Tetrahedron 65 (2009) 9657–9672

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 890

Recent advances and applications in asymmetric aza-Michael addition chemistry

Palakodety Radha Krishna *, Aare Sreeshailam, Ravula Srinivas

D-211, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 607, India

ARTICLE INFO

Article history:
Received 10 July 2009
Available online 13 August 2009

Keywords:
Diastereoselective aza-Michael addition
Enantioselective aza-Michael addition
Double aza-Michael addition

Contents

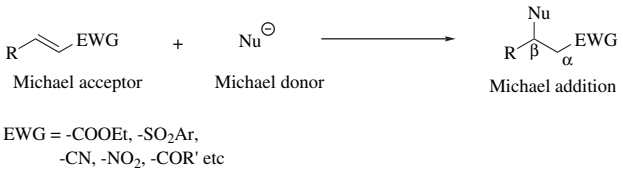
1. Introduction

Organic chemistry is an ever-evolving science. Each new discovery adds to the glory of organic synthesis. Even the reactions, which were discovered a century ago have promising new dimensions being added each day. Michael addition is one such reaction. As originally defined by Michael,[1] the reaction is the addition of an enolate of a ketone or aldehyde to an α,β-unsaturated carbonyl compound at the β carbon. A newer definition, proposed by Kohler,[2] is the 1,4-addition of a doubly stabilized carbon nucleophile to an α,β-unsaturated carbonyl compound. Some examples of nucleophiles include β-ketoesters, malonates, and β-cyanoesters. When the nucleophile is nitrogen based, the reaction is named as an aza-Michael addition. Ever since its discovery, Michael addition has been a very popular reaction among organic chemists.[3]

During our work on the total synthesis of natural products, we planned to use an asymmetric aza-Michael addition reaction as the crucial step and, hence, scanned the literature. We found that the earlier literature or erstwhile review(s) on asymmetric aza-Michael reactions were either embedded or dedicated mostly to the generation of β-amino acids.[4] It was therefore felt necessary to compile the literature under one heading for the benefit of the readers and the potential users.

* Corresponding author. Tel.: +91 40 27193158; fax: +91 40 27160387.
E-mail address: prkgenius@iict.res.in (P.R. Krishna).

0040-4020/$ – see front matter
doi:10.1016/j.tet.2009.08.021



2. Asymmetric aza-Michael addition

Conjugate addition has been used as an efficient tool in organic synthesis for over a century now, but the versatility of aza-Michael addition, i.e., conjugate addition, using nitrogen-based nucleophiles has become evident only recently. Aza-Michael addition is an excellent way of forming C–N bonds and is of tremendous significance in asymmetric synthesis. In this review, we discuss the scope of asymmetric aza-Michael addition as an efficient tool in organic synthesis by citing various examples from the literature and from the work carried out in our own laboratories. This review is confined to the chiral version of the reaction and the vast literature on other types is excluded. The asymmetric aza-Michael reaction will now be broadly discussed under several categories.

3. Diastereoselective aza-Michael addition

The diastereoselectivity in the aza-Michael addition can be achieved by employing one of the following methods.

3.1. Using chiral amines

Lithium amides, the universally known strong bases, have recently been recognized as potential nucleophiles in stereocontrolled aza-Michael additions. The first asymmetric aza-Michael addition was reported by Hawkins et al.[5] They demonstrated the first diastereoselective conjugate addition of the homochiral lithium amide derived from **2** to a range of α,β-unsaturated acceptors. Lithium amides, derived from readily available chiral amines (**1**–**5**), have been extensively used as synthetic equivalents of ammonia in these transformations (Fig. 1).

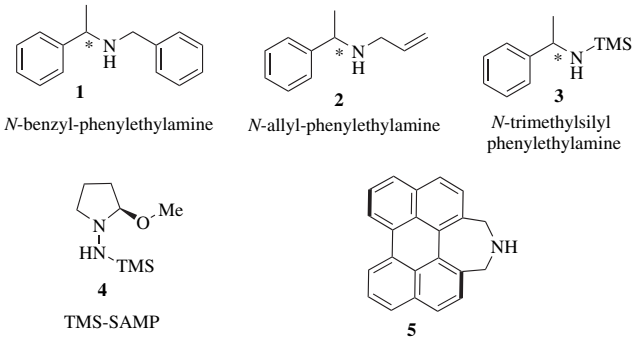
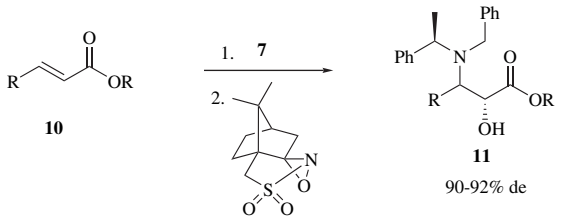


Figure 1.

The extensive work of Davies et al. has demonstrated that secondary homochiral lithium amides such as **7** undergo highly diastereoselective conjugate addition to a range of α,β-unsaturated esters **6**.[6] The subsequent product **8** on debenzylation results in the corresponding β-amino acids **9** in high yields and high ees (Scheme 1).[7]

The formation of product **8** was rationalized by a proposed transition-state model A (Scheme 1), based on molecular modeling studies. The lowest energy transition state was that in which the α,β-unsaturated acceptor adopts an *S-cis* conformation, lithium is chelated to the carbonyl oxygen as well as to the nitrogen lone pair, and the two phenyl groups are almost parallel to each other, as shown in model A (Scheme 1), to facilitate the *si*-face addition as the most favored, generating the desired product **8**.[8]

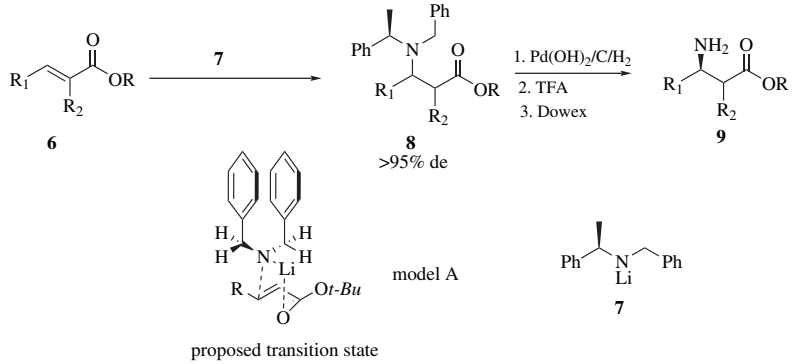
Trapping of the intermediate enolate electrophile, realized from **10** undergoes Michael addition with concomitant hydroxylation to furnish α-hydroxy β-amino acids **11** in excellent diastereoselectivities (Scheme 2).



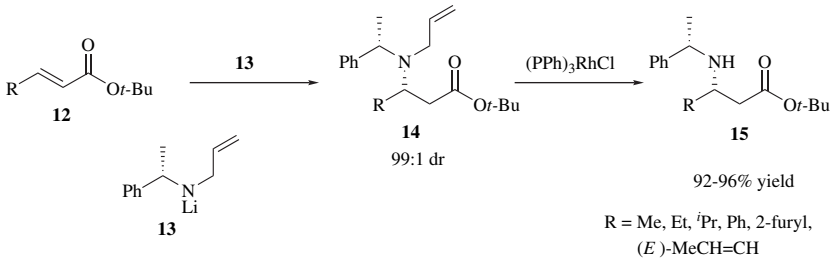
Scheme 2.

One limitation of the above methodology is that, however, since the end products posses the benzyl groups their removal requires hydrogenolysis reaction. Consequently, the amide (α-methylbenzyl phenyl amide) cannot be used for the synthesis of unsaturated β-amino acid derivatives that are encountered in nature such as (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6-8-trimethyl-10-phenyl-4,6-decadienoic acids, commonly known as ADDA (**16**, Scheme 4), or in the antibiotics, cyanovirin-N, nodularin, and microcystin. In order to bring the synthesis of these β-amino acids within the scope of the lithium amide methodology, a slight modification of the protocol was therefore desirable.

To overcome this difficulty, Davies et al.[9] have demonstrated the use of lithium (α-methylbenzyl)allylamide (*S*)-**13** in the conjugate addition of the enolates **12** and, later, the *N*-allyl group present in compound **14** could be preferentially removed in the presence of the *N*-α-methylbenzyl group upon treatment with Wilkinson's catalyst (Scheme 3). Subsequently, the *N*-α-methylbenzyl group in



Scheme 1.



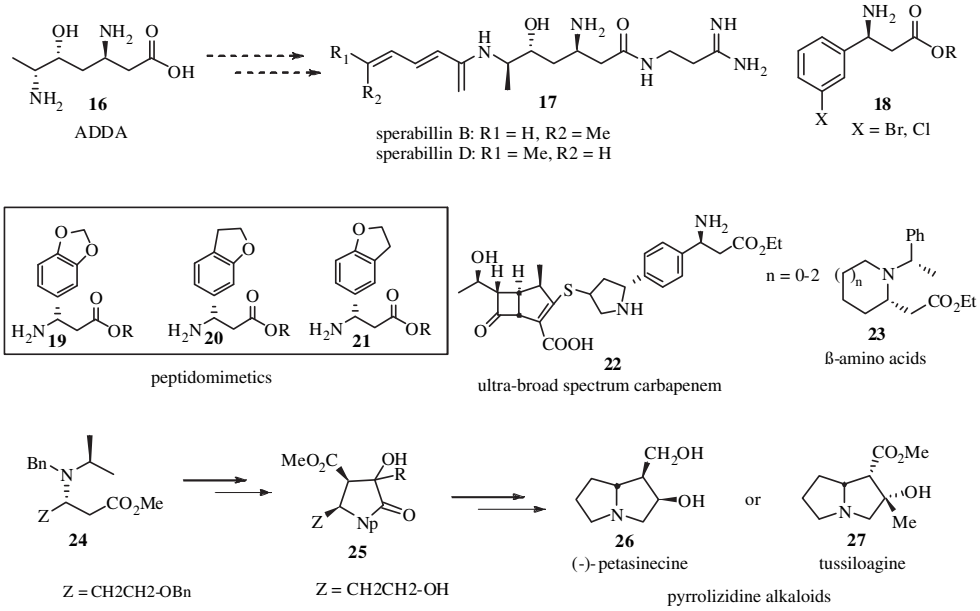
Scheme 3.

15 can be removed from β-lactam ring systems using a dissolving metal reduction without affecting the unsaturated side chain.

