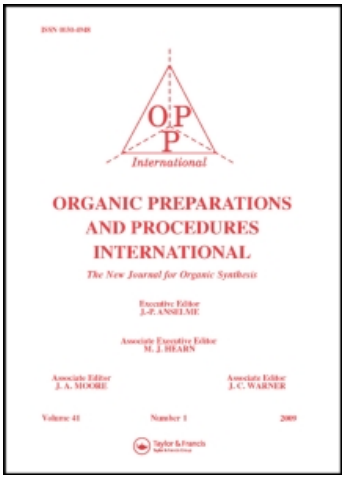

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THE ASYMMETRIC *AZA*-MICHAEL REACTION. A REVIEW

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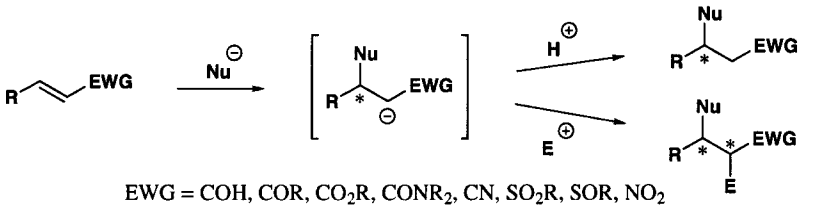
INTRODUCTION

The conjugate addition reaction is regarded as one of the most powerful methods for the preparation of complex molecules.[1] In this transformation, a nucleophile (also referred to as donor) adds to the β-carbon of an electron-deficient olefin (usually known as acceptor) giving a stabilized carbanion intermediate which, after protonation or subsequent treatment with another electrophile furnishes the final addition product (*Scheme 1*). The synthetic versatility of this reaction relies mainly upon the broad spectrum of donors and acceptors that may be employed. The nucleophiles can be either carbon- or heteroatom-centered and the acceptors are usually α,β-unsaturated carbonyl compounds (aldehydes, ketones, esters, amides, nitriles, *etc.*), although other activating groups like nitro, sulfonate, sulfoxide, phosphate or phosphonate have also been successfully employed.



EWG = COH, COR, CO_2R, $CONR_2$, CN, SO_2R, SOR, NO_2

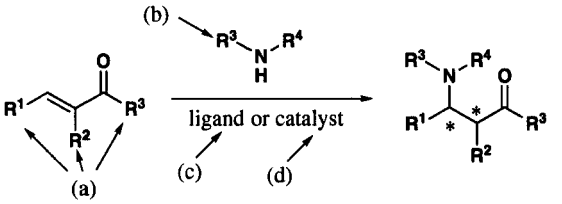
General Scheme for the Conjugate Addition Reaction

Scheme 1

Among this already mentioned broad range of nucleophiles and activated olefins that can be employed in this transformation, a particularly interesting version of this reaction is the conjugate addition of nitrogen nucleophiles, the so-called *aza*-Michael reaction, which represents one of the most attractive procedures for the asymmetric synthesis of β-amino carbonyl compounds or related derivatives. These are extremely important molecules not only because of

their ubiquitous occurrence as constituents of a plethora of biologically important natural and synthetic products but also because they have shown to be very versatile intermediates in the synthesis of other nitrogen-containing compounds.[2] Furthermore, the substitution of α-amino acids for β-amino acids in biologically active peptides is a promising tactic to prepare peptide analogues with increased potency and/or enzymatic stability.[3]

In addition, when the activated olefin substrate contains prochiral centers at the α and/or β-position, the generation of one or more stereogenic centers occurs concomitant with the conjugate addition process, which means that highly functionalized enantiomerically enriched nitrogen-containing compounds can be obtained once the stereochemical outcome of the reaction becomes suitably controlled. In this context, the different strategies employed in order to achieve the desired high stereocontrol can be classified according to the position in which the chiral information is incorporated (*Scheme 2*): (a) the use of conjugate acceptors carrying chiral auxiliaries that can be easily removed from the final product, (b) the use of chiral nitrogen nucleophiles, (c) performing the reaction in the presence of a stoichiometric amount of a chiral ligand and (d) the asymmetric catalysis methodology.



The general Scheme for the aza-Michael reaction. Arrows indicate the different positions at which the chiral information can be introduced.

Scheme 2

Several review articles have been published in recent years which comprehensively cover the main features of the asymmetric conjugate addition reaction in general and in which the importance of the *aza*-Michael variant is specially highlighted.[4] This review will focus specifically on the different methodologies reported for performing stereocontrolled *aza*-Michael reactions and will be presented according to the strategy applied for the introduction of the initial chirality source, that is, in relation to the use of the chiral auxiliary methodology either incorporated at the acceptor or at the nitrogen nucleophile, the use of chiral ligands or the use of asymmetric catalysis conditions.

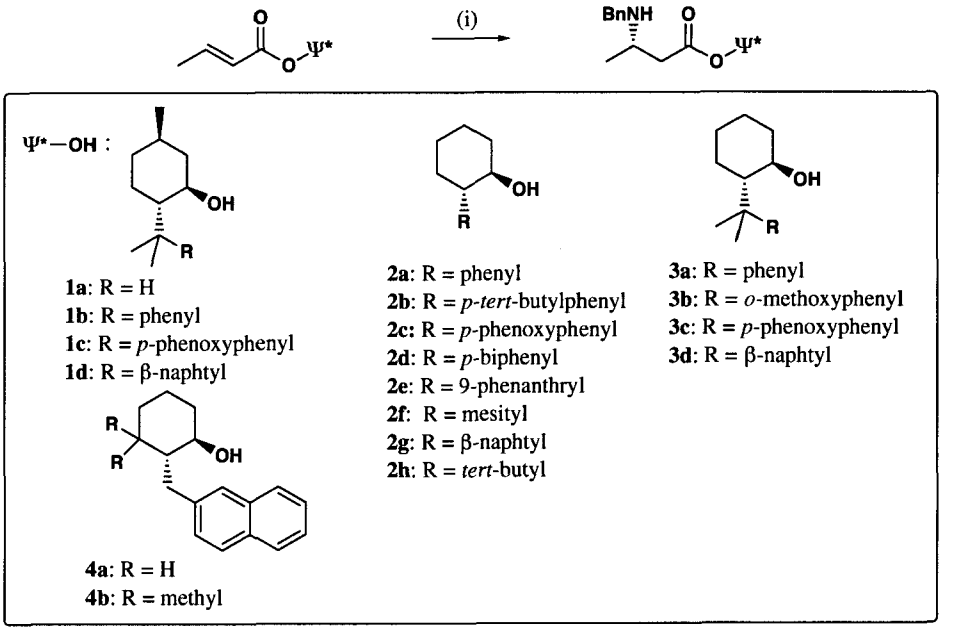
I. ASYMMETRIC *AZA*-MICHAEL REACTIONS USING CHIRAL AUXILIARIES

This methodology involves the attachment of a chiral auxiliary to the achiral acceptor in order to induce chirality transfer during the addition process and final removal/detachment from the *aza*-Michael adduct. Therefore, a good chiral auxiliary should fulfill some requirements: The chiral auxiliary has to be able to efficiently control the stereochemical outcome of the conjugate

addition step. In addition, the reactions employed to attach or remove the chiral auxiliary from the starting/final compounds should be simple and high-yielding procedures. Furthermore, it is highly desirable that the chiral auxiliary could be recovered and recycled for further uses once it has been removed from the final product. The fact that stoichiometric quantities of the chirality source are needed, together with the requirement of additional synthetic steps for the attachment/removal of the auxiliary constitute the major disadvantages of this methodology. However, the broad substrate tolerance and operational simplicity (*e. g. product isolation and purification by crystallization*) found in most cases, together with the implementation of recycling protocols for the recovery of the chiral auxiliary very often outweigh these limitations.

Nevertheless, the strategy that involves the use of chiral auxiliaries directly attached to the carbonyl moiety of the α,β-unsaturated acceptor in asymmetric *aza*-Michael reactions has not been as widely employed as other methodologies, mainly due to the fact that, in this case, the chiral information remains located too far away from the position in which the new stereocenter is going to be formed. In fact, the systems that have been tested with good results in this particular case, have employed extremely hindered substrates or functionalized moieties that can interact with the conjugate system, either at the carbonyl group or at the C=C double bond, thus reaching a rigid, well-organized intermediate.

