Asymmetric Synthesis with (S)-2-Methoxymethylpyrrolidine (SMP) – a Pioneer Auxiliary

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Dedicated to the memory of Professor Shun-ichi Yamada, a pioneer in asymmetric synthesis

Since the pioneering times of the mid seventies (S)-2-methoxymethylpyrrolidine SMP and its enantiomer RMP belong to the most generally useful chiral auxiliaries in stoichiometric asymmetric synthesis with a very broad range of different applications. As a proline derivative, it generally shows high stereoselectivities due to the rigidity of the five-membered ring and the ability to coordinate metal fragments. The intention of this treatise is to demonstrate the synthetic utility of this important chiral auxiliary covering the literature up to 1996.

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1. Introduction

Since the pioneering times of the mid seventies (S)-2-methoxymethylpyrrolidine SMP and its enantiomer RMP belong to the most generally useful chiral auxiliaries in asymmetric synthesis with a very broad range of different applications.\(^1\)

\[ \text{SMP} \quad \text{RMP} \]

Scheme 1

A basic requirement for a practicable asymmetric synthesis using stoichiometric amounts of a chiral auxiliary is that the reagent is relatively cheap, that both enantiomers are easily available in large amounts and, of course, excellent asymmetric inductions are reached. Two major facts were decisive for the design of the new auxiliary. On the one hand the successful use of the amino acid (S)-proline and its derivatives in asymmetric C-C bond forming reactions, as demonstrated in the early work of Yamada et al.\(^2\) and in the Eger–Sauer–Wiechert–Hajos reaction, a very efficient, (S)-proline catalyzed Robinson annulation technique.\(^3\) On the other hand, in 1974 Meyers et al.\(^4\) demonstrated with their oxazoline method the importance of an intramolecular methylene ligand using chiral organolithium compounds. Based on these roots the idea was born in 1975 to combine the cheap chirality information and conformational rigidity of the five-membered ring amino acid (S)-proline with the intramolecular methoxy chelation trick. Thus by a simple reduction of the acid group followed by etherification, the title auxiliary SMP was created.\(^5\) The intention of this treatise is to depict the synthetic utility of this important chiral auxiliary. The literature until 1996 has been scanned as thoroughly as possible and, although the most significant studies are represented herein, some surely have eluded careful search. For this the authors apologize and hope readers will inform them of any omissions so such work may be included in a future discussion. Following an old tradition in the journal *Synthesis*, important and typical procedures are given throughout this review.

(S)-2-Methoxymethylpyrrolidine (SMP):\(^6\)

In a 4-L three-necked round-bottomed flask equipped with a heating mantle, an overhead stirrer, an effective reflux condenser with a drying tube packed with silica gel and a plastic stopper, LiAlH\(_4\) (60 g, 1.6 mol) was placed in anhyd THF (2.5 L) and heated to reflux for 15 min. The heating mantle was switched off, (S)-proline (115.1 g, 1.0 mol) was added in small portions and the mixture was heated for 1 h to reflux. Excess LiAlH\(_4\) was decomposed by cautiously adding a solution of KOH (28 g) in H\(_2\)O (112 mL). After stirring for 15 min the mixture was filtered through a large Büchner funnel and the remaining salts were extracted with THF (1.5 L) under reflux conditions. The combined organic filtrates were concentrated under reduced pressure at 30 °C to yield (S)-2-hydroxymethylpyrrolidine (115–125 g). In a 1-L flask methyl formate (80 mL) was added at 0 °C over a period of 1 h to the crude product and stirred for 2 h. Excess methyl formate was evaporated at 30 °C in vacuum affording a dark oil which was taken up in CH\(_2\)Cl\(_2\) (600 mL) and dried (Na\(_2\)SO\(_4\)). The mixture was filtered and concentrated under reduced pressure at 30 °C. The procedure yielded 130 g (ca. 1 mol) of the N-formyl compound which was dissolved in anhyd THF (1.5 L) in a 4-L three-necked round-bottomed flask equipped with an overhead stirrer, reflux condenser and dropping funnel. The solution was cooled to ~ 50 to −60 °C, Mel (81 mL, 1.2 mol) and then NaN\(_3\) (28.8 g, 1.2 mol) were added carefully. The solution was allowed to warm up to r.t. (caution: H\(_2\) gas formation!), heated to reflux for 15 min, quenched by slow addition of 6 M HCl
(91 mL) and filtered. THF was evaporated under reduced pressure yielding a dark oil. A solution of KOH (180 g) in H₂O (720 mL) was added to the crude product under vigorous stirring at r.t. and then heated at reflux for 5 h. (S)-2-Methoxyethylpyrrolidine was extracted in a 2-L perforator over a period of 48 h with Et₂O. The organic layer was dried (Na₂SO₄), Et₂O was evaporated and the residue distilled (bp 62°C/40 Torr). The procedure yielded 86 to 92 g (75 to 80%) of a colourless liquid ([α]D²⁰ = +3 to +4 (neat)) which was stored at 0 to −4°C under Ar. The enantiomer (R)-2-methoxyethylpyrrolidine (RMP) can be prepared from (R)-proline or alternatively from the commercially available relatively cheap (R)-glutamic acid, (R)-prolinol, and then along the lines given above.⁵

2. Asymmetric Synthesis with SMP-formamides

Lithiated SMP-formamides and -thioformamides were among the first chiral acyl anion equivalents (d₁-synths) in asymmetric synthesis.⁶ The α-hydroxy amides 1 could be obtained in good yields via asymmetric nucleophilic carbamoylation by addition of lithium tetramethylpiperidide (LTMP) to a mixture of the SMP-formamide and ketones at low temperatures. After chromatographic separation of the diastereomers the enantio-merically pure α-hydroxy amides 1 may be converted to α-hydroxy ketones and aldehydes, α-hydroxy acids and vicinal diols in high yields and excellent enantiomeric purities.