Further, Davies et al. described the enormous synthetic utility of the protocol shown in Schemes 1–3, as exemplified by its application in the synthesis of antibiotic ADDA (**16**),[10] sperabillins B and D (**17**),[11] β-haloaryl-β-amino acids (**18**),[12] peptidomimetics (**19**–**21**),[13] cyclic β-amino acids (**23**),[14] an ultra-broad spectrum carbapenem (**22**),[15] pyrrolizidine alkaloids (**26** and **27**),[16] etc. (Scheme 4). Thus, the initial Michael addition product **24** upon simple conversions led to highly substituted lactam **25**, which on further extrapolation led to **26** and **27** as the case maybe.

corresponding β-amino ester **29** exclusively. Extrapolating further, a second aza-Michael addition of chiral amine **30** with alkynoic ester **31** gave enamine **32**, which eventually led to the synthesis of (−)-8-*epi*-hyperaspine **33** in good yields.

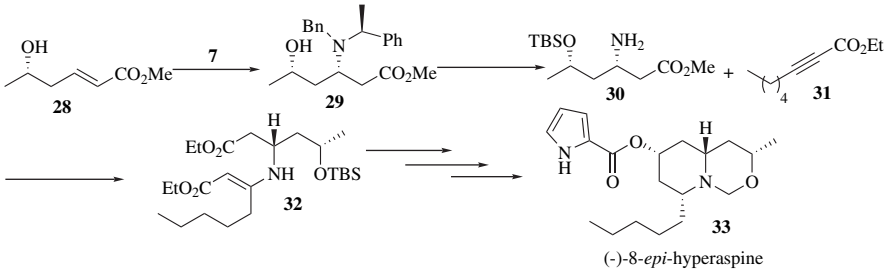
A similar strategy was employed for the synthesis of hyperaspine (Scheme 6).[18] Thus, enantiopure β-amino ester **35** was obtained exclusively in 89% yield by the diastereoselective aza-Michael addition of lithium (*S*)-*N*-benzyl-α-methylbenzylamide to (*E*)-2-nonenoic acid ethyl ester **34** followed by a hydrogenolysis reaction. Further, this β-amino ester **35** on next Michael addition to the alkynoic ester **36** gave diester **37** and on further transformations gave hyperaspine **38**.



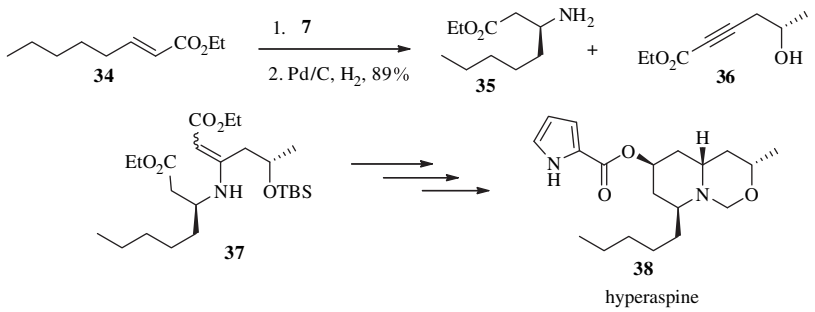
Scheme 4.

Zhu and Ma have applied the above methodology in the construction of the 3-oxaquinolizidine skeleton of hyperaspine (Scheme 5).[17] The diastereoselective conjugate addition of lithium (*S*)-*N*-benzyl-α-methyl benzylamide to δ-hydroxy α,β-unsaturated ester **28** and subsequent hydrogenolysis provided the

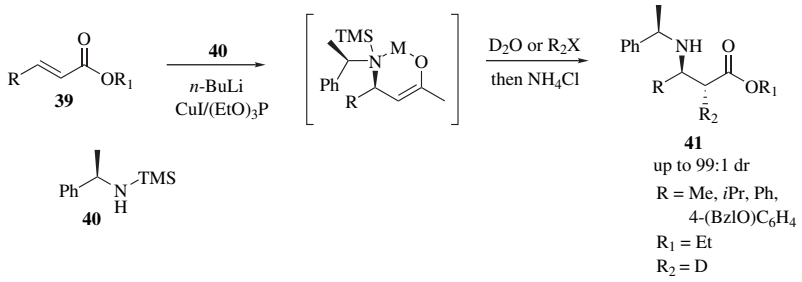
Sewald et al.[19] demonstrated the use of *N*-trimethylsilyl-phenylethylamine as a nucleophile (Scheme 7). Thus, the conjugate addition of homochiral amidocuprates or lithium amides based on (*R*)-*N*-(1-phenylethyl)-(trimethylsilyl)amine **40** to α,β-unsaturated esters **39** proceeds stereoselectively to afford the corresponding β-amino



Scheme 5.



Scheme 6.



Scheme 7.

acids (Scheme 7). Trapping of the intermediate enolate with D_2O furnished the corresponding α-deuterated β-amino acid compounds **41**. *anti*-α-Alkyl-β-amino acids are obtained stereoselectively after transmetalation of the lithium/copper ester enolate to the titanium ester enolate and trapping with carbon electrophiles. The *anti*/*syn*-selectivity can be explained by assuming transition-state geometries where the delivery of the nitrogen nucleophile is controlled by lithium 'chelation' between the reagent and substrate. While in one case the product configuration could be controlled by the reagent irrespective of the substrate stereochemistry, in other examples the topicity of the addition is complementary to published results. For instance, *erythro*- or *threo*-configured 2,3-dideoxy-3-aminopentoses are accessible via this route.

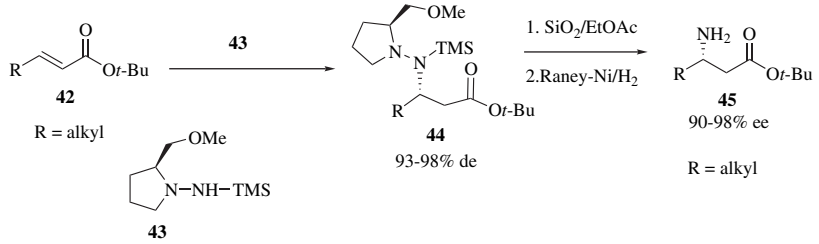
In a similar way, Enders et al.[20] have developed a diastereo- and enantioselective synthesis of α-alkyl/aryl-β-amino acids by a tandem 1,4-addition/α-alkylation strategy (Scheme 8). Thus, the 'chiral ammonia' utilized by these authors is (*S*)-(−)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine (TMS-SAMP) **43**, readily prepared from the well-established auxiliary (*S*)-(−)-1-amino-2-methoxymethylpyrrolidine (SAMP). By adding the lithium salt of TMS-SAMP to various methyl and *tert*-butyl α,β-unsaturated esters such as **42**, the corresponding (*S*,*S*)-3-amino ester derivatives **44** were obtained in 93–98% de and in varying yields of 32–67%. These products were readily transformed into the corresponding (*S*)-β-amino acids **45** by the reductive cleavage of the SAMP moiety with Raney Ni/H_2 (Scheme 8).

Further, if the addition of the lithium salt of TMS-SAMP was followed by treatment of the reaction mixture with HMPA (3 equiv) and the appropriate alkyl halide, both the α- and the β-position were functionalized in favor of the *anti*-stereoisomer with diastereomeric excesses ranging from 63 to ≥96% (Scheme 9).

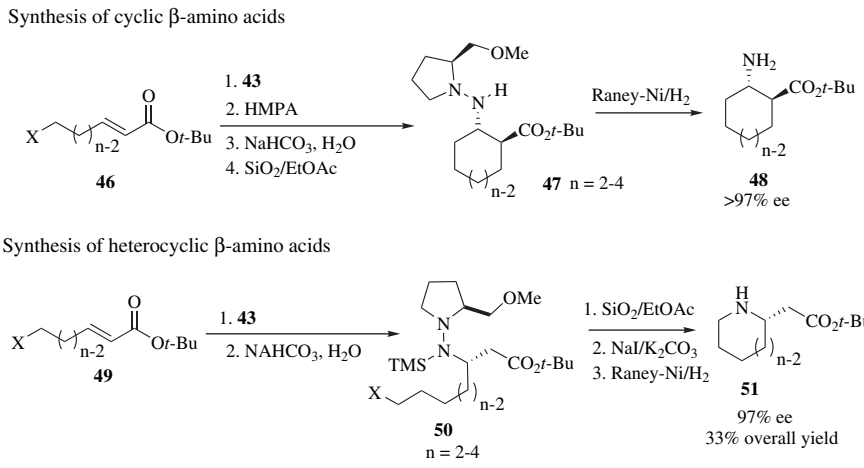
An application of this methodology[21] was the synthesis of *trans*-2-aminocyclopentane-, cyclohexane-, and cycloheptane-1-carboxylic acids **48** (Scheme 9) in high diastereo- and enantiomeric purity (de≥96–98%, ee≥98%) utilizing the stereoselective conjugate addition of lithiated (*S*)-(−)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine (TMS-SAMP) **43** to ω-halide-substituted α,β-unsaturated enolates to afford **47** followed by subsequent ring closure of the intermediate ester enolate (MIRC reaction). Likewise **49** on aza-Michael addition as adopted in earlier case with **43** gave acyclic hydrazide **50**, which on different set of reactions led to the piperidine derivative **51**, thus showcasing the diverse utility of this reaction.

3.2. Using chiral substrates

Stereoselective 1,4-addition of an achiral amine nucleophile to a chiral acceptor has been investigated by a number of scientists.[22] Achiral amines have also been shown to undergo exemplary diastereoselective conjugate additions. Following this strategy, d'Angelo et al. achieved a very high stereocontrol in the conjugate addition of achiral amines to chiral (α,β-ethylenic esters) crotonates **52**, albeit under high pressure, to produce β-amino esters **53** in

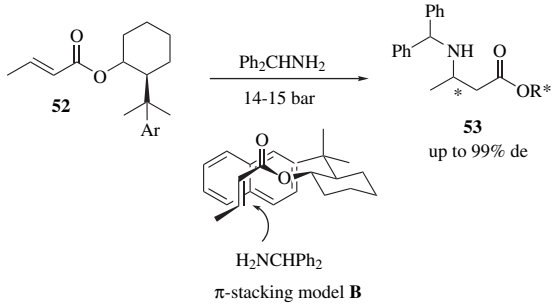


Scheme 8.



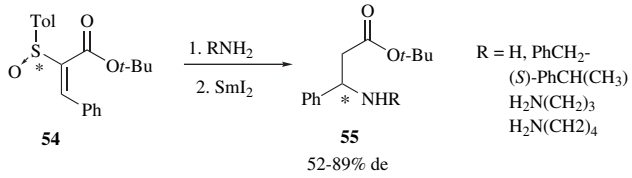
Scheme 9.

good chemical yield and variable des ranging from 5 to ≥99%[23] (Scheme 10). A π-stacking model B was proposed to rationalize the observed high selectivities, which were consistent with the preferential attack of the amine from the less hindered enoate π-*face* of the crotonate existing in its *S-trans* conformation. The aryl group of the inductor shields the α-face of the crotonate unit and an *anti* addition of the amine across the double bond was also suggested by the authors via the addition of $CHND_2$.



