Glyoxylates as Versatile Building Blocks for the Synthesis of α-Amino Acid and α-Alkoxy Acid Derivatives via Cationic Intermediates

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Glyoxylic acid and its derivatives are versatile ester-substituted aldehyde equivalents that can be used efficiently to generate precursors for reactive cationic intermediates such as iminium ions, *N*-acyliminium ions, *N*-sulfonyliminium ions, and oxycarbenium ions. These intermediates have been extensively used for the synthesis of (cyclic) α-amino acid and α-alkoxyester derivatives. The research presented in this review is largely dedicated to the evaluation of the scope and limitations of glyoxylate-derived cationic intermediates in intra- and intermolecular reactions with suitable nucleophiles. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2003)

1. Introduction

Glyoxylic acid (**1**)[1] is a reactive aldehyde, which is stable (and commercially available) in its hydrated form **2**. When applied in organic reactions, the acid is often protected as an ester, with the aldehyde present variously as such (**3**), as the corresponding acetal **4**, or as a hemiacetal **5**. The esters **3**, for example, are conveniently prepared by ozonolysis of a double bond (usually of the corresponding maleate or fumarate ester)[2] or oxidative cleavage of tartrate esters.[3]

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(From left to right: Schoemaker/Maarseveen/Meester/Hiemstra)

Hans Schoemaker was born in Haarlem, The Netherlands, in 1952. He studied chemistry at the University of Amsterdam and received his Ph.D. at the same university with Prof. W. Nico Speckamp in 1979. That year, he joined DSM Research (Geleen, The Netherlands), where he is now corporate scientist in advanced synthesis and (bio-)catalysis. In 1994, he was appointed part-time professor of Industrial Fine Chemistry at the Institute of Molecular Chemistry, University of Amsterdam.

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Wim Meester was born in Diemen, The Netherlands, in 1975. He received his M.Sc. from the University of Amsterdam in 1998 and his Ph.D. from the same university under the supervision of Prof. Henk Hiemstra and Prof. Floris Rutjes in 2002. Currently, he is conducting postdoctoral studies with Prof. Hidde Ploegh at Harvard Medical School in Boston, USA. His research interests include the use of combinatorial chemistry in organic synthesis, biocatalysis, and biological applications.

Henk Hiemstra was born in Dronrijp, Friesland, The Netherlands, in 1952. He studied chemistry at the University of Groningen and received his Ph.D. at this university with Prof. Hans Wynberg in 1980. After a postdoctoral stay with Prof. Barry M. Trost at the University of Wisconsin, Madison, USA, he was appointed at the University of Amsterdam in 1982. He was promoted to full professor of organic synthesis in 1997. His favorite research areas are new synthetic methodology and the total synthesis of natural products.

Floris Rutjes was born in Heiloo, The Netherlands, in 1966. He studied chemistry at the University of Amsterdam, where he also received his Ph.D. with Prof. W. Nico Speckamp in 1993. After conducting postdoctoral studies in the group of Prof. K. C. Nicolaou (the Scripps Research Institute, La Jolla, USA), he was appointed at the University of Amsterdam in 1995. Four years later, he became full professor in synthetic organic chemistry at the University of Nijmegen. In 2002, he was awarded the Golden Medal of the Royal Netherlands Chemical Society (KNCV). His research interests include the use of enzymes in organic synthesis and the development of novel synthetic methodology.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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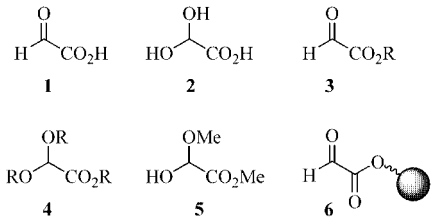
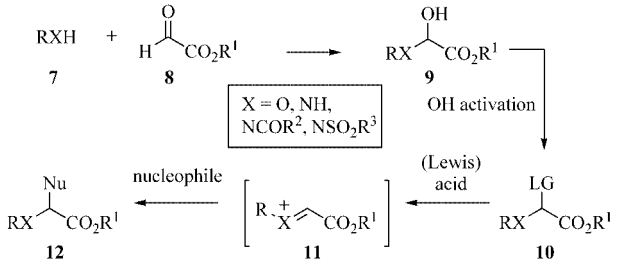
Straightforward acid-mediated acetalization of the aldehyde function provides the acetals **4**. Methyl hemiacetal **5** is produced on an industrial scale at DSM (Linz, Austria) by ozonolysis of dimethyl maleate in methanol, followed by hydrogenation in the presence of Pt.[4] The stable hemiacetal is a synthetically useful glyoxylate derivative, somewhat more reactive than the related acetal. Glyoxylates are usually stored in their hydrated or acetal forms, as the free aldehyde is rapidly transformed into a viscous liquid as a result of polymerization. Both hydrates and hemiacetals of glyoxylates can readily be converted into the reactive aldehyde form by distillation from P_2O_5.[5] To prevent polymerization of the free aldehyde, the compound has to be collected at −78 °C and should be used directly after the distillation. Finally, a number of immobilized derivatives of glyoxylate (**6**) have been described more recently.[6]



Thanks to the reactive aldehyde functionality, glyoxylates **8** are susceptible to nucleophilic attack of heteronucleophiles, resulting in the corresponding acetal-type compounds **9**. This species is often a stable compound, which can then be transformed into the corresponding alkoxy or amino ester **12** by conversion of the hydroxy function into a suitable leaving group (LG; **10**), followed by acid-mediated nucleophilic attack at the resulting carbocation **11**.



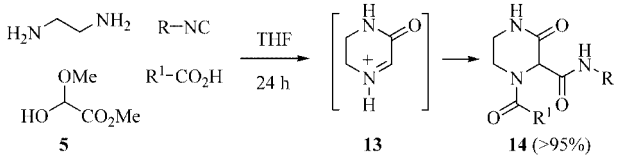
Scheme 1

This sequence − either in one-pot reactions or in different sequential steps − has been exploited by various groups, using nitrogen and oxygen nucleophiles. In this overview, we briefly summarize interesting recent examples that make use of amine nucleophiles (resulting in Mannich-type addition reactions), but focus especially on applications in which the less nucleophilic amides, sulfonamides, and alcohols have been applied. Use of these nucleophiles eventually results in the synthesis of amino and alkoxy acids by C−C bond formation at the corresponding strongly electrophilic *N*-acyliminium (**11**, X = $NCOR^2$), *N*-sulfonyliminium (**11**, X = NSO_2R^3), and oxycarbenium (**11**, X = O) ion intermediates. Alternative approaches to these cationic intermediates not involving the use of glyoxylic acid derivatives, such as the use of elimination/addition reactions of α-bromoglycine[7] or addition reactions to *N*-acylimines,[7b,8,9] also exist. The use of these types of α-cation equivalents[10] is only briefly discussed here.

2. Addition Reactions of Amines

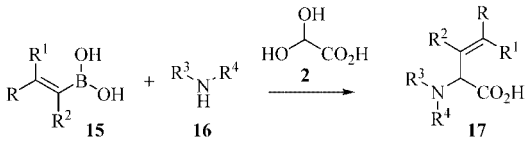
Because the combination of amines with glyoxylates may give rise to a wide variety of different reactions (such as Pictet-Spengler reactions[11] and reductive aminations),[12] we will focus on some particularly interesting applications of the sequence described above in multi-component reactions.

A first example concerns the Ugi reaction, a multi-component reaction in which a carboxylic acid, an amine, an aldehyde, and an isocyanide react by initial condensation of the aldehyde and amine to form an iminium ion, which is then attacked by the isocyanide. Although there are only few examples, glyoxylate has been used in this application.[13] As shown in Scheme 2, ethylenediamine reacts with glyoxylate derivative **5** to form the cyclic Mannich intermediate **13**,[14] which then reacts in Ugi fashion to give the product **14**. The reaction proceeds for a variety of different substituents in nearly quantitative yield.



