Conformational Control of Flexible Molecules: Design and Synthesis of Novel Chiral 1,5-Diaza-*cis*-decalins

Zhenrong Xu and Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104

marisa@sas.upenn.edu

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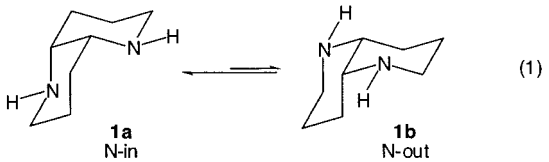
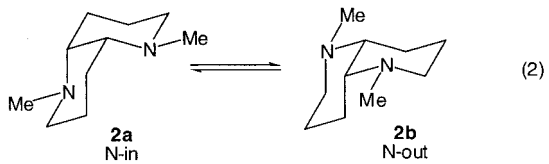
Control of the conformational equilibria of 1,5-diaza-*cis*-decalins, a new class of chiral diamine ligands, has been investigated. Chiral 2,6- and 3,7-substituted derivatives of 1,5-diaza-*cis*-decalins were designed to stabilize the conformational form needed to chelate a lithium. These derivatives were synthesized in optically pure form starting from 1,5-diaza-*cis*-decalin. Due to the rigid and conformationally well-defined nature of these compounds, the potential of these compounds as chiral diamine ligands was investigated. Asymmetric lithiation−substitution reactions of *N*-Boc-pyrrolidine and *N*,*N*-diisopropyl-*o*-ethylbenzamide were performed using these ligands and up to 60% ee was obtained. For the latter substrate, results spanning a range from 32% ee (*R*) to 60% ee (*S*) were obtained (Δee = 92%) with 1,5-diaza-*cis*-decalin ligands differing only in the location of two methyl substituents. Unlike many other diamines that have been employed in asymmetric lithiation−substitution reactions, the limited conformational flexibility of the 1,5-diaza-*cis*-decalins is analogous to (−)-sparteine such that these results may permit the construction of structure−activity relationships.

Introduction

Asymmetric synthesis has become a major focal point of synthetic chemistry in the past three decades. For metal-mediated and metal-catalyzed reactions, the design and synthesis of appropriate chiral ligands is crucial.[1] Recently, we developed a new class of chiral diamine ligands, 1,5-diaza-*cis*-decalins, on the basis of computer-aided identification of novel ligand scaffolds.[2] 1,5-Diaza-*cis*-decalin (**1**) is a unique chiral diamine ligand, in which there are two conformational isomers, N-in and N-out (eq 1). The N-in conformer has a well-defined chiral cavity with two nitrogens that can chelate a metal.[3,4] A previous study[5] showed that the parent compound **1** prefers the N-in conformation **1a**; however, the *N*,*N*′-dimethyl derivative **2** partitions equally between the N-in and N-out forms (**2a** and **2b**, eq 2).



(1)



(2)

In the prior studies, we have shown that 1,5-diaza-*cis*-decalin (**1**) is the ligand of choice in catalytic enantioselective oxidative biaryl coupling reactions providing high selectivity (90−93% ee).[4] However, when **2** was employed in the asymmetric lithiation−substitution of benzylic substrates, only moderate selectivity was achieved (42−45% ee).[3] These results stimulated us to further examine conformational control of this flexible molecule by means of suitably located methyl substituents. "The conformation of a ligand is particularly important in the development of optimum polydentate ligands. The coordination of the ligand is most favorable when its ground-state conformation resembles that of the complex."[6] Thus, conformationally locked derivatives of **2** would facilitate coordination of a metal since there would be no energetic penalty associated with the chelating conformation. Such a trait is particularly desirable in ligands for species which form weak coordination bonds, such as alkyllithiums. For the 1,5-diaza-*cis*-decalins, this goal cannot be accomplished by simple substitution at the nitrogen atom since *N*- or *N*,*N*′-substitution perturbs the equilibrium toward the N-out conformation.[5,7] To overcome this problem 2,6- and 3,7-substituted-1,5-diaza-*cis*-decalins were designed (Scheme 1).

