Combinatorial applications of N-acyliminium ion intermediates in the synthesis of homoallylic amines.

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CHAPTER 1

GENERAL INTRODUCTION

1.1 Combinatorial and solid phase synthesis

Combinatorial and solid phase chemistry have their origin in the revolutionary and Nobel Prize-winning work of Merrifield in 1963.\textsuperscript{1} Merrifield was the first scientist to use an insoluble polymer support as a synthesis tool for the preparation of a range of tetrapeptides and this approach has since inspired many scientists. Nevertheless, besides a few exceptions in the 1970’s and 1980’s,\textsuperscript{2} solid phase chemistry was solely focused on peptide synthesis until the early 1990’s. In particular the work of Ellman\textsuperscript{3} and Hobbs DeWitt\textsuperscript{4} in 1992/1993 caused a revival in solid phase chemistry by its application in the organic synthesis of benzodiazepines. This renaissance of solid phase chemistry can be attributed to the development of automation in biology at that time, in combination with the practical advantages of solid-supported chemistry. There are a number of practical advantages of solid phase chemistry compared to classical solution phase chemistry, (1) simplified purification procedures by using filtration, (2) forcing reactions to completion by the addition and facile removal of reagents in excess, (3) suppressing of side reactions such as dimerization and cross-linking by the principle of high dilution, (4) standardization of synthetic procedures to enable automation. The automation in biology led to the need for large numbers of new, potentially biologically active compounds to be tested by the efficient method of high throughput screening. As a consequence the automation of solid phase chemistry took place and created the ability to very quickly generate large numbers (libraries) of chemical compounds, which is the core of combinatorial synthesis. More precisely, the IUPAC recommendations defines the term ‘combinatorial’ as follows: “A combinatorial library is a set of compounds prepared by combinatorial synthesis. Combinatorial synthesis is a process to prepare large sets of organic compounds by combining sets of building blocks.”\textsuperscript{5,6} A particularly efficient example of combinatorial synthesis can be found in the split-and-mix procedure, which was described for the first time in the literature by Houghten and Lam in 1991 and resulted in the preparation of large peptide libraries.\textsuperscript{7} Since then, combinatorial and solid phase organic synthesis have become important tools for the preparation of large libraries of organic compounds to be tested for biological activity, particularly in the field of drug discovery.

Although several techniques for the immobilization on a solid support are known, the cross-linked polystyrene resin beads that were originally used by Merrifield still remain the most popular ones.\textsuperscript{8} Nowadays, these gel-like resins are commercially available and are
usually prepared in a copolymerization process with styrene and a small amount of divinylbenzene (DVB, around 1%), resulting in the desired cross-linked network. A 1% degree of cross-linking is sufficient to give the required mechanical strength and insolubility, while swelling of the resin in a solvent to allow diffusion of the reagents throughout the whole polymer backbone is still possible. Although polystyrene resins are inert under a wide range of reaction conditions, it should be kept in mind that the polymer is unstable towards highly electrophilic reagents and at temperatures above ~120 °C.

In order to use a polymer support as a tool in the synthesis of (organic) compounds, a chemical handle has to be introduced. This can either be done by the use of a functionalized monomer prior to polymerization, or by chemical modification of the polystyrene resin itself. The chemical handle is used to attach a group, which allows for further functionalization. A chloromethylated resin, which is also known as Merrifield resin, is most commonly used as the handle, but other groups such as aminomethylene, hydroxymethylene and carboxyl functionalities are also known and commercially available. The resin can be used as such, but most often an additional spacer and/or linker moiety is used as the actual attachment point. Spacer moieties might be used for more flexibility or to reduce steric influence of the polymer backbone. A linker moiety allows for the efficient loading of the polymer and conversely, should facilitate ready cleavage of the desired products. Clearly, the choice of the linker system is dependent on the chemistry to be performed and is one of the most significant factors for the success of any solid phase synthesis.

