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Synthesis of Novel Derivatives of (1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]heptane and Their Evaluation as Potential Ligands in Asymmetric Catalysis

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Thirty-seven (most of them novel) chiral derivatives of (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane (**2**–**36**, **38**, **39**) were prepared from (*S*)-*trans*-4-hydroxyproline. A selection of these chiral ligands were examined as potential ligands in the preparation of catalysts for the enantioselective addition of diethylzinc to aldehydes and as chiral Lewis acid activators in the asymmetric Diels–Alder reaction. In the former system, diamine **30** induced up to 92 % enantiomeric excess in the formation of (*S*)-phenyl ethyl carbinol, whereas in the case of the cycloaddition reaction between cyclopentadiene and 3-acryloyloxazolidin-2-one the catalytic complex formed between dimeric derivative **8** and copper triflate [$Cu(OTf)_2$] afforded the expected product in a 95:5 *endo*/*exo* ratio and up to 72 % *ee* for the major diastereomeric product. Finally, some of the novel chiral diamines prepared in this work were also evaluated as potential organocatalysts in the asymmetric amination of ethyl α-phenyl-α-cyano acetate. Bifunctional derivative **12** provided the aminated product in excellent yield and with up to 40 % *ee*.

Introduction

One of the most active areas in modern synthetic organic chemistry involves the development of asymmetric reactions leading to the generation of enantiopure products.[1] Particularly relevant is the creation of protocols involving the use of complexes of homochiral ligands and transition metals, which generally act as Lewis acids in catalysis of the enantioselective formation of carbon–carbon and carbon–heteroatom bonds.[2]

As a consequence, the search for ever more efficient chiral ligands that, in addition to promoting reactions in high yields and with high enantioselectivities, also possess the ability to distinguish between substrates that are closely related structural analogues has attracted the attention of many chemists over nearly three decades, and the pace of development has shown no sign of abating in recent years.[3] Furthermore, a significant number of the chiral ligands employed in the preparation of organometallic catalysts have been found to be efficient organocatalysts; that is, they are capable of promoting the enantioselective formation of carbon–carbon and carbon–heteroatom bonds in the absence of metals.[4]

A current challenge in this area consists of the development of readily available, structurally simple organocatalysts that induce high enantioselectivities in the final products.[5]

Asymmetric organozinc additions to aldehydes and ketones allow the synthesis of chiral alcohols, which are ubiquitous in the structures of natural products and pharmaceutical drugs. Since the initial reports by Oguni and Omi[6] and by Noyori and co-workers[7] in the mid-1980s, research on asymmetric addition of dialkylzinc compounds to carbonyl compounds has expanded enormously.[8] Indeed, the reaction between Et_2Zn and benzaldehyde has become a classical test in the design of new ligands for catalytic enantioselective synthesis.[8e]

Another important reaction that can proceed diastereo- and enantioselectively with catalysis by chiral Lewis acids is the Diels–Alder reaction.[9]

Motivated by the extraordinary success of (–)-sparteine, a natural alkaloid presenting a suitable disposition of two nitrogen atoms in tertiary amine segments, as a chiral ligand in stereoselective organolithium chemistry,[10] we deemed it important to search for novel chiral diamines as potential ligands in the enantioselective addition of Et_2Zn to benzaldehyde. In contrast with the large number of reports describing the use of chiral amino alcohols and aminothiols as activators in this reaction,[8] very little effort has

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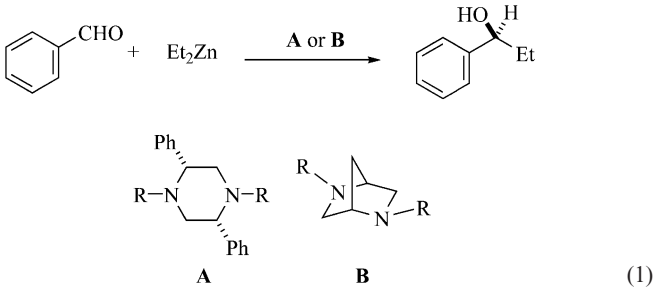
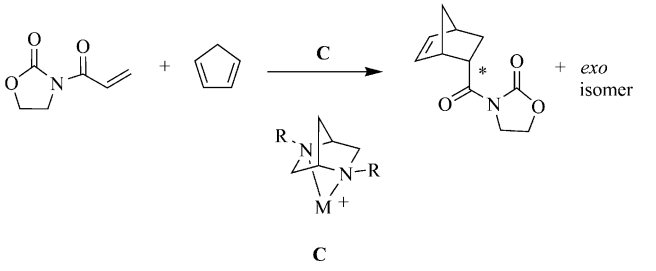
been dedicated to the study of chiral diamines in this endeavor.[11–13]

Perhaps most pertinent to this study is the report by Fuji and co-workers[12d] describing the use of chiral piperazine **A** as an activator for the reaction between Et_2Zn and benzaldehyde to afford low enantioselectivity in the product. We considered that conformationally rigid analogues **B**[14] might induce greater enantiomeric excesses in the resulting carbinol, see Equation (1).



(1)

Furthermore, metal ions other than zinc would be expected to associate with ligands **B**, affording chiral Lewis acids **C**, which should catalyze the cycloaddition reaction between cyclopentadiene and 3-acryloyloxazolidin-2-one, see Equation (2).

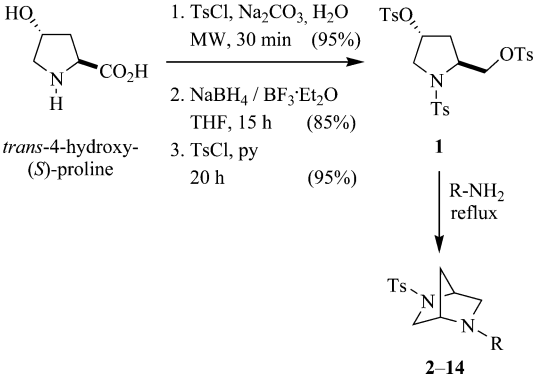


(2)

The synthesis of (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane from the readily available (*S*)-*trans*-4-hydroxyproline has been described by several research groups.[15] In this report thirty-seven novel derivatives have been prepared, and some synthetic steps have been improved by the use of microwave irradiation.[16]

Results and Discussion

(2*S*,4*R*)-*N*-Tosyl-4-tosyloxy-2-(tosyloxymethyl)pyrrolidine (**1**, Scheme 1) was prepared from (*S*)-*trans*-4-hydroxyproline by treatment with *p*-toluenesulfonyl chloride and aqueous sodium carbonate. Interestingly, use of conventional heating required a reaction time of 48 h, whereas under microwave irradiation conditions the reaction was complete (95% isolated yield) in only 30 min. The carboxylic group in **1** was then reduced with diborane as described in the literature,[15c] and treatment with additional *p*-toluenesulfonyl chloride in pyridine afforded tritosylate **1** in 77% overall yield (Scheme 1).



Scheme 1.

Cyclization of tritosylate **1** with selected primary amines afforded the desired 5-alkyl-2-tosyl-2,5-diazabicyclo[2.2.1]-heptanes **2**–**14** (Scheme 1). For instance, diazabicyclo derivative **2** was obtained with benzylamine (1.2 equiv.). Relative to the conditions described in the literature,[15a,15d] it was found that this reaction proceeds more rapidly by heating to reflux for 2 h in the absence of solvent. Furthermore, under microwave irradiation conditions this reaction takes place in a mere 30 min (95% isolated product). The preparation of diazabicyclic derivatives **9** and **10** (Entries 8–9 in Table 1) was also improved by the use of microwave irradiation. The conditions used for the preparation of diazabicyclo derivatives **2**–**14** are summarized in Table 1.

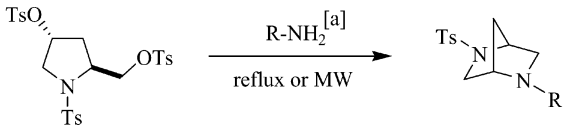
In the cases of **8** and **9**, these diazabicyclic derivatives were obtained as side products of one another; nevertheless, either one could be prepared as major product by adjustment of the synthetic protocol. Indeed, when substrate **1** and spacer ethylenediamine in a 1:1 ratio are heated at reflux for 50 h, "dimeric" ligand **8** is isolated as the main product although in low yield; however, in the presence of an excess of ethylenediamine and with a shorter reaction time product **9** is obtained in 71% yield (Table 1).

N-Benzyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptane (**2**) was a precursor of several derivatives. To this end, **2** was detosylated under microwave irradiation conditions over 30 min with 6 equiv. of hydrobromic acid (48%) at reflux to give a 98% yield of **15**. (For comparison, conventional heating requires 2–6 h at reflux for reaction completion[15c,15d]). *N*-Benzylated diazabicyclo compound **15** was modified in three different ways: a) *N*-methylation under Eschweiler–Clarke conditions[17] afforded the dialkylated derivative **16**, b) debenzylation of **15** by hydrogenolysis with palladium on charcoal provided the parent (1*S*,4*S*)-2,5-diazabicyclo-[2.2.1]heptane **17** in 94% isolated yield, and c) treatment of **15** with 2-bromoethanol gave derivative **18** in 77% isolated yield (Scheme 2).

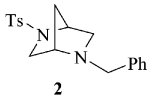
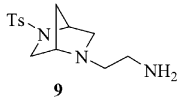
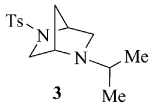
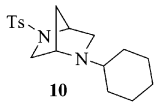
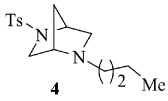
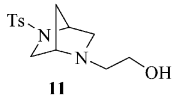
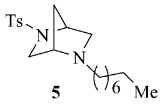
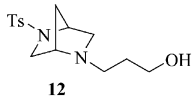
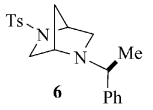
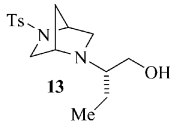
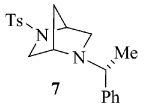
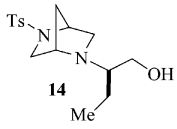
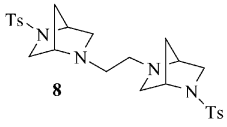
In this context, *N*-methylation of amine **9** under Eschweiler–Clarke conditions[17] afforded dimethylated derivative **19** in 37% isolated yield [Equation (3)].

Bis-sulfonamide **21** was prepared by debenzylation of **2**, followed by treatment with *p*-toluenesulfonyl chloride. C_2-Symmetric diazabicyclo[2.2.1]heptanes **22**, **24**, **26**, and **28** were obtained by detosylation of **2**–**5** (48% hydrobromic

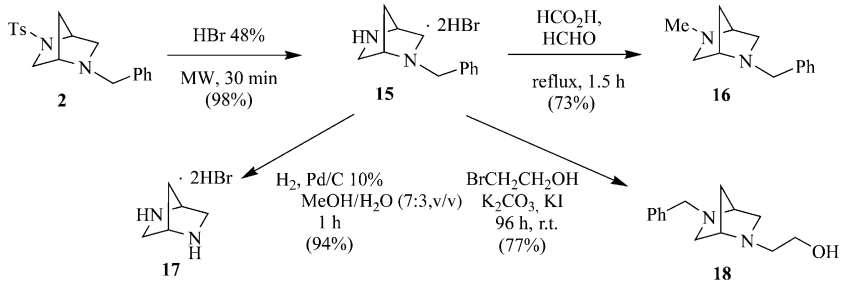
Table 1. Cyclization of tritosylate **1** with different primary amines to afford diazabicyclo derivatives **2**–**14**.



1 **2-14**

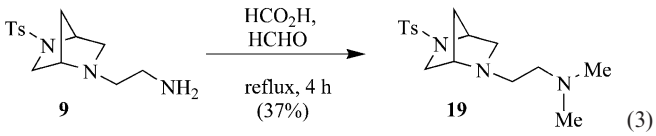
Entry	Product	Time [h]	% Yield	Entry	Product	Time [h]	% Yield
1	 **2**	2 (0.5 h)[b]	93 (95)[b,c]	8	 **9**	24 (1.5)[b]	71[c] (77)[b]
2	 **3**	5	95[c]	9	 **10**	18 (1)[b]	87[c] (73)[b]
3	 **4**	2	85	10	 **11**	1	83
4	 **5**	3	77	11	 **12**	1	89
5	 **6**	5.5	70	12	 **13**	2	84
6	 **7**	5.5	72	13	 **14**	2	79
7	 **8**	50	22[c]				

[a] Equivalents of primary amine: for **2**, 4 equiv.; for **3**, 14 equiv.; for **4**, 17.5 equiv.; for **5**, 9 equiv.; for **6**, 11 equiv.; for **7**, 11 equiv.; for **8**, 1 equiv.; for **9**, 5 equiv.; for **10**, 4.4 equiv.; for **11**, 25 equiv.; for **12**, 19 equiv.; for **13**, 12 equiv.; for **14**, 9 equiv. [b] Under microwave irradiation conditions. [c] Acetonitrile or toluene.



Scheme 2.

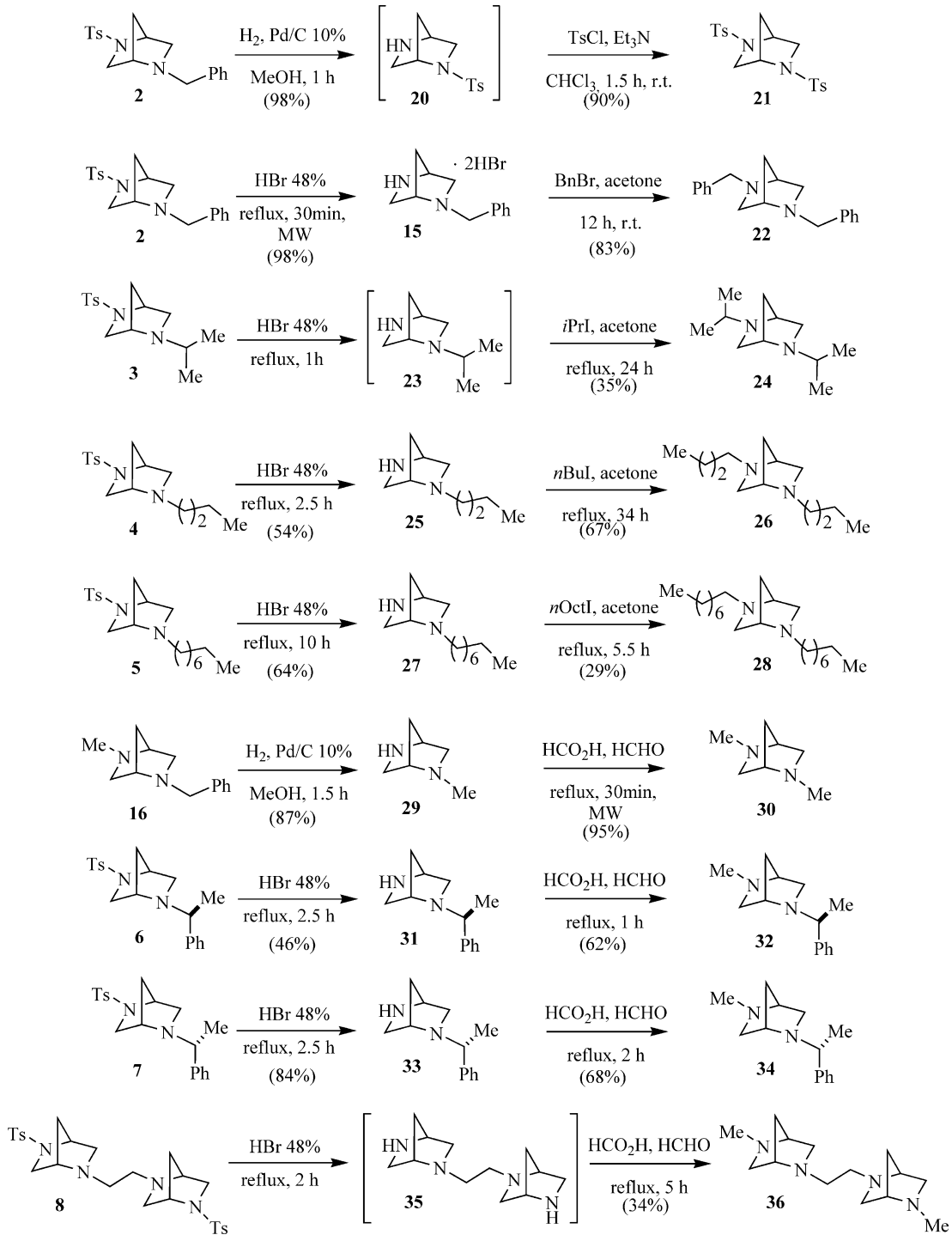
acid), followed by alkylation (Scheme 3). Hydrogenolysis of **16** under mild conditions afforded debenzylated product **29**, which was methylated under Eschweiler–Clarke conditions either by conventional heating (5 h) or with microwave irradiation (30 min). Diamines **32** and **34**, containing the α-phenylethyl segment, were prepared by detosylation of **6**



(3)

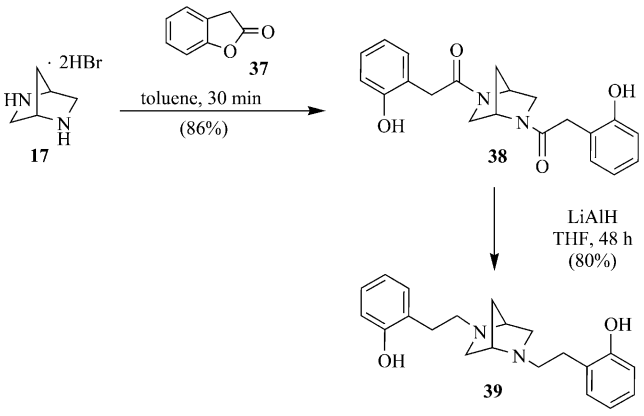
and **7**, followed by methylation under Eschweiler–Clarke conditions (Scheme 3).