We anticipated that the methyl groups of these substituted diazadecalins would be equatorial in the N-in form thereby "locking" the conformation. In addition, these methyl substituents would extend the asymmetric environment of the metal binding cavity. In this paper, the synthesis and conformational properties of these

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(2) Kozlowski, M. C.; Panda, M. *J. Mol. Graph. Modell.* **2002**, *20*, 399−409.

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(5) Santos, A. G.; Klute, W.; Torode, J.; Böhm, V. P. W.; Cabrita, E.; Runsink, J.; Hoffmann, R. W. *New J. Chem.* **1998**, 993−997.

(6) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124−1134.

(7) Ganguly, B.; Freed, D. A.; Kozlowski, M. C. *J. Org. Chem.* **2001**, *66*, 1103−1108.

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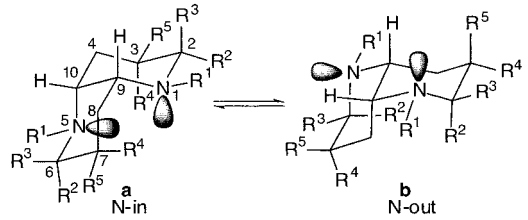
Scheme 1

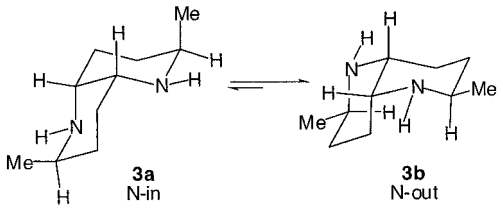


compd	R^1	R^2	R^3	R^4	R^5
1	H	H	H	H	H
2	Me	H	H	H	H
3	H	H	Me	H	H
4	H	Me	H	H	H
5	Me	Me	H	H	H
6	H	Ph	H	H	H
7	H	H	H	Me	Me
8	Me	H	H	Me	Me
9	H	H	H	H	Me
10	Me	H	H	H	Me
17	H	H	H	Me	H

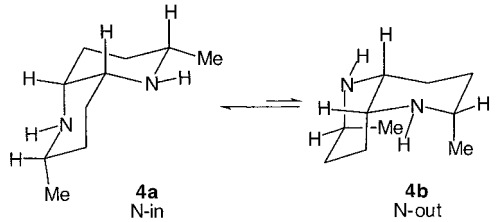
chiral 1,5-diaza-*cis*-decalins are reported along with their application to asymmetric lithiation−substitution.

Results and Discussion

Synthesis and Conformational Analysis of 2,6-Substituted-1,5-diaza-*cis*-decalins. In a prior paper,[8] we reported the syntheses of 2,6-dimethyl-1,5-diaza-*cis*-decalins **3** and **4**. On the basis of NMR analyses, isomer **3**, with the C-2, C-6 methyl groups syn to the angular hydrogens, was found to exist in the N-out conformation (eq 3) while isomer **4**, with the C-2, C-6 methyl groups anti to the angular hydrogens, was found to exist in the N-in conformation (eq 4). As such, **4** could act as a rigid chelating diamine ligand due to the N-in conformational preference. In this case, the metal would be positioned in a well-defined extended chiral cavity.



(3)



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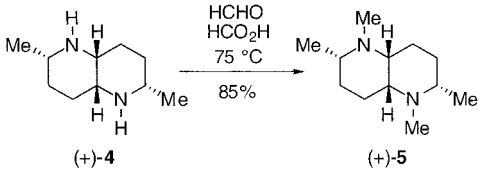
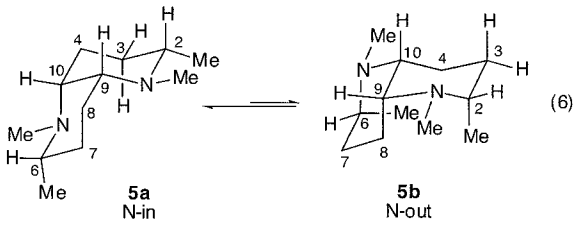
The *N*,*N*′-dimethyl substituted derivative **5** was prepared from **4** by Eschweiler−Clarke methylation (eq 5).



