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The SAMP-/RAMP-hydrazone methodology in asymmetric synthesis

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1. Introduction

The formation of carbon–carbon or carbon–heteroatom bonds adjacent to a carbonyl group in a regio-, diastereo- and enantioselective manner is one of the most important procedures in organic synthesis. While the classical carbonyl enolate chemistry is usually accompanied by the problem of side reactions, the imine derivatives give better

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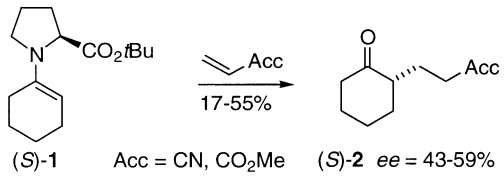
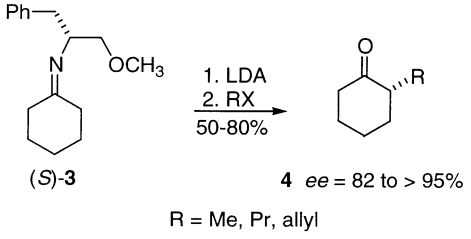


Scheme 1.

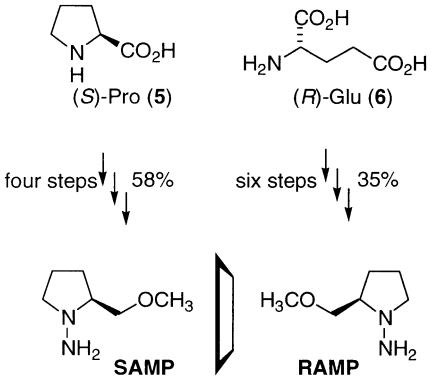
yields and selectivities.[1] The first asymmetric synthesis via enamine chemistry based on an (*S*)-proline-derived auxiliary was published by Yamada et al. in 1969 (Scheme 1).[2] The enantiomeric excesses for the reaction of the enamine (*S*)-**1** with Michael acceptors to afford the 1,4-adducts (*S*)-**2** were moderate.

A further early example of the use of proline in asymmetric synthesis is the Eder–Sauer–Wiechert–Hajos-reaction[3] affording up to 93% ee in cyclisation reactions to form steroid building blocks. The alkylation of metallated azaenolates with an acyclic amino acid-based auxiliary reported by Meyers in 1976 gave good results in alkylation reactions of cyclohexanone (**3→4**, Scheme 2).[4] During this time, other azaenolate equivalents, the dimethylhydrazones (DMHs), proved to be a powerful tool in organic synthesis.[5] Compared with the free carbonyl compounds the DMHs are more reactive and show higher regio- and stereoselectivity. Cleavage of the hydrazone moiety to regenerate the carbonyl functionality is possible under various mild conditions, even at pH 7.[6]

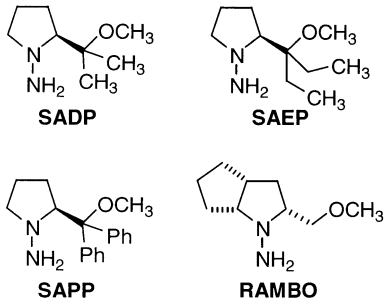
The combination of the useful hydrazone technique with a cyclic amino acid derivative resulted in the now widely used auxiliary, (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP), introduced in 1976 by our group.[7,8] Starting from (*S*)-proline (**5**), the auxiliary SAMP is available in a



Scheme 2.



Scheme 3.



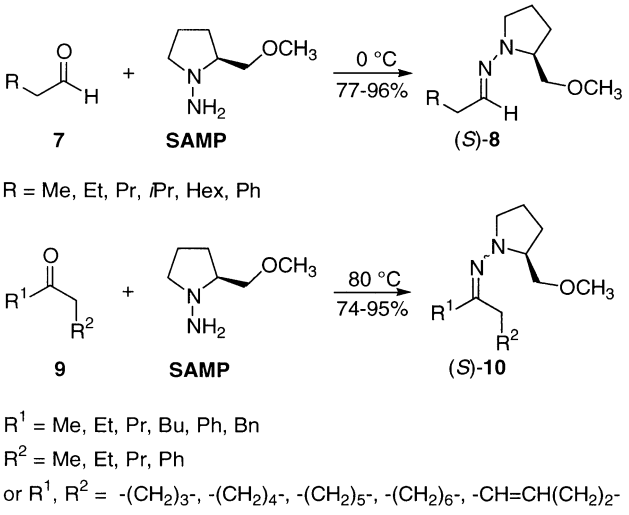
Scheme 4.

four-step procedure with 58% yield, while the (*R*)-enantiomer (RAMP) is obtained in six steps in 35% yield from (*R*)-glutamic acid (**6**, Scheme 3).[9] The enantiomeric purity of SAMP or RAMP can be controlled by measurement of the optical rotation or alternatively by GC measurement of the urea derivatives of the hydrazines on a chiral stationary phase.[10]

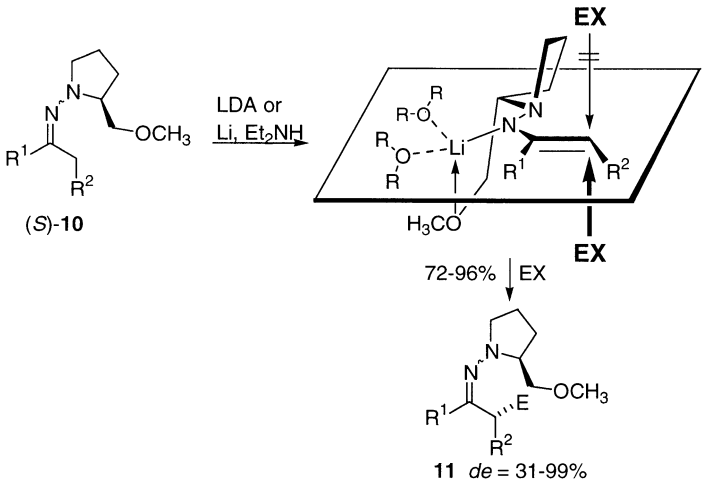
The possibly toxic nitrosamine, 1-nitroso-2-methoxymethylpyrrolidine, an intermediate in the reaction sequence, can be avoided by applying the Hofmann degradation reaction of a urea derivative.[11] If more steric demand of the auxiliary is needed, the SAMP analogues, SADP, SAEP and SAPP (Scheme 4), can be generated in a seven-step sequence.[12] The even more sterically-demanding derivative RAMBO can be prepared from the corresponding amino acid derivative according to the usual SAMP-protocol.[13,14]

The chiral hydrazones are easily obtained by mixing SAMP or its analogues and the carbonyl compound under water separation conditions. With the aldehydes (**7**), the reaction runs at 0°C without any solvent, while the ketones (**9**) have to be refluxed with catalytic amounts of acid in benzene or cyclohexane using a Dean and Stark separator (Scheme 5).[9] The hydrazones **8** and **10** can be purified by distillation or chromatography, although purification is often unnecessary, and they can be stored at −20°C under an inert atmosphere without decomposition.

Deprotonation of SAMP-hydrazones by means of lithium



Scheme 5.

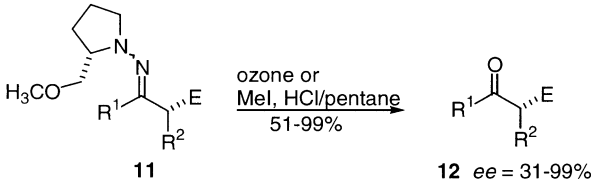


R^1 = H, Me, Et, Pr; R^2 = Me, Et, Pr, *i*Pr, Hex, Ph
and R^1, R^2 = -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -CH=CH$(CH_2)_2$-
R = Et, -$(CH_2)_4$-
E = Me, Et, Pr, Bn, allyl
X = Br, I

Scheme 6.

diisopropylamide or other lithium bases results in azaenolates that can be trapped by electrophiles to obtain diastereomerically enriched compounds. In the deprotonation step, four geometrical isomers can theoretically be generated. Investigations concerning the *E*/*Z*-geometry showed that deprotonation with lithium diisopropylamide in both cyclic ketones and more flexible acyclic systems results only in the $E_{CC}Z_{CN}$-species (Scheme 6). This has been confirmed by trapping experiments,[7,9,15] MNDO calculations,[16] spectroscopic investigations[17] and X-ray analysis.[18] Further determination of freezing point depression values of lithiated 2-acetylnaphthalene-SAMP-hydrazones confirmed the monomeric structure of the azaenolate.[19] In this monomeric structure, the lithium atom of the lithio enehydrazide is located about 20° below the CCNN-plane and intramolecularly chelated by the methoxy group. Electrophilic attack on this rigid intermediate proceeds under high diastereofacial differentiation, resulting in the highly diastereomerically enriched hydrazones **11** (Scheme 6).

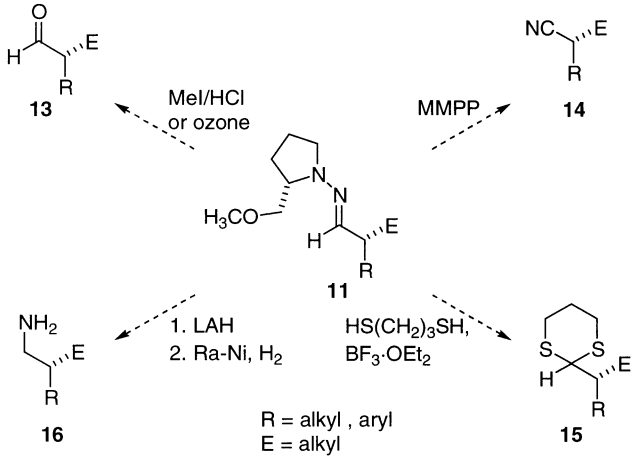
The stereochemical outcome of the reaction can be explained by an S_E2'-front (metalloretentive) mechanism.[20] On account of the single reaction pathway, it is possible to predict the resulting diastereomer. The synthesis of the desired product can therefore be controlled by the use of either SAMP or RAMP as the chiral inductor. Suitable electrophiles are alkyl halides, Michael acceptors, carbonyl compounds, halide-substituted esters, oxiranes, aziridines and various hetero electrophiles (for details vide infra). After workup, the crude α-substituted hydrazones can be purified by distillation or column chromatography. Subsequent cleavage of the hydrazones restores the original carbonyl function to provide substituted ketones or aldehydes (**12**) (Scheme 7).[9]



R^1 = H, Et
R^2 = Me, Et, Pr, *i*Pr, Hex, Ph
R^1, R^2 = -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -CH=CH$(CH_2)_2$-
E = Me, Et, Pr, Bn, allyl, $CH_2C(OEt)=CHCO_2Et$

Scheme 7.

Starting from the substituted aldehyde-SAMP-hydrazones **11**, the cleavage reaction can further generate, besides the parent aldehydes **13**, new functionalities such as nitrile (**14**),[21] dithian (**15**)[22] or amino groups (**16**)[23] (Scheme 8). For details concerning the cleavage of hydrazones, a recently-published review may be consulted by the reader.[6]



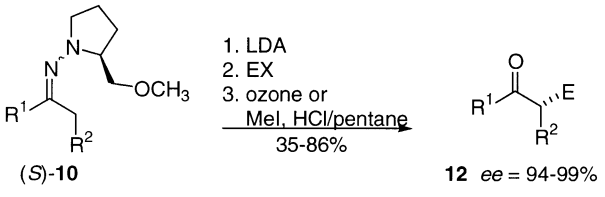
Scheme 8.

The following chapters cover the literature up to the year 2000. Early applications of the SAMP-/RAMP-hydrazone methodology are collected in a previous review.[8a]

2. Alkylation reactions

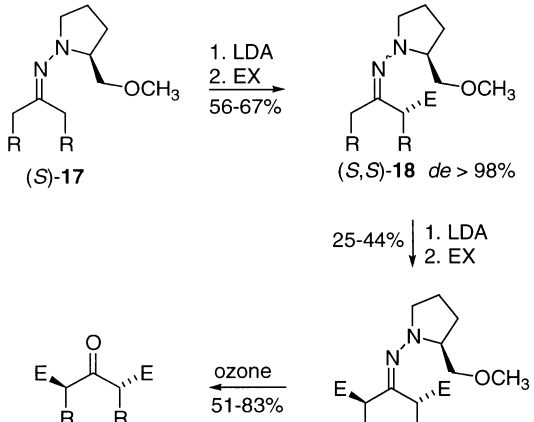
2.1. Carbon–carbon bond formation

2.1.1. Ketone derivatives. In 1976, our group demonstrated that alkylation reactions starting from SAMP hydrazones proceed in a highly diastereoselective manner.[7] After optimisation of the reaction conditions, a powerful methodology for the synthesis of virtually enantiomerically pure ketones was developed. SAMP derivatives (*S*)-**10** of acyclic ketones can easily be converted into α-substituted ketones **12** with high enantiomeric purity (Scheme 9). On account of the reaction mechanism described above, the configuration of the new stereogenic centre is predictable. The SAMP-/RAMP-hydrazone method was therefore also used as a reliable standard procedure for the determination of the absolute configuration of chiral compounds.[24]



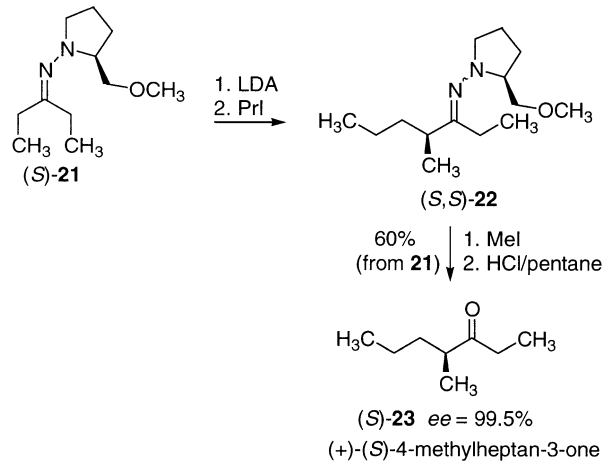
R^1 = Me, Et, Pr, Bu, Ph, Bn;
R^2 = Me, Et, Pr, Ph
E = Me, Et, Pr, CH_2cHex, $CH_2(CH_3)C{=}CHCH_3$, CH_2CO_2tBu, $CH_2C(COEt){=}CHCO_2Et$
X = Br, I

Scheme 9.



R = Me, Ph
E = $(CH_2)_2O(CH_2)_2OCH_3$, $(CH_2)_2OCH_3$
X = Br

Scheme 10.

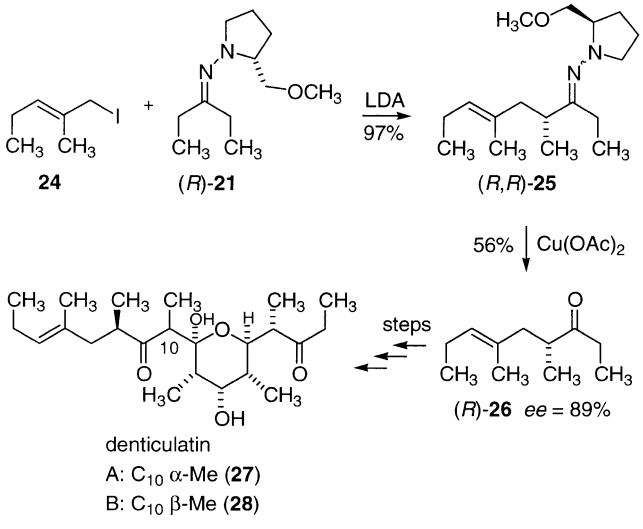


Scheme 11.

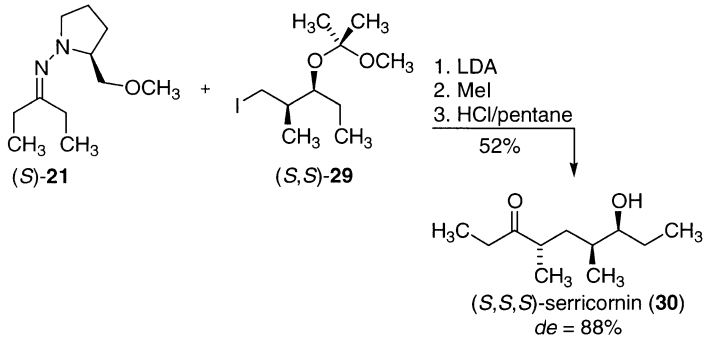
Monosubstituted hydrazones (*S*,*S*)-**18**, obtained by α-alkylation of (*S*)-**17**, can undergo a second regioselective α′-alkylation reaction, giving rise to pseudo-C_2-symmetric hydrazones (*S*,*S*,*S*)-**19** with complete diastereoselectivity (Scheme 10).[25] Subsequent treatment with ozone provided only a single diastereomer of the C_2-symmetric ketones **20**.

One of the first applications of this protocol, which was one of the first asymmetric pheromone syntheses, was the reaction of diethyl ketone SAMP-hydrazone (*S*)-**21** with iodopropane providing, after oxidative cleavage of the auxiliary from (*S*,*S*)-**22**, the alarm pheromone (*S*)-**23** of the ant *Atta texana* in 99.5% ee and good overall yield (Scheme 11).[26]

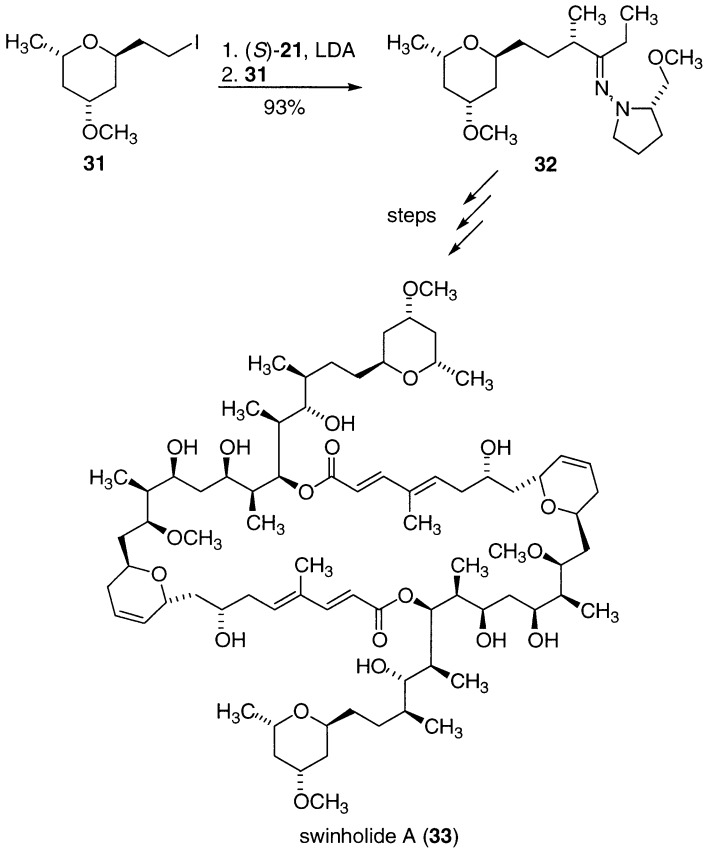
Starting from the analogous RAMP-derivative (*R*)-**21**, Ziegler et al. trapped the corresponding azaenolate with the allylic iodide **24** to obtain the desired α-alkylated hydrazone (*R*,*R*)-**25** in excellent yield (Scheme 12).[27] Treatment with copper(II) acetate gave rise to the ketone (*R*)-**26** with 89% enantiomeric excess, which is a key intermediate in the total synthesis of denticulatins A (**27**) and B (**28**), structurally intriguing polypropionate metabolites isolated from *Siphonaria denticulata*.



Scheme 12.



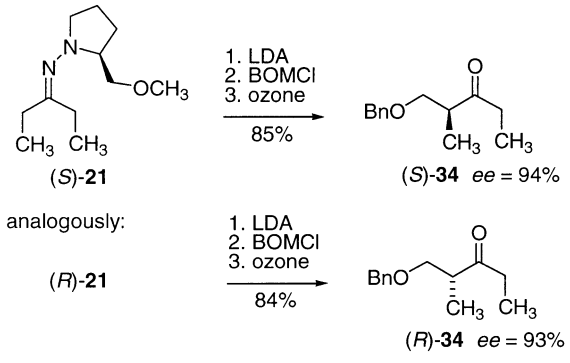
Scheme 13.



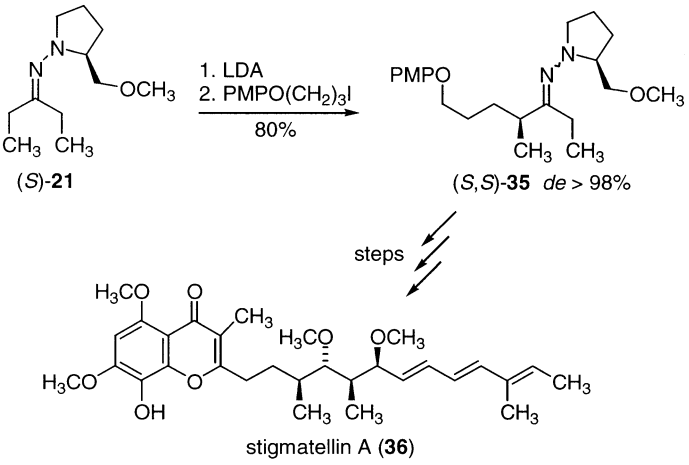
Scheme 14.

Mori et al. used this protocol for the generation of the third stereogenic centre of serricornin (**30**), the female-produced sex pheromone of the cigarette beetle *Lasioderma serricorne* (Scheme 13).[28] The reaction of the iodide (*S*,*S*)-**29** with the hydrazone (*S*)-**21** and subsequent cleavage afforded (*S*,*S*,*S*)-serricornin (**30**) directly with good diastereomeric excess. The two stereogenic centres present in the iodide electrophile appeared to have no noticeable effect on the selectivity in the sense of the double stereodifferentiation concept.[29]

A similar situation occurs during the total synthesis of swinholide A (**33**), an antifungal and cytotoxic agent of marine origin (Scheme 14).[30] The reaction of the iodide **31** with the deprotonated hydrazone (*S*)-**21** resulted in the



Scheme 15.



Scheme 16.

substituted hydrazone **32**. A loss of selectivity on account of the chiral centres in the iodide was not observed and again the asymmetric induction of the SAMP auxiliary overrides the pre-existing chirality.

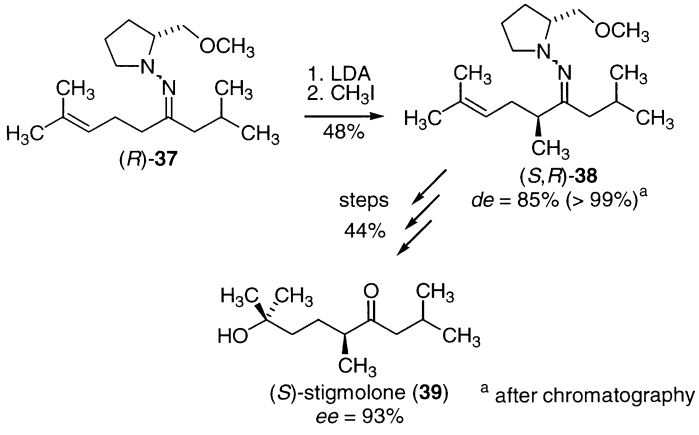
Reaction of the hydrazone (*S*)-**21** with benzyloxymethyl chloride (BOMCl) and subsequent treatment with ozone provided the ketone (*S*)-**34** in very good enantiomeric excess and yield (Scheme 15).[31] Starting from the enantiomer (*R*)-**21**, the analogous procedure provided the enantiomeric ketone (*R*)-**34** with similar selectivity. This compound, known as Paterson-ketone,[32] serves as an important intermediate in aldol reactions for the synthesis of polyketides[33] and of many propionate-based natural products, e.g. muamvatin,[34] denticulatin A and B[35] (**27** and **28**), *sec*-acids of 9,12-anhydroerythronolide-aglycons,[36] serricornin[31] (**30**), membrenone C,[37] scytophycin C[38] and discodermolide.[39]

Another application of this methodology was the first total synthesis of stigmatellin A (**36**), isolated from the gliding bacteria *Stigmatella aurantiaca* and a potent electron transport inhibitor both in chloroplasts and mitochondria (Scheme 16).[40] Deprotonation of (*S*)-**21** with lithium diisopropylamide, followed by alkylation with *p*-methoxyphenyl (PMP)-protected 1-hydroxy-3-iodopropane, led to diastereomerically pure (*S*,*S*)-**35**. Further transformations provided enantiomerically and diastereomerically pure stigmatellin A (**36**).

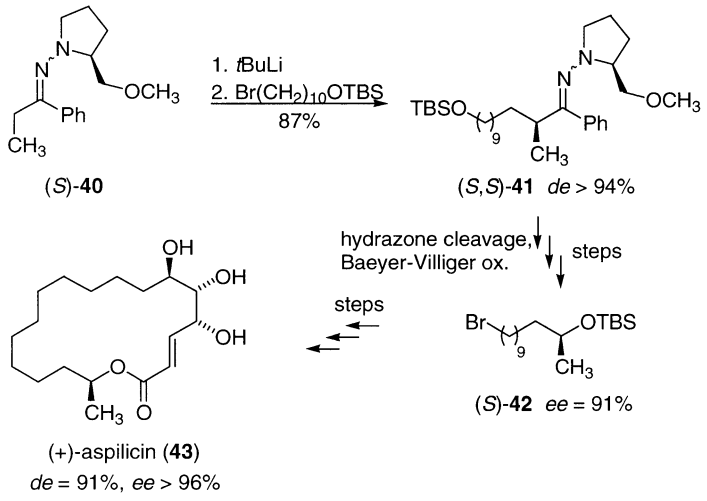
The first total synthesis of stigmolone (**39**), the fruiting body-inducing pheromone of the myxobacterium *S. aurantiaca*, could be accomplished starting from the hydrazone (*R*)-**37** (Scheme 17).[41] Deprotonation and subsequent trapping with iodomethane gave the corresponding hydrazone (*S*,*R*)-**38** in 85% de. After separation of the minor diastereomer via chromatography, further steps led to (*S*)-stigmolone (**39**) with an ee of 93%.

The substituted hydrazone (*S*,*S*)-**41** could be obtained from propiophenone SAMP-hydrazone [(*S*)-**40**] and 1-bromo-10-*tert*-butyldimethylsilyloxydecane in good yield and selectivity (de>94%, Scheme 18). Hydrazone cleavage and subsequent Baeyer–Villiger oxidation provided the silyl-protected ω-bromoalcohol (*S*)-**42** in 91% ee, a key intermediate in the synthesis of aspilicin (**43**), an 18-membered macrolide isolated from a lichen source in south-west Germany.[42] This method represents a versatile route to highly enantiomerically enriched secondary alcohols, as shown for bromo-substituted (*S*)-**42**.

While lithiated hydrazones do not usually react with



Scheme 17.

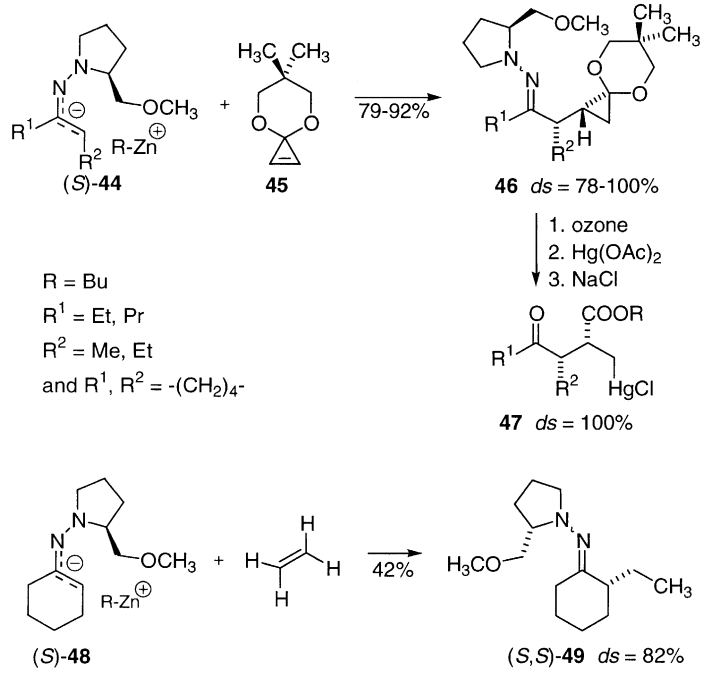


Scheme 18.

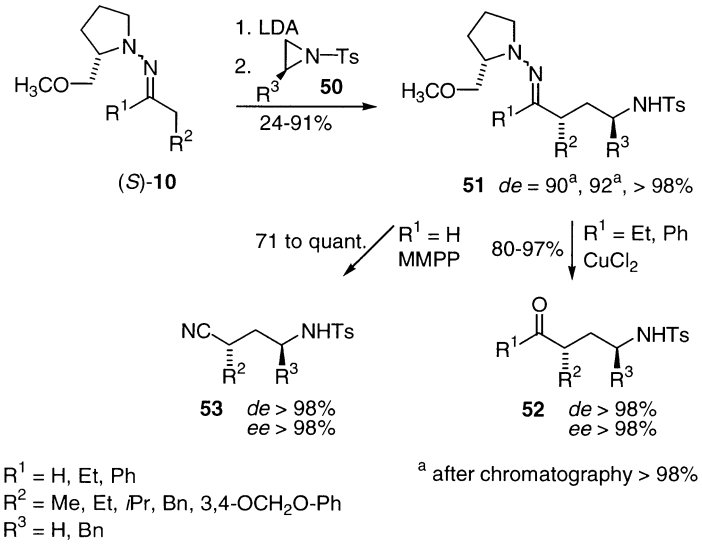
unactivated olefins, Nakamura et al. reported that the hydrazone anions (*S*)-**44** bearing a zinc(II) countercation react smoothly with cyclopropene acetal **45** (Scheme 19).[43] The resulting hydrazones **46** were generally obtained in high diastereoselectivity. Subsequent steps provided the compound **47**, which can undergo further transformations. Even ethene can be used in this reaction to obtain the substituted hydrazone (*S*,*S*)-**49** with a diastereoselectivity of 82%. The zincated hydrazones **44** and **48** were generated from lithiated species via transmetallation with zinc chloride and butyl lithium. A second equivalent of BuLi is needed to prepare the alkyl dummy ligand, which is necessary for good yields. The identity of the zinc enolate-like reagent is not yet known. Reactions with a chlorozinc countercation were either too slow to be useful or low yielding.

Deprotonated SAMP derivatives of aldehydes and ketones can further be trapped with tosylaziridines **50** (Scheme 20).[44] The resulting hydrazones **51** were obtained in 90 and 92% de or in diastereomerically pure form, respectively. If substituted chiral aziridines were used, the hydrazones formed bear an additional stereogenic centre in the 4-position. Subsequent treatment of ketone-hydrazones with aqueous copper(II) chloride solution yielded the corresponding γ-aminoketones **52** as pure stereoisomers (de, ee>98%), while the aldehyde derivatives **51** (R^1=H) were oxidised with MMPP to the corresponding nitriles **53**. This reaction provided an access to γ-amino acids. Earlier attempts to react lithiated SAMP-hydrazones with ethylene oxide provided the desired products in good overall yields but with low selectivities (ee=30%).[45]

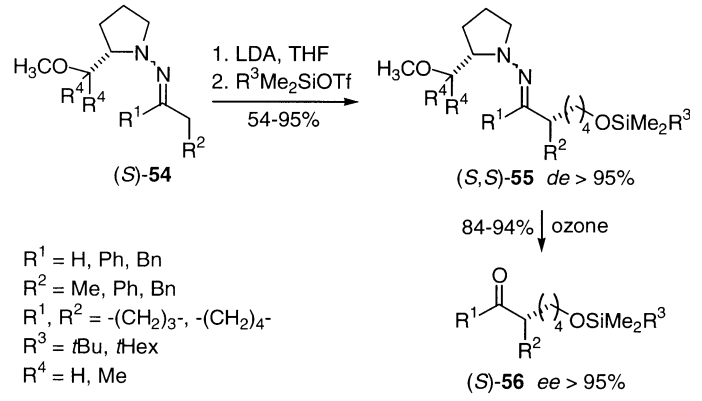
While trying to silylate lithiated hydrazones in an asymmetric manner, a ring-opening reaction of THF was



Scheme 19.



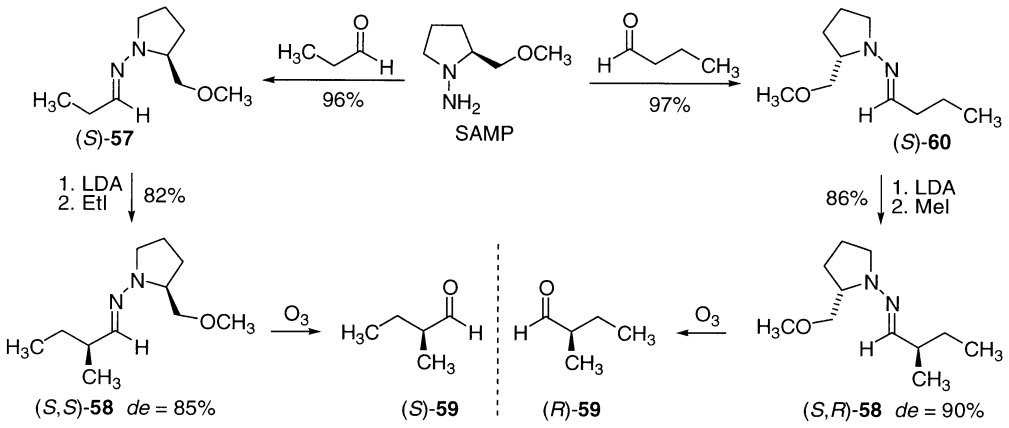
Scheme 20.



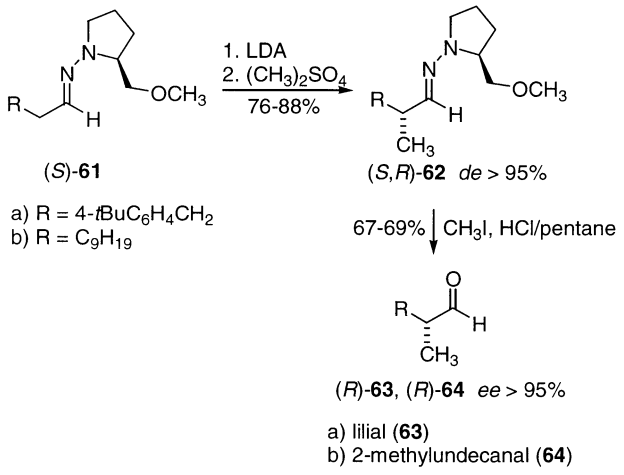
Scheme 21.

discovered (Scheme 21).[46] When the lithiated SAMP derivatives (*S*)-**54** were treated with a trialkylsilyl trifluoromethanesulfonate in tetrahydrofuran, a ring opening of THF occurs resulting in the α-silyloxybutylated hydrazones (*S*,*S*)-**55** with complete diastereoselection. Ozonolysis afforded the corresponding ketones (*S*)-**56** in very good yields and ee>95%. If the reaction was carried out in ether with 5 equiv. THF, the yield of hydrazone (*S*,*S*)-**55** was 77% accompanied by 10% α-trialkylsilyl hydrazone. In contrast, when tetrahydropyran was used as the solvent, only 10% of the ring-opened product was isolated, along with 85% of the corresponding α-silylated hydrazone.

2.1.2. Aldehyde derivatives. The general methodology of



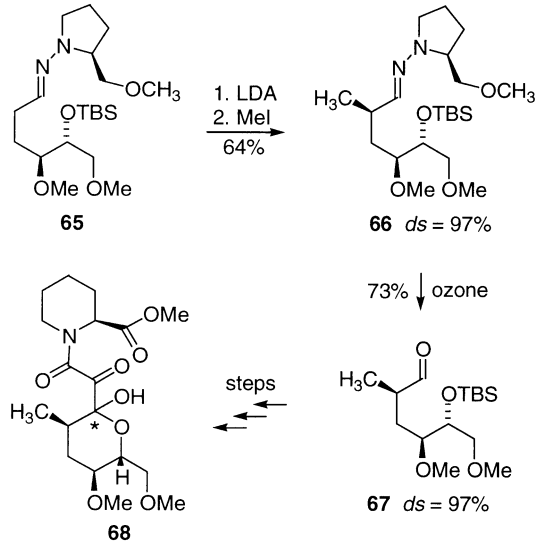
Scheme 22.



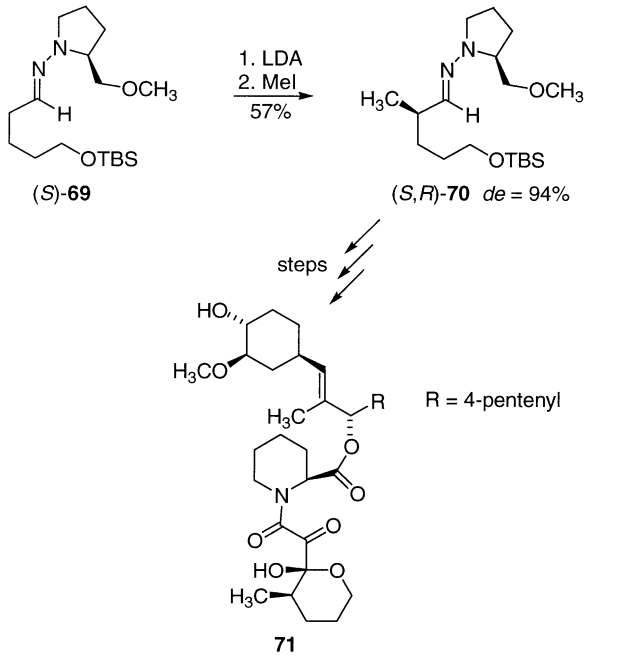
Scheme 23.

the alkylation of aldehyde-SAMP-hydrazones is depicted in Scheme 5 (Section 1). A noticeable feature concerning the α-alkylation of SAMP-hydrazones is the sequence-dependent stereogenic control of the reaction. As depicted in Scheme 22, condensation of SAMP with propanal or butanal provided the corresponding SAMP-hydrazones (*S*)-**57** and (*S*)-**60** in near-quantitative yield.[47] Alkylation of **57** with iodoethane and **60** with iodomethane furnished the epimeric SAMP-hydrazones (*S*,*S*)-**58** and (*S*,*R*)-**58** in good yield and selectivity. Ozonolytic cleavage afforded both enantiomers (*S*)-**59** and (*R*)-**59** using only SAMP as the chiral auxiliary (synthon control of enantioselectivity).

The diastereoselective alkylation of aldehyde-SAMP-hydrazones is a widely-used technique for the synthesis of natural products. Starting from linear aldehydes, methylation of the corresponding hydrazones (*S*)-**61** followed by cleavage of the auxiliary of **62** provided lilial (**63**) and 2-methylundecanal (**64**), two artificial fragrances, which are used to a large extent in the perfume industry (Scheme 23).[48] (*R*)-**63** and (*R*)-**64** were obtained starting from the hydrazones (*S*)-**61**, while the enantiomers (*S*)-**63** and (*S*)-**64** were available using the RAMP-hydrazones. Evaluation of the odour characteristics of the two enantiomeric pairs in dilute solutions by a professional perfumer has shown that the optical antipodes of lilial (**63**) and 2-methylundecanal (**64**) exhibit only slight differences in their odour quality and intensity.



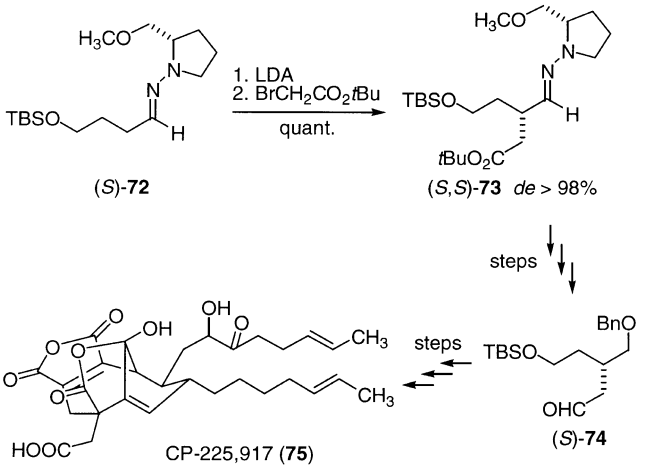
Scheme 24.



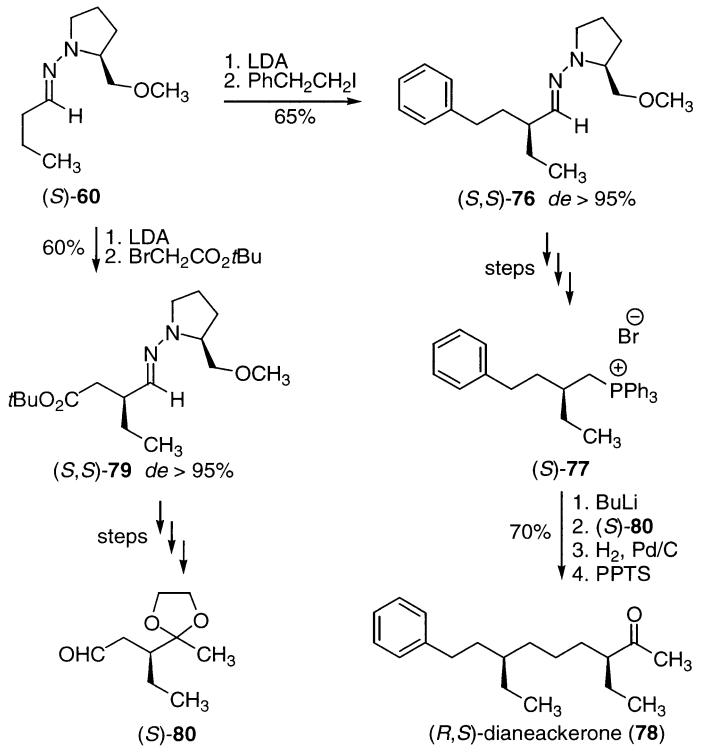
Scheme 25.

Kocienski et al. have used the α-methylation reaction for the synthesis of **68**, a substructure of tsukubaenolide, a powerful immunosuppressant isolated from *Streptomyces tsukubaensis* (Scheme 24).[49] The hydrazone **65** was treated with iodomethane furnishing the methylated hydrazone **66** in very good diastereoselectivity. Reaction with ozone provided the aldehyde **67** in 97% ds, based on the newly generated stereogenic centre. Further steps provided the desired key structure **68**.

