Asymmetric Michael Additions to Nitroalkenes

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The asymmetric conjugate addition of various carbon and heteroatom nucleophiles to nitroalkenes as a tool for the construction of highly functionalized synthetic building blocks is presented. Diastereoselective, substrate-controlled 1,4-additions are also included. Besides auxiliary controlled asymmetric Michael additions, external asymmetric versions employing enantiopure additives, addition-elimination processes with enantiopure leaving groups, and catalytic asymmetric syntheses are described. The use of the highly reactive nitroalkenes as Michael acceptors opens the way to synthetically very useful C–C and C–X bond-forming reactions and subsequent transformations as is demonstrated by various applications.

1. Introduction

The asymmetric conjugate addition[1] is one of the most powerful bond-forming reactions to construct enantioenriched, highly functionalised carbon skeletons for the total synthesis of natural and biologically active compounds. Its strategic importance is evident by considering that a Michael addition can represent the initiating step of more complex inter- and intramolecular tandem processes.[2] Among the Michael acceptors, nitroalkenes are very attractive, because the nitro group[3] is the most electron-withdrawing group known.[4] Often described as a "synthetic chameleon"[5] it can serve as masked functionality to be further transformed after the addition has taken place. The Nef reaction,[6] the nucleophilic displacement,[7] the reduction to an amino group,[8] the Meyer reaction,[9] and the conversion into a nitrile oxide [10] are only some examples of the possible transformations that nitro groups can undergo (Scheme 1).

To make the employment of nitroalkenes even more attractive, a number of new efficient synthetic methods have been developed in recent years.[11] In the present paper we report on the application of nitroalkenes as Michael acceptors in asymmetric conjugate additions. Related substrate-controlled diastereoselective Michael additions to nitroalkenes are also covered briefly to give a more complete picture.

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Dieter Enders (center) was born in 1946 in Butzbach, Hessen. He studied chemisty at the Justus Liebig Universität Gießen and received his Dr. rer. nat. in 1974 under the direction of Prof. D. Seebach. After postdoctoral studies at the Harvard University with Prof. E. J. Corey he went back to Gießen and obtained his habilitation in 1979. In 1980 he moved to the Universität Bonn as an Associate Professor and in 1985 to his present postion as Professor of Organic Chemistry at the Reinisch-Westfälische Technische Hochschule Aachen. His current research interests are asymmetric synthesis, new synthetic methods using organometallics and the stereoselective synthesis of biologically active compounds.

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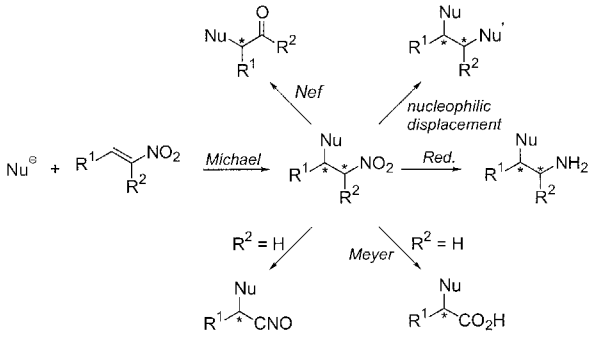
MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

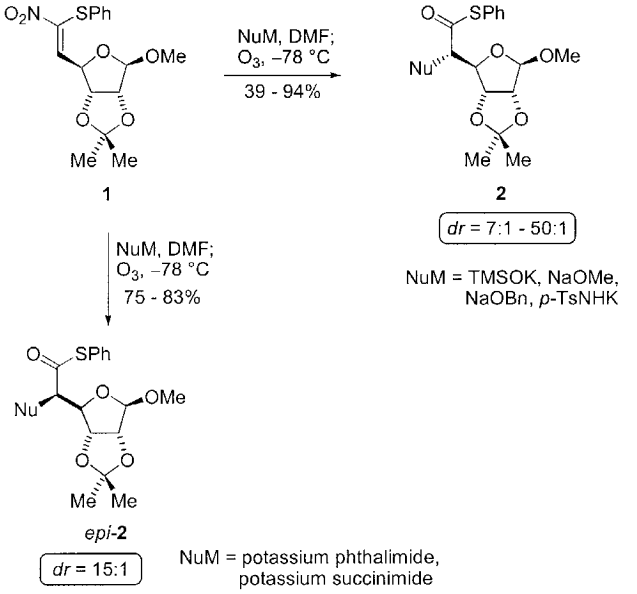


Scheme 1

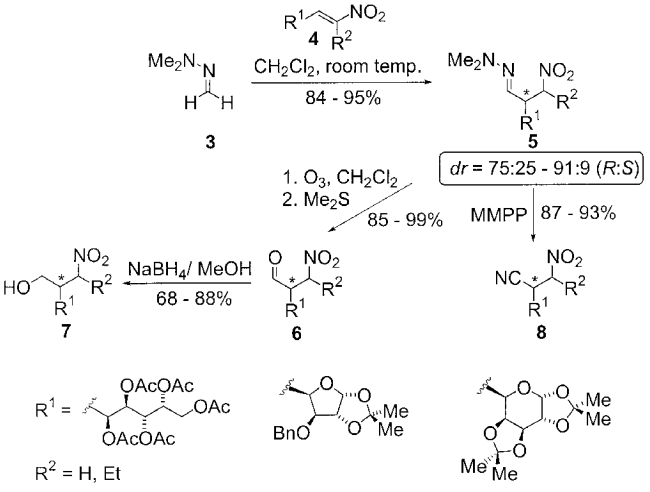
2. Substrate-Controlled Diastereoselective Michael Addition to Nitroalkenes

There are numerous examples of substrate-controlled conjugate additions to nitro olefins, especially to carbohydrates containing an α,β-unsaturated nitro moiety. It is not the purpose of this microreview to list all such applications but rather to give some representative examples. Moreover, further examples can be found in the review of Barrett.[12]

Barrett and co-workers[13] have investigated the stereochemical outcome of the reaction between different nucleophiles and 1-nitro-1-(phenylthio)alkenes **1** bearing a chiral sugar residue. The results show that the 1,4-addition followed by ozonolysis gave thioesters **2** in moderate to very good yields and with excellent diastereoselectivities. In addition, recrystallization resulted in diastereomerically pure products **2**. Interestingly, with smaller nucleophiles, such as alkoxylates, the absolute configuration of the newly formed center was (*S*) whereas with aerofoil bulky nucleophiles, such as potassium phthalimide and potassium succinimide the (*R*)-configured epimers *epi*-**2** were obtained (Scheme 2). This demonstrates the danger of assigning configurations by analogy. Moreover, the methodology has been applied to the total synthesis of polyoxin C[14] and nikkomycin B.[15]



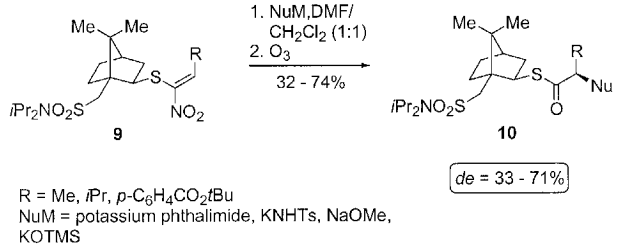
Scheme 2



Scheme 3

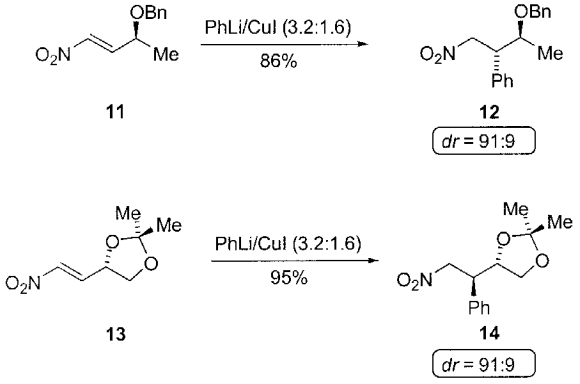
Lassaletta and co-workers[16] studied the 1,4-addition of formaldehyde dimethylhydrazone (**3**) to sugar nitro olefins **4**. The reaction proceeds under mild and neutral conditions based on the aza-enamine reactivity of the hydrazone to give the desired 1,4-adducts **5** in high yield and in good diastereofacial selectivity, which is derived from the asymmetric control of the sugar moiety (Scheme 3). In addition, both epimers could be separated by column chromatography. Release of the aldehyde moiety was achieved by ozonolysis and reductive workup in good yield to give the β-nitro aldehydes **6**. Due to the sensitivity of these aldehydes, a sodium borohydride reduction was performed leading to the corresponding alcohols **7**. Furthermore, the hydrazones **5** can be converted into the corresponding nitriles **8** with magnesium monoperoxyphthalate. Both processes take place without racemization.

Barrett and co-workers[17] also examined the addition of different nitrogen and oxygen nucleophiles on (+)-camphorsulfonic acid derived nitroalkenes **9**. The conjugate addition, followed by ozonolysis, provided the adducts **10** in moderate yields and stereoselectivities. The aryl-substituted **9** failed to react with all nucleophiles except for KOTMS. In all cases the absolute configuration of the newly formed stereogenic center was (*R*) (Scheme 4).



Scheme 4

The 1,4-addition of organometallic carbon nucleophiles to chiral nitro olefins of type **11** and **13** was investigated by Ayerbe et al.[18] Several organometallic nucleophiles with different additives were examined and in the case of phenyllithium, for example, best diastereoselectivities were obtained with compounds **11** and **13** when CuI was used as an additive to give the products **12** and **14** in high yield (Scheme 5). This method has also been extended to functionalized nucleophiles.[19]

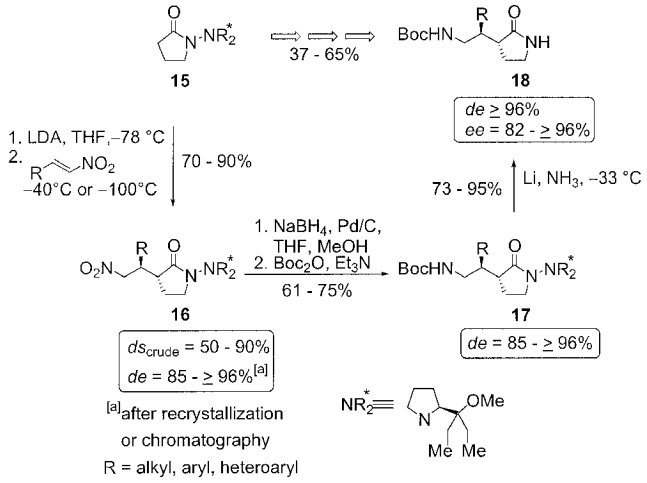


Scheme 5

3. Auxiliary-Controlled Conjugate Addition

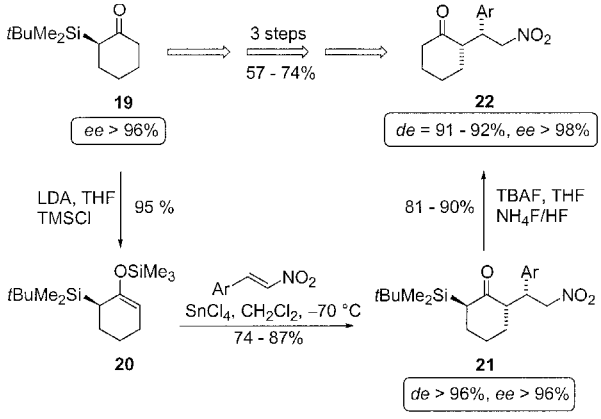
3.1 Michael Additions of Carbon-Centered Nucleophiles to Nitroalkenes

In our research group we have prepared α-(β-aminoalkyl)-substituted γ-lactams **18**, which are pharmacologically interesting compounds as they constitute enantioenriched precursors of double GABA analogues.[20] Key step is the conjugate addition of the γ-lactam **15** bearing a sterically demanding, (*S*)-proline-derived auxiliary on the lactam nitrogen atom to nitroalkenes. The conjugate addition to aliphatic nitroalkenes provided higher diastereoselectivities (ds_{crude} = 80−90%) of the 1,4-adducts **16** than the aromatic counterparts (ds_{crude} = 50−78%). In both cases the diastereoselectivities could be significantly increased by recrystallization or chromatography. Reduction of the nitro group, Boc protection and cleavage of the N−N bond of the resulting lactam **17** with lithium in liquid ammonia provided lactams **18** in good overall yields and high diastereo- and enantiomeric excesses (Scheme 6).