3. Asymmetric Synthesis with SMP-aminonitriles

Metalated SMP-aminonitriles are eligible d₁-synths as Enders, Mazaleyrat et al. demonstrated.⁷ After deprotonation of the SMP-aminonitriles with lithium disopropylamide (LDA) in THF the corresponding anions were trapped with various aldehydes at −78°C. The cleavage of the intermediate adducts afforded the α-hydroxy ketones 2 in moderate yields (31–55%) and enantiomeric excesses (5–65%). High enantiomeric purities were obtained after recrystallization of the intermediate adducts. Mazaleyrat et al.⁸ carried out the “Brüllants reaction” of SMP-aminonitriles with Grignard reagents. In this

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**Biographical Sketches**

**Dieter Enders** was born in 1946 in Butzbach, Hessen. He studied chemistry at the Justus Liebig Universität Gießen and received his Dr. rer. nat. in 1974 under the direction of Prof. D. Seebach. After postdoctoral studies at Harvard University with Prof. E. J. Corey he went back to Gießen and obtained his habilitation in 1979. In 1980 he moved to the Universität Bonn as an associate professor and in 1985 to his present position as Professor of Organic Chemistry and director 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.

**Martin Klatt**, born in November 1965 in Essen, Germany received his diploma of chemistry and his PhD from the RWTH Aachen under the supervision of Prof. Dr. D. Enders in 1994. In 1991 he won the Springorum-Gedenkmünze from the same university. He has been a post-doctoral research associate with Prof. Dr. Masami Otsuka in the group of Prof. Yukio Sugiiura at the Institute for Chemical Research of Kyoto University, Uji, Japan. Since 1996 he works in the research and development department of BASF AG, Ludwigshafen.
Scheme 3

process the cyano group of the α-aminonitriles is replaced by a nucleophilic attack of an organometallic reagent. The reaction yielded tertiary amines in high diastereomeric purity. As depicted in Scheme 4 by simple exchange of the groups within the electrophile and nucleophile employed both diastereomers are obtainable (synthon control).

Scheme 4

4. Asymmetric Synthesis with SMP-enamines

SMP-enamines have a very broad range of applications as d2-synths which was demonstrated by various research groups. Seebach et al.9 reported on the efficient Michael addition of cyclohexanone-SMP-enamine 3 to Knoevenagel acceptors 4 and nitroalkenes 5. These reactions occurred with good yields (35–81%) and excellent stereoselectivities. The authors discussed the stereochemical course and a possible mechanism involving a gauche orientation of the donor and acceptor double bonds as a general topological rule.

Scheme 5

In a more recent work [3 + 3]-carbocyclization reactions of enamines with nitroalkenes were investigated.10 While reactions of enantiomerically pure nitroalkenes with achiral enamines gave only unsatisfactory results, the enantioselective [3 + 3] carbocyclization of enamine 3 with the nitroallylic ester 6 proceeded with excellent stereoselectivities (ds > 95%, ee > 95%).

Scheme 6

(+)-(R,S,3.3.3)-Nitro-2-phenylbicyclo[3.3.1]nonan-9-one:10

A solution of cyclohexanone-SMP-enamine 3 (3.87 g, 20 mmol), prepared under standard conditions (TsOH, benzene, Dean–Stark trap), in CH2Cl2 (5–10 mL) was added to a solution of the nitroallylic ester 6 (5.35 g, 20.3 mmol) in CH2Cl2 (30 mL) at −78°C under Ar. After warming up to r.t. over 14 h, the mixture was hydrolyzed by addition of 1 M HCl (10 mL) and H2O (5 mL) and then heated under reflux for 1 h. The mixture was then cooled to r.t. and the phases were separated. The aqueous phase was extracted with CH2Cl2 (3 × 40 mL), the combined organic layers were washed with 1 M HCl (2 × 20 mL), brine (20 mL), dried (MgSO4) and then concentrated in vacuo. Flash chromatography (CH2Cl2/petroleum ether, 2:1) of the residue followed by recrystallization from boiling Et2O afforded the product (1.73 g, 34%, ds > 95%, ee > 95%) as colourless crystals (mp: 101–102°C).

