‘Super Electron Donors’

Powerful Reductions Performed by Neutral Organic Molecules

by

Franziska Schönebeck

A thesis submitted to the University of Strathclyde

In part fulfilment of regulations for the degree of

Doctor of Philosophy in Chemistry

WestCHEM, Department of Pure and Applied Chemistry

University of Strathclyde, Thomas Graham Building

295 Cathedral Street, Glasgow G1 1XL, UK

2007

Acknowledgments

I would like to thank Prof. John Murphy for his guidance throughout the past years, for his constant help, encouragement and discussions as well as the teaching.

Further thanks go to the members of the Murphy group – past and present – especially to Douglas Thomson, Dr. Sheng-ze Zhou and Dr. Mahesh Mohan.

I am grateful to Neil Findlay and Stuart Park for electrochemical measurements and to Dr. Tell Tuttle for computational investigations and advise.

Finally, I would like to thank all Technical Staff for their support.

DECLARATION OF COPYRIGHT

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ABBREVIATIONS

Ac	acetyl
AIBN	azo*iso*butyronitrile
AM1	Austin Model 1
Ar	aryl
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
BT	benzothiazole
Bu	butyl
°C	degree(s) centigrade
cat.	catalytic
CI	chemical ionisation
Cp	cyclopentadienyl
d	doublet or day(s)
DCM	dichloromethane
de	diastereomeric excess
DIAD	di*iso*propyl azodicarboxylate
DMA	dimethylacetamide
DNA	2'-deoxyribonucleic acid
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
E°	standard reduction potential
$E_{1/2}$	half-wave potential [cyclic voltammetry]
$E'_{1/2}$	half-wave potential [polarography]
E_p	peak potential [cyclic voltammetry]
ee	enantiomeric excess
e.g.	*exempli gratia*
EI	electron impact
Et	ethyl
equiv.	Equivalent(s)
ESI	electrospray ionisation
Et	ethyl
g	gram or grams
h	hour/hours
HMPA	hexamethylphosporamide
HOMO	highest occupied molecular orbital
i.e.	*id est*
IR	infrared

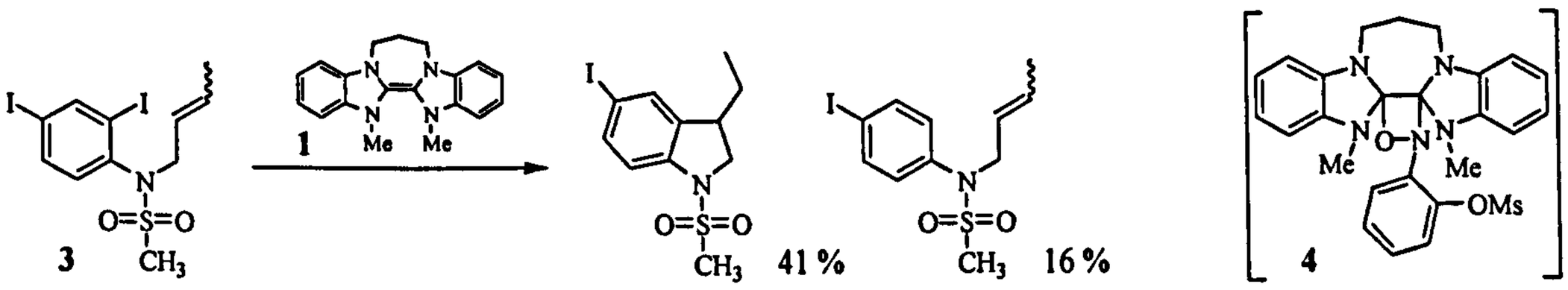
ir.	irreversible
J	coupling constant
JMOD	J modulated
KHMDS	potassium bis(trimethylsilyl)amide
Lit	literature
LUMO	lowest unoccupied molecular orbital
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute(s)
ml	millilitre(s)
mol	mole(s)
mmol	millimole(s)
Ms	methanesulfonyl
mp	melting point
m/z	ratio of mass to charge
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
Ph	phenyl
ppm	parts per million
Pr	propyl
sat.	saturated
SET	single electron transfer
SOMO	singly occupied molecular orbital
t or *tert*	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TDAE	tetrakis(dimethylamino)ethylene
THF	tetrahydrofuran
TLC	thin layer chromatography
Tf	trifluoromethanesulfonate
TS	*p*-toluenesulfonyl
TTF	tetrathiafulvalene
TTMSS	tris(trimethylsilyl)silane
UHF	unrestricted Hartree-Fock
UV-Vis	ultraviolet visible
vs.	*versus*
X	halogen
y	yield

ABSTRACT

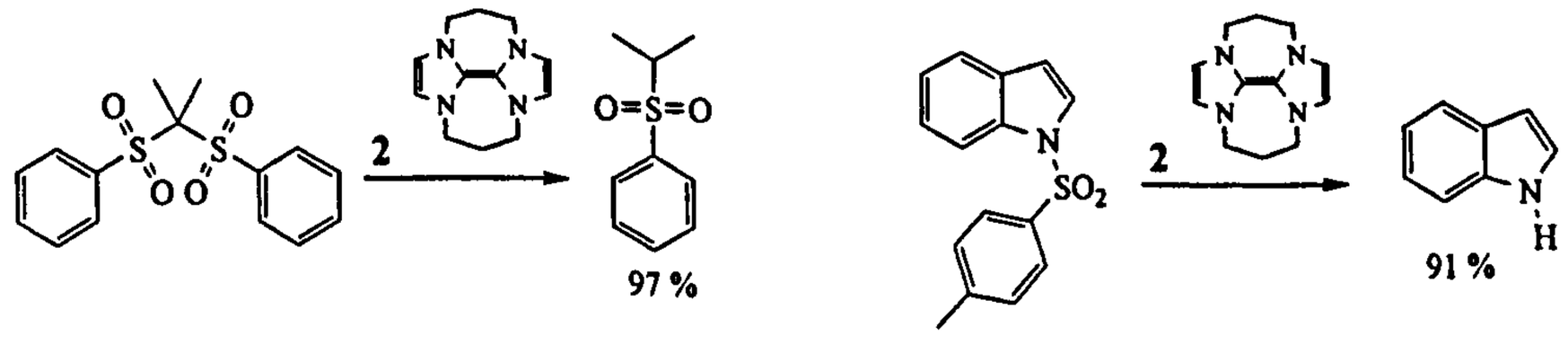
This project aims to explore the ability of organic molecules to transfer electrons and is based on the recent development within the Murphy group of a novel organic molecule, called Super-S.E.T. reagent **1**, that allows the reduction of unactivated aryl and alkyl iodides. My study investigates the scope of donor **1** as a reducing agent and extends the study to a more powerful donor **2**.

Chapter One provides an introduction to the world of electron transfer. After giving a theoretical background, synthetic applications of electron transfer are highlighted, in particular using metal chemistry, electrochemical and photochemical methods. This chapter also discusses the use of sulfones and sulfonamides as challenging substrates for electron transfer. Finally the field of neutral organic electron-donors, which form the basis of my studies, is introduced.

Chapters Two to ***Seven*** then summarise my work. ***Chapter Two*** and the second part of ***Chapter Six*** highlight my adventures in investigating the chemistry of donor **1**. Until now, donor **1** is known to reduce efficiently only specific aryl and alkyl iodides. This report (i) highlights the scope and limitations of donor **1** in the reduction of different aryl iodide substrates and of aryl halides other than iodides and (ii) discusses the application of donor **1** in the selective reduction of an *ortho*- over an analogous *para*-aryl iodide in substrate **3** and (iii) recounts the successful isolation of the first adduct of the donor, *i.e.* **4**.

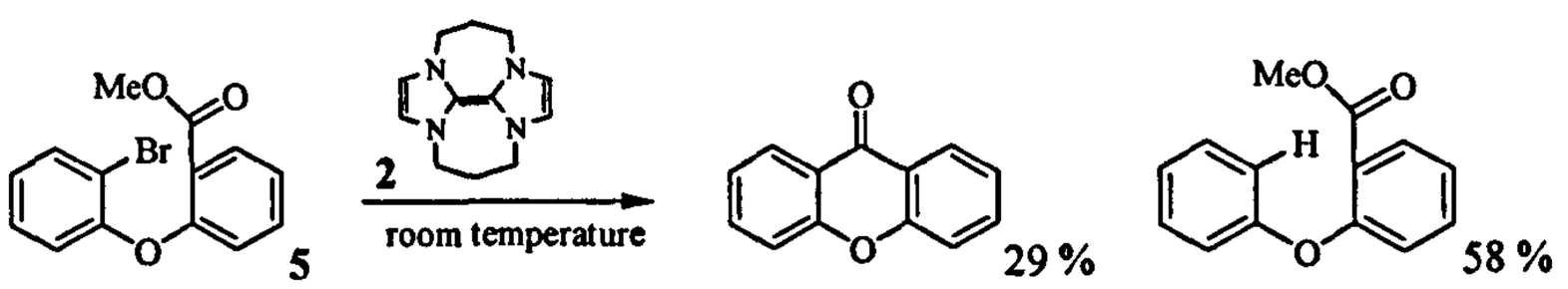


Chapter Three to ***Six*** deal with the exploration of the power of Super-S.E.T. reagent **2**. This donor was successfully applied as a powerful reducing agent in the reductive cleavages of a number of activated sulfones and sulfonamides, giving the reduced counterparts in excellent yields. Further, strong evidence for the first example of a Julia olefination using a neutral organic electron donor has been given.

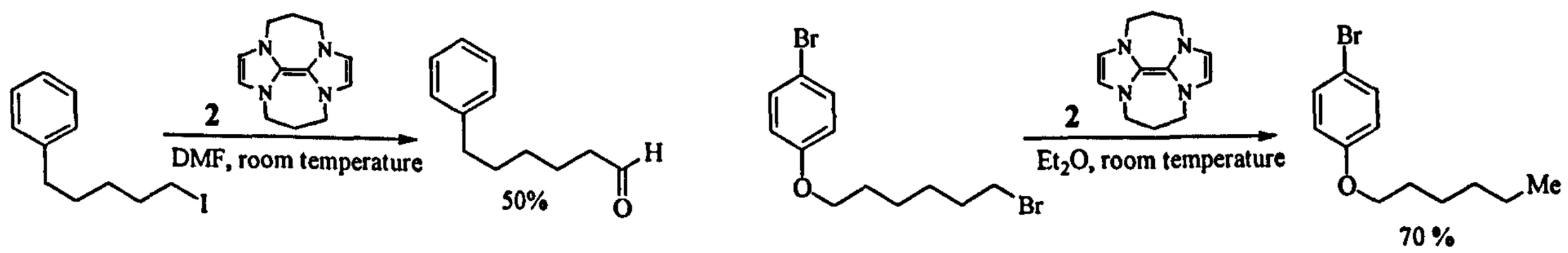


It was also shown that the reagent has remarkable reducing power, being the first neutral organic reagent to generate highly reactive aryl anion intermediates in the reduction of aryl

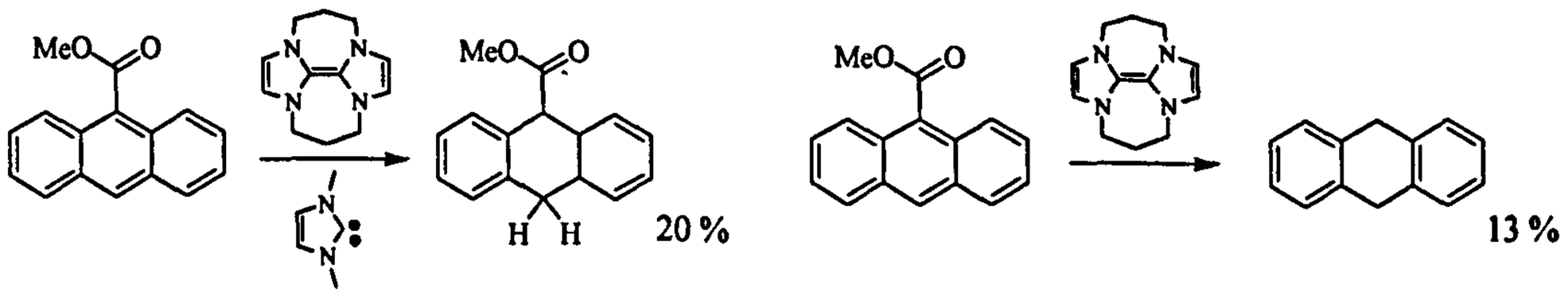
bromides and iodides. Ester substrates **5**, **6** and **7** were synthesised and investigated as mechanistic probes in that context.



The chemistry of donor **2** with aliphatic halides was investigated, leading to the formation of aldehydes in DMF or DMA. It was found that the proportion of aldehyde can be increased with more equivalents of donor **2**, ultimately leading to the aldehyde being the exclusive product. Using non-polar solvents, such as diethyl ether, donor **2** was transformed into a powerful reducing agent for alkyl bromides, reacting at room temperature and showing radical chemistry. Selective reduction of an alkyl over aryl bromide was achieved also.



Intriguing reactivity was observed with anthracene esters, giving the dihydroester as one of the major products, if a carbene is added, and dihydroanthracene, if not.



After a summary of results in ***Chapter Seven***, ***Chapter Eight*** presents the experimental procedures and analytical data for the compounds discussed in ***Chapters Two*** to ***Six***.

Introduction

Introduction

1.1 Theoretical background

The following section discusses theoretical aspects of electron-transfer. Marcus theory is introduced firstly, redox potentials are then considered, followed by the chemistry of radical-anions, highlighting the factors and mechanisms governing reductive bond cleavages. The understanding of redox potentials as well as reduction processes is particularly important for the research discussed in this thesis.

1.1.1 *Marcus Theory*

Rudolph A. Marcus was awarded the Nobel Prize in 1992 for his contribution to the field of electron-transfer. He developed the theory that became later famous as Marcus theory,[1] covering the physical and theoretical background to allow a deep understanding of electron-transfer processes.

To understand Marcus' new idea and development in the theory of electron-transfer, a little background is required:[2]

If two molecules in solution are considered that exchange an electron, both molecules will undergo a considerable change in structure by accepting or donating the transferred electron. The environment, however (the solvent molecules in this case), needs to undergo change also, as two new ionic species are formed that require different solvation to stabilise them with respect to the starting molecules. Hence, a number of changes is required for the electron-transfer to occur and, therefore, a considerable rise in energy can be expected. The amount of energy required, or in other words the size of the energy barrier, determines the rate of the electron-transfer reaction.

At this point Marcus' new concept came into play.[3] He assumed that the two molecules undergoing electron exchange have to be bound loosely. Further, he named the energy required for such structural changes the "reorganisation energy" and termed it as λ.

In **Figure 1.1**[4] two curves are shown, with the left representing the energies of the starting molecules and the right representing the energies of the product molecules after the electron-transfer step. The minima illustrate the equilibrium positions of the molecules before and after the reaction. The point where both curves intercept, is the point where electron-transfer occurs. λ is the energy difference between the bottom of the left curve

and a point vertically above on the upper part of the other curve (representing the reaction products before any atomic positions have been changed).

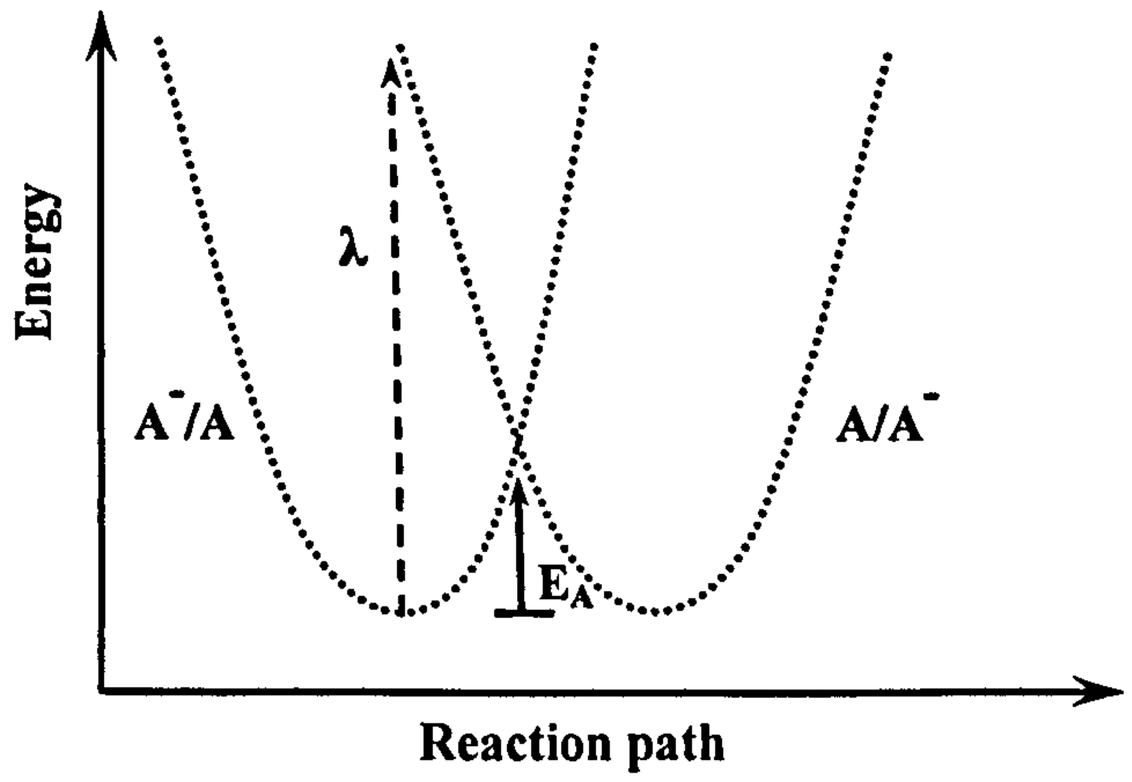


Figure 1.1 **Potential energy diagram of self-exchange electron-transfer reaction**

$A^- + A \rightleftharpoons A + A^-$

As can be seen in the above **Figure 1.1** the activation energy ($E_a = \Delta G^*$) to undergo the electron-transfer reaction is only a part of the overall reorganisation energy λ. This was incorporated by Marcus by adding the factor ¼ into his general equations (2) describing the rate of electron-transfer reaction.

(1) $$k = A \cdot \exp\left(\frac{-\Delta G^*}{k_B T}\right)$$ (2) $$\Delta G^* = \frac{\lambda}{4}\left(1 + \frac{\Delta G^0}{\lambda}\right)^2$$

(3) $$\lambda = \lambda_O + \lambda_i$$ (4) $$\lambda_O = (\Delta e)^2\left(\frac{1}{2a_1} + \frac{1}{2a_2} - \frac{1}{R}\right)\left(\frac{1}{D_{OP}} - \frac{1}{D_S}\right)$$

The rate of electron-transfer (*k*) is given by equation (1). ΔG*, the energy barrier of the reaction, is described further in equation (2). λ is composed of solvational (λ_0) and vibrational (λ_i) components [equation (3)]. k_B Is the Boltzmann constant, A depends on the nature of the electron-transfer reaction (*e.g.* intra- or intermolecular), T is the absolute temperature at which the reaction occurs and R is the centre-to-centre separation distance between the reactants. ΔG^0 Is the standard free energy of reaction (driving force), a_1 and a_2 are the ionic radii of the reactants, D_{op} and D_s are optical and static dielectric constants of the solvent and Δe represents the charge transferred from one reactant to the other.

For a reaction in which energy E is liberated, the upper diagram will change slightly. The curve representing the products (marked as D^+/A^-) will now move down by the amount of energy liberated, E, and the activation energy (E_a) is decreased (**Figure 1.2**).[4]

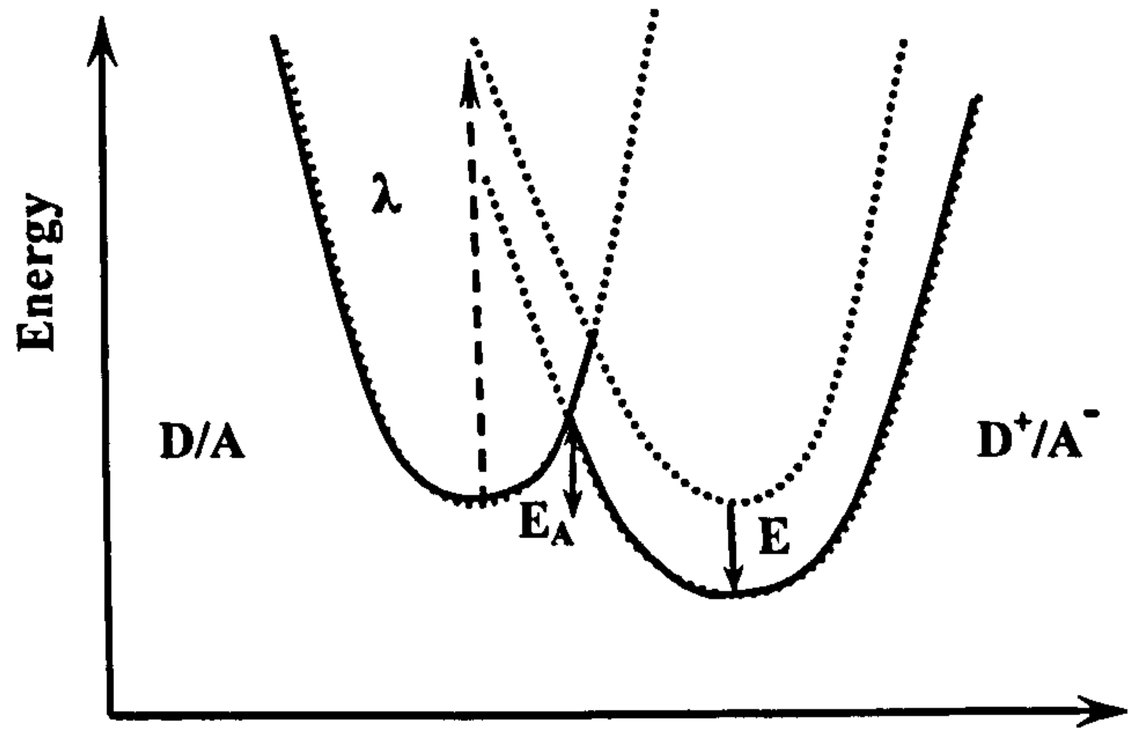


Figure 1.2 **Potential energy diagram of energy-liberating electron-transfer reaction**
$D + A \rightleftharpoons D^+ + A^-$

If the driving force of the reaction increases, *i.e.* the amount of energy liberated increases, which corresponds to a very negative change in free energy, the right curve will move down even further and eventually E becomes greater than the reorganisation energy λ **(Figure 1.3).**[4]

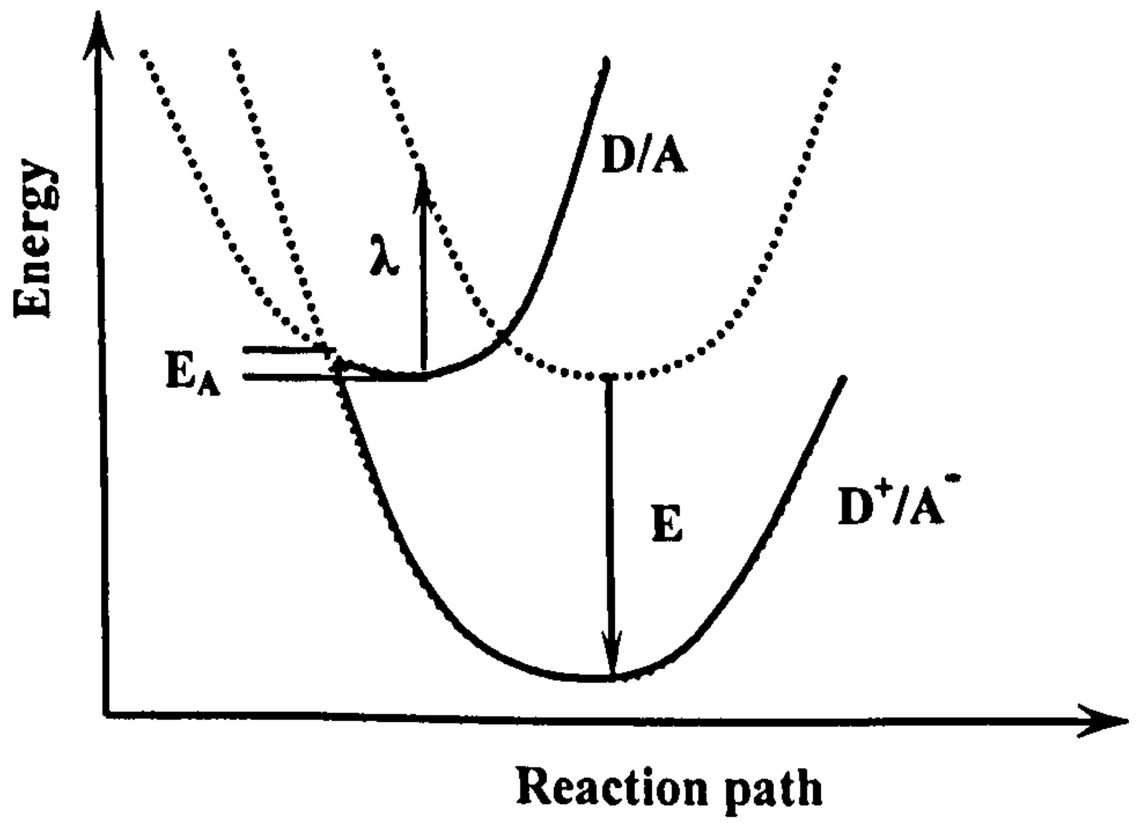


Figure 1.3 **Potential energy diagram of electron-transfer reaction $D + A \rightleftharpoons D^+ + A^-$**
Illustration of inverted region

This situation became famous as the "inverted region" of electron-transfer. This is the novel and most revolutionary feature of the Marcus theory, because in contrast to any existing understanding of reactions at that time when Marcus published his work, in this region the rate of electron-transfer reactions decreases with increasing driving force as shown in **Figure 1.4.** Therein, the changeover from normal (left) to inverse (right) behaviour can clearly be seen.

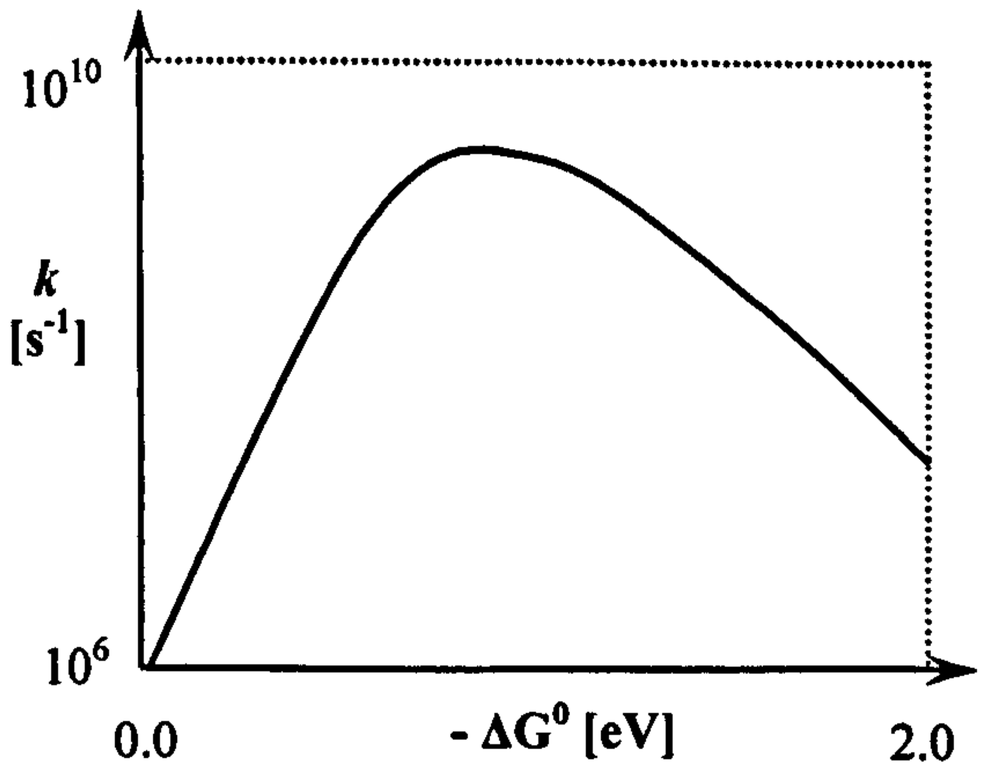


Figure 1.4 **Connection between reaction speed (k) and driving force (ΔG°) for an electron-transfer reaction**

Twenty-five years after being predicted by Marcus, the existence of the inverted region was confirmed experimentally for the back electron-transfer process in a radical ion pair that was produced by intermolecular electron-transfer reaction,[5] and also in a number of intramolecular electron-transfer systems, exhibiting donor and acceptor connected covalently at a fixed distance.[6,7]

1.1.2 *Fundamentals of Electrochemistry*

Standard potentials – what they mean and what they tell us.[8]

When considering a reaction between a possible electron donor and a possible electron acceptor, it is important to decide in the first place whether the reaction will occur. The question can frequently be answered by comparing the standard reduction potentials $E°$ of the reactants. For the following reaction (**Scheme 1.1**),

$$A + D \rightleftharpoons A^- + D^+$$

Scheme 1.1

the corresponding equilibrium constant K is related to the difference between the standard reduction potentials $E°_{A/A^-}$ and $E°_{D^+/D}$ of the A/A^- and D^+/D couples, respectively. From the expression (5) below it follows for K, that if $E°_{A/A^-}$ is much greater than $E°_{D^+/D}$, the equilibrium of the reaction shown in **Scheme 1.1** will be displaced to the right-hand side. The equilibrium will be displaced to the left-hand side accordingly, if the reverse is true (*i.e.* $E°_{A/A^-} << E°_{D^+/D}$). If both potentials are of similar magnitude, the reactant and product concentrations obviously depend on the potential difference.

$$(5) \qquad K = \exp[F(E^0_{A/A^-} - E^0_{D^+/D})/R \cdot T]$$

This equation (5) arises from the usual thermodynamic equilibrium expression (6), replacing the standard free energy difference with its electrochemical counterpart (7), the standard potential.

$$(6) \qquad K = e^{\frac{-\Delta G°}{RT}} \qquad (7) \qquad \Delta G° = -\nu \cdot F \cdot \Delta E°$$

K: equilibrium constant; $\Delta G°$: difference in standard free energy; R: universal gas constant; T: absolute temperature; ν: number of exchanged electrons; F: Faraday constant.

Rearranged further, this expression appears in the form of the Nernst equation (8), that is named after 1920's Nobel Prize winner, Walther H. Nernst, and correlates the free energy with the electromotive force of the galvanic cell. It allows the calculation of the potentials depending on concentrations and conditions (*i.e.* temperature, see equation).

$$(8) \quad \Delta E = \Delta E° + \frac{RT}{F} \ln \frac{[A] \cdot [D]}{[A^-] \cdot [D^+]}$$

According to its definition, the standard (reduction) potential of the A/A^- couple is the standard electromotive force of a cell in which an A/A^- electrode is opposed to a standard electrode [usually hydrogen electrode, but among others a saturated calomel electrode (SCE) might also be used] whose potential is assigned 0 by convention. Thus, the standard reduction potential $E°$ is then ascribed to the 'half-reaction' illustrated in **Scheme 1.2.**

$$A + e^- \rightleftharpoons A^- \qquad (E°)$$

Scheme 1.2

The Nernst equation for this half-cell reaction then simplifies to appear in the form below (9):

$$(9) \qquad E = E° + \frac{RT}{F} \ln \frac{[A]}{[A^-]} .$$

Strong electron donors will generally have very negative reduction potentials and acceptors generally more positive reduction potentials, whereupon with increasing negative value the acceptor becomes more difficult to be reduced.

For completeness it has to be mentioned, that the potential E is dependent also on the pH and solvent used, or more generally, the ionic strength of the solution. This is normally accommodated in the Nernst equation by replacing the concentrations with activities.

1.1.3 *Radical-anions*

Reductive Bond Cleavage

Radical-anions have received much attention,[9] as the transition into a radical-anion state activates organic molecules and gives rise to several interesting transformations, such as their reactions with free radicals,[10] fragmentation[11] or dimerisation[12] or even leads to DNA damage in a biological context.[13] Radical-anions are usually generated by one electron reduction, *i.e.* an electron is injected into the LUMO of the molecule. If the LUMO is the antibonding orbital of a characteristic bond (σ*-orbital), this bond will be weakened (due to the decrease in bond order) and subsequently cleaved (**Scheme 1.3**). This is generally the case for alkyl halides.[14]

$$A\text{-}B \xrightarrow{e^-} A\bullet + B^-$$

Scheme 1.3

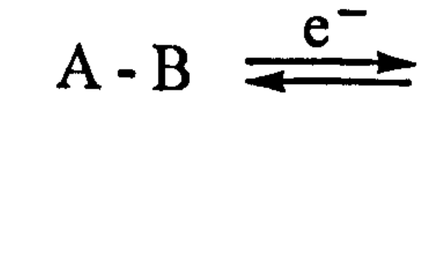
However, bond cleavage can also occur if the LUMO is a π-type orbital, as long as a relatively low-lying σ*-orbital is available to which the excess electron can be transferred. Di-*para*-nitroaryl disulfides typically undergo this "stepwise" bond dissociation (of the S-S bond).[11] Therein, the electron is initially transferred into a π*-orbital, which becomes the SOMO. The SOMO is weakly coupled with the σ*-orbital of the A-B bond, and the electron transition is accompanied by considerable stretching of the A-B bond and its subsequent cleavage (**Scheme 1.4**).

$$A\text{-}B \rightleftharpoons (A\text{-}B)^{\bullet -} \longrightarrow A\bullet + B^-$$

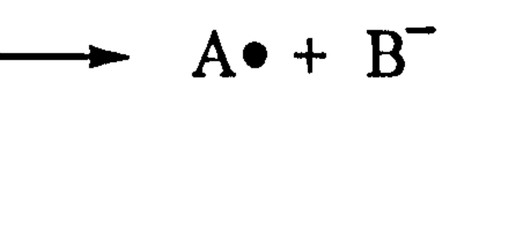
Scheme 1.4

Benzyl and aryl halides are further interesting examples of a predominantly stepwise cleavage mechanism. For aryl halides, as opposed to benzylic halides, the σ*-orbital, to which the electron transition occurs, is orthogonal to the π-system, *i.e.* there is no overlap between the orbitals (**Scheme 1.5**).

Scheme 1.5

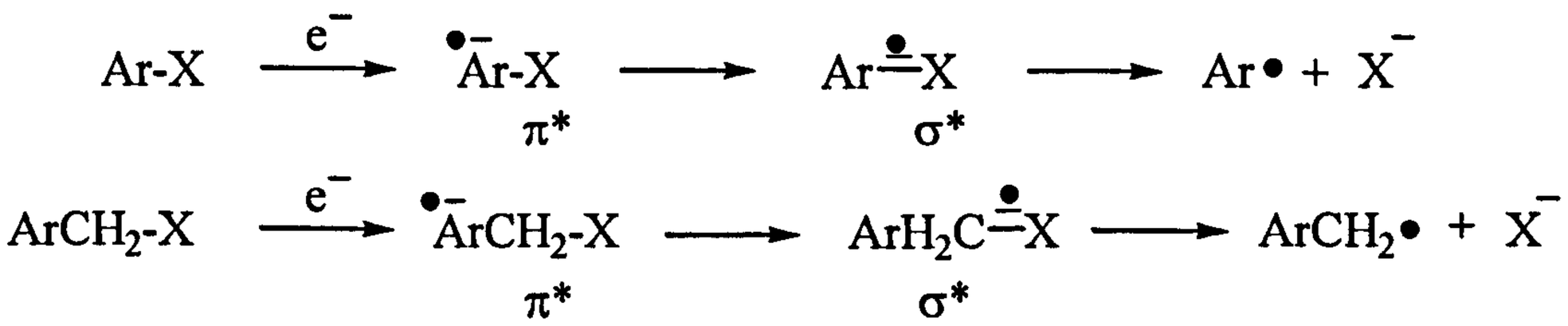


aryl halides
no π*-σ* overlap



benzyl halides
good π*-σ* overlap

Nevertheless, electron-transfer from π^* to σ^*, although being formally forbidden, can occur. It requires out-of-plane vibrations that lead to bending of the aromatic-halogen bond.[15] After electron transition from the π-system to the σ^* orbital, a three-electron bond radical-anion intermediate is formed that dissociates further into a carbon-centred radical and the anion of the leaving group (**Scheme 1.6**).[16]



Scheme 1.6

Savéant describes[17] the bond-cleaving process without the presence of the three-electron-bond radical intermediate. He suggests that the cleavage of the anion radical may be viewed as an intramolecular concerted electron-transfer-bond breaking process. While the breaking bond is stretched, the energy of its antibonding orbital is lowered and once the energy is low enough to match with the energy of the initial LUMO (π^* for many aromatic systems), where the extra electron is located, the electron is transferred and the bond cleaved concertedly.

In contrast to aryl halides, benzyl halides are not in π-conjugation with the aromatic ring, [leading to a stronger carbon-halogen bond for aryl halides] and show considerable π^*-σ^* overlap (see **Scheme 1.5**), which explains the much weaker C-halogen bond and hence the observed faster bond dissociation after electron-transfer.[18]

This introduces the main factors governing the reductive bond dissociation: the nature of the halogen and its relative position towards substituents in the ring are of importance for the rate of dehalogenation of benzyl and aryl halides. The rate increases for decreasing bond strength of the C-X bond (cleavage rate: I > Br > Cl)[14] and is greater if an electron-withdrawing group is located in the *ortho*- rather than the *para*-position relative to the leaving halide. It is assumed that this behaviour is due to steric effects. For *ortho*-nitroaryl halides the halogen atom is believed to influence the nitro group sterically, so that conjugation is prevented and hence stabilisation of the radical-anion is diminished. Therefore, dissociation of the C-halogen bond is favoured.[19] *Meta*-substitution leads to even slower dehalogenation than *ortho* and *para* because of the very low spin density at

the *meta*-position which disfavours intramolecular electron-transfer from the nitro-group (to which the initial electron transfer occurs) to the halide.

A further crucial factor influencing the rate of reductive bond cleavage is the standard potential ($E°$) for the formation of the radical anion of the substrate. $E°$ is a measure of the energy of the π*-orbital (for most aromatic compounds) or, more generally, any other low-lying orbital to which the electron may be transferred.[17] In other words, a low reduction potential (in absolute value) corresponds to a low-energy LUMO and hence fast and easy initial electron-transfer to form the radical-anion.

The above stated factors are not the only ones governing the driving force of reductive bond cleavage. Further variables, such as entropic terms and oxidation potential of the leaving group also contribute, but will remain undiscussed within the scope of this review.[14]

However, comment must be made on the uncertainty of stepwise or concerted mechanisms for the reductive bond cleavage of aryl and benzyl halides. In this context, it has been shown by Savéant and co-workers[20] with cyclic voltammetry that both iodobenzene and 3-methyliodobenzene follow a concerted pathway in the cleavage of the C-halogen bond; upon increase of driving force of the reaction (*i.e.* scan rate in electrochemical terms), however, the mechanism changes to stepwise.

Benzyl halides are on the borderline between stepwise and concerted mechanisms as they feature a π-system to accommodate an incoming electron, but at the same time their C-X bond is considerably weaker (see discussion above). Hence, either pathway is possible, depending on the ring-substitution pattern of the benzyl compound. Nitrobenzyl halides, for instance, have been shown to undergo stepwise cleavage, whereas no substituents or weakly electron-withdrawing substituents, such as a cyano group, lead to concerted reductive cleavage of the corresponding benzyl compound, benzyl chloride and cyanobenzyl bromide respectively.[21,22]

However, the reaction medium, *i.e.* the solvent, has also an influence on the mechanism of the reductive cleavage. Thus it has been observed by UV-Vis spectroscopy that the radical-anion of 3-cyanobenzyl bromide dissociates in water in a stepwise manner with a rate constant of $k = 1.3 \times 10^7\ s^{-1}$.[23] In DMF during electrochemical reduction, electron-transfer

and bond cleavage seem to occur concertedly. This different behaviour is presumed to be based on solvation effects.[22,24,25]

Reductive bond formation

To address the variety in reactivity of radical-anions, the following paragraph will deal with bond formation processes. Although reductive bond dissociations may lead to bond formation in follow-up reactions from the radical intermediate, radical-anions can also undergo bond-forming processes right at the stage of the anionic radical intermediate. This is possible, if the LUMO contains significant π^*-character and transition to σ^*, followed by irreversible bond cleavage, is precluded due to the absence of low lying σ^*-orbitals of suitable leaving groups. Such radical-anions will react with electrophiles (proton, cation, unsaturated electron-poor system) or another odd-electron species (charged or neutral radical) to form new bonds.[9]

Synthetic examples and applications of reductive bond formation, such as the Birch reduction or the pinacol reaction as the most famous representatives of this process, will be discussed in chapter 1.2.1.

1.2 Electron-transfer in synthesis

Electron-transfer based chemical reactions can be found across many different areas of organic synthesis. Various metal-based reactions, photochemical processes and the entire branch of electro-organic chemistry can be assigned to electron-transfer.

Therefore, this section attempts to give a broad overview and to cover many different kinds of synthetic applications of electron-transfer.

1.2.1 *Metals as electron-transfer reagents*

(i) Alkali metals

Alkali metals (Li, Na, K) are the strongest reducing agents, with standard potentials of about -3 V relative to SCE in aqueous systems. Their redox potentials vary considerably with solvent (±1V) due to the variation in solvation of the cation. Sodium (Na/Na^+), for instance, exhibits a 1V less negative potential (*i.e.* -2 V) in ammonia than in DMF; it reacts with ammonia to give solvated sodium cations and a deep-blue solution of solvated electrons (**Scheme 1.7**):[26]

$$Na + (n+m)NH_3 \xrightarrow{NH_3} [Na(NH_3)_n^+] + [e(NH_3)_m]^-$$

Scheme 1.7

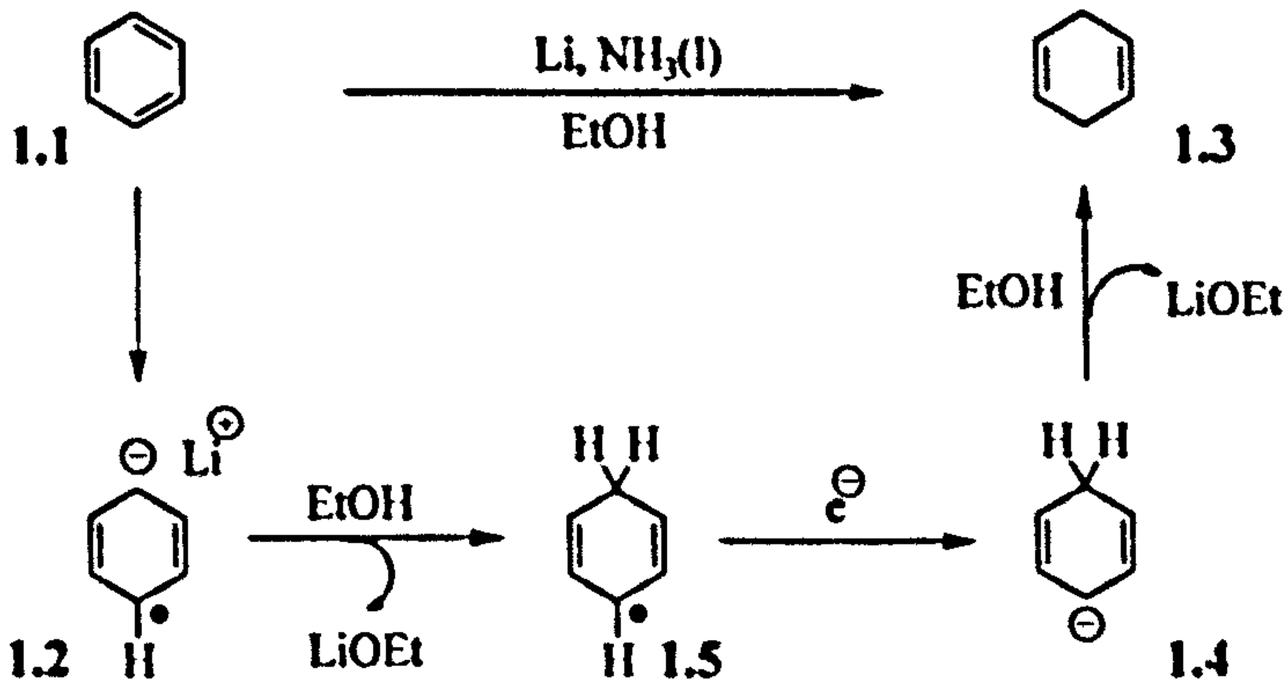
The redox potentials of the most commonly used reducing agents in water are given in **Figure 1.5**[26] to provide an indication of the metals' reducing power.

Reaction	$E°$(V)
$Li^+ + e^- \rightarrow Li$	- 3.045
$K^+ + e^- \rightarrow K$	- 2.925
$Na^+ + e^- \rightarrow Na$	- 2.714
$Al^{3+} + 3\ e^- \rightarrow Al$	- 1.660
$Zn^{2+} + 2\ e^- \rightarrow Zn$	- 0.763
$Fe^{2+} + 2\ e^- \rightarrow Fe$	- 0.440
$Sn^{2+} + 2\ e^- \rightarrow Sn$	- 0.140

Figure 1.5 Most common metals used as reducing agents

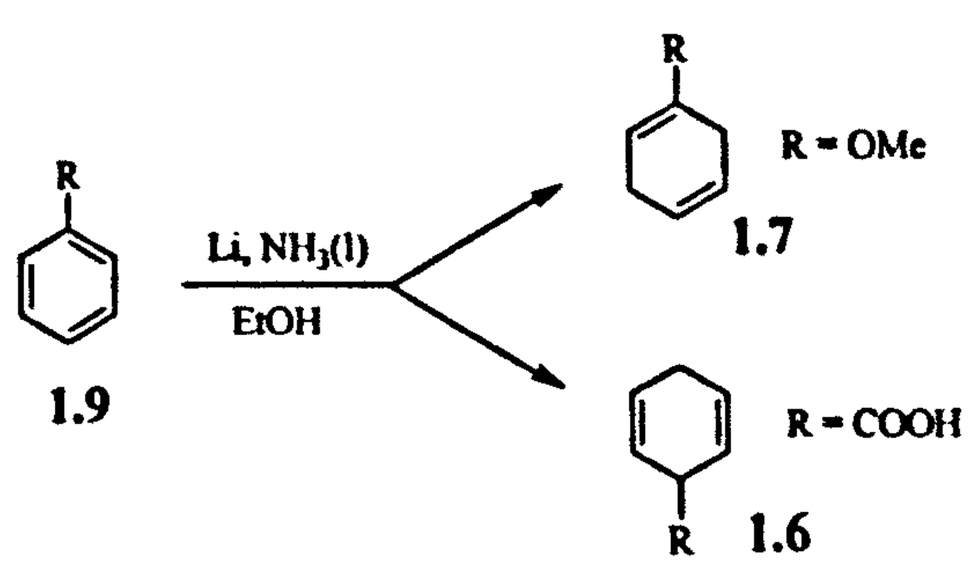
Perhaps the most famous reaction involving alkali metals is the Birch reduction,[27] which is used to reduce aromatic systems to their dihydro-counterparts as well as alkynes to alkenes, and can also be applied to reduce other functional groups.

After the metal is dissolved in liquid ammonia as shown below in **Scheme 1.8**, an electron is transferred to the substrate, here benzene **1.1**, to form a radical-anion **1.2**. This is then protonated, traditionally by an alcohol, such as ethanol or tertiary butanol, and reduced further, followed by another protonation to give cyclohexadiene **1.3** (**Scheme 1.8**).



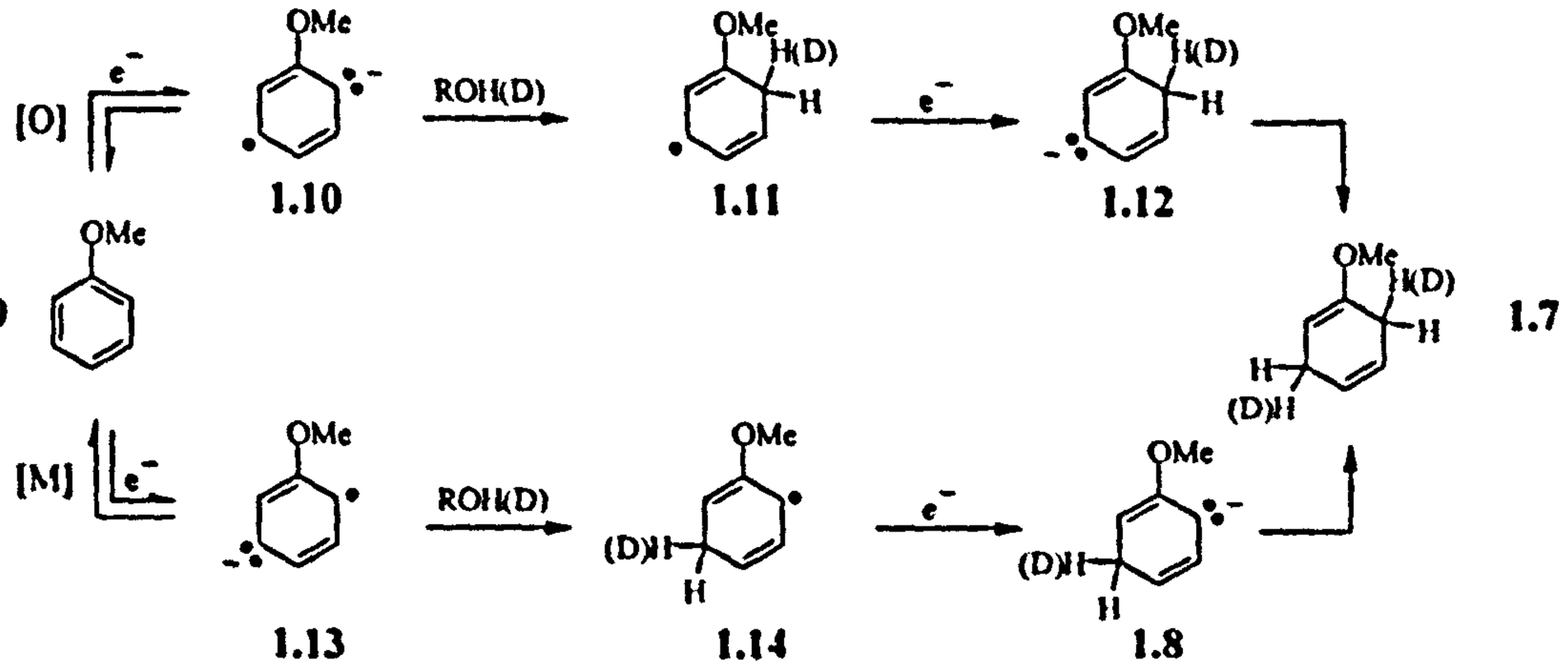
Scheme 1.8

Substituted benzenes are reduced in a regioselective fashion (**Scheme 1.9**). This issue of selectivity has been studied extensively by theoreticians throughout the decades.



Scheme 1.9

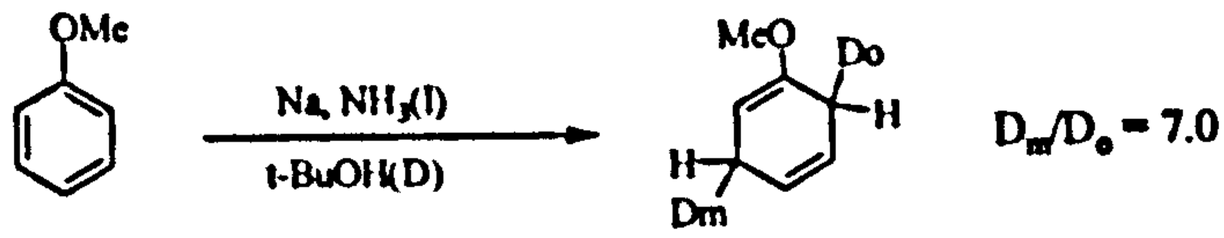
Considering anisole, there are two possible reaction paths that will lead to the identical regioisomer. Whereas the generation of the above isomer **1.7** has clearly been accepted and widely proven by various experiments, the mechanism of its formation remains widely discussed by theoreticians.



Scheme 1.10

As shown in Scheme 1.10 there are two possible mechanisms of formation of the regioisomer formed by reduction of anisole 1.9. The path [O] describes initial electron-transfer to form the aryl radical-anion 1.10, bearing the greatest anionic character *ortho* to the methoxy group. Protonation of this species [which is the rate determining step of the process] will give rise to radical 1.11 that is then reduced further to the carbanion *meta* to the methoxy group 1.12. After rapid protonation of the carbanion, regioisomer 1.7 is formed. Alternatively, the radical-anion may be illustrated as shown in the lower reaction path, 1.13, where the anionic charge is greatest located *meta* to the methoxy group. Both mechanisms will give rise to the same isomer. Birch proposed originally mechanism [M] to be valid, assuming the greatest electron density in the *meta* position of the radical-anion.[28] Hückel calculations on anisole revealed that it is the position *ortho* to the methoxy group which is most electron-rich in the radical-anion.[29] Thus mechanism [O] was suggested and followed. In a more recent publication Birch *et al.* suggest protonation at both sites with a slight preference for *ortho*, *i.e.* both mechanisms are operating.[30] Since the literature has not been consistent in favouring one mechanism over the other, Zimmerman and Wang had a practical as well as theoretical approach to the problem. Their approach[31] was based on the expected greater primary deuterium isotope effect expected for the protonation of less basic anions relative to more basic anions. Since the radical-anion [formed in the initial step of the Birch reduction] is less basic[32] than the carbanion and hence its rate of protonation is lower,[33] the radical-anion should be more selective in deuterium incorporation than the carbanion. Accordingly, if mechanism [O] is followed in the reduction of anisole, then the anion of the radical-anion is located *ortho* to the methoxy group and should have a lower deuterium incorporation than the *meta* position, where the anion in 1.12 will be formed. This anion is more reactive and hence less selective towards deuterium incorporation. If mechanism [M] is followed on the other hand, the *meta*

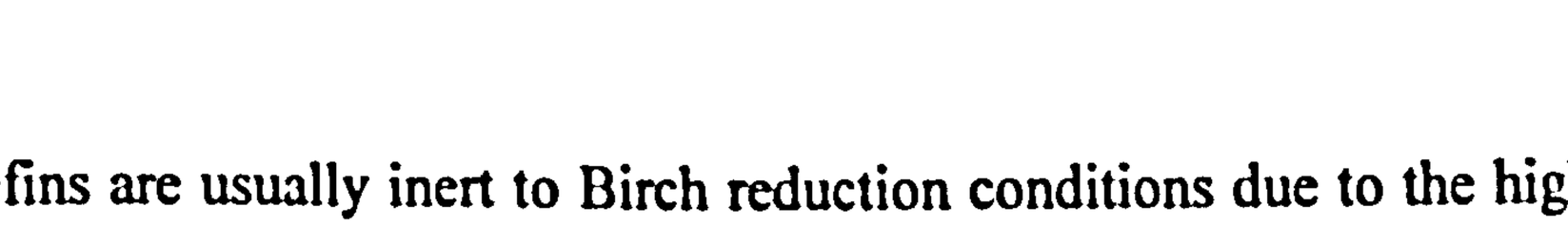
position should be deficient in deuterium relative to *ortho*. When the experiment was carried out using sodium as the metal and *tert*-butanol (1-2 % ^{t}BuOD) as the proton source at –78°C in ammonia, it was found that a seven-fold preference in deuterium incorporation in the *meta* position had taken place, consistent with mechanism [O]. There was concern that the products resulting from Birch reduction might undergo an exchange reaction and might incorporate deuterium, so that the deuterium distribution would not be based on kinetics anymore. Thus, blank experiments were carried out, in which dienes were exposed to basic conditions simulating the Birch reduction, but no deuterium incorporation was observed.[31]



1.9 **1.7**

From further theoretical considerations it was concluded that the stability of the produced radical after protonation of the radical anion and thus its effect on the transition state is important also. Thus, radical **1.11** experiences resonance stabilisation from the methoxy group, where **1.14** does not. This is in agreement with calculations (UHF/3-21G), where it was determined that there is a 3.3 kcal/mol preference for *ortho* protonation.[31] Overall, Zimmerman and Wang concluded that mechanism [O] is not the exclusive one, and that both mechanisms, [O] and [M], operate, with a preference for [O].

Ordinary olefins are usually inert to Birch reduction conditions due to the high energy of their π^*-orbital. However, conjugated or phenyl-substituted double-bonds are reduced [conjugation lowers energy of π^*] as well as isolated alkynes to their corresponding *E*-alkenes, where the selectivity arises from protonation of the thermodynamically more stable anionic precursor intermediate, which adopts *E*-configuration (**Scheme 1.11**).[34,38]

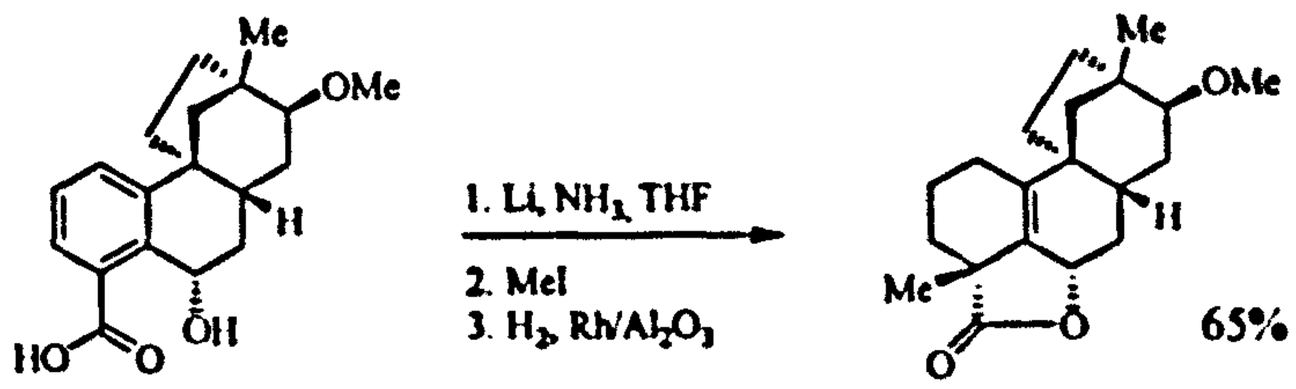


1.19 **1.20** **1.17** **1.18**

1.16 **1.15**

Scheme 1.11

Recently, Overman *et al.*[35] applied the Birch reduction, followed by *in situ* alkylation of the anionic intermediate to generate an alkylated cyclohexadiene moiety, in their synthesis of **1.22** (Scheme 1.12).

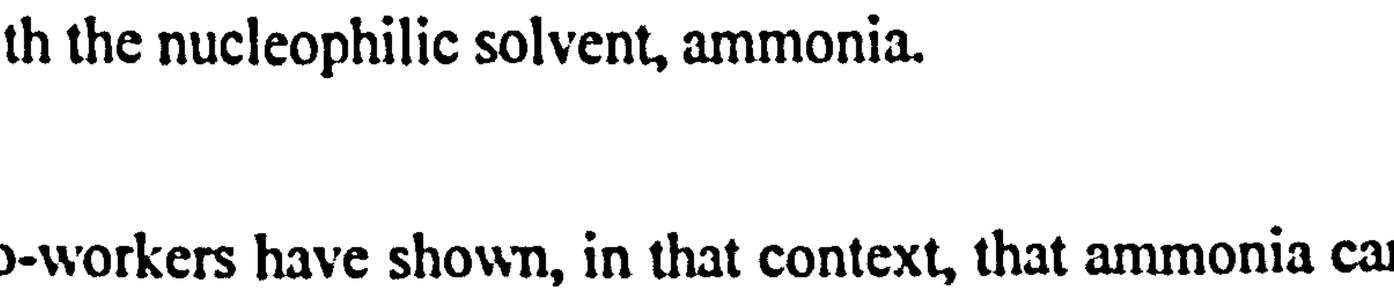


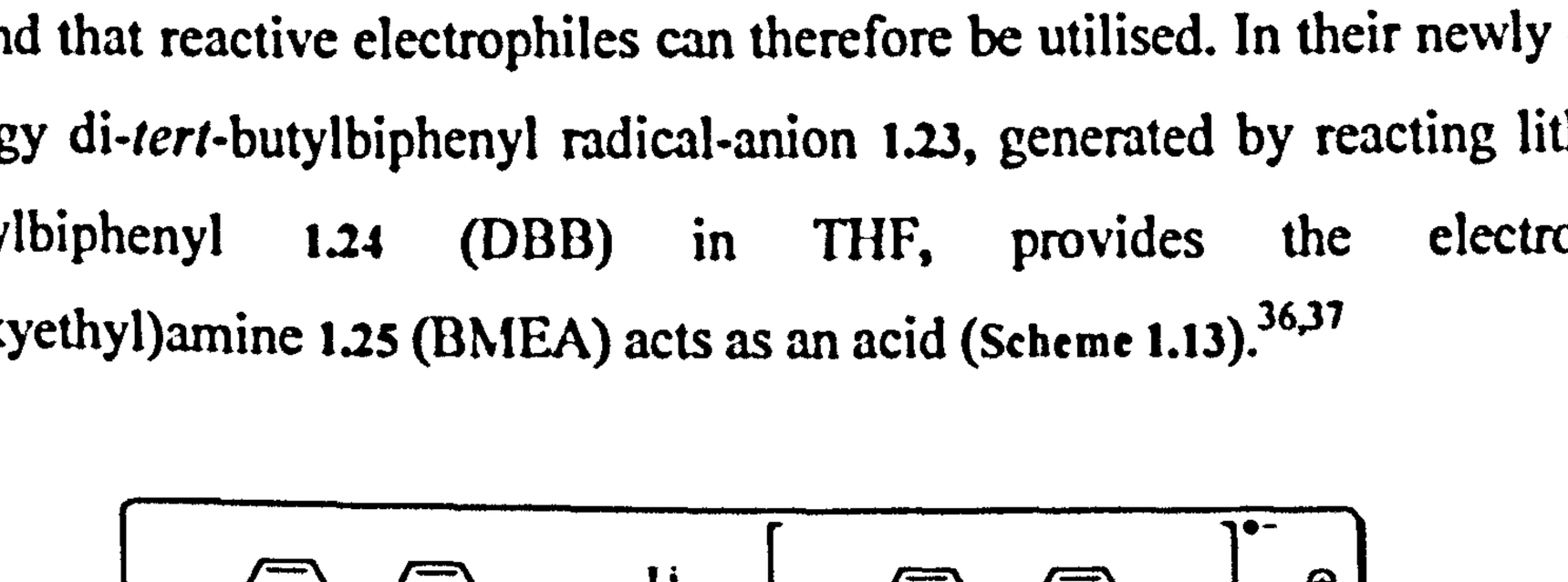
1.21 **1.22**

Scheme 1.12

Research is ongoing to avoid the relatively harsh reduction conditions and to increase the number of electrophiles that could be used to trap the anionic intermediate beyond the alkyl halides as illustrated in the previous synthesis by Overman *et al.* The limitation is that very reactive electrophiles, such as enolisable aldehydes, silyl halides or acid chlorides are incompatible with the nucleophilic solvent, ammonia.

Donohoe and co-workers have shown, in that context, that ammonia can be fully replaced by THF, and that reactive electrophiles can therefore be utilised. In their newly developed methodology di-*tert*-butylbiphenyl radical-anion **1.23**, generated by reacting lithium with di-*tert*-butylbiphenyl **1.24** (DBB) in THF, provides the electrons, and bis(methoxyethyl)amine **1.25** (BMEA) acts as an acid (Scheme 1.13).[36,37]

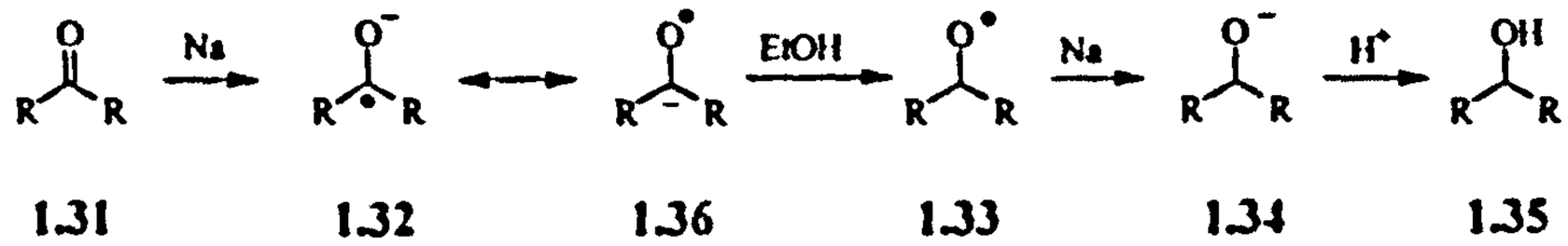




Scheme 1.13

Exposing alkali metals to certain functional groups leads to their reduction. Thus, carbonyl groups are reduced by sodium *via* single electron-transfer giving an alcohol if a suitable

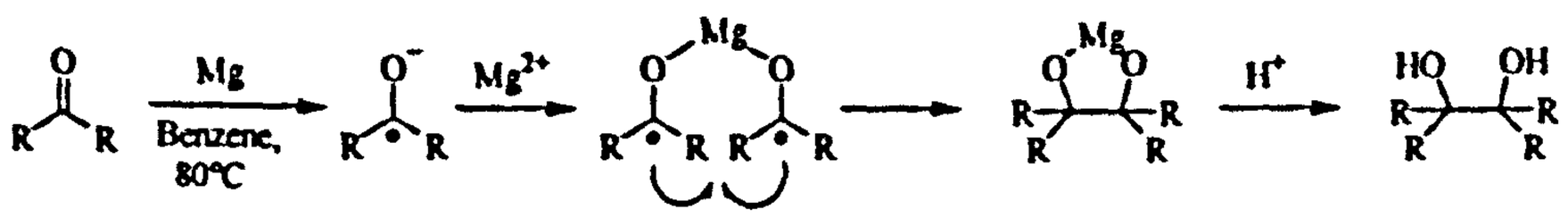
proton-source is present. This is known as the Bouveault-Blanc reaction.[38] Therein, **1.31** accepts an electron to give the corresponding ketyl anion **1.32** that is then protonated to afford **1.33**. Another electron-transfer gives the anionic species **1.34** that is protonated to give alcohol **1.35** (**Scheme 1.14**).



1.31 **1.32** **1.36** **1.33** **1.34** **1.35**

Scheme 1.14

In the absence of any proton source, the concentration of ketyl radicals will steadily increase, eventually leading to coupling of the ketyl radicals. However, due to the repulsion of the negative charges located on the oxygen atoms, dimerisation will take place only if a suitable metal cation is present that is capable of binding to the oxygens, holding them together to allow coupling of the radicals (**Scheme 1.15**). Alkali-metals are not capable of binding simultaneously both oxygen anions. Therefore, this so-called 'pinacol' reaction is carried out with Mg, Al or Zn.



1.37 **1.38** **1.39** **1.40** **1.41**

Scheme 1.15

(ii) Transition metals

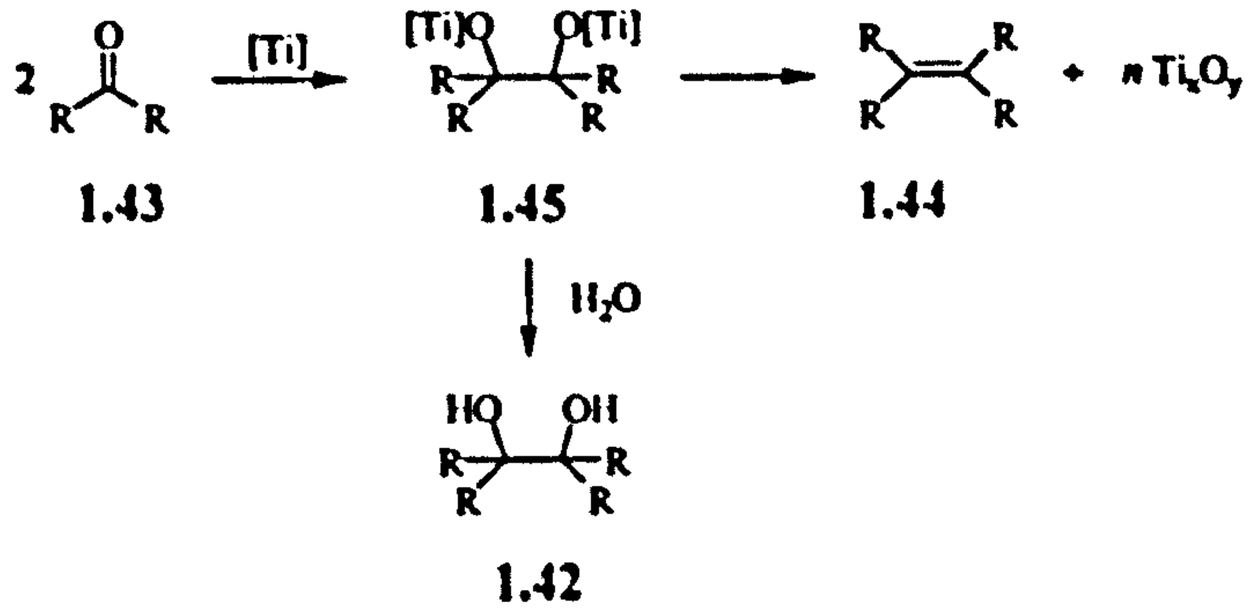
Various transition metals, such as Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn show electron-transfer chemistry and are therefore frequently used in synthesis. However, as many reactions utilising metals differ not significantly from each other, only a few selected examples will be presented below.

Titanium

In the early 1970s Mukaiyama, Tyrlik and McMurry made the independent and nearly simultaneous discovery of low-valent titanium being able to couple aldehydes or ketones and this became famous as the McMurry reaction, shown in **Scheme 1.16**.[39,40,41] The titanium

species is generated by reduction of $TiCl_3$ or $TiCl_4$ with a suitable reducing agent, such as Zn, and is based on the high reducing ability and oxophilicity of Ti.

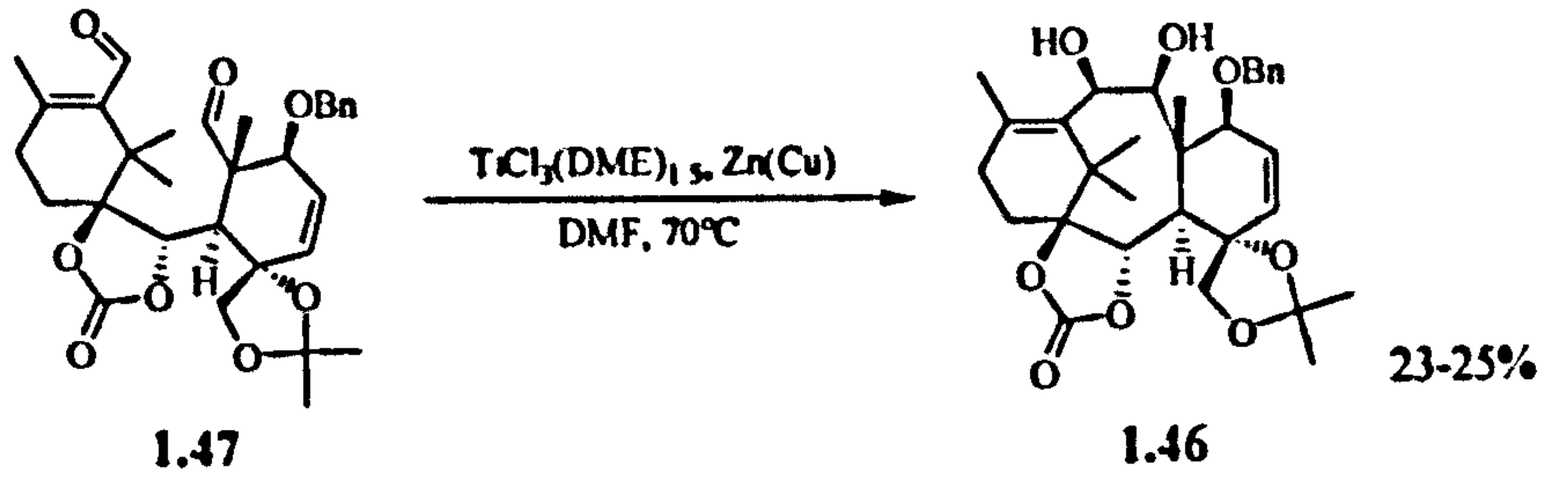
The reaction can be stopped at the pinacol intermediate stage **1.42** by lowering the temperature [generally from solvent reflux temperature] to 0°C.[42]



1.43 **1.45** **1.44** **1.42**

Scheme 1.16

A great achievement was the total synthesis of taxol by Nicolaou *et al.*, a promising anti-cancer agent. In that case, the central 8-membered ring of the precursor compound **1.46** was synthesised *via* McMurry coupling of the two aldehydes in **1.47** (**Scheme 1.17**).[43]

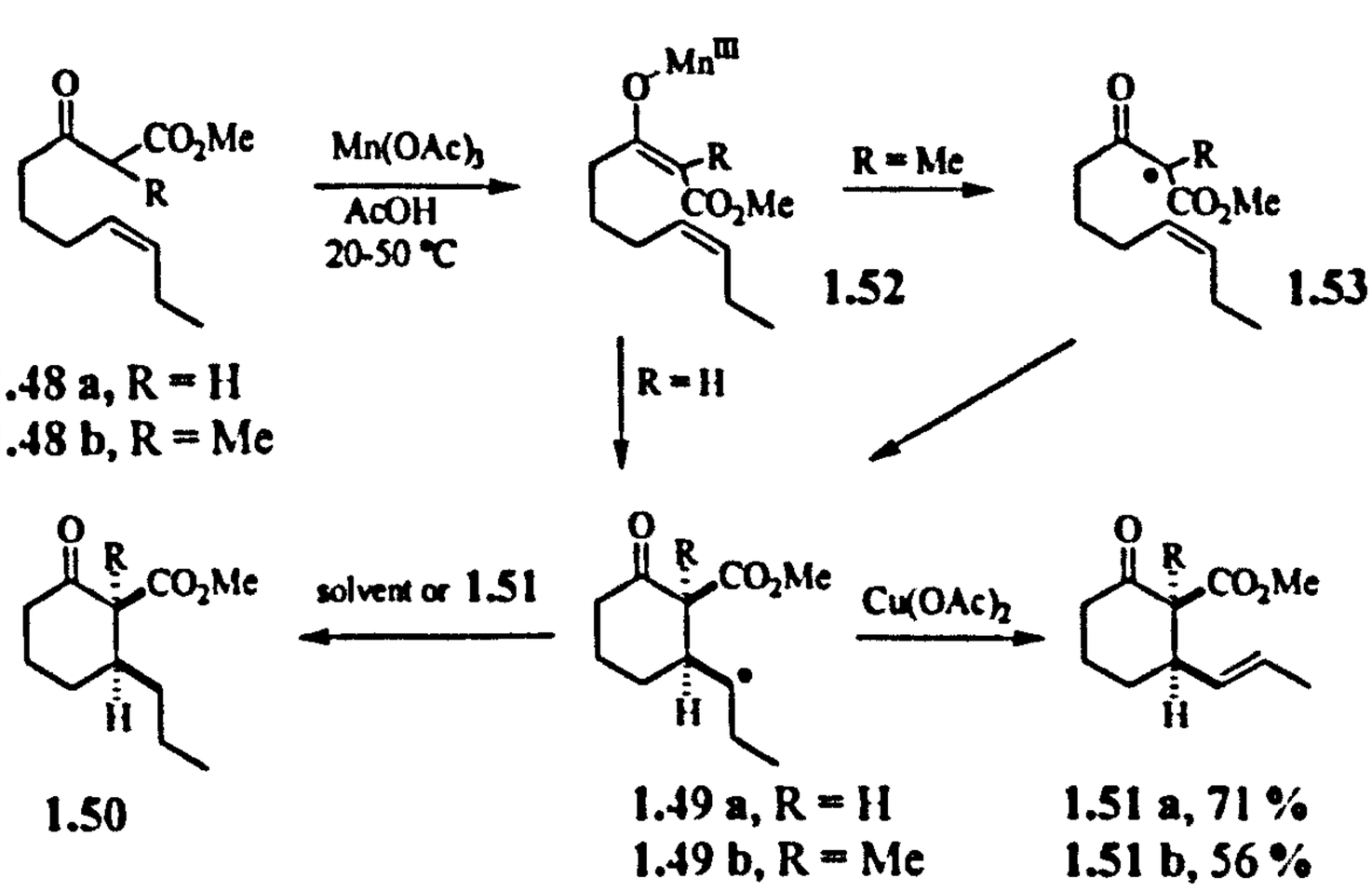


1.47 **1.46**

Scheme 1.17

Manganese

The manganese(III)-based oxidative free-radical cyclisations of **1.48 a** and **1.48 b** (see **Scheme 1.18**) highlight the factors that need to be understood to use manganese in synthesis.[44]



1.48 a, R = H
1.48 b, R = Me

1.52 **1.53**

1.50

1.49 a, R = H
1.49 b, R = Me

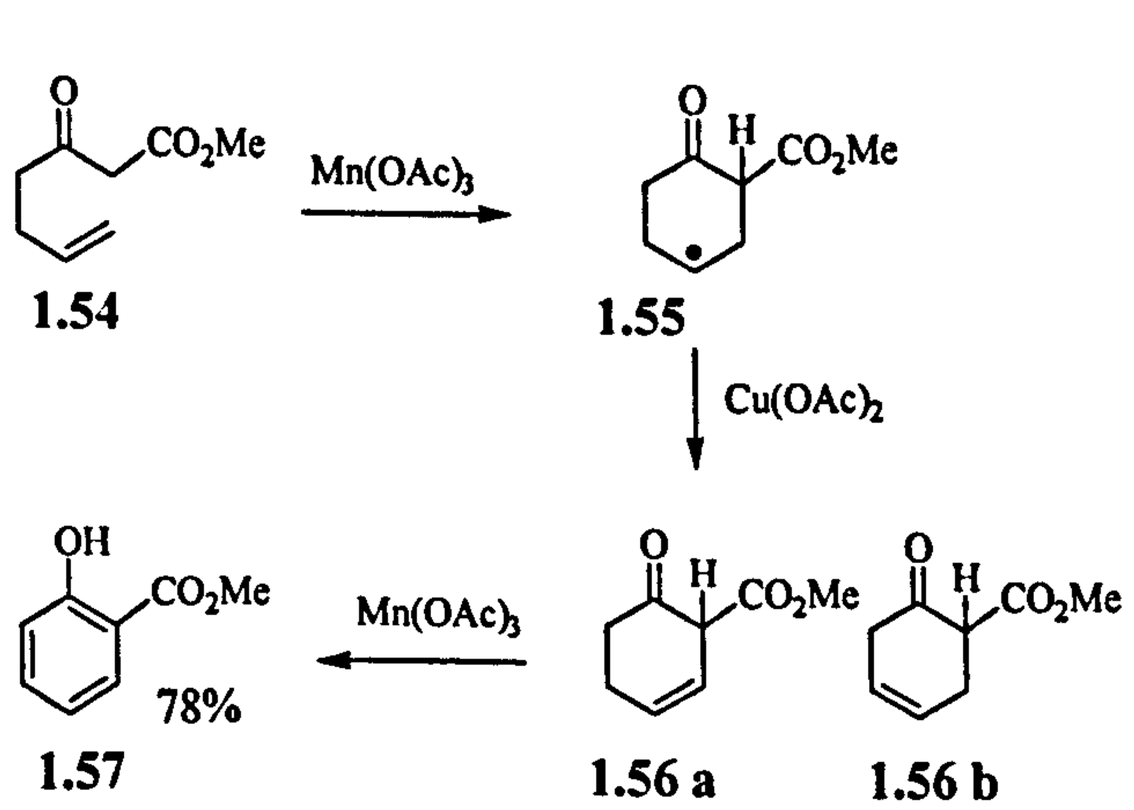
1.51 a, 71 %
1.51 b, 56 %

Scheme 1.18

Oxidative cyclisation of β-keto ester **1.48** with $Mn(OAc)_3$ occurs to give radical intermediate **1.49**. This radical then either abstracts a hydrogen atom from the solvent or from the starting substrate **1.48** to give **1.50**, or is oxidised to afford **1.51**.

Mn(III) is not capable of oxidising radical **1.49** to its corresponding cation, but Heiba and Dessau found that $Cu(OAc)_2$ oxidises secondary radicals 350 times faster than $Mn(OAc)_3$ and that both reagents can be used together.[45] The first step in this reaction sequence involves the loss of a proton of **1.48a, b** to afford the Mn(III) enolate **1.52**. In the next step, it is believed that Mn(II) loss occurs (for R=Me) to give the free radical **1.53** that then cyclises to **1.49b** in a stereo- and regiospecific fashion. The pathway undergone if R=H, is assumed to be the cyclisation of the unsaturated Mn(III) enolate **1.52** to give radical **1.49a**, *i.e.* there is no free-radical intermediate at that stage.

A general problem in the manganese-promoted oxidations is that the product molecule might be oxidised further, if it bears another H-atom in the α-position to the ester carbonyl group, as the same reaction cycle could be undergone again with the next available hydrogen. An example is given in **Scheme 1.19**. Oxidative cyclisation of **1.54** gives radical **1.55** that is then oxidised further to **1.56**, probably as a mixture of double-bond positional isomers (**1.56a** and **b**). The unsaturated cyclic *β*-keto ester **1.56a** is more acidic than **1.55** and is rapidly oxidised further by two equivalents of Mn(III) to give a cyclohexadienone that tautomerises to phenol **1.57**.[46]

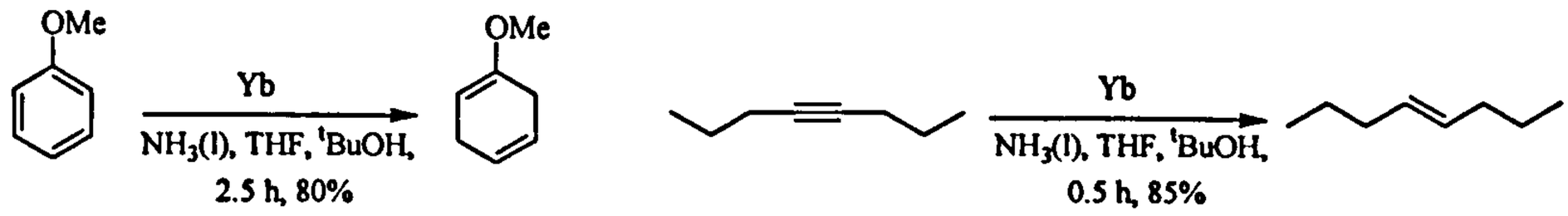


Scheme 1.19

(iii) Lanthanide reagents

Lanthanides are used to transform functional groups and to form new C-C bonds by single-electron-transfer. They can be applied to selective reductions of alkynes and aromatic

systems, for which they were first used as an alternative to alkali metals in the Birch reduction (**Scheme 1.20**).[47]

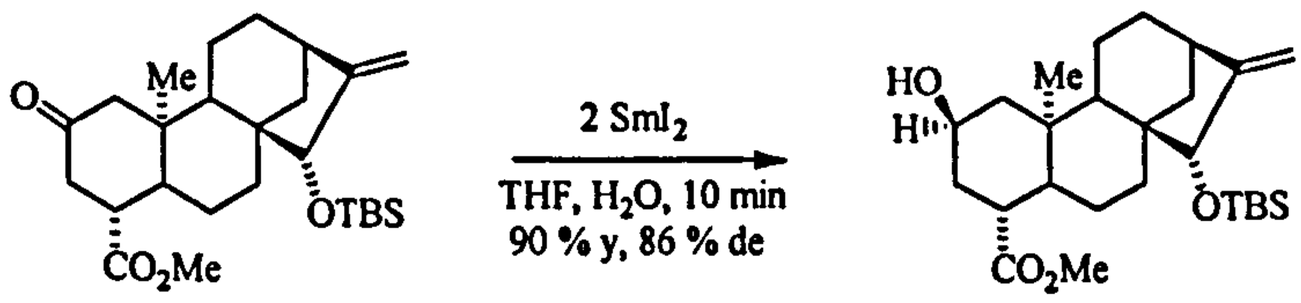


1.58 **1.59** **1.60** **1.61**

Scheme 1.20

Probably the most used representative of its class is samarium (II) diiodide (SmI_2). It has been developed as a mild, ether-soluble, single-electron donor and is capable of a wide range of chemistry, of which selected examples are presented in the following section.

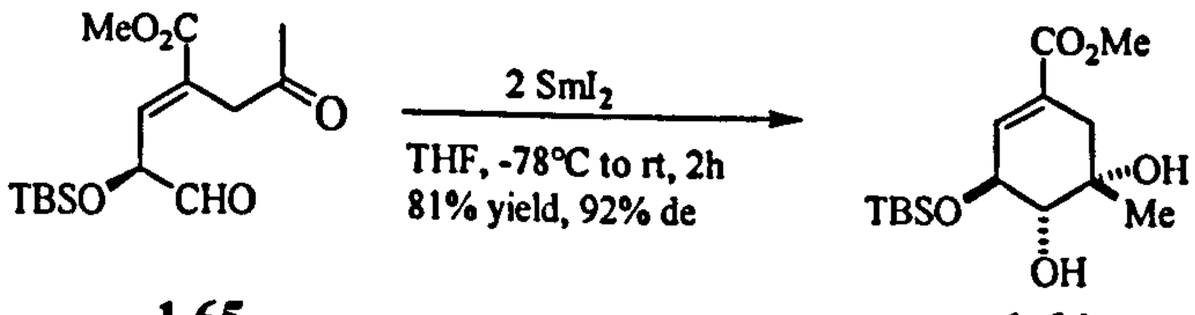
Samarium (II) iodide is usually prepared from metallic samarium in the presence of 1,2-diiodoethane in THF. It reduces carbonyl compounds to the corresponding alcohols in the presence of a proton source, such as water or alcohol, as illustrated in Corey's synthesis of **1.63 (Scheme 1.21).**[48]



1.62 **1.63**

Scheme 1.21

However, in the absence of protons, pinacolic coupling is observed. Intramolecular examples carried out by Hanessian *et al.* gave *cis*-diols after highly stereoselective reduction of dicarbonyl compounds in excellent yield (**Scheme 1.22**).[49]

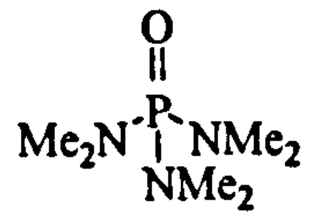


1.65 **1.64**

Scheme 1.22

Another carbon-carbon bond formation reaction that is frequently carried out using SmI_2 is the Barbier-type reaction. Its efficiency is highly dependent on the substrate as well as the reaction conditions employed. Primary organic iodides, for instance, undergo Barbier-type coupling with ketones, but require heating for 8-12 h in boiling THF.[50] Alkyl bromides are less reactive and alkyl chlorides are virtually inert. However, if catalytic quantities of

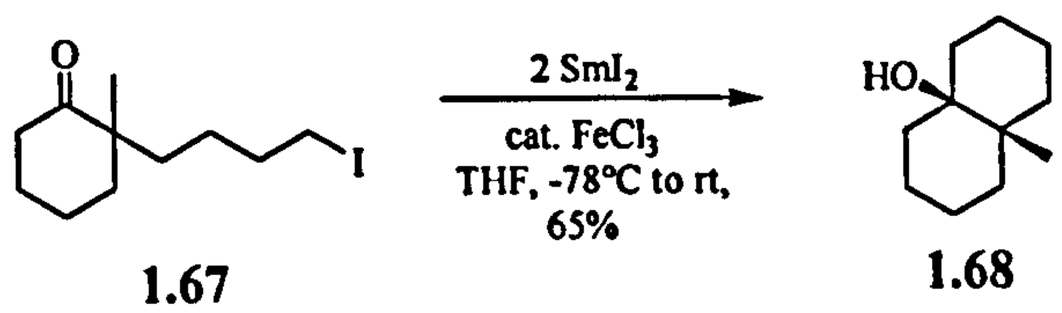
Fe(III) salts are added, the reaction can be carried out under much milder conditions (at room temperature and short reaction times).[50] Further increase of reactivity can be gained by utilising HMPA as a co-solvent with THF.[51] In the presence of this solvent system, alkyl bromides are now reduced within 1 min at room temperature.



HMPA

1.66

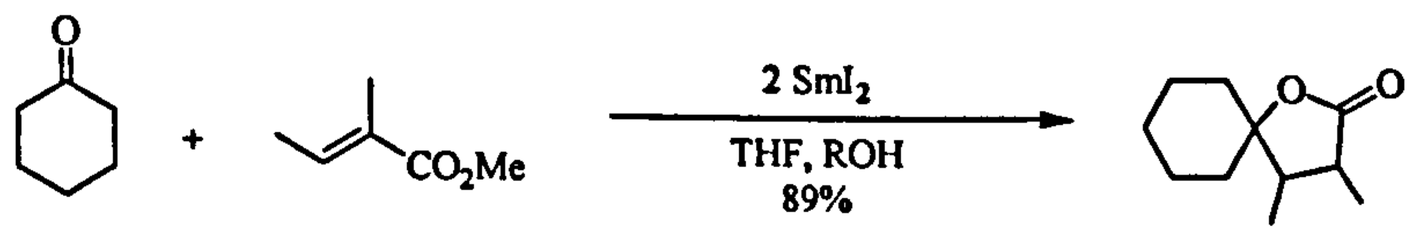
SmI_2 is particularly useful for the annulation of 5- and 6-membered rings *via* an intramolecular Barbier process. Prior to Molander's and Etter's discovery, there existed no reliable and convenient method to generate bicyclic systems by Barbier reaction. Considerable diastereoselectivity was observed also (**Scheme 1.23**).[52]



1.67 **1.68**

Scheme 1.23

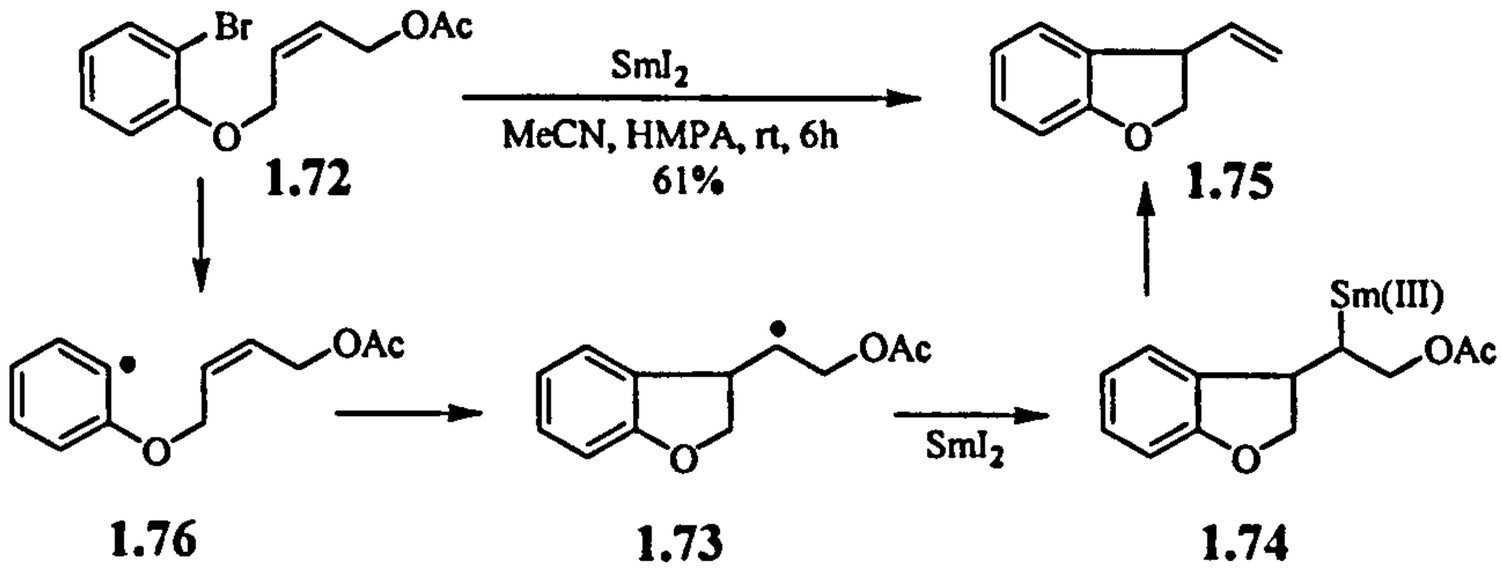
Ketyl radicals derived from SmI_2 reaction with aldehydes or ketones can be coupled with alkenes and alkynes in a radical fashion. Both inter- and intramolecular versions have been described. Thus it has been shown, for instance, that conjugated esters react with aldehydes and ketones in the presence of SmI_2 to afford the corresponding lactones (**Scheme 1.24**).[53]



1.69 **1.70** **1.71**

Scheme 1.24

Radical cyclisation reactions are particularly well suited to SmI_2 as the aryl radical **1.72** produced by single-electron-transfer is not reduced further to the corresponding anion. However, the alkyl radical **1.73** obtained after cyclisation, couples with another SmI_2 species to give the organosamarium (III) intermediate **1.74**, which may lead to further reactions, if desired (**Scheme 1.25**).[54]



Scheme 1.25

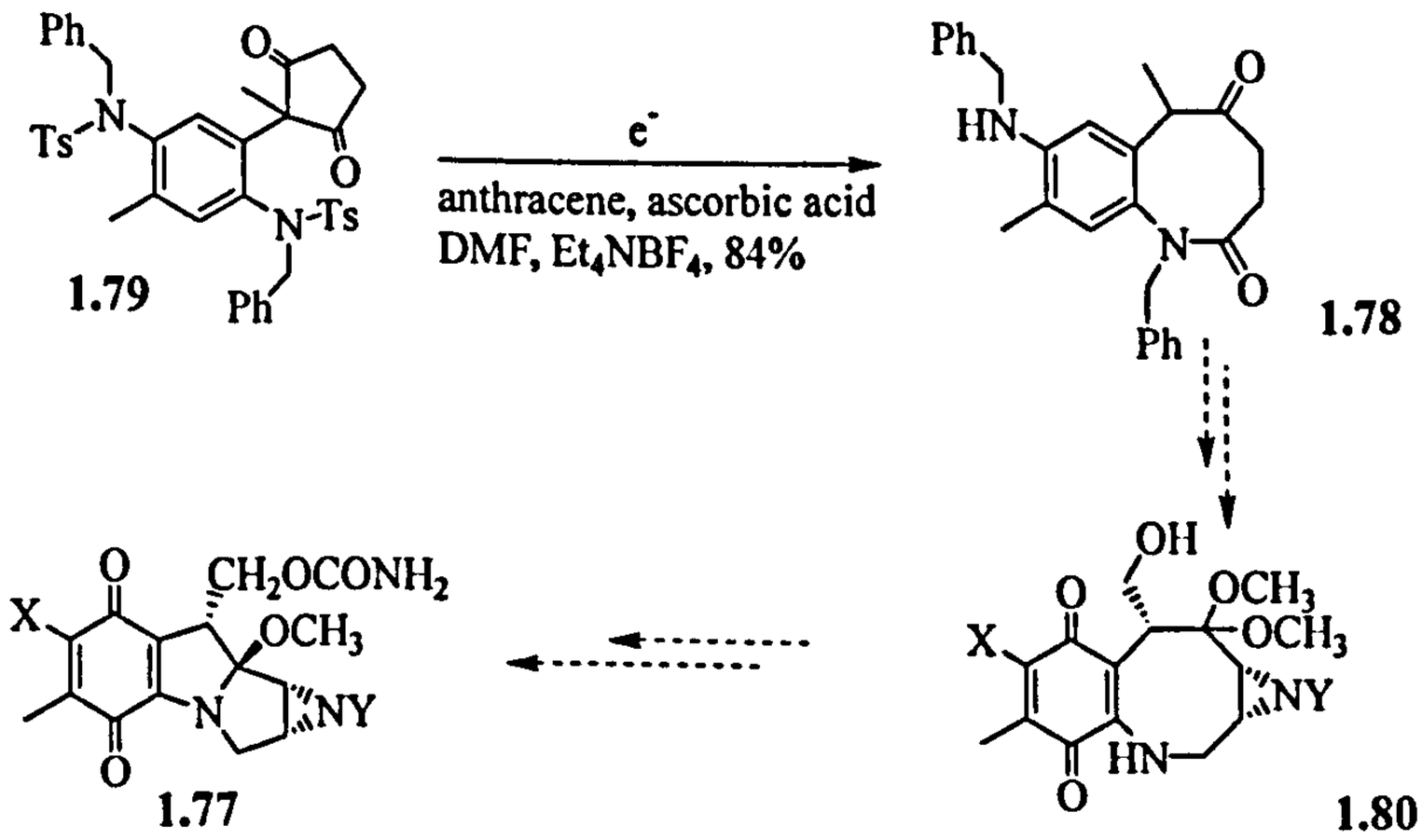
However, the frequent requirement for carcinogenic HMPA make SmI_2, although a versatile reagent, rather unpopular and has led to a considerable drive towards replacing the reagent by 'cleaner' alternatives.

1.2.2 *Electrochemical methods*

A very clean and effective way to transfer single electrons, without the requirement of any additional, not to mention carcinogenic, reagents is the generation of radicals or anions by electrochemical reduction. Electrochemistry allows the formation of bonds by typical radical reactions and the transformation of electron-poor functional groups, such as carbonyl-, cyano- or nitro-groups to their corresponding nucleophiles *via* cathodic reduction, giving reactive intermediates that enable further chemistry to be carried out. Similarly, electrons can be removed from electron-rich functionalities, *e.g.* amines, to generate electrophiles (anodic oxidation). However, as this is a separate issue that is not so closely related to our research, it will not be illustrated further in this review. Nevertheless, information about anodic oxidation can be obtained, following the references in this section.[55]

Electrochemistry provides a convenient method to synthesise a variety of building blocks, some of which have proven to be useful in total synthesis of natural products.

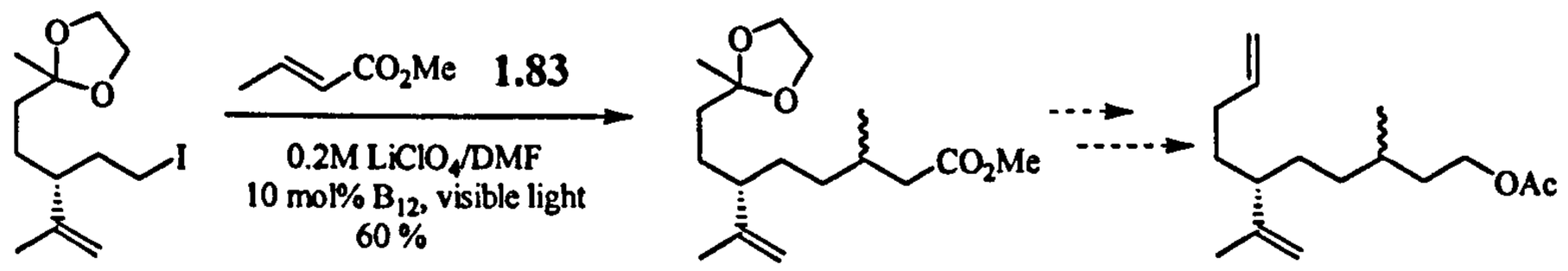
Mitomycins (**1.77**), for instance, have attracted much attention due to their interesting structure and their possible anticancer properties. One approach involving electrochemical reduction as the key step is illustrated in **Scheme 1.26**.[56] Keto-amide **1.78** was synthesised by *N*-tosyl group cleavage, followed by cyclisation and fragmentation. Ascorbic acid functions as a proton source as well as a reductant in combination with anthracene.



Scheme 1.26

The California red scale pheromone **1.81** was synthesised *via* an indirect electrochemical reaction, involving vitamin B_{12} as a mediator for cyclisation (**Scheme 1.27**).[57] Vitamin B_{12} reacts with alkyl halide **1.82** to give a cobalt(III) alkyl intermediate that fragments to a

carbon-centred radical and a cobalt(II) species upon irradiation with visible light. The cobalt(II) is electrochemically reduced to Co(I) and undergoes further reaction with another alkyl halide molecule **1.82** and hence re-enters the catalytic cycle. The so formed radical is capable of undergoing a variety of transformations, including a conjugate addition to the Michael acceptor **1.83** leading to the synthesis of the California red scale pheromone (**1.81**). [Note: The radical could undergo further cathodic reduction to the carbanion. Both species, however, lead to the same outcome in this case. The advantage of indirect methods is generally that reduction can be carried out at lower potentials and milder conditions. Over-reduction and resulting side-products are therefore avoided.[58,59]]



1.82 **1.84** **1.81**

Scheme 1.27

Direct electrochemical reduction of a diazonium salt, giving rise to an aryl radical that subsequently cyclises, was recently utilised by the Murphy group[60] for the preparation of indolines (**Scheme 1.28**). The advantage in using the diazonium acceptor was that the reduction could be carried out under quite mild conditions, allowing the presence of sensitive functional groups.[61]

1.85a, R, R' = H, H **1.86a, 60 %**

1.85b, R, R'= $(CH_2)_2$ **1.86b, 68 %**

1.85c, R, R' = $(CH_2)_3$ **1.86c, 34 %**

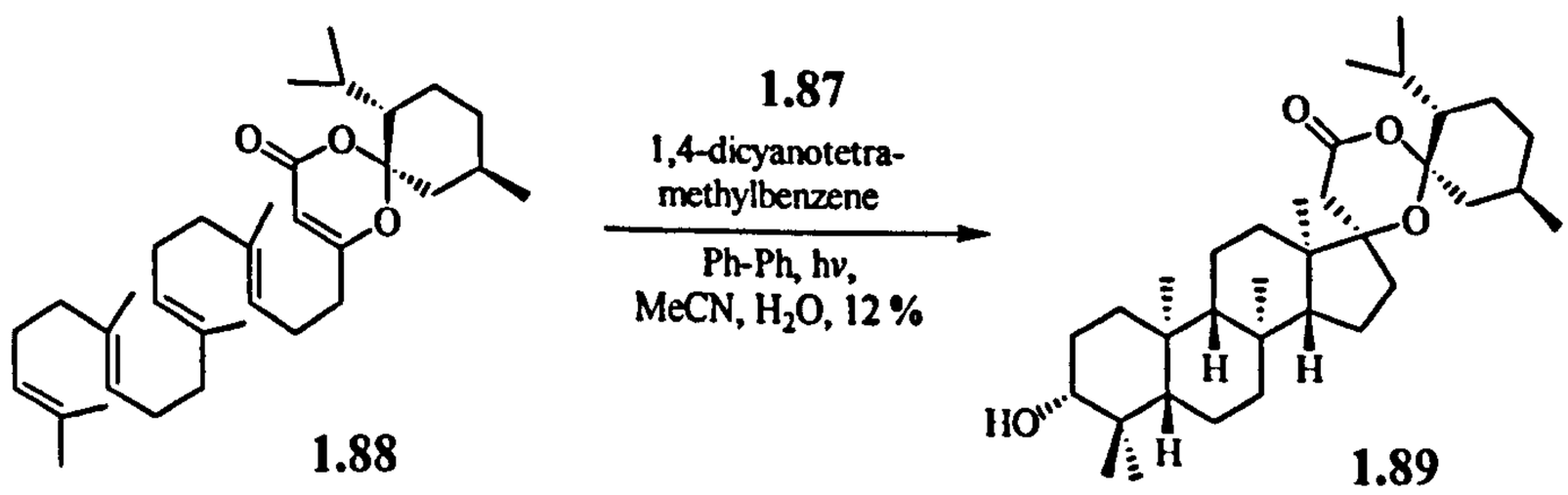
Scheme 1.28

1.2.3 *Photochemistry*

Photochemical electron-transfer reactions are based on the high reactivity of the excited state of a molecule. Neutral organic molecules can be excited by UV-light and transformed into highly reactive intermediates as will be discussed below. Thus, this section is supposed to address general principles and selected examples of photochemically induced electron-transfer reactions, since these contrast with the fundamentally different reactivities of neutral organic ground state donors that are investigated in our research and are discussed later in this thesis.

Photochemical transformations frequently provide routes to synthetic targets that cannot be attained by conventional reactions.[62] Generally, a photosensitiser, which is a molecule that absorbs UV-light leading to the promotion of an electron from its HOMO to its LUMO, is utilised. Thus the photosensitiser is transformed into its excited species, exhibiting a hole in a low-lying orbital (that is capable of taking up an electron and hence oxidising another molecule)[62] and an electron in a high-lying orbital (that can be donated and reduce another molecule).[63] After being oxidised by a sensitiser, the organic molecule is transformed into a reactive intermediate that can undergo further reaction(s).

An application of the principle can be found in the synthesis of polycyclic molecules by photo-induced cascade reactions. The photosensitiser **1.87** is excited by UV-light, leading to oxidation of the substrate **1.88** to give a radical-cation that subsequently undergoes nucleophile-assisted cascade cyclisation to afford the steroid ring system **1.89** (**Scheme 1.29**).[64]

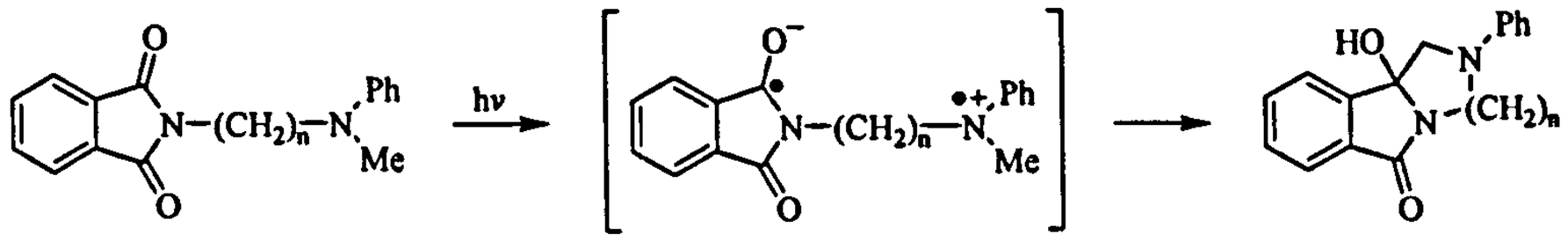


1.88 **1.89**

Scheme 1.29

The synthesis shown below in **Scheme 1.30** does not, in contrast to the previous example, require the use of sensitisers. Instead the substrate itself, phthalimido-amine **1.90**, is excited by UV-light, leading to intramolecular single electron-transfer from the amine moiety to

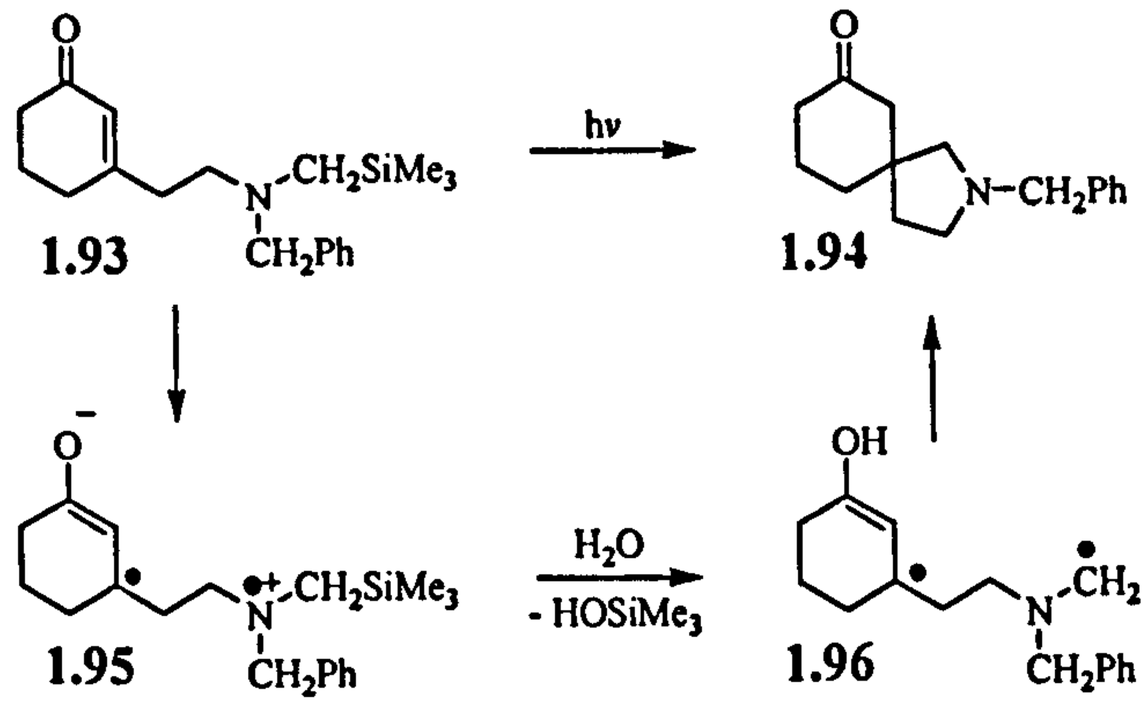
the carbonyl acceptor which gives rise to the zwitterionic intermediate **1.91** that upon proton transfer cyclises to afford the heterocycle **1.92**.[65,66]



1.90 **1.91** **1.92**

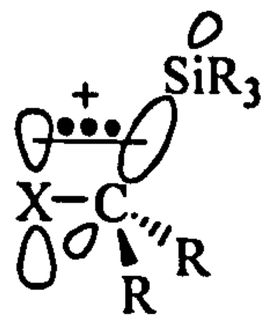
Scheme 1.30

This reaction was developed further by Mariano *et al.*, applying the novel concept of desilylation after intramolecular electron-transfer from the photo-excited silyl amine **1.93** which enables further cyclisation to give spiro compound **1.94** (**Scheme 1.31**).[67]



Scheme 1.31

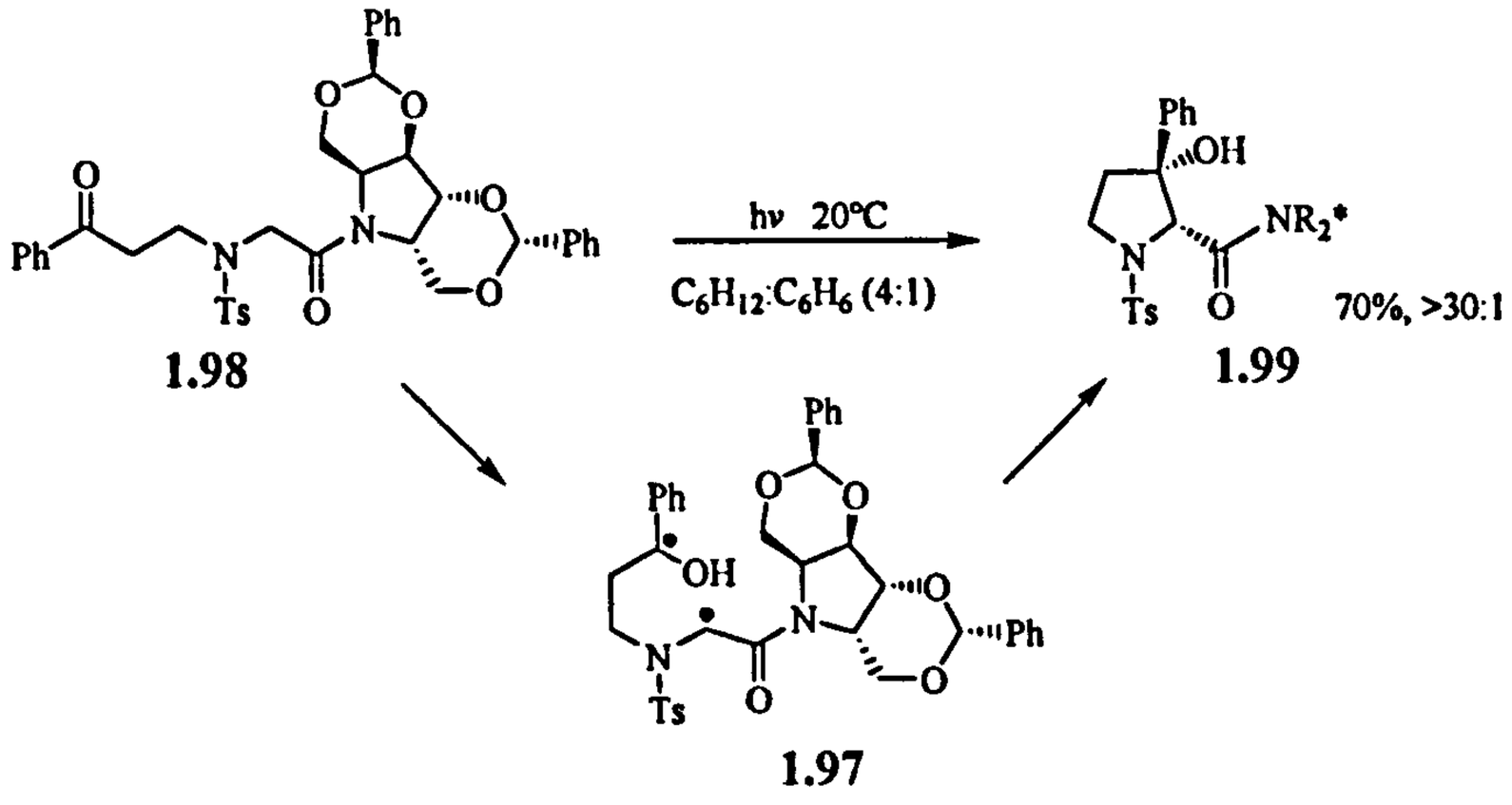
This desylilation-based synthesis was developed upon theoretical and experimental studies by Yoshida *et al.*[68] who predicted that the half-filled orbital of the heteroatom would overlap with the relatively large and energetically high-lying C-Si σ-orbital, resulting in bond weakening and thus C-SiR_3 cleavage (**Scheme 1.32**).



Scheme 1.32

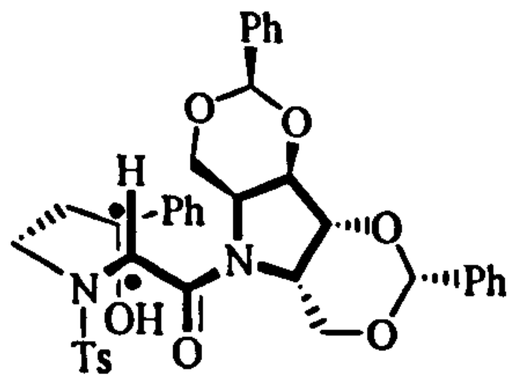
Yoon *et al.* are actively involved in the development of new photochemically promoted radical and biradical cyclisation reactions. They have studied a variety of desilylation type cyclisations and provided evidence for the zwitterionic intermediates with trapping experiments, such as cycloaddition or deuteration.[69,70]

To finish this section the last example is one by Giese *et al.* who have shown that it is possible to introduce stereochemistry into target molecules *via* photo-induced biradical cyclisation.[71] Stereoselective radical reactions are possible by means of chiral auxiliaries, chelation control or substrate control (featuring a strained radical precursor).[72] However, stereoselectivity arising from reaction between two radicals is very unusual. Nevertheless it is possible, as shown by Giese and co-workers who generated biradical **1.97** photolytically from **1.98** and examined its cyclisation behaviour to give **1.99** (**Scheme 1.33**). The intermediate **1.97** arises from H-atom abstraction by the photoexcited carbonyl group.



Scheme 1.33

In another experiment, a triplet quencher (naphthalene) was added and no cyclisation was observed anymore. Hence the biradical **1.97** must be a triplet excited state that cannot undergo immediate cyclisation due to the forbidden spin compatibility and has a relatively long-lifetime that allows the molecule to adopt a preferential cyclisation conformation as shown in **Scheme 1.34**. Here the benzyl radical attacks the partner radical from the less hindered face.



Scheme 1.34

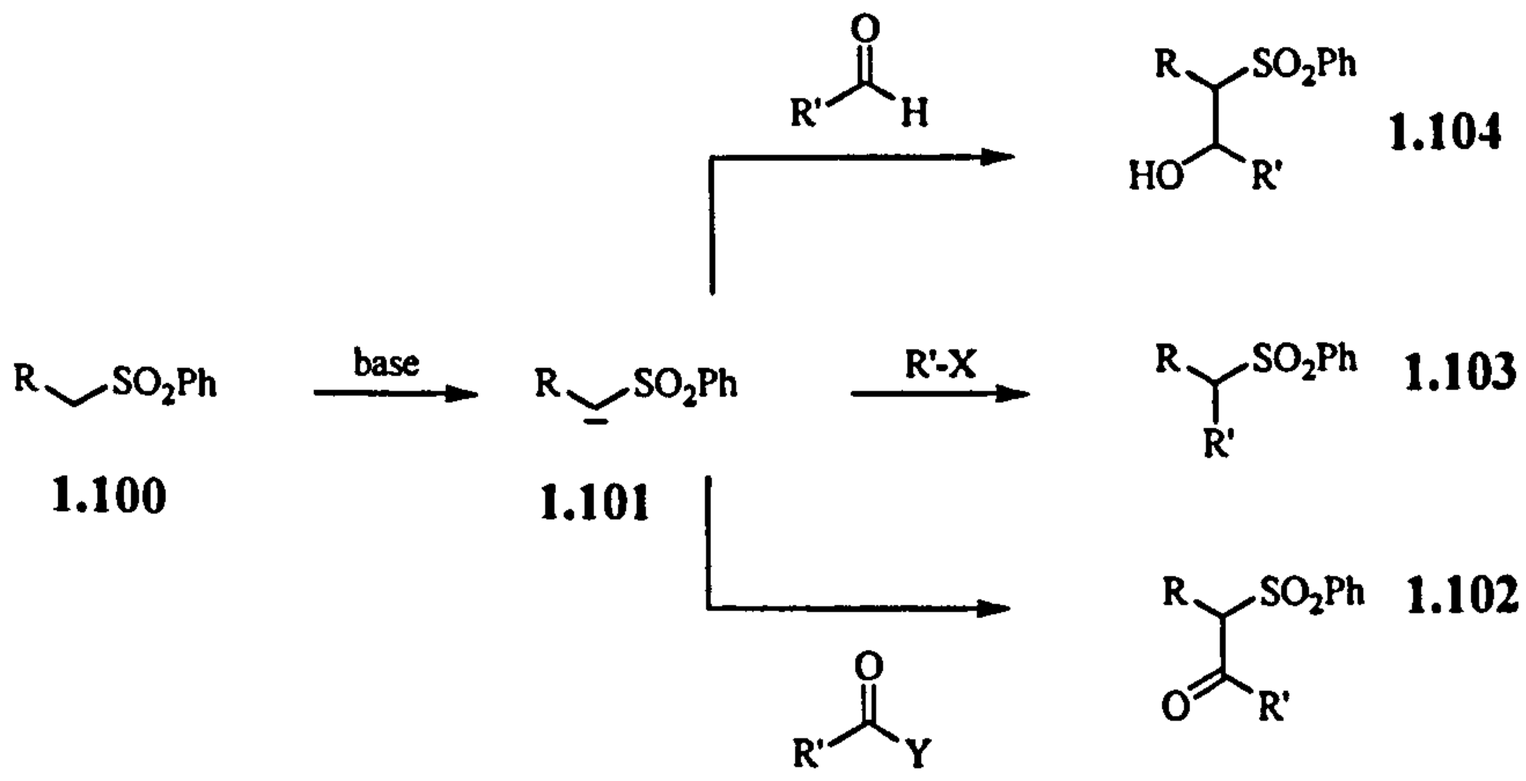
To allow cyclisation, a triplet-singlet interconversion must take place, which occurs *via* partial overlap of the radical orbitals. This brings the radical centres close together. They approach each other with minimum hindrance and eventually cyclise rapidly, as soon as conversion to the singlet state is completed, giving rise to the observed stereoselectivity.[71]

1.3 Sulfones and sulfonamides

As part of my study, Super-S.E.T. reagents were investigated for their ability to cleave sulfone and sulfonamide groups. This will be presented in the later discussion of this thesis. Thus, the following section is intended to address the general utility and reactivity of sulfones. Furthermore, general methods to remove the sulfone group will be presented.

1.3.1 *Synthetic application of sulfones*

Sulfones have found extensive application in organic synthesis.[73a] Numerous natural product syntheses contain sulfones *en route* to the final target molecule. However, the sulfone group is generally removed prior to the end of synthesis. The sulfone group has become such a popular synthetic tool for numerous reasons. A sulfone is generally easily prepared by high yielding routes. It is a robust group that gives easy access to carbanions *alpha* to the sulfone group that can be utilised further in efficient C-C bond formation *via* alkylation, acylation or aldol-like-reactions (**Scheme 1.35**).[73a]



Scheme 1.35

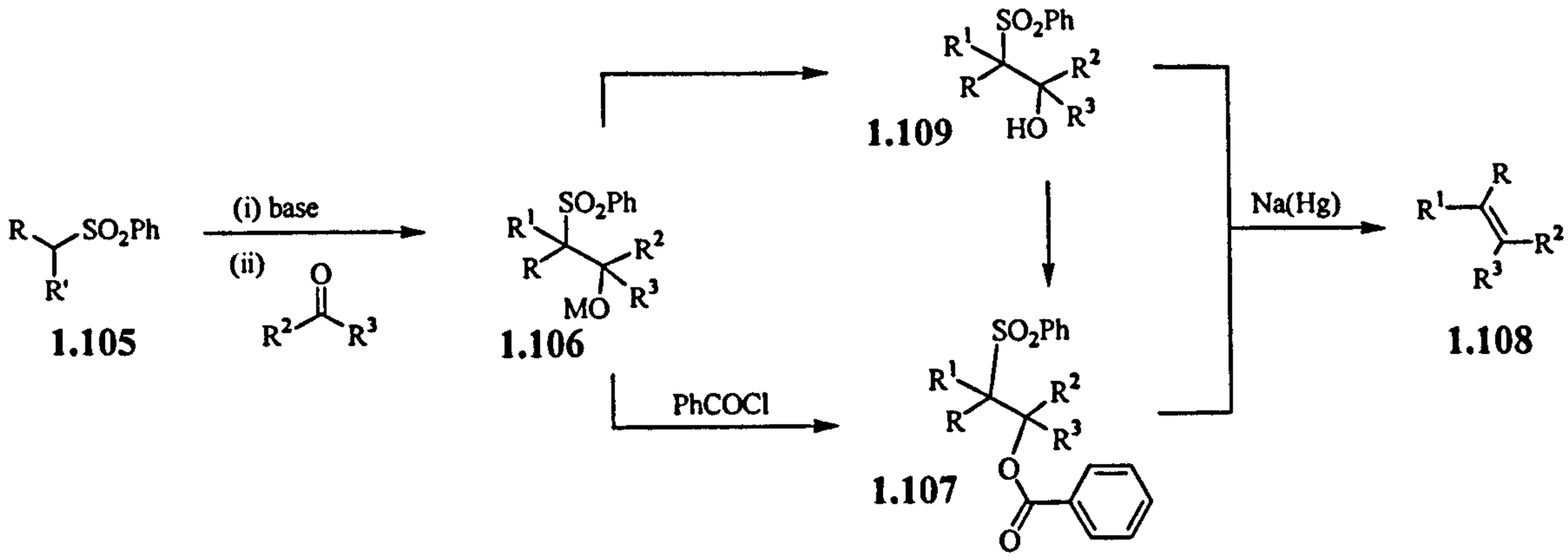
Phenyl sulfones (RSO_2Ph) and tolyl sulfones (RSO_2Tol) are most frequently used in synthesis, since they give rise to regiochemically unambiguous deprotonation.

Classical Julia reaction

The most important type of C-C double bond formation using sulfones is the Julia reaction.[74]

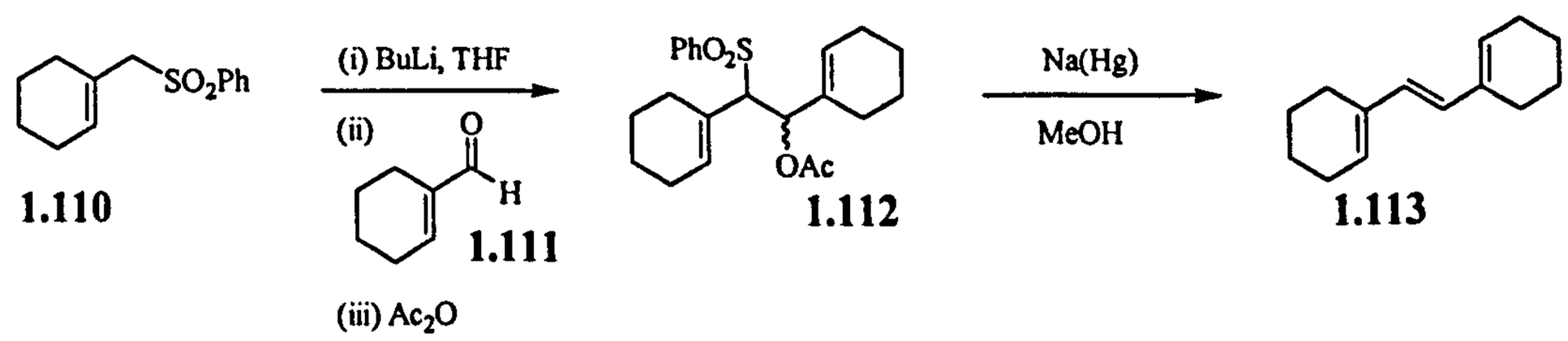
It is frequently used in total syntheses of natural products and was first reported by M. Julia and Paris.[75] As shown in **Scheme 1.36**, sulfone **1.105** is deprotonated firstly to an α-sulfonyl carbanion. This then attacks an aldehyde or ketone, giving rise to a metal alkoxide adduct **1.106** that is usually derivatised *in situ* [*e.g.* by PhCOCl to afford adduct **1.107**].

Treatment of **1.107** with sodium amalgam then gives rise to the olefin **1.108**. In very rare cases, direct treatment of **1.109** with sodium amalgam may lead to the alkene **1.108** also. However, usually isolation of intermediate **1.109** is preferred and derivatisation carried out in an additional step, giving rise to greater overall elimination yield in the final alkene formation.



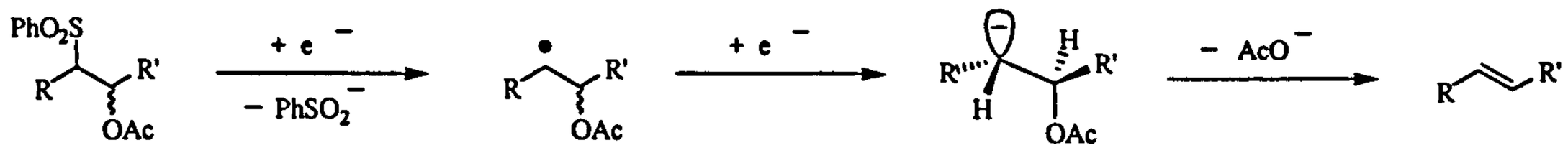
Scheme 1.36

Kocienski and Lythgoe have investigated the Julia reaction further, addressing its scope and stereochemical outcome.[73a,76,77] They modified the original Julia protocol, and used methanol as a solvent at low temperatures (-20 °C) with added ethyl acetate or THF to improve substrate stability. These conditions minimise unwanted side-reactions, such as hydrolysis of the derivative **1.107** (**Scheme 1.36**) or elimination of benzoic acid to form a vinyl sulfone. An example is shown in **Scheme 1.37**. After generation of the carbanion of **1.110**, aldehyde **1.111** is added and subsequently trapped with acetic anhydride to give **1.112** which upon reductive elimination gives triene **1.113**. Despite the formation of diastereomers for intermediate **1.112**, *E*-stereochemistry was obtained exclusively in the final product **1.113**.



Scheme 1.37

This can be rationalised as follows (see **Scheme 1.38**): Electron-transfer to the aryl sulfone group leads to C-S bond cleavage, generating a sulfinate anion and an intermediate radical **1.114** that is then reduced to the carbanion **1.116**. Either at the radical or the carbanion stage, equilibration of the intermediate occurs and elimination proceeds in an *anti*-periplanar fashion to give the *E*-alkene.[73a,78]

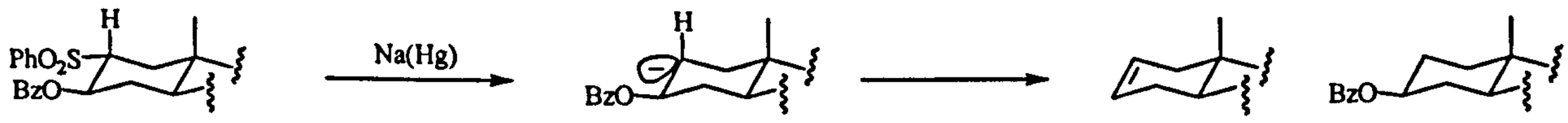


1.115 **1.114** **1.116** **1.117**

Scheme 1.38

The product distribution (*E*:*Z*-isomer) reflects the thermodynamic distribution of the intermediate **1.116** or **1.114** that is dependent on the interactions of R and R'. The bulkier the substituents R and R', the greater is the *E*-selectivity of the product.

For more substituted systems, leading to fully substituted alkenes, the selectivity is lower. Another limitation of the Julia reaction is found in cyclic systems, when the elimination of the leaving group (AcO^-) cannot occur as readily since an *anti*-periplanar conformation cannot be adopted due to ring-strain. An example is shown below. The Julia reaction is low-yielding and the alternative product, the protonated carbanion **1.120**, is obtained as a side-product (**Scheme 1.39**).[73a,77]

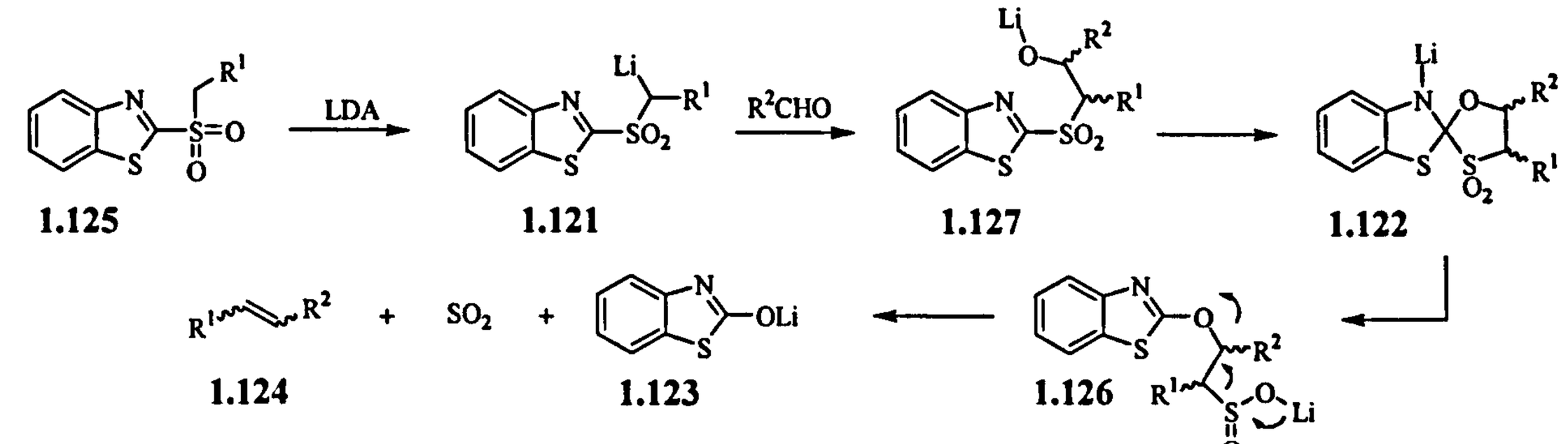


1.118 **1.119** **1.121** **1.120**

Scheme 1.39

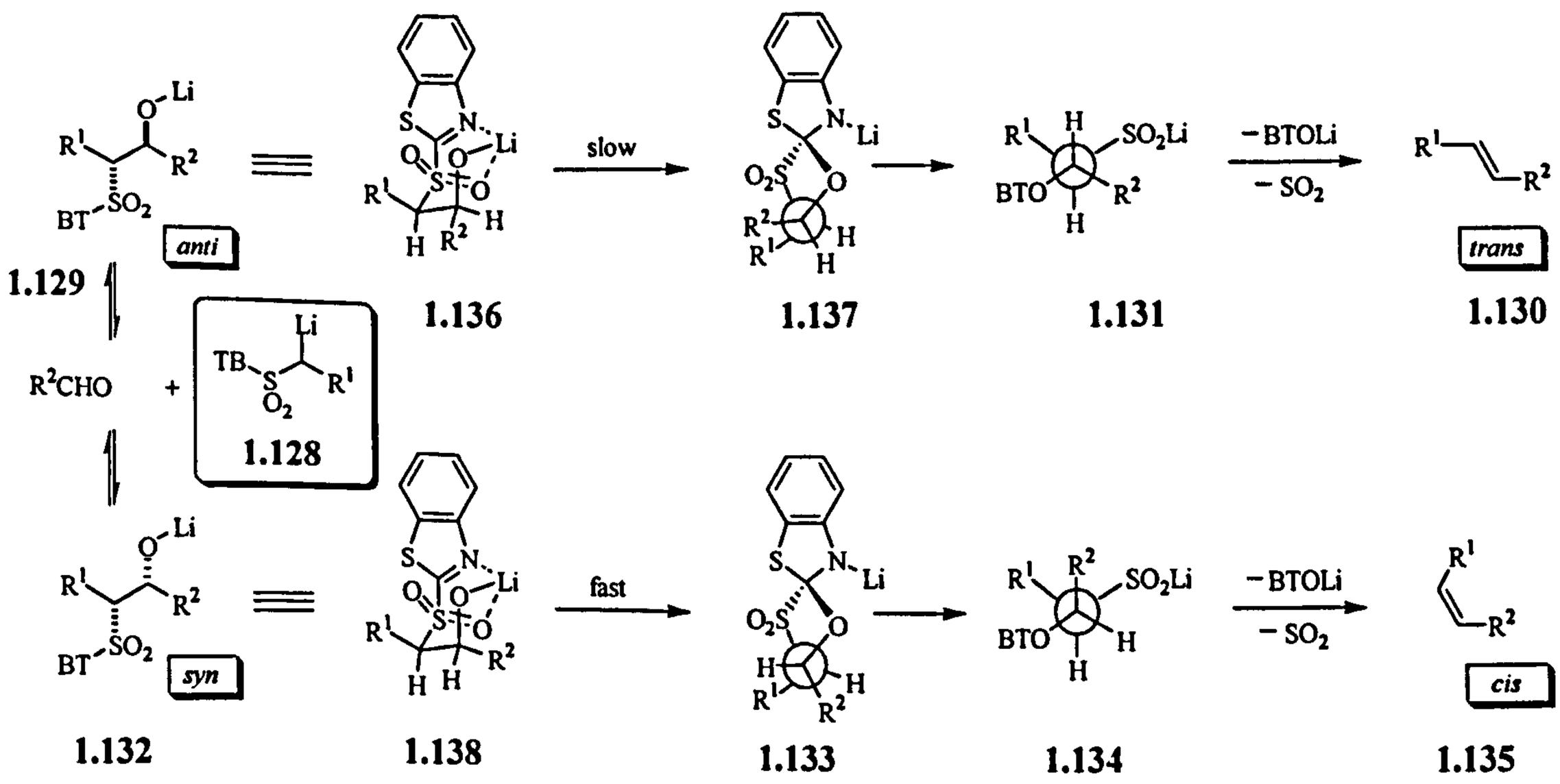
Modified Julia reaction

S. Julia and co-workers replaced the phenyl substituent on the sulfone, traditionally used in the Julia reaction, by a heterocycle. This heterocycle is quite elctrophilic, giving rise to altered reactivity. The first steps, deprotonation and addition to the aldehyde electrophile, are analogous to the classical Julia olefination (see **Scheme 1.40**). The difference in the modified version is that the metallated adduct **1.121** is inherently unstable and undergoes a facile Smiles rearrangement[78,79] to give spirocycle **1.122**. Elimination of sulfur dioxide and heterocycle **1.123** yields the alkene product **1.124** directly in one pot.



Scheme 1.40

The stereochemical outcome in the modified Julia reaction is substrate-controlled.[78] Addition of the aldehyde onto the *alpha* deprotonated sulfone **1.128** can give rise to *anti* and *syn* diastereoisomers. The *anti* diastereoisomer yields a *trans*-alkene while the *syn* diastereoisomer gives a *cis*-alkene. Low selectivities in alkene formation are thus ascribable to low diastereocontrol in the initial nucleophilic addition (**Scheme 1.41**).

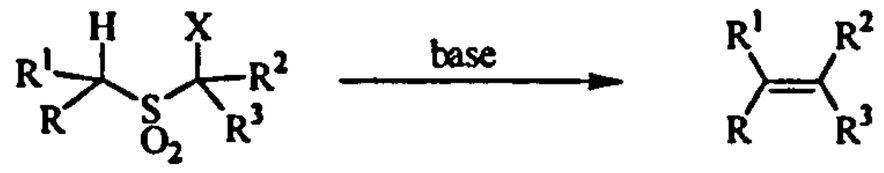


Scheme 1.41

It is believed that the initial addition step of **1.128** onto the aldehyde can be reversible since the carbanion is highly stabilised. Thus, equilibration between *syn* and *anti* intermediate occurs *via* addition and retroaddition between the aldehyde and **1.128**. The energy barrier for Smiles rearrangement is believed to be greater for the *anti* isomer **1.136** due to the eclipsed arrangement of R^2 and R^1 in **1.137**. Equilibration between **1.136** and **1.138** as well as the faster rearrangement/ elimination for **1.138** provides notable *cis* selectivity.[78]

Ramberg-Bäcklund reaction

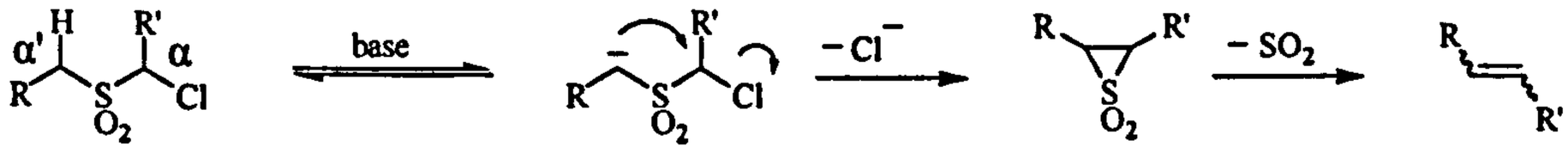
The Ramberg-Bäcklund reaction is a rearrangement of a sulfone having a leaving group in the *alpha* position. A new C=C double bond is formed by loss of sulfur dioxide (see **Scheme 1.42**).[73b]



1.139 **1.140**

Scheme 1.42

The reaction is mostly conducted with α-chlorosulfones, and an α'-hydrogen is required for the reaction to occur. The mechanism was intensively studied, suggesting the following:[80]

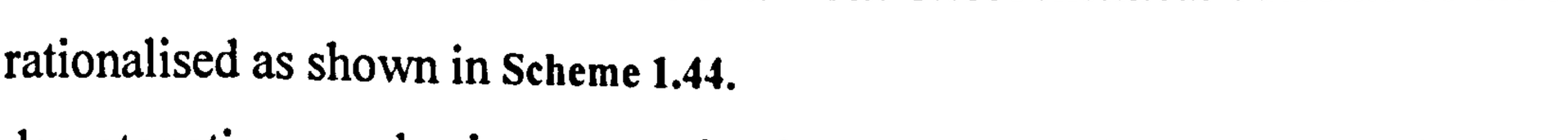


1.141 **1.142** **1.143** **1.144**

Scheme 1.43

After deprotonation of the sulfone **Scheme 1.43** to give the carbanion **1.142** intramolecular nucleophilic attack occurs by the latter on the α-carbon centre to displace the chloride, forming intermediate **1.143**. This intermediate is unstable under the basic conditions and loss of SO_2 occurs to afford the alkene **1.144**.[73] The stereochemical outcome of the reaction can be rationalised as shown in **Scheme 1.44.**

After deprotonation, carbanion **1.146** is formed and this undergoes intramolecular nucleophilic attack more rapidly than epimerisation, to form intermediate **1.147.** The final alkene reflects the stereochemistry of the intermediate **1.147.** If the intermediate episulfone has an acidic α-hydrogen, then epimerisation of the intermediate may occur to form the less hindered episulfone intermediate, giving rise to the *E*-alkene as the final product.

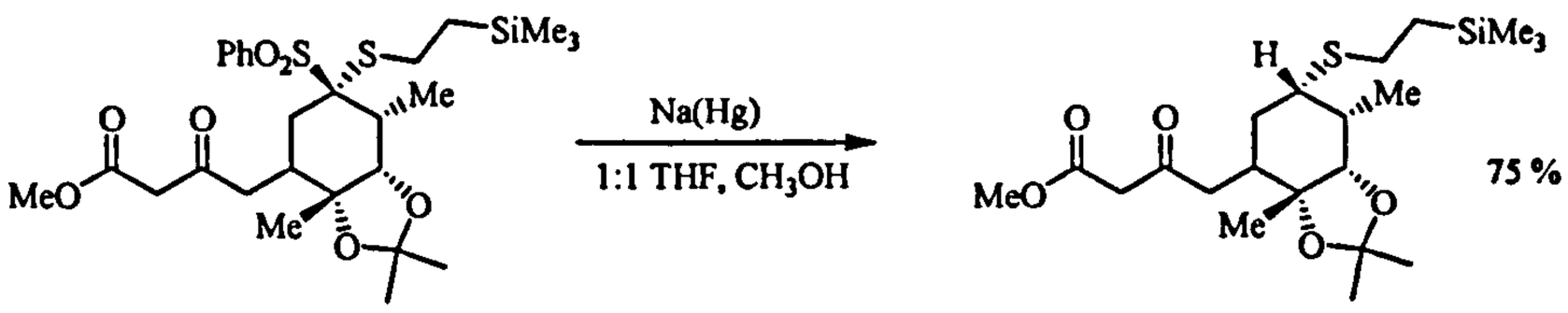


1.145 **1.146** **1.147** **1.148**

Scheme 1.44

1.3.1 *Reductive Desulfonation*

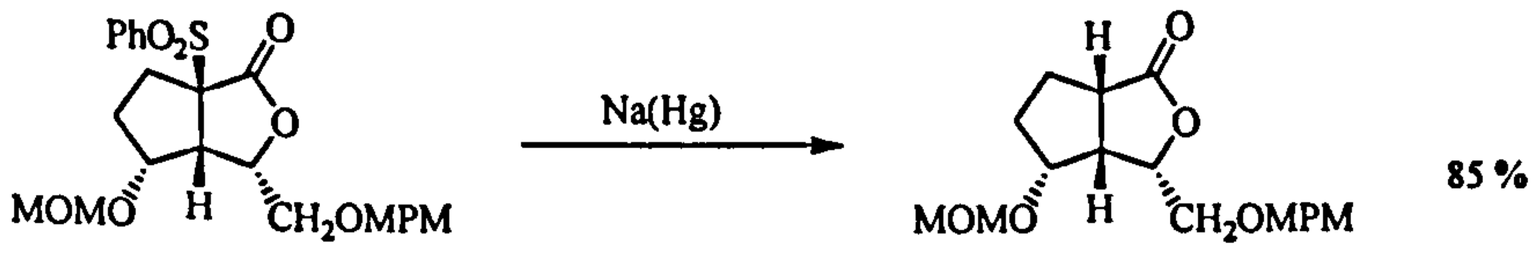
Several reductive desulfonation methods are reported.[73a] Apart from electrochemical methods,[81] they all involve strongly reducing metals. Trost *et al.* developed a desulfonation method using sodium amalgam in methanol at temperatures between –20°C and room temperature.[82] Synthetic application of this method by Fuchs *et al.* demonstrates that the method is compatible with several functional groups (**Scheme 1.45**).[83]



1.149 **1.150**

Scheme 1.45

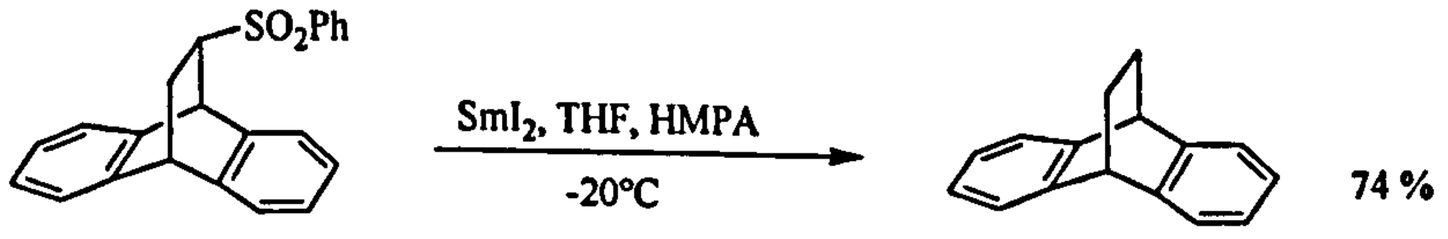
In the synthesis of the marine eicosanoid bacillariolide II from (*R*)-malic acid, the intermediate sulfonyl lactone **1.151** was reduced stereoselectively by sodium amalgam to lactone **1.152.**[84]



1.151 **1.152**

Scheme 1.46

Another method for the removal of phenylsulfonyl groups is the use of SmI_2 in a mixture of THF and HMPA. HMPA is a very toxic and carcinogenic reagent, however, it is a crucial co-solvent for the reaction to proceed (**Scheme 1.47**).[85]



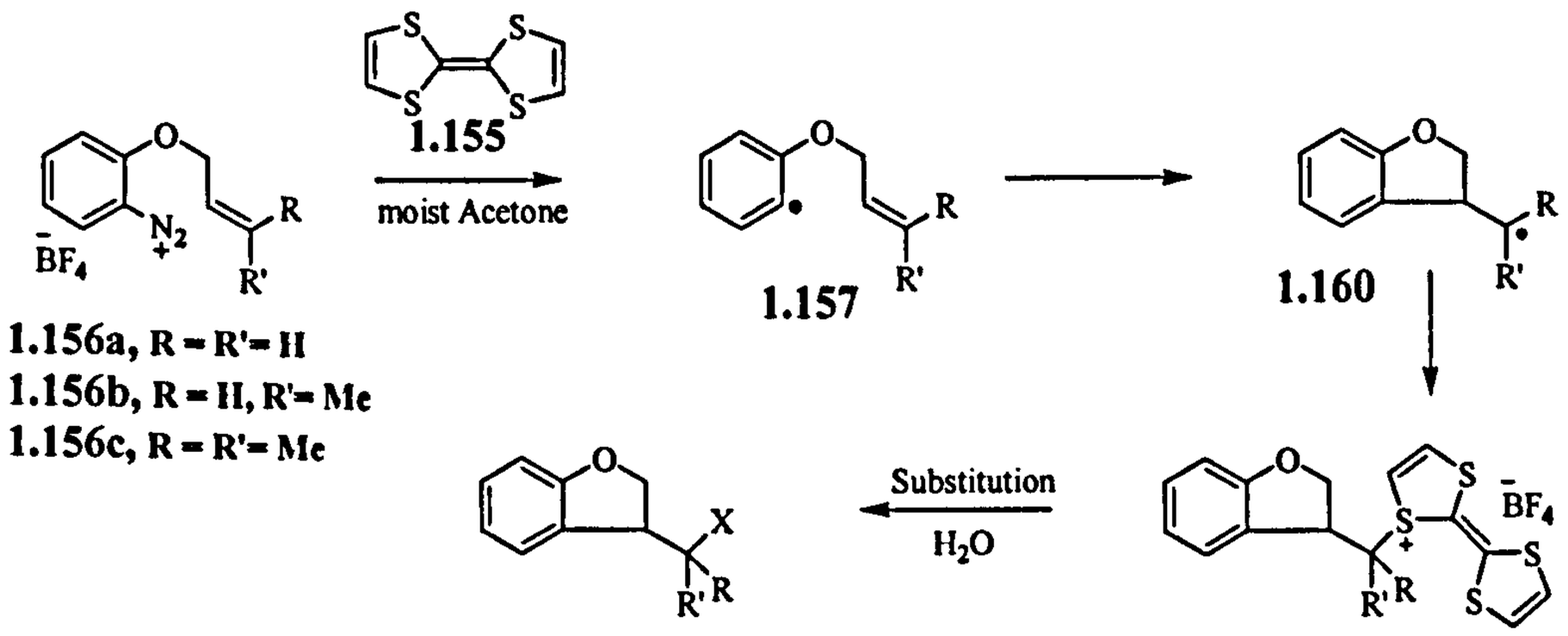
1.153 **1.154**

Scheme 1.47

Various nickel reagents have been applied to reductive desulfonations.[86] Among them are Raney Nickel or nickel-containing complexes.

1.4 Neutral organic electron donors

Neutral organic molecules that are capable of electron donation in their ground state to substrates of suitable reduction potential are a clean, metal-free alternative in the multitude of electron-transfer methods and reagents. Tetrathiafulvalene (TTF) **1.155** has proven to be such a reagent.[87] It transfers an electron to a diazonium salt acceptor **1.156** at room temperature, giving rise to an aryl radical **1.157** that subsequently cyclises (**Scheme 1.48**). The TTF radical-cation formed after electron donation then traps the radical intermediate to form salt **1.158** and this is further converted to the alcohol **1.159** in a polar fashion (substitution reaction), therefore giving this discovery its name – the radical-polar crossover reaction.



Scheme 1.48

The driving force for TTF to donate its electron is based on the aromatisation energy gained by the formation of the radical-cation species $TTF^{+\bullet}$ (**Scheme 1.49**). The newly formed aromatic system (bold) can clearly be seen in resonance structure **1.161b**. The reduction potential for the uptake of the first electron from TTF^{2+} (**1.162**) to $TTF^{+\bullet}$ (**1.161**) is quoted to be $E^{\circ} = 0.71$ V (*vs.* SCE in MeCN); the potential for the second electron uptake from $TTF^{+\bullet}$ to TTF is $E^{\circ} = 0.32$ V.[88]

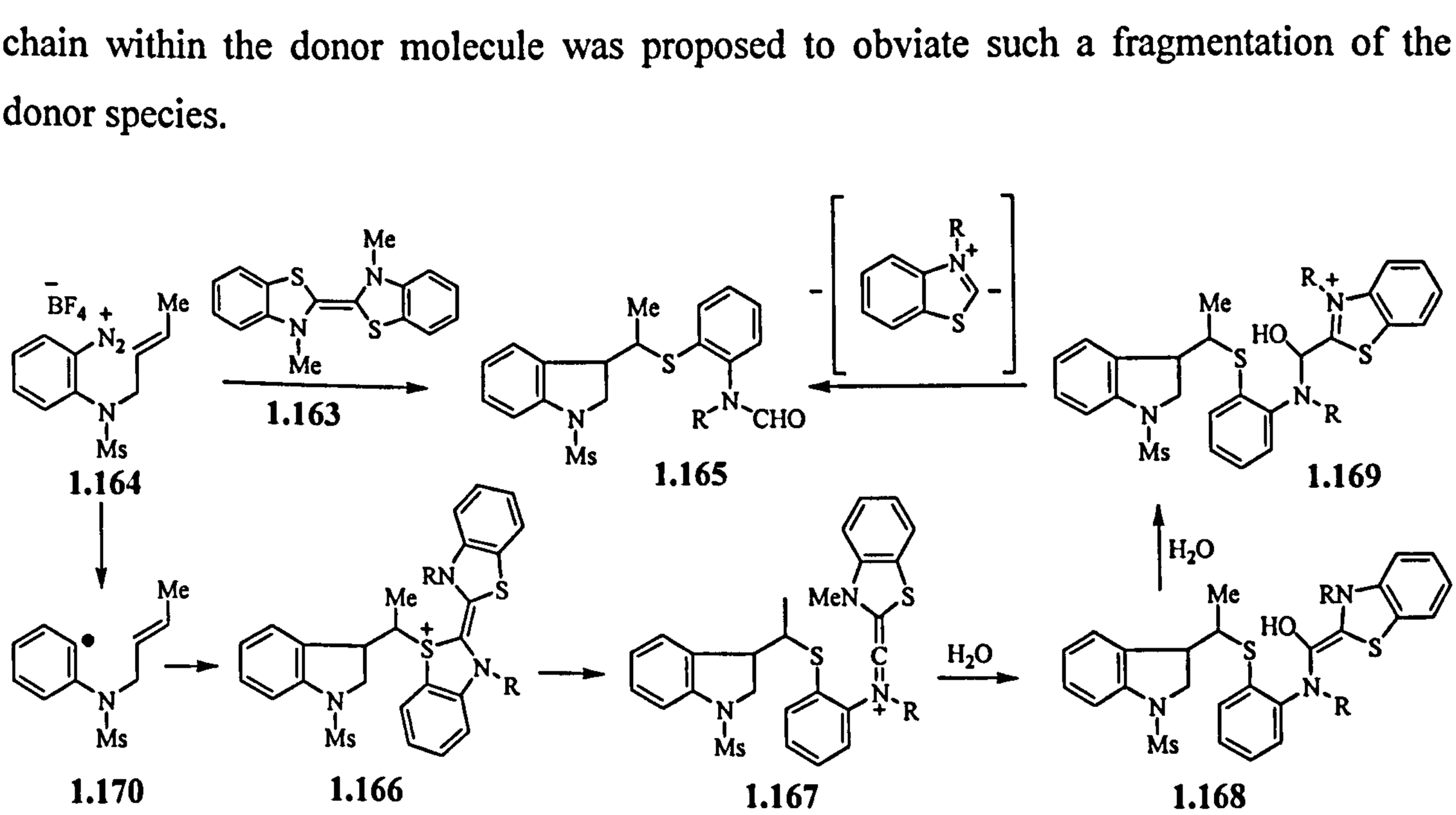
1.155 **1.161a** **1.161b** **1.162**

Scheme 1.49

Research proceeded in the development of a stronger electron donor. A donor was sought that might have the ability of reducing more challenging substrates, such as alkyl and aryl halides. Accordingly, dithiadiaza compound **1.163** was prepared. It consists of a mixed 2-

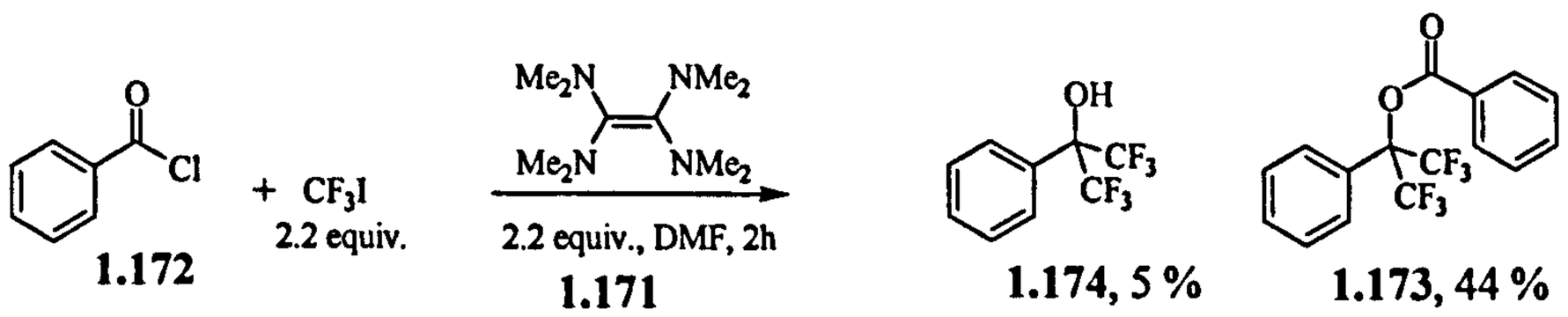
nitrogen, 2-sulfur system. Nitrogen was incorporated due to the stronger π-donation of nitrogen as opposed to sulfur, which would lead to a greater stabilisation of the generated radical-cation after electron-transfer and hence might increase the driving force for the electron-transfer reaction. The initial test was carried out on diazonium salt acceptor **1.164**. However, surprisingly, **1.165** was isolated and its formation was rationalised as shown in **Scheme 1.50**. After electron-transfer-initiated aryl radical formation and cyclisation, trapping of the resulting radical-cation of dithiadiaza compound **1.163** with the aliphatic radical occurs to give adduct **1.166**. This then undergoes fragmentation to give the keteniminium salt **1.167** due to the greater ability of nitrogen in stabilising the positive charge. Subsequent hydrolysis affords the product **1.165** (**Scheme 1.50**). In further experiments donor **1.163** proved not to be powerful enough to react with C-I bonds.[89,90]

This clearly highlights the requirement of changes in the molecular design of the donor, to increase its reducing power and to prevent any fragmentation side-reactions. A bridging chain within the donor molecule was proposed to obviate such a fragmentation of the donor species.



Scheme 1.50

Meanwhile, Médebielle *et al.* developed the more powerful organic donor TDAE[91] **1.171** that was successfully applied in the reduction of highly activated halides. CF_3I and benzoyl chloride **1.172** were coupled by an electron-transfer mechanism, possibly involving even trifluoromethyl anionic intermediates (**Scheme 1.51**).[92]

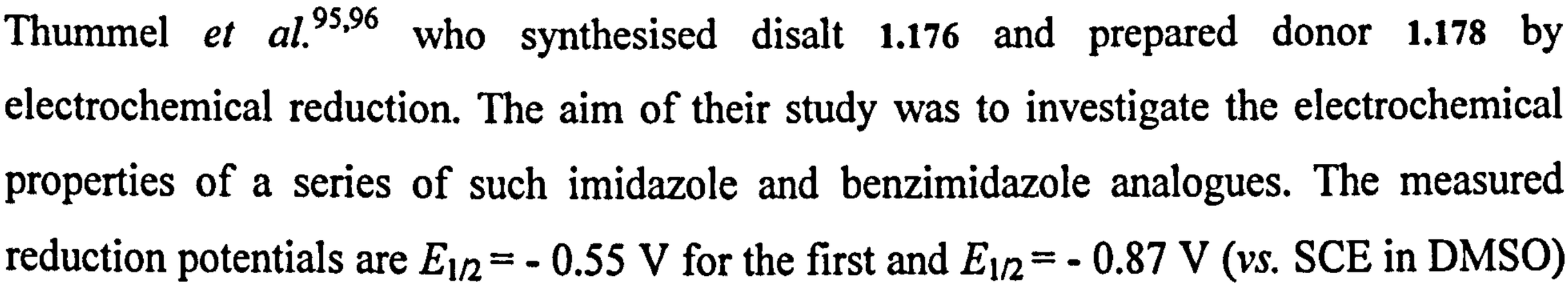


1.172 **1.171** **1.174, 5 %** **1.173, 44 %**

Scheme 1.51

The reduction potentials of TDAE were measured[93] to be $E°$ = - 0.61 V for the first ($TDAE^{2+} \rightarrow TDAE^{+\cdot}$) and $E°$ = - 0.78 V (*vs.* SCE in MeCN) for the second electron uptake ($TDAE^{+\cdot} \rightarrow TDAE$). In DMF only a single reduction peak was seen with $E°$ = - 0.62 V (*vs.* SCE in DMF).[93] The greater reducing power of TDAE in comparison to TTF can be ascribed to the greater π-donating power of nitrogen as opposed to sulfur.

Having these three concepts in mind, the aromatisation principle as shown by TTF, the great ability of nitrogen in π-donation highlighted by TDAE and the requirement of a bridging side-chain to avoid fragmentation, the donor **1.175** was developed recently within the Murphy group.[94] The very similar donor **1.178** has been studied before by Shi, Thummel *et al.*[95,96] who synthesised disalt **1.176** and prepared donor **1.178** by electrochemical reduction. The aim of their study was to investigate the electrochemical properties of a series of such imidazole and benzimidazole analogues. The measured reduction potentials are $E_{1/2}$ = - 0.55 V for the first and $E_{1/2}$ = - 0.87 V (*vs.* SCE in DMSO) for the second electron uptake (see **Scheme 1.52**). Donor **1.175** was prepared electrochemically also and reduction potentials of $E_{1/2}$ = - 0.76 V and $E_{1/2}$ = - 0.82 V (*vs.* SCE in DMF) were measured.[97]



1.176 **1.177** **1.178**

Scheme 1.52

The reduction potentials of the previously introduced donors are summarised below. The further left on this chart the indicated reduction is, the more difficult it is to achieve and hence the easier is the corresponding oxidation process.