Solid phase synthesis also has its limitations. Loading and cleavage of the resin require additional reaction steps, while the choice of the linker system could limit the scope of possible chemistry. Furthermore, solid phase synthesis is a new field that is still under development, and analytical monitoring of the reactions is therefore not yet well developed. Moreover, the development of new reactions on solid phase is rather time consuming.
Although a plethora of different reactions on solid support has been reported in the past few years,\textsuperscript{10} the development of novel reactions on solid support still remains important. Over these years the focus of solid phase chemistry seems to have shifted from the preparation of libraries containing large numbers of compounds (mixtures) to the preparation of smaller libraries, which contain more diverse and highly functionalized, discrete compounds. In addition, the developments in solid phase chemistry have also led to developments in related fields, such as (1) parallel synthesis in solution phase, which for example can be applied to the optimization of reaction conditions, (2) the use of solid-supported reagents,\textsuperscript{11} (3) the use of polymer-supported catalysts,\textsuperscript{12} (4) the screening of catalysts,\textsuperscript{13} and (5) automated synthesis in general. From Merrifield's work in the early 1960's onward, combinatorial and solid phase synthesis have contributed to some major revolutions in the way chemists think and how synthesis can be performed more rapidly and more efficiently. Therefore, particularly in an era in which time is considered as one of the most valuable commodities, research in solid phase synthesis has been and will remain of major importance.

1.2 Functionalized aldehydes in N-acyliminium ion chemistry

\textit{N}-Acyliminium ion chemistry is an effective tool for the formation of C–C bonds and has been successfully used in the synthesis of highly complex molecules.\textsuperscript{14} The introduction of substituents at the $\alpha$-position of acylated amines is accomplished by the addition of a suitable nucleophile to the intermediate $N$-acyliminium ion 2 (eq 1.1). The ionic species itself is generated \textit{in situ} by the protic or Lewis acid treatment of an $N$-acylated compound 1 bearing a leaving group (LG) at the $\alpha$-position.

\begin{equation}
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\begin{array}{c}
\text{O} \\
\text{R}^1
\end{array}
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\text{N} \\
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\rightarrow
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\text{O} \\
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\end{equation}

\text{Lewis acid}

\text{nucleophile}

(1.1)

Several methodologies for the preparation of appropriate $N$-acyliminium ion precursors exist.\textsuperscript{14} Amongst these, the most important techniques include (1) the reduction of imides\textsuperscript{15} (route A, Scheme 1.1), (2) the (electro)chemical oxidation of amides\textsuperscript{16} (route B) and (3) the addition of aldehydes to amides or carbamates to afford the corresponding $N,O$-hemiacetals (route C). Despite the relative instability of the $N$-acyl $N,O$-hemiacetal functionality, the latter methodology is an efficient approach for the incorporation of an aldehyde in the desired $N$-acyliminium ion precursor and the $N,O$-(hemiacetal functionality
is even found in some natural products. However, the intermolecular addition of amides or carbamates to aldehydes is an equilibrium process in which the formation of the desired adduct is usually disfavored. Regular aliphatic and aromatic aldehydes are not sufficiently electrophilic to react with amides or carbamates and as a result the adducts cannot be isolated. Therefore, the use of these aldehydes is restricted to some specific cases in which the resulting N,O-hemiacetal is trapped. Efficient additives to trap the intermediate N,O-hemiacetal adduct are phosphorous acid or esters, silylated amides in combination with SiMe₃OTf, DABCO or trimethyl orthoformate.

Panek and Veenstra developed a particularly interesting approach, in which the desired N,O-hemiacetal 9 was generated as an intermediate and subsequently transformed into the N-acyliminium ion species 10, which resulted in a one-pot three component N-acyliminium ion reaction (Scheme 1.2). Thus, starting from carbamate or sulfonamide 8 (R¹ = CO₂R, SO₂R), aldehyde 7, allylsilane 11 and BF₃·OEt₂, the desired homoallylic amine 12 was obtained. Via the application of aliphatic and aromatic aldehydes a wide range of homoallylic amines was prepared.