Enders, Steglich et al.11 developed the synthesis of acyclic and cyclic γ-oxo-α-amino acids by nucleophilic addition of SMP-enamines 7 to the enantiomerically pure imine 8 using the principle of double asymmetric induction. The chiral acylimino acetate 8 constitutes a highly reactive electrophile. The C—C bond formation of this enamine reaction occurred at −100°C. In the case of X = S a desulfurization with Raney nickel afforded the corresponding acyclic products.
Risch and Esser\textsuperscript{12} examined the aminalkylation of cyclohexanone SMP-enamine 3 and related enamines with iminium tetrachloroaluminate yielding optically active Mannich bases 9 with moderate enantioselectivities. The diastereoselective reduction of 9 gave the $\gamma$-amino alcohol 10 in good diastereomeric excess of the trans isomer.

\[
\begin{align*}
\text{Scheme 8}
\end{align*}
\]

Overman et al.\textsuperscript{15} developed a general strategy for the synthesis of C\textsubscript{15}-halogenated tetrahydrofuranoid lipids from red algae of the genus \textit{Laurencia}. The key step is the convenient formation of racemic hydrobenzofuranone 16 on a large scale with complete stereocontrol. An enantioselective approach was achieved by addition of vinylmagnesium bromide to cyclopentanedione-SMP-enamine 15 followed by hydrolysis and conversion to 16 with an enantiomeric excess of ee = 84%. The total synthesis of \textit{trans}-kumausyne (17) from racemic 16 was accomplished in 13 steps and an overall yield of ca. 5%.

\[
\begin{align*}
\text{Scheme 11}
\end{align*}
\]

Node et al.\textsuperscript{16} described the asymmetric $\gamma$-methylation of a tetronic acid derivative using SMP as chiral auxiliary and its application in the total synthesis of (+)-blastymincinone (19). The methylation of the SMP-enamine 18 afforded the key intermediate in 91% yield and a diastereomeric excess of 82%.

\[
\begin{align*}
\text{Scheme 12}
\end{align*}
\]

Hiroi et al.\textsuperscript{17} reported a novel method for the palladium-catalyzed asymmetric $\alpha$-alkylation of carbonyl compounds via their chiral enamines or imines with allyl esters. In particular the palladium-catalyzed reaction of the chiral enamine 20 with allyl acetate occurred with only moderate yields and stereoselectivities creating a quaternary stereogenic center.

\[
\begin{align*}
\text{Scheme 10}
\end{align*}
\]
The asymmetric oxidation of the acyclic disubstituted SMP-amide enolate 23 with the enantipure oxaziridine 24 and its enantiomer was practised by Davis et al.\textsuperscript{21} The asymmetric \(\alpha\)-hydroxylation (double asymmetric induction) afforded the tertiary \(\alpha\)-hydroxy amide 25 in high diastereomeric excess (de up to 90\%). The diastereoselectivity for the mismatched case, reaction with (+)-24, was improved from 48\% to 89\% by addition of HMPA after enolate generation. No effect was observed in the reaction of the matched case.

The synthetic utility of this method was demonstrated in the synthesis of (R)-10-methyldecadienyl acetate (22), a component of the pheromone bouquet of the little tea moth, *Adoxophyes sp.*\textsuperscript{20}

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Fujisawa et al.\textsuperscript{23} added several organometallics to benzoylformamide 27 prepared from benzoylformic acid and SMP. Best selectivities were realized when MeMgBr in the presence of ZnCl\(_2\) was used, whereas the reaction with Me\(_2\)TiCl\(_2\) in dichloromethane afforded the epimeric \(\alpha\)-hydroxy SMP-amide with the opposite configuration of the new stereogenic center.
which controlled the regioselectivity of the subsequent oxidation step of the cycloadducts. The ketenimminium salt 29 prepared from $N$-tosylsarcosine and SMP reacted with high facial selectivities with cyclic alkenes like cyclohexene and cyclopentene, whereas poor enantiomeric excesses were observed in the reaction with terminal alkenes like styrene.

Scheme 18

(S)-$N$-Benzoylformyl-2-(methoxymethyl)pyrrolidine:
To an EtOAc solution (10 mL) of benzoylformic acid (666 mg, 4.44 mmol) was added an EtOAc solution (3 mL) of (S)-2-methoxymethylpyrrolidine (SMP) (467 mg, 4.05 mmol) at $-16^\circ$C under Ar. After being stirred for 30 min at that temperature, an EtOAc solution (3 mL) of cyclohexylcarbodiimide (882 mg, 4.28 mmol) was added and then the solution was gradually warmed to r.t. for 12 h. The resulting precipitate was filtered off and the condensed filtrate was dissolved in CH$_2$Cl$_2$ and washed with 1 M HCl, sat. aq NaHCO$_3$ solution and H$_2$O. The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Column chromatography (silica gel, hexane/EtOAc, 1:1) gave 27 (641 mg, 64%).

Stereoselective Reaction of 27 with MeMgBr/ZnCl$_2$ in Diethyl Ether:
To an Et$_2$O solution (8 mL) of ZnCl$_2$ (151 mg, 1.10 mmol) was added an Et$_2$O solution (5 mL) of 27 (204 mg, 0.83 mmol) at 0°C under Ar and stirred for 1 h at that temperature. After being cooled to $-78^\circ$C, MeMgBr (4.7 mL of a 0.71 M solution in Et$_2$O) was added and the solution was stirred for 7 h at $-78^\circ$C. The reaction was quenched with sat. aq NH$_4$Cl and extracted with CH$_2$Cl$_2$. The separated organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Purification by preparative TLC on silica gel (hexane/EtOAc, 3:2) gave (S)-[N-(S)-2-hydroxy-2-phenylpropionyl]-2-(methoxymethyl)pyrrolidine (157 mg, 72%).

As Effenberger et al. showed, the stereoselective addition of thio carboxylic acids to the 1-(methacryloyl)-substituted SMP 28 yielded the corresponding Michael adduct 1-[3-(acylthio)-2-methylpropionyl]-substituted SMP. The less soluble diastereomers were obtained in high diastereomeric excesses (de $\geq 98\%$) by digestion of the crude product in diethyl ether. After acidic hydrolysis (R)-3-mercapto-2-methylpropionic acid was obtained.