Asymmetric α-methylation of (*S*)-**69** afforded the corresponding hydrazone (*S*,*R*)-**70** in 94% de (Scheme 25).[50]



Scheme 26.

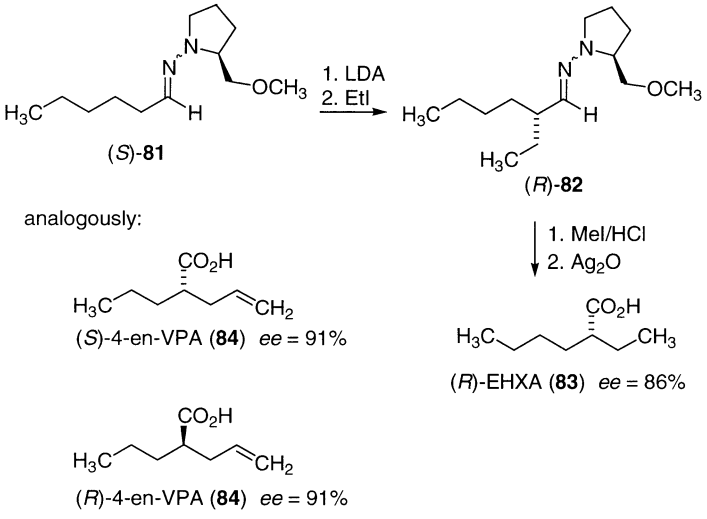


Scheme 27.

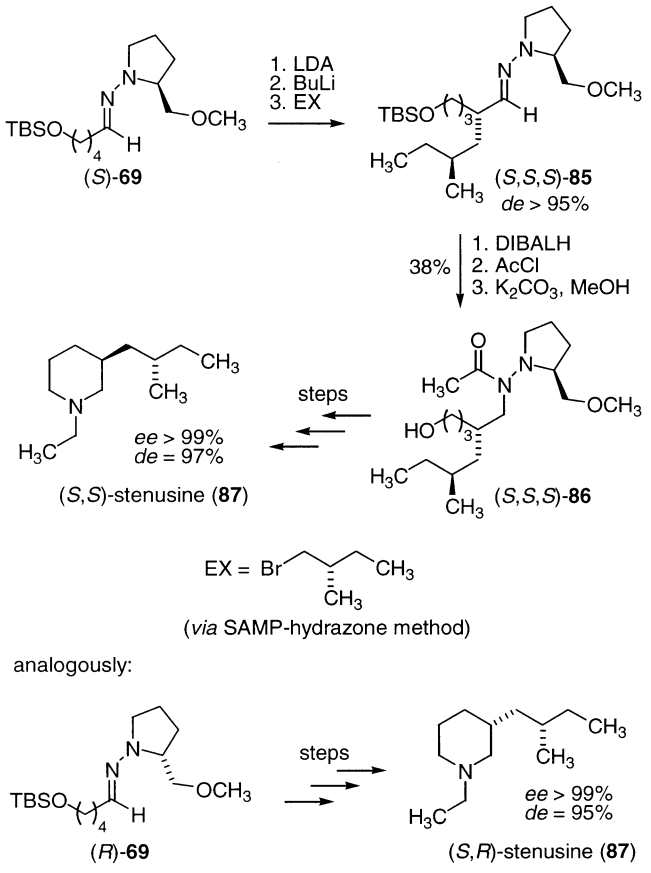
Additional steps provided **71**, a model compound for the examination of the binding properties of FK-506 to the immunophilin protein FKBP-12.

Nicolaou et al. used the hydrazone methodology for the asymmetric introduction of a *tert*-butoxycarbonylmethyl functionality (Scheme 26).[51] Trapping of the corresponding azaenolate of the hydrazone (*S*)-**72** led to the substituted hydrazone (*S*,*S*)-**73** as a single diastereomer in quantitative yield. Further transformations of the hydrazone (*S*,*S*)-**73** furnished the aldehyde (*S*)-**74**, used as a chiral building block for the total synthesis of the compound CP-225,917 (**75**), a potent inhibitor of squalene synthase and Ras farnesyl transferase.

Dianeackerone (**78**) is a secretory product from the adult African dwarf crocodile *Osteolaemus tetraspis* and was isolated and characterised by Whyte and Meinwald et al. (Scheme 27).[52] In the asymmetric synthesis using butanal-SAMP-hydrazone [(*S*)-**60**], both stereogenic centres in the corresponding hydrazones **76** and **79** were generated in excellent diastereoselectivities accomplishing the standard reaction sequences. The Wittig salt (*S*)-**77** and the aldehyde (*S*)-**80** were then connected via olefination. Subsequent steps provided enantiomerically pure dianeackerone (*R*,*S*)-**78**. In addition, when RAMP-hydrazone (*R*)-**60** was used for the synthesis of the Wittig salt (*R*)-**77** dianeackerone (**78**) was also obtained in an (*S*,*S*)-configuration.[52c] It was eludicated that both epimers are present in the natural



Scheme 28.



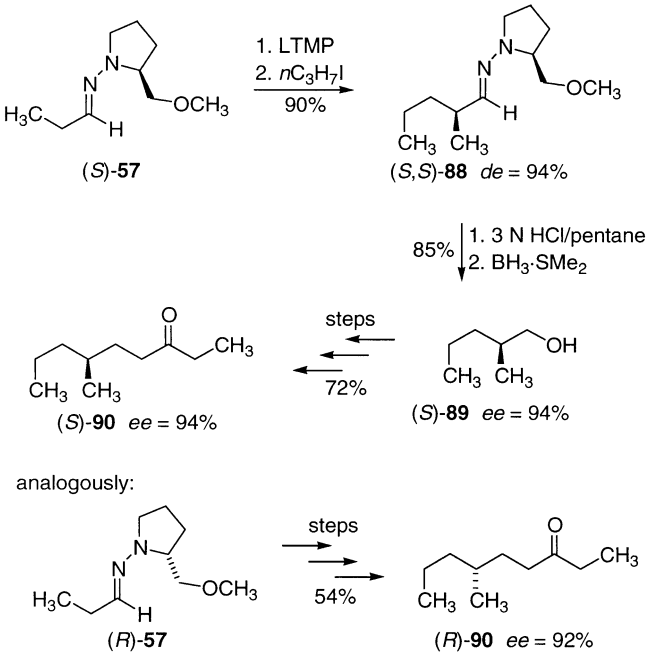
Scheme 29.

secretion of the crocodiles, but in individually different ratios. The first suspicion that the stereoisomeric dianeackerones might be indicators of gender proved untenable, leaving the exact role of these glandular constituents unknown.

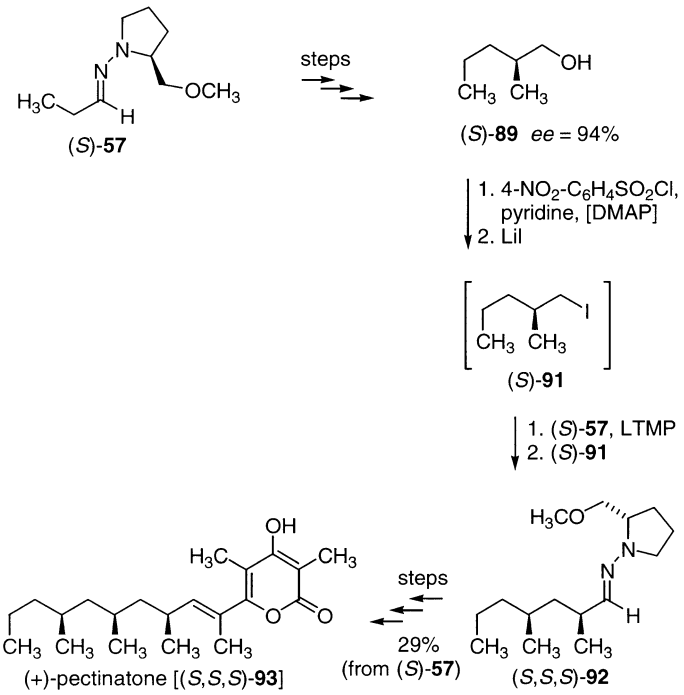
Application of the SAMP-hydrazone method has provided both enantiomers of 2-ethylhexanoic acid (EHXA, **83**), a metabolite of the widely-used plasticiser di-(2-ethylhexyl)phthalate (Scheme 28). Its teratogenic activity was investigated by Hauck and co-workers.[53] Alkylation of hexanal-SAMP-hydrazone and -RAMP-hydrazone (**81**) with iodoethane to the substituted hydrazone **82**, subsequent cleavage of the auxiliary and oxidation of the aldehyde to the corresponding acid yielded (*R*)- and (*S*)-EHXA (**83**), respectively. While (*S*)-EHXA exhibited no significant activity in mice, the optical antipode (*R*)-EHXA was highly teratogenic and embryotoxic.

Analogously, both enantiomers of 4-en-valproic acid (4-en-VPA, **84**), a metabolite of the human and animal teratogenic antiepileptic drug valproic acid (VPA), was obtained.[54] Hauck et al. found that the (*S*)-enantiomer is significantly more teratogenic and embryotoxic than (*R*)-4-en-VPA.

Alkylation of the protected hydroxyaldehyde hydrazone (*S*)-**69** with the enantiopure electrophile 1-bromo-2-methylbutane yielded (*S*,*S*,*S*)-**85** as a single diastereomer (Scheme 29).[55] Subsequent transformations via hydrazine **86** furnished (*S*,*S*)-stenusine (**87**), a propulsion fluid produced by the beetle *Stenus comma*. If the coupling of the chiral electrophile was accomplished with the enantiomeric hydrazone (*R*)-**69**, the reaction sequence provided the epimeric stenusine (*S*,*R*)-**87**. α-Alkylation of propanal-SAMP-hydrazone (*S*)-**57** with iodopropane afforded (*S*,*S*)-**88** in 90% yield with a de of 94% (Scheme 30).[56] The substituted hydrazone (*S*,*S*)-**88** was cleaved by hydrolysis and the volatile aldehyde, obtained as an intermediate, was reduced in situ by the borane–dimethylsulfide complex. The resulting alcohol (*S*)-**89** was isolated in 85% yield and an ee of 94%, determined by GC analysis on chiral stationary phases. Further steps provided (*S*)-6-methyl-nonan-3-one (**90**), the sex pheromone of the caddisfly *Hesperophylax occidentalis*. Starting from the enantiomeric hydrazone (*R*)-**57** the

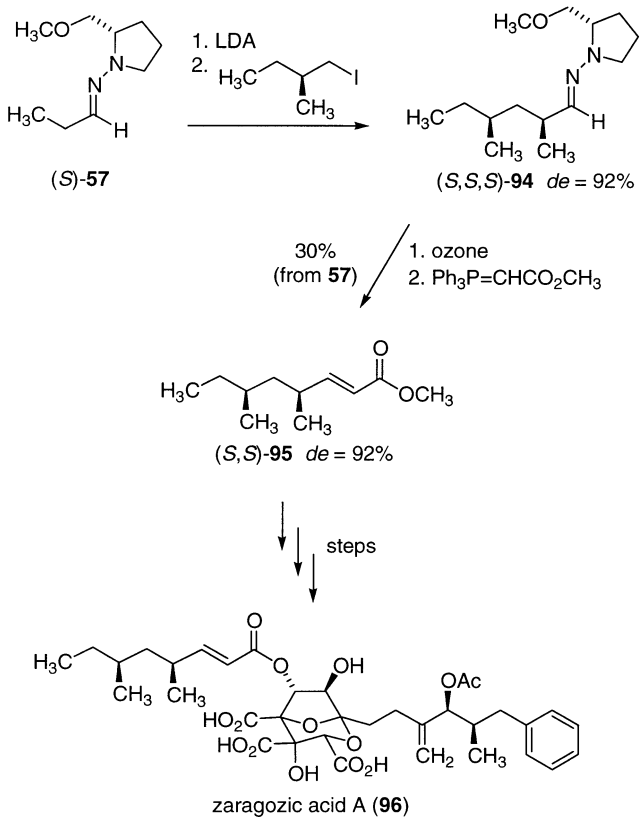


Scheme 30.



Scheme 31.

analogous procedure provided the enantiomer (*R*)-**90** in 92% ee. A biological evaluation of both enantiomers of the sex pheromone showed that the (*R*)-enantiomer of **90** is much more active than the (*S*)-configured ketone.[57]



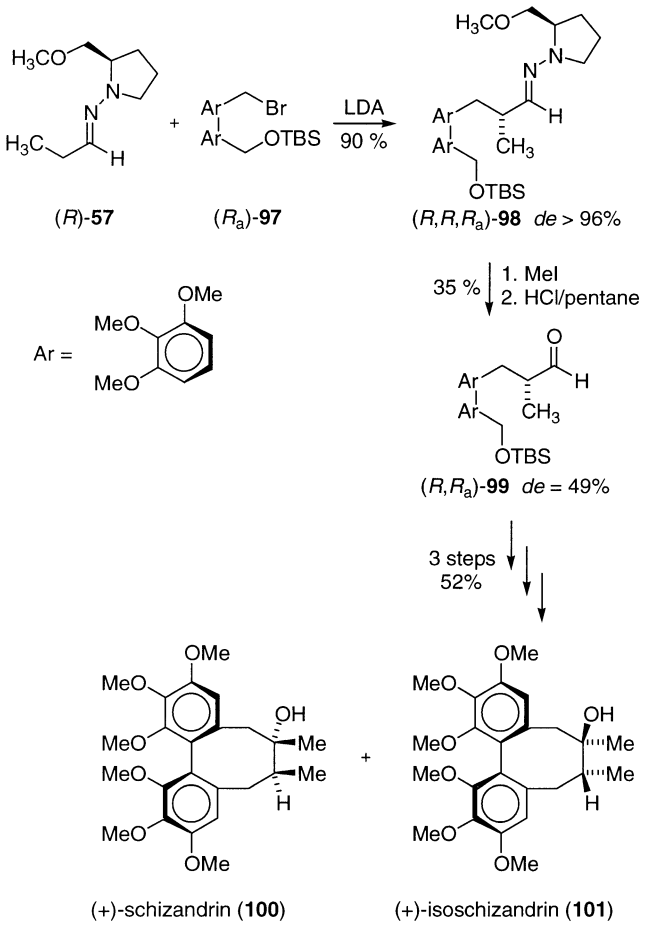
Scheme 32.

As depicted in Scheme 31, iterative application of the SAMP-hydrazone method afforded structures containing 'skip' 1,3-dimethyl stereocenters,[58] employed in the synthesis of (+)-pectinatone (**93**), isolated from *Siphonaria* sp. molluscs, which displays antibacterial, antifungal and cytotoxic activity.[59] As previously demonstrated, the alcohol (*S*)-**89** may be obtained from the hydrazone (*S*)-**57** in 94% ee. This alcohol was transferred to the corresponding iodide (*S*)-**91** in situ and trapped with the azaenolate of hydrazone (*S*)-**57** to obtain (*S*,*S*,*S*)-**92**. Repetition of this sequence afforded all stereogenic centres of the pectinatone side chain.

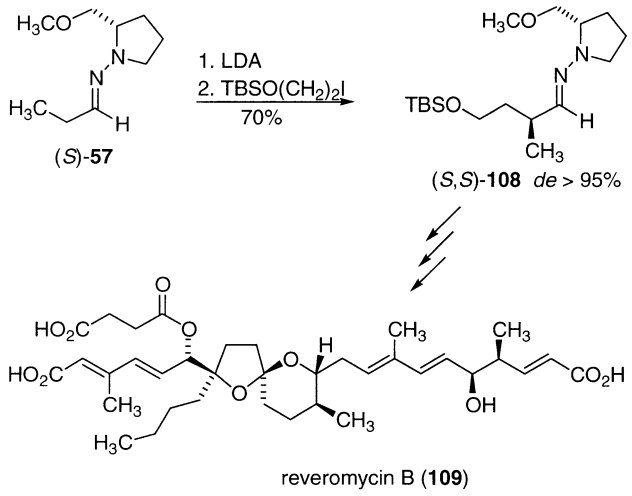
Using a similar technique, Nicolaou et al. have generated a 1,3-dimethyl-substituted hydrazone (*S*,*S*,*S*)-**94** as a key structure for the side chain **95** of zaragozic acid A (**96**, Scheme 32).[60] This class of natural products inhibits squalene synthase, which is responsible for the biosynthetic generation of cholesterol—a principal cause of coronary heart disease.

Meyers et al. used the hydrazone method to combine elements of central and axial chirality (Scheme 33).[61] Treatment of deprotonated RAMP-hydrazone (*R*)-**57** with the biaryl bromide (R_a)-**97** furnished the hydrazone (*R*,*R*,R_a)-**98** in >96% de, based on the newly generated stereogenic centre. Subsequent cleavage of the auxiliary provided the desired aldehyde (*R*,R_a)-**99**, but, unfortunately, a significant epimerisation occurred during this reaction. A following three-step procedure, however, led to the lignans (+)-schizandrin (**100**) and (+)-isoschizandrin (**101**), which occur in the fruits of *Schizandra chinesis* Baill.

In the synthesis of epothilones A and B, the SAMP-hydrazone method was applied to two different synthetic pathways (Scheme 34). In the first of these, the hydrazone (*S*)-**57**



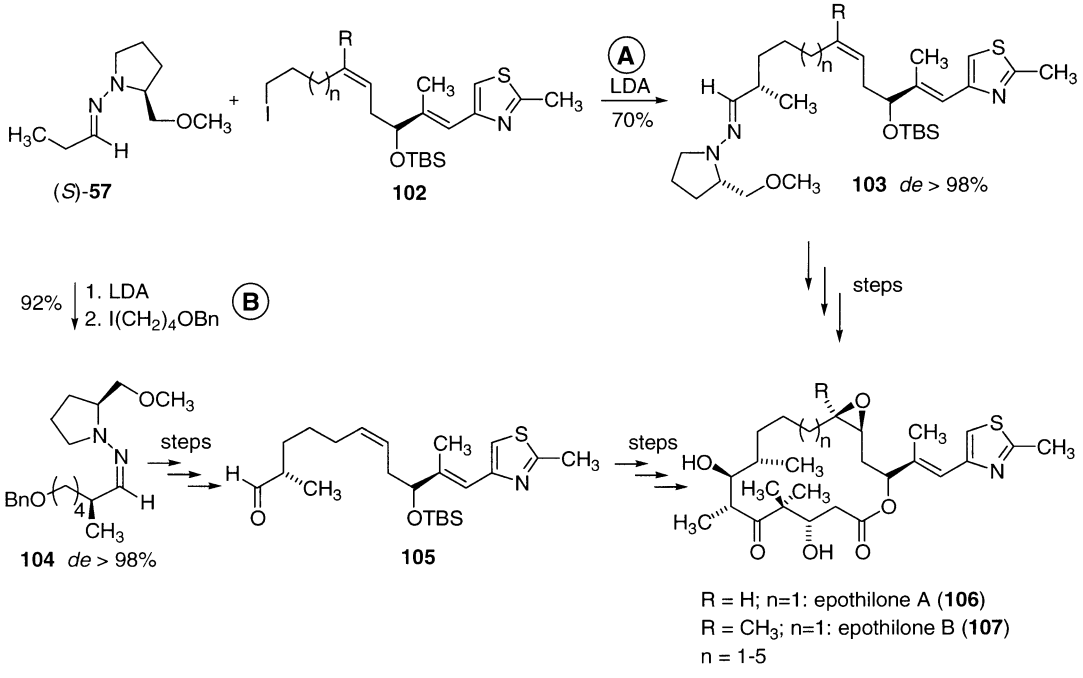
Scheme 33.



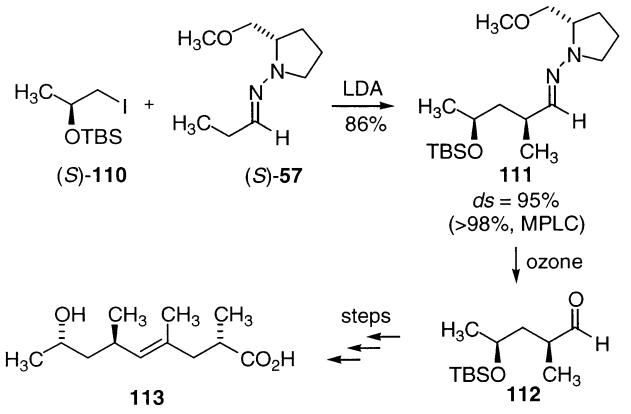
Scheme 35.

was deprotonated with lithium diisopropylamide and subsequently trapped with various iodides **102** (R=H, CH_3), providing the desired products **103** as single diastereomers (pathway A, Scheme 34).[62] Further steps yielded epothilones A (**106**) and B (**107**), which exhibit potent taxol-like cytotoxic activity. For investigations concerning ring size-activity relationships, the reaction sequence was also accomplished with iodides of varying chain lengths giving rise to epothilones of different ring sizes (n=1–5).[63] The SAMP-alkylation protocol was additionally used for the synthesis of various derivatives requiring further biological activity investigations of this lead structure.[64]

The second approach for the construction of the C_7–C_{22} substructure of epothilones is depicted in Scheme 34, pathway B.[65] Alkylation of the hydrazone (*S*)-**57** afforded the substituted derivative (*S*,*S*)-**104** as a single diastereomer.



Scheme 34.

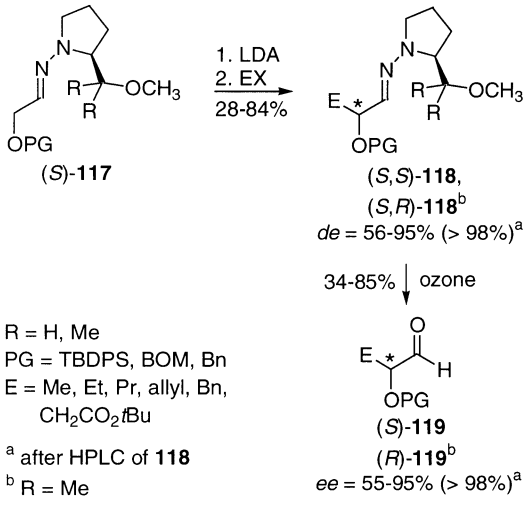


Scheme 36.

Additional steps furnished the aldehyde **105** as a key intermediate in the syntheses of the epothilones.

Propanal-SAMP-hydrazone (*S*)-**57** was converted by Theodorakis et al. according to the standard procedure with a TBS-protected iodoalcohol to the substituted hydrazone (*S*,*S*)-**108**, providing a chiral building block for the synthesis of reveromycin B (**109**), a potent eukaryotic cell growth inhibitor isolated from a soil actinomycete of the genus *Streptomyces* (Scheme 35).[66]

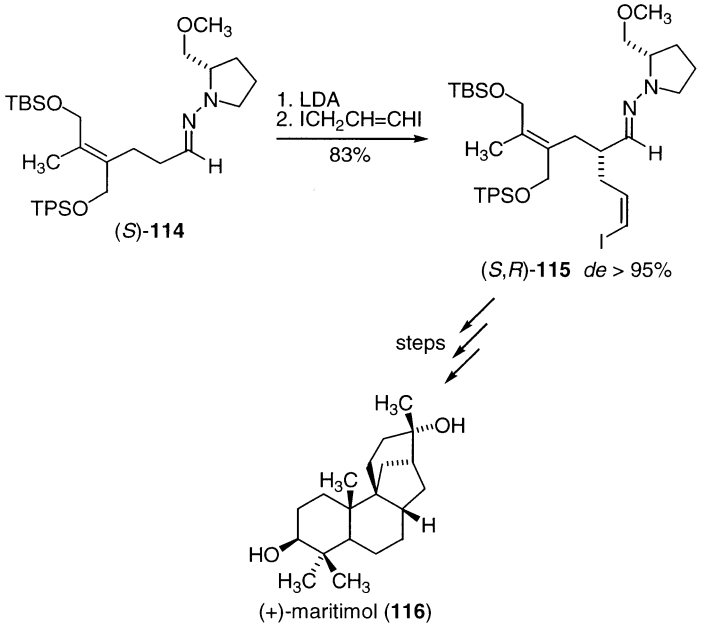
Starting from the same hydrazone (*S*)-**57** and the iodide (*S*)-**110**, Schmidt et al. obtained the hydrazone (*S*,*S*,*S*)-**111** bearing three stereogenic centres in 95% ds (Scheme 36)[67] and, fortunately, the undesired diastereomer could be separated by MPLC. Subsequent treatment with ozone provided the optically pure aldehyde (*S*,*S*)-**112**. Further transformations gave rise to the acid **113**, which is a subunit of jaspamide and geodiamolide A and B, which are biologically active peptides isolated from lower marine organisms.



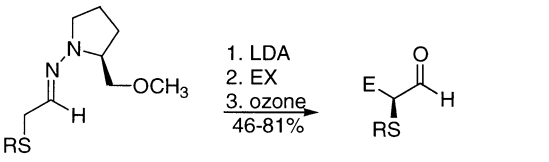
Scheme 38.

Deslongchamps and co-workers synthesised (+)-maritimol (**116**), a member of the stemodane diterpenoids isolated from *Stemodia maritima* L, employing the SAMP-alkylation protocol (Scheme 37).[68] Deprotonation of the hydrazone (*S*)-**114** with lithium diisopropylamide and subsequent trapping with 1,3-diiodopropene furnished the vinyl iodide-substituted hydrazone (*S*,*R*)-**115**. Additional transformations provided the desired target molecule, which is used as a Caribbean folk medicine for the treatment of veneral diseases.

Another class of substances is available starting from α-heterosubstituted aldehydes. Deprotonation of the protected glycol aldehyde hydrazones (*S*)-**117** and trapping with alkyl halides provided the α-hydroxy-substituted hydrazones **118** in up to 95% de (Scheme 38).[69] In some cases, the undesired diastereomer could be separated by HPLC. Subsequent cleavage furnished protected α-hydroxy



Scheme 37.

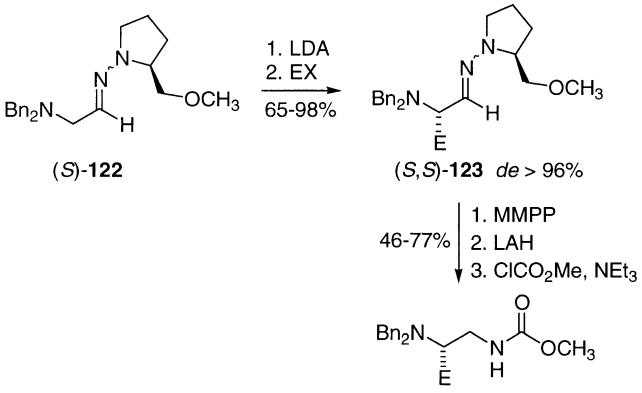


R = Me, *i*Pr, *t*Bu, Ph
E = Et, Pr, Bu, Hex, Oct, Dec, Undec, *c*HexCH$_2$
X = I

Scheme 39.

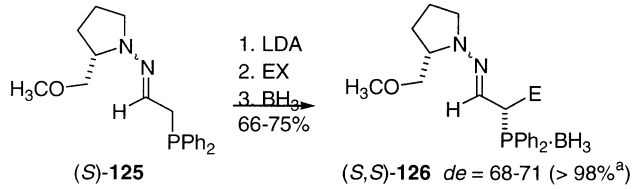
aldehyde building blocks **119**. Using SAMP as the auxiliary, the resulting hydrazones **118** showed (*S*,*S*)-configuration in agreement with the general SAMP-alkylation mechanism. Changing the auxiliary to SADP (R=Me, Scheme 38) led to hydrazones with the opposite (*R*)-configuration at the new stereogenic centre.

Based on the same concept, α-sulfenylated aldehydes (*S*)-**121** may be prepared via chemoselective ozonolysis of the C=N double bond in the presence of a thioether function in (*S*)-**120** (Scheme 39)[70] and *N*,*N*-dibenzyl-amino-SAMP-hydrazones (*S*,*S*)-**123** (Scheme 40)[71] are available from (*S*)-**122**. As depicted for the amino-substituted hydrazones (*S*,*S*)-**123**, the MMPP-induced cleavage with subsequent reduction led to the specifically protected chiral diamines (*S*)-**124** of high enantiomeric purity (ee=91–99%). These compounds are of great importance in medicinal chemistry and are useful as chiral ligands and auxiliaries in asymmetric synthesis.[72]



E = Me, Et, *i*Pr, Bn, allyl, BnOCH$_2$
X = Cl, Br, I

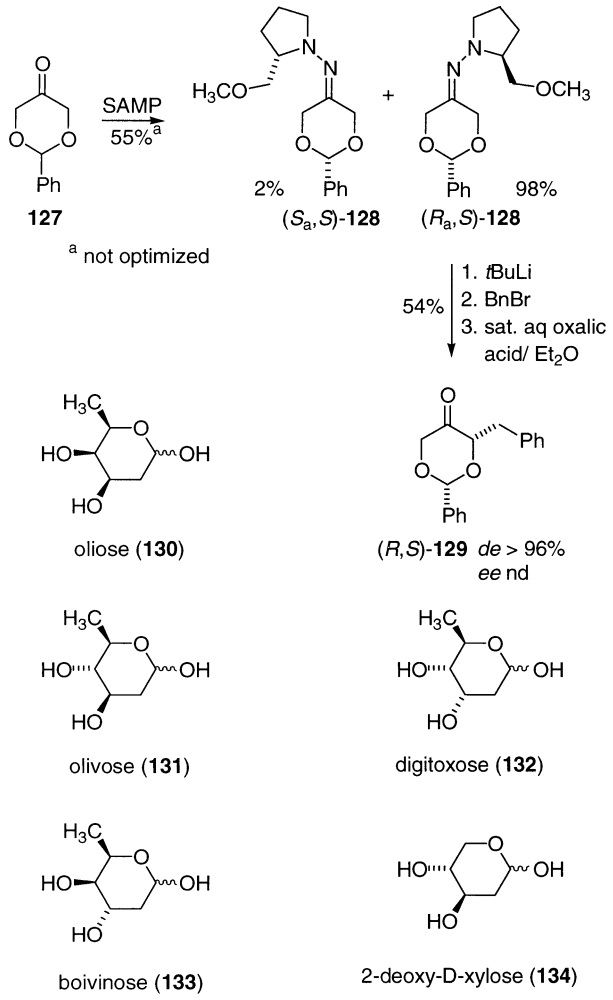
Scheme 40.



E = Me, Et, Pr, Bu

[a] after HPLC

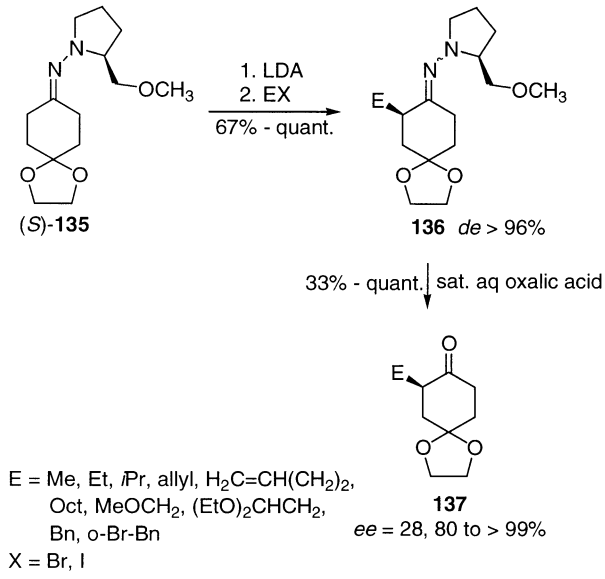
Scheme 41.



Scheme 42.

Alkylation of the α-phosphino-substituted hydrazones (*S*)-**125** and subsequent protection resulted in the borane-protected hydrazones (*S*,*S*)-**126** bearing a new stereogenic centre (Scheme 41).[73] Separation of the epimers by HPLC afforded the diastereomerically pure (*S*,*S*)-**126**. Further transformations of these hydrazones furnished P∪O-ligands for asymmetric catalysis (vide infra). Because of the uniform reaction mechanism for all the electrophilic substitutions with α-heterosubstituted aldehyde hydrazones mentioned here, the opposite absolute configurations compared with the versions employing heteroatom electrophiles (vide infra) were observed.

2.1.3. Cyclic ketone derivatives. The general reaction sequence for the alkylation of cyclic ketones via SAMP-hydrazones proceeds according to the usual mechanism and generates the new stereogenic centre with the same configuration as that for the open-chain ketones (Section 1). The chiral hydrazones of cyclic ketones were synthesised in the same manner as the acyclic ketones (Section 1, Scheme 5). A notable difference occurs with C_S-symmetric ring systems. The reaction of 2-phenyl-1,3-dioxan-5-one (**127**) with SAMP yielded the hydrazone **128** (Scheme 42) containing two stereogenic elements, i.e. central chirality in the pyrrolidine ring system and axial chirality in the dioxanone system.[74] The major diastereomer

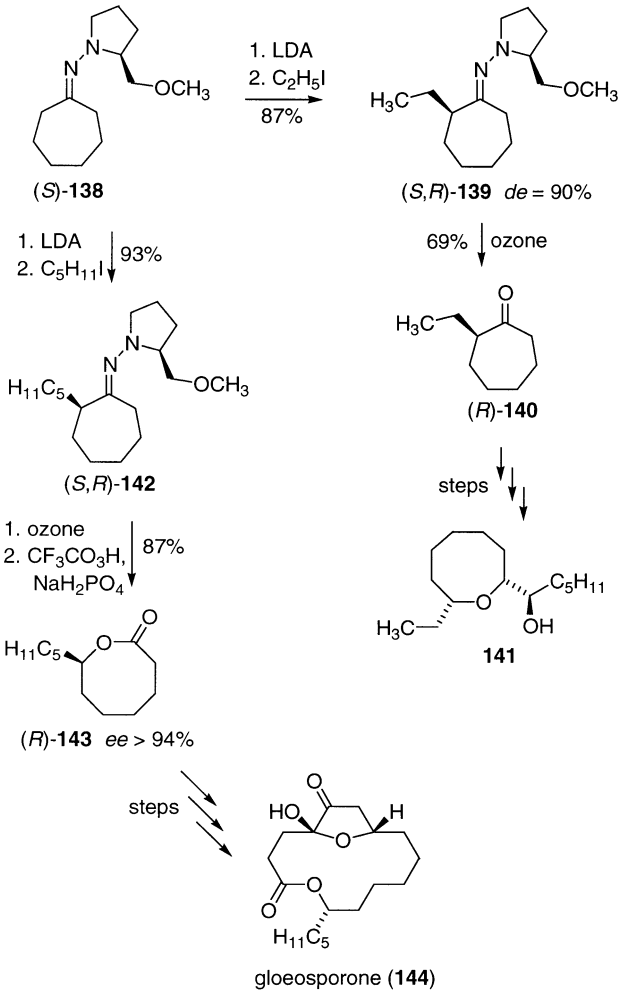


Scheme 43.

(R_a,*S*)-**128** was obtained in 96% de. Storage at −20°C under an argon atmosphere maintains this configuration, whilst heating in benzene or storage at room temperature leads to epimerisation. Subsequent alkylation of the major diastereomer provided the optically active and diastereomerically pure ketone (*R*,*S*)-**129**, the enantiomeric excess of which has not yet been determined. Application of this method led to all diastereomers of the medicinally interesting 2,6-dideoxyhexoses, oliose (**130**), olivose (**131**), digitoxose (**132**), boivinose (**133**) and 2-deoxy-D-xylose (**134**).[75] The desired enantiomer of these compounds can be obtained from **127** by choosing either SAMP or RAMP as the chiral auxiliary.

The monoprotected cyclohexadione derivative (*S*)-**135** can be alkylated with different electrophiles in excellent diastereoselectivity (Scheme 43).[76] Subsequent cleavage of **136** with oxalic acid provided the protected cyclohexanedione derivatives (*S*)-**137** or (*R*)-**137** in up to 99% ee, which are important intermediates for the total synthesis of (±)-dolasta-1(15),7,9-trien-14-ol,[77] (±)-sordidin,[78] (±)-pyrenolide B,[79] (*R*)-4-hydroxy-4-methylcyclohexanone,[80] (+)-sporogen-AO 1,[81] (+)-aphidicolin[82] and substituted octalones.[83]

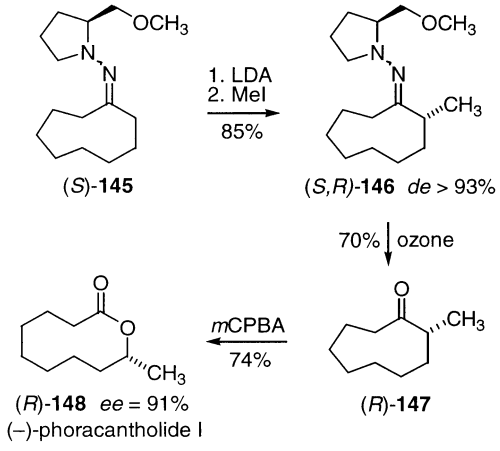
The α-alkylation method can be combined with Baeyer–Villiger oxidation to obtain asymmetrically-substituted lactones with a one-oxygen atom extended ring system (Scheme 44). Alkylation of suberone-SAMP-hydrazone (*S*)-**138** with iodopentane afforded the substituted hydrazone (*S*,*R*)-**142**. Subsequent ozonolytic cleavage followed by oxidation with trifluoroperoxyacetic acid provided the lactone (*R*)-**143**. During the Bayer–Villiger reaction, the absolute configuration of the stereogenic centre was maintained (retention). Applying further transformations, the lactone (*R*)-**143** was converted to gloeosporone (**144**), which has been isolated from conidia of *Colletotrichum gloeosporiodes*.[84] Starting from the same hydrazone (*S*)-**138**, alkylation with iodoethane furnished (*S*,*R*)-**139** in good diastereoselectivity. Treatment with ozone afforded



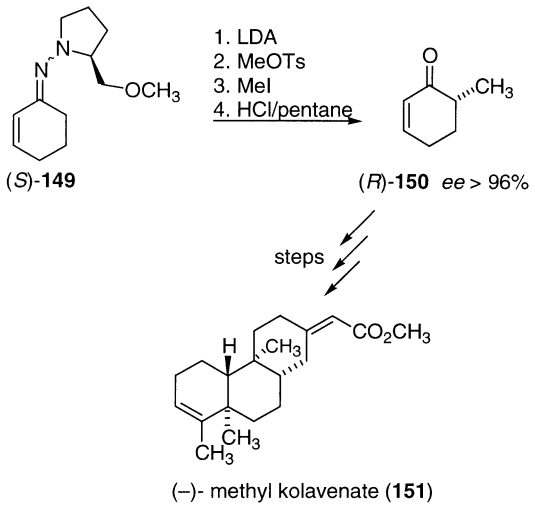
Scheme 44.

the corresponding ketone (*R*)-**140**, which can be converted in several steps including the Baeyer–Villiger protocol to the degradation product **141** of laurencin.[85] Based on this protocol, Murai et al.[86] accomplished the total synthesis of lauthisan, which was isolated from marine algae of the species *Laurencia*, analogously to laurencin.

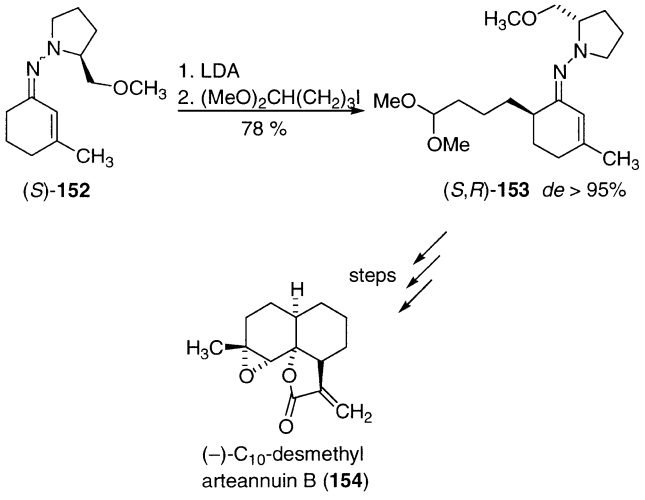
According to the same concept, the 9-membered ring



Scheme 45.



Scheme 46.



Scheme 47.

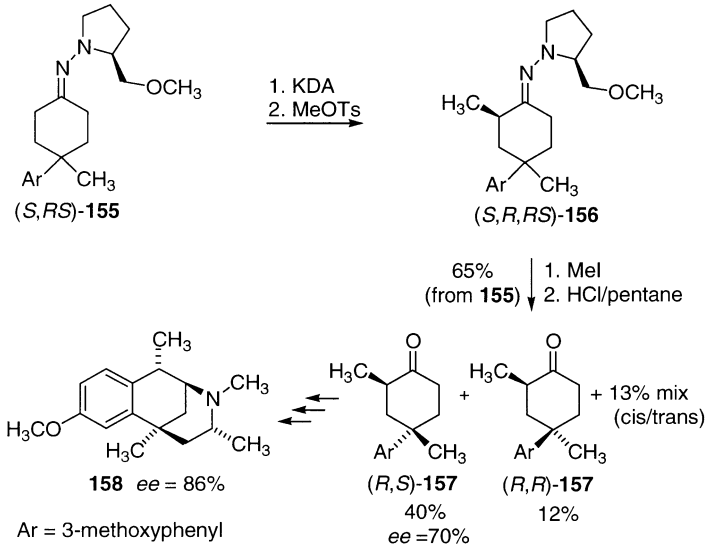
SAMP-hydrazone (*S*)-**145** was converted by α-methylation to (*S*,*R*)-**146** in >93% de (Scheme 45).[87] Ozonolytic cleavage of the auxiliary to the ketone (*R*)-**147** and treatment with *m*CPBA resulted in the 10-membered methyl lactone (−)-phoracantholide I (**148**), which is a constituent of the defensive secretion of the eucalypt longicorn *Phoracantha synonyma* and a major component of the metasternal gland secretion.[88]

Applying analogous techniques, Meinwald et al. obtained (*R*)-15-hexadecanolide, which is a constituent of the male-released sex pheromone system of the stink bug *Piezodorees hybneri*.[89] Behavioural observation showed that the non-natural enantiomer is neither a beneficial nor a behavioural antagonist.

