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Evaluation of the Chiral DIANANE Backbone as Ligand for Organolithium Reagents

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Abstract: Novel *endo,endo*-2,5-diaminonorbonane-derived tertiary C_2-symmetrical diamines were synthesized *via* the one-pot reductive amination of enantiomerically pure norbornane-2,5-dione. These ligands were applied to various catalytic reactions such as asymmetric deprotonation, asymmetric bromine-lithium exchange, and enantioselective addition of aryl- and allkylithium reagents to aromatic aldimines.

Keywords: asymmetric catalysis; bromine-lithium exchange; deprotonation; *endo,endo*-2,5-diaminonorbonane derivatives; nucleophilic addition; organolithium compounds

Introduction

The elaboration of new chiral ligands for enantioselective catalytic reactions, leading to optically active scaffolds, remains one of the major challenges in organic synthesis. Non-racemic diamines, classically used as chiral auxiliaries or chiral reagents, have recently received widespread application as external ligands as well.[1] Indeed, this class of bidentate ligands has shown great ability to coordinate to alkali and transition metals.[1,2a]

In organic synthesis, organolithium reagents are widely employed, due to their ability to act as powerful bases and nucleophiles. However, the high tendency of these reagents to form aggregates markedly modifies their reactivity. This inconvenient behaviour can be controlled by the addition of coordinating etheral solvents such as diethyl ether and THF, or bidentate ligands such as diamines. Coordinating solvents and diamine ligands are known to affect both the solubility and the reactivity of organolithium species by decreasing the aggregation state of these compounds.[2] Most importantly, chirality can be brought into organolithium compounds through complexation with a chiral diamine ligand. This allows a large panel of asymmetric transformations with organolithium reagents.[3]

In this area, it is important to mention the widely employed naturally occurring alkaloid (−)-sparteine **1** (see Scheme 10), largely exploited for its ability to form chiral complexes with conventional organolithium reagents. In 1968, this pseudo-C_2-symmetric bidentate diamine ligand was firstly introduced by Nozaki et al. for carbanion reactions.[4a–c] Few years later, Beak and Hoppe obtained highly enantioenriched products by asymmetric deprotonations, with *s*-BuLi coordinated to chiral diamine **1**.[5]

Following these pioneering examples, various other asymmetric transformations catalyzed with (−)-sparteine **1** were disclosed.[6] However, development of new chiral diamine ligands remains crucial if further advances in this area are to be made. The problem of the lack of availability of unnatural (+)-sparteine was elegantly solved by O'Brien with his sparteine surrogate.[4d] However, a new problem arose, this last year, when even natural (−)-sparteine **1** became non-available commercially.[4e]

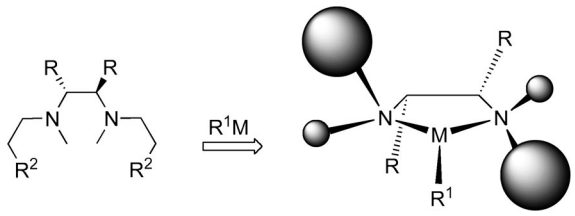
Previously, our group described a new class of chiral tertiary 1,2-diamines derived from the rigid *trans*-cyclohexanediamine or the more flexible diphe-

nylethanediamine backbones. These diamines were employed as ligands for lithium in enantioselective additions of alkyl- and aryllithium reagents to activated aldimines.[7] We postulated that a transfer of chirality from the backbone to the nitrogen atoms took place in the diamine-lithium complex, through a *trans* relationship between the bulky substituent on the nitrogen atom and the R group of the chiral backbone (Scheme 1).

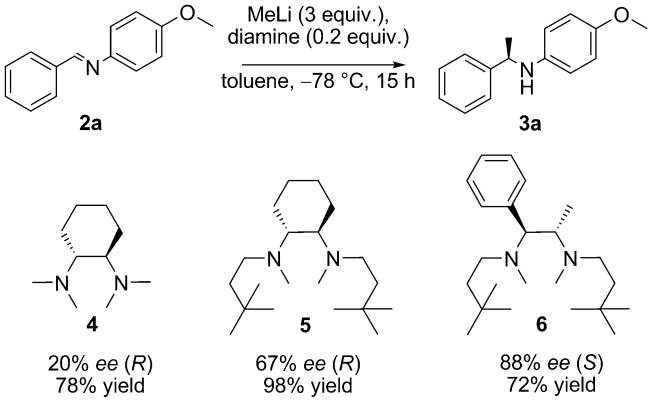
In most cases, best results were obtained with diamines possessing a two-methylene units spacer between the stereogenic nitrogen atom and bulky groups like *tert*-butyl or phenyl at the termini. However, *tert*-butyl groups were preferred to phenyl ones, because the latter could be deprotonated by some organolithium reagents leading to ligand damage.[7,8a,b] Ligand **6**, derived from the pseudo-ephedrine backbone (Scheme 2) was particularly effective.[7a,f]

However, this concept could not be extended to the addition of aryllithium reagents to aromatic aldimines. In this case, better results were obtained with simpler tetramethylated diamines such as **4** and **9** (Scheme 3).[7b,d]

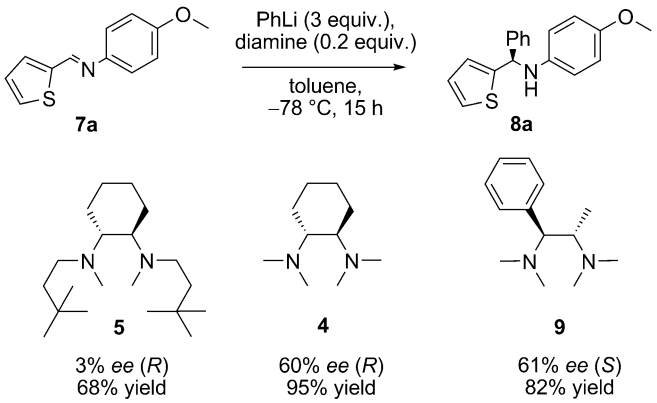
These promising results prompted us to apply our new diamine ligands to various other organolithium-mediated transformations, such as the asymmetric deprotonation or the enantioselective bromine-lithium exchange reactions.[8]



Scheme 1. Postulated chelate complex of a tertiary, chiral 1,2-diamine with an alkyllithium reagent.