The first attempts in this field were performed using chiral crotonates derived from menthol (**1a**).[5] The direct addition of primary amines to this chiral substrate under thermal conditions led to the corresponding β-amino ester with a rather poor degree of diastereoselection (*Scheme 3*).[5a] Further development in the structure of the chiral auxiliary led to the use of different

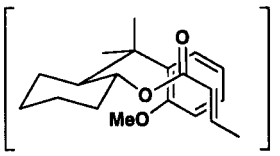


Reagents and Conditions: (i) $BnNH_2$, MeOH, 20°C, 14 kbar.

Scheme 3

8-arylmenthol derivatives **1b-d** as auxiliaries in which improvement of the diastereoselectivity of the reaction was observed upon increasing the steric bulk of the aromatic moiety.[6] *trans*-2-Phenylcyclohexanol **2a** and other related derivatives **2b-d** were also tested in the same context with similar results. Later on, the "simplified" alcohol **3a**, in which a methyl substituent at the cyclohexane ring of menthol was missing, proved to be an excellent chiral auxiliary in the high pressure-mediated *aza*-Michael reaction of diphenylmethylamine to crotonate-type substrates.[7]

Soon thereafter, the same authors completed a systematic study directed toward the optimization of the structure of the chiral auxiliary,[8] showing that the general structure of "8-arylmenthyl"-type auxiliaries **3a-d** led to the best results concerning to the diastereoselectivity of the reactions, the 8-methoxyphenyl substituted derivative **3b** being the most efficient one (*Scheme 3*). These results were interpreted in terms of a well ordered transition state in which the aryl moiety interacts with the conjugated acceptor system *via* π-stacking interactions,[9] thus effectively blocking one of the diastereotopic faces of the α,β-unsaturated acceptor in its *s-trans* conformation (*Fig. 1*).



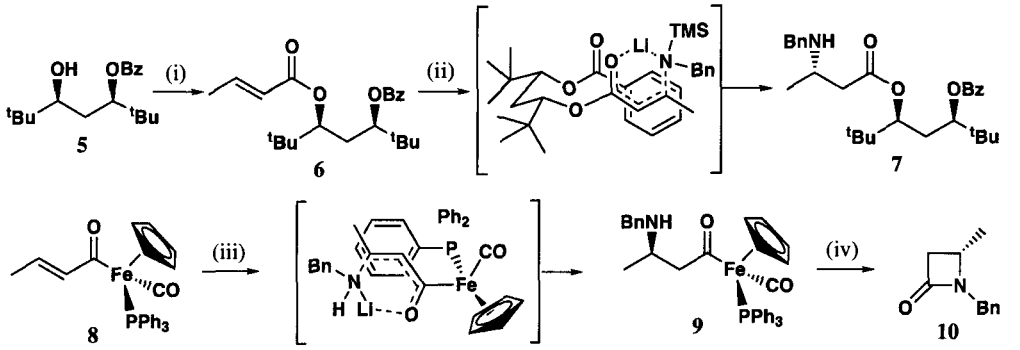
(π-Stacking interaction)

Fig. 1

Other alcohols like the 2-arylcyclohexanol-derived substrates **2e-h**, in which X-ray analysis of their crystal structure indicated that such an interaction between the aromatic moieties and the α,β-unsaturated substrate was not possible, led to a dramatic drop in the diastereoselectivity. Interestingly, the presence of the geminal methyl groups at the benzylic position was also found to be an essential requisite for the reaction to proceed with good stereocontrol, which was proven after chiral auxiliary **4a** was employed, leaving to an almost 1:1 mixture of diastereoisomers. The presence of a *gem*-dimethyl substitution at the cyclohexane ring, as in **4b**, overcame this limitation, furnishing only one out of the two possible isomers.

Following a similar design, Yamamoto has employed the fully acyclic chiral diol derivative **5** as a very effective auxiliary in the asymmetric *aza*-Michael reaction of lithium benzyltrimethylsilylamide (*Scheme 4*).[10] The *tert*-butyl groups present in this auxiliary, together with a π-stacking interaction between the benzoyl moiety and the conjugate acceptor, are proposed to provide a rigid arrangement in the transition state in which one of the faces of the electrophile, now in a *s-cis* conformation, became shielded by the presence of the benzoyl group, resulting in excellent stereochemical control in the incoming of the nucleophile. Davies has also applied the π-stacking concept using chiral complexes of ferrocene **8**, in which one of the phenyl rings of the triphenylphosphine ligand connects to the acceptor *via* these kind of interactions (*Scheme 4*).[11] In this work, the tandem reaction involving conjugate addition of lithium benzyl-

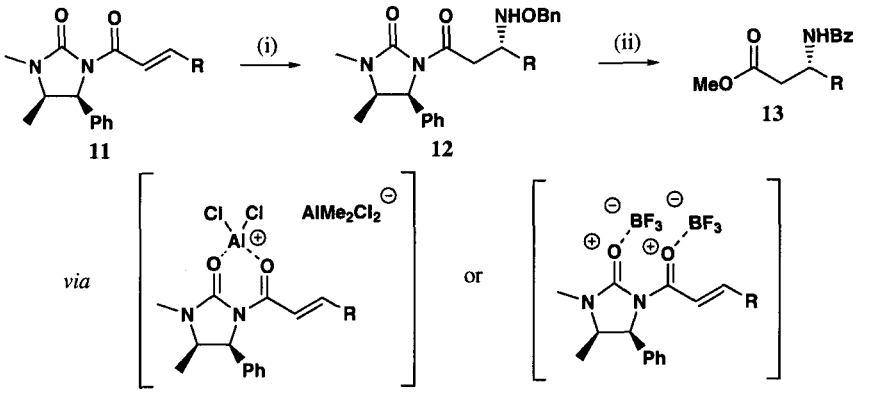
amide followed by alkylation of the intermediate enolate with methyl iodide was also successfully performed and, very recently, the same authors have explored the tandem *aza*-Michael/aldol reaction with good results.[12]



Reagents and Conditions: (i) 1. $CH_3CH_2CH_2COCl$, pyridine, THF; 2. LDA, PhSeSePh, H_2O_2; (ii) BnTMSNLi, THF, –78°C; (iii) BnNHLi, THF, -78°C; 2. MeOH, –78°C; (iv) 1. Br_2, CH_2Cl_2, –78°C; 2. Et_3N, r.t.

Scheme 4

A conceptually different approach has been exploited by Cardillo in the Lewis acid mediated asymmetric conjugate addition of *O*-benzylhydroxylamine to α,β-unsaturated imide **11**. In this case, the Lewis acid greatly enhanced the electrophilicity of the β-carbon and ensured good facial discrimination by chelation to both carbonyl oxygens present at the acceptor.[13] Further elaboration of the obtained adducts allowed the authors to prepare highly enantioenriched *N*-benzoyl-β-amino esters **13** (*Scheme 5*). The authors also found that the stereochemical



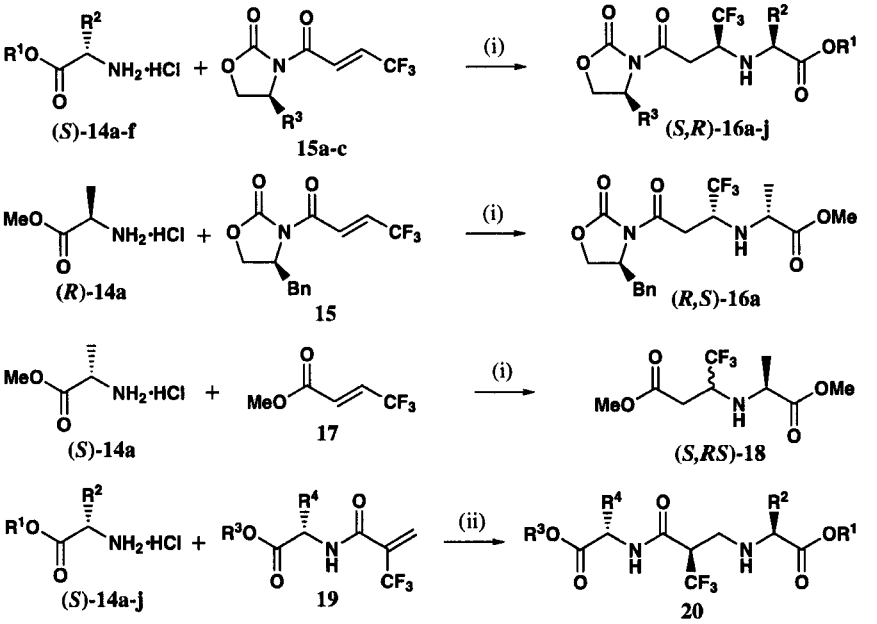
Reagents and Conditions: (i) $BnONH_2$, $AlClMe_2$ or $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78°C; (ii) 1. Zn/Cu(OAc)$_2$/AcOH, 70°C; 2. LiOH, THF/H_2O, r.t.; 3. BzCl, NaOH (aq.)/acetone, r.t.; 4. TMSCl, MeOH, r.t.