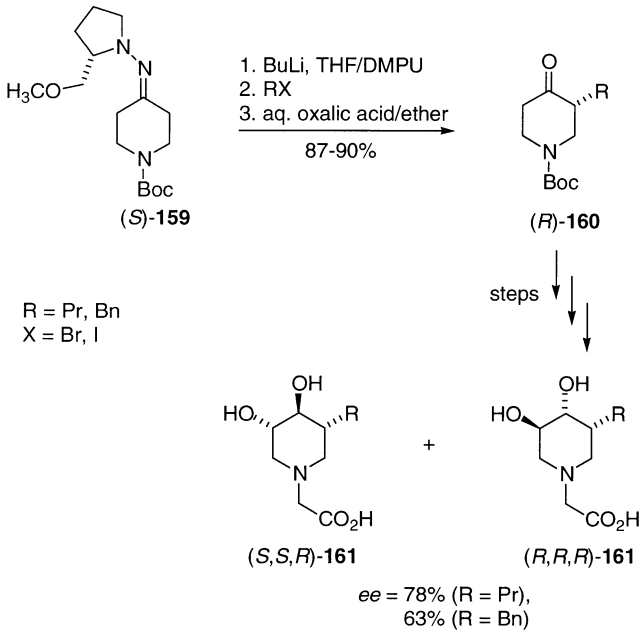
Another application to the synthesis of natural products started from cyclohexenone-SAMP-hydrazone [(*S*)-**149**] following the standard reaction sequence leading to the methylated cyclohexenone (*R*)-**150** as single enantiomer (Scheme 46).[90] Further transformations provided the diterpenoid (−)-methylkolavenate (**151**). Analogously, Little et al. obtained the hydrazone (*S*,*R*)-**153** from (*S*)-**152** in diastereomerically pure form (Scheme 47).[91] Several following steps provided (−)-C_{10}-desmethyl arteannuin B (**154**), a structural analogue of artemisinin,[92] which is an efficient antimalarial agent even against drug-resistant strains.

Sainsbury et al. converted the epimeric mixture of the hydrazone (*S*,*RS*)-**155** in a four-step procedure via **156** into the substituted cyclic ketones **157** (Scheme 48).[93] The major isomer (*R*,*S*)-**157** was isolated in 40% yield and 70% ee. Several following steps afforded 6,7-benzomorphan **158**, which represents a class of drugs exhibiting analgesic properties.[94]

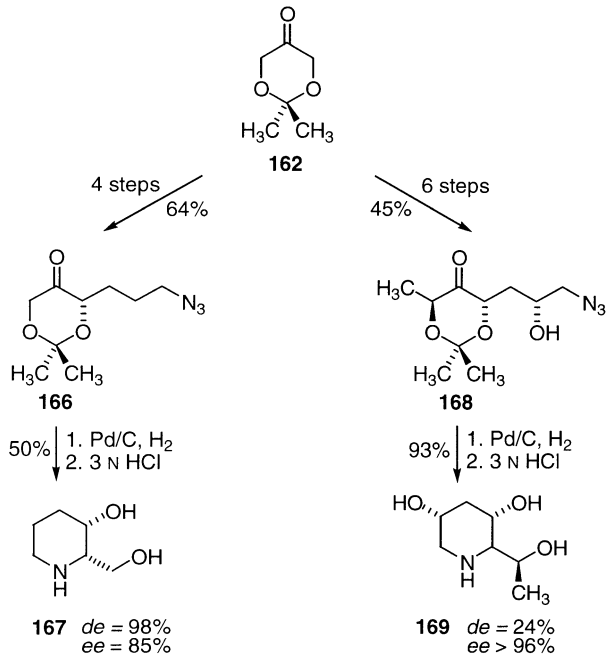
Even heteroatom-containing cyclic ketones were successfully substituted according to this protocol. Horenstein et al.[95] obtained the α-alkylated ketones (*R*)-**160** from



Scheme 48.



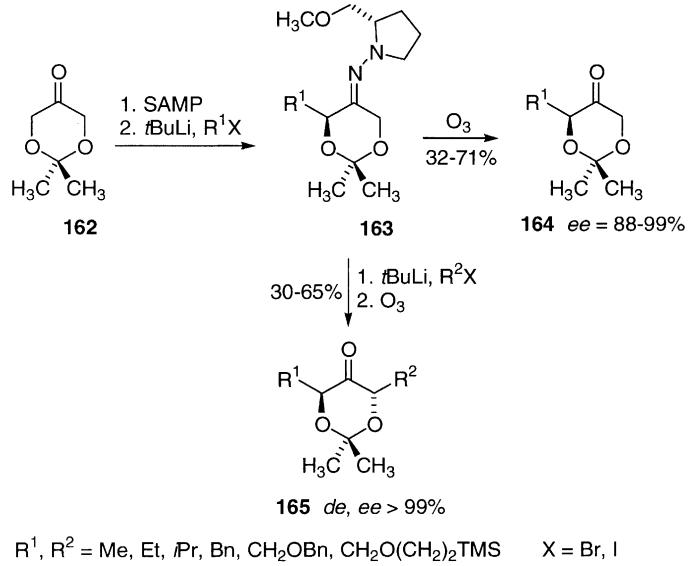
Scheme 49.



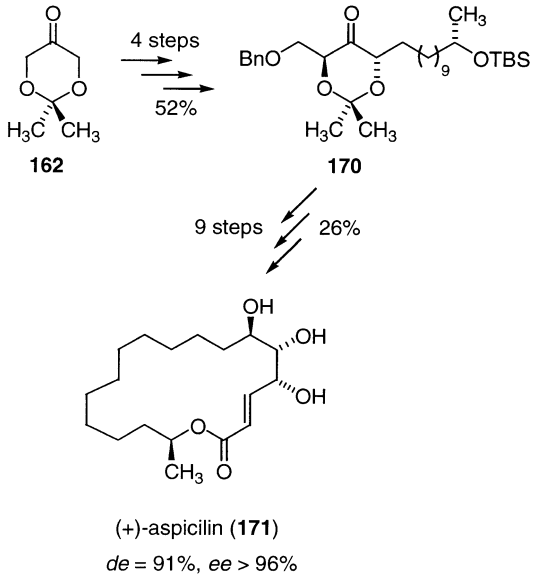
Scheme 51.

SAMP-hydrazone (*S*)-**159** in high yields (Scheme 49). Further transformations led to two potential glycosidase inhibitors, the 3,4-dihydroxy-5-alkylpiperidines (*S*,*S*,*R*)-**161** and (*R*,*R*,*R*)-**161** in 78 and 63% enantiomeric excess, respectively. The optical purity of neither the α-alkylated hydrazone, nor the ketone (*R*)-**160** was determined. Therefore the moderate ees of the piperidines **161** may correspond to a racemisation during the transformation of the ketone **160** into the target molecules.

2.1.4. Dioxanone derivatives. 2,2-Dimethyl-1,3-dioxan-5-one **162**[96] constitutes a versatile C_3-building block and a dihydroxyacetone phosphate (DHAP) equivalent in asymmetric synthesis.[97] In combination with the SAMP-/RAMP-hydrazone method, the dioxanone **162** has turned out to be broadly applicable in this aspect and can be used to carry out highly diastereo- and enantioselective C–C bond formations. Transformation into the corresponding SAMP-hydrazone together with α-alkylation afforded the hydrazones **163**, which were oxidatively cleaved to the α-alkylated ketones **164** in good overall yields and with excellent enantiomeric excesses (Scheme 50).[98] A second alkylation of the monoalkylated hydrazone **163** is possible in the same manner, occurring regioselectively at the α′-position, with diastereomeric and enantiomeric excesses of de, ee>98% to afford, after cleavage of the chiral auxiliary, *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanones **165**. Using this methodology, C_2-symmetric ketones[99] and unsymmetric α,α′-bisalkylated ketones[100] are available in good overall yields. Recently, additional methods for the recovery of the ketone moiety have been developed which comprise



Scheme 50.

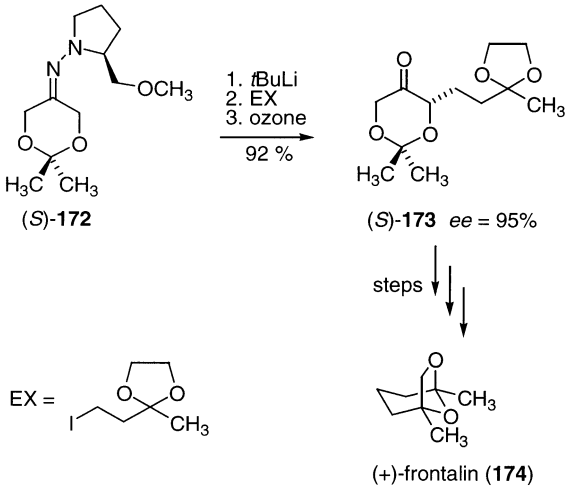


Scheme 52.

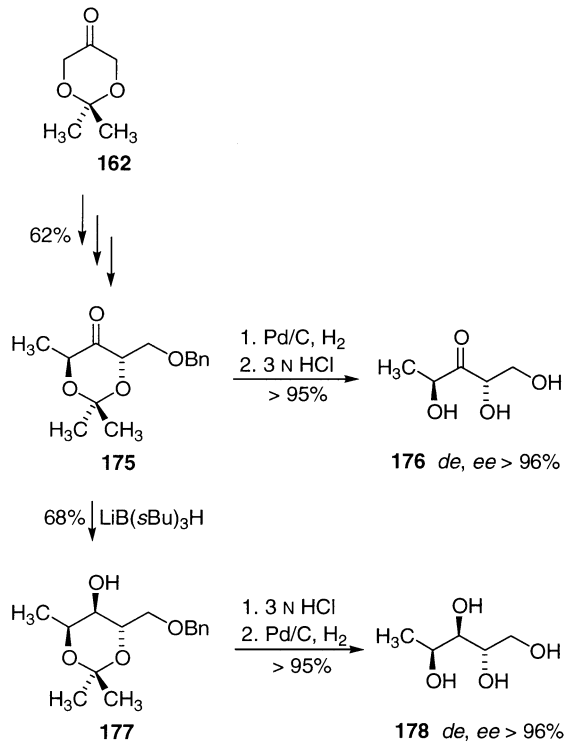
mild hydrolysis of the hydrazones **163** with an aqueous solution of copper(II) chloride[101] or oxalic acid[102]—allowing recycling of the auxiliary—to give considerably higher yields. For extremely acid sensitive compounds, aqueous ammonium hydrogen phosphate is recommended.[103]

As depicted in Scheme 51, the protocol can be extended by the introduction of a nitrogen functionality, leading finally to hydroxylated piperidines (azasugars). The reaction with substituted alkyl halides via **166**, for example, led to the piperidine **167** after intramolecular reductive amination and acetonide cleavage. Alternatively, the oxirane azide ring-opening variant via **168** gave rise to the polyhydroxylated piperidine **169**.[104]

The methodology could be successfully applied to various natural product syntheses. Employing the RAMP-hydrazone of **162**, the 18-membered lichen macrolide (+)-aspilicin (**171**) was synthesised via the key intermediate **170** (Scheme 52).[42]



Scheme 53.

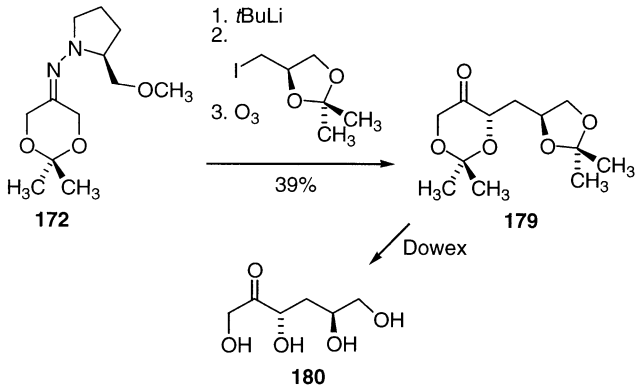


Scheme 54.

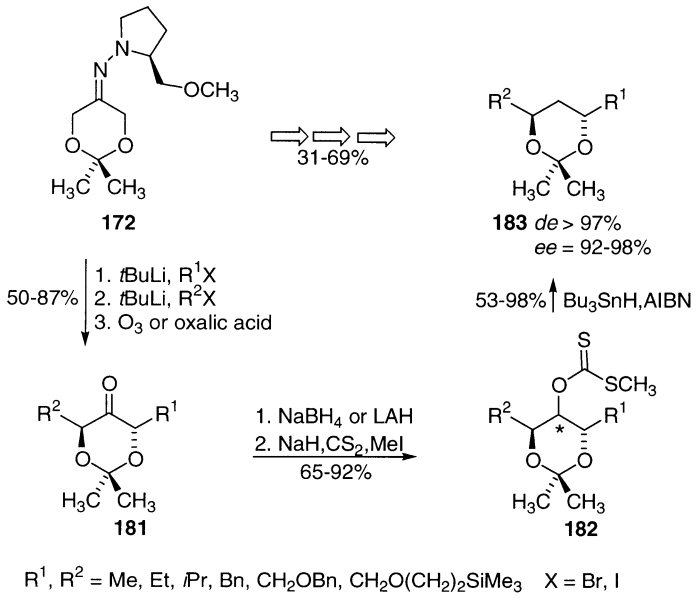
(+)-Frontalin (**174**), the aggregation pheromone of *Dendroctonus* beetles, was synthesised in eight steps and 40% overall yield via alkylation of the hydrazone **172** (Scheme 53). This method provided the key intermediate (*S*)-**173** with an ee of 95%. The levorotatory isomer could be obtained by using the RAMP derivative.[105]

The de novo synthesis of C_5- to C_9-desoxy sugars is possible by means of this protocol. As illustrated in Scheme 54, for example, the α,α′-bisalkylated ketone **175** could be converted into the polyhydroxyketone **176** after cleavage of the protecting groups. After reduction of **175** with L-selectride® to **177** and subsequent cleavage of the protecting groups, the corresponding polyols **178** are available in high yields and with excellent diastereo- and enantiomeric excesses.[106]

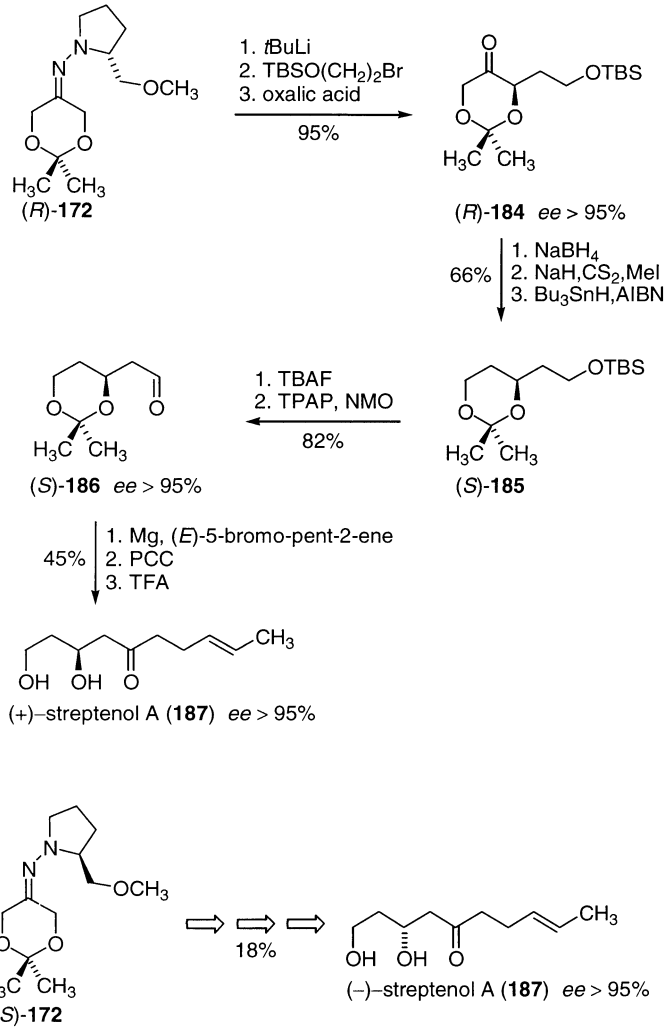
Desoxysugars are an important tool to understand biological



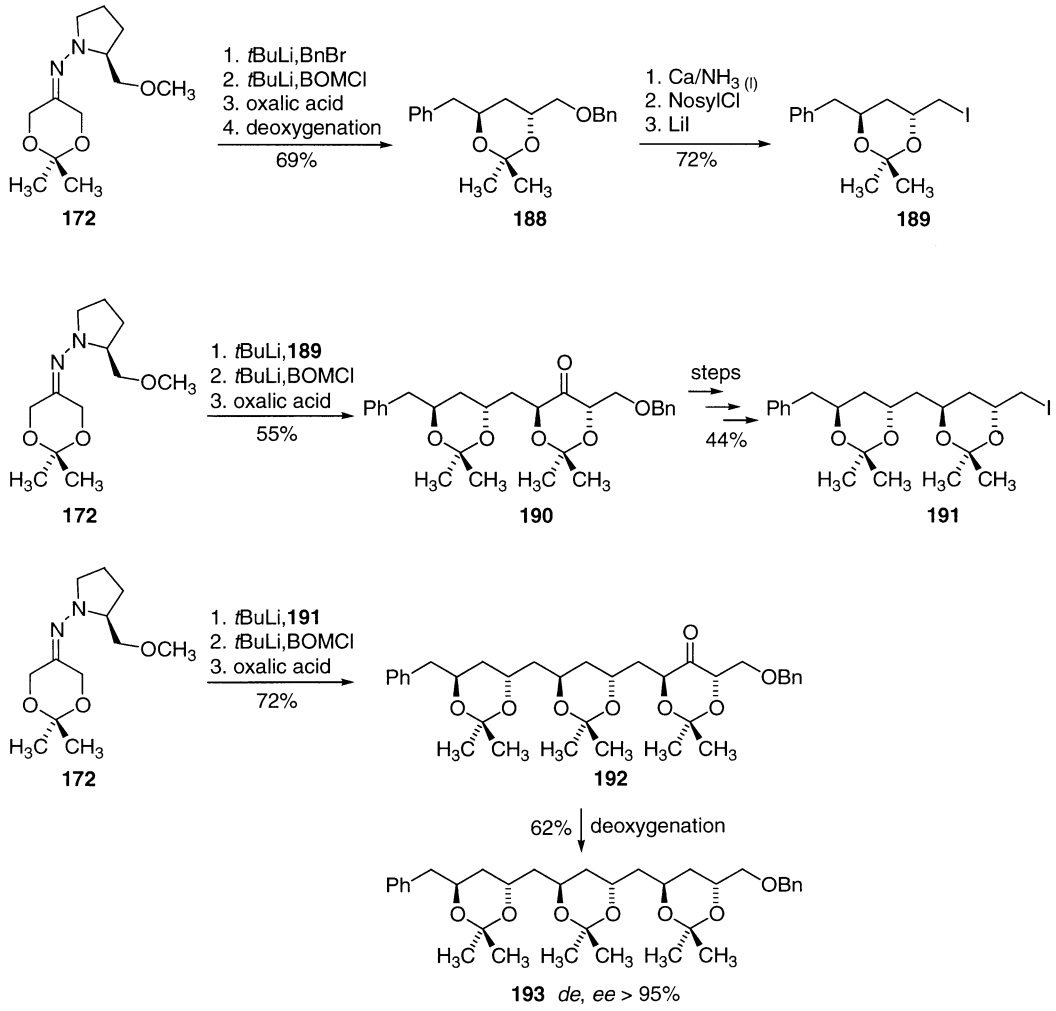
Scheme 55.



Scheme 56.



Scheme 57.



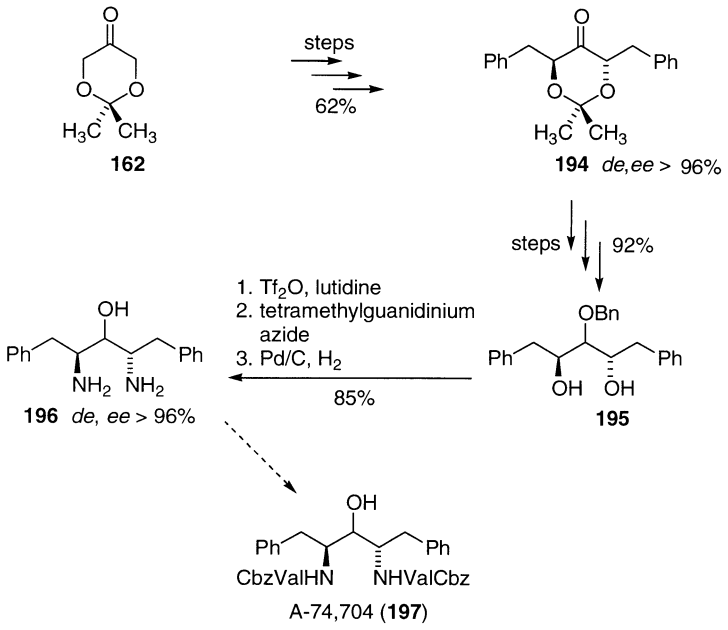
Scheme 58.

systems. In order to be able to study the mechanism and action of the glycolysis pathway, 4-deoxy-D-fructose **180** was prepared according to the method described above by alkylation of the hydrazone **172** with (*R*)-2,2-dimethyl-4-(iodomethyl)-1,3-dioxolane (Scheme 55).[107] Conversion of the protected ketopolyol **179** by acidic hydrolysis led to an aqueous solution of the desoxysugar **180**.

Using the dioxanone-SAMP-hydrazones as key building blocks for the synthesis of 1,3-diols, a reliable method of removal of the ketone functionality was crucial. Reduction of the α,α′-bisalkylated ketones **181** with sodium borohydride or lithium aluminium hydride gave rise to a diastereomeric mixture of the corresponding alcohols (Scheme 56). Conversion to the xanthate **182** set the stage for the Barton–McCombie[108] deoxygenation, which was accomplished with tributyltin hydride or a polymer-bound organotin hydride. This reaction sequence afforded the acetonide-protected *anti*-1,3-diols **183** in an overall yield of 31–69% starting from the hydrazone **172** and excellent de and ee values.[100]

The potential of this protocol could be proved by the synthesis of (+)-streptenol A (**187**, Scheme 57). The RAMP-hydrazone of 2,2-dimethyl-1,3-dioxan-5-one (*R*)-**172** was metallated with *t*BuLi, followed by alkylation of the resulting lithio azaenolate with 2-bromo-1-*tert*-butyldimethylsilyloxyethane. The chiral auxiliary was cleaved with oxalic acid to afford the ketone (*R*)-**184** in two steps in 95% yield and ee>95%. Removal of the ketone functionality in three steps led to the triol (*S*)-**185**. After removal of the protecting group with tetrabutylammonium fluoride (TBAF), subsequent oxidation with tetrapropylammonium perruthenate (TPAP) furnished the chiral aldehyde (*S*)-**186**. In the final steps, this aldehyde was submitted to a Grignard reaction, oxidation and removal of the acetonide-protecting group to yield (+)-streptenol A (**187**) in an overall yield of 23%. The same reaction sequence employing SAMP-hydrazone (*S*)-**172** gave (−)-streptenol A (**187**) in 18% yield.[109]

The development of a highly stereoselective synthesis of 1,3-polyol chains has received considerable attention in recent years, mainly due to the growing interest in polyenmacrolides as challenging synthetic targets with desirable pharmacological features.[110] Based on the results described above, an iterative asymmetric synthesis of protected *anti*-1,3 polyols was developed using the SAMP-hydrazone of 2,2-dimethyl-1,3-dioxan-5-one (Scheme 58).[111] Employing the previously-described reaction sequence, the protected diol **188** was synthesised in 69% yield. The use of



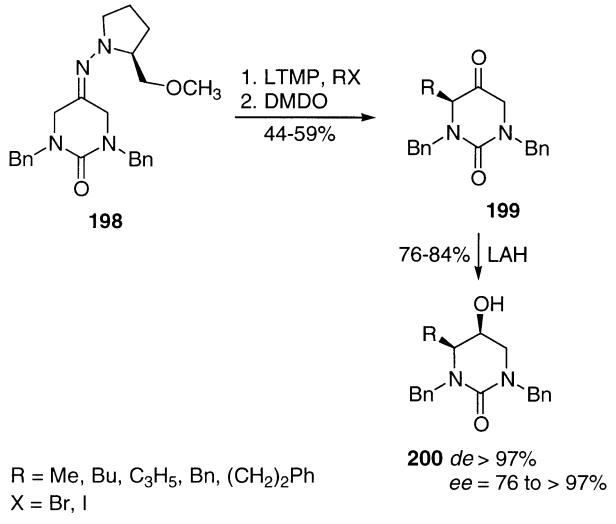
Scheme 59.

BOMCl in the second alkylation allows the conversion of the benzyl ether into the corresponding alcohol with calcium in liquid ammonia. A two-step conversion into the iodide via nucleophilic displacement of the corresponding nosylate gave **189**, which in turn can be used as a new electrophile in the iterative alkylation procedure. Sequential α,α′-bisalkylation with the iodide **189** and BOMCl led to the dioxanone **190** in 55% yield. Subsequent deoxygenation and conversion into the corresponding iodide gave **191**. Repetition of the reaction sequence with this electrophile gave via **192**, finally, the protected polyol **193** (de, ee>95%).

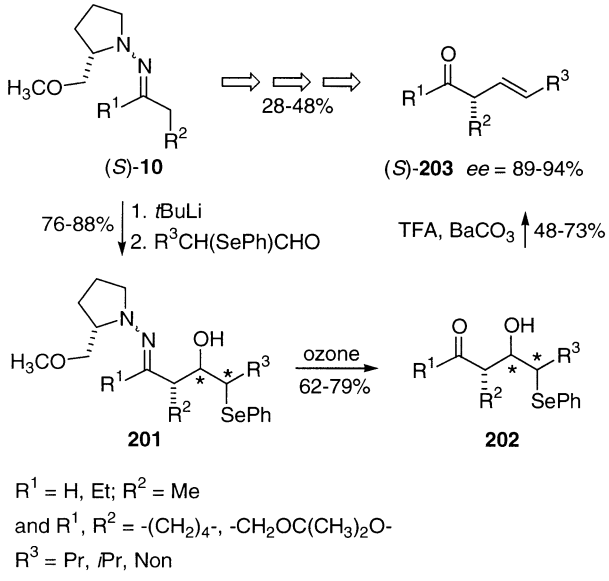
An efficient entry to C_2-symmetric HIV-1 protease inhibitors, e.g. A-74,704 (**197**) of Abbott, was opened up by using the α,α′-bisbenzylated ketone **194**. The 1,3-diol **195** was converted with tetramethylguanidinium azide and subsequent hydrogenation into the 1,3-diamine **196**, which was obtained with complete asymmetric induction as a general precursor for this class of inhibitors (Scheme 59).[112]

A different class of potential HIV-1 protease inhibitors is available by alkylation of the aza-analogous dioxanone-SAMP-hydrazone **198** (Scheme 60). Cleavage of the chiral auxiliary with dimethyldioxirane yielded the corresponding ketones **199**, which could be reduced diastereoselectively with lithium aluminium hydride to obtain the hexahydropyrimidin-2-on-5-ol-type heterocycles **200** in excellent diastereomeric and good to excellent enantiomeric excesses.[113]

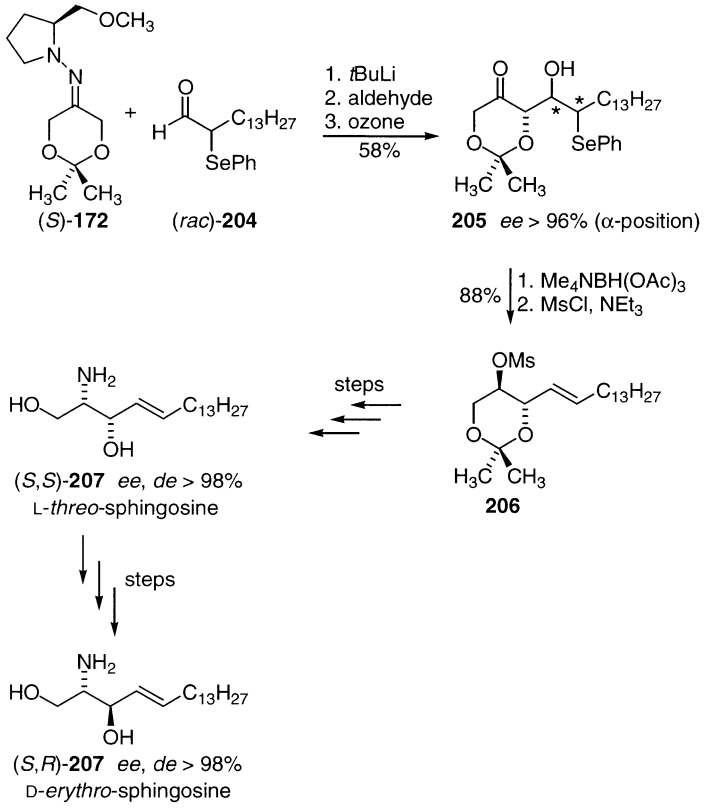
2.1.5. Miscellaneous. Chiral α-substituted β,γ-unsaturated aldehyde or ketone subunits are found in a very broad range



Scheme 60.

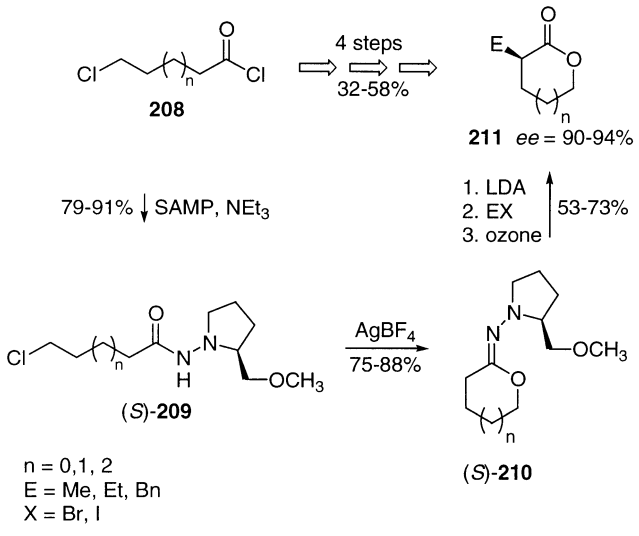


Scheme 61.



Scheme 62.

of bioactive compounds and natural products, e.g. pseudomonic acid,[114] stigmastatriene[115] and levuglandin.[116] The synthesis of this β,γ-unsaturated carbonyl unit has therefore received considerable attention. An asymmetric α-alkenylation took place in the reaction sequence depicted in Scheme 61.[117] The SAMP-hydrazones (*S*)-**10** could be deprotonated with *tert*-butyl lithium and subsequently treated with α-selenylaldehydes, alkenyl cation equivalents, to obtain the hydroxyhydrazones **201** with high asymmetric induction at the α-position. Cleavage of the auxiliary by ozonolysis to **202** and treatment with trifluoroacetic acid provided the α-alkenylated ketone derivatives (*S*)-**203** in good yield and with high enantiomeric excess.

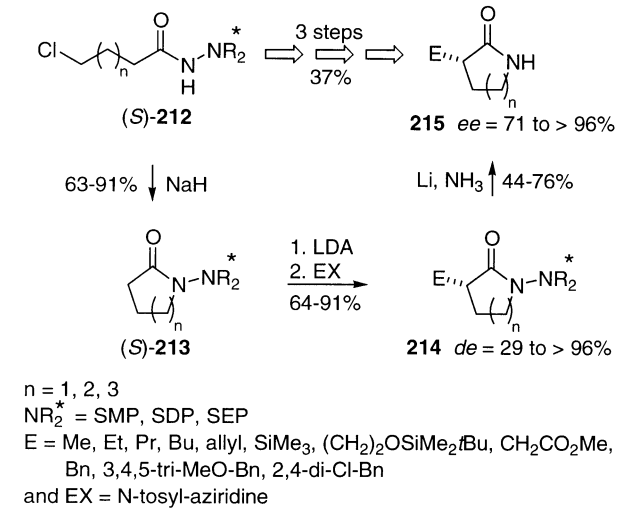


Scheme 63.

The same protocol was accomplished with dioxanone-SAMP-hydrazone (**172**) and *rac*-**204** providing the dioxanone derivative **205** in high enantiomeric purity based on the α-position (Scheme 62).[118] Subsequent transformations, including an elimination step, afforded the α-alkenylated triol **206**, which was further converted into optically pure L-*threo*- and D-*erythro*-sphingosine (**207**). This important compound shows broad biological activities, inhibiting protein kinase C in vivo and in vitro and playing a pivotal role in cell recognition, cell growth modulation and signal transduction.[118]

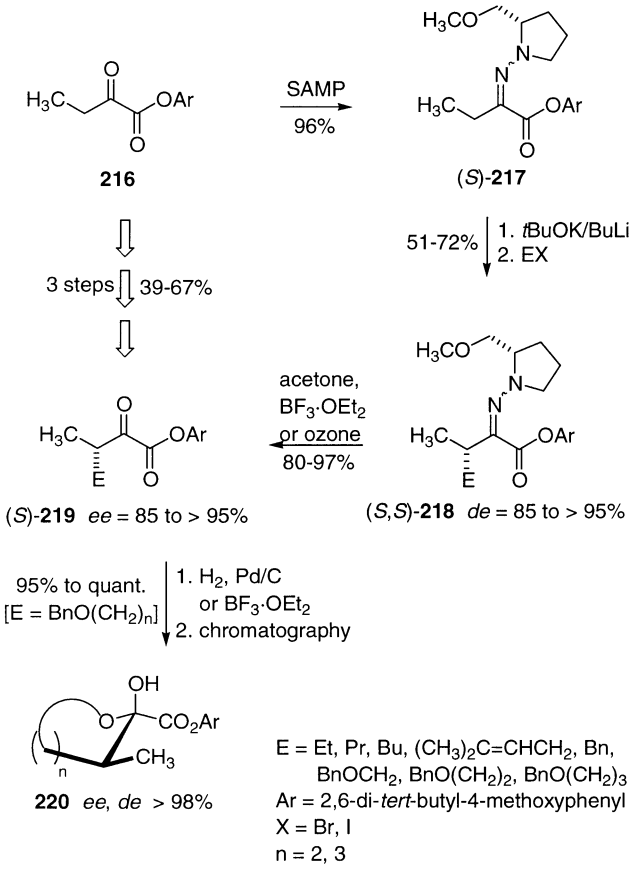
The lactone SAMP-hydrazones (*S*)-**210** could be prepared for the first time in a two-step procedure from the chloroalkanoyl chlorides **208** and the hydrazine SAMP (Scheme 63).[119] The key step was an ambidoselective cyclisation of the intermediate ω-chlorohydrazide **209** in the presence of silver tetrafluoroborate (C–O bond formation). These compounds undergo alkylation reactions with good yields and high selectivity.[120] Subsequent cleavage of the hydrazones furnished the α-substituted lactones **211** in up to 94% ee.

Starting from the chloroalkanoyl hydrazides **212**, an ambidoselective cyclisation reaction by means of sodium hydride furnished the lactams **213** (C–N bond formation,

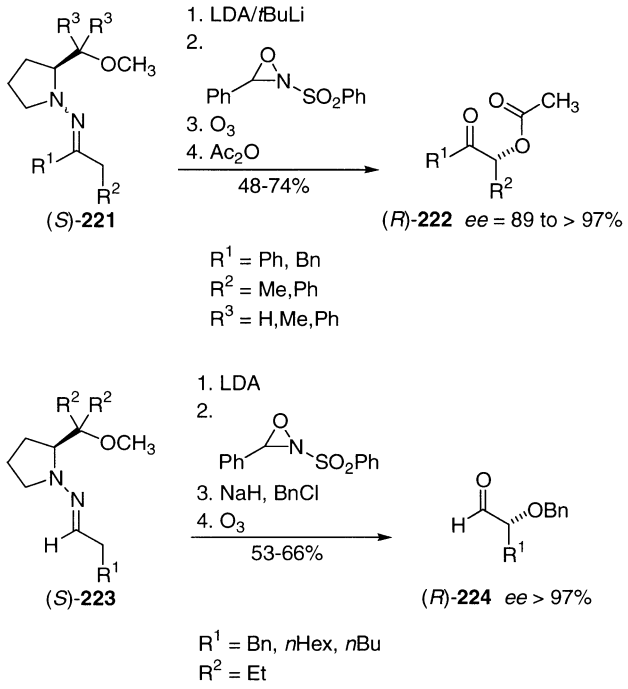


Scheme 64.

Scheme 64).[119] α-Alkylation and subsequent reductive N–N cleavage generated the α-substituted lactams **215**.[121] In this reaction, auxiliaries with a greater steric demand such as SADP or SAEP must be used for good selectivities. The undesired diastereomers of **214** could be separated in some cases. During the treatment with lithium in ammonia, a slight loss of optical purity was observed for the aziridine tosylate derivative. Reaction with 12 equiv. of lithium gave rise to the desired product in 55% yield with 83% ee, while



Scheme 65.



Scheme 66.

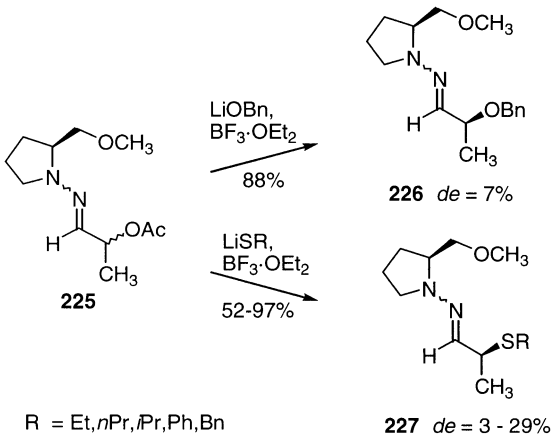
treatment with 10 equiv. of lithium yielded only 30% product with 95% ee.

As phosphoenolpyruvate (PEP), pyruvic acid plays a central role in the biosynthesis of diverse natural products, whereby PEP undergoes C–C linkage to aldehydes by means of aldol reactions catalysed by aldolases.[122] The 2-oxoester-SAMP-derivative (*S*)-**217**, obtained from **216** and SAMP, represents a chemical chiral equivalent to natural PEP (Scheme 65).[123] Alkylation of (*S*)-**217** afforded 3-substituted 2-oxoester derivatives **218** in very good diastereoselectivities. Self-condensation of the azaenolate ester was prevented by a sterically demanding ester substituent. Cleavage of the auxiliary with acetone/$BF_3{\cdot}OEt_2/H_2O$ yielded the ketoesters **219** without loss of optical purity. Removal of the benzylic protective group gave rise to deoxygenated ulosonic acid derivatives **220** in very good yields and selectivities.[124]

2.2. Carbon–heteroatom bond formation

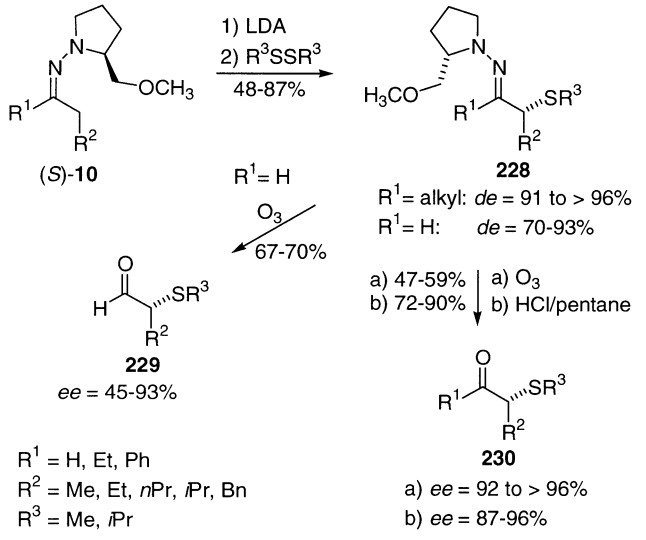
As discussed previously (Section 2.1.2), one possible pathway to α-heteroatom-substituted aldehydes was accomplished via carbon alkylation of the corresponding SAMP-/RAMP-hydrazones. Alternatively, by the use of heteroatom electrophiles, these chiral building blocks are accessible in the same way. As expected, the new stereogenic centre generated by this second pathway shows the opposite absolute configuration based on a uniform reaction mechanism for all electrophilic substitutions via the SAMP-/RAMP-hydrazone methodology.

As an example, the asymmetric α-hydroxylation of carbonyl compounds was achieved by employing an *N*-sulfonyl-oxaziridine according to Davis et al.[125] After deprotonation of the parent hydrazone **221** with LDA or *t*BuLi, the resulting azaenolate underwent facile oxidation by treatment with 2-(phenylsulfonyl)-3-phenyloxaziridine (Scheme 66). With



Scheme 67.

the ketones no other diastereomer was detectable, whereas the aldehyde hydrazones **223** showed lower diastereomeric excesses and separation of the minor diastereomer was necessary by flash chromatography at this stage. The ketone hydrazones were cleaved with ozone and protected with acetic anhydride to yield the highly enantiomerically enriched α-hydroxyketones **222**, while the aldehyde hydrazones were first benzylated with NaH/BnCl. Finally, ozonolysis led to the enantiomerically pure α-benzyloxyaldehydes **224**.[126]



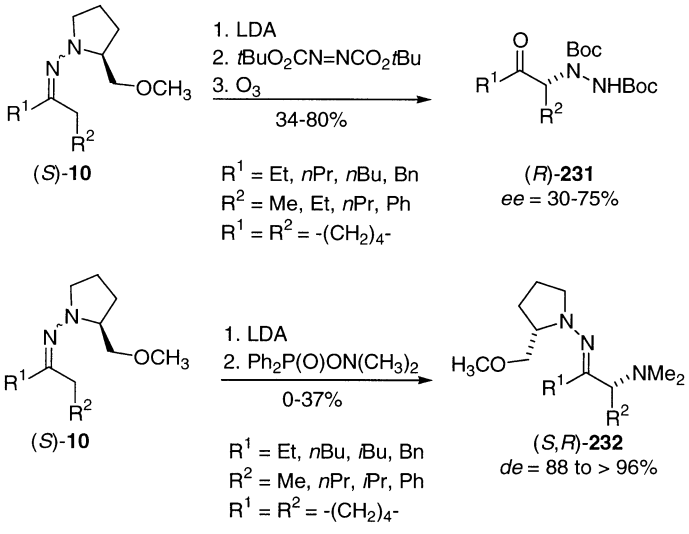
Scheme 68.

A different approach to α-benzyloxyaldehydes was tried using a 1:1 epimeric mixture of the α-acetoxyhydrazones **225**. An asymmetric nucleophilic displacement reaction with lithiated benzyl alcohol in the presence of BF_3·etherate afforded the 2-benzyloxypropanol SAMP-hydrazone **226** in 88% yield but with only 7% diastereomeric excess (Scheme 67).