Scheme 1.1:

Scheme 1.2:
In contrast to regular aliphatic and aromatic aldehydes, the use of more electrophilic aldehydes can shift the equilibrium of the intermolecular reaction with amides and carbamates in favor of the desired adduct. Thus, the use of formaldehyde (13),\textsuperscript{24} chloral (14)\textsuperscript{25} and glyoxylic acid derivatives (15-18) results in the formation of stable N,O-hemiacetals. Glyoxylates are particularly useful aldehydes as their corresponding N,O-hemiacetals are precursors for the preparation of α-amino acids \textit{via} N-acyliminium ion chemistry. Related approaches towards amino acids that involve α-cation equivalents\textsuperscript{26} are nucleophilic additions to bromoglycine\textsuperscript{27} or acyl imines.\textsuperscript{28}

\[
\begin{align*}
\text{H} & \text{H} \\
\text{Cl}_3\text{C} & \text{H} \\
\text{HO} & \text{O} \\
\text{O} & \text{H} \\
\text{MeO} & \text{O} \\
\text{MeO} & \text{OH}
\end{align*}
\]

\text{13} \quad \text{14} \quad \text{15} \quad \text{16} \quad \text{17} \quad \text{18}

Glyoxylic acid (15) and methyl glyoxylate (17) are both colorless liquids. However, in their pure form the aldehydes are not stable and transformed into viscous liquids due to self-polymerization. Therefore, glyoxylic acid is usually available as its crystalline monohydrate 16 or as a solution in water, while methyl glyoxylate is normally used as the hydrate or in its hemiacetal form 18. Pure methyl glyoxylate can be readily obtained from the corresponding hemiacetal by distillation from P₂O₅.\textsuperscript{29} To prevent polymerization, the compound can only be prepared prior to use and has to be collected at a low temperature (-78 °C). Alternative methods have been developed to generate the aldehyde \textit{in situ} by refluxing the hemiacetal in benzene.\textsuperscript{30} An even more sophisticated way to generate the aldehyde \textit{in situ} was reported by van Benthem.\textsuperscript{31} In this approach hemiacetal 18 was refluxed in CH₂Cl₂ and MeOH was azeotropically removed from the reaction mixture. MeOH was trapped by 4Å molecular sieves, which were positioned above the reaction mixture to prevent polymerization of the aldehyde on its aluminum silicate surface. In this approach, CH₂Cl₂ appeared a superior solvent, which may be caused by the fact that the low boiling point of CH₂Cl₂ allowed the aldehyde a longer lifetime in the reaction mixture.\textsuperscript{32}

Starting from the amide or carbamate 19, several suitable N-acyliminium ion precursors can be readily prepared (Scheme 1.3). The N,O-hemiacetal 20 – made \textit{via} either of the aforementioned approaches – can be subsequently transformed into (1) N,O-acetal 21 by acid catalyzed methanolysis,\textsuperscript{30b} (2) chloride 22 by either PCl₃-mediated chlorination of 21 or directly from 20 by treatment with SOCl₂,\textsuperscript{30b} and (3) acetate 23 by base-mediated acylation.\textsuperscript{24a}
In 1975 the first example of an intermolecular N-acyliminium ion reaction with a glyoxylate-derived precursor was reported. In that year, Ben-Ishai described the use of N,O-hemiacetal in the protic acid-mediated N-acyliminium ion reaction with a variety of mercaptans (eq 1.2).

The addition of mercaptans to N-acyliminium ion precursor in a mixture of concentrated H₂SO₄ and acetic acid afforded the desired N,S-acetals in good yields. Using a different approach by starting from N,O-acetal, the N-acyliminium ion intermediate was generated with a catalytic amount of 2-naphthalenesulfonic acid (NSA) in refluxing 1,2-dichloroethane to give the corresponding thioaminals in yields of 68-92%. Analogously, the development of N-acyliminium ion reactions with glyoxylate-derived precursors was extended to aromatic nucleophiles. A wide range of aromatic nucleophiles was successfully used in combination with N,O-hemiacetal as the N-acyliminium ion precursor in concentrated H₂SO₄ to deliver the desired products in moderate to excellent yields of 41-92%. In the case of acid sensitive furan-derived nucleophiles, the reaction conditions were changed. Starting from N,O-acetal, with the use of BF₃·OEt₂ as the Lewis
acid in ether, the furan adducts were obtained in 67 and 84% yields, respectively. Aromatic nucleophiles have since extensively been used in the synthesis of $\alpha$-aromatic amino acids.\(^3\)

![Chemical structures](image)

Harding introduced a stereoselective approach for the use of an aromatic nucleophile in the intermolecular N-acyliminium ion reaction with a glyoxylate-derived precursor (eq 1.3).\(^3\) Oppolzer's auxiliary was used to prepare $N,O$-hemiacetal 20a as a mixture of diastereoisomers. The treatment of 20a with BF$_3$OEt$_2$ and anisole (29) resulted in an essentially quantitative yield of (R,S)-36 and a diastereoselectivity of $>96:4$. The same diastereoisomer was obtained when the reaction was performed in H$_2$SO$_4$/AcOH, albeit with a slightly lower stereoselectivity of 91:9.