Scheme 19

Moeller et al. employed an anodic SMP-amide oxidation in the synthesis of a rigid Phe-Pro building block. The SMP-amide 30 was oxidized under constant current conditions in a methanol/dichloromethane electrolyte solution. The methoxylated amide product derived from methanol trapping of the desired $N$-acyliminium ion was obtained in a yield of 60%. The regeneration of the $N$-acyliminium ion and completion of the annulation procedure was accomplished with titanium tetrachloride in high yield (92%). The desired Phe-Pro building block 31 was finally obtained by subsequent hydrogenolysis, hydroxylation with Davis' reagent, oxidation of the resulting alcohol and enamine formation with the use of ammonia in methanol.

Scheme 20

Ghosez et al. observed asymmetric inductions in [2 + 2] cycloadditions of chiral keteniminium salts generated from the corresponding SMP-amides with alkenes. The keteniminium ions 29 turned out to be ideal reagents due to their high reactivity in cycloaddition reactions, even with nonactivated alkenes, giving crystalline easily purified products and bearing a heterosubstituent at C-2.

Scheme 21
5.3 Asymmetric Birch Reductions

Detailed investigations on Birch reductions of various aromatic SMP-amides with subsequent alkylation were carried out by Schultz et al. in the last decade. The factors which control the stereoselectivity of the alkylation of SMP-amide enolates generated during Birch reduction were carefully studied and excellent yields and stereoselectivities were generally observed. 27

\[
\text{O} \quad \begin{array}{c}
\text{N} \\
\text{CH}_{3}
\end{array} \\
\text{OCH}_{3}
\]

1. liq. NH_{3}, THF, t-BuOH
2. CH_{4}, -78°C
3. 62 - 79%

\[
\text{O} \\
\text{OCH}_{3}
\]

\[
\text{C} \\
\text{OCH}_{3}
\]

1. NBS, CCl_{4}
2. SMP, K_{2}CO_{3}
3. 70%

\[
\text{O} \\
\text{OCH}_{3}
\]

1. Li, NH_{3}, t-BuOH
2. PhX, -78°C
3. 50 - 83%

\[
\text{R: H, allyl, allyl, benzyl, CH}_{2}O(CH_{2})_{2}SiMe_{3}
\]

\[
\text{de = 90 - 98%}
\]

Scheme 22

The synthetic utility of this method was demonstrated in the asymmetric synthesis of various natural products. Recently, the first asymmetric total synthesis of (+)-1-deoxylycorine (33), an Amaryllidaceae alkaloid, which possesses antiviral, antineoplastic and short-term hypotensive activity, has been accomplished with virtually complete stereo- and regiocontrol. 28

The key step of the synthesis was the Birch reduction of the chiral amide 32, followed by alkylation of the resulting enolate with 2-bromoethyl acetate. The subsequent ester saponification gave the cyclohexadiene derivative in 96% yield as one single diastereomer, which finally was converted to deoxylycorine 33.

\[
\text{O} \quad \begin{array}{c}
\text{N} \\
\text{OCH}_{3}
\end{array} \\
\text{OMe}
\]

1. K, NH_{3}, t-BuOH
2. Br(CH_{2})_{2}OAc, 2 eq.
3. KOH, MeOH
4. 96%

\[
\text{de = 100%}
\]

Scheme 23

The synthesis of chiral 2-methylenecycloalkanones 36, which are important intermediates for inter- and intra-
molecular Michael additions and Diels–Alder reactions, was worked out by the same research group. In these cases the key step was the Birch reduction of aromatic methyl esters bearing a SMP moiety. 29 Excellent diastereoselectivities were observed for subsequent alkylation, propargyl- and cyanomethylations to afford 35. The chiral auxiliary was removed in two steps by acid-catalyzed enol ether hydrolysis and subsequent treatment with m-chloroperbenzoic acid (MCPBA).

\[
\text{OCMe} \\
\text{OCH}_{3}
\]

1. NBS, CCl_{4}
2. SMP, K_{2}CO_{3}
3. 70%

\[
\text{R: Me, allyl, CH}_{2}C=CH, CH_{2}CN, CH_{2}Ph}
\]

1. Li, NH_{3}, t-BuOH
2. PhX, -78°C
3. 50 - 83%

\[
\text{R: Me, allyl, CH}_{2}C=CH, CH_{2}CN, CH_{2}Ph}
\]

1. TeO, 2. MCPBA
2. 31 - 78%

\[
\text{de = 66 - 95%}
\]

Scheme 24

(5′)-Methyl 3-Methoxy-2-[(2-methoxymethylpyrrolidinyl)methyl]benzoate (34):

A solution of methyl 3-methoxy-2-methylbenzoate (1.00 g, 5.55 mmol), NBS (1.18 g, 6.63 mmol) and benzoyl peroxide (6.0 mg, 0.25 mmol) in CCl_{4} (75 mL) was heated at reflux and carefully monitored by thin-layer chromatography (silica gel, hexane/EtOAc, 9:1). After 90 min, the mixture was cooled to r.t., filtered through glass wool into an injection funnel, and added dropwise to a stirred solution of (5′)-methyleneoxypyrrolidin-2-yl)benzoic (700 mg, 6.09 mmol), K_{2}CO_{3} (1.00 g, 7.25 mmol) and H_{2}O (10 mL) in CH_{2}Cl_{2} (75 mL) at 0°C. The mixture was allowed to warm to r.t. and stirred for 15 h. The mixture was transferred to a separatory funnel and washed with H_{2}O (2 × 50 mL), Na_{2}S_{2}O_{3} (5%), 2 × 50 mL) and brine (50 mL). The organic layer was dried (MgSO_{4}) and concentrated to give a yellow oil. Flash chromatography (alumina, hexane/EtOAc, 3:1) gave 34 as a pale oil (1.25 g, 70%).

