New Chiral I^+ Complexes for *Reagent*-controlled Reactions: A Combined Computational and Synthetic Approach

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- "Amine-Iodine Monochloride Complexes - New Chiral Electrophiles" *Fullpaper in preparation*

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A Combined Computational and Synthetic Approach"

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J. Haas, T. Wirth
"Chiral I^+ - a Theoretical Investigation"

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J. Haas, T. Wirth
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J. Haas, T. Wirth
"Chiral I^+ in *Reagent*-Controlled Stereoselective Iodolactonizations"

1-5/4/2001 221st ACS National Meeting, San Diego, USA
S. J. Burpee, A. N. French, J. Haas, T. Wirth
"Progress in a Computational Investigation of Conformers of Chiral Hypervalent Iodine Compounds"

15/12/2000 South-West Regional Meeting RSC, Reading, UK
J. Haas, T. Wirth
"Stereoselective Halocyclisations: now *Reagent*-Controlled"

14-16/9/2000 ORCHEM, Bad Nauheim, Germany
J. Haas, T. Wirth
"Stereoselektive Iodcyclisierungen: Jetzt reagenzkontrolliert"
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J. Haas, T. Wirth
"New Approach to Asymmetric Lactonization Reactions"

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Not everything that can be counted counts,

and not everything that counts can be counted.

- Albert Einstein

Meiner Familie gewidmet

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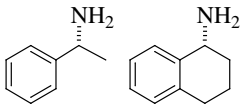
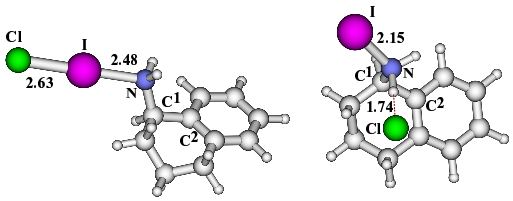
Summary

Amines are known to form strong complexes with ICl, their potential in organic synthesis is therefore of high interest. Thus chiral complexes with enantiomerically pure amines were investigated by synthetic, spectroscopical and computational means.



A **B**

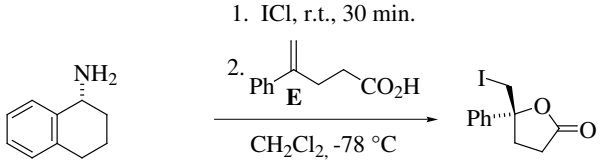
The complex formed between (*R*)-1-phenyl-ethylamine **A** and ICl has been investigated in NMR titrations, which showed the formation of a 1:1 complex and indicated subsequent transformations. These compounds have been investigated experimentally and also have been described by quantum chemical investigations. Furthermore with the aid of *ab initio* and DFT calculations a



C **D**

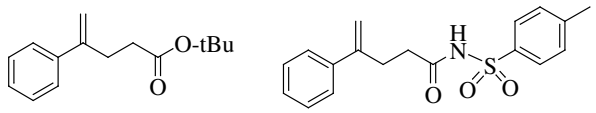
chiral complex **C**, formed by **B** and ICl could be identified. The charge transfer complex **C** between (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **B** and ICl resembles a chiral electrophile and after a proton-iodine exchange the *N*-iodo species **D** is formed. This is supported by time-dependent UV/VIS studies and also NMR titration experiments. If the reaction between **B** and ICl is continued for two hours, followed by an aequeous workup, the formation of α-tetralone was observed, which is also strongly supporting the conversion of **C** to **D**.

In the iodolactonisation reaction of 4-phenyl-4-pentenoic acid **E** to 5-iodomethyl-5-phenyl-dihy-



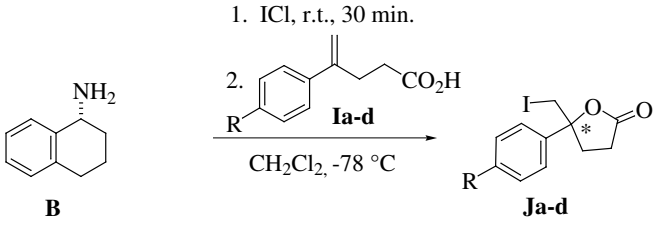
B 80% 45% *ee* (*R*)-**F**

drofuran-2-one **F**, an enantiomeric excess (*ee*) of 45% was observed. This result was obtained after stirring **B** and ICl for 30 minutes, bevor the actual lactonisation was performed at −78 °C. If this time was shortened lower enantioselectivites were observed (without stirring: 31% *ee*). Cyclisations of *tert.*-butyl-ester **G** as well as *N*-(4-phenyl-4-pentenoyl)-4-toluolsulfonamide **H** could achieve similar selectivities (34% *ee* and 37% *ee*, respectively).



G **H**

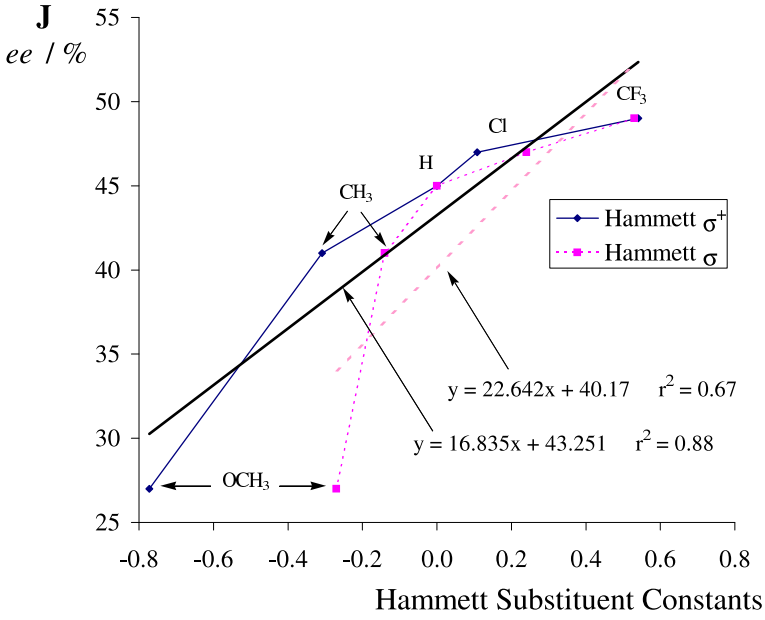
In a series of modifications on the aryl moiety, due to the introduction of a CF_3 moiety in the 4-position of the phenyl system, the highest selectivity of 50% *ee* was found.



B **Ja-d**

R= CF_3	**Ja**	50% *ee*	CH_3	**Jc**	41% *ee*
Cl	**Jb**	47% *ee*	OCH_3	**Jd**	27% *ee*

The results of these lactonisations were incorporated in a correlation of the *ee* with Hammett values σ_p^+ and σ_p. The linear relationship found for this type of transformation suggests the existence of a benzylic cation in the selectivity determining step. A range of ligands, mostly with the



motive of (*R*)-1-phenylethylamine **A** have been synthesised and the stereoselective lactonisation performed with these amine-ICl complexes. Transfer of chirality was also investigated in 1,2-iodofunctionalisations and iodocylisations of unsaturated alcohols.

1 Introduction

1.1 Iodiranium Ions in Iodocyclisations

Halocyclisations have been known since the late 1800s[1] and iodolactonisations were first mentioned by Bougault early last century.[2] They have been key intermediates in many natural product syntheses, since they resemble versatile building blocks, often used in lactonisation-HI elimination or in lactonisation-deiodination sequences.[3]

The mechanism of halolactonisations was thoroughly investigated and it is accepted that, depending on the reaction conditions,[4] it can proceed in two possible ways.[5] In aqueous media in presence of a base the reaction sequence proceeds via iodiranium ion **A** to the desired lactone. In aprotic media a π-complex $\mathbf{\Pi^1}$ is initially formed, which incorporates the electrophile, the double bond and the internal nucleophile. Subsequent deprotonation in the π-complex $\mathbf{\Pi^2}$ yields the lactone. Additionally the formation of the π-complexes is regarded to be reversible.

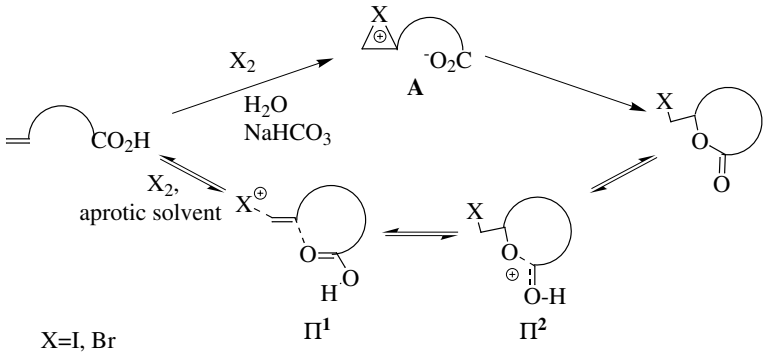
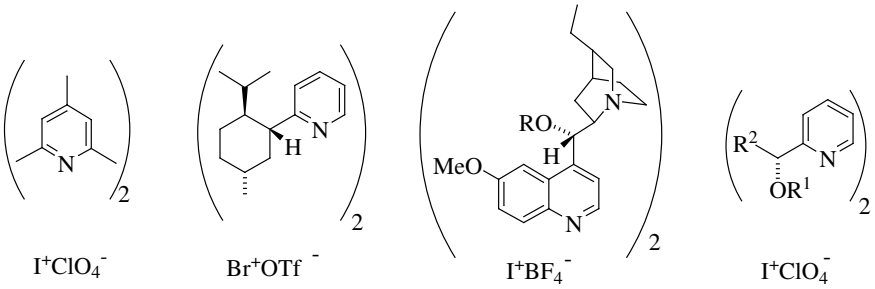


Figure 1: Possible Mechanisms in Lactonisations

Many examples of stereoselective cyclisations have been reported using *substrate*-controlled conditions, in which chiral auxiliaries[6] were used as a source of stereochemical information. The disadvantage of this approach is that auxiliaries have to be attached prior to the required transformation and also removed afterwards.

Reagent-controlled iodolactonisations exhibit several advantages over the *substrate*-controlled approach. Halogens, complexed by one or more chiral ligand molecules, are responsible for the stereoselectivity found in the product. Moreover to achieve a catalytic and enantioselective cycle the requirements of ligand accelerated reactions must be fulfilled, which is not possible with the *substrate*-controlled approach.
There are only two other attempts in the literature to realise the *reagent*-controlled approach. Both approaches were similar to bis-*sym*-collidine-iodoniumperchlorate (BCIP) **1a**,[7] with *sym*-collidine substituted by chiral ligands. Selectivities have been reported of up to 14% *ee* (using **1c** as a ligand in a 5-*exo*-iodolactonisation),[8] the other was a bromo analoguous system **1b** and reported selectivities of 5% *ee* (**1b** was used as a ligand in a 5-*exo*-bromocyclisation).[9]



1a **1b** **1c** **1d**

Also in the research group of T. Wirth this approach had been independently followed (**1d**).[10] The typical procedure for applying theses complexes as reagents is mostly a two-step synthesis, where firstly $AgClO_4$ is reacted with two equivalents of the ligand molecule. In a second disproportionating step AgI is precipitated, when I_2 is added to the silver complex to generate the reagent *in situ*. In a 5-*exo*-iodolactonisation the selectivities achieved with **1d** were very low.

1.2 Iodiranium Ions in Computational Investigations

The vast majority of calculations in the field of electrophilic additions to double bonds by halogens have been done on bromo- or chloroiranium ions.[11] This is mostly for practical reasons, since in many well-defined and widely applied basis sets iodine is not treated relativistically or is not included.[12]

In all of the work reported so far mostly bromoiranium ions are discussed, followed by chloroiranium ions. In these investigations the addition of halogens or interhalogens to double bonds were explored in detail, bromoiranium ions of cyclohexane and ethene being the most detailed studied ones.

The formation of donor-acceptor complexes of the halogens with electron donor compounds, prior to the addition to the double bond to form the halo-iranium ion, was not reported so far. On the other hand the interaction of ICl and carbonyls has been studied,[13] but not in conjunction with an attack to a double bond.

The field of donor-acceptor complexes is a classic domain of electron correlated methods, such as MP2 and only recently there has been development of DFT functionals towards accurate descriptions in this area.[14]

2 Task and Concept

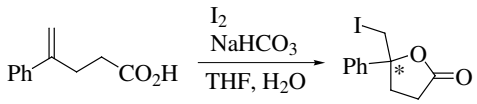
The examples of stereoselective iodolactonisations that have been reported, were either *auxiliary*-controlled versions or lactonisations of molecules already bearing a stereogenic center in the course of a total synthesis. Up to date there is no efficient *reagent*-controlled protocol known for this type of reaction. Therefore the formation, the chemical properties and possible applications of chiral electrophilic complexes of iodine(+1) are of high interest, since iodolactones have been important key intermediates in many organic syntheses. *Reagent*-controlled iodolactonisations were therefore to be investigated by means of synthetic, spectroscopic and computational methods. The stereoselectivities found in model lactonisations were to be used to make assumptions about the possible intermediates formed between the source of I^+ and the chiral ligand.
The interaction between the most efficient source of I^+ and electron donor molecules was to be investigated computationally (by *ab initio* and DFT calculations). Studies on iodiranium ions would be completing the computational results.
The experimental and computational results are then combined to deduce a working hypothesis, which is verified experimentally.

3 Synthetic Results and Discussion

3.1 5-*exo*-Lactonisations

Strategy: Halogens and interhalogens generally form strong complexes with N-donor molecules.[15] Chiral versions of these complexes can be used to perform stereoselective halo-transformations, such as iodolactonisations.

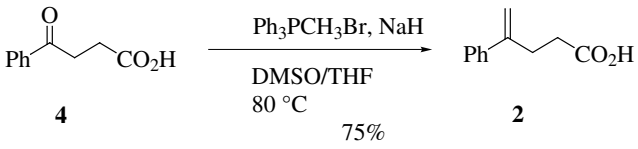
In order to be able to investigate the efficiency and selectivity of stereoselective iodolactonisations complex 4-phenyl-4-pentenoic acid **2** was chosen as a model compound. Analysis and stability of 5-iodomethyl-5-phenyl-dihydrofuran-2-one **3** was expected to be superior to products of other iodolactonisations, possibly eliminating HI. In this lactonisation the formation of the 6-*endo*-lactone was not observed, which is according to Baldwin.[16]



2 **3**

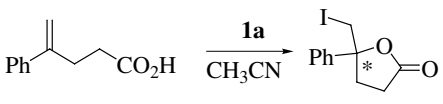
3.1.1 Cyclisation of 4-Phenyl-4-pentenoic Acid

Compound **2** was synthesised from 3-benzoyl-propionic acid **4** by a Wittig reaction in 75% yield. Carboxylic acid **4** had to be deprotonated with NaH beforehand to achieve high yields.



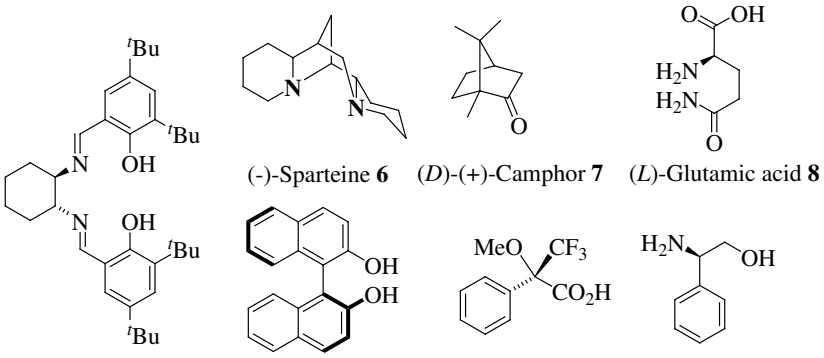
4 **2**

The iodolactonisation of **2** $\longrightarrow$ **3** with the standard iodolactonisation protocol[2b] ($NaHCO_3$, iodine and aq. THF) proceeded in less than 30 minutes to completion with an excellent yield (90%).
Also under alternative iodolactonisation conditions (**1a** in CH_3CN)[17] this reaction proved to be efficient. The analysis of the racemate was achieved by chiral HPLC;[18] all in all the reaction times were short and the reaction product **3** could be analysed in a straightforward manner.
In earlier work on stereoselective iodolactonisations a chiral pyridine moiety was used to substitute *sym*-collidine in **1a**. Nonetheless **1b** did not lead to selectivities higher than 5% *ee*.[19] Similar results were also reported in the literature in bromocyclisations using compound **1b**.[20] A different approach was chosen, in using ICl as source of I^+.



2 **3**

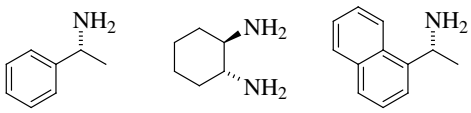
ICl was used as a source of I^+, in order to form a chiral donor-acceptor complex with a ligand to yield a chiral complexed electrophile. Potentially this approach is very promising, since in this way also a catalytic version would be possible, which was no option with *substrate*-controlled procedures.[21] The racemic iodolactonisation of **2** ⟶ **3** with ICl in CH_2Cl_2 proceeded with excellent yields (90%). Various compounds from different classes were then used as ligands (in a 1:1 ratio to ICl), since it was known that ICl forms 1:1 complexes with amines such as ammonia,[15] pyridines[22] and triethylamine.[23] Compounds such as Jacobsen's ligand **5**,[24] (−)-sparteine **6**,[25] (*D*)-(+)-camphor **7**, (*L*)-glutamic acid **8**, (*R*)-(+)-[1,1']-binaphthalenyl-2,2'-diol **9**, (*S*)-Moshers acid **10**,[26] (*L*)-phenylglycinol **11** were applied as ligands. The use of these resulted in the formation of racemic **3**, while a variety of primary amines were showing more promising results.



Jacobsen's ligand **5** (-)-BINOL **9** (*S*)-Moshers Acid **10** (*L*)-Phenyl-glycinol **11**

(-)-Sparteine **6** (*D*)-(+)-Camphor **7** (*L*)-Glutamic acid **8**

This initial screening clearly showed the potential of amines, only a small selection shall be shown here, since a more detailed discussion will follow. Amines such as (*R*)-1-phenylethylamine **12** or (*1R,2R*)-(−)-1,2-diaminocyclohexane **13** showed low to moderate stereoselectivity. Stereoselectivities of up to 30% *ee* (in (*R*)-**3** using (*R*)-1-(1-naphthyl)-ethylamine **14**) were achieved with this initial unoptimised procedure.



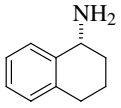
12 **13** **14**

The conditions for the generation of the chiral complex for use in this iodolactonisation were then optimised.

Optimisations To enhance the selectivity and reproducibility in these lactonisation, several parameters were optimised. Among these parameters were the handling of the ICl itself, the effect of solvents and the ratio of amine to ICl used in the reaction.

Handling of ICl: Initially the reaction gave varying selectivities under similar conditions. While within a larger batch of ICl solution the results were perfectly reproducible, they varied from one batch to the next. Different concentrations of the solutions, which were prepared from solid ICl, was the only plausible cause for this variation. Recrystallised ICl did not enhance reproducibility, only with a commercial 1 M solution of ICl in CH_2Cl_2 the results were reproducible ($\pm 2\%$ *ee* for the selectivities up to 20% *ee*).

The Stereoselective Lactonisation - a Two Step Procedure: In early experiments it was found, that ligand **12** gave (*R*)-**3** in 12% *ee*. Furthermore after ICl and **12** had been stirring at -78 °C for 25 minutes, the selectivity was 18% *ee*. This effect could be amplified even further by stirring at r.t. and for longer periods (30-45 minutes), before cooling to −78 °C for the actual iodolactonisation. In case of amine **12** an enantioselectivity of 26% *ee* (*R*)-**3** was obtained.



15

Other amines, such as (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **15** showed even higher selectivities with this optimised procedure. Amine **15** was allowed to stirr at r.t. for 0 minutes (31% *ee* (*R*)-**3**) and 15 minutes (36% *ee* (*R*)-**3**), 30-45 minutes (45% *ee* (*R*)-**3**). After more than 90 min. no reaction occurred anymore, indicating a decomposition of the chiral complex.
In case of **15** the temperature of these initial 30 minutes was increased to reflux, but the selectivities of the reaction performed at -78 °C after refluxing for 5 and 10 minutes remained the same. After 15 minutes there was an slight increase by 3% *ee*. If ICl and **15** were stirred at r.t. for 30 minutes, the enantioselectivity was 14% higher, than directly mixing amine **15** and ICl at −78 °C and the iodolactonisation performed immediately.
In this first stage of the procedure a change in composition of the initially formed charge-transfer complex between the amine and ICl, is responsible for the increased selectivities. This reaction eventually even led to complete inactivity of the mixture in iodolactonisations, when amine and ICl were stirred for more than 90 minutes at room temperature.

The optimised procedure therefore constisted always of stirring the amine (0.1 M in CH_2Cl_2) and ICl (1 M in CH_2Cl_2) at room temperature for 35 minutes. The reaction mixture was then cooled down to -78 °C and the iodolactonisation was performed by adding **2** in CH_2Cl_2.

Ligand : ICl ratio As expected, it was found that changes in the ratio of amine **15** to ICl influences the stereoselectivity in the reaction. Moreover, it was necessary, in order to obtain best results, to use 2 equivalents of amine and 1 equivalent of ICl.

Variations of multiples thereof only led to smaller stereoselectivities, because the amount of **2** in the lactonisation remained constant. Any other change in ratio showed the same effect, possibly one equivalent of the amine traps the HCl formed in the reaction.

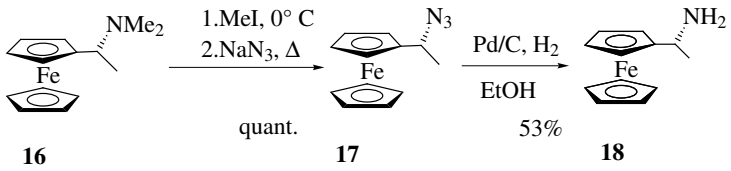
Table 1: Effects on Stereoselectivities by changing Ratios of **15**:ICl

eq. **15**: eq. ICl	*ee* / % in **3**
1:2	0
1:1	34
1.5:1	36
2:1	45
2.5:1	28
4:2	37
6:3	41
4:1	30

Ligands: The initial strategy was to either use commercially available or easily accessible amines to have a straightforward access to new ligands.

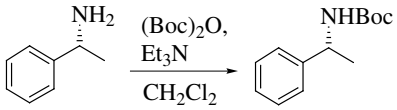
Syntheses:

(*R*)-(−)-*N*,*N*-dimethyl-1-ferrocenyl-ethylamine **16** was converted in in two steps via (*R*)-(−)-1-ferrocenyl-ethylazide **17** in 53% yield to (*R*)-(−)-1-Ferrocenyl-ethylamine **18**.[27]

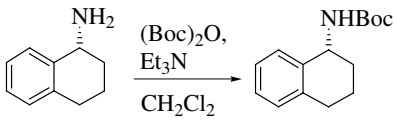


16 **17** **18**

Amines **12** and **15** were reacted with di-*tert*.butyldicarbonate and triethylamine to obtain (*R*)-1-Phenylethyl-carbamic acid *tert*.butylester **19** and (*R*)-1,2,3,4-tetrahydro-1-naphthylcarbamic acid *tert*.butylester **20** in a straightforward (95% and quantitative yield) way.

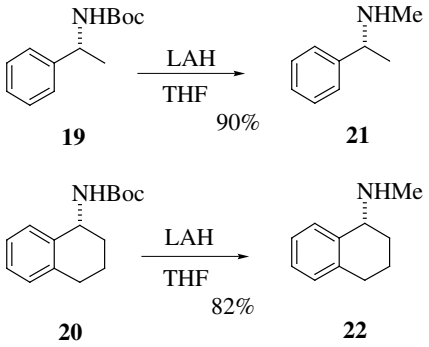


12 **19**

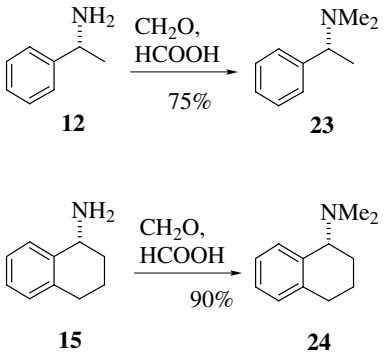


15 **20**

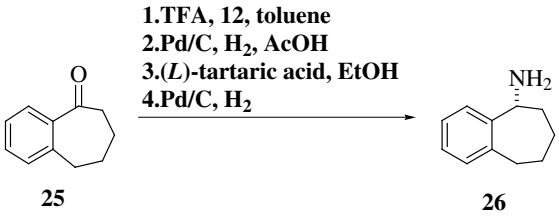
Reducing esters **19** and **20** with lithium aluminum hydride yielded *N*-methylated amines **21** and **22** in 90% and 82% yield, respectively.



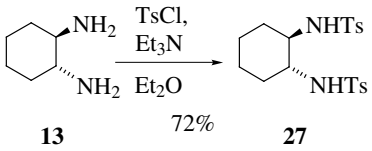
In a reductive amination using formaldehyde and formic acid compound **12** was converted into *N*,*N*-dimethylated amine **23** in 90% yield. *N*,*N*-Dimethylated **24** was obtained from **15** in 75% yield following the same procedure.



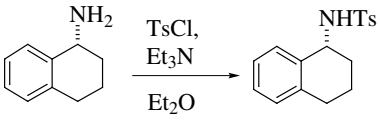
(*R*)-5-Amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene **26** was synthesised to further study the influence of varying the ring size. In a first step *(R)*-1-phenylethylamine **12** and 1-benzosuberone **25** formed a ketimine, which, after hydrogenating the imine bond, was resolved with (*L*)-(+)-tartaric acid by fractional recrystallisation. The last step was a palladium catalysed cleavage of the benzylic bond, which led to a product mixture of (*R*)-1-phenylethylamine **12** and amine **26**.[28]



Adding tosylchloride and triethylamine to etheral solutions of amines **13** and **15** tosylates **27** and **28** were synthesised in 72 % and 85% yield, respectively.



13 72% **27**



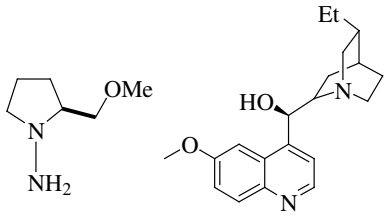
15 85% **28**

The structural features and the patterns which emerged from the trends in selectivity allowed the ligands to be divided into three main groups:

- Group I: Structural motif of **12** is not present at all
- Group II: Compounds contain variations of structural motif of **12**
- Group III: bis-amines.

Group I:

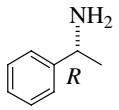
There were only a few compounds which, at a low level of selectivity, were successful. Two examples are SAMP **29**,[29] where a selectivity of 14% *ee* (*S*)-**3** was observed and hydrochinidine **30** which gave (*S*)-**3** in 5% *ee*.[30]



29 **30**

Group II:

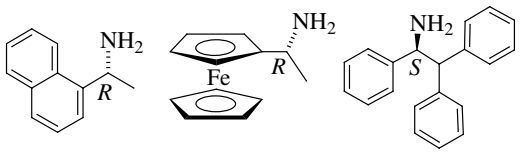
Far more successful were primary amines, the structural motif of **12** emerged to be crucial for selectivity. All the selectivities given below show the configuration in **3**, which was found to be the major enantiomer. In the lactonisation of **2** to **3** the major enantiomer differed from ligand to ligand. Hence all ligands discussed bear the configuration of the enantiomer used in the reaction, noted as *S* or *R* in the individual schemes.



12

(26% *ee* (***S***)-**3**)

A variation in the aromatic moiety and the substitution pattern at the ethyl moiety showed that the opposite stereoisomer is induced (compared to **12**), if the phenyl moiety is swapped with entities of higher spacious requirements like naphthyl (**14**) or ferrocenyl (**18**) moieties.

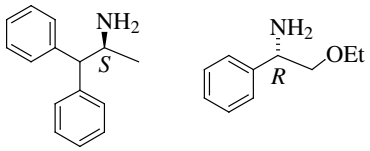


14 **18** **31**

(30% *ee* (***R***)-**3**) (19% *ee* (***R***)-**3**) (5% *ee* (***S***)-**3**)

In case of (*S*)-1,2,2-triphenyl-ethylamine **31** and (*S*)-1-methyl-2,2-diphenyl-ethylamine **32** low selectivities were observed and the major enantiomer in the lactone has the same configuration as the stereogenic center in the ligand.

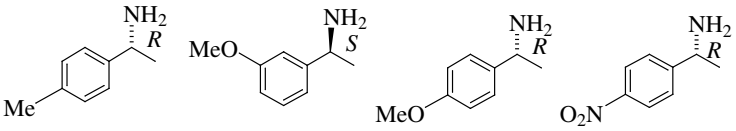
On the contrary a sterically smaller ethoxy group in (*R*)-2-ethoxy-1-phenyl-ethylamine **33** induced an excess of stereoisomer ((*S*)- **3**).



32 **33**

(3% *ee* (*S*)-**3**) (10% *ee* (*S*)-**3**)

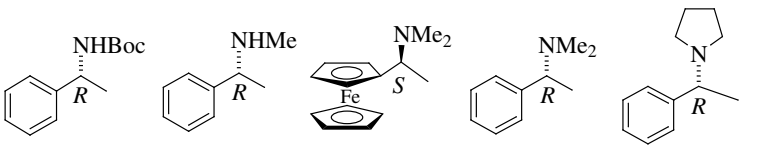
In a small set of substitutions on the aromatic system, a *para*-methyl substitution in **34** and *meta*-methoxy substitution in **35** gave similar selectivities. A *para*-methoxy substitution on the phenyl moiety in **36** led to an enantioselectivity, which was expected to be higher. With an increase in electron density, a stronger donor-acceptor interaction was expected. In (*R*)-1-(4-nitro-phenyl)-ethylamine **37** the electron density in the conjugated π-system was expected to be lowered. A change in selectivity (lower compared to **12**) was observed in this case.



34 **35** **36** **37**

(24% *ee* (*S*)-**3**) (26% *ee* (*R*)-**3**) (11% *ee* (*S*)-**3**) (11% *ee* (*S*)-**3**)

Much different was the situation, when substituents on the nitrogen were introduced. In all cases the selectivity dropped dramatically, it often racemic product was observed, (*R*)-1-(1-phenyl-ethyl)-pyrrolidine **38** showed 13% *ee* (*S*)-**3**.



19 **21** **16** **23** **38**

(2% *ee* (*S*)-**3**) (0% *ee* **3**) (0% *ee* **3**) (0% *ee* **3**) (13% *ee* (*S*)-**3**)

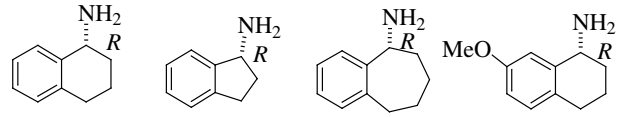
From this first selection of experiments it already can be seen that primary amines are much better ligands, in spite of the low selectivities observed, when applying **31** and **32**. All the results discussed so far are summarised in Table 2. Undoubtedly the best results were obtained with **15**.

Changing of the size of the annelated ring to either 5 or 7 membered ring systems did only lead to reduced selectivities (18% *ee* and 10% *ee* obtained with (*R*)-aminoindan **39** and (*R*)-5-amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene **26** resp.). 7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-ylamine **40** achieved a lower selectivity than **15** (41% *ee*).

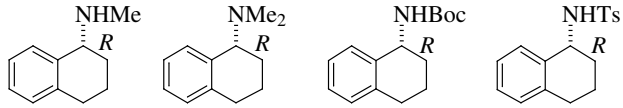
Table 2: Selectivities Achieved with First Set of Variations of **12**

Ligand	*ee* / % in **3**	Ligand	*ee* / % in **3**
12	26 (*S*)	**36**	11 (*S*)
14	30 (*R*)	**37**	11 (*S*)
18	19 (*R*)	**19**	2 (*S*)
31	3 (*S*)	**21**	0
32	5 (*S*)	**16**	0
33	10 (*S*)	**23**	0
34	24 (*S*)	**38**	13 (*S*)
35	26 (*R*)	**15**	45 (*R*)

Any substitution on the nitrogen, as seen above, again only lowered the selectivity dramatically.



