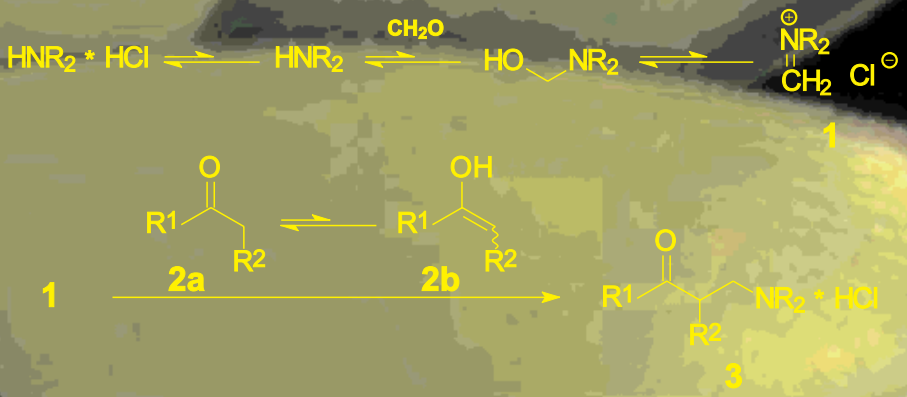
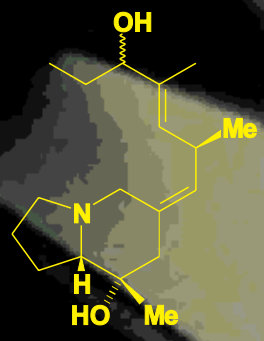
What does Carl Mannich



Dendrobates pumilio
(Costa Rica)



Pumiliotoxin

have to do with frogs ?

Modern Variants of the Mannich Reaction

Michael Arend, Bernhard Westermann, and Nikolaus Risch*

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

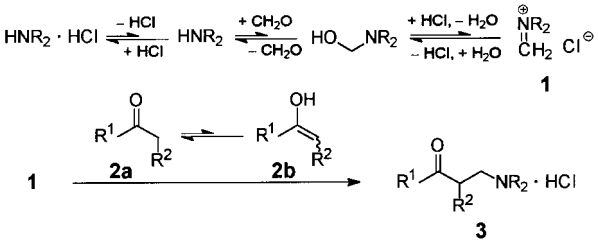
The Mannich reaction is a classical method for the preparation of β-amino ketones and aldehydes (Mannich bases) and, as such, is one of the most important basic reaction types in organic chemistry. It is the key step in the synthesis of numerous pharmaceuticals and natural products. Mannich bases and derivatives such as 1,3-amino alcohols or Michael acceptors, which are easily formed from Mannich bases, are particularly versatile synthetic intermediates and find great use in, for example, medicinal chemistry. Nevertheless, when seen from a modern viewpoint, the potential of the classical intermolecular Mannich reaction is rather modest. Thus the range of application is limited (e.g. confined to aminomethylation), and in many cases undesired side products are formed. Additionally, the ability to control regio- and stereoselectivity is generally unsatisfactory. However, the exceptional attractiveness of Mannich bases and their derivatives makes the challenge of overcoming these drawbacks worthwhile. Modern variants, whose range of applications is much wider than that of the classical methodology, and which can be carried out with effective control of regio- and stereoselectivity, form the focus of this review. Intramolecular Mannich reactions are much more versatile than corresponding intermolecular versions. Because of this, they have always excited the imagination of chemists. For example, such intramolecular reactions are used for the biomimetic preparation of natural products, and for many other applications. In general, one can use the Mannich reaction as part of a tandem reaction sequence for the elegant and often deceptively simple construction of complex target molecules. Current applications of this chemistry in the preparation of pharmaceutical and natural products will be presented.

Keywords: aminoalkylation · asymmetric synthesis · biomimetic synthesis · domino reactions · Mannich bases

1. Introduction

The aminoalkylation of CH-acidic compounds was described by several authors as early as the 19th. century. However, it was Carl Mannich who was the first to recognize the enormous significance of this reaction type, and it was he who extended the chemistry into a broad based synthetic methodology through systematic research. Since than this reaction that now carries his name has developed into one of the most important C–C bond-forming reactions in organic chemistry.[1, 2]

In practice, enolizable aldehydes or ketones serve as the CH-acidic substrate for Mannich reactions. In the most important variation, the carbonyl compound is heated with formaldehyde and an amine hydrochloride in a protic solvent. A simplified mechanism is given in Scheme 1. It is assumed that methylene iminium salts **1** are formed in tiny amounts, by a series of equilibrium reactions. These then react with the enol tautomer **2b** of the carbonyl compound **2a**, also present in very small equilibrium concentrations, to give the hydrochloride of the β-aminocarbonyl compound **3**. These so-called Mannich bases are versatile synthetic building blocks, which can easily be converted into a range of useful and valuable derivatives (Scheme 2). Such derivatives include Michael acceptors **4** (elimination of the amine HNR_2), 1,3-amino alcohols **5** (reduction or addition of organometallic com-



Scheme 1. Simplified mechanism of the Mannich reaction.

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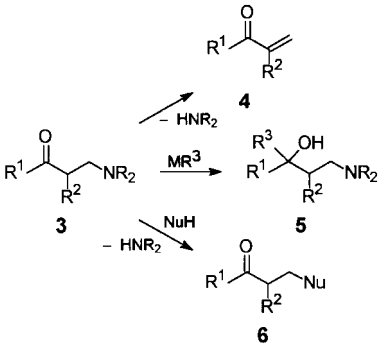
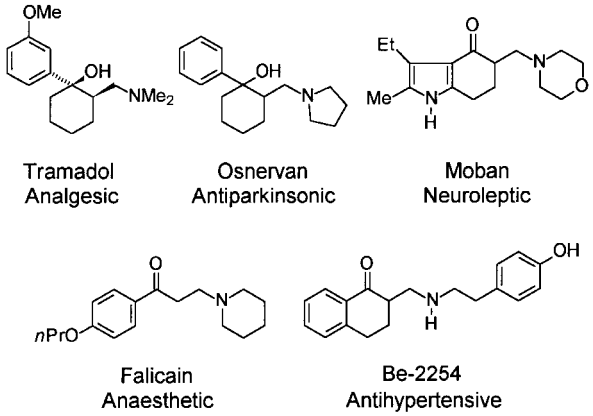


Scheme 2. Mannich bases as synthetic building blocks.



Scheme 3. Application of Mannich bases and their derivatives in medicine.

pounds) and functionalized carbonyl compounds **6** (substitution of NR_2 by nucleophiles).[1] Mannich bases and their derivatives have many attractive applications, for example in plant protection and in paint and polymer chemistry (hardeners, cross-linkers, and reaction accelerators).[1] However, the most important application by far is in the area of pharmaceutical products.[1, 3] A small selection of these is represented in Scheme 3. At the moment, the use of Mannich bases in cancer therapy (as cytostatics) is one of several current areas of research.[3c, d]

The classical intermolecular Mannich reaction is, however, plagued by a number of serious disadvantages:[1] Due to the drastic reaction conditions and the long reaction times, unwanted side reactions often take place. Major problems here are deamination and the formation of methylene bisketones **7**. Single products **3** are generally only obtained when secondary amines are used. If one uses a primary amine or ammonia as the amine component, reaction can continue until all the H atoms on the nitrogen are replaced. As a consequence, one obtains, in addition to the desired product **3**, the other Mannich bases **8** and **9** as major components. Ketones with two reactive α-positions must be used in large

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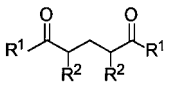
Nikolaus Risch, born in 1949 in Lemgo (Germany) studied chemistry at the Technische Universität Braunschweig, completing his course there in 1975 with a doctorate on the structure elucidation and partial synthesis of bacteriochlorophylls under the supervision of H. Brockmann. After a year as postdoc in the division Niedermolekulare Naturstoffe of the Gesellschaft für Biotechnologische Forschung (GBF) in Braunschweig he became scientific assistent at the Faculty of Chemistry of the newly founded Universität Bielefeld in 1976, where he was involved with the establishment of the new university. In 1984 he completed his habilitation in the field of organic synthesis. He accepted a professorship at the Universität Paderborn in 1992. His research interests are the development and application of modern synthesis methods (domino reactions, novel fragmentations, building blocks for supramolecular chemistry, stereoselective reactions) and the preparative and analytic aspects of photodynamic therapy with derivatives of natural tetrapyrrole dyes.

Michael Arend, born in 1966 in Paderborn, studied chemistry at the Universität Paderborn (1987 – 1993) and obtained his doctorate in 1996 in the research group of N. Risch with a thesis on regio- and stereoselective synthesis of Mannich bases. In the summer of 1997 he was awarded a Feodor-Lynen fellowship by the Alexander-von-Humboldt Foundation and has since been working as postdoc at the University of Florida, Gainesville (USA) with A. R. Katritzky.

Bernhard Westermann, born in 1962 in Oelde (Germany), studied chemistry (1981 – 1986) at the Universität Paderborn and completed his doctorate there in 1989 under the supervision of H.-J. Altenbach with a thesis on ferroelectric liquid crystals. After a postdoctoral fellowship at the University of Toronto with J. B. Jones, he began his habilitation (1992), which he completed in 1997. He focuses his research on the enzyme-catalyzed preparation of enantiomerically pure building blocks and natural product synthesis.



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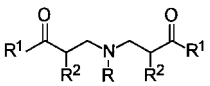

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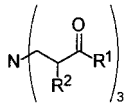

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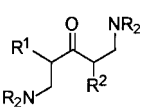

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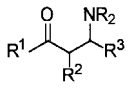
excess, in order to avoid the production of bis-Mannich bases **10**. In the case of unsymmetrical ketones a further problem is encountered. The regioselectivity cannot be controlled to any significant extent and is often strongly dependent on reaction conditions. Additionally, and with very few exceptions, one can only use formaldehyde.[4] Therefore, Mannich bases such as **11**, which would very probably also be extremely attractive intermediates, are not accessible by this method. A further limitation is that only aldehydes and ketones can normally be used, and other carbonyl compounds such as carboxylic acids and their derivatives cannot be aminomethylated. In addition, the classical Mannich reaction is not suited to the enantioselective synthesis of β-amino ketones and amino aldehydes. Thus, the majority of pharmaceutical products, which are derived from the Mannich reaction, are used in the form of racemates. The application of enantiomerically pure Mannich bases is only possible when these are available by separation of the racemate.[1, 3a,b] This problem becomes more severe when one takes into consideration the increasing importance of stereochemically pure pharmaceuticals (the avoidance of "isomer ballast" and of undesirable side effects).[5]



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Due to the very attractive nature of Mannich bases, there have been many attempts to find alternative synthetic routes to these compounds, which do not suffer the severe drawbacks of the classical procedure. Thus, numerous methods have been developed for the indirect synthesis of β-amino aldehydes and ketones,[6] as well as β-amino carboxylic acid derivatives,[7] which do not proceed by aminomethylation or aminoalkylation. Modern versions of the Mannich reaction usually allow a distinctly simpler entry into β-aminocarbonyl compounds through the use of preformed electrophiles (e.g., iminium salts or imines) or nucleophiles (enolates, enol ethers, and enamines). These methods allow, at least in principle, all the limitations of the classical method to be overcome. The level of performance and the versatility of these methods have already been powerfully demonstrated in the synthesis of β-amino acid derivatives and β-lactams. Since this work has already been adequately documented,[7a, 8, 9] we will restrict ourselves here to modern methods of β-aminomethylation and β-aminoalkylation of aldehydes, ketones, and their derivatives. Emphasis is placed on regioselective and stereoselective variants. Recently, several notable advances have been made in these areas.

Intramolecular Mannich reactions possess a significantly wider range of applications than their intermolecular counterparts. Their extremely high value—particularly as the key step in domino reaction sequences—has long been recognized and used, amongst other applications, in biomimetic natural product synthesis. Since the first ground-breaking work, such as Robinsons' synthesis of tropinone,[10a] this work has had a stormy development. Modern methods such as the combination of [3,3] sigmatropic rearrangements with intramolecular aminoalkylation, or powerful new methods for the generation of iminium salts under mild reaction conditions have allowed simple highly regio- and stereoselective access to a large number of complex target molecules. Thanks to this unique synthetic potential—perfectly characterized by the title "Mannich Magic" by Heathcock[10b]—the intramolecular Mannich reaction has never lost its fascination. It is in the best traditions an eternally young classic, ever ready for the challenges of modern synthetic chemistry. In the context of this review modern variants and current applications of the intramolecular Mannich reaction will be discussed.

Vinylogous versions of the Mannich reaction (γ-aminoalkylation of α,β-unsaturated carbonyl compounds or their derivatives) have rarely been reported. The enormous potential of this method is only now beginning to be employed synthetically. In particular, the possibility of using the vinylogous Mannich reaction to access complex, highly functionalized compounds, which would otherwise be accessible only with great difficulty (if at all), is now exercising the imagination of chemists. Current applications of this chemistry will also be described.

2. Preformed Mannich Reagents: Rejuvenation of the Classic

2.1. General Discussion

The serious limitations of the classical Mannich reaction on the one hand, and the versatility of β-aminocarbonyl compounds on the other,[1] has led to the search for significantly simpler synthetic methodologies. The key to success is the use of preformed Mannich reagents:[8c] In comparison to the classical Mannich conditions, these preformed reagents guarantee a higher concentration of the electrophile, leading to lower reaction temperatures and much shorter reaction times. As a consequence, many undesired side reactions, which so often cause problems in the Mannich reaction, are avoided, even with sensitive substrates. Furthermore, one can avoid the use of protic solvents. In this way the carbonyl component can be replaced with much more reactive synthetic equivalents such as enolates. This leads to a greatly extended spectrum of application for the reaction. One can therefore also successfully use reagents which are normally impossible under the classical conditions (e.g. sterically very demanding substrates or carboxylic acid derivatives). In addition, the reaction is not restricted to aminomethylation, but aminoalkylation is also possible. It is also possible to carry out the reaction with high degrees of regio- and stereoselectivity. The most important Mannich reagents will now be briefly discussed.

2.2. Imines

Imines **12** (R^1 = alkyl, aryl)[11] are generally much less electrophilic than the corresponding aldehyde. This drawback can, however, often be overcome by activation with Lewis acids. The use of enolizable imines should allow the reaction to proceed under very mild conditions with the avoidance of aldol-type self-condensation reactions.[8c] Formaldehyde imines (R^1 = H) are generally only stable at low temperatures. They are therefore best generated in situ or, alternatively, a synthetic equivalent can be used.[8c, 12]

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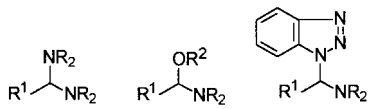
Imines **12** and related compounds have often been used with a great deal of success in the stereoselective aminoalkylation of carboxylic acid derivatives.[7a, 8, 9] It is therefore astonishing that so little work exists on the application of imines in the stereoselective synthesis of β-amino ketones.[13] The possibilities of such chemistry should be thoroughly explored.

2.3. Aminals and N,O-Acetals

Aminals **13** and N,O-acetals **14** resemble imines in terms of their electrophilicity. They must, therefore, normally be activated by Lewis acids, in order to react with nucleophiles.