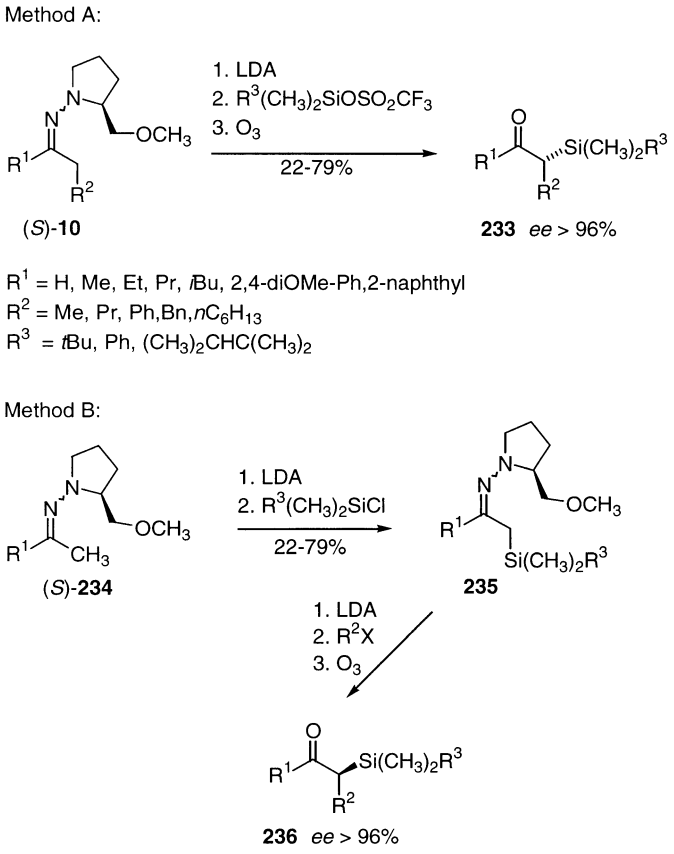
In order to introduce a sulfur atom α to the carbonyl functionality, the 2-thiolated SAMP-hydrazones **227** prepared in the same manner were obtained in good to excellent yields but low de values.[127]

Alternatively, the asymmetric α-sulfenylation of lithiated SAMP ketone hydrazones (*S*)-**10** with disulfides afforded the α-thiolated hydrazones **228** in good yields and high diastereomeric excesses (91–96%, Scheme 68). The relative and absolute configuration of the α-thiolated products was confirmed by X-ray structure analysis.[128] The chiral auxiliary could be removed by ozonolysis without racemisation to afford the α-thiolated ketones **230**. The competing oxidation of the thioether moiety to the corresponding sulfoxides, however, limited this method and gave moderate yields. Better yields of **230** were obtained when the hydrazones were vigorously stirred in a two-phase system of 2N hydrochloric acid/pentane, but partial racemisation occurred under these relatively harsh reaction conditions.

The synthesis of the α-thiolated aldehydes **229** via α-sulfenylated aldehyde hydrazones **228** proceeded in the same manner. Cleavage of the chiral auxiliary with hydrochloric acid/pentane resulted in racemisation while the oxidative cleavage with ozone gave rise to the α-thiolated aldehydes **229** in 67–70% yield without racemisation.[129] This methodology is a flexible alternative to the previously described



Scheme 69.



Scheme 70.

α-alkylation of thiolated acetaldehyde SAMP hydrazones, giving rise to the other enantiomer (see Section 2.1.2).

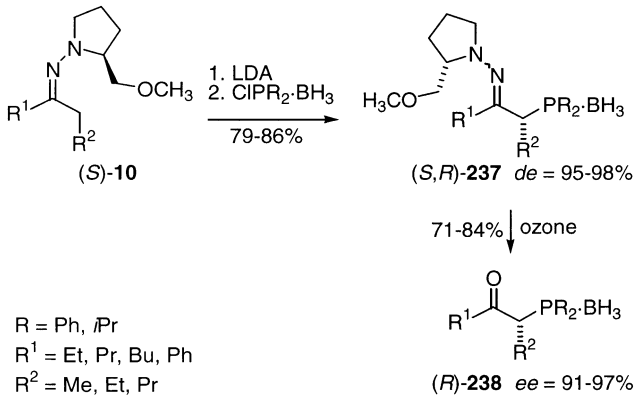
The asymmetric α-amination of SAMP-hydrazones **10** has been difficult to achieve to date. The best results were obtained using di-*tert*-butyl azodicarboxylate (DBAD) as the electrophile, leading to the α-hydrazino ketones (*R*)-**231** in moderate yields and enantiomeric excesses (Scheme 69). Cleavage of the N–N bond to obtain the α-aminated hydrazones has not yet been accomplished.

Alternatively, the asymmetric α-amination of SAMP-hydrazones **10** with diphenylphosphinyl-*N*,*N*-dimethylaminohydroxylamine gave the α-dimethylaminohydrazones (*S*,*R*)-**232** only in low yields but with good to excellent diastereoselectivities. Cleavage of the chiral auxiliary to regenerate the ketone moiety, however, has not been successful so far.[130]

The first enantioselective synthesis of α-silylated ketones and aldehydes **233** was developed using the SAMP methodology, whereas two pathways have been investigated (Scheme 70).[131] In method A, SAMP-hydrazones (*S*)-**10** were metallated with LDA or *t*BuLi in anhydrous diethyl ether (the use of THF results in ring opening and alkylation of the solvent, as mentioned above)[46] and treated with the appropriate silyl triflate to obtain the α-silylated hydrazones. Subsequent treatment with ozone afforded the α-silylated ketones and aldehydes **233** in virtually enantiomerically pure form (ee>96%) and excellent yields. The absolute and relative configuration of the silylated compounds was confirmed by X-ray structure analysis.[132]

Due to the poor regioselectivity of the α-alkylation of unsymmetric dialkyl ketone hydrazones, an alternative method B was developed. The starting material consisted of a methyl ketone hydrazone **234**, which was treated with commercially available chlorosilanes to obtain the silylated hydrazone **235**, followed by stereoselective α-alkylation with the corresponding alkyl halide. Since silicon stabilises the negative charge in the α-position of the carbonyl functionality, only the desired regioisomer was observed. This regiocontrol was also studied in detail by Rickards et al.[133] After cleavage of the chiral auxiliary with ozone, the α-silylated carbonyl compounds **236** were obtained in excellent enantiomeric excess.[134] Formally, the order of alkylation and silylation in method A and B is reversed. This results in the possibility of providing both enantiomerically pure α-silyl carbonyl compounds using the same chiral auxiliary.

The importance of these α-silyl carbonyl compounds has been shown by their use as versatile precursors for a wide range of transformations such as aldol-, Michael- and Darzens-type reactions. Employing the α-silyl carbonyl moiety as a traceless directing group, the first practical asymmetric Mannich reaction with these compounds was accomplished.[135] A variety of enantiomerically enriched α-heteroatom-substituted ketones (het=O, F, Br, I, N) has additionally been obtained by this method.



Scheme 71.

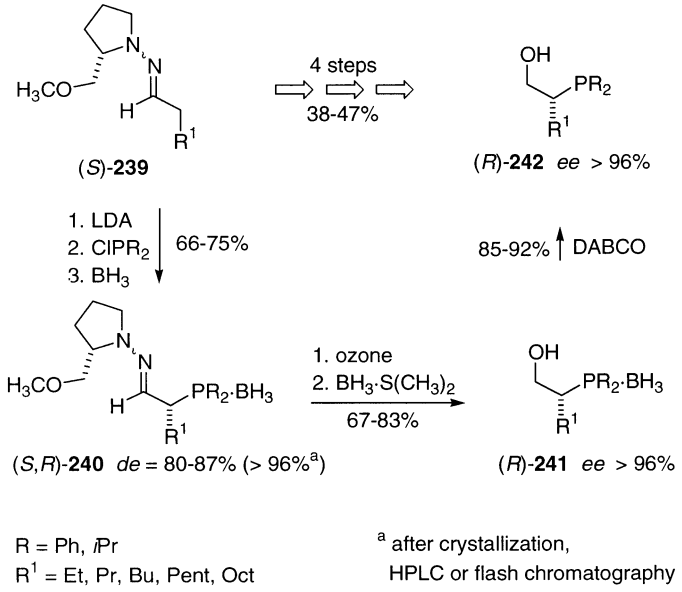
Functionalised phosphanes containing an additional oxygen donor functionality, e.g. esters,[136] ketones,[137] ethers[138] and alcohols,[139] were used as hemilabile ligands in homogeneous catalysis.[140] α-Phosphanyl ketones, for example, were successfully used as ligands in the Shell Higher Olefin Process (SHOP).[141] Despite the potential use of enantiopure α-phosphanyl ketones and phosphanyl alcohols in enantioselective catalysis, asymmetric syntheses of these important classes of compounds have hardly been investigated. The first attempts of the reaction of deprotonated SAMP-hydrazones with chlorodiphenylphosphane provided phosphinylated hydrazones with up to de=85%, but cleavage of the oxygen-sensitive substances could not be realised in a satisfactory manner.[73] Acidic hydrolysis under two-phase conditions furnished substituted ketones with 50% yield and only 21% ee, while ozonolysis afforded 72% of the corresponding phophane oxides as a racemic mixture.

Introduction of the borane protective group provided oxygen-stable compounds. Treatment of the hydrazones (*S*)-**10** with a borane-protected chlorodialkyl- or diphenylphosphane afforded the phosphinylated hydrazones (*S*,*R*)-**237** with nearly complete diastereoselectivity (Scheme 71). Subsequent cleavage of the auxiliary furnished the borane-protected phosphinylated ketones (*R*)-**238** in up to 97% ee.[142] The phosphinylation proceeds according to the same mechanism discussed for the alkylation reactions. The absolute configuration of the hydrazones (*S*,*R*)-**237** was established by NOE measurements and X-ray structure analysis.

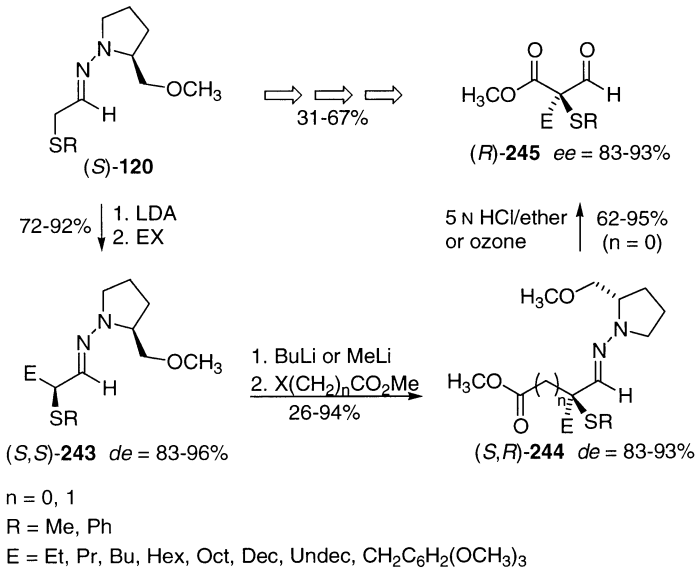
Based on the same concept, phosphinylation of aldehyde-SAMP derivatives was accomplished analogously (Scheme 72).[143] Deprotonation of the aldehyde hydrazones (*S*)-**239** with LDA, followed by treatment with chlorodialkyl- or diphenylphosphane and subsequent protection with borane afforded the phosphinylated aldehyde derivatives (*S*,*R*)-**240** in good yield and good selectivities. The undesired diastereomers are, with one exception, separable by chromatography. Instead of separate carbon–phosphorous bond generation and subsequent phosphorous protection, the transformation has also been carried out in one step. The reaction of the deprotonated hydrazones (*S*)-**239** with a protected chlorodialkyl- or diphenylphosphane therefore furnished the corresponding compounds (*S*,*R*)-**240**. Both the yields and selectivities were a little lower in the latter reaction. The auxiliary was subsequently cleaved by ozonolysis and the resulting aldehydes could be reduced in situ with the borane dimethylsulfide complex providing the phosphinylated alcohols (*R*)-**241**. Deprotection of the phosphorous group was carried out with diazabicyclooctane, furnishing the corresponding non-protected alcohols (*R*)-**242**.

2.3. Quaternisation

Application of the SAMP-/RAMP-hydrazone method offers an efficient and flexible access to compounds bearing a quaternary stereogenic centre. As mentioned above, sulfenylated hydrazones (*S*)-**120** can undergo alkylation reactions resulting in substituted hydrazones (*S*,*S*)-**243** with good yield and high diastereolectivity (Scheme 73).[144,145] Treatment with butyl or methyl lithium provided an



Scheme 72.

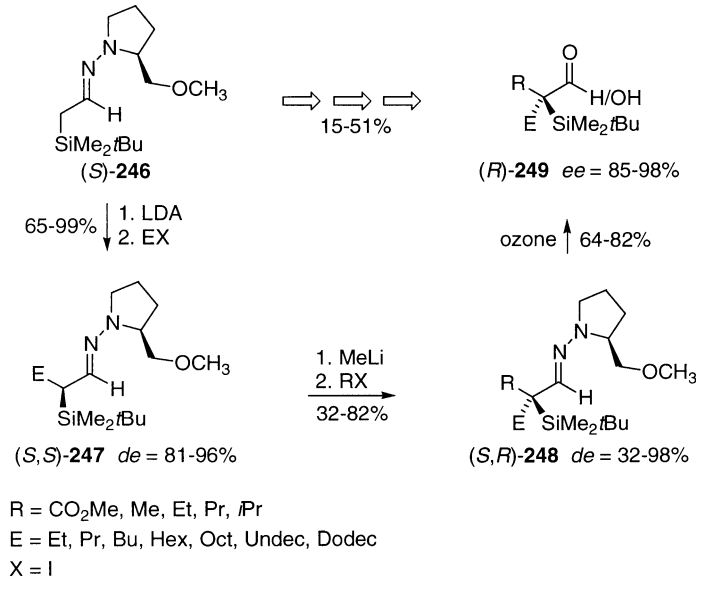


Scheme 73.

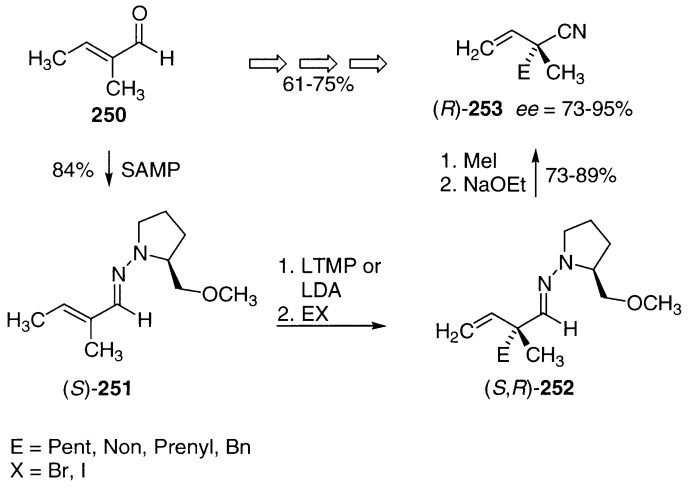
α-deprotonated hydrazone intermediate that can be trapped with another electrophile giving rise to the compounds (*S*,*R*)-**244** with a quaternary stereogenic centre. The hydrazones (*S*,*R*)-**244** were hydrolytically cleaved with HCl in a two-phase system or treated with ozone, giving rise to the corresponding aldehydes (*R*)-**245** in good yield and excellent enantioselectivities. The de values were determined by ^{13}C NMR spectroscopy of the hydrazones (*S*,*R*)-**244** and the ees by ^{19}F NMR spectroscopy of the Mosher ester derivatives of the corresponding alcohols, respectively. The absolute configuration of the aldehydes (*R*)-**245** was elucidated by X-ray analysis. These findings confirmed the postulated mechanism for electrophilic substitutions via SAMP-hydrazones for quaternisations.

Further studies concerning the absolute configuration of the conformationally flexible aldehyde ester have been made with methyl 2-formyl-2-(phenylsulfanyl)-3-(3,4,5-trimethoxyphenyl)-propanoate as a model system in order to compare the measured and calculated CD spectra.[146] The results were in good agreement with the former confirmation by X-ray structure analysis.

The analogous reaction sequence was accomplished for the silylated hydrazone (*S*)-**246** (Scheme 74).[144,145] Starting from the substituted hydrazones (*S*,*S*)-**247**, deprotonation with methyl lithium and subsequent treatment with different electrophiles provided the α-quaternary compounds (*S*,*R*)-**248**. Cleavage of the auxiliary with ozone furnished the quaternary 3-oxoesters (*R*)-**249** (R=CO_2Me) in good yields and high enantiomeric excesses. Ozonolysis of the alkyl-substituted hydrazones (*S*,*R*)-**248** (R=alkyl) gave rise to the corresponding carboxylic acids (*R*)-**249**. The absolute configuration was determined by X-ray structure



Scheme 74.

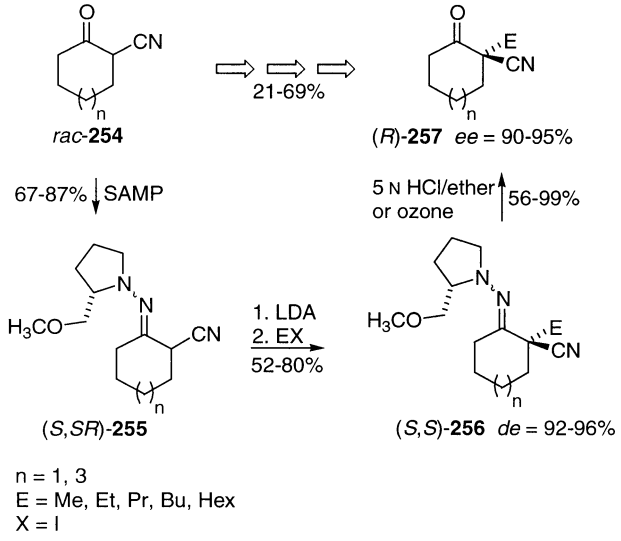


Scheme 75.

analysis of a single crystal of one of the carboxylic acid derivatives (*R*)-**249**.

Yamashita and co-workers have used the SAMP protocol for the asymmetric synthesis of α-quaternary β,γ-unsaturated nitriles (Scheme 75). The unsaturated aldehyde **250** was condensed with SAMP providing the hydrazone (*S*)-**251** in good yield.[147] Deprotonation and subsequent trapping with various electrophiles afforded the hydrazones (*S*,*R*)-**252**, in which a migration of the double bond to the terminal position occurs. Cleavage of the auxiliary gave the quaternary nitriles (*R*)-**253** in good yield and up to 95% ee.

Cyclic α-cyano-substituted hydrazone derivatives **255** obtained from the racemic ketones *rac*-**254** and SAMP could be deprotonated in the α-position with lithium diisopropylamide and subsequently trapped with various electrophiles affording the quaternary hydrazones (*S*,*S*)-**256** in good yield and excellent selectivity (Scheme 76).[148] Diastereomeric excesses were determined by ^{13}C NMR spectroscopy, while the absolute configuration of the new stereogenic centre was determined by X-ray analysis.

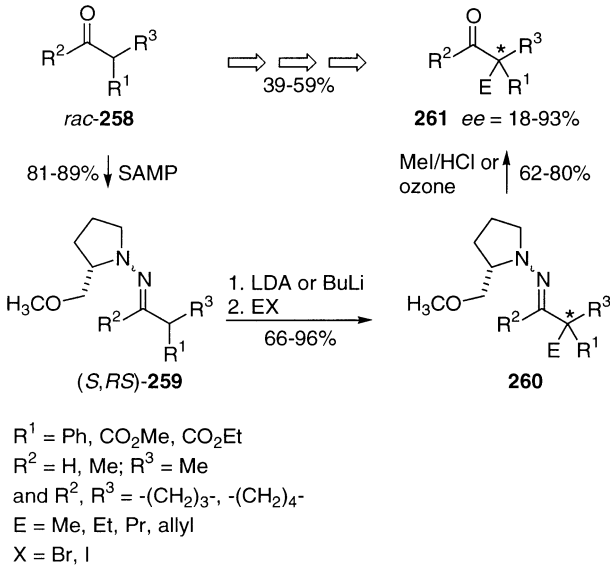


Scheme 76.

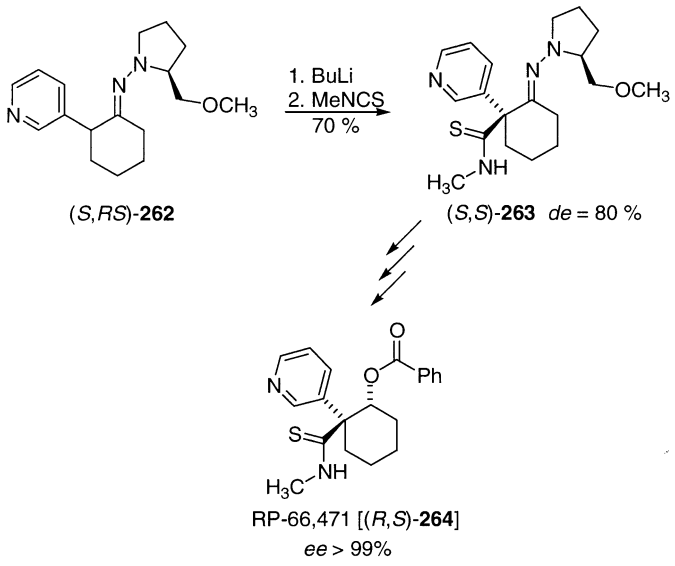
Acidic hydrolysis in a two-phase system or treatment with ozone furnished the cyclic ketones (*R*)-**257** bearing an α-quaternary centre (ee=90–95%).

A similar protocol led to open-chain derivatives with quaternary stereocenters (Scheme 77).[145] Starting from various SAMP derivatives (*S*,*RS*)-**259** derived from racemic aldehydes or ketones **258**, the reaction sequence provided the hydrazones **260** and subsequent cleavage afforded the quaternary building blocks **261**. The enantiomeric excess of the obtained substances was measured by NMR shift experiments, but the absolute configuration has not yet been determined.

Hart et al. applied this protocol using an α-substituted cyclic ketone system to provide the potent potassium channel opener RP-66,471 (**264**, Scheme 78).[149] Deprotonation of the hydrazone (*S*,*SR*)-**262** with butyl lithium and subsequent treatment with methyl isothiocyanate furnished the quaternary hydrazone (*S*,*S*)-**263** in 70% yield and 80% de. Further transformations and separation of the minor diastereomer



Scheme 77.



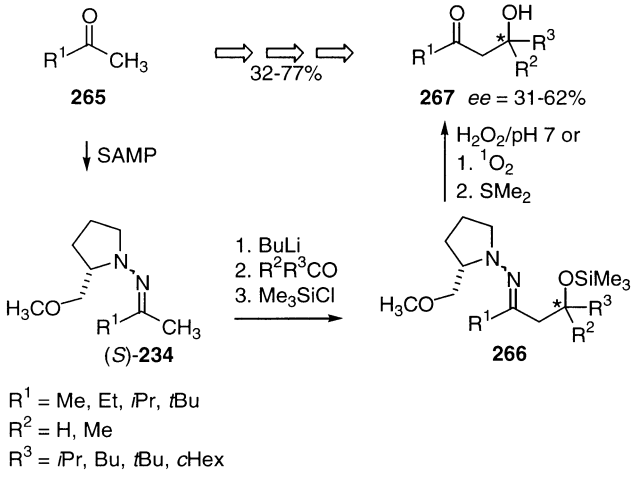
Scheme 78.

gave rise to the biologically active compound RP-66,471 (**264**) in enantiomerically pure form.

Further asymmetric syntheses providing building blocks that contain quaternary centres are described below.

3. Aldol reactions

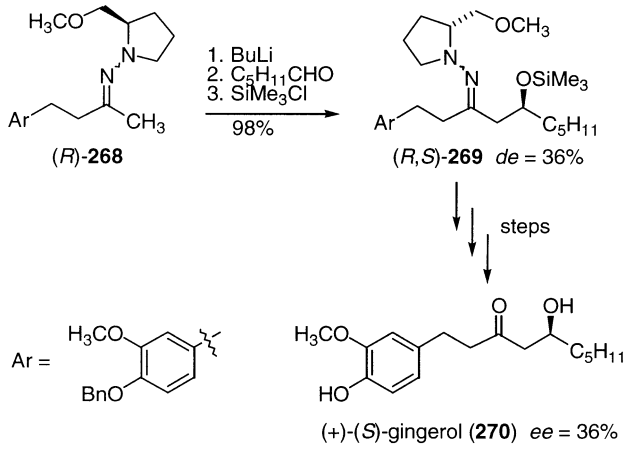
The aldol reaction is one of the fundamental methods for carbon–carbon bond formation and has shown a wide applicability. The first asymmetric intermolecular aldol reaction was accomplished by the SAMP-hydrazone method in 1978. The methyl ketones **265** were condensed with SAMP, furnishing the hydrazones (*S*)-**234** as the starting materials (Scheme 79).[150] Deprotonation with butyllithium and treatment with carbonyl compounds gave rise to β-hydroxyhydrazones as intermediates. In situ trapping with chlorotrimethylsilane opened access to the protected hydroxyhydrazones **266**. Cleavage of the auxiliary afforded the β-hydroxyketones **267** in moderate enantiomeric excesses. The latter step was performed by two alternative methods: treatment with hydrogen peroxide at pH 7 gave rise to the desired aldol adduct directly, while cleavage of the auxiliary with singlet oxygen made deprotection of the hydroxy group necessary in a second step. The abolute configuration of the resulting products was not determined.



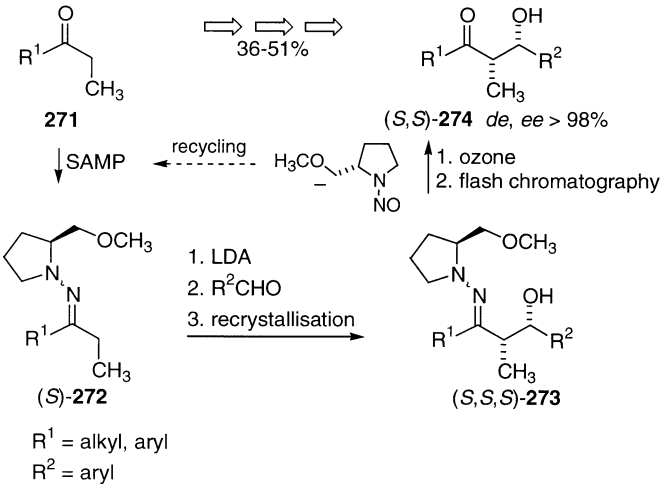
Scheme 79.

Using this protocol, the synthesis of enantiomerically enriched (+)- and (−)-[6]-gingerol (**270**), the pungent principle of ginger, could be accomplished (Scheme 80).[151] Starting from RAMP-hydrazone (*R*)-**268**, the reaction protocol depicted in Scheme 79 yielded the silyl-protected hydrazone (*R*,*S*)-**269** in 36% de. Further transformations gave rise to (+)-[6]-gingerol (**270**) with the same ee of 36%. Analogously, the reaction sequence starting from SAMP-hydrazone (*S*)-**268** yielded (−)-[6]-gingerol (**270**) with similar ee values.

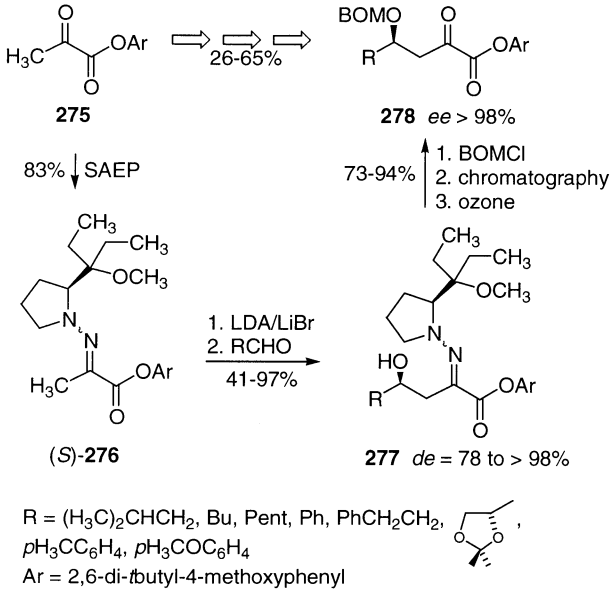
Additional investigations of this protocol showed that the reactions of α-substituted hydrazones with symmetric carbonyl compounds provided the new stereogenic centre in the α-position with >77% ee. Reactions with unsymmetric ketones and α-substituted hydrazones yielded β-hydroxyketones bearing a stereogenic centre in the α- and



Scheme 80.



Scheme 81.

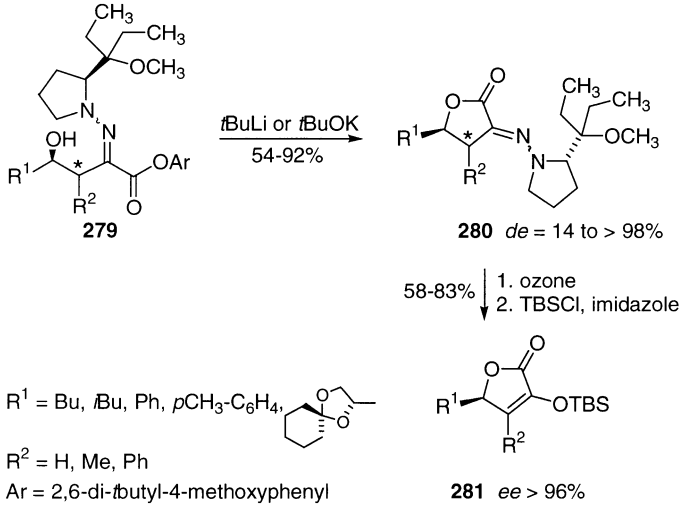


Scheme 82.

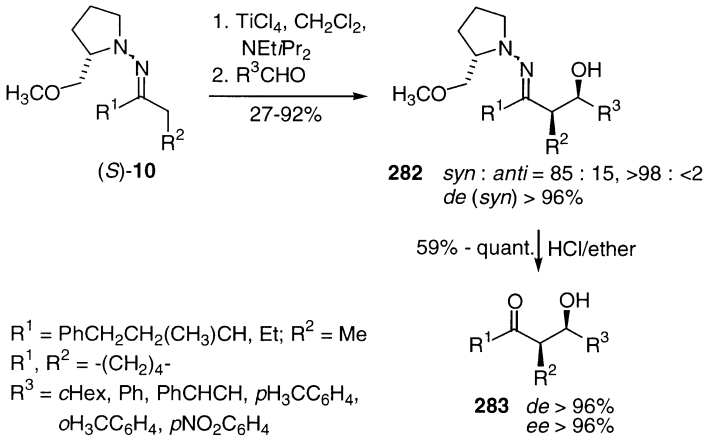
β-positions and led to stereoselectivities with changing de and ee values. Variation of the countercation from Li^+ to $Ti(OiPr)_3^+$, $MgBr^+$ or $SnCl^+$ sometimes led to higher asymmetric induction.[152]

As depicted in Scheme 81, the asymmetric aldol reaction of the ethyl ketones **271** with aldehydes via the SAMP-hydrazones (*S*)-**272** gave rise to the *syn*-aldol adducts (*S*,*S*,*S*)-**273** with de=51–80% and ee=70–80%. A single recrystallisation, however, afforded the pure stereoisomers (*S*,*S*,*S*)-**273**, which, after ozonolysis and recycling of the auxiliary, allowed the asymmetric synthesis of a variety of diastereo- and enantiomerically pure *syn*-aldol adducts (*S*,*S*)-**274** for the first time. The relative and absolute configurations could be determined by X-ray structure analysis.[20]

Condensation of the α-ketoester **275** with SAEP provided the hydrazone (*S*)-**276**, which represents a chiral PEP equivalent (see Section 2.1.5, Scheme 65).[123] Deprotonation with lithium diisopropylamide in the presence of lithium bromide and subsequent addition of an aldehyde furnished the β-hydroxyhydrazones **277** in good yield and good to excellent diastereoselectivity (Scheme 82).[153] Self-condensation



Scheme 83.



Scheme 84.

of the highly reactive azaenolate ester was prevented by sterically blocking the ester reactivity as the 2,6-di-*tert*-butyl-4-methoxyphenyl ester. Protection with benzyloxymethyl chloride and separation of the minor diastereomer by chromatography gave the diastereomerically pure hydrazones. Ozonolysis afforded the enantiomerically pure γ-hydroxy-α-ketoesters **278** in very good yields.

Lactonisation of the hydrazones **279** with an additional stereogenic centre in the 3-position obtained by the latter reaction sequence provided the γ-butyrolactone derivatives **280** (Scheme 83).[154] Ozonolytic cleavage of the auxiliary and subsequent treatment with chloro-*tert*-butyldimethylsilane afforded the protected isotetronic acid derivatives **281** in excellent enantiomeric purity. These compounds are important due to their wide range of biological activity and their use as building blocks in organic synthesis.

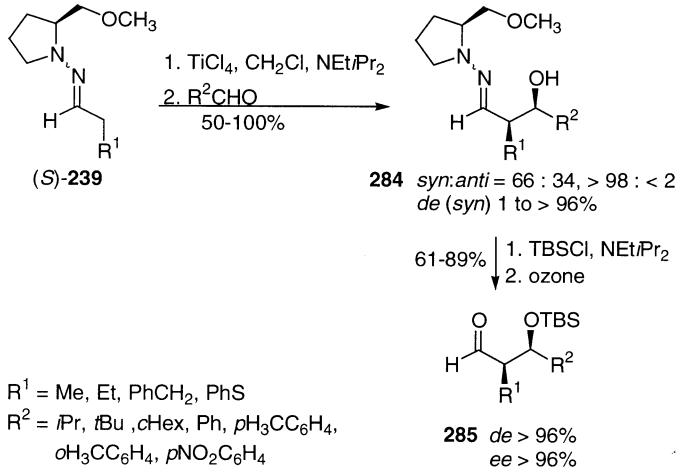
Recent progress in asymmetric aldol reactions via SAMP-hydrazones was achieved by the use of titanated azaenolates (Scheme 84).[155] In this variant, SAMP-hydrazones (*S*)-**10** were treated with titanium tetrachloride and Hünig's base providing the titanium complex as a deep red solution in dichloromethane. Subsequent trapping with an aldehyde furnished the β-hydroxyhydrazones **282** as single *syn*-diastereomers. Only one example showed a lower *syn*/*anti*-ratio of 85:15. Acidic hydrolysis in a two-phase system afforded the β-hydroxyketones **283** in up to quantitative yields and with excellent de and ee values. No single crystals of the red titanium azaenolate species have yet been obtained, and further details concerning the transition state and reaction mechanism have to be investigated.

The same procedure was applied to aldehyde-SAMP-hydrazones (*S*)-**239** (Scheme 85).[155] Reaction with various aldehydes provided the hydroxyhydrazones **284** with a lower selectivity compared to the ketone derivatives. After protection of the hydroxy functionality as a silyl ether, ozonolysis furnished the corresponding protected β-hydroxyaldehydes **285**. If the ozonolysis is performed without protection of the newly generated hydroxy group, none of the desired product was obtained, and this may be due to a retro-aldol reaction of the unprotected products.

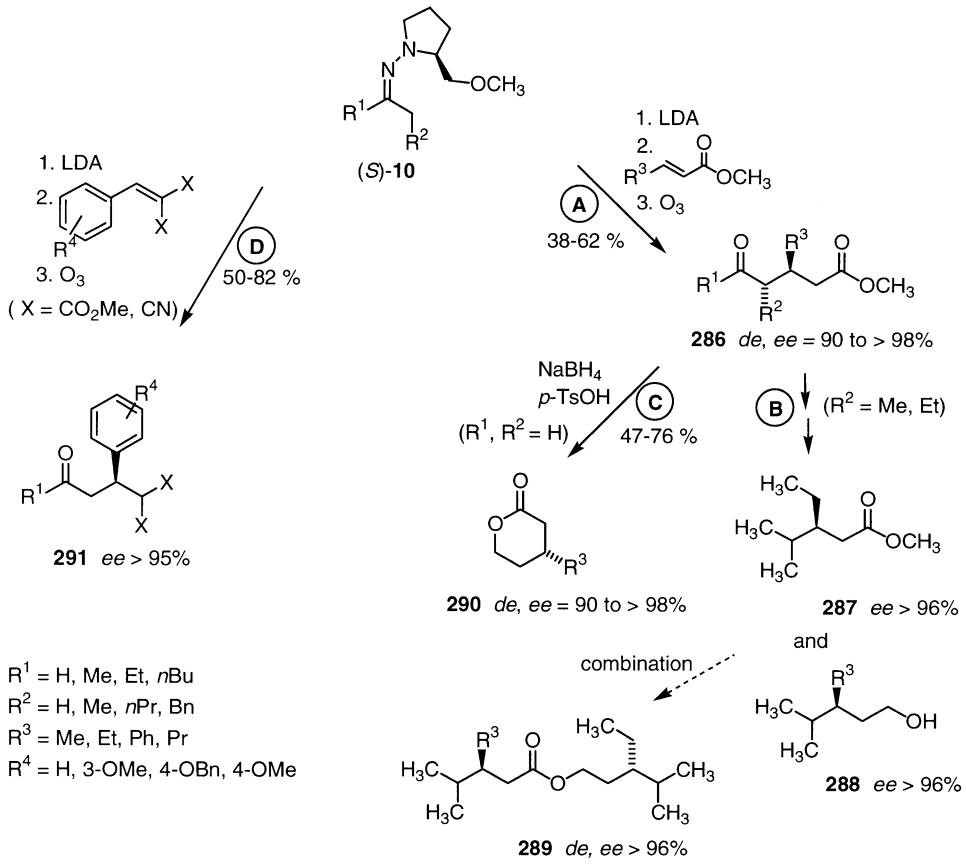
Other asymmetric aldol reactions related to this methodology have been accomplished via silylated ketone derivatives.[135,156,157]

4. Michael reactions

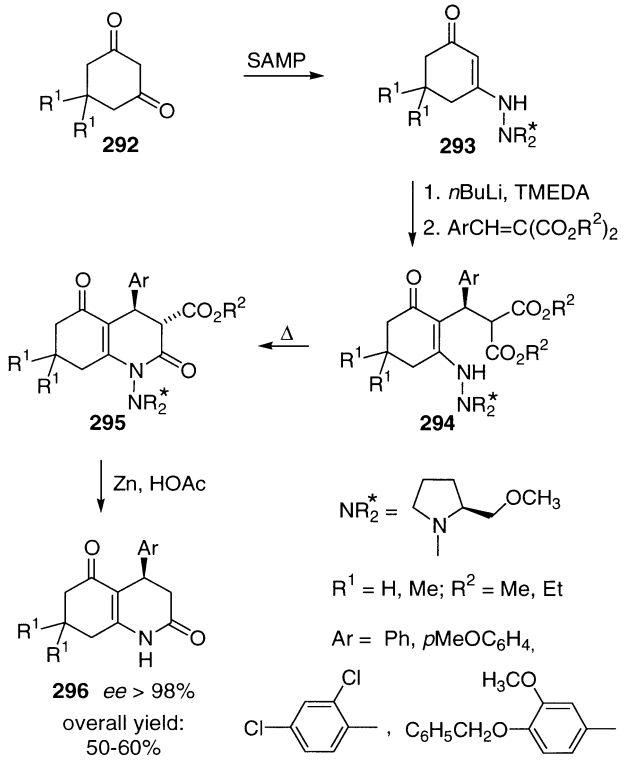
Asymmetric conjugate addition reactions have proved to be



Scheme 85.



Scheme 86.