15 (45% *ee* (*R*)-**3**) **39** (18% *ee* (*R*)-**3**) **26** (10% *ee* (*R*)-**3**) **40** (41% *ee* (*R*)-**3**)



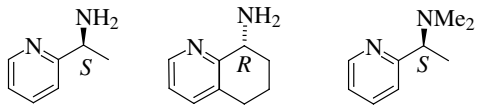
22 (20% *ee* (*R*)-**3**) **24** (13% *ee* (*R*)-**3**) **20** (0% *ee* **3**) **27** (0% *ee* **3**)

Exceptions were *N*-methyl- (**22**) and *N*,*N*-dimethyl-derivatives (**24**), where low selectivities were obtained (20% *ee* and 13% *ee* respectively).

Table 3: Second Set of Variations of **12**

Ligand	*ee* / % in **3**	Ligand	*ee* / % in **3**
15	45 (*R*)	**22**	20 (*R*)
39	18 (*R*)	**24**	13 (*R*)
26	10 (*R*)	**20**	0
40	41 (*R*)	**27**	0

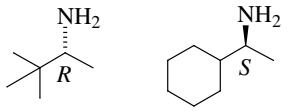
If the compounds contained two nitrogen atoms like in 1-pyridin-2-yl-ethylamine **41** and (*R*)-8-amino-5,6,7,8-tetrahydroquinoline **42** very low selectivities were observed (**41**: 2% *ee* (*S*); **42**: 3% *ee* (*R*)), despite the close resemblance to **12** and **15**.



41 (2% *ee* (*S*)-**3**) **42** (3% *ee* (*R*)-**3**) **43** (0% *ee* **3**)

The coordination to the pyridyl-nitrogen atom seems to have a strong influence on the orientation to the double bond in the moment of the formation of the iodiranium ion. When using (*S*)-*N*,*N*-dimethyl-1-pyridin-2-yl-ethylamine **43**, racemic product was observed.

To take the variations one step further, the phenyl moiety in **12** was substituted with a *tert.*-butyl and cyclohexyl moiety ((*R*)-1,2,2-trimethyl-propylamine **44** and (*R*)-1-cyclohexyl-ethylamine **45**, respecively). But the aromatic moiety seems be crucial and lacking thereof did not lead to high selectivities (**44**: 3% *ee* (*S*); **45**: 16% *ee* (*S*)).

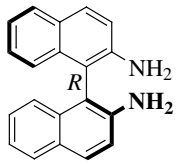


44 (0% *ee* **3**) **45** (16% *ee* (*S*)-**3**)

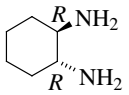
Group III:

For using *bis*-amines the procedure was adapted, so that an additional 2 equivalents of ICl was used, to keep the ration of amine functional groups:ICl constant at 2:1. With (*R*)-(+)-2,2'-diamino-1,1'-binaphthalene **46** and **28** racemic results were obtained, when **13** and (*1R,2S*)-1,2-diphenyl-ethane-1,2-diamine **47** were used as ligands low selectivities were obtained.

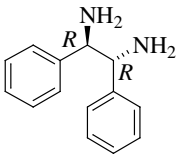
In this case the yields were low (30%) as well.



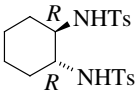
46
(0% *ee* **3**)



13
(16% *ee* (*S*)-**3**)



47
(16% *ee* (*R*)-**3**)

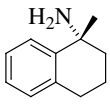


28
(3% *ee* (*R*)-**3**)

More convenient would be to use the HCl salts of the amines, since most of them are air sensitive. In case of **15** and **37** the corresponding HCl salts have been prepared (as well as sparteinesulfate), but in each case racemic product **3** was obtained in the iodolactonisations.

In summary only primary amines gave significant enantiomeric excesses, the motif of **12** has emerged to be crucial for the formation of a selective I^+-complex and the best amine was **15**.
Any substitution on the nitrogen interferes strongly with the course of the reaction and leads to very low selectivities or even racemic product.
The decay of the amine-ICl complex clearly poses a problem, it could procced via the corresponding imime. Thus the *N*,*N*-dimethylated compounds **23** and **24** were synthesised to inhibit this route, but they led to low selectivities.
Crystal structures of primary amines and ICl are not known (complex decomposes due to imine formation), but Et_3N was reported.[23]

A new type of primary amines, such as (*R*)-1-methyl-1,2,3,4-tetrahydro-naphthalen-1-ylamine **48** has therefore been designed and is illustrated below:



48

This compound containing a quaternary stereogenic center has posed a number of problems in different routes and is therefore only presented as an outlook.[31]

Counterions: To investigate the effect of different counterions on the selectivity in the iodolactonisation **2** $\longrightarrow$ **3**, ICl was treated with the $AgClO_4$, $AgPF_6$, $AgBF_4$ and AgOTf respectively. The preformed electrophile was then filtered over a 0.45 micron filter and subsequently used in the lactonisation. After that the optimised procedure (chapter 3.1.1 on page 6) was followed with no further modifications.

While hexafluorophosphate did yield selectivities and yields in a very similar range (40% *ee*), triflate (28% *ee*) and perchlorate (11% *ee*) counterions partly diminished the selectivities. Among the various counterions investigated, tetrafluoroborate showed the most dramatic change, where only racemic traces of product were observed.

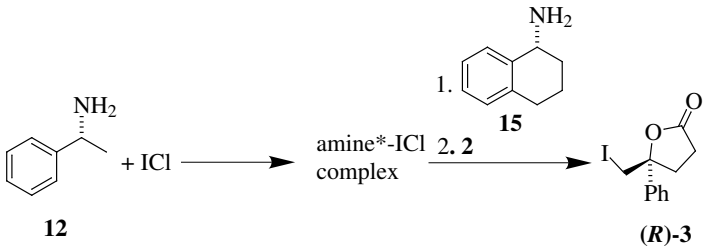
External Bases: Since a twofold excess of chiral ligand is a disadvantage as such, substituting one equivalent of chiral amine (**12** and **15** in this case) with one equivalent of a base was considered. It is to be noted that pyridine and triethylamine can also influence the equilibrium between the ICl and the chiral ligand by complexing ICl as well.

Table 4: Influence of External Bases on the Stereoselectivity

Base	*ee* / %[a] in **3**	*ee* / %[b] in **3**
$NaHCO_3$	11 (*S*)	-
Et_3N	11 (*S*)	30 (*R*)
Na_2CO_3	15 (*S*)	33 (*R*)
pyridine	8 (*S*)	35 (*R*)

The following chiral amines were used as ligands: a) **12** b) **15**.

Crossover Experiments: The results of the external bases proved that the amine-ICl complexes can be altered in composition. Therefore a second chiral amine was added after the preforming of the complex was complete (30 minutes). This second amine was known to give the opposite enantiomer in **3**.



The crossover experiments have been divided into two phases. First one equivalent of ICl was mixed with one equivalent of **12** in CH_2Cl_2 and stirred for 30 minutes. After this preforming of the complex one equivalent of **15** was added at room temperature. In the second phase the reaction mixture was then cooled down to -78 °C and the lactonisation reaction was performed in which 6% *ee* (*R*)-**3** was observed. Reversing the order of addition of amines (first **15** then after preforming the complex **12**) resulted in 7% *ee* (*R*)-**3**.
Lowering the temperature at the time of the addition of the second amine resulted in 10% *ee* (*R*)-**3** (first **15**, second **12**) and 1% *ee* (*R*)-**3** (first **12** second **15**) respectively.

The first four experiments were confirming, that although **12** is used in the preforming stage, **15** alters the complex to a 1:1 situation (1:1 with **12** and 1:1 with **15**). From this mixture 10% *ee* (*R*)

Table 5: Stereoselectivities when Adding a Second Ligand

amine 1	amine 2	T / °C	*ee* obs. / %
1 eq. **15**	1 eq. **12**	25	7 (*R*)
1 eq. **12**	1 eq. **15**	25	6 (*R*)
1 eq. **15**	1 eq. **12**	−78	10 (*R*)
1 eq. **12**	1 eq. **15**	−78	1 (*R*)
2 eq. **15**	2 eq. **12**	−78	15 (*R*)
2 eq. **12**	2 eq. **15**	−78	2 (*S*)

were expected and the experimental results of 6% *ee* (*R*) and 7% *ee* (*R*) are indeed representing this assumption. The last two entries represent each an attempt to influence the enantioselectivity even further by using two equivalents of both amines.

Solvents: CH_2Cl_2 was found to be the solvent of choice. Substituting it with others resulted in lower selectivities. Although benzene (and also *o*-xylene) showed very promising results (30% *ee* at r.t.). Unfortunately a mixture of benzene and CH_2Cl_2 did not improve selectivities, since with higher ratios of benzene, the latter would freeze and therefore not participate in the reaction.

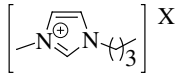
Table 6: Solvent Effects on the Stereoselectivity

solvent	T /° C	ee^a / %	ee^b / %
CH_2Cl_2	25	9 (*S*)	-
benzene	25	7 (*S*)	30 (*R*)
CH_2Cl_2	0	15 (*S*)	25 (*R*)
$C_6H_5CF_3$	0	6 (*S*)	20 (*R*)
CH_2Cl_2	-78	21 (*S*)	45 (*R*)
CH_3Cl	-78	5 (*S*)	5 (*R*)
CCl_4	-78	3 (*S*)	13 (*R*)
Et_2O	-78	7 (*S*)	0
CH_3CN	-78	5 (*S*)	5 (*R*)

a) using **12** b) using **15**

Also further investigations were done to improve the reaction conditions using alternative chlorinated solvents to substitute CH_2Cl_2, but with neither dibromomethane nor 1,2-dichloroethane, trifluorotoluene nor tetrachloromethane better selectivites were obtained. Furthermore diluting the solution of CH_2Cl_2 by a factor of 10, did not change the selectivity. Room temperature ionic liquids (RTIL) have been reported to form trihalide based RTILs, which are solvent and reagent in one. In these media iodobromination as well as iodochlorination of alkenes and alkynes have been investigated with good to very good yields.[32]

Thus 3-butyl-1-methyl-3*H*-imidazol-1-ium-hexafluorophosphate (BMIM[PF_6]) **49** and 3-butyl-1-methyl-3*H*-imidazol-1-ium-tetrafluoroborate (BMIM[BF_4]) **50** were used, but the selectivities were found to be low.



BMIM$^+$[X]

X=PF_6^- **49**

BF_4^- **50**

From the vast amount of RTILs available (or possible) only two examples were tried[33] and to fully discuss the use of these successful solvent systems many more should be tried.

Table 7: Additional Solvent Effects on the Stereoselectivity

solvent	T /° C	*ee*[a] / % in (*R*)-**3**
CH_2Br_2	25	30
BMIM[BF_4]	25	7
BMIM[PF_6]	25	6
EtOH:H_2O[b]	25	8
THF:H_2O 1:1	25	0
o-xylene	0	30
DME	0	0
$Cl(CH_2)_2Cl$	0	30
10% HFP[c]	-78	0
CD_2Cl_2	-78	41

a) using **15** b) ratio was 9:1 EtOH:H_2O c) 10% 1,1,1,3,3,3-hexafluoro-propanol in CH_2Cl_2

Also mixtures of RTILs with other solvents proved to be promising, while recent developments have combined the chiral ligand and solvent function, by extending the range of and using chiral RTILs.[34]

Alternative Sources of I^+: Interhalogens differ from halogens in reactivity, therefore also iodine and IBr were used to correlate the selectivity with the reactivity. Additionally *N*-iodosuccinimide (NIS) was applied a reagent often used as a convenient source of I^+.

Iodine was also applied with **12** used as a ligand. In the lactonisation 7% *ee* (*S*)-**3** were obtained and with **15** 11% *ee* (*R*)-**3** were found.

IBr: Within the interhalogens IBr was also used as a source of I^+, the lactonisation to form **3** clearly proceeded less selective, so that IBr could not provide as a replacement to ICl.

***N*-iodosuccinimide (NIS)** was used in reactions following the optimised procedure 3.1.1 on page 6. Since in a lactonisation reaction with NIS and **12** (ratio 1:2) virtually racemic

Table 8: Comparing Selectivities in **3**: ICl vs. IBr

Ligand	*ee* (IBr) / %	*ee* (ICl) / %
12	8 (*S*)	26 (*S*)
15	17 (*R*)	45 (*R*)
13	0	14 (*S*)

product was obtained (1% *ee*), only **15** has been studied in greater detail. Table 9 shows four parameters which were changed: the temperature the reaction was performed at (column 1), the solvent (column 2), the ratio of NIS to **15** (column 3) and also the time which NIS and **15** were allowed to react before the actual reaction was commenced (column 4). Reactions were stirred at -78 °C for approximately an hour, after all reactants had been added.
Similarly to the ICl method there was no reactivity observed at all if NIS and amine **15** were allowed to react for 120 min. at r.t., but unlike observed with ICl, the selectivity could not be improved by stirring a mixture of NIS and **15** at r.t. (times from 0-60 min. were tested).

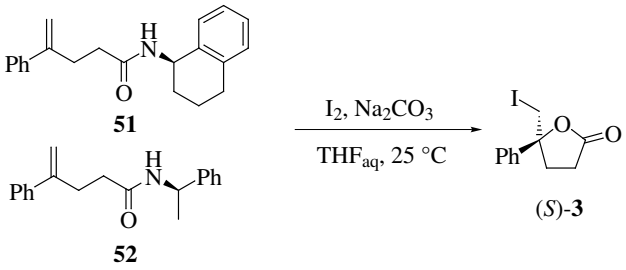
Table 9: Substituting ICl with NIS

temperature	solvent	equivalents **15**:NIS[a]	time/min at r.t.	*ee*/%	yield/%
r.t.	CH_2Cl_2	1:1	0	3	-
-78 °C	CH_2Cl_2	2:1	0	17	-
-78 °C	CH_2Cl_2	1:2	0	9	quant.
-78 °C	CH_2Cl_2	2:2	0	13	83
-78 °C	CH_2Cl_2	4:2	15	10	very low
-78 °C	CH_2Cl_2	4:2	30	12	very low
-78 °C	CH_2Cl_2	4:2	60	15	-
-78 °C	CH_2Cl_2	4:2	120	-	n.r.
-78 °C	THF	2:2	0	0	69
-78 °C	CH_3CN	2:2	0	0	-

a) In all cases one equivalent of **2** was used.

3.1.2 Comparison to Chiral Auxiliary Approach

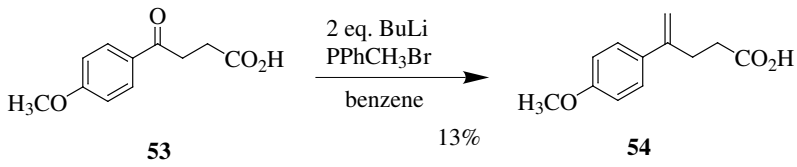
The comparison of the chiral auxiliary (*substrate*-controlled) approach and the *reagent*-controlled approach was realised in amide **51** and amide **52**. In this way a direct comparison between the two approaches was possible. They were cyclised with iodine in aqueous THF, in presence of Na_2CO_3 to form (*S*)-**3**. The *substrate*-controlled approach showed low selectivities (**51**: 11% *ee*; **52**: 20% *ee* resp.) and was clearly outperformed by the *reagent*-controlled approach (**12**: 25% *ee*; **15**: 45% *ee*).
In both lactonisations the same major stereoisomer was obtained, while in case of the *reagent*-controlled approach amine **12** led to more (*S*)-enantiomer, **15** to a majority of (*R*)-enantiomer. This may be an indication of a different mechanism, in which the selectivity determining step is the same, due to the chirality being present in the molecule to be cyclised.



3.1.3 Differently Substituted 4-Aryl Acids

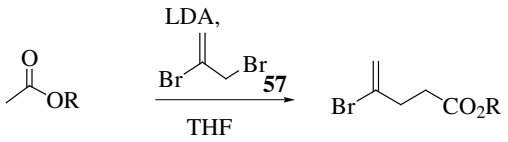
Hammett Investigations: The relationship between the substituents on an aromatic moiety and the change in various properties (reaction rate, thermodynamic properties and others) due to these substituent is known as the Hammett relation.[35] The Hammett equation links the log of the ratio of the rate for the substituted and the rate for the unsubstituted compound in a reaction to the parameters σ and ρ: $\rho\sigma = log(K_Y/K_H) = \Delta G^0_Y - \Delta G^0_H$. The scale of σ was defined for the acid dissociation of benzoic acids. σ accounts for the substituent itself and is empirically determined (for values see reference).[36] ρ is the reaction constant and reflects the sensitivity of a reaction mechanism to the effects of electronic perturbation. Furthermore σ^+ and ρ^+ have been defined for reactions, in which a strong acceptor, such as a carbocation, develops at the phenyl moiety. According to this equation produce changes in structure proportional changes in the activation energies for all such reactions. This type of correlation is analogous to a linear free energy relationship (LFER).

Synthesis: Since substitutions on the aromatic moiety of **2**, are influencing the charge in the benzylic position, they were expected to influence the stereoselectivity of iodolactonisations as well. Four different *para*-substituted analogues of **2** were prepared, starting from 4-(4-methoxy-phenyl)-4-oxo-butyric acid **53** (prepared from anisole and succinic acid anhydride), which was converted into 4-(4-methoxy-phenyl)-4-pentenoic acid **54** via a Wittig reaction.



Since this first approach was exhibiting a very low yield (13%) the strategy was changed for other substituents, to a more flexible approach.

The reaction of ethylacetate **55**, LDA and 2,3-dibromoprop-1-ene **57** yielded 4-bromo-4-pentenoic acid-ethylester **58** in only 28%. The procedure was optimised using *tert.*-Butylacetate **56**, LDA and 2,3-dibromoprop-1-ene **57** to yield 4-bromo-4-pentenoic acid-*tert.*-butylester **59** in 74%. From vinyl bromides **58** and **59** Suzuki coupling reactions[37] would lead to the esters of desired compounds.

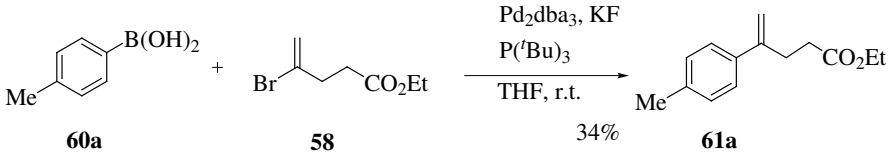


R=Et **55**
^{t}Bu **56**

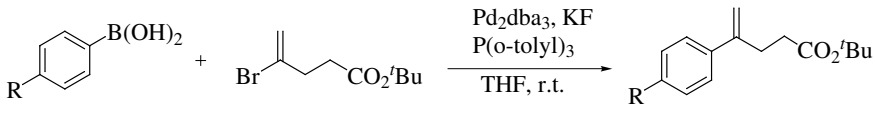
58 28%
59 74%

The palladium catalysed Suzuki coupling of *para*-methyl-phenyl-boronic acid **60a** and compound **58** was used to synthesise **61a** in 34% yield.

Suzuki reactions between the *para*-substituted boronic acids **60b**, **60c** and 4-bromo-4-pentenoic acid-*tert.*-butylester **59** achieved the coupling products **61b** and **61c** in 60% and 64% yield respectively.



60a **58** **61a**

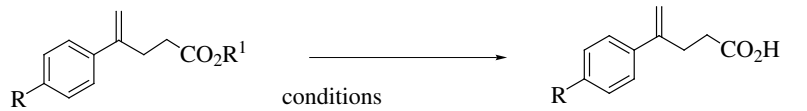


59

R=CF_3 **60b**
Cl **60c**

61b 64%
61c 60%

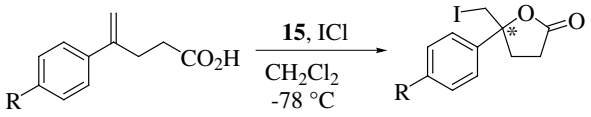
The saponification to the free acids required different conditions each time to achieve best yields.



R= Me	**61a**	R^1=Et	LiOH (60% in EtOH)	R= Me	**62a**	55%
CF_3	**61b**	R^1=^{t}Bu	HCOOH	CF_3	**62b**	93%
Cl	**61c**	R^1=^{t}Bu	SiO_2, toluene, Δ	Cl	**62c**	71%

4-(4-Methyl-phenyl)-4-pentenoic acid **62a** was obtained upon treatment of 4-(4-methyl-phenyl)-4-pentenoic acid-ethylester **61a** with LiOH (60% in EtOH) in 55% yield. To prepare 4-(4-trifluoromethyl-phenyl)-4-pentenoic acid **62b** the corresponding *tert.*-butylester **61b** was cleaved with formic acid in 93% yield. Cleavage of 4-(4-chloro-phenyl)-4-pentenoic acid-*tert.*-butylester **61c** by refluxing over silica gel in toluene yielded 4-(4-chloro-phenyl)-4-pentenoic acid **62c** in 71% yield.[38]

Stereoselective Iodolactonisations: Investigation of the stereoselective lactonisation of **62a**, **62b**, **62c** and **54** showed clearly, that the more electron withdrawing the substituent was the higher the observed stereoselectivity in the iodolactonisation. The obtained selectivities were 41% *ee*, 50% *ee*, 47% *ee* and 27% *ee* in **63a** - **63d** respectively.



R=CH_3	**62a**	**63a**	41% *ee*
CF_3	**62b**	**63b**	50% *ee*
Cl	**62c**	**63c**	47% *ee*
OCH_3	**54**	**63d**	27% *ee*

Correlation with Hammett substituent constants revealed a stabilisation of positive charge at the benzylic position, since a much better fit was achieved when σ_p^+ values were used instead of σ_p. Furthermore a better selectivity with electronwithdrawing groups has been established, although the overall effect is low and does not contribute to a large difference in enantioselectivity. The correlation of the enantiomeric excess with the Hammett σ_p^+ from five experiments shows a r^2 of 0.88. If instead of *ee* values the logs of the enantioselectivities were used, the correlation with Hammett σ_p^+ was found to be very similar (r^2=0.86) and ρ^+ was +0.202.

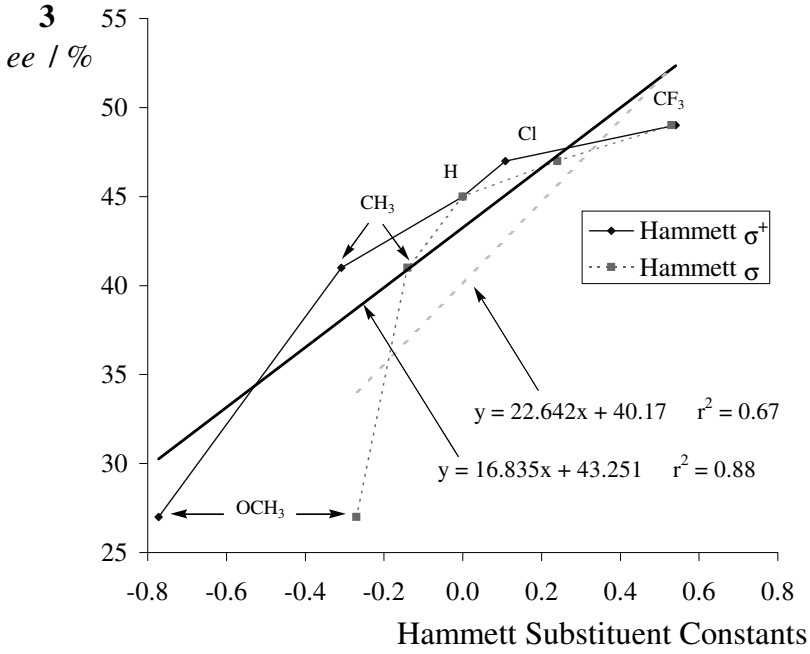
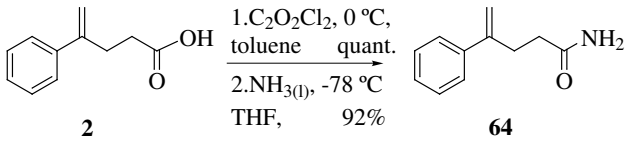


Figure 2: Correlation of Enantioselectivities with Hammett Substituent Constants

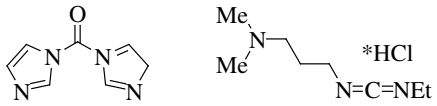
3.1.4 Derivatives of 4-Phenyl-4-pentenoic Acid

4-Phenyl-4-pentenamide: Generally also amides can undergo efficient lactonisation or lactamisation.[39] To investigate the mode of cyclisation several amides with an *exo*-double bond as contained in 4-phenyl-4-pentenoic acid **2** were synthesised. 4-Phenyl-4-pentenoic acid **2** was converted to 4-phenyl-4-pentenamide **64** by condensing liquid ammonia onto the *in situ* prepared acid chloride in THF at -78 °C.[40]



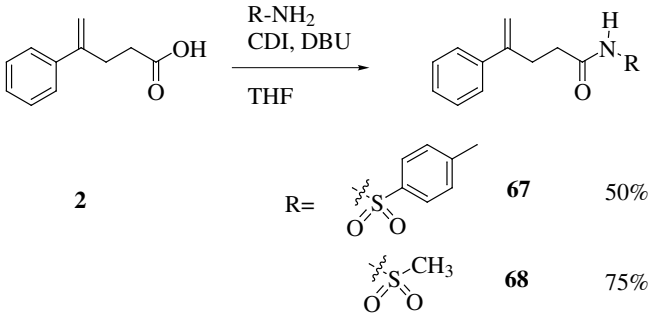
2 **64**

Among the various coupling agents carbonyldiimidazole (CDI)[41] **65** and the watersoluble ethyl--3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI)[42] **66** have been chosen for the following amide syntheses.



65 **66**

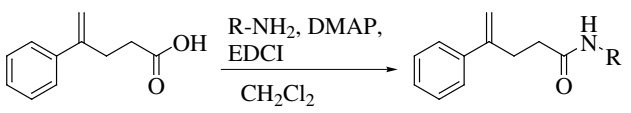
Refluxing acid **2** with CDI **65** in THF, then cooling and adding DBU, then *p*-toluenesulfonamide to obtain *N*-(4-phenyl-4-pentenoyl)-4-toluolsulfonamide **67**. *N*-(4-Phenyl-4-pentenoyl)-methylsulfonamide **68** was prepared accordingly using methylsulfonamide.[43]



2 **67** 50%

68 75%

N-Propyl-4-phenyl-4-pentenamide **69** and *N*-benzyl-4-phenyl-4-pentenamide **70** were synthesised from **2** in a EDCI mediated reaction using propylamine and benzylamine to yield **69** and **70**, respectively.



2

R=n-propyl **69** 70%

R=benzyl **70** 66%

All these amides have been subjected to two different lactonisation conditions, but only **67** formed lactone **3**. No lactams could be detected, independently of the conditions applied.[39a] It was however possible to cyclise **64**, **67**, **68**, **69** and **70** to lactone **3,** if aqueous THF was applied. Only compound **67** also formed lactone **3** in aprotic conditions, when the optimised procedure (chapter 3.1.1 on page 6) was applied 37% *ee* (*R*)-**3** were observed (Table 10).

Table 10: Lactonisations of Amides

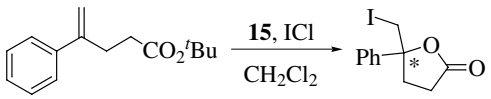
Substrates	**yield** / %[a]	**yield** / %[b]
2	80	quant.
64	-	quant.
67	43	low yield
68	-	83
69	-	54
70	-	quant.

a) Optimised Lactonisation Conditions Chapter10; b) Iodine, THF:H_2O 1:1

The fact that amides of type **67** can be cyclised with a selectivity similar to the cyclisation of 4-phenyl-4-pentenoic acid **2** implies that the selectivity defining step here is rather the attack of the double bond by the amine-ICl complex than a precomplexation in an acid-base reaction.

Cyclisations of Esters: This experiment was performed to investigate the the acid-base interaction of the carboxylic acid with the amine used as ligand, because theoretically the chiral information could also be transferred in this way. By using esters this possibility is suppressed.

4-Phenyl-4-pentenoic acid-*tert.*-butylester **71** was synthesized via a Suzuki reaction like discussed before.



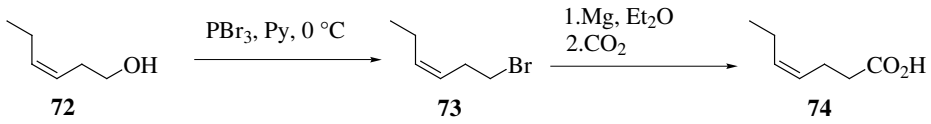
71 (*R*)-**3**

Treatment of ester **71** with ICl led to product **3** in 70% yield. It was possible to cyclise esters to 3 racemically, but applying the optimised procedure (chapter 3.1.1 on page 6) did not lead to any lactonisation product. Only when the ratio of amine:ICl was changed from 1:2 to 1:1.5 the reaction also proceeded stereoselectively to yield (*R*)-**3** in 34% *ee* and 66% yield.

3.1.5 Substrates without Aryl Moiety

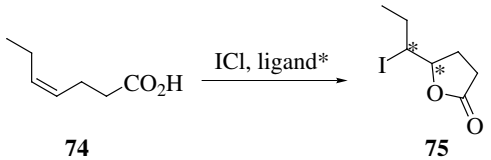
Cyclisation of *cis*-4-Heptenoic Acid: In the first ever reported *reagent*-controlled stereoselective iodolactonisation Grossman investigated lactonisations of *cis*-4-heptenoic acids.[8]
Thus *cis*-4-heptenoic acid **74** was synthesised starting from *cis*-3-hexenol **72**, which was converted

to *cis*-1-bromo-hex-3-ene **73** using PBr_3 and pyridine. Homologation was done in a Grignard reaction utilising CO_2 leading to *cis*-4-heptenoic acid **74** in a low 20% yield, due to a major dimeric byproduct (formed in a Wurtz-type coupling reaction).[44]



72 **73** **74**

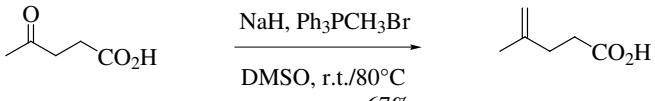
Formation of the *unlike*-5,6-iodo-γ-heptanolactone **75** was achieved in 83% by following the optimised procedure (chapter 3.1.1 on page 6).



74 **75**

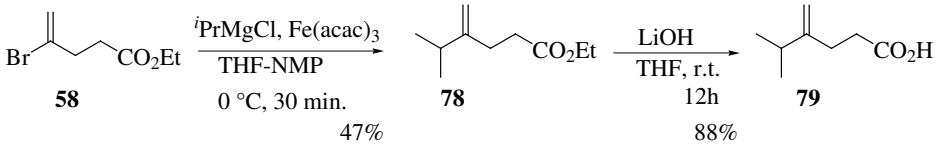
In the lactonisation of **74**, however, only racemic product **75** was found with all of the ligands tested (**13**, **12**, **46**, **23**). Amine **15** was not used in these experiments.

Analogues to 2: The preparation of 4-methylpent-4-enoic acid **77** was achieved via a Wittig reaction of levulinic acid **76** in 67% yield.

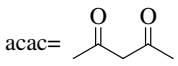


76 **77**

4-Isopropylpent-4-enoic acid **79** was prepared in a two-step procedure.

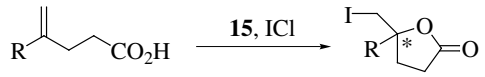


58 **78** **79**



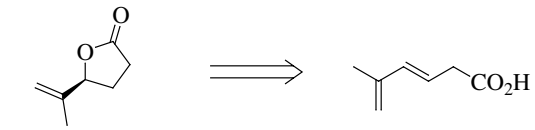
In this reaction $Fe(acac)_3$ was used as a catalyst in THF/*N*-methyl-2-pyrrolidone (NMP).[45] The cross coupling reaction with compound **58** was carried out with ^{i}PrMgCl in the presence of 1% of $Fe(acac)_3$ in THF-NMP to afford 4-isopropyl-pent-4-enoic acid ethyl ester **78** in 47% yield. Upon saponification of the ester using LiOH, carboxylic acid **79** was prepared in 88% yield.

Following the optimised procedure (chapter 3.1.1 on page 6) the lactonisation of **77** and **79**, showed racemic product in both 5-iodomethyl-5-methyl-dihydro-furan-2-one **80a** and 5-iodomethyl-5-isopropyl-dihydro-furan-2-one **80b**.



R=Me	**77**	**80a**	76%
^{i}Pr	**79**	**80b**	56%

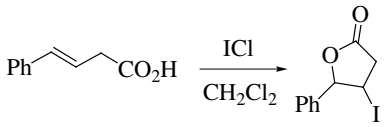
3.2 5-*endo*-Lactonisation



(*S*)-(+)-hoplactone **81** **82**

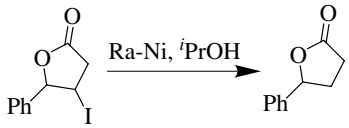
(*S*)-(+)-Hoplactone **81** is naturally occurring in hop, this lactone **81** can be synthesised via a 5-*endo*-lactonisation and a subsequent deiodination starting from 5-methyl-hexa-3,5-dienoic acid **82**.