13 **14** **15**

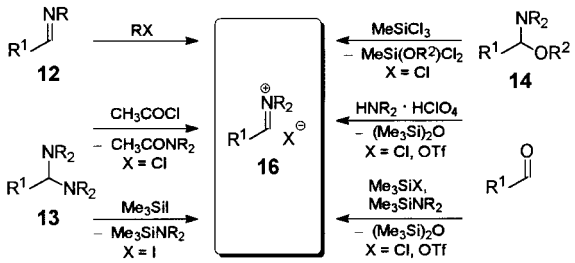
In this context, the formation of iminium intermediates has often been postulated (many times without real investigation) in an S_N1-type of reaction. There are, however, indications that this behavior—even in the presence of Lewis acids—is not necessarily always the case.[14] Only aminals **13** and N,O-acetals **14** which are derived from non-enolizable aldehydes (generally R^1 = H or aryl) have been used as Mannich reagents. The reason for this may be that derivatives of aldehydes with α-H atoms have a tendency to decompose on heating or under acid catalysis (elimination of amines or alcohols, respectively).[15] The benzotriazole aminals **15** represent a special case. These easily accessible compounds are very well suited for aminoalkylation, when derivatives of enolizable aldehydes or ketones are used, or when derivatives of primary amines are involved.[12b] Benzotriazole aminals **15** have been used in the synthesis of, amongst others, β-aminocarbonyl compounds.[16]

The application of aminals **13** and N,O-acetals **14** as Mannich reagents is still in its infancy. Nevertheless, noteworthy results have already been achieved. Particularly interesting examples are the regio- and enantioselective syntheses of β-amino ketones by the aminomethylation of silyl enol ethers,[17] the use of the N,O-acetal $MeOCH_2N(SiMe_3)_2$[18] as a synthetic equivalent for $[CH_2NH_2]^+$, the diastereoselective aminoalkylation of enolates with aminals[16b, d, 19] and in situ generated N,O-acetals.[20]

2.4. Iminium Salts

Iminium salts are generally readily accessible from basic chemicals.[21] One can obtain them from, for example, the alkylation of imines **12**,[21b] by cleavage of aminals **13** (e.g. with CH_3COCl[8a, 22a, b] or Me_3SiI[22c]), or N,O-acetals **14** (e.g. with $MeSiCl_3$:[22d, e] this is also suitable for the preparation of sterically hindered iminium salts such as $[H_2C{=}N(iPr)_2]^+Cl^-$[22f]). Aldehydes can be converted to iminium salts by direct reaction with $HNR_2 \cdot HClO_4$[22g, h] and with Me_3SiNR_2 and Me_3SiX (X = CF_3SO_3, Cl)[22i, j] (Scheme 4). Other powerful synthetic methods are the conversion of enamines with protonic acids such as HCl[22k] or the generation of iminium salts from amine oxides with the aid of the Polonovski–Potier reaction.[22m]

The iminium salts **16** are the most commonly applied Mannich reagents in the synthesis of β-amino ketones and

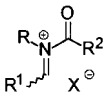


Scheme 4. Synthesis of iminium salts.

aldehydes.[8c, 23] This is because they are more powerfully electrophilic than imines, aminals, and N,O-acetals. They are also suitable for the preparation of β-amino carboxylic acid derivatives.[8c, 24] Basically, the preparative uses of these materials have been limited to three compounds: Eschenmoser's salt $[H_2C{=}NMe_2]^+I^-$ (**16a**),[22c, 25a] the corresponding chloride salt (**16b**) made popular by Kinast and Tietze,[22b] and the trifluoroacetate (**16c**) introduced by Potier et al.[25b] In contrast to the typical salts **16a** and **16b** (both are commercially available), the trifluoroacetate **16c** is a distillable liquid.[25c] Ternary iminium salts **16** ($R^1 \neq H$) have rarely been used for the Mannich reaction.[24a, 26] There is much to suggest that these derivatives have clear advantages over other Mannich reagents. Their use makes possible several features, including effective control over the regio- and stereoselectivity of aminoalkylation.[24a, 26a–d]

Iminium salts **16** are normally hygroscopic and sensitive towards hydrolysis. Under exclusion of moisture, they can, however, be stored over long periods. Nonetheless, salts with α-H atoms are often less stable.[21, 22k] In such cases perchlorates are recommended, as are salts with complex anions (e.g. $[AlCl_4]^-$, $[SbCl_6]^-$).[8a, 22k, 27] Typically, these are significantly more stable and less sensitive towards hydrolysis than salts with simple anions such as Cl^-. On the grounds of convenience, it is quite common to generate these salts **16** in situ.[26a, 28] The reactivity of **16** towards nucleophiles[29] decreases, as would be expected, in the sequence R^1 = H > aryl > alkyl. However, there is no simple rule relating to the influence of the anion on the reactivity of iminium salts.

Differences in reactivity are likely to be related, at least in part, to differences in solubility.[25c] In order to achieve the best possible solubility of the iminium salts, and thereby the smoothest and most rapid course of reaction, it is recommended to use polar, aprotic solvents (e.g. MeCN, DMF, CH_2Cl_2). Significant effects of the anion of the iminium salts **16** on the stereochemical course of the addition of nucleophiles are generally not observed[26a–d, 30a] (an exception is the aminomethylation of the trimethylsilyl enol ether of camphor[30b] with **16a** or **16b**). However, anions can cause side reactions. Thus, it is known that, for example, iodide can promote the formation of undesired side products.[8c] When one considers the latest developments and the numerous attractive applications of the related N-acyliminium salts **17**,[31] it is obvious that the preparative opportunities for iminium salts **16**—despite their lower electrophilicity than **17**—are nowhere near exhausted.



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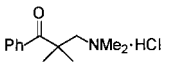
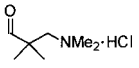
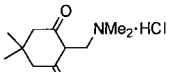
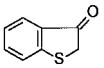
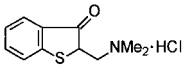
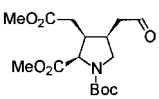
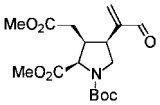
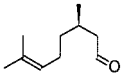
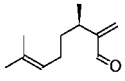
3. Intermolecular Aminomethylations and Alkylations: Control of Regio- and Stereoselectivity and Methods for the Efficient Synthesis of Novel β-Amino Ketones and Aldehydes

3.1. Carbonyl Compounds

Methylene iminium salts **16** ($R^1 = H$) are extremely well suited to the aminomethylation of carbonyl compounds. In particular, ketones[22b, 32] and aldehydes[22b, 33] can be converted under mild conditions into the corresponding Mannich bases.

Table 1. Aminomethylation of carbonyl compounds with $[CH_2{=}NMe_2]^+Cl^-$ (**16b**).

No.	Carbonyl compound	Product	Yield [%]	Ref.
1			53[a]	[22b]
2			82[b]	[22b]
3			87[c]	[32e]
4			83[c,d]	[32g]
5			62[e]	[33b]
6			78[e]	[33b]

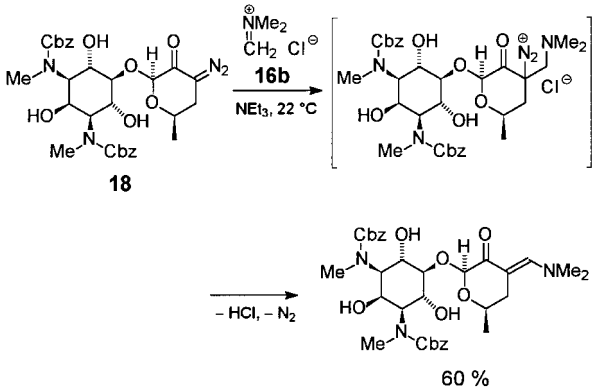
[a] MeCN, reflux, 45 min. [b] MeCN, 20°C, 2 h. [c] If the hydrochloride is dissolved in water, it decomposes immediately. [d] MeCN, 20°C, 3 min. [e] CH_2Cl_2, 20°C, 15 h. The aldehyde is generated in situ from the corresponding alcohol by Swern oxidation (DMSO, $(COCl)_2$, NEt_3). The yield is based on the alcohol. Under the reaction conditions, the primarily formed β-amino aldehyde is deaminated. Boc = *tert*-butoxycarbonyl.

In general, this methodology yields good results, even when the classical Mannich reaction fails or results in low yields. For example, this route is possible for the aminomethylation of sterically hindered carbonyl compounds (Table 1, No. 1, 2) or in the synthesis of sensitive Mannich bases (Table 1, No. 3, 4). In the course of aminomethylation of aldehydes RCH_2CHO, often only the α-methylene aldehydes are isolated despite the mild reaction conditions. This is due to the relative instability of the initially formed β-amino aldehydes (Table 1, No. 5, 6). Particularly notable is the fact that one can often convert even highly functionalized carbonyl compounds such as **18** into β-aminocarbonyl products with methylene iminium salts.[34] This can be done without the formation of side products. There have also been some attempts to improve the regioselectivity of aminomethylation of ketones by use of iminium salts. The choice of reaction medium is crucial in these cases. Reaction in trifluoroacetic acid (reflux, 12–48 h) leads to preferential reaction at the more highly substituted α-position of the ketone. In acetonitrile (reflux, 72–96 h) the opposite selectivity is seen.[35] However, a range of regioselective variants of the Mannich reaction exists, which are clearly milder and more efficient than these (see the following sections).

Apart from methylene iminium salts, many other reagents have been used to convert aldehydes and ketones into the corresponding α-methylenecarbonyl compounds. In general these are imines **12** (usually derivatives of aromatic aldehydes and amines),[8c] aminals **13**,[36a–e] N,O-acetals **14**[36f] or ternary iminium salts **16** ($R^1 \neq H$).[26e, h]

3.2. Enolates

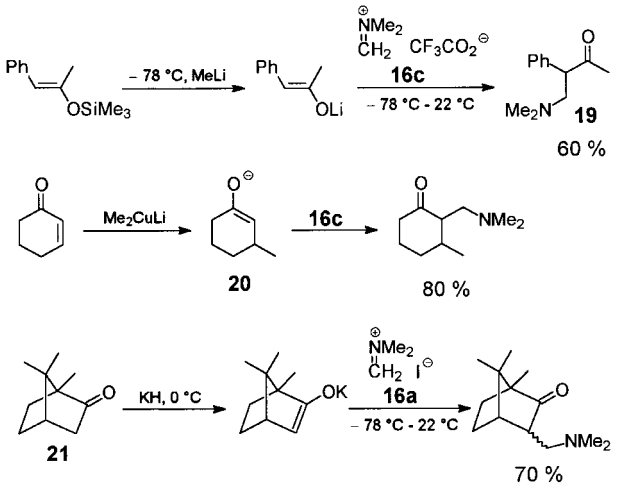
Traditionally the methylene iminium salts **16a**, **16b**, and **16c**[16b, 25c, 30b, 37] are used to react with aldehyde or ketone enolates. These are normally generated in situ by the reaction of trimethylsilyl enol ethers[25c, 37c, e] or enol carbonates[37a, f] with MeLi or by deprotonation of the carbonyl compound with KH[25c, 30b, 37d] or $Li[N(SiMe_3)_2]$[16b] (in contrast to the deprotonation of carboxylic acid derivatives, the use of LDA is much less suitable[25c, 37d]). Due to the additional experimental effort required, one is well-advised to use enolates in certain cases. Thus, for example, for the regioselective synthesis of β-amino ketones such as **19**[25c] (Scheme 5), the extra



Scheme 5. Aminomethylation of the highly functionalized carbonyl compound **18** as example of the aminomethylation of enolates with iminium salts. Cbz = benzyloxycarbonyl.

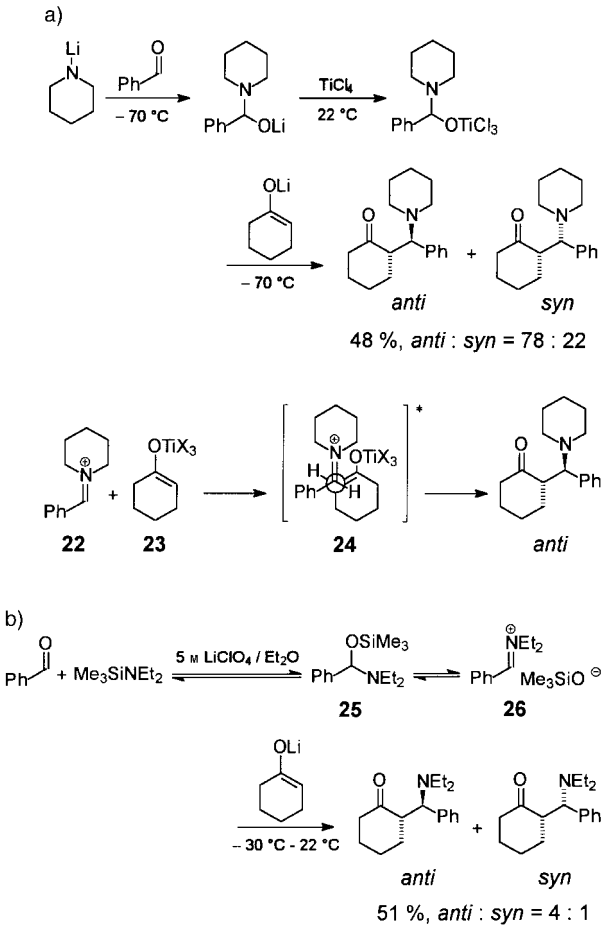
effort would be worthwhile. An elegant variation is the aminomethylation of enolates such as **20**,[37e] which are generated in situ by the addition of nucleophiles to α,β-unsaturated ketones. By conversion into enolates, even sterically hindered ketones such as camphor (**21**)[30b, 25c] can be aminomethylated without problems (Scheme 5).

Due to their high nucleophilicity, ketone enolates react with Mannich reagents not derived from formaldehyde in a similar way to ester enolates.[8c] Their use allows the scope of the classical Mannich reaction to be extended from aminomethylation to aminoalkylation. The reaction of lithium enolates (derivatives of cyclohexanone, acetone, or acetophenone) with in situ generated N,O-acetals (derivatives of secondary amines and aromatic or aliphatic aldehydes) is the first generally applicable method for the aminoalkylation of ketones.[20c] During the aminoalkylation of cyclohexanone enolates one observes that the corresponding *anti*-Mannich bases are preferentially formed. The *anti*:*syn* diastereoisomer ratio is generally about 4:1. A typical example is given in Scheme 6.[20c] Seebach et al. have postulated that the cause of



Scheme 6. Diastereoselective aminoalkylation of an enolate with a N,O-acetal generated in situ.

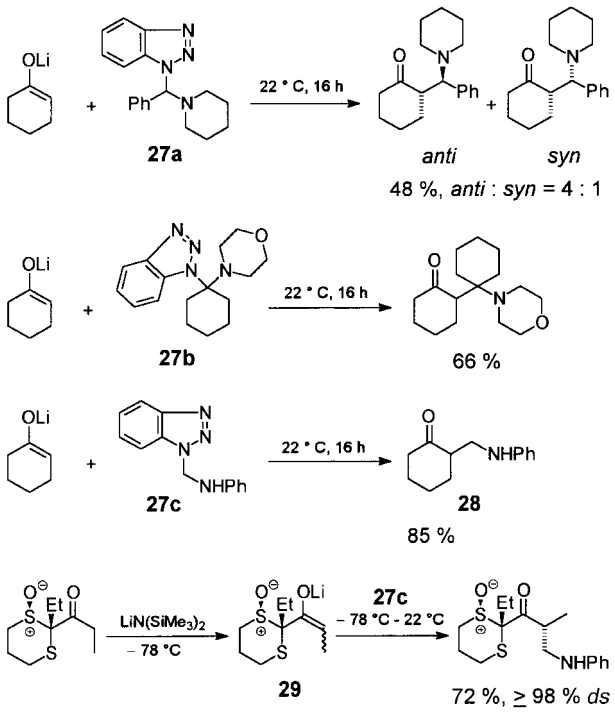
the *anti*-diastereoselectivity may be the formation of an iminium intermediate (**22**). This should react with the in situ generated titanium enolate **23** by an aldol-like reaction sequence involving the electrostatically stabilized transition state **24** (Scheme 6).[20b] The mechanism cannot yet be considered proven, because a thorough investigation is still lacking.[38] A related method is the "$LiClO_4$-induced three-component aminoalkylation": Here, for example, lithium cyclohexanone enolate is aminoalkylated with N-trimethylsilyldiethylamine and benzaldehyde in a 5 M ether solution of $LiClO_4$.[20a] It can be assumed that the first step is the formation of the N,O-acetal **25**, which might exist in equilibrium with the iminium salt **26**. Salt **26** then reacts with the enolate to give the corresponding diastereomeric β-amino ketones (Scheme 7). The preferential formation of the *anti*-diastereoisomers can be explained by an analogous mechanism to that of Seebach et al. (cf. **24**) mentioned previously—that is, by an aldol-type reaction proceeding through an electrostatically stabilized transition state.[20a]



Scheme 7. a) Diastereoselective aminoalkylation of an enolate with an N,O-acetal. b) Diastereoselective $LiClO_4$-induced three-component aminoalkylation of a ketone enolate.

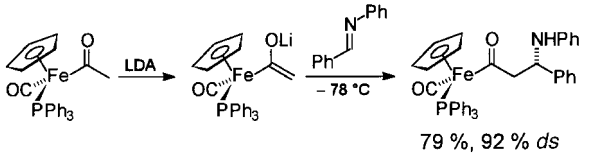
Apart from the in situ generated N,O-acetals, a preformed benzotriazole aminal **27** has been used in aminoalkylation and aminomethylation of ketone enolates (Scheme 8). The advantages of this methodology are the broad applicability and the simple reaction conditions. Thus, one can use benzotriazole aminals such as **27a**[16d] for the synthesis of Mannich bases. Katritzky and Harris have postulated that the observed *anti*-diastereoselectivity[39] can be explained by the preferential deamination of the *syn*-diastereoisomer.[16d] A 25% yield of benzylidenecyclohexanone is obtained, which is presumably formed by elimination of piperidine. Apart from benzotriazole aminals derived from benzaldehyde, derivatives of enolizable aldehydes (acetaldehyde, isobutyraldehyde) can also be used for the synthesis of β-amino ketones. Additionally, enolates will even undergo aminomethylation with ketone benzotriazole aminals such as **27b**.[16d] It is also possible to prepare secondary Mannich bases such as **28** by this method. This requires the use of derivatives of primary amines (e.g. **27c**).[16d] Amine **27c** is also very well suited to the highly diastereoselective aminomethylation of chiral enolates such as **29**.[16b] Other Mannich reagents such as Eschenmoser's salt (**16a**) deliver poorer yields in this case.[16b]

Astonishingly, imines have been used almost exclusively in the conversion of ester enolates or related compounds.[8]



Scheme 8. Aminoalkylation of enolates with benzotriazole aminals.