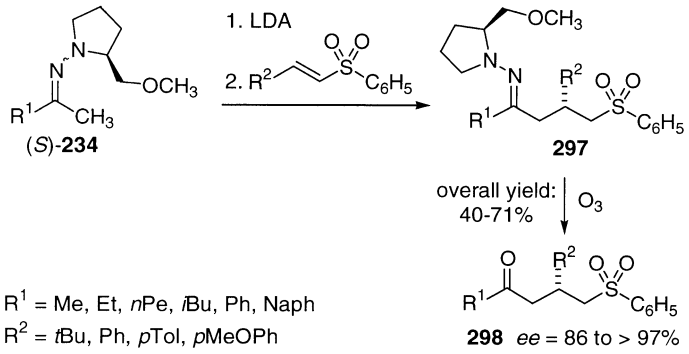
Scheme 87.

a powerful tool in organic synthesis to provide new carbon–carbon and carbon–heteroatom bond formations with asymmetric induction.[158] In the stoichiometric versions on the one hand, achiral nucleophiles can be added to Michael acceptors bearing the chiral auxiliary, and on the other hand, enantiopure nucleophiles are used with achiral acceptors leading finally to high ees. In addition, especially by the use of heteronucleophiles, the asymmetric Michael addition forming a carbon–heteroatom bond has been extensively investigated.[159]

4.1. Asymmetric Michael additions via SAMP-hydrazones

The first asymmetric Michael additions using SAMP/RAMP as the chiral auxiliary were the addition of lithiated SAMP-/RAMP-hydrazones of ketones (*S*)-**10** to α,β-unsaturated enoates. The desired aldehydes or ketoesters **286** could be obtained via the corresponding 1,4-adducts followed by cleavage of the C=N bond with ozone in 38–62% overall yield and very high diastereo- and enantiomeric excesses (Scheme 86, pathway A).[160] The optical antipode of **286** could be prepared in the same manner by using RAMP instead of SAMP as the chiral auxiliary. Applying this method, Katzenellenbogen et al. used both enantiomers of the ketoesters **286** (R^1=Me, R^2=Ph) to synthesise serine protease inhibitors by the formation of acyl enzyme complexes with α-chymotrypsin.[161]

This method could be successfully applied in the overall



Scheme 88.

enantioselective synthesis of pheromones of the small forest ant *Formica polyctena* and the red wood ant *F. rufa*. The simple esters and alcohols **287**–**289** have been isolated by Francke and co-workers.[162] The ester **287**, found in *F. pratensis*, showed a particularly strong aggression-inhibiting effect in laboratory bioassays. All of these volatile ant pheromone constituents could be prepared starting from simple precursors such as propanal, methyl 2-butenoate and methyl 2-pentenoate via 1,4-addition of the corresponding SAMP-hydrazones (Scheme 86, pathway B).[163]

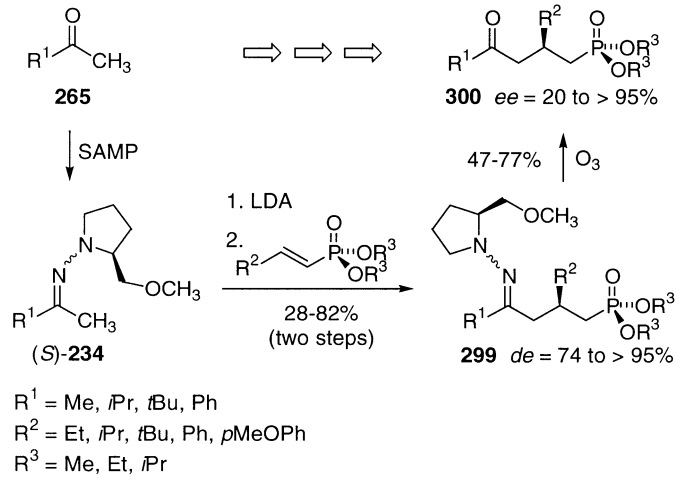
Using this conjugate addition as the key step, the achieved β-substituted δ-oxopentanoates **286** (R^1, R^2=H) could be transformed without racemisation to the corresponding δ-valerolactones **290** via reduction with sodium borohydride and cyclisation with toluenesulfonic acid (Scheme 86, pathway C).[164] Further extensions including the use of the different Michael acceptors 2-benzylidenemalonates and -dinitriles could be achieved. Employing the conjugate addition of SAMP-/RAMP-hydrazones, the 2-substituted 4-oxo-diesters and -dinitriles **291** were synthesised after oxidative cleavage of the 1,4-adducts by ozonolysis in good overall yields of 50–82% and high ees (Scheme 86, pathway D).[165]

Using the cyclic 1,3-diketones **292** diastereo- and enantioselective annulation to tetrahydro-quinolinediones of the types **295** and **296** in good overall yields (50–60%) is possible. The key step is again the Michael addition of the corresponding lithiated SAMP-/RAMP-hydrazones **293** to arylidenemalonates followed by lactamisation of **294**, observing virtually complete asymmetric induction (Scheme 87).[166]

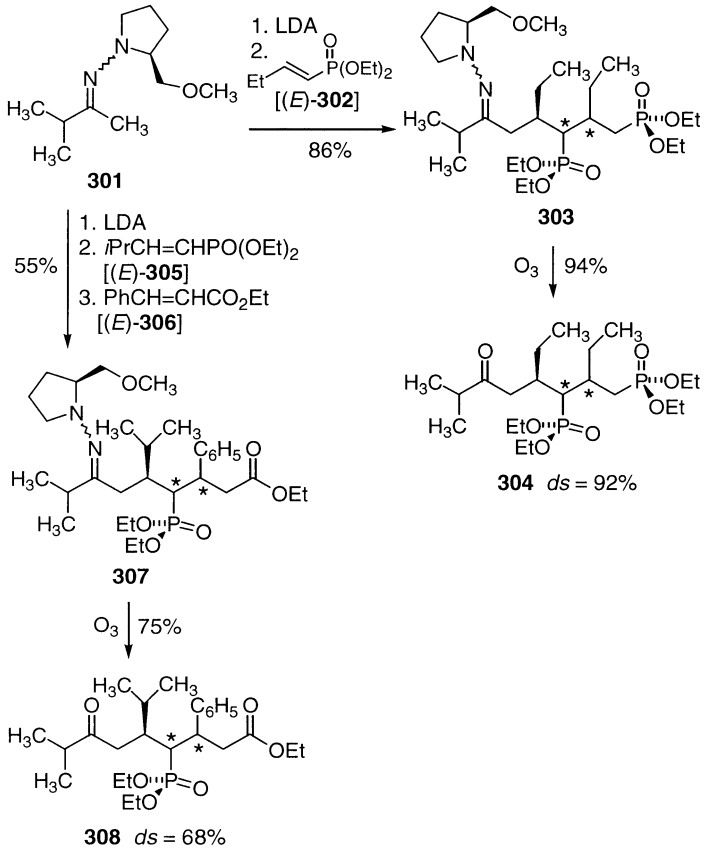
In the asymmetric conjugate addition, enoates, alkylidene malonates and the corresponding dinitriles have proved to be efficient Michael acceptors, and a useful extension of these methods is therefore the preparation of 2-substituted 4-oxosulfones **298** using alkenylsulfones as Michael acceptors. The desired products **298** could be obtained in 40–71% overall yield and ees of 86–>97%. In this procedure, the SAMP-hydrazones (*S*)-**234** were metallated with lithium diisopropylamide and treated with the alkenylsulfones. After oxidative cleavage of the crude Michael adducts **297** by ozonolysis, the desired oxosulfones **298** could be obtained (Scheme 88).[167] The use of RAMP as the chiral auxiliary led, as expected, to the corresponding enantiomers.

Since alkenylphosphonates should also be excellent Michael acceptors, a simple and efficient enantioselective 1,4-addition to alkenylphosphonates using metallated SAMP-/RAMP-hydrazones as nucleophiles has been accomplished.[168] The resulting 2-substituted 4-oxophosphonates **300** represent an interesting novel class of chiral bifunctional compounds.

As depicted in Scheme 89, the methyl ketones **265** were

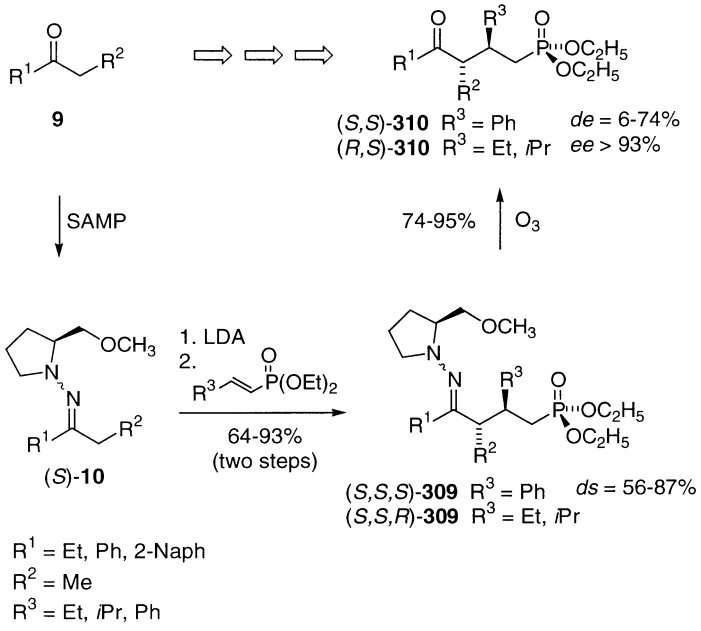


Scheme 89.

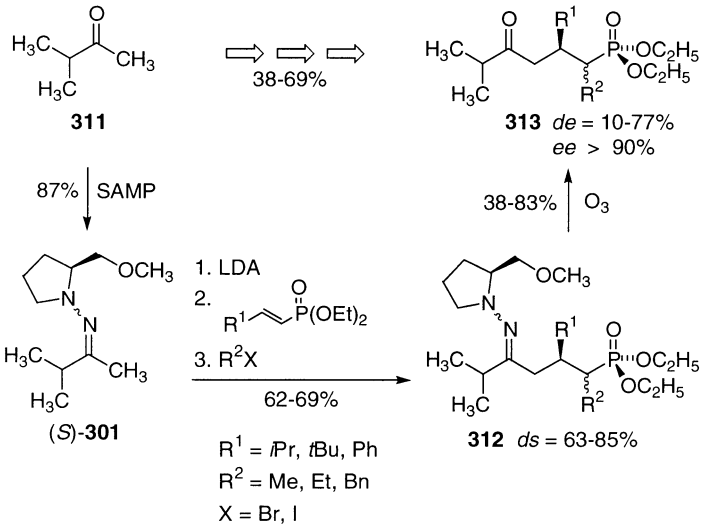


Scheme 90.

transformed into their corresponding SAMP hydrazones (*S*)-**234**, which were then metallated with lithium diisopropylamide in tetrahydrofuran. Next, the (*E*)-alkenylphosphonates were added and, after hydrolysis, the resulting adduct hydrazones **299** could be obtained. Their oxidative cleavage by ozonolysis furnished the 2-substituted 4-oxophosphonates **300** in good overall yields of 47–77%, if Michael acceptors of lower reactivity (R^2=*i*Pr, *t*Bu) were employed. With more reactive Michael acceptors (R^2=Et, Ph, *p*MeOPh), anionic dimerisation occurred as a side reaction, which reduced the chemical yields remarkably (overall 14–42%). The ees ranged from poor (20%) to excellent (>95%), depending on the substituents R^1, R^2 and R^3. Generally, the ees were high if sterically hindered



Scheme 91.



Scheme 92.

ketones **265** (R^1=*i*Pr, *t*Bu) and less reactive acceptors with sterically demanding substituents R^2 and R^3 were employed.

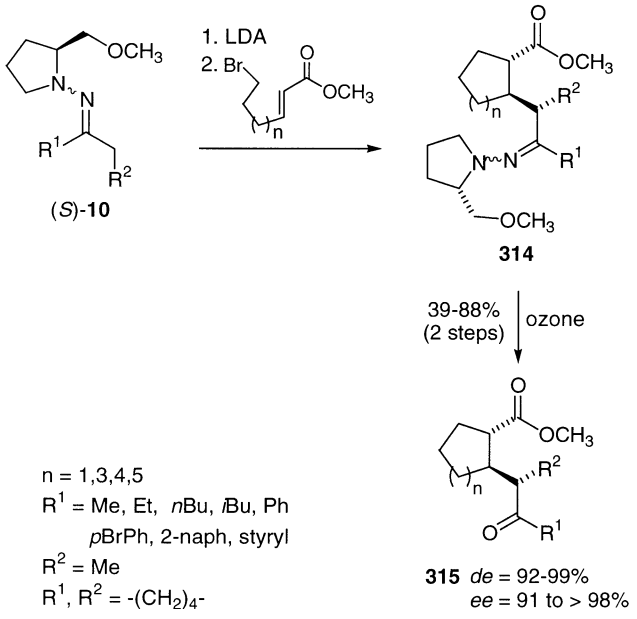
The P=O-stabilised lithio anions, which were generated primarily by the Michael addition, are themselves reactive nucleophiles in the tandem reaction with the substrate Michael acceptor.[169] As shown in Scheme 90, 3-methylbutanone-SAMP-hydrazone **301** and 2 equiv. of the very reactive butenylphosphonate **302** afforded the double Michael adduct **303**. After removal of the auxiliary, the keto derivative **304** was obtained with a high diastereoselectivity and in excellent yield.

This Michael tandem protocol can be used to build up long carbon chains with variable substitution patterns. The phosphonate Michael acceptor **305**, for example, was added to the hydrazone **301** as described and the primary 1,4-adduct anion was trapped with (*E*)-ethyl cinnamate **306**. The double Michael adduct **307**, bearing three new stereocentres, was obtained in an overall yield of 55% and ozonolysis generated the ketophosphonate ester **308**.

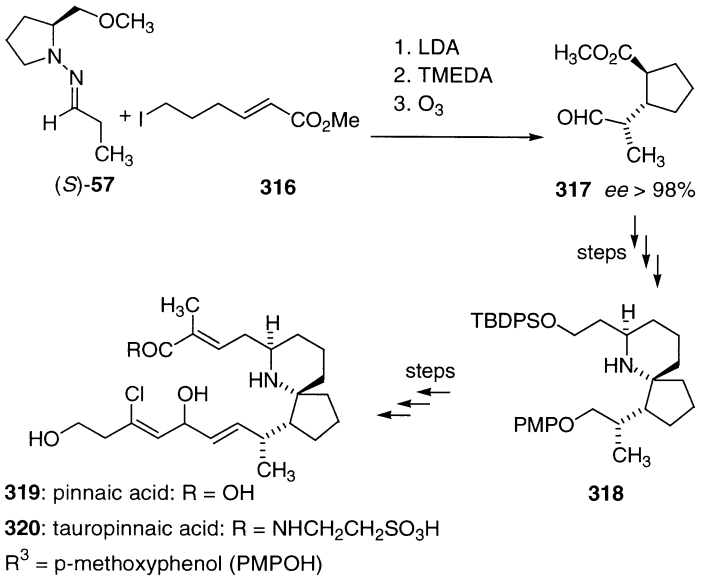
In order to extend this synthetic method, the synthesis of 2,3- and 1,2-disubstituted 4-oxophosphonates via diastereo- and enantioselective 1,4-additions to alkenylphosphonates was investigated.[170] A variety of aryl ethyl ketones and diethyl ketone **9** were transformed to the corresponding SAMP-hydrazones (*S*)-**10** and then metallated with lithium diisopropylamide. The Michael reactions were carried out by addition of the (*E*)-alkenylphosphonates (R^3=Et, *i*Pr, Ph) to the azaenolates. The Michael adducts **309** were obtained as yellow oils in good yield and with moderate to good diastereoselectivities (Scheme 91). Cleavage of the adduct hydrazones **309** was readily achieved by ozonolysis, leading to the 2,3-disubstituted 4-oxophosphonates **310**.

When further exploring this methodology, the synthesis was directed towards 1,2-disubstituted 4-oxophosphonates. In Scheme 92, a simple and efficient diastereo- and enantioselective synthesis of this class of compounds **313** is presented.[170] 3-Methylbutan-2-one (**311**) was converted to the corresponding SAMP-hydrazone (*S*)-**301**, which was metallated and then added to various alkenylphosphonates following the standard protocol. The intermediate P=O-stabilised adduct anions were trapped with alkyl bromides, iodides or sulfates, giving the tandem adduct hydrazones **312** in good yields and with moderate to good diastereoselectivities. The 1,2-disubstituted hydrazonephosphonates **312** were cleaved by ozonolysis, furnishing the compounds **313** with moderate to good overall yields and diastereomeric excesses of 10–77% and good enantiomeric excesses of >90%.

An elegant method for constructing carbocycles is a combination of a Michael addition, followed by an intramolecular trapping of the resulting acceptor enolate, the Michael-Initiated Ring Closure (MIRC reaction).[171] As shown above, metallated SAMP-/RAMP-hydrazones have proved to be excellent chiral Michael donors in a broad range of reactions. Adapting the MIRC reaction method therefore

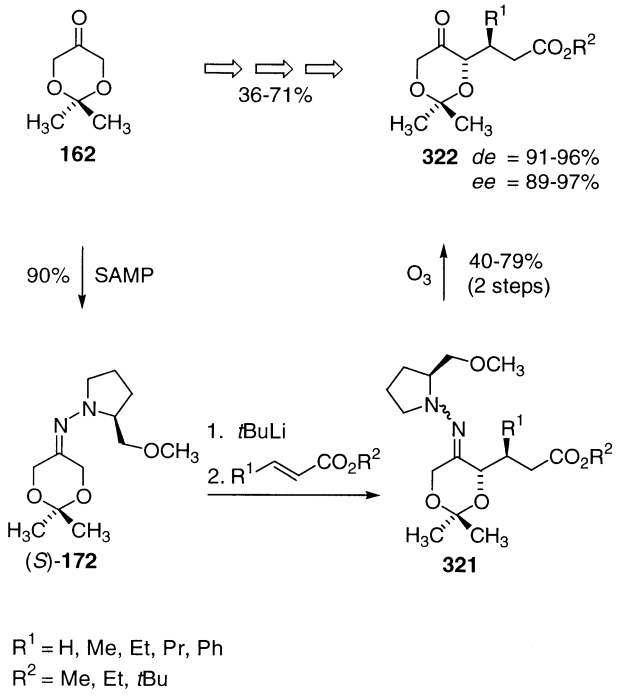


Scheme 93.



Scheme 94.

opened a highly diastereo- and enantioselective route to the *trans*-disubstituted cyclopentanoates **315** (Scheme 93). Metallation of the hydrazones (*S*)-**10** with LDA, for example, followed by addition to the ω-functionalised Michael acceptor methyl (*E*)-6-bromo-hex-2-enoate, led after oxidative cleavage of **314** with ozone to the *trans*-disubstituted cyclopentanoates **315** in good overall yields with excellent diastereo- and enantioselectivities.[172] This method has a broad applicability, because 3-, 5-, 6- and 7-membered rings may be prepared, other Michael acceptors such as sulfones can be used and excellent control of the three contiguous stereocenters was achieved.



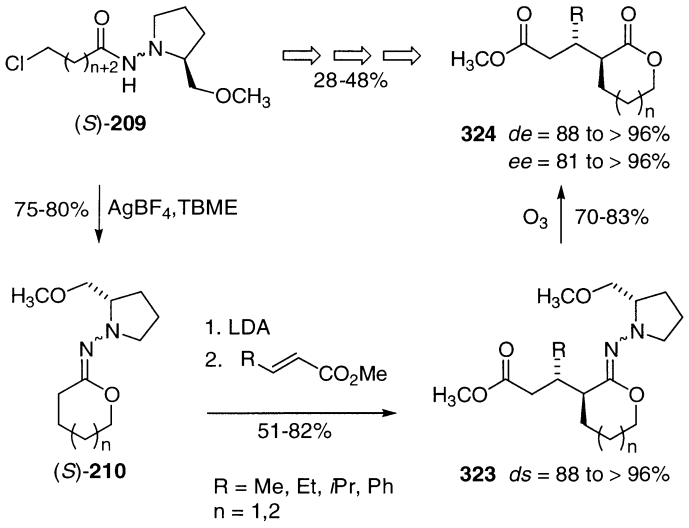
Scheme 95.

Application of this method resulted in the synthesis of the azaspiro core of pinnaic acids by Uemura et al.[173] While searching for biologically active substances from marine bivalves, they found the potent PLA_2 inhibitors, pinnaic acid **319** and tauropinnaic acid **320**, both from *Pinna muricata*.[174] These bioactive compounds have potential therapeutic value in the treatment of inflammation and by inhibiting cytosolic phospholipases. As an aspect of their synthetic strategy leading to these bioactive compounds, the azaspiro moiety had to be built up. The asymmetric MIRC-reaction was used, starting from propanal-SAMP-hydrazone (*S*)-**57**, which after reaction with the Michael acceptor **316** and removal of the chiral auxiliary led to the cyclic aldehyde **317** as a single stereoisomer (ee>98%). Further reactions provided the desired azaspiro compound **318** (Scheme 94).

As part of the continuing work on asymmetric synthesis of polyoxygenated compounds, the highly diastereo- and enantioselective Michael addition of SAMP-hydrazones (*S*)-**172** to α,β-unsaturated (*E*)-esters was investigated.[175] As shown in Scheme 95, after deprotonation of (*S*)-**172** with *t*BuLi and addition of the enoate to the azaenolate, the desired Michael adducts **321** could be achieved. In order to obtain good yields, the crude hydrazones **321** were directly subjected to the oxidative removal of the chiral auxiliary with ozone. The resulting oxoesters **322** were obtained in good yields and with excellent diastereo- and enantiomeric excesses.

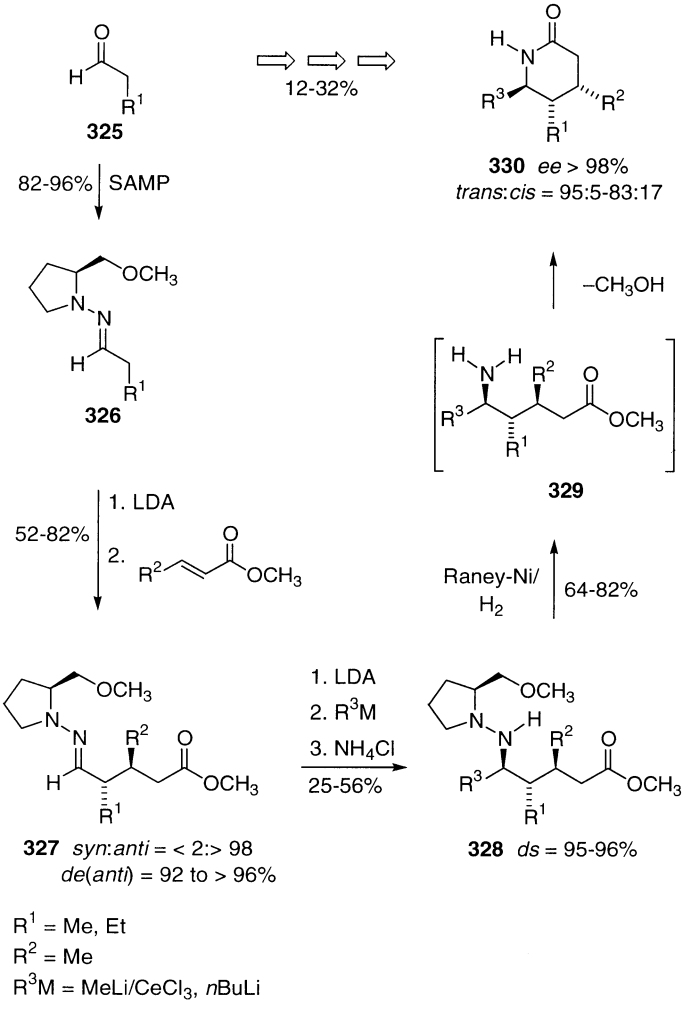
Lactones and their derivatives are of great importance as structural elements in a wide range of natural products such as sesquiterpene lactones[176] or functionalised γ- and δ-lactones.[177] As they show important biological activitities, e.g. as semiochemicals, flavours and fragrances, antibiotics or cytostatics, their diastereo- and enantioselective synthesis is of great interest.

As shown in Scheme 63, one pathway to 2-alkyl-substituted lactones is the alkylation of metallated lactone

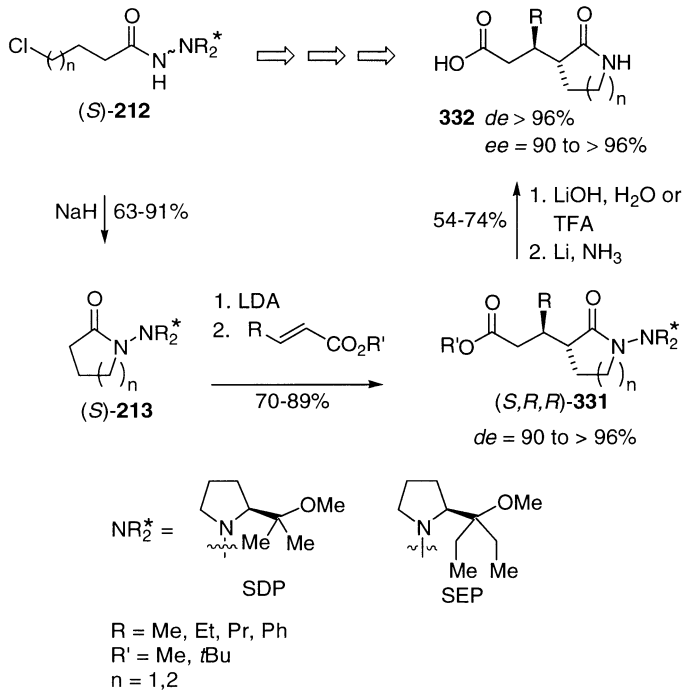


Scheme 96.

SAMP-hydrazones and subsequent oxidative removal of the chiral auxiliary.[120] A second pathway is the diastereo- and enantioselective Michael addition of metallated lactone SAMP-hydrazones (*S*)-**210** obtainable from the ω-chloro-alkanoyl-SAMP-hydrazides (*S*)-**209** to the α,β-unsaturated (*E*)-esters.[178] The crude Michael adducts **323** were obtained in good yields and high diastereoselectivities. After removal of the chiral auxiliary, the lactone esters **324** were obtained in good overall yields and high diastereo- and enantiomeric excesses (Scheme 96).



Scheme 97.



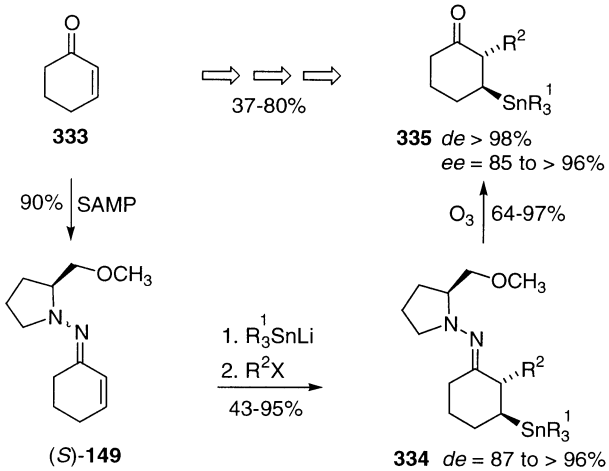
Scheme 98.

The lactam moiety is also a commonly occurring structural feature of various biologically active compounds and natural products,[179,180] and is a useful building block for alkaloids.[181] As lactams are cyclic amides, they can be converted to their corresponding amino acids by ring opening.

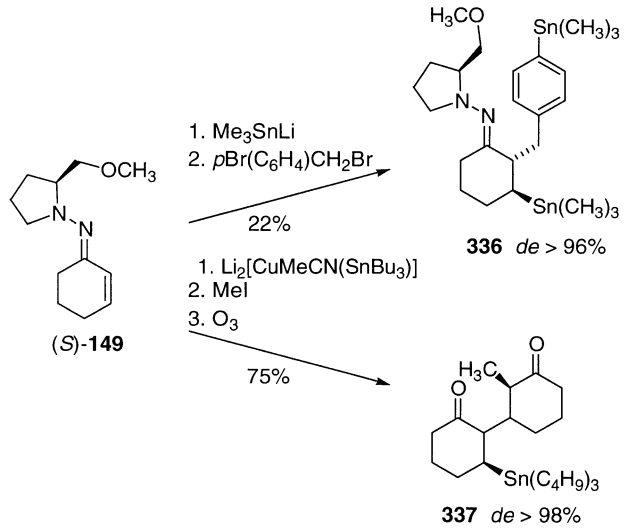
On the basis of the experience with azaenolates of SAMP-/RAMP-hydrazones as chiral nucleophiles, the basic strategy for the synthesis of the 4,5,6-trisubstituted piperidin-2-ones **330** involved the d^2- and a^1-reactivity of SAMP-/RAMP-hydrazones. The first key step for the generation of a defined stereotriad in two consecutive C–C connective procedures is the asymmetric Michael addition followed by an alkylative amination and a lactamisation, as shown in Scheme 97. The first reaction sequence forming two stereogenic centres was the asymmetric Michael addition of the metallated hydrazone **326**, derived from aldehyde **325**, to methyl 2-butenolate. After work up, the resulting 3,4-disubstituted 5-oxopentanoate hydrazones **327** were obtained in good yields and with excellent diastereoselectivities. After protection of the reactive ester function as an enolate, chemoselective nucleophilic 1,2-addition of organolithium compounds to the C=N double bond followed by reductive cleavage of the auxiliary from the adduct **328** and lactamisation of the intermediate δ-aminoesters **329** gave rise to the desired trisubstituted piperidin-2-ones **330**.[182]

The stereoselective synthesis of γ- and δ-lactams bearing a substituted propionic acid α-side chain has also been investigated (Scheme 98).[183] The lactams (*S*)-**213** were synthesised by cyclisation of the corresponding ω-chloroalkanohydrazides (*S*)-**212** (*n*=1, 2). Deprotonation of the lactams (*S*)-**213** and 1,4-addition to enoates afforded the Michael adducts **331** in good yields and excellent diastereoselectivities. Removal of the auxiliary was achieved by reductive cleavage of the N–N bond using lithium in liquid ammonia. To avoid decomposition in the cleavage reaction, it was necessary to first generate the corresponding carboxylic acids. The lactam carboxylic acids **332** were obtained in moderate to good yields with high diastereo- and enantioselectivities.

Organotin compounds have been shown to be valuable building blocks for C–C bond formation and tin–lithium exchange under mild conditions has been used extensively for the construction of complex organic molecules. Recently, the 1,4-addition of trialkylstannyllithium to



Scheme 99.



Scheme 100.

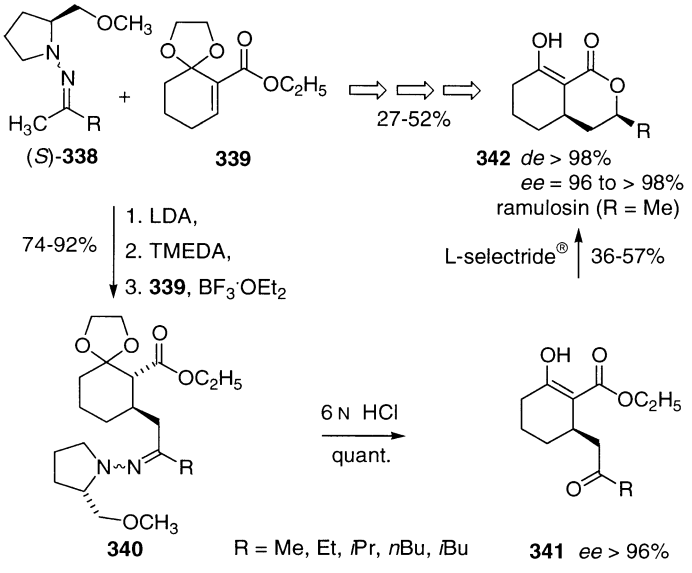
α,β-unsaturated carbonyl compounds has been investigated.[184] Due to the fact that optically active 3-trialkylstannylketones have mostly been prepared by diastereoselective addition to enantiomerically pure cyclohexenones,[185] the Michael addition of organostannyllithium compounds to cyclohexenone SAMP-/RAMP-hydrazones led for the first time to a regio-, diastereo- and enantioselective pathway to 2-substituted 3-trialkylstannylcyclohexanones **335** (Scheme 99).[184]

Starting from cyclohexenone (**333**), the corresponding SAMP-hydrazone (*S*)-**149** is readily available in 90% yield. Using trimethyl- and tributylstannyllithium in the conjugate addition to the hydrazone **149**, led regioselectively to the 4-substituted Michael adducts **334**. The simple adducts (R^2=H) could only be achieved in moderate diastereomeric excesses, whereas the *trans* tandem adducts **334** ($R^2 \neq$H) with equatorial substituents are obtained in very good diastereomeric excess in the trapping reaction with alkyl iodides or bromides. By oxidative cleavage, the hydrazones **334** are subsequently converted to the 3-trialkylstannylketones **335** in very good yield without epimerisation and racemisation. With *p*-bromobenzyl bromide as the electrophile, the bromine atom is exchanged for a trimethylstannyl group in a side reaction leading to the bis-stannylated hydrazone **336** (de>96%, Scheme 100). The conjugate addition of cyano-(tributylstannyl)methylcuprate as the nucleophile to (*S*)-**149** and trapping the resulting azaenolate with methyl iodide provided, after oxidative cleavage, the Michael adduct **337** as the major product with a yield of 75% and excellent diastereomeric excess (de>98%), together with the simple tandem adduct **335** (R^1=*n*Bu, R^2=Me) in 16% yield and good selectivity.

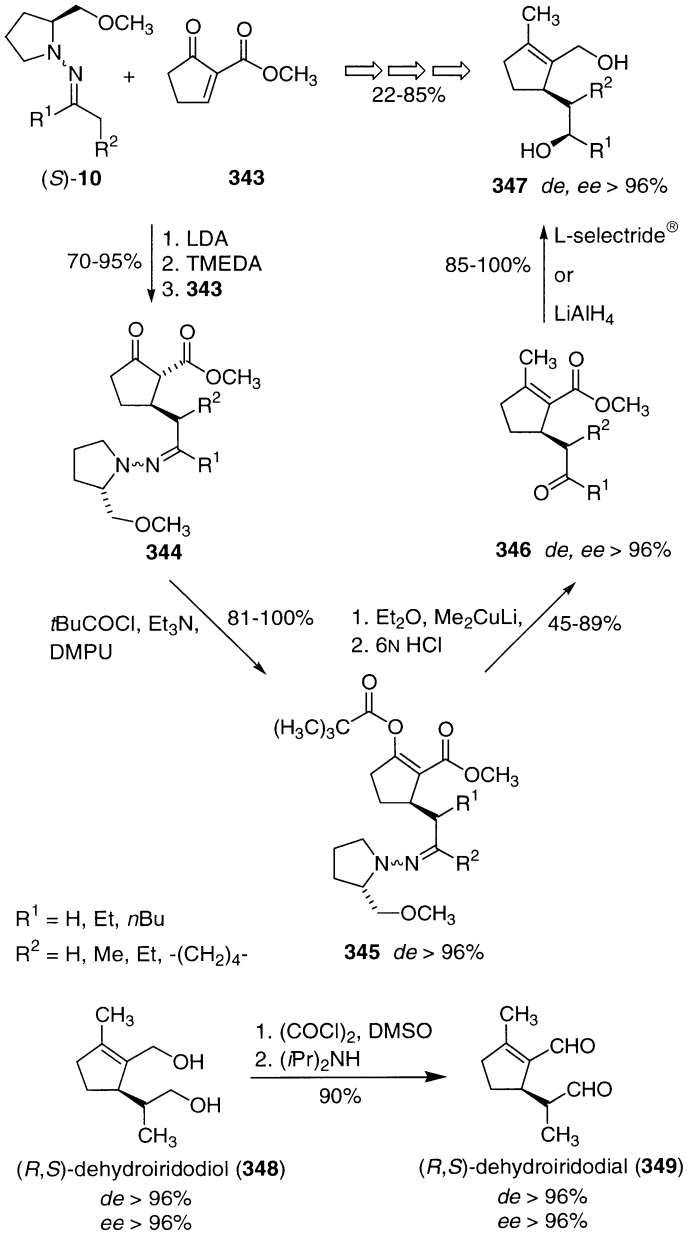
The asymmetric Michael addition method using SAMP-hydrazones has been further applied to the synthesis of natural products, including the asymmetric synthesis of both enantiomers of ramulosin and its analogues.

(+)-Ramulosin (**342**, R=Me), the simplest member of a class of biogenetically-related δ-lactone antibiotics, was first isolated from the fungus *Pestalotia ramulosa* by Stodola et al. in the early 1960s and inhibits the germination of seeds and spores of microorganisms.[186,187] The asymmetric conjugate addition using the SAMP-/RAMP-hydrazone method provided a very short asymmetric synthesis of (+)-ramulosin (**342**, R=Me) and its enantiomer, as well as of some analogues.[188]

As depicted in Scheme 101, the methyl ketone SAMP-hydrazones (*S*)-**338** were metallated with lithium diisopropylamide and tetramethylethylenediamine (TMEDA) was added to the azaenolate generated. Subsequent reaction with the protected cyclic β-ketoenoate **339** in the presence of $BF_3 \cdot Et_2O$ resulted in a clean 1,4-addition. Acetal protection of the β-carbonyl group of the Michael acceptor **339** turned out to be essential, presumably because of a more favourable γ-deprotonation of the parent β-ketoesters by the lithiated hydrazones instead of 1,4-addition, thus resulting in the isolation of only starting material after an aqueous work up. In order to achieve conjugate addition,



Scheme 101.



Scheme 102.

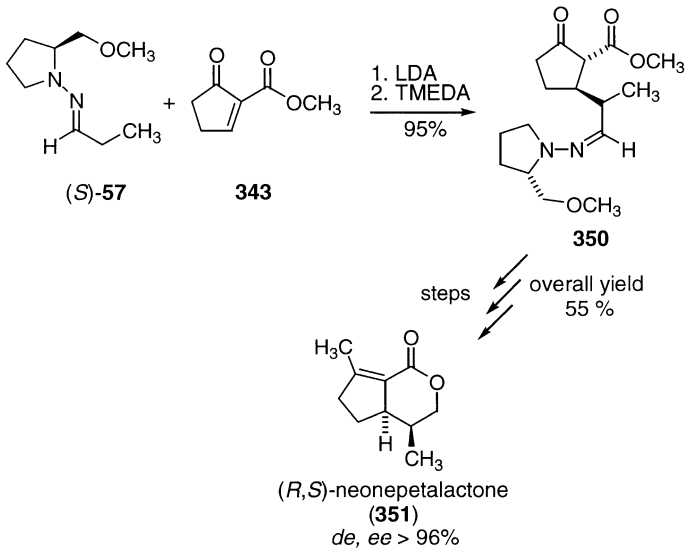
activation of the Michael acceptor with $BF_3{\cdot}Et_2O$ was also essential.

For removal of the chiral auxiliary and the acetal protecting group, the crude hydrazones **340** were hydrolysed with hydrochloric acid to obtain the 6-substituted 2-hydroxy-cyclohex-1-ene-carboxylates **341** in practically quantitative yields and with excellent ees. In the final step of the total synthesis of ramulosin (R=Me) and related 3-substituted 8-hydroxy-hexahydroisocoumarins **342**, the ketoesters **341** were diastereoselectively reduced with L-selectride®, which after an aqueous quench gave direct lactonisation. (−)-Ramulosin (**342**, R=Me) and its analogues were obtained in moderate yields, but with excellent diastereomeric and enantiomeric excesses. For the total synthesis of the naturally occurring (+)-ramulosin, RAMP had to be used instead of SAMP as the chiral auxiliary.

Following this reactions sequence, the total syntheses of (*R*,*S*)-dehydroiridodial **349**, (*R*,*S*)-dehydroiridodiol **348** and its analogues were accomplished.[189]

Dehydroiridodiol, isolated from the dry leaves of the cat-attracting plant *Actinidia polygama* Miq, is known to be an attractant for the male adults of *Chrysopidae* and shows activity in amounts as small as 10^{-4} μg.[190] Dehydroiridodial, a further oxidised product, was isolated as a pungent principle of *A. polygama* Miq and was characterised by Sakan et al. in 1978.[191] Its stereoisomer, chrysomelidial, is a component of the defence secretion of chrysomelid larvae.[192] The absolute configuration of dehydroiridodiol-(dial) was determined in 1980 by Sakan and co-workers.[193]

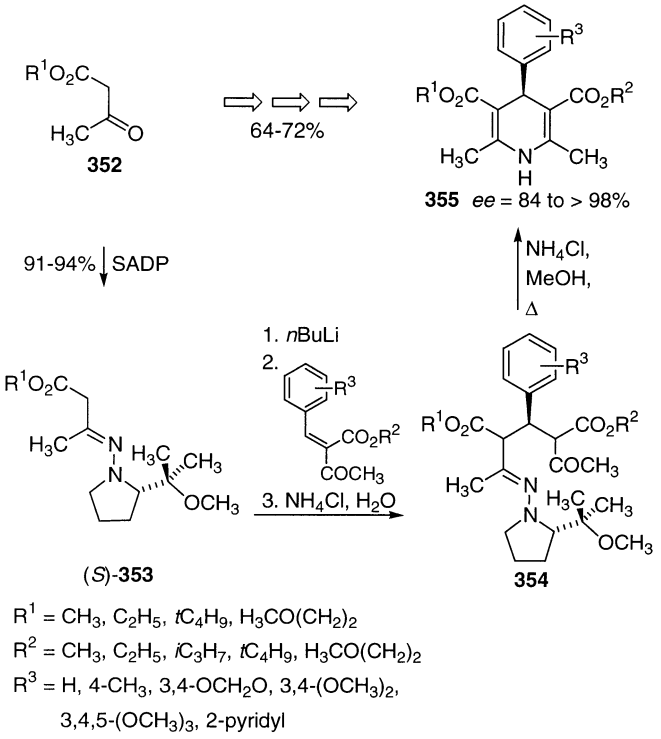
As depicted in Scheme 102, the azaenolate could again be generated from the aldehyde or ketone SAMP-hydrazones



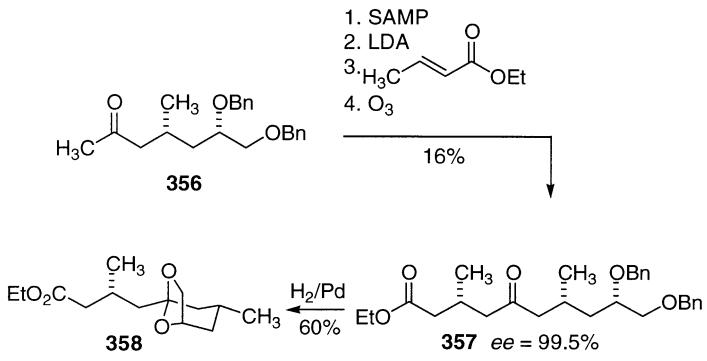
Scheme 103.

(*S*)-**10** by metallation with lithium diisopropylamide/TMEDA. Subsequent reaction with 2-cyclopentenecarboxylate **343** resulted in a clean 1,4-addition and the hydrazone Michael adducts **344** could be obtained in good to excellent yields. Introduction of the methyl group was achieved by a two-step procedure. The hydrazone Michael adducts **344** were first converted into the enol pivaloates **345**. Treatment with lithium dimethylcuprate and subsequent removal of the chiral auxiliary furnished the 5-substituted 2-methyl-cyclopentenecarboxylates **346**. Reduction with lithium aluminium hydride or L-selectride® provided dehydroiridodiol (*R*,*S*)-**347** (R^1=Me, R^2=H) and its analogues in excellent yields and with excellent diastereomeric and enantiomeric excesses. Swern oxidation of (*R*,*S*)-dehydroiridodiol (**348**) gave rise to virtually diastereo- and enantiopure (*R*,*S*)-dehydroiridodial (**349**) in very good yield.

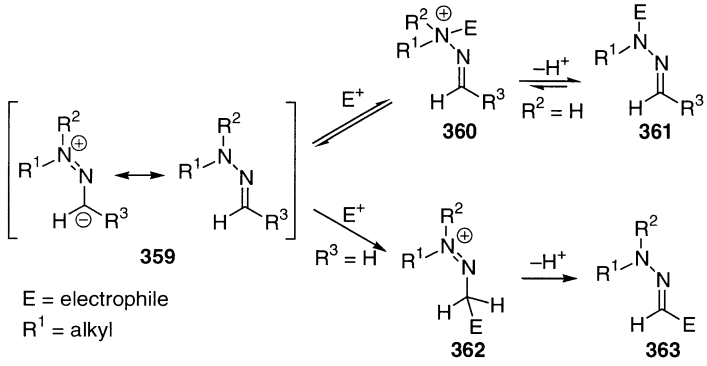
Following the same reaction sequence, the conjugate addition of SAMP-hydrazone (*S*)-**57** to 2-cyclopentenecarboxylate **343** provided a short asymmetric pathway to neonepetalactone (**351**),[194] a naturally occuring lactone, isolated in 1965 from the leaves and galls of *A. polygama* by Sakan et al.[195] which was found to be quite attractive to cats (Scheme 103). The natural product could be synthesised via the Michael adduct **350** with an overall yield of 55% and high diastereo- and enantioselectivity (de, ee>96%).



Scheme 104.



