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Synthesis and Resolution of a Novel Chiral Diamine Ligand and Application to Asymmetric Lithiation–Substitution

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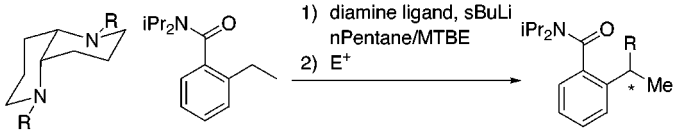
ABSTRACT



A short, efficient synthesis of chiral 1,5-diaza-*cis*-decalins (7) is presented. In the lithiation of *N*-Boc pyrrolidine, the ligands with the smallest most electron rich R groups (Me > Et > $CH_2{}^tBu$ > CH_2CF_3 ≈ Bn) were most effective. In the asymmetric deprotonation/substitution of benzylic substrates, (*R*,*R*)-7 (R = Me, R′ = H) conferred modest selectivity. The ready availability of both enantiomers of the 1,5-diaza-*cis*-decalins and the ability to tune steric and electronic properties renders these compounds an attractive new class of diamine ligands.

Despite the host of applications of chiral diamine ligands in asymmetric synthesis, few significantly different structures have found general utility. The most widely used chiral diamines (**1**−**6**) are outlined in Figure 1, and extensive

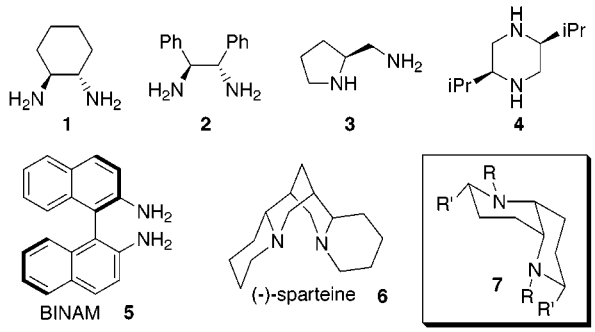
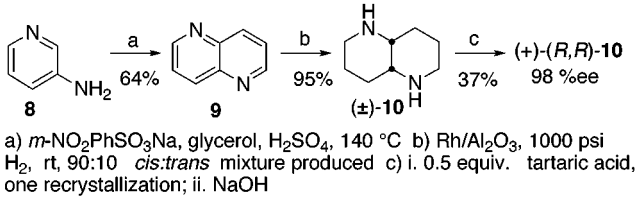


Figure 1.

reviews on these compounds can be found.[1,2] Compound **7** was identified as a potential lead from our efforts in the computer-aided identification of novel ligand scaffolds.[3] Interestingly, while diaza-*cis*-decalins (**7**, R = H) are known compounds, ligands of this type have not been employed in asymmetric synthesis. On the basis of the well-defined chiral cavity of **7**, we believe diaza-*cis*-decalins could add significantly to the utility of this group of compounds.

In this Letter, we outline the synthesis and application of bis-tertiary amines **11** (Figure 3) based upon diaza-*cis*-decalin skeleton **7**. These compounds can be synthesized in a straightforward manner in three−four steps (Figure 2). As



a) *m*-NO_2PhSO_3Na, glycerol, H_2SO_4, 140 °C b) Rh/Al_2O_3, 1000 psi H_2, rt, 90:10 *cis*:*trans* mixture produced c) i. 0.5 equiv. tartaric acid, one recrystallization; ii. NaOH

Figure 2.

the first step, commercially available 3-aminopyridine (**8**) is readily converted to known 1,5-naphthyridine (**9**) in 64% yield via a Skraup reaction.[4] The reduction of naphthyridine **9** to the saturated derivative was improved greatly over that

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reported[5] by employing rhodium/alumina as the hydrogenation catalyst[6] with acetic acid to yield a 90:10 mixture of *cis*:*trans* isomers of **10** in 95% yield. The more crystalline *trans* isomer could be readily removed by extraction or recrystallization to yield (±)-**10** in a ≥95:5 *cis*:*trans* ratio.[7] At this point, precipitation of the racemic diamine **10** with 0.5 equiv of (*R*,*R*)-tartaric acid and recrystallization from water/ethanol gave a 37% yield (74% of the total possible yield) of the (*R*,*R*)-**10** (*R*,*R*)-tartrate salt in ≥98% ee free of any residual *trans* isomer.[8] The mother liquors from these recrystallizations could be treated with the (*S*,*S*)-tartaric acid to generate (*S*,*S*)-**10** with similar selectivity.