Scheme 6

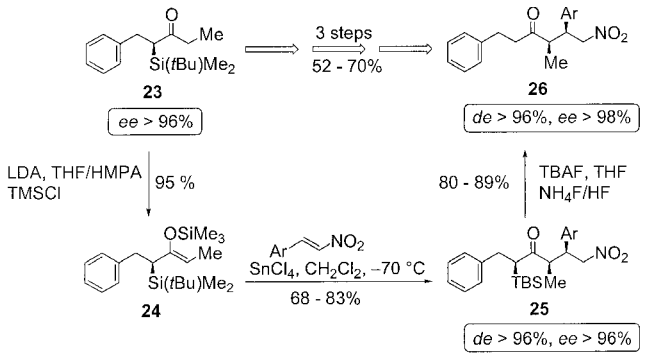
Our group used the concept of α-silyl ketone control[21a] in the asymmetric synthesis of α,β-disubstituted γ-nitro ketones **22**.[21b] The practically enantiopure cyclic α-silylated ketone **19** was regioselectively converted into the corresponding silyl enol ether **20** by treatment with lithium diisopropylamide and chlorotrimethylsilane. No racemization was observed at the α-position due to the steric bulk of the *tert*-butyldimethylsilyl group. Tin tetrachloride promoted 1,4-addition to aryl-substituted nitroalkenes occurred smoothly providing the products **21** with high asymmetric induction. Removal of the silyl group was achieved by using tetrabutylammonium fluoride and NH_4F/HF as buffer system. Without the buffer epimerization occurred at the α-position, which could be reduced but not completely avoided by using NH_4F/HF (Scheme 7).



Scheme 7

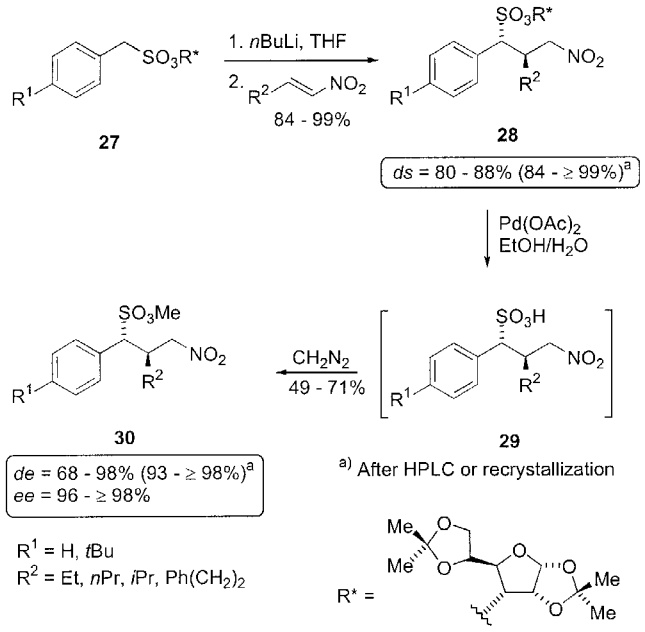
In addition, the same procedure was investigated in an acyclic α-silyl ketone **23**.[21b] In the acyclic case the problem of (*E*)/(*Z*) selectivity regarding the enolate geometry arises, which could be solved by employing HMPA as an additive. Otherwise, the procedure follows the one developed for the cyclic examples via **24** and **25** with the exception that in the deprotection step with TBAF and NH_4F/HF no epimerization was observed. In this manner, the *syn*-configured α,β-disubstituted γ-nitro ketones **26** were obtained with excellent overall yields and stereoselectivities (*de* > 96%, *ee* > 98%, Scheme 8).

Recently, a diastereo- and enantioselective synthesis of α,β-disubstituted γ-nitro methyl sulfonates **30** has been reported by our group.[22] Such compounds are valuable bifunctional building blocks and constitute chiral disubstituted precursors of pharmacologically interesting homotaurine derivatives (3-aminopropanesulfonic acid). Lithiated enantiopure sulfonates **27** using 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as chiral auxiliary were allowed to react with nitroalkenes to give the Michael adducts **28** in high yield (84−99%) and induction (*ds* = 80−88%). The diastereoselectivities could be further increased by preparative HPLC or recrystallization (*ds* =



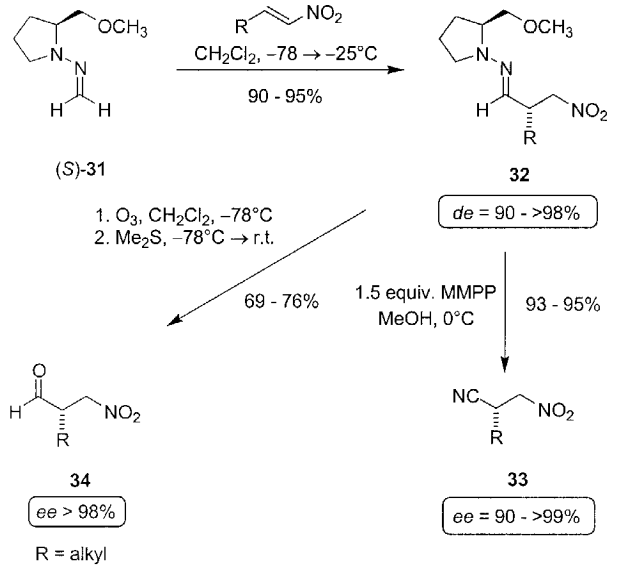
Scheme 8

84−99%). Removal of the sugar auxiliary was achieved by refluxing the products in an EtOH/H_2O solution containing 20 mol % $Pd(OAc)_2$. The resulting sulfonic acids **29** were directly converted into the corresponding methyl sulfonates **30** with diazomethane to facilitate the isolation of the desired products (Scheme 9).



Scheme 9

The aza-enamine reactivity of formaldehyde SAMP-hydrazone **31** was investigated by employing it as a chiral formyl anion and cyanide equivalent.[23] SAMP-hydrazone **31** reacted with nitroalkenes under neutral and very mild conditions to give in high yield and diastereoselectivity the Michael adducts **32**. Cleavage of the chiral auxiliary was carried out by either magnesium monoperoxyphthalate (MMPP) or ozonolysis, followed by reductive workup to yield α-substituted β-nitrocarbonitriles **33** and β-nitro aldehydes **34**, respectively. In both cases, the hydrazone cleavage occurs without racemization providing the desired compounds in good yields and high enantiomeric purity. The asymmetric Michael addition can also be performed with aromatic nitroalkenes, but with lower yields (60−95%) and diastereoselectivities (*de* = 82−89%, Scheme 10).



Scheme 10

A mechanism was proposed to explain the high diastereoselectivity of the 1,4-addition and the observed absolute configuration of the products. The formaldehyde SAMP-hydrazone attacks the *Si* face of the nitroalkene forming a closed, chair-like transition state which is stabilized by the attractive electrostatic interactions between the developing charges $N^{\delta+}/NO_2^{\delta-}$ (Figure 1).

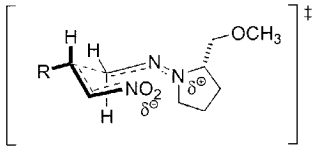
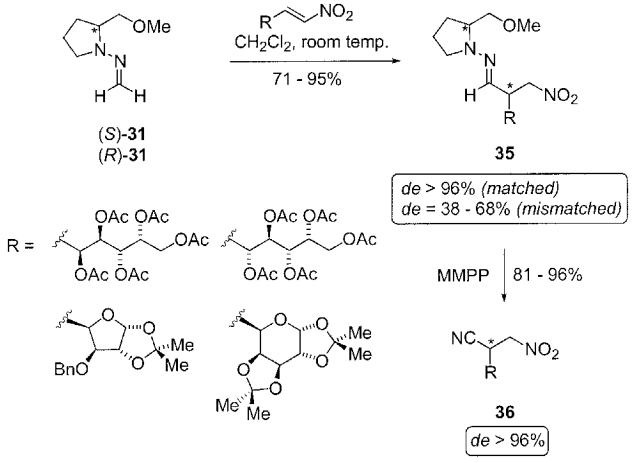


Figure 1. Proposed transition state

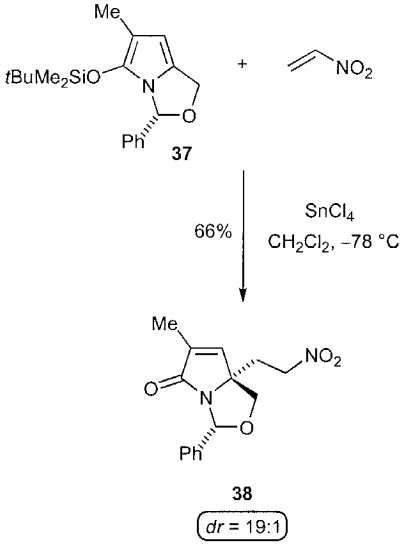
Furthermore, double-induction experiments with chiral Michael acceptors *and* donors were undertaken.[24] Allowing formaldehyde SAMP- or RAMP-hydrazone (*S*)- or (*R*)-**31** to react with chiral sugar-derived nitro olefins produced the 1,4-adducts in good to excellent yields. The diastereoselectivity of the "matched" pairs **35** was very high (*de* > 96%). In the "mismatched" case moderate to good selectivities were obtained with the configuration of the newly formed stereogenic center being opposite to that induced by the sugar moiety indicating a strong dominance of induction caused by the SAMP/RAMP auxiliary over that of the chiral sugar. Furthermore, the epimers resulting from the "mismatched" case could be separated by column chromatography to give after oxidative cleavage the β-nitro-

carbonitriles **36** with high diastereomeric excesses (*de* > 96%, Scheme 11).