Finally, in order to prepare diazabicyclo derivatives containing phenolic substituents, parent precursor **17** was treated with lactone **37**,[18] to provide the diamide **38** in 86%



Scheme 3.

isolated yield. The rather complex NMR spectra suggest dynamic equilibria between several conformers that interconvert by slow rotation around the N–C=O segments. Reduction of **38** with lithium aluminumhydride provided the C_2-symmetric diaminephenol **39** in 80% isolated yield (Scheme 4).



Scheme 4.

Heterocycles **4**, **10**, **13**, **14**, and **21** afforded crystals suitable for structural analysis by X-ray diffraction.[19] Figure 1 presents the solid-state conformations of these diazabicyclo[2.2.1]heptanes. Salient observations are the preference of the *N*-sulfonyl moiety for adopting an *exo* orientation, whereas *N*-alkyl groups occupy the *endo* position. Significantly, both *N*-sulfonyl substituents in the bis-sulfonamide **21** are oriented in the *exo* positions, and this might suggest that the nitrogen lone pairs should be available for bidentate coordination with Lewis acids and metal ions.

Applications in Asymmetric Catalysis

A. Attempted Lithiation–Substitution Reactions

Motivated by the reports describing enantioselective substitution of enantiotopic acidic hydrogens by lithiation with butyllithium/(–)-sparteine,[20] we explored the application of (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptanes **22**, **24**, **26**, **28**, and **30** as potential chiral ligands for *sec*-butyllithium. As it turned out, no metallation reaction of amide **40** took place, apparently owing to destruction of the alkyllithium, as sug-

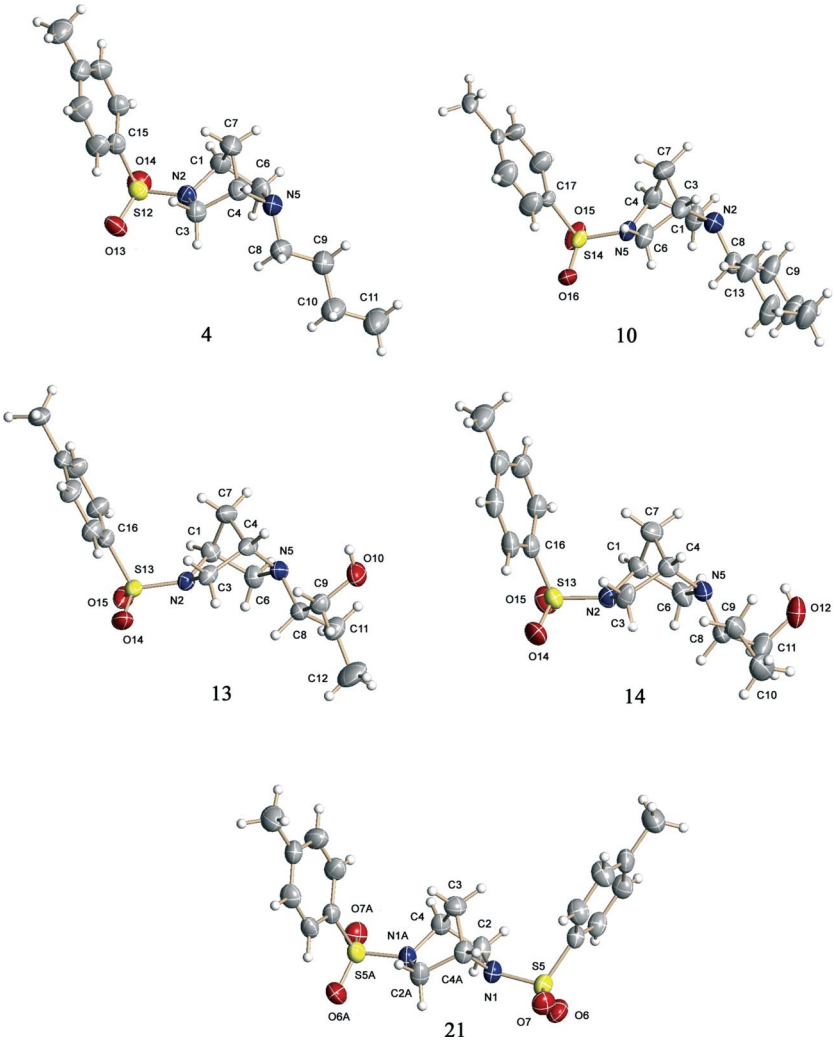
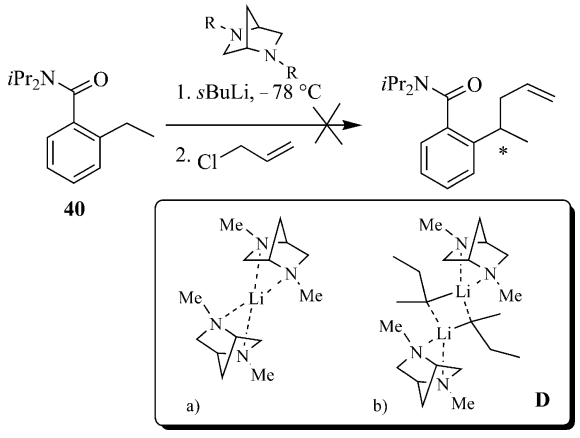


Figure 1. X-ray crystallographic structures and solid-state conformations of **4**, **10**, **13**, **14**, and **21**.[19]

gested by the disappearance of the purple color obtained after its mixing with the diamines (Scheme 5). Interestingly, Bailey and co-workers[21a] have described similar results with diazabicyclo compound **30** in failed olefin cyclization reactions. We surmise that *s*-butyllithium is trapped and inactivated by formation of complex **D** (Scheme 5). Indeed, when the progress of the reaction was followed by ^{7}Li NMR, we observed that the purple color generated upon addition of *sec*-butyllithium to substrate **40** (δ = –2.43 ppm) disappears after the addition of **30**, giving rise to a new signal at δ = –1.69 ppm. Following the observations reported by Collum et al.[21b,21c] we assign this signal to species **Da** or **Db** in Scheme 5.



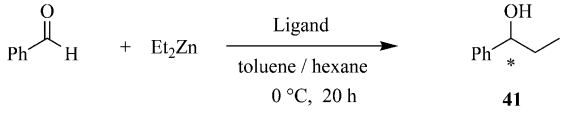
Scheme 5.

B. Addition of Diethylzinc to Benzaldehyde

Most ligands employed as activators of diethylzinc addition to aldehydes and ketones present at least one acidic hydrogen, which is involved in the accepted reaction mechanism.[22] In those few examples of the use of chiral tertiary amines,[12a,12e] rather low (<20% *ee*) enantioselectivities were observed.

Table 2 (Entries 1–18) summarizes the results of diethylzinc addition to benzaldehyde in the presence of several chiral tertiary amines. With (–)-sparteine as ligand, 1-phenylpropan-1-ol (**41**) of 8% *ee* was obtained. Moderately higher enantioselectivities were observed with diazabicyclic *N*-sulfonamides **19** (24% *ee*) and **28** (30% *ee*), whereas significant enantioinduction was achieved with *N*,*N*-dimethylated derivative **30** [60% *ee* (*R*), Entry 14 in Table 2]. It is possible that the lower enantioselectivity encountered with the derivatives that incorporate longer *N*-alkyl chains (cf. **28**; Entries 12 and 13 in Table 2) is a consequence of the more flexible natures of the N-substituents, which give rise to additional competing transition states of nearly similar energy. In the case of the diazabicyclic derivatives containing an additional hydroxylic chain, **13** afforded carbinol **41** in 50% *ee* (*S*), whereas diastereomeric **14** led to the predominant formation of (*R*)-**41** in 32% *ee*. The opposite configuration in the main products suggests the determining role of the stereogenic center in the hydroxylated chain.

Table 2. Addition of diethylzinc to benzaldehyde catalyzed by 2,5-diazabicyclo[2.2.1]heptanes.

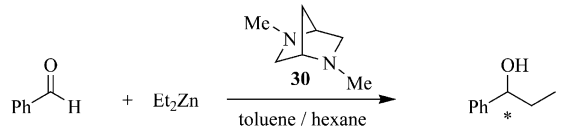


Entry	Ligand	mol-%	% Yield	% *ee*[a] (major configuration)[b]
1	(–)-sparteine	10	71	8 (*R*)
2	**7**	5	30	4 (*S*)
3	**8**	5	37	4 (*R*)
4	**10**	10	84	–
5	**16**	10	93	6 (*S*)
6	**19**	10	29	24 (*S*)
7	**25**	10	51	10 (*S*)
8	**29**	10	71	16 (*S*)
9	**22**	10	60	6 (*S*)
10	**22**	50	44	10 (*S*)
11	**24**	10	65	–
12	**28**	20	42	12 (*R*)
13	**28**	50	71	30 (*R*)
14	**30**	10	64	60 (*S*)
15	**32**	10	94	8 (*S*)
16	**34**	10	93	4 (*S*)
17	**36**	10	87	14 (*S*)
18	**39**	10	47	6 (*R*)
19	**11**	10	48	12 (*R*)
20	**12**	10	70	10 (*R*)
21	**13**	10	98	50 (*R*)
22	**14**	10	97	32 (*S*)
23	**18**	5	70	–

[a] Enantiomeric excess values were determined by chiral HPLC analysis. [b] The assignment of the configuration was based on literature precedent.[23]

Once we had established that the C_2-symmetric ligand **30** afforded the highest enantioinduction in the reaction, a search for optimum conditions was undertaken. Table 3 presents the effect of ligand concentration (mol-%) on chemical yield and enantiomeric excess. Best results were observed with 50 mol-% of **30**, with 88% *ee* (*S*) and 95% yield (Table 3, Entry 5).

Table 3. Addition of diethylzinc to benzaldehyde catalyzed by ligand (*S*,*S*)-**30**.

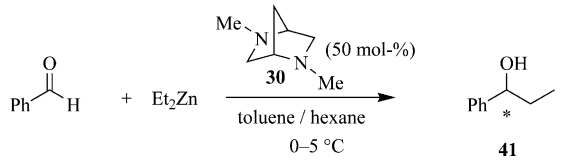


Entry	mol-%	% Yield	% *ee*[a] (major configuration)[b]
1	5	80[c]	24 (*S*)
2	10	64	60 (*S*)
3	30	57	72 (*S*)
4	40	65	84 (*S*)
5	50	95	88 (*S*)
6	75	82	88 (*S*)
8	100	61	84 (*S*)

[a] Enantiomeric excess values were determined by chiral HPLC analysis. [b] The assignment of the configuration was based on literature precedent.[23] [c] The reaction was carried out at 25 °C.

The addition reaction of diethylzinc to benzaldehyde in the presence of (*S*,*S*)-**30** was also monitored as it progressed. Table 4 shows higher enantioselectivity at shorter reaction times, reaching 92% *ee* at *t* = 4–8 h (Table 4, Entries 2–4). As already noted above, the highest yield was achieved after 15–20 h of reaction, but enantioselectivity was slightly lower (88% *ee*, Table 4, Entries 6 and 7).

Table 4. Addition of diethylzinc to benzaldehyde catalyzed by ligand **30**. Effect of the reaction time.



Entry	Time [h]	% Yield	% *ee*[a] (major configuration)[b]
1	2	40	92 (*S*)
2	4	46	92 (*S*)
3	6	50	92 (*S*)
4	8	60	92 (*S*)
6	15	98	88 (*S*)
7	20	98	88 (*S*)

[a] Enantiomeric excess values were determined by chiral HPLC analysis. [b] The assignment of the configuration was based on literature precedent.[23]

Interestingly, the amino alcohol derivatives reported by Jordis et al.[14a] induce the moderately selective formation of the enantiomer (*R*)-**41**, whereas diamine **30** affords the (*S*) enantiomer. A model that could account for the observed enantioselectivity is presented in Figure 2. This proposal takes account of the fact that zinc metal ion is able to present bi-, tetra-, and pentacoordination numbers.[24] Thus, Figure 2 suggests association of zinc to both nitrogen atoms to form tetracoordinate species **E**, which binds further to the carbonyl oxygen in benzaldehyde to give transition state **F** before transfer of an ethyl group on the less hindered *Si* face, affording (*S*)-**41** via zincate **G**. It is noted that the multinuclear complexes **E** and **F** involve bidentate coordination modes for zinc when the crystal structures in Figure 1 show one nitrogen lone pair adopting an *exo* orientation. Nevertheless, nitrogen inversion in these heterocycles is rapid, and it is apparent that the stabilization attained by the coordination counterbalances the original conformational preference. The model advanced in Figure 2 is not able to explain the failure of ligands **32** and **34**, where the additional center of chirality in the *N*-phenethyl substituent was expected to have a positive effect.

C. Diels–Alder Reaction

Asymmetric induction in the intermolecular Diels–Alder cycloaddition reaction can be achieved with chiral Lewis acid catalysts.[25] Several diazabicyclo derivatives prepared in this study were treated with $Cu(OTf)_2$ and examined as potential chiral Lewis catalysts in the cycloaddition reaction between cyclopentadiene and 3-acryloyloxazolidin-2-one (**42**). The results are summarized in Table 5.

The complex formed from (–)-sparteine and $Cu(OTf)_2$ catalyzed the Diels–Alder reaction with low diastereoselectivity (*endo*/*exo* = 75:25) and no enantioselectivity (*ee* = 0%, Table 5, Entry 1). Diazabicyclo compound **8** provided a better diastereoselectivity (*endo*/*exo* = 90:10 and good enantioselectivity (*ee* = 72%, Table 5, Entries 4 and 5). By the same token, the complex formed from diazabicyclo compound **9** induced moderate enantioselectivity (46% *ee*) and a good *endo*/*exo* ratio of 85:15. With a full equivalent of ligand, this reaction proceeded with essentially complete diastereoselectivity (greater than 98:2 *endo*/*exo* ratio) and moderate enantioselectivity (*ee* = 46%, Table 5, Entry 13). On the other hand, an unexpected observation was that ligand **30**, which had induced highest enantioselectivity in the addition reaction of diethylzinc to benzaldehyde (see above), was totally inefficient in the asymmetric Diels–Alder reaction (Entry 19 in Table 5). In contrast, it is noted that Evans et al.[25e,25f] have achieved enantioselectivities higher than 98% with catalysts derived from C_2-symmetric

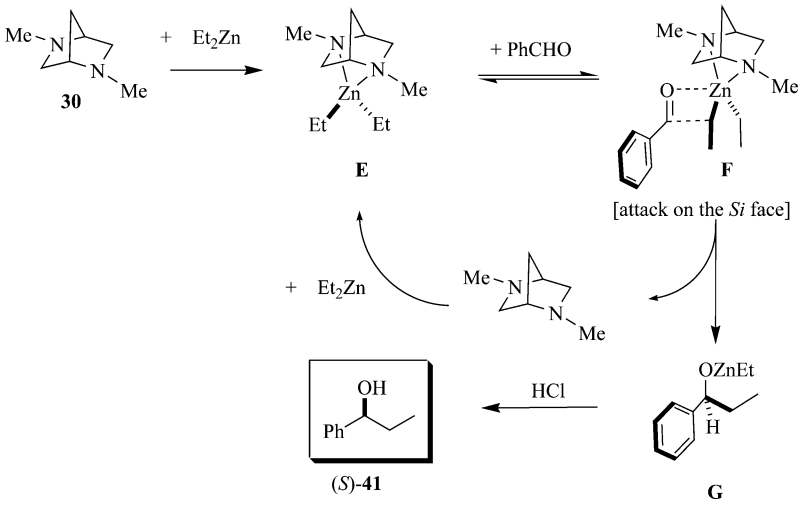
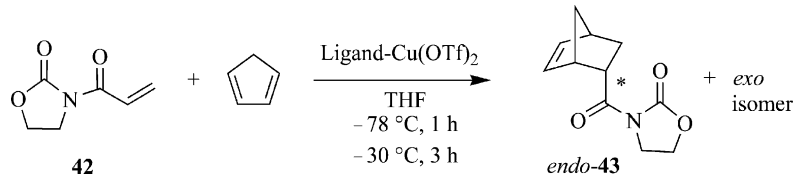


Figure 2. Proposed model to account for the observed enantioselectivities reported in Table 2.

