CHEMICAL REVIEWS

REVIEW

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# Bicyclic Conformationally Restricted Diamines

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## 1. INTRODUCTION

The term "conformational restriction" can be found very often in contemporary chemical literature. Despite the lack of strict definitions, this term is usually intuitively understood and used by scientists to discuss the molecules possessing structural features that cause decreased freedom of intramolecular motion, particularly of rotation around chemical bonds.[1] Molecules containing cycles and polycycles, extended networks of intramolecular hydrogen bonds or other weak interactions, or bulky substituents are most often regarded as conformationally restricted.

The subject of this review is the synthesis and use in chemistry and related sciences of a particular class of conformationally restricted molecules, namely, bicyclic conformationally restricted diamines (CRDA). There are several reasons for the high interest in CRDA and their derivatives, among these being their usefulness as biologically active compounds, stereoselective catalysts, and as compounds of interest in coordination, supramolecular, and other areas of chemistry. CRDA provide sufficiently restricted molecular scaffolds to hold the nitrogen atoms at well-defined distances and mutual orientation in space; CRDA scaffolds are thus preorganized, which can be beneficial for achieving efficient intramolecular interactions of CRDA or their derivatives with other molecules. The amino groups or the functional groups attached to CRDA can take part in many types of inter- and intramolecular interactions, such as hydrogen bonding, dipole−dipole or electrostatic interactions, as well as coordination with metal ions. It is important that the relative disposition of the nitrogen atoms in space varies widely across the library of CRDA, which is valuable for various structure−property relationship studies and, particularly, in SAR (structure−activity relationship) studies in medicinal chemistry. The chemistry of the amino group is very well studied, and the wealth of available methodology offers numerous approaches for rational and selective chemical modification of CRDA and, in particular, regioselective transformations of the two nitrogen atoms. Last

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but not least, the structural rigidity of CRDA makes computational approaches to the study of their derivatives easier. For example, computer simulation of a flexible ligand binding to a biological target is still a challenge due to difficulties in accounting for numerous possible conformations of the ligand.[2] This problem is alleviated when the ligand is conformationally restricted.

To the best of our knowledge, conformationally restricted diamines have not been reviewed previously in full. Several reviews on vicinal (1,2-) di- and polyamines can be found in the literature, but none of them highlight conformationally restricted and/or cyclic compounds.[3−6] This is contrary to the case of conformationally restricted amino acids (CRAA), which have comparable distinctive characteristics and are also used in many branches of chemistry. The synthesis and application of CRAA have been reviewed extensively in recent years (see refs 7−9 for recent examples); it is therefore surprising that CRDA have received much less attention.

The CRDA discussed in the following sections can be divided into three types, as shown schematically in Figure 1. We have limited the scope of this review to saturated compounds possessing only primary and secondary amino groups, thus focusing on diamines that can be considered as bifunctional linkers and can be modified at both nitrogen atoms without quaternization. Bicyclic diamines that have one or two tertiary amino groups are also valuable; suffice it to say that many of their derivatives are found in nature, for example, alkaloids.[10] The same could be said about stereochemically defined monocyclic diamines (e.g., *trans*-1,2-diaminocyclohexane or *cis*-1,5-diaminocyclooctane); examples of their use in medicinal chemistry,[3] catalysis,[11] and model studies[12] can be given, to name just a few. The principles guiding the use of the monocyclic diamines in chemistry and related branches of science are similar to those described in this review. However, these diamines, as well as derivatives of poly- (three and more) cyclic conformationally restricted scaffolds could be the subjects of separate reviews. The length of the bridges in the molecules of CRDA was limited to four non-hydrogen atoms for fused and bridged compounds and to five non-hydrogen atoms for spirocyclic compounds to ensure sufficient conformational restriction of the molecule. As an exception, we have included in the discussion spirocyclic diamines containing five non-hydrogen atoms in the bridge, as these CRDA were rather frequently encountered in the literature.

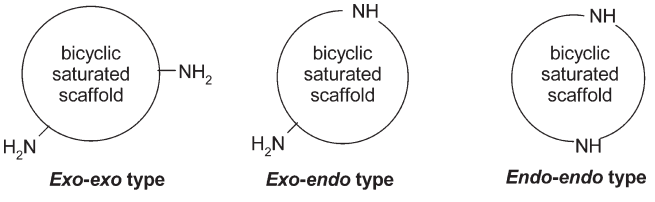


**Figure 1.** Three types of bicyclic CRDA to be discussed in the review: exo−exo type contains two primary amino (exocyclic) groups, exo−endo type possesses one primary and one secondary amino group, and endo−endo type is characterized by two secondary (endocyclic) amino groups.

The ultimate purpose of this review is to draw the attention of the chemical community to the part of the chemical space covered by CRDA and their derivatives, first of all to encourage developing novel and more convenient methods for the synthesis of both reported and previously unknown CRDA and to illustrate the structural diversity of the CRDA available for drug design and other applications. We will focus here on synthetic methods for all three subtypes of CRDA mentioned above (exo−exo, exo−endo, and endo−endo types) and describe the literature on the subject dating from the 1930s to 2009 (although several newer publications are also included). The material of each section will be grouped into three subdivisions corresponding to the type of the bicyclic cores (fused, bridged, and spirocyclic). Only syntheses of parent (unsubstituted) diamines and their monoprotected derivatives will be presented. The literature on synthesis of other numerous derivatives is too large to be reviewed in full, but we should notice that syntheses of the derivatives often starts from the corresponding parent compounds; if not, the strategies used for the synthesis of the parent CRDA and its derivatives are in most cases similar.

The structural characteristics and reactivity make CRDA very popular first of all in medicinal chemistry. The use of CRDA in drug discovery is discussed in a separate section of this review. However, insight into the use of CRDA in other areas such as catalysis, polymer synthesis, inorganic chemistry, asymmetric synthesis, model studies, and supramolecular chemistry is also given. An exhaustive discussion of all these applications is beyond the scope of this review. However, we have attempted to include all the papers where the *synthesis* of CRDA and their monoprotected derivatives is described.

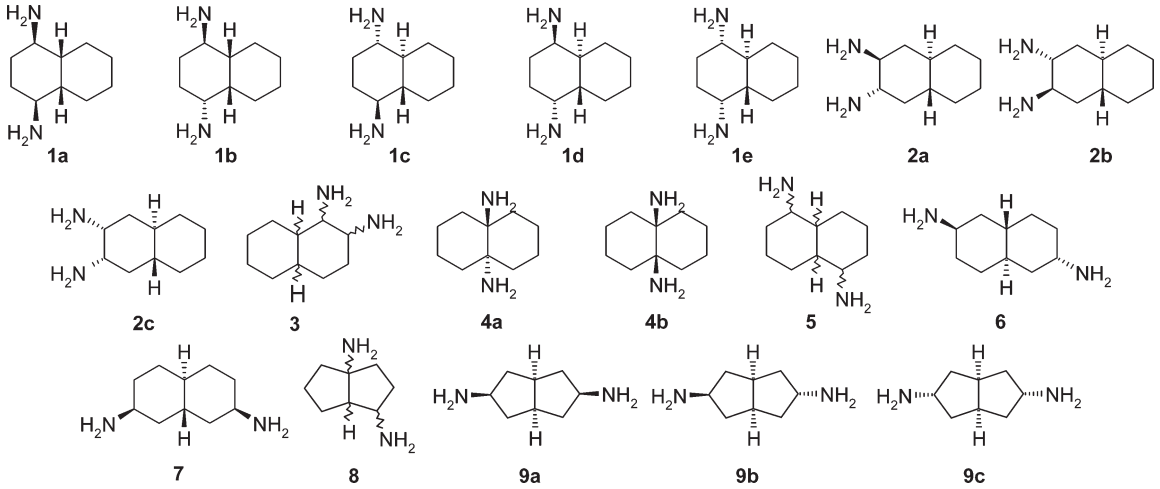


**Figure 2.** Fused bicyclic CRDA of exo−exo type.


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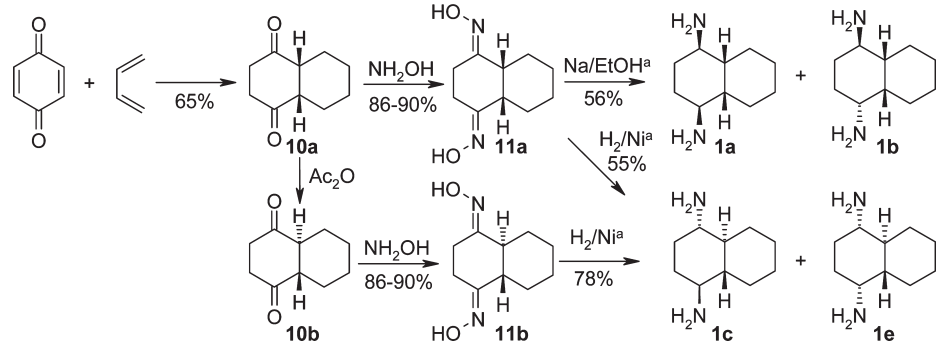
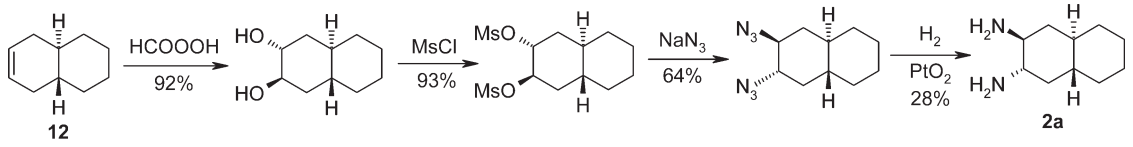
**Scheme 1**[a]

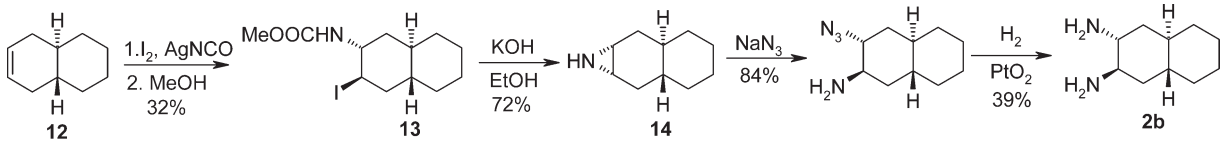



[a] Only major products of the reduction are shown.

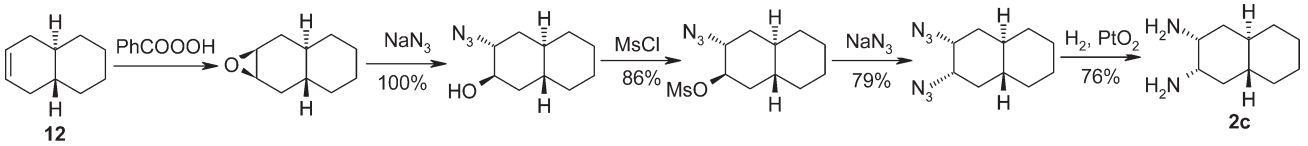
**Scheme 2**



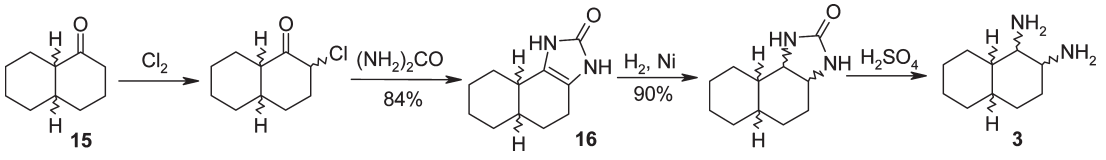

**Scheme 3**



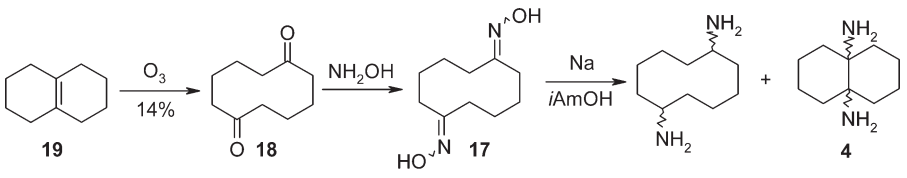

**Scheme 4**




**Scheme 5**




**Scheme 6**



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Throughout the following sections discussing the synthesis of CRDA, the yields in all the schemes are given if they were clearly stated in the literature source. Furthermore, the relative configurations of all the compounds are shown unless noted otherwise.

## 2. SYNTHESIS OF BICYCLIC CRDA WITH TWO EXOCYCLIC NITROGEN ATOMS

### 2.1. Fused Bicyclic CRDA of Exo−Exo Type

Despite overwhelming possibilities for the design of diamines provided by bicyclo[*m.n.*0]alkane (i.e., fused bicyclic) scaffolds, only bicyclo[4.4.0]decane and bicyclo[3.3.0]octane derivatives **1**−**9** (Figure 2) have been reported to date. Diamine **8** was mentioned in the literature without a detailed description of its preparation.[13]

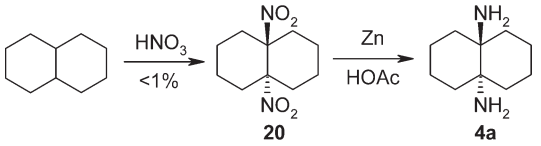
Syntheses of compounds **1a**−**e** commenced from *cis*-decalin-1, 4-dione **10a**, which, in turn, was obtained by [4 + 2]-cycloaddition of 1,4-benzoquinone and butadiene (Scheme 1). The syntheses were not enantioselective, but control of the relative configuration of the chiral centers was attempted by variation of the reagents and reaction conditions. Heating of **10a** in acetic anhydride led to its epimerization to give the thermodynamically more stable *trans*-decalin-1,4-dione **10b**. Further transformations included oxime formation and subsequent reduction, which was achieved by a set of reagents (Na/EtOH, $LiAlH_4$, $H_2$/Ni, $H_2$/Pt) leading to the formation of **1a**−**e** mixtures, which were subjected to further separation (only the major diamine products are shown in the Scheme 1). It is interesting to note that whereas reduction of **11** with Na/EtOH allowed cis- or trans-configuration of the decalin system to be substantially retained (i.e., **1a,b** were obtained predominantly from **11a** and **1c,e** from **11b**), hydrogenation of cis-isomer with $H_2$/Ni was accompanied by epimerization (thus giving predominantly **1c,e** in both **11a** and **11b** cases). Direct reductive amination of **10a,b** ($H_2$/Ni, $NH_3$) was also described, leading mainly to the formation of **1c** and **1e**.[14]

All three diastereomers **2a**−**c** were prepared from a common starting material: *trans*-$\Delta^2$-octalin **12**. To obtain diamine **2a**, alkene **12** was oxidized with performic acid, mesylated, treated with sodium azide, and then hydrogenated (Scheme 2). In the case of **2b**, compound **12** reacted with in situ generated INCO and then methanol to give carbamate **13** in 32% yield (Scheme 3). Heating of **13** with ethanolic alkali gave aziridine **14**, which was subjected to ring-opening followed by hydrogenation. In the synthesis of **2c**, compound **12** was epoxidized, treated with sodium azide, mesylated, treated with azide again, and then hydrogenated (Scheme 4). All the diamines **2a**−**c** were isolated as dihydrochlorides.[15]

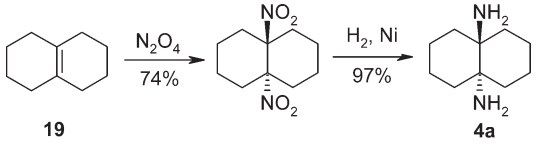
In the synthesis of diamine **3**, 2-decalone **15** was chlorinated and then reacted with urea to give the imidazolone **16** (Scheme 5). The compound **16** was hydrogenated and then hydrolyzed to give the diamine **3**.[16] Although the stereochemistry of the compounds was not specified in the original source, the relative cis-configuration of the amino groups in **3** might be assumed.

The diamines **4a,b** were obtained as byproducts in the reduction of the oxime **17** with sodium in isoamyl alcohol (Scheme 6). Synthesis of **17** commenced from the diketone **18**, which was obtained by ozonolysis of $\Delta^{9,10}$-octalin **19**. Alternatively, the diamine

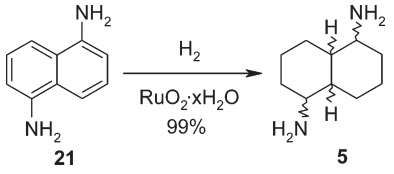
**Scheme 7**



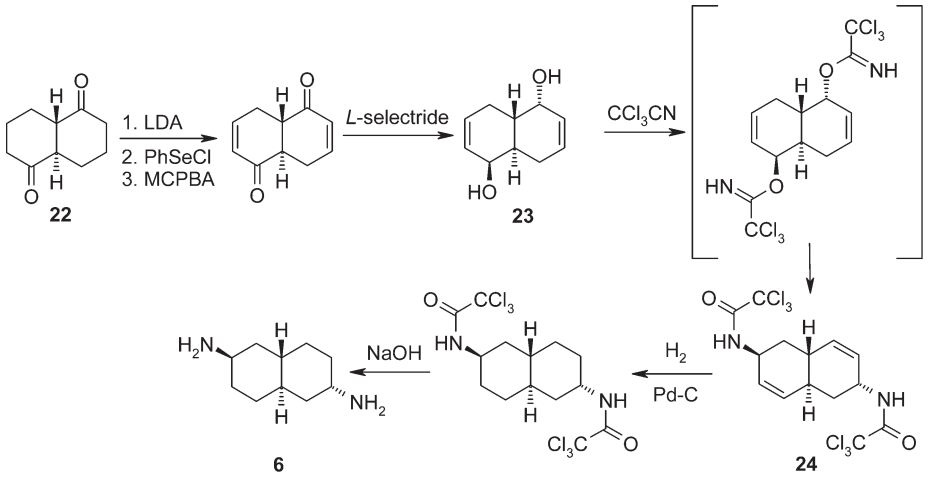

**Scheme 8**




**Scheme 9**




**Scheme 10**





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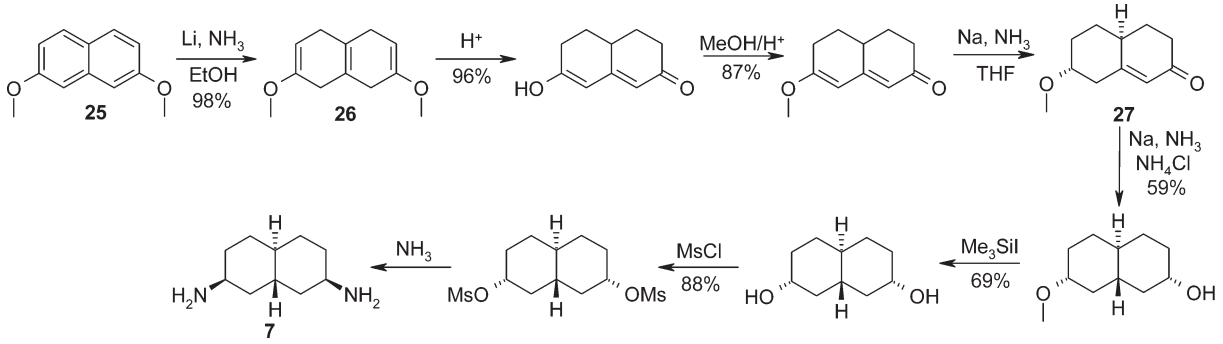
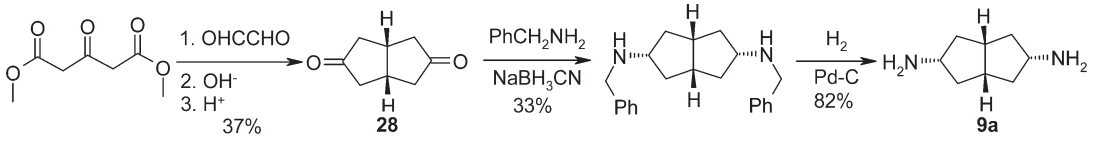
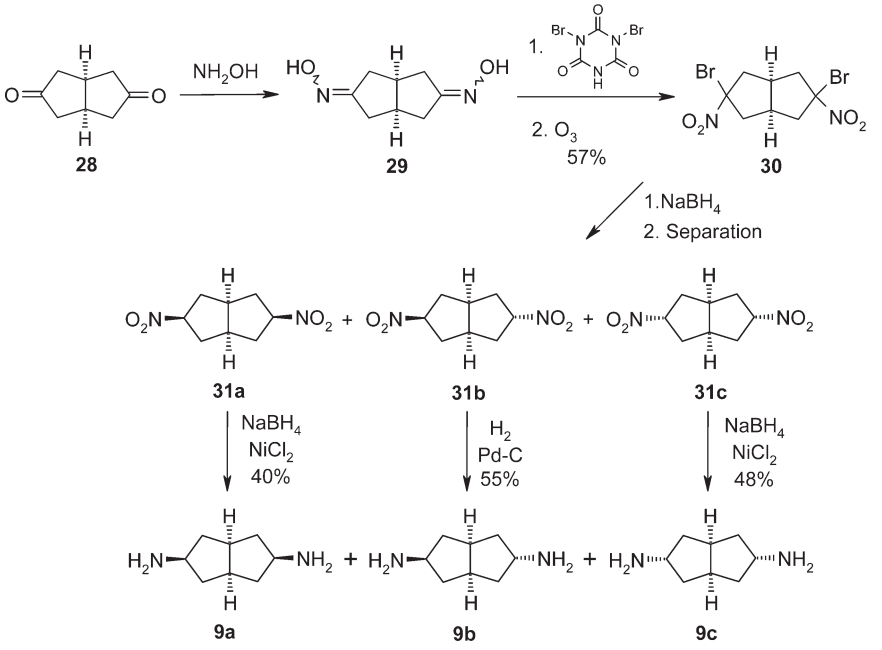
**Scheme 11**




**Scheme 12**




**Scheme 13**




**4a** was prepared by reduction of dinitrodecalin **20**. Compound **20** was obtained in less than 1% yield by nitration of decalin (Scheme 7)[17] or by reaction of **19** with dinitrogen tetroxide (Scheme 8).[18]

Compound **5** was formed in almost quantitative yield by the Ru-catalyzed hydrogenation of the corresponding naphthalene derivative **21** (Scheme 9).[19] The stereochemistry of **21** was not specified in the original source.

Compound **6** was prepared from commercially available *trans*-decalin-1,5-dione **22** (Scheme 10). The diketone **22** was transformed into the diol **23** in several steps. Reaction of **23** with trichloroacetonitrile resulted in a double [3,3]-sigmatropic reaction (Overman rearrangement) to give the diamide derivative **24**, which was hydrogenated and then hydrolyzed to give the diamine **6**.[20]

Synthesis of the diamine **7** commenced from 3,6-dimethoxynaphtalene **25**, which was subjected to Birch reduction to give compound **26** (Scheme 11). The latter was transformed into the $\alpha,\beta$-unsaturated ketone **27** in three steps. Reduction of the compound **27** followed by demethylation, mesylation, and amination gave **7** as a single diastereomer.[21]

The diamine **9a** was synthesized from bicyclo[3.3.0]octan-3,7-dione **28**, which was obtained in 37% yield from 1,3-acetonedicarboxylate (Scheme 12).[22] Reductive amination of **28** followed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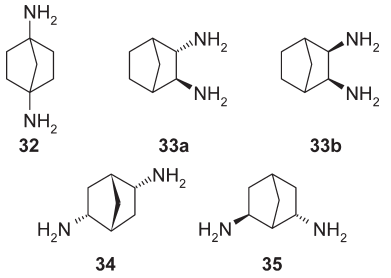
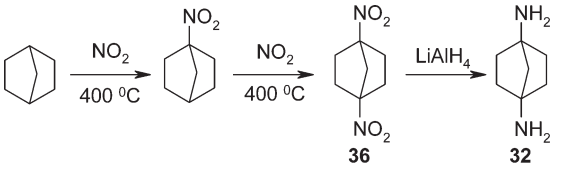
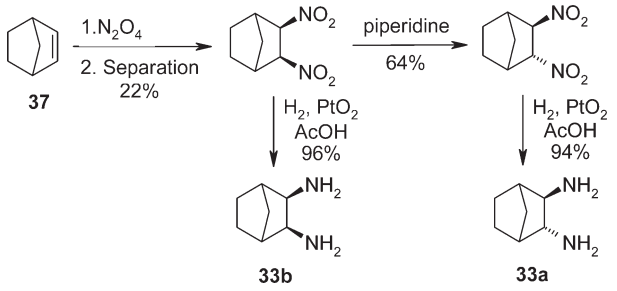



**Figure 3.** Diaminonorbornanes.

**Scheme 14**




**Scheme 15**




by catalytic hydrogenation allowed the diamine **9a** to be obtained as a single diastereomer.[23]

In another approach, the ketone **28** was transformed into the bis-oxime **29**, which was brominated and then oxidized to give bicyclo[3.3.0]octane derivative **30** (Scheme 13).[24] The latter was reduced with sodium borohydride to give a mixture of diastereomers **31a**−**c** (**31a**:**31b**:**31c** = 1.6:1:1), which were separated and transformed into the diamines **9a**−**c**.[25]

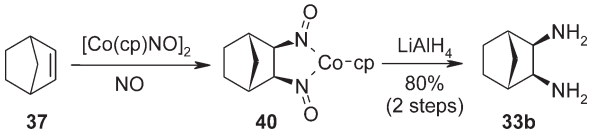
## 2.2. Bridged Bicyclic CRDA of Exo−Exo Type

**2.2.1. Bicyclo[2.2.1]heptane Derivatives (Diaminonorbornanes).** Bicyclo[2.2.1]heptane, or norbornane, is a scaffold with derivatives that are widespread in nature and are easy to obtain in the laboratory. Therefore, it is not surprising that many of the theoretically possible bicyclo[2.2.1]heptane diamines are described in the literature, i.e. compounds **32**−**35** (Figure 3). Due to the special role of the norbornane derivatives in organic chemistry, they are discussed in a separate section.

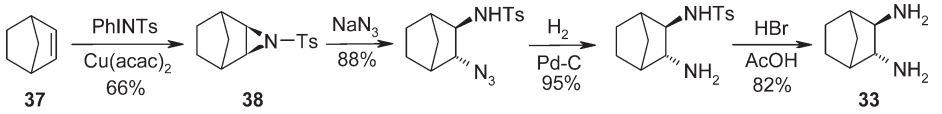
Synthesis of the diamine **32** included reduction of the dinitro derivative **36**, which was obtained in less than 1% yield by two-step nitration of norbornane (Scheme 14).[26] Obviously, this method is not suitable as a practical synthesis of **32**.

The diamine **33a** was prepared via $N_2O_4$ addition to norbornene **37** followed by reduction (Scheme 15),[18] aziridine **38** ring-opening (Scheme 16),[27] or double Curtius rearrangement of the corresponding dicarboxylic acid **39**. In the latter approach, enantiopure compounds were obtained using either enantioselective anhydride ring-opening (Scheme 17)[28] or resolution with

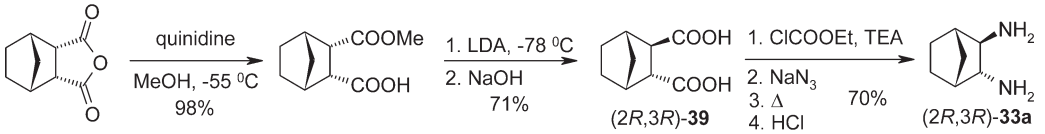
**Scheme 19**




**Scheme 16**

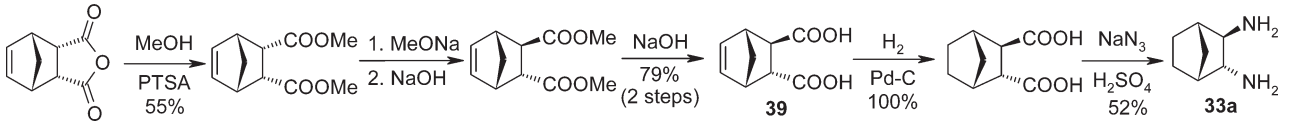



**Scheme 17**[a]




[a] Absolute configurations are shown.

**Scheme 18**





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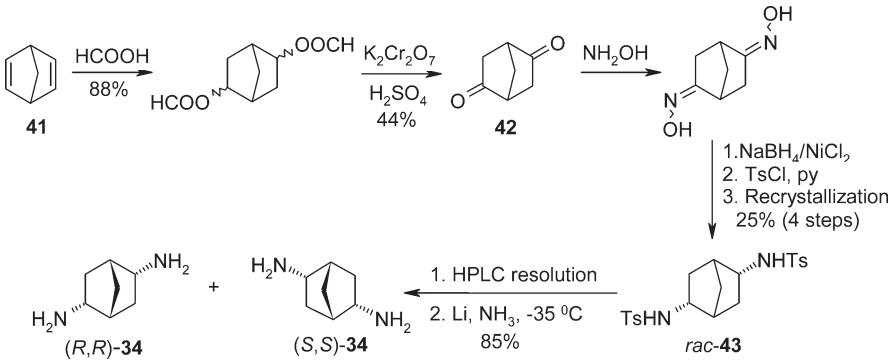
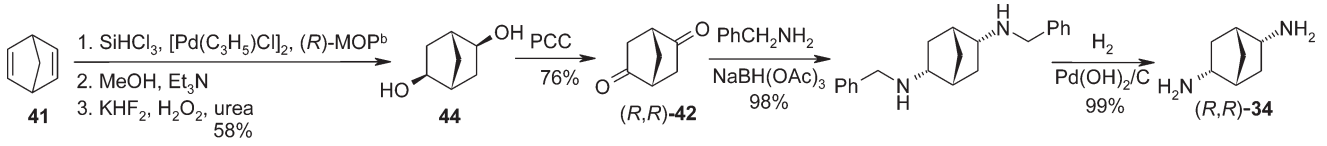
**Scheme 20**

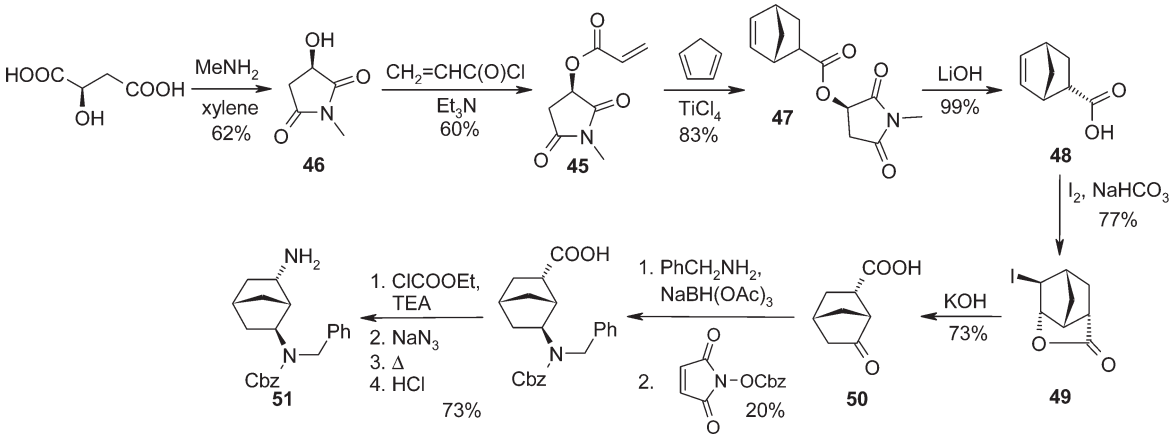



**Scheme 21**[a]




[a] Absolute configurations are shown. [b] (*R*)-MOP, (*R*)-2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl.

**Scheme 22**[a]




[a] Absolute configurations are shown.

(−)-dibenzoyltartaric acid ((−)-BTA) (Scheme 18; the resolution step is not shown).[29]

The diamine **33b** was prepared from norbornene analogously to trans-isomer **33a** (see Scheme 15). An alternative synthesis of the diamine **33b** relied on the reaction of norbornene **37**, cobalt complex $[Co(cp)(NO)]_2$, and nitrogen oxide followed by reduction of the intermediate **40** with $LiAlH_4$ (Scheme 19).[30]

2,5-Diaminonorbornane **34** (DIANANE) was obtained from norbornadiene **41** via diketone **42** by two synthetic approaches. The first method included reaction of the diene **41** and formic acid followed by Jones oxidation (Scheme 20). The racemic ketone **42** thus obtained was transformed into an oxime which was reduced with $NaBH_4$−$NiCl_2$, tosylated, and purified by recrystallization to give the bis-tosylate **43** (25% from **42**). The compound **43** was subjected to HPLC resolution using a chiral stationary phase followed by deprotection to give both enantiomers of **34**.[31]

In an alternative and more practical approach, the diene **41** was subjected to palladium-catalyzed enantioselective silylation followed by Tamao−Fleming oxidation to give the enantiopure bis-*exo*-diol **44** (Scheme 21). Attempts to transform the diol **44** into the corresponding azide turned out to be unfruitful; hence, **44** was oxidized to the ketone **42**. The compound **42** was subjected to reductive amination; after the debenzylation step, enantiopure **34** was synthesized. It should be noted that the latter method allowed both enantiomers of **34** to be obtained with high enantioselectivity using either (*R*)- or (*S*)-MOP at the corresponding step.[32]

An enantioselective Diels−Alder reaction of the acrylic acid ester **45** (obtained from chiral alcohol **46**) with cyclopentadiene was used as a key step to construct the bicyclic core of the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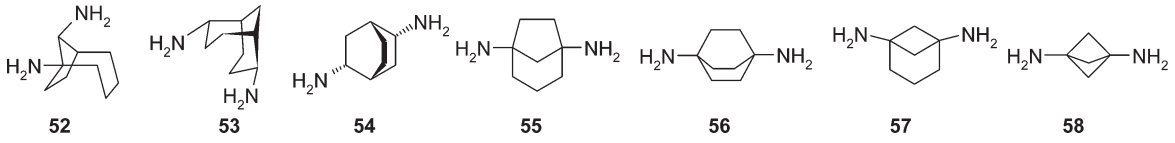
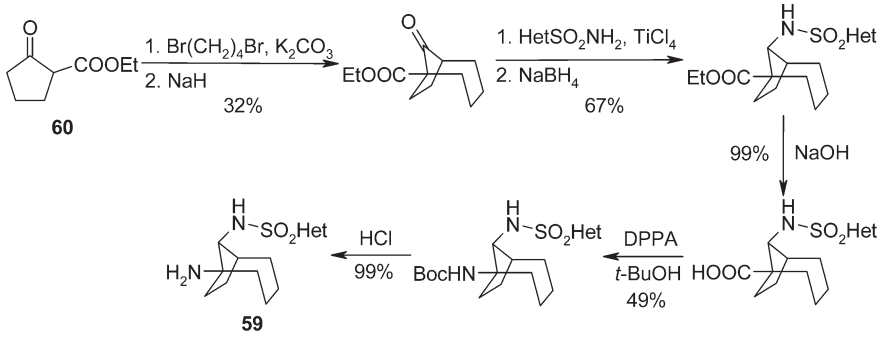


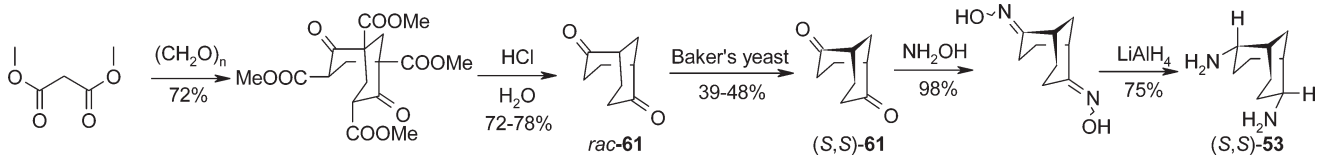

**Figure 4.** Other bicyclo[*m.n.k*]alkane diamines.

**Scheme 23**[a]



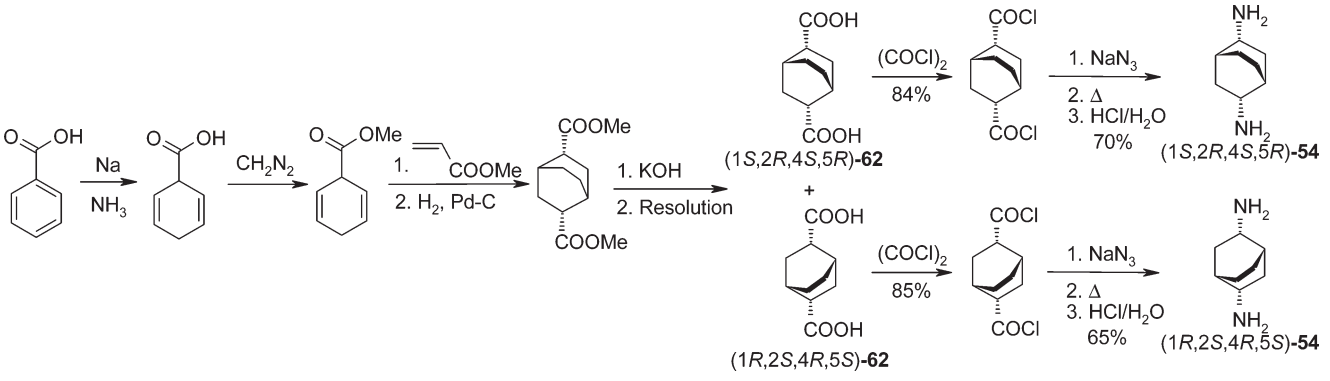

[a] Het, 2-(5-chlorothienyl); DPPA, diphenylphosphoryl azide.