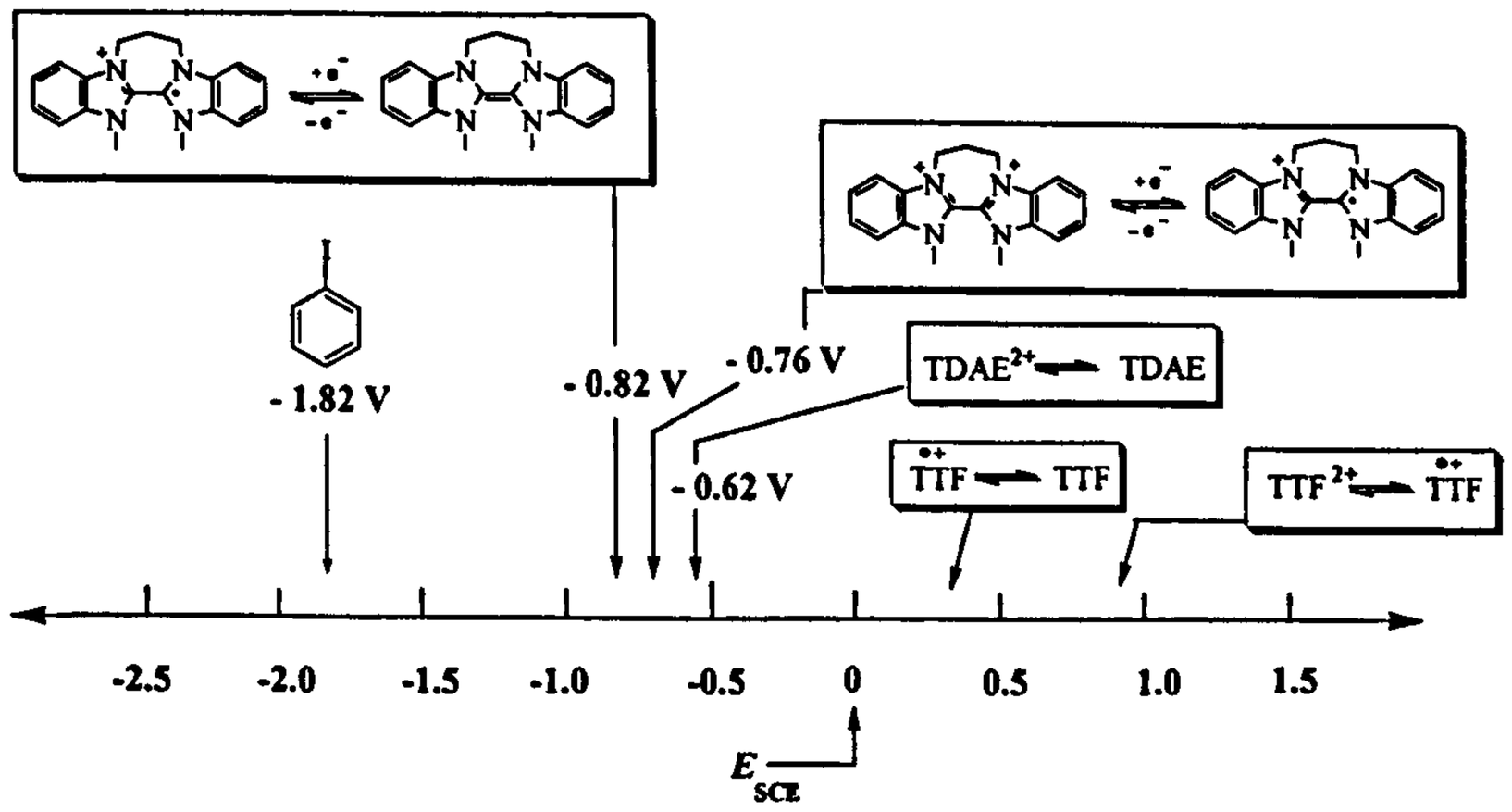


Figure 1.6 **Reduction potential chart***

In order to use donor **1.175** in synthesis a direct route to prepare donor **1.175** was developed within the Murphy group (see **Scheme 1.54** on page 43). The synthesis started from methylbenzimidazole that was refluxed in acetonitrile with 1,3-diiodopropane to give disalt **1.179**. Deprotonation of this benzimidazole salt then results in the formation of a carbene intermediate (*e.g.* **1.180** below) that will then initiate the 'dimerisation' process. A carbene is a neutral, divalent species, exhibiting two non-bonding orbitals and two electrons to distribute in the latter. These two orbitals are a lower energy sp^2-orbital and a higher energy p-orbital. If both electrons are located in the energetically lower sp^2-orbital, this will be a singlet state carbene. However, if the spin-pairing energy to accommodate both electrons in the sp^2-orbital is larger than the energy gap between sp^2- and p-orbital, the triplet state carbene will be favoured, having one electron in each orbital with parallel spin.[98]

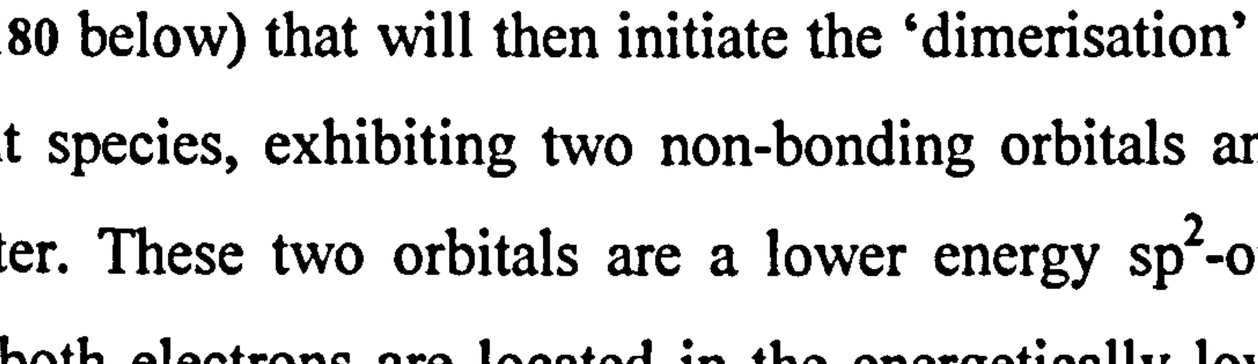


Figure 1.7 **Singlet- and triplet-state carbene of 1.180**

Considering the carbene **1.180** in **Figure 1.7**, one factor stabilising this carbene is steric shielding around the carbene centre by R groups, so that due to steric hindrance, dimerisation is prevented.[99] However, bulky substituents R also favour the adoption of the

---

* Iodobenzene: Voltammetry: $E_{1/2}$ = -1.77 V (*vs.* Ag/ AgCl, in H_2O) = -1.815 V (*vs.* SCE, in H_2O)
Polarography: $E''_{1/2}$ = - 1.62 V (*vs.* SCE, in H_2O/ Dioxane)

triplet state, as both non-bonding orbitals are forced towards a linear structure, so that they are degenerate as p_x and p_z orbitals.[100]

Further stability of the singlet state is gained, if the carbene carbon is bound to an electronegative atom, *e.g.* nitrogen or oxygen, as inductive effects within the σ-system lead to lowering of the sp^2-orbital and hence singlet-state stabilisation.[101] The model carbene **1.180** shown in **Figure 1.7** also has strong π-donors, the nitrogens in the α-positions. The nitrogen lone pairs overlap with the empty p-orbital and hence stabilise the entire molecular structure, but also stabilise the singlet state, as the energy gap between the orbitals is increased (**Figure 1.8**).[102]

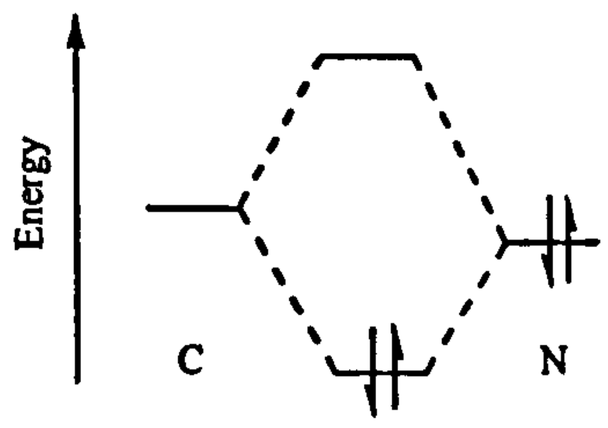
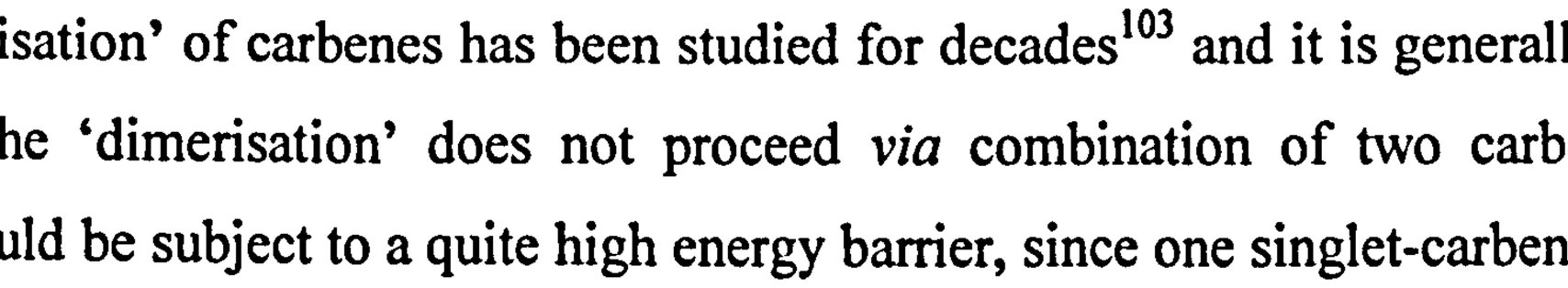


Figure 1.8 **Stabilisation by π-donation of nitrogen lone pair into the empty p-orbital of carbene**

The 'dimerisation' of carbenes has been studied for decades[103] and it is generally believed now that the 'dimerisation' does not proceed *via* combination of two carbenes. This process would be subject to a quite high energy barrier, since one singlet-carbene lone pair would have to interact with the LUMO of the partner molecule and hence the high-lying π-orbital (high in energy due to the N-donation, **Figure 1.8**) of the other carbene. Instead it is proposed that the dimerisation occurs between the singlet carbene and its conjugate acid as illustrated in **Scheme 1.53**.[104]

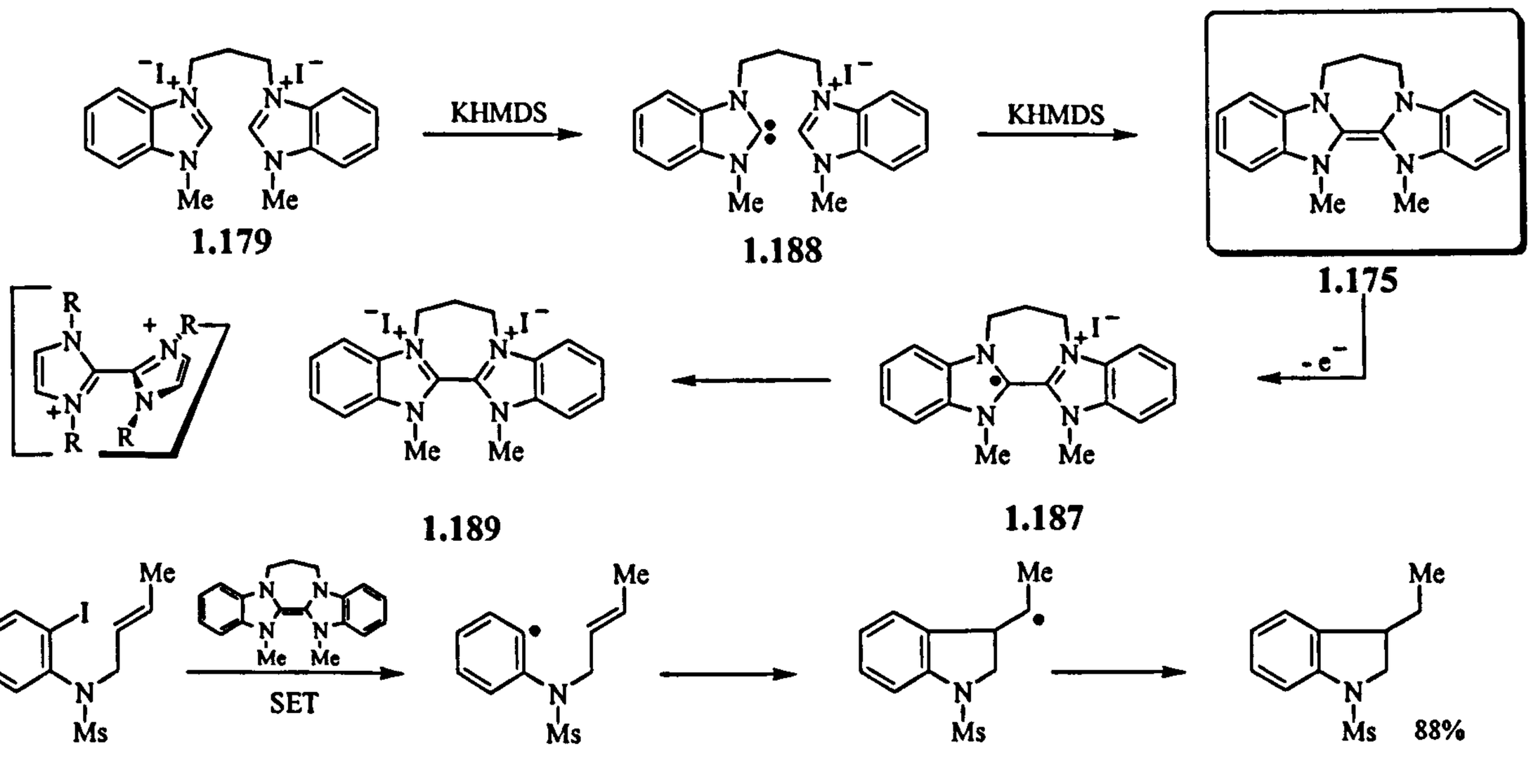


1.180 **1.181** **1.182** **1.183**

Scheme 1.53

Thus, disalt **1.179** was treated with a strong, non-nucleophilic irreversible base, KHMDS, and donor **1.175** was formed as a highly yellow, moisture and air-sensitive reagent *in situ*. This electron donor is now capable of transferring a single electron to an unactivated aryl iodide **1.184** to produce an aryl radical **1.185** that then undergoes typical radical cyclisation

to give **1.186** in excellent yield (**Scheme 1.54**) with the donor radical-cation **1.187** as by-product.[94]

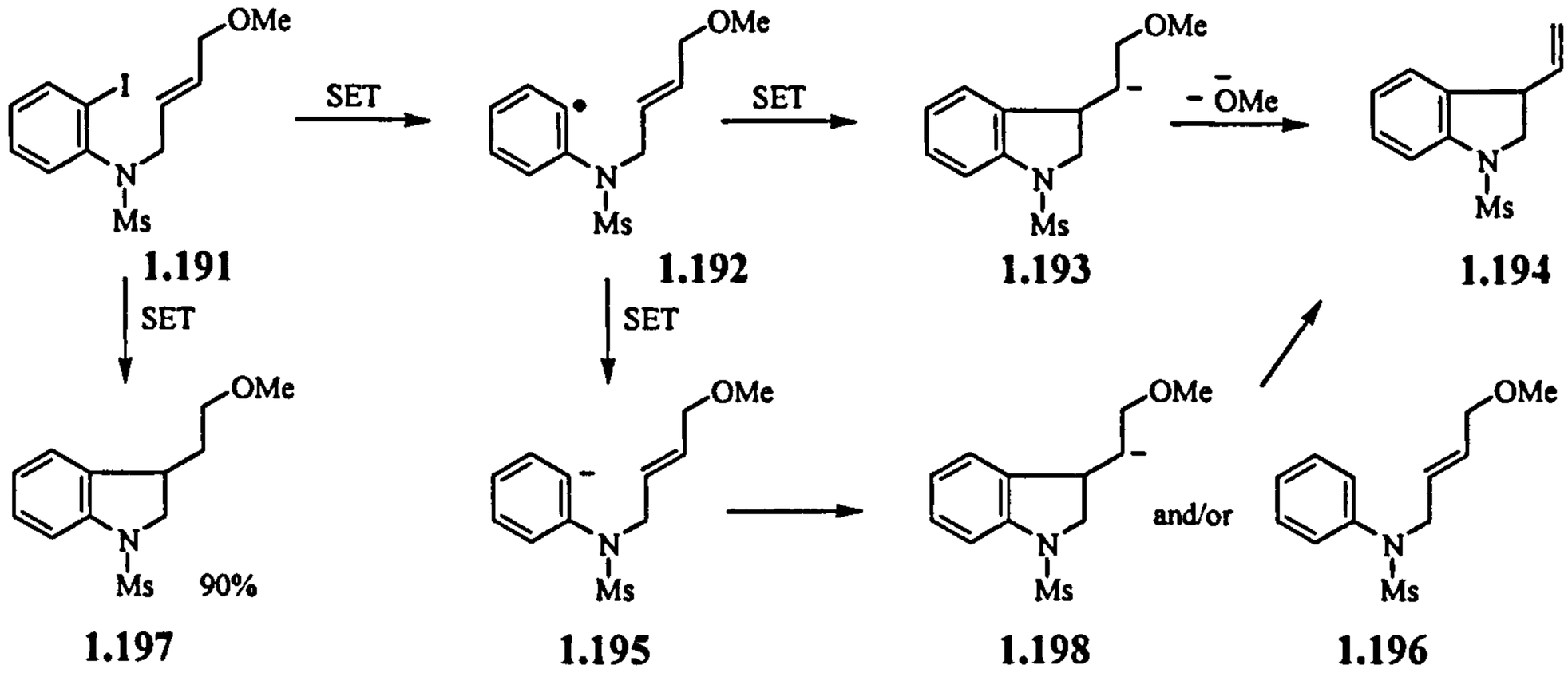


1.179 **1.188** **1.175**

1.184 **1.185** **1.189** **1.190** **1.187** **1.186**

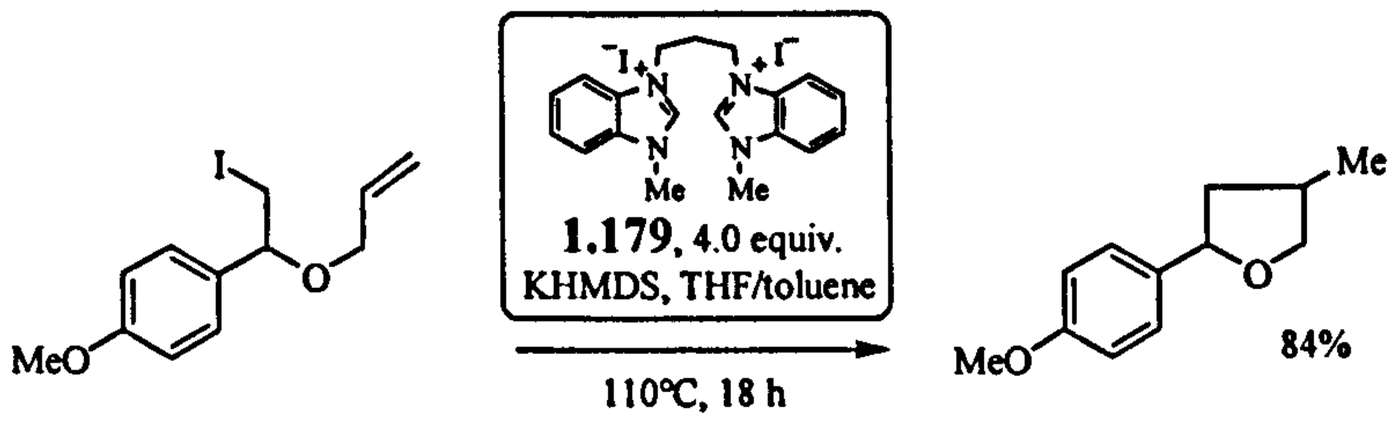
Scheme 1.54

In contrast to the chemistry of TTF, the donor radical-cation **1.187** of benzimidazole donor **1.175** that is formed after electron-transfer, does not couple to the intermediate radical **1.190**, so that the radical-polar crossover reaction was not observed. In further experiments it has been established that donor **1.175** is an exclusive 'radical reagent' under the conditions used. The possibility of forming aryl or alkyl anions has been investigated with the following methoxy substrate **1.191**. If a second electron was transferred after cyclisation of the aryl radical **1.192**, the anionic intermediate **1.193** would form that should subsequently eliminate methoxide to afford **1.194**. Similarly, if a second electron-transfer took place at the aryl radical stage **1.192**, before cyclisation, this would give the aryl anion **1.195** which could be reduced to give **1.196** or cyclise[105] and would subsequently eliminate methoxide to afford **1.194**. However, only **1.197** was isolated in high yield, hence precluding any other pathway than the radical one.[94]



Scheme 1.55

Benzimidazole donor **1.175** was further applied to the reduction of aliphatic iodides, giving **1.200** resulting from cyclisation of the radical intermediate arising from alkyl iodide **1.199**.

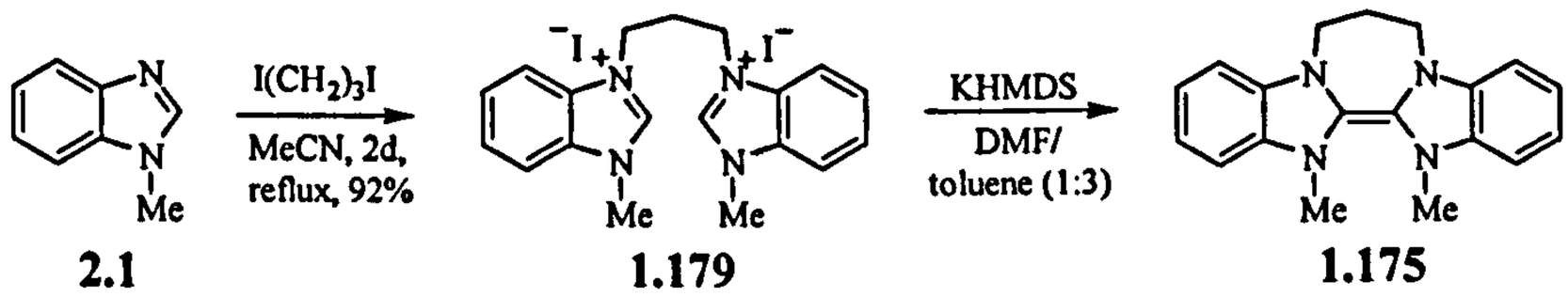


At this point my study started with the investigation of the general scope and power of donor **1.175** as a reducing agent.

Results and Discussion

Study and scope of benzimidazole donor 1.175

As introduced in the previous chapter, benzimidazole donor **1.175** was found to be reactive with aryl iodides, forming products in high yields arising from aryl radical intermediates. Aryl iodides with an *ortho*-NMs substituent (*e.g.* **1.184** on page 43) as well as alkyl iodides were found to react efficiently with benzimidazole donor **1.175**. However, hardly any studies had been undertaken to investigate *ortho*-iodoaryl ether substrates or aryl halides different from iodides, *i.e.* aryl bromides and chlorides. Thus, the goal of the following study was to explore the reductive power and scope of benzimidazole donor **1.175** on those substrates.

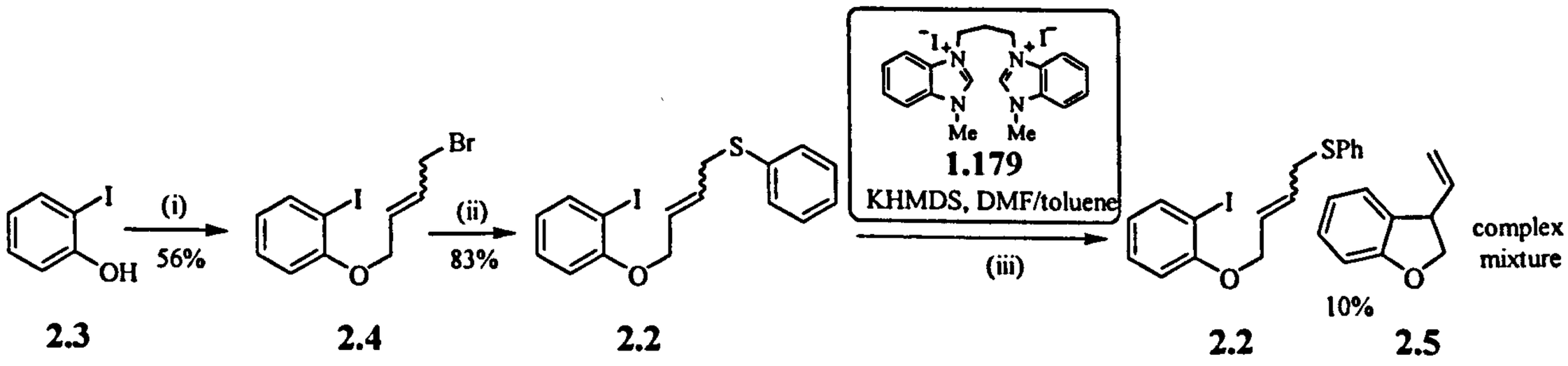


2.1 **1.179** **1.175**

Scheme 2.1

Benzimidazole salt **1.179** was prepared as reported[94] by refluxing *N*-methylbenzimidazole **2.1** and diiodopropane in acetontrile and **1.179** precipitated as a white solid from the solution.

In an initial approach to study the reductive power of donor **1.175**, *ortho*-iodoaryl ether substrates were prepared to study the influence of the *ortho*-side chain on the reduction of the leaving halide. *Ortho*-iodo-NMs substrates were found to react efficiently with donor **1.175** using 1.2 equivalents of donor in DMF/ toluene (1:3) and KHMDS as the base. However, the reaction on sulfide substrate **2.2** [that was prepared in a facile two-step synthesis and investigated under the identical reaction conditions as the NMs series] was less successful.

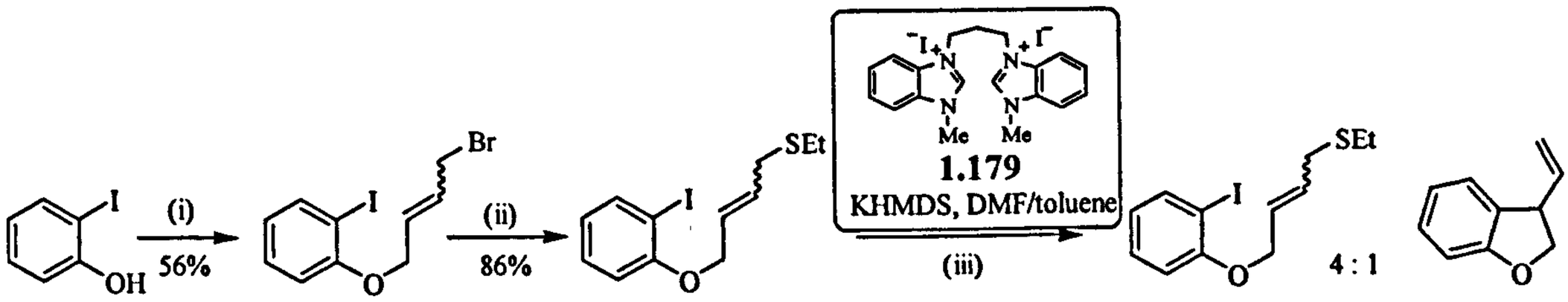


2.3 **2.4** **2.2** **2.2** **2.5**

***Reagents and conditions*: (i)** 1,4-dibromobut-2-ene (2.5 equiv.), NaH (1.2 equiv.), THF, 0°C to r.t., 2.5 h; **(ii)** thiophenol (1 equiv), NaH (1.2 equiv.), THF, 0°C to r.t., 15 h; **(iii) 1.179** (1.2 equiv.), KHMDS (2.4 equiv.), DMF/toluene (1:3), 110°C, 18h.

Scheme 2.2

Substrate **2.2** did not undergo efficient cyclisation under the successful NMs-reduction conditions. Instead a complex mixture was obtained. In purification attempts on the mixture, product **2.5** was isolated in 10 % yield, and starting material **2.2** was observed in a mixture with other compounds by ^{1}H-NMR analysis. To simplify this substrate, the SPh-radical-leaving group was replaced by an S-alkyl group in a parallel approach. Substrate **2.6** was prepared by nucleophilic substitution of the common intermediate **2.4** and then examined in the reaction with donor **1.175** [that was prepared *in situ* from salt **1.179**].



***Reagents and conditions*: (i)** *trans*-1,4-dibromobut-2-ene (2.5 equiv.), NaH (1.2 equiv.), THF, 0°C to r.t., 2.5 h; **(ii)** ethanethiol (1.2 equiv), NaH (1.3 equiv.), THF, 0°C to r.t., 18 h; **(iii) 1.179** (1.2 equiv.), KHMDS (2.4 equiv.), DMF/toluene (1:3), 110°C, 18 h.

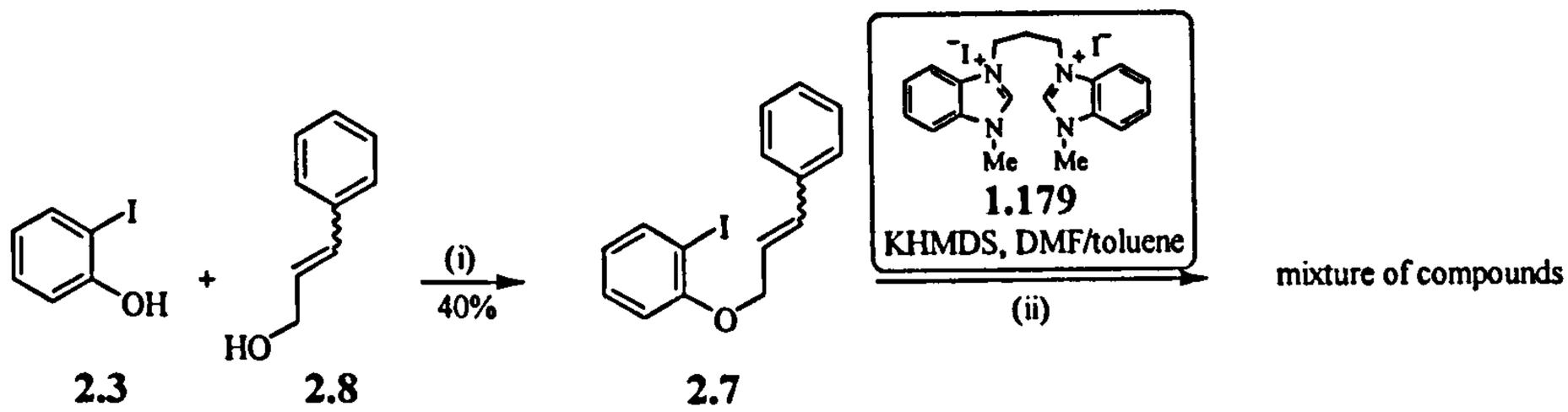
Scheme 2.3

^{1}H-NMR spectroscopic analysis of the crude mixture indicated that the reaction did not go to completion; a 4:1 ratio of starting material **2.6** to cyclised product **2.5** was seen. This result confirms the observation made in the previous experiment. The electron-donating oxygen side-chain must alter the electronic environment of the starting iodide making it into a worse electron acceptor in comparison to the NMs-series. Thus, the applied reductive conditions are not sufficiently powerful to achieve the desired conversion. It is reported that methylphenylsulfide, PhSMe, exhibits a reduction potential* of $E''_{1/2}$ = -2.27 V (*vs.* Ag/AgCl in DMF).[108] For a rough comparison, iodobenzene is quoted to have a potential of $E''_{1/2}$ = -1.62 (*vs.* SCE in 75% dioxane/water) [= -1.57 V (*vs.* Ag/AgCl)].[106] The ArS-moiety should, therefore, not be reduced in preference over the Ar-I bond in substrate **2.2**. The thiyl radical produced however is easily reduced to the sulfide anion. This might be an alternative reason for the inefficient reactivity of those *ortho*-iodoaryl ethers; perhaps the thiyl radical reduction was in competition with the iodide reduction. However, if this was the sole reason, at least 50 % overall conversion would have been expected. Thus, it seems as if *ortho*-iodoaryl ethers need greater reducing power to be converted completely. This assumption seems indeed confirmed by the reduction potentials* estimated by N. Findlay from our group, for an aryl iodide with an *ortho*-NMs

* *E* corresponds to the reduction potential measured by cyclic voltammetry and the quoted value differs significantly from *E*'' obtained by polarography; the values cannot be compared between one another.

substituent the potential is E_p = -2.30 V (*vs.* Ag/AgCl in DMF)]. In comparison, an aryl iodide with an *ortho*-ether chain shows a potential of E_p = -2.48 V (*vs.* Ag/AgCl in DMF), suggesting that the reduction of the aryl iodo ether is more difficult, which is in line with the experimental observations [the cyclic voltammograms of the corresponding structures and information about their LUMOs can be found in the Appendix, chapter 9].

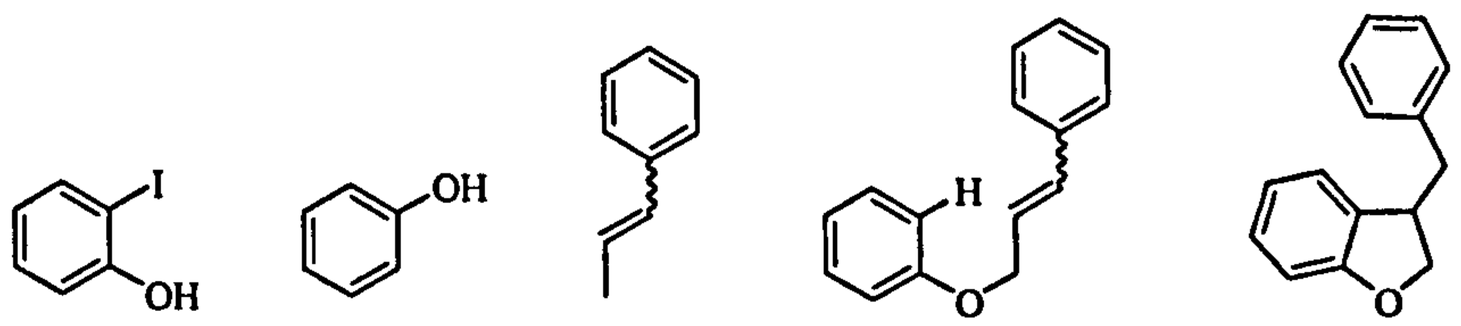
Another substrate investigated was **2.7**. It was obtained under Mitsunobu conditions starting from iodophenol and cinnamyl alcohol. After donor formation, using KHMDS, **2.7** was added and the mixture heated at reflux overnight (**Scheme 2.4**).



***Reagents and conditions*: (i)** PPh_3, DIAD, THF, 0°C to r.t., 2.5h; **(ii)** **1.179** (1.2 equiv.), KHMDS (2.4 equiv.), DMF/toluene (1:3), 110°C, 18h.

Scheme 2.4

It was found that **2.7** did not cyclise efficiently in the reaction with benzimidazole donor **1.175**. Instead starting material **2.7** was recovered in 44 % yield, and a mixture of several compounds was observed by GC-MS analysis, among them phenol, iodophenol, **2.10**, some **2.11** or **2.12** (both have identical masses) and several other unidentified compounds.



2.3 **2.9** **2.10** **2.11** **2.12**

A molecular modelling study[107] of the LUMO of **2.7** indicated the highest LUMO density (which indicates where the electron is accepted with greatest probability, indicated in blue in **Figure 2.3**) to be located on the allylic side-chain of the molecule, suggesting that the electron is transferred there in preference to the aryl iodide moiety, possibly giving rise to the cleavage products **2.3**, **2.9** and **2.10**.

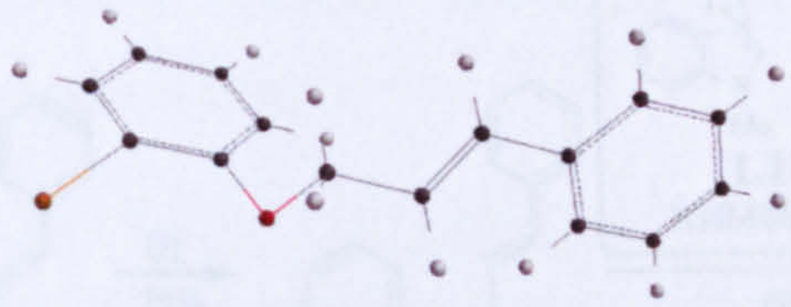


Figure 2.1 Substrate 2.7

Figure 2.2 LUMO of 2.7

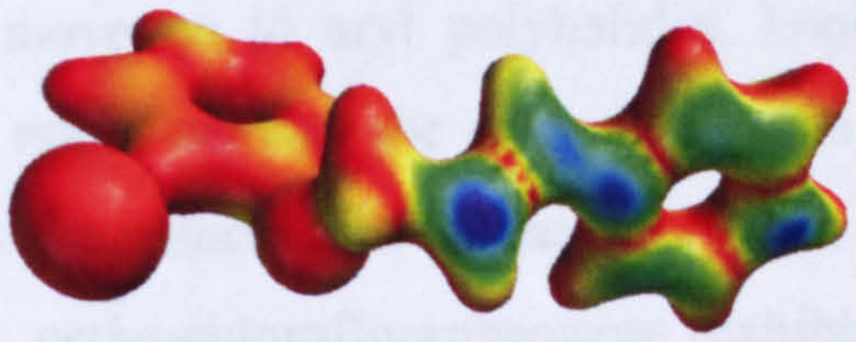
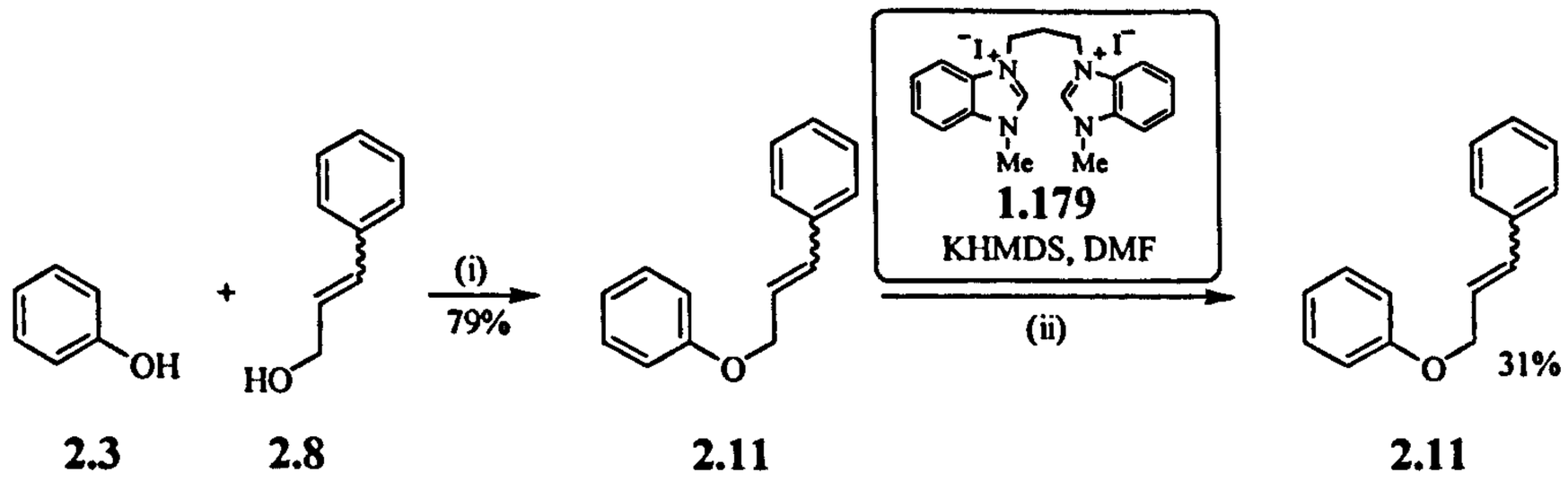


Figure 2.3 LUMO density of 2.7

To test whether this observation could have synthetic utility in the cleavage of benzylic protecting groups for instance, the substrate was simplified to **2.11**, which was synthesised (as shown below) in 79 % yield and subjected to the reaction with *in situ*-prepared benzimidazole donor under more concentrated conditions. DMF was chosen as the only solvent to achieve greater temperature and hence more reductive power by donor **1.175** (reduction potential is concentration- and temperature-dependent, compare section **1.1.2**). However, a complex mixture was obtained again, partially unidentified even by GC-MS. Since starting material **2.11** was recovered in 31 % yield and isomeric compounds of the same molecular mass were seen by GC-MS that probably arose by rearrangement under the high temperature conditions, it was decided that this reaction does not have synthetic utility (**Scheme 2.5**).



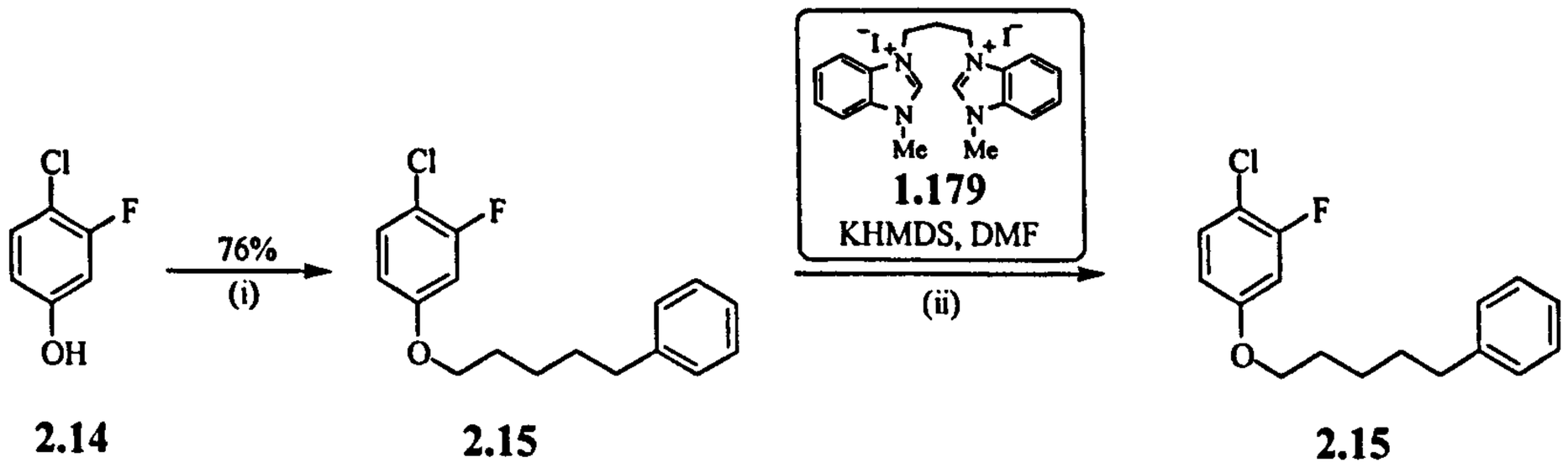
2.3 **2.8** **2.11** **2.11**

***Reagents and conditions*: (i)** PPh_3, DIAD, THF, 0°C to r.t., 5 h; **(ii)** **1.179** (1.2 equiv.), KHMDS (2.4 equiv.), DMF, 120°C, 18 h.

Scheme 2.5

These results highlight the importance of the nature of the side-chain on the reduction of aryl halides. Benzimidazole donor **1.175** seems to be at a fine borderline of being able to reduce more electron-deficient aryl iodides and to be rather limited in reducing slightly more electron-rich ones. Therefore, benzimidazole donor **1.175** could have scope as a selective reagent, and this will be investigated in later chapters.

It was then decided to move on to aryl polyhalides, hoping that additional electron-withdrawing substituents might activate the aromatic system towards electron acceptance and might therefore allow the reduction of halides other than iodides. A study of reduction potentials revealed that *ortho*-chlorofluorobenzene exhibits a reduction potential of $E''_{1/2}$ = -1.89 V (*vs.* SCE in H_2O).[108] This is slightly higher than iodobenzene ($E''_{1/2}$ = -1.62 V *vs.* SCE in 75% dioxane-water). Thus, it was thought that if the number of equivalents of the donor was increased, reduction might be possible under those more forcing conditions. Since the reduction of *ortho*-chlorofluorobenzene would give rise to a volatile product, *para*-chlorofluorophenol was used instead, and a large group was attached to make it non-volatile (**2.15, Scheme 2.6**).



2.14 **2.15** **2.15**

***Reagents and conditions*: (i)** 5-phenyl-1-pentanol **2.13** (1 equiv.), PPh_3 (1 equiv.), DIAD (1equiv.), THF, 0°C to r.t., 2.5 h; **(ii)** see **Table 2.1**.

Scheme 2.6

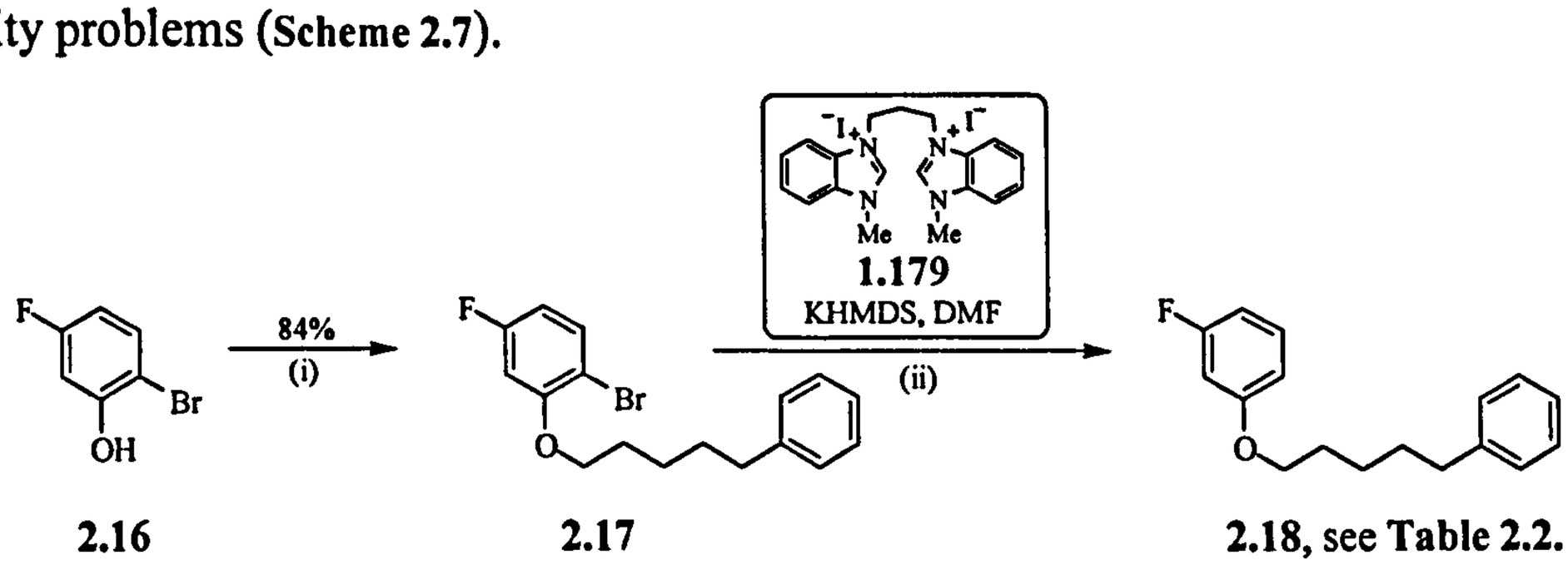
Two reactions were carried out (see **Table 2.1** for conditions), one using standard aryl NMs-iodide reduction conditions except that DMF was used as the exclusive solvent, while in

the second experiment more concentrated conditions were applied. However, only starting material was recovered in both cases.

Entry	Conditions	Outcome
1	**1.179** (1.2 equiv., 0.26 mmol), KHMDS (2.4 equiv.), DMF (17ml), 118°C, 3d.	**2.15**, 90%
2	**1.179** (5 equiv., 1.5 mmol), KHMDS (10 equiv.), DMF (14ml), 118°C., 3d.	**2.15**, 95%

Table 2.1 Attempted reduction of chloride 2.15

Since fluorochloride **2.15** did not lead to any conversion, it was decided to move on to bromo-fluorobenzene, because *ortho*-bromofluorobenzene is reported to have a lower and possibly more accessible reduction potential of $E^{red}_{1/2}$ = -1.69 V (*vs.* SCE in H_2O).[108] No corresponding phenol bearing the fluoride and bromide *ortho* to each other was commercially available. It was decided, therefore, to use **2.16** instead, since at least the oxygen is located *ortho* to the bromide (compare previous discussion of rate of bond cleavage, page 13). Again, a suitable derivative, this time **2.17**, was prepared to avoid any volatility problems (**Scheme 2.7**).



2.16 **2.17** **2.18, see Table 2.2.**

***Reagents and conditions*: (i)** 5-phenyl-1-pentanol (1 equiv.), PPh_3 (1 equiv.), DIAD (1equiv.), THF, 0°C to r.t., 3 h; **(ii)** see **Table 2.2.**

Scheme 2.7

Two different conditions were applied; the first using five equivalents of benzimidazole salt **1.179**. This led to a 50:50 mixture of **2.17** and its reduced counterpart **2.18**. Using ten equivalents of salt under very concentrated conditions in the second experiment, pleasingly led to increase in reduction of the bromide to give **2.18** as the major compound. The reduced compound **2.18** turned out to be inseparable from its starting material **2.17** (**Table 2.2**).

Entry	Conditions	Outcome
1	**1.179** (5 equiv., 1.5 mmol), KHMDS (10 equiv.), DMF (15ml), 110°C, 18h	**2.17:2.18** 1:1
2	**1.179** (10 equiv., 3.0mmol), KHMDS (20 equiv.), DMF (8ml), 110°C., 18h	**2.17:2.18** 2:3

Table 2.2 Attempted reduction of bromide 2.17

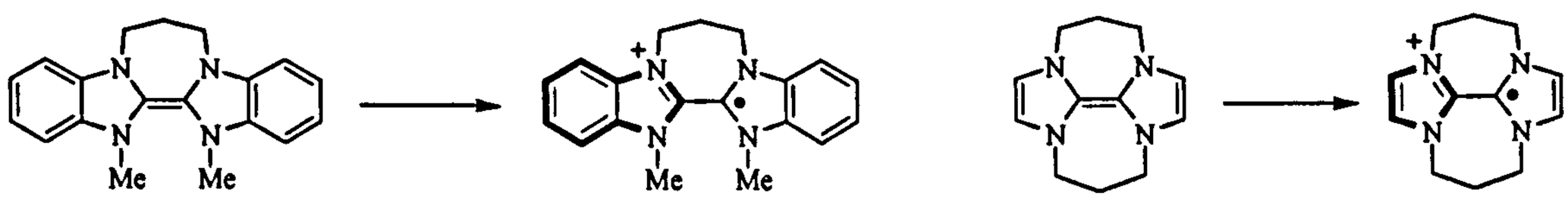
Complete reduction could not be achieved. This initiated a study of reduction potentials of aryl halides with different substitution patterns in more detail. Unexpectedly, great differences in reduction potentials are reported for the relative positions of the halides to each other; for *ortho*-bromofluorobenzene a reduction potential of $E''_{1/2}$ = - 1.69 V (*vs.* SCE in H_2O) is reported, as stated above. Changing the halide positions to *para*-bromofluorobenzene, tremendously changes the reduction potential to $E''_{1/2}$ = - 2.00 V (*vs.* SCE in H_2O).[108] The observation of incomplete reduction of 2-bromo-5-fluoro-1-(5-phenylpentyloxy)benzene **2.17** is therefore rather unsurprising, as an enormous potential of approximately $E''_{1/2}$ = - 2.00 V has to be overcome which is beyond the power of donor **1.175**, even under very concentrated conditions.

In conclusion, it has been shown that benzimidazole donor **1.175** has limited reducing power in reductions of substrates other than *ortho*-iodo NMs-substrates. Its scope as an all-round reducing agent is rather limited and to achieve reductions with low numbers of equivalents of donor and milder conditions (*e.g.* reaction at room temperature), a more powerful neutral organic reducing agent of more negative reduction potential needed to be developed and this will be discussed in the following chapter.

Powerful reductions and generation of aryl anions

3.1 New electron donor – imidazole donor 2.20

In the previous chapter, it has been shown that benzimidazole donor **1.175** is not powerful enough to reduce halides with a low number of equivalents of donor. To achieve these types of reductions, a more powerful donor was required. Considering the driving force of electron donation, the aromatisation energy gained by the donor molecule when undergoing transformation from the neutral donor towards the radical-cation (or dication) is crucial, as discussed in the introduction (*e.g.* TTF, benzimidazole donor). Thus, it was thought, that by omission of the benzene ring in the benzimidazolium system, greater aromatisation energy could be gained, having a single ring becoming aromatic after electron transfer and thus overcoming the annellation effect[109] that leads to smaller aromatisation energy and hence less driving force in the case of benzimidazole donor **1.175.**



1.175 **1.187** **2.20** **2.19**

Scheme 2.8

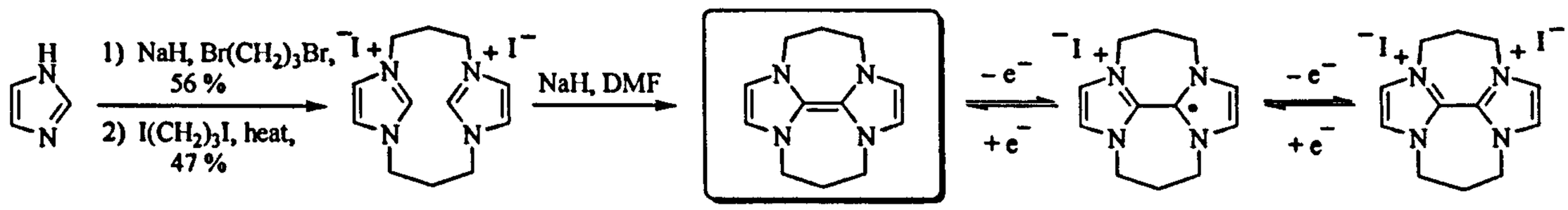
Imidazole donor **2.20** had been prepared by Ames, Thummel and Taton *et al.*[110,111,112] to study the electrochemical properties of this compound. Disalt **2.21** was synthesised and subsequently reduced in an electrochemical fashion to donor **2.20**. The measured reduction potentials are $E_{1/2}$ (MeCN) = -1.12 V and -1.28 V [(ir.) *vs.* SCE];[111] $E_{1/2}$ (DMF) = -1.20 V (*vs.* SCE)[110] for the first and second electron.

2.21 **2.19** **2.20**

Scheme 2.9

However, they neither succeeded in isolating donor **2.20** nor in preparing it in a more practical synthetic manner. A successful route to synthesise disalt **2.22** in bulk, developed by S.-Z. Zhou from our group, is *via* deprotonation of imidazole with NaH, treatment of it with 1,3-dibromopropane, followed by isolation of the intermediate and further treatment

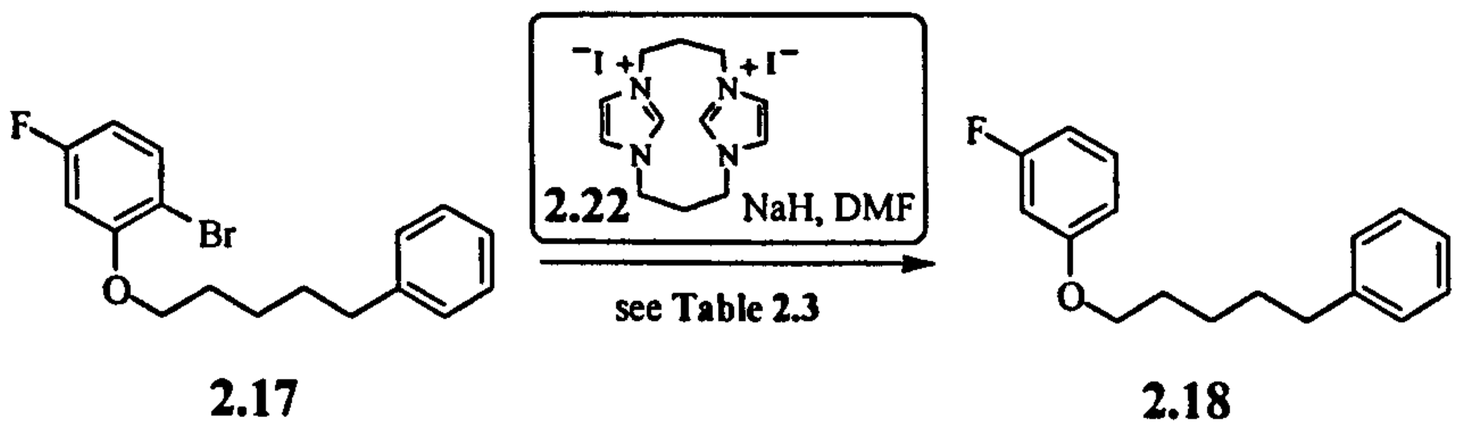
with 1,3-diiodopropane (see **Scheme 2.10**). This gave rise to the stable, white precursor salt **2.22**. The donor can then be generated *in situ* by dissolving the salt **2.22** in DMF and treating it with NaH. After sufficient 'dimerisation' time, the mixture is centrifuged and the resulting supernatant liquid transferred to the substrate.



2.23 **2.22** **2.20** **2.19** **2.24**

Scheme 2.10

The first experiments carried out with this new donor were to attempt the reductions of substrates **2.17** and **2.15** again. In the first experiment, 1.5 equiv. of donor **2.20** were prepared using an excess of NaH. After centrifugation, the resulting yellow solution of donor **2.20** was transferred *via* cannula to substrate **2.17** at room temperature. No change in colour was observed. However, after heating the mixture at 100°C overnight, the colour changed from yellow to deep red. Pleasingly, nearly complete reduction of bromide **2.17** to **2.18** was achieved (see **Table 2.3**). Increase to two equivalents in a second experiment then gave **2.18** in a successful 76 % yield as the exclusive product (**Scheme 2.11**).



2.17 **2.18**

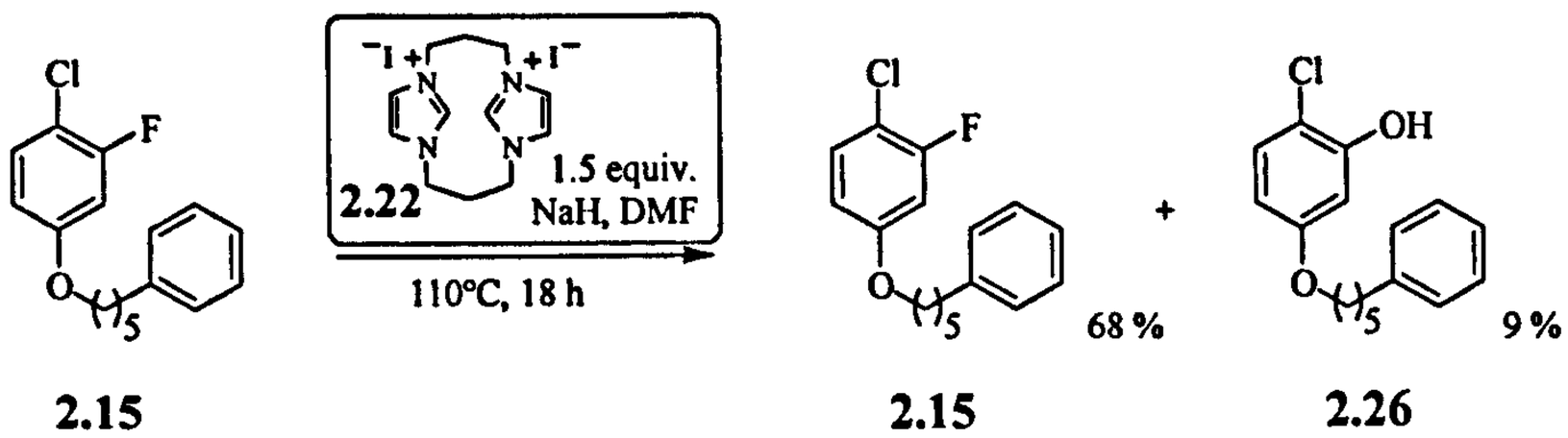
Scheme 2.11

Entry	Conditions	Outcome
1	**2.22** (1.5 equiv., 0.45 mmol), NaH (12 equiv.), DMF (15ml), 100°C, 18h	**2.17 : 2.18** 1:6
2	**2.22** (2.0 equiv., 0.50 mmol), NaH (16 equiv.), DMF (15 ml), 100°C., 18h	**2.18**, 76 %

Table 2.3 **Reduction of bromide 2.17**

This result highlights the exceptionally great reducing power of donor **2.20**. With benzimidazole donor **1.175**, in contrast, reduction of **2.17** could only be achieved to about 60 %, using salt **1.179** in 10 equivalents and under very concentrated conditions.

Next to be reduced was substrate **2.15**. Using benzimidazole donor **1.175**, chloride substrate **2.15** had remained untouched, and only starting material had been recovered. Accordingly, 1.5 equiv. of donor **2.20** were prepared from salt **2.22** in solution and added to **2.15**. Again, no colour change was observed at room temperature. Heating at 100°C overnight led to an orange solution. However, 68 % of starting material **2.15** were recovered along with phenol **2.26** in 9 % yield (**Scheme 2.12**). Reduction of the chloride did not take place. Possibly **2.26** arose from nucleophilic aromatic substitution by hydroxide on the fluoride. Substitution of an analogous aromatic fluoride has been observed by Davies *et al.* in the reaction of 6-chloro-5-fluoro-1,2,3-benzothiadiazoles with hydroxide for instance.[113]



Scheme 2.12

Since the reduction potential of chlorofluorobenzene ($E''_{1/2}$ = -1.69 V)[108] should be in the range of the power of donor **2.20**, there might be a different reason, why reduction was not observed. Possibly, electron transfer into the π*-system of **2.15** occurred (of which the reduction potential is a measure) to form the corresponding radical-anion; the second step, however, involving stretching of the C-Cl bond with lowering of the σ*-orbital and subsequent π*-σ* transition with concerted C-Cl cleavage, seems to be of too high energy to be achieved.

In a theoretical study carried out by Pierini and Vera, the energy required to undergo the π*-σ* transition was calculated for halobenzenes. They report[114] that the antibonding a_1 (σ*) orbital of the C-X bond lies more than 4 eV above the π* LUMO for X = F. In case of X = Cl this energy decreases to 1.11 eV, and for X = Br it is estimated to be 0.59 eV. Further, the a_1 (σ*) orbital becomes LUMO for X = I.

This study agrees with the experimental outcome stated above. Seemingly, the high energy barrier for the π*-σ* transition disfavours the reduction of aryl chloride **2.15**.

3.2 Mechanism of aryl halide reduction

3.2.1 *Ester cyclisation as a probe for aryl anion*

The question then arose, by which mechanism the reduction of halides occurs. Does it proceed *via* a radical mechanism or possibly by an anionic mechanism? Given the reduction potentials of **2.20** that were investigated in acetonitrile, little difference was observed in the potential of the 1st and 2nd electron (see above). However, in DMF only a single potential was measured for the bromide salt **2.21**. S. Park of our research group carried out electrochemical measurements[115] on the corresponding iodide salt **2.22** in DMF, starting from the disalt **2.24**, and he obtained the following cyclic voltammogram for donor **2.20**.

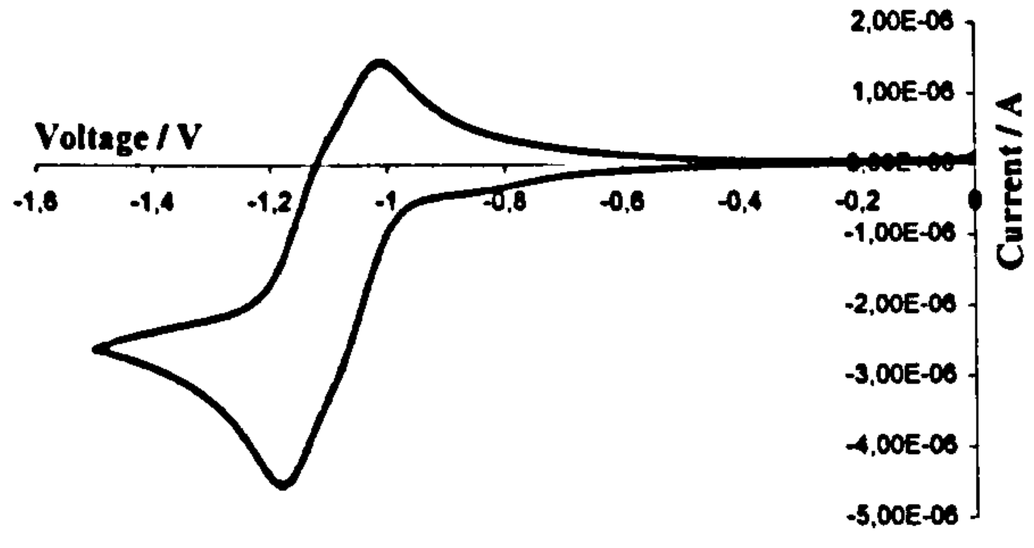
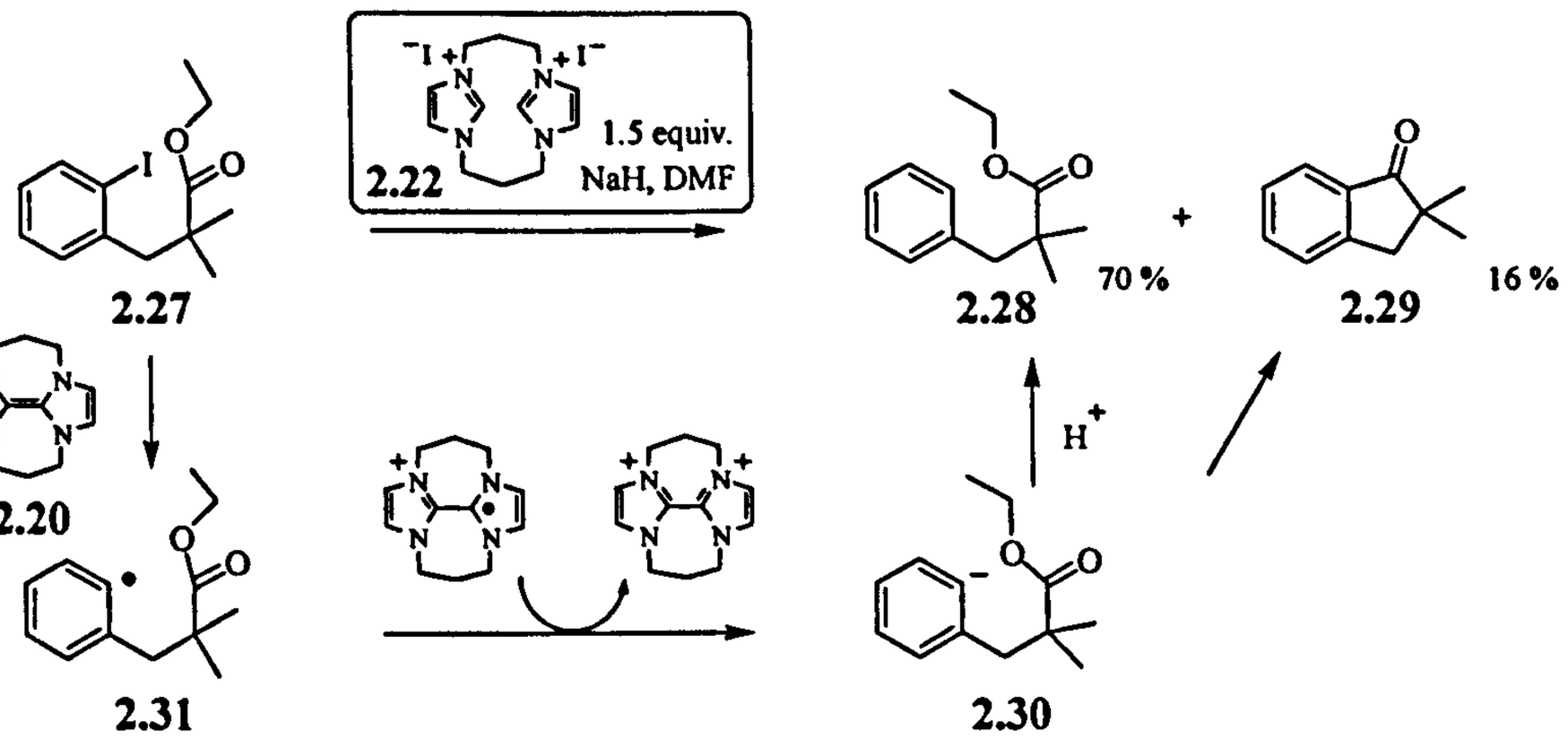


Figure 2.4

Thus, both electrons of the donor are, under the experimental conditions [*i.e.* DMF as the solvent] taken up at almost the same reduction potential, which can be seen in the cyclic voltammogram (**Figure 2.4**). Only one 'wave' is seen that also exhibits a little 'shoulder' corresponding to the second electron being taken up at that potential. Further, from the peak height it was estimated that it indeed corresponds to two electrons being transferred (calibrated against ferrocene). If both electrons were donated to the donor precursor salt at different potentials, two separate waves would be expected. Since this is a reversible peak, this indicates in turn, that both electrons of the donor are almost equally powerful and this suggests that donor **2.20** might be capable of transferring two electrons to a halide acceptor.

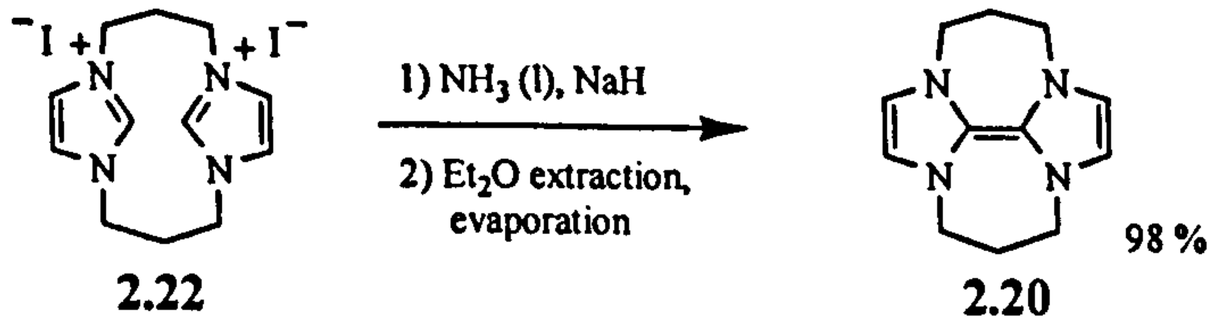
This was investigated synthetically by S.-Z. Zhou. A substrate was designed that would lead to unambiguous discrimination between aryl anions and aryl radicals. Iodoester **2.27** was selected as it should differentiate between an aryl anion and an aryl radical intermediate. If an aryl anion was produced, this should cyclise onto an ester. Aryl radicals, however, should not (see also later discussion). When the experiment was carried out, it was found[116] that donor **2.20** reacts instantaneously at room temperature with the iodoester to give the reduced ester **2.28** (70 %) as well as the ketone **2.29** (16 %). This outcome was

rationalised as follows: upon exposure of the aryl iodide to the donor, the aryl anion **2.30** was formed, which subsequently attacked the ester functionality to form ketone **2.29** or was protonated to give rise to the reduced ester **2.28** (**Scheme 2.13**). Alternatively reduced ester **2.28** could also arise from hydrogen atom abstraction by the aryl radical **2.31**.



Scheme 2.13

In this reaction, the donor **2.20** was formed *in situ*, by use of sodium hydride as a base to trigger the donor formation. This results in the generation of sodium iodide as a byproduct that is slightly soluble in DMF.[117] Thus, metal ions, present in the reaction mixture, could complex to the aryl anion and thus lower its reactivity. In order to form highly reactive, non-chelated aryl anions and to establish the uniqueness of generating a 'naked' anion with a completely organic positive counter-ion, a metal-free protocol was developed.[118] To this end, donor **2.20** was generated as a pure compound, a yellow solid. This was achieved by reacting salt **2.22** with sodium hydride in liquid ammonia. After sufficient reaction time (4 h), the ammonia was then evaporated and the residue transferred into a glove-box, where it was extracted with diethyl ether, and subsequently the solvent was removed by distillation. This method afforded donor **2.20** as a highly moisture-sensitive and air-sensitive, yellow solid that was stable under glove-box conditions.*



Scheme 2.14

Repetition of the previously discussed cyclisation experiment of iodoester **2.27** using the pure donor, gave a very similar outcome. The cyclised product, ketone **2.29**, was isolated in slightly lower yield this time (**Scheme 2.15**).[116]

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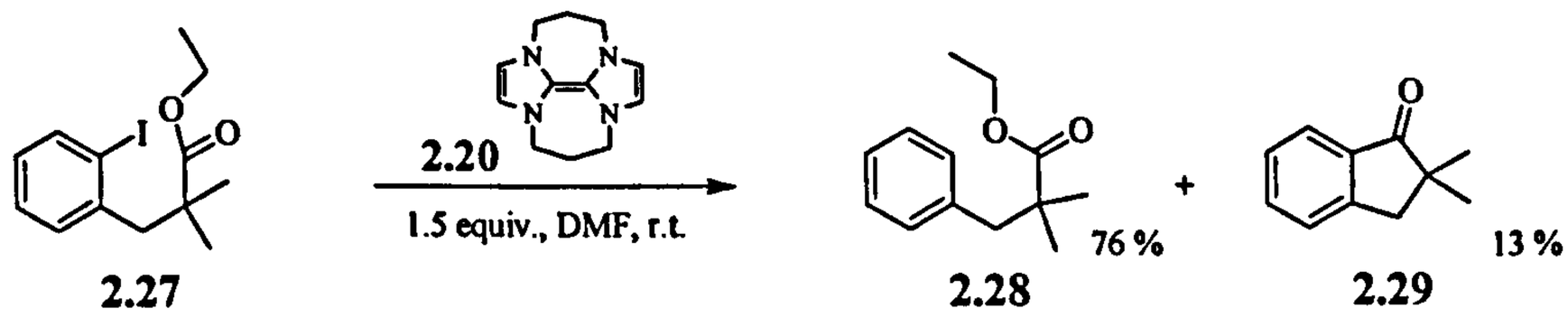
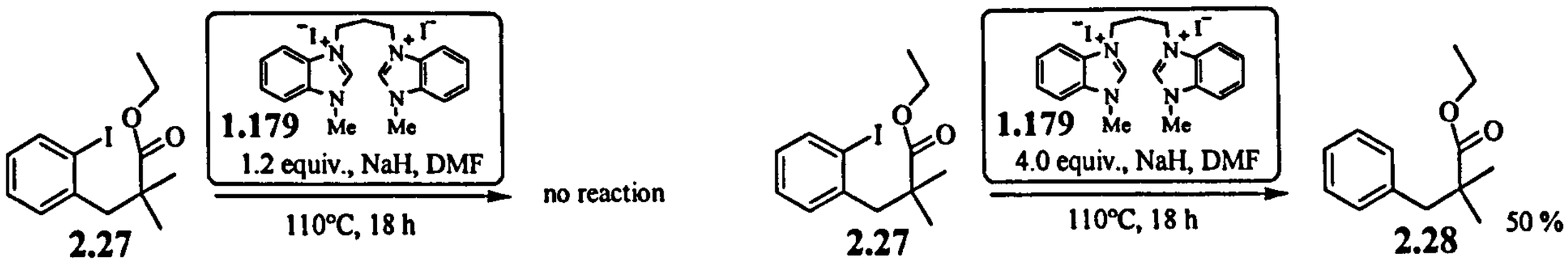
* Atomic absorption (AAS) analysis: 0.005 mg of Na in 100.0 mg of donor **2.20** (0.047 mol%), evaluated by S.-Z. Zhou with an AAnalyst 200 Atomic Absorption Spectrometer [PerkinElmer instruments, Ltd].



2.27 **2.28** **2.29**

Scheme 2.15

To prove that radicals do not cyclise onto esters and to verify iodoester **2.27** as a valid mechanistic probe for aryl anions, it was decided to react iodoester **2.27** with benzimidazole donor **1.175** which has been shown to produce aryl radical intermediates, but no anions.[94] Reaction of **2.27** with one equivalent of donor **1.175** did not give rise to any conversion, *i.e.* only starting material was recovered.[119] This can be rationalised as follows: due to the carbon side-chain *ortho* to the iodide leaving group as opposed to the electron-deficient NMs group [which fully reacts with one equivalent of donor],[94] less inductive activation takes place. This has the consequence that the LUMO energy will be higher for the carbon side-chain substrate **2.27** and therefore a greater reductive power is necessary to reduce this substrate [analogous to what has been observed in the reactions of benzimidazole donor **1.175** with aryl iodo *ortho*-ethers, compare chapter 2 and appendix]. Thus, it was decided to carry out the experiment under more concentrated conditions, *i.e.* four equivalents of salt **1.179** were used in an identical amount of solvent to the original experiment.



2.27 **2.27** **2.28**

Scheme 2.16

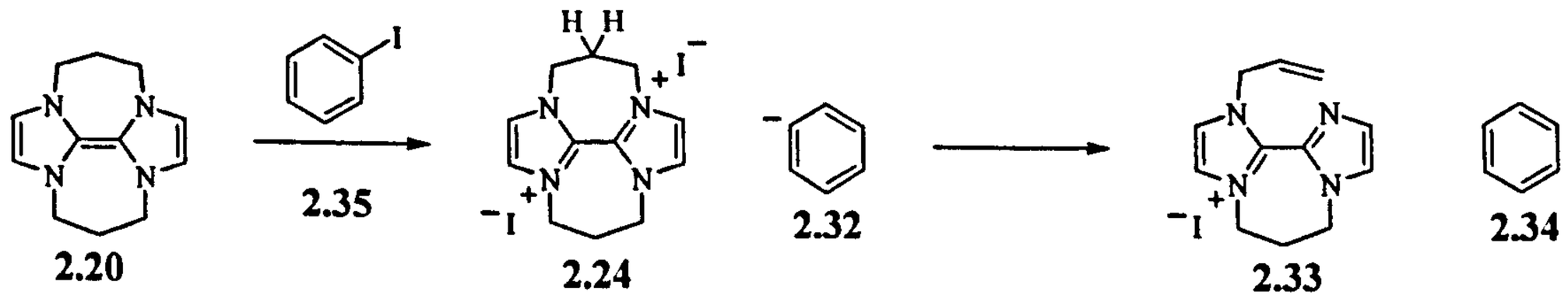
The change to more concentrated conditions led to full conversion of the starting material and the ketone **2.29** was not formed [as judged from ^{1}H-NMR spectroscopic analysis of the crude mixture]. Thus, the ester is a valid probe to test for aryl anions. However, after purification, the reduced compound **2.28** was isolated in 50 % yield only as the sole product. It was questioned whether this low yield might be due to the presence of traces of water, either in the salt starting material or in the DMF. If this was the case, sodium hydroxide would have formed in the 'dimerisation process' since an excess of sodium hydride had been used. The sodium hydroxide might then have hydrolysed the ester under the reaction conditions [DMF, 110°C, 18 h] and the acid formed might have been washed into the aqueous layer in work-up. Therefore, benzimidazole disalt **1.179** was freshly made by refluxing methylbenzimidazole with diiodopropane in acetonitrile for 2 d. After

filtration and various washings with dichloromethane, the salt was stored under vacuum for 20 h, then heated to 120°C under vacuum for 2 h prior to use and new sodium hydride was used as well as anhydrous DMF for the reaction. However, despite the careful drying of reagents, the isolated yield of the reduced ester **2.28** did not improve, and ester **2.28** was isolated in 51 % yield only. This suggests that side-reactions due to the excess of donor might have taken place that could be responsible for the low mass-balance. [Similar observations will be discussed later in this thesis (see section **3.2.2**) and possible explanations will be presented in more detail.] Decreasing the number of equivalents of donor to 2.5, reduced ester **2.28** was isolated pleasingly in 67 % yield.[120]

The significance of the 15 % yield of cyclised ketone **2.29** was next considered. Did this mean only 15 % of aryl anions were present and the reduced ester **2.28** might arise from aryl radical intermediates upon hydrogen atom abstraction? Or is there a much greater proportion of aryl anion **2.30** formed in the reaction, but the competing protonation of the aryl anion is just too rapid to allow more cyclisation? This raises further questions, *i.e.* (i) where would the proton be abstracted from and (ii) how can the real proportion of aryl anion intermediate be estimated?

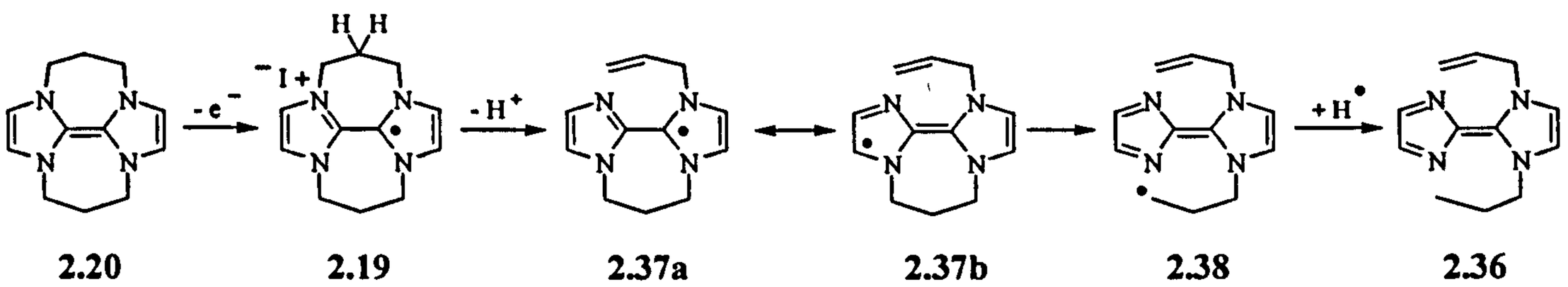
3.2.2 *What is the proton source?*

Considering the mechanism of electron transfer, it is likely that a sandwich π-complex[121] of donor and acceptor is formed in the transition state to ensure sufficient orbital overlap [HOMO of donor with LUMO of acceptor], so that the transfer of electron from the HOMO to the LUMO can take place. Upon single electron transfer, a donor radical-cation and acceptor radical-anion will be formed [or donor dication **2.24** and acceptor anion **2.32** in the case of double electron transfer] and these two charged species are likely to stay attached to each other due to the stabilising attraction of the opposite charges. The donor radical-cation [or donor dication] could then become a source of proton due to its positive charge and induced acidity (**Scheme 2.17**) and since it is closely associated with the acceptor anion in a sandwich-like complex the proton-abstraction should be a very favourable process.



Scheme 2.17

Evidence in support of this assumption was the isolation of the donor-derived species **2.36** (see below) that was detected in a reduction reaction of a sulfone, using 3 equivalents of donor **2.20**, formed *in situ* using the sodium hydride technique. Heat [110°C for 18 h] was applied in the reaction. [Reductions of sulfones will be discussed in chapter five in this thesis.] A possible mechanism for the formation of **2.36** is shown in **Scheme 2.18** below.



2.20 **2.19** **2.37a** **2.37b** **2.38** **2.36**

Scheme 2.18

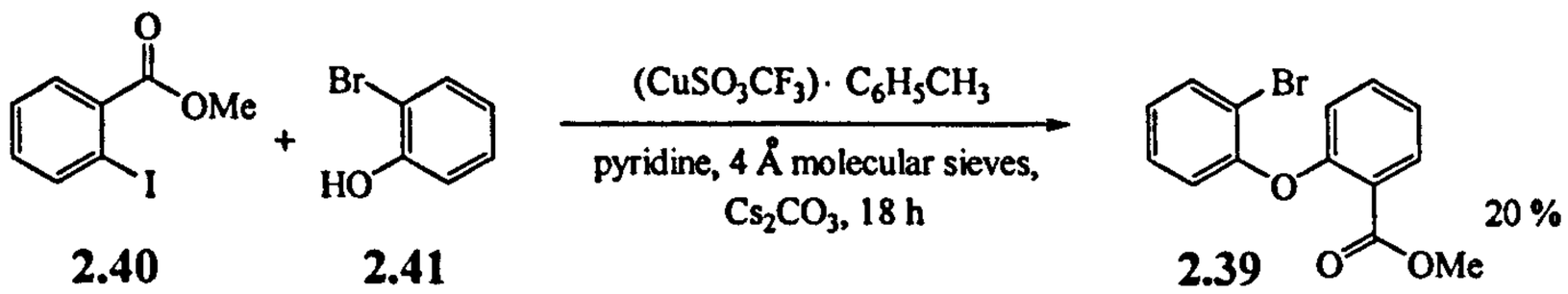
Upon single-electron donation, the radical-cation **2.19** was formed that then acted as a proton source to form **2.37** (or alternatively, two electrons were transferred from **2.20** and the corresponding dication was reduced by excess donor to the illustrated radical-cation species **2.19**). This radical species might have triggered C-C bond cleavage of the side-chain to give **2.38**, and after hydrogen atom abstraction, species **2.36** was generated.

Since the proton source is located so favourably close to the aryl anion in the proposed sandwich-like complex, it is obvious that it will be quite challenging to answer question (ii), *i.e.* to reveal the real aryl anion proportion in the reaction.

3.2.3 *Alternative ester substrate to reveal the anion proportion - bromo diaryl ether*

It was thought that a structural change in the cyclisation substrate towards a more rigid system might favour cyclisation a little more over the competing very fast proton-abstraction. Therefore, diaryl ether ester **2.39** was selected. The bromide was chosen to allow easier synthesis of the substrate. Synthesis of diaryl ether **2.39** was accomplished by Ullmann-type copper(I) coupling of iodobenzoate **2.40** and 2-bromophenol **2.41**. Due to the inductive activation of the methyl ester *ortho* to the iodide, the Cu(I) species should preferentially insert into the C-I bond. There is literature precedent[122] for the greater reactivity difference of the C-I over the C-Br bond insertions by Cu(I). Due to this kinetic preference, the bromoester **2.39** was chosen for preparation. Molecular sieves were utilised to mop up water in the reaction, since this could cause hydrolysis of the ester to the acid. Ester **2.39** was synthesised successfully in 20 % yield, which is in accord with the literature, given the highly disfavouring effect of *ortho*-substituents on the coupling reaction.[123] In

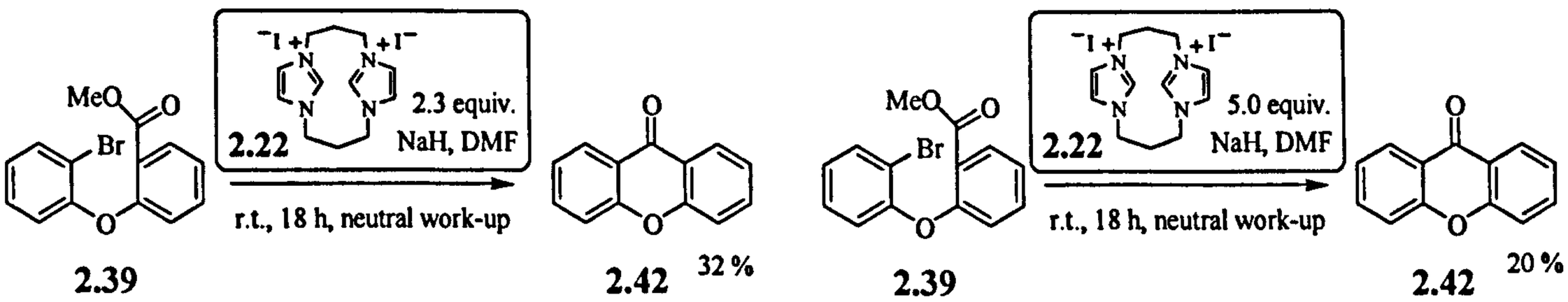
this reaction, two hindering *ortho*-substituents were present, so that the overall yield is quite pleasing.



2.40 **2.41** **2.39**

Scheme 2.19

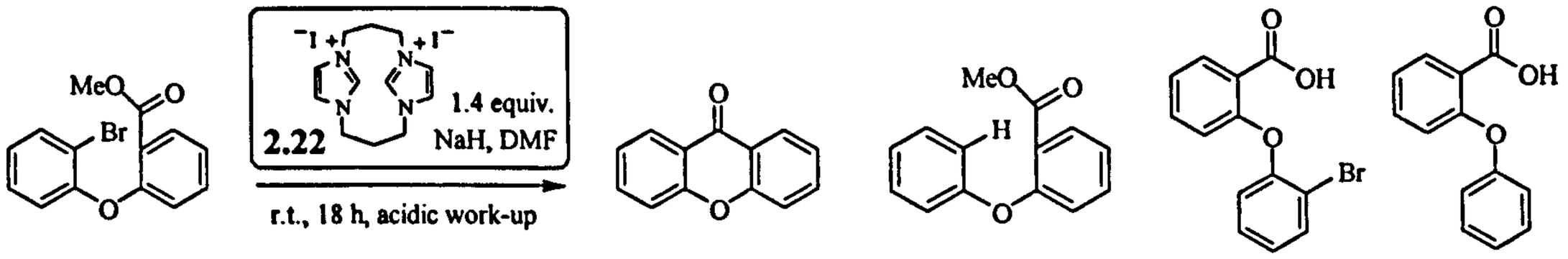
In ester **2.39** the two phenyl rings should give rise to a conformationally restrained system, generating the anion in close proximity to the ester and hence possibly favouring the cyclisation. The initial test experiment was carried out as follows: 2.5 equiv. of salt **2.22** were dissolved in anhydrous and deoxygenated DMF and transferred onto washed sodium hydride. This was then stirred at room temperature for 4 h and centrifuged. The resulting supernatant liquid was added to bromoester **2.39** and the mixture was stirred overnight at room temperature, resulting in a colour change from yellow to red. After neutral work-up, a ^{1}H-NMR spectrum of the crude mixture was taken and xanthone **2.42** was seen as the sole product. Column chromatography on silica gel was then carried out and xanthone **2.39** was isolated in 32 % yield. This proves the assumption of more favoured cyclisation of the anion over protonation in this rigid system to be true. Intriguingly, in a repetition experiment using 5 equivalents of donor **2.20**, the mass balance decreased and xanthone **2.42** was now isolated in 20 % yield (**Scheme 2.20**).



Scheme 2.20

That multiple equivalents of donor **2.20** have a lowering effect on the mass-balance has been observed before (see previous discussion, page 58). However, the very low mass balance of only 32 % in the first experiment led to questions. This low mass balance might be ascribable to the presence of hydroxide in the reaction mixture that would form in the donor formation process by deprotonation of water by NaH, leading to the formation of carboxylic acid that might have been lost into the aqueous layer in work-up. Evidence for the presence of hydroxide was the formation of phenol derivative **2.26** in the reaction presented in **Scheme 2.12**, page 55. Thus, the experiment was repeated with fewer

equivalents of **2.22** (for a better mass balance) and this time an acidic work-up was carried out (**Scheme 2.21**).

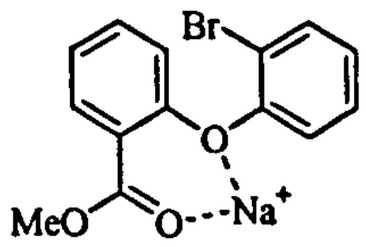


2.39 **2.42** **2.43** **2.44** **2.45**

Scheme 2.21

Two fractions were isolated after column chromatography this time, the first less polar, containing xanthone **2.42** and, for the first time, the reduced compound **2.43** was also detected (ratio 1:1). The second, more polar fraction contained two compounds, bromocarboxylic acid **2.44** and reduced carboxylic acid **2.45** (in ratio 1:2). [2-Phenoxybenzoic acid **2.45** was identified by comparison of the ^{1}H-NMR spectrum with that of the commercial material and bromocarboxylic acid **2.44** was identified by comparison of the ^{1}H-NMR spectrum with that of the synthesised compound, see experimental section for further details].

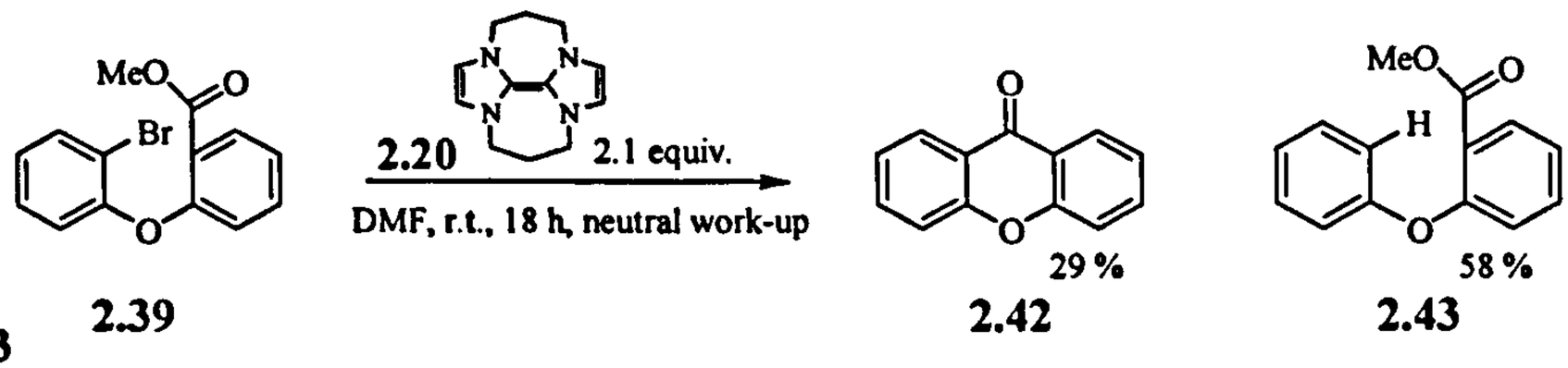
The reduced ester **2.43** was formed, but surprisingly was detected only if acidification was carried out. This suggests that the reduced compound **2.43** must somehow have been liberated upon acidification. This intriguing observation would not be expected to be due to the presence of hydroxide in the reaction mixture. It was thought, therefore, that the presence of metal ions, *i.e.* sodium iodide, might have caused this reaction outcome. Metal chelation *via* a favourable 6-membered structure (**Scheme 2.22**) might have activated the ester functionality in **2.39** towards attack by a nucleophile, *i.e.* hydroxide or possibly donor **2.20** acting as a nucleophile, the former leading to carboxylic acid. However, it seems unlikely that the metal-complexed reduced ester might be water-soluble [to explain why it is lost in neutral work-up].



Scheme 2.22

To test for this further, it was investigated how donor **2.20**, free of metal salts, would react with bromoester **2.39** in the absence of any metals or hydroxide. Thus, bromoester **2.39** was reacted with 2.1 equivalents of pure donor **2.20** in the glove-box. Upon addition of the solution of ester **2.39** in DMF to the pure donor solid, the yellow colour changed instantaneously to bright red-orange. After stirring at room temperature overnight, a

neutral work-up was carried out and xanthone **2.42** was isolated in 29 % yield as well as the reduced ester **2.43** in 58 % yield. This time the reduced compound **2.43** was detected, despite the absence of acid treatment.



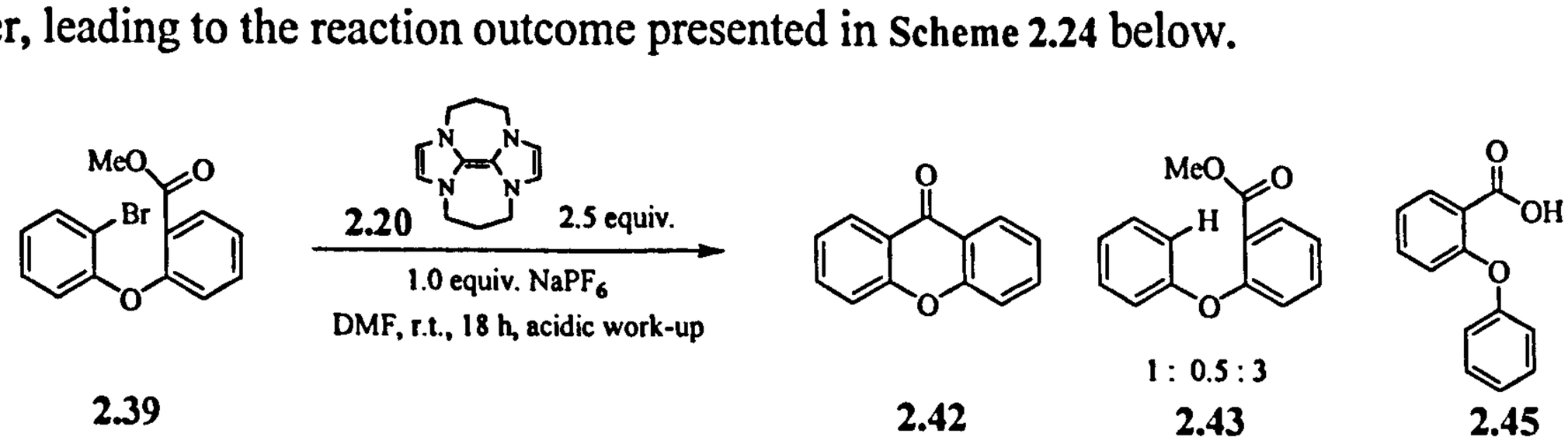
2.39 **2.42** **2.43**

Scheme 2.23

In another experiment, 2.5 equivalents of pure donor **2.20** were reacted with ester **2.39** in the glove-box and this time acidic work-up was carried out. No acid was detected. Only xanthone **2.42** and reduced ester **2.43** were seen in the ^{1}H-NMR spectrum of the crude mixture.

This time, under metal-free conditions, the reduced ester **2.43** was isolated after neutral work-up. Addition of acid was not necessary to liberate it. In the next experiment it was investigated therefore whether metal chelation might indeed play a role in this behaviour.

Thus, pure donor **2.20** was reacted in the presence of an added metal salt. One equivalent of sodium hexafluorophosphate (to avoid possibly nucleophilic iodide counterions) was added to the reaction of the pure donor **2.20** with ester **2.39**. The sodium hexafluorophosphate was heated at 150°C under vacuum for 5 h prior to use, then dissolved in 5 ml DMF. The substrate **2.39** was dissolved in 10 ml DMF and transferred *via* cannula to the sodium salt solution under argon. The resulting solution was transferred into the glove-box and added to the pure donor solid. A red-orange colour was observed. After stirring overnight at room temperature, a TLC was taken to monitor the reaction. For this a little amount of the reaction mixture was diluted with water (neutral!) and extracted with ether. Only a single spot was seen [with the identical R_f value to that of xanthone **2.42**]. Then, acidic work-up was carried out and two more spots appeared on TLC of the organic layer, leading to the reaction outcome presented in **Scheme 2.24** below.



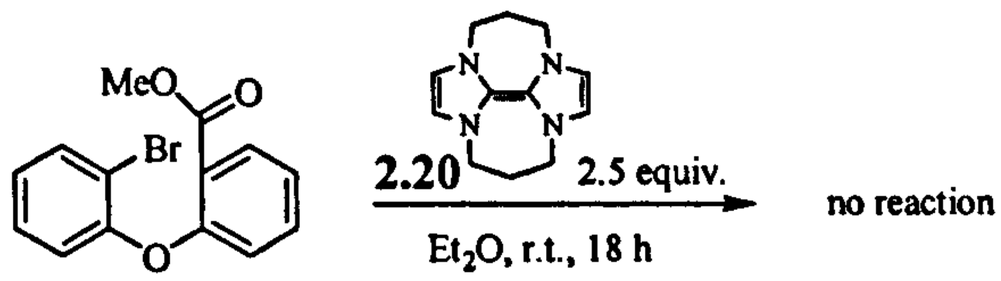
2.39 **2.42** **2.43** **2.45**

Scheme 2.24

Interestingly, in the presence of sodium cations the identical reaction outcome was observed as in the reactions in which the donor **2.20** was generated *in situ* with sodium

hydride (compare **Scheme 2.21**). In the presence of metal ions, the reduced ester **2.43** is not liberated into the organic layer until acidification, and the acid **2.45** is formed also. The presence of hydroxide is less likely in this reaction, however, water might be present, if the drying of the metal salt was not sufficient. Why the reduced ester **2.43** is liberated only upon acid treatment remains a mystery.

It was also questioned whether the solvent might have an effect on the cyclisation efficiency. When diethyl ether was used as the solvent with the pure donor **2.20** and ester **2.39** were reacted in the glove-box at room temperature for 18 h, only starting material **2.39** was recovered. Presumably electron transfer is disfavoured in a less polar solvent since the transition state (charged) and products (charged) are unstabilised. This finding was confirmed in other experiments also [in reaction of the donor **2.20** with alkyl halides; this will be presented in chapter 4].



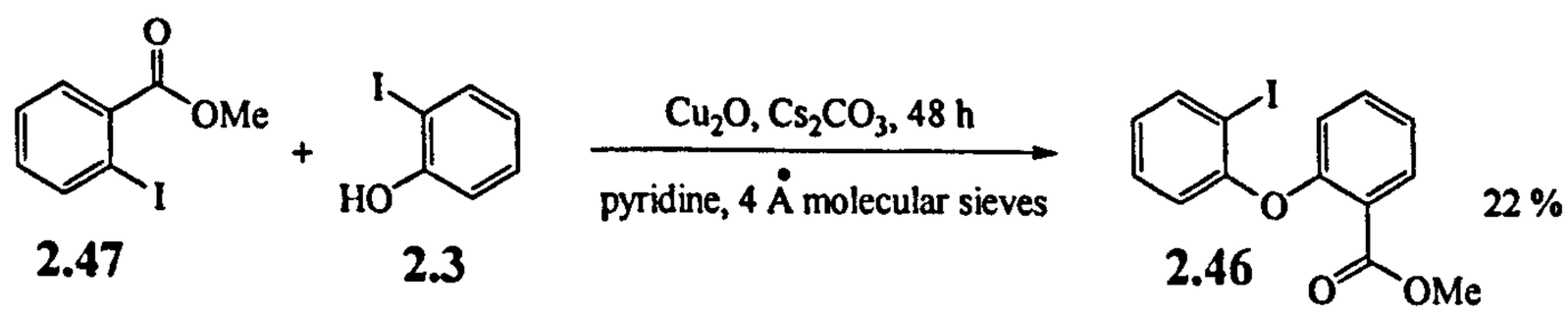
2.39

Scheme 2.25

It was then of interest to discover how benzimidazole donor **1.175** would behave in the reaction with ester **2.39**. However, aryl bromides do not react efficiently with benzimidazole donor (see previous chapter). Therefore, it was decided to prepare the iodide analogue to bromoester **2.39**.

3.2.4 *Investigations with iodo diaryl ether ester analogue*

Iodoester **2.46** was prepared by Ullmann-Cu(I) coupling also, using a different Cu(I) source, but both copper species are possible, since they differ only slightly in reactivity.[123] Due to the even bulkier *ortho*-substituent (iodine *vs.* bromine) and the extensive purification (various washings and extraction, column chromatography, followed by Kugelrohr distillation) it is not surprising that the yield of the reaction was not very high either. However, iodoester **2.46** was satisfyingly made in 22 % yield.

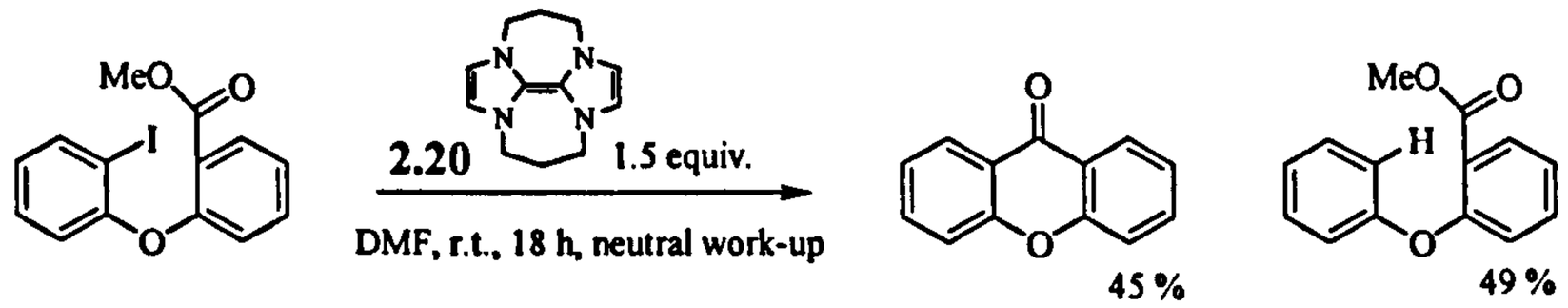


2.47 **2.3** **2.46**

Scheme 2.26

Having substrate **2.46** in hand, it was decided to test it in a reaction with the pure donor **2.20**. For the initial cyclisation substrate, ester **2.27**, no difference in reaction outcome was observed, whether the iodide or the corresponding bromide ester was used in the reaction.[116]

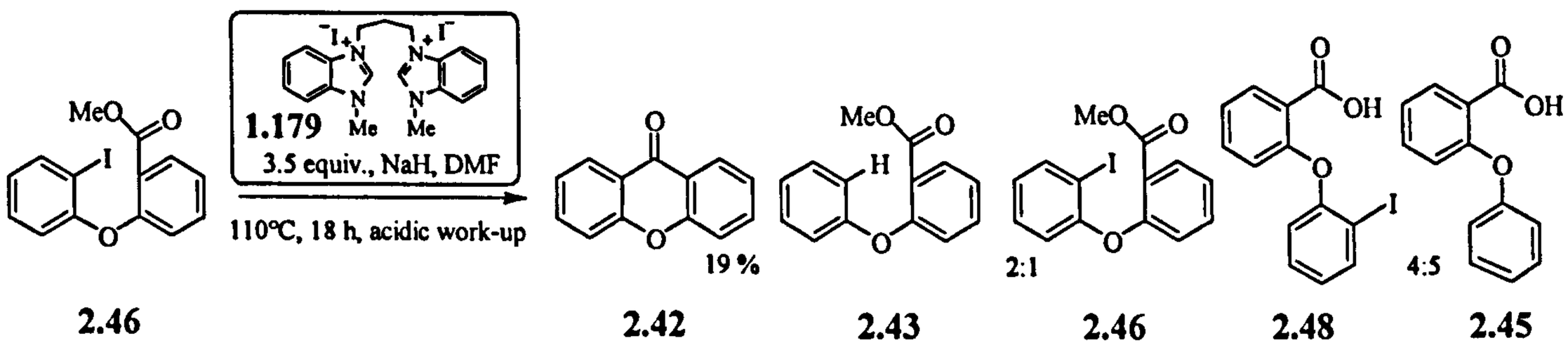
However, this was not seen for iodoester **2.46**. Here the cyclisation was considerably enhanced in comparison to the reaction with bromoester **2.39** (compare **Scheme 2.23**). An increase from 29 % cyclisation to 45 % was observed. This may be due to smaller reorganization energies and activation barriers associated with the electron transfer to the aryl iodide, giving rise to less anion formation in the bromide case (more detailed discussion on the theoretical aspects of anion formation will follow in section **3.2.9**).



2.46 **2.42** **2.43**

Scheme 2.27

The reaction of iodoester **2.46** with benzimidazole donor **1.175** was next assayed to verify also in this case that radical intermediates do not cyclise onto the ester. Thus, xanthone **2.42** was not expected as a product. To achieve conversion of the iodoester to the aryl radical, high temperature and multiple equivalents of donor **1.175** are necessary. It was decided to use 3.5 equivalents of donor **1.175**, that was prepared by the NaH method *in situ* and the yellow donor solution was then reacted with ester **2.46** at 110°C for 18 h (**Scheme 2.28**).



2.46 **2.42** **2.43** **2.46** **2.48** **2.45**

Scheme 2.28

Unexpectedly, cyclisation took place to give xanthone **2.42** in 19 % yield. Further, the reduced ester **2.43** was isolated in an inseparable mixture with starting material **2.46** (ratio 2:1 in ^{1}H-NMR spectrum, 31 mg) and both iodocarboxylic acid **2.48** and reduced acid **2.45** were isolated in an inseparable mixture (5:4 ratio) [the presence of the iodoacid **2.48** was verified by synthesis of the compound, *i.e.* by separate reaction of **2.46** with NaOH in DMF and heating overnight, see experimental section for further details. The reduced acid **2.45** was authenticated by comparison with commercially available material].

That both acids had formed was not surprising, since hydroxide is likely to be present in the reaction mixture. Metal ions were present also that seemingly activate the ester moiety towards attack by a nucleophile as seen previously (compare with **Scheme 2.24**). It was questioned, however, how xanthone was formed. The reduction potential* of iodoester **2.46** was estimated to be E_p= -2.13 V (*vs.* Ag/AgCl in DMF)[130] and thus is almost identical to that of carbon ester **2.27** (E_p = -2.10 V *vs.* Ag/AgCl in DMF);[130] the transfer of the first electron to iodoester **2.46** should therefore be similarly difficult. However, it is currently unknown by which mechanism aryl anions form in the reaction with imidazole donor **2.20**. Aryl anions could form directly *via* a concerted or successive two electron transfer from the donor to the aryl halide without the formation of an aryl radical intermediate. Alternatively, the aryl anion could be formed by further reduction of a 'real' aryl radical intermediate. Iodoallyl ether substrates (as discussed in chapter 2) give rise, if at all, to the simple cyclised compound arising from radical intermediates [if anion intermediates were present no such cyclisation would be expected]. However, the situation might be different for iodoester **2.46**, since the derived aryl radical would have a longer life-time to be reduced further (since the fast radical cyclisation is not an option). Nevertheless, reaction of benzimidazole donor **1.175** with carbon ester **2.27** did not lead to the formation of a ketone, and the lifetime of a possible aryl radical intermediate should be similar in that case. Also, the aryl radical intermediate, derived from ester **2.46**, would not expected to be able to cyclise onto the ester, since the activation barrier for a radical to cyclise onto a carbonyl moiety is, due to the strong C=O π-bond, relatively high and therefore rather disfavoured.

3.2.5 *Can an aryl radical cyclise onto an ester?*

Not many studies have been carried out investigating the cyclisation of aryl radicals onto esters and the available literature is limited. However, with rate studies that were done by Beckwith and Hay,[124] it became clear that the cyclisation of *alkyl* radicals (*e.g.* **2.49, Scheme 2.29**) onto carbonyl moieties is challenging due to the reversibility of the formed oxyl radical **2.50** (back reaction is faster than cyclisation). If the cyclisation is made irreversible,[125] however, *e.g.* by rapid trapping of the intermediate oxyl radical **2.50** by titanium salts[126] or rapid loss of a very good radical leaving group *alpha* to the carbonyl as in **2.53**,[125] then cyclisation is possible (see **Scheme 2.29**).

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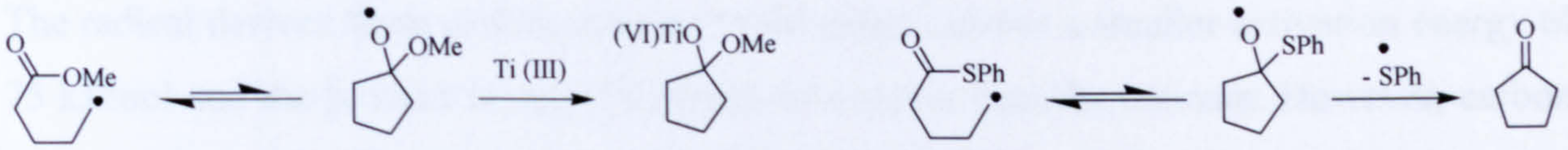
* The reduction potentials were obtained by cyclic voltammetry, explaining to the large differences compared to the potentials that were estimated by polarography and discussed previously.



2.49 **2.50** **2.51** **2.52** **2.53** **2.54**

Scheme 2.29

However, the cyclisation of ***aryl*** radicals on esters has not been studied or discussed in the literature. A *semi-empirical*, AM1 gas-phase modelling approach using S*PARTAN* to study radical cyclisations onto esters was therefore next assayed (**Figure 2.5**). Three cases were considered, the cyclisation of the alkyl radical **2.49** and the cyclisations of the aryl radicals derived from carbon ester **2.27** and diaryl ether **2.46** were investigated. The activation energies for the cyclisations were obtained by stretching of the C-C bond in the product as indicated (**Figure 2.5**, below), leading to the transition state at the top of the graph, reactant at the right-hand side and product at the left-hand side of the graph.

The alkyl radical **2.49** needs to overcome an activation barrier of 99.3 kJ/mol to cyclise (green graph); and the calculation showed that the reverse process is indeed more favourable, since the product radical (- 278.18 kJ/mol) is by far less stable than the starting radical (- 338.96 kJ/mol).

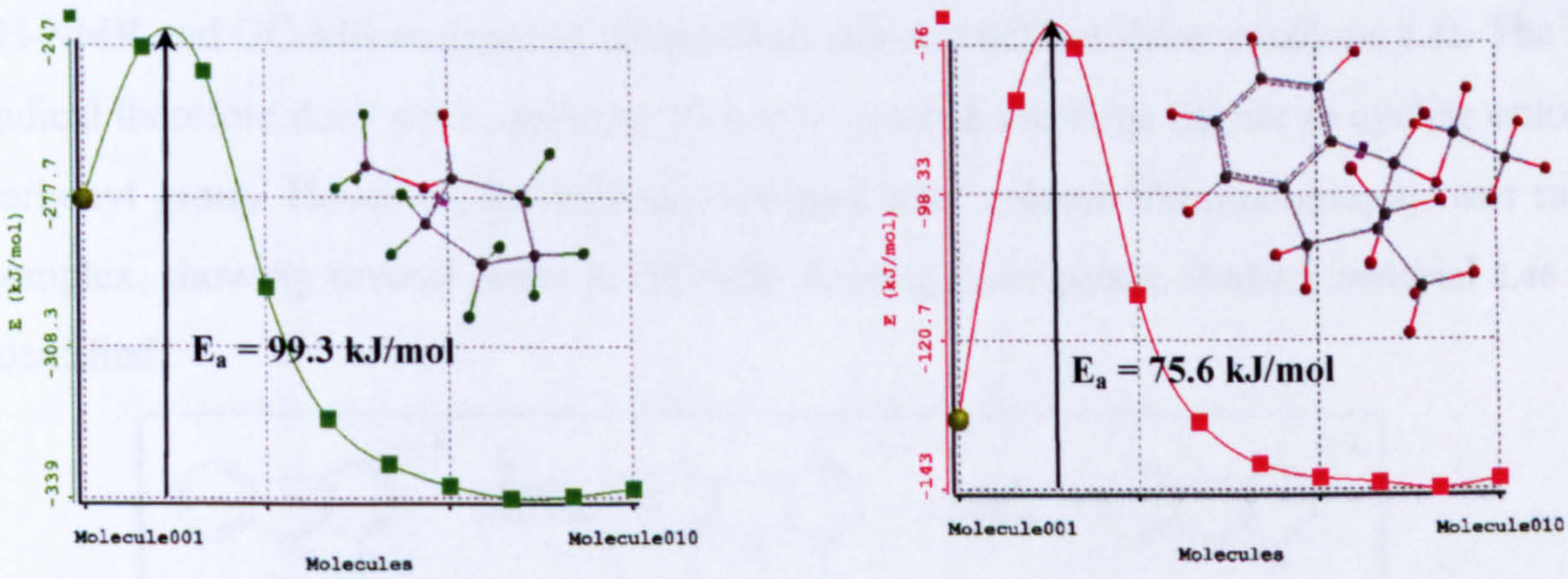
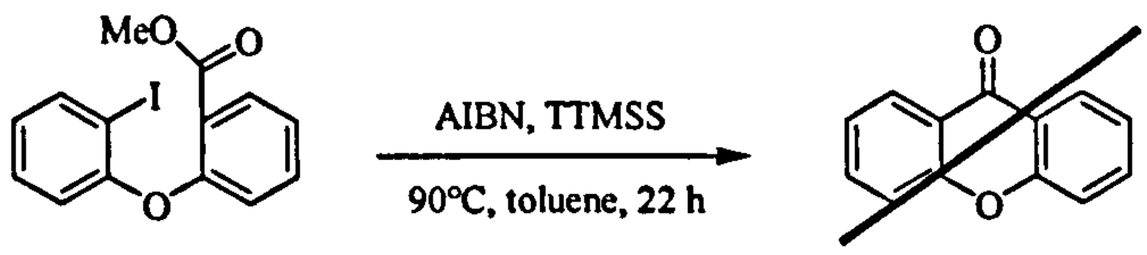


Figure 2.5 **Cyclisation path for radicals 2.49a (green), 2.27* (red) and 2.46* (blue)**

The radical derived from carbon ester **2.27** (red graph) shows a smaller activation energy of 75 kJ/mol and the product is only 10 kJ/mol less stable than the reactant. However, carbon ester **2.27** did not cyclise when it was reacted with benzimidazole donor **1.175**. This suggests that the competing H-atom abstraction and quenching of the aryl radical is more favourable than 75 kJ/mol and undergone more rapidly.

The radical derived from diaryl ether **2.46** (blue graph) showed an even smaller activation energy (49.9 kJ/mol) and the product radical was now more stable than the reactant **2.46*** (by 21 kJ/mol). This might suggest that cyclisation of the aryl radical might indeed be a favoured process for diaryl ether ester **2.46**.

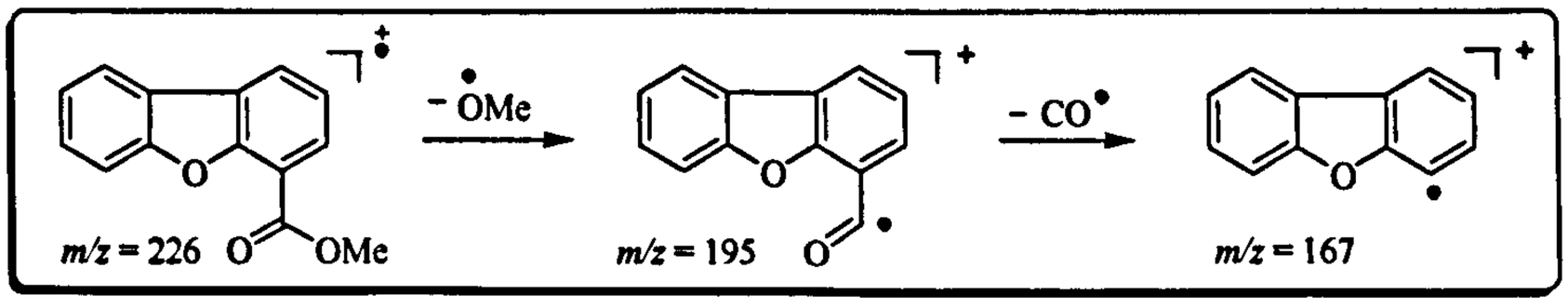
To test whether this thermodynamic preference for radical cylisation does indeed allow the aryl radical to cyclise in the case of diaryl ether **2.46**, standard radical chemistry using AIBN and TTMSS was employed (**Scheme 2.30**).



2.46 **2.42**

Scheme 2.30

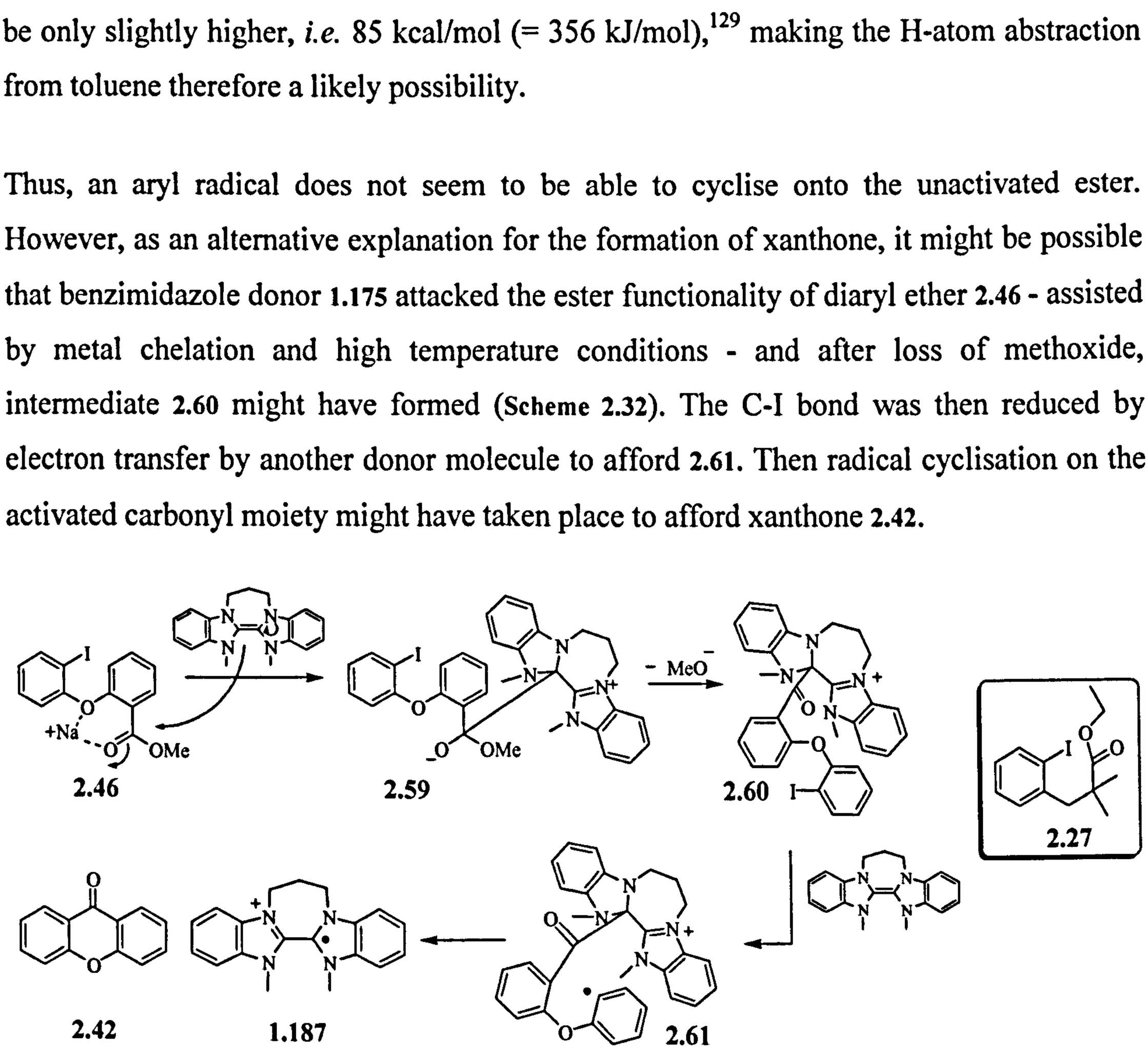
^{1}H-NMR and GC-MS analyses of the purified mixture did not show xanthone **2.42**. The aryl radical therefore does not seem to be able to overcome the large barrier to cyclise onto the carbonyl group. However, the mixture obtained after column chromatography was rather complex, showing several peaks in GC-MS. Among these peaks, starting material **2.46** was identified.



Scheme 2.31

Reduced ester **2.43** was seen, as well as a peak corresponding to a mass of the molecular ion of 226. The fragmentation of the latter peak suggests a loss of OMe-radical first, followed by a loss of a CO-radical, which would match with the structure **2.55**[127] in **Scheme 2.31.** This compound shows that cyclisation of the aryl radical onto the aromatic ring is more favourable than cyclisation onto the ester functionality. A higher molecular mass peak at 318 was seen also, which could correspond to the addition of a benzyl radical onto the reduced ester **2.43**, however, the fragmentation does not support this straightforward solution too strongly and is rather complex (see experimental chapter for further details).
If the structure corresponding to the molecular ion peak of 318 is indeed the benzyl radical adduct **2.57**, then this would explain why starting material **2.46** was not consumed completely in the reaction. Preferential H-atom abstraction from toluene rather than TTMSS might have taken place, which stopped the radical chain. The Si-H bond strength in TTMSS[128] is 79 kcal/mol (= 331 kJ/mol) and the $PhCH_2$-H bond strength was found to be only slightly higher, *i.e.* 85 kcal/mol (= 356 kJ/mol),[129] making the H-atom abstraction from toluene therefore a likely possibility.

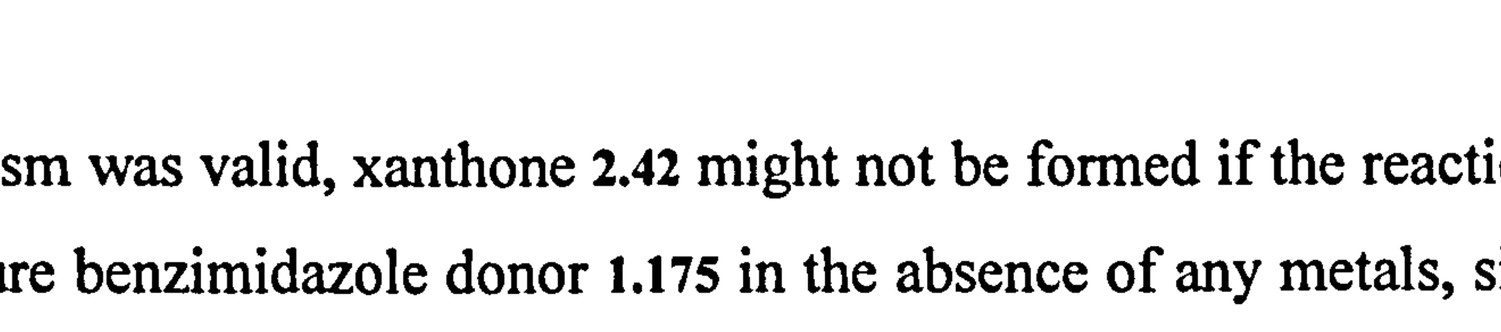
Thus, an aryl radical does not seem to be able to cyclise onto the unactivated ester. However, as an alternative explanation for the formation of xanthone, it might be possible that benzimidazole donor **1.175** attacked the ester functionality of diaryl ether **2.46** - assisted by metal chelation and high temperature conditions - and after loss of methoxide, intermediate **2.60** might have formed (**Scheme 2.32**). The C-I bond was then reduced by electron transfer by another donor molecule to afford **2.61.** Then radical cyclisation on the activated carbonyl moiety might have taken place to afford xanthone **2.42.**



Scheme 2.32

In this mechanism two crucial factors play a role: an inductively activated and therefore more reactive carbonyl group moiety is present that should pose a lower activation barrier for a radical cyclisation. Further, the radical cation **1.187** features an excellent radical leaving group, making the cyclisation irreversible. Carbon side-chain ester **2.27** (see **Scheme 2.32**), in contrast, perhaps cannot undergo such 'favourable' and 'activating' chelation with metal salts and also the ester functionality is not activated by an electron withdrawing heteroatom, such as oxygen, and therefore nucleophilic attack by the donor species **1.175** onto the ester functionality might be disfavoured, hence cyclisation is not seen for that substrate.

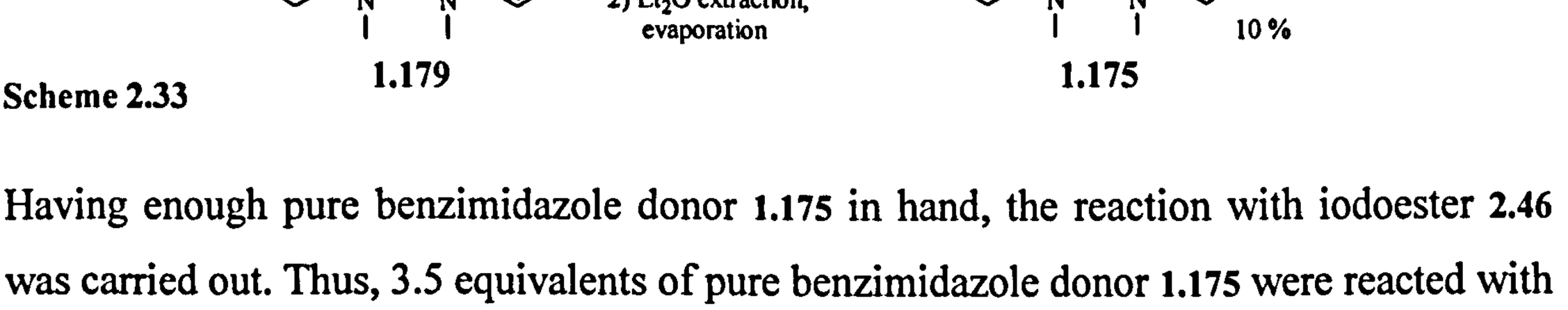
If this mechanism was valid, xanthone **2.42** might not be formed if the reaction was carried out with the pure benzimidazole donor **1.175** in the absence of any metals, since activation towards nucleophilic attack by metal ions could not take place. Thus, pure benzimidazole donor **1.175** was prepared according to the previously described method, *i.e.* by dissolving the precursor salt **1.179** in liquid ammonia and reacting it with NaH. After evaporation of ammonia, the residue was transferred into a glove-box and there repeatedly extracted with diethyl ether. Due to the low solubility of benzimidazole donor **1.175** in diethyl ether, only 10 % yield of pure donor **1.175** was obtained (after 15 extractions and evaporation of the solvent).



1.179 **1.175**

Scheme 2.33

Having enough pure benzimidazole donor **1.175** in hand, the reaction with iodoester **2.46** was carried out. Thus, 3.5 equivalents of pure benzimidazole donor **1.175** were reacted with iodoester **2.46** in DMF at 110°C for 18 h. Colour change to dark red occurred as usual and after acidic work-up and further purification by column chromatography, xanthone **2.42** was again isolated, this time in an even greater amount, *i.e.* in 27 % yield. The reduced ester **2.43** was again isolated in an inseparable mixture with starting material **2.46** (4:1 ratio) and both acids, **2.48** and **2.45**, were formed also (1:1 mixture).



2.46 **2.42** **2.43** **2.46** **2.48** **2.45**

Scheme 2.34

Although the reaction was carried out under 'metal-free' conditions, xanthone **2.42** as well as both acids had formed. This may be due to the heat that was applied in the reaction, since this is a difference to the pure imidazole donor [**2.20**] reaction, possibly giving the extra energy to allow nucleophilic attack by the donor onto the ester functionality also under unactivated, 'metal-free' conditions and therefore the mechanism in **Scheme 2.32** above might still be undergone. Alternatively, since multiple ether extractions were applied to obtain benzimidazole donor **1.175** (15 extractions as opposed to 1-2 for imidazole donor **2.20**) the proportion of NaI might be far greater now, so that the conditions are not as 'metal-free' as assumed.

3.2.6 *Biradical coupling – a possible reaction path?*

When LUMO density calculations were carried out on iodoester **2.46**, it was found that the highest LUMO density [indicated in blue] is located on the bold π-system (**Figure 2.6** and **Scheme 2.35**), suggesting that the electron is transferred there with greatest probability.

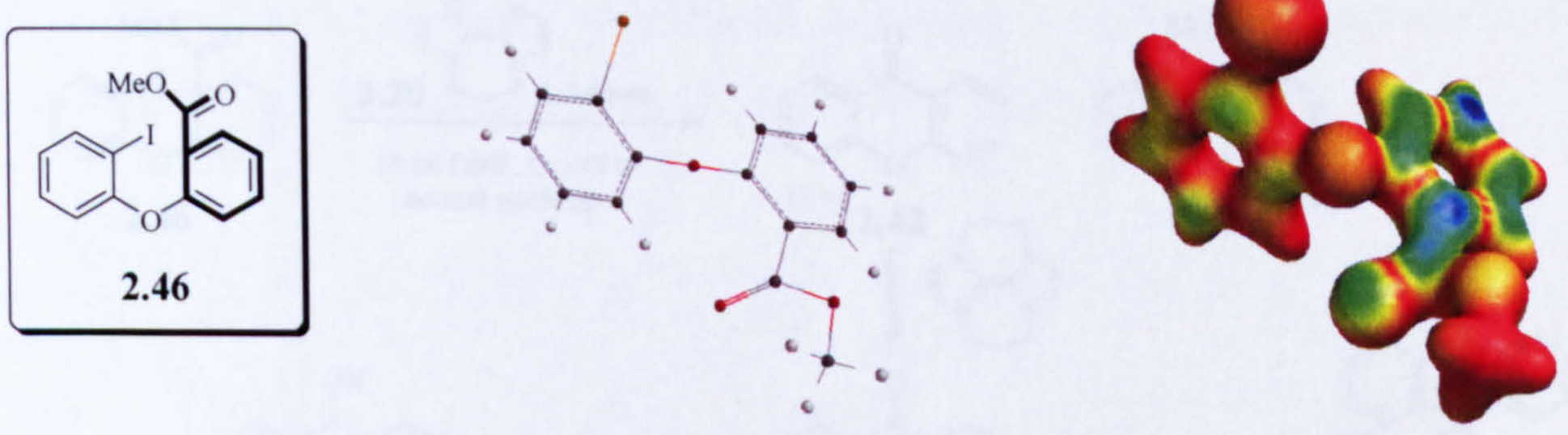
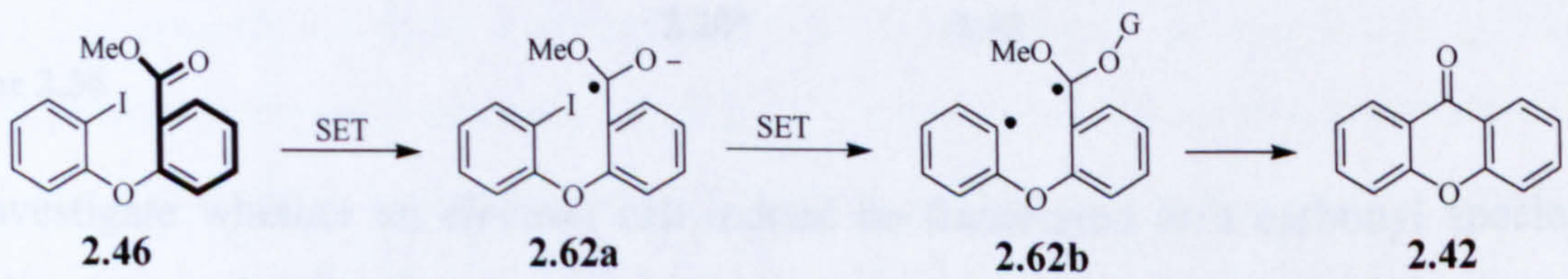


Figure 2.6 **Structure and LUMO density of diaryl ether 2.46**

A further mechanistic possibility may hence be that a ketyl anion intermediate **2.62a** was formed initially and then biradical cyclisation took place after reduction of the carbon-iodine bond (**Scheme 2.35**).

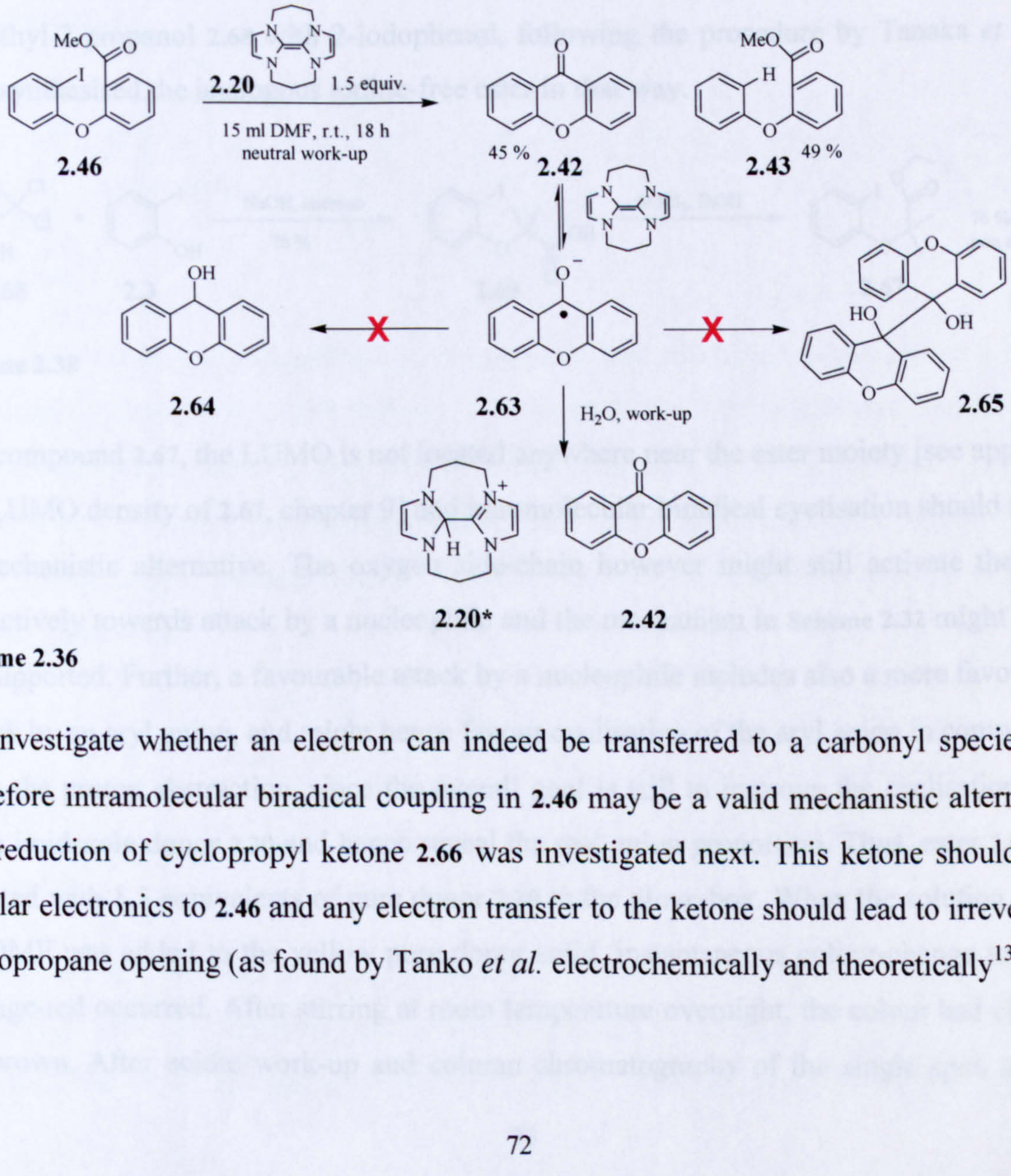


2.46 **2.62a** **2.62b** **2.42**

Scheme 2.35

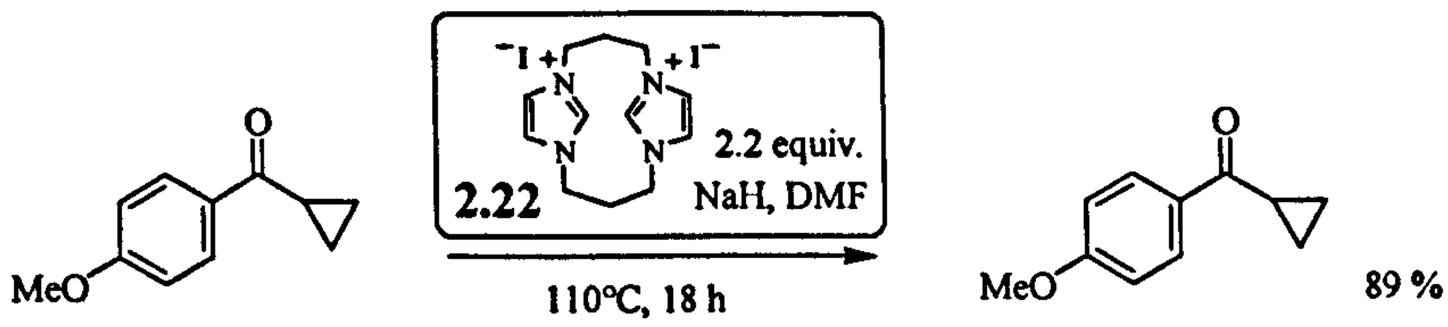
Indicated by G, a stabilising component, either a metal cation or, in the metal-free reaction, the donor radical-cation, may assist the intramolecular biradical coupling by decreasing the negative charge density on the oxygen in **2.62b**.

However, from the previously discussed experiments, it is evident that the ketone formed in the experiment is not reduced further to the alcohol, nor is ketyl radical coupling undergone (**Scheme 2.36** below). Even greater donor equivalents led to a decrease in mass balance only, but not to the detection of a species arising from carbonyl reduction. Electrochemical measurement of the reduction potential, in contrast, suggests that ketone **2.42**, with a reduction potential of $E_{1/2}$ = - 1.6 V, is reduced slightly more readily than the starting iodide **2.46** (whose reduction potential is around 0.5 V more negative).[130] However, this non-reduction of the ketone might simply be a phenomenon of reversibility. Considering ketyl anion intermediate **2.63**, its conjugate acid has a pK_a[131] of 10.5. The donor however is likely to be more basic. Therefore the donor species might always be protonated preferentially to **2.20***, which could drive the equilibrium back to the starting ketone **2.42** upon work-up (**Scheme 2.36**). Irreversible intermolecular pinacol coupling to **2.65** might be disfavoured here, due to the absence of metals or steric bulk of the donor radical cation, if that is acting as the stabilising component.



Scheme 2.36

To investigate whether an electron can indeed be transferred to a carbonyl species and therefore intramolecular biradical coupling in **2.46** may be a valid mechanistic alternative, the reduction of cyclopropyl ketone **2.66** was investigated next. This ketone should have similar electronics to **2.46** and any electron transfer to the ketone should lead to irreversible cyclopropane opening (as found by Tanko *et al.* electrochemically and theoretically[132]).

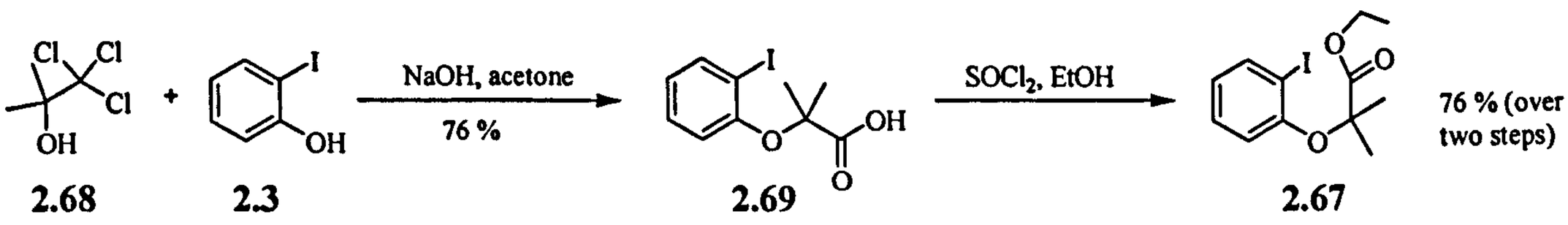


Scheme 2.37

Cyclopropane opening was not observed, however, neither at room temperature nor when heat was applied, despite the observation of colour change from yellow to deep red. This suggests that electron transfer to form a ketyl anion intermediate, despite the seemingly feasible reduction potential of E_p = -2.24 V (*vs.* Ag/AgCl in DMF),[149] might not be possible to aryl carbonyl compounds. [For cyclic voltammogram and LUMO of **2.66**, see appendix, chapter 9.]

3.2.7 *Studies with iodoaryl ether ester* 2.67

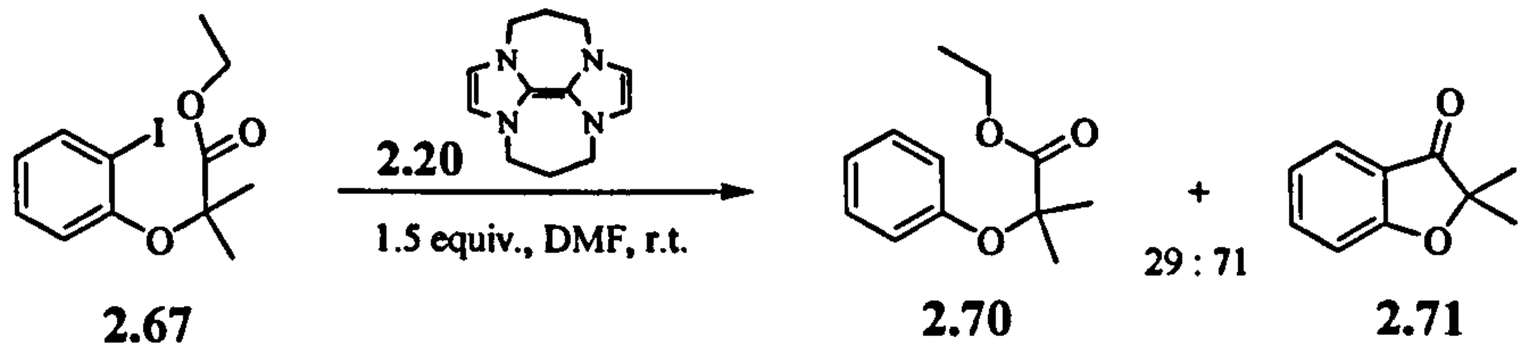
Due to the various mechanistic possibilities of the diaryl ether ester reaction, it was decided to synthesise substrate **2.67**. This was accomplished by reaction of 1,1,1-trichloro-2-methyl-2-propanol **2.68** with 2-iodophenol, following the procedure by Tanaka *et al.*[133] who synthesised the analogous iodine-free ester in that way.



Scheme 2.38

For compound **2.67**, the LUMO is not located anywhere near the ester moiety [see appendix for LUMO density of **2.67**, chapter 9] and intramolecular biradical cyclisation should not be a mechanistic alternative. The oxygen side-chain however might still activate the ester inductively towards attack by a nucleophile and the mechanism in **Scheme 2.32** might hence be supported. Further, a favourable attack by a nucleophile includes also a more favourable attack by an aryl anion, and might hence favour cyclisation of the aryl anion in competition with the proton abstraction, since the overall goal is still to improve the cyclisation yield with imidazole donor **2.20** and hence reveal the real anion proportion. Thus, ester **2.67** was reacted with 1.5 equivalents of pure donor **2.20** in the glove-box. When the solution of **2.67** in DMF was added to the yellow pure donor solid, instantaneous colour-change to bright orange-red occurred. After stirring at room temperature overnight, the colour had changed to brown. After acidic work-up and column chromatography of the single spot, a 29:71

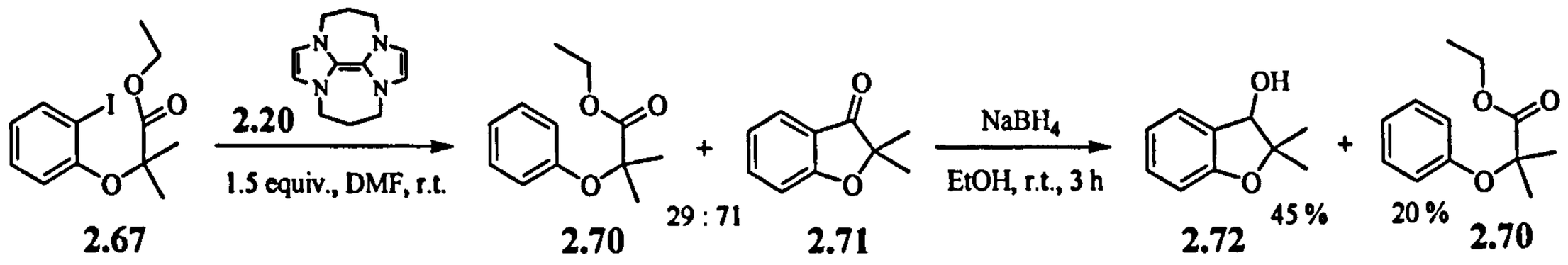
mixture of reduced ester **2.70** and ketone **2.71** was observed by ^{1}H-NMR spectroscopic analysis (**Scheme 2.39**).



2.67 **2.70** **2.71**

Scheme 2.39

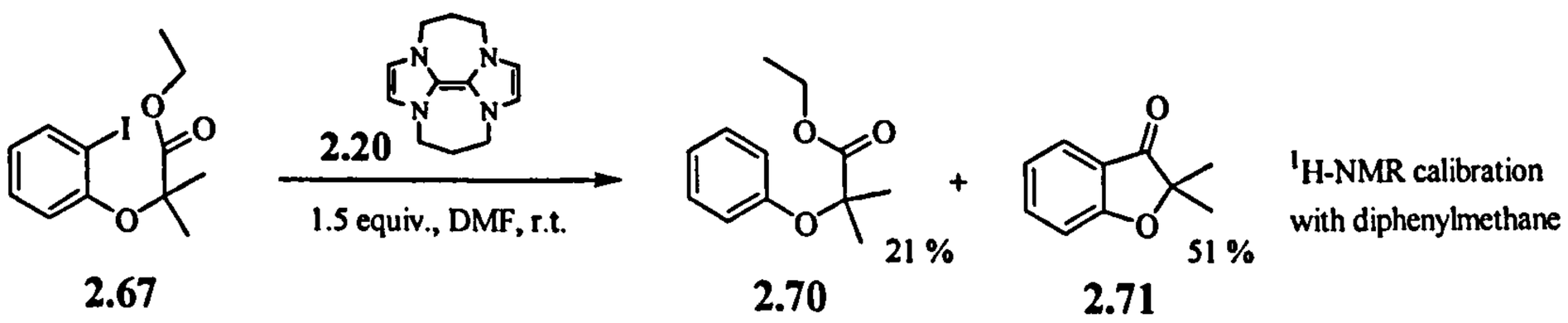
The ketone **2.71** now seemed to be the major product, which suggests that there was really quite a high percentage of anion intermediates in the reaction. In order to get a quantitative estimate, it was decided to reduce the ketone selectively with sodium borohydride in ethanol, in order to make a separation and characterisation of both compounds possible. Thus, the reaction was repeated and after work-up, the crude mixture was dissolved in ethanol and sodium borohydride was added. This led to 45 % of benzyl alcohol **2.72** and 20 % of reduced ester **2.70** (**Scheme 2.40**). The overall mass balance was a little low and it was presumed that this might be due to the relatively high boiling point of ethanol leading to loss of material.



2.67 **2.70** **2.71** **2.72** **2.70**

Scheme 2.40

Thus, the purified and isolated benzyl alcohol **2.72** was reoxidised to the ketone **2.71** and subsequently characterised. The reaction of **2.67** with the pure donor **2.20** was then repeated, purified by acidic work-up and column chromatography and a calibration ^{1}H-NMR-experiment was carried out [diphenylmethane was added as the calibration standard]. The ^{1}H-NMR-calibration indicated that 51 % of ketone and 21 % of reduced ester had been formed (**Scheme 2.41**).

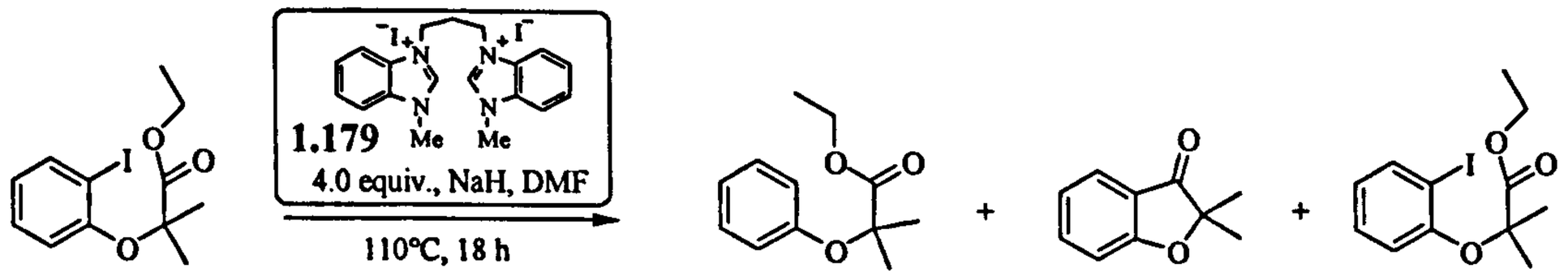


2.67 **2.70** **2.71**

Scheme 2.41

It was then checked whether the cyclisation of the corresponding aryl radical would be consistent with the previously discussed mechanism in **Scheme 2.32** (after nucleophilic attack by the donor at high temperature and under activating metal-chelation). Ester **2.67**

was reacted with benzimidazole donor **1.175** generated by the NaH method *in situ*. Salt **1.179** was used in 3.5 equivalents and the mixture was heated at 110°C overnight. After acidic work-up, column chromatography was carried out and the ^{1}H-NMR spectrum of the collected fraction showed reduced ester **2.70**, starting material **2.67** and indeed ketone **2.71**.



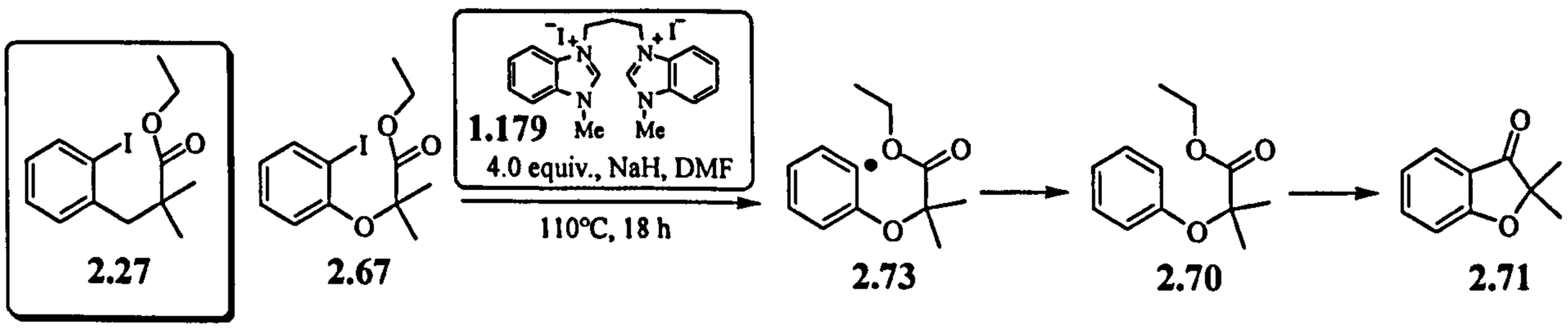
2.67 **2.70** **2.71** **2.67**

Scheme 2.42

This formation of ketone **2.71** would be consistent with the mechanism proposed in **Scheme 2.32.**

3.2.8 *Is a radical anion Friedel-Crafts reaction a mechanistic possibility?*

The ether oxygen atom could be responsible for the fundamental difference in reactivity of the oxygen-containing ester substrates compared to the carbon-side chain ester **2.27** (that did not cyclise to the corresponding ketone) also in a different way (see **Scheme 2.43**). After formation of the reduced ester **2.70** *via* radical **2.73** and subsequent hydrogen atom abstraction, the oxygen atom might have assisted a thermal cyclisation of the reduced ester, and this Friedel-Crafts type process might be responsible for the observed cyclisation in the case of oxygen side-chain esters.



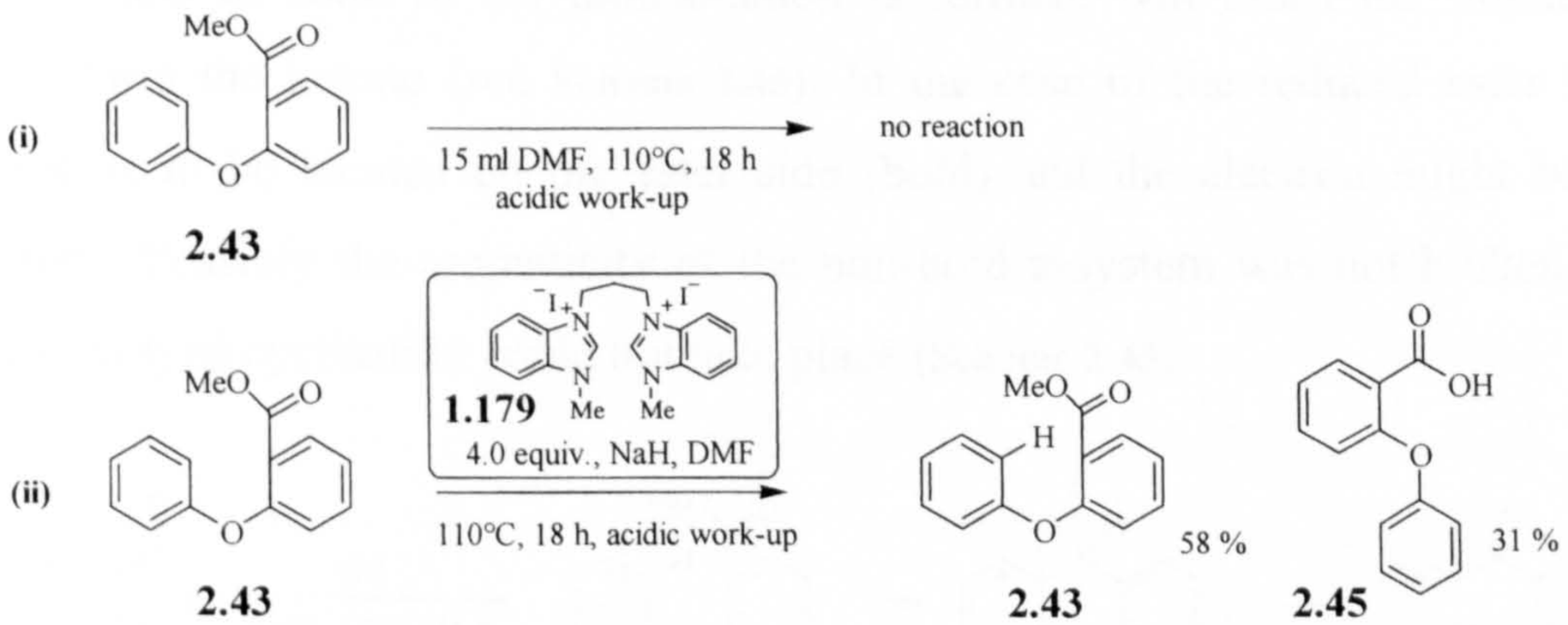
2.27 **2.67** **2.73** **2.70** **2.71**

Scheme 2.43

To test for this possibility, (i) the reduced ester **2.43** [since xanthone and reduced ester **2.43** are separable by column chromatography] was heated at 110°C for 18 h in anhydrous DMF (**Scheme 2.44**). However, only starting material **2.43** was recovered which rules out the possibility of thermal self-cyclisation of the reduced ester. In another experiment (ii), 4.0 equivalents of benzimidazole donor **1.175** were prepared *in situ* using the NaH method and reacted with reduced ester **2.43** at 110°C for 18 h in DMF to test whether activation of the ester by metal salts and/ or the nucleophilic donor is necessary to allow the Friedel-Crafts

process. This time, 58 % of the reduced ester **2.43** were recovered, and 31 % of acid **2.45** had formed, indicating either the interaction of the donor with the ester functionality or the presence of water, hydroxide respectively.

It was then tested (iii) whether reaction of the reduced ester **2.43** with pure imidazole donor **2.20** occurred at room temperature (to check whether a Friedel-Crafts process was responsible here for cyclisation), but this was not the case (see **Scheme 2.44**). And finally (iv), the carboxylic acid did not undergo self-cyclisation at 110°C either and was thus not responsible for the produced xanthone either.



