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Additional and Supplementary Volumes to the 4th Edition
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Vol. E 21 f

Stereoselective Synthesis:

Appendix, Author Index and Compound Index

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Overview of Contents

Volume E 21 f

Appendix: Survey of Chiral Auxiliaries, Solvents, Reagents, and Catalysts

For Contents to all Volumes see p VII
For Detailed Table of Contents to Volume E 21 f see p XI
For List of Abbreviations see inside back cover

METHODS OF
ORGANIC CHEMISTRY

METHODS OF ORGANIC CHEMISTRY

(HOUBEN-WEYL)

ADDITIONAL AND SUPPLEMENTARY VOLUMES TO THE 4TH EDITION

GEORG THIEME VERLAG STUTTGART · NEW YORK

VOLUME E 21 f

STEREOSELECTIVE SYNTHESIS

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19 96

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Preface

There was a time when stereoselectivity of a reaction was mostly of mechanistic interest and reactions that could result in the formation of stereoisomers were considered a nuisance and had to be avoided at best. However, this situation has changed over the past two decades, during which stereoselective synthesis has grown into a reliable methodology. This development began with the remodelling of readily available chiral compounds from nature. More recently, these "ex-chiral-pool" synthetic strategies have been complemented and, in many cases, surpassed by the powerful techniques of asymmetric synthesis.

Originally, only a few laboratories were concerned with the design of routes to enantiomerically pure compounds. Since the demand for nonracemic chiral drugs and pesticides has enormously increased, methods of asymmetric synthesis are now bound to be applied by almost every practising chemist. However, newcomers to the field soon find themselves confronted with a confusing vocabulary, with no guidance as to the appropriate method to solve their problem, and with lack of well-documented procedures. This situation frequently leads to frustration or at least to unnecessary work.

This called for the present volume set of the HOUBEN-WEYL series *Methods of Organic Chemistry*. Since the 1950s HOUBEN-WEYL has served the synthetic community by giving comprehensive critical reviews of the existing synthetic methods in a consistent style and with high reliability. The editors, authors and publisher of HOUBEN-WEYL "Stereoselective Synthesis" have worked together to confer this philosophy to the field of asymmetric synthesis. Thus, we hope to supply a treatise which should become the standard reference in the field.

"Stereoselective Synthesis" gives a comprehensive treatment of chemical transformations in which a new stereocenter is created, i.e., all enantio- and those diastereodifferentiating reactions which allow the absolute and relative configuration of a new stereogenic unit to be controlled. Consequently, mechanism-controlled reactions (e.g. S_N2 displacements), "ex-chiral-pool" syntheses which do not lead to new stereogenic units, and *E*/*Z* selective formation of alkenes are not covered.

Following the general introductory chapters covering principles, nomenclature, separation and analysis, the chapters on individual synthetic methods are organized by the type of bond that is broken or formed. Only starting material and products are considered as a basis for the classification, not the reaction mechanism. In the typical HOUBEN-WEYL style, the scope of the most important methods is illustrated with tables of selected examples. Insight into the practical application of the methods can be obtained from the experimental procedures provided.

The wealth of material forced us to break up the work into five volumes (E21a through f). Access to and properties of the common chiral auxiliaries, solvents, reagents and catalysts which are used in various different reactions is covered comprehensively in Volume E 21e avoiding duplication of information in the individual chapters.

The transition of HOUBEN-WEYL from German to English brought about changes in the layout and in the style of presentation without, however, sacrificing the high standard of quality and reliability that is the hallmark of HOUBEN-WEYL.

Special thanks go to our 101 authors who have spent a great deal of time and effort to achieve the goals we have set. We are also indebted to the editorial staff in Stuttgart, who had to cope with the special challenges of editing and publishing a gigantic amount of complex material.

May 1995

Günter Helmchen
Reinhard W. Hoffmann
Johann Mulzer
Ernst Schaumann

Contents to all Volumes

Table of Contents

Volume E 21 f

Appendix

Survey of Chiral Auxiliaries, Solvents, Reagents, and Catalysts

R. HERRMANN

Introduction

The purpose of this appendix is to survey chiral auxiliaries, solvents, reagents, and catalysts which are often used in stereoselective bond-forming reactions, thus avoiding repetition of details on the synthesis of these compounds in the other sections of Houben-Weyl Volume E21 which discuss specific reaction types. It will not contain every chiral compound ever used in asymmetric synthesis, but will focus on compounds mentioned in this Houben-Weyl volume. Reagents used exclusively for the resolution of racemates are not included, as these are treated in more detail in Section A.2. Enzymes, which can also be considered as chiral catalysts, are also not discussed; they are beyond the scope of this section, which concentrates on chemical techniques.

This survey is structured by functional groups and/or common structures present in the compounds considered. This implies that structural analogy rather than synthetic logic defines the place where a specific compound can be found; there are only a few exceptions to this principle. For example, compounds mimicking the typical reactivity of others are treated together, such as chiral oxaziridines and sultams, which are included in Section 3.4.11., although they do not contain the bicyclo[2.2.1]skeleton which is the general topic of Section 3.4. This section also contains a subsection on ring-enlarged (3.4.9.) and ring-cleaved (3.4.10.) derivatives of camphor, where synthetic logic has been chosen as the ordering principle. In cases of doubt, the reader should use the tabular survey at the end of the section which they expect to contain the compound. Generally, the logic is applied that a compound should appear as early as possible if it can be attributed to more than one section. A few exceptions are made for closely related compounds such as phosphorus and sulfur compounds which are listed in specific sections, as their syntheses are often closely related. Wherever possible, cross-references are made to sections where their precursors are described.

Table 1. Abbreviations Used for Commercial Suppliers

Abbrev.	Supplier	Address
A	Sigma-Aldrich-Chemie GmbH & Co. KG	Postfach 1120, D-89555 Steinheim
B	Boehringer Ingelheim KG	Chemicals Division, D-55216 Ingelheim
C	Carl Roth GmbH & Co.	Schoemperlenstr. 1–5, D-76185 Karlsruhe
D	Degussa AG	GB Industrie- und Feinchemikalien, Postfach 110533, D-60287 Frankfurt
F	Fluka Chemie AG	Industriestr. 25, CH-9470 Buchs
J	Acros Chimica	Postfach 23, D-61130 Nidderau
M	Merck KGaA	D-84271 Darmstadt
R	Riedel-de-Haën AG	Postfach 100262, D-30918 Seelze
T	Tokyo Kasei Kogyo Co. Ltd. (TCI)	3-1-13, Nihonbashi-Honcho, Chuo-Ku, Tokyo 103, Japan

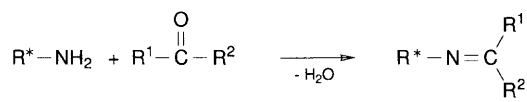
for references see p 5765

After every section, a tabular survey is given of the auxiliaries, reagents, and catalysts, which includes common names and synonyms, acronyms, leading references to synthesis, cross-references to the sections in this volume where they are described and/or applied, and commercial sources. The last item is based on information from specific suppliers and is not comprehensive. Information has only been considered which allows comparison of the enantiomeric purity, e.g., by citing optical rotation or enantiomeric excess. The abbreviations used for suppliers are given in Table 1. The address is given for each company, however, readers may find it more convenient to contact a local supplier for the same company.

1. Amines

1.1. Monoamines

Among monoamines, both enantiomers of 1-phenylethylamine and their derivatives play a prominent role. They are commercially available, but can also be prepared by resolution of the racemate, obtainable by Leuckart–Wallach reaction of acetophenone[1], with malic acid[2] or, more conveniently, with tartaric acid in methanol[3]. They are used as chiral additives for the addition of zinc alkyls to aldehydes in Section D.1.3.1.4., as copper complexes for the synthesis of biaryls in Section B.2., as lithium salts for enantioselective deprotonation in Section C., and as imines in Sections D.1.1.1.3.1., D.1.1.1.4., D.1.4.4., D.1.5.2., D.1.5.8., D.1.6.1.2.1., D.2.3.1., and D.8. A general procedure for the synthesis of imines from carbonyl compounds and primary amines, with many examples of both chiral carbonyl compounds and chiral amines is given in reference 4.