**Scheme 24**[a]




[a] Starting from (*S*,*S*)-**61**; absolute configurations are shown.

**Scheme 25**[a]




[a] Starting from **62**; absolute configurations are shown.

diamine **35** (Scheme 22). The adduct **47** thus obtained was hydrolyzed to give the enantiopure carboxylic acid **48**. Iodolactonization of the latter led to the formation of the tricyclic compound **49**, which was transformed into the keto acid **50** by alkaline hydrolysis. Reductive amination of **50** followed by protection and Curtius rearrangement gave the selectively protected derivative **51** of the diamine (1*S*,2*S*,4*R*,6*S*)-**35** as a single enantiomer.[33]

**2.2.2. Derivatives of Other Bicyclo[*m.n.k*]alkanes.** Unlike the bicyclo[*m.n*.0]alkane and norbornane diamines discussed in the previous sections, other bicyclo[*m.n.k*]alkane derivatives are represented rather sparsely (compounds **52**−**58**, Figure 4). Compounds **55**−**58**, which have an antiparallel (or almost antiparallel) orientation of the C−N bonds, form an interesting subset of these diamines.

Diamine **52** was reported in the literature as its 5-chlorothiophene-2-sulfonamide derivative **59** (Scheme 23). Bis-alkylation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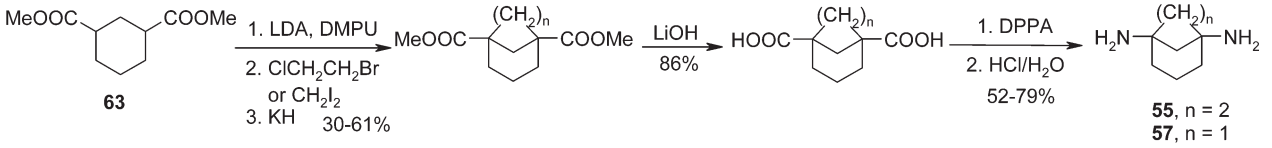
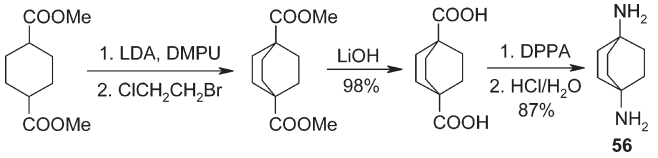
**Scheme 26**[a]



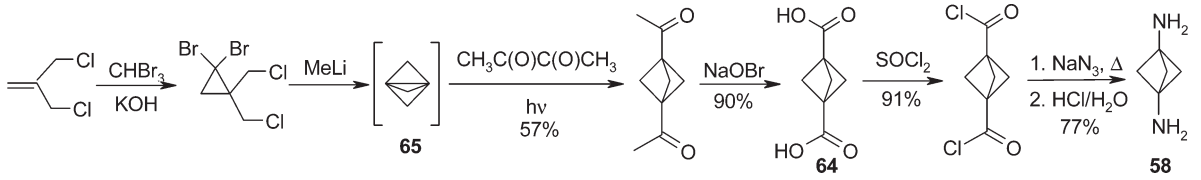

[a] DPPA, diphenylphosphoryl azide.

**Scheme 27**[a]




[a] DPPA, diphenylphosphoryl azide.

**Scheme 28**



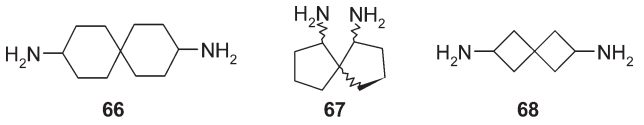




**Figure 5.** Diaminospiroalkanes.

of β-keto ester **60** was a key step in a sequence used for the construction of the bicyclic core of **59**.[34]

Diamine **53** was obtained from diketone **61** (Scheme 24). Synthesis of **61** was first described by Meerwein and Schurmann in 1913.[35] An enantioselective approach to **53** that included an enzymatic resolution of **61** was also reported.[36]

Synthesis of the diamine **54** proceeded via the dicarboxylic acid **62** as the key intermediate using the Curtius rearrangement (Scheme 25).[37] Both enantiomers of **62** (and hence **54**) were obtained starting from benzoic acid via Diels–Alder cycloaddition as the key step.[38] Racemic **54** was also obtained using an analogous reaction sequence.

Compounds **55** and **57** were prepared from the corresponding dicarboxylic acids, which were themselves obtained by bis-alkylation of 1,3-cyclohexanedicarboxylate **63** (Scheme 26).[39] An analogous approach was used in the synthesis of diamine **56** (Scheme 27).[39,40]

Bicyclo[1.1.1]pentane ([1]staffane) derivative **58** was prepared by Curtius rearrangement of the corresponding dicarboxylic acid **64** (Scheme 28).[41] Synthesis of **64** relied on [1.1.1]propellane **65** ring-opening as a key step.[42]

## 2.3. Spirocyclic CRDA of Exo–Exo Type

Only a few examples of bicyclic spiroalkane diamines of the exo–exo type were reported in the literature, i.e., compounds **66**–**68** (Figure 5).

Two distinct synthetic pathways were used to obtain the compound **66**. One of them started from methanetetraacetic acid **69** (Scheme 29). Compound **69** was subjected to multistep quadruple homologation, which included formation of the tetrabromide **70** as the key intermediate. It should be noted that while **70** could be prepared by the reaction of the tetraol **71** with a mixture of hydrobromic and sulfuric acids, the product was difficult to purify. Hence, the two-step sequence was used instead. The tetraester **72** obtained after homologation underwent double Dieckmann condensation followed by hydrolysis and decarboxylation to give the diketone **73**, which was transformed into the dioxime **74** and then reduced by catalytic hydrogenation to give the racemic diamine **66**.[43]

In another approach, 4-carboxycyclohexanone **75** was transformed into Guareschi imide **76** by treatment with ammonia and ethyl cyanoacetate (Scheme 30). Hydrolysis of the compound **76** followed by esterification and reduction gave triol **77**. Compound **77** was transformed into dibromide **78** via 3-oxaspiro-[5.5]undecane derivative **79**. Formation of the 3-oxaspiro-[5.5]undecane ring system played a dual role. It was used to differentiate the three hydroxy groups in **77** and at the same time to increase the overall yield of the transformations, as in the case of tetrabromide **70** formation discussed above. Compound **78** was used to alkylate diethyl malonate, and the triester so obtained was hydrolyzed and decarboxylated to give dicarboxylic acid **80**. Finally, **80** was transformed into diamine **66** via a Schmidt rearrangement step.[43]

The diamine **67** was obtained from the diketone **81** via reduction of the oxime **82** (Scheme 31).[44] Synthesis of the diketone **81** included a two-step alkylation of the malonate followed by hydrolysis, Dieckmann-type cyclization, and decarboxylation.[45]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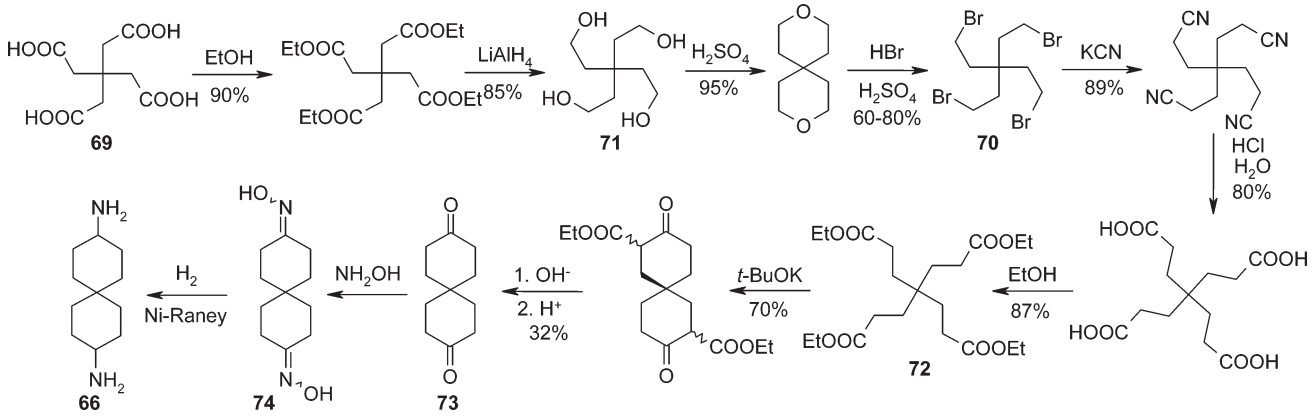
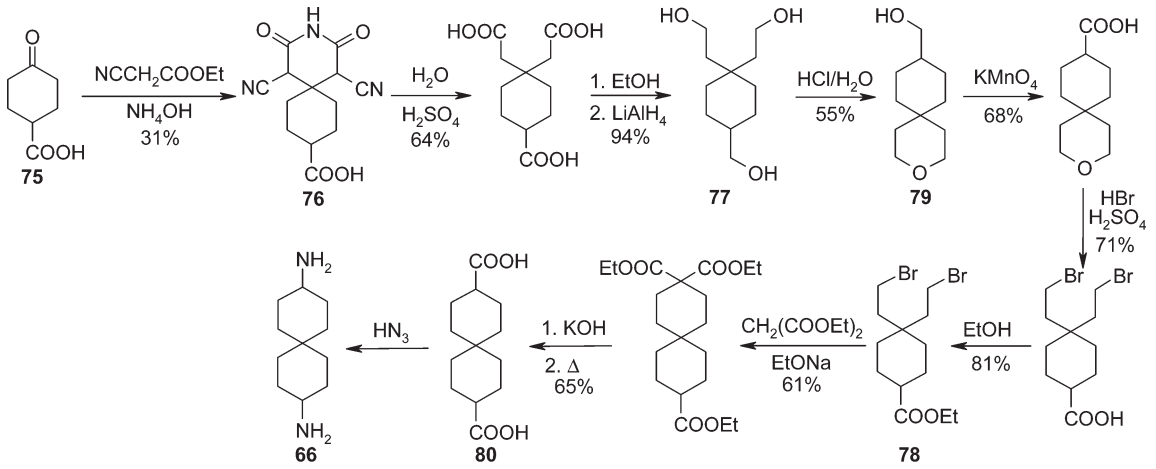
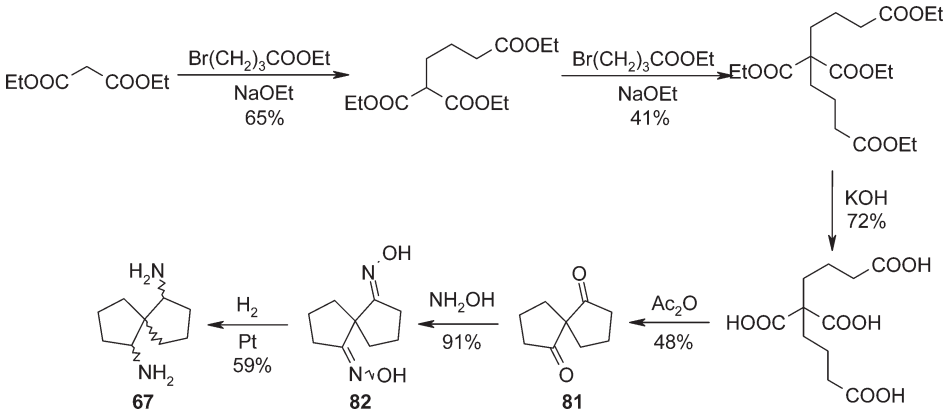
**Scheme 29**




**Scheme 30**




**Scheme 31**




Synthesis of enantiopure **67** was also reported (Scheme 32). In this case, the ketone **81** was subjected to CBS reduction, leading to the formation in 50% yield and at more than 99% ee of the diol **83** and its diastereomer, which were separated by column chromatography.[46] The compound **83** was transformed into diamine (1*R*,5*R*,6*R*)-**67** via azide formation.[47]

Synthesis of the diamine **68** started from Fecht acid **84** (Scheme 33), which was first reported more than a century ago.[48] Transformation of **84** to the diamine **68** was achieved by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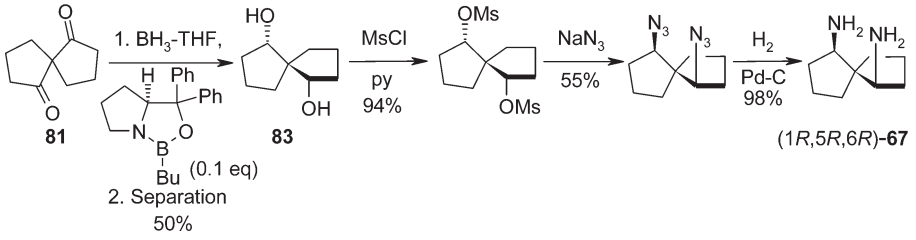
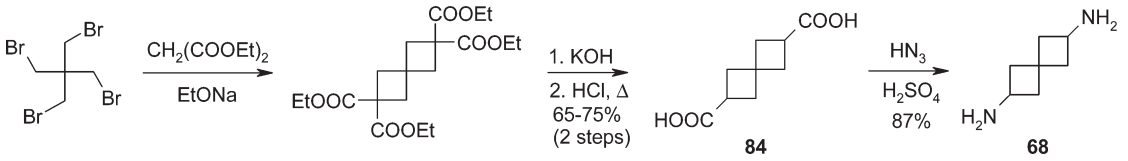
**Scheme 32**[a,b]




[a] Absolute configurations are shown.

**Scheme 33**



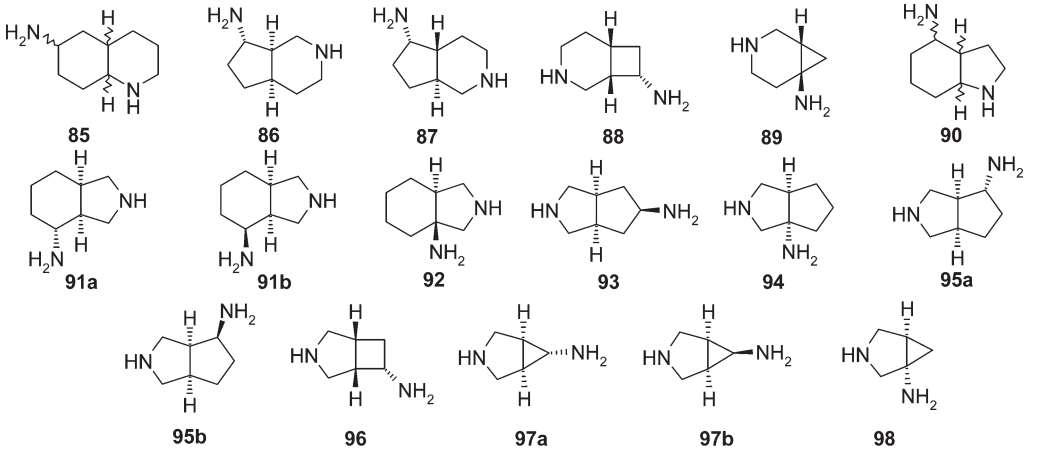
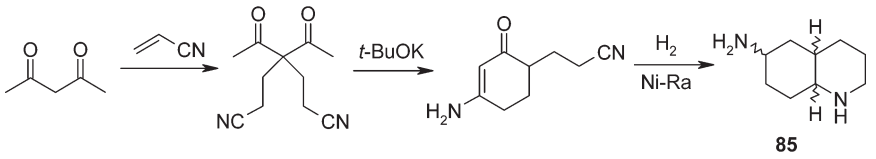




**Figure 6.** Aminoazabicyclo[*m.n.*0]alkanes.

**Scheme 34**




means of Schmidt rearrangement.[49] To obtain compound **68** as a single enantiomer, optical resolution was applied either to the dicarboxylic acid **84** (with brucine)[49] or the diamine **68** (with camphorsulfonic acid).[50]

## 3. SYNTHESIS OF BICYCLIC CRDA WITH ONE ENDOCYCLIC AND ONE EXOCYCLIC NITROGEN ATOM

### 3.1. Fused Bicyclic CRDA of Exo−Endo Type

In this section, conformationally rigid diamines derived from fused bicyclic scaffolds are discussed. Aminoazabicyclo[*m.n.*0]alkanes reported in the literature are presented as compounds **85**−**98** (Figure 6). It should be noted that all the diamines **85**−**98** have a common feature: the primary amino group is located in a carbocyclic ring of the bicyclic system, or at least at a bridgehead position, not in the heterocyclic ring. All the compounds **85**−**98** can be considered as fused derivatives of either pyrrolidine or piperidine; in most cases, fusion at the [*c*] edge of the heterocycle is observed (except **85** and **90**). It should be noted that many of the theoretically possible amino azabicyclo[*m.n.*0]alkanes are yet to be synthesized.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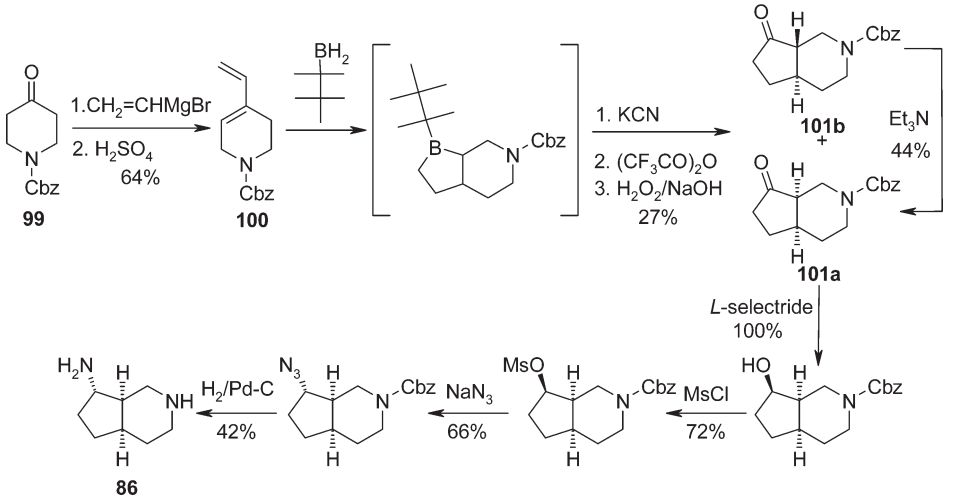
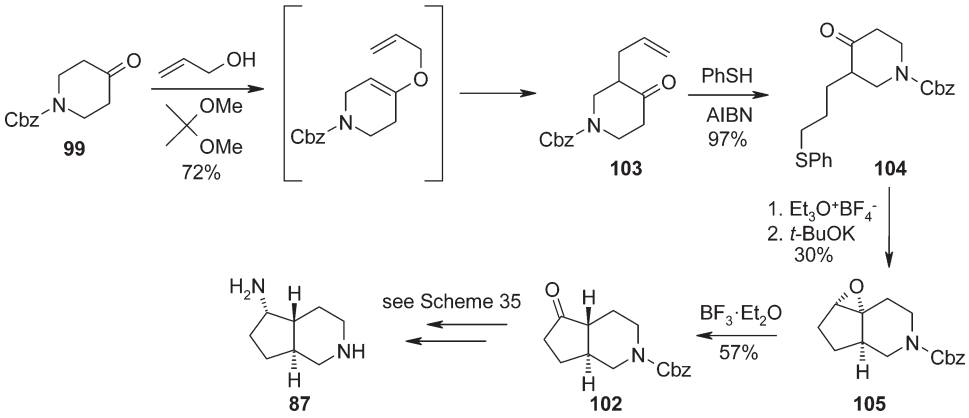
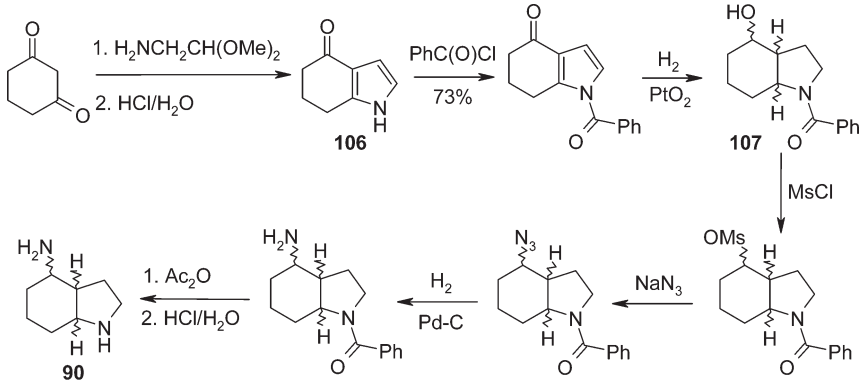
**Scheme 35**




**Scheme 36**




**Scheme 37**




Synthesis of compound **85** started with acetylacetone cyanoethylation followed by base-induced cyclization (Scheme 34). The resulting intermediate was subjected to catalytic hydrogenation; at this step, the second ring of the molecule of the diamine **85** was formed. The last step of the synthesis included three reactions: nitrile reduction, intramolecular imine formation, and hydrogenation of the double bonds. An analogous approach was successfully applied to the synthesis of other 7-aminodecahydroquinoline derivatives.[51]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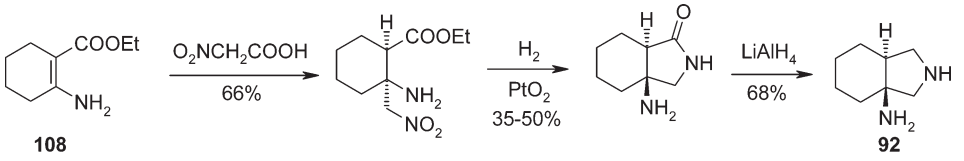
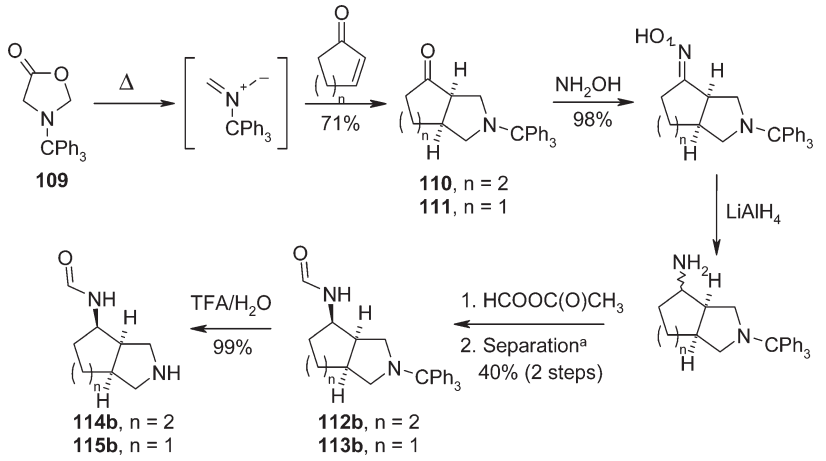
**Scheme 38**

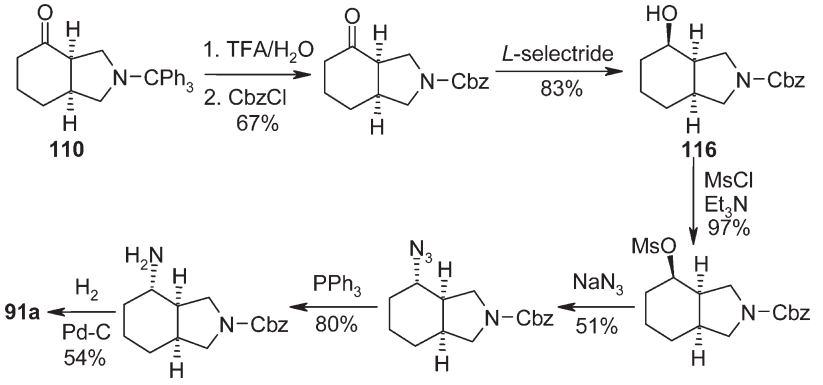



**Scheme 39**[a]




[a] Both diastereomers **112a,b** (**113a,b**) were obtained after the separation; further transformations are shown for **112b** (**113b**) only.

**Scheme 40**




The compound **86** was obtained from the 4-piperidone derivative **99** in seven steps (Scheme 35). A vinylmagnesium bromide addition−dehydration sequence gave the diene **100**. Treatment of **100** with thexylborane and potassium cyanide according to the Brown−Negishi method gave ketone **101** as a mixture of the diastereomers **101a,b**. The less stable trans-isomer **101b** was transformed into the cis-isomer **101a** by triethylamine-catalyzed epimerization. Further transformations of **101a** included reduction with L-Selectride, mesylation, substitution with azide, and catalytic hydrogenation to give finally the diamine **86**.[52]

An analogous idea was behind the synthesis of diamine **87** (Scheme 36). An elegant four-step sequence was used to transform **99** into the trans-fused ketone **102**. Compound **99** reacted with allyl alcohol to undergo enol ether formation followed by Claisen rearrangement leading to the ketone **103**. Compound **103** was treated with thiophenol in the presence of AIBN to give an addition product **104**. Reaction of **104** with triethyloxonium tetrafluoroborate and then with potassium *tert*-butylate resulted in intramolecular Corey−Chaikovsky epoxydation to give epoxide **105**, which was isomerized to ketone **102**. Compound **102** was transformed into diamine **87** by the reactions described above for **86**.[52]

The synthesis of 4-aminooctahydroindole **90** started from 4-oxotetrahydroindole **106**, which is easily obtainable from 1, 3-cyclohexanedione (Scheme 37).[53] Benzoylation of **106** followed by catalytic hydrogenation gave the *N*-protected amino alcohol **107**, which was transformed into diamine **90** by a mesylation−substitution with azide−catalytic reduction sequence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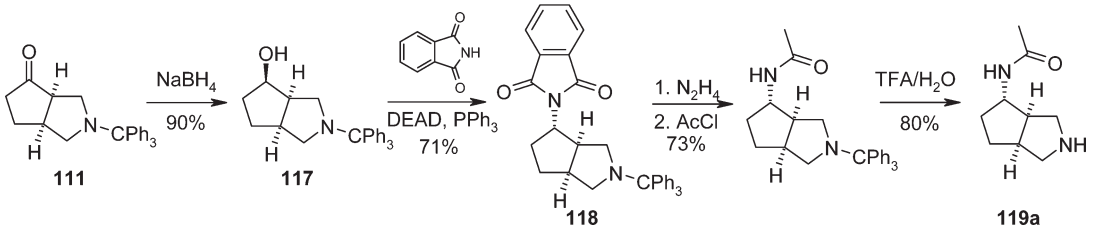
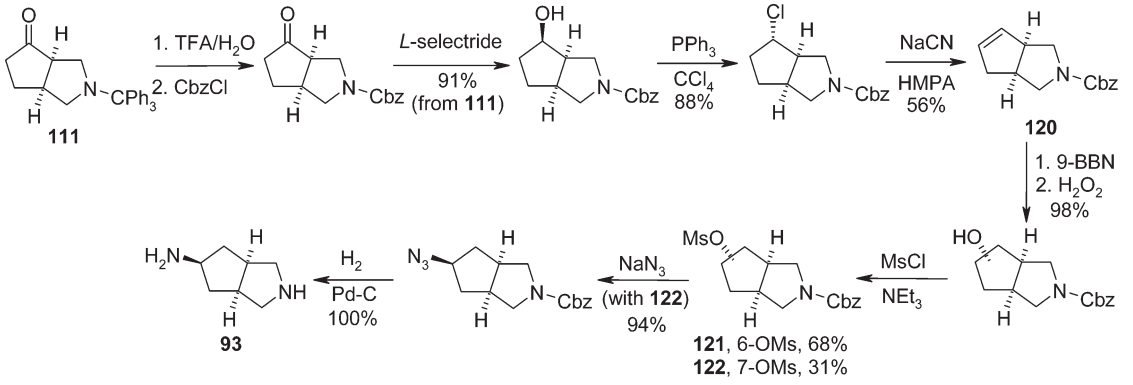
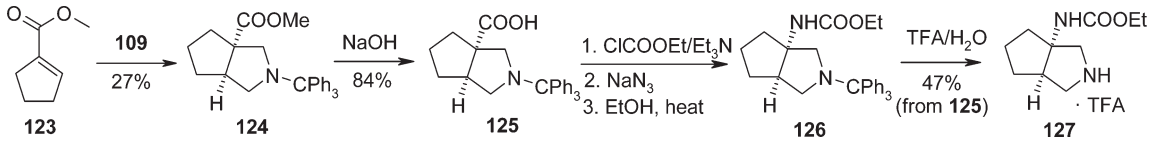
**Scheme 41**



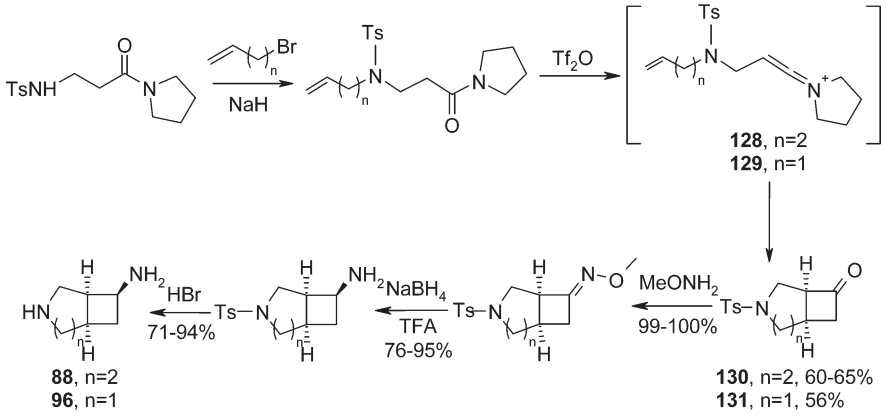

**Scheme 42**




**Scheme 43**




**Scheme 44**




followed by hydrolysis. To isolate pure **90**, derivatization with acetic anhydride was done prior to the last step.[54]

3a-Aminooctahydroisoindole **92** was obtained from ethyl 2-aminocyclohex-1-ene-1-caroxylate **108** in three steps including reaction with nitroacetic acid, catalytic hydrogenation accompanied with lactam formation, and subsequent reduction (Scheme 38). The synthesis proceeded in a stereoselective manner to give the trans-isomer **92**.[55]

The diamines **91** and **95** were obtained as their *N*-formyl derivatives from cyclohexenone and cyclopentenone, respectively (Scheme 39). Reaction of the cycloalkenones with the oxazolidinone **109** resulted in [3 + 2]-cycloaddition to give the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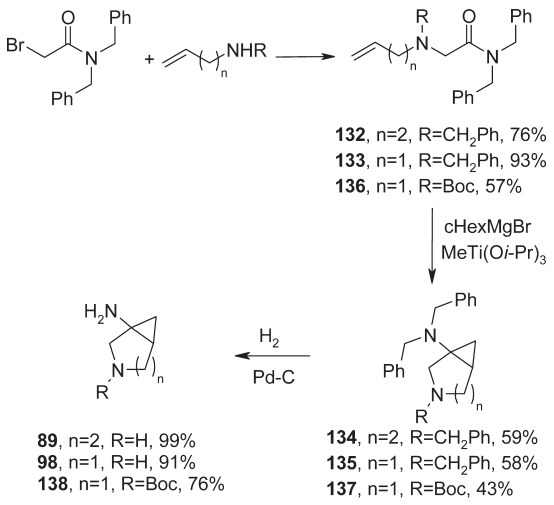
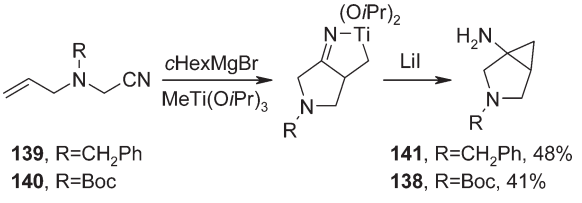
bicyclic amino ketones **110** and **111**. The compounds **110** and **111** were transformed into the corresponding derivatives **112a,b** and **113a,b** (diastereomeric mixtures) by an oxime formation−reduction sequence, which was followed by a formylation reaction. The diastereomers of the derivatives **112** and **113** were then separated by column chromatography. Removal of the triphenylmethyl protecting group in these products gave **114a,b** and **115a,b**, the formyl derivatives of the parent **91a,b** and **95a,b** (only synthesis of the isomers **114b** and **115b** is shown).[52]

Alternatively, ketones **110** and **111** were transformed into alcohols **116** and **117** using reduction with L-Selectride or $NaBH_4$ at the corresponding steps (Schemes 40 and 41). Compound **116** was subjected to mesylation followed by the reaction with azide, reduction, and deprotection to give the diamine **91a**. Mitsunobu reaction of alcohol **117** with phthalimide gave compound **118**, which was transformed into the derivative **119a** of the diamine **95a** by standard protecting group manipulations.[52]

**Scheme 45**




**Scheme 46**




Ketone **111** was also used as the key intermediate in the synthesis of diamine **93** (Scheme 42). After changing the protecting group, the corresponding Cbz derivative was transformed in three steps to alkene **120**, which was subjected to a hydroboration−oxidation sequence followed by mesylation to give a ca. 1:2 mixture of mesylates **121** and **122**. After a chromatographic separation of isomers, compound **122** was used as the substrate in a reaction sequence analogous to those described above for the synthesis of **91a** to give the diamine **93**.[52]

[3 + 2]-Cycloaddition of the ylide generated from the oxazolidinone **109** (see Scheme 39) was used in the synthesis of the derivative of the diamine **94** (Scheme 43). Reaction of **109** with the ester **123** led to the formation of the amino acid derivative **124**, which was hydrolyzed to give the carboxylic acid **125**. The latter was subjected to Curtius rearrangement to give the carbamate **126**. Deprotection of the compound **126** gave the monoprotected derivative **127** of the diamine **94**.[52]

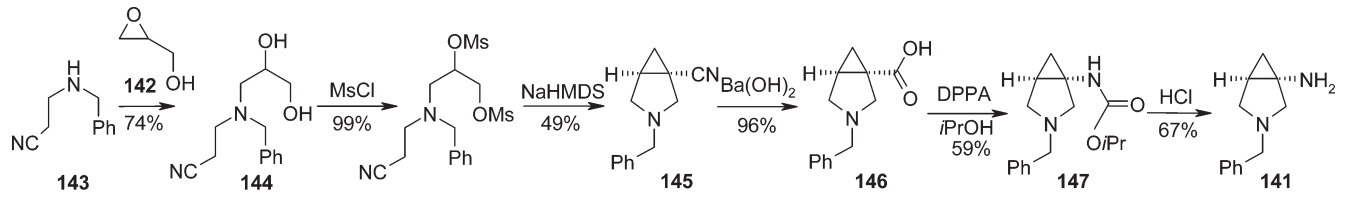
The key step in the synthesis of compounds **88** and **96** was an intramolecular [2 + 2]-cycloaddition of the keteneiminium salts **128** and **129**, respectively (Scheme 44).[56] The ketones **130** and **131** obtained in these reactions were transformed into the diamines **88** and **96** by subsequent *O*-methyloxime formation, reduction, and deprotection.[57]

The intramolecular Kulinkovich reaction is a highly useful method for preparation of bicyclic cyclopropane-containing amines.[58] In particular, this method was applied to the synthesis of diamines **89** and **98**. The intramolecular Kulinkovich reaction applied to amides **132** and **133** gave diamines **134** and **135** in 58−59% yield (Scheme 45). This reaction was also applied to the compound **136**; in this case, the desired product **137** was isolated in 43% yield. Hydrogenation of **134** and **135** gave the diamines **89** and **98**, whereas **137** gave the selectively protected derivative **138**. Analogous transformations were also applied to the nitriles **139** and **140** (Scheme 46); in this case, the selectively protected derivatives **141** and **138** of the diamine **98** were obtained in 41−48% yield.[59]

Alternatively, glycidol **142** and benzyl(2-cyanoethyl)amine **143** reacted to give the diol **144** (Scheme 47). The compound **144** was mesylated and then treated with sodium hexamethyldisilazide to give the nitrile **145** in 49% yield. This step was the key transformation in which the bicyclic skeleton was constructed from the acyclic precursor by double intramolecular nitrile-stabilized carbanion alkylation. Alkaline hydrolysis of **145** gave the *N*-protected amino acid **146**. Further transformations in the synthesis of the derivative **141** of the diamine **98** included Curtius rearrangement of **146** and the subsequent deprotection of the intermediate **147**.[60]

Several different approaches to the synthesis of **97a** and its derivatives have been reported in the literature and/or patented,

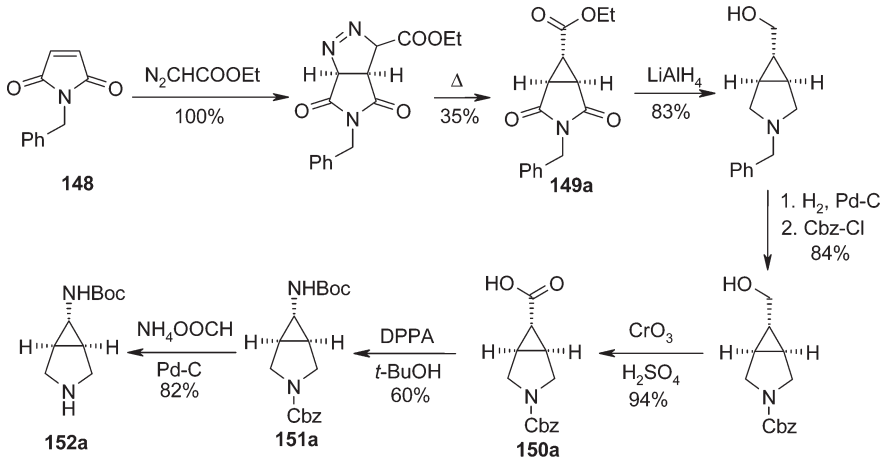
**Scheme 47**[a]




[a] DPPA, diphenylphosphoryl azide.