Early studies were done on an analogous model system treating 4-phenyl-but-3-enoic acid **83** with ICl to give 4-iodo-5-phenyl-dihydro-furan-2-one **84** (75% yield).[46] Compound **84** failed analysis by chiral HPLC or GC.[47]



83 **84**

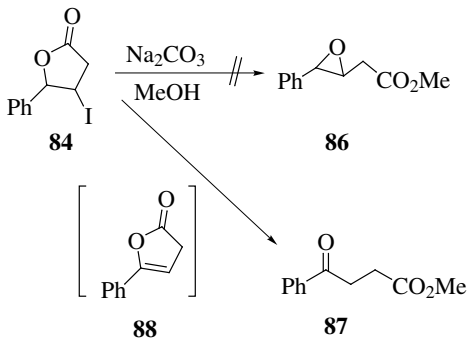
It was possible to reduce iodolactone **84** to 5-phenyl-dihydro-furan-2-one **85** following a literature procedure.[48] However, when the optimised procedure (chapter 3.1.1 on page 6) was followed to achieve stereoselective lactonisation, this deiodination did not proceed, moreover also a radical reaction with AIBN and Bu_3SnH did fail to yield the deiodination product.



84 **85**

Hence, in order to determine the stereoselectivity a conversion to the corresponding epoxide was chosen.[49]

This did not form (3-phenyl-oxiranyl)-acetic acid methyl ester **86** but it converted **84** cleanly to 4-oxo-4-phenyl-butyric acid methyl ester **87** under methanloysis conditions, possibly via butenolide **88**.

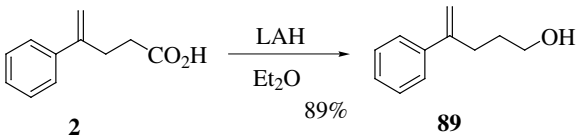


The same ketone **87** was obtained when **84** was treated with Pd/C and hydrogen with a small amount of triethylamine added to trap the forming HI. The benzylic proton was acidic enough to be abstracted by the base upon which a formal elimination of HI was completed by forming a butenolide, the attack by MeOH led to **87**. When tried without the addition of Et_3N, only decomposition products were detected, probably due to a higher rate of decomposition than displacement.

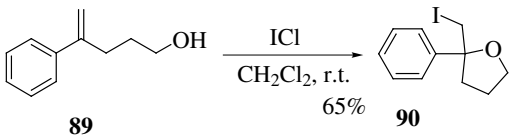
Another strategy was followed when in the workup of the stereoselective iodolactonisation HCl was applied to extract any basic compounds into the aqueous phase. This was tried, in order to overcome the problems of the inacitvity of the deiodination reaction, but again decomposition of **84** complicated matters, column chromatography itself decomposes the product as well.
At this stage this *endo*-lactone was not pursued any further and therefore no further attempts have been made to synthesise **82** stereoselectively.

3.3 Formation of Tetrahydrofuranes

Cyclisation of 5-phenyl-5-iodomethyl Tetrahydrofuran: 4-Phenyl-4-pentenol **89** was obtained by reducing **2** with LAH in Et_2O in a 89% yield.



Amine **15** was used in the cyclisation reaction (following the optimised procedure, chapter 3.1.1 on page 6) of 4-phenyl-4-pentenol **89** to tetrahydrofuran **90.**



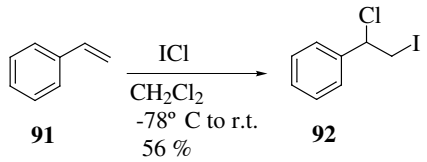
In case compound **15** was used as a ligand, no product was formed. This is most likely due to the reaction time which is several hours at (r.t.), where it has been shown, that the chiral complex is not reactive at all after 90 min. at this temperature. Since this is a general pattern recurring with different primary amines, no further amines have been tried.

3.4 Iodo-Functionalisation of Styrenes

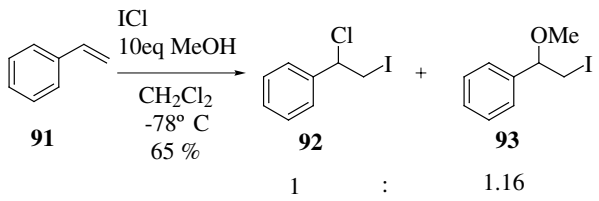
3.4.1 1,2-Iodo-Functionalisation

The procedures to perform 1,2-halo functionalisations reported so far, exhibit disadvantages such as the use of mercury[50] or silver, the latter, when left in the reaction mixture could cause unwanted side reactions. Other direct methods have been investigated with a small number of reagents.[51] A stereoselective version applying $CuO{\cdot}HBF_4$ has been reported.[52]

Addition of ICl to Styrene: The investigations of 1,2-iodofunctionalisation of olefins, with an adapted version of the stereoselective lactonisation protocol reported above, were initially done on the addition of ICl to styrene. ICl was reacted with styrene **91** in CH_2Cl_2 at -78 °C, which resulted in a straightforward formation of (1-chloro-2-iodo-ethyl)-benzene **92**.[53] Since this product is instable at r.t. the analysis of the enantiomers proved to be unsuccessful on both chiral HPLC and chiral GC.

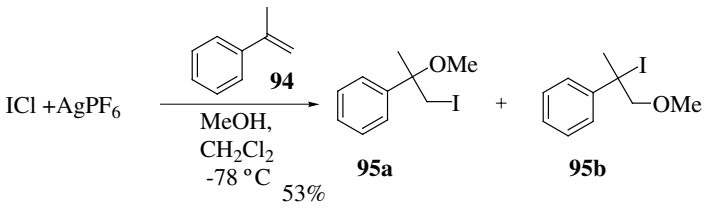


Formation of 1,2-Iodoethers from Styrene: Although the reaction was quenched with MeOH, the addition product was found to be compound **92**, indicating that the attack of the chloride anion is much faster than the attack of MeOH. In a different version MeOH was added to styrene prior to the addition of ICl, which then resulted in a mixture of **92** and 2-iodo-1-methoxy-ethyl-benzene **93** (1.00:1.16).



Since **93** was instable due to HI elimination and resolution was only partially achieved on chiral GC,[54] α-methyl styrene was chosen for further investigations.

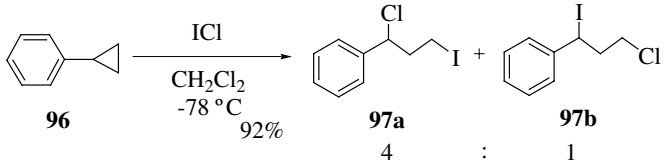
Formation of 1,2-Iodoethers from α-methyl styrene : Since the opening of the iodiranium moiety by Cl^- competed with the attack by methanol, the addition sequence was altered and preformed IPF_6 was used instead of ICl, the reaction of α-methyl styrene **94** and IPF_6 then was quenched as above by MeOH and an aqueous solution of $Na_2S_2O_3$ to yield 2-iodo-1-methoxy-1-methyl-ethyl-benzene **95a** and the anti-Markovnikov product **95b** in a 3.5:1 ratio. Analysis of the racemate of **95a** and **95b** was achieved by chiral HPLC.



The adaptation of the optimised procedure (chapter 3.1.1 on page 6) included the preforming of IPF_6 by mixing $AgPF_6$ and ICl in CH_2Cl_2 which then after filtration over a 0.45 micron filter, was added to a solution of **15** in CH_2Cl_2 to form the chiral complex as discussed above.
The reaction, however, did not take place at all at -78 °C, 0 °C or r.t., therefore the ratio of ICl and **15** was altered from 1:2 to 1:1.5 and finally to 1:1, respectively. Although the IPF_6 amine complex was visibly formed (color change from bright orange to dark red during the formation of the complex) no traces of product were detected and complete starting material has been reisolated.
At this stage these investigations were not pursued any further.

3.4.2 1,3-Iodo-Functionalisation

Upon opening a cyclopropane system with ICl, 1,3-iodo-functionalised compounds can be synthesised. Initial experiments showed that it is possible to open cyclopropylbenzene **96** with ICl to 1-chloro-3-iodo-propyl-benzene **97a** and 3-chloro-1-iodo-propyl-benzene **97b** in excellent total yields (92%). Influencing the ratio of **97a** to **97b** to minimize the amount of **97b** product by changing the temperature the reaction was run at was unsuccessful. The reaction was performed at -78 °C, where this ratio was found to be 4:1 (by NMR analysis of the product).



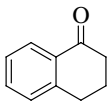
Similar to the 1,2-iodomethoxylation the stereoselective 1,3-iodomethoxylation was unsuccessful. After the amine-IPF_6 complex was formed, it is not reactive enough (at r.t.) to open the cyclopropyl moiety. Complete starting material was recovered.

3.5 Amine-ICl Complexes: Additional Studies

3.5.1 Investigation into the Reaction of Primary Amines and ICl

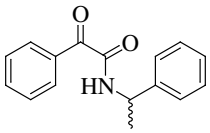
Reaction of ICl and (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **15**

The reaction produced α-tetralone (**98**, 21%)[55] among other minor compounds, which could not be identified. No amine could be detected after workup with $Na_2S_2O_3$. NMR measurements clearly indicated an imine signal (^{13}C), but due to many other signals it was impossible to interprete the spectrum, because the reaction between a primary amine and ICl proceeds with many byproducts.



98

In further investigations of the reaction **12** and ICl 2-oxo-2-phenyl-*N*-(1-phenyl-ethyl)-acetamide **99** was found (3% yield), its structure was assigned by NMR and its composition strongly supported by elemental analysis.[56]



99

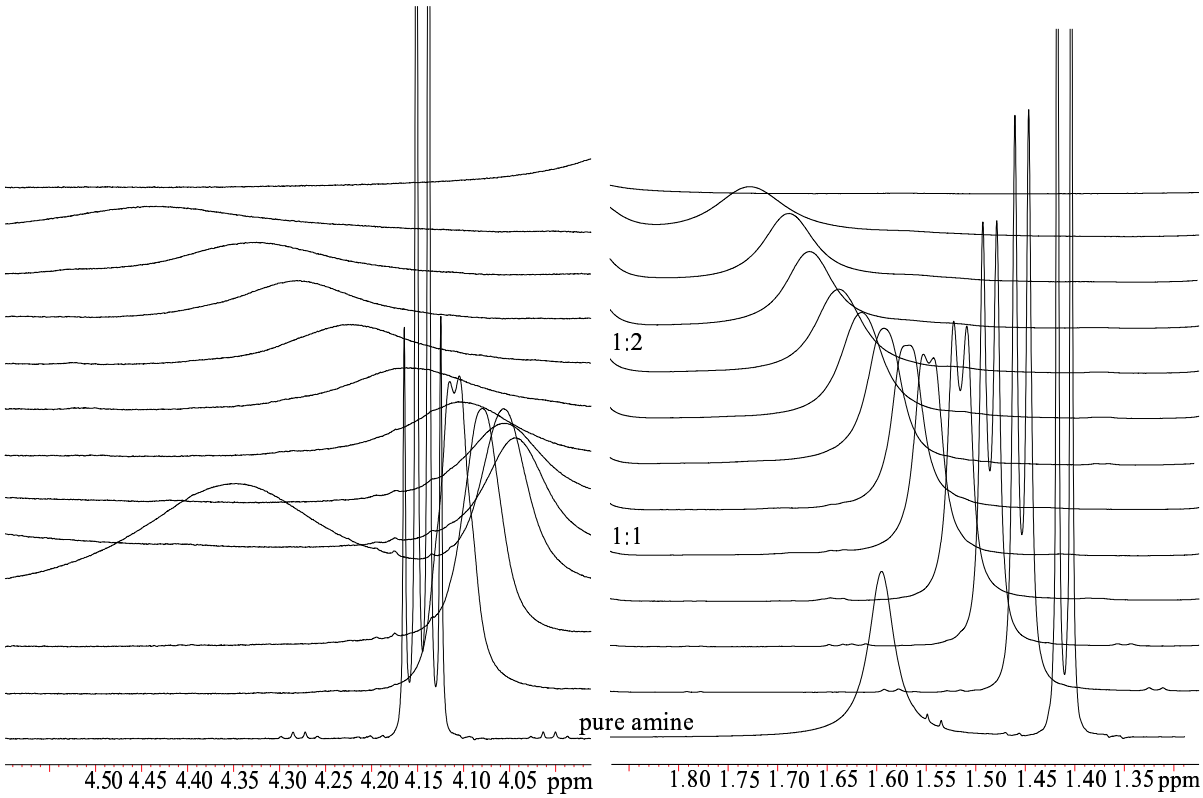
However it is unclear how this product was formed, but this compound shows again the diversity of the reaction between a primary amine and ICl. These byproducts can pose problems, if the reaction is scaled up.

3.5.2 Reversibility of the Complex Formation

It was known that several byproducts form in the reaction of a primary amine and ICl. Therefore it was checked, if the formation of the complex was reversible or not. A 2:1 mixture of amine:ICl in CH_2Cl_2 was prepared (the yellow solution of the **12** in CH_2Cl_2 turned dark yellow to orange, when adding ICl to the amine). This mixture was extracted with an aqueous solution of 0.5N HCl, to release the amine from the (*R*)-1-phenylethylamine–ICl-complex. It was possible to reisolate amine **12** in 85% yield, the enantiomeric purity remained unchanged (checked by $[\alpha]_D^{25}$). It therefore could be shown that the formation of the complex is reversible, if the reaction time is kept under 5 minutes at r.t.

3.5.3 NMR Investigations

Formation of the complex: The results from the titration of (*R*)-1-phenyl-ethylamine **12** with a solution of ICl in $CDCl_3$ imply a complex sequence of reactions taking place.



12

Figure 3: NMR Titration of **12** in Steps of 0.25 Equivalents of ICl

Protons of interest were the quartet of the benzylic proton H^1 and the doublet of the protons H^2, where any of the stacked spectra is taken after addition of ca. 0.25 equivalents ICl, starting from a solution of the pure amine. In case of the benzylic proton, a shift is appearing first to lower ppm and at approximately 1:1 mixture to higher ppm. This indicates a more complex reaction, since a 1:1 ratio would be recognizable by the typical change in shift in one direction and a stabilisation

thereafter. In contrast to the quartet, the doublet shows a steady shift to higher ppm.

3.5.4 Attempts to Obtain an X-ray Structure Analysis

While crystal structures of ICl and different pyridines,[22b] ICl and triethylamine,[23] ICl and thiocarbonyls[57] or selenocarbonyls are known,[58] crystallisation of a complex of ICl and (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **15** was unsuccessful, because **15** decomposed under crystallisation conditions. However a crystal structure of the HCl adduct of **15** was obtained,[59] indicating a proton-iodine exchange on the nitrogen leading to an *N*-iodo-amine and HCl. In the iodolactonisation HCl is possibly complexed by the second equivalent of **15**, because two equivalents of amine have been found to give highest enantioselectivities.
It was further tried to crystallise the complex formed by **24** and ICl, but only an oily residue was obtained.

A yellow powder was successfully obtained from mixing a 1M solution of ICl in CH_2Cl_2 and neat (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **15**, but it has not been possible to recrystallise this material, to achieve a quality which would allow powder diffraction analysis. An elemental analysis of this solid was in excellent agreement with the theoretical values for a 1:1 complex.[60]
Using this powder instead of following the optimised procedure (chapter 3.1.1 on page 6) in the lactonisation reaction of **2** $\longrightarrow$ **3**, an enantiomeric excess of 37% *ee* (*R*)-**3** was observed.

3.5.5 UV/VIS Studies

Job´s Method of continuous variation[61] was applied and two technically different procedures were tried. In the first procedure the ratio of ICl and (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **15** at constant volume was changed from pure amine to pure ICl solutions. For each ratio a spectrum has been taken and the absorbance at 288 nm was recorded and plottet against the mole fraction of the sample the spectrum was taken of. A value of 0.4 was obtained by mixing the two components each time from two stock solutions and allowing them to equilibrate after mixing for 30 minutes similar to the iodolactonisation procedure. A value of 0.5 translates to a 1:1 composition, since this value was not observed the changes occurring during these 30 minutes are possibly responsible for the difference.
If a titration was used instead, which was has the advantage that in the area of composition interest many points can be obtained easily, again a value of 0.4 on the mole fraction scale was found. Once the titration is started, the solution continuously changes composition. Since the whole experiment took more than 90 minutes, it is likely, that also this result is inaccurate.

The method of continuous variation of concentration therefore cannot be applied in this case, because this method does not allow to detect changes in composition within the studied system.

Time dependent studies were done concerning the first 30 minutes of the experiment, where the chiral electrophilic complex is formed. During this time is has been shown that the most selective composition is obtained, since the stereoselectivity in the iodolactonisation increased

compared to the low temperature case like discussed earlier (chapter 3.1.1).
It could be shown, that after 30 minutes the UV/VIS spectra of a 1:1 mixture of **15** and ICl were superimposable on the ones taken thereafter.

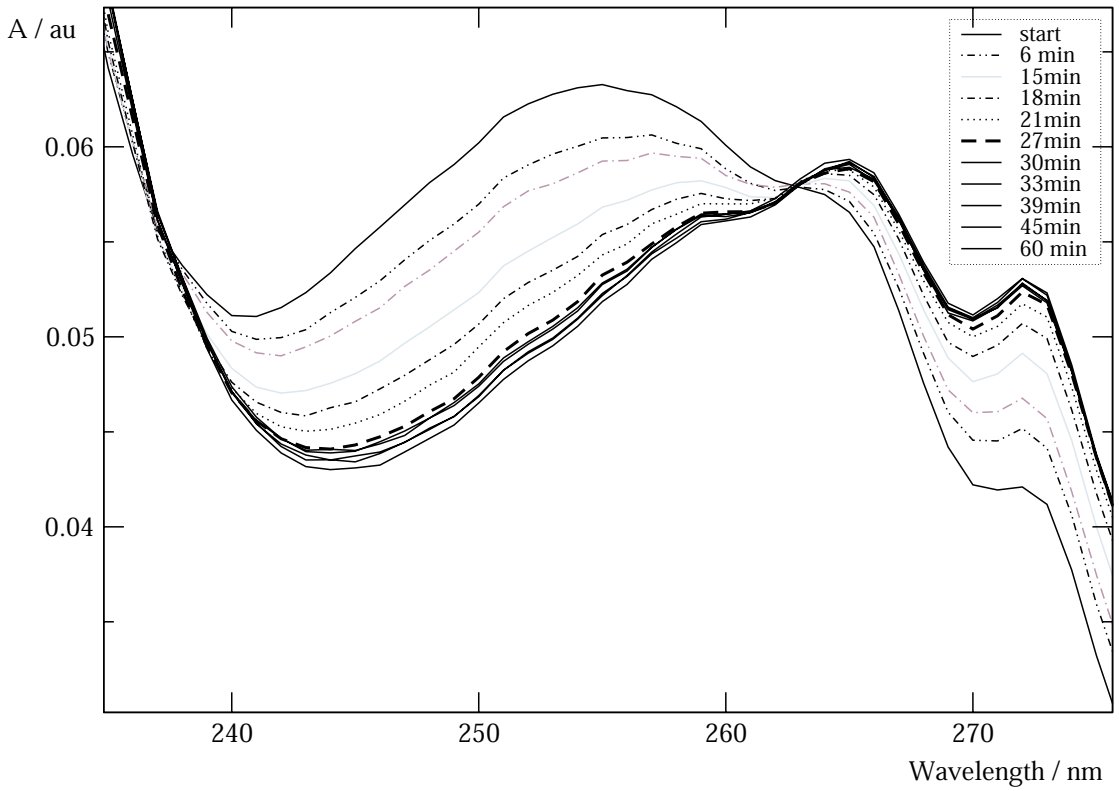


Figure 4: UV Investigations of a 1:1 mixture (**15**:ICl)

This time corresponds to the time which was found to lead to the highest selectivities in the iodolactonisations. With two isosbestic points found (237 nm and 263 nm) it could be shown, that there is a complex reaction going on between at least three components.

3.6 Summary of Experimental Part

In this chapter experimental evidence has been compiled to illustrate the potential of primary amines in chiral complexes with ICl. These are the first thorough investigations of such complexes and their practical use is illustrated in iodolactonisations. The achieved enantioselectivity is therefore regarded as high, although it does not exceed a ratio of 1:3 (50% *ee*). In these investigations mainly amines from commercial sources or easily accessible amines have been used to allow straightforward variations of the experiments.
The model iodolactonisation reaction of **2** $\longrightarrow$ **3** has been found to be the reaction of choice. Optimisations of this reaction led to an unprecedented enantioselectivity of 45% *ee*. In the *reagent-*

controlled iodolactonisation of *para*-substituted analogues of **2** 50% *ee* were achieved (in case of CF_3). An excellent correlation between Hammett σ_p^+ and the enantioselectivity (r^2=0.88) was observed in a series of iodolactonisations of these analogues of **2**. If enantioselectivities were replaced by logarithmic enantiomeric ratios the correlation with Hammett σ_p^+ was better (r^2=0.93) and in this case the slope of this correlation corresponds to the resonance parameter ρ^+, which was +0.202. The small value of ρ indicates, that the enantioselectivity is not greatly depended on the substituents and indeed in the experiments with the exception of *para*-methoxy all other substituents showed only little changes in the enantioselectivity (±5% *ee*).

The ligands for ICl which contained the structural motif of amine **12**, were the most successful, the best being **15**. Substitutions on the nitrogen, as well as a presence of a second nitrogen, also within molecules bearing this motif, always led to lower selectivities. The best solvent was CH_2Cl_2, in benzene or CH_2Br_2 good selectivities of 30% *ee* were achieved in the iodolactonisation at room temperature. Other sources of I^+ were applied as well, but NIS, IBr and iodine did show much lower selectivities. Different ratios of amine and ICl were investigated, but clearly 2:1 (amine:ICl) was favoured. HCl, which is formed during the iodolactonisation is probably complexing the second equivalent of amine. This gave reason to investigate the effect of external bases on the enantioselectivity, unfortunately the bases tried ($NaHCO_3$, Na_2CO_3, pyridine and triethylamine) were lowering the selectivities. The complex which formed in the reaction between an amine and ICl was probably altered by adding other potential ligands (certainly in case of the amines), hence the enantioselectivities were then found to be lower.
In crossover experiments it could be shown, that the formation of the reagent from amines such as **12** can be dynamically altered. An equilibrium between the two different amines used and ICl was achieved, if they were mixed at room temperature. Equal contributions of both complexes were then found in the iodolactonisation of **2** $\longrightarrow$ **3**.
Changing counterions did show a great effect, especially in case of BF_4^-. In that reaction only traces of product were formed, possibly this mixture attacks and iodinates the aromatic moiety in the ligand during the precomplexation step. Also hexafluorophosphate and triflate were tested, but the effects on the selectivities were smaller (41% *ee* and 27 % *ee*)
The most efficient complex between **15** and ICl decomposes gradually during longer reaction times. Amines **23** and **24** were the most straightforward attempts to overcome decomposition issues, since they inhibit any H-I exchange on the nitrogen. Unfortunately they were unsuccessful replacements for **15**, since selectivities were much lower. This could be caused due to different steric requirements, which in the diastereomeric transition state leads to unfavourable interactions. It also could indicate the necessity of a primary amine for an efficient transfer of chirality.
The procedure itself was not successfully adapted to reactions which take more than 30 minutes at room temperature. Also unsuccessful were attempts to iodo-functionalise styrenes, since the complex formed from the amine-ICl mixture was not reactive enough to allow an attack at the double bond and subsequent trapping (e.g. by methanol).
Comparison to the *substrate*-controlled approach showed that, with the auxiliaries chosen, the *reagent*-controlled approach was much more selective.
A possible interdependence between compounds responsible for the enantioselectivity could be derived from further mechanistic studies. Both NMR titrations and UV/VIS time dependence studies indicated a subsequent reaction after the formation of a 1:1 complex.

Equilibria of Complexes: From a mechanistic point of view it is clear, that the complexation of ICl by the amine is followed by at least one subsequent reaction, which eventually alters the composition of the complex and leads to inactivity. UV/VIS and NMR studies suggest that a 1:1 complex is formed, which then reacts further to convert the amine into a imine functionality (in case of **15**: α-tetralone was isolated upon aqueous workup). Further mechanistic details have been collected by proving the reversibility of the complex. The dynamic behaviour of these complexes formed were illustrated in the crossover experiments. These clearly show that the preformed complex, despite the fact that it has altered its composition (selectivities were found to be higher during optimisations of the general procedure), can be changed instantly upon adding another N-donor (this certainly happened, when pyridine or triethylamine were added to substitue one equivalent of chiral amine). Together with the observed ketone formation a hypothesis was formulated, that during the complex formation several compounds could be connected via a series of equilibria. **100** is instantly formed by a donor acceptor reaction, while the proton iodine

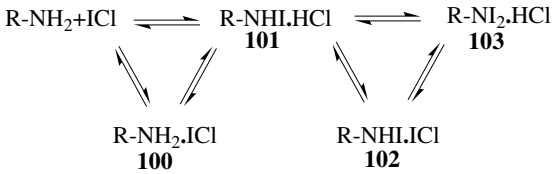


Figure 5: Equilibria of Chiral Complexes

exchange on the nitrogen is slower (possibly this corresponds to the 30 minutes preforming time which led to the highest selectivities) and **101** is formed. In **101** itself HCl can be changed exchanged against ICl to form **102**. Another H-I exchange on the nitrogen finally leads to **103**. While with the exception of **100**, each of these species listed could be potentially leading to the ketone during the workup, **102** and **103** are less likely to be important. For them to be formed, it requires a second molecule ICl. In the experiments a 2:1 ratio amine:ICl was used, therefore all ICl is likely to be incorporated into molecules **100** or **101**. This requires the second molecule ICl to be released out of **100**. This path becomes therefore a side reaction, if the formation of **100** is favoured. The complexation energies in **100** and **101** will help discussing the importance of this pathway. If these complexation energies are lower than in **100** and **102** is not thermodynamically favoured, then this reaction will not be important. However, if the second equivalent of amine traps the HCl, which has been formed in **101**, the transition from **101** to **102** could be assisted. This rather complex situation could not be analysed to complete satisfaction and is therefore subject of computational investigations of this reaction in chapter 4.5.

Very promising is the solid reagent which precipitated from mixing neat amine **15** and ICl solution. This compound resembles an excellent practical way of utilising these amine-ICl complexes in a very straightforward fashion, avoiding the recurrence of using ICl in every reaction.

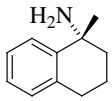
3.7 Outlook

3.7.1 Additional Types of Reactions

The model iodolactonisation reaction of **2** ⟶ **3** has been found to be the only type of halotransformation studied in this work, which actually showed selectivities. In 1,2-iodo additions and the ring opening of cyclopropylbenzene, which allow very flexible and versatile routes to new 1,2- and 1,3- halo compounds, the current method is not applicable. Compounds, which do not decompose or maybe a less strong interaction between the lonepair donor (such as phosphorous instead of nitrogen) and ICl are favourable as ligands of the next generation.

3.7.2 New Ligands

The limitation to a short reaction time clearly narrows the reactions which this protocol could be applied to, therefore attempts were made to overcome this obstacle. 2-(4-Isopropyl-4,5-dihydro-oxazol-2-yl)-aniline **103** showed a result of only 12% *ee*, which is a low selectivity, but it indicates the basic potential of this class of compounds, beside the fact that it contains two nitrogens, in which case the better lone pair donor will complex ICl, possibly the nitrogen of the oxazoline. Compounds such as amines **105** and **106** are also important examples to learn more about the steric requirements in the moment of attack at the double bond.



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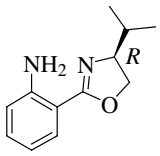
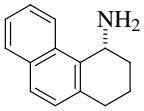


104



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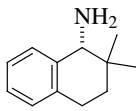


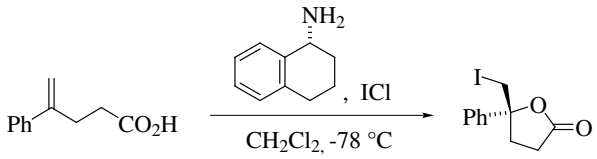
106

A further way out of the decomposition problem, which caused several other reactions to fail, when the chiral protocol was applied, are substances bearing R_3-*C* -NH_2 groups such as compound **48**. The synthesis of this proved to be somewhat demanding and remains unfinished to this date, although it is a structurally simple molecule.[62] Therefore no application of compound **48** has been investigated so far.

4 Computational Results and Discussion

4.1 Introduction

The reaction of 4-phenyl-4-pentenoic acid **2** ⟶ 5-iodomethyl-5-phenyl-dihydrofuran-2-one **3** was used as a measure of efficiency in transferring chirality. Quantum chemical *ab initio* and density functional theory (DFT) calculations were performed on appropriate model systems to support experimental findings in the reaction of amines with ICl as well as the formation of iod iranium ions. The latter is considered to be the selectivity determining step from the experimental point of view. Since iodine is not included in many high quality basis sets such as 6-31+G(d,p) and 6-311+G(d,p), different approaches were to be considered and compared. There are not many computational precedences of haloiranium ions in the literature, the few existing examples focus on chlorine and bromine, possibly for this reason.[63]



2 (*R*)-**3**

4.2 Methodology

4.2.1 Basis Sets

Basis sets play an important role, since are used to construct the molecular orbitals (MOs) in a calculation. They are inherent approximations in ab initio calculations, due to an impracticality: a complete basis with an infinite number of functions can technically not be used in actual calculations. The basis set therefore limits the molecular orbitals, which can be constructed, because the set of atomic orbital functions which describe each atom involved in the calculation determine these MOs.
Since iodine is a fifth row element, a relativistic approach using effective core potentials (ECP) has been chosen. In this approach a pseudo potential describes the inner shell electrons, which are not involved in the chemical bonding. This core potential solves two problems in one step. Firstly, it allows the expensive relativistic calculation to be reduced from the full set to only the valence orbitals (VO). Secondly, the large number of basis sets which were needed to describe the VO's properly (otherwise using a small number of basis sets would lead to a poor electron-electron repulsion) is reduced to a core potential and the VO's.

The following two ECP's have been applied:

LANL2DZ consists of Dunning and Huzinaga full double-zeta[64] for the first row in the periodic table and the Los Alamos ECP[65] plus DZ on sodium to bismuth.

SDD consists of Dunning and Huzinaga valence double-zeta[63] for first row elements and the Stuttgart/Dresden ECP's[66] for the remaining atoms in the periodic table.

Mixed Basis atoms *C, H, N* were treated at a MP2/6-31+G(d,p) and *I* at a MP2/SDD level of theory(denoted MP2/6-31+G(d,p),SDD).

4.2.2 Methods

DFT: From the DFT methods the established Becke's 3 parameter exchange functional combined with the correlation functionals developed by Lee, Yang and Parr (and is denoted B3LYP)[67] was chosen to model the iodiranium ions. For the formation of the chiral complexes the performance of density functionals are dependent on how much a charge transfer interaction is represented by dispersive effects (which are covered with limitations in conventional DFT) and Coulomb interactions (which are covered very well).[68]

ab initio: For the description of the complexes between ICl and the primary amine also an electron correlation method, Møller-Plesset second order perturbation theory (MP2),[69] was used to account for dispersive effects and charge transfer interactions. MP2 covers these interactions very well by the frozen core electron correlation approach.[70]

For the sake of computational resources especially at a MP2 level of theory all atoms have been treated with the SDD basis set.[71]
A short investigation revealed, that it would be computationally too costly, if mixed basis sets (MP2/6-31+G(d,p),SDD) were applied.[72] Hence no such modifications were made to overcome the contracted nature of the SDD basis set. At a B3LYP/6-31+G(d,p),SDD level of theory much slower convergence resulted and the relative energy differences between the individual complexes, were found to be very similar to the pure SDD results.[73]
All geometries shown are local minima, except otherwise noted and were obtained using Gaussian98;[74] they were optimised without constrains and the correct number of negative eigenvalues has been confirmed in frequency calculations.

4.3 Model Systems

Quantum chemical investigations of carbonyl-ICl complexes,[13] ICl-pyridine complexes[75] and as mentioned above halogen additions to double or triple bonds are known.[11a] An investigation of the effects of different electrophiles and substitution patterns in the substrate on the stereoselectivity in the product has also been reported.[11b]
Since there is no precedence of computational description of a complexed I^+ attacking a double bond, initial investigations were done at a B3LYP/LANL2DZ level of theory. The mechanistic model used here involved an electrophilic attack of a preformed complex (between I^+ and methylamine) on ethene. Methanol opens the iodiranium ion to give **111**.