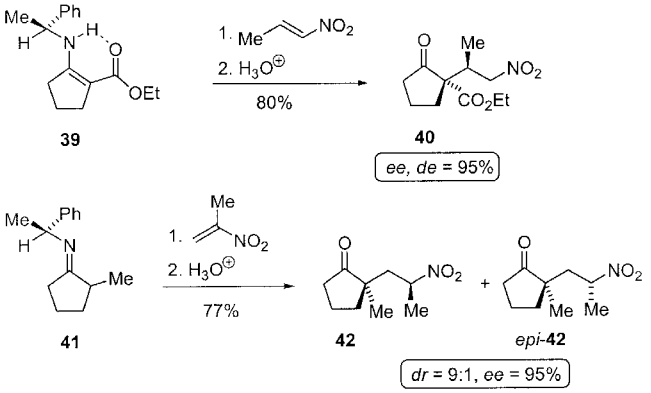
Scheme 11

Uno et al.[25] used (3*R*)-5-(*tert*-butyldimethylsiloxy)-3-phenyl-1*H*-pyrrolo[1,2-*c*]oxazole for the construction of a quaternary stereocenter. As an example, the Lewis acid promoted Michael addition of oxazole **37** to nitroethene gave the 1,4-adduct in good yield and diastereomeric ratio (Scheme 12). Other α-nitro-substituted compounds were converted into α-branched serine derivatives.



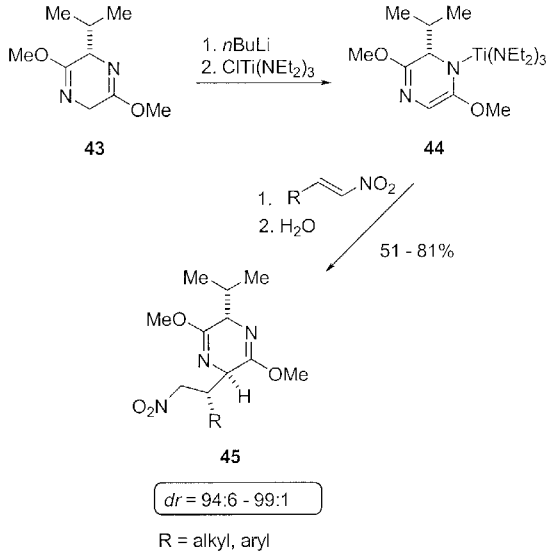
Scheme 12

A different approach to synthesize quaternary stereocenters was disclosed by d'Angelo and co-workers.[26] The asymmetric Michael addition of enantiopure imines/enamino esters **39** and **41**, prepared from the corresponding ketones using (*S*)-1-phenylethylamine as chiral auxiliary, to nitroalkenes gave the 1,4-adducts **40** and **42** with excellent *de* and *ee* (Scheme 13). The enantiomeric excesses of compounds **40** and **42** were determined from the corresponding methyl ketones easily available by the Nef reaction.



Scheme 13

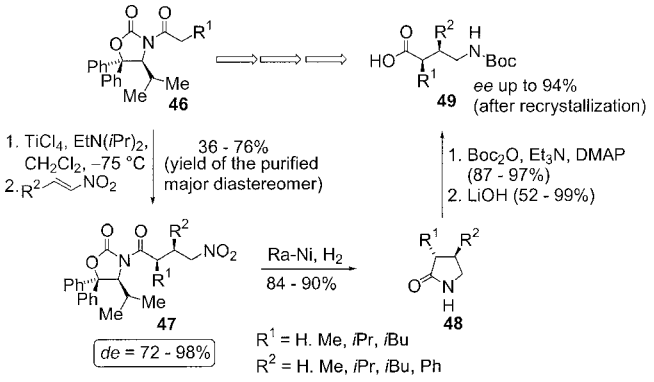
Schöllkopf and co-workers have explored the Michael addition of the bis(lactim ether) **43** of cyclo(−L-Val−Gly−) to nitro olefins.[27] The lithiated species of **43** gave only a moderate selectivity in the 1,4-addition, whereas the titanated bis(lactim ether) **44** provided excellent diastereomeric ratios in good yield (Scheme 14). Changing the titanated species from titanium tris(diethylamide) to titanium tris(isopropoxide) gave the Michael adducts in comparable yield with slightly lower inductions. Some of the products **45** were converted into α-amino-γ-nitro esters and upon hydrogenation to lactams. Also an oxazoline-containing amino acid ester was prepared by transformation of the nitro group into a nitrile oxide, followed by a dipolar cycloaddition and hydrolysis.



Scheme 14

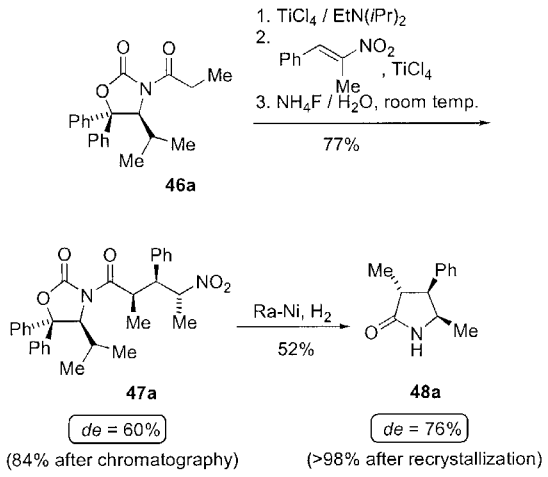
Seebach and co-workers[28] reported on the asymmetric Michael addition of enolates derived from acyloxazolidinones to various aliphatic and aromatic nitro olefins, and the application of this reaction as the key step in the synthesis of differently substituted pharmacologically active γ-lactams and γ-amino acid derivatives[29] (Scheme 15). The

best results concerning the stereoselectivity were obtained using Ti enolates, prepared by treating **46** with $TiCl_4$ and Hünig's base. Subsequent addition of the nitroalkene and another equiv. of $TiCl_4$ yielded the Michael adducts **47** in good to excellent diastereomeric excess (72−98%). Separation of the diastereomers was possible in all cases by crystallization, giving the pure major diastereomer. Catalytic hydrogenation of the nitro derivatives **47** led directly to the γ-lactams **48**. The oxazolidinone auxiliary was cleaved off during the lactam formation and recovered in very good yield (95%). Some of the lactams were finally Boc-protected and subjected to ring opening to yield γ-amino acids **49**. Unfortunately, partial racemization occurred at this stage but the enantiomeric excess of the final products could be increased through recrystallization.



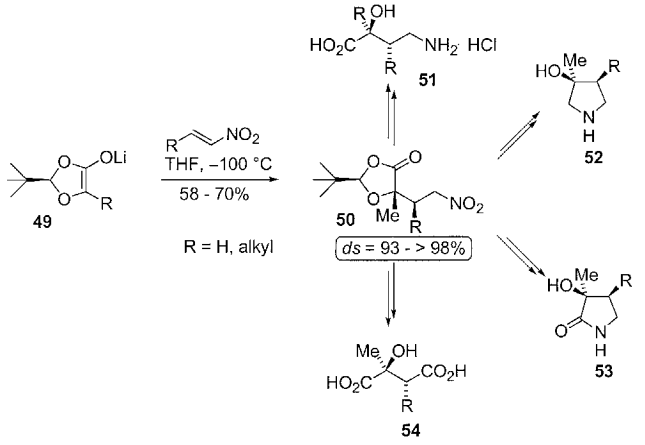
Scheme 15

A very interesting extension of this method involves the addition of the oxazolidinones **46a** to 1,2-disubstituted nitroethene derivatives[28] to generate **47a** and thus three stereogenic centers in a single step. In this process two stereocenters are formed by differentiation between the *Re* and *Si* faces of the enolate and the nitroalkene and the third one by diastereoselective protonation of the nitronate intermediate. Subsequent reduction and cyclization afforded the trisubstituted γ-lactam **48a** (Scheme 16).



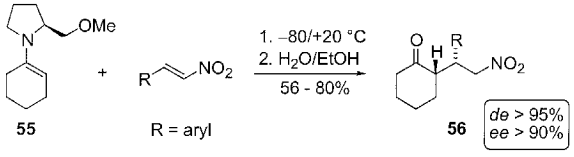
Scheme 16

Carboxylic acids derivatives with heteroatom substituents in α-position, such as hydroxy, amino or thio groups, represent valuable starting materials to build chiral lithium enolates, which can be used as nucleophiles in asymmetric conjugate additions to nitroalkenes. The addition of the dioxolano enolate **49** to nitroalkenes for example proceeded in good yields giving the addition products **50** in very high diastereomeric excesses as it was shown by Seebach and coworkers.[30] Taking advantage of the versatility of the nitro group, it was possible to convert the Michael adducts **50** into γ-aminobutyric acid **51**, pyrrolidine **52**, γ-lactam **53** and succinic acid derivatives **54** (Scheme 17). Very good results were also obtained with chiral enolates derived from α-amino acids.[30]



Scheme 17

Conjugate additions of the enantiopure cyclohexanone enamine **55** employing the (*S*)-methoxymethylpyrrolidine (SMP)[31a,31b] auxiliary to aromatic nitroalkenes are pioneering investigations in this field by Seebach's group.[31c,31d] The 1,4-addition proceeded in good yields and high diastereo- and enantioselectivity to afford the Michael adducts **56** (Scheme 18).

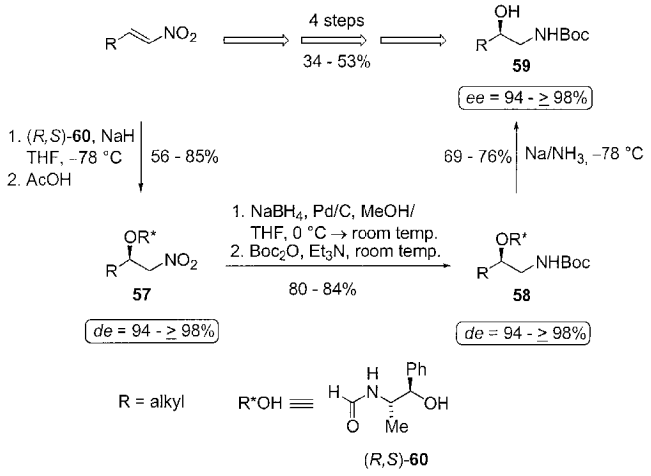


Scheme 18

3.2 Oxa Michael Addition to Nitroalkenes

Enantioenriched vicinal amino alcohols, easily available by oxa Michael addition to nitroalkenes and subsequent reduction of the nitro group, are valuable building blocks as auxiliaries, ligands for transition metal catalyzed reactions and for natural product synthesis.[32] In our group[33] we developed the first auxiliary-based asymmetric oxa Michael reaction using *N*-formylnorephedrine (*R*,*S*)-**60** as chiral hydroxide equivalent. Allowing the sodium salt of **60** to react with aliphatic nitroalkenes yielded the Michael adducts **57** in good yields and diastereomeric excesses, which

could be further increased in most cases by column chromatography (*de* = 94 to ≥ 98%). Reduction of the nitro group, Boc protection of the amine to afford **58** and cleavage of the ether bond provided the vicinal amino alcohols **59** without loss of stereochemical information (Scheme 19). Aromatic and α-substituted nitroalkenes gave generally lower yields and diastereoselectivities. The oxa Michael products were further applied in the synthesis of 2-amino-1,4-diols involving as key step inter- and intramolecular 1,3-dipolar cycloaddition reactions of a nitrile oxide to give the products in excellent diastereomeric and enantiomeric purity (*de*, *ee* ≥ 96%).[34]