Table 5. Asymmetric Diels–Alder reaction between 3-(acryloyl)oxazolidin-2-one and cyclopentadiene, catalyzed by $Cu(OTf)_2$/2,5-diazabicyclo[2.2.1]heptanes.

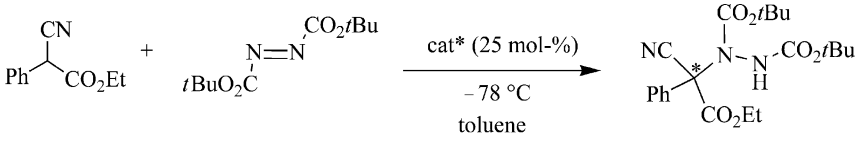


42 *endo*-**43**

Entry	Ligand	mol-%	% Yield	*endo*/*exo*[a]	% *ee*[b] (major configuration)[c]
1	(–)-sparteine	10	50	75:25	–
2	**8**	5	94	80:20	56 (*R*)
3	**8**	10	90	86:14	60 (*R*)
4	**8**	20	91	90:10	72 (*R*)
5	**8**	50	70	95:5	70 (*R*)
6	**9**	10	87	90:10	20 (*R*)
7	**9**	20	82	90:10	26 (*R*)
8	**9**	50	88	85:15	42 (*R*)
9	**11**	5	93	90:10	12 (*R*)
10	**11**	10	99	90:10	22 (*R*)
11	**11**	20	99	92:8	26 (*R*)
12	**11**	50	99	90:10	46 (*R*)
13	**11**	100	86	>98:<2	46 (*R*)
14	**13**	20	89[d]	88:12	–
15	**14**	20	95[d]	86:14	4 (*R*)
16	**18**	10	95[d]	85:15	–
17	**19**	10	96	83:17	12 (*R*)
18	**22**	50	70	90:10	4 (*R*)
19	**30**	10	99	86:14	–
20	**36**	10	65[d]	88:12	–
21	**39**	10	79[d]	85:15	–

[a] *endo*/*exo* ratios were determined by ^{1}H NMR and chiral HPLC analysis. [b] Enantiomeric excess values were determined by chiral HPLC analysis for *endo* isomers. [c] The assignment of the configuration was based on literature precedent.[26] [d] The reaction was concluded in 12 h.

Table 6. Amination of ethyl α-phenyl-α-cyanoacetate with 2,5-diazabicyclo[2.2.1]heptanes as organocatalysts.



(±)-**44** **45**

Entry	Cat.*	Time	% Yield	% *ee*[a] (major configuration)[b]
1	**8**	30 h	88	6 (*S*)
2	**11**	24 h	99	20 (*S*)
3	**12**	24 h	76	40 (*R*)
4	**13**	24 h	67	6 (*R*)
5	**14**	24 h	97	10 (*R*)
6	**15**[c]	2 h	91	10 (*S*)
7	**18**[c]	1.5 h	93	30 (*S*)
8	**19**	24 h	96	6 (*R*)
9	**22**[c]	10 h	94	18 (*R*)
10	**24**	1 h	96	10 (*S*)
11	**26**	10 h	89	12 (*S*)
12	**28**	10 h	82	12 (*S*)
13	**30**	10 min	99	4 (*S*)
14	**32**	10 min	99	4 (*S*)
15	**34**	10 min	99	16 (*S*)
16	**36**	90 min	98	–
17	**39**[d]	24 h	57	4 (*R*)

[a] Enantiomeric excess values were determined by chiral HPLC analysis. [b] The assignment of the configuration was based on literature precedent.[27c,27d] [c] The reaction was carried out with 50 mol-% of the organocatalyst, which was partially soluble. [d] The reaction was carried out with 15 mol-% of the organocatalyst.

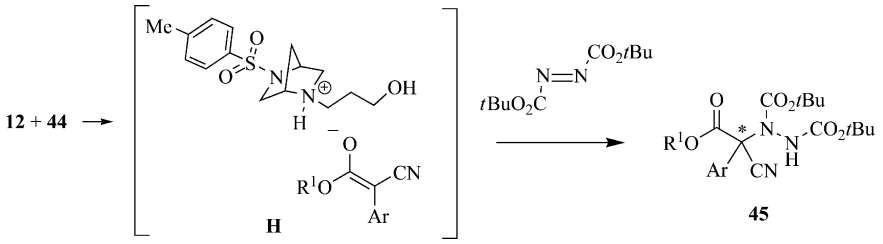


Figure 3. Diastereotopic faces of the prochiral enolate in complex **H** allow for enantioselective amination.

chiral bis-oxazolines and $Cu(OTf)_2$. Apparently, the asymmetric environment around the reaction site in the diazabicyclic complexes examined in the present study is less effective than that attained in propeller-like ligands.

D. Enantioselective Amination

An additional application of the diazabicyclic heterocycles prepared in this work consisted of their use as chiral Brønsted bases (organocatalysts) in the enantioselective amination of racemic ethyl α-phenyl-α-cyanoacetate [(±)-**44**] with di-*tert*-butyl azodicarboxylate.[27] Indeed, the α-aminated products thus formed have the potential to be converted into either α- or β-amino acids,[28] which play crucial roles in biology, chemistry, and medicine.

Table 6 summarizes our results. It will be appreciated that *N*-*p*-toluenesulfonyl derivatives required long (24 h) reaction times, whereas most of the rest of the amines required less than 10 min for complete reaction. Best results were found with diazabicyclo compound **12**, with an *N*-hydroxylpropyl chain, which afforded aminated product **45** with 40% *ee*. By comparison, several chiral amines containing the phenethyl auxiliary proved to be more efficient in this asymmetric amination reaction (84–98% *ee*).[27d] Apparently, the chiral environment that is created with the *N*-phenylethyl chiral auxiliary is more effective than that achieved with the diazabicyclo framework in this particular system.

A plausible interpretation for the enantioselectivity encountered in the formation of **45** can be advanced in terms of a noncovalent interaction between the enolate of **44**, generated by proton abstraction by the chiral amine, and the conjugated acid of such a Brønsted base, forming the chiral ammonium salt **H**, where the prochiral faces of the enolate become diastereotopic. Attack by the electrophilic aminating agent within the chiral environment (see **H** in Figure 3) allows for differentiation of the prochiral faces of the enolate.

Conclusions

The synthetic protocol for the preparation of the (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane system from (*S*)-*trans*-4-hydroxyproline has been optimized by the use of microwave irradiation instead of conventional heating in relevant steps. Thirty-seven novel, structurally simple, chiral derivatives were prepared, and a selection of them were evaluated as potential ligands in three different catalytic asymmetric reactions. In particular, *N*,*N*-dimethyl derivative **30** (previously reported by Bailey et al.[21a]) proved to be an efficient tertiary diamine ligand in the enantioselective addition of diethylzinc to benzaldehyde. On the other hand, the Lewis acid complex formed between diazabicyclic ligand **8** and $Cu(OTf)_2$ catalyzed the stereoselective Diels–Alder reaction in 95:5 *endo*/*exo* ratio and with 72% *ee*. Finally, modest (40% *ee*) enantioselectivity was induced by Brønsted base amine **12**, which acted as a chiral Brønsted base organocatalyst.

Experimental Section

General Information: All manipulations of organometallic compounds were carried out under nitrogen. Commercially available reagents and solvents were used as received. Toluene, tetrahydrofuran, and hexane were distilled from sodium and benzophenone before use. Flash column chromatography was performed on silica gel (230–400 mesh). Melting points were measured with a Melt-Temp "Electrothermal" apparatus and are uncorrected. Optical rotations were determined on Perkin–Elmer 241 and 341 polarimeters. IR spectra were recorded on a Perkin–Elmer FT-IR spectrum-Gx instrument. NMR spectra were obtained with JEOL GSX-270 (270 MHz), Bruker Advance 300 (300 MHz), and JEOL Eclipse+400 (400 MHz) spectrometers. Chemical shifts (δ) are in ppm downfield from tetramethylsilane as a internal reference. MS were registered on a Hewlett–Packard 5989-AMS-ENGINE, Thermo Electron Trace-DSQ, all at 20 eV. HRMS were taken on JEOL JMS-SX 102a and Agilent-MSD-TOF1069A spectrometers. Elemental analyses were obtained with a Thermo Finnegan CHNS/O-1112 apparatus. Microwave heating was carried out with a single-mode cavity Discover Microwave Synthesizer (CEM Corporation, NC). Analytical HPLC was carried out with Waters 600 E and UV/Vis Waters 2487 chromatographs. The enantiomeric excesses of the chiral products were determined with Chiralcel OD (250 × 4.6 mm) and Chiralpak AD (250 × 4.6 mm) columns, with elution with hexane/*i*PrOH mixtures. The structural X-ray crystallographic data were obtained with an Enraf–Nonius Kappa CCD diffractometer.

Synthesis of (1*S*,4*S*)-5-Alkyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptanes (2–14). General Procedure 1 (GP 1): The required amount of tritosylate **1**[15c,15e] and the corresponding amount of alkylamine was placed in a round-bottomed flask provided with a magnetic stirrer and condenser, and the resulting mixture was heated at reflux for 1 to 10 h, the reaction progress being monitored by tlc (hexane/EtOAc, 50:50). The reaction mixture was cooled to ambient temperature before purification of the product of type **2**–**14**; in some cases addition of water with stirring for several hours induced precipitation, but in others extraction with EtOAc (following addition of water to the crude product) and concentration provided a par-

tially purified material that was crystallized from a suitable solvent (see below).

Synthesis of (1*S*,4*S*)-2-Alkyl-2,5-diazabicyclo[2.2.1]heptanes 15, 23, 25, 27, 29, 31, 33, 35. General Procedure 2 (GP 2): The required amount of a (1*S*,4*S*)-5-alkyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptane of type **2**–**8** and hydrobromic acid (48%, 6 equiv.) were placed a round-bottomed flask provided with magnetic stirrer and condenser. The resulting mixture was heated at reflux, the reaction progress being monitored by tlc (chloroform/methanol, 9:1). Excess water and HBr were removed at reduced pressure and the product was purified by recrystallization of the corresponding hydrobromide salt. In some cases, no crystallization was observed, so purification was achieved by liberation of the free amine with KOH, extraction with an organic solvent, concentration, and distillation at reduced pressure.

Eschweiler–Clarke Reaction. General Procedure 3 (GP 3): The required amount of a (1*S*,4*S*)-2-alkyl-2,5-diazabicyclo[2.2.1]heptane of type **15**, **23**, **29**, **31**, **33**, or **35** was placed in a round-bottomed flask provided with magnetic stirrer and condenser. The reaction flask was cooled to 5–10 °C before the addition of aqueous formic acid (96%, 4 equiv.) and aqueous formaldehyde (37%, 2 equiv.). The resulting mixture was heated at reflux for 2–5 h, the reaction progress being monitored by tlc (methanol/EtOAc/NH_4OH, 9:1:0.1). The reaction mixture was concentrated in a rotary evaporator, treated with KOH in methanol (2 equiv., to adjust the pH to 10–12), and stirred for 1 h at 5 °C. The mixture was then filtered, the filtrate was concentrated, and the residue was distilled at reduced pressure.

Synthesis of (1*S*,4*S*)-2,5-Dialkyl-2,5-diazabicyclo[2.2.1]heptanes (22, 24, 26, 28). General Procedure 4 (GP 4): The required amount of a (1*S*,4*S*)-2-alkyl-2,5-diazabicyclo[2.2.1]heptane of type **15**, **23**, **25**, or **27** in acetone was placed in a round-bottomed flask provided with magnetic stirrer and condenser before the addition of the corresponding alkyl halide. The resulting mixture was heated to reflux, the reaction progress being monitored by tlc (chloroform/methanol, 9:1). The solvent was removed in a rotary evaporator, and water was added to the residue, which was brought to pH 10–12 with aqueous NaOH (50%), extracted, and either distilled at reduced pressure or treated with HCl to induce the precipitation of the corresponding hydrochloride salt.

General Procedure for Diethylzinc Addition to Aldehydes (Section B): The required amount of the (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]-heptane ligand (0.188 mmol for 10% and 1.88 mmol for 100%) was placed under nitrogen in a round-bottomed flask containing a magnetic stirrer and was dissolved in anhyd. toluene (6 mL). The resulting mixture was cooled to 0 °C in an ice bath before the slow addition of a hexane solution of diethylzinc (1.0 M, 5.0 mL, 4.7 mmol). The reaction mixture was allowed to react at ambient temperature for 20 min, cooled, treated dropwise with aldehyde (1.8 equiv.), and allowed to react at the specified temperature (see below). Excess Et_2Zn was destroyed by slow addition of HCl (1 N, 20 mL, ***CAUTION:*** vigorous evolution of gases!). The white suspension that developed was stirred for 30 min, extracted with Et_2O, and washed with brine solution until neutral pH. The combined organic extracts were dried with anhyd. Na_2SO_4 and concentrated in a rotary evaporator to remove the diethyl ether, and then the excess toluene was distilled under vacuum. The residue was purified by flash chromatography (hexane/EtOAc, 1:0→8:2) to give the main product, 1-phenylpropan-1-ol (**41**). From benzaldehyde (0.2 g, 1.88 mmol, 0.19 mL). The enantiomeric excess was determined by HPLC with a Chiralcel OD chiral column, detector at λ = 210 nm, mobile phase hexane/*i*PrOH (95:5), flow 1 mL min^{-1}. The observed retention times are as follows: 7.4 min for the (*R*) enantiomer and 8.7 min for the (*S*) enantiomer.

General Procedure for Diels–Alder Reactions (Section C): A (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane ligand (0.106 mmol for 10% and 1.06 mmol for 100%), the corresponding amount of triflate (0.106 mmol for 10% and 1.06 mmol for 100%), and anhyd. THF (5.0 mL) were placed under nitrogen in a 25 mL round-bottomed flask containing a magnetic stirrer. The resulting mixture was stirred for 2 h at ambient temperature, and then 3-(acryloyl)oxazolidinone (**42**, 0.15 g, 1.06 mmol) was added, followed by 3 h additional stirring at ambient temperature. The temperature was lowered to –78 °C before the addition of cyclopentadiene (0.35 g, 5.3 mmol, 0.45 mL), and stirring was continued for 3 h at –30 °C, and then at ambient temperature, the reaction progress being monitored by tlc (EtOAc/hexane, 70:30). The THF was removed in a rotary evaporator, and the residue was purified by flash column chromatography (hexane→hexane/EtOAc, 1:1, using a 1% potassium permanganate solution to develop the tlc plates) to provide product *endo*-**43**. $[\alpha]_D^{20}$ = +93.2 (*c* = 1, $CHCl_3$) for 72% *ee*, 90:10 *endo*/*exo* [ref.[26a] $[\alpha]_D^{20}$ = +126.7 (*c* = 1, $CHCl_3$) for the (*R*) enantiomer]. The *endo*/*exo* ratio was determined by ^{1}H NMR and the enantiomeric ratio was determined by HPLC with a chiral Chiralcel OD column, detector at λ = 230 nm, mobile phase hexane/*i*PrOH (97:3), and flow 1 mL min^{-1}. The observed retention times were 20–21 min for the *exo* enantiomers, 23 min for the *endo*-(*S*) enantiomer, and 25 min for the *endo*-(*R*) enantiomer[26b].

General Procedure for the Amination Reaction (Section D): A (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane ligand (0.125 mmol for 25% and 0.25 mmol for 50%), ethyl α-phenyl-α-cyanoacetate (0.104 g, 0.55 mmol, 0.1 mL), and 2.0 mL of dry toluene (or 9.0 mL of toluene/hexane, 1:1, v/v) were placed in a 25 mL round-bottomed flask provided with magnetic stirrer. The resulting mixture was stirred for 1 h at ambient temperature and at –78 °C (or –100 °C) under nitrogen before the dropwise addition of di-*tert*-butyl azodicarboxylate (0.115 g, 0.5 mmol) in 1.0 mL of toluene (or 2.0 mL of a toluene/hexane, 1:1, v/v mixture). The reaction mixture initially turned bright yellow, and disappearance of this color indicated that the reaction was complete (5 min to 30 h). At that point the reaction temperature was allowed to increase to ambient temperature, and the reaction mixture was concentrated under vacuum and purified by flash column chromatography (hexane→hexane/EtOAc, 8:2), to give the aminated product **45** as a viscous oil that eventually solidified, m.p. 94–96 °C. The enantiomeric excess was determined by HPLC with a Chiralpak AD chiral column, UV detector λ = 220 nm, mobile phase hexane/*i*PrOH (85:15), and flow 1.0 mL min^{-1}. The observed retention times were 11.0 min for the (*R*) enantiomer of **45** and 33.0 min for the (*S*) enantiomer.