The mechanism is envisaged as follows: The preformed electrophilic complex initially forms a π-complex with ethene (**107**) which leads to the three membered cyclic intermediate (iodiranium ion) **108**. The attack of methanol as a nucleophile opens up this iodiranium ion from the opposite

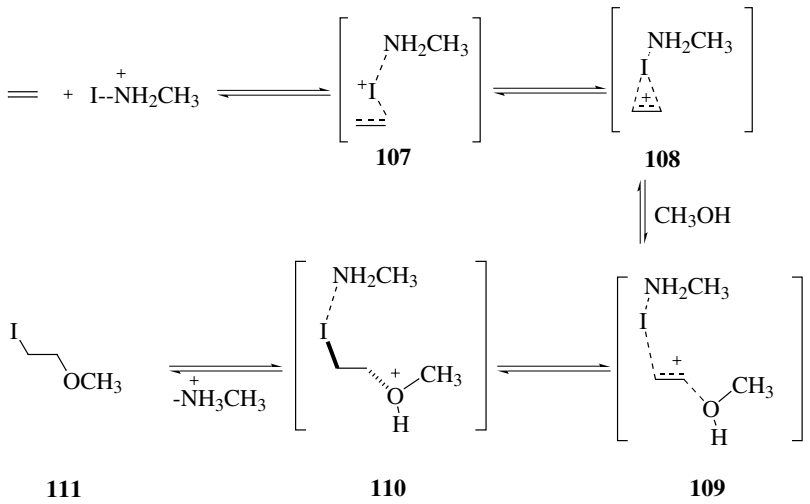


Figure 6: General Mechanism of a 1,2-Iodo-Functionalisation of Ethene

side leading, via a second π-complex (**109**), to the second intermediate **110**. Decomplexation and deprotonation finally forms product **111**.

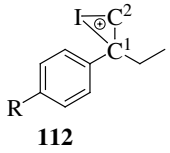
This general reaction mechanism was successfully modelled at a B3LYP/LANL2DZ level of theory. The length of each of the two C-I bonds in **108** and **110** are 3.60/3.70 Å and 3.90/3.96 Å, respectively. The N-I distance in both **108** and **110** is 2.14 Å. The C-I distance ethene-ICl complex at a B3LYP/LANL2DZ level of theory was 3.01 Å.[76] The complexes **107** and **109** could not be located in these gas phase calculations, while intermediates **108** and **110** as well as a transition state in the formation of **110** were successfully calculated. The N-I bonds were shorter than the sum of the van der Waals radii involved (3.65 Å),[77] in either the iodiranium ion or the intermediate which formed after an attack at the double bond by MeOH.

Investigations on larger model systems were initiated by dividing the reaction sequence displayed above into three steps, focusing on iodiranium ions and the formation of the electrophilic amine-I^+ complex. The coordination of the amine-ICl complex to styrene would allow to draw conclusions from the lowest energy conformation on the design of structures of new ligands. This approach, however, is on one hand computationally very expensive and on the other hand a selectivity of 50% *ee* resembles a mere difference of 2.6 kJ·mol^{-1}, which is too small to be modelled reliably with these two initial approaches, on one hand combining *ab initio* and SDD, on the other combining conventional DFT with SDD. Again it is important to stress, that using SDD as a basis set for all atoms without adding polarising functions has been done out of computational cost and also due to the lack of precedence of computational description of these systems. In order to get an overview of the system it was neccessary to choose a compromise between the accuracy of the energies and the time required for each calculation.

4.4 Properties of Iodiranium Ions

These investigations shown in the previous section (4.3) served as a general framework, emphasis is now put on the iodiranium ions as a first step in that reaction. The computation of the initial

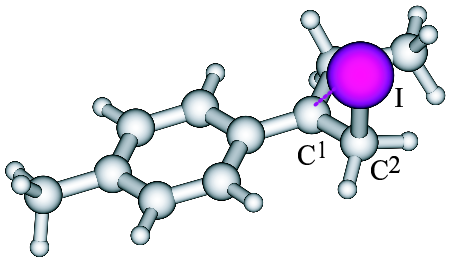
formation of the iodiranium ions and the evaluation of the structural features was approached by modelling reactions of I^+ with α substituted-styrenes.
Structures of positively charged species **112** were optimized at a B3LYP/SDD level of theory.[78] Intermediates **112** serve as models of iodiranium ions of the substrate in the reaction **2** $\longrightarrow$ **3**, as well as formal additions of IOMe (or IN_3 etc.) to α-substituted styrenes.



112

R		R	
$N(CH_3)_2$	**a**	F	**f**
OH	**b**	Cl	**g**
OCH_3	**c**	I	**h**
CH_3	**d**	CF_3	**i**
H	**e**	NO_2	**j**

All optimized geometries showed an unsymmetric iodiranium ion for all substituents R for both levels of theory applied. The distance of C^2 to I remains essentially constant at 2.24 Å (B3LYP/SDD).



112d

Figure 7: Structure of **112d**

The bond lengths of C^1-I in these iodiranium ion are, as can be expected based on the change in

Table 11: Distances C^1-I at a B3LYP/SDD Level of Theory

B3LYP/SDD	C^1-I /Å	B3LYP/SDD	C^1-I /Å
112a	3.10	**112f**	2.98
112b	3.02	**112g**	3.03
112c	3.03	**112h**	3.00
112d	3.04	**112i**	2.93
112e	3.03	**112j**	2.97

the charge density in the benzylic carbon atom, influenced by the nature of the group in 4-position of the aryl moiety.
Hence the relationship between the substituent R and the charge on C^1 itself, as well as the charge on the iodiranium moiety were investigated. Mulliken charges are compared to charges taken from a natural bond orbital (NBO) analysis.[79] Mulliken charges are resulting from an equal

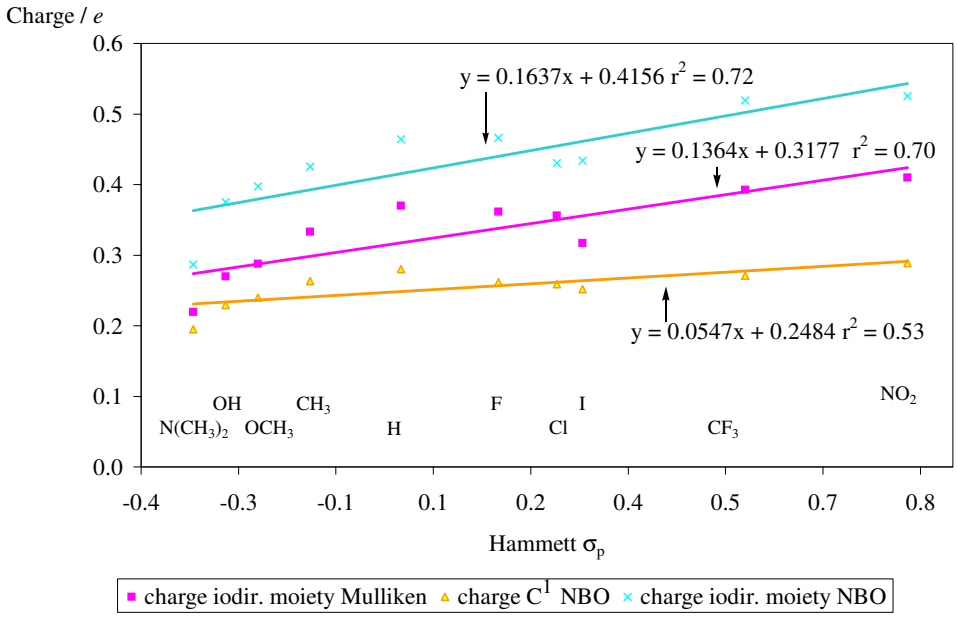
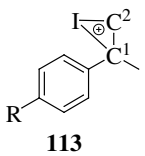


Figure 8: Correlation of Hammett σ_p and Benzylic Charges at a B3LYP/SDD Level of Theory

contribution of the atomic orbitals of the two atoms to the electron density. In an NBO analysis the atomic orbitals are formed from the electron density matrix, hence the contribution to the charge is according to this matrix. The correlation of Hammett[80] σ_p^+ (8) values vs. the charge of iodiranium moiety shows slightly better r^2 values for NBO (r^2=0.91) than for Mulliken (r^2=0.90), the latter proved to give non correlated results at C^1, which shows the limits of Mulliken charge analysis, where the effect of the ch100ange in electron density and the change in bond length cancel each other.[81] These calculations have been performed at a B3LYP/SDD level of theory, where the geometries and the charge correlations (C^1_{NBO}, r^2=0.84) were in very good agreement with the ones obtained at a B3LYP/LANL2DZ level of theory (C^1_{NBO}, r^2=0.86).[82]

A smaller representative set of structures of types **113** was also investigated at a B3LYP/LANL2DZ level of theory, the correlations obtained show the same trend as the ones discussed above.



113

R	
OCH_3	**a**
CH_3	**b**
H	**c**
Cl	**d**
CF_3	**e**
NO_2	**f**

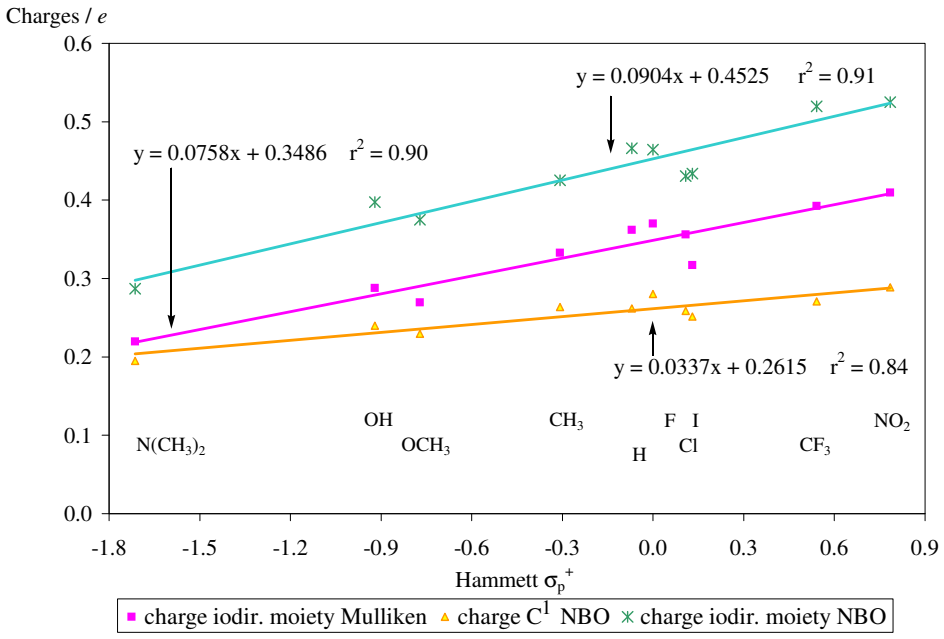


Figure 9: Correlation of Hammett σ_p^+ and Benzylic Charges at a B3LYP/SDD Level of Theory

Excellent correlations of σ_p^+ vs. charges at C^1 with both **112** (C^1_{NBO,σ_p^+} B3LYP/ LANL2DZ: r^2=0.94) and **113** (C^1_{NBO,σ_p^+} B3LYP/ LANL2DZ: r^2=0.97) could again be obtained.

Summary Iodiranium Ions: All iodiranium ions were found to be distorted, with the bond of C^1 to I being significantly shorter than to C^2. This may be explained by the stabilisation of positive charge in the benzylic position. It was found that, the more electron-withdrawing (the higher the Hammett value) a substituent in the 4-position of the aromatic moiety, the shorter the bond length $C^1 - I$. NBO charges of the iodiranium moiety and also the NBO charges at C^1 correlated better with Hammett σ_p^+ than with Hammett σ_p.

4.5 Amine-ICl Complexes

4.5.1 General Part

In the experimental procedure it was shown shown, that the enantioselectivity could be increased by 14%, if a solution of ICl and (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **15** (this also accounts for all other primary amines tested, with the structural motif of **12**) were stirred at room temperature

for 30 minutes. This increase does not correspond to a large energy difference between diastereomeric transition states leading to the enantiomers. Nevertheless it is important to understand the reaction in greater detail for further designing new ligands for ICl. Once a working model was established, other ligands of similar type could be investigated in a very straightforward fashion. Investigations were therefore focussed on the reaction of amines and ICl.
The increase can be rationalised (Figure 10) generally by assuming a chiral complex **100**, which is in equilibrium with **101** and possibly also with ICl and the free amine itself.

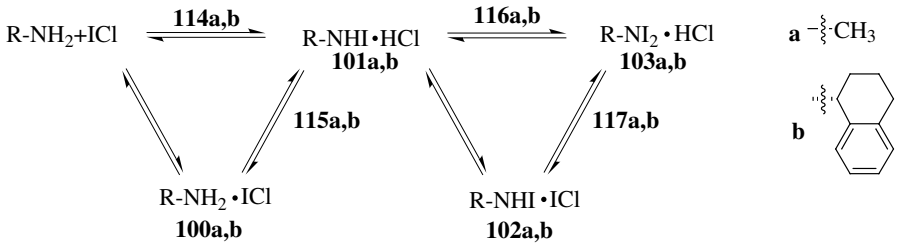


Figure 10: Equilibria of Chiral Complexes

Furthermore **102** and **103** are also possible candidates, resulting from a ICl-HCl exchange (**102**) and from another H-I exchange on the nitrogen (**103**).[83]

4.5.2 Methylamine-ICl Complex

In order to simplify this system, complexes of methylamine were investigated at a MP2/SDD level of theory.[84] Figure 11 shows a 3D visualisation of two representative complexes **100a** and **101a**.

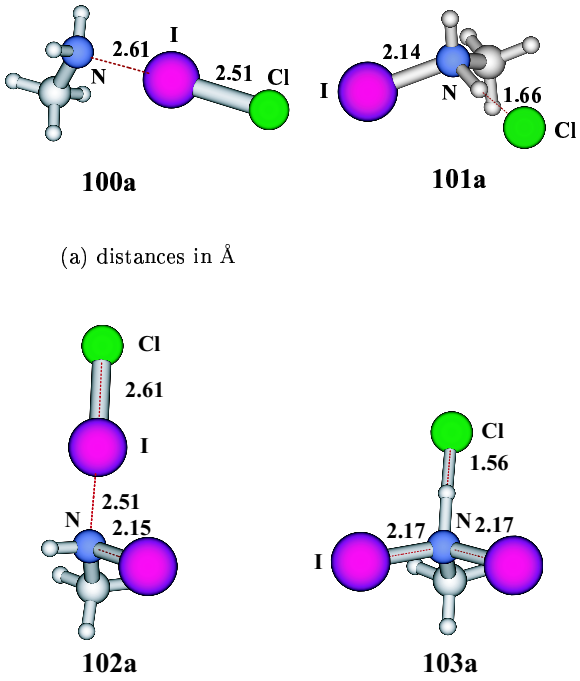
The geometries of 100a to 103a are shown, the N-I bond is shorter (2.14 - 2.17 Å), if the iodine is covalently bound to the nitrogen, rather than forming a coordinative complex (2.51 / 2.61 Å). For

Table 12: Geometries of Methylamine Model System

MP2/SDD	N-I / Å	N-XCl / Å	X-Cl / Å	C-N-I / °
100a (X=I)	-	2.51	2.61	111.0
101a (X=H)	2.14	1.22	1.66	114.1
102a (X=I)	2.15	2.51	2.61	112.3
103a (X=H)	2.17	1.31	1.56	110.1[a]

a) The N-I distance is the same for both iodine atoms.

comparison the complex between ICl and ammonia was chosen. In the $NH_3 \cdots ICl$ complex the N-I bond was found to be 2.71 Å;[15] The N-I distance in the triethylamin$\cdots$ICl crystal structure is 2.30 Å, the same distance was found in the Py$\cdots$ICl crystal structure.[23]



(a) distances in Å

Figure 11: 3D Representations of **100a - 103a**

A more positive charge (NBO) was assigned to the iodine, if the N-I bond was of covalent nature ($\sim$ 2.10 Å in 101a and 103a), while the charge on the nitrogen is only marginally higher in the molecules complexing HCl (Table 13).

Table 13: Charge distributions in **100a** - **103a**

MP2/SDD	N-*I* / *e*	N-*X*Cl / *e*	*X*-Cl / *e*	C-*N*-I / *e*
100a (X=I)	-0.88	-	-0.40	0.20
101a (X=H)	-0.82	0.35	-0.62	-
102a (X=I)	-0.86	0.33	-0.38	0.21
103a (X=H)	-0.82	0.36[a]	-0.52	-

Charges are given in units of elementary charge *e*;
a) The charge on the iodine is the same for both atoms.

The relative total energies (Table 14) show a clear preference of the amine-ICl complex. No free ICl is thought be available to be incorporated in a reaction from 101a to 102a, which in turn makes the conversion of 101a into 102a a side reaction. On the other hand the second equivalent of amine could promote the conversion of the *N*-iodoamine to the corresponding imine via a H-I elimination, by complexing the HCl.[85]
All transition states in Figure 10 have proven to be very difficult to localise, presumably the potential energy surface (PES) is very flat for this reaction.

Table 14: Total Energies of Methylamine Complexes

MP2/SDD	E / kJ·mol^{-1}	MP2/SDD	E / kJ·mol^{-1}
100a	−85.8	**102a**	−39.8
101a	−27.4	**103a**	+10.9

The investigations of the different possible compounds suggest an initial formation of an amine-ICl complex, which can react further to form **101a** and in a side reaction also **102a** and are therefore involved in the above mentioned reaction of a primary amine with ICl. **103a** was found to have a higher energy on the reaction profile than the corresponding free amine. The transition states, however, have not been successfully located, possibly due to a flat PES.
Good agreement with reported literature values for bond lengths has been found.

4.5.3 (*R*)-1,2,3,4-Tetrahydro-1-naphthylamine-ICl Complex

Amine **15** was the second amine, which was investigated, because the stereoselectivity achieved in the reaction of **1** ⟶ **2** was the highest. Hence it is the most interesting compound to model, despite the large number of atoms present in the molecule. The different complexes, which were taken into account are the possible compounds in the system of equilibria shown above in the general part (Figure 10, p.42). All structures shown were obtained in a conformational analysis at a MP2/SDD level of theory as shown representatively for the location of **101b**. For **101b** and **102b** the configuration at the nitrogen is in principle chiral and therefore the rotation around the dihedral was performed for both diastereomers to determine the difference in energy.

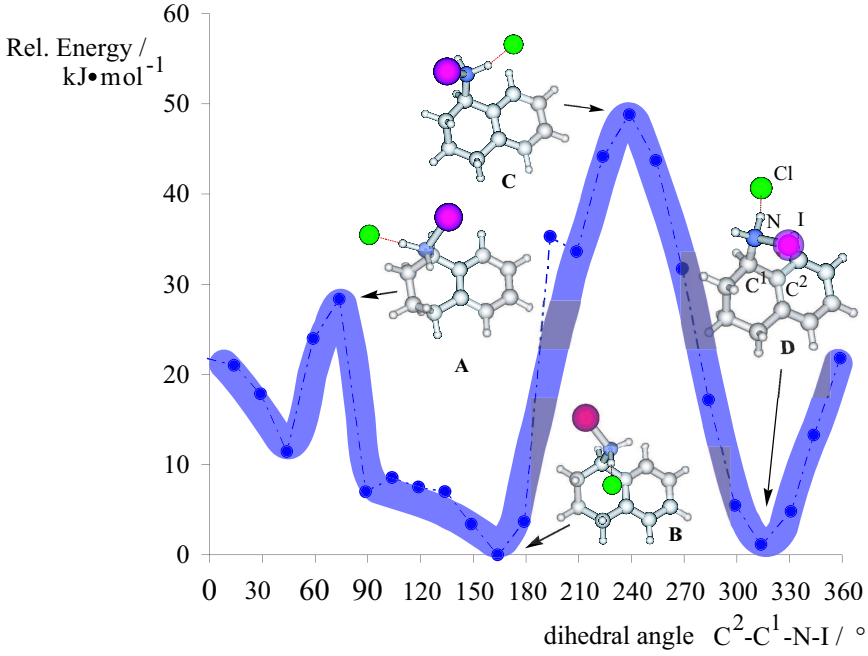


Figure 12: Visualisation of Dihedral Scan around C^2-C^1-N-I of **101b**

The dihedral angular scan of **101b** at a MP2/SDD level of theory is shown, illustrating a 360° rotation around C^2-C^1-N-I. The first local maximum **A** was found at 75°, it was 7 kJ·mol^{-1} higher than the original starting point. The global minimum **B** was located at 165°, it was 22 kJ·mol^{-1} lower than at 0°. The highest point in energy **C** was reached at 240° at 49 kJ·mol^{-1} higher than originally started from. The second minimum **D** was found at 315° and the difference to **B** was just +1 kJ·mol^{-1}, which is well within the error limits of the method applied.

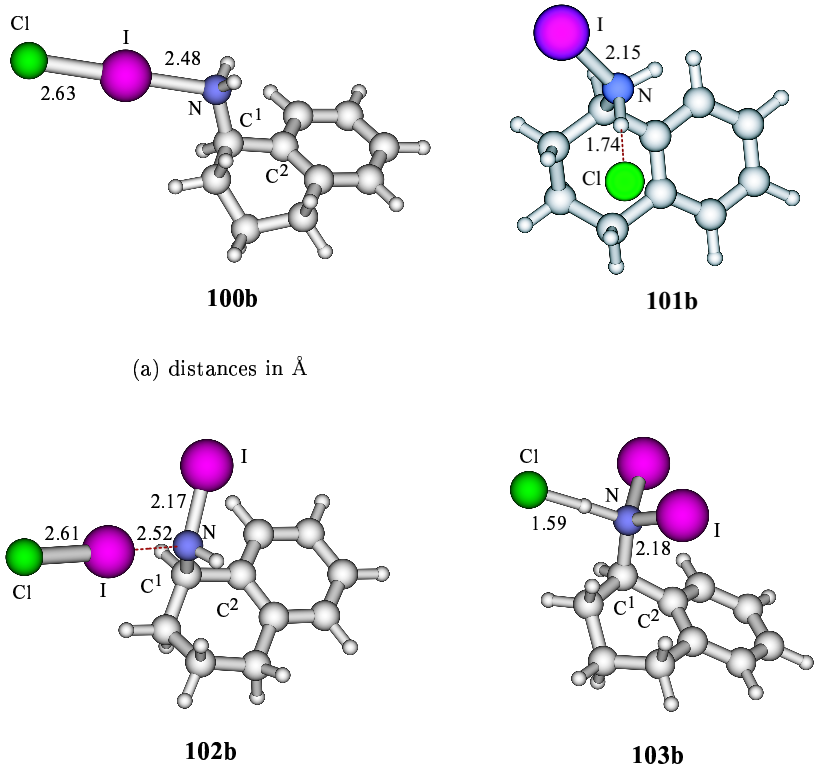


Figure 13: 3D Representations of **100b**-**103b**

The MP2 geometries for the individual species **100b**-**103b** are shown in figure 13, the structures for the transitions states will be shown on page 47. The length of the nitrogen-iodine bonds of each of the species in question are comparable to the ones mentioned in the previous subsection 4.5.2, the sum of the van-der-Waals-radii is reported to be 3.65 Å.[77] The interatomic distances are therefore contracted, which shows significant electron transfer to form a at least partially covalent N-I bond. Likewise the charge distribution found by NBO calculations show picture very similar to the investigations on the complexes of methylamine. In case the bond length N-I was approximately 2.16 Å, an increased charge (+0.1 e) was localised on the iodine atom.

The diastereomer of **101b** differs 3.7 kJ·mol^{-1} in energy compared to **101b**. For each of stereoisomers two different local minimum geometries were found, which appeared to be very similar in energy. Similarly a second minimum was located for **100b**, with ICl being positioned above the tetrahydronaphthyl system. Molecules **102b** and **103b** generally were found to have minima, which differ only little in energy.

Table 15: Geometries of **100b**-**103b**

MP2/SDD	N-I / Å	N-XCl / Å	X-Cl / Å	C^2-C^1-N-I / °	C^1-N-I / °
100b (X=I)	–	2.48	2.63	166.4	112.6
101b (X=H)	2.15	1.17	1.74	−160.5	119.4
101b (X=H)[a]	2.15	1.17	1.74	165.2	114.2
102b (X=I)	2.17	2.53	2.61	−169.1	115.0
103b (X=H)	2.18	1.17	1.59	78.3	114.0

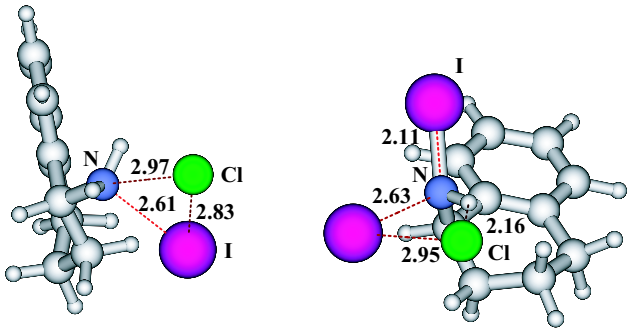
a) This entry represents the diastereomer of **101b** with respect to the *N*-chirality.

Table 16: Charge Distributions of **100b**-**103b**

MP2/ SDD	N / *e*	I / *e*	Cl / *e*	N-*I*-Cl / *e*
100b	−0.87	–	−0.42	0.20
101b	−0.82	0.35	−0.68	–
101b[a]	−0.80	0.34	−0.67	–
102b	−0.86	0.31	−0.39	0.22
103b	−0.80	0.35[b]	−0.54	–

a) Diastereomer of **101b**; b) Same charge on both iodine atoms.

The calculations were done at three different levels (dihedral scans and geometry optimisation for each of the compounds on each level), to investigate the importance of electron correlated methods for this type of complexes. Similar reaction profiles were obtained at B3LYP/LANL2DZ , B3LYP/SDD and MP2/SDD levels of theory.[86] The B3LYP/SDD barriers from the free amine to **101b**, from **100b** to **101b** and from **101b** to **103b** were found to be +30 kJ·mol^{-1}, +97 kJ·mol^{-1} and +135 kJ·mol^{-1}, respectively. These barriers are gas phase energies, which are certainly different from the situation in solution. Similar results have been obtained at B3LYP/LANL2DZ (+30 kJ·mol^{-1}, +89 kJ·mol^{-1} and +133 kJ·mol^{-1}) and also at a MP2/SDD (+50 kJ·mol^{-1}, +74 kJ·mol^{-1}, **116b** was not confirmed) level of theory. These values allow the interpretation that the transformation from **100b** to **101b** is possible, while **103b** is unlikely to be formed and will not be included in further calculations. With all three methods a direct transition from **101b** to **103b** could not be located. The direct formation of **101b** from the free amine showed a barrier which can be overcome farily quickly, the straightforward formation of **100b** is, however, much faster.

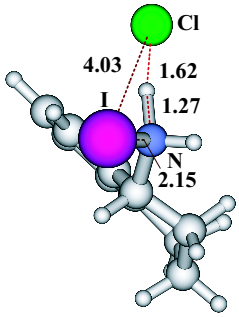


114b **116b**

(a) distances in Å

Figure 14: Structures of **114b** and **116b**

Furthermore, the diastereomer for **102b**, mentioned above, was less than 0.2 kJ·mol^{-1} different in energy and are at the present level of accuracy and this stage of the investigations not regarded to be of significance.[87]



115b

Figure 15: Structure of **115b**

Table 17: Total Energies of **100b**-**103b**

Total Energies	**15**	**100b**	**114b**	**101b**	**115b**	**102b**	**116b**	**103b**
B3LYP/LANL2DZ	0	−88.6	29.5	−33.0	−0.2	−12.4	100.1	55.1
B3LYP/SDD	0	−92.0	29.5	−28.6	4.5	−2.7	105.9	63.5
MP2/SDD	0	−87.2	49.6	−46.3	−13.0	−44.9	−[a]	6.9

a) **116b** on a MP2/SDD level of theory was located, but could not be confirmed by frequency calculations; **117b** was not located; All energies are given in kJ·mol^{-1}

The ICl complexes **100b** and **102b** exhibited a very large dipole moment(∼13 debye), thus proving

the ionic character of these compounds. The dipole moment in the HCl complex **101b** is smaller (~6 debye), but still a significant charge separation.[88]

The various molecules have been optimized and the PES was scanned for the lowest energy conformation.
The lowest conformation was **100b**, which can be converted into **101b** via a barrier of about 80 kJ·mol^{-1} (MP2 energies). A small positive relative energy to the free amine was observed for **103b**. The existence of **102b** at a very similar energy level than **101b** shows the possibility of this HCl-ICl exchange, which was already found in the investigations of the complexes of methylamine. Due to the lack of free ICl at this stage of the reaction sequence, it is assumed that any further molecule ICl is only available, by decomplexing **100b**. This aspect will be discussed with the help of complexation energies.

4.5.4 Incorporation of Solvents

In the reactions different solvents have been used hence solvent models were included to assist discussing the reaction pathways. The Conductor Polarizable Continuum Model (CPCM), which was applied, places the solute in a cavity created via a series of overlapping spheres.[89] B3LYP/SDD calculations included geometry optimisation in presence of the solvents, focussing on compounds **100b**, **101b** and **114b**.
The results allow the same conclusion obtained by the gas phase calculations in terms of the difference in the total energy of the species. All species are lowered in total, which results in an easier transition from the free amine directly to **101b**. Acetonitrile has the highest dielectric

Table 18: Relative Energies (CPCM Solvent Model)

B3LYP/SDD[a]	**100b**	**101b**	**114b**	$\epsilon_{\mathbf{R}}$
benzene	−107.1	−41.3	7.0	2.25
Et_2O	−119.9	−52.1	26.2	4.36
CH_2Cl_2	−119.6	−51.3	2.5	8.93
CH_3CN	−123.1	−54.1	−33.7	36.64

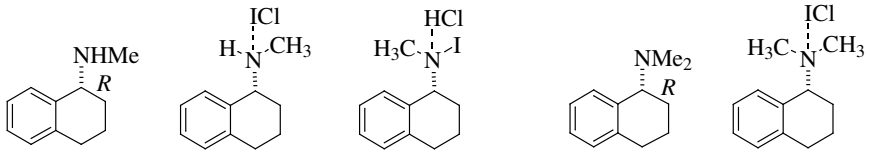
a) Energies are given in kJ·mol^{-1} relative to the free amine.

constant (ϵ_r=36.64) and shows the greatest stabilisation effect among the four different solvents. This may be explained by the high dipolar moments observed in these complexes. In contrast to the gas phase calculations the solvent can interact and charge will be redistributed accordingly. Benzene (ϵ_r=2.25) is the least polar of the solvents included, it shows a higher energy for **100b** relative to the free amine than in all other solvent calculations, allowing the formation of **101b**.

The solvent played an important role in the stereoselectivity of the iodolactonisations. The formation of the iodiranium ion, seems to be the stereoselectivity determining step, in which the complex formed in the reaction of the amine and ICl attacks at a double bond (the N-I bond is weakened and the iodiranium moiety is established). This extensive model however is not included in the present approach.

4.5.5 *N*-Substituted Amines

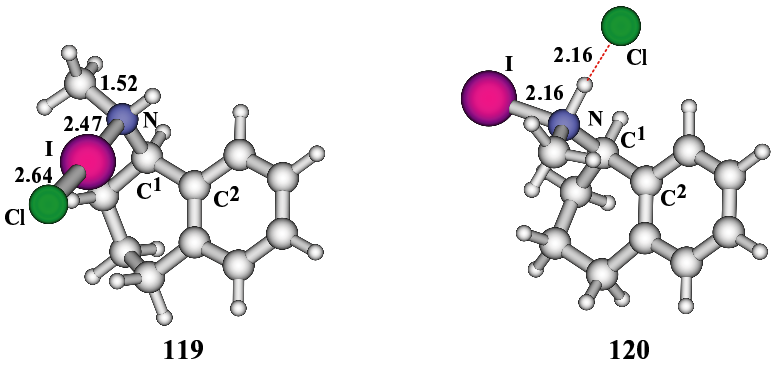
N-Alkyl substituted amines were investigated, because in the iodolactonisation experiments these compounds always showed a lower selectivity or even racemic product. Charge distributions and optimised geometries could indicate reasons for this observation, hence complexes of **22** (**119**, **120**) and of **24** (**121**) have been considered.[90]



22 **119** **120** **24** **121**

The N-I bond varies in length (2.17 Å for **120**, 2.45 Å for **119** and **121**), as seen before in the studies of both primary amine, where the N-I bond in **101b** and **103b** was also shorter than the corresponding coordinative bond in **100b** and **102b**. The charge on the nitrogen in **119** (-0.72 *e*) and in **120** (-0.62 *e*) is considerably lower than in **101b**. The charge on the iodine remains virtually unchanged.