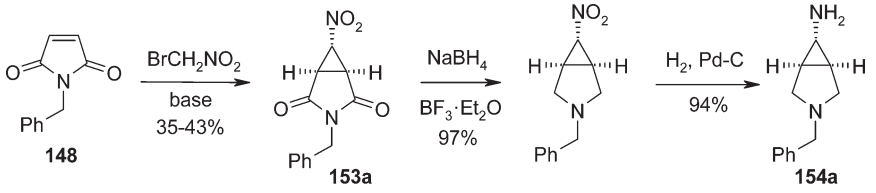

dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 48**[a]

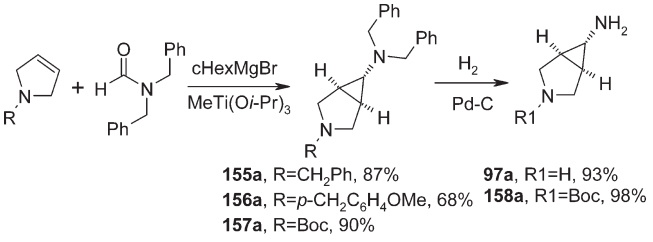



[a] DPPA, diphenylphosphoryl azide.

**Scheme 49**




**Scheme 50**




most likely because this compound was incorporated as a scaffold into the quinolone antimicrobial trovafloxacin.

One of the approaches patented by Pfizer Inc. relied on a two-step cyclopropanation of *N*-benzylmaleimide **148** with ethyl diazoacetate (Scheme 48). The bicyclo[3.1.0]hexanedione derivative **149a** thus obtained in 35% yield was reduced by lithium aluminum hydride and, after changing the protecting group, oxidized by Jones reagent to give the carboxylic acid **150a**. The latter was subjected to a Curtius rearrangement to give the orthogonally protected derivative **151a**, which was transformed into the mono-*N*-Boc-protected derivative of the diamine **97a**, i.e., compound **152a**.[60,61]

Cyclopropanation of *N*-benzylmaleimide **148** by a tandem Michael addition−nucleophilic cyclization was the key step in the synthesis of a derivative of **97a** reported by Norris et al. (Scheme 49). In this case, bromonitromethane and a base [tetra-*n*-butylammonium 2,6-di-*tert*-butylphenoxide or 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine (DMTHP)] were used to assemble the bicyclic ring system. However, the yield of the product **153a** in this step was moderate (35−43%). Compound **153a** was reduced to the derivative **154a** of the diamine **97a** with $NaBH_4$−$BF_3 \cdot Et_2O$ followed by catalytic hydrogenation. Synthesis of **152a** from **153a** was also described.[62]

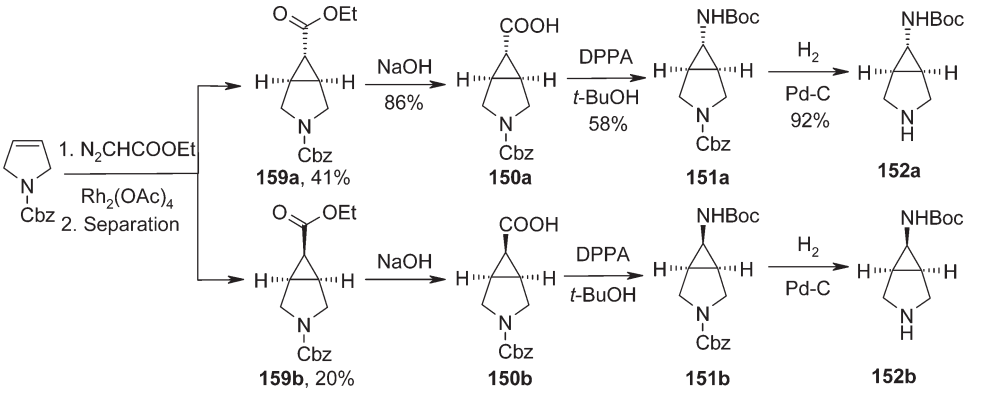
Another approach to the synthesis of **97a** and its derivatives relied on a Kulinkovich reaction of pyrrolines mediated by the *c*HexMgBr−MeTi(O*i*-Pr)$_3$ system (Scheme 50). In this reaction, the bicyclo[3.1.0]hexane derivatives **155a**−**157a** were obtained in 68−90% yields. Compounds **155a** and **157a** were transformed into diamine **97a** and its monoprotected derivative **158a**, respectively, by catalytic hydrogenation.[63]

One more reaction that has been applied in the synthesis of monoprotected **97a** and **97b** from pyrrolines exploited ethyl diazoacetate as the cyclopropanation reagent and $Rh_2(OAc)_4$ as the catalyst (Scheme 51). In this case, compounds **159a** and **159b** were obtained in 41% and 20% yields, respectively, and separated by column chromatography. After hydrolysis, both the corresponding carboxylic acids **150a** and **150b** reacted with diphenylphosphoryl azide (DPPA) and *t*-BuOH to give the Curtius rearrangement products **151a** and **151b**, which were selectively deprotected by catalytic hydrogenation.[61,64]

The method for cyclopropane ring formation described above was not stereoselective. Another approach—nucleophile-induced chloroenamine cyclization—was used for the diastereoselective synthesis of a monoprotected derivative of **97b** (Scheme 52). It began with the 4-piperidinone derivative **160**, which was transformed into the enamine **161** and then chlorinated with NCS. The compound **162** thus obtained was treated with sodium methylate and then reduced with lithium aluminum hydride to

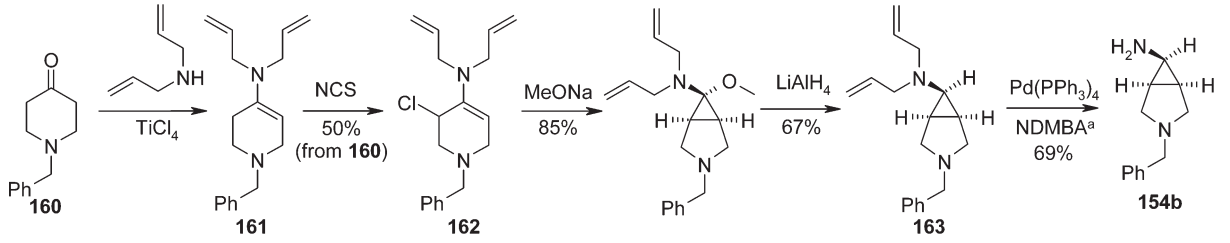

dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 51**[a]




[a] DPPA, diphenylphosphoryl azide.

**Scheme 52**[a]




[a] NDMBA, *N,N*′-dimethylbarbituric acid.

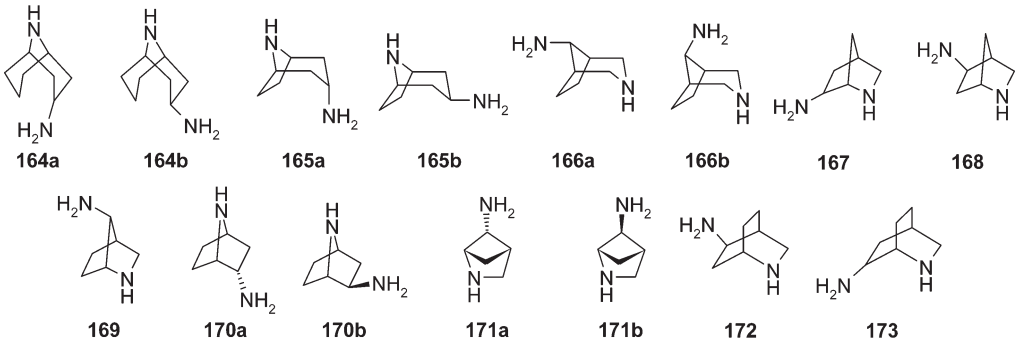



**Figure 7.** Amino azabicyclo[*m.n.*1]alkanes and -[2.2.2]octanes.

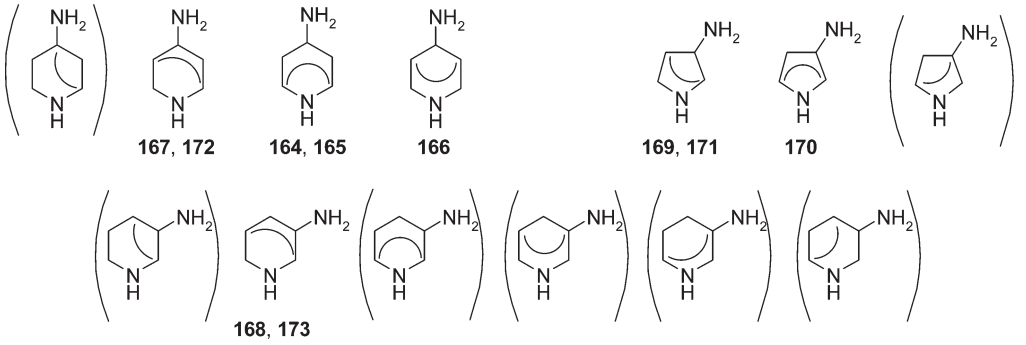



**Figure 8.** Three subtypes of bridged CRDA with one endocyclic and one exocyclic nitrogen atom (structures not reported in the literature are shown in parentheses). The curved bridge represents a one-, two-, or three-carbon chain.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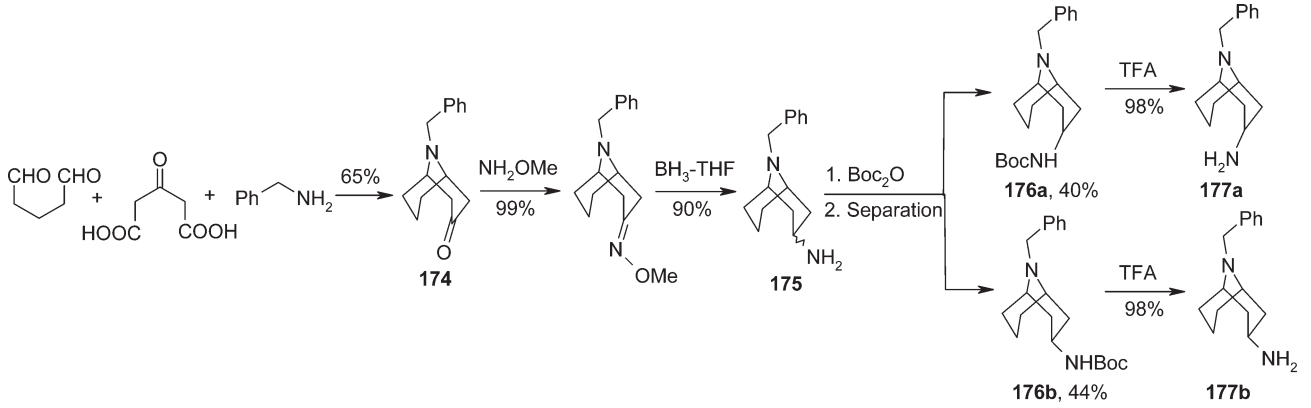
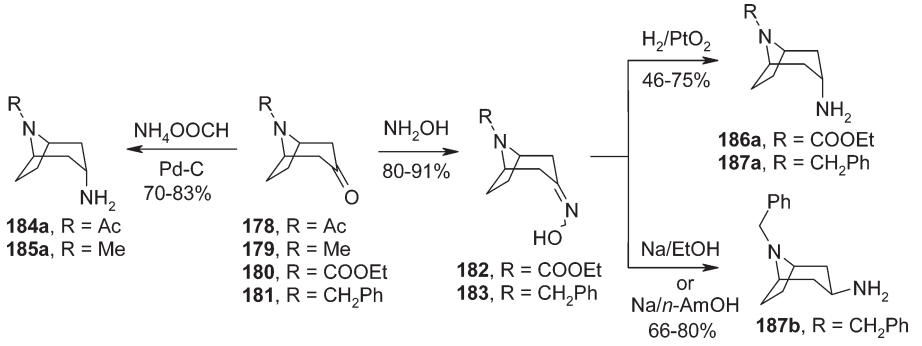
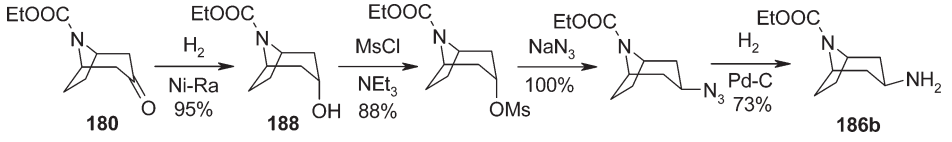
**Scheme 53**



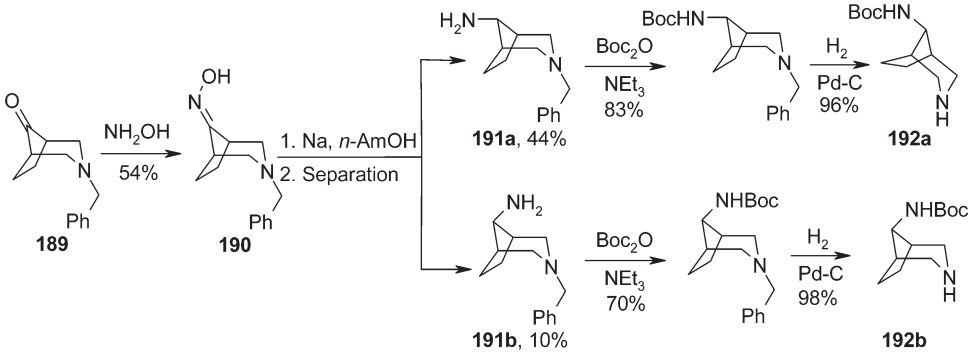

**Scheme 54**




**Scheme 55**




**Scheme 56**




give the diamine derivative **163**. The latter was selectively deprotected with $Pd(PPh_3)_4$ to give compound **154b**, a mono-protected derivative of **97b**.[65]

### 3.2. Bridged Bicyclic CRDA of Exo−Endo Type

In this section, diamines derived from bridged aza-substituted bicyclic scaffolds are discussed. They are represented mainly by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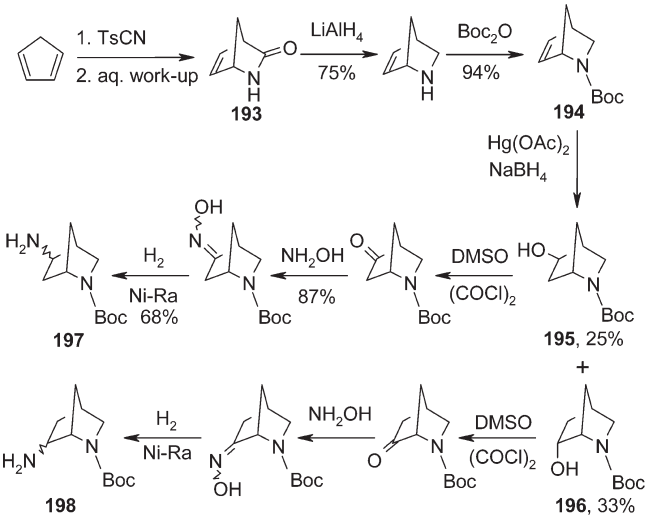
amino azabicyclo[*m.n.*1]alkanes (compounds **164**−**171**); apart from those, azabicyclo[2.2.2]octane derivatives **172** and **173** were described in the literature (Figure 7).

All the known diamines discussed in this section can be subdivided into three groups defined as those consisting of conformationally constrained derivatives of 4-aminopiperidine, 3-aminopiperidine, and 3-aminopyrrolidine (Figure 8). Other structures are theoretically possible, e.g., conformationally constrained derivatives of 3-aminoazetidine, but they are not represented by known diamines. As can be seen from Figures 7 and 8, syntheses of nearly three-quarters of the theoretically possible bridged bicyclic CRDA of exo−endo type are yet to be reported.

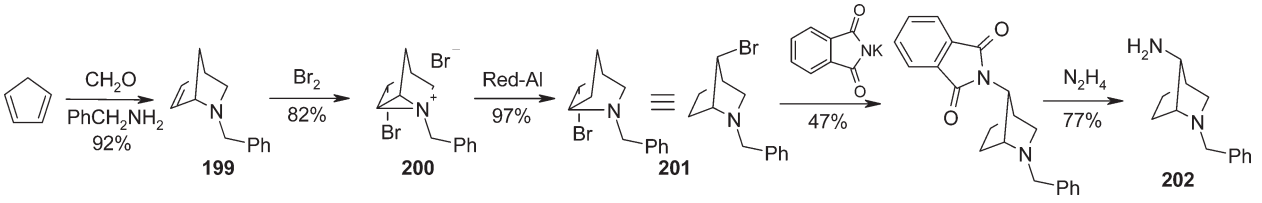
The synthesis of derivatives of the diamines **164a** and **164b** used a Robinson−Schopf reaction to give the homotropanone derivative **174** (Scheme 53). The latter was transformed into *O*-methyloxime and then reduced with borane to give diamine **175** as a 1:1 mixture of diastereomers. To obtain the single diastereomers of these compounds, they were transformed into Boc-derivatives **176** and then separated by chromatography. Selective deprotection of the primary amino group in **176a** and **176b** yielded monoprotected derivatives **177a** and **177b** of the diamines **164a** and **164b**.[66]

Analogously, the tropanone derivatives **178**−**181** were the key starting compounds in the synthesis of the monoprotected diamines **165a** and **165b** (Schemes 54 and 55). To obtain the derivatives **184a** and **185a** of the endo-isomer **165a**, the ketones **178** and **179** were subjected to direct reductive amination ($NH_4OOCH/Pd-C$).[67,68] Alternatively, the compounds **180** and **181** were transformed into the oximes **182** and **183** and then reduced by catalytic hydrogenation to give **186a** and **187a**.[69−71] Derivatives of the exo-isomer **165b** were obtained using different reaction conditions. In particular, reduction of **183** by sodium in ethanol or 1-pentanol gave the derivative **187b** of the *exo*-diamine **165b**.[70,71] The derivative **186b** of the diamine **165b** was also obtained by the transformation of **180** into the alcohol **188** followed by mesylation, substitution with azide, and catalytic hydrogenation.[71]

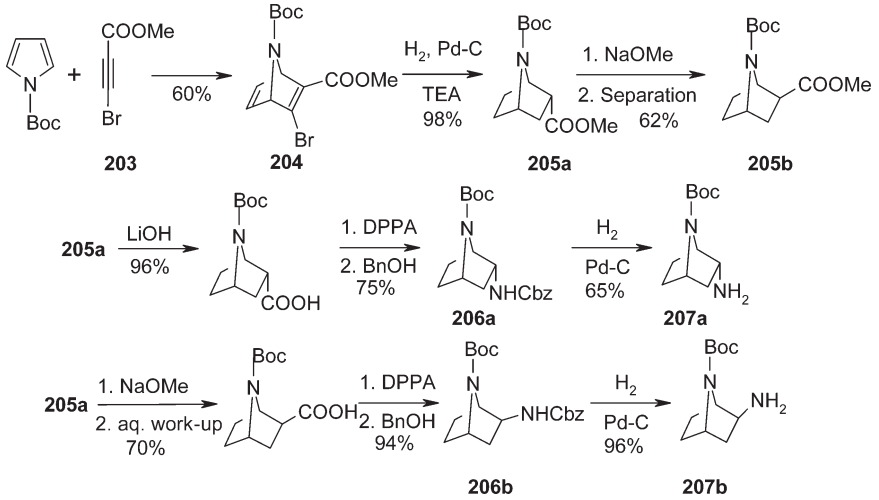
**Scheme 57**




**Scheme 58**




**Scheme 59**[a]




[a] DPPA, diphenylphosphoryl azide.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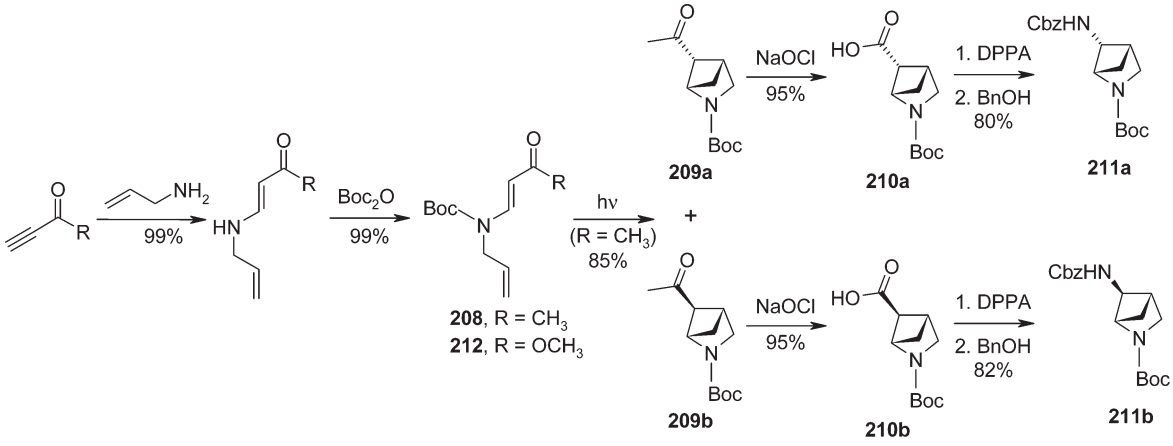
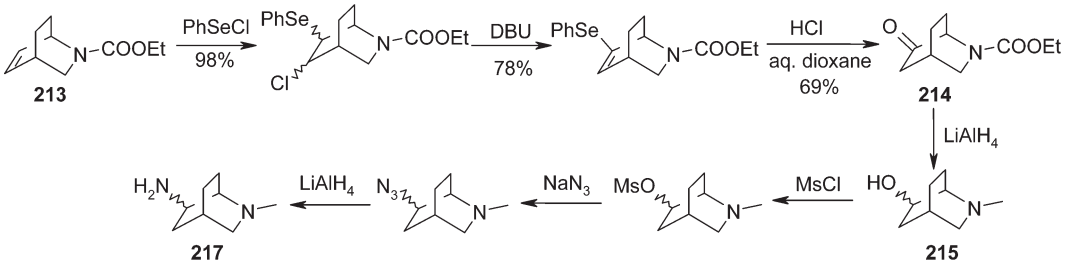
**Scheme 60**[a]




[a] DPPA, diphenylphosphoryl azide.

**Scheme 61**




An analogous approach was applied to the synthesis of monoprotected derivatives of the diamines **166a,b** (Scheme 56). In this case, ketone **189**[72] was used as a starting compound. Compound **189** was transformed into oxime **190**, which was reduced with sodium in 1-pentanol to give a mixture of the amines **191a** and **191b**. After separation by column chromatography, compounds **191a,b** were transformed into Boc derivatives **192a** and **192b** of the diamines **166a,b**.[73]

Synthesis of monoprotected derivatives of the diamines **167** and **168** commenced from Vince lactam **193** (Scheme 57). Compound **193** was reduced with lithium aluminum hydride and then *N*-protected to give **194**. Compound **194** was transformed into a mixture of the alcohols **195** and **196** (ca. 1:1), which were separated by column chromatography. Swern oxidation of **195** and **196** gave the corresponding ketones, which were then transformed into oximes and reduced to give the monoprotected derivatives **197** and **198** of **167** and **168**, respectively.[74]

Synthesis of a derivative of the diamine **169** relied on an exciting reductive rearrangement in the 2-azabicyclo[2.2.1]-heptane series (Scheme 58). First, cyclopentadiene, benzylamine, and formaldehyde were reacted to give amine **199**. The latter was brominated to give the azoniatricyclo[2.2.1.0$^{2,6}$]heptane derivative **200**. Reduction of the compound **200** with sodium bis(methoxyethyl)aluminum hydride (Red-Al) resulted in aziridine ring-opening, which led to the formation of the bromide **201**.[75] Reaction of **201** and potassium phtalimide followed by hydrazine-mediated deprotection gave the diamine **169** as the monoprotected derivative **202**.[76]

An approach to the synthesis of the diamines **170a** and **170b** (as the Boc derivatives) was based on Diels−Alder cycloaddition of the activated alkyne **203** to *N*-Boc-pyrrole (Scheme 59). The adduct **204** was hydrogenated to give the *endo*-ester **205a**. Since **205a** is the thermodynamically less stable isomer, it was transformed into **205b** by epimerization with sodium methoxide. An equilibrium mixture of **205a** and **205b** contained 75% of the *exo*-ester **205b** and was easily separated by column chromatography.[77] Both **207a** and **207b** were obtained from the endo-isomer **205a** via a Curtius rearrangement step. In the synthesis of **207b**, epimerization and hydrolysis of the ester moiety were combined into a single step without isolation of **205b**. The (1*S*,2*R*,4*R*)-isomer of the compound **207b** was obtained in optically pure form via separation of **206b** on a chiral stationary phase.[78,79]

The synthesis of monoprotected derivatives of the diamines **211a** and **211b** relied on intramolecular photochemical [2 + 2]-cycloaddition of the dienone **208** (Scheme 60). Compound **208** was obtained in two steps from 3-butyn-2-one.[80] Irradiation of **208** gave a mixture of the ketones **209a** and **209b** enriched in the syn-isomer **209b** (more than 80%). Both isomers of **209** were oxidized to the $\beta$-amino acid derivatives **210** by sodium hypochlorite.[81] Curtius rearrangement of the carboxylic acids **210a,b** then gave the differentially protected derivatives **211a,b** of the diamines **171**. It is interesting to note that irradiation of the ester **212**, an analog of **208**, gave none of the desired product.[82]

An approach to *N*-methyl derivatives of diamines **172** and **173** starting from the isoquinuclidine derivative **213**, which can be prepared by a Diels−Alder reaction (Schemes 61 and 62), has been described. Reaction of **213** with PhSeCl followed by treatment with DBU and acidic hydrolysis gave the protected amino ketone **214**,[83] which was reduced to give alcohol **215**. On the contrary, an oxymercuration−reduction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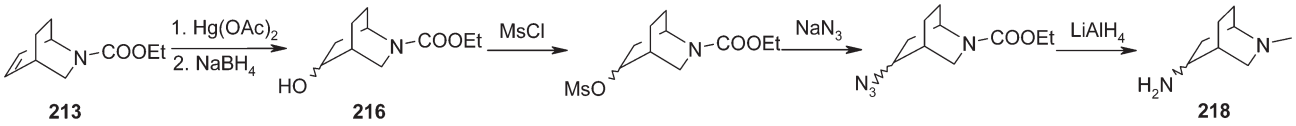
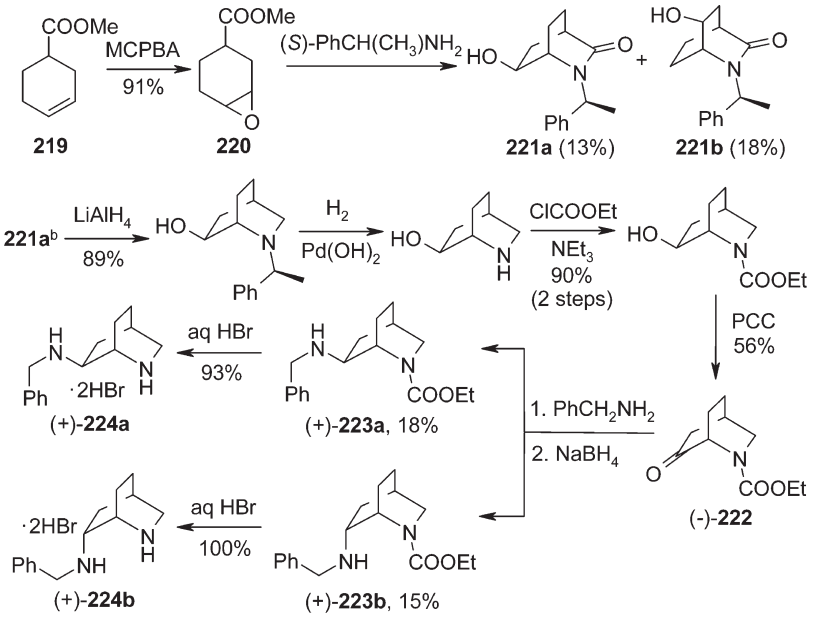
**Scheme 62**




**Scheme 63**[a]




[a] Absolute configurations are shown. [b]The same transformations were performed with **221b** to give (−)-**224a,b**.

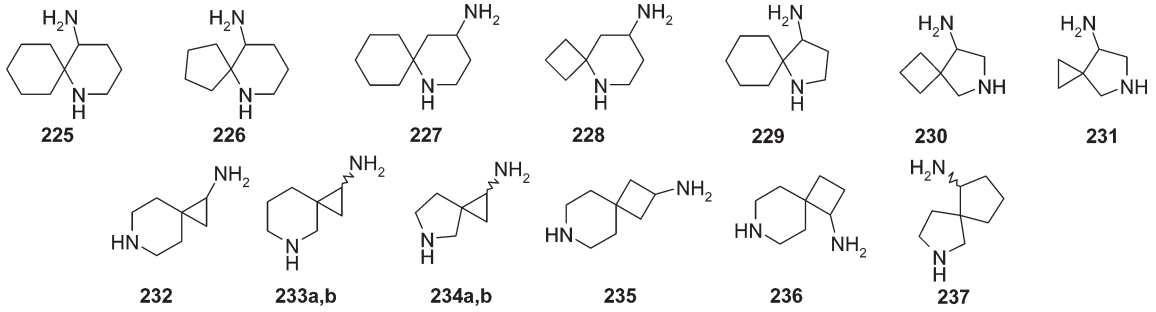



**Figure 9.** Aminoazaspiroalkanes.

reaction on **213** gave 5-hydroxy-substituted isoquinuclidine **216**. Regioselectivity of the initial steps in both the syntheses is noticeable. The alcohols **215** and **216** were transformed into derivatives **217** and **218** of the diamines **172** and **173** by a mesylation, azide substitution, and $LiAlH_4$ reduction sequence.[84]

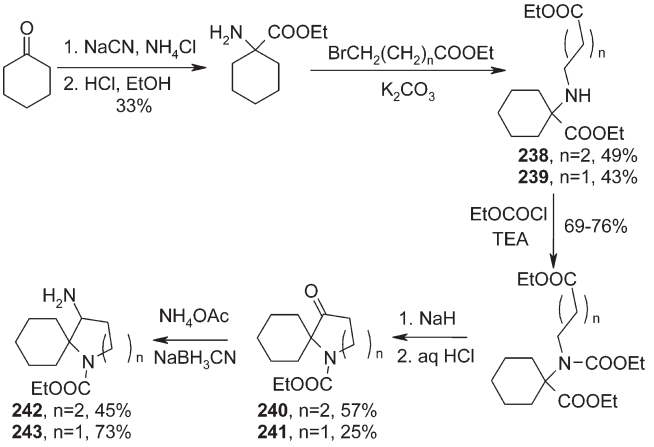
An approach to an optically pure derivative of the diamine **173** protected at the exocyclic amino group, i.e., compound (+)-**224b**, started from methyl 3-cyclohexene-1-carboxylate **219** (Scheme 63). The ester **219** was transformed into a mixture of the *cis*- and *trans*-epoxides **220**.[85] Reaction of **220** with (*S*)-α-phenylethylamine resulted in epoxide ring-opening accompanied by bicyclic lactam formation and gave a mixture of diastereomers which were separated by flash chromatography to yield **221a** (13%) and **221b** (18%). Both enantiomers of the compound **221** were reduced by $LiAlH_4$ and then, after a change of the protecting group, oxidized by pyridinium chlorochromate. The resulting ketones **222** were transformed into the corresponding imines and then reduced by $NaBH_4$ to give a mixture of the diamines **223a** and **223b**, which was separated by flash chromatography. Deprotection of the compounds **223a** and **223b** allowed the corresponding stereoisomers of the derivatives of **173** [compounds (+)-**224a,b**] to be obtained [only transformations of **221a** are shown in the Scheme 63, but the same transformations were performed with **221b** to give (−)-**224a,b**]. Racemic endo- and exo-isomers of the derivatives of **173** were also obtained when benzyl amine was used instead of (*S*)-α-phenylethylamine at the corresponding step of the synthesis.[86]


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

### 3.3. Spirocyclic CRDA of Exo−Endo Type

Compounds **225**−**237** (Figure 9) are the known spirocyclic CRDA with one exocyclic and one endocyclic amino group. Amino azaspiroalkanes can be subdivided into two groups: those in which both amino functions are in the same ring and those in which the exocyclic amino group is not on the heterocyclic ring. The known diamines of the first group (**225**−**231**) can be considered as derivatives of 3-aminopyrrolidine or 4-aminopiperidine, similar to the case of the bridged CRDA discussed in the previous section. The number of theoretically possible structures in the second group is rather large; nevertheless, all of the diamines described in the literature (**232**−**237**) are the derivatives of only azaspiro[4.4]-, -[5.3]-, -[5.2]-, or -[4.2]alkane cores.

**Scheme 64**



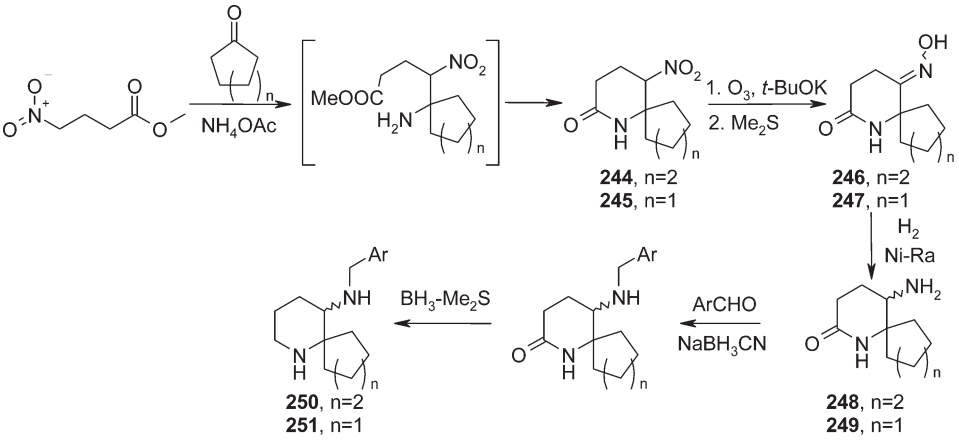

The syntheses of the monoprotected derivatives of the diamines **225** and **229** started from ethyl 1-aminocyclohexane carboxylate, which was reacted with the corresponding bromo ester (or acrylate) to give amino esters **238** and **239** (Scheme 64). Compounds **238** and **239** were subjected to *N*-protection followed by Dieckmann condensation, hydrolysis, and decarboxylation. This step completed construction of the spirocyclic system. The amino ketone derivatives **240** and **241** obtained were subjected to reductive amination to give **242** and **243**.[87]

In another synthesis, derivatives of **225** and **226** were obtained from methyl 4-nitrobutanoate (Scheme 65). This starting compound was reacted with the corresponding cycloalkanone and ammonium acetate to undergo imine formation—a Mannich-type reaction—and a lactam formation sequence to give the spiropiperidones **244** and **245**.[88] The latter were converted to the oximes **246** and **247** via the modified Nef reaction. Reduction of the compounds **246** and **247** with Raney Nickel gave the amines **248** and **249**. The compounds **248** and **249** can be directly reduced by $BH_3 \cdot Me_2S$ to give **225** and **226**, as was described for their *N*′-*o*-methoxybenzyl derivatives **250** and **251**.[89]

The amino spiropiperidines **227** and **228** (as the Boc derivatives) were obtained by reaction of the corresponding cycloalkanones and the 4-amino-2-butanone ketal **252** to form the spiropiperidones **253** and **254** (Scheme 66).[90] The key step of the sequence was a Mannich-type intramolecular cyclization which presumably was preceded by the dioxolane ring-opening. The compounds **253** and **254** were Boc-protected and then subjected to reductive amination to give the Boc-protected derivatives **255** and **256**.[91]

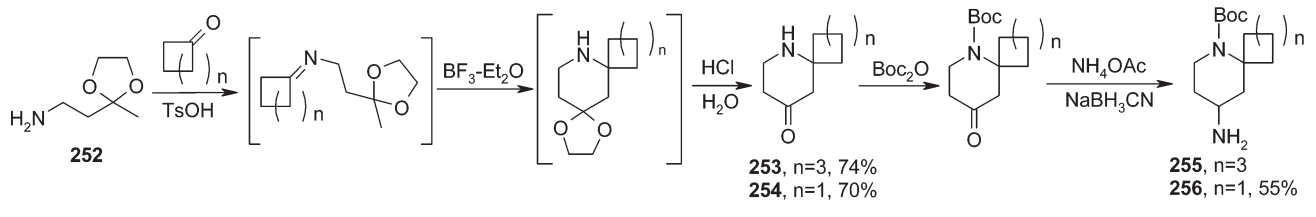
Synthesis of an optically pure derivative of the diamine **230** started with diethyl cyclobutane-1,1-dicarboxylate, which was

**Scheme 65**[a]




[a] Ar, 2-methoxyphenyl.