(2′,3′,5′,5′-Carboxymethoxy-1-methoxy-2-[(2-methoxymethyl)-
pyrrolidinyl]methyl]-3-methylcyclohexa-1,4-diene, (R = CH_{3}, 35):

A solution of 34 (200 mg, 0.68 mmol) in anhyd THF (5 mL) and t-BuOH (51 mg, 0.68 mmol) was cooled to −78°C and liquid NH_{3} (30 mL) was added. Li (10 mg, 0.15 mmol) was added in small pieces and the resulting blue solution was stirred for 20 min. The excess Li was consumed with cyclopenta-l,3-diene (10 μL) to give a yellow coloured solution of enolate. Mel (87 μL, 1.3 mmol) was added at −78°C and the mixture stirred for 30 min. After addition of sat. NH_{4}Cl (5 mL), the NH_{3} was removed by slow evaporation and the resulting mixture partitioned between EtOAc and H_{2}O. The aqueous layer was washed with EtOAc (50 mL) and the combined organic extracts were washed with brine (50 mL) and dried (K_{2}CO_{3}). The solvent was removed to give a yellow oil (13:1 mixture of diastereomers). Flash chromatography (silica gel, hexane/EtOAc, 3:1) gave 35 as a pale yellow oil (186 mg, 89%, 13:1 mixture of diastereomers).
(S)-3-Carbomethoxy-3-methyl-2-exo-methylene cyclohex-5-en-1-one (R = CH₃, 36):
A mixture of 35 (2.10 g, 6.80 mmol) and TsOH·H₂O (1.42 g, 7.48 mmol) in benzene (75 mL) was heated at reflux for 2 h and then cooled to rt. The benzene solution was diluted with EtOAc (75 mL) and washed with aq NaHCO₃ (30 mL, 10%), H₂O (50 mL) and brine (50 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo to give a yellow oil. The crude material was dissolved in CH₂Cl₂ (50 mL) and MCPBA (1.28 g, 7.48 mmol) was added. The mixture was stirred for 1 h and then diluted with CH₂Cl₂ (50 mL). The mixture was transferred to a separatory funnel and washed with aq NaHCO₃ (50 mL, 10%), H₂O (50 mL) and brine (50 mL). The organic layer was dried (Na₂SO₄) and concentrated. Flash chromatography (silica gel, hexane/EtOAc, 10:1) gave 36 as a colourless oil (0.95 g, 78%).

6. Asymmetric Synthesis with Metalated SMP-allylamines and SMP-enamines
Metalated SMP-allylamines and -enamines were used by Ahlbrecht, Enders et al.⁴⁵ as the first chiral homoenoate equivalents (d⁴-synthons). The stereoselectivities obtained in the alkylation of metalated cinnamylamines 37 with SMP as chiral auxiliary leading to phenylpropionaldehydes or ketones depend strongly on the solvent. The best results were obtained with tert-butyl methyl ether as solvent (ee = 80 to 86%). In the case of cinnamaldehydes (R¹ = H) the nature of the alkylation agent is not important in contrast to the synthesis of the phenyl ketones (R¹ = Ph). Ahlbrecht, Boche et al.³¹ were able to determine the structure of the dimeric, intramolecularly chelated (3S)-3-lithio-1-[(3S)-2-(methoxymethyl)pyrrolidin-1,3-diphenylpropene (lithiated 37; R¹, R² = Ph). MNDO calculations reproduced the results of the X-ray structure determination satisfactorily and allowed some insight into possible structures in solution.

Scheme 25

7. SMP as Chiral Auxiliary in [4 + 2]-Cycloaddition Reactions
SMP was found to be useful as a chiral auxiliary in various [4 + 2]-cycloaddition reactions. Enders et al.⁴² and later Barluenga et al.⁴³ used chiral 2-amino-1,3-dienes in the Diels–Alder reaction with 2-aryl-1-nitroethenes. The reaction of 3-[(S)-2-(methoxymethyl)pyrrolidin-1-yl]buta-1,3-diene (38) with various 2-aryl-1-nitroethenes afforded after hydrolysis the 5-aryl-2-methyl substituted 4-nitrocyclohexanones in excellent enantiomeric purities (ee = 95–99%) and with high diastereoselectivities (ds = 75–95%).