Scheme 2. Asymmetric addition of MeLi to aldimine **2a** promoted by enantiopure diamines **4**, **5** and **6**.[7a,c,e,f]



Scheme 3. Asymmetric addition of PhLi to aldimine **7a** promoted by enantiopure diamines **4**, **5** and **9**.[7b,d]

Very recently, we turned our attention to a novel C_2-symmetric chiral diamine, namely *endo,endo*-2,5-diaminonorbonane (DIANANE, **16**, Scheme 5). Besides possessing a much more rigid backbone, it exhibits a larger nitrogen-nitrogen interatomic separation than the conventional *trans*-1,2-diaminocyclohexane and diphenylethane-derived diamines. Initially, Berkessel et al. used this 1,4-diamine as a backbone for salen-type ligands. These were successfully employed to catalyze asymmetric Nozaki–Hiyama–Kishi reactions, kinetic resolutions of epoxides, and hetero-Diels–Alder reactions.[9]

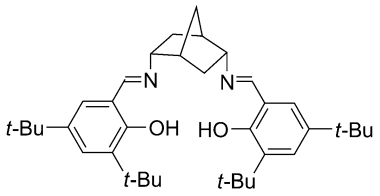
In this article, we describe the use of new DIANANE-derived tertiary diamines as chiral ligands in prototypical organolithium-mediated reactions, including: (i) asymmetric addition of alkyl- and aryllithium reagents to aromatic aldimines, (ii) asymmetric deprotonation reactions, and (iii) enantioselective bromine-lithium exchange reactions.

Results and Discussion

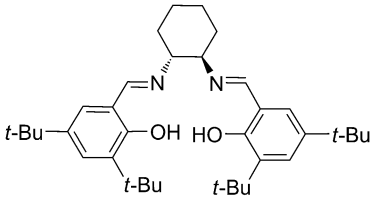
General Considerations

Very recently, Berkessel et al. published an X-ray diffraction structure of the new salen-type ligand **10** derived from (*R*,*R*)-DIANANE (Scheme 4). The corresponding structure of *trans*-1,2-diaminocyclohexane-derived salen ligand **11** was already known in the literature.[10] Comparison of these two structures revealed a striking difference in the corresponding N–N interatomic separations. This distance is considerably larger for the former (3.59 Å *versus* 2.91 Å).[9b]

The bridged DIANANE backbone is significantly more rigid than that of (–)-sparteine **1**, and hence conformational equilibria are no longer an issue.[5c,9b] Unlike that of (–)-sparteine **1**, this structure can be easily modified.[4d] Moreover, both enantiomers of



(*R,R*)-**10**



(*R,R*)-**11**

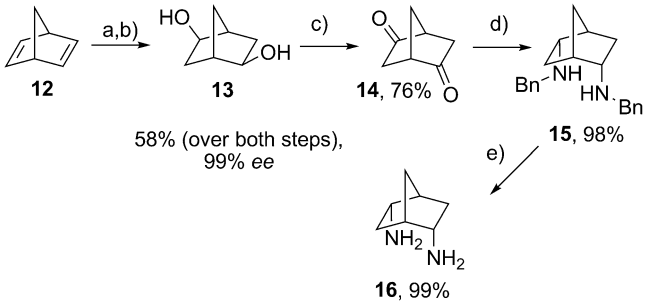
Scheme 4. Comparison between cyclohexanediamine- (**11**) and DIANANE-derived (**10**) salen ligands.

DIANANE-derived diamines are readily available, and that is with excellent enantiomeric excesses.

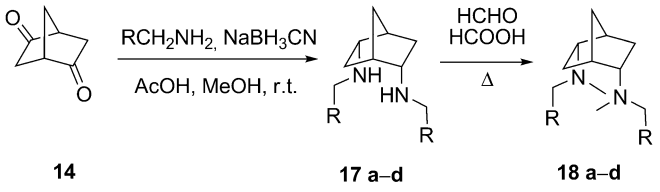
Ligands Synthesis

Enantiomerically pure diketone **14** was obtained in three steps starting from commercially available norbornadiene following a procedure described previously by Berkessel et al.[9b] Accordingly, an asymmetric Hayashi-type hydrosilylation of norbornadiene, followed by a Tamao–Fleming oxidation of the resulting disilane afforded diol **13** in essentially enantiopure form (99% *ee*, *vide infra*). Subsequent PCC oxidation furnished the desired norbornane-2,5-dione **14** (Scheme 5).[9b,11]

We envisaged the synthesis of the desired bis-tertiary diamines, directly from diketone **14**, thus avoiding



Scheme 5. Synthesis of *endo,endo*-2,5-diaminonorbornane (DIANANE) **16**. *Reaction conditions:* (a) $HSiCl_3$ (2.4 equiv.), 0.05 mol% $[Pd(C_3H_5)Cl]_2$, 0.2 mol% (*S*)-MOP, −3 °C; (b) (1) MeOH, NEt_3, (2) KHF_2, H_2O_2·urea (c) PCC, CH_2Cl_2, room temperature; (d) Bn-NH_2 (2.5 equiv.), $NaBH(OAc)_3$; (e) H_2 (1 atm), Pearlman catalyst.



18a : R = Ph 25% yield
18b : R = CH_2-Ph 56% yield
18c : R = CH_2-OMe 29% yield
18d : R = CH_2-$C(CH_3)_3$ 62% yield

Scheme 6. Reductive amination and Eschweiler–Clarke reactions, leading to ligands **18a–d**.

going through DIANANE **16**. At the beginning of our investigations, reductive amination of dione **14** was carried out using standard methodology (RCH_2NH_2, $NaBH_3CN$, AcOH) for the synthesis of C_2-symmetric tertiary diamines[7a,d,f,8b] Without purification, the bis-secondary diamines **17a–d** were methylated under Eschweiler–Clarke conditions (Scheme 6).