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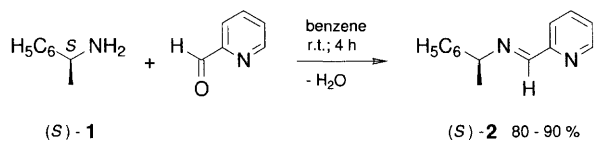
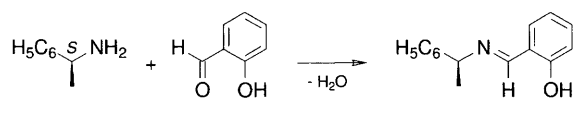
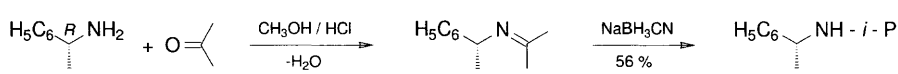






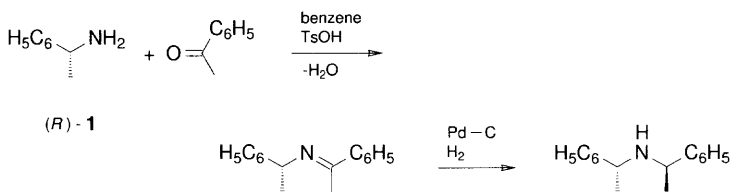
(*S*)-*N*-(2-Pyridinylmethylene)-1-phenylethylamine [(*S*)-PPEI, (*S*)-2][4]:
To a solution of 10.7 g (0.10 mol) of 2-pyridinecarboxaldehyde in 150 mL of dry benzene are added 13.3 g (0.11 mol) of (–)-(*S*)-1-phenylethylamine. The water formed in the reaction is removed by the addition of Na_2SO_4 (about 10 g is required). After stirring for 4 h at r.t., the Na_2SO_4 is filtered off, the solvent is evaporated, and the residue is purified by Kugelrohr distillation, bath temperature 140–150 °C (high vacuum); yield: 80–90%.

(*R*)-*N*-Isopropyl-1-phenylethylamine [(*R*)-5][6]:
To a stirred solution of 12.1 g (0.10 mol) of (*R*)-1-phenylethylamine in 50 mL of CH_3OH is added a 6 M methanolic solution of HCl to adjust the pH to 6–7. 7.54 g (0.13 mol) of acetone are added, followed by 4.16 g (0.068 mol) of $NaBH_3CN$ and the mixture is stoppered and stirred at r.t. for 17 h. The CH_3OH is then removed under reduced pressure, and 50 mL of H_2O and solid KOH are added to adjust the pH to >10. The aqueous layer is saturated with solid NaCl and then extracted three times with 50-mL portions of Et_2O. The combined organic extracts are washed twice with 40-mL portions of 20% aq $FeSO_4$ and dried over $MgSO_4$. The solvent is removed under reduced pressure and the residue distilled (bp 60–66 °C/0.5 Torr). The amine is poured into 120 mL of hot 2 M HCl, and the white crystals obtained on cooling are collected. The free amine is recovered by stirring the salt with 120 mL of 2 M aq KOH, saturating the mixture with solid NaCl, and extracting the amine three times with 50-mL portions of Et_2O. The combined extracts are dried with $MgSO_4$, and the solvent is removed under reduced pressure. Distillation of the residue at 0.5 Torr gives a colorless oil; yield: 9.1 g (56%); $[\alpha]_D^{22}$ +61.4 (c = 2.23, $CHCl_3$).

Such imines can be used as ligands for catalytic enantioselective hydrosilylation of ketones (Section D.2.3.1.[4]) or asymmetric hydroformylation [Section D.1.5.8. which uses (*S*)-*N*-(2-hydroxybenzylidene)-1-phenylethylamine (**2**)[5]] or reduced further to chiral amines, e.g., by sodium borohydride[4]. A convenient one-pot synthesis of such secondary amines uses sodium cyanoborohydride as the reducing agent[6].

The same technique can be applied to the synthesis of many other secondary amines containing the 1-phenylethyl moiety; they are used as the lithium salt for deprotonation reactions (Section C.).

The introduction of a second chiral residue in simple primary amines such as 1-phenylethylamine to give a secondary amine is also possible by catalytic hydrogenation of an imine[7].



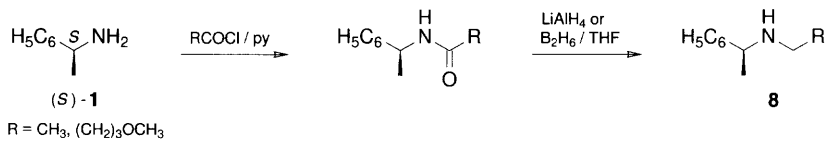
(*R*)-**1** **6** 65 % (*R*, *R*)-**7** 61%

(+)-(*R*,*R*)-Bis(1-phenylethyl)amine [(*R*,*R*)-7][7]:
(−)-(R)-N-(*1-Phenylethylidene*)-*1-phenylethylamine* (**6**):
A solution of 12.7 g (0.10 mol) of (+)-(*R*)-1-phenylethylamine {$[\alpha]_D$ +29.7 (c = 10.85, neat)} and 12.0 g (0.10 mol) of freshly distilled acetophenone in 120 mL of anhyd benzene containing a catalytic amount of 4-methylbenzenesulfonic acid is refluxed under N_2 while H_2O is continuously removed by means of a Dean–Stark trap. A total of 2.2 mL (0.12 mol) of H_2O is collected overnight, whereupon the solvent is removed under reduced pressure and the residue is distilled to yield the title compound as a colorless oil; yield: 14.5 g (65%); bp 124 °C/0.05 Torr; $[\alpha]_D$ −73.3 (c = 2.14, $CHCl_3$).
(+)-(R,R)-*Bis*(*1-phenylethyl*)*amine* [(R,R)-7]:
A solution of 12.6 g (0.56 mol) of (−)-(*R*)-*N*-(1-phenylethylidene)-1-phenylethylamine in 80 mL of THF containing 0.50 g of 10% palladium on carbon is shaken in a Paar hydrogenator for 2 h. After filtration of the catalyst, the solvent is evaporated at reduced pressure, and the residue is distilled to give a colorless oil; yield: 10 g (80%); bp 98–104 °C/0.20 Torr. The amine is converted to the hydrochloride salt and fractionally crystallized by slow addition to a stirred hot solution of 250 mL of H_2O containing 8 mL of conc aq HCl. After slow cooling, the salt is filtered and washed with cold water. The solid is then treated with aq KOH with stirring for 1 h, and the mixture is extracted twice with Et_2O. The combined organic layers are washed with H_2O and brine and are dried over anhyd $MgSO_4$. Removal of solvent leaves an oil that is purified by distillation, yielding the title compound; yield: 6.1 g (61%); bp 86–96 °C/0.05 Torr; $[\alpha]_D$ +167.6 (c = 1.1, $CHCl_3$).

for references see p 5765

This amine has been used as the lithium salt for deprotonation reactions (Sections D.1.6.3.2. and C.).

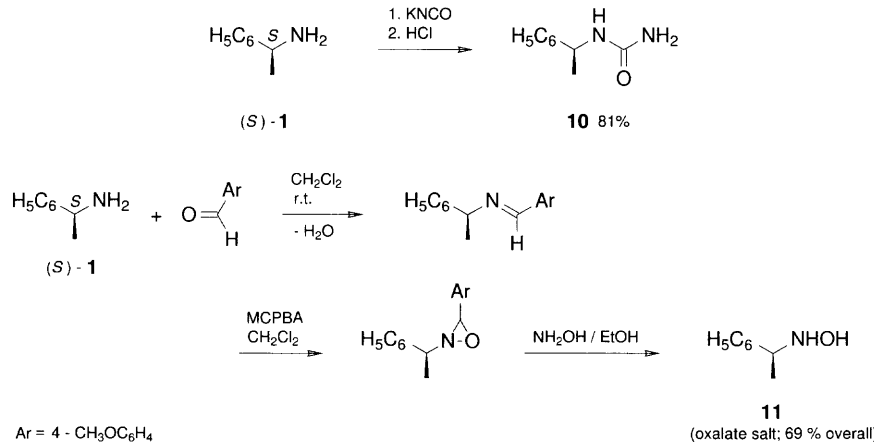
Other *N*-substituents may be more conveniently introduced by reduction of the corresponding amide, e.g., formation of **8**[8].