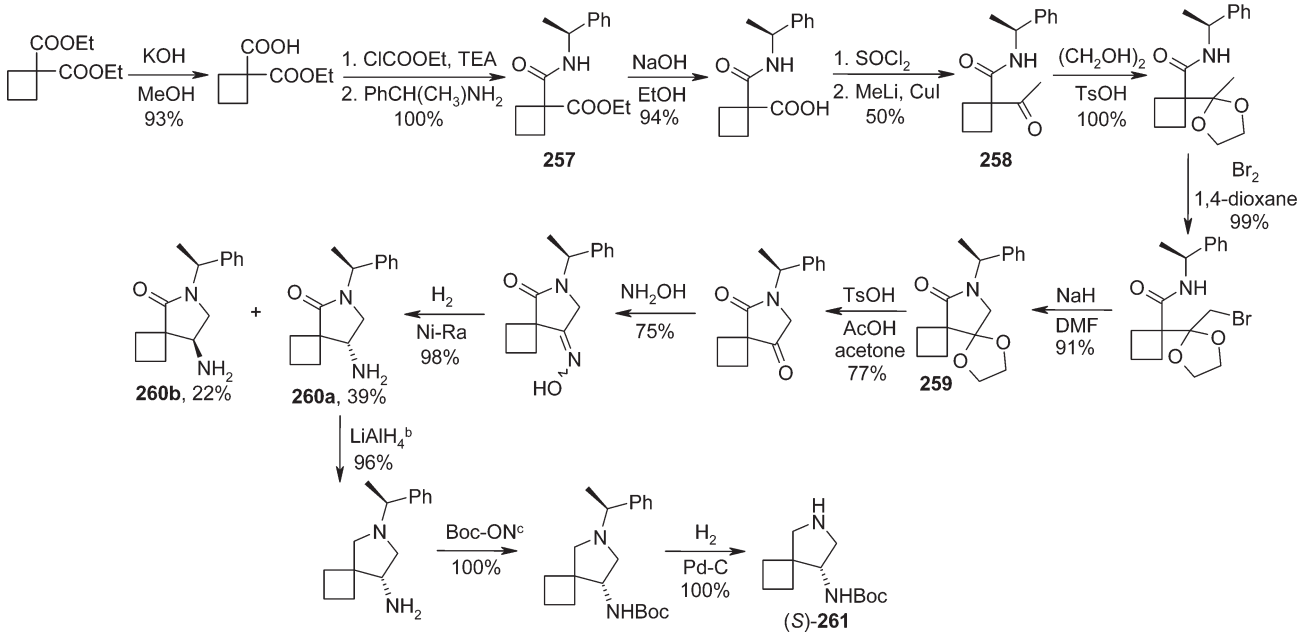
**Scheme 66**





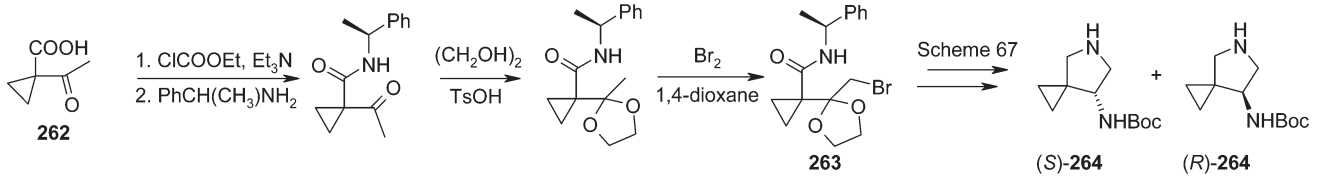
dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 67**[a]



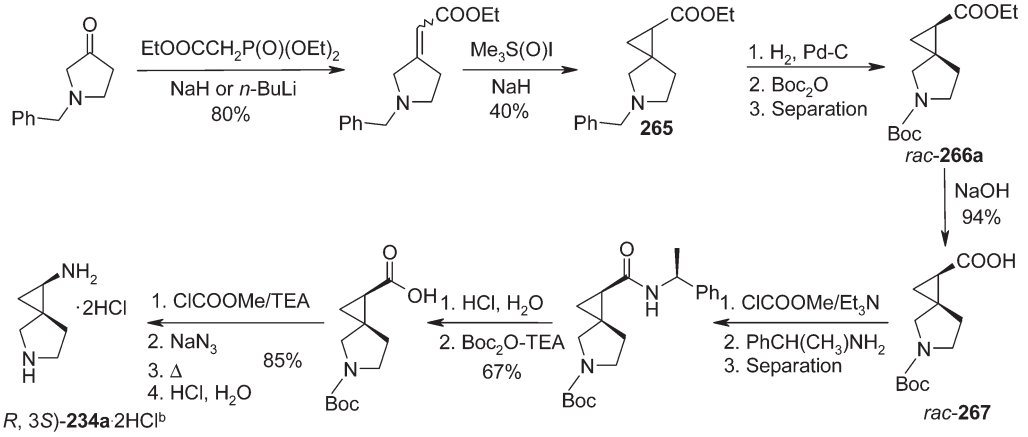

[a] Absolute configurations are shown. [b]The same transformations were performed with **260b** to give (*R*)-**261**. [c]Boc-ON, Boc-imino-2-phenylacetonitrile.

**Scheme 68**[a]




[a] Absolute configurations are shown.

**Scheme 69**[a]

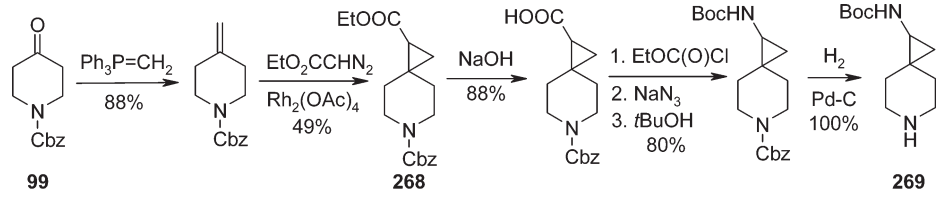



[a] Except **266a** and **267**, absolute configurations are shown. All four stereoisomers of **234** were obtained in this reaction sequence; only the (1*R*, 3*S*)-**234a** synthesis is shown.

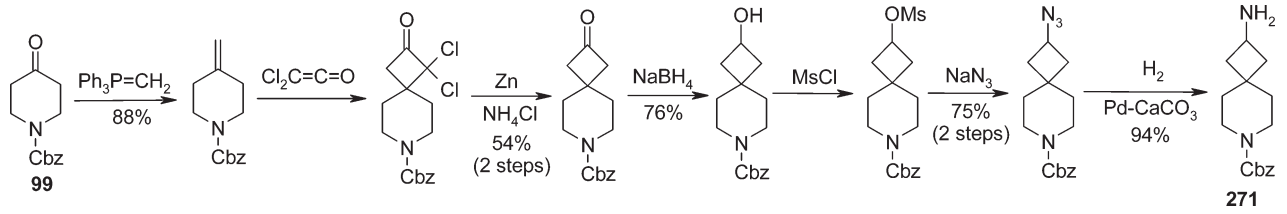
transformed into the monoamide **257** in four steps (Scheme 67). The latter was converted to ketone **258** via Cu(I)-mediated methyllithium addition to the corresponding acid chloride. (Compound **258** was synthesized by using this rather lengthy reaction sequence instead of by using the double alkylation of the corresponding acetoacetic acid derivative since the latter failed.)


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

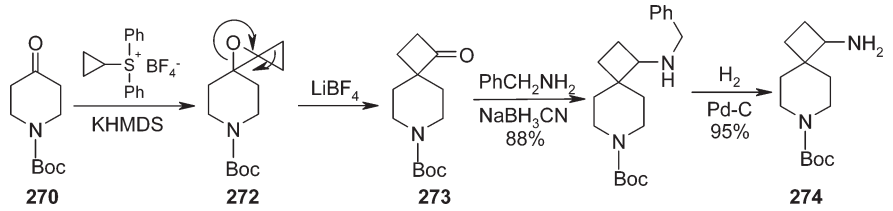
**Scheme 70**



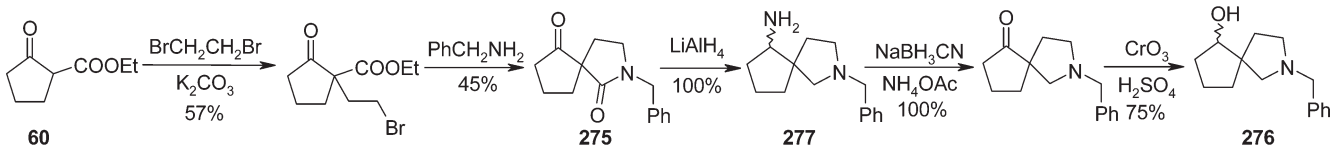

**Scheme 71**




**Scheme 72**




**Scheme 73**



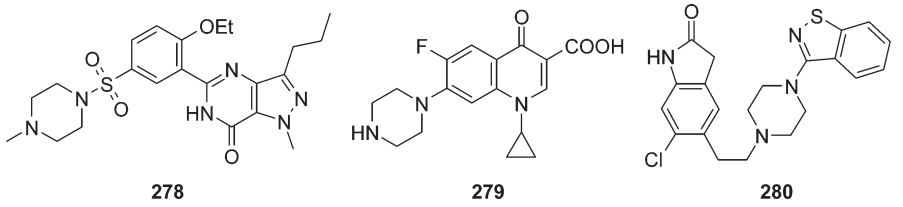




**Figure 10.** Examples of marketed drugs containing a piperazine scaffold.

After protection of the carbonyl group in **258**, it was brominated and then treated with sodium hydride to give the spiro compound **259**. Further transformations included deprotection, oxime formation, and reduction to get the amine **260**. Diastereomers of **260** were separated by column chromatography and then reduced with $LiAlH_4$, reacted with Boc-imino-2-phenylacetonitrile (Boc-ON), and hydrogenated to give the optically pure monoprotected derivatives **261** of diamines (*R*)- and (*S*)-**230**. (The synthesis of the (*S*)-isomer is shown in Scheme 67).[92]

An analogous approach was applied to the synthesis of a protected derivative of the diamine **231** (Scheme 68). In this case, the $\beta$-keto acid **262** was used as a starting compound and transformed into the bromide **263** in three steps. The synthetic


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

route **263** → **264** was exactly the same as described above for the synthesis of **261**.[93]

Syntheses of cyclopropane-containing diamines **232**−**234** started with 1-benzyl-4-piperidone, 1-benzyl-3-piperidone, and 1-benzyl-3-pyrrolidone, respectively. For example, in the synthesis of diamine **234** (Scheme 69), 1-benzyl-3-pyrrolidone was subjected to the Horner−Wadsworth−Emmons reaction followed by Corey−Chaikovsky cyclopropanation to give ester **265**. After changing the protecting group, the diastereomers of **266** were separated by column chromatography. The resulting esters **266a,b** were hydrolyzed to give *N*-Boc-protected amino acid derivatives **267a,b**. Enantiomers of the compounds **267a,b** were separated via column chromatography of the corresponding *N*-(α-phenylethyl)amides and then subjected to Curtius rearrangement. Thus, optically pure diamines **234a,b** were obtained. Syntheses of diamines **232** and **233a,b** were done in an analogous way. Racemic compounds **232**−**234** were also obtained using this approach.[94]

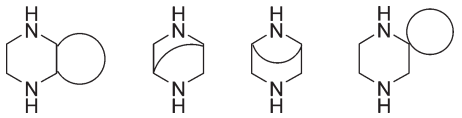


**Figure 11.** Conformationally restricted piperazine analogs.

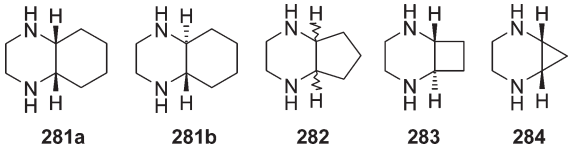
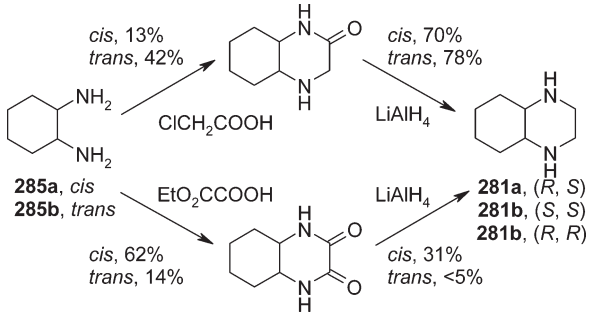
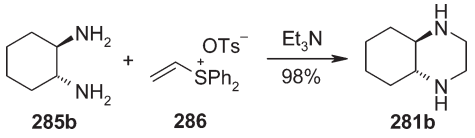



**Figure 12.** Fused conformationally restricted piperazine analogs.

**Scheme 74**




**Scheme 75**

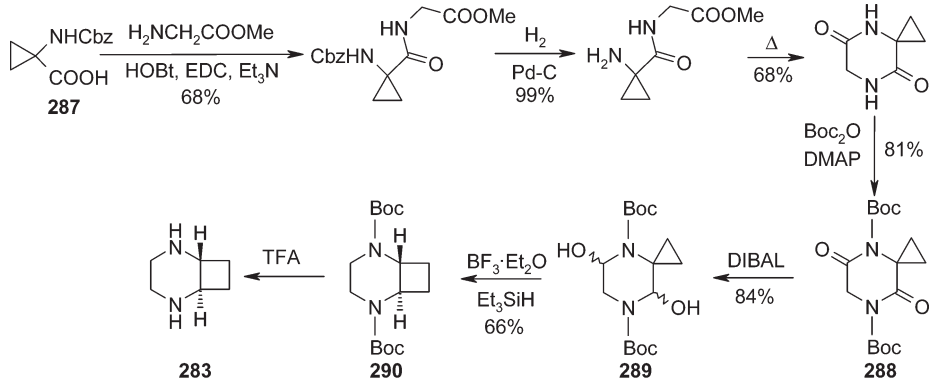



## 4. SYNTHESIS OF BICYCLIC CRDA WITH TWO ENDOCYCLIC NITROGEN ATOMS

### 4.1. Piperazine Analogs

The piperazine scaffold has been widely used in drug discovery; in particular, it can be found in the molecules of sildenafil (Viagra) (**278**),[99] ciprofloxacin (**279**),[100] and ziprasidone (**280**)

**Scheme 76**[a]




[a] HOBt, hydroxybenzotriazole; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

(Figure 10).[101] Therefore, it is not surprising that piperazine analogs are among the most numerous of the diamines discussed in this review. Several ways are illustrated in Figure 11 to attach an element such as a (poly)methylene bridge to the piperazine structure to restrict its conformational flexibility. To date, most of these compound types have been synthesized. Because of the importance of the piperazine scaffold for drug design, the piperazine-derived CRDA are discussed in a separate section.

**4.1.1. Fused Bicyclic CRDA.** The diamines **281**−**284** shown in Figure 12 are fused piperazines; syntheses of **281**, **283**, and **284** have been reported in the literature. No synthesis of **282** has been reported, but it was identified among the components of roasted almond flavor using GS−MS analysis.[102]

The *cis*-diamine **281a** was obtained by catalytic hydrogenation of quinoxaline,[103] tetrahydroquinoxaline,[104] or 2-(β-aminoethylamino) cyclohexanol.[105] In another approach, all three isomers of the compound **281** were obtained from the corresponding 1,2-diaminocyclohexanes **285a** and **285b** (Scheme 74); the enantiomers (+)-**281b** and (−)-**281b** were separated by resolution with dibenzoyl-D-tartaric acid (DBTA).[106,107] A newer approach to the synthesis of **281b** included reaction of the diamine **285b** with the vinyl sulfonium salt **286** (Scheme 75). The bis-electrophile **286** was successfully used to form the piperazine ring via a tandem Michael addition−intramolecular nucleophilic substitution.[108]

The synthesis of piperazine **283** started from compound **287**, a derivative of 1-aminocyclopropanecarboxylic acid (Scheme 76). This was transformed into the di-*N*-Boc-piperazine-2,5-dione **288** and then reduced with DIBAL to give compound **289**. The latter underwent ring expansion to **290** upon treatment with $BF_3 \cdot Et_2O-Et_3SiH$. Deprotection of **290** gave the diamine **283**. The authors reported an unusual trans-fusion of the cyclobutane and piperazine rings in **283**.[109]

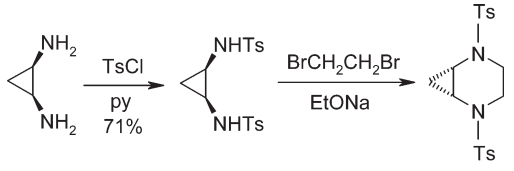
The diamine **284** was reported as its bis-tosyl derivative **291**, which was prepared from *cis*-1,2-diaminocyclopropane **292** via double alkylation (Scheme 77).[110]

**4.1.2. Bridged Bicyclic CRDA.** Two types of bridged piperazine analogs are possible depending on which atoms of the parent piperazine are connected by the bridge. Known "2,5-bridged" piperazine analogs, compounds **293**−**296**, are shown in Figure 13. In these diamines, the piperazine ring is fixed in a (distorted) boat conformation. On the other hand, in the known "2,6-bridged" piperazine analogs (**297**−**300**), the piperazine ring is fixed in a chair conformation by the bicyclic core of the diamine molecules.

Synthesis of the diamine **293** started from the allylglycine ester **301**, which was transformed into the dipeptide **302** using standard procedures (Scheme 78). The azocine derivative **303** was then obtained through a ring-closing metathesis of **302**.[111] This was followed by intramolecular cyclization of **303** to give the diketopiperazine **304**,[112] which was transformed into the piperazine **293** in several steps.[113]

Synthesis of the diamine **294** started from 2,6-diaminoheptanedioic acid **305**, which was converted into the dimethyl ester **306** and then transformed into the diamide **307** upon heating (Scheme 79). Transformation of **307** into the diamine **294** was

**Scheme 77**




292 291

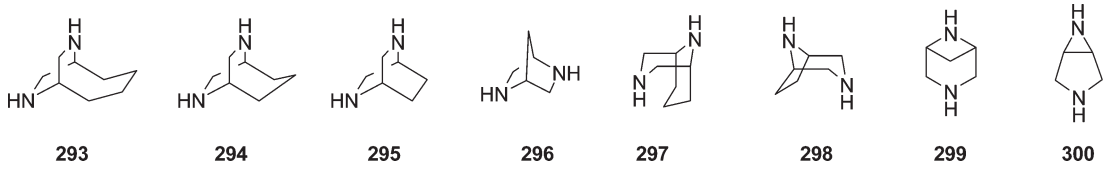
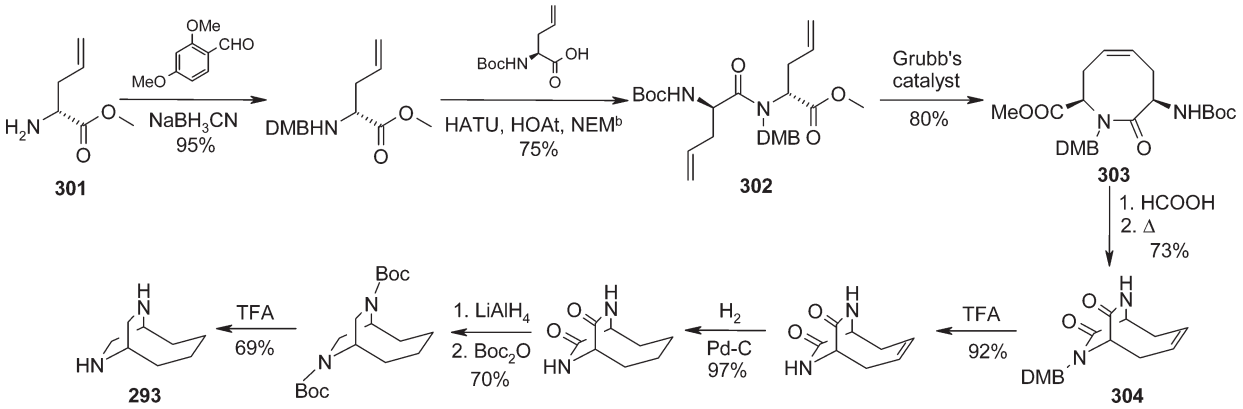



**Figure 13.** Bridged conformationally constrained piperazine analogs.

**Scheme 78**[a]

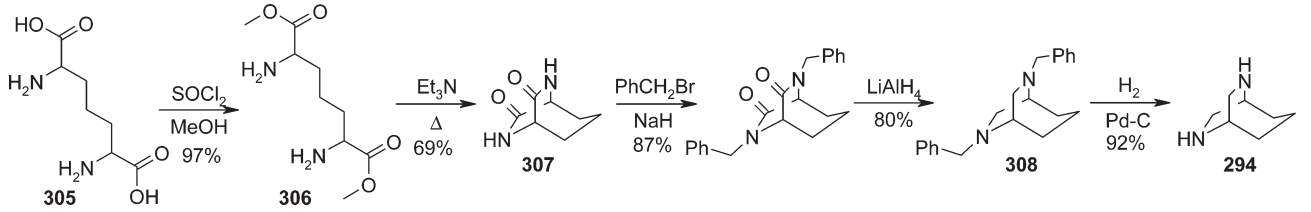



301 302 303 304 293

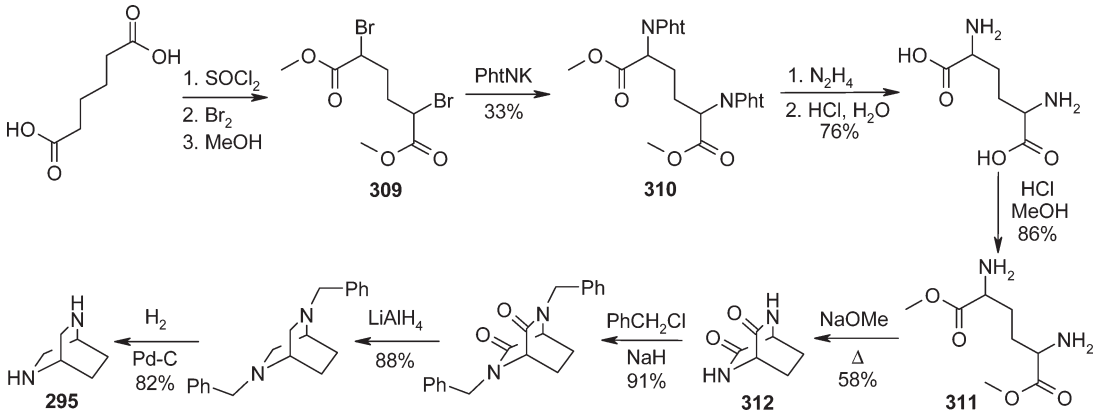
[a] Absolute configurations are shown. HATU, 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOAt, 1-hydroxy-7-azabenzotriazole; NEM, *N*-ethylmorpholine; DMB, 2,4-dimethoxybenzyl.


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 79**

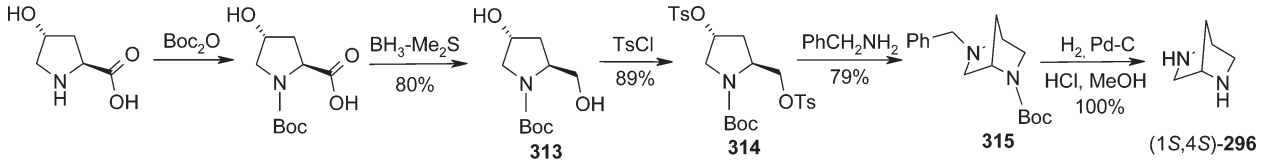



**Scheme 80**[a]



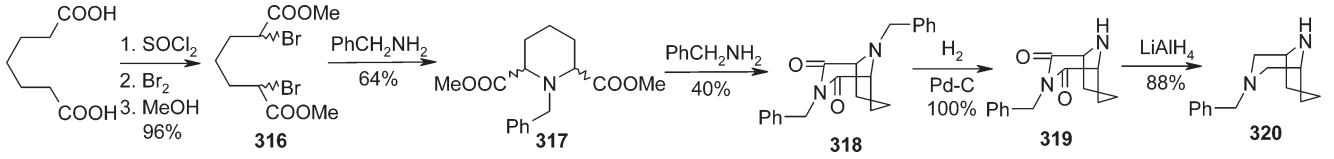

[a] Pht, phtaloyl.

**Scheme 81**[a]




[a] Absolute configurations are shown.

**Scheme 82.** [118b]




achieved either via the dibenzyl derivative **308**[114] or by direct reduction.[115]

An analogous approach was used to obtain the diamine **295** (Scheme 80). In this case, adipic acid was converted to the α,α′-dibromo ester **309**, which was reacted with an excess of potassium phtalimide and then deprotected to give the derivative **310**. Hydrolysis of **310** followed by esterification gave the diester **311,** which underwent base-promoted cyclization to give the diketopiperazine **312.** Compound **312** was then transformed into the diamine **295** in a way analogous to the synthesis of **294** from **307**.[116]

Both enantiomers of the diamine **296** were synthesized from L-4-hydroxyproline as the starting compound.[117] In particular, L-4-hydroxyproline was transformed into the diol **313** and then tosylated to give the derivative **314** (Scheme 81). Refluxing of **314** with benzyl amine in toluene yielded the diazanorbornane **315**. The diamine (1*S*,4*S*)-**296** was then finally obtained from deprotection of **315**. Synthesis of (1*R*,4*R*)-**296** was performed analogously via the enantiomer of compound **314** that was obtained from D-4-hydroxyproline. The latter was prepared from the L-isomer via inversion of both of the chiral centers.[117a]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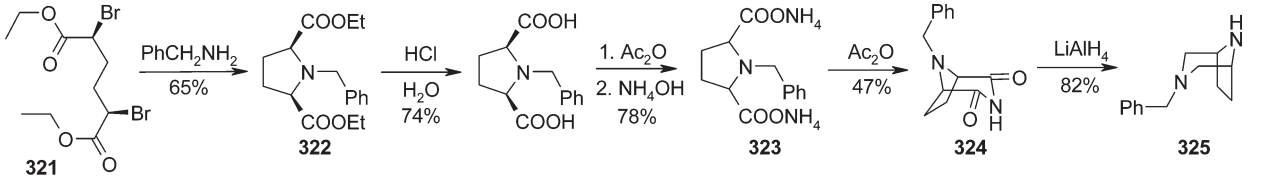
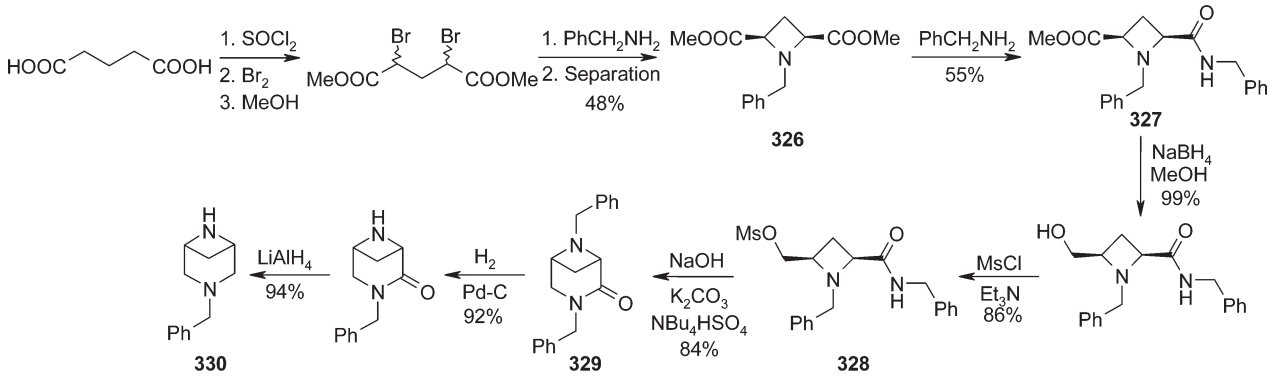
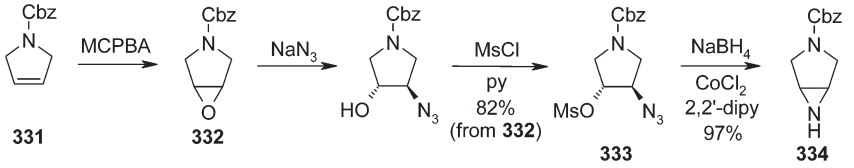
**Scheme 83.** [119c]




**Scheme 84**




**Scheme 85.** [122a]



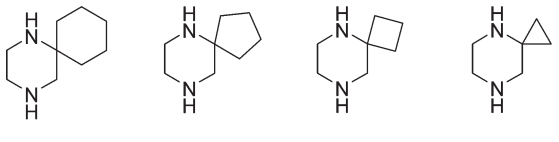
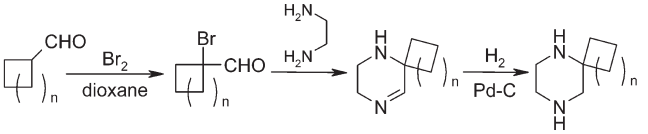




**Figure 14.** Spirocyclic conformationally constrained piperazine analogs.

Synthesis of the monoprotected derivative of the diamine **297** started from pimelic acid, which was transformed into the α,α′-dibromo ester **316** (Scheme 82). Compound **316** was reacted with benzylamine to give the piperidine **317** as a mixture of diastereomers, which, as such, was reacted with benzylamine to form the imide **318** (isolated as the hydrochloride). Apparently, only *cis*-**317** underwent the cyclization but this simpler procedure was preferred to that involving a preliminary separation of the diastereomers by flash chromatography followed by condensation of *cis*-**317** with benzylamine because the simpler procedure gave a comparable overall yield of **318**. Catalytic hydrogenation of **318** resulted in selective deprotection to give amine **319**. Finally, compound **319** was reduced with lithium aluminum hydride to give the monoprotected derivative **320**.[118]

**Scheme 86**

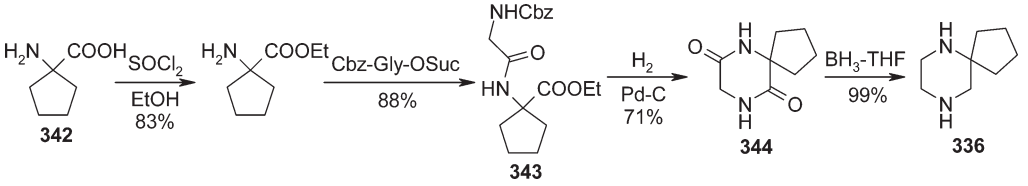



A derivative of the diamine **298** was prepared analogously starting from *meso*-α,α′-dibromoadipate **321** (Scheme 83).[119] Reaction of the diester **321** with benzylamine gave the pyrrolidine derivative **322**, which was transformed into the ammonim salt **323** followed by cyclization to give **324** upon heating in acetic anhydride. The imide **324** thus obtained was reduced by lithium aluminum hydride to give the monoprotected derivative **325**. Selective protection of **298** at each of the nitrogen atoms was achieved (not shown).[120]

A similar method was used to obtain the monoprotected derivative of the diamine **299** (Scheme 84). Analogously to the preparation of **320** and **325**, the first steps of the synthesis included cyclization, in this case with formation of the azetidine

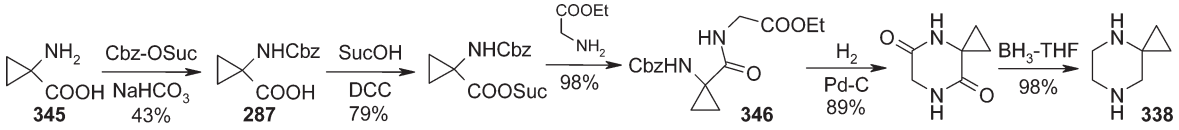

dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 87**[a]




[a] Suc, succinimide residue.

**Scheme 88**[a]




[a] Suc, succinimide residue.

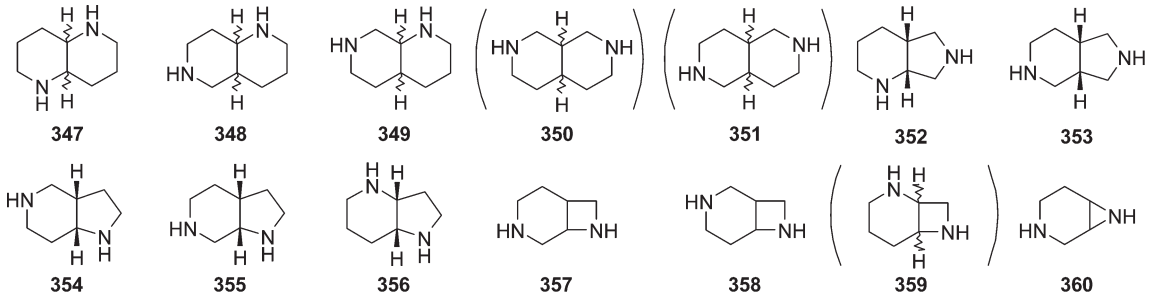
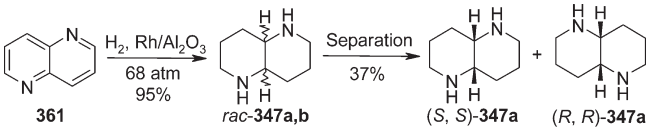
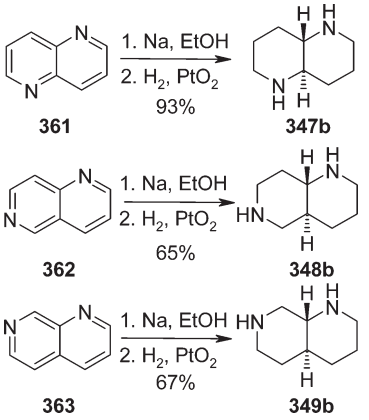



**Figure 15.** Diazabicyclo[4.*n*.0]alkanes.

**Scheme 89**




**Scheme 90**




**326**. Reaction of **326** with benzylamine gave the amide **327**; further cyclization, however, did not occur. To make the cyclization step more favorable, the compound **327** was transformed into mesylate **328**, which further reacted smoothly with a base to give the diazabicyclo[3.1.1]heptane derivative **329**. Further transformations of **329** were analogous to those described for **318** and led to the formation of the monoprotected derivative **330**.[121]

Synthesis of the monoprotected derivative of the aziridine-containing diamine **300** started from pyrroline **331**, which was transformed into the epoxide **332** (Scheme 85). Reaction of **332** with sodium azide followed by mesylation gave the compound **333**, which was reduced by $CoCl_2$−$NaBH_4$−2,2′-dipy to give the monoprotected derivative **334**.[122]

**4.1.3. Spirocyclic CRDA.** All of the theoretically possible spiro analogs of piperazine containing up to six-membered spiro-connected rings have been described in the literature (compounds **335**−**338**, Figure 14).