With the chiral diamine **10** in hand, a variety of substituted derivatives were readily made (Figure 3). Dimethyl analogue

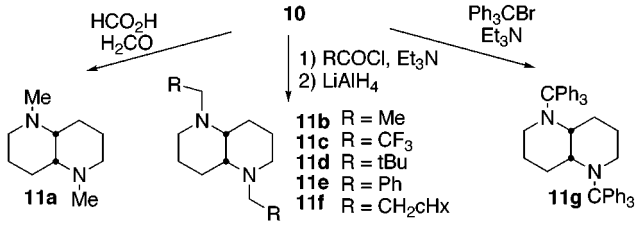

Figure 3. *N*,*N*′-Dialkylation of diamine **10**.

(*R*,*R*)-**11a** was produced by Eschweiler−Clarke reductive amination. Other dialkylated derivatives, (*R*,*R*)-**11b**−**f**, were produced by acylation with the corresponding acyl chloride followed by reduction with $LiAlH_4$.[9] This protocol was superior when compared to direct alkylation in that the amide intermediates are oxidatively stable, easily purified, and can be stored indefinitely.

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(5) Decahydronaphthyridine has been produced in about 20% yield from naphthyridine as a 2:1 *cis:trans* mixture in the presence of 1 equiv of PtO_2: Albert, A. *J. Chem. Soc.* **1960**, 1790−3.

(6) Hoffmann et al. have independently shown that similar reaction conditions result in similar improvement (see ref 12a).

(7) To **9** (8.15 g, 62.7 mmol) in absolute EtOH were added 5% Rh/Al_2O_3 (0.817 g) and HOAc (70 mL). The mixture was hydrogenated at 1200 psi of H_2 for 12 h. After filtration, the residue was washed with MeOH and the filtrates were saturated with HCl. Removal of the solvent gave a solid (10.5 g, 95%). Recrystallization from MeOH and H_2O yielded pure *trans* HCl salt. The mother liquor was concentrated and dissolved in H_2O which was made basic with NaOH, saturated with NaCl, and extracted with Et_2O. Drying the Et_2O extracts with Na_2SO_4 and removal of the Et_2O afforded a 94:6 mixture of *cis*-**10** and the *trans* isomer. Distillation (89−90 °C, 3 mmHg) afforded pure **10** (4.2 g, 48%) as a waxy white solid. See Supporting Information for analytical data.

(8) (*R*,*R*)-**10** (*R*,*R*)-tartrate was prepared by dissolving racemic **10** (0.98 g, 7.0 mmol) in MeOH (5 mL) and then adding this solution slowly to a MeOH (5 mL) solution of L-(+)-tartaric acid (525 mg, 3.5 mmol) at rt. After the solution clarified, acetic acid (0.36 mL, 6.3 mmol) was added. H_2O (2 mL) was added, and the mixture was warmed. Upon standing at 0 °C overnight, the tartrate salt of **5** (887 mg, 44%) was isolated in 87% ee. Recrystallization of a portion (550 mg) from EtOH/H_2O caused enrichment to ≥98% ee (458 mg, 83%). See Supporting Information for analytical data.