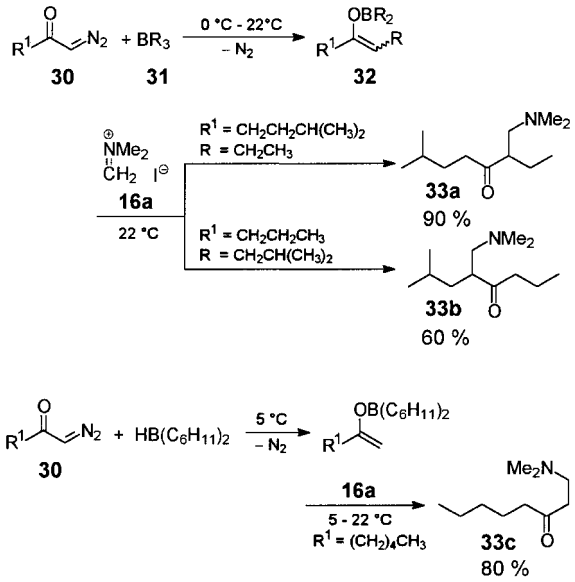
Reactions with other enolates have only sporadically been described.[13b–d] An example is shown in Scheme 9.[13c]



Scheme 9. Diastereoselective aminoalkylation of a chiral acyliron complex.

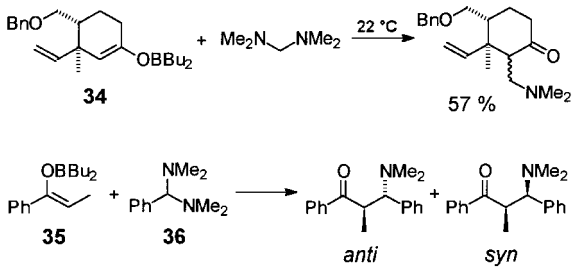
3.3. Boron Enol Ethers

The reaction of boron enol ethers with Eschenmoser's salt (**16a**) is a powerful method for the regioselective preparation of β-amino ketones (Scheme 10).[40] This method consists of the conversion of α-diazoketones **30** with trialkylboranes **31** to give the boron enol ethers **32**, which are then aminomethylated by the iminium salt **16a** which is itself generated in situ. A typical example is the synthesis of the two regioisomeric β-amino ketones **33a** and **33b**.[40b] The use of dicyclohexylborane in the generation of the boron enol ether can also allow the preparation of specific derivatives of methyl ketones such as **33c**.[40a] Aminomethylation of boron enol ethers makes possible the synthesis of regioisomerically pure Mannich bases in good to very good yields. Their use is, unfortunately, associated with a difficult experimental methodology. The particular advantage of this method lies in the fact that one can prepare, in a highly regioselective manner, β-amino ketones, which are derived from ketones with almost identical α-positions (e.g. **33a** and **33b**.).



Scheme 10. Regioselective synthesis of β-amino ketones by aminomethylation of boron enol ethers with Eschenmoser's salt.

On the basis of the Lewis acidic nature of boron enol ethers, these reagents will also react (in contrast to the lithium enolates) with aminals, species which are much less electrophilic than the iminium salts (Scheme 11).[19] In this manner



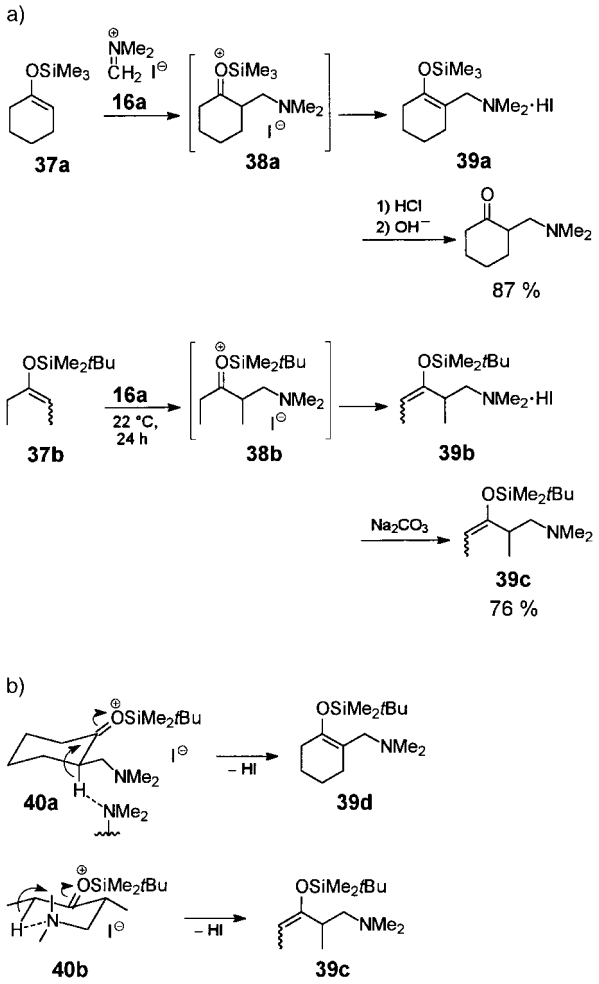
Scheme 11. Aminomethylation and aminoalkylation of boron enol ethers with aminals.

one can also successfully aminomethylate even sterically hindered substrates such as **34**.[19b] In addition, boron enol ethers can be aminoalkylated, with high diastereoselectivity, with aminals (only derivatives of non-enolizable aldehydes are suitable; see Section 2.3).[19a] Conversion of boron enol ether **35** with the aminal **36** shows that the diastereoisomeric ratio is influenced decisively by the temperature and time of reaction. At -78°C (5 to 20 min) (that is, under kinetic control) the *syn*-Mannich base is preferred (33 %, *anti*:*syn* = 1:4). If the reaction is carried out at room temperature, it begins to equilibrate, and after 6 h a diastereoisomeric mixture (90 %, *anti*:*syn* = 1:1) is formed. After 16 to 20 h the almost pure *anti*-Mannich base is obtained (90 %, *anti*:*syn* = 17:1). Nevertheless, similar results are not obtained in every case. If, for example, the corresponding piperidine derivative is used in place of **36**, the diastereoselectivity is marginal at both -78°C and at room temperature.

3.4. Silyl Enol Ethers

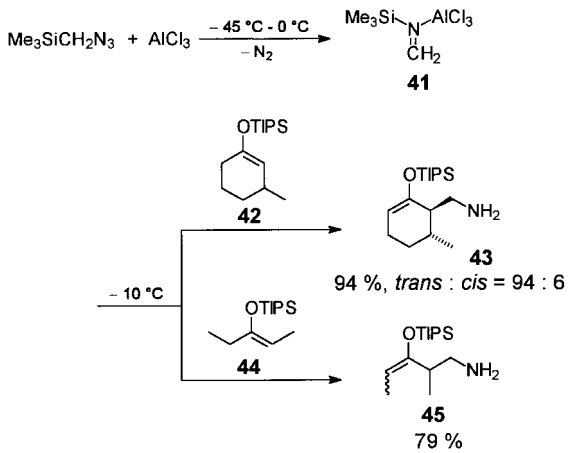
Silyl enol ethers are significantly better nucleophiles than the corresponding carbonyl derivatives. This allows them to be used in the Mannich reaction under much milder conditions. With this method, Mannich bases not accessible with the classical route become available. It is possible, for example, to extend the methodology from aminomethylation to encompass aminoalkylation too.[13a, 41] This methodology can also be used to achieve effective levels of stereoselectivity in the synthesis of β-aminocarbonyl compounds.[13a, 17, 30b, 41a] A further advantage is that one can generally convert ketones into silyl enol ethers with a high degree of regioselectivity, and thereby achieve effective control of regioselectivity in the Mannich reaction.[25c, 28b, e, 37c, 42]

The most commonly used variant of this method is aminomethylation using preformed,[25c, 30b, 37c, 42a, c, d, f, 43] or in situ generated methylene iminium salts.[28a–e] Two typical examples are given in Scheme 12. The mechanism has not yet been investigated in detail. Danishefsky et al. have assumed that oxonium salts such as **38a** are initially formed, which are then converted into compounds such as **39a** by deprotonation (formation of **39a** is backed up by evidence from NMR spectroscopy).[42f] *t*-Butyldimethylsilyl derivatives such as **39b** can even be converted into the free base (**39c**) by aqueous workup and isolated.[42c] Interestingly, intermediates such as **38a**, which are derived from cyclic ketones, undergo regioselective α-deprotonation;[42c, f] that is, formation of the double bond takes place exclusively at the original double-bond position. Derivatives of acyclic ketones such as **38b** display the opposite selectivity, that is, deprotonation takes place exclusively at the α'-position, and the double bond is shifted.[42c] Akiba et al. have tried to explain this phenomenon on the basis of the transition state **40**. In the case of cyclic ketones, a transition state with equatorial aminomethyl groups (e.g. **40a**) should be energetically more favorable. Due to steric hindrance deprotonation can only take place in an intermolecular manner, and this leads to the formation of the more highly substituted double bond—that is, the more thermodynamically favored product is formed (e.g. **39d**).[42c] The fact that the deprotonation takes place in a highly regioselective manner at the sterically more hindered α-position may be explained by the acidifying $-$I effect of the dimethylamino group,[44] which may be substantially reinforced by complexation of the nitrogen with the silicon. For derivatives of acyclic ketones such as **38b**, a cyclic transition state **40b** has been postulated, which allows an intramolecular deprotonation. This results in a shift of the double bond and thus to the formation of products such as **39c**.[42c]



Scheme 12. a) Aminomethylation of silyl enol ethers with a methylene iminium salt. b) Postulated transition states for the aminomethylation of cyclic and acyclic ketones.

These results cannot be directly applied to reactions involving other Mannich reagents. Thus, in reactions involving the $H_2NCH_2^+$ synthetic equivalent **41** (easily prepared from trimethylsilylmethyl azide and $AlCl_3$ in situ), both cyclic (like **42**) and acyclic silyl enol ethers (like **44**) are deprotonated at the α'-position (Scheme 13). After workup in aqueous NaOH

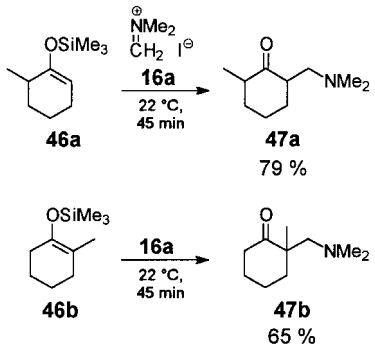


Scheme 13. Aminomethylation of silyl enol ethers with the Mannich reagent **41**, generated in situ. TIPS = triisopropylsilyl.

solution, products such as **43** and **45** are obtained (the corresponding β-amino ketones are generally not stable under basic aqueous conditions).[42b] Whether reaction with other Mannich reagents such as N,O-acetals or imines leads to α- or α'-deprotonation has not yet, to the best of our knowledge, been ascertained. This question is of particular importance in the interpretation of the stereochemical pathway of aminomethylation and aminoalkylation of silyl enol ethers where α-

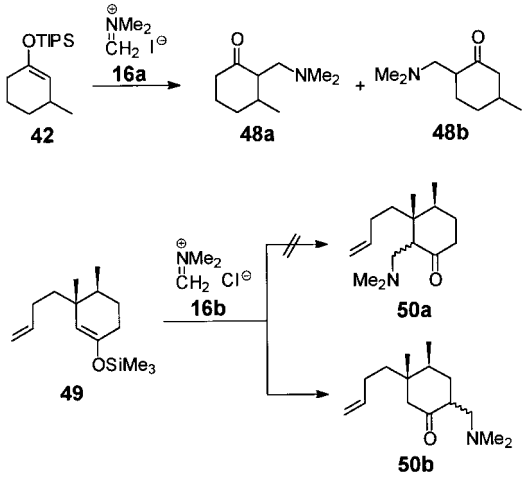
stereogenic centers are formed. The stereochemical information will be lost upon α-deprotonation. The observed stereoisomeric ratios are, therefore, generally not the result of a stereoselective Mannich reaction, but are rather (wholly or, in the case of a mixture of α- and α'-deprotonation, in part) a result of reprotonation during workup. The aminomethylated and aminoalkylated silyl enol ethers which are thus accessible, potentially in a highly regioselective manner, should prove to be synthetic building blocks with many attractive applications.

The aminomethylation of silyl enol ethers with methylene iminium salts is a popular method for the regioselective synthesis of β-amino ketones[25c, 28b, e, 37c, 42a, c, d, f] such as **47a** and **47b**. (Scheme 14).[42d] It is worth noting that, upon



Scheme 14. Regioselective synthesis of β-amino ketones by aminomethylation of silyl enol ethers with a methylene iminium salt.

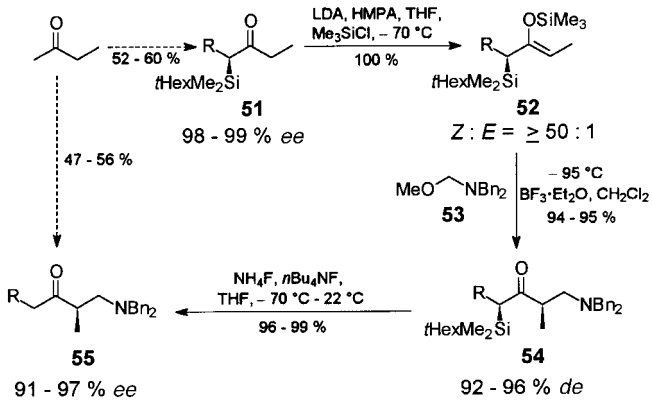
aminomethylation of **46a**, **47b** is formed (about 4%) alongside **47a**, even when the silyl enol ether contains no detectable quantity of the regioisomeric **46b**.[42d] Really serious deviations from the normal reaction pathway had previously only been seen with the silyl enol ethers **42** and **49** (Scheme 15):



Scheme 15. Unusual behavior in the aminomethylation of silyl enol ethers with methylene iminium salts. TIPS = triisopropylsilyl.

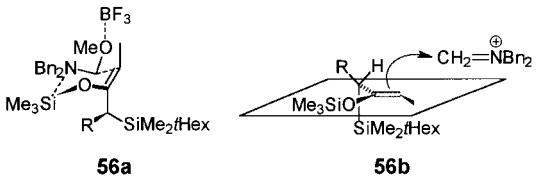
Thus, on aminomethylation of **42** with **16a**, no predominant product, in contrast to the analogous reaction with **41** (compare Scheme 13), but rather a mixture of the regioisomeric β-amino ketones **48a** and **48b** are obtained.[42b, 45] Upon reaction of **49** with **16b** the expected Mannich base **50a** is not formed, the product being the other regioisomer **50b**. However, if one transforms **49** into the corresponding lithium enolate with MeLi before the addition of **16b**, one obtains only **50a**.[37c, 45]

In the presence of Lewis acids, silyl enol ethers react readily with aminals[16a, 46] and with N,O-acetals.[14d, 17, 28a] In this way one can, for example, synthesize acyclic β-amino ketones **55** in a highly regio- and enantioselective manner (Scheme 16).[17]

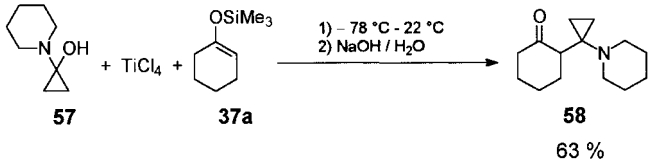


Scheme 16. Regio- and enantioselective synthesis of acyclic β-amino ketones by diastereoselective aminomethylation of silyl enol ethers with an N,O-acetal. *t*Hex = 1,1,2-trimethylpropyl.