The methyl substitutions on the nitrogen did not show a significant difference in neither the N-I bond lengths, nor the charges localised on the iodine atoms, when compared to the complexes of **15**.



(a) distances in Å

Figure 16: Structures of **119**, **120**

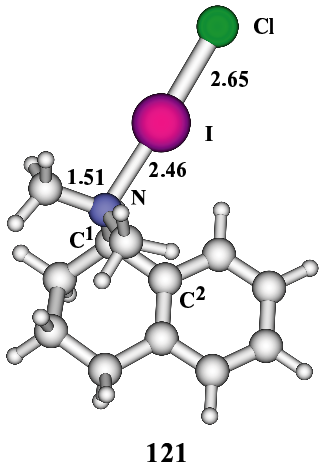


Figure 17: 3D Representation of **121**

Table 19: Geometries of **119**, **120**, **121**

MP2/SDD	N-XCl / Å	X-Cl / Å	C^2-C^1-N-I / °	C^1-N-I / °
119 (X=I)	2.45	2.64	173.1	111.4
120 (X=H)	2.17	1.78	164.3	109.6
121 (X=I)	2.45	2.65	175.0	108.5

Table 20: Charge Distributions of **119**, **120**, **121**

MP2/SDD	N / *e*	I / *e*	Cl / *e*	N-*I*-Cl / *e*
119	−0.72	–	−0.43	0.19
120	−0.62	0.35	−0.69	–
121	−0.87	–	−0.42	0.20

4.5.6 Trends in Complexation Energies

In the series of the primary amine, the complexation energies are the smaller, the more iodine atoms are incorporated into the molecule,[91] showing the strongest complex for **100b** in all cases. The energies calculated at a MP2/SDD level of theory do not show much variation for **101b**, **102b** and **103b**).

When calculating the complexation by simply subtracting the energy of each of the monomers from the total energy of a dimer a phenomenon called the basis set superposition error (BSSE)[92] is encountered. It arises from the fact that when using more basis functions a better description of the systems results. This discrepancy was estimated to be ca. 6.5 kJ·mol^{-1} for **100b** and **102b**, the estimations for the HCl complexes (**101b** and **103b**) differed considerably from this value.[93]

Table 21: Complexation Energies of **100b** - **103b**

Level of Theory	**100b**	**101b**	**102b**	**103b**
MP2/SDD	87.2	73.4	71.9	71.8
BSSE MP2/SDD	6.2	−78.0	6.6	−57.2
B3LYP/LANL2DZ	88.6	34.3	29.5	66.4
B3LYP/SDD	92.0	79.2	53.3	61.8

All Energies are given in kJ·mol^{-1}

The complexation energies of the *N*-alkylated amines **119**, **120** and *N*,*N*-dialkylated amine **121** at a MP2/SDD level of theory are much higher for both of the ICl complexes (**119** and **121**) than for the HCl complex (**120**). In case of **121** the +I effect of the alkyl groups increases the electron density on the nitrogen, which results in a stronger coordination of ICl. A higher complexation energy resembles a stronger interaction, which should lead to better selectivities in the lactonisation, due to a prolonged close contact at the moment of forming the iodiranium ion with the double bond. Future investigations at a MP2/6-31+G(d,p),SDD//B3LYP/6-31+G(d,p),SDD level of theory will be aimed at more precise complexation and also total energies.

Table 22: Complexation Energies of **119**, **120** and **121**

Level of Theory	**119**	**120**	**121**
MP2/SDD	102.2	76.9	108.8

All Energies are given in kJ·mol^{-1}

4.5.7 Summary Chiral Amine-ICl Complexes

The complexes of methylamine and tetrahydronaphthylamine with ICl yielded geometries, in which N-I bonds are close in length to comparable known complexes (EtN_3·ICl and NH_3·ICl).
The relative total energies vary in reasonable range and suggest, additionally to the species hypothesised from the experimental evidence (**100** and **101**), a complex of type **102** should also be taken into account, although this compound chemically is regarded a side product.
The charge distributions at a level of MP2/SDD show that the charge difference on the iodine only is of small nature (0.1 e). Compounds with a higher positive charge on the iodine should be better electrophiles towards double bonds.
The N-substituted molecules should be as efficient as electrophiles originating from primary amines in terms of electrophilicity, since the change in charge on the iodine atom is only marginal.

In case a solvent was present in the calculations, all energies were lower compared to the gas phase results. All in all the energy differences obtained were in agreement with the reaction path suggested from gasphase calculations.

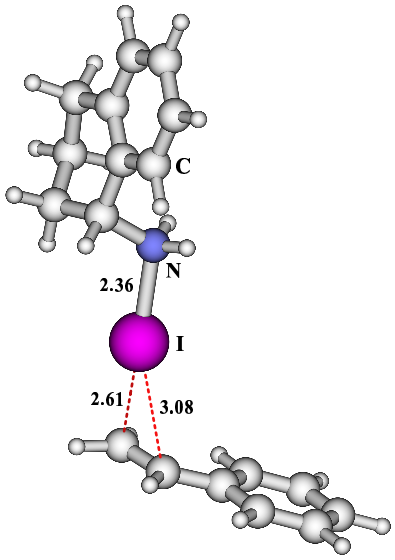
4.6 Summary of Computational Part

The methodologies applied proved to be consistent with comparable literature experimental and computational results although there were limitations of the basis as discussed.
In the Hammett investigations of the positively charged iodiranium moiteies an excellent correlation of the NBO charge on the benzylic carbon with Hammett σ_p^+ constants was observed. Not surprisingly the NBO charge of the iodiranium moieties also correlate well with Hammett σ_p^+ constants. The geometries of these iodiranium moieties showed a clearly distorted iodiranium ion, which varied according to the substituent in *para*-position.

The investigation into the reaction of ICl and primary amines was clearly showing a preference for an amine$\cdots$ICl complex at all levels of theory considered (values in parenthesis correspond to relative energies (compared to free amines methylamine **a**/(*R*)-1,2,3,4-tetrahydro-1-naphthylamine **b**) at MP2/SDD level of theory). This is implied first of all by the relative total energies, independent from the amine investigated. The results comprise a complex, which is a product of two subsequent reactions on the nitrogen: After formation of complex **100** (-85.8/-87.0 kJ·mol^{-1}) in a first step the proton is exchanged with an iodine atom. Secondly the resulting *N*-iodo HCl complex **101** (-27.4/-43.6 kJ·mol^{-1}) is undergoing a decomplexation-recomplexation step, where the HCl is exchanged against an ICl molecule to give product **102** (-39.8/-44.9 kJ·mol^{-1}). Although all methods give different energies to the latter molecule, they consistently suggest an exothermic pathway. The reaction to reach the *N*,*N*-diiodo HCl complex **103** (+10.9/+6.9 kJ·mol^{-1}) was found to be endothermic in all calculations.
The hypothesis deducable from this data includes two scenarios. One possibility is that free amine is still present and there is an equilibrium between the free amine (and ICl as well), **100** and **101** (The iodolactonisation performed in such an environment should show lower selectivities, since the free ICl causes a racemic background reaction). It, however, is likely that the concentration of free amine and free ICl is considerably high, because the formation of complexe **100** was favoured at all levels of theory. On the other hand considering **100**, **101** and **102** leads to a new, more complex situation, since all complexes formed can in principle transfer stereochemical information, although **102** is regarded a byproduct, which is thought to be formed by exchanging HCl with ICl (the latter needs to be liberated from **100**); this seems unfavourable at present on the basis of the complexation energies (**MP2/SDD 100b**: 87.2 kJ·mol^{-1} compared to **102b**: 71.9 kJ·mol^{-1} as well as the relative energies *vide supra*).
The *N*-alkyl substituted amines investigated showed higher complexation energies than the unsubstituted ones, in complexes **119** and **121** it was much higher (105 ±3 kJ·mol^{-1} than in the the bondlengths in complexes are slightly shorter (-0.03Å− 0.08 Å) .
Including solvents into the calculations did show that **101** is more likely to be formed, because the energy barriers were generally found to be lower. The differences in relative total energies of **100** and **101** did not change much.
Charge distributions in complexes **100**-**103** show a slightly higher positive charge on the iodine for covalent N-I bonds (**101**, **102**, **103**) in contrast to the coordinative bonds. (The *N*-substituted molecules should be as efficient as electrophiles originating from primary amines in terms of electrophilicity, since the change in charge on the iodine atom is only marginal, a higher positive charge indicates a more iodinating compound and the extend observed was 0.1 *e*.

4.7 Outlook

Formation of Iodiranium Ions with Chiral ICl-Complexes These initial calculations were done first at HF/SDD and B3LYP/SDD levels of theory, the observed geometries showed an arrangement of **101b** essentially perpendicular to the plane of the styrene π-system, without the counter ion being included in the calculation.



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Including the counter ion caused the calculations to be much longer, also convergence was much harder to achieve. Incorporation of solvent models (CPCM, CH_2Cl_2) at both levels of theory did not change the perpendicular arrangement, but the distance of the double bond carbon atoms to the iodine increased, while the N-I distance decreased, accounting for the lack of description of dispersive effects needed to describe the dative bond between N and I.

The existence of more than one minimum for each species **100b**-**102b** suggests, that during the interaction with a double bond in the stereoselective step different minima could be of importance. Hence the global minimum found here might not be the geometry most favourable in the attack at the double bond.

When combining these results with the experimental results in the following chapter, it is important to remember that th findings of the calculations are resembling only two examples of amines (methylamine and **15**) and that more calculations applying solvent models must be done as well before one can quantitatively rely on the energy barriers to the transition states calculated. For more accurate descriptions mixed basis sets should be applied, also including polarising and diffuse functions (*vide supra*), for which we do not have computational resources at present time.

5 Combined Summary

This chapter is regarded to be read in conjunction with the individual summaries (chapter 3.6 on page 32 and chapter 4.5.7 on page 52). From combining the experimental evidence with the results of the computational part where the results of both chapters were available, the interpretations have been mostly consistent, differences are outline when occured.

5.1 Complexes formed by Amines and ICl

From both, the experimental and also the computational part, it is assumed that there exists an alternative pathway of the initial formation of the amine-ICl complex **100**. In a second transformation (it also could be concerted), a H-I exchange takes place on the nitrogen (which forms **101**). It remains unclear at this stage, which of these two complexes is the dominant one, although the calculations clearly show **100** as the most stable compound relative to the free amine.
It has been excluded, that further reactions, taking place after this first H-I exchange are playing a substantial part in the selectivity determining step of the iodolactonisation. To form complex **102** decomplexation of ICl from **100** seems necessary, if all ICl is incorporated in **100** or **101**. This aspect is supported by the total energies of species **100**-**103**. It can be clearly stated, that compound **100** is favoured to a great extend at all levels of theory over all other species considered. The energy barrier to reach **101** starting from the free amine is in a range, which can be overcome at r.t. (B3LYP/SDD: In gas phase +30 kJ·mol^{-1}; In solution (CPCM:CH_2Cl_2:+7) kJ·mol^{-1}). Therefore the above mentioned equilibrium between **100** and **101** is likely to be of importance and serves as an explanation for the experimental observation, that after stirring the amine and ICl at r.t. for 30 minutes the stereoselectivity is changed (+14% *ee*) in the iodolactonisation **2** to **3**.
Assigning a role to **102** proved more difficult, because there is little experimental evidence of its existence, but from the calculations the total energy is similar to **101**, as is the complexation energy (MP2/SDD). The complexation energy was lower than in **100** (which means, it is unlikely that it decomplexes ICl in **100**), furthermore **102** is also much higher in total energy (compared to **100**).
Therefore an equilibrium between free amine and free ICl (at very low concentrations), **100** and **101** is favoured. This is also supported by the experimental findings, where from UV/VIS studies additionally to the donor acceptor complex formation a second transformation was observed.[94]

The fact that *N*-substituted amines gave so much lower enantioselectivities could not be reasoned by the calculations, where the charges on the iodine are only marginally different. More likely is the importance of the actual geometry of the complex formed, when the **100** or **101** attack at the double bond. The investigations into solvent effects did not lead to agreement, because in the experiment only chlorinated solvents (and at r.t. benzene) showed good enantioselectivities. This might be due to the lack of a computational description of the iodiranium ion, formed by a chiral complex **100** or **101** and styrene (as a straightforward example). It therefore should be noted, that the solvent effects in the reaction of a primary amine and ICl may not be conclusive for stereoselectivities found in the experiments. It is assumed that the change in stereoselectivity,

which was found when applying other solvents than CH_2Cl_2 is inherent to the circumstances present at the time of the actual formation of the iodiranium ion rather than to the individual molecules formed in the reaction of amines and ICl.

5.2 Electronic Effects

The Hammett investigations showed, that the more electron-withdrawing (the higher the Hammett value) a substituent in the 4-position of the aromatic moiety, the shorter the bond length C^1-I and, moreover, the higher the selectivities in reaction of 2 $\longrightarrow$ 3. Correlations of the charge at the benzylic carbon in iodiranium ions **112** and **113** have been shown to be excellent as well. The calculations are therefore clearly supporting the experimental evidence in the selectivity of the reaction of **2** to **3** and *para*-substituted analogs of **2**.

6 Experimental Details

6.1 General Working Techniques and Equipment

Standard laboratory equipment of the appropriate size was used for all experiments, unless otherwise stated. In case degassed solvents were to be used, degassing was achieved by freezing the solvent in a closed vessel and subsequent evaporation on a high vacuum (HV) pump. The solvent was then allowed to warm up to room temperature and the whole procedure was repeated twice again, before the vessel was finally flushed with argon. Experiments requiring water exclusion were carried out under argon (argon balloon) in a beforehand vacuum dried vessel.
Solvents were removed using a *Büchi R-124* rotation evaporator at a final vaccum of 15 mbar and a water bath temperature of 40 °C. Further vacuum was applied using a rotatory pump at about 0.05 mbar. Vacuum destillations were performed on a bulb to bulb destillation apparature manufactured by *Büchi*.

Absolute (abs.) Solvents were used when appropriate, when not otherwise stated, distilled laboratory solvents were used.

TLC/Preparative TLC Thin layer chromatography was performed on *Merck silica gel 60 F254* precoated aluminum/glass backed plates.

Flash Column Chromatography was performed with 0.025 mm-0.040 mm pore sized Merck silica

GC-MS

1. *Hewlett Packard (HP) 5890 A Series II* GC equipped with column SE30, 25 m and detector *HP 5970A*.
2. *Hewlett Packard (HP) 5890 A Series II* GC with column DB5MS, 30 m and detector *VG Instruments Trio-1*

HPLC Systems The analytical columns used were: Daicel Chemical Industries OD, OD-H with a length of 25 cm, a diameter of 4.6 mm and a flow rate of 0.5 ml/min. The semi-preparative column used was a Daicel Chemical Industries OD, length 25 cm, diameter 21 mm, flow rate 6 ml/min.

1. *Hitachi/Merck L-6200* gradient pump with *Merck/Hitachi L-4200* UV/VIS detector and a *Merck/Hitachi L-2500* integrator.
2. *Shimadzu LC-10 ATVP*quaternary pump, *Shimadzu SCL-10AVP* controller, *Shimadzu SPD-M10AVP* diode array detector and a *Shimadzu CTO 10 AVP* column oven. This system was controlled by *Shimadzu Class VP* software (v5.032).

Inert Atmospheric Conditions were generated by heating the whole vessel with a heat gun from all sides under a applied vacuum and allowing it to cool down with the vacuum still applied, before flushing the reaction vessel with argon.

Infrared (IR) Spectra were recorded on a *Perkin Elmer FT1600* as a liquid film on NaCl plates (neat) or as pressed tablets in potassium bromide (KBr).

Mass Spectra (MS) Low resolution MS were recorded on a *Finnegan MT 8200* and a *Fisons VG* Platform. either with electrochemical ionisation (EI, 70eV) or by fast atom bombardment (FAB). High resolution MS were recorded on a *Finnegan MT 95.*

Elemental Analysis (EA) All EAs were submitted to Warwick Analytical Services, UK.

Melting Points were recorded on a *Kofler* hot stage apparatus and are uncorrected.

NMR spectra were recorded on a *Varian Gemini* 300 MHz (^{1}H)/75 MHz (^{13}C), a *Bruker DPX* 400 MHz (^{1}H)/100 MHz (^{13}C) NMR or on a *Bruker DRX* 500 MHz (^{1}H)/125 MHz (^{13}C) spectrometer as stated, using TMS as an internal standard.

Optical Rotatory Power ($[\alpha]_D^{25}$) values were measured on either a *Optical Activity Ltd. AA-1000 Polarimeter* with a cuvette of a path length of 5 cm or a *Perkin Elmer PE 141-Polarimeter* with a cuvette of 10 cm path length. The values were recorded three times at a wavelength of 589 nm at 25 °C and the mean value is stated. The concentrations are given in g/100 ml.

ICl was purchased as a 1M solution in CH_2Cl_2 at Aldrich. The following compounds were purchased from various companies and used without any further purfication, unless otherwise stated. In case enantiomerically pure substances were purchased $[\alpha]_D^{25}$ measurements were done to assure enantiomerical purity.

The following table serves as a guide to the individual compounds, where *P* stands for compound was *purchased*, the indices A, F and L represent the companies Aldrich, Fluka and Lancaster respectively. The abbreviation *K* stands for *Known* compound, which was synthesised (a reference will be given) and *S* for *Synthesised* compound, with the procedure and the experimental data presented below.

no.		**no.**		**no.**		**no.**		**no.**		**no.**		**no.**	
2	**K**	**20**	**S**	**31**	$\mathbf{P}_A$[e]	**41**	**K**	**54**	**S**	**70**	**S**	**87**	K
3	**S**	**21**	$\mathbf{K}$[b]	**32**	$\mathbf{P}_A$[e]	**42**	**K**	**58**	**K**	**73**	**K**	**89**	K
12	$\mathbf{P}_A$	**22**	$\mathbf{K}$[b]	**34**	$\mathbf{P}_L$	**43**	**K**	**59**	**K**	**74**	**K**	**90**	**S**
13	$\mathbf{P}_A$	**23**	$\mathbf{K}$[b]	**34**	$\mathbf{P}_L$	**44**	$\mathbf{P}_L$	**61a-c**	**S**	**75**	**K**	**92**	**K**
14	$\mathbf{P}_L$	**24**	$\mathbf{K}$[c]	**35**	$\mathbf{P}_L$	**45**	$\mathbf{P}_L$	**62a-c**	**S**	**77**	**K**	**93**	**K**
15	$\mathbf{P}_L$	**26**	**K**	**36**	$\mathbf{P}_L$	**46**	$\mathbf{P}_A$	**63a-d**	**S**	**78**	**K**	**95a/b**	**K**
16	$\mathbf{P}_L$	**27**	$\mathbf{K}$[c]	**37**	$\mathbf{P}_L$	**47**	$\mathbf{P}_A$	**64**	**S**	**79**	**K**	**97a/b**	**K**
17	**K**	**28**	**K**	**38**	**K**	**49**	$\mathbf{P}$[g]	**67**	**S**	**80a/b**	**S**	**99**	**K S**
18	**K**	**29**	$\mathbf{P}_F$	**39**	$\mathbf{P}_L$	**50**	$\mathbf{P}$[g]	**68**	**S**	**83**	**K**		
19	**K**	**30**	$\mathbf{P}_A$	**40**	**K**	**53**	**K**	**69**	**S**	**84**	**K**		

a) bought as **5***H_2SO_4*****$5H_2O$; b) also available from Fluka;
c) also available from Aldrich; d) also available from Lancaster;
e) supplemental chiral compounds catalog; f) obtained as **37***HCl from Aldrich;
g) obtained from Solvent Innovation GmbH

6.2 Experiments

General procedure 1 (GP1) for Iodocyclisations The iodolactone was prepared in a two step procedure, when $2.28*10^{-1}$ mmol ICl (1M in CH_2Cl_2) and $4.54*10^{-1}$ mmol of chiral enantiomerically pure amine,[95] dissolved in 4 ml CH_2Cl_2 were stirred for 35 minutes at room temperature. After cooling to -78 °C, $1.14*10^{-1}$ mmol of the substrate in 1 ml CH_2Cl_2 were added. The reaction was allowed to react for 10 minutes. After adding an aqueous 10% $Na_2S_2O_3$ solution the reaction mixture was allowed to warm up to room temperature. Extracting twice with ca. 6 ml CH_2Cl_2 and drying over $MgSO_4$, the product was purified by preparative TLC (1:2 TBME:Pentane).[96]

General procedure 2 (GP2) for Suzuki reactions to yield *para*-substituted 4-aryl-4-pentenoic acids: 1 eq boronic acid, 3.3 eq KF and 1.5 mol% $Pd_2(dba)_3$ were dissolved in 5 ml THF (dry) and 1.1 eq *tert.*butyl-2-bromo-1-pentenoate and 4 mol% *tris*-(o-tolyl)-phosphine were added. After 4-10 hours the reaction was stopped by filtering over celite and washing the celite pad with large quantities of ethylacetate. The crude products were purified by flash chromatography using a 1:10 mixture of TBME and petrolether destillates. All products obtained were colourless clear oils.

General Procedure for Iodoadditions (GP3):

Non Chiral Version:

1 mmol of styrene (or cyclopropylbenzene) and 380 $/mu$l MeOH were stirred in 5ml CH_2Cl_2, when 1.10 mmol ICl was added at $-78°C$. The reaction was allowed to warm up to r.t. and continuously stirred. Addition of 15 ml aqueous 10% $Na_2S_2O_3$ solution, followed by extracting with CH_2Cl_2 (three times) and drying over $MgSO_4$ yielded the crude product. If MeOH was added after ICl then only the iodochlorinated product was observed.

Chiral version:

GP1 was adapted so that prior to the preforming stage, when the amine and ICl were stirred for 30 minutes at r.t., the Cl^- counterion was exchanged against PF_6^-, by adding solid 200 mg (0.79 mmol) $AgPF_6$ to 800 μl of ICl (1M in CH_2Cl_2). This mixture was continued to stirr for 15 minutes, until the formation of a yellow precipitate stopped. A solution of 470 mg (3.19 mmol) (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **15** in 2ml CH_2Cl_2 was added and stirred for 30 minutes 1.5 ml of this solution were transferred into a freshly dried vessel, 130 μl MeOH and α-methyl styrene **94** (also styrene **91** or cyclopropylbenzene **96** were used) were added. GCMS and TLC showed only starting material for all iodofunctionalisations tried.

General Procedure for Lactonisation of Amides in CH_2Cl_2 (GP4):

In a dried apparatus under argon, 2 equivalents ICl ($2.28*10^-1$ mmol, 1 M in CH_2Cl_2) were added to 4 ml CH_2Cl_2. $1.14*10^-1$ mmol (1 eq.) of the amide was dissolved in 2 ml CH_2Cl_2 and then dripped onto the ICl solution. In case completion of the lactonisation was not complete after 30 min. at r.t. a condenser was fitted and the mixture was refluxed for 30 minutes. The reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted three times with CH_2Cl_2. Organic

aliquots were combined and washed with saturated NaCl solution. Product was dried over $MgSO_4$ and concentrated by rotary evaporation. Purification by preparatory TLC in a 1:1 TBME:pentane eluent gave iodolactone **3**.

General Procedure for Lactonisation of Amides in aqueous THF (GP5): To 4 ml of a 1:1 mixture THF:H_2O, 2 equivalents ICl ($2.28*10^{-1}$ mmol, 1 M in CH_2Cl_2) were added. $1.14*10^{-1}$ mmol (1 eq.) of the amide was dissolved in 2 ml of THF-water solution and transferred to the reaction flask. Reaction was performed at r.t. monitored by TLC and worked-up upon completion. The reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted three times with CH_2Cl_2. Organic aliquots combined and washed with saturated NaCl solution. Product dried over $MgSO_4$ and concentrated by rotary evaporation. The lactone was purified by preparatory TLC in a 1:1 TBME:pentane eluant.

General Procedure for Iodolactonisations in solvents other than CH_2Cl_2 (GP6): For this procedure see **GP1**, CH_2Cl_2 was substituted against the desired solvent, ICl however was added from a stock solution in CH_2Cl_2 (1M).

Procedure for NMR Titrations:

A solution of 1 mg ($6.79 *10^{-6}$ mol) (*R*)-1-phenyl-ethylamine **12** in 600 μl $CDCl_3$ was titrated in an NMR tube, by adding 35 μl (0.25 equivalents) of ICl ($4.85*10^{-2}$ M in CH_2Cl_2) in each step.[97]

Procedure for UV/VIS Time Dependent Studies:

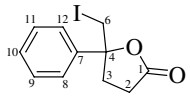
A 1:1 (0.01 mmol) mixture of (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **15** and ICl in CH_2Cl_2 was stirred for 60 min. at r.t. and a UV/VIS spectrum aqcuired every 4 minutes.[98]

Procedure for Cross Over Experiments:

In **GP1** the stage of the preforming of the chiral complex was adapted. After stirring one equivalent of the first amine at r.t. for 30 min., one equivalent of the second amine was added at r.t. (-78 °C in the second series of experiments). Each experiment was rerun with a swapped order of amines in the reaction, so that each amine was once stirred at r.t. with ICl for 30 min. and once added after this time when of the preforming of the chiral complex.

4-Phenyl-4-pentenoic acid 2

For preparation and spectral data see reference.[99]

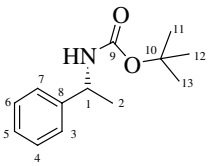


5-Iodomethyl-5-phenyl-dihydro-furan-2-one 3

Following **GP1** 5-iodomethyl-5-phenyl-dihydro-furan-2-one **3** was obtained in 78% yield (TBME :Pentane=1:2). This experiment was repeated with 200 mg (1.14 mmol) **2** to obtain 260 mg **3** (76% yield). ^{1}H-NMR δ/ppm ($CDCl_3$, 300 MHz): 7.35-7.41 (m, 5 H, C7-C12), 3.63 (s, 2 H, C6), 2.44-2.82 (m, 4 H, C2, C3);^{13}C-NMR δ/ppm ($CDCl_3$, 75 MHz): 175.2 (1 C, C1), 140.6 (1 C, C7), 128.8 (2 C, C8, C12), 128.6 (1 C, C10), 124.8 (2 C, C9, C11), 86.0 (1 C, C4), 33.9 (1 C, C3), 29.2 (1 C, C2), 16.3 (1 C, C6). IR $\tilde{\nu}$ / cm $^{-1}$: 3054 (w), 3012 (w), 2362 (st), 1780 (st), 1420 (m), 1180 (st). MS (m / z) (relative intensity): [M^+]= 302(1); [M-I^+]=175 (43); 161 (100); 115 (9). HRMS ($C_{11}H_{11}IO_2$): *calc*: 301.9802, *found*: 301.9813. Analysis of the enantiomeric excess was done by chiral HPLC using a 80 : 20 mixture of hexane:2-propanol, a flow at 0.5 ml*min^{-1} and a wavelength of 272 nm, R_f(R)=19 min. and R_f(S)=21 min. (OD-H).

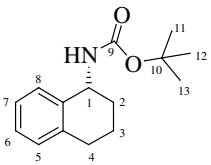
(*R*)-(−)-1-Ferrocenyl-ethylazide 17 and 18

For preparation and spectra see reference.[27]



(*R*)-1-Phenylethyl-carbamic acid *tert.*butylester 19

726 mg (6.0 mmol) (R)-1-Phenylethylamine and 1.3 ml Et_3N were dissolved in 10 ml CH_2Cl_2 and cooled to 0 °C, when 1.96 g (9.0 mmol) di-tert.-butyldicarbonate was added and allowed to warm to r.t. overnight. Diluting with H_2O, extracting twice with CH_2Cl_2 yielded the crude product. After flash chromatography (1:2 TBME:pentane) (R)-1-phenylethyl-carbamic acid *tert.*butylester **19** was obtained in 95% yield. For spectra see reference.[100]

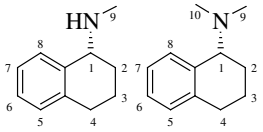


(*R*)-1,2,3,4-Tetrahydro-naphthyl carbamic acid *tert.*butylester 20

1.00 g (7.0 mmol) (R)-1,2,3,4-tetrahydro-1-naphthylamine **15** and 1.5 ml Et_3N were dissolved in 10 ml CH_2Cl_2 and cooled to 0 °C, when 1.96 g (9.0 mmol) di-tert.-butyldicarbonate was added

and allowed to warm to r.t. overnight. Diluting with H_2O, extracting three times with CH_2Cl_2 yielded the crude product. After flash chromatography (1:2=TBME:pentane) (*R*)-1,2,3,4-tetrahydro-naphthylcarbamic acid *tert.*butylester **20** was obtained quantitatively (1.75 g).

^{1}H-NMR δ/ppm ($CDCl_3$, 400 MHz): 7.26-7.21 (m, 1 H, C7-*H*), 7.09-7.02 (m, 2 H, C5/C8-*H*), 6.96-6.92 (m, 1 H, C6-*H*), 4.75 (m, 2 H, N-*H*/C1-*H*), 2.73-2.57 (m, 2 H, C2-*H*), 1.95-1.86 (m, 1 H, C3-*H*), 1.95-1.86 (m, 1 H, C4-*H*, C3-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 100 MHz): IR $\tilde{\nu}$ /cm^{-1} 3328.0 (w), 3054.2 (w), 3012.8 (s), 1694.0 (s), 1493.7 (m), 1453.8 (s), 1390.5 (s), 1173.9 (s). MS (m/z) (relative intensity): [M+H$^+$]=248 (25); 218 (45); 158 (50); 148 (100); 130 (55); 100 (78); HRMS ($C_{15}H_{21}NO_2$+H$^+$): *calc*: 248.1644, *found*: 248.1644. mp 76-78 °C.



(*R*)-*N*-Methyl-1-phenylethylamine 21 and (*R*)-*N*-Methyl-1,2,3,4-tetrahydro-1-naphthylamine 22

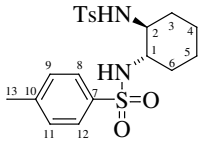
Reducing 700 mg (3.10 mmol) [1.00 g (4.05 mmol)] of the carbamic acid *tert.*-butylester **20** [**21**] with 600 mg (15.8 mmol) [780 mg (20.0 mmol)] LAH in 4ml THF yielded (*R*)-*N*-methyl-1-phenylethylamine **21** [(*R*)-*N*-methyl-1,2,3,4-tetrahydro-1-naphthylamine **22**] in 90% [82%] yield. For spectral data see reference.[101]

(*R*)-*N*,*N*-Dimethyl-1-phenylethylamine 23 and (*R*)-*N*,*N*-Dimethyl-1,2,3,4-tetrahydro-1-naphthylamine 24

For preparation and spectral data see reference.[102]

***(R)*-5-Amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene 26**

The hydrogenations were done in a Parr flask at 4 bar H_2 pressure. For full experimental details and spectra see reference.[28]



(*1R,2R*)-*N*,*N*'-Ditosyl-1,2-diaminocyclohexane 27

To 0.46 g (4.0 mmol) (*R,R*)-1,2-diaminocyclohexane in 5 ml CH_2 Cl_2 , 2.22 g (18 mmol, 3.1 ml) diisopropylamine were added at 0 °C. The mixture was cooled down to -40 °C and 1.50 g tosylchloride were added. It was allowed to warm to r.t. and the contents were poured onto 1N aqueous HCl. Three times extracting with Et_2O, drying over $MgSO_4$, evaporation of the solvent and recrystallisation from Hexan-CH_2Cl_2 gave 1.20 g **27** (72%). Evaporation of part of the solvent and recrystallisation from the mother liquor yielded additional 0.41 g **27**. This compound is also available from Aldrich.