N-Phenyl groups and other tertiary groups cannot be introduced by such reduction techniques. To obtain these compounds, simple imines, such as *N*-benzylideneaniline, are treated with Grignard reagents to obtain secondary amines **9**[9] which are resolved with (+)-10-camphorsulfonic acid[10].

Both enantiomers of the tertiary amine *N*,*N*-dimethyl-1-phenylethylamine are readily available by conventional Leuckart–Wallach reaction (formaldehyde/formic acid) of the enantiomers of 1-phenylethylamine[12, 13]. The reaction is most conveniently performed by the technique developed for the racemate[14]. Both enantiomers are also commercially available and have been used for enantioselective deprotonations (Section C.) and as catalysts for the addition of dialkylzinc to aldehydes (Section D.1.3.1.4.).

Other derivatives of 1-phenylethylamines include the urea **10**, which is used in the preparation of chiral aminophosphonic acid (Section D.8), and which is formed by the action of potassium isocyanate on the amine **1**[11], and (*S*)-*N*-phenylethylhydroxylamine **11**, used for the formation of chiral nitrones for 1,3-dipolar cycloadditions (Section D.1.6.1.2.1.)[15].



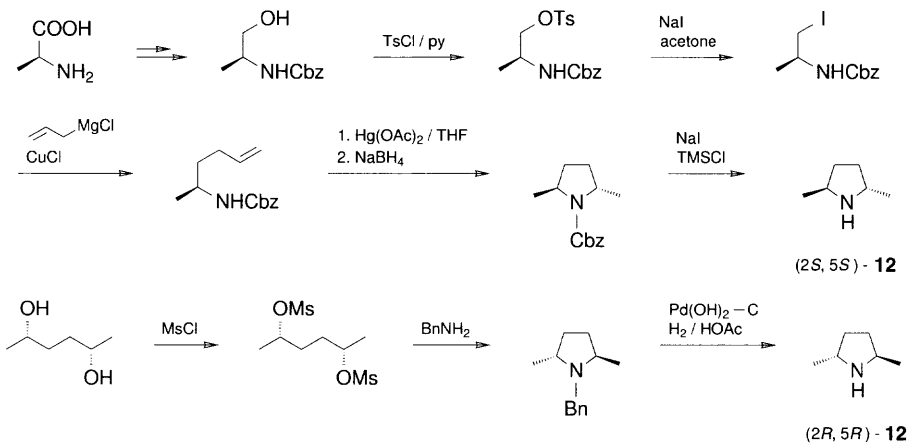
(−)-(*S*)-*N*-Hydroxy-1-phenylethylammonium Oxalate (11)[15]:
A mixture of 200 g of $MgSO_4$, 600 mL of CH_2Cl_2, 96.3 g (0.79 mol) of (−)-(*S*)-1-phenylethylamine, and 110 mL (0.90 mol) of methoxybenzaldehyde is stirred under Ar at r.t. overnight. The filtrate is transferred to a flask equipped with a mechanical stirrer and cooled to 0 °C under Ar. Then, 208 g (1.02 mol) of 85% MCPBA slurried in 400 mL of CH_2Cl_2 are added. The temperature rises to 17 °C, and then declines. Stirring is continued for 2.5 h. The mixture is filtered, the solid is washed with 500 mL of CH_2Cl_2, and the filtrate

is washed successively with 600 mL of 0.5 M Na_2SO_3, 800 mL of 0.5 M K_2CO_3, 200 mL of H_2O, and finally dried with Na_2SO_4. Removal of the solvent in vacuo (water bath below 30 °C) gives 221 g of a residue which is dissolved in 1 L of dry EtOH, cooled to 0 °C under Ar, and treated with 75.5 g (1.09 mol) of $NH_2OH \cdot HCl$. The mixture is stirred overnight during which time the mixture is allowed to reach r.t. 1.5 L of $CHCl_3$ is added to precipitate excess of $NH_2OH \cdot HCl$. After 2 h, the mixture is filtered and the solvents are removed under reduced pressure. The residue is dissolved in 500 mL of H_2O and washed twice with 500-mL portions of Et_2O. The aqueous phase is treated with 500 mL of sat. aq $NaHCO_3$ and extracted five times with 500-mL portions of Et_2O. The combined extracts are dried over Na_2SO_4 and filtered into a flask containing 94 g (1.04 mol) of anhyd oxalic acid in 600 mL of Et_2O. The precipitated salt is recrystallized from $EtOH/CH_3OH$ to give the product; yield: 123.6 g (69%); mp 177–180 °C (dec.); $[\alpha]_D^{25}$ −2.6 (c = 1.02, CH_3OH).

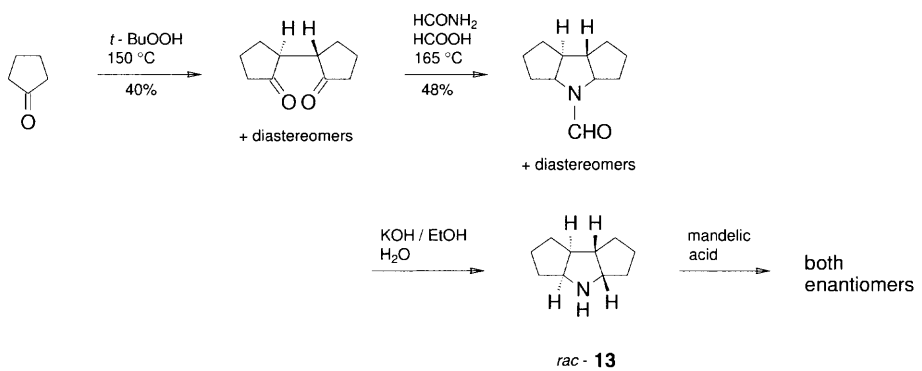
As a close analog to 1-phenylethylamine but possessing greater steric hindrance, (*S*)-1-naphthylethylamine has been employed as an auxiliary for the alkylation of azaenolates via imines (Section D.1.1.1.4.) and amides (Section D.1.5.1.). The racemate (obtained by reductive amination of 1-acetylnaphthalene) is best resolved with tartaric acid[16] (see also ref 17).

Another simple amine used as an auxiliary in [2,3] sigmatropic rearrangements (Section D.1.6.3.2.) is (*S*)-2-butanamine. It is commercially available, but expensive, and can be obtained from the inexpensive racemate by resolution with tartaric acid[18,19].

Several heterocyclic monoamines have also found applications (Section C.). Both enantiomers of 2,5-dimethylpyrrolidine **12** can be prepared from (*R*)- or (*S*)-alanine in several steps[20], but a more convenient access[21] to the (2*R*,5*R*)-enantiomer uses (2*S*,5*S*)-2,5-hexanediol as the starting material, which is readily available by baker's yeast reduction of 2,5-hexanedione[22].



The interesting C_2-symmetric tricyclic compound 1*H*-decahydrodicyclopenta[*b*,*d*]pyrrole (**13**) is prepared as a mixture of diastereomers from cyclopentanone in several steps, and separated as the racemate by selective hydrolysis of the intermediate formamide. The final resolution to obtain the enantiomers is achieved with mandelic acid[23].