Scheme 2

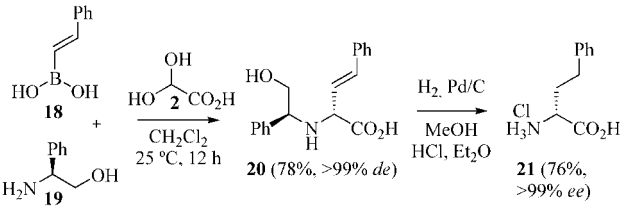
A recently developed multi-component reaction is the Petasis reaction,[15] in which an amine, an aldehyde, and a vinyl- or arylboronic acid are combined. Initial condensation of the amine **16** and aldehyde **2**, followed by delivery of the boron substituent to the intermediate Mannich-type intermediate, gives the coupling product. Application of glyoxylic acid derivatives in this reaction proceeds smoothly to produce the corresponding amino acids **17** (Scheme 3).[16]



Scheme 3

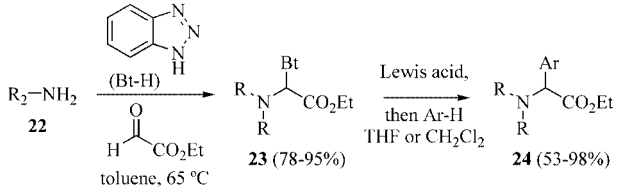
The same authors showed that this route may also provide enantiomerically pure amino acids by employment of enantiopure (*S*)-phenylglycinol (**19**) as the amine (Scheme 4).[17] The three-component coupling results in the diastereomerically pure amino acid **20**, which provides en-

antiomerically pure homophenylalanine **21** upon hydrogenolysis of the auxiliary.



Scheme 4

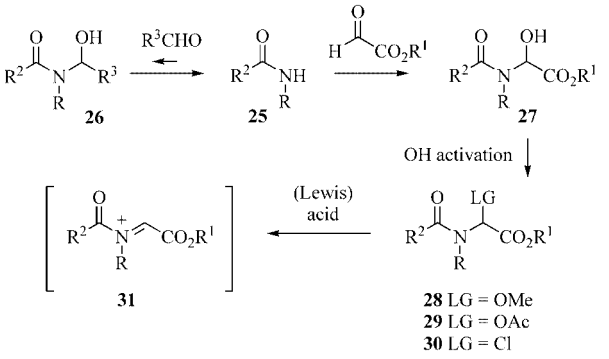
Yet another useful sequence − although not carried out in a one-pot fashion − was reported by Risch and co-workers.[18] Condensation of a secondary amine, benzotriazole, and ethyl glyoxylate according to a procedure previously established by Katritzky[19] gave rise to the aminals **23** in good yields (Scheme 5). Lewis acid treatment, followed by introduction of a range of aromatic nucleophiles gave the arylglycine derivatives **24** in generally good to excellent yields.



Scheme 5

3. Addition Reactions of Amides

Despite the significantly less nucleophilic natures of *N*-acylamines relative to amines, they readily react with glyoxylate derivatives, thanks to the strongly electrophilic character of the glyoxylate aldehyde function, to form stable N,O-hemiacetals **27** (Scheme 6). This contrasts strongly with the intermolecular addition of amides or carbamates to − less electrophilic − ordinary aliphatic and aromatic aldehydes (R^3 = Ar or alkyl): the latter case is an equilibrium process in which the formation of the desired adduct (**26**) is usually disfavored. Treatment of amides or carbamates with glyoxylate often involves stirring with freshly prepared glyoxylate (distilled from P_2O_5) at room temperature, giving the adduct **27** in good yield. Alternative procedures in which the free aldehyde is prepared in situ have also been developed. One example involves heating of the glyoxylate hemiacetal at reflux in benzene (with azeotropic removal of methanol) in the presence of the nitrogen nucleophile.[20] A more sophisticated way was reported by Van Benthem et al.[21] In this approach, the hemiacetal **5** was heated at reflux in CH_2Cl_2, and MeOH was azeotropically removed from the reaction mixture. The MeOH was trapped by molecular sieves (4 Å) in a Soxhlet apparatus to prevent polymerization of the aldehyde on the aluminum silicate surface. CH_2Cl_2 appeared to be a superior solvent for this approach, which may be due to the fact that the low boiling point of CH_2Cl_2 would allow a longer lifetime for the aldehyde in the reaction mixture.[22]



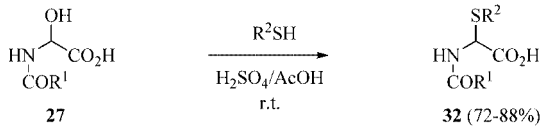
Scheme 6

Transformation of the hydroxy group into an appropriate leaving group can be carried out in different ways, including: (a) acid-catalyzed methanolysis, resulting in the corresponding N,O-acetal **28**[20a] (b) acetylation with an acetylating agent (**29**),[23] (c) chlorination of **27** with $SOCl_2$, resulting in the corresponding chloro derivative **30**,[20b] or (d) chlorination of the methyl N,O-acetal **28** with PCl_5.[20b]

The resulting products are all suitable precursors for the (Lewis) acid mediated formation of the corresponding *N*-acyliminium ion intermediates **31**. Because of the strongly electrophilic natures of these cations, they are reactive towards a wide range of (weak) nucleophiles and therefore constitute important intermediates for the formation of C−C bonds.[24] The enormous potential of these intermediates can be illustrated with successful applications in the synthesis of highly complex natural products.

3.1 Glyoxylates in Intermolecular *N*-Acyliminium Ion Reactions

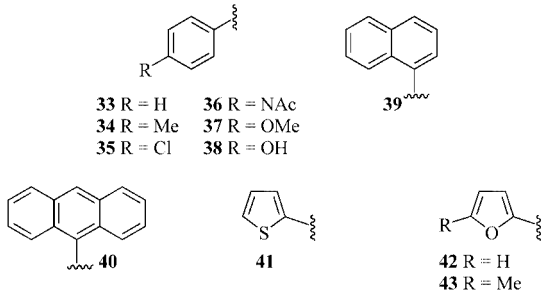
The first example of an intermolecular *N*-acyliminium ion reaction with a glyoxylate-derived precursor was reported in 1975.[20a] In that year, Ben-Ishai described the use of N,O-hemiacetal **27** in the protic acid mediated *N*-acyliminium ion addition of a variety of mercaptans (Scheme 7).



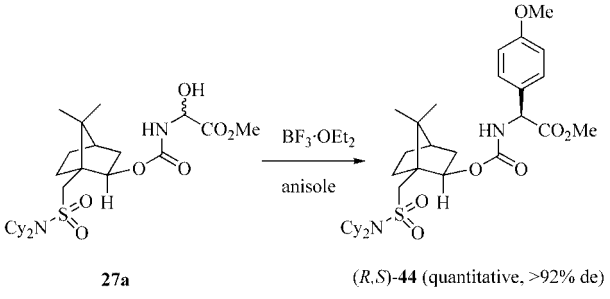
Scheme 7

The addition of mercaptans to *N*-acyliminium ion precursor **27** proceeded in a mixture of concentrated H_2SO_4 and acetic acid to afford the desired N,S-acetals **32** in good yields. By a different approach, starting from N,O-acetal **28**, 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 ranging from 68 to 92%.