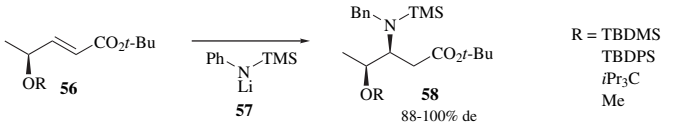
Scheme 10.

Matsuyama et al. demonstrated the addition of different acyclic nitrogen nucleophiles to chiral *p*-tolylsulfinyl cinnamate **54** to produce the adducts **55** with moderate-to-good selectivities[24] (Scheme 11). Most notably, the addition of NH_3 to **54** proceeded smoothly at room temperature, followed by reductive cleavage of the sulfinyl group to give the product **55** (R=H) in 81% ee.



Scheme 11.

Other similar instances were described by Yamamoto et al.[25] and Meyers and Shimano,[26] respectively, as outlined in Schemes 12 and 13. The conjugate addition of achiral lithium amide **57** to chiral enoates **56** (Scheme 12) produced a mixture of the *syn* and *anti* products in high yields (83–99%). Sterically bulky groups such as



Scheme 12.

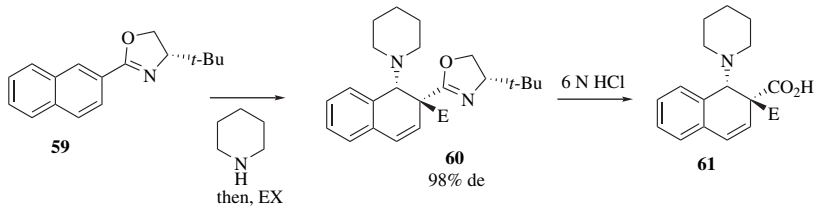
trityloxy and TBDPS gave the *syn*-diastereomer **58** either exclusively or predominantly. The *syn*-selectivity may be explained by a modified Felkin–Anh (C) model. Similarly, chiral oxazolidine **59** (Scheme 13) on Michael addition with piperidine and simultaneous trapping with several electrophiles gave corresponding adducts **60**, which on hydrolysis afforded dihydroaryl α-substituted β-amino acids **61** in equally good yields and selectivities as obtained in acyclic substrates.

There are numerous other examples, which employ conjugate addition of simple achiral benzylamine to chiral enoates. For instance, Costa et al.[27] were able to add $BnNH_2$ to the chiral ester **62** to give **63**, in 90% yield and in good diastereoselectivity (85% de) (Scheme 14).

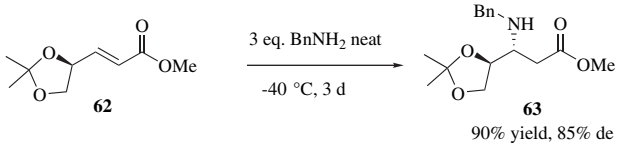
Similarly, Sharma et al.[28] demonstrated the aza-Michael addition of $BnNH_2$ to sugar-based γ-alkoxy α,β-unsaturated esters **64a–e** to give the corresponding β-amino esters **65a–e** by utilizing TBAF as a base (Scheme 15). The use of TBAF in the reaction is to suppress the 1,2-addition pathway, while enhancing the rate of the reaction.

In another report, Perlmutter and Tabone utilized the diastereoselective conjugate addition of $BnNH_2$ to various alkenoates **66** in methanol at room temperature to give the adducts **67** with virtually complete *anti*-diastereoselectivity (up to 90% de) for the synthesis of *anti*-α-substituted-β-amino esters via 1,3-asymmetric induction[29] (Scheme 16). It was found that the presence of a β-substituent led to a dramatic reduction in yield, although the same *anti*-diastereoselectivity was maintained.

Fustero et al.[30] planned the synthesis of partially modified retro (PMR)-Ψ[$NHCH_2$] peptide mimetics, using an aza-Michael-enolate protocol to incorporate a chemically stable group [$CH_2CH(CF_3)CO$] to access trifluoromethyl-Ala in a stereodefined way. The smooth and general synthesis of PMR-Ψ[$NHCH_2$]-tripeptides **70** (Scheme 17) by tandem asymmetric aza-Michael addition–enolate protonation of α-amino esters **68** with *N*-(α-trifluoromethyl)acryloyl-α-amino esters **69** is demonstrated. This sequence furnishes products in good-to-excellent diastereoselective 1,4-asymmetric induction (up to 95% de), depending upon the substrate. Very high stereocontrol was observed upon fine tuning the key reaction parameters such as the solvent and the base.

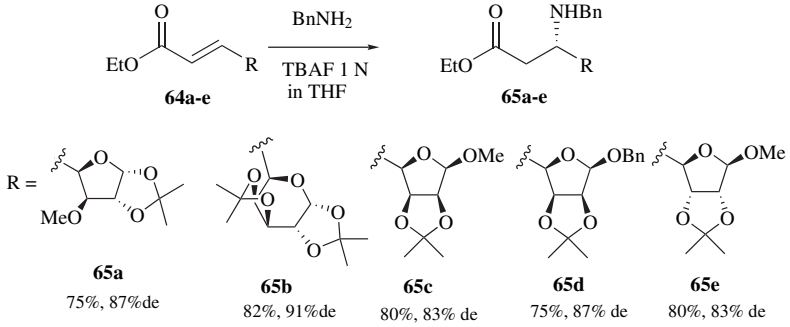


Scheme 13.

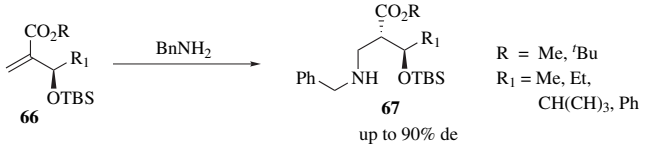


Scheme 14.

carbonyls in order to produce a rigid chiral unsaturated system (to control the rotamer population) which, in turn, reacts with the nucleophile from the preferred face and thus enhances the reactivity of the electrophilic imide. Various Lewis acids were used as chelating agents and the best results were obtained with $TiCl_4$ and $AlMe_2Cl$. Indeed, when the reaction was performed in the absence of a Lewis acid no addition product was obtained.

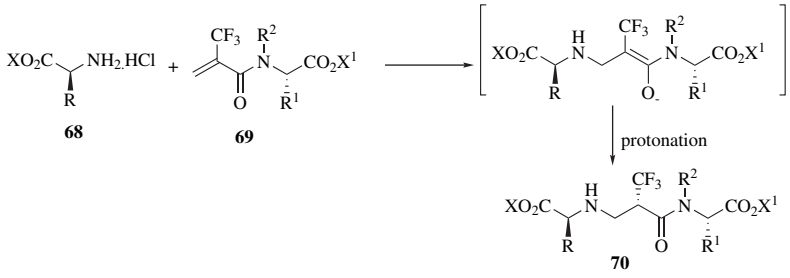


Scheme 15.



Scheme 16.

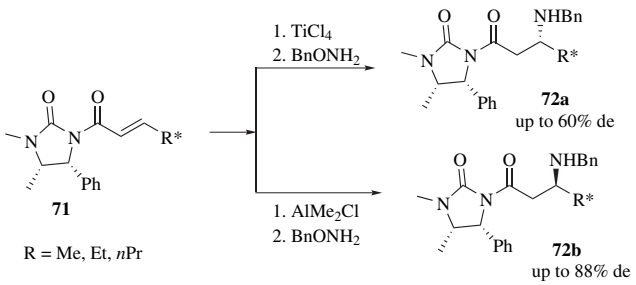
In particular, the addition of *O*-benzylhydroxylamine catalyzed by 2 equiv of $AlMe_2Cl$ furnished the β-amino derivative **72b** in an 89:11 diastereomeric ratio and 83% yield. The nucleophilic attack of the aluminum-chelated crotonyl imide derivative would preferably occur from the Cβ-*re* face of the *syn* conformation. Conversely, titanium mediated addition led to lower ratios as in **72a** in favor of α-amino derivate as major product.



Scheme 17.

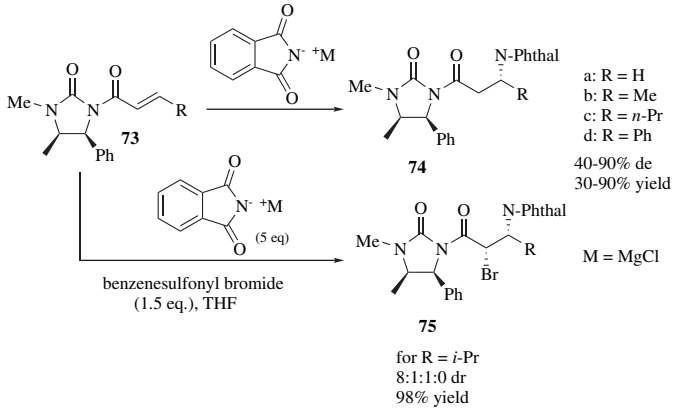
3.3. Using chiral auxiliaries

Cardillo et al. demonstrated another significant protocol involving aza-Michael addition with chiral substrates in which the Lewis-acid-mediated addition of *O*-benzylhydroxylamine to chiral imides **71**[31] (Scheme 18) played a crucial role. Initially, the reaction of various α,β-unsaturated acyl chlorides with (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one afforded the corresponding acylated oxazolidinones **71**, which were used in a Michael addition later in the presence of a Lewis acid. The beauty of this reaction was the dual mechanistic role of the Lewis acid in chelating both the



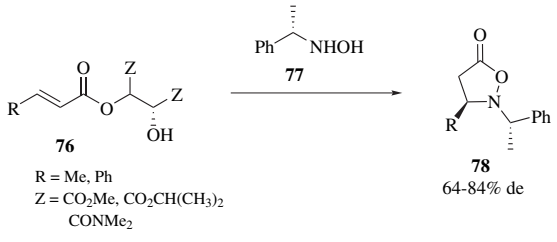
Scheme 18.

In yet another method, Cardillo et al. reported the diastereoselective functionalization of both the α- and the β-position of chiral enamides **73** with the addition of chloromagnesium phthalimide[32] (Scheme 19). The reaction afforded the corresponding β-phthalimido derivatives **74** in 95:5 diastereomeric ratio and in 90% yield. Incidentally, the reaction was performed with 5 equiv of the nucleophile. Furthermore, the resulting enolate was trapped by performing the reaction in the presence of benzenesulfonyl bromide to offer the *syn*-2-bromo-3-phthalimido derivative **75** in good yield and high diastereoselectivity, and thus was then transformed into the corresponding *anti*-2-azido-3-phthalimido derivative by displacement of the bromide with azide.



Scheme 19.