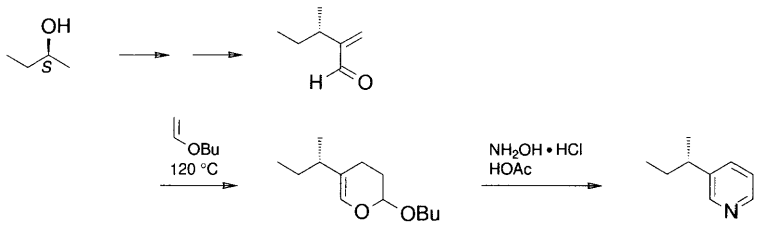


for references see p 5765

Table 2. Survey of Monoamines

Compound	No.	Synonyms and Acronyms	Section	Ref	Commercial Sources
(*R*)-1-phenylethylamine	(*R*)-**1**	(*R*)-α-methylbenzenemethaneamine, (+)-PEA	B.2.; D.1.4.4.; D.1.5.2.1.; D.6.	1–3	A, F, M, T, J
(*S*)-1-phenylethylamine	(*S*)-**1**	(*S*)-α-methylbenzenemethaneamine, (−)-PEA	B.2.; C.; D.1.1.1.3.1.; D.1.1.1.4.; D.1.3.1.4.; D.1.4.4.; D.1.5.2.1.; D.1.6.1.2.1.; D.6.	1–3	A, F, M, T, J
(*S*)-*N*-(2-pyridinylmethylene)-1-phenylethylamine	(*S*)-**2**	(*S*)-PPEI	D.2.3.1.	4	–
(*S*)-*N*-(2-hydroxybenzylidene)-1-phenylethylamine	(*S*)-**3**	(*S*)-*N*-α-methylbenzylsalicylaldimine	D.1.5.8.	5	–
(*R*)-*N*-isopropyl-1-phenylethylamine	(*R*)-**5**	–	C.	4, 6	–
(+)-(*R*,*R*)-bis(1-phenylethyl)amine	(*R*,*R*)-**7**	–	C.; D.1.6.3.2.	7	–
(*R*)-*N*-phenyl-1-phenylethylamine	(*R*)-**9**	–	C.	9, 10	–
(*R*)-*N*,*N*-dimethyl-1-phenylethylamine		(*R*)-*N*,*N*,α-trimethylbenzenemethanamine	C.	12	A, F, J
(*S*)-*N*,*N*-dimethyl-1-phenylethylamine		(*S*)-*N*,*N*,α-trimethylbenzenemethanamine	C.; D.1.3.1.4.	13	A, F, J
(*S*)-1-phenylethylurea	**10**	–	D.6.	11	–
(*S*)-*N*-(1-phenylethyl)hydroxylamine	**11**	–	D.1.6.1.2.1.	15	–
(*S*)-*N*-1-naphthylethylamine		(*S*)-α-methyl-1-naphthalenemethanamine	D.1.1.1.4.; D.1.5.1.	17	J
(*S*)-2-butanamine		(*S*)-*sec*-butylamine	D.1.6.3.2.	18, 19	A, F
(2*R*,5*R*)-2,5-dimethylpyrrolidine	(2*R*,5*R*)-**12**	–	C.	20, 21	–
(2*S*,5*S*)-2,5-dimethylpyrrolidine	(2*S*,5*S*)-**12**	–	C.	20	–
3a*S*-(3aα,4aβ,7aβ,7bα)-decahydro-1*H*-dicyclopenta[*b*,*d*]pyrrole	**13**	–	C.	23	–
(*S*)-3-(1-methylpropyl)pyridine	**14**	(+)-3-*sec*-butylpyridine	D.1.5.8.	24, 25	–

(+)-3-*sec*-Butylpyridine (**14**) has been used as a ligand for asymmetric hydroformylations (Section D.1.5.8.). Together with its 2- and 4-substituted isomers, the compound was prepared from commercial (+)-(*S*)-2-butanol in several steps[24, 25].



14

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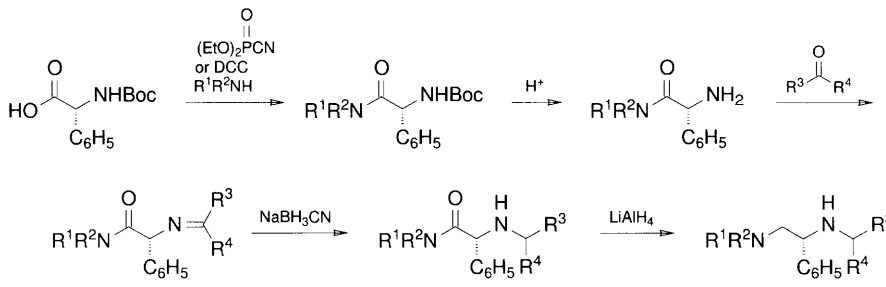
1.2. Di- and Triamines

Amides of amino acids react with complex hydrides resulting in reduction of the carbonyl to a methylene group. Thus, it is possible to obtain a variety of diamines (not containing α-hydroxy groups) in an enantiomerically pure form. The amino acids generally employed are phenylglycine[1] and proline[2,3]. The majority of amines discussed in this section were used as the lithium salt in enantioselective deprotonation and elimination (Section C.).



1-6

R^1, R^2 = H, CH_3; CH_3, CH_3; $-(CH_2)_4-$; $-(CH_2)_5-$; $-CH_2CH_2N(CH_3)CH_2CH_2-$
R^3, R^4 = H, H; CH_3, CH_3; H, *t*-Bu; H, C_6H_5; H, 1-adamantyl; $-(CH_2)_5-$

Cpd	R^1	R^2	R^3	R^4	Cpd	R^1	R^2	R^3	R^4
1	CH_3	CH_3	CH_3	CH_3	**4**	$-(CH_2)_5-$		H	*t*-Bu
2	$-(CH_2)_5-$		CH_3	CH_3	**5**	$-CH_2CH_2N(CH_3)CH_2CH_2-$		CH_3	CH_3
3	$-(CH_2)_4-$		CH_3	CH_3	**6**	$-(CH_2)_5-$		H	H

(*R*)-*N*-Isopropyl-*N'*,*N'*-dimethyl-1-phenyl-1,2-ethanediamine; Typical Procedure[1]:

(R)-*2*-(tert-*Butoxycarbonylamino*)-N,N-*dimethyl-2-phenylethanamide*:

To an ice-cold solution of 12.55 g (50 mmol) of (*R*)-*N*-*tert*-butoxycarbonyl-α-phenylglycine in 100 mL of DMF are added 4.90 g (60 mmol) of dimethylamine hydrochloride, 9.78 g (60 mmol) of diethyl phosphorocyanidate in 25 mL of DMF and 12.23 g (120 mmol) of Et_3N in 25 mL of DMF. The mixture is stirred in an ice bath for 1 h and at r.t. overnight. After dilution with 1200 mL of EtOAc/benzene (2:1), the organic layer is successively washed with 10% aq citric acid, H_2O, sat. aq $NaHCO_3$, H_2O, and brine, and dried over Na_2SO_4. Removal of the solvent gives almost pure product which is used in the next step without further purification; yield: 88%; mp 109–110.5 °C (hexane); $[\alpha]_D^{27}$ −164.1 (*c* = 1, CH_3OH).