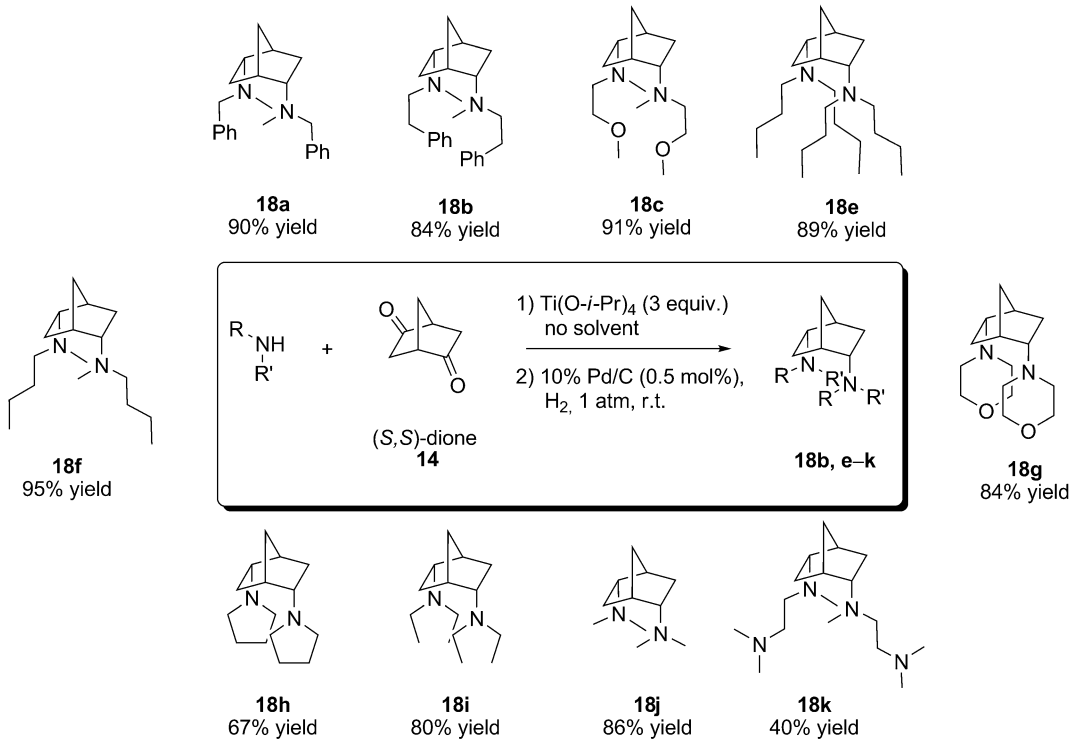
Given the moderate yields obtained *via* this route, we decided to adopt a more direct one, based on recent developments in our laboratory on making C_2-symmetric secondary diamines.[12] To this end, we used the combination of $Ti(O\text{-}i\text{-}Pr)_4$ with H_2/Pd-C to perform a one-pot reductive amination of dione **14** directly to bis-tertiary diamines **18a–d**, as well as **18e–k** (Scheme 7). The reduction was completely in favour of the *endo*-diastereomer, and very good yields and purity were obtained. This new procedure proved economical, efficient and environmentally friendly, as it did not require an organic solvent, for most cases.[12]

With enantiomerically pure DIANANE-derived tertiary diamines **18a–k** in hand, the catalytic behaviour of these novel external ligands in organolithium-mediated transformations was studied next.

Asymmetric Addition to Imines

Previously in our laboratory, a variety of optically active amines was obtained by asymmetric addition of alkyl- and aryllithium reagents to aromatic aldimines, using chiral tertiary 1,2-diamines as sub-stoichiometric promoters.[1e,7]

For this class of diamines, the chiral information is brought closer to the reactive site by the two sterically very different substituents at the stereogenic nitrogen atoms. Indeed, a *trans*-relationship between the bulkiest N-substituent and the R group at the backbone was postulated to explain the configurational stability at nitrogen after formation of a chelate complex with the organolithium reagent (Scheme 1). This concept was recently supported by the X-ray diffraction struc-

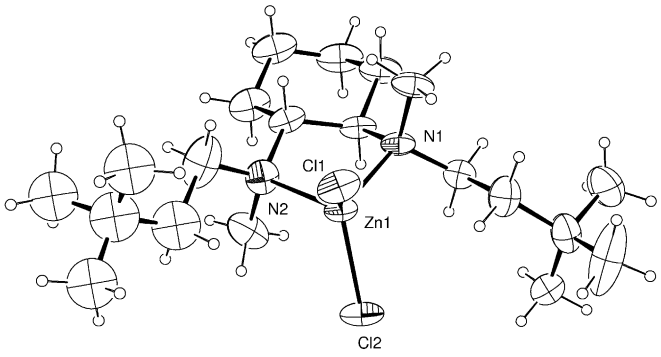


Scheme 7. One-pot reductive amination of enantiopure diketone **14** using the combination of $Ti(O\text{-}i\text{-}Pr)_4$ and H_2/Pd.

ture of the complex formed between ligand **5**, derived from the *trans*-cyclohexanediamine and zinc chloride (Scheme 8). A *trans* relationship between the hindered neohexyl substituent at nitrogen and the alkyl group at the backbone can clearly be observed.

Following this work, we evaluated the performance of our new diamine ligands with enantiomerically pure DIANANE backbone.

As stated in the introduction, the enantioselective addition of MeLi to imines worked best with ligands having a homobenzyl or neohexyl *N*-substituent. Unfortunately, no selectivity was induced for the addition of MeLi to imine **2a** (Scheme 9) Only DIANANE **18c**, bearing chelating methoxy groups afforded a moderate *ee* of 35%.



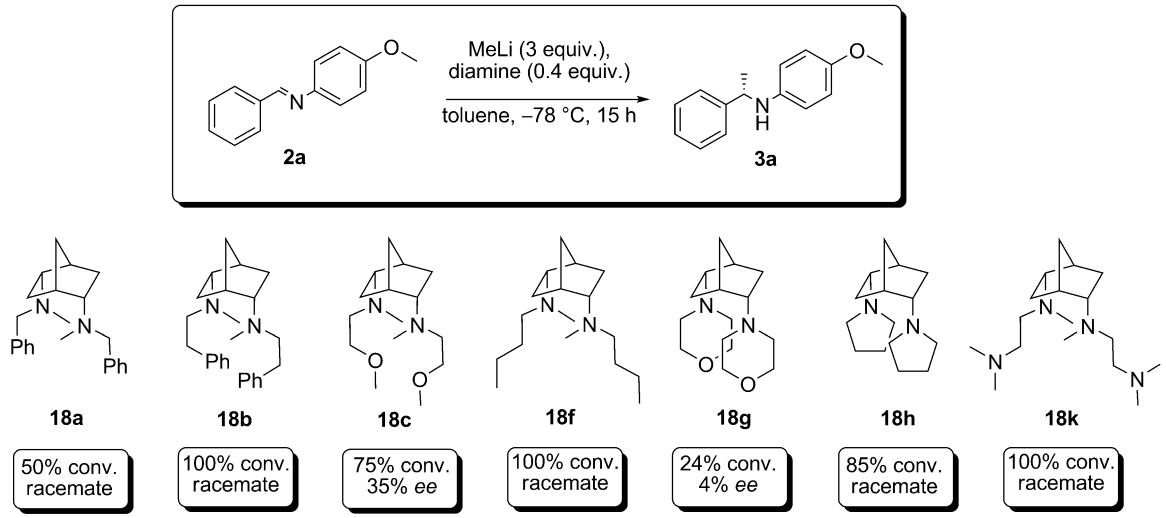
Scheme 8. X-ray structure of the monomeric diamine **5**/$ZnCl_2$ complex.

Knowing that PhLi is sensitive to a different type of diamine (see Scheme 3 and diamine **4**), we also explored its addition to imines, in the presence of a panel of DIANANE ligands (Table 1). Again, racemates were mostly obtained. The only exceptions were a hindered diamine **18b** (entry 2) and the least encumbered one **18j** (entry 6).

The behaviour of these new DIANANE ligands for asymmetric nucleophilic additions of organolithium reagents differs completely from the previous diamines we had tested. This behaviour may be ascribed to the significantly larger distance between the two nitrogen atoms (3.59 Å *versus* 2.91 Å).