![Reaction scheme](image)

Next to mercaptans and aromatic nucleophiles, the application of olefinic nucleophiles was also developed by Ben-Ishai.\(^3\) Glyoxylate-derived $N,O$-acetal 21, several styrene derivatives and 2-naphthalenesulfonic acid were reacted to afford the substituted vinylglycines 38 in good yields (Scheme 1.4). When the phenyl amide-protected $N,O$-acetal 21a ($R^1 = $Ph) was used in combination with BF$_3$OEt$_2$, oxazine 39 was afforded as the product. Both reactions were believed to occur via a nucleophilic cycloaddition reaction in which the protonated oxazine 39 was generated as an intermediate. With the use of asymmetric olefins, products 38 and 39 were obtained as (E)/(Z) and cis/trans isomeric mixtures, respectively.
The intermolecular $N$-acyliminium ion reaction of $N,O$-hemiacetal 20 with olefins 37 resulted in the formation of cis/trans mixtures of lactone 40 in mostly moderate yields (eq 1.4). The reaction was performed in a mixture of concentrated sulfuric acid and dioxane, in which the lactone was obtained after rearrangement of a protonated oxazine intermediate (cf. formation of 39). Similar results were obtained by using an ethylthio function as the leaving group. Further applications of the cyclic compounds 39 and 40 were also investigated, particularly those in the synthesis of unsaturated $\alpha$-amino acids.

Concentrated sulfuric acid is the most commonly used acid and solvent for the $N$-acyliminium ion reaction of $N,O$-hemiacetal 20. However, its use is limited to nucleophiles that are stable under these strongly acidic conditions. For example, in the case of $\alpha$-diketones and $\alpha$-keto esters, deacylation or decarboxylation of the desired products was observed as a side reaction and therefore milder reaction conditions had to be found (Scheme 1.5). The use of MsOH, TFA or a H$_2$SO$_4$/AcOH solvent mixture proved to be sufficiently acidic to generate the intermediate $N$-acyliminium ion, while it was mild enough to produce product 43. The desired products were isolated as isomeric mixtures. The application of $\alpha$-diketones and $\alpha$-keto esters as nucleophiles was also investigated in the $N$-acyliminium ion reaction of glyoxylate-derived $N$-acyliminium ion precursor 21. Again, the stability of the nucleophile and the desired product required the use of mild reaction conditions. Several acids were tried and the best results were obtained when the intermediate $N$-acyliminium ion was generated in TFA or with BF$_3$OEt$_2$ in CH$_2$Cl$_2$. [8]
In 1988 the first example of the use of allyltrimethylsilane in a reaction with a glyoxylate-derived precursor was reported (eq 1.5).\textsuperscript{40} Substituted allylsilanes were also successfully applied, which resulted in the preparation of a wide range of allylglycine derivatives \textsuperscript{45,41} In the case of N,O-acetal 21, the best results were obtained with the use of BF\textsubscript{3}-OEt\textsubscript{2} as the Lewis acid, while in the case of chloroglycine 22 SnCl\textsubscript{4} gave the best results. Where appropriate, diastereoisomers were obtained in low selectivity. Modifications of this procedure involving silicon-based \(\pi\)-nucleophiles include the use of vinylsilane,\textsuperscript{42} alkynylsilanes and stannanes,\textsuperscript{43} cyclopentadienylsilane,\textsuperscript{44} a menthyl ester as chiral auxiliary,\textsuperscript{45} cyclic N,O-acetals,\textsuperscript{46} and \(\beta\)-lactams.\textsuperscript{47}