Thus, α-silylketones **51** (obtainable by the successive silylation and alkylation of the hydrazone derived from butanone and (*S*)-1-amino-2-methoxymethylpyrrolidone)[47] can be converted into the silyl enol ether **52** with a high degree of regioselectivity and diastereoselectivity. Aminomethylation of **52** with equimolar quantities of the N,O-acetal **53** and $BF_3 \cdot Et_2O$ yields the product **54** in very good yields and high diastereoselectivities. After cleavage of the α-silyl group, which proceeds with almost no racemization, the Mannich bases **55** are obtained in enantiomeric excesses of 91 to 97% *ee* (Scheme 16). Enders et al. have proposed that the excellent diastereoselectivity of the aminomethylation of **52** can be explained, either by the reaction proceeding through the cyclic transition state **56a** (S_N2 type mechanism) or via the open transition state **56b** (S_N1 type mechanism). In both cases the *Re* side of the silyl enol ether **52** is shielded by the bulky dimethyl-*t*-hexyl group.[17]

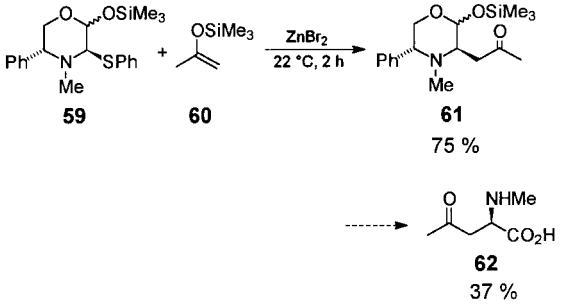


Silyl enol ethers also react with N,O-acetals that are not derived from formaldehyde.[41c, d, f] Thus, the Mannich base **58** can be synthesized under mild conditions by reacting the silyl enol ether **37a** with the cyclopropane derivative **57** and $TiCl_4$ (Scheme 17). It has been assumed that the reaction proceeds via an iminium intermediate.[41d, f] N,S-acetals[48] are also well suited to the aminoalkylation of silyl enol ethers. An excellent



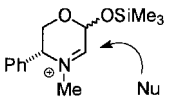
Scheme 17. Aminoalkylation of a silyl enol ether with a N,O-acetal.

example is given by the synthesis of the γ-oxoamino acid **62** (Scheme 18).[41a] The key step is the highly diastereoselective

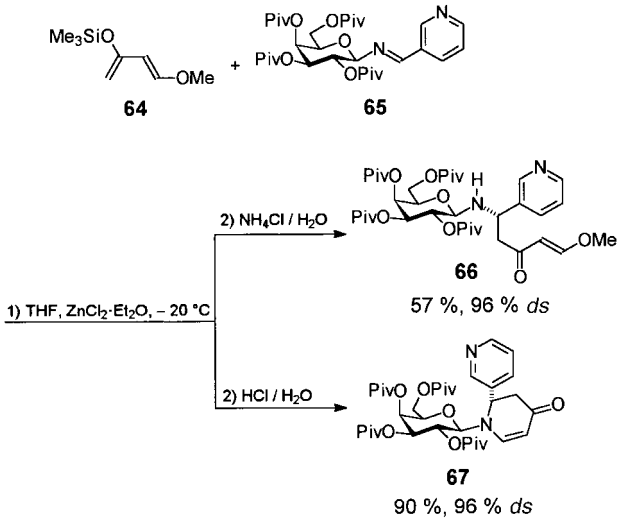


Scheme 18. Enantioselective synthesis of a γ-oxoamino acid by diastereoselective aminoalkylation of a silyl enol ether with a N,S-acetal.

aminoalkylation of the silyl enol ether **60** with the chiral N,S-acetal **59** (glyoxal derivative) in the presence of three equivalents of $ZnBr_2$. In this case the β-amino ketone **61** is obtained exclusively. This can be converted into the enantiomerically pure product **62** (three steps, 37 %). Agami et al. have rationalized the high diastereoselectivity as being due to the attack of the nucleophile occurring almost exclusively on the front side (the *Re* face) of the initially formed iminium ion **63**, the rear side being effectively shielded by the phenyl group. Silyl enol ethers can also be aminoalkylated with high diastereoselectivity with nucleophiles other than the N,S-acetal **59**.[41a]

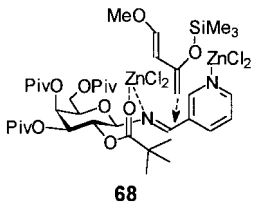


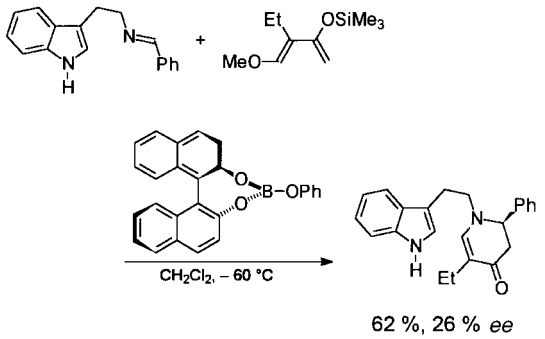
Activation with Lewis acids such as trimethylsilyl triflate,[41c, e] ytterbium triflate,[41b] or $ZnCl_2$[13a] allows the reaction of in situ generated,[41b] or preformed,[13a, 41c, e] imines with silyl enol ethers to give β-amino ketones. Both enolizable[13a, 41b] and non-enolizable[13a, 41b, c, e] derivatives of aldehydes can be used. The great potential of this method was demonstrated by Kunz and Pfrengle in the aminoalkylation of Danishefsky's diene **64** with enantiomerically pure imines (derivatives of 2,3,4,6-tetra-*O*-pivaloyl-β-galactopyranosylamine).[13a] After workup with NH_4Cl solution, almost diastereomerically pure β-amino ketones were obtained. Thus, for example, the Mannich base **66** can be synthesized in a highly diastereomerically pure form by the reaction of **64** with the imine **65** in the presence of two equivalents of $ZnCl_2$ (Scheme 19). If hydrochloric acid is used in the workup rather than NH_4Cl solution, other reactions take place (intramolecular Michael addition and cleavage of methanol). Dehydropiperidones such as **67** are formed with retention of the initially formed stereogenic center. These molecules are of use in the synthesis of, amongst others, piperidine alkaloids.[13a, 49] The stereochemical progress of the



Scheme 19. Diastereoselective aminoalkylation of a silyl enol ether with an enantiomerically pure imine. Piv = CO*t*Bu.

aminoalkylation of **64** with the imine **65** can be explained on the basis of the transition state **68**. One equivalent of $ZnCl_2$ is bonded to the nitrogen and therefore made inactive. Then the second equivalent activates the C=N double bond by coordination to the imine nitrogen and the carbonyl oxygen of the 2-pivaloyl group (derivatives of nonbasic aldehydes require only one equivalent of $ZnCl_2$). The attack of the silyl enol ether takes place preferentially on the back face (*Si* face) of the imine, because the front face is shielded by the 2-pivaloyl group.[13a, 50] As has been demonstrated by Waldmann et al., other imines (from aldehydes and esters of amino acids) can also be used in the highly diastereoselective synthesis of dehydropiperidones.[52] An enantioselective variant of this reaction has also recently been described (Scheme 20).[52a, b]

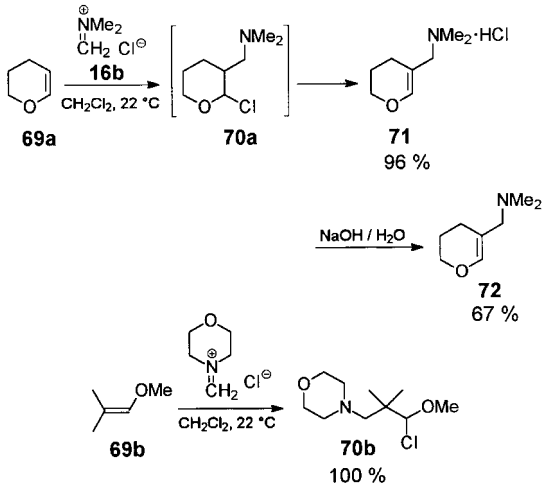




Scheme 20. Enantioselective domino Mannich – Michael reaction.

3.5. Alkyl Enol Ethers

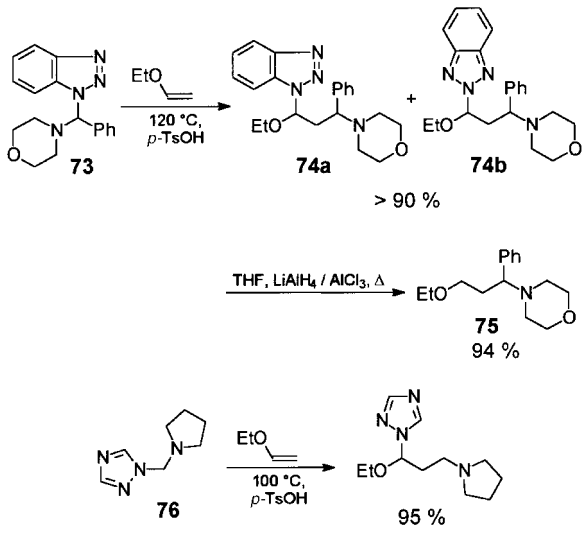
There are relatively few reports of the use of alkyl enol ethers in the Mannich reaction.[53] Thus, alkyl enol ethers such as **69a** can be aminomethylated with methylene iminium salts such as **16b** under mild conditions (Scheme 21).[53d] The



Scheme 21. Aminomethylation of alkyl enol ethers with methylene iminium salts.

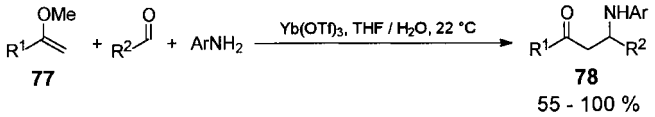
products generally formed are the hydrochlorides of aminomethylated alkyl enol ethers such as **71**, which one can easily convert into the free base (**72** in this example). Böhme and Wagner have proposed that the initially formed product is the α-chloroether (**70a**), which is then instantly transformed into compounds such as **71** by dehydrohalogenation. This assumption is backed up by the observation that the α-chloroether **70b**, which cannot undergo the second reaction step, is formed in quantitative yield by aminomethylation of the alkyl enol ether **69b** (Scheme 21).[53d]

It is possible to aminoalkylate alkyl enol ethers by use of benzotriazole aminals such as **73**. This method results in the formation of α-benzotriazole ethers **74a** and **74b** (Scheme 22).[53c] These compounds are valuable synthetic building blocks, since the benzotriazole moiety can easily be displaced by nucleophiles (e.g. Grignard reagents). A further application is the reduction of α-benzotriazole ethers to γ-amino ethers such as **75**.[53c] 1,2,4-Triazole aminals, for example **76**, can be employed in place of benzotriazole aminals for analogous Mannich reactions.[53a]



Scheme 22. Aminoalkylation of alkyl enol ethers with benzotriazol- and 1,2,4-triazolaminals.

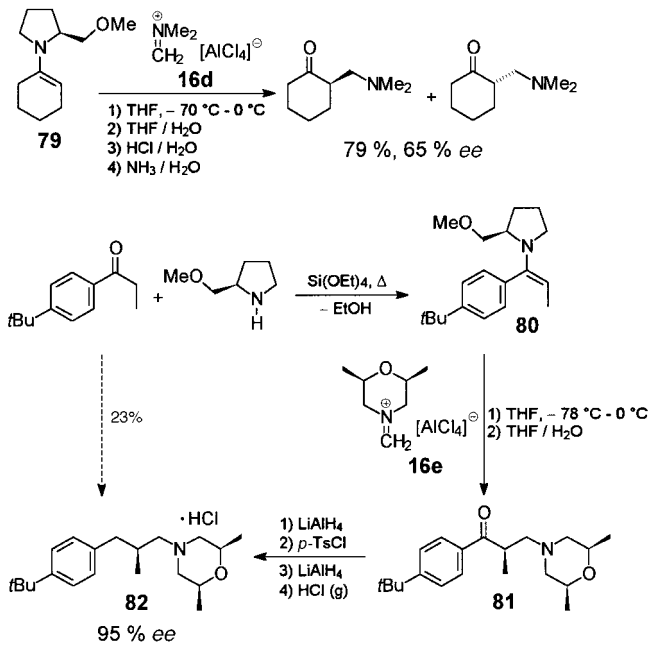
The use of lanthanide triflate catalysts such as ytterbium (III) triflate ($Yb(OTf)_3$) makes possible the synthesis, in aqueous medium, of secondary β-amino ketones **78** by the aminoalkylation of alkyl enol ethers **77** (R^1 = Me, Ph) with aldehydes (R^2 = H, alkyl, Ph, COPh, etc.) and aromatic amines (Scheme 23). Kobayashi and Ishitani have proposed that the reaction proceeds via imines formed in situ.[53b]



Scheme 23. Lanthanide triflate catalyzed aminoalkylation of alkyl enol ethers in aqueous medium.

3.6. Enamines and Imines

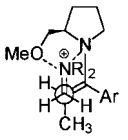
So far, iminium salts have been the preferred reagents for the aminomethylation and aminoalkylation of enamines.[26a, c, d, g, h, 54] In comparison to iminium salts, other Mannich reagents such as N,O-acetals,[55] aminals,[36a, 56] and imines[57] have played only a minor supporting role. For example, Risch and Esser have shown that methylene iminium salts such as **16d** (tetrachloroaluminates are significantly less sensitive towards hydrolysis and are therefore much more easily handled than the corresponding chlorides)[26a, c] and enamines such as **79** (derivatives of (*S*)- or (*R*)-2-methoxymethylpyrrolidines) are excellent reaction partners for the enantioselective synthesis of β-amino ketones (Scheme 24).[54d] The



Scheme 24. Enantioselective synthesis of β-amino ketones by aminomethylation of enamines with iminium salts.

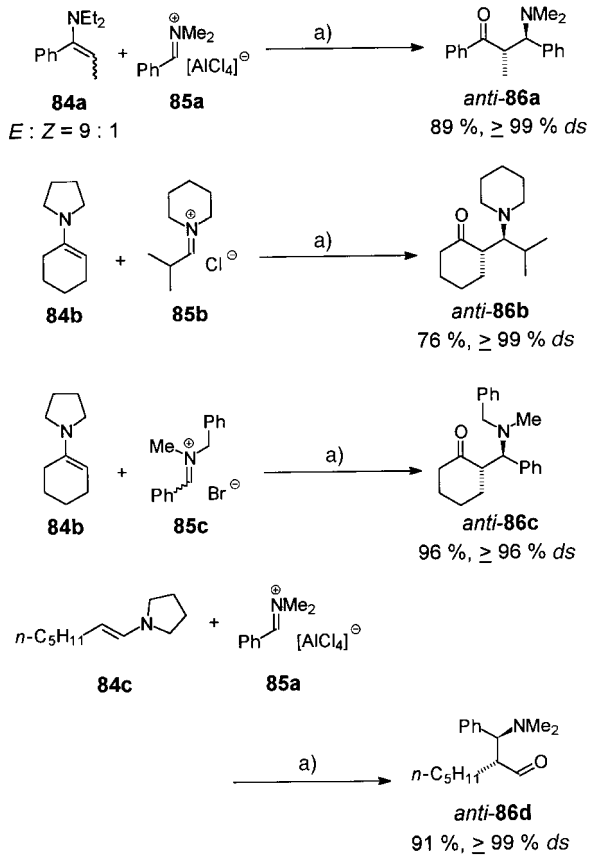
execution of the procedure is simple, but gives only moderate *ee* values (30–66 % *ee*). More recent results indicate that this is predominantly due to partial racemization of the Mannich bases during the traditional workup procedure.[54a,b] Omission

of the workup step can yield almost enantiomerically pure β-amino ketones such as **81** for direct use in subsequent reactions, for example the synthesis of the fungicide (*S*)-fenpropimorph **82** (Scheme 24).[54a] Vinkovic and Sunjic have tried to explain the stereochemical progress of the aminomethylation of 2-methoxymethylpyrrolidine enamines, for example **80**, with methylene iminium salts such as **16e**, on the basis of the aldol-type transition state **83**. This transition state is stabilized by electrostatic interactions. It is noteworthy that the iminium ion attacks the more sterically hindered side of the enamine preferentially. This is likely to be due to Coulombic interations between the positively charged nitrogen atom and the oxygen.[54a]



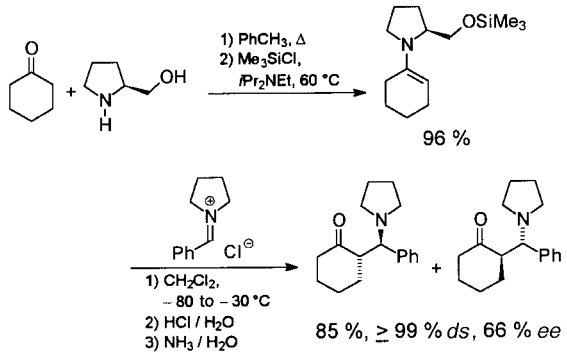
83

Ternary iminium salts are extremely good in the aminoalkylation of enamines. Thus, β-amino ketones and aldehydes *anti*-**86** can be synthesized in good to very good yields (Scheme 25) and excellent diastereoselectivities (constantly $\geq$96 % *ds*).[26c, d] From those investigations carried out so far, it has been possible to obtain almost diastereomerically pure products in most cases even at room temperature. It is only under significantly more drastic conditions (e.g. THF, reflux) that significant quantities of the corresponding *syn*-diastereoisomers are observed. The type of iminium salt used has no appreciable effect on the diastereoselectivity of the reaction.



Scheme 25. Diastereoselective aminoalkylation of enamines with ternary iminium salts. Reaction conditions: a) 1. CH_2Cl_2, -80 to -30°C; 2. HCl/H_2O; 3. NH_3/H_2O.