(2*S*,4*R*)-1,4-Bis(tosyl)-2-(tosylmethyl)pyrrolidine (1). Microwave-Assisted Preparation: (*S*)-*trans*-4-Hydroxyproline (2.0 g, 15.26 mmol) and water (20 mL) were placed in a 50 mL round-bottomed flask containing a magnetic stirrer before the addition of Na_2CO_3 (3.4 g, 32.04 mmol). The resulting solution was cooled to 0 °C before the dropwise addition of *p*-toluenesulfonyl chloride (3.5 g, 18.32 mmol). The reaction mixture was heated with microwave irradiation (100 W) for 30 min at 100 °C, cooled to room temp., and treated with aqueous HCl (10%) to pH 2–3. At this point a white solid precipitated, and this was filtered, washed with water, and dried under vacuum at 40 °C to provide the desired (2*S*,4*R*)-4-hydroxy-*N*-tosylproline (4.21 g, 97% yield) as a white solid, m.p. 154–156 °C, $[\alpha]_D^{20}$ = –94.1 (*c* = 2, EtOH) [ref.[15a,15c] m.p. 153–155 °C, $[\alpha]_D^{20}$ = –105.4 (*c* = 2, EtOH)].

This monotosylated product was treated according to the procedures described in the literature as follows.[15c] i) Reduction with

diborane to provide (3*R*,5*S*)-3-hydroxy-5-(hydroxymethyl)-*N*-tosylpyrrolidine (1.6 g, 85% yield) as a white solid, m.p. 128–130 °C, $[a]_D^{20}$ = –47.1 (*c* = 2, EtOH) [ref.[15c] m.p. 132–133 °C, $[a]_D^{20}$ = –43.3 (*c* = 1.85, EtOH)]. ii) This intermediate was treated with additional *p*-toluenesulfonyl chloride to provide tritosylate **1** (3.65 g, 95% yield) as a white solid, m.p. 135–136 °C, $[a]_D^{20}$ = –57.0 (*c* = 1.9, acetone) [ref.[15c] m.p. 134–136 °C, $[a]_D^{20}$ = –56.0 (*c* = 1.16, acetone)]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.05 (m, 2 H), 2.42 (s, 3 H), 2.45 (s, 6 H), 3.51 (m, 2 H), 3.80 (m, 1 H), 4.10 (dd, $J_{H,H}$ = 6.2, 10.2 Hz, 1 H), 4.30 (dd, $J_{H,H}$ = 3.2, 10.2 Hz, 1 H), 4.77 (m, 1 H) 7.27–7.78 (m, 12 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 21.6, 21.7, 21.7, 35.8, 54.7, 56.8, 71.6, 78.1, 127.7, 127.8, 128.0, 129.9, 130.0, 130.1, 132.7, 133.2, 133.3, 144.5, 145.3, 145.4 ppm. MS (EI): *m*/*z* (%) = 580 [M + 1]$^+$ (0.2), 394 (32), 222 (100), 155 (24), 80 (22).

(1*S*,4*S*)-5-Benzyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptane (2): This compound was produced as described in GP 1, with tritosylate **1** (10 g, 17.3 mmol) and benzylamine (22 g, 20.6 mmol, 22.5 mL). The reaction time was 2 h, and the product was purified by recrystallization from ethanol (5.5 g, 93% yield). White solid, m.p. 122–124 °C, $[a]_D^{20}$ = +14.3 (*c* = 1.6, acetone) [ref.[29] m.p. 124 °C, $[a]_D^{20}$ = –15.7 (*c* = 1.6, acetone) for the (*R*,*R*) enantiomer].

Microwave Modification: Tritosylate **1** (0.5 g, 0.86 mmol) and toluene (1 mL) were placed in a 10 mL reactor tube contaiing a magnetic stirrer and the resulting solution was treated with benzylamine (0.37 g, 3.45 mmol, 0.37 mL). The reaction mixture was heated with microwave irradiation (50 W) for 30 min at 130 °C, cooled to room temp., diluted with EtOAc and water, extracted with EtOAc, washed with HCl solution (1 N) and brine, and dried with anhyd. Na_2SO_4. The product was concentrated in a rotary evaporator, and the residue was crystallized from ethanol to afford **2** (0.28 g, 95% yield), white solid, m.p. 120–122 °C, $[a]_D^{20}$ = +13.8 (*c* = 1.6, acetone). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.09 (d, $^2J_{H,H}$ = 9.8 Hz, 1 H, CHC*H*$_2$CH), 1.70 (d, $^2J_{H,H}$ = 9.8 Hz, 1 H, CHC*H*$_2$CH), 2.44 (s, 3 H, ArC*H*$_3$), 2.66 [d, $^2J_{H,H}$ = 9.9 Hz, 1 H, NC*H*$_{2(endo)}$CH], 2.82 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.03 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.40 (s, 1 H, NC*H*CH$_2$), 3.64 [m, 3 H, NC*H*$_{2(endo)}$-CH, C*H*$_2$Ph], 4.28 (s, 1 H, NC*H*CH$_2$), 7.21–7.28 (m, 5 H, C*H*Ar), 7.32 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar), 7.73 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 21.6 (ArCH$_3$), 35.2 (CH$_2$), 50.8 (CH$_2$), 57.6 (CH$_2$), 59.6 (CH$_2$Ph), 60.9 (CH), 61.1 (CH), 127.1, 127.6, 128.4, 128.5, 129.8, 137.3, 139.2, 143.5 ppm. MS (EI): *m*/*z* (%) = 343 [M + 1]$^+$ (5), 265 (1), 187 (100), 158 (84), 91 (97).

(1*S*,4*S*)-5-Isopropyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptane (3): GP 1 was followed with tritosylate **1** (4.0 g, 6.9 mmol) and isopropylamine (5.6 g, 94.7 mmol, 8.0 mL) in acetonitrile (8 mL). The reaction time was 5 h, and the product was purified by recrystallization from ethanol (1.9 g, 95% yield). White solid, m.p. 88–89 °C, $[a]_D^{20}$ = +27.2 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.97 [d, $^3J_{H,H}$ = 5.9 Hz, 6 H, CH(C*H*$_3$)$_2$], 1.03 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CHC*H*$_2$CH), 1.65 (d, $^2J_{H,H}$ = 9.8 Hz, 1 H, CHC*H*$_2$CH), 2.41 (s, 3 H, ArC*H*$_3$), 2.58 [m, 2 H, C*H*(CH$_3$)$_2$, NC*H*$_{2(endo)}$CH], 2.93–2.96 [dd, $^2J_{H,H}$ = 9.5, $^3J_{H,H}$ = 1.8 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.02–3.05 [dd, $^2J_{H,H}$ = 9.8, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.56 [d, $^2J_{H,H}$ = 9.8 Hz, 1 H, NC*H*$_{2(endo)}$CH], 3.58 (s, 1 H, NC*H*CH$_2$), 4.22 (s, 1 H, NC*H*CH$_2$), 7.30 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, C*H*Ar), 7.70 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 21.6, 21.9, 22.6, 36.0, 48.9, 50.6, 58.6, 58.9, 60.6, 127.5, 129.8, 135.7, 143.6 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3437, 2977, 2855, 1596, 1343, 1158, 673 cm^{-1}. MS (EI): *m*/*z* (%) = 293 [M + 1]$^+$ (1), 279 (5), 139 (100), 110 (42), 68 (25). $C_{15}H_{22}N_2O_2S$ (294.41): calcd. C 61.19, H 7.53, N 9.52; found C 60.94, H 7.91, N 9.58.

(1*S*,4*S*)-5-Butyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptane (4): GP 1 was followed with **1** (10.0 g, 17.3 mmol) and butylamine (22.2 g, 303.6 mmol, 30 mL). The reaction time was 2 h, and the product was purified by recrystallization from propan-2-ol to provide **4** (4.5 g, 85% yield), white solid, m.p. 69–70 °C, $[a]_D^{20}$ = +26.8 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.84 [t, $^3J_{H,H}$ = 7.3 Hz, 3 H, NCH$_2$(CH$_2$)$_2$C*H*$_3$], 1.02 (d, $^2J_{H,H}$ = 9.8 Hz, 1 H, CHC*H*$_2$CH), 1.29 [m, 4 H, NCH$_2$(C*H*$_2$)$_2$CH$_3$], 1.62 (d, $^2J_{H,H}$ = 9.8 Hz, 1 H, CHC*H*$_2$CH), 2.39 [m, 5 H, NC*H*$_2$(CH$_2$)$_2$CH$_3$, ArC*H*$_3$], 2.54 [d, $^3J_{H,H}$ = 8.8 Hz, 1 H, NC*H*$_{2(endo)}$CH], 2.86–2.89 [dd, $^2J_{H,H}$ = 9.5, $^3J_{H,H}$ = 2.5 Hz, 1 H, NC*H*$_{2(exo)}$CH], 2.94–2.97 [dd, $^2J_{H,H}$ = 9.5, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.38 (s, 1 H, NC*H*CH$_2$), 3.53 [d, $^2J_{H,H}$ = 9.5 Hz, 1 H, NC*H*$_{2(endo)}$CH], 4.21 (s, 1 H, NC*H*CH$_2$), 7.28 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar), 7.69 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 14.1, 20.5, 21.6, 31.4, 35.3, 49.9, 53.2, 59.7, 60.7, 61.4, 127.5, 129.8, 135.6, 143.5 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3446, 2935, 2407, 1595, 1465, 1337, 1222, 818 cm^{-1}. MS (EI): *m*/*z* (%) = 309 [M + 1]$^+$ (1), 265 (11), 153 (100), 124 (82), 68 (14), 44 (4). $C_{16}H_{24}N_2O_2S$ (308.44): calcd. C 62.30, H 7.84, N 9.08; found C 62.20, H 7.86, N 9.28.

(1*S*,4*S*)-5-Octyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptane·HCl (5): GP 1 was followed with **1** (10.0 g, 17.3 mmol) and octylamine (19.6 g, 151.7 mmol, 25 mL). The reaction time was 3 h, and the product was purified by recrystallization of the hydrochloride salt from EtOAc, to provide **5** (5.3 g, 77% yield), white solid, m.p. 197–199 °C, $[a]_D^{20}$ = +8.5 (*c* = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.86 [t, $^3J_{H,H}$ = 6.6 Hz, 3 H, NCH$_2$(CH$_2$)$_6$C*H*$_3$], 1.03 (d, $^2J_{H,H}$ = 10.2 Hz, 1 H, CHC*H*$_2$CH), 1.23–1.36 [m, 12 H, NCH$_2$(C*H*$_2$)$_6$-CH$_3$], 1.65 (d, $^2J_{H,H}$ = 9.8 Hz, 1 H, CHC*H*$_2$CH), 2.42 [m, 5 H, NC*H*$_2$(CH$_2$)$_6$CH$_3$, ArC*H*$_3$], 2.56 [d, $^2J_{H,H}$ = 9.9 Hz, 1 H, NC*H*$_{2(endo)}$CH], 2.89–2.92 [dd, $^2J_{H,H}$ = 9.8, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 2.95–2.98 [dd, $^2J_{H,H}$ = 9.8, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.40 (s, 1 H, NC*H*CH$_2$), 3.55 [d, $^2J_{H,H}$ = 9.5 Hz, 1 H, NC*H*$_{2(endo)}$CH], 4.23 (s, 1 H, NC*H*CH$_2$), 7.31 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar), 7.71 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 14.2, 21.6, 22.7, 27.5, 29.2, 29.3, 29.7, 31.9, 35.4, 49.8, 53.5, 59.7, 60.7, 61.3, 127.5, 129.8, 135.5, 143.5 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3401, 2925, 2422, 1597, 1460, 1338, 1215, 823 cm^{-1}. MS (EI): *m*/*z* (%) = 364 [M + 1]$^+$ (0.1), 265 (5), 209 (100), 180 (5), 111 (8), 68 (9). $C_{20}H_{32}N_2O_2S$·HCl (401.01): calcd. C 59.90, H 8.29, N 6.99; found C 60.01, H 8.51, N 7.00.

(1*S*,4*S*)-5-[(*S*)-1-Phenylethyl]-2-tosyl-2,5-diazabicyclo[2.2.1]-heptane·HCl (6): GP 1 was followed with **1** (20.0 g, 34.5 mmol) and (*S*)-phenylethylamine (46.0 g, 379.5 mmol, 48.5 mL). The reaction time was 5.5 h, and the product was purified by recrystallization of the hydrochloride salt from EtOAc, to provide **6**·HCl (9.5 g, 70% yield), white solid, m.p. 232–236 °C, $[a]_D^{20}$ = –18.9 (*c* = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.12 (d, $^2J_{H,H}$ = 11.4 Hz, 1 H, CHC*H*$_2$CH), 1.75 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CHC*H*$_3$), 2.38 (s, 3 H, ArC*H*$_3$), 2.57 (d, $^2J_{H,H}$ = 11.4 Hz, 1 H, CHC*H*$_2$CH), 2.91 [d, $^2J_{H,H}$ = 11.8 Hz, 1 H, NC*H*$_{2(endo)}$CH], 3.30 [d, $^2J_{H,H}$ = 11.0 Hz, 1 H, NC*H*$_{2(endo)}$CH], 3.69–3.73 [m, 2 H, NC*H*$_{2(exo)}$CH, NC*H*CH$_2$], 4.0–4.08 [m, 1 H, NC*H*$_{2(exo)}$CH], 4.25 (m, 1 H, C*H*CH$_3$), 4.43 (s, 1 H, NC*H*CH$_2$), 7.30–7.40 (m, 5 H, C*H*Ar), 7.65 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, C*H*Ar), 7.71 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 20.4 (CH*C*H$_3$), 21.7 (ArCH$_3$), 35.2 (CH*C*H$_2$CH), 46.9, 59.0, 59.9, 62.7, 63.8, 127.5, 127.9, 129.6, 129.9, 130.7, 133.7, 136.3, 145.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3447, 2987, 2880, 2451, 1596, 1348, 1158, 684 cm^{-1}. MS (EI): *m*/*z* (%) = 357 [M + 1]$^+$ (1), 341 (2), 201 (100), 105 (71), 97 (73), 68 (28). $C_{20}H_{24}N_2O_2S$ (356.48): calcd. C 67.38, H 6.79, N 7.86; found C 67.29, H 6.81, N 7.94.

(1*S*,4*S*)-5-[(*R*)-1-Phenylethyl]-2-tosyl-2,5-diazabicyclo[2.2.1]heptane (7): GP 1 was followed with **1** (25.0 g, 43.1 mmol) and (*R*)-phenylethylamine (46.0 g, 57.5 g, 474 mmol, 60 mL). The reaction time was 5.5 h, and the product was purified by recrystallization from EtOAc to provide **7** (11.0 g, 72% yield), white solid, m.p. 117–119 °C, $[\alpha]_D^{20}$ = +36.5 (*c* = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.11 (d, $^2J_{H,H}$ = 9.8 Hz, 1 H, CHC*H*$_2$CH), 1.21 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CHC*H*$_3$), 1.67 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CHC*H*$_2$CH), 2.43 (s, 3 H, ArC*H*$_3$), 2.47 [d, $^2J_{H,H}$ = 10.2 Hz, 1 H, NC*H*$_{2(endo)}$CH], 2.66–2.79 [dd, $^2J_{H,H}$ = 10.2, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.02–3.04 [dd, $^2J_{H,H}$ = 9.5, $^3J_{H,H}$ = 1.8 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.44 (q, $^3J_{H,H}$ = 6.6 Hz, 1 H, C*H*CH$_3$), 3.57–3.63 [m, 2 H, NC*H*$_{2(endo)}$, NC*H*CH$_2$], 4.22 (s, 1 H, NC*H*CH$_2$), 7.17–7.27 (m, 5 H, C*H*Ar), 7.31 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar), 7.71 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 21.6, 23.6, 35.3, 50.2, 58.8, 60.8, 61.4, 127.1, 127.2, 127.6, 128.5, 129.8, 135.8, 143.5, 145.5 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3448, 2974, 2872, 1597, 1343, 1165, 685 cm^{-1}. MS (EI): *m*/*z* (%) = 357 [M + 1]$^+$ (7), 341 (4), 201 (100), 105 (76), 97 (72), 68 (28). $C_{20}H_{24}N_2O_2S$ (356.48): calcd. C 67.38, H 6.79, N 7.86; found C 67.66, H 6.46, N 8.01.