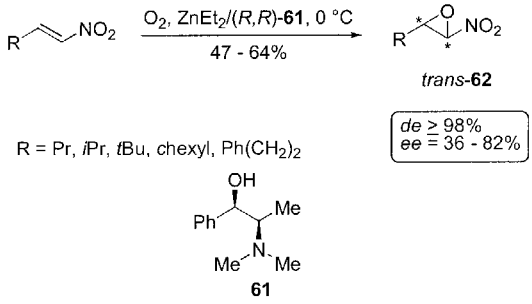


Scheme 19

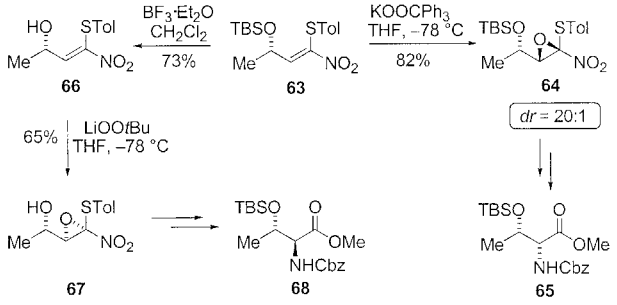
The epoxidation of nitroalkenes can be considered as an oxa Michael reaction as it involves a 1,4-addition of oxygen to the nitro olefin moiety. Our group reported an enantioselective zinc-mediated epoxidation of nitroalkenes using oxygen as oxidant.[35a]

Treatment of (*E*)-configured nitroalkenes with diethylzinc and oxygen in the presence of the enantiopure amino alcohol (*R*,*R*)-*N*-methylpseudoephedrine (**61**), which can be recycled after the reaction in virtually quantitative yield, provide the *trans*-oxiranes **62** in moderate yields, complete diastereoselectivity and good enantiomeric excesses (Scheme 20). The absolute configuration of the products remains to be determined but tentatively (2*R*,3*S*) was proposed based on related asymmetric epoxidations of enones.[35b][35c] Colonna and Juliá[36] have also reported an enantioselective epoxidation of nitroalkenes by utilizing $NaOH/H_2O_2$ in the presence of polypeptides but only very low enantiomeric excesses (up to 7%) were obtained.

Furthermore, the synthesis of enantiopure nitrooxiranes can also be achieved by diastereoselective epoxidation of chiral nitro olefins as is exemplified by the work of Jackson et al.[37] When they applied their methodology[37a] they accomplished efficient stereoselective syntheses of protected D-threonine **65** and L-*allo*-threonine **68**. The stereochemical outcome of the epoxidation can be controlled by the appropriate choice of substrate and oxidizing agent. Minimizing the coordination ability by using the TBS-protected substrate **63** and potassium triphenylmethyl peroxide as oxidizing agent gives via the *anti*-oxirane **64** (*dr* = 20:1) the protected D-threonine ester **65** in good overall yield. On the other hand, maximizing coordination abilities by using the unprotected alcohol **66** and lithium *tert*-butyl peroxide leads via the *syn*-oxirane **67** (single diastereomer) to the protected L-*allo*-threonine ester **68** (Scheme 21).



Scheme 20



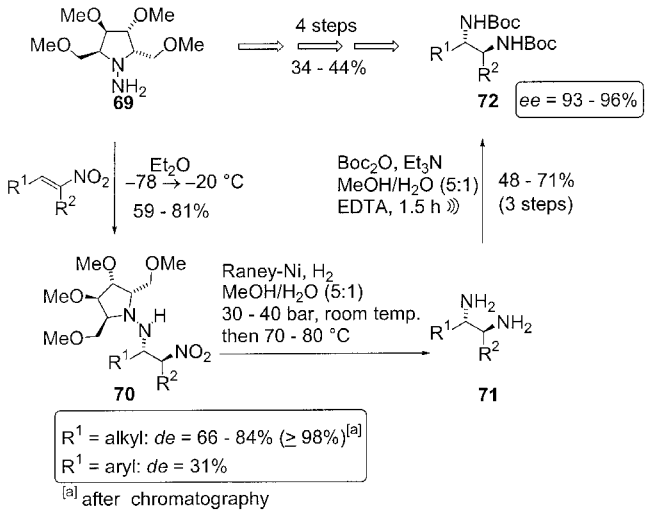
Scheme 21

3.3 Aza Michael Addition to Nitroalkenes

The 1,4-addition of chiral nitrogen nucleophiles to nitro olefins can provide vicinal diamines or α-amino acids depending on the transformation of the nitro group. Vicinal diamines are important building blocks in several natural products as well as chiral ligands in transition metal complexes and auxiliaries in asymmetric synthesis. Moreover, the high utility of an asymmetric synthesis leading to α-amino acids is evident due to their biological activity and application e.g. in peptide synthesis.

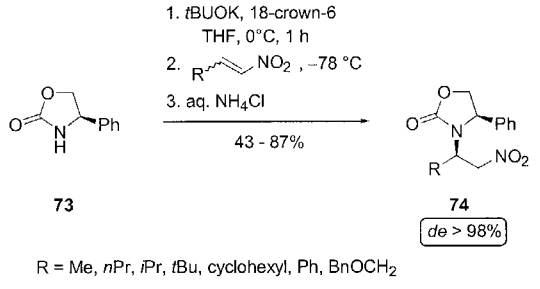
Recently, our group reported an auxiliary-controlled diastereo- and enantioselective synthesis of 1,2-diamines by an aza Michael reaction applying (−)-(2*S*,3*R*,4*R*,5*S*)-1-amino-3,4-dimethoxy-2,5-bis(methoxymethyl)pyrrolidine (ADMP) (**69**) as a chiral equivalent of ammonia (Scheme 22).[38] Allowing ADMP to react with nitroalkenes provided the Michael adducts **70** in good yields and diastereoselectivities. In nearly all cases, purification of the crude product by column chromatography using deactivated silica gel resulted in the separation of the major diastereomer thus increasing the diastereomeric excesses to ≥ 98%. Reduction of the nitro group and removal of the auxiliary gave the vicinal diamines **71**. Subsequent Boc protection of **71** provided the desired products **72** in good overall yield. All steps were performed without isolation of the intermediates and since

the last sequence caused only little racemization, excellent enantioselectivities were obtained.



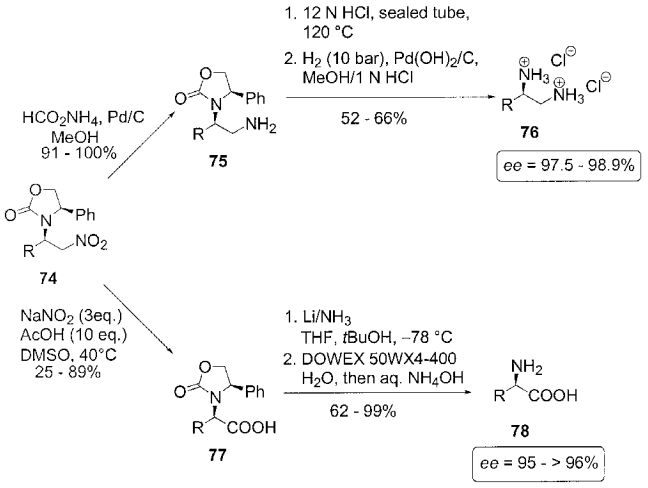
Scheme 22

Recently, Lucent et al.[39] have used the potassium salt of (*R*)- and (*S*)-4-phenyl-2-oxazolidinone (**73**) as enantiopure nucleophile in the aza Michael reaction. Deprotonation of **73** with *t*BuOK in the presence of 18-crown-6 provided the 1,4-adducts **74** in good yield as a single diastereomer regardless of which enantiomer of the oxazolidinone was used. Interestingly, when (*E*)/(*Z*) mixtures of nitroalkenes were applied, a single product was still obtained (Scheme 23).



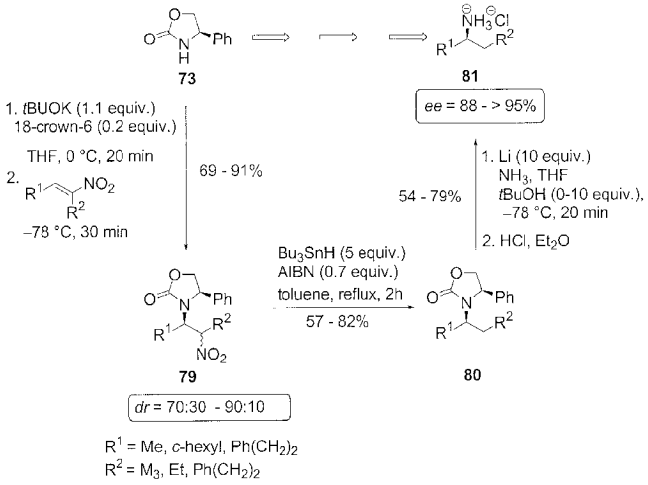
Scheme 23

The resulting conjugate addition products **74** were then converted into the corresponding diamino salts **76** or α-amino acids **78**. Reduction of the nitro group of **74** afforded the diamine **75**, which was treated with 12 N HCl and subjected to catalytic hydrogenation under acidic conditions to give **76** as hydrochloride salts with high *ee*. On the other hand, the α-amino acids **78** were prepared in high enantiomeric purity by oxidation and Birch reduction of the intermediate **77** (Scheme 24).[39] This methodology was applied to the synthesis of natural D-dethiobiotin and its three diastereomers.[40]



Scheme 24

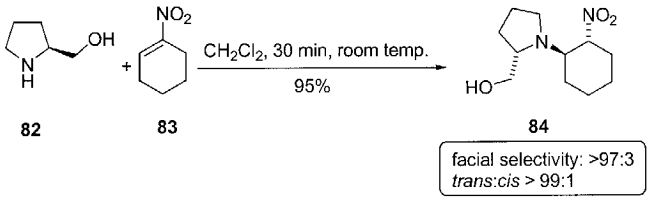
Very recently, the same group[41] expanded its methodology to the asymmetric synthesis of α,α-disubstituted amines by a three-step sequence, which commences with the 1,4-addition of the potassium salt of 4-phenyloxazolidin-2-one (**73**) to disubstituted nitroalkenes to give a mixture of epimers **79** in good yield. Removal of the nitro group by a radical-mediated reaction provides the diastereomerically pure products **80**. Finally, after cleavage of the oxazolidinone ring, the desired products **81** were isolated as their hydrochloride salts (Scheme 25).



Scheme 25

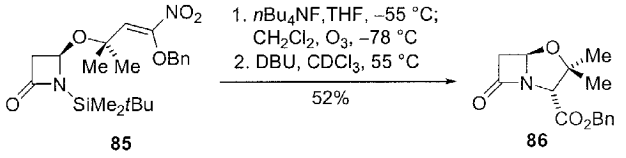
Addition of chiral amines to nitroalkenes was investigated by Morris and Sturgess.[42] Best results were obtained when (*S*)-prolinol (**82**) was used as a nucleophile in the reaction with 1-nitrocyclohexene (**83**) giving the 1,4-product **84**

in a short reaction time with high yield and facial selectivity (Scheme 26).