Scheme 26

Substituted 4-Nitrocyclohexanones; General Procedure:³²
The amino butadiene 38, prepared from SMP and buta-2,3-diene by a modified Weingarten method with a subsequent Wittig alkenation, was added with stirring to a slurry of 2-arylnitroethene in Et₂O (50 mL) at -78°C over 10 min. The resulting suspension was allowed to warm to r.t. during 6 h. Stirring was continued at r.t. until no 2-arylnitroethene could be detected by TLC. The solvent was removed and the oil passed through a column of silica gel (Merck, 230–400 mesh, 100 g per 1 g oil) with Et₂O (1 L) saturated with H₂O as eluent. The solvent was removed and the colourless solids were washed with 3 portions of petroleum ether (50 mL). To obtain analytically pure substituted nitrocyclohexanones the solids may be recrystallized from MeOH/Et₂O.

Döpp et al.³⁴ carried out the photo-Diels–Alder reaction of SMP-acrylonitrile 39 with electronically excited 1-acectynaphthalene. After hydrolysis of the adducts chiral 1,4-diketones were obtained with excellent enantiomeric purity (ee ≥ 97%).

Scheme 27

Ghosez et al.³⁵ studied the Lewis acid catalyzed Diels–Alder reaction of 1,3-disiloxycyclohexadiene 40 with the RMP-acrylamide 41. Mild hydrolysis (H₂O or HCl 0.25 M) of the primary adducts smoothly regenerated the carbonyl function. The endo : exo ratio was strongly controlled by the choice of the catalyst. A high diastereomeric excess was observed by Streith et al.³⁶ in the double asymmetric induction of a Diels–Alder reaction of chiral diene 42 with N-acetylnitrosodiphenyl, formed in situ by oxidation of the corresponding
Reinhoudt et al. synthesized chiral four-membered cyclic nitrones by asymmetric [4 + 2] cycloaddition of nitroalkenes with SMP-ynamines 44 via oxazine oxides. The subsequent stereoselective addition of allylmagnesium bromide enabled the synthesis of chiral N-hydroxyazetidines.

Scheme 28

Hydroxamic acids 43 with tetra-n-propylammonium periodate. While the RMP-dienophile afforded high diastereoselectivities (de = 96%) the SMP-dienophile gave only poor induction (de = 4%).

Scheme 29

Bäckvall et al. used SMP-ynamines in the diastereoselective inverse electron demand Diels–Alder reaction with 2-phenylsulfonfyl-1,3-dienes. Moderate to very good yields (up to 92%) and diastereoselectivities (up to 73%) were observed at the stage of the [4 + 2] cycloadducts.

Scheme 30

The chiral organosilicon compound 47 was used for the enantioselective synthesis of arylmethanos by alkylation and subsequent oxidative cleavage of the carbon–silicon bond. The high diastereoselectivities in the alkylation step resulted from internal chelation of the intermediate.
carbanion in which the bulky phenyl group is placed exo to the bicyclic system.\(^{40}\)

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\text{Scheme 33}
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The alkylation of \(\alpha\)-silylcinnamyl carbanions\(^{44}\) 48 gave, with good regio- and stereoselectivities and high yields in toluene, mostly the \(\alpha\)-alkylation product 49. When the reaction was carried out in tetrahydrofuran poor selectivities were observed. Secondary alkyl iodides reacted preferentially at the \(\gamma\)-centre and good levels of stereoselectivities were still obtained, despite the rather long distance between the reacting centre and chiral auxiliary.

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\text{Scheme 34}
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Alkylation to Afford 49: General Procedure:\(^{41}\)

To a solution of cinnamylsilane 48 (1 mmol) in toluene (6 mL) at -78 °C was added sec-BuLi (2 mmol). The mixture was stirred for 15–30 min at -78 °C and the alkylating agent was then added. The mixture was quenched with \(\text{NH}_2\text{Cl}\) when THF was the solvent or warmed up to r.t. prior to quenching when \(\text{Et}_2\text{O}\) or toluene were used. Extraction with \(\text{Et}_2\text{O}\) followed by washing with brine and drying (\(\text{MgSO}_4\)) afforded the crude mixture of essentially pure alkylated products. In all cases, regioisomers could be separated by column chromatography on silica gel using \(\text{EtOAc}\) (10 to 100%) in hexane elution.

Chiral 1,3-diols were prepared in high enantiomeric purity (ee > 97%) from the reaction of silylcarbanions, obtained from 50, with epoxides followed by oxidative cleavage of the carbon–silicon bond with hydrogen peroxide.\(^{52}\)

Recently silylpropargyl carbanions bearing SMP on the silicon moiety have been alkylated with excellent regio- and diastereoselectivity. In this way, propargyl alcohols were synthesized with excellent yields and enantiomeric excesses.\(^{43}\)

9. SMP as Chiral Leaving Group in Asymmetric Synthesis

The elegant application of SMP as a chiral leaving group in addition–elimination processes was studied especially by Fuji et al. and by Tamura et al.

Fuji et al.\(^{44}\) reported on a method for the asymmetric synthesis of \(\alpha,\alpha\)-disubstituted lactones by reaction of SMP nitro enamines 51 with zinc enolates of \(\alpha\)-substituted lactones in an addition–elimination process. The Michael-type addition of the enolate onto the nitro enamine was kinetically controlled and decided the absolute stereochemistry of the product.