(1*S*,4*S*)-5-{2-[5-Tosyl-2,5-diazabicyclo(2.2.1)heptane]ethyl}-2-tosyl-2,5-diazabicyclo[2.2.1]heptane (8): Tritosylate **1** (5.79 g, 10.0 mmol) dissolved in toluene (17 mL) and methanol (8 mL) was placed in a 50 mL round-bottomed flask provided with a magnetic stirrer and a condenser. Ethylenediamine (0.6 g, 10.0 mmol, 0.7 mL) and triethylamine (4.8 g, 47.0 mmol, 6.5 mL) were added to this solution. The reaction mixture was heated at reflux (ca. 100 °C) for 50 h, the reaction progress being monitored by tlc (EtOAc/hexane, 1:1). The reaction mixture was cooled to room temp. and concentrated before the addition of HCl (10%, 20 mL) and EtOAc (20 mL), and was then stirred for 30 min. The precipitate that developed was filtered, washed with water, and dried under vacuum at 40 °C to provide of **8**·2HCl (1.3 g, 22% yield) as a white solid, m.p. 242–244 °C. The free amine **8** was liberated by treatment with aqueous NaOH (2 equiv.), extracted with EtOAc, and concentrated to give **8** as a white solid, m.p. 178–180 °C, $[\alpha]_D^{20}$ = +40.6 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.01 (d, $^2J_{H,H}$ = 9.5 Hz, 2 H, CHC*H*$_2$CH), 1.57 (d, $^2J_{H,H}$ = 9.5 Hz, 2 H,CHC*H*$_2$CH), 2.40 (s, 6 H, ArC*H*$_3$), 2.48 [m, 6 H, N(C*H*$_2$)$_2$N, NC*H*$_2$CH], 2.81 (d, $^2J_{H,H}$ = 9.5 Hz, 2 H, NC*H*$_2$CH), 2.95 (d, $^2J_{H,H}$ = 9.5 Hz, 2 H, NC*H*$_2$CH), 3.35 (s, 2 H, NC*H*CH$_2$), 3.45 (d, $^2J_{H,H}$ = 9.5 Hz, 2 H, NC*H*$_2$CH), 4.20 (s, 2 H, NC*H*CH$_2$), 7.27 (d, $^3J_{H,H}$ = 7.3 Hz, 4 H, C*H*Ar), 7.68 (d, $^3J_{H,H}$ = 7.6 Hz, 4 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 21.6 35.3, 50.3, 53.3, 60.3, 60.6, 62.1, 127.5, 127.9, 135.5, 143.6 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3435, 2941, 2849, 1596, 1455, 1338, 1156, 675 cm^{-1}. EM (IE) *m*/*z* (%): 531 [M + 1]$^+$ (1), 375 (2), 265 (100), 155 (3), 111 (1), 44 (13). $C_{26}H_{34}N_4O_4S_2$·2HCl (603.62): calcd. C 51.73, H 6.01, N 9.28; found C 51.74, H 6.21, N 9.25.

(1*S*,4*S*)-5-Aminoethyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptane (9): GP 1 was followed with **1** (5.8 g, 10.0 mmol) and ethylenediamine (3.0 g, 3.35 mL, 50 mmol) in toluene (17 mL). The reaction time was 24 h, to provide **9** (2.1 g, 71% yield) as a colorless oil, which was treated with aqueous HCl (10%) to induce the precipitation of hydrochloride **9**·2HCl as a white solid, m.p. 204–206 °C, $[\alpha]_D^{20}$ = +17.5 (*c* = 1, $CHCl_3$).

Microwave Modification: Tritosylate **1** (2.0 g, 3.45 mmol) and toluene (6 mL) were placed in a 50 mL reactor flask provided with magnetic stirrer, and the resulting solution was treated with ethylenediamine (1.04 g, 17.25 mmol, 1.15 mL). The reaction mixture was heated with microwave irradiation (200 W) for 1.5 h at 115 °C to provide **9** (0.79 g, 77% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.05 (d, $^2J_{H,H}$ = 11.0 Hz, 1 H, CHC*H*$_2$CH), 1.62 (d, $^2J_{H,H}$ = 10.2 Hz, 1 H, CHC*H*$_2$CH), 1.67 (br., 2 H, NH$_2$), 2.49–2.66 [m, 5 H, N(C*H*$_2$)$_2$NH$_2$, NC*H*$_{2(endo)}$CH], 2.82–2.85 [dd, $^2J_{H,H}$ = 9.8, $^3J_{H,H}$ = 2.5 Hz, 1 H, NC*H*$_{2(exo)}$CH], 2.97–3.02 [dd, $^2J_{H,H}$ = 9.8, $^3J_{H,H}$ = 2.5 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.36 (s, 1 H, NC*H*CH$_2$), 3.50 [d, $^2J_{H,H}$ = 9.5 Hz, 1 H, NC*H*$_{2(endo)}$CH], 4.24 (s, 1 H, NC*H*CH$_2$), 7.29 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar), 7.69 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 21.6 (ArCH$_3$), 35.2 (CH$_2$), 40.9 (CH$_2$), 50.9 (CH$_2$), 56.6 (CH$_2$), 59.8 (CH$_2$), 60.7 (CH), 61.9 (CH), 127.5 (CHAr), 129.8 (CHAr), 135.6 (C), 143.5 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3419, 3532, 1648, 1492, 1340, 1155, 1097, 815, 713 cm^{-1}. MS (EI): *m*/*z* (%) = 296 [M + 1]$^+$ (1), 265 (100), 222 (3), 172 (24), 155 (10), 140 (23), 91 (28), 68 (17). $C_{14}H_{21}N_3O_2S$·2HCl (368.32): calcd. C 45.65, H 6.29, N 11.41; found C 45.38, H 6.65, N 11.60.

(1*S*,4*S*)-5-Cyclohexyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptane (10): GP 1 was followed, with **1** (25.0 g, 43.1 mmol) and cyclohexylamine (8.0 g, 190 mmol, 21.7 mL) in toluene (100 mL). The reaction time was 18 h, and the product was purified by recrystallization from EtOAc to provide **10** (12.5 g, 87% yield) as a white solid, m.p. 96–98 °C, $[\alpha]_D^{20}$ = +34.1 (*c* = 1, $CHCl_3$).

Microwave-Assisted Reaction: Tritosylate **1** (2.0 g, 3.45 mmol) in cyclohexylamine (20 mL, 174.85 mmol, 17.34 g) was placed in a 50 mL reactor flask containing a magnetic stirrer. The reaction mixture was heated with microwave irradiation (120 W) for 1 h at 110 °C to provide **10** (0.84 g, 73% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.02–1.23 (m, 6 H), 1.58–1.71 (m, 6 H), 2.18 (m, 1 H), 2.42 (s, 3 H, ArC*H*$_3$), 2.56 [d, $^2J_{H,H}$ = 9.8 Hz, 1 H, NC*H*$_{2(endo)}$CH], 2.94–2.97 [dd, $^2J_{H,H}$ = 9.8, $^3J_{H,H}$ = 1.8 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.02–3.04 [dd, $^2J_{H,H}$ = 9.8, $^3J_{H,H}$ = 1.8 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.54 [d, $^2J_{H,H}$ = 9.8 Hz, 1 H, NC*H*$_{2(endo)}$CH], 3.62 (s, 1 H, NC*H*CH$_2$), 4.22 (s, 1 H, NC*H*CH$_2$), 7.31 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, C*H*Ar), 7.71 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 21.6 (ArCH$_3$), 24.6, 24.7, 26.0, 32.0, 32.8, 36.1, 48.7, 57.7, 58.1, 58.7, 60.3, 127.6 (CHAr), 129.8 (CHAr), 135.5 (C), 143.5 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3446, 2934, 2658, 2412, 2190, 1917, 1596, 1452, 1342, 1163, 816, 687 cm^{-1}. MS (EI): *m*/*z* (%) = 335 [M + 1]$^+$ (3), 291 (2), 179 (100), 150 (33), 97 (19), 68 (53). $C_{18}H_{26}N_2O_2S$ (334.48): calcd. C 64.64, H 7.84, N 8.38; found C 64.85, H 7.71, N 8.31.

(1*S*,4*S*)-5-Hydroxyethyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptane (11): GP 1 was followed, with **1** (6.0 g, 10.4 mmol) and 1,2-ethanolamine (16.0 g, 261.9 mmol). The reaction time was 1 h, and the excess ethanolamine was distilled at reduced pressure in a kugelrohr (52–58 °C/2 Torr). The residue was treated with water (40 mL) and extracted with EtOAc in a continuous liquid–liquid extractor for 8 h. The organic layer was dried with anhyd. Na_2SO_4 and concentrated. The residue was recrystallized from EtOAc/hexane (9:1) to provide **11** (2.54 g, 83% yield) of **11** as a slightly yellow solid, m.p. 78–80 °C, $[\alpha]_D^{20}$ = +24.3 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.09 (d, $^2J_{H,H}$ = 9.9 Hz, 1 H, CHC*H*$_2$CH), 1.64 (d, $^2J_{H,H}$ = 9.9 Hz, 1 H, CHC*H*$_2$CH), 2.41 (s, 3 H, ArC*H*$_3$), 2.59–2.70 [m, 4 H, NC*H*$_{2(endo)}$CH, NC*H*$_2$CH$_2$O*H*], 2.86 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.02 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.39 (s, 1 H, NC*H*CH$_2$), 3.47–3.50 [m, 3 H, NC*H*$_{2(endo)}$CH, NCH$_2$C*H*$_2$OH], 4.27 (s, 1 H, NC*H*CH$_2$), 7.30 (d, $^3J_{H,H}$ = 8.04 Hz, 2 H, C*H*Ar), 7.70 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 21.6 (ArCH$_3$), 35.3 (CH*C*H$_2$CH), 51.2 (N*C*H$_2$CH), 55.6 (N*C*H$_2$CH$_2$OH), 59.7 (NCH$_2$CH$_2$OH), 59.8 (NCH$_2$*C*H$_2$OH), 60.6 (N*C*HCH$_2$), 62.0 (N*C*HCH$_2$), 127.5 (CHAr), 129.9 (CHAr), 135.4 (C), 143.7 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3444, 2864, 1920, 1597, 1452, 1341, 1154, 1051, 810, 671 cm^{-1}. MS (EI): *m*/*z* (%) = 295 [M + 1]$^+$ (0.2),

265 (10), 141 (100), 112 (51), 94 (11), 68 (9), 44 (8). $C_{14}H_{20}N_2O_3S$ (296.39): calcd. C 56.73, H 6.80, N 9.45; found C 56.40, H 6.95, N 9.56.

(1*S*,4*S*)-5-Hydroxypropyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptane (12): GP 1 was followed with **1** (20.0 g, 34.5 mmol) and 3-hydroxypropylamine (49.0 g, 652.4 mmol). The reaction time was 1 h, and the product was purified by recrystallization from EtOAc/hexane (9:1) to provide **12** (9.5 g, 89% yield), pale yellow solid, m.p. 85–86 °C, $[\alpha]_D^{20}$ = +17.5 (*c* = 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.05 (d, $^2J_{H,H}$ = 10.2 Hz, 1 H, CHC*H*$_2$CH), 1.58 (d, $^2J_{H,H}$ = 10.2 Hz, 1 H, CHC*H*$_2$CH), 1.52–1.69 (m, 2 H, NCH$_2$C*H*$_2$CH$_2$OH), 2.41 (s, 3 H, ArC*H*$_3$), 2.66–2.72 (m, 1 H, NC*H*$_2$CH$_2$CH$_2$OH), 2.70 [d, $^2J_{H,H}$ = 9.5 Hz, 1 H, NC*H*$_{2(endo)}$CH], 2.77–2.82 (m, 1 H, NC*H*$_2$CH$_2$CH$_2$OH), 2.90 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 2.99 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.48 (s, 1 H, NC*H*CH$_2$), 3.50 [d, $^2J_{H,H}$ = 10.6 Hz, 1 H, NC*H*$_{2(endo)}$CH], 3.74 (t, $^3J_{H,H}$ = 4.9 Hz, 2 H, NCH$_2$CH$_2$C*H*$_2$OH), 4.25 (s, 1 H, NC*H*CH$_2$), 4.41 (br., 1 H, O*H*), 7.30 (d, $^3J_{H,H}$ = 8.04 Hz, 2 H, C*H*Ar), 7.69 (d, $^3J_{H,H}$ = 8.08 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 21.6 (ArCH$_3$), 29.3 (NCH$_2$*C*H$_2$CH$_2$OH), 35.0 (CH*C*H$_2$CH), 50.1 (N*C*H$_2$CH), 54.1 (N*C*H$_2$CH$_2$CH$_2$OH), 60.0 (N*C*H$_2$CH), 60.4 (N*C*HCH$_2$), 61.7 (N*C*HCH$_2$), 64.4 [N(CH$_2$)$_2$*C*H$_2$OH], 127.5 (CHAr), 129.9 (CHAr), 135.3 (C), 143.7 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3172, 2859, 1974, 1596, 1449, 1331, 1163, 1058, 820, 688 cm^{-1}. MS (EI): *m*/*z* (%) = 311 [M + 1]$^+$ (1), 265 (4), 155 (100), 126 (60), 111 (27), 80 (8), 68 (9), 44 (8). $C_{15}H_{22}N_2O_3S$ (310.41): calcd. C 58.04, H 7.14, N 9.02; found C 58.18, H 7.31, N 9.33.

(1*S*,4*S*)-5-[(2*S*)-(1-Hydroxymethyl)propyl]-2-tosyl-2,5-diazabicyclo-[2.2.1]heptane (13): GP 1 was followed, with **1** (27.4 g, 47.3 mmol) and (*S*)-2-aminobutan-1-ol (50.0 g, 560.9 mmol). The reaction time was 2 h, and the product was purified by initial removal of excess (*S*)-2-aminobutan-1-ol by distillation at reduced pressure (50–55 °C/0.25 Torr) followed by recrystallization of the residue from water to provide **13** (12.85 g, 84% yield), white solid, m.p. 125–126 °C, $[\alpha]_D^{20}$ = +37.1 (*c* = 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.86 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, CHCH$_2$C*H*$_3$), 1.11 (d, $^2J_{H,H}$ = 9.9 Hz, 1 H, CHC*H*$_2$CH), 1.31–1.49 (m, 2 H, CHC*H*$_2$CH$_3$), 1.61 (d, $^2J_{H,H}$ = 9.9 Hz, 1 H, CHC*H*$_2$CH), 2.34–2.41 (m, 1 H, C*H*CH$_2$CH$_3$), 2.42 (s, 3 H, ArC*H*$_3$), 2.58 (br., 1 H, O*H*), 2.79 [d, $^2J_{H,H}$ = 9.5 Hz, 1 H, NC*H*$_{2(endo)}$CH], 2.90 [dd, $^2J_{H,H}$ = 9.5, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.05 [dd, $^2J_{H,H}$ = 9.5, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.40 (dd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 5.1 Hz, 1 H, CHC*H*$_2$OH), 3.45 [d, $^2J_{H,H}$ = 9.5 Hz, 1 H, NC*H*$_{2(endo)}$CH], 3.55 (dd, $^2J_{H,H}$ = 11.2, $^3J_{H,H}$ = 3.5 Hz, 1 H, CHC*H*$_2$OH), 3.59 (s, 1 H, NC*H*CH$_2$), 4.29 (s, 1 H, NC*H*CH$_2$), 7.31 (d, $^3J_{H,H}$ = 8.08 Hz, 2 H, C*H*Ar), 7.71 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 10.7 (CHCH$_2$*C*H$_3$), 21.6 (ArCH$_3$), 21.7 (CH*C*H$_2$CH$_3$), 35.8 (CH*C*H$_2$CH), 51.8 (N*C*H$_2$CH), 57.3 (N*C*H$_2$CH), 58.0 (N*C*HCH$_2$), 60.4 (N*C*HCH$_2$), 61.3 (CH*C*H$_2$OH), 62.6 (*C*HCH$_2$CH$_3$), 127.5 (CHAr), 129.9 (CHAr), 135.5 (C), 143.7 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3551, 2953, 1924, 1595, 1330, 1090, 814 cm^{-1}. MS (EI): *m*/*z* (%) = 325 [M + 1]$^+$ (1), 293 (100) 169 (72), 140 (39), 68 (41). $C_{16}H_{24}N_2O_3S$ (324.44): calcd. C 59.23, H 7.46, N 8.63; found C 59.33, H 7.67, N 8.63.