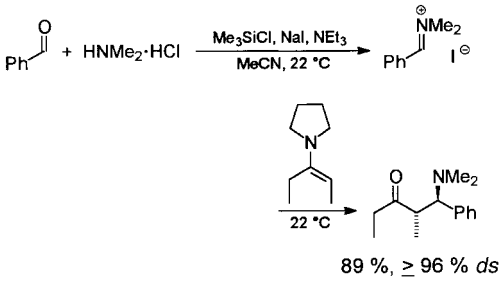
For example, it does not matter whether arylidene iminium salts such as **85a** or alkylidene iminium salts such as **85b** are used. The configuration of the iminium salt employed has no significant influence on the stereochemical progress of the reaction. Thus, even when a diastereoisomeric mixture such as **85c** is used (two diastereoisomers in the ratio 85:15), the almost diastereomerically pure Mannich base *anti*-**86c** is produced. The choice of anion likewise exerts no detectable influence on the diastereoselectivity of the aminoalkylation. Quaternary iminium salts (ketone derivatives) do not react with enamines. Similarly, the type (cyclic or acyclic ketone derivatives such as **84a** or **84b**, or aldehyde derivatives, for example **84c**) or the configuration of the enamine used has no effect on the stereochemical outcome of the reaction. Thus, the aminoalkylation of the diastereoisomeric mixture **84a** yields the β-amino ketone *anti*-**86a** in a highly diastereoselective fashion. Ternary iminium salts can also be utilized in enantioselective syntheses of Mannich bases. An example is shown in Scheme 26 (the β-amino ketone can be readily obtained in enantiomerically pure form by recrystallization).[26d]



Scheme 26. Asymmetric aminoalkylation of a chiral enamine with a ternary iminium salt.

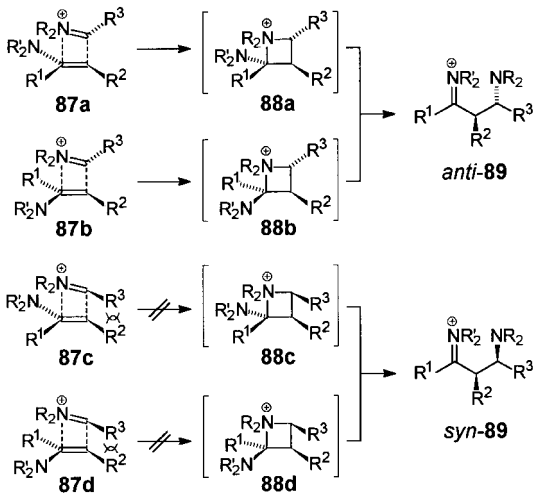
Iminium salts can be generated in situ almost quantitatively from secondary amines (or their hydrochlorides) and non-enolizable aldehydes. These iminium salts can then be used directly, without isolation or purification, in the reaction with enamines or other nucleophiles such as imines or electron rich arenes ("silylogous" Mannich reaction). An example is given in Scheme 27. The experimental effort required can be dramatically reduced with this approach.[26a, d] The results (yields, diastereoselectivities) are essentially indistinguishable from those obtained with pre-formed iminium salts.[8a, 26b, c, 58] A further benefit is that iminium salts that are otherwise difficult or impossible to obtain can easily be generated (e.g., derivatives of benzylamine).[59]

An aldol-type transition state, which has been postulated for the aminomethylation of enamines with methylene iminium salts (e.g. **83**),[54a] does not fit the consistently high *anti*-diastereoselectivities obtained for the aminoalkylation of enamines with iminium salts. In particular, the fact that the use of a mixture of *E* and *Z* isomers such as **84a** or an aldehyde amine (e.g. **84c**) does not lead to a reduction in diastereoselectivity (Scheme 25) is not consistent with an



Scheme 27. The silylogous Mannich reaction. Aminoalkylation of enamines with iminium salts generated in situ.

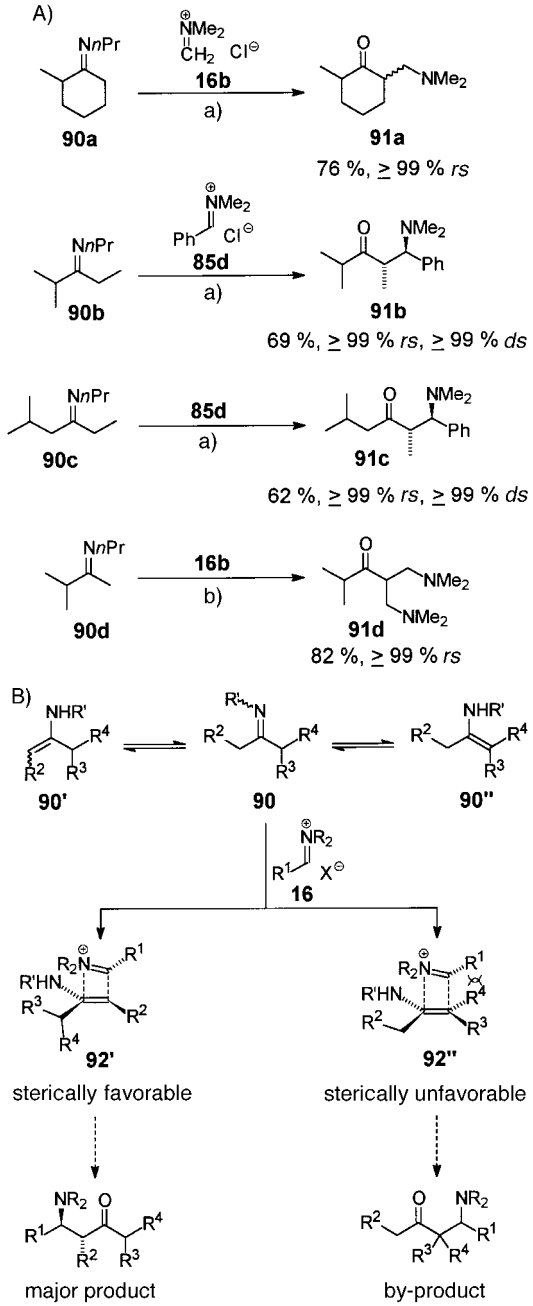
aldol-type reaction mechanism (compare **83**). In contrast, the results can be explained satisfactorily by a [2+2] cycloaddition mechanism. Such a mechanism has already been proposed by Viehe et al. for the closely related reaction between ynamines and iminium salts.[60] The fact that the diastereoselectivities are always high lends weight to the postulate that the aminoalkylation of enamines with iminium salts proceeds in a concerted manner. As has already been put forward for reactions between very electron rich and very electron deficient alkenes, this reaction is supposedly a polar [2s+2s] cycloaddition (Scheme 28).[8a, 26c, d] In these reactions, the diastereoselectivity is controlled principally by the steric



Scheme 28. Possible cycloaddition mechanism of the aminoalkylation of enamines with iminium salts.

interaction of the groups R^2 and R^3. Cycloadducts such as **88a** or **88b** are only formed from transition states (e.g. **87a** or **87b**) that have relatively little steric hindrance. These rearrange immediately to the iminium salts *anti*-**89**, which can be hydrolyzed to the corresponding β-amino ketones,[8a, 26c, d] or can be reduced in situ to the 1,3-diamines (>98% *ds*).[26d, 62] Transition states such as **87c** or **87d**, which lead to the formation of iminium salts *syn*-**89**, are energetically very unfavorable due to the eclipsed conformation between R^2 and R^3. They therefore do not, in general, lead to appreciable quantities of products. This idea also finds support in the fact that enamines do not react, even under drastic reaction conditions, with iminium salts derived from ketones (such salts lead inevitably to eclipsed interactions).[26d] On the other hand, the same iminium salts react smoothly with ynamines.[60] This is also easily explicable on the basis of a cycloaddition mechanism, since the transition state cannot involve sterically unfavorable eclipsed interactions, due to the linear structure of the ynamine.

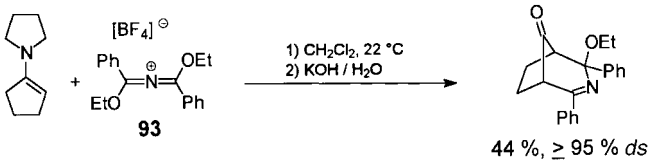
The reaction of imines (or of the tautomeric enamines, with which they are in equilibrium) with iminium salts is a simple method for the highly regioselective preparation of β-amino ketones (Scheme 29A).[26b, d] In general, Mannich bases (e.g. **91a**, **91b** or **91c**) can be prepared in high yield and excellent regioselectivity, independent of the nature both of the imine



Scheme 29. A) Regioselective aminoalkylation of imines with iminium salts. Reaction conditions: a) 1. CH_2Cl_2, −80 to −30°C; 2. AcOH/H_2O; 3. HCl/H_2O; 4. NH_3/H_2O; b) 1. CH_2Cl_2, −80 to −30°C; 2. HCl/H_2O; 3. NH_3/H_2O. B) Transition states for the regioselective aminoalkylation of imines with iminium salts.

used (derivatives of cyclic ketones such as **90a** or acyclic ketones such as **90b** and **90c**) and of the iminium salt. This methodology also allows the preparation of bis-Mannich bases such as **91d** (Scheme 29A). Attack of the iminium salt takes place almost exclusively on the sterically less hindered α-C atom of the imine. Very good selectivity is achieved, even when the α- and α'-positions are only marginally different (for example **90c**). Aminoalkylation with ternary iminium salts such as **85d** is, in addition, highly diastereoselective. As has been seen in the case of the corresponding reaction with enamines (see, for comparison, Scheme 25), the *anti*-diastereoisomer is the only isomer obtained. This result can also be explained on the basis of a polar [2s+2s] cycloaddition mechanism. This model incorporates all the features of the stereochemical reaction profile (analogous to Scheme 28). Additionally, it is also obvious, on the basis of the highly ordered transition states **92′** and **92″**, why even small differences in the regioisomeric secondary enamines **90′** and **90″**, which are in tautomeric equilibrium with the imines **90**, play such a major role and can influence the regioselectivity of the reaction (Scheme 29B).[26b, d]

An interesting and powerful new variant of the Mannich reaction involves the use of in situ generated[63] or preformed 2-azaallenium salts.[64] For example, Würthwein et al. have shown that the reaction of enamines with 2-azaallenium salts[65] such as **93** can be used to allow the simple and highly diastereoselective synthesis of complex heterocyclic ketones (Scheme 30).[64b]



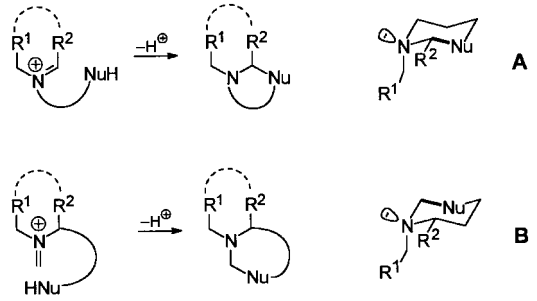
Scheme 30. The use of 2-azaallenium salts for Mannich-type reactions.

4. Intramolecular Mannich Reactions—A Key Step in the Synthesis of Natural Products

4.1. Preparative and Stereochemical Aspects

Both the inter- and intramolecular versions of the Mannich reaction are undoubtedly amongst the most versatile and powerful methods for the preparation of azacyclic products from acyclic precursors. The practicality of the Mannich reaction is well documented in a multitude of syntheses of alkaloids.[1a, 2, 66] The reasons for the use of this popular method are just as multifacetted as the reaction itself. In contrast to the intermolecular Mannich reaction, the intramolecular variant is not restricted to aminomethylation, but can be applied in its widest sense to aminoalkylations. Its chemoselectivity also offers a much wider range of potential applications. The carbonyl compound, as is the case with the intermolecular variant, can be used in the form of an acetal or a (silyl) enol ether in the intramolecular reaction (see Section 3). Whereas in the presence of aqueous mineral acid the protecting group is cleaved and the enol is the reactive species, under anhydrous conditions the enol ether is the nucleophile and the iminium ion is trapped.[2]

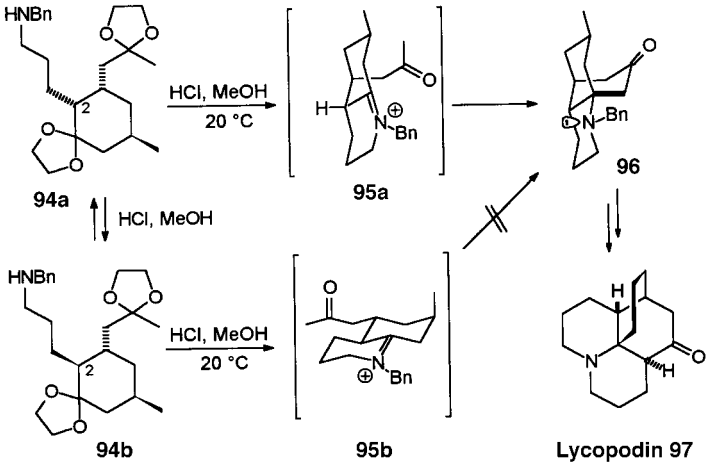
Furthermore, the regioselectivity and stereoselectivity of the intramolecular Mannich reaction are governed by a series of rules that allow the prediction of the reaction path—an important precondition for the synthesis of natural products. Thus, Baldwins' selection rules, developed for the cyclization of olefins, can be applied to iminium ions. Cyclic products can be formed according to either an *exo*-cyclic-trigonal (**A**) or an *endo*cyclic-trigonal process (**B**; Scheme 31).[2, 67]



Scheme 31. Stereoelectronic control in the cyclization initiated by iminium ions to form *exo-trig* (**A**) and *endo-trig* (**B**) products.

The stereochemical pathway of a nucleophilic attack on an iminium ion is often controlled by stereoelectronic factors (Scheme 31)[68] because of the antiperiplanar conformation of the developing electron pair and the incoming electrophile in the product. Reliable predictions can therefore be made about the stereoselectivity of the cyclization.

An excellent example of this stereocontrolled reaction is the synthesis of Lycopodium alkaloid **97** (Scheme 32).[69] The starting material **94a**,**b**, which is epimeric at C-2, cyclizes to

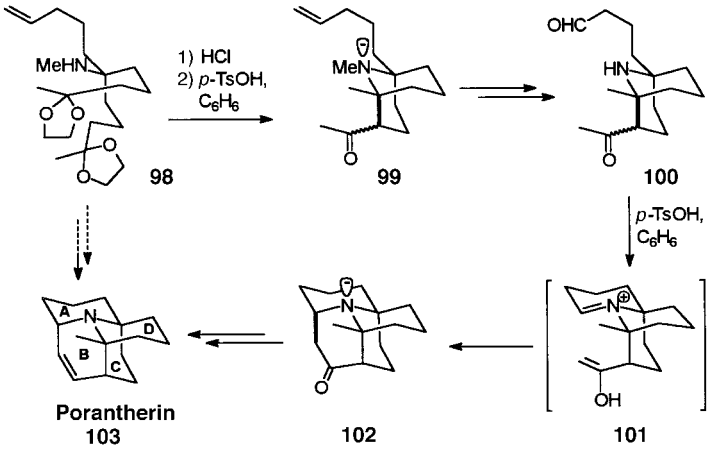


Scheme 32. Redundant synthesis of Lycopodium alkaloid **97**.

give the single isomer **96** in 66% yield. This result can only be explained by assuming an equilibration of the starting material after hydrolysis of the protecting group; a cyclization via the transition state **95b** is impossible on stereoelectronic grounds. In this synthetic sequence another major advantage of *redundant* or *degenerate synthesis* is exemplified. This is a feature of many Mannich cyclizations.[70] Regio- and stereo-

chemical considerations are reduced to a minimum, and the total number of subsequent steps is thus dramatically reduced.

Similarly, the stereoelectronically controlled Mannich cyclization is responsible for the diastereoselective construction of the quadricycle in the synthesis of the Porantherin alkaloid **103**. The principle of *redundant synthesis* is again exemplified in the formation of the C/D rings (Scheme 33).[71] Starting



Scheme 33. Stereoelectronically controlled synthesis of Porantherin alkaloid **103**.

from the symmetrical starting material **98**, a cyclic enamine is initially formed, with the help of *p*-toluene sulfonic acid. This enamine then yields the bicyclic compound **99** by means of a Mannich cyclization. Due to the symmetry of the starting material, the initial formation of the enamine can take place equally well with either carbonyl group in **98**. The subsequent preparation of the iminium species and cyclization to **99**, starting from the initially formed enamine, is achieved with catalytic quantities of acid. The subsequent transformation of the ω-olefin to the aldehyde **100** follows the same sequence as for the formation of the A/B rings. The complete reaction sequence to **99** and **102** (cleavage of the acetal protecting group, Mannich cyclization) is carried out sequentially, in order to guarantee water-free conditions for the Mannich reaction. The construction of the A/B and C/D rings in the presence of water proceeds with very modest yield.