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\text{Scheme 35}
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\text{Scheme 36}
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\text{Scheme 37}
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Tamura et al.\(^{45}\) developed a novel addition–elimination reaction of \((S)-2-[(2-(methoxymethyl)-1-pyrrolidinyl)methyl]alk-2-en-1-ones 52 with organocuprates and zincates affording 3-substituted 2-exo-methylenealkanones with high enantiomeric purity. The enantiomeric excess was highly dependent on the structure of the enone, the organometallic reagent, the chiral auxiliary and added Lewis acids. In the reaction of lithium diorganocuprates, which led to the best results, the enantiomeric excess decreased in the following order by varying the structure of the main framework of the enones: cycloheptanones
(96–97%), cyclohexanones (95%), cyclopentanones (82–85%), acyclic enones (55–70%). The existence of the methoxy oxygen atom in the chiral auxiliary was essential to achieve high enantioemic excesses.

Scheme 38

Conjugate Addition–Elimination Reaction of Organocupper Reagents to the Chiral Enone 52; General Procedure:
A mixture of the chiral amino enone 52 (1.0 mmol) and the Lewis acid (1.0–2.0 mmol) in THF (5 mL) was stirred at 25°C for 10 min and cooled to -90°C in a dry ice/MeOH bath. A THF or Et₂O solution of the organocupper reagent precool to -90°C was added to the THF solution of the amino enone 52 at -90°C using a cannula. The resulting mixture was slowly warmed to 0°C during 1 h. The workup procedure was dependent on the substrate structure used; sat. aq NH₄Cl (10 mL) was used for cycloheptanone and cyclohexanone derivatives, while H₂O (10 mL) was used in the other cases. After extraction of the aqueous solution with Et₂O (3 × 30 mL), the combined organic phases were dried (MgSO₄) and concentrated in vacuo. The crude 2-methylene ketones were purified by column chromatography on Florisil (hexane/EtOAc, 20:1).

Scheme 39

10. Asymmetric Michael Additions with SMP as Chiral Auxiliary
Several groups were engaged in the asymmetric conjugate addition using SMP as chiral auxiliary ligand. Various enantiopure amines, SMP included, were lithiated by Bertz et al. with methylthiium or butyllithium and added to phenylcopper to give chiral organocuprates. Treatment of cyclohexenone with these chiral cuprates gave (R)- and (S)-3-phenylcyclohexanones with only moderate enantiomeric excesses and yields. The reaction conditions were studied in detail. In the case of SMP an ee value of 20% and a yield of 36% were observed.

Dieter et al. examined the reaction of cyclopentenone, cyclohexenone, (E)-pent-3-en-2-one and (E)-oct-3-en-2-one with chiral organoheterocuprates containing methyl, n-butyl or t-butyl transferrable ligands. The adducts were obtained in optical yields of 41 to 83% when SMP was used as ligand.

Scheme 40

Conjugate Addition of SMP Organocuprates to α,β-Enones; General Procedure:
Methylthiium (0.68 mL, 1.14 mmol) was added dropwise to a 0°C cold solution of the chiral amine (1.14 mmol) and 2 mL of solvent in a septum-sealed, 25-mL round bottomed flask under N₂. After 15 min, the yellow solution was transferred under N₂ by using a double tipped needle to a two-necked flask which contained CuBr (162.7 mg, 1.13 mmol) and 5 mL of solvent (Et₂O or THF) at -40°C. The appropriate alkylthiium was added via syringe, and the mixture was slowly warmed to 0°C over 30 min. The cuprate (Me: light brown, n-Bu: black, t-Bu: orange-brown) was then cooled to -78°C, and the enone (1.00 mmol) was added in 2.0 mL of sol-

vent via syringe. After 60 to 90 min, the reaction was quenched with sat. aq NH₄Cl (5 mL). The mixture was allowed to warm to r.t. and filtered through Celite to remove the copper salts, and the residue was washed with Et₂O (10 mL). The filtrate was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with 2 M HCl (2 × 10 mL) and once with brine. After drying (MgSO₄), the organic layer was concentrated in vacuo to afford the addition product which was purified by medium-pressure liquid chromatography (MPLC) (pentane containing 5-25% Et₂O).

Quinkert et al. employed the enantioselective conjugate addition of chiral ligand-modified organocuprates to 2-methylcyclopent-2-en-1-one in the total synthesis of the pseudoguaninolide (+)-confertin (53). Good yields (76%) and enantioselectivities (ee = 75%) were observed when SMP was used.

Scheme 41

Schulte et al. added allylsilanes (Sakurai reaction) and silyl enol ethers (Mukaiyama–Michael reaction) to chiral amidocycloalkenes 54 with excellent yields and with
high diastereoselectivities. Treatment of the SMP-amidocycloalkenone 54 with titanium tetrachloride and allyltrimethylsilane in dichloromethane at $-78^\circ$C followed by reaction with $N$-methylhydroxylamine hydrochloride gave the 1-methyltetrahydrobenzisoxazolin-3-one with an enantiomeric excess of $ee = 80\%$ in a yield of $92\%$. Subsequent Birch reduction with lithium in ammonia at $-78^\circ$C followed by alkylation with iodomethane produced the cyclohexanone derivative.

Chelucci et al. used the ligand 56 in the enantioselective addition of diethylzinc to benzaldehyde, while the equilibrium behaviour of the chiral ligand 57 in copper(II) complexes was studied by Bernauer et al., Steckhan et al.\textsuperscript{54} carried out the synthesis of a new potential $C_2$-symmetrical ligand 58.

Sturgess et al.\textsuperscript{50} studied the Michael addition of chiral $N$-nucleophiles to achiral nitroalkenes. While amino alcohols, like (S)-prolinol, reacted fast and with very high facial selectivities, SMP showed only moderate results.