Scheme 26

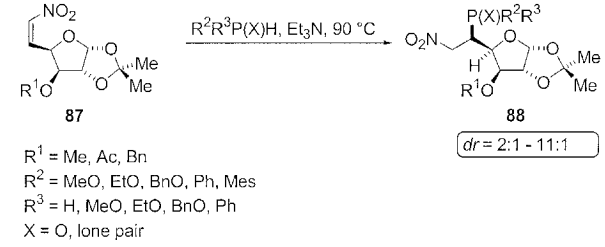
An intramolecular variant of the aza Michael reaction was used by Shibyua et al.[43] in the construction of 2,2-dimethyl-1-carbapenam. The approach has been adapted by Barrett and co-workers to the synthesis of the oxapenam **86**.[44] Treatment of **85** with TBAF resulted in deprotection and cyclization which was followed by ozonolysis in situ to afford the oxapenams as a mixture of diastereomers (1:1). Furthermore, epimerization with DBU gave exclusively the *exo* isomer (Scheme 27). The approach has further been used in the total syntheses of penicillanic acid *S*,*S*-dioxide and 6-aminopenicillanic acid.[45]



Scheme 27

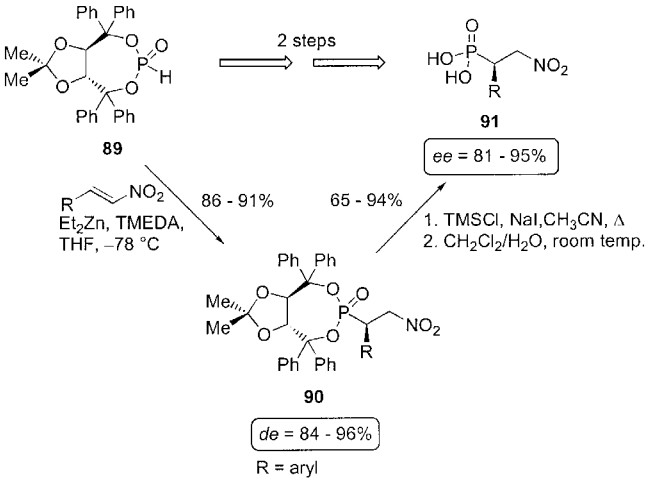
3.4 Phospha Michael Addition to Nitroalkenes

Phosphonates bearing a heteroatom at the α- or β-position are known to possess significant biological activity as antibiotics, antitumor drugs, herbicides and enzyme inhibitors.[46] Moreover, aminophosphonic acids are of special interest. Michael addition of phosphanes to chiral, sugar-derived unsaturated nitro compounds have been reported.[47] Yamashita et al.[47a] achieved stereoselectivities up to 11:1 in the reaction between different phosphorus nucleophiles and the nitro sugars **87** to give the 1,4-addition products **88** (Scheme 28).



Scheme 28

Recently, we developed the first auxiliary-controlled phospha Michael addition to aromatic nitroalkenes using TADDOL as chiral auxiliary.[48] The enantiopure phosphite **89** was allowed to react in the presence of diethylzinc and TMEDA with nitroalkenes to give the 1,4-adducts **90** in high yield and diastereomeric excesses. Removal of the chiral auxiliary could be achieved racemization-free providing the α-substituted γ-nitrophosphonic acids with high *ee*. The obtained products are valuable bifunctional building blocks and constitute precursors of β-aminophosphonic acids (Scheme 29). In the case of aliphatic nitroalkenes excellent yields were obtained (85−95%), but the induction remained unsatisfactory.



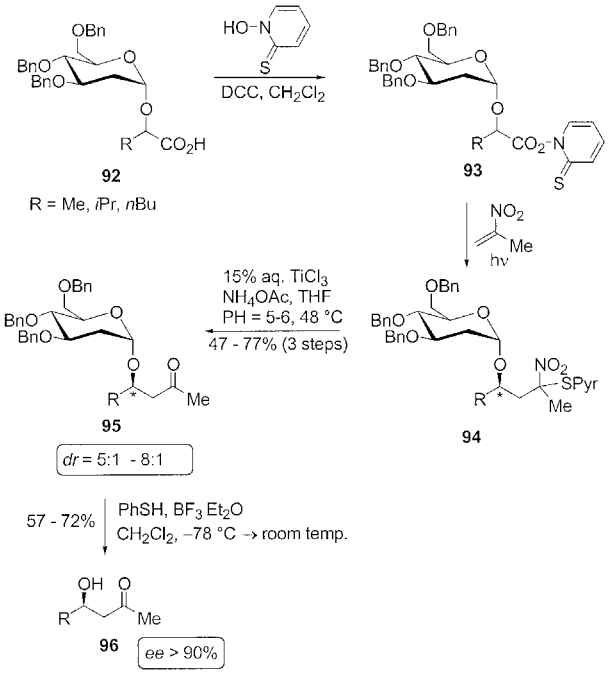
Scheme 29

3.5 Radical Michael Addition to Nitroalkenes

A radical approach to the 1,4-addition to nitro olefins has been pioneered by Barton and co-workers,[49] which was used in an asymmetric aldol synthesis by Garner et al.[50] Esterification of **92** with *N*-hydroxy-2-thiopyridone to yield **93** was followed by the free-radical reaction with 2-nitropropene to give **94**. The subsequent Nef reaction afforded the products **95** in very good overall yield. The diastereoselectivity of the radical reaction showed temperature dependence and by lowering the temperature to −100 °C diastereoselectivities up to 8:1 could be obtained. Finally, glycoside cleavage of compounds **95** after diastereomeric enrichment by flash chromatography released the (*R*)-configured free aldols **96** with an *ee* > 90% (Scheme 30). Recently, Garner and Anderson obtained diastereomeric ratios up to 35:1 at −78 °C through appropriate modifications to the chiral auxiliary.[51] In addition, Hanessian and co-workers applied the Barton reaction to synthesize functionalized carbapenem precursors.[52]

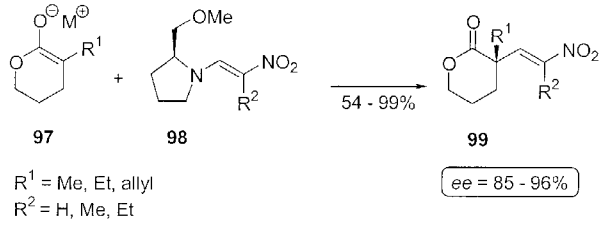
3.6 Addition-Elimination Processes Involving Chiral Leaving Groups

The construction of quaternary carbon stereocenters[53] is of interest as many natural products possess such moieties. The addition-elimination process involving 1,4-addition to an optically active nitroalkene, followed by elimination of the enantiopure leaving group, is a convenient method to produce tetrasubstituted centers. It directly leads to a chiral product avoiding the cleavage of an auxiliary at a later stage. Fuji and co-workers[54] developed an efficient



Scheme 30

method to synthesize enantioenriched α-disubstituted δ-valerolactones in high enantiomeric excesses (Scheme 31). The best results were obtained when Zn^{2+} was used as a counterion for the enolate. In terms of *ee* the substituted nitro enamines gave better results. Extension of this methodology to α-substituted ketones, esters and amides proceeded but failed to give high asymmetric induction.



Scheme 31

As the previous procedure provided only moderate enantioselectivities in the case of γ-butyrolactones further optimizations were undertaken. It was found that by increasing the steric bulk at either R^1 [55] or R^2 [56] of the chiral nitro enamines **100** significantly higher inductions were obtained (Figure 2).

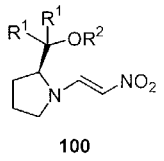
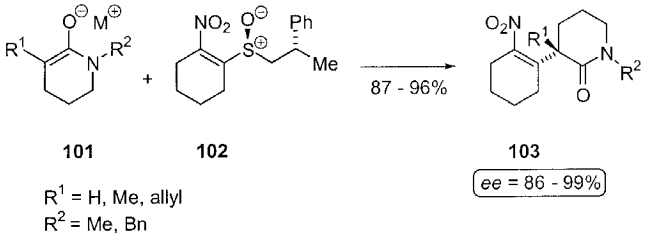


Figure 2. Differently substituted nitro enamines

Fuji and co-workers[57] extended their addition-elimination strategy by using the chiral sulfoxide **102** as a leaving group instead of an amine (Scheme 32). Again, the best results were obtained with zinc enolates of δ-lactams **101** (M^+ = Zn), which afforded nitrolactams **103** as addition-elimination products. γ-Lactams gave the Michael adducts in comparable yield but lower *ee* values, whereas various ketones, lactones and esters underwent the conjugate addition in good yield but poor *ee*. The absolute configuration of the products were determined by conversion into a known natural product.[58]

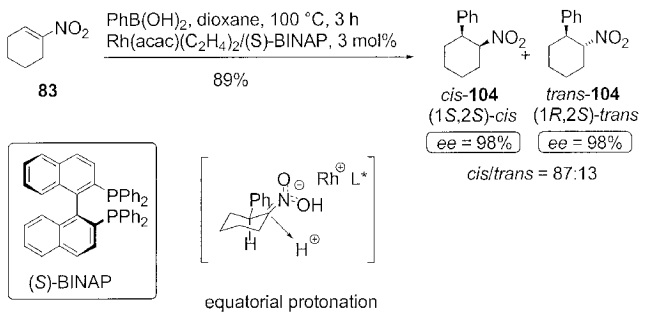


Scheme 32

4. Asymmetric Michael Additions to Nitroalkenes Employing Enantiopure Additives or Catalysts

In addition to auxiliary-based methods, various enantioselective 1,4-additions to nitroalkenes have been described employing stoichiometric amounts of enantiopure additives or substoichiometric quantities of enantiopure catalysts.

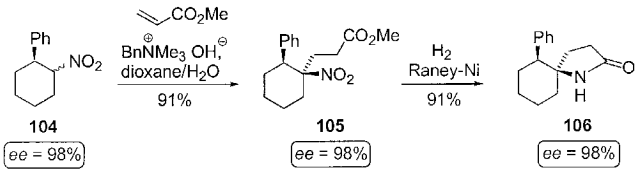
Hayashi and co-workers[59] found that 1-nitroalkenes undergo a rhodium-catalyzed 1,4-addition of boronic acids. The asymmetric reaction of phenylboronic acid with 1-nitrocyclohexene (**83**) in the presence of the rhodium/(*S*)-BINAP catalyst proceeded with high enantioselectivity and high diastereoselectivity giving preferentially the thermodynamically less stable *cis* isomer **104** (*cis*/*trans* = 87:13) in 89% yield. Both *cis* and *trans* diastereoisomers **104** were of high enantiomeric purity (*ee* = 98%). The preferential formation of *cis*-**104** may indicate an equatorial protonation of the rhodium nitronate intermediate in the catalytic cycle (Scheme 33).



Scheme 33

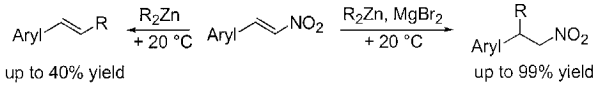
The resulting chiral nitroalkanes **104** could be readily converted into a variety of optically active compounds by taking advantage of the versatile reactivity of the nitro

group. The synthesis of the spirolactam **106** (Scheme 34) via the intermediate **105** represents an elegant application.