One of the approaches to the synthesis of the diamines **335**−**337** used the aldehydes **339**−**341** as starting compounds to be brominated in dioxane and then reacted with ethylenediamine to give imines (Scheme 86), which were then hydrogenated to give **335**−**337**.[123]

Another approach to the synthesis of the diamine **336** used the amino acid **342** as the starting material (Scheme 87). It transformed into the dipeptide derivative **343** using activation of the glycine carboxylic group via formation of the *N*-hydroxysuccinimide ester. Upon deprotection, the compound **343** so formed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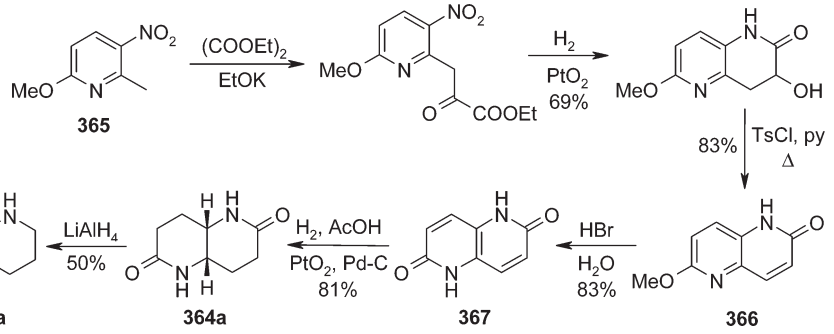
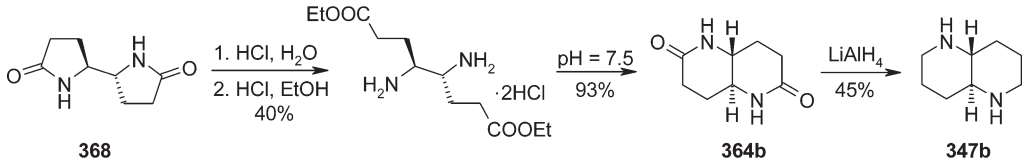
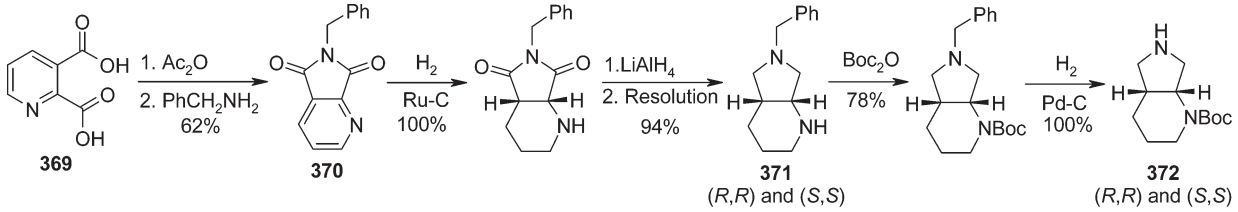
Scheme 91




Scheme 92




Scheme 93[a]




[a] After the resolution step, absolute configuration is shown for only (*R*,*R*)-isomers.

underwent cyclization to give the diketopiperazine **344**, which was reduced to yield the piperazine derivative **336**.[124]

A slightly different method was used for the synthesis of the piperazine analog **338** (Scheme 88). In this case, amino acid **345** was first transformed into dipeptide **346**. Further reactions of **346** were then analogous to those described above for the synthesis of **336** (however, see also ref 109 and Scheme 76).[124]

## 4.2. Other Fused Bicyclic CRDA of Endo−Endo Type

**4.2.1. Diazabicyclo[4.*n*.0]alkanes.** All of the theoretically possible diazabicyclo[4.*n*.0]alkanes ($n \leq 4$) (except for the piperazine analogs discussed in the previous section) are shown as compounds **347**−**360** (Figure 15). Of these diamines, only the compounds shown in parentheses (**351** and **359**) have not been described in the literature. Although compound **350** was used as a building block in the design of nicotinic acetylcholine receptor ligands,[125] its synthesis was not reported.

Synthesis of the diamine **347a** started from 1,5-naphthyridine **361** (Scheme 89). High-pressure catalytic hydrogenation of **361** resulted in the formation of a mixture of the cis- and trans-isomers **347a** and **347b** in which the cis-isomer **347a** predominated (cis:trans = 9:1). After recrystallization, racemic **347a** was resolved using (+)-tartaric acid.[126−128]

Trans-isomers of the diamines **347**−**349** were obtained by a two-step reduction of the corresponding naphthyridines **361**−**363** (Scheme 90). The intermediate products were not characterized.[127]

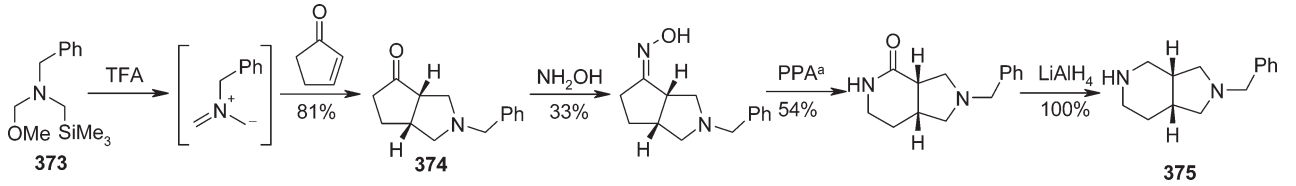
Alternatively, the cis- and trans-isomers of **347** were obtained by reduction of the corresponding lactams **364a,b** (Schemes 91 and 92, respectively). Synthesis of **364a** started from the pyridine derivative **365**, which was transformed into the naphthyridine derivative **366** in three steps. Compound **366** was hydrolyzed to give naphthyridine-2,6-dione **367**. Reduction of **367** gave the lactam **364a**, which was then reduced further to give the diamine **347a**. The *trans*-isomer **347b** was obtained from the pyrrolidin-2-one photodimer **368** in three steps.[129]

A derivative of the diamine **352** was obtained from pyridine-2,3-dicarboxylic acid **369** (Scheme 93). Compound **369** was transformed into the imide **370** via the corresponding anhydride. The benzyl derivative **371** was obtained by hydrogenation of **370** followed by $LiAlH_4$ reduction. The enantiomers of the **371** so obtained were resolved using tartaric acid. The Boc-derivative **372** was also prepared.[130]

[3 + 2]-Cycloaddition reactions using ylide precursor **373** have been widely used as key steps for the construction of bicyclic CRDA. For example, the synthesis of a derivative of the diamine **353** started from cyclopentenone, which underwent [3 + 2]-cycloaddition with **373** to give the bicyclic ketone **374** (Scheme 94). The compound

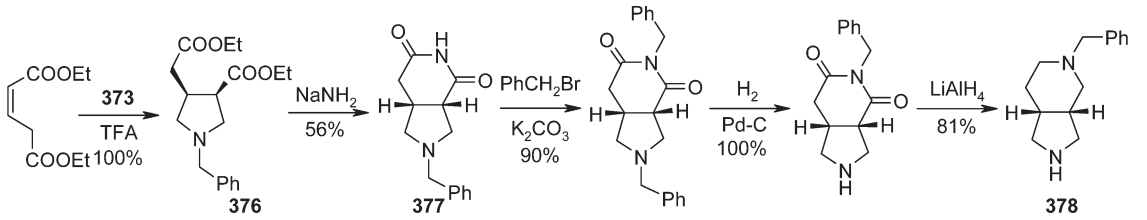

dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 94**[a]

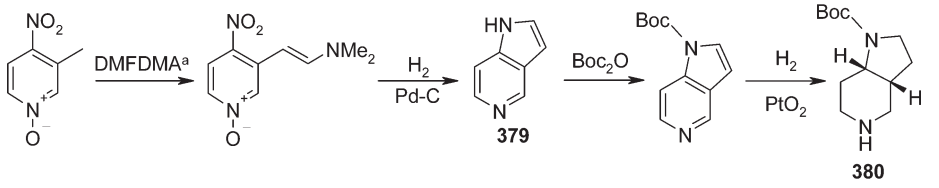



[a] PPA, polyphosphoric acid.

**Scheme 95**

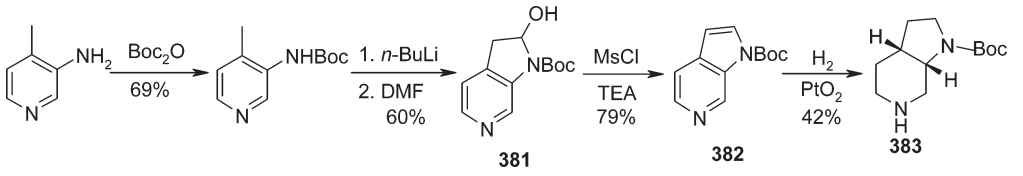



**Scheme 96**[a]

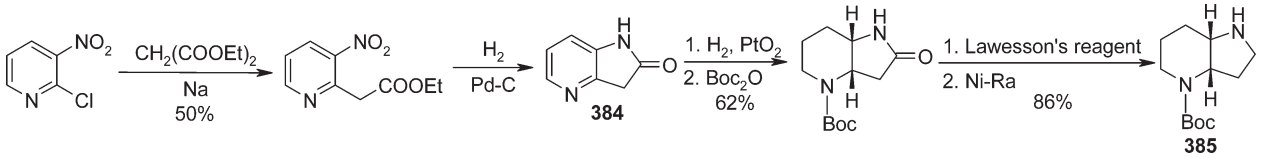



[a] DMFDMA, dimethylformamide dimethyl acetal.

**Scheme 97**




**Scheme 98**



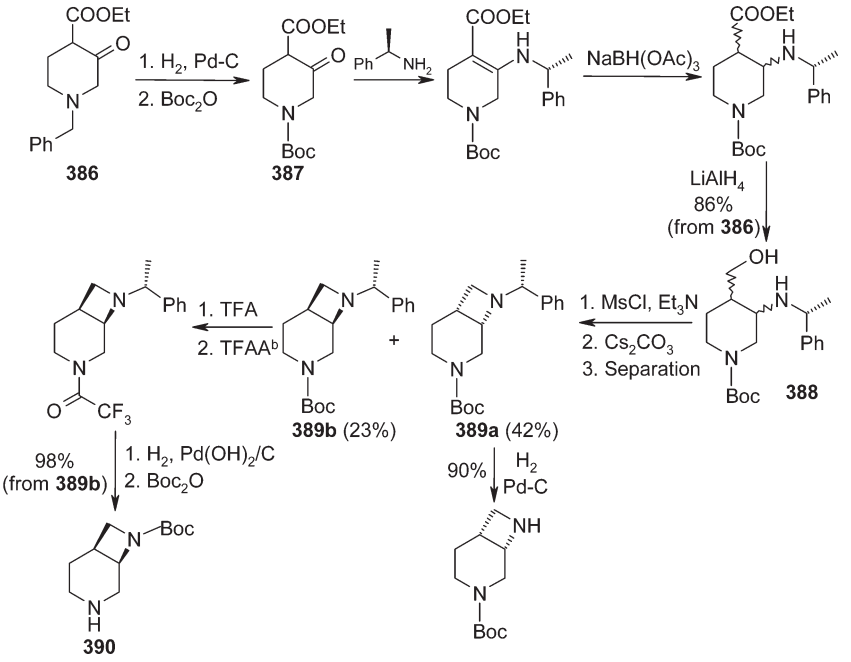

**374** was transformed into oxime in 33% yield and then subjected to Beckmann rearrangement followed by reduction to give the monoprotected derivative of **353** (compound **375**).[131]

Another derivative of the compound **353** was obtained using a more straightforward approach starting from diethyl glutaconate (Scheme 95), which upon [3 + 2]-cycloaddition with **373** gave the diester **376**. The compound **376** so obtained was then reacted with sodium amide to give the imide **377**, which was transformed into the monoprotected derivative **378** in three steps.

The Boc-protected derivative of the diamine **354** was obtained from 5-azaindole **379** (Scheme 96), which was prepared from 3-methyl-4-nitropyridine-1-oxide in two steps. The compound

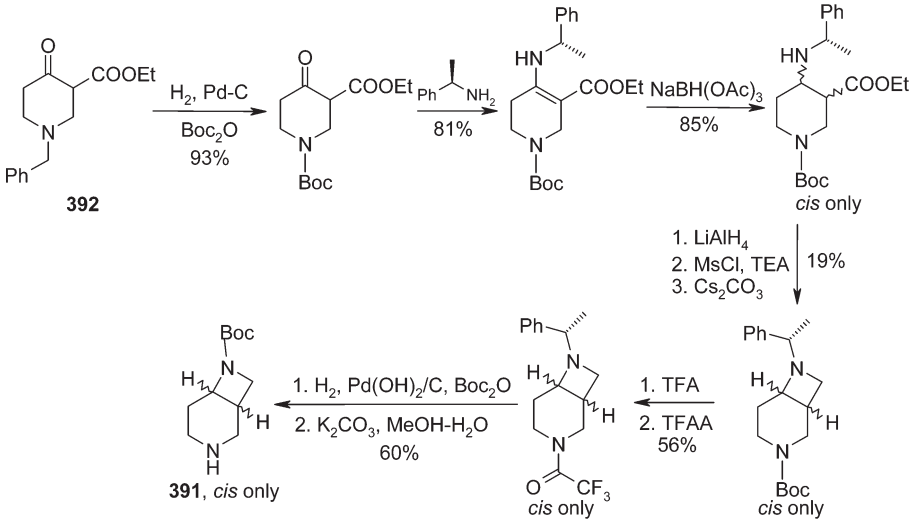

dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 99**[a]



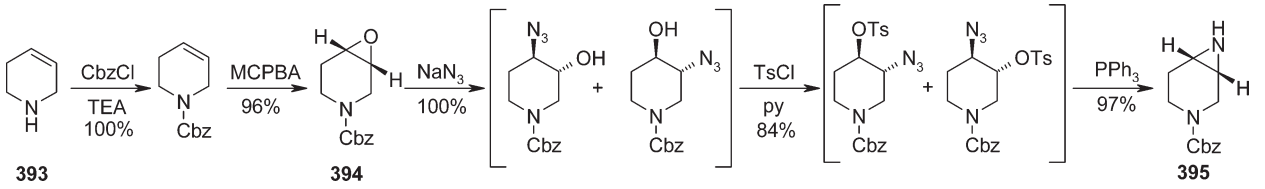

[a] Absolute configurations are shown. TFAA, trifluoroacetic anhydride.

**Scheme 100**[a]




[a] Absolute configuration of the α-phenylethylamine moiety is shown.

**Scheme 101**




**379** was reacted with Boc-anhydride and then hydrogenated to give the monoprotected derivative **380**.[132]

Synthesis of the Boc-protected derivative of the diamine **355** was performed starting from 3-amino-4-methylpyridine (Scheme 97),


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

which was *N*-protected and treated with *n*-BuLi and then with DMF to give the fused heterocyclic compound **381**. Dehydration of **381** via a mesylation step gave the pyrrolo[2,3-*c*]pyridine derivative **382**. The latter was hydrogenated to obtain the monoprotected derivative **383**.[133]

Hydrogenation of the dihydropyrrolo[3,2-*b*]pyridine derivative **384** was used as the key step to obtain the monoprotected diamine derivative **385** (Scheme 98).[98]

Synthesis of optically pure derivatives of the azetidine **357** started from commercially available 1-benzyl-3-oxo-4-piperidinecarboxylate **386** (Scheme 99). After the change of protecting group as a first step, the resulting compound **387** was subjected to a two-step reductive amination followed by reduction with $LiAlH_4$ to give the amino ester **388**. Mesylation and $Cs_2CO_3$-induced cyclization of **388** gave a mixture of fused azetidines **389a** (42%) and **389b** (23%), which were readily separated by column chromatography. Monodeprotection of **389a** via direct hydrogenation succeeded; in the case of **389b**, additional protecting group manipulations were done to obtain **390**.[131,133a,134]

A monoprotected derivative of the diamine **358**, compound **391**, was obtained in racemic form (despite the use of a chiral auxiliary) in an analogous way starting from the 1-benzyl-4-oxo-3-piperidinecarboxylate **392** (Scheme 100).[128]

Synthesis of the Cbz derivative of the fused aziridine **360** started from 1,2,3,6-tetrahydropyridine **393** (Scheme 101), which was *N*-protected and then transformed into the epoxide **394**. The compound **394** underwent ring-opening followed by tosylation and aziridine ring formation to give the monoprotected derivative **395**.[135]

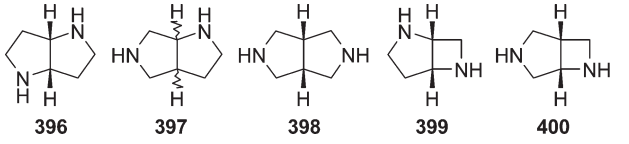
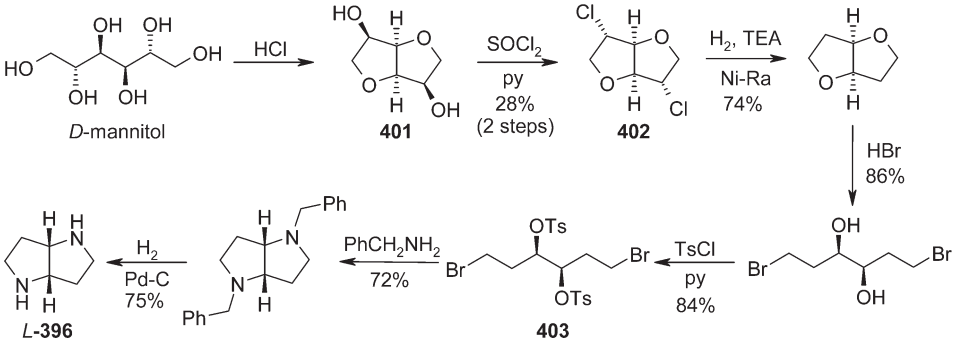


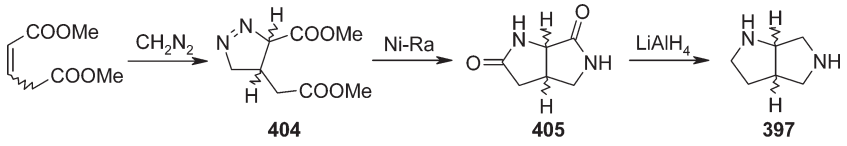

**Figure 16.** Diazabicyclo[3.*n*.0]alkanes.

**Scheme 102**[a]

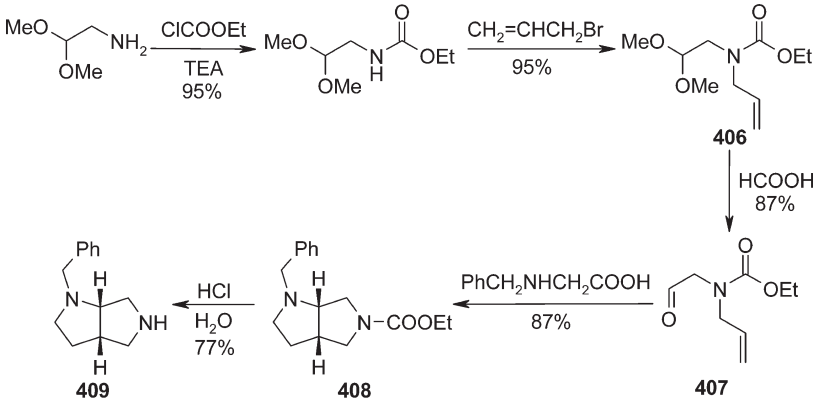



[a] Absolute configurations are shown.

**Scheme 103**




**Scheme 104**





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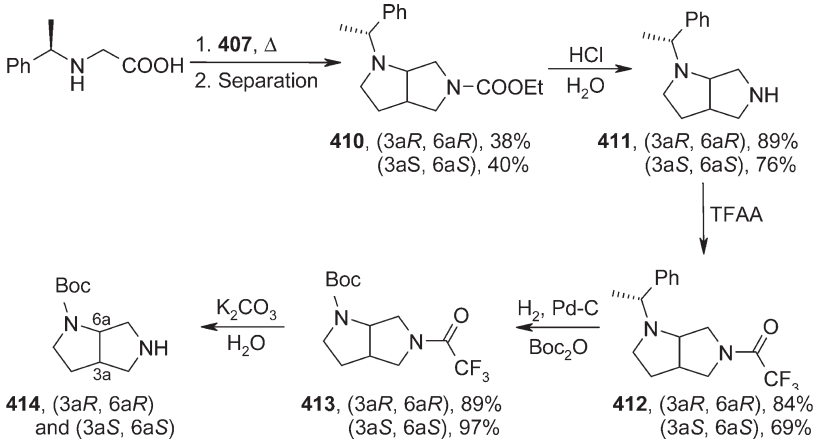
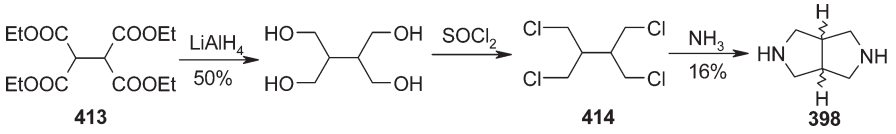
**Scheme 105**[a]

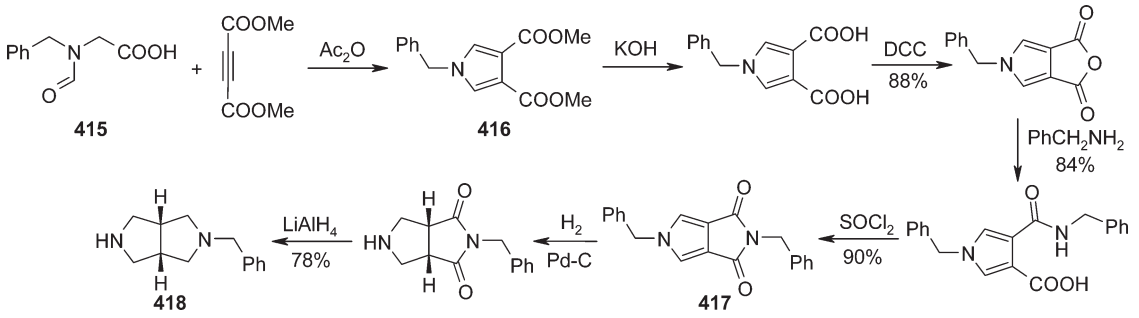



[a] Syntheses of both enantiomers of **410**−**414** are shown in the same scheme; configurations at C-3a and C-6a in the formulas are not shown. TFAA, trifluoroacetic anhydride.

**Scheme 106**




**Scheme 107**




**4.2.2. Diazabicyclo[3.*n*.0]alkanes.** Syntheses of all of the theoretically possible diazabicyclo[3.*n*.0]alkanes ($n$ = 2, 3) **396**−**400** have been reported in the literature (Figure 16).

The optically pure diamine **396** was obtained from D-mannitol, which was transformed into isomannide **401** by heating with fuming hydrochloric acid (Scheme 102). The diol **401** was then treated with thionyl chloride to give the dichloride **402**.[136] The compound **402** was hydrogenated, allowed to react with hydrogen bromide, and then tosylated to give the ditosylate **403**. Reaction of **403** with benzylamine followed by catalytic hydrogenation gave the diamine L-**396**. Partial deprotection was also achieved in the latter transformation, giving thereby the monobenzyl derivative of **396** in 52% yield.[137]

An early synthesis of the diamine **397** included reaction of dimethyl glutaconate with diazomethane to obtain the pyrazoline **404** (Scheme 103), which smoothly underwent a recyclization reaction upon catalytic hydrogenation to give the diamide **405**, which was in turn reduced with lithium aluminum hydride to obtain diamine **397**.[138]

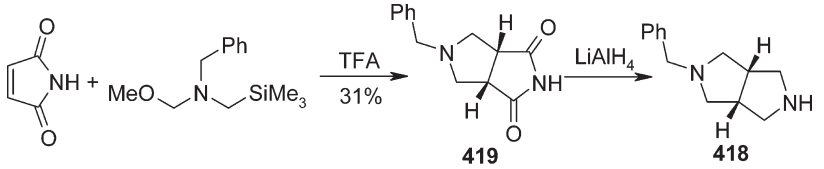
A more recent approach to derivatives of **397** started from aminoacetaldehyde dimethyl acetal, which, after protection, was alkylated to give the carbamate **406** (Scheme 104). Compound **406** was deprotected, and the aldehyde **407** so formed was treated with *N*-benzylglycine to give **408**. The mechanism of this elegant transformation was not given in the original publications, but presumably it included iminium salt formation, decarboxylation, and intramolecular [3 + 2]-cycloaddition. The derivative **408** was transformed into the monoprotected diamine **409** upon acidic hydrolysis.[139]

In an analogous synthesis, both enantiomers of a derivative of the diamine **397** were obtained using α-phenylethylamine as a chiral auxiliary (Scheme 105).[133a]

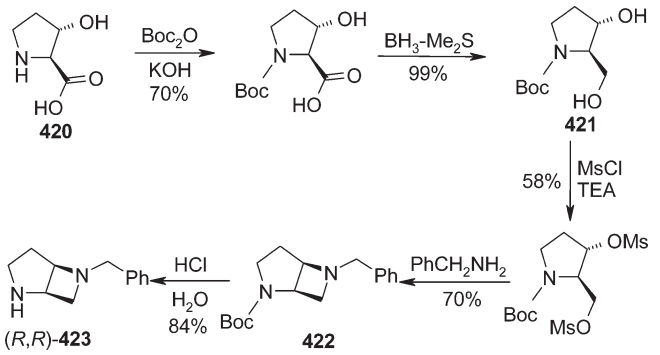
Several approaches to the synthesis of diamine **398** and its derivatives have been reported in the literature. In particular, compound **398** was obtained from tetraester **413** (Scheme 106),


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 108.** [98]

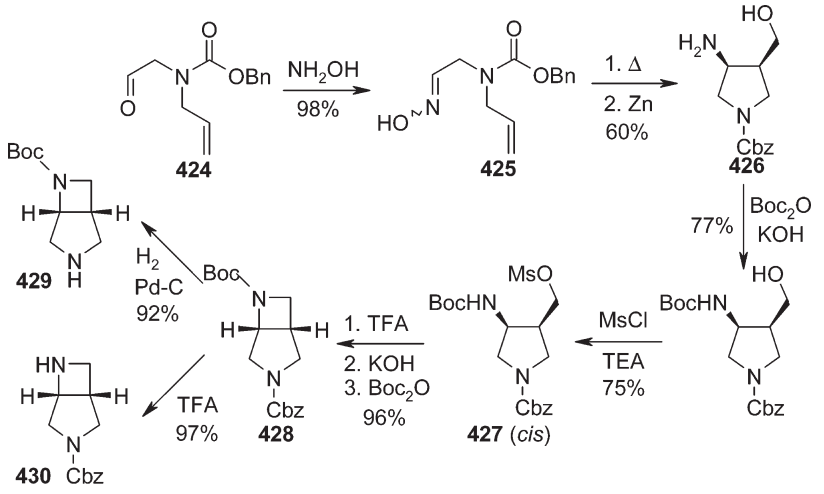



**Scheme 109**[a]




[a] Absolute configurations are shown.

**Scheme 110**




which was transformed into tetrachloride **414** in two steps and then allowed to react with ammonia to give **398**.[140] Another approach relied on [3 + 2]-cycloaddition of dimethyl acetylenedicarboxylate and the ylide generated by acylation of the glycine derivative **415** (Scheme 107). The pyrrole **416** so formed was transformed into imide **417** and then reduced in two steps to give the monoprotected diamine **418**.[141] In the recent publications, another [3 + 2]-cycloaddition reaction was used as the key step of the synthesis, namely, the transformation of maleimide leading to the formation of **419** (Scheme 108), which was then reduced to **418**.[98,131,133a]

Synthesis of an optically active derivative of the diamine **399** was reported starting from (2*S*,3*S*)-3-hydroxyproline **420** (Scheme 109). Protection of **420** followed by reduction with $BH_3-Me_2S$ gave the alcohol **421**. Treatment of **421** with mesyl chloride followed by benzylamine gave the 2,6-diazabicyclo-[3.2.0]heptane derivative **422**, and hydrolysis of **422** gave the monoprotected derivative **423** as a single enantiomer.[133a]

Finally, the derivatives of the diamine **400** were synthesized from the aldehyde **424** (prepared analogously to **407**; see Scheme 104), which was transformed into the oxime **425** (Scheme 110). Under reflux in xylene, **425** underwent intramolecular [3 + 2]-cycloaddition to yield the intermediate isoxazolidine, which was treated with zinc powder to give the pyrrolidine derivative **426**. Protection of **426** followed by mesylation gave the mesylate **427**, which cyclized upon deprotection. The product of this transformation was isolated as the derivative **428**. Either of the protecting groups in the molecule of **428** can be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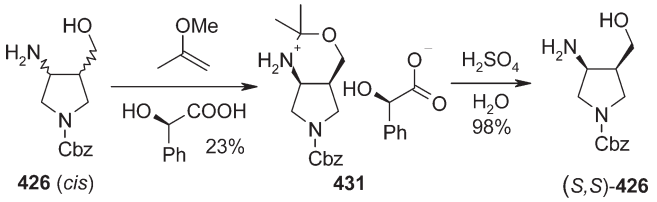
removed selectively, thus giving the monoprotected derivatives of the diamine **400**, compounds **429** and **430**.[133a]

**Scheme 111**[a]




[a] Absolute configurations are shown.

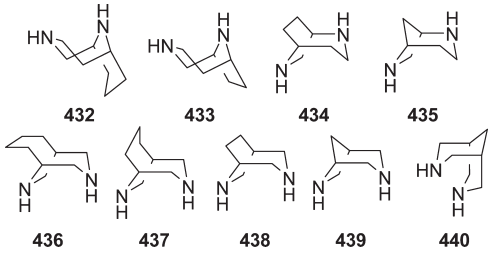



**Figure 17.** Bridged bicyclic CRDA of endo−endo type.

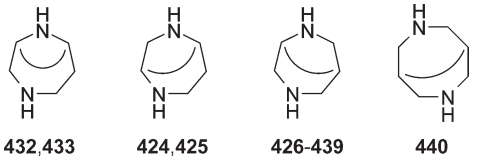



**Figure 18.** Four types of bridged bicyclic CRDA. The curved bridge represents a one-, two-, or three-carbon chain.

Synthesis of the optically pure derivative of **400** via resolution of racemic **426** was also reported (Scheme 111). In order to separate the enantiomers of **426**, it was treated with 2-methoxypropene and (*R*)-mandelic acid to give the hexahydropyrrolo[3,4-*d*][1.3]oxazine derivative **431** in 23% yield. Compound **431** was then hydrolyzed to give enantiopure (*S*,*S*)-**426**. Further transformations were analogous to those described above for the racemate (Scheme 110) and led to (*S*,*S*)-**430**. Another enantiomer, (*R*,*R*)-**430**, was also obtained when (*S*)-mandelic acid was used for the resolution.[131,133a]

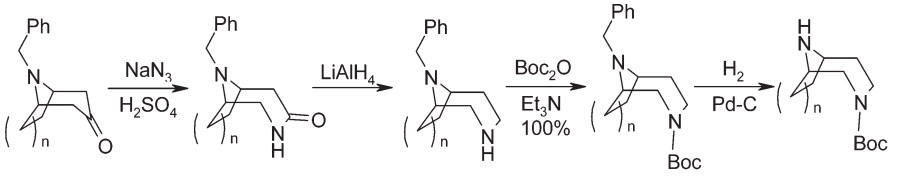
### 4.3. Other Bridged Bicyclic CRDA of Endo−Endo Type

Apart from the diazabicyclo[*m.n.k*]alkanes that were discussed in sections 4.1 and 4.2, there are other examples of bridged bicyclic CRDA of endo−endo type, in particular, compounds **432**−**440** (Figure 17). Of these, compounds **432**−**439** can be considered as bridged 1,4-diazepane derivatives, but **440** is instead a conformationally constrained bicyclic 1,5-diazocane analog (Figure 18).

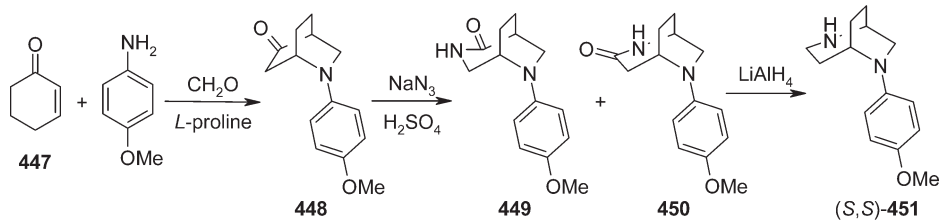
The synthesis of derivatives of the diamines **432** and **433** (Scheme 112) relied on the Schmidt rearrangement of the corresponding bicyclic ketones **174** and **181** (see section 3.2). The amides **441** and **442** obtained in these reactions were reduced with lithium aluminum hydride to give the monoprotected derivatives **443** and **444**, respectively. Compounds **445** and **446** protected at the other nitrogen atoms were also obtained.[142]

An optically pure derivative of the diamine **434** was synthesized using an L-proline-catalyzed reaction of *p*-anisidine, cyclohexen-2-one **447**, and formaldehyde that led to the formation of ketone **448** (Scheme 113). The authors claimed that the transformation was the first example of a direct enantioselective organocatalytic aza-Diels−Alder reaction.[143] Schmidt rearrangement of **448** gave amides **449** and **450** in a mixture that was subsequently separated. Compound **450** was reduced with lithium aluminum hydride to give the monoprotected derivative **451** of the diamine (*S*,*S*)-**443**. Cerium ammonium nitrate (CAN) oxidation removed the *p*-methoxyphenyl protecting group in subsequent steps of the synthesis.[144]

**Scheme 112**



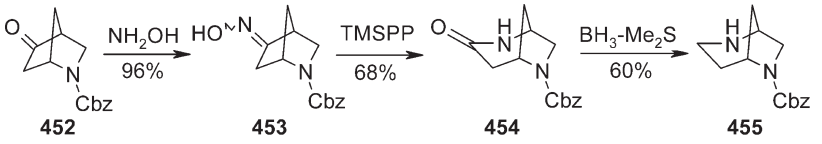

**Scheme 113**[a]




[a] Absolute configurations are shown.

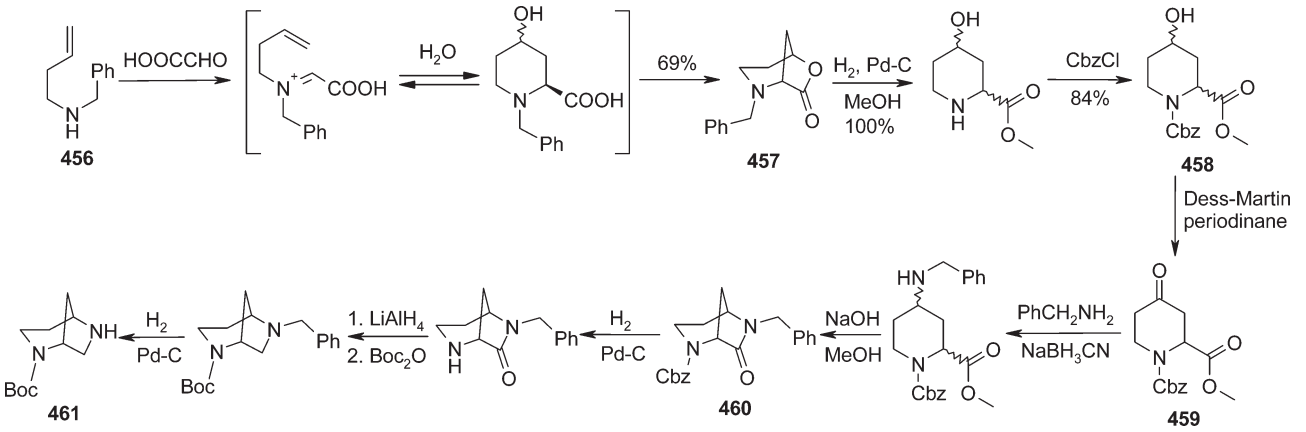

dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 114**[a]

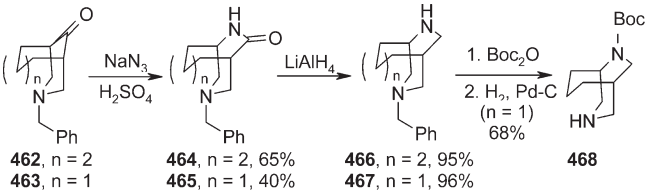



[a] TMSPP, poly(trimethylsilyl phosphate).