Saito et al. went a step further to prepare the isoxazolidinone precursors via an aza-Michael addition.[33] One of the traditional synthetic routes to isoxazolidinones **78** consists of two elementary processes, namely a Michael addition of a hydroxylamine to an α,β-unsaturated ester **76** and a cyclization process involving an intramolecular transesterification between the ester group and the *N*-hydroxyl group of the resulting adduct (Scheme 20). It should be noted, however, that the second step requires a strong base such as LDA or LHMDS at −78 °C, which makes this method rather less attractive. After endeavors to remedy these drawbacks, Saito et al. found that switching the ethyl group of acrylate to a particular alkyl group bearing an α-CO_2R moiety can facilitate not only the Michael addition of (*N*-benzyl)hydroxylamine (BHA), but also the ensuing transesterification step at 0 °C to room temperature without relying on any base, although in this case the yields with BHA are very high, albeit in low diastereoselectivity (1–10% ee).



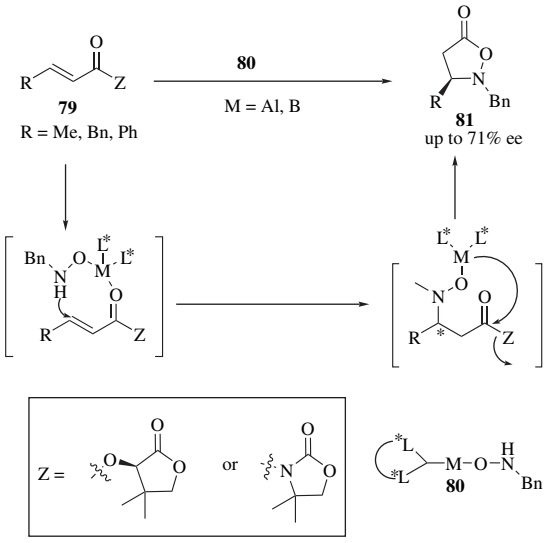
Scheme 20.

Using chiral (*N*-α-methylbenzyl)hydroxylamine [(*S*)- or (*R*)-MBHA] **77** in lieu of BHA totally changed the above-mentioned product profile in terms of stereoselectivity. The product was formed in 70% yield and in a 9:1 ratio (80% de). These values can be explained by the phenomenon of double stereodifferentiation. In this work, they used (*N*-methylbenzyl)hydroxylamine as a bifunctional nucleophile, since isoxazolidinone **78** can be visualized as a masked β-amino acid moiety through the reductive N–O bond cleavage.

Similarly, using this methodology, Zanda et al.[34] prepared a small library of enantiomerically modified retropeptides having a ψ[NHCH(CF_3)] unit as a possible mimic of the classical ψ(NHCO) retropeptide unit using a double stereodifferentiation approach.[29]

The above-mentioned protocol, however, contains a common drawback in the sense that the stereocenters of chiral amines such as (*S*)-MBHA are destroyed during the deprotection step in order to generate free β-amino acids. Hence, more economical chiral amine nucleophiles bearing removable and recyclable chiral auxiliaries are desirable.

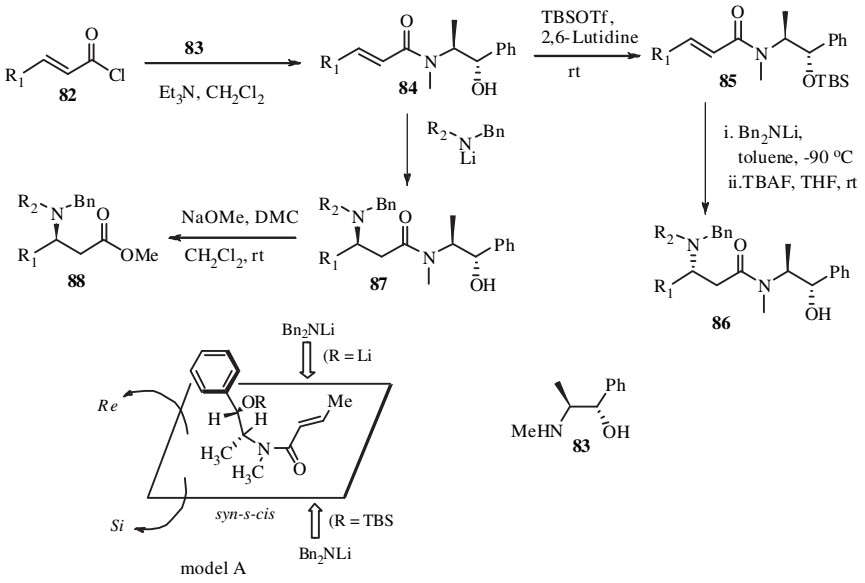
Consequently, Saito et al. designed Lewis acid-hydroxylamine hybrid reagents (LHHRs) **80**.[35] The chiral auxiliary was tethered by an appropriate metal to its hydroxyl group and the hydroxylamine acts as the chiral amine nucleophile. In the work involving this 'LHHR concept', because the tethered atom (Al, B, etc.) can play the role of a Lewis acid (Scheme 21), it was exploited as the methodology. Thus, LHHR **80** can be prepared via a two-step transformation involving the reaction of 2,3-dimethyl-2,3-butanediol (1 equiv) with a borane·THF complex (1.0 equiv/THF/0 °C, 30 min) and subsequent reaction with *N*-benzylhydroxylamine (1.0 equiv, 0 °C, 30 min) and crotonate **79** to give the corresponding isoxazolidinone derivatives **81**.



Scheme 21.

Much better results with regard to the enantioselectivity, although moderate (43–71% ee), have been achieved when Al-based LHHRs were reacted with crotonates, compared to the borane reagents.

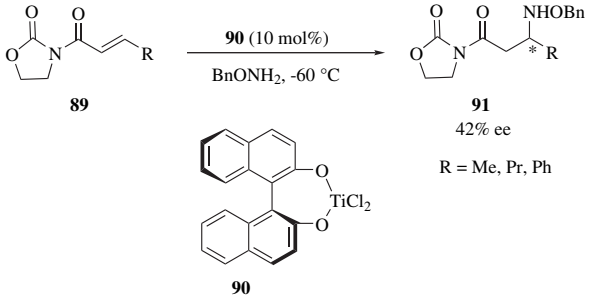
Cardillo et al.[36] utilized (*S*,*S*)-(+)-pseudoephedrine **83** as a chiral auxiliary in the conjugate addition reaction of nitrogen nucleophiles to α,β-unsaturated amides **84** derived from corresponding crotyl chlorides **82** (Scheme 22) to afford products in good-to-excellent yields (52–73%) and diastereoselectivities (60–99%) via a 1,5-asymmetric induction. Several β-aminoamide adducts were prepared using different conjugate acceptors and two different lithium benzylamides as nucleophiles. The resulting differently substituted enantiomerically enriched β-aminoamides **87** prepared could be transformed afterward into several interesting compounds, such as β-amino esters **88**, γ-amino alcohols, and β-amino ketones. Products with an opposite configuration at the newly generated stereogenic center could be generated when the protection of the free OH group of the auxiliary was changed to a bulky silyl ether **85** prior to the conjugate addition to afford the respective products **86**. Transition-state model A explains the preferential conjugate addition.



Scheme 22.

4. Enantioselective (organocatalytic) aza-Michael addition

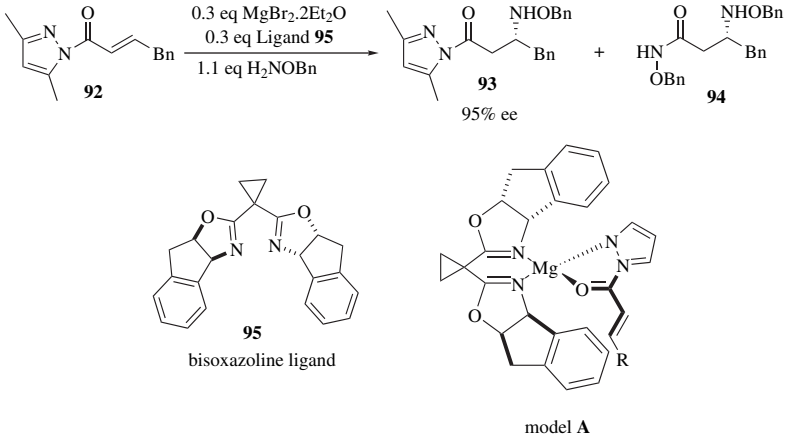
In the last five years, the asymmetric aza-Michael reaction has emerged as a powerful tool for the synthesis of chiral β-amino carbonyl compounds. Various research groups around the world have achieved tremendous success in organocatalytic based strategy towards aza-Michael addition.[4] The first example was reported by Jørgensen et al. in 1996, in which a titanium–BINOL catalyst **90** was used to catalyze the addition of $BnONH_2$ to *N*-acyloxazolidinones **89**.[37] This resulted in high conversions into **91**, albeit in 42% enantioselectivity (Scheme 23).



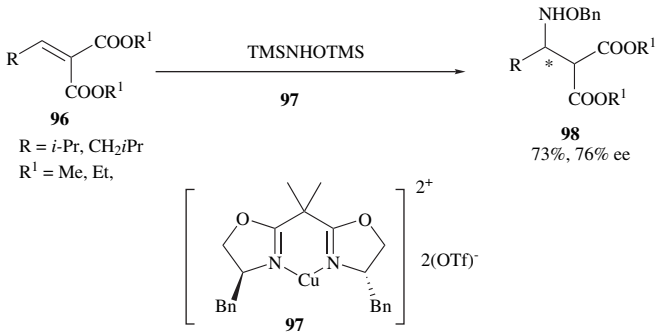
Scheme 23.

Sibi et al. have recently achieved a highly enantioselective protocol for the conjugate addition of *O*-benzylhydroxylamine to a 3,5-dimethylpyrazole-derived enoate **92** using catalytic amounts of a chiral Lewis acid prepared from $MgBr_2 \cdot OEt_2$ and a bisoxazoline **95**, thus generating β-amino acid derivatives **93** in good chemical yields and upto 97% ee,[38] together with **94** (Scheme 24). The control of the product configuration by the Lewis acid was also noteworthy. The opposite enantiomer of the product was produced in 59% ee when a lanthanide Lewis acid was employed in conjunction with the same ligand. The effects of temperature and the stoichiometry of the chiral Lewis acid on the reaction were also investigated. These workers also presented a hypothesis for the observed high selectivity with $MgBr_2$. After the amine addition to an *S-cis* substrate/Lewis acid/ligand complex, a tetrahedral or a cis-octahedral arrangement accounts for the observed product configuration (model A, Scheme 24).

Cardillo reported the conjugate addition of $BnONH_2$ to doubly activated acceptors, alkylidene or arylidene malonates **96**, in the presence of a Cu(II)–box-complex **97**, resulting in **98** in low ees (up to 29%)[39] (Scheme 25). The selectivity was further increased to as high as 76% by the use of a bulkier amine nucleophile, *N,O*-bis(trimethylsilyl)hydroxylamine.



Scheme 24.