Scheme 5

outcome of the reaction became strongly influenced by the nature of the Lewis acid employed. Studies performed more recently revealed that Lewis acids with only one coordination site like BF_3 could also be employed in the same context because the formation of a coordination compound between the acceptor and two molecules of BF_3, each one coordinated to one

carbonyl group, could simulate chelation.[14] The same authors have also reported the use of phtalimide magnesium chloride as nitrogen nucleophile with the same kind of acceptors with excellent results.[15] In this related work, activation of the acceptor by Lewis acid coordination was also established.

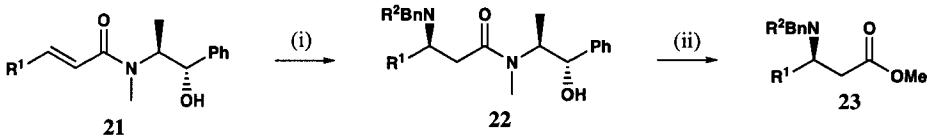
α,β-Unsaturated imide-type chiral acceptors have also been used recently by Volonterio and Zanda in the synthesis of modified peptidomimetics incorporating trifluoromethyl units (*Scheme 6*). In their first work, the β-trifluoromethyl substituted acceptor **15** linked to an Evans oxazolidinone moiety was employed as the electrophile and several chiral α-amino esters (***S*)-14** or (***R*)-14** were utilized as nucleophiles.[16] Under these conditions, a double stereodifferentiation process is operating; although the chiral information incorporated at the acceptor had a strong influence in the de's obtained, the sense of the facial diastereoselectivity was controlled mainly by the chiral information at the α-amino ester nucleophile. The use of **(*S*)-14a-f** afforded the adducts **(*S,R*)-16a-j** in moderate de (50-78%) while the addition of **(*R*)-14a** to the same chiral acceptor afforded the final product **(*R,S*)-16a-j** with the opposite configuration at the newly created stereogenic center, although in much lower de (21%). When the achiral enoate **17** was employed as the electrophile, the *aza*-Michael reaction of α-amino ester **(*S*)-14a** afforded a 1:1 mixture of diastereoisomers, which confirmed that the double asymmetric induction process was really operating. More recently,[17] the same authors applied this methodology to the α-CF_3 substituted acceptor **19** in which α-amino esters are also employed as chiral auxiliaries linked covalently to the substrate.



Reagents and Conditions: (i) 2,4,6-trimethylpyridine, CH_2Cl_2, r.t.; (ii) DABCO, CCl_4, r.t.

Scheme 6

We have also developed conditions to perform a highly stereoselective asymmetric *aza*-Michael reaction using lithium benzylamides as nucleophiles and the β-amino alcohol (*S,S*)-(+)-pseudoephedrine as chiral auxiliary directly attached to the conjugate acceptor *via* an amide bond linkage.[18] This amino alcohol is able to exert a very effective 1,5-asymmetric induction, thus affording the corresponding β-amino amides in good to excellent yields and diastereoselectivities, although the experimental conditions have to be changed depending upon the nature of the β-substituents at the α,β-unsaturated chain (*Scheme 7*).[19] The differently substituted, enantiomerically enriched β-amino amides **22** could be subsequently transformed into several interesting compounds by exploiting the intrinsic reactivity of the amide functionality. We have succeeded in converting these β-amino amides into β-amino esters **23** in a single step, with excellent yields and with no loss of the stereochemical integrity. Other compounds like γ-amino alcohols and β-amino ketones, are also amenable to be easily prepared from the same starting materials.

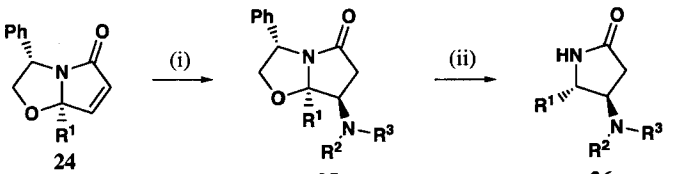


21 22 23

Reagents and Conditions: (i) R^2BnNLi or R^2BnNLi/TMEDA, toluene, –90°C; (ii) NaOMe, Me_2CO_3, CH_2Cl_2, r.t.

Scheme 7

Other β-amino alcohols have been used as auxiliaries in asymmetric *aza*-Michael reactions linked to the carbonyl acceptor through the nitrogen atom. In fact, Meyers has surveyed the asymmetric *aza*-Michael reaction throughout the development of his well-known chiral bicyclic lactam chemistry.[20] In this context, primary and secondary amines underwent clean conjugate addition reaction with bicyclic lactams **24** derived from (*S*)-phenylglycinol, affording the expected adducts **25** with excelent stereocontrol (*Scheme 8*).[21] The use of chiral amines as nucleophiles was also surveyed in order to determine whether the reaction proceeded under double stereodifferentiation conditions; however, the stereochemistry of the adducts was always found to be the same regardless the configuration of the chiral amine nucleophile employed, showing that the chiral auxiliary was the main - and probably the sole - factor operating in the stereochemical control of the reaction. Reductive cleavage of the chiral appendage allowed the authors to prepare a wide variety of 5-alkyl-4-aminopyrrolidin-2-ones **26** in highly enantioenriched form.

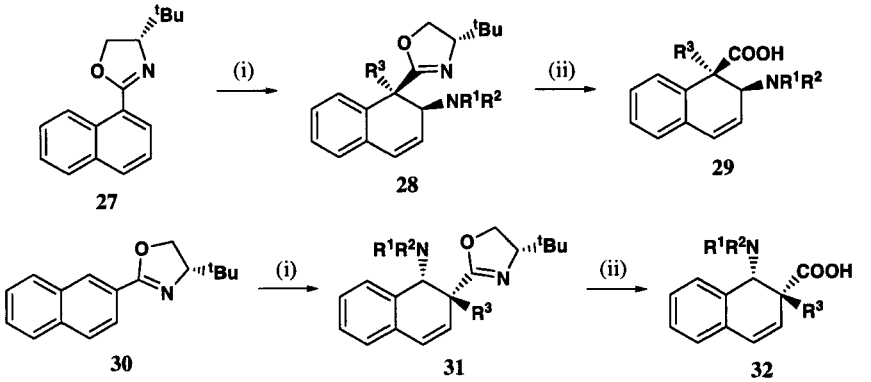


24 25 26

Reagents and Conditions: (i) R^2R^3NH, H_2O, CH_2Cl_2, r.t.; (ii) 1. AlH_3, THF, –78°C to r.t.; 2. H_2, Pd/C, EtOH, r.t.