Further examples of stereoelectronically controlled syntheses of natural products are given by the syntheses of the structurally unusual 2-azaspiro[5.5]undecane alkaloid nitramine (**104a**) and its regioisomer isonitramine (**104b**),[72] and the analgesics (−)-morphine (**105a**) and (−)-codeine (**105b**) (Scheme 34).[73]

Nitramine **104a**
R^1 = H, R^2 = OH
Isonitramine **104b**
R^1 = OH, R^2 = H

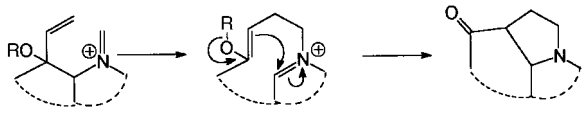
(−)-Morphine **105a**
R = H
(−)-Codeine **105b**
R = CH_3

Scheme 34. Alkaloids synthesized by stereoelectronically controlled Mannich reactions.

In the following, syntheses of natural products will be discussed, in which Mannich cyclizations have been used to construct a) pyrrolidines, b) piperidines, c) bicyclo[x.y.1(N)]-alkaloids with nitrogen as the bridge atom, and d) carbocyclic products.

4.2. Mannich Cyclizations Leading to Pyrrolidones

The sequence of cationic aza-Cope rearrangement and Mannich cyclization (Scheme 35) in which pyrrolidines (both mono- and polycyclic) are formed has served many groups in



Scheme 35. Schematic reaction path of the aza-Cope–Mannich cyclization. R = H, alkyl.

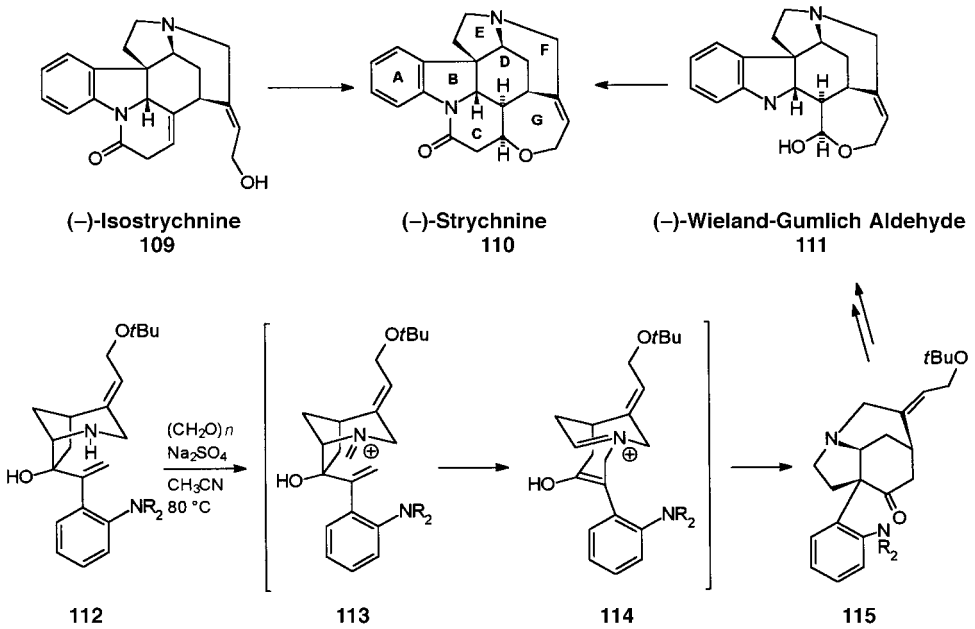
their work relating to the total synthesis of alkaloids. In the simplest case, a *homo*-allylamine functionalized at C-2 with a hydroxyl or alkoxy group is treated with an aldehyde or ketone to give **106**. The cationic iminium component is then converted into **107** by a subsequent aza-Cope rearrangement. Simultaneously, the nucleophile is also activated by the formation of either enol (R = H) or enol ether (R = alkyl). This simple, versatile, and, most of all, regioselective accessibility of the iminium species, coupled with the intermediate activation of the nucleophile, has led to the method's very wide applicability. In all cases, the intermediate is cyclized to the corresponding pyrrolidine **108** by a 5-*exo*-*trig* process. The 7-*endo*-*trig* cyclization, which is possible after equilibration of the enolate, though allowed, is not observed. In the case of a carbocyclic starting material, the process leads, overall, to a ring expansion by one carbon.

The possibilities of obtaining enantiomerically pure starting materials are numerous. Not only are amino acid derivatives from the chiral pool utilized, but homochiral starting materials from biocatalytic racemate separations are also used.

One of the characteristics of the cationic aza-Cope rearrangement is the mild conditions of the reaction.[74] The reaction proceeds at room temperature or slightly above upon addition of one equivalent of acid (commonly 0.9 eq.). Furthermore, the reaction takes place with a high degree of stereocontrol. Two factors which are responsible for this positive effect are the stereoelectronic control of the Mannich reaction and the characteristic stereoselectivity of [3,3]-sigmatropic rearrangements.[75]

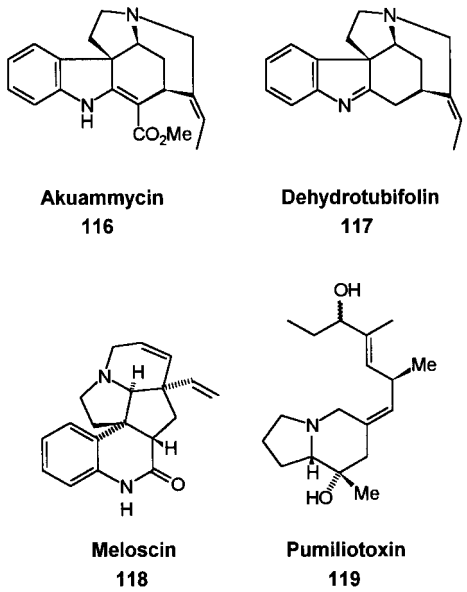
The synthesis of (−)-strychnine (**110**) by Overman et al. represents one of the highlights of the cationic aza-Cope rearrangement–Mannich reaction strategy.[76] In contrast to the route of Woodward, who chose to prepare strychnine from isostrychnine (**109**), Overman utilized a route involving the Wieland–Gumlich aldehyde (**111**) (Scheme 36).[77]

The conversion of the azabicyclooctane **112** with an excess of paraformaldehyde in the presence of Na_2SO_4 as drying agent gives the tricyclic diamine **115** in almost quantitative



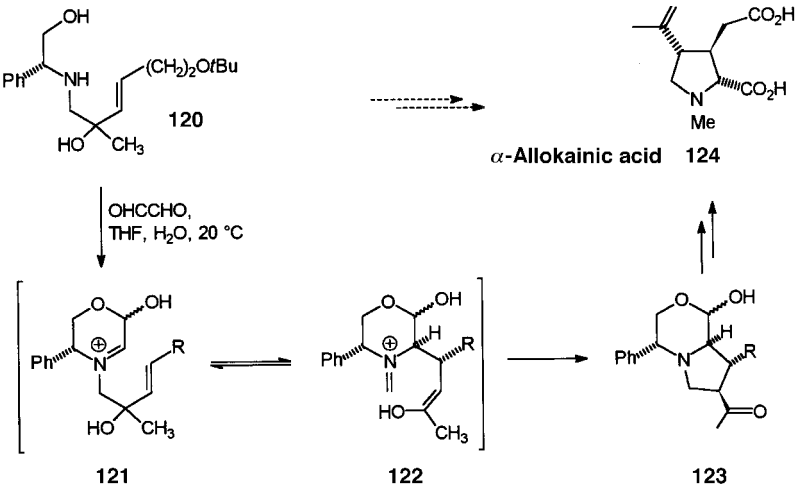
Scheme 36. Synthesis of (–)-strychnine (**110**).

yield as a single diastereoisomer. The formation of the iminium ion **113** from the homoallylamine **112** initiates the domino reaction, and the product of the aza-Cope rearrangement **114** is converted diastereoselectively into the amine **115** by the Mannich cyclization. The critical synthesis of the DEF ring system of strychnine thus proceeds with complete stereocontrol. This conversion underlines dramatically the power of this method. The following six steps leading to the enantiomerically pure (–)-Wieland–Gumlich aldehyde (**111**) can be carried out in an overall yield of 24%. The structurally related strychnine alkaloids akuammycin **116** and dihydrotubifolin **117** can also be prepared following this route.[78a] Besides these examples, the possibilities of this tandem sequence appear to set the imagination no limits, since the class of pumillotoxins **119**[78b] and the aspidosperma and melodinus alkaloids **118**[78c, d] can also be synthesized in this way (Scheme 37).



Scheme 37. Alkaloids accessible by aza-Cope/Mannich cyclization.

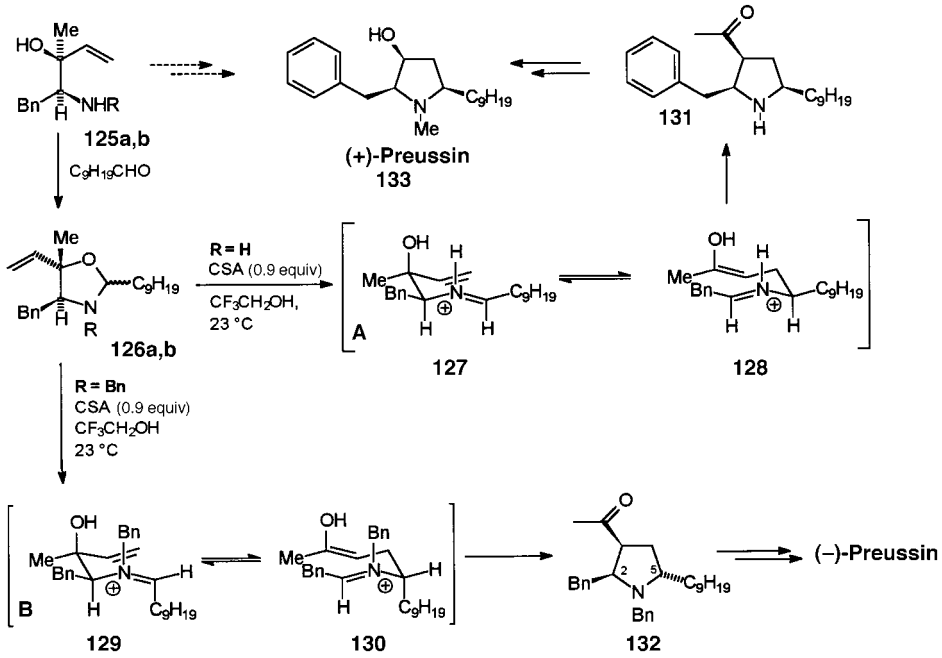
This methodology is not restricted to these very complex structures. Monocyclic, highly functionalized pyrrolidinines, such as allokainic acid (**124**)[79] and the antibiotic preussin (**133**)[80] can also be prepared along this route. The synthesis of *allo*-kainic acid is an EPC synthesis with a chiral auxiliary (Scheme 38). While the nitrogen of the phenylglycinol is incorporated into the product, the stereogenic center is used as a messenger so that the three stereogenic centers in the pyrrolidine can be generated stereoselectively. Condensation of the *homo*-allylamine **120** with glyoxal forms the intermediate epimeric hemiacetal **121**, which is cyclized diastereoselectively to the pyrrolidine **123** via **122** in a 5-*exo*-*trig* Mannich reaction. Finally, phenylethanol is removed, and with it the chiral auxiliary. In this way



Scheme 38. Synthesis of α-allokainic acid (**124**).

one can also synthesize proline derivatives, which are of great interest as building blocks for peptide mimetics.[81]

On the other hand, the synthesis of preussin is a classical synthesis ex chiral pool (or better: "conversion of natural chiral building blocks"[82]), which starts from phenylalanine. In this case too, the aza-Cope–Mannich sequence delivers the required control over the stereogenic centers. The synthesis of the natural (+)-preussin (**133**) and of its enantiomer can be carried out enantiodivergently (Scheme 39). The use of the primary amino alcohol starting material (R = H) **125a** leads,

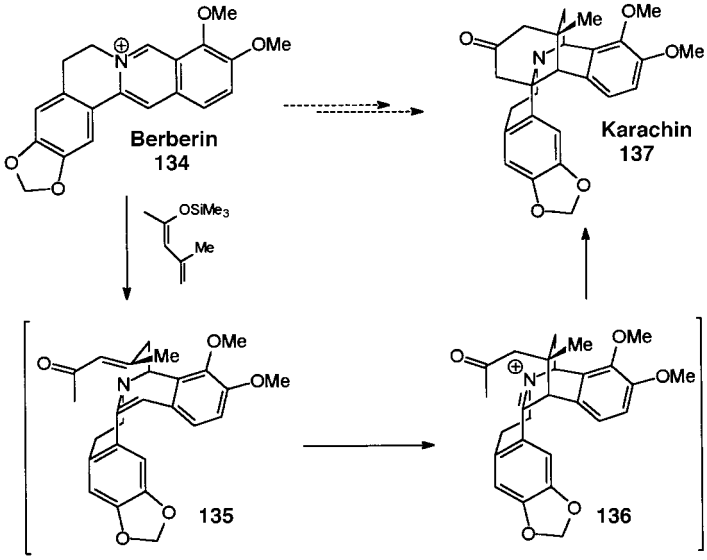


Scheme 39. Enantiodivergent synthesis of preussin (**133**). CSA = camphorsulfonic acid.

after reaction with decanal and subsequent generation of the iminium species with camphor sulfonic acid, to the all-*cis* product **131**, which can be converted into the natural product. The configuration of the transition state can be concluded from the chair configuration of the intermediate **127** (*E*-iminium stereoisomer) in the rearrangement/cyclization sequence.

Starting from the N-benzyl protected derivative **126b**, the major product obtained is the C(2)-C(5)-*trans*-configured pyrrolidine **132**. The transition state is thought to be the *Z*-configured iminium ion **129**. During a sequence of reaction steps (which contain, amongst others, a retro-Mannich–Mannich cyclization) the configuration is inverted at C-2 and C-3, and thus **132** is converted into (–)-preussin.

This application clearly underlines the potential of the aza-Cope/Mannich cyclization sequence, which offers a high level of stereocontrol even in open chain transition states. Despite this situation, this synthetic strategy seems only to have been applied at first to complex polycyclic derivatives, on the basis that their rigidity offers limited scope for epimerization.



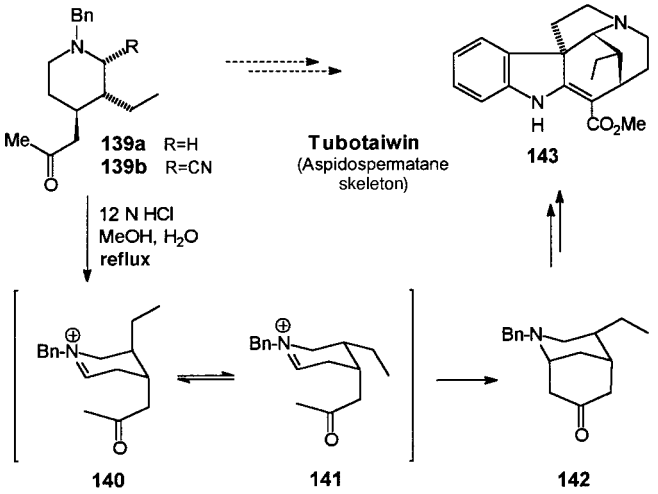
Scheme 40. Domino Mannich–Michael–Mannich cyclization of karachin (**137**).