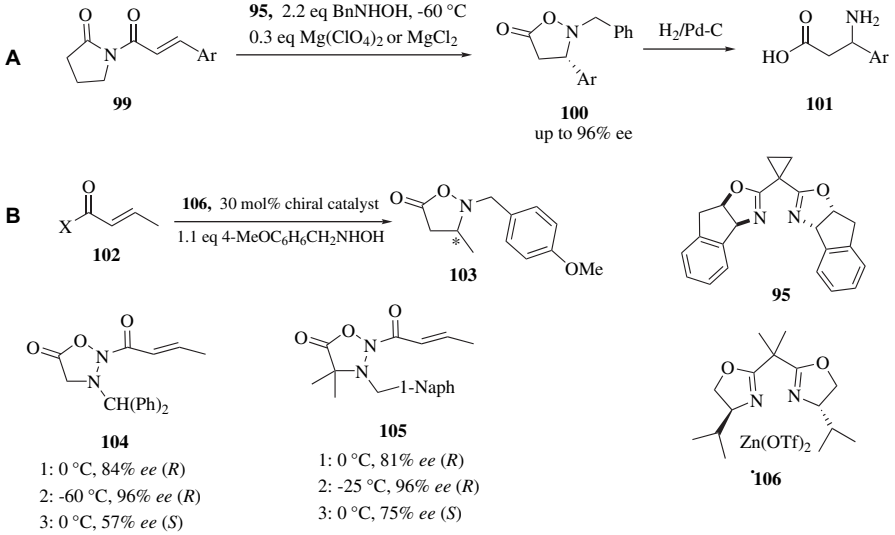


Scheme 25.

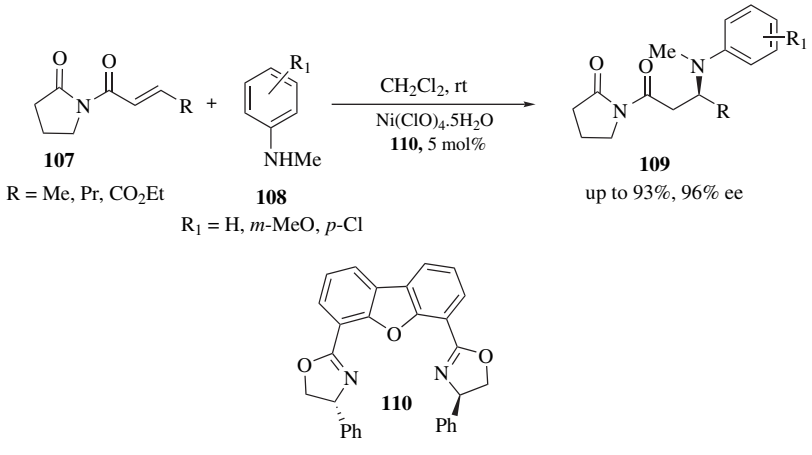
It is a well-established fact that *N*-substituted hydroxylamines, which are more nucleophilic than *O*-substituted hydroxylamines, can undergo conjugate addition to α,β-unsaturated enoates to generate isoxazolidinones, precursors for β-amino acids.[40] Sibi and Liu utilized the high reactivity of BnNHOH and developed an efficient method for the conjugate addition of BnNHOH to pyrrolidinone-derived enoates **99**[41] and **102**. Thus, the protocol afforded respective isoxazolidinones **100** and **103**. This proved to be an excellent protocol for obtaining β-aryl-β-amino acid derivatives in high enantiomeric purity using catalytic amounts of a chiral Lewis acid **95** (Scheme 26A). Improvement of the selectivity of the conjugate addition at moderate reaction temperatures and using simple ligands have been extensively discussed by Sibi et al. in their reports.[42] Furthermore, catalysts **104** and **105** provided enantiomeric products with high purity at practical reaction conditions (Scheme 26B). Catalyst **106** proved to be equally good.

Jørgensen et al. investigated the first stereoselective addition of secondary aromatic amines **108** to acylpyrrolidinones **107**.[43] The selectivity and chemical efficiency were found to be dependent upon the reaction conditions including solvents, catalysts, and Lewis acids. DBFOX-Ph **110** effectively catalyzed the addition of substituted *N*-methyl anilines to acylpyrrolidinones, providing β-amino acid derivatives **109** in varying selectivities (up to 90% ee) (Scheme 27). The absolute configuration of the product was determined to be *S*, which agreed with a trigonal bipyramidal geometry around the metal with ligand **110** occupying three sites, while the substrate took up the other two positions, leaving the *re* face of the alkene available for amine additions.

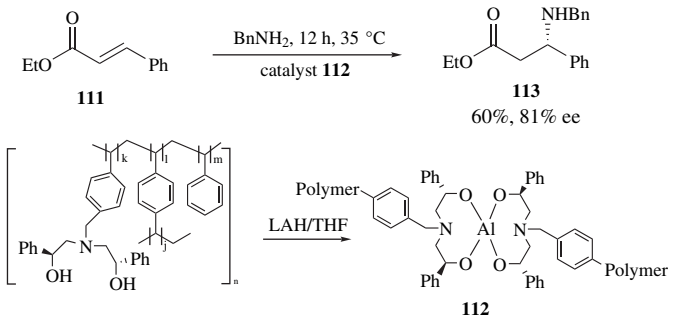
A novel polymer-supported chiral catalyst **112** was utilized by Sundararajan and Prabagaran in the 1,4-addition of $BnNH_2$ to ethyl cinnamate **111** for the synthesis of chiral β-aryl-β-amino ester **113** in high enantioselectivity (81% ee)[44] (Scheme 28). It should be noted that the work up of this reaction is simple: only a filtration step is needed for purification of the final product and the catalyst can be easily recovered by washing with 1 N HCl. Numerous reports



Scheme 26.



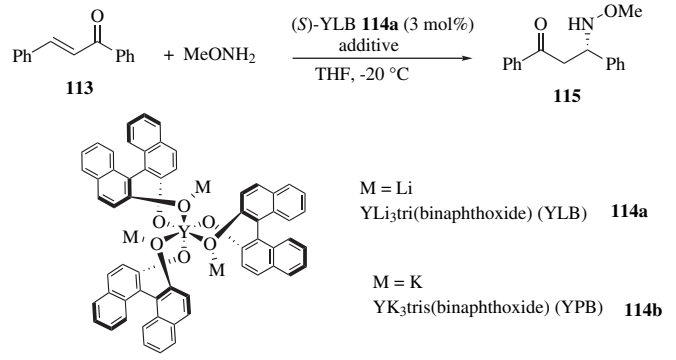
Scheme 27.



Scheme 28.

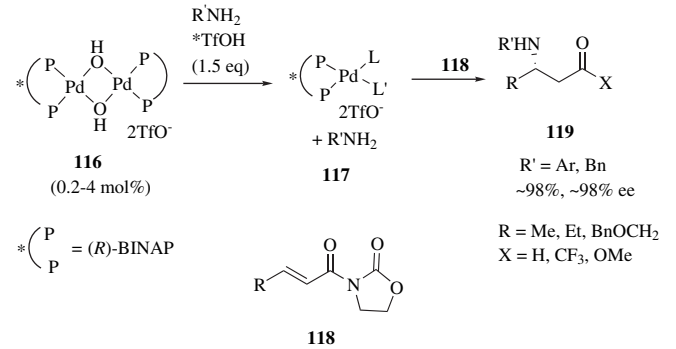
have been cited to establish the efficacy of asymmetric catalysis as an efficient tool for aza-Michael addition.[45]

Shibasaki et al. came up with a practical, more amine-tolerant, asymmetric catalysis for aza-Michael addition (Scheme 29).[46] They demonstrated the utility of heterobimetallic multifunctional catalysis[47] in an asymmetric 1,4-addition of an *O*-alkylhydroxylamine to enone **113** to afford corresponding aminoketone **115** as the product. High ees and yields were achieved using as little as 3 mol % of YLi_3tris(binaphthoxide) YLB **114a**, while **114b** was not effective. High catalyst turnovers (0.5–3 mol % of YLB) and good yields (80–98%) and ees (81–96%) were achieved under concentrated conditions (1.1–2.5 M), although the substrate scope was somewhat limited. These results implied that neither the amine nor the product inhibited the heterobimetallic catalysis, unlike standard Lewis-acid catalysis. The same authors have exemplified the utility of the 1,4 adducts, and converted them into acylaziridines, *syn*-1,3-amino alcohols, and *anti*-1,3-amino alcohols.[48]



Scheme 29.

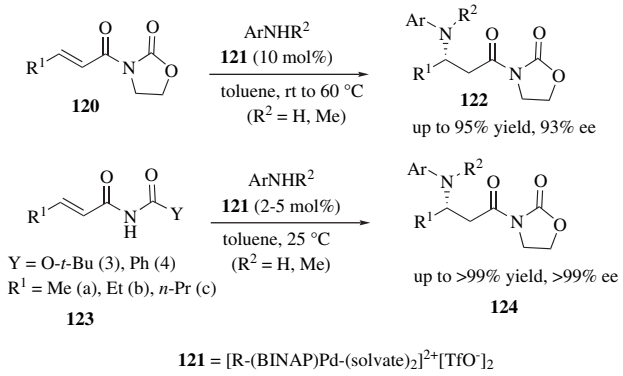
Hamashima et al.[49] employed a combination of a chiral Pd complex **116** and an amine salt, enabling a completely regulated release of free nucleophilic amine (Scheme 30). This combination



Scheme 30.

suppressed both the decomposition of the catalyst by the amine and the uncontrolled spontaneous reaction thus ensuring an efficient catalytic asymmetric conjugate addition of various amines on alkenoyl 1,3-oxazolan-2-ones **118** to afford β-amino acid derivatives **119** in high chemical yields with ees up to 98%. In addition, a highly enantioselective protonation in 1,4-addition of amines was also developed using this novel reaction system. These workers suggested a mechanism in which the generated complex **117** could activate the enone in a bidentate fashion. The *re*-face of the double bond was blocked preferentially by one of the phenyl groups in (*R*)-BINAP, the addition of amine proceeded from the *si*-face in a highly enantioselective manner, and the Pd enolate was found to give subsequent protonation of this Pd enolate, followed by dissociation of the product as the salt, which would complete the catalytic cycle.

Phua et al.[50] have demonstrated that [R-(BINAP)Pd-(solvate)$_2$]$^{2+}$[TfO$^-$]$_2$ **121** catalyzes the addition of aromatic amines to α,β-unsaturated *N*-oxazolidinones **120**,[49,51] carbamates **123**,[52] and imides[53] to afford the corresponding products **122** and **124** in excellent yields (95%) and enantioselectivities (>98%) (Scheme 31). They have performed extensive studies in parallel ligand screening and identified that $Pd(OTf)_2 \cdot 2H_2O$ can be used as a precursor in the rapid construction of asymmetric hydroamination catalysts.