(1*S*,4*S*)-5-[(2*R*)-(1-Hydroxymethyl)propyl]-2-tosyl-2,5-diazabicyclo-[2.2.1]heptane (14): GP 1 was followed, with **1** (5.0 g, 8.6 mmol) and (*R*)-2-aminobutan-1-ol (7.0 g, 78.5 mmol). The reaction time was 2 h, and the product was purified by initial removal of excess (*R*)-2-aminobutan-1-ol by distillation at reduced pressure (50–55 °C/0.25 Torr) followed by recrystallization of the residue from water to provide **14** (2.2 g, 79% yield), white solid, m.p. 117–118 °C, $[\alpha]_D^{20}$ = +18.8 (*c* = 1, MeOH). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.84 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, CHCH$_2$C*H*$_3$), 1.06 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CHC*H*$_2$CH), 1.38–1.42 (m, 2 H, CHC*H*$_2$CH$_3$), 1.59 (d, $^2J_{H,H}$ = 9.8 Hz, 1 H, CHC*H*$_2$CH), 2.33–2.36 (m, 1 H, C*H*CH$_2$CH$_3$), 2.38 (s, 3 H, ArC*H*$_3$), 2.52 (br., 1 H, O*H*), 2.58 [d, $^2J_{H,H}$ = 9.5 Hz, 1 H, NC*H*$_{2(endo)}$CH], 3.00 [dd, $^2J_{H,H}$ = 9.5, $^3J_{H,H}$ = 2.2 Hz, 2 H, NC*H*$_{2(exo)}$CH], 3.48–3.90 [m, 3 H, NC*H*$_{2(endo)}$CH, CHC*H*$_2$OH], 3.53 (s, 1 H, NC*H*CH$_2$), 4.23 (s, 1 H, NC*H*CH$_2$), 7.27 (d, $^3J_{H,H}$ = 8.08 Hz, 2 H, C*H*Ar), 7.66 (d, $^3J_{H,H}$ = 8.08 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 10.4 (CHCH$_2$*C*H$_3$), 21.6 (ArCH$_3$), 21.7 (CH*C*H$_2$CH$_3$), 36.0 (CH*C*H$_2$CH), 50.7 (N*C*H$_2$CH), 57.7 (N*C*H$_2$CH), 58.5 (N*C*HCH$_2$), 60.3 (N*C*HCH$_2$), 60.4 (CH*C*H$_2$OH), 62.8 (*C*HCH$_2$CH$_3$), 127.5 (CHAr), 129.8 (CHAr), 135.4 (C), 143.7 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3507, 2938, 1947, 1595, 1341, 1090, 826 cm^{-1}. MS (EI): *m*/*z* (%) = 325 [M + 1]$^+$ (7), 293 (100), 169 (53), 140 (24), 68 (19). $C_{16}H_{24}N_2O_3S$ (324.44): calcd. C 59.23, H 7.46, N 8.63; found C 59.61, H 7.59, N 8.81.

(1*S*,4*S*)-2-Benzyl-2,5-diazabicyclo[2.2.1]heptane·2 HBr (15): GP 2 was followed, with **2** (25.0 g, 73.0 mmol) and hydrobromic acid (48%, 35.4 g, 438 mmol, 50 mL). The reaction time was 2 h, and the product was purified as the dihydrobromide by recrystallization from propan-2-ol to provide **15**·2 HBr (23.5 g, 92% yield), white solid, m.p. 269 °C, $[\alpha]_D^{20}$ = +16.5 (*c* = 3, 2 N NaOH) [ref.[30] m.p. 270 °C (dec.) $[\alpha]_D^{20}$ = +16.5 (*c* = 3, 2 N NaOH)].

Microwave-Assisted Reaction: 2-Tosyl-diazabicyclo derivative **2** (0.25 g, 0.73 mmol) and 48% hydrobromic acid (0.35 g, 4.38 mmol, 0.50 mL) were placed in a 25 mL round-bottomed flask provided with magnetic stirrer and condenser. The reaction mixture was heated in the microwave apparatus for 30 min (75 W) at 110 °C. Product **15**·2 HBr was purified by recrystallization from propan-2-ol (0.25 g, 98% yield) as a white solid, m.p. 275 °C, $[\alpha]_D^{20}$ = +16.3 (*c* = 3, 2 N NaOH). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.51, (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CHC*H*$_2$CH), 1.77 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CHC*H*$_2$CH), 1.92 (br., 1 H, N*H*), 2.38 [d, $^2J_{H,H}$ = 9.5 Hz, 1 H, NC*H*$_{2(endo)}$CH], 2.74–2.77 [dd, $^2J_{H,H}$ = 10.2, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 2.84–2.87 [dd, $^2J_{H,H}$ = 9.8, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC*H*$_{2(exo)}$CH], 3.15 [d, $^2J_{H,H}$ = 10.2 Hz, 1 H, NC*H*$_{2(endo)}$CH], 3.30 (s, 1 H, NC*H*CH$_2$), 3.48 (s, 1 H, NC*H*CH$_2$), 3.66 (q, $^2J_{H,H}$ = 13.5 Hz, 2 H), 7.16–7.31 (m, 5 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 35.6 (CH*C*H$_2$CH), 48.4 (N*C*H$_2$CH), 57.1 (N*C*H$_2$CH), 58.5 (*C*H$_2$Ph), 60.7 (N*C*HCH$_2$), 62.6 (N*C*HCH$_2$), 126.8 (CHAr), 128.3 (CHAr), 128.5 (CHAr), 139.9 (C) ppm. MS (EI): *m*/*z* (%) = 188 [M]$^+$ (63), 158 (100), 132 (8), 97 (40), 91 (95), 68 (40).

(1*S*,4*S*)-2-Benzyl-5-methyl-2,5-diazabicyclo[2.2.1]heptane (16): Compound **15**·2 HBr (10 g, 28.5 mmol) and methanol (15 mL) were placed in a 250 mL Erlenmeyer flask containing a magnetic stirrer. The resulting solution was treated with KOH (2 equiv.) in methanol (15 mL) and stirred at 5–10 °C for 1.5 h. The resulting mixture was filtered, and the solid was washed three times with methanol (15 mL portions) and three times with EtOAc. The combined filtrates were concentrated in a rotary evaporator to give the free amine as a viscous oil. General procedure 3 was then followed, with formic acid (96%, 8.06 g, 175.2 mmol, 6.9 mL) and aqueous formaldehyde (37%, 2.6 g, 87.9 mmol, 6.5 mL). The reaction time was 1.5 h, to give **16** (4.2 g, 73% yield) as a colorless oil b.p. 82–92 °C/0.1 Torr, $[\alpha]_D^{20}$ = +35.1 (*c* = 1, $CHCl_3$). This oil was dissolved in methanol (25 mL) and bubbled with HCl(g), to afford **16**·2 HCl as a white solid, m.p. 234–236 °C [ref.[15b] m.p. 200 °C]. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.70 (d, $^2J_{H,H}$ = 11.3 Hz, 1 H, CHC*H*$_2$CH), 1.73 (d, $^2J_{H,H}$ = 11.3 Hz, 1 H, CHC*H*$_2$CH), 2.38 (s, 3 H, NC*H*$_3$), 2.58 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.5 Hz, 1 H, NC*H*$_{2(exo)}$CH], 2.68 [dd,

$^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC$H_{2(exo)}$CH], 2.72 [d, $^2J_{H,H}$ = 9.9 Hz, 1 H, NC$H_{2(endo)}$CH], 2.89 [d, $^2J_{H,H}$ = 9.9 Hz, 1 H, NC$H_{2(endo)}$CH], 3.18 (s, 1 H, NC*H*CH_2), 3.26 (s, 1 H, NC*H*CH_2), 3.67 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H, CH_2Ph), 3.74 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H, CH_2Ph), 7.19–7.34 (m, 5 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 33.5 (CH*C*H_2CH), 41.4 (ArCH_3), 56.2 (N*C*H_2CH), 57.6 (N*C*H_2CH), 58.1 (*C*H_2Ph), 62.0 (N*C*HCH$_2$), 63.9 (N*C*HCH$_2$), 126.8 (CHAr), 128.3 (CHAr), 128.5 (CHAr), 140.1 (C) ppm. MS (EI): *m*/*z* (%) = 202 $[M]^+$ (44), 158 (80), 111 (46), 91 (93), 82 (100), 68 (28).

(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]heptane·2 HBr (17): Compound **15**·2 HBr (6.0 g, 17.1 mmol) and Pd/C (10%, 1.5 g, 25% w/w), methanol (75 mL) and water (25 mL) were placed in a hydrogenation flask. The reaction flask was pressurized to 65 psi of hydrogen for 1 h. Filtration over Celite and concentration afforded **17**·2 HBr (4.2 g, 94% yield) as a white solid, m.p. 290 °C (dec.), $[\alpha]_D^{20}$ = +22.6 (*c* = 1, H_2O) [ref.[31] m.p. 300 °C (dec.), $[\alpha]_D^{20}$ = +22.0 (*c* = 1, H_2O)]. ^{1}H NMR (D_2O, 400 MHz): δ = 2.32 (s, 2 H, CHCH_2CH), 3.65 [s, 4 H, NC$H_{2(exo,endo)}$CH], 4.71 (s, 2 H, NC*H*CH_2) ppm. ^{13}C NMR (D_2O, 100.5 MHz): δ = 34.9 (CH*C*H_2CH), 47.2 (N*C*H_2CH), 56.5 (N*C*HCH$_2$) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3449, 2940, 1543, 1450, 1375, 1254, 1169, 821 cm^{-1}.

(1*S*,4*S*)-5-Benzyl-2-hydroxyethyl-2,5-diazabicyclo[2.2.1]heptane (18): KOH (85%, 0.95 g, 16.8 mmol) in methanol (10 mL) was placed in a 25 mL Erlenmeyer flask. Compound **15**·2 HBr (2.0 g, 5.71 mmol) was added to this solution, and the resulting mixture was stirred for 30 min at ambient temperature, before the addition of EtOAc (10 mL). The white solid that precipitated was removed by filtration, the filtrate was concentrated, and the residue was redissolved in toluene (15 mL) before treatment with K_2CO_3 (0.79 g, 6.38 mmol), KI (0.015 g, 0.09 mmol), and 2-bromoethanol (0.8 g, 6.38 mmol, 0.45 mL). The resulting reaction mixture was stirred for 96 h at room temp. The white solid that formed was removed by filtration, and the filtrate was concentrated in a rotary evaporator to give a pale yellow oil (1.2 g) that was purified by flash column chromatography ($CHCl_3$/MeOH, 7:3→1:1) to give **18** (1.02 g, 77% yield) as a colorless oil. This oil was dissolved in methanol (25 mL) and bubbled with HCl(g), to afford of **18**·2 HCl (1.28 g, 96% yield) as a white solid, m.p. 226–228 °C (dec.), $[\alpha]_D^{20}$ = –9.4 (*c* = 1, MeOH) (ref.[32] NMR). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.70 (d, $^2J_{H,H}$ = 8.8 Hz, 1 H, CHCH_2CH), 1.80 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CHCH_2CH), 2.63–2.84 [m, 5 H, NCH_2CH$_2$OH, NC$H_{2(exo,endo)}$CH, NC$H_{2(exo)}$CH], 2.89 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 1.1 Hz, 1 H, NC$H_{2(endo)}$CH], 3.19 (br., 1 H, O*H*), 3.32 (s, 2 H, NC*H*CH_2), 3.57 (t, $^3J_{H,H}$ = 5.5 Hz, 2 H, NCH$_2$CH_2OH), 3.68 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H, CH_2Ph), 3.73 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H, CH_2Ph), 7.22–7.36 (m, 5 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 33.9 (CH*C*H_2CH), 56.3 (N*C*H_2CH$_2$OH), 56.5 (N*C*H_2CH), 56.8 (N*C*H_2CH), 58.5 (CH$_2$Ph), 59.7 (NCH$_2$*C*H$_2$OH), 61.3 (NCHCH$_2$), 62.8 (NCHCH$_2$), 127.0 (CHAr), 128.4 (CHAr), 128.6 (CHAr), 139.7 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3406, 3010, 2561, 1627, 1451, 1209, 1080, 739 cm^{-1}. MS (EI): *m*/*z* (%) = 232 $[M]^+$ (8), 202 (16), 158 (100), 141 (46), 112 (85), 91 (74), 82 (34), 68 (15). $C_{14}H_{20}N_2O$·2 HCl (305.24): calcd. C 55.09, H 7.26, N 9.18; found C 54.88, H 7.33, N 9.51.

(1*S*,4*S*)-5-(Dimethylamino)ethyl-2-tosyl-2,5-diazabicyclo-[2.2.1]heptane·2 HCl (19): GP 3 was followed, with **9** (5.0 g, 16.9 mmol), formic acid (96%, 18.5 g, 402 mmol, 15.8 mL), and formaldehyde (37%, 6.06 g, 202 mmol, 15 mL). The reaction mixture was heated at reflux for 4 h to give **19**·2 HCl (2.5 g, 37% yield) as a white solid, m.p. 210 °C (dec.), $[\alpha]_D^{20}$ = +15.0 (*c* = 1, MeOH). ^{1}H NMR (D_2O, 400 MHz): δ = 1.31 (d, $^2J_{H,H}$ = 12.5 Hz, 1 H, CHCH_2CH), 2.02 (d, $^2J_{H,H}$ = 12.5 Hz, 1 H, CHCH_2CH), 2.38 (s, 3 H, ArCH_3), 2.96 [s, 6 H, N(CH_3)$_2$], 3.38 [d, $^2J_{H,H}$ = 12.0 Hz, 1 H, NC$H_{2(endo)}$CH], 3.48 [d, $^2J_{H,H}$ = 11.0 Hz, 1 H, NC$H_{2(endo)}$CH], 3.56–3.66 [m, 3 H, N(CH_2)$_2$N(CH$_3$)$_2$, NC$H_{2(exo)}$CH], 3.71–3.79 [m, 3 H, N(CH_2)$_2$N(CH$_3$)$_2$, NC$H_{2(exo)}$CH], 4.45 (s, 1 H, NC*H*CH_2), 4.66 (s, 1 H, NC*H*CH_2), 7.42 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar), 7.70 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar) ppm. ^{13}C NMR (D_2O, 100.5 MHz): δ = 21.1, 33.6, 43.8, 48.6, 49.9, 51.7, 59.1, 63.0, 66.6, 127.7, 130.8, 131.9, 146.5 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3435, 2416, 1598, 1466, 1346, 1158, 687 cm^{-1}. MS (EI): *m*/*z* (%) = 224 $[M + 1]^+$ (1), 223 (0.2), 265 (100), 222 (3), 152 (14), 140 (10), 91 (5), 58 (77), 44 (23). $C_{16}H_{25}N_3O_2S$·2 HCl (396.38): calcd. C 48.48, H 6.87, N 10.60; found C 48.34, H 7.19, N 10.97.

(1*S*,4*S*)-2-Tosyl-2,5-diazabicyclo[2.2.1]heptane·HCl (20): Compound **2** (15.0 g, 43.8 mmol), Pd/C (10%, 1.5 g, 10% w/w), and concd. aqueous HCl (3.5 mL) were placed in a hydrogenation flask. The reaction flask was pressurized to 65 psi of hydrogen for 1 h. Filtration over Celite and concentration afforded **20**·2 HCl (12.4 g, 98% yield) as a white solid, m.p. 242–245 °C, $[\alpha]_D^{20}$ = +12.0 (*c* = 1, MeOH). This salt was treated with aqueous NaOH (1.5 equiv.) and extracted with EtOAc to give **20** (quantitative yield) as a pale yellow solid, m.p. 123–125 °C, $[\alpha]_D^{20}$ = +14.5 (*c* = 2, $CHCl_3$) [ref.[15a] m.p. 130–132 °C, $[\alpha]_D^{20}$ = +19.3 (*c* = 2, $CHCl_3$)]. ^{1}H NMR ([D$_6$]-DMSO, 400 MHz): δ = 0.95 (d, $^2J_{H,H}$ = 10.9 Hz, 1 H, CHCH_2CH), 1.62 (d, $^2J_{H,H}$ = 10.9 Hz, 1 H, CHCH_2CH), 2.40 (s, 3 H, ArCH_3), 3.14–3.17 [m, 3 H, NC$H_{2(exo)}$CH, NC$H_{2(endo)}$CH], 3.60 [d, $^2J_{H,H}$ = 10.9 Hz, 1 H, NC$H_{2(endo)}$CH], 4.26 (s, 1 H, NC*H*CH_2), 4.53 (s, 1 H, NC*H*CH_2), 7.45 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, C*H*Ar), 7.73 (d, $^3J_{H,H}$ = 8.13 Hz, 2 H, C*H*Ar), 9.77 (br., 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]-DMSO, 100.5 MHz): δ = 21.9 (ArCH_3), 35.0 (CH*C*H_2CH), 51.2 (N*C*H_2CH), 52.4 (N*C*HCH$_2$), 57.9 (N*C*H_2CH), 58.8 (N*C*HCH$_2$), 128.3 (CHAr), 131.0 (CHAr), 134.9 (C), 144.9 (C) ppm. MS (EI): *m*/*z* (%) = 253 $[M + 1]^+$ (2), 187 (29), 158 (10), 97 (100), 91 (17), 68 (71).