Analogously, the development of *N*-acyliminium ion reactions with glyoxylate-derived precursors was extended to aromatic nucleophiles.[25] A wide range of aromatic nucleophiles (**33**−**41**) was successfully used in combination with N,O-hemiacetal **27** as the *N*-acyliminium ion precursor in concentrated H_2SO_4 to deliver the desired products in moderate to excellent yields of 41−92%. In the case of the acid-sensitive furan-derived nucleophiles **42** and **43**, the reaction conditions were changed. In these cases it turned out that, when starting from N,O-acetal **28**, the furan adducts were obtained in 67 and 84% yields, respectively, in the presence of the Lewis acid $BF_3{\cdot}OEt_2$. Since then, aromatic nucleophiles have been extensively used in the synthesis of α-aromatic amino acids.[26]

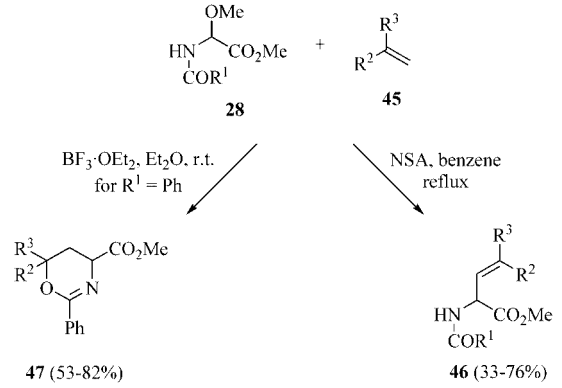


Harding reported an extension of this principle in the form of a diastereoselective addition of an aromatic nucleophile to a glyoxylate-derived precursor (Scheme 8).[27] Oppolzer's auxiliary was used to prepare N,O-hemiacetal **27a** as a mixture of diastereoisomers. Subsequent treatment of **27a** with $BF_3{\cdot}OEt_2$ and anisole resulted in an essentially quantitative yield of (*R*,*S*)-**44** in a *de* of > 92%. The same diastereoisomer was obtained when the reaction was performed in H_2SO_4/AcOH, albeit with a slightly lower *de* of 82%.



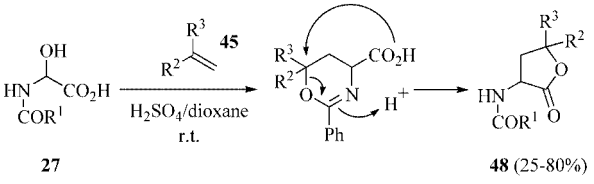
Scheme 8

In addition to that of mercaptans and aromatic nucleophiles, the application of olefinic nucleophiles has been developed by Ben-Ishai.[28] Glyoxylate-derived N,O-acetal **28**, several styrene derivatives **45**, and 2-naphthalenesulfonic acid (NSA) were allowed to react to afford the substituted vinylglycines **46** in good yields (Scheme 9). On the other hand, use of the benzoyl-protected N,O-acetal **28a** (R^1 = Ph) in combination with $BF_3{\cdot}OEt_2$ afforded oxazine **47** as the product. Both reactions were believed to occur through a cycloaddition reaction, in which the protonated oxazine **47** was generated as an intermediate. With the use of asymmetric olefins, products **46** and **47** were obtained as (*E*)/(*Z*) and *cis*/*trans* isomeric mixtures, respectively.



Scheme 9

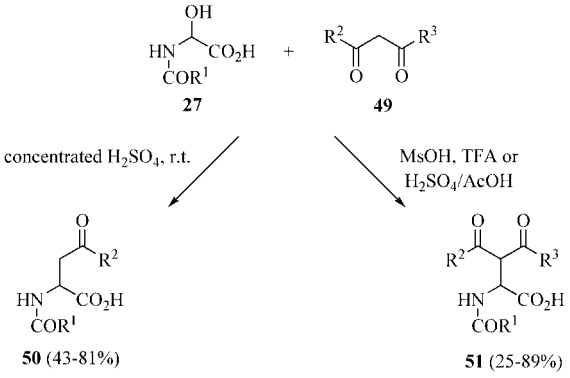
Intermolecular *N*-acyliminium ion reactions between N,O-hemiacetal **27** and olefins **45** resulted in the formation of *cis*/*trans* mixtures of lactone **48**, mostly in moderate yields (Scheme 10). The reactions were performed in mixtures of concentrated sulfuric acid and dioxane, in which the lactones were obtained after rearrangement of protonated oxazine intermediates (cf. the formation of **47**). Similar results were obtained by use of ethanethiol as the leaving group.[29] Further applications of the cyclic compounds **47** and **48** were investigated, particularly in the synthesis of unsaturated α-amino acids.[28,30]



Scheme 10

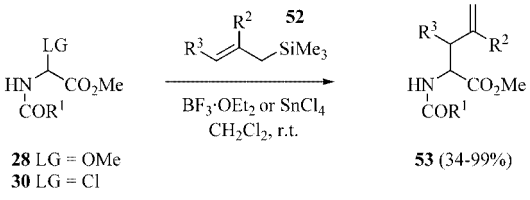
Concentrated sulfuric acid is the most commonly used acid and solvent for the *N*-acyliminium ion reaction of N,O-hemiacetal **27**. However, its use is limited to nucleophiles that are stable under these strongly acidic conditions. In the cases of α-diketones and α-oxo esters, for example, deacylation or decarboxylation of the desired products was observed as a side reaction, and so milder reaction conditions had to be found (Scheme 11).[31] MsOH, TFA, or H_2SO_4/AcOH solvent mixtures proved to be sufficiently acidic to generate the intermediate *N*-acyliminium ion, while being mild enough to produce product **51**. The desired products were isolated as isomeric mixtures. The application of α-diketones and α-oxo esters as nucleophiles was also investigated in the *N*-acyliminium ion reaction behavior of glyoxylate-derived *N*-acyliminium ion precursor **28**. Again, the stabilities 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 $BF_3{\cdot}OEt_2$ in CH_2Cl_2.



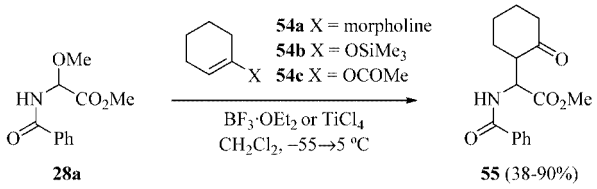
Scheme 11

The first example of the use of allyltrimethylsilane in a reaction with a glyoxylate-derived precursor was reported in 1988 (Scheme 12).[32] Substituted allylsilanes were also successfully applied, resulting in the preparation of a wide range of allylglycine derivatives **53**.[33] In the case of the N,O-acetal **28**, the best results were obtained by use of $BF_3{\cdot}OEt_2$ as the Lewis acid, while in the case of chloroglycine **30**, $SnCl_4$ gave the best results. Where appropriate, mixtures of diastereoisomers were obtained. Modifications of this procedure involving silicon-based π-nucleophiles include the use of vinylsilanes,[34] alkynylsilanes and stannanes,[35] cyclopentadienylsilane,[36] a menthyl ester as chiral auxiliary,[37] cyclic N,O-acetals,[38] and β-lactam-derived N,O-acetals.[39]



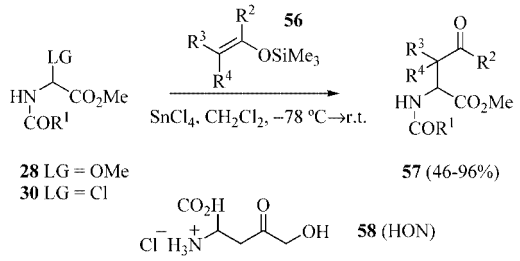
Scheme 12

Steckhan − who prepared the N,O-acetal **28a** by electrochemical methoxylation rather than by 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 (Scheme 13).[40] Several reaction conditions were evaluated, and the best results with the use of enamine **54a** were achieved in combination with $TiCl_4$, the *anti* diastereoisomer of **55** being obtained in yields of up to 90% and with *de* values of up to 86%. Silyl enol ether **54b** also gave its best results in combination with $TiCl_4$. With silyl enol ether **54b**, the *syn* diastereoisomer was surprisingly obtained as the major product, with *de* values of up to 38%. Enol acetate **54c** was much less reactive and only produced the desired product in combination with $BF_3{\cdot}OEt_2$ in a 50% yield and a maximum of 31% *de* in favor of the *anti* isomer.