4-Methyl-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-benzenesulfonamide 28

4-Methyl-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-benzenesulfonamide **28** was prepared by reacting 710 mg (3.70 mmol) TsCl in presence of 380 μl Et_3N in 4 ml Et_2O (abs.) from **15** in 85% yield (846 mg). For spectral data see reference.[103]

(*R*)-1-(1-Phenyl-ethyl)-pyrrolidine 38

For preparation and spectral data see reference.[104]

(*R*)-7-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylamine 40

7-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylamine **40** was prepared from the corresponding azide by reduction with LAH in quantitative yield. For spectral data see references.[105]

(*S*)-1-(1-Pyridinyl)-ethylamine 41

For spectral data and preparation see reference.[106]

(*R*)-8-Amino-5,6,7,8-tetrahydroquinoline 42

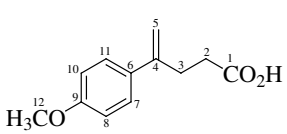
In order to prepare (*R*)-8-amino-5,6,7,8-tetrahydroquinoline **42**, *rac*-8-hydroxy-5,6,7,8-tetrahydroquinoline was separated into the enantiomers by semipreparative chiral HPLC (Daicel Chiraldex OD, diameter 2.1 cm, length 25 cm;6ml/min;2-propanol:hexane=2:8; retention times: $R_f(S)$=18 min. and $R_f(R)$=24 min.) and the (*S*)-enantiomer then converted into amine **42** following reported procedures.[107]

(*S*)-*N*,*N*-Dimethyl-1-pyridyl-ethylamine 43

For spectral data and preparation see reference.[108]

4-(4-Methoxy-phenyl)-4-oxo-butyric acid 53

To a cold stirred solution of anisole (1.00 g, 9.20 mmol), aluminum trichloride (3.00 g, 22.5 mmol) in 12 ml of CH_2Cl_2 was added succinic anhydride (922 mg, 9.20 mmol). The reaction mixture was allowed to warm up to room temperature overnight. Then it was poured into water at 0 °C, followed by acidification with 1N HCl. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and evaporation of the solvent gave a residue, which was purified by flash chromatography (1:9=TBME:pentane, followed by TBME). 384 mg 4-(4-Methoxy-phenyl)-4-oxo-butyric acid **53** were obtained (20% yield).
For spectral data see reference.[109]



4-(4-Methoxy-phenyl)-4-pentenoic acid 54

To a stirred suspension of methyl triphenylphosphonium bromide (436 mg, 1.22 mmol) in 3 ml of C_6H_6 was added dropwise 760 μl *n*-BuLi (1.2 mmol, 1.6 M in hexane). The resulting yellow suspension was stirred for 30 min. at room temperature before adding ketoacid **53** (114 mg, 0.547

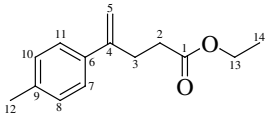
mmol). The reaction was refluxed for 5 days then quenched with water and 1N HCl. The aqueous phase was extracted with TBME. and the combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and evaporation of the solvent gave a residue which was purified by preparative TLC with 1:1=TBME:pentane. The alkene **54** (14.6 mg) was isolated in 13% yield. ^{1}H-NMR δ/ppm ($CDCl_3$, 300 MHz): 7.35 (d, J=8.9 Hz, 2H, C8-*H*/C10-*H*), 6.86 (d, J=8.8 Hz, 2H, C11-*H*/C7-*H*), 5.14 (d, J=67 Hz, 2H, C5-*H*), 3.81 (s, 3H, C12-*H*), 2.82 (t, J=8.3 Hz, 2H, C2-*H*), 2.53 (t, J=9.1 Hz, 2H, C3-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 75 MHz): 178.8 (1 C, C1), 159.2 (1 C, C9), 145.8 (1 C, C4), 132.7, 127.1 (2 C, C7/C11), 113.7 (2 C, C8/C10), 111.4 (1 C, C5), 55.2 (1 C, C12), 32.9 (1 C, C3), 30.2 (1 C, C2). IR (neat) $\tilde{\nu}$ /cm^{-1}: 2955 (m), 2916 (m), 1694 (s), 1623 (m), 1606 (m), 1514 (m), 1428 (m), 1299 (m), 1255 (m), 1181 (m). MS m/z (relative intensity): 206 (99%) [M^+], 161 (100%) [M^+-CO_2H].

4-Bromo-4-pentenoic acid ethyl ester 58

For experimental and spectral data see reference.[110]

4-Bromo-4-pentenoic acid *tert.*-butyl ester 59

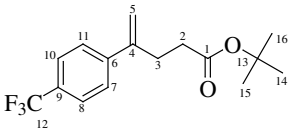
For experimental and spectral data see reference.[111]



4-(4-Methyl-phenyl)-4-pentenoic acid ethyl ester 61a

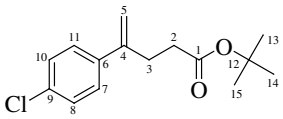
630 mg (4.60 mmol) 4-Methyl-benzeneboronic acid, 1.10 g (13.8 mmol) potassium fluoride and 19.0 mg (0.5 mol%) $Pd_2(dba)_3$ were dissolved in 4 ml dry THF. To the well-stirred solution 840 mg (4.20 mmol) ethyl-2-bromo-1-pentenoate and 250μl of tris-*tert.*butylphosphine (0.2 M in dioxane, 1.2 mol%) were added and stirred for three hours. The reaction mixture was filtered over a pad of celite and washed with Et_2O. After flashchromatography (1:10 TBME:pentane) of the crude 4-(4-methyl-phenyl)-4-pentenoic acid ethyl ester **61a** was obtained in 34% yield (260 mg).

^{1}H-NMR δ/ppm ($CDCl_3$, 400 MHz): 7.34 (d, J=8.0 Hz, 2 H, C7/C11-*H*), 7.17 (d, J=8.0 Hz, 2 H, C8/C10-*H*), 5.31 (s, 1 H, C5-*H*), 5.08 (s, 1 H, C5-*H*), 4.15 (q, J=7.2 Hz, 2 H, C13-*H*), 2.86 (t, J=7.8 Hz, 2 H, C2-*H*), 2.50 (t, J=7.8 Hz, 2 H, C3-*H*), 2.38 (s, 3 H, C12-*H*), 1.27 (t, J=7.2 Hz, 3 H, C14-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 100 MHz): 173.6 (1 C, C1), 147.1 (1 C, C4), 139.4 (1 C, C9), 133.8 (1 C, C6), 129.5 (2 C, C8, C10), 126.4 (2 C, C7, C11), 112.4 (1 C, C5), 60.8 (1 C, C13), 33.8 (1 C, C3), 30.9 (1 C, C2), 21.9 (1 C, C12), 14.6 (1C, C14). IR (neat) $\tilde{\nu}$ /cm^{-1}: 3104 (m), 3041 (m), 2979 (st), 1735 (st), 1628 (m), 1492 (m), 1370 (m). MS m/z (relative intensity): [M^+]=218 (42); [M - $C_3H_5O_2^+$]=145 (100); 129 (50); 115 (92); 91 (12.6); 77 (7.5); 55 (9.5). HRMS ($C_{14}H_{18}O_2$+H^+) *calc.:* 219.1385, *found:* 219.1386.



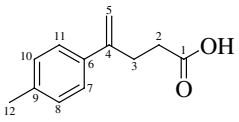
4-(4-Trifluoromethyl-phenyl)-4-pentenoic acid *tert.*butylester 61b

Following **GP2** 680 mg (2.90 mmol) **59** were converted into 560 mg (64%) 4-(4-trifluoro-phenyl)-4-pentenoic acid *tert.*butylester **61b** (after flash chromatography as described in **GP2**). ^{1}H-NMR δ/ppm ($CDCl_3$, 400 MHz): 7.49 (d, J=8.9 Hz, 2H, C9/10-*H*), 7.40 (d, J=8.2 Hz, 2H, C7/8-*H*), 5.30 (s, 1H, C5-*H*), 5.12 (s, 1H, C5-*H*), 2.75 (t, J=7.5 Hz, 2H, C3-*H*), 2.32 (t, J=7.7 Hz, 2H, C2-*H*), 1.36 (s, 9H, C14/15/16-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 100 MHz): 172.6 (1C, C1), 146.5 (1C, C6), 144.8 (1C, C4), 130.0 (q, 1C, $^2J_{C,F}$=30 Hz, C9), 126.9 (2C, C7/C11), 125.7 (2C, C8/C10), 124.5 (1C, $^1J_{C,F}$=260 Hz, C12), 113.2 (1C, C5), 80.4 (1C, C13), 34.2 (1C, C3), 30.5 (1C, C2), 28.1 (3C, C13/14/15). IR (neat) $\tilde{\nu}$ /cm^{-1}: 3086 (w), 3005 (m), 2980 (m), 1730 (st), 1616 (m), 1573 (w), 1455 (m), 1368 (m), 1325 (s), 1150 (s). MS m/z (relative intensity): [M+NH_4^+]=318 (100): 262 (67); 228 (5); 199 (18); 115 (11); 77 (6.5). HRMS ($C_{16}H_{19}F_3O_2$+NH_4^+) *calc.*: 318.1681, *found:* 318.1676.



4-(4-Chloro-phenyl)-4-pentenoic acid *tert.*butylester 61c

Following **GP2** 982 mg (4.20 mmol) **59** was converted into 660 mg (60%) 4-(4-chloro-phenyl)-4-pentenoic acid *tert.*butylester **61c** (after flash chromatography as described). ^{1}H-NMR δ/ppm ($CDCl_3$, 400 MHz): 7.40-7.28 (m, 4H, C7/8-*H*, C9/10-*H*), 5.20 (s, 1H, C5-*H*), 5.02 (s, 1H, C5-*H*), 2.69 (t, J=7.6 Hz, 2H, C3-*H*), 2.30 (t, J=7.7 Hz, 2H, C2-*H*), 1.36 (s, 9H, C13/14/15-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 100 MHz): 178.4 (1C, C1), 146.0 (1C, C4), 139.2 (1C, C9), 133.3 (1C, C6), 129.0 (2C, C7, C11), 128.4 (2C, C8, C10), 113.2 (1C, C5), 80.4 (1C, C12), 34.2 (1C, C3), 30.5 (1C, C2), 28.1 (3C, C13/14/15). IR (neat) $\tilde{\nu}$ /cm^{-1}: 3083 (m), 2978 (m), 1729 (st), 1628 (m), 1492 (m), 1455 (m), 1148 (s). MS m/z (relative intensity): 284 (40) [M+NH_4^+], 228 (100), 194 (18), 165 (8), 108 (18), 91 (13). HRMS ($C_{15}H_{19}ClO_2$+NH_4^+) *calc.*: 284.1417, *found:* 284.1426.

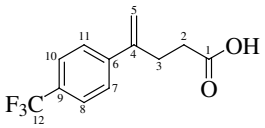


4-Tolyl-4-pentenoic acid 62a

280 mg (1.28 mmol) 4-(4-methyl-phenyl)-4-pentenoic acid ethyl ester **61-a** have been stirred for 10 hours in a 1 M solution of LiOH*H_2O in EtOH (60%). After evaporation, dilution with water and extraction with CH_2Cl_2, the organic extracts were dried over $MgSO_4$ and evaporated to give a crude yield of 240 mg. Recrystallized from petrolether 4-tolyl-4-pentenoic acid **62a** was obtained in 55% yield (90 mg).

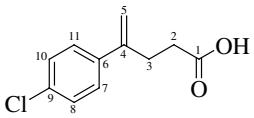
^{1}H-NMR δ/ppm ($CDCl_3$, 400 MHz): 7.31 (d, J=7.8 Hz, 2H, C7/C11-*H*), 7.16 (d, J=7.7 Hz, 2H, C8/C10-*H*), 5.31 (s, 1H, C5-*H*), 5.07 (s, 1H, C5-*H*), 2.84 (t, J=7.6 Hz, 2H, C2-*H*), 2.54 (t, J=8.1 Hz, 2H, C3-*H*), 2.36 (s, 3H, C12-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 100 MHz): 178.4 (1 C, C1), 146.2

(1 C, C4), 137.4 (1 C, C9), 137.3 (1 C, C6), 129.1 (2 C, C7/C11), 125.9 (2 C, C8/C10), 112.2 (1 C, C5), 33.0 (1 C, C3), 30.1 (1 C, C2), 21.1 (1 C, C12). IR (KBr) $\tilde{\nu}$ /cm^{-1}: 3066 (m), 3028 (m), 1693 (st), 1623 (m), 1514 (m), 1440 (m), 1415 (m), 1332 (m). MS m/z (relative intensity): [M$^+$]= 190 (48); 175 (7); 145 (100); 129 (31); 115 (48); 105 (24). HRMS ($C_{12}H_{14}O_2$+NH_4^+) *calc.:* 208.1338, *found:* 208.1331.



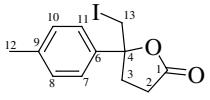
4-(4-Trifluoromethyl-phenyl)-4-pentenoic acid 62b

270 mg (1.10 mmol) **60b** and 10 g of silica were refluxed in toluene for two hours. After filtration over celite, a basic extraction with 1N NaOH and 1N HCl yielded 280 mg 4-(4-trifluoromethyl-phenyl)-4-pentenoic acid **62b** (93%). ^{1}H-NMR δ/ppm ($CDCl_3$, 400 MHz): 11.0 (s, 1H, OH), 7.50 (d, J=8.4 Hz, 2H, C8/10-*H*), 7.40 (d, J=8.4 Hz, 2H, C7/11-*H*), 5.30 (s, 1H, C5-*H*), 5.12 (s, 1H, C5-*H*), 2.76 (t, J=7.8 Hz, 2H, C2-*H*), 2.44 (t, J=8.0 Hz, 2H, C3-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 100 MHz): 179.4 (1 C, C1), 145.4 (1 C, C6), 144.0 (1 C, C4), 129.7 (q, 1 C, $^2J_{C,F}$=32 Hz, C9), 126.4 (2 C, C8/C10), 125.4 (2 C, C7/C11), 124.1 (q, 1 C, $^1J_{C,F}$=270 Hz, C12), 114.9 (C5), 32.3 (1 C, C3), 29.9 (1 C, C2). IR (neat) $\tilde{\nu}$ /cm^{-1}: 3056, 3025, 1697, 1626, 1572, 1541, 1444, 1404, 1340, 1182, 1139. MS m/z (relative intensity): 244 (1) [M$^+$], 225 (30), 199 (100), 151 (6), 115 (53), 91 (4). HRMS *calc.*($C_{12}H_{11}F_3O_2$+NH_4^+): 262.1055, *found:* 262.1060.



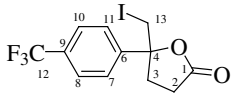
4-(4-Chloro-phenyl)-4-pentenoic acid 62c

500 mg (2.0 mmol) **62c** and 10 g of silica were refluxed in toluene for two hours. After filtration over celite, a basic extraction with 1N NaOH and 1N HCl yielded 250 mg 4-(4-chloro-phenyl)-4-pentenoic acid **62c** (60%). ^{1}H-NMR δ/ppm ($CDCl_3$, 400 MHz): 7.22 (m, 4H, C7/8-*H*, C9/10-*H*), 5.24 (s, 1H, C5-*H*), 5.05 (s, 1H, C5-*H*), 2.84 (t, J=7.6 Hz, 2H, C3-*H*), 2.45 (t, J=7.3 Hz, 2H, C2-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 100 MHz): 178.8 (1 C, C1), 145.4 (1 C, C4), 138.8 (1 C, C9), 133.5 (1 C, C6), 128.6 (2 C, C7/C11), 127.4 (2 C, C8/C10), 113.5 (1 C, C5), 32.7 (1 C, C3), 30.0 (1 C, C2). IR (neat) $\tilde{\nu}$ /cm^{-1}: 3066 (m), 2926 (m), 1689 (st), 1629 (m), 1494 (m), 1413 (m). MS m/z (relative intensity): 210 (4) [M$^+$], 195 (72), 167 (11), 155 (25), 149 (51), 141 (17), 139 (43), 111(18), 91 (13), 75 (27), 40 (100). HRMS ($C_{11}H_{11}ClO_2$) *calc.*: 210.0448, *found:* 210.0449.



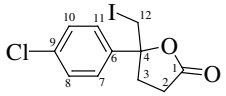
5-Iodomethyl-5-p-tolyl-dihydrofuran-2-one 63a

Following **GP1** 5-iodomethyl-5-p-tolyl-dihydrofuran-2-one **63a** was prepared on an analytical scale. ^{1}H-NMR δ/ppm ($CDCl_3$, 400 MHz): 7.13 - 7.28 (m, 4H, C7/8/10/11-*H*), 3.54 (s, 2H, C13-*H*), 2.42 - 2.70 (m, 4H, C2/3-*H*), 2.29 (s, 3H, C12-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 100 MHz): 175.9 (1 C, C1), 137.9 (1 C, C9), 135.2 (1 C, C6), 129.9 (2 C, C8/C10), 125.2 (2 C, C7/C11) , 85.6 (1 C, C4), 34.2 (1 C, C2), 29.6 (1 C, C3), 21.1 (1 C, C12), 15.7 (1 C, C13). IR (neat) $\tilde{\nu}$ /cm^{-1}: 3026 (m), 3016 (m), 3001 (m), 1778 (s), 1614 (m), 1513 (m), 1455 (m), 1414 (m), 1315 (m), 1294 (m), 1238 (m), 1153 (m). MS m/z (relative intensity): [M+H$^+$]=316 (1), 175 (18), 141 (100), 126 (92), 119 (43), 115 (40), 105 (24), 91 (76), 89 (66), 77 (34), 65 (61), 63 (74). HRMS ($C_{12}H_{13}IO_2$) *calc.*: 315.9960, *found:* 315.9928. Separation of the enantiomers by HPLC (hexane:2-propanol = 8:2); Chiralcel OD-H; 0.5 ml*min^{-1}; 272 nm; R_f(first enantiomer)=17.9 min; R_f(second enantiomer)=19.8 min.



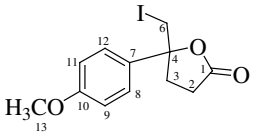
5-Iodomethyl-5-(4-trifluoromethyl-phenyl)-dihydrofuran-2-one 63b

5-Iodomethyl-5-(4-trifluoromethyl-phenyl)-dihydrofuran-2-one **63b** was prepared on an analytical scale according to **GP1**. ^{1}H-NMR δ/ppm ($CDCl_3$, 400 MHz): 7.68 (d, J=8.4 Hz, 2H, C8/C10-*H*), 7.54 (d, J=8.4 Hz, 2H, C11/C7-*H*), 3.60 (s, C13-*H*), 2.52-2.84 (m, 4H, C2/C3-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 100 MHz): 174.8 (1 C, C1), 144.7 (1 C, C6), 129.7 (q, $^{2}J_{C,F}$=33 Hz, C9), 129.0 (2 C, C8/C10), 124.1 (q, $^{1}J_{C,F}$=270 Hz, C12), 125.4 (2 C, C11/C7), 85.5 (1 C, C4), 34.0 (1 C, C3), 29.0 (1 C, C2), 15.1 (1 C, C13). IR (neat) $\tilde{\nu}$ /cm^{-1}: 3480, 2960, 2884, 1787, 1726, 1460, 1413, 1328, 1168, 1126, 1069. MS m/z (relative intensity): 244 (1) [M-I$^+$], 179 (5), 151 (10), 128 (16), 115 (15), 87 (21), 75 (60), 73 (100), 60 (81). HRMS ($C_{12}H_{10}F_3IO_2$+H$^+$): *calc*: 370.9755, *found*: 370.9763. Separation of the enantiomers by HPLC (hexane:2-propanol = 8:2); Chiralcel OD-H; 0.5 ml*min^{-1}; 272 nm; R_f(first enantiomer)=24.3 min; R_f(second enantiomer)=26.9 min.



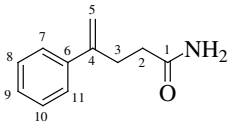
5-(4-Chloro-phenyl)-5-iodomethyl-dihydrofuran-2-one 63c

Compound 5-(4-chloro-phenyl)-5-iodomethyl-dihydrofuran-2-one **63c** was obtained following **GP1** on an analytical scale. ^{1}H-NMR δ/ppm ($CDCl_3$, 400 MHz): 7.28 (m, 4H, arH-*H*), 3.54 (d, J=11.1 Hz, 1H, C12-*H*), 3.50 (d, J=11.1 Hz, 1H, C12-*H*) , 2.59 (m, 4H, C2/3-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 100 MHz): 175.0 (1 C, C1), 139.1 (1 C, C9), 134.6 (1 C, C6), 129.0 (2 C, C11/C7), 126.4 (2 C, C10/C8), 85.6 (1 C, C4), 33.8 (1 C, C3), 29.1 (1 C, C2), 15.6 (1 C, C12). IR (neat) $\tilde{\nu}$ /cm^{-1}: 3045, 3015, 2955, 1781, 1599, 1491, 1454, 1414, 1241, 1151. MS m/z (relative intensity): 336 (5) [M$^+$], 209 (23), 195 (100), 167 (15), 151 (6), 139 (32), 125 (27), 115 (8), 102 (7), 89 (8), 75 (7), 55 (6). HRMS ($C_{11}H_{10}ClIO_2$+NH_4^+): *calc*: 353.9758, *found*: 353.9760. Separation of the enantiomers by HPLC (hexane:2-propanol = 8:2); Chiralcel OD-H; 0.5 ml*min^{-1}; 272 nm; R_f(first enantiomer)=33.1 min.; R_f(second enantiomer)=35.6 min.



5-Iodomethyl-5-(4-methoxy-phenyl)-dihydro-furan-2-one 63d

The reaction was carried out according to **GP1** using 4-(2-methoxy)phenylpent-4-enoic acid **54** (14.6 mg, 0.071 mmol), (*R*)-1,2,3,4-tetrahydro-1-naphtylamine **15** (41 μl, 0.285 mmol) and ICl (145 μl, 1 M in CH_2Cl_2). The crude was purified by preparative TLC with 2:5=TBME:pentane and the γ-lactone **63d** (36.9 mg, 48%) was isolated as a pale yellowoil.^{1}H-NMR δ/ppm ($CDCl_3$, 300 MHz): 7.32 (d, J=6.7 Hz, 2H, C12-*H*, C8-*H*), 6.90 (d, J=6.7 Hz, 2H, C9-*H*, C11-*H*), 3.81 (s, 3H, C13-*H*), 3.60 (m, 2H, C6-*H*), 2.66 (m, 4H, C2-*H*, C3-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 75 MHz): 175.3 (1 C, C1), 159.6 (1 C, C10), 132.3 (1 C, C7), 126.2 (2 C, C8, C12), 114.1 (2 C, C9, C11), 85.9 (1 C, C4), 55.3 (1 C, C13), 33.7 (1C, C2), 29.2 (1C, C3), 16.5 (1C, C6). IR (neat) $\tilde{\nu}$ /cm^{-1}: 2939 (m), 2837 (m), 1778 (st), 1613 (st), 1585 (m), 1503 (m). MS m/z (relative intensity): 332 (9%) [M$^+$], 191 (100%) [M-CH_2I]. HRMS ($C_{12}H_{13}IO_3$) *calc*: 331.9909 *found*: 331.9896. The enantiomeric excess was analysed on chiral HPLC (Daicel OD-H) using a mixture of 10% 2-propanol in hexane (R_f(first enantiomer)= 29.4 min.; R_f(second enantiomer)=32.9 min.).



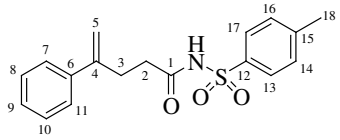
4-Phenyl-4-pentenamide 64

2.01 g (11.4 mmol) 4-phenyl-4-pentenoic acid 2 and 1 drop DMF in 120 ml toluene were cooled to 0 °C under argon. 2.46 g (19.4 mmol) Oxalyl chloride was added dropwise. The flask was warmed to room temperature and stirred for 1 hour. Product was dried through $MgSO_4$ and was concentrated by rotary evaporation. The acid chloride was dissolved in 120 ml THF, the flask was fitted with a gas condensation apparatus and cooled to -78 °C. Gaseous ammonia was condensed onto the reaction for several minutes. The reaction was then allowed to warm to room temperature. The product was poured into 120 ml water and extracted five times with chloroform, then dried over $MgSO_4$. Purification by flash chromatography gave 1.83 g of 4-phenyl-4-pentenamide **64** (92%).

^{1}H-NMR δ/ppm ($CDCl_3$, 300 MHz): 7.42-7.24 (m, 5 H, C7-C11-*H*); 5.94-5.82 (s, 1 H, N-*H*); 5.55-5.48 (s, 1 H, N-*H*) 5.31 (1 H, s, C5-*H*); 5.12 (s, 1 H, C5-*H*); 2.85 (t, 7.8 Hz, 2 H, C3-*H*); 2.35 (t, 7.8 Hz, 2 H, C2-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 75 MHz): 174.93 (1 C, C1); 146.91 (1 C, C4); 140.33 (1 C, C6); 128.41 (2 C, C8, C10); 127.62 (1 C, C9); 126.06 (2 C, C7, C11); 116.11 (1 C, C5); 34.53 (1 C, C2); 30.84 (1 C, C3). IR $\tilde{\nu}$ /cm^{-1}: 3388.4 (s), 3185.8 (m), 2959.3 (w), 2915.1 (w), 1654.7 (s), 1623.5 (m), 1443.6 (m), 1414.8 (m), 901.8 (s), 779.8 (m), 702.6 (s). MS (m / z) (relative intensity): [M$^+$]=176 (100); [M- NH_2]$^+$=159 (9.5); [M - $CONH_2$]$^+$=131 (23.0); [M - $CH_2CONH_2^1$]=117 (9.4); 91 (12.6); 77 (7.5); 55 (9.5). HRMS ($C_{11}H_{13}NO$+H$^+$): *calc*: 176.1030, *found*:176.1078. mp 112-114 °C.

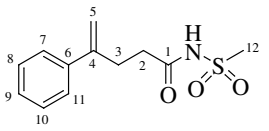
***N*-(4-Phenyl-4-pentenoyl)-4-toluolsulfonamide 67** and ***N*-(4-Phenyl-4-pentenoyl)-methylsulfonamide 68**

4-phenyl-4-pentenoic acid **2** (400 mg, 2.27 mmol) was dissolved in 5 ml THF. Carbonyldiimidazole (CDI 368 mg, 2.27 mmol) was added dropwise in 5 ml THF. The reaction was stirred for 30 minutes, then heated to reflux for 30 minutes and cooled to room temperature. 428 mg (2.5 mmol) *p*-toluenesulfonamide (methanesulfonamide) was added in one portion and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU / 339 μl, 2.27 mmol) was dissolved in 2 ml THF and added. The product was poured onto 1 M HCl and extracted three times with TBME. The extracts were dried over $MgSO_4$ and concentrated by rotary evaporation. Flash chromatography with 1:2=ethylacetate:pentane and 100:1 CH_2Cl_2/methanol successively yielded 367 mg (50%) of **67** (**68:** 430 mg, 75%).



***N*-(4-Phenyl-4-pentenoyl)-4-toluolsulfonamide 67**

^{1}H-NMR δ/ppm ($CDCl_3$, 300 MHz): 7.92 (d, 8.4 Hz , 2 H, C13-*H*, C17-*H*); 7.30-7.23 (m, 7 H, C7-C11-*H*, C14-C16-*H*); 5.20 (s, 1 H, C5-*H*); 4.96 (s, 1 H, C5-*H*); 2.71 (t, 8.4 Hz, 2 H, C3-*H*); 2.39 (m, 5 H, C2-*H*, N-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 75 MHz): 170.71 (1 C, C1); 145.89 (1 C, C4); 144.97 (1 C, C15); 139.91 (1 C, C12); 135.42 (1 C, C6); 129.48 (2 C, C14, C18); 128.77 (1 C, C9); 128.30 (2 C, C8, C10); 127.56 (2 C, C7, C11); 125.85 (2 C, C13, C17); 113.11 (1 C, C5); 34.87 (1 C, C2); 29.48 (1 C, C3); 21.53 (1 C, C18). IR $\tilde{\nu}$ /cm^{-1} 3346.0 (s), 1826.4 (w), 1712.3 (s), 1495.8 (m), 1428.2 (s), 1440.1 (s), 1340.2 (s), 1477.0 (s), 1113.9 (s), 1085.8 (s), 1038.0 (m), 911.3 (s), 850.1 (s), 815.3 (s), 778.6 (m), 704.4 (s), 666.3 (s). MS (m/z) (relative intensity): [M$^+$]=330 (100); [M - $SO_2C_7H_7^+$]=174 (37.6); [$SO_2C_7H_7^+$]=155 (24.7); [M - $COSO_2C_7H_7^+$]=131 (28.4); 117 (12.1); 103 (10.0); 91 (58.1); 77 (20.2); 55 (25.6); 43 (17.9). HRMS ($C_{18}H_{19}NO_3S$+H$^+$): *calc*: 330.1119, *found*: 330.1161. mp 74-76 °C.



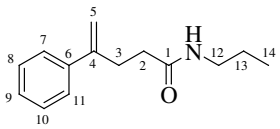
***N*-(4-Phenyl-4-pentenoyl)-methylsulfonamide 68**

^{1}H-NMR δ/ppm ($CDCl_3$, 300 MHz): 7.41-7.26 (m, 5H, C7-C11-*H*); 5.34 (s, 1 H, C5-*H*); 5.12 (s, 1 H, C5-*H*); 3.21 (s, 3 H, C12-*H*); 2.88 (t, 7.8 Hz, 2 H, C3-*H*); 2.46 (t, 7.8 Hz, 2 H, C2-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 75 MHz): 171.28 (1 C, C1); 146.08 (1 C, C4); 139.83 (1 C, C6); 128.58 (2 C, C8, C10); 127.90 (1 C, C9); 126.09 (2 C, C7, C11); 113.86 (1 C, C5); 41.46 (1 C, C12); 35.33 (1 C, C2); 29.92 (1 C, C3). IR $\tilde{\nu}$ /cm^{-1}: 3246.0 (s), 3081.7 (w), 3051,6 (w), 3030.6 (m), 2983.2 (w), 2932.4 (w), 2883.2 (w), 1811.4 (w), 1717.8 (s), 1700.0 (s), 1626.0 (m), 1465.8 (s), 1401.9 (s), 1332.0 (s), 1181.8 (s), 1126.2 (s), 980.1 (m), 901.2 (m), 894.2 (m), 868.9 (m), 779.3 (m), 518.0 (m), 509.4 (m).

MS (m/z) (relative intensity): [M^+]=254 (100); [M - $SO_2CH_3^+$]=174 (9.1); [M - $HNSO_2CH_3^+$]=159 (27.4); [M - $CONHSO_2CH_3^+$]=131 (34.4); [M - $H_2CCONHSO_2CH_3^+$]=117 (14.0); 91 (16.8); 89 (10.0). HRMS ($C_{12}H_{15}NO_3S+H^+$): *calc*, 254.0806, *found*: 254.0851. mp 121-124 °C.

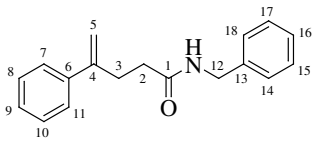
_N_-Propyl-4-phenyl-4-pentenamide 69 and **_N_-Benzyl-4-phenyl-4-pentenamide 70**

A catalytic amount of DMAP (0.227 mmol) was dissolved in 2 ml CH_2Cl_2 and cooled to 0°C. The coupling agent *N*-(3-dimethylaminopropyl)-*N*'-ethyl-carbondiimide hydrochloride (EDCI) (436 mg, 2.27 mmol) was dissolved in 5 ml CH_2Cl_2 and dripped onto the reaction, with a 2 ml CH_2Cl_2 wash. 4-phenyl-4-pentenoic acid **2** (400 mg, 2.27 mmol) was added dropwise in 5 ml CH_2Cl_2. One equivalent propyl amide (205 μl, 2.27 mmol) [benzylamide 273μl, 2.27 mmol] was added slowly to the reaction. The mixture was warmed slowly to room temperature over 2 hours, poured into water and extracted three times with CH_2Cl_2. Organic extracts were combined, washed with brine, and dried with $MgSO_4$. Product was concentrated by rotary evaporation and purified by flash chromatography with an eluant of 1:1 TBME/pentane yielded 346 mg (70%) **69** [400 mg 66% **70**].