Scheme 2.44

Friedel-Crafts acylation reactions are generally carried out in the presence of a metal-based-Lewis acid, *e.g.* $AlCl_3$. In a theoretical investigation, the effect of $AlCl_3$ has been studied and it was suggested that besides its action as a Lewis acid, $AlCl_3$ breaks the aromaticity of the aromatic ring and introduces a negative charge on carbon *via* bonding to the Al and backbonding from the 3p Cl orbital to the benzene HOMO (**Figure 2.7**).[134]

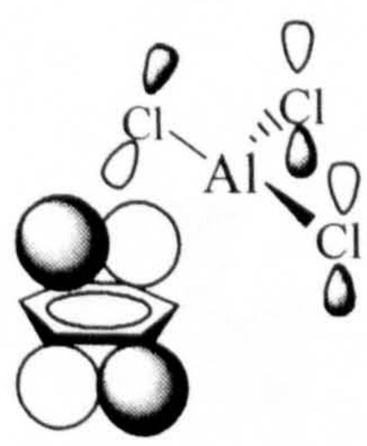
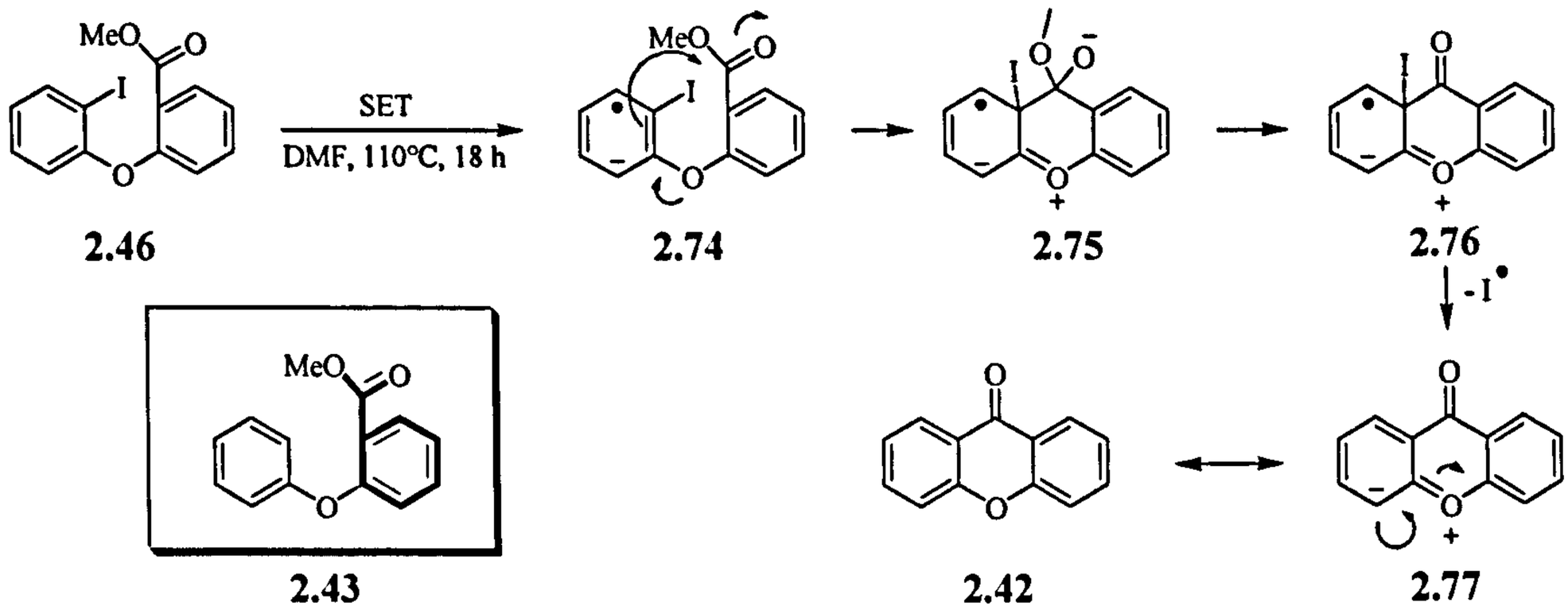


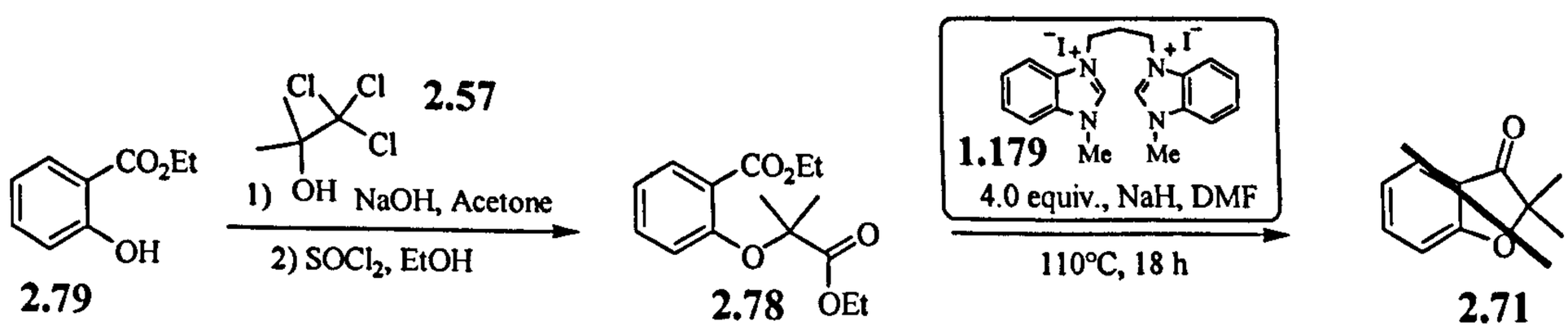
Figure 2.7 **Backbonding from the 3p Cl orbital to the benzene HOMO**

This introduced partial negative charge makes benzene more nucleophilic and hence reactive towards acylation. Thus, this study suggests that some kind of activation of the aromatic ring assists a Friedel-Crafts reaction. This might be the reason why the simple reduced ester **2.43** did not show any Friedel-Crafts reaction, as it contains a stable π-system and the aromaticity is not partially broken. However, this may be different for iodoester starting materials. In the process of the electron transfer reaction with benzimidazole donor **1.175**, the aromaticity will be partially broken in the formation of the radical-anion. Since the radical-anion only forms if heat is applied, the oxygen will be ready waiting at high temperature, and as soon as the radical-anion is formed, will assist the Friedel-Crafts process to form the ketone (see **Scheme 2.45**). In the case of the reduced ester **2.43**, the LUMO seems to be located on the ester side (bold) and the electron might be highly located there. Possibly the aromaticity of the non-bold π-system was not broken, so that Friedel-Crafts type cyclisation could not take place (**Scheme 2.45**).



Scheme 2.45

Whether such a radical-anion initiated Friedel-Crafts reaction was responsible for the formation of ketones in the reaction of benzimidazole donor **1.175** was next investigated. A π-activating (LUMO-lowering) group that is unambiguously not a leaving group was sought, and the choice resulted in the synthesis and study of diester **2.78**, since this diester should be electron-deficient enough to accept an electron from benzimidazole donor **1.175** (as confirmed by simple S*PARTAN* calculation of the LUMO energy and comparison with that of iodoester **2.56**).



Scheme 2.46

However, no ketone formation took place in the reaction of **2.78** with benzimidazole donor **1.175** (that was generated *in situ* from salt **1.179**) as judged from the ^{1}H-NMR spectrum of the crude mixture. Further GC-MS analysis of the reaction mixture showed considerable amount of starting material and no peak corresponding to ketone **2.71**, making the radical-anion Friedel-Crafts process therefore a less likely mechanistic alternative. The mechanistic proposal in which radical cyclisation on the benzimidazolium activated ester takes place, is thus favoured.

3.2.9 *Theoretical investigations of aryl anion formation*

To establish further that aryl anions are indeed favourable intermediates in reaction with imidazole donor **2.20** and at the same time unfavourable intermediates in reactions with benzimidazole donor **1.175**, a computational investigation of the corresponding electron transfer processes was undertaken by T. Tuttle.[135] The structural changes upon electron loss of the electron donors **1.175** and **2.20** were studied and it was found that donor **2.20** gets increasingly planar towards the dication species, whereas benzimidazole donor **1.175** undergoes a considerable twist upon electron loss (see **Figure 2.8**). Furthermore, the formation of positive charge was found to be in total ca. 20 kcal/mol* more favourable for imidazole donor **2.20** (ca. 10 kcal/mol more favourable for the formation of the radical cation, and 10 kcal/mol for the dication).[135]

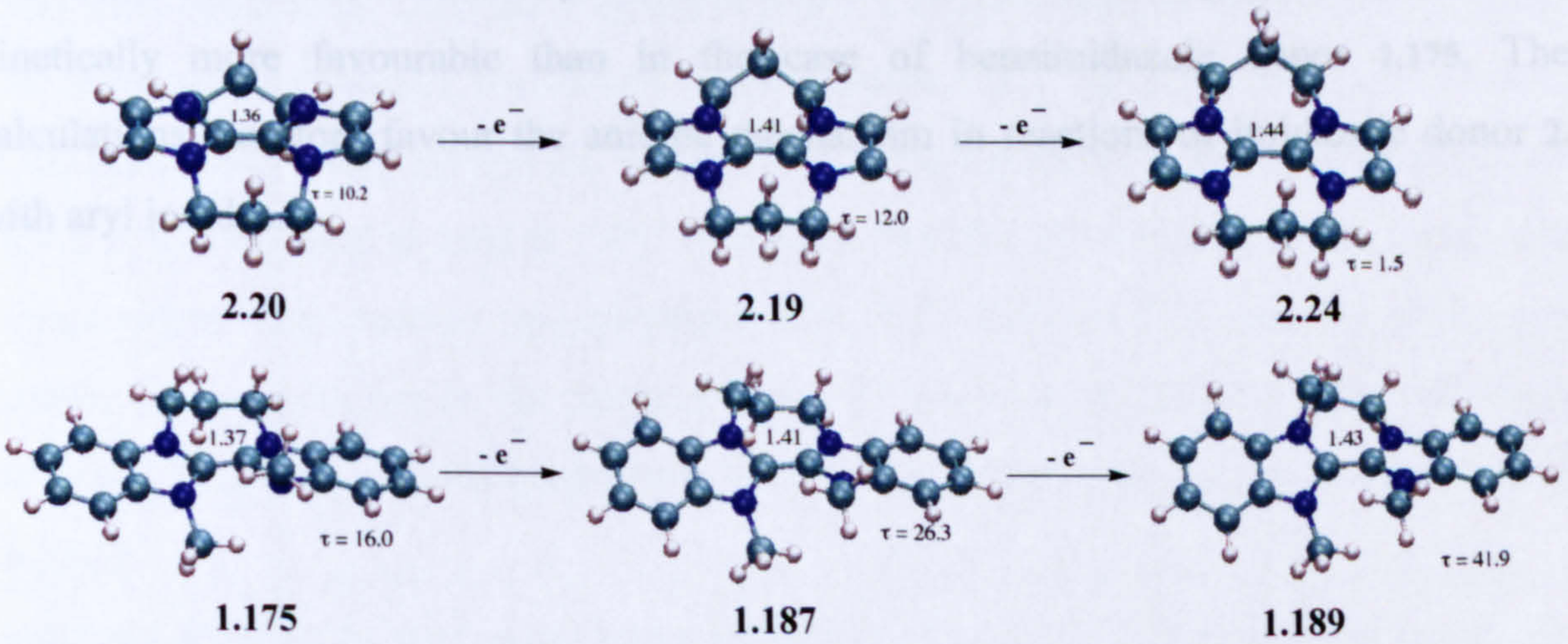


Figure 2.8

The reorganisation energies as well as activation barriers for the formation of aryl anions were calculated next for each of the donors using Marcus theory. It was found that imidazole donor **2.20** exhibits slightly greater reorganisation energies[135] than benzimidazole

* Conversion factor: 1 kcal = 4.1868 kJ

donor **1.175** which has to overcome an activation barrier of 12.8 kcal/mol to form aryl anions and the overall process is endergonic. Imidazole donor **2.20**, in contrast, has with 6.9 kcal/mol a considerable smaller activation energy to overcome to form an aryl anion in the reduction of iodobenzene, and also the process was found to be slightly exergonic.[135]

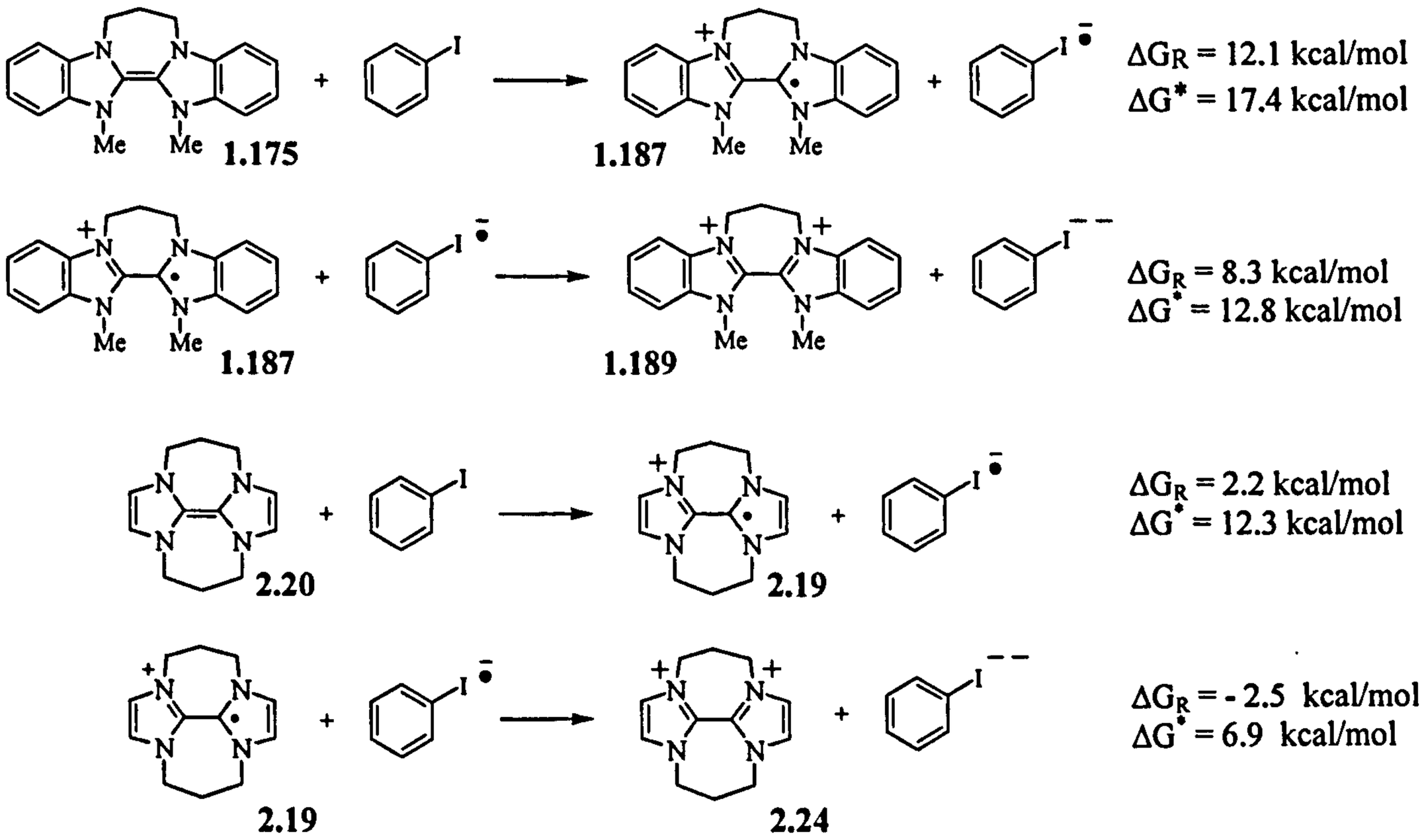
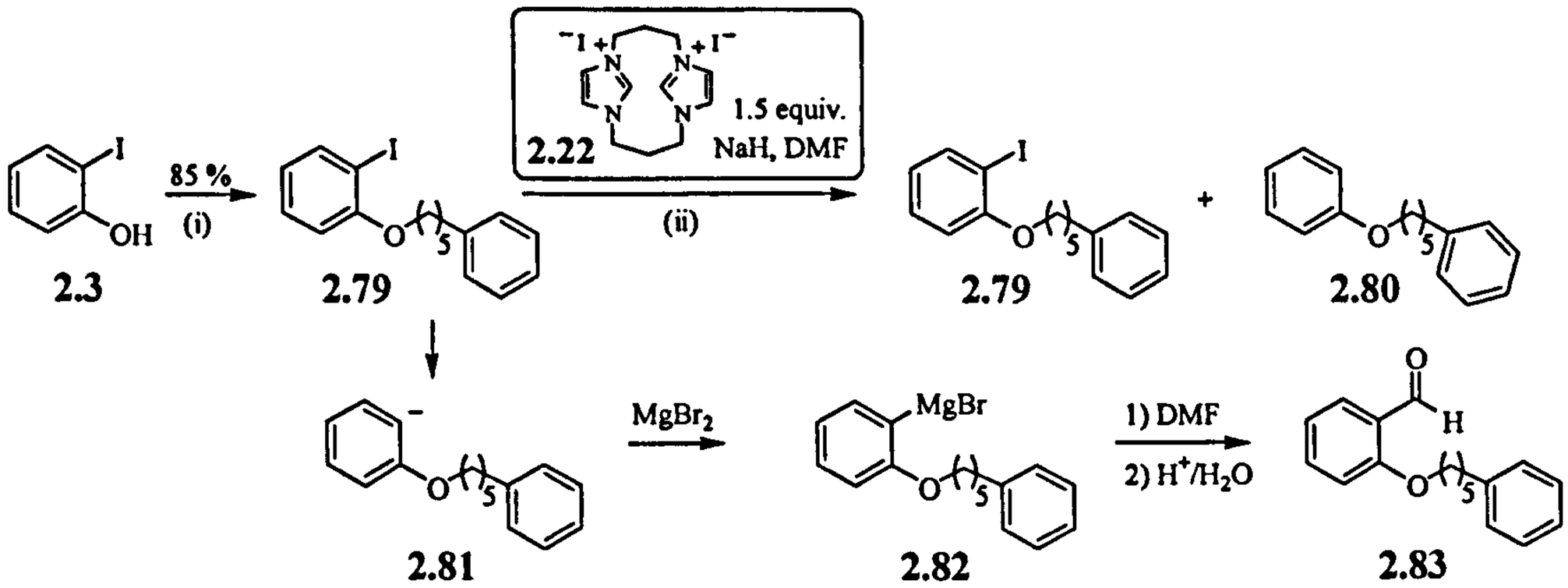


Figure 2.9 Activation energies (ΔG^*) and reaction free energies (ΔG_R) for electron transfer

The formation of aryl anions by imidazole donor **2.20** is thermodynamically as well as kinetically more favourable than in the case of benzimidazole donor **1.175.** These calculations therefore favour the anionic mechanism in reactions of imidazole donor **2.20** with aryl iodides.

3.3 Further investigations to prove aryl anion intermediates - benzynes

This indication of aryl anions needed further experimental evidence. Since the aryl anion seems to have at least enough life-time to cyclise onto an ester, it was thought that the addition of an anhydrous metal salt in the reaction of an aryl halide with imidazole donor **2.20** might stabilise the anion and lead to the formation of an organometallic intermediate **2.82**, which should then have the lifetime to carry out subsequent chemistry, *i.e.* attack onto the solvent DMF,[136] giving rise to aldehyde **2.83** after work-up.



***Reagents and conditions*: (i)** 5-phenyl-1-pentanol (1 equiv.), PPh_3 (1 equiv.), DIAD (1equiv.), THF, 0°C to r.t., 3.5 h; **(ii)** a) $MgBr_2$ (1.2 equiv.), 70°C, 18 h; b) D_2O.

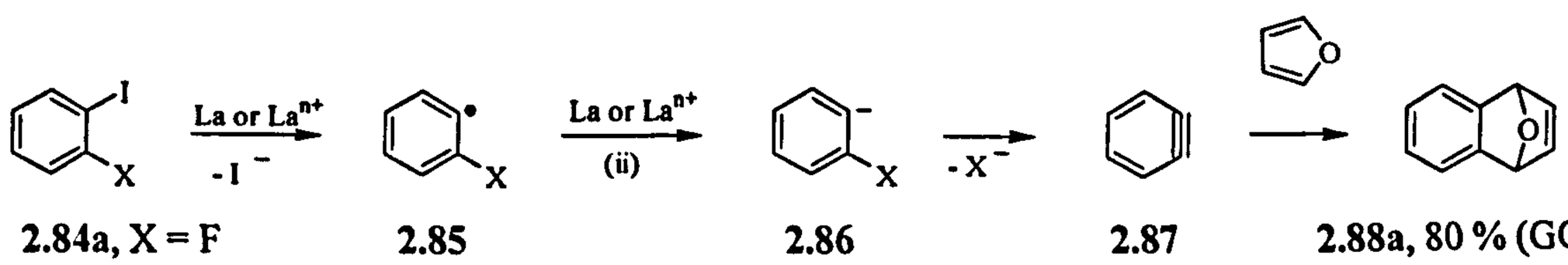
Scheme 2.47

Accordingly **2.79** was prepared in 85 % yield under Mitsunobu conditions. Anhydrous magnesium bromide was weighed in a glove-box and substrate **2.79** was transferred to it under inert conditions. Then the solution of donor **2.20** (generated by NaH method) in DMF was added and the mixture was stirred at room temperature. Since the usual colour change in the reduction of aryl iodides did not occur at room temperature when the reagents were added, it was decided to heat at 70°C overnight, but this did not lead to the usual colour change either. The reaction was quenched with D_2O. However, IR-analysis of the crude mixture did not give rise to the characteristic C-D vibration at 2200 cm^{-1}. Instead starting material **2.79** and its reduced counterpart **2.80** were isolated as an inseparable mixture in a 1:1 ratio.

Questions arose as to why quantitative reduction of aryl iodide **2.79** did not occur, since aryl iodides are normally immediately reduced at room temperature after adding the reagents. The reason could be that the added Mg^{2+} ions stabilise the radical-anion formed after the first single electron transfer which corresponds to an increase in $E°_{RX/RX^{\cdot-}}$, and thus leads to significant decrease in fragmentation rate. This was observed for 4-chlorobenzophenone for instance, where a decrease in fragmentation rate by a factor of 20

was estimated after the addition of metal-pairing ions.[137] However, $MgBr_2$ being a Lewis acid, might also have led to interaction with the donor and might have lowered its HOMO energy, hence lowering its reducing power and thus partially preventing it from electron transfer.

Another alternative attempt to prove the existence of the aryl anion intermediate was to investigate the formation of benzyne intermediates. Generally, benzynes are formed by elimination of a very good leaving group, such as triflate, *ortho* to the aryl anion centre. However, the strongly reducing donor **2.20** can cleave a triflate group [this will be discussed later in more detail]. Therefore, only limited leaving groups can be utilised for the benzyne formation. Kawabata *et al.* have reported[138] in that context that cyclo-adduct **2.88** was formed after electron transfer from lanthanum to iodofluoro- or iodochlorobenzenes, **2.84a,b** with furan, justifying the assumed benzyne intermediate **2.87** **(Scheme 2.48).**



2.84a, X = F **2.85** **2.86** **2.87** **2.88a, 80 % (GC)**

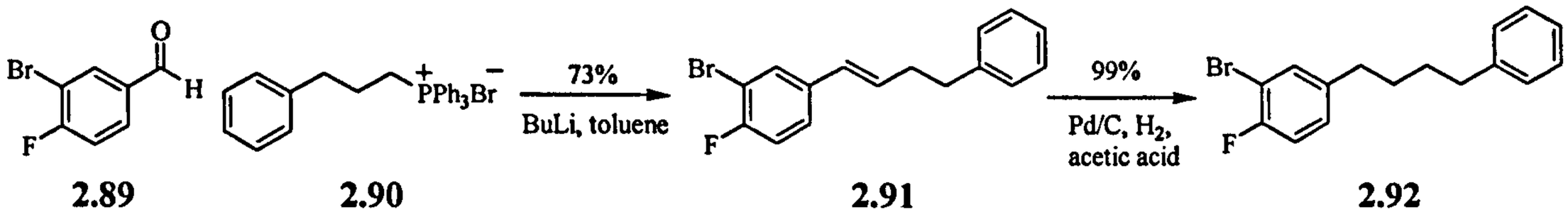
2.84b, X = Cl **2.88b, 100 % (GC)**

Scheme 2.48

From the previous studies on aryl chlorides and fluorides it was seen that those do not react under the reductive conditions using imidazole donor **2.20**. Thus, the literature precedent was felt to be ideal. Accordingly, **2.84a** and **b** along with furan [that was purified from its stabiliser beforehand and deoxygenated] were exposed to donor **2.20** (**Scheme 2.48**), which led to instantaneous colour change to deep red. The mixture was stirred at room temperature overnight and then quenched with D_2O. However, no product could be isolated. Possibly, benzyne **2.87** did not form and only the usual reduction took place, leading to fluoro- and chlorobenzene that have boiling points of 85°C and 132°C and were thus too volatile to be detected. The second option is that the electrophilic benzyne intermediate did form, but underwent preferential cycloaddition with another donor molecule **2.20** (which exhibits a very high-lying HOMO). Possible addition could lead to a positively charged species that would subsequently be lost into the aqueous layer in work-up. However, starting material would then have been recovered in 50 % yield.

It was decided to synthesise a benzyne precursor that would lead to a non-volatile dehalogenated product, to test whether simple reduction might have taken place in the

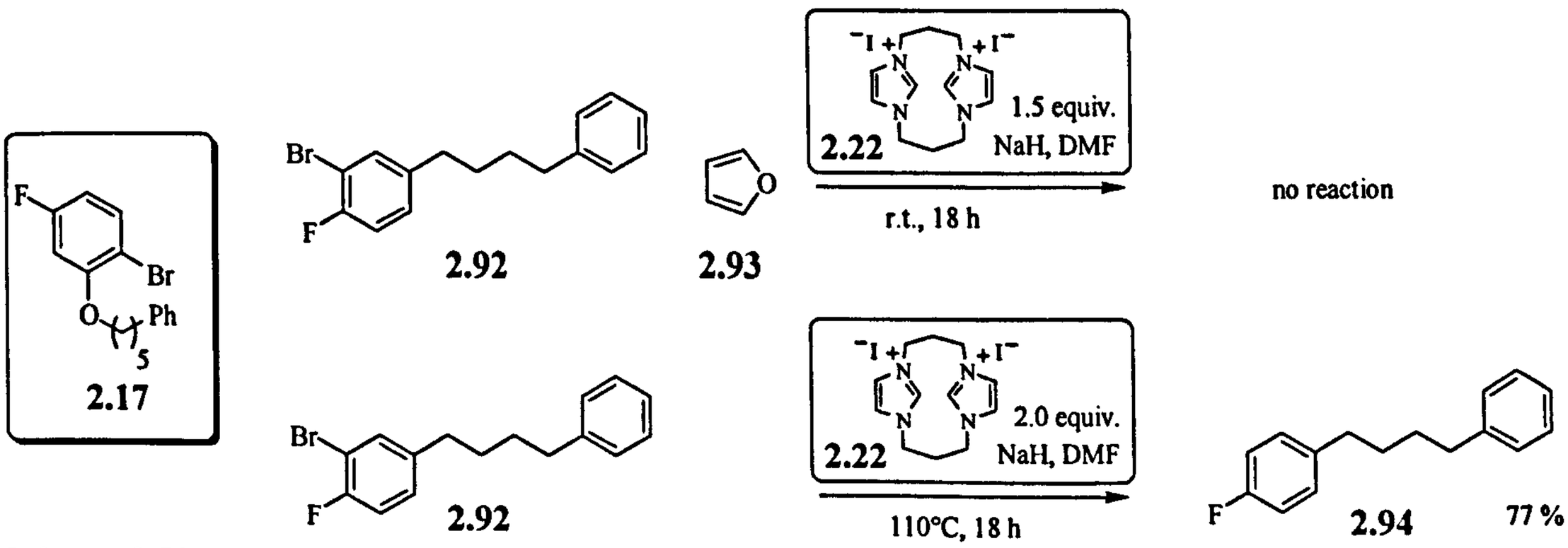
previous experiments and the volatile products were subsequently lost. Thus, commercially available aldehyde **2.89** was reacted with phosphonium salt **2.90**[139] in a Wittig reaction. The mixture of *E*- and *Z*-alkene **2.91** was then hydrogenated using a Pd/C catalyst; the solvent acetic acid was found to be crucial for the reaction to take place.



2.89 **2.90** **2.91** **2.92**

Scheme 2.49

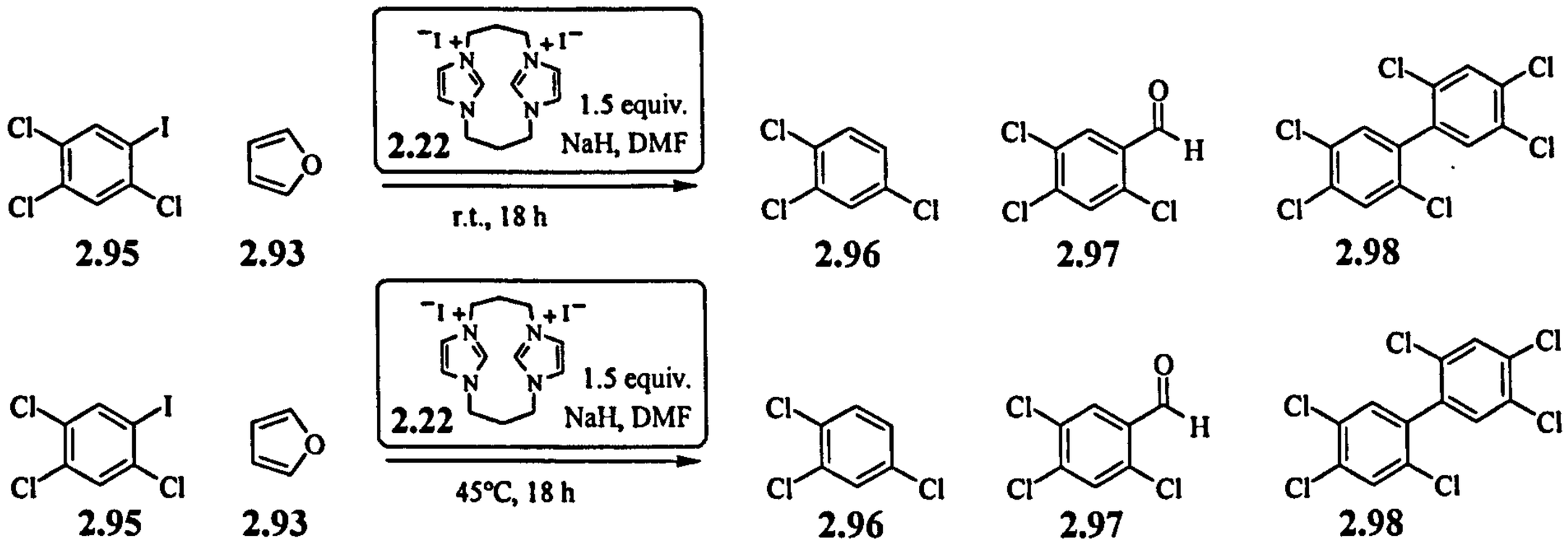
In the initial experiment, substrate **2.92** was reacted with 1.5 equivalents of donor **2.20** along with furan at room temperature in DMF. However, no reaction took place and starting material **2.92** was recovered (**Scheme 2.50**). This is in line with the experimental observation made in the reduction of **2.17** where 2.0 equivalents of donor **2.20** and heat were necessary to reduce the bromo-fluoro system completely (see below). Since the reduction from the aryl radical to the aryl anion should be easier than the initial reduction of the halide to the aryl radical,[140] an aryl anion should also form at high temperature. The fact that the reduction takes place only at high temperature might be advantageous, since the elimination of the fluoride leaving group might be favoured at higher temperature (due to greater molecular/ bond vibrations) and thus, the benzyne formation might be facilitated. Thus **2.92** was reacted with 2 equivalents of donor at high temperature in the absence of furan (which has too low a boiling point). However, only simple reduction to afford **2.94** took place without any indication of successful benzyne formation (**Scheme 2.50**).



Scheme 2.50

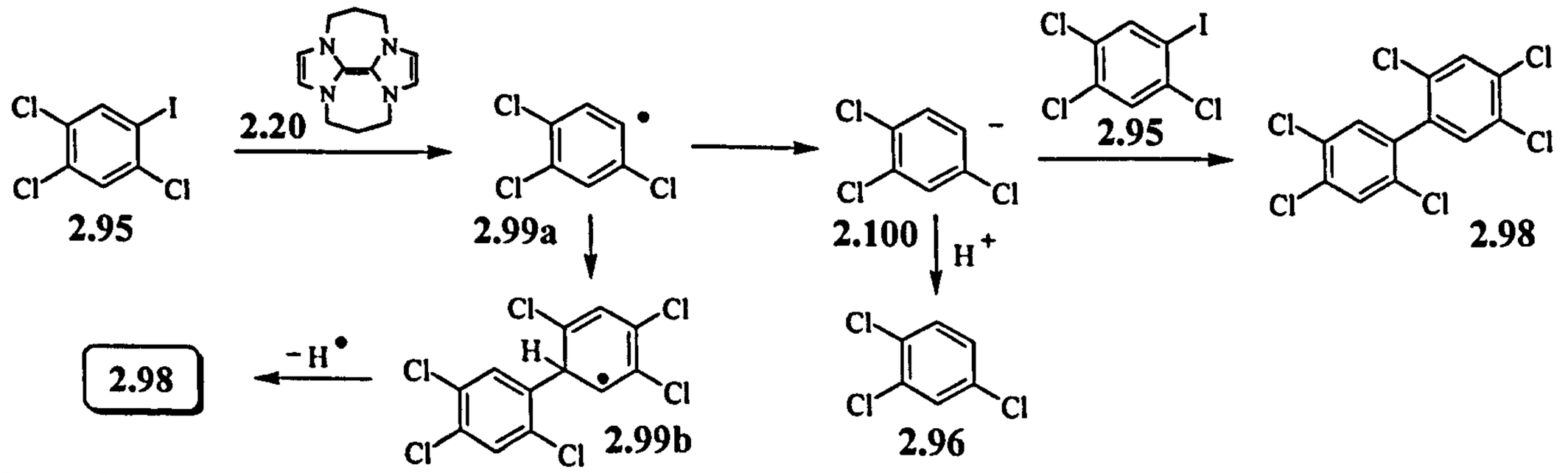
Kawabata *et al.* used benzyne precursor trichloroiodobenzene **2.95** to form a cycloadduct with furan and lanthanum. The yield of the detected cycloadduct was significantly lower than in the case of 2-iodochlorobenzene, for instance. This may be attributed to the intermediate anion being more stabilised by the additional chlorine atoms, making the

benzyne formation slow and disfavoured. However, it did take place to some extent. Trichlorobenzene is non-volatile also, making this substrate another candidate for a qualitative benzyne intermediate test. Arene **2.95** was reacted with 1.5 equivalents of donor **2.20** and purified furan in DMF at room temperature for 18 h. After work-up and column chromatography (to remove donor residues), the mixture was analysed by GC-MS. Several products were detected, but there was no sign of the cycloadduct arising from a benzyne intermediate. A second experiment was carried out, identical to the first with the only difference being that gentle heat was applied (45°C), but again, there was no sign of any products from a benzyne intermediate (see **Scheme 2.51**). The major compound formed in both experiments (although a GC-MS calibration with standards was not carried out) was trichlorobenzene **2.96**. Aldehyde **2.97** had also formed [a possible mechanism of formation will be discussed in the next section in great detail] and biphenyl product **2.98**.



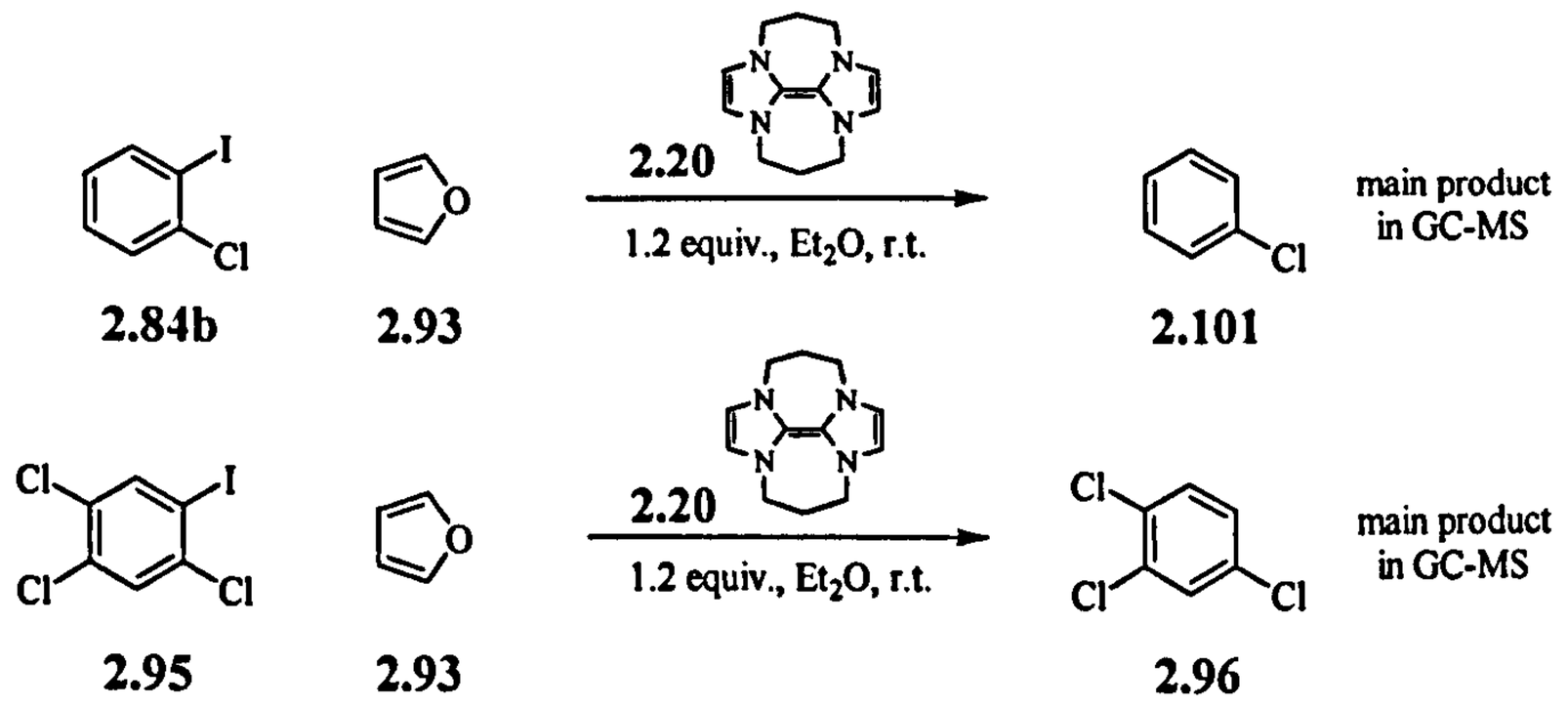
Scheme 2.51

The probability that biphenyl product **2.98** could form *via* coupling of two aryl radicals **2.99a (Scheme 2.52)** is rather low. More likely, the aryl anion **2.100** could undergo nucleophilic substitution on the activated iodide **2.95**, leading to the biphenyl product **2.98**. Further, an aryl radical **2.99a** could, in principle, add to trichlorobenzene **2.96**, giving biphenyl **2.98** after loss of an H-atom from **2.99b**.[141]



Scheme 2.52

One more approach to form benzynes was chosen. It was thought that a change of solvent might be advantageous for the formation of benzynes. Diethyl ether or THF are generally used in benzyne reactions (but this may be only to address the metal reactivity, *e.g.* breakdown of aggregation in such donating solvents). Nevertheless, the use of diethyl ether was felt to be advantageous, since the radical-cation or dication of the donor, after electron transfer, precipitates from solution. Thus, the precipitate can simply be removed by filtration and the solution can be analysed by GC-MS analysis. This allows the detection of more volatile products. Iodochlorobenzene and iodotrichlorobenzene were reacted with the pure donor **2.20** in deoxygenated and dry diethyl ether and purified furan for 18 h at room temperature. The precipitate was removed by filtration and the solution analysed by GC-MS. In both experiments the major product (judged by peak height, no calibration was carried out) was the one arising from simple reduction of the C-I bond (**Scheme 2.53**).



2.84b **2.93** **2.101**

2.95 **2.93** **2.96**

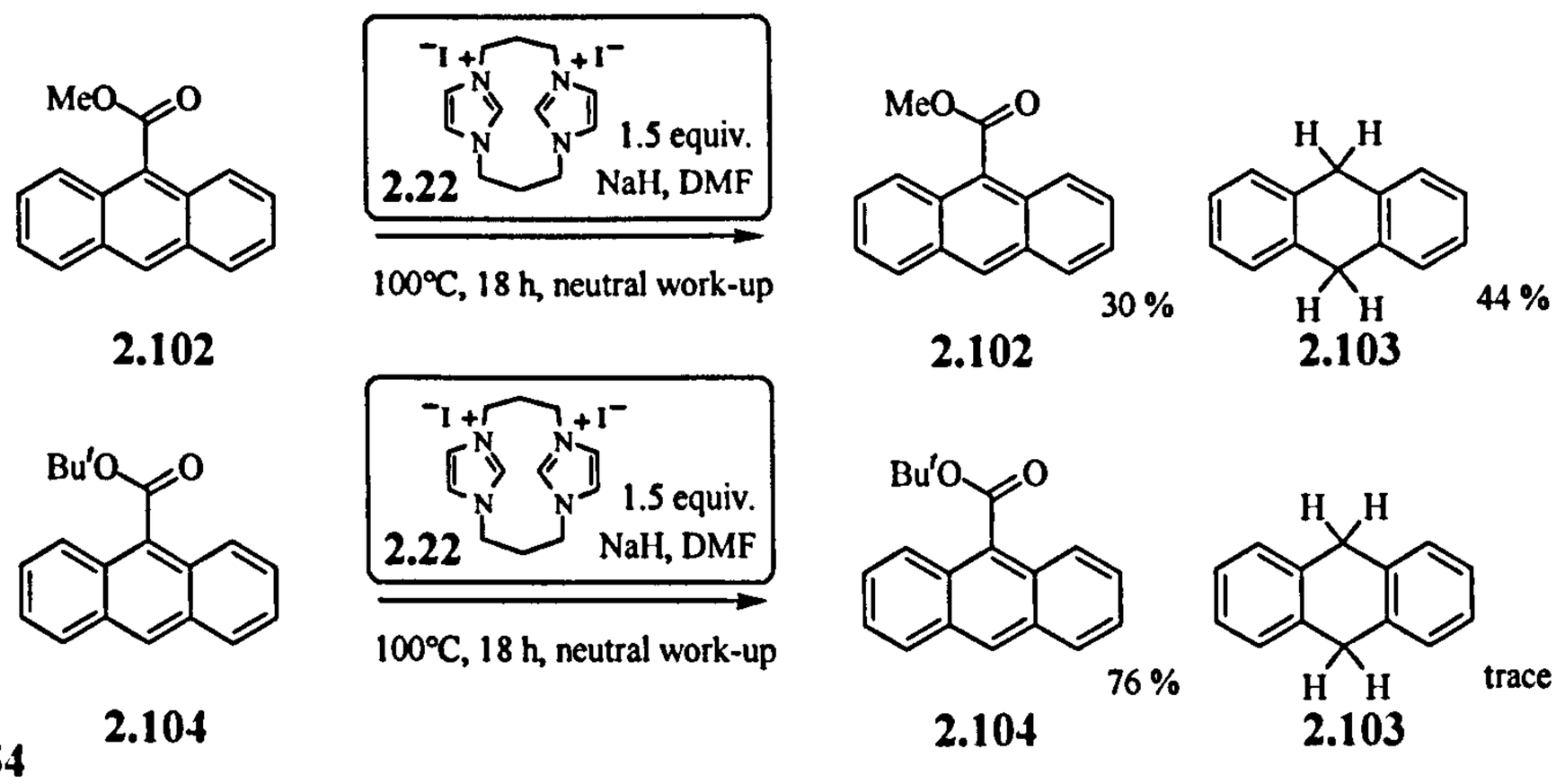
Scheme 2.53

In conclusion, benzynes could not be formed. This may be due to the fact that the donor dication is in close proximity to the aryl anion after double electron donation, and proton transfer from the side-chain of the donor dication salt occurs more rapidly than elimination of an *ortho* leaving group to form a benzyne. Also, the tested leaving groups are less efficient than others (*e.g.* triflate) and give rise to slow benzyne formation. However, more efficient leaving groups cannot be used for the formation of benzynes, since imidazole donor **2.20** is able to react with those.

3.4 To be nucleophile or electron donor – that is the question

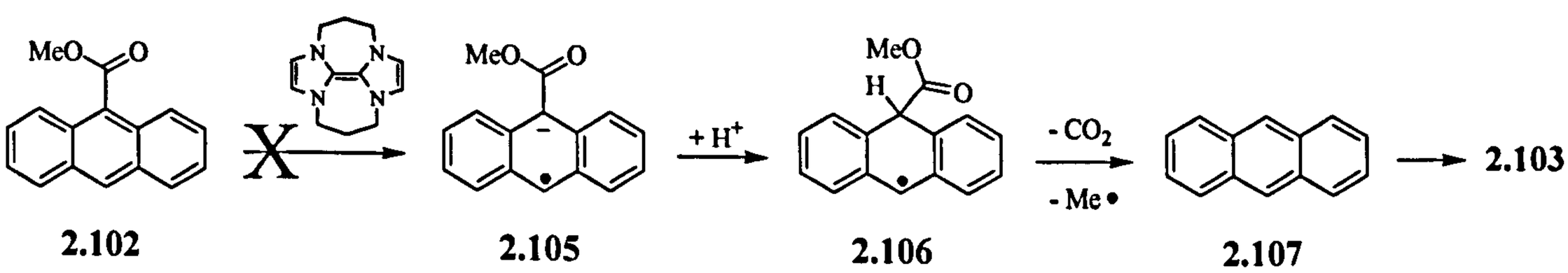
3.4.1 *Reductions of anthracene esters with donor* 2.20

In section **3.2** above, the formation of aryl anions using donor **2.20** was discussed. Further it was assumed that benzimidazole donor **1.175** might be capable of attacking an ester nucleophilically, if heat is applied. Aryl radical cyclisation onto the formed intermediate was proposed to lead to the cyclised ketone *via* a radical mechanism also, rather than *via* an anionic pathway. This interplay in reactivity between nucleophilicity and electron transfer ability was observed also in different reactions within the Murphy group. D. Thomson in our group studied the two reductions of anthracene methyl ester **2.102** and *tert*-butyl ester **2.104** below using imidazole donor **2.20**.[142] Along with starting material, he isolated in both cases dihydroanthracene, achieving with that a Birch-type reduction.



Scheme 2.54

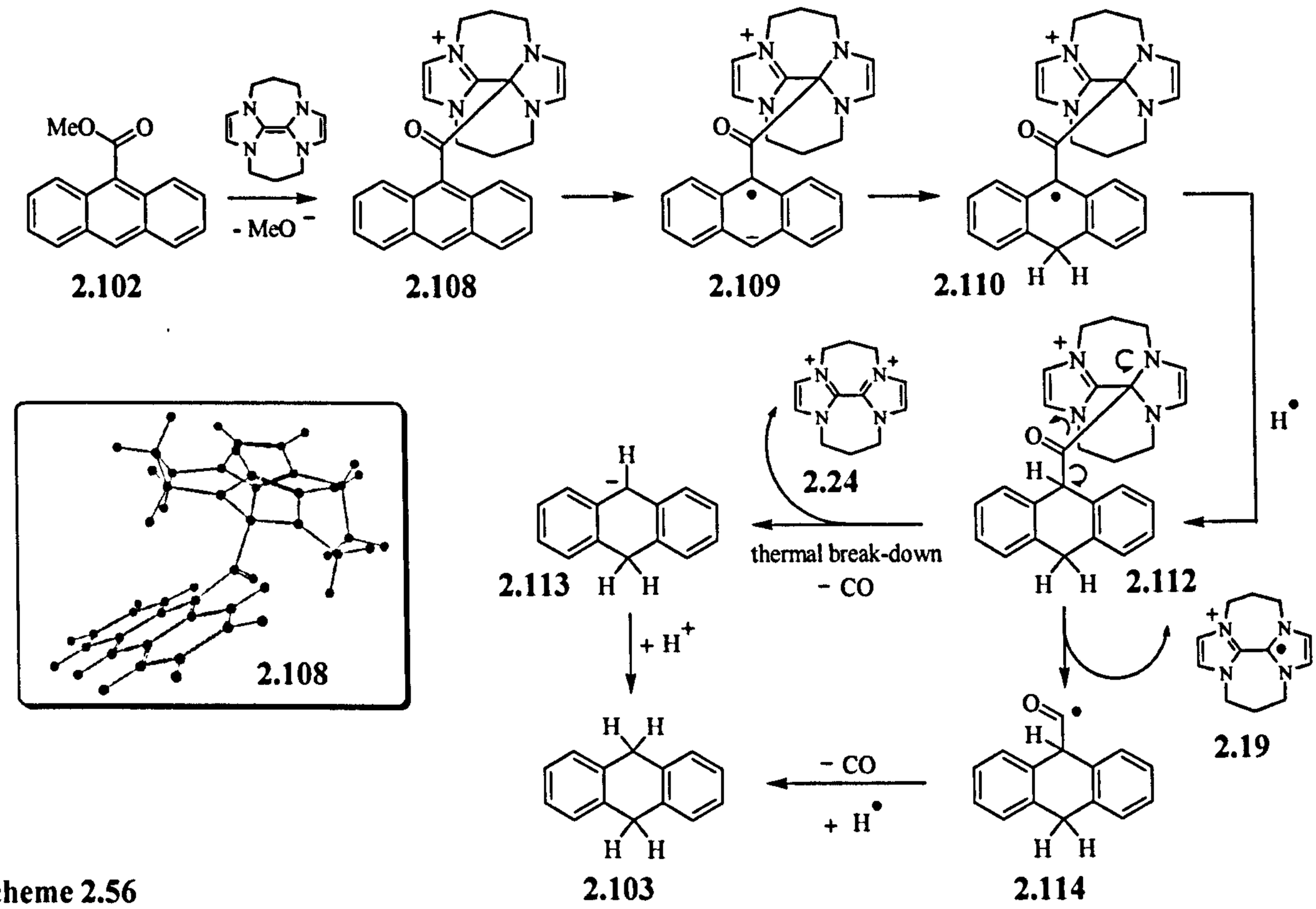
The mechanistic rationalisation of the observed results was the following (see also **Scheme 2.55**): since *tert*-butyl ester **2.104** gave only a trace of dihydroanthracene in the reaction with donor **2.20**, it is assumed that dihydroanthracene **2.103** should not be produced by initial reduction of the anthracene moiety, followed by loss of the ester functionality, as the LUMOs, *i.e.* π^* orbitals are expected to be of very similar energy for both esters (see appendix for LUMOs and geometries of the esters).



Scheme 2.55

Anthracene **2.107** is not reduced to dihydroanthracene, under the reaction conditions shown in **Scheme 2.54**,[142] suggesting that the ester group is not lost until the anthracene π-system is

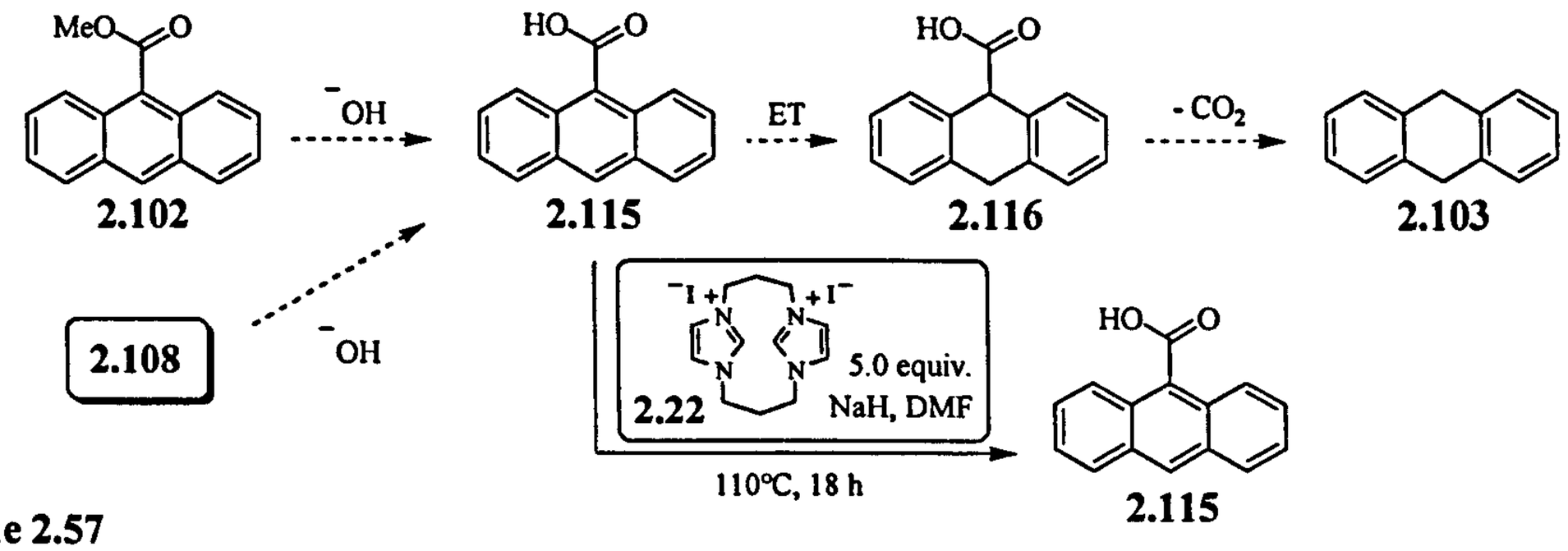
reduced towards the dihydro analogue. It was assumed that the ester functionality is attacked initially by the nucleophilic donor, with methoxide and *tert*-butoxide respectively, being displaced. This would account for the poorer conversion to dihydroanthracene in the case of *tert*-butyl ester **2.104**, where the carbonyl group is more protected by the crowded *tert*-butyl group towards attack by a nucleophile. Also, methoxide is a better leaving group (the corresponding acid has a pK_a = 16; *tert*-butanol: pK_a = 19).[143] The formed activated intermediate **2.108** might then be reduced more readily and after protonation might undergo thermal decarbonylation from **2.112** (**Scheme 2.56**) *via* the red mechanism indicated below, or alternatively by a radical mechanism as indicated in blue.



Scheme 2.56

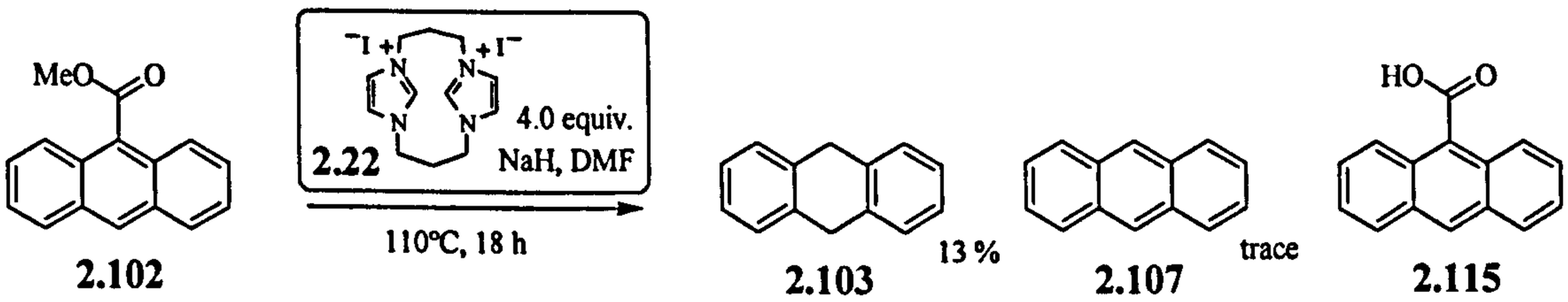
If **2.108** was indeed an intermediate in the mechanism, it would be expected that perhaps anthracene-9-carboxylic acid might be formed by displacement of the activated intermediate **2.108** by hydroxide or possibly hydrolysis of any activated intermediate (**2.108** or **2.112**) in work-up.

To rule out that any anthracene-9-carboxylic acid **2.115**, that had formed in the reaction mixture, is subsequently converted to the dihydroanthracene **2.103** *via* reduction to the dihydroacid **2.116**, followed by decarboxylation, anthracenecarboxylic acid **2.115** was reacted with *in situ* generated donor **2.20**.



Scheme 2.57

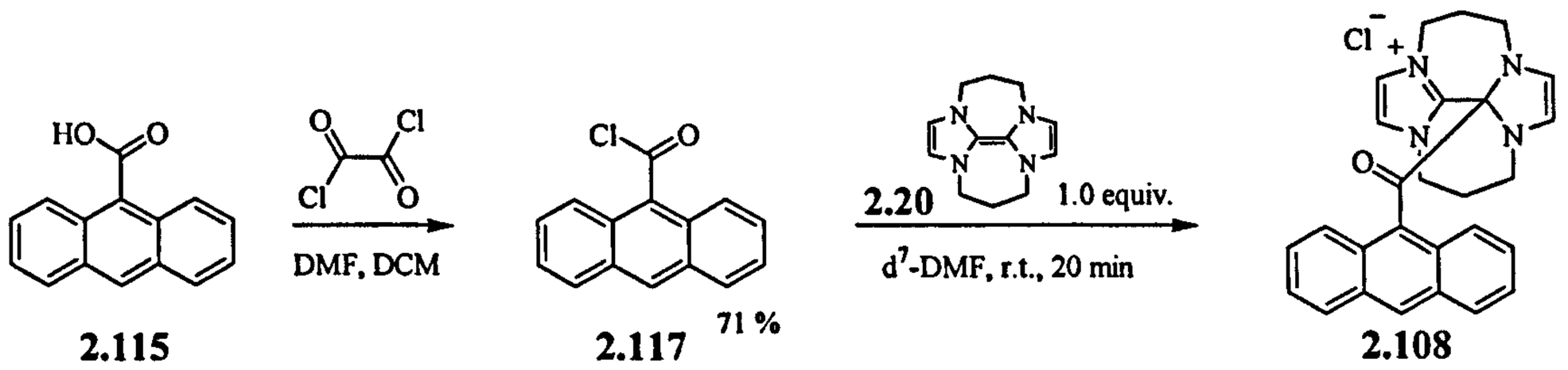
However, this led to a recovery of starting material only, which means that any acid formed in the reaction mixture does not react further. To see whether acid had formed in D. Thomson's original experiment, methyl ester **2.102** was reacted with imidazole donor **2.20** and acidic work-up was carried out (**Scheme 2.58**). A greater number of equivalents of donor (4 equiv.) was applied under more concentrated conditions, and this time no starting material was observed. Acid extraction was carried out and dihydroanthracene **2.103** was isolated in 13 % yield. Surprisingly anthracene **2.107** was observed as a trace in the ^{1}H-NMR spectrum also. The lower yield of dihydroanthracene **2.103** as compared to the original experiment may be due to the higher boiling point of ethyl acetate that was used in work-up (for solubility of carboxylic acid), leading to loss due to volatility. Carboxylic acid **2.115** was identified by LC-MS analysis of the fraction that was obtained from acid extraction in a mixture with other unidentified compounds. No peak corresponding to the dihydroacid **2.116** was observed in LC-MS.



Scheme 2.58

The finding of carboxylic acid **2.115** might be a hint for the existence of a donor adduct intermediate **2.108**. However it is not a proof, as acid **2.115** could also form by displacement of methoxide in **2.102** with hydroxide that might be present in the reaction mixture. It was therefore attempted to prove the existence of adduct intermediate **2.108**.

Anthracene-9-carbonyl chloride **2.117** was synthesised for that purpose. It was hoped that upon exposure of 1.0 equivalent of pure donor **2.20** in the glove-box to 1.0 equivalent of anthracene-9-carbonyl chloride **2.117** in fully deuterated DMF, the species **2.108** might form and might be observable by NMR analysis of the reaction mixture (**Scheme 2.59**).

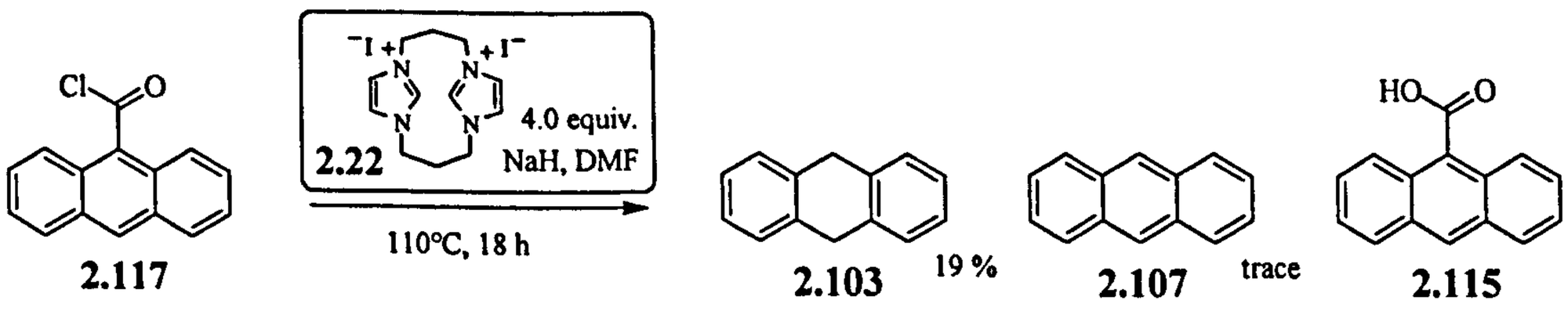


2.115 **2.117** 71 % **2.108**

Scheme 2.59

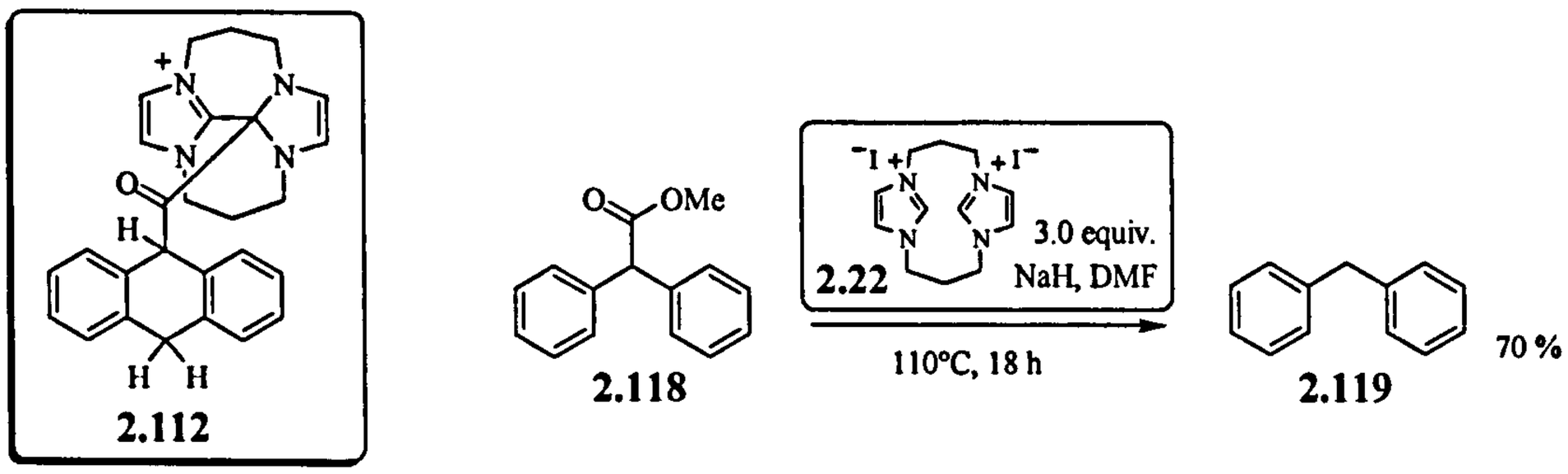
A solution of donor **2.20** in deoxygenated and deuterated DMF was transferred dropwise *via* pipette to anthracene-9-carbonyl chloride **2.117** in the glove-box at room temperature, leading to a black reaction mixture that was analysed by ^{1}H-NMR and ^{13}C-NMR after 20 min reaction time. However, the NMR spectra were rather complex and did not give any definite answer about whether the species **2.108** had formed. It was decided therefore to add diethyl ether to the reaction mixture in order to precipitate polar intermediates (*i.e.* the charged species **2.108**). LC-MS analysis of the precipitate pleasingly showed a peak corresponding to $[M+H]^+$ at 422 with a ^{13}C isotope peak-intensity of ~31 % relative to the $[M+H]^+$ peak-intensity, which would match the 27 carbon atoms at a relative abundance of 1.1 % and the contributions of the nitrogen and oxygen isotopes (relative abundances: ^{15}N: 0.36 %; ^{17}O: 0.04 %). This is evidence for the formation of species **2.108** (or an isomer of it) as an intermediate.

As the next task it had to be proven that dihydroanthracene **2.103** indeed formed by reduction of acid chloride **2.117** (and therefore possibly *via* reduction of the intermediate species **2.108**). Four equivalents of yellow donor solution **2.20** were added to anthracene-9-carbonyl chloride **2.117** *via* cannula, leading to the same black reaction mixture at room temperature. The mixture was then heated at reflux for 18 h and then exposed to acid extraction using ethyl acetate as extracting solvent (**Scheme 2.60**). A very similar reaction outcome to that discussed previously in **Scheme 2.58** was observed. Dihydroanthracene was formed in 19 % yield and a trace of anthracene was observed also in the ^{1}H-NMR spectrum. Further the acid **2.115** was once again identified by LC-MS analysis of the fraction that was obtained by acid extraction.



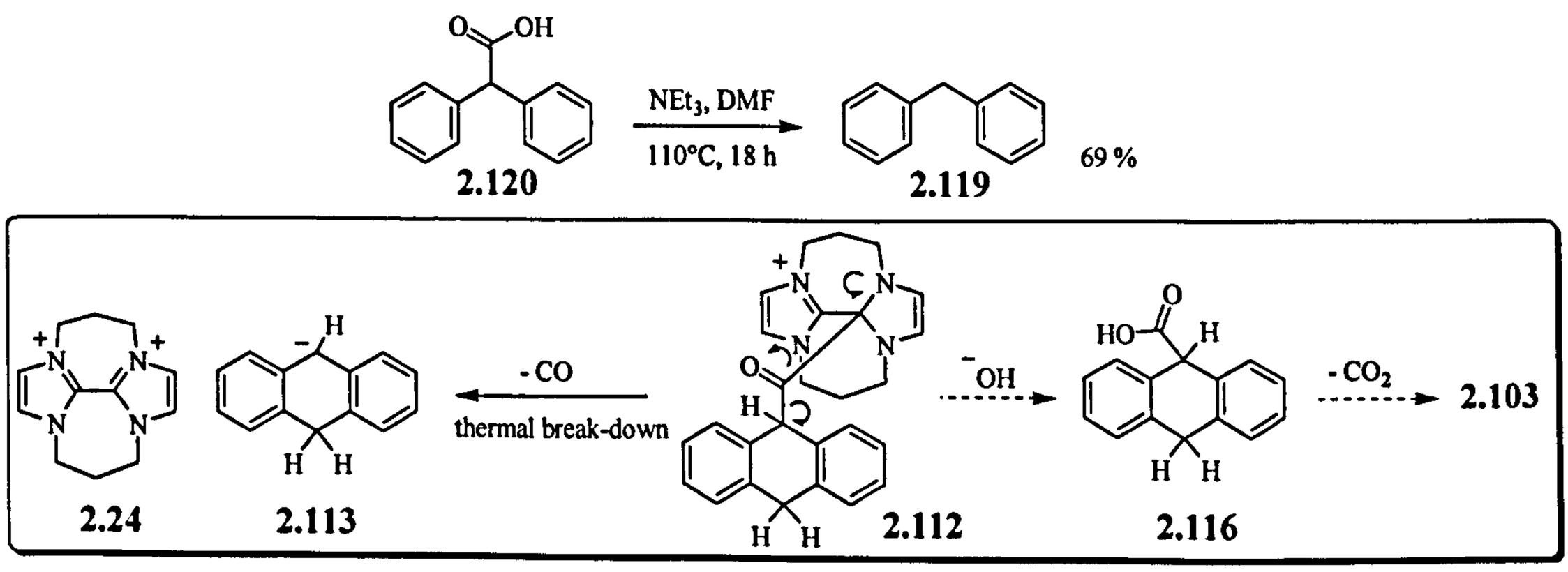
Scheme 2.60

This would be consistent with the previously proposed mechanism, in which initial attack by the donor onto the ester functionality was postulated. Later in the mechanism shown in **Scheme 2.56**, the loss of ester was described from a dihydroester species derivative **2.112** (below). If this is indeed the case, a dihydroester or similar species should lose the ester group also upon exposure to imidazole donor **2.20**. This was tested by S.-Z. Zhou, and he indeed found loss of the ester group in substrate **2.118** to form diphenylmethane **2.119** in 70 % yield. This might suggest that the breakdown from **2.112** to **2.113** could indeed be a favourable process.



Scheme 2.61

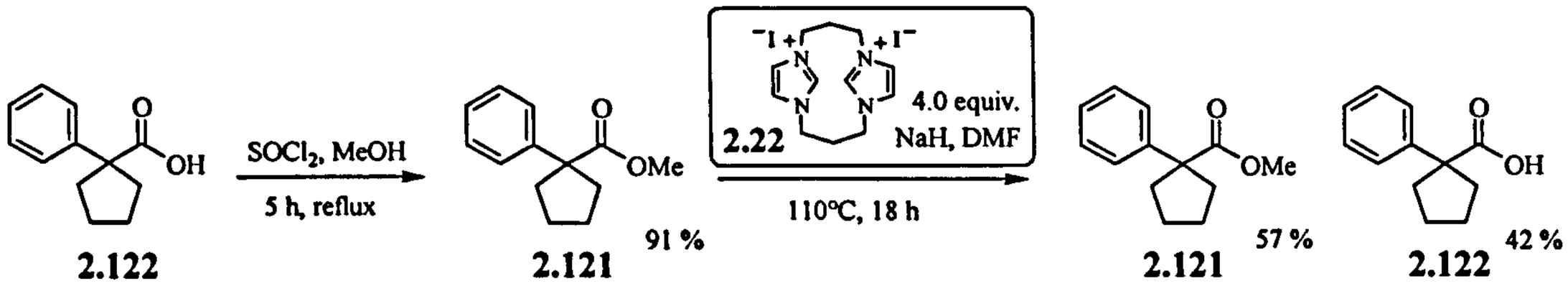
In a blank experiment (**Scheme 2.62**), exposing triethylamine to diphenylacetic acid **2.120**, followed by heating of the mixture overnight, diphenylmethane **2.119** was produced in 69 % yield also. Thus, any hydroxide present in the reaction mixture may attack intermediate **2.112**, giving rise to the dihydroacid **2.116**, which would convert also to dihydroanthracene. This explains why the dihydroacid was never detected in LC-MS.



Scheme 2.62

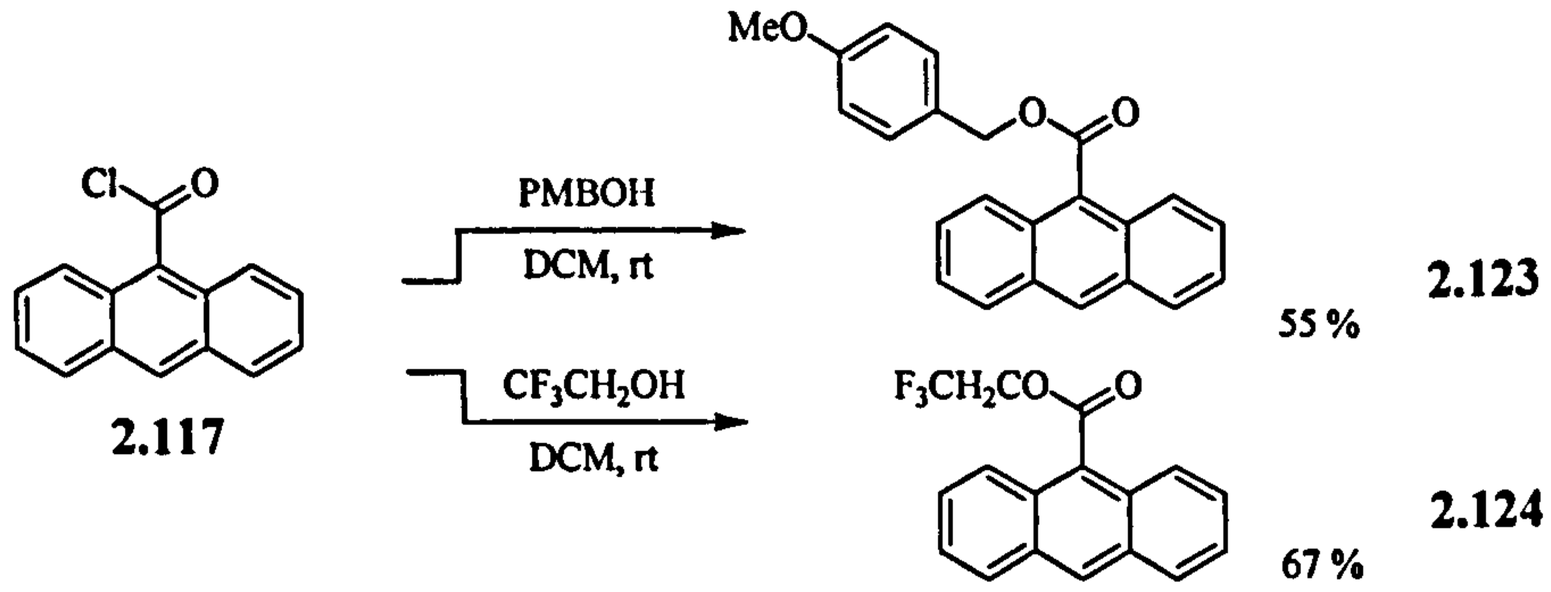
To see whether such a de-esterification has general applicability as a synthetic method, ester **2.121** was synthesised (**Scheme 2.63**). Here, only one stabilising aryl group is present. When ester **2.121** was reacted with donor **2.20**, this time loss of the ester group was not seen. Starting material **2.121** was recovered in 57 % yield. Also, hydrolysis of the ester had taken

place to form acid **2.122** in 42 % yield, limiting the de-esterification therefore to substrates that contain more than one stabilising unit.



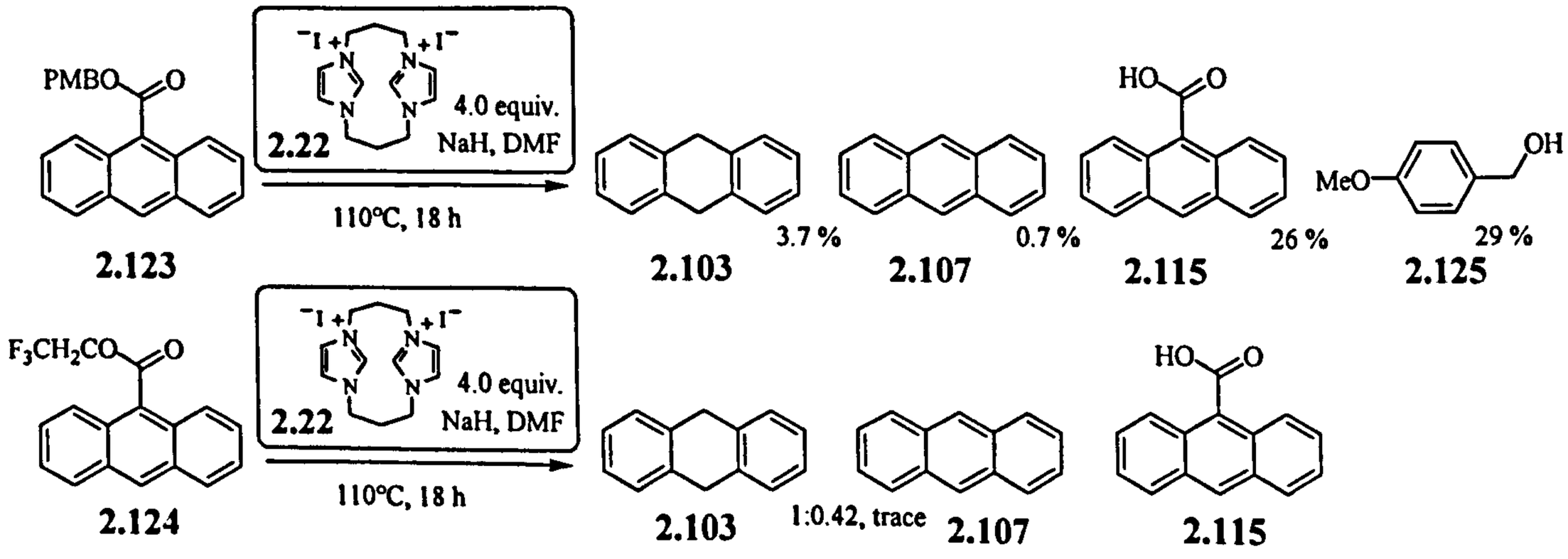
Scheme 2.63

To increase the yield of dihydroanthracene **2.103** formed after reduction of an anthracene ester, the reductions of two more ester substrates were explored. Benzyl ester **2.123** as well as trifluoroethyl ester **2.124** were prepared readily *via* the acid chloride intermediate **2.117** (**Scheme 2.64**). With respect to the anthracene-9-carboxylic acid methyl ester **2.102**, both esters (**2.123** and **2.124** below) feature a slightly more positive carbonyl group, which is hence similarly activated towards attack by a nucleophile and might give rise to conversion to dihydroanthracene **2.103** (see appendix, chapter 9 for structures, LUMOs and partial charge on the carbonyl group). Furthermore, benzyl ester **2.123** should allow the isolation of benzyl alcohol **2.125**, if the alkoxide is displaced in the initial step of the mechanism.



Scheme 2.64

When both esters were tested using 4.0 equivalents of *in situ* generated imidazole donor **2.20**, only very poor conversions to dihydroanthracene were observed (**Scheme 2.65**).

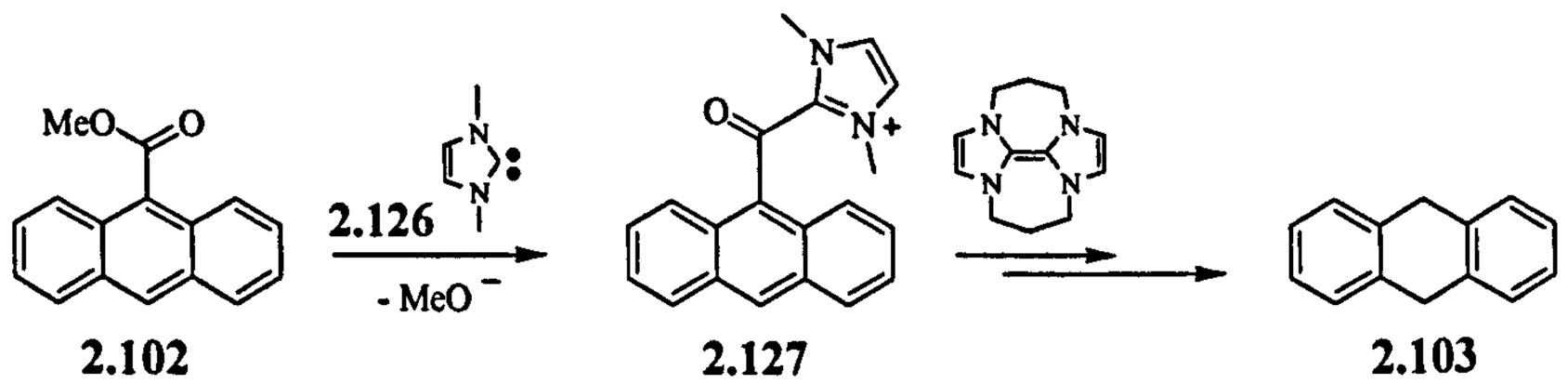


Scheme 2.65

Trifluoroethyl ester **2.124** gave a trace (~1mg) of conversion to an inseparable mixture of dihydroanthracene **2.103** and anthracene **2.107** (1:0.42 ratio), despite its more activated carbonyl group. This result supports the assumption that the increased steric hindrance by the additional CF_3 group might prevent nucleophilic attack by the donor. Acid **2.115** was detected by ^{1}H-NMR and LC-MS analyses also. *Para*-methoxybenzyl ester **2.123** gave slightly more dihydroanthracene, and a large amount of *para*-methoxybenzyl alcohol **2.115** as well as acid **2.115** were isolated. However, in both reactions the mass balance is poor and starting material was not recovered.

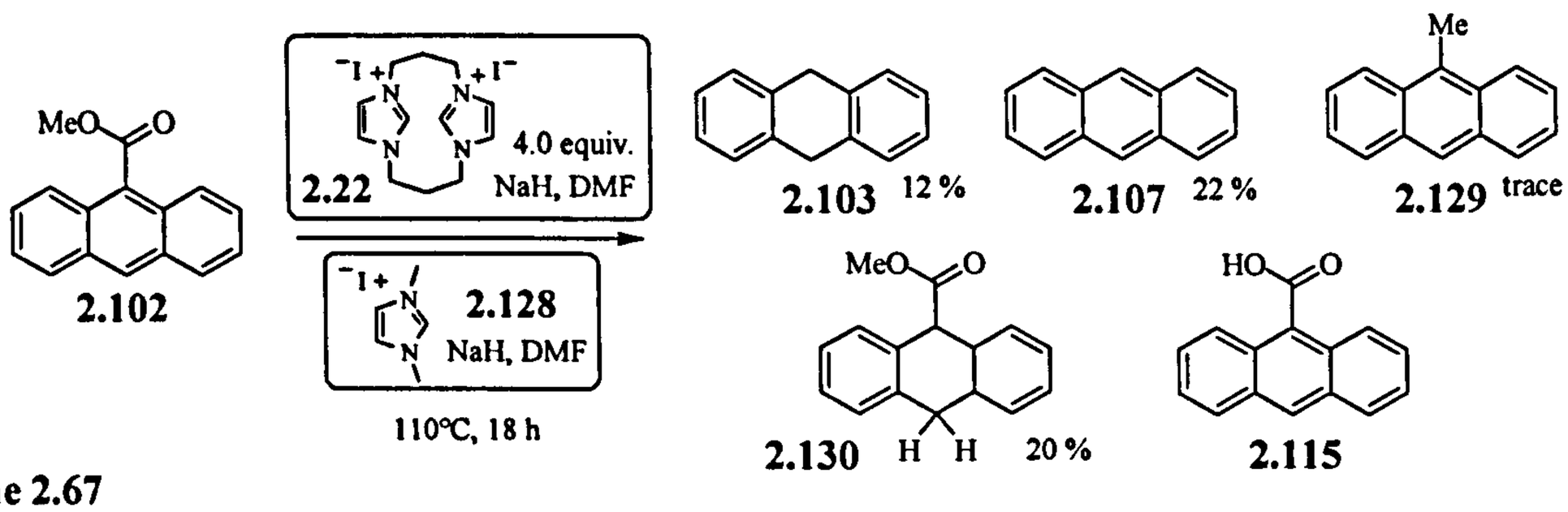
3.4.2 *Anthracene ester reduction in the presence of a carbene*

From the investigations so far, it seems that the steric hindrance of the ester is important for the efficiency of the reductive process towards dihydroanthracene. The crucial step of the mechanism seems to be the first, *i.e.* the attack of the donor molecule on the carbonyl group to form species **2.108**. It was thought that a smaller nucleophile, such as 1,3-dimethyl-1*H*-imidazolium carbene **2.126** below, might attack the ester group with greater efficiency than imidazole donor **2.20** and the intermediate formed (**2.127**) might then be reduced further by the imidazole donor **2.20** (**Scheme 2.66**).



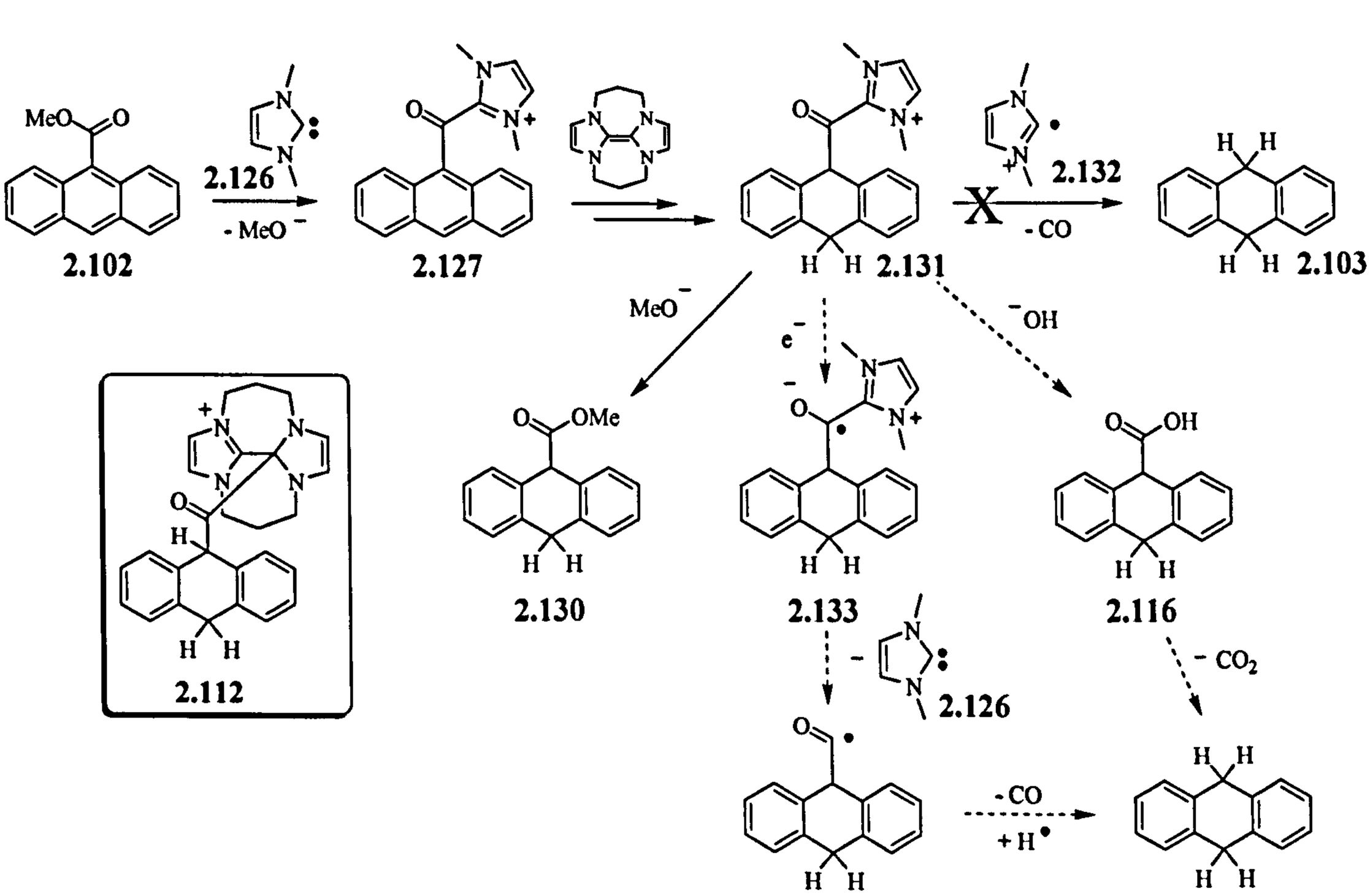
Scheme 2.66

Thus, carbene **2.126** solution was prepared analogously to the *in situ* preparation of donor **2.20**. The slightly yellow carbene solution was transferred *via* cannula to methyl ester **2.102**, resulting in a colour change to dark-green. This mixture was stirred for 5 min at room temperature and then the solution of donor **2.20** was added; the colour remained unchanged. The reaction mixture was heated overnight and after acidic work-up, surprisingly, dihydroanthracene-9-carboxylic acid methyl ester **2.130** was isolated in 20 % yield. Also, anthracene was detected this time as a major component in the inseparable mixture with dihydroanthracene and unexpectedly another compound was seen as a trace (NMR-yields based on the ratio in ^{1}H-NMR spectrum shown in **Scheme 2.67**). ^{1}H-NMR and GC-MS analyses suggest that this trace might be 9-methylanthracene **2.129**. Acid **2.115** was detected only as a small peak in LC-MS at [M-H]: 221 in the negative ion mode.



Scheme 2.67

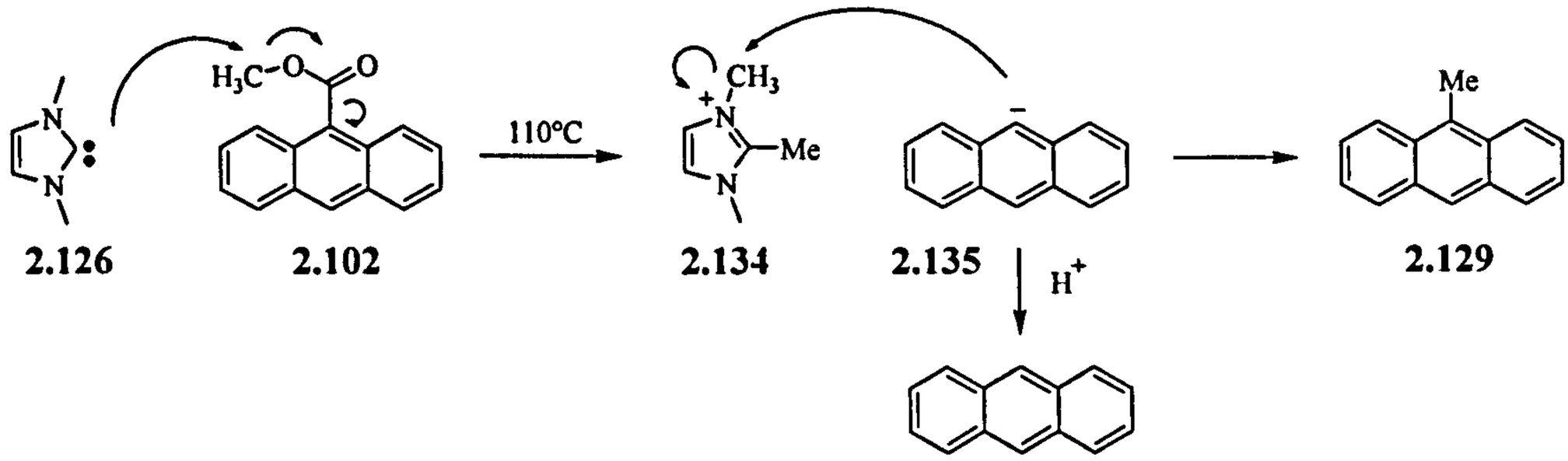
The formation of dihydroanthracene-9-carboxylic acid methyl ester **2.130** was very intriguing. Presumably, the mechanism of its formation is analogous to the one proposed previously in **Scheme 2.56** (compare below in **Scheme 2.68**), however, the last step of thermal breakdown from **2.112** cannot occur analogously from the imidazolium species **2.131**. Also, the species **2.132** does not feature a good radical leaving group either. Thus, there will be a competition between displacement of **2.131** by methoxide or, alternatively, further reduction of **2.131** to **2.133**, which should make a breakdown possible by regeneration of carbene **2.126** and decarbonylation, producing dihydroanthracene **2.103** after H-atom abstraction. If displacement by hydroxide takes place to give dihydroacid **2.116**, dihydroanthracene **2.103** would be formed also, as discussed previously.



Scheme 2.68

The formation of anthracene **2.107** and methylanthracene **2.129** is rather mysterious. Both species might form by a Krapcho-type mechanism, *i.e.* by nucleophilic attack of the carbene onto the methyl group of the ester, followed by decarboxylation at high

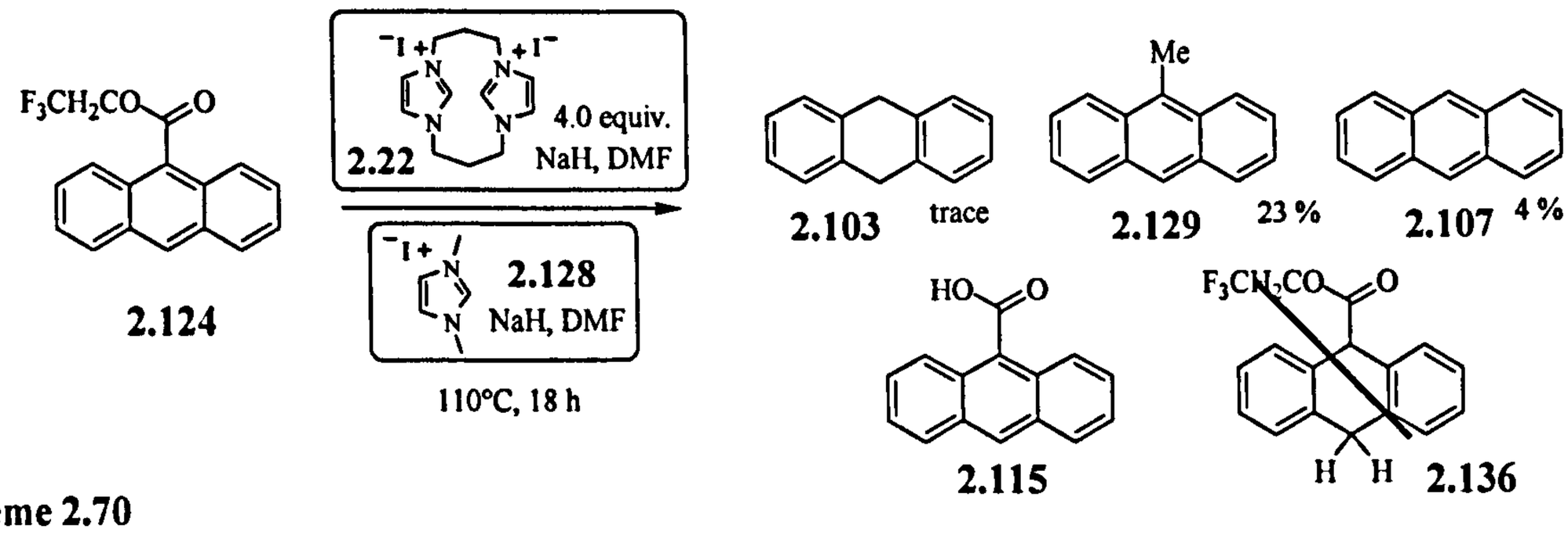
temperature. For instance, demethylation of *N*-methylpyridinium salts by the nucleophile triphenylphosphine is a known process.[144] [This Krapcho mechanism could also occur on **2.130** which would lead to **2.103** directly]. However, anthracene-9-carboxylic acid **2.115** does, under basic conditions, not undergo decarboxylation, making the Krapcho mechanism therefore perhaps to a less likely possibility.



2.126 **2.102** **2.134** **2.135** **2.129** **2.107**

Scheme 2.69

However, the Krapcho proposal would be consistent with the following observation: when trifluoroester **2.124** was reacted with carbene **2.126** (generated from **2.128**) and donor **2.20** analogously to the latter experiment, anthracene **2.107** was detected as well as methylanthracene **2.129** and a small amount of dihydroanthracene **2.103** (**Scheme 2.70**).

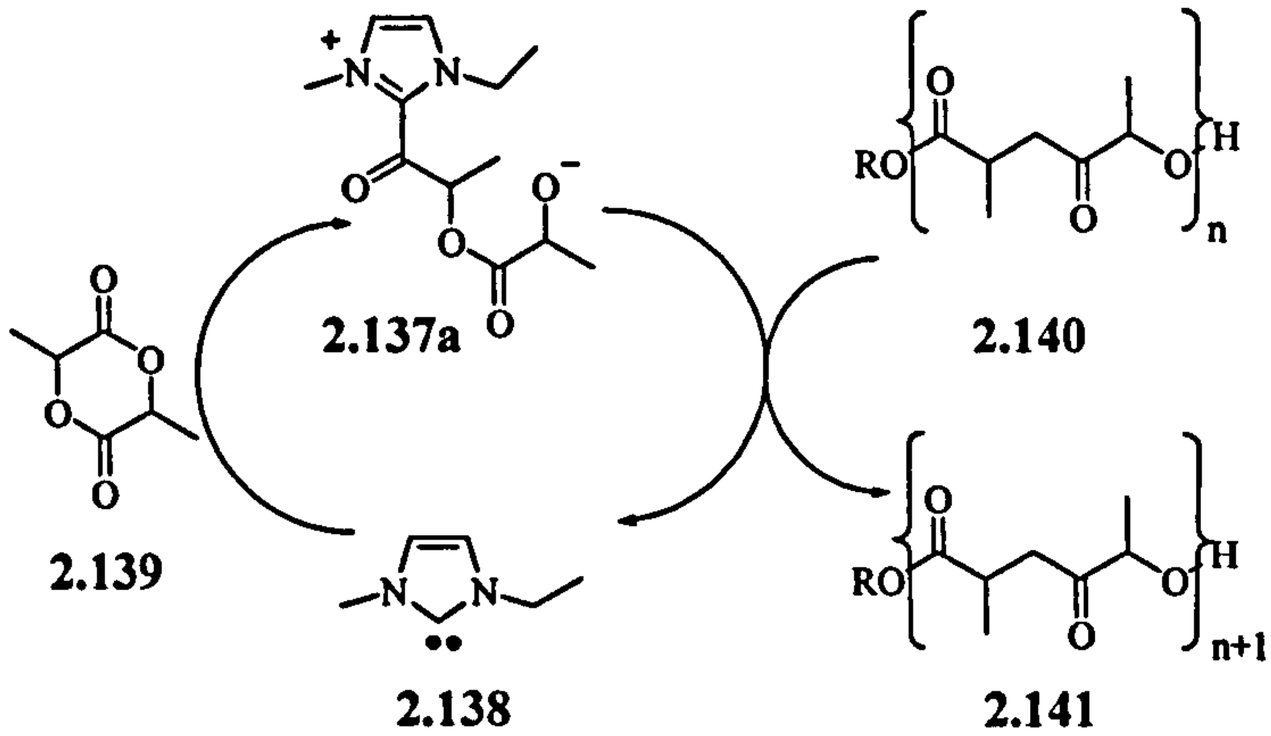


2.124 **2.103** trace **2.129** 23 % **2.107** 4 % **2.115** **2.136**

Scheme 2.70

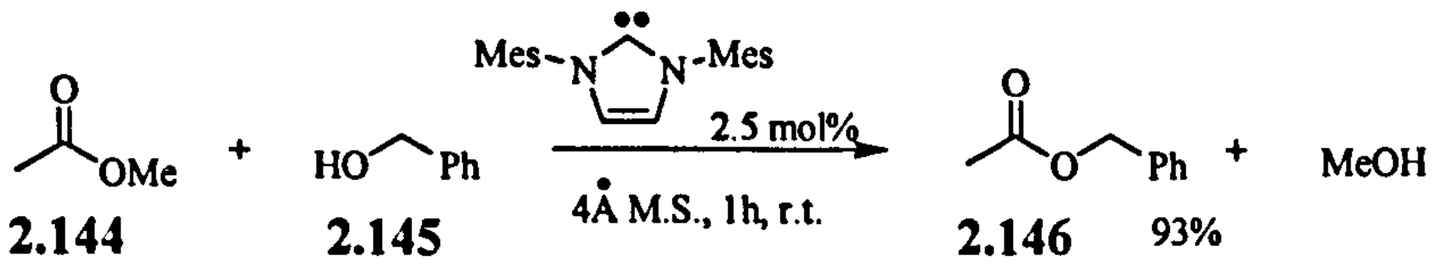
Dihydrotrifluoroester **2.136** was not seen in this reaction, consistent with the trace amount of dihydroanthracene that was observed, which suggests that only a little reductive pathway was undergone. Carbene **2.126** seems to be too large also to attack the sterically more hindered carbonyl group in **2.124** from where further reduction towards **2.136** would occur; thus the Krapcho-type reaction as a competing process is undergone preferentially.

N-heterocyclic carbenes (NHCs) are popular in organic synthesis. Their reactivity has been utilised in many synthetically useful transformations, such as 1,2-addition reactions[145] or ring-opening polymerisation[146] (see **Scheme 2.71** below). In those cases initial attack by the carbene onto the carbonyl moiety has been proposed as a mechanistic rationalisation.



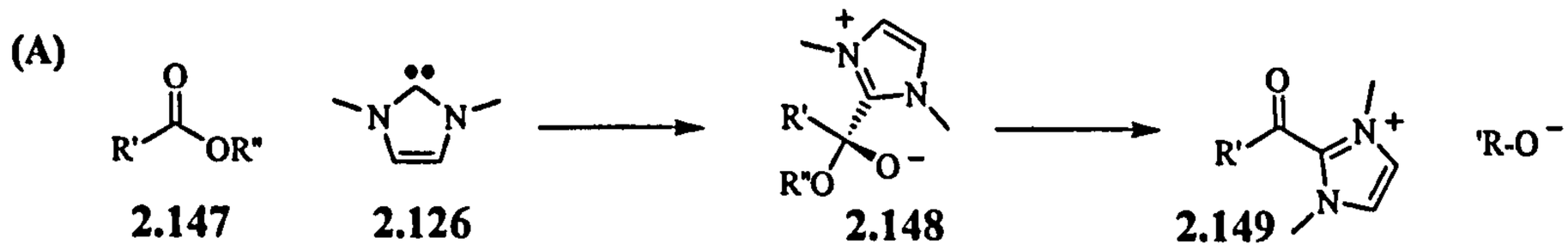
Scheme 2.71: ROP (left) and 1,2 additions (right) catalysed by NHC

Sterically hindered *N*-heterocyclic carbenes are also utilised in transesterification reactions,[147] such as shown in **Scheme 2.72** below. Recently, a computational study was undertaken by Lai *et al.*[148] to reveal the mechanism of carbene-catalysed transesterification and to explain the role of the carbene.



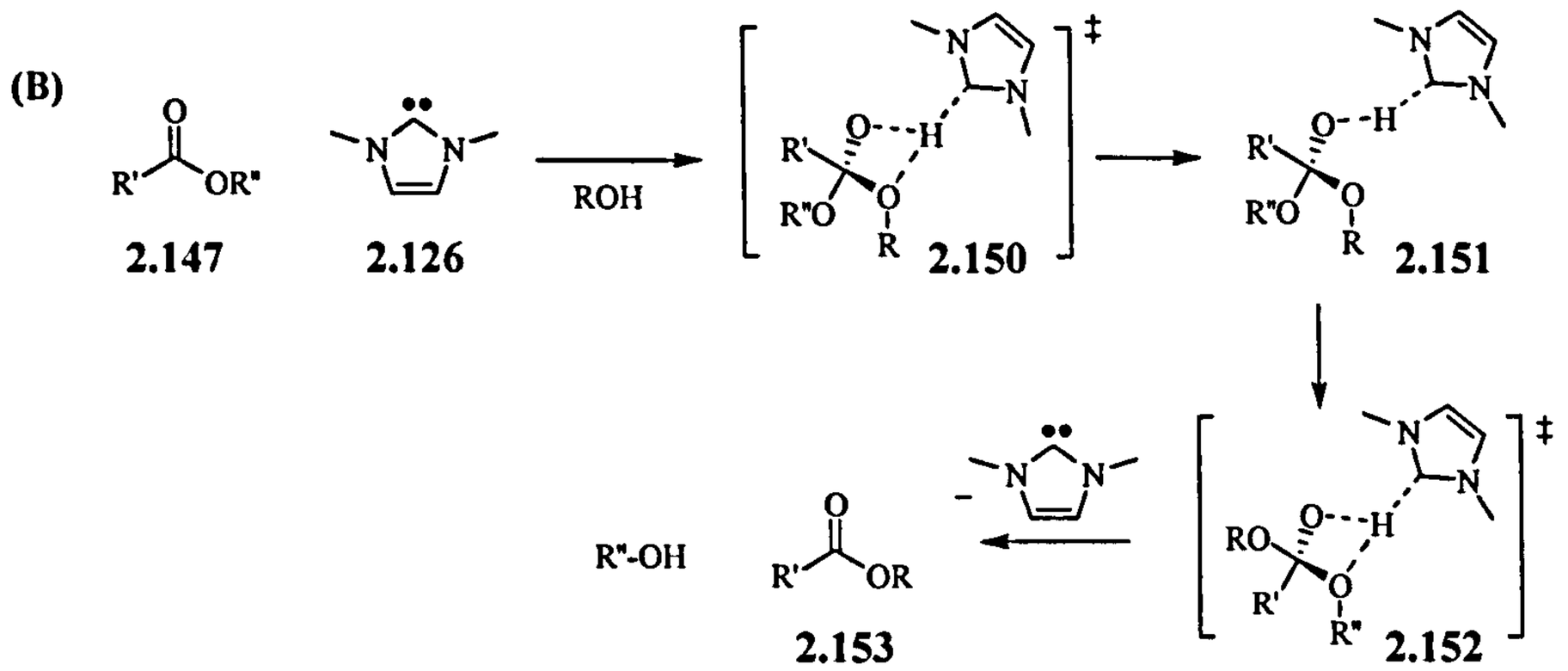
Scheme 2.72

According to this study, carbene attack onto the ester **2.147** to form **2.149** *via* tetrahedral intermediate **2.148** is a quite high energy process (**Scheme 2.73**), making alternative mechanisms more favourable (free energies of 22.5 kcal/mol for **2.148** and 60 kcal/mol for **2.149** relative to **2.147** were quoted for R'=Me and R''=Me).



Scheme 2.73

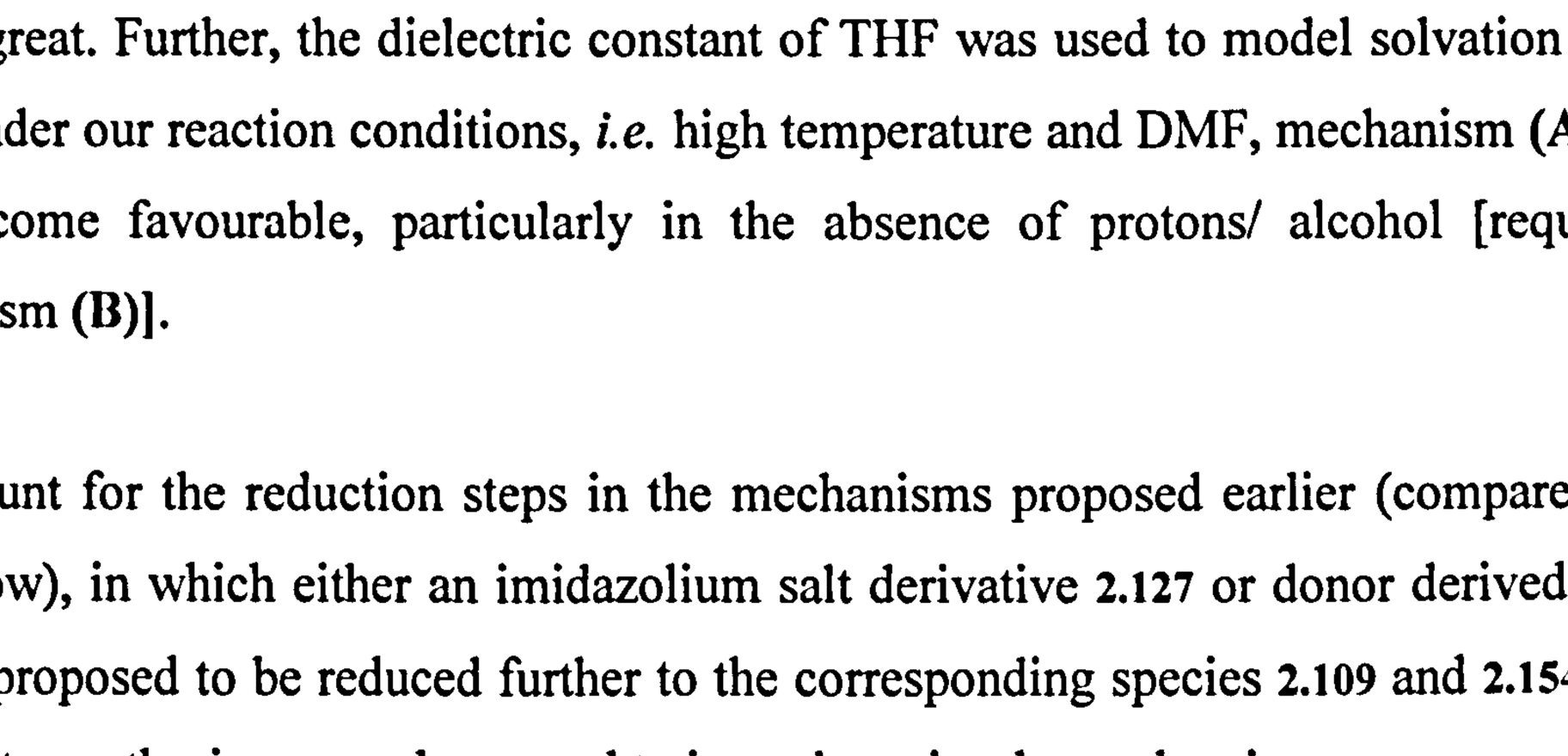
Mechanism **(B)**, illustrated in **Scheme 2.74** was found to be an energetically more favourable reaction path with an activation energy of 27 kcal/mol (the transition states **2.150** and **2.152** have a relative energy of 27 kcal/mol with respect to **2.147** for R'=R''=Me); intermediate **2.151** was computed to have an energy of 16 kcal/mol (relative to **2.147**, with R'=R''=Me) and is therefore of lower energy than the intermediates in mechanism **(A)**. The role of the carbene is described to be as an organocatalyst, assisting the proton transfer from the alcohol to the carbonyl oxygen. The tetrahedral intermediate is then formed and subsequently decomposes to the acylated product.



Scheme 2.74

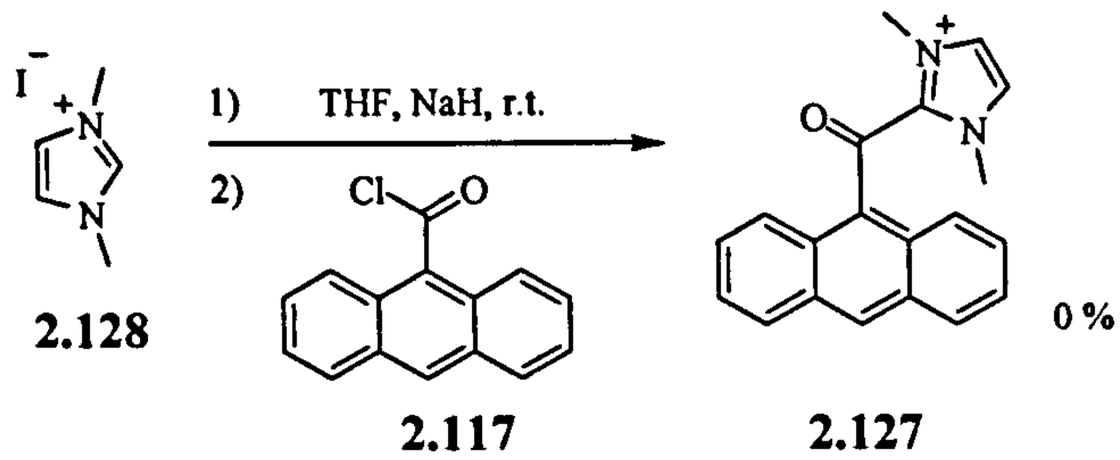
However, the energetic differences between the intermediates in mechanisms **(A)** and **(B)** are not great. Further, the dielectric constant of THF was used to model solvation effects. Thus, under our reaction conditions, *i.e.* high temperature and DMF, mechanism **(A)** could well become favourable, particularly in the absence of protons/ alcohol [required in mechanism **(B)**].

To account for the reduction steps in the mechanisms proposed earlier (compare **Scheme 2.75** below), in which either an imidazolium salt derivative **2.127** or donor derived species **2.108** is proposed to be reduced further to the corresponding species **2.109** and **2.154**, it was decided to synthesise an analogue and to investigate its electrochemistry.



Scheme 2.75

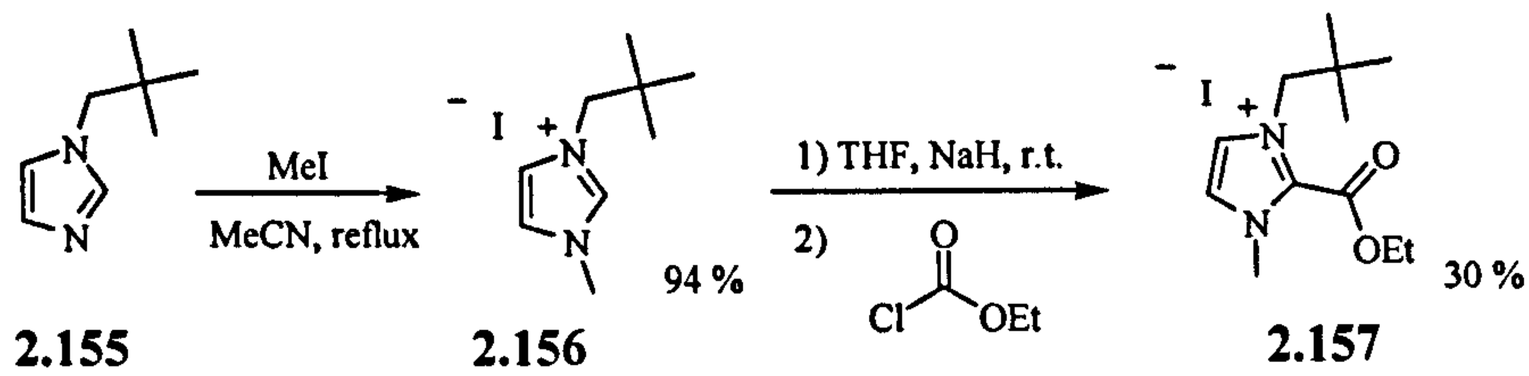
The attempted synthesis of anthracene derivative **2.127** *via* nucleophilic displacement by carbene **2.126** onto anthracene acid chloride **2.117** (**Scheme 2.76**) was not straightforward and led to a complex mixture.



2.128 **2.117** **2.127**

Scheme 2.76

However, synthesis of ester analogue **2.157** under identical conditions was successful **(Scheme 2.77).**



2.155 **2.156** **2.157**

Scheme 2.77

Subsequent cyclic voltammetry of the compound **2.157** gave[115,149] the following diagram **(Figure 2.10).**

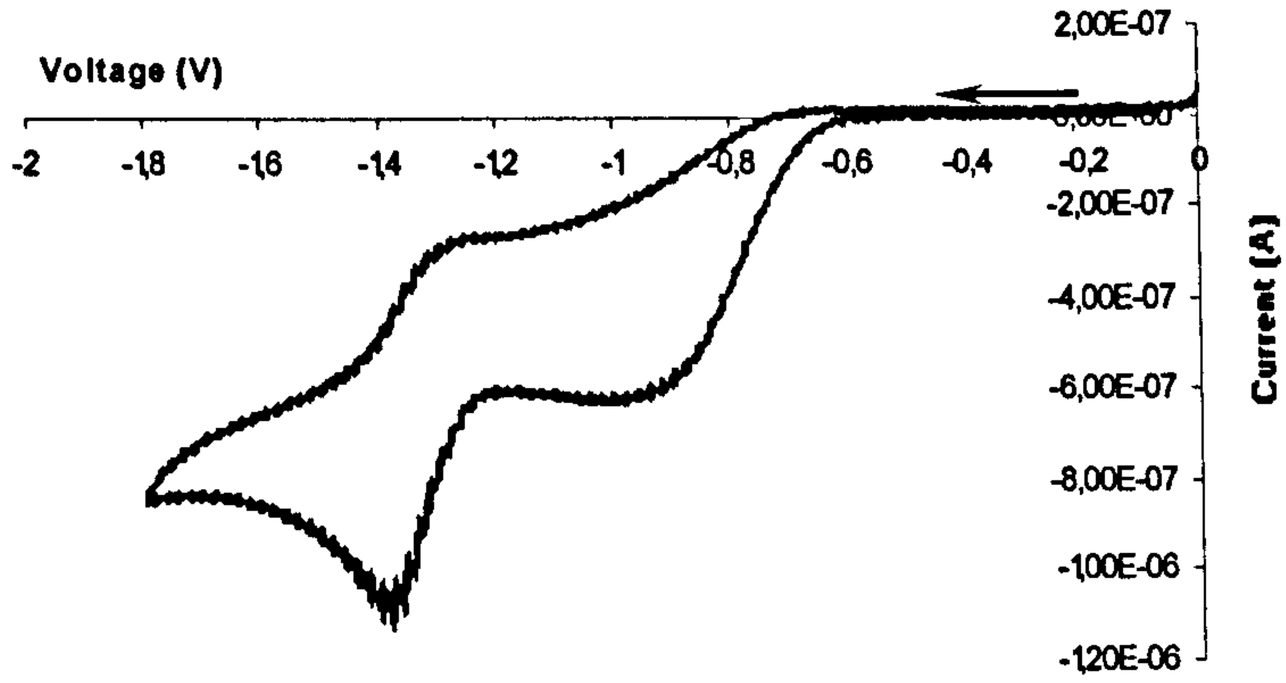
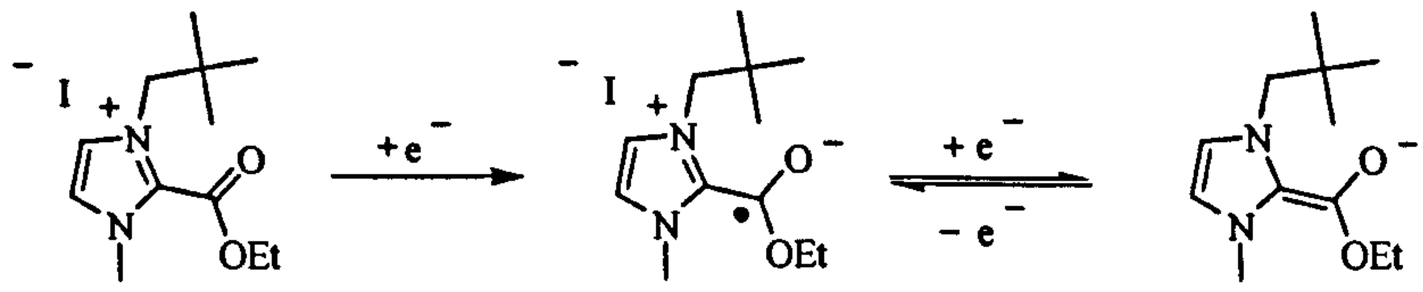


Figure 2.10 Cyclic voltammogram of compound 2.157 *vs.* Ag/AgCl

Starting from the right-hand side of the graph (as indicated by the arrow), imidazolium ester **2.157** (**Scheme 2.78**) is reduced to the corresponding radical, showing an irreversible peak. Further reduction of the radical **2.158** to the anion **2.159** occurs at a peak potential of E_p = -1.40 V. Calibration with ferrocene indicated that the peak height corresponds to a single electron being transferred.



2.157 **2.158** **2.159**

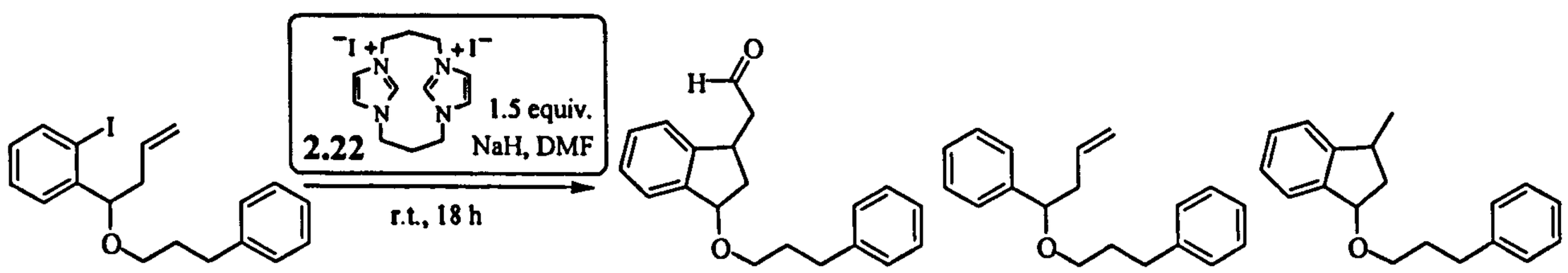
Scheme 2.78

The reduction from species **2.157** to **2.158** occurs in a region more positive than -1.2 V, where donor **2.20** transfers its electrons (peak potential for the oxidation of the donor considered) under identical conditions (*i.e.* in DMF *vs.* Ag/AgCl electrode, identical concentration and temperature). The anthracene-derived species **2.127** should be reduced even more readily, as the alkoxy oxygen in the ester functionality **2.157** is expected to impede electron uptake. This shows that the required reduction step in the carbene mechanism (red mechanism in **Scheme 2.76**) is indeed achievable. Furthermore, with species **2.159** a novel, more powerful, anionic organic electron donor was possibly generated, showing a peak potential of E_p= -1.40 V (for the reduction to species **2.159**). Scope exists for further exploration of the latter electron donor in the future.

Overall, a novel reductive reactivity of imidazole donor **2.20** has been observed in reactions with anthracene esters, and there is scope for optimisation of the reaction to make the reaction path leading to dihydroester **2.130** in the presence of a carbene **2.126** the most favourable.

Formation of aldehydes with imidazole donor 2.20

D. Thomson[150] from our research group carried out investigations on the reductive behaviour of imidazole donor **2.20** on aryl iodides. He investigated whether substrate **2.160** would cyclise upon treatment with donor **2.20** to give **2.163** or would give rise to the reduced product **2.162**, which would normally be expected if aryl anions had formed (**Scheme 2.79**). Upon donor formation using salt **2.22** in DMF and NaH as a base, he exposed the yellow donor solution to the substrate **2.160**. This gave rise to instantaneous reaction at room temperature (based on colour change from yellow to deep red). Upon aqueous work-up, D. Thomson discovered that apart from the reduced compound **2.162**, the aldehyde **2.161** was formed. In further investigations, S.-Z. Zhou from our group found the simple cyclised product **2.163** in trace amounts also.

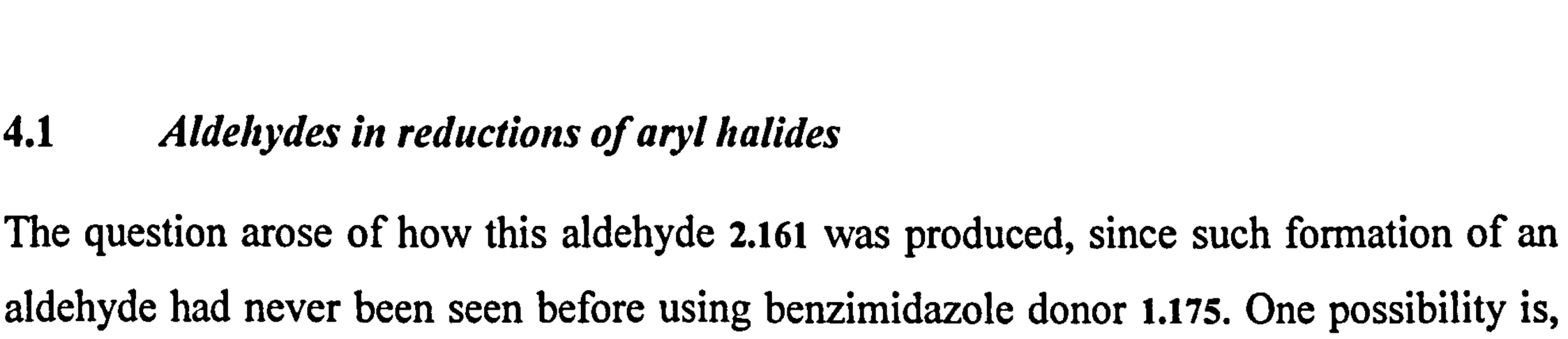


2.160 **2.161** **2.162** **2.163**

Scheme 2.79

4.1 *Aldehydes in reductions of aryl halides*

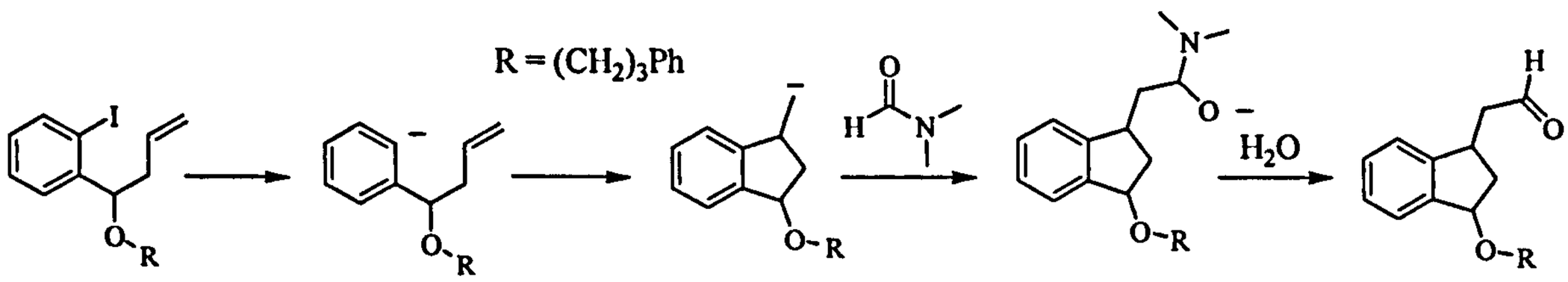
The question arose of how this aldehyde **2.161** was produced, since such formation of an aldehyde had never been seen before using benzimidazole donor **1.175**. One possibility is, that upon exposure of donor **2.20** to substrate **2.160**, the aryl radical **2.164** was formed which then cyclised to give the radical **2.165**. Radical species **2.165** might then have been reduced further by another electron to the aliphatic anion **2.166** which could subsequently attack the solvent, DMF, and give rise to the observed aldehyde **2.161** after work-up (**Scheme 2.80**, Route A).



2.160 **2.164** **2.165** **2.166** **2.167** **2.161**

Scheme 2.80 Route A

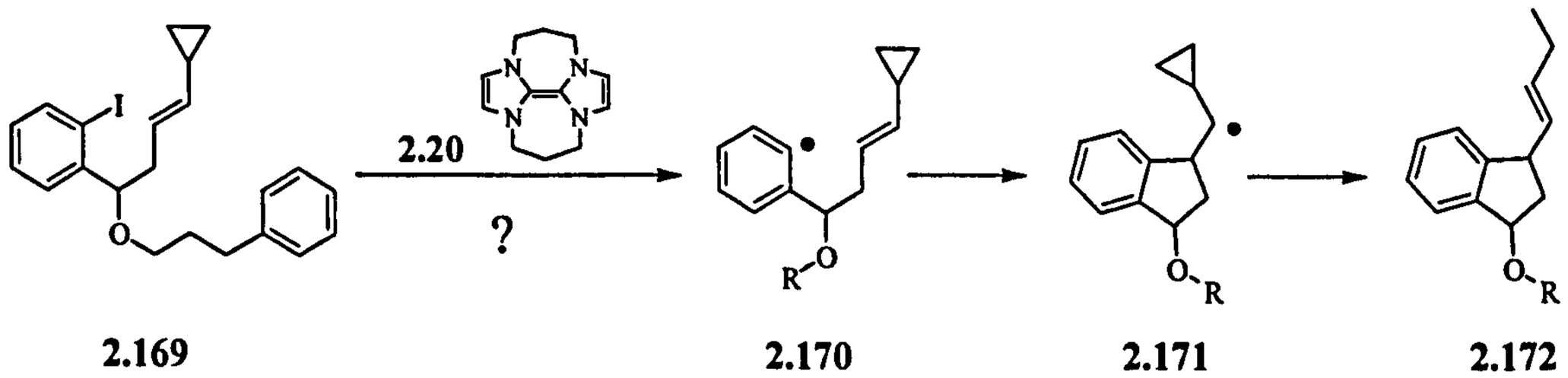
There is literature precedent that aryl anions can undergo cyclisation onto alkenes also. This was seen in electrochemical reductions of aryl iodides and using organometallics.[151] If this was the case here, the aryl anion **2.168** must have been formed. This would then have undergone cyclisation to give anion **2.166** that would attack the solvent (DMF), and upon breakdown in work-up the aldehyde **2.161** would form (**Scheme 2.81**, Route B).



2.160 **2.168** **2.166** **2.167** **2.161**

Scheme 2.81 Route B

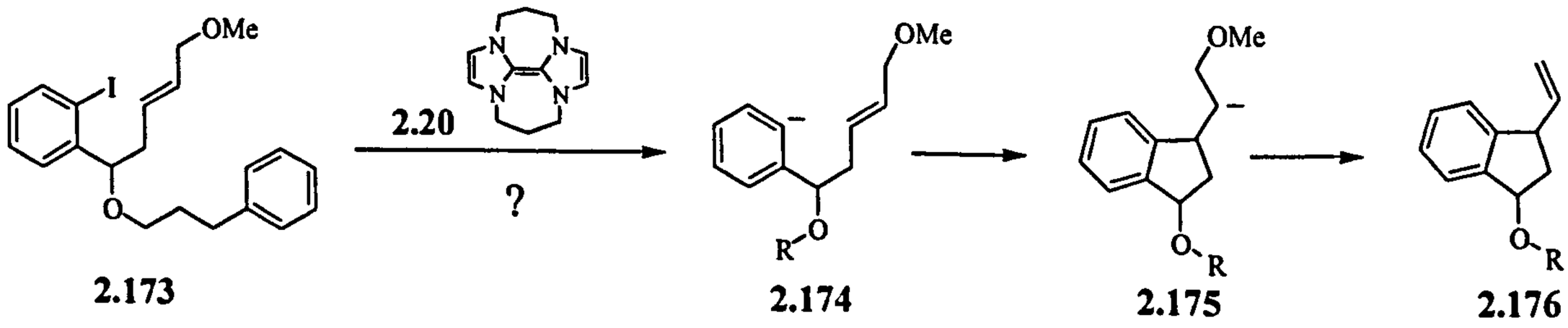
To test for route A, it was decided to prepare cyclopropane substrate **2.169**. The cyclopropane is a very strained ring that is easily opened, if a radical is placed *alpha* to it. It has been utilised as a radical probe by Oshima *et al.* who investigated whether aryl radical intermediates are present in the reactions of tributylmanganate.[152] Thus, if the aryl radical **2.170** gave rise to the observed cyclisation, then the cyclopropane should undergo very fast ring-opening [before any further reduction of the radical to the aliphatic anion occurred] to give rise to compound **2.172** after H-atom abstraction (**Scheme 2.82**).



2.169 **2.170** **2.171** **2.172**

Scheme 2.82

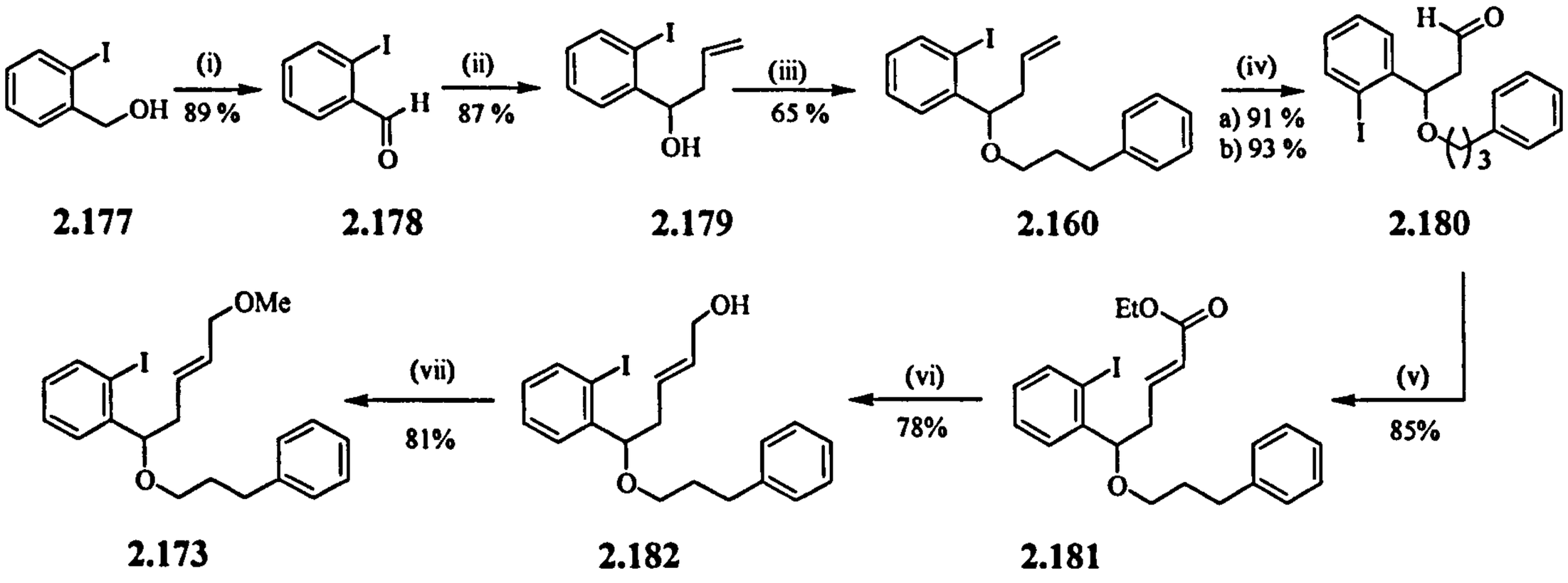
On the other hand, methoxy compound **2.173**, shown below, would be a suitable probe to test for anionic cyclisation (Route B). If the aryl anion **2.174** was produced and subsequently cyclised, the methoxy group should be eliminated and product **2.176** would be observed (**Scheme 2.83**).



2.173 **2.174** **2.175** **2.176**

Scheme 2.83

The synthesis of methoxy substrate **2.173** was accomplished successfully in eight efficient steps *via* the route shown in **Scheme 2.84.** Iodobenzyl alcohol **2.177** was oxidised under Swern conditions, followed by Grignard attack of allylmagnesium bromide onto the aldehyde **2.178.** Nucleophilic substitution using 3-phenylpropanol and sodium hydride in DMF gave aryl iodide substrate **2.160,** following D. Thomson's previous synthesis[150] of this compound.

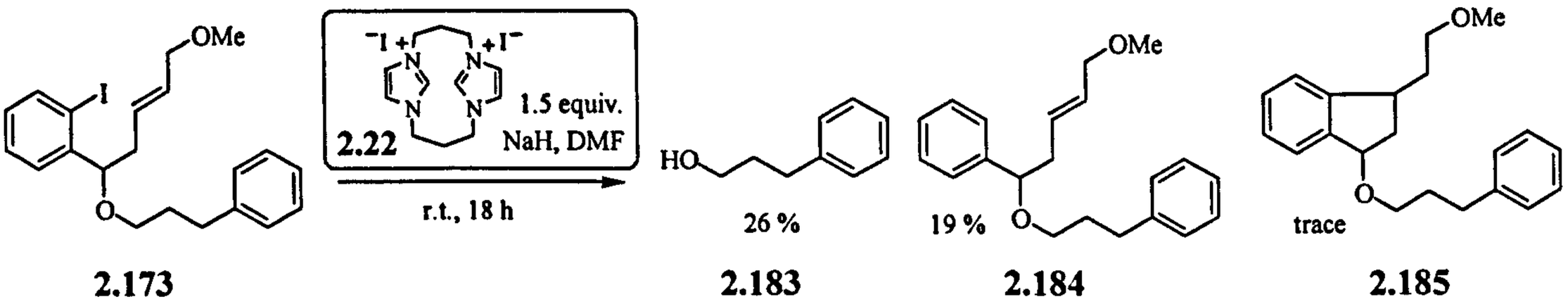


***Reagents and conditions*: (i)** oxalyl chloride (2.0 equiv.), DMSO (3.0 equiv.), NEt_3 (5.5 equiv.), DCM, -78°C to r.t., 1 h; **(ii)** allylMgBr (1.2 equiv.), THF, 0°C to r.t., 18 h; **(iii)** NaH (1.2 equiv.), 1-bromo-3-phenylpropane (1.5 equiv.), DMF, 0°C to r.t., 18 h; **(iv)** a) OsO_4/ $NaIO_4$ or b) O_3/Me_2S; **(v)** $C_{22}H_{21}O_2P$ (1.1 equiv.), DCM, reflux; **(vi)** DIBAL-hexane (2.3 equiv.), hexane, -78°C, then r.t.; **(vii)** MeI (1.1 equiv.), NaH (1.1 equiv.), DMF, r.t., 18 h.

Scheme 2.84

The double-bond in compound **2.160** was then oxidatively cleaved using osmium tetroxide and alternatively, by ozonolysis; both routes were highly efficient in generating aldehyde **2.180.** This aldehyde was then reacted in a Wittig reaction with ethyl (triphenylphosphoranyliden)acetate to give conjugated ester **2.181.** Complete reduction to the allyl alcohol **2.182** was accomplished using diisobutylaluminium hydride (DIBAL) in hexane. After methylation with iodomethane in the final step, methoxy test substrate **2.173** was satisfyingly made.

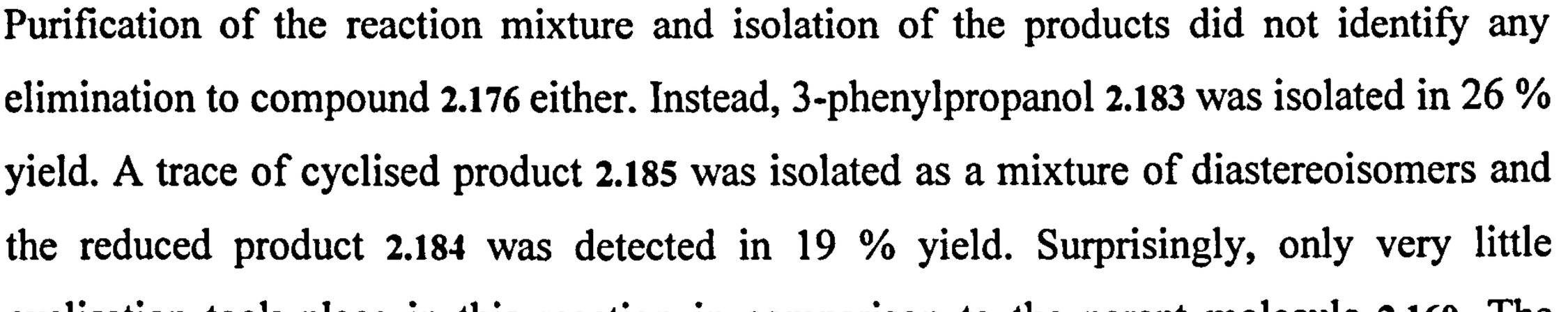
Having substrate **2.173** in hand, the molecule was tested for the elimination of the methoxy group. Thus, imidazole donor **2.20** was prepared in the usual way in a centrifuge tube using sodium hydride as a base and anhydrous DMF as the solvent. After centrifugation, the supernatant yellow liquid was transferred *via* cannula to the test substrate **2.173** at room temperature. This resulted in instantaneous colour change to deep red. After stirring for 18 h at room temperature, followed by aqueous work-up and purification, the following products were isolated (shown in **Scheme 2.85**).



2.173 **2.183** **2.184** **2.185**

Scheme 2.85

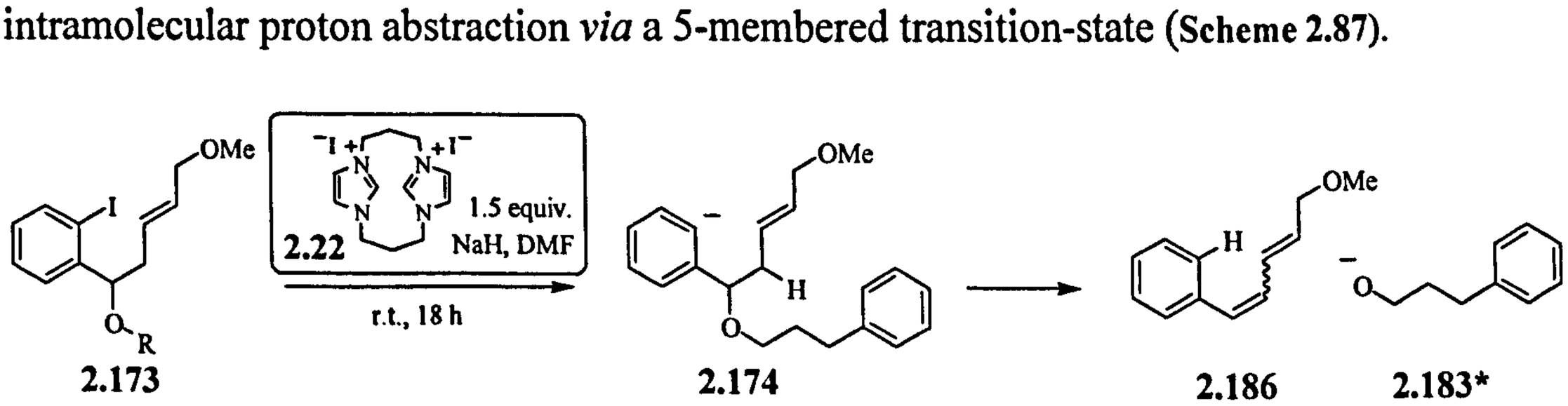
However, elimination of the methoxy group was not observed. The ^{1}H-NMR spectrum of the crude mixture did not show any signal near δ 6.0, characteristic of a terminal alkene. Purification of the reaction mixture and isolation of the products did not identify any elimination to compound **2.176** either. Instead, 3-phenylpropanol **2.183** was isolated in 26 % yield. A trace of cyclised product **2.185** was isolated as a mixture of diastereoisomers and the reduced product **2.184** was detected in 19 % yield. Surprisingly, only very little cyclisation took place in this reaction in comparison to the parent molecule **2.160**. The formation of 3-phenylpropanol **2.183** is intriguing also, and might be rationalised as follows: donor **2.20** was used in 1.5 equivalents and the excess donor could have acted as a base (**Scheme 2.86**). Removal of the proton indicated in bold in **Scheme 2.86** would give rise to a stabilised product **2.186** that bears an extended conjugated system. However, **2.186** was not observed.



2.173 **2.184** **2.186** **2.187** **2.183***

Scheme 2.86

Alternatively, an aryl anion might have formed upon reduction of the aryl iodide by the donor **2.20**. This might have caused elimination of 3-phenylpropanoxide by an intramolecular proton abstraction *via* a 5-membered transition-state (**Scheme 2.87**).

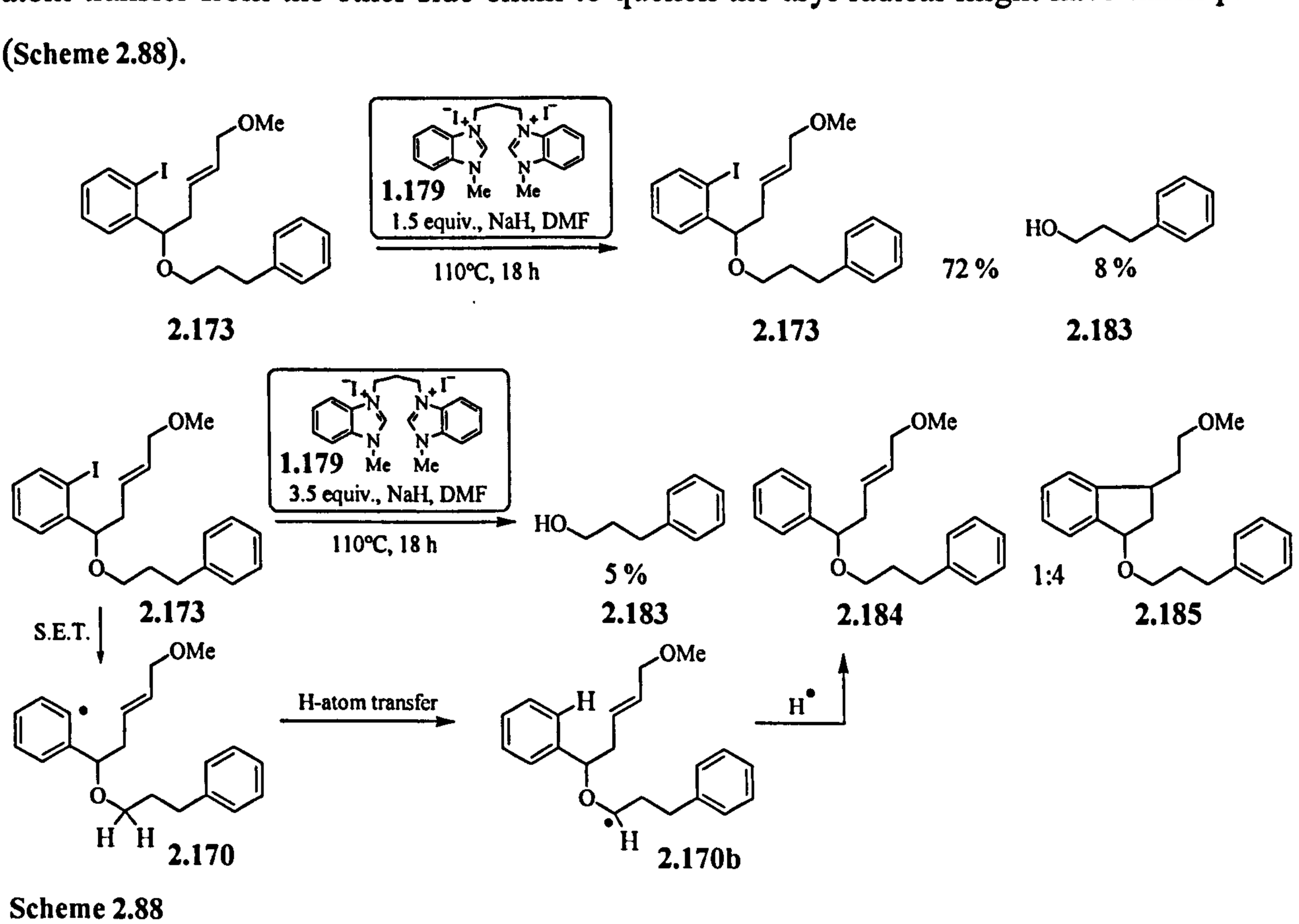


2.173 **2.174** **2.186** **2.183***

Scheme 2.87

To investigate this further, it was decided to test methoxy substrate **2.173** with benzimidazole donor **1.175**. Donor **1.175** is known to reduce aryl iodides highly efficiently

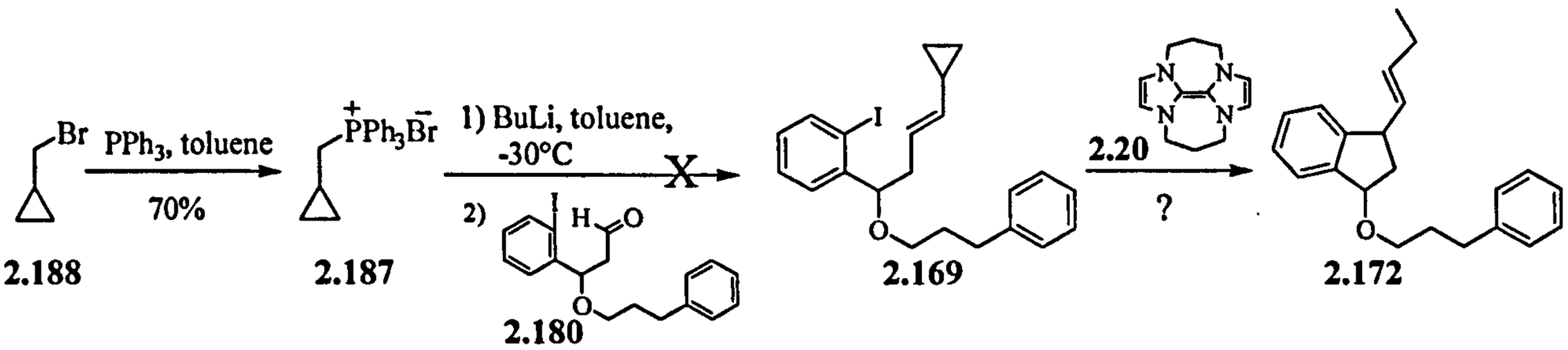
to the corresponding aryl radicals. Under 'pure radical conditions' the formation of 3-phenylpropanol **2.183** would then not be expected, if it was really arising from intramolecular deprotonation by an aryl anion. Benzimidazole donor **1.175** was prepared identically to imidazole donor **2.20** using NaH in DMF and the centrifugation technique. Reaction of methoxy substrate **2.173** was carried out with 1.5 equivalents of donor **1.175** and heating of the mixture overnight (**Scheme 2.88**). However, the C-I bond was not reduced under these conditions; only starting material was recovered (72 %) along with phenylpropanol (8 %). This indicates that the formation of the alcohol **2.183** is induced by the basic donor. Also, the more negative reduction potential of the substrate **2.173** in comparison to previously studied *ortho*-NMs-aryl iodides[94] is highlighted again. This can be ascribed to the less electron-withdrawing *ortho*-carbon side chain. Increase to 3.5 equivalents of donor **1.175** under otherwise identical conditions (dilution, temperature, reaction time) forced the reaction to go to completion. 3-Phenylpropanol **2.183** was again isolated (5 %) along with reduced compound **2.184** and cyclised product **2.185** (in a 1:4 mixture, 81 % overall yield). The detection of reduced compound **2.184** under pure radical conditions could suggest that the radical cyclisation is rather slow[153]. On the other hand, H-atom transfer from the ether side chain to quench the aryl radical might have taken place **(Scheme 2.88).**



Scheme 2.88

Synthesis of cyclopropane substrate **2.169** was attempted by Wittig reaction of the previously made aldehyde **2.180** with phosphonium salt **2.187**. This reaction afforded an

inseparable mixture of compounds and **2.169** could not be obtained. However, since methoxy substrate **2.173** did not cyclise efficiently in the previously discussed experiments, synthesis of substrate **2.169** has become unnecessary anyway.



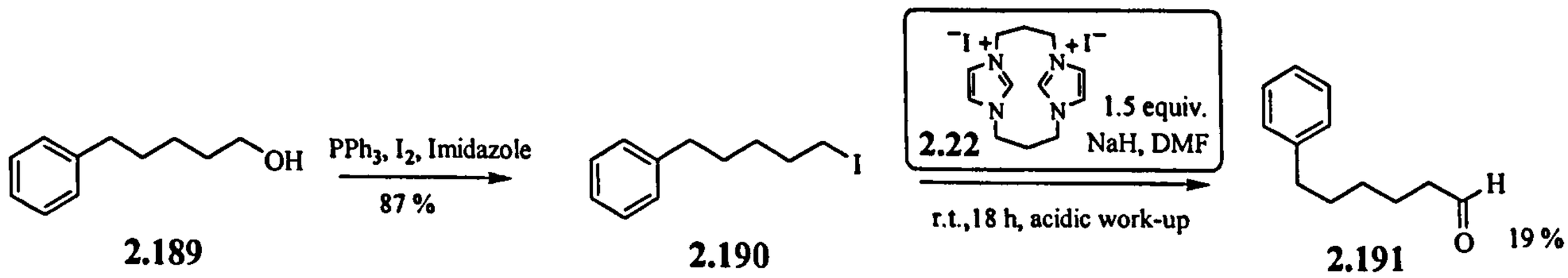
2.188 **2.187** **2.180** **2.169** **2.172**

Scheme 2.89

4.2 *Aldehydes in reductions of alkyl halides*

This study was rather inconclusive. Therefore, it was decided to explore the formation of the aldehyde in an alternative approach. If an alkyl anion (formed by anionic cyclisation [route B] or by further reduction of the cyclised radical [route A]) was responsible for the aldehyde formation, then it is worthwhile to test for the reductive behaviour of donor **2.20** on alkyl halides. If an aldehyde was not formed upon reduction of an alkyl halide, then this would suggest that donor **2.20** is not capable of reducing alkyl radicals to the alkyl anion and one mechanistic possibility (route A) could be excluded.

Iodomethane is reported to have a reduction potential of $E''_{1/2}$ = -1.38 V (*vs.* SCE)[154] which is less negative than the reduction potential of aryl iodides and thus the compound should be readily reducible [for comparison, iodobenzene is quoted to have a potential of $E''_{1/2}$ = -1.62V (*vs.* SCE)].[155] Thus, 5-phenyliodopentane **2.190** was synthesised by conversion of 5-phenylpentanol to the corresponding iodide using triphenylphosphine, imidazole and iodine. It was then tested in a reaction with donor **2.20**: 1.5 equiv. of donor were used, formed in DMF using NaH and the centrifugation technique and reacted with the substrate at room temperature for 18 h (**Scheme 2.90**).

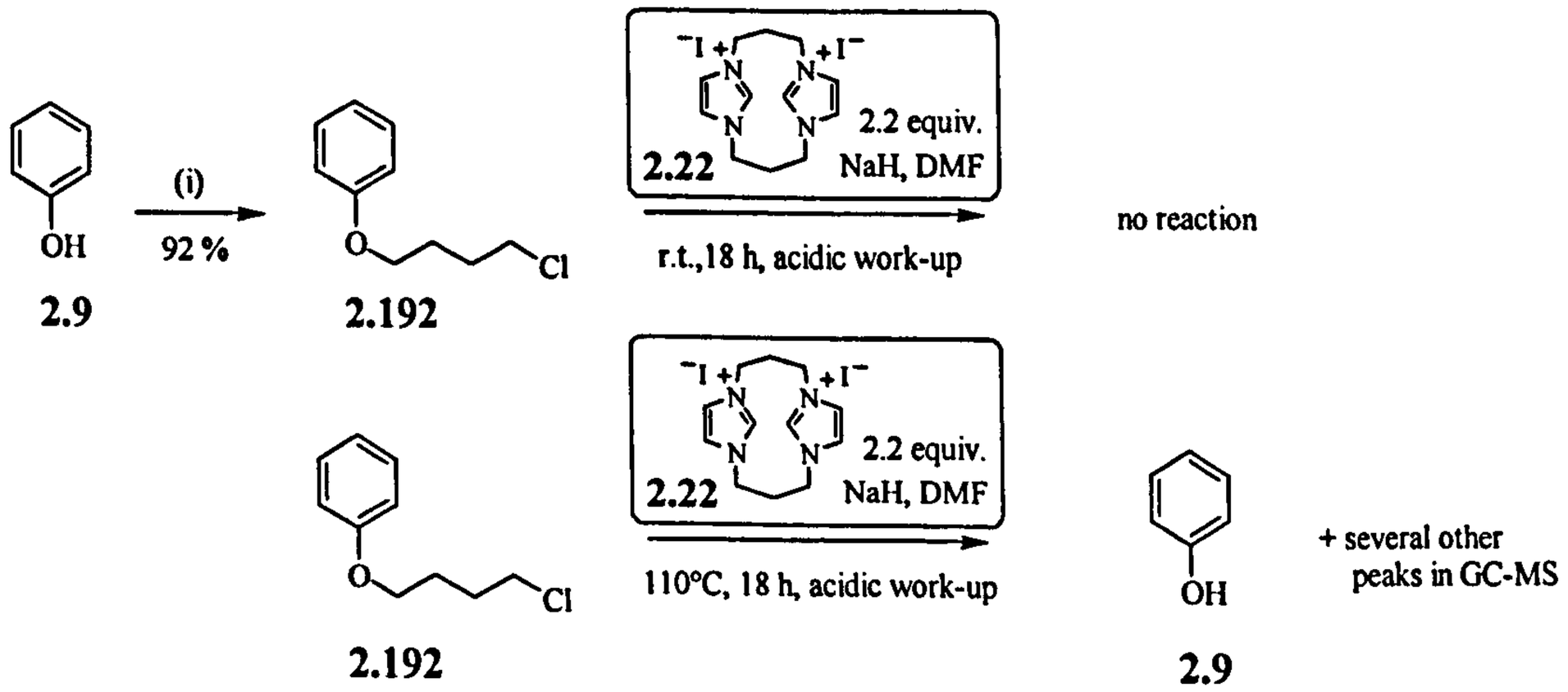


2.189 **2.190** **2.191**

Scheme 2.90

The colour did not change instantaneously, however, after several hours a change from yellow to deep red had occurred. After aqueous work-up a ^{1}H-NMR spectrum of the crude mixture was taken and a triplet signal at δ 9.85 was seen that would be characteristic for an

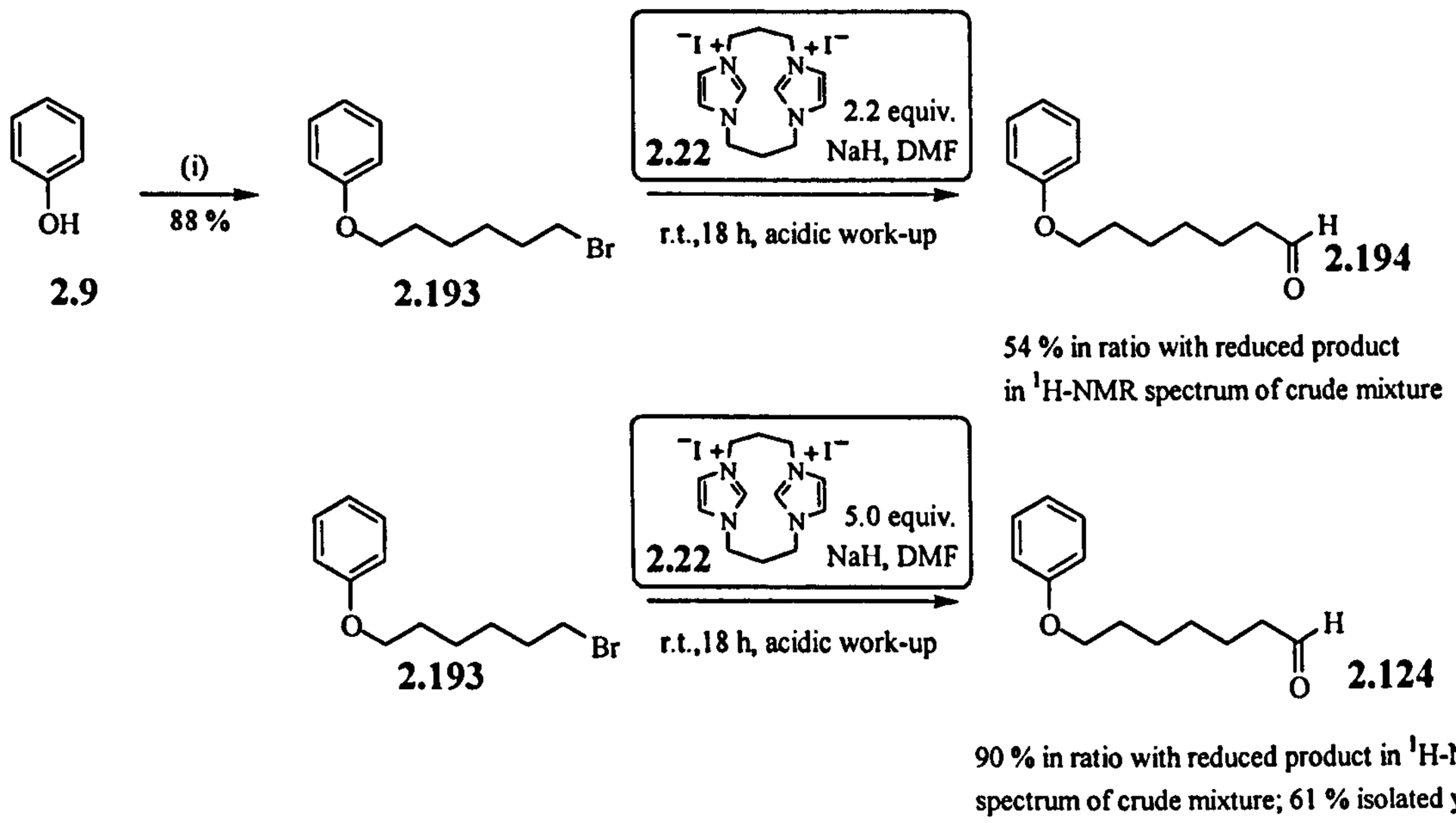
aliphatic aldehyde. However, this signal was very small, corresponding only to a trace amount of the aldehyde **2.191**. It was decided to repeat the reaction under identical conditions and to acidify in work-up this time, in order to aid the breakdown of the intermediate that possibly arises upon attack of the alkyl anion onto DMF. Upon addition of 2 N hydrochloric acid (20 ml), the reaction mixture heated up, changed its colour from red to pale yellow and bubbles were observed. Subsequent ^{1}H-NMR analysis of the crude mixture showed the aliphatic aldehyde **2.191** in considerable amount in a mixture with the simple reduced compound. The aldehyde **2.191** was isolated in 19 % yield after column chromatography on silica gel. This was very exciting as it suggested that donor **2.20** was possibly capable of producing alkyl anions by reducing an alkyl radical further. It was questioned whether it would be possible to reduce alkyl bromides and alkyl chlorides also. This would be synthetically advantageous since the starting materials bear greater stability in comparison to alkyl iodides. Alkyl bromides have a reduction potential of $E''_{1/2}$ = -1.77 V [*vs.* SCE (MeCN)][154] and $E''_{1/2}$ = -1.94 V [*vs.* SCE (DMF)][154] and should thus be in the range of the power of donor **2.20**. Alkyl chlorides have a more negative potential, reflecting the greater carbon-halogen bond strength. Both alkyl bromide **2.193** and alkyl chloride **2.192** were prepared by Mitsunobu reaction and then tested using slightly greater donor (2.2 equiv.) concentrations in order to accommodate the more negative potentials with greater reductive power (**Scheme 2.90** and **Scheme 2.91**). The alkyl chloride did not show any reaction at room temperature after 18 h [as judged by ^{1}H- NMR analysis of the crude mixture after acidic work-up]. Hence, the reaction was repeated and this time heat was applied. This resulted in a very complex mixture that was analysed by GC-MS. Among more than 20 peaks in GC-MS, phenol **2.9** was identified.



***Reagents and conditions*: (i)** 4-chlorobutanol, PPh_3, DIAD, THF, 0°C to r.t.

Scheme 2.91

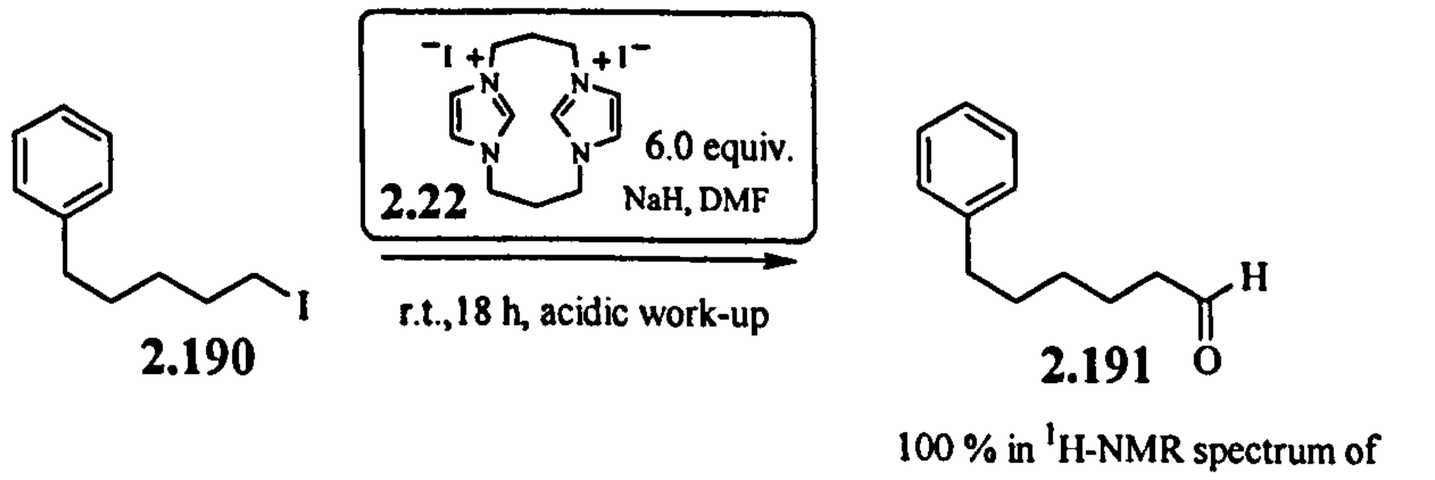
The alkyl bromide **2.193** showed much more promise. After 18 h of reaction at room temperature the reaction mixture had turned deep red and upon acidic work-up, a ^{1}H-NMR spectroscopic analysis was done. The aldehyde signal was seen, thus bromide **2.193** reacted to the aldehyde **2.194** also, just like the alkyl iodide (**Scheme 2.92**). Furthermore, its proportion increased to 54 %, suggesting that more reducing power is required to give a greater amount of aldehyde. Therefore, bromide **2.193** was reacted in another experiment using 5 equiv. of donor **2.20** under otherwise identical conditions (same solvent amount, temperature, reaction time) and now an increase to 90 % in ratio was seen. After further purification, aldehyde **2.194** was isolated in 61 % yield.