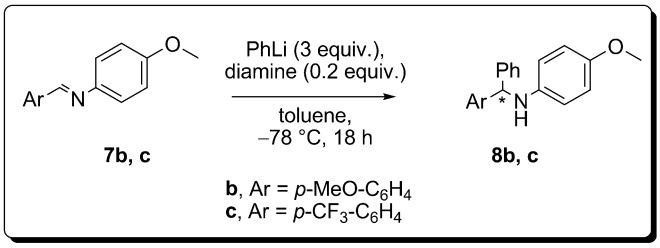
Asymmetric Deprotonation

Asymmetric deprotonation, with organolithium reagents, was an extensively studied reaction during the two past decades, largely due to its application in organic synthesis. The groups of Beak and Hoppe pioneered the field by developing the first highly enantioselective deprotonation of carbamate substrates, such as *N*-Boc-pyrrolidine **19**, with *sec*-BuLi, and (−)-sparteine **1** as chiral diamine (87% yield, 96% *ee*).[5] The group of O'Brien disclosed the first highly enantioselective deprotonation of *N*-Boc-pyrrolidine with a non-sparteine ligand **5**, a C_2-symmetric tertiary chiral diamine, developed in our laboratory.[7f,8e] This



Scheme 9. Asymmetric addition of MeLi to *N*-*p*-methoxyphenylimine **2a** mediated by sub-stoichiometric amounts of DIANANE-derived ligand.

Table 1. Addition of phenyllithium to aldimines **7b**, **c**.



Entry	Ligand	Product	% Conversion[a]	*ee* [%][b,c]
1	**18a**	**8c**	55	5 (+)
2	**18b**	**8c**	68	18 (+)
3	**18b**	**8b**	15	racemate
4	**18c**	**8b**	18	6 (−)
5	**18h**	**8b**	15	racemate
6	**18j**	**8c**	>99	14 (+)

[a] Conversions were evaluated by ^{1}H NMR spectroscopy of the crude reaction mixtures.

[b] Enantiomeric excesses were determined by SFC analysis on Chiralpak AS-H (**8c**) and Chiracel OD-H (**8b**) columns.

[c] The (+) or (−) signs refer to the absolute direction of optical rotations.

diamine **5** was also used as a sparteine surrogate in many other asymmetric lithiations.[8d–k]

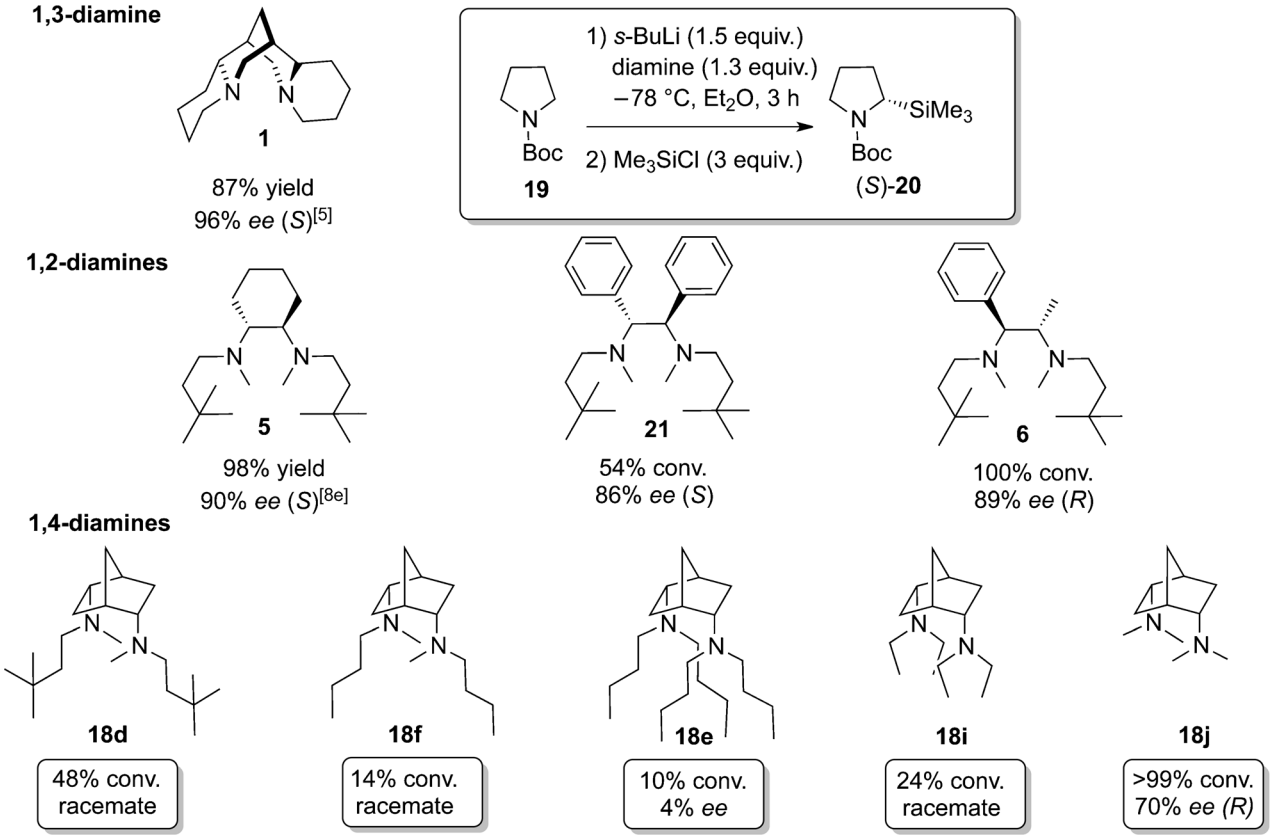
In our laboratory, we tested many other chiral 1,2-diamines previously synthesized in our group (Scheme 10). Commonly, diamines bearing neohexyl subsituents (**5**, **6**, **21**) perform the best, with selectivity similar to that of the (−)-sparteine **1** ligand. A small difference in efficiency is nevertheless observed, depending on the diamine backbone. The backbones adapted best are represented by the derivative of *trans*-1,2-diaminocyclohexane **5**, the 1,2-diphenylethane-1,2-diamine **21**, and the pseudo-ephedrine derivative **6**.

Building on these promising results, we decided to use our new 1,4-diamines derived from DIANANE (Scheme 10). Unfortunately, diamine **18d** bearing neohexyl substituents did not furnish an enantiomerically enriched product.