(5)

The nature of the predominant conformation in solution of the 1,5-diaza-*cis*-decalins could be discerned from the vicinal coupling constants along the molecular backbone.[9] In the N-in conformation of **5**, the nitrogen atoms are gauche (eq 6). Thus, the angular hydrogens (H-10/H-9) are equatorial with respect to the cyclohexyl ring containing the adjacent H-4/H-8 protons. As a result, small coupling constants are observed for H-10/H-9 in this form. In the N-out conformation, the nitrogen atoms are anti, placing the angular hydrogens axial (eq 6). As a result, H-10/H-9 have one large (axial−axial) and one small (axial−equatorial) coupling constant with the adjacent H-4/H-8 protons. The ^{1}H NMR spectrum of **5** showed H-10/H-9 as a deformed doubled doublet with small coupling constants (J = 2.6, 1.8 Hz; Table 1), implying that H-10/H-9 are equatorial. In other words, the conformational equilibrium of **5** predominantly populates the N-in conformation (eq 6).



(6)

The stereochemistry of the C-2, C-6 substituents could also be determined by the coupling constants, particularly between H-2/H-6 and H-3/H-7. For compound **5**, H-2/H-6 participate in one large (J = 12.3 Hz) and one small (J = 2.9 Hz) coupling with the adjacent H-3/H-7 protons, implying that H-2/H-6 must be axial. In other words, the C-2/C-6 methyl substituents occupy equatorial positions. On this basis, **5** populates mainly the N-in conformation with the C-2, C-6 methyl groups anti to the angular hydrogens.

It is noteworthy that the equatorial disposition of the C-2, C-6 methyl groups substitution in **5** greatly stabilizes the N-in conformation and even overcomes the torsional effects of *N*,*N*′-dimethyl substitution which ordinarily stabilizes an N-out arrangement (compare eq 1 and eq 2).[7] This result confirmed that the conformational equilibria of 1,5-diaza-*cis*-decalins can be completely controlled to favor the N-in conformation by suitably locating substituent groups. On this basis, the 2,6-diphenyl-substituted derivative **6** was designed, which should also possess a higher conformational preference for the N-in conformation relative to the parent compound **1**.

Preparation of **6** began with the L-tartrate salt of 1,5-diaza-*cis*-decalin (**11**) which was directly converted to the corresponding *N*,*N*′-diBoc compound **12** by treatment with di-*tert*-butyl dicarbonate in the presence of aqueous NaOH (Scheme 2). Protected diamine **12** was conveniently oxidized to the corresponding bislactam **13** using catalytic RuO_2 with excess 10% aqueous $NaIO_4$ in a two-phase EtOAc/H_2O system.[10] Compound **13** was then converted to the corresponding enol triflate **14** with *N*-(5-chloro-2-pyridyl)triflimide using the procedure of Comins.[11] The subsequent Pd-catalyzed Suzuki coupling reaction

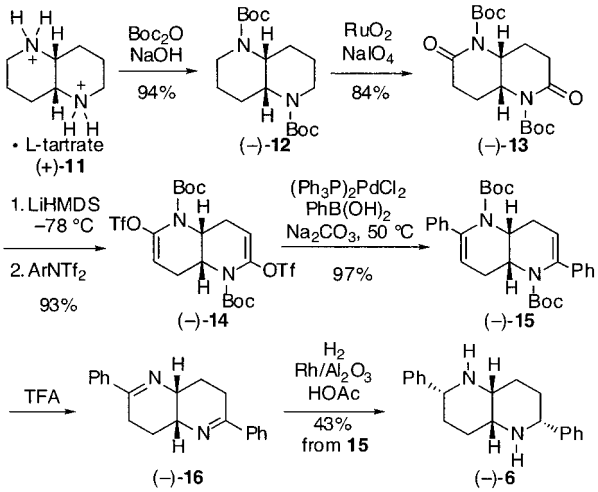
(8) Kozlowski, M. C.; Xu, Z.; Santos, A. G. *Tetrahedron* **2001**, *57*, 4537−4542.
(9) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054−2070.
(10) Tanaka, K.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1988**, *36*, 3125−3129.
(11) Foti, C. J.; Comins, D. L. *J. Org. Chem.* **1995**, *60*, 2656−2657.