***Reagents and conditions*: (i)** 6-bromohexanol, PPh_3, DIAD, THF, 0°C to r.t.

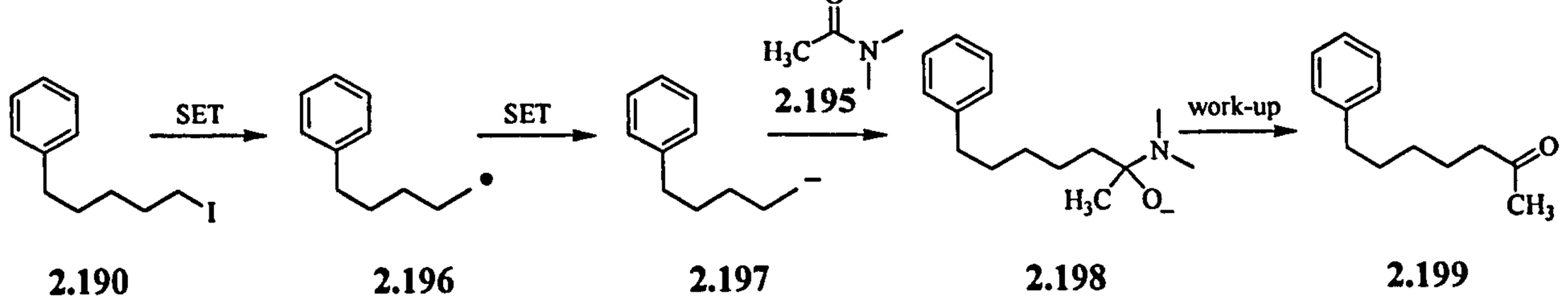
Scheme 2.92

It was felt that even further increase of donor concentration might give rise to complete aldehyde formation. Thus, iodide **2.120** was exposed to 6.0 equiv. of donor for 18 h at room temperature. ^{1}H-NMR spectroscopic analysis of the crude mixture after acidic work-up showed the aldehyde **2.191** this time as the sole product.



Scheme 2.93

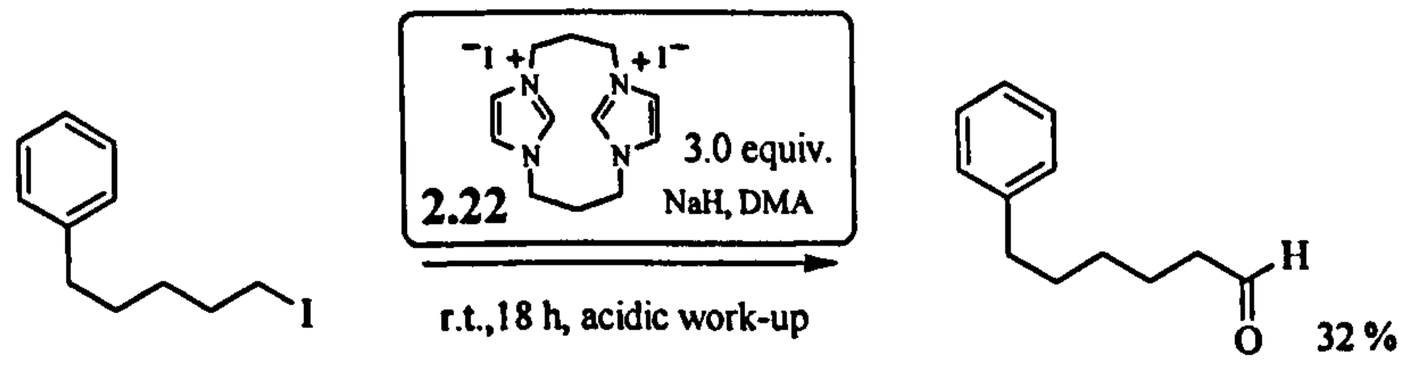
However, after column chromatography, the aldehyde was isolated in 50 % yield only. This might be due to the instability of aliphatic aldehydes on silica gel, leading to loss of material. A more stable product might give rise to better yields. Ketones are far more stable than aldehydes and should be formed, if the solvent was changed to dimethylacetamide **2.195**. Formation of the alkyl anion **2.197** would then lead to attack on dimethylacetamide which upon work-up would afford ketone **2.199 (Scheme 2.94)**.



2.190 **2.196** **2.197** **2.198** **2.199**

Scheme 2.94

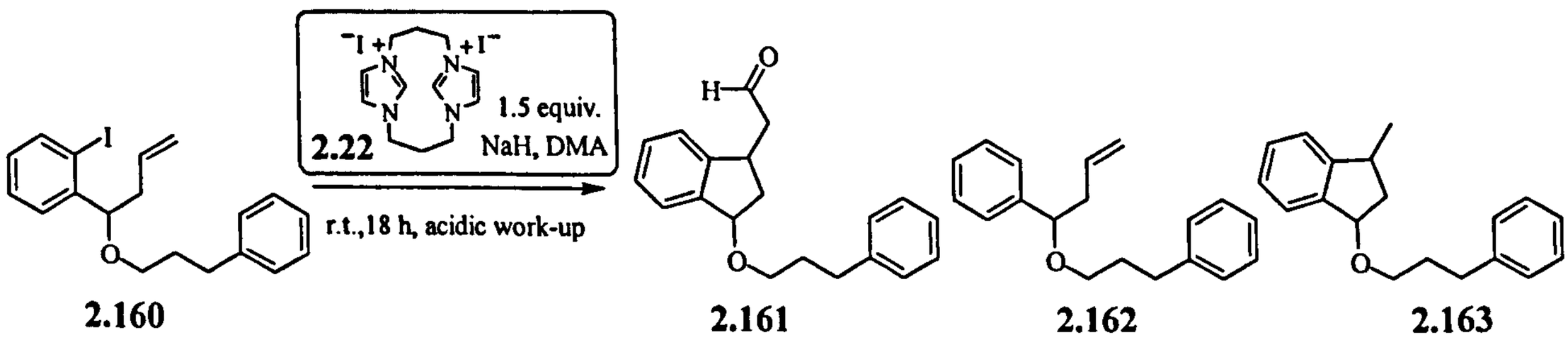
Thus donor **2.20** was prepared in freshly distilled and deoxygenated dimethylacetamide using sodium hydride as a base. After centrifugation, the supernatant yellow liquid was transferred to alkyl iodide **2.190** and the mixture was stirred for 18 h at room temperature. A deep red solution resulted that was subjected to acidic work-up. A ^{1}H-NMR spectrum of the crude mixture, surprisingly, showed the characteristic aldehyde signal at δ 9.8 again. And indeed, aldehyde **2.191** was isolated in 32 % yield after further purification by column chromatography, which is identical to the previous experiments in DMF.



2.190 **2.191**

Scheme 2.95

This result was highly unexpected and shows that the product formation is independent of the solvent used. This means that the aldehydes cannot arise from alkyl anions attacking the solvent. D. Thomson's substrate that gave rise to aldehyde **2.161** was subsequently tested in dimethylacetamide also, to investigate whether the situation is identical.

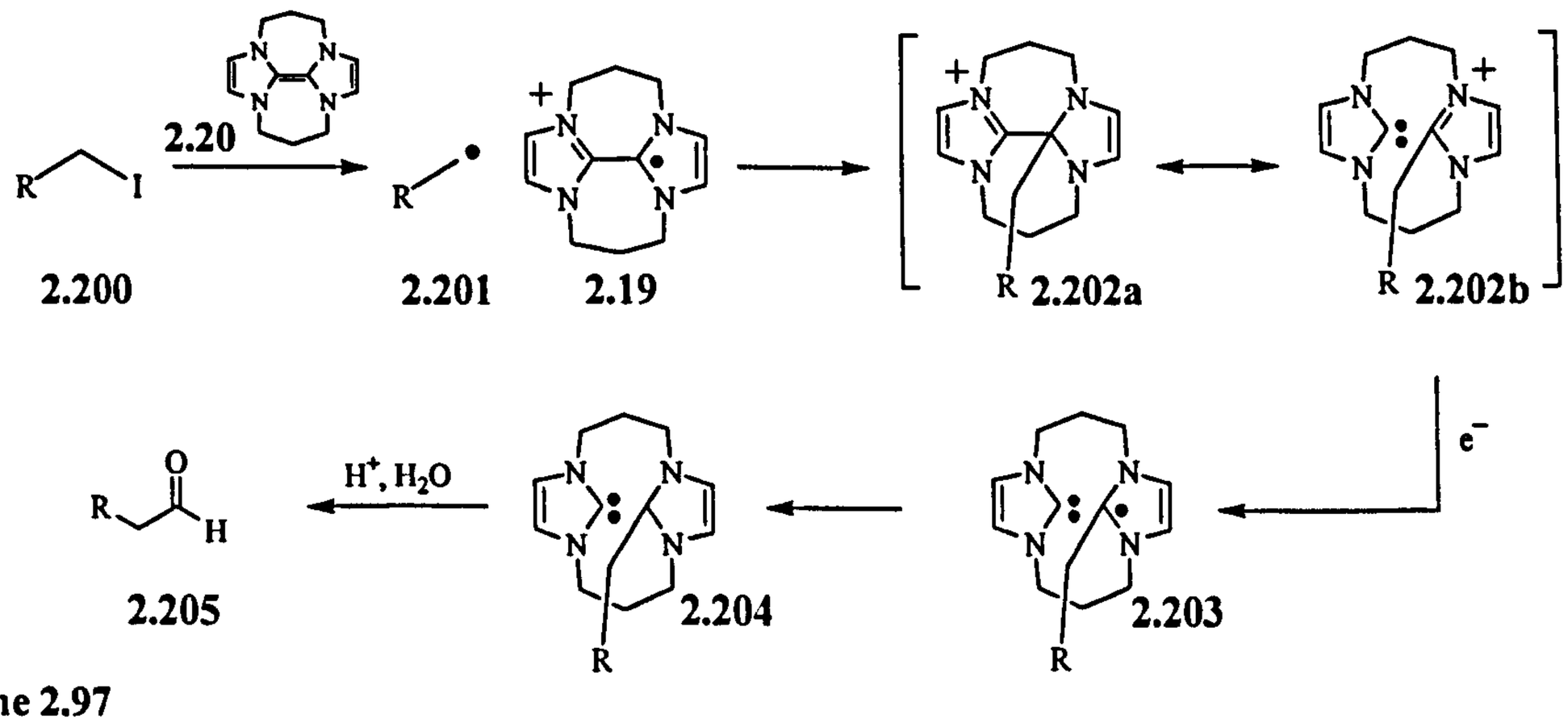


2.160 **2.161** **2.162** **2.163**

Scheme 2.96

Donor **2.20** was formed in freshly distilled and deoxygenated dimethylacetamide and after centrifugation added to substrate **2.160**. Instantaneous colour change from yellow to deep red occurred. After stirring for 18 h at room temperature, the mixture was subjected to acidic work-up, as usual, and ^{1}H-NMR analysis of the crude mixture was carried out. Again, the characteristic aldehyde peak at δ 9.9 was seen; there was no sign of ketone. Further, reduced compound **2.162** and cyclised product **2.163** were identified also in the NMR spectrum.

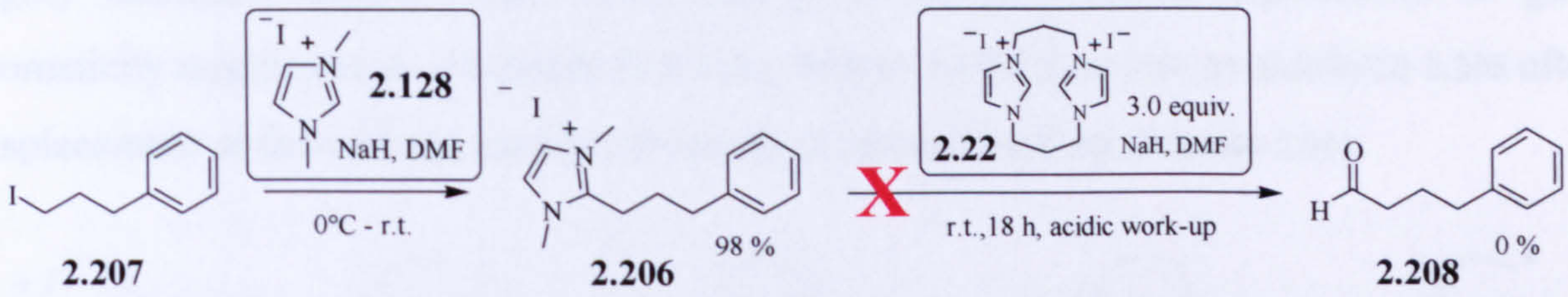
This was a very intriguing result that raises the question how those aldehydes form. Since the additional CHO seems not to be arising from the solvent, the imidazolium moieties may be the source and origin of aldehyde formation and this might be rationalised as follows (**Scheme 2.97**): after reduction of the alkyl halide **2.200** to the alkyl radical, addition to the radical-cation **2.19** might have occurred to form adduct **2.202a**. This adduct could alternatively form by nucleophilic substitution by the nucleophilic donor **2.20** onto the primary alkyl halide [however, the fact that aldehyde **2.161** of the cyclised compound is formed, rules out that S_N2 is the exclusive mechanism]. Reduction of the adduct species **2.202** to **2.203** might then have occurred, addressing the observation that an increase of donor equivalents led to an increase in aldehyde formation. Hydrogen atom abstraction, followed by proton-catalysed hydrolysis might then have taken place to afford the aldehyde **2.205**.



Scheme 2.97

To test for the validity of the proposed mechanism the reduction step from **2.202b** to **2.203** was investigated further. For that puropose, 2-substituted imidazolium salt **2.206** was synthesised *via* nucleophilic substitution of alkyl iodide **2.207** with carbene **2.126**. Three equivalents of *in situ*-prepared donor **2.20** were then exposed to species **2.206** and stirred at room temperature overnight, followed by acidic work-up, analogous to the previous

experiments in which aldehyde formation had taken place. However, this time no such aldehyde was observed, suggesting that the proposed mechanism is not valid.



Scheme 2.98

A computational investigation* of the SOMO, spin-density and spin of the radical cation of imidazole donor **2.20** (*i.e.* **2.19**) shows that, as expected, the unpaired electron is highly delocalised. Further, the highest spin-density (indicated in blue in **(B)**) as well as spin **(C)** is located on the central carbon atoms as well as nitrogen atoms (see **Figure 2.11**).

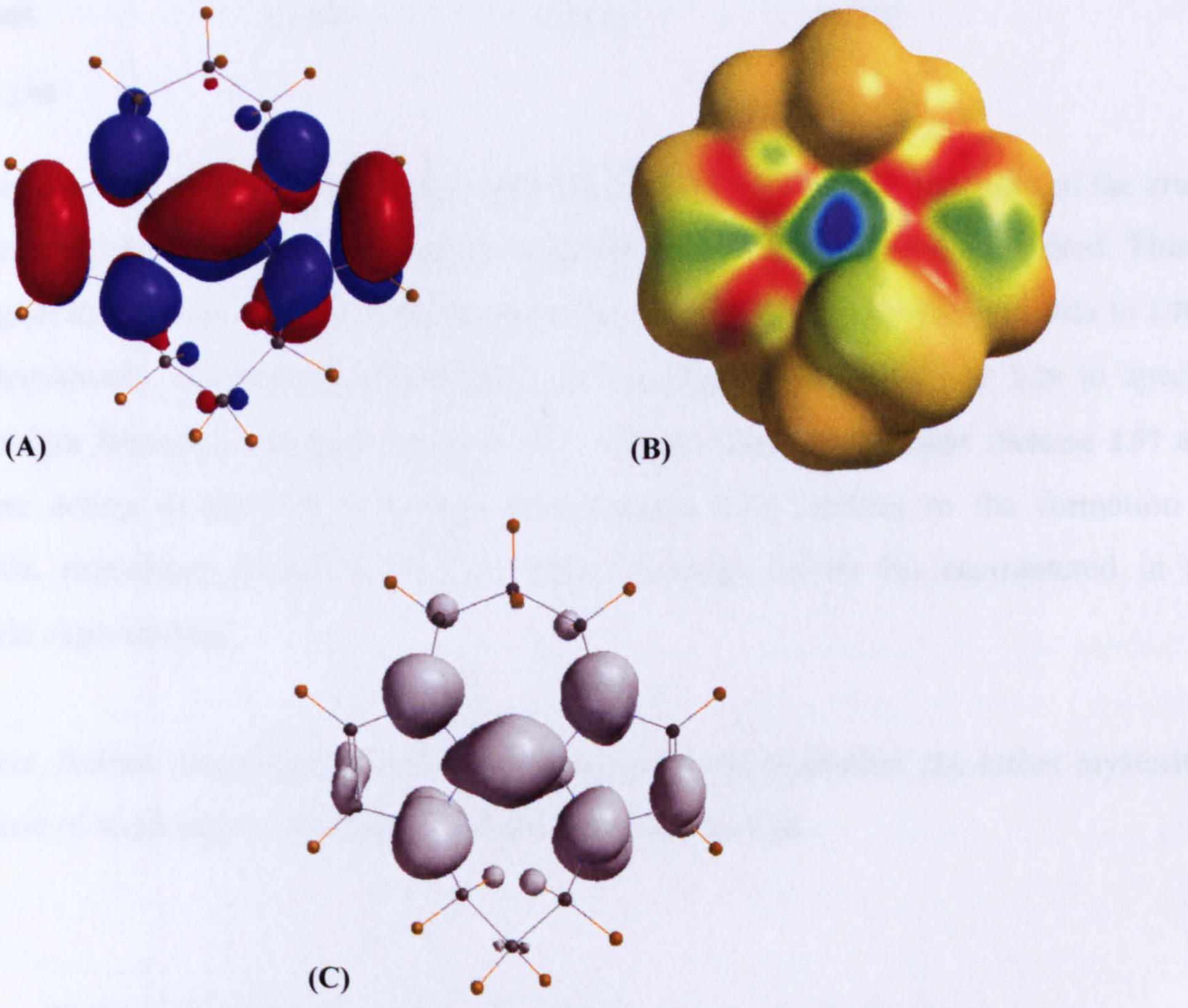
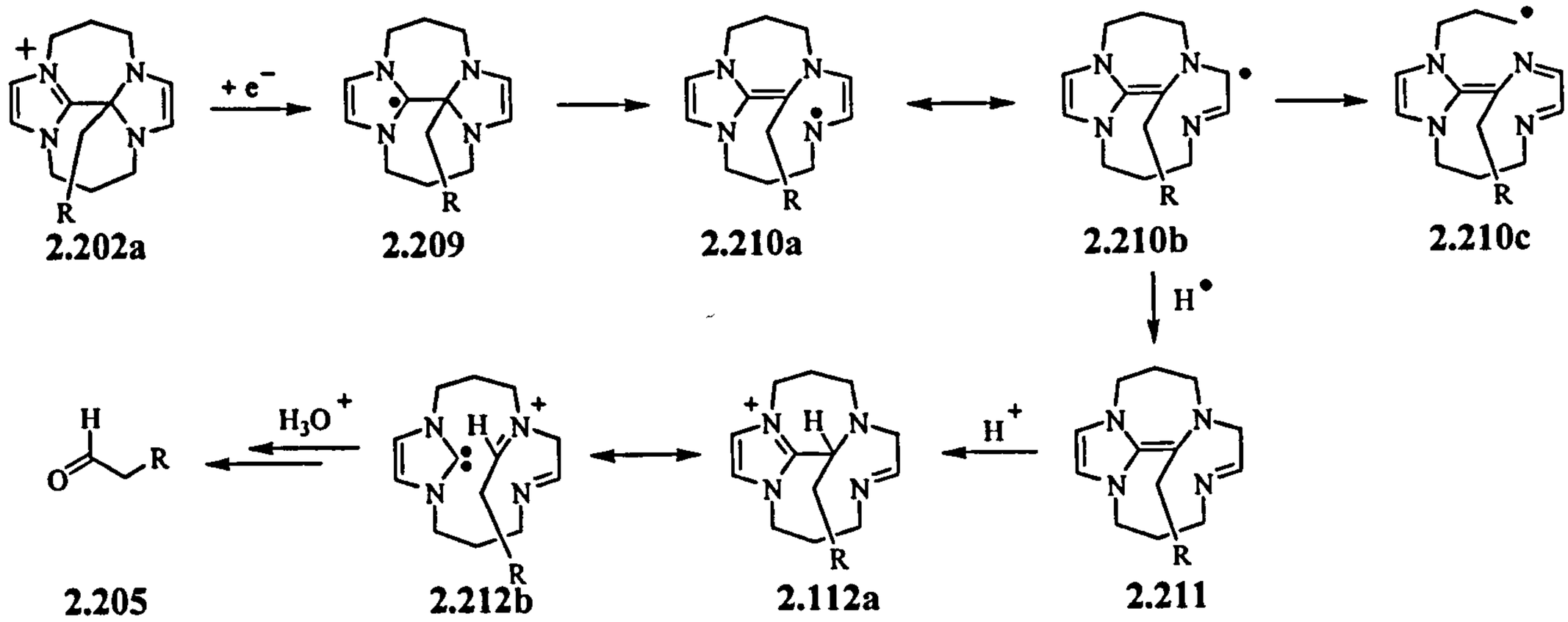


Figure 2.11 SOMO (A), spin density (B) and spin (C) of donor radical cation 2.19

Addition of the radical would therefore be most favourable at the central carbon atoms, as investigated above. The formation of aldehydes might alternatively be rationalised as

* S*PARTAN*, Single-point, Hartree-Fock, 3-21 G*

shown below in **Scheme 2.99**. In this mechanism it is assumed that species **2.202a** does not convert to **2.202b** and instead is reduced at that stage to **2.209**. *Beta*-cleavage to afford a highly stabilised radical might then take place to give **2.210a**. Protonation to gain aromaticity might lead to intermediate **2.112a**, which would give rise to aldehyde **2.205** after displacement of the carbene moiety and aqueous acidic work-up (**Scheme 2.99**).



Scheme 2.99

In order to see the aldehyde as the exclusive product in the ^{1}H-NMR spectrum of the crude mixture, multiple equivalents and high concentrations of donor **2.20** were required. This is once again incorporated in the mechanism by the additional reduction step (**2.202a** to **2.209**) and alternatively, nucleophilic substitution of the alkyl halide by donor **2.20** to species **2.202a** might become a competitive pathway. Perhaps both mechanisms (**Scheme 2.97** and **2.99**) are acting in parallel, with only one (**Scheme 2.99**) leading to the formation of aldehyde, explaining therefore the low mass balances (30-60 %) encountered in the aldehyde experiments.

However, further investigations have to be undertaken to rationalise the rather mysterious formation of aldehydes in reactions with imidazole donor **2.20**.

4.3 Disfavouring the formation of aldehydes and selective reductions

Addition of the alkyl radical to the radical cation **2.19** has to occur to give rise to the formation of aldehydes. Thus, in order to prevent the formation of those aldehydes and to achieve simple reduction of an alkyl halide, this coupling process of the radical to the radical cation of the donor needs to be prevented. This might be achievable by changing

the reaction solvent from DMF to a less polar one, such as toluene or diethyl ether. Because in those apolar solvents, the radical-cation of the donor might not be soluble anymore and might precipitate from solution, so that it is not able to couple with the radical. Thus, the alkyl radical would then not add to the radical-cation anymore, as this would be a heterogeneous reaction and would therefore be disfavoured.

This was investigated by using the pure donor **2.20** in toluene on substrate **2.213**. This substrate contains two C-Br bonds, one being of aryl and one being of aliphatic nature. The previous reactions on alkyl halides showed that complete consumption of the starting material took place at room temperature. With aryl bromides the situation is different. *Ortho*-bromide **2.39** was found to react at room temperature, while **2.92**, in contrast, required heat despite the presence of the *ortho*-fluorine. This highlights the fine borderline of reactivity at which the donor acts. Studying the reported reduction potentials of bromophenols,[154] there should be a considerable reactivity difference between a *para*- and *ortho*-substituted halide, *i.e. para*-bromophenol shows a more negative reduction potential than *ortho*-bromophenol (**Figure 2.12**).

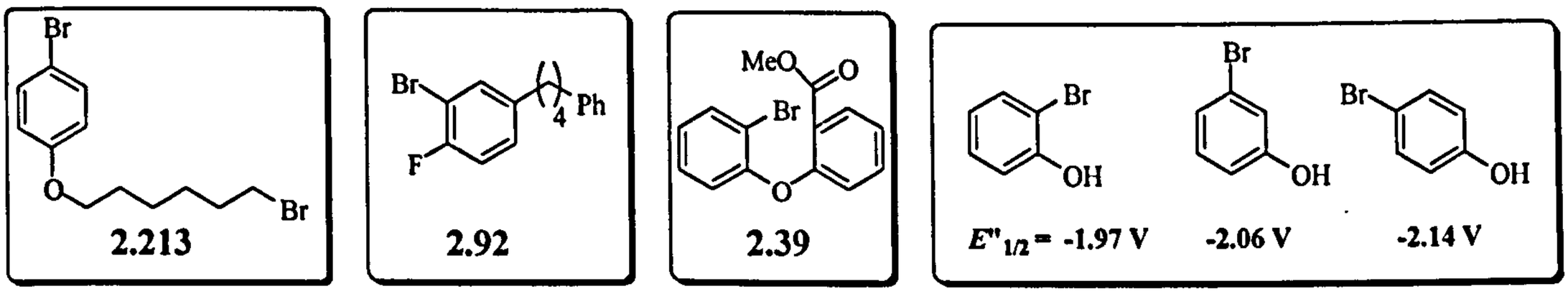
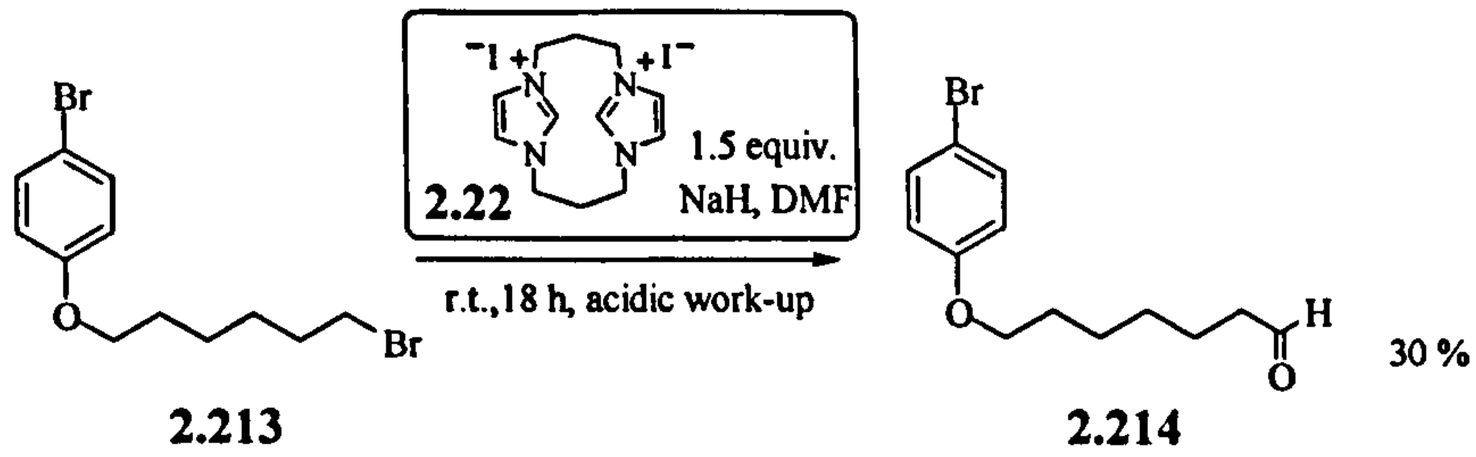


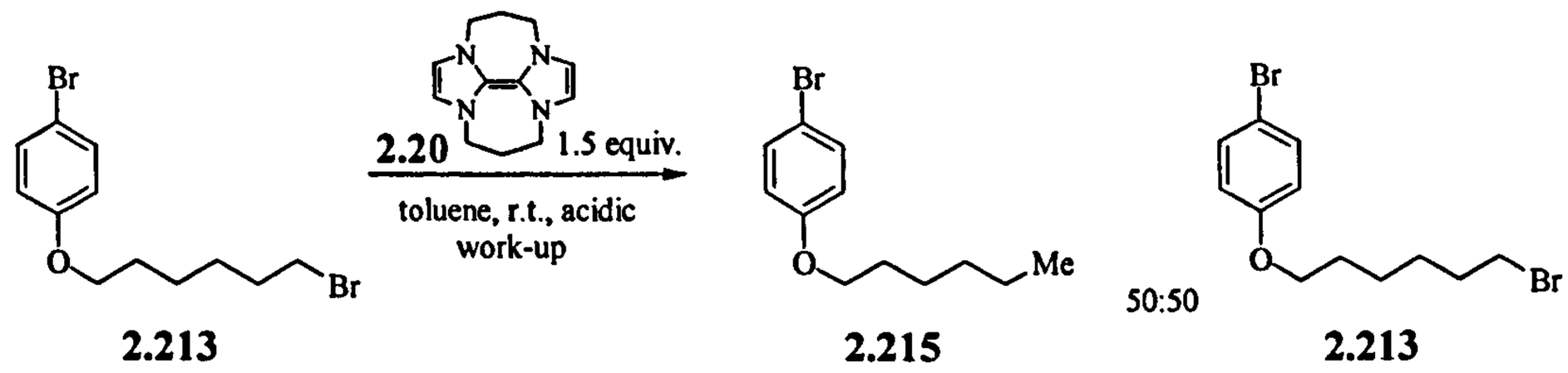
Figure 2.12 Substrates and reduction potentials of bromophenols

Thus, a *para*-substituted aryl bromide should be more difficult to reduce, probably requiring heat to achieve the reduction. It was thought, therefore, that if the experiment was carried out at room temperature, then selectivity might be observed in the competitive reduction of the alkyl and aryl bromide, reducing the aliphatic C-Br bond in preference and leaving the aromatic C-Br bond untouched in this particular substrate. To test for a qualitative answer, substrate **2.213** was reacted in DMF with *in situ*-formed donor **2.20** at room temperature. This showed in the ^{1}H-NMR spectrum of the crude mixture that reduction of the aryl bromide bond had not taken place, only the aliphatic C-Br bond was reduced, however, as expected, aldehyde formation took place also in 30 % isolated yield.



Scheme 2.100

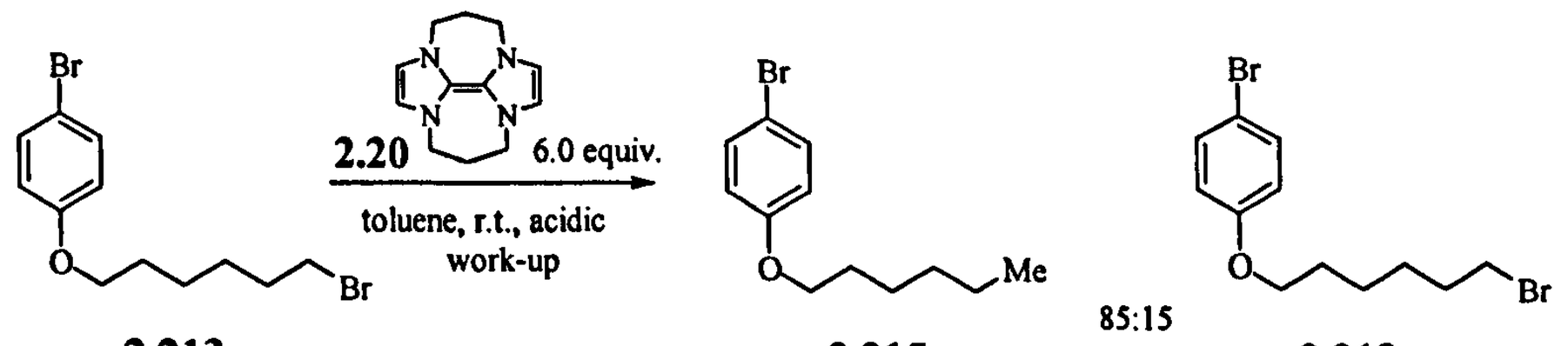
Since selectivity in reactivity seemed to be the case, it was then tested whether the formation of aldehyde **2.214** could be avoided by using an apolar solvent. Thus, 1.5 equivalents of pure donor **2.20** were dissolved in toluene in the glove-box and reacted with dibromide **2.213.** After work-up a ^{1}H-NMR analysis of the crude mixture was carried out, and this showed starting material **2.213** and its reduced counterpart **2.215** in a 50:50 mixture.



Scheme 2.101

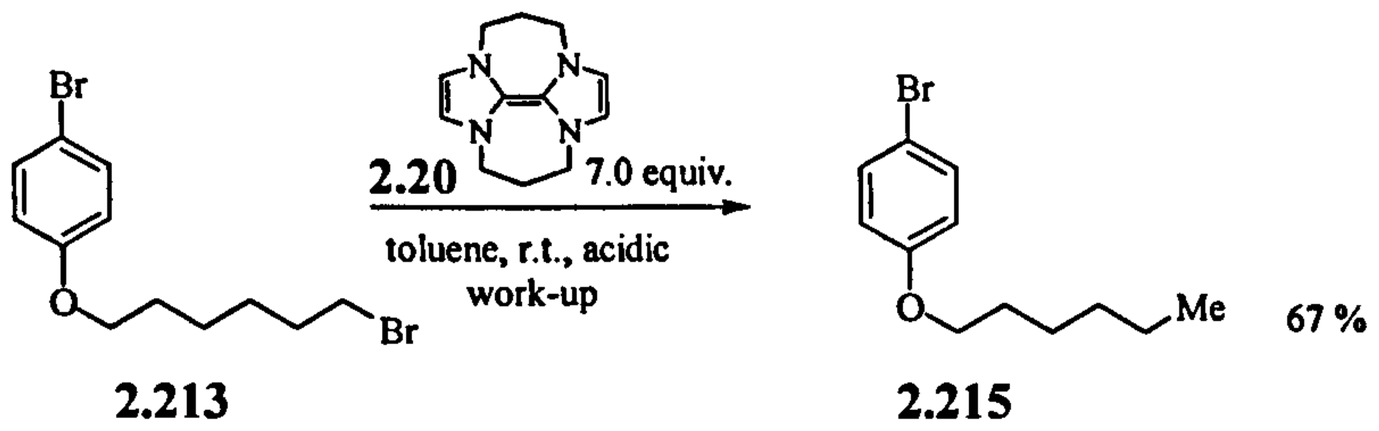
This result was intriguing, since it contrasts to results obtained in DMF, where complete conversion was seen using 1.5 equivalents of donor **2.20**. This suggests again, as observed previously, that donor **2.20** has got lower reducing power in a less polar solvent than in DMF. Possibly, the formation of the polar electron transfer transition state is disfavoured in an apolar, less stabilising solvent.

It was decided to increase the concentration of donor **2.20** by using 6.0 equivalents under otherwise identical conditions. This time, the reaction nearly went to completion.



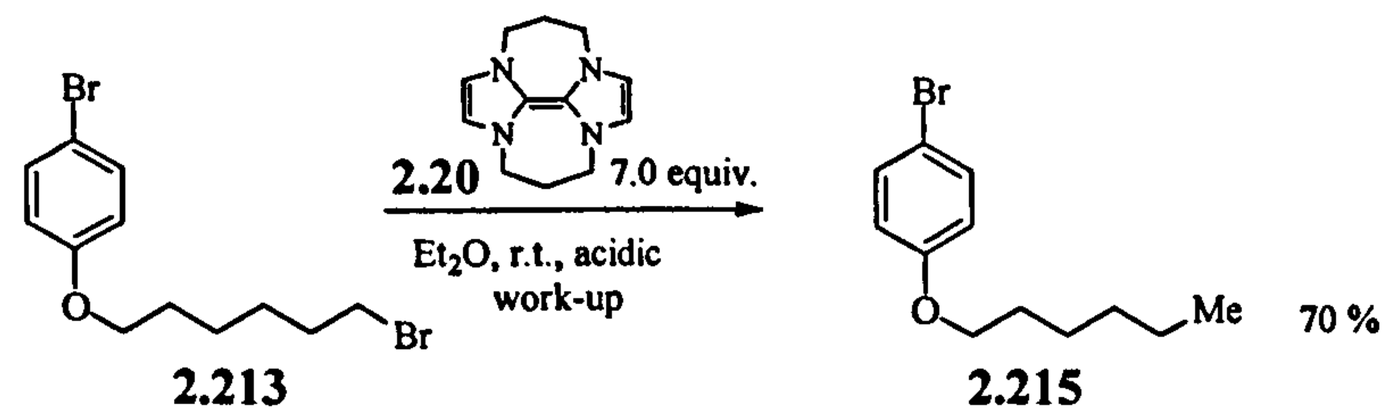
Scheme 2.102

Finally, using 7.0 equivalents of donor **2.20** led to success and only the product arising from reduction of the aliphatic C-Br bond was formed. Thus, complete selectivity was achieved as well as unique difference in reactivity observed by changing the solvent towards a less polar one.



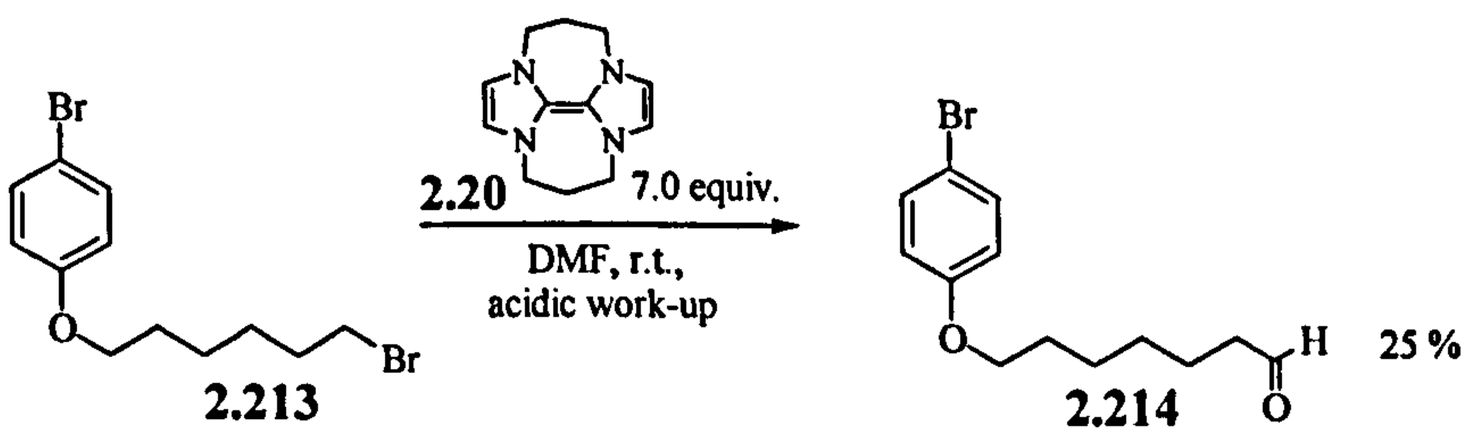
Scheme 2.103

The moderate 67 % yield of aryl bromide product **2.215** might have been caused by the relatively high boiling point of toluene that was utilised in the reaction, and thus loss of the product may have occurred due to volatility. It was, therefore, decided to do the reaction in diethyl ether, since it has a relatively low boiling point and the radical-cation of the donor would not be soluble in it either, so that aldehyde formation is prevented.



Scheme 2.104

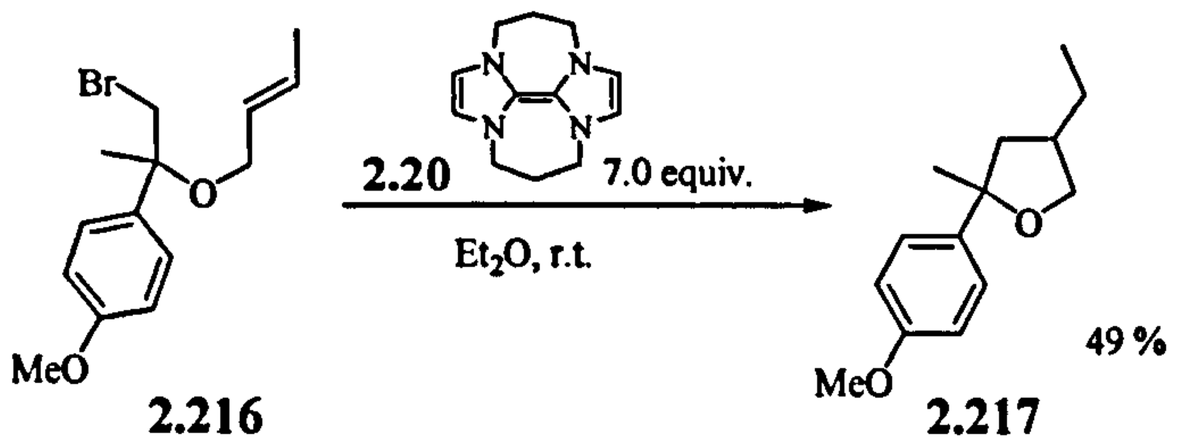
But again, the yield of **2.215** (70 %) was not great and did not improve considerably. Possibly, although being disfavoured in apolar solvents, some nucleophilic substitution might have taken place and the intermediate **2.202** (compare **Scheme 2.99**) precipitated from the solution and was subsequently lost in work-up into the aqueous layer [or alkyl radical and donor radical-cation coupled before precipitation of the salt had taken place].
Nevertheless, the assumption of avoiding the formation of aldehydes by using an apolar solvent was valid and it also confirmed that the source of aldehyde formation was the imidazole moiety. The question remained of whether the presence of metals is crucial for the formation of aldehydes, *i.e.* is there a difference whether the donor is formed *in situ* or whether the pure donor is used in DMF? This was investigated in another experiment.



Scheme 2.105

Again, aldehyde **2.214** was formed and thus, no matter whether the pure donor is used in DMF or the one generated *in situ* by the NaH-method, aldehydes form.

One more question was asked, *i.e.* whether the reduced compound **2.215** arises from a radical or an anionic intermediate. This was tested in a reaction of cyclisation substrate[156] **2.216** with 7.0 equivalents of donor in diethyl ether at room temperature (**Scheme 2.106**). After acidic work-up the cyclised product **2.217** was isolated as the exclusive product, indicating that reductions of alkyl halides in non-polar solvents proceed by a radical mechanism. However, the mass balance of the reaction was low, with **2.217** being isolated in 49 % yield only.

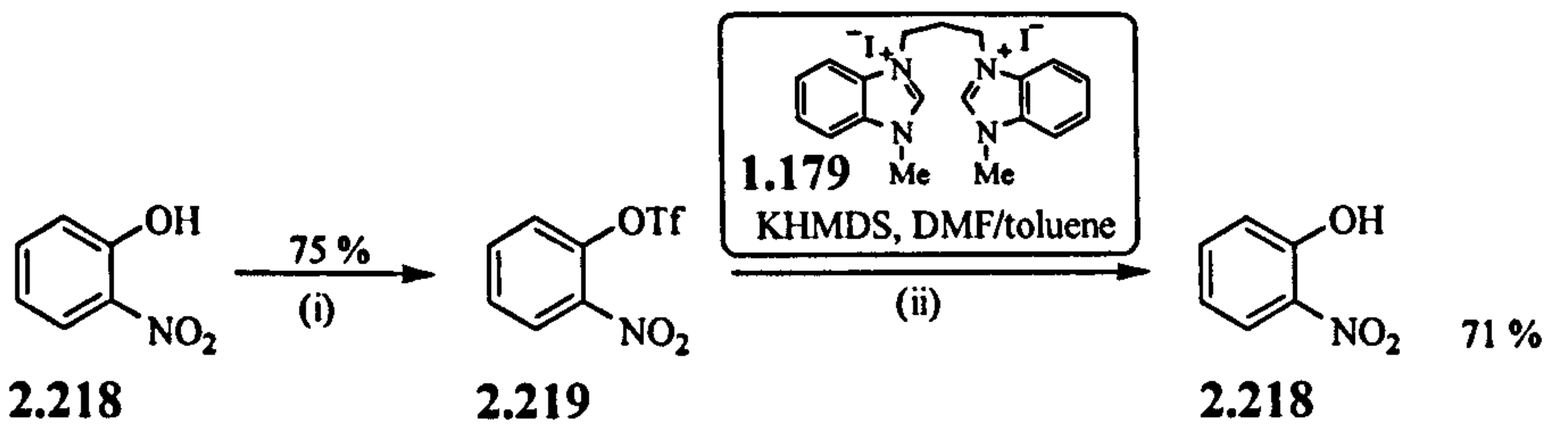


Scheme 2.106

5 Reductive cleavage of sulfones and sulfonamides

5.1 *Reduction of triflates and mesylates*

In attempts to produce an aryl radical based on deoxygenation using benzimidazole donor **1.175** on nitro triflate substrate **2.219**, it was observed that the O-S bond of the triflate group was cleaved in preference to the aryl C-O bond, giving rise to nitrophenol **2.218** (**Scheme 2.107**).

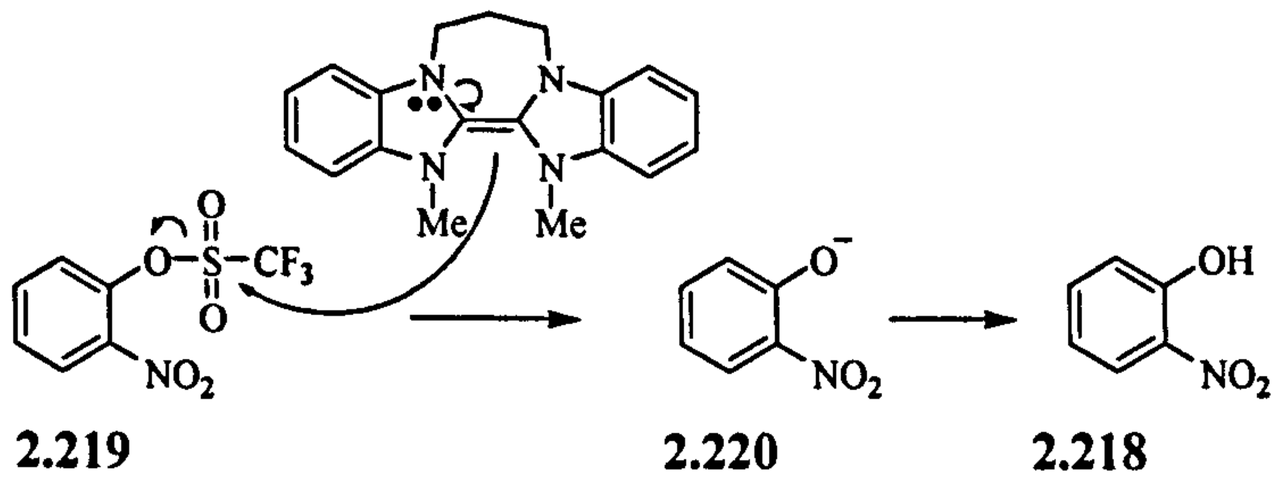


2.218 **2.219** **2.218**

***Reagents and conditions*: (i)** Tf_2O (2.0 equiv.), triethylamine (4.0 equiv.), DCM, 0°C to r.t., 18 h; **(ii) 1.179** (1.2 equiv.), KHMDS (2.4 equiv.), DMF/toluene (1:3), 110°C, 18 h.

Scheme 2.107

This cleavage could, in principle, be induced by the donor acting as a nucleophile (**Scheme 2.108**) or by single electron transfer from the donor to the substrate.

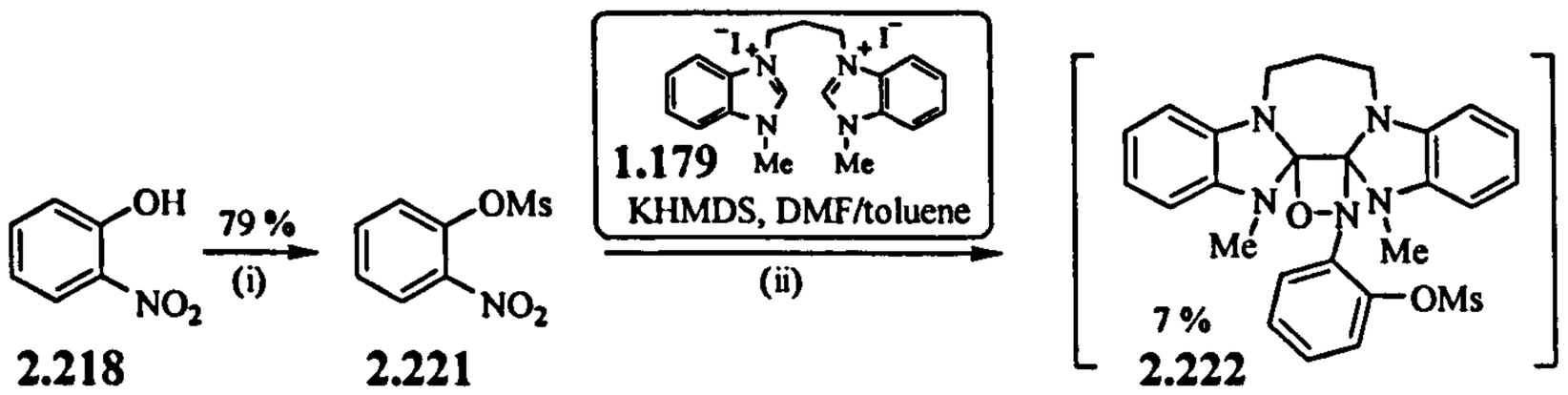


2.219 **2.220** **2.218**

Scheme 2.108

Therefore, a more stable substrate, nitro mesylate **2.221** was prepared that might be less prone to attack by a nucleophile, but might still be activated towards reduction. It was reacted with benzimidazole donor **1.175**. The most UV-active spot on TLC was isolated from the reaction mixture and fully characterised (**Scheme 2.109**). The isolated compound **2.222** did not show aromatic proton signals at a higher chemical shift than δ 7.2, which suggests that there was no nitro group present anymore. Twelve aromatic protons were counted. Further, three singlet signals (with 3H each) were seen that were likely to correspond to the two methyl groups on the nitrogen atoms of the benzimidazole moieties and the methyl group of the mesylate. The proton signals for the 3-carbon bridge were clearly seen, but both CH_2 groups next to the nitrogen atoms have identical chemical shift

of δ 3.9. This indicates that the benzimidazole moieties must be neutral, since a benzylic CH_2 group next to a positively charged nitrogen would be expected to have a chemical shift slightly downfield of δ 5. A molecular ion peak of 506 $[M+H]^+$ was found by ESI mass spectrum analysis and confirmed by high-resolution mass spectrometry for M+H, matching the proposed structure **2.222** below.

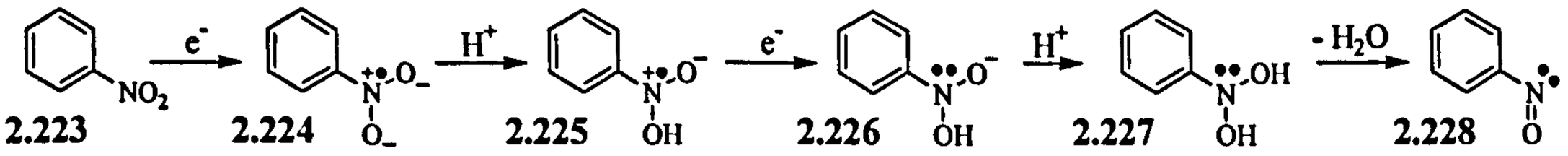


2.218 **2.221** **2.222**

***Reagents and conditions*: (i)** MsCl (2 equiv.), triethylamine (4 equiv.), DCM, 0°C to r.t., 18 h; **(ii) 1.179** (1.2 equiv.), KHMDS (2.4 equiv.), DMF/toluene (1:3), r.t., 2 h.

Scheme 2.109

Structure **2.222** arises probably from reduction of the nitro group, and an intermediate species, (either of radical or anionic nature) is formed that subsequently attacks the radical-cation or dication species resulting from donor **1.175**. It is reported for nitroaryl compounds that the single electron transferred to the substrate is located mainly on the nitro group, rather than being fully delocalised over the aromatic ring.[155] For the reduction of nitro groups, several electron transfer steps and also proton transfers are required. Many intermediates are likely to form and even dimerisation can occur (**Scheme 2.110**).[157]

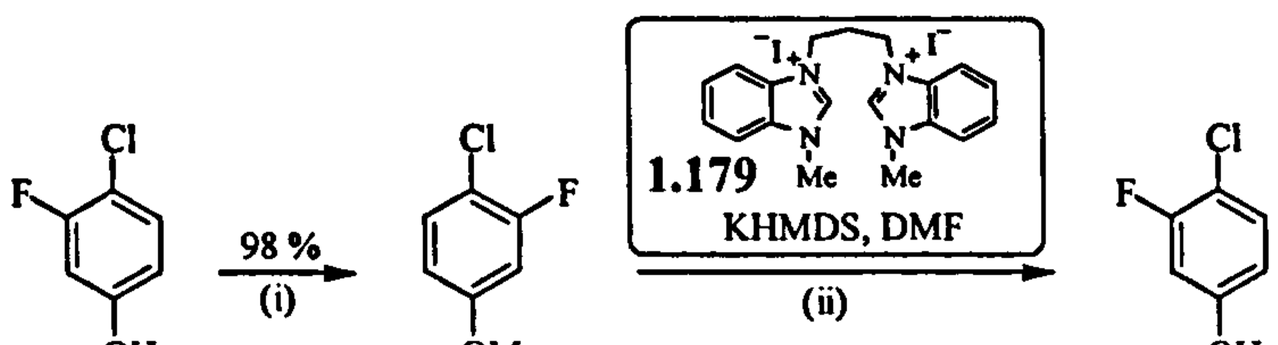


Scheme 2.110

This sort of adduct species **2.222** suggests that the radical-cation (or dication), arising from the donor **1.175** after electron transfer, has sufficient lifetime and stability to be attacked by a nucleophile. This might be useful information in moves to make the electron-transfer process catalytic.

Isolation of adduct species **2.222** in which the mesylate group is still present, suggests that the mesylate might be a stable protecting group in reactions with donor **1.175**. This initiated use of the mesylate group as a possible electron deficient system that might facilitate the

reduction of the carbon-chlorine bond in substrate **2.232**. However, upon reaction with benzimidazole donor **1.175** deprotection occurred, again to cleave the O-S bond rather than C-O bond. It was found that one equivalent of electron donor and heat is required to deprotect completely (see **Table 2.4**, Entry 3).



2.233 **2.232** **2.233**

***Reagents and conditions*: (i)** MsCl (2 equiv.), NEt_3 (2 equiv.), DCM, 0°C to r.t., 2.5 h; **(ii)** see **Table 2.4**

Scheme 2.111

Entry	Conditions	Outcome
1	**1.179** (1.2 equiv., 1.3 mmol), KHMDS (2.4 equiv.), DMF (20 ml), r.t., 18 h	**2.233**, 45 % **2.232**, 49 %
2	**1.179** (2.2 equiv., 1.0 mmol), KHMDS (4.4 equiv.), DMF (15 ml), r.t., 18 h	**2.233**, 60 % **2.232**, 25 %
3	**1.179** (1.2 equiv., 0.48 mmol), KHMDS (2.4 equiv.), DMF (7 ml), 118°C., 18 h	**2.233**, 75 % **2.232**, 0 %

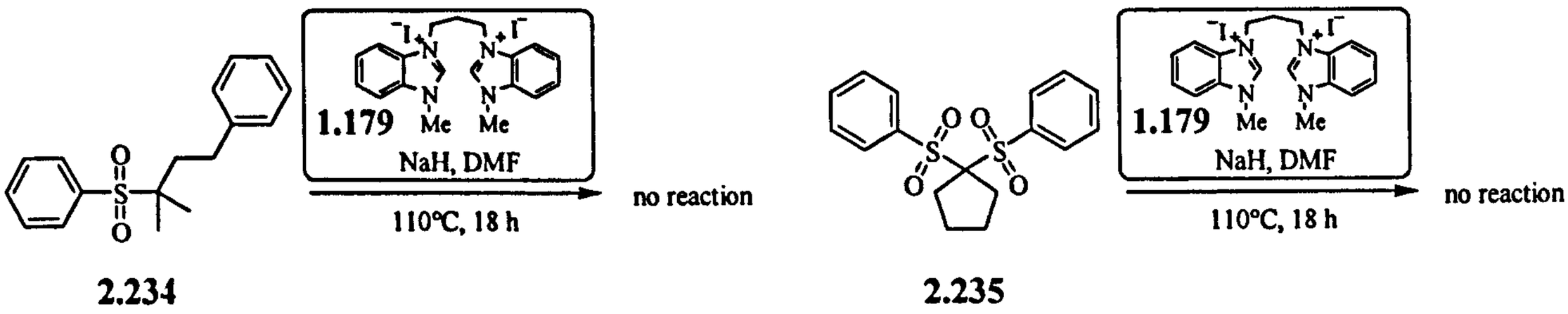
Table 2.4

It is reported that electrochemical reduction of triflates and mesylates occurs at relatively high potentials (in absolute value). Thus, phenyl triflate is quoted to have a reduction potential of E° = -2.63 V.[158] Incorporation of a cyano group changes the potential considerably to E° = -1.8 V for *para*-cyanophenyl triflate.[158] A nitro group is more strongly electron-withdrawing and might therefore make the potential even more positive, so that the reduction of triflates and mesylates becomes achievable for donor **1.175**. Also, it is reported that the O-S bond is cleaved preferentially over the Ar-O bond in the intermediate radical-anion of phenyl triflates, hence indicating that deoxygenation based on triflates and mesylates is rather disfavoured (as attempted) and that the deprotection requires one electron only (as observed).[158]

5.2 *Reduction of activated sulfones*

Overall, the question of whether the deprotection of mesylates and triflates was induced by the donor acting as a nucleophile or electron transfer, cannot be answered. Thus, it was decided to move on to an unambiguous system, *i.e.* a sulfone. Sulfones exhibit a strong C-S bond that is not prone to an attack by nucleophiles.

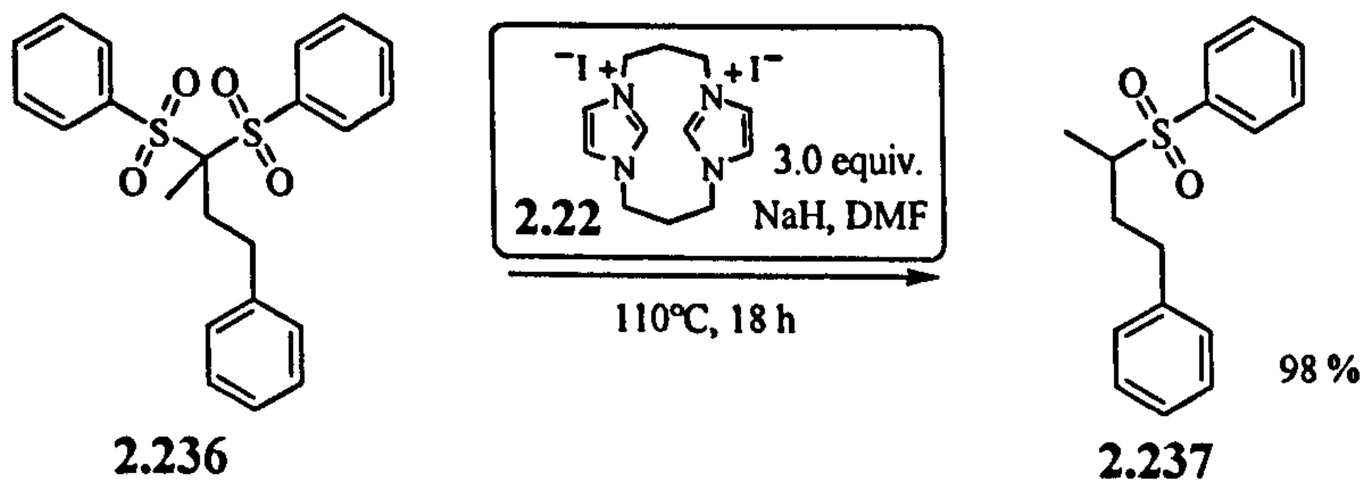
Y. Miclo in our research group tested benzimidazole donor **1.175** on sulfone **2.234** and on the more activated *bis*sulfone **2.235**.[167] He did not observe any reaction at all, highlighting the strong C-S bond and the associated highly negative reduction potential of sulfones.



2.234 **2.235**

Scheme 2.112

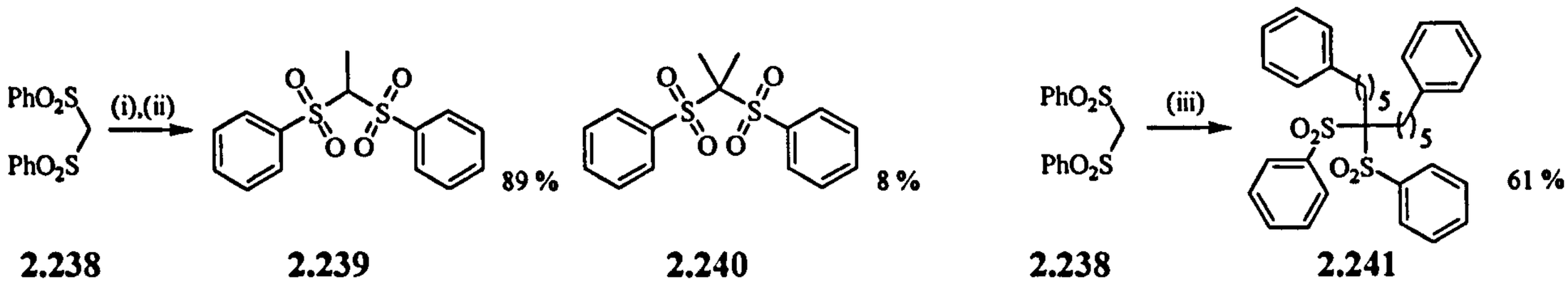
It is reported that monosulfones are electrochemically reduced at a potential of $E°$ = -2.27 V (*vs.* SCE)[165] for $PhSO_2CH_3$, and as discussed in the introduction, strong reducing conditions (such as sodium amalgam) are generally required for the deprotection. Even though benzimidazole donor **1.175** is a powerful donor, it is not powerful enough to reach those potentials. Thus, Y. Uenoyama from our group applied the more powerful imidazole donor **2.20** to the reductive cleavage of the *bis*-sulfone **2.236** (shown in **Scheme 2.113**).[167] Using 3 equivalents of donor and heating at 110°C for 18 h, he observed the complete cleavage of *bis*sulfone **2.236** to the corresponding monosulfone **2.237** (**Scheme 2.113**). After work-up and purification, its monosulfone counterpart **2.237** was isolated in excellent yield by Uenoyama, which was a very promising result.



2.236 **2.237**

Scheme 2.113

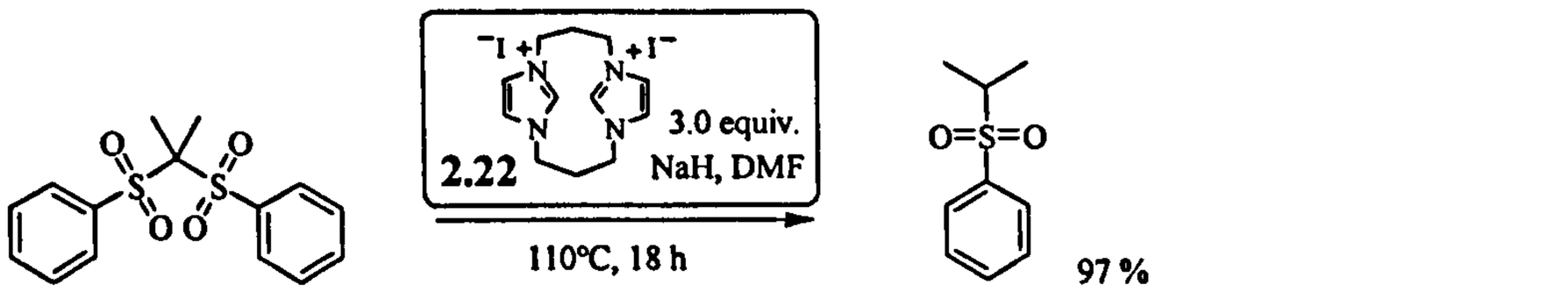
As part of my studies, two more bissulfones, **2.240** and **2.241** were prepared [the former was obtained as a side-product in the synthesis of substrate **2.239**, **Scheme 2.114**] and examined for their cleavage behaviour in the reaction with imidazole donor **2.20**. Again, clean cleavages to the monosulfones were observed (**Scheme 2.115**).



2.238 **2.239** **2.240** **2.238** **2.241**

***Reagents and conditions*: (i) 2.238** (1.0 equiv.), NaH (1.1 equiv.), DMF, 0°C to r.t.; **(ii)** MeI (1.3 equiv.), r.t., DMF, 18 h; **(iii) 2.138** (1.0 equiv.), 1-iodo-5-phenylpentane (2.0 equiv.), K_2CO_3 (5 equiv.), r.t., 5 d.

Scheme 2.114

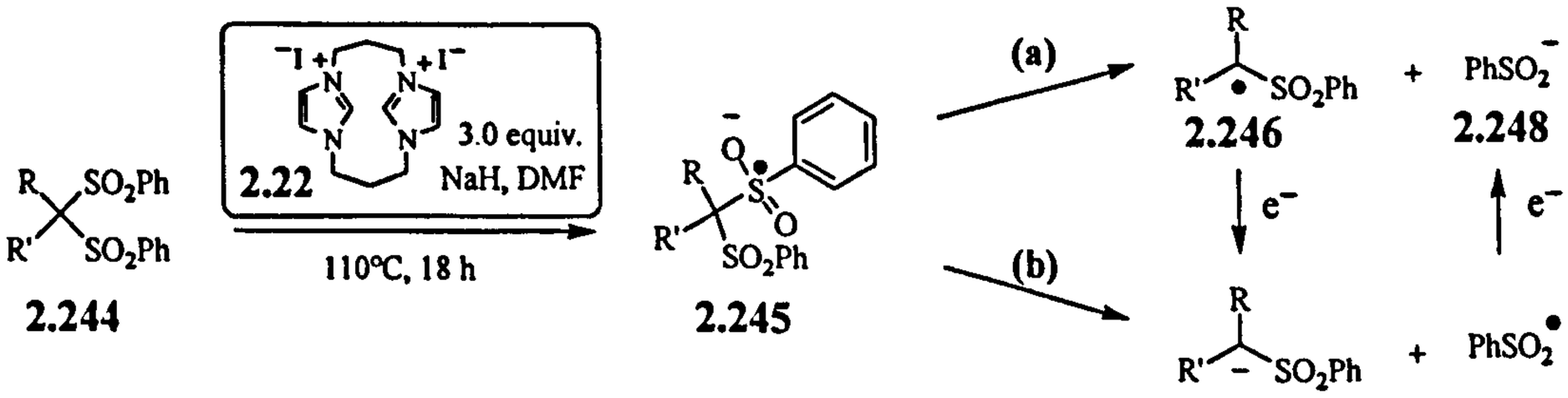


2.240 **2.242**

2.241 **2.243**

Scheme 2.115

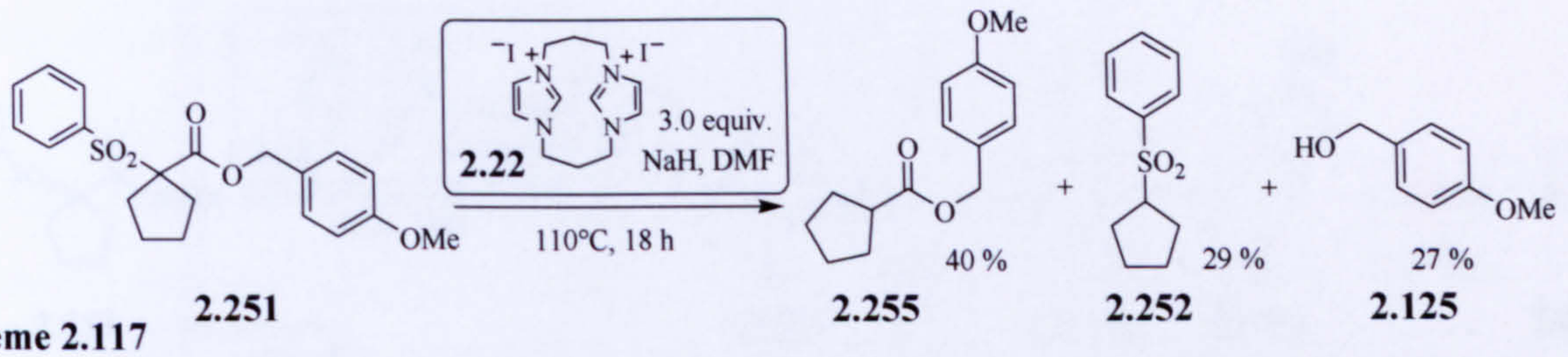
The sulfone cleavage can occur principally *via* the following mechanisms: upon electron donation to the arenesulfonyl group, heterolytic scission of the C-S bond can occur either to produce a sulfinate anion **2.248** and a carbon-centred radical **2.246** that could then undergo further reduction to the carbanion **2.247** under the reaction conditions (**route a**). Or the reduction could proceed initially to produce a carbanion **2.247** and a sulfonyl radical **2.249** [that should readily undergo further reduction to the sulfinate anion **2.248**] (**route b**).



2.244 **2.245** **2.246** **2.248** **2.247** **2.249**

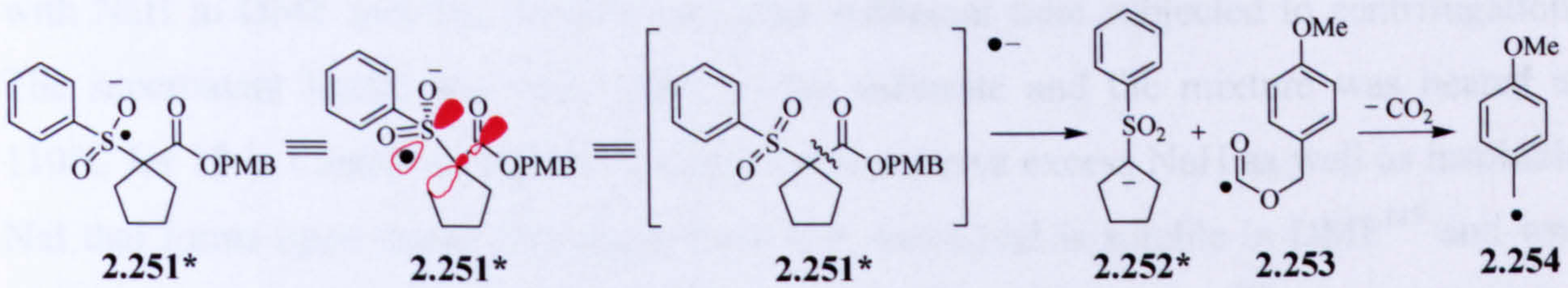
Scheme 2.116

As an alternative substrate ester sulfone **2.251**[162] was explored. It was hoped that the ester group takes over the role of activation in place of a second sulfonyl group and reductive desulfonation would occur also. Thus, ester sulfone **2.251**[162] was reacted with three equivalents of imidazole donor **2.20** while heating at 110°C for 18 h. The outcome is shown in **Scheme 2.117.**



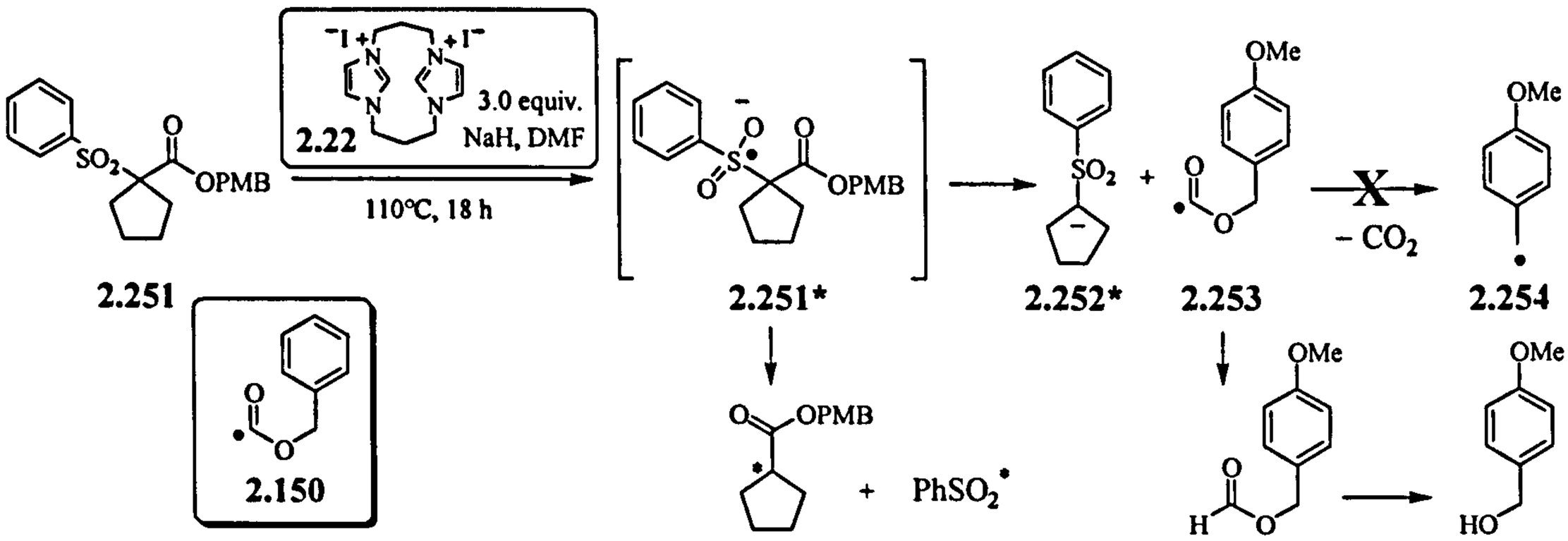
Scheme 2.117

As before, desulfonation occurred to give ester **2.255**, this time in 40 % yield. In addition to that, cleavage of the C-C bond occurred to form sulfone **2.252** in 29 % yield. This might be rationalised as depicted in **Scheme 2.118**. It has been suggested in the literature that the unpaired electron of the radical-anion **2.251*** is mainly located on the sulfur rather than being fully delocalised over the aromatic ring.[159] Thus, the C-C bond cleavage might have been induced by overlap of the unpaired electron with the σ* of the C-C=O bond to give *para*-methoxytoluene after decarboxylation (see **Scheme 2.118**) [LUMO of sulfone ester **2.251** is shown in Chapter 9, Appendix].



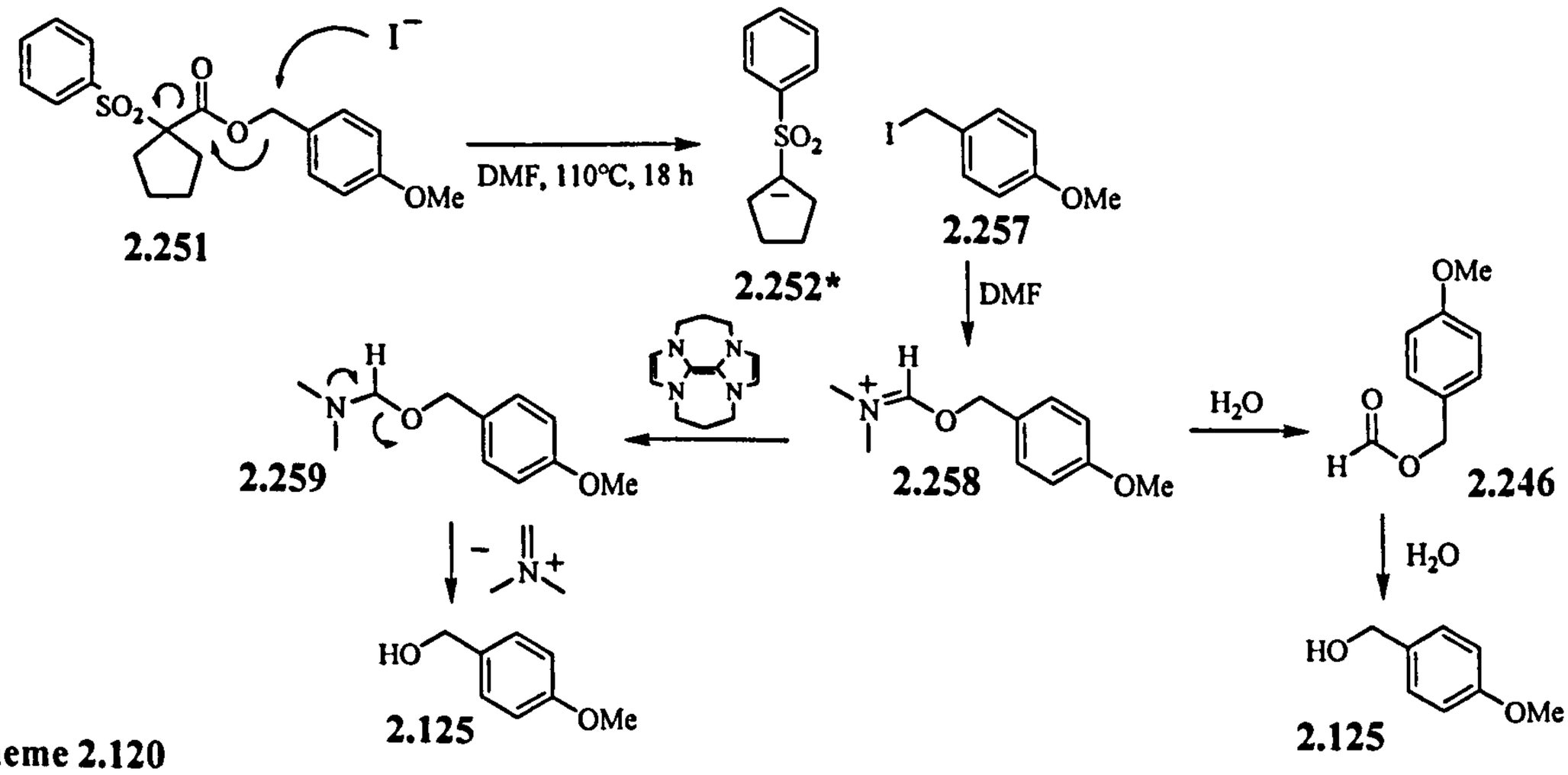
Scheme 2.118

In almost identical yield to sulfone **2.252**, *para*-methoxybenzyl alcohol **2.125** was formed, which is rather surprising. Its formation could suggest that the decarboxylation to form *para*-methoxytoluene was rather slow. The acyl radical might have been quenched to species **2.256** very rapidly before loss of CO_2 could occur. Upon work-up, the alcohol **2.125** would then have formed. This, however, would be a rather unlikely scenario as the rate of decarboxylation for the analogous benzylalkoxycarbonyl radical **2.150** (**Scheme 2.119**) was determined by Beckwith and Bowry[160] to be $k = 2.2 \times 10^8$ s^{-1} at 79°C, suggesting that the decarboxylation is a very fast process.



Scheme 2.119

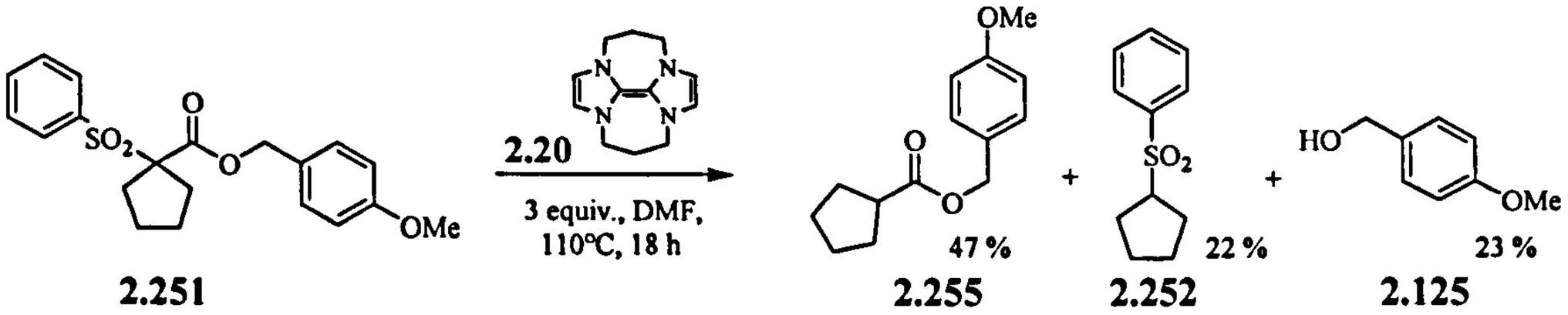
Considering the reaction conditions, an alternative mechanism might be responsible for the observed reaction outcome of **Scheme 2.117**: imidazole donor **2.20** was formed from its precursor salt **2.22** that bears iodide counterions. To form donor **2.20**, salt **2.22** was treated with NaH in DMF and this mixture was after sufficient time subjected to centrifugation. The supernatant liquid was then added to the substrate and the mixture was heated at 110°C for 18 h. Centrifugation was carried out to remove excess NaH as well as insoluble NaI that forms upon donor formation. However, some NaI is soluble in DMF[117] and was probably transferred to the reaction mixture. Thus, Krapcho reaction[161] that involves the decarboxylation of an ester in the presence of halide ions might have occurred here (**Scheme 2.120**).



Scheme 2.120

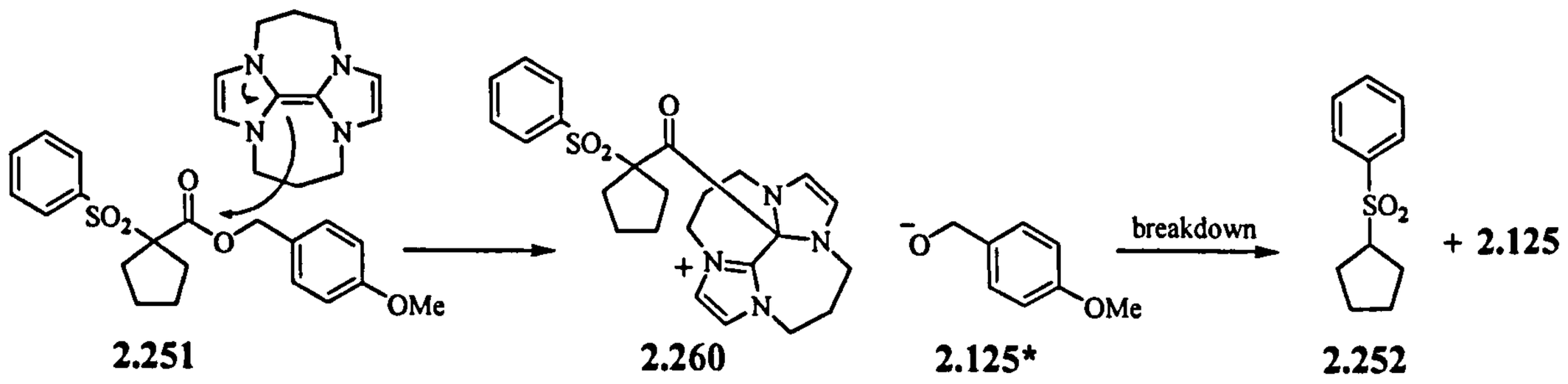
Attack of the iodide at the benzylic position of sulfone ester **2.251**, followed by decarboxylation would give rise to anion **2.252*** and *para*-methoxy benzyl iodide **2.257**. This benzyl iodide should be highly unstable under the conditions (110°C, DMF), so that it might be nucleophilically attacked by DMF to form **2.258**. The formed species might either

be reduced further by the donor to **2.259** or break down in work-up to *para*-methoxybenzyl alcohol. Due to the different mechanistic possibilities, it was decided to test for the Krapcho reaction by performing the reaction in the absence of iodide. Pure imidazole donor **2.20** was used and the reaction was carried out under otherwise identical conditions [DMF, 110°C for 18 h].* Satisfyingly, a very similar reaction outcome was observed as shown in **Scheme 2.121**, therefore, excluding a Krapcho-type interference.



Scheme 2.121

A likely mechanistic possibility for the formation of *para*-methoxybenzyl alcohol **2.125** is the displacement of the alkoxide **2.125*** by the nucleophilic donor **2.20** (compare section **3.4**, *i.e.* anthracene ester reactivity), since the ester functionality is inductively activated by the sulfone group. This would once again lead to an activated donor complex **2.260**, and decarbonylation would here also give rise to a stabilised carbanion (or radical) *alpha* to the sulfone group. This time, pure donor **2.20** was used in the reaction, thus, the concentration of hydroxide should, if present at all, be rather small, which suggests that hydrolysis of the ester by hydroxide attack, followed by decarboxylation should not be an alternative in this case.

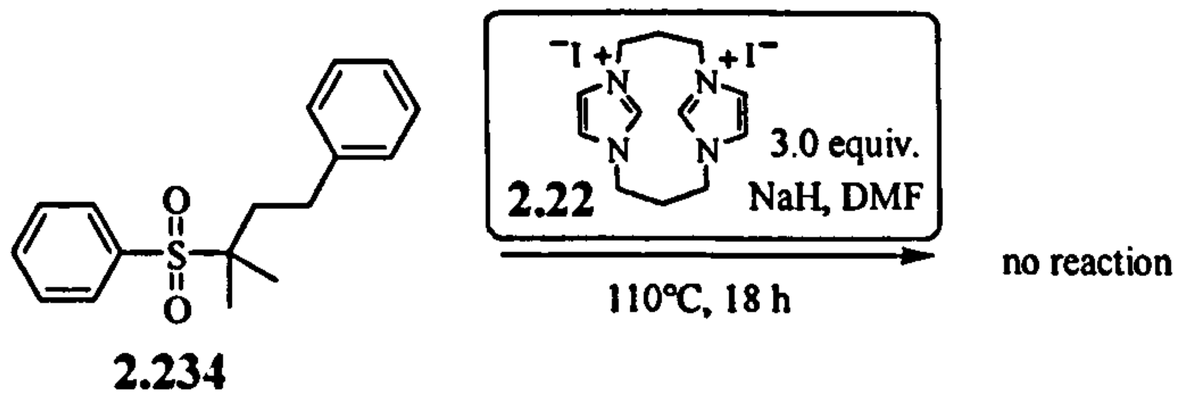


Scheme 2.122

It was next questioned, whether a monosulfone that is not activated by a second sulfone or ester group, would undergo cleavage under the reductive conditions also. Monosulfone **2.234**[162] was subsequently exposed to three equivalents of donor and the mixture was heated at 110°C for 18 h. However, no reaction occurred as judged by ^{1}H-NMR of the crude mixture.

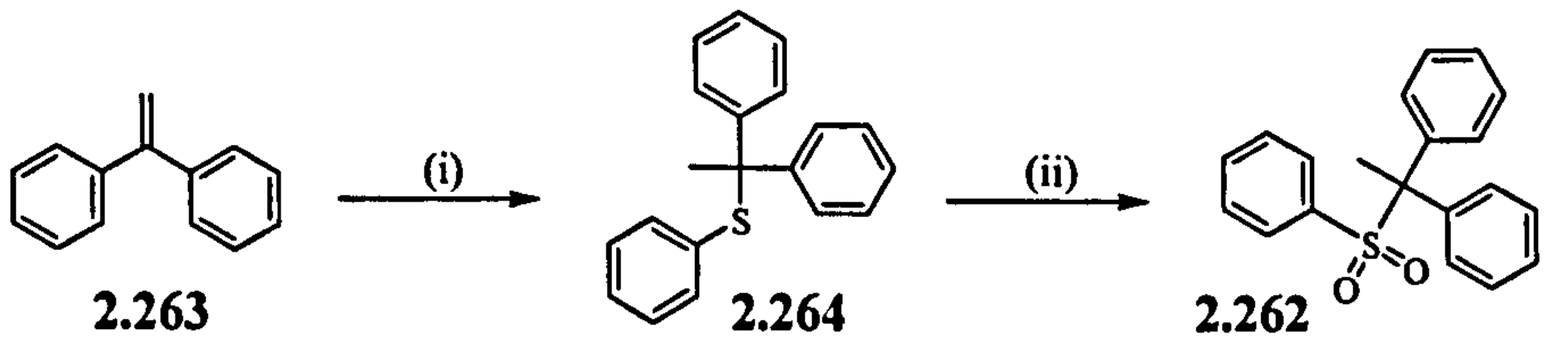
---

* Atomic absorption (AAS, done by S.-Z. Zhou) analysis: 0.005 mg of Na in 100.0 mg of donor **2.20** (0.047 mol %). This corresponds to the maximum content of NaI in donor **2.20**.



Scheme 2.123

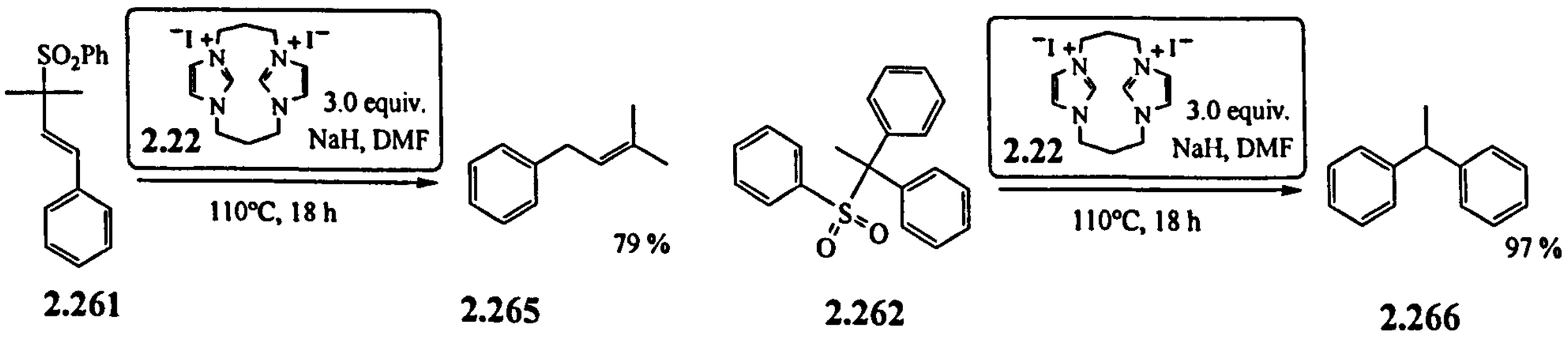
This suggests that imidazole donor **2.20** acts as a selective reagent, being just at the borderline with its reducing power between the potentials of more activated and unactivated sulfones. Thus, two further activated sulfones were synthesised to test for this hypothesis. This time, the activation was induced by an extended carbon-based π-system. This should, once again, aid the formation of the product, *i.e.* the developing radical or anion in the transition state should be stabilised by delocalisation due to the extended π-system, and hence this should favour the transformation in comparison to the unactivated monosulfone **2.234** above. Also, the overall LUMO energy of the molecule would be lowered, easing therefore the electron transfer process (this will be discussed in **section 5.4** in more detail). Thus, monosulfones **2.261**[163] and **2.262** were envisaged (see **Scheme 2.125**). The latter was synthesised *via* addition of thiophenol to the protonated counterpart of diphenylethylene **2.263**, followed by oxidation of sulfide **2.264** using *meta*-chloroperbenzoic acid (**Scheme 2.124**).



***Reagents and conditions*: (i)** thiophenol (1.3 equiv.), perchloric acid, **2.263** (1.0 equiv.), 0°C to r.t., 2 h; **(ii) 2.264** (1.0 equiv.), *m*-CPBA (6.0 equiv.), DCM, 0°C to r.t., 18 h.

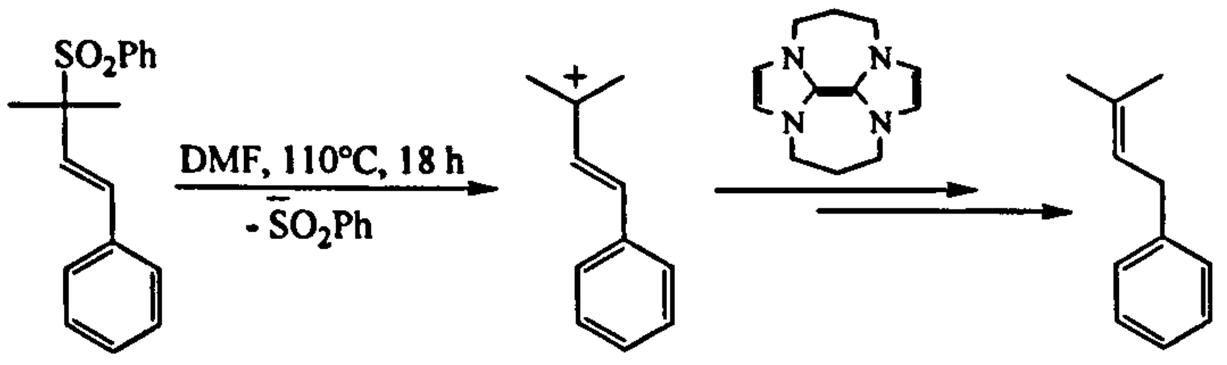
Scheme 2.124

Both monosulfones gave rise to complete desulfonation upon reaction with donor **2.20**, giving rise to alkene **2.265** and 1,1-diphenylethane **2.266** as the sole products. Alkene **2.265** was isolated in lower yield, presumably due to its volatility (**Scheme 2.125**).



Scheme 2.125

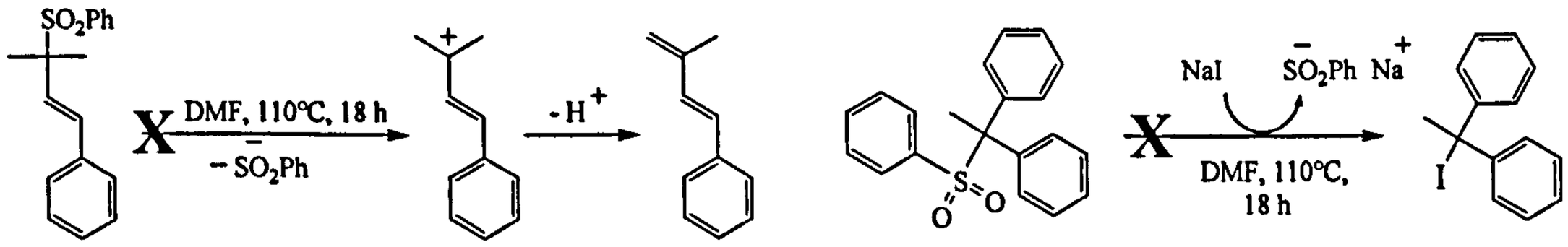
The cleavages of monosulfones **2.261** and **2.262** are rationalised above by an electron transfer mechanism to the arenesulfonyl group. However, an alternative mechanism for the observed cleavage could lead to the identical products. If the sulfone cleavages from **Scheme 2.125** proceeded *via* S_N1 reaction alternatively, highly stabilised carbocation intermediates would result (*e.g.* **2.267, Scheme 2.126**). The resulting carbocation might then have been reduced by electron transfer, leading to the isolated alkene after protonation (of a carbanion) or H-atom abstraction (of a radical intermediate).



2.261 **2.267** **2.265**

Scheme 2.126

To test whether loss of the sulfonyl group is possible *via* S_N1, both substrates, **2.261** and **2.262**, were reacted in the absence of imidazole donor **2.20**, once in pure DMF and in the other experiment in DMF with thoroughly dried NaI. If carbocations indeed formed, a diene, such as **2.268** or the iodide species **2.269** as shown in **Scheme 2.127** would be expected to form among possible products. [In the reactions with imidazole donor **2.20**, iodide **2.269** could principally form also due to the presence of NaI. Reduction of the iodide by electron transfer could then take place, giving 1,1-diphenylethane **2.266** also].



2.261 **2.267** **2.268** **2.262** **2.269**

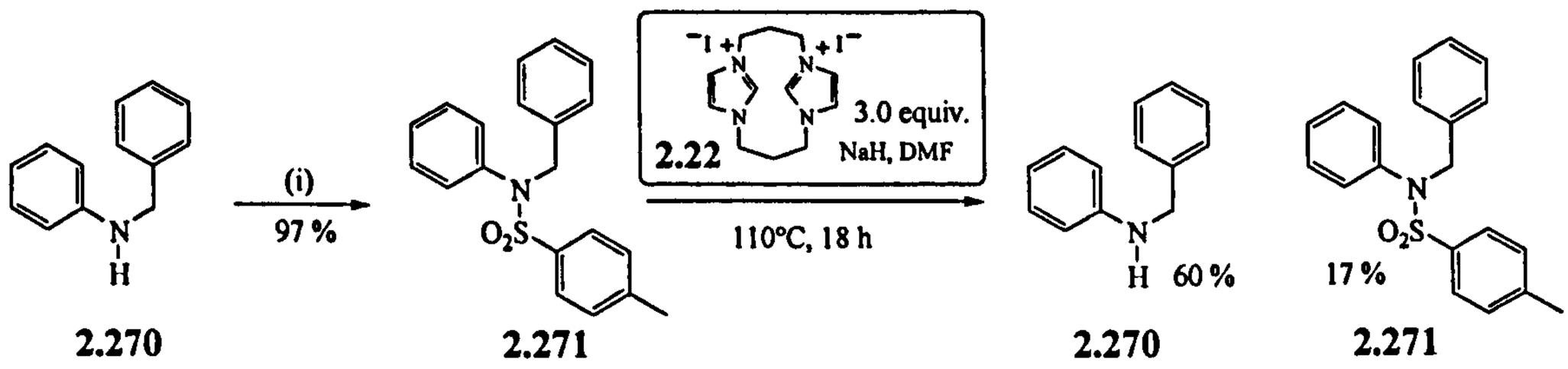
Scheme 2.127

However, both experiments gave rise to starting materials only [as judged by ^{1}H-NMR spectroscopic analysis of the crude mixture after work-up], disfavouring therefore the possibility of S_N1 reaction.

In conclusion, it was shown that imidazole donor **2.20** is capable of cleaving inductively- and π-activated sulfones in excellent yields, making it a possible selective reagent in desulfonation reactions.

5.3 *Reductive cleavage of sulfonamides*

Due to the success in the deprotection of activated sulfones, sulfonamides were next examined for their cleavage with imidazole donor **2.20**. Sulfonamides are tough challenges also; the S-N bond cleavage usually requires vigorous hydrolysis or strongly reducing metals.[164] The reduction potential for sulfonamides typically are around E° = -2.3 to -2.4 V (*vs.* SCE).[165] Sulfonamide **2.271** was prepared and examined for its cleavage behaviour using imidazole donor **2.20**. The successful protocol that was found for desulfonation was applied in the initial experiment. However, this led only to 60 % deprotection (see **Scheme 2.128**).

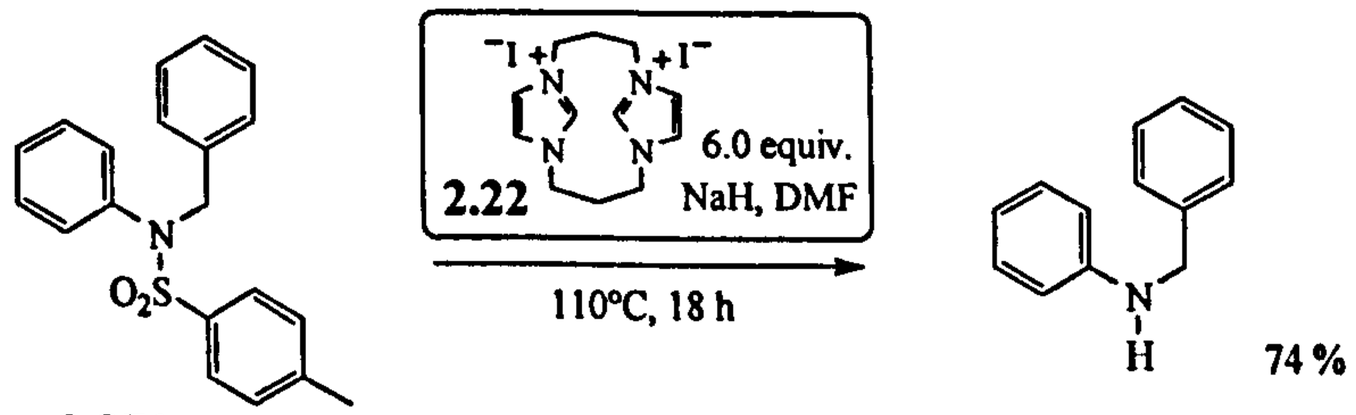


2.270 **2.271** **2.270** **2.271**

***Reagents and conditions*:** (i) *N*-phenylbenzylamine (1.0 equiv.), *p*-toluenesulfonyl chloride (1.2 equiv.), pyridine, reflux, overnight.

Scheme 2.128

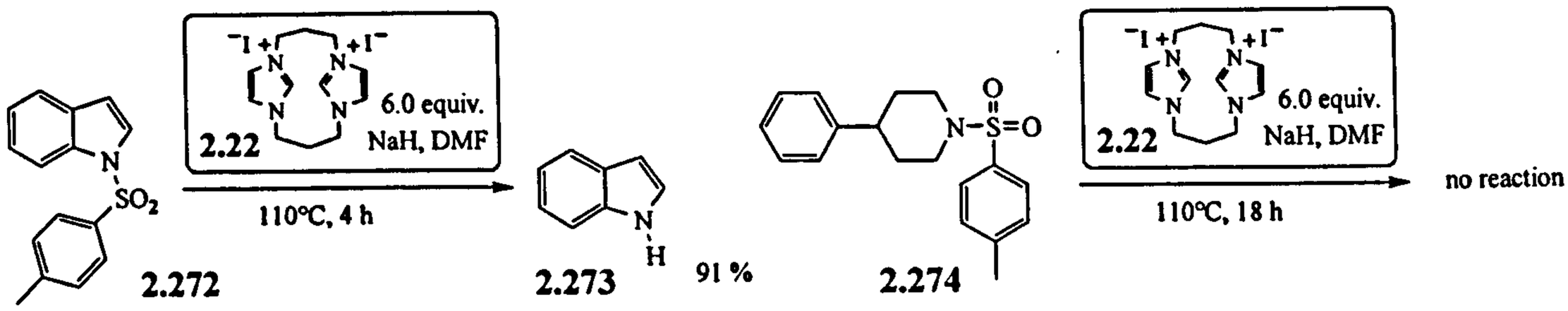
It was thought that more forcing reducing conditions, *i.e.* greater equivalent numbers of donor under more concentrated conditions, might drive the reaction to completion. Thus six equivalents of donor **2.20** under twice as concentrated conditions in DMF and 110°C for 18 h were applied, and it was found that this led to a complete conversion, giving phenylbenzylamine **2.270** in 74 % yield (**Scheme 2.129**).



2.271 **2.270**

Scheme 2.129

Two more sulfonamides, **2.272** and **2.274**, were then considered that should differ in their S-N bond strengths and stability of deprotection products. For protected indole **2.272** it was found that a decrease in reaction time to 4 h only, led to considerable increase in yield, reflecting indole's high reactivity and instability over longer reaction times (see **Scheme 2.130**).

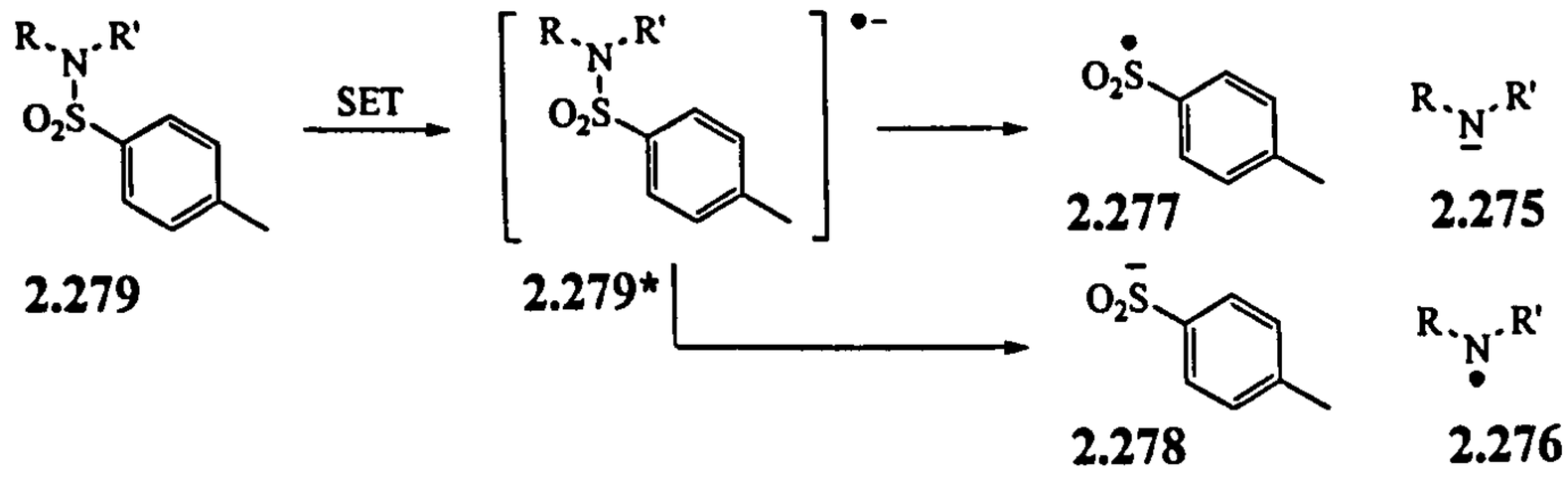


Scheme 2.130

Piperidide **2.274** did not show reaction, which is in accord with its greater S-N bond strength in comparison to the other tested sulfonamides.

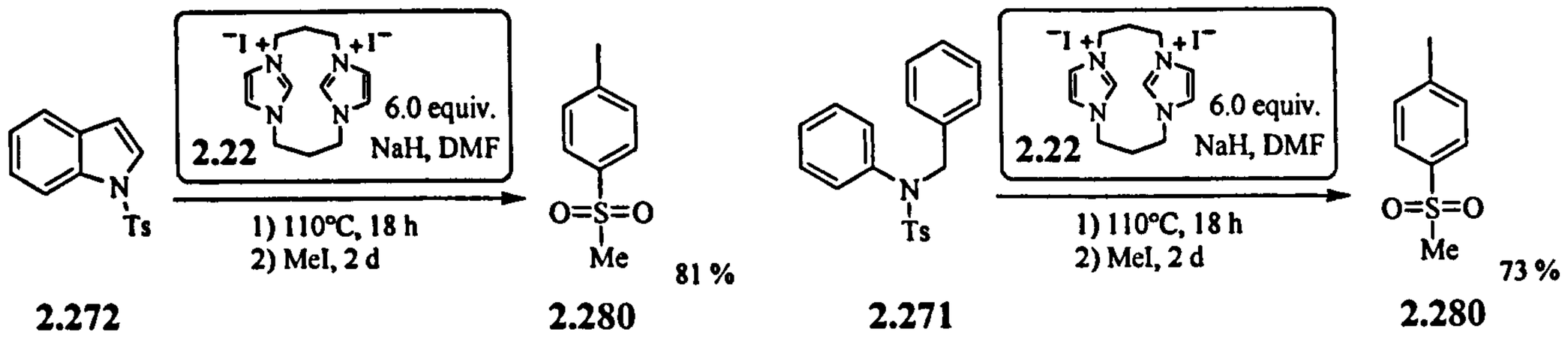
In terms of the cleavage mechanism (see **Scheme 2.131**), there is the possibility that the N-S bond cleavage proceeds to form a nitrogen-centred anion **2.275** and tolylsulfinyl radical **2.276**. Sulfonamides **2.271** and **2.272** would presumably give rise to anions with the additional lone pair being accommodated in an sp^2 orbital. Piperidide **2.274**, in contrast, would perhaps lead to an anion having the extra lone pair in an sp^3 orbital which should be less stable (this is confirmed by the trend of pK_a's). Alternatively, the bond cleavage could occur as to produce a nitrogen-centred radical **2.276** and sulfinate anion **2.278**.

Further theoretical investigations to resolve the mechanism of reductive bond cleavage will follow in section **5.4**).



Scheme 2.131

To test whether sulfinate anion **2.278** was indeed produced in the reactions with donor **2.20** as shown in **Scheme 2.131**, iodomethane was added to the reaction mixture to trap the sulfinate anion. Thus, sulfonamide **2.199** and **2.200** were reacted (see **Scheme 2.132**) with six equivalents of imidazole donor **2.20** for 18 h at 110°C. After cooling the reaction mixture, iodomethane was added and this mixture was then stirred for 2 d at room temperature. In both experiments tolyl methyl sulfone **2.280** was isolated, showing that **2.278** was formed in the reaction and possibly supporting the reductive mechanism.



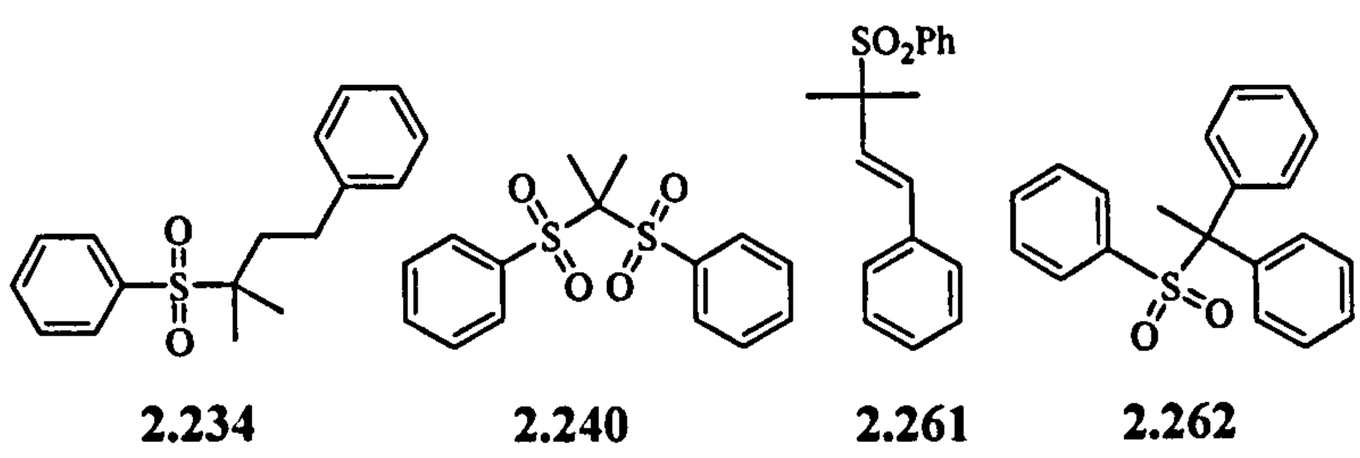
2.272 **2.280** **2.271** **2.280**

Scheme 2.132

5.4 *Theoretical investigations of the reduction of sulfones and sulfonamides*

To understand the basis of the selectivity seen in the reactions above as well as to get insight into the mechanism of reductive cleavage, computational investigations [(DFT, B3LYP/6-31G(d,p)] were carried out by T. Tuttle from our Department. These studies show that the activation energy ΔG^{*} required (calculated with Marcus theory) for the electron transfer to monosulfone **2.234** is much greater than for the activated sulfones **2.240**, **2.261** or **2.262** (see **Table 2.5**).

Acceptor	ΔG^{*}	ΔG_R
2.234	25.4	24.9
2.240	13.9	-1.7
2.261	6.1	-8.7
2.262	5.1	-13.3
2.271	10.7	-5.2
2.272	10.8	-1.5
2.274	27.0	26.7



2.234 **2.240** **2.261** **2.262**

Table 2.5 **Reaction free energy (ΔG_R) and activation energy (ΔG^{*}) for electron transfer**

Further it was shown that this initial electron transfer must be the crucial factor associated with reaction or non-reaction of the corresponding sulfone or sulfonamide, because for monosulfone **2.234** it was calculated that after electron acceptance to form the radical anion, the generated radical anion has to overcome a small barrier of only 2 kcal/mol to fragment. For **2.240**, **2.261** and **2.262**, lower activation energies are associated with the initial electron transfer, and the dissociation into a sulfinate anion occurs concertedly with electron acceptance as indicated below (see **Figure 2.13**).

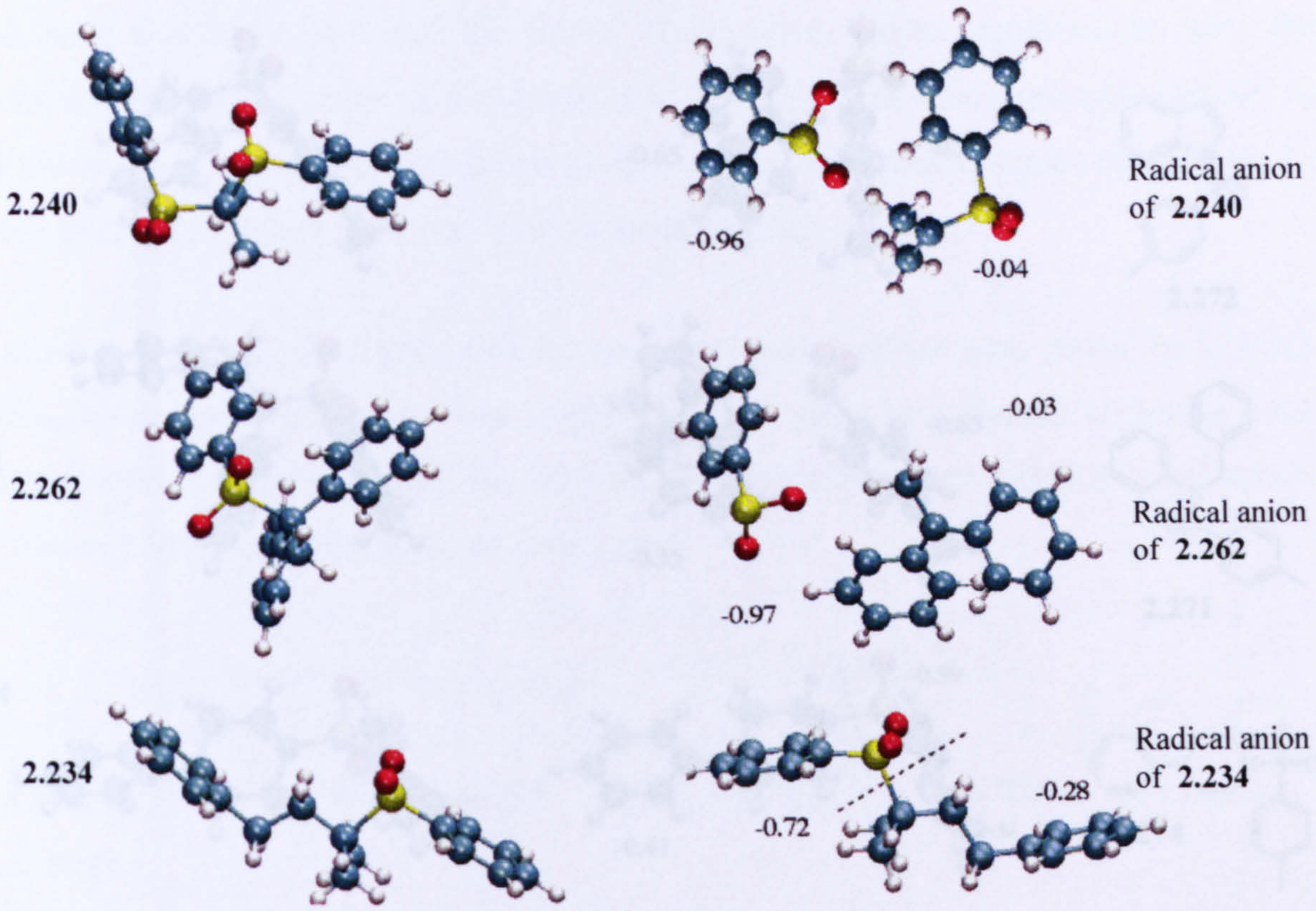


Figure 2.13

This favourable dissociation can be explained with the relevant orbitals also, *i.e.* the LUMO of **2.261**, for instance, is more extended and the additional π-substitution leads to much greater overlap than in **2.234** with the σ*-orbital of the C-S bonds, and therefore this bond will be far more weakened (**Figure 2.14**).

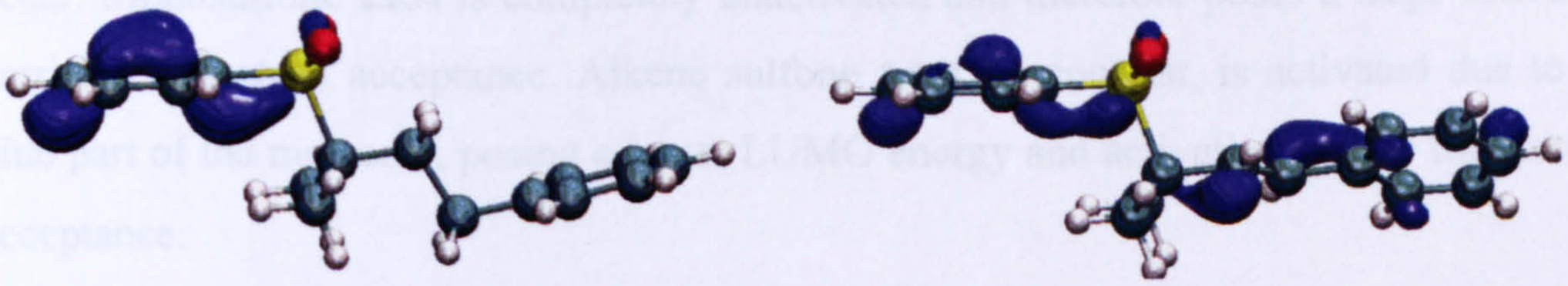


Figure 2.14 LUMO of 2.234 (left) and 2.261 (right)

For the studied sulfonamides the activation barriers to form the corresponding radical anions were found to be the most difficult step in the reductive bond cleavage also (see **Table 2.5** above). Sulfonamides **2.271** and **2.272** show smaller activation energies for electron acceptance than piperidide **2.274**, agreeing therefore with the experimental observation.[166] Upon reductive bond cleavage of **2.271** and **2.272**, the negative charge was found to reside primarily on the sulfinate for benzyl sulfonamide **2.271**, but the charge distribution was found to be reversed for the indole sulfonamide **2.272**, and a loose associated complex was formed that could be described by a three-electron bond (see **Figure 2.15** and **Appendix**).[166,167]

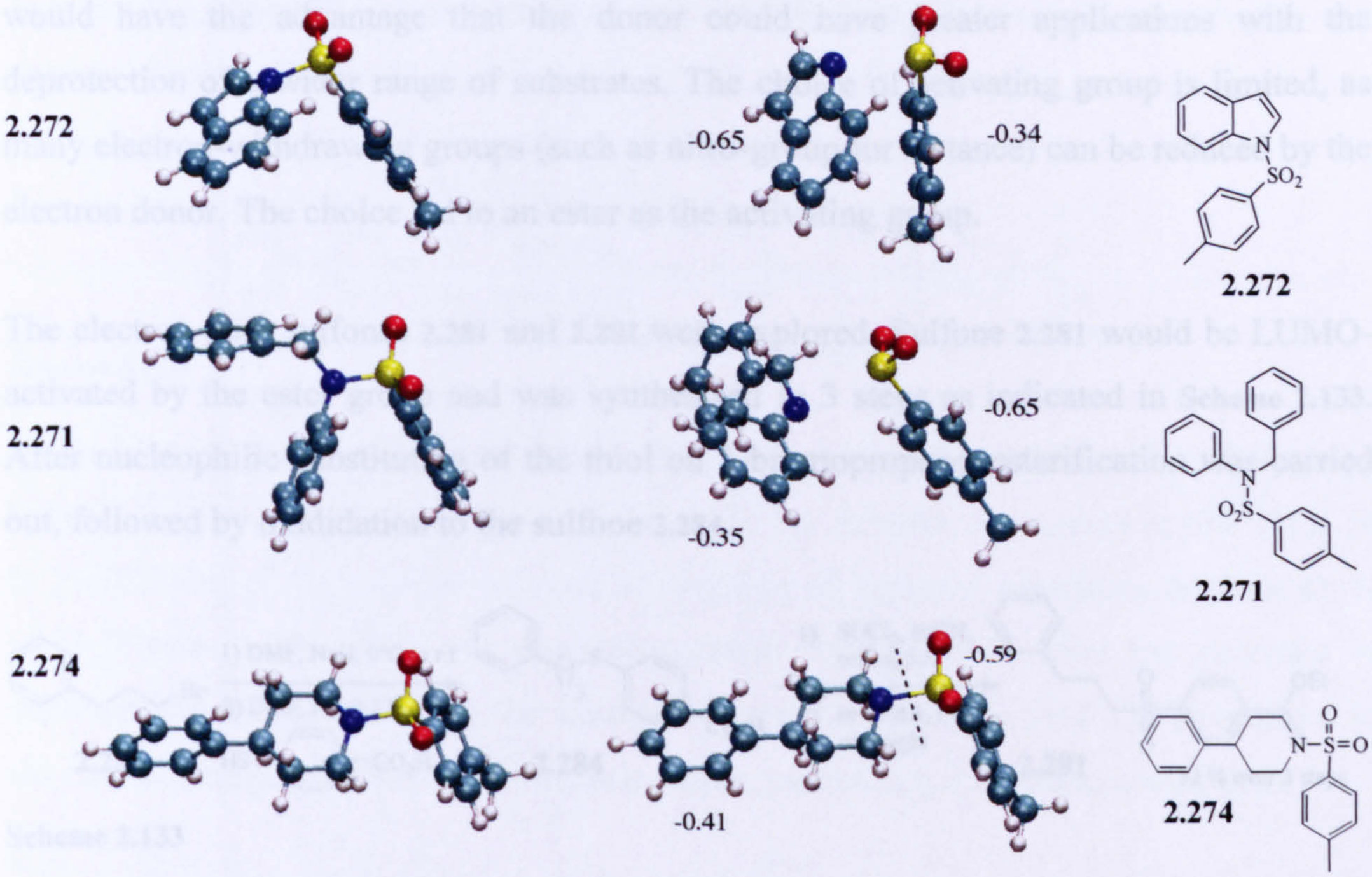


Figure 2.15 **Sulfonamides (left) and corresponding radical anions (right) with charge distribution**

5.5 *Activation of the arylsulfonyl moiety*

Based on the computational results above, the LUMO energy of the sulfone or sulfonamide is a crucial factor for the electron transfer and therefore for reductive bond cleavage to occur. Monosulfone **2.234** is completely unactivated and therefore poses a large activation barrier for electron acceptance. Alkene sulfone **2.261**, in contrast, is activated due to the blue part of the molecule, posing a lower LUMO energy and activation barrier for electron acceptance.

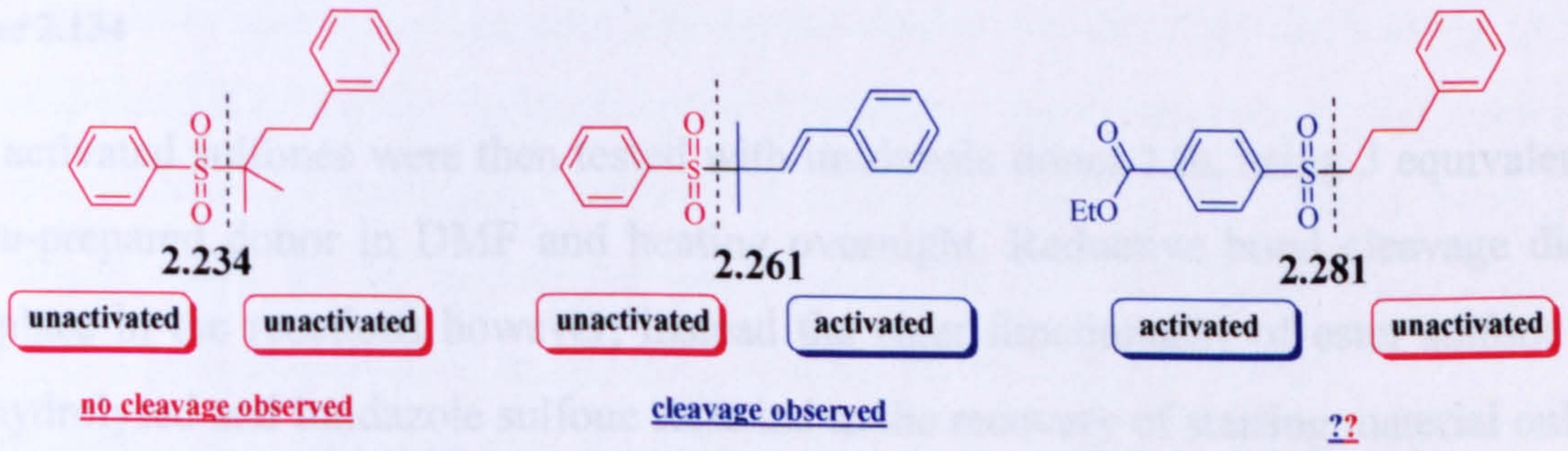
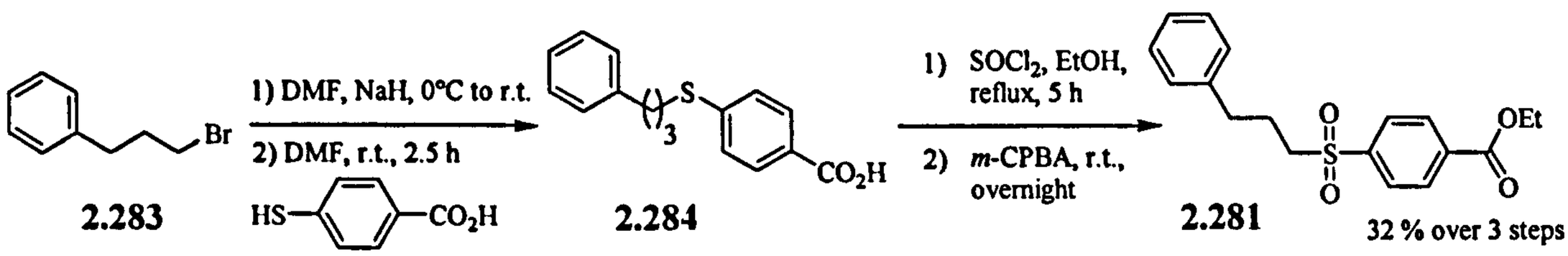


Figure 2.16

Perhaps, a lowering of the LUMO energy could be introduced into the protecting group also, instead of activating the substrate itself (as for **2.261**, indicated in blue), *i.e.* by using an electron-poor arylsulfonyl group. The lowering of the LUMO would then be achieved by imposing the activation onto the protecting group as shown in blue for **2.281** above, and

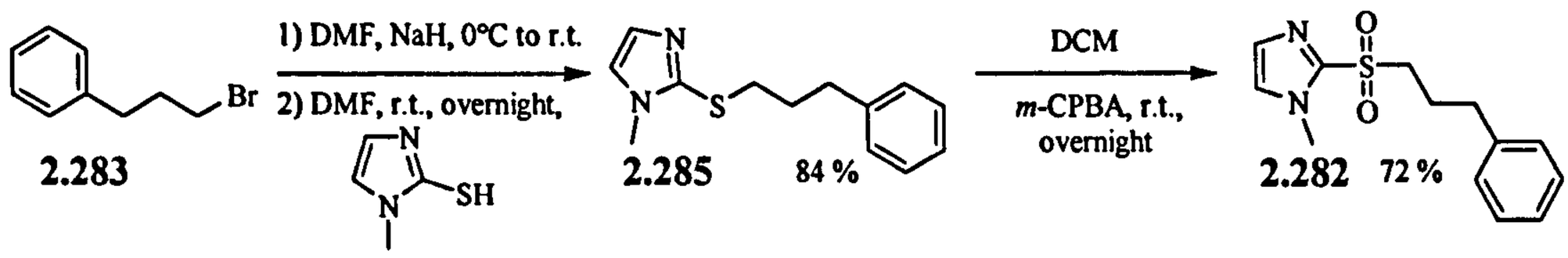
would have the advantage that the donor could have greater applications with the deprotection of a wider range of substrates. The choice of activating group is limited, as many electron-withdrawing groups (such as nitro-group for instance) can be reduced by the electron donor. The choice led to an ester as the activating group.

The electron-poor sulfones **2.281** and **2.282** were explored. Sulfone **2.281** would be LUMO-activated by the ester group and was synthesised in 3 steps as indicated in **Scheme 2.133.** After nucleophilic substitution of the thiol on 3-bromopropane, esterification was carried out, followed by oxididation to the sulfone **2.284.**



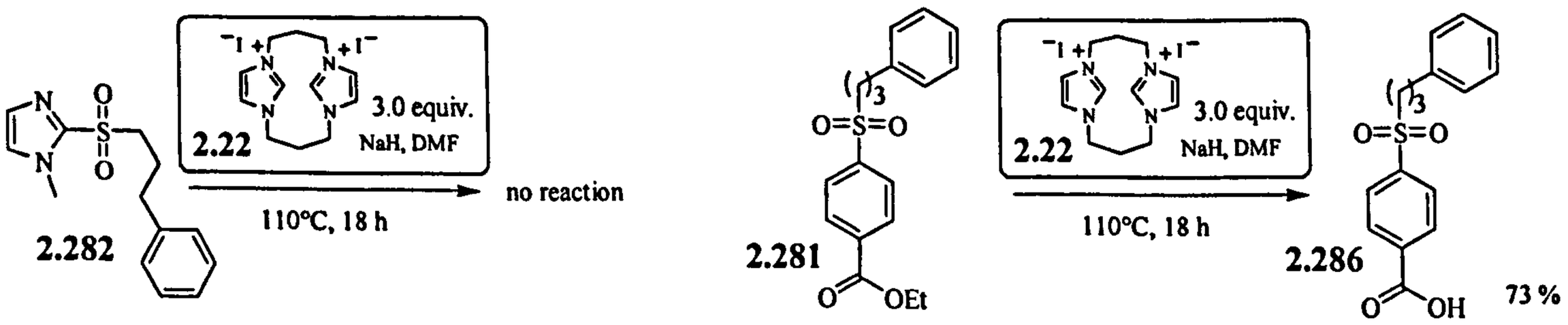
Scheme 2.133

Imidazole derived sulfones (such as **2.282** below) are more readily reduced than phenyl sulfones according to Kende *et al.*[168] who compared the reactivities in reactions with SmI_2 and found reductive cleavage only with imidazole sulfones, but not with phenyl sulfones. Additives, such as HMPA or DMPU, lead to the reductive bond cleavage of phenylsulfones with SmI_2.[169,170] Imidazole sulfone **2.282** was synthesised readily in two steps **(Scheme 2.134).**



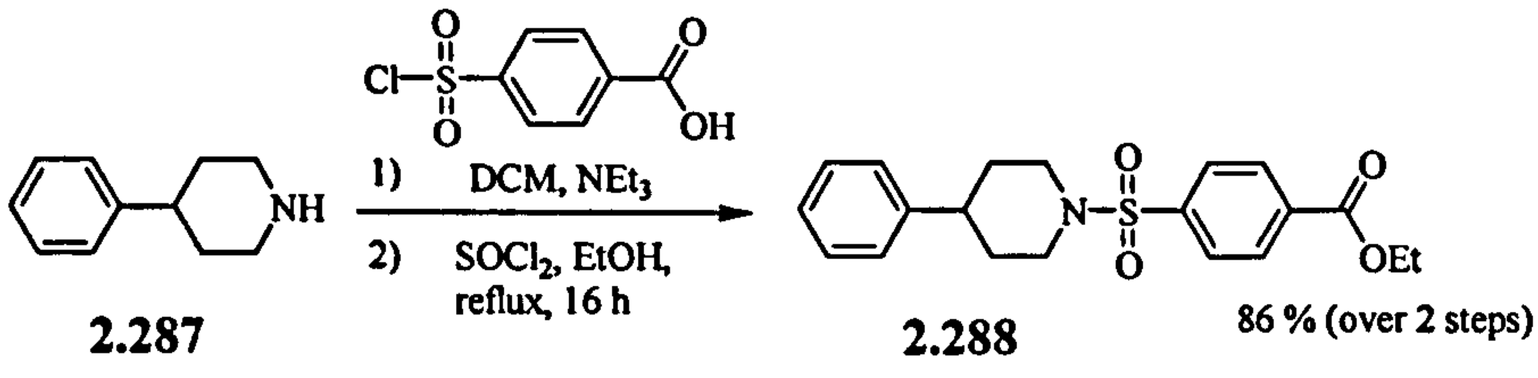
Scheme 2.134

Both activated sulfones were then tested with imidazole donor **2.20**, using 3 equivalents of *in situ*-prepared donor in DMF and heating overnight. Reductive bond cleavage did not take place in the reactions however; instead the ester functionality of ester sulfone **2.281** was hydrolysed and imidazole sulfone **2.282** led to the recovery of starting material only.



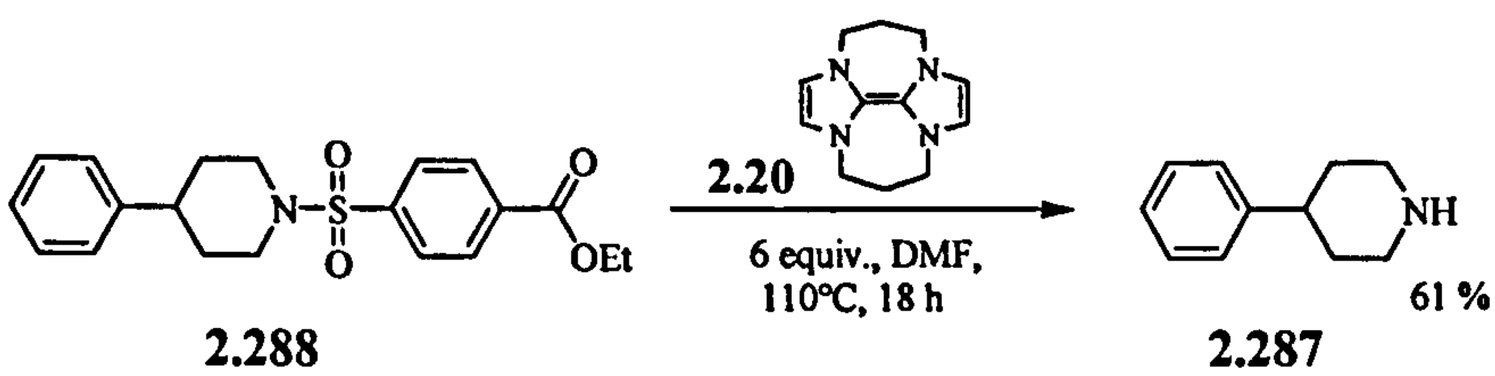
Scheme 2.135

In a parallel approach, an electron-poor sulfonamide (**2.288**) was prepared readily in two steps as shown in **Scheme 2.136.**



Scheme 2.136

It was tested using 6 equivalents of pure donor **2.20** (to avoid possible ester hydrolysis by hydroxide, if *in situ*-prepared donor **2.20** is used). The mixture was heated at 110°C for 18 h. Purification of the mixture resulted in isolation of 4-phenyl piperidine **2.287** in 61 % yield (**Scheme 2.137**). This was a pleasing result as this now makes the cleavage of sulfonamides independent from the substrate. The rather moderate yield can be ascribed to the challenging purification of an aliphatic amine, particularly in a mixture with DMF.



Scheme 2.137

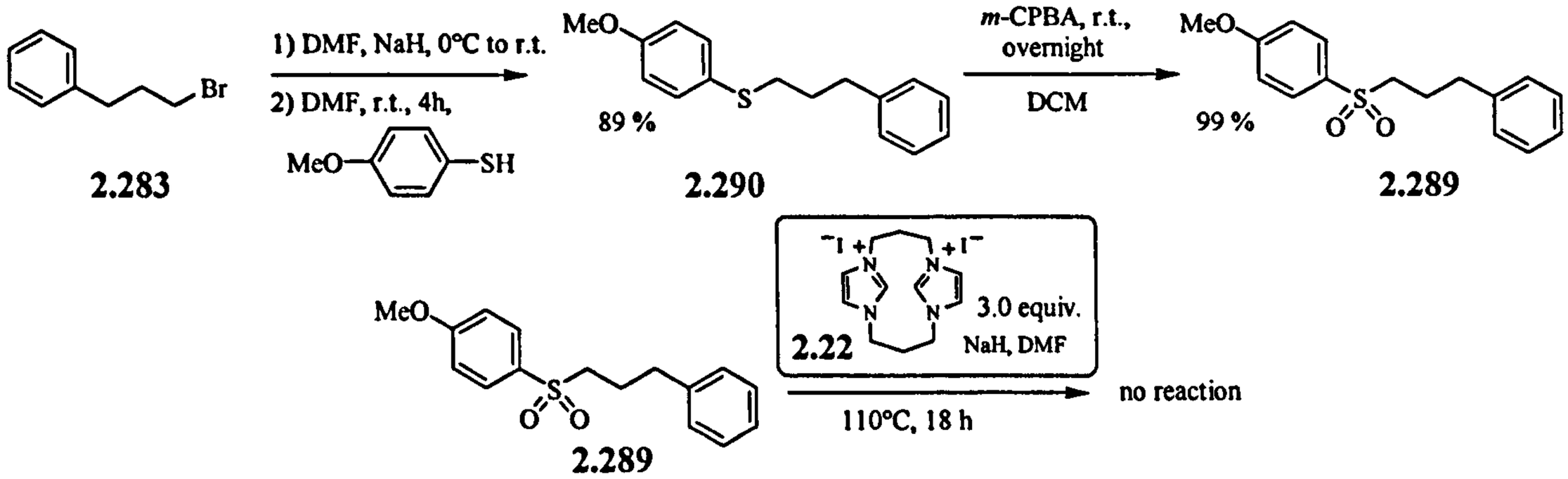
However, comparing the reductive bond cleavage of sulfonamide **2.288** with the attempted reductive cleavage of **2.281**, the cleavage of the more activated N-S bond could have been induced by nucleophilic attack of the donor or hydroxide also and further investigation would be necessary to support the proposed electron transfer mechanism.

Returning to the electron transfer induced reductive bond cleavage, the non-reaction in the first two sulfone cases (**Scheme 2.135**) might be due to the fact that the leaving group is unstabilised. So far, sulfones led to successful reductive bond cleavage, if they were π- and inductively-activated, leading to stabilised (conjugated) radicals. A primary alkyl radical (that would result in the two upper cases) would be less stabilised, leading therefore perhaps to a greater activation barrier also, despite the low-energy LUMO.

Alternatively, it was thought that the initial electron-transfer into the π* (LUMO) might take place, however, the intramolecular electron transfer from the π* to the σ* of the C-S bond, that is necessary to trigger bond cleavage, might be disfavoured now. Because the π* was lowered by the electron-withdrawing substituent, but the orthogonal σ-system was not (or less) affected, hence the gap between π* and σ* might be too large now to be overcome. This was explored with the next substrate, *i.e.* electron-rich methoxy sulfone

2.289 below. Again, an unstable alkyl radical would result from reductive bond cleavage, but this time, the $\pi^* \rightarrow \sigma^*$ gap should be significantly smaller in energy, as the π-donating methoxy group should raise the energy of the π^*-system, and the inductively withdrawing effect of the methoxy group should affect the σ^*- system, *i.e.* lower its energy.

Methoxy sulfone **2.289** was prepared in two efficient steps and tested under identical conditions to those used for the two electron-poor sulfones (**2.282** and **2.281**).



Scheme 2.138

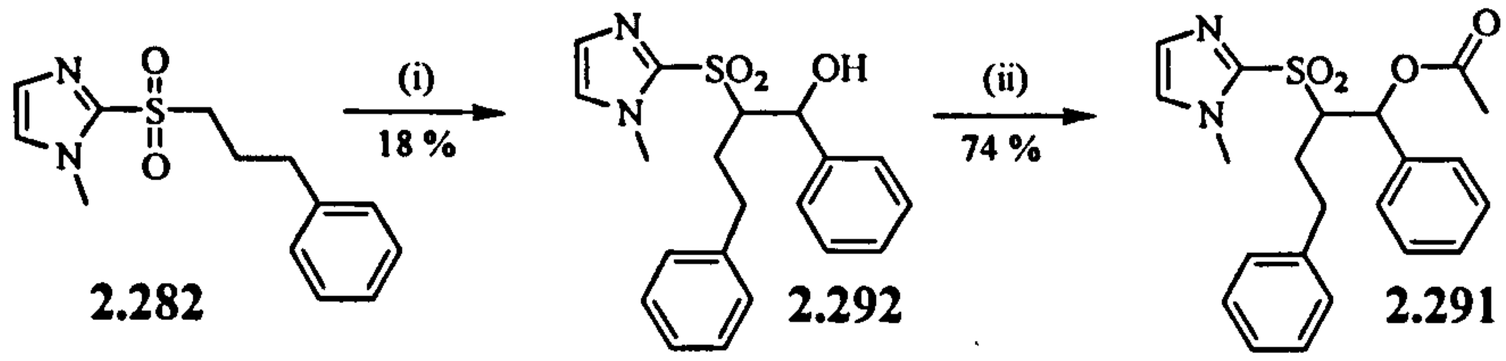
However, **2.289** did not give rise to any bond cleavage either, suggesting therewith that the unstabilised alkyl radical leaving group might indeed be responsible here for the non-reaction in these cases. Thus, the leaving group stability is just as crucial as the LUMO energy for the activation barrier of electron transfer and therefore the reaction or non-reaction of the bond cleavage.

Thus, in order to obtain a great driving-force for the sulfone to leave, more stabilised products might need to result from the reductive bond cleavage of low LUMO species. One alternative to producing a highly stabilised radical or anion, might also be to induce further reactivity in the resulting radical or anion after reductive bond cleavage. In other words, if the resulting cleavage product would react further, resulting in a highly stable product, this might lower the transition state energy for reductive bond cleavage also. Thus, the Julia olefination was envisaged next.

5.6 *Investigations towards the Julia olefination*

As discussed in the introduction, the classical Julia olefination is carried out with sodium amalgam as the reducing agent and after sulfone reduction a very good leaving group (*e.g.* acetate) is eliminated, giving rise to an alkene with *E*-selectivity.

Kende, Keck and co-workers[168,170] found that the reduction of imidazole-containing Julia substrates, such as **2.291** below, is feasible using SmI_2. The reduction of $PhSO_2$ analogues however, is much more difficult to achieve. Imidazole sulfone **2.291** was thus synthesised, by alkylation of sulfone **2.282** (its synthesis is described above) using NaHMDS as the base and benzaldehyde as the electrophile. The alcohol obtained was then converted to the corresponding ester **2.291** using acetic anhydride (see **Scheme 2.139**).

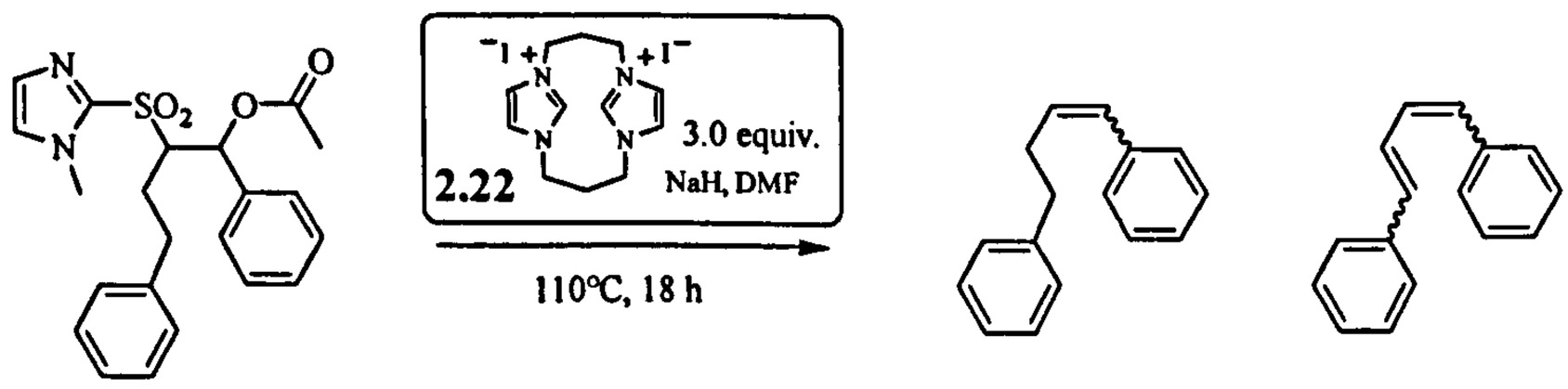


2.282 **2.292** **2.291**

***Reagents and conditions*: (i)** NaHMDS (1.0 equiv.), benzaldehyde (1.0 equiv.), THF, -78°C, 1 h; **(ii)** triethylamine (2.4 equiv.), DMAP, acetic anhydride (1.2 equiv.), DCM, 0°C to r.t., overnight.

Scheme 2.139

Having sulfone ester **2.291** in hand, its behaviour in the presence of electron donor **2.20** was next explored. Three equivalents of donor were used and the mixture was heated at 110°C overnight (**Scheme 2.140**). This resulted in a complete consumption of starting material and, after column chromatography, an inseparable mixture of alkenes was isolated in ca. 73 % yield.



2.291 **2.293** **2.294**

Scheme 2.140

The mixture was analysed by ^{1}H-NMR and GC-MS. The latter analysis is given in **Figure 2.17** below. Column **A** shows the GC-chromatogram. Two major peaks corresponding to a mass of 208 (identical with the mass of alkene **2.293**) are present, which is illustrated in column **C**. Three other major peaks corresponding to a mass of 206 are present also (illustrated in column **B**) and this mass is identical to the molecular mass of diene **2.294**. Comparison of the mass spectra of the peaks in column **C** with the known library spectrum of alkene **2.293** indicates a very good match (see **Figure 2.18**). Furthermore, alkene **2.293** has a characteristic fragmentation peak at 117; only the peaks from column **C** show this peak in the corresponding mass spectra, which is illustrated in **D** (**Figure 2.17**). The mass spectra corresponding to the peaks at the retention times 12.76 min and 13.17 min are identical,

hence suggesting that the peaks might correspond to the two possible isomers (*E* and *Z*) of alkene **2.293** (the mass spectra are shown in the appendix, section **9.3**).

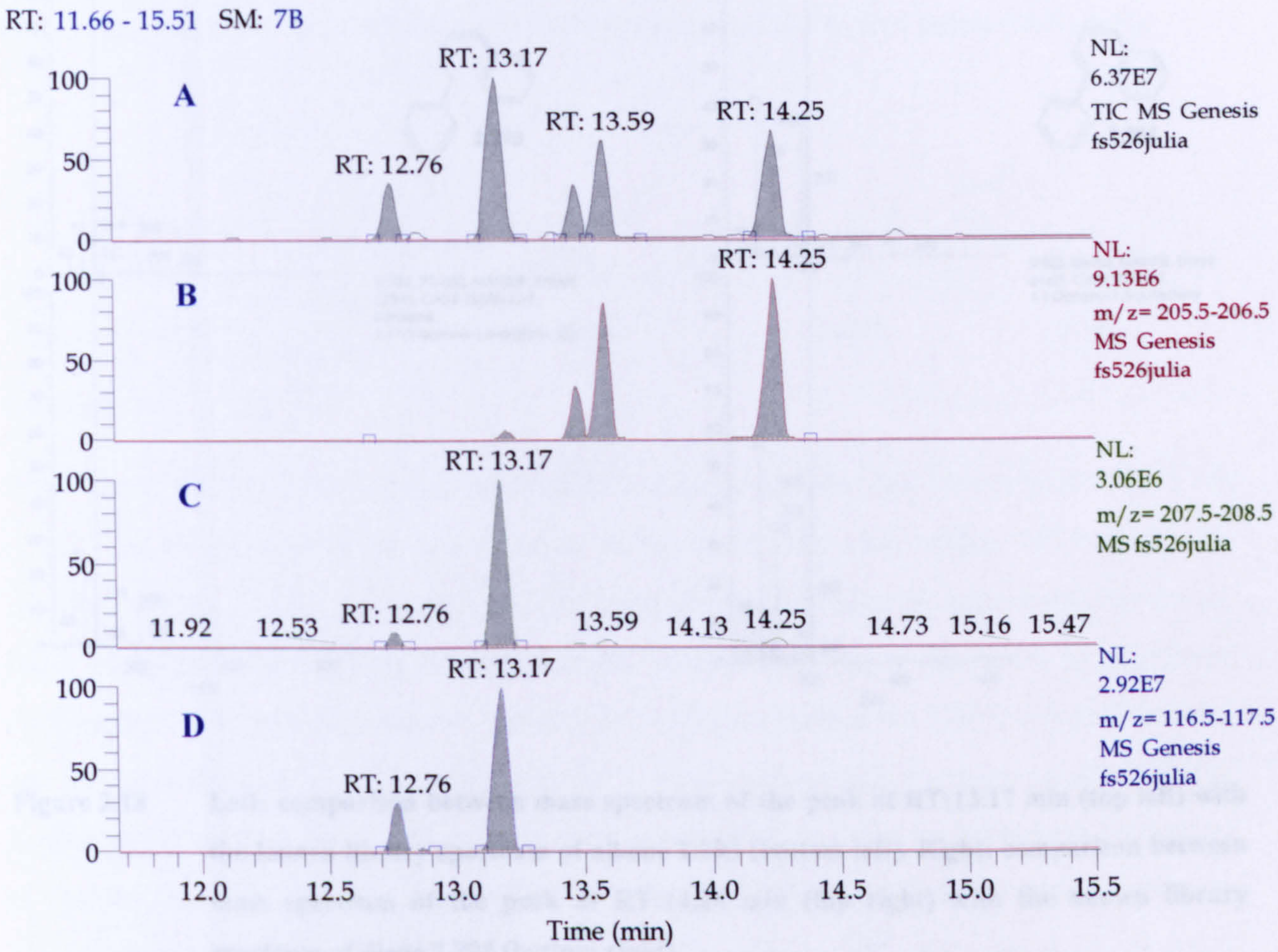


Figure 2.17 **GC-MS analysis of the reaction from Scheme 2.291, with A: GC-chromatogram, B: peaks from A that show *m/z* = 206 in the MS; C: peaks from A that show *m/z* = 208 in the MS; D: peaks from A that show *m/z* = 117 in the MS.**

The fragmentation spectra of the three peaks in **B** in **Figure 2.17**, likely corresponding to diene **2.294,** show a very good match with the known library spectrum also (see **Figure 2.18**).

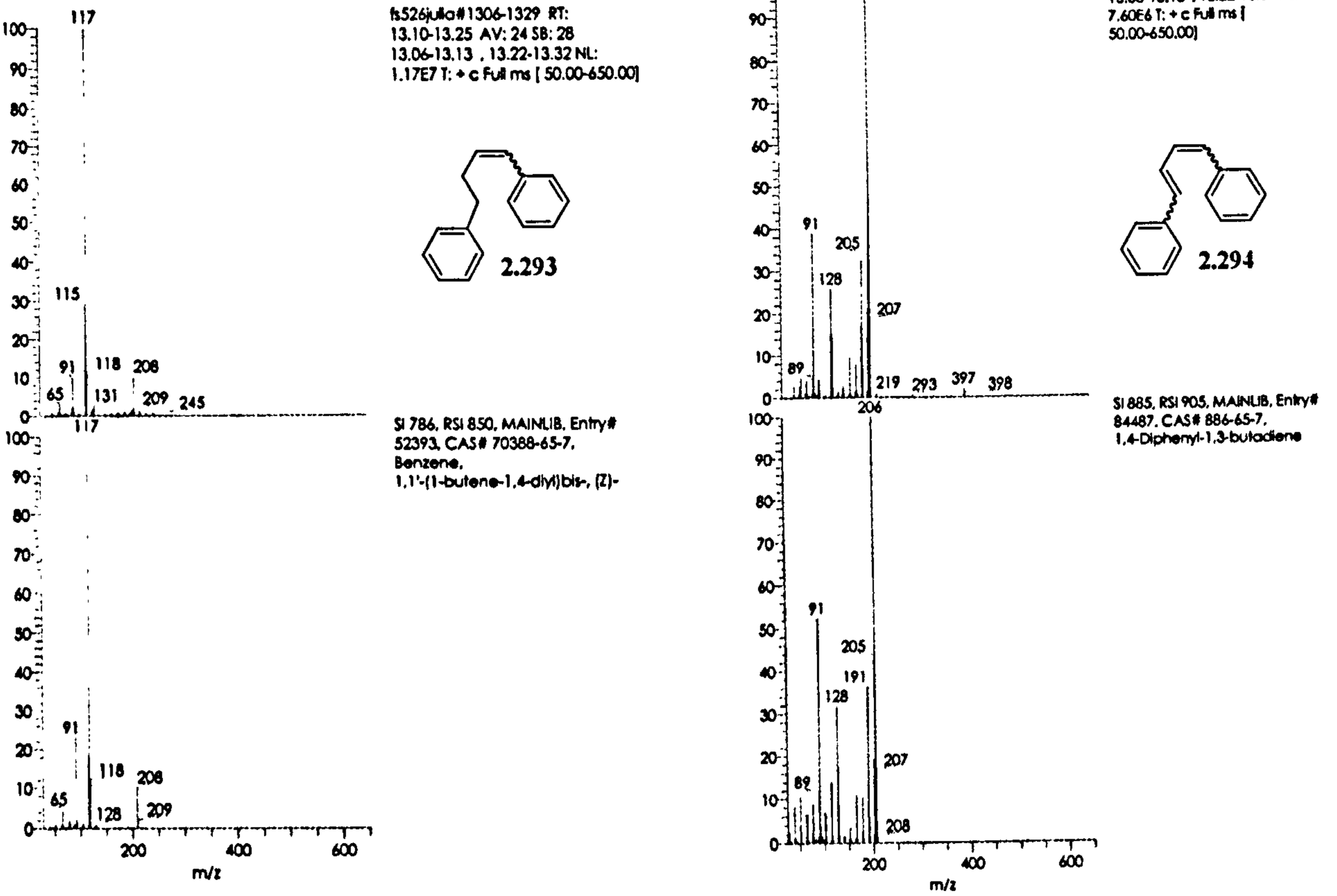
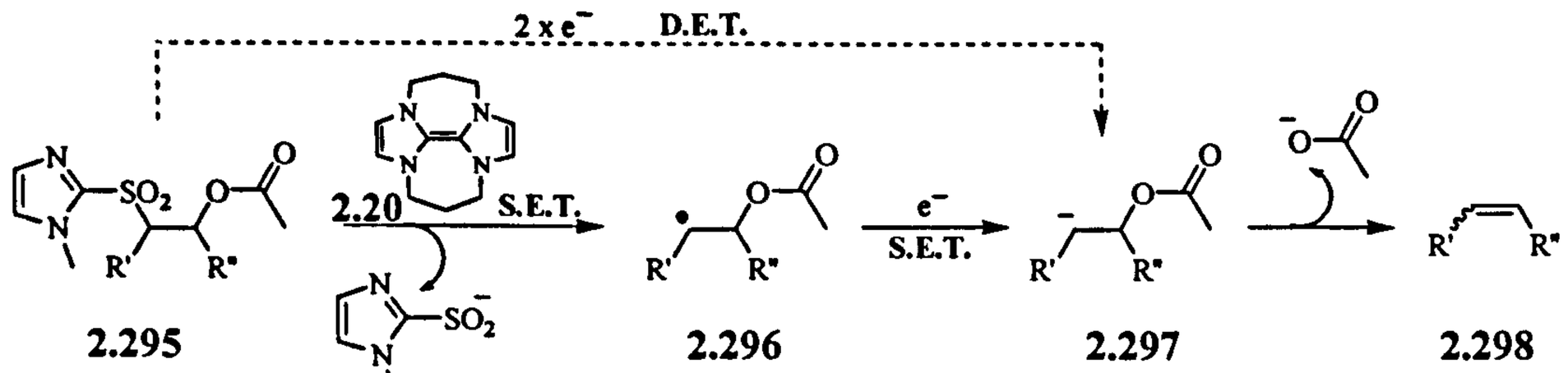


Figure 2.18 Left: comparison between mass spectrum of the peak at RT:13.17 min (top left) with the known library spectrum of alkene 2.293 (bottom left). Right: comparison between mass spectrum of the peak at RT:14.24 min (top right) with the known library spectrum of diene 2.294 (bottom right).

Furthermore, the three peaks in **B** in **Figure 2.17** have an identical fragmentation pattern (see Appendix for the mass spectra, section **9.3**), which would suggest that the three peaks might correspond to the three possible isomers, *i.e. E/Z*, *Z/Z* and *E/E*. Attempts to purify the mixture of alkene **2.293** and diene **2.294** by HPLC were unsuccessful. [The ^{1}H-NMR spectra of the mixture of diene **2.293** and alkene **2.294** after column chromatography and after HPLC purification can be found in the Appendix, section **9.3**].

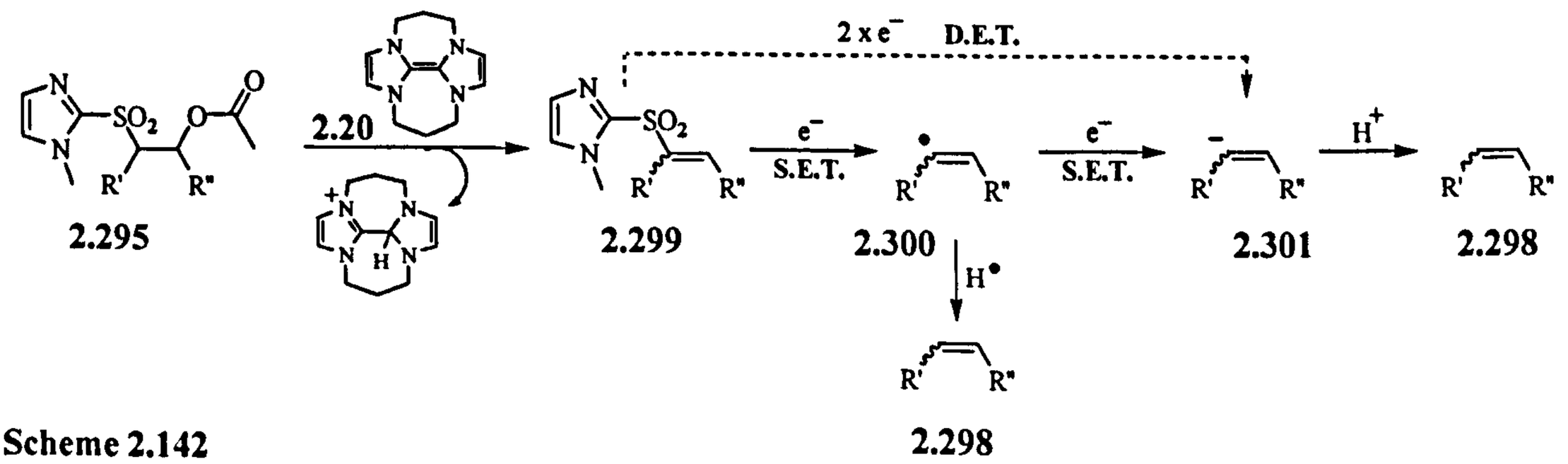
Alkene **2.293** would be the first example of a Julia reaction in the absence of metals, using a completely neutral organic electron donor. Its formation can be rationalised by two possible mechanisms. The originally proposed mechanism for the classical Julia olefination includes the formation of an alkyl anion *via* two successive electron transfers and subsequent elimination of the acetate (compare with Introduction, section **1.3**). For the reactions with electron donor **2.20** this path (**Scheme 2.141**) is a less likely alternative, since

reduction of an alkyl radical (**2.296**) to the alkyl anion (**2.297**) has as yet not been observed in reactions with donor **2.20** (compare section **4.2**, *i.e.* aldehyde formation). The only possibility would therefore be that the arylsulfonyl group accepts two electrons before undergoing reductive bond cleavage (possibly analogous to the aryl anion formation).