Scheme 13

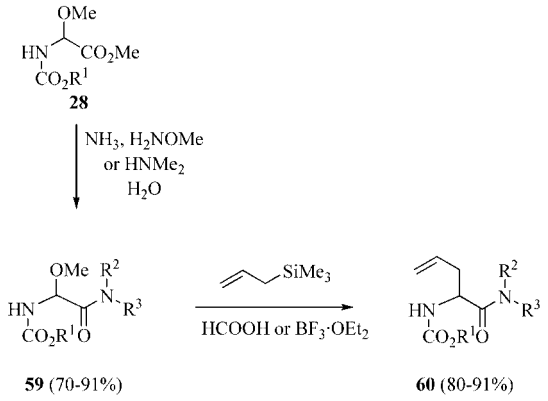
A more detailed study on the use of silyl enol ethers was demonstrated in the synthesis of α-amino γ-oxo acids.[41] In contrast to the use of bromoglycine (**28**, LG = Br),[42] the generation of an *N*-acylimino acetate from chloroglycine **30** (by treatment with Et_3N) and subsequent addition of silyl enol ethers resulted only in low yields of the anticipated product **57**. This difference in reactivity was attributed to the better leaving group ability of bromide with respect to chloride. Interestingly, the use of N,O-acetal **28** as an *N*-acyliminium ion precursor resulted in poor yields of the desired product. Nevertheless, a range of α-amino γ-oxo acids **57** was prepared from chloroglycine **30** by the $SnCl_4$-mediated *N*-acyliminium ion reaction with silyl enol ethers (Scheme 14). A particularly useful application of this approach was found in the synthesis of the natural product 5-hydroxy-4-oxonorvaline (HON, **58**). Fluorinated α-amino γ-oxo acids were prepared in a similar fashion by McCarthy.[43]



Scheme 14

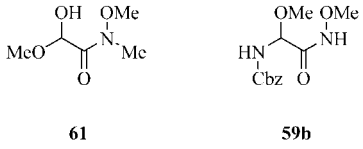
The scope of intermolecular *N*-acyliminium ion reactions was also extended to α-methoxyglycinamide precursors **59**.[44] The desired amides were obtained from N,O-acetal **28** and subsequently used in *N*-acyliminium ion chemistry with allyltrimethylsilane (Scheme 15). Formic acid and $BF_3{\cdot}OEt_2$ were found to be the most efficient reagents for the formation of the cationic intermediate. The reaction was also performed with substituted allylsilanes and afforded the products in reasonable yields and with low diastereoselectivities. 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 involving the use of *Pseudomonas putida* whole cells to produce the corresponding α-amino acids in enantiomerically pure form. Recently, the scope of the *N*-acyliminium ion step was extended with the use of a Weinreb amide-functionalized N,O-acetal (**59a**,

R^2 = OMe, R^3 = Me).[45] In the latter case, the required N,O-acetal **59a** was obtained directly from a carbamate by treatment with the Weinreb amide functionalized glyoxylate derivative **61**.



Scheme 15

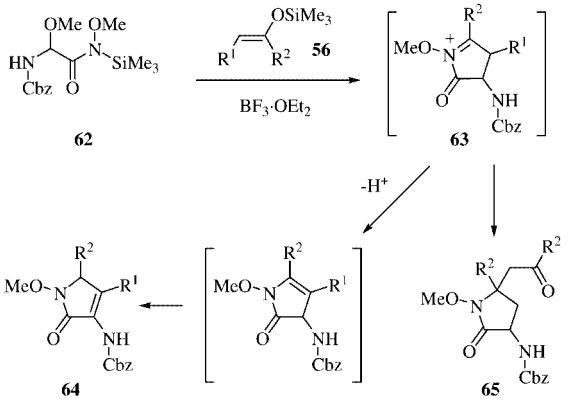
The use of silyl enol ethers in the *N*-acyliminium ion reaction with amide **59** was also investigated.[46] Unfortunately, the desired reaction between *N*-methoxycarboxamide **59b** and silyl enol ethers failed completely, which then resulted in the use of the in situ silylation approach described above.



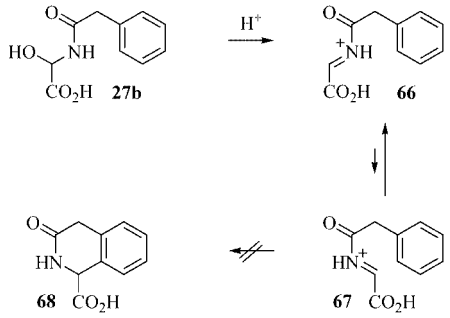
Interestingly, use of silylamide **62** in combination with silyl enol ethers resulted in the formation of dihydropyrrolone **64** and, in the cases of reactive or unhindered silyl enol ethers, in the formation of pyrrolidinones **65** in reasonable yields (Scheme 16). The formation of these rather unexpected cyclic products was explained in terms of the intermediacy of the cyclic *N*-acyliminium ion **63**, formed by attack of the reasonably nucleophilic amide nitrogen atom 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 by the same group.[47]

3.2. Glyoxylates in Intramolecular *N*-Acyliminium Ion Reactions

In 1980, Ben-Ishai reported the first investigations towards intramolecular *N*-acyliminium ion cyclization reactions with glyoxylate-derived precursors.[48] However, the intramolecular reaction between N,O-hemiacetal **27b** and an aromatic nucleophile appeared troublesome (Scheme 17). The reason for the anticipated product **68** not being formed was mainly attributed to the preferred *s-cis* conformation of the ionic heterodiene **66**, which disfavors the endotrigonal cyclization step (**67** → **68**).

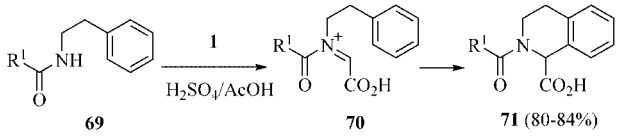


Scheme 16



Scheme 17

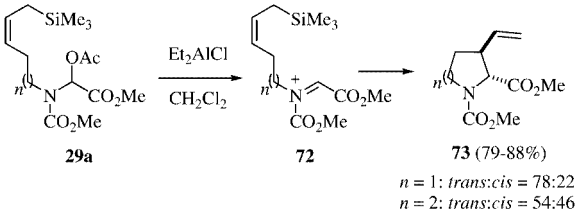
A slight modification of the starting material resulted in the cyclization precursor **69**, which successfully reacted in an endotrigonal fashion (Scheme 18).[49] The reaction with glyoxylic acid (**1**) and the subsequent cyclization step were performed in a one-pot fashion, which made this process 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-cis* conformation of the amide bond is therefore less pronounced, while the desired tetrahydroisoquinoline **71** was obtained in good yields. Ben-Ishai also reported the extension of this methodology to the cyclization of dipeptides.[50]



Scheme 18

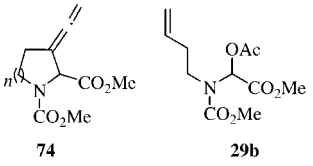
Subsequently, the use of silyl nucleophiles in intramolecular *N*-acyliminium ion chemistry with glyoxylate-derived precursors was examined (Scheme 19).[23] The Lewis acid mediated cyclization of allylsilane **29a** afforded the corresponding pyrrolidine or piperidine **73** in good yields. Especially in the case of the five-membered ring formation, the *trans* diastereoisomer was obtained with high selectivity.

Comparable results were obtained when product **73** was prepared from the corresponding N,O-hemiacetal by mesylation and subsequent generation of the ionic intermediate **72** under thermal conditions (MsCl and Et_3N, then heat). Propargylsilanes were also cyclized under Lewis acidic or thermal conditions to give the endocyclic allenes **74**.