Scheme 8

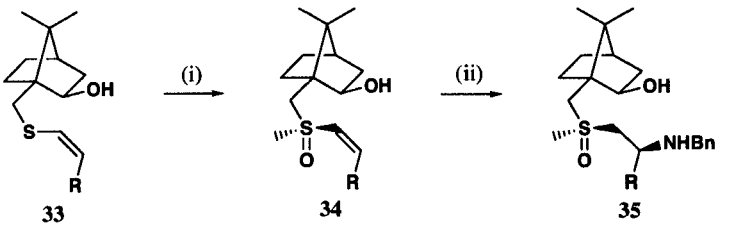
In a completely different approach, the same group has reported the asymmetric conjugate addition of lithium amides to chiral naphthyloxazolines derived form (*S*)-*tert*-leucinol **27** and **30** (*Scheme 9*).[22] The reaction was shown to be highly stereoselective after optimization of the reaction conditions, especially the solvent and the use of HMPA as additive, which increased notably the yield in which the final adducts were obtained. In addition, the fact that the reaction could be quenched in all cases with different alkyl halides implies that the intermediate enolate underwent a subsequent alkylation, thus generating two contiguous stereogenic centers in a fully stereocontrolled way. The adducts obtained (**28** or **31**) were subsequently converted into the corresponding β-amino acids **29** or **32** respectively using standard hydrolytic procedures.



Reagents and Conditions: (i) 1. R^1R^2NLi, HMPA, THF, –78°C to –50°C; 2. R^3X, THF, –78°C to –25°C; (ii) 6M HCl, reflux

Scheme 9

To conclude this section, it should be mentioned that non-carbonylic chiral acceptors like enantiomerically pure sulfoxides were also used as acceptors in asymmetric *aza*-Michael reactions by Pyne some time ago.[23] These sulfoxides were prepared in enantiomerically pure form by diastereoselective oxidation of the corresponding 10-isobornyl vinyl sulfides **33**. The obtained chiral vinyl sulfoxides **34** underwent diastereoselective conjugate addition of benzylamine, affording the corresponding β-amino sulfoxides **35** in good yields although with moderate diastereoselectivities (*Scheme 10*).

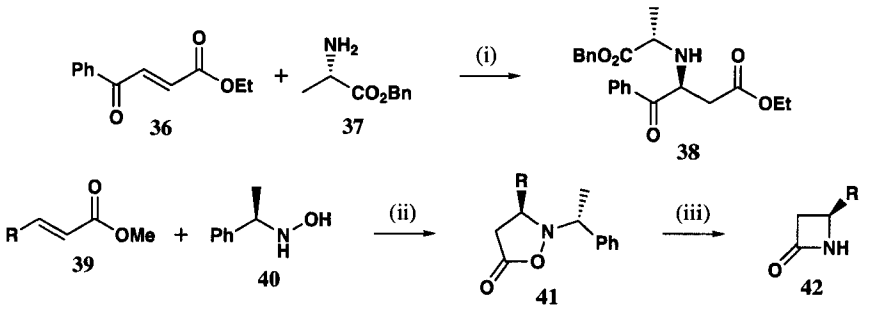


Reagents and Conditions: (i) *m*-CPBA, CH_2Cl_2, r.t.; (ii) $BnNH_2$, EtOH, 80°C

Scheme 10

II. ASYMMETRIC *AZA*-MICHAEL REACTION WITH CHIRAL NUCLEOPHILES

The second possibility to exert stereochemical control in the *aza*-Michael reaction is the incorporation of chiral nitrogen nucleophiles in the reaction scheme. In this context, one of the first reports found in the literature corresponds to the asymmetric conjugate addition of (*S*)-alanine benzyl ester **37** to ethyl 4-oxo-4-phenyl-2-butenoate **36**, yielding the 1,4-addition product in good yield but as an undetermined mixture of diastereoisomers in which the major isomer **38** could be separated from the minor one by precipitation in the reaction solvent (*Scheme 11*).[24]



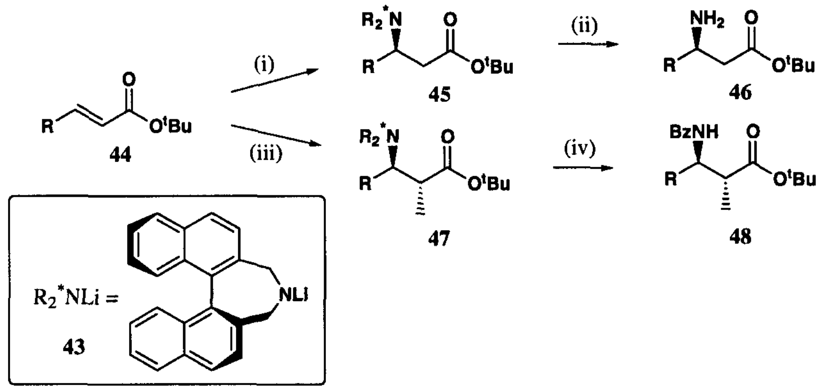
Reagents and Conditions: (i) Et_3N, EtOH, r.t.; (ii) Toluene, K_2CO_3, 80°C; (iii) 1. H_2, Pd/C, EtOH; 2. $^nBu_4NHSO_4$, $KHCO_3$ (aq.); 3. MsCl, $CHCl_3$; 4. Na/NH_3

Scheme 11

The other pioneering report in this area deals with the addition of chiral *N*-(α-methylbenzyl)hydroxylamines **40** to several methyl enoates **39**[25] to yield the expected isoxazolidinone adducts **41** in moderate to good diastereoselectivity; they were subsequently transformed into 4-alkylazetidin-2-ones **42** using standard procedures (*Scheme 11*). The diastereoselectivity of the reaction was subsequently increased by using chiral crotonate acceptors under double stereodifferentiation conditions;[26] in these cases, the stereochemical outcome of the reaction was always dominated by the chiral nucleophile, although the nature of the chiral auxiliary linked to the substrate was crucial in order to attain the desired high degree of diastereoselection. More recently, the same approach has been applied to α-substituted acrylates, and also in this case the reaction was not completely diastereoselective.[27]

Soon thereafter, Hawkins reported the use of atropisomeric benzylic lithium amide **43** as an excellent chiral nitrogen nucleophile in the *aza*-Michael reaction with α,β-unsaturated esters (*Scheme 12*).[28] The reaction proceeded with excellent diastereoselectivity furnishing β-amino esters **45** in excellent yields and these could be easily converted into the corresponding primary β-amino esters **46** due to the presence of easily removable benzyl groups on the nitrogen atom. This methodology also allowed tandem *aza*-Michael/alkylation reactions in which the intermediate enolate generated in the conjugate addition step reacted smoothly with methyl iodide leading to the fully stereoselective generation of two consecutive stereogenic centers in the adducts **47**, which could be easily converted into *N*-benzoyl-β-amino esters **48**.[29]

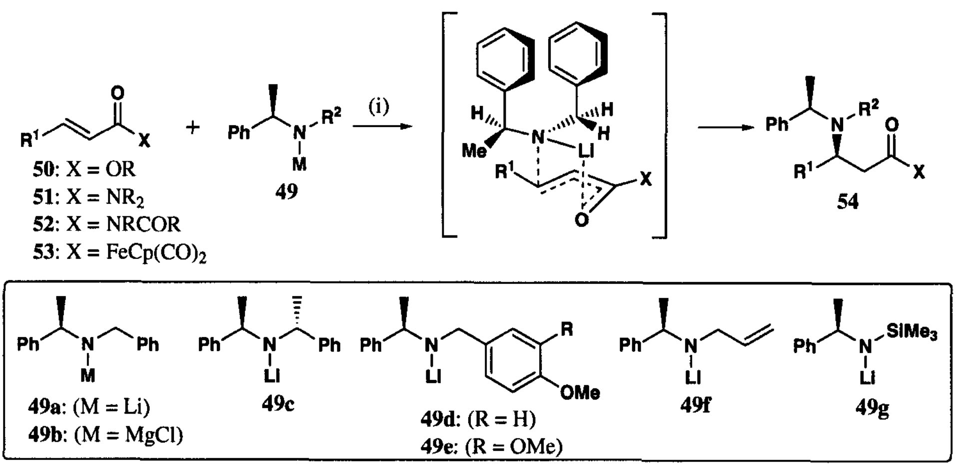
However, the most widely employed and exploited methodology in this context is that developed by Davies, which involves the use of metal α-methylbenzylamides as nucleophiles. In his first paper,[30] Davies reported a highly diastereoselective conjugate addition of lithium amide **49a** to several α,β-unsaturated esters, showing that the addition proceeded with almost complete