Table 1. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) Spectral Data of 2,6- and 3,7-Substituted-1,5-diaza-*cis*-decalins

compound	H-10/H-9	H-2/H-6
3[a]	3.09 (ddd, J = 13.6, 5.6, 4.0 Hz, 2H)	2.85 (dqd, J = 11.3, 6.2, 2.7 Hz, 2H)
4[a]	2.68 (ddd, J = 4.0, 2.8, 2.7 Hz, 2H)	2.64 (dqd, J = 11.2, 6.3, 2.4 Hz, 2H)
5	2.04 (deformed dd, J = 2.6, 1.8 Hz, 2H)	1.98 (dqd, J = 12.3, 6.2, 2.9 Hz, 2H)
6	2.97 (dd, J = 2.5, 2.3 Hz, 2H)	3.75 (dd, J = 11.2, 2.8 Hz, 2H)
7	2.84 (br s, 2H)	2.58 (d, J = 12.7 Hz, 2H) 2.27 (d, J = 12.7 Hz, 2H)
8	3.06 (br d, J = 13.1 Hz, 2H)	2.16 (d, J = 11.5 Hz, 2H) 1.96 (dd, J = 11.5, 1.7 Hz, 2H)
9	2.63 (dd, J = 2.6, 2.2 Hz, 2H)	3.00 (ddd, J = 12.3, 3.9, 2.4 Hz, 2H) 2.20 (dd, J = 11.9, 11.3 Hz, 2H)
10	1.86 (deformed dd, J = 2.4, 1.8 Hz, 2H)	2.86 (ddd, J = 10.9, 3.2, 2.4 Hz, 2H) 1.62 (dd, J = 11.0, 10.9 Hz, 2H)

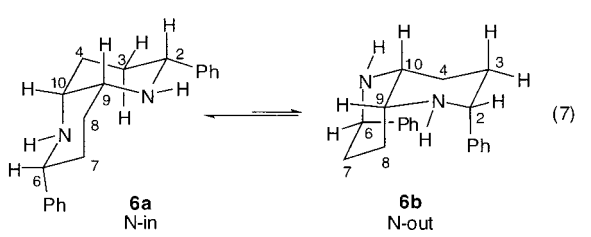
[a] Coupling constants determined by simulation with PPC gNMR to reproduce the second-order multiplets observed in the ^{1}H NMR spectra.[8]

Scheme 2



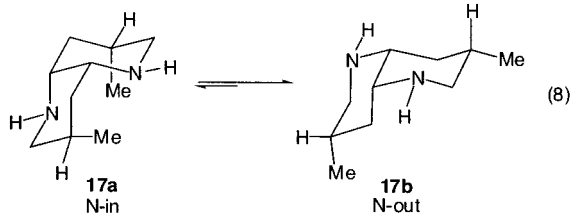
of **14** with phenylboronic acid provided the corresponding 2,6-diphenyl-substituted bisenamide **15** in high yield.[12] Several attempts to hydrogenate **15** using palladium black as the catalyst were unsuccessful, even though this catalyst was successful for a closely related transformation.[13] Compound **15** was then treated with TFA which removed the Boc groups and isomerized the resultant bisenamine to provide bisimine **16**. However, the subsequent reduction of **16** with DIBALH afforded a complex mixture. The desired compound **6** was finally achieved by the hydrogenation of bisimine **16** with 5% Rh/Al_2O_3 in the presence of acetic acid.