The absolute configuration of the 1,5-diaza-*cis*-decalin (+)-**10**, and subsequent derivatives, was determined by an X-ray crystallographic analysis of the (*R*,*R*)-tartrate salt (Figure 4). The structure definitively indicates that the (*R*,*R*)-

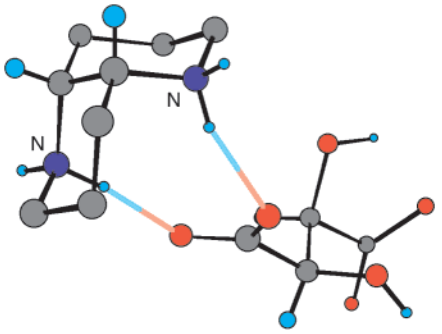


Figure 4. X-ray structure of (*R*,*R*)-tartaric acid (*R*,*R*)-**10** complex (hydrogens, except on heteroatoms or stereogenic centers, omitted for clarity).

tartrate crystallized with (*R*,*R*)-**10**.[8] Notably, the *cis*-decalin component adopts the conformation expected under acidic conditions (see below, Figure 5 **11-in**, R = H), and only

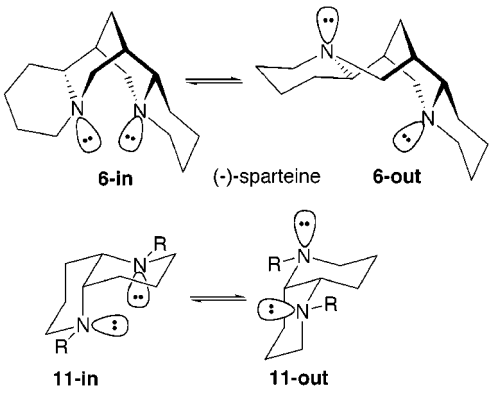


Figure 5. Conformations of (−)-sparteine and 1,5-diaza-*cis*-decalins.

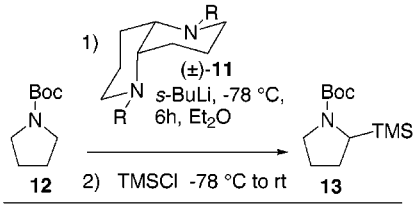
one carboxylic acid of the tartrate interacts with the diamine from the concave face. Examination of the crystal packing diagram reveals that the second carboxylate of the tartrate interacts with a neighboring diamine from the convex face.

(9) For example, **11e** was produced from **10** (75:25 *cis:trans* HCl salt, 1.92 g, 10.9 mmol) in CH_2Cl_2 (40 mL) at 0 °C by addition of Et_3N (7.6 mL, 54.5 mmol), DMAP (221 mg, 1.8 mmol), and PhCOCl (4.2 mL, 36.0 mmol). After being stirred at rt overnight, the insoluble solid was filtered off and the resultant oil was purified by silica chromotography (2:1 EtOAc:hexanes) to afford the bisamide (2.45 g, 65%) as a white solid. The bisamide (1.15 g, 3.3 mmol) was reduced with $LiAlH_4$ (570 mg, 15.0 mmol) in anhydrous THF (50 mL) by heating to reflux for 1 h and then stirring 12 h at room temperature. After the reaction was quenched with an aqueous NaOH solution, the mixture was filtered and purified by silica chromotography (95:5 CH_2Cl_2:MeOH) to afford **11e** (0.98 g, 93%) as a waxy white solid. See Supporting Information for analytical data.

The potential application of bis-tertiary amines (**11**) derived from 1,5-diaza-*cis*-decalin as sparteine alternates is particularly interesting (Figure 5). Much effort has been devoted to the development of efficient asymmetric synthetic methods based upon chiral carbanions.[2] Chiral carbanions undergo a wide range of selective alkylation, carbonyl addition, and most recently conjugate addition reactions.[10] The key to the ready utility of this rich chemistry has been in the generation of enantiomerically enriched lithium carbanion pairs in which the carbanionic center carries chiral information. Substitution of the lithium occurs stereospecifically, often with retention of configuration. Chiral lithium carbanions are typically generated by the action of an achiral alkyllithium base (i.e., BuLi) in the presence of a chiral ligand. Many chiral ligands have been utilized in this chemistry with the natural alkaloid (−)-sparteine (**6**) enjoying the most widespread utility. This methodology suffers in that the (+)-enantiomer of sparteine is not readily available. A host of diamine ligands have been screened in the hope of solving this dilemma, but the utility of these replacements tends to fall short of the parent.[11]