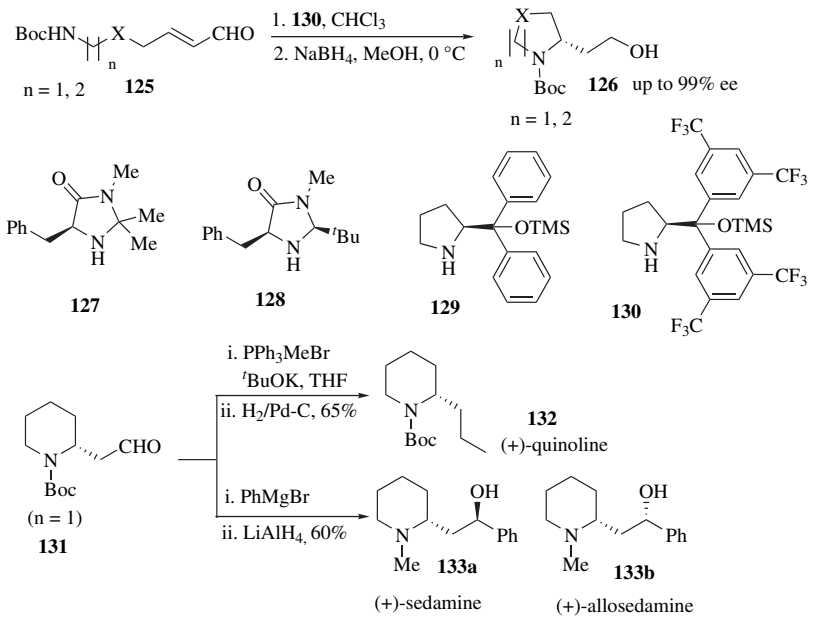
Scheme 31.

Fustero et al. described a very highly enantioselective organocatalytic intramolecular aza-Michael reaction (IMAMR) of carbamates bearing remote α,β-unsaturated aldehydes **125** as Michael acceptors (Scheme 32)[54] under organocatalytic conditions to afford the corresponding products **126** in good yields (80%) and in excellent ees (99%). When a Jørgensen catalyst **130** was used to effect the same conversion, facile enantioselective formation of several five- and six-membered heterocycles was observed. A similar methodology was applied to access the common advance intermediate **131** en route to the synthesis of three piperidine alkaloids, namely (+)-quinoline **132**, (+)-sedamine **133a**, and (+)-allosedamine **133b**. The catalysts **127**–**129** mediated conjugate addition resulted in products with comparable yields, however the optical yields varied from 5 to 75% ees, respectively.

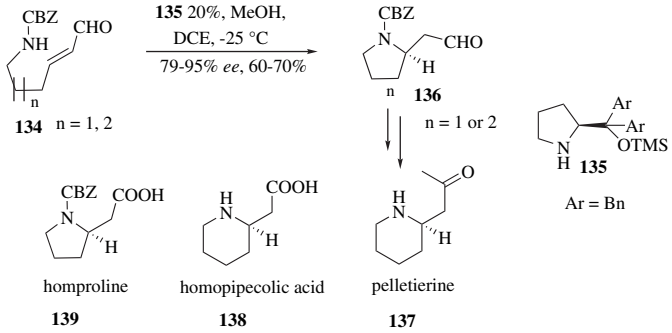
Carter et al.[55] described an intramolecular aza-Michael addition of 5- or 6-protected amino α,β-unsaturated aldehydes such as **134** (n=1 or 2) to produce cyclic β-amino aldehydes such as **136** (n=1, 2) in good yield (80%) and high enantioselectivity (95%), (Scheme 33) promoted by prolinol derivative **135**. Applying this methodology, homoproline **139**, homopipecolic acid **138**, and pelletierine **137** have been synthesized in enantiopure form.

5. Asymmetric aza-Michael addition catalyzed by cinchona alkaloids

Jørgensen and Perdicchia[56] have developed the first example of organocatalyst-assisted asymmetric aza-Michael addition of

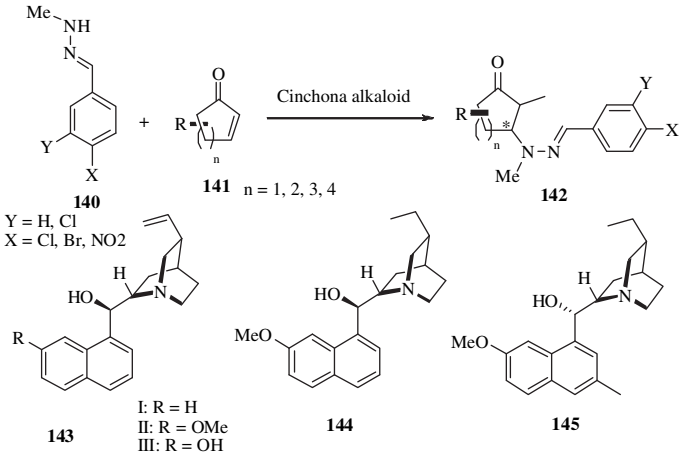


Scheme 32.



Scheme 33.

hydrazones **140** to cyclic enones **141** in good yields (up to 100%) and ee >77% using inexpensive and commercially available cinchona alkaloids **143**, **144**, and **145** as catalysts (Scheme 34).



Scheme 34.

The products **142** can be recrystallized to give nearly enantiopure compounds and, furthermore, it was shown that they could be reduced to the corresponding 1,3-benzylidenehydrazino alcohol derivatives with high diastereoselectivity. These workers have proposed a model in which the free hydroxyl group establishes a hydrogen bond with the carbonyl moiety and the quinuclide group that is linked to the hydrazone, forming a tight transition state.

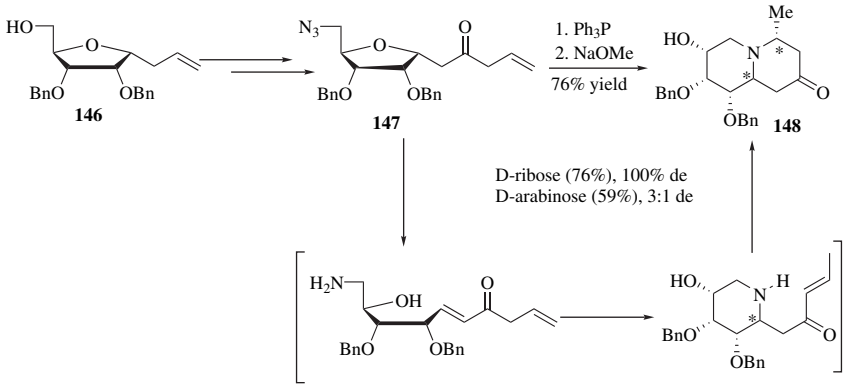
6. Double aza-Michael addition

This review would not be complete without a discussion of the marvel of two aza-Michael additions in succession, i.e., double aza-Michael addition. For instance, Zhou et al. achieved stereoselective synthesis of polyhydroxylated quinolizidines **148** from *C*-glycosides **146** by a one-pot, double-conjugate addition[57] (Scheme 35). The stereoselectivity of the first conjugate addition, giving azasugar **147**, was affected by the stereochemistry of the monosaccharide substrate, whereas the stereoselectivity in the second conjugate addition was entirely directed by steric repulsion due to the large azasugar moiety.

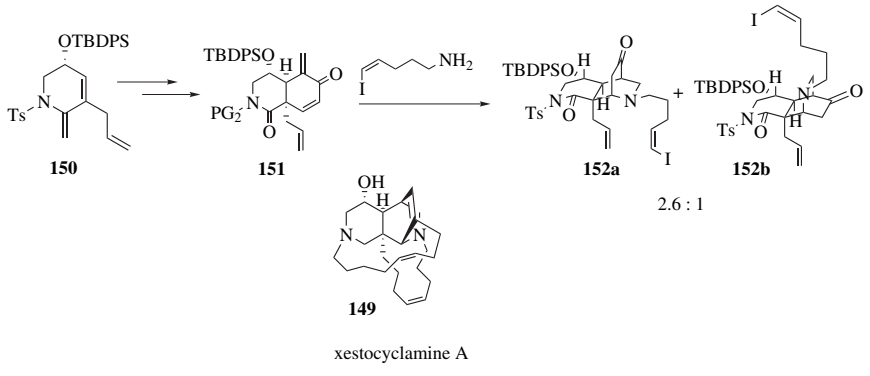
Another interesting example was cited by Danishefsky et al.,[58] while attempting the synthesis of xestocyclamine **149**. They investigated the double Michael addition between **151**, obtained in few steps from **150**, and a vinyliodoamine (Scheme 36). The reaction produced a mixture of diastereomeric products **152a** and **152b** in favor of the desired adduct (2.6:1). The diastereoselectivity was found to be largely unaffected by permutations of the solvent, temperature, and additives. The synthesis could not, however, be completed via this approach and an alternative route was undertaken, the discussion of which is beyond the scope of this review.

The work carried out in our laboratories for the synthesis of (+)-hyperaspine presents another classical example of an aza-Michael addition.[59] Hyperaspine **38** belongs to the class of ladybird alkaloids isolated from *Hyperaspia campestris* and possessing a unique 3-oxaquinolizidine skeleton.

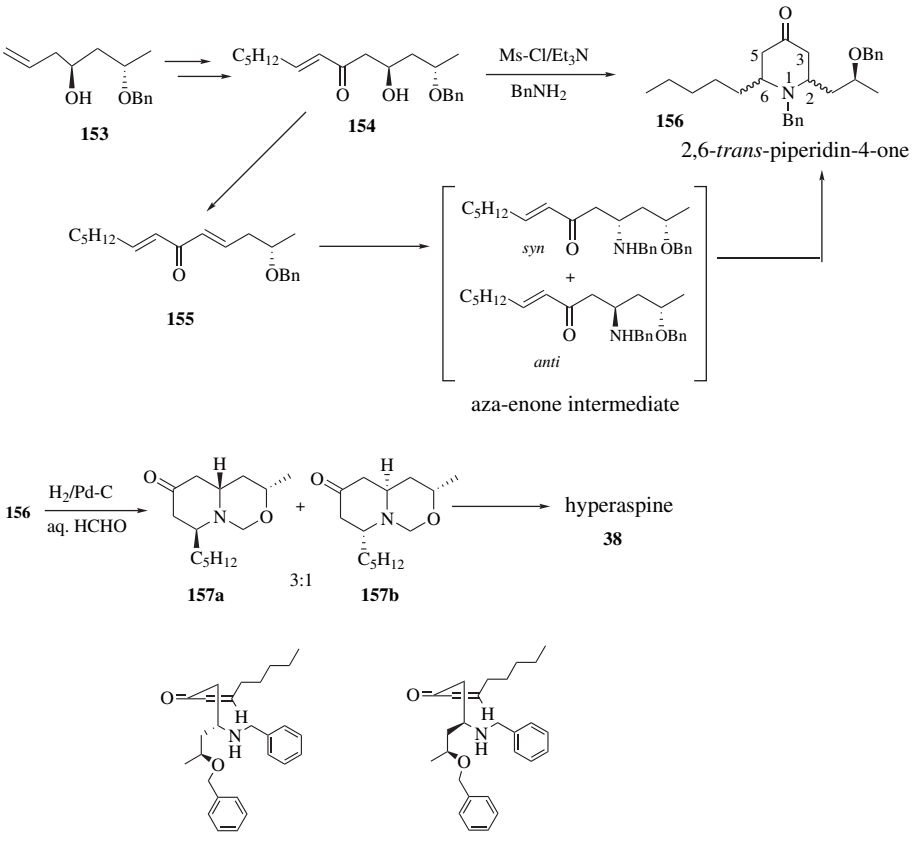
As depicted in Scheme 37, the synthesis started with the known homoallylic alcohol **153**. After some sequential reactions, the α,β-unsaturated ketone **154** was obtained. Compound **154** was identified as an ideal substrate for an S_N2 reaction of its corresponding mesylate with benzylamine followed by an intramolecular aza-Michael addition to afford the piperidinone derivative **156**, which could eventually be transformed into 3-oxaquinolizidine. Piperidinone **156** was, however, resolved into two oxaquinolizidines



Scheme 35.