Reagents and Conditions: (i) 1. **43**, DME, –63°C; 2. NH_4Cl (aq.); (ii) NH_4HCO_2, $Pd(OH)_2/C$, EtOH, 60°C; (iii) 1. **43**, DME, –63°C; 2. MeI; (iv) 1. NH_4HCO_2, $Pd(OH)_2/C$, EtOH, 60°C; 2. PhCOCl, pyridine

Scheme 12

diastereoselection in all cases (*Scheme 13*). A mechanistic rationale which accounts for the observed high level of diastereoselection has also been provided.[31] As it is shown in *Scheme 13*, it is proposed that the lithium amide adds to the α,β-unsaturated carbonyl compound *via* a cyclic six member ring-type transition state in which the lithium atom coordinates with the oxygen of the acceptor and this remains in a *s-cis* conformation. Therefore, the α-methylbenzyl amide moiety selects the face in which non-bonding interactions between the α-methyl group and the α,β-unsaturated substrate are minimized. This methodology has been further extended to a wide range of different acceptors like

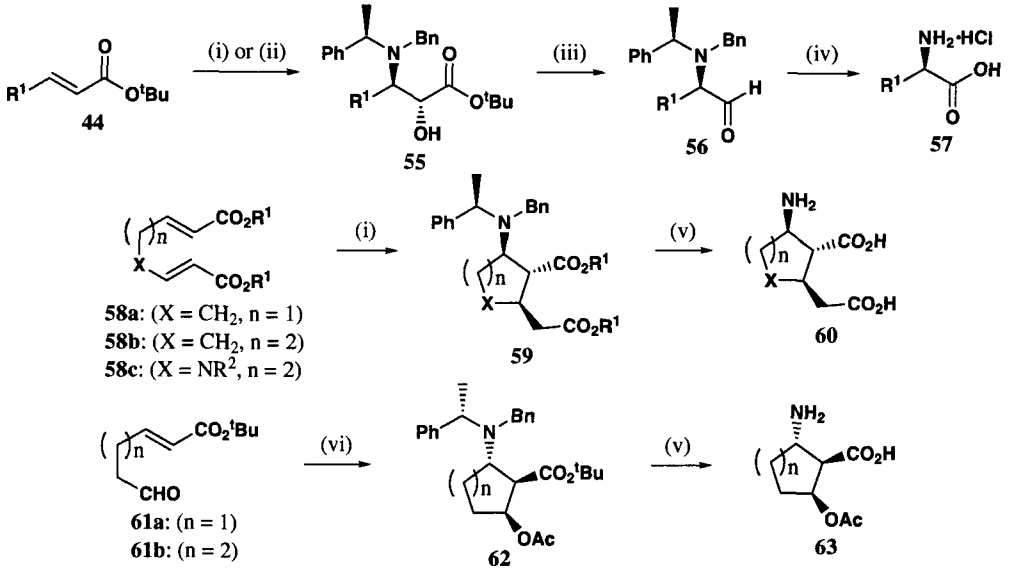


Reagents and Conditions: (i) 1. THF, –78°C; 2. NH_4Cl (aq.)

Scheme 13

other enoates,[32] α,β-unsaturated amides,[33] imides,[34] and iron acyl complexes.[35] In addition, modified chiral amide nucleophiles like magnesium amide **49b**[36] and benzylamides **49c-g**[37] have been investigated. The use of these modified nucleophiles has opened the way to an increased synthetic versatility of this methodology due to the possibility of performing selective protective group manipulation when converting the obtained adducts into other valuable compounds. This has notably increased the applicability of this protocol in total synthesis.[38]

Perhaps the most interesting point of this methodology is that it is possible to trap the intermediate enolate generated after the conjugate addition step with several electrophiles, in a typical tandem reaction sequence. In this context, the conjugate addition of lithium benzylamide **49a** to several enoates followed by concomitant diastereoselective enolate oxidation with (-)-camphorsulfonyloxaziridine has been reported (*Scheme 14*).[39] In this sequence, *anti*-β-amino-α-hydroxy esters **55** were obtained in very high enantio- and diastereomeric excesses and these



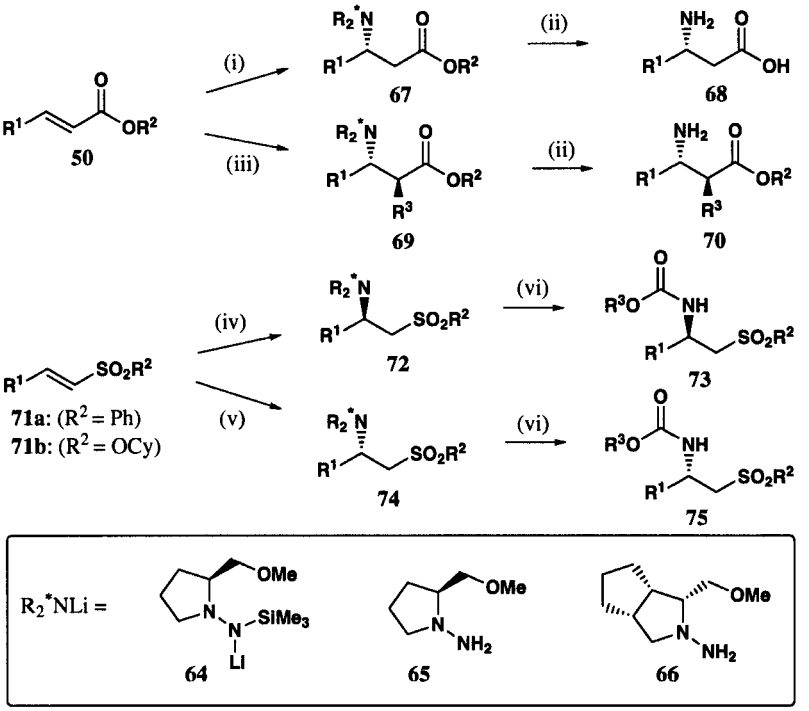
Reagents and Conditions: (i) 1. **49a**, THF, –78°C; 2. (-)-camphorsulfonyloxaziridine, –78°C to r.t; (ii) 1. **49a**, THF, –78°C; 2. NH_4Cl (aq.); 3. LDA, THF, –78°C; 4. (-)-camphorsulfonyloxaziridine, –78°C to r.t. (iii) 1. LAH, THF, –78°C to r.t.; 2. H_5IO_6, CH_2Cl_2/H_2O, 0°C; (iv) 1. $NaIO_4$, $RuCl_3$, CCl_4, r.t.; 2. HCO_2H, Pd/C, MeOH, 40°C; 3. HCl (aq.); (v) 1. H_2, $Pd(OH)_2/C$, MeOH; 2. LiOH, THF/H_2O, r.t.; 3. TFA, CH_2Cl_2, r.t; (vi) 1. **49a**, THF, –78°C to –20°C; 2. Ac_2O, DMAP, pyridine, CH_2Cl_2, r.t.

Scheme 14

adducts have shown to be versatile building blocks in the synthesis of many other chiral compounds, especially α-amino aldehydes **56** and acids **57**. The diastereofacial selectivity of the enolate hydroxylation is claimed to occur under predominantly substrate-controlled asymmetric induction, although a measurable degree of chirality recognition with the oxaziridine reagent is also reported. Alternatively, the same compounds with the same stereochemistry were obtained by stepwise *aza*-Michael reaction/protonation followed by deprotonation of the β-amino ester and oxidation of the formed enolate. This methodology has been successfully applied in the synthesis of the taxol and taxotere C-13 side chains.[40]

In a similar way the tandem *aza*-Michael/amination[41] and aza-Michael/alkylation[42] have been developed affording α-diazo-β-amino esters and α-alkyl-β-amino esters respectively with excellent stereocontrol. The aza-Michael/Michael and aza-Michael/aldol tandem sequences have also been surveyed in dienoates such as **58** and formyl enoates like **61,** affording cyclic β-amino acid derivatives of type **60** or **63** respectively after the subsequent deprotection steps (*Scheme 14*).[43]

Enantiopure hydrazines **64-66** have been also developed as extremely useful chiral ammonia equivalents in aza-Michael reactions (*Scheme 15*). Enders has brilliantly shown that lithium amide **64** derived from (*S*)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine (TMS-SAMP) adds to α,β-unsaturated esters in an extremely high diastereoselective fashion, furnishing