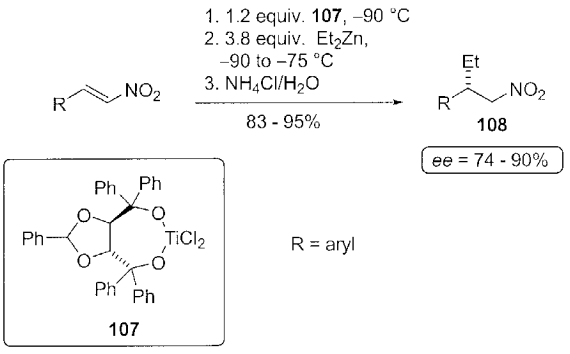
Scheme 34

Probably the most investigated conjugate addition to nitroalkenes is the addition of dialkylzinc reagents. It was first noted by Seebach and Schäfer[60] that, surprisingly, the direct reaction of dialkylzinc compounds with nitroalkenes proceeds with replacement of the nitro group, although nitroalkenes are the strongest Michael acceptors. Only in the presence of Lewis acids such as $MgBr_2$ a 1,4-addition takes place (Scheme 35).



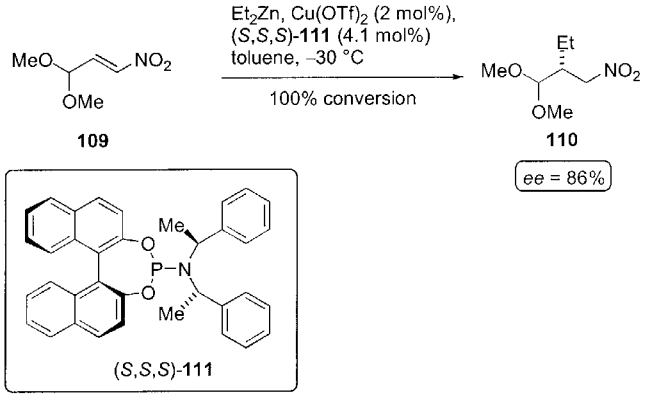
Scheme 35

The same group[60] showed that a 1,4-addition can also be induced by transition metal complexes. The chiral Ti-TADDOLate **107**, for example, mediates the enantioselective addition of diethylzinc to aromatic nitroalkenes to afford Michael adducts **108** in very high yields and high enantiomeric excesses (Scheme 36).



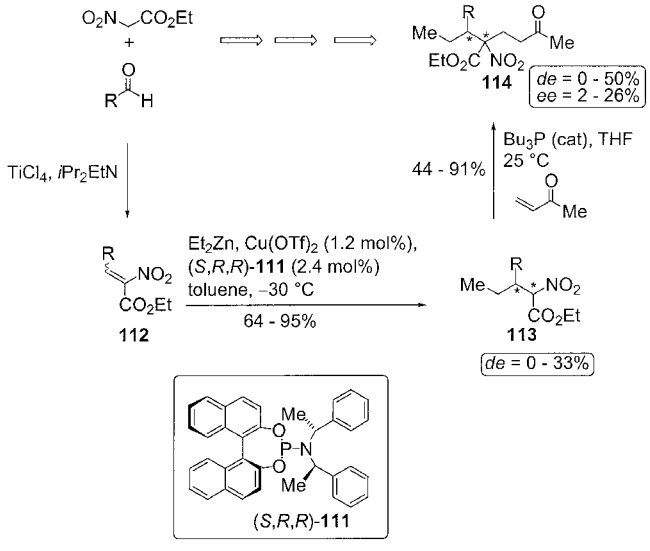
Scheme 36

Sewald and Wendisch [61] reported a catalytic enantioselective conjugate addition of Et_2Zn to the nitroalkene **109**. By employing the binaphthol-based homochiral copper phosphoramidite complex (*S*,*S*,*S*)-**111**, originally developed by Feringa et al.[62] for the addition of Et_2Zn to cyclic enones, it was possible to obtain **110** in quantitative yield and with high enantiomeric excess. The extension of the method to nitrostyrene resulted in good conversion (90%) but only moderate enantiomeric excesses (*ee* = 48%, Scheme 37).



Scheme 37

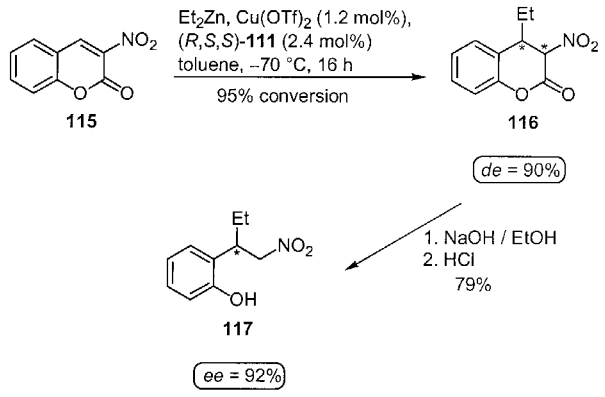
The diastereomeric ligand (*S*,*R*,*R*)-**111** was applied by Feringa et al.[63] to the conjugate addition of Et_2Zn to unsaturated nitroacetates **112**,[64] which can be considered as precursors of α-amino acids. The resulting β-substituted nitroacetates **113** were obtained in excellent yields but with a near 1:1 diastereomeric ratio, probably due to the fact that the reaction was performed on (*E*)/(*Z*) mixtures of nitroacetates. The addition products were then subjected to a second Michael addition to methyl vinyl ketone to give the quaternary nitroacetates **114** in moderate enantiomeric excesses (Scheme 38). Surprisingly, a complete lack of enantioselectivity was observed in the conjugate addition of Et_2Zn to isomerically pure (*Z*)-**112**. This was attributed to the unfavourable interaction of the *cis*-oriented aryl and nitro group for the formation of a productive catalyst–substrate complex.



Scheme 38

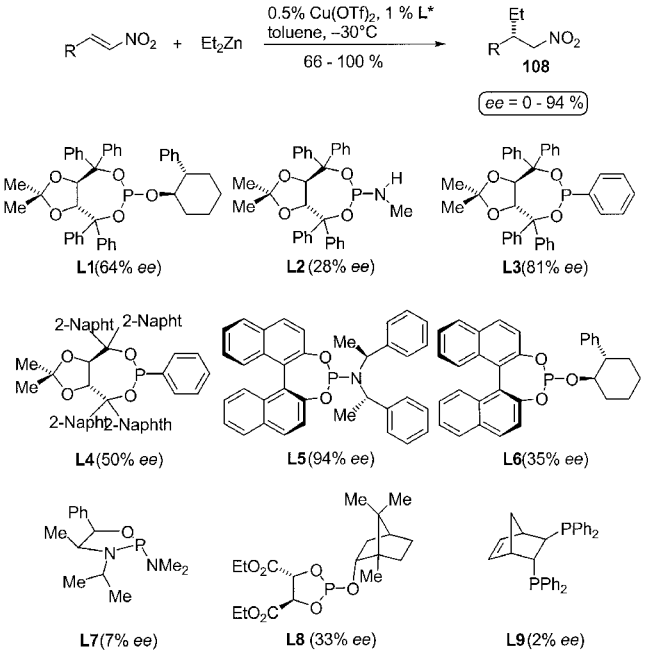
In case of the *cis*-oriented nitrocoumarine **115** asymmetric addition of Et_2Zn followed by hydrolysis with ring open-

ing of the addition product **116** led to the (−)-nitrophenol **117** in very high enantiomeric excess (Scheme 39).



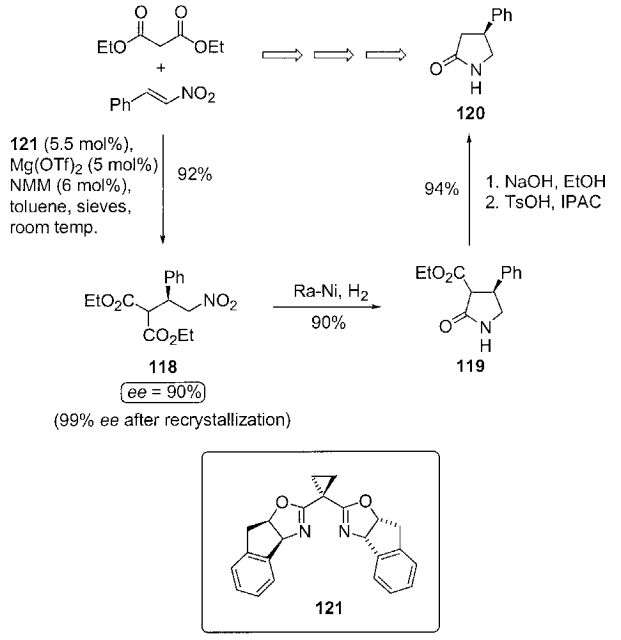
Scheme 39

Alexakis and co-workers[65] tested a whole series of ligands for the addition of Et_2Zn to several nitroalkenes, most of them based on TADDOL or binaphthol. As little as 0.5% of copper salt and 1% trivalent phosphorus ligand were needed to give **108** in high yields and although Feringa's ligand **L5** remained the ligand of choice for this reaction, it was still possible to improve Sewald's results up to 92% *ee* for the addition to β-nitrostyrene by performing the reaction under higher dilution (Scheme 40).



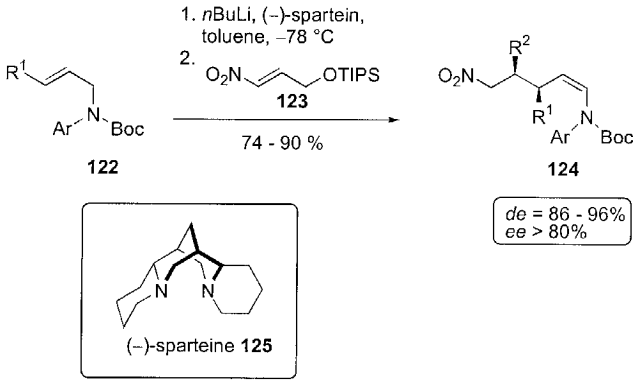
Scheme 40

In order to obtain highly functionalized derivatives, enantioselective catalytic conjugate additions of oxo esters and malonates to nitroalkenes have been developed. The first example was reported by Barnes et al.,[66] who made use of bis(oxazoline) ligand **121** in the presence of $Mg(OTf)_2$. This reaction is catalytic in ligand−metal complex and employs an amine cocatalyst. Notably, in the absence of ligand, the reaction did not proceed. Particularly good selectivities were obtained in the case of malonates and they could be further improved through a single recrystallization to obtain the addition products **118** in enantiomerically pure form. In order to establish the sense of induction and to show the synthetic utility of the method, the γ-nitromalonate **118** was converted in three steps into the substituted pyrrolidinone **120** of known configuration by cyclization and subsequent deethoxycarbonylation of the intermediate **119** (Scheme 41).



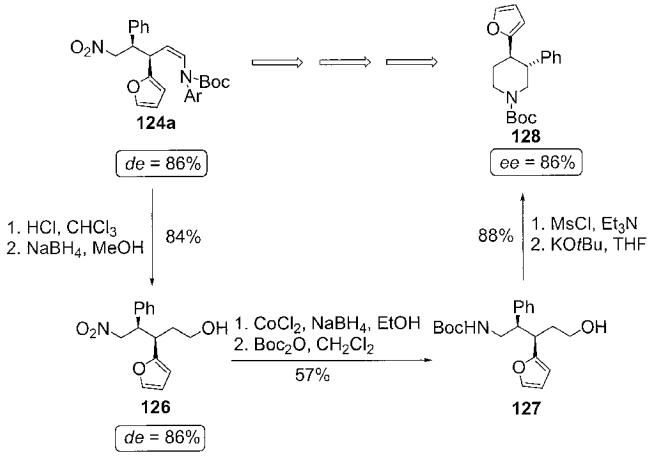
Scheme 41

The asymmetric conjugate addition of *N*-Boc-*N*-(*p*-methoxyphenyl)allylamines **122** to nitroalkenes proved to give efficient access to substituted six-membered rings such as piperidinones and piperidines, which are common structures in many natural and bioactive compounds.[67] Treatment of the *N*-protected allylamines **122** with *n*BuLi in the presence of (−)-sparteine (**125**) at −78 °C in toluene for 1 h generated a lithiated intermediate, which underwent conjugate addition to nitroalkene **123** to provide **124** in good yields and with high diastereo- and enantiomeric excesses (Scheme 42).