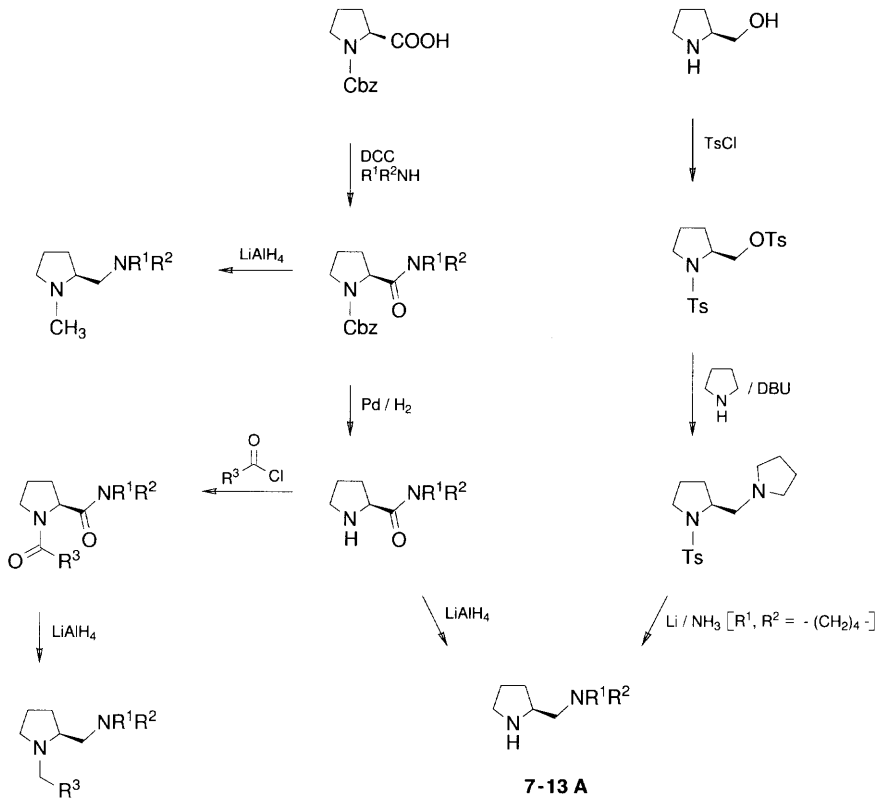
(R)-*2-Isopropylamino*-N,N-*dimethyl-2-phenylethanamide*:

13.90 g (50 mmol) of (*R*)-2-(*tert*-butoxycarbonylamino)-*N*,*N*-dimethyl-2-phenylethanamide are dissolved in 100 mL of trifluoroacetic acid in an ice bath, and the mixture is stirred for 30 min. After concentration in vacuo, benzene is added to the residue, and the solvent is evaporated in vacuo. This workup using benzene is repeated three times. 100 mL of H_2O are added to the residue, and the solution made basic with 10% aq NaOH. NaCl is added, the mixture is extracted with Et_2O, and the organic layer dried over Na_2SO_4. After removal of the solvent, the residue is dissolved in 100 mL of dry CH_3OH, and 3.14 g (50 mmol) of $NaBH_3CN$ and 3.48 g (60 mmol) of acetone are added. The pH of the mixture is adjusted to ca. 6 by adding HOAc. The solution is stirred at r.t. for 3 h. If the reaction does not proceed completely, another 3.48 g (60 mmol) of acetone can be added, and the mixture is stirred overnight. The solution is cooled with ice/CH_3OH, and then 200 mL of 40% aq K_2CO_3 are added. After extraction with Et_2O, the organic layer is washed twice with brine and dried over Na_2SO_4. Concentration in vacuo gives the residue which is purified by recrystallization from hexane; yield: 98%; mp 102–103 °C; $[\alpha]_D^{27}$ −145.2 (*c* = 1, CH_3OH).

(R)-N-*Isopropyl*-N',N'-*dimethyl-1-phenyl-1,2-ethanediamine*:

A solution of 3.30 g (15 mmol) of (*R*)-2-isopropylamino-*N*,*N*-dimethyl-2-phenylethanamide in 25 mL of THF is added dropwise to an ice-cold suspension of 1.14 g (30 mmol) of $LiAlH_4$ in 50 mL of THF, and the mixture is stirred at r.t. for 3–6 h. 6 mL of EtOAc, 6 mL of 10% aq NaOH, and 18 mL of H_2O are added successively dropwise to the mixture in an ice bath, and the mixture is stirred at r.t. for several hours. After filtration, the precipitate is washed with Et_2O. The organic layer is dried over Na_2SO_4 and concentrated in vacuo. The residue is purified by Kugelrohr distillation; yield: 70%; bp 92–93 °C/0.6 Torr; $[\alpha]_D^{26}$ −74.9 (*c* = 1, CH_3OH).

In close analogy, many proline derived diamines were prepared by reduction of amides of proline[2, 7, 13].



R^1, R^2 = H, cyclohexyl; H, (*S*)-1-phenylethyl; H, C_6H_5; H, 2,6-$(CH_3)_2C_6H_3$; H, 1-naphthyl; Et, Et; CH_3, C_6H_5; $-(CH_2)_4-$; $-(CH_2)_5-$; $-CH_2CH_2OCH_2CH_2-$; $CH_2CH_2N(CH_3)CH_2CH_2-$

R^3 = H, CH_3, *i*-Pr, *t*-Bu

Cpd	R^1	R^2	Cpd	R^1	R^2	R^3
7A	H	C_6H_5	**14B**	H	cyclohexyl	H
8A	H	2,6-$(CH_3)_2C_6H_3$	**15B**	H	cyclohexyl	*i*-Pr
9A	$-(CH_2)_4-$		**16B**	H	(*S*)-1-phenylethyl	H
10A	$-(CH_2)_5-$		**17B**	H	C_6H_5	H
11A	Et	Et	**18B**	$-(CH_2)_5-$		H
12A	$-CH_2CH_2OCH_2CH_2-$		**19B**	H	1-naphthyl	H
13A	H	cyclohexyl				

for references see p 5775

The products are versatile auxiliaries not only for enantioselective deprotonation and elimination (Section C.), but are also valuable chiral ligands for complex hydrides in the enantioselective reduction of ketones (Section D.1.4.5.). They are also applied in enolate reactions (Section D.1.5.2.1., D.1.5.2.4.), transition-metal-catalyzed Michael additions (Section D.1.5.8.), 1,3-dipolar cycloadditions (Section D.1.6.1.2.1.), and additions of Grignard reagents (Section D.1.3.1.4.2.5.). (*S*)-2-(Phenylaminomethyl)pyrrolidine has found most application and is also commercially available. Several methods exist for the preparation of such compounds. Two typical procedures for the synthesis of (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine are presented here. The methodology can be readily extended to other amides and alkylamino derivatives of proline.

(*S*)-2-(1-Pyrrolidinylmethyl)pyrrolidine; Typical Procedures:

1. From (*S*)-*N*-Benzyloxycarbonylproline:

(S)-*1-Benzyloxycarbonyl*-N,N-*tetramethylene-2-pyrrolidinecarboxamide*[2]:

To a solution of 24.9 g (0.10 mol) of (*S*)-*N*-benzyloxycarbonylproline in 30 mL of CH_2Cl_2 are added 20.6 g (0.10 mol) of DCC in 60 mL of CH_2Cl_2 at 0 °C under N_2. After stirring for 30 min, a solution of 7.1 g (0.1 mol) of pyrrolidine in 40 mL of CH_2Cl_2 is slowly added to the mixture at 0 °C and the mixture is slowly warmed to r.t. and further stirred overnight. After removal of the precipitate by filtration, the filtrate is washed successively with 2% aq HCl, 4% $NaHCO_3$, H_2O, and brine and dried with anhyd Na_2SO_4. The solvent is evaporated in vacuo, and the crude product is purified by recrystallization or column chromatography. The title compound is isolated as colorless crystals; yield: 63%; mp 130–132 °C (EtOAc), 130–133 °C (acetone); $[\alpha]_D^{29}$ −13.0 (*c* = 1.67, CH_3OH), $[\alpha]_D^{22}$ −14.1 (*c* = 1.16, CH_3OH).

(S)-*2-(1-Pyrrolidinylmethyl)pyrrolidine*[2]:

21.1 g (70 mmol) of (*S*)-1-benzyloxycarbonyl-*N*,*N*-tetramethylene-2-pyrrolidinecarboxamide and 1.3 g of 5% palladium on carbon are stirred vigorously in 100 mL of CH_3OH under a H_2 atmosphere overnight. The reaction mixture is then filtered through Celite and the filtrate is concentrated in vacuo to give the crude *N*,*N*-disubstituted (*S*)-prolinamide as a viscous oil. The crude material in 75 mL of THF is slowly added to a suspension of 9.1 g (0.24 mol) of $LiAlH_4$ in 75 mL of THF at 0 °C under N_2 and the mixture is refluxed for 20 h. Sat. aq Na_2SO_4 is then added to the mixture at 0 °C. After removal of the inorganic material by decantation and removal of the solvent in vacuo, fractional distillation of the residue under reduced pressure affords the title compound as a colorless oil; yield: 69%; bp 84 °C/5 Torr; $[\alpha]_D^{29}$ +8.2 (*c* = 2.38, EtOH).