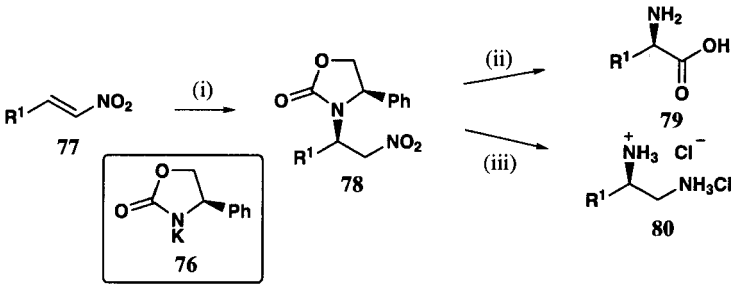
Reagents and Conditions: (i) 1. **64**, THF, 78°C; 2. NH_4Cl (aq.); (ii) H_2, Ra-Ni, H_2O or MeOH, 75°C; (iii) 1. **64**, THF, –78°C; 2. R^3X, HMPA, THF, –78°C; (iv) **65**, $Yb(OTf)_3$, THF, r.t. (for **71a**) or $ZnCl_2$, MeOH, r.t. (for **71b**); (v) **66**, $Yb(OTf)_3$, THF, r.t. (for **71a**) or $ZnCl_2$, MeOH, r.t. (for **71b**); (vi) 1. BH_3, THF, reflux; 2. Boc_2O, Et_3N, MeOH, r.t. or CbzCl, Na_2CO_3, CH_2Cl_2/H_2O, reflux

Scheme 15

a direct and efficient method for the preparation of enantiopure β-amino acids.[44] The tandem *aza*-Michael/alkylation sequence has also been reported to proceed with an equal high degree of stereoselection, furnishing highly enantioenriched α-alkyl-β-amino esters in excellent overall yields after reductive *N-N* bond cleavage.[45] The same authors have reported a very efficient Lewis acid-catalyzed asymmetric conjugate addition of hydrazines to α,β-unsaturated sulfones **71a**[46] and sulfonates **71b**.[47] Both enantiomers of the corresponding β-amino sulfones or β-amino

sulfonates can be selectively obtained using either (*S*)-1-amino-2-metoxymethylpyrrolidine (SAMP) **65** or (*R,R,R*)-2-amino-3-methoxymethyl-2-azabicyclo[3.3.0]octane (RAMBO) **66** as nucleophiles. Very recently, Fernandez and Lassaletta have also reported the asymmetric conjugate addition of a *D*-mannitol derived hydrazine to alkylidene malonates, which proceeds spontaneously without the need of any Lewis acid catalyst.[48]

Finally, a cyclic carbamate has also been employed as chiral nitrogen nucleophile in the conjugate addition to nitroalkenes (*Scheme 16*). The potassium amide **76**, generated in a first step



Reagents and Conditions: (i) 1. **76**, THF, 0°C; 2. **77**, 0°C; 3. NH_4Cl (aq.); (ii) 1. $NaNO_2$, AcOH, DMSO, 40°C; 2. Li/NH_3, THF, ^{t}BuOH, –78°C; (iii) 1. NH_4HCO_2, Pd/C, MeOH; 2. 12M HCl, sealed tube, 120°C; 3. H_2, $Pd(OH)_2$/C, MeOH/1M HCl

Scheme 16

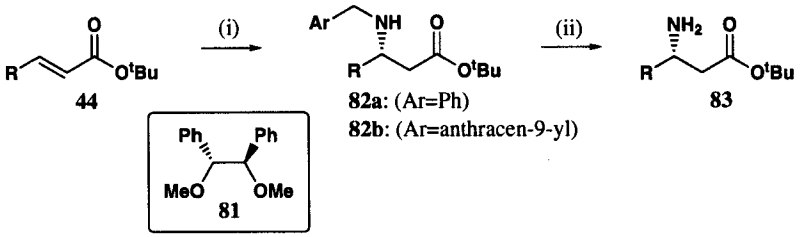
by deprotonation of the starting oxazolidinone with ^{t}BuOK in the presence of 18-crown-6, reacted with several nitroalkene acceptors **77** affording the expected adducts **78** as single diastereoisomers, which were afterwards converted into α-amino acids **79** and 1,2-diamonium chlorides **80** by standard procedures.[49]

III. ASYMMETRIC *AZA*-MICHAEL REACTIONS IN THE PRESENCE OF CHIRAL LIGANDS

Another possibility to effect stereochemical control in the *aza*-Michael reaction is the incorporation of chiral ligands in stoichiometric amounts in the reaction medium. Typically, these ligands have to remain attached to the nucleophile during the reaction for the final adduct to be obtained with the desired high degree of diastereoselectivity; this is achieved provided that a well organized transition state is reached, in which one of the enantiotopic faces of the acceptor results effectively shields the incoming the nucleophile with respect to the other. A clear practical advantage of the use of chiral ligands over the chiral auxiliaries and chiral nitrogen nucleophiles relies upon the fact that no additional synthetic steps are needed for the attachment/detachment to/from the starting/final compounds. Despite this, there are not so many reports for these kind of asymmetric *aza*-Michael reactions.

The most remarkable result made in this area is that reported by Tomioka, using the *bis*-chelating chiral ether **81** as ligand (*Scheme 17*). The reaction of α,β-unsaturated ester **44** with lithium benzyltrimethylsilyl amide in the presence of a stoichiometric amount of **81** led to the corresponding *N*-benzyl-β-amino ester **82a** in excellent yields and enantioselectivities, which

could be easily transformed into the *N*-deprotected derivative **83** after simple hydrogenolytic treatment.[50] Further progress on this topic led to optimization of the lithium amide structure; it

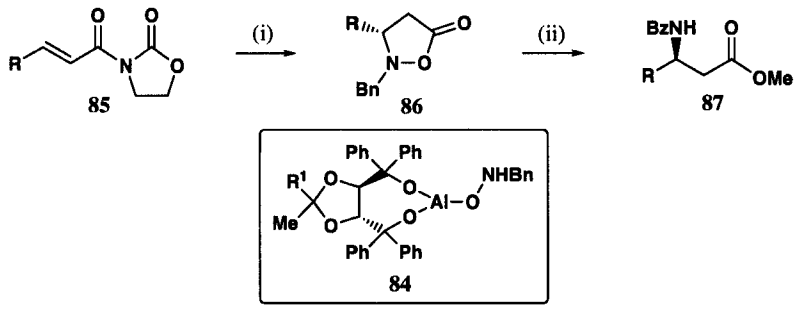


Reagents and Conditions: (i) LiNBnTMS or LiN(anthracen-9-ylmethyl)TMS, **81**, toluene, –78°C; (ii) H_2, $Pd(OH)_2/C$, MeOH, r.t.

Scheme 17

was determined that anthracen-9-ylmethyltrimethylsilyl amide was the reagent of choice in the enantioselective *aza*-Michael reaction in the presence of chiral ligand **81**.[51] Very recently, a paper reported the asymmetric conjugate addition of benzylamines to *N*-phenylmaleimide in the presence of (1*R*,2*R*)-*N*,*N*,*N*',*N*'-tetramethyl-cyclohexanediamine as chiral ligand, although with little degree of enantioselection.[52]

In a different approach, *O*-metalated hydroxylamines incorporating chiral ligands linked to the metal center have been employed as stoichiometric reagents in *aza*-Michael reactions to α,β-unsaturated imides **85** (*Scheme 18*). The use of this kind of nitrogen nucleophile led



Reagents and Conditions: (i) **84**, THF, 0°C to r.t; (ii) 1. H_2, Pd/C, EtOH, r.t.; 2. BzCl, Et_3N, CH_2Cl_2, r.t.; 3. $TMSCHN_2$, MeOH, r.t.