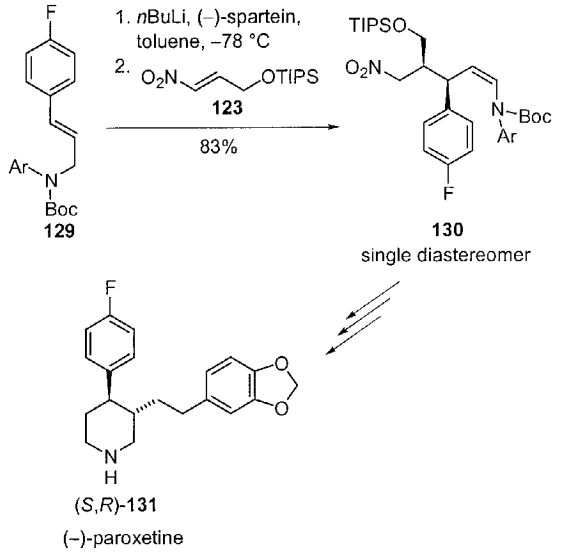
Scheme 42

The ene-carbamate **124a** was then hydrolyzed and reduced to provide the nitro alcohol **126**. Further reduction and Boc protection gave the Boc-amino alcohol **127**. Cyclization was achieved by mesylation and treatment with KO*t*Bu to provide the Boc-protected piperidine **128** in good yield and high *ee*. (Scheme 43)



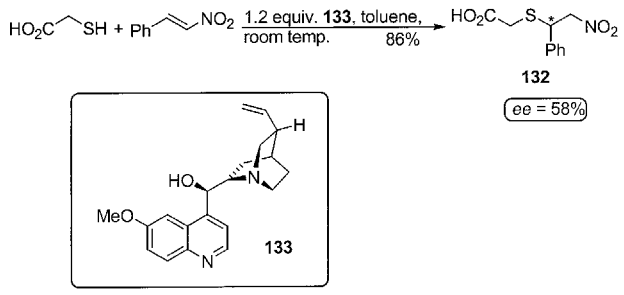
Scheme 43

This methodology was also applied to the synthesis of (−)-paroxetine **131**, a selective serotonin reuptake inhibitor (Scheme 44). The key step, which establishes the relative and absolute stereochemistry of the target molecule is the sparteine-mediated asymmetric Michael addition of **129** to the nitroalkene **123** to yield the intermediate **130**.



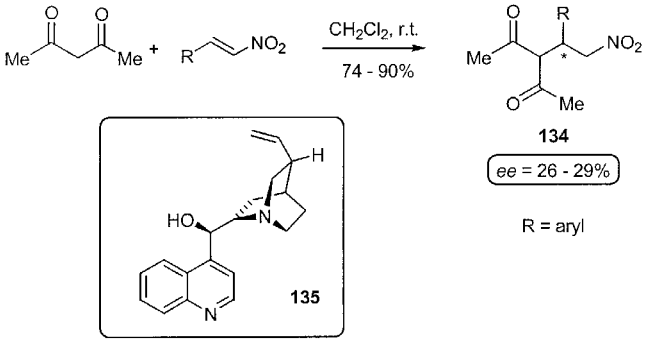
Scheme 44

A very early example of enantioselective conjugate addition based on chiral catalysts was reported by the group of Kobayashi.[68] In the presence of quinine (**133**) they were able to achieve the asymmetric Michael addition of thioglycolic acid to (*E*)-nitrostyrene. The reaction proceeded in very good yield, giving enantiomerically enriched **132**. The enantiomeric excess was determined through the optical rotation of **132** and based on the calculated rotation of the pure compound (Scheme 45). To the best of our knowledge this constitutes the only case of asymmetric Michael addition to nitroalkenes involving sulfur nucleophiles.



Scheme 45

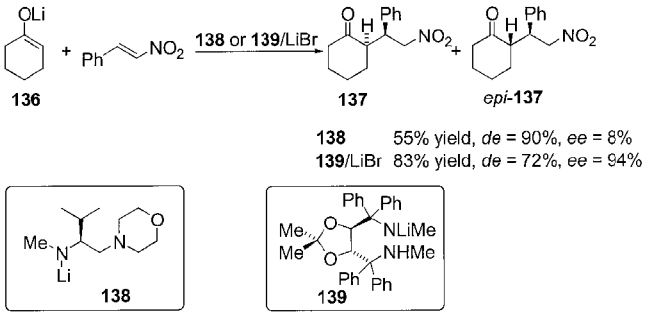
Cinchona alkaloids[69] exerted also some degree of stereocontrol in the conjugate addition of 1,3-dicarbonyl compounds to nitro olefins, although only moderate enantiomeric excesses of the products **134** were observed with cinchonidine **135** as a base catalyst (Scheme 46).[70]



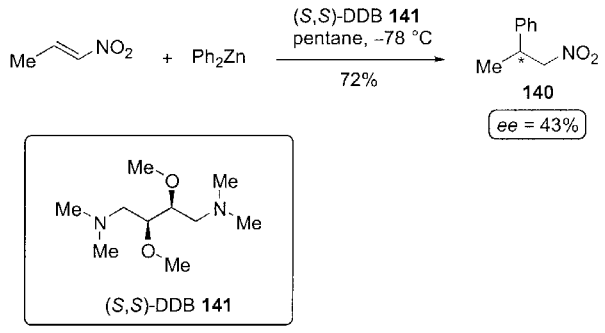
Scheme 46

The influence of chiral additives like amines or amides on the stereoselectivity of the Michael addition of enolates to nitroalkenes was demonstrated by Seebach et al.[71] in the addition of the lithium enolate **136** of cyclohexanone to (*E*)-nitrostyrene to give the 1,4-adducts **137** (Scheme 47). The best results were obtained with TADDAMIN (**139**) in the presence of 1 equiv. of LiBr. The application of [(*S*)-1-isopropyl-2-morpholinoethyl](methyl)amine (**138**) led to high diastereomeric excess, but the enantioselectivity of the reaction was very low. This reaction is based on the observation that temporary incorporation of chiral amines or lithium amides into achiral lithium aggregates through an interaction, which is simply broken during an aqueous workup, can lead to enantiomerically enriched products.

Among the different strategies which can be applied to achieve control of the enantioselectivity, the use of a chiral solvent is a very attractive possibility. In pioneering experiments it was shown[72] that the readily available C_2-symmetric 2,3-dimethoxy-1,4-bis(dimethylamino)butane (*S*,*S*)-DDB (**141**), used as a cosolvent in a 1:1 ratio with pentane, was responsible for the enantioselective addition of Ph_2Zn to nitropropene. The reaction proceeds in good yield giving an enantiomerically enriched product **140** (Scheme 48).

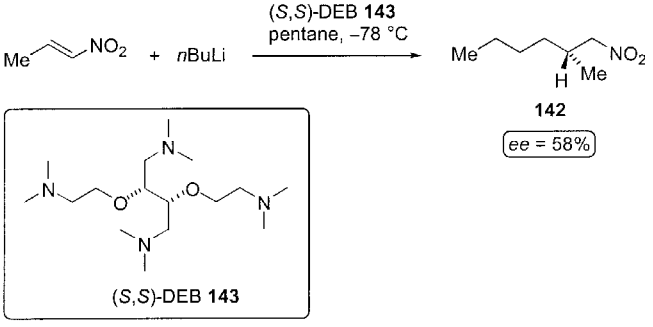


Scheme 47



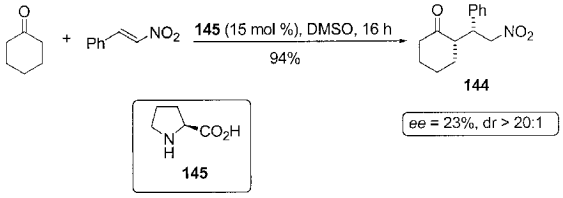
Scheme 48

In search for new chiral solvents and complexing reagents Seebach and co-workers[73] increased the number of heteroatoms in DDB (**141**) in order to obtain more stable complexes with multidentate ligands. The resulting (*S*,*S*)-DEB (**143**), prepared from *N*,*N*,*N*′,*N*′-tetramethyl-2,3-bis(methoxycarbonyl)succinamide and dimethylamine, and subsequent reduction was used in a 2:1 ratio with pentane in the addition of *n*BuLi to (*E*)-nitropropene yielding 2-methyl-1-nitrohexane (**142**) in 58% enantiomeric excess (Scheme 49).



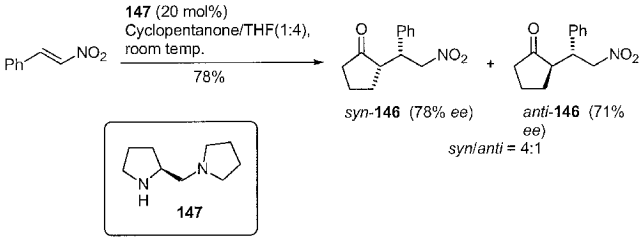
Scheme 49

Among the reactions which employ small organic molecules as catalysts, proline-catalyzed conjugate additions have gained considerable attention. They can proceed through iminium or enamine catalysis. A first asymmetric example involving nitroalkenes, although with only modest enantioselectivity, was reported by List et al.[74] Symmetrically substituted ketones such as acetone or cyclohexanone were treated with (*E*)-nitrostyrene in the presence of (*S*)-proline (**145**) to give the corresponding nitro ketones such as **144** (Scheme 50). The reaction was conducted in DMSO as a solvent and proceeded with very good yield but virtually no selectivity in the case of acetone (*ee* = 7%) or only modest enantioselectivity in the case of cyclohexanone (*ee* = 23%).



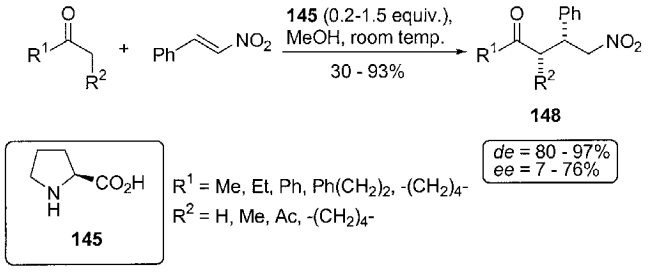
Scheme 50

This enantioselective addition followed a report by Barbas III and co-workers,[75] who also made use of L-proline (**145**) as a catalyst in the addition of acetone to (*E*)-nitrostyrene in DMSO, but could only obtain racemic products. In a subsequent paper[76] the same group investigated the addition of cyclopentanone to (*E*)-nitrostyrene catalysed by (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (**147**). The addition products **146** were obtained in good yield and a *syn*/*anti* ratio of 4:1, with the highest enantiomeric excess for the *syn* diastereomer (Scheme 51).