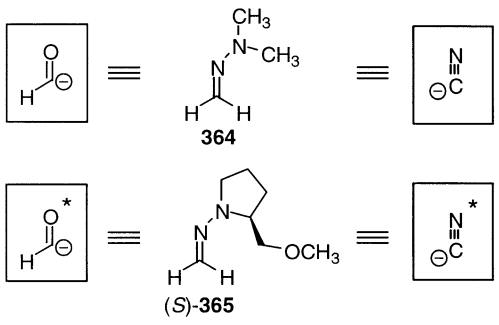
Scheme 105.



Scheme 106.

The asymmetric 1,4-dihydropyridines **355**, which are analogues was of the potent calcium channel blockers, nifedipine® and nitrendipine®, could also be obtained by the SAMP-hydrazone method. After metallation of the SAMP-hydrazones (*S*)-**353**, which were easily prepared from the corresponding α-ketoesters **352**, addition of α,β-unsaturated ketoesters furnished the Michael adducts **354** (Scheme 104).[196] Refluxing of the crude adducts in an MeOH/aqueous NH_4Cl solution releases the chiral auxiliary and effects ring closure to give the 1,4-dihydropyridines **355**.

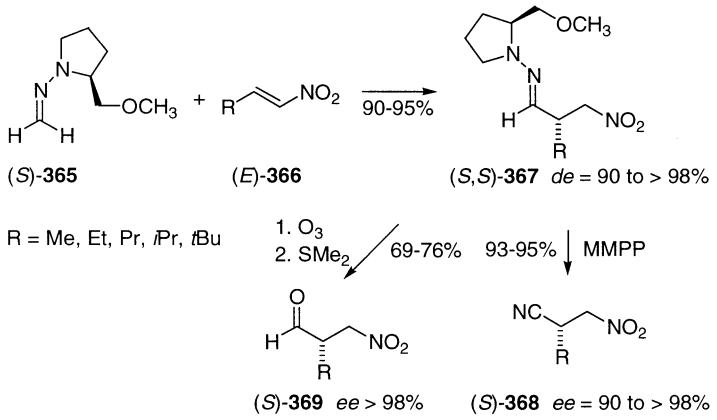
Another example of the application of the SAMP-/RAMP-hydrazone method to the synthesis of natural products was published by Kitching and co-workers.[197] The desired ketoester **357** serves as a model substance to confirm the proposed stereochemistry of the bicyclic ketal system **358** of the shellfish toxin pinnatoxin D. Starting from the ketone **356**, the SAMP-hydrazone was synthesised, metallated with lithium diisopropylamide and added in a conjugate addition to ethyl crotonate. After removal of the chiral auxiliary, the desired product **357** could be obtained with excellent enantiomeric purity (Scheme 105).



Scheme 107.

4.2. Reactions via formaldehyde SAMP-hydrazone

The formyl group is an important functional group in synthetic chemistry. Nucleophilic formylation based on the concept of Umpolung[198] is an especially important C–C bond formation process. A variety of formyl carbanion equivalents, including asymmetric analogues, have been developed in recent years.[199] In the late 1960 s, Brehme and Nikolajewski recognised that aldehyde *N*,*N*-dialkylhydrazones **359** can be regarded as azaenamines and reported electrophilic substitutions at the aldehyde hydrazone carbon on treatment with reactive electrophiles.[200] As depicted in Scheme 106, the hydrazones **359** are ambident nucleophiles, which can react with electrophiles either at the amine nitrogen or at the azomethine carbon. The former atom is usually the most nucleophilic centre and the primary products **360** of its reaction with electrophiles contain a new N–C bond. If at least one of the substituents of the amine nitrogen is a hydrogen, the loss of a proton in **360** would yield *N*-substituted hydrazones **361**. This pathway is not, however, feasible for *N*,*N*-disubstituted hydrazones. Due to lack of a hydrogen atom, addition to the nitrogen atom is reversible and, additionally, the energy associated with the formation of a new C–C bond will make its formation an essentially irreversible process, as the subsequent loss of a proton in **362** will result in the new hydrazones **363**.[201]



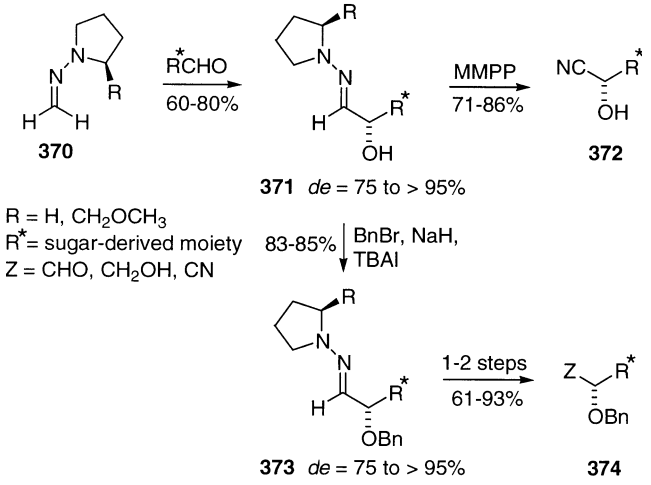
Scheme 108.

After transformation of the hydrazone group into the aldehyde or the nitrile function (Section 1, Scheme 8), a nucleophilic formylation or cyanation of the electrophile under neutral conditions is the overall result. The, formaldehyde hydrazones **364** and **365** are, therefore, indeed the synthetic equivalents of the formyl and cyanide anion synthons (Scheme 107).[202]

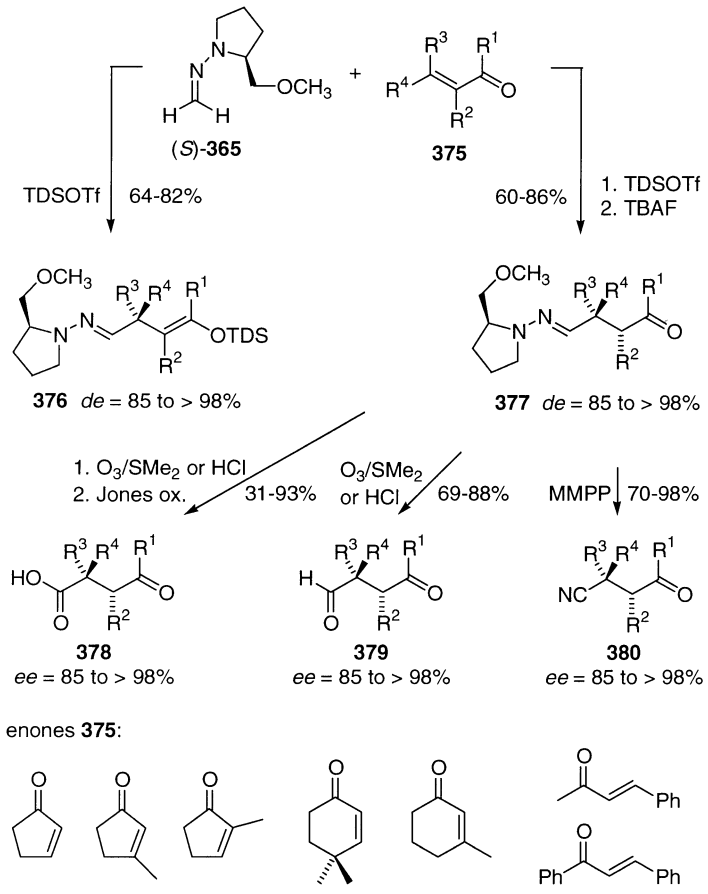
Lassaletta et al. reported that the formaldehyde dimethylhydrazone undergoes a 1,4-addition with nitroalkenes **366** as Michael acceptors.[203] Employing the commercially available formaldehyde SAMP-hydrazone (*S*)-**365**,[204] this reaction proceeded with almost quantitative yield and excellent diastereoselection to give **367** (Scheme 108).[205] Cleavage of the auxiliary could be achieved with magnesium monoperoxyphthalate,[21] providing the nitriles **368**, or with ozone,[9] affording the corresponding aldehydes **369**, in excellent enantiomeric purity, respectively. The diastereoselective synthesis of sugar-derived β-nitrodialkylhydrazones was also achieved using enantiopure sugar nitroalkenes.[201] The double asymmetric induction with formaldehyde SAMP- and RAMP-hydrazone **365** led to the desired products in very good yields (71–95%) and, in the 'matched' case, with nearly complete asymmetric induction (de>96%). Oxidative cleavage with MMPP afforded the corresponding sugar β-nitronitriles in excellent yields (81–96%) without epimerisation.

This methodology was later extended to sugar-derived aldehydes to allow the one-carbon homologation of aldoses and dialdoses.[206] The addition of formaldehyde dialkylhydrazones such as **370** to sugar-derived aldehydes gave rise to the α-hydroxyhydrazones **371** with good yields and selectivities in the range 57–>95% de (Scheme 109). Formaldehyde SAMP- or RAMP-hydrazone did not give better diastereoselectivities than, or different stereochemical results from, achiral pyrrolidine hydrazones. This indicates that the diastereofacial selectivity of the addition to sugar aldehydes is determined by the α-substituent and the chiral reagent has a limited influence. Only the pyrrolidine hydrazones **370** were therefore converted to cyanohydrins **372** in high yields. In addition, the α-benzyloxyhydrazones **373** were cleaved, leading in one or two steps to α-hydroxyaldehydes, monoprotected diols and cyanohydrins **374**.

As depicted in Scheme 110, formaldehyde SAMP-hydrazone (**365**) can further undergo a thexyldimethylsilyl triflate (TDSOTf)-promoted stereoselective 1,4-addition to α,β-unsaturated ketones.[207] The azaenamine reactivity was not high enough to allow spontaneous conjugate addition to the enones **375** in contrast to the more electrophilic nitroalkenes or sugar aldehydes. It was therefore necessary to use trialkylsilyl triflates as promoters giving rise to the Michael adducts as their corresponding silyl enol ethers **376**. The rich chemistry of the latter derivatives makes the primary adducts promising synthetic intermediates that are not only protected forms of the corresponding ketones, but should also allow further regioselective electrophilic α-substitutions typical for silyl enol ethers. The reaction always proceeded cleanly and the 1,2-adducts could not be detected. Both the silyl enol ethers **376**, the primary products of the reaction, and the corresponding deprotected ketones **377** could be isolated in good yields and with excellent diastereomeric excesses. Quaternary stereogenic centres are easily created and are within the highest diastereoselectivity (de>98%) in the series. The reaction proceeded with similar results in the presence of equimolar amounts of triethylamine, which may allow the 1,4-reaction to proceed in the presence of acid-sensitive groups. Racemisation-free cleavage of **377** yielded the acids **378**, aldehydes



Scheme 109.

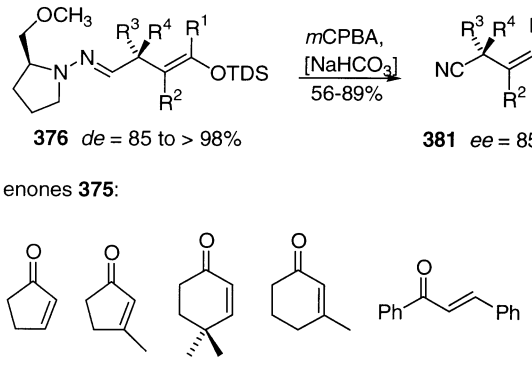


Scheme 110.

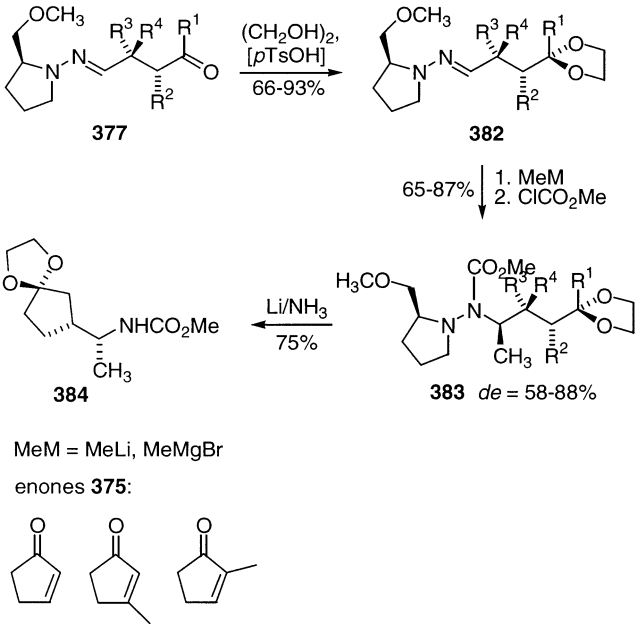
379 or nitriles **380** in good to excellent yield with ee values 85 to >98%. The absolute configuration of the newly-created stereogenic centre was determined using different methods such as X-ray structure analysis,[208] polarimetry and the empirical rule developed by Lemière and co-workers.[209]

Cleavage of the silyl enol ether hydrazones **376** obtained by the latter reaction were achieved by treatment with *m*-chloroperbenzoic acid giving rise to the nitriles **381** in good yield without racemisation (Scheme 111).[210] This reaction needs to be run with a small amount of solid $NaHCO_3$ to prevent partial cleavage of the silyl enol ethers.

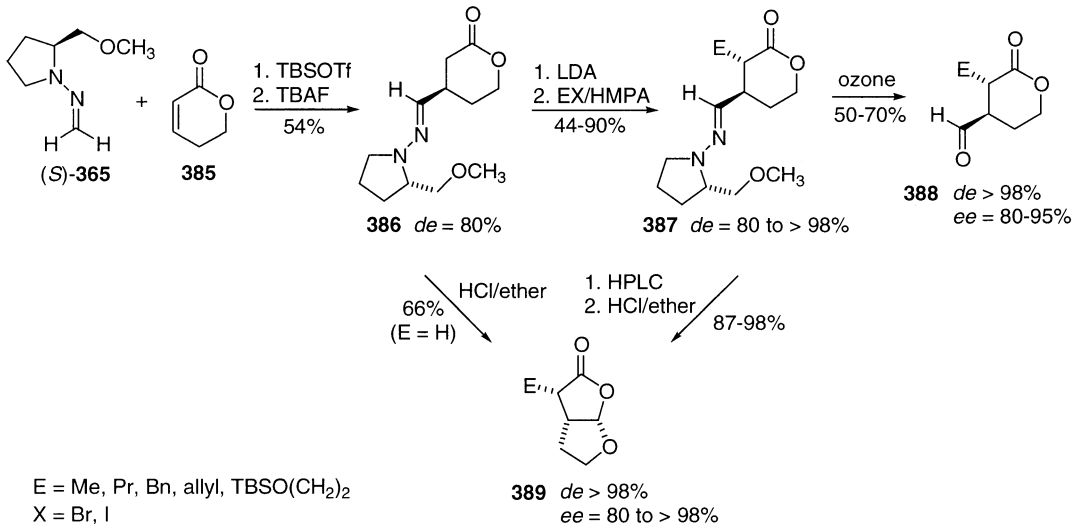
Additionally, the ketone-functionalised hydrazones **377** obtained from the 1,4-addition protocol were used for the synthesis of protected γ-aminoketones (Scheme 112).[211] The hydrazones **377** were initially converted into the corresponding ethylene acetals **382**. The key step, a 1,2-addition to the C=N double bond, was performed with methyl lithium or methyl magnesium bromide; subsequent trapping with methyl chloroformate (MOCCl) afforded the stable



Scheme 111.



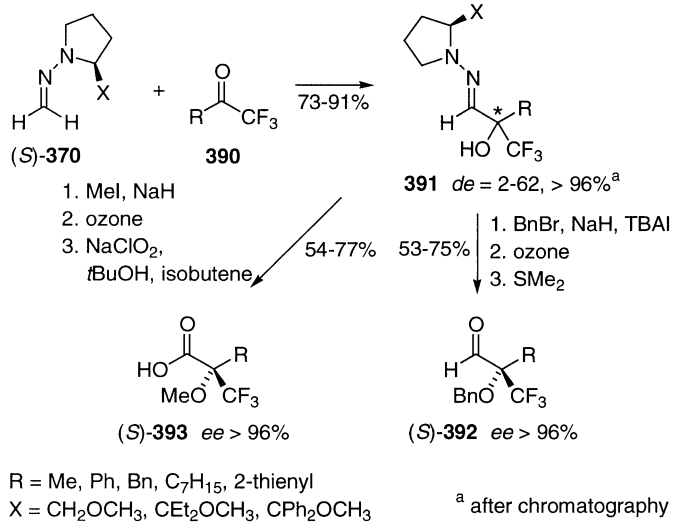
Scheme 112.



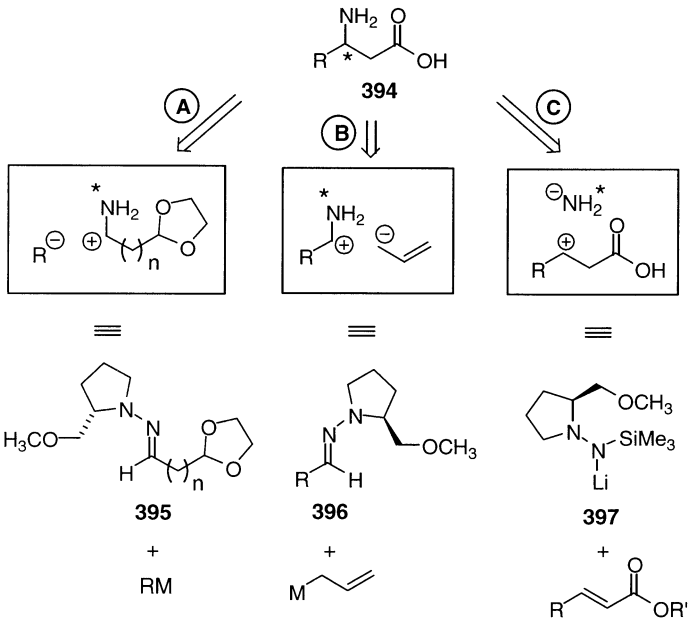
Scheme 113.

compounds **383**. Quenching the reaction with methanol generated the corresponding unstable hydrazine derivatives, which were difficult to isolate. The stereochemistry of the addition is assumed to be controlled by chelation of the organometallic reagent by the oxygen in the methoxymethyl group and the hydrazone π-system.[212,213] According to this model, the *R* configuration is assigned to the new stereogenic centre generated by the addition of the organometallic reagent to SAMP-hydrazones. Additionally, the configuration was established following the methodology developed by Nájera et al.[214] and further by ab initio MO calculations. Treatment with lithium in liquid ammonia furnished the MOC-protected amine derivative **384** in good yield. Alternatively, a one-pot synthesis of γ-aminoketone derivatives could be achieved from the acetals **382** by addition of the organometallic reagent followed by Raney nickel-catalysed hydrogenolysis. The unstable amines in the crude mixture were protected in situ by adding Boc_2O and triethylamine to the resulting solution. The corresponding *N*-Boc-derivatives could be isolated in satisfactory yields (53–65% overall from **377**) and with diastereoselectivities very similar to those observed for the compounds **384**. In the overall reaction, formaldehyde SAMP-hydrazone (*S*)-**365** behaves as an ambiphilic chiral aminomethine synthon. During the reaction sequence, the azomethine carbon of the SAMP-hydrazones serves as a nucleophilic centre (1,4-addition) and an electrophilic centre (1,2-addition), respectively. This special behaviour provides the possibility of generating up to three adjacent stereogenic centres.

A similar concept is shown in Scheme 113. Formaldehyde SAMP-hydrazone (*S*)-**365** was added under silyl triflate activation to the α,β-unsaturated lactone **385**.[215] Subsequent treatment with TBAF yielded the corresponding 1,4-adduct **386**. Deprotonation with lithium diisopropylamide and electrophilic trapping afforded the α-substituted lactone derivatives **387** in good yield and a de of 80%. Fortunately, the minor diastereomer could usually be separated by column chromatography or HPLC. Ozonolytic cleavage of **387** restored the aldehyde functionality and gave rise to the aldehyde lactone derivative **388** in excellent optical purity. Cleavage of the hydrazones **386** and **387** under acidic



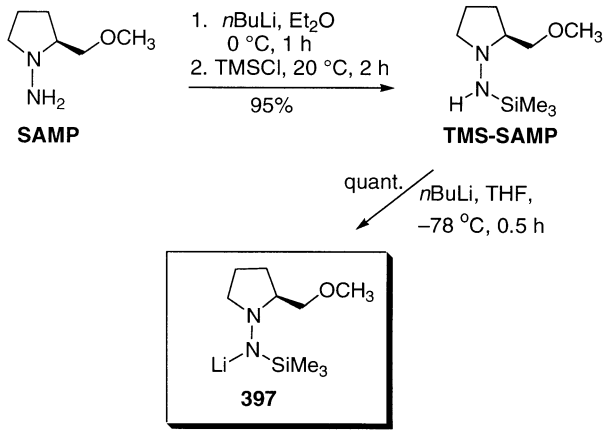
Scheme 114.



Scheme 115.

conditions furnished the furofuran lactones **389**, which constitute valuable building blocks for the synthesis of clerodane derivatives, a class of substances showing insect antifeedant properties.

The introduction of the important trifluoromethyl group was also perfomed by this protocol (Scheme 114).[216] Addition of SAMP-hydrazone (*S*)-**370** to the trifluoromethyl ketone derivatives **390** resulted in the hydroxy hydrazones **391** in good yield but low selectivities. Better diastereomeric excesses were obtained applying auxiliaries with more steric demand such as SAEP or SAPP. Additionally, the diastereomers could be separated by chromatography to furnish the hydrazones **391** as single diastereomers. The absolute configuration of the newly generated stereogenic centre was determined by X-ray structure analysis and assigned as *S*,*S*. Protection of the new hydroxy group with benzyl bromide and subsequent cleavage of the auxiliary provided the aldehydes **392** in enantiomerically pure form. Protection of **391** with iodomethane and treatment with ozone and subsequent oxidation yielded the trifluoromethyl-substituted acids **393** as single enantiomers.



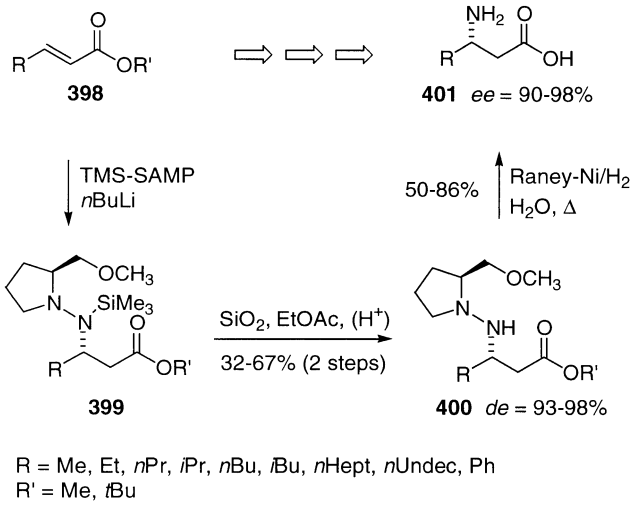
Scheme 116.

4.3. Michael additions with heteronucleophiles

Since the use of SAMP as a chiral auxiliary in C–C bond formation via Michael addition of SAMP-hydrazones to α,β-unsaturated acceptors has proved to be a versatile method, heteronucleophiles have been investigated to build up carbon–heteroatom bonds, especially focussing on nitrogen nucleophiles for the synthesis of β-amino acids and β-aminosulfones.

4.3.1. Enantioselective synthesis of β-amino acids. β-Amino acids **394**, although of less importance than the parent α-amino acids, are crucial structural features of numerous biologically active natural products as well as building blocks for β-lactam antibiotics. This is reflected by the increasing research activity in the field of their stereoselective synthesis, employing C–C bond formations via the aldehyde SAMP-hydrazones **395** and **396** (pathways A and B) as well as C–N bond connections (pathway C) according to the retrosynthetic analysis shown in Scheme 115.[159] Following this pathway, the aza-analogous Michael addition of the commercially available enantiopure nitrogen nucleophiles TMS-SAMP or TMS-RAMP as chiral equivalents **397** of ammonia to enoates opened an enantioselective access to a wide range of β-amino acids.

The hydrazine auxiliary, (*S*)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine (TMS-SAMP), and the optical antipode, TMS-RAMP, can be prepared from SAMP and RAMP, respectively, via deprotonation with *n*-butyllithium in diethyl ether at 0°C and subsequent silylation with chlorotrimethylsilane. The desired enantiopure nitrogen nucleophile **397** can be formed via deprotonation of TMS-SAMP with *n*-butyllithium at −78°C in tetrahydrofuran (Scheme 116).[217]



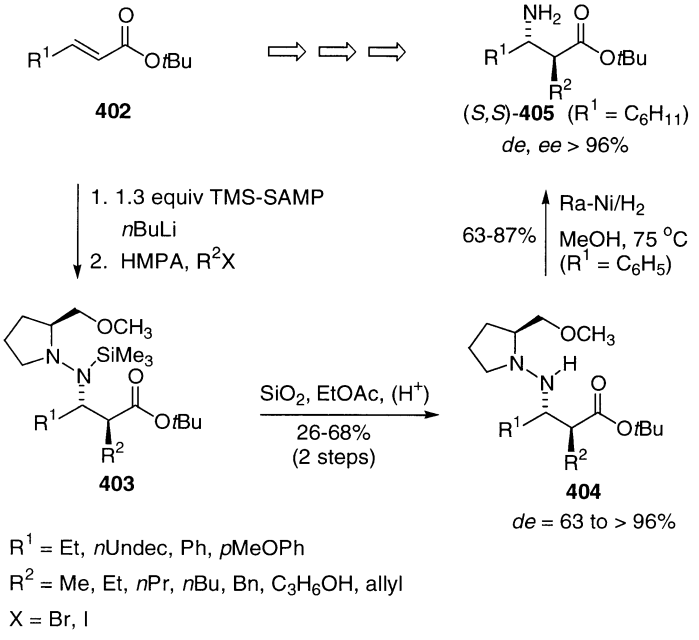
Scheme 117.

In the synthesis of β-amino acids (Scheme 117),[218] the *N*-lithiated TMS-SAMP was treated with the α,β-unsaturated esters **398** at −78°C, affording the *N*-silylated β-hydrazinoesters **399** through aza-analogous Michael addition. Using simple methyl esters as Michael acceptors, 1,2-addition occurs as a side reaction leading to the generation of the corresponding α,β-unsaturated acid hydrazides in 10% yield. Employing the sterically more demanding *tert*-butyl esters (R′=*t*Bu), the problem of 1,2-addition can be avoided. After desilylation and purification, the β-hydrazinoesters **400** were obtained with high diastereomeric excesses. Finally, the hydrazinoesters **400** were converted to the corresponding β-amino acids (*S*)-**401** by hydrogenolytic N–N bond cleavage with concomitant saponification of the ester function using freshly-prepared Raney nickel.[219]

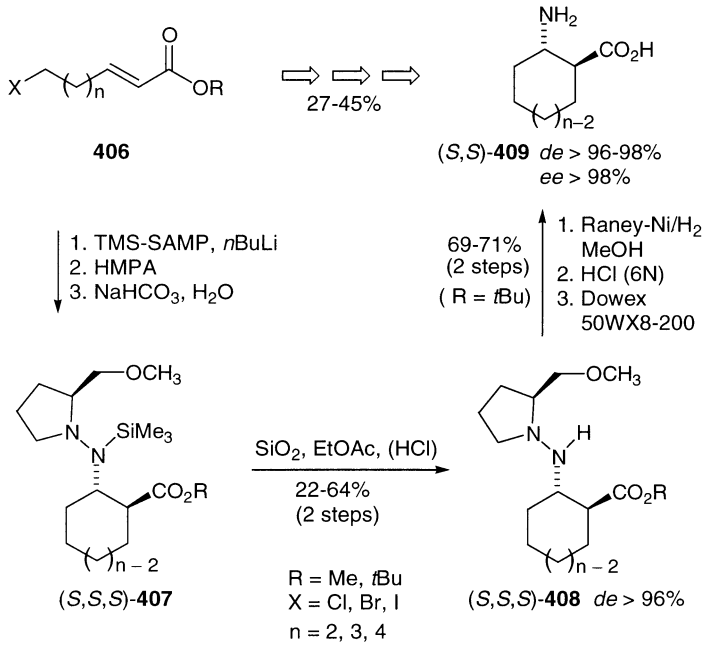
By an extension of this protocol to α-substituted β-amino acids, a highly stereoselective tandem heteroMichael addition/α-esterenolate alkylation could be developed.[218b] As depicted in Scheme 118, the 1,4-addition of lithiated TMS-SAMP as chiral *N*-nucleophile to the enoates **402** followed by α-alkylation with the appropriate halides R^2X led after desilylation of the intermediates **403** to the α-substituted β-hydrazinoesters **404** with good to excellent stereoselectivity. As Yamamoto et al. have demonstrated, control of the enolate geometry leads to the generation of either the *syn*- or *anti*-configured β-amino acid esters, respectively.[220] Following this strategy, we were able to demonstrate, although in lower yield, that, after a consecutive deprotonation of the β-hydrazinoester **399** (R=Ph) with LDA and subsequent trapping with allyl bromide, followed by desilylation, the *syn*-β-hydrazinoester **404** (R^1=Ph, R^2=allyl) could be prepared with high diastereo- and enantiomeric excess. In conclusion, this example demonstrates that, in principle, both diastereomers of the β-hydrazinoesters **404** are accessible.

Finally, reductive N–N bond cleavage of the hydrazinoesters **404** applying modified conditions (Raney-nickel in methanol), afforded the α-substituted β-amino acid esters (*S*,*S*)-**405** in good yields. Using this route, the prepared amino acid esters were formed with excellent diastereo- and enantiomeric excesses. During the cleavage reaction SMP is formed as a by-product and can be recycled in the synthesis of SAMP for further transformations.

A logical extension of the tandem hetero Michael addition/α-ester-enolate alkylation protocol is the intramolecular variant leading to diastereo- and enantiomerically pure *trans*-configured 2-aminocycloalkanoic acids (MIRC reaction).[171] As shown in Scheme 119, the ω-halo-enoate **406** was added to a solution of lithiated TMS-SAMP. Depending on the desired ring size, cyclisation of the intermediate ester enolate must be promoted by addition of HMPA to activate the ester enolate towards intramolecular cyclisation. Whereas cyclisation to the 7-membered ring system



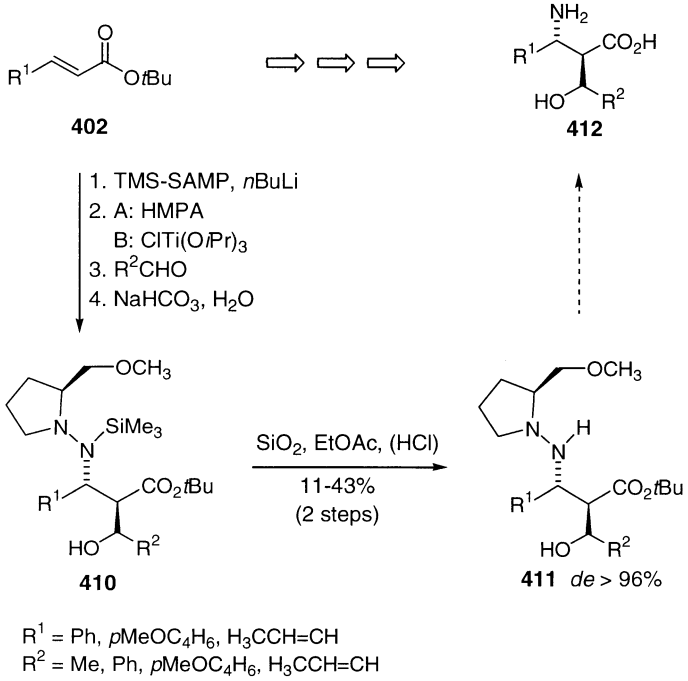
Scheme 118.



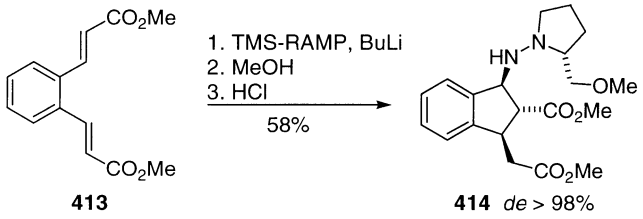
Scheme 119.

could only be achieved if the iodide was used and HMPA was added, the 5- and 6-membered rings were obtained using the bromides without the addition of co-solvent. The crude trimethylsilyl-protected hydrazines **407** were directly desilylated, leading to the desired β-hydrazinoesters **408** in good overall yield from **406** (Scheme 119). Interestingly, no β-hydrazinoester **408** (R=Me) was obtained via the initial route in the 1,4-addition of lithiated TMS-SAMP to methyl 1-cyclohexenylcarboxylate,[218a] since the corresponding hydrazide was formed via 1,2-addition of the nucleophile to the ester group. Reductive N–N bond cleavage of **408** with neutral Raney nickel, followed by hydrolysis and purification by ion-exchange chromatography, afforded the β-amino acids **409** in good yields and excellent diastereo- and enantiomeric purity.

In an analogous manner, aldehydes could be used as electrophiles in a tandem Michael aldol reaction.[221] The products **412** prepared by this method are highly interesting precursors for the important class of carbapenem antibiotics.[222] After addition of the metallated TMS-SAMP to the enoate **402**, two different methods were applied. In the first route (method A), the intermediate ester enolate was activated by the addition of HMPA followed by addition of



Scheme 120.

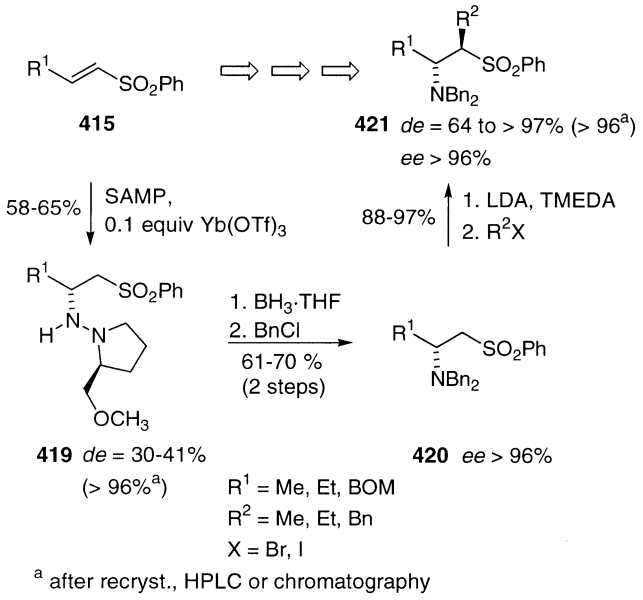


Scheme 121.

the aldehyde. Upon desilylation of the crude products **410** the aldol-type products **411** were obtained with diastereomeric excesses ranging from 20 to >96%. In the second synthetic strategy (method B), the intermediate ester enolate was not activated by the addition of HMPA, but treated with chlorotriisopropoxytitanium(IV)chloride to generate the chiral titanium enolate complex. After addition of the aldehyde, the silyl-protected β-hydrazino-β′-hydroxy-esters **410** were directly desilylated using the common procedure.

By comparison with method A, a distinct increase of the diastereoselectivities could be observed with method B and, after enrichment via column chromatography, all diastereomeric excesses were >96%. By comparison with the results obtained in the tandem-Michael addition and the high stereoselectivity of these reactions the observed diastereomers are presumably epimers of the β′-centre (Scheme 120).

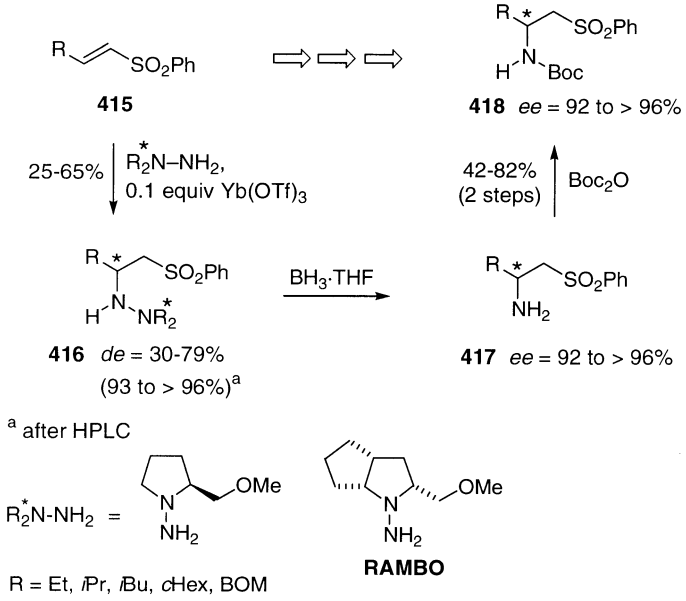
De Meijere et al. have used this method in a diastereoselective Michael addition a conveniently access enantiomerically pure six-ring annelated cispetacin derivatives.[223] Via palladium-catalyased coupling reactions, the *o*-diethenylarene **413** could be synthesised. Starting from **413** the use of TMS-RAMP led to the corresponding indane derivative **414** in 58% yield achieving only one stereoisomer (Scheme 121).



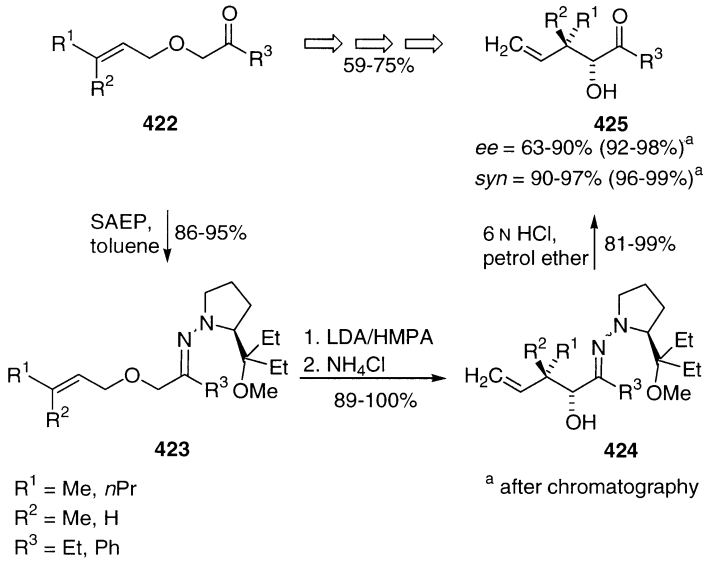
Scheme 123.

4.3.2. Enantioselective synthesis of β-aminosulfones. Sulfones have become increasingly important in organic synthesis in recent years. Since α,β-unsaturated sulfones are known to be excellent Michael acceptors and react with a number of carbon- and heteroatom-nucleophiles, the aza Michael addition has been investigated to provide a new method for the synthesis of β-aminosulfones.

Several procedures are currently employed for intramolecular[224] and intermolecular[225] aza Michael additions to alkenylsulfones. The first enantioselective aza Michael addition with a nitrogen nucleophile bearing chirality information, which may subsequently be cleaved, could be realised using SAMP as the chiral ammonia equivalent. As is shown in Scheme 122, conjugate addition of SAMP to the (*E*)-alkenylsulfones (*E*)-**415** afforded the Michael adducts **416** in the



Scheme 122.

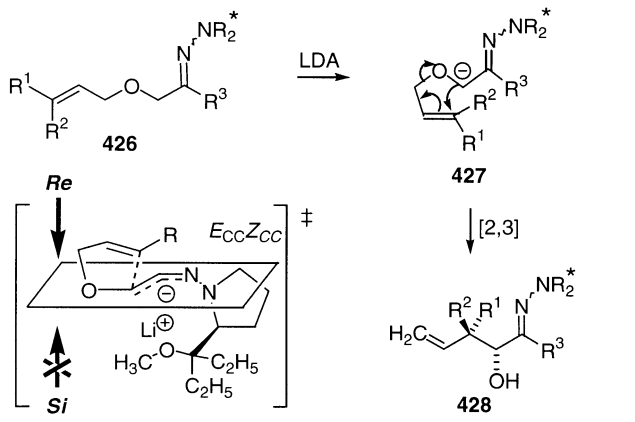


Scheme 124.

presence of catalytic amounts of ytterbium(III) triflate with moderate yields and moderate to good diastereoselectivities.[14] The epimers could be separated by HPLC, yielding the virtually diastereomerically pure β-hydrazinosulfones **416**.

Alternatively, (*R*,*R*,*R*)-2-amino-3-methoxymethyl-azabicyclo-[3.3.1]octane [RAMBO], first synthesised as its epimer SAMBO by Martens et al.[13] can be employed as the nitrogen nucleophile (Scheme 122). Considerably higher selectivities were obtained using RAMBO compared to those achieved with SAMP and separation of the diastereomers by HPLC was also feasible. Reductive cleavage of the chiral auxiliary from the β-hydrazinosulfones **416** with BH_3·THF afforded the β-aminosulfones **417** without racemisation.[226] Introduction of the Boc protecting group was effected using di-*tert*-butyldicarbonate and triethylamine in methanol to give the *N*-Boc-protected β-aminosulfones **418** without prior purification of the amines **417**.

An important extension to the previous protocol is the appropriate α-alkylation to generate two adjacent stereogenic centres. In order to reach this goal, the protection of the β-amino function was changed. After removal of the chiral auxiliary of **419** with excess BH_3·THF, subsequent N,N-dibenzylation allowed access to the N,N-dibenzyl-protected β-aminosulfones **420** in good yields, which were finally alkylated to afford the desired β-aminosulfones **421** (Scheme 123).[14]



Scheme 125.