**Scheme 115**




**Scheme 116**




Analogously, the ketone **452**[145] was transformed into the oxime **453**, which was subjected to Beckmann rearrangement to give the amide **454** (Scheme 114). Reduction of compound **454** with $BH_3-Me_2S$ gave the monoprotected derivative **455** of the diamine **435**.[131,146]

Alternatively, a derivative of the diamine **435** was prepared starting from the amine **456**, which was reacted with glyoxylic acid to form the bicyclic lactone **457** (Scheme 115). The mechanism of this step suggested by the authors included a concerted olefin−iminium ion cyclization followed by lactionization. Hydrogenation of **457** followed by N-protection gave the alcohol **458**,[147] which was oxidized to give the ketone **459**. The compound **459** was subjected to reductive amination followed by alkaline cyclization to give the lactam **460**. The latter was transformed into the monoprotected derivative **461** by standard functional group transformations.[144]

By analogy to the synthesis of the derivatives of **445** and **446** described above, the diamines **436** and **437** were obtained as the monoprotected derivatives **466**−**468** (Scheme 116) via Schmidt rearrangement of the corresponding bicyclic ketones **462** and **463**[148] (the bicyclic lactams **464** and **465** were the key intermediates).[149]

The derivatives of the diamines **438** and **439** were obtained from the corresponding N-protected azabicyclo[2.2.*n*]alkenes **213** and **194**, respectively, (for which, see section 3.2) by reductive ozonolysis followed by reductive amination and partial deprotection. Scheme 117 shows, for example, the synthesis of **469**, which is the Boc derivative of **439**.[131,133a,142,144,150,151]

Numerous reports on the synthesis of the diamine **440** (the so-called "bispidine") occur in the literature. Early syntheses were based on hydrogenation of dinicotinic acid derivatives as the key step.[152] For example, diethyl dinicotinate **470** was hydrogenated and then reduced with lithium aluminum hydride to give the diol **471** (Scheme 118). Reaction of **471** with hydrobromic acid followed by amination then gave the diamine **440** in moderate yield.[152b]

More recent reports on the synthesis of bispidine are based on double Mannich annelations of 4-piperidone derivatives.[153] For example, reaction of *N*-benzyl-4-piperidone **160**, benzylamine, and formaldehyde resulted in a double Mannich annelation to give the 9-bispidinone derivative **472** (Scheme 119). The compound **472** was subjected to Wolff−Kishner reduction followed by catalytic hydrogenation to give bispidine **440**.[153b] Synthesis of an orthogonally bis-protected derivative of the diamine **440** (namely, 3-*tert*-butoxycarbonyl-7-benzyl-) has also been reported.[154]

### 4.4. Other Spirocyclic Diamines of Endo−Endo Type

Spirocyclic diamines of endo−endo type (diazaspiroalkanes) have attracted much attention, partially because of the occurrence of aza-substituted spiro compounds in nature.[10] Many of the theoretically possible diamines of this type have been reported (i.e., compounds **473**−**490**, Figure 19).

The diazaspiro[5.5]decane **473** was obtained from the readily available chiral building block **491** (Scheme 120).[155] Alkylation of **491** proceeded stereoselectively to give the chloride **492** as a single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enantiomer after recrystallization. Reduction of **492** with lithium aluminum hydride resulted in cyclization to form the tricyclic aminal **493**, which was hydrogenated to yield the enantiopure diamine (+)-**473**.[156]

Alternatively, 1-*tert*-butoxycarbonyl-3-piperidone was heated with allylamine and the boronic ester **494** (Scheme 121) to undergo the Petasis (borono Mannich) reaction[157] to give the diallyl derivative **495**. The compound **495** was trifluoroacetylated and then subjected to a ring-closing metathesis reaction, giving the unsaturated diamine derivative **496**. Hydrogenation of **496** then gave the orthogonally bis-protected derivative **497** of the diamine **473**.[158] This approach was also applied to the synthesis of the derivatives of the diamine **474**. In this case, the corresponding 4-piperidone derivative was used as the starting material.[97,158,159]

In yet another approach to the spirocyclic core of **473**, the pipecolic acid derivative **498** was transformed into the nitrile **499** in two steps and then alkylated to give the chloride **500** (Scheme 122). Hydrogenation of **500** over Raney nickel yielded the monoprotected derivative **501**.[160]

The literature syntheses of the diamine **475** started from various nitrile derivatives of pentane-1,3,3,5-tetracarboxylic acid that are 1:2 Michael adducts of the corresponding derivatives of malonic and acrylic acids.

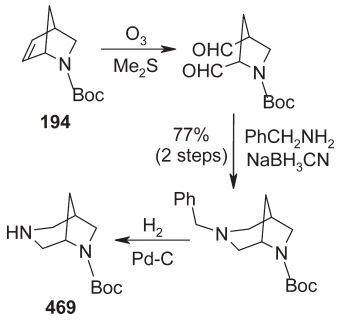
For example, compound **502**, the product of the double cyanoethylation of diethyl malonate, gave upon catalytic hydrogenation the bis-lactam **503**, which after benzylation followed by reduction and deprotection gave the diamine **475** (Scheme 123).[169] Direct reduction of **503** by $LiAlH_4$ gave **475** in moderate yield (30%),[168] so that the three-step procedure was more practical.

The Boc-protected derivative of the diamine **476** was prepared from 1-benzyl-3-piperidone, which underwent reaction with ammonia and ethyl cyanoacetate (giving the corresponding Guareshi imide; see also Scheme 30) followed by acidic hydrolysis and esterification to give the diester **504** (Scheme 124). Compound **504** was reduced with lithium aluminum hydride and, after changing the amine protecting group, mesylated to give the bis-mesylate **505**. Compound **505** was used to alkylate ammonia to give the monoprotected derivative **506**.[161] A modification of this scheme using a polymer-supported analog of compound **505** has also been reported.[162]

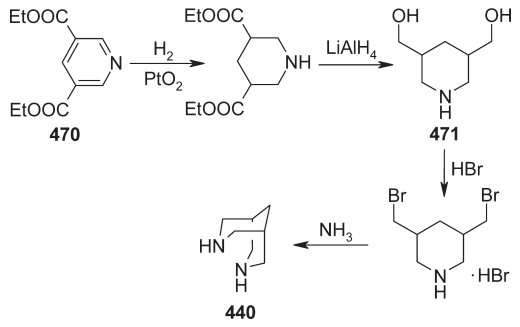
The synthesis of a derivative of 3,9-diazaspiro[5.5]undecane **477** was essentially the same as that for **476**, except that the 4-piperidone derivative was used as the starting material.[161,163]

Both of the methods for the synthesis of derivatives of the 2,6-diazaspiro[5.4]decane **478** were analogous to those described for its homologue **473**. In particular, the 2-trifluoroacetyl-6-*tert*-butoxycarbonyl derivative of **478** was obtained if the transformations described in the Scheme 121 were applied to 1-*tert*-butoxycarbonyl-3-pyrrolidone as the starting compound.[158]

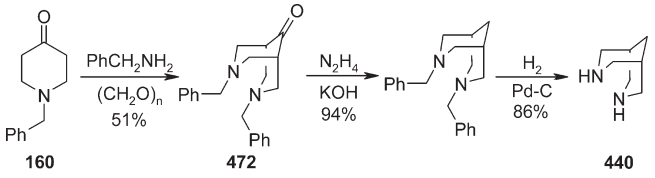
**Scheme 117.** [131]




**Scheme 118**




**Scheme 119**



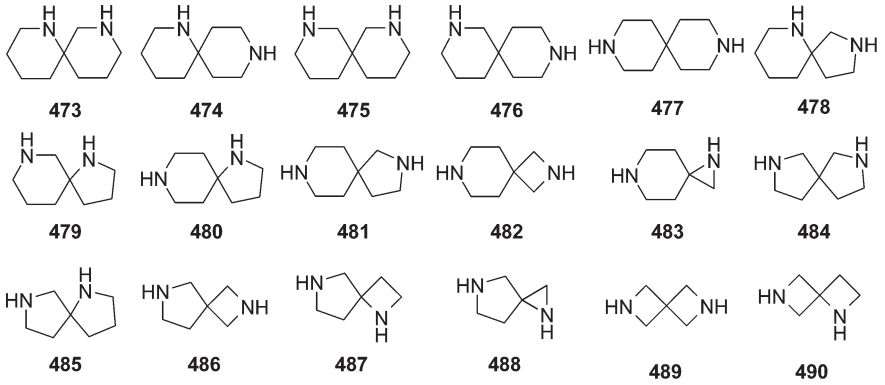
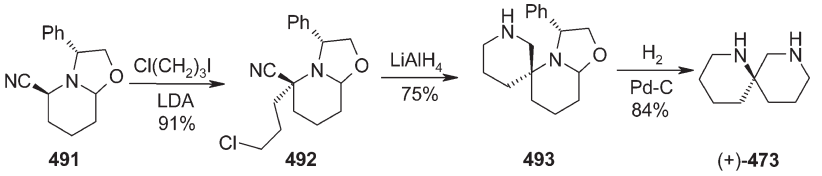




**Figure 19.** Diazaspiroalkanes.

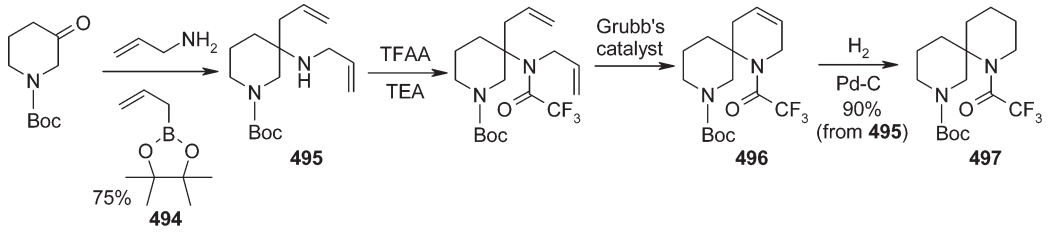

dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 120**[a]

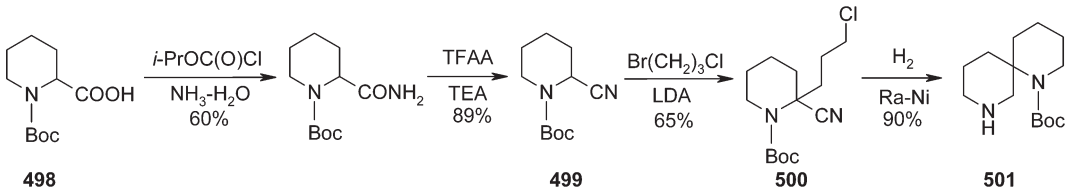



[a] Absolute configurations are shown.

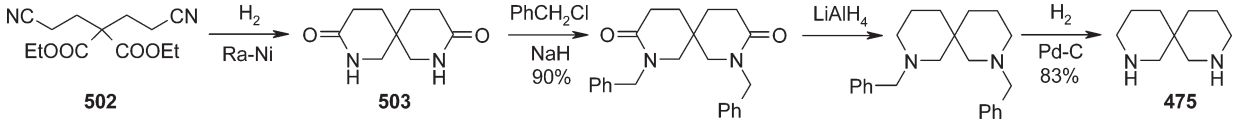
**Scheme 121**



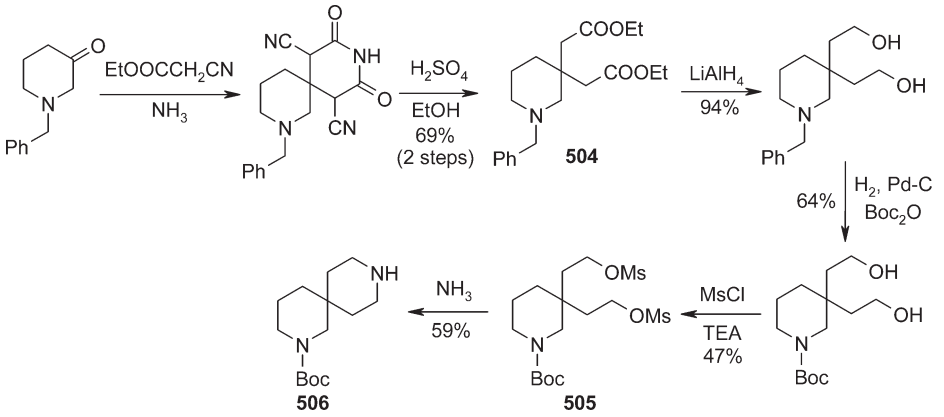

**Scheme 122**




**Scheme 123**



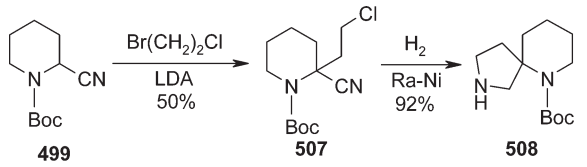

**Scheme 124**





dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

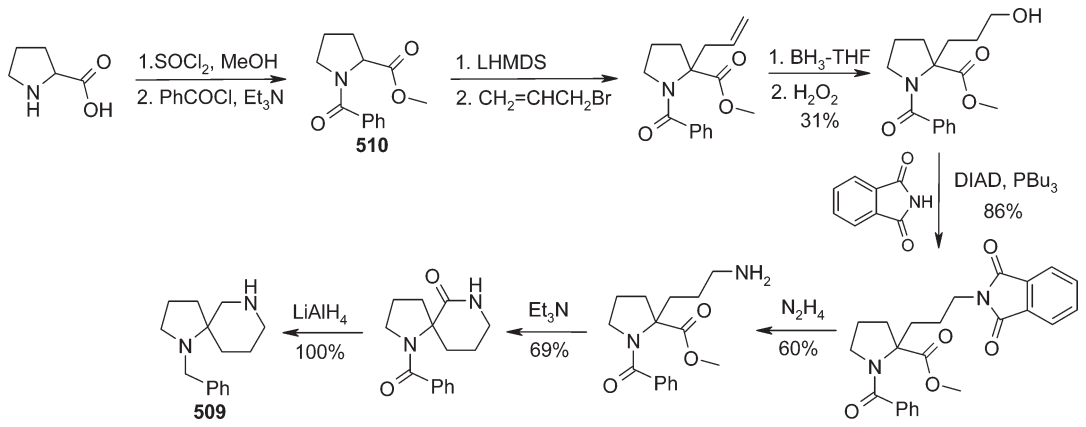
**Scheme 125**




Alternatively, the nitrile **499** (prepared as shown in Scheme 122) was alkylated with 1-bromo-2-chloroethane to give the chloride **507**, which was hydrogenated to give the Boc-derivative of **478** (Scheme 125).

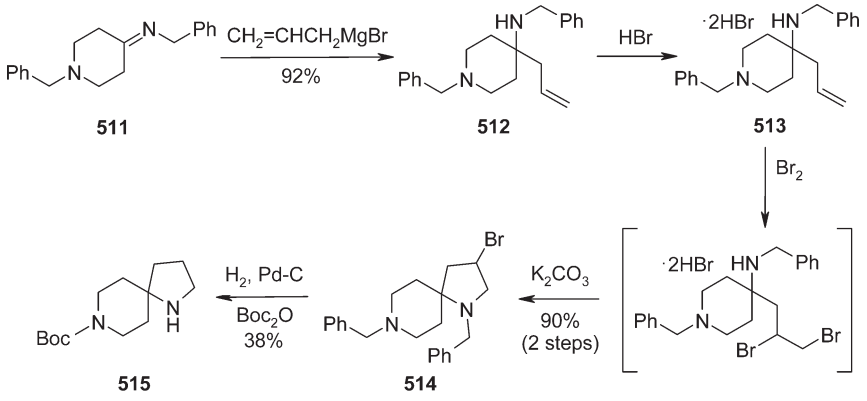
The latter strategy can be also applied to the synthesis of a derivative of **479** (compound **509**) by taking *N*-Boc-proline as the starting compound in the transformations shown in Scheme 122 for the *N*-Boc-pipecolic acid **498**.[160]

**Scheme 126**[a]

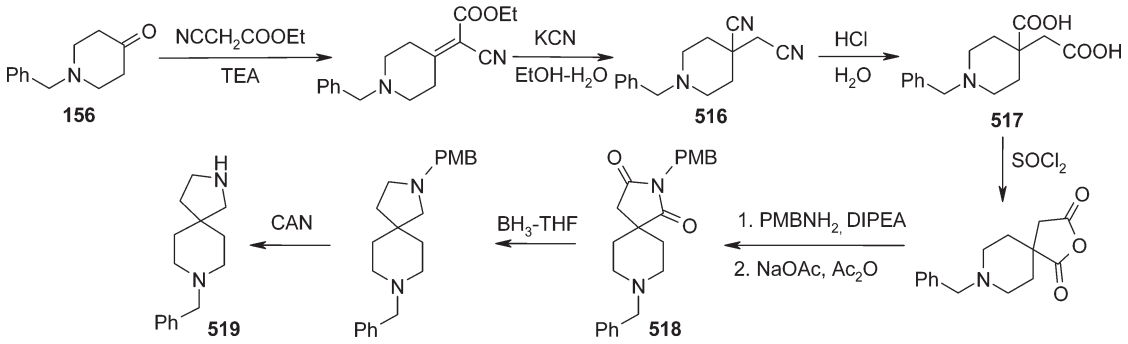



[a] DIAD, diisopropyl azodicarboxylate.

**Scheme 127**




**Scheme 128**[a]




[a] PMB, *p*-methoxybenzyl; DIPEA, *N*,*N*-diisopropylethylamine; CAN, cerium ammonium nitrate.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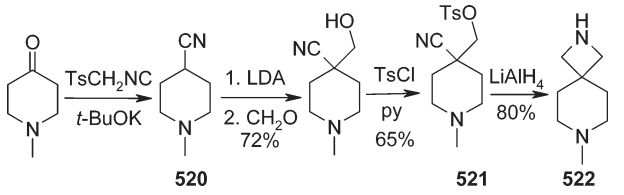
An alternative pathway to **509** starting from proline has also been reported (Scheme 126). This method included allylation at the C2-position of the proline derivative **510** followed by hydroboration−oxidation, Mitsunobu amination, deprotection, cyclization, and reduction with lithium aluminum hydride.[164]

The *N*-protected diamine **480** was prepared from the imine **511** (Scheme 127), which was readily obtained from 1-benzyl-4-piperidone. Reaction of **511** with allyl magnesium bromide gave the diamine **512**, which was converted to the dihydrobromide **513**. Bromination of **513** followed by base-induced cyclization led to the spirocyclic bromide **514**. Compound **514** was hydrogenated in the presence of Boc-anhydride to give the mono-protected diamine **515**.[97]

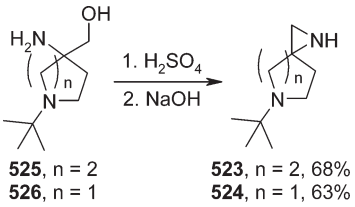
Synthesis of a derivative of the diamine **481** also started from 1-benzyl-4-piperidone (Scheme 128). In this case, a Knoevenagel condensation−Michael addition−decarboxylation sequence was used to obtain the dinitrile **516**. The latter was subjected to hydrolysis to give the dicarboxylic acid **517**, which was transformed into the imide **518** in two steps. Reduction of **518** and subsequent deprotection gave the desired derivative of the diamine **481**, i.e., compound **519**.[165,166]

4-Piperidone derivatives were also the proper starting materials for the synthesis of derivatives of the diamine **482**. In particular, 1-methyl-4-piperidone was reacted with tosylmethylisocyanide (TosMIC)[167] to give the corresponding nitrile **520** (Scheme 129). Compound **520** was then hydroxymethylated and tosylated to give **521**, which was reduced with lithium

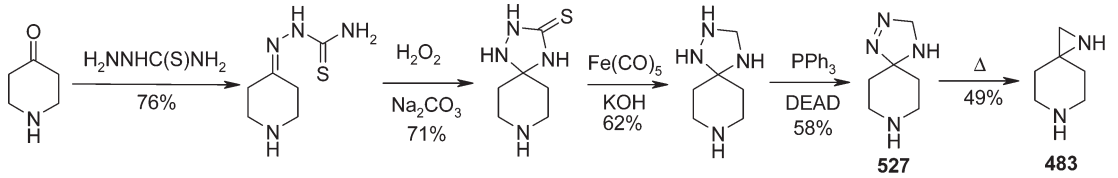
**Scheme 129**



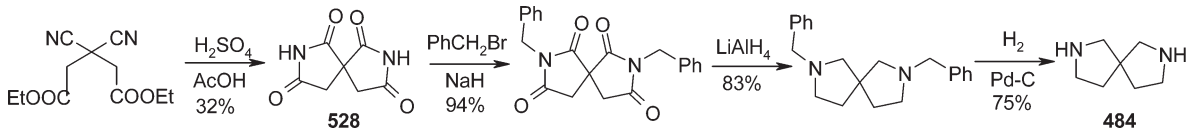

**Scheme 130**



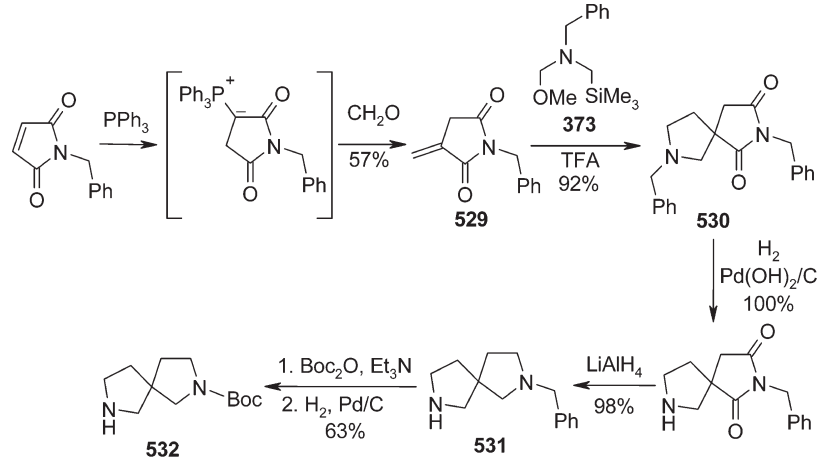

**Scheme 131**




**Scheme 132.** [169]



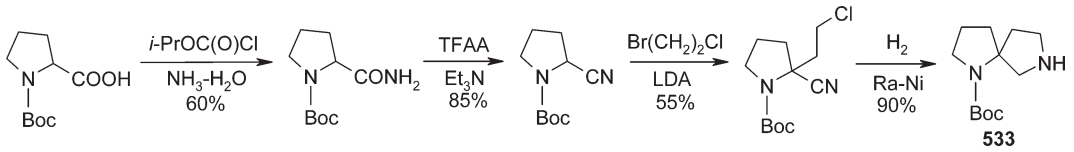

**Scheme 133**





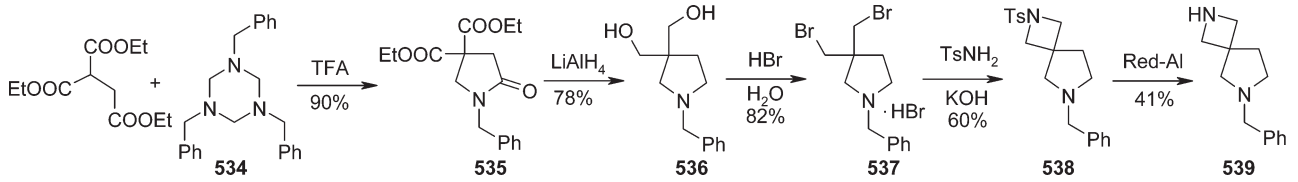
dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 134**[a]




[a] TFAA, trifluoroacetic anhydride.

**Scheme 135**




aluminum hydride to give compound **522**, an *N*-methyl derivative of the diamine **482**.[168]

The aziridines **483** and **488** were obtained as the *tert*-butyl derivatives **523** and **524** starting from the amino alcohols **525** and **526** (Scheme 130).[169] An alternative approach to **483** relied on extrusion of nitrogen from the dihydrotriazole derivative **527**, which was obtained in four steps from 4-piperidone (Scheme 131).[170]

Diamine **484** was synthesized starting from diethyl 3,3-dicyanopentanedioate, which was transformed into the bis-imide **528** in acidic media (Scheme 132). The compound **528** so obtained was then benzylated, reduced with lithium aluminum hydride, and finally hydrogenated to give the diamine **484**.[169,171] Enantiomers of **484** were resolved using L-6,6′-dinitro-2,2′-diphenic acid.[171]

Alternatively, *N*-benzylmaleimide **148** was transformed into the α,β-unsaturated imide **529** via a one-pot Michael addition−Wittig reaction sequence (Scheme 133).[172] The compound **529** so obtained was subjected to a [3 + 2]-cycloaddition reaction with the ylide generated from **373** to give **530**, and partial deprotection of **530** followed by reduction gave the benzyl derivative **531**. The Boc-derivative of **484** (compound **532**) was also obtained.[173]

Several interrelated approaches were reported for the synthesis of the monoprotected derivative **533** of the diamine **485**.[160,169,174] For example, one of the synthetic schemes started from Boc-proline (Scheme 134) and used transformations analogous to those described above in Schemes 122 and 125.[160]

The pyrrolidine core of the spirobicyclic diamine **486** was constructed by the reaction of triethyl 1,1,2-ethanetricarboxylate with the triazine **534** to give compound **535** (Scheme 135). Although the mechanism of this step was not given in the original publication, it presumably included tandem Mannich reaction−lactonization. Compound **535** was then reduced with lithium aluminum hydride to give the diol **536**, which was reacted with hydrobromic acid to give the dibromide **537**, and this was used to alkylate tosylamide to yield the spirobicyclic sulfamide **538**. Detosylation of **538** with sodium bis(methoxyethyl)alanate (RedAl) yielded the monoprotected derivative of **486**, i.e., compound **539**.[175]

The diamine **487** scaffold was constructed starting from azetidine-2-carboxylic acid **540** (Scheme 136). After compound **540** was first protected to give **541**, it was then alkylated and subjected to reductive ozonolysis to give the aldehyde **542**. Reductive amination of **542** was accompanied by lactonization to give the spirocyclic lactone **543**. The final steps of the synthesis included deprotection, reduction with $LiAlH_4$, Boc-derivatization, and debenzylation to give the Boc derivative **544**.[173]

The synthesis of the diamine **489** started from pentaerythritol (Scheme 137), which was transformed into the tribromide **545**. Compound **545** yielded the oxetane **546** upon alkaline treatment. Amination of **546** with liquid ammonia followed by acidic workup gave the salt **547**, which smoothly underwent ring-opening−double ring closure to give diazaspiro[3.3]heptane **489**.[176,177]

Recently, an optimized procedure for the synthesis of a monoprotected derivative of **489** was developed (Scheme 138). This synthesis started from the tribromide **545**, which was transformed into the spirocyclic oxetane **548**.[178] The compound **548** was subjected to oxetane ring-opening with HBr to give the bromo alcohol **549**, which was then transformed into the 2,6-diazaspiro[3.3]heptane derivative **550** in two steps. Changing the protecting group in **550** followed by detosylation gave the monoprotected derivative of diamine **489**, which was isolated as the oxalate salt **551**.[179] It should be noted that using the oxetane ring formation in the two syntheses shown in Schemes 137 and 138 allowed regioselective functionalization of the tribromide **545** (see also Scheme 30).

Synthesis of a derivative of the diamine **490** started from the azetidine **552**, which was subjected to Wittig olefination to give the ester **553** (Scheme 139). Michael addition of benzylamine to **553** followed by reduction with $LiAlH_4$ led to the formation of the amino alcohol **554**. Reaction of **554** with $CBr_4/PPh_3$ resulted in cyclization, giving the 1,6-diazaspiro[3.3]heptane derivative **555**. As in the case of its isomer described above, detosylation of **555** gave the monoprotected derivative of diamine **490**, which was isolated as the oxalate salt **556**.[180]

## 5. RETROSYNTHETIC APPROACHES TO CRDA: AN OVERVIEW

In this section, we summarize the transformations frequently encountered in the schemes described above. The retrosynthetic presentation of the literature data will hopefully facilitate the design of new syntheses of both known CRDA and those which are theoretically possible but still not synthesized. The reactions are subdivided into three groups: those used for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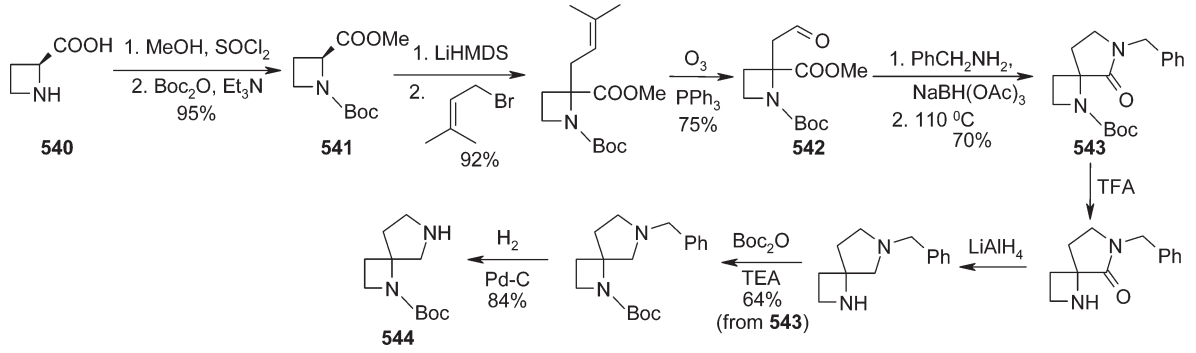
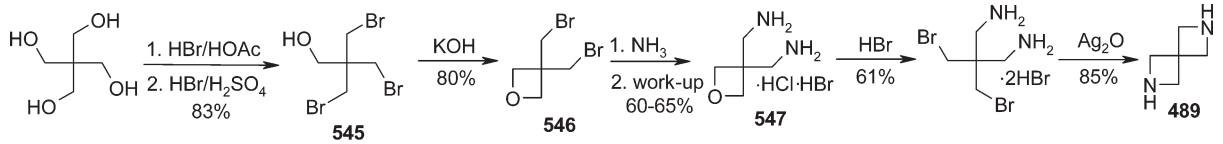
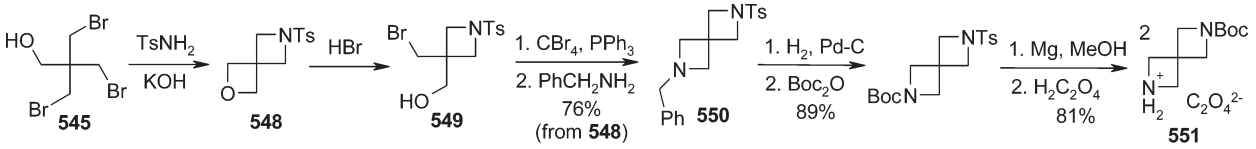
**Scheme 136**



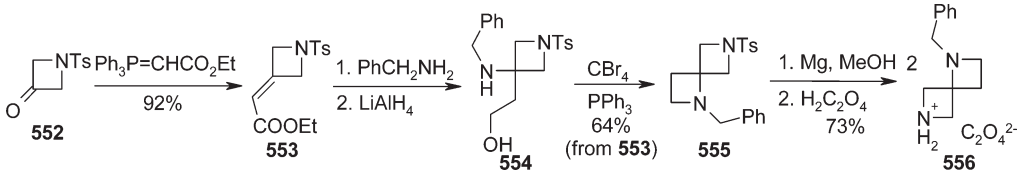

**Scheme 137.** [177]




**Scheme 138**




**Scheme 139**




introduction of the primary (exocyclic) amino group, for construction of the carbocyclic skeleton, and for formation of the heterocyclic ring.

### 5.1. Introduction of Exocyclic Amino Groups into Bicyclic Cores

Several functional groups can be considered as synthetic equivalents for exocyclic amino groups in the retrosynthetic analysis of a CRDA molecule.

(1) A secondary hydroxy group can be transformed into an amino group either via Mitsunobu reaction or via a mesylation−azide substitution−reduction sequence. The corresponding alcohols are often obtained from the corresponding ketones (see below).

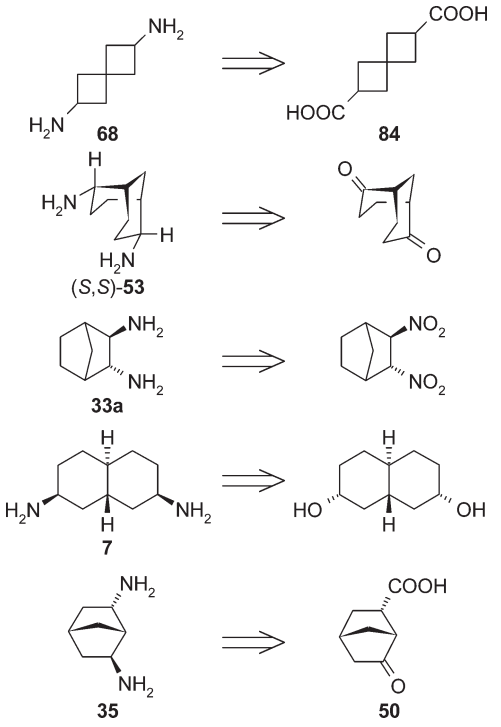
(2) A ketone moiety can be transformed into an amino group either via direct reductive amination or via reduction of an oxime derivative. Alternatively, ketones can be reduced to alcohols, which can be transformed into amines as described above. This approach is especially valuable because all of the steps of the corresponding sequences can in principle be performed stereoselectively. Obviously, secondary hydroxy groups and ketone functions can be synthetic equivalents for amino groups that are not at bridgehead positions.

(3) A carboxyl group is another functional group that can be considered as a precursor of a primary amino group; Curtius rearrangement is a common way to achieve this transformation. This approach is especially effective for the synthesis of CRDA with amino groups at the bridgehead positions.

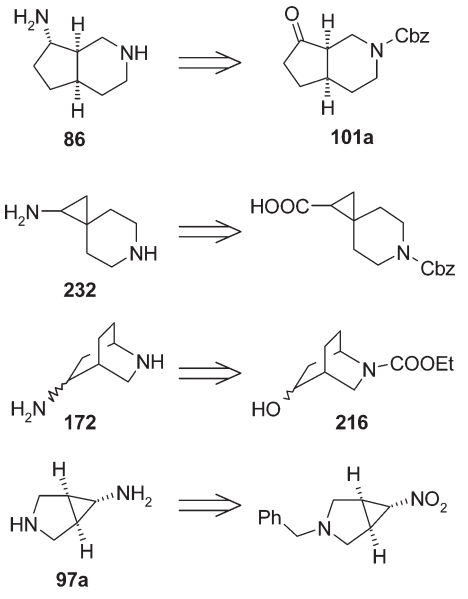
(4) Reduction of nitro derivatives can be also used for the synthesis of CRDA.


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Scheme 140**



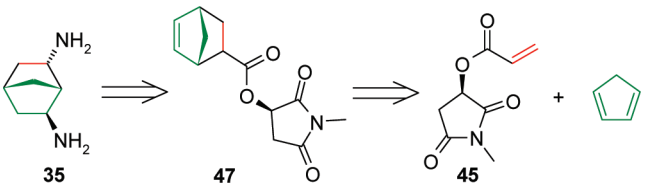

**Scheme 141**



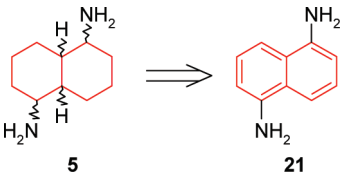

As follows from the above discussion, compounds of the following classes can be the key intermediates for the synthesis of CRDA possessing exocyclic amino groups (see Schemes 140 and 141 for representative examples):

- dicarboxylic acids
- diketones
- dinitro derivatives
- diols and epoxides

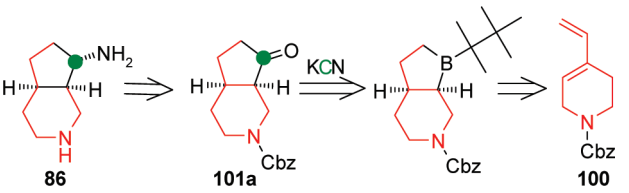
**Scheme 142.** [181]



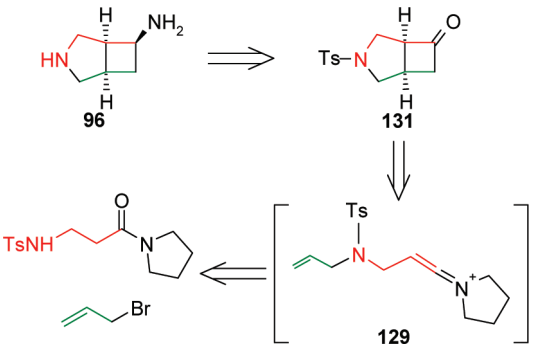

**Scheme 143**



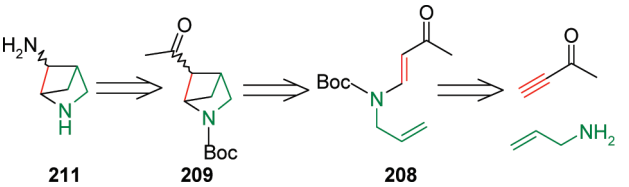

**Scheme 144**




**Scheme 145**




**Scheme 146**




- keto acids
- amino ketones
- amino acids
- amino alcohols
- nitroamines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### 5.2. Construction of Carbocyclic Rings of Bicyclic Cores

The type of the transformation used for the construction of carbocyclic rings of a bicyclic CRDA depends strongly on the size of the ring formed in the reaction. All of the few methods that are more or less general and can be applied to four-, five-, and six-membered rings originate from classical enolate chemistry.