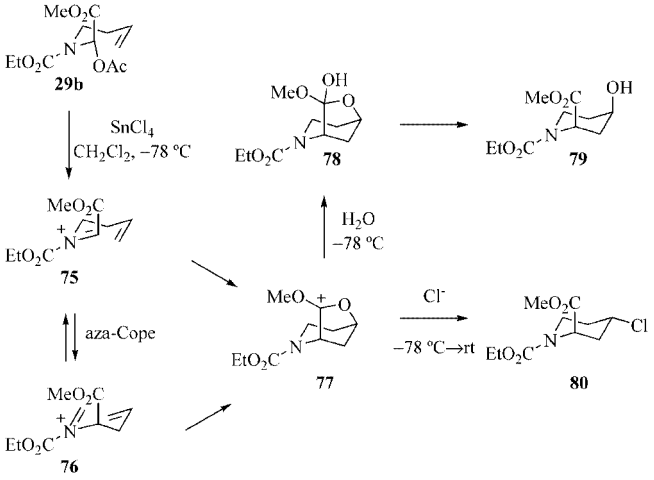
Scheme 19

The use of intramolecular nucleophiles was extended to the $SnCl_4$-mediated cyclization of olefin **29b**. The reaction was quenched with water either at −78 °C or after warming to room temp. to afford the axial alcohol **79** and the equatorial chloro derivative **80**, respectively.[51] Substituted olefins resulted in the formation of similar alcohols and chloro compounds.

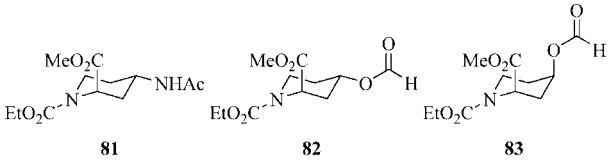


An important goal in this study was to investigate the cyclization mechanism, which might proceed through a cationic aza-Cope rearrangement. The proposed mechanism explaining the formation of the different products is shown in Scheme 20. Cyclization of both *N*-acyliminium ions **75** and **76** resulted in the formation of the dioxycarbenium ion **77**. Hydrolytic quenching resulted in the formation of **79**, while at higher temperatures the cation was quenched by an S_N2 attack of chloride to give **80**. Interestingly, in the case of allylsilane **72** ($n = 1$, Scheme 19) the cyclization step was apparently faster than the aza-Cope rearrangement of the 1,5-diene moiety, since the latter would have led to a six-membered ring. On the other hand, reductive trapping of the cationic intermediates **75**/**76** by the addition of Et_3SiH and trifluoroacetic acid resulted in the exclusive isolation of the reduced form of *N*-acyliminium ion **76**. This clearly proved the presence of a cationic aza-Cope rearrangement in this kind of cyclization reaction.

The same precursor was used for the $SnCl_4$-mediated cyclization in MeCN − analogous to the reactions with acetate **29b** described above − to afford the Ritter product **81**[44] and for the formic acid-induced reaction to give products **82** and **83**.[52] The formation of **82** was explained by equatorial attack of formic acid onto **79** (cf. formation of **76**), whereas formation of **83** was explained by the formation of intermediate **80**, due to traces of water in the formic acid.

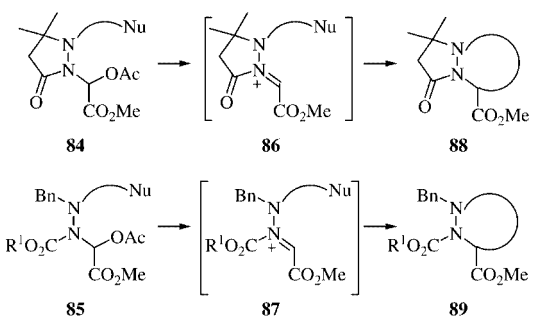


Scheme 20

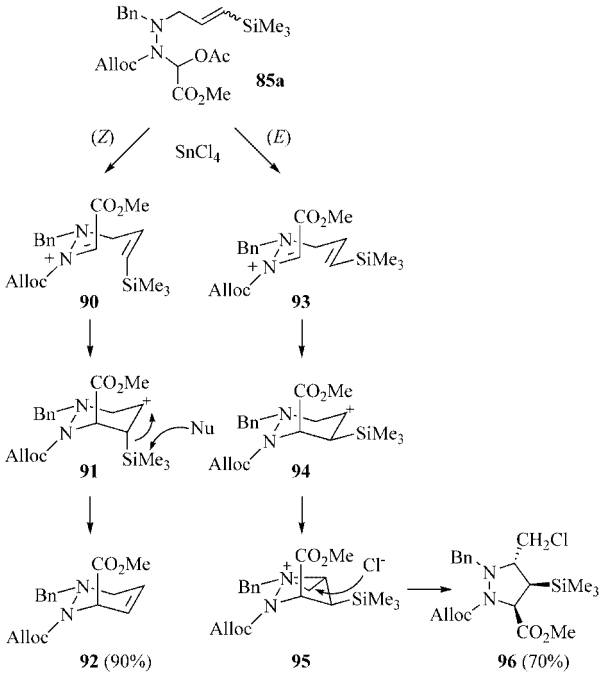


The application of glyoxylates in combination with hydrazine derivatives in intramolecular *N*-acyliminium reactions was demonstrated by cyclization reactions of the pyrazolidinones **84**[53] and monobenzylated carbazates **85**.[54] This resulted − through the intermediacy of the *N*-acylhydrazonium ions **86** and **87** − in the preparation of a wide range of bicyclic hydrazino acids **88** and functionalized cyclic α-hydrazino acids **89**, respectively.

Mechanistic studies of these intramolecular *N*-acyliminium reactions showed a striking difference between the cyclization of (*E*)- and (*Z*)-vinylsilanes **85a**. The two chair-like transition-state conformations of the cationic intermediates are shown in Scheme 21. Cyclization of the (*Z*) precursor **85a** occurs via intermediates **90** and **91**, in which the trimethylsilyl group occupies an axial position. This orientation produces a maximal σ−π hyperconjugative stabilization of the developing positive charge, followed by a fast elimination to give the unsaturated six-membered ring **92**. The reaction of the (*E*)-vinylsilane **85a** occurs via intermediates **93** and **94**, in which the trimethylsilyl group occu-



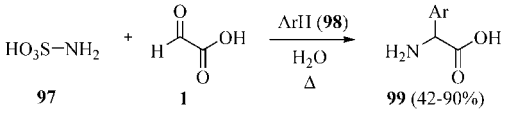
pies an equatorial position. In this position the β-C−Si bond is not oriented coplanar to the vacant p-orbital and stabilization of the positive charge by the silicon atom is not likely to take place. Stabilization of the cationic six-membered ring therefore occurs by formation of the aziridinium intermediate **95**, thus resulting in a ring-contraction. Subsequent intermolecular attack of a nucleophile affords the final product **96**.



Scheme 21

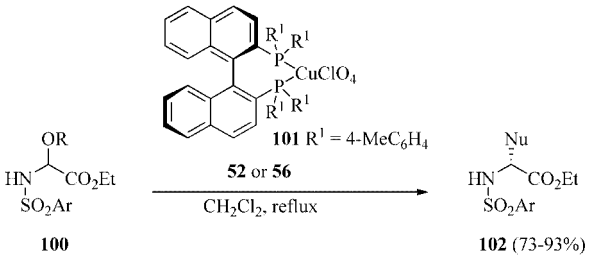
4. Addition Reactions of Sulfonamides

As well as the *N*-acyliminium group, the *N*-sulfonyliminium group has also been successfully used for the acid-mediated introduction of carbon nucleophiles.[55] In combination with glyoxylate derivatives, *N*-sulfonyliminium ion chemistry results in the formation of *N*-sulfonyl-protected amino acids. A particularly nice example of *N*-sulfonyliminium ion chemistry was reported by Boesten and De Heij (Scheme 22).[56] In a multi-component fashion, sulfamic acid (**97**), glyoxylic acid (**1**), and an aromatic nucleophile **98** reacted to afford the corresponding α-amino acids **99** in yields up to 90%.