Scheme 36.

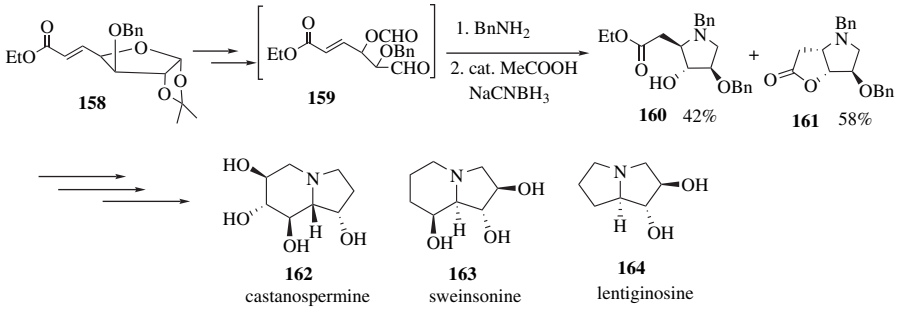


Scheme 37.

157a and **157b** in a 3:1 product ratio upon cyclization. The formation of **157b** could be logistically explained if a double aza-Michael addition of dienone **155** was envisaged as the intervening reaction to result initially in **156**, which was later converted into **157a** and **157b**.

Further, the formation of **157a**/**157b** in an isomeric ratio of 3:1 and the stereochemical preferential formation could be explained by considering the fact that the first Michael reaction of the dienone **155** with benzylamine was indeed a regio- and diastereoselective intermolecular aza-Michael reaction to afford an aza–enone intermediate (*syn* and *anti*, Scheme 37), which on second aza-Michael reaction (intramolecular) provided the 2,6-disubstituted-*trans*-piperidinones as exclusive products. While, the former regioselective Michael addition can possibly be explained by a transient 10-membered H-bonding between the ketone and benzyl ether groups, resulting in a diastereomeric ratio of 3:1 in favor of the requisite isomer, the exclusive *anti*-selectivity of the second aza-Michael reaction was mainly due to less prevalence of steric repulsions due to the substituents in the transition states (models A and B, Scheme 37).

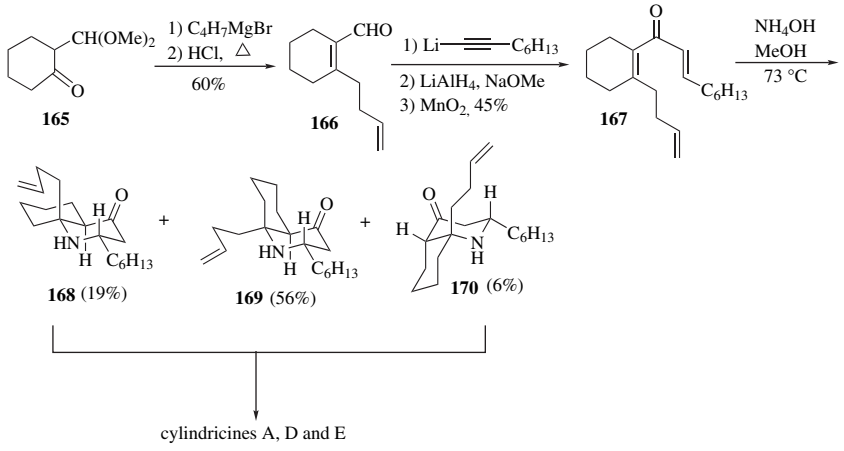
surveyed. For instance, Dhavale et al. achieved the synthesis of 1,4,5-trideoxy-1,4-imino-L-*xylo*-hexitol **160** and 1,4,5-trideoxy-1,4-imino-D-*arabino*-hexitol **161** using the intramolecular aza-Michael addition of benzylamine, generated in situ, to the α,β-unsaturated ester **159** derived from D-glucose[60] (Scheme 38), which was realized from **158** upon acetonide unmasking and periodate cleavage. These intermediates were efficiently converted into (−)-lentiginosine **164**, castanospermine **162**, and swainsonine **163** in overall good yields (Scheme 38).



Scheme 38.

Various research groups have frequently used an aza-Michael addition as the key step for the synthesis of cylindricines **168**–**170**. The first total synthesis of a cylindricine alkaloid was reported by Snider and Liu in 1997.[61] The key steps included in this approach are: a double Michael reaction of ammonia on a dienone **167**, obtained from **165** via a Grignard and dehydration reaction to afford **166**, to form the fused A/B-ring system and a copper-catalyzed *N*-chloroamine/olefin radical cyclization for the C-ring construction (Scheme 39).

Liu and Heathcock's approach toward the synthesis of cylindricines A and B also employs the aza-Michael addition as the key



Scheme 39.

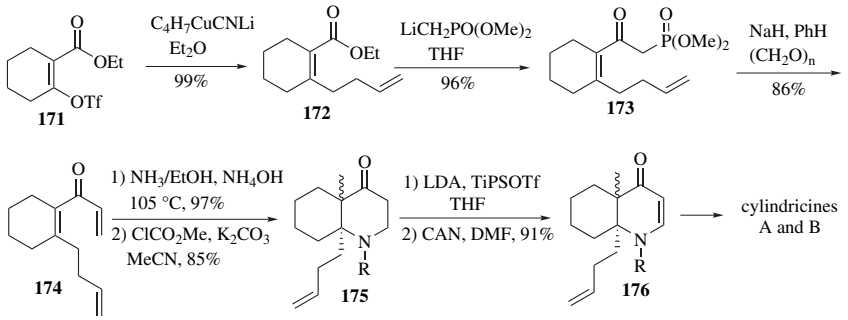
Thus, a highly stereocontrolled double aza-Michael reaction played a crucial role in minimizing the number of products. The synthesis took advantage of the lone stereogenic center of the starting material in creating additional chiral centers in a stereodefined fashion.

7. Application of aza-Michael addition in natural product synthesis

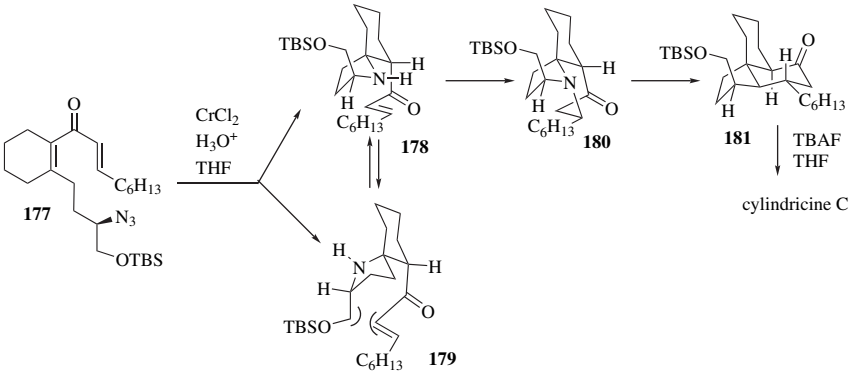
Although numerous applications were discussed while explaining the various strategies of the aza-Michael addition, some more representative examples in natural product synthesis are now briefly

step, in which a dienone **174** was generated following a series of reactions involving the alkylation reaction of **171** to diene **172** first, which was converted to ketophosphonate **173** on way to dienone **174** via Wittig–Horner reaction. Heating this compound with ammonia/ammonium hydroxide in ethanol resulted in a double Michael reaction to afford the desired 1-azadecalin **175** in high yield as a 1:1 mixture of cis and trans isomers[62] (Scheme 40). These were separated using HPLC, converted to octahydro-4-quinolinone derivatives **176** and were independently used in the synthesis of cylindricines A and B.

In 1999, Molander and Ronn described an enantioselective total synthesis of (−)-cylindricine C, which featured an intramolecular



Scheme 40.



Scheme 41.

double Michael addition of an amine to a dienone[63] (Scheme 41). An initial Michael reaction of the amine derived from the reduction of the azide **177** led to diastereomeric spirocycles. Stereoelectronic factors promoted the conjugate addition of the amino group in enone **178** to form the tricycle **180**, a relatively stable ring system. Subsequent epimerization of ketone **180** at C(5) then produces the thermodynamically more stable cylindricine C system **181**. The second Michael addition did not take place in the case of the diastereomeric spirocycle **179**, due to an unfavorable interaction between the enone and the siloxymethyl group.

8. Conclusions

The asymmetric aza-Michael addition reaction has great potential in organic synthesis, primarily because of the ubiquitous presence of β-amino acids or alcohols in many natural products as partial structures or in designed hybrid scaffolds containing β-amino acids/alcohols due to their role played in bioprocesses as isosteres of α-amino acids. More importantly, the factors that govern the 1,2-selectivity via induction, optimization of the methodology/enrichment of isomeric mixtures in favor of one isomer, use of chiral catalysts in enantioselective versions of the reaction and the corresponding advantages are discussed. Thus, various asymmetric aza-Michael protocols available at the disposal of an organic chemist to access such moieties in highly stereoselective manner have been reviewed. Some applications in the total synthesis of natural products are also showcased in an appreciation of this protocol.

Acknowledgements

The authors thank Dr. Rachna Sachwani for proofreading the manuscript. Two of the authors (A.S and R.S.) thank CSIR and UGC, New Delhi for financial support.