Scheme 2.141

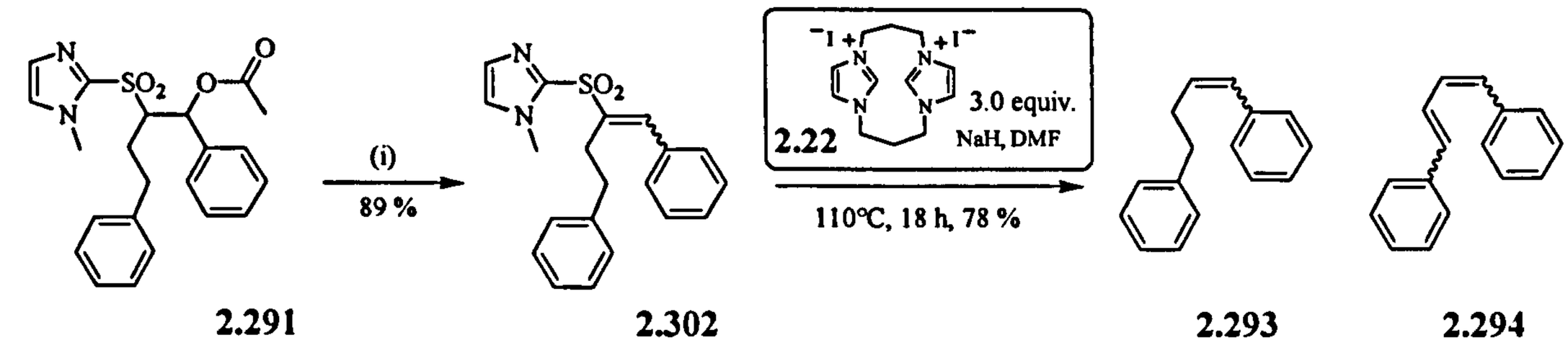
However, the second mechanistic possibility would be the one that was proposed by Keck *et al.*[170] as an alternative for the classical Julia olefination mechanism. With deuterium labelling studies as well as SmI_2 reactivity comparisons, Keck *et al.* concluded that a very likely mechanistic possibility for the classical Julia olefination is the initial base-induced elimination of the acetate group by methoxide (sodium-amalgam in THF/methanol solution are the standard conditions), giving rise to a vinyl sulfone that is subsequently reduced further to the alkene. The vinyl sulfone intermediate was verified by premature quenching of the reaction. This mechanism could be a very likely reaction path for the reduction by donor **2.20** (**Scheme 2.142**). Reduction of the vinyl sulfone **2.299** might proceed *via* single electron transfer (S.E.T.) to give the vinyl radical **2.300** that would then be quenched with an H-atom, or alternatively, further reduction to the vinyl anion might take place, giving alkene **2.298** after protonation of the latter. Vinyl anion **2.301** could also be formed by double electron transfer (D.E.T.) directly from vinyl sulfone **2.299**.



Scheme 2.142

To test for this mechanistic possibility, vinyl sulfone **2.302** was prepared by DBU-triggered elimination of the acetate group in THF at room temperature, giving vinyl sulfone **2.302** in excellent yield (**Scheme 2.143**). Subsequent testing of **2.302** with donor **2.20** under identical

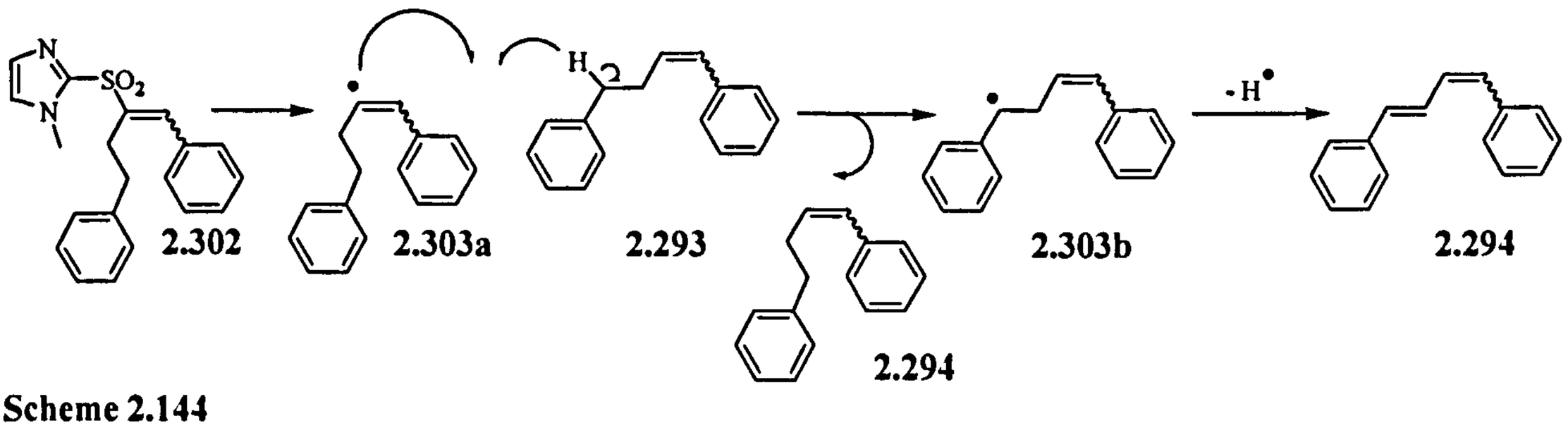
conditions as before, gave the identical reaction outcome. Once again, a mixture of alkenes **2.293** and **2.294** was obtained in *ca.* 78 % yield.



***Reagents and conditions*:** (i) DBU (6.0 equiv.), THF, r.t., overnight.

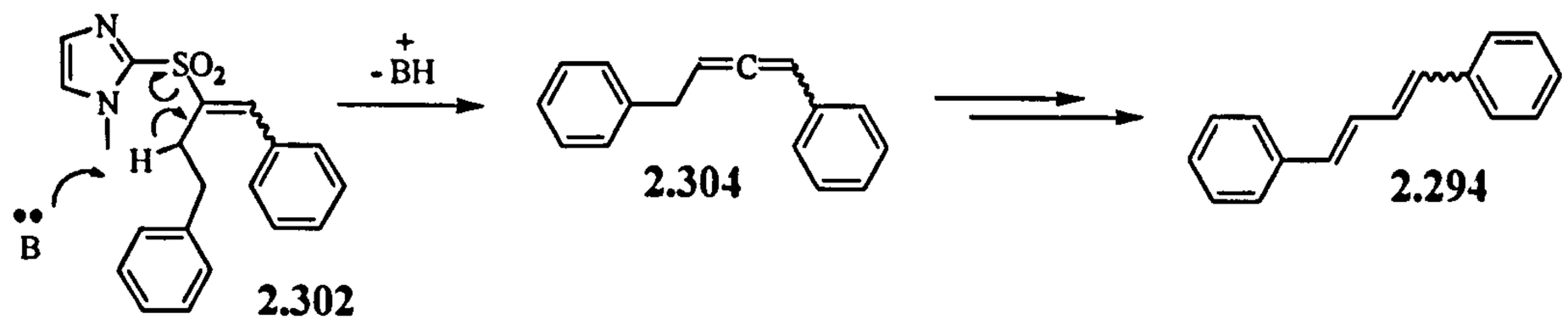
Scheme 2.143

Diene **2.294** might form by H-atom abstraction by a vinyl radical intermediate **2.303a**, assisted by high temperature and the driving force of forming a highly conjugated system.



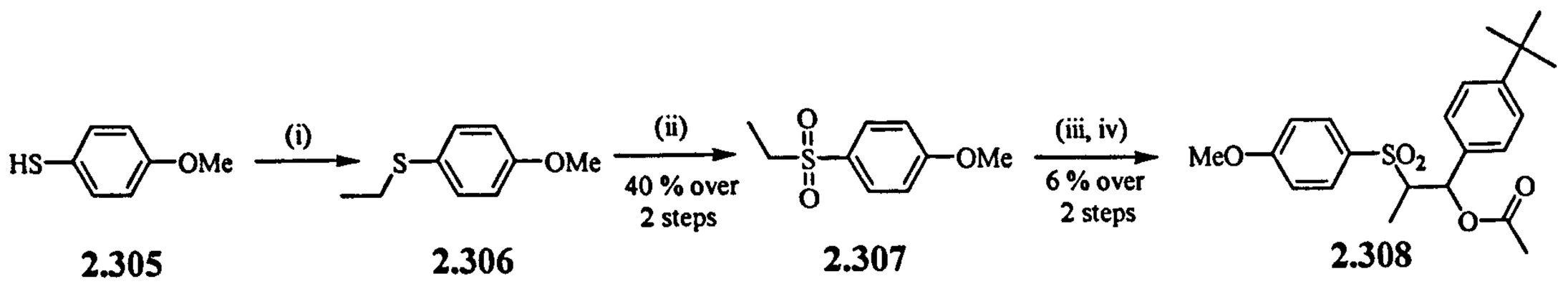
Scheme 2.144

Alternatively, diene **2.294** might form *via* allene species **2.304** that could result from base-induced elimination of the heterocyclic sulfonyl group.



Scheme 2.145

The mechanism for the formation of diene species **2.294** could at this stage not completely be resolved. Therefore two more ester sulfone analogues were prepared, bearing a different aliphatic chain length that would not impose a driving force towards a conjugated species. Furthermore, two different aryl sulfonyl groups were explored in order to investigate the scope of the Julia-type olefination by electron donor **2.20**. SmI_2 was found to be inefficient in achieving the Julia reaction on phenylsulfonyl derivatives due to the more negative reduction potential of the latter group. How imidazole donor **2.20** stands in comparison to SmI_2 was thus of interest next.

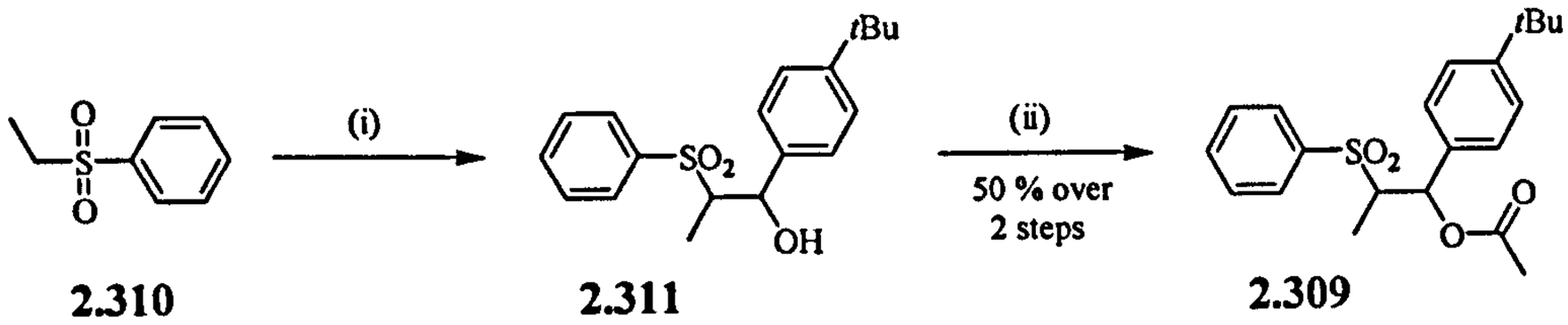


2.305 **2.306** **2.307** **2.308**

***Reagents and conditions*: (i)** EtI, DMF, NaH, 0°C to r.t., 2.5 h; **(ii)** *m*-CPBA, DCM, r.t., overnight, **(iii)** NaHMDS (1.1 equiv.), *tert*-butyl-benzaldehyde (1.2 equiv.), THF, -78°C, 1 h; **(iv)** triethylamine (2.4 equiv.), DMAP, acetic anhydride (1.2 equiv.), DCM, 0°C to r.t., overnight.

Scheme 2.146

Para-methoxysulfone ester **2.308** as well as phenylsulfonyl ester **2.309** were prepared as indicated in **Schemes 2.146** and **2.147**, analogously to previously described procedures.

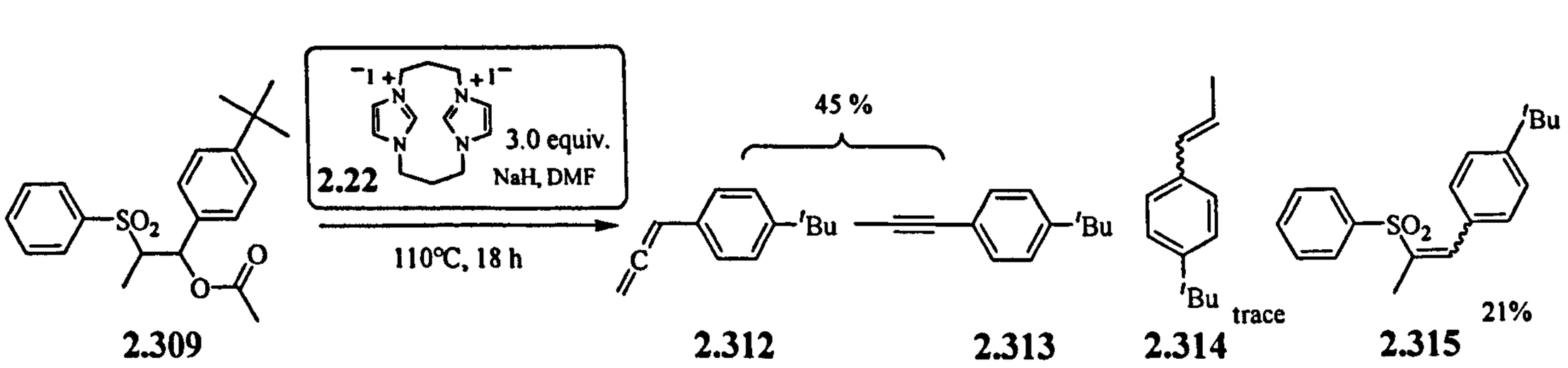


2.310 **2.311** **2.309**

***Reagents and conditions*: (i)** NaHMDS (1.1 equiv.), *tert*-butyl-benzaldehyde (1.2 equiv.), THF, -78°C, 1 h; **(ii)** triethylamine (2.4 equiv.), DMAP, acetic anhydride (1.2 equiv.), DCM, 0°C to r.t., overnight.

Scheme 2.147

Phenylsulfone ester **2.309** was then tested with electron donor **2.20**, using 3 equivalents of donor at 110°C overnight. The result of the experiment is illustrated in **Scheme 2.148**. This time, two fractions were isolated. The first apolar fraction was analysed by ^{1}H-NMR and GC-MS. The two major peaks in GC-MS had a molecular ion peak at a mass of 272, and further comparison with the ^{1}H-NMR of the mixture indicated that those two peaks most likely correspond to allene **2.312** and alkyne **2.313**. Two small peaks were also seen in GC-MS, corresponding to a mass of 174, which would match alkene **2.314** (2 peaks corresponding possibly to *E*- and *Z*-isomer of the alkene). However, alkene **2.314** was not observed in the ^{1}H-NMR analysis, suggesting that it was formed only in trace amount. Vinyl sulfone **2.315** was isolated as the second fraction.

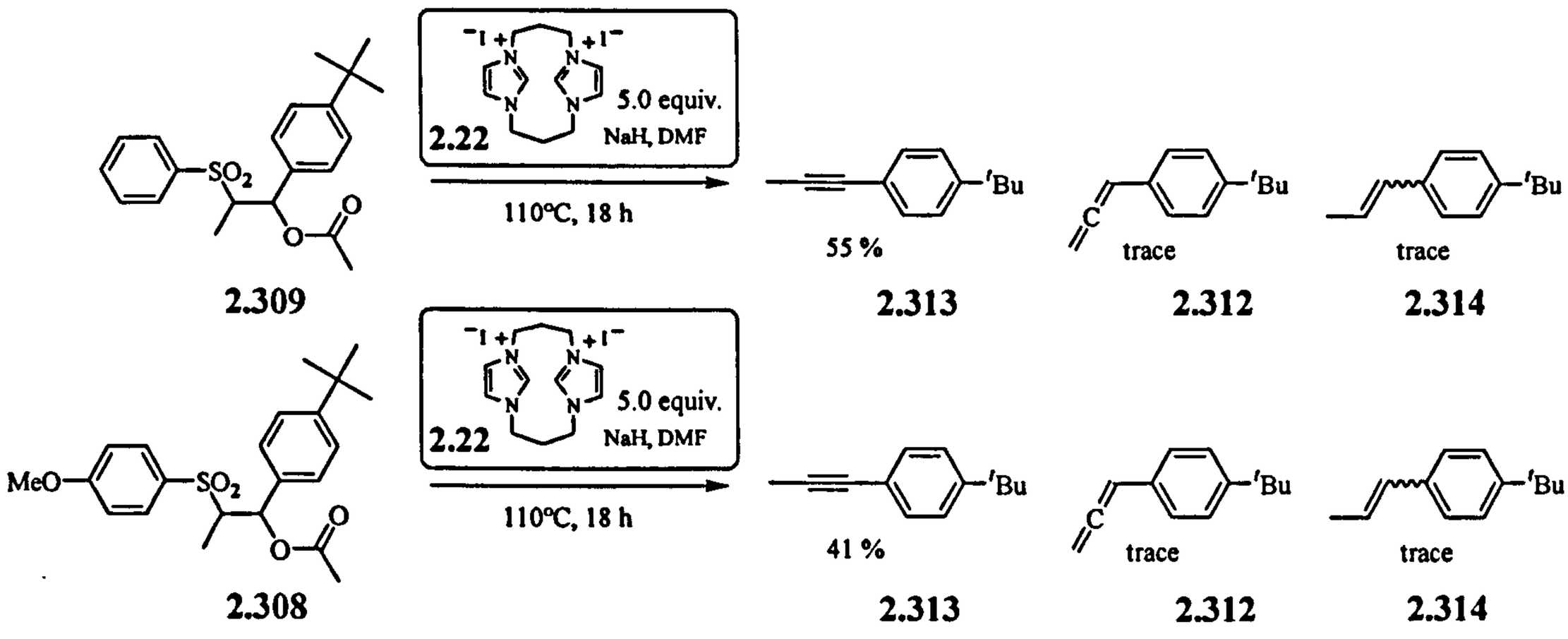


2.309 **2.312** **2.313** **2.314** **2.315**

Scheme 2.148

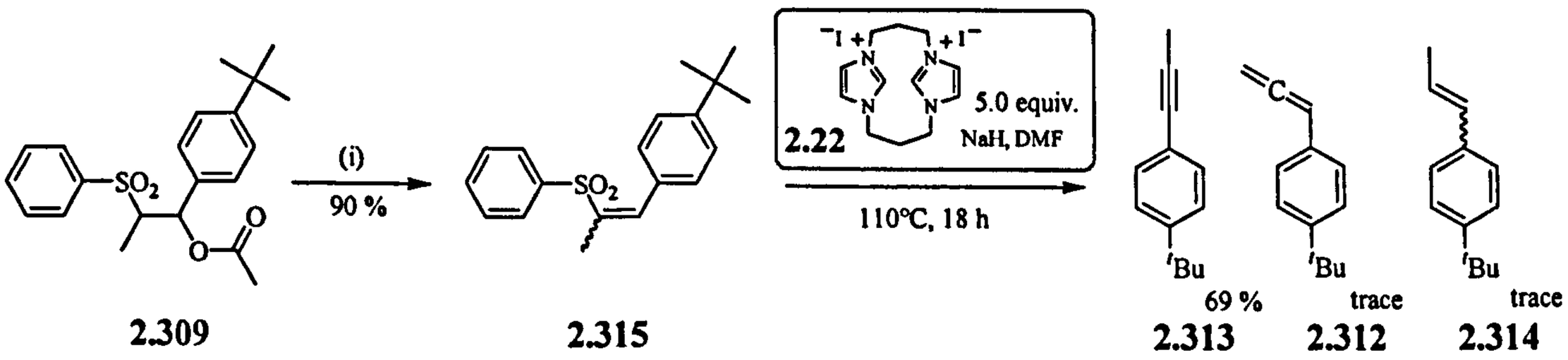
Repeat of the experiment using 5 equivalents of donor to increase the reducing power and therefore perhaps favour alkene **2.314** formation and to achieve full reduction of vinyl

sulfone intermediate **2.315**, led then to almost exclusive alkyne formation in the reaction with *para*-methoxy sulfone substrate **2.308** and aryl sulfone **2.309**. In both cases, GC-MS and ^{1}H-NMR analyses revealed traces of allene **2.312** and alkene **2.314** (two peaks with a mass of 174, identical retention time as previously, possibly corresponding to *E*- and *Z*-isomer) being formed also (**Scheme 2.149**).



Scheme 2.149

Vinyl sulfone **2.315** that was prepared *via* DBU-induced elimination of acetate, gave rise to the identical reaction outcome with 5 equivalent of *in situ*-prepared donor **2.20**.



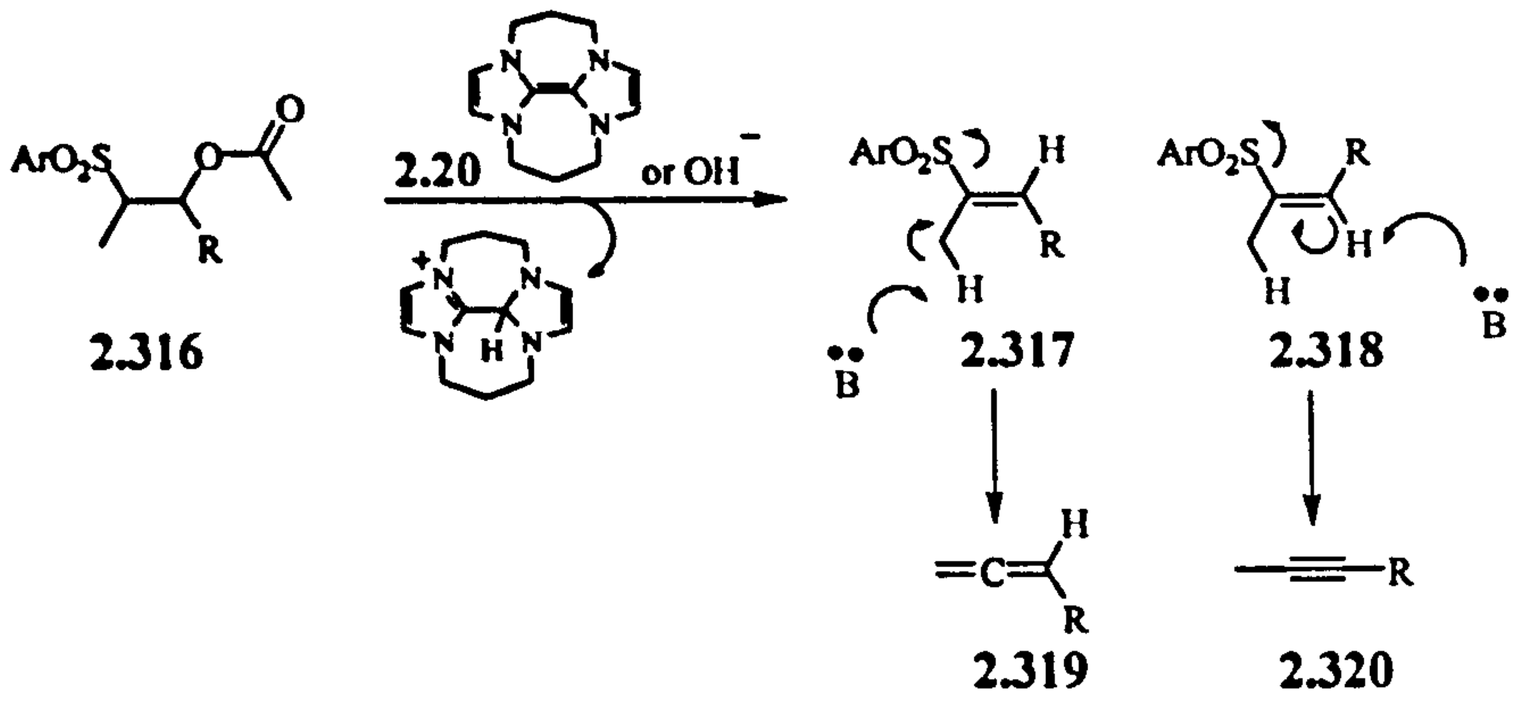
***Reagents and conditions*: (i)** DBU (6.0 equiv.), THF, r.t., overnight.

Scheme 2.150

The varying mass balances in these reactions can most likely be ascribed to the rather low boiling points of the species formed. Observation of alkene **2.314** by GC-MS in only trace amounts in all cases suggests that the reduction potential of aryl sulfonyl groups either in ester sulfone species **2.309** or vinyl sulfone **2.315** is too negative to achieve complete reductive bond cleavage by electron donor **2.20**, as is the case in reaction with SmI_2 (without the help of additives, such as HMPA or DMPU) also.

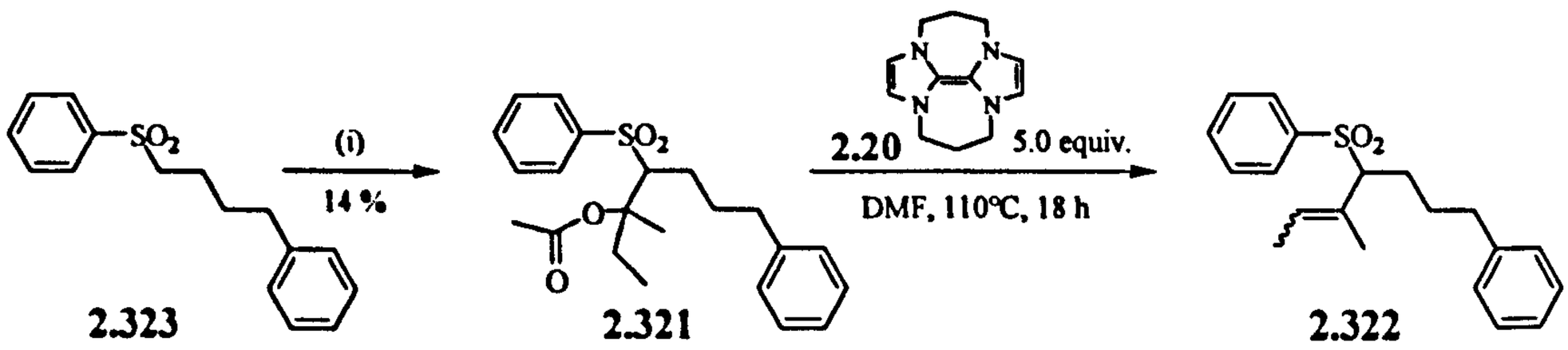
Alkyne **2.313** as well as allene **2.312** most likely form *via* base-induced elimination. As the reductive pathway seems to be too difficult for donor **2.20** to undergo, it chooses to react by an alternative pathway and acts as a base to eliminate the sulfinate anion. This highlights

once again, the fine reactivity borderlines of the neutral organic electron donors, reacting at the intersection between electron donor, nucleophile or, as observed here, a base (**Scheme 2.151**). Alternatively, hydroxide, that is likely to be present in the reaction mixture might have acted as the base also and might have caused the observed eliminations. Perhaps both species are reactive.



Scheme 2.151

As the final substrate, sulfone **2.321** was synthesised as shown in **Scheme 2.152** and investigated, this time with pure donor **2.20** (*i.e.* hydroxide should not be present in the reaction mixture). This substrate now is derived from a ketone, bearing a methyl group instead of the (acidic) proton. Thus the elimination path towards alkyne **2.320** would be disfavoured. However, the extra methyl group seems to increase the steric hindrance to such an extent that now a completely different proton is abstracted, leading to species **2.322** as the exclusive product. This reaction outcome might be a combination of both, increased steric hindrance around the *alpha*-sulfonyl position and the absence of hydroxide as the possible (small) base.



***Reagents and conditions*:** (i) NaHMDS (1.0 equiv.), 2-butanone (1.0 equiv.), THF, -78°C, 1 h, then quenched with Ac_2O (1.2 equiv.).

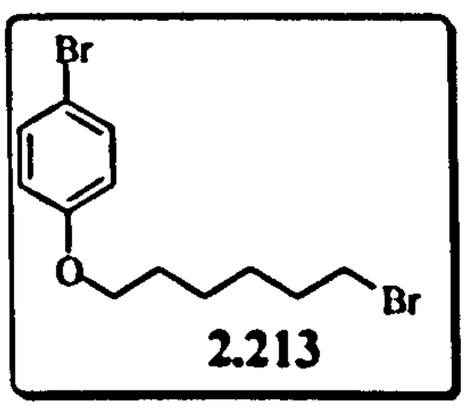
Scheme 2.152

In conclusion, imidazole donor **2.20** was applied to the successful and clean deprotection of activated sulfones and sulfonamides, proving to be a selective and highly powerful reagent. This selectivity was found to be based on the greater activation barriers for the electron transfer step to form the radical anions in the unactivated sulfone and sulfonamide cases and depends both on the LUMO energy and the stability of the leaving groups.

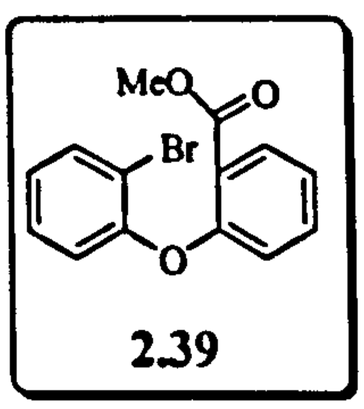
Strong evidence was presented for the first example of a Julia olefination using the neutral organic electron donor **2.20** on an imidazole based sulfone ester, and the limited scope for other aryl sulfones has been shown. Promise lies in further investigation of imidazole or derivatives of similarly low reduction potential to make the reductive pathway most favourable in competition with base-induced side-reactions. Applications of 'metal-free' Julia reactions in synthesis are then likely to follow in the future.

5 Can neutral organic donors achieve selective reductions?

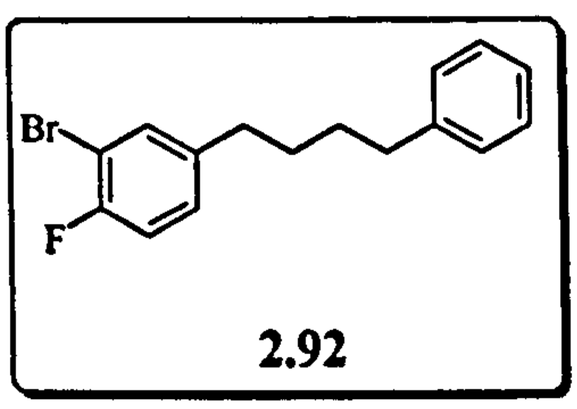
Following the results that were obtained in the previous chapters in the reduction of aryl iodides, bromides and sulfones, significant differences in reactivities were observed depending on the reaction conditions. It seems that there is a very fine borderline in reactivity of the neutral organic electron donors. The investigations that were carried out on sulfones show that it should be possible to reduce a *bis*sulfone over a monosulfone, if present in the same molecule or reaction mixture. Further, the experiments done on aryl iodides highlighted how important the nature of the *ortho*-substituent to the leaving iodide is for an efficient departure of the iodide. Great differences in reactivity were observed also, depending on whether additional substitution was on the aromatic system. Thus, it was observed that aryl bromide **2.39** reacts at room temperature, where fluorobromide **2.92** reacts only if heat is applied.



2.213



2.39



2.92

Further, *para*-bromide **2.213**, in contrast to **2.39**, required heat also. This reaction outcome is in line with electrochemical observations. *Para*-bromophenol exhibits a more negative reduction potential than 2-bromophenol. A similar trend is observed with iodophenol: *para*-iodophenol is significantly more difficult to reduce than *ortho*-iodophenol (see **Table 2.6** below).[154]

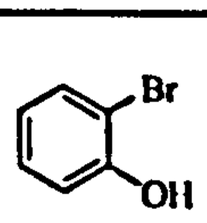
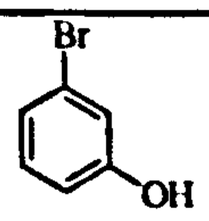
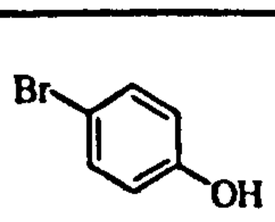
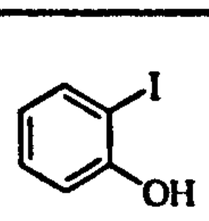
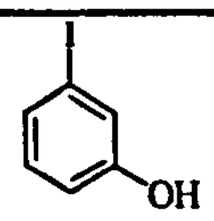
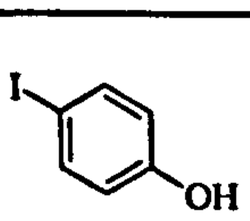
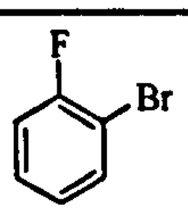
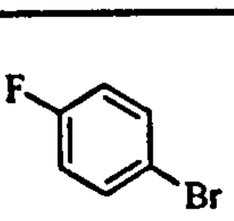
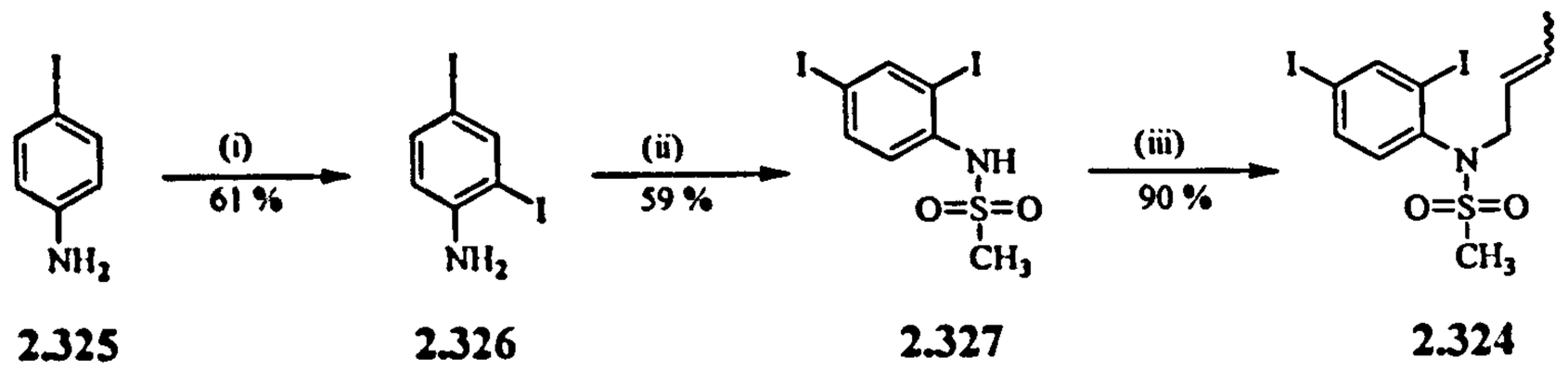
Compound								
$E^{red}_{1/2}$ *vs.* SCE in H_2O	**-1.97 V**	**-2.06 V**	**-2.14 V**	**-1.53 V**	**-1.63 V**	**-1.70 V**	**-1.69 V**	**-2.00 V**

Table 2.6

Thus, it was thought that it might be possible to make use of this trend and to achieve selective reduction of an *ortho*- over a *para*-iodide, if both are present in the same molecule. Diiodo-substrate **2.324** was synthesised for that purpose by iodination of 4-

iodoaniline, following the procedure by Shirtcliff *et al.*[171] Subsequent mesylation and Mitsunobu reaction gave rise to diiodide **2.324**.

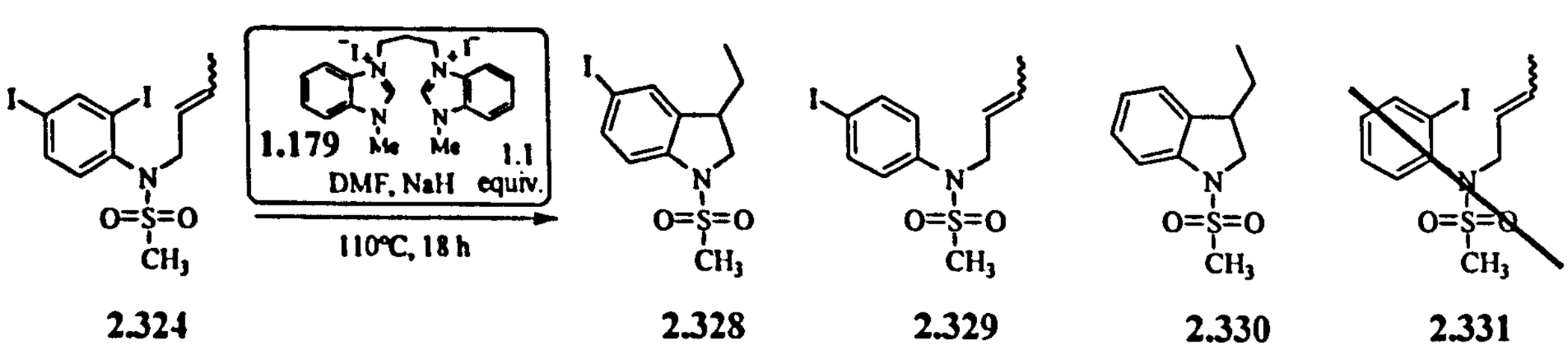


2.325 **2.326** **2.327** **2.324**

***Reagents and conditions*: (i) 4-iodoaniline (1.0 equiv.), tetramethylammonium iodochlorate (1.15 equiv.), $CaCO_3$ (1.4 equiv.), DCM/ MeOH (5:1), r.t., overnight; (ii) 2.326 (1.0 equiv.), DMAP, MsCl (1.1 equiv.), pyridine, reflux, 18 h; (iii) 2.327 (1.0 equiv.), but-2-en-1-ol (1.2 equiv.), PPh_3 (1.2 equiv.), DIAD (1.2 equiv.), THF, r.t., 4 h.**

Scheme 2.153

Substrate **2.324** was then investigated with benzimidazole donor **1.175**, since this donor had been shown to be at the borderline of being able to reduce aryl iodides. Thus, only this donor would give the desired selectivity in that case. In the initial experiment, 1.1 equiv. of donor **1.175** were formed *in situ* using the NaH method. After centrifugation, the supernatant yellow liquid was added to substrate **2.324** which gave a colour change from yellow to orange and the mixture was then heated at 110°C for 18 h. After neutral work-up and further purification by column chromatography, ^{1}H-NMR spectroscopic analysis of the obtained mixture was carried out and a rather complex composition was observed. By ^{1}H-NMR spectroscopic comparison with the NMR data of the authentic sample, compound **2.331** could be excluded; it was not formed in this reaction (**Scheme 2.154**). The sample was then further analysed by GC-MS, revealing that two compounds with identical mass were formed in the reaction, but showing a different fragmentation pattern. Comparison with the proton NMR spectrum indicated that these compounds might be **2.328** and **2.329**. Furthermore, compound **2.330** was formed, indicating that over-reduction had taken place.

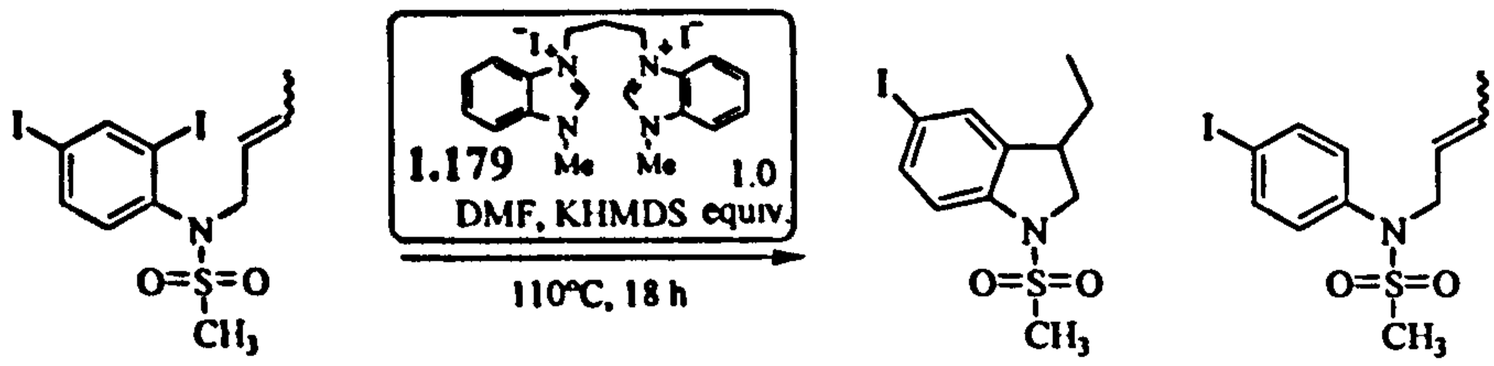


2.324 **2.328** **2.329** **2.330** **2.331**

Scheme 2.154

In the experiment 1.1 equivalents of donor **1.175** were used since loss of donor solution was feared by centrifugation and subsequent transfer *via* cannula to the reactant. However, to ensure that only 1.0 equivalent of donor was present in the reaction mixture, donor **1.175**

was formed differently in another experiment, this time forming it with KHMDS and adding the substrate to it. By this method, more precise amounts of reagents should have been in the mixture. Again, the reaction outcome was rather complex (**Scheme 2.155**). More than one product had formed. In purification attempts reduced iodide **2.329** and cyclised iodide **2.328** were isolated.

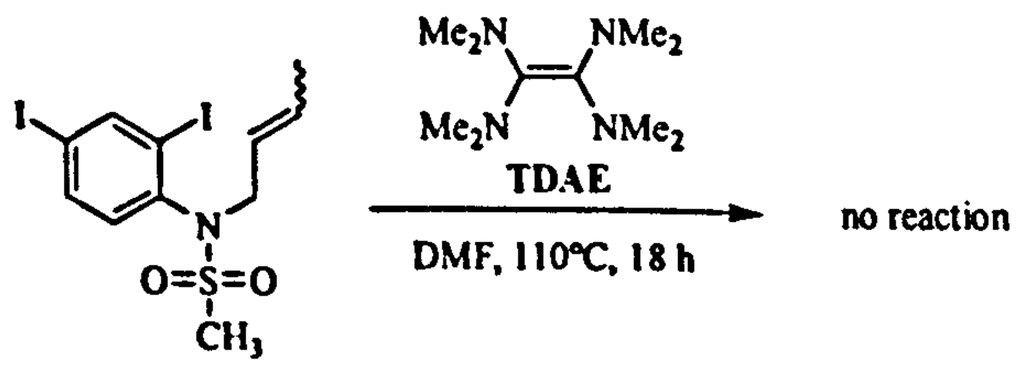


2.324 **2.328** **2.329**

Scheme 2.155

The isolation of reduced iodide **2.329** was intriguing. If an aryl radical had formed selectively on the *ortho*-iodide, this radical should have cyclised in a very rapid and efficient manner. Reduced, uncyclised products were never seen using benzimidazole donor **1.175** on iodo NMs substrates.[94] The presence of the second iodine should not have affected the conformation of the molecule to the extent that a cyclisation would now be slow and disfavoured in competition with hydrogen-atom abstraction. However, the second iodine might have an effect on the aromatic system (information about the LUMO of **2.324** can be found in the Appendix, section **9.4**). Two electron-withdrawing iodine substituents might lower the LUMO energy considerably, and hence might activate the system towards reduction. This would agree with the observation that colour had changed at room temperature. This is generally only observed when heat is applied in reaction with benzimidazole donor **1.175** with iodo-NMs substrates. Thus, double electron transfer might have taken place onto this highly activated diiodo-substrate **2.324** at room temperature analogously to the chemistry of imidazole donor **2.20** on unactivated aryl iodides.

To test for this greater reactivity of the diiodo-substrate **2.324** towards electron acceptance, the reaction was tried with TDAE, which is a less powerful electron donor that does not react with mono-iodo NMs aryl iodides,[172] but might give rise to selective and exclusive aryl radical formations on this more activated system.

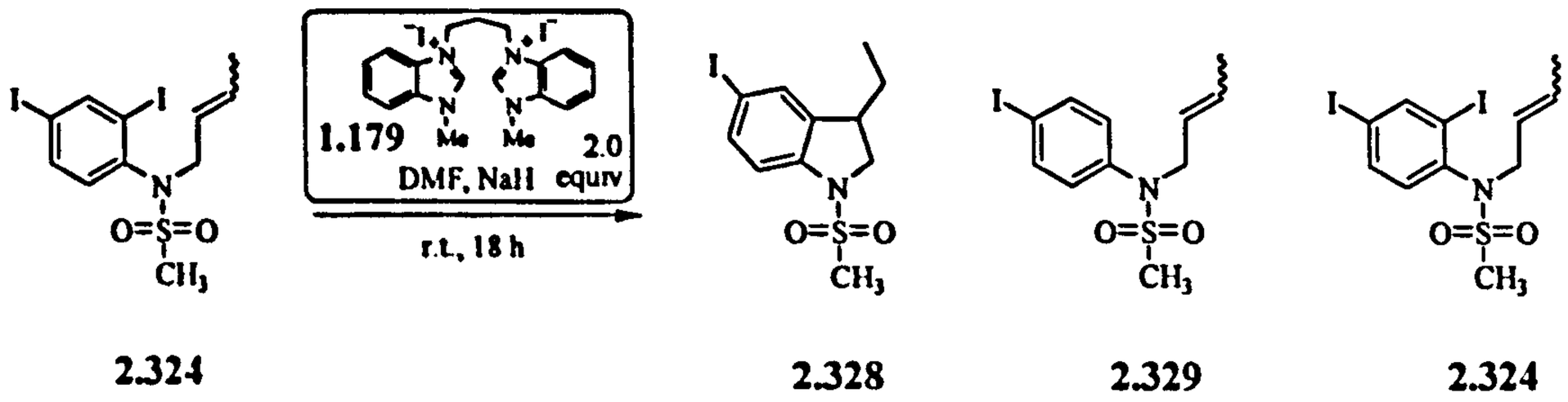


2.324

Scheme 2.156

Thus, one equivalent of TDAE was reacted with diiodide **2.324** at DMF at 110°C overnight. After work-up ^{1}H-NMR of the crude mixture showed only starting material, the reaction did not proceed.

In another attempt, diiodo-substrate **2.324** was reacted with two equivalents of benzimidazole donor **1.175** generated by the NaH method (**Scheme 2.157**), and this time heat was not applied. Monoaryl iodides do not react at room temperature with benzimidazole donor **1.175**, thus, if selective reduction was possible at room temperature due to the greater activation of the diiodide system, then over-reduction should not take place, even if excess amounts of donor were used.

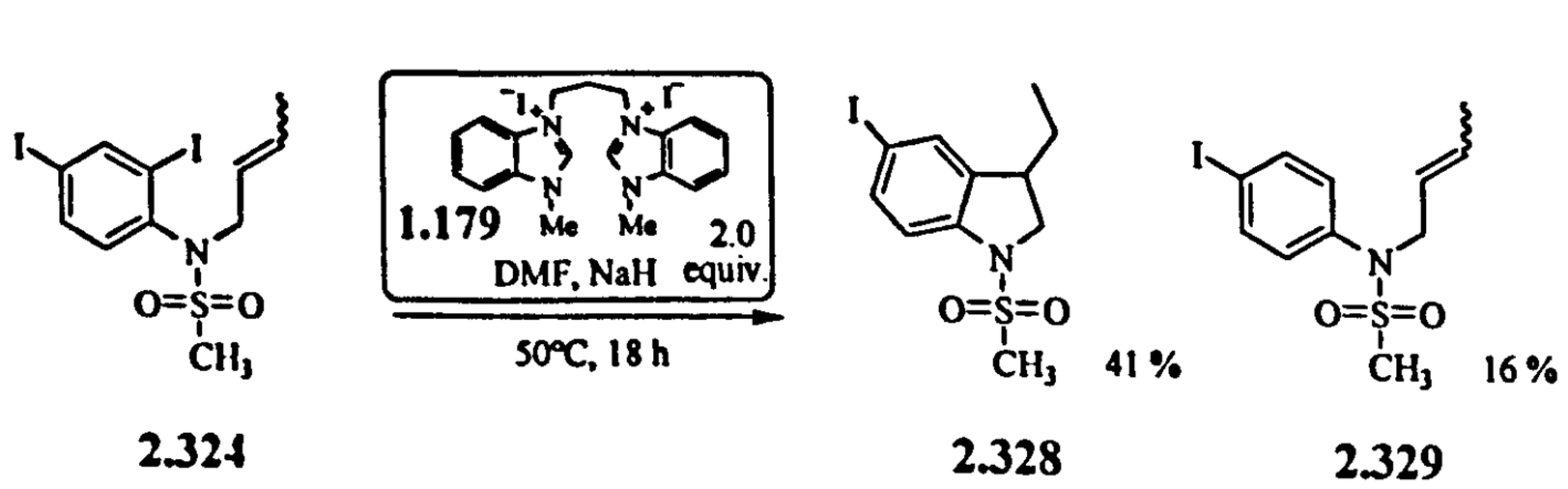


2.324 **2.328** **2.329** **2.324**

Scheme 2.157

When the yellow donor-solution was added to the substrate, instantaneous colour change to orange took place. After 30 min reaction time, the mixture was deep red, and after stirring for 18 h at room temperature, surprisingly, the mixture was yellow again (**Scheme 2.157**). ^{1}H-NMR analysis of the crude mixture after work-up indicated that the reaction did take place to some extent. Starting material **2.324** was seen in a mixture with cyclised iodide **2.328** and reduced compound **2.329**.

The experiment was repeated and this time only gentle heat was applied (50°C for 18 h; 110°C are required to convert a mono-iodoarene[94]) to drive the reaction to completion. And indeed, pleasingly no starting material was observed anymore (**Scheme 2.158**).



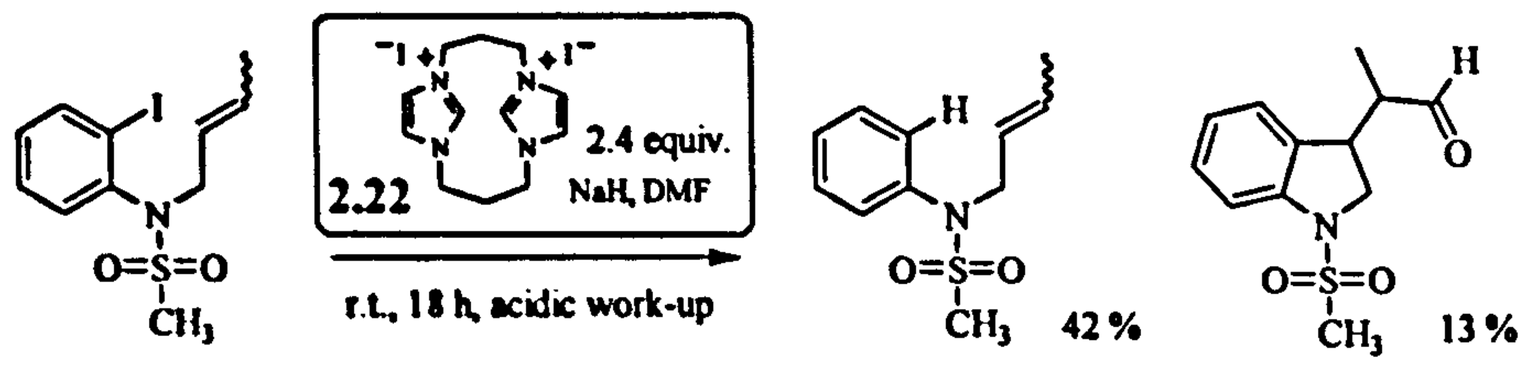
2.324 **2.328** **2.329**

Scheme 2.158

Under these conditions, the benzimidazole donor was 100 % selective and reacted exclusively with the *ortho*-iodide. However, the reduced product **2.329** was observed again

(16 % NMR yield) and the overall mass balance was rather moderate (57 %). It seems that benzimidazole donor **1.175** is capable of forming aryl anions on an activated diiodo-system.

To test why the mass balance is rather low, imidazole donor **2.20** that presumably had formed aryl anions on unactivated aryl iodides, was exposed to an aryl iodide cyclisation substrate. If the low mass balance can be attributed to the aryl anion intermediate, then imidazole donor **2.20** might show similarly low mass balances on analogous cyclisation substrates. Thus iodide **2.332** was reacted with 1.5 equivalents of donor **2.20** at room temperature. After acidic work-up and purification, the reduced product **2.333** was isolated (42 %) as well as aldehyde **2.334** (13 %).



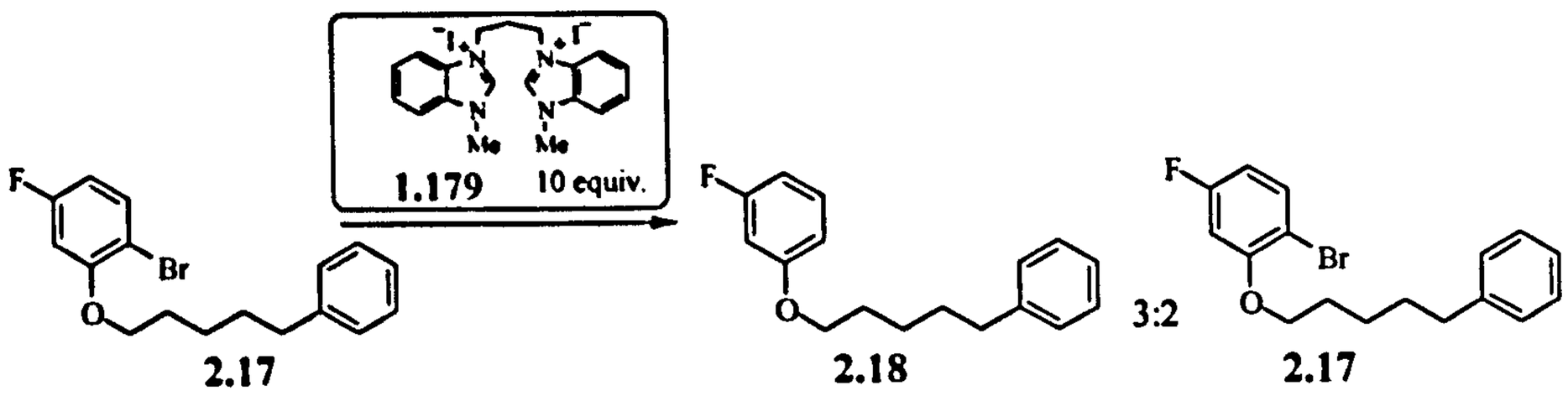
2.332 **2.333** **2.334**

Scheme 2.159

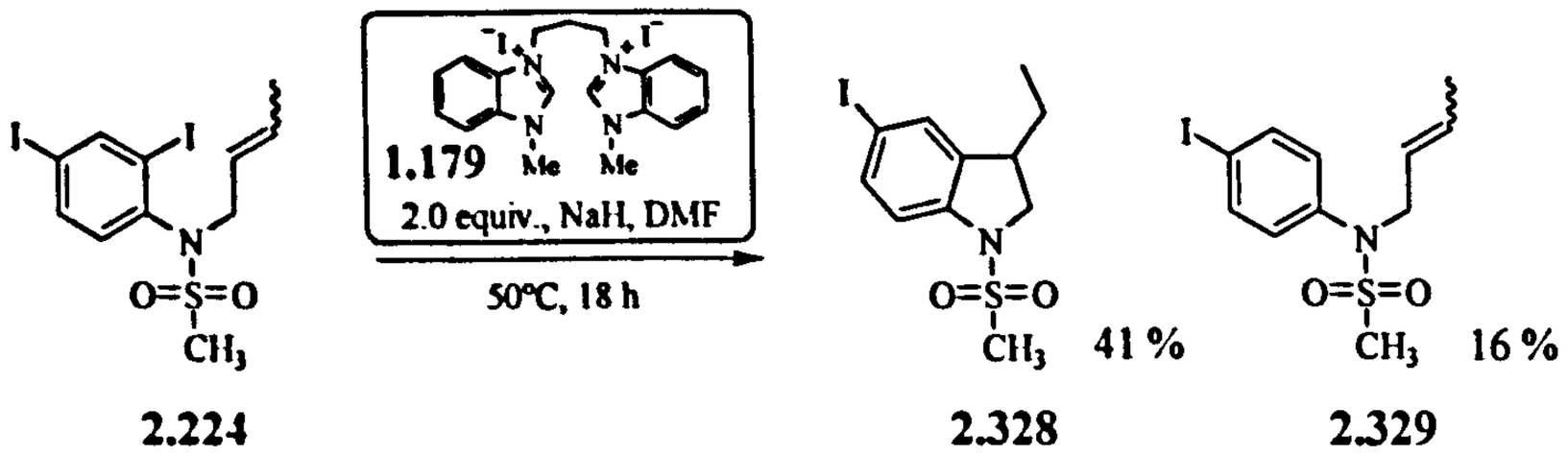
The mass balance was almost identical to the reaction described above (**Scheme 2.158**). However, when the reaction with diiodide **2.224** was repeated and acidic work-up was carried out also, no aldehyde was observed, and the only products formed were cyclised **2.328** and reduced compound **2.329**.

7 Conclusions

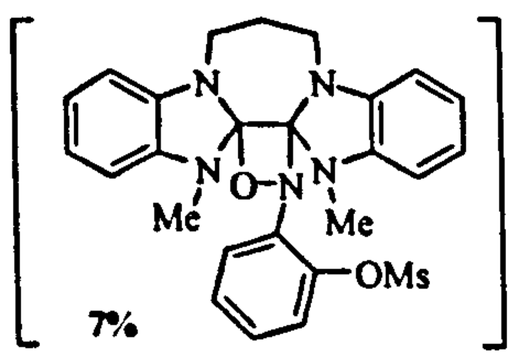
It has been shown that the scope of benzimidazole donor **1.175** as a reducing agent is rather limited to specific *ortho*-iodo NMs substrates. More electron-donating *ortho*-side chains (*i.e.* containing an oxygen or carbon heteroatom) are only reduced with a greater number of equivalents of donor under more concentrated conditions. Halides other than iodides are reduced rather inefficiently, *e.g.* **2.17** below.



Thus the scope of benzimidazole donor **1.175** lies in the ability to be a selective reagent. This has been shown in the selective reduction of the *ortho*-iodide in the highly activated diiodo-substrate **2.224**, that possibly led to the formation of an anion in this position even. This would be the first time that benzimidazole donor **1.175** generated an aryl anion.

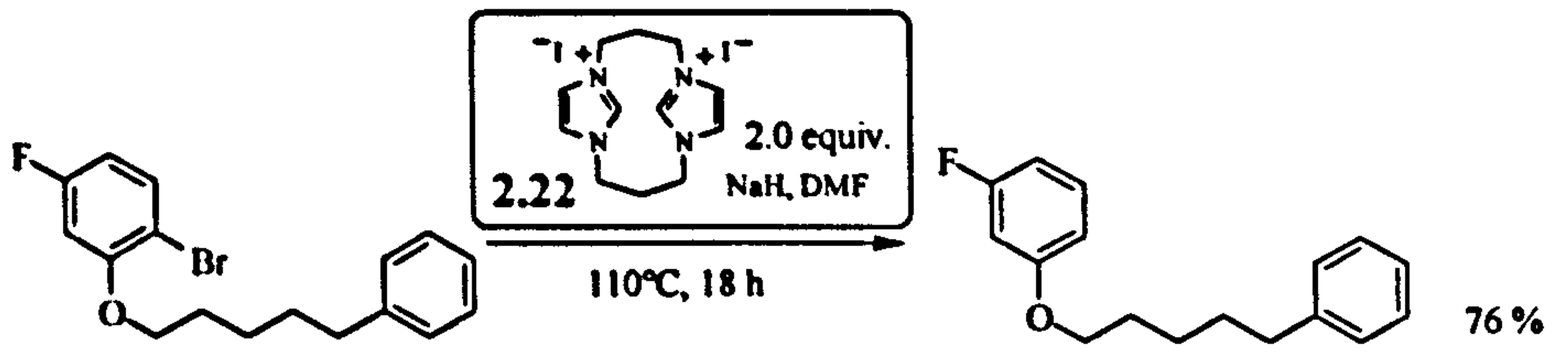


In the reduction of an aryl nitro compound by benzimidazole donor **1.175**, adduct species **2.222** was isolated, that might arise from the addition of nucleophilic intermediates, formed by the reduction of the nitro group, giving important mechanistic information of the chemistry of those donors.

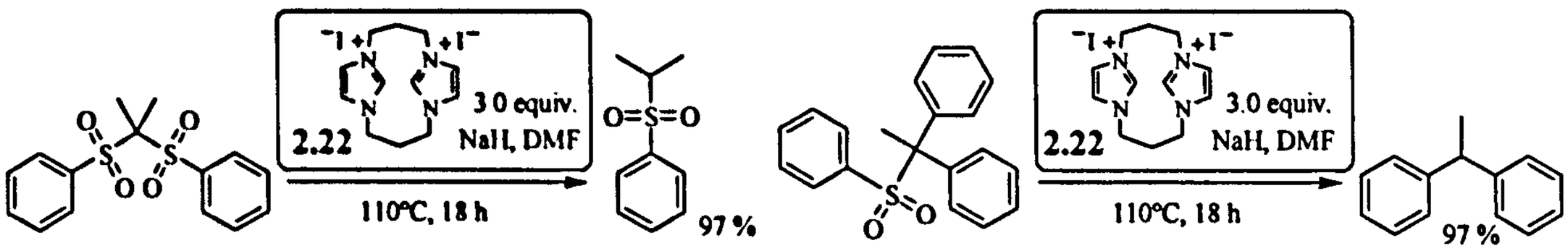


2.222

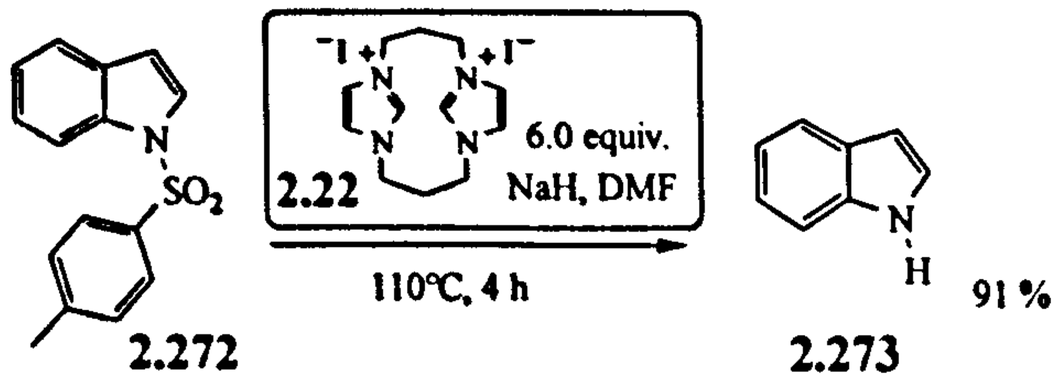
It was shown that imidazole donor **2.20** is a more powerful reducing agent, leading to complete reduction of aryl bromides, using low equivalent numbers of donor. Further, donor **2.20** was applied in the reduction of activated sulfones and sulfonamides, leading to products in high yields.



2.17 **2.18**

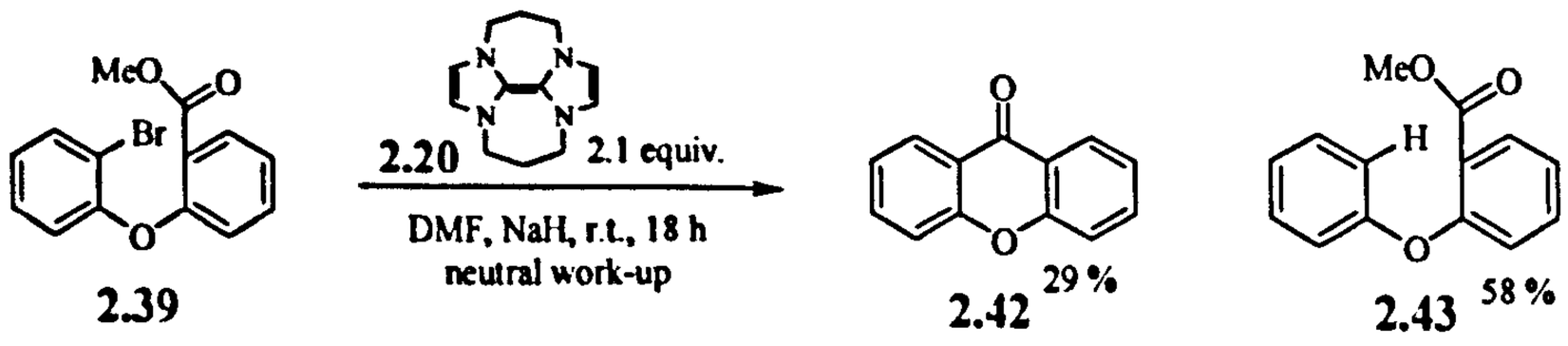


2.240 **2.242** **2.262** **2.266**

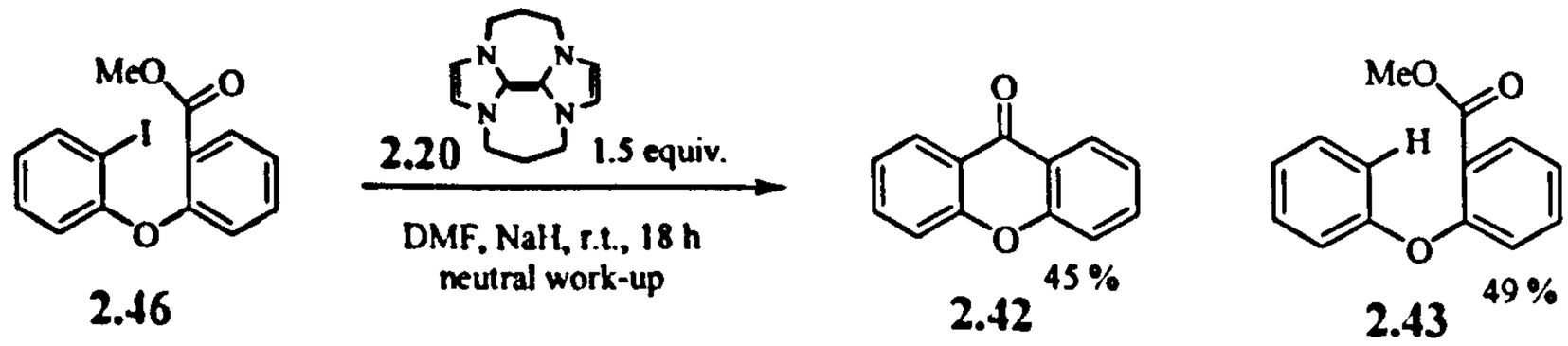


2.272 **2.273**

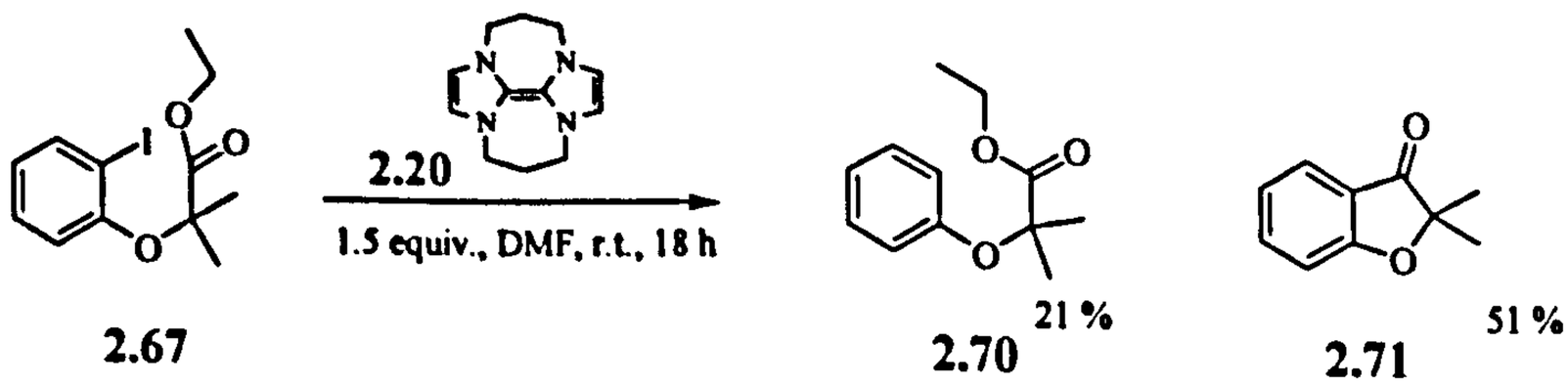
Ortho-iodoarenes and *ortho*-bromoarenes even react at room temperature with donor **2.20**, highlighting its greater reducing power, and it was shown that aryl anion intermediates seem to be involved in the mechanism, since cyclisation of several ester substrates was observed.



2.39 **2.42** **2.43**

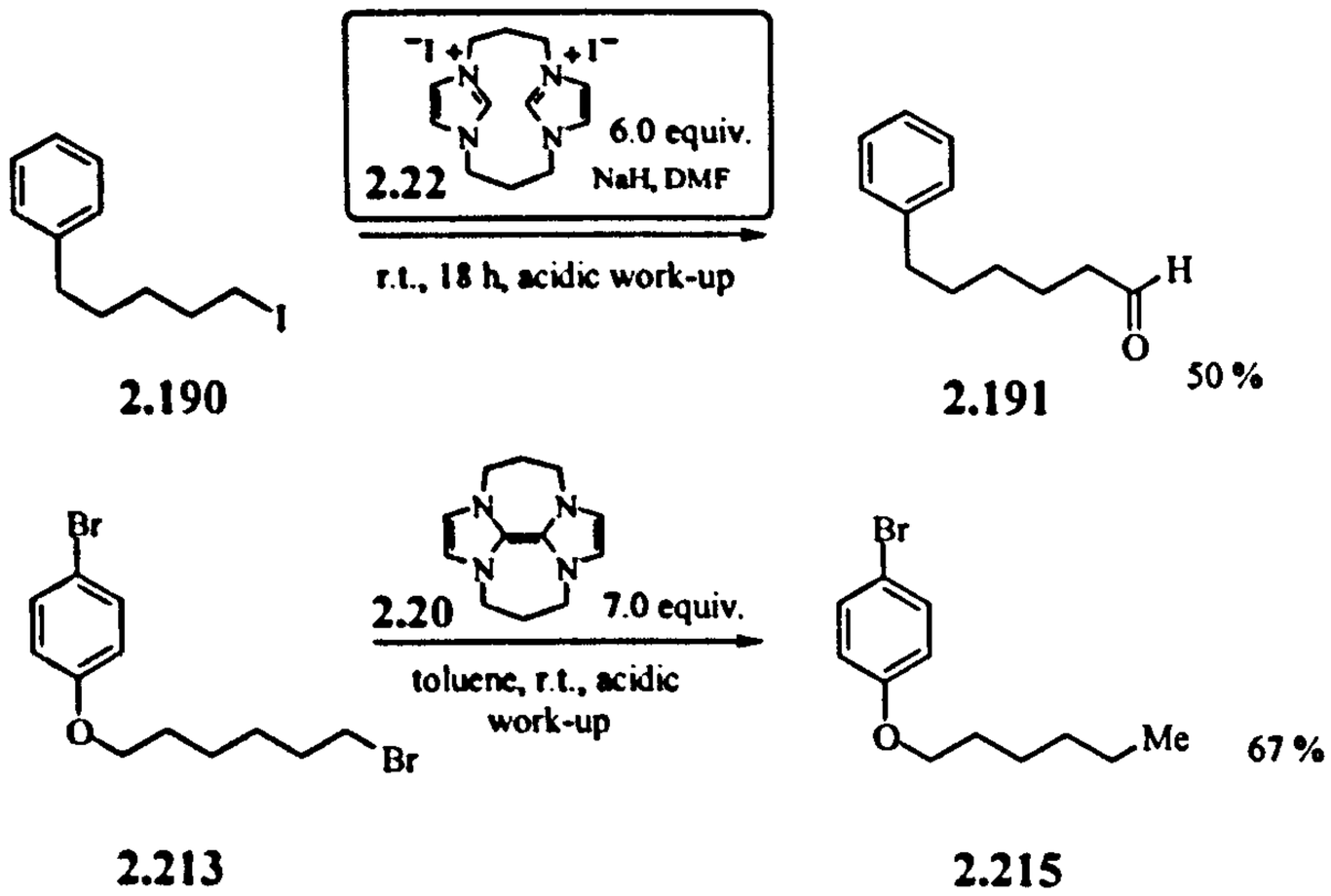


2.46 **2.42** **2.43**

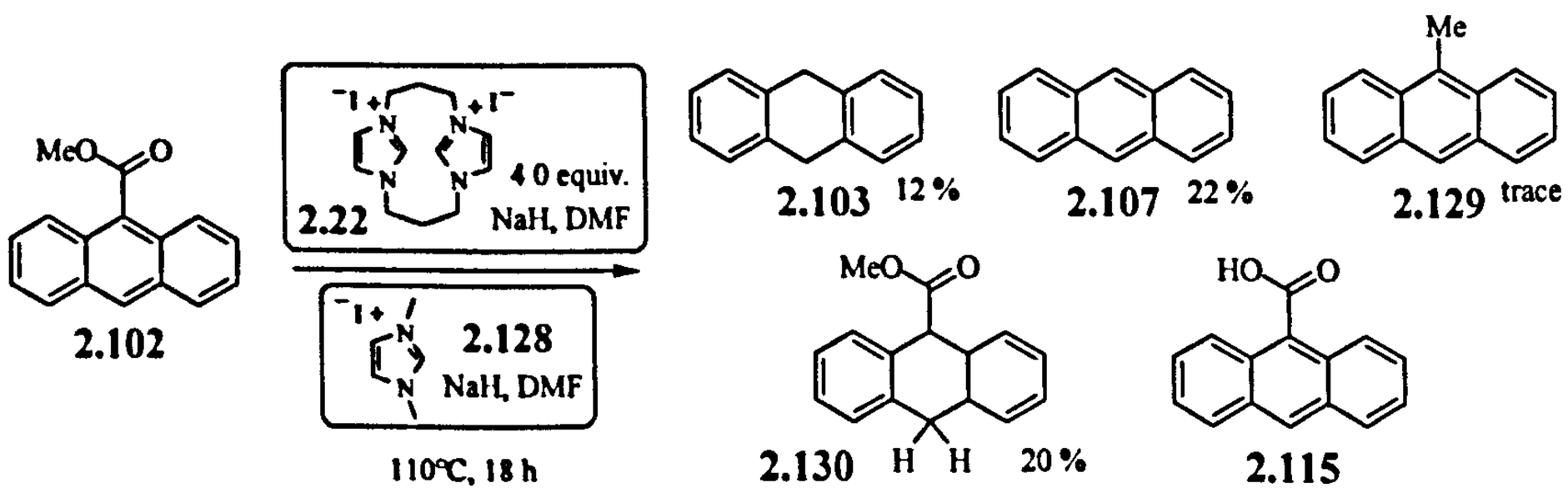


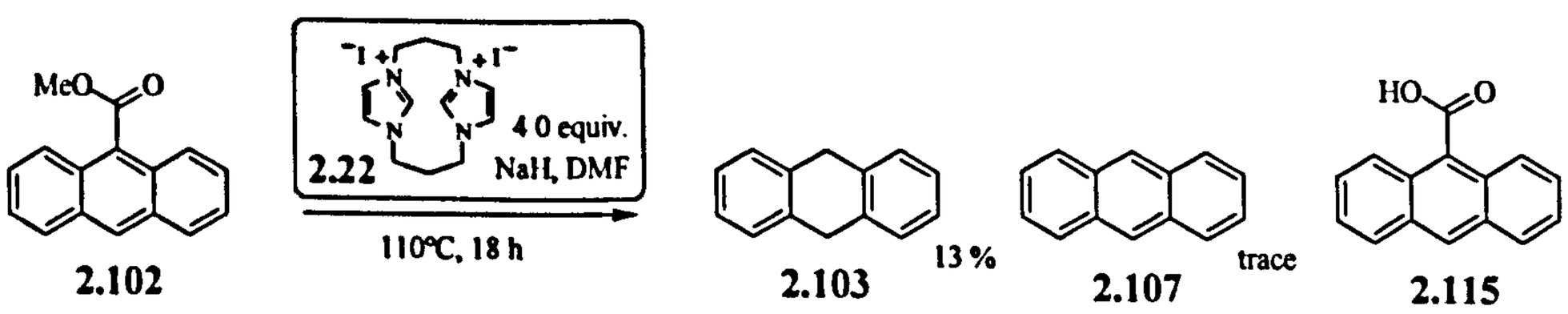
2.67 **2.70** **2.71**

With aliphatic halides, donor **2.20** intriguingly forms aldehydes, if DMF is used as the solvent. The proportion of aldehyde was increased with greater number of equivalents and concentration of donor. It has been shown that those aldehydes can be avoided by changing the solvent to diethyl ether or toluene, giving then radical chemistry at room temperature on alkyl bromides and iodides. Further, donor **2.20** has been applied to the selective reduction of an aryl bromide over an alkyl bromide.

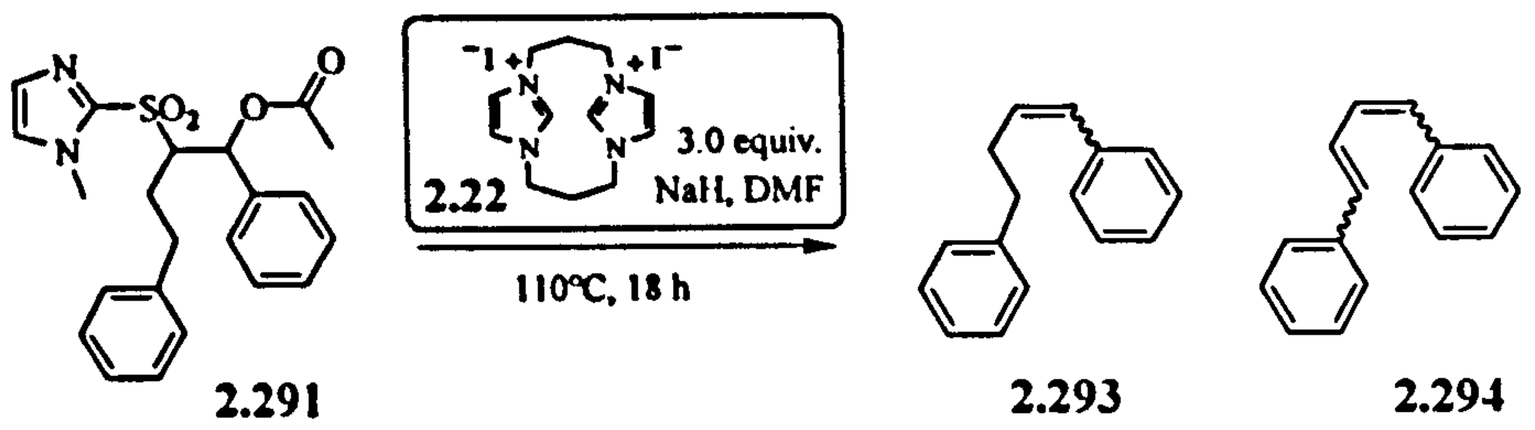


Intriguing reactivity was explored with anthracene esters, giving a dihydroanthracene ester (**2.130**) as one of the major products, if carbene **2.126** (derived from **2.128**) was added, and dihydroanthracene, if not.

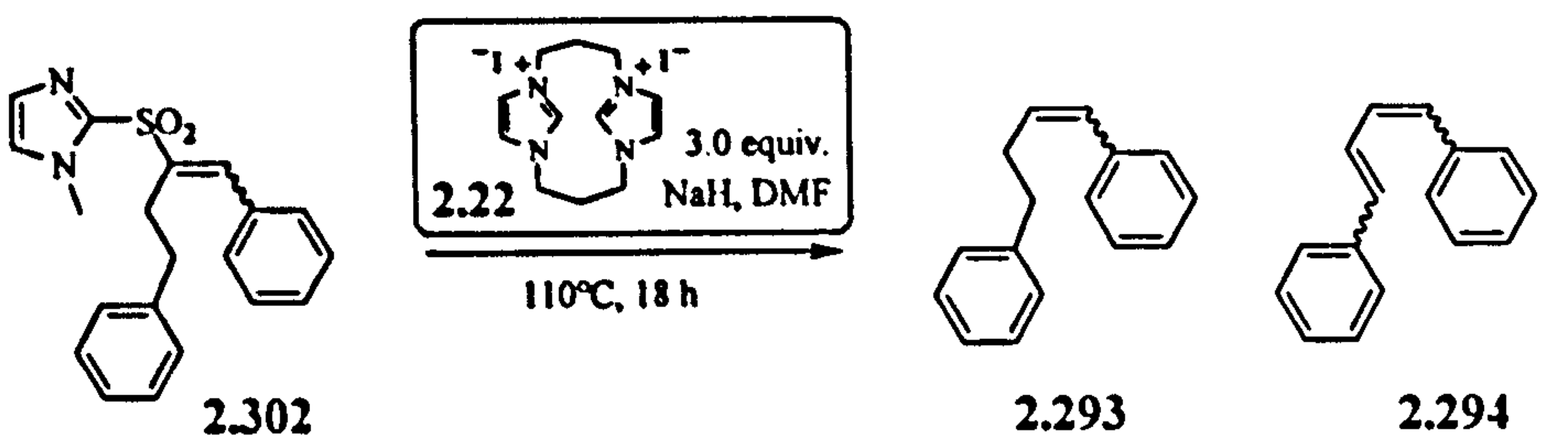




Furthermore, strong evidence was presented for the 1st example of a Julia olefination using a neutral organic electron donor.



2.291 **2.293** **2.294**



2.302 **2.293** **2.294**

In terms of future developments, once the Julia reaction with donor **2.20** has been optimised, applications in synthesis could follow. Further mechanistic investigations to reveal the mechanism of aldehyde formation in the reduction of alkyl halides would be valuable. Also, the possibility of anion formation on activated aryl iodides by benzimidazole donor **1.175** would be an interesting subject for further studies in the future. Scope exists also for further optimisation and studies in the reduction of anthracene esters in the presence of a carbene.

Experimental Section

8 Experimental Section

8.1 *General information*

^{1}H-NMR spectra were recorded at 400.13 MHz on a Bruker DPX400 spectrometer and 400.03 MHz on an AV400 (AVANCE) and at 500.13 MHz on an AV/DRX500 spectrometer. ^{13}C NMR spectra were recorded at 100.6 MHz (DMX/ AV400) and at 125.758 MHz (AV/DRX500) using a broadband decoupled mode on the same spectrometers. JMOD and ^{13}C-decoupled spectra were used to determine the multiplicities of the carbon resonances. Experiments were carried out using deuterochloroform ($CDCl_3$) unless otherwise stated and chemical shifts are reported in parts per million (ppm). Coupling constants *J* are reported in Hertz (Hz). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; b, broad.

Infrared spectra were recorded on a Perkin Elmer "spectrum One FT-IR" spectrometer. Melting points were recorded using either a Griffin or a Gallenkamp melting point apparatus.

Mass spectrum analysis was carried out by the EPSRC national mass spectrometry service centre using a JLZX 102, VG ZAB-E or VG micromass instrument.

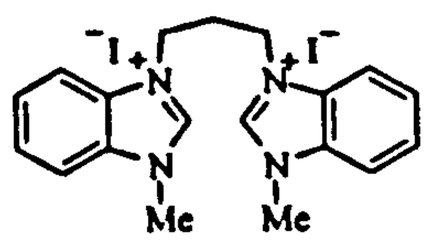
Column chromatography was performed using Prolabo 35-75 μm particle sized silica gel 60 (200-400 mesh) or activated neutral alumina. Reactions were followed using thin layer chromatography (TLC) carried out on Merck silica gel 60 F_{254} pre-coated aluminium plates. Visualisation was achieved under UVP mineralight UVG-11 lamp or by developing plates with methanolic vanillin or phosphomolybdic acid.

All reagents were obtained from commercial suppliers. Tetrahydrofuran, dichloromethane, hexane, diethyl ether and toluene were dried with a Pure-Solv 400 solvent purification system (by Innovative Technology Inc., USA). Dimethylformamide was obtained from commercial suppliers as anhydrous (99.98%) and used directly. Sodium hydride was supplied as a 60% suspension in mineral oil and was washed with hexane to remove the oil prior to use.

For references given in the experimental section the following convention is used. References given with the name of the compound in the title of an experiment were used for the procedures carried out in that experiment. References contained within the body of the report are from previous syntheses of that particular compound, not exclusively by the methods described, and were used for comparison of spectroscopic and analytical data.

8.2 Experiments from chapter 2: *Reaction with benzimidazole donor* 1.175

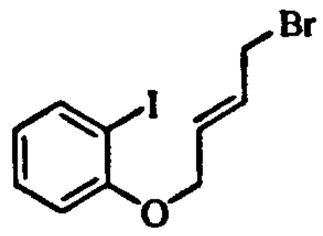
1,3-*bis*[3-Methyl-3*H*-benzimidazolium]propane diiodide 1.179[94]



1.179

N-Methylbenzimidazole (5.00g, 37.82 mmol, 2.5 equiv.) and 1,3-diiodopropane (1.74 ml, 15.13 mmol, 1.0 equiv.) were dissolved in acetonitrile (20 ml) and heated under reflux for 4 d. After cooling, the precipitate was collected by filtration and washed with DCM. The salt was ground to a fine powder and washed further with more DCM. This gave 1,3-bis[3-methyl-3*H*-benzimidazolium]propane[94] **1.179** as a white salt (7.817 g, 92 %), dec. at 276-277°C; ν_{max} (KBr)/cm^{-1} 3034 (Ar-H), 1570 (Ar-H), 1462 (C-H), 1434 (C-H); δ_H (DMSO) 2.60 (2H, quintet, *J* 7.3, CH_2), 4.08 (6H, s, NCH_3), 4.67 (4H, t, *J* 7.3, CH_2), 7.68-7.47 (4H, m, Ar*H*), 8.02-8.08 (4H, m, Ar*H*), 9.72 (2H, s, 2 x NC*H*C$^+$); δ_C (DMSO) 28.4 (CH_2), 33.8 (CH_3), 44.2 (CH_2), 113.9 (CH), 114.0 (CH), 126.9 (CH), 127.0 (CH), 131.2 (C), 132.2 (C), 143.2 (CH).

1-(4-Bromobut-2-enyloxy)-2-iodobenzene 2.4

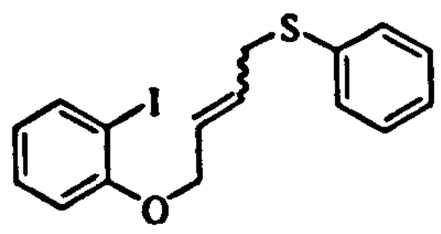


2.4

A solution of 2-iodophenol (5.60 g, 25.45 mmol, 1.0 equiv.) in THF (75 ml) was added dropwise to a suspension of washed sodium hydride (1.22 g, 30.55 mmol, 1.2 equiv.) in THF (150 ml) while cooling to 0°C. The mixture was allowed to warm to room temperature, stirred for 1h and was then cooled to 0°C again. Subsequently, 1,4-*trans*-dibromobut-2-ene (13.60 g, 63.60 mmol, 2.5 equiv.) dissolved in THF (75 ml) was added rapidly and the mixture was stirred for 2.5 h. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (5:95 DCM/ petroleum ether) which afforded *1-(4-bromo-but-2-enyloxy)-2-iodobenzene* **2.4** as a white solid (5.03 g, 56 %); mp 41-42 °C; (Found: [M+NH$_4$]$^+$, 369.9299. $C_{10}H_{10}BrIO$ requires [*M*+*NH*$_4$]$^+$, 369.9299 for ^{79}Br); ν_{max} (KBr)/cm^{-1} 3055 (Ar-H), 3020 (Ar-H), 2895 (C-H), 2850 (C-H), 1581 (Ar), 1475 (C-H), 1437 (C-H); δ_H ($CDCl_3$) 4.02 (2H, m, CH_2Br), 4.63 (2H, d, *J* 4.2,

CH_2O), 5.98-6.04 (1H, m, CH=C*H*CH$_2$Br), 6.16-6.24 (1H, m, OCH$_2$C*H*=CH), 6.72-6.76 (1H, m, Ar*H*), 6.80 (1H, dd, *J* 8.2, 1.2, Ar*H*), 7.28-7.32 (1H, m, Ar*H*), 7.80 (1H, dd, *J* 7.8, 1.6, Ar*H*); δ_C ($CDCl_3$) 32.3 (CH_2), 68.5 (CH_2), 87.0 (C), 112.8 (CH), 123.2 (CH), 129.3 (CH), 129.8 (CH), 129.8 (CH), 139.8 (CH), 157.1 (C); *m/z* (EI) 354 (M^+, 3 % ^{81}Br), 352 (M^+, 3 % ^{79}Br), 219 (55), 92 (37), 63 (50), 53 (100).

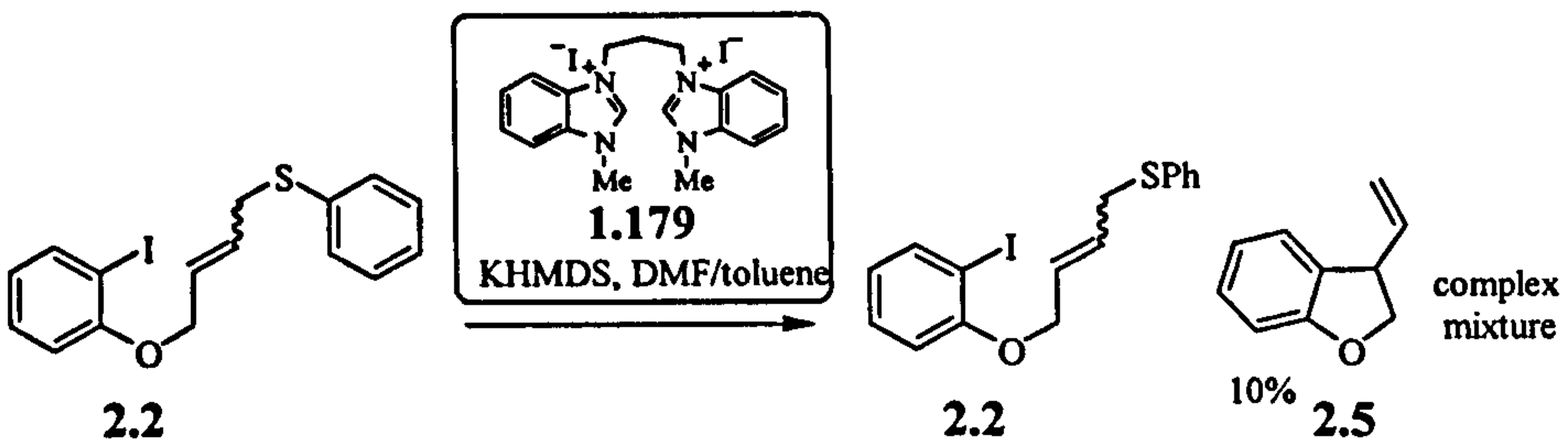
1-Iodo-2-(4-phenylsulfanylbut-2-enyloxy)benzene 2.2[172]



2.2

To a suspension of washed sodium hydride (134.4 mg, 3.36 mmol, 1.2 equiv.) in THF (5 ml), a solution of thiophenol (0.29 ml, 2.80 mmol, 1.0 equiv.) in THF (5 ml) was added dropwise while cooling to 0°C. The mixture was allowed to warm to room temperature and was stirred for 0.5 h. A solution of 1-(4-bromobut-2-enyloxy)-2-iodobenzene **2.4** (1.0 g, 2.80 mmol, 1.0 equiv.) in THF (5 ml) was then added dropwise at 0°C and upon complete addition, the mixture was warmed to room temperature again and stirred for 15 h. After quenching the reaction with water, the solvent was removed under reduced pressure and the residue was dissolved in diethyl ether (100 ml) and water (100 ml). The aqueous phase was extracted with diethyl ether (2 x 100 ml) and the combined organic phase was washed with water (2 x 100 ml) and sat. sodium bicarbonate solution (5 x 50 ml), dried over sodium sulfate and evaporated. The residue was subjected to column chromatography (10:90, then 20:80 toluene/ petroleum ether), which afforded *1-iodo-2-(4-phenylsulfanylbut-2-enyloxy)benzene* **2.2** as a white solid (0.890 mg, 83 %); mp 51-52°C; (Found: $[M+NH_4]^+$ 400.0231. $C_{16}H_{15}IOS$ requires $[M+NH_4]^+$, 400.0227); ν_{max} (KBr)/cm^{-1} 3057 (Ar-H), 2915 (C-H), 1581 (Ar), 1473 (C-H); δ_H ($CDCl_3$) 3.62 (2H, dd, *J* 6.9, 1.1, CH_2S), 4.53 (2H, dd, *J* 5.1, 1.2, CH_2O), 5.76-5.84 (1H, m, C*H*=CH), 5.99-6.07 (1H, m, CH=C*H*), 6.71-6.75 (1H, m, Ar*H*), 7.20-7.33 (4H, m, Ar*H*), 7.36-7.39 (2H, m, Ar*H*), 7.80 (1H, dd, *J* 8.1, 1.6, Ar*H*); δ_C ($CDCl_3$) 36.1 (CH_2), 68.8 (CH_2), 86.8 (C), 112.6 (CH), 122.8 (CH), 126.5 (CH), 127.7 (CH), 129.0 (CH), 129.1 (CH), 129.5 (CH), 130.3 (CH), 135.7 (C), 139.6 (CH), 157.1 (C); *m/z* (EI) 382 (M^+, 2 %), 163 (100), 146 (18), 135 (42), 108 (52), 65 (29).

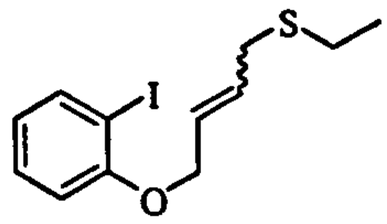
Attempted cylisation of 2.2 using benzimidazole donor 1.175



2.2 **2.2** **2.5**

Salt **1.179** (201.6 mg, 0.36 mmol, 1.2 equiv.) was dissolved in DMF (5 ml) and toluene (10 ml) and purged with argon for 30 min. KHMDS (1.9 ml, 0.72 mmol, 2.4 equiv., c = 0.38 mol/l) was added dropwise and the reaction mixture was stirred for 1h at room temperature. A purged solution of substrate **2.2** (115.0 mg, 0.3 mmol, 1.0 equiv.) in toluene (5 ml) was then added to the reaction mixture. After heating at reflux for 18 h, the mixture was poured into water (50 ml) and diethyl ether (50 ml), and the aqueous phase was extracted with diethyl ether (2 x 50 ml). The organic phases were combined and washed with water (3 x 50 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. A complex mixture was obtained, in which starting material **2.2** was identified by ^{1}H-NMR comparison. Further purification of the mixture by by column chromatography (2:98 ethyl acetate/ petroleum ether) gave the desired product 3-vinyl-2,3-dihydrobenzofuran **2.5**[173] as a colourless liquid (4.3 mg, 10 %); ν_{max} (NaCl)/cm^{-1} 3076 (Ar-H), 2959 (C-H), 1640 (Ar), 1596 (Ar), 1481 (C-H); δ_H ($CDCl_3$) 4.10-4.17 (1H, m, C*H*), 4.23-4.27 (1H, m, CH_2O), 4.72 (1H, dd, *J* 9.0, 9.0, CH_2O), 5.15-5.25 (2H, m, CH=CH_2), 5.83-5.92 (1H, m, C*H*=CH$_2$), 6.81-6.91 (2H, m, Ar*H*), 7.12-7.17 (2H, m, Ar*H*); δ_C ($CDCl_3$) 47.2 (CH_2), 76.4 (CH), 109.9 (CH_2), 116.9 (CH), 120.8 (CH), 125.1 (CH), 128.7 (C), 129.5 (CH), 138.1 (CH), 160.1 (C); *m/z* (EI) 146 (M^+, 24 %), 131 (100), 115 (35), 91 (28).

1-(4-Ethylsulfanylbut-2-enyloxy)-2-iodobenzene 2.6

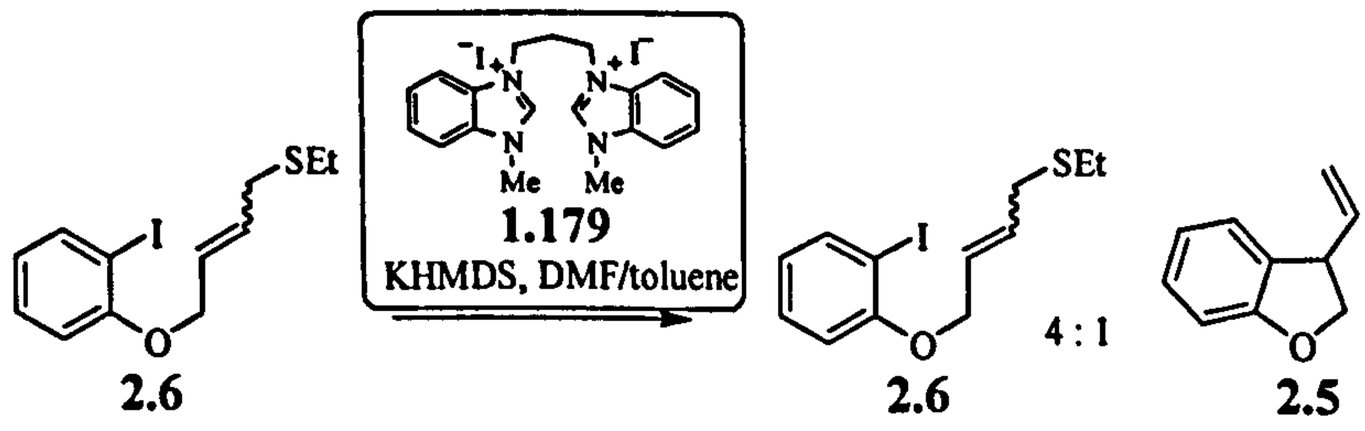


2.6

To a suspension of washed sodium hydride (36.9 mg, 0.923 mmol, 1.3 equiv.) in THF (2 ml) a solution of ethanethiol (0.064 ml, 0.85 mmol, 1.2 equiv.) in THF (2 ml) was added dropwise while cooling to 0°C. The mixture was allowed to warm to room temperature and was stirred for 0.5 h. A solution of 1-(4-bromobut-2-enyloxy)-2-iodobenzene **2.4** (250.0

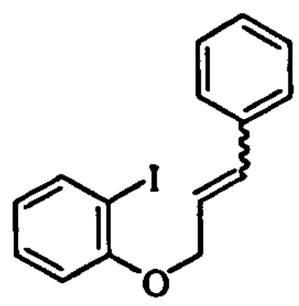
mg, 0.71 mmol, 1.0 equiv.) in THF (3 ml) was then added dropwise at 0°C and the mixture was allowed to warm to room temperature again. After stirring for 18 h at room temperature the solvent was removed *in vacuo* and the residue was dissolved in water (20 ml) and diethyl ether (50 ml). The organic phase was washed with water (2 x 20 ml) and sat. sodium bicarbonate solution (3 x 20 ml), was then dried over sodium sulfate and evaporated. The residue was purified by column chromatography and *1-(4-ethylsulfanylbut-2-enyloxy)-2-iodobenzene* **2.6** was isolated as a yellow oil (203 mg, 86 %); (Found: $[M+NH_4]^+$ 352.0229. $C_{12}H_{15}IOS$ requires $[M+NH_4]$, 352.0227); ν_{max} (NaCl)/cm^{-1} 2963 (C-H), 2923 (C-H), 1471 (C-H), 1438 (C-H); δ_H ($CDCl_3$) 1.23 (3H, t, *J* 7.4, CH_3), 2.47 (2H, q, *J* 7.4, SCH_2CH$_3$), 3.19 (2H, dd, *J* 7.1, 0.8, CHCH_2S), 4.58 (2H, m, OCH_2), 5.74-5.81 (1H, m, C*H*=CH), 5.87-5.94 (1H, m, CH=C*H*), 6.71 (1H, m, Ar*H*), 6.80 (1H, dd, *J* 8.3, 1.2, Ar*H*), 7.25-7.29 (1H, m, Ar*H*), 7.77 (1H, dd, *J* 7.8, 1.6, Ar*H*); δ_C ($CDCl_3$) 14.6 (CH_3), 24.7 (CH_2), 33.1 (CH_2), 69.1 (CH_2), 87.0 (C), 112.8 (CH), 122.8 (CH), 126.9 (CH), 129.5 (CH), 130.6 (CH), 139.6 (CH), 157.1 (C); *m/z* (EI) 334.1 (M^+, 20 %), 272 (20), 220 (100), 203 (32), 190.9 (80).

Attempted cyclisation of 2.6 using benzimidazole donor 1.175



Salt **1.179** (201.6 mg, 0.36 mmol, 1.2 equiv.) was dissolved in DMF (5 ml) and toluene (10 ml) and purged with argon for 30 min. KHMDS (1.6 ml, 0.72 mmol, 2.4 equiv., c = 0.45 mol/l) was added dropwise and the reaction mixture was stirred for 1h at room temperature. A solution of substrate **2.6** (115.0 mg, 0.3 mmol, 1.0 equiv.) in toluene (5 ml) was purged with argon for 20 min and then added. The reaction mixture was heated at reflux for 18 h. The mixture was then poured into water (50 ml) and diethyl ether (50 ml) and the aqueous phase was extracted with diethyl ether (2 x 50 ml). The organic phases were combined and washed with water (3 x 50 ml), dried over sodium sulfate, filtered and evaporated. A ^{1}H-NMR spectrum of the crude mixture showed a 4:1 ratio of starting material **2.6** and 3-vinyl-2,3-dihydrobenzofuran[173] **2.5**; for data, see above.

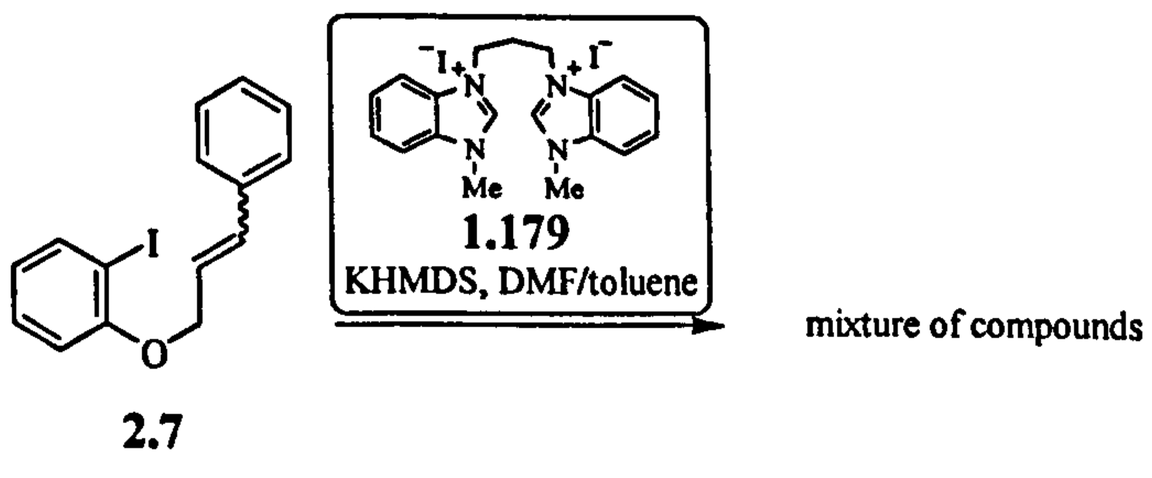
1-Iodo-2-(3-phenylallyloxy)benzene 2.7[174]



2.7

Cinnamyl alcohol (1.220 g, 9.09 mmol, 1.0 equiv.), 2-iodophenol (2 g, 9.09 mmol, 1.0 equiv.) and triphenylphosphine (2.384 g, 9.09 mmol, 1.0 equiv.) were dissolved in THF (30 ml), and the mixture was cooled to 0°C. DIAD (1.79 ml, 9.09 mmol, 1.0 equiv.) was then added dropwise and the mixture was allowed to warm to room temperature and stirred for 2.5 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (10:90 toluene/ petroleum ether). 1-Iodo-2-(3-phenylallyloxy)benzene **2.7**[175] was isolated as a colourless liquid (0.801 g, 40 %); (Found: $[M+NH_4]^+$ 354.0348. $C_{15}H_{13}IO$ requires $[M+NH_4]$, 354.0349); ν_{max} (NaCl)/cm^{-1} 3058 (Ar-H), 3025 (Ar-H), 2864 (C-H), 1581 (Ar), 1473 (C-H), 1438 (C-H); δ_H ($CDCl_3$) 4.79 (2H, dd, *J* 5.4, 1.6, CH_2O), 6.47 (1H, m, C*H*=CH), 6.79 (1H, m, CH=C*H*), 6.90 (2H, m, Ar*H*), 7.34 (2H, m, Ar*H*), 7.41 (2H, m, Ar*H*), 7.49 (2H, m, Ar*H*), 7.87 (1H, dd, *J* 7.8, 1.6, Ar*H*); δ_C ($CDCl_3$) 70.1 (CH_2), 87.3 (C), 113.2 (CH), 123.2 (CH), 122.4 (CH), 127.1 (CH), 128.3 (CH), 129.1 (CH), 129.9 (CH), 133.3 (CH), 136.9 (C), 140.0 (CH), 157.6 (C); *m/z* (EI) 336 (M^+, 100 %), 307 (29), 254 (30), 233 (70).

Attempted cylisation of 2.7 using benzimidazole donor 1.175



2.7

Salt **1.179** (201.6 mg, 0.36 mmol, 1.2 equiv.) was dissolved in toluene (15 ml) and DMF (5 ml) and purged with argon for 30 min. KHMDS (1.76 ml, 0.72 mmol, 2.4 equiv., c = 0.41 mol/l) was then added dropwise and the mixture was stirred for 1h at room temperature. A solution of 1-iodo-2-(3-phenylallyloxy)benzene **2.7** (101 mg, 0.3 mmol, 1.0 equiv.) in toluene (5 ml) was purged with argon for 20 min and then added to the reaction mixture *via* cannula. The mixture was heated at reflux for 18 h, poured into water (50 ml) and diethyl ether (50 ml) and the aqueous phase was extracted with diethyl ether (2 x 50 ml).

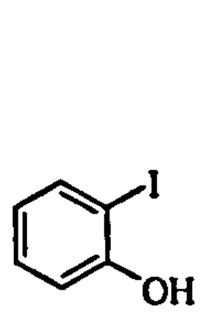
The combined organic layer was washed with water (3 x 50 ml), dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (2.5:2.5:95 toluene/ DCM/ petroleum ether) to afford starting material **2.7** (44 mg, 44 %) and two other complex fractions, one less polar than starting material **2.7** (26 mg), the other more polar than **2.7** (5 mg). Both fractions were subjected together to GC-MS analysis. Found:

Phenol **2.9**[176]: *m/z* (EI) 94 (M^+, 100 %), 66 (73), 65 (52), 63 (11).

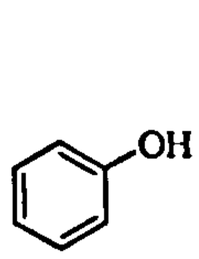
Iodophenol **2.3**[177]: *m/z* (EI) 220 (M^+, 100 %), 93 (16), 65 (26), 63 (12).

Propenylbenzene **2.10**[178]: *m/z* (EI) 118 (M^+, 37 %), 117 (100), 91 (18), 63 (9).

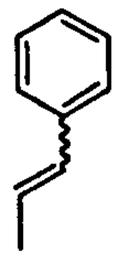
Phenyl-cinnamyl ether **2.11**[180] or 3-benzyl-2,3-dihydrobenzofuran **2.12**[179]: *m/z* (EI) 210 (M^+, 12 %), 117 (100), 115 (68), 91 (12), 77 (8).



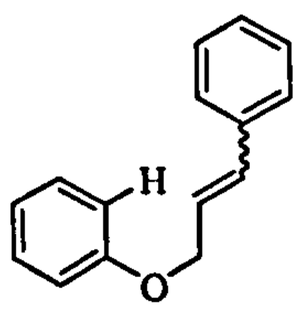
2.3



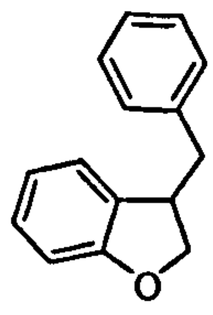
2.9



2.10

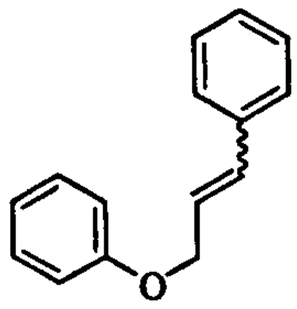


2.11



2.12

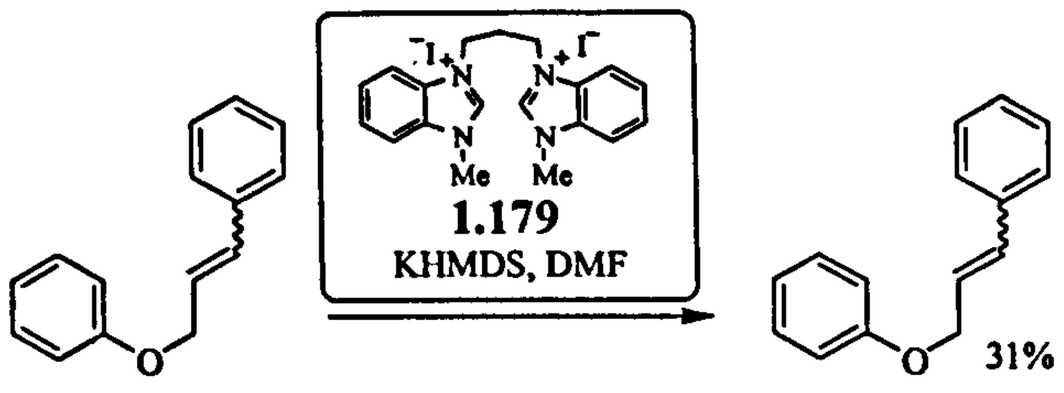
Phenyl cinnamyl ether 2.11[174]



2.11

Cinnamyl alcohol (1.43 g, 10.6 mmol, 1.0 equiv.), phenol (1.0 g, 10.6 mmol, 1.0 equiv.) and triphenylphosphine (2.78 g, 10.6 mmol, 1.0 equiv.) were dissolved in THF (15 ml), and cooled to 0°C. Subsequently, DIAD (2.3 ml, 11.7 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for 5 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (10:90 toluene/ petroleum ether) to give phenyl cinnamyl ether **2.11**[180] as a white solid (1.76 g, 79 %), mp 65-66°C (lit.[181] 68-69.7°C); ν_{max} (KBr)/cm^{-1} 3027 (Ar-H), 2908 (C-H), 2862 (C-H), 1599 (Ar), 1448 (C-H); δ_H ($CDCl_3$) 4.72 (2H, dd, *J* 5.8, 1.4, CH_2O), 6.41-6.48 (1H, m, C*H*=CHPh), 6.76 (1H, d, *J* 16.5, CH=C*H*Ph), 6.97-7.00 (3H, m, Ar*H*), 7.25-7.37 (5H, m, Ar*H*), 7.42-7.45 (2H, m, Ar*H*); δ_C ($CDCl_3$) 68.8 (CH_2), 115.0 (CH), 121.1 (CH), 124.7 (CH), 126.8 (CH), 128.1 (CH), 128.8 (CH), 129.7 (CH), 133.2 (CH), 136.7 (C), 158.8 (C); *m/z* (EI) 210 (M^+, 12 %), 117 (100), 115 (75), 91 (15), 77 (12).

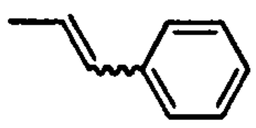
Attempted cyclisation of 2.11 using benzimidazole donor 1.175



2.11 **2.11**

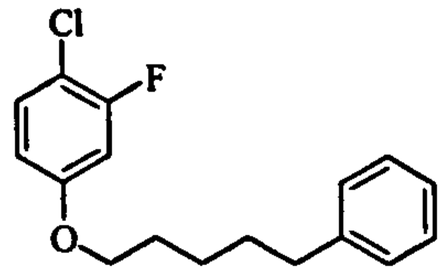
Salt **1.179** (403.2 mg, 0.72 mmol, 1.2 equiv.) was dissolved in DMF (13 ml) and purged with argon for 30 min. KHMDS (3.79 ml, 1.44 mmol, 2.4 equiv., c = 0.38 mol/l) was then added dropwise and the mixture was stirred for 1h at room temperature. An argon-purged solution of substrate **2.11** (126.2 mg, 0.6 mmol, 1.0 equiv.) in DMF (7 ml) was then added to the reaction mixture *via* cannula and the mixture was heated at reflux for 18h, poured into water (50 ml) and diethyl ether (50 ml) and the aqueous phase was acidified and extracted with diethyl ether (2 x 50 ml). The combined organic phases were washed with dilute hydrochloric acid (3 x 50 ml), dried over Na_2SO_4, filtered and evaporated. The residue was subjected to column chromatography (10:90 ethyl acetate/ petroleum ether) and two main fractions were separated, the first afforded starting material **2.11** (39 mg, 31%) and the second fraction (33 mg) was a complex mixture that was subjected to GC-MS analysis which gave along with unidentified compounds:

Propenylbenzene **2.10**[178]: *m/z* (EI) 118 (M^+, 37 %), 117 (100), 91 (18), 63 (9).



2.10

1-Chloro-2-fluoro-4-(5-phenylpentyloxy)benezene 2.15[174]

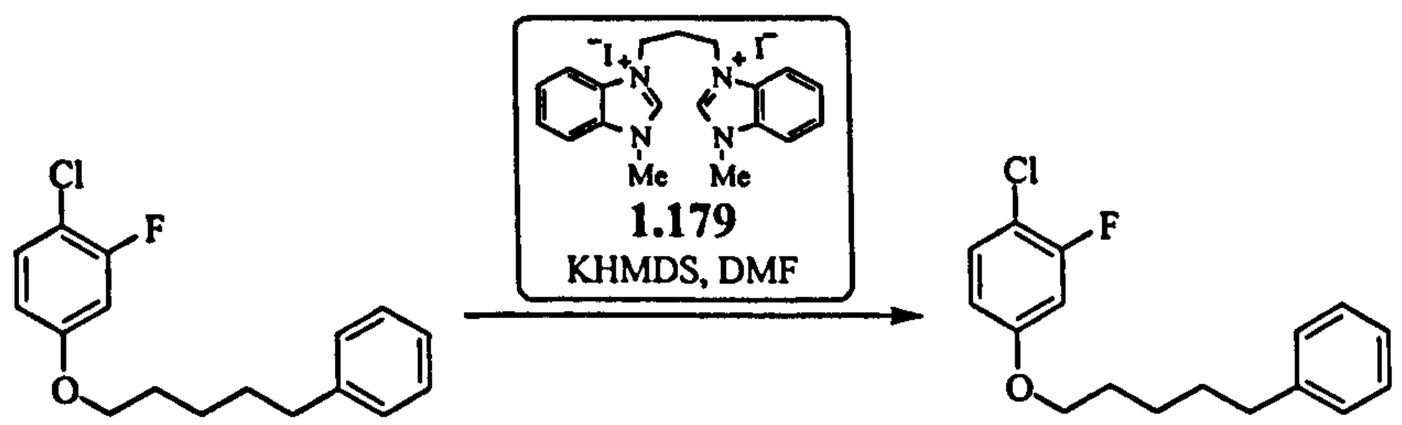


2.15

5-Phenyl-1-pentanol (0.144 ml, 0.854 mmol, 1.0 equiv.), 4-chloro-3-fluorophenol (125.1 mg, 0.854 mmol, 1.0 equiv.) and triphenylphosphine (223.9 mg, 0.854 mmol, 1.0 equiv.) were dissolved in THF (5 ml), and the mixture was cooled to 0°C. DIAD (0.168 ml, 0.854 mmol, 1.0 equiv.) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 2.5 h. The solvent was removed under reduced pressure and the

residue was exposed to column chromatography (10:90 DCM/ petroleum ether). *1-Chloro-2-fluoro-4-(5-phenylpentyloxy)benzene* **2.15** was isolated as a colourless liquid (189 mg, 76 %); (Found: $[M+NH_4]^+$ 310.1370. $C_{17}H_{18}ClFO$ requires $[M+NH_4]$, 310.1368 for ^{35}Cl); ν_{max} (NaCl)/cm^{-1} 3027 (Ar-H), 2938 (C-H), 2859 (C-H), 1609 (Ar), 1493 (C-H), 1470 (C-H); δ_H ($CDCl_3$) 1.55 (2H, m, CH_2), 1.75 (2H, m, CH_2), 1.86 (2H, m, CH_2), 2.70 (2H, t, *J* 7.7, CH_2), 3.96 (2H, t, *J* 6.3, CH_2), 6.67 (1H, dd, *J* 8.8, 2.8, Ar*H*), 6.73 (1H, dd, *J* 10.9, 2.7, Ar*H*), 7.24 (2H, m, Ar*H*), 7.33 (4H, m, Ar*H*); δ_C ($CDCl_3$) 25.8 (CH_2), 29.1 (CH_2), 31.3 (CH_2), 36.0 (CH_2), 68.7 (CH_2), 103.5 (d, ^2J 24.1, CH), 111.4 (d, $^3J_{C\text{-}F}$ 3.2, CH), 112.1 (d, ^2J 18.0, C), 125.9 (CH), 128.5 (CH), 128.6 (CH), 130.6 (d, $^4J_{C\text{-}F}$ 1.1, CH), 142.6 (C), 158.6 (d, $^1J_{C\text{-}F}$ 247.6, C), 159.1 (d, $^3J_{C\text{-}F}$ 9.7, C); *m/z* (EI) 294 (M^+, 4 %, ^{37}Cl), 292 (M^+, 11%, ^{35}Cl), 146 (25), 148 (8), 91 (100).

Attempted reduction of 1-chloro-2-fluoro-4-(5-phenylpentyloxy)benezene 2.15 with 1.175



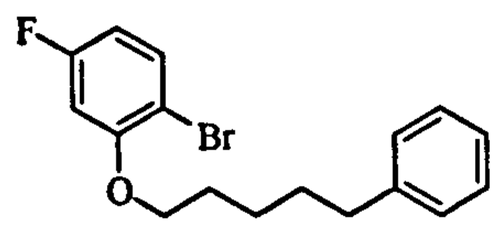
2.15 **2.15**

(i) Salt **1.179** (147.8 mg, 0.264 mmol, 1.2 equiv.) was dissolved in DMF (12 ml) and purged with argon for 30 min. KHMDS (1.39 ml, 0.528 mmol, 2.4 equiv., c = 0.38 mol/l) was added dropwise and the reaction mixture was stirred for 1h at room temperature. An argon-purged solution of **2.15** (64.4 mg, 0.220 mmol, 1.0 equiv.) in DMF (5 ml) was then added and the reaction mixture was heated at 118°C for 3d. The mixture was poured into water (50 ml) and diethyl ether (50 ml). The aqueous phase was extracted with diethyl ether (2 x 50 ml) and the combined organic phases were washed with water (3 x 50 ml), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (5:95 ethyl acetate/ petroleum ether) to afford starting material **2.15** (58.0 mg, 91%).

(ii) Salt **1.179** (827.3 mg, 1.477 mmol, 5.0 equiv.) was dissolved in DMF (10 ml) and purged with argon for 30 min. KHMDS (9.0 ml, 2.954 mmol, 10 equiv., c = 0.33 mol/l) was added dropwise and the reaction mixture was stirred for 1h at room temperature. An argon-purged solution of **2.15** (200 mg, 0.295 mmol, 1.0 equiv.) in DMF (4 ml) was then

added and the reaction mixture was heated at 118°C for 3d. The mixture was poured into water (50 ml) and diethyl ether (50 ml). The aqueous phase was extracted with diethyl ether (2 x 50 ml) and the combined organic phases were washed with water (3 x 50 ml), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (4:95 ethyl acetate/ petroleum ether) to afford starting material **2.15** (190 mg, 95 %).

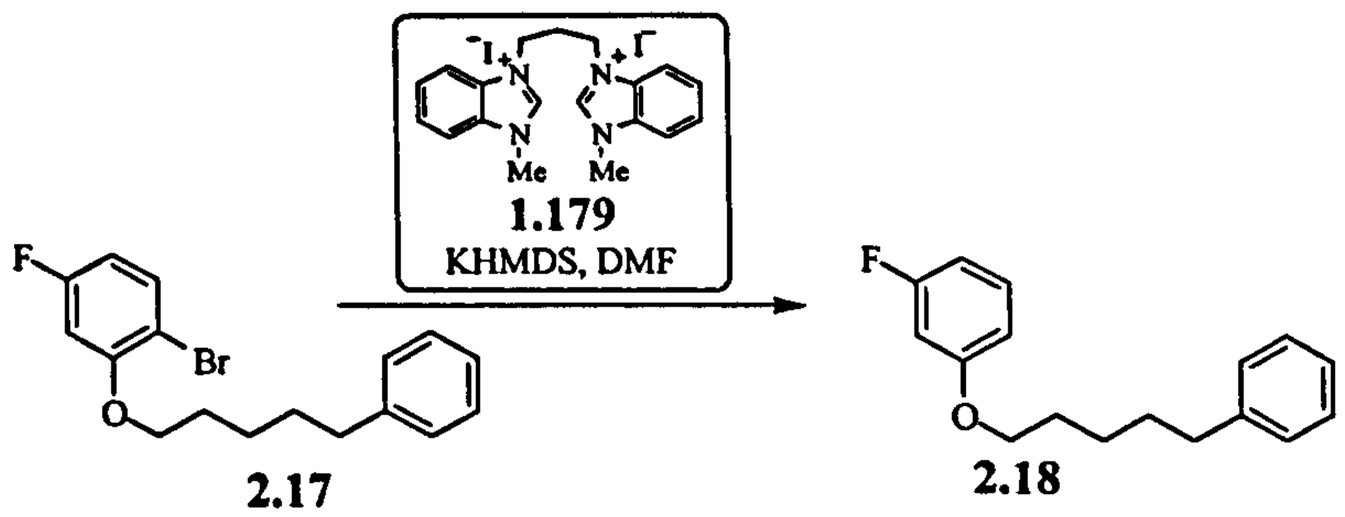
2-Bromo-5-fluoro-1-(5-phenylpentyloxy)benzene 2.17[174]



2.17

5-Phenyl-1-pentanol (0.44 ml, 2.60 mmol, 1.0 equiv.), 2-bromo-5-fluorophenol (0.3 ml, 2.60 mmol, 1.0 equiv.) and triphenylphosphine (0.687 g, 2.60 mmol, 1.0 equiv.) were dissolved in THF (8 ml), and the mixture was cooled to 0°C. DIAD (0.51 ml, 2.60 mmol, 1.0 equiv.) was then added dropwise and the mixture was allowed to warm to room temperature and stirred for 3 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (5:95 ethyl acetate/ petroleum ether) to give *2-bromo-5-fluoro-1-(5-phenylpentyloxy)benzene* **2.17** as a yellow oil (823.9 mg, 84 %); (Found: $[M+NH_4]^+$ 354.0870. $C_{17}H_{18}BrFO$ requires $[M+NH_4]$, 354.0863 (for ^{79}Br); ν_{max} (NaCl)/ cm^{-1} 3084 (Ar-H), 3026 (Ar-H), 1605 (Ar), 1483 (C-H), 1423 (C-H); δ_H ($CDCl_3$) 1.64-1.72 (2H, m, CH_2), 1.85 (2H, quintet, *J* 6.5, CH_2), 1.99 (2H, m, CH_2), 2.79 (2H, t, *J* 7.6, CH_2), 4.06 (2H, t, *J* 6.4, CH_2), 6.69 (2H, m, Ar*H*), 7.32 (3H, m, Ar*H*), 7.42 (2H, m, Ar*H*), 7.57 (1H, dd, *J* 8.6, 6.2, Ar*H*); δ_C ($CDCl_3$) 25.8 (CH_2), 28.9 (CH_2), 31.3 (CH_2), 35.9 (CH_2), 69.3 (CH_2), 101.4 (d, $^2J_{C\text{-}F}$ 26.7, CH), 106.5 (d, $^4J_{C\text{-}F}$ 3.6, C), 108.3 (d, $^2J_{C\text{-}F}$ 22.4, CH), 125.9 (CH), 128.5 (CH), 133.5 (CH), 142.5 (C), 156.5 (d, $^3J_{C\text{-}F}$ 10.2, C), 162.8 (d, $^1J_{C\text{-}F}$ 246.0, C); *m/z* (EI) 338 (M^+, 5 %, ^{81}Br), 336 (M^+, 5 %, ^{79}Br), 192 (6, ^{81}Br), 190 (6, ^{79}Br), 117 (28), 91 (100).

Attempted reduction of 2-bromo-5-fluoro-1-(5-phenylpentyloxy)benzene 2.17 with 1.175



(i) Salt **1.179** (828.8 mg, 1.48 mmol, 5.0 equiv.) was dissolved in DMF (10 ml) and purged with argon for 30 min. KHMDS (7.43 ml, 2.97 mmol, 10 equiv., c = 0.40 mol/l) was added dropwise and the reaction mixture was stirred for 1h at room temperature. An argon-purged solution of **2.17** (100 mg, 0.297 mmol, 1.0 equiv.) in DMF (5 ml) was then added and the reaction mixture was heated at 118°C for 18 h. The mixture was poured into water (50 ml) and diethyl ether (50 ml). The aqueous phase was extracted with diethyl ether (2 x 50 ml) and the combined organic phases were washed with water (3 x 50 ml), dried over sodium sulfate, filtered and evaporated. The residue was subjected to column chromatography (5:95 ethyl acetate/ petroleum ether) to afford an inseparable mixture of starting material **2.17** and *1-fluoro-3-(5-phenylpentyloxy)-benzene* **2.18** in 1:1 ratio (analysed by ^{1}H-NMR and comparison with the data of **2.18** on page 167).

(ii) Salt **1.179** (1.33 g, 2.37 mmol, 10.0 equiv.) was dissolved in DMF (6 ml) and purged with argon for 30 min. KHMDS (11.8 ml, 4.74 mmol, 20 equiv., c = 0.40 mol/l) was added dropwise and the reaction mixture was stirred for 1h at room temperature. An argon-purged solution of **2.17** (80 mg, 0.240 mmol, 1.0 equiv.) in DMF (5 ml) was then added and the reaction mixture was heated at 118°C for 18 h. The mixture was poured into water (50 ml) and diethyl ether (50 ml). The aqueous phase was extracted with diethyl ether (2 x 50 ml) and the combined organic phases were washed with water (3 x 50 ml), dried over sodium sulfate, filtered and evaporated. The residue was subjected to column chromatography (5:95 ethyl acetate/ petroleum ether) to afford an inseparable mixture of starting material **2.17** and *1-fluoro-3-(5-phenylpentyloxy)benzene* **2.18** in 2:3 ratio (analysed by ^{1}H-NMR and comparison with the data of **2.18** on page 167).

8.3 Experiments from chapter 3: *Reductions and anions by imidazole donor* 2.20

General Procedure for 'sodium hydride-method' to generate the donor in situ

Imidazole salt **2.22** or benzimidazole salt **1.179** was heated at 110°C for 1h under vacuum in a centrifuge tube, then cooled to room temperature and sodium hydride (60% suspension with mineral oil, 10 x salt equivalents) was added under argon atmosphere. This mixture was then washed with hexane (2 x 20 ml) and subsequently dried under argon. Dry DMF (15 ml) was deoxygenated with argon for 20 min [alternatively DMA (15 ml) was dried by vacuum distillation and purged with argon for 1 h prior to use] and then added dropwise to the salt/ sodium hydride residue. This mixture was stirred for 4h at room temperature under argon and then exposed to centrifugation. The resulting supernatant liquid was transferred *via* cannula to the particular substrate [dried beforehand under vacuum at room temperature for 3 h]. The reaction mixture was stirred at room temperature for 18 h [alternatively heated at 110°C for 18 h] under argon atmosphere [see experiment for exact conditions]. Work-up was then carried out.

General Procedure for 'pure donor-method'

The particular substrate was dried under vacuum at room temperature for 3h. Anhydrous DMF (15 ml) was then added under argon atmosphere and the mixture was deoxygenated with argon for 20 min. This mixture was then transferred into a glove-box. Pure imidazole donor **2.20** was weighed into a dry round-bottomed flask in a glove-box and the solution of the reactant in DMF was then added to it by pipette. The reaction mixture was stirred for 18 h at room temperature in the glove-box. Work-up was then carried out.

Work-up procedures

If '*neutral* work-up' is stated in the experiment, the following procedure was carried out:
The reaction mixture was poured into water (20 ml). The aqueous layer was extracted with diethyl ether (3 x 20 ml) and the combined organic layer was then washed with water (4 x 20 ml) and brine (20 ml), dried over sodium sulfate, filtered and removed *in vacuo*.

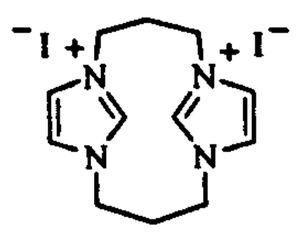
If '*acidic* work-up' is stated in the experimental procedure, the following was applied:
2 N hydrochloric acid (20 ml) was added and the aqueous layer was extracted with diethyl ether (3 x 20 ml). The combined organic layer was then washed with 2N hydrochloric acid (4 x 20 ml), followed by brine/ hydrochloric acid (20 ml + 10 ml), was subsequently dried over sodium sulfate, filtered and evaporated.

Which particular work-up procedure was carried out is stated in the experimental part below.

General furan purification

For each reaction furan was freshly purified from its stabiliser (2,6-di-*tert*butyl-4-methyl-phenol) prior to use according to this procedure:[182] Furan was washed with 7 % aqueous potassium hydroxide solution (5 x 10 ml), dried over sodium sulfate, filtered and subsequently distilled under argon atmosphere over KOH pellets. The resulting furan was degassed with argon.

1,1-3,3-Bistrimethylene diimidazolium diiodide 2.22

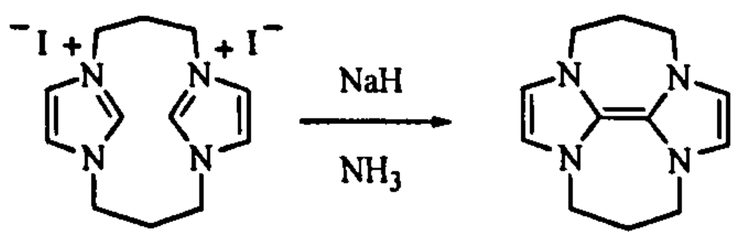


2.22

Stage 1 Sodium hydride (27 g, 0.675 mol, 2.2 equiv.) was washed with hexane (2 x 200 ml), then dried under vacuum. Anhydrous DMF (20 ml) was added and the mixture was cooled to 0°C. A solution of imidazole (40.6 g, 0.614 mol, 2.0 equiv) in DMF (30 ml) was added dropwise *via* cannula. After stirring for 1 h at room temperature the mixture was cooled to 0°C. 1,3-Dibromopropane (31 ml, 0.307 mol, 1.0 equiv) was then added dropwise, and the reaction mixture was subsequently stirred at room temperature overnight. DCM (1.5 l) was then added, the precipitate removed by filtration and the solvent evaporated. The residue was purified by vacuum distillation (1 mbar, 175°C) to afford 1-[3-(1*H*-imidazol-1-yl)propyl]-1*H*-imidazole as a colourless liquid (30.6 g, 56 %); which was reacted in the next step.

Stage 2 A five-litre three-necked flask, equipped with a mechanical stirrer and a condenser was filled with acetonitrile (4.0 litres), 1-[3-(1*H*-imidazol-1-yl)propyl]-1*H*-imidazole (1.53 g, 8.68 mmol, 1.0 equiv.) and 1,3-diiodopropane (1 ml, 8.68 mmol, 1.0 equiv.). The mixture was heated at reflux for 24 h, and then another batch of starting materials (of same quantity) was added. One batch of starting material was added every 24 h. White precipitate appeared gradually. After 20 days, a total of 1-(3-(1*H*-imidazol-1-yl)propyl)-1*H*-imidazole (30.6 g, 0.173 mmol) and 1,3-diiodopropane (51.4 g, 0.173 mmol) had been added. The mixture was further heated at reflux for an additional four days. The hot solution was decanted and acetonitrile was removed. The resulting solid was recrystallised from methanol to afford 1,1-3,3-bistrimethylene diimidazolium diiodide **2.22** (38.8 g, 47 %) as a white solid; mp 284 °C (dec.); δ_H (DMSO) 2.29-2.41 (2H, m, CH_2), 2.42-2.56 (2H, m, CH_2), 4.43-4.48 (4H, m, 2 × CH_2), 4.58-4.65 (4H, m, 2 × CH_2), 7.65 (4H, s, Ar*H*), 9.07 (2H, s, 2 × N=C*H*N$^+$); consistent with the data collected previously within the group.[183]

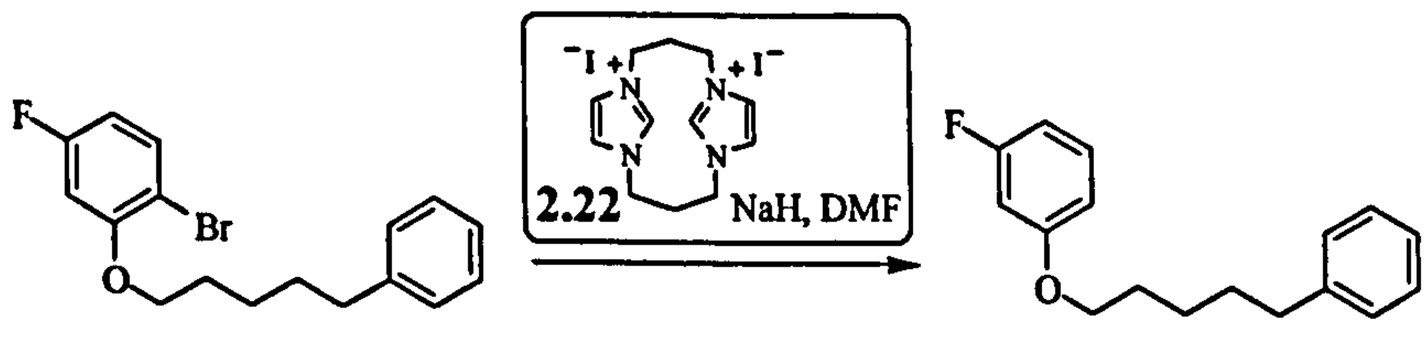
1-(3-(1*H*-imidazol-1-yl)propyl)-1*H*-imidazole 2.20



2.22 **2.20**

A 250 ml Schlenk flask with a magnetic stirbar was flame-dried in vacuum, backfilled with argon and charged with 1,1-3,3-bistrimethylene diimidazolium diiodide **2.22** (6.0 g, 12.7 mmol, 1.0 equiv.). The salt was dried *in vacuo* at 100 °C for 2 h, then cooled to room temperature, purged with argon gas and sodium hydride (5.0 g, 127.0 mmol, 10.0 equiv.) was added. The mixture was washed with dry hexane (3 × 100 ml) under an argon atmosphere and a dry-ice condenser was attached to the flask. The residual hexane in the reaction mixture was removed under vacuum and the system was back-filled with argon gas. Ammonia (150 ml) was condensed into the flask while a steady flow of argon gas was maintained at all times during the course of the reaction. The suspension turned yellow, was stirred and refluxed at room temperature for 2 h and then left overnight at room temperature while the ammonia evaporated slowly. The flask was transferred into a glove box. The yellow solid mixture was extracted with dry ether (3 × 80 ml, deoxygenated). The yellow suspension was filtered and the filtrate was evaporated under reduced pressure by distillation to afford a yellow solid. This was dried *in vacuo* to afford 1-(3-(1*H*-imidazol-1-yl)propyl)-1*H*-imidazole **2.20** (2.7 g, 98 %) as a yellow solid which was stored under nitrogen; δ_H (C_6D_6) 1.38-1.43 (4H, m, 2 × C*H*$_2$), 2.43-2.45 (8H, m, 4 × C*H*$_2$), 5.48 (4H, s, 4 × =C*H*); the data were consistent with those reported in the literature[184] and collected within the group.[183]

Reduction of 2-bromo-5-fluoro-1-(5-phenylpentyloxy)benzene 2.15 with donor 2.20

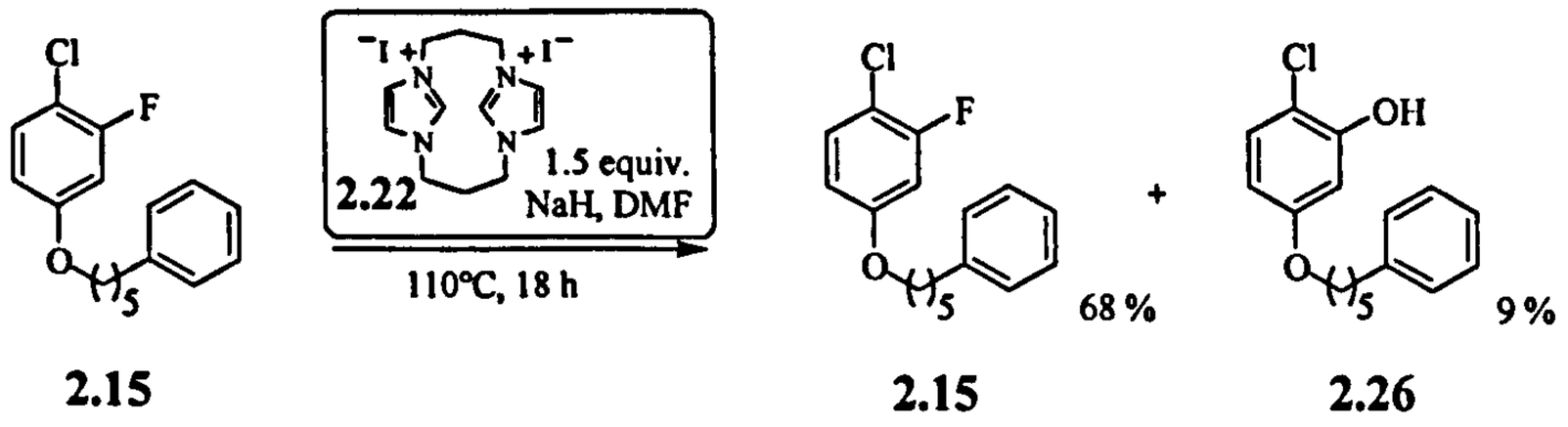


2.17 **2.18**

(i) The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: Room temperature for 1.5 h, then 110°C overnight, DMF (15 ml), salt **2.22** (212 mg, 0.45 mmol, 1.5 equiv.), 2-bromo-5-fluoro-1-(5-phenylpentyloxy)benzene **2.17** (101.1 mg, 0.3 mmol, 1.0 equiv.). The purification of the crude mixture after *neutral* work-up was carried out by column chromatography on silica gel (5:95 ethyl acetate/ petroleum ether) to afford an inseparable mixture of **2.17** and **2.18** (56 mg) in 1:6 ratio (analysed by ^{1}H-NMR and comparison with data below).

(ii) The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: Room temperature for 1.5 h, then 110°C overnight, DMF (15 ml), salt **2.22** (472 mg, 0.5 mmol, 2.0 equiv.), 2-bromo-5-fluoro-1-(5-phenylpentyloxy)benzene **2.17** (95.0 mg, 0.28 mmol, 1.0 equiv.). The purification of the crude mixture after *neutral* work-up was carried out by column chromatography on silica gel (5:95 ethyl acetate/ petroleum ether) to afford *1-fluoro-3-(5-phenylpentyloxy)benzene* **2.18** as a colourless oil (55 mg, 76 %); (Found: $[M+NH_4]^+$ 276.1754. $C_{17}H_{19}FO$ requires [*M+NH4*], 276.1758); ν_{max} (NaCl)/cm^{-1} 3027 (Ar-H), 2938 (C-H), 1592 (Ar), 1491 (C-H); δ_H ($CDCl_3$) 1.54-1.62 (2H, m, C*H*$_2$), 1.73-1.81 (2H, m, C*H*$_2$), 1.85-1.92 (2H, m, C*H*$_2$), 2.72 (2H, t, *J* 7.7, C*H*$_2$Ph), 3.99 (2H, t, *J* 6.5, C*H*$_2$O), 6.65-6.75 (3H, m, Ar*H*), 7.24-7.38 (6H, m, Ar*H*); δ_C ($CDCl_3$) 26.2 (CH_2), 29.5 (CH_2), 31.7 (CH_2), 36.4 (CH_2), 68.7 (CH_2), 102.6 (d, $^2J_{C-F}$ 24.6, CH), 107.7 (d, $^2J_{C-F}$ 21.3, CH), 110.9 (CH), 126.3 (CH), 128.8 (CH), 128.9 (CH), 130.6 (d, $^3J_{C-F}$ 10.1, CH), 142.9 (C), 161.0 (d, $^3J_{C-F}$ 10.9, C), 164.2 (d, $^1J_{C-F}$ 244.8, C); *m/z* (EI) 258 (M^+, 10 %), 146 (10), 117 (14), 91 (100), 83 (5), 65 (9).

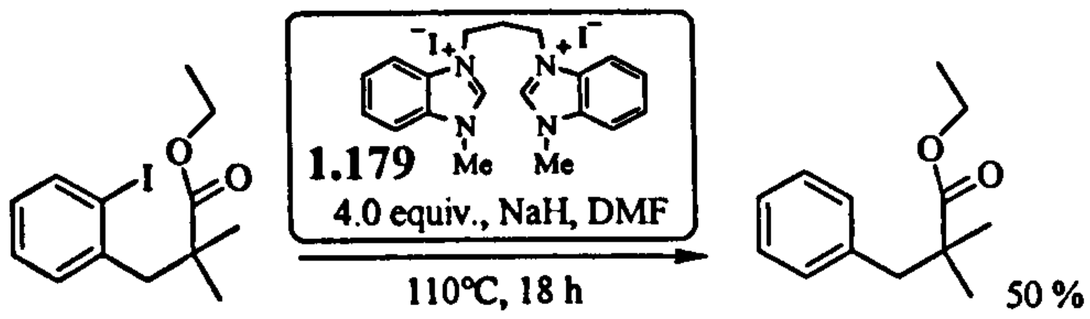
Attempted reduction of 1-chloro-2-fluoro-4-(5-phenylpentyloxy)benzene 2.15



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), salt **2.22** (212 mg, 0.45 mmol, 1.5 equiv.), 1-chloro-2-fluoro-4-(5-phenylpentyloxy)benzene **2.15** (87.8 mg, 0.3 mmol, 1.0 equiv.). The purification of the crude mixture after *neutral* work-up was carried out by column chromatography on silica gel (5:95 ethyl acetate/ petroleum ether) to afford starting material **2.15** (60 mg, 68 %) and *2-chloro-5-(5-phenylpentyloxy)phenol* **2.26** as a colourless oil (6 mg, 9 %); (Found: $[M+NH_4]^+$ 308.1415. $C_{17}H_{19}ClO_2$ requires [*M+NH4*], 308.1412); δ_H ($CDCl_3$) 1.49-1.57 (2H, m, C*H*$_2$), 1.67 (2H, quintet, *J* 7.6, C*H*$_2$), 1.77-1.83 (2H, m, C*H*$_2$), 2.65 (2H, t, *J* 7.6, C*H*$_2$), 3.91 (2H, t, *J* 6.5, C*H*$_2$), 6.43 (1H, dd, *J* 8.9, 2.8, Ar*H*), 6.57 (1H, d, *J* 2.8, Ar*H*), 7.16-7.29 (6H, m, Ar*H*); *m/z* (EI) 290 (M^+, 62%), 144 (91), 91 (100), 65 (14), 41 (12).

Reaction of benzimidazole donor 1.175 with iodoester 2.27

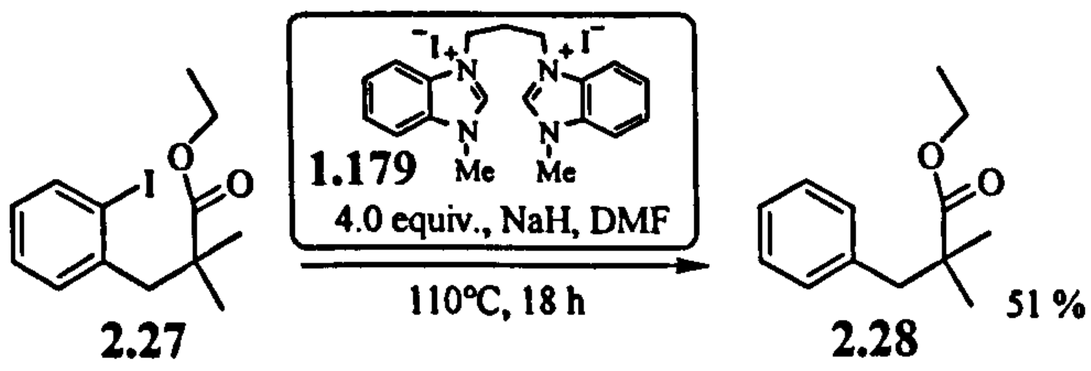
(i)



2.27 **2.28**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), benzimidazole salt **1.179** (668 mg, 1.19 mmol, 4.0 equiv.), 3-(2-iodophenyl)-2,2-dimethylpropionic acid ethyl ester **2.27** (99.0 mg, 0.298 mmol, 1.0 equiv.). The purification of the crude mixture after *neutral* work-up was carried out by column chromatography on silica gel (10:90 ethyl acetate/ petroleum ether) to afford 2,2-dimethyl-3-phenyl-propionic acid ethyl ester **2.28** as a colourless liquid (32 mg, 51 %); δ_H ($CDCl_3$) 1.22 (6H, s, CH_3), 1.27 (3H, t, *J* 7.1, CH_2CH_3), 2.90 (2H, s, CH_2), 4.15 (2H, q, *J* 7.1, OCH_2CH_3), 7.12-7.18 (2H, m, Ar*H*), 7.20-7.33 (3H, m, Ar*H*); this is consistent with the data collected previously in the group.[185,183]

(ii)

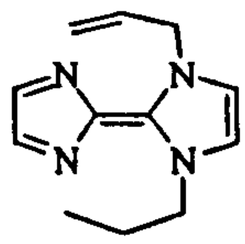


2.27 **2.28**

Salt **1.179** was freshly prepared according to the above quoted procedure. The salt **1.179** (694 mg, 1.24 mmol, 4.0 equiv.) was stored under vacuum at room temperature prior to use [20 h], was then dried under vacuum at 120°C for 2 h and then cooled to room temperature. Sodium hydride (60% suspension with mineral oil, 360 mg, 9.0 mmol, 30 equiv.) was added under argon atmosphere. This mixture was then washed with hexane (2 x 20 ml) and subsequently dried under argon. Dry DMF (15 ml) was deoxygenated with argon for 20 min and then added dropwise to the salt/sodium hydride residue. This mixture was stirred for 4h at room temperature under argon and then exposed to centrifugation. The resulting supernatant liquid was transferred *via* cannula to 3-(2-iodophenyl)-2,2-dimethylpropionic acid ethyl ester **2.27** (103 mg, 0.310 mmol, 1.0 equiv.) [dried beforehand under vacuum at room temperature for 3 h]. The reaction mixture was heated at 110°C for 18 h under argon atmosphere. After allowing to cool to room temperature the reaction mixture was poured into water (20 ml). The aqueous layer was extracted with diethyl ether

(3 x 20 ml) and the combined organic layer was then washed with water (4 x 20 ml) and brine (20 ml), dried over sodium sulfate and removed *in vacuo*. The residue was purified by column chromatography (10:90 ethyl acetate/ petroleum ether) to afford 2,2-dimethyl-3-phenyl-propionic acid ethyl ester **2.28** as a colourless liquid (32 mg, 51 %); for ^{1}H-NMR data see above.

3-Allyl-1-propyl-1,3-dihydro-[2,2']biimidazolylidene 2.36

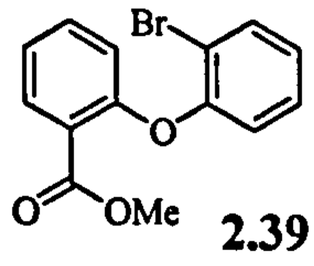


2.36

(Found: $[M+H]^+$ 217.1449. $C_{12}H_{16}N_4$ requires $[M+H]^+$, 217.1448); ν_{max} (NaCl)/cm^{-1} 3109 (Ar-H), 2961 (C-H), 2934 (C-H), 1422 (C-H); δ_H ($CDCl_3$) 0.89 (3H, t, *J* 7.4, C*H*$_3$), 1.76-1.82 (2H, m, $CH_3CH_2CH_2$), 4.42 (2H, t, *J* 7.2, $CH_3CH_2CH_2N$), 5.06-5.19 (4H, CH_2=CHC*H*$_2$N), 5.94-6.02 (1H, m, CH_2=C*H*CH$_2$), 7.01 (2H, s, Ar*H*), 7.13 (2H, d, *J* 7.4, ArH); δ_C ($CDCl_3$) 11.0 (CH_3), 24.3 (CH_2), 49.1 (CH_2), 49.9 (CH_2), 117.4 (CH_2), 129.9 (CH), 121.4 (CH), 133.9 (CH), [2 x central C were not shown]; *m/z* (EI) 216 (16), 201 (18), 173 (21), 159 (38), 147 (19), 94 (9), 57 (17), 43 (40), 41 (100).

Further details about the experiment in which **2.36** was isolated can be found on page 232.

2-(2-Bromophenoxy)benzoic acid methyl ester 2.39[186]



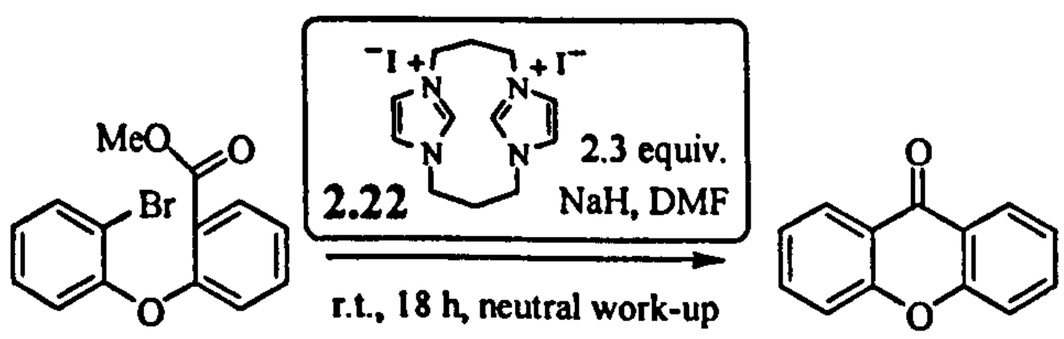
2.39

Methyl-2-iodobenzoate (3g, 11.45 mmol, 1.0 equiv.) and 2-bromophenol (1.2 ml, 11.45 mmol, 1.0 equiv.) were dissolved in pyridine (20 ml) under argon. To this mixture cesium carbonate (4.1 g, 12.59 mmol, 1.1 equiv.), $(CF_3SO_3Cu)_2 \cdot C_6H_5CH_3$ (0.5 g, 0.93 mmol, 0.08 equiv.) and 4 Å molecular sieves (50 mg) were added under argon. The reaction mixture was heated at 110°C for 36 h under argon. After allowing to cool to room temperature, the mixture was poured into diethyl ether (200 ml) and water was added (200 ml). The aqueous layer was extracted with diethyl ether (150 ml) and the combined organic layer was washed with 2 N hydrochloric acid (3 x 200 ml), followed by 2 N sodium hydroxide solution (3 x 200 ml) and brine (200 ml). After drying over sodium sulfate the solvent was

removed under reduced pressure and the residue was purified by column chromatography (20:20:60 toluene/ dichloromethane/ petroleum ether) to give *2-(2-bromophenoxy)benzoic acid methyl ester* **2.39** as a colourless liquid (0.7 g, 20 %); (Found: $[M+H]^+$ 306.9965. $C_{14}H_{11}BrO_3$ requires $[M+H]^+$, 306.9964); ν_{max} (NaCl)/cm^{-1} 3066 (Ar-H), 2950 (C-H), 1732 (C=O), 1603 (Ar), 1471 (C-H); δ_H ($CDCl_3$) 3.87 (3H, s, CH_3), 6.87 (1H, dd, *J* 8.2, 1.4, Ar*H*), 6.98 (1H, dd, *J* 8.2, 0.8, Ar*H*), 7.02-7.06 (1H, m, Ar*H*), 7.45-7.30 (2H, m, Ar*H*), 7.51-7.55 (1H, m, Ar*H*), 7.69 (1H, dd, *J* 8.0, 1.5, Ar*H*), 8.02 (1H, dd, *J* 7.8, 1.7, Ar*H*); δ_C ($CDCl_3$) 52.2 (CH_3), 113.9 (C), 118.9 (CH), 120.3 (CH), 122.8 (C), 123.9 (CH), 124.6 (CH), 128.6 (CH), 132.1 (CH), 133.7 (CH), 133.8 (CH), 154.2 (C), 155.5 (C), 165.8 (C); *m/z* (EI) 308 (M^+, 5 % ^{81}Br), 306 (M^+, 5 % ^{79}Br), 277 (6 ^{81}Br), 275 (6 ^{79}Br), 227 (100), 196 (34), 139 (38), 92 (31).

Test reactions on 2-(2-bromophenoxy)benzoic acid methyl ester 2.39

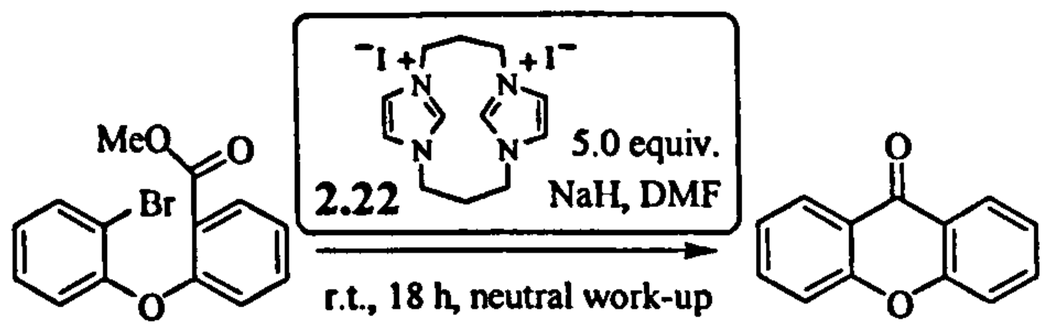
(i)



2.39 **2.42** 32 %

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), salt **2.22** (333 mg, 0.706 mmol, 2.3 equiv.), 2-(2-bromophenoxy)benzoic acid methyl ester **2.39** (94.3 mg, 0.307 mmol, 1.0 equiv.). *Observation:* Upon addition of yellow donor solution, instantaneous colour change to red-orange occurred. The purification of the crude mixture after *neutral* work-up was carried out by column chromatography on silica gel (20:80 ethyl acetate/ hexane) to afford xanthone **2.42**[187] as a white solid (19 mg, 32 %); mp 168-170°C (lit.[187] 172-173°C); (Found: $[M+H]^+$ 197.0596. $C_{13}H_8O_2$ requires $[M+H]^+$, 197.0597); ν_{max} (KBr)/cm^{-1} 3054 (Ar-H), 2987 (C-H), 1655 (C=O), 1609 (Ar); δ_H ($CDCl_3$) 7.38-7.42 (2H, m, Ar*H*), 7.51 (2H, d, *J* 8.3, Ar*H*), 7.72-7.76 (2H, m, Ar*H*), 8.36 (2H, dd, *J* 7.9, 1.6, Ar*H*); δ_C ($CDCl_3$) 118.2 (CH), 122.1 (C), 124.1 (CH), 127.0 (CH), 135.0 (CH), 156.5 (C), 177.5 (C); *m/z* (EI) 196 (M^+, 100 %), 168 (59), 139 (53), 92 (11), 74 (17), 63 (25).

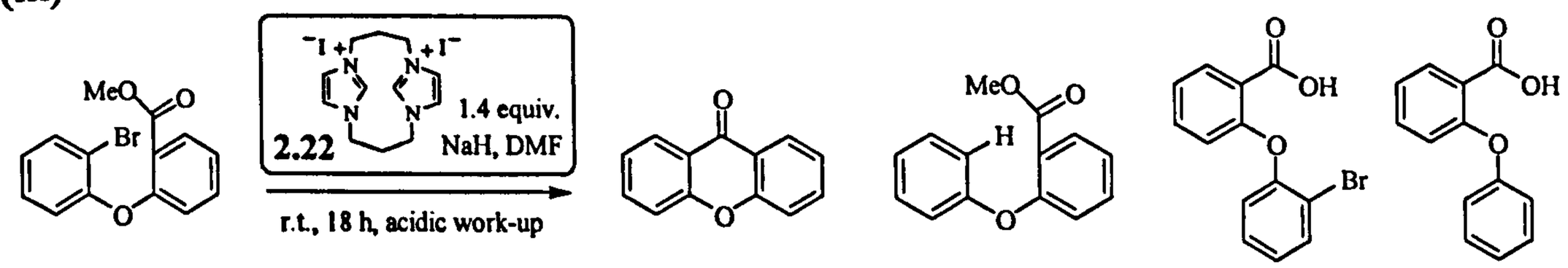
(ii)



2.39 **2.42** 20 %

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), salt **2.22** (776 mg, 1.64 mmol, 5.0 equiv.), 2-(2-bromophenoxy)benzoic acid methyl ester **2.39** (101 mg, 0.329 mmol, 1.0 equiv.). *Observation:* Upon addition of yellow donor solution instantaneous colour change to red-orange occurred. The purification of the crude mixture after *neutral* work-up was carried out by column chromatography on silica gel (20:80 ethyl acetate/ hexane) to afford xanthone **2.42**[187] as a white solid (15 mg, 20 %); for data see above.

(iii)

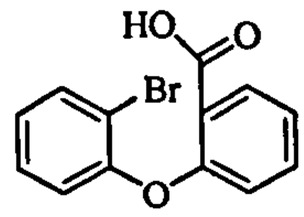


2.39 **2.42** **2.43** **2.46** **2.45**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), salt **2.22** (230.5 mg, 0.488 mmol, 1.4 equiv.), 2-(2-bromophenoxy)benzoic acid methyl ester **2.39** (104 mg, 0.339 mmol, 1.0 equiv.). The purification of the crude mixture after *acidic* work-up was carried out by column chromatography on silica gel (20:80 ethyl acetate/ hexane) to afford two fractions. The first fraction (21 mg, yellow liquid) contained xanthone **2.42**[187] as a white solid and 2-phenoxybenzoic acid methyl ester **2.43**[188] in a 1:1 mixture; for data see above. The second fraction (15 mg, white solid) contained both acids **2.46** and **2.45** in a 1:2 mixture (15 mg, white solid), as judged by comparison of the ^{1}H-NMR spectrum of the fraction with the data of those compounds (see below).

2-Phenoxybenzoic acid **2.45**[218]: mp 103-104°C (lit.[218] 112°C); δ_H ($CDCl_3$) 6.85 (1H, dd, *J* 7.6, 0.7, Ar*H*), 7.13-7.16 (2H, m, Ar*H*), 7.21-7.30 (2H, m, Ar*H*), 7.43-7.51 (3H, m, Ar*H*), 8.23 (1H, dd, *J* 7.9, 1.7, Ar*H*).

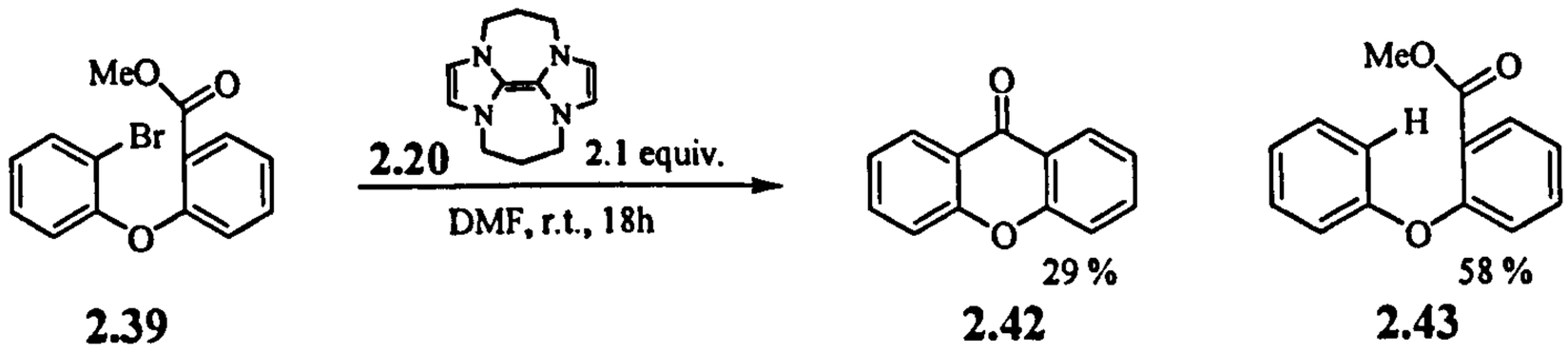
2-(2-Bromo-phenoxy)-benzoic acid 2.46



2.46

2-(2-bromophenoxy)benzoic acid methyl ester **2.39** (94 mg, 0.32 mmol, 1.0 equiv) was dissolved in DMF (12 ml). A solution of sodium hydroxide (128 mg, 3.2 mmol, 10 equiv.) in water (2 ml) was added and the mixture was heated at 100°C overnight. Acidic work-up was carried out and the residue purified by column chromatography (60:40 ethyl acetate/ hexane) to afford *2-(2-bromo-phenoxy)-benzoic acid* **2.46** as a white solid; mp 112-115°C; (Found: $[M+NH_4]^+$ 310.0077. $C_{13}H_9BrO_3$ requires $[M+NH_4]^+$, 310.0073 {for ^{79}Br}); ν_{max} (KBr)/cm^{-1} 3380 (O-H), 3078 (Ar-H), 2918 (C-H), 1697 (C=O), 1601 (Ar); δ_H ($CDCl_3$) 6.76 (1H, d, *J* 8.3, Ar*H*), 6.95-6.97 (1H, m, Ar*H*), 7.09-7.13 (1H, m, Ar*H*), 7.19-7.23 (1H, m, Ar*H*), 7.31-7.35 (1H, m, Ar*H*), 7.46-7.51 (1H, m, Ar*H*), 7.66 (1H, dd, *J* 7.9, 1.2, Ar*H*), 8.16 (1H, dd, *J* 7.8, 1.5, Ar*H*); δ_C ($CDCl_3$) 115.4 (C), 117.7 (CH), 119.9 (C), 121.4 (CH), 123.6 (CH), 126.3 (CH), 128.9 (CH), 133.3 (CH), 134.1 (CH), 134.8 (CH), 152.1 (C), 156.7 (C), 168.3 (C); *m/z* (CI) 312 ($[M+NH_4]^+$, 37 % ^{81}Br), 310 ($[M+NH_4]^+$, 36 % ^{79}Br), 232 (100), 215 (43), 197 (32), 168 (24), 121 (15), 83 (18).