In the ^{1}H NMR spectrum of **6**, H-10/H-9 showed a doubled doublet with small coupling constants (J = 2.5, 2.3 Hz), implying that H-10/H-9 are equatorial (eq 7). On the other hand, H-2/H-6 showed a doubled doublet with a large (J = 11.2 Hz) and a small (J = 2.8 Hz) coupling constant implying that H-2/H-6 are axial. From this analysis, the N-in conformer predominates for **6** and the C-2, C-6 phenyl groups are anti to the angular hydrogens.



(7)

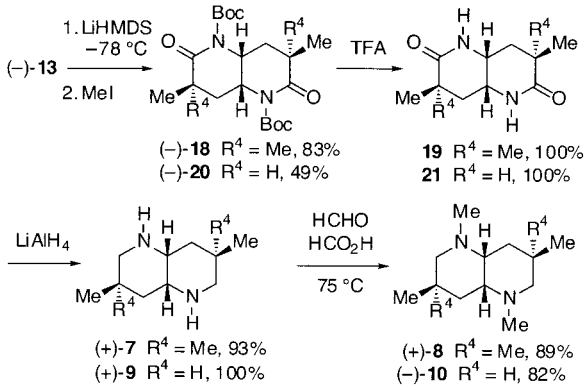
Synthesis and Conformational Analysis of 3,7-Substituted-1,5-diaza-*cis*-decalins. To gain further insight into the conformational control of this flexible molecule, 3,7-substituted derivatives were also examined. Substitution of R^4 appears to create a well-defined chiral cavity in the N-in conformation (Scheme 1). However, **17** (R^4 = Me, R^5 = H) will populate mainly the N-out conformation to minimize the 1,3-diaxial steric interactions (eq 8).



(8)

Generation of a derivative in the N-in conformation with R^4 = Me could be accomplished by geminal dimethyl substitution of C-3 and C-7 to yield derivative **7**. Compound **7** was made from **13** by exhaustive methylation of the bisenolate, followed by *N*-deprotection and reduction[14] (Scheme 3).

Scheme 3



The ^{13}C NMR spectrum of **7** showed broad signals at room-temperature implying the presence two conformers. Interestingly, the low temperature ^{13}C NMR at 250 K indicated ca. 4:1 ratio of conformers with a predominance of N-in **7a** (eq 9). The N-in form **7a** predominates *despite the two 1,3-interactions in the concave face of the ring*

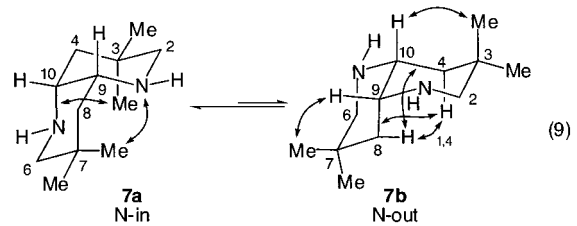
(12) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *Org. Lett.* **2000**, *2*, 1241−1242.
(13) Yamaguchi, R.; Nakazono, Y.; Matsuki, M.; Hata, E.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 215−222.
(14) Frydman, B.; Los, M.; Rapoport, H. *J. Org. Chem.* **1971**, *36*, 450−454.

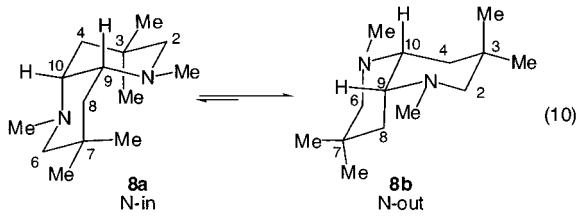
Table 2. Experimental Ratios and Relative Energies (kcal/mol) Calculated with MM2*, Amber*, and HF/6-31G* for the Conformers of 2,6- and 3,7-Substituted-1,5-diaza-*cis*-decalins

	3a	**3b**	**4a**	**4b**	**5a**	**5b**	**6a**	**6b**	**7a**	**7b**	**8a**	**8b**	**9a**	**9b**	**10a**	**10b**
expt. ratio[a]	<10	>90	>90	<10	>90	<10	>90	<10	80	20	<10	>90	>90	<10	>90	<10
rel *E* (MM2*)	1.9	0.0	0.0	10.7	0.0	8.3	0.0	9.3	0.0	1.0	0.0	0.0	0.0	5.9	0.0	5.0
rel *E* (Amber*)	0.0	1.3	0.0	10.6	0.0	4.3	0.0	11.6	0.0	0.3	3.4	0.0	0.0	3.9	0.0	1.2
rel *E* (HF/6-31G*)	4.0	0.0	0.0	11.4	0.0	1.1	0.0	16.3	0.0	0.7	4.2	0.0	0.0	5.6	0.0	1.9

[a] Determined from the NMR data. See text.