Other DIANANE derivatives (**18e**, **f**, **i**) were screened for the asymmetric deprotonation of *N*-Boc-pyrrolidine **19**, but the results were equally frustrating. A surprising result was obtained with tetramethylated DIANANE derivative **18j**, reaching an *ee* of 70% for the deprotonation of *N*-Boc-pyrrolidine **19**. Here, it is important to note that, in the past, no enantioselectivity was obtained when 1,2-bis-(*N*,*N*-dimethylamino)cyclohexane **4** was employed, presumably due to the non-stereogenic nature of the nitrogen atoms involved in chelation.[8c,e] It appears that the behaviour of this new DIANANE 1,4-diamine is closer to that of the naturally occurring ligand (−)-sparteine **1**, at least when asymmetric deprotonation is concerned. In this case, increasing the steric bulk on nitrogen atoms is detrimental for high selectivity.

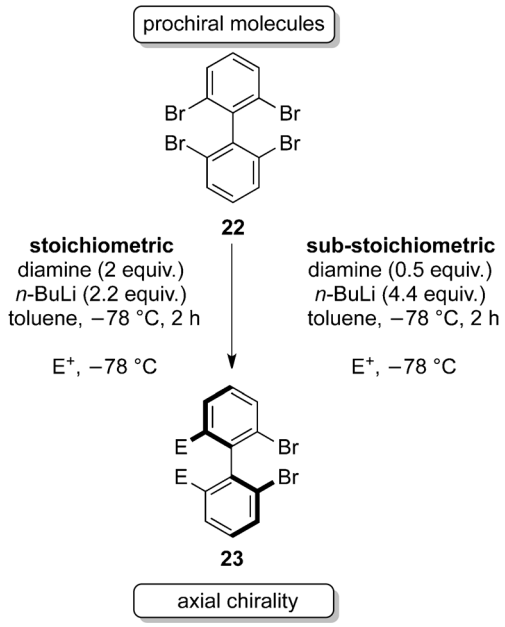
Asymmetric Bromine-Lithium Exchange

Asymmetric deprotonation and nucleophilic addition with organolithium reagents are well known concepts in organic synthesis. On the other hand, asymmetric variants of bromine-lithium exchange are scarce. This is rather surprising since halogen-lithium exchange is widely employed for the *in situ* generation of organolithium reagents and to elaborate valuable building blocks for asymmetric synthesis.



Scheme 10. Asymmetric deprotonation of *N*-Boc-pyrrolidine **19** with *sec*-BuLi, promoted by different chiral diamine ligands.

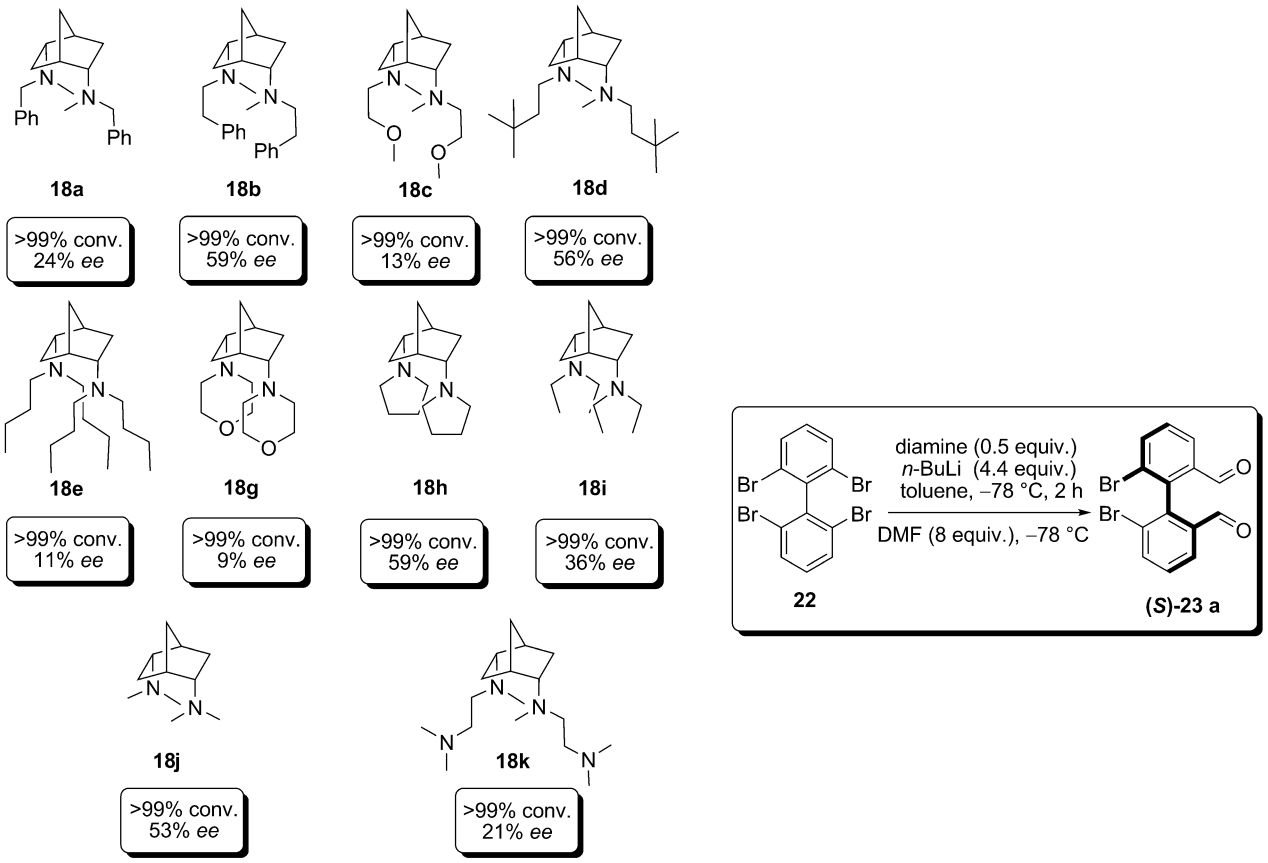
The first enantioselective variants of halogen-lithium exchange were introduced simultaneously by the group of Kagan and our group in 2008.[8a,b,13] The idea of using chiral diamines to perform asymmetric bromine-lithium exchange was an issue arising from prior observations made in our laboratory. Accordingly, we observed that bromine-lithium exchange did not occur at low temperature in an apolar solvent, like toluene, without the presence of a diamine ligand.[14] At the beginning of our studies, different classes of prochiral polybrominated aromatic compounds were efficiently desymmetrized with stoichiometric amounts of diamine ligands, with enantiomeric excess ranging up to 63% (Scheme 11).[8a] Enantiomeric excesses were then improved by using sub-stoichiometric amounts of chiral 1,2-diamine or chiral 1,2-diether ligands (0.5 equiv.) with an excess of *n*-BuLi (4.4 equiv.).



Scheme 11. General procedure for an asymmetric bromine-lithium exchange.