Scheme 51

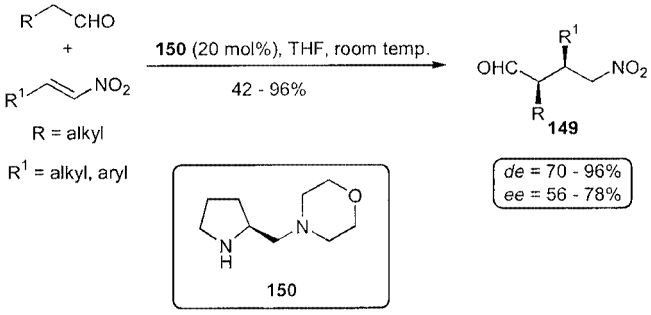
The best results in the proline-catalyzed addition of ketones to (*E*)-nitrostyrene up to now have been achieved by our group,[77] employing small amounts of methanol to improve the solubility of proline (**145**) and increase the diastereo- and enantioselectivity of the conjugate addition products **148** (Scheme 52).



Scheme 52

Finally, in a very recent report, Barbas III and co-workers[78] performed an extended screening of L-proline-based catalysts for the addition of aldehydes to aromatic and aliphatic nitroalkenes, obtaining the best results with the morpholine derivative (*S*)-**150**. The reaction proceeded in good yields to give the *syn* diastereomer **149** as a major

product in moderate to good enantioselectivities (Scheme 53).



Scheme 53

5. Applications to the Synthesis of Natural and Biologically Active Products

In this section some applications of asymmetric Michael addition to nitro olefins will be presented. The list is not intended to be comprehensive but rather to show representative examples in the synthesis of pharmacologically interesting compounds as well as natural products.[79]

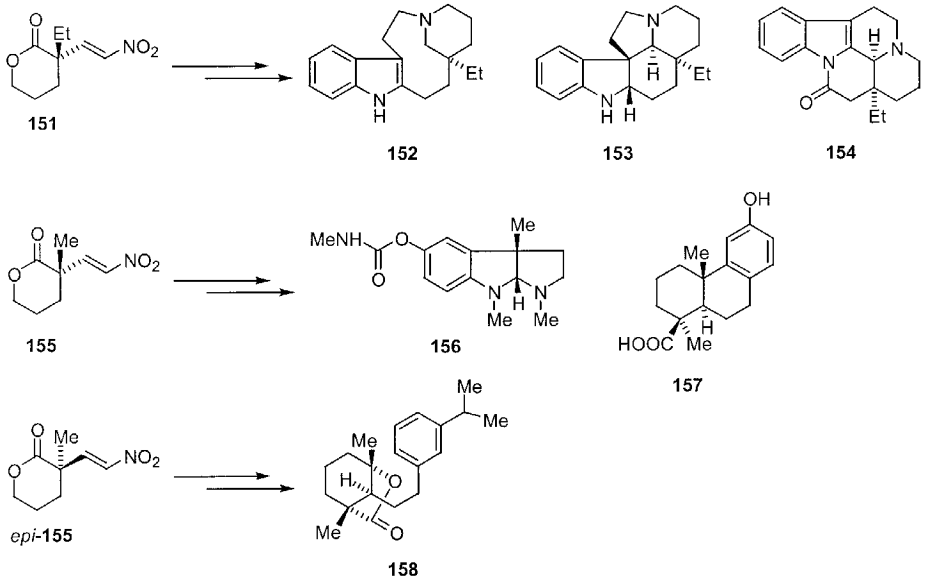
The group of Fuji[80] has elegantly utilized their methodology of creating chiral quaternary carbon centers by an addition-elimination process to produce optically active nitroalkenes in the total synthesis of natural products (Scheme 54). The resulting nitro compounds **151** and **155** were used as key building blocks to synthesize a multitude of natural products, which include the pharmacologically interesting indole alkaloids (+)-quebrachamine (**152**), (−)-aspidospermidine (**153**), and (−)-eburnamonine (**154**).[81] Furthermore, the principle alkaloid of calabar bean, (−)-physostigmine (**156**),[82] as well as different diterpenoids such as **158**[83] and (+)-podocarpic acid **157**[84] were synthesized by this method.

Fuji and co-workers have further applied this technique to the synthesis of oxindole alkaloids. After optimization of the nitro enamine structure **160**, determining the appropriate protecting group for the oxindole nitrogen atom, as well as the reaction conditions, the total synthesis of (−)-pseudophrynaminol (**162**) and (−)-horsfiline (**164**) could be achieved in high enantiomeric purity. The key intermediates **161** and **163** were obtained by addition-elimination reaction of **159a**−**b** to nitro enamine **160** (Scheme 55).[85,86]

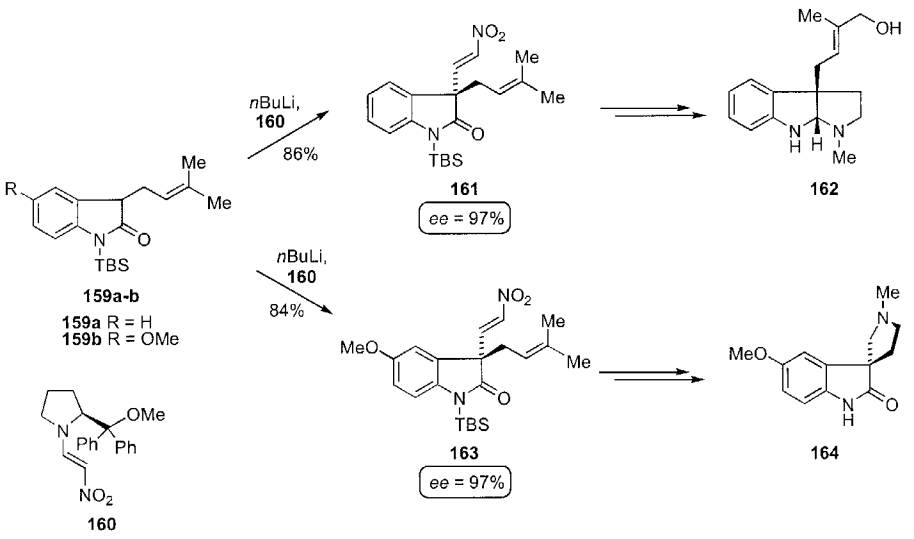
Asymmetric conjugate addition of acylated oxazolidinones to nitroalkenes has been frequently applied in the synthesis of pharmacological interesting products. Mulzer and co-workers[87] used this approach to prepare the antidepressant rolipram (**169**). The addition of the sodium enolate of the oxazolidinone **165** to **166** gave the Michael product **167** with good diastereoselectivity (94:6), which could be increased to > 99% by a recrystallization in 65% yield. Reduction of the nitro group, followed by intramolecular cyclization, gave **168**. Finally, *O*-alkylation of the phenolate with cyclopentyl bromide afforded the target compound **169** in 60% yield (Scheme 56).

Recently, the H_3 agonist Sch 50971 (**173**) was prepared by applying as a key step the 1,4-addition of oxazolidinone **170** to nitroalkene **171** to generate the precursor **172**.[88] After optimization of transition metal, ligand stoichiometry, temperature and solvent conditions a diastereomeric excess of 88% in 77% yield was achieved, which could be further increased by recrystallization to 91% (Scheme 57).

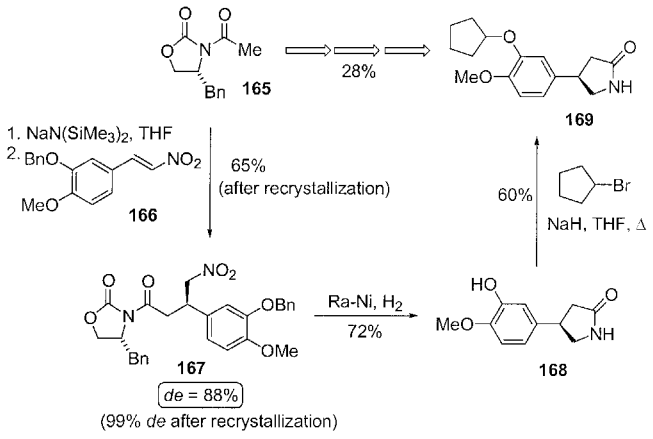
Recently, Mulzer and Riether have applied the 1,4-addition of ethyl acetate to compound **174** in the synthesis of the D-ring fragment **176** of cobyric acid. The diastereomeric ratio of the reaction product **175** was 86:14 (Scheme 58).[89]



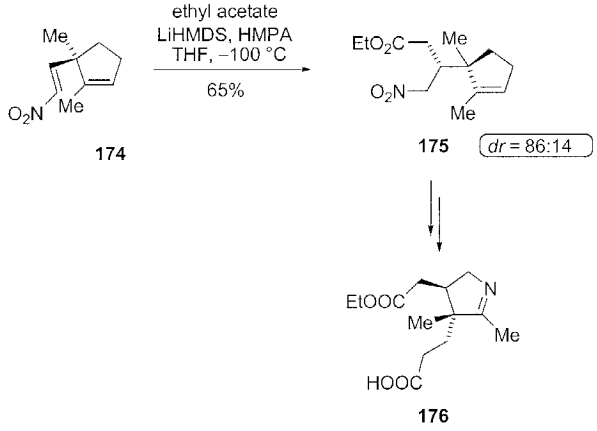
Scheme 54



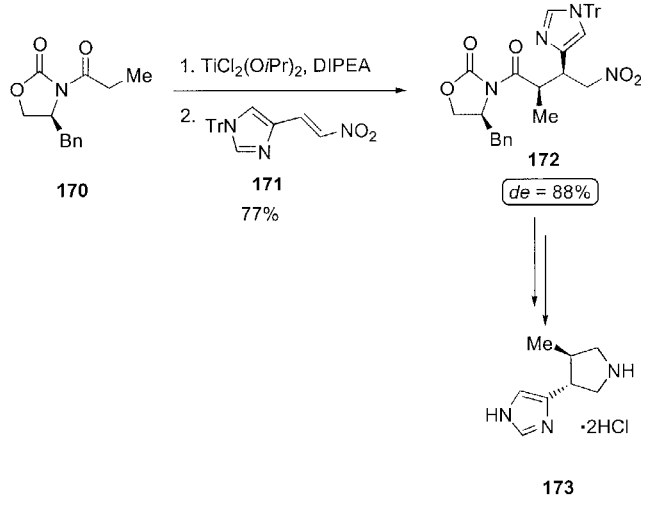
Scheme 55



Scheme 56



Scheme 58



Scheme 57

6. Conclusion

The asymmetric Michael addition to nitroalkenes provides an efficient way to synthesize enantioenriched, highly functionalized synthetic building blocks. The high degree of stereocontrol that can be achieved in conjugate additions to nitroalkenes has been thoroughly shown by substrate-, auxiliary- and additive-controlled reactions as well as catalytic versions. The enormous versatility of the nitro group, the high reactivity of nitroalkenes and their good availability make them ideal starting materials for the construction of complex, polyfunctional molecules, which would be difficult to obtain so easily by other known methods.

Acknowledgments

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AG, BASF AG, Bayer AG, Wacker Chemie and the former Hoechst AG for the donation of chemicals.

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