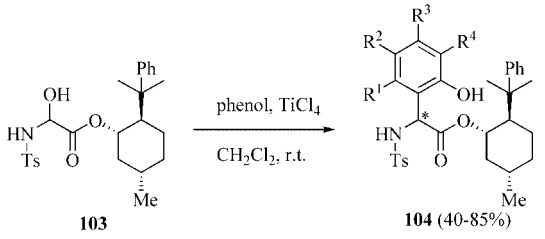
Scheme 22

Lectka described the use of different silyl nucleophiles in combination with a variety of aromatic *N*-sulfonyl N,O-acetals **100** and a chiral Cu^{I}-based Lewis acid catalyst (**101**, Scheme 23) to provide the optically active sulfonyl-protected amino acids **102**.[57] Yields ranged from 73 to 93%, while *ee* values of up to 96% were reported.



Scheme 23

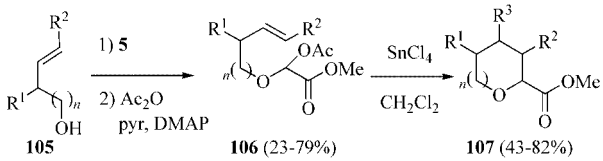
Recently, the 8-phenylmenthyl ester derived N,O-acetal **103** was applied as a chiral auxiliary in the diastereoselective addition of phenols to *N*-sulfonyliminium ion intermediates (Scheme 24).[58] With the use of the appropriate Lewis acid ($TiCl_4$), the desired products **104** were obtained in good yields (40−85%) and with excellent *de* values (up to 99%).



Scheme 24

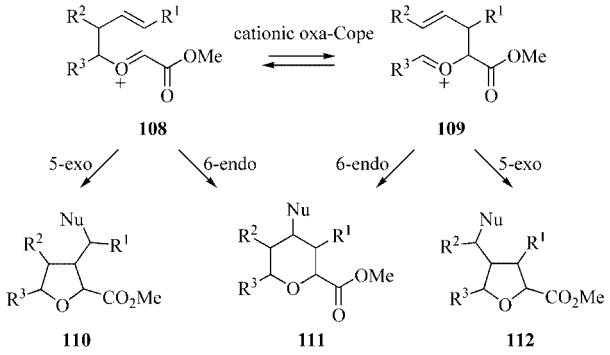
5. Intramolecular Oxycarbenium Ion Reactions

Oxycarbenium ions have reactivities comparable to those of *N*-acyliminium ions, and so can also be used as reactive intermediates derived from glyoxylate derivatives. The use of oxycarbenium ions, however, results in the formation of oxacyclic esters rather than the cyclic α-amino acid derivatives described with *N*-acyliminium ion intermediates (Scheme 25).[59] The appropriate cyclization precursors **106** were obtained from the corresponding alcohols **105** after condensation with methyl glyoxylate and subsequent acylation. The acetate function was found to be the most suitable leaving group for the subsequent formation of the anticipated oxycarbenium ion. Cyclization was accomplished by treatment with $SnCl_4$, the intramolecular π-nucleophile reacting with the transient oxycarbenium ion.



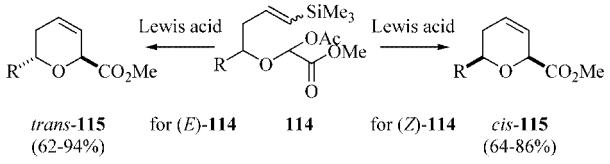
Scheme 25

Depending on the substitution pattern of the cyclization precursor and the equilibration of the cationic oxa-Cope rearrangement, several cyclization modes are possible.[60] When starting from oxycarbenium ion **108**, for example, cationic oxa-Cope rearrangement gives oxycarbenium ion **109**, while both cationic intermediates can cyclize in either 5-*exo* or 6-*endo* fashion to afford tetrahydrofurans **110** or **112**, or tetrahydropyran **111**, respectively (Scheme 26).



Scheme 26

Dihydropyrans were obtained by the stereoselective cyclization of vinylsilane-substituted oxycarbenium ions (Scheme 27).[61] The geometry of the double bond proved to have a remarkable influence on the stereochemistry of the product, (*E*)-**114** giving the *trans* product **115** (*cis*/*trans* ratio up to 11:89), whereas (*Z*)-**114** provided *cis*-**115** (*cis*/*trans* ratio up to > 98:2). The selectivity of the cyclization reaction was explained by the difference in the cyclization rates of the several intermediates resulting from a cationic oxa-Cope rearrangement and subsequent chair-chair interconversion.



Scheme 27

6. Conclusion

In conclusion, glyoxylic acid and its derivatives are extremely useful ester-substituted aldehyde equivalents for the generation of precursors for reactive cationic intermediates such as iminium ions, *N*-acyliminium ions, *N*-sulfonyliminium ions, and oxycarbenium ions. These intermediates have been applied to a broad range of examples of the synthesis of (cyclic) α-amino acids and α-alkoxy esters. Most of the research presented in this review has been dedicated to evaluation of the scope and limitations of the cationic intermediates with respect to the type of nucleophiles in intra- and intermolecular reactions. In view of the abundance of existing applications, future developments in the use of glyoxylate derivatives for such purposes may include the development of stereoselective methods and combinatorial or solid-phase approaches.