2. From (*S*)-Prolinol:

(−)-(S)-*1-(4-Methylphenylsulfonyl)-2-[(4-methylphenylsulfonyloxy)methyl]pyrrolidine*[13]:

A solution of 10 g (0.10 mol) of (*S*)-prolinol, 21.4 mol (0.20 mol) of Et_3N and 46 g (0.20 mol) of 4-methylbenzenesulfonyl chloride in 200 mL of CH_2Cl_2 is refluxed for 24 h. After cooling, the mixture is washed twice with 25-mL portions of H_2O, and the organic layer is dried with $MgSO_4$ and evaporated. The crude material is recrystallized from EtOH to provide the title compound as white needles; yield: 26.4 g (65%); mp 92–94 °C; $[\alpha]_D^{25}$ −123.2 ($CHCl_3$).

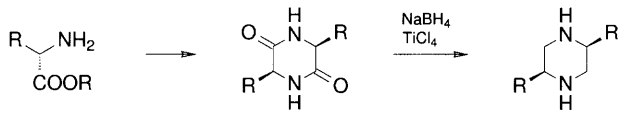
(S)-*1-(4-Methylphenylsulfonyl)-2-(1-pyrrolidinylmethyl)pyrrolidine*[13]:

A solution of 24.54 g (0.06 mol) of the above pyrrolidine, 17 g (0.24 mol) of pyrrolidine and 0.91 g (5.98 mmol) of DBU in 400 mL of toluene is heated at reflux for 24 h, or until no starting material remains, as indicated by TLC. The solvent is then removed on a rotary evaporator and the product is crystallized from EtOH/H_2O. If crystallization proves difficult, the material can be purified by flash chromatography. The title compound is isolated as pale yellow crystals; yield: 70%; mp 80–82 °C; $[\alpha]_D^{25}$ −128.4 ($CHCl_3$).

(S)-*2-(1-Pyrrolidinylmethyl)pyrrolidine*[13]:

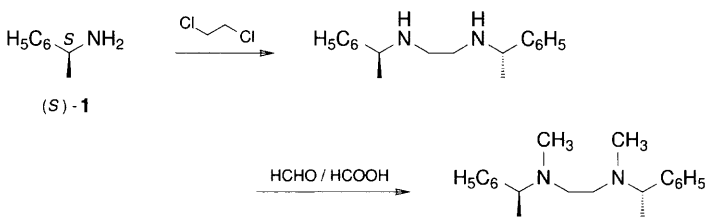
To a solution of 12.40 g (0.04 mol) of the above pyrrolidine in a mixture of 200 mL of anhyd THF, 10 mL of anhyd EtOH and 200 mL of anhyd liquid ammonia, under N_2 at −78 °C, is added excess lithium and the mixture is then allowed to reflux for 15 min. The condenser is then removed and after the ammonia has evaporated, the mixture is diluted with 50 mL of H_2O and extracted twice with 200-mL portions of EtOAc. The combined organic layers are dried and concentrated, leaving a brown oil, which is purified by bulb-to-bulb distillation. The title compound is isolated as a colorless oil; yield: 68%; $[\alpha]_D^{25}$ +8.3 (*c* = 2.4, EtOH).

Amino acid esters can be dimerized to dioxopiperazines, which are conveniently reduced with sodium borohydride/titanium(IV) chloride to give the corresponding chiral piperazine derivatives. Thus, from valine and phenylalanine, useful auxiliaries **20** and **21** were obtained[9], and used for the alkylation of carbanions (Section D.1.1.1.3.1.) and as catalysts for the addition of zinc alkyls to aldehydes (Section D.1.3.1.4.), as well as for enantioselective deprotonation and elimination (Section C.).



20 R = *i*-Pr
21 R = Bn

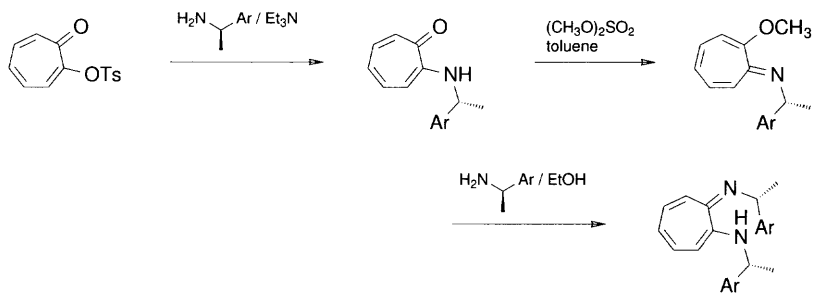
(*S*,*S*)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(1-phenylethyl)-1,2-ethanediamine was prepared from (*S*)-phenylethylamine by reaction with 1,2-dichloroethane, followed by the introduction of the *N*-methyl group with formaldehyde/formic acid[10] and used as a chiral additive in transition-metal-catalyzed Michael additions to enones (Section D.1.5.2.1.).



(*S*)-**1**

22

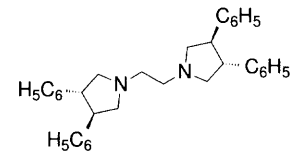
(*R*)-1-Phenylethylamine is the chiral starting material for the preparation of the CHIRAMT ligands[11] which were similarly used (Sections D.1.5.2.1. and D.1.5.8.). Analogously, H R-NEAT was prepared from (*R*)-1-(1-naphthyl)ethylamine[12].



23 Ar = C_6H_5; H(R-CHIRAMT)
24 Ar = 1-naphthyl; H(R-NEAT)

for references see p 5775

1,2-Bis[(*R*,*R*)-3,4-diphenyl-1-pyrrolidinyl]ethane (**25**) was developed as a chiral additive for dihydroxylation reactions catalyzed by osmium tetroxide (Section D.4.4.). The key intermediate in the synthesis is (*R*,*R*)-3,4-diphenylpyrrolidine; reaction with oxalyl chloride, followed by lithium aluminum hydride reduction, leads directly to the compound[14]. The intermediate is accessible from (*R*,*R*)-2,3-diphenyl-1,4-butanediol[15] or the corresponding (*R*,*R*)-2,3-diphenylbutanedioic acid, which is obtained by resolution of the racemic acid with 1-phenylethylamine.