Steckhan – who prepared N,O-acetal 21a by electrochemical methoxylolation rather than using a glyoxylate – was the first to report studies on the nucleophilic addition of an enamine, a silyl enol ether and an enol acetate to these compounds (eq 1.6).\textsuperscript{48} Several reaction conditions were evaluated, and with the use of enamine 46a the best results were achieved in combination with TiCl\textsubscript{4} where the \textit{anti}-diastereoisomer of 47 was obtained in yields up to 90\% and de’s up to 86\%. Silyl enol ether 46b gave also the best results in combination with TiCl\textsubscript{4}. Surprisingly, with silyl enol ether 46b the \textit{syn}-diastereoisomer was obtained as the major product in de’s up to 38\%. Enol acetate 46c was much less reactive and only produced the desired product in combination with BF\textsubscript{3}-OEt\textsubscript{2} in a 50\% yield and a maximum of 31\% de in favor of the \textit{anti}-isomer.
Mooiweer reported a more detailed study on the use of silyl enol ethers in the synthesis of γ-oxo-α-amino acids. In contrast to the use of bromoglycine (22, LG = Br), the generation of an N-acylimino acetate from chloroglycine 22 (by treatment with Et₂N) and subsequent addition of silyl enol ethers only resulted in low yields of the anticipated product 49. This difference in reactivity was assigned to the better leaving group ability of bromide with respect to chloride. Interestingly, the use of N,O-acetal 21 as an N-acyliminium ion precursor resulted in poor yields of the desired product. Nevertheless, a range of γ-oxo-α-amino acids 49 was prepared from chloroglycine 22 by the SnCl₄-mediated N-acyliminium ion reaction with silyl enol ethers (Scheme 1.6). A particularly useful application of this approach was found in the synthesis of the natural product 5-hydroxy-4-oxonorvaline (HON, 50). In a similar fashion, fluorinated γ-oxo-α-amino acids were prepared by McCarthy.

Scheme 1.6:

Roos extended the scope of intermolecular N-acyliminium ion reactions with glycine-derived precursors to α-methoxy glycinamides 51. The desired amides were obtained from N,O-acetal 21 and subsequently used in N-acyliminium ion chemistry with allyltrimethylsilane (Scheme 1.7). Formic acid and BF₃·OEt₂ were found to be the most efficient reagents for the formation of the ionic intermediate. The reaction was also performed with substituted allylsilanes and afforded the products in reasonable yields and low diastereoselectivity. In some cases, the poor solubility and reactivity of the amide precursors required an in situ silylation step prior to the actual addition of a carbon nucleophile.
Moreover, the obtained α-amino amides were subsequently used in an enzymatic resolution process with *Pseudomonas putida* to produce the corresponding α-amino acids in enantiopure form.

Scheme 1.7:

The use of silol enol ethers in the *N*-acyliminium ion reaction with amide 51 was also investigated. However, the desired reaction of *N*-methoxycarboxamide 51a with silyl enol ethers failed completely, which forced the use of the aforementioned *in situ* silylation approach. Interestingly, silylamide 53 in combination with silyl enol ethers resulted in the formation of dihydropyrrrolone 54 and in the case of reactive or unhindered silyl enol ethers in the formation of pyrrrolidinone 55 in reasonable yields. The formation of these rather unexpected cyclic products was explained by the generation of a cyclic *N*-acyliminium ion 56, which proceeded *via* attack of the reasonably nucleophilic amide at the carbonyl group in the side chain. Comparable *N*-acyliminium ion reactions of pyruvate-derived *N*,*O*-acetals with allylsilanes and silyl enol ethers were also reported.

In 1980, Ben-Ishai reported the first investigations towards intramolecular *N*-acyliminium ion cyclization reactions with glyoxylate-derived precursors. However, the intramolecular reaction of *N*,*O*-hemiacetal 20b with an intramolecular aromatic nucleophile appeared troublesome (Scheme 1.8). The reason that the anticipated product 59 was not formed, was mainly attributed to the preferred *s-trans* conformation 57 of the ionic intermediate, which disfavors the endotrigonal cyclization step (58→59).
Slight modification of the starting material resulted in the cyclization precursor 60 that successfully reacted in an endotrigonal fashion (Scheme 1.9). The reaction with glyoxylic acid and the subsequent cyclization step were performed in one pot, which made this process an extension of the Pictet-Spengler reaction of less reactive aromatic systems. The amide carbonyl is not incorporated into the newly formed ring and the interference of the preferred s-trans conformation of the amide bond is therefore less pronounced, while the desired tetrahydroisoquinoline 62 was obtained in good yields. Ben-Ishai also reported the extension of this methodology to the cyclization of dipeptides.