(iv)

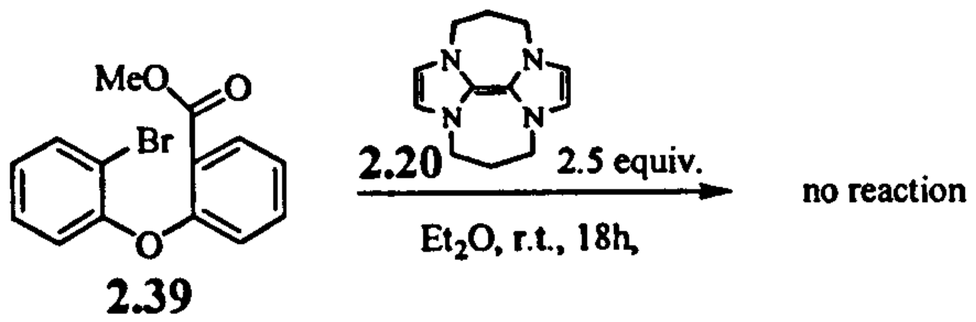


2.39 **2.42** **2.43**

The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), donor **2.20** (135.9 mg, 0.629 mmol, 2.1 equiv.), 2-(2-bromophenoxy)benzoic acid methyl ester **2.39** (92 mg, 0.299 mmol, 1.0 equiv.). *Observation:* Upon addition of yellow donor solution instantaneous colour change to red-orange occurred. The purification of the crude mixture after *neutral* work-up was carried out by column chromatography on silica gel (20:20:60 DCM/ toluene/ hexane, then 100:0 methanol) to afford xanthone **2.42**[187] as a white solid (17 mg, 29 %), for data see above and 2-phenoxybenzoic acid methyl ester **2.43**[188] as a colourless liquid (39.6 mg, 58 %); (Found: $[M+H]^+$ 229.0859. $C_{14}H_{12}O_3$ requires $[M+H]^+$, 229.0859); ν_{max} (NaCl)/cm^{-1} 3068 (Ar-H), 3039 (Ar-H), 2951 (C-H), 1732 (C=O), 1603 (Ar), 1483 (C-H);

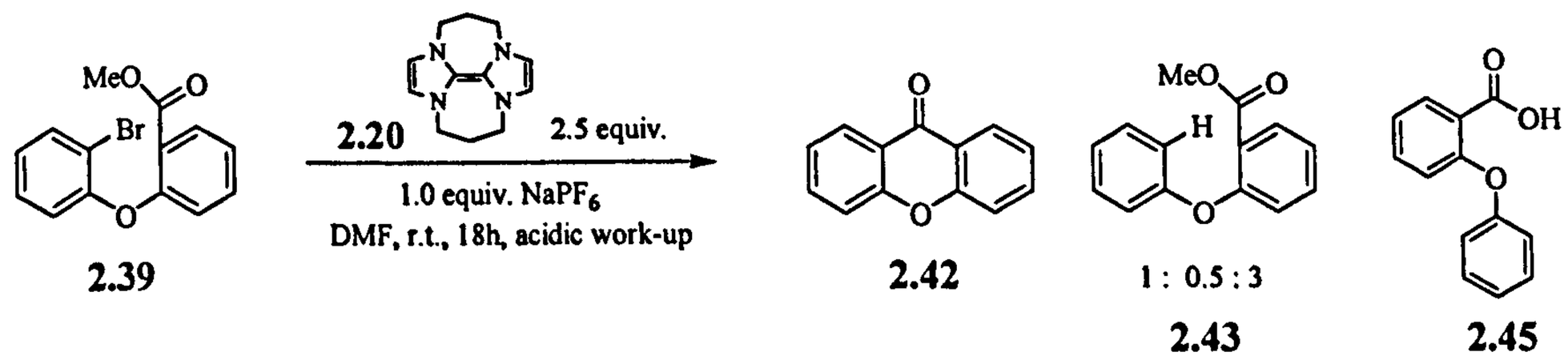
δ_H ($CDCl_3$) 3.89 (3H, s, C*H*$_3$), 7.04-7.09 (3H, m, Ar*H*), 7.09-7.19 (1H, m, Ar*H*), 7.27 (1H, ddd, *J* 7.6, 7.6, 1.1, Ar*H*), 7.39-7.43 (2H, m, Ar*H*), 7.52-7.57 (1H, m, Ar*H*), 8.01 (1H, dd, *J* 7.8, 1.8, Ar*H*); δ_C ($CDCl_3$) 52.3 (CH_3), 118.4 (CH), 121.1 (CH), 123.3 (CH), 123.4 (C), 123.7 (CH), 129.9 (CH), 132.0 (CH), 133.8 (CH), 156.4 (C), 157.8 (C), 166.4 (C); *m/z* (EI) 228 (M^+, 76 %), 197 (100), 168 (28), 108 (57), 77 (78).

(v)



The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), donor **2.20** (162 mg, 0.75 mmol, 2.5 equiv.), 2-(2-bromo-phenoxy)-benzoic acid methyl ester **2.39** (93 mg, 0.30 mmol, 1.0 equiv.). *Observation:* The yellow colour persisted and a white precipitate formed. ^{1}H-NMR analysis of the crude mixture after *acidic* work-up (93 mg) showed only starting material **2.39**; the reaction did not procced.

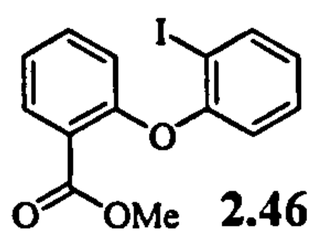
(vi)



Sodium hexafluorophosphate (50.38 mg, 0.3 mmol, 1.0 equiv.) was dried under vacuum at 150°C for 5 h. To this was added a solution of 2-(2-bromophenoxy)benzoic acid methyl ester **2.39** (93 mg, 0.30 mmol, 1.0 equiv.) in anhydrous and deoxygenated DMF (5 ml) [dried under vacuum at room temperature for 3 h prior to use] under argon atmosphere. Donor **2.20** was weighed into a dry flask in the glove-box and then dissolved in anhydrous and deoxygenated DMF (10 ml) under argon. The yellow donor solution was then added to the $NaPF_6$-substrate solution *via cannula*, which resulted in an orange-yellow reaction mixture. This was stirred for 18 h at room temperature. An aliquotwas taken from the reaction mixture and diluted with water and diethyl ether. A TLC of the organic layer showed only one spot (identical polarity as xanthone **2.42**). *Acidic* work-up of the reaction mixture was then carried out and a TLC of the residue showed then three spots. ^{1}H-NMR

of the residue showed xanthone **2.42**, 2-phenoxybenzoic acid methyl ester **2.43** and 2-phenoxybenzoic acid **2.45** (ratio: 1:0.5:3); for data see (iii) above

2-(2-Iodophenoxy)benzoic acid methyl ester 2.46[189]

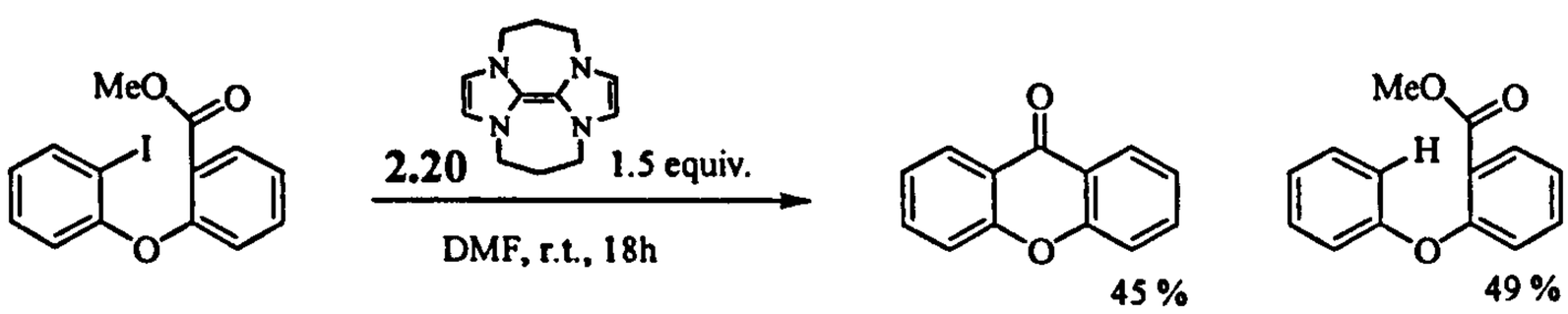


2.46

Methyl-2-iodobenzoate (4 g, 15.3 mmol, 1.0 equiv.) and 2-iodophenol (3.36 g, 15.3 mmol, 1.0 equiv.) were dissolved in pyridine (30 ml) under argon. Cesium carbonate (5.5 g, 16.79 mmol, 1.1 equiv.), copper (I) oxide (400 mg, 2.8 mmol, 0.18 equiv.) and 4 Å molecular sieves (50 mg) were added to this mixture under argon. The reaction mixture was heated at 110°C for 48 h under argon. After allowing to cool to room temperature, the mixture was poured into ethyl acetate (200 ml) and water was added (200 ml). The aqueous layer was extracted with ethyl acetate (150 ml) and the combined organic layer was washed with 2 N hydrochloric acid (5 x 200 ml), followed by 2 N sodium hydroxide solution (5 x 200 ml) and brine (200 ml). After drying over sodium sulfate and filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography (20:20:60 toluene/ dichloromethane/ petroleum ether), followed by Kugelrohr distillation (150°C, 2 mbar) to give *2-(2-iodophenoxy)benzoic acid methyl ester* **2.46** as a colourless liquid (1.19 g, 22 %); (Found: $[M+NH_4]^+$ 372.0092. $C_{14}H_{11}IO_3$ requires $[M+NH_4]^+$, 372.0091); ν_{max} (NaCl)/cm^{-1} 3062 (Ar-H), 2998 (C-H), 2949 (C-H), 1732 (C=O), 1603 (Ar), 1465 (C-H); δ_H ($CDCl_3$) 3.81 (3H, s, C*H*$_3$), 6.73 (1H, dd, *J* 8.2, 1.4, Ar*H*), 6.85 (1H, ddd, *J* 7.6, 7.6, 1.4, Ar*H*), 6.94 (1H, dd, *J* 8.2, 1.0, Ar*H*), 7.21-7.27 (2H, m, Ar*H*), 7.47-7.51 (1H, m, Ar*H*), 7.87 (1H, dd, *J* 7.9, 1.6, Ar*H*), 7.96 (1H, dd, *J* 7.9, 1.8, Ar*H*); δ_C ($CDCl_3$) 52.7 (CH_3), 88.2 (C), 118.1 (CH), 121.1 (CH), 123.5 (C), 124.4 (CH), 125.3 (CH), 130.0 (CH), 132.6 (CH), 134.1 (CH), 140.3 (CH), 155.8 (C), 157.5 (C), 166.4 (C); *m/z* (EI) 354 (M^+, 7 %), 227 (100 %), 196 (48), 168 (47), 139 (36), 63 (38).

Test reactions on 2-(2-iodophenoxy)benzoic acid methyl ester 2.46

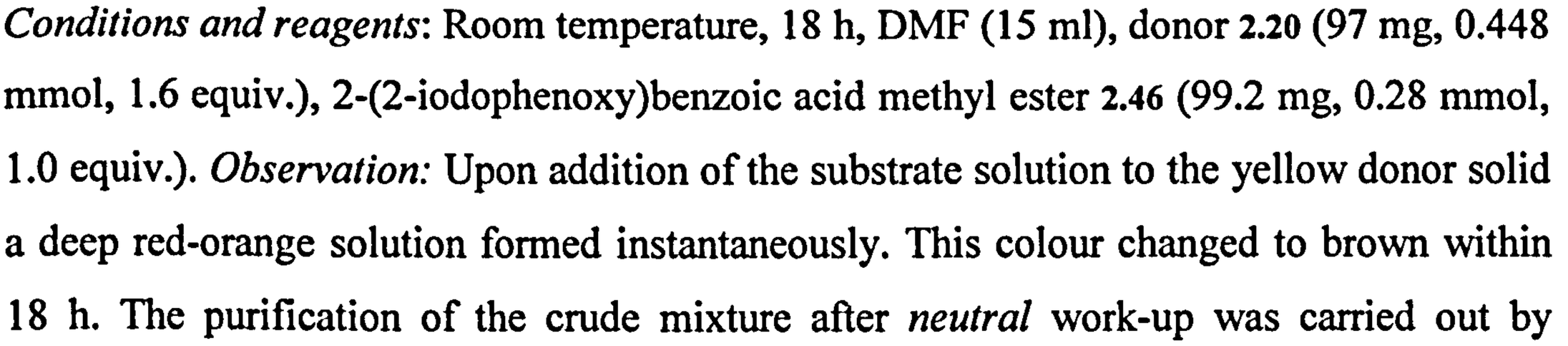
(i)



2.46 **2.42** **2.43**

The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), donor **2.20** (97 mg, 0.448 mmol, 1.6 equiv.), 2-(2-iodophenoxy)benzoic acid methyl ester **2.46** (99.2 mg, 0.28 mmol, 1.0 equiv.). *Observation:* Upon addition of the substrate solution to the yellow donor solid a deep red-orange solution formed instantaneously. This colour changed to brown within 18 h. The purification of the crude mixture after *neutral* work-up was carried out by column chromatography on silica gel (20:20:60 DCM/ toluene/ hexane, then 100:0 methanol) to afford xanthone **2.42**[187] as a white solid (25 mg, 45 %) and 2-phenoxybenzoic acid methyl ester **2.43**[188] as a colourless liquid (32 mg, 49 %); for data see above.

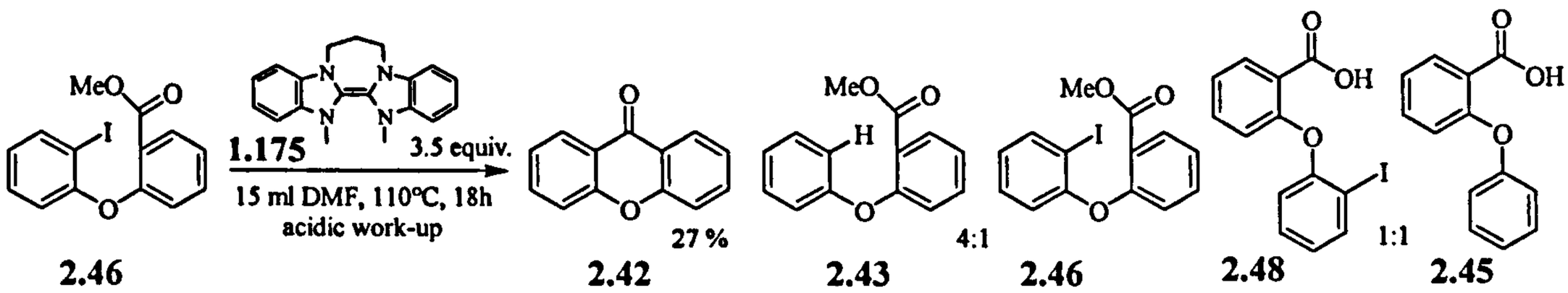
(ii)



2.46 **2.42** **2.43** **2.46** **2.48** **2.45**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), benzimidazole salt **1.179** (566 mg, 1.01 mmol, 3.5 equiv.), 2-(2-iodophenoxy)benzoic acid methyl ester **2.46** (102 mg, 0.288 mmol, 1.0 equiv.). *Observation:* The yellow donor colour did not change at room temperature, while heating a colour change to deep red took place. The purification of the crude mixture after *acidic* work-up was carried out by column chromatography on silica gel (20:20:60 toluene/ DCM/ petroleum ether, then 20:80 ethyl acetate/ petroleum ether) to afford a mixture of starting material **2.46** and 2-phenoxybenzoic acid methyl ester **2.43**[188] (1:2 mixture, 31.3 mg) and xanthone **2.42**[187] as a white solid (11 mg, 19 %), for data see above, and a mixture (5:4, 14 mg) of 2-(2-iodophenoxy)benzoic acid **2.48** and 2-phenoxybenzoic acid **2.45**; for data see **(iii)** below.

(iii)

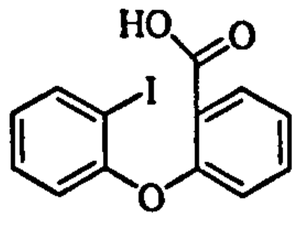


2.46 **2.42** **2.43** **2.46** **2.48** **2.45**

1,1'-Dimethyl-3,3'-(trimethylene)-2,2'-bibenzimidazolinylidene **1.175** (303 mg, 1.0 mmol, 3.5 equiv.) was weighed into a dry round-bottomed flask in a glove-box. DMF (15 ml) was deoxygenated and added to the pure donor under argon. The donor solution was then transferred to 2-(2-iodophenoxy)benzoic acid methyl ester **2.46** (101 mg, 0.285 mmol, 1.0 equiv.) [dried beforehand under vacuum at room temperature] and the mixture was heated at 110°C for 18 h under argon. This led to a colour change from yellow to deep red. Acidic work-up was then carried out and the residue was purified by column chromatography on silica gel (20:20:60 DCM/ toluene/ hexane, then 100:0 methanol) to afford xanthone **2.42**[187] as a white solid (15.6 mg, 27 %) and a mixture of 2-phenoxybenzoic acid methyl ester **2.43**[188] and starting material 2-(2-iodophenoxy)benzoic acid methyl ester **2.46** (4:1 mixture, 33.6 mg, for data see above), and a mixture of 2-(2-iodophenoxy)*benzoic acid* **2.48** *and* 2-phenoxybenzoic acid **2.45** (11.6 mg, 1:1 mixture, judged by ^{1}H-NMR and comparison with authentic compounds, see below for data).

2-phenoxybenzoic acid **2.45**[218] as a white solid (19.2 mg, 31 %); mp 103-104°C (lit.[218] 112°C); δ_H ($CDCl_3$) 6.85 (1H, dd, *J* 7.6, 0.7, Ar*H*), 7.13-7.16 (2H, m, Ar*H*), 7.21-7.30 (2H, m, Ar*H*), 7.43-7.51 (3H, m, Ar*H*), 8.23 (1H, dd, *J* 7.9, 1.7, Ar*H*).

2-(2-iodophenoxy)benzoic acid 2.48

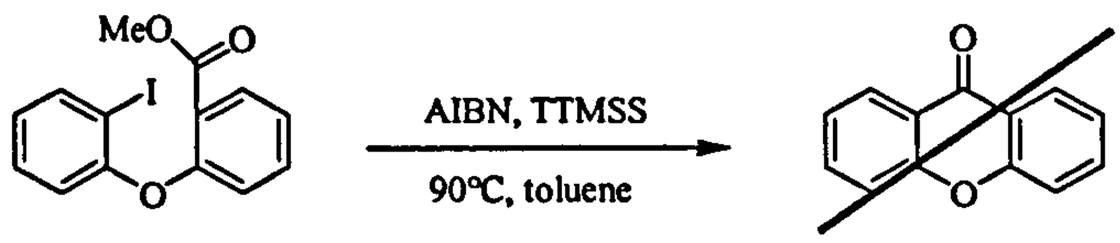


2.48

2-(2-iodophenoxy)benzoic acid methyl ester **2.46** (90 mg, 0.25 mmol, 1.0 equiv) was dissolved in DMF (12 ml). A solution of sodium hydroxide (102 mg, 2.5 mmol, 10 equiv.) in water (2 ml) was added and the mixture was heated at 100°C overnight. Acidic work-up was carried out and the residue purified by column chromatography (60:40 ethyl acetate/ hexane) to afford *2-(2-iodophenoxy)benzoic acid* **2.48** as a white solid; mp 99-100°C; (Found: $[M+NH_4]^+$ 357.9935. $C_{13}H_9IO_3$ requires $[M+NH_4]^+$, 357.9935); ν_{max} (NaCl)/cm^{-1} 3382 (O-H), 3066 (Ar-H), 2917 (C-H), 2840 (C-H), 1694 (C=O); δ_H ($CDCl_3$) 6.82 (1H, d,

J 8.2, Ar*H*), 6.93-7.02 (2H, m, Ar*H*), 7.23-7.29 (1H, m, ArH), 7.40-7.47 (1H, m, Ar*H*), 7.51-7.55 (1H, m, Ar*H*), 7.94 (1H, dd, *J* 8.3, 1.5, Ar*H*), 8.21 (1H, dd, *J* 7.8, 1.6, Ar*H*); δ_C ($CDCl_3$) 88.3 (C), 118.2 (CH), 120.5 (CH), 123.9 (CH), 125.9 (CH), 126.7 (CH), 130.2 (CH), 133.6 (CH), 134.9 (CH), 140.7 (C), 155.3 (C), 156.7 (C), 168.3 (C); *m/z* (ESI) 341 ($[M+H]^+$, 100 %), 215 (18), 105 (19), 79 (32).

Standard radical chemistry on 2-(2-iodophenoxy)benzoic acid methyl ester 2.46



2.46 **2.42**

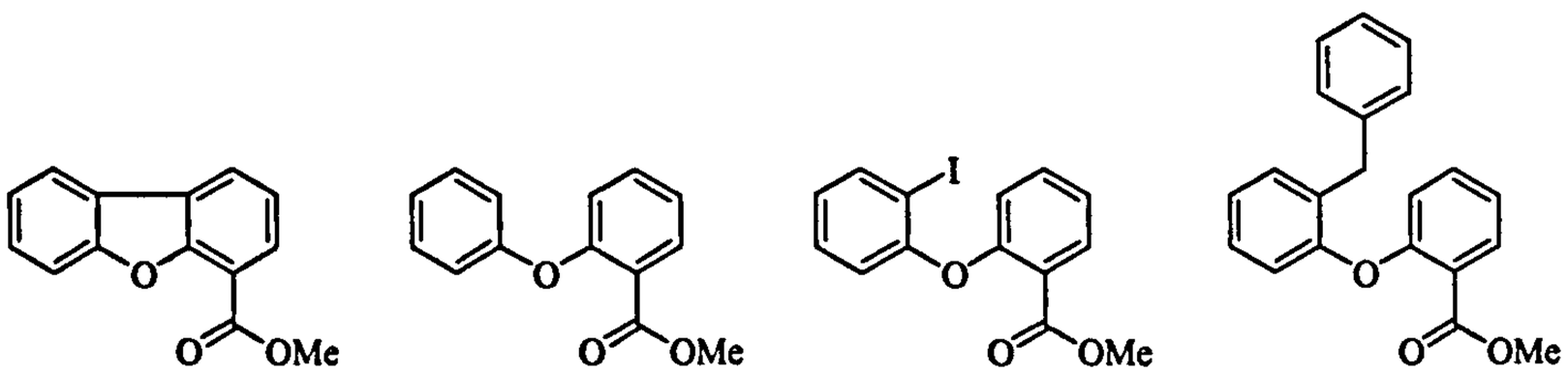
2-(2-Iodophenoxy)benzoic acid methyl ester **2.46** (105 mg, 0.293 mmol, 1.0 equiv.) was dissolved in dry toluene (3 ml) and the solution was deoxygenated with argon for 40 min, then heated at 90°C. A deoxygenated solution of tris(trimethylsilyl)silane (TTMSS) (89.5 mg, 0.36 mmol, 1.2 equiv.) and azobisisobutyronitrile (AIBN) (69 mg, 0.42 mmol, 1.4 equiv.) in dry toluene (7 ml) was loaded into a syringe and added dropwise to the reaction mixture using a syringe pump over 4 h under argon atmosphere. The mixture was stirred and continued to heat at 90°C for another 18 h. The reaction mixture was then concentrated under reduced pressure and dissolved in diethyl ether (20 ml). 2 N hydrochloric acid (20 ml) was added and the aqueous layer was extracted with diethyl ether (20 ml). The combined organic layer was dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (0:100, then 5:95, then 20:80 ethyl acetate/ hexane) to give a mixture of compounds that was analysed further by GC-MS, which showed possibly the following compounds:

Dibenzofuran-4-carboxylic acid methyl ester[190] **2.55**: *m/z* (EI) 226 (M^+, 60 %), 195 (100), 167 (18), 139 (80).

2-Phenoxybenzoic acid methyl ester **2.43**: *m/z* (EI) 228 (M^+, 66 %), 197 (100), 168 (14), 108 (40).

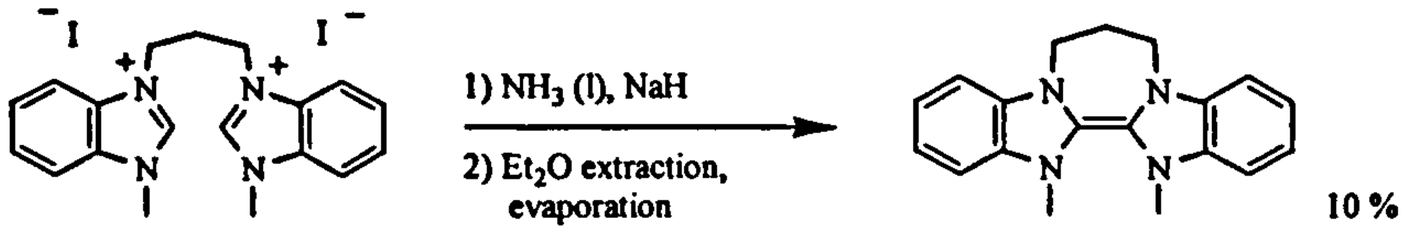
2-(2-Iodophenoxy)benzoic acid methyl ester **2.46**: *m/z* (EI) 354 (M^+, 34 %), 228 (227 (100 %), 196 (52), 168 (35), 139 (42).

2-(2-Benzylphenoxy)benzoic acid methyl ester **2.57**: *m/z* (EI) 318 (M^+, 90 %), 287 (44), 286 (100), 269 (38), 215 (26), 165 (36), 152 (29).



2.55 **2.43** **2.46** **2.57**

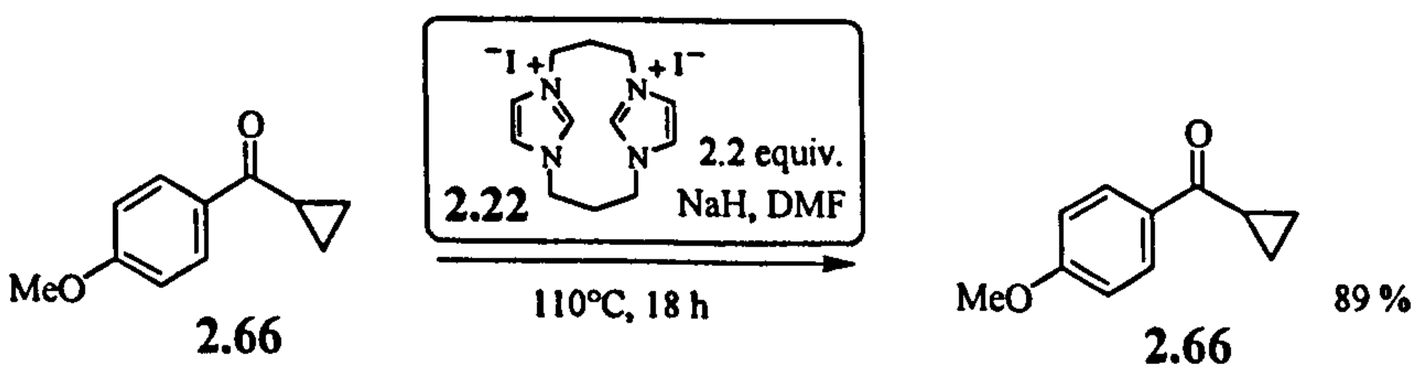
1, 1'- Dimethyl-3,3'-(trimethylene)-2,2'-bibenzimidazolinylidene 1.175



1.179 **1.175**

Benzimidazole salt **1.179** (4.8 g, 8.58 mmol, 1.0 equiv.) was dried under vacuum at 100°C for 1h in a Schlenk flask. After allowing to cool to room temperature sodium hydride (3.43 g, 85.8 mmol, 10.0 equiv.) was added under argon. The mixture was washed with dry and deoxygenated hexane (5 x 100 ml) and subsequently dried under vacuum. The mixture was then cooled to –78°C and the system filled with argon. Ammonia (150 ml) was subsequently added and condensed at –78°C under argon and the resulting yellow mixture was stirred at –78°C for 4 h. Ammonia then evaporated slowly overnight while allowing the mixture to warm to room temperature. The condenser was removed and the sealed Schlenk flask transferred into a glove-box. The solid residue of the reaction was extracted with dry and deoxygenated diethyl ether (15 x 50 ml) and the solvent removed by distillation in the glove-box. This afforded *1,1'-dimethyl-3,3'-(trimethylene)-2,2'-bibenzimidazolinylidene* **1.175** as a yellow solid (600 mg, 10 %); δ_H (deoxygenated C_6D_6) 1.54 (2H, quintet, *J* 5.6, $CH_2CH_2CH_2$), 2.90 (6H, s, CH_3), 3.16 (4H, t, *J* 5.6, NCH_2), 6.42 (2H, d, *J* 7.3, Ar*H*), 6.60 (2H, dd, *J* 7.4, 1.0, Ar*H*), 6.86-6.96 (4H, m, Ar*H*); δ_C (deoxygenated C_6D_6) 29.0 (CH_2), 36.5 (CH_3), 48.0 (CH_2), 106.3 (CH), 109.5 (CH), 120.2 (CH), 121.5 (CH), 123.6 (C), 141.9 (C), 143.2 (C).

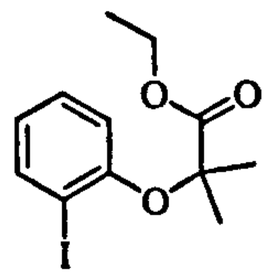
Attempted opening of cyclopropyl-(4-methoxyphenyl)methanone



2.66 **2.66**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (311 mg, 0.66 mmol, 2.2 equiv.), cyclopropyl-(4-methoxyphenyl)methanone **2.66** (54 mg, 0.306 mmol, 1.0 equiv.). *Observation:* The yellow donor colour did not change at room temperature; while heating a colour change to deep-red took place. The purification of the crude mixture after *neutral* work-up was carried out by column chromatography on silica gel (10:90 ethyl acetate/ petroleum ether) to afford starting material **2.66** (48 mg, 89 %).

2-(2-Iodophenoxy)-2-methylpropionate 2.67[123]

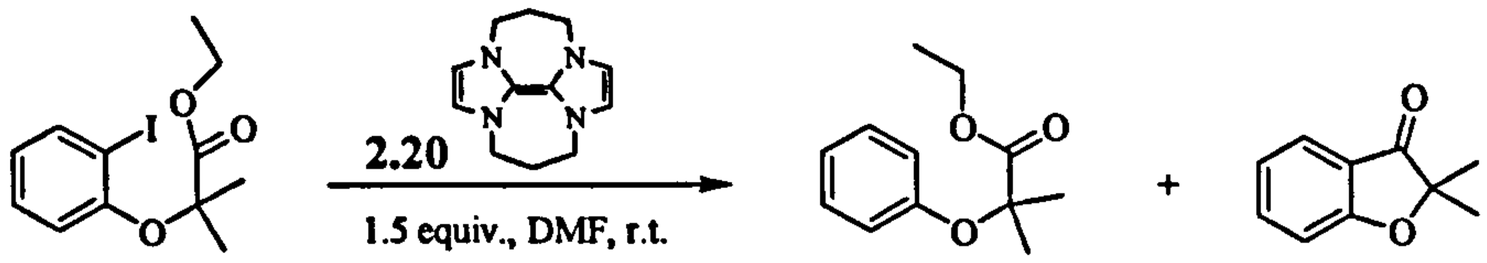


2.67

2-Iodophenol (4.0 g, 18.18 mmol, 1.0 equiv.), 1,1,1-trichloro-2-methylpropanol hemihydrate (6.78 g, 36.36 mmol, 2.0 equiv.) and sodium hydroxide (5.8 g, 145 mmol, 8.0 equiv.) were dissolved in acetone (200 ml) and the mixture was stirred at room temperature overnight. The solvent was then removed *in vacuo*, and the residue was dissolved in water (250 ml). The aqueous layer was extracted with diethyl ether (3 x 200 ml) and then acidified with concentrated hydrochloric acid. The aqueous layer was then extracted with diethyl ether (3 x 200 ml), and the combined organic layer was dried over sodium sulfate, flitered and evaporated. The residue was dissolved in ethanol (100 ml) and thionyl chloride (2.65 ml, 36.36 mmol, 2.0 equiv.) was added dropwise at room temperature. The mixture was then heated at reflux for 6 h and subsequently concentrated under reduced pressure. The residue was purified by Kugelrohr distillation (150°C, 1 mbar) to afford *2-(2-iodophenoxy)-2-methylpropionate* **2.67** as a slightly yellow liquid (4.6 g, 76 %); (Found: $[M+NH_4]^+$ 352.0407. $C_{12}H_{15}O_3$ requires $[M+NH_4]^+$, 352.0404); ν_{max} (NaCl)/cm^{-1} 3061 (Ar-H), 2987 (C-H), 2938 (C-H), 1735 (C=O), 1580 (Ar), 1468 (C-H); δ_H ($CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 1.72 (6H, s, 2 x C*H*$_3$), 4.32 (2H, q, *J* 7.1, C*H*$_2$), 6.78-6.85 (2H, m, Ar*H*), 7.23-7.29 (1H, m, Ar*H*), 7.85 (1H, dd, *J* 7.8, 1.1, Ar*H*); δ_C ($CDCl_3$) 14.2 (CH_3), 25.5 (CH_3), 61.6 (CH_2), 81.0 (C), 91.3 (C), 117.8 (CH), 124.1 (CH), 129.1 (CH), 139.8 (CH), 155.2 (C), 174.2 (C); *m/z* (EI) 334 (M^+, 12 %), 261 (26), 220 (100), 134 (23), 87 (49), 76 (44), 59 (67).

Test reactions on 2-(2-iodophenoxy)-2-methylpropionate 2.67

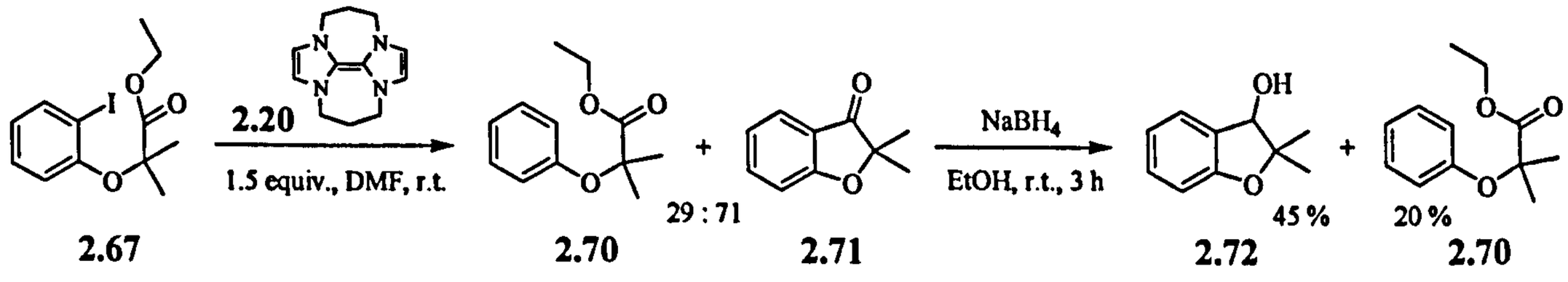
(i)



2.67 **2.70** **2.71**

The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), donor **2.20** (122 mg, 0.48 mmol, 1.5 equiv.), 2-(2-iodophenoxy)-2-methylpropionate **2.67** (106 mg, 0.317 mmol, 1.0 equiv.). *Observation:* Upon addition of the substrate solution to the yellow donor solid a bright red-orange solution formed. The colour changed further to brown after stirring for 18 h at room temperature. *Neutral* work-up was carried out and the residue was purified by column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether, then 100 % dichloromethane) to give an inseparable mixture of 2-methyl-2-phenoxypropionic acid ethyl ester **2.70**[191] (21 % NMR analysis yield) and 2,2-dimethylbenzofuran-3-one **2.71**[194] (51 % NMR analysis yield). The NMR analysis yields of the products were determined from standardised ^{1}H-NMR spectroscopic analysis of 1 ml solution of the total amount of the isolated mixture of **2.70** and **2.71** in $CDCl_3$ along with diphenylmethane (17.27 mg, 0.1026 mmol) as an internal standard and comparison with the authentic compounds; for data see below.

(ii)

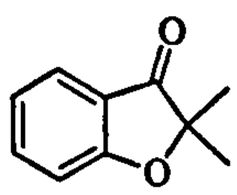


2.67 **2.70** **2.71** **2.72** **2.70**

The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), donor **2.20** (100 mg, 0.46 mmol, 1.5 equiv.), 2-(2-iodophenoxy)-2-methylpropionate **2.67** (103.6 mg, 0.310 mmol, 1.0 equiv.). *Observation:* Upon addition of the substrate solution to the yellow donor solid a bright red-orange solution formed. The colour changed further to brown after stirring for 18 h at room temperature. *Neutral* work-up was carried out and the residue was dissolved in ethanol (15 ml). Sodium borohydride (34 mg, 0.899 mmol, 2.9 equiv.) was added while

cooling to 0°C. The reaction mixture was then stirred at room temperature for 3 h. After removing the solvent under reduced pressure, the residue was dissolved in diethyl ether (50 ml) and water (50 ml). 2 N hydrochloric acid was added and the aqueous layer was extracted with diethyl ether (2 x 50 ml). The combined organic layer was washed with 2 N hydrochloric acid (2 x 50 ml), was then dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on neutral alumina (5:95 ethyl acetate/ hexane) to afford 2-methyl-2-phenoxypropionic acid ethyl ester **2.70**[191] as a colourless liquid (13 mg, 20 %); (Found: $[M+NH_4]^+$ 226.1440. $C_{12}H_{16}O_3$ requires $[M+NH_4]^+$, 226.1438); ν_{max} (NaCl)/cm^{-1} 3064 (Ar-H), 2989 (C-H), 2940 (C-H), 1733 (C=O), 1580 (Ar), 1495 (C-H); δ_H ($CDCl_3$) 1.28 (3H, t, *J* 7.1, C*H*$_3$), 1.64 (6H, s, C*H*$_3$), 4.27 (2H, q, *J* 7.1, C*H*$_2$), 6.88-6.90 (1H, m, Ar*H*), 6.99-7.03 (1H, m, Ar*H*), 7.25-7.30 (2H, m, Ar*H*); δ_C ($CDCl_3$) 14.2 (CH_3), 25.5 (CH_3), 61.5 (CH_2), 79.1 (C), 119.2 (CH), 122.2 (CH), 129.9 (CH), 155.6 (C), 174.4 (C); *m/z* (EI) 208 (M^+, 99 %), 135 (100), 94 (56), 66 (14) and 2,2-dimethyl-2,3-dihydrobenzofuran-3-ol **2.72**[192] as a colourless liquid (23 mg, 45 %); ν_{max} (NaCl)/cm^{-1} 3307 (O-H), 2977 (C-H), 2932 (C-H), 1599 (Ar), 1478 (C-H); δ_H ($CDCl_3$) 1.36 (3, s, C*H*$_3$), 1.51 (3H, s, C*H*$_3$), 1.74-1.76 (1H, m, O-*H*), 4.75-4.76 (1H, m, ArC*H*OH), 6.81 (1H, d, *J* 8.1, Ar*H*), 6.92 (1H, ddd, *J* 7.4, 7.4, 0.8, Ar*H*), 7.23-7.29 (1H, m, Ar*H*), 7.39-7.42 (1H, m, Ar*H*); δ_C ($CDCl_3$) 20.9 (CH_3), 26.5 (CH_3), 78.8 (CH), 89.4 (C), 110.9 (CH), 120.8 (CH), 126.5 (CH), 128.9 (C), 130.9 (CH), 159.1 (C); *m/z* (EI) 164 (M^+, 17 %), 145 (13), 131 (33), 121 (63), 105 (31), 39 (100).

2,2-Dimethylbenzofuran-3-one 2.71[193]

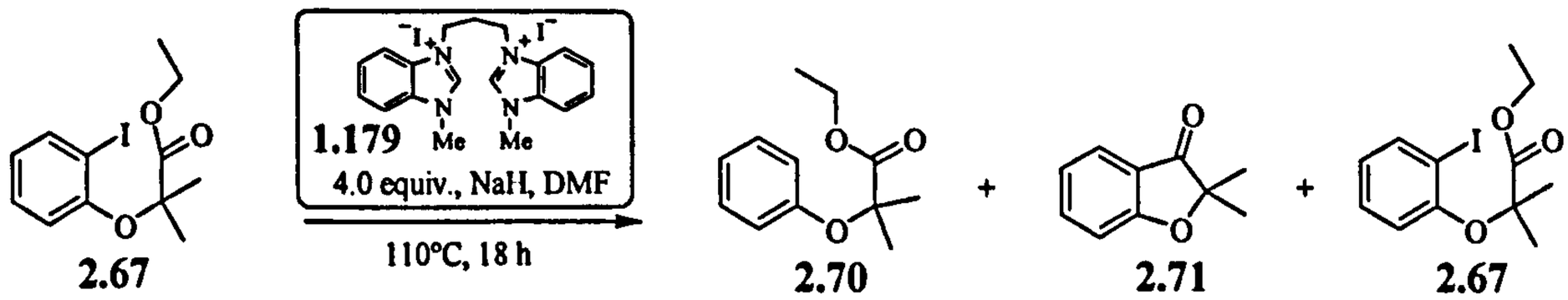


2.71

2,2-Dimethyl-2,3-dihydrobenzofuran-3-ol **2.72** (37 mg, 0.225 mmol, 1.0 equiv.) was dissolved in DCM (10 ml) and the solution was cooled to 0°C. Dess-Martin periodinane (115 mg, 0.271 mmol, 1.2 equiv.) was added and the mixture was allowed to warm to room temperature and was stirred for 3 h at that temperature. DCM (50 ml) and water (50 ml) were then added and the aqueous layer was extracted with DCM (2 x 50 ml). The combined organic layer was washed with sat. sodium bicarbonate solution (3 x 50 ml) and brine (50 ml), was then dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (5:95 ethyl acetate petroleum ether) to afford a mixture of compounds. This mixture was dissolved in methanol (10 ml) and

potassium carbonate was added (93 mg, 0.67 mmol, 3.0 equiv.). The mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue dissolved in diethyl ether (50 ml) and water (50 ml). The aqueous layer was extracted with diethyl ether (2 x 50 ml) and the combined organic layer was then washed with water (50 ml) and brine (50 ml), dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on neutral alumina (5:95 ethyl acetate/ hexane) to afford 2,2-dimethylbenzofuran-3-one **2.71**[194] as a colourless liquid (15 mg, 41 %); (Found: $[M+H]^+$ 163.0735. $C_{10}H_{10}O_2$ requires $[M+H]^+$, 163.0754); ν_{max} (NaCl)/cm^{-1} 2973 (C-H), 2918 (C-H), 1721 (C=O), 1615 (Ar), 1464 (C-H); δ_H ($CDCl_3$) 1.48 (6H, s, 2 x CH_3), 7.06-7.10 (2H, m, Ar*H*), 7.61 (1H, dd, *J* 7.2, 1.3, Ar*H*), 7.64.7.69 (1H, m, Ar*H*); δ_C ($CDCl_3$) 23.2 (CH_3), 88.1 (C), 113.8 (CH), 119.8 (C), 121.9 (CH), 125.1 (CH), 138.3 (CH), 171.1 (C), 204.6 (C); *m/z* (EI) 162 (M^+, 100 %), 147 (54), 91 (14); *m/z* (EI) 162 (M^+, 100 %), 147 (54), 91 (14).

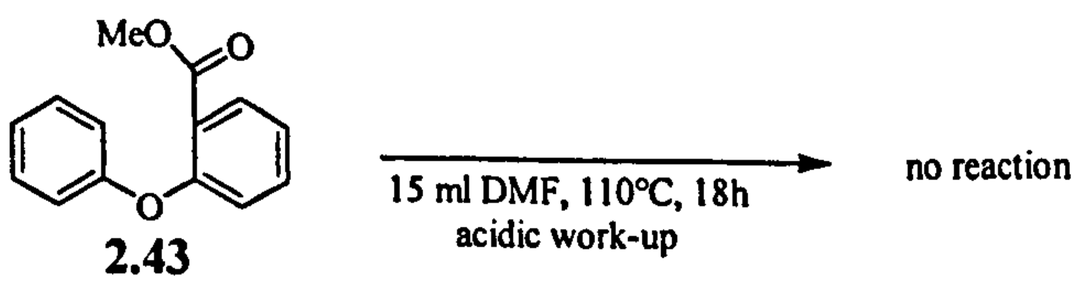
(ii)



The experiment was carried out according to the 'general sodium hydride-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), salt **1.179** (672 mg, 1.2 mmol, 4.0 equiv.), 2-(2-iodophenoxy)-2-methylpropionate **2.67** (100 mg, 0.299 mmol, 1.0 equiv.). *Observation:* The yellow donor colour did not change at room temperature, while heating a colour change to deep red took place. *Acidic* work-up was carried out and the residue was purified by column chromatography on silica gel (10:90 ethyl acetate/ hexane). ^{1}H-NMR analysis of the purified mixture showed 2,2-dimethylbenzofuran-3-one **2.71**, starting material **2.67** and 2-methyl-2-phenoxypropionic acid ethyl ester **2.70**; for data see above.

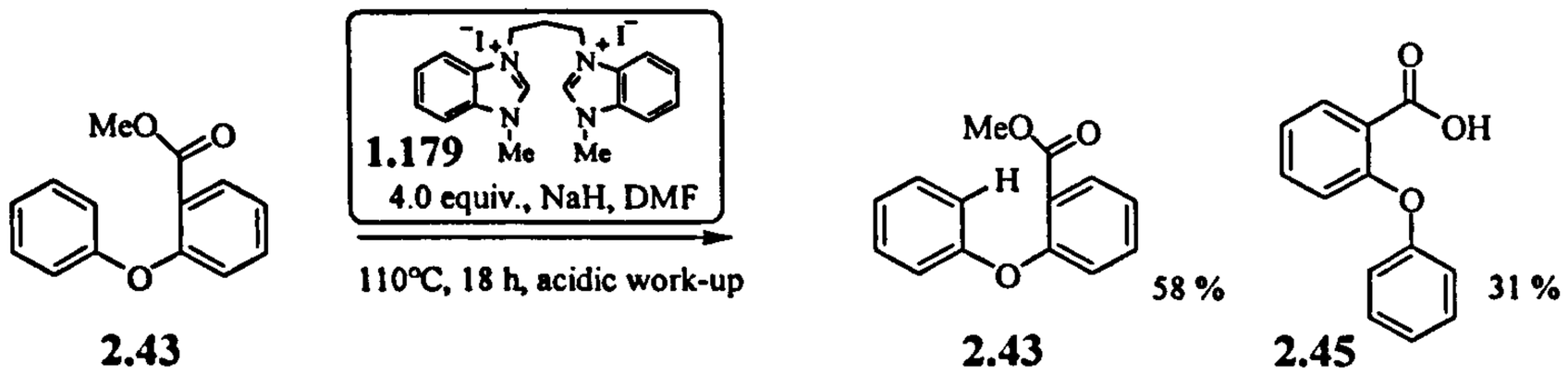
Test reactions on 2-phenoxybenzoic acid methyl ester 2.43

(i)



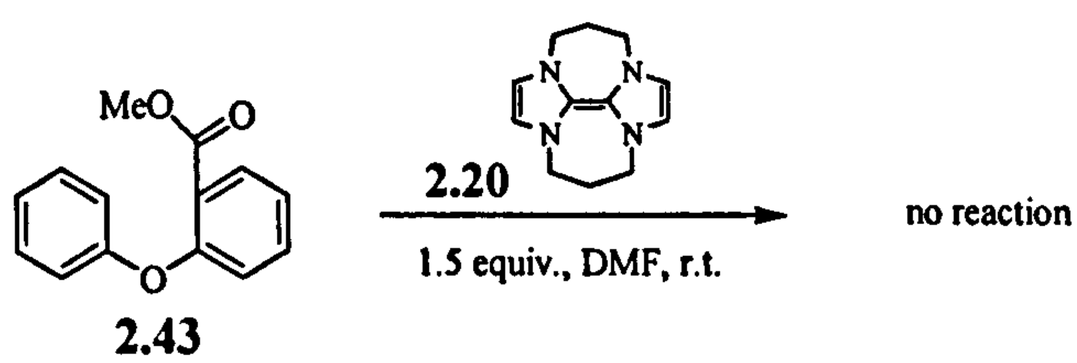
2-Phenoxybenzoic acid methyl ester **2.43** (38.9 mg, 0.1706 mmol, 1.0 equiv.) was dissolved in anhydrous DMF (7 ml) and the mixture was heated at 110°C overnight. After allowing to cool to room temperature, acidic work-up was carried out. ^{1}H-NMR spectroscopic analysis of the crude mixture showed only starting material **2.43**; no reaction had occurred.

(ii)



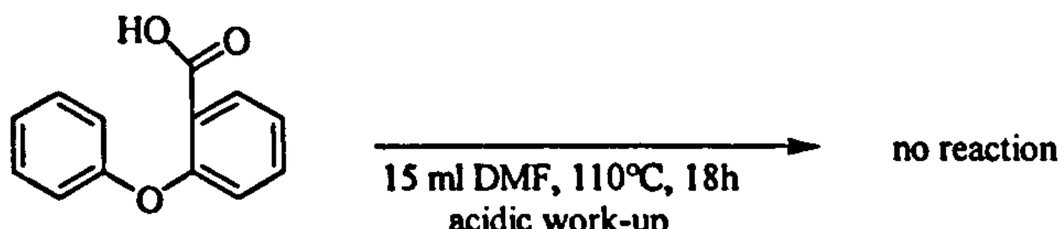
The experiment was carried out according to 'general sodium hydride-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), benzimidazole salt 1.179 (672 mg, 1.2 mmol, 4.0 equiv.), 2-phenoxybenzoic acid methyl ester 2.43 (66 mg, 0.289 mmol, 1.0 equiv.). *Observation:* The mixture turned from yellow to orange while heat was applied. *Acidic* work-up was carried out and the residue was purified by column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether) to afford starting material **2.43** (38.3 mg, 58 %) and 2-phenoxybenzoic acid **2.45**[218] as a white solid (19.2 mg, 31 %); mp 103-104°C (lit.[218] 112°C); δ_H ($CDCl_3$) 6.85 (1H, dd, *J* 7.6, 0.7, Ar*H*), 7.13-7.16 (2H, m, Ar*H*), 7.21-7.30 (2H, m, Ar*H*), 7.43-7.51 (3H, m, Ar*H*), 8.23 (1H, dd, *J* 7.9, 1.7, Ar*H*).

(iii)



The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), donor **2.20** (97 mg, 0.45 mmol, 1.5 equiv.), 2-phenoxybenzoic acid methyl ester **2.43** (65.9 mg, 0.289 mmol, 1.0 equiv.). *Observation:* The reaction mixture stayed yellow. *Acidic* work-up was carried out and the residue was analysed by ^{1}H-NMR spectroscopy which showed starting material **2.43** only; the reaction did not proceed.

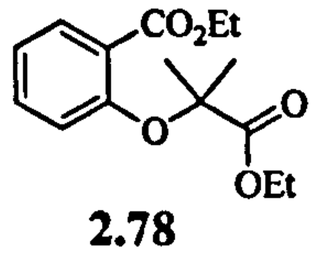
Test reactions of 2-phenoxybenzoic acid 2.45



2.45

2-Phenoxybenzoic acid **2.45** (93 mg, 0.434 mmol, 1.0 equiv.) was dissolved in anhydrous DMF (7 ml) and the mixture was heated at 110°C overnight. After allowing to cool to room temperature, acidic work-up was carried out. ^{1}H-NMR spectroscopic analysis of the crude mixture showed only starting material **2.45**; no reaction had occurred.

2-(1-Ethoxycarbonyl-1-methylethoxy)benzoic acid ethyl ester 2.78

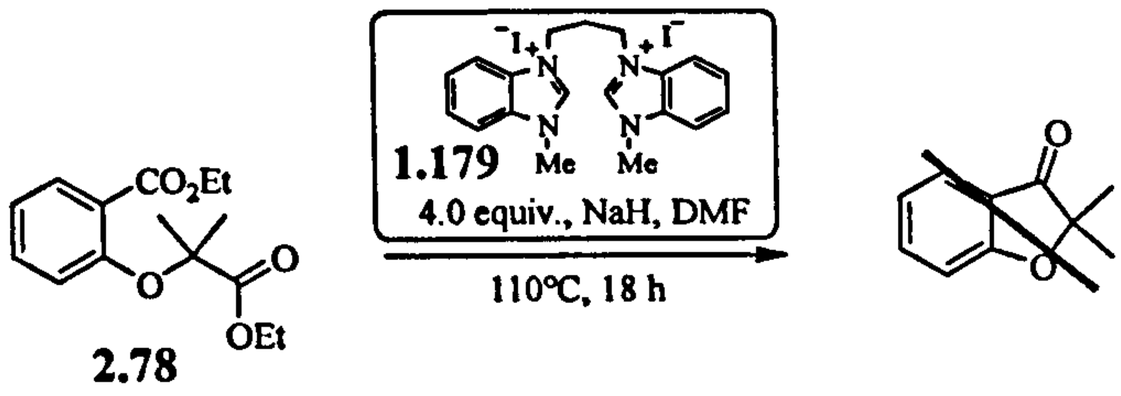


2.78

Ethyl salicylate (1.5 g, 9.03 mmol, 1.0 equiv.), 1,1,1-trichloro-2-methylpropanol hemihydrate (3.2 g, 18.05 mmol, 2.0 equiv.) and sodium hydroxide (2.8 g, 72.2 mmol, 8.0 equiv.) were dissolved in acetone and the reaction mixture was stirred at room temperature overnight. The solvent was then removed *in vacuo* and the residue dissolved in water and extracted with diethyl ether (3 x 100 ml). The combined organic layer was acidified with conc. hydrochloric acid and extracted with diethyl ether (3 x 100 ml). The combined organic layer was dried over sodium sulfate, filtered and evaporated. The residue was dissolved in ethanol (75 ml) and thionyl chloride (0.66 ml, 1.0 equiv.) was added and the reaction mixture was heated at reflux for 6 h. After cooling, the solvent was removed *in vacuo* and the residue dissolved in diethyl ether (200 ml) and water (200 ml). The aqueous layer was extracted with diethyl ether (3 x 200 ml), and the combined organic layer was washed with water (3 x 200 ml), then dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (10:90 ethyl acetate/petroleum ether) to give 2-(1-ethoxycarbonyl-1-methylethoxy)benzoic acid ethyl ester[195] **2.78** as a colourless liquid (2.05 g, 81 %); (Found: $[M+H]^+$ 281.1386 $C_{15}H_{20}O_5$ requires $[M+H]$, 281.1384); ν_{max} (NaCl)/cm^{-1} 3077 (Ar-H), 2986 (C-H), 2940 (C-H), 1732 (C=O), 1601 (Ar), 1487 (C-H), 1080 (C-O); δ_H ($CDCl_3$) 1.26 (3H, t, *J* 7.1 CH_2CH_3), 1.39 (3H, t, *J* 7.1, CH_2CH_3), 1.62 (6H, s, 2 x CH_3), 4.25 (2H, q, *J* 7.1, CH_2CH_3), 4.36 (2 H, q, *J* 7.1, CH_2CH_3), 6.83-6.85 (1H, m, Ar*H*), 7.01-7.05 (1H, m, Ar*H*), 7.32-7.37 (1H, m, Ar*H*), 7.74 (1H, dd, *J* 7.7, 1.8,

Ar*H*); δ_C ($CDCl_3$) 14.2 (CH_3), 14.4 (CH_3), 25.2 (CH_3), 60.6 (CH_2), 61.3 (CH_2), 80.1 (C), 118.9 (CH), 121.8 (CH), 123.2 (C), 131.1 (CH), 132.3 (CH), 154.8 (C), 166.6 (C), 174.3 (C); *m/z* (CI) 298 ($[M+NH_4]^+$, 37 %), 281 (100), 167 (18), 52 (22).

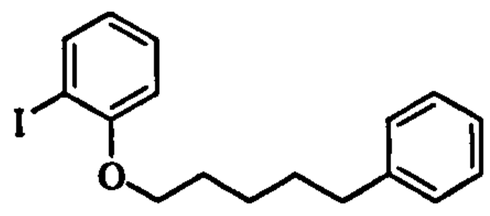
Test reaction on 2-(1-ethoxycarbonyl-1-methylethoxy)benzoic acid ethyl ester 2.78



2.78

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), benzimidazole salt **1.179** (668 mg, 1.19 mmol, 4.0 equiv.), 2-(1-ethoxycarbonyl-1-methylethoxy)benzoic acid ethyl ester **2.78** (83.0 mg, 0.3 mmol, 1.0 equiv.). *Acidic* work-up was carried out and the ^{1}H-NMR spectrum of the crude mixture showed predominantly starting material **2.78**, which was confirmed by further analysis by GC-MS: *m/z* (EI) 280 (M^+, 100 %), 207 (89), 166 (20), 120 (37), 92 (21).

1-Iodo-2-(5-phenylpentyloxy)benzene 2.79[174]

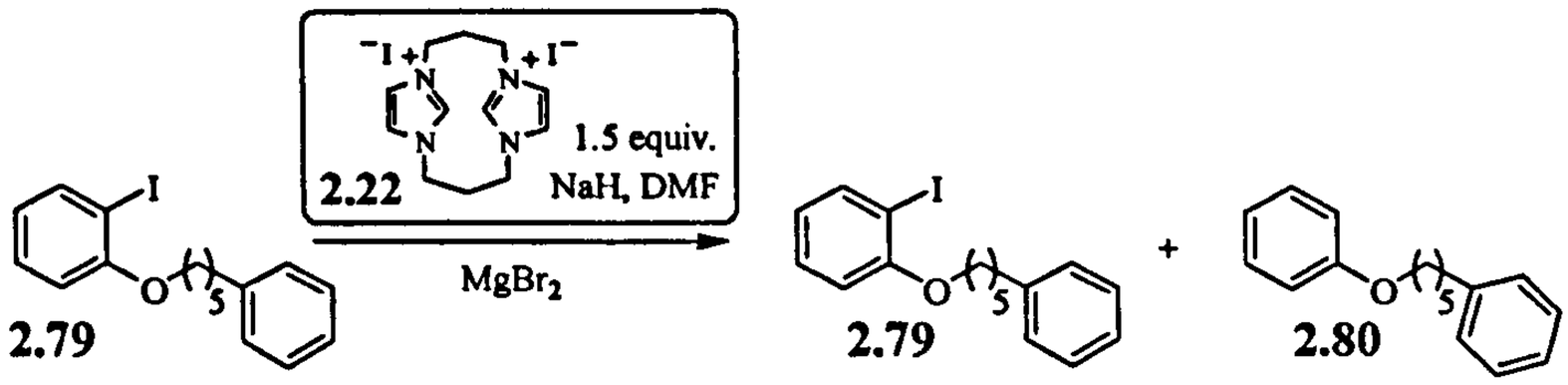


2.79

5-Phenylpentanol (1.530 ml, 9.09 mmol, 1.0 equiv.), 2-iodophenol (2 g, 9.09 mmol, 1.0 equiv.) and triphenylphosphine (2.384 g, 9.09 mmol, 1.0 equiv.) were dissolved in THF (30 ml), and the mixture was cooled to 0°C. DIAD (1.97 ml, 10.00 mmol, 1.1 equiv.) was then added dropwise and the mixture was allowed to warm to room temperature and stirred for 3.5 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (3:97 ethyl acetate/ petroleum ether) to afford *1-iodo-2-(5-phenylpentyloxy)benzene* **2.79** as a colourless liquid (2.830 g, 85 %); (Found: $[M+NH_4]^+$ 384.0818. $C_{17}H_{19}IO$ requires [*M+NH*$_4$], 384.0819); ν_{max} (NaCl)/cm^{-1} 3060 (Ar-H), 3025 (Ar-H), 2935 (C-H), 2855 (C-H), 1581 (Ar), 1463 (C-H); δ_H ($CDCl_3$) 1.54-1.66 (2H, m, CH_2), 1.69-1.75 (2H, m, CH_2), 1.87 (2H, q, *J* 6.8, $CH_2CH_2CH_2$), 2.68 (2H, t, *J* 7.3, CH_2CH_2Ph), 4.00 (2H, t, *J* 6.3, CH_2O), 6.65-6.79 (2H, m, Ar*H*), 7.14-7.31 (6H, m, Ar*H*),

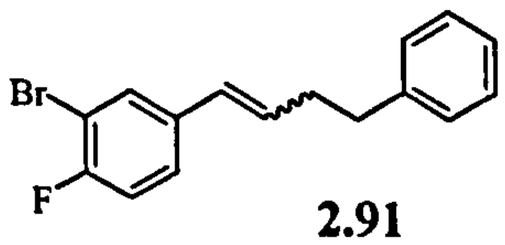
7.76 (1H, dd, *J* 7.8, 1.6, Ar*H*); δ_C ($CDCl_3$) 26.2 (CH_2), 29.4 (CH_2), 31.5 (CH_2), 36.2 (CH_2), 69.3 (CH_2), 87.2 (C), 112.5 (CH), 122.7 (CH), 126.0 (CH), 128.7 (CH), 128.8 (CH), 129.7 (CH), 139.7 (CH), 142.8 (C), 157.9 (C); *m/z* (EI) 366 (M^+, 8%), 220 (19), 146 (14), 91 (100), 65 (22).

Attempted aldehyde formation from 1-iodo-2-(5-phenylpentyloxy)benzene 2.69



Anhydrous magnesium bromide (200 mg, 1.09 mmol, 3.6 equiv.) was weighed in a glove-box and added to substrate **2.79** (110 mg, 0.3 mmol, 1.0 equiv.). Imidazolium salt **2.22** (212 mg, 0.45 mmol, 1.5 equiv.) was stirred under vacuum for 1h, then dissolved in DMF (15 ml). The solution was added to a residue of washed sodium hydride (144 mg, 3.6 mmol, 12 equiv.) and the mixture was stirred for 4 h and was then centrifuged. The solution was then added to the mixture of anhydrous magnesium bromide and substrate **2.79**. The reaction mixture was stirred at room temperature for 2h and the yellow, cloudy mixture was then heated at 70°C for 18 h. Deuterated water (1.5 ml) was added and the mixture was stirred at room temperature for 15 min, then poured into water (50 ml) and diethyl ether (50 ml). The aqueous layer was acidified (2 N hydrochloric acid) and extracted with diethyl ether (2 x 50 ml). The organic phases were combined and washed with dilute hydrochloric acid (3 x), dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (5:95 ethyl acetate/ petroleum ether) to afford a yellow oil (80 mg) that was a 50:50 mixture of starting material **2.79** and its reduced counterpart 1-(5-phenoxylpentyl)benzene **2.80**[196] (determined by ^{1}H-NMR spectroscopic analysis).

2-Bromo-1-fluoro-4-(4-phenyl-but-1-enyl)benzene 2.91

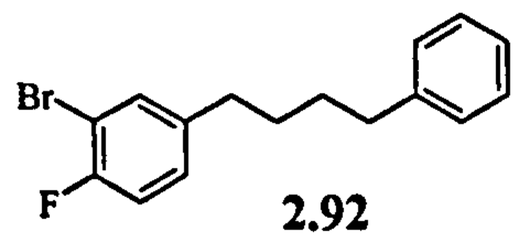


2.91

A solution of triphenyl-(3-phenylpropyl)phosphonium bromide[197] (2.95 g, 6.4 mmol, 1.3 equiv.) in THF (10 ml) was cooled to –78°C and n-BuLi (2.48 ml, 5.9 mmol, 1.2 equiv., c

= 2.38 mol/l) was added dropwise. The mixture was stirred for 1h at room temperature and then re-cooled to –30°C. A solution of A solution of 3-bromo-4-fluorobenzaldehyde **2.89** (1.0 g, 4.93 mmol, 1.0 equiv.) in THF (10 ml) was added dropwise and the reaction mixture was stirred at room temperature over night, was then poured into water (150 ml) and diethyl ether (150 ml). The aqueous layer was extracted with diethyl ether (150 ml) and the combined organic layer was washed with water (150 ml) and brine (150 ml), was then dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (5:95 ethyl acetate/ petroleum ether) to afford *2-bromo-1-fluoro-4-(4-phenylbut-1-enyl)benzene* **2.91** (1.09 g, 73 %) as a mixture of *E* and *Z*-isomers as a colourless liquid, which was reacted further directly.

2-Bromo-1-fluoro-4-(4-phenylbutyl)benzene 2.92

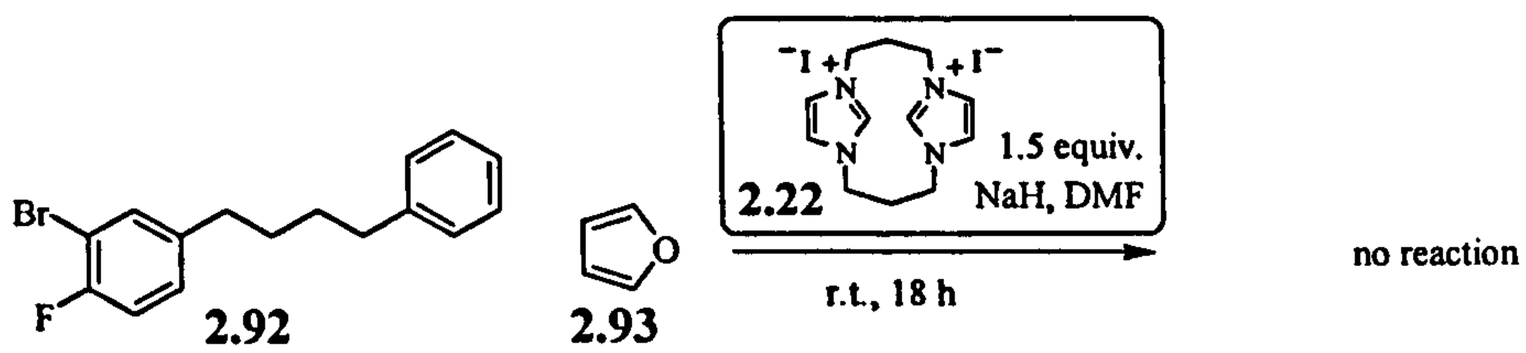


2.92

To a solution of 2-bromo-1-fluoro-4-(4-phenylbut-1-enyl)benzene **2.91** (1.09 g, 3.57 mmol, 1.0 equiv.) in acetic acid (5 ml) was added palladium (10 % Pd on activated carbon, 20 mg) and this mixture was stirred under hydrogen atmosphere (H_2-balloon used) at room temperature for 5 h. The mixture was then filtered using Kieselguhr and the resulting solution was neutralised with sodium bicarbonate solution at 0°C. Ethyl acetate (100 ml) was then added and the aqueous layer was extracted further with ethyl acetate (2 x 100 ml). The combined organic layer was washed with brine (200 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (5:95 ethyl acetate/ petroleum ether) to give *2-bromo-1-fluoro-4-(4-phenylbutyl)benzene* **2.92** as a white semi-solid (1.08 g, 99 %); (Found: M^+ 306.0412. $C_{16}H_{16}BrF$ requires M^+, 306.0414 {for ^{79}Br}); ν_{max} (NaCl)/cm^{-1} 3026 (Ar-H), 2934 (C-H), 1601 (Ar), 1496 (C-H); δ_H ($CDCl_3$) 1.73-1.74 (4H, m, CH_2), 2.67-2.80 (4H, m, CH_2), 7.02-7.18 (2H, m, Ar*H*), 7.20-7.44 (6H, m, Ar*H*); δ_C ($CDCl_3$) 31.0 (CH_2), 34.9 (CH_2), 35.2 (CH_2), 35.9 (CH_2), 108.8 (d, $^2J_{C\text{-}F}$ 20.7, C), 116.2 (CH), 126.0 (CH), 128.6 (CH), 128.9 (CH), 133.3 (CH), 140.1 (d, $^4J_{C\text{-}F}$ 20.7, C), 142.5 (C), 157.6 (d, $^1J_{C\text{-}F}$ 244.9, C); *m/z* (EI) 308 (M^+, 18 %, ^{81}Br), 306 (M^+, 18 %, ^{79}Br), 228 (6), 187 (15), 149 (27), 109 (47), 91 (100), 65 (38).

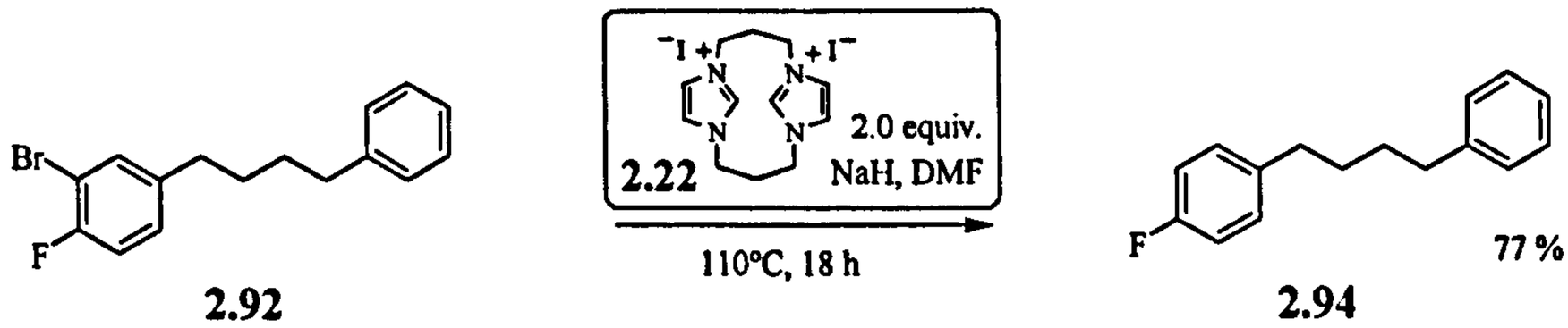
Test reactions with 2-bromo-1-fluoro-4-(4-phenylbutyl)benzene 2.80

(i) *Attempted benzyne formation*



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: room temperature, 18 h, DMF (15 ml), salt **2.22** (212 mg, 0.45 mmol, 1.5 equiv.), 2-bromo-1-fluoro-4-(4-phenylbutyl)benzene **2.92** (92 mg, 0.3 mmol, 1.0 equiv.), furan (0.65 ml, 9 mmol, 30 equiv.). Furan was purified and treated as stated in the general procedure. ^{1}H-NMR spectrum of the crude mixture after work-up showed only starting material **2.92**; the reaction did not proceed.

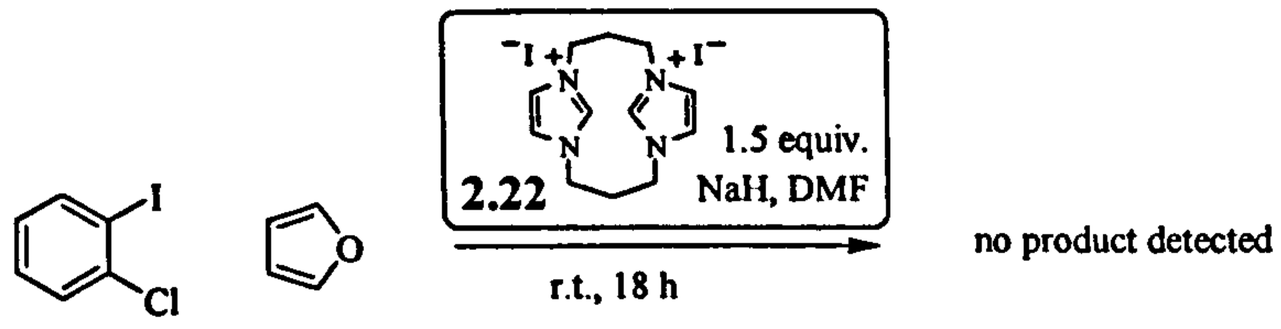
(ii) *Formation of 1-fluoro-4-(4-phenylbutyl)benzene* 2.94



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C for 18 h, DMF (15 ml), salt **2.22** (283 mg, 0.6 mmol, 2.0 equiv.), 2-bromo-1-fluoro-4-(4-phenyl-butyl)benzene **2.92** (92 mg, 0.3 mmol, 1.0 equiv.). Purification after work-up carried out by column chromatography on silica gel (4:20:76 ethyl acetate/ toluene/ petroleum ether) to afford *1-fluoro-4-(4-phenylbutyl)benzene* **2.94** as a colourless liquid (53 mg, 77 %); (Found: M^+ 228.1308 $C_{16}H_{17}F$ requires M^+, 228.1309) ν_{max} (NaCl)/cm^{-1} 3048 (Ar-H), 2931 (C-H), 2856 (C-H), 1508 (Ar), 1463 (C-H); δ_H ($CDCl_3$) 1.70-1.79 (4H, m, CH_2), 2.68-2.75 (4H, m, CH_2), 7.01-7.07 (2H, m, Ar*H*), 7.18-7.21 (2H, m, Ar*H*), 7.25-7.31 (3H, m, Ar*H*), 7.35-7.39 (2H, m, Ar*H*); δ_C ($CDCl_3$) 31.2 (CH_2), 31.4 (CH_2), 35.2 (CH_2), 36.0 (CH_2), 115.3 (CH), 125.9 (CH), 128.5 (CH), 129.8 (CH), 138.3 (d, $^4J_{C\text{-}F}$ 3.2, C), 142.7 (C), 161.4 (d, $^1J_{C\text{-}F}$ 242.9, C); *m/z* (EI) 228 (M^+, 9 %), 185 (2), 136 (4), 109 (100), 91 (38), 65 (6).

Attempted benzyne formations from 1-chloro-2-iodobenzene 2.84b

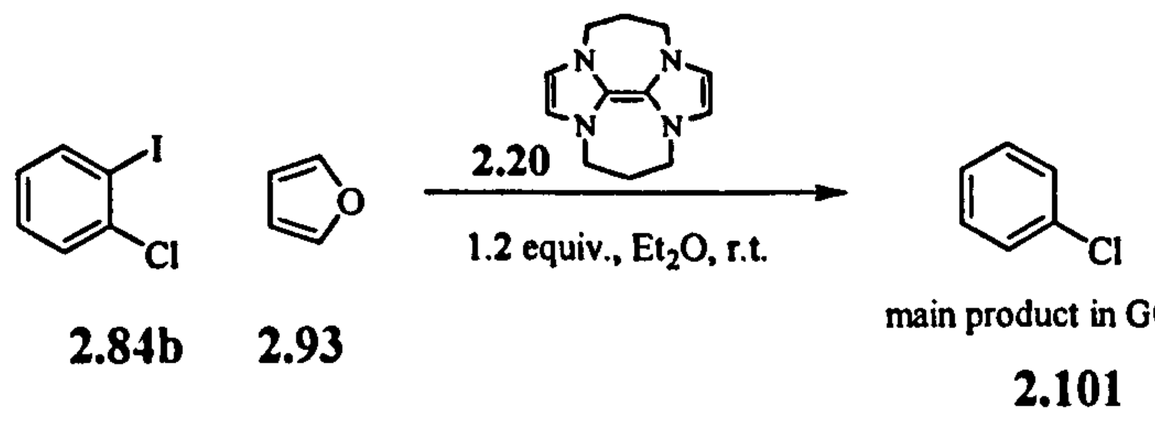
(i)



2.84b **2.93**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: Room tempearture, 18 h, DMF (15 ml), salt **2.22** (212 mg, 0.45 mmol, 1.5 equiv.), 1-chloro-2-iodobenzene **2.84b** (71.5 mg, 0.3 mmol, 1.0 equiv.), furan (0.65 ml, 9 mmol, 30 equiv.). Furan was purified and treated as stated in the general procedure. No material was obtained after work-up of the reaction mixture.

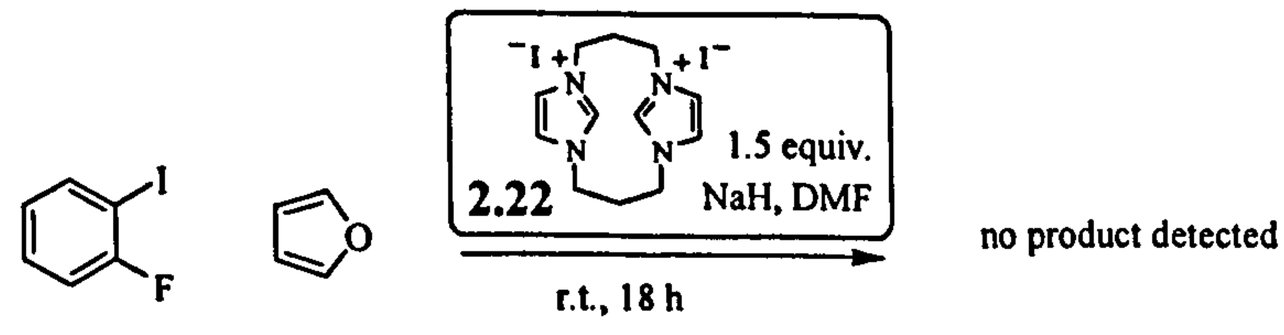
(ii)



2.84b **2.93** **2.101**

The experiment was carried out according to the 'general pure donor-method' procedure. *Conditions and reagents*: Room temperature for 18 h, diethyl ether (15 ml), donor **2.20** (78 mg, 0.36 mmol, 1.2 equiv.), 1-chloro-2-iodobenzene **2.84b** (71.5 mg, 0.3 mmol, 1.0 equiv.), furan (0.65 ml, 9 mmol, 30 equiv.). Furan was purified and treated as stated in the general procedure. *Observation*: A precipitate formed during the reaction. Thus, the reaction mixture was filtered and the resulting solution subjected to GC-MS analysis which suggested, among other compounds, chlorobenzene **2.101** as the main compound. No cycloadduct arising from benzyne intermediate was detected by GC-MS. Chlorobenzene **2.101**[198] was identified with 96.66 % probability match with the known library compound; *m/z* (EI) 114 (M^+, 33 %, ^{37}Cl), 112 (M^+, 100 %, ^{35}Cl), 77 (46).

Attempted benzyne formations on 2-fluoroiodobenzene 2.84a

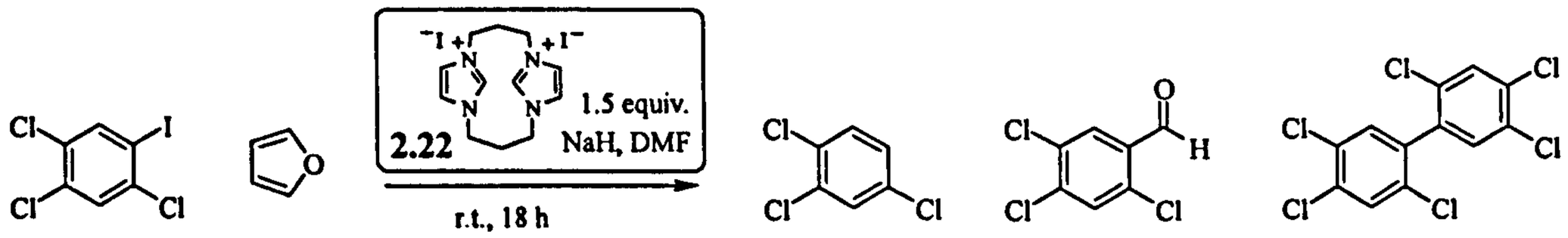


2.84a **2.93**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), salt **2.22** (212 mg, 0.45 mmol, 1.5 equiv.), 1-fluoro-2-iodobenzene **2.84a** (66 mg, 0.3 mmol, 1.0 equiv.), furan (0.65 ml, 9 mmol, 30 equiv.). Furan was purified and treated as stated in the general procedure. No material was obtained after work-up of the reaction mixture.

Attempted benzyne formation on trichloroiodobenzene

(i)



2.95 **2.93** **2.96** **2.97** **2.98**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), salt **2.22** (212 mg, 0.45 mmol, 1.5 equiv.), 1,2,4-trichloro-5-iodobenzene **2.95** (92 mg, 0.3 mmol, 1.0 equiv.), furan (0.65 ml, 9 mmol, 30 equiv.). Furan was purified and treated as stated in the general procedure. The crude mixture after work-up was subjected to column chromatography on silica gel (10:90 ethyl acetate/ petroleum ether) and the resulting mixture was subjected to GC-MS analysis which suggested the following compounds:

1,2,4-Trichlorobenzene **2.96**: *m/z* (EI) 186 (M^+, 3 %, $^{37}Cl^{37}Cl^{37}Cl$), 184 (M^+, 33 %, $^{35}Cl^{37}Cl^{37}Cl$), 182 (M^+, 94 %, $^{35}Cl^{35}Cl^{37}Cl$), 180 (M^+, 100 %,$^{35}Cl^{35}Cl^{35}Cl$), 147 (18), 145 (27), 111 (6), 109 (22), 74 (17).

Literature mass spectrum from library of mass spectrometry program:

1,2,4-Trichlorobenzene **2.96**: *Masses and relative abundances*: 187 (0.2), 186 (4.1), 185 (2.1), 184 (35.6), 183 (6.3), 182 (97.2), 181 (6.8), 180 (99.9), 149 (4.7), 148 (2.0), 147 (28.1), 146 (5.2), 145 (44.9), 144 (4.3), 112 (1.3), 111 (8.5)110 (5.4), 109 (26.7), 74 (19.3), 75 (9.3), 76 (0.5).

2,4,5-Trichlorobenzaldehyde **2.97**: *m/z* (EI) 213 (M^+, 10 %, $^{37}Cl^{37}Cl^{37}Cl$), 211 (M^+, 34 %, $^{35}Cl^{37}Cl^{37}Cl$), 209 (M^+, 100 %, $^{35}Cl^{35}Cl^{37}Cl$), 207 (M^+, 98 %,$^{35}Cl^{35}Cl^{35}Cl$), 181 (24), 179 (25), 143 (8), 145 (13), 109 (22), 74 (20).

Literature mass spectrum from library of mass spectrometry program:

2,4,5-Trichlorobenzaldehyde **2.97**: *Masses and relative abundances*: 213 (4.4), 212 (18.7), 211 (30.8), 210 (54.5), 209 (92.2), 208 (62), 207 (100), 184 (3.6), 183 (8.8), 182 (11.6),

179 (26.7), 148 (3.2), 147 (11.4), 146 (15.0), 145 (20.4), 144 (21.1), 143 (10.5), 111 (11.1), 110 (7.7), 109 (323), 108 (12.3), 107 (2.2), 75 (12.3), 74 (47.1), 73 (21.5), 29 (11.3), 28 (1.7).

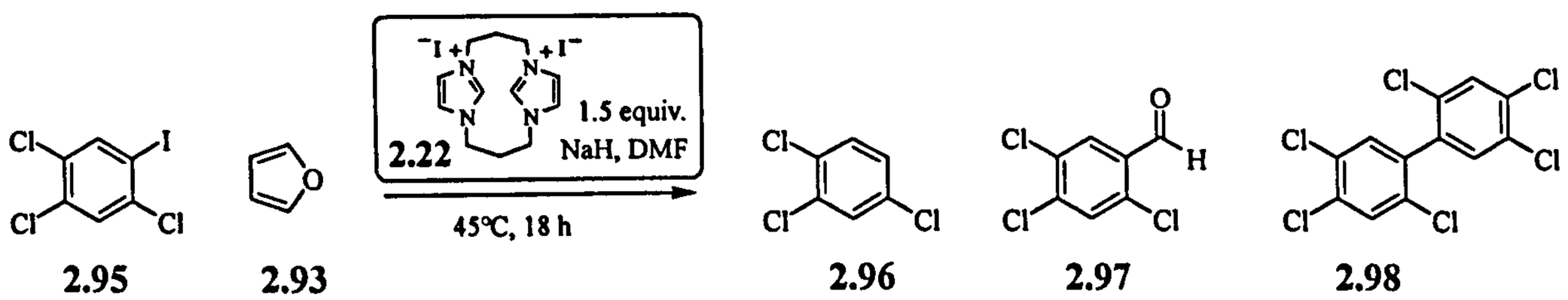
2,4,5,2',4',5'-Hexachlorobiphenyl **2.98**: *m/z* (EI) 368 (1 %, 1 x ^{35}Cl, 5 x ^{37}Cl), 366 (8 %, 2 x ^{35}Cl, 4 x ^{37}Cl), 364 (35 %, 3 x ^{35}Cl, 3 x ^{37}Cl), 362 (77 %, 4 x ^{35}Cl, 2 x ^{37}Cl), 360 (100 %, 5 x ^{35}Cl, 1 x ^{37}Cl), 358 (50 %, 6 x ^{35}Cl), 327 (34), 325 (53), 323 (35), 292 (34), 290 (66), 288 (48), 257 (3), 255 (11), 220 (18), 218 (30), 182 (11), 144 (16), 109 (9), 73 (3).

Literature mass spectrum from library of mass spectrometry program:

2,4,5,2',4',5'-Hexachlorobiphenyl **2.98**: *Masses and relative abundances*:

370 (trace), 369 (0.1), 368 (1.3), 367 (1.2), 366 (10.3), 365 (5.1), 364 (41.5), 363 (11.0), 362 (91.8), 360 (99.9), 359 (3.7), 358 (70.5), 230 (1.6), 329 (3.1), 328 (4.9), 327 (9.0), 326 (3.1), 325 (13.6), 324 (5.7), 323 (8.7), 322 (0.8), 294 (8.4), 293 (4.7), 292 (36.8), 291 (10.3), 290 (73.1), 289 (8.5), 288 (60.4), 258 (1.3), 257 (2.4), 256 (5.7), 255 (7.1), 254 (9.9), 253 (7.3), 252 (7.0), 222 (3.5), 221 (3.4), 220 (22.3), 219 (7.6), 218 (35.5), 217 (6.0), 216 (2.1), 185 (3.5), 184 (6.8), 183 (13.1), 182 (20.7), 181 (23.5), 180 (23.0), 179 (13.0), 147 (20.4), 146 (53.5), 145 (85.5), 144 (77.2), 111 (11.6), 110 (35.9), 109 (56.9), 108 (23.3), 107 (8.1), 79 (6.5), 78 (8.4), 77 (1.4), 75 (4.5), 74 (30.0), 73 (28.6), 72 (11.8).

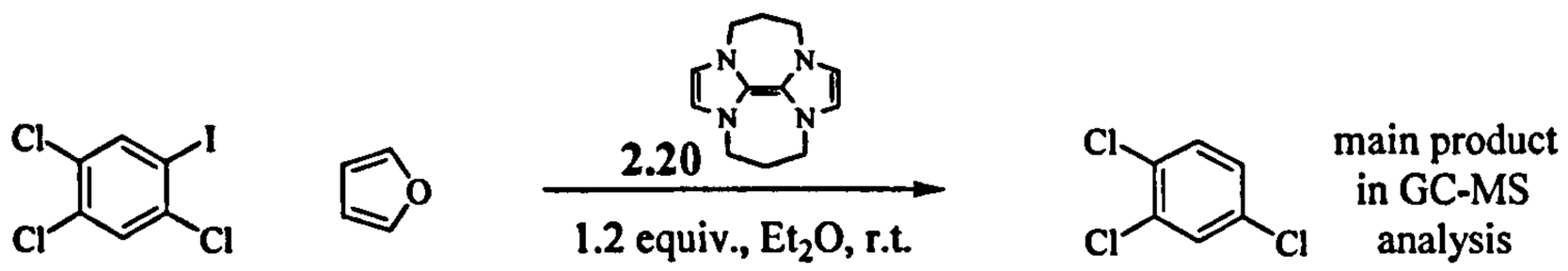
(ii)



2.95 **2.93** **2.96** **2.97** **2.98**

Furan was purified and treated as stated in the general procedure. A mixture of furan (0.65 ml, 9 mmol, 30 equiv.) and 1,2,4-trichloro-5-iodobenzene **2.95** (92 mg, 0.3 mmol, 1.0 equiv.) was heated at 45°C under argon and the donor solution [prepared according to 'general NaH-method' procedure, 212 mg of salt **2.22**, 0.45 mmol, 1.5 equiv.] was added at 45°C and stirred for 30 min at that temperature, then stirred overnight at room temperature. The crude mixture after work-up was subjected to column chromatography on silica gel (10:90 ethyl acetate/ petroleum ether) and the resulting mixture was subjected to GC-MS analysis which suggested the formation of 1,2,4-trichlorobenzene **2.96**, 2,4,5-trichlorobenzaldehyde **2.97** and 2,4,5,2',4',5'-hexachlorobiphenyl **2.98**; see above for mass spectra of the compounds.

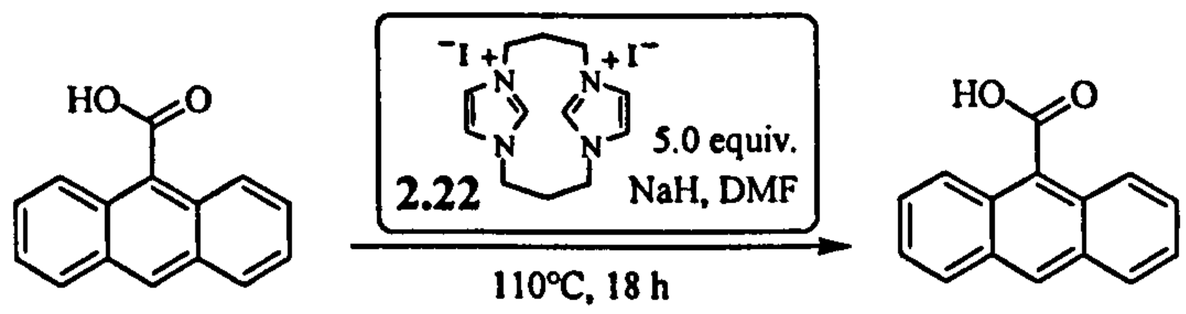
(iii)



2.95 **2.81** **2.96**

The Experiment was carried out according to the general 'pure donor method' procedure. *Conditions and reagents*: Room temperature, 18 h, diethyl ether (15 ml), donor **2.20** (78 mg, 0.36 mmol, 1.2 equiv.), 1,2,4-trichloro-5-iodobenzene **2.95** (92 mg, 0.3 mmol, 1.0 equiv.), furan (0.65 ml, 9 mmol, 30 equiv.). Furan was purified and treated as stated in the general procedure. A precipitate formed during the reaction. Thus, the reaction mixture was filtered and the resulting solution subjected to GC-MS analysis which suggested trichlorobenzene **2.96** [for mass spectrum see above] as the major product, no cycloadduct was observed.

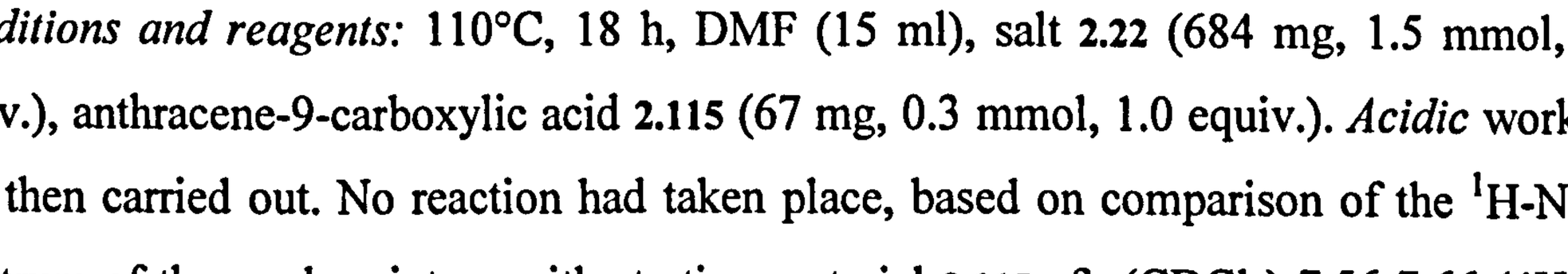
Attempted reduction of anthracene-9-carboxylic acid 2.115



2.115 **2.115**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (684 mg, 1.5 mmol, 5.0 equiv.), anthracene-9-carboxylic acid **2.115** (67 mg, 0.3 mmol, 1.0 equiv.). *Acidic* work-up was then carried out. No reaction had taken place, based on comparison of the ^{1}H-NMR spectrum of the crude mixture with starting material **2.115**; δ_H ($CDCl_3$) 7.56-7.66 (4H, m, ArH), 8.04 (2H, dd, *J* 8.3, 4.7, Ar*H*), 8.16 (2H, dd, *J* 8.3, 4.7, Ar*H*). 13.9 (1H, s, CO_2H); *m/z* (ESI) 222 (M^+, 28 %), 221 (100), 205 (36), 179 (17).

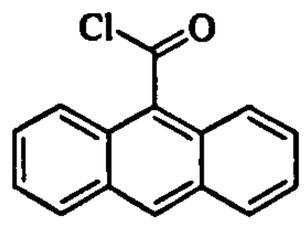
Reduction of anthracene-9-carboxylic acid methyl ester 2.102



2.102 **2.103** **2.107** **2.115**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (566 mg, 1.2 mmol, 4.0 equiv.), anthracene-9-carboxylic acid methyl ester **2.102** (70 mg, 0.296 mmol, 1.0 equiv.). *Observation:* Upon addition of the yellow donor solution to the reactant at room temperature the colour changed to orange and upon heating overnight to dark-red. After heating at 110°C for 18 h, ethyl acetate was added (20 ml) and 2 N hydrochloric acid (20 ml). The aqueous layer was extracted with ethyl acetate (2 x 20 ml) and the combined organic layer was washed with 2 N hydrochloric acid (3 x 20 ml). The organic layer was then washed with aqueous NaOH solution (3 x 20 ml), then dried over sodium sulfate and evaporated. The residue was purified by column chromatography on silica gel (3:97 ethyl acetate/ hexane) to give 9,10-dihydro-anthracene **2.103** as a white solid (7 mg, 13 %) and anthracene **2.107** as a white solid (trace); for data see below. The basic aqueous layer was acidified with conc. hydrochloric acid and extracted with ethyl acetate (3 x 20 ml). This organic layer was then combined, dried over sodium sulfate and evaportated. The residue (12.2 mg) contained anthracene-9-carboxylic acid **2.115** (based on comparison of the ^{1}H-NMR spectrum of the crude mixture with the commercial material of **2.115**) and LC-MS mass spectrum analysis showed, among other unidentified peaks, a signal at *m/z* (ESI-) 221 ($[M-H]^+$), corresponding to anthracene-9-carboxylic acid **2.115.**

Anthracene-9-carbonyl chloride 2.117

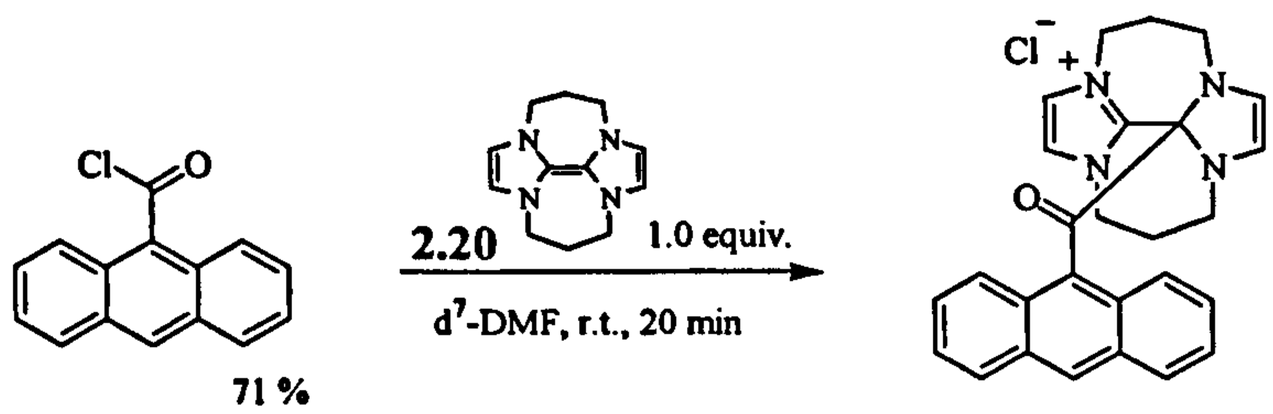


2.117

Anthracene-9-carboxylic acid **2.115** (2.0 g, 8.99 mmol, 1.0 equiv.) was dissolved in DCM (20 ml) and oxalyl chloride (0.94 ml, 10.7 mmol, 1.2 equiv.) was added. The reaction mixture was cooled to 0°C and four drops of anhydrous DMF were added. After stirring the mixture at 0°C for 1 h the stirring was continued for another 2 h at room temperature. The solvent was removed *in vacuo* and the residue was recrystallised (DCM/hexane) to give *anthracene-9-carbonyl chloride* **2.117** as a yellow solid (1.53 g, 71 %); mp 153°C (dec.); (Found: M^+ 240.0334. $C_{15}H_9ClO$ requires M^+, 240.0336 for ^{35}Cl); ν_{max} (KBr)/cm^{-1} 3059 (Ar-H), 1797 (C=O); δ_H ($CDCl_3$) 7.27-7.58 (2H, m, Ar*H*), 7.59-7.62 (2H, m, Ar*H*), 8.06-8.08 (2H, d, *J* 8.7 Ar*H*), 8.12-8.15 (2H, dd, *J* 8.7, 0.8 Ar*H*), 8.60 (1H, s, Ar*H*); δ_C ($CDCl_3$) 123.9 (CH), 125.9 (CH), 125.9 (C), 127.9 (CH), 128.7 (CH), 130.7 (CH), 170.6

(C); *m/z* (EI) 242 (M^+, 6 %, ^{37}Cl), 240 (M^+, 18 %, ^{35}Cl), 205 (100), 177 (64), 151 (23), 88 (26).

Formation of salt species 2.108 from anthracene-9-carbonyl chloride 2.117



71 %

2.117 **2.108**

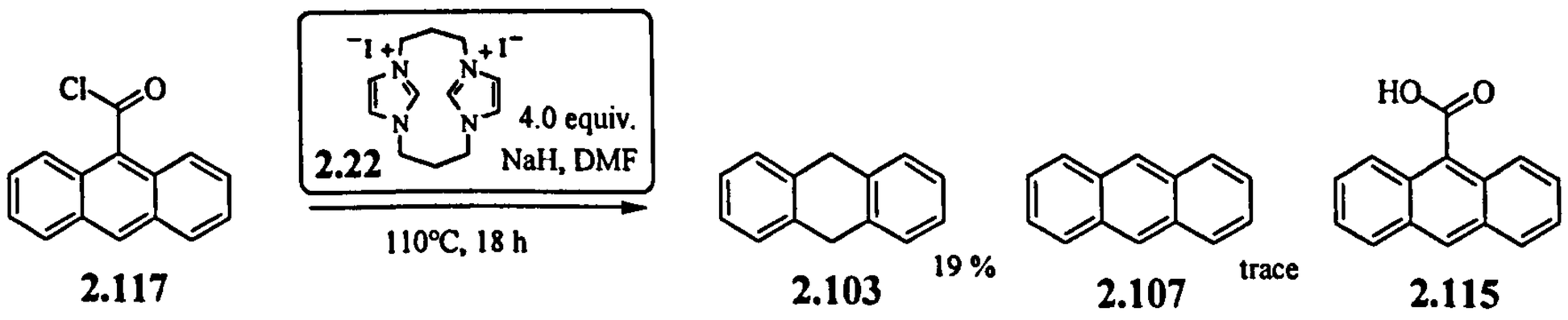
Anthracene-9-carbonyl chloride **2.117** (98.1 mg, 0.407 mmol, 1.0 equiv.) was dried under vacuum at room temperature for 3 h. Imidazole donor **2.20** (88 mg, 0.407 mmol, 1.0 equiv.) was dissolved in d^7-DMF (2 ml) [that was deoxygenated with argon for 20 min prior to usage] in a glove-box. The solution was transferred dropwise *via* pipette to anthracene-9-carbonyl chloride **2.117** in the glove-box at room temperature. After stirring for 20 min, the reaction mixture was analysed by ^1H and ^{13}C NMR spectroscopy. Diethyl ether (20 ml) was added to the reaction mixture and the precipitate was filtered and washed with diethyl ether. The obtained brown solid was analysed by LC mass spectroscopy, showing the desired peak for species **2.108**:

LC-MS analysis: $[M+H]^+$ 422 (21 %);

MS-MS at 422: 422 ($[M+H]^+$, 78 %), 421 (M^+, 100 %), 394 (16), 327 (23), 314 (19), 217 (68), 150 (98).

^{13}C isotope peak at : $[M+H]^+$ 422: 31 corresponding to 27 carbon atoms at 1.1 % relative abundance and the isotope contributions of ^{17}O and ^{15}N.

Reduction of anthracene-9-carbonyl chloride 2.117

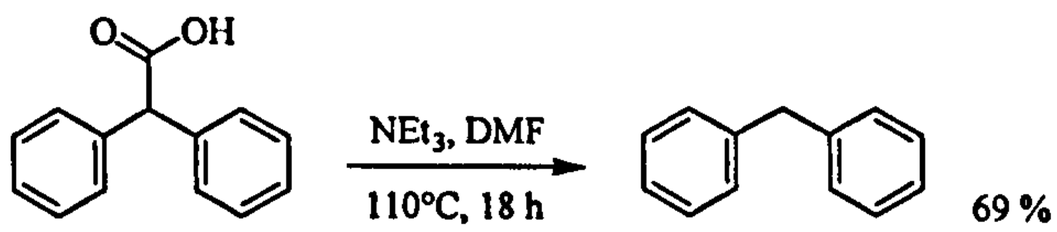


2.117 **2.103** 19 % **2.107** trace **2.115**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (566 mg, 1.2 mmol, 4.0 equiv.), anthracene-9-carbonyl chloride **2.117** (69 mg, 0.287 mmol, 1.0 equiv.). *Observation:* Upon addition of the yellow donor solution to the substrate at room

temperature the colour changed to dark green-black. After heating at 110°C for 18 h, ethyl acetate was added (20 ml) and 2 N hydrochloric acid (20 ml). The aqueous layer was extracted with ethyl acetate (2 x 20 ml) and the combined organic layer was washed with 2 N hydrochloric acid (3 x 20 ml). The organic layer was then washed with aqueous NaOH solution (3 x 20 ml), then dried over sodium sulfate and evaporated. The residue was purified by column chromatography on silica gel (3:97 ethyl acetate/ hexane) to give an inseparable mixture of 9,10-dihydro-anthracene **2.103** as a white solid (9.6 mg, 19 %); δ_H ($CDCl_3$) 4.01 (4H, s, C*H*$_2$), 7.26 (4H, dd, *J* 5.5, 3.3, Ar*H*), 7.36 (4H, dd, *J* 5.5, 3.3, Ar*H*); and anthracene[203] **2.107** as a white solid (trace); δ_H ($CDCl_3$) 7.48 (4H, ddd, *J* 6.3, 6.3, 2.8, Ar*H*), 8.02 (4H, dd, *J* 6.5, 3.3, Ar*H*), 8.44 (2H, s, Ar*H*); consistent with the data quoted by D. Thomson.[203]The basic aqueous layer was acidified with conc. hydrochloric acid and extracted with ethyl acetate (3 x 20 ml). This organic layer was then combined, dried over sodium sulfate and evaporated to give a residue (20.5 mg) that contained anthracene-9-carboxylic acid **2.115**, based on comparison of the ^{1}H-NMR spectrum of the fraction with the commercial material of **2.115** and LC-MS analysis showed among other unidentified peaks a signal at 221 ($[M-H]^+$) with a MS-MS: *m/z* (ESI+) 223 ($[M+H]^+$, 89 %), 205 (100), 179 (37), corresponding to anthracene-9-carboxylic acid **2.115**.

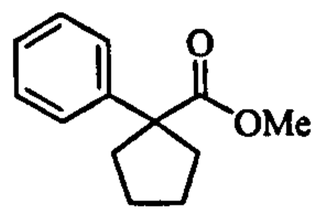
Triethylamine blank experiment



2.120 **2.119**

Diphenylacetic acid **2.120** (250 mg, 1.18 mmol, 1.0 equiv.) was dissolved in DMF (15 ml) and triethylamine was added (0.45 ml, 3.54 mmol, 3.0 equiv.). The reaction mixture was heated at 110°C for 18 h. Diethyl ether (50 ml) and 2 N hydrochloric acid (50 ml) were added and the aqueous layer was extracted with diethyl ether (50 ml). The combined organic layer was washed with 2 N hydrochloric acid (4 x 50 ml), dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (5:95 diethyl ether/ hexane) to afford diphenylmethane[199] **2.119** as a colourless liquid (136 mg, 69 %); ν_{max} (NaCl)/cm^{-1} 3085 (Ar-H), 3062 (Ar-H), 3027 (Ar-H), 2910 (C-H), 2843 (C-H), 1599 (Ar), 1494 (C-H); δ_H ($CDCl_3$) 4.06 (2H, s, C*H*$_2$), 7.15-7.30 (6H, m, Ar*H*), 7.31-7.45 (4H, m, Ar*H*); δ_C ($CDCl_3$) 42.2 (CH_2), 126.3 (CH), 128.8 (CH), 129.1 (CH), 114.1 (C); *m/z* (EI) 168 (M^+, 100 %), 167 (97), 165 (45), 153 (37), 152 (27), 91 (13).

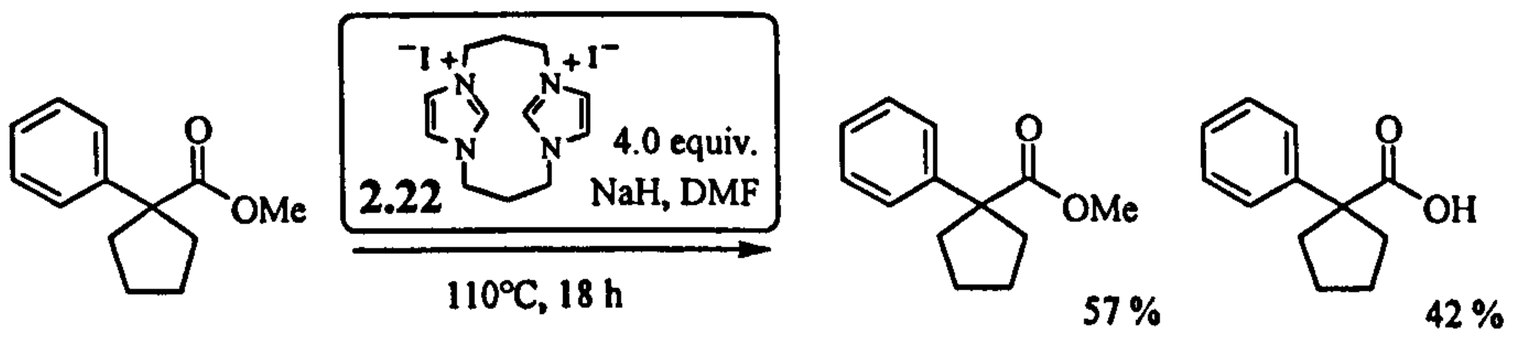
1-Phenylcyclopentanecarboxylic acid methyl ester 2.121



2.121

1-Phenylcyclopentanecarboxylic acid (1.5 g, 7.88 mmol, 1.0 equiv.) was dissolved in methanol and thionyl chloride (2.3 ml, 31.5 mmol, 4.0 equiv.) was added dropwise at 0°C. After heating the mixture at reflux for 5 h, the solvent was removed *in vacuo* and the residue purified by column chromatography (15:75 ethyl acetate/ petroleum ether) to afford the 1-phenylcyclopentanecarboxylic acid methyl ester **2.121** as a colourless liquid (1.46 g, 91 %); (Found: $[M+NH_4]^+$ 222.1492. $C_{13}H_{16}O_2$ requires $[M+NH_4]^+$, 222.1489); ν_{max} (NaCl)/cm^{-1} 2952 (C-H), 2874 (C-H), 1729 (C=O), 1448 (C-H), 1012 (C-O); δ_H ($CDCl_3$) 1.71-1.79 (4H, m, $CH_2CH_2CH_2CH_2$), 1.91-1.98 (2H, m, CH*H*CCH*H*), 2.64-2.71 (2H, m, C*H*HCC*H*H), 3.63 (3H, s, OCH_3), 7.12-7.26 (1H, m, Ar*H*), 7.31-7.33 (2H, m, Ar*H*), 7.50-7.58 (2H, m, Ar*H*); δ_C ($CDCl_3$) 23.6 (CH_2), 36.2 (CH_2), 52.3 (CH_3), 59.1 (C), 126.6 (CH), 126.8 (CH), 128.3 (CH), 143.3 (C), 176.5 (C); *m/z* (EI) 204 (M^+, 4 %), 145 (93), 115 (18), 91 (100), 77 (10), 67 (16), 59 (19).

Attempted reduction of 1-phenyl-cyclopentanecarboxylic acid methyl ester 2.121

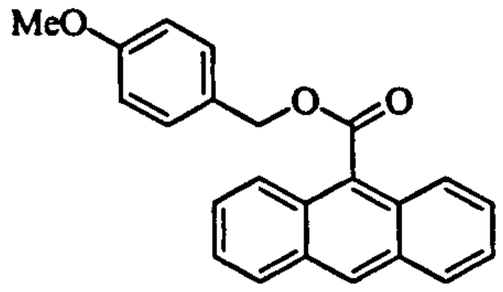


2.121 **2.121** **2.122**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (566 mg, 1.2 mmol, 4.0 equiv.), 1-phenyl-cyclopentanecarboxylic acid methyl ester **2.121** (70 mg, 0.342 mmol, 1.0 equiv.). *Observation:* Upon addition of the yellow donor solution to the reactant at room temperature the colour changed to orange and upon heating overnight to dark-red. *Acidic* work-up was carried out and the residue was purified by column chromatography on silica gel (2:98, then 20:80 diethyl ether/ hexane) to give starting material **2.121** as a colourless liquid (40 mg, 57 %) and 1-phenylcyclopentanecarboxylic acid **2.122** as a white solid (27.3 mg, 42 %); mp 153-155°C (lit.[218] 159-161°C); ν_{max} (KBr)/cm^{-1} 3402 (O-H), 2873 (C-H), 1681 (C=O), 1443 (C-H); δ_H ($CDCl_3$) 1.71-1.80 (4H, m, $CH_2CH_2CH_2CH_2$), 1.91-1.97 (2H,

m, CH*H*CCH*H*), 2.63-2.73 (2H, m, C*H*HCC*H*H), 7.23-7.28 (1H, m, Ar*H*), 7.31-7.35 (2H, m, Ar*H*), 7.40-7.43 (2H, m, Ar*H*); δ_C ($CDCl_3$) 23.6 (CH_2), 36.0 (CH_3), 58.9 (C), 126.9 (CH), 127.3 (CH), 128.3 (CH), 142.7 (C), 182.3 (C); *m/z* (ESI) 190 (M^+, 18 %).

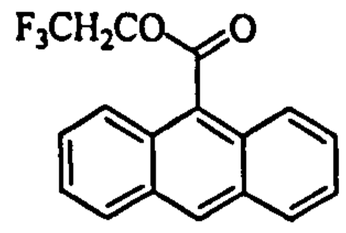
Anthracene-9-carboxylic acid 4-methoxybenzyl ester 2.123



2.123

Anthracene-9-carbonyl chloride **2.117** (382 mg, 1.58 mmol, 1.0 equiv.) was dissolved in DCM (15 ml) and cooled to 0°C. A solution of 4-methoxybenzyl alcohol (241.3 mg, 1.74 mmol, 1.1 equiv.) in DCM (5 ml) was then added dropwise. The mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel (5:95 ethyl acetate/ petroleum ether) to give *anthracene-9-carboxylic acid 4-methoxybenzyl ester* **2.123** as a yellow solid (296 mg, 55 %); mp 148-150°C; (Found: M^+ 342.1253 $C_{23}H_{18}O_3$ requires M^+, 342.1250); ν_{max} (KBr)/cm^{-1} 3056 (Ar-H), 3003 (Ar-H), 2908 (C-H), 2836 (C-H), 1718 (C=O), 1612 (Ar), 1199 (C-O); δ_H ($CDCl_3$) 3.83 (3H, s, OCH_3), 5.64 (2H, s, CH_2O), 6.92-6.96 (2H, m, Ar*H*), 7.46-7.54 (6H, m, Ar*H*), 7.97-8.03 (4H, m, Ar*H*), 8.50 (1H, s, Ar*H*); δ_C ($CDCl_3$) 55.4 (CH_3), 67.2 (CH_2), 114.1 (CH), 124.9 (CH), 125.5 (CH), 126.9 (CH), 127.9 (C); 128.4 (C), 128.7 (CH), 129.3 (CH), 130.5 (CH), 131.2 (C), 159.7 (C), 169.5 (C); *m/z* (EI) 342 (M+, 6 %), 298 (2), 178 (11), 121 (100), 91 (15), 77 (11).

Anthracene-9-carboxylic acid 2,2,2-trifluoroethyl ester 2.124

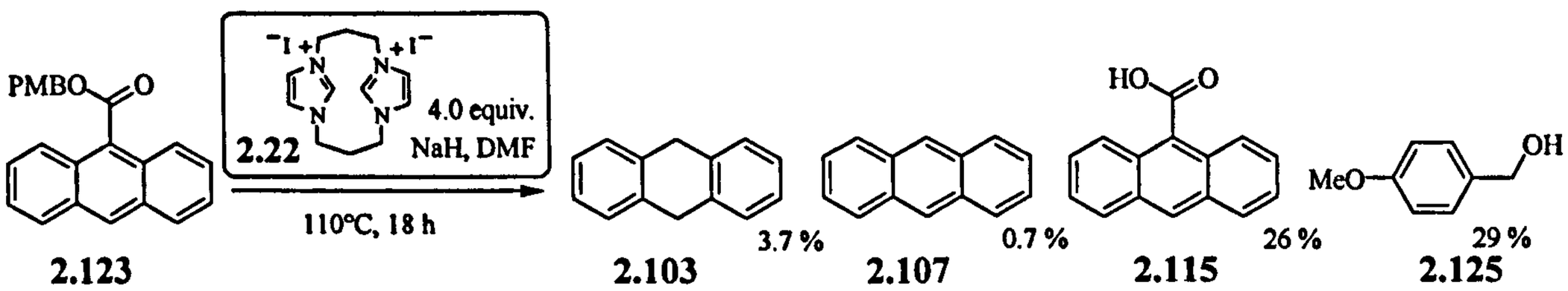


2.124

Anthracene-9-carbonyl chloride **2.117** (386 mg, 1.60 mmol, 1.0 equiv.) was dissolved in DCM (15 ml) and cooled to 0°C. Trifluoroethanol (5 ml) was then added dropwise. The mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel (5:95 ethyl acetate/ petroleum ether) to give *anthracene-9-carboxylic acid 2,2,2-trifluoro-*

ethyl ester **2.124** as a yellow solid (324 mg, 67 %); mp 121-122°C; (Found: M^+ 304.0707 $C_{17}H_{11}F_3O_2$ requires M^+, 304.0706); ν_{max} (KBr)/cm^{-1} 3059 (Ar-H), 2968 (C-H), 1738 (C=O), 1416 (C-H), 1169 (C-O); δ_H ($CDCl_3$) 5.06 (2H, q, *J* 8.4, CH_2), 7.48-7.52 (2H, m, Ar*H*), 7.57-7.61 (2H, m, Ar*H*), 8.07-8.09 (2H, m, Ar*H*), 8.09-8.10 (2H, m, Ar*H*), 8.53 (1H, s, Ar*H*); δ_C ($CDCl_3$) 61.0 (q, $^2J_{C-F}$ 36.6, CH_2), 121.7 (C), 124.5 (CH), 125.4 (C), 125.6 (CH), 127.4 (CH), 127.5 (C), 128.7 (CH), 130.5 (CH), 130.8 (C), 167.9 (C); *m/z* (EI) 304 (M^+, 100 %), 205 (55), 177 (75), 176 (57), 151 (19), 88 (39).

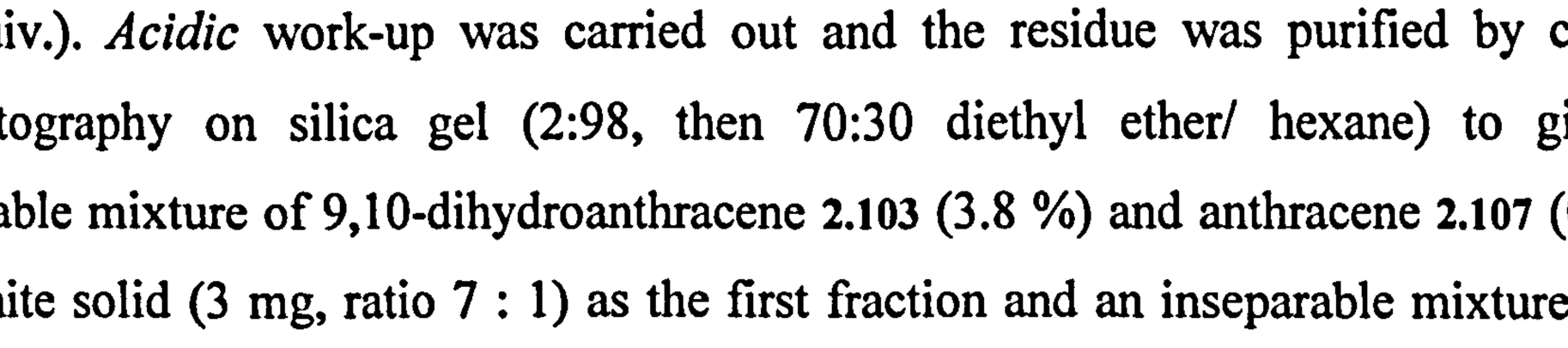
Reduction of anthracene-9-carboxylic acid 4-methoxybenzyl ester 2.123



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (566 mg, 1.2 mmol, 4.0 equiv.), anthracene-9-carboxylic acid 4-methoxy-benzyl ester **2.123** (100 mg, 0.292 mmol, 1.0 equiv.). *Acidic* work-up was carried out and the residue was purified by column chromatography on silica gel (2:98, then 70:30 diethyl ether/ hexane) to give an inseparable mixture of 9,10-dihydroanthracene **2.103** (3.8 %) and anthracene **2.107** (0.7 %) as a white solid (3 mg, ratio 7 : 1) as the first fraction and an inseparable mixture of (4-methoxyphenyl)methanol **2.125** (29 %) and anthracene-9-carboxylic acid **2.115** (26 %) as a yellow solid (29 mg, ratio 1 : 0.899) as the second fraction; for data see above and on page 232.

Attempted reduction of anthracene-9-carboxylic acid 2,2,2-trifluoroethyl ester 2.124

(i)

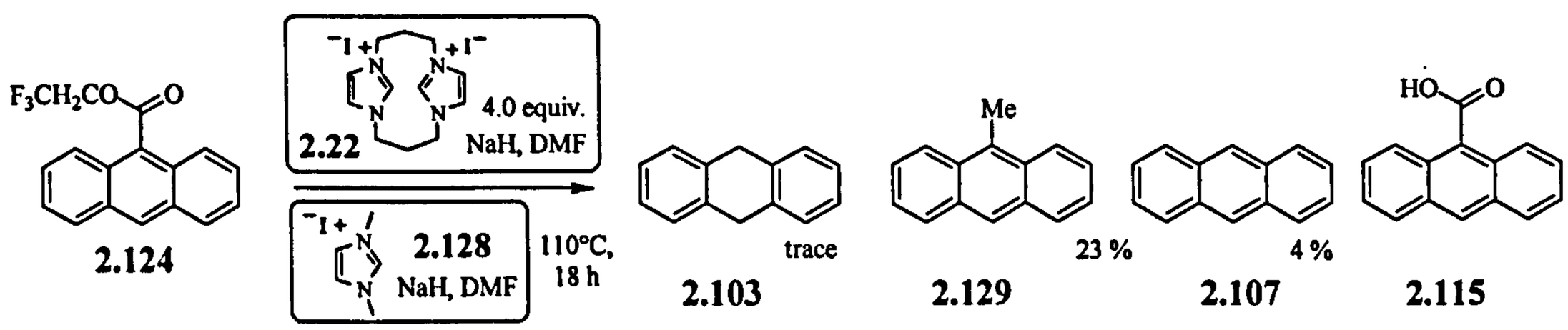


The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (566 mg, 1.2 mmol, 4.0

equiv.), anthracene-9-carboxylic acid 2,2,2-trifluoroethyl ester **2.124** (91 mg, 0.299 mmol, 1.0 equiv.). *Acidic* work-up was carried out and the combined organic layer was additionally washed with aqueous NaOH solution (3 x 20 ml). The residue was purified by column chromatography on silica gel (2:98 diethyl ether/ hexane) to give an inseparable mixture of 9,10-dihydro-anthracene **2.103** (trace) and anthracene **2.107** (trace) as a white solid (1 mg, ratio 1 : 0.426); for data see above.

The basic aqueous layer was acidified with conc. hydrochloric acid and extracted with ethyl acetate (3 x 20 ml). This organic layer was then combined, dried over sodium sulfate and evaporated to give a residue (8.6 mg) that contained anthracene-9-carboxylic acid **2.115,** based on comparison of the ^{1}H-NMR spectrum of the crude mixture with the commercial sample of **2.115** and LC-MS analysis showed among other unidentified peaks a signal at *m/z* (ESI-) 221 ($[M-H]^{+}$), corresponding to anthracene-9-carboxylic acid **2.115.**

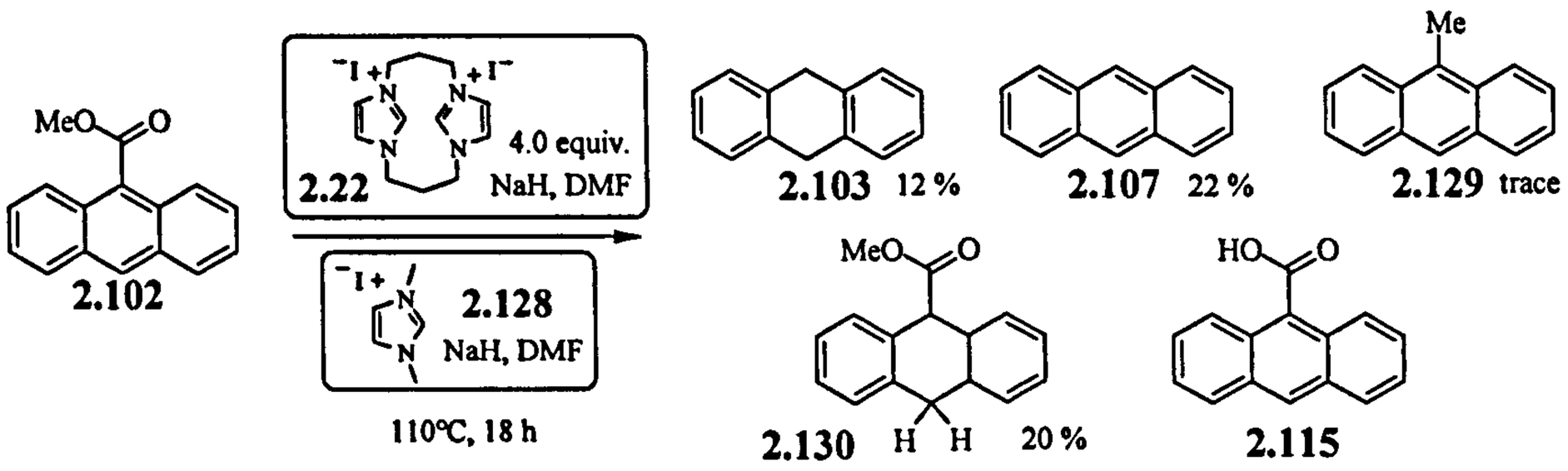
(ii)



The yellow donor solution was prepared according to the 'general NaH-method' procedure using salt **2.22** (566 mg, 1.2 mmol, 4.0 equiv.) and anhydrous DMF (10 ml). 1,3-Dimethyl-1*H*-imidazolium salt iodide **1.128** (168 mg, 0.75 mmol, 2.5 equiv.) was heated at 90°C for 1h under vacuum in a centrifuge tube, then cooled to room temperature and sodium hydride (60% suspension in mineral oil, 300 mg, 7.5 mmol, 25 equiv.) was added under argon atmosphere. This mixture was then washed with hexane (2 x 20 ml) and subsequently dried under argon. Dry DMF (5 ml) was deoxygenated with argon for 20 min and then added dropwise to the salt/sodium hydride residue. This mixture was stirred for 4h at room temperature under argon and then exposed to centrifugation. The resulting supernatant liquid was transferred *via* cannula to anthracene-9-carboxylic acid 2,2,2-trifluoroethyl ester **2.124** (94.0 mg, 0.308 mmol, 1.0 equiv.) [dried beforehand under vacuum at room temperature for 3 h]. The reaction mixture turned dark-green and was stirred at room temperature for 5 min. The donor solution prepared from salt **2.22** was then added *via* cannula and the mixture was heated at 110°C for 18 h under argon atmosphere. After heating the reaction mixture at 110°C for 18 h, *acidic* work-up was carried out. The

residue was purified by column chromatography on silica gel (2:98, then 20:80, then 90:10 diethyl ether/ hexane) to give an inseparable mixture, tentatively identified as 9,10-dihydroanthracene **2.103** (trace), anthracene **2.107** (4 %) and 9-methyl-anthracene[200] **2.129** (23 %) as a white solid (16 mg, yields determined based on the ratio in the ^{1}H-NMR spectrum of the mixture) as the first fraction. The second fraction (12.8 mg) contained mainly anthracene-9-carboxylic acid **2.115** based on comparison of the ^{1}H-NMR spectrum of the crude mixture with the commercial **2.115** and LC-MS analysis of the fraction showed a signal at *m/z* (ESI-) 221 ($[M-H]^+$), corresponding to anthracene-9-carboxylic acid **2.115**.

Reduction of anthracene-9-carboxylic acid methyl ester 2.102 in the presence of 2.126

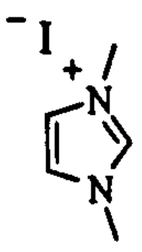


The yellow donor solution was prepared according to the 'general NaH-method' procedure using salt **2.22** (566 mg, 1.2 mmol, 4.0 equiv.) and anhydrous DMF (10 ml). 1,3-Dimethyl-1*H*-imidazolium salt iodide **2.128** (168 mg, 0.75 mmol, 2.5 equiv.) was heated at 90°C for 1 h under vacuum in a centrifuge tube, was then cooled to room temperature and sodium hydride (60 % suspension in mineral oil, 300 mg, 7.5 mmol, 25 equiv.) was added under argon atmosphere. This mixture was then washed with hexane (2 x 20 ml) and subsequently dried under argon. Dry DMF (5 ml) was deoxygenated with argon for 20 min and was then added dropwise to the salt/ sodium hydride residue. This mixture was stirred for 4 h at room temperature under argon and then exposed to centrifugation. The resulting supernatant liquid was transferred *via* cannula to anthracene-9-carboxylic acid methyl ester **2.102** (70.0 mg, 0.296 mmol, 1.0 equiv.) [dried beforehand under vacuum at room temperature for 3 h]. The reaction mixture turned dark-green and was stirred at room temperature for 5 min. The donor solution prepared from salt **2.22** was then added *via* cannula and the mixture was heated at 110°C for 18 h under argon atmosphere. After heating the reaction mixture at 110°C for 18 h, diethyl ether (20 ml) and 2 N hydrochloric acid (20 ml) were added. The aqueous layer was extracted with diethyl ether (2 x 20 ml) and the combined organic layer was washed with 2 N hydrochloric acid (3 x 20 ml). The organic layer was then washed with aqueous NaOH solution (3 x 20 ml), then dried over

sodium sulfate and evaporated. The residue was purified by column chromatography on silica gel (2:98, then 20:80 diethyl ether/ hexane) to give an inseparable mixture of 9,10-dihydroanthracene **2.103** (12 %), anthracene **2.107** (22 %) and 9-methyl-anthracene[200] **2.129** (trace) as a white solid (18 mg, yields determined based on the ratio in the ^{1}H-NMR spectrum of the mixture) as the first fraction. As the second fraction was isolated 9,10-dihydroanthracene-9-carboxylic acid methyl ester **2.130** as a yellow liquid (14 mg, 20 %); (Found: $[M+NH_4]^+$ 256.1328. $C_{16}H_{14}O_2$ requires $[M+NH_4]^+$, 256.1332); ν_{max} (NaCl)/cm^{-1} 3066 (Ar-H), 2945 (C-H), 2923 (C-H), 1735 (C=O), 1449 (C-H), 1152 (C-O); δ_H ($CDCl_3$) 3.60 (3H, s, OC*H*$_3$), 3.92 (1H, d, *J* 18.2, ArC*H*HAr), 4.33 (1H, d, *J* 18.2, ArH*H*Ar), 5.02 (1H, s, ArC*H*CO), 7.24-7.32 (4H, m, Ar*H*), 7.35-7.37 (2H, m, Ar*H*), 7.40 (2H, dd, *J* 7.9, 1.5, ArH); δ_C ($CDCl_3$) 36.3 (CH_2), 52.4 (CH), 52.8 (CH_3), 126.4 (CH), 127.5 (CH), 128.1 (CH), 128.6 (CH), 133.9 (C), 136.9 (C), 172.5 (C); *m/z* (CI) 256 ($[M+H]^+$, 100 %), 239 (8), 195 (10), 179 (12), 52 (4).

The basic aqueous layer was acidified with conc. hydrochloric acid and extracted with ethyl acetate (3 x 20 ml). This organic layer was then combined, dried over sodium sulfate and evaporated to give a residue (16 mg) that contained anthracene-9-carboxylic acid **2.115**, based on comparison of the ^{1}H-NMR spectrum of the crude mixture with the commercial **2.115**, and LC-MS analysis of the fraction showed among other unidentified peaks a signal at *m/z* (ESI-) 221 ($[M-H]^+$), corresponding to anthracene-9-carboxylic acid **2.115**.

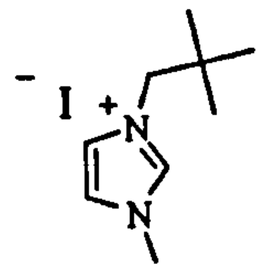
1,3-Dimethyl-1*H*-imidazolium salt iodide 2.128



2.128

1-Methyl-1*H*-imidazole (2.91 ml, 36.5 mmol, 1.0 equiv.) was dissolved in acetonitrile and iodomethane (2.73 ml, 43.8 mmol, 1.2 equiv.) was added dropwise at room temperature. After heating the reaction mixture at 65°C for 20 h the solvent was removed *in vacuo* and the solid residue was washed with diethyl ether to give 1,3-dimethyl-1*H*-imidazolium salt iodide **2.128** as a yellow semi-solid (7.6 g, 93 %); ν_{max} (KBr)/cm^{-1} 3149 (Ar-H), 3090 (C-H), 1575, 1450, 1173; δ_H (DMSO) 3.84 (6H, s, C*H*$_3$), 7.76 (2H, s, Ar*H*), 9.12 (1H, s, NC*H*N$^+$); δ_C (DMSO) 34.3 (CH_3), 121.3 (CH), 135.0 (CH); *m/z* (ESI) 97 ($[M-I]^+$, 100 %).

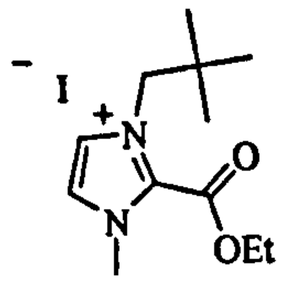
3-(2,2-Dimethylpropyl)-1-methyl-1*H*-imidazolium salt iodide 2.156



2.156

1-(2,2-Dimethylpropyl)-1*H*-imidazole (3.0 g, 21.7 mmol, 1.0 equiv.) **2.155** was dissolved in acetonitrile (20 ml) and iodomethane (2.03 ml, 32.5 mmol, 1.5 equiv.) was added at room temperature. After heating the mixture at reflux for 18 h the solvent was removed *in vacuo* and the residue washed with diethyl ether to give 3-(2,2-dimethylpropyl)-1-methyl-1*H*-imidazolium salt iodide **2.156** as an orange oil (5.7 g, 94 %); (Found: $[M\text{-}I]^+$ 153.1387. $C_9H_{17}IN_2$ requires $[M\text{-}I]^+$, 153.1386); ν_{max} (KBr)/cm^{-1} 3139 (Ar-H), 3078 (Ar-H), 2960 (C-H), 2871 (C-H), 1481 (C-H); δ_H ($CDCl_3$) 0.89 [9H, s, C(CH_3)], 5.11 (5H, s, NCH_2 and NCH_3), 7.42-7.43 (1H, m, Ar*H*), 7.65-7.66 (1H, m, Ar*H*), 9.86 (1H, s, NC*H*N^+); *m/z* (ES+) 153 ($[M\text{-}I]^+$, 100 %), 83 (3).

3-(2,2-Dimethylpropyl)-1-methyl-1*H*-imidazolium-2-carboxylic acid ethyl ester iodide 2.157



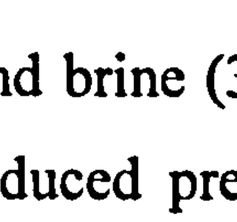
2.157

Sodium hydride (1.43 g, 35.69 mmol, 10.0 equiv.) was washed with hexane (2 x 30 ml) and was subsequently dried with argon. 3-(2,2-dimethyl-propyl)-1-methyl-1H-imidazolium salt iodide **2.128** (1 g, 3.569 mmol, 1.0 equiv.) was dried under vacuum at 100°C for 2 h and was then dissolved in THF (30 ml, deoxygenated with argon for 30 min beforehand). The solution was transferred *via* cannula to the sodium hydride and the mixture was stirred at room temperature for 4 h under argon. After centrifugation the supernatant liquid was transferred to ethyl chloroformate (0.37 ml, 3.926 mmol, 1.1 equiv.) while cooling to 0°C under argon. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was then removed under reduced pressure and the residue was purified by column chromatography on silica gel (20:80 DCM/ acetonitrile) to afford *3-(2,2-dimethylpropyl)-1-methyl-1H-imidazolium-2-carboxylic acid ethyl ester iodide* **2.157** as a yellow semi-solid (376.5 mg, 30 %); (Found: $[M\text{-}I]^+$ 225.1600. $C_{12}H_{21}IN_2O_2$ requires $[M\text{-}I]^+$, 225.1598); ν_{max} (KBr)/cm^{-1} 3089 (Ar-H), 2960 (C-H), 1733 (C=O), 1440 (C-H),

1186 (C-O); δ_H ($CDCl_3$) 0.95 [9H, s, C(CH_3)], 1.45 (3H, t, *J* 7.1, OCH_2CH_3), 4.33 (3H, s, NCH_3), 4.55 (2H, q, *J* 7.1, OCH_2CH_3), 4.61 (2H, s, NCH_2), 8.04 (1H, d, *J* 1.8, Ar*H*), 8.38 (1H, d, *J* 1.8, Ar*H*); δ_C ($CDCl_3$) 19.9 (CH_3), 27.3 (CH_3), 33.4 (C), 40.6 (CH_3), 60.9 (CH_2), 64.9 (CH_2), 126.9 (CH), 127.0 (CH), 132.4 (C), 153.9 (C); *m/z* (ES+) 225 ($[M-I]^+$, 84 %), 211 (100), 153 (9), 141 (6).

8.4 Experiments from chapter 4: *Formation of aldehydes*

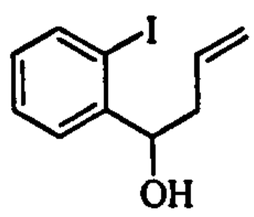
2-Iodobenzaldehyde 2.178



2.178

A solution of oxalyl chloride (5.5 ml, 0.0854 mol, 2.0 equiv.) in dichloromethane (40 ml) was cooled to –78°C and dimethylsulfoxide (9.1 ml, 0.128 mol, 3.0 equiv.) was added dropwise under argon. This mixture was stirred for 10 min at –78°C. A solution of 2-iodobenzyl alcohole in dichloromethane (40 ml) was then added dropwise. After stirring for 30 min at –78°C, triethylamine (35.62 ml, 0.235 mol, 5.5 equiv.) was added dropwise and the reaction mixture was allowed to warm to room temperature, was stirred for 30 min at room temperature and then poured into diethyl ether (500 ml). The organic phase was washed with water (2 x 500 ml) and brine (300 ml), was then dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10:90 ethyl acetate/ petroleum ether) to give 2-iodobenzaldehyde **2.178**[201] as a yellow solid (8.5 g, 86 %); mp 32-34°C (lit.[201] 34°C); δ_H ($CDCl_3$) 7.27-7.32 (1H, m, Ar*H*), 7.44-7.50 (1H, m, Ar*H*), 7.89 (1H, dd, *J* 7.7, 1.8, Ar*H*), 7.97 (1H, dd, *J* 7.9, 1.0, Ar*H*), 10.08 (1H, s, OC*H*); consistent with the data quoted by D. Thomson.[203]

1-(2-Iodophenyl)but-3-en-1-ol 2.179[203]

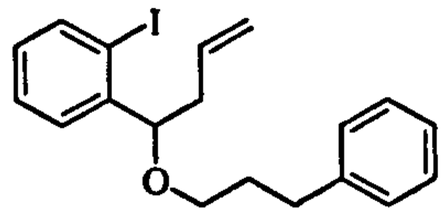


2.179

A solution of 2-iodobenzaldehyde **2.178** in tetrahydrofuan (60 ml) was cooled to 0°C and a solution of allylmagnesium bromide (43.97 ml, 43.9 mmol, 1.2 equiv.) was added dropwise under argon. After allowing to warm to room temperature the reaction mixture was stirred overnight and was then quenched with ammonium chloride solution (100 ml). Ethyl acetate (100 ml) was added and the organic layer was washed with water (100 ml) and brine (100 ml), was subsequently dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (20:80 ethyl acetate/ petroleum ether) to give 1-(2-iodophenyl)but-3-en-1-ol **2.179**[202] as a white solid (12.5 g, 87 %); 38-39°C (lit.[202] 42°C); δ_H ($CDCl_3$) 2.13 (1H, s, O*H*), 2.28-2.30 (1H, m, CH*H*), 2.60-2.65 (1H, m,

CH*H*), 4.94 (1H, dd, *J* 8.6, 3.4, C*H*), 5.19-5.26 (2H, m, =CH_2), 5.86-5.96 (1H, m, =C*H*), 6.96-7.00 (1H, m, Ar*H*), 7.37-7.40 (1H, m, Ar*H*), 7.53 (1H, dd, *J* 7.8, 2.5, Ar*H*), 7.81 (1H, dd, *J* 7.9, 1.6, Ar*H*); consistent with the data quoted by D. Thomson.[203]

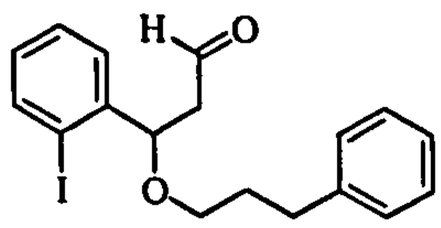
1-Iodo-2-[1-(2-phenylpropyloxy)but-3-enyl]benzene 2.160[203]



2.160

To a suspension of washed sodium hydride (1.633 g, 0.041 mol, 1.2 equiv.) in DMF (20 ml) was added a solution of 1-(2-iodophenyl)but-3-en-1-ol **2.179** in DMF (20 ml) under argon while cooling to 0°C. The mixture was allowed to warm to room temperature and after stirring for 1 h, the mixture was cooled to 0°C again. 1-bromo-3-phenylpropane (7.76 ml, 0.051 mol, 1.5 equiv.) was then added dropwise and the mixture was stirred at room temperature overnight. Ethyl acetate (100 ml) and water (100 ml) were then added and the aqueous layer was extracted further with ethyl acetate (3 x 100 ml). The combined organic layer was subsequently washed with water (8 x 100 ml) and brine, was dried over sodium sulfate, filtered and removed *in vacuo*. The residue was purified by column chromatography on silica gel (2:98 ethyl acetate, petroleum ether) to afford 1-iodo-2-[1-(2-phenylpropyloxy)but-3-enyl]benzene **2.160**[204] as a colourless liquid (6.9 g, 52 %); δ_H ($CDCl_3$) 1.86-1.93 (2H, m, $CH_2CH_2CH_2$), 2.36-2.50 (2H, m, $CHCH_2CH$=), 2.65-2.78 (2H, m, CH_2Ph), 3.29-3.41 (2H, m, OCH_2), 4.57 (1H, dd, *J* 8.1, 4.4, OC*H*), 5.07-5.16 (2H, m, =CH_2), 5.90-6.01 (1H, m, =C*H*), 6.98 (1H, ddd, *J* 9.1, 7.7, 1.8, Ar*H*), 7.17-7.21 (3H, m, Ar*H*), 7.21-7.30 (2H, m, Ar*H*), 7.38 (1H, ddd, *J* 9.1, 7.9, 1.1, Ar*H*), 7.45 (1H, dd, *J* 7.7, 1.1, Ar*H*), 7.81 (1H, dd, *J* 7.9, 1.8, Ar*H*); consistent with the data quoted by D. Thomson.[203]

3-(2-Iodophenyl)-3-(3-phenyl-propoxy)propionaldehyde 2.180



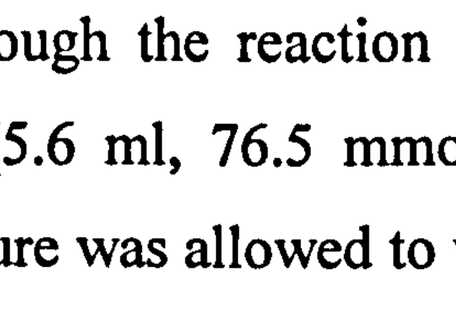
2.180

(i)[205] 1-Iodo-2-[1-(2-phenylpropyloxy)but-3-enyl]benzene **2.160** (103 mg, 0.263 mmol, 1.0 equiv.), sodium periodate (225 mg, 1.052 mmol, 4.0 equiv.) and 2,6-lutidine (0.061 ml, 0.526 mmol, 2.0 equiv.) were dissolved in dioxane and water solution (3 ml, 3:1). Osmium

tertroxide solution (in *tert*-butanol) (1.33 mg, 0.00526 mmol, 1/50 equiv.) was added at room temperature and the mixture was stirred for 4 h at that temperature. The mixture was then filtered through Kieselguhr. The filtrate was dissolved in diethyl ether (20 ml) and water (20 ml) and the organic layer was washed with water (2 x 20 ml) and brine (20 ml), was subsequently dried over sodium sulfate, filtered and evaporated. The residue was subjected to column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether) to give *3-(2-iodophenyl)-3-(3-phenylpropyloxy)propionaldehyde* **2.180** as a colourless oil (94 mg, 91 %); ν_{max} (NaCl)/cm^{-1} 3061 (Ar-H), 3026 (Ar-H), 2942 (C-H), 2864 (C-H), 2713 (CO-H), 1727 (C=O), 1455 (C-H); δ_H ($CDCl_3$) 1.95-2.01 (2H, m, CH_2CH_2CO), 2.71-297 (4H, m, CH_2Ph and CHCH_2COH), 3.43-3.53 (2H, m, OCH_2), 5.16 (1H, t, *J* 6.3, OC*H*CH_2), 7.09 (1H, ddd, *J* 7.6, 7.6, 1.8, Ar*H*), 7.25-7.28 (3H, m, Ar*H*), 7.34-7.38 (2H, m, Ar*H*), 7.48 (1H, ddd, *J* 7.7, 7.7, 1.0, Ar*H*), 7.56 (1H, dd, *J* 7.8, 1.8, Ar*H*), 7.91 (1H, dd, *J* 7.9, 1.1, Ar*H*), 9.94 (1H, t, *J* 2.1, CO*H*); due to the instability of the compound further data were not collected.

(ii) 1-Iodo-2-[1-(2-phenylpropyloxy)but-3-enyl]benzene **2.160** (3.0 g, 7.65 mmol, 1.0 equiv.), was dissolved in dichloromethane and the solution was cooled to –78°C. Ozone was bubbled through the solution at –78°C until a deep blue colour appeared (*ca.* 30 min). Then oxygen gas was bubbled through the reaction mixture until the blue colour had disappeared and dimethyl sulfide (5.6 ml, 76.5 mmol, 10.0 equiv.) was added in one portion at –78°C. The reaction mixture was allowed to warm to room temperature and was stirred for 4d at that temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether) to afford *3-(2-iodo-phenyl)-3-(2-phenylpropyloxy)propionaldehyde* **2.180** as a colourless oil (2.8 g, 93 %); for data see above.

5-(2-Iodophenyl)-5-(3-phenylpropyloxy)pent-2-enoic acid ethyl ester 2.181

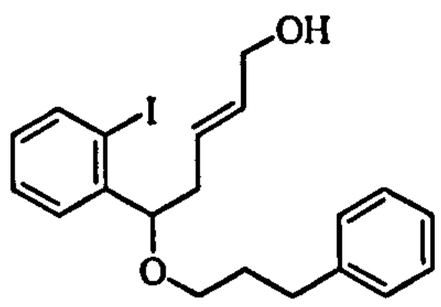


2.181

3-(2-Iodophenyl)-3-(3-phenylpropyloxy)propionaldehyde **2.180** (78.5 mg, 0.199 mmol, 1.0 equiv.) and ethyl (triphenylphosphoranyliden)acetate (76.35 mg, 0.219 mmol, 1.1 equiv.)

were dissolved in dichloromethane (5 ml) and the mixture was heated at reflux for 3 h. After removing the solvent under reduced pressure, the residue was purified by column chromatography (20:80 ethyl acetate/ petroleum ether) to afford *5-(2-iodophenyl)-5-(3-phenylpropyloxy)pent-2-enoic acid ethyl ester* **2.181** as a colourless liquid (78 mg, 85 %); (Found: $[M+NH_4]^+$ 482.1189. $C_{22}H_{25}IO_3$ requires $[M+NH_4]^+$, 482.1187); ν_{max} (NaCl)/cm^{-1} 3061 (Ar-H), 3026 (Ar-H), 2980 (C-H), 2940 (C-H), 1729 (C=O), 1655 (Ar), 1455 (C-H); δ_H ($CDCl_3$) 1.35 (3H, t, *J* 7.1, CH_3CH_2O), 1.92-1.99 (2H, m, $CH_2CH_2CH_2$), 2.51-2.68 (2H, m, $CHCH_2C{=}C$), 2.70-2.81 (2H, m, CH_2Ph) 3.33-3.46 (2H, m, OCH_2CH_2), 4.27 (1H, q, *J* 7.1, CH_3CH_2CO), 4.66 (1H, dd, *J* 8.5, 3.8, $ArCHOCH_2$), 5.99 (1H, dt, *J* 15.7, 1.37, $CH_2CH{=}CH$), 7.04 (1H, ddd, *J* 7.5, 7.5, 1.8, Ar*H*), 7.12-7.19 (1H, m, $CH_2CH{=}CH$), 7.23-7.25 (3H, m, Ar*H*), 7.31-7.36 (2H, m, Ar*H*), 7.41-7.45 (1H, m, Ar*H*), 7.50 (1H, dd, *J* 7.8, 1.8, Ar*H*), 7.87 (1H, dd, *J* 7.9, 1.1, Ar*H*); δ_C ($CDCl_3$) 14.7 (CH_3), 31.8 (CH_2), 32.8 (CH_2), 40.1 (CH_2), 60.7 (CH_2), 68.9 (CH_2), 84.3 (CH), 98.7 (C), 126.2 (CH), 127.7 (CH), 128.8 (CH), 128.9 (CH), 129.1 (CH), 129.9 (CH), 139.9 (CH), 142.3 (C), 144.1 (C), 145.4 (CH), 166.8 (C); *m/z* (CI) 482 ($[M+NH_4]^+$, 100 %), 465 (6), 356 (88), 329 (10), 220 (86), 203 (14), 152 (14).

5-(2-Iodophenyl)-5-(3-phenylpropyloxy)-pent-2-en-1-ol 2.182

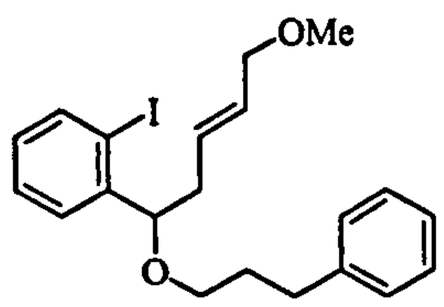


2.182

A solution of 5-(2-iodophenyl)-5-(3-phenylpropyloxy)-pent-2-enoic acid ethyl ester **2.181** (1.162 g, 2.504 mmol, 1.0 equiv.) in hexane (15 ml) was cooled to –78°C and diisobutyl aluminium hydride (1 M solution in hexane, 5.76 ml, 5.76 mmol, 2.3 equiv.) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 2.5 h. After quenching with water, the mixture was poured into water (200 ml) and diethyl ether (200 ml). The aqueous layer was acidified with 2 N hydrochloric acid and extraceted with diethyl ether (2 x 100 ml). The combined organic layer was washed with brine, dried over sodium sulfate and evaporated. Purification by column chromatography (20:80 ethyl acetate/ petroleum ether) gave rise to *5-(2-iodophenyl)-5-(3-phenylpropyloxy)-pent-2-en-1-ol* **2.182** as a colourless oil (0.888 g, 84 %); (Found: $[M+NH_4]^+$ 440.1077. $C_{20}H_{23}IO_2$ requires $[M+NH_4]^+$, 440.1081); ν_{max} (NaCl)/cm^{-1} 3367 (O-H), 3060 (Ar-H),

3025 (Ar-H), 2938 (C-H), 1603 (Ar), 1496 (C-H); δ_H ($CDCl_3$) 1.04-2.02 (2H, m, $CH_2CH_2CH_2$), 2.45-2.53 (2H, m, $CHCH_2C{=}C$), 2.71-2.85 (2H, m, CH_2Ph), 3.38-3.48 (2H, m, OCH_2CH_2), 4.19 (2H, dd, *J* 5.6, 0.8, $CH{=}CHCH_2O$), 4.63 (1H, dd, *J* 7.8, 4.8, $ArCHOCH_2$), 5.76-5.83 (1H, m, $CH{=}CHCH_2OH$), 5.86-5.97 (1H, m, $CH{=}CHCH_2OH$), 7.06 (1H, ddd, *J* 7.5, 7.5, 1.8, Ar*H*), 7.23-7.28 (3H, m, Ar*H*), 7.32-7.38 (2H, m, Ar*H*), 7.41-7.47 (1H, m, Ar*H*), 7.51 (1H, dd, *J* 7.8, 1.8, Ar*H*), 7.89 (1H, dd, *J* 7.9, 1.1, Ar*H*); δ_C ($CDCl_3$) 31.9 (CH_2), 32.9 (CH_2), 40.4 (CH_2), 64.1 (CH_2), 68.9 (CH_2), 85.1 (CH), 99.2 (C), 126.3 (CH), 128.0 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 129.7 (CH), 132.2 (CH), 139.8 (CH), 142.5 (C), 144.7 (C); *m/z* (CI) 440 ($[M+NH_4]^+$, 100 %), 351 (12), 314 (58), 296 (24), 269 (22), 178 (38), 143 (31).

1-Iodo-2-[5-methoxy-1-(3-phenylpropyloxy)pent-3-enyl]benzene 2.173



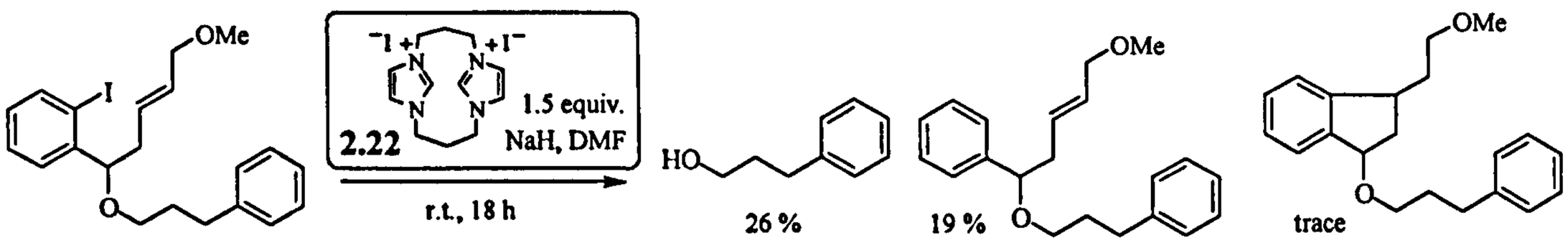
2.173

To a suspension of washed sodium hydride (92.5 mg, 2.313 mmol, 1.1 equiv.) in DMF (5 ml) was added a solution of 5-(2-iodophenyl)-5-(3-phenylpropyloxy)pent-2-en-1-ol **2.182** (888 mg, 2.103 mmol, 1.0 equiv.) in DMF (15 ml) while cooling to 0°C. The mixture was allowed to warm to room temperature and was stirred for 1 h. After re-cooling to 0°C, iodomethane (0.144 ml, 2.313 mmol, 1.1 equiv.) was added dropwise and the reaction mixture was stirred at room temperature overnight. Water was then added and the aqueous phase was extracted with diethyl ether (3 x 70 ml). The combined organic layer was washed with water and brine, was then dried over sodium sulfate, filtered and removed under reduced pressure. The residue was subjected to column chromatography (10:90 ethyl acetate/ petroleum ether) to give *1-iodo-2-[5-methoxy-1-(3-phenylpropyloxy)pent-3-enyl]benzene* **2.173** as a colourless liquid (709 mg, 77 %); (Found: $[M+NH_4]^+$ 454.1238. $C_{21}H_{25}IO_2$ requires $[M+NH_4]^+$, 454.1237); ν_{max} (NaCl)/cm^{-1} 3060 (Ar-H), 3025 (Ar-H), 2926 (C-H), 1603 (Ar), 1455 (C-H); δ_H ($CDCl_3$) 1.96-2.03 (2H, m, $CH_2CH_2CH_2$), 2.47-2.61 (2H, m, $CHCH_2CH{=}C$), 2.74-2.87 (2H, m, CH_2Ph), 3.38-3.51 (5H, m, OCH_3 and OCH_2CH_2), 3.99 (2H, d, *J* 6.1, $CH{=}CHCH_2O$), 4.67 (1H, dd, *J* 8.0, 4.5, $ArCHOCH_2$), 5.72-5.79 (1H, m, $CH{=}CHCH_2OMe$), 5.92-5.99 (1H, m, $CH{=}CHCH_2OMe$), 7.05 (1H, ddd, *J* 7.5, 7.5, 1.7, Ar*H*), 7.27-7.29 (3H, m, Ar*H*), 7.35-7.41 (2H, m, Ar*H*), 7.43-7.47 (1H, m,

Ar*H*), 7.54 (1H, dd, *J* 7.7, 1.7, Ar*H*), 7.89 (1H, d, *J* 7.1, Ar*H*); δ_C ($CDCl_3$) 32.0 (CH_2), 32.9 (CH_2), 40.5 (CH_2), 58.1 (CH_3), 68.8 (CH_2), 73.5 (CH_2), 85.2 (CH), 99.2 (C), 126.3 (CH), 127.9 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 129.5 (CH), 129.7 (CH), 130.7 (CH), 139.8 (CH), 142.5 (C), 144.8 (C); *m/z* (CI) 454 ($[M+NH_4]^+$, 100 %), 438 (8), 351 (13), 328 (28), 269 (11), 192 (15), 143 (12).

Test reaction on 1-iodo-2-[5-methoxy-1-(3-phenyl-propoxy)-pent-3-enyl]benzene 2.173

(i)

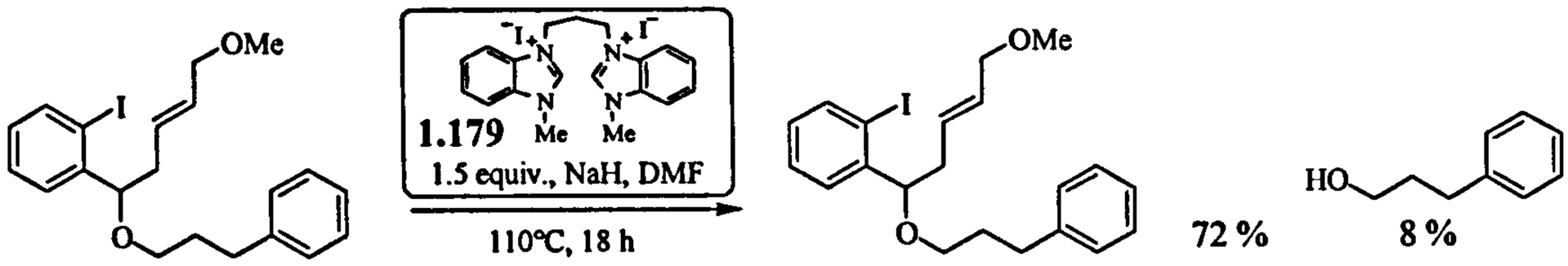


2.173 **2.183** **2.184** **2.185**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMF (15 ml), salt **2.22** (212 mg, 0.45 mmol, 1.5 equiv.), 1-iodo-2-[5-methoxy-1-(3-phenylpropoxy)pent-3-enyl]benzene **2.173** (131 mg, 0.3 mmol, 1.0 equiv.). *Neutral* work-up was carried out and the residue was purified by column chromatography on silica gel (100:0, then 95:5, then 80:20 petroleum ether/ ethyl acetate) to afford *1-(2-methoxyethyl)-1-methyl-3-(3-phenylpropoxy)indane* **2.185** (trace), for data see **(iii)** below; and *2-[5-methoxy-1-(3-phenylpropoxy)pent-3-enyl]benzene* **2.184** (18 mg, 19 %); (Found: $[M+NH_4]^+$ 328.2272 $C_{21}H_{26}O_2$ requires $[M+NH_4]^+$, 328.2271; ν_{max} (NaCl)/cm^{-1} 3022 (Ar-H), 2926 (C-H), 1605 (Ar), 1454 (C-H); δ_H ($CDCl_3$) 1.56-1.91 (2H, m, $CH_2CH_2CH_2$), 2.38-2.47 (1H, m, $CHCH_2CH$=C), 2.56-2.77 (3H, m, 1H: $CHCH_2CH$=C and 2H: CH_2Ph), 3.26-3.54 (5H, m, OCH_3 and OCH_2CH_2), 3.86-3.40 (2H, m, CH=$CHCH_2O$), 4.24 (1H, dd, *J* 7.6, 5.8, $ArCHOCH_2$), 5.56-5.63 (1H, m, CH=$CHCH_2OMe$), 5.68-5.76 (1H, m, CH=$CHCH_2OMe$), 7.15-7.25 (3H, m, Ar*H*), 7.27-7.37 (7H, m, Ar*H*); δ_C ($CDCl_3$) 31.7 (CH_2), 32.6 (CH_2), 41.5 (CH_2), 57.8 (CH_3), 68.2 (CH_2), 73.3 (CH_2), 82.3 (CH), 125.9 (CH), 126.9 (CH), 127.7 (CH), 128.6 (CH), 130.9 (CH), 142.3 (C), 142.6 (C); *m/z* (CI) 328 ($[M+NH_4]^+$, 100 %), 225 (15), 192 (38), 175 (33), 143 (76), 52 (54); and 3-phenylpropan-1-ol **2.183**[206] (11 mg, 26 %); (Found: $[M+NH_4]^+$ 154.1227. $C_9H_{12}O$ requires $[M+NH_4]^+$, 154.1226; ν_{max} (NaCl)/cm^{-1} 3350 (O-H), 3027 (Ar-H), 2939 (C-H), 1603 (Ar), 1454 (C-H); δ_H ($CDCl_3$) 1.92-1.99 (2H, m, $CH_2CH_2CH_2$), 2.75-2.79 (2H, m, CH_2Ph), 3.74 (2H, t, *J* 6.4, $HOCH_2CH_2$), 7.15-7.25 (3H, m, Ar*H*), 7.28-

7.35 (2H, m, Ar*H*); δ_C ($CDCl_3$) 32.3 (CH_2), 34.5 (CH_2), 62.5 (CH_2), 126.1 (CH), 128.6 (CH), 142 (C); *m/z* (CI) 154 ($[M+NH_4]^+$, 100 %), 118 (14), 91 (5).