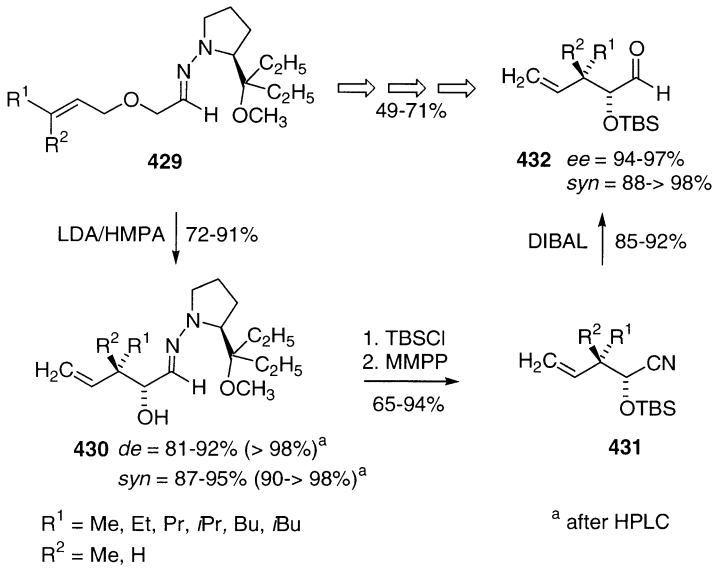
5. Rearrangements

5.1. 2,3-Wittig rearrangement

The [2,3]-Wittig rearrangement has been established as a powerful tool for stereoselective C–C bond formations.[227] In order to use this reaction in combination with the protocol of the SAMP-/RAMP-hydrazone method, an asymmetric [2,3]-Wittig rearrangement employing the SAEP derivative has been developed. This novel variant offers an efficient entry to γ,δ-unsaturated α-hydroxyketones, α-hydroxyaldehydes and cyanohydrins with variable substitution in the β-position and high *syn*-selectivities and enantiomeric excesses, starting from readily available precursors.[228]

The α-allyloxy ketone hydrazones **423**, obtained from **422** and SAEP, were metallated with lithium diisopropylamide in THF or THF/HMPA at low temperature and, after column chromatography or HPLC, the rearranged product hydrazones **424** were obtained in good to excellent yields (Scheme 124). The chiral auxiliary was removed with 5N HCl in petrol ether to afford the γ,δ-unsaturated α-hydroxyketones **425** in excellent yields, *syn*-selectivities and good enantiomeric excesses. The use of HMPA as a co-solvent was essential to achieve good selectivities for the rearrangement of aliphatic ketone hydrazones, whereas it diminishes the asymmetric inductions for the rearrangement of aromatic hydrazones.[229]

The proposed mechanism for the [2,3]-Wittig rearrangement of SAEP-hydrazones starting from the hydrazone **426** via the deprotonated species **427** to the rearranged product **428** is shown in Scheme 125. The assigned stereochemistry is in accordance with the cyclic transition state



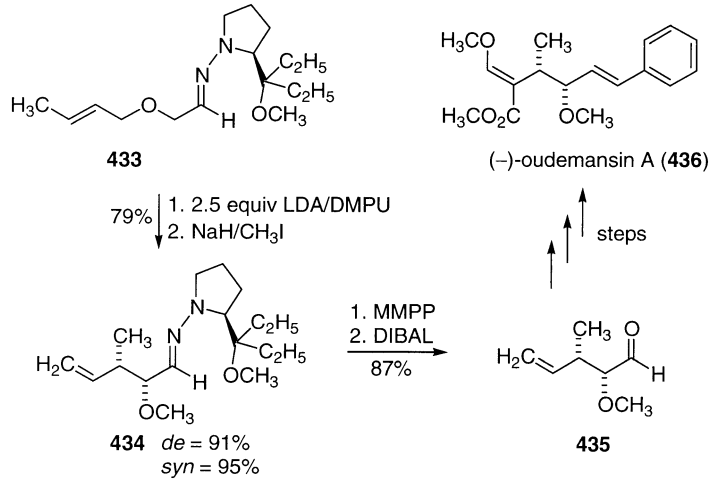
Scheme 126.

shown.[228] It is interesting to note that the diastereofacial selectivity of this orbital-controlled sigmatropic rearrangement is opposite that of the usual intermolecular electrophilic substitutions (metalloretentive) via metallated SAMP-hydrazones.

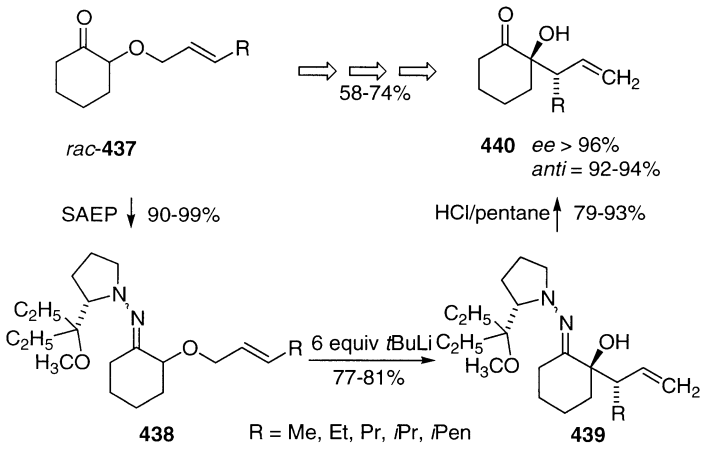
This protocol could also be applied to the α-allyloxyaldehyde hydrazones **429**, which were metallated with lithium diisopropylamide in THF/HMPA (Scheme 126). After protection of the α-hydroxyl functionality of the product **430** using TBSCl and removal of the chiral auxiliary with magnesium monoperoxyphthalate (MMPP), the γ,δ-unsaturated cyanohydrins **431** could be obtained. Reductive conversion of the nitrile functionality with diisobutyl aluminium hydride provided the γ,δ-unsaturated α-hydroxyaldehydes **432** with high *syn*-selectivities and enantiomeric excesses.[230]

This methodology was applied to the diastereo- and enantioselective synthesis of (−)-oudemansin A (**436**). This natural product, isolated from mycelial cultures of *Oudemansiella mucida*, has received much attention lately due to its strong antifungal activity.[231] Metallation of crotyloxyacetaldehyde hydrazone **433** with lithium diisopropylamide in THF/DMPU at −78°C afforded the rearranged product hydrazone with 95% *syn*-selectivity and a diastereomeric excess of 91% (Scheme 127). Methylation of the hydroxyl functionality led to the hydrazone **434** in good yields. The removal of the chiral auxiliary was accomplished with MMPP and DIBAL (as shown above) to provide the aldehyde **435**, which was converted in six steps and an overall yield of 29% into (−)-oudemansin A (**436**).[232]

Starting from the racemic α-hydroxyketones **437**, an efficient entry to the virtually enantiopure γ,δ-unsaturated cyclic α-hydroxyketones **440** with neighbouring quaternary and tertiary stereogenic centres via [2,3]-Wittig rearrangement has been developed. Condensation of the ketones **437** with SAEP resulted in excellent yields of the hydrazones **438**, which were obtained as a 1:1 mixture of diastereomers



Scheme 127.

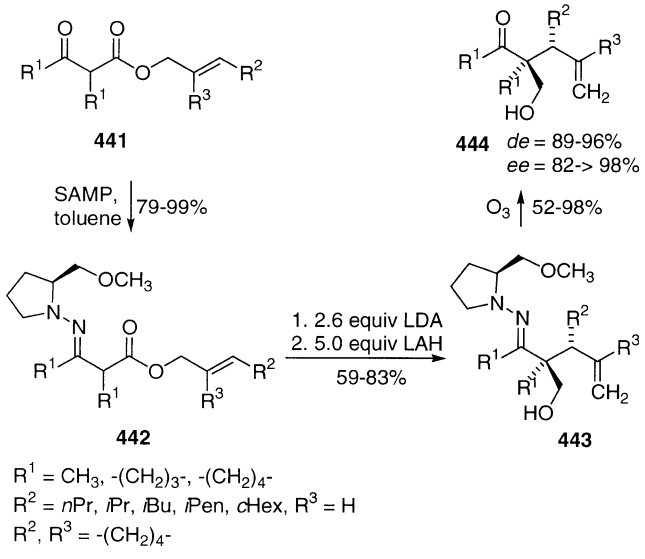


Scheme 128.

(Scheme 128). Metallation with a large excess of *t*BuLi gave rise to the rearranged hydrazones **439**. Acidic cleavage of the chiral auxiliary with hydrochloric acid in pentane afforded the γ,δ-unsaturated α-hydroxyketones **440** in good yields and excellent *syn*-selectivities and enantiomeric excesses.[233]

5.2. Carroll rearrangement

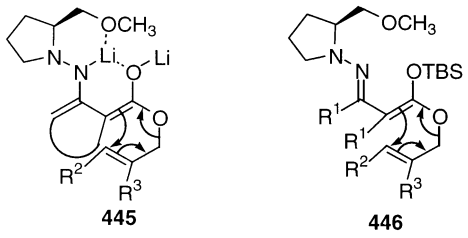
The [3,3]-sigmatropic Carroll rearrangement[234] is an efficient C–C bond-forming method and can lead to the highly-functionalised ketones **444** with vicinal quaternary and tertiary stereogenic centres. Using the SAMP hydrazone method, an asymmetric Carroll rearrangement has been developed.[235] The β-ketoallyl esters **441** were transformed into the corresponding SAMP-hydrazones **442**, which underwent, after double deprotonation with lithium diisopropylamide, the Carroll rearrangement. The intermediate carboxylic acids were directly reduced with lithium aluminium hydride to the alcohols **443** to avoid the usual decarboxylation (Scheme 129). Oxidative cleavage of the auxiliary led smoothly to the β-ketoalcohols **444** with excellent diastereo- and enantiomeric excesses in good overall yields.



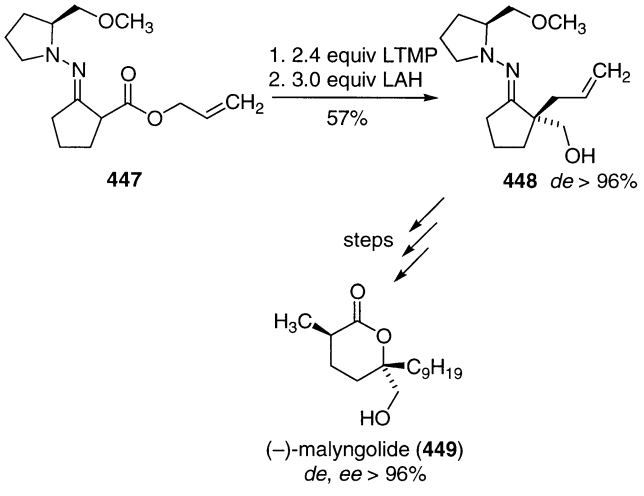
Scheme 129.

The proposed transition state is shown in Scheme 130 for the hydrazone dienolate **445**. An intramolecular chelation of lithium by the methoxymethyl group directs the approach of the allylic moiety from the sterically less hindered side (re-re attack) with the formation of a new σ-bond. Assuming the [3,3]-sigmatropic Carroll rearrangement occurs via a chair-like transition state, the configuration of the new tertiary stereogenic centre is easily assigned and could be confirmed by X-ray structure analysis.

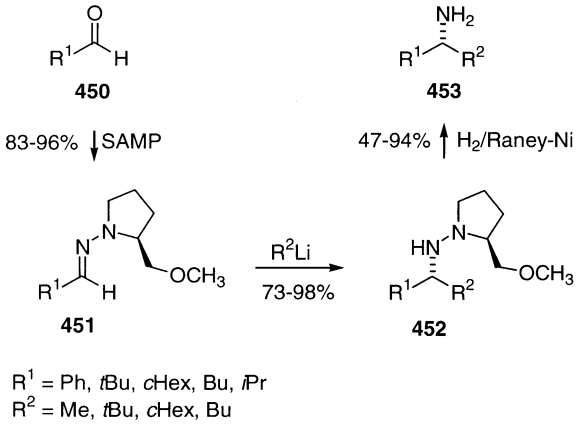
In comparison to the dianionic rearrangement, a Lewis acid-mediated [3,3]-sigmatropic Carroll rearrangement led to



Scheme 130.



Scheme 131.



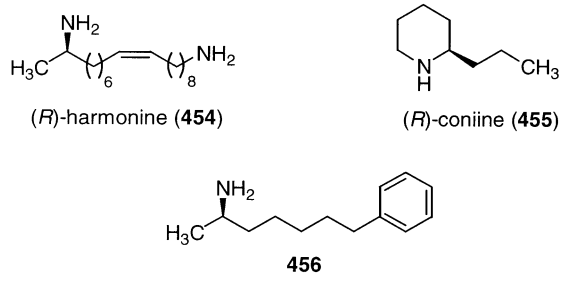
Scheme 132.

products of lower selectivity (de=5–41%, ee=39–86%). The proposed transition state is shown in Scheme 130 for compound **446**. Interestingly, this time the other diastereomer was found to be the main product resulting from a *si–si* attack.[236]

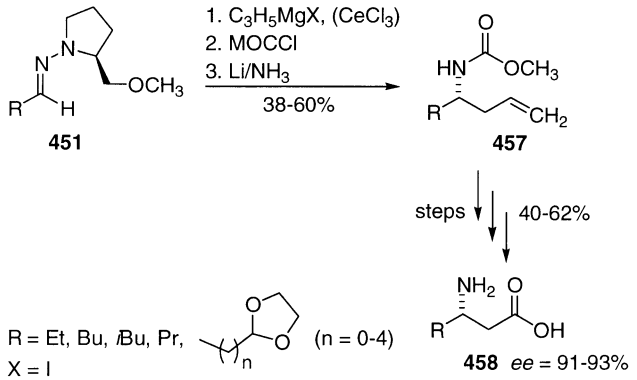
The dianionic protocol was applied to the asymmetric synthesis of the antibiotic (−)-malyngolide (**449**), a lactone isolated from the blue–green marine algae *Lyngbya majuscula*. The hydrazone **447** was metallated with 2.4 equiv. of LTMP and gave, after rearrangement, the hydrazone **448** in 57% yield with complete diastereoselectivity (Scheme 131). Further transformations gave rise to the diastereo- and enantiomerically pure natural product **449** in seven steps and 10% overall yield.[237]

6. Nucleophilic addition to the C=N double bond

The asymmetric synthesis of amines via nucleophilic 1,2-addition of organometallic reagents to CN double bonds has been reviewed recently.[238] In this section, the general scope of the 1,2-addition to SAMP-hydrazones and some recent applications will be presented. The SAMP-hydrazones **451** derived from the aldehyde **450** react with organometallic reagents in a highly stereoselective manner, the best results being obtained using organolithium, organocerium, organo-ytterbium or Grignard reagents. Reductive N–N bond cleavage of the resulting hydrazines **452** afforded the primary amines or their derivatives **453** in good overall yields and with high diastereo- and enantioselectivities (Scheme 132).[212]



Scheme 133.



Scheme 134.

This reaction was studied independently by Denmark et al.[213] A different protocol for the cleavage of the chiral auxiliary includes the trapping of the metallated nitrogen with MOCCl followed by reductive cleavage of the hydrazine N–N bond with lithium in ammonia.[239] A very mild and efficient reductive N–N bond cleavage with borane–tetrahydrofuran complex was described recently.[226]

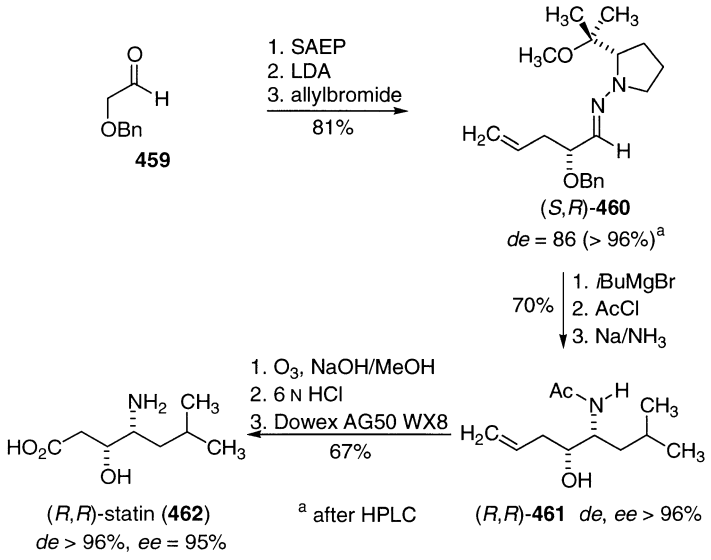
The 1,2-addition of organometallic reagents to SAMP-hydrazones was applied to the asymmetric synthesis of the ladybug defence alkaloid harmonine (**454**),[240] both enantiomers of coniine (**455**),[241] and a compound of medicinal interest (**456**) (Scheme 133).[242]

α-Amino acetals and α-amino acids[243] as well as β-amino acetals and β-amino acids[244] could also be obtained using this reaction sequence. In a representative example, the SAMP-hydrazones **451** were treated with an allyl-cerium reagent in THF or an allyl-Grignard reagent in toluene, followed by protection of the resulting hydrazine with MOCCl (Scheme 134). Cleavage of the chiral auxiliary with lithium in liquid ammonia gave rise to the homoallylamino products **457**, which could be transformed into the β-amino acids **458** with enantiomeric excesses of 91–93%.

1,2-Addition of a Grignard reagent to the SAMP-hydrazone obtained from the hydroxyaldehyde **459**, combined with an α-alkylation, led to statin (**462**), the essential component of pepstatin and aphatinin, which are natural peptidic HIV-protease inhibitors. The substituted SAMP-hydrazone **460** was reacted with an *iso*-propyl-Grignard reagent to obtain, after N–N bond cleavage, the hydroxyamine **461** in virtually diastereo- and enantiomerically pure form (Scheme 135).[245] Further steps gave rise to (*R*,*R*)-statin (**462**) in 67% yield.

N-protected aminoaldehydes,[246] β-aminoalcohols,[245] homoallylamines,[247] vicinal diamines,[248] C_2-symmetric 1,*n*-diamines (*n*=2, 4, 5),[249] ferrocenylalkylamines[250] (see Section 8) and β-silylamines[251] were also synthesised following this methodology.

Besides the use of organolithium, -cerium, -ytterbium and Grignard reagents, organobarium compounds have been used successfully in the 1,2-addition of SAMP-hydrazones (Scheme 136). The reaction of benzaldehyde SAMP-hydrazone (*S*)-**463** and prenylbariumchloride **464** afforded at 0°C

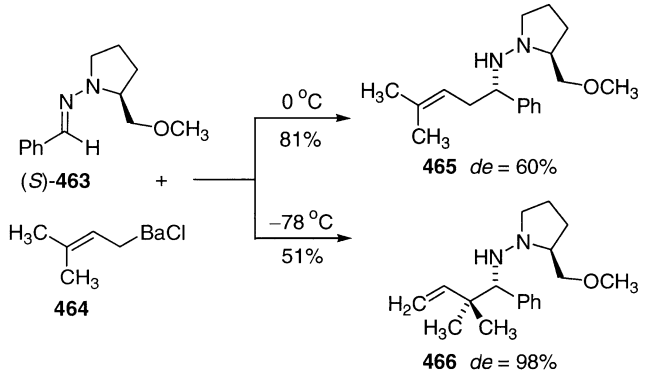


Scheme 135.

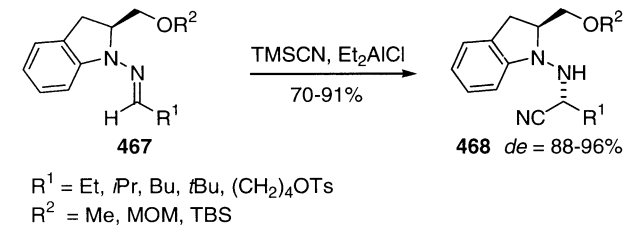
the α-allylated hydrazine **465** with a diastereomeric excess of 60%, whilst the reaction at −78°C furnished the γ-adduct **466** as the major product with complete stereocontrol, albeit only with 51% yield. Nevertheless, the use of organobarium reagents appears to be an interesting alternative to the standard reaction protocol.[252]

The 1,2-addition of trimethylsilyl cyanide (TMSCN) to (*S*)-1-amino-2-methoxymethylindoline (SAMI)-hydrazones **467** in the presence of diethylaluminium chloride afforded the corresponding chiral α-hydrazinonitriles **468** in good to excellent yields and diastereoselectivities (Scheme 137). Cleavage of the chiral auxiliary turned out to be difficult and was achieved for one compound with $H_2/Pd(OH)_2/C$ to give the corresponding diamine.[253]

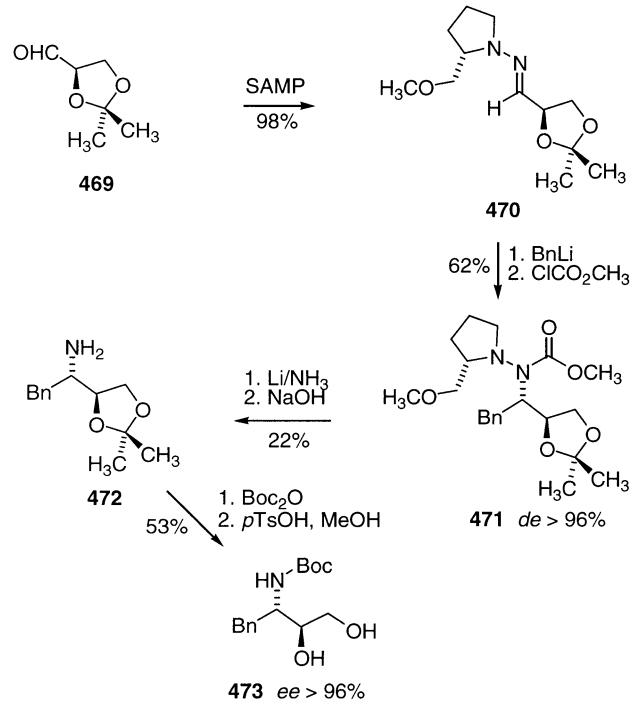
Unnatural (D)-phenylalaninol derivatives, which serve as potential synthetic building blocks for HIV-1 protease inhibitors, were also obtained by the 1,2-addition protocol. Starting from the SAMP-hydrazone of protected (D)-glyceric aldehyde **470**, the addition of benzyl lithium followed by carbamate formation afforded the hydrazine **471** with excellent diastereoselectivity (Scheme 138). Former investigations of the addition of methyl lithium to both SAMP- and RAMP-hydrazone of protected (D)-glyceric aldehyde (**469**), revealed that the asymmetric



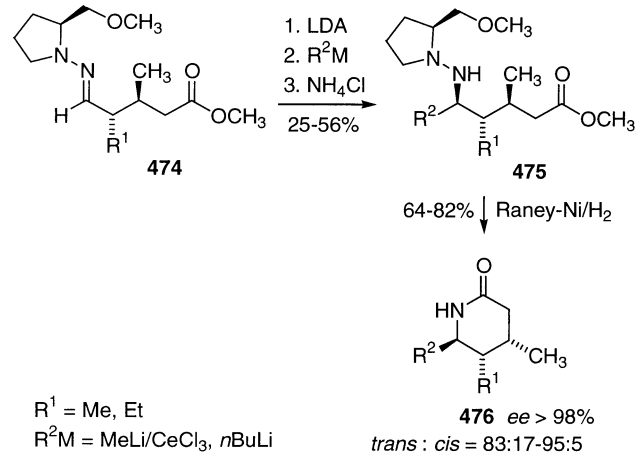
Scheme 136.



Scheme 137.



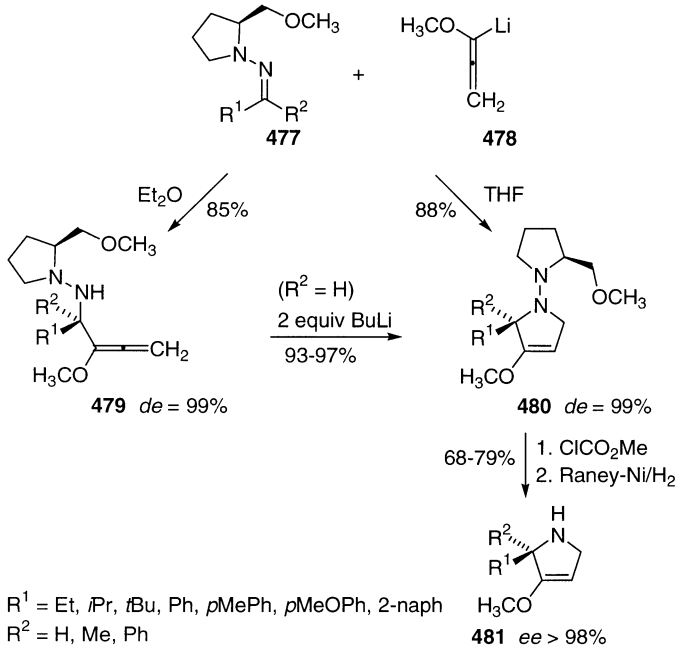
Scheme 138.



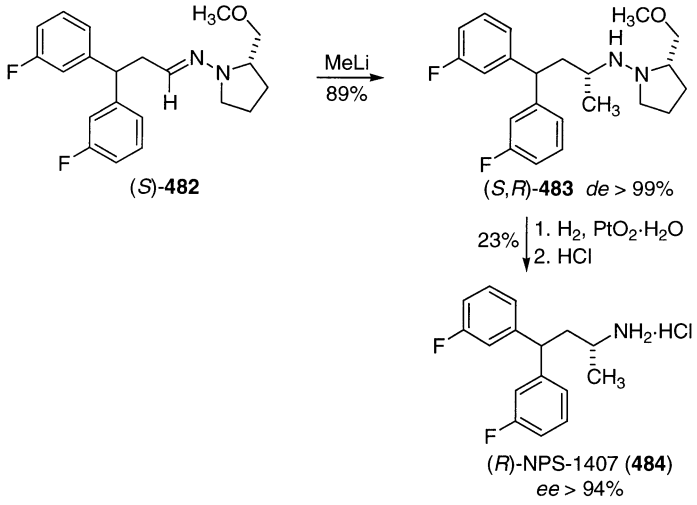
Scheme 139.

induction of the chiral auxiliary exceeded the pre existing chirality.[254] Cleavage of the chiral auxiliary with lithium in liquid ammonia and reaction of the carbamate with sodium hydroxide gave rise to the amine **472**, which was transformed into the Boc-protected (D)-phenylalaninol **473**.[255]

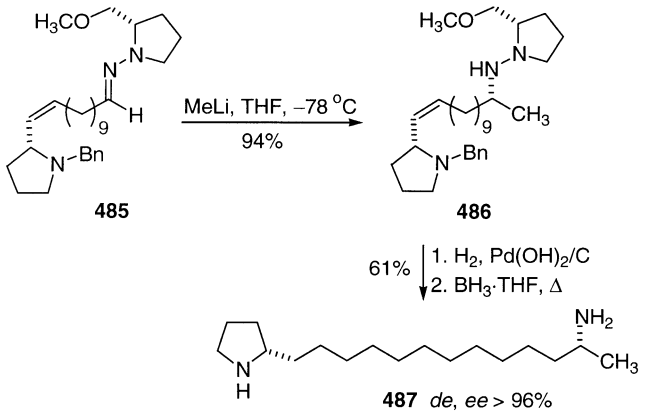
A synthesis of trisubstituted piperidin-2-ones was achieved using a combination of a Michael reaction and 1,2-addition, both using the SAMP-hydrazone methodology (Scheme 139). The aldehyde hydrazones **474**, which were obtained in high selectivities in a Michael-reaction sequence (see Section 4), were metallated with LDA. This step is necessary to mask the more electrophilic ester as an ester enolate. Using an excess of the organometallic reagent, the 1,2-addition proceeds in the usual manner to furnish the hydrazines **475**. In the last step, the chiral auxiliary was cleaved with hydrogen and Raney-nickel as catalyst.



Scheme 140.



Scheme 141.



Scheme 142.

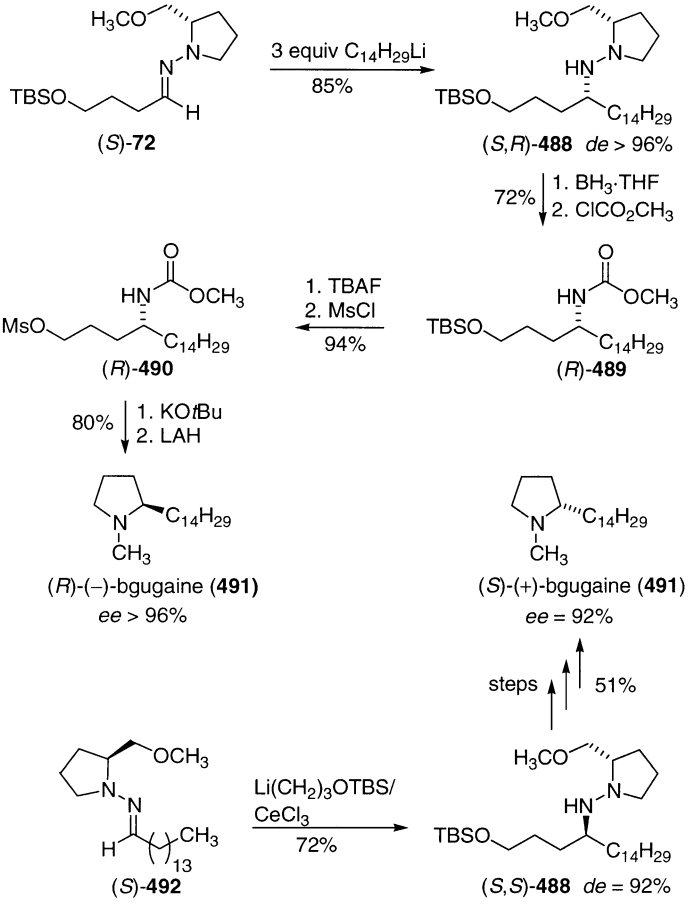
Under these reaction conditions, the product underwent cyclisation to give the virtually enantiopure 6-membered lactam derivates **476** in high *trans*/*cis*-selectivities.[182]

An asymmetric synthesis of pyrrolines via 1,2-addition to SAMP-hydrazones was reported by Goré and co-workers. The lithio derivative of methoxyallene **478** was reacted with the hydrazones **477** to afford—depending on the solvent used—the α-allenic hydrazine **479** with excellent yields and diastereoselectivities or the pyrrolines **480** (Scheme 140). Using aromatic aldehyde hydrazones, high diastereoselectivities were obtained. The chiral auxiliary of the hydrazinopyrrolines was removed by the use of MOCCl. Consecutive catalytic hydrogenation afforded the pyrrolines **481** with high enantiomeric excesses. It is interesting to note that 1,2-addition of the methoxyallene **478** also proceeded with ketone hydrazones.[256]

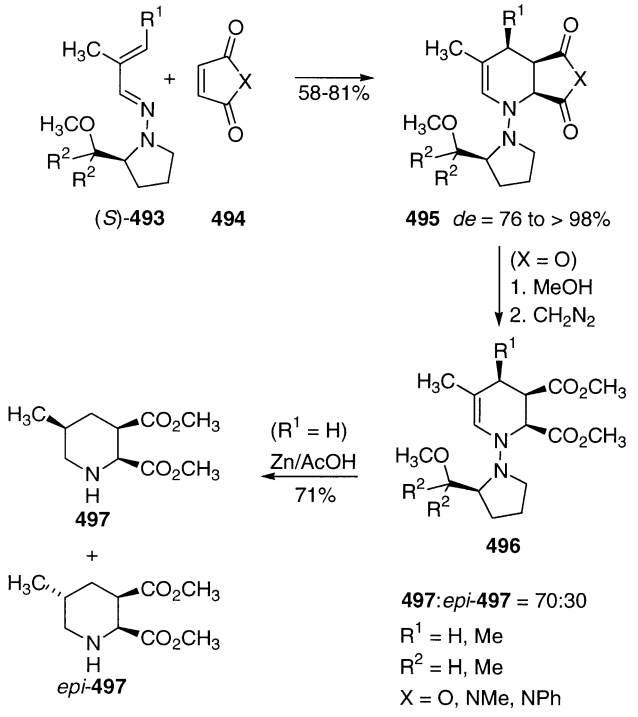
The 1,2-addition of methyl lithium to the fluorosubstituted SAMP-hydrazone (*S*)-**482** gave rise to the diastereomerically pure hydrazone (*S*,*R*)-**483** in good yield (Scheme 141).[257] N–N bond cleavage led to enantiopure (*R*)-NPS-1407 (**484**), which is a potent NMDA receptor antagonist.

The use of the 1,2-addition protocol remains to be useful for the synthesis of alkaloids. We recently prepared the defence alkaloid of the Mexican bean beetle, *Epilachana varivestis* (Coccinellidae), **487** in an efficient manner (Scheme 142). Starting from (*R*)-proline, the hydrazone **485** was obtained in four steps and an overall yield of 61%. 1,2-Addition of methyl lithium resulted in the formation of a single diastereomer of the hydrazine **486**. Removal of the benzyl protective group occurred along with hydrogenation of the double bond. Finally, the chiral auxiliary was cleaved with borane–tetrahydrofuran complex to provide the natural product **487** with excellent diastereo- and enantiomeric excess (de, ee>96%).[258]

The flexibility of the SAMP-hydrazone methodology employing the concept of synthon control of enantioselectivity was demonstrated in the synthesis of both enantiomers



Scheme 143.



Scheme 144.

of bgugaine **491**, a pyrrolidine alkaloid extracted from the tubers of *Arisarum vulgare*, showing antibacterial and antimycotic activity (Scheme 143). The SAMP-hydrazone (*S*)-**72** was treated with tetradecyl lithium to provide the hydrazine (*S*,*R*)-**488** with excellent diastereoselectivity (de>96%). Removal of the chiral auxiliary with borane–tetrahydrofuran complex followed by protection of the resulting amine with MOCCl gave rise to (*R*)-**489**, which was transformed via the mesylate (*R*)-**490** into the naturally occurring (*R*)-(−)-bgugaine (**491**) with complete stereocontrol (ee>96%). Starting from the SAMP-hydrazone (*S*)-**492**, the 1,2-addition using an organocerium-reagent gave rise to the hydrazine (*S*,*S*)-**488** with a diastereoselectivity of 92%. Repetition of the sequence described above furnished the enantiomer (*S*)-(+)-bgugaine (**491**) with an enantiomeric excess of 92%.[259]

7. Diels–Alder reactions

The asymmetric Diels–Alder reaction is a powerful method for the synthesis of enantiomerically pure 6-membered ring systems.[260] Asymmetric induction can be achieved by the use of chiral dienes, dienophiles or Lewis acids. The application of chiral 1-azadienes in asymmetric hetero-Diels–Alder reactions is depicted in Scheme 144.[261] The hydrazones (*S*)-**493**, which can be obtained from the corresponding aldehyde and SAMP or SADP, respectively, were treated with the dienophiles **494** at room temperature, affording the bicyclic compounds **495** with good to excellent diastereomeric excesses. A significant increase of facial selectivity was observed by using the sterically more demanding auxiliary. Anhydride opening and esterification provided the bisester **496**. Cleavage of the auxiliary was effected with zinc in acetic acid, furnishing the corresponding piperidine derivatives **497** without epimerisation or racemisation. During the cleavage, the double bond was reduced and a slight asymmetric induction (70:30) of the new stereogenic centre was observed.

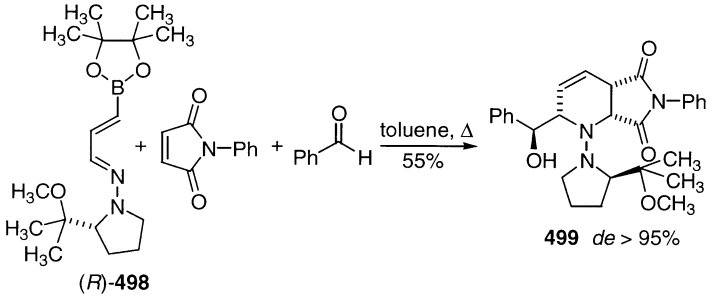
Recently, Hall et al. demonstrated that this protocol is useful as first step in a multicomponent reaction, namely in a tandem aza [4+2]/allylboration (Scheme 145).[262] RADP-hydrazone (*R*)-**498** underwent a one-pot conversion with *N*-phenylsuccinimide and benzaldehyde to afford the highly-substituted piperidines **499** as a single diastereomer (Scheme 145). The cleavage of the auxiliary or further tranformations of **499** have yet not been reported.

The isoquinuclidine ring system, azabicyclo[2.2.2]octane, is of special interest because of its role as precursor for the synthesis of bioactive compounds. The pyridinium salt **500** was treated with SAMP and subsequently reduced with sodium borohydride providing the corresponding SAMP-dihydropyridine derivative (*S*)-**501** (Scheme 146).[263] Diels–Alder reaction with methyl acrylate provided the isoquinuclidine derivatives **502** and **503** with a high *endo*/*exo* selectivity but low diastereoselectivity (45:23). Separation of the diastereomers by chromatography yielded **502** and **503** in diastereomerically pure form. Reductive cleavage of the auxiliary and treatment with MOCCl furnished the isoquinuclidines **504** and *ent*-**504**.

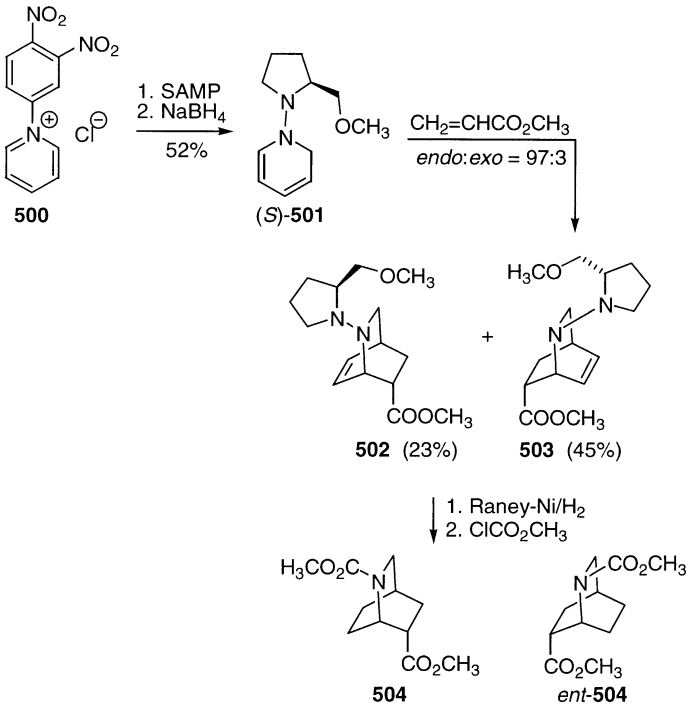
Further examples of asymmetric Diels–Alder reactions of 2-amino-1,3-dienes are summarised in a recent review.[264]

8. Applications to organometallic chemistry

SAMP-hydrazones have found several applications in the asymmetric synthesis of organometallic compounds, particularly in the synthesis of chiral ferrocene derivatives.



Scheme 145.



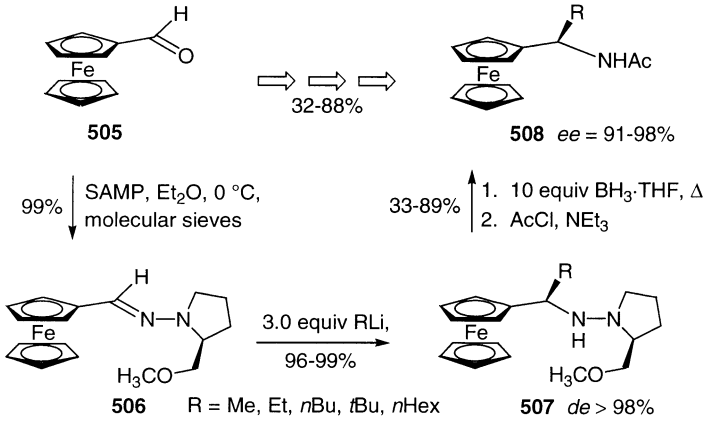
Scheme 146.

8.1. Ferrocenes

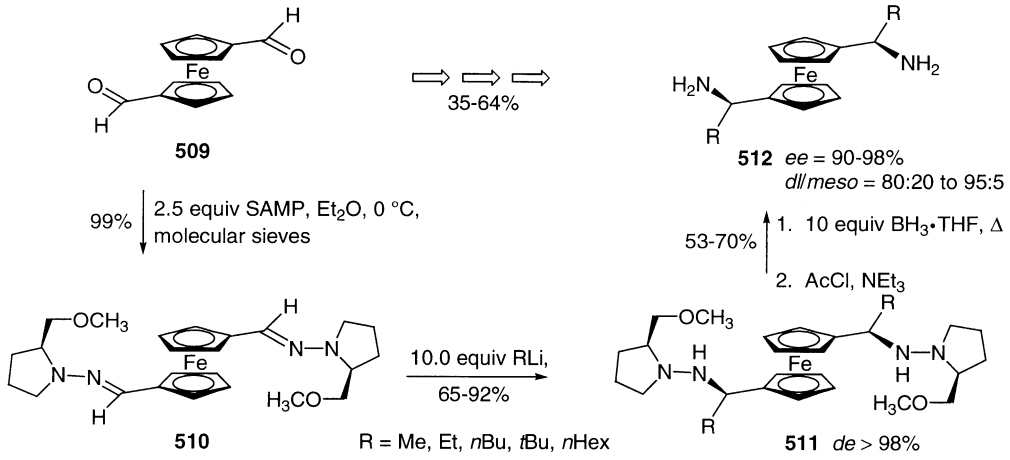
In recent years, chiral ferrocenes have proved to be extraordinarily efficient ligands for asymmetric catalysis in academic research and industry.[265] There has been a renaissance of interest since the pioneering work of Ugi et al.[266] in developing modern methods for the asymmetric synthesis of chiral ferrocenyl ligands, thus enabling an extention to the variety of accessible derivatives. The SAMP-/RAMP-hydrazone method allows the highly-stereocontrolled synthesis of ferrocene derivatives with planar chirality and/or stereogenic centres at the α- or β-position.

8.1.1. Ferrocenes bearing stereogenic centres in the α-position. Ferrocenes bearing stereogenic centres in the α-position are important precursors en route to planar chiral ferrocenyl ligands and the current interest in synthesising such compounds via asymmetric synthesis has grown.[265] Nucleophilic 1,2-addition of organolithium reagents to ferrocenecarbaldehyde SAMP-hydrazone **506**, easily accessible in almost quantitative yield starting from ferrocenecarbaldehyde **505**, afforded the hydrazines **507** (Scheme 147).[267] In order to obtain nearly quantitative yields (96–99%), the use of 3.0 equiv. of the alkyl lithium compound turned out to be necessary. The additions occurred with virtually complete asymmetric induction. The 1,2-addition of phenyl lithium gave the corresponding hydrazine in 96% yield, but the enantiomeric excess was determined to be only 84%. Owing to the air sensitivity of the hydrazines **507**, N–N cleavage was immediately carried out in order to remove the chiral auxiliary. This task was accomplished by treatment with an excess of BH_3·THF (10 equiv.) in refluxing THF furnishing the (1-ferrocenylalkyl)amines, which could be isolated as their acetamide derivatives **508** with high enantiomeric excesses (ee=91–98%) and good overall yields (32–88%).