Mooiweer investigated the use of intramolecular silyl nucleophiles in N-acyliminium ion chemistry with glyoxylate-derived precursors (Scheme 1.10). The Lewis acid-mediated cyclization of allylsilane 23a afforded the corresponding pyrrolidine or piperidine 64 in good yields. Particularly in the case of the five-membered ring formation, the trans-diastereoisomer was obtained in high selectivity. Comparable results were obtained when product 64 was prepared from the corresponding N,O-hemiacetal by mesylation and subsequent generation of the ionic intermediate 63 under thermal conditions (MsCl and Et3N, then Δ). Propargylsilanes were also cyclized under Lewis acidic or thermal conditions to give the endocyclic allenes 65.
Esch extended the use of intramolecular nucleophiles to the SnCl₄-mediated cyclization of olefin 23b. The reaction was quenched with water either at -78 °C or after warming-up at rt to afford the axial alcohol 66 and the equatorial chloride 67, respectively. Substituted olefins resulted in the formation of similar alcohols and chlorides.

An important goal in this study was to investigate the cyclization mechanism, which might include an aza-Cope rearrangement. The proposed mechanism that explains the formation of the different products, is shown in Scheme 1.11. Cyclization of both N-acyliminium ions 68 and 69 led to the formation of the dioxycarbenium ion 70. Hydrolytic quenching resulted in the formation of 66, while at higher temperatures the cation was quenched by an S_N2 attack of chloride to give 67. In the case of allylsilane 63 (n = 1, Scheme 1.10) the cyclization step was apparently faster than the aza-Cope rearrangement of the 1,5-diene moiety, since the latter would have led to an exocyclic six-membered ring. However, reductive trapping by the addition of Et₃SiH to the intermediates that are formed in the reaction with 23b, resulted in the exclusive isolation of the reduced N-acyliminium ion 69. This clearly proved the presence of an aza-Cope rearrangement in this kind of cyclization reaction.
Analogous to the reactions with acetate 23b described above, the same precursor was used for the SnCl₄-mediated cyclization in MeCN to afford the Ritter product 72₅¹ and for the formic acid-induced reaction to give products 73 and 74.²⁴b Formation of 73 was explained by equatorial attack of formic acid onto 70 (cf. formation of 67), whereas formation of 74 was explained by the formation of intermediate 71 due to traces of water in formic acid.

In conclusion, glyoxylic acid and derivatives thereof have been widely used in the preparation of suitable N-acyliminium ion precursors and subsequently applied in the synthesis of α-amino acids and its derivatives. Most of the research presented in this overview was dedicated to the determination of the scope and limitations with respect to the nucleophile and herewith has shown its high potential. New developments in the use of glyoxylate-derived cationic glycine equivalents may include the further development of highly stereoselective methods and combinatorial or solid phase approaches.⁵⁸

1.3 Purpose and outline of this investigation

Unlike other great achievements, it is clear that combinatorial and solid phase chemistry are still under development and require the translation of efficient solution phase processes to the solid phase. An example of such a solution phase process is the N-
acyliminium ion-mediated C–C bond formation, which due to the versatility of amines and their facile condensation with aldehydes to give suitable precursors has over the years turned into a well-developed and highly efficient technology. Therefore, a combination of the two – solid phase and N-acyliminium ion chemistry – could lead to a powerful combinatorial methodology and forms the basis of this thesis.

Chapter 2 describes the initial results of the translation process of the one-pot three component N-acyliminium ion reaction of an immobilized carbamate, an aldehyde and an allylsilane on the Wang linker system. In Chapter 3 the development of novel dedicated linker systems for solid phase N-acyliminium chemistry is presented. The investigation of the scope and limitations of the one-pot three component N-acyliminium ion reaction in solution and on solid phase is described in Chapter 4. Finally, in Chapter 5 the diastereoselective synthesis of β-amino alcohols via a new technology that combines glyoxylates, Weinreb amides and N-acyliminium ion chemistry will be detailed.

Parts of this thesis have been published, or will be published in the near future.

1.4 References and notes

6. For comments on terminology in combinatorial and solid phase chemistry, see: Link, A. Angew. Chem. Int. Ed. 2000, 39, 4039.


25. For a review on chloral, see: Luknitskii, F. I. Chem. Rev. 1975, 75, 259.  
Chapter 1


General introduction


Chapter 1