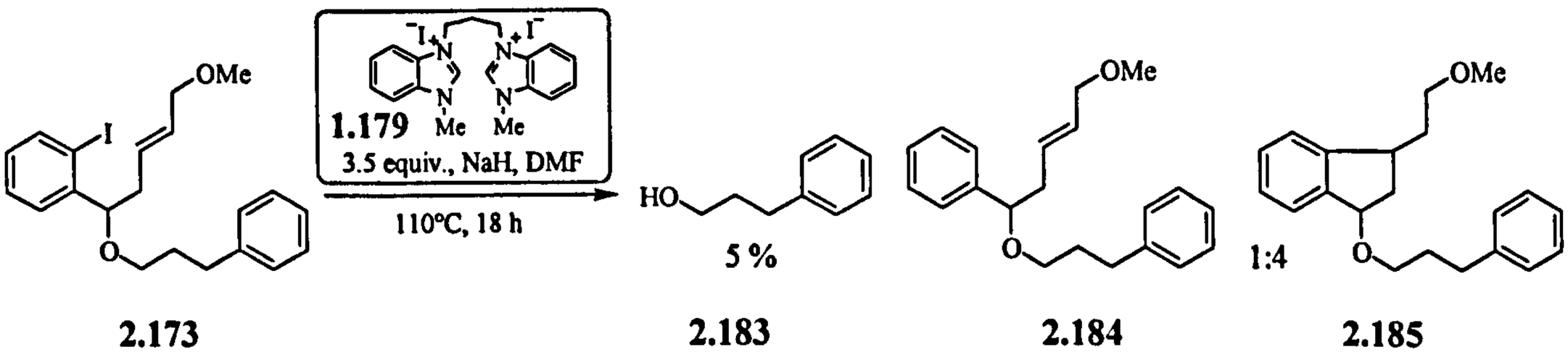
(ii)



2.173 **2.173** **2.183**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (10 ml), salt **1.179** (170 mg, 0.303 mmol, 1.5 equiv.), 1-iodo-2-[5-methoxy-1-(3-phenylpropyloxy)pent-3-enyl]benzene **2.173** (88 mg, 0.202 mmol, 1.0 equiv.). *Neutral* work-up was carried out and the residue was purified by column chromatography on silica gel (95:5 petroleum ether/ ethyl acetate) to afford starting material **2.173** (63 mg, 72 %) and 3-phenylpropan-1-ol **2.183**[206] (2.3 mg, 8 %); for data see **(i)** above.

(iii)

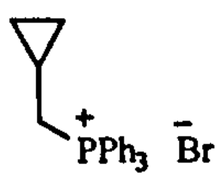


2.173 **2.183** **2.184** **2.185**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (10 ml), salt **1.179** (171 mg, 0.305 mmol, 3.5 equiv.), 1-iodo-2-[5-methoxy-1-(3-phenyl-propoxy)-pent-3-enyl]benzene **2.173** (38 mg, 0.087 mmol, 1.0 equiv.). *Neutral* work-up was carried out and the residue was purified by column chromatography on silica gel (95:5 petroleum ether/ ethyl acetate) to afford 3-phenylpropan-1-ol **2.183** as a colourless liquid (0.6 mg, 5 %) and *2-[5-methoxy-1-(3-phenylpropyloxy)pent-3-enyl]benzene* **2.184** and *1-(2-methoxyethyl)-1-methyl-3-(3-phenylpropoxy)indane* **2.185** as a colourless liquid in a 1:4 mixture (28 mg, 61 %); for data of **2.183** and **2.184** see **(i)** above. The mixture was purified further by HPLC (5:95 ethyl acetate/ petroleum ether) to give one diastereomer of *1-(2-methoxyethyl)-1-methyl-3-(3-phenylpropoxy)indane* **2.185** pure as a colourless liquid; δ_H ($CDCl_3$) 1.59-1.66 (2H, m,

$CH_2CH_2CH_2$), 1.88-1.99 (3H, m, CH_2CH_2OMe and $OCHCH_2CH$), 2.14-2.20 (1H, m, $OCHCHHCH$), 2.31-2.38 (1H, m, $OCHCHHCH$), 2.70-2.74 (2H, m, CH_2Ph), 3.39 (3H, s, OCH_3), 3.50-3.54 (4H, m, $OCH_2CH_2CH_2Ph$ and CH_2OMe), 4.89 (1H, dd, *J* 6.4, 3.2, $ArCHOCH_2$), 7.16-7.21 (3H, m, Ar*H*), 7.23-7.33 (5H, m, Ar*H*), 7.38 (1H, d, *J* 7.4, Ar*H*); δ_C ($CDCl_3$) 31.7 (CH_2), 31.9 (CH_2), 322.6 (CH_2), 35.4 (CH_2), 39.3 (CH_2), 58.9 (CH_3), 67.8 (CH_2), 71.5 (CH), 82.1 (CH), 124.2 (CH), 124.9 (CH), 125.2 (CH), 125.9 (CH), 128.7 (CH), 128.9 (CH), 142.3 (CH), 142.8 (C), 143.5 (C), 146.6 (C).

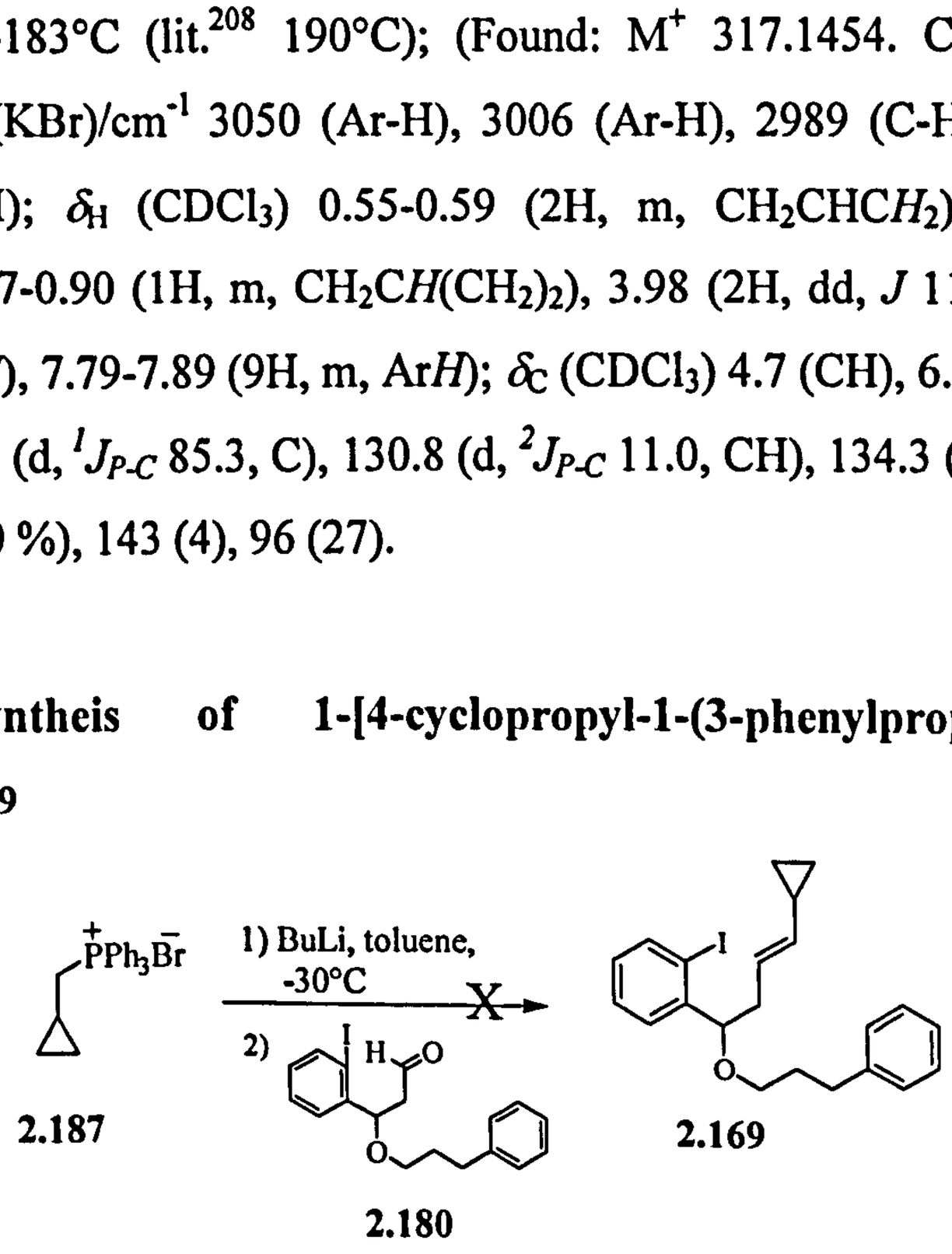
Cyclopropylmethyltriphenylphosphonium bromide 2.178[207]



2.178

Bromomethylcyclopropane (1.0 g, 7.41 mmol, 1.0 equiv.) and triphenylphosphine (1.943 g, 7.41 mmol, 1.0 equiv.) were dissolved in toluene (10 ml) and the mixture was heated at reflux for 2 d. After allowing to cool to room temperature, the precipitate was filtered and the solid was repeatadly washed with toluene and diethyl ether and dried under vacuum to afford cyclopropylmethyltriphenylphosphonium bromide **2.178**[208] as a white solid (1.65 g, 70 %); mp 181-183°C (lit.[208] 190°C); (Found: M^+ 317.1454. $C_{22}H_{22}P^+$ requires M^+, 317.1454); ν_{max} (KBr)/cm^{-1} 3050 (Ar-H), 3006 (Ar-H), 2989 (C-H), 2862 (C-H), 1586 (Ar), 1437 (C-H); δ_H ($CDCl_3$) 0.55-0.59 (2H, m, CH_2CHCH_2), 0.62-0.66 (2H, m, CH_2CHCH_2), 0.87-0.90 (1H, m, $CH_2CH(CH_2)_2$), 3.98 (2H, dd, *J* 11.5, 6.7, PCH_2), 7.68-7.73 (6H, m, Ar*H*), 7.79-7.89 (9H, m, Ar*H*); δ_C ($CDCl_3$) 4.7 (CH), 6.7 (CH_2), 28.2 (d, $^1J_{P-C}$ 49.2, CH_2), 118.7 (d, $^1J_{P-C}$ 85.3, C), 130.8 (d, $^2J_{P-C}$ 11.0, CH), 134.3 (CH), 135.4 (CH); *m/z* (EI) 317 (M^+, 100 %), 143 (4), 96 (27).

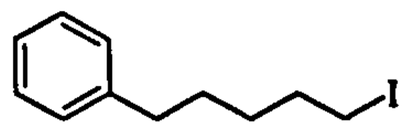
Attempted syntheis of 1-[4-cyclopropyl-1-(3-phenylpropyloxy)but-3-enyl]-2-iodobenzene 2.169



2.187 **2.180** **2.169**

Cyclopropylmethyltriphenylphosphonium bromide **2.187** (160 mg, 0.371 mmol, 1.3 equiv.) was dissolved in THF (5 ml) and cooled to –20°C. BuLi (0.15 ml, 0.37 mmol, 1.2 equiv., c = 2.47 mol/l) was added dropwise and the mixture was stirred at –20°C for 1 h. The mixture was then cooled to –30°C and a solution of aldehyde **2.180** (122 mg, 0.309 mmol, 1.0 equiv.) in THF (5 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred overnight and then poured into diethyl ether (100 ml) and washed with water (100 ml) and brine (100 ml), was dried over sodium sulfate, filtered and evaporated. The residue was subjected to column chromatography on silica gel (2:98 ethyl acetate/ petroleum ether) to give a complex mixture of compounds of identical polarity.

5-Iodopentylbenzene 2.190

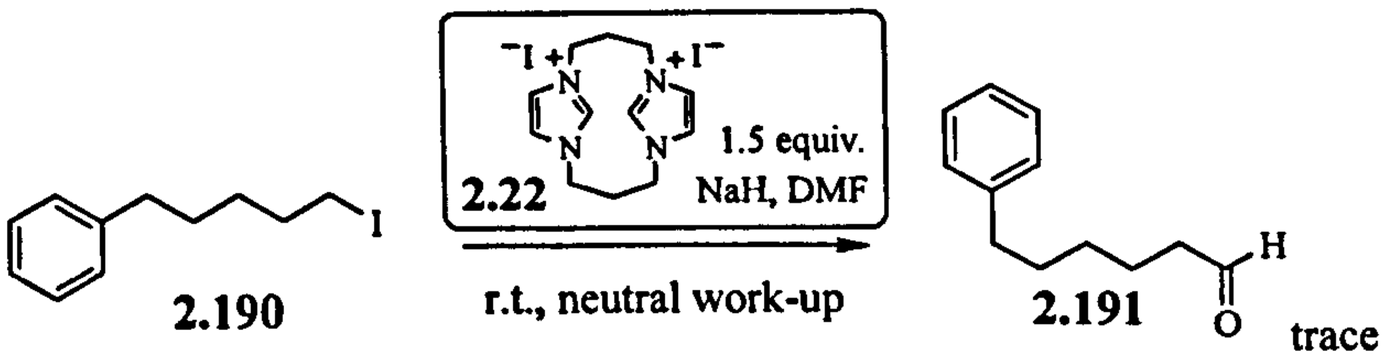


2.190

Triphenylphosphine (2.69 g, 0.01025 mol, 1.0 equiv.) was dissolved in dichloromethane (60 ml) at 0°C under an argon atmosphere. To this was added imidazole (0.698 g, 0.1025 mol, 1.0 equiv.) followed by dropwise addition of 5-phenylpentanol (2.59 ml, 15.38 mmol, 1.5 equiv.). The resulting mixture was stirred at 0°C for 30 min, after which iodine (3.9 g, 0.01538 mol, 1.5 equiv.) was added and reaction mixture was stirred at room temperature for 3 hours. Diethyl ether (150 ml) was then added and the organic layer was washed with sodium thiosulfate solution (2 x 150 ml), brine (150 ml), was then dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was filtered through silica gel (petroleum ether) to afford 5-iodopentylbenzene **2.190**[209] as a colourless liquid (3.66 g, 87 %); (Found: M^+ 274.0211. $C_{11}H_{15}I$ requires M^+, 274.0213); ν_{max} (NaCl)/cm^{-1} 3061 (Ar-H), 3025 (Ar-H), 2931 (C-H), 2855 (C-H), 1603 (Ar), 1453 (C-H), 1426 (C-H); δ_H ($CDCl_3$) 1.42-1.50 (2H, m, CH_2), 1.66 (2H, quintet, *J* 7.7, CH_2), 1.87 (2H, quintet, *J* 7.3, CH_2), 2.64 (2H, t, *J* 7.7, ArCH_2), 3.20 (2H, t, *J* 7.0, CH_2I), 7.18-7.21 (3H, m, Ar*H*), 7.27-7.31 (2H, m, Ar*H*); δ_C ($CDCl_3$) 7.1 (CH_2), 30.4 (CH_2), 30.6 (CH_2), 33.7 (CH_2), 35.9 (CH_2), 126.0 (CH), 128.5 (CH), 128.6 (CH), 142.2 (C); *m/z* (EI) 274 (M^+, 8 %), 183 (3), 147 (19), 105 (18), 91 (100), 65 (21).

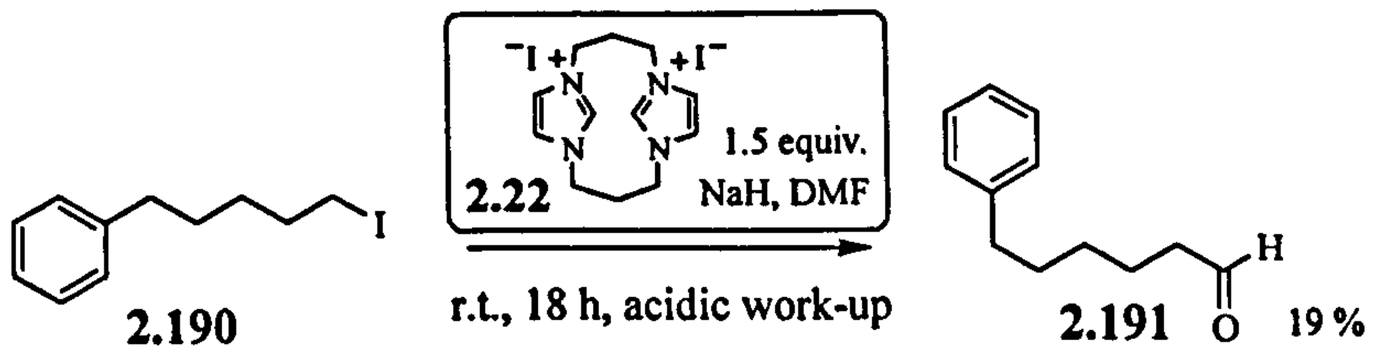
Test reactions with 5-iodopentylbenzene 2.190

(i)



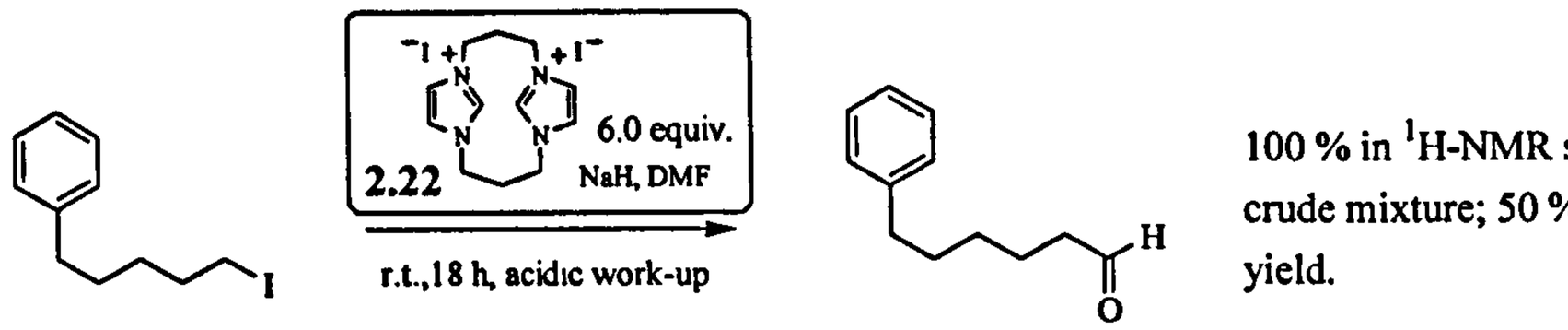
The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMF (15 ml), salt **2.22** (212 mg, 0.45 mmol, 1.5 equiv.), 5-iodopentylbenzene **2.190** (82 mg, 0.3 mmol, 1.0 equiv.). *Neutral* work-up was carried out and ^{1}H-NMR spectroscopic analysis of the crude mixture showed the characteristic aldehyde peak at δ9.85 of **2.122** in trace amount; for data see below.

(ii)



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMF (15 ml), salt **2.22** (204 mg, 0.432 mmol, 1.5 equiv.), 5-iodopentylbenzene (79 mg, 0.288 mmol, 1.0 equiv.). The purification of the crude mixture after *acidic* work-up was carried out by column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether) to afford 6-phenylhexanal **2.191**[210] as a colourless liquid (9.7 mg, 19 %); ν_{max} (NaCl)/cm^{-1} 2944 (C-H), 2863 (C-H), 2726 (CO-H), 1723 (C=O), 1605 (Ar), 1482 (C-H); δ_H ($CDCl_3$) 1.43-1.51 (2H, m, $CH_2CH_2CH_2$), 1.70-1.79 (4H, m, $CH_2CH_2CH_2$), 2.51 (2H, td, *J* 7.3, 1.8, CH_2COH), 2.71 (2H, t, *J* 7.7, CH_2Ph), 7.25-7.29 (3H, m, Ar*H*), 7.35-7.39 (2H, m, Ar*H*), 9.85 (1H, t, *J* 1.8, CO*H*); δ_C ($CDCl_3$) 22.1 (CH_2), 29.0 (CH_2), 31.4 (CH_2), 35.9 (CH_2), 44.0 (CH_2), 125.9 (CH), 128.5 (CH), 128.6 (CH), 142.6 (C), 202.9 (CO*H*); *m/z* (EI) 176 (M^+, 17 %), 158 (13), 143 (18), 130 (31), 98 (40), 91 (100), 65 (22).

(iii)

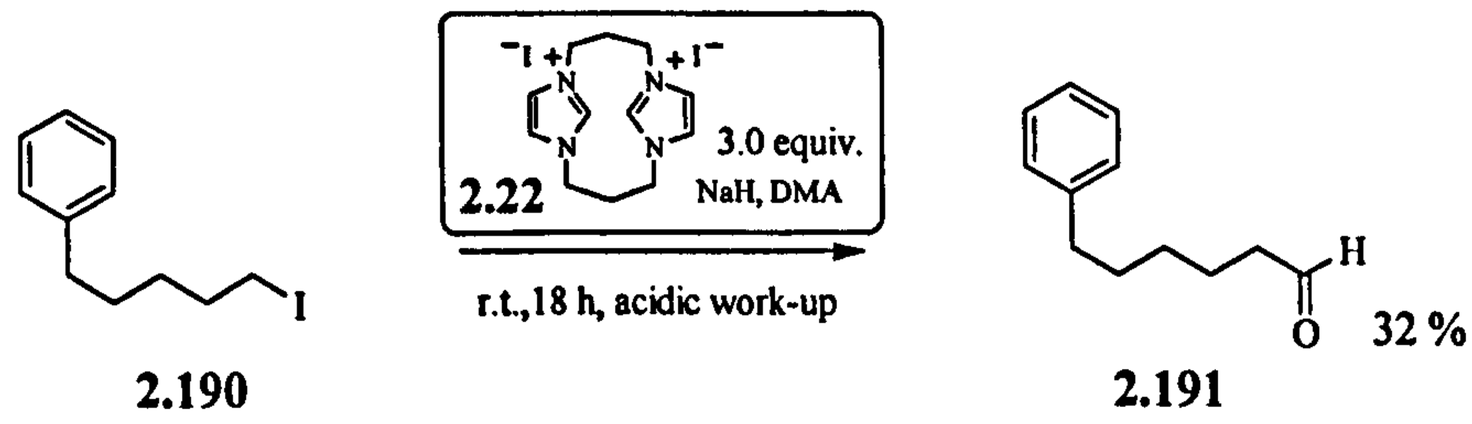


2.190 **2.191**

100 % in ^{1}H-NMR spectrum of crude mixture; 50 % isolated yield.

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMF (15 ml), salt **2.22** (850 mg, 1.8 mmol, 6.0 equiv.), 5-iodopentylbenzene **2.190** (81.0 mg, 0.295 mmol, 1.0 equiv.). ^{1}H-NMR analysis of the crude mixture after acidic work-up showed 6-phenylhexanal **2.191** as the exclusive product. The purification of the crude mixture after *acidic* work-up was carried out by column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether) to afford 6-phenylhexanal **2.191**[210] as a colourless liquid (9.7 mg, 19 %); for data see (ii) above.

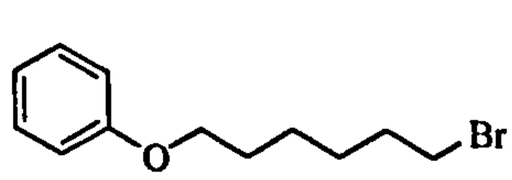
(iv)



2.190 **2.191**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMA (15 ml), salt **2.22** (425 mg, 0.9 mmol, 3.0 equiv.), 5-iodopentylbenzene **2.190** (80.0 mg, 0.292 mmol, 1.0 equiv.). The purification of the crude mixture after *acidic* work-up was carried out by column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether) to afford 6-phenylhexanal **2.191**[210] as a colourless liquid (16.5 mg, 32 %); for data see experiment (ii) above.

6-Bromohexyloxybenzene 2.193[174]



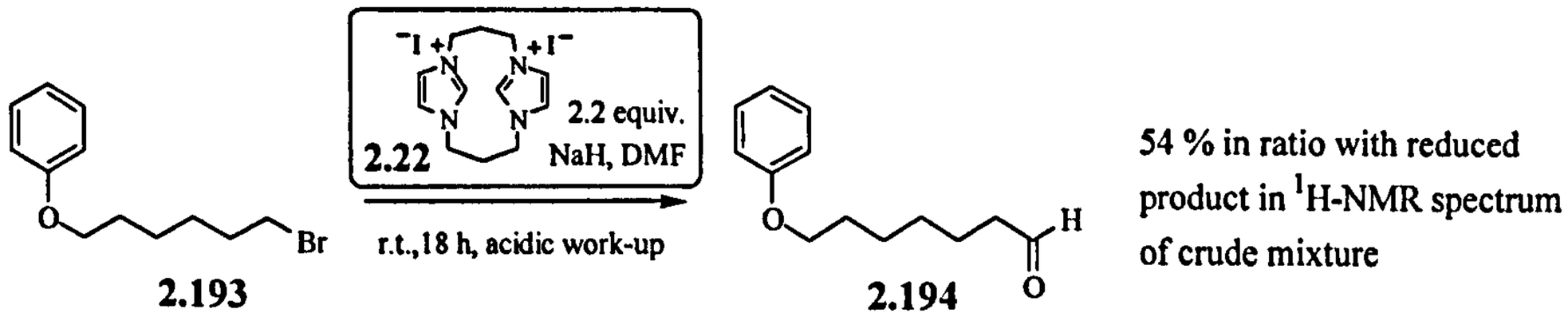
2.193

6-Bromohexan-1-ol (0.38 ml, 2.93 mmol, 1.0 equiv.), phenol (275 mg, 2.93 mmol, 1.0 equiv.) and triphenylphosphine (767 mg, 2.93 mmol, 1.0 equiv.) were dissolved in

tetrahydrofuran (5 ml) under argon and cooled to 0°C. DIAD (0.62 ml, 3.22 mmol, 1.1 equiv.) was then added dropwise and the reaction mixture was stirred at room temperature overnight. The mixture was then concentrated under reduced pressure, loaded onto silica and purified by column chromatography (2:98, then 5:95 ethyl acetate/ petroleum ether) to afford 6-bromohexyloxybenzene **2.193**[211] as a colourless liquid (660 mg, 88 %); (Found: M^+ 256.0455. $C_{12}H_{17}BrO$ requires M^+, 256.0457); ν_{max} (NaCl)/cm^{-1} 3039 (Ar-H), 2938 (C-H), 2861 (C-H), 1600 (Ar), 1497 (C-H); δ_H ($CDCl_3$) 1.51-1.54 (4H, m, $CH_2CH_2CH_2$), 1.80-1.83 (2H, m, $CH_2CH_2CH_2$), 1.88-1.93 (2H, m, $CH_2CH_2CH_2$), 3.44 (2H, t, *J* 6.8, CH_2Br), 3.97 (2H, t, *J* 6.4, CH_2OPh), 6.89-6.96 (3H, m, Ar*H*), 7.28-7.31 (2H, m, Ar*H*); δ_C ($CDCl_3$) 25.4 (CH_2), 28.0 (CH_2), 29.2 (CH_2), 32.8 (CH_2), 33.8 (CH_2), 67.6 (CH_2), 114.5 (CH), 120.6 (CH), 129.5 (CH), 159.1 (C); *m/z* (EI) 258 (M^+, 4 % ^{81}Br), 256 (M^+, 4 % ^{79}Br), 107 (5), 94 (100), 77 (18), 65 (22), 55 (24).

Test reactions with 6-bromohexyloxybenzene 2.193

(i)

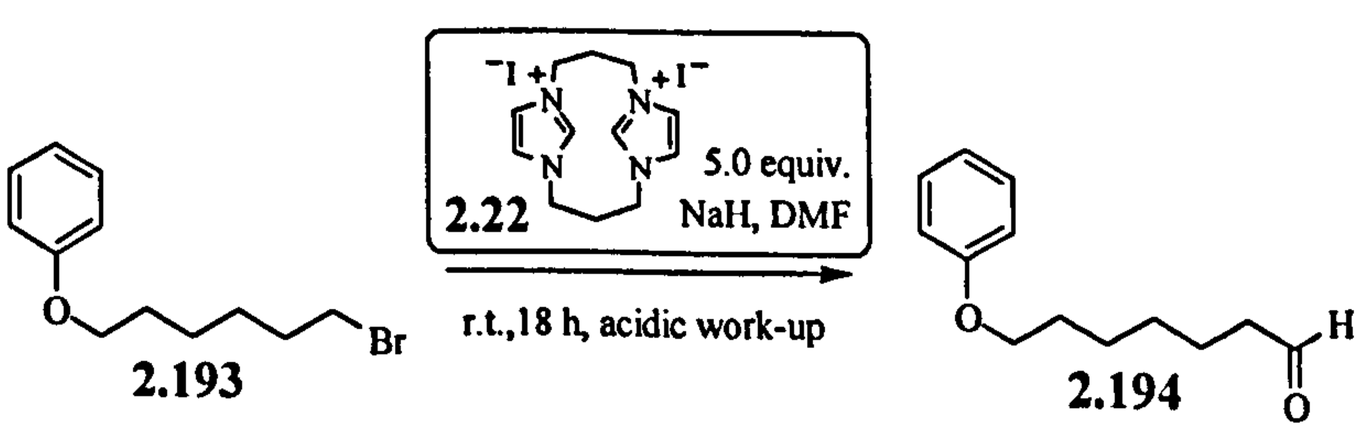


2.193 **2.194**

54 % in ratio with reduced product in ^{1}H-NMR spectrum of crude mixture

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMF (15 ml), salt **2.22** (223 mg, 0.473 mmol, 2.2 equiv.), 6-bromohexyloxybenzene **2.193** (55.4 mg, 0.215 mmol, 1.0 equiv.). ^{1}H-NMR analysis of the crude mixture after *acidic* work-up was carried out and *7-phenoxyheptanal* **2.194** was seen in 54 % ratio with presumably hexyloxybenzene; for data see below in (ii).

(ii)

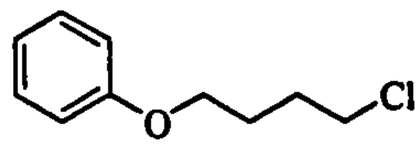


2.193 **2.194**

90 % in ratio with reduced product in ^{1}H-NMR of crude mixture; 61 % isolated yield

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMF (15 ml), salt **2.22** (708 mg, 1.5 mmol, 5.0 equiv.), 6-bromohexyloxybenzene **2.193** (74.3 mg, 0.289 mmol, 1.0 equiv.). ^{1}H-NMR analysis of the crude mixture after *acidic* work-up showed 7-phenoxyheptanal **2.194** in 90% ratio. The purification of the crude mixture was carried out by column chromatography on silica gel (10:90 ethyl acetate/ petroleum ether) to afford *7-phenoxyheptanal* **2.194** as a colourless liquid (30.4 mg, 61 %); (Found: M^+ 206.1299. $C_{13}H_{18}O_2$ requires M^+, 224.1645); ν_{max} (NaCl)/cm^{-1} 2938 (C-H), 2861 (C-H), 2722 (CO-H), 1724 (C=O), 1601 (Ar), 1497 (C-H); δ_H ($CDCl_3$) 1.39-1.44 (2H, m, $CH_2CH_2CH_2$), 1.46-1.55 (2H, m, $CH_2CH_2CH_2$), 1.65-1.72 (2H, m, $CH_2CH_2CH_2$), 1.77-1.84 (2H, m, $CH_2CH_2CH_2$), 2.46 (2H, td, *J* 7.3, 1.8, CH_2COH), 3.97 (2H, t, *J* 6.4, CH_2O), 6.89-6.97 (3H, m, Ar*H*), 7.26-7.32 (2H, m, Ar*H*), 9.79 (1H, t, *J* 1.8, CO*H*); δ_C ($CDCl_3$) 22.2 (CH_2), 26.1 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 44.0 (CH_2), 67.9 (CH_2), 114.7 (CH), 120.8 (CH), 129.6 (CH), 159.3 (C), 202.9 (CH); *m/z* (EI) 206 (M^+, 8 %), 94 (100), 77 (13), 55 (22), 41 (37).

4-Chlorobutoxybenzene 2.194[174]

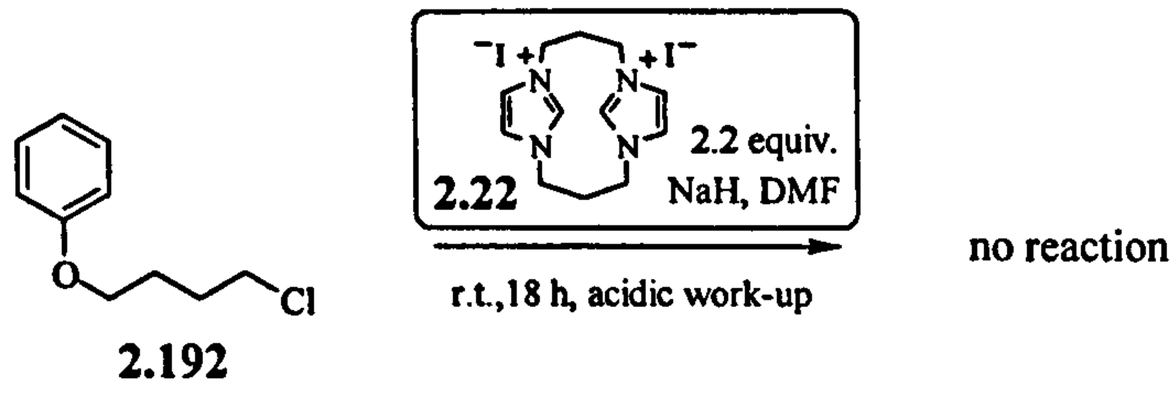


2.194

4-Chlorobutan-1-ol (1.06 ml, 10.6 mmol, 1.0 equiv.), phenol (1 g, 10.6 mmol, 1.0 equiv.) and triphenylphosphine (2.79 g, 10.6 mmol, 1.0 equiv.) were dissolved in tetrahydrofuran (20 ml) under argon and cooled to 0°C. DIAD (2.47 ml, 10.6 mmol, 1.2 equiv.) was then added dropwise and the reaction mixture was stirred at room temperature overnight. The mixture was then concentrated under reduced pressure and loaded onto silica. Purification was carried out by column chromatography (1:99 ethyl acetate/ petroleum ether) to give 4-chlorobutoxy-benzene as a colourless liquid **2.194**[212] (1.79 g, 92 %); (Found: M^+ 184.0650. $C_{10}H_{13}ClO$ requires M^+, 184.0649); ν_{max} (NaCl)/cm^{-1} 3063 (Ar-H), 3040 (Ar-H), 2956 (C-H), 2873 (C-H), 1600 (Ar), 1497 (C-H); δ_H ($CDCl_3$) 1.92-2.04 (4H, m, $CH_2CH_2CH_2$), 3.64 (2H, t, *J* 6.3, CH_2Cl), 4.02 (2H, t, *J* 5.8, CH_2OPh), 6.87-6.97 (3H, m, Ar*H*), 7.27-7.32 (2H, m, Ar*H*); δ_C ($CDCl_3$) 26.9 (CH_2), 29.6 (CH_2), 45.0 (CH_2); 67.1 (CH_2), 114.7 (CH), 121.0 (CH), 129.7 (CH), 159.1 (C); *m/z* (EI) 186 (M^+, 4 %, ^{37}Cl), 184 (M^+, 12 %, ^{35}Cl), 94 (100), 77 (18), 65 (27), 55 (33).

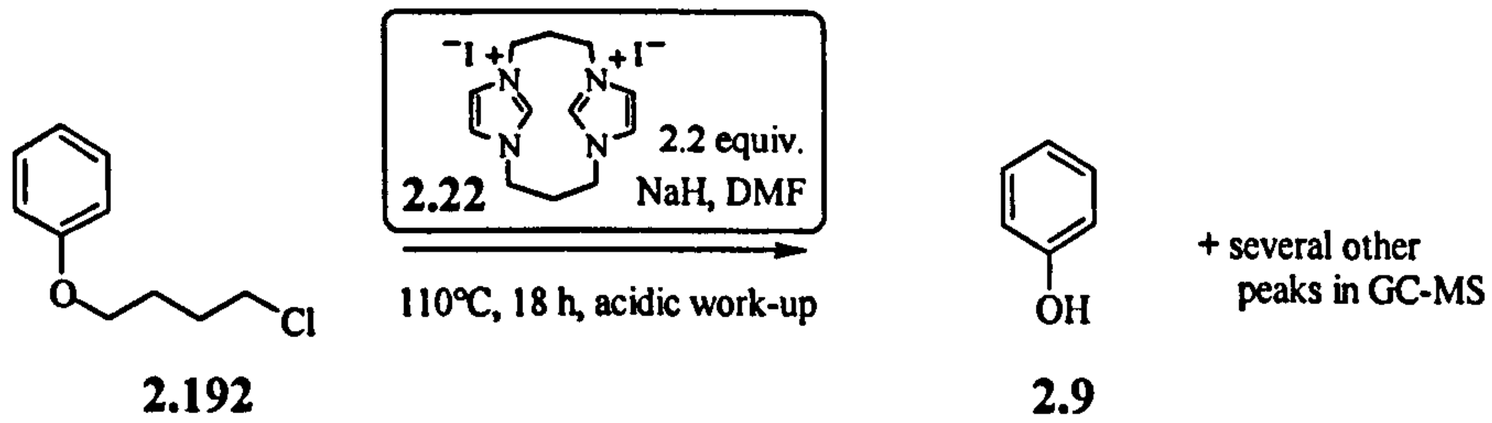
Test reactions on 4-chlorobutoxybenzene 2.192

(i)



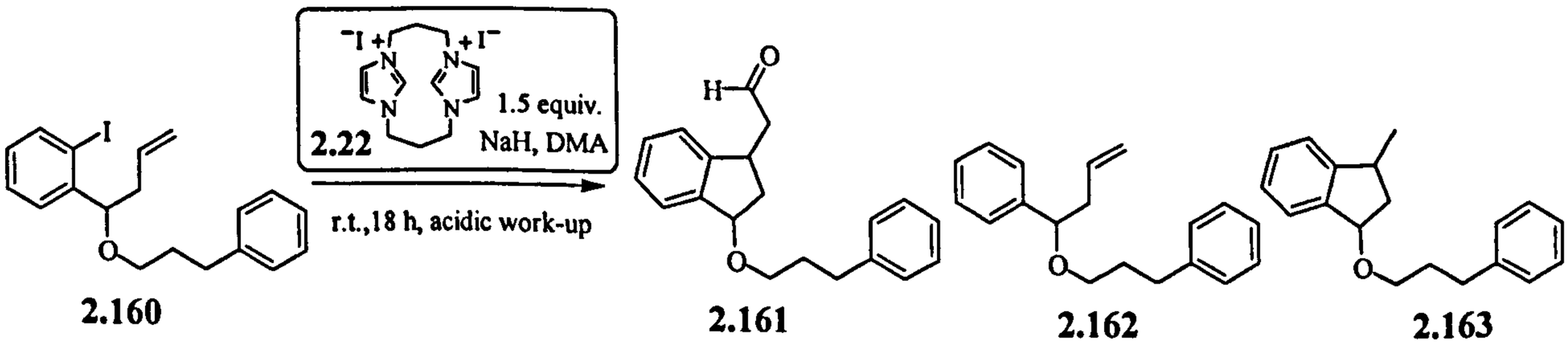
The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMF (15 ml), salt **2.22** (312 mg, 0.66 mmol, 2.2 equiv.), 4-chlorobutoxybenzene **2.192** (55 mg, 0.3 mmol, 1.0 equiv.). *Observation:* Upon addition of the yellow donor, the colour did not change; overnight the colour changed to red-orange. The purification of the crude mixture after *acidic* work-up was carried out by column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether) to afford starting material **2.192** only (54 mg, 98 %) .

(ii)



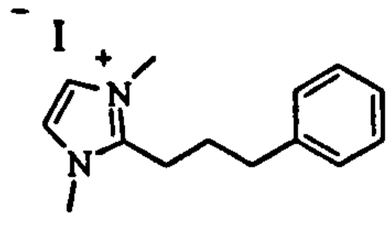
The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (283 mg, 0.66 mmol, 2.2 equiv.), 4-chlorobutoxy benzene **2.192** (55.4 mg, 0.3 mmol, 1.0 equiv.). *Observation:* Upon addition of the yellow donor, no colour change took place; upon heating overnight colour changed to red-brown. *Acidic* work-up was carried out and the crude mixture was analysed by GC-MS analysis. Among several unidentified compounds, phenol **2.9**[176] was observed; *m/z* (EI) 94 (M^+, 100 %), 66 (29).

Test reaction on 1-iodo-2-[1-(3-phenylpropoxy)but-3-enyl]benzene 2.160



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMA (15 ml), salt **2.22** (708 mg, 1.5 mmol, 5.0 equiv.), 1-iodo-2-[1-(3-phenylpropoxy)but-3-enyl]benzene **2.160** (74.3 mg, 0.289 mmol, 1.0 equiv.). ^{1}H-NMR analysis of the crude mixture of after *acidic* work-up showed [3-(3-phenylpropyloxy)indan-1-yl]acetaldehyde **2.161**,[203] 1-methyl-3-(3-phenyl-propyloxy)indane **2.163**[161] and [1-(3-phenylpropyloxy)but-3-enyl]benzene **2.162**.[203] The compounds were identified by comparison of the ^{1}H-NMR spectrum of the crude mixture with the ^{1}H-NMR of the isolated and within the group fully characterised compounds.[203]

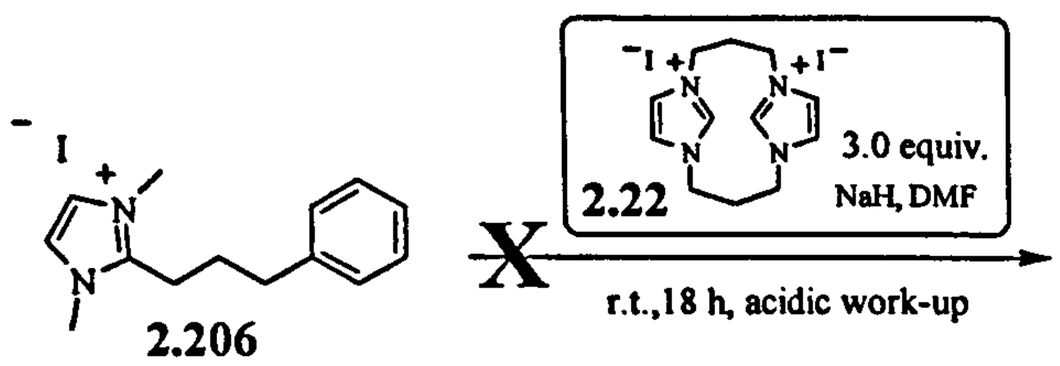
1,3-Dimethyl-2-(3-phenyl-propyl)-1*H*-imidazolium salt iodide 2.206



2.206

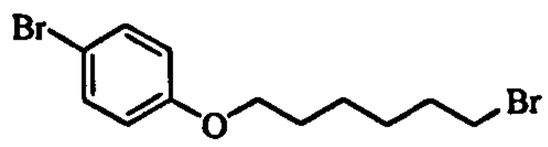
Sodium hydride was washed with hexane (2 x 20 ml) and was subsequently dried under argon. To this was added a solution of 1,3-dimethyl-1*H*-imidazolium salt iodide **2.128** (0.5 g, 2.23 mmol, 1.0 equiv.) in THF (25 ml, degassed beforehand for 30 min) *via* cannula. After stirring for 4 h at room temperature centrifugation of the mixture was carried out, and the supernatant liquid was transferred *via* cannula to (3-iodopropyl)benzene **2.207** (0.6 g, 2.45 mmol, 1.1 equiv.) while cooling to 0°C. The resulting mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was washed with diethyl ether to give *1,3-dimethyl-2-(3-phenylpropyl)-1H-imidazolium salt iodide* **2.206** as a yellow solid (750 mg, 98 %); mp 136-139°C; (Found: $[M\text{-}I]^+$ 215.1455. $C_{14}H_{19}N_2I$ requires $[M\text{-}I]^+$, 215.1543); ν_{max} (KBr)/cm^{-1} 3073 (Ar-H), 2923 (C-H), 1633 (Ar), 1445 (C-H); δ_H (DMSO) 1.87-1.91 (2H, m, $CH_2CH_2CH_2$), 2.69 (2H, t, *J* 7.7, CH_2Ph), 3.00 (2H, t, *J* 7.9, $NCCH_2$), 3.75 (6H, s, 2 x NCH_3), 7.19-7.31 (5H, m, Ar*H*), 7.58 (2H, s, Ar*H*); δ_C (DMSO) 22.0 (CH_2), 26.9 (CH_2), 34.2 (CH_2), 34.6 (CH_3), 122.3 (CH), 126.1 (CH), 128.2 (CH), 128.4 (CH), 140.7 (C), 146.6 (C); *m/z* (ES+) 215 ($[M\text{-}I]^+$, 100 %), 97 (2).

Attempted aldehyde formation with 1,3-dimethyl-2-(3-phenyl-propyl)-1*H*-imidazolium salt iodide 2.206



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMF (15 ml), salt **2.22** (428 mg, 0.9 mmol, 3.0 equiv.), 1,3-dimethyl-2-(3-phenyl-propyl)-1*H*-imidazolium salt iodide **2.206** (102 mg, 0.3 mmol, 1.0 equiv.). *Acidic* work-up was carried out and analysis of the crude mixture by ^{1}H-NMR spectroscopy did not show an aldehyde.

1-Bromo-4-(6-bromohexyloxy)benzene 2.213[174]

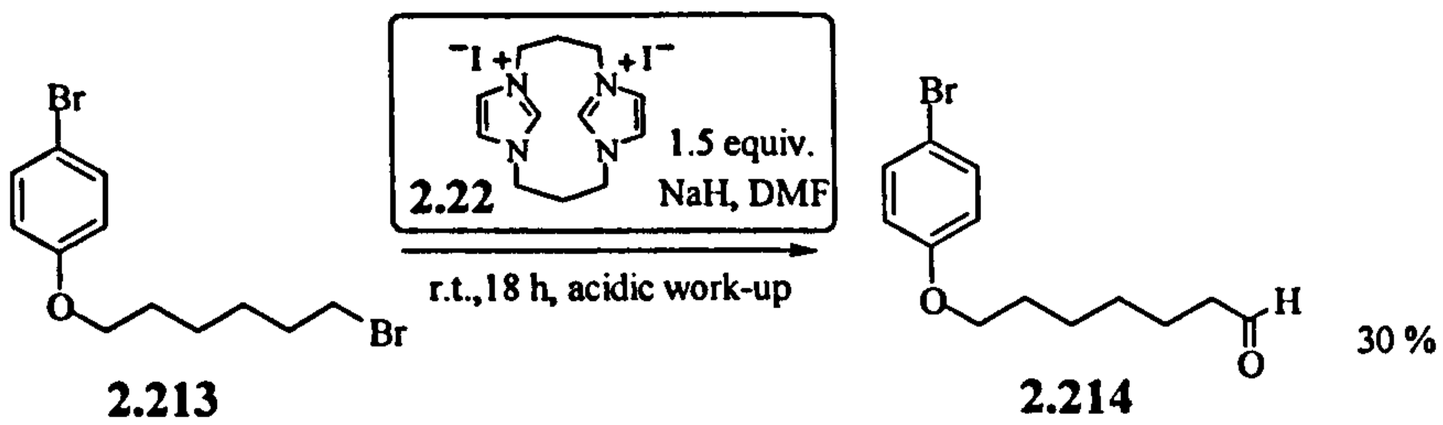


2.213

6-Bromohexan-1-ol (0.76 ml, 5.78 mmol, 1.0 equiv.), 4-bromophenol (1.0 g, 5.78 mmol, 1.0 equiv.) and triphenylphosphine (1.52 g, 5.78 mmol, 1.0 equiv.) were dissolved in THF (25 ml) under argon and cooled to 0°C. DIAD (1.24 ml, 6.35 mmol, 1.1 equiv.) was then added dropwise and the reaction mixture was stirred at room temperature overnight. The mixture was then concentrated under reduced pressure, loaded onto silica and purified by column chromatography (2:98 ethyl acetate/ petroleum ether) to afford 1-bromo-4-(6-bromohexyloxy)benzene **2.213**[213] as a white solid (1.14 g, 89 %); mp 37-38°C (lit.[213] 41-42°C); (Found: M^+ 333.9557. $C_{12}H_{16}Br_2O$ requires M^+, 333.9562); ν_{max} (KBr)/cm^{-1} 2943 (C-H), 2868 (C-H), 1676 (Ar), 1489 (C-H); δ_H ($CDCl_3$) 1.45-1.51 (4H, m, CH_2), 1.80 (2H, quintet, *J* 6.8, $CH_2CH_2CH_2$), 1.91 (2H, quintet, *J* 6.8, $CH_2CH_2CH_2$), 3.43 (2H, t, *J* 6.8, CH_2Br), 3.93 (2H, t, *J* 6.4, CH_2O), 6.78 (2H, d, *J* 8.9, Ar*H*), 7.37 (2H, d, *J* 8.9, Ar*H*); δ_C ($CDCl_3$) 25.5 (CH_2), 28.1 (CH_2), 29.2 (CH_2), 32.9 (CH_2), 33.9 (CH_2), 68.2 (CH_2), 112.9 (C), 116.5 (CH), 132.5 (CH); 158.4 (C); *m/z* (EI) 338 (M^+, 3 % ^{81}Br ^{81}Br), 336 (M^+, 6 % ^{81}Br ^{79}Br), 334 (M^+, 3 % ^{79}Br ^{79}Br), 174 (32), 172 (38), 143 (18), 55 (45), 41 (100).

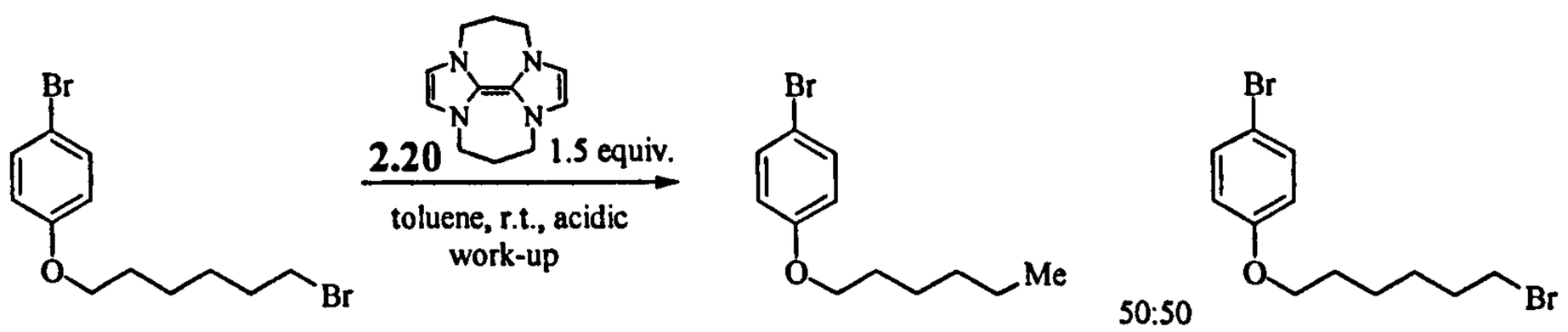
Selectivity test reactions on 1-bromo-4-(6-bromohexyloxy)benzene 2.213

(i)



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMF (15 ml), salt **2.22** (212 mg, 0.45 mmol, 1.5 equiv.), 1-bromo-4-(6-bromohexyloxy)benzene **2.213** (101 mg, 0.3 mmol, 1.0 equiv.). The purification of the crude mixture after *acidic* work-up was carried out by column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether) to afford *7-(4-bromophenoxy)heptanal* **2.214** as a colourless liquid (25 mg, 30 %); (Found: M^+: 284.0411. $C_{13}H_{17}BrO_2$ requires M^+, 284.0406); ν_{max} (NaCl)/cm^{-1} 2937 (C-H), 2863 (C-H), 2714 (CO-H), 1724 (C=O), 1489 (C-H); δ_H ($CDCl_3$) 1.37 (4H, m, $CH_2CH_2CH_2$), 1.47-1.53 (2H, m, $CH_2CH_2CH_2$), 1.75-1.82 (2H, m, $CH_2CH_2CH_2$), 2.46 (2H, dt, *J* 7.3, 1.7, CH_2COH), 3.92 (2H, t, *J* 6.4, OCH_2), 6.77 (2H, d, *J* 8.9, Ar*H*), 7.37 (2H, d, *J* 8.9, Ar*H*); δ_C ($CDCl_3$) 22.2 (CH_2), 26.1 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 44.0 (CH_2), 68.3 (CH_2), 112.9 (C), 116.5 (CH), 132.5 (CH), 158.4 (C), 202.8 (COH); *m/z* (EI) 286 (M^+, 5 % ^{81}Br), 284 (M^+, 5 % ^{79}Br), 174 (100, ^{81}Br), 172 (100, ^{79}Br), 95 (27), 69 (28), 55 (44), 41 (88).

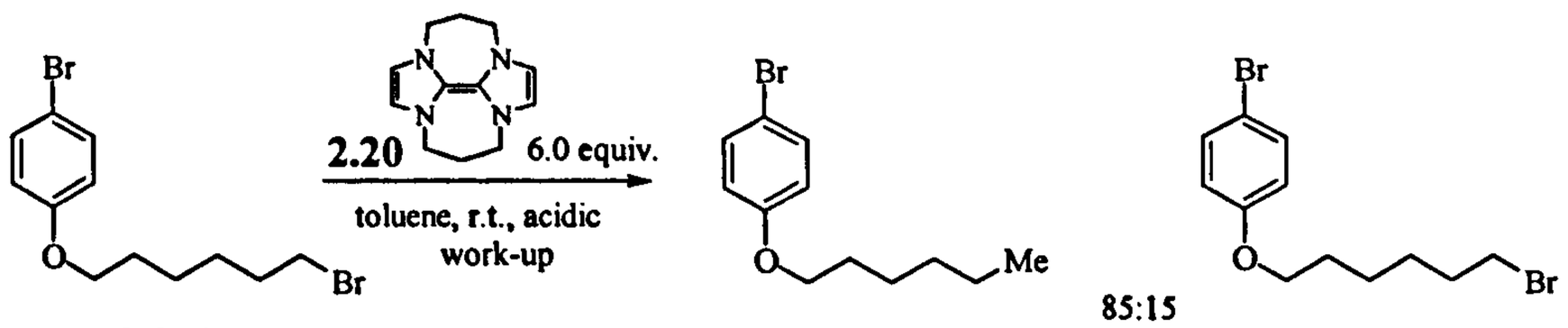
(ii)



The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, toluene (15 ml), pure donor **2.20** (97 mg, 0.45 mmol, 1.5 equiv.), 1-bromo-4-(6-bromohexyloxy)benzene **2.213** (101 mg, 0.3 mmol, 1.0 equiv.). Toluene was deoxygenated with argon prior to use. *Observation:* The colour changed from yellow to slightly orange overnight and a precipitate formed. ^{1}H-NMR spectrum of the crude mixture after *acidic* work-up showed a 50:50 mixture of 1-

bromo-4-hexyloxybenzene **2.215** and starting material **2.213** as judged by comparison of ^{1}H-NMR spectrum with that of authentic compounds; for data see (iv) below.

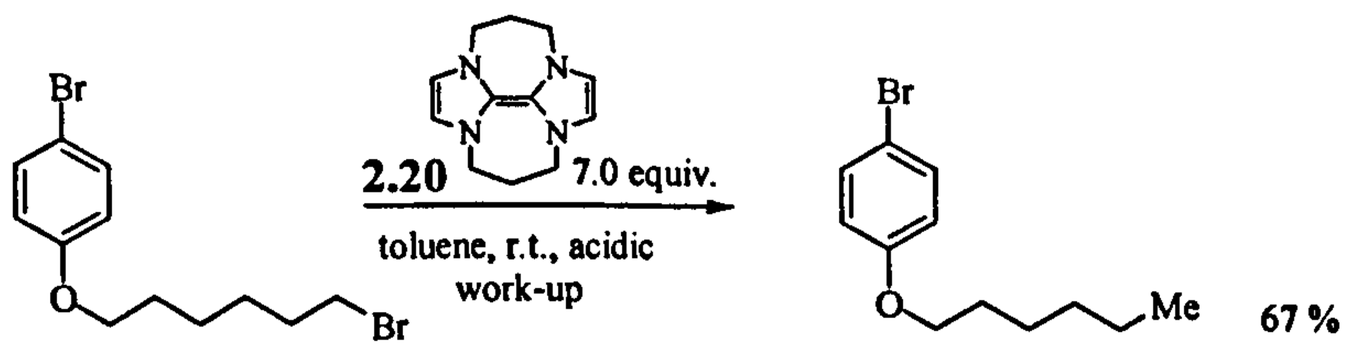
(iii)



2.213 **2.215** **2.213**

The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, toluene (15 ml), donor **2.20** (389 mg, 0.1.8 mmol, 6.0 equiv.), 1-bromo-4-(6-bromohexyloxy)benzene **2.213** (102 mg, 0.303 mmol, 1.0 equiv.). Toluene was deoxygenated with argon prior to usage. *Observation:* The colour changed from yellow to slightly orange overnight and a precipitate formed. ^{1}H-NMR spectrum of the crude mixture after *acidic* work-up showed a 85:15 mixture of 1-bromo-4-hexyloxybenzene **2.2215** and starting material **2.213** as judged by comparison of ^{1}H-NMR with that of authentic compounds; for data see (iv) below.

(iv)

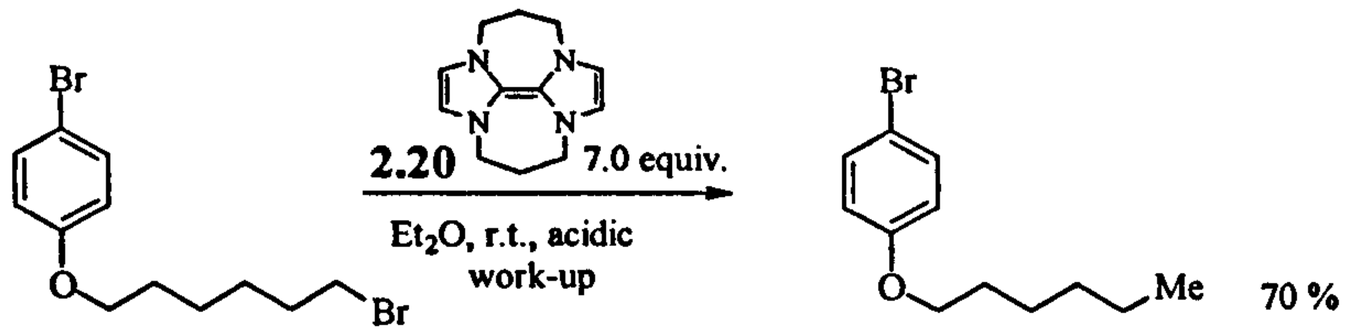


2.213 **2.215**

The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, toluene (15 ml), donor **2.20** (441 mg, 2.04 mmol, 7.0 equiv.), 1-bromo-4-(6-bromohexyloxy)benzene **2.213** (98 mg, 0.291 mmol, 1.0 equiv.). Toluene was deoxygenated with argon prior to usage. *Observation:* The colour changed from yellow to orange overnight and a precipitate formed. ^{1}H-NMR spectrum of the crude mixture after *acidic* work-up showed 1-bromo-4-hexyloxybenzene **2.215** as the sole product. The purification of the crude mixture was carried out by column chromatography on silica gel (2:98 ethyl acetate/ petroleum ether) to afford 1-bromo-4-(6-bromohexyloxy)benzene **2.215**[214] as a colourless liquid (50 mg, 67 %); (Found: M^+ 256.0456. $C_{12}H_{17}BrO$ requires M^+, 256.0457); ν_{max} (NaCl)/cm^{-1} 2929 (C-H), 2858 (C-H), 1591 (Ar), 1489 (C-H); δ_H ($CDCl_3$) 0.91-0.94 (3H, m, CH_3), 1.33-1.37 (4H, m,

$CH_2CH_2CH_2CH_3$), 1.46-1.49 (2H, m, $CH_2CH_2CH_2CH_3$), 1.74-1.81 (2H, m, $ArOCH_2CH_2$), 3.93 (2H, t, *J* 3.2, $ArOCH_2$), 6.78 (2H, d, *J* 8.9, Ar*H*), 7.37 (2H, d, *J* 8.9, Ar*H*); δ_C ($CDCl_3$) 14.6 (CH_3), 23.1 (CH_2), 26.2 (CH_2), 29.7 (CH_2), 32.1 (CH_2), 68.8 (CH_2), 113.1 (C), 116.9 (CH), 132.7 (CH), 158.2 (C); *m/z* (EI) 258 (M^+, 8 % ^{81}Br), 256 (M^+, 8 % ^{79}Br), 172 (98), 105 (18), 55 (70), 43 (100).

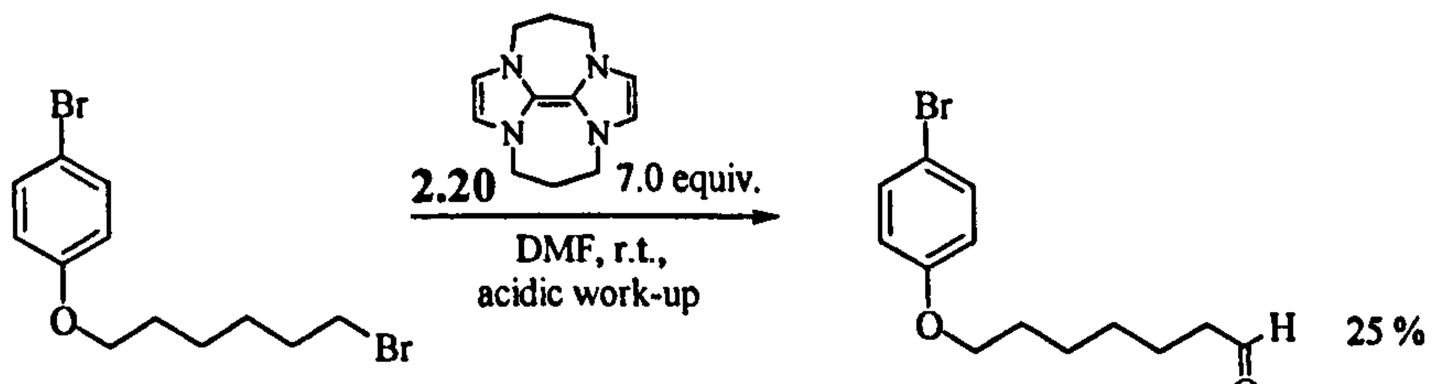
(v)



2.213 **2.215**

The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, toluene (15 ml), donor **2.20** (239 mg, 1.1 mmol, 7.0 equiv.), 1-bromo-4-(6-bromo-hexyloxy)-benzene **2.213** (53 mg, 0.158 mmol, 1.0 equiv.). Diethyl ether was deoxygenated with argon prior to usage. *Observation:* The colour changed from yellow to orange overnight and a precipitate formed. The purification of the crude mixture after acidic work-up was carried out by column chromatography on silica gel (2:98 ethyl acetate/ petroleum ether) to afford 1-bromo-4-(6-bromohexyloxy)benzene **2.215**[214] as a colourless liquid (28 mg, 70 %); for data see (iv) above.

(vi)

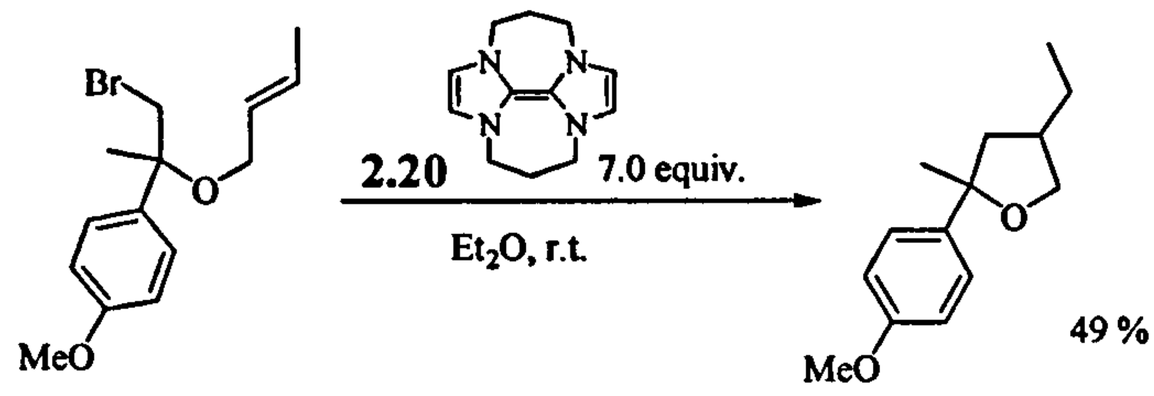


2.213 **2.214**

The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, DMF (15 ml), donor **2.20** (445 mg, 2.06 mmol, 7.0 equiv.), 1-bromo-4-(6-bromohexyloxy)benzene **2.213** (99 mg, 0.295 mmol, 1.0 equiv.). *Observation:* An orange-red solution formed overnight. The purification of the crude mixture after *acidic* work-up was carried out by column chromatography on silica

gel (10:90 ethyl acetate/ petroleum ether) to afford *7-(4-bromophenoxy)heptanal* **2.214** as a colourless liquid (21.4 mg, 25 %); see (i) above for data.

Test reaction with 1-(2-bromo-1-but-2-enyloxy-1-methyl-ethyl)-4-methoxybenzene 2.216

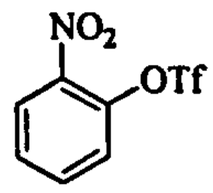


2.216 **2.217**

The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: Room temperature, 18 h, diethyl ether (8 ml), donor **2.20** (253 mg, 1.16 mmol, 7.0 equiv.), 1-(2-bromo-1-but-2-enyloxy-1-methyl-ethyl)-4-methoxybenzene **2.216** (50 mg, 0.167 mmol, 1.0 equiv.). *Observation:* Upon addition of yellow donor solution, colour changed to orange-red. The purification of the crude mixture after *acidic* work-up was carried out by column chromatography on silica gel (5:95 ethyl acetate/ petroleum ether) to afford *4-ethyl-2-(4-methoxyphenyl)-2-methyltetrahydrofuran* **2.217** as a colourless liquid (14 mg, 38 %) as a mixture of diastereomers; (Found: $[M+H]^+$ 221.1534. $C_{14}H_{20}O_2$ requires $[M+H]$, 221.1536); ν_{max} (NaCl)/cm^{-1} 2963 (C-H), 2926 (C-H), 2835 (C-H), 1509 (Ar), 1246 (C-H); δ_H ($CDCl_3$) 0.76-0.82 (3H, m, CH_2CH_3), 1.21-1.27 and 1.30-1.36 (2H, 2 x m, CH_2CH_3), 1.45 and 1.39 (3H, 2 x s, CCH_3), 1.51-1.55 and 1.65-1.70 (1H, 2 x m, $CHCH_2CH_3$), 1.91-1.99 and 2.18-2.50 (1H, 2 x m, CCH_2CH), 2.27-2.34 (1H, m, CCH_2CH), 3.38 and 3.49 (1H, t, *J* 8.4 and 8.3, OCH_2), 3.72 (3H, s, CH_3OAr), 3.97 and 4.07 (1H, t, *J* 8.0 and 7.7, OCH_2), 6.78 (2H, d, *J* 8.5, Ar*H*), 7.23 (2H, m, Ar*H*); δ_C ($CDCl_3$) 13.3 (CH_3), 13.3 (CH_3), 26.3 (CH_2), 26.7 (CH_2), 30.8 (CH), 30.9 (CH), 41.4 (CH_3), 42.4 (CH_3), 46.6 (CH_2), 46.8 (CH_2), 55.7 (CH_3), 73.2 (CH_2), 73.6 (CH_2), 84.4 (C), 84.6 (C), 113.8 (CH), 113.9 (CH), 126.1 (CH), 126.1 (CH), 140.5 (C), 141.9 (C), 158.3 (C); *m/z* (EI) 220 (M^+, 8 %), 205 (95), 135 (100), 91 (23), 77 (30), 55 (27).

8.5 Experiments from chapter 5: *Sulfones and Sulfonamides*

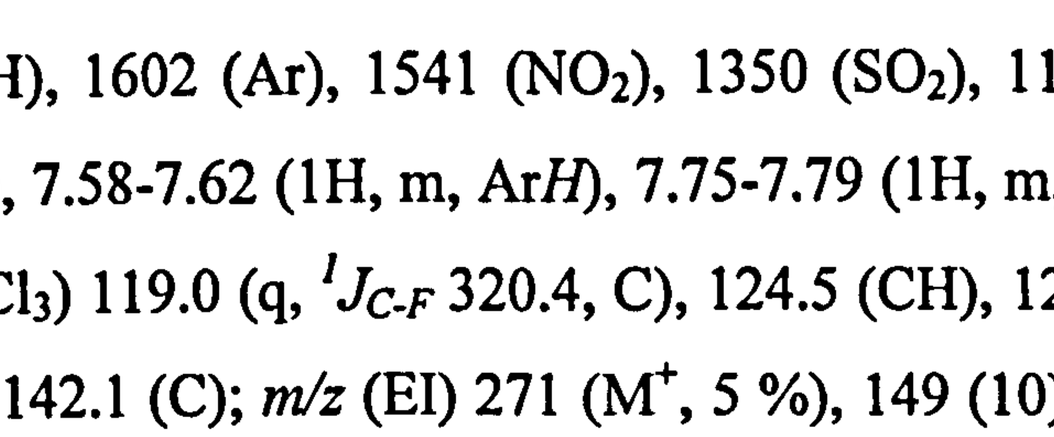
Trifluoromethanesulfonic acid 2-nitrophenyl ester 2.219[215]



2.219

2-Nitrophenol (1.00g, 7.186 mmol, 1.0 equiv.) and triethylamine (4.04 ml, 28.744 mmol, 4.0 equiv.) were dissolved in DCM (15 ml) and cooled to 0°C. Trifluoromethanesulfonic anhydride (2.418 ml, 14.372 mmol, 2.0 equiv.) was then added dropwise and the reaction mixture was allowed to warm to room temperature. After stirring for 18 h at room temperature the mixture was poured into DCM (50 ml) and water (50 ml). The water layer was acidified with 2 N hydrochloric acid and extracted with DCM (3 x 50 ml). The combined organic phase was washed further with 2 N hydrochloric acid and water (2 x 50 ml) and brine (50 ml), was dried over sodium sulfate, evaporated and the residue purified by column chromatography (40:60 DCM/ petroleum ether) to afford trifluoromethanesulfonic acid 2-nitrophenyl ester **2.219**[216] as a yellow liquid (1.46 g, 75 %); (Found: $[M+NH_4]^+$ 289.0102. $C_7H_4F_3O_5NS$ requires $[M+NH_4]$, 289.0101); ν_{max} (NaCl)/cm^{-1} 3110 (Ar-H), 1602 (Ar), 1541 (NO_2), 1350 (SO_2), 1136 (SO_2); δ_H ($CDCl_3$) 7.48-7.50 (1H, m, Ar*H*), 7.58-7.62 (1H, m, Ar*H*), 7.75-7.79 (1H, m, Ar*H*), 8.19 (1H, dd, *J* 8.2, 1.7, Ar*H*); δ_C ($CDCl_3$) 119.0 (q, $^1J_{C-F}$ 320.4, C), 124.5 (CH), 127.0 (CH), 129.9 (CH), 136.1 (CH), 141.8 (C), 142.1 (C); *m/z* (EI) 271 (M^+, 5 %), 149 (10), 122 (12), 95 (26), 69 (100).

Attempted reduction of trifluoro-methanesulfonic acid 2-nitrophenyl ester 2.219

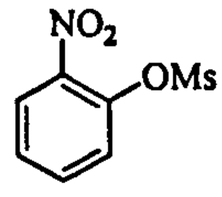


2.219 **2.218**

Salt **1.179** (360 mg, 0.64 mmol, 1.2 equiv.) was dissolved in toluene (10 ml) and DMF (5 ml) and purged with argon for 30 min. KHMDS (2.57 ml, 1.28 mmol, 2.4 equiv., c = 0.5 mol/l) was added dropwise and the reaction mixture was stirred for 1h at room temperature. A purged solution of **2.219** (146.3 mg, 0.54 mmol, 1.0 equiv.) in toluene (5

ml) was then added and the reaction mixture was refluxed for 18 h. The mixture was poured into water (50 ml) and diethyl ether (50 ml). The aqueous phase was acidified and extracted with diethyl ether (2 x 50 ml). Then the organic phases were combined and washed with dilute hydrochloric acid (3 x 50 ml), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (10:90 ethyl acetate/ petroleum ether) to afford 2-nitrophenol **2.218** as a yellow solid (53 mg, 71 %), mp 93-95°C (lit.[218] 102°C); ν_{max} (NaCl)/cm^{-1} 3400 (O-H), 1614 (Ar), 1531 (NO_2), 1374 (NO_2); δ_H ($CDCl_3$) 6.93-7.02 (1H, m, Ar*H*), 7.17 (1H, dd, *J* 8.5, 1.6, Ar*H*), 7.57-7.61 (1H, m, Ar*H*), 8.11 (1H, dd, *J* 8.5, 1.6, Ar*H*); δ_C ($CDCl_3$) 120.2 (CH), 120.4 (CH), 125.3 (CH), 137.6 (CH), 137.7 (C), 155.4 (C).

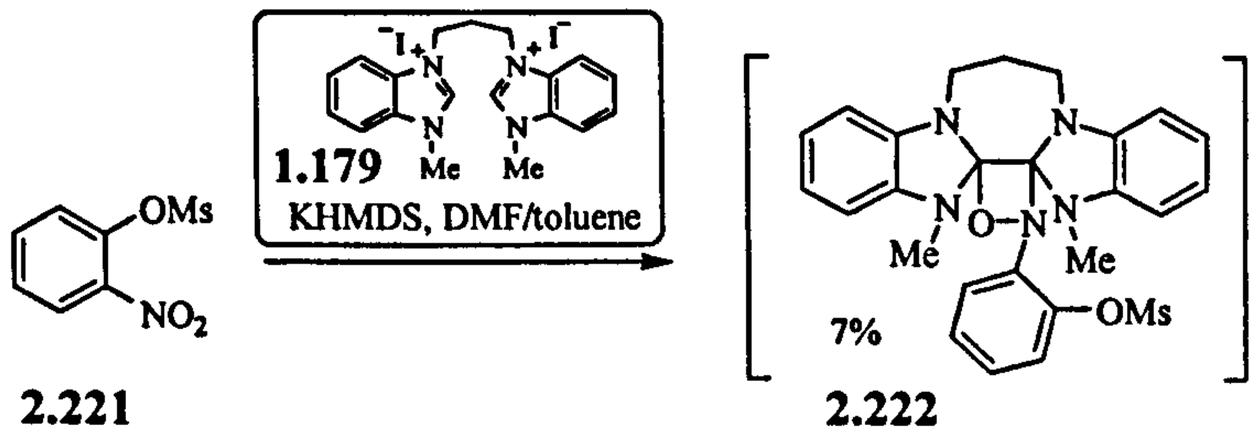
Methanesulfonic acid 2-nitrophenyl ester 2.221[217]



2.221

2-Nitrophenol (1.50 g, 10.78 mmol, 1.0 equiv.) and triethylamine (6.06 ml, 43.13 mmol, 4 equiv.) were dissolved in DCM (20 ml) and cooled to 0°C. Methanesulfonyl chloride (1.669 ml, 21.566 mmol, 2.0 equiv.) was then added dropwise and the reaction mixture was warmed to room temperature. After stirring for 2.5 h at room temperature, the mixture was poured into diethyl ether (50 ml) and water (50 ml). The water layer was acidified with 2 N hydrochloric acid and extracted with diethyl ether (3 x 50 ml). The combined organic phase was washed further with 2 N hydrochloric acid and water (2 x 50ml) and brine (50 ml), dried over sodium sulfate and evaporated. Further purification by column chromatography (30:70 ethyl acetate/ petroleum ether) gave *methanesulfonic acid 2-nitrophenyl ester* **2.221** as a yellow solid (1.85 g, 79 %), mp 83-84°C; (Found: $[M+NH_4]^+$ 235.0383. $C_7H_7O_5NS$ requires [*M+NH*$_4$], 235.0383); ν_{max} (NaCl)/cm^{-1} 3104 (Ar-H), 3030 (Ar-H), 2936 (C-H), 1522 (NO_2), 1365 (NO_2), 1350 (SO_2), 1142 (SO_2); δ_H ($CDCl_3$) 3.36 (3H, s, C*H*$_3$), 7.47-7.51 (1H, m, Ar*H*), 7.59 (1H, dd, *J* 8.3, 1.3, Ar*H*), 7.67-7.72 (1H, m, Ar*H*), 8.06 (1H, dd, *J* 8.2, 1.6, Ar*H*); δ_C ($CDCl_3$) 39.5 (CH_3), 125.8 (CH), 126.6 (CH), 128.3 (CH), 135.2 (CH), 141.5 (C), 142.8 (C); *m/z* (EI) 217 (M^+, 8 %), 139 (35), 79 (83), 63 (100).

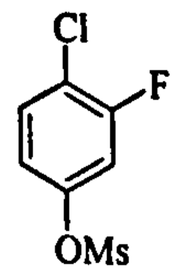
Attempted reduction of methanesulfonic acid 2-nitrophenyl ester 2.221



2.221 **2.222**

Salt **1.179** (619 mg, 1.1 mmol, 1.2 equiv.) was dissolved in toluene (12 ml) and DMF (7 ml) and purged with argon for 30 min. KHMDS (5.53 ml, 2.2 mmol, 2.4 equiv., c = 0.40 mol/l) was added dropwise and the reaction mixture was stirred for 1h at room temperature. An argon-purged solution of **2.221** (200 mg, 0.92 mmol, 1.0 equiv.) in toluene (10 ml) was then added and the reaction mixture was stirred at room temperature for 2h. The mixture was poured into water (50 ml) and diethyl ether (50 ml). The aqueous phase was extracted with diethyl ether (2 x 50 ml) and the combined organic phases were washed with water (3 x 50 ml), dried over Na_2SO_4, filtered and removed *in vacuo*. The residue was purified by column chromatography (10:90 ethyl acetate/ petroleum ether, then 50:50 ethyl acetate/ petroleum ether) to afford *adduct compound* **2.222** as a yellow oil (31 mg, 7 %); (Found: $[M+H]^+$ 506.1856. $C_{26}H_{27}N_5O_4S$ requires $[M+H]$, 506.1857); ν_{max} (NaCl)/cm^{-1} 2934 (C-H), 1590 (Ar), 2936 (C-H), 1445 (C-H), 1360 (SO_2), 1151 (SO_2); δ_H ($CDCl_3$) 2.17 (2H, quintet, *J* 7.1, $CH_2CH_2CH_2$), 3.13 (3H, s, SO_2CH_3), 3.17 (3H, s, NCH_3), 3.38 (3H, s, NCH_3), 3.87-3.94 (4H, m, NCH_2CH_2), 6.85-6.97 (6H, m, Ar*H*), 7.03-7.14 (5H, m, Ar*H*), 7.18 (1H, dd, *J* 8.1, 1.4, Ar*H*); δ_C ($CDCl_3$) 26.8 (CH_2), 26.9 (CH_3), 29.7 (CH_3), 38.9 (CH_3), 38.9 (CH_2), 40.4 (CH_2), 107.0 (CH), 107.4 (CH), 107.5 (CH), 107.6 (CH), 121.1 (CH), 121.2 (CH), 121.3 (CH), 123.7 (CH), 124.1 (CH), 127.5 (CH), 128.9 (C), 130.1 (C), 131.3 (C), 132.6 (C), 142.0 (C), 142.3 (C), 146.4 (C), 154.3 (C); *m/z* (ESI) 506 ($[M+H]^+$, 34 %), 427 (66), 319 (53), 189 (100), 161 (20).

Methanesulfonic acid 4-chloro-3-fluorophenyl ester 2.232[217]

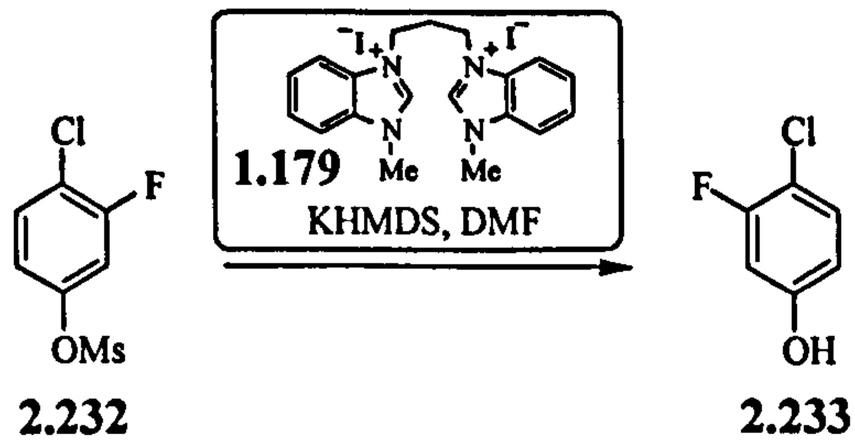


2.232

4-Chloro-3-fluorophenol (200.0 mg, 1.365 mmol, 1.0 equiv.) and triethylamine (0.767 ml, 5.460 mmol, 4.0 equiv.) were dissolved in DCM (3 ml) and cooled to 0°C. Methanesulfonyl chloride (0.211 ml, 2.730 mmol, 2.0 equiv.) was then added dropwise and

the reaction mixture was warmed to room temperature. After stirring for 2.5 h at room temperature the mixture was poured into diethyl ether (20 ml) and water (20 ml). The water layer was acidified with 2 N hydrochloric acid and extracted with diethyl ether (3 x 20 ml). The combined organic phase was washed further with 2 N hydrochloric acid (2 x 20 ml) and brine (20 ml), dried over sodium sulfate and evaporated. Further purification by column chromatography (10:40 ethyl acetate/ petroleum ether) gave *methanesulfonic acid 4-chloro-3-fluorophenyl ester* **2.232** as a yellow solid (293.0 mg, 96 %), mp 41-42 °C; (Found: $[M]^+$ 223.9704. $C_7H_6ClFO_3S$ requires $[M]^+$ 223.9705 {for ^{35}Cl}); ν_{max} (KBr)/cm^{-1} 3116 (Ar-H), 3074 (Ar-H), 3032 (Ar-H), 2939 (C-H), 1594 (Ar), 1481 (C-H), 1370 (SO_2), 1121 (SO_2); δ_H ($CDCl_3$) 3.18 (3H, s, C*H*$_3$), 7.05-7.08 (1H, m, Ar*H*), 7.13-7.16 (1H, m, Ar*H*), 7.42-7.46 (1H, m, Ar*H*); δ_C ($CDCl_3$) 37.8 (CH_3), 111.5 (d, $^2J_{C\text{-}F}$ 24.2, CH), 118.8 (d, ^4J 4.0, CH), 120.2 (d, $^2J_{C\text{-}F}$ 17.6, C), 131.4 (CH), 147.9 (d, $^3J_{C\text{-}F}$ 9.5, C), 158.1 (d, $^1J_{C\text{-}F}$ 252.2, C); *m/z* (EI) 226 (M^+, 3 %, ^{37}Cl), 224 (M^+, 9 %, ^{35}Cl), 146 (53, ^{35}Cl), 148 (17, ^{37}Cl), 117 (100, ^{35}Cl), 119 (33, ^{37}Cl), 79 (56).

Attempted reduction of methanesulfonic acid 4-chloro-3-fluorophenyl ester 2.232



2.232 **2.233**

(i) Salt **1.179** (748 mg, 1.336 mmol, 1.2 equiv.) was dissolved in DMF (15 ml) and purged with argon for 30 min. KHMDS (6.68 ml, 2.672 mmol, 2.4 equiv., c = 0.40 mol/l) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. An argon-purged solution of **2.232** (259 mg, 1.113 mmol, 1.0 equiv.) in DMF (5 ml) was then added and the reaction mixture was stirred at room temperature for 18 h. The mixture was poured into water (50 ml) and diethyl ether (50 ml). The aqueous phase was acidified (2 N hydrochloric acid) and extracted with diethyl ether (2 x 50 ml). The organic phases were combined and washed with dilute hydrochloric acid (3 x 50 ml). The organic phase was then washed with dilute sodium hydroxide solution (3 x), dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (10:90 diethyl ether/ petroleum ether) to afford starting material **2.232** (122.5 mg, 49 %). The remaining basic aqueous layer was neutralised with 2 N hydrochloric acid and extracted with diethyl ether (3 x 50 ml). The organic phases were combined, dried over sodium

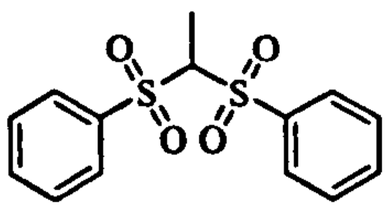
sulfate, filtered and evaporated. The residue was purified by column chromatography (10:90 diethyl ether/ petroleum ether) to afford 4-chloro-3-fluorophenol **2.233**[218] as a white solid (73 mg, 45 %); for data see below.

(ii) Salt **1.179** (548 mg, 0.979 mmol, 2.2 equiv.) was dissolved in DMF (10 ml) and purged with argon for 30 min. KHMDS (4.9 ml, 1.958 mmol, 4.4 equiv., c = 0.40 mol/l) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. An argon-purged solution of mesylate **2.232** (100 mg, 0.445 mmol, 1.0 equiv.) in DMF (5 ml) was then added and the reaction mixture was stirred at room temperature for 18 h. The mixture was poured into water (50 ml) and diethyl ether (50 ml). The aqueous phase was acidified (2 N hydrochloric acid) and extracted with diethyl ether (2 x 50 ml). The organic phases were combined and washed with dilute hydrochloric acid (3 x 50 ml). The organic phase was then washed with dilute sodium hydroxide solution (3 x), dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (10:90 diethyl ether/ petroleum ether) to afford starting material **2.232** (25 mg, 25 %). The remaining basic aqueous layer was neutralised with 2 N hydrochloric acid and extracted with diethyl ether (3 x 50 ml). The organic phases were combined, dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (10:90 diethyl ether/ petroleum ether) to afford 4-chloro-3-fluorophenol **2.233**[218] as a white solid (39 mg, 60 %); for data see below.

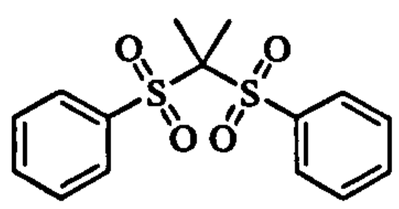
(iii) Salt **1.179** (269 mg, 0.481 mmol, 1.2 equiv.) was dissolved in DMF (5 ml) and purged with argon for 30 min. KHMDS (2.4 ml, 0.96 mmol, 2.4 equiv., c = 0.40 mol/l) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. An argon-purged solution of mesylate **2.232** (90 mg, 0.40 mmol, 1.0 equiv.) in DMF (2 ml) was then added and the reaction mixture was heated at 118°C for 18 h. The mixture was poured into water (50 ml) and diethyl ether (50 ml). The aqueous phase was acidified (2 N hydrochloric acid) and extracted with diethyl ether (2 x 50 ml). The organic phases were combined and washed with dilute hydrochloric acid (3 x 50 ml). The organic phase was then washed with dilute sodium hydroxide solution (3 x), dried over sodium sulfate, filtered and evaporated. TLC analysis of this crude mixture did not show anything. The remaining basic aqueous layer was neutralised with 2 N hydrochloric acid and extracted with diethyl ether (3 x 50 ml). The organic phases were combined, dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography

(10:90 diethyl ether/ petroleum ether) to afford 4-chloro-3-fluorophenol **2.233**[218] as a white solid (105 mg, 75 %), 49-50°C (lit.[218] 54-56°C); ν_{max} (KBr)/cm^{-1} 3351 (OH), 1603 (Ar); δ_H ($CDCl_3$) 5.41 (1H, s, O*H*), 6.61-6.74 (1H, m, Ar*H*), 6.72 (1H, dd, *J* 10.2, 2.8 Ar*H*), 7.25-7.31 (1H, m, Ar*H*); δ_C ($CDCl_3$) 104.8 (d, $^2J_{C\text{-}F}$ 24.0 CH), 112.3 (d, $^3J_{C\text{-}F}$ 3.4, CH), 112.8 ($^2J_{C\text{-}F}$ 22.4, C), 131.0 (d, $^4J_{C\text{-}F}$ 1.1, CH), 155.5 (d, $^3J_{C\text{-}F}$ 10.1 C), 158.6 (d, $^1J_{C\text{-}F}$ 248.2, C); *m/z* (EI) 146 (M^+, 32 %), 145 (93).

1-[2-(Phenylsulfonyl)propan-2-ylsulfonyl]benzene 2.240



2.239

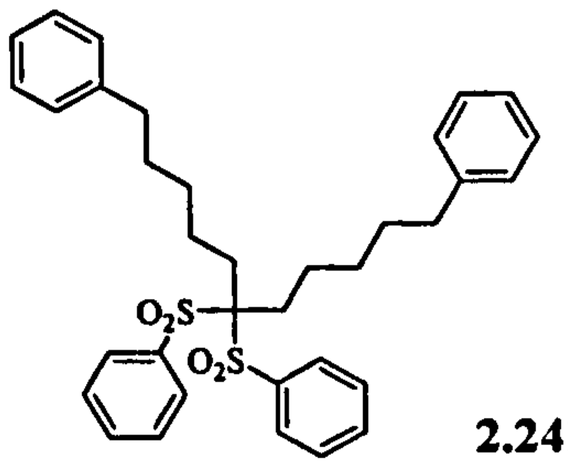


2.240

To a suspension of washed sodium hydride (60 %, 742 mg, 18.55 mmol, 1.1 equiv.) in DMF (5 ml) a solution of *bis*(phenylsulfonyl)methane in DMF (15 ml) was added dropwise under argon *via* cannula while cooling to 0°C. The mixture was allowed to warm to room temperature and was stirred for 1 h, then cooled to 0°C and iodomethane (1.37 ml, 21.93 mg, 1.3 equiv.) was added dropwise. The reaction mixture was stirred for 18 h at room temperature. Water was then added (100 ml) and the aqueous layer was extracted with diethyl ether (2 x 100 ml). The combined organic layer was washed with brine (100 ml) and was then dried over sodium sulfate, filtered and removed under reduced pressure. The residue was purified by column chromatography (10:10:80 ethyl acetate/ petroleum ether/ toluene) to give 1-[1-(phenylsulfonyl)ethylsulfonyl]benzene **2.239**[219] as a white solid (4.6 g, 89 %); mp 94-95°C (lit.[219] 101°C); (KBr)/cm^{-1} 3069 (Ar-H), 2994 (C-H), 2930 (C-H), 1447 (C-H), 1332 (SO_2), 1155 (SO_2); δ_H ($CDCl_3$) 1.70 (3H, d, *J* 7.3, CH_3), 4.53 (1H, q, *J* 7.3, C*H*CH_3), 7.57-7.62 (4H, m, Ar*H*), 7.69-7.74 (2H, m, Ar*H*), 7.95-7.98 (4H, m, Ar*H*); δ_C ($CDCl_3$) 11.1 (CH_3), 79.1 (CH), 129.2 (CH), 129.7 (CH), 134.6 (CH), 137.3 (C); *m/z* (EI) 310 (M^+, 9 %), 169 (1), 153 (5), 141 (13), 125 (139), 121 (100).

It was also isolated 1-(2-(phenylsulfonyl)propan-2-ylsulfonyl)benzene **2.240**[220] as a white solid (446 mg, 8 %); mp 189-190°C (lit.[220] 187-188°C); (Found: $[M+NH_4]^+$ 342.0829. $C_{15}H_{16}O_4S_2$ requires $[M+NH_4]^+$, 342.0829); (KBr)/cm^{-1} 3095 (Ar-H), 3073 (Ar-H), 2986 (C-H), 1582 (Ar), 1448 (C-H), 1327 (SO_2), 1144 (SO_2); δ_H ($CDCl_3$) 1.74 (6H, s, CH_3), 7.59-7.63 (4H, m, Ar*H*), 7.71-7.75 (2H, m, Ar*H*), 8.02-8.04 (4H, m, Ar*H*); δ_C ($CDCl_3$) 19.6 (CH_3), 84.0 (C), 129.1 (CH), 131.5 (CH), 134.8 (CH), 136.2 (C); *m/z* (CI) 342 ($[M+NH_4]^+$, 23 %), 219 (4), 202 (100), 151 (3), 94 (3), 78 (4), 52 (6).

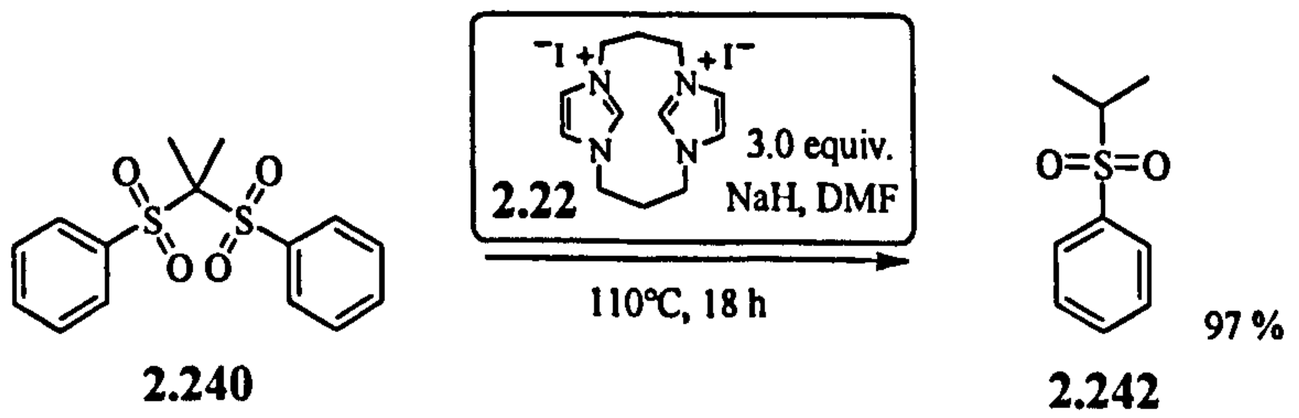
1,11-Diphenyl-6,6-bis(phenylsulfonyl)undecane 2.241



2.241

1-Iodo-5-phenylpentane (495 mg, 1.81 mmol, 2.0 equiv.), *bis*(phenylsulfonyl)methane (268 mg, 0.903 mmol, 1.0 equiv.) and potassium carbonate (624 mg, 4.515 mmol, 5.0 equiv.) were dissolved in dimethyl sulfoxide (15 ml) under argon and stirred at room temperature for 5 d. The mixture was then poured into water (50 ml) and the aqueous layer was extracted with diethyl ether (3 x 50 ml). The combined organic layer was washed with water (3 x 50 ml), brine (50 ml), dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (10:10:80 ethyl acetate/ toluene/ petroleum ether) to give *1,11-diphenyl-6,6-bis(phenylsulfonyl)undecane* **2.241** as a colourless oil (324 mg, 61 %); (Found: $[M+NH_4]^+$ 606.2706. $C_{35}H_{40}O_4S_2$ requires $[M+NH_4]^+$, 606.2702); ν_{max} (NaCl)/cm^{-1} 3060 (Ar-H), 3025 (Ar-H), 2928 (C-H), 1447 (C-H), 1327 (SO_2), 1144 (SO_2); δ_H ($CDCl_3$) 1.34-1.43 (4H, m, CH_2), 1.69-1.77 (8H, m, CH_2), 2.22-2.28 (4H, m, CH_2), 2.68 (4H, t, *J* 7.5, CH_2), 7.25-7.30 (6H, m, Ar*H*), 7.36-7.40 (4H, m, Ar*H*), 7.57-7.61 (4H, m, Ar*H*), 7.72-7.75 (2H, m, Ar*H*), 8.08-8.11 (4H, m, Ar*H*); δ_C ($CDCl_3$) 23.5 (CH_2), 28.6 (CH_2), 29.7 (CH_2), 30.9 (CH_2), 35.7 (CH_2), 92.8 (C), 125.9 (CH), 128.5 (CH), 131.1 (CH), 134.5 (CH), 137.3 (C), 142.3 (C); *m/z* (CI) 606 ($[M+NH_4]^+$, 8 %), 465 (44), 325 (25), 160 (23), 126 (48), 108 (78), 94 (100), 78 (81).

Reduction of 1-[2-(phenylsulfonyl)propan-2-ylsulfonyl]benzene 2.240

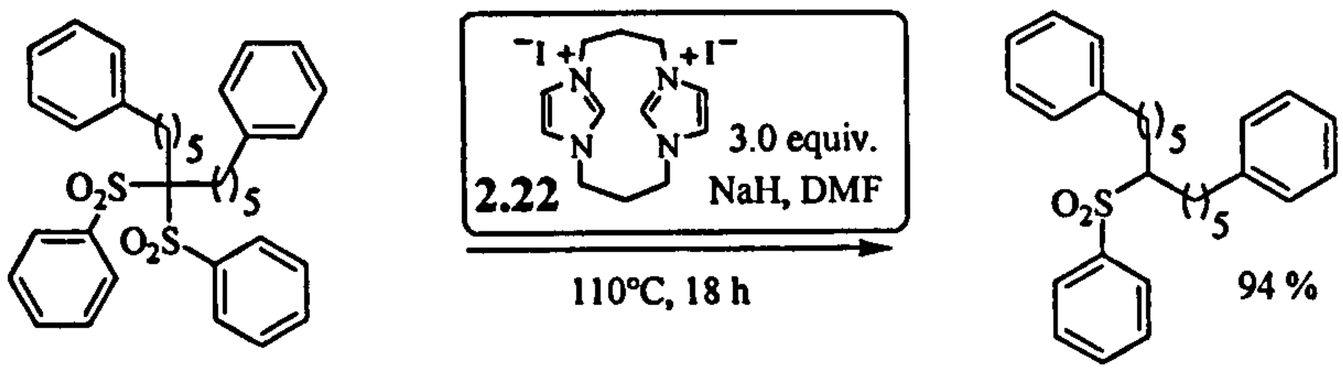


2.240 **2.242**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (425 mg, 0.9 mmol, 3.0 equiv.), 1-[2-(phenylsulfonyl)propan-2-ylsulfonyl]benzene **2.240** (95 mg, 0.292 mmol). The purification of the residue after work-up was carried out by column chromatography on

silica gel (10:90 ethyl acetate/ hexane) to give isopropylsulfonylbenzene **2.242**[221] as a colourless oil (52 mg, 97 %); (Found: $[M+NH_4]^+$ 202.0896. $C_9H_{12}O_2S$ requires $[M+NH_4]^+$, 202.0896); ν_{max} (NaCl)/cm^{-1} 3066 (Ar-H), 2938 (C-H), 1447 (C-H), 1305 (SO_2), 1144 (SO_2); δ_H ($CDCl_3$) 1.27 (6H, d, *J* 6.9, CH_3), 3.18 (1H, septet, *J* 6.9, C*H*), 7.53-7.57 (2H, m, Ar*H*), 7.62-7.67 (1H, m, Ar*H*), 7.86-7.88 (2H, m, Ar*H*); δ_C ($CDCl_3$) 15.9 (CH_3), 55.7 (CH), 129.2 (CH), 133.8 (CH), 137.2 (C); *m/z* (EI) 184 (M^+, 4 %), 142 (49), 78 (100), 51 (97).

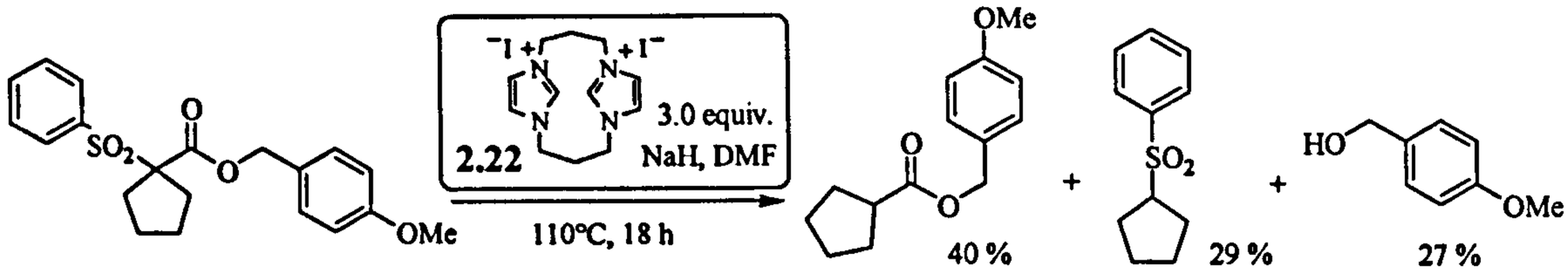
Reduction of 1,11-diphenyl-6,6-bis(phenylsulfonyl)undecane 2.241



2.241 **2.243**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (293 mg, 0.6 mmol, 3.0 equiv.), 1,11-diphenyl-6,6-*bis*(phenylsulfonyl)undecane **2.241** (122 mg, 0.207 mmol). The purification of the residue after work-up was carried out by column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether) to give *1,11-diphenyl-6-(phenylsulfonyl)undecane* **2.243** as a colourless oil (87 mg, 94 %); (Found: $[M+NH_4]^+$ 466.2774. $C_{29}H_{36}O_2S$ requires $[M+NH_4]^+$, 466.2774); ν_{max} (NaCl)/cm^{-1} 3061 (Ar-H), 3026 (Ar-H), 2931 (C-H), 2857 (C-H), 1603 (Ar), 1447 (C-H), 1303 (SO_2), 1144 (SO_2); δ_H ($CDCl_3$) 1.36-1.51 (6H, m, CH_2), 1.51-1.60 (2H, m, CH_2), 1.62-1.73 (6H, m, CH_2), 1.90-1.98 (2H, m, CH_2), 2.69 (4H, t, *J* 7.6, CH_2Ph), 2.97-3.00 (1H, m, SO_2C*H*), 7.25-7.31 (6H, m, Ar*H*), 7.36-7.41 (4H, m, Ar*H*), 7.63-7.67 (2H, m, Ar*H*), 7.27-7.76 (1H, m, Ar*H*), 7.97-7.99 (2H, m, Ar*H*); δ_C ($CDCl_3$) 26.8 (CH_2), 28.0 (CH_2), 29.2 (CH_2), 31.1 (CH_2), 35.9 (CH_2), 64.7 (CH), 125.9 (CH), 128.5 (CH), 129.0 (CH), 129.2 (CH), 133.6 (CH), 138.5 (C), 142.6 (C); *m/z* (CI) 466 ($[M+NH_4]^+$, 60 %), 326 (100), 160 (31), 126 (39), 108 (52), 94 (85), 78 (66).

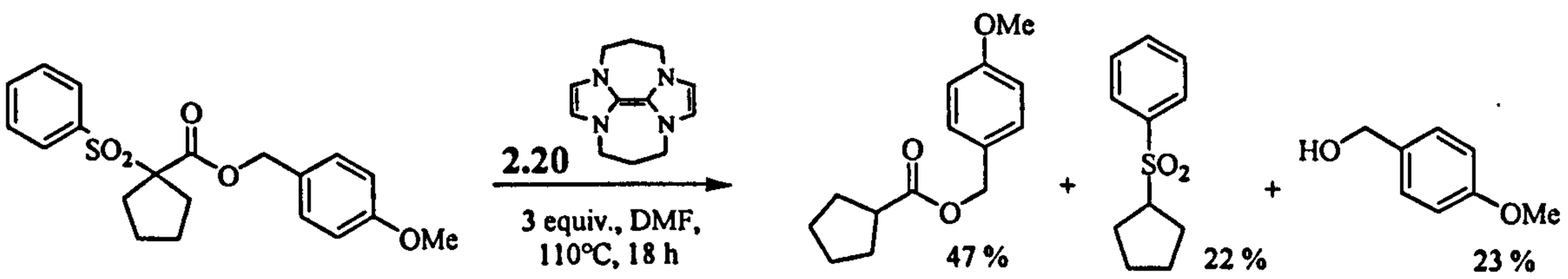
Reaction of 4-methoxybenzyl (1-benzenesulfonyl)cyclopentane carboxylate 2.251



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (425 mg, 0.9 mmol, 3.0 equiv.), 4-methoxybenzyl(1-benzenesulfonyl)cyclopentane carboxylate **2.254** (114 mg, 0.304 mmol). The purification of the residue after work-up was carried out by column chromatography on silica gel (100:0, then 80:20 hexane/ ethyl acetate) to give *cyclopentanecarboxylic acid 4-methoxybenzyl ester* **2.255** as a colourless oil (29 mg, 41 %); (Found: $[M+Na]^+$ 257.1147 $C_{14}H_{18}O_3$ requires $[M+Na]^+$, 257.1148); ν_{max} (NaCl)/cm^{-1} 3064 (Ar-H), 3030 (Ar-H), 2956 (C-H), 2871 (C-H), 2837 (C-H), 1730 (C=O), 1453 (C-H), 1248 (C-O ether), 1171 (C-O ester); δ_H ($CDCl_3$) 1.55-1.70 (2H, m, CH_2), 1.70-1.80 (2H, m, CH_2), 1.80-2.00 (4H, m, CH_2), 2.80 (1H, quintet, *J* 7.9, C*H*), 3.85 (3H, s, CH_3), 5.10 (2H, s, OCH_2), 6.93 (2H, d, *J* 8.6, Ar*H*), 7.34 (2H, d, *J* 8.6, Ar*H*); δ_C ($CDCl_3$) 26.3 (CH_2), 30.5 (CH_2), 44.4 (CH), 55.8 (CH_3), 66.3 (CH_2), 114.4 (CH), 129.0 (C), 130.4 (CH), 160.0 (C), 177.1 (C); *m/z* (EI) 234 (M^+, 12 %), 138 (8), 121 (100), 91 (15), 77 (20), 41 (32); and cyclopentanesulfonylbenzene[222] **2.252** as a white solid (23 mg, 29 %), mp 58-60°C (lit.[223] 60.1-61.5°C); (Found: $[M+NH_4]^+$: 228.1053. $C_{11}H_{14}O_2S$ requires $[M+NH_4]^+$, 228.1053); ν_{max} (KBr)/cm^{-1} 3064 (Ar-H), 2960 (C-H), 2872 (C-H), 1446 (C-H), 1302 (SO_2), 1146 (SO_2), 691 (Ar), 761 (Ar); δ_H ($CDCl_3$) 1.50-1.65 (2H, m, CH_2), 1.65-1.80 (2H, m, CH_2), 1.80-1.90 (2H, m, CH_2), 1.95-2.05 (2H, m, CH_2), 3.45 (1H, quintet, *J* 7.9, C*H*), 7.53 (2H, dd, *J* 7.9, 7.3, Ar*H*), 7.62 (1H, t, *J* 7.3, Ar*H*), 7.88 (2H, d, *J* 7.9, Ar*H*); δ_C ($CDCl_3$) 26.3 (CH_2), 27.7 (CH_2), 64.7 (CH), 128.9 (CH), 129.6 (CH), 133.9 (CH), 139.5 (C); *m/z* (EI) 211 (M^+, 2 %), 143 (77), 125 (20), 77 (71), 51 (55), 41 (100); and (4-methoxyphenyl)methanol **2.125**[224] as a white solid (11 mg, 27 %); mp 22-24°C (lit.[224] 25-26°C); (Found: M^+ 138.0674. $C_8H_{10}O_2$ requires M^+, 138.0675); ν_{max} (KBr)/cm^{-1} 3337 (O-H), 3060 (Ar-H), 3032 (Ar-H), 3000 (Ar-H), 2956 (C-H), 2934 (C-H), 2914 (C-H), 2862 (C-H), 2838 (C-H), 1248 (C-O ether); δ_H ($CDCl_3$) 3.82 (3H, s, CH_3), 4.62 (2H, s, CH_2), 6.90 (2H, d, *J* 8.7, Ar*H*), 7.30 (2H, d, *J* 8.7, Ar*H*); δ_C ($CDCl_3$) 55.8 (CH_3), 65.5 (CH_2), 114.5 (CH), 129.1 (CH), 133.7 (C), 159.7 (C); *m/z* (EI) 138 (M^+, 28 %), 121 (20), 109 (44), 77 (100), 63 (49). Another fraction was isolated, that upon further purification by

column chromatography on silica gel (60:20:1:19 acetonitrile/ DCM/ methanol/ petroleum ether) gave *3-allyl-1-propyl-1,3-dihydro-[2,2']biimidazolylidene* **2.36** as a colourless oil; (Found: $[M+H]^+$ 217.1449. $C_{12}H_{16}N_4$ requires $[M+H]^+$, 217.1448); ν_{max} (NaCl)/cm^{-1} 3109 (Ar-H), 2961 (C-H), 2934 (C-H), 1422 (C-H); δ_H ($CDCl_3$) 0.89 (3H, t, *J* 7.4, CH_3), 1.76-1.82 (2H, m, $CH_3CH_2CH_2$), 4.42 (2H, t, *J* 7.2, $CH_3CH_2CH_2N$), 5.06-5.19 (4H, CH_2=CHCH_2N), 5.94-6.02 (1H, m, CH_2=C$H$$CH_2$), 7.01 (2H, s, Ar$H$), 7.13 (2H, d, *J* 7.4, ArH); δ_C ($CDCl_3$) 11.0 (CH_3), 24.3 (CH_2), 49.1 (CH_2), 49.9 (CH_2), 117.4 (CH_2), 129.9 (CH), 121.4 (CH), 133.9 (CH), [2 x central C were not shown]; *m/z* (EI) 216 (16), 201 (18), 173 (21), 159 (38), 147 (19), 94 (9), 57 (17), 43 (40), 41 (100); the structure is presented on page 169.

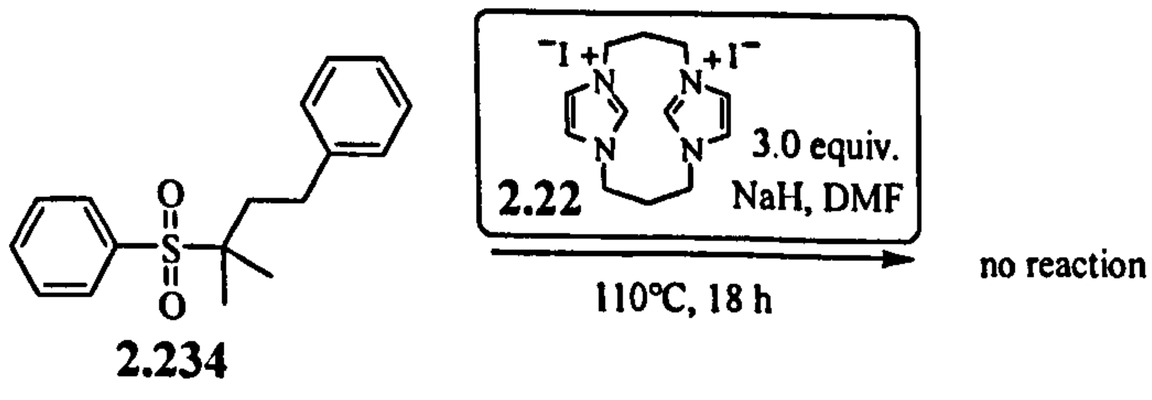
Reaction of 4-methoxybenzyl (1-benzenesulfonyl)cyclopentane carboxylate 2.251 with iodide-free pure donor 2.20



2.251 **2.255** **2.252** **2.125**

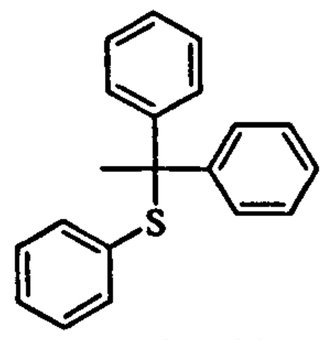
The experiment was carried out according to the 'pure donor-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), donor **2.20** (179 mg, 0.833 mmol, 2.8 equiv.), (1-benzenesulfonyl)cyclopentane carboxylate **2.251** (103.6 mg, 0.277 mmol, 1.0 equiv.). *Observation:* Upon addition of yellow donor solution, colour change to orange-red. The purification of the crude mixture after *neutral* work-up was carried out by column chromatography on silica gel (5:95 ethyl acetate/ petroleum ether) to afford *cyclopentanecarboxylic acid 4-methoxybenzyl ester* **2.255** as a colourless oil (33 mg, 47 %), (4-methoxyphenyl)methanol[224] **2.125** as a white solid (8 mg, 23 %) and cyclopentane-sulfonylbenzene[225] **2.252** as a white solid (13.4 mg, 22 %); for data see above.

Reaction of 1,1-dimethyl-3-phenylpropyl phenylsulfone 2.234



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), salt **2.22** (425 mg, 0.9 mmol, 3.0 equiv.), 1,1-dimethyl-3-phenylpropyl phenylsulfone **2.234** (86.4 mg, 0.3 mmol, 1.0 equiv.). *Observation:* Upon addition of yellow donor solution, the colour change to orange-red. *Neutral* work-up was carried out and ^{1}H-NMR of the crude mixture showed only starting material **2.234**; the reaction did not proceed.

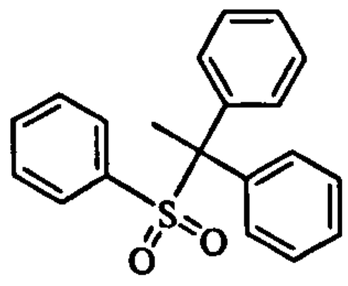
Phenyl-(1,1-diphenylethyl)sulfane 2.264[226]



2.264

Thiophenol (1.71 ml, 16.6 mmol, 1.2 equiv.) and perchloric acid (70 %, 0.1 ml) were added to a dry flask under argon and the mixture was cooled to 0°C. To this, diphenylethylene (2.45 ml, 13.8 mmol, 1.0 equiv.) was added dropwise at 0°C and the reaction mixture was stirred for 2 h at room temperature. Benzene (100 ml) was then added to the reaction mixture, followed by sodium hydroxide solution (5 %). The organic layer was separated and dried over sodium sulfate. The solvent was subsequently removed and the residue was recrystallised from hexane. Phenyl-(1,1-diphenylethyl)sulfane[226] **2.264** was obtained as a white solid (3.44 g, 86 %); mp 145-148°C (lit.[226] 148-149°C); (Found: [M-H]$^+$ 289.1043. $C_{20}H_{18}S$ requires [*M-H*]$^+$, 289.1045); (KBr)/cm^{-1} 3057 (Ar-H), 3019 (Ar-H), 2965 (C-H), 2923 (C-H), 1590 (Ar), 1535 (Ar); δ_H ($CDCl_3$) 2.14 (3H, s, C*H*$_3$), 7.26-7.28 (4H, m, Ar*H*), 7.37-7.47 (7H, m, Ar*H*), 7.60-7.62 (4H, m, Ar*H*); δ_C ($CDCl_3$) 30.5 (CH_3), 59.8 (C), 126.8 (CH), 128.0 (CH), 128.5 (CH), 128.5 (CH), 132.7 (C), 136.7 (CH), 146.5 (C); *m/z* [CI (CH_4)] 289 ([M-H]$^+$, 2%), 209 (9), 181 (100), 103 (3).

1,1-Diphenyl-1-(phenylsulfonyl)ethane 2.262

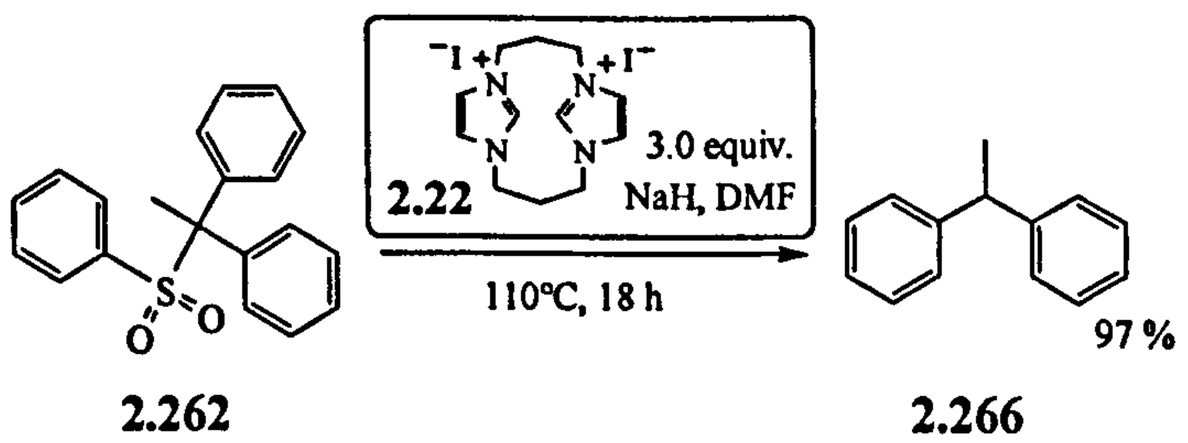


2.262

Phenyl-(1,1-diphenylethyl)sulfane **2.264** (1.04 g, 3.58 mmol, 1.0 equiv.) was dissolved in dichloromethane (10 ml) under argon. A solution of 3-chloroperbenzoic acid (77 %, 3.7 g, 21.49 mmol, 6.0 equiv.) in dichloromethane (30 ml) was then added dropwise under argon

while cooling to 0°C. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was filtered and the solution was washed with aqueous sodium hydroxide solution (3 x 30 ml) and brine (30 ml). The organic layer was dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (50:50 petroleum ether/ dichloromethane, then 100:0 dichloromethane) to give 1,1-diphenyl-1-(phenylsulfonyl)ethane[227] **2.262** as a white solid (1.13 g, 98 %); mp 171-172°C (lit.[227] 174-175°C); (Found: $[M+NH_4]^+$ 340.1366. $C_{20}H_{18}O_2S$ requires $[M+NH_4]^+$, 340.1366); ν_{max} (KBr)/cm^{-1} 3058 (Ar-H), 2999 (C-H), 1497 (Ar), 1445 (C-H), 1293 (SO_2), 1128 (SO_2); δ_H ($CDCl_3$) 2.12 (3H, s, C*H*$_3$), 7.23-7.34 (10H, m, Ar*H*), 7.45-7.48 (1H, m, Ar*H*), 7.53-7.55 (4H, m, Ar*H*); δ_C ($CDCl_3$) 26.5 (CH_3), 75.6 (C), 128.5 (CH), 130.0 (CH), 130.7 (CH), 133.6 (CH), 137.1 (C), 139.7 (C); *m/z* (CI) 340 ($[M+NH_4]^+$, 7 %), 200 (4), 181 (100), 160 (6), 94 (5), 52 (7).

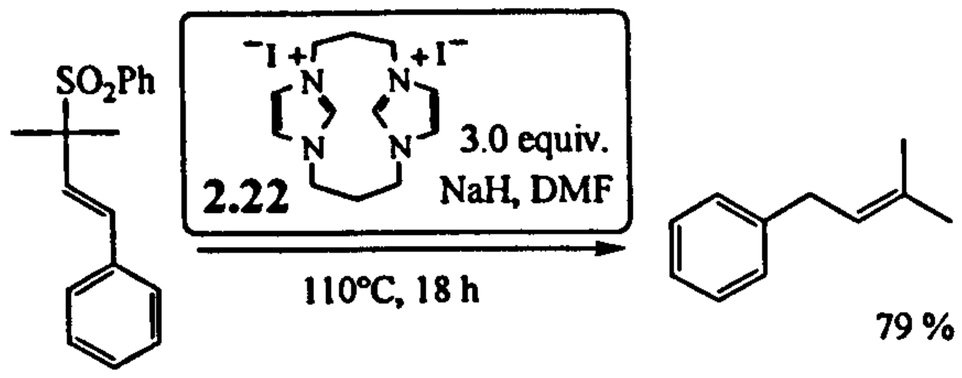
Reduction of 1,1-diphenyl-1-(phenylsulfonyl)ethane 2.262



2.262 **2.266**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), salt **2.22** (425 mg, 0.9 mmol, 3.0 equiv.), 1,1-diphenyl-1-(phenylsulfonyl)ethane **2.262** (96.7 mg, 0.3 mmol). The purification of the residue after work-up was carried out by column chromatography on silica gel (5:95 ethyl acetate/ hexane) to give 1,1-diphenylethane **2.266**[228] as a colourless liquid (53 mg, 97 %); (Found: M^+ 182.1091. $C_{14}H_{14}$ requires M^+, 182.1090); ν_{max} (NaCl)/cm^{-1} 3061 (Ar-H), 3026 (Ar-H), 2967 (C-H), 2930 (C-H), 1493 (C-C), 1450 (C-H); δ_H ($CDCl_3$) 1.74 (3H, d, *J* 7.2, C*H*$_3$), 4.25 (1H, q, *J* 7.2, C*H*), 7.24-7.39 (10H, m, Ar*H*); δ_C ($CDCl_3$) 22.1 (CH_3), 45.0 (CH), 126.2 (CH), 127.8 (CH), 128.6 (CH), 146.6 (C); *m/z* (EI) 182 (M^+, 89 %), 167 (100), 152 (52), 77 (48), 51 (34).

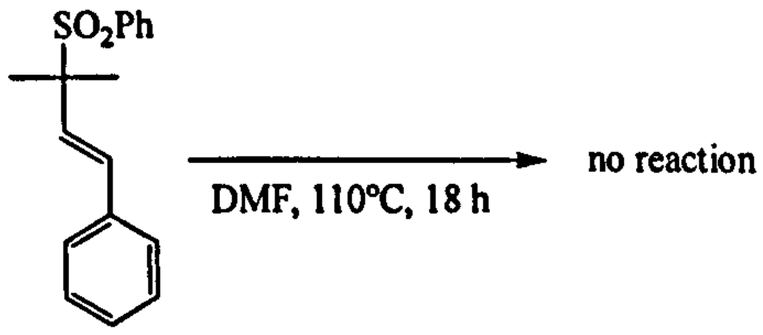
Reduction of 1-[2-methyl-4-phenylbut-3-en-2-ylsulfonyl]benzene 2.265



2.261 **2.265**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), salt **2.22** (425 mg, 0.9 mmol, 3.0 equiv.), 1-[2-methyl-4-phenylbut-3-en-2-ylsulfonyl]benzene **2.261** (84 mg, 0.293 mmol). The purification of the residue after work-up was carried out by column chromatography on silica gel (hexane) to give 1-(3-methylbut-2-enyl)benzene[229] **2.265** as a colourless liquid (33.8 mg, 79 %); (Found: M^+ 146.1088. $C_{11}H_{14}$ requires M^+, 146.1090); ν_{max} (NaCl)/cm^{-1} 3063 (Ar-H), 3028 (Ar-H), 2925 (C-H), 1603 (Ar), 1494 (C-H), 1452 (C-H); δ_H ($CDCl_3$) 1.81 (3H, s, CH_3), 1.83 (3H, s, CH_3), 3.43 (2H, d, *J* 7.3, PhCH_2), 5.40-5.44 (1H, m, C*H*), 7.23-7.27 (3H, m, Ar*H*), 7.32-7.42 (2H, m, Ar*H*); δ_C ($CDCl_3$) 25.9 (CH_3), 34.5 (CH_2), 123.4 (CH), 125.9 (CH), 128.5 (CH), 132.7 (C), 142.1 (C); *m/z* (EI) 146 (M^+, 8 %), 131 (12), 91 (48), 57 (63), 41 (100).

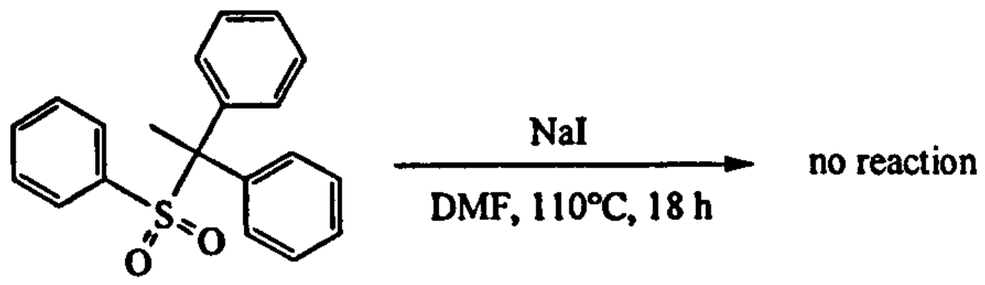
Reaction of 1-[2-methyl-4-phenylbut-3-en-2-ylsulfonyl]benzene 2.261 in DMF



2.261

1-[2-Methyl-4-phenylbut-3-en-2-ylsulfonyl]benzene **2.261** (85.8 mg, 0.3 mmol, 1.0 equiv.) was dissolved in anhydrous DMF (15 ml) and the mixture was heated at 110°C for 18 h. After cooling to room temperature the mixture was poured into water (20 ml). The aqueous layer was extracted with diethyl ether (3 x 20 ml) and the combined organic layer was washed with water (3 x 20 ml) and brine (20 ml). The organic layer was then dried over sodium sulfate, filtered and evaporated. ^{1}H-NMR of this crude mixture showed only starting material **2.261.**

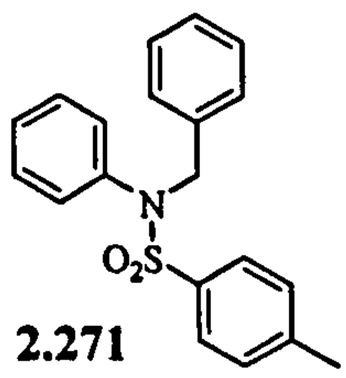
Reaction of 1,1-diphenyl-1-(phenylsulfonyl)ethane 2.262 with NaI in DMF



2.262

Sodium iodide (269.6 mg, 1.8 mmol, 6.0 equiv.) was dried under vacuum and 130°C for 6 h and then cooled to room temperature. A solution of 1,1-diphenyl-1-(phenylsulfonyl)-ethane **2.262** (96.7 mg, 0.3 mmol, 1.0 equiv.) in dry DMF (15 ml) was added under argon and the reaction mixture was heated at 110°C for 18 h. After cooling to room temperature the mixture was poured into water (20 ml). The aqueous layer was extracted with diethyl ether (3 x 20 ml) and the combined organic layer was washed with water (3 x 20 ml) and brine (20 ml). The organic layer was then dried over sodium sulfate, filtered and evaporated. ^{1}H-NMR of this crude mixture showed only starting material **2.262.**

***N*-Benzyl-4-methyl-*N*-phenylbenzenesulfonamide 2.271**

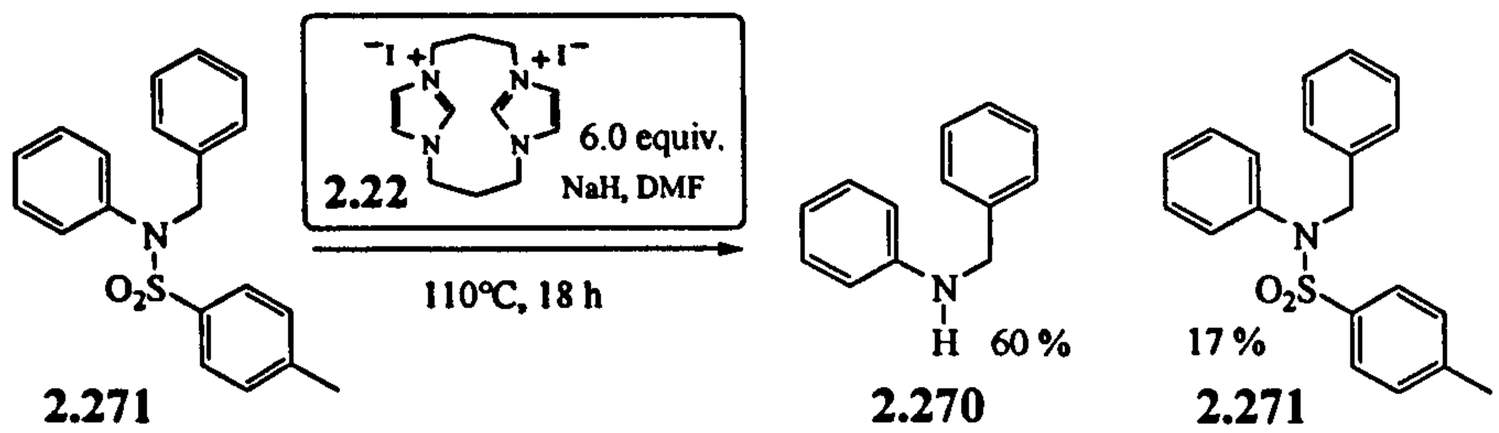


2.271

N-Phenylbenzyl mine (1.50 g, 8.18 mmol, 1.0 equiv.) and *p*-toluenesulfonyl chloride (1.87 g, 9.82 mmol, 1.2 equiv.) were dissolved in pyridine (40 ml) under argon. The reaction mixture was heated at reflux overnight. After cooling to room temperature, the mixture was poured into diethyl ether (300 ml) and subsequently washed with 2 N hydrochloric acid (3 x 150 ml), 2 N aqueous sodium hydroxide solution (150 ml) and brine (100 ml). The organic layer was dried over sodium sulfate and removed under reduced pressure. The residue was purified by column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether) to give *N*-benzyl-4-methyl-*N*-phenylbenzenesulfonamide **2.271**[230] as a white solid (2.67 g, 97 %); 138-140°C (lit.[230] 139-140°C); found: $[M+H]^+$ 338.1208. $C_{20}H_{19}NO_2S$ requires $[M+H]^+$, 338.1209); ν_{max} (KBr)/cm^{-1} 3064 (Ar-H), 3028 (Ar-H), 2920 (C-H), 1596 (Ar), 1456 (C-H), 1345 (SO_2), 1166 (SO_2); δ_H ($CDCl_3$) 2.51 (3H, s, C*H*$_3$), 4.86 (2H, s, C*H*$_2$), 7.10-7.12 (2H, m, Ar*H*), 7.24-7.32 (6H, m, Ar*H*), 7.35-7.37 (4H, m, Ar*H*), 7.66 (2H, d, *J* 8.3, Ar*H*); δ_C ($CDCl_3$) 21.9 (CH_3), 55.1 (CH_2), 127.9 (CH), 128.1 (CH), 128.7 (CH), 128.8 (CH), 129.2 (CH), 129.3 (CH), 129.9 (CH), 136.0 (C), 133.4 (C),

139.4 (C), 143.9 (C); *m/z* (EI) 337 (M^+, 7 %), 181 (29), 104 (16), 91 (100), 77 (43), 65 (29), 51 (16).

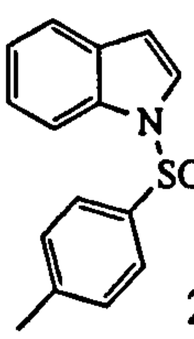
Reduction of *N*-benzyl-4-methyl-*N*-phenylbenzenesulfonamide 2.271



2.271 **2.270** **2.271**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), salt **2.22** (850 mg, 1.8 mmol, 6.0 equiv.), *N*-benzyl-4-methyl-*N*-phenylbenzenesulfonamide **2.271** (100 mg, 0.296 mmol). The DMF was evaporated and the resulting residue dissolved in water (20 ml) and extracted with diethyl ether (3 x 20 ml). The combined organic layer was dried over Na_2SO_4 and removed under reduced pressure. The residue was purified by column chromatography on silica gel (5:95 ethyl acetate/ hexane) to give *N*-benzyl-*N*-phenylamine **2.270**[218] as a white solid (40.6 mg, 74 %); mp 34-36°C (lit.[218] mp 35-38°C); (Found: $[M+H]^+$ 184.1119. $C_{13}H_{13}N$ requires $[M+H]^+$, 184.1121); ν_{max} (KBr)/cm^{-1} 3417 (N-H), 3022 (Ar-H), 2926 (C-H), 1603 (Ar), 1514 (Ar); δ_H ($CDCl_3$) 4.14 (1H, s, N*H*), 4.42 (2H, s, CH_2), 6.72-6.75 (2H, m, Ar*H*), 6.79-6.83 (1H, m, Ar*H*), 7.21-7.29 (2H, m, Ar*H*), 7.33-7.42 (1H, m, Ar*H*), 7.44-7.48 (4H, m, Ar*H*); δ_C ($CDCl_3$) 48.6 (CH_2), 113.1 (CH), 117.8 (CH), 127.5 (CH), 127.7 (CH), 128.9 (CH), 129.5 (CH), 139.6 (C), 148.4 (C); *m/z* (EI) 183 (M^+, 19 %), 106 (16), 91 (100), 77 (31), 65 (43), 51 (38).

1-Tosyl-1*H*-indole 2.272[231]

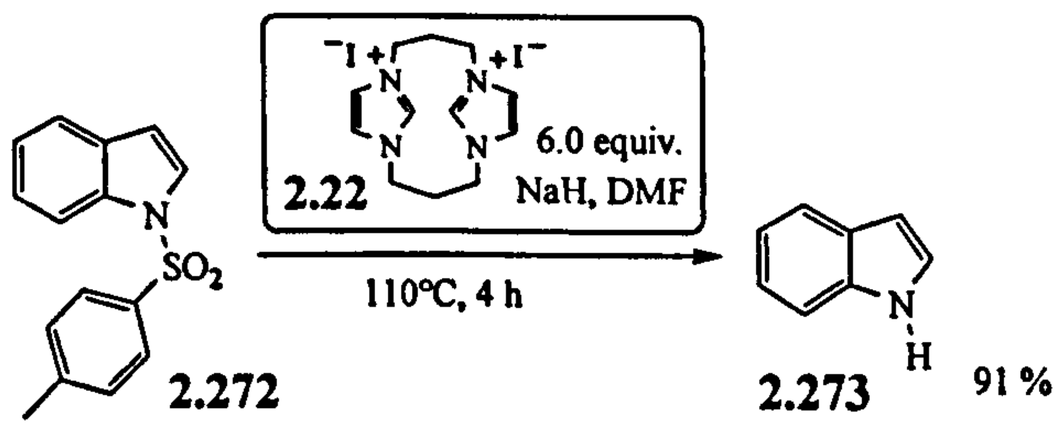


2.272

Crushed potassium hydroxide pellets (2.5 g, 0.045 mol, 3.5 equiv.) were added to anhydrous DMSO (20 ml) under argon. To this a solution of indole (1.5 g, 0.013 mol, 1.0 equiv.) in diethyl ether (10 ml) was added dropwise *via* cannula at room temperature. The mixture was stirred for 1 h and a solution of *p*-toluenesulfonyl chloride (2.44 g, 0.013 mol, 1.0 equiv.) in diethyl ether (10 ml) was then added *via* cannula at room temperature. After

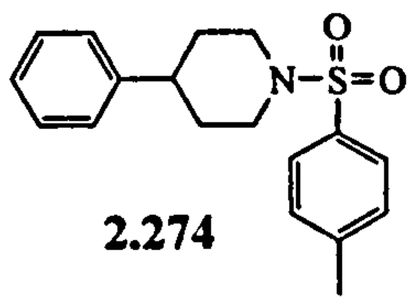
stirring for 30 min at room temperature under argon, water (50 ml) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 50 ml). The organic phases were combined and washed with water (3 x 50 ml) and brine (50 ml), then dried over sodium sulfate, filtered and evaporated. The resulting solid was recrystallised from hexane/ dichloromethane to afford 1-tosyl-1*H*-indole **2.272**[232] as a white solid (1.6 g, 45 %); 82-84°C (lit.[232] 83-84°C); (Found: $[M+NH_4]^+$ 289.1007. $C_{15}H_{13}NO_2S$ requires $[M+NH_4]^+$, 289.1005); ν_{max} (KBr)/cm^{-1} 3068 (Ar-H), 2918 (C-H), 1596 (Ar), 1370 (SO_2), 1260 (SO_2); δ_H ($CDCl_3$) 2.38 (3H, s, C*H*$_3$), 6.73 (1H, d, *J* 3.7, Ar*H*), 7.25-7.33 (3H, m, Ar*H*), 7.38-7.42 (1H, m, Ar*H*), 7.59-7.61 (1H, m, Ar*H*), 7.65-7.66 (1H, m, Ar*H*), 7.84-7.86 (2H, m, Ar*H*), 8.09-8.10 (1H, d, *J* 8.3, Ar*H*); δ_C ($CDCl_3$) 21.6 (CH_3), 109.2 (CH), 113.7 (CH), 121.5 (CH), 123.4 (CH), 124.7 (CH), 126.5 (CH), 126.9 (CH), 130.0 (CH), 130.9 (C), 135.0 (C), 135.5 (C), 145.1(C); *m/z* (EI) 271 (M^+, 50 %), 155 (66), 116 (89), 91 (100), 65 (67), 51 (19).

Reduction of 1-tosyl-1*H*-indole 2.272



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 4 h, DMF (15 ml), salt **2.22** (850 mg, 1.8 mmol, 6.0 equiv.), 1-tosyl-1*H*-indole **2.272** (81.39 mg, 0.3 mmol). The DMF was evaporated and the resulting residue dissolved in water (20 ml) and extracted with diethyl ether (3 x 20 ml). The combined organic layer was dried over Na_2SO_4 and removed under reduced pressure. The residue was purified by column chromatography on silica gel (5:95 ethyl acetate/ hexane) to give 1*H*-indole **2.273**[218] as a white solid (32 mg, 91 %); mp 52-53°C (lit.[218] mp 51-54°C); (Found: $[M+H]^+$ 118.0651. C_8H_7N requires $[M+H]^+$, 118.0651); ν_{max} (KBr)/ cm^{-1} 3397 (N-H), 3048 (Ar-H), 1455 (C=C); δ_H ($CDCl_3$) 6.64-6.65 (1H, m, Ar*H*), 7.19-7.32 (3H, m, Ar*H*), 7.46-7.48 (1H, m, Ar*H*), 7.74-7.76 (1H, m, Ar*H*), 8.17 (1H, s, N*H*); δ_C ($CDCl_3$) 102.8 (CH), 111.2 (CH), 120.0 (CH), 120.9 (CH), 122.2 (CH), 124.4 (CH), 128.1 (C), 136.0 (C); *m/z* (EI) 117 (M^+, 100 %), 89 (37), 63 (34), 49 (33).

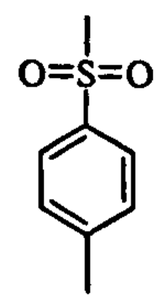
4-Phenyl-1-*p*-tolylpiperidine 2.274



2.274

4-Phenylpiperidine (800 mg, 4.96 mmol, 1.0 equiv.) and triethylamine (1.67 ml, 12.0 mmol, 2.4 equiv.) were dissolved in dichloromethane (10 ml) under argon and cooled to 0°C. A solution of *p*-toluenesulfonyl chloride (1.134 g, 5.95 mmol, 1.2 equiv.) in dichloromethane (10 ml) was then added dropwise at 0°C. The reaction mixture was allowed to warm to room temperature and was stirred over night. The reaction mixture was then poured into 2 N hydrochloric acid (30 ml) and the organic layer was washed further with 2 N hydrochloric acid (2 x 30 ml) and aqueous sodium hydroxide solution (2 x 30 ml) and brine (30 ml). The organic layer was then dried over sodium sulfate, filtered and removed under reduced pressure. The residue was recrystallised (hexane/ dichloromethane) to give *4-phenyl-1-p-tolylpiperidine* **2.274** as a white solid (954 mg, 61 %); mp 151-152°C; (Found: $[M+H]^+$ 316.1365. $C_{18}H_{21}NO_2S$ requires $[M+H]^+$, 316.1366); ν_{max} (KBr)/cm^{-1} 3026 (Ar-H), 2944 (C-H), 2840 (C-H), 1594 (Ar), 1493 (C-H), 1334 (SO_2), 1162 (SO_2); δ_H ($CDCl_3$) 1.79-1.89 (4H, m, CH_2CHPh), 2.33-2.44 (3H, m, NCH_2, CH), 2.50 (3H, s, CH_3), 3.91-3.96 (2H, m, NCH_2), 7.14-7.16 (2H, m, ArH), 7.20-7.23 (1H, m, ArH), 7.28-7.32 (2H, m, ArH), 7.35-7.37 (2H, m, ArH), 7.69 (2H, d, J 8.3, ArH); δ_C ($CDCl_3$) 21.7 (CH_3), 32.8 (CH_2), 42.1 (CH), 47.1 (CH_2), 126.8 (CH), 126.9 (CH), 128.0 (CH), 128.8 (CH), 129.8 (CH), 143.7 (C), 145.1 (C); *m/z* (CI) 333 ($[M+NH_4]^+$, 4 %), 316 (10), 162 (100), 108 (8), 52 (14).

1-Methyl-4-(methylsulfonyl)benzene 2.280

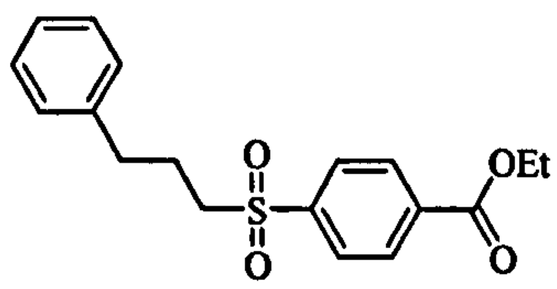


2.280

Salt **2.22** (850 mg, 1.8 mmol, 6.0 equiv.) was heated to 110°C for 1h under vacuum in a centrifuge tube, then cooled to room temperature and sodium hydride (60 % suspension with mineral oil, 576 mg, 14.4 mmol, 48 equiv.) was added under argon atmosphere. This mixture was then washed with hexane (2 x 20 ml) and subsequently dried under argon. Dry DMF (15 ml) was deoxygenated with argon for 20 min and then added dropwise to the

salt/ sodium hydride residue. This mixture was stirred for 4 h at room temperature under argon and then exposed to centrifugation. The resulting supernatant liquid was transferred *via* cannula to (i) *N*-benzyl-4-methyl-*N*-phenylbenzenesulfonamide **2.271** (101 mg, 03 mmol, 1.0 equiv.) [(ii) 1-tosyl-1H-indole **2.272** (81 mg, 0.3 mmol, 1.0 equiv.)] that was dried beforehand under vacuum at room temperature for 3 h. The reaction mixture was heated to 110°C for 18 h under argon atmosphere, then allowed to cool to room temperature and then iodomethane (0.75 ml, 12 mmol, 40 equiv.) was added. The mixture was stirred at room temperature for 2 d and was then poured into water (20 ml). The aqueous layer was extracted with diethyl ether (3 x 20 ml) and the combined organic layer was then washed with water (4 x 20 ml) and brine (20 ml), dried over sodium sulfate and removed *in vacuo*. The residue was purified by column chromatography on silica gel (10:90, then 50:50 ethyl acetate/ hexane) to give 1-methyl-4-(methylsulfonyl)benzene **2.280**[233] as a white solid [(i) 37 mg, 73 %] [(ii) 41 mg, 81 %]; mp 84-85°C (lit.[234] mp 88°C); (Found: $[M+NH_4]^+$ 188.0740. $C_8H_{10}O_2S$ requires $[M+NH_4]^+$, 188.0740); (KBr)/cm^{-1} 3018 (Ar-H), 2926 (C-H), 1300 (SO_2), 1148 (SO_2); δ_H ($CDCl_3$) 2.45 (3H, s, CH_3), 3.03 (3H, s, CH_3), 7.36 (2H, d, *J* 7.9, Ar*H*), 7.82 (2H, m, Ar*H*); δ_C ($CDCl_3$) 22.1 (CH_3), 45.1 (CH_3), 128.4 (CH), 130.5 (CH), 128.3 (C), 145.2 (C); *m/z* (EI) 170 (M^+, 27%), 155 (40), 107 (40), 91 (100), 77 (40), 65 (78), 51 (32).

4-(3-Phenyl-propane-1-sulfonyl)benzoic acid ethyl ester 2.281



2.281

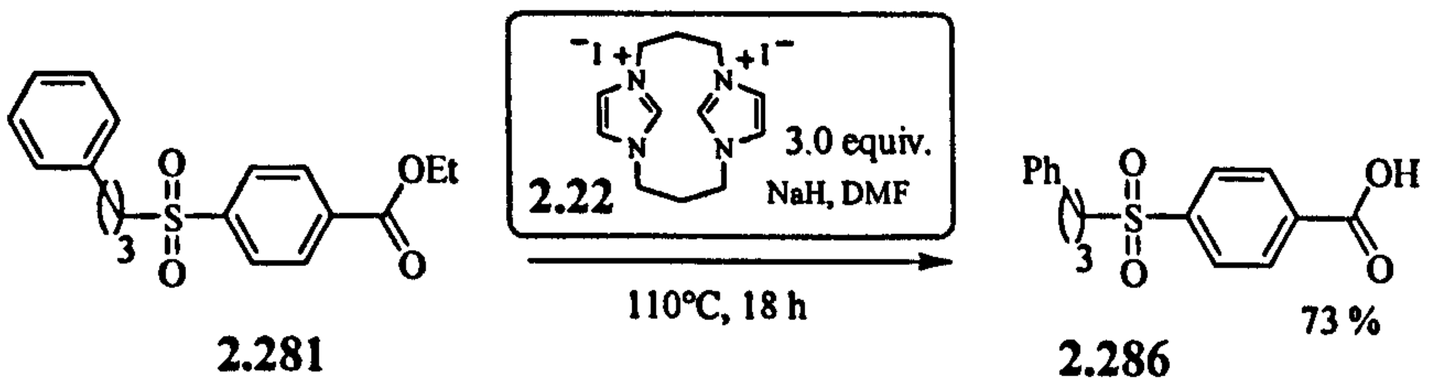
Stage (i) A solution of 4-mercaptobenzoic acid (2.0 g, 12.9 mmol, 1.0 equiv.) in DMF (10 ml) was transferred *via* cannula to a suspension of washed sodium hydride (1.14 g, 28.0 mmol, 2.2 equiv.) in DMF while cooling to 0°C. After stirring the mixture for 0.5 h a solution of (3-bromopropyl)benzene (2.07 ml, 13.6 mmol, 1.05 equiv.) in DMF (20 ml) was added dropwise at 0°C. The mixture was then stirred at room temperature for 2.5 h. Ethyl acetate (150 ml) and 2 N hydrochloric acid (150 ml) were added. The aqueous layer was extracted with ethyl acetate (150 ml). The combined organic layer was washed with 2 N hydrochloric acid (3 x 150 ml), then dried over sodium sulfate and evaporated.

Stage (ii) The residue (2.36 g) was dissolved in ethanol (40 ml) and thionyl chloride (1.26 ml, 17.2 mmol, 2.0 equiv.) was added drowise at 0°C. After heating the mixture at

reflux for 5 h, the solvent was removed *in vacuo* and the residue purified by column chromatography (20:80 ethyl acetate/ petroleum ether) to afford the desired crude intermediate (2.11 g) which was reacted further in the next stage.

Stage (iii) The crude intermediate from *stage (ii)* (2.11 g) was dissolved in DCM (10 ml) and a solution of 3-chloroperoxybenzoic acid (6.08 g, 35.0 mmol, 5.0 equiv., 77 %) in DCM (30 ml) was added *via* cannula at 0°C. The mixture was then stirred at room temperature overnight. The precipitate was filtered and the solution diluted with DCM (200 ml). The organic layer was washed with aqueous NaOH solution (4 x 150 ml), dried over sodium sulfate and evaporated. The residue was recrystallised from hexane/ DCM to give *4-(3-phenylpropane-1-sulfonyl)benzoic acid ethyl ester* **2.281** as a white solid (1.34 g, 32 % over 3 steps); mp 90-91°C; (Found: $[M+NH_4]^+$ 350.1418. $C_{18}H_{20}O_4S$ requires $[M+NH_4]^+$, 350.1421); ν_{max} (KBr)/cm^{-1} 3085 (Ar-H), 3022 (Ar-H), 2988 (C-H), 2942 (C-H), 2869 (C-H), 1717 (C=O), 1279 (SO_2), 1153 (SO_2); δ_H ($CDCl_3$) 1.43 (3H, t, *J* 7.1, CH_3), 2.01-2.09 (2H, m, $CH_2CH_2CH_2$), 2.71 (2H, t, *J* 7.4, ArCH_2), 3.08-3.12 (2H, m, SO_2CH_2), 4.43 (2H, q, *J* 7.1, CH_2O), 7.09-7.11 (2H, m, Ar*H*), 7.19-7.23 (1H, m, Ar*H*), 7.26-7.30 (2H, m, Ar*H*), 7.94-7.97 (2H, m, Ar*H*), 8.20-8.23 (2H, m, Ar*H*); δ_C ($CDCl_3$) 14.3 (CH_3), 24.1 (CH_2), 34.0 (CH_2), 55.3 (CH_2), 61.8 (CH_2), 126.5 (CH), 128.2 (CH), 128.4 (CH), 128.7 (CH), 130.4 (CH), 135.2 (C), 139.6 (C), 142.7 (C), 165.0 (C); *m/z* (ESI) 350 ($[M+NH_4]^+$, 100 %), 333 (78), 149 (18), 111 (37), 72 (58).

Attempted reduction of 4-(3-phenylpropane-1-sulfonyl)benzoic acid ethyl ester 2.281

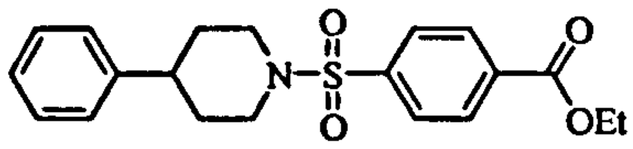


2.281 **2.286**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), salt **2.22** (425 mg, 0.9 mmol, 3.0 equiv.), 4-(3-phenyl-propane-1-sulfonyl)-benzoic acid ethyl ester **2.281** (95.5 mg, 0.287 mmol, 1.0 equiv.). *Acidic* work-up was carried out and the solid residue washed with diethyl ether to give *4-(3-phenyl-propane-1-sulfonyl)-benzoic acid* **2.286** as white solid (64 mg, 73 %); mp 80-81°C; ν_{max} (KBr)/cm^{-1} 3409 (O-H), 1682 (C=O), 1284 (SO_2), 1141 (SO_2); δ_H (DMSO) 1.77-1.85 (2H, m, $CH_2CH_2CH_2$), 2.62 (2H, t, *J* 7.7, CH_2Ar), 3.33 (2H, t, *J* 7.8, CH_2SO_2), 4.43 (2H, q, *J* 7.1, CH_2O), 7.12-7.18 (3H, m, Ar*H*), 7.23-7.27 (2H, m,

Ar*H*), 7.99 (2H, d, *J* 8.5, Ar*H*), 8.15 (2H, d, *J* 8.5, Ar*H*); δ_C (DMSO) 24.2 (CH_2), 33.1 (CH_2), 53.9 (CH_2), 126.1 (CH), 128.0 (CH), 128.3 (CH), 128.5 (CH), 130.2 (CH), 135.5 (C), 140.5 (C), 142.3 (C), 160.1 (C); *m/z* (ESI) 303 ($[M-H]^+$, 100 %), 259 (7).

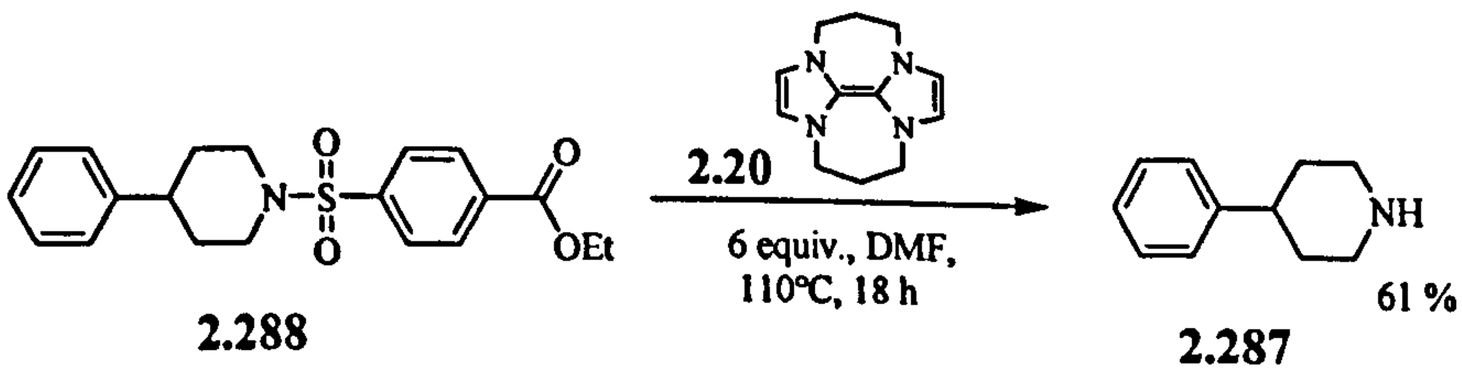
4-(4-Phenylpiperidine-1-sulfonyl)benzoic acid ethyl ester 2.288



2.288

4-Phenylpiperidine (1.20 g, 7.45 mmol, 1.0 equiv.) and triethylamine (4.19 ml, 29.8 mmol, 4.0 equiv.) were dissolved in DCM (20 ml) and cooled to 0°C. A solution of 4-chlorosulfonylbenzoic acid (1.65 g, 7.45 mmol, 1.0 equiv.) in DCM (20 ml) was then added dropwise at 0°C. The reaction mixture was subsequently stirred for 3 h at room temperature. The solvent was removed *in vacuo* and the residue dissolved in ethanol (40 ml). Thionylchloride (1.09 ml, 14.9 mmol, 2.0 equiv.) was added dropwise while cooling to 0°C. After heating the mixture overnight at reflux, the solvent was removed under reduced pressure and the mixture loaded onto silica. Purification by column chromatography (20:80 ethyl acetate/ petroleum ether) was then carried out to give *4-(4-phenylpiperidine-1-sulfonyl)benzoic acid ethyl ester* **2.288** as a white solid (2.27 g, 82 %); mp 124-125°C; (Found: $[M+H]^+$ 374.1414. $C_{20}H_{23}NO_4S$ requires $[M+H]^+$, 374.1421); ν_{max} (KBr)/cm^{-1} 3027 (Ar-H), 2978 (C-H), 2942 (C-H), 1722 (C=O), 1340 (SO_2), 1164 (SO_2); δ_H ($CDCl_3$) 1.43 (3H, t, *J* 7.2, CH_3), 1.83-1.92 (4H, m, CH_2CHCH_2), 2.35-2.44 (3H, m, C*H*HNC*H*H and C*H*Ar), 3.97-3.99 (2H, m, CH*H*NCH*H*), 4.44 (2H, q, *J* 7.2, CH_2O), 7.14-7.16 (2H, m, Ar*H*), 7.20-7.24 (1H, m, Ar*H*), 7.29-7.33 (2H, m, 2 x Ar*H*), 7.87 (2H, d, *J* 8.6, 2 x Ar*H*), 8.22 (2H, d, *J* 8.6, 2 x Ar*H*); δ_C ($CDCl_3$) 14.3 (CH_3), 32.5 (CH_2), 41.8 (CH), 46.8 (CH_2), 61.7 (CH_2), 126.6 (CH), 126.6 (CH), 127.5 (CH), 128.6 (CH), 130.1 (CH), 134.3 (C), 140.2 (C), 144.6 (C), 165.2 (C); *m/z* (ESI) 374 ($[M+H]^+$, 100 %), 144 (4), 129 (5), 111 (8), 60 (22).

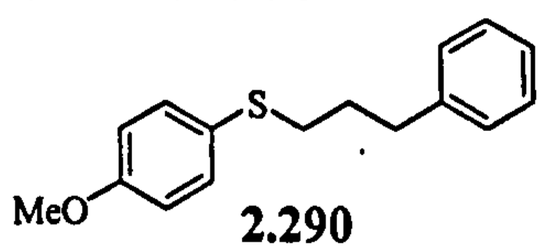
Reduction of 4-(4-phenylpiperidine-1-sulfonyl)benzoic acid ethyl ester 2.288



2.288 **2.287**

The experiment was carried out according to the general 'pure donor-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), donor **2.20** (388 mg, 1.8 mmol, 6.0 equiv.), 4-(4-phenylpiperidine-1-sulfonyl)benzoic acid ethyl ester **2.288** (108 mg, 0.289 mmol, 1.0 equiv.). After heating for 18 h at 110°C, the DMF was evaporated and the resulting residue dissolved in water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic layer was washed with water (20 ml) and brine (20 ml), dried over Na_2SO_4 and removed under reduced pressure. The residue was purified by column chromatography on silica gel (6:2:92 MeOH/ triethylamine/ DCM) to give 4-phenyl-piperidine **2.287**[218] as a colourless liquid (28 mg, 61 %); ν_{max} (NaCl)/cm^{-1} 3305 (N-H), 3059 (Ar-H), 3028 (Ar-H), 2930 (C-H), 2846 (C-H), 1493 (C-H); δ_H ($CDCl_3$) 1.61-1.71 (2H, m, NCH_2CH_2), 1.82-1.86 (2H, m, NCH_2CH_2), 2.59-2.66 (1H, m, CH_2CHCH_2), 2.71-2.78 (2H, m, NCH_2), 3.18-3.21 (2H, m, NCH_2), 7.20-7.33 (3H, m, Ar*H*), 7.407.53 (2H, m, Ar*H*); δ_C ($CDCl_3$) 34.5 (CH_2), 43.1 (CH), 47.1 (CH_2), 126.0 (CH), 126.8 (CH), 128.4 (CH), 146.8 (C); *m/z* (ESI) 162 ($[M+H]^+$, 100 %).

1-Methoxy-4-(3-phenylsulfonyl)benzene 2.290

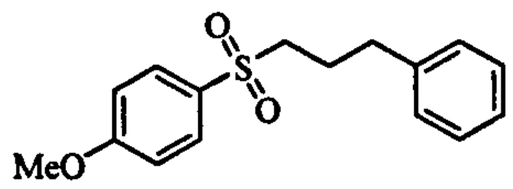


2.290

A solution of 4-methoxythiophenol (0.50 ml, 4.06 mmol, 1.0 equiv.) in DMF (5 ml) was added to a suspension of washed sodium hydride (178 mg, 4.46 mmol, 1.1 equiv.) in DMF (10 ml) while cooling to 0°C. After stirring for 30 min at room temperature the mixture was re-cooled to 0°C and a solution of (3-iodopropyl)benzene (1.0 g, 4.06 mmol, 1.0 equiv.) in DMF (10 ml) was added dropwise *via* cannula. The mixture was allowed to warm to room temperature and was stirred for 4 h. Water (200 ml) and diethyl ether (200 ml) were then added and the aqueous layer extracted further with diethyl ether (200 ml). The combined organic layer was washed with water (3 x 200 ml) and brine (200 ml), dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (10:90 ethyl acetate/ petroleum ether) to give *1-ethoxy-4-(3-phenylsulfonyl)benzene* **2.290** as a colourless liquid (932 mg, 89 %); (Found: M^+ 258.1076. $C_{16}H_{18}OS$ requires M^+, 358.1073); ν_{max} (NaCl)/cm^{-1} 3061 (Ar-H), 3026 (Ar-H), 2937 (C-H), 2834 (C-H), 1493 (C-H); δ_H ($CDCl_3$) 1.92 (2H, quintet, *J* 7.4, $CH_2CH_2CH_2$), 2.75 (2H, t, *J* 7.4, CH_2Ar), 2.85 (2H, t, *J* 7.4, SCH_2), 3.82 (3H, s, OCH_3), 6-84-6.88 (2H, m, Ar*H*), 7.17-7.23 (3H, m, Ar*H*), 7.28-7.32 (2H, m, Ar*H*), 7.34-7.38 (2H, m, Ar*H*); δ_C ($CDCl_3$)

30.8 (CH_2), 34.6 (CH_2), 35.1 (CH_2), 55.4 (CH_3), 114.5 (CH), 125.9 (CH), 126.5 (C), 128.3 (CH), 128.5 (CH), 133.2 (CH), 141.5 (C), 158.8 (C); *m/z* (EI) 258 (M^+, 13 %), 140 (100), 139 (52), 91 (98), 65 (17).

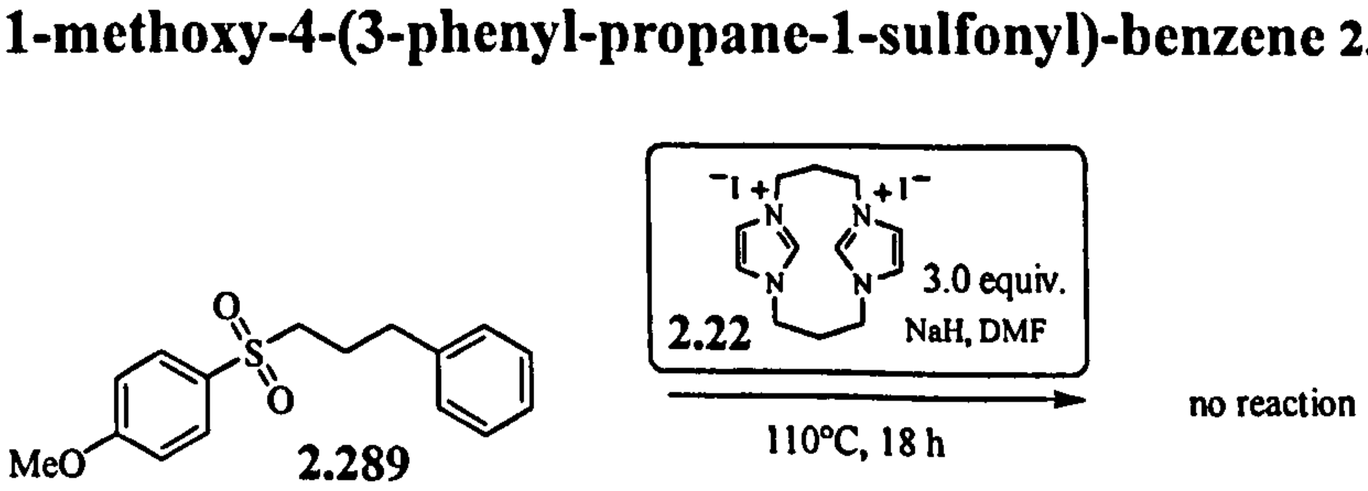
1-Methoxy-4-(3-phenyl-propane-1-sulfonyl)benzene 2.289



2.289

1-Methoxy-4-(3-phenylsulfonyl)benzene **2.290** (0.804 g, 3.11 mmol, 1.0 equiv.) was dissolved in DCM (5 ml) and a solution of 3-chloroperoxybenzoic acid (3.20 g, 18.6 mmol, 6.0 equiv., 77 %) in DCM (35 ml) was added *via* cannula at 0°C. The mixture was then stirred at room temperature overnight. The precipitate was filtered and the solution diluted with DCM (150 ml). The organic layer was washed with aqueous NaOH solution (4 x 100 ml), dried over sodium sulfate and concentrated *in vacuo*. The residue was loaded onto silica and purified by column chromatography on silica gel to give *1-methoxy-4-(3-phenyl-propane-1-sulfonyl)benzene* **2.289** as a white solid (0.894 g, 99 %); mp 96-98°C; (Found: $[M+NH_4]^+$ 308.1313. $C_{16}H_{18}O_3S$ requires $[M+NH_4]^+$, 308.1315); ν_{max} (KBr)/cm^{-1} 3093 (Ar-H), 3026 (Ar-H), 2921 (C-H), 2856 (C-H), 2869 (C-H), 1498 (C-H), 1263 (SO_2), 1145 (SO_2), 1024 (C-O), 756 (Ar-H); δ_H ($CDCl_3$) 2.04 (2H, m, $CH_2CH_2CH_2$), 2.70 (2H, t, *J* 7.4, CH_2Ar), 3.07 (2H, t, *J* 7.8, SO_2CH_2), 3.88 (3H, s, OCH_3), 7.01-7.03 (2H, m, Ar*H*), 7.11-7.13 (2H, m, Ar*H*), 7.19-7.23 (1H, m, Ar*H*), 7.27-7.30 (2H, m, Ar*H*), 7.80-7.83 (2H, m, Ar*H*); δ_C ($CDCl_3$) 24.3 (CH_2), 34.0 (CH_2), 55.6 (CH_2), 55.6 (CH_3), 114.5 (CH), 126.4 (CH), 128.3 (CH), 128.6 (CH), 130.1 (CH), 130.3 (C), 140.0 (C), 163.7 (C); *m/z* (CI) 308 ($[M+NH_4]^+$, 100 %), 118 (18), 108 (21), 91 (12).