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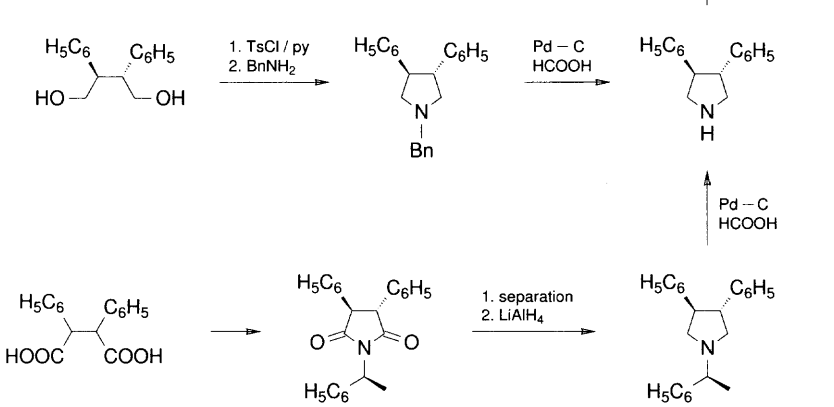
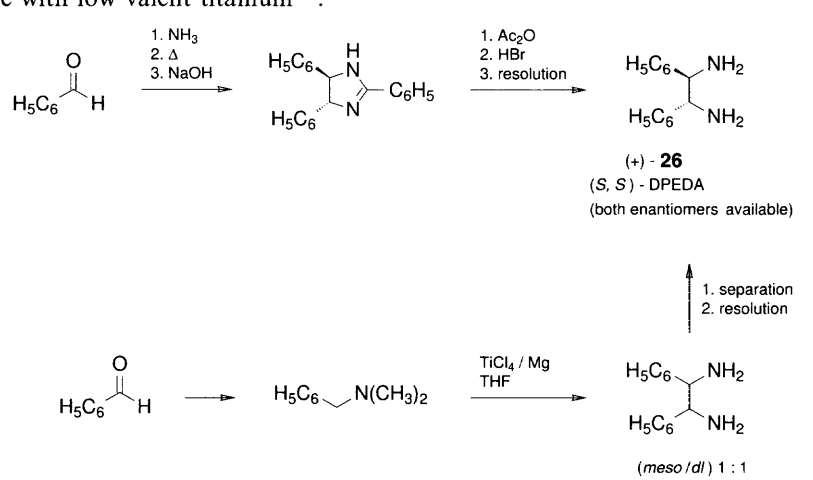
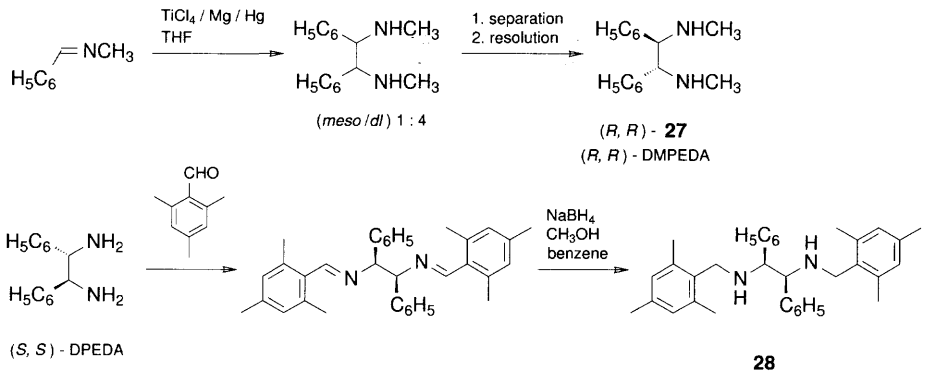


(*S*,*S*)-1,2-Diphenyl-1,2-ethanediamine [(*S*,*S*)-DPEDA, (+)-**26**] is a useful auxiliary in the Michael addition (Section D.1.5.8.) and in enantioselective deprotonation and elimination reactions (Section C.). The imine with 4,6-di-*tert*-butylsalicylaldehyde forms a manganese complex which catalyzes enantioselective epoxidations by sodium hypochlorite (Section D.4.5.2.3.). In addition, the sulfonamides with aromatic sulfonic acids[20] are used as ligands for chiral Lewis acids in enantioselective Diels–Alder reactions (Section D.1.6.1.1.1.). Although commercially available, the diamine is readily prepared by resolution of the racemate with mandelic acid, following an improved procedure[16]. More difficult, but less expensive, is the use of tartaric acid[17]. The racemate is obtained either via an imidazolidine[17,18], or by reductive coupling of benzaldehyde imine with low valent titanium[19].

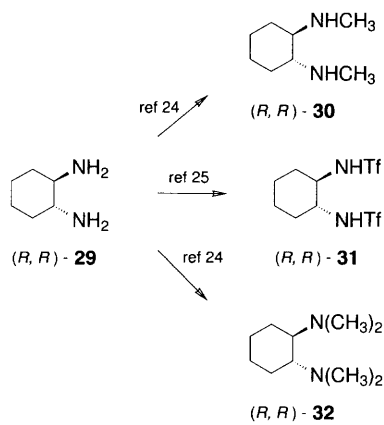


The corresponding *N*,*N*'-dimethyl compound [DMPEDA, (*R*,*R*)-**27**] was similarly obtained by reductive coupling, together with the *meso*-compound[21,22], purified by flash chromatography, and resolved with tartaric acid[22]. It has been used for the formation of chiral enamines with aldehydes (Section D.1.5.2.1.) or dicarbonyl compounds and for enantioselective Grignard addition (Section D.1.3.1.4.).

In addition, a more sterically hindered derivative of DPEDA, the 2,4,6-trimethylphenyl-substituted derivative **28**, was obtained by reduction of the diimine from 2,4,6-trimethylbenzaldehyde with sodium borohydride[23] and used as an additive in osmium tetroxide catalyzed dihydroxylations (Section D.4.4.).

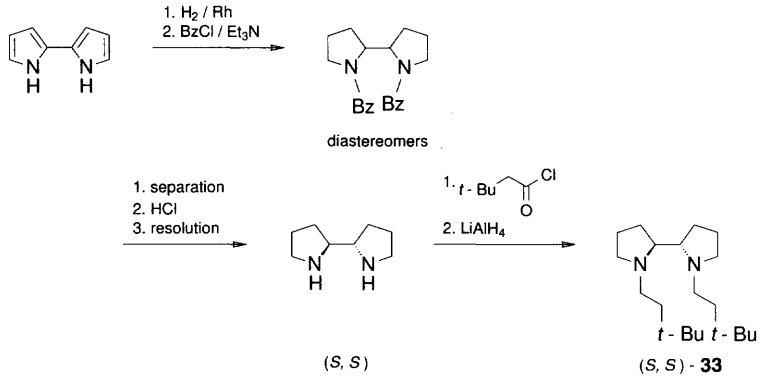


(*R*,*R*)-1,2-Diaminocyclohexane [(*R*,*R*)-DACH, (*R*,*R*)-**29**] is commercially available, but expensive. The racemate is a byproduct of the technical synthesis of Nylon 60 and may be resolved with tartaric acid[24]. The imine with 4,6-di-*tert*-butylsalicylaldehyde forms a manganese complex which catalyzes epoxidations with sodium hypochlorite (see Section D.4.5.2.3.). From (*R*,*R*)-DACH, (*R*,*R*)-1,2-bis(methylamino)cyclohexane [(*R*,*R*)-**30**] and (*R*,*R*)-1,2-bis(dimethylamino)-cyclohexane [(*R*,*R*)-**32**] are obtained[24]. The former has been used in the formation of chiral enamines with aldehydes (Section D.1.5.2.1.), and the latter as a chiral ligand for osmium tetroxide catalyzed dihydroxylations of alkenes (Section D.4.4.). Finally, the amino groups may be converted to sulfonamides[20,25]. (*R*,*R*)-1,2-Bis(trifluoromethylsulfonamido)cyclohexane [(*R*,*R*)-**31**] is an efficient ligand for titanium-catalyzed additions of dialkylzinc to aldehydes (Section D.1.3.1.4.1.5.) and is used as a chiral acid for enantioselective protonation of lactam enolates (Section D.2.1.).

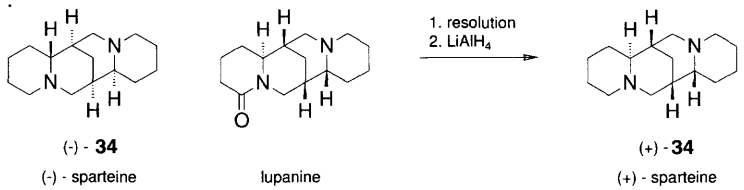


for references see p 5775

A diamine containing two directly connected pyrrolidine rings has been used as an additive in osmium tetroxide catalyzed dihydroxylations (Section D.4.4.). The synthesis from 2,2′-bipyrrole involves catalytic reduction, benzoylation, separation of the *meso* and *dl* forms by chromatography, amide hydrolysis, and resolution with tartaric acid[26]. The (*S*,*S*)-2,2′-bipyrrolidine thus obtained is then converted to the sterically hindered (*S*,*S*)-*N*,*N*′-bis(3,3-dimethylbutyl)-2,2′-bipyrrolidine [(*S*,*S*)-**33**] by acylation and reduction with lithium aluminum hydride[27].



(−)-Sparteine [(−)-**34**] is an alkaloid frequently occurring in *Fabiaceae*. It is commercially available, mostly as the sulfate, and comparatively inexpensive, so there is no need for synthesis. The other enantiomer, named (+)-pachycarpine [(+)-**34**], can be obtained by partial synthesis from racemic lupanine, involving resolution with camphorsulfonic acid and lithium aluminum hydride reduction[28].