Süss-Fink et al.\textsuperscript{55} applied SMP in the chiral modification of trinuclear ruthenium clusters 59, which were tested in the catalytic isomerization of nerol to give citronellal with an enantiomeric excess of $12.4\%$.

Recently, Wulff et al.\textsuperscript{51} reported on the first Michael addition of aminocarbene complex anions to $\alpha,\beta$-unsaturated carbonyl compounds. The conjugate addition of the chiral amino complex 55 to cyclic enones represent the first examples of asymmetric reactions of any type of enolates of either alkoxy- or amino-stabilized group 6 Fischer carbene complexes. Both enantiomers of 55 based on SMP and RMP were examined with cyclohexenone and found to give asymmetric inductions in the range of $65\text{--}95\% ee$, which is comparable with the best yet induction reported for the addition of a chiral acetalddehyde equivalent to cyclohexenone.

11. Miscellaneous

Various other applications should be mentioned briefly. Chiral ligands bearing a SMP-motety were synthesized by Chelucci et al.\textsuperscript{52} and Bernauer et al.\textsuperscript{53}.
X-ray structure of 60 and the configuration of the product phosphates suggest that these substitutions occurred with preponderant inversion of configuration at phosphorus.

The asymmetric, ultrasound-promoted perfluoralkylation of SMP-enamines 63 with perfluoroalkylzine halides in the presence of dichlorocyclopentadienyltitanium was carried out by Kitazume et al. leading to z-perfluoroalkylated ketones of moderate enantiomeric excess.

Scheme 46

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\text{Scheme 46}
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Keim, Enders et al. described the enantioselective telomerization of SMP-cyclohexanone enamine with butadiene using triphenylphosphine which gave enantiomeric selectivities up to 72%.

Scheme 49

Sampson et al. prepared (S)-2-(methoxymethyl)pyrrol-1-ylsulfur trifluoride (62), the first enantiopure amino-fluorosulfurane which is one of the most stable yet reported. It was shown that it is an effective fluorodehydroxylation reagent in the kinetic resolution of alcohols to form optically active organofluorine compounds.

Scheme 47

Collet et al. prepared N-Boc-(4-cyanophenyl)oxaziridine 64, which transfers its N-Boc fragment under mild conditions to primary and secondary amines to give N-Boc-protected hydrazines. In this way, SMP can be transformed to N-Boc-protected (S)-1-amino-2-(methoxymethyl)pyrrolidine 65.

Scheme 50

In a recent work Enders et al. presented an enantioselective synthesis of allylic alcohols by oxidation of readily available chiral allylamines followed by an asymmetric 2,3-sigmatropic Meisenheimer rearrangement. While the C_{3}-symmetric auxiliary 66 yielded the allylic alcohols with very high enantiomeric excesses, SMP gave only a low asymmetric induction.

Scheme 51
Liebscher et al.\textsuperscript{63} reported the diastereoselective \(\alpha\)-alkylation of (S)-(prolinoylmethyl)oxadiazole 67 prepared from the corresponding halomethyl heterocycle and SMP. Deprotonation of 67 with lithium diisopropylamide (LDA) and subsequent trapping with iodomethane afforded the alkylated product in good yield (77\%) and moderate diastereomeric excess (\(\text{de} = 74\%\)).

Engels et al.\textsuperscript{64} synthesized P-prolyl-nucleoside-P-methylphosphonamidites which are P-chiral building blocks for nucleoside methylphosphonate synthesis. Starting from dichloromethylphosphane and SMP the prochiral bis-SMP-methylphosphane 68 was prepared. The reaction with tritylthymidine 69 under acidic conditions furnished the amidite 70. By oxidation of the amidite 70 to the corresponding amide with tert-butyl hydroperoxide the absolute configuration of the phosphorus centre could be determined by single crystal X-ray diffraction.

Ganter et al.\textsuperscript{65} described the 2-metalation of the enantiopure (S)-[(2-methoxypyrrolidin-1-yl)methyl]ferrocene (71) with butyllithium which proceeded with high diastereomeric excess (up to \(\text{de} \geq 98\%\)) to yield \(\text{Ph}_2\text{P}\)-substituted ferrocene derivative 72 after quenching with \(\text{Ph}_2\text{PCl}\). The SMP moiety was removed by heating the alkylated product in acetic anhydride at reflux to give the planar chiral (\(S_\text{p}\))-2-diphenylphosphanylferrrocenyl-

methyl acetate which was further hydrolyzed to the corresponding alcohol.

12. Conclusions

The aim of this review has been to demonstrate the synthetic utility of (S)-methoxymethylpyrrolidine, one of the pioneering chiral auxiliaries which has found a broad range of applications since its introduction into asymmetric synthesis in the mid seventies. The fact that it is easily available from the amino acid (S)-proline and generally gives high asymmetric inductions in various fields of synthetic chemistry has contributed to its acceptance and popularity. Scheme 56 summarizes the main applications in which it has been used so far. Asymmetric syntheses with the N-amine derivative of the title auxiliary, namely the hydrizine (S)-1-amino-2-methoxymethylpyrrolidine (SAMP), will be covered in a separate review.\textsuperscript{66}

\begin{itemize}
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Scheme S6

(13) Renaud, P.; Schuberti, S. Synlct 1990, 624.
(82) Enders, D.; Betray, W. manuscript in preparation.