In a typical case, desymmetrization of 2,2′,6,6′-tetrabromobiphenyl **22** gave access to new atropoisomers with an enantiomeric excess of 82%, using the diether of Tomioka (diphenylethanediol dimethyl ether).[8b,15]

Concerning 1,2-diamines, the best results were obtained with **21** and **6** (72% *ee*, 50% *ee*, respectively), clearly showing that hindered N-substituents were the best. Again, we tested several new chiral 1,4-diamines derived from DIANANE as sub-stoichiometric promoters of asymmetric bromine-lithium exchange (Scheme 12). As expected, promising selectivities were obtained with diamines bearing a β-*tert*-butyl



Scheme 12. Enantioselective bromine-lithium exchange promoted by substoichiometric amounts of DIANANE-derived ligands **18a–k**.

group **18d** or a β-phenyl group **18b** as the sterically demanding substituent on the nitrogen atoms (*ee* up to 59%). We also observed that the selectivity decreased when switching to ligands in which the steric bulk is closer to the reactive centre such as ligand **18a**, with an α-phenyl (24% *ee*).

Rather surprisingly, and similar to the unexpectedly high enantioselectivity observed for asymmetric deprotonation with tetramethylated DIANANE derivative **18j**, an enantiomeric excess of 53% for asymmetric bromine-lithium exchange of 2,2′,6,6′-tetrabromobiphenyl **22** was obtained when employing the latter ligand. Notably, this was one of the best results obtained for the DIANANE series. A slight increase resulted (up to 59% *ee*) from rigidifying the substituent on the nitrogen atoms by a five-membered pyrrolidine ring, as in **18h**.

It is important to mention that all chiral diamines were recycled at the end of each bromine-lithium exchange reaction by a simple acid-base extraction followed by distillation on a Kugelrohr apparatus.

Conclusions

To conclude, we have disclosed an efficient one-pot synthesis of tertiary DIANANE derivatives. These new chiral ligands with their rigid backbone and fixed larger distance between the two nitrogen atoms were tested in asymmetric synthesis using organolithium reagents and compared with our previous 1,2 chiral diamine ligands. Unfortunately, additions of alkyl- or aryllithium reagents to imines produced essentially racemic products.

In contrast, for the asymmetric deprotonation of *N-Boc*-pyrrolidine **19**, an enantiomeric excess of 70% with full conversion was observed with the least hindered ligand: the tetramethylated DIANANE **18j**.

The new ligands were highly efficient in asymmetric bromine-lithium exchange: in the desymmetrization of 2,2′,6,6′- tetrabromobiphenyl **22**, enantioselectivities around 53–59% *ee* were obtained with *n*-BuLi and DIANANE ligands **18b**, **d, h, j**, comparable to the results obtained with previous 1,2-diamines ligands. Building on these promising results, research in our laboratory is devoted to improvement of the performance of ligand **18h** in enantioselective bromine-lithium exchange.

Experimental Section

General Remarks

^{1}H (400 MHz or 300 MHz), ^{13}C (100 MHz or 75 MHz) NMR spectra were recorded on either a Bruker 300 MHz, or 400 MHz spectrometer at room temperature and are reported as chemical shift (δ) in ppm relative to solvent peak. Spin multiplicities are reported as singlet (s), doublet (d), triplet (t), and multiplet (m) and the coupling *J* is given in Hz. The reaction progress was followed by using a Hewlett Packard GC-MS (EI mode) HP6890–5973 or analytical thin-layer chromatography (TLC, visualization was performed with UV, anisaldehyde, $KMnO_4$, phosphomolybdic acid). Electrospray mass spectra (HR-MS) were obtained with the Sciences Mass Spectrometry (SMS) platform at the Faculty of Sciences (University of Geneva) on a QStar pulsar instrument from AB/MDS Sciex, ESI (positive). Optical rotations were measured at 20 °C in a cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}(concentration *c* given as g/100 mL). Enantiomeric excesses were determined by chiral GC (capillary column, 10 psi H_2) or chiral supercritical fluid chromatography (SFC) with an appropriate program using a gradient of methanol. Flash chromatography was performed using silica gel 32–63 μm, 60 Å.

Reactions were generally carried out under an atmosphere of nitrogen or argon using flame-dried glassware. All solvents were dried on alumina columns and TMSCl (98%, Acros) distilled from calcium hydride. *n*-BuLi (1.6 M in hexane, Acros), *s*-BuLi (1.3 M in cyclohexane/hexane 98:2, Acros), PhLi (2.0 M in dibutyl ether, Acros), MeLi (1.6 M in diethyl ether, Acros), palladium on carbon (10%) (50% wet with water for safety, Acros), DMF (99.5%, Acros), Ti(O-*i*-Pr)$_4$ (Acros) were purchased and used as received. The following substrates were prepared according to literature procedures **2a**,[15a] **7b**,[16a] **7c**,[16b] **19**,[17] and **22**[8b]. Imines were generated by condensation of *p*-anisidine with the corresponding aldehyde. The following products (**3a**,[7c] **8b**,[7d] **8c**,[7d] **20**,[5a] and **23a**[8b]) have been described previously and were identified by comparison of their physical and spectroscopic data (^{1}H NMR, ^{13}C NMR, GC/MS, chiral-GC and SFC). Ligands (**4**,[7d] **5**,[7c] **6**,[7f] and **21**[8b]) were synthesized as described in the literature.

General Procedures for asymmetric reactions are described in detail in the Supporting Information.

General Procedures for the Synthesis of DIANANE Derivatives

General procedure for the preparation tertiary diamines in two steps: In the first step, to a solution of (1*S*,4*S*)-bicyclo-[2.2.1]heptane-2,5-dione **14** (2.42 mmol) in methanol (3 mL) was added the amine (2.9 mmol), sodium cyanoborohydride (5.33 mmol) and acid acetic (69 μL, 1.2 mmol). The mixture was stirred for 2 days, methanol was then evaporated and the residue was diluted in dichlorormethane (DCM) (6 mL). The organic layer was washed with NaOH (15%) (2×6 mL) and with brine, dried over K_2CO_3 filtered and concentrated under reduced pressure.

The crude diamine (2.9 mmol) was dissolved in formic acid 98% (52.2 mmol) and formaldehyde 40% (1.1 mL, 40.6 mmol) was added slowly at room temperature. The mixture was heated to reflux for 6 h. After cooling, the reaction mixture was adjusted to pH 14 and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified.