As is the case for sparteine, 1,5-diaza-*cis*-decalins are conformationally mobile and interconvert between two stable conformations by ring inversion (Figure 5). For sparteine, the desired conformation for bidentate coordination of a cation, **6-in**, is actually slightly less stable than **6-out**.[2a] Nevertheless, the addition of lithium species appears to perturb this equilibrium and complexes of the **6-in** conformation are generally regarded as responsible for the selectivities observed in sparteine-mediated carbanion chemistry. In the case of the 1,5-diaza-*cis*-decalins, the position of the equilibrium between the desired conformation capable of bidentate coordination, **11-in**, and the other major conformation, **11-out**, varies depending upon substituents (R), solvent, and additive. In an elegant study, Hoffmann and co-workers[12] have shown that when the R groups are small, **11-in** is favored and when the R groups are large, **11-out** becomes favored. Regardless, the two conformations are energetically similar enough that the addition of acid or $LiClO_4$ shifts the equilibrium toward **11-in**. Visual examination of **11-in** reveals an asymmetric environment upon coordination of a tetrahedral ion such as lithium. With these considerations in mind, derivatives of **11** were examined as reagents for asymmetric lithiation.

In initial studies, the *s*-BuLi complexes with **11** were tested for reactivity in the deprotonation of *N*-Boc pyrrolidine **12** (Figure 6).[13] This case is especially useful for assaying the utility of ligands as almost no lithiation occurs in the absence



entry	diamine	R	conv. (%)[a]
1	**11a**	Me	100
2	**11b**	Et	45
3	**11c**	CH_2CF_3	0
4	**11d**	CH_2tBu	28[b]
5	**11e**	CH_2Ph	0
6	(-)-sparteine		76[c]

[a]GC conversion. [b]When the anion was treated with MeOD , 73% deuteration seen by ^{1}H NMR. [c]Isolated yield (93% ee). When the anion was treated with MeOD, 98% deuteration. See reference 13.

Figure 6.

of a diamine. Not surprisingly, the more hindered versions of **11** (larger R groups) were less reactive.[11a] The larger R groups shield the lithium significantly, which may account for the lower reactivity following the series Bn < ^{t}BuCH$_2$ < Et < Me. Interestingly the trifluoroethyl derivative **11c** proved to be completely unreactive. The strongly electron withdrawing trifluoro groups undoubtedly create a less electron rich ligand. Whether this ligand possesses a lower affinity for the lithium species or its lesser donicity renders the *sec*-butyl anion less nucleophilic remains to be delineated. Examination of the resolved form of the optimal ligand (*R,R*)-**11a** in this reaction led to a disappointingly low selectivity (12% ee).

A second test substrate, **14**,[14] was surveyed with the 1,5-diaza-*cis*-decalins **11a** and **11e** (Figure 7). Lithiation of **14** in the presence of the less hindered (*R,R*)-**11a** and treatment with acetone yielded tertiary alcohol **15a** in 39% ee which was comparable to the 39% ee achieved by (−)-sparteine except that the opposite configuration of **15a** was produced.

Further studies with substrate **14** using allyl electrophiles revealed that the degree of enantioselectivity imparted by diamine **11a** is remarkably independent of the electrophile and the sense of enantioselection was again opposite that of (−)-sparteine (Figure 7). As is the case for (−)-sparteine, allyl halides appear to give reaction via an inversion pathway and allyl tosylate via a retention pathway. Warming of deprotonated **14** to −20 °C prior to treatment with the electrophile caused only small changes in selectivity (entries 5 vs 6 and 7 vs 8). Most likely, a dynamic kinetic resolution in which one diastereomeric anion is more reactive that the other is operative. This result is analogous to that observed by Beak for substrate **14** with (−)-sparteine.[14] As such, it appears that diamine **11a** causes reaction pathways similar to those observed with (−)-sparteine.