References and notes

1. (a) Michael, A. *J. Prakt. Chem.* **1887**, *35*, 349–356; (b) Michael, A. *J. Prakt. Chem.* **1894**, *49*, 20–29.
2. (a) Kohler. *J. Am. Chem. Soc.* **1907**, *37*, 385; (b) Kohler, E. P.; Potter, H. *J. Am. Chem. Soc.* **1935**, *57*, 1316–1321.
3. Reviews: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196; (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061; (c) Leonard, J.; Dı′ez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051–2061; (d) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806; (e) d'Angelo, J.; Desmaele, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459–505.
4. (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035; (b) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633–639.
5. (a) Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820–2822; (b) Rudolf, K.; Hawkins, J. M.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1988**, *53*, 3879–3881; (c) Hawkins, J. M.; Lewis, T. A. *J. Org. Chem.* **1992**, *57*, 2114–2121.
6. (a) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183–186; (b) Davies, S. G.; Chihara, O.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1141–1147.
7. Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2373–2384.
8. Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999–2008.
9. (a) Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1109–1110; (b) Brackenridge, I.; Davies, S. G.; Fenwick, D. R.; Ichihara, O.; Polywka, M. E. C. *Tetrahedron* **1999**, *55*, 533–540.
10. (a) Davies, S. G.; Fenwick, D. R.; Ichihara, O. *Tetrahedron: Asymmetry* **1997**, *8*, 3387–3391; (b) Namikoshi, M.; Rinehart, K. L. *Tetrahedron Lett.* **1989**, *30*, 4349–4352.
11. Davies, S. G.; Ichihara, O. *Tetrahedron Lett.* **1999**, *40*, 9313–9316.
12. Bull, S. D.; Davies, S. G.; Delgado-Ballester, S.; Fenton, G.; Kelly, P. M.; Smith, A. D. *Synlett* **2000**, 1257–1260.
13. Coleman, P. J.; Hutchinson, J. H.; Hunt, C. A.; Lu, P.; Delaporte, E.; Rushmore, R. *Tetrahedron Lett.* **2000**, *41*, 5803–5806.
14. O'Brien, P.; Porter, D. W.; Smith, N. M. *Synlett* **2000**, 1336–1338.
15. (a) Imamura, H.; Shimizu, A.; Sato, H.; Sugimoto, Y.; Sakuraba, S.; Nakajima, S.; Abe, S.; Miura, K.; Nishimura, I.; Yamada, K.; Morishima, H. *Tetrahedron* **2000**, *56*, 7705–7713; (b) Yamamoto, Y.; Maeda, K.; Tomimoto, K.; Mase, T. *Synlett* **2002**, 561–564.
16. Ma, D.; Zhang, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1703–1707.
17. Zhu, W.; Ma, D. *Tetrahedron Lett.* **2003**, *44*, 8609–8612.
18. Zhu, W.; Ma, D. *Org. Lett.* **2003**, *5*, 5063–5066.
19. (a) Sewald, N.; Hiller, K. D.; Helmreich, B. *Liebigs Ann.* **1995**, 925–928; (b) Sewald, N.; Hiller, K. D.; Körner, M.; Findeisen, M. *J. Org. Chem.* **1998**, *63*, 7263–7274.

20. Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 455–457.
21. (a) Enders, D.; Wiedemann, J.; Bettray, W. *Synlett* **1995**, 369–371; (b) Enders, D.; Wiedemann, J. *Liebigs Ann./Recueil* **1997**, 699–706.
22. (a) Sewald, N. *Amino Acids* **1996**, *11*, 397–408; (b) In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, NY, 1997; Chapter 7.
23. Dumas, F.; Mezrhab, B.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 2293–2304.
24. (a) Matsuyama, H.; Itoh, N.; Yoshida, M.; Kamigata, N.; Sasaki, S.; Iyoda, M. *Chem. Lett.* **1997**, 375–376; (b) Matsuyama, H.; Itoh, N.; Yoshida, M.; Iyoda, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *120–121*, 475–476.
25. Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274–6282.
26. Shimano, M.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7450–7455.
27. Lima, P. G.; Sequeira, L. C.; Costa, P. R. R. *Tetrahedron Lett.* **2001**, *42*, 3525–3527.
28. Sharma, G. V. M.; Reddy, V. G.; Chander, A. S.; Reddy, K. R. *Tetrahedron: Asymmetry* **2002**, *13*, 21–24.
29. Perlmutter, P.; Tabone, M. *J. Org. Chem.* **1995**, *60*, 6515–6522.
30. Sani, M.; Bruch, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060–2063.
31. (a) Amaroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trere, A. *J. Org. Chem.* **1993**, *58*, 5615–5619; (b) Bongini, A.; Cardillo, G.; Gentilucci, L.; Tomasini, C. *J. Org. Chem.* **1997**, *62*, 9148–9153; (c) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Tetrahedron Lett.* **1999**, *40*, 8261–8264.
32. Cardillo, G.; De Simone, A.; Gentilucci, L.; Sabatino, P.; Tomasini, C. *Tetrahedron Lett.* **1994**, *35*, 5051–5054.
33. Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1995**, 1171–1173.
34. Volonterio, A.; Bravo, P.; Zanda, M. *Org. Lett.* **2000**, *2*, 1827–1830.
35. Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1998**, 1291–1293.
36. (a) Etxebarria, J.; Vicario, J. L.; Badia, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790–8800; (b) Etxebarria, J.; Vicario, J. L.; Badia, D.; Carrillo, L. *J. Org. Chem.* **2004**, *69*, 2588–2590.
37. Falborg, L.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2823–2826.
38. Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615–6616.
39. Cardillo, G.; Gentilucci, L.; Gianotti, M.; Kim, H.; Perciaccante, R.; Tolomelli, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2395–2398.
40. (a) Baldwin, S. W.; Aubé, J. *Tetrahedron Lett.* **1987**, *28*, 179–182; (b) Baldwin, J. E.; Harwood, L. M.; Lombard, M. J. *Tetrahedron* **1984**, *40*, 4363–4370; (c) Stamm, H.; Steudle, H. *Tetrahedron Lett.* **1976**, 3607–3610; For the conversion of isoxazolidinones to β-amino acids, see: (d) Keirs, D.; Moffat, D.; Overton, K.; Tomanek, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1041–1051.
41. Sibi, M. P.; Liu, M. *Org. Lett.* **2000**, *2*, 3393–3396.
42. (a) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181–4184; (b) Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444–8445 and references cited therein.
43. Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240–1241.
44. Sundararajan, G.; Prabagaran, N. *Org. Lett.* **2001**, *3*, 389–392.
45. (a) Lakshmipathi, P.; Rao, A. V. R. *Tetrahedron Lett.* **1997**, *38*, 2551–2552 and references cited therein; (b) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959–8960; (c) Guerin, D. J.; Horstmann, T. E.; Miller, S. J. *Org. Lett.* **1999**, *1*, 1107–1109; (d) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635–3638; (e) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134–2136; (f) Nelson, S. G.; Spencer, K. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1323–1325.
46. Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178–16179.
47. Review: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187–2210; (b) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 1236–1256; For the preparation and structure of YLB **1a**, see: (c) Aspinall, H. C.; Dwyer, J. L.; Greeves, N.; Steiner, A. *Organometallics* **1999**, *18*, 1366–1368.
48. (a) Sugihara, H.; Daikai, K.; Jin, X. L.; Furuno, H.; Inanaga, J. *Tetrahedron Lett.* **2002**, *43*, 2735–2739; (b) Jin, X. L.; Sugihara, H.; Daikai, K.; Takeishi, H.; Jin, Y. Z.; Furuno, H.; Inanaga, J. *Tetrahedron* **2002**, *58*, 8321–8329.
49. Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004**, *6*, 1861–1864.
50. Phua, P. H.; White, A. J. P.; deVries, J. G.; Hiia, K. K. *Adv. Synth. Catal.* **2006**, *348*, 587–592.
51. (a) Li, K.; Hii, K. K. *Chem. Commun.* **2003**, 1132–1133; (b) Li, K.; Phua, P. H.; Hii, K. K. *Tetrahedron* **2005**, *61*, 6237–6243.
52. Li, K.; Cheng, X.; Hii, K. K. *Eur. J. Org. Chem.* **2004**, 959–964.
53. Phua, P. H.; deVries, J. G.; Hii, K. K. *Adv. Synth. Catal.* **2005**, *347*, 1775–1780.
54. Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; Pozo, C. *Org. Lett.* **2007**, *9*, 5283–5286.
55. Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155–5158.
56. Perdicchia, D.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 3565–3568.
57. Zou, W.; Sandbhor, M.; Bhasin, M. *J. Org. Chem.* **2007**, *72*, 1226–1234.
58. Yun, H.; Gangon, A.; Danishefsky, S. J. *Tetrahedron Lett.* **2006**, *47*, 5311–5315.
59. Krishna, P. R.; Sreeshailam, A. *Tetrahedron Lett.* **2007**, *48*, 6924–6927.
60. (a) Choudhari, V. D.; Kumar, K. S. A.; Dhavale, D. D. *Tetrahedron Lett.* **2004**, *45*, 8363–8366; (b) Choudhari, V. D.; Kumar, K. S. A.; Dhavale, D. D. *Tetrahedron* **2006**, *62*, 4349–4354.
61. Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630–5633.
62. Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263–8266.
63. Molander, G. A.; Ronn, M. *J. Org. Chem.* **1999**, *64*, 5183–5187.

Biographical sketch

Palakodety Radha Krishna obtained his Ph.D. from Pune University in 1989 under the supervision of Dr. A.V. Rama Rao. He pursued his postdoctoral research with Prof. N.K. Kochetkov at the N.D. Zelinsky Institute of Organic Chemistry, Moscow, Russia and with Prof. David G.I. Kingston, Virginia Tech, US. He joined the Organic Chemistry Division at the Indian Institute of Chemical Technology, Hyderabad in 1991 and is currently a Senior Scientist. He has more than 100 peer-reviewed research papers, 11 US patents, and 2 book chapters and reviews to his credit. His current interests are asymmetric Baylis–Hillman reactions, organocatalysis, complex natural product synthesis, carbohydrate chemistry, and multicomponent reactions. He visited POSTECH, Korea on a '*Brainpool fellowship*' and worked on '*Dynamic Kinetic Resolution*'.

Aare Sreeshailam obtained his B.Sc. from Kakatiya University and his Masters in Organic Chemistry from Osmania University, Hyderabad. He is the third year graduate student of Dr. Palakodety Radha Krishna at the Indian Institute of Chemical Technology, Hyderabad. His research work includes the asymmetric Baylis–Hillman reaction, its applications in the synthesis of higher carbon non-natural sugars and the synthesis of bioactive natural products.

Ravula Srinivas obtained his B.Sc. from Kakatiya University and his Masters in Organic Chemistry from Osmania University, Hyderabad. He is a fourth year graduate student of Dr. Palakodety Radha Krishna at the Indian Institute of Chemical Technology, Hyderabad. His research work revolves around the stereoselective total synthesis of polyfunctional bioactive natural products and, more recently, has been focused on spirocyclic natural products.