Scheme 18

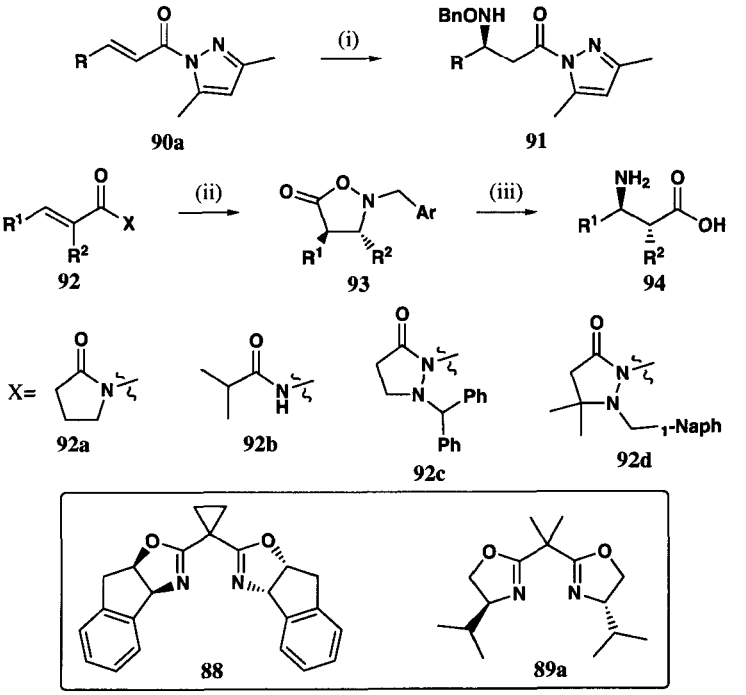
to the formation of isoxazolidinones **86** as final compounds, which could be converted into the target β-amino acids by reductive treatment.[53] The authors surveyed many chiral ligands derived from several diols but moderate enantioselectivities were obtained in all cases, concluding that the best results were afforded by the TADDOL-containing hydroxylamine **84**.

IV. CATALYTIC ASYMMETRIC *AZA*-MICHAEL REACTIONS

Covalently linked chiral auxiliaries or promoters used in stoichiometric amounts provide high stereoselectivities in a reliable way and with a broad substrate tolerance, as it has been stated in the previous sections. However, the methods based on the use of catalytic amounts

of the chirality source are clearly preferable over the others, especially from the economical point of view in the case of large scale preparations.

Metal complexes of *bis*-oxazoline-type chiral ligands have been used by several authors as efficient catalysts in many cases of asymmetric *aza*-Michael reactions. Sibi has reported a highly enantioselective protocol for the conjugate addition of *O*-benzyl hydroxylamine to unsaturated imides **90a**, using a Mg(II) catalyst containing chiral ligand **88** (*Scheme 19*).[54] The same author has

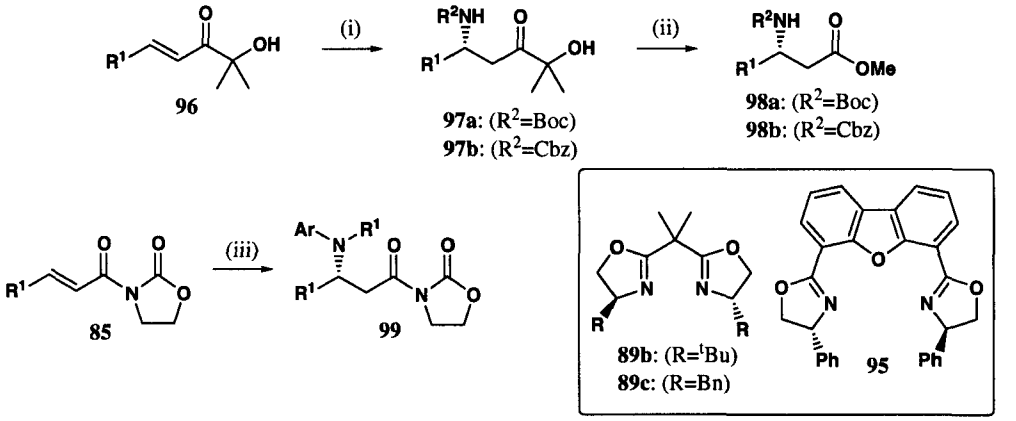


Reagents and Conditions: (i) H_2NOBn, **88**, $MgBr_2$, CH_2Cl_2, –60°C; (ii) $ArCH_2NHOH$, $Mg(ClO_4)_2$ or $Mg(NTf_2)_2$ or MgI_2, **88**, CH_2Cl_2, –40°C; (iii) H_2, Pd/C, dioxane, 60°C

Scheme 19

also reported the *aza*-Michael addition of hydroxylamine to several enimides **92a-d** using Lewis acids like $Mg(ClO_4)_2$ or $Mg(NTf_2)_2$ as catalysts in the presence of chiral *bis*-oxazoline ligands **88** and **89a**,[55] obtaining the corresponding isoxazolidinone adducts **93** in good yields, which could be afterwards converted into the target β-amino acids by standard reductive treatment. It was also found that the nature of the imide substituent plays an important role in the enantioselectivity and the yield of the reaction. In this context, the authors have employed their "chiral relay method",[56] in which functional groups introduced in the achiral template present in one reagent play a crucial role in enantioselective transformation. The use of the pyrazoli-dinone based relay template acceptors **92c** and **92d**, provided a significant amplification of selectivity in the reaction.[57] Besides, the use of $Mg(ClO_4)_2$/**88** or $Zn(OTf)_2$/**89a** combination of reagents as catalysts furnished the final products in opposite configuration at the newly created stereogenic center.

Other examples of catalytic asymmetric *aza*-Michael reactions employing chiral *bis*-oxazolines as ligands are shown in *Scheme 20*. Palomo has very recently reported the enantioselective conjugate addition of carbamates to α,β-unsaturated hydroxyketones **96** using ligand **89b**/Cu(OTf)$_2$ as catalyst,[58] furnishing directly almost enantiopure *N*-protected β-amino-α'-hydroxyketones **97** which, after oxidative cleavage of the hydroxyketone moiety followed by