(1*S*,4*S*)-2,5-Ditosyl-2,5-diazabicyclo[2.2.1]heptane (21): Tosylation of **20**·HCl (4.0 g, 13.9 mmol) was achieved with *p*-toluenesulfonyl chloride (3.2 g, 16.7 mmol), and triethylamine (2.4 g, 23.7 mmol, 3.3 mL). This reaction mixture was stirred at room temp. for 1.5 h. The usual workup procedure afforded **21** (5.0 g, 90% yield) as a white solid, m.p. 124–125 °C, $[\alpha]_D^{20}$ = –31.8 (*c* = 1.1, MeOH) [ref.[15a] m.p. 122–123 °C]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.06 (s, 2 H, CHCH_2CH), 2.41 (s, 6 H, ArCH_3), 3.12–3.15 [dd, $^2J_{H,H}$ = 9.7, $^3J_{H,H}$ = 2.5, Hz, 2 H, NC$H_{2(exo)}$CH], 3.40 [d, $^2J_{H,H}$ = 9.6 Hz, 2 H, NC$H_{2(endo)}$CH], 4.36 (br., 2 H, NC*H*CH_2), 7.28 (d, $^3J_{H,H}$ = 8.2 Hz, 4 H, C*H*Ar), 7.64 (d, $^3J_{H,H}$ = 8.2 Hz, 4 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 21.6 (ArCH_3), 35.4 (CH*C*H_2CH), 55.2 (N*C*H_2CH), 60.1 (N*C*HCH$_2$), 127.3 (CHAr), 129.9 (CHAr), 135.1 (C), 143.9 (C) ppm. MS (EI): *m*/*z* (%) = 407 $[M + 1]^+$ (1), 251 (100), 222 (36), 155 (40), 91 (26), 68 (5).

(1*S*,4*S*)-2,5-Dibenzyl-2,5-diazabicyclo[2.2.1]heptane (22): Compound **15**·2 HBr (10.0 g, 28.5 mmol) and methanol (15 mL) were placed in a 250 mL Erlenmeyer flask provided with a magnetic stirrer. KOH (2 equiv.) in methanol (15 mL) was added to this solution. The resulting mixture was stirred for 1.5 h at 5–10 °C and filtered, and the solid was washed three times with methanol (15 mL portions) and three times with EtOAc (15 mL portions). The combined organic layer was concentrated in a rotary evaporator to give the free amine as a viscous oil that was alkylated with benzyl bromide (5.4 g, 31.4 mmol, 3.7 mL). The crude product was treated with HCl (30%, 20 mL), and the hydrochloride salt precipitated with propan-2-ol to give **22**·2 HCl (8.3 g, 83% yield) as a white solid, m.p. 231–233 °C, $[\alpha]_D^{20}$ = –20.1 (*c* = 1, H_2O). This salt

was treated with aqueous NaOH (2 equiv.), extracted with EtOAc, and concentrated to give **22** as a pale yellow solid, m.p. 53–54 °C, $[\alpha]_D^{20}$ = +19.5 (*c* = 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ = 1.74 (s, 2 H, $CHCH_2CH$), 2.65–2.70 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.5 Hz, 2 H, $NCH_{2(exo)}CH$], 2.86 [d, $^3J_{H,H}$ = 9.9 Hz, 2 H, $NCH_{2(endo)}CH$], 3.28 (s, 2 H, $NCHCH_2$), 3.74 (q, $^2J_{H,H}$ = 13.4 Hz, 4 H, CH_2Ph), 7.19–7.37 (m, 10 H, CHAr) ppm. ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 33.5 ($CHCH_2CH$), 56.5 (NCH_2CH), 58.4 (CH_2Ph), 61.6 ($NCHCH_2$), 126.7 (CHAr), 128.2 (CHAr), 128.4 (CHAr), 128.5 (CHAr), 140.1 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3446, 2839, 1960, 1599, 1450, 1363, 1296, 1178, 818, 749 cm^{-1}. MS (IE) *m*/*z* (%): 278 $[M]^+$ (9), 187 (70), 158 (98), 91 (100), 68 (9). $C_{19}H_{22}N_2$ (278.39): calcd. C 81.97, H 7.97, N 10.06; found C 81.71, H 7.96, N 10.32.

(1*S*,4*S*)-2,5-Diisopropyl-2,5-diazabicyclo[2.2.1]heptane (24): This compound was produced as described in GP 2; compound **3** (14 g, 47.5 mmol) and hydrobromic acid (48%, 22.9 g, 283 mmol, 32 mL, 1 h reflux time) afforded crude **23** (3.5 g, 53% yield) as a viscous oil, which was then alkylated without further purification according to General Procedure 4 [acetone (15 mL), isopropyl iodide (5.3 g, 31.3 mmol, 3.1 mL), and Na_2CO_3 (2.6 g, 25 mmol)]. Dialkylated derivative **24** (0.71 g, 16% yield) was obtained as a colorless oil, b.p. 59–60 °C/2 Torr. $[\alpha]_D^{20}$ = +30.0 (*c* = 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.96 [d, $^3J_{H,H}$ = 6.2 Hz, 6 H, $NCH(CH_3)_2$], 1.03 [d, $^3J_{H,H}$ = 6.2 Hz, 6 H, $NCH(CH_3)_2$], 1.72 (s, 2 H, $CHCH_2CH$), 2.56 (d, $^2J_{H,H}$ = 10.2 Hz, 2 H, $NCH_{2(endo)}CH$], 2.61 [septet, $^3J_{H,H}$ = 6.2 Hz, 2 H, $NCH(CH_3)_2$], 2.80 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.5 Hz, 2 H, $NCH_{2(exo)}CH$], 3.46 (s, 2 H, $NCHCH_2$) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 22.0 [$NCH(CH_3)_2$], 22.9 [$NCH(CH_3)$], 36.6 ($CHCH_2CH$), 50.1 [$NCH(CH_3)_2$], 52.6 (NCH_2CH), 58.7 ($NCHCH_2$) ppm. IR (film): $\tilde{\nu}_{max}$ = 3363, 2969, 2951, 2601, 1471, 1367, 1205, 971 cm^{-1}. MS (EI): *m*/*z* (%) = 182 $[M]^+$ (42), 167 (5), 139 (27), 110 (100), 96 (54), 68 (46). $C_{11}H_{22}N_2$ (182.31): calcd. C 72.47, H 12.16, N 15.37; found C 72.17, H 12.26, N 15.24.

(1*S*,4*S*)-2-Butyl-2,5-diazabicyclo[2.2.1]heptane (25): GP 2 was followed, with **4** (13.2 g, 42.8 mmol) and hydrobromic acid (48%, 20.8 g, 256.8 mmol, 29.1 mL). The reaction time was 2.5 h, and the product **25** (3.5 g, 54% yield) was purified by distillation (b.p. 60 °C/0.1 Torr) to give **25** (3.5 g, 54% yield) as a viscous, colorless oil. $[\alpha]_D^{20}$ = +28.6 (*c* = 1, MeOH). ^1H NMR ($CDCl_3$, 270 MHz): δ = 0.79 [t, $^3J_{H,H}$ = 7.2 Hz, 3 H, $N(CH_2)_3CH_3$], 1.14–1.37 [m, 4 H, $NCH_2(CH_2)_2CH_3$], 1.44 (d, $^2J_{H,H}$ = 9.6 Hz, 1 H, $CHCH_2CH$), 1.66 (d, $^2J_{H,H}$ = 9.6 Hz, 1 H, $CHCH_2CH$), 2.23 [d, $^2J_{H,H}$ = 9.6 Hz, 1 H, $NCH_{2(endo)}CH$], 2.27–2.49 [m, 2 H $NCH_2(CH_2)_2CH_3$], 2.63 (br., 1 H, NH), 2.65 [dd, $^2J_{H,H}$ = 10.4, $^3J_{H,H}$ = 2.2 Hz, 1 H, $NCH_{2(exo)}CH$], 2.81 [dd, $^2J_{H,H}$ = 9.6, $^3J_{H,H}$ = 2.4 Hz, 1 H, $NCH_{2(exo)}CH$], 3.02 [d, $^2J_{H,H}$ = 10.1 Hz, 1 H, $NCH_{2(endo)}CH$], 3.26 (s, 1 H, $NCHCH_2$), 3.38 (s, 1 H, $NCHCH_2$) ppm. ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.0 (CH_3), 20.7 (CH_2), 31.3 (CH_2), 35.7 (CH_2), 47.4 (CH_2), 54.1 (CH_2), 56.6 (CH_2), 60.8 (CH), 62.5 (CH) ppm. MS (EI): *m*/*z* (%) = 154 $[M]^+$ (32), 139 (8), 124 (46), 112 (20), 97 (10), 82 (100), 68 (30), 57 (20). $C_9H_{18}N_2$ (154.25) HRMS (FAB): calcd. $[M + H]^+$ 155.1548; found 155.1553.

(1*S*,4*S*)-2,5-Dibutyl-2,5-diazabicyclo[2.2.1]heptane (26): This compound was produced as described in GP 4; compound **25** (2.6 g, 17 mmol) and butyl iodide (3.7 g, 20 mmol, 2.3 mL) in acetone (11 mL) were heated at reflux for 34 h to give **26** (2.4 g, 67% yield) as a colorless oil, b.p. 75–78 °C/0.05 Torr, $[\alpha]_D^{20}$ = +15.2 (*c* = 1, MeOH). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.85 [t, $^3J_{H,H}$ = 7.0 Hz, 6 H, $N(CH_2)_3CH_3$], 1.23–1.40 [m, 8 H, $NCH_2(CH_2)_2CH_3$], 1.63 (s, 2 H, $CHCH_2CH$), 2.33–2.40 [m, 2 H, $NCH_2(CH_2)_2CH_3$], 2.45–2.51 [m, 2 H, $NCH_2(CH_2)_2CH_3$], 2.62 [s, 4 H, $NCH_{2(endo,exo)}CH$], 3.21 (s, 2 H, $NCHCH_2$) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 14.1 (CH_3), 20.8 (CH_2), 31.6 (CH_2), 34.2 (CH_2), 53.9 (CH_2), 55.5 (CH_2), 61.7 (CH) ppm. IR (film): $\tilde{\nu}_{max}$ = 3356, 2957, 2860, 1681, 1459, 1377, 1217, 1104, 967 cm^{-1}. MS (EI): *m*/*z* (%) = 210 $[M]^+$ (20), 167 (6), 153 (9), 124 (100), 82 (71), 68 (15). $C_{13}H_{26}N_2$ (210.36). HRMS (FAB): calcd. $[M + H]^+$ 211.2174; found 211.2176.

(1*S*,4*S*)-2-Octyl-2,5-diazabicyclo[2.2.1]heptane (27): GP 2 was followed, with **5**·HCl (15.0 g, 37.4 mmol) and hydrobromic acid (48%, 18.2 g, 224.4 mmol, 25.4 mL). The reaction time was 10 h, and the product **27** (8.9 g, 64% yield) was isolated as its hydrobromide, m.p. 176–178 °C. This salt was treated with KOH in methanol (2 equiv.), and the free amine (viscous oil) was distilled at reduced pressure (b.p. 80 °C/0.1 Torr). $[\alpha]_D^{20}$ = +13.0 (*c* = 1, MeOH). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.84 [t, $^3J_{H,H}$ = 6.2 Hz, 3 H, $N(CH_2)_7CH_3$], 1.24 [m, 9 H, $N(CH_2)_7CH_3$], 1.40 [m, 2 H, $N(CH_2)_7CH_3$], 1.56 (d, $^2J_{H,H}$ = 9.9 Hz, 1 H, $CHCH_2CH$), 1.77 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, $CHCH_2CH$), 2.35–2.54 [m, 3 H, $N(CH_2)_7CH_3$], 2.75 [d, $^2J_{H,H}$ = 9.9 Hz, 1 H, $NCH_{2(endo)}CH$], 2.89 [d, $^2J_{H,H}$ = 9.8 Hz, 1 H, $NCH_{2(exo)}CH$], 3.15 [d, $^2J_{H,H}$ = 10.2 Hz, 1 H, $NCH_{2(endo)}CH$], 3.32–3.36 [m, 3 H, $NCH_{2(exo)}CH$, $NCHCH_2$, NH], 3.54 (s, 1 H, $NCHCH_2$) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 14.2 (CH_3), 22.7 (CH_2), 27.6 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 35.7 (CH_2), 47.3 (CH_2), 54.4 (CH_2), 56.7 (CH_2), 60.7 (CH), 61.7 (CH) ppm. MS (EI): *m*/*z* (%) = 210 $[M]^+$ (23), 180 (45), 124 (4), 140 (18), 111 (25), 97 (9), 82 (100), 68 (24), 44 (12). $C_{13}H_{26}N_2$ (210.36) HRMS (FAB): calcd. $[M + H]^+$ 211.2174; found 211.2176.

(1*S*,4*S*)-2,5-Dioctyl-2,5-diazabicyclo[2.2.1]heptane (28): This compound was produced as described in GP 4; compound **27** (15.0 g, 71.4 mmol) and octyl iodide (18.8 g, 78.5 mmol, 14.2 mL) in acetone (100 mL) were heated at reflux for 5.5 h to give **28** (6.7 g, 29% yield) as a yellowish oil, b.p. 160 °C/0.4 Torr, $[\alpha]_D^{20}$ = +20.8 (*c* = 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.84 [t, $^3J_{H,H}$ = 7.0 Hz, 6 H, $N(CH_2)_7CH_3$], 1.16–1.34 [m, 20 H, $NCH_2(CH_2)_6CH_3$], 1.38–1.46 [m, 4 H, $NCH_2(CH_2)_6CH_3$], 1.65 (s, 2 H, $CHCH_2CH$), 2.34–2.41 [m, 2 H, $NCH_2(CH_2)_6CH_3$], 2.46–2.53 [m, 2 H, $NCH_2(CH_2)_6CH_3$], 2.64 [s, 4 H, $NCH_{2(endo,exo)}CH$], 3.24 (s, 2 H, $NCHCH_2$) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 14.1 (CH_3), 22.7 (CH_2), 27.6 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 34.3 (CH_2), 54.2 (CH_2), 55.5 (CH_2), 61.7 (CH) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2926, 2854, 1466, 1378, 1221, 1106, 966, 723 cm^{-1}. MS (EI): *m*/*z* (%) = 322 $[M]^+$ (11), 279 (4), 223 (6), 180 (100), 82 (21). $C_{21}H_{42}N_2$ (322.57) HRMS (FAB): calcd. $[M + H]^+$ 323.3426; found: 323.3430.

(1*S*,4*S*)-2-Methyl-2,5-diazabicyclo[2.2.1]heptane (29): Compound **16** (1.0 g, 4.94 mmol) and Pd/C (10%, 0.15 g, 15% w/w) in methanol (10 mL) were placed in a hydrogenation flask. The reaction flask was pressurized to 65 psi of hydrogen for 1 h. Filtration over Celite and concentration afforded **29** (0.48 g, 87% yield) as a colorless oil, b.p. 40 °C/3 Torr, $[\alpha]_D^{20}$ = +40.4 (*c* = 1.1, MeOH). Treatment with hydrobromic acid (48%, 2 equiv.) afforded **29**·2 HBr as a white solid, m.p. 257–258 °C, $[\alpha]_D^{20}$ = +13.7 (*c* = 1, MeOH), [ref.[15c] m.p. 258–259 °C, $[\alpha]_D^{20}$ = +13.2 (*c* = 0.94, MeOH)]. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.45 (d, $^2J_{H,H}$ = 9.7 Hz, 1 H, $CHCH_2CH$), 1.70 (d, $^2J_{H,H}$ = 9.7 Hz, 1 H, $CHCH_2CH$), 2.27 (s, 3 H, NCH_3), 2.32 [d, $^2J_{H,H}$ = 9.9 Hz, 1 H, $NCH_{2(endo)}CH$], 2.69 [dd, $^2J_{H,H}$ = 10.4, $^3J_{H,H}$ = 2.4 Hz, 1 H, $NCH_{2(exo)}CH$], 2.72 (br., NH), 2.75 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.2 Hz, 1 H, $NCH_{2(exo)}CH$], 3.04 [d, $^2J_{H,H}$ = 10.3 Hz, 1 H, $NCH_{2(endo)}CH$], 3.17 (s, 1 H, $NCHCH_2$), 3.41 (s, 1 H, $NCHCH_2$) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 35.3 ($CHCH_2CH$), 41.0 (NCH_3), 47.7 (NCH_2CH), 57.2 ($NCHCH_2$), 62.6 ($NCHCH_2$), 63.7 (NCH_2CH) ppm. MS (EI): *m*/*z* (%) = 112 $[M]^+$ (26), 97 (5), 82 (100), 68 (31), 57 (15), 42 (52).

(1*S*,4*S*)-2,5-Dimethyl-2,5-diazabicyclo[2.2.1]heptane (30): GP 3 was followed, with **29** (16.0 g, 142 mmol), formic acid (96%, 26.0 g, 568 mmol, 22.3 mL), and formaldehyde (37%, 8.5 g, 284 mmol, 21.2 mL). The reaction mixture was heated at reflux for 5 h to give **30** (17.2 g, 96% yield) as a colorless oil, b.p. 30 °C/2.5 Torr, $[\alpha]_D^{20}$ = +41.9 (*c* = 1, MeOH) [ref.[21a] b.p. 60 °C/13 Torr].