[1] See, e.g.: *Glyoxylic Acid*, in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: L. A. Paquette), John Wiley & Sons, New York, **1995**, vol. 4, p. 2620−2622.
[2] For examples, see: M. E. Jung, K. Shishido, L. H. Davis, *J. Org. Chem.* **1982**, *47*, 891−892 and references cited therein.
[3] J. G. Haggerty, T. R. Kelly, T. E. Schmidt, *Synthesis* **1972**, 544−545.
[4] A. Sajtos, M. Wechsberger, E. Roithner, AT 376197B, **1984**.
[5] J. M. Hook, *Synth. Commun.* **1984**, *14*, 83−87.
[6] [6a] J. Rademann, M. Meldal, K. Bock, *Chem. Eur. J.* **1999**, *5*, 1218−1225. [6b] N. Schlienger, M. R. Bryce, T. K. Hansen, *Tetrahedron Lett.* **2000**, *41*, 5147−5150. [6c] S. Kobayashi, R. Akiyama, H. Kitagawa, *J. Comb. Chem.* **2000**, *2*, 438−440. [6d] S. Kobayashi, R. Akiyama, H. Kitagawa, *J. Comb. Chem.* **2001**, *3*, 196−204.
[7] [7a] R. Kober, K. Papadopoulos, W. Miltz, D. Enders, W. Steglich, *Tetrahedron* **1985**, *41*, 1693−1701. [7b] P. Münster, W. Steglich, *Synthesis* **1987**, *3*, 223−225. [7c] P. Hartmann, J.-P. Obrecht, *Synth. Commun.* **1988**, *18*, 553−557. [7d] P. Ermert, J. Meyer, C. Stucki, J. Schneebeli, J.-P. Obrecht, *Tetrahedron Lett.* **1988**, *29*, 1265−1268. [7e] T. Bretschneider, W. Miltz, P. Münster, W. Steglich, *Tetrahedron* **1988**, *44*, 5403−5414. [7f] R. M. Williams, D. J. Aldous, S. C. Aldous, *J. Org. Chem.* **1990**, *55*, 4657−4663. [7g] C. J. Easton, I. M. Scharfbillig, *J. Org. Chem.* **1990**, *55*, 384−386. [7h] D. P. G. Hamon, R. A. Massy-Westropp, P. Razzino, *Tetrahedron* **1992**, *48*, 5163−5178. [7i] Y. Yamamoto, S. Onuki, M. Yumoto, N. Asao, *J. Am. Chem. Soc.* **1994**, *116*, 421−422. [7j] H. Dialer, W. Steglich, W. Beck, *Tetrahedron* **2001**, *57*, 4855−4861.
[8] [8a] Y. Yamamoto, S. Onuki, M. Yumoto, N. Asao, *Heterocycles* **1998**, *47*, 765−780. [8b] S. Yao, S. Saaby, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2000**, *6*, 2435−2448. [8c] S. Saaby, X. Fang, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2000**, *112*, 4280−4282; *Angew. Chem. Int. Ed.* **2000**, *39*, 4114−4116. [8d] S. Kobayashi, R. Akiyama, H. Kitagawa, *J. Comb. Chem.* **2000**, *2*, 438−440. [8e] S. Kobayashi, R. Akiyama, H. Kitagawa, *J. Comb. Chem.* **2001**, *3*, 196−204.
[9] For an excellent recent review on the use of α-imino esters, see: A. E. Taggi, A. M. Hafez, T. Lectka, *Acc. Chem. Res.* **2003**, *36*, 10−19.
[10] P. D. Bailey, J. Clayson, A. N. Boa, *Contemp. Org. Synth.* **1995**, *2*, 173−187.
[11] For examples, see e.g.: [11a] S. P. Hollinshead, M. L. Trudell, P. Skolnick, J. M. Cook, *J. Med. Chem.* **1990**, *33*, 1062−1069. [11b] S.-D. Cho, S.-Y. Song, E.-J. Hur, M. Chen, W.-H. Joo, J. R. Falck, Y.-J. Yoon, D.-S. Shin, *Tetrahedron Lett.* **2001**, *42*, 6251−6253.
[12] [12a] A. Ahmad, *Bull. Chem. Soc., Jpn.* **1974**, *47*, 1819. [12b] Y. Watanabe, S. C. Shim, T. Mitsudo, M. Yamashita, Y. Takegami, *Chem. Lett.* **1975**, 699−700. [12c] W. M. Hearon, L. C. Fan, US 4073804, **1978**. [12d]A. Papanikos, J. Rademann, M. Meldal, *J. Am. Chem. Soc.* **2001**, *123*, 2176−2181.
[13] A. V. Zychlinski, I. Ugi, *Heterocycles* **1998**, *49*, 29−32.
[14] For an excellent review on Mannich reactions, see: M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096−1122; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044−1070.
[15] [15a] N. A. Petasis, I. Akritopoulou, *Tetrahedron Lett.* **1993**, *34*, 583−586. [15b] N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1998**, *120*, 11798−11799.
[16] N. A. Petasis, A. Goodman, I. A. Zavialov, *Tetrahedron* **1997**, *53*, 16463−16470.
[17] N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445−446.