(1) The Diels−Alder reaction (Scheme 142) can be considered a common approach to the construction of the cyclohexane rings of CRDA cores. In particular, this method was used for the synthesis of norbornane and bicyclo[2.2.2]octane derivatives.
(2) Catalytic reduction of aromatic compounds can in principle be used for cyclohexane-containing CRDA (Scheme 143); however, this method has found limited application.
(3) The hydroboration of dienes−carbonylation sequence (Scheme 144) is a promising approach to the synthesis of CRDA containing five-membered carbocyclic rings. This method was used for the synthesis of fused CRDA.
(4) Different types of [2 + 2]-cycloadditions (Schemes 145 and 146) can be used to obtain CRDA containing cyclobutane fragments in their molecules. In some cases, both rings of the bicyclic core can be constructed in one step.
(5) Another approach to cyclobutane-derived CRDA relies on expansion of three-membered rings (Scheme 147).
(6) Cyclopropanation reactions involving diazoalkanes (Scheme 148) or sulfur ylides (Scheme 149) provide a general method for the synthesis of cyclopropane-containing CRDA.
(7) The Kulinkovich reaction and its modifications (Scheme 150) seem to be an alternative and promising method for the synthesis of CRDA containing cyclopropane fragments.
(8) Tandem aldol-type reaction−Michael addition (Schemes 151 and 152) was used to obtain the diamines **9a** and **53**; five- and six-membered rings were constructed in these transformations. Both of the sequences shown in the schemes are rather specific, but in principle they might be extended to some other bicyclic cores.
(9) Dieckmann cyclization and its variations (Scheme 153) were used for the construction of five- and six-membered rings in the spirocyclic CRDA.
(10) Double alkylation of malonate with bis-electrophiles (Scheme 154) was applied to the synthesis of spirocyclic CRDA containing four- and six-membered rings. In principle, this method can also be extended to five-membered rings.
(11) Another type of enolate bis-alkylation (Scheme 155) was used for the synthesis of bridged CRDA of exo−exo type. In this case, enolates were generated from diesters, which allowed bridges containing one or two carbon atoms to be added to the parent molecule.

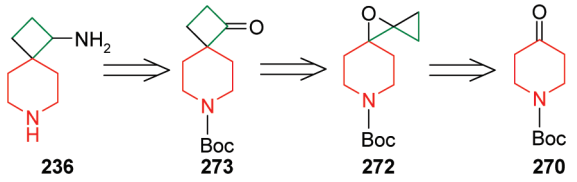
### 5.3. Construction of Heterocyclic Rings of Bicyclic Cores

Methods for the construction of the heterocyclic rings in molecules of CRDA are rather diverse. Many of them rely on nucleophilic cyclizations and are not too specific to the size of the ring formed. In contrast, [4 + 2]- and [3 + 2]-cycloadditions can be applied only to the construction of six- and five-membered rings, respectively. An important approach to the synthesis of CRDA of the exo−endo and endo−endo types includes catalytic hydrogenation of heteroaromatic rings. Other methods involving the use of Mannich condensation, Schmidt rearrangement, and metathesis reactions should also be mentioned.

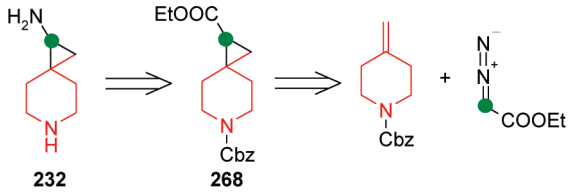
(1) A general approach to the synthesis of CRDA containing piperidine and pyrrolidine cores includes formation of lactams from amino esters followed by reduction (Schemes 156 and 157). Amino esters are often generated in situ by, for example, reduction of the corresponding cyano and nitro esters. This method was used for the synthesis of almost all subtypes of CRDA containing one or more endocyclic amino groups.
(2) A related approach relies on generation of lactams by cyclization of $\omega$-functionalized primary or secondary amides under strong basic conditions (Scheme 158). Bromides and mesylates containing an amide function were used as substrates in this transformation. This method can be used for the construction of four-, five-, and six-membered nitrogen-containing rings.
(3) In another related approach that includes the formation of imides followed by their reduction (Scheme 159), derivatives of dicarboxylic acids are the key intermediates. This method can be used for the construction of five- and six-membered rings.
(4) Intramolecular cyclizations of $\omega$-functionalized amines (containing bromo, chloro, mesyloxy, or other electrophilic functions in their molecules) (Schemes 160 and 161) are an alternative group of the methods that can be used for the construction of nitrogen-containing rings of almost any size. The corresponding substrates for the cyclization are often generated in situ.
(5) Double alkylations of ammonia equivalents with bis-electrophiles (Schemes 162 and 163) is another group of CRDA synthesis strategies that relies on nucleophilic cyclization. The scope of bis-electrophiles that were used as the substrates in these transformations is broad and includes dibromides, bis-mesylates and bis-tosylates, dichlorides, and even dialdehydes.
(6) The hetero-Diels−Alder reaction (Scheme 164) can be a valuable method for the construction of bicyclic systems containing piperidine rings. In particular, the method was used for the synthesis of bridged CRDA of exo−endo type.
(7) [3 + 2]-Cycloaddition (Scheme 165) is a method that has been widely used for the synthesis of CRDA containing the pyrrolidine ring. This approach is particularly important for the preparation of fused and spirocyclic diamines.
(8) Reduction of heteroaromatic compounds (i.e., pyrroles, pyridines, pyrazines, and their fused analogs) (Scheme 166) is useful for the synthesis of fused CRDA containing five- and six-membered heteroaromatic rings. Reduction of aromatic rings is mainly achieved by catalytic hydrogenation.
(9) Double Mannich condensation (Scheme 167) can be applied for the synthesis of various bridged piperidine analogs. The Robinson−Schöpf synthesis of tropane derivatives is a classical example of this transformation. The synthesis of bispidine **440** also can be mentioned as an example.
(10) Schmidt and Beckmann rearrangements (Scheme 168) have also been used in the synthesis of CRDA. These transformations are especially significant for the synthesis of large bridged bicyclic systems, which are hardly achievable by other methods.
(11) Recent advances in the synthesis of CRDA include the use of a metathesis reaction (Scheme 169). This method


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

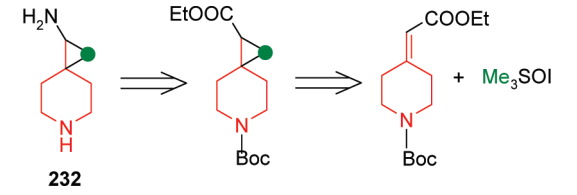
Scheme 147



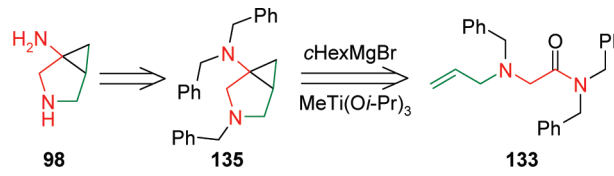

Scheme 148



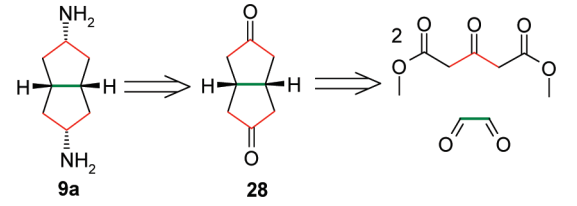

Scheme 149




Scheme 150




Scheme 151

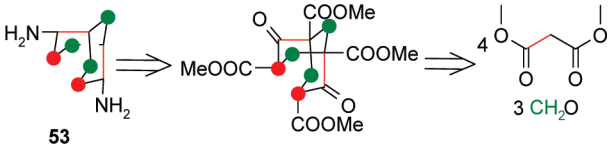



was used for the preparation of spirocyclic and bridged CRDA of endo−endo type. In our opinion, the potential of this approach has scarcely been explored to date.

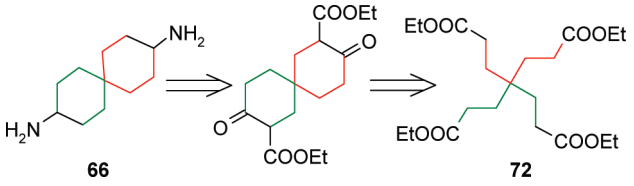
## 6. OVERVIEW OF CRDA APPLICATIONS

As was pointed out in the Introduction, the distinctive features of the CRDA made them very popular for constructing molecules possessing properties with practical usefulness. The literature describing the application of CRDA in chemistry and related branches of science is extremely vast. Obviously, a discussion of the whole literature on the applications of CRDA is impossible in

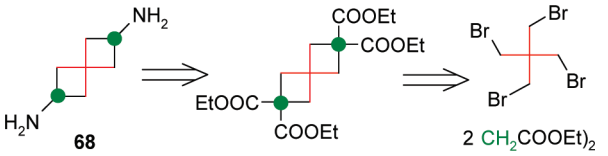
Scheme 152



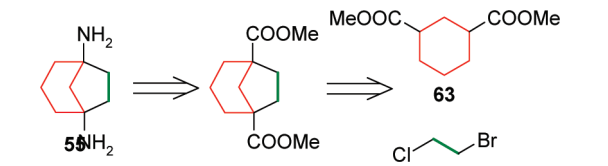

Scheme 153



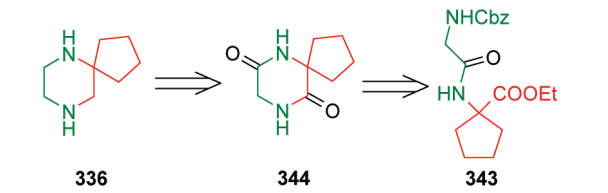

Scheme 154



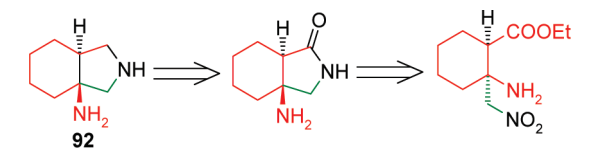

Scheme 155




Scheme 156



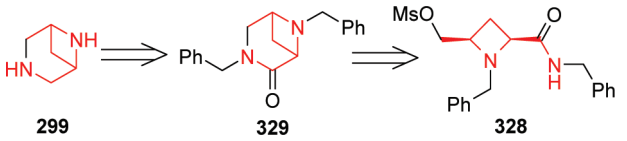

Scheme 157



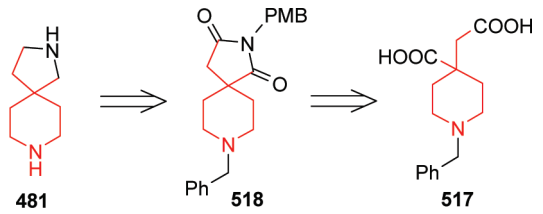


dx.doi.org/10.1021/cr100352k |Chem. Rev. 2011, 111, 5506–5568

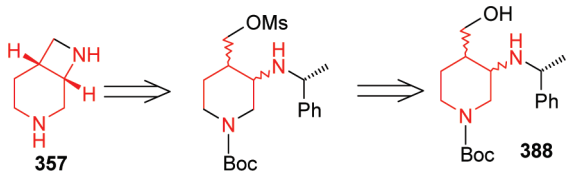
Scheme 158



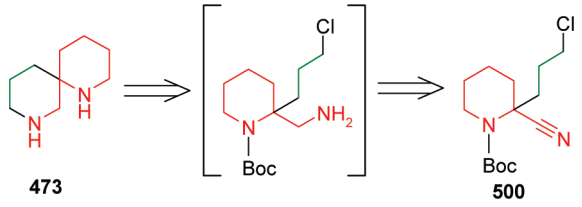

Scheme 159



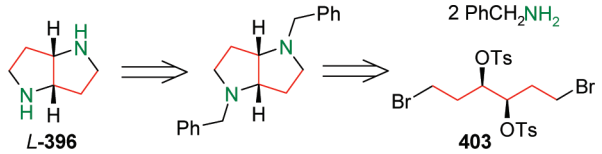

Scheme 160



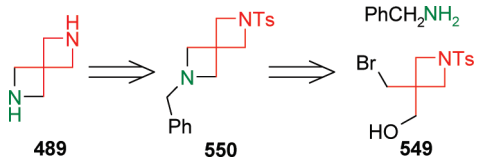

Scheme 161



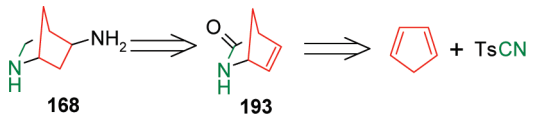

Scheme 162



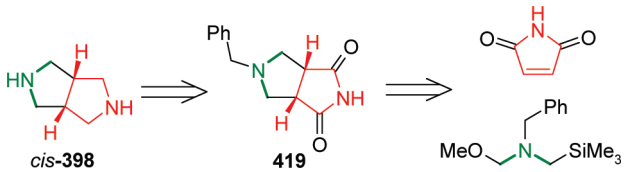

Scheme 163



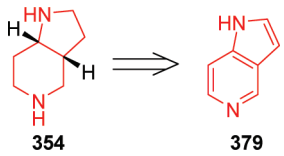

Scheme 164



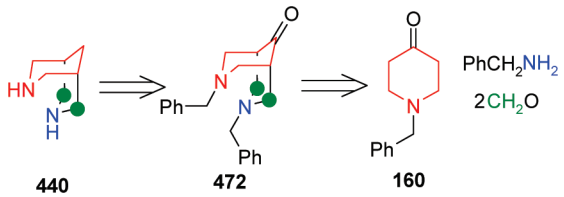

Scheme 165



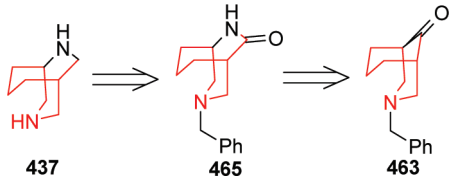

Scheme 166



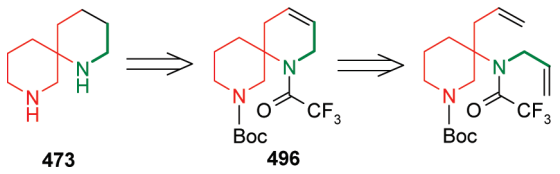

Scheme 167




Scheme 168




Scheme 169




this review because of the sheer volume of the data (this is an indirect proof of the utility of CRDA). Instead, we would just like to exemplify different aspects of the CRDA applications using


dx.doi.org/10.1021/cr100352k |Chem. Rev. 2011, 111, 5506–5568

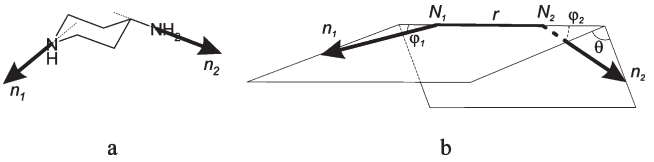



**Figure 20.** (a) Definition of vectors $\mathbf{n}_1$ and $\mathbf{n}_2$ (4-aminopiperidine used as an example) and (b) definition of geometric parameters $r$, $\varphi_1$, $\varphi_2$, and $\theta$. Reprinted with permission from ref 189. Copyright 2010 American Chemical Society.

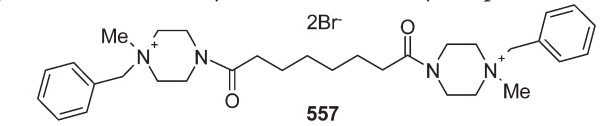
vivid recent examples, citing the pioneering papers and published reviews where possible. We apologize here for not including the many other interesting reports contributing to the field equally as much as do these examples and hope that this section will stimulate generation of new ideas and encourage other research work based on applications for CRDA.

### 6.1. CRDA in Medicinal Chemistry

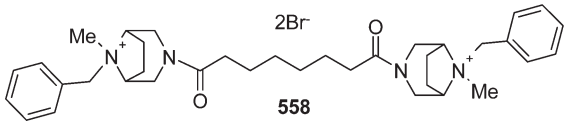
Analyzing the literature on the CRDA, one might conclude that their synthesis and subsequent studies were first of all driven by the needs of drug discovery. Indeed, the major part of the literature references given in the preceding sections describing the synthesis of CRDA is connected to this rapidly evolving subject. Moreover, discovery of a promising drug candidate containing a CRDA fragment stimulated development of new and more efficient syntheses of the corresponding CRDA. For example, early syntheses of the diamine **96a** described in section 3.1 were tedious and low-yielding. The use of this diamine in the preparation of the antimicrobial trovafloxacin prompted further synthetic studies and application, in particular of the Kulinkovich reaction, in a novel synthetic strategy leading to this compound (Schemes 48−51).

The structural features of CRDA have already proved their advantages in drug design: many drugs on the market today have CRDA residues as parts of their molecules. Table 1 summarizes a search in the MDL Drug Data Report Database[185] for compounds containing CRDA fragments and presently available on the market. Even more CRDA derivatives that did not reach the market or clinical studies were found to be biologically active. Nearly 1000 records for biologically active compounds containing CRDA fragments were found in the MDL Drug Data Report Database.

There are several reasons for the enhanced interest in the CRDA in medicinal chemistry. The first reason is the rigidity of the CRDA molecules, which might be beneficial for achieving efficient and selective binding of the CRDA or their derivatives to biological targets. The idea of using rigid or conformationally restricted units as the building blocks for drug design is well-precedented.[186] Suggestions for using the restriction of the conformational mobility of the CRDA or their derivatives in the search for new drugs or in finding the biologically active conformations of the ligands can be found in the open literature published almost a half a century ago.[117a,187] As was stated in the Introduction, the preorganization of the CRDA fragments could decrease the entropy penalty of the drug−target interaction, thus leading to increased drug selectivity and potency. However, this approach should not be oversimplified. In a carefully planned model study,[188] the entropy of binding a conformationally restricted ligand to a biological target was shown to be in fact less favorable than that of a flexible analog, despite the overall efficiency of the rigid ligand−target interaction being higher. This fact might not be general, but it certainly reflects the formidable complexity of the drug−target interaction mechanisms. Therefore, the use of conformationally restricted building blocks in drug design does not automatically mean improvement of affinity of the drug candidates to their targets, their target specificity, or the favorability of their ADME (absorption, distribution, metabolism, and excretion) parameters. The building blocks must be optimal for achieving desirable pharmacokinetic and pharmacodynamic characteristics. As far as CRDA are concerned, an instructive example in this respect is described in a paper reporting the loss of biological activity after replacing the conformationally flexible piperazine ring in piperazine-derived analgetics with a CRDA (3,8-diazabicyclo-[3.2.1]octane) residue.[119c] Compound **557** was taken as the lead, and the conformational restriction was achieved by incorporation of the endoethylenic bridge in the piperazine rings to get the 3,8-diazabicyclo[3.2.1]octane derivative **558**. Almost complete loss of analgesic activity was observed for compound **558** and its homologues; instead, the toxicity increased dramatically compared to **557**.




**557**




**558**

This example stresses the demand for libraries of structurally diverse conformationally restricted building blocks that differ in the spatial disposition of functional groups and thus enable fine-tuning of the ligands to a receptor in order to achieve the highest binding efficiency. CRDA comprise one of only a few classes of compounds satisfying this demand, and this is the second reason why CRDA are so popular in drug design. The exceptional structural diversity of CRDA enables the use of libraries of them to achieve very diverse mutual disposition of the groups directly participating in the biologically relevant interactions. That the amine functions in the CRDA are rigidly fixed at different distance and spatial orientation within the whole library of the known CRDA makes it possible to probe the "three-dimensional space" around the scaffold. In a recent report,[189] the structural diversity of CRDA scaffolds was analyzed by introducing the simple geometric parameters schematically shown in Figure 20.

It was shown by analysis of the geometric parameters $r$, $\varphi_1$, $\varphi_2$, and $\theta$ calculated from X-ray structural data for some mono-, bi-, and spirocyclic diamine derivatives that CRDA scaffolds might open a route into scarcely explored three-dimensional molecular structures, which is very valuable for drug design.

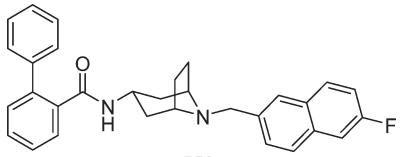
Two closely related general strategies for the use of CRDA in a search for new drugs can be envisaged. One strategy is based on the use of a CRDA fragment as a molecular scaffold or a template, which is assumed to be relatively inert in interactions with the biological targets. Another strategy uses CRDA fragments as units directly involved in the drug−target interactions.

In the former strategy, the nitrogen atoms, or in rare cases the carbon atoms of the skeleton, are used to attach fragments that participate in the biologically relevant interactions. In order to achieve optimal interaction of a drug candidate with biological targets, the nature as well as relative disposition of the fragments in space should be fine-tuned, both by variations in the scaffold and in the fragments themselves.

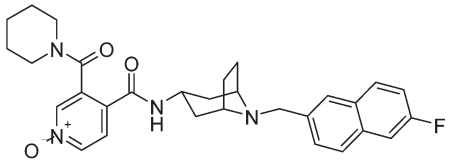
An example of successful variation around a CRDA scaffold can be found in a recent report.[190] The authors identified a CRDA derivative, compound **559**, as a novel antagonist of a


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

CC chemokine receptor CCR3. The CCR3 antagonists were shown to be potential therapeutic agents for some allergic diseases. However, compound **559** also inhibited human cytochrome P450 2D6 (CYP2D6), which might cause unfavorable drug−drug metabolizing interactions. In order to reduce the CYP2D6 inhibitory activity, modifications of the biphenyl fragment were undertaken to find less lipophilic compounds with the attenuated CYP2D6 activity. The result was the discovery of compound **560**, which showed CCR3 activity comparable to **559** but possessed reduced CYP2D6 inhibitory activity.

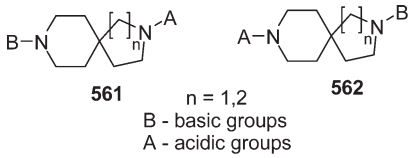


**559**



**560**

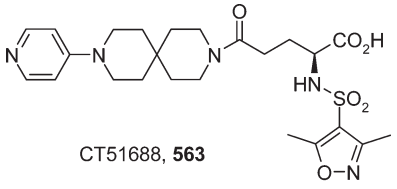
In a series of papers,[166,191,192] both the central spirocyclic template and the peripheral functional groups in compounds of general formula **561** and **562** were varied to find potent glycoprotein IIb-IIIa antagonists, nonpeptide RGD mimetics that prevent platelet aggregation and might be used to treat thrombotic disease. Highly active GPIIb-IIIa inhibitors containing 3,9-diazaspiro[5.5]undecane and 2,8-diazaspiro[4.5]decane scaffolds (compounds **563** and **564**, respectively) were discovered.



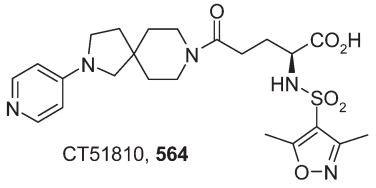
**561** n = 1,2 **562**

B - basic groups

A - acidic groups

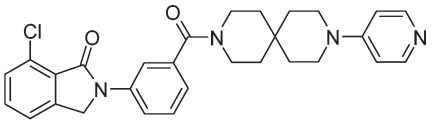


CT51688, **563**



CT51810, **564**

It is relevant to emphasize here the interest in the spirocyclic CRDA that rose in the past decade in medicinal chemistry. Papers describing the synthetic approaches[90,156,159,168] to the spirodiamine scaffolds stressed their utility in drug design; indeed, novel biologically active spirocyclic CRDA derivatives were found recently. In adddition to the example discussed above, discovery of a spirocyclic bradykinin B1 receptor antagonist ELN441958 (**565**)—a promising therapeutic agent to reduce pain and inflammation—could be mentioned.[193]



ELN441958, **565**

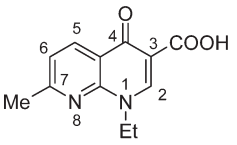
Spirocyclic frameworks can be mounted onto scaffolds of known drugs to give active compounds with similar or even improved metabolic stability. For example, heteroatom-substituted derivatives of 2,6-diazaspiro[3.3]heptane **489**—a structural surrogate for piperazine ("homospiropiperidine"[180])—showed higher aqueous solubility than their piperazine analogs as well as a trend toward higher metabolic stability.[194]

**489**

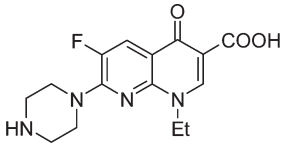
A different CRDA drug design strategy, that which uses the CRDA fragments not as "inert" scaffolds but as units directly involved in the biologically relevant interaction, received much more attention from medicinal chemists than that described above. Strictly speaking, CRDA scaffolds, like any other molecular fragments used to construct a drug candidate, cannot be completely inert in the drug−target interaction. They inevitably contribute to the final pharmacokinetic and pharmacodynamic properties of the drug candidate, and the drug design strategies which make advantageous use of this contribution are of great value in medicinal chemistry.

Many successful drug discovery projects relied on the screening of a large number of candidates with variation of the CRDA fragment in the molecules as the main part of the pharmacophore.

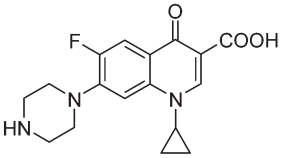
One such example that should be mentioned here is the discovery of the quinolone antimicrobial agents.[195] The story began when the first compound of this class possessing antimicrobial activity, nalidixic acid (**566**), was isolated in 1962.[196] Compound **566**, however, had limited clinical use because of its activity against only Gram-negative organisms and the rapid development of bacterial resistance to it. A breakthrough in this area was made in the early 1980s, with the development of enoxacin (**567**) and then ciprofloxacin (**279**).



Nalidixic acid **566**



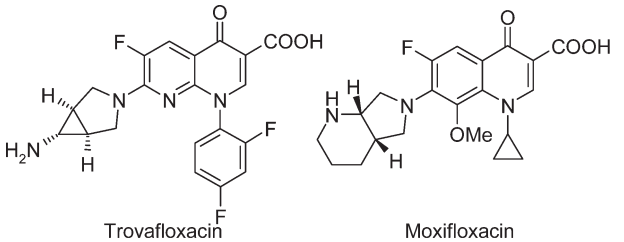
Enoxacin **567**



Ciprofloxacin **279**

The quinolones and fluoroquinolones act on bacterial nucleic acid transcription and replication by inhibiting the vital bacterial enzyme topoisomerase II (DNA gyrase) or topoisomerase IV, thus preventing bacterial protein synthesis. The selectivity for the bacterial enzymes over the corresponding enzymes in human cells displayed by enoxacin, ciprofloxacin, and their analogs ensured their wide use in

chemotherapy of lower respiratory tract infections, skin and soft tissue infections, sexually transmitted diseases, and urinary tract infections. Still, there was a need for broadening the activity spectrum, especially against the bacterial strains resistant to known drugs. It was found that modification of the diamine fragment at the 7-position of the 4-oxo-1,4-dihydronaphthyridine or 4-oxo-1,4-dihydroquinoline template is an efficient instrument for activity and selectivity modulation. Extensive SAR and QSAR (quantitative SAR) studies followed on the above-mentioned central cores as well as on the modified ones, 6*H*-6-oxo-pyrido[1,2-*a*]pyrimidine and 4*H*-4-oxoquinolizine. Most of the CRDA described in this review were tested, and thousands of the derivatives were synthesized and screened against pathogens, which made possible establishing structure/antibacterial,[197] antituberculosis,[198] or antiparasitical relationships.[199] These studies culminated in the development of the new-generation antimicrobial agents, and among these were the bicyclic CRDA derivatives trovafloxacin (**568**) and moxifloxacin (**569**), both of which showed improved antibacterial activity. It was clearly shown that steric and electronic properties, conformation, and the absolute stereochemistry of the diamine substituent are very important to the antibacterial profiles.

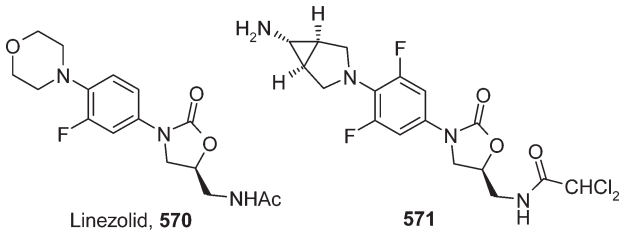



Notably, the 6-amino-3-azabicyclo[3.1.0]hexane residue in trovafloxacin is achiral. This property might be regarded at first sight as a deficiency: development of new drugs often requires the use of chiral building blocks. The main fundamental reason behind this lies in the fact that almost all biological targets are chiral, and the drug−receptor interaction requires a strict match of chirality. However, chirality might also cause serious problems in development and market launch of a new drug, because of the cost of synthesis and analysis for chiral nonracemic compounds as well as the strengthening in many countries of the regulatory guidelines for submitting new drug applications for chiral drug substances. Therefore, if using an achiral building block leads to a drug candidate as good as using a chiral building block, then it could be considered beneficial. The development of trovafloxacin is one of several examples demonstrating this.

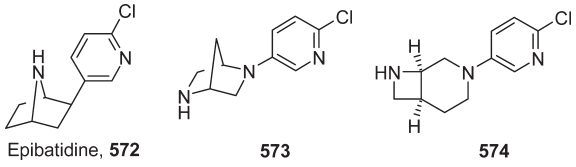
Recently, the 6-amino-3-azabicyclo[3.1.0]hexane building block was used in SAR studies[64] on another class of synthetic antibacterial agents, the oxazolidinones. Like quinolone antibacterials, oxazolidinones also inhibit bacterial protein synthesis, but at another stage via binding to 23S RNA of the 50S ribosomal subunit of the prokaryotes.[200]

Linezolid **570** was the first compound of this class to reach the market, in 2000.[201] In the work cited above,[64] the morpholine ring of linezolid was replaced by the isosteric 3-azabicyclo[3.1.0]hexane building block. Substituent variations allowed identifying SAR trends in a series of synthesized compounds. Several analogs, among them the 6-amino-3-azabicyclo[3.1.0]hexane derivative **571**, were found to be more potent than linezolid against key Gram-positive and fastidious Gram-negative pathogens.

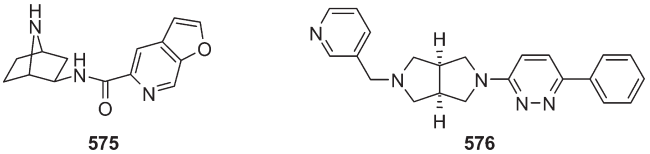
Another area of medicinal chemistry where CRDA have played a




central role in the design of potential therapeutic agents is the search for potent and selective neuronal nicotinic acetylcholine receptor (nAChR) ligands. Human nAChRs, the pentameric ligand-gated ion channels located in the central nervous system (CNS), were recognized as potential targets for the treatment of several CNS disorders, as well as for the treatment of pain.[202] A very large family of neuronal nAChRs exists and it is believed that the selective action of ligands at specific subtypes of the receptors should facilitate treatment of the disease states associated with the corresponding subtypes and also diminish unwanted side effects. For example, there is a strong body of evidence that the central $\alpha4/\beta2$ nAChR subtype plays the central role in the antinociceptive effect of nicotinic agonists such as epibatidine (**572**). Epibatidine is an extremely potent but nonselective nAChR agonist whose adverse effects are thought to be associated with activation of the $\alpha3/\beta4$ nAChR subtype.[203] Therefore, medicinal chemists targeted selective agonists at the $\alpha4/\beta2$ nAChR in order to find an analgesic with an improved therapeutic index. Along the way in this search, many CRDA analogs of **572** were tested.[134,146] A number of novel nAChR agonists were discovered with binding and functional potencies rivaling that of epibatidine, for example, compounds **573** and **574**.



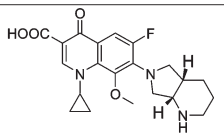
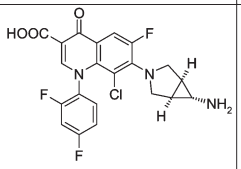
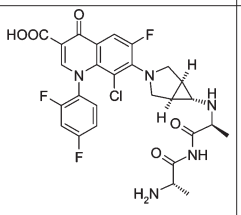
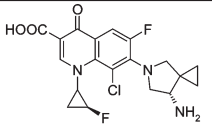
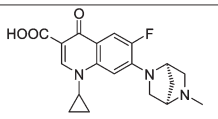
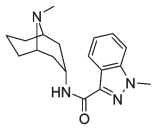
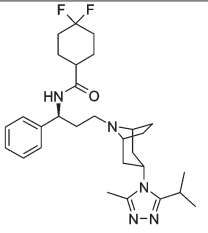
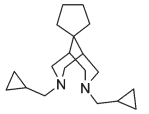

Selectivity at another nAChR subtype, $\alpha7$, was the main goal of other medicinal chemistry projects.[79,204] This subtype has been proposed to modulate a variety of attention and cognitive processes.[205,206] Among the compounds studied, 7-azanorbornane analogs (for example, **575**),[79] and octahydropyrrolo[3,4-*c*]pyrrole derivatives (exemplified by **576**)[204] showed excellent potency and affinity toward $\alpha7$ nAChR and selectivity over other nicotinic receptors. Gratifyingly, these compounds were shown to be functionally efficacious by in vivo assays.




In most of the examples cited above, the nitrogen atoms of a CRDA scaffold or the substituents attached to them participated in the intermolecular drug−target interactions. It should be noted, however, that the hydrocarbon skeleton of CRDA fragments may also take part in the interaction by fitting into


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

**Table 1. Launched Drugs Based on CRDA**

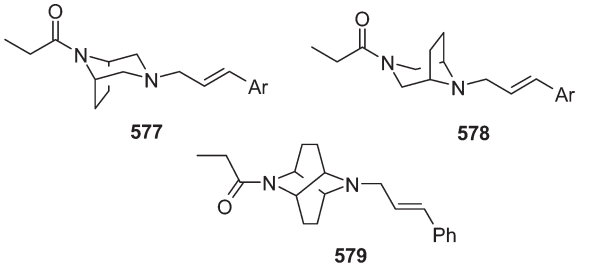
| No | Structure | US adopted name | Trade name | Launched Year (country) | Company | Comments | Ref |
|---|---|---|---|---|---|---|---|
| 1 |  | Moxifloxacin | Avelox | 1999 (USA) | Bayer | Quinolone antimicrobial | 182 |
| 2 |  | Trovafloxacin | Trovan | 1998 (USA) | Pfizer | Quinolone antimicrobial | 182 |
| 3 |  | Alatrofloxacin | Trovan IV | 1998 (USA) | Pfizer | Quinolone antimicrobial | 182 |
| 4 |  | Sitafloxacin | Gracevit | 2008 (Japan) | Daiichi Sankyo | Quinolone antimicrobial | 183 |
| 5 |  | Danofloxacin | Advocin | 2002 | Pfizer | Quinolone antimicrobial used in veterinary | 184 |
| 6 |  | Granisetron | Kytril | 1991 (UK) 1994 (US) | Roche Laboratories, Beecham | 5-HT3 receptor antagonist | 182 |
| 7 |  | Maraviroc | Selzentry (Celsentri outside the U.S.) | 2007 (USA, EU) | Pfizer, Sandwich | Treatment of HIV infection | 182 |
| 8 |  | Tedisamil | Pulzium | Under regulatory review on FDA, Submitted 2007 | Solvay | class III antiarrhythmic | 182 |

corresponding lipophilic pockets of targets. For example, the endoethylenic bridge of the 3,8-diazabicyclo[3.2.1]octane fragment in opioid receptor ligands **577** and **578** was suggested to play an essential role in modulating activity toward $\mu$ opioid receptors.[207] This hypothesis was used to design even more potent ligands containing two bridges; one of the synthesized compounds, **579**, displayed an in vivo (mice) analgesic potency 6 times that of morphine.