Examination of the structures of (−)-sparteine and decalin derivative (*R,R*)-**11a** provides insight into the important

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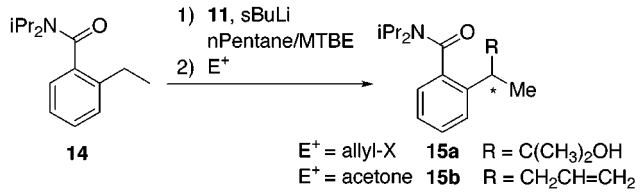

entry	ligand	E^+	ee (%)
1	(*R*,*R*)-**11a**	acetone	39 (*R*)
2	(*R*,*R*)-**11e**	acetone	3 (*R*)
3	(-)-sparteine[a]	acetone	39 (*S*)
4	(*R*,*R*)-**11a**	CH_2=$CHCH_2Cl$	6 (*S*)
5	(*R*,*R*)-**11a**	CH_2=$CHCH_2Br$	45 (*S*)
6	(*R*,*R*)-**11a**	CH_2=$CHCH_2Br$	38 (*S*)[b]
7	(*R*,*R*)-**11a**	CH_2=$CHCH_2OTs$	42 (*R*)
8	(*R*,*R*)-**11a**	CH_2=$CHCH_2OTs$	30 (*R*)[b]
9	(-)-sparteine[a]	CH_2=$CHCH_2Cl$	92 (*R*)
10	(-)-sparteine[a]	CH_2=$CHCH_2Br$	52 (*R*)
11	(-)-sparteine[a]	CH_2=$CHCH_2OTs$	88 (*S*)

[a]See reference 14. [b]Anion solution warmed to -20 °C.

Figure 7.

topological features relevant to the stereoselectivity in these reactions. Figure 8 shows a view of lithium coordinated to

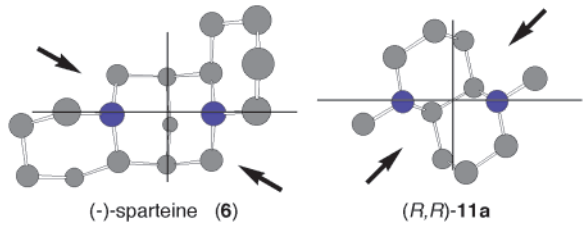

Figure 8. View of the stereochemically accessible quadrants of lithium-coordinated (−)-sparteine and (*R*,*R*)-**11a**. The lithium ion (not shown) is located at the crosshair defining the accessible quadrants.

(−)-sparteine and (*R*,*R*)-**11a** in which the plane of the two nitrogens and a bound lithium ion (not shown) are perpendicular to the plane of the page. Comparison of the stereochemically accessible quadrants reveals that these ligands block enantiomeric quadrants, which is consistent with the observation of enantiomeric products (see above) This result signifies that, in principle, diamines based on **11** can allow access to enantiomeric forms not readily achieved with (−)-sparteine.

Notably, the energy differences imparted by these chiral ligands is very small. For example, an energy difference of 1.26 kcal/mol between reaction pathways would account for the 92% ee observed with (−)-sparteine (Figure 7, entry 9) and a difference of 0.40 kcal/mol would account for the 45% ee observed with the decalin derivative (*R*,*R*)-**11a** (Figure 7, entry 5). As such, minor modifications may result in substantial differences in selectivity.[11] To this end, modified derivatives of **7** (R′ = alkyl, Figure 1) are being explored.

In conclusion, the preparation of a unique class of chiral ligands, the 1,5-diaza-*cis*-decalin derivatives, has been described. These compounds have been shown to be moderately effective in asymmetric carbanion chemistry. Future efforts will be directed toward modifying the steric and electronic characteristics of this family of ligands which can be readily accomplished by variation of the substituent *N*-alkyl groups. Because of the well-defined and easily modulated chiral environment of these 1,5-diaza-*cis*-decalins, it is anticipated that this new class of diamine ligands will find a number of applications in asymmetric synthesis.

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Supporting Information Available: Experimental details and characterization of all new compounds is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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