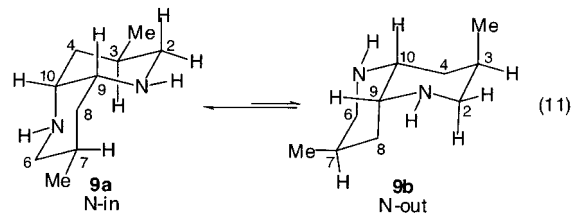
system arising from the two axial methyl groups at C-3 and C-7. Apparently, the disfavorable interactions in **7a** (two 1,3 Me-NHR interactions) incur less of an energetic penalty compared to those in **7b** (one 1,4 H−H and four 1,3 H−CH_2R interactions; see eq 9).

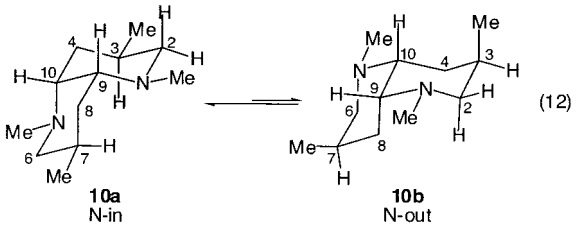




Diamine **7** was also converted to the corresponding *N*,*N*′-dimethyl-substituted derivative **8** by the same Eschweiler−Clarke procedure used for **5** (Scheme 3). In the case of **8**, the H-10/H-9 protons showed a broad doublet with a large coupling constant (J = 13.1 Hz) which implies that H-10/H-9 are axial and that the undesired N-out conformation predominates (eq 10). From the calculations (see below), diamine **7** possesses one of the lowest proclivities for the N-in form (ΔH **7a**/**7b** ≤ 1 kcal/mol). *N*-Methylation to form **8** introduces torsional strain between the *N*-Me groups and the C-4/C-8 positions[7] which offsets the marginal stabilization of the N-in form in these tetramethyl C-3, C-7 variants. Since **8** did not favor the desired N-in conformation, we reevaluated the 1,5-diaza-*cis*-decalins and designed 3,7-dimethyl-substituted derivatives **9** and **10**.

Compounds **9** and **10** were synthesized by stereoselective alkylation[15] of **13** as the key step followed by deprotection, reduction, and methylation (Scheme 3). NMR analyses of **9** and **10** indicated that the angular H-10/H-9 protons are equatorial with respect to the cyclohexyl ring containing the adjacent H-4/H-8 protons since only small coupling constants were observed (Table 1). Thus, **9** and **10** predominantly populate the N-in conformation. In addition, the stereochemistry of the C-3, C-7 methyl groups of **9** and **10** was determined by the coupling constants of H-3/H-7 with the adjacent H-2/H-6 protons. Since the H-2/H-6 axial proton signals are a doubled doublet with large coupling constants (J = 11.9, 11.3 Hz for **9** and J = 11.0, 10.9 Hz for **10**), H-3/H-7 must be axial and the C-3/C-7 methyl substituents occupy equatorial positions. On this basis, the C-3, C-7 methyl groups of **9** and **10** are syn to the angular hydrogens, and these compounds predominantly populate the N-in conformations, **9a** and **10a**, respectively (eq 11 and 12). Thus, full conformational control of 1,5-diaza-*cis*-decalins to favor either the N-in or N-out forms has been achieved.