_N_-Propyl-4-phenyl-4-pentenamide 69

^{1}H-NMR ($CDCl_3$, δ/ppm): 7.41-7.23 (m, 5 H, C7-C11-*H*); 5.74(s, 1 H, N-*H*); 5.29 (s, 1 H, C5-*H*); 5.09 (s, 1 H, C5-*H*); 3.15 (q, 6.6 Hz, 2 H, C12-*H*); 2.85 (t, 8.1 Hz, 2 H, C3-*H*); 2.29 (t, 8.1 Hz, 2 H, C2-*H*); 1.50-1.43 (m, 2 H, C13-*H*); 0.89 (3 H, t, C14-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 75 MHz): 172.15 (1C, C1); 147.07 (1 C, C4); 140.36 (1 C, C6); 128.28 (2 C, C8, C10); 127.47 (1 C, C9); 125.98 (2 C, C7, C11); 112.88 (1 C, C5); 41.09 (1 C, C12); 35.32 (1 C, C3); 31.11 (1 C, C2); 22.72 (1 C, C13); 11.26 (1 C, C14). IR $\tilde{\nu}$ /cm^{-1}: 3302.8 (s), 3079.5 (m), 2957.7 (s), 2871.8 (s), 1955.9 (w), 1893.6 (w), 1797.8 (w), 1638.0 (s), 1542.1 (s), 1492.2 (m), 1444.1 (s), 1372,4 (m), 1339.5 (m), 1263.1 (m), 1231.6 (m), 1169.1 (s), 1025,44 (m), 895.3 (s), 776.6 (s), 703.8 (s). MS (m / z) (relative intensity): [M^+]=218 (100); [M - $CONHiPr^+$]=132 (16.0); [M - $CH_2CONHiPr^+$]=117 (7.0); [M - H_3NiPr^+]=60 (12.7); 55 (11.7); 43 (33.7). HRMS ($C_{14}H_{19}NO+H^+$): *calc*: 218.1500, *found*: 218.1548. mp 54-56 °C.



_N_-Benzyl-4-phenyl-4-pentenamide 70

^{1}H-NMR ($CDCl_3$, δ/ppm): 7.36-7.18 (m, 10 H, C7-C11-*H*, C14-C18-*H*); 6.04 (s, 1 H, N-*H*); 5.26 (s, 1 H, C5-*H*); 5.06 (s, 1 H, C5-*H*); 4.32 (d, 5.4 Hz, 2 H, C12-*H*); 2.83 (t, 7.5 Hz, 2 H, C3-*H*); 2.30 (t, 7.5 Hz, 2 H, C2-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 75 MHz): 172.07 (1 C, C1); 146.91 (1 C, C4); 140.28 (1 C, C13); 138.20 (1 C, C6); 128.47 (2 C, C8, C10); 128.29 (2 C, C15, C17); 127.64 (2 C,

C14, C18); 127.47 (1 C, C9); 127.28 (1 C, C16); 125.97 (2 C, C7, C11); 113.01 (1 C, C5); 43.38 (1 C, C12); 35.16 (1 C, C2); 31.01 (1 C, C3). IR $\tilde{\nu}$ /cm^{-1}: 3297.7 (s), 3049.9 (m), 2946.7 (m), 1951.7 (w), 1880.9 (w), 1804.6 (w), 1786.3 (w), 1752.2 (w), 1631.9 (s), 1551.4 (s), 1493.3 (m), 1453.8 (m), 1381.4 (m), 1223.0 (m), 1160.3 (m), 1075.1 (m) 1029.4 (m), 995.6 (m), 889.9 (s), 778.0 (s), 747.4 (s), 694.5 (s). MS (m / z) (relative intensity): [M+H$^+$]=266 (79.7); [$CH_2CONHBn^+$]=147 (5.4); [M - $CONHBn^+$]=131 (10.3); [M- $CH_2CONHBn^+$]=117 (6.7); [$NHBn^+$]=106 (11.3); [Bn^+]=91. HRMS ($C_{18}H_{19}NO$): *calc*: 265.1467, *found*: 265.1543. mp 88-90 °C.

cis-3-Hexenylbromide 73

4.60 g (17.0 mmol) PBr_3 were weight into a threenecked flask, a mixture of 4.30 g (42.0 mmol, 5 ml) *cis*-3-hexenol **72** and 1.20 g (15.0 mmol) pyridine were slowly added at 0 °C. After standing for 3.5 h, water was added and the aqueous phase was extracted three times with CH_2Cl_2. Drying over $MgSO_4$ and purification using Kugelrohr destillation yielded 3.00 g (44%) of *cis*-3-hexenylbromide **73**.
For experimental data see reference.[112]

cis-4-Heptenoic acid 74

For preparation and spectral data see reference.[113]

2-Iodo-1-(4-furanon)-propan 75

Following **GP1** 0.03 g (0.23 mmol) **74** were converted into **75** yielding 0.04 g (80%). Conditions to separate enantiomers: column: γ-CD, 60kPa, 100-160 °C, rate: 1°/min; retention times: 54 min, 56 min. resp. For spectral data see reference.[8]

4-Methylpent-4-enoic acid 77

Under argon, sodium hydride (1.94g, 48.5 mmol, 60% in dispersion in oil) and 67 ml of DMSO were heated at 80 °C for 30 min. and then cooled to r.t. before adding 66 ml of THF and methyltriphenylphosphoniumbromide (17g, 47.5 mmol) in five portions. The resulting yellow suspension was stirred for an additional 30 min. A solution of levulinic acid (5g, 43 mmol) in 30 ml of THF was added to a suspension of sodium hydride (1.76g, 44 mmol, 60% in dispersion in oil) in 33 ml of THF. After stirring for 30 min., this solution was added to the above yellow suspension. The resulting mixture was refluxed for 4 hours. TBME was added and hydrolysation was achieved with a 1M HCl solution. The aqueous phase was extracted with TBME and the combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent, a yellow viscous oil was obtained which was further purified by flash chromatography over silicagel (10-40% TBME in pentane). 4-methylpent-4-enoic acid **77** (3.3g, 67%) was isolated as a yellow oil.
For spectral data see reference.[114]

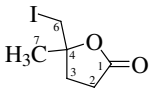
4-Isopropyl-pent-4-enoic acid ethyl ester 78

To a solution of ethyl 4-bromopent-4-enoate **58** (706 mg, 3.41 mmol) and 1% $Fe(acac)_3$ in a mixture of THF (4 ml) and NMP (3 ml, 29.3 mmol) was added dropwise (over 10 min.) at 0 °C a 2 M solution of isopropylmagnesium chloride in Et_2O (2.2 ml, 4.4 mmol). Stirring was continued for 30 min. then the reaction mixture was hydrolyzed with 1N HCl. The aqueous layer was extracted

with TBME and the combined organic phases were successively washed with a saturated aqueous $NaHCO_3$ solution, brine and dried over $MgSO_4$. Solvents were removed in vacuo and the product (277 mg, 47%) was isolated as a colorless oil, after purification by flash chromatography with 1% TBME in pentane. For spectral data see references.[115]

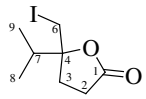
4-isopropyl-pent-4-enoic acid 79

For experimental and spectral data see reference.[114]



5-Iodomethyl-5-methyl-dihydro-furan-2-one 80a

The reaction was carried out following the general procedure using 4-methyl-4-pentenoic acid **77** (20.7 mg, 0.181 mmol), (*R*)-1,2,3,4-tetrahydro-1-naphtylamine (104 μl, 0.723 mmol) and ICl (370 μl, 0.37 mmol). The crude was purified by preparative TLC with TBME:Pentane/1:1 and the γ-lactone (26.3 mg, 60%) was isolated as a yellow pale oil. ^{1}H-NMR δ/ppm ($CDCl_3$, 300 MHz): 3.39 (m, 2 H, C6-*H*), 2.67 (m, 2 H, C2-*H*), 2.33 (m, 1 H, C3-*H*), 2.14 (m, 1 H, C3-*H*), 1.62 (s, 3 H, C7-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 75 MHz): 175.6 (1 C, C1), 83.7 (1 C, C4), 32.8 (1 C, C2), 29.3 (1 C, C3), 25.8 (1 C, C7), 14.1 (1 C, C7). IR (neat), $\tilde{\nu}$ /cm^{-1}: 2977 (m), 2933 (m), 1769 (st), 1453 (m), 1416 (m), 1380 (m), 1273 (st). MS m/z (relative intensity): 240 (11%) [M^+], 99 (100%) [M-CH_2I^+]. HRMS ($C_6H_9IO_2$) *calc.*: 239.9647, *found*: 239.9648. The enantiomeric excess was measured on chiral HPLC (Daicel, Chiraldex OB-H) using a mixture of 20% 2-propanol in heptane; R_f(first enantiomer)=31.7 min; R_f(second enantiomer)= 35.7 minutes.



5-Iodomethyl-5-isopropyl-dihydro-furan-2-one 80b

The reaction was carried out as in the general procedure using 4-isopropylpent-4-enoic acid **79** (40.4 mg, 0.284 mmol), (*R*)-1,2,3,4-tetrahydro-1-naphtylamine (170 μl, 1.18 mmol) and ICl (570 μl, 0.57 mmol).

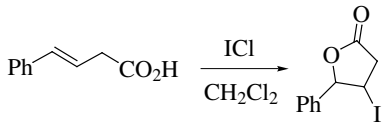
The crude was purified by preparative TLC with 30% TBME in pentane and the γ-lactone **80b** (36.9 mg, 48%) was isolated as a colorless oil. ^{1}H-NMR δ/ppm ($CDCl_3$, 300 MHz): 3.46 (m, 2 H, C6-*H*), 2.75 (m, 1 H, C3-*H*), 2.56 (m, 1 H, C3-*H*), 2.19 (m, 3 H, C7-*H*, C2-*H*), 0.99 (d, J=6.6 Hz, 3 H; C8-*H*), 0.98 (d, J=6 Hz, 3 H; C9-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 75 MHz): 176.0 (1 C, C1), 87.9 (1 C, C4), 35.6 (1 C, C7), 29.6 (1 C, C2), 28.4 (1 C, C3), 17.0 (1 C, C8), 16.9 (1 C, C9), 14.4 (1 C, C6). IR (neat): $\tilde{\nu}$ /cm^{-1}: 2968 (m), 1766 (st), 1469 (m), 1417 (m). MS m/z (relative intensity): 268 (6%) [M^+], 225 (100%) [M-$C_3H_7^+$]. HRMS ($C_8H_{13}IO_2$) *calc.*: 267.9960, *found*: 267.9953. The enantiomeric excess was measured on chiral HPLC (OD-H) using a mixture of 1% 2-propanol in hexane; R_f(first enantiomer)=33.3 min; R_f(second enantiomer)= 35.5 minutes.

4-Phenyl-but-3-enoic acid 83

Synthesised by addition of malonic acid to phenylacetaldehyde. Spectral data see reference.[116]

4-Iodo-5-phenyl-dihydro-furan-2-one 84

4-Iodo-5-phenyl-dihydro-furan-2-one **84** was synthesised from 110 mg (0.68 mmol) **83** by dissolving **83** in 2 ml CH_2Cl_2 and adding 810 μl ICl (1.2eq, 1 M in CH_2Cl_2) to obtain in (75% yield).[117] Compound **84** failed analysis by chiral HPLC or GC.[118]



83 **84**

5-Phenyl-dihydro-furan-2-one 85

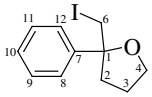
For preparation and spectral data see reference.[48]

4-oxo-4-phenyl-butyric acid methyl ester 87

For preparation see reference[49]. This compound is also commercially available from various major companies.

4-Phenyl-penten-4-ol 89

4-Phenyl-penten-4-ol **89** was prepared from **2** by a lithium aluminum hydride reduction in Et_2O. For spectroscopic data see reference.[119]



5-Phenyl-5-iodmethan-tetrahydrofuran 90

Following **GP1** compound **90** was prepared in 15% yield. The reaction was racemic using (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **15** as a ligand.

^{1}H-NMR δ/ppm ($CDCl_3$, 300 MHz): 7.39-7.20 (m, 5 H, C7-C11-*H*), 4.10-3.75 (m, 2 H, C4-*H*), 3.55 (d, 2 Hz, 1 H, C5-*H*), 2.37-2.25 (m, 2 H, C3-*H*), 2.11-1.70 (m, 2 H, C2-*H*). ^{13}C-NMR δ/ppm ($CDCl_3$, 75 MHz): 143.9 (1 C, C6), 128.2 (2 C, C7/C11), 127.2 (1 C, C9), 125.3 (2 C, C8/C10), 84.3 (1 C, C1), 68.4 (1 C, C4), 37.6 (1 C, C3), 26.2 (1 C, C2), 19.1 (1 C, C5). IR $\tilde{\nu}$ /cm^{-1}: 3260 (st), 3073 (w), 1684 (m), 1635 (st), 1557 (m), 1449 (m), 1221 (m); MS m/z (relative intensity): 254 [M+H$^+$](27%), 150 (13%), 105 (100%), 91 (7%), 73 (17%), 55 (18%).

(1-Chloro-2-iodo-ethyl)-benzene 92

Adapting **GP3** for use without MeOH and ICl directly (1-chloro-2-iodo-ethyl)-benzene **92** was prepared in 56 % yield, for spectral data see reference.[53]

2-Iodo-1-methoxy-ethyl-benzene 93

GP3 was modified to obtain 2-iodo-1-methoxy-ethyl-benzene **93** by mixing MeOH and CH_2Cl_2 prior to adding ICl and the styrene A 1:1.6 mixture of **92** to **93** was isolated in 65%, for experimental data see reference.[120]

2-Iodo-1-methoxy-1-methyl-ethyl-benzene 95a and **1-Iodo-2-methoxy-1-methyl-ethyl-benzene 95b**

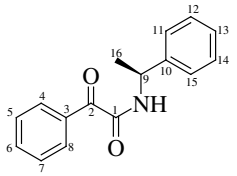
Following **GP3** was prepared, for experimental data see reference.[121]

1-Chloro-3-iodo-propyl-benzene 97a and 3-Chloro-1-iodo-propyl-benzene 97b

Following **GP3** was prepared, for experimental data see reference.[122]

Investigating the reaction of ICl and (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **15**:

71 μl ($4.92*10^{-1}$ mmol) (*R*)-1,2,3,4-Tetrahydro-1-naphthylamine **15** and 246 μl ($2.46*10^{-1}$ mmol) of a 1M solution of ICl in CH_2Cl_2 was stirred at r.t. for 2.5 hours. After addition of 5 ml 10% aqueous $Na_2S_2O_3$ solution and extracting three times with CH_2Cl_2, the organic layers were combined and dried over $MgSO_4$. Purification by preperative TLC (TBME:Pentane=2:1) gave 15 mg (21%) of tetralone (**98**).



2-Oxo-2-phenyl-*N*-(1-phenyl-ethyl)-acetamide 99

368 mg ICl (2.30 mmol) and 550 mg *R*-1-phenylethylamine **12** (4.59 mmol) were dissolved in CH_2Cl_2 and after cooling down to -78 °C for 30 minutes, 200 mg **2** ($1.14*10^{-1}$ mmol) were dissolved in a separate flask and added. After waiting for 30 minutes the reaction was allowed to warm up to room temperature. The reaction mixture was extracted twice with 0.5N HCl to remove the amine, the organic layers were combined and 2 ml of 10%-aqueous $Na_2S_2O_3$ solution was added. After separating the phases the solution was extracted with 1 N NaOH, but no starting material could be detected. After flash chromatography of the crude reaction mixture (370 mg) with a 1:2 mixture TBME:pentane yielded *S*-**3** (76%) and **99** (3%). For spectral data see reference.[123]

6.3 Abbreviations

$[\alpha]_D^{25}$	optical rotation (at 25 °C, υ=589 nm)
abs.	absolute
Ar	aryl moiety
^{t}Bu	*tert.*-butyl
Boc	*tert.*-butyloxycarbonyl
c	concentration
CDI	carbonyldiimidazole
conc.	concentrated
CPCM	conductor polarizable continuum model
δ	chemical shift in ppm, TMS was used as reference signal at 0.0 ppm
DMAP	dimethylaminopyridine
DMSO	dimethyl sulfoxide
EA	elemental analysis / microanalysis
EDCI	*N*-(3-dimethylaminopropyl)-*N*'-ethyl-carbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact ionisation (MS)
EtOH	ethanol
HPLC	high performance liquid chromatography
HV	high vacuum($5*10^{-2}$-10^{-3} mbar)
IR	infrared spectroscopy/spectra
J	coupling constant in Hz
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine
mp	melting point
MS	mass spectrometry
Ms/mesyl	methanesulfonyl
NBO	natural bond orbitals
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
PES	potential energy hypersurface
Py	pyridine
r.t.	room temperature
R_f	retention factor
TBME	*tert.*-butylmethylether
Tf/triflyl	trifluoromethansulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin/thick layer chromatography
TMS	tetramethyl silane (NMR standard reference) or trimethylsilyl
Ts/tosyl	*para*-toluene sulfonyl

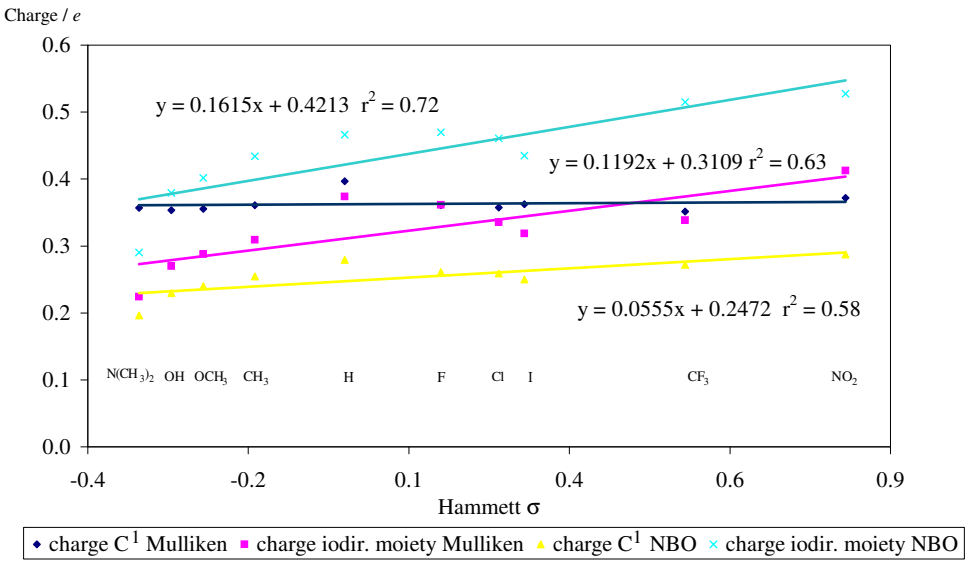
A Appendix A

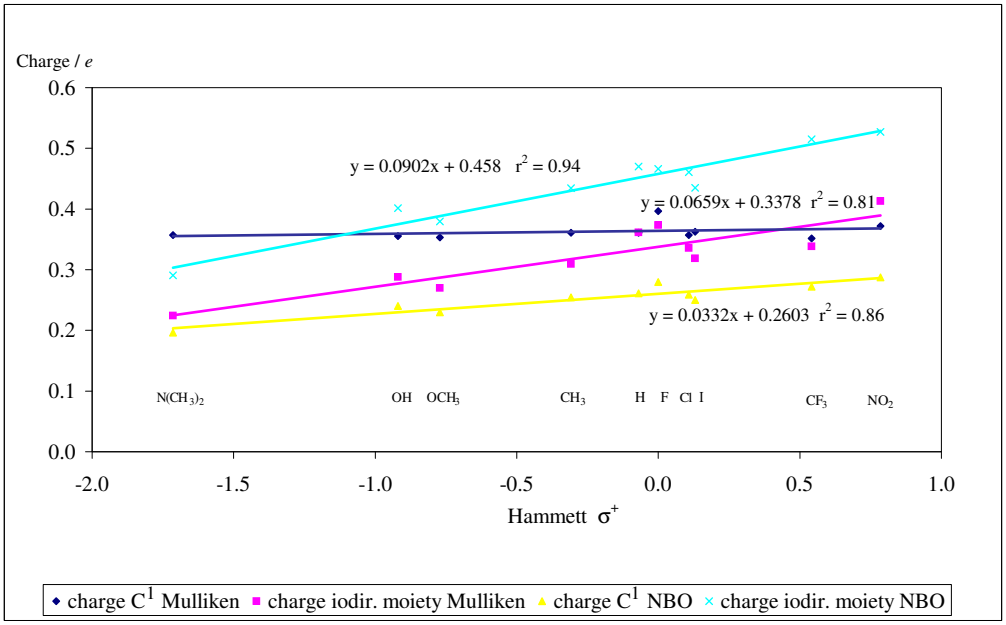
Further Data and Comments from Calculations B3LYP/LANL2DZ geometries of iodiranium ions **112** and **113**

B3LYP/LANL2DZ	C^1-I	B3LYP/LANL2DZ	C^1-I
112a	3.09	**112f**	2.98
112b	3.02	**112g**	2.98
112c	3.03	**112h**	2.99
112d	3.00	**112i**	2.98
112e	3.02	**112j**	2.97

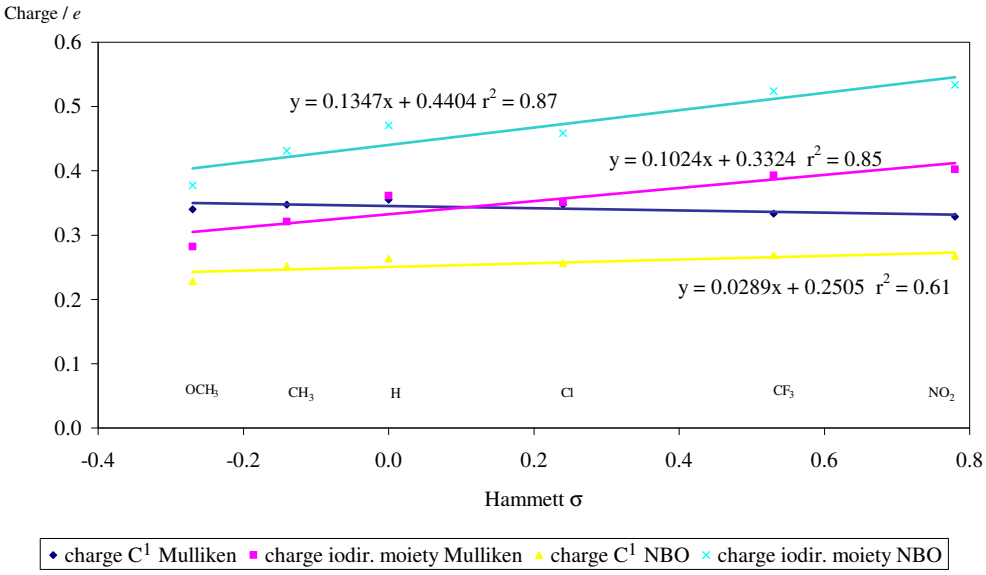
B3LYP/LANL2DZ	C^1-I	B3LYP/LANL2DZ	C^1-I
113a	3.02	**113d**	2.98
113b	3.00	**113e**	2.93
113c	2.97	**113f**	2.92

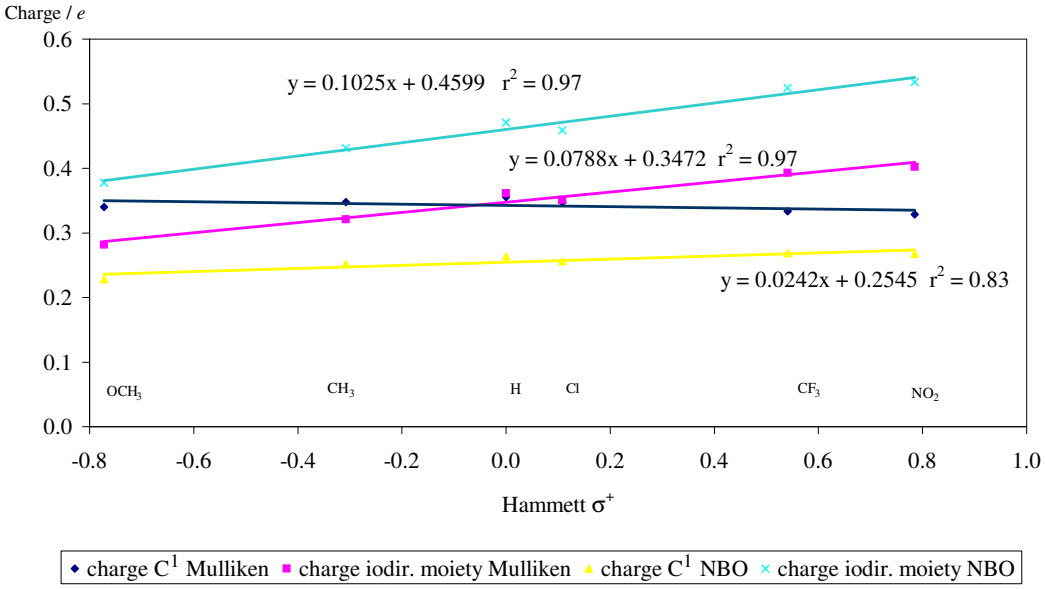
Further Hammett plots of iodiranium ions **112** at a B3LYP/LANL2DZ level of theory:





Further Hammett plots of iodiranium ions **113** at a B3LYP/LANL2DZ level of theory:

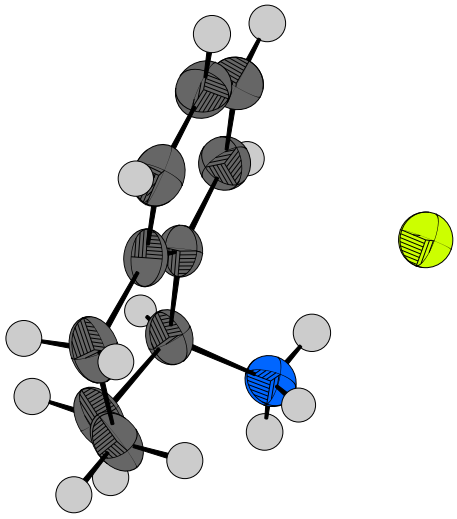



Charge / e
0.6
0.5
0.4
0.3
0.2
0.1
0.0
y = 0.1025x + 0.4599 r2 = 0.97
y = 0.0788x + 0.3472 r2 = 0.97
y = 0.0242x + 0.2545 r2 = 0.83
OCH3
CH3
H
Cl
CF3
NO2
-0.8
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
Hammett σ+
charge C1 Mulliken
charge iodir. moiety Mulliken
charge C1 NBO
charge iodir. moiety NBO

B Appendix B

X-ray Structures Upon crystallisation a crystal structure was obtained, but it turned out to be the HCl-salt of **15**, but in this way valuable information about the reaction pathway could be obtained as discussed above.

Experimental Crystal Data



formula: $C_{10}H_{14}ClN$

molecular weight
M_r =183.68 g*mol^{-1}

crystal system: orthorhombic

spacegroup: $P2_12_12_1$

a = 5.8592 (1) Å

b = 11.8976 (3) Å

c = 14.6031(3) Å

Volume = 1017.99 (4) Å^3

Z = 4

measured reflections = 3538

independent reflections = 3516

reflections in refinement = 2786

final R = 0.0336

weighted R = 0.0436

S = 1.0404

source of radiation Mo K_α

λ = 0.71073 Å

temperature = 293 K

crystal colour: colourless

crystal size: $0.48 \times 0.45 \times 0.25$ mm

Θ_{max} = 32.577

Table 1. Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters

	x	y	z	Ueq
$Cl1$	0.17018(5)	0.26350(3)	0.62962(2)	0.0523
$N1$	0.6742(2)	0.1700(1)	0.58250(8)	0.0470
$C1$	0.7262(2)	0.04857(12)	0.6042(1)	0.0477
$C2$	0.7620(3)	0.03522(17)	0.70662(12)	0.0622
$C3$	0.5377(3)	0.03174(17)	0.75758(11)	0.0624
$C4$	0.4008(3)	0.07038(16)	0.72700(11)	0.0603
$C5$	0.3833(2)	0.07922(11)	0.62419(11)	0.0478
$C6$	0.2130(3)	0.14508(13)	0.58441(14)	0.0589
$C7$	0.1957(3)	0.15695(14)	0.49077(14)	0.0649
$C8$	0.3500(3)	0.10352(14)	0.43408(12)	0.0617
$C9$	0.5200(3)	0.03792(13)	0.47157(11)	0.0538
$C10$	0.5378(2)	0.02443(11)	0.5664(1)	0.0447
$H1$	0.6630(2)	0.1772(1)	0.52184(8)	0.0500
$H2$	0.5320(2)	0.1920(1)	0.61246(8)	0.0500
$H3$	0.7940(2)	0.2102(1)	0.60288(8)	0.0500
$H11$	0.8705(2)	0.02356(12)	0.5739(1)	0.0549
$H21$	0.8534(3)	0.10017(17)	0.72992(12)	0.0740
$H22$	0.8462(3)	0.03635(17)	0.71880(12)	0.0740
$H31$	0.5638(3)	0.02943(17)	0.82523(11)	0.0709
$H32$	0.4486(3)	0.10069(17)	0.74158(11)	0.0709
$H41$	0.4801(3)	0.13892(16)	0.75066(11)	0.0671
$H42$	0.2439(3)	0.06614(16)	0.75369(11)	0.0671
$H61$	0.1021(3)	0.18493(13)	0.62511(14)	0.0659
$H71$	0.0708(3)	0.20369(14)	0.46378(14)	0.0749
$H81$	0.3399(3)	0.11314(14)	0.36617(12)	0.0719
$H91$	0.6320(3)	0.00150(13)	0.43107(11)	0.0626

Table 2. Anisotropic Displacement Parameters

	U11	U22	U33	U12	U13	U23
$Cl1$	0.03823(14)	0.06027(18)	0.05845(18)	0.00137(12)	0.00511(13)	0.00053(14)
$N1$	0.0345(4)	0.0552(6)	0.0511(6)	0.0018(5)	0.0029(5)	0.0016(4)
$C1$	0.0330(6)	0.0587(7)	0.0513(7)	0.0053(5)	0.0017(4)	0.0042(5)
$C2$	0.0455(7)	0.0831(11)	0.0580(9)	0.0036(7)	0.0148(6)	0.0105(8)
$C3$	0.056(1)	0.0880(12)	0.0430(7)	0.0126(8)	0.0042(6)	0.0061(7)
$C4$	0.0470(7)	0.079(1)	0.0545(8)	0.0084(7)	0.0046(6)	0.0177(7)
$C5$	0.0366(6)	0.0491(6)	0.0576(7)	0.0076(4)	0.0024(5)	0.0085(6)
$C6$	0.0457(8)	0.0509(7)	0.080(1)	0.0004(5)	0.0031(7)	0.0051(7)
$C7$	0.055(1)	0.0545(8)	0.0850(12)	0.0030(7)	0.0133(8)	0.0046(7)

$C8$	0.068(1)	0.0586(8)	0.0584(8)	0.0024(8)	0.0099(8)	0.0035(6)
$C9$	0.0570(8)	0.0530(7)	0.0514(7)	0.0004(6)	0.0010(6)	0.0027(6)
$C10$	0.0375(6)	0.0463(6)	0.0502(6)	0.0051(5)	0.0008(5)	0.0030(5)

Table 3. Selected Geometric Parameters

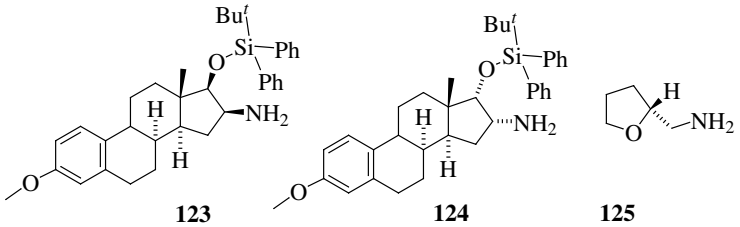
$N1-C1$	1.5101(18)	$C1-N1-H1$	108.42(7)	$C3-C4-H41$	107.75(9)
$N1-H1$	0.892	$C1-N1-H2$	109.51(7)	$C5-C4-H41$	108.58(8)
$N1-H2$	0.977	$H1-N1-H2$	110.851	$C3-C4-H42$	109.26(9)
$N1-H3$	0.900	$C1-N1-H3$	106.39(7)	$C5-C4-H42$	109.19(8)
$C1-C2$	1.518(2)	$H1-N1-H3$	109.521	$H41-C4-H42$	109.467
$C1-C10$	1.509(2)	$H2-N1-H3$	111.993	$C4-C5-C6$	120.14(14)
$C1-H11$	1.000	$N1-C1-C2$	109.58(13)	$C4-C5-C10$	121.58(13)
$C2-C3$	1.511(2)	$N1-C1-C10$	109.0(1)	$C6-C5-C10$	118.26(15)
$C2-H21$	1.000	$C2-C1-C10$	113.67(13)	$C5-C6-C7$	121.52(15)
$C2-H22$	1.000	$N1-C1-H11$	111.20(7)	$C5-C6-H61$	118.9(1)
$C3-C4$	1.523(3)	$C2-C1-H11$	106.79(8)	$C7-C6-H61$	119.6(1)
$C3-H31$	1.000	$C10-C1-H11$	106.54(7)	$C6-C7-C8$	119.97(15)
$C3-H32$	1.000	$C1-C2-C3$	111.58(12)	$C6-C7-H71$	120.1(1)
$C4-C5$	1.509(2)	$C1-C2-H21$	109.17(9)	$C8-C7-H71$	119.9(1)
$C4-H42$	1.000	$C3-C2-H21$	108.64(11)	$C7-C8-C9$	119.71(16)
$C4-H41$	1.000	$C1-C2-H22$	109.42(9)	$C7-C8-H81$	120.2(1)
$C5-C10$	1.3987(19)	$C3-C2-H22$	108.6(1)	$C9-C8-H81$	120.1(1)
$C6-C7$	1.379(3)	$H21-C2-H22$	109.467	$C8-C9-C10$	120.80(15)
$C6-H61$	1.000	$C2-C3-C4$	109.60(15)	$C8-C9-H91$	120.3(1)
$C7-C8$	1.381(3)	$C2-C3-H31$	110.75(8)	$C10-C9-H91$	118.90(9)
$C7-H71$	1.000	$C4-C3-H31$	110.39(8)	$C1-C10-C5$	121.37(13)
$C8-C9$	1.379(2)	$C2-C3-H32$	108.4(1)	$C1-C10-C9$	118.89(13)
$C8-H81$	1.000	$C4-C3-H32$	108.12(9)	$C5-C10-C9$	119.73(13)
$C9-C10$	1.398(2)	$H31-C3-H32$	109.467		
$C9-H91$	1.000	$C3-C4-C5$	112.55(13)		

If ICl (1M in CH_2Cl_2) was reacted with neat **15** a yellow powder was obtained, which powder diffraction was performed on, but unfortunately the solid obtained was too fine for a successful Rietveld analysis so no conclusions about the structure in this solid could be made. Recrystallisation attempts(EtOAc, Hexane and mixtures thereof) all lead to a decomposition of the solid.