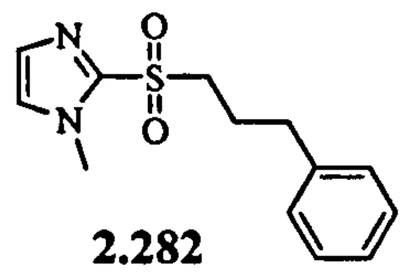
Test reaction of 1-methoxy-4-(3-phenyl-propane-1-sulfonyl)-benzene 2.289



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), salt **2.22** (425 mg, 0.9 mmol, 3.0 equiv.), 1-methoxy-4-(3-phenyl-propane-1-sulfonyl)-benzene **2.289** (87 mg, 0.3 mmol, 1.0

equiv.). Observation: Upon addition of the yellow donor solution to **2.289**, the colour changed to dark-red at room temperature. ^{1}H-NMR of the crude mixture after *neutral* work-up showed only starting material **2.289**; the reaction did not proceed.

1-Methyl-2-(3-phenyl-propane-1-sulfonyl)-1*H*-imidazole 2.282



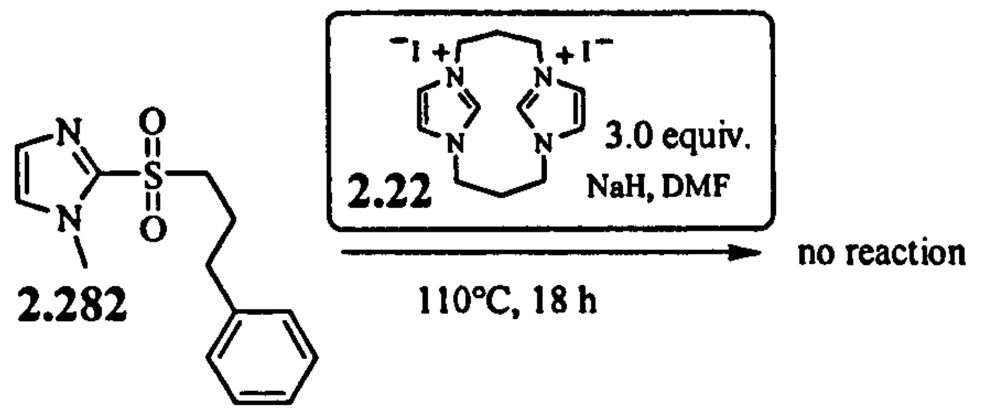
2.282

Stage (i) A solution of 2-mercapto-1-methylimidazole (3.0 g, 26.0 mmol, 1.0 equiv.) in DMF (15 ml) was added to a suspension of washed sodium hydride (1.26 g, 31.0 mmol, 1.2 equiv.) in DMF (10 ml) while cooling to 0°C. After stirring for 30 min at room temperature the mixture was re-cooled to 0°C and a solution of (3-bromopropyl)benzene (4 ml, 26.0 mmol, 1.0 equiv.) in DMF (5 ml) was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 3 h. Water (200 ml) and ethyl acetate (200 ml) were then added and the aqueous layer extracted further with ethyl acetate (200 ml). The combined organic layer was washed with water (3 x 200 ml) and brine (200 ml), dried over sodium sulfate and evaporated. The residue was purified by column chromatography on silica gel to afford *1-methyl-2-(3-phenyl-propylsulfanyl)-1H-imidazole* **2.285** as a colourless liquid (5.1 g, 84 %); which was reacted further in the next step without further characterisation.

Stage (ii) 1-Methyl-2-(3-phenyl-propylsulfanyl)-1*H*-imidazole **2.285** (3.8 g, 16.3 mmol, 1.0 equiv.) was dissolved in DCM (10 ml) and potassium carbonate (6.78 g, 49.0 mmol, 3.0 equiv.) was added. A solution of 3-chloroperoxybenzoic acid (14.1 g, 81.7 mmol, 5.0 equiv., 77 %) in DCM (50 ml) was added *via* cannula at 0°C. The mixture was then stirred at room temperature overnight. The precipitate was filtered and the solution diluted with DCM (250 ml). The organic layer was washed with aqueous NaOH solution (4 x 200 ml), dried over sodium sulfate and concentrated *in vacuo*. The residue was recrystallised (hexane/ DCM) to give *1-methyl-2-(3-phenyl-propane-1-sulfonyl)-1H-imidazole* **2.282** as a white solid (3.1 g, 72 %); mp 139°C; (Found: $[M+H]^+$ 265.1006. $C_{13}H_{16}N_2O_2S$ requires $[M+H]^+$, 265.1005); ν_{max} (KBr)/cm^{-1} 3114 (Ar-H), 3027 (Ar-H), 2951 (C-H), 2867 (C-H), 1455 (C-H), 1324 (SO_2), 1121 (SO_2); δ_H ($CDCl_3$) 2.15-2.22 (2H, m, $CH_2CH_2CH_2$), 2.77 (2H, t, *J* 7.5, CH_2Ar), 3.43-3.47 (2H, m, SO_2CH_2), 3.97 (3H, s, NCH_3), 7.14 (1H, d, *J* 1.0, Ar*H*), 7.13-7.18 (3H, m, Ar*H*), 7.19-7.24 (1H, m, Ar*H*), 7.28-

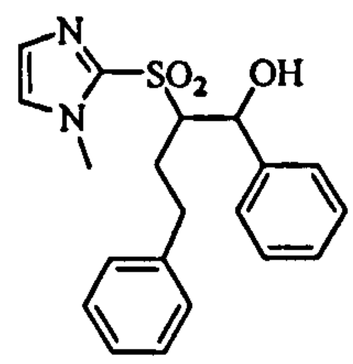
7.32 (2H, m, Ar*H*); δ_C ($CDCl_3$) 22.7 (CH_2), 34.1 (CH_2), 35.1 (CH_3), 54.2 (CH_2), 125.4 (CH), 126.5 (CH), 128.4 (CH), 128.6 (CH), 129.1 (CH), 139.9 (C); *m/z* (CI) 265 ($[M+H]^+$, 37 %), 172 (6), 108 (4), 83 (100).

Test reaction of 1-methyl-2-(3-phenyl-propane-1-sulfonyl)-1*H*-imidazole 2.282



The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), salt **2.22** (425 mg, 0.9 mmol, 3.0 equiv.), 1-methyl-2-(3-phenyl-propane-1-sulfonyl)-1*H*-imidazole **2.2282** (79 mg, 0.3 mmol, 1.0 equiv.). Observation: Upon addition of the yellow donor solution to **2.289**, the colour changed to orange and upon heating to dark-red. ^{1}H-NMR of the crude mixture after *neutral* work-up showed only starting material **2.282**; the reaction did not proceed.

2-(1-Methyl-1*H*-imidazole-2-sulfonyl)-1,4-diphenyl-butan-1-ol 2.292[235]

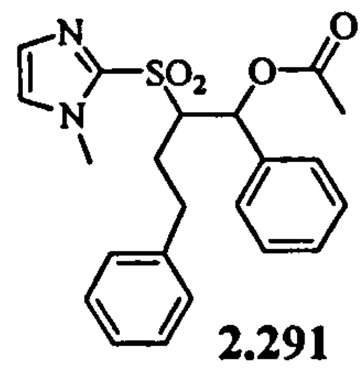


2.292

1-Methyl-2-(3-phenylpropane-1-sulfonyl)-1*H*-imidazole **2.282** (1.07 g, 4.059 mmol, 1.0 equiv.) was dissolved in THF (8 ml) and cooled to –78°C. Sodium hexamethyldisilazide [NaHMDS] (6.75 ml, 4.059 mmol, 1.0 equiv., c = 0.6 mol/l) was added dropwise and the mixture was stirred for 30 min at –78°C. A solution of benzaldehyde (0.41 ml, 4.059 mmol, 1.0 equiv.) in THF (1 ml) was then added dropwise *via* cannula at –78°C. After stirring for 30 min at –78°C, sat. ammonium chloride solution was added, followed by water and ethyl acetate. The aqueous layer was extracted further with ethyl acetate (200 ml). The combined organic layer was dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (15:85 acetonitrile/ toluene) to afford 2-(1-methyl-1*H*-imidazole-2-sulfonyl)-1,4-diphenyl-butan-1-ol[235] **2.292**

as a white solid (265 mg, 18 %) that was used in the next step without further characterisation.

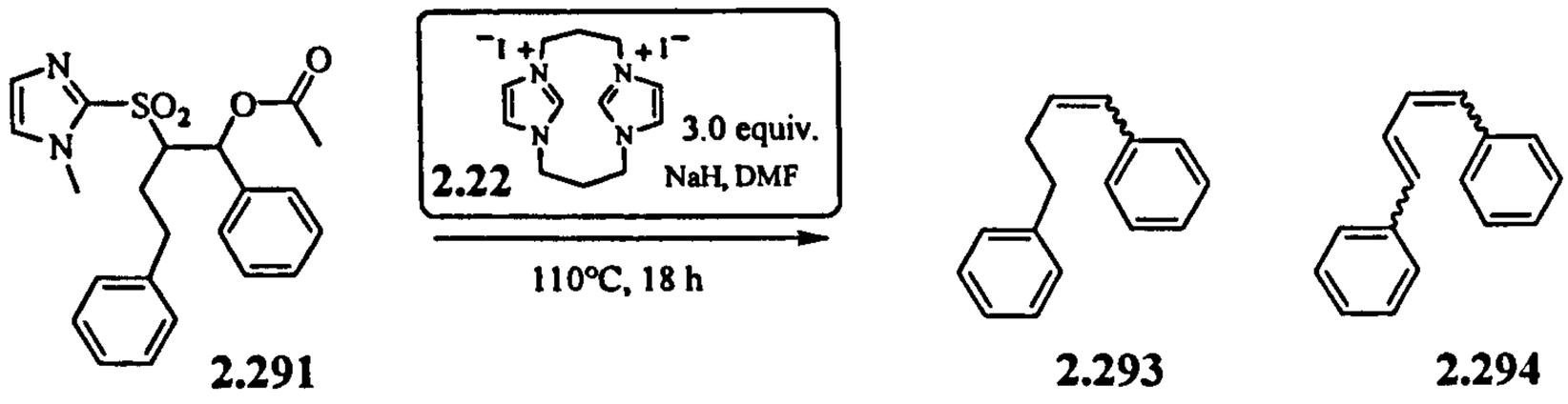
Acetic acid 2-(1-methyl-1*H*-imidazole-2-sulfonyl)-1,4-diphenyl-butyl ester 2.291[236]



2.291

2-(1-Methyl-1*H*-imidazole-2-sulfonyl)-1,4-diphenyl-butan-1-ol **2.292** (149 mg, 0.402 mmol, 1.0 equiv.), triethylamine (0.05 ml, 0.965 mmol, 2.4 equiv.) and 4-DMAP (5 mg, 0.04 mmol, 0.1 equiv.) were dissolved in DCM (3 ml). Acetic anhydride (0.045 ml, 0.4826 mmol, 1.2 equiv.) was then added while cooling to 0°C. The reaction mixture was allowed to warm to room temperature and was stirred overnight. DCM (100 ml) was then added and the organic layer was washed with water (100 ml) and was subsequently dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (8:92 acetonitrile/ toluene) to afford *acetic acid 2-(1-methyl-1H-imidazole-2-sulfonyl)-1,4-diphenylbutyl ester* **2.291** as a single diastereomer as a colourless oil (123 mg, 74 %); (Found: $[M+H]^+$ 413.1535. $C_{22}H_{24}N_2O_4S$ requires $[M+H]^+$, 413.1530); ν_{max} (NaCl)/cm^{-1} 3055 (Ar-H), 3033 (Ar-H), 2923 (C-H), 1746 (C=O), 1451 (C-H), 1311 (SO_2), 1124 (SO_2); δ_H ($CDCl_3$) 1.77 (3 H, s, $COCH_3$), 1.82-1.91 (1H, m, $CHCHHCH_2Ph$), 2.13-2.20 (1H, m, $CHCHHCH_2Ph$), 2.49-2.59 (2H, m, CH_2Ph), 3.89 (3H, s, NCH_3), 4.14-4.18 (1H, m, $ArSO_2CH$), 6.21 (1H, d, *J* 7.2, $PhCHO$), 6.87 (2H, d, *J* 5.6, Ar*H*), 7.03 (1H, s, Ar*H*), 7.13-7.22 (4H, m, Ar*H*), 7.31-7.39 (5H, m, Ar*H*); δ_C ($CDCl_3$) 20.9 (CH_3), 33.2 (CH_2), 28.0 (CH_2), 35.5 (CH_3), 66.2 (CH), 73.8 (CH), 125.6 (CH), 126.3 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.1 (CH), 129.5 (CH), 136.4 (C), 140.2 (C), 142.4 (C), 168.9 (C); *m/z* (CI) 413 ($[M+H]^+$, 17 %), 286 (21), 226 (100), 208 (59), 117 (38), 91 (52).

Reduction of acetic acid 2-(1-methyl-1*H*-imidazole-2-sulfonyl)-1,4-diphenylbutyl ester 2.291



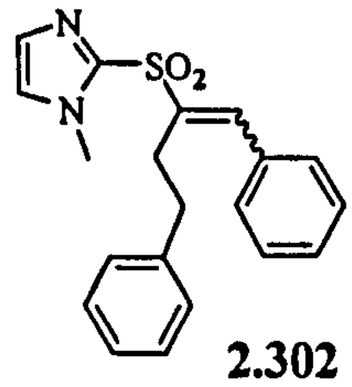
2.291 **2.293** **2.294**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (8 ml), salt **2.22** (141 mg, 0.297 mmol, 3.0), acetic acid 2-(1-methyl-1*H*-imidazole-2-sulfonyl)-1,4-diphenyl-butyl ester **2.291** (40.8 mg, 0.099 mmol, 1.0 equiv.). Observation: Upon heating of the mixture the colour changes from yellow to dark red. The purification of the residue after *neutral* work-up was carried out by column chromatography on silica gel (4:96 ethyl acetate/ hexane) to give 1,4-diphenyl-1-butene[237] **2.293** and 1,4-diphenyl-1,3-butadiene[238] **2.294** as an inseparable mixture as a white semi-solid (15.0 mg, ~ 73 %); the ^{1}H-NMR spectrum of the mixture can be found in the Appendix, Chapter 9. Further analysis of the fraction by GC-MS showed 5 major peaks at different intensities, possibly corresponding to 3 isomers of **2.294** (E/E, Z/Z, E/Z) and 2 isomers of **2.293** (E, Z): 1,4-diphenyl-1-butene[237] **2.293**: *m/z* (EI) 208 (M^+, 3 %), 117 (100), 115(55), 91 (13).

1,4-diphenyl-1,3-butadiene[238] **2.294**: *m/z* (EI) 206 (M^+, 100 %), 205 (47), 191 (46), 128 (29), 91 (44).

Further attempts to purify the mixture by HPLC were unsuccessful (the ^{1}HNMR spectrum can be found in the Appendix).

2-(1,4-Diphenyl-but-1-ene-2-sulfonyl)-1-methyl-1*H*-imidazole 2.302[236]

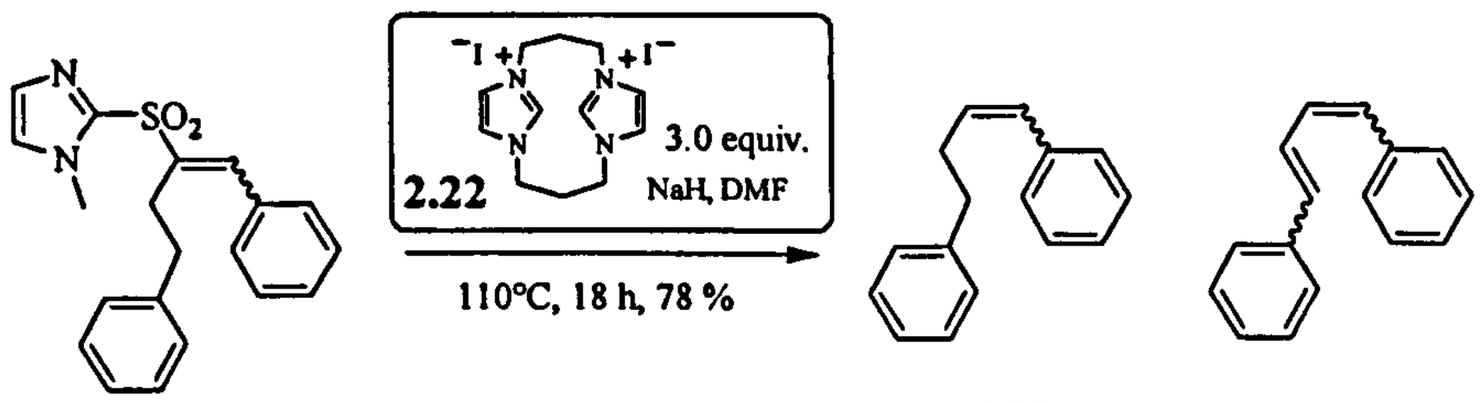


2.302

Acetic acid 2-(1-methyl-1*H*-imidazole-2-sulfonyl)-1,4-diphenyl-butyl ester **2.291** (72 mg, 0.174 mmol, 1.0 equiv.) was dissolved in THF (10 ml) and DBU [1,8-diazabicyclo[5.4.0]undec-7-en] (0.16 ml, 1.047 mmol, 6.0 equiv.) was added dropwise at room temperature. The mixture was stirred overnight at room temperature, then concentrated under reduced pressure and purified by column chromatography on silica gel

(18:82 acetonitrile/ toluene) to afford *2-(1,4-diphenyl-but-1-ene-2-sulfonyl)-1-methyl-1H-imidazole* **2.302** as a slightly yellow semi-solid (55 mg, 89 %); (Found: $[M+H]^+$ 353.1317. $C_{20}H_{20}N_2O_4S$ requires $[M+H]^+$, 353.1318); ν_{max} (NaCl)/cm^{-1} 3104 (Ar-H), 3022 (Ar-H), 2962 (C-H), 1454 (C-H), 1321 (SO_2), 1123 (SO_2); δ_H ($CDCl_3$) 2.79 (2H, m, CH_2CH_2Ar), 2.97-3.01 (2H, m, CH_2CH_2Ar), 3.97 (3H, s, NCH_3), 7.05 (1H, d, *J* 0.6, Ar*H*), 7.12-7.14 (2H, m, Ar*H*), 7.18-7.20 (2H, m, Ar*H*), 7.26-7.30 (2H, m, Ar*H*), 7.39-7.48 (5H, m, Ar*H*), 7.88 (1H, s, ArC*H*=C); δ_C ($CDCl_3$) 29.2 (CH_2), 34.1 (CH_2), 35.2 (CH_3), 126.2 (CH), 126.4 (CH), 128.4 (CH), 128.6 (CH), 129.0 (CH), 129.6 (CH), 129.9 (CH), 130.0 (CH), 133.2 (C). 140.0 (CH), 140.3 (C), 140.5 (C), 141.5 (C); *m/z* (CI) 353 ($[M+H]^+$, 4 %), 226 (8), 117 (7), 83 (100), 44 (16).

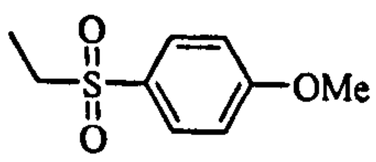
Reduction of 2-(1,4-diphenyl-but-1-ene-2-sulfonyl)-1-methyl-1*H*-imidazole 2.302



2.302 **2.293** **2.294**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents*: 110°C, 18 h, DMF (8 ml), salt **2.22** (205 mg, 0.432 mmol, 3.0), acetic acid 2-(1-methyl-1*H*-imidazole-2-sulfonyl)-1,4-diphenyl-butyl ester **2.302** (40.8 mg, 0.099 mmol, 1.0 equiv.). Observation: Upon heating of the mixture the colour changed from yellow to dark red. The purification of the residue after *neutral* work-up was carried out by column chromatography on silica gel (4:96 ethyl acetate/ hexane) to give **2.293** and **2.294** as an inseparable mixture as a white semi-solid (22 mg, ~ 78 %). Further analyses of the mixture by ^{1}H-NMR spectroscopy and GC-MS showed the identical composition as described above (in the reaction with **2.291**).

1-Ethanesulfonyl-4-methoxybenzene 2.307



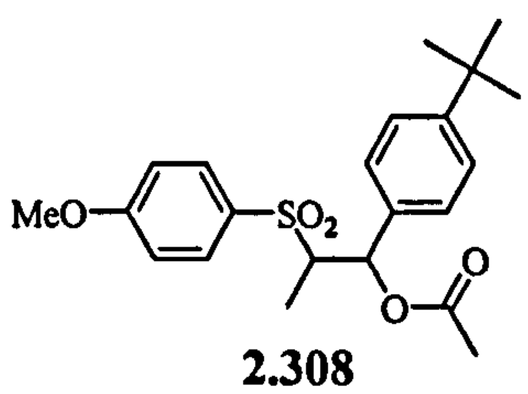
2.307

<u>*Stage (i)*</u> A solution of 4-methoxythiophenol (4.0 ml, 0.03 mol, 1.0 equiv.) in DMF (15 ml) was transferred *via* cannula to a suspension of washed sodium hydride (1.56 g,

0.039 mol, 1.2 equiv.) in DMF (5 ml) while cooling to 0°C. After stirring the mixture for 0.5 h at room temperature the mixture was re-cooled to 0°C, and a solution of iodoethane (2.86 ml, 0.0357 mol, 1.1 equiv.) in DMF (5 ml) was added dropwise. The mixture was then stirred at room temperature for 2.5 h. Water (200 ml) and ethyl acetate (200 ml) were added and the organic layer was washed further with brine (200 ml), was then dried over sodium sulfate, filtered and evaporated. The residue (3.945 g) was not exposed to further purification and reacted in the next step directly.

<u>*Stage (ii)*</u> The crude intermediate from *stage (i)* (3.945 g) was dissolved in DCM (20 ml) and a solution of 3-chloroperoxybenzoic acid (24.3 g, 0.1408 mol, 6.0 equiv., 77 %) in DCM (200 ml) was added *via* cannula at 0°C. The mixture was then stirred at room temperature overnight. The precipitate was filtered and the solution diluted with DCM (300 ml). The organic layer was washed with aqueous NaOH solution (4 x 200 ml), dried over sodium sulfate and evaporated. The residue was recrystallised from hexane/ DCM to give *1-ethanesulfonyl-4-methoxybenzene* **2.307** as a white solid (2.42 g, 40 % over 2 steps); mp 56-58°C; (Found: $[M+NH_4]^+$ 218.0844. $C_9H_{12}O_3S$ requires $[M+NH_4]^+$, 218.0845); ν_{max} (KBr)/cm^{-1} 3069 (Ar-H), 3016 (Ar-H), 2972 (C-H), 2934 (C-H), 2848 (C-H), 1496 (C-H), 1275 (SO_2), 1139 (SO_2); δ_H ($CDCl_3$) 1.24 (3H, t, *J* 7.4, CH_2CH_3), 3.07 (2H, q, *J* 7.4, CH_2CH_3), 3.87 (3H, s, OCH_3), 6.99-7.05 (2H, m, Ar*H*), 7.81-7.86 (2H, m, Ar*H*); δ_C ($CDCl_3$) 7.5 (CH_3), 50.9 (CH_2), 55.7 (CH_3), 114.5 (CH), 130.2 (C), 130.4 (CH), 163.7 (C); *m/z* (EI) 200 (M^+, 77 %), 171 (100), 155 (24), 123 (26), 107 (37), 92 (32), 77 (39).

Acetic acid 1-(4-*tert*-butyl-phenyl)-2-(4-methoxybenzenesulfonyl)propyl ester 2.308



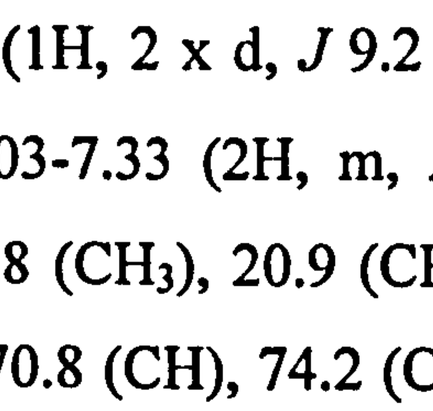
2.308

<u>*Stage (i)*</u> 1-Ethanesulfonyl-4-methoxybenzene **2.307** (1.13 g, 5.67 mmol, 1.0 equiv.) was dissolved in THF (12 ml) and cooled to –78°C. Sodium hexamethyldisilazide [NaHMDS] (10.4 ml, 6.24 mmol, 1.1 equiv., c = 0.6 mol/l) was added dropwise and the mixture was stirred for 30 min at –78°C. A solution of 4-*tert*-butyl-benzaldehyde (1.14 ml, 6.807 mmol, 1.2 equiv.) in THF (2 ml) was then added dropwise *via* cannula at –78°C. After stirring for 30 min at –78°C, sat. ammonium chloride solution was added, followed by water and ethyl acetate. The aqueous layer was extracted further with ethyl acetate (200

ml). The combined organic layer was dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (10:90 diethyl ether/ toluene) to afford *1-(4-tert-butylphenyl)-2-(4-methoxybenzenesulfonyl)propan-1-ol* in a mixture with starting material **2.307** (0.724 g) that was reacted in the next step without further purification.

Stage (ii) The crude mixture from *stage (i)* (0.724 g), triethylamine (0.59 ml, 4.29 mmol, 2.4 equiv.) and 4-DMAP (22 mg, 0.17 mmol, 0.1 equiv.) were dissolved in DCM (30 ml). Acetic anhydride (0.2 ml, 2.14 mmol, 1.2 equiv.) was then added while cooling to 0°C. The reaction mixture was allowed to warm to room temperature and was stirred overnight. DCM (200 ml) was then added and the organic layer was washed with water (200 ml) and was subsequently dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (3:97 diethyl ether/ toluene) to afford *acetic acid 1-(4-tert-butylphenyl)-2-(4-methoxybenzenesulfonyl)propyl ester* **2.308** as a mixture of diastereoisomers as a colourless liquid (131 mg, 6 % over 2 steps); **%);** (Found: $[M+NH_4]^+$ 422.1996. $C_{22}H_{28}O_5S$ requires $[M+NH_4]^+$, 422.1996); ν_{max} (NaCl)/cm^{-1} 3016 (Ar-H), 2965 (C-H), 2906 (C-H), 1749 (C=O), 1595 (Ar), 1498 (C-H), 1319 (SO_2), 1143 (SO_2), 1028 (C-O); δ_H ($CDCl_3$) 1.03 and 1.27 (3H, d, *J* 7.2, CHCH_3), 1.26 and 1.28 (9H, s, C(CH_3)), 1.79 and 1.97 (3H, s, COCH_3), 3.24-3.30 and 3.61-3.69 (1H, m, SO_2C*H*), 3.87 (3H, s, OCH_3), 5.96 and 6.44 (1H, 2 x d, *J* 9.2 and 1.2, C*H*Ar), 7.01-7.05 (3H, m, Ar*H*), 7.18-7.22 (1H, m, Ar*H*), 7.03-7.33 (2H, m, Ar*H*), 7.80-7.89 (2H, m, Ar*H*); δ_C ($CDCl_3$) 7.5 (CH_3), 11.8 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 31.2 (CH_3), 34.5 (C), 34.6 (C), 55.7 (CH_3), 63.4 (CH), 65.6 (CH), 70.8 (CH), 74.2 (CH), 114.4 (CH), 125.2 (CH), 125.6 (CH), 127.2 (CH), 129.1 (C), 130.5 (C), 130.9 (CH), 131.3 (CH), 134.1 (C), 134.9 (C), 151.1 (C), 151.8 (C), 163.7 (C), 163.8 (C), 169.2 (C); *m/z* (CI) 422 ($[M+NH_4]^+$, 100 %), 362 (20), 281 (13), 252 (12), 232 (10), 192 (19), 175 (34), 159 (20).

Acetic acid 2-benzenesulfonyl-1-(4-*tert*-butyl-phenyl)-propyl ester 2.309



2.309

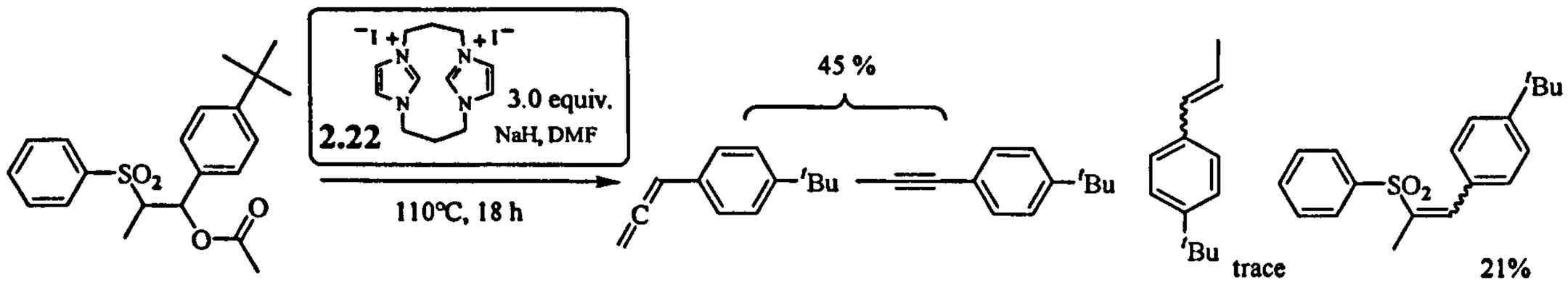
Stage (i) Ethanesulfonylbenzene **2.310** (1.435 g, 8.43 mmol, 1.0 equiv.) was dissolved in THF (12 ml) and cooled to –78°C. Sodium hexamethyldisilazide [NaHMDS] (15.4 ml,

9.27 mmol, 1.1 equiv., c = 0.6 mol/l) was added dropwise and the mixture was stirred for 30 min at –78°C. A solution of 4-*tert*-butylbenzaldehyde (1.7 ml, 10.12 mmol, 1.2 equiv.) in THF (4 ml) was then added dropwise *via* cannula at –78°C. After stirring for 30 min at –78°C, sat. ammonium chloride solution was added, followed by water and ethyl acetate. The aqueous layer was extracted further with ethyl acetate (200 ml). The combined organic layer was dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (10:90 diethyl ether/ toluene) to afford *2-benzenesulfonyl-1-(4-tert-butylphenyl)propan-1-ol* **2.311** in a mixture with starting material (1.952 g) that was reacted in the next step without further purification.

Stage (ii) The crude mixture from *stage (i)* (1.952 g), triethylamine (1.96 ml, 14.09 mmol, 2.4 equiv.) and 4-DMAP (71 mg, 0.58 mmol, 0.1 equiv.) were dissolved in DCM (40 ml). Acetic anhydride (0.66 ml, 7.04 mmol, 1.2 equiv.) was then added while cooling to 0°C. The reaction mixture was allowed to warm to room temperature and was stirred overnight. DCM (250 ml) was then added and the organic layer was washed with water (250 ml) and was subsequently dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (3:97 diethyl ether/ toluene) to afford *acetic acid 2-benzenesulfonyl-1-(4-tert-butylphenyl)propyl ester* **2.309** as a mixture of diastereoisomers as a white solid (1.58 g, 50 % over 2 steps); mp 139-142°C; (Found: $[M+NH_4]^+$ 392.1888 $C_{21}H_{26}O_4S$ requires $[M+NH_4]^+$, 392.1890); ν_{max} (KBr)/cm^{-1} 3055 (Ar-H), 2961 (C-H), 2863 (C-H), 1744 (C=O), 1447 (C-H), 1301 (SO_2), 1141 (SO_2), 1076 (C-O); δ_H ($CDCl_3$) 1.09 and 1.41 (3 H, d, *J* 7.3, CH_3CH), 1.28 and 1.29 [9H, s, C(CH_3)$_3$], 1.67 and 1.94 (3H, s, CH_3CO), 3.29-3.34 and 3.67-3.75 (1H, m, CH_3CHSO_2), 5.97 and 6.46 (1H, 2 x d, *J* 9.2 and 1.3, ArC*H*O), 7.05-7.10 (1H, m, Ar*H*), 7.18-7.20 (1H, m, Ar*H*), 7.31-7.35 (2H, m, Ar*H*), 7.57-7.62 (2H, m, Ar*H*), 7.66-7.70 (1H, m, Ar*H*), 7.90-7.95 (2H, m, Ar*H*); δ_C ($CDCl_3$) 7.5 (CH_3), 11.5 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.2 (CH_3), 34.6 (C), 34.5 (C), 63.4 (CH), 65.5 (CH), 70.8 (CH), 74.3 (CH), 125.2 (CH), 125.6 (CH), 127.1 (CH), 128.6 (CH), 129.1 (CH), 129.2 (CH), 133.5 (CH), 133.8 (CH), 133.9 (C), 134.7 (C), 137.9 (C), 139.5 (C), 151.2 (C), 151.9 (C), 169.0 (C), 169.1 (C); *m/z* (CI) 392 ($[M+NH_4]^+$, 100 %), 332 (50), 252 (52), 192 (35), 175 (60), 159 (36), 94 (17).

Reduction of acetic acid 2-benzenesulfonyl-1-(4-*tert*-butyl-phenyl)-propyl ester 2.309

(i)



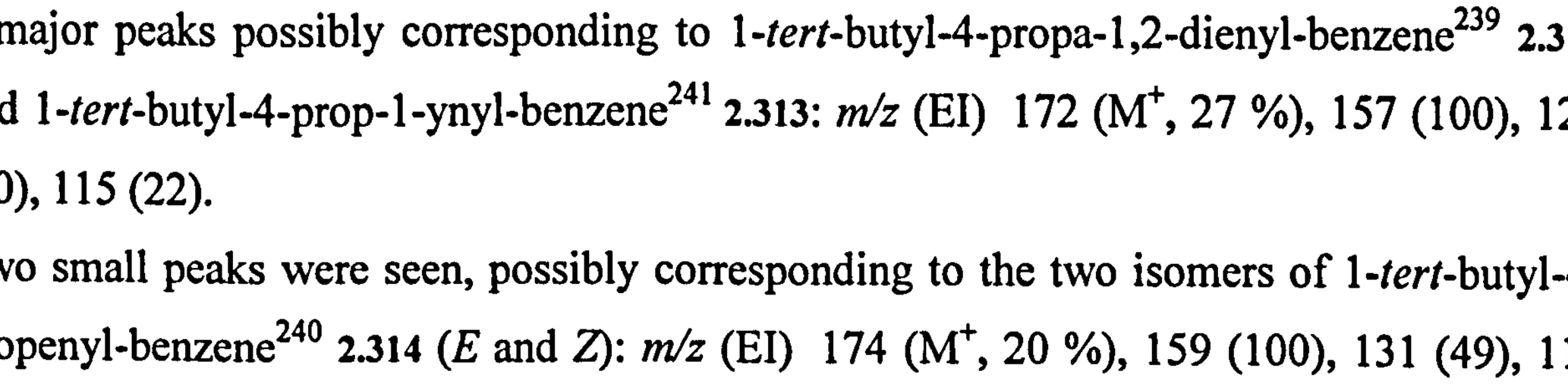
2.309 **2.312** **2.313** **2.314** **2.315**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (428 mg, 0.9 mmol, 3.0 equiv.), acetic acid 2-benzenesulfonyl-1-(4-*tert*-butylphenyl)propyl ester **2.309** (116 mg, 0.309 mmol, 1.0 equiv.). Purification of the residue after *neutral* work-up was carried out (1:99, then 50:50 diethyl ether/ hexane) to afford an inseparable mixture of 1-*tert*-butyl-4-propa-1,2-dienyl-benzene[239] **2.312** and 1-*tert*-butyl-4-prop-1-ynyl-benzene[241] **2.313** as a colourless liquid (23.7 mg, ~ 45 %); δ_H ($CDCl_3$) 1.32 and 1.33 (17H, 2 x s, C(CH_3)$_3$), 2.07 (3.7H, s, CH_3), 5.14 (1H, d, *J* 6.8, C*H*=CH), 6.2 (0.49H, t, *J* 6.6, C*H*=CH), 7.27-7.30 (1.4H, m, Ar*H*), 7.32-7.39 (6H, m, Ar*H*). Further analysis by GC-MS showed 3 peaks: 2 major peaks possibly corresponding to 1-*tert*-butyl-4-propa-1,2-dienyl-benzene[239] **2.312** and 1-*tert*-butyl-4-prop-1-ynyl-benzene[241] **2.313**: *m/z* (EI) 172 (M^+, 27 %), 157 (100), 129 (40), 115 (22).

Two small peaks were seen, possibly corresponding to the two isomers of 1-*tert*-butyl-4-propenyl-benzene[240] **2.314** (*E* and *Z*): *m/z* (EI) 174 (M^+, 20 %), 159 (100), 131 (49), 117 (30), 91 (27).

As the second fraction 1-(2-benzenesulfonylpropenyl)-4-isopropylbenzene **2.315** was isolated as a colourless liquid (21 mg, 21 %); for data see below.

(ii)



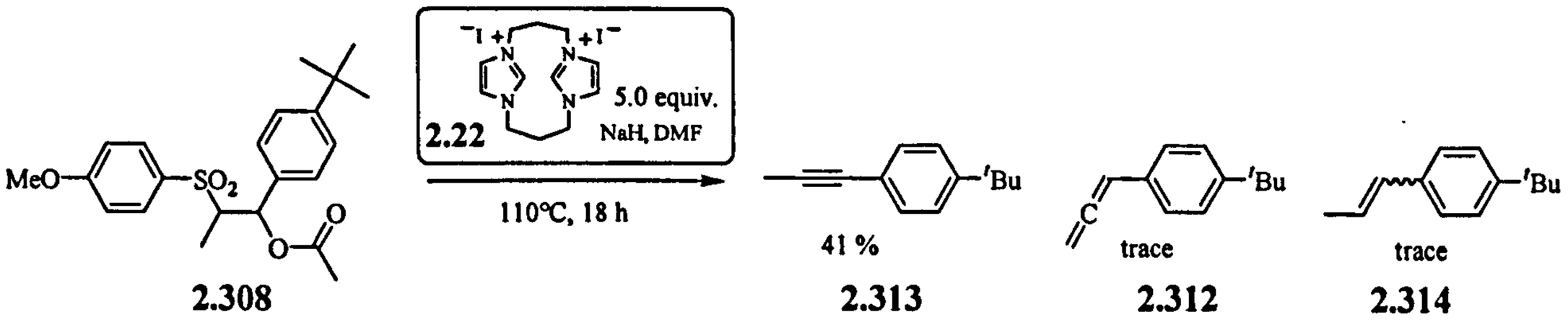
2.309 **2.313** **2.312** **2.314**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (708 mg, 1.5 mmol, 5.0

equiv.), acetic acid 2-benzenesulfonyl-1-(4-*tert*-butylphenyl)propyl ester **2.309** (104 mg, 0.277 mmol, 1.0 equiv.). Purification of the residue after *neutral* work-up was carried out (1:99, then 50:50 diethyl ether/ hexane) to afford 1-*tert*-butyl-4-prop-1-ynylbenzene[241] **2.313** as a colourless liquid (26.2 mg, 55 %); (Found: M^+ 172.1247. $C_{13}H_{16}$ requires M^+, 172.1246; ν_{max} (NaCl)/cm^{-1} 3038 (Ar-H), 2963 (C-H), 2863 (C-H), 1504 (Ar), 1462 (C-H); δ_H ($CDCl_3$) 1.32 [9H, s, C(CH_3)$_3$], 2.06 (3H, s, CH_3), 7.30-7.35 (4H, m, Ar*H*); δ_C ($CDCl_3$) 4.4 (CH_3), 31.1 (CH_3), 34.6 (C), 79.7 (C), 84.9 (C), 121.0 (C), 125.3 (CH), 131.2 (CH), 150.6 (C); *m/z* (EI) 172 (M^+, 38 %), 157 (100), 142 (17), 129 (28), 114 (27).

GC-MS analysis and comparison with the ^{1}H-NMR spectrum showed trace amounts of 1-*tert*-butyl-4-propa-1,2-dienyl-benzene[239] **2.312** being formed also. Further two peaks in GC-MS possibly correspond to the *E*- and *Z*-isomers of 1-*tert*-butyl-4-propenylbenzene[240] **2.314.**

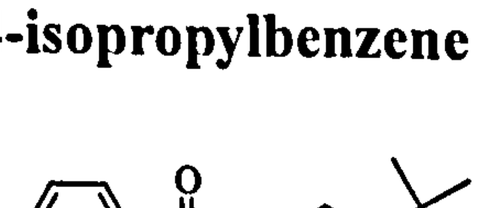
Test reaction of acetic acid 1-(4-*tert*-butyl-phenyl)-2-(4-methoxy-benzenesulfonyl)propyl ester 2.308



2.308 — 41 % **2.313** — trace **2.312** — trace **2.314**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (708 mg, 1.5 mmol, 5.0 equiv.), acetic acid 2-benzenesulfonyl-1-(4-*tert*-butyl-phenyl)propyl ester **2.308** (92 mg, 0.227 mmol, 1.0 equiv.). Purification of the residue after *neutral* work-up was carried out (1:99, then 50:50 diethyl ether/ hexane) to afford 1-*tert*-butyl-4-prop-1-ynylbenzene[241] **2.313** as a colourless liquid (16 mg, 41 %); for data see above. GC-MS analysis and comparison with the ^{1}H-NMR spectrum showed trace amounts of 1-*tert*-butyl-4-propa-1,2-dienylbenzene[239] **2.312** being formed also, as well as two peaks in GC-MS possibly corresponding to the *E*- and *Z*-isomers of 1-*tert*-butyl-4-propenylbenzene[240] **2.314.**

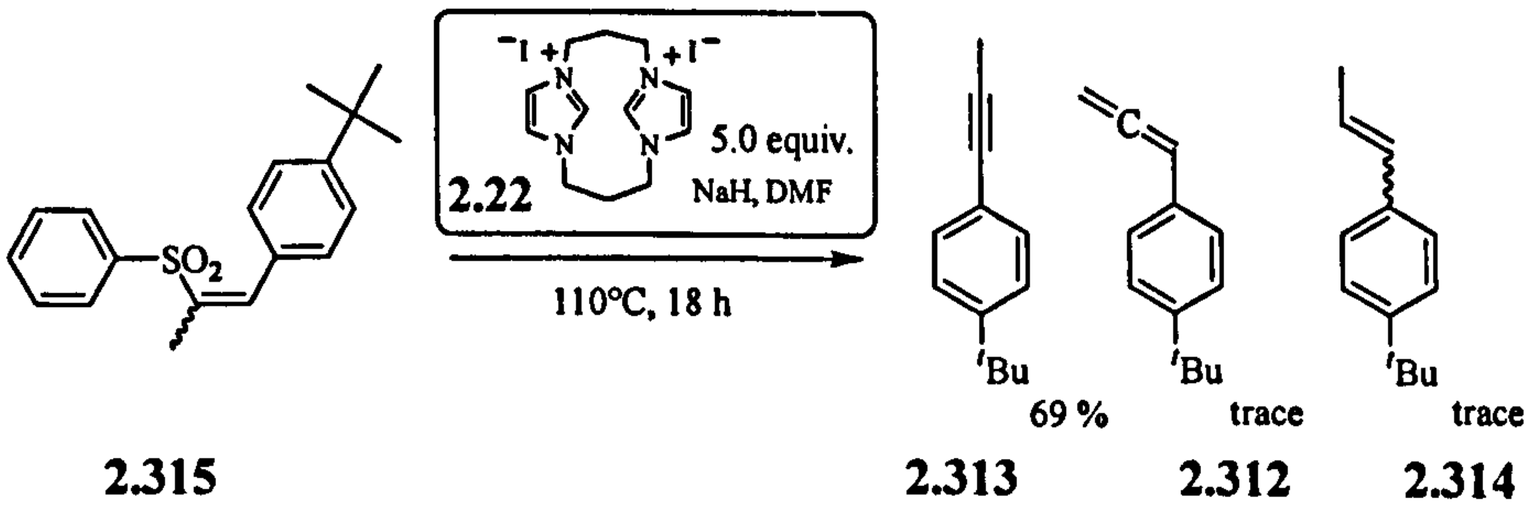
1-(2-Benzenesulfonyl-propenyl)-4-isopropylbenzene 2.315[236]



2.315

Acetic acid 2-benzenesulfonyl-1-(4-*tert*-butyl-phenyl)-propyl ester **2.309** (595 mg, 1.59 mmol, 1.0 equiv.) was dissolved in THF (40 ml) and diaza(1,3)bicyclo[5.4.0]undecane (1.42 ml, 9.53 mmol, 6.0 equiv.) was added dropwise at room temperature. The mixture was stirred overnight at room temperature, then concentrated under reduced pressure and purified by column chromatography on silica gel (2:98 diethyl ether/ toluene) to afford *1-(2-benzenesulfonyl-propenyl)-4-isopropylbenzene* **2.315** as a white solid (449 mg, 90 %); mp 100-103°C; (Found: $[M+NH_4]^+$ 322.1676. $C_{19}H_{22}O_2S$ requires $[M+NH_4]^+$, 322.1679); ν_{max} (KBr)/cm^{-1} 3066 (Ar-H), 2963 (C-H), 2873 (C-H), 1633 (Ar), 1446 (C-H), 1303 (SO_2), 1153 (SO_2); δ_H ($CDCl_3$) 1.34 (9H, s, C(C*H*$_3$)), 2.14 (3H, s, C*H*$_3$), 7.37-7.43 (2H, m, Ar*H*), 7.43-7.46 (2H, m, Ar*H*), 7.53-7.57 (2H, m, Ar*H*), 7.60-7.66 (1H, m, Ar*H*), 7.81-7.82 (1H, m, Ar*H*), 7.91-7.95 (2H, m, Ar*H*); δ_C ($CDCl_3$) 13.3 (CH_3), 31.1 (CH_3), 34.8 (C), 125.7 (CH), 128.1 (CH), 129.2 (CH), 129.6 (CH), 130.9 (C), 133.2 (CH), 136.2 (C), 137.5 (C), 139.4 (C), 152.9 (C); *m/z* (EI) 314 (M^+, 31 %), 299 (37), 172 (66), 157 (96), 128 (38), 115 (63), 77 (100), 57 (30).

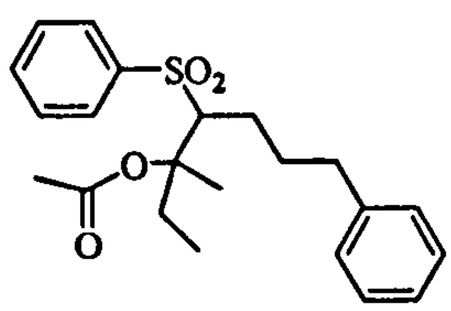
Test reaction of 1-(2-benzenesulfonylpropenyl)-4-isopropylbenzene 2.315



2.315 **2.313** **2.312** **2.314**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **2.22** (425 mg, 0.9 mmol, 3.0 equiv.), 1-(2-benzenesulfonylpropenyl)-4-isopropylbenzene **2.315** (92.5 mg, 0.294 mmol, 1.0 equiv.). Purification of the residue after *neutral* work-up was carried out (1:99, then 50:50 diethyl ether/ hexane) to give 1-*tert*-butyl-4-prop-1-ynylbenzene[241] **2.313** as a colourless liquid (35 mg, 69 %); for data see above. ^{1}H-NMR analysis showed trace amounts most likely corresponding to 1-*tert*-butyl-4-propa-1,2-dienylbenzene **2.312** and further analysis by GC-MS showed very small peaks, possibly corresponding to 1-*tert*-butyl-4-propenylbenzene[240] **2.314**.

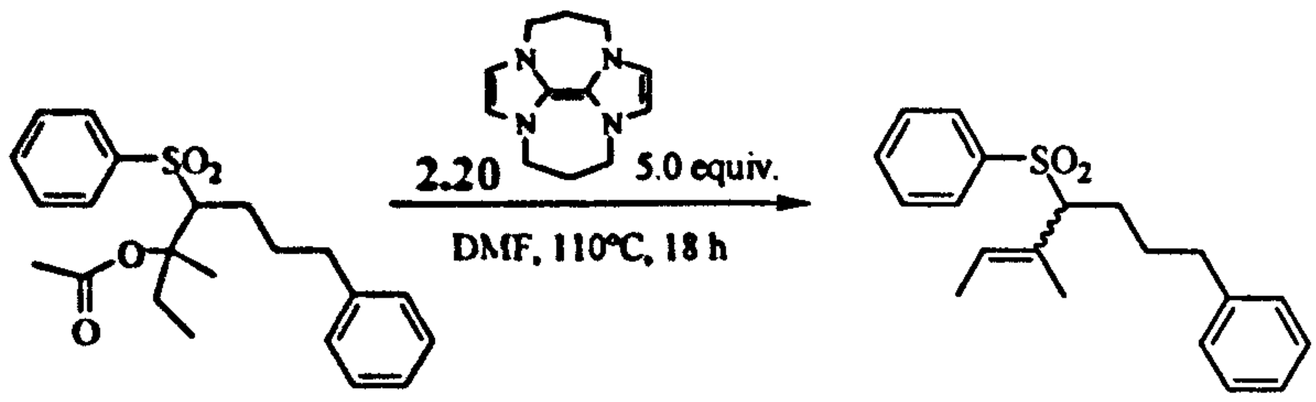
Acetic acid 2-benzenesulfonyl-1-ethyl-1-methyl-5-phenylpentyl ester 2.321



2.321

(4-Phenyl-butane-1-sulfonyl)benzene[242] **2.323** (1.07 g, 3.9 mmol) was dissolved in THF (5 ml) and cooled to –78°C. Sodium hexamethyldisilazide [NaHMDS] (6.5 ml, 3.9 mmol, 1.0 equiv., c = 0.6 mol/l) was added dropwise and the mixture was stirred for 30 min at –78°C. A solution of 2-butanone (0.35 ml, 3.9 mmol, 1.0 equiv.) in THF (2 ml) was then added dropwise *via* cannula at –78°C. After stirring for 30 min at –78°C, acetic anhydride (0.44 ml, 4.68 mmol, 1.2 equiv.) were added dropwise and the mixture was allowed to warm to room temperature. After stirring at room temperature overnight, water (200 ml) and ethyl acetate (200 ml) were added. The aqueous layer was extracted further with ethyl acetate (200 ml). The combined organic layer was dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (15:25:60 diethyl ether/ toluene/ petroleum ether) to afford acetic acid 2-benzenesulfonyl-1-ethyl-1-methyl-5-phenylpentyl ester **2.321** as a mixture of diastereomers (210 mg, 14 %); (Found: $[M+H]^+$ 406.2048. $C_{22}H_{28}O_4S$ requires [*M+H*], 406.2047); ν_{max} (NaCl)/cm^{-1} 3063 (Ar-H), 2971 (C-H), 2941 (C-H), 1732 (C=O), 1447 (C-H), 1303 (SO_2), 1140 (SO_2); δ_H ($CDCl_3$) 0.85 and 0.91 (3H, t, *J* 7.3, CH_2CH_3), 1.05-1.08 and 1.17-1.23 (2H, m, CCH_2CH_3), 1.43-1.56 (1H, m, CH_2CHHCH_2), 1.59 and 1.64 (3H, s, CH_3), 1.66-1.72 (1H, m, CH_2CHHCH_2), 1.81 and 1.89 (3H, s, CH_3), 1.89-2.03 and 2.09-2.18 (2H, m, SO_2CHCH_2), 2.35-2.42 (2H, m, CH_2Ph), 4.23-4.26 (SO_2CH), 6.94-6.99 (2H, m, Ar*H*), 7.15-7.18 (1H, m, Ar*H*), 7.22-7.26 (2H, m, Ar*H*), 7.49-7.55 (2H, m, Ar*H*), 7.59-7.64 (1H, m, Ar*H*), 7.82-7.86 (2H, m, Ar*H*); δ_C ($CDCl_3$) 6.2 (CH_3), 7.1 (CH_3), 21.4 (CH_3), 21.8 (CH_3), 22.3 (CH_3), 29.4 (CH_2), 31.4 (CH_2), 32.8 (CH_2), 35.5 (CH_2), 68.3 (CH), 84.9 (C), 85.5 (C), 121.6 (CH), 127.7 (CH), 128.1 (CH), 128.7 (CH), 128.9 (CH), 140.6 (C), 141.0 (C), 170.8 (C); *m/z* (CI) 406 (M^+, 100 %), 346 (38), 266 (44), 204 (40), 187 (69), 104 (27), 52 (24).

Reaction of acetic acid 2-benzenesulfonyl-1-ethyl-1-methyl-5-phenyl-pentyl ester 2.321

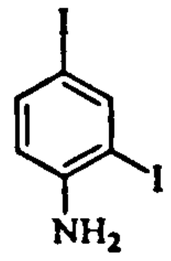


2.321 **2.322**

The experiment was carried out according to the 'pure donor-method.' *Conditions and reagents*: 110°C, 18 h, DMF (15 ml), imidazole donor **2.20** (324 mg, 1.5 mmol, 5.0 equiv.), acetic acid 2-benzenesulfonyl-1-ethyl-1-methyl-5-phenyl-pentyl ester **2.321** (128.6 mg, 0.331 mmol, 1.0 equiv.). *Neutral* work-up was carried out and the residue was purified by column chromatography on silica gel (30:70 diethyl ether/ hexane) to give *(7-Phenyl-3-methylhept-2-ene-4-sulfonyl)benzene* **2.322** as a colourless liquid (93.7 mg, 86 %); (Found: $[M+H]^+$ 346.1835. $C_{20}H_{24}O_2S$ requires $[M+H]$, 346.1835); ν_{max} (NaBr)/cm^{-1} 3062 (Ar-H), 2923 (C-H), 2856 (C-H), 1447 (C-H), 1304 (SO_2), 1144 (SO_2); δ_H ($CDCl_3$) 1.48 (3H, dd, *J* 6.8, 1.0, C*H*$_3$CH), 1.51-1.59 (2H, m, $CH_2CH_2CH_2Ph$), 1.63 (3H, d, *J* 1.0, CC*H*$_3$), 1.91-1.99 (1H, m, SO_2CHCHH), 2.08-2.18 (1H, m, SO_2CHCHH), 2.54-2.69 (2H, m, C*H*$_2$Ph), 3.48 (1H, dd, *J* 11.6, 3.7, SO_2CHCH_2), 5.10-5.15 (1H, m, CH_3CH=C), 7.12-7.14 (2H, m, Ar*H*), 7.17-7.21 (1H, m, Ar*H*), 7.25-7.32 (3H, m, Ar*H*), 7.49-7.52 (2H, m, Ar*H*), 7.58-7.62 (1H, m, Ar*H*), 7.77-7.99 (2H, m, Ar*H*); δ_C ($CDCl_3$) 13.1 (CH_3), 13.7 (CH_3), 24.5 (CH_2), 28.6 (CH_2), 35.4 (CH_2), 74.2 (CH), 125.8 (CH), 127.2 (C), 128.5 (CH), 128.9 (CH), 129.3 (CH), 130.5 (CH), 133.4 (CH), 137.9 (C), 141.5 (C); *m/z* (CI) 346 (M^+, 100 %), 234 (18), 204 (24), 187 (57), 159 (8), 52 (16).

8.6 Experiments from chapter 6: *Selective reductions*

2,4-Diiodophenylamine 2.326[142]



2.326

4-Iododoaniline (3.5 g, 15.98 mmol, 1.0 quiv.), tetramethylammonium iodochlorate (5 g, 18.38 mmol, 1.15 equiv.) and calcium carbonate (2.24 g, 22.37 mmol, 1.4 equiv.) were dissolved in dichloromethane (100 ml) and methanol (20 ml). This mixture was stirred at room temperature overnight, then filtered and concentrated *in vacuo*. The residue was dissolved in diethyl ether (200 ml) and washed with 10 % sodium hydrogensulfite solution (4 x 100 ml) and brine (100 ml). The organic layer was then dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (10:20:70 ethyl acetate/ toluene/ petroleum ether) to give 2,4-diiodophenylamine **2.326**[243] as a pink solid (3.37 g, 61 %); mp 90-91°C (lit.[243] 91-94 °C); (Found: $[M+H]^+$ 345.8586. $C_6H_5I_2N$ requires $[M+H]^+$, 345.8586); ν_{max} (KBr)/cm^{-1} 3378 (N-H), 3284 (N-H), 3021 (Ar-H), 1621 (Ar); δ_H ($CDCl_3$) 4.13 (2H, s, NH_2), 6.52 (1H, d, *J* 8.4, Ar*H*), 7.38 (1H, dd, *J* 8.4, 2.9, Ar*H*), 7.90 (1H, d, *J* 2.0, Ar*H*); δ_C ($CDCl_3$) 79.1 (C), 85.1 (C), 116.5 (CH), 138.1 (CH), 146.5 (CH), 146.7 (C); *m/z* (EI) 345 (M^+, 100 %), 218 (31 %), 127 (51), 91 (84), 63 (47).

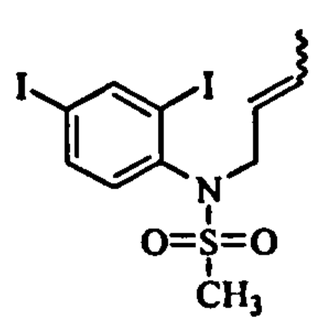
N-(2,4-Diiodophenyl)methanesulfonamide 2.327

2.227

2,4-Diiodophenylamine **2.326** (1.54 g, 4.45 mmol, 1.0 equiv.) and DMAP (54 mg, 0.445 mmol, 0.1 equiv.) were dissolved in pyridine (15 ml) and methane sulfonyl chloride (0.38 ml, 4.89 mmol, 1.1 equiv.) was added dropwise at room temperature. The reaction mixture was then heated at reflux for 18 h. The mixture was then poured into diethyl ether (200 ml) and water (200 ml). The organic layer was washed with 2 N hydrochloric acid (3 x 100 ml) and brine (100 ml), was then dried over sodium sulfate and evaporated. The residue was recrystallised (petroleum ether, ethyl acetate) to afford *N-(2,4-diiodophenyl)-methanesulfonamide* **2.327** as a yellow solid (1.115 g, 59 %); mp 109°C; (Found: M^+

422.8278. $C_7H_7I_2NO_2S$ requires M^+, 422.8278); ν_{max} (KBr)/cm^{-1} 3256 (N-H), 3008 (Ar-H), 2925 (C-H), 1462 (C-H), 1328 (SO_2), 1154 (SO_2); δ_H ($CDCl_3$) 3.02 (3H, s, C*H*$_3$), 6.62 (1H, s, N*H*), 7.40 (1H, d, *J* 8.6, Ar*H*), 7.67 (1H, dd, *J* 8.6, 1.9, Ar*H*), 8.15 (1H, d, *J* 1.9, Ar*H*); δ_C ($CDCl_3$) 40.5 (CH_3), 90.2 (C), 93.1 (C), 123.7 (CH), 137.8 (C), 139.1 (CH), 150.0 (CH); *m/z* (EI) 423 (M^+, 46 %), 344 (76), 217 (53), 127 (24), 90 (48), 63 (100).

N-but-2-enyl-N-(2,4-diiodophenyl)methanesulfonamide 2.324[174]

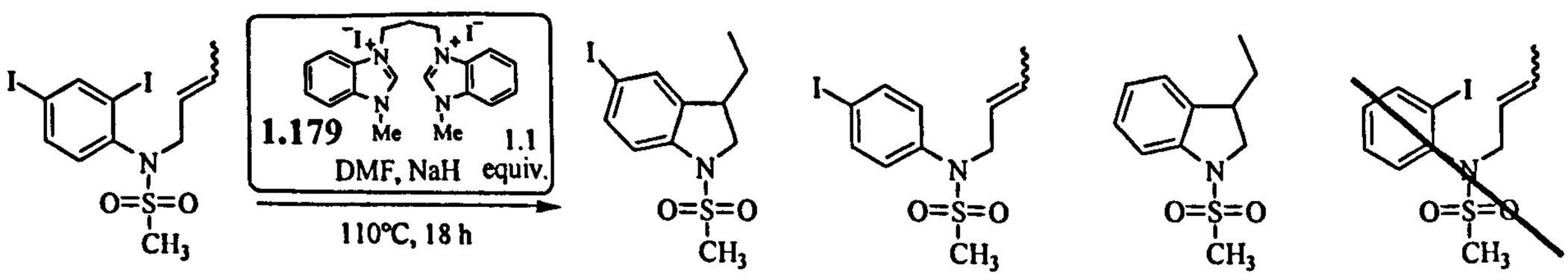


2.324

N-(2,4-diiodophenyl)methanesulfonamide **2.327** (0.476 g, 1.123 mmol, 1.0 equiv.), but-2-en-1-ol (78.3 mg, 1.123 mmol, 1.2 equiv.) and triphenylphosphine (353.3 mg, 1.347 mmol, 1.2 equiv.) were dissolved in THF and the mixture was cooled to 0°C. DIAD (0.26 ml, 1.347 mmol, 1.2 equiv.) was added dropwise and after stirring for 4 h at room temperature the solvent was removed under reduced pressure. The residue was purified by column chromatography to give *N-but-2-enyl-N-(2,4-diiodophenyl)methanesulfonamide* **2.324** as colourless liquid (482 mg, 90 %); (Found: $[M+NH_4]^+$ 494.9096. $C_{11}H_{13}I_2NO_2S$ requires $[M+NH_4]^+$, 494.9095; ν_{max} (NaCl)/cm^{-1} 3006 (Ar-H), 2923 (C-H), 1469 (C-H), 1338 (SO_2), 1154 (SO_2); δ_H ($CDCl_3$) 1.65 (3H, d, *J* 5.2, C=CHC*H*$_3$), 3.10 (3H, s, SO_2C*H*$_3$), 3.91 (1H, m, NMsC*H*$_2$HC=), 4.26 (1H, m, NMsC*H*$_2$HC=), 5.44-5.59 (2H, m, C*H*=C*H*), 7.06 (1H, d, *J* 8.3, Ar*H*), 7.69 (1H, dd, *J* 8.3, 2.0, Ar*H*), 8.26 (1H, d, *J* 2.0, Ar*H*); δ_C ($CDCl_3$) 17.8 (CH_3), 41.5 (CH_3), 53.5 (CH_2), 95.1 (C), 103.5 (C), 124.9 (CH), 132.1 (CH); 133.8 (CH), 138.3 (CH), 114.1 (C), 147.8 (CH); *m/z* (EI) 466 (M^+, 6 %), 423 (46), 344 (49), 270 (22), 143 (37), 79 (33), 55 (100).

Test experiments on *N*-but-2-enyl-*N*-(2,4-diiodophenyl)methanesulfonamide 2.324

(i)



2.324 **2.328** **2.329** **2.330** **2.331**

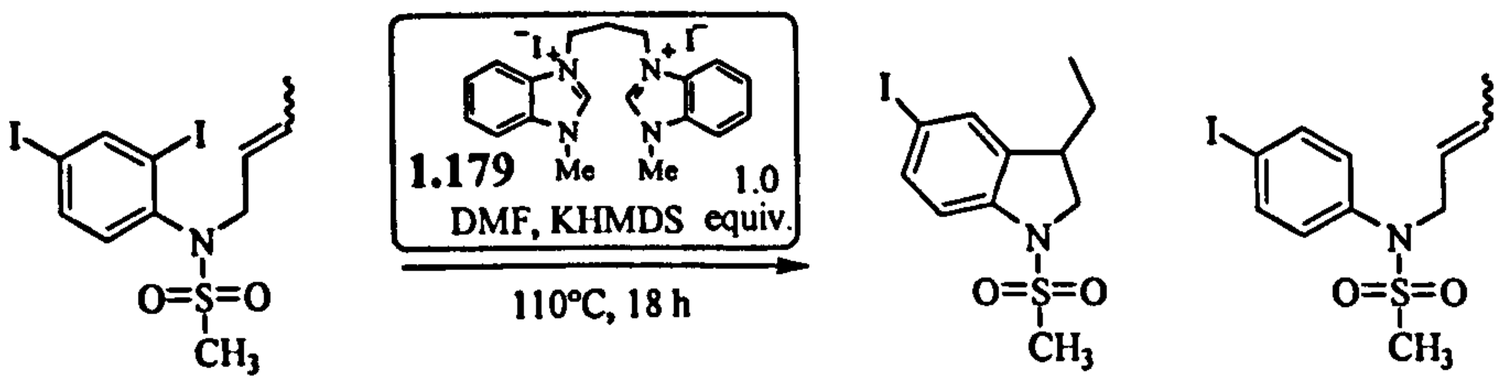
The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 110°C, 18 h, DMF (15 ml), salt **1.179** (207 mg, 0.368 mmol, 1.1 equiv.), *N*-but-2-enyl-*N*-(2,4-diiodo-phenyl)-methanesulfonamide **2.330** (160 mg, 0.335 mmol, 1.0 equiv.). The purification of the residue after *neutral* work-up was carried by column chromatopgraphy on silica gel (30:70 ethyl acetate/ petroleum ether) to afford a mixture of compounds (29 mg). The ^{1}H-NMR spectrum of this mixture was rather complex; *3-ethyl-5-iodo-1-methanesulfonyl-2,3-diydro-1H-indole* **2.328** [for data see below] was observed and possibly *N-but-2-enyl-N-(4-iodophenyl)methanesulfonamide* **2.329**. *N*-but-2-enyl-*N*-(2-iodophenyl)methanesulfonamide **2.331** could be excluded by ^{1}H-NMR spectrum comparison with the authentic sample. GC-MS analysis of the mixture was then carried out and three major peaks [and other minor unidentified] were observed:

m/z (EI) 351 (M^+, 24 %), 297 (100), 218 (78), 144 (26), 91 (18); presumably corresponds to **2.329.**

m/z (EI) 351 (M^+, 52 %), 272 (49), 144 (100), 130 (83), 117 (20); corresponds to **2.328.**

3-Ethyl-1-methanesulfonyl-2,3-dihydro-1*H*-indole **2.330**: *m/z* (EI) 225 (M^+, 41 %), 196 (43), 130 (42), 118 (100), 91 (22); the data is consistent with the mass spectrum of the authentic compound.[94]

(ii)

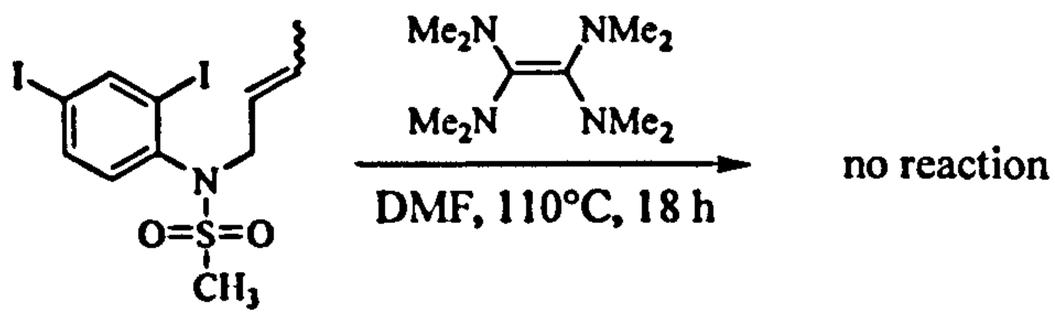


2.324 **2.328** **2.329**

Salt **1.179** (126 mg, 0.224 mmol, 1.0 equiv.) was dissolved in DMF (7 ml) and purged with argon for 30 min. KHMDS (0.90 ml, 0.448 mmol, 2.0 equiv., c = 0.495 mol/l) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. An argon-purged solution of substrate **2.324** (107 mg, 0.224 mmol, 1.0 equiv.) in DMF (5 ml) was then added to the reaction mixture. Observation: Upon addition of the substrate-solution the yellow colour changed to orange. After heating at 110°C for 18 h the now deeply red-coloured mixture was exposed to *neutral* work-up. The residue was purified by column chromatography on silica gel (30:70 ethyl acetate/ petroleum ether) to afford a rather complex mixture (24 mg) of which *3-ethyl-5-iodo-1-methanesulfonyl-2,3-diydro-1H-*

indole **2.328** and *N-but-2-enyl-N-(4-iodo-phenyl)methanesulfonamide* **2.329** were partially purified and identified; for data see below.

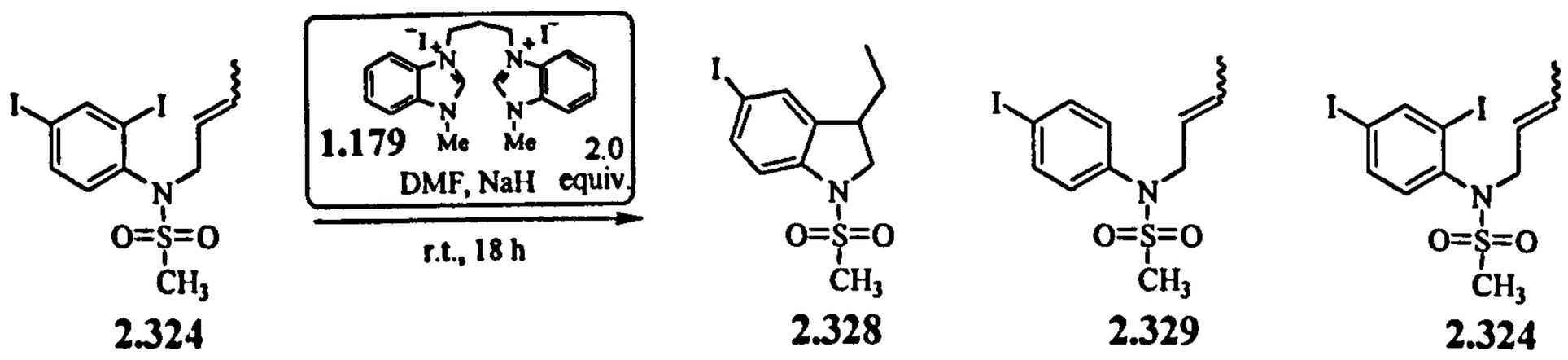
(iii)



2.324

N-but-2-enyl-*N*-(2,4-diiodophenyl)methanesulfonamide **2.324** (58 mg, 0.1215 mmol, 1.0 equiv.) was dried under vacuum at room temperature for 3 h. Anhydrous DMF (10 ml) was then added under argon atmosphere and the mixture was deoxygenated with argon for 20 min. This mixture was then transferred into a glove-box. TDAE (24.3 mg, 0.1215 mmol, 1.0 equiv.) was weighed into a dry round-bottomed flask in a glove-box and the solution of the reactant in DMF was then added to it by pipette. The reaction mixture was heated at 110°C for 18 h. *Neutral* work-up was then carried out. ^{1}H-NMR spectroscopic analysis of the crude mixture showed only starting material **2.324**; the reaction did not proceed.

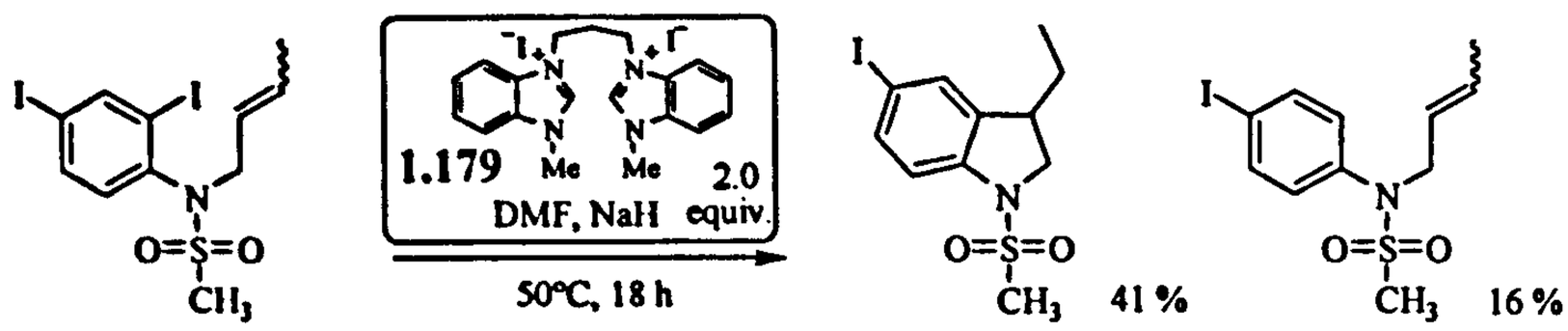
(iv)



2.324 **2.328** **2.329** **2.324**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMF (15 ml), salt **1.179** (336 mg, 0.6 mmol, 2.0 equiv.), *N*-but-2-enyl-*N*-(2,4-diiodophenyl)methanesulfonamide **2.324** (112 mg, 0.293 mmol, 1.0 equiv.). ^{1}H-NMR analysis of the crude mixture after *neutral* work-up showed that the reaction did not go to completion. Starting material **2.324** was identified along with *3-ethyl-5-iodo-1-methanesulfonyl-2,3-diydro-1H-indole* **2.328** and *N-but-2-enyl-N-(4-iodophenyl)methanesulfonamide* **2.329** ; for data see below.

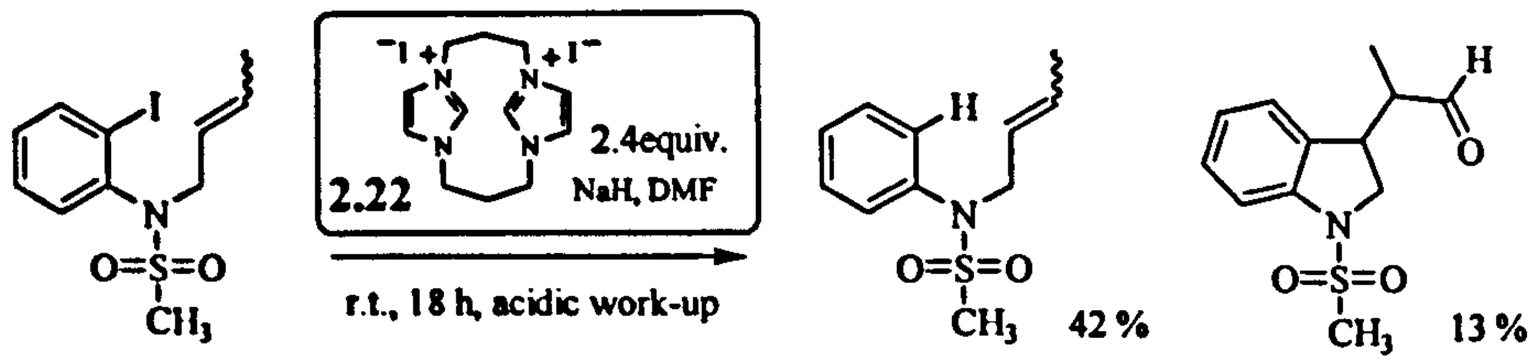
(v)



2.324 **2.328** **2.329**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* 50°C, 18 h, DMF (15 ml), salt **1.179** (263 mg, 0.469 mmol, 2.0 equiv.), *N*-but-2-enyl-*N*-(2,4-diiodophenyl)methanesulfonamide **2.324** (112 mg, 0.235 mmol, 1.0 equiv.). The residue after *acidic* work-up was purified by column chromatography on silica gel (20:80 ethyl acetate/ petroleum ether) to afford a mixture of **2.328** and **2.329** (47 mg, 57 %) of which *3-ethyl-5-iodo-1-methanesulfonyl-2,3-diydro-1H-indole* **2.328** (41 % NMR spectrum yield) was purified as a colourless liquid; (Found: $[M+NH_4]^+$ 369.0130. $C_{11}H_{14}INO_2S$ requires $[M+NH_4]^+$ 369.0128); ν_{max} (NaCl)/cm^{-1} 2961 (C-H), 2928 (C-H), 2873 (C-H), 1348 (SO_2), 1161 (SO_2); δ_H ($CDCl_3$) 1.09 (3H, t, *J* 7.4, C*H*$_3$), 1.67-1.72 (1H, m, CHC*H*$_2$CH$_3$), 1.88-1.98 (1H, m, CHC*H*$_2$CH$_3$), 2.96 (3H, s, SO_2C*H*$_3$), 3.38-3.42 (1H, m, NCH$_2$C*H*), 3.72 (1H, dd, *J* 10.3, 6.5, NC*H*$_2$CH), 4.12-4.18 (1H, m, NC*H*$_2$CH) 7.29 (1H, d, *J* 8.3, Ar*H*), 7.58-7.61 (2H, m, Ar*H*); δ_C ($CDCl_3$) 11.4 (CH_3), 27.7 (CH_2), 34.9 (CH), 41.5 (CH_3), 56.1 (CH_2), 86.7 (C), 115.7 (CH), 133.9 (CH), 137.3 (CH), 137.8 (C), 142.0 (C); *m/z* (EI) 351 (M^+, 30 %), 272 (28), 144 (42), 130 (100), 117 (37), 79 (38); and *N-but-2-enyl-N-(4-iodophenyl)methanesulfonamide* **2.329** (16 % NMR spectrum yield) as a colourless liquid; (Found: $[M+NH_4]^+$ 369.0129. $C_{11}H_{14}INO_2S$ requires $[M+NH_4]^+$ 369.0128); ν_{max} (NaCl)/cm^{-1} 2961 (C-H), 2923 (C-H), 1482 (C-H), 1333 (SO_2), 1155 (SO_2); δ_H ($CDCl_3$) 1.64 (3H, dd, *J* 5.1, 1.3, C=CHC*H*$_3$), 2.91 (3H, s, SO_2C*H*$_3$), 4.20 (2H, d, *J* 6.6, NC*H*$_2$), 5.44-5.49 (1H, m, C*H*=CH), 5.57-5.62 (1H, m, CH=C*H*), 7.07 (2H, dd, *J* 6.7, 2.0, Ar*H*), 7.72 (2H, dd, *J* 6.7, 2.0, Ar*H*); δ_C ($CDCl_3$) 17.9 (CH), 36.6 (CH), 53.2 (CH_2), 93.3 (C), 125.5 (CH), 130.5 (CH), 131.5 (CH), 128.7 (CH), 139.5 (C); *m/z* (EI) 351 (M^+, 10 %), 297 (52), 218 (60), 130 (16), 76 (26), 55 (100).

Reduction of *N*-but-2-enyl-*N*-(2-iodophenyl)methanesulfonamide 2.324 with donor 2.20



2.324 **2.333** **2.334**

The experiment was carried out according to the 'general NaH-method' procedure. *Conditions and reagents:* Room temperature, 18 h, DMF (15 ml), salt **2.22** (348 mg, 0.74 mmol, 2.4 equiv.), *N*-but-2-enyl-*N*-(2-iodophenyl)methanesulfonamide **2.324** (108 mg, 0.308 mmol, 1.0 equiv.). The residue after *acidic* work-up was purified by column chromatopgraphy on silica gel (10:90 ethyl acetate/ petroleum ether) to afford *N*-but-2-enyl-*N*-phenyl-methanesulfonamide **2.333** (29 mg, 42 %) as a colourless oil; (Found: $[M+NH_4]^+$ 243.1161. $C_{11}H_{15}NO_2S$ requires $[M+NH_4]^+$ 243.1162); δ_H ($CDCl_3$) 1.56 (3H, d, *J* 6.9, C*H*$_3$), 2.91 (3H, s, SO_2CH_3), 4.22 (2H, d, *J* 6.4, C*H*$_2$), 5.45-5.53 (1H, m, CH=C*H*), 5.56-5.64 (1H, m, C*H*=CH), 7.23-7.33 (3H, m, Ar*H*), 7.35-7.42 (2H, m, Ar*H*); *m/z* (EI) 225 (M^+, 15 %), 171 (80), 104 (60), 92 (100), 77 (80), 55 (75); data consistent with those reported by D. Thomson.[203]

It was also isolated *2-(1-methanesulfonyl-2,3-dihydro-1H-indol-3-yl)propionaldehyde* **2.334** as a colourless oil (14 mg, 13 %); (Found: $[M+NH_4]^+$ 271.1107. $C_{12}H_{15}NO_3S$ requires $[M+NH_4]^+$ 271.1111); δ_H ($CDCl_3$) 1.12 and 1.17 (3H, d, *J* 7.4, C*H*$_3$CH), 2.79-2.98 (4H, m, SO_2CH_3 and C*H*CH$_3$), 3.74-3.84 (2H, m, NC*H*$_2$), 4.05-4.07 (1H, m, NCH$_2$C*H*), 7.02-7.08 (1H, m, Ar*H*), 7.17 (1H, d, *J* 7.4, Ar*H*), 7.23-7.27 (1H, m, Ar*H*), 7.42 (1H, d, *J* 8.1, Ar*H*), 9.72 and 9.78 (1H, s, CO*H*); *m/z* (CI) 271 ($[M+NH_4]^+$, 100 %), 243 (12), 176 (10), 118 (3).

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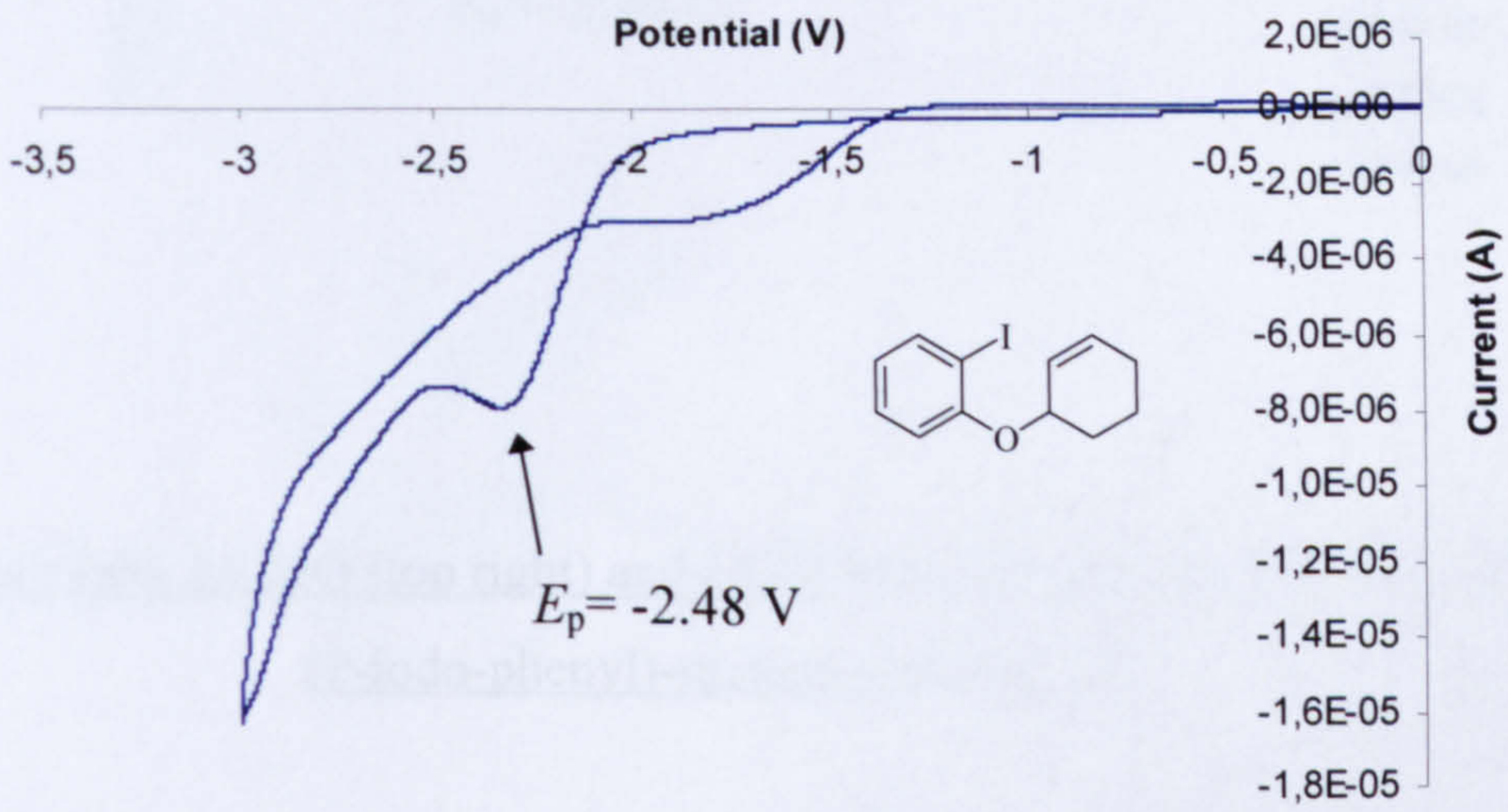
Appendix

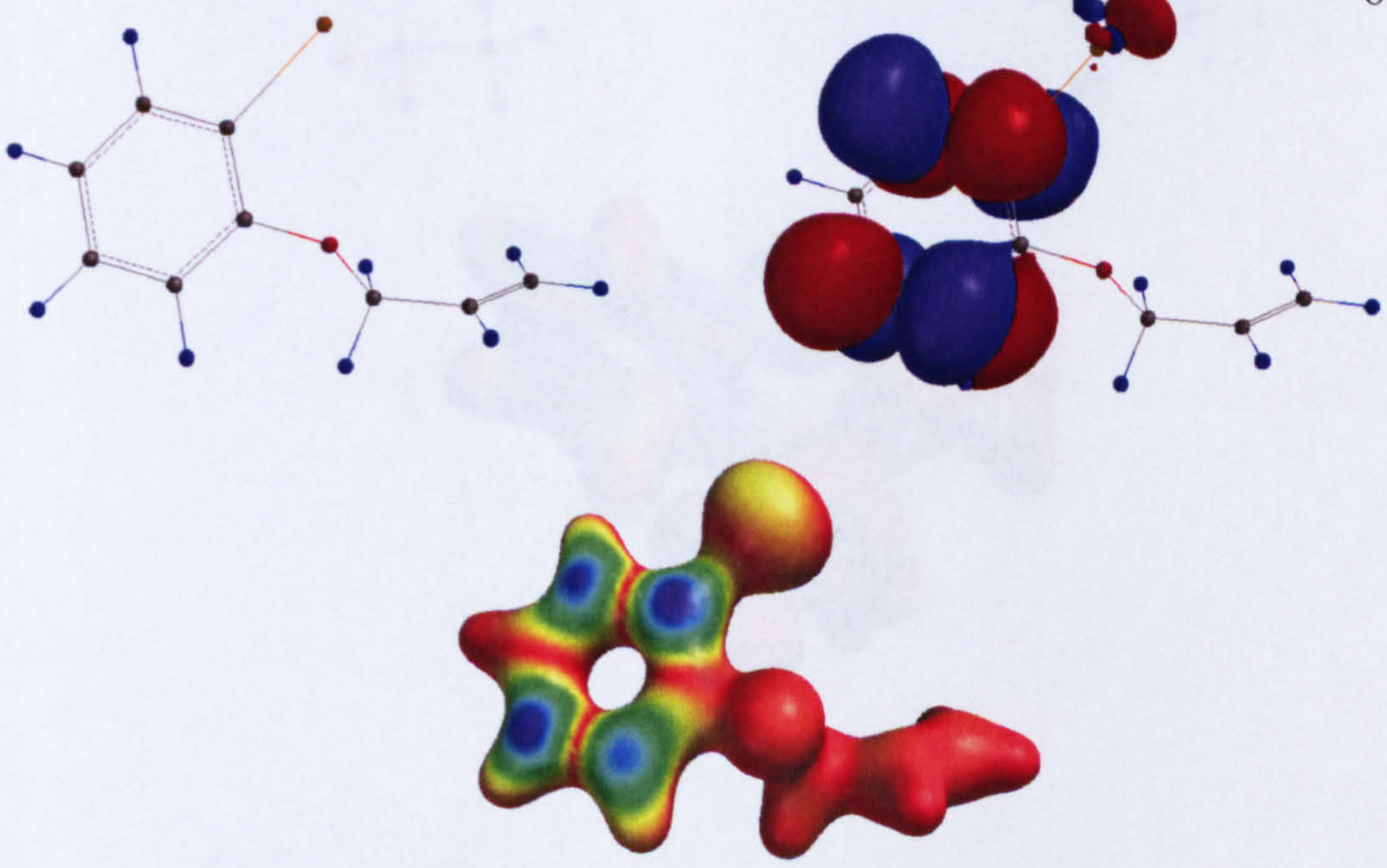
9 Appendix

9.1 Supplementary material for *Chapter Two*

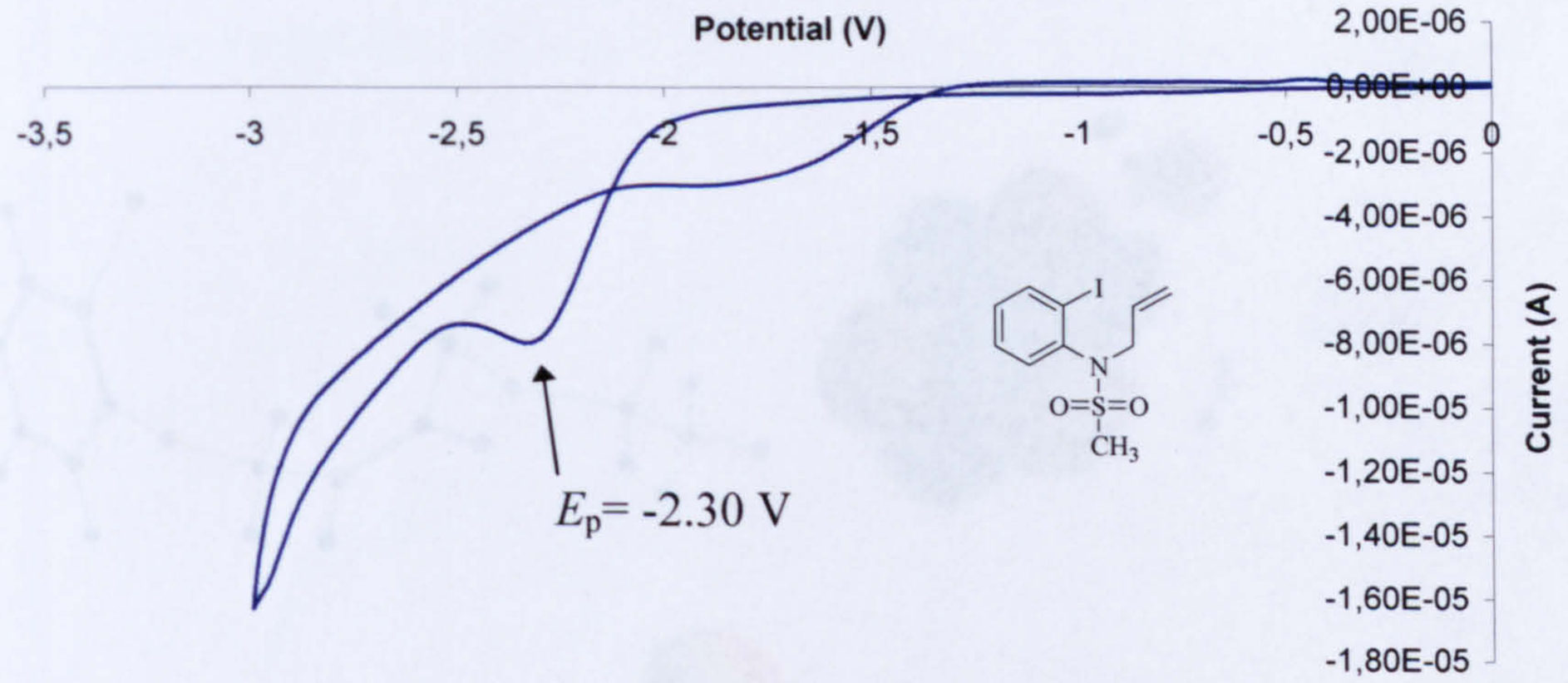
Cyclic Voltammogram of 1-(cyclohex-2-enyloxy)-2-iodo-benzene[i]



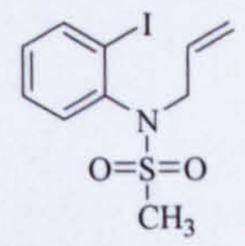
Structure (top left), LUMO (top right) and LUMO density (middle bottom) of 1-allyloxy-2-iodo-benzene[ii]

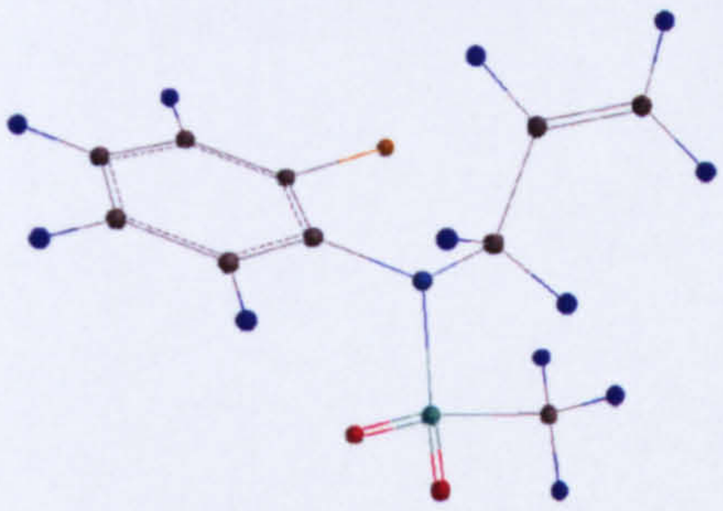


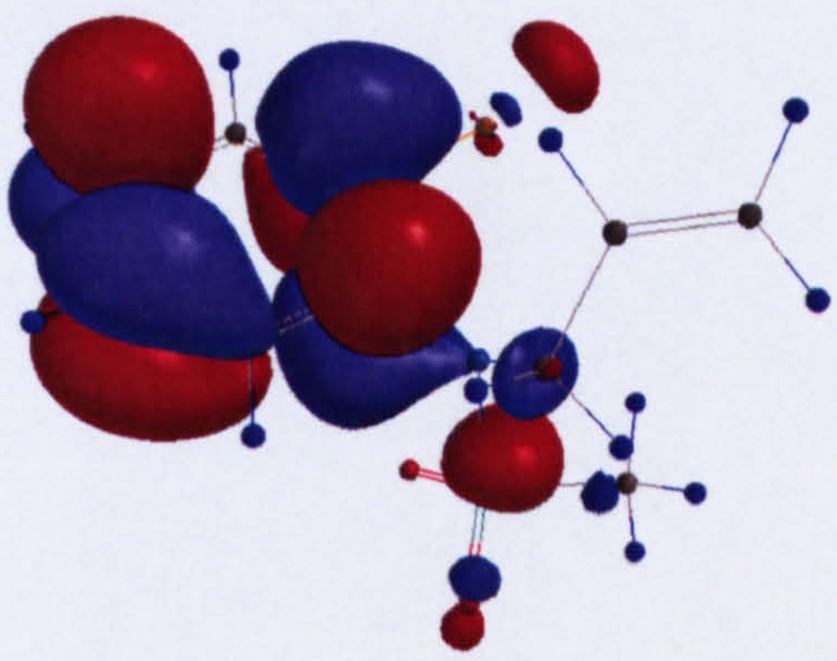
Cyclic Voltammogram of *N*-allyl-*N*-(2-iodo-phenyl)-methanesulfonamide[i]

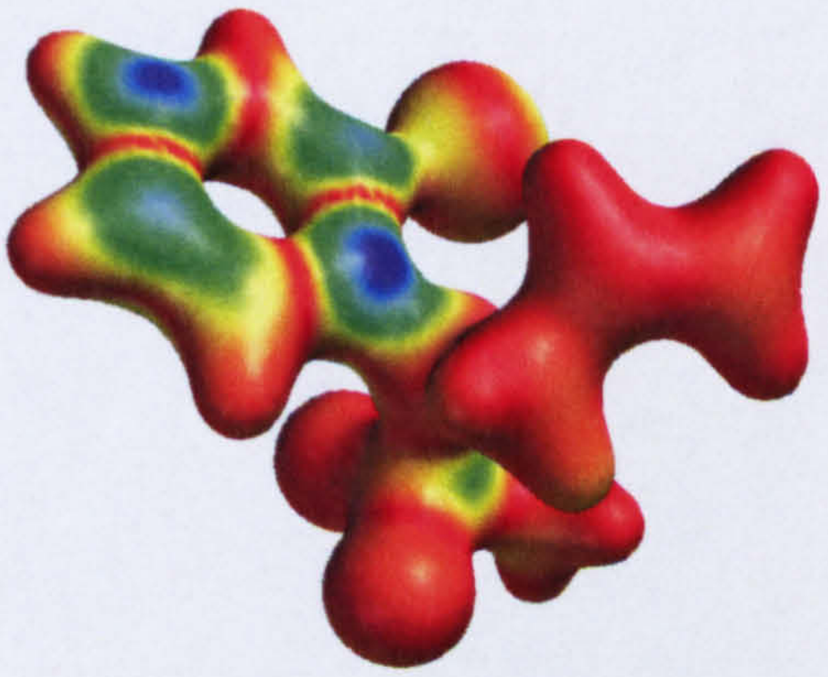


Structure (top left), LUMO (top right) and LUMO density (middle bottom) of *N*-allyl-*N*-(2-iodo-phenyl)-methanesulfonamide[ii]

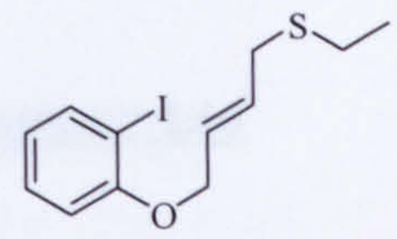


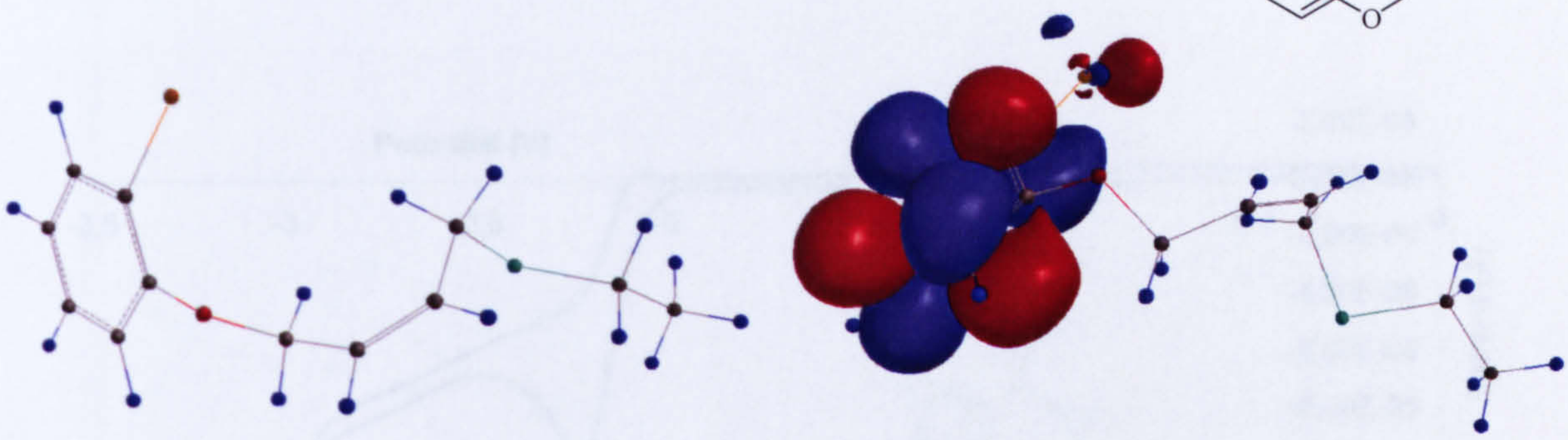


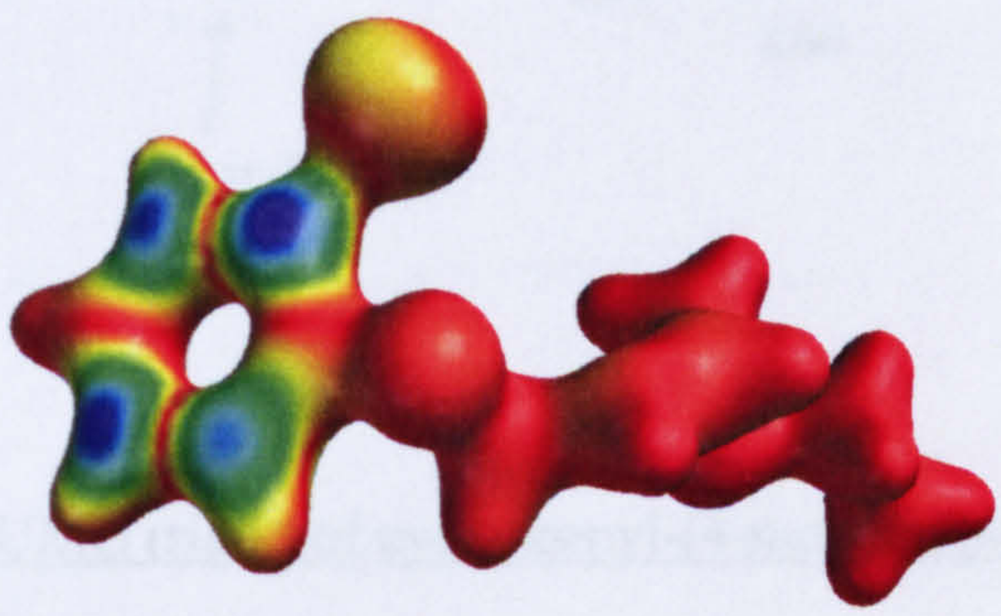




Structure (top left), LUMO (top right) and LUMO density (middle bottom) of 1-(4-Ethylsulfanyl-but-2-enyloxy)-2-iodo-benzene[ii]

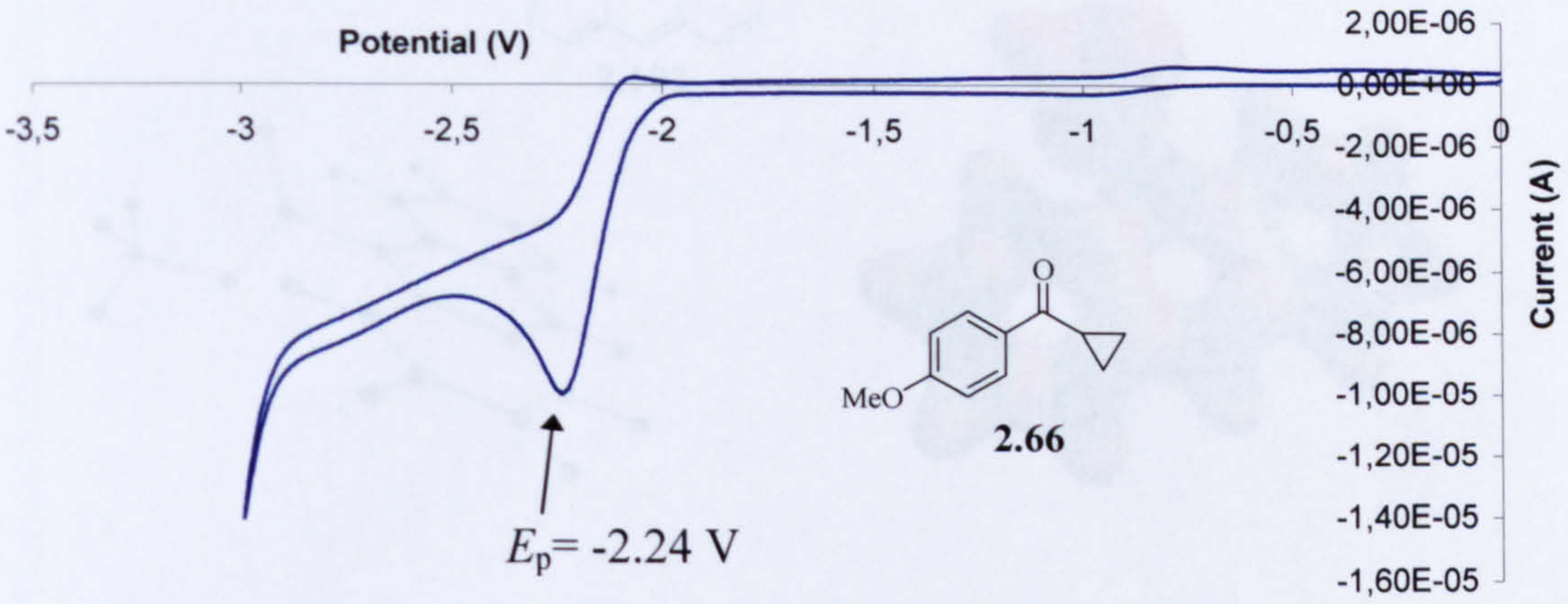




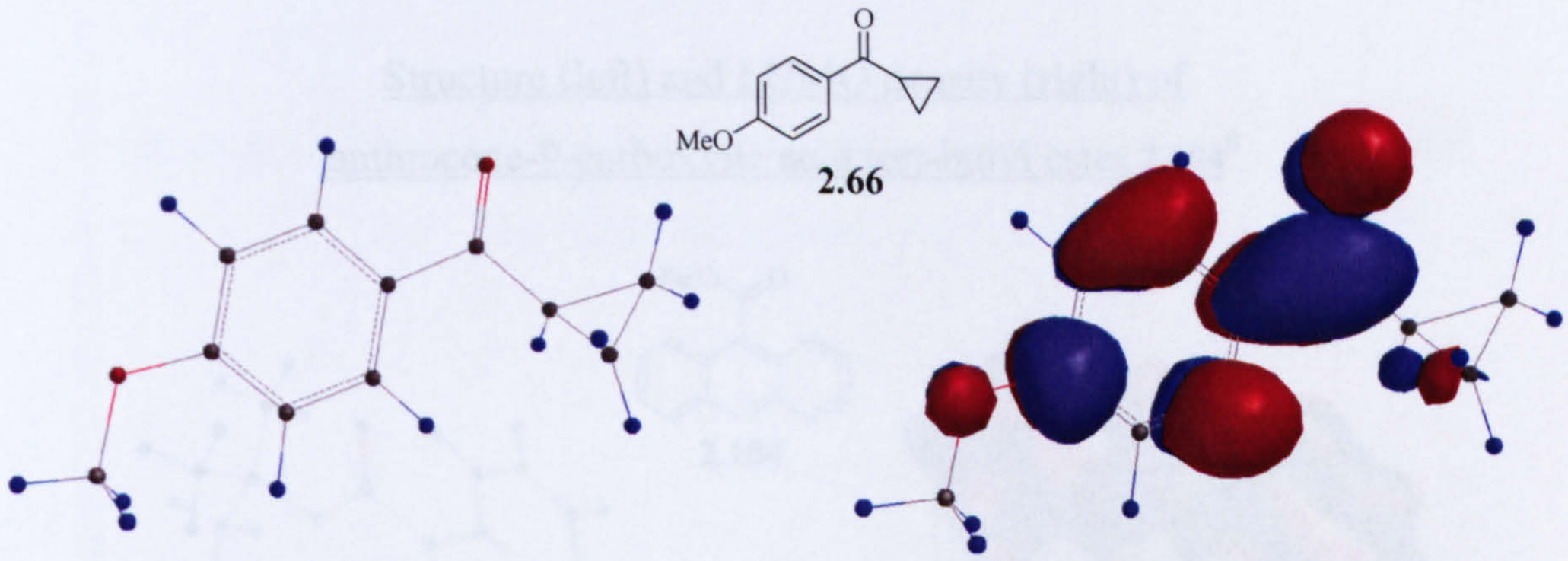


9.2 Supplementary material for *Chapter Three*

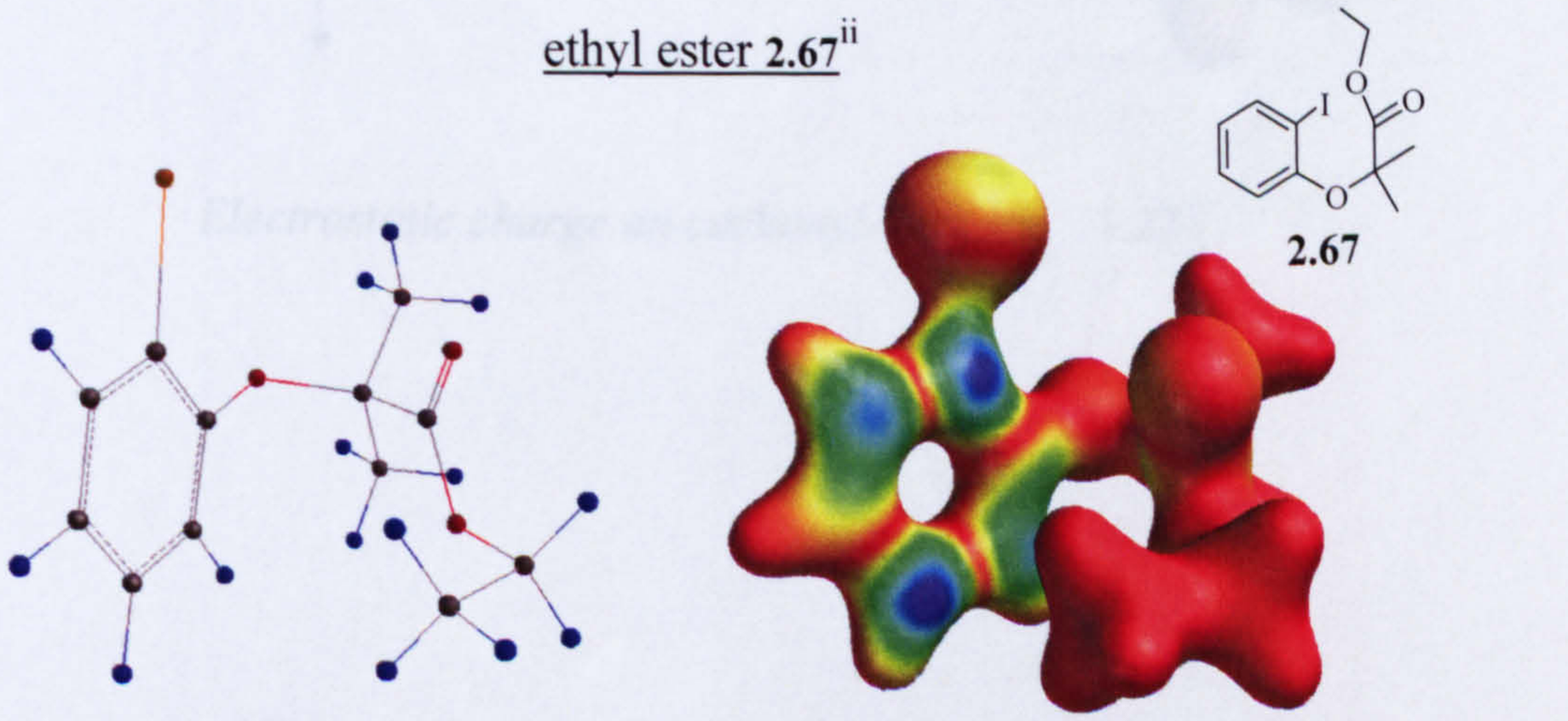
Cyclic Voltammogram of cyclopropyl-(4-methoxyphenyl)methanone **2.66**[i]



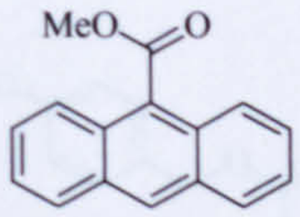
Structure (left) and LUMO (right) of cyclopropyl-(4-methoxyphenyl)methanone **2.66**[ii]



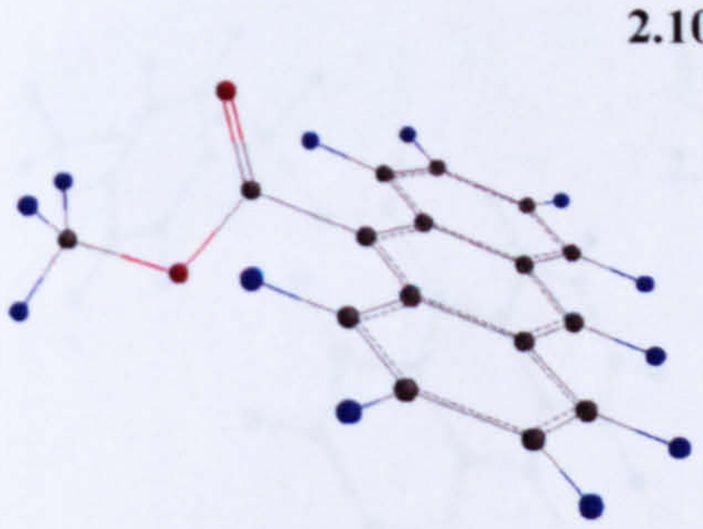
Structure (left) and LUMO density (right) of 2-(2-Iodophenoxy)-2-methylpropionic acid ethyl ester **2.67**[ii]

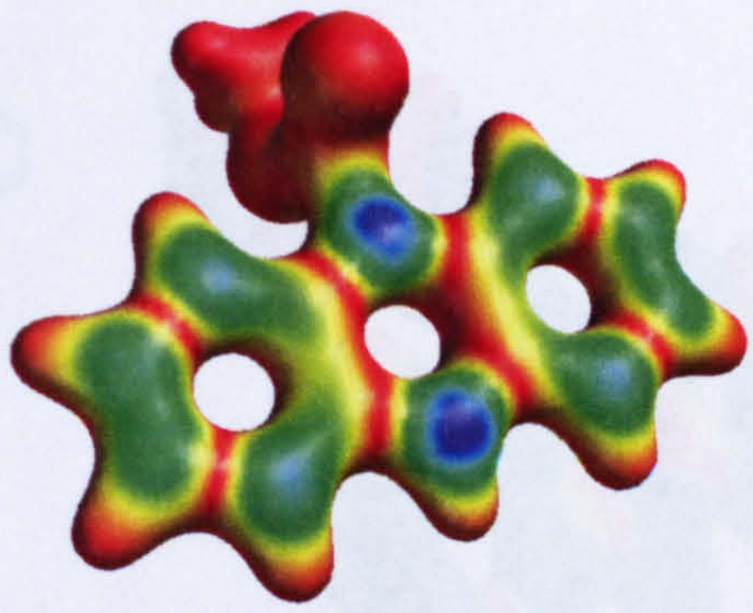


Structure (left) and LUMO density (right) of anthracene-9-carboxylic acid methyl ester **2.102**[ii]



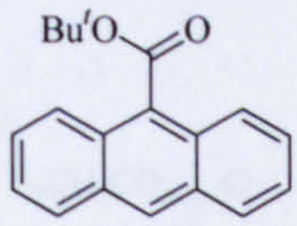
2.102



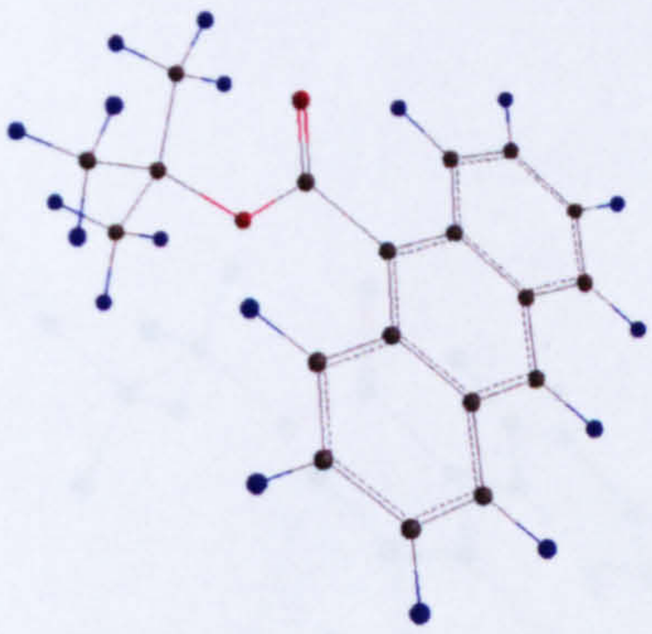


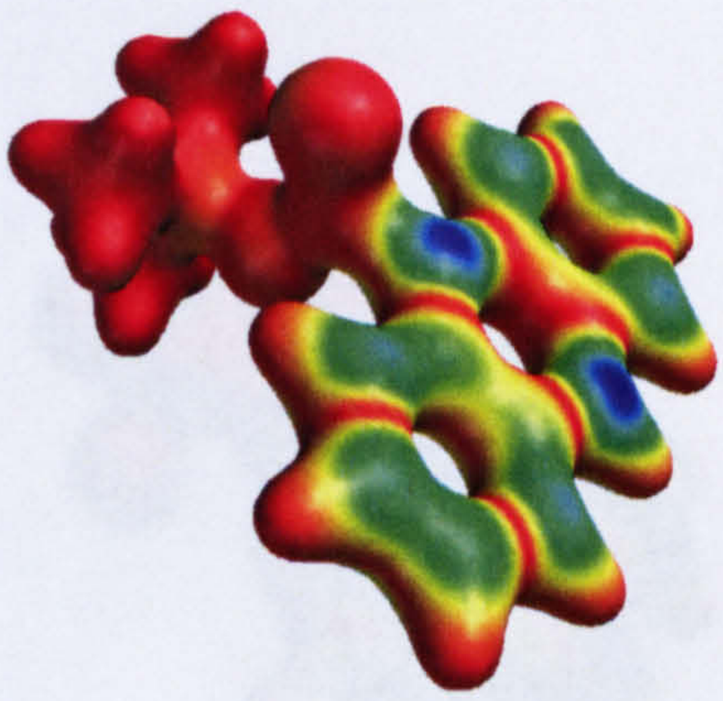
Electrostatic charge on carbonyl-carbon: 1.227

Structure (left) and LUMO density (right) of anthracene-9-carboxylic acid tert-butyl ester **2.104**[ii]



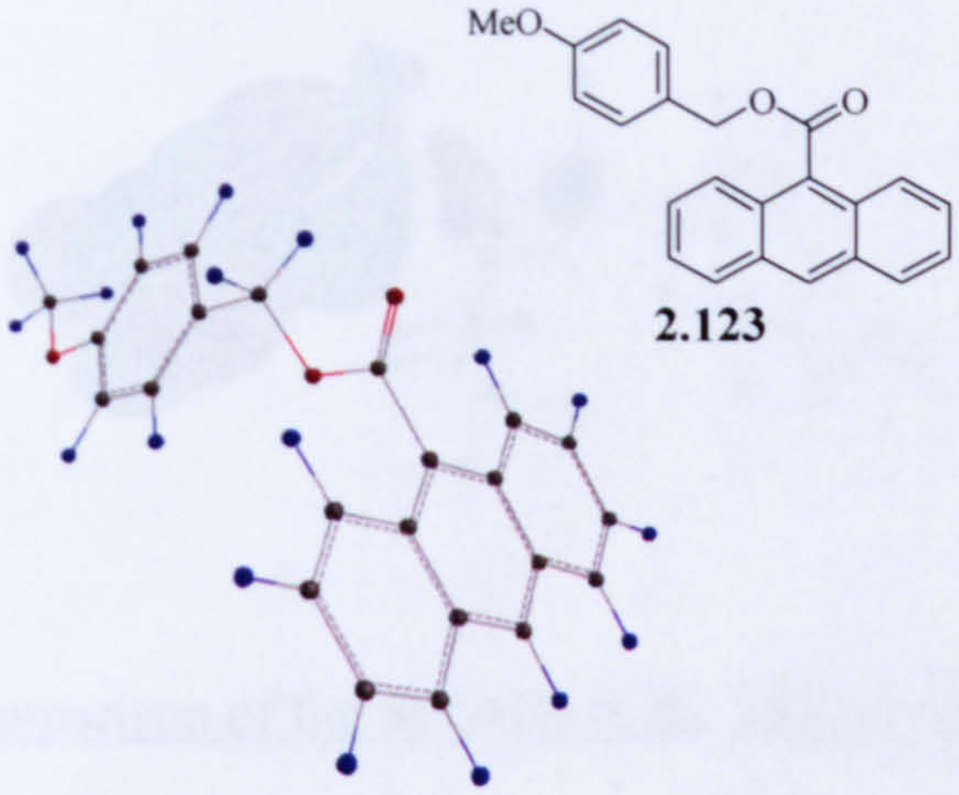
2.104



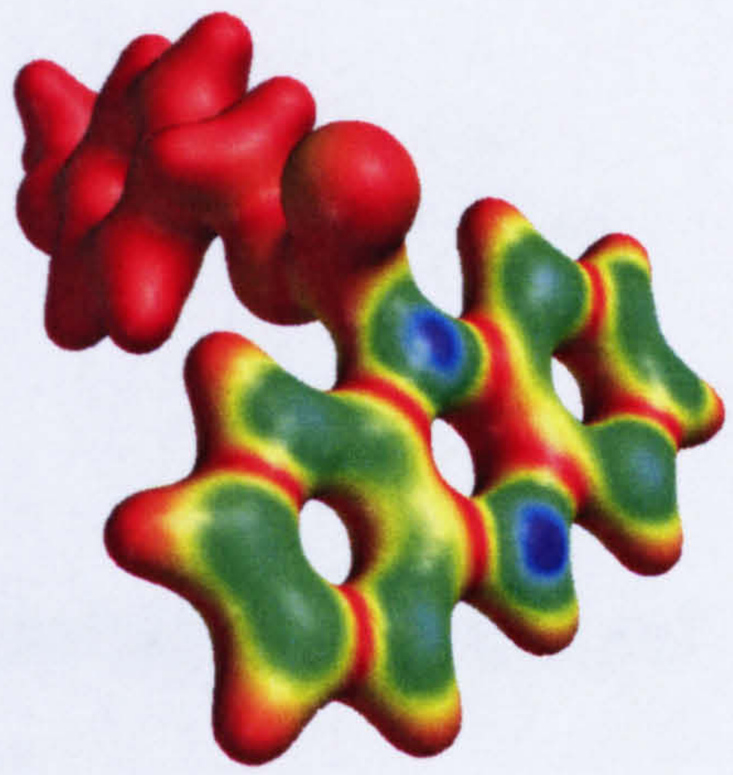


Electrostatic charge on carbonyl-carbon: 1.227

Structure (left) and LUMO density (right) of anthracene-9-carboxylic acid 4-methoxy-benzyl ester **2.123**[ii]

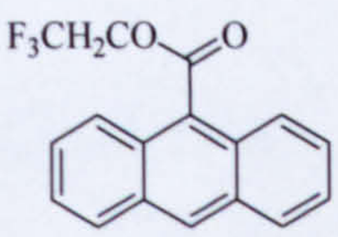


2.123

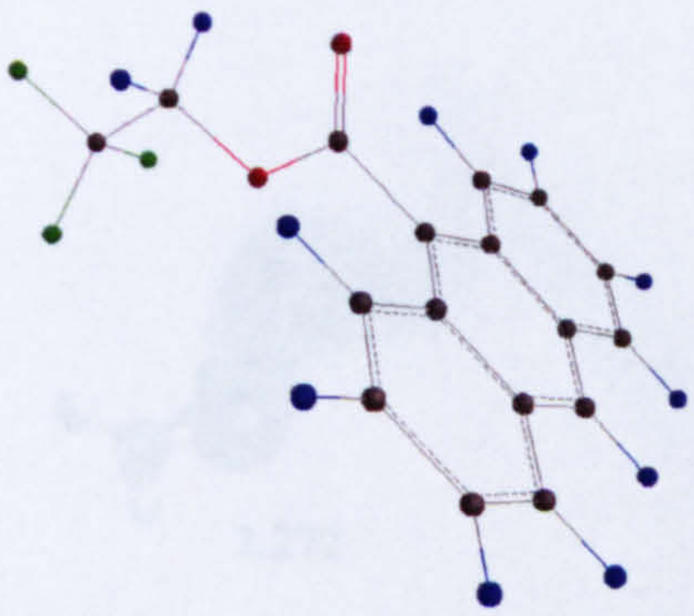


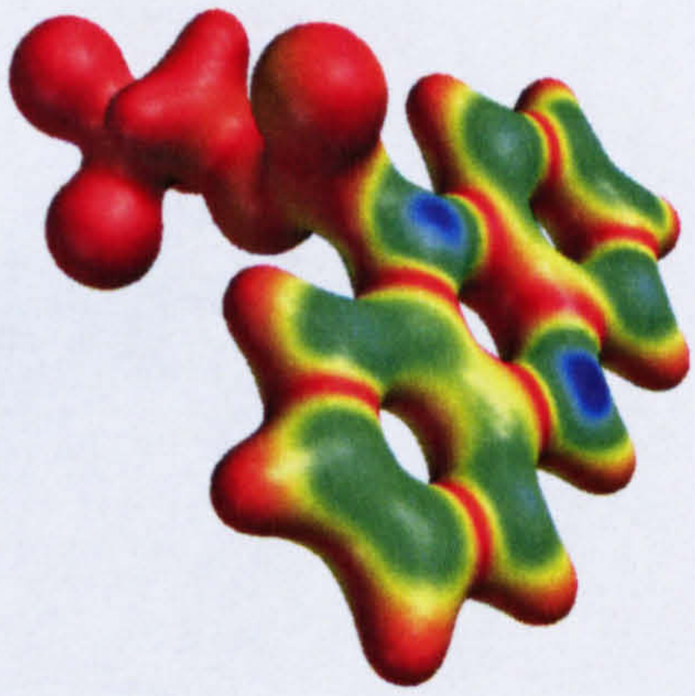
Electrostatic charge on carbonyl-carbon: 1.250

Structure (left) and LUMO density (right) of anthracene-9-carboxylic acid 2,2,2-trifluoro-ethyl ester **2.124**[ii]



2.124

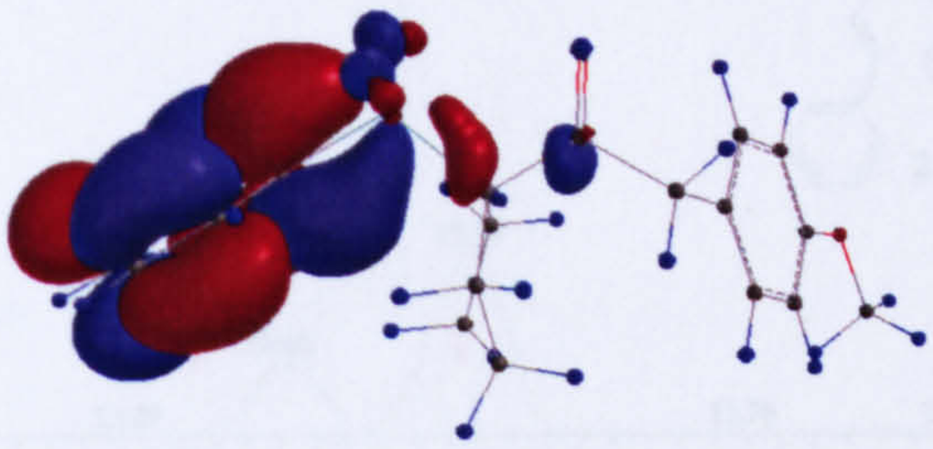


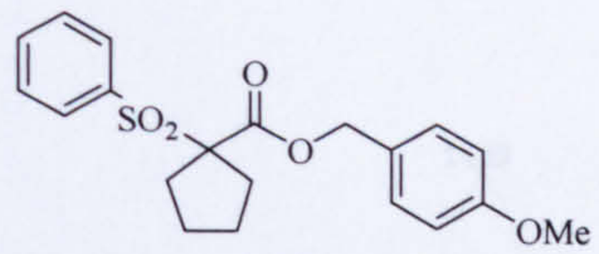


Electrostatic charge on carbonyl-carbon: 1.260

9.3 Supplementary material for *Chapter Five*

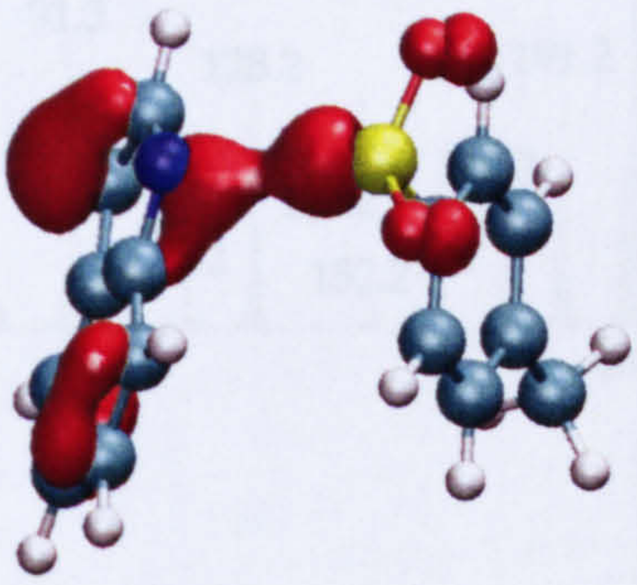
LUMO of sulfone ester **2.251**[ii]



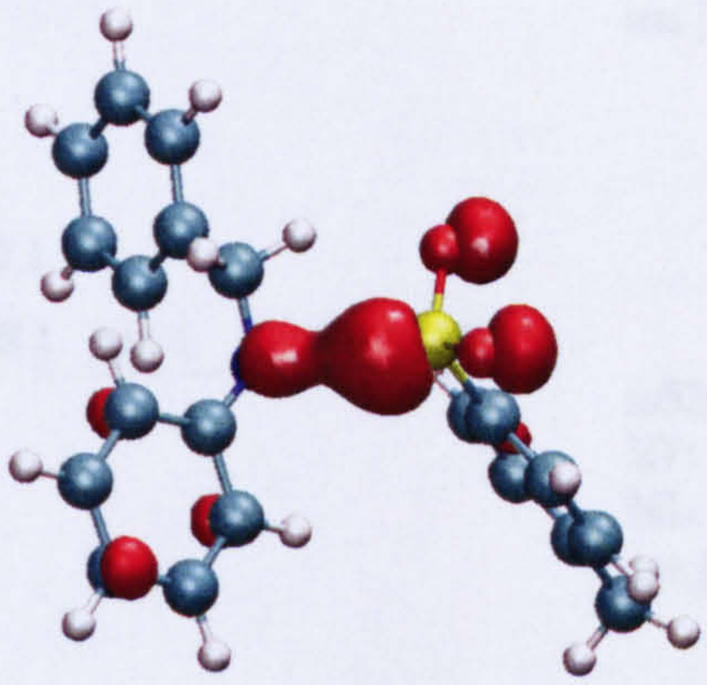


2.251

Comparison of the SOMOs in the radical anions derived from **2.272** and **2.271**[iii]

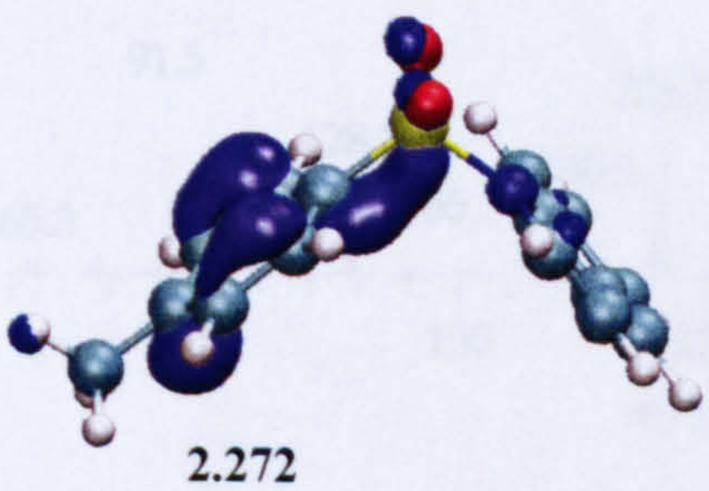


Radical anion of
2.272

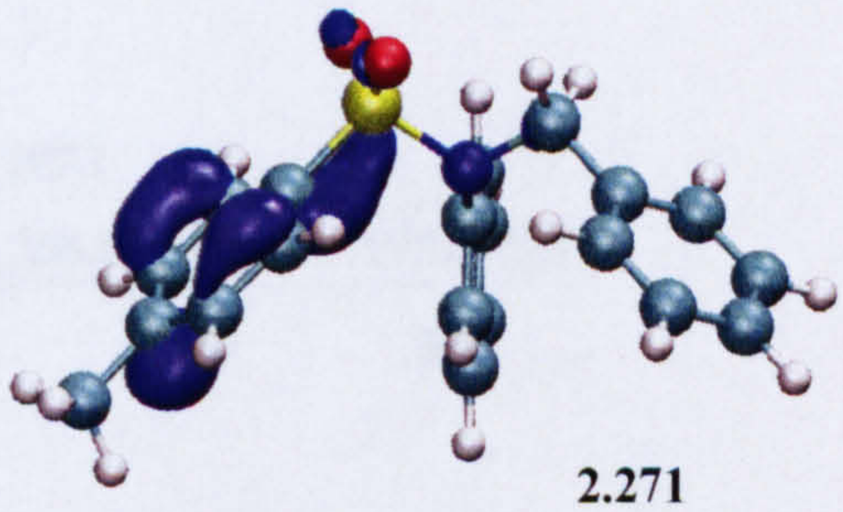


Radical anion of
2.271

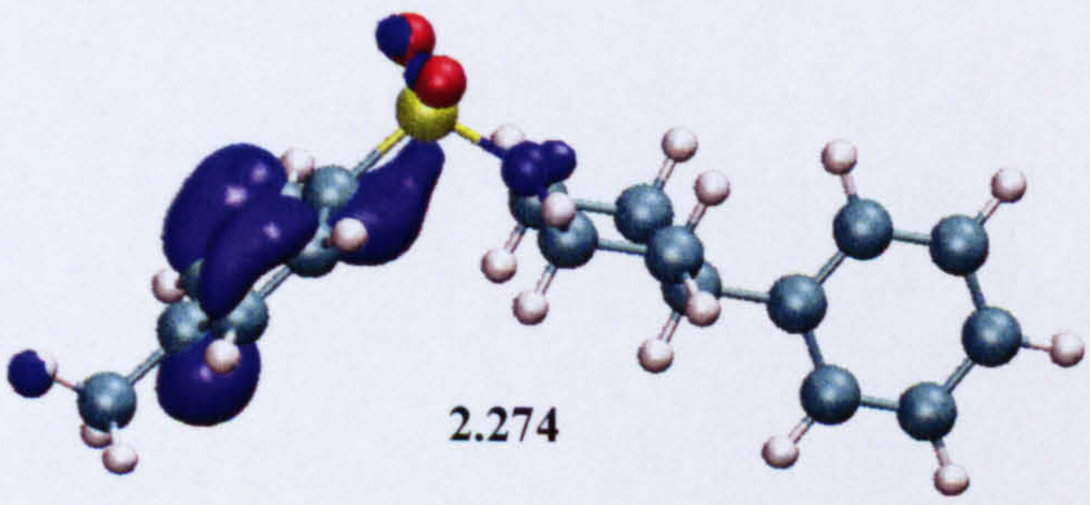
LUMOs of sulfonamides **2.272**, **2.271** and **2.274**[iii]



2.272

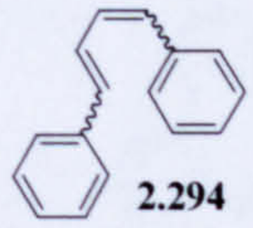


2.271

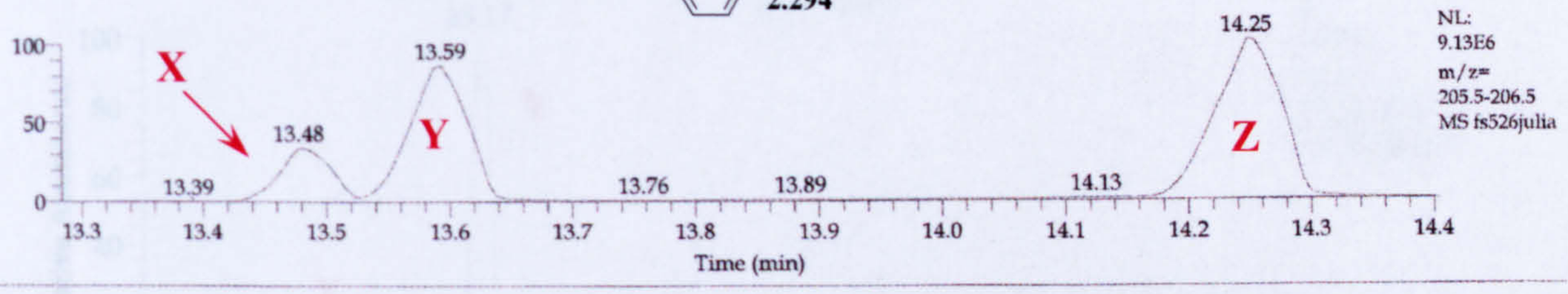


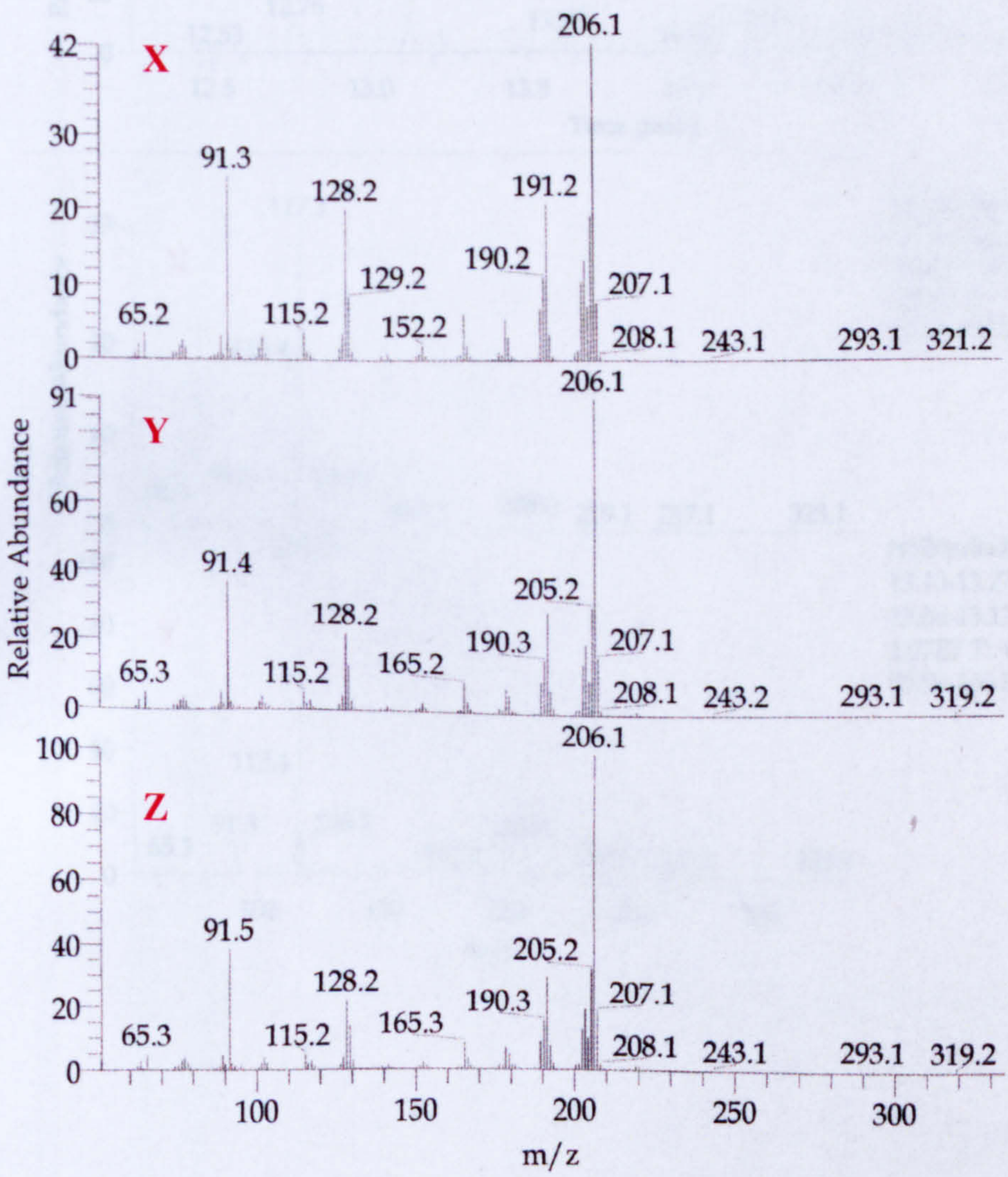
2.274

Comparison of the mass spectra of the three peaks corresponding to a molecular mass of 206, matching diene 2.294



2.294



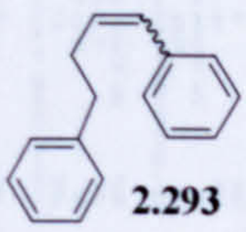


fs526julia#1363-1367
RT: 13.47-13.50 AV: 5
NL: 3.63E6 T: + c Full
ms [50.00-650.00]

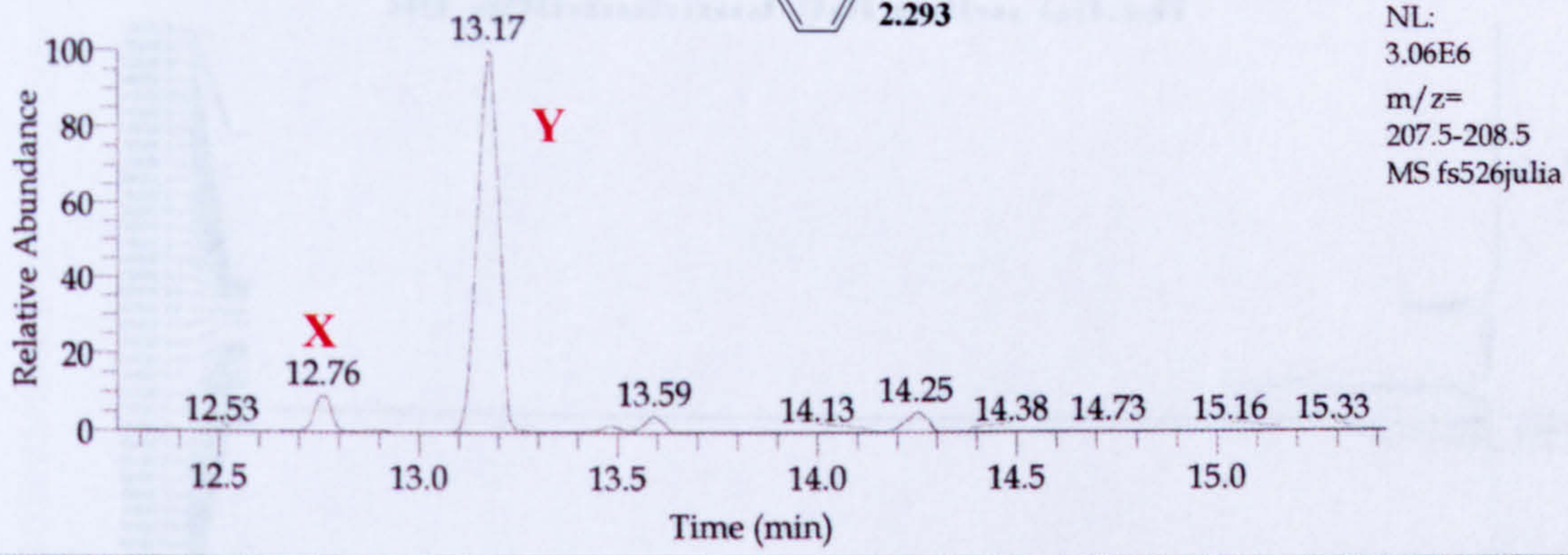
fs526julia#1379-1385
RT: 13.57-13.61 AV: 7
NL: 7.86E6 T: + c Full
ms [50.00-650.00]

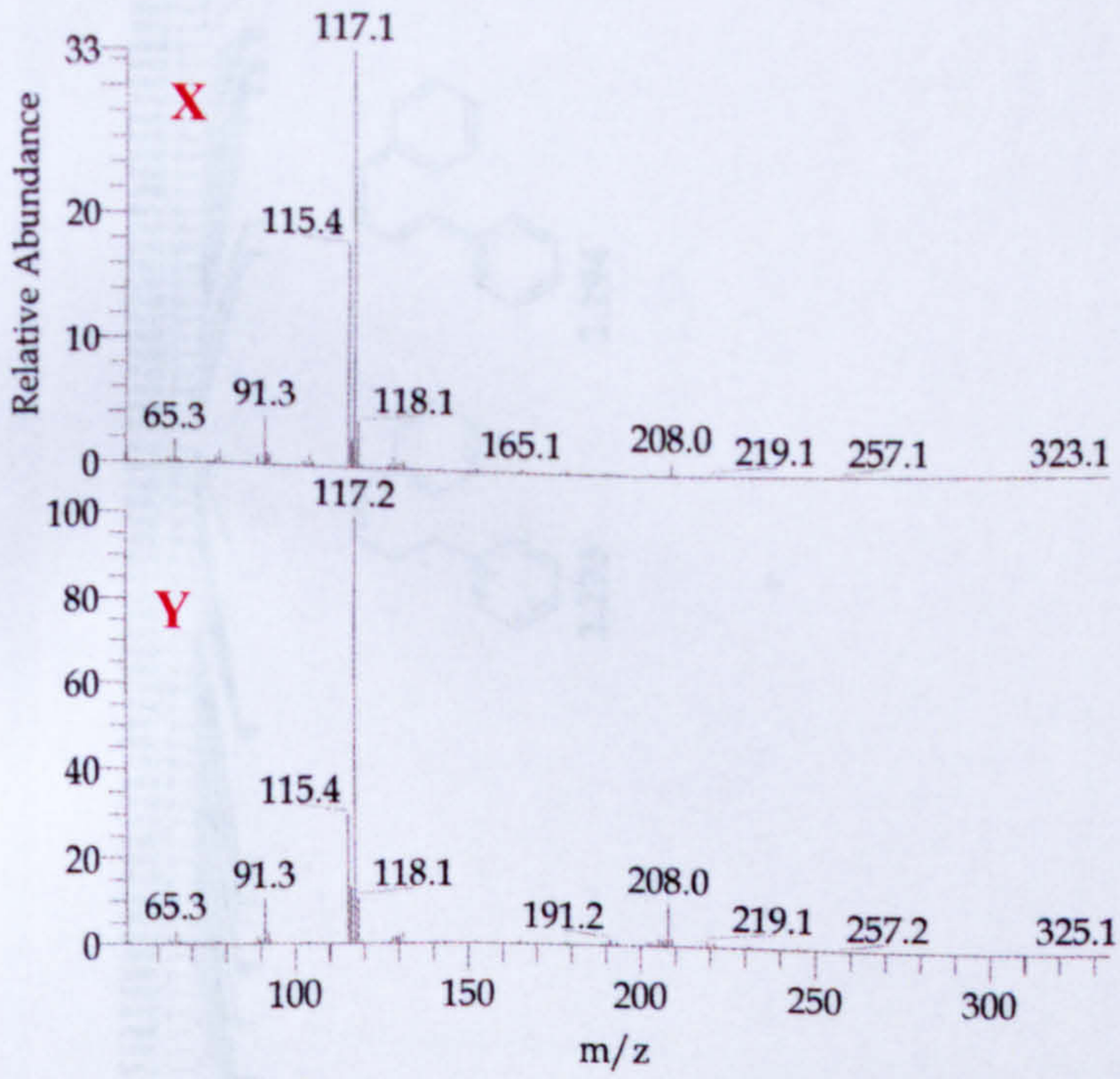
fs526julia#1478-1485
RT: 14.23-14.27 AV: 8
NL: 8.67E6 T: + c Full
ms [50.00-650.00]

Comparison of the mass spectra of the three peaks corresponding to a molecular mass of 208, matching alkene 2.293



2.293

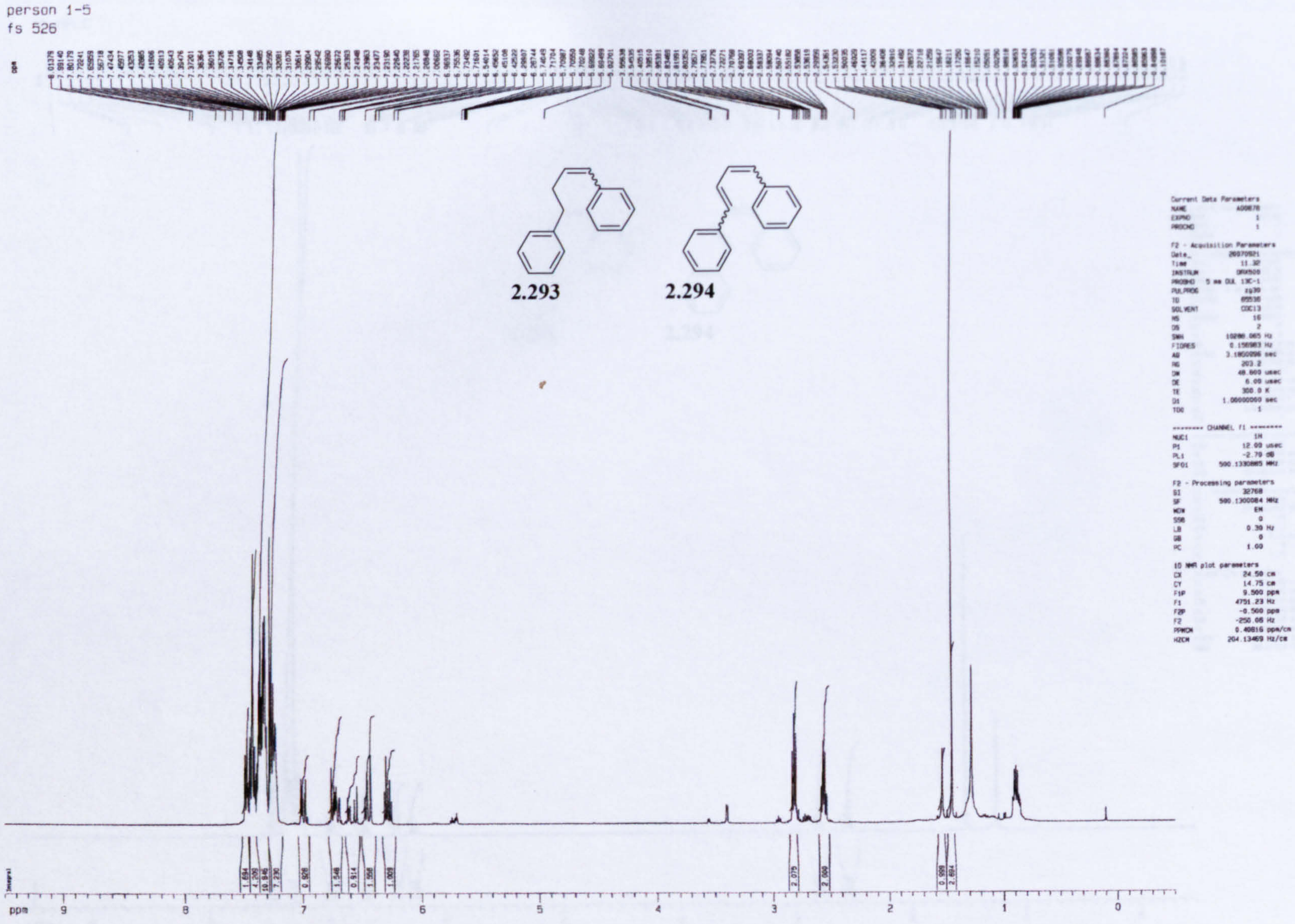




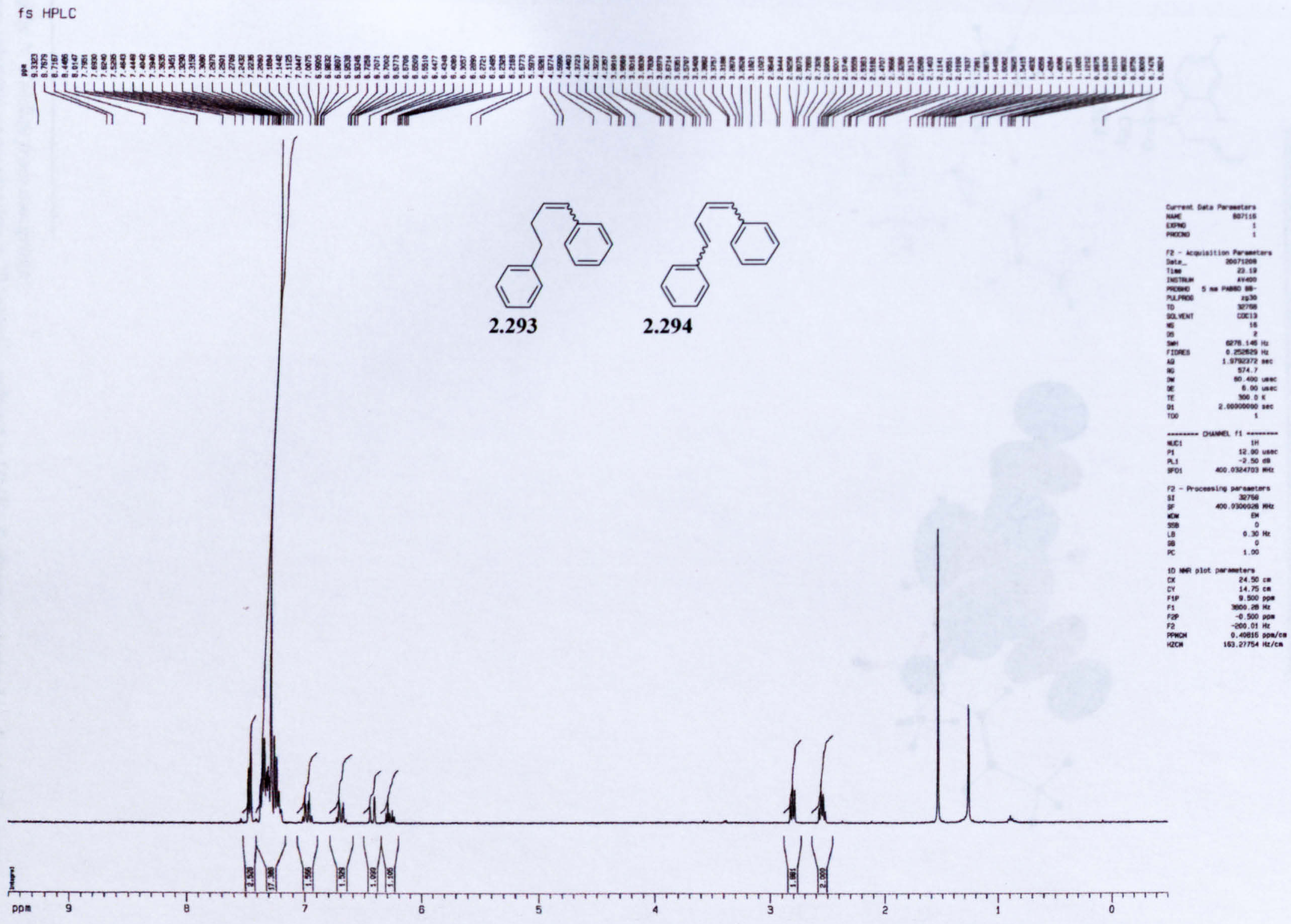
fs526julia#1246-1265 RT: 12.70-12.82 AV: 20 SB: 17 12.65-12.69 , 12.81-12.87 NL: 3.50E6 T: + c Full ms [50.00-650.00]

fs526julia#1306-1332 RT: 13.10-13.27 AV: 27 SB: 24 13.04-13.12 , 13.23-13.29 NL: 1.07E7 T: + c Full ms [50.00-650.00]

^{1}H-NMR spectrum of the mixture of 2.293 and 2.294 after column chromatography

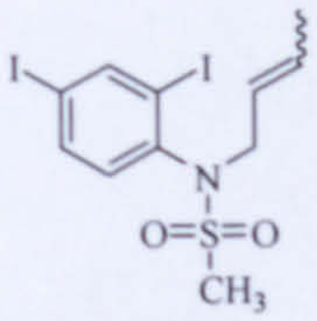


^{1}H-NMR spectrum of the mixture of 2.293 and 2.294 after HPLC

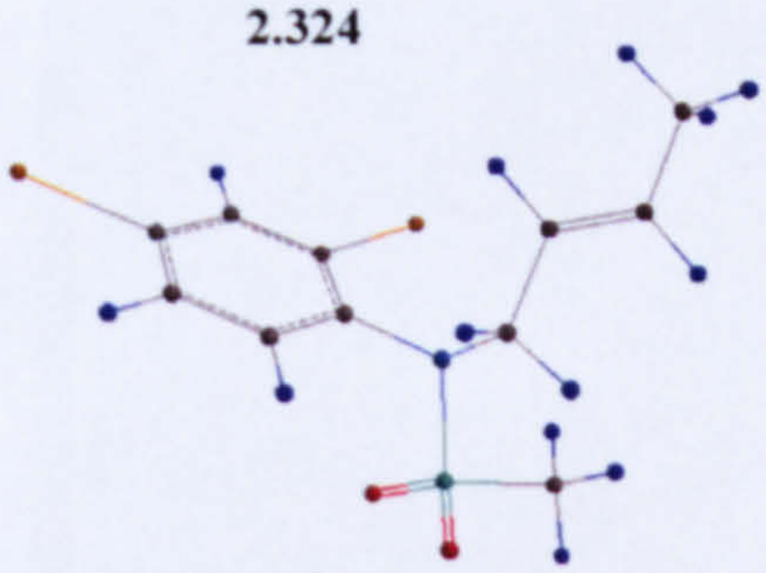


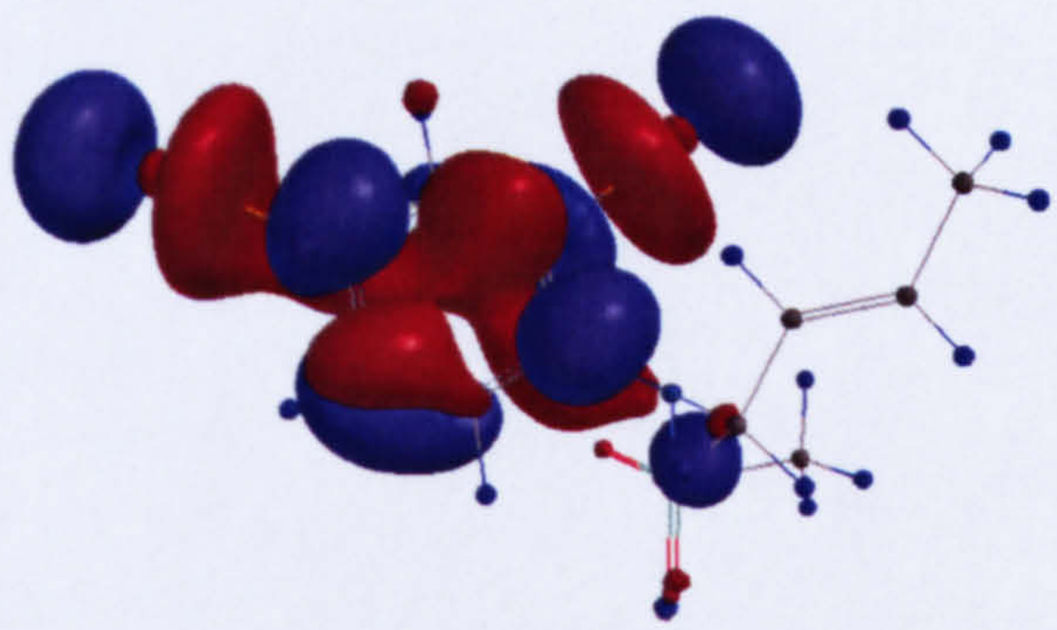
9.4 Supplementary material for *Chapter Six*

Structure (left) and LUMO (right) of diiodide **2.324**[ii]



2.324





[i] *Mesured by N. Findlay from our group:*
Conditions: substrate concentration = 20 mmol/l ; solvent = DMF ; Reference electrode : Ag/AgCl ; room temperature

[ii] Calculation: S*PARTAN*, Single-Point Energy, 3-21 G*, Hartree-Fock

[iii] *Calculated by T. Tuttle from our Department*: Gaussian03 program, DFT, B3LYP 6-311++G(d,p)