The numerous applications of (−)-sparteine include the synthesis of allenes (Section B.1., both enantiomers), enantioselective Michael additions (Section D.1.5.2.1.), asymmetric acylations of allyl anions (Section D.1.3.3.3.), and the enantioselective introduction of electrophilic groups at α-carbons in primary alcohols via carbamates (Section D.9.).

Finally, a chiral triamine **35**, derived from (−)-proline, has been used as the lithium salt for the deprotonation of amines (Section D.2.1.). It is obtained from *N*-benzyloxycarbonylproline by forming the amide with *N*,*N*,*N*′-trimethyl-1,2-ethanediamine, cleavage of the protecting group, and lithium aluminum hydride reduction[29].

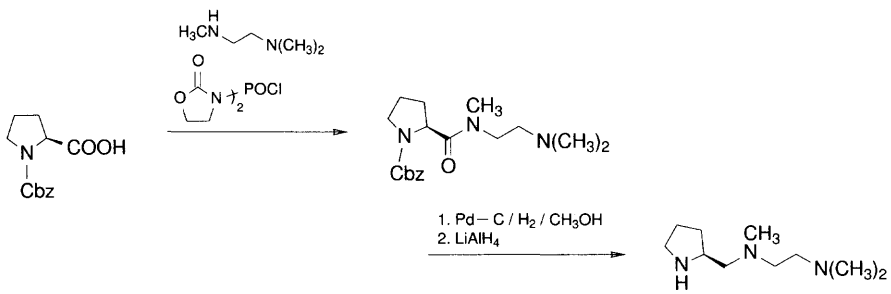


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Table 3. Survey of Di- and Triamines

Compound	No.	Synonyms and Acronyms	Section	Ref	Commercial Sources
(*R*)-*N*-isopropyl-*N'*,*N'*-dimethyl-1-phenyl-1,2-ethanediamine	**1**	–	C.	1	–
1-(*R*)-2-isopropylamino-2-phenylethylpiperidine	**2**	–	C.	1	–
1-(*R*)-2-isopropylamino-2-phenylethylpyrrolidine	**3**	–	C.	4	–
1-(*R*)-2-(2,2-dimethylpropyl)amino-2-phenylethylpiperidine	**4**	–	C.	5	–
1-[(*R*)-2-isopropylamino-2-phenylethyl]-4-methylpiperazine	**5**	–	C.	4	–
1-(*R*)-2-methylamino-2-phenylethylpiperidine	**6**	MAPP	D.1.5.2.1.6	6	
(*S*)-2-(phenylaminomethyl)pyrrolidine	**7A**	(*S*)-2-anilinomethylpyrrolidine	D.1.3.1.4.; D.1.5.2.1.; D.1.5.8.; D.1.6.1.2.1.	3	A, F, M, T
(*S*)-2-(2,6-dimethylphenylaminomethyl)pyrrolidine	**8A**	(*S*)-2-xylidinomethylpyrrolidine	D.1.4.5.	3	T
(*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine	**9A**		C.	2, 13	A
(*S*)-2-(1-piperidinylmethyl)pyrrolidine	**10A**		C.	2	–
(*S*)-2-(diethylaminomethyl)pyrrolidine	**11A**	–	C.	2	–
(*S*)-2-(4-morpholinylmethyl)pyrrolidine	**12A**	–	C.	2	–
(*S*)-2-(cyclohexylaminomethyl)pyrrolidine	**13A**	–	C.	7	–
(*S*)-2-(cyclohexylaminomethyl)-1-methylpyrrolidine	**14B**	–	C.	7	–
(*S*)-2-(cyclohexylaminomethyl)-1-isopropylpyrrolidine	**15B**	–	C.	7	–
(*S*)-2-[(*S*)-1-phenylethylaminomethyl]-1-methylpyrrolidine	**16B**	–	C.	7	–
(*S*)-1-methyl-2-phenylaminopyrrolidine	**17B**	(*S*)-1-methyl-2-(anilinomethyl)pyrrolidine	C.	7	–
(*S*)-1-methyl-2-(1-piperidinylmethyl)pyrrolidine	**18B**	–	D.1.5.2.4.	7	F
(*S*)-1-methyl-2-(1-naphthylaminomethyl)pyrrolidine	**19B**	–	D.1.5.2.4.	8	T
(*S*,*S*)-2,5-diisopropylpiperazine	**20**	–	D.1.1.1.3.1.; D.1.3.1.4.; C.	9	–
(*S*,*S*)-2,5-dibenzylpiperazine	**21**	–	D.1.1.1.3.1.	9	–
(*S*,*S*)-*N*,*N'*-dimethyl-*N*,*N'*-bis(1-phenylethyl)-1,2-ethanediamine	**22**	–	D.1.5.2.1.	10	–
1-[(*R*)-α-methylbenzylamino]-7-[(*R*)-α-methylbenzylimino]-1,3,5-cycloheptatriene	**23**	H (R-CHIRAMT)	D.1.5.2.1.; D.1.5.8.	11	–
1-[(*R*)-1'-(1''-naphthyl)ethylamino]-7-[(*R*)-1'-(1''-naphthyl)ethylimino]-1,3,5-cycloheptatriene	**24**	H (R-NEAT)	D.1.5.8.	12	–
1,2-bis[(*R*,*R*)-3,4-diphenyl-1-pyrrolidinyl]ethane	**25**	–	D.4.4.	14	–
(*S*,*S*)-1,2-diphenyl-1,2-ethanediamine	(+)-**26**	(+)-1,2-diphenylethylenediamine; (*S*,*S*)-DPEDA	D.1.5.8.; D.4.5.2.; C.	16, 17	A, F

for references see p 5775

Table 3 (cont.)

Compound	No.	Synonyms and Acronyms	Section	Ref	Commercial Sources
(*S*,*S*)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine	(*S*,*S*)-**27**	(*S*,*S*)-DMPEDA	D.1.3.1.4.; D.1.5.2.1.	21, 22	–
(*S*,*S*)-*N*,*N*′-bis(2,4,6-trimethylbenzyl)-1,2-diphenyl-1,2-ethanediamine	**28**	–	D.4.4.	23	–
(*R*,*R*)-1,2-diaminocyclohexane	(*R*,*R*)-**29**	(*R*,*R*)-DACH, (*R*,*R*)-1,2-cyclohexanediamine	D.4.5.2.3.	24	A, F
(*R*,*R*)-1,2-bis(methylamino)cyclohexane	(*R*,*R*)-**30**	(*R*,*R*)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine	D.1.5.2.1.	24	–
(*R*,*R*)-1,2-bis(trifluoromethylsulfonylamino)cyclohexane	(*R*,*R*)-**31**	(*R*,*R*)-*N*,*N*′-bis(trifluoromethylsulfonyl)-1,2-cyclohexanediamine	D.1.3.1.4.; D.2.1.	20, 25	–
(*R*,*R*)-1,2-bis(dimethylamino)cyclohexane	(*R*,*R*)-**32**	(*R*,*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine	D.4.4.	24	–
(*S*,*S*)-*N*,*N*′-bis(3,3-dimethylbutyl)-2,2′-bipyrrolidine	(*S*,*S*)-**33**	–	D.4.4.	26, 27	–
(−)-sparteine	(−)-**34**	lupinidine, [(7*S*)-(7α,7aα,14α,14aβ)]-dodecahydro-7,14-methano-2*H*,6*H*-dipyrido[1,2-*a*:1′,2′-*e*][1,5]diazocine	B.1.; D.1.3.3.3.; D.1.5.2.; D.9.	–	A, F, J
(+)-sparteine	(+)-**34**	(+)-pachycarpine, [(7*R*)-(7α,7aα,14α,14aβ)]-dodecahydro-8,14-methano-2*H*,6*H*-dipyrido[1,2-*a*:1′,2′-*e*][1,5]diazocine	B.1.	28	–
(*S*)-2-[(2-dimethylaminoethyl)methylaminomethyl]pyrrolidine	**35**	–	D.2.1.	29	–