C Appendix C

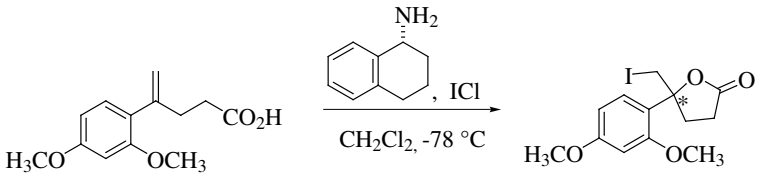
Further Experimental Data

Ligands: These are additional ligands which were tested in the lactonisation of **1** ⟶ **2**, but gave poor stereoselectivity or even racemic product (**123** 4% *ee*(S)-**3**, **124** 5% *ee* (R)-**3**, **125** 0% *ee* **3**).



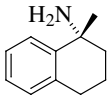
123 **124** **125**

The iodolactonisation of the 2,4-dimethoxy-phenyl analogue of **2** (**126**) to lactone **127** gave an enantioselectivity of 10% *ee*.



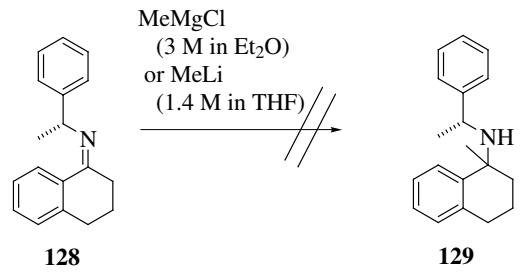
126 **127**

The preparation of amine **48** was tried unsuccessfully by the first three routes shown below.

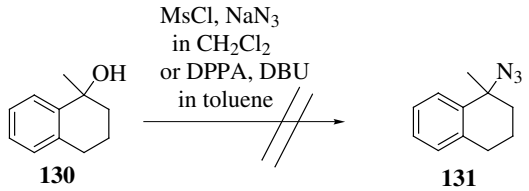


48

Compound **128** was reacted with either a solution of methylmagnesium chloride in Et_2O (3 M) or a solution of methyllithium in THF (1.4 M). No traces of **129** have been detected, upon addittion of either MeLi or methylmagnesiumbromide a formation of a gas was observed. Most likely the purity of **128** was the reason for the failure, because it was not possible to purify it bulb to bulb destillation.
the second attempt involved the conversion of 1-methyl-1-tetralol **130** into the corresponding azide **131**, but both methods applied failed also in variations such as lower temperature and different solvents.



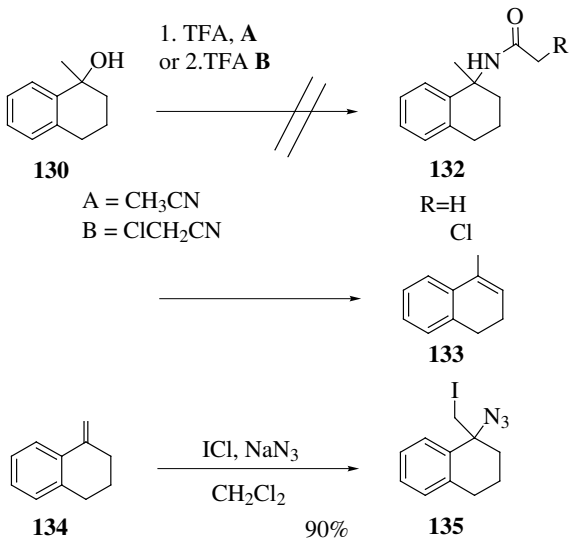
128 **129**



130 **131**

DPPA=Diphenyldiphosphorylazide

In case of the third route Ritter reactions of **130** were leading only to the elimination product **133** instead of yielding compound **132**.
A fourth way has been worked on successfully, where 1-methylene-1,2,3,4-tetrahydro-naphthalene **134** was converted to 1-azido-1-iodomethyl-1,2,3,4-tetrahydro-naphthalene **135** in a 1,2 addition of IN_3.



130 **132** **133** **134** **135**

This route remained unfinished at **135**.

References

[1] a) H. Stobbe, *Liebigs Ann. Chem.* **1899**, *308*, 77; b) H. Stobbe, *Liebigs Ann. Chem.* **1902**, *321*, 119; c) R. Fittig, *Liebigs Ann. Chem.* **1884**, *224*, 366; d) R. Fittig, E. Hjelt, *Liebigs Ann. Chem.* **1883**, *216*, 52; e) R. Fittig, *Liebigs Ann. Chem.* **1898**, *304*, 211; f) R. Fittig, *Liebigs Ann. Chem.* **1904**, *331*, 142.

[2] a) M. J. Bougault, *Compt. rend.* **1904**, *139*, 864; b) M. J. Bougault, *J. Ann. Chim. Phys.* **1908**, *14*, 145; c) M. J. Bougault, *J. Ann. Chim. Phys.* **1908**, *15*, 296; d) M. J. Bougault, *J. Ann. Chim. Phys.* **1911**, *22*, 125.

[3] a) E. J. Corey, J. Mann, *J. Am. Chem. Soc.* **1973**, *95*, 6832; b) S. Danishefsky, P. F. Schuda, T. Kitahara, S. J. Etheredge, *J. Am. Chem. Soc.* **1977**, *99*, 6066; c) C. Neukom, D. P. Richardson, J. H. Myerson, P. A. Bartlett, *J. Am. Chem. Soc.* **1986**, *108*, 5559; d) A. G. Schultz, J. S. Kirincich, *J. Org. Chem.* **1996**, *61*, 5626; e) M. Jung, J. Ham, J. Song, *Org. Lett.* **2002**, 4, 2763; f) J. C. Anderson, M. Whiting, *J. Org. Chem.* **2003**, *68*, 6160.

[4] A. R. Chamberlin, R. L., Jr., Mulholland, S. D. Kahn, W. J. Hehre, *J. Am. Chem. Soc.* **1987**, *109*, 672.

[5] a) E. E. van Tamelen, M. Shamma, *J. Am. Chem. Soc.* **1954**, *76*, 2315; b) L. do Amaral, S. C. Melo, *J. Org. Chem.* **1973**, *38*, 800; c) M. D. Dowle, D. I. Davies, *Chem. Soc. Rev.* **1979**, *8*, 171.

[6] a) J. H., III, McDonald, W. C. Still, *Tetrahedron Lett.* **1980**, *21*, 1031; Still, W. C., J. A. Schneider *Tetrahedron Lett.* **1980**, *21*, 1035. b) D. B. Collum, J. H., III, McDonald, W. C. Still, *J. Am. Chem. Soc.* **1980**, *102*, 2117; c) D. B. Collum, J. H., III, McDonald, W. C. Still, *J. Am. Chem. Soc.* **1980**, *102*, 2118; d) D. B. Collum, J. H., III, McDonald, W. C. Still, *J. Am. Chem. Soc.* **1980**, *102*, 2120; e) D. B. Collum, J. H., III, McDonald, W. C. Still, *J. Am. Chem. Soc.* **1980**, *102*, 2117; f) S. Najdi, D. Reichlin, M. J. Kurth, *J. Org. Chem.* **1990**, *55*, 6241; g) H.-S. Moon, S. W. E. Eisenberg, M. E. Wilson, N. E. Schore, M. J. Kurth, *J. Org. Chem.* **1994**, *59*, 6504; h) Wissner, Pat. US 5428167, **1995**; R. W. Hoffmann, R. Sturmer, K. Harms, *Tetrahedron Lett.* **1994**, *35*, 6263; i) K. Fuji, M. Node, Y. Naniwa, T. Kawabata, *Tetrahedron Lett.* **1990**, *31*, 3175.

[7] a) J. H. Schauble, J. W. Magee, R. D. Evans, *Synthesis* **1988**, 863; b) J. Barluenga, *Pure Appl. Chem.* **1999**, *71*, 431.

[8] R. B. Grossman, R. J. Trupp, *Can. J. Chem.* **1998**, *76*, 1233.

[9] R. S. Brown, X. L. Cui, *J. Org. Chem.* **2000**, *65*, 5653.

[10] J. Haas, Diploma Thesis **1999**, University of Basel.

[11] a) D. Lenoir, C. Chiappe, *Chem. Eur. J.* **2003**, *9*, 1037; b) R. Damrauer, M. D. Leavell, C. M. Hadad, *J. Org. Chem.* **1998**, *63*, 9476; c) H. Slebocka-Tilk, A. Neverov, S. Motallebi, R. S. Brown, O. Donini, J. L. Gainsforth, M. Klobukowski, R. S. Brown, *J. Am. Chem. Soc.* **1998**, *120*, 2578.

[12] In many commercial packages basis sets which include iodine, however, the standard option to treat the elements of the first two rows with polarized or diffused functions is not available. This leads to a variety of approaches for different fields of research, the results of which are therefore more difficult to compare.

[13] A. M. Lamsabhi, W. Bouab, M. Esseffar, M. Alcami, M. Yáñez, J.-L. M. Abboud, *New J. Chem.* **2001**, *25*, 509.

[14] a) E. Ruiz, D. R. Salahub, A. Vela, *J. Am. Chem. Soc.* **1995**, *117*, 1141; b) Y. Zhang, C.-Y. Zhao, X.-Z. You, *J. Phys. Chem. A* **1997**, *101*, 2879; c) D. Reha, M. Kabelac, F. Ryjacek, J. Sponer, J. E. Sponer, M. Elstner, S. Suhai, P. Hobza, *J. Am. Chem. Soc.* **2002**, *124*, 3366; d) D. Reha, M. Kabelac, F. Ryjacek, J. Sponer, J. E. Sponer, M. Elstner, S. Suhai, P. Hobza, *J. Am. Chem. Soc.* **2003**, *125*, 5581; e) X. Wang, C. Lu, A. Endou, M. Kubo, A. Miyamoto, *J. Organomet. Chem.* **2003**, *678*, 156.

[15] A. C. Legon, *Chem. Phys. Lett.* **1999**, *314*, 472.

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

[17] J. H. Schauble, J. W. Magee, R. D. Evans, *Synthesis* **1988**, 863.

[18] The actual configuration of the (−) and (+) enantiomers was assigned by comparison to the literature value of $[\alpha]_D^{25}$ after radical dehalogenation applying AIBN and Ph_3SnH; A. Albinati, P. Bravo, F. Ganazzoli, G. Resnati, F.

Viani, *J. Chem. Soc., Perkin Trans. 1* **1986**, 1405.

[19] J. Haas, Diploma Thesis **1999**.

[20] R. S. Brown, X. L. Cui, *J. Org. Chem.* **2000**, *65*, 5653.

[21] Ligand acceleration is a condition to achieve a catalytic cycle; a) E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schroeder, B. K. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968; b) E. N. Jacobsen, I. Marko, M. B. France, J. S. Svendsen, B. K. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 737; c) D. J. Berrisford, C. Bolm, B. K. Sharpless, *Angew. Chem. Int. Ed.* **1995**, *34*, 1059.

[22] a) J. Yarwoodl, W. B. Person, *J. Am. Chem. Soc.* **1968**, *90*, 3930; b) O. Hassel, C. Rømming, *Acta Chem. Scand.* **1956**, *10*, 696.

[23] O. Hassel, H. Hope, *Acta Chem. Scand.* **1960**, *2*, 391.

[24] E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, *J. Am. Chem. Soc.* **1991**, *113*, 7063.

[25] D. Hoppe, T. Hense, *Angew. Chem. Int. Ed.* **1997**, *36*, 2282.

[26] G. R. Sullivan, J. A. Dale, H. S. Mosher, *J. Org. Chem.* **1973**, *38*, 2143.

[27] D. W. Gokel, D. Marquarding, I. K. Ugi, *J. Org. Chem.* **1972**, *37*, 3052.

[28] A. Gutmann, M. Etinger, G. Nisnevich, F. Polyak, *Tetrahedron: Asymmetry* **1998**, *9*, 4369.

[29] A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253.

[30] Some additional ones are mentioned in appendix C.

[31] For different approaches see appendix C.

[32] O. Bortolini, M. Bottai, C. Chiappe, V. Conte, D. Pieraccini, *Green Chem.* **2002**, *4*, 621.

[33] At the moment commercial sources are quite expensive and preparation requires special equipment and sometimes is still not straightforward.

[34] S. T. Handy, *Chem. Eur. J.* **2003**, *9*, 2938; and references cited therein.

[35] a) L. P. Hammett, *Chem. Rev.* **1935**, *17*, 225; b) L. P. Hammett, *J. Chem. Ed.* **1966**, *43*, 464; c) G. N. Burckhardt, *Nature* **1935**, *136*, 884; d) G. N. Burckhardt, W. G. K. Ford, E. Singleton, *J. Chem. Soc.* **1936**, 17; e) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, NY, p194 (2nd ed. **1970**); f) C. Hansch, A. Leo, R. Taft, *Chem. Rev.* **1991**, *91*, 165; g) D. W. Nelson, A. Gypser, P. T. Ho, H. C. Kolb, T. Kondo, H.-L. Kwong, D. V. McGrath, A. E. Rubin, P.-O. Norrby, K. P. Gable, K. B. Sharpless, *J. Am. Chem. Soc.* **1997**, *119*, 1840.

[36] N. Isaacs in *Physical Organic Chemistry*, 2nd ed., Longman Scientific and Technical, Essex, UK, **1995**.

[37] a) A. Suzuki, *J. Organomet. Chem.* **1999**, 57, 147; b) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020.

[38] R. W. Jackson, *Tetrahedron Lett.* **2001**, *42*, 5163.

[39] a) A. T. Levorse, S. Knapp, *J. Org. Chem.* **1988**, *53*, 4006; b) S. Knapp *Iodolactamisation: Aspects and Applications* Advances in Heterocyclic Natural Product Synthesis, Vol 3, 57-98, *1996* JAI Press Inc.; c) S. Robin, G. Rousseau, *Tetrahedron* **1998**, 13681; d) C. Chuang, J. C. Galluci, D. J. Hart, *J. Org. Chem.* **1988**, *53*, 3210.

[40] The acid chloride was formed quantitatively in a first step with oxalylchloride in toluene at 0 °C and was used directly without further purification.

[41] H. A. Staab, *Liebigs Ann. Chem.* **1957**, *609*, 75.

[42] a) J. C. Sheehan, G. P. Hess, *J. Am. Chem. Soc.* **1955**, *77*, 1067; b) J. C. Sheehan, P. A. Cruickshank, G. L. Boshart, *J. Org. Chem.* **1961**, *26*, 2525.

[43] J. T. Drummond, G. Johnson, *Tetrahedron Lett.* **1988**, *29*, 1653.

[44] a) A. Wurtz, *Ann. Chim. Phys.* **1855**, *44*, 275; b) A. Wurtz, *Ann.* **1855**, *96*, 364; c) D. C. Billington, *Comp.*

Org. Syn. **1991**, *3*, 413.

[45] G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199.

[46] Already during formation of the lactone decomposition products were found by TLC, while starting material was still present.

[47] Analysis was done on Daicel's Chiralcel OD-H, OB-H, OJ and Whelk-01 (HPLC) and on Chiralsil γ-CD and β-CD (GC). In all cases decomposition was found.

[48] R. C. Mebane, K. D. Grimes, S. R. Jenkins, J. D. Deardorff, B. H. Gross, *Synth. Commun.* **2002**, *32*, 2049.

[49] P. A. Bartlett, J. Myerson, *J. Am. Chem. Soc.* **1978**, *100*, 3950.

[50] J. Barluenga, J. M. Gonzalez, P. J. Campos, G. Asensio, *Angew. Chem. Int. Ed.* **1985**, *97*, 341.

[51] a) S. A. Glover, A. Goosen, *Tetrahedron Lett.* **1980**, *21*, 2005; b) M. S. Yusubov, R. Y. Yusubova, V. D. Filimonov, K.-W. Chi, *Russ. J. Org. Chem. (Translation of Zhurnal Organicheskoi Khimii)* **2002**, *38*, 902.

[52] J. Barluenga, M. A. Rodriguez, P. J. Campos, *J. Chem. Soc., Perkin Trans. 1* **1990**, *10*, 2807.

[53] Compound **92** can also be obtained by reacting styrene with $KICl_2$; N. S. Zefirov, G. A. Sereda, S. E. Sosonuk, N. V. Zyk, T. I. Likhomanova, *Synthesis* **1995**, 1359.

[54] column : Chiraldex β-CD 25m

[55] Similar to the *N*-chloro case, this ketone can be formed via the imine; *Reagents for Organic Synthesis*, 1st Vol. L. & F. Fieser, John Wiley & Sons, NY, **1967**, p487;

[56] The configuration at the stereogenic center has not been determined.

[57] M. Esseffar, W. Bouab, A. Lamsabhi, J.-L. M. Abboud, R. Notario, M. Yáñez, *J. Am. Chem. Soc.* **2000**, *122*, 2300.

[58] F. Demartin, F. A. Devillanova, A. Garau, F. Isaia, V. Lippolis, G. Verani, *Polyhedron* **1999**, *18*, 3107.

[59] See appendix B for X-ray structure.

[60] Elemental analysis ($C_{10}H_{13}NICl$): calc.: C: 38.80%, H: 4.23%, N: 4.52%; found: C: 38.58%, H: 4.23%, N: 4.44%

[61] a) P. Job, *Ann. Chim.* **1928**, *9*, 113; b) P. MacCarthy, *Analyt. Chem.* **1978**, *50*, 2165 and references cited therein.

[62] See appendix C for further details.

[63] a) see reference [11a]; b) see reference [11b]; c) V. I. Teberekidis, M. P. Sigalas, *Tetrahedron* **2003**, *59*, 4749.

[64] T. H. Dunning Jr., P. J. Hay in *Modern Theoretical Chemistry*, Ed. F. H. Schaefer III, Plenum, New York, **1976**, vol 3, p1.

[65] a) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 270; b) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 284; c) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299.

[66] a) P. Fuentealba, H. Preuss, H. Stoll, L. v. Szentpaly, *Chem. Phys. Lett.* **1989**, *89*, 418; b) L. v. Szentpaly, P. Fuentealba, H. Preuss, H. Stoll, *Chem. Phys. Lett.* **1982**, *93*, 555; c) P. Fuentealba, H. Stoll, L. v. Szentpaly, P. Schwerdtfeger, H. Preuss, *J. Phys. B* **1983**, *16*, 1323; d) H. Stoll, P. Fuentealba, P. Schwerdtfeger, J. Flad, L. v. Szentpaly, H. Preuss, *J. Chem. Phys.* **1984**, *81*, 2732; e) P. Fuentealba, L. v. Szentpaly, H. Preuss, H. Stoll, *J. Phys. B* **1985**, *18*, 1287; f) U. Wedig, M. Dolg, H. Stoll, H. Preuss in *Quantum Chemistry: The Challenge of Transition Metals and Coordination Chemistry*, Ed. A. Veillard, Reidel and Dordrecht **1986**, p.79; g) M. Dolg, U. Wedig, H. Stoll, H. Preuss, *J. Chem. Phys.* **1987**, *86*, 866; h) G. Igel-Mann, H. Stoll, H. Preuss, *Mol. Phys.* **1988**, *65*, 1321; i) G. Dolg, H. Stoll, H. Preuss, *J. Chem. Phys.* **1989**, *90*, 1730; j) P. Schwerdtfeger, M. Dolg, W. H. E. Schwarz, G. A. Bowmaker, P. D. Boyd, *J. Chem. Phys.* **1989**, *91*, 1762; k) G. Dolg, H. Stoll, A. Savian, H. Preuss, *Theor. Chim. Acta* **1989**, *75*, 173; l) D. Andrae, U. Haeussermann, M. Dolg, H. Stoll, H. Preuss, *Theor.Chim.acta* **1990**, *77*, 123; m) M. Kaupp, P. v. R. Schleyer, H. Stoll, H. Preuss, *J. Chem. Phys.* **1991**, *94*, 1360; o) W. Kuechle, M. Dolg, H. Stoll, H. Preuss, *Mol. Phys.* **1991**, *74*, 1245; p) M. Dolg, P. Fulde, W. Kuechle,

C.-S. Neumann, H. Stoll, *J. Chem. Phys.* **1991**, *94*, 3011; q) M. Dolg, H. Stoll, H.-J. Flad, H. Preuss, *J. Chem. Phys.* **1992**, *97*, 1162; r) A. Bergner, W. Kuechle, H. Stoll, H. Preuss, *Mol. Phys.* **1993**, *80*, 1431; s) M. Dolg, H. Stoll, H. Preuss, R. M. Pitzer, *Theor. Chim. Acta* **1993**, *85*, 441; t) M. Dolg, H. Stoll, H. Preuss, R. M. Pitzer, *J. Chem. Phys.* **1993**, *97*, 5852; u) U. Haeussermann, M. Dolg, H. Stoll, H. Preuss, *Mol. Phys.* **1993**, *78*, 1211; v) W. Kuechle, M. Dolg, H. Stoll, H. Preuss, *J. Chem. Phys.* **1994**, *100*, 7535; w) A. Nicklass, M. Dolg, H. Stoll, P. Schwerdtfeger, *J. Chem. Phys.* **1995**, *102*, 8942; x) T. Leininger, A. Nicklass, H. Stoll, M. Dolg, P. Schwerdtfeger, *J. Chem. Phys.* **1996**, *105*, 1052.

[67] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B*, **1988**, *37*, 785.

[68] a) G. Alagona, C. Ghio, S. Monti, *Int. J. Quant. Chem.* **1999**, *73*, 115; b) M. Elstner, P. Hobza, T. Frauenheim, S. Suhai, E. Kaxiras, *J. Chem. Phys.* **2001**, *114*, 5149; c) J. Ŝpooner, J. Leszczynski, P. Hobza, *J. Comput. Chem.* **1996**, *17*, 841; d) C. Rauwolf, A. Mehlhorn, J. Fabian, *Collect. Czech. Chem. Commun.* **1998**, *63*, 1223.

[69] a) M. J. Frisch, M. Head-Gordon, J. A. Pople, *Chem. Phys. Lett.* **1990**, *166*, 275; b) M. J. Frisch, M. Head-Gordon, J. A. Pople, *Chem. Phys. Lett.* **1990**, *166*, 281; c) M. Head-Gordon, T. Head-Gordon, *Chem. Phys. Lett.* **1994**, *220*, 122; d) M. Head-Gordon, J. A. Pople, M. J. Frisch, *Chem. Phys. Lett.* **1988**, *153*, 503; e) C. Møller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618;

[70] a) see reference [14a]; b) J. Ŝpooner, J. Leszczynski, P. Hobza, *Chem. Phys. Lett.* **1997**, *267*, 263; c) G. Alagona, C. Ghio, S. Monti, *J. Phys. Chem. A* **1998**, *102*, 6125; d) G. Alagona, C. Ghio, A. Giolitti, S. Monti, *Theor. Chem. Acc.* **1999**, *101*, 143.

[71] This limitation may lead to energies, which are overestimated, because no polarisation functions are present.

[72] There are, however, approaches to apply uncontracted basis sets for iodine described. a) Relativistic compact potentials (RCEP), Y. Zhang, C.-Y. Zhao, X.-Z. You, *Can. J. Chem.* **1992**, *70*, 612; orbital exponent from: "Gaussian Basis Sets for Molecular Calculations" in "Physical Sciences Data 16", S. Huzinaga, ed., Elsevier, Amsterdam, **1985**; b) D. Danovich, J. Hrusak, S. Shaik, *J. Phys. Chem.* **1997**, *23*, 4085.

[73] S. Bissmire, Master Thesis, Cardiff University, **2002**.

[74] a) Gaussian 98, Revision A.7 and A.9, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1998**.

[75] O. Kh. Poleshchuk, I. Latoshinska, Ya. Koput, *Russ. J. Coord. Chem.* **1998**, *24*, 72.

[76] From rotational spectroscopy, this distance is 3.03 Å; see reference [15].

[77] L. Pauling in *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, NY, **1960**, p260.

[78] B3LYP/LANL2DZ data available in appendix A.

[79] a) A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899; b) F. Weinhold in *Encyclopedia of Computational Chemistry*, Vol. 3, p. 1792, P. v. Schleyer, N. L. Allinger, P. A. Kollmann, T. Clark, H. F. Schaefer, J. J. Gasteiger, P. R. Schreiner, Wiley-VCH, Chichester, **1998**.

[80] For a brief introduction into the Hammett notation and also for references see chapter 3.1.3.

[81] J. B. Foresman, Æ. Frisch, *Exploring Chemistry with Electronic Structure Methods*, 2nd ed.,Gaussian Inc. Pittsburgh, **1996**.

[82] For additional graphs (**112**: B3LYP/LANL2DZ; **113**: B3LYP/LANL2DZ) see appendix A.

[83] To consider a further HCl - ICl exchange in **103a** was abandoned during the course of the calculations, because of *N*,*N*-diiodomethylamine being higher in energy than the starting materials, methylamine and ICl.

[84] This system was also investigated at a MP2/6-31+G(d,p),SDD level of theory. The geometries and energies obtained were almost identical (less than 0.1 Å and less than 0.5 kJ·mol^{-1} difference, the computational cost, however, tripled. It therefore was decided against the use of this methodology.

[85] According to the analogous *N*-chloro case in *Reagents for Organic Synthesis*, 1st Vol. L. & F. Fieser, John Wiley & Sons, NY, **1967**, p487; this possibility has not been included in the calculations as an explicit model.

[86] In case the zero-point energy (which corrects for the energy at the true equilibrium state at 0 K) is added the interpretation of the data remains the same, with the exception that **103b** becomes stable. This however does not change the overall picture, because **102b** and **103b** are regarded as less important.

[87] The error limits of these relative energies are within ± 2 kJ·mol^{-1}.

[88] The pyridine-iodine complex was experimentally found to have a dipolemoment of 4.9 D; K. Toyoda, W. B. Person, *J. Am. Chem. Soc.* **1966**, *88*, 1629.

[89] C. S. Pomelli, J. Tomasi, M. Cossi, V. Barone, *J. Comp. Chem.* **1999**, *20*, 1693.

[90] Other -substituted amines were not yet taken into account, mainly due to computational cost.

[91] except for B3LYP/LANL2DZ calculations: **103b** shows a higher complexation energy than **101b** and **102b**.

[92] a) S. F. Boys, F. Bernardi, *Mol. Phys.* **1970**, *19*, 553; b) J. A. Sordo, *THEOCHEM* **2001**, *537*, 245.

[93] At this stage the contracted nature of the SDD basis set is assumed to be partly responsible for it. Future B3LYP/6-31+G(d,p)/SDD calculations are aimed at refining these complexation energies.

[94] Two isosbestic points were observed, one at shorter (237 nm) and one at longer wavelength (262 nm), indicating the participation of three species.

[95] If not otherwise stated, amine **15** was used as a ligand.

[96] In case other substrates than **2** have been cyclised, the configuration of the major stereoisomer has not been determined (like it has been done for **3**).

[97] Concentration achieved by diluting more concentrated solutions, starting from 5 mg **15** and 1 M ICl in CH_2Cl_2.

[98] Concentration achieved by diluting more concentrated solutions, starting from 14.7 mg **15** and 1 M ICl in CH_2Cl_2.

[99] S. Handa, K. Jones, G. C. Newton, *Tetrahedron Lett.* **1988**, *29*, 3841.

[100] Y. S. Park, M. L. Boys, P. Beak, *J. Am. Chem. Soc.* **1996**, *118*, 3757.

[101] X. Verdaguer, U. E. W. Lange, M. T. Reding, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 6784.

[102] **22:** Compound has been prepared accoring to the literature given, it is also commercially available from Aldrich, Fluka or Acros; **24:** G. van Koten, J. T. B. H. Jastrzebski, J. G. Noltes, W. M. G. F. Pontenagel, J. Kroon, A. L. J. Spek, *J. Am. Chem. Soc.* **1978**, *100*, 5021.

[103] B. M. Chanda, R. Vyas, A. V. Bedekar, *J. Org. Chem.* **2001**, *66*, 30.

[104] N. Baba, K. Nishiyama, J. Oda, Y. Inouye, *Agric. Biol. Chem.* **1976**, *40*, 1441.

[105] R. Weidmann, J.-P. Guett, *Synthesis* **1986**, 900.

[106] F. R. Keene, M. J. Ridd, M. R. Snow, *J. Am. Chem. Soc.* **1983**, *105*, 7075.

[107] J. Uenishi, M. Hamada, *Synthesis* **2002**, 625.

[108] M. Falorni, G. Chelucci, S. Conti, G. Giacomelli, *Synthesis* **1992**, 972.

[109] A. Bolognese, G. Scherillo, *J. Org. Chem.* **1977**, *42*, 3867.

[110] T. L. Gilchrist, P. D. Kemmitt, A. L. Germain, *Tetrahedron* **1997**, *53*, 4447.

[111] G. D. Jr., Harris, R. J. Herr, S. M. Weinreb, *J. Org. Chem.* **1993**, *58*, 5452.

[112] I. Matsuda, S. Murata, Y. Izumi, *J. Org. Chem.* **1980**, *45*, 237.

[113] T. Sato, K. Toshio, S. Tatsuo, F. T. Kazumi, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 505.

[114] E. J. Enholm, M. E. Gallagher, S. Jiang, W. A. Batson, *Org. Lett.* **2000**, *2*, 3355.

[115] K. Mori, M. Ohki, M. Matsui, *Tetrahedron* **1970**, *26*, 2821.

[116] T. R. Hoye, W. S. Richardson, *J. Org. Chem.* **1989**, *54*, 688.

[117] Already during formation of the lactone decomposition products were found by TLC, while starting material was still present.

[118] Analysis was done on Daicel's Chiralcel OD-H, OB-H, OJ and Whelk-01 (HPLC) and on Chiralsil γ-CD and β-CD (GC). In all cases decomposition was found.

[119] E. Wenkert, E. L. Michelotti, C. S. Swindell, M. Tingoli, *J. Org. Chem.* **1984**, *49*, 4894.

[120] G. Spengler, A. Weber, *Brennstoff-Chemie* **1959**, *40*, 22.

[121] A. Citterio, M. Gandolfi, C. Giordano, G. Castaldi, *Tetrahedron Lett.* **1985**, *26*, 1665.

[122] J. Barluenga, J.-M. Martinez-Gallo, C. Najera, M. Yus, *Synthesis* **1987**, 582.

[123] Y. Takeuchi, N. Itoh, T. Satoh, T. Koizumi, K. Yamaguchi, *J. Org. Chem.* **1993**, *58*, 1812.

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Eidesstattliche Erklärung

Hiermit erkläre ich, dass ich die Dissertation

"New Chiral I^+ Complexes for *Reagent*-controlled Reactions:
A Combined Computational and Synthetic Approach"

selbstständig nur mit der darin angegebenen Hilfe verfasst und bei keiner anderen Fakultät eingereicht habe.

Basel, den 27. Oktober 2003

Jürgen Haas