(1*S*,2*S*,4*S*,5*S*)-*N*^{2},*N*^{5}-Dibenzyl-*N*^{2},*N*^{5}-dimethylbicyclo-[2.2.1]heptane-2,5-diamine (18a): Following the general procedure to obtain the tertiary diamine in two steps using benzylamine as amine component. Chromatographic separation on silica gel with cyclohexane/AcOEt (8/2) +1% Et_3N gave a white solid; yield: 26%; mp 53.8–54 °C; $[\alpha]_D^{20}$: −15.7 (*c* 1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.46–7.48 (m, 4H), 7.31–7.24 (m, 6H), 3.68 (d, 2H, *J* = 13.5 Hz), 3.34 (d, 2H, *J* = 13.5 Hz), 2.55–2.5 (m, 2H), 2.34 (s, 6H), 1.96 (dd, 2H, *J* = 5.3, 11.8 Hz), 1.63–1.56 (m, 2H), 1.54 (s, 2H); ^{13}C NMR ($CDCl_3$): δ = 140.6, 129, 128.2, 126.7, 68.3, 60.7, 41.1, 40.4, 37.6, 27.6; HR-MS: $[M+H]^+$ *m/z* = 335.2481, cacld. for $C_{23}H_{31}N_2$: 335.2481.

(1*S*,2*S*,4*S*,5*S*)-*N*^{2},*N*^{5}-Dimethyl-*N*^{2},*N*^{5}-diphenethylbicyclo-[2.2.1]heptane-2,5-diamine (18b): Following the general procedure to obtain the tertiary diamine in two steps using 2-phenylethylamine as amine component. Chromatographic separation on silica gel with cyclohexane/AcOEt (8/2) +1% Et_3N gave a pale yellow oil; yield: 56%; $[\alpha]_D^{20}$: 2.5 (*c* 1.14, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.21–7.15 (m, 10H), 2.82–2.55 (m, 8H), 2.54–2.41 (m, 2H), 2.27 (s, 6H), 1.9–1.7 (m, 2H), 1.61–1.2 (m, 6H); ^{13}C NMR ($CDCl_3$): δ = 141.38, 128.9, 128.5, 125.8, 67.9, 62.6, 58.2, 45.6, 41.17, 40, 37.3, 32.2, 27.1; HR-MS: *m/z* = 363.2808 $[M+H]^+$, cacld. for $C_{25}H_{34}N_2$: 363.2794.

(1*S*,2*S*,4*S*,5*S*)-*N*^{2},*N*^{5}-Bis(2-methoxyethyl)-*N*^{2},*N*^{5}-dimethylbicyclo[2.2.1]heptane-2,5-diamine (18c): Following the general procedure to obtain the tertiary diamine in two steps using 2-methoxyethylamine as amine component. Chromatographic separation on silica gel with cyclohexane/AcOEt, (3/7, 1% NEt_3) gave a pale yellow oil; yield: 29%; $[\alpha]_D^{20}$: 3.4 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.39 (s, 2H), 1.41–1.46 (m, 2H), 1.55–1.59 (m, 2H), 2.17 (s, 6H), 2.2 (s, 2H), 2.35–2.4 (m, 2H), 2.48–2.56 (m, 4H), 3.33 (s, 6H), 3.49 (t, 4H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$): δ = 27.0, 37.2, 40, 42, 55.4, 59, 68.7, 70.9; HR-MS: $[M+H]^+$ *m/z* = 271.2374, calcd. for $C_{15}H_{31}N_2O_2$: 271.238.

(1*S*,2*S*,4*S*,5*S*)-*N*^{2},*N*^{5}-bis(3,3-dimethylbutyl)-*N*^{2},*N*^{5}-dimethylbicyclo[2.2.1]heptane-2,5-diamine (18d): Following the general procedure to obtain tertiary diamine in two steps using 3,3-dimethylbutylamine as amine component. Chromatographic separation on silica gel with cyclohexane/AcOEt (3/7, 1% NEt_3) gave a colourless oil in 62% yield; $[\alpha]_D^{20}$: 210.34 (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 2.36-2.11 (m, 8H), 2.1 (s, 1H), 1.6–1.25 (m, 8H), 0.88 (s, 18H); ^{13}C NMR ($CDCl_3$): δ = 68.3, 51.9, 41.1, 40, 39, 37.4, 30, 29.7,27.2; HR-MS: *m/z* = 323.3426 $[M+H]^+$, calcd. for $C_{21}H_{43}N_2$: 323.342.

General Procedure for the One-Step Preparation of Tertiary Diamines[12]

A mixture of (1*S*,4*S*)-bicyclo[2.2.1]heptane-2,5-dione **14** (0.81 mmol), secondary amine (4.5 mmol) and titanium(IV) isopropoxide (2.43 mmol) was stirred at room temperature for 30 min. The mixture was then hydrogenated at 1 atm with 10% palladium on charcoal (32 mg, 4 mol%) under vig-

orous stirring at room temperature. The reaction was monitored by GC/MS. The reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide. After stirring for 10 min, the solution was extracted fives times with pentane/ether. The combined organic layers were filtered over Celite, dried over potassium carbonate and evaporated under reduced pressure. The product is typically sufficiently pure to be used without further purification.

(1*S*,2*S*,4*S*,5*S*)-*N*^{2},*N*^{5}-Dibenzyl-*N*^{2},*N*^{5}-dimethylbicyclo-[2.2.1]heptane-2,5-diamine (18a): Following the one-step procedure, using *N*-methyl-2-phenethylamine as the amine component. The crude product was purified by Kugelrohr distillation (220 °C/0.05 mm Hg) to afford a white solid; yield: 90%.

(1*S*,2*S*,4*S*,5*S*)-*N*^{2},*N*^{5}-Dimethyl-*N*^{2},*N*^{5}-diphenethylbicyclo-[2.2.1]heptane-2,5-diamine (18b): Following the one-step procedure, using *N*-methylbenzylamine as the amine component. The crude product was purified by Kugelrohr distillation (190 °C/0.05 mm Hg) to afford a pale yellow oil; yield: 84%.

(1*S*,2*S*,4*S*,5*S*)-*N*^{2},*N*^{5}-Bis(2-methoxyethyl)-*N*^{2},*N*^{5}-dimethylbicyclo[2.2.1]heptane-2,5-diamine (18c): Following the one-step procedure, using methyl-(2-methoxyethyl)amine as the amine component. A pale yellow oil was obtained; yield: 91%.

(1*S*,2*S*,4*S*,5*S*)-*N*^{2},*N*^{2},*N*^{5},*N*^{5}-Tetrabutylbicyclo[2.2.1]heptane-2,5-diamine (18e): Following the one-step procedure, using dibutylamine as the amine component. The crude product was purified by Kugelrohr distillation (150 °C/0.05 mm Hg) to afford a colourless oil; yield: 89%; $[\alpha]_D^{20}$: 24.2 (*c* 0.45, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.68–2.63 (m, 2H), 2.44–2.40 (m, 8H), 2.12 (m, 2H), 1.64 (dd, 2H, ^3J = 5.8 and 11. 8 Hz), 1.38–1.27 (20H), 0.9 (t, 12H, ^3J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 14.4, 21, 27, 27.9, 37.0, 40.1, 51.4, 65.4; HR-MS: *m/z* = 351.3730 $[M+H]^+$, calcd. for $C_{23}H_{47}N_2$: 351.3733.