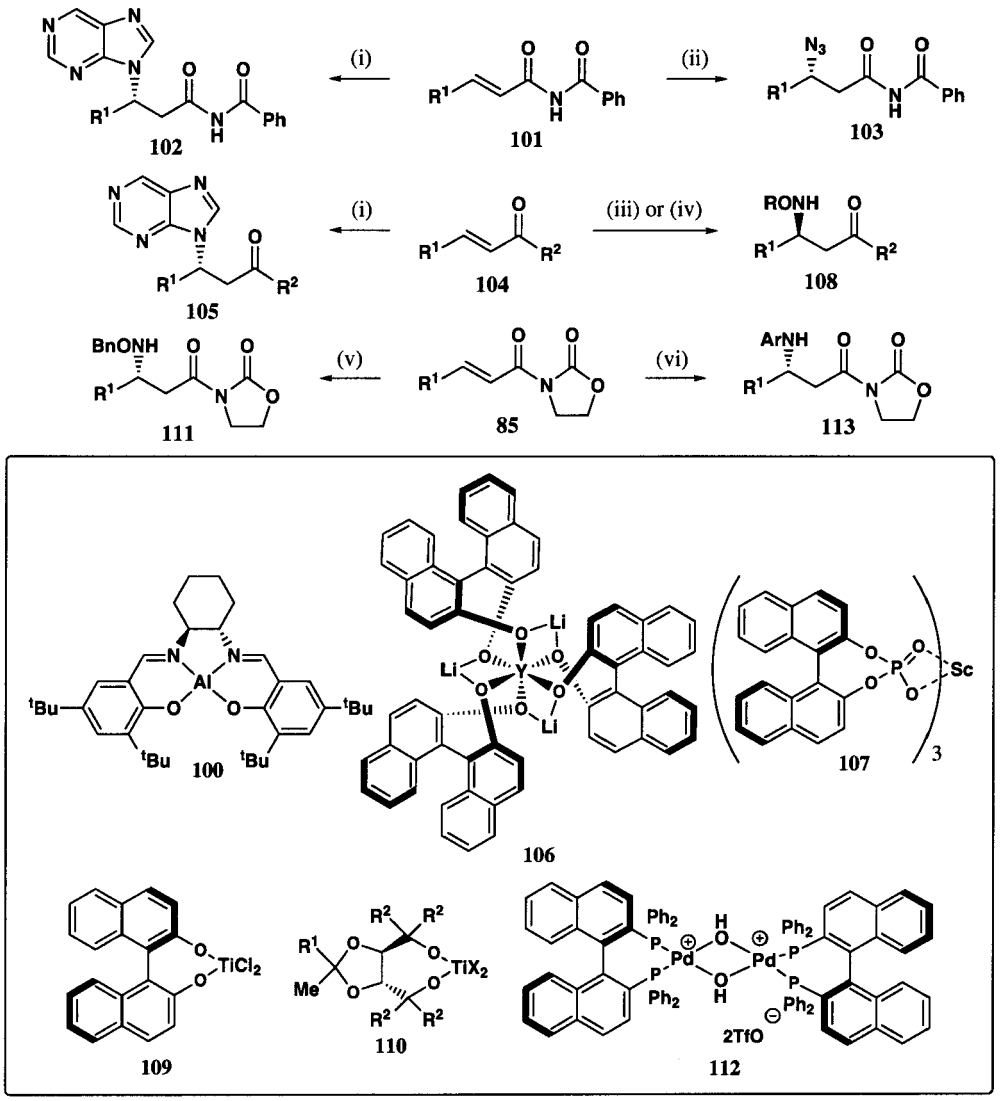


Reagents and Conditions: (i) R^2NH_2, **89b**, $Cu(OTf)_2$, CH_2Cl_2, r.t.; (ii) 1. $NaIO_4$, H_2O/MeOH, r.t.; 2. $TMSCHN_2$, MeOH, C_6H_6, r.t.; (iii) $Ni(ClO_4)_2 \cdot 6H_2O$, **95**, CH_2Cl_2, r.t.

Scheme 20

esterification provided an easy and direct access to β-amino esters **98**. This is the only example found in the literature in which carbamates can be activated as nucleophiles in an asymmetric *aza*-Michael reaction. In another interesting paper, Jorgensen has set up a very effective Ni(II)-catalyzed enantioselective 1,4-addition of secondary aromatic amines to α,β-unsaturated imides **85** using *bis*-oxazoline **95** as chiral ligand (*Scheme 20*).[59] On the other hand, Cardillo has employed a copper(II) catalyst incorporating *bis*-oxazoline ligand **89c** in the asymmetric conjugate addition of *O*-trimethylsilylhydroxylamine to alkylidenemalonates,[60] and Kanemasa has studied the enantioselective *aza*-Michael addition of aldoximes to enimide **85** using a Zn(II) catalyst based on chiral ligand **95**,[61] both reporting moderate enantioselectivities.

Another conceptually different catalyst design is the aluminium-salen complex **100**, which has been brilliantly employed by Jacobsen in the asymmetric conjugate addition of *N*-heterocycles to α,β-unsaturated imides **101** and enones **104**[62] and in the *aza*-Michael reaction of hydrazoic acid to enimides **101**,[63] obtaining excellent enantioselectivities in almost all cases studied (*Scheme 21*). Shibasaki has also applied his well-known heterobimetallic catalyst **106** in the asymmetric 1,4-addition of *O*-benzylhydroxylamine to enones **104**, with excellent degrees of enantioselection.[64] Good results were also obtained by Inanaga in the same reaction using chiral scandium complex **107**.[65] On the other hand, Jorgensen has surveyed the use of Ti(IV)-BINOL complex **109** and Ti(IV)-TADDOL complex **110** as catalysts in the asymmetric conjugate addition of *O*-benzylhydroxylamine to α,β-unsaturated imides **85** but moderate enantioselectivities



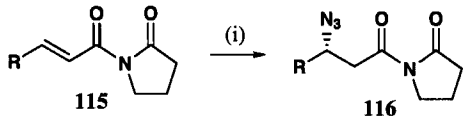
Reagents and Conditions: (i) Purine, **100**, toluene, r.t.; (ii) HN_3, **100**, toluene, r.t.; (iii) $RONH_2$, **106**, drierite, THF, –20°C; (iv) $RONH_2$, **107**, toluene, r.t.; (v) $BnONH_2$, **109** or **110**, toluene, r.t.; (vi) $ArNH_2$•TfOH, **112**, THF, r.t.

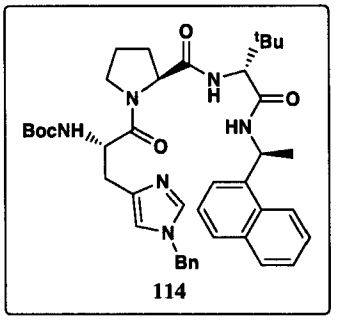
Scheme 21

were obtained.[66] The addition of aromatic amines to the same kind of acceptors using different chiral BINAP-Pd complexes like **112** has also been reported to proceed with good results in some cases.[67]

The increasingly growing field of the asymmetric organocatalysis has also been applied to the *aza*-Michael reaction.[68] This methodology avoids the use of metallic reagents, which is a key advantage over the other previously mentioned "classic" transition metal-based catalysts and therefore it has become a progressively more interesting subject of research in the last few years,

not only for the evident synthetic advantages reported but also due to the possibility of expanding the model to other synthetic reactions. In this case, a simple peptide like that shown in *Scheme 22* has been found to be an excellent promoter for the 1,4-addition of $TMSN_3$ to α,β-unsaturated imides, affording the corresponding β-azidocarbonyl adducts in excellent yields and in moderate to good enantioselectivities.[69]

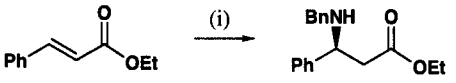


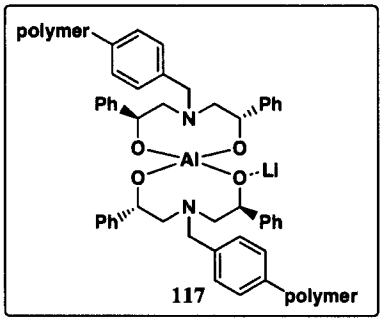


Reagents and Conditions: (i) $TMSN_3$, **114**, $^tBuCO_2H$, Toluene, r.t.

Scheme 22

Finally, it has to be mentioned that an example of an asymmetric *aza*-Michael reaction under heterogeneous catalysis conditions has been recently reported by Sundarajan in which the polymer-anchored chiral aluminium catalyst **117** resulted to be an effective promoter for the enantioselective conjugate addition of benzylamine to ethyl cinnamate, yielding the corresponding *N*-benzyl-β-amino ester in ca. 80% e.e. and with good yield (*Scheme 23*).[70]





Reagents and Conditions: (i) $BnNH_2$, **117**, THF, 35°C

Scheme 23

V. CONCLUDING REMARKS

We have shown that the asymmetric *aza*-Michael reaction is a very well developed transformation in stereoselective organic synthesis which allows the straightforward preparation of differently functionalized β-amino carbonyl compounds in good yields and as optically pure compounds. In principle, it can be said that the methods involving the use of chiral nitrogen

nucleophiles are the best developed and the most employed, especially in total syntheses. The methodology that involves the use of chiral auxiliaries linked to the carbonyl acceptor has also been widely studied but the fact that the chiral information is placed quite far away from the point in which the new stereocentre is formed makes that the stereoselectivity of the reactions becomes very dependent upon the reaction conditions. Nevertheless, in both methodologies, the available methods give good yields and predictable stereochemical outcome in the reactions in which they are involved and these features, together with the fact that the chirality sources employed to obtain these auxiliaries or nitrogen nucleophiles are usually cheap and/or readily available, overcomes the need for stoichiometric amounts of chiral reagents and the additional synthetic steps required for the attachment and removal of the chiral appendage. The strategies based on the use of chiral ligands overcome the use of these additional synthetic steps although they have not been as thoroughly studied as the former methodologies. On the other hand, in the last years much effort has been devoted to the development of new chemical entities capable of catalyzing the asymmetric *aza*-Michael reaction with high efficiency. This methodology, in which all the theoretical advantages of a synthetic transformation converge (high yield and stereo-selectivities, atom economy, reduction of synthetic steps and catalytic use of chirality source) seems to be the most promising field of research in this area. It is expected that new exciting contributions will appear in the next few years, especially related to the field of the asymmetric organocatalysis.

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