Microwave-Assisted Reaction: Derivative **29** (0.8 g, 7.13 mmol), formic acid (96%, 1.3 g, 28.5 mmol, 1.1 mL), and aqueous formaldehyde (37%, 0.43 g, 14.3 mmol, 1.1 mL) were placed in a 25 mL round-bottomed flask provided with magnetic stirrer and condenser. The reaction mixture was heated in the microwave apparatus for 30 min (100 W) at 100 °C. The product was purified by distillation (b.p. 37 °C/3 Torr) to give pure **30** (0.85 g, 95% yield) $[\alpha]_D^{20}$ = +38.9 (*c* = 1, MeOH). ^{1}H NMR (CD_3OD, 400 MHz): δ = 1.75 (s, 2 H, CHCH_2CH), 2.36 (s, 6 H, NCH_3), 2.59 [dd, $^2J_{H,H}$ = 10.5, $^3J_{H,H}$ = 2.7 Hz, 4 H, NC$H_{2(exo)}$CH], 2.80 [d, $^2J_{H,H}$ = 10.3 Hz, 4 H, NC$H_{2(endo)}$CH], 3.25 (s, 2 H, NC*H*CH$_2$) ppm. ^{13}C NMR (CD_3OD, 100.5 MHz): δ = 32.2 (CH*C*H$_2$CH), 40.1 (NCH$_3$), 56.6 (N*C*H$_2$CH), 63.7 (N*C*HCH$_2$) ppm. IR (film): $\tilde{\nu}_{max}$ = 3369, 2964, 2856, 1670, 1454, 1337, 1227, 937 cm^{-1}. MS (EI): *m*/*z* (%) = 126 [M + 1]$^+$, (31), 111 (3) 82 (100), 70 (19), 55 (2), 42 (29). $C_7H_{14}N_2$ (126.20) HRMS (FAB): calcd. [M + H]$^+$ 127.1235; found 127.1228.

(1*S*,4*S*)-2-[(*S*)-1-Phenylethyl]-2,5-diazabicyclo[2.2.1]heptane (31): GP 2 was followed, with **6**·HCl (9.0 g, 22.9 mmol) and hydrobromic acid (48%, 11.1 g, 137.4 mmol, 15.5 mL). The reaction time was 2.5 h. The product was isolated as its hydrobromide and subsequently redissolved in water, treated with aqueous NaOH to pH = 11, extracted with toluene, dried with Na_2SO_4, concentrated, and distilled to give **31** (2.1 g, 46% yield) as a viscous oil, b.p. 102–110 °C/0.01–0.05 Torr $[\alpha]_D^{20}$ = –13.6 (neat). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CHCH_3), 1.42 (d, $^2J_{H,H}$ = 8.4 Hz, 1 H, CHCH_2CH), 1.75 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CHCH_2CH), 2.01 (br., 1 H, N*H*), 2.28 [dd, $^2J_{H,H}$ = 9.5, $^3J_{H,H}$ = 1.1 Hz, 1 H, NC$H_{2(endo)}$CH], 2.56 [dd, $^2J_{H,H}$ = 10.6, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC$H_{2(exo)}$CH], 3.10–3.19 [m, 3 H, NC$H_{2(endo,exo)}$CH, NC*H*CH$_2$], 3.46 (s, 1 H, NC*H*CH$_2$), 3.55 (q, $^3J_{H,H}$ = 6.2 Hz, 1 H, C*H*CH$_3$), 7.15–7.31 (m, 5 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 23.9 (CH*C*H$_3$), 36.9 (CH*C*H$_2$CH), 46.5 (N*C*H$_2$CH), 57.1 (N*C*HCH$_2$), 58.6 (N*C*HCH$_2$), 61.3 (N*C*H$_2$CH), 61.4 (*C*HCH$_3$), 126.9 (CHAr), 127.5 (CHAr), 128.5 (CHAr), 146.4 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3370, 2877, 2443, 1636, 1456, 1385, 1213, 1166, 921, 812, 703 cm^{-1}. MS (EI): *m*/*z* (%) = *m*/*z* 202 [M]$^+$ (46), 187 (6), 172 (45), 158 (25), 105 (100), 97 (92), 68 (63). $C_{13}H_{18}N_2$ (202.30) HRMS (TOF-ESI): calcd. [M + H]$^+$ 203.1542; found 203.1544.

(1*S*,4*S*)-2-[(*S*)-1-Phenylethyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane (32): GP 3 was followed, with **31** (2.0 g, 9.9 mmol), formic acid (96%, 2.7 g, 59.4 mmol, 2.3 mL), and formaldehyde (37%, 0.9 g, 29.7 mmol, 2.2 mL). The reaction mixture was heated at reflux for 1 h to give **32** (1.34 g, 62% yield) as a colorless oil, b.p. 83 °C/0.05 Torr, $[\alpha]_D^{20}$ = –35.8 (*c* = 1.2, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CHCH_3), 1.59 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CHCH_2CH), 1.65 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CHCH_2CH), 2.29 [dd, $^2J_{H,H}$ = 10.2, $^3J_{H,H}$ = 2.6 Hz, 1 H, NC$H_{2(exo)}$CH], 2.33 (s, 3 H, NCH_3), 2.58 [d, $^2J_{H,H}$ = 9.5 Hz, 1 H, NC$H_{2(endo)}$CH], 2.89–2.96 [m, 2 H, NC$H_{2(endo,exo)}$CH], 3.10 (s, 1 H, NC*H*CH$_2$), 3.13 (s, 1 H, NC*H*CH$_2$), 3.59 (q, $^3J_{H,H}$ = 6.6 Hz, 1 H, C*H*CH$_3$), 7.14–7.33 (m, 5 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 24.1 (CH*C*H$_3$), 34.1 (CH*C*H$_2$CH), 41.7 (NCH$_3$), 55.5 (N*C*H$_2$CH), 56.0 (N*C*H$_2$CH), 59.9 (N*C*HCH$_2$), 60.9 (*C*HCH$_3$), 63.9 (N*C*HCH$_2$), 126.9 (CHAr), 127.5 (CHAr), 128.4 (CHAr), 145.5 (C) ppm. IR (film): $\tilde{\nu}_{max}$ = 3300, 2970, 2852, 1686, 1451, 1304, 1216, 767 cm^{-1}. MS (EI): *m*/*z* (%) = 216 [M]$^+$ (46), 172 (100), 158 (18), 111 (67), 82 (63), 68 (49) 44 (16). $C_{14}H_{20}N_2$ (216.32) HRMS (FAB): calcd. [M + H]$^+$ 217.1705; found 217.1712.

(1*S*,4*S*)-2-[(*R*)-1-Phenylethyl]-2,5-diazabicyclo[2.2.1]heptane·2 HBr (33): GP 2 was followed, with **7** (5.0 g, 14.0 mmol) and hydrobromic acid (48%, 6.8 g, 84.2 mmol, 9.5 mL). The reaction time was 1 h. The product was isolated as its hydrobromide, which was recrystallized from propan-2-ol/EtOAc (1:1) to give **33**·2 HBr (4.7 g, 94% yield) as a white solid, m.p. 238–240 °C, $[\alpha]_D^{20}$ = +14.4 (*c* = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (d, $^3J_{H,H}$ = 6.2 Hz, 3 H, CHCH_3), 1.54 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CHCH_2CH), 1.76 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CHCH_2CH), 2.23 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 1.4 Hz, 1 H, NC$H_{2(endo)}$CH], 2.28 (br., 1 H, N*H*), 2.76 [dd, $^2J_{H,H}$ = 9.7, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC$H_{2(exo)}$CH], 2.78 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.2 Hz, 1 H, NC$H_{2(exo)}$CH], 3.17 [dd, $^2J_{H,H}$ = 10.0, $^3J_{H,H}$ = 1.0 Hz, 1 H, NC$H_{2(endo)}$CH], 3.45 (s, 1 H, NC*H*CH$_2$), 3.50 (s, 1 H, NC*H*CH$_2$), 3.51 (q, $^3J_{H,H}$ = 6.4 Hz, 1 H, C*H*CH$_3$), 7.16–7.34 (m, 5 H, C*H*Ar) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 23.7 (CH*C*H$_3$), 35.9 (CH*C*H$_2$CH), 47.7 (N*C*H$_2$CH), 57.0 (N*C*HCH$_2$), 58.4 (N*C*HCH$_2$), 61.8 (N*C*H$_2$CH), 62.2 (*C*HCH$_3$), 126.9 (CHAr), 127.3 (CHAr), 128.4 (CHAr), 146.2 (C) ppm. MS (EI): *m*/*z* (%) = 202 [M]$^+$ (48), 172 (39), 158 (26), 105 (99), 97 (100), 68 (81). $C_{13}H_{18}N_2$·2HBr (364.12): calcd. C 42.88, H 5.54, N 7.69; found C 42.93, H 5.22, N 7.66.

(1*S*,4*S*)-2-[(*R*)-1-Phenylethyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane (34): Compound **33**·2 HBr (2.0 g, 5.5 mmol) and methanol (20 mL) were placed in a 125 mL Erlenmeyer flask containing a magnetic stirrer. KOH (2 equiv.) in methanol (10 mL) was added to this solution. The resulting mixture was stirred for 1.5 h at 5–10 °C and filtered, and the solid was washed three times with methanol (15 mL portions) and three times with EtOAc (15 mL) portions. The combined organic layer was concentrated in a rotary evaporator to give the free amine as a viscous oil that was methylated as described in General Procedure 3 with formic acid (96%, 1.52 g, 33.1 mmol, 1.3 mL) and formaldehyde (37%, 0.49 g, 16.5 mmol, 1.2 mL) to give **34** (1.4 g, 68% yield) as a colorless oil, b.p. 80 °C/0.005 Torr, $[\alpha]_D^{20}$ = –82.2 (neat). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.19 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CHCH_3), 1.65 (s, 2 H, CHCH_2CH), 2.33 (s, 3 H, NCH_3), 2.42–2.51 [m, 2 H, NC$H_{2(endo,exo)}$CH], 2.57 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.5 Hz, 1 H, NC$H_{2(exo)}$CH], 2.86 [d, $^2J_{H,H}$ = 9.8 Hz, 1 H, NC$H_{2(endo)}$CH], 3.06 (s, 1 H, NC*H*CH$_2$), 3.39 (s, 1 H, NC*H*CH$_2$), 3.52 (q, $^3J_{H,H}$ = 6.4 Hz, 1 H, C*H*CH$_3$), 7.11–7.34 (m, 5 H, *CH*Ar) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 23.6 (CH*C*H$_3$), 33.6 (CH*C*H$_2$CH), 41.3 (NCH$_3$), 55.5 (N*C*H$_2$CH), 56.5 (N*C*H$_2$CH), 59.4 (N*C*HCH$_2$), 61.3 (*C*HCH$_3$), 63.5 (N*C*HCH$_2$), 126.6 (CHAr), 127.0 (CHAr), 128.2 (CHAr), 146.2 (C) ppm. IR (film): $\tilde{\nu}_{max}$ = 3300, 2970, 2853, 1686, 1451, 1311, 1226, 766 cm^{-1}. MS (EI): *m*/*z* (%) = 216 [M]$^+$ (44), 172 (62), 158 (13), 111 (88), 82 (100), 68 (67) 44 (26). $C_{14}H_{20}N_2$ (216.32) HRMS (FAB): calcd. [M + H]$^+$ 217.1705; found 217.1707.

(1*S*,4*S*)-5-Methyl-2-[2-(5-methyl-2,5-diazabicyclo[2.2.1]heptane)-ethyl]-2,5-diazabicyclo[2.2.1]heptane (36): GP 2 was followed, with **8**·2 HCl (10.0 g, 16.5 mmol) and hydrobromic acid (48%, 8.0 g, 100 mmol, 11.2 mL). The reaction time was 2 h. The product was methylated as described in General Procedure 3 with formic acid (96%, 6.1 g, 132 mmol, 5.2 mL) and formaldehyde (37%, 2.0 g, 66 mmol, 5 mL) (the reaction time was 5 h) to give **36** (1.4 g, 34% yield) as a colorless oil, b.p. 130–140 °C/0.5 Torr, $[\alpha]_D^{20}$ = +35.6 (*c* = 1.1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.63 (d, $^2J_{H,H}$ = 10.8 Hz, 2 H, CHCH_2CH), 1.66 (d, $^2J_{H,H}$ = 10.8 Hz, 2 H, CHCH_2CH), 2.31 (s, 6 H, NCH_3), 2.47–2.61 [m, 6 H, NC$H_{2(exo)}$-CH, N(CH_2)$_2$N], 2.63 [d, $^2J_{H,H}$ = 10.3 Hz, 2 H, NC$H_{2(endo)}$CH],

2.69 [dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.6 Hz, 2 H, NC$H_{2(exo)}$CH], 2.74 [d, $^2J_{H,H}$ = 10.3 Hz, 2 H, NC$H_{2(endo)}$CH], 3.12 (s, 2 H, NCHCH_2), 3.25 (s, 2 H, NCHCH_2) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 33.9 (CHCH$_2$CH), 40.9 (NCH_3), 53.8 (NCH$_2$CH), 56.3 (N(CH$_2$)$_2$N), 56.8 (NCH$_2$CH), 62.9 (NCHCH$_2$), 63.5 (NCHCH$_2$) ppm. MS (EI): *m*/*z* (%) = 251 [M + 1]$^+$ (2), 206 (1), 156 (26), 125 (71), 82 (100), 44 (23). IR (film): $\tilde{\nu}_{max}$ = 3350, 2959, 2848, 1450, 1296, 1224, 939 cm^{-1}. $C_{14}H_{26}N_4$ (250.38) HRMS (FAB): calcd. [M + H]$^+$ 251.2236; found 251.2240.

(1*S*,4*S*)-2,5-Bis[2-(2-hydroxyphenyl)acetyl]diazabicyclo[2.2.1]heptane (38): Compound **17**·2HBr (1.3 g, 5.1 mmol) and methanol (2.5 mL) were placed in a 250 mL Erlenmeyer flask containng a magnetic stirrer. The resulting solution was treated with a solution of KOH (2 equiv.) in methanol (5 mL) and stirred at 5–10 °C for 1 h. The resulting mixture was filtered under vacuum, and the solid was washed with methanol (three 5 mL portions) and EtOAc (three 5 mL portions). The combined filtrates were concentrated in a rotary evaporator to afford the free amine, which was redissolved in toluene (20 mL), treated with benzofuranone **37** (1.45 g, 11.0 mmol), and stirred for 5 min at ambient temperature before the addition of mixture of hexane and toluene (9:1, 50 mL) to induce the crystallization of **38**. Purification by flash column chromatography (CH_2Cl_2/AcOEt/MeOH, 4.5:4.5:1), afforded **38** (1.6 g, 86% yield) as a white solid, m.p. 162–164 °C, $[\alpha]_D^{20}$ = –161.0 (*c* = 1, MeOH). ^{1}H NMR ([D$_6$]DMSO, 400 MHz, 120 °C): δ = 1.82 (s, 2 H, CHCH_2CH), 3.40–3.62 [m, 8 H, NC$H_{2(endo,exo)}$CH, NCOCH_2], 4.78 (s, 2 H, NCHCH$_2$), 6.70–7.07 (m, 8 H, CHAr), 9.17 (br., 2 H, OH) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3218, 2960, 2343, 1913, 1623, 1594, 1459, 1251, 755 cm^{-1}. MS (EI): *m*/*z* (%) = 366 [M]$^+$ (99), 232 (22), 165 (67), 134 (28), 107 (29), 68 (100).

(1*S*,4*S*)-2,5-Bis[2-(2-Hydroxyphenyl)ethyl]diazabicyclo[2.2.1]heptane (39): Diamide **38** (0.25 g, 0.68 mmol) was reduced with $LiAlH_4$ (0.18 g, 4.92 mmol) in dry THF (40 mL). The product was purified by flash column chromatography (EtOAc) followed by recrystallization from hexane to give diol **39** (0.185 g, 80% yield) as a white solid, m.p. 138–140 °C, $[\alpha]_D^{20}$ = –16.6 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.89 (s, 1 H, CHCH_2CH), 2.70–2.87 [m, 6 H, NC$H_{2(endo,exo)}$CH, N(CH_2)$_2$], 2.91–2.93 (m, 2 H), 3.00–3.04 (m, 4 H), 3.55 (s, 2 H), 6.74–7.16 (m, 8 H), 12.83 (br., 2 H, OH) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 33.1, 34.3, 56.1, 56.2, 62.2, 117.6, 119.0, 127.3, 128.5, 131.1, 157.3 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3427, 2969, 2876, 2412, 1802, 1579, 1484, 1429, 1277, 760 cm^{-1}. MS (EI): *m*/*z* (%) = 338 [M]$^+$ (8), 231 (100), 188 (28), 151 (7), 121 (4), 82 (6).

Supporting Information (see also the footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of the described compounds.

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