[18] H.-J. Grumbach, B. Merla, N. Risch, *Synthesis* **1999**, 1027−1033.
[19] A. R. Katritzky, L. Urogdi, A. Mayence, *Synthesis* **1989**, 323−327.
[20] [20a] U. Zoller, D. Ben-Ishai, *Tetrahedron* **1975**, *31*, 863−866. [20b] Z. Bernstein, D. Ben-Ishai, *Tetrahedron* **1977**, *33*, 881−883.
[21] R. A. T. M. van Benthem, H. Hiemstra, W. N. Speckamp, *J. Org. Chem.* **1992**, *57*, 6083−6085.
[22] R. A. T. M. van Benthem, PhD Dissertation ("Palladium cluster catalyzed oxidative cyclizations in the synthesis of aminoalkenols and diamines"), University of Amsterdam, **1995**.
[23] H. H. Mooiweer, H. Hiemstra, H. P. Fortgens, W. N. Speckamp, *Tetrahedron Lett.* **1987**, *28*, 3285−3288.
[24] For reviews on *N*-acyliminium ion chemistry, see: [24a] W. N. Speckamp, H. Hiemstra, *Tetrahedron* **1985**, *41*, 4367−4416. [24b] H. Hiemstra, W. N. Speckamp in *The Alkaloids* (Ed.: A. Brossi), Academic, Oxford, **1988**, vol. 32, p. 271−339. [24c] H. Hiemstra, W. N. Speckamp in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, vol. 2, p. 1047−1082. [24d] H. de Koning, M. J. Moolenaar, H. Hiemstra, W. N. Speckamp in *Bioactive Natural Products*, part A ("Studies in Natural Products Chemistry") (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1993**, vol. 13, p. 473−518. [24e] H. de Koning, W. N. Speckamp in *Houben-Weyl, Methods in Organic Chemistry* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, vol. E21b, p. 1953−2009. [24f]W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817−3856.
[25] D. Ben-Ishai, I. Sataty, Z. Bernstein, *Tetrahedron* **1976**, *32*, 1571−1573.
[26] [26a] A. Schouteeten, Y. Christidis, G. Mattioda, *Bull. Soc. Chim. Fr.* **1978**, *II*, 248−254. [26b] A. Schouteeten, Y. Christidis, G. Mattioda, M. J. Brienne, J. Jacques, *Bull. Soc. Chim. Belg.* **1979**, *88*, 897−904. [26c] G. J. Lofthouse, *J. Chem. Soc., Perkin Trans. 1* **1979**, 1634−1639. [26d] D. Ben-Ishai, N. Peled, I. Sataty, *Tetrahedron Lett.* **1980**, *21*, 569−572. [26e] M. L. Edwards, *J. Heterocycl. Chem.* **1980**, *17*, 383−384. [26f] E. H. W. Böhme, R. E. Bambury, R. J. Baumann, R. C. Erickson, B. L. Harrison, P. F. Hoffman, F. J. McCarthy, R. A. Schnetter, M. J. Vaal, D. L. Wenstrup, *J. Med. Chem.* **1980**, *23*, 405−412. [26g] I. T. Barnish, P. E. Cross, J. C. Danilewicz, R. P. Dickinson, D. A. Stopher, *J. Med. Chem.* **1981**, *24*, 399−404. [26h] T. Sadeh, M. A. Davis, R. Gil, U. Zoller, *J. Heterocycl. Chem.* **1981**, *18*, 1605−1607. [26i] S. Kukolja, S. E. Draheim, J. L. Pfeil, R. D. G. Cooper, B. J. Graves, R. E. Holmes, D. A. Neel, G. W. Huffman, J. A. Webber, M. D. Kinnick, R. T. Vasileff, B. J. Foster, *J. Med. Chem.* **1985**, *28*, 1886−1896. [26j] M. A. Ciufolini, C. Y. Wood, *Tetrahedron Lett.* **1986**, *27*, 5085−5088. [26k] N. L. Dirlam, B. S. Moore, F. J. Urban, *J. Org. Chem.* **1987**, *52*, 3587−3591. [26l] D. Ben-Ishai, S. Hirsh, *Tetrahedron* **1988**, *44*, 5441−5449. [26m] C. F. Bigge, J. T. Drummond, G. Johnson, T. Malone, A. W. Probert Jr., F. F. Marcoux, L. L. Coughenour, L. J. Brahce, *J. Med. Chem.* **1989**, *32*, 1580−1590. [26n] E. A. Cutmore, A. W. Guest, J. D. I. Hatto, C. J. Moores, T. C. Smale, *J. Chem. Soc., Perkin Trans. 1* **1990**, 847−853. [26o] J. J. Barlow, T. P. Blackburn, G. F. Costello, R. James, D. J. Le Count, B. G. Main, R. J. Pearce, K. Russel, J. S. Shaw, *J. Med. Chem.* **1991**, *34*, 3150−3158. [26p] F. J. Urban, B. S. Moore, *J. Heterocycl. Chem.* **1992**, *29*, 431−438. [26q] C. A. Lipinski, C. E. Aldinger, T. A. Beyer, J. Bordner, D. F. Burdi, D. Bussolotti, P. B. Linskeep, T. W. Siegel, *J. Med. Chem.* **1992**, *35*, 2169−2177. [26r] S. Sheffer-Dee-Noor, D. Ben-Ishai, *Tetrahedron* **1994**, *50*, 7009−7018. [26s] M.-J. Brienne, J. Gabard, M. Leclercq, J.-M. Lehn, M. Cheve, *Helv. Chim. Acta* **1997**, *80*, 856−875. [26t] M. Schmitt, J.-J. Bourguignon, G. B. Barlin, G. B. Davies, *Aust. J. Chem.* **1997**, *50*, 779−785.
[27] K. E. Harding, C. S. Davis, *Tetrahedron Lett.* **1988**, *29*, 1891−1894.
[28] [28a] J. Altman, R. Moshenberg, D. Ben-Ishai, *Tetrahedron Lett.* **1975**, *16*, 3737−3740. [28b] D. Ben-Ishai, R. Moshenberg, J. Altman, *Tetrahedron* **1977**, *33*, 1533−1542.
[29] D. Plusquellec, Y. Le Floc'h, D. Papillon-Jegou, *Bull. Soc. Chim. Fr.* **1979**, *II*, 552−558.
[30] [30a] D. Ben-Ishai, S. Hirsch, *Tetrahedron Lett.* **1983**, *24*, 955−958. [30b] D. Ben-Ishai, S. Hirsch, *Tetrahedron* **1988**, *44*, 5441−5449.
[31] [31a] D. Ben-Ishai, Z. Berler, J. Altman, *J. Chem. Soc., Chem. Commun.* **1975**, 905−906. [31b] D. Ben-Ishai, J. Altman, Z. Bernstein, N. Peled, *Tetrahedron* **1978**, *34*, 467−473.
[32] A. L. Castelhano, S. Horne, G. J. Taylor, R. Billedeau, A. Krantz, *Tetrahedron* **1988**, *44*, 5451−5466.
[33] H. H. Mooiweer, H. Hiemstra, W. N. Speckamp, *Tetrahedron* **1989**, *45*, 4627−4636.
[34] S. C. Ebeling, D. Matthies, D. McCarthy, *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *60*, 265−273.
[35] [35a] P. Casara, B. W. Metcalf, *Tetrahedron Lett.* **1978**, *19*, 1581−1584. [35b] C. Danzin, P. Casara, N. Claverie, B. W. Metcalf, *J. Med. Chem.* **1981**, *24*, 16−20. [35c] R. M. Williams, D. J. Aldous, S. C. Aldous, *J. Chem. Soc., Perkin Trans. 1* **1990**, 171−172. [35d] R. M. Williams, D. J. Aldous, S. C. Aldous, *J. Org. Chem.* **1990**, *55*, 4657−4663.
[36] H. Dialer, W. Steglich, W. Beck, *Tetrahedron* **2001**, *57*, 4855−4861.
[37] [37a] S. C. Ebeling, D. J. Matthies, *J. Prakt. Chem.* **1994**, *336*, 271−272. [37b] S. C. Ebeling, *J. Prakt. Chem.* **1994**, *336*, 330−332.
[38] [38a] G. Kardassis, P. Brungs, E. Steckhan, *Tetrahedron* **1998**, *54*, 3471−3478. [38b] G. Kardassis, P. Brungs, C. Nothhelfer, E. Steckhan, *Tetrahedron* **1998**, *54*, 3479−3488.
[39] A. G. M. Barrett, M. Ahmed, S. P. Baker, S. P. D. Baugh, D. C. Braddock, P. A. Procopiou, A. J. P. White, D. J. Williams, *J. Org. Chem.* **2000**, *65*, 3716−3721.
[40] K.-D. Ginzel, P. Brungs, E. Steckhan, *Tetrahedron* **1989**, *45*, 1691−1701.
[41] H. H. Mooiweer, K. W. A. Ettema, H. Hiemstra, W. N. Speckamp, *Tetrahedron* **1990**, *46*, 2991−2998.
[42] T. Bretschneider, W. Miltz, P. Münster, W. Steglich, *Tetrahedron* **1988**, *44*, 5403−5403.
[43] J. P. Whitten, C. L. Barney, E. W. Huber, P. Bey, J. R. McCarthy, *Tetrahedron Lett.* **1989**, *30*, 3649−3652.
[44] E. C. Roos, H. H. Mooiweer, H. Hiemstra, W. N. Speckamp, B. Kaptein, W. H. J. Boesten, J. Kamphuis, H. E. Schoemaker, *J. Org. Chem.* **1992**, *57*, 6769−6778.
[45] W. J. N. Meester, R. van Dijk, J. H. van Maarseveen, F. P. J. T. Rutjes, P. H. H. Hermkens, H. Hiemstra, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2909−2911.
[46] E. C. Roos, H. Hiemstra, W. N. Speckamp, B. Kaptein, J. Kamphuis, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 360−364.
[47] E. C. Roos, M. C. López, M. A. Brook, H. Hiemstra, W. N. Speckamp, B. Kaptein, J. Kamphuis, H. E. Schoemaker, *J. Org. Chem.* **1993**, *58*, 3259−3268.
[48] D. Ben-Ishai, N. Peled, I. Sataty, *Tetrahedron Lett.* **1980**, *21*, 569−572.
[49] D. Ben-Ishai, I. Sataty, N. Peled, R. Goldshare, *Tetrahedron* **1987**, *43*, 439−450.
[50] [50a] D. Ben-Ishai, A. R. McMurray, *Tetrahedron* **1993**, *49*, 6399−6410. [50b] A. Rabi-Barakay, D. Ben-Ishai, *Tetrahedron* **1994**, *50*, 10771−10782.
[51] P. M. Esch, I. M. Boska, H. Hiemstra, R. F. de Boer, W. N. Speckamp, *Tetrahedron* **1991**, *47*, 4039−4062.
[52] C. Danzin, P. Casara, N. Claverie, B. W. Metcalf, *J. Med. Chem.* **1981**, *24*, 16−20.
[53] [53a] F. P. J. T. Rutjes, J. H. Udding, H. Hiemstra, W. N. Speckamp, *Heterocycles* **1992**, *33*, 81−85. [53b] F. P. J. T. Rutjes, J. H. Udding, H. Hiemstra, W. N. Speckamp, *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 145−152.
[54] F. P. J. T. Rutjes, N. M. Teerhuis, H. Hiemstra, W. N. Speckamp, *Tetrahedron* **1993**, *49*, 8605−8628.
[55] For a review on *N*-sulfonylimines, see: S. M. Weinreb, *Top. Curr. Chem.* **1997**, *190*, 131−184.
[56] W. H. J. Boesten, N. A. de Heij, EP 530879 A1, **1993**.

[57] [57a] D. Ferraris, T. Dudding, B. Young, W. J. Drury, III, T. Lectka, *J. Org. Chem.* **1999**, *64*, 2168−2169. [57b] D. Ferraris, B. Young, T. Dudding, W. J. Drury, III, T. Lectka, *Tetrahedron* **1999**, *55*, 8869−8882. [57c] D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. Drury, III, L. Ryzhkov, A. E. Taggi, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 67−77.
[58] C.-S Ge, Y.-J. Chen, D. Wang, *Synlett* **2002**, 37−42.
[59] [59a] L. D. M. Lolkema, H. Hiemstra, H. H. Mooiweer, W. N. Speckamp, *Tetrahedron Lett.* **1988**, *29*, 6365−6368. [59b] L. D. M. Lolkema, H. Hiemstra, C. Semeyn, W. N. Speckamp, *Tetrahedron* **1994**, *50*, 7115−7128.
[60] L. D. M. Lolkema, C. Semeyn, L. Ashek, H. Hiemstra, W. N. Speckamp, *Tetrahedron* **1994**, *50*, 7129−7140.
[61] C. Semeyn, R. H. Blaauw, H. Hiemstra, W. N. Speckamp, *J. Org. Chem.* **1997**, *62*, 3426−3427.

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