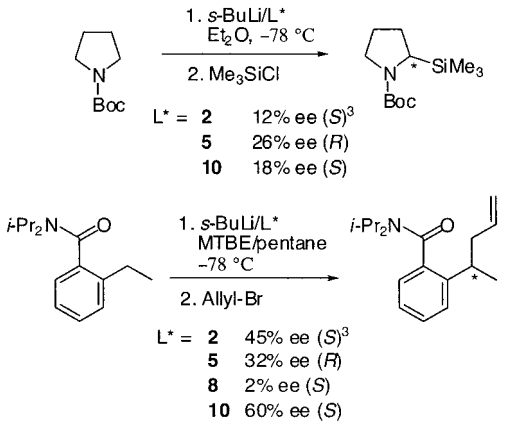


To further examine the conformational equilibria of 1,5-diaza-*cis*-decalins the relative energies of the conformers of 2,6- and 3,7-substituted derivatives were calculated using MM2*, Amber*, and HF/6-31G* (Table 2). Generally, the calculated results support the experimental observations. For the majority of the cases, the molecular mechanics calculations were adequate; however, neither the MM2* or the Amber* calculations were entirely reliable (see **8** and **3**, respectively). These discrepancies may arise from stereoelectronic interactions in these 1,2-diamines which are not evaluated in the force field treatments. The relevant interactions include (i) negative hyperconjugation between the nitrogen lone-pair and a antiperiplanar σ*-acceptor (C−H and C−C bonds) and (ii) donation from the best σ-donor (C−H bond) to the best σ*-acceptor (C−N bond). Previously, we had shown that Hartree−Fock calculations are the most reliable for the 1,5-diaza-*cis*-decalins.[7] In line with these results, the HF/6-31G* geometry optimized energies are the most accurate for the entire series. On the basis of the calculated energies, the N-in form is strongly favored (by 5.6−16.3 kcal/mol) for the secondary amines **4**, **6**, and **9**. The *N*-methyl derivatives **5** and **10** are still predisposed toward the N-in form, but the energy differences (1.1 and 1.9 kcal/mol, respectively) are substantially smaller, and some of the N-out form may be present. The calculations indicate that *N*-methylation always decreases the stability of the N-in form relative to the parent secondary amines (**5** vs **4**, **8** vs **7**, **10** vs **9**) due to the introduction of torsional interactions.[7] From these results, it appears that calculations can be used to determine if 1,5-diaza-*cis*-decalin derivatives are predisposed to one conformational form or the other.

Asymmetric Lithiation−Substitutions of *N*-Boc-Pyrrolidine and *N*,*N*-Diisopropyl-*o*-ethylbenzamide.

(15) Casimir, J. R.; Didierjean, C.; Aubry, A.; Rodriguez, M.; Briand, J.; Guichard, G. *Org. Lett.* **2000**, *2*, 895−897.