In the last several decades, computational approaches to drug discovery have become increasingly important.[208] They actually changed the landscape of medicinal chemistry and now play a significant role in rational drug design. Modern pharmaceutical research is based on target-focused drug discovery, in which the goal is to affect the biological activity of a particular biological target to provide a cure or treatment for a disease.


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

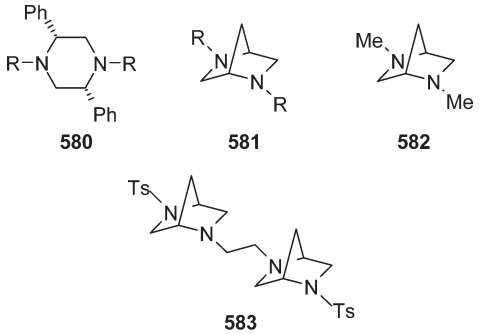
Constantly increasing knowledge about the structure of the molecular targets and their biological role, on the one hand, and development of efficient computational algorithms and computer power, on the other hand, have made it possible to assess the mode and relative energy of the interaction of a chemical compound (ligand) with a target and predict the consequences of that interaction before undertaking a tedious synthesis of that compound. We have already mentioned an advantage of CRDA-derived ligands for the theoretical evaluation of their mode and relative energy of interaction with biological targets. In such evaluations, generation of the possible molecular conformations of the ligands is the first step of numerous modern algorithms in which the ligand molecules are first docked to the targets and then scored as to relative interaction energy. Restricted conformational mobility of the ligands containing CRDA fragments ensures greater predictability of the docking and scoring algorithms and thus significantly reduces the computational time. In a recent survey of different docking programs and scoring functions,[209] the authors showed that most modern programs cannot generate correct flexible (containing more than eight rotatable bonds) ligand poses in the ligand−target complex. This will certainly be improved in the future, but today the rigidity of the CRDA-derived ligands seems to be beneficial not only for efficiency of the drug−target interaction but also for its computational assesment.



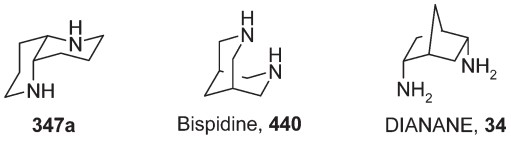

## 6.2. Use of CRDA as Ligands and Catalysts in Asymmetric Synthesis

Another area of chemistry where the CRDA have enjoyed extensive use is asymmetric synthesis. Many of the CRDA are chiral and those that are not can be easily transformed into chiral derivatives. Due to the presence of the amino groups or other functional groups attached to them, optically pure chiral CRDA or their derivatives can serve as ligands to prepare metal complexes for catalytic or stoichiometric asymmetric transformations or can themselves be used as organocatalysts. Before giving examples, we first comment on the role of the rigidity of the CRDA molecules in their use in stereoselective catalysis. It can be speculated that steric constraints imposed by a rigid chiral metal-based or organocatalyst might increase the energy difference between the two diastereomeric transition states formed with a prochiral substrate in the stereodifferentiating step. This would lead to increased stereoselectivity of the asymmetric transformations. This statement still needs very careful theoretical and experimental proof, but it has been used by many chemists as a guide in designing highly selective catalysts. However, it should be noted that catalytic processes are multistage, and transformation of the starting compounds through intermediates to final products might involve conformational changes in the catalyst so that excessive rigidity might decrease overall efficiency of the catalytic system. This subtle balance between rigidity and flexibility, as well as the particular electronic and steric requirements for the chiral molecules to be "good" for asymmetric catalysis, is extremely difficult to predict. Just as in the search for biologically active compounds, screening of a library of candidates is still the method of choice for finding the most efficient catalytic systems. We will illustrate this by several examples.

In a recent paper,[210] 37 chiral derivatives of (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane were prepared and examined as ligands in preparation of the catalysts for enantioselective addition of diethylzinc to aldehydes and as chiral Lewis acid activators in the asymmetric Diels−Alder reaction. The previously reported compound **580** was taken as the "lead"; this piperazine derivative was shown to activate the addition of diethylzinc to aldehydes, although with low enantioselectivity. The authors reasoned that conformationally restricted analogs such as **581** might induce greater enantiomeric excess of the resulting carbinols than would **580**. Indeed, one of the compounds screened, the ligand **582**, gave the highest enantioinduction in the reaction, yielding products with up to 88% ee. The complex between another derivative, **583**, and $Cu(OTf)_2$ catalyzed the stereoselective Diels−Alder reaction in 95:5 endo/exo ratio and with 72% ee.




Three other CRDA, i.e., 1,5-diaza-*cis*-decalin (**347a**), 3,7-diazabicyclo[3.3.1]nonane ("bispidine") (**440**), and *endo*,*endo*-2,5-diaminonorbornane ("DIANANE") (**34**), need special attention here in view of their exceptionally successful use in asymmetric synthesis.




The bicyclic core of the 1,5-diaza-*cis*-decalin was identified using a computational approach as a potential "lead" for the design of new ligand chemotypes for asymmetric synthesis.[211] Early attempts at application of N-alkylated derivatives of **347a** as stoichiometric additives to *s*-BuLi in asymmetric lithiation reactions were only moderately successful[126] (although a recent paper[212] reports on an improvement in the enantioselectivity of asymmetric cyclization of achiral olefinic organolithiums in the presence of the *N*,*N*-dimethyl derivative of **347a**). However, highly efficient enantioselective oxidative biaryl coupling catalyzed by 1,5-diaza-*cis*-decalin metal complexes was discovered subsequently. In a typical example (Scheme 170), a BINOL analog (*R*)-**584** was formed from **585** in 85% yield and in 90−93% ee in the presence of 2−10 mol % of (*S*,*S*)-**337a**, 2−10 mol % of CuI, and with oxygen as the oxidant.[213]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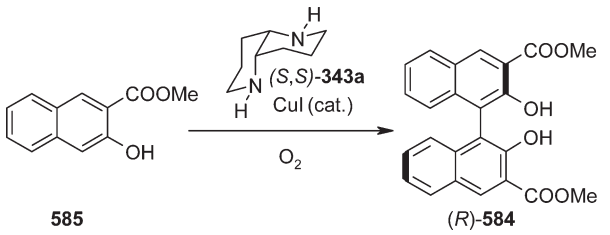
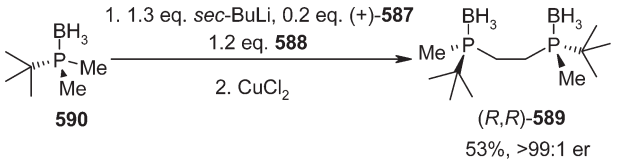
**Scheme 170**




**Scheme 171**

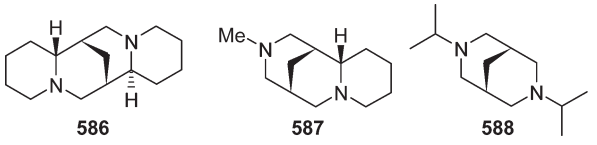



Extensive work was done to find optimal conditions, the scope of the reaction, and to get a more detailed understanding of its mechanism.[214]

Bispidine **440** is the central structural core of the alkaloid (−)-sparteine (**586**). (−)-Sparteine is widely used as a chiral diamine ligand in various stoichiometric asymmetric transformations involving enantiomerically enriched lithium−carbanion pairs.[215] The (−)-sparteine proved to be a unique ligand for this chemistry. The disadvantages of **586**, however, consist in its relatively high cost and practical unavailability of the other enantiomer—only the (−)-enantiomer occurs in nature. It was desirable, therefore, to find analogous ligands, especially those that induce enantioselectivity opposite to that induced by (−)-sparteine, and to develop catalytic variants of the corresponding stoichiometric transformations.

Despite much effort spent to find good sparteine surrogates, the efficiency of the (−)-sparteine was rarely surpassed; compound **587** is an exception. It was synthesized in three steps from (−)-cytisine and introduced as a (+)-sparteine surrogate with selectivity enantiocomplementary to (−)-sparteine.[216]

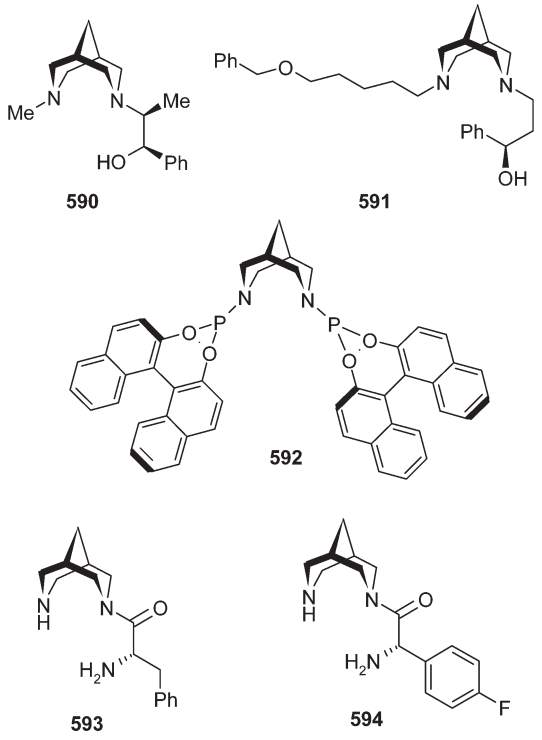
Highly efficient asymmetric reactions requiring catalytic amounts of the (−)-sparteine or (+)-sparteine surrogate in asymmetric deprotonation by *s*-BuLi were also reported.[217] The idea was to find a cheap diamine that would displace the chiral ligand from the complex formed after the lithiation, thus regenerating *s*-BuLi/(−)-sparteine complex for re-entering the catalytic cycle. This "ligand-exchange" approach indeed worked excellently when the nonchiral bispidide derivative **588** was used for the displacement.




Using the novel ligand-exchange methodology, deprotonation and carbanion trapping by electrophiles were performed successfully with *N*-Boc-pyrrolidine, *O*-alkyl carbamates (Hoppe's reaction), and phosphine−boranes. For example (Scheme 171), the compounds (*R*,*R*)- and (*S*,*S*)-**589**, which are chiral precursors of bis-phosphines widely used as ligands in Rh-based homogeneous asymmetric hydrogenation catalysts, were synthesized from **590** with high stereoselectivity using this methodology.

The bispidine molecule **440** is achiral. However, the unique mutual disposition of the nitrogen atoms and the rigidity of the bicyclic skeleton in **440** led chemists to design ligands for asymmetric synthesis by placing chiral moieties on the nitrogens in this molecule. Again, screening of libraries of ligand candidates with various *N*-substituents proved to be useful in finding the best ligands. In this way, chiral bispidine-derived amino alcohol ligands for the enantioselective addition of diethylzinc to aldehydes, as exemplified by **590**[153b] and **591**,[218] were found. Phosphoramidite ligands (for example, **592**) proved to be selective in the Cu-catalyzed 1,4-addition of dialkylzinc reagents to cyclic and acyclic enones.[219b] Polymer-bound analogs of **591** and **592** were also tested in corresponding asymmetric transformations.[233,219b]

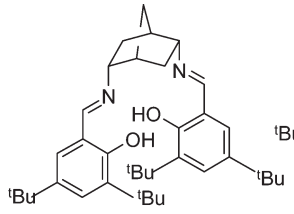
The bispidine framework was also used to develop organocatalysts for asymmetric organic transformations. Asymmetric direct aldol reactions of functionalized ketones,[220] as well as the asymmetric Michael addition of ketones to nitroolefins,[221] were catalyzed by α-amino acid derivatives of bispidine. A number of derivatives were tested to find the most selective catalysts (for example, **593** and **594**), which led to the products with up to 99% ee after optimization of the reaction conditions.



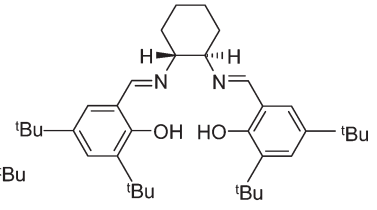

*endo*,*endo*-2,4-Diaminonorbornane ("DIANANE") was recently proposed as the scaffold to prepare salen ligands, e.g., **595**.[31,32] The corresponding *trans*-diaminocyclohexane-derived ligands, for example, **596**, found application in a very broad range of catalytic transformations.[222] It was suggested that alteration of the spatial disposition of the nitrogen atoms in analogous ligands might play an important role in further


dx.doi.org/10.1021/cr100352k |*Chem. Rev.* 2011, 111, 5506–5568

improving the catalytic properties.[31] The DIANANE-derived salen ligands indeed proved to be efficient and selective in the nucleophilic addition of organochromium reagents to aldehydes (Nozaki−Hiyama−Kishi reaction). Recently, Cr(III)−DIANANE−salen complexes were tested in a completely different transformation, i.e., the Diels−Alder reaction of Danishefsky's diene with various aldehydes.[223] The reactions gave the corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-ones in high yields and enantioselectivities (up to 96% ee). It can be suggested that DIANANE-derived salen ligands will find application in other catalytic reactions just as did the 1,2-diaminocyclohexane salen ligands.




595




596

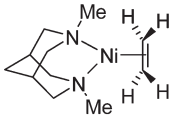
As a recent example, which also demonstrates the use of chiral spirocyclic CRDA, we cite here the work of Chan et al.[47] The rigid diamine **67** possessing axial chirality was used as the scaffold to prepare a spiro bisphosphinamidite ligand **597** (SpiroNP). The rhodium-based catalyst [**597**-Rh(COD)]$BF_4$ was tested in hydrogenation of "standard" α,β-unsaturated carboxylic acids and showed excellent activity and enantioselectivity, giving products of up to >99% ee.

### 6.3. CRDA-Derived Compounds Possessing Useful Properties Apart from Their Biological Activity and Synthetic Utility

The use of CRDA is by no means restricted to medicinal chemistry and asymmetric synthesis. Less numerous, but still highly interesting, papers can show how diverse are the areas of chemistry and other branches of science where CRDA found application. The examples below will hopefully encourage other interesting ideas in this field.

The molecular scaffold of the bispidine discussed in the previous section was used to construct a molecule with the nitrogen atoms incorporated in a rigid polycycle, **598**.[224] The authors found that **598** was a very strong base: it was capable of abstracting the proton from chloroform to form dichlorocarbene. Further studies including X-ray analysis have shown that the proton was drawn into a molecular cavity formed by the four nitrogen atoms; the p$K_a$ for **598** was estimated to be 24.9, slightly higher than that for DBU. This behavior prompted the authors to name compound **598** the "real proton sponge". The rigid framework of this molecule forces the nitrogen lone pairs to be located in close proximity, like in the naphthalene-derived proton sponge **599**. Strong hydrogen bonding of the proton by such molecules is the cause for their exceptionally high basicity.[225] Similar systems were recently studied theoretically.[226] There is a striking difference between **598** and the previously known strong bases like DBU or the proton sponge **599**. While the basicities of DBU and **598** are close, the former cannot abstract the proton completely from chloroform. This was ascribed to the particular geometry of **598** and the steric hindrance at the nitrogen atoms.[224]

The spatial disposition of nitrogen atoms in the bispidine is ideal for coordination of certain metal centers. In a work of Pörschke et al.,[227] this property of the bispidine core was used to synthesize unique diamine nickel(0)−ethene and −ethyne complexes (**600** and **601**), which provide limiting cases of the Pearson hard−soft/acid−base concept. The rigidity and preorganization of the bicyclic skeleton acted as the powerful stabilizing factor, allowing the hard diamine ligand to chelate the soft Ni(0) in combination with nonactivated alkenes or alkynes, an unprecedented fact in Ni(0) coordination chemistry.

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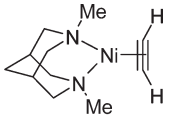


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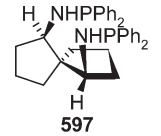
The bispidine scaffold has also been used to construct chiral ligands for determination of the absolute configuration of chiral palladium complexes.[228] Namely, the chelating ligand (*S*,*S*)- or (*R*,*R*)-*N*,*N*′-bis(phenylethyl)bispidine **602** allowed straightforward determination of the absolute configuration of chiral (π-allyl)Pd complexes. Compound **602** and the π-allyl ligand accommodated themselves around the metal center in a well-defined fashion (with the bulky phenyl substituents pointing "outward"), determined by the steric demands and rigidity of **602**. Consequently, the chiral auxiliary **602** served as a reporter: the absolute configuration of the π-allyl ligand can easily be deduced from characteristic interligand NOEs in the $^1$H NMR spectra, as shown in Figure 21 for (*R*)-4-acetoxy-1,2,3-$\eta^3$-cyclohexenyl. It is interesting to note that an analogous ligand was proposed by the same authors[229] to act as a "conformational brake" that forced flexible π-allyl chains to adopt one single conformation, as illustrated in Figure 21. The restricted rotation was achieved even for those π-allyl ligands possessing no bulky substituent, apparently because of the great steric demands of the CRDA-derived ligand.

The preorganization in the other diamine molecule, **33a**, was the factor that dictated the mode of Pt(II) coordination.[27] While *trans*-cyclohexane diamine forms mononuclear Pt(II) complexes, the rigid diamine **32a** led to formation of single μ-ligand dinuclear platinum complexes. "Quantum screening" of the norbornane-derived CRDA **33a** and **603**−**605** at the HF/6-31G level identified **33a** as the one of those ligands having the most favorable bite angle for the formation of dinuclear Pt(II) complexes.

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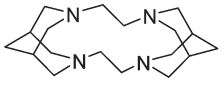


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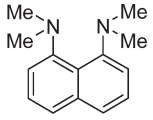


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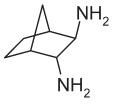


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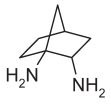


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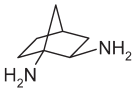


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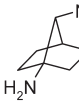


605

In the previous section, another norbornane-based diamine, DIANANE (**34**), was mentioned as useful in preparing salen-type ligands for asymmetric catalysis. It was also used to prepare an unusual diaminotetracarboxylic ligand NorDATA (**606**), a "preorganized" analog of the known ligand EDTA


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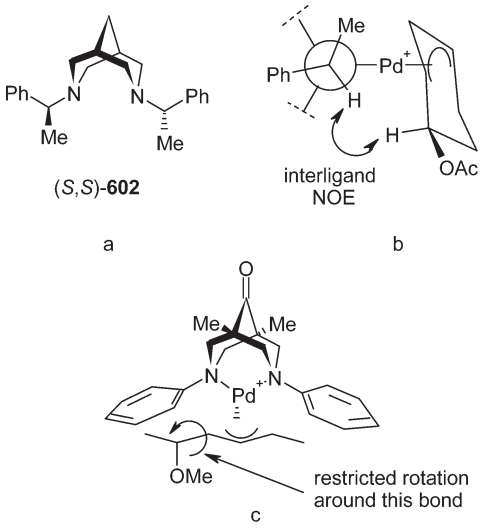
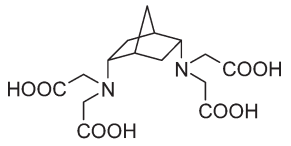


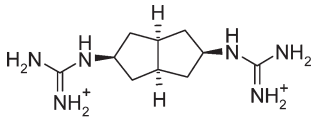

**Figure 21.** (a) Structure of the auxiliary ligand (*S*,*S*)-**602**. (b) Newman projection showing the characteristic interligand NOE in the Pd(0) complex with (*S*,*S*)-**602** and (*R*)-4-acetoxy-1,2,3-$\eta^3$-cyclohexenyl proposed in ref 228 for determining the absolute configuration of ($\pi$-allyl) Pd complexes. (c) "Molecular brake" employing a bispidine-derived ligand.

(ethylenediaminetetraacetate), which has long been used extensively in science and industry. The complexation behavior of the NorDATA (prepared as a racemate) was studied and compared with that of EDTA and other known analogs. Enhanced selectivity was found for complexation of the NorDATA with different metal ions, which might be the consequence of the rigid fixation of the nitrogen atoms on the rigid norbornane skeleton. The functional groups in **606** form a cavity that matched or mismatched the size of different metal ions upon coordination.[230]




NorDATA, **606**

CRDA open up versatile opportunities for the needs of supramolecular chemistry. The restricted conformational mobility and preorganization of the CRDA scaffolds is exactly what is needed for constructing different supramolecular systems. As supramolecular interaction is a central event in the recognition of drugs by molecular targets, many parallels can be drawn between medicinal and supramolecular chemistry. Thus, bicyclo[3.3.0]octane derivative **607** was designed as an artificial receptor for sequence-selective binding of proteins.[23a] Two guanidinium groups in this receptor are so organized in space as to be complementary to a specific interaction with aspartate carboxylates on protein surfaces. Indeed, this and subsequent studies[23b] showed that model α-helical peptides with two aspartates separated by two other amino acid residues [($i$ + 3) peptides] bind **607** with high affinity in competitive solvents. Moreover, significant stabilization of the helical structure was observed for the ($i$ + 3) peptides upon receptor binding. The experimental results and molecular modeling suggested that the receptor and the corresponding peptide formed a 1:1 supramolecular complex through specific hydrogen-bonding interactions between each receptor guanidinium and each substrate carboxylate when the peptide adopted a helical conformation. Potential applications of these results might be the disruption of physiologically important protein−protein interactions or protein purification by polymer-bound receptors.




**607**

Another rigid scaffold, bicyclo[1.1.1]pentane, provides an opportunity to design rod-shaped construction elements for the assembly of molecular structures of the "Tinkertoy" type.[231] Bicyclo[1.1.1]pentane ([1]staffane) derivative **58** with collinear CN bonds was suggested as one such construction element.[41] The strained but stable bicyclic core in **58** ensures the overall stability of molecular constructions.


**58**

At the end of this section we discuss examples of the use of CRDA in materials science. A recent paper[232] reported application of quaternized derivatives of CRDA, among other cyclic and polycyclic amines and diamines, as "templates" or structure-directing agents (SDA) in preparing zeolites. The templates stabilized void regions within the inorganic framework of zeolites, being included in the crystallizing products as guest molecules and then easily removed simply by washing with water. The size and shape of the SDA were purposely designed in order to obtain novel zeolite structures. By screening a number of SDA, the authors found the design strategy that led to novel, uncommon zeolite phases. In particular, the SDA molecules which are too large or of the wrong geometry to stabilize commonly encountered competing phases can be used to synthesize novel, unusual zeolitic phases, designated as SSZ-35, SSZ-36, and SSZ-39. For example, selective formation of the SSZ-35 zeolitic phase was observed in the presence of the bispidine derivative **608** (Figure 22).

Bifunctional diamine molecules are perfectly suited for polycondensation reactions as themselves or after transformation into reactive intermediates, for example, *bis*-isocyanates. It is therefore not surprising that CRDA were used for preparing polymeric materials. In fact, many early CRDA syntheses were patented by companies active in this field.[233] Studies have shown that polymers derived from rigid monomers have improved mechanical and thermal properties.[234] A regular conformation may exist in a polymer made of rigid monomers. For example, in ref 177 this was confirmed by preparing optically active polyamides from (+)-(*S*)-*trans*-1,2-cyclopropanedicarboxylic acid or (+)- and (-)-*trans*-1,2-cyclohexanedicarboxylic acid and the rigid spirodiamine 2,6-diazaspiro[3.3]heptane (**489**).

### 6.4. CRDA and Their Derivatives as Model Compounds

The overview of CRDA applications would not be complete without mentioning their use as model compounds. Under the term "model compound" we mean here a compound that is studied in chemistry or other branches of science to obtain new knowledge about another object of study, so that the model serves as an appropriate surrogate of the object (which is usually difficult to study directly).

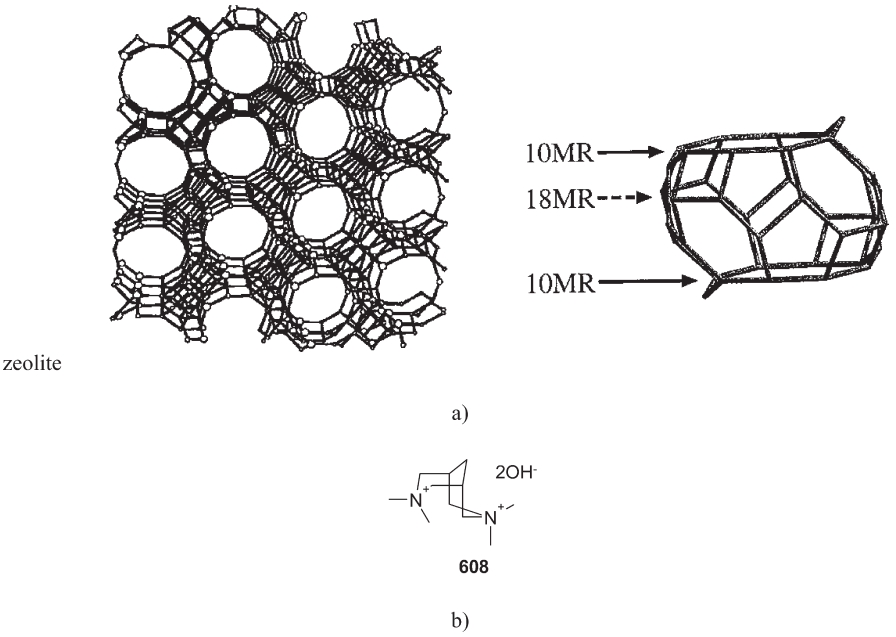
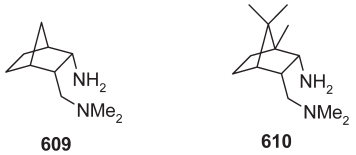



**Figure 22.** (a) Framework representation of the zeolitic phase SSZ-35. (b) Structure-directing agent used to selectively obtain the SSZ-35. (Adapted from ref 232.)

The objects of studies using model compounds are very diverse.[235] For example, other chemical compounds for which the models serve as simpler surrogates can be studied; concepts in theoretical chemistry or stereochemistry (e.g., aromaticity, empirical rules) can be verified; reaction mechanisms and synthetic paths toward complex molecules can be tested.

Applications of CRDA and their derivatives in model studies are relatively rare, which seems surprising in view of the extensive use of CRDA in other branches of science exemplified in the previous sections. Nevertheless, we would like to bring the reader's attention to this aspect of the use of CRDA because we believe that the potential of CRDA in this area is far from being exploited in full. We refer here to papers in the area of bioorganic chemistry, where modeling (in the sense outlined above) is one of the main instruments of the research into biological systems. In particular, enzyme models—compounds that model specific aspect(s) of enzyme chemistry — have long been successfully used to study enzyme structure and the mechanisms of their catalytic activity.[236] In this case, the use of model molecules is justified by the formidable complexity of both the enzyme molecules and the mechanisms of their catalytic action. Many known efficient enzyme modeling systems are constructed using rigid or conformationally restricted building blocks. Rigid scaffolds allow chemists to bring together functional groups that model the catalytic functions and adjust their mutual disposition in space to find closest resemblance of the putative enzyme active site. By restriction of conformational freedom in enzyme models one could exclude structural variability of the models and thus simplify the interpretation of the experimental results. Although acyclic and cyclic diamines have been extensively used to construct various enzyme models (for some examples, see ref 237), their rigidified counterparts have received almost no attention. An exception—a series of papers devoted to the use of diamines (including bicyclic compounds **609** and **610**) as the enzyme models[12,238]—is worth mentioning in this section. Although synthesis of **609** and **610** was not discussed in this review (the structures are beyond the scope outlined in the Introduction), the above-mentioned papers[238] are among the first that used conformationally restricted diamines as enzyme models and vividly illustrated the benefit of rigidifications in achieving polyfunctional catalysis relevant to enzymatic transformations. The authors found that some acyclic diamines (for example, $Me_2N(CH_2)_3NH_2$) were capable of catalyzing removal of α-hydrogen from aldehydes and ketones, a process that is widespread in nature and is catalyzed by many enzymes. Prompted by an examination of the hypothetical transition state of a model reaction (hydrogen—deuterium exchange in ketones catalyzed by the diamines), the authors suggested the most favorable spatial disposition of the nitrogen atoms involved in the catalysis and proposed constraining the catalyst to this disposition by a rigid scaffold as in **609** and **610**. Compounds **609** and **610** turned out to be the most efficient catalysts of all compounds studied [(1*R*,2*S*,3*R*,4*R*)-**610** was stereoselective], thus confirming the hypothesis on the mechanism of the catalysis and possibly pointing out how the corresponding enzymes[239] might work.




Most of the uses of CRDA-based model molecules can be found in medicinal chemistry. CRDA and their derivatives have been used to map the ligand-binding domains of enzymes, receptors, or other molecules suggested as drug targets. In these cases, just as in enzyme modeling, the use of model molecules is justified by the complexity of the drug targets and by the difficulties in studying the biochemical processes in which they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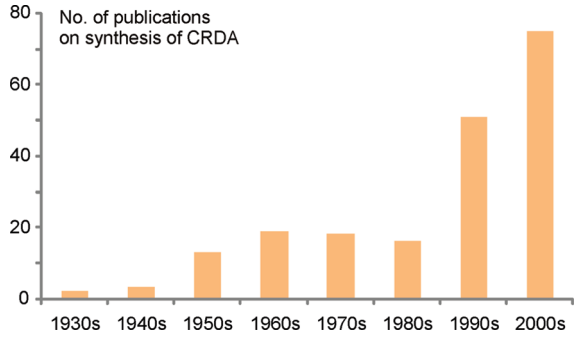
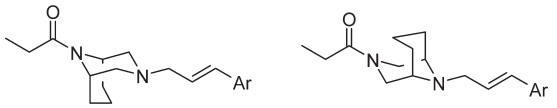
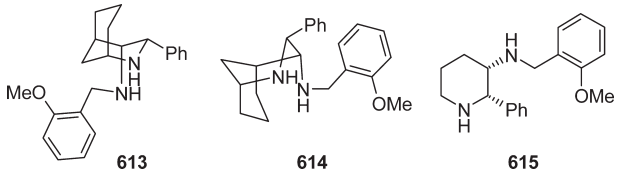



**Figure 23.** Number of the publications describing the synthesis of CRDA (parent and N-protected) over the period from the 1930s to 2000s.

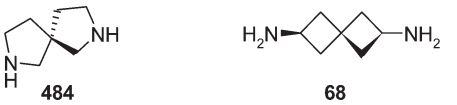
are involved. The model studies are especially valuable when detailed structural information about the molecular drug target is scarce. For example, compounds **611** and **612** (analogs of **577** and **578** described in the section 6.1) were synthesized and tested for binding affinity toward opioid receptor subtypes $\mu$, $\delta$, and $\kappa$, the detailed structures of which were unknown. Strongly selective $\mu$-affinity of these compounds was found, and the results were used to refine and verify the hypothesis concerning the existence of two hydrophobic pockets in the receptor able to accommodate the endoethylenic bridge in **577** and **578** on the mode of interaction of such compounds with the $\mu$-receptor.[118a]




Model compounds with restricted conformational mobility are used to find the so-called biologically active conformation of flexible drug molecules. In ref 240, two 2-azabicyclo[3.3.1]nonane derivatives **613** and **614** were suggested as models of the known nonpeptidic substance P antagonist, **615**. Compound **615** can adopt either a chair or a boat conformation when bound to the receptor. In **613** and **614**, these conformations are locked by the bridges. A study of the biological activity of the model molecules might shed light on the mode of the interaction of **615** with its biological target.




As a successful example of the use of CRDA as model compounds in stereochemistry, we cite here early reports on the study of axial chirality. The diamines **484** and **68** are simple examples of compounds possessing axial chirality, and interest in them arose more than a half of a century ago.[50] In a series of papers,[49,171,241] compounds **484** and **68** have been used to verify empirical rules and theoretical models for establishing absolute configuration of chiral compounds on the basis of their chiroptical properties. A striking invalidity of the empirical rules was found for these particular spiro systems.




Finally, the conformationally restricted diamines and their derivatives are expected to form discrete homo- and heterochiral associations and therefore serve as interesting model compounds for the study of the self-disproportionation of enantiomers via achiral chromatography[242] and sublimation.[243]

## 7. CONCLUSIONS

A continuing and constantly increasing interest in synthesis of CRDA, which has lasted for more than half of a century (Figure 23), resulted in the development of efficient and practical procedures for obtaining many of the theoretically possible molecules of this type. This interest was fuelled by the prospect of many interesting applications of CRDA. Still, there exists a great unused potential of CRDA in chemistry and related branches of science. The structural diversity, molecular rigidity and preorganization, and ease of chemical modification were the main factors determining the success of numerous published applications of CRDA. It should be stressed, however, that CRDA may not be regarded as uniquely possessing these features, since other compounds, for example, conformationally restricted amino acids, have found similarly broad application. We hope that the ideas highlighted in this review can also be projected to other classes of organic compounds characterized by conformational restrictions.

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## BIOGRAPHIES

Oleksandr O. Grygorenko was born in Brody, Lviv region, Ukraine, in 1982. He received his M.S. in chemistry (2004) and Ph.D. in organic chemistry (2007) from Kyiv National Taras Shevchenko University under the supervision of Prof.

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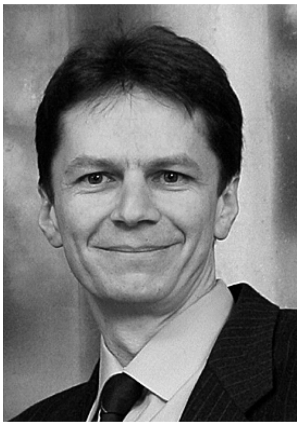
Dmytro S. Radchenko was born in Zaporizhya, Ukraine, in 1985. He received his B.S. (2006) and M.S. (2007) in chemistry from Kyiv National Taras Shevchenko University under the supervision of Prof. Dr. Sci. Igov V. Komarov. At present, he is a Synthetic Chemist at Enamine Ltd. He is also working toward his Ph.D. in organic chemistry on conformationally restricted amino acids at Kyiv National Taras Shevchenko University.

Dmitriy M. Volochnyuk was born in 1980 in Irpen, Kyiv region, Ukraine. He graduated from Kyiv State Taras Shevchenko University in 2002 and was awarded his M.S. degree in chemistry. He received his Ph.D. in organic chemistry in 2005 from the Institute of Organic Chemistry, National Academy of Sciences of Ukraine under the supervision of Dr. A. Kostyuk for research on the chemistry of enamines. At present, he divides his time between the Institute of Organic Chemisty, as Deputy Head of Organophosphorus Department and Senior Researcher, and Enamine Ltd (Kyiv, Ukraine), as Director of Chemistry. His main scientific interests are related to fluoroorganic, organophosphorus, heterocyclic and combinatorial chemistry, and multistep organic synthesis. He is a coauthor of more than 80 papers.

Andrey A. Tolmachev was born in Kyiv, Ukraine, in 1957. He graduated from Kyiv State Taras Shevchenko University in 1979. He received his Ph.D. (1986) and Doctor of Sciences degree (1997) in organic chemistry from the Institute of Organic Chemistry, National Academy of Sciences of Ukraine, where he worked from 1979 to 2001. In 2002, he moved to Kyiv National Taras Shevchenko University. At the moment, he is the Director of ChemBioCenter at this university. He is also Scientific Advisor at Enamine Ltd. (Kyiv, Ukraine). His scientific interests include the chemistry of heterocycles and elementoorganic chemistry (organophosphorus, organosilicon). He is a coauthor of more than 160 papers.



Igor V. Komarov was born in Irkliev, Cherkasy region, Ukraine, in 1964. He obtained his Ph.D. degree in 1991 in organic chemistry at Kyiv National Taras Shevchenko University under the supervision of Prof. Mikhail Yu. Kornilov. Two postdoctoral fellowships followed: at the University Chemical Laboratory (Cambridge, UK) with Prof. Anthony J. Kirby FRS (NATO Postdoctoral Fellowship Award) and at the Institut für Organische Katalyseforschung (Rostock, Germany) with Prof. Armin Börner (Alexander von Humboldt Fellowship Award). He joined the Organic Chemistry Department of Kyiv National Taras Shevchenko University in 1997 as an Assistant Professor and has been working there since then, presently holding positions of Professor at the Organic Chemistry Department and Vice-Director of the Institute of High Technologies. He received the Doctor of Sciences degree in 2003 for his work on the synthesis of model molecules to solve problems in stereochemistry, physical organic chemistry, and catalysis. His research work and that of his scientific group is directed to the study molecular rigidity and its use in diverse areas of science—

medicinal chemistry, bioorganic chemistry, stereochemistry, theoretical chemistry, and catalysis. Synthesis of model molecules, unusual amino acids, including fluorine-substituted and peptides from them, conformationally restricted diamines, and other building blocks for drug design are within his interests. Special effort is placed in his group on the development of new synthetic approaches toward strained and polycyclic compounds. He is a coauthor of more than 100 papers.

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