(1*S*,2*S*,4*S*,5*S*)-*N*^{2},*N*^{5}-Dibutyl-*N*^{2},*N*^{5}-dimethylbicyclo-[2.2.1]heptane-2,5-diamine (18f): Following the one-step procedure, using *N*-methyl(dibutyl)amine as the amine component. A yellow oil was obtained; yield: 95%; $[\alpha]_D^{20}$: 19.6 (*c* 1.07, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.24–2.29 (m, 6H), 2.17–1.18 (m, 2H), 2.09 (s, 6H), 1.59 (dd, 2H, *J* = 5.7 and 11.88 Hz), 1.37–1.43 (m, 8H), 1.27–1.33 (m, 4H), 0.9 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 14.3, 20.9, 27.2, 28.6, 37.3, 40.0, 41.02, 56.0, 68.6; HR-MS: *m/z* = 267.2799 $[M+H]^+$, calcd. for $C_{17}H_{34}N_2$: 267.2794.

(1*S*,2*S*,4*S*,5*S*)-2,5-Dimorpholinobicyclo[2.2.1]heptane (18g): Following the one-step procedure, using morpholine as the amine component. A white solid was obtained; yield: 84%; mp 96–98 °C; $[\alpha]_D^{20}$: 22.45 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.35–1.43 (4H, m), 1.6 (m, 2H), 2.22–2.31(m, 8H), 2.38 (s, br, 4H), 3.67–3.75 (8H); ^{13}C NMR ($CDCl_3$): δ = 68.9, 67.1, 53.1, 38.6, 37.0, 25.8; HR-MS: $[M+H]^+$ *m/z* = 267.2068, cacld. for $C_{15}H_{27}N_2O_2$: 267.2067.

(1*S*,2*S*,4*S*,5*S*)-2,5-Di(pyrrolidin-1-yl)bicyclo[2.2.1]heptane (18h): Following the one-step procedure, using pyrrolidine as the amine component. The crude product was purified by Kugelrohr distillation (120 °C/0.05 mm Hg) to afford a white solid; yield: 67%; mp. 72–74 °C; $[\alpha]_D^{20}$: 23.15 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.37 (s, 2H), 1.42–1.49 (m, 2H), 1.64–1.68 (dd, 2H, *J* = 5.5 and 12.3 Hz), 1.72–1.77(m, 8H), 2.13 (s, 2H), 2.20–2.25 (m, 2H), 2.33–2.46 (m, 8H); ^{13}C NMR ($CDCl_3$): δ = 23.5, 27.2, 37.5, 41.3, 53.8, 68.8; IR (neat): $\tilde{\nu}$ = 2948, 2871, 2771, 2722, 2677, 1476, 1455, 1439, 1369, 1339, 1303, 1283, 1249, 1233, 1202, 1165, 1133, 1109, 1081, 1046, 950, 939, 908, 863, 625 cm^{-1}; HR-MS: *m/z* = 235.2168 $[M+H]^+$, calcd. for $C_{17}H_{34}N_2$: 235.2163.

(1*S*,2*S*,4*S*,5*S*)-*N*^{2},*N*^{2},*N*^{5},*N*^{5}-Tetraethylbicyclo-[2.2.1]heptane-2,5-diamine (18i): Following the one-step procedure, using diethylamine as the amine component. The crude product was purified by Kugelrohr distillation (120 °C/0.05 mm Hg) to afford a colourless oil; yield: 80%; $[\alpha]_D^{20}$: 22.8 (*c* 0.45, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.93(t, 12H, *J* = 7.1 Hz), 1.37 (s, 2H), 1.42(td, 2H, ^3J = 5.4 and 10.4 Hz), 1.6 (dd, 2H, *J* = 5.8,11.8 Hz), 2.16 (m, 2H), 2.56 (dd, 8H, *J* = 5.8 and 11.8 Hz), 2.71–2.66 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 64.2, 43.8, 39.8, 37.1, 26.7, 10.2; HR-MS: *m/z* = 239.2479 $[M+H]^+$, calcd. for $C_{23}H_{47}N_2$: 239.2481.

(1*S*,2*S*,4*S*,5*S*)-*N*^{2},*N*^{2},*N*^{5},*N*^{5}-Tetramethylbicyclo-[2.2.1]heptane-2,5-diamine (18j): Following the one-step procedure, using dimethylamine as the amine component. The crude product was purified by Kugelrohr distillation (40–50 °C/15 mm Hg) to afford a colourless oil; yield: 86%; $[\alpha]_D^{20}$: 40.6 (*c* 1.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.35–2.15 (m, 2H), 2.13 (s, 12H), 2.1–2.04 (m, 2H), 1.57–1.42 (m, 4H), 1.4 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 70.3, 45.36, 40.34, 37.7, 27.6; HR-MS: *m/z* = 183.1856 $[M+H]^+$, calcd. for $C_{23}H_{47}N_2$: 183.1855.

***N*^{1},*N*$^{1'}$-[(1*S*,2*S*,4*S*,5*S*)-Bicyclo[2.2.1]heptane-2,5-diyl)-bis(*N*^{1},*N*^{2},*N*^{2}-trimethylethane-1,2-diamine] (18k):** Following the one-step procedure, using trimethylethylenediamine as the amine component. The crude product was purified by Kugelrohr distillation (90 °C/0.05 mm Hg) to afford a colourless oil; yield: 40%; $[\alpha]_D^{20}$: 12.4 (*c* 0.85, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.51–2.3 (m, 12H), 2.23 (s, 12H), 2,12 (s, 6H), 1.58 (dd, 2 H , *J* = 5.6, 12.0 Hz), 1.49–1.42 (m, 2H), 1.39 (s, 2H); ^{13}C NMR ($CDCl_3$): δ = 68.8, 56.9, 54.5, 46.1, 41.5, 40, 37.3, 27.2; HR-MS: *m/z* = 297.3020 $[M+H]^+$, calcd. for $C_{17}H_{37}N_2$: 297.3012.

X-Ray Crystallography

For a summary of the crystal data, intensity measurements and structure refinement for the monomeric diamine (**5/ZnCl$_2$**) complex, see the Supporting Information. The crystal was mounted on quartz fibres with protection oil. Cell dimensions and intensities were measured at 180 K on a STOE IPDS diffractometer with graphite-monochromated Mo[Kα] radiation (λ = 0.71073 Å). Data were corrected for Lorentz and polarization effects and for absorption. The structure was solved by direct methods (SIR97),[18] all other calculation were performed with ShelX97 systems[19] and ORTEP 3 programs[20]. CCDC 859054 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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