4.3. Mannich Cyclizations in the Construction of Alkaloids Containing Piperidine Moieties

Intermolecular Mannich–Michael domino reactions have been successfully applied to the synthesis of a range of piperidine alkaloids (cf. Section 3.4). These domino sequences can also be applied intramolecularly, as the synthesis of the alkaloid karachin (**137**) proves (Scheme 40). In this impressive example, a domino reaction takes place as follows: a vinylogous Mannich reaction (to **135**) is succeeded by a Michael reaction (to **136**) and then another Mannich reaction (to **137**). Three C–C bonds are formed sequentially. This example can also be used as proof of the efficiency with which Mannich cyclizations can be carried out, and thus displays Trost's atom economy.[83] When berberin **134** is treated with 20 equivalents of the diene **138** for 18 h at 100°C, the yield of the sequence is 66%.[84]

The alkaloids of the Strychnos family (e.g. tubotaiwin (**143**)) have been the subject of much synthetic endeavor. This activity is in part due to their pharmacological properties, but also partly because of their spectacular structures. The synthesis of 2-azabicyclo[3.3.1]nonane, a substructure of this family, can be achieved with the Mannich reaction (Scheme 41).[85] The starting point of the sequence is the suitably substituted piperidine **139a**, which can be converted into the iminium ion **140** by oxidation with $Hg(OAc)_2$.[86] More recently, the iminium ion can be generated by cleavage of the cyano group from the α-cyano-substituted piperidine **139b**, itself accessed by the Polonovski–Potier reaction.[22m, 87]

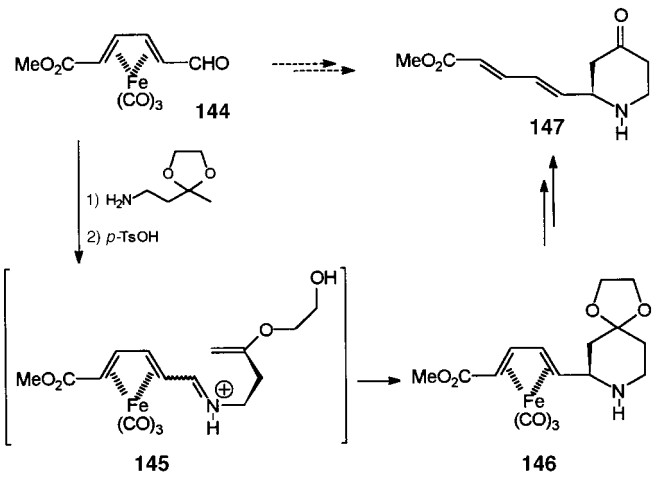
Interestingly, the iminium compound **140** epimerizes to the *cis*-isomer **141** in an equilibrium preceding the Mannich cyclization. The cyclization can only take place with an axial carbonyl side chain. Therefore, the more stable *cis*-isomer **141** serves as the compound to be cyclized. The final cyclization to **142** is again an example of the stereoelectronic control of the Mannich reaction and allows efficient control of the relative conformation.



Scheme 41. Synthesis of tubotaiwin (**143**).

Unfortunately, the preceding Polonovski–Potier reaction leading to **139b** proceeds with very unsatisfactory regioselectivity. Thus, the regioisomeric α'-cyanopiperidine is formed in approximately the same quantity as the desired compound **139b**. Furthermore, the conditions required for the conversion into the iminium cation are often very drastic, although in this case help is at hand in the form of a Lewis acid such as $TiCl_4$.[88] A further possibility for the cleavage of the cyano group is the use of *tert*-butyldimethylsilyltrifluoromethyl sulfonate (TBDMSOTf). The elimination takes place even at $-78^\circ C$ in the presence of hydrolysis-sensitive functionalities (e.g. enol ethers) and has been successfully employed in the synthesis of the insect pheromone precoccinellin.[89]

An interesting variation for the synthesis of homochiral piperidine derivatives like **147** is provided by the use of planar chiral tricarbonyl-diene-iron complexes (Scheme 42).[90] The Mannich cyclization proceeds stereoselectively on the opposite side of the iron tricarbonyl blocking group, with the *E* configuration of the iminium ion in the diastereoisomeric mixture **145** preferentially cyclization. The resulting 4-piperidinone **146** is formed in high diastereoisomeric excess (9:1).



Scheme 42. Synthesis of enantiomerically pure piperidines (**147**).

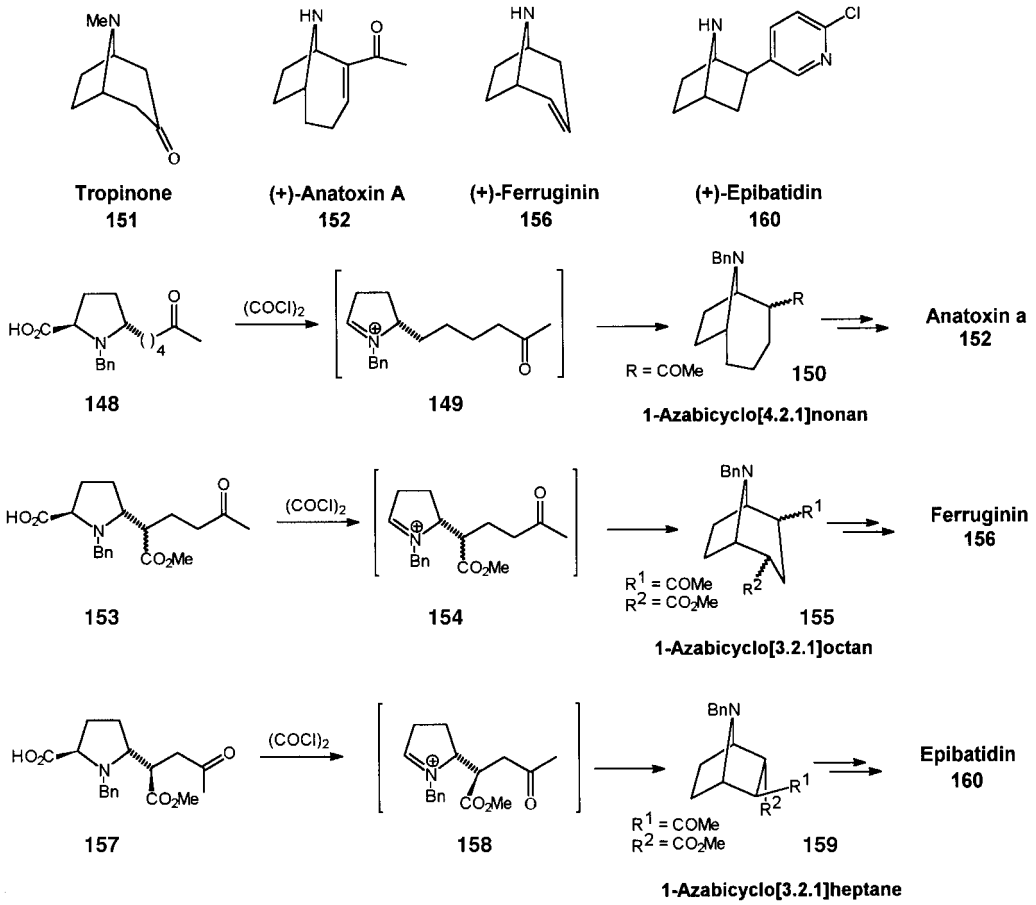
4.4. Mannich Cyclizations for the Construction of Bicyclo[*x.y.*1(N)] alkaloids

The synthesis of bicyclic systems which, in analogy to tropinone **151**, have nitrogen as the bridging atom is considered as a classic example of this methodology. This synthesis, first carried out by Robinson in 1917, is still frequently used today for the synthesis of these pharmacologically interesting materials.[10, 91]

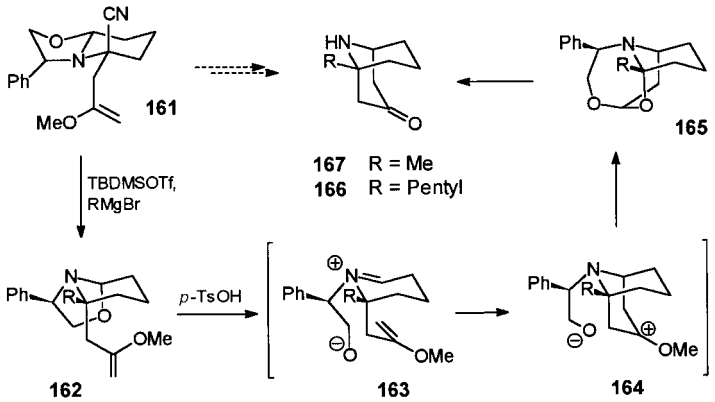
To synthesize alkaloids such as the neurotoxin anatoxin A (**152**, Scheme 43) by intramolecular Mannich reaction, a suitable side chain must be incorporated α to the imine nitrogen. In their fundamentally important work Rapoport et al. demonstrated that iminium ions of the type **149**, **154**, or **158** very readily undergo Mannich reactions to give bicyclic products.[92] They chose tertiary α-amino acid chlorides as starting materials and could show that these decarbonylate very easily to the corresponding iminium ion. This methodology offers the advantage that the generation of cationic intermediates can be performed regioselectively under mild conditions. Whereas in earlier work $POCl_3$ was used to form the acid chloride, today it is mostly $(COCl)_2$ that is the reagent of choice. Analogously, this reaction can also take place by the conversion of amino acids with dicyclohexylcarbodiimide (DCC).[93] L-glutamic acid serves in all cases as the chiral-pool building block. This is converted into the 5-thioproline derivative. Eschenmoser coupling[94] is used to incorporate the side chain required for the Mannich cyclization. By variation of the α-side chain, a variety of bicyclic natural products can be prepared, all of which contain the same basic bicyclic structure.[95] The enantiodivergent synthesis of natural products, leading to both enantiomers, is also possible. Examples of this are given by the syntheses of anatoxin a (**152**), ferruginin (**156**), and epibatidin (**160**).[96]

One restriction to this method is that the carbonyl component must be a ketone. Aldehydes and β-dicarbonyl compounds lead only to polymerized products.

Nonetheless, bicyclic alkaloids such as the alarm pheromone (−)-euphococcinin (**167**) and related compounds (e.g. adalin, **166**) can be prepared in homochiral form using the CN (*R,S*) method (Scheme 44).[97] α-Cyanoamines **161** are again used in this method—phenylglycinol serves as chiral auxiliary. After the cleavage of the cyano group under mild conditions, the quaternary center in **162** is formed by alkylation of the intermediate iminium ion. The Mannich cyclization then follows from **163**, which is itself formed by cleavage of the *N,O*-acetal. The resulting product, the acetal **165**, is converted into the natural product in a one-pot reaction involving hydrolysis and hydrogenolysis of the benzylamine. This synthesis underlines the efficiency of the method, which is



Scheme 43. Synthesis of bicyclic alkaloids.



Scheme 44. Synthesis of bicyclic insect pheromones (−)-adalin (**166**) and (−)-euphococcinin (**167**). TBDMSOTf = *tert*-butyldimethylsilyltrifluoromethane sulfonate.

due, most of all, to the ease of access to the cationic iminium species **163**.

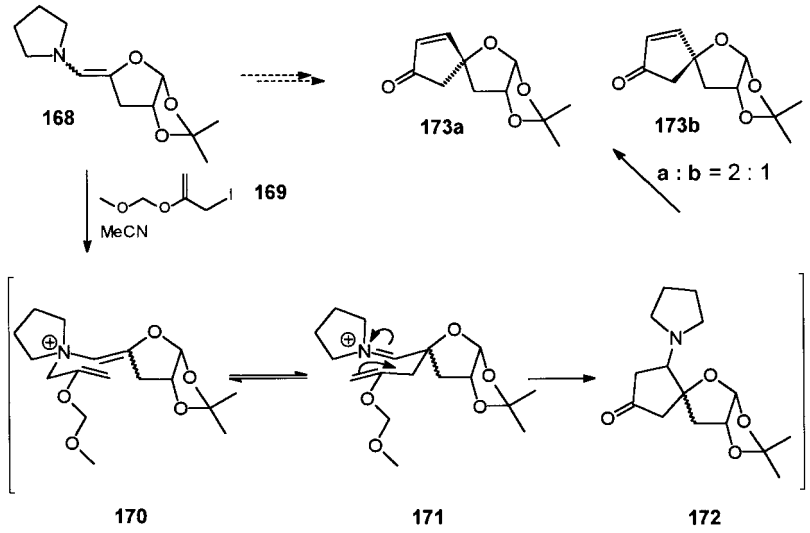
4.5. Mannich Cyclization to Carbocycles

The following synthesis represents a special case in the discussion of the Mannich cyclization to alkaloids. This is because the cyclization leads to cyclopentyl products, with the nitrogen being lost by β-elimination, a side reaction often associated with the Mannich reaction.[98] However, this is not the only interesting aspect of this synthesis; the method of generation of the iminium ion is itself worthy of discussion. While the cationic aza-Cope rearrangement is characterized by the fact that the iminium species is already present in the molecule, the use of the aza-Claisen rearrangement offers the possibility of generating the iminium ion in the course of the reaction. This has already been documented in the synthesis of highly functionalized cyclopentenones, which find use as building blocks for the pharmacologically active prostaglandin derivatives (Scheme 45).

The quaternary ammonium compound **170**, formed by N-alkylation of the enamine **168** (*Z*/*E* isomeric mixture) with the allyl halide **169**, serves as the starting material for the aza-Claisen rearrangement. The iminium ion **171**, formed as an intermediate, is trapped by a Mannich reaction, in which a carbonyl compound in the form of an enol ether functions as the nucleophile. Subsequent β-elimination of the piperidine leads to the spirocyclic product **173a**,**b** in a ratio of **a**:**b** = 2:1.

This example of the synthesis of carbocyclic compounds displays all the advantages of the use of the Mannich reaction as a key step of a rearrangement/cyclization sequence. Thus, the Mannich reaction will play a much more important role in the synthesis of carbocyclic products in the future.

The method of preparation of the carbocyclic part of perhydroindoles consists of a sequence of [2+2] photocyclization, retro-Mannich, and Mannich cyclization to yield dihydroindoles.[99] A cyclohexyl ring is formed as part of this sequence (Scheme 46). The hydroaromatic part of the struc-



Scheme 45. Domino aza-Claisen/Mannich cyclization to give cyclopentenone **173**.

turally very interesting polycyclic alkaloid manzamin A (**179**) is synthesized with this methodology.[100]

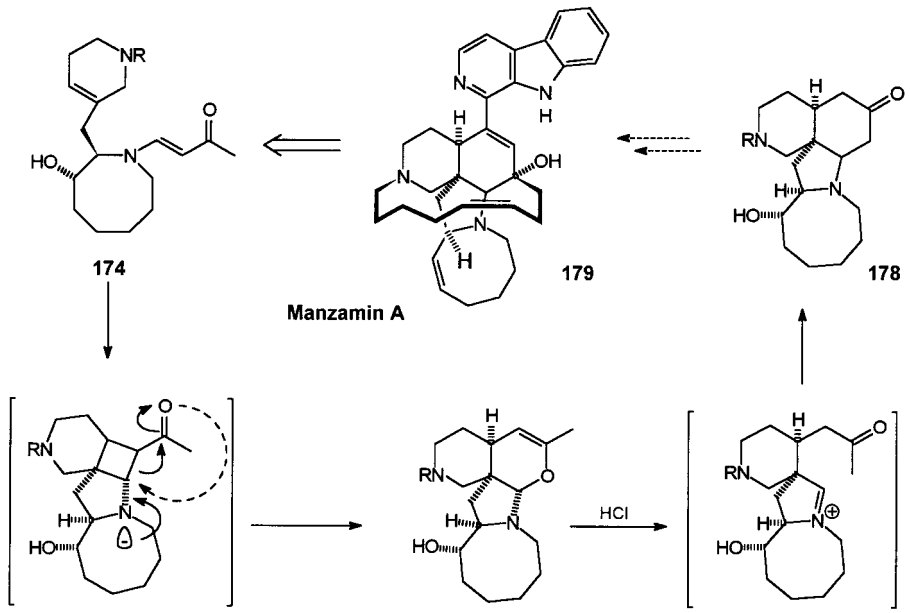
Manzamin A contains four stereocenters, which are built up from the 2,3-*trans*-configurated cyclooctylamine **174** in the correct relative configuration. Irradiation of the vinylogous amide **174** yields the tetracyclic aminal **176** in a [2+2] photocyclization/retro-Mannich domino reaction at $-78^{\circ}C$ in a diastereoselective manner. Subsequent acid-catalyzed cleavage of the aminal to give the iminium ion **177** leads, by a Mannich cyclization, to the desired tetracycle **178** in only four reaction steps.