The procedure described has been extended to the synthesis



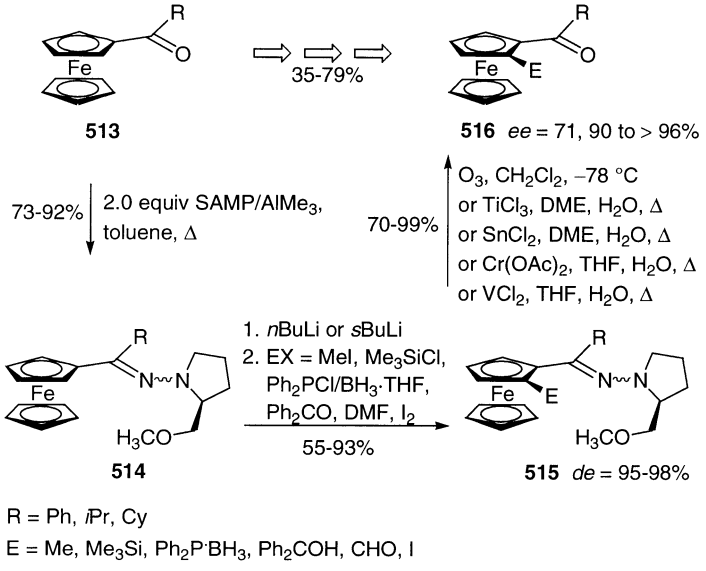
Scheme 147.



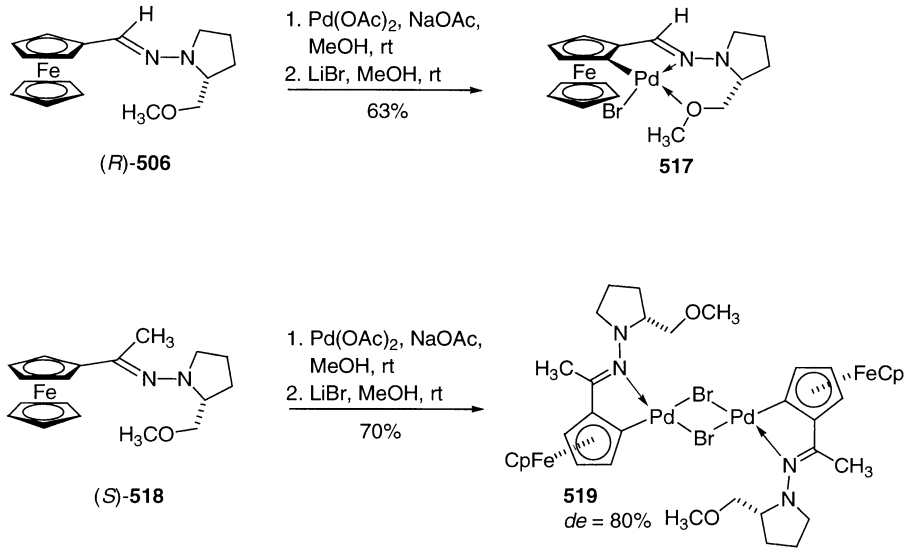
Scheme 148.

of C_2-symmetric 1,1′-bis(1-aminoalkyl)ferrocene derivatives **512** (Scheme 148).[250b,267b] In order to achieve high yields in the double 1,2-addition to the bishydrazone **510**, obtained from the corresponding bisaldehyde **509** and SAMP, a large excess (10 equiv.) of the organolithium reagent was required. This did not however appear to have any negative effect on the stereoselectivities. The best results were obtained by the use of small alkyl lithium compounds (R=Me, Et), while the bulky *tert*-butyl derivative was isolated in only moderate yield (65%), presumably due to steric hindrance. N–N bond cleavage of the hydrazine **511** and subsequent acylation of the generated primary amine functionalities provided the protected C_2-symmetric compounds **512** in 35–64% overall yield, enantiomeric excesses of 90–98% and *dl*/*meso* ratios ranging from 80:20 to 95:5.

8.1.2. Planar chiral ferrocenyl ketones. The SAMP-/RAMP-hydrazone method is also applicable to the synthesis of planar chiral ferrocene derivatives lacking stereogenic centres starting from the simple ferrocenyl ketones **513**. Since the electron-donating character of the ferrocenyl core reduces the electrophilicity of the carbonyl moiety, the ketones **513** cannot be transformed to their corresponding SAMP-hydrazones **514** using conventional methods. In 1994, Bildstein et al. presented a method that allows the conversion of electron-rich ketones into their corresponding *N*,*N*-dimethylhydrazones by activating both the hydrazine and the ketone with $AlMe_3$.[268] It was found that this method is also applicable to the synthesis of the SAMP-hydrazones **514**. The key step in the synthesis of the planar chiral ketones **516** is the diastereoselective *o*-metallation of the hydrazones **514** proceeding smoothly in diethyl ether or THF using 1.1 equiv. of *n*-BuLi or *s*-BuLi (Scheme 149).[269] The carbanions generated may be trapped by a variety of electrophiles to give the planar chiral hydrazones **515** in good yields (55–93%) and high diastereomeric excesses (87–98%). The broad applicability was demonstrated by an alkylation (EX=MeI), silylation (EX=Me_3SiCl), phosphinylation (EX=Ph_2PCl), hydroxyalkylation (EX=Ph_2CO), formylation (EX=Me_2NCHO) and iodination (EX=I_2), respectively.

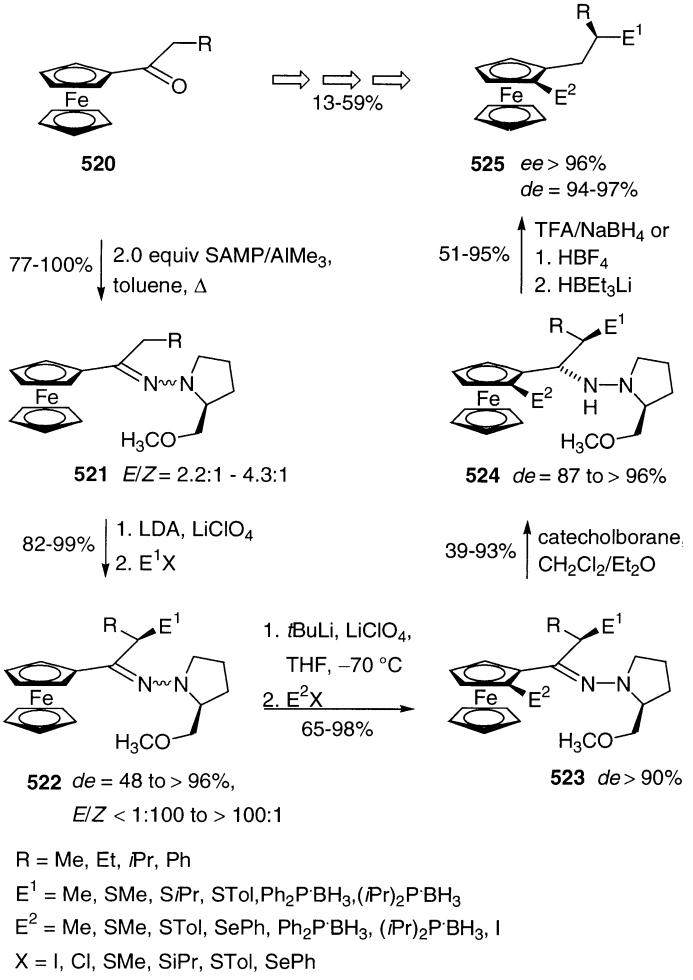


Scheme 149.

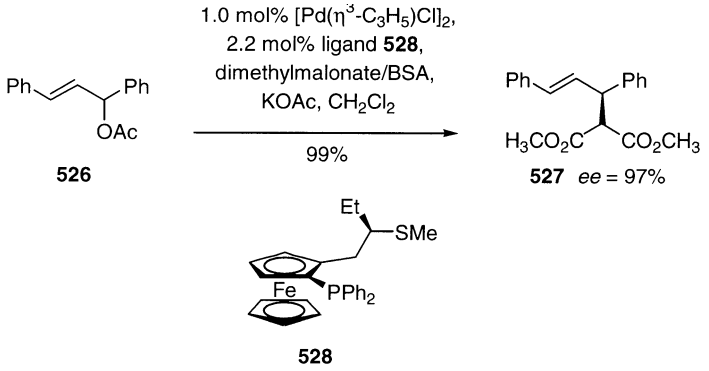


Scheme 150.

Cleavage of the auxiliary to regenerate the ketone functionality was generally accomplished by ozonolysis in dichloromethane at −78°C. The planar chiral hydrazones **515**, however, frequently turned out to be rather sensitive towards oxidative reaction conditions and, in addition, these compounds are not compatible with organic and mineral acids. It was therefore investigated whether **515** could be converted into the ketones **516** employing reducing Lewis acids that would first cleave the N–N bond, providing a ketimine that would subsequently be readily hydrolysed.



Scheme 151.



Scheme 152.

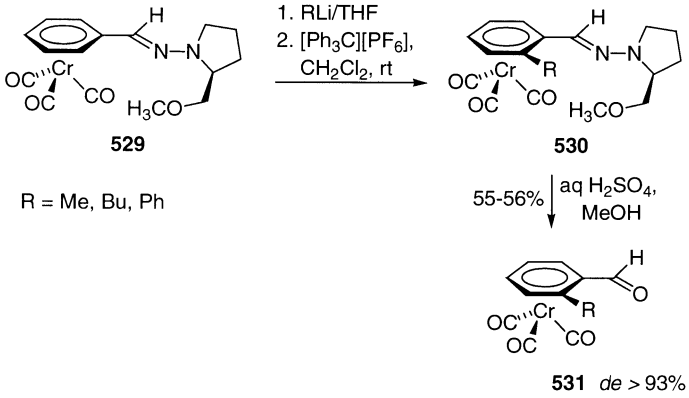
$TiCl_3$, $SnCl_2$, VCl_2 and $Cr(OAc)_2$ were found to be efficient reductive cleavage reagents.[6] All cleavage procedures mentioned above are accompanied by a slight degree of racemisation. The *o*-functionalised ferrocenyl ketones **516** could, however, be obtained, with one exception, in high enantiomeric purity (ee=90–>96%).

In a related study, Mak et al. have examined the cyclopalladation of ferrocene carbaldehyde RAMP-hydrazone (*R*)-**506** and acetylferrocene RAMP-hydrazone **518** proceeding with high diastereoselectivity.[270] While (*R*)-**506** furnished the monomeric Pd-complex **517**, **518** provided the bromo-bridged dimeric complex **519** (Scheme 150). Interestingly, *o*-lithiation and cyclopalladation of the ferrocenylketone SAMP-/RAMP-hydrazones proceeded at different *o*-positions.

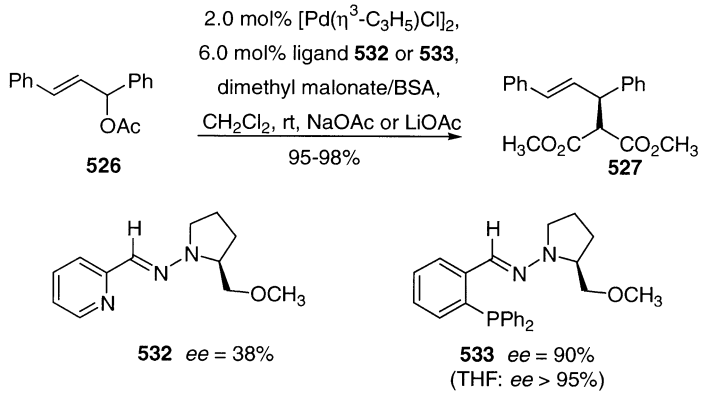
8.1.3. Planar chiral ferrocenyl ligands bearing a stereogenic centre in the β-position. The SAMP-/RAMP-hydrazone method seemed to be appropriate for the asymmetric synthesis of the planar chiral ferrocenes **525** bearing a stereogenic centre at the β-position of the ferrocene side chain. Since planar chiral ferrocenes which additionally possess a stereogenic centre in the α-position have shown efficiency as ligands for catalytic asymmetric synthesis,[265] the effect of changing the position of the stereogenic centre from α- to β- on the levels of asymmetric induction for the catalytic processes was investigated. The field of such planar chiral ferrocenes had been little studied, since there was no stereoselective access to these compounds.

After conversion of the ferrocenyl ketones **520** bearing α-protons to the corresponding hydrazones **521**, regioselective metallation of the side chain was accomplished with LDA in diethyl ether at room temperature (Scheme 151).[271] The addition of $LiClO_4$ turned out to be essential in order to achieve high *E*/*Z*-hydrazone ratios, since the (*E*)- and (*Z*)-isomers were unexpectedly found to afford products bearing opposite configurations. Through trapping of the metallated species at −100°C with the requisite electrophile, the α-functionalised hydrazones **522** were available in good yields and with *E*/*Z*-ratios varying from 5:1 to >100:1, the (*E*)-isomers of **522** being diastereomerically pure (de>96%). Regio- and diastereoselective metallation of **522** at the Cp-ring *ortho* to the directing hydrazone moiety was achieved using the combination *t*BuLi/$LiClO_4$/THF at −70°C. Trapping of the carbanions generated with alkyl, phosphorous, sulfur or selenium electrophiles yielded the planar chiral hydrazones **523** in good yields (65–98%) and with high de values (>90%). This methodology allows the successive highly diastereoselective introduction of two different donor groups. Removal of the auxiliary was accomplished by diastereoselective reduction, giving rise to the hydrazines **524** bearing two contiguous stereogenic centres in the α- and β-positions. Subsequent protonation provided the corresponding α-ferrocenyl carbocations, which could be trapped by hydride reagents. This asymmetric synthesis opens up an efficient and very flexible approach to the novel ferrocenyl ligands **525** (de=94–97%, ee>96%) for asymmetric catalysis.

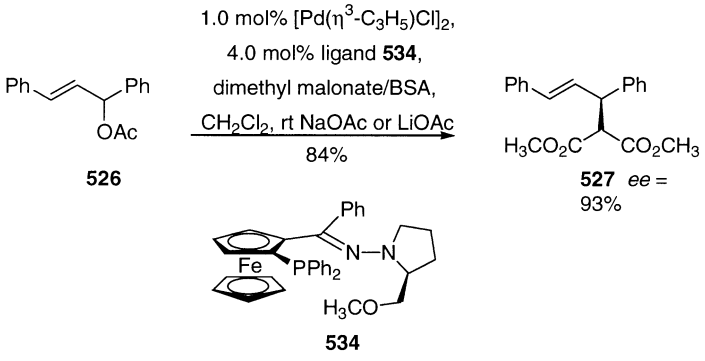
The chiral ligands **525** were investigated in Pd-catalysed enantioselective allylic substitution reactions (Scheme 152).[271b,272] By employing 2.2 mol% of the P∪S-ligand



Scheme 153.



Scheme 154.

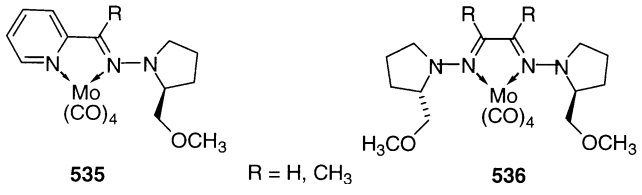


Scheme 155.

528 and 1.0 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, alkylation of the standard test system (±)-(*E*)-1,3-diphenyl-2-propenyl acetate (**526**) using dimethyl malonate/BSA as nucleophile proceeded in quantitative yield to provide **527** with an ee of 97%, which is the best value reported so far in this reaction using a P∪S-ligand.

8.2. Arene tricarbonylchromium(0) complexes

From a stereochemical point of view, planar chiral (η^6-arene)tricarbonylchromium(0) complexes are related to their more robust ferrocene counterparts.[273] Kündig et al. investigated the reaction of organolithium compounds with arenes bound to the electron-withdrawing $Cr(CO)_3$ fragment.[274] The hydrazone complex **529**, readily prepared in 88% yield from [$Cr(CO)_3$(benzaldehyde)] and SAMP, was employed in a nucleophilic addition/hydride abstraction sequence (Scheme 153). Isolation of the planar chiral hydrazone complexes **530** is not required. The three-step transformation of **529** into the aldehyde complexes **531** could be carried out as a one-pot procedure (overall yield 55–56% from **529**, de>93%).



Scheme 156.

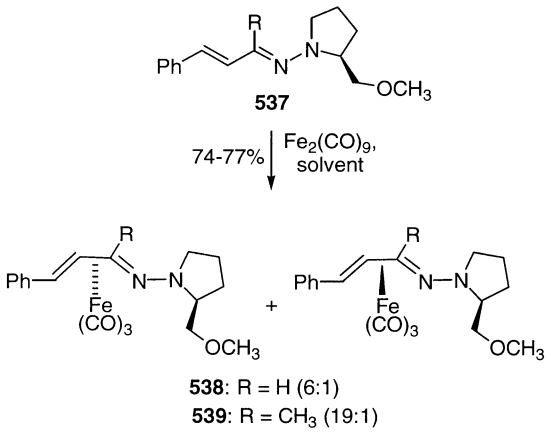
8.3. Applications to asymmetric catalysis

SAMP-hydrazones may also act as chiral ligands in asymmetric catalysis. Yamashita et al. investigated the Pd-catalysed asymmetric allylic alkylation[275] of 1,3-diphenyl-2-propenyl acetate (**526**, Scheme 154).[276] Using the N∪N-type pyridine–hydrazone ligand **532**, the substitution product **527** was obtained in nearly quantitative yield, but the enantiomeric excess was low (ee=38%). Employing the P∪N ligand **533**, however, the ee value was increased to 90%. Application of THF as the solvent in the latter reaction led to the enantiopure malonate **527**.[277]

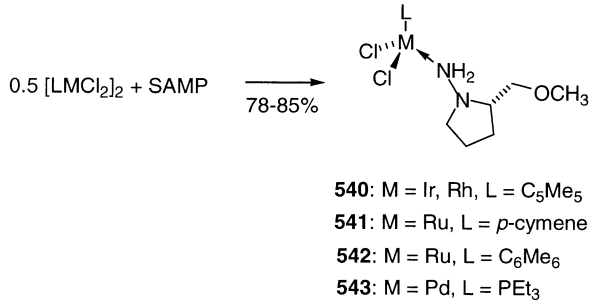
The ferrocene phosphinohydrazone **534** turned out to be an efficient P∪N ligand in the same catalytic reaction (Scheme 155).[269b] Employing 4.0 mol% of the ligand **534** and 1.0 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ yields **527** with an ee of 93% at room temperature in dichloromethane (yield 84%).

8.4. Miscellaneous

The complexation of the SAMP-hydrazones of glyoxal, biacetyl, pyridine-2-carbaldehyde or 2-acetylpyridine to $Mo(CO)_6$ was investigated by tom Dieck and co-workers.[278] The hydrazones were found to coordinate through the imino nitrogen atoms, furnishing the chelate hydrazone tetracarbonylmolybdenum complexes **535** and **536** (Scheme 156). A single crystal X-ray diffraction study proved the conjugate interaction of the sp^2-hybridised amino nitrogen with the chelating π-system resulting in a relatively short N–N distance (1.38 Å).



Scheme 157.



Scheme 158.

Pearson et al. have studied a chiral auxiliary-directed asymmetric tricarbonyliron complexation of azadienes (Scheme 157).[279] The α,β-unsaturated SAMP-hydrazones **537** were treated with $Fe_2(CO)_9$ providing the η^4-complexes **538** and **539** with diastereofacial selectivities up to 95:5.

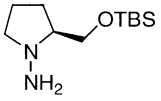
SAMP may also act as a chiral N-ligand. The chloro-bridged complexes $[Cp^*MCl_2]_2$ ($Cp^*=C_5Me_5$, M=Ir, Rh), $[(p\text{-cymol})RuCl_2]_2$, $[(C_6Me_6)RuCl_2]_2$ and $[(PEt_3)PdCl_2]_2$ react with SAMP by cleavage of the chloro-bridges, yielding the monomeric η^1-SAMP complexes **540**–**543** (Scheme 158).[280] X-Ray structural determinations proved coordination of the amino group.

From the chloro-bridged complexes, SAMP and sodium α-ketocarboxylates, the hydrazone N∪O-chelate complexes **544**–**547** were obtained providing new stereogenic centres at the metal atom with some degree of diastereoselectivity (60:40, Scheme 159).

9. Miscellaneous

Besides the use of SAMP as a versatile chiral auxiliary in asymmetric synthesis, its applicability as a reagent for the determination of enantiomeric excesses of ketones and aldehydes has been demonstrated, usually by NMR spectroscopic methods or gas chromatography.[281]

On a preparative scale, the separation of racemic ketones or aldehydes can additionally be accomplished by chromatography of SAMP derivatives, to lead after cleavage of the auxiliary to the corresponding enantiopure ketones and aldehydes.[282] During investigations in the HPLC separation of SAMP-hydrazones, the SAMP derivative **548** (SASP, Scheme 160) proved to be the most efficient compound for this purpose.[283] Additionally, SAMP was applied to the resolution of racemic ketones via fractional crystallisation of the diastereomeric hydrazones.[284]

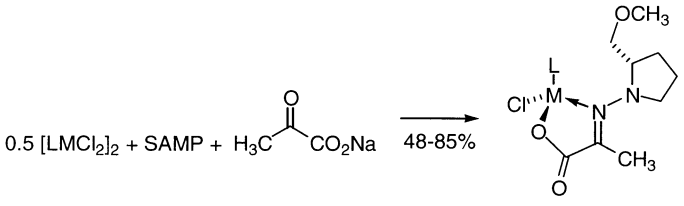


SASP (548)

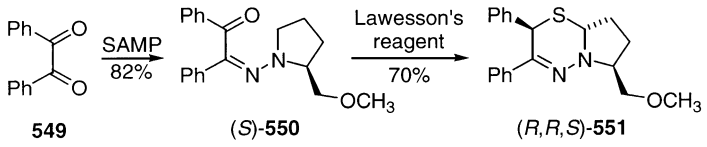
Scheme 160.

As an example, benzil (**549**) was treated with SAMP resulting in the corresponding benzil monohydrazone **550** in good yield (Scheme 161). Reaction with Lawesson's reagent thiolated the remaining carbonyl functionality. A subsequent intramolecular cyclisation afforded the bicyclic 1,3,4-thiadiazine **551** as a pure stereoisomer with the absolute configuration 4*R*,6*R*,9*S* shown by X-ray analysis.[285]

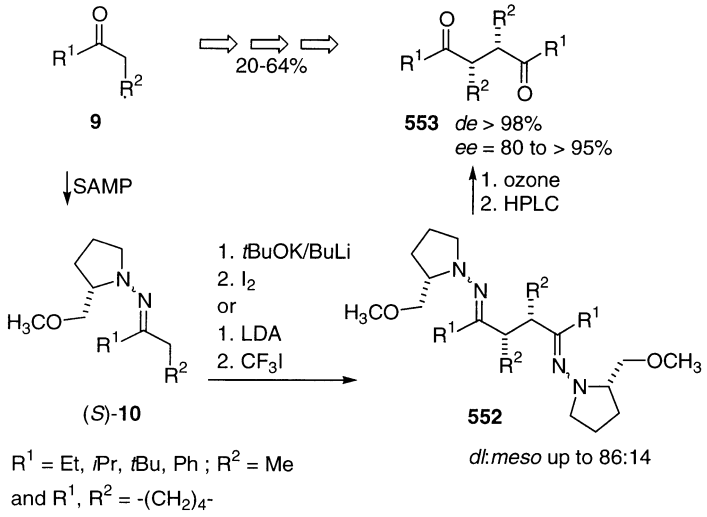
1,4-Diketones are important precursors of cyclopentanoids and 5-membered heteroaromatics.[286] Starting from the hydrazones (*S*)-**10** obtained from the ketones **9** and SAMP, deprotonation and oxidative coupling with iodine yielded the bishydrazones **552** (Scheme 162).[287] The same products with similar selectivity but lower yield were obtained by applying trifluoromethyl iodide on the corresponding azaenolates. Subsequent ozonolytic cleavage afforded the 1,4-diketones **553** in good overall yield. MPLC separation of the undesired *meso*-compounds



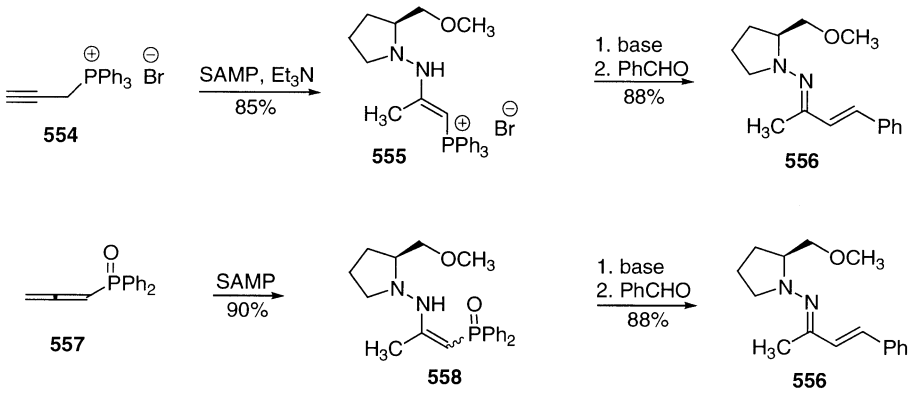
Scheme 159.



Scheme 161.



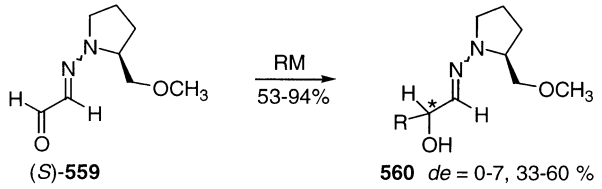
Scheme 162.



Scheme 163.

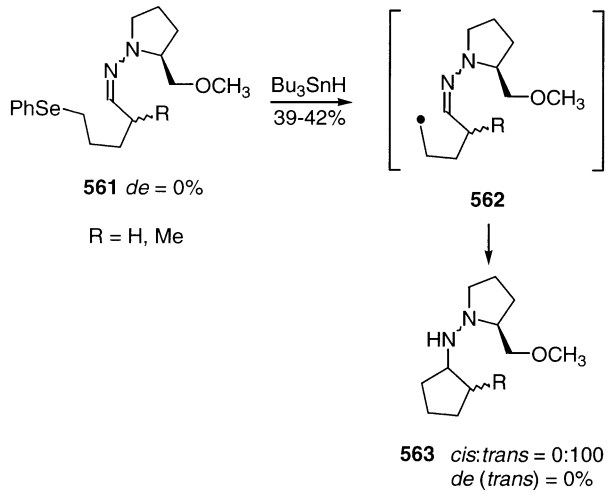
provided the diketones with excellent diastereo- and enantiomeric purity.

Palacios et al. provided a flexible protocol for the synthesis of α,β-unsaturated SAMP-hydrazone derivatives used for Diels–Alder reactions (Section 7) or in organometallic reactions (Section 8). Addition of propargyltriphenylphosphonium bromide (**554**) to SAMP afforded the corresponding hydrazino phosphonium salt **555** in complete *E*-selectivity (Scheme 163).[288] The analogous addition of the allene derivative **557** to SAMP gave the phosphine oxide **558** in excellent yield. Such compounds can also be alkylated in a further step providing the α-branched hydrazono phosphine oxides.[288] Both SAMP derivatives are precursors for olefination reactions and were added to benzaldehyde resulting in the corresponding α,β-unsaturated hydrazones **556** in

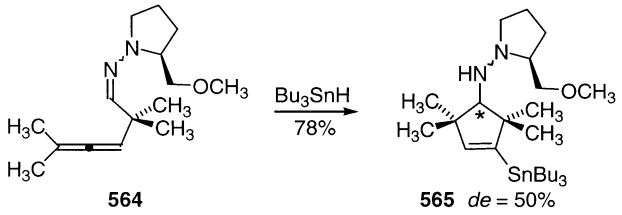


RM = MeLi, *t*BuLi, *t*Bu$_2$CuLi, H$_2$C=CHMgBr, H$_2$C=C(CH$_3$)MgBr, allyl$_4$Sn

Scheme 164.



Scheme 165.



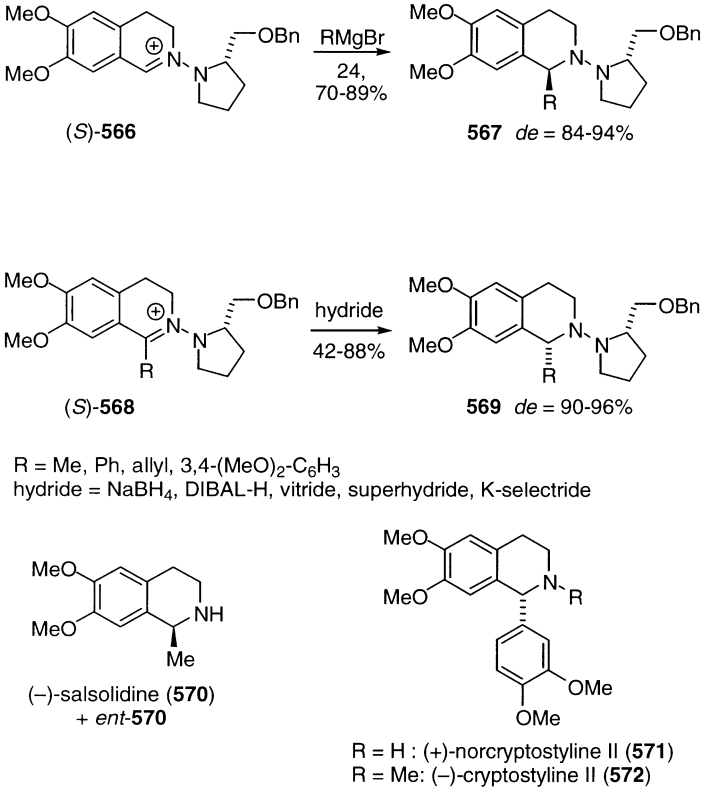
Scheme 166.

high *E*-selectivity. Variation of both coupling reagents and carbonyl compounds should yield a broad variety of α,β-unsaturated SAMP-hydrazones as precursors for further reactions.

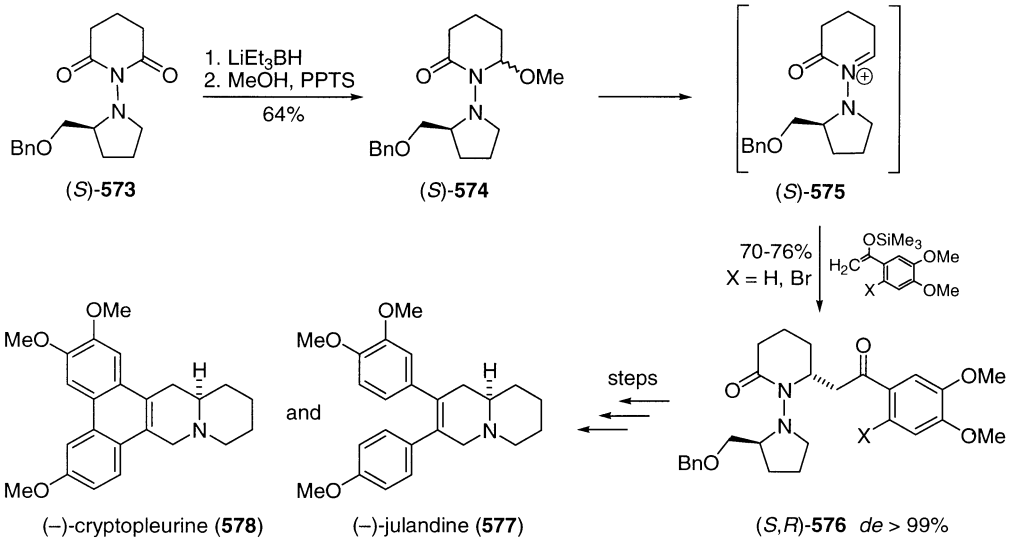
Addition of organometallic reagents to glyoxal mono-SAMP-hydrazone (*S*)-**559** obtained from glyoxal and SAMP gave the α-hydroxy hydrazones **560** (Scheme 164). With organo lithium or cuprate reagents a diastereoselectivity is hardly noticeable, but addition of Grignard reagents or tetraallyltin furnished the hydrazones **560** with up to 60% de.[289]

Radical cyclisation of the selenylated the aldehyde hydrazones **561** with tributyltin hydride yielded via the intermediate **562** the cyclic hydrazines **563** with excellent *trans*-selectivity (R=Me, Scheme 165).[290] Due to the epimeric mixture of the hydrazone **561** (R=Me, de=0%), the de value of the *trans*-product was 0%. Radical cyclisation of the allene derivative **564** proceeds under similar conditions with 78% yield and a diastereomeric excess of 50% to the hydrazine **565** (Scheme 166).[291]

Nucleophilic addition of Grignard reagents to the hydrazonium ions (*S*)-**566** yielded the 1-substituted tetrahydroisoquinolines **567** in good yields and very good diastereoselectivities (Scheme 167).[292] Starting from the substituted hydrazonium ions (*S*)-**568**, reaction with various hydride reagents furnished the opposite diastereomer **569** in excellent selectivity. This protocol was applied to the synthesis of the alkaloids (−)-salsolidine (**570**) and its enantiomer *ent*-**570**, (+)-norcryptostyline II (**571**) and (−)-cryptostyline II (**572**, Scheme 167).[292]



Scheme 167.



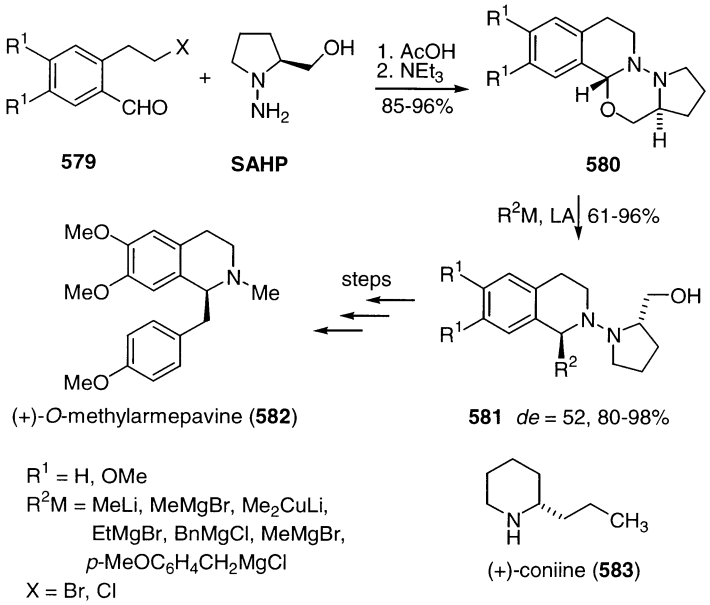
Scheme 168.

Analogously, the *N*-pyrrolidinylimide (*S*)-**573**, which was obtained from the corresponding hydrazine and glutaric anhydride, can be converted in situ via (*S*)-**574** into the hydrazonium ion (*S*)-**575** (Scheme 168).[293] Subsequent trapping of this reactive intermediate with silyl enol ethers yielded the substituted lactams (*S*,*R*)-**576** as single diastereomers. Further transformations afforded the natural products (−)-cryptopleurine (**577**) and (−)-julandine (**578**).

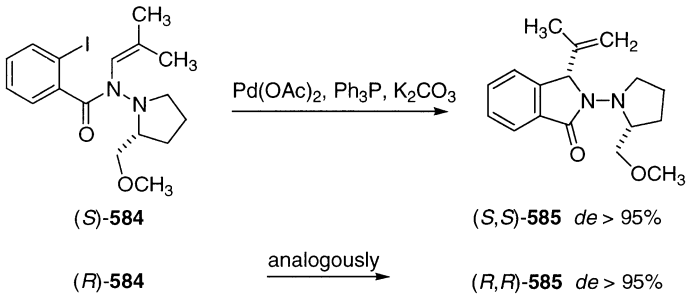
The same class of compounds was also obtained by a second concept. Treatment of the haloethyl benzaldehydes **579** with (*S*)-1-amino-2-hydroxymethylpyrrolidine (SAHP) yielded the chiral 1,3,4-oxadiazine derivatives **580** (Scheme 169).[294] Lewis acid-mediated addition of carbon nucleophiles to the latter compounds afforded the formerly-discussed 1-substituted tetrahydroisoquinolines **581** in good yield and good selectivity. Further transformations of one derivative of **581** yielded the alkaloid (+)-*o*-methylarmepavine (**582**) in enantiopure form. The reaction sequence was also employed on a starting material without an aromatic ring system providing enantiomerically pure (+)-coniine (**583**).[295]

Another cyclisation reaction was accomplished with the SAMP derivative (*S*)-**584** according to the Heck reaction protocol (Scheme 170).[296] Both starting materials (*S*)-**584** and (*R*)-**584** provided the desired products (*S*,*S*)-**585** and (*R*,*R*)-**585**, respectively, in very good diastereoselectivity. The absolute configuration of the isoindolinone derivative (*S*,*S*)-**585** was proved by X-ray structure analysis.

Palladium-catalysed allylation of the chiral hydrazone

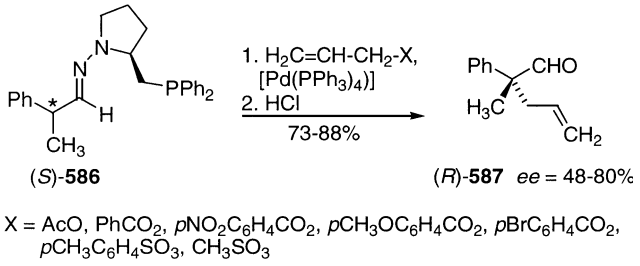


Scheme 169.



Scheme 170.

(*S*)-**586** bearing a diphenylphosphine group was performed by Hiroi et al. (Scheme 171).[297] Various leaving groups in the allyl moiety were investigated and the allyl tosylate showed the best results. In the latter reaction, the allylated aldehyde (*R*)-**587** was isolated in 73% yield and 80% ee. If the reaction was performed with (*S*)-valine- and (*S*)-phenylalanine-derived hydrazones, the stereochemical outcome of the intramolecular asymmetric allylation furnished the opposite absolute configuration of the aldehyde **587**.



Scheme 171.

The auxiliary SAMP was also used for the synthesis of enantiomerically-enriched precursors for the synthesis of shape-persistent two-dimensional polymers.[298] Those polymers consist of rigid chiral molecules, which form a bilayer on account of self-assembly phenomena. The necessary molecular recognition events also include homochiral interactions.

10. Conclusions and outlook

Since the pioneering times of the mid 1970s, when the first practical and generally applicable methods in stochiometric asymmetric synthesis were developed, such as the oxazoline method of Meyers and the SAMP-/RAMP-hydrazone method described in this review, we have seen a tremendous growth in this research area. Only 25 years later, efficient methods for almost all important asymmetric C–C and carbon–heteroatom bond formations are now at our disposal and enzyme-like enantioselectivities can generally be reached. It is fascinating to see that the next innovation steps, namely the development of catalytic versions of all these processes, are developed even more rapidly in the near future. Asymmetric synthesis—'vivat, crescat, floriat'!

Acknowledgements

D. E. wishes to express his deep gratitude to a large number of co-workers, who have contributed significantly over the past 25 years with hard work, skill and enthusiasm to the field of asymmetric synthesis. We thank the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Alexander von Humboldt Foundation, the Volkswagen-Stiftung and the Max-Planck-Gesellschaft for financial support. The donation of chemicals mainly by Degussa AG, BASF AG, Bayer AG, the former Hoechst AG and Wacker Chemie is gratefully acknowledged.

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Biographical sketch

Andreas Job was born in 1972 in Neuwied am Rhein, Germany. He studied chemistry at the RWTH Aachen, where he received his Dr rer. nat. in 2001 in the group of Professor Enders. As a member of the Graduiertenkolleg he was working on the asymmetric synthesis of natural products, e.g. argentilcatone, goniothalamin, serricornin and callystatin A. He is currently a postdoctoral fellow at the Scripps Research Institute in the laboratories of Professor J. Rebek, Jr. where he is working in the area of supramolecular chemistry (Feodor Lynen fellowship, Alexander von Humboldt foundation).

Wolfgang Bettray was born in 1963 in Kalkar, Germany. He studied chemistry at the RWTH Aachen, where he received his Dr rer. nat. in 1993 in the group of Professor D. Enders on the asymmetric synthesis of β-amino acids and their derivatives via hetero Michael Addition using TMS-SAMP as a chiral equivalent of ammonia. Since 1993 he has been responsible for the administration of the Sonderforschungsbereich 380 'Asymmetric Synthesis with Chemical and Biological Methods' and the Chair I of Organic Chemistry (Professor Enders) at the Institute of Organic Chemistry of the RWTH Aachen. Furthermore he is leading the laboratories for Mass- and IR-Spectroscopy as well as Combinatorial Chemistry.

Carsten Janeck was born in 1969 in Rotenburg, Germany. He studied chemistry at the RWTH Aachen, where he received his Dr rer. nat. in 2000 in the group of Professor D. Enders on the asymmetric synthesis of natural products and the application of aziridines in asymmetric synthesis. Since 2000 he has been working for Merck KGaA in Darmstadt, Germany.

René Peters was born in 1971 in Simmerath, Germany. He studied chemistry at the RWTH Aachen (1992–1997). In 2000, he received his Dr rer. nat. in the group of Professor Dieter Enders on the asymmetric synthesis of novel ferrocenyl ligands and their application to catalysis. Attracted by the work of Professor Yoshito Kishi on total syntheses of most complex natural products, he moved to Harvard University (Cambridge, MA, USA) for postdoctoral studies (2000/2001) working on the syntheses of marine macrocylic poyether toxins. Recently, he has taken a position in Process Research at F. Hoffmann-La Roche in Basel/ Switzerland.

Dieter Enders was born in 1946 in Butzbach, Germany. He studied chemistry at the Justus Liebig University Gießen and received his Dr rer. nat. in 1974 under the supervision of Professor D. Seebach. After post-doctoral studies at Harvard University with Professor E. J. Corey he returned to Gießen obtaining his Habilitation in 1979. In 1980 he moved to the University of Bonn as an associate professor and in 1985 to his present position as Professor of Organic Chemistry at the Rheinisch–Westfälische Technische Hochschule Aachen. His current research interests are asymmetric synthesis, new synthetic methods using organometallics and the stereoselective synthesis of biologically active compounds. He has been the recipient of many prizes, among them the Leibniz prize (Deutsche Forschungsgemeinschaft), the Yamada Prize (Japan), and the Max Planck Research Award (Max Planck Gesellschaft and Alexander von Humboldt Foundation).