5. Vinylogous Mannich Reactions—A Logical Development

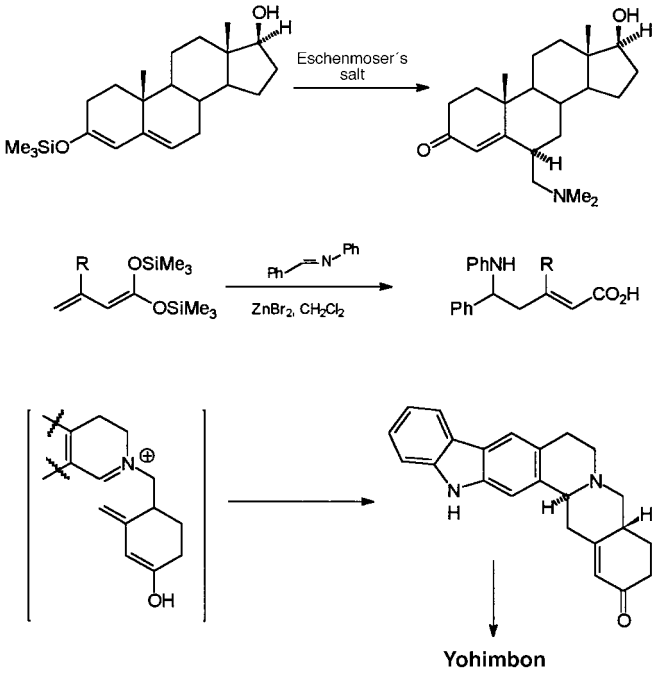
The vinylogous variant of the Mannich reaction is the γ-aminoalkylation of α,β-unsaturated carbonyl compounds (Scheme 47).[42a, b, 101] As has already been demonstrated in the synthesis of the alkaloid karachin (**137**) (cf. Scheme 40), the reaction of an iminium ion with a silyloxydiene can be carried out in the sense of an intermolecular vinylogous Mannich reaction. This type of reaction can also be applied to the synthesis of yohimbon if the tautomer of the β,γ-unsaturated cyclohexenone is prepared.[102]

This intermolecular methodology has been successfully applied to the EPC synthesis of the heteroyohimbon alkaloid (−)-ajmalycin (**184**) and its epimer (Scheme 48).[103] Starting from the imine **180**, which is itself derived from tryptophan, the Mannich reaction is carried out with the silyl ketene acetal of the methyl crotonate **181**. The reaction proceeds in CH_2Cl_2 under mild conditions, and a single diastereoisomer **182** is obtained in 69% yield. After subsequent Michael addition of the resulting amine with methyl vinyl ketone, Diels–Alder reaction to **183**, and further transformations (including the Barton decarboxylation), the natural product is obtained after a total of nine steps.[104]

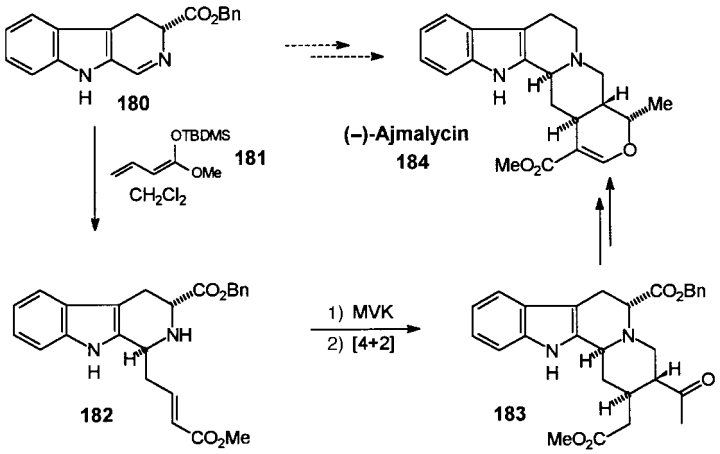
Since trimethylsilyloxybutadiene **191** is not sufficiently nucleophilic to undergo an analogous reaction, the electrophilicity of the iminium reaction partner must be increased. This is done by the in situ generation of an acyliminium ion (Scheme 49).[105] First, the acyliminium ion is generated from **192** by treatment with crotonyl chloride. This activated iminium species can now undergo a vinylogous Mannich reaction with **190** to give **193**. In this one-pot process, not only the diene but also the dienophile are introduced in 80% yield. Subsequent Diels–Alder reaction leads to a pentacycle in which the product **194** with the *cis* configuration is present in a ratio of 1:2 to the corresponding *trans* isomer. Further transformations lead to products that can be used in the



Scheme 46. Synthesis of a structural fragment of the alkaloid manzamin A (**179**).



Scheme 47. Vinylogous Mannich reactions.

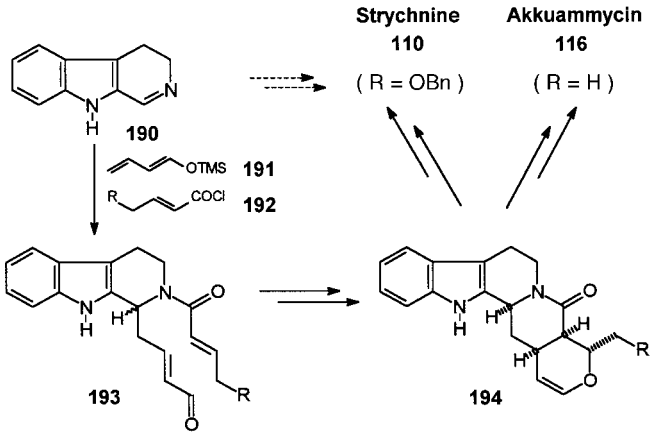


Scheme 48. Synthesis of (−)-ajmalycin (**184**).

synthesis of, for example, (±)-strychnine (**110**) (see Scheme 36). Thus, the formal total synthesis of strychnine of Martin et al. serves as a benchmark for the use of the vinylogous Mannich reaction as a key step in the total synthesis of natural products.

Further application of the vinylogous Mannich reaction are illustrated by the use of 2-alkoxyfurans **196** as nucleophilic, α,β-unsaturated components.[106] Conversion of these building blocks with iminium cations is illustrated in Scheme 50. The structural elements (**197**) thus formed are to be found in alkaloids of the Stemona family (e.g. croomin, **211**)[107] and the rugulovasines A and B (**202a**, **b**).[108]

The two last-mentioned natural products from the ergot alkaloid class differ only in the configuration at the tertiary stereogenic center. In the synthesis of this alkaloid, the reaction of the siloxyfuran **200** with the cationic iminium compound **199** leads to two diasteroisomeric products **201a**, **b**



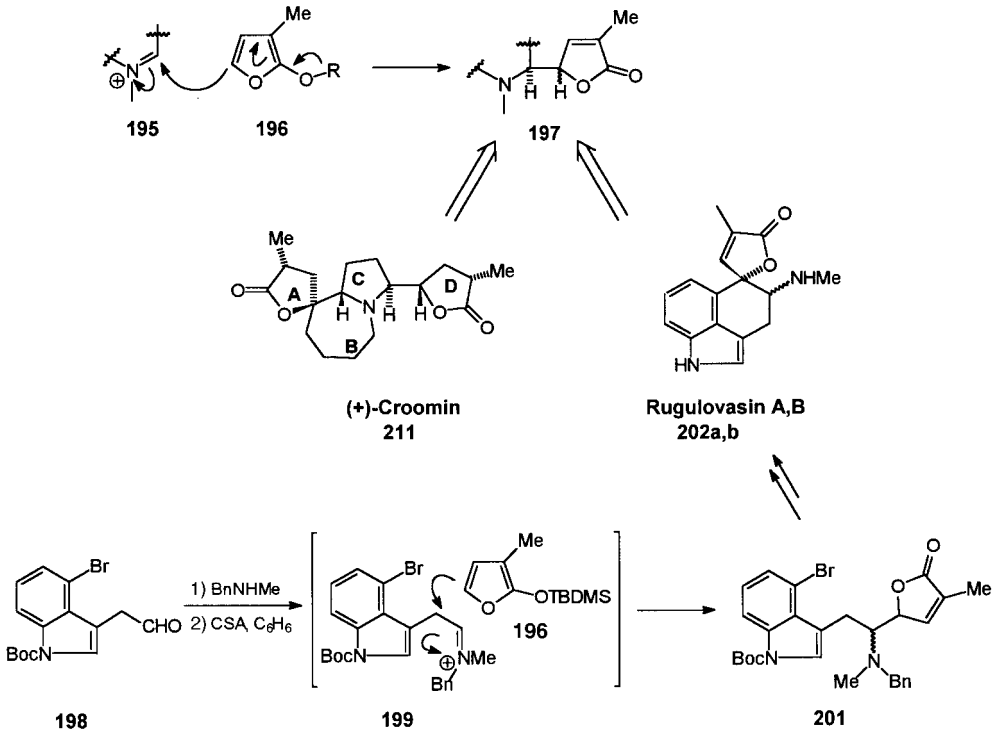
Scheme 49. Formal total synthesis of strychnine (**110**) and akkuammycin (**116**). TMS = trimethylsilyl.

(**a**:**b** = 2:1) in 80% yield based on aldehyde **198**. Subsequent photocyclization yields the spirocyclic lactone **202a, b**.

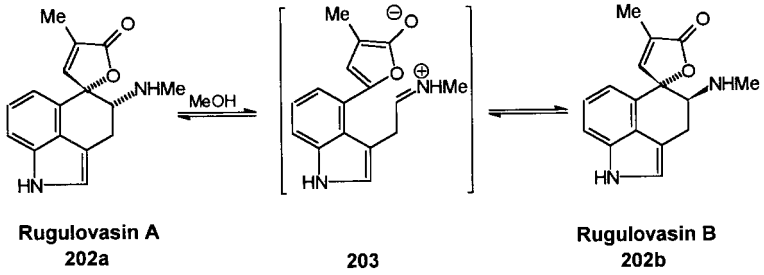
An intramolecular variant of the vinylogous Mannich reaction has helped to clarify the epimerization of the tertiary stereocenter of rugulovasine (Scheme 51).[109] The epimerization proceeds spontaneously by a retro Mannich–vinylogous Mannich sequence in which the zwitterionic structure **203** has been assumed to be an intermediate.

Two vinylogous Mannich reactions are the key steps in the synthesis of (+)-croomin (**211**) (Scheme 52).[107] The first step is a nucleophilic attack of the alkoxyfuran **204** on the acyliminium ion (**205**). This reactive intermediate is used not for its enhanced electrophilicity, but rather to protect the amino functionality. The major product is the diastereoisomer **206**, which has the *threo* configuration. Subsequent construction of the B ring leads to the bicyclic amine **207**, and then to an intermediate which, under conditions of decarbonylation, is converted into the cationic species **208** (cf. Scheme 43). Repeated vinylogous Mannich reaction with the iminium cation thus formed yields the C–C connected quadricycle **210** with a *threo*:*erythro* selectivity of 2:1. Finally, stereoselective hydrogenation gives the extremely complex natural product, whose synthesis requires a total of eleven steps.

Similarly, a vinylogous Mannich reaction can be formulated which is applicable to the preparation of dibenzo[*a,g*]quinolidine (**217**), a suitable precursor in the synthesis of (−)-emetin (Scheme 53).[110] Hydrolysis of the enol ether **212** and subsequent reaction with formaldehyde generates a β,γ-unsaturated carbonyl compound, which exists in equilibrium with its tautomer **213**. This undergoes a spontaneous [3,3]-sigmatropic rearrangement to **214**. This rearrangement is responsible for the synthesis of racemic products from homochiral precursors. It could be proved beyond doubt that this racemization cannot be traced back to a retro-Mannich–Mannich sequence. Its source is the aza-Cope rearrangement. This undesired rearrangement can be completely suppressed by reduction of the carbonyl group, and the synthesis of enantiomerically pure products can be successfully carried out with a Mannich-analogous cyclization. Similar observations have also been in the synthesis of (−)-yohimbon (cf. Scheme 47).[102b]



Scheme 50. 2-Alkoxyfurans as vinylogous Mannich nucleophiles. Boc = *tert*-butoxycarbonyl; CSA = camphorsulfonic acid; TBDMS = *tert*-butyldimethylsilyl.

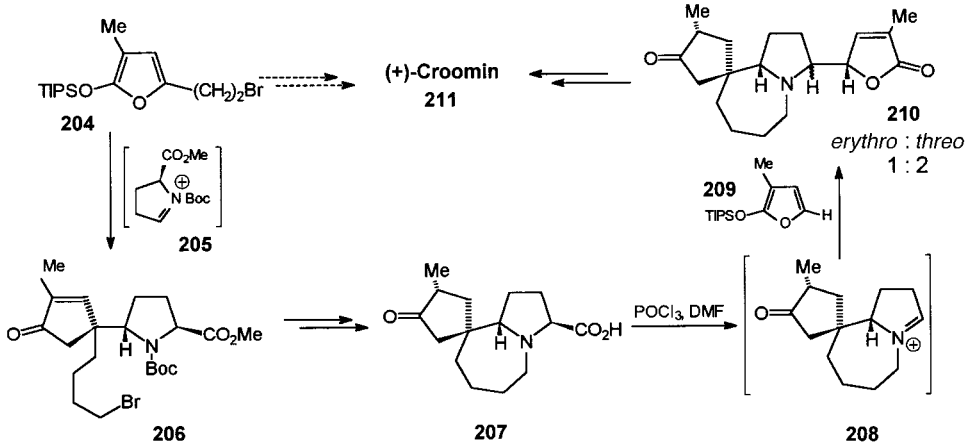


Scheme 51. Epimerization by vinylogous Mannich reaction.

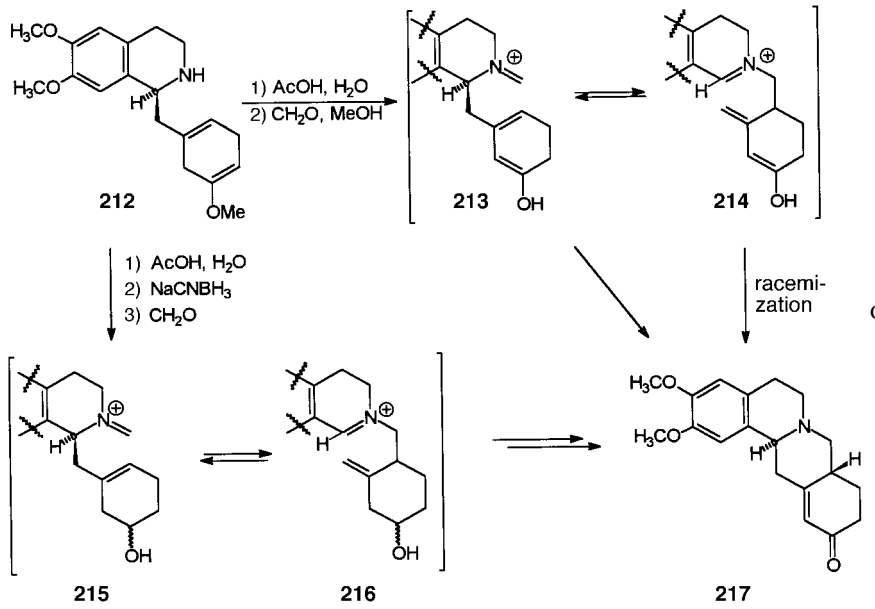
6. Summary and Future Perspectives—The End Is Still Not in Sight

The aspects of the Mannich reaction which we have chosen to discuss represent only a small fraction of the huge body of work that can be associated with the name of Carl Mannich. We wanted to, and indeed had to, limit ourselves to the area defined by us at the start of the article, namely, the aminocarbonyl compounds, and in particular to the more recent work, bearing in mind that earlier studies had already been covered by good quality reviews.

It is clear that this reaction type is unusually valuable and has a remarkably wide range of applications. This means, more specifically, that it starts from cheap starting materials and provides key building blocks for pharmaceuticals and natural products in an inexpensive manner. It is efficient in terms of yields and resources. That the conditions of the Mannich reaction are such that many multistage processes (domino reaction sequences) can be carried out as "one-pot" reactions increases its worth even more. This methodology is, however, more than just an economic process. The intensive research



Scheme 52. Synthesis of (+)-croomin (**211**).



Scheme 53. Vinylogous Mannich cyclization leading to azacyclic fragments of alkaloids.

carried out on the classical Mannich reaction over the last few years has satisfied the requirements of modern selective chemistry (that is, chemo-, regio-, and diastereoselectivity). The reason for this success is not only the creativity of the chemists involved in the recognition, planning, and realization of its synthetic potential, but also the skilful use of synthetic tools such as preformed aminoalkylation reagents (iminium salts etc.).

The fascination generated by the application of this chemistry has, not without good reason, led to the catch phrase "Mannich Magic"—a term which embodies the fascination and motivation inspired by this chemistry.

In addition to the iminium ions prepared in situ, which have a well-established place in modern Mannich chemistry (particularly in the intramolecular variant), many forms of aminomethylating and aminoalkylating agents now enrich the synthetic palette of selective chemical reagents. Their electrophilic character makes them predestined to react with almost any nucleophile, thereby expanding the potential functionalities. Iminium systems with an increasing variety of selectively deblockable substitution patterns will no doubt follow. Many new routes and preparative chances have been proposed, or at least hinted at.

Despite many studies, and some notable successes, penetration into enantiomerically pure Mannich bases is still only beginning. That the configurational stability of β-aminocarbonyl compounds cannot easily be secured makes this field of endeavor appear less attractive. However, when one thinks of the many in situ and racemization-free routes to derivatization of the kinetic products (to, for example, amino alcohols, diamines, amines etc.), it becomes understandable that the possibility of developing efficient and effective routes to products of controlled absolute configuration may indeed be realizable. Catalytic processes, which are established in many other areas of stereochemistry, are almost completely untouched.

We thank our colleagues in the research groups for their motivation within the teams and our colleagues for useful discussions and advice. We thank the Deutschen Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Universität Paderborn for the financial support of our work.

Received: March 7, 1997 [A 217 IE]
German version: *Angew. Chem.* **1998**, *110*, 1096 – 1122
Translated by Dr. D. J. Macquarrie, York, England

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[39] In the original publication, both ^1H and ^{13}C NMR data were given; however, the relative configuration of the predominant diastereoisomer was not indicated.[16d] By comparing the NMR data of the *anti* Mannich base, described in the literature,[20d, 26d] the *anti* configuration can be assigned to the predominant isomer in this case.

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