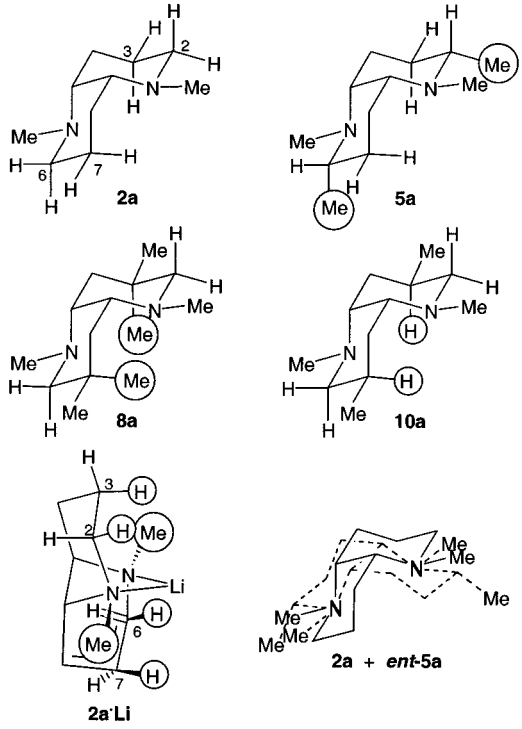
Scheme 4



To test the effect of the modified ligands, the asymmetric lithiation−substitution reactions of *N*-Boc-pyrrolidine[16] and *N*,*N*-diisopropyl-*o*-ethylbenzamide[17] were examined (Scheme 4). Initial results from **2a** gave 12% ee (*S*) and 45% ee (*S*), respectively, in these reactions. To improve these results, a model of **2a** bound to lithium (**2a·Li**, Scheme 5) was constructed.[18,19] In this model, the *N*-alkyl groups, the axial H-3/H-7, and the equatorial H-2/H-6 hydrogens (circled groups in **2a·Li**) would have the closest contact to reactants bound to the lithium center. Modification of the *N*-alkyl groups was not viable since larger groups perturbed the equilibria of the 1,5,-diaza-*cis*-decalins to the N-out form[7] which does not undergo facile chelation with alkyllithiums.[20] Substitution at C-3/C-7 was next considered since these positions are the closest to the lithium center and may play an important role in asymmetric induction (Scheme 5). To enhance the stereochemical environment of the concave decalin cavity in which the alkyllithium reagent presumably resides, compound **8** with C-3/C-7 geminal dimethyl substitution was designed. If the N-in conformation of **8** was predominant the axial methyl groups (circled portions of **8** in Scheme 5) in the chiral cavity would be expected to have a dramatic effect. However, very low selectivity (Scheme 4) was observed since **8** populated the N-out conformation **8b** almost exclusively and most likely did not form a chelated complex with the alkyllithium base.

Since the tetramethyl C-3/C-7 variant **8** was not viable the dimethyl C-3/C-7 derivative **10** was examined. As expected, 3,7-dimethyl derivative **10** gave better results than **2**. This result may arise from the higher conformational preference for the N-in conformation with **10** compared to **2**. Thus, **10** may act as the optimum form of **2**. Alternatively, steric compression of the axial H-3/H-7 protons (circled portions of **10** in Scheme 5) in **10** may attenuate the stereochemical environment of the 1,5-diaza-*cis*-decalin cavity, resulting in the slight improvement in selectivities (12 to 18% ee and 45 to 60% ee, see Scheme 4).

Scheme 5



Substitution at the more distal C-2/C-6 positions (circled portions of **5** in Scheme 5) was examined next using **5**. With this compound a dramatically different effect on the reaction selectivities was observed. Surprisingly, the reactions mediated by **5** produced products with the *opposite configuration* compared to **2**. In an attempt to discern the cause of this effect, the chiral environment was analyzed by generating overlays of **2a** and *ent*-**5a** via the nitrogen atoms (Scheme 5). A topological analysis of **2a** superimposed with **5a** and with *ent*-**5a**, revealed that the shapes of **2a** and *ent*-**5a** were more analogous than those of **2a** and **5a**. In other words, there is a greater degree of similarity between **2a** and *ent*-**5a** relative to **2a** and **5a** when the overall lowest energy "absolute" conformations (including the *N*-Me groups) are compared. This analysis and the fact that the absolute stereochemistry is dominated by the substituents rather than the stereochemistry of the ligand core suggests that the periphery of ligand is much more important in defining the stereochemical approach of the substrates in these reactions.

Notably, the substituent effect is different for the 2,6-substituted derivative **5** and the 3,7-substituted derivative **10**. In the case of **5**, the methyl substituents not only caused the conformational equilibrium to favor the N-in conformation but also increased steric bulk of the C-2/C-6 positions, providing completely different stereochemical results. With **10**, however, the methyl substituents serve primarily as conformational locks. That is, **5** directly alters the stereochemical environment while **10**

(16) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231−3239.

(17) Thayumanavan, S.; Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 8209−8216.

(18) For reviews of asymmetric lithiation/substitution and chiral ligand−Li complexes, see: (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282−2316. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560.

(19) The observed selectivity differences could also arise due to different oligomeric species. On the basis of prior work in this field, we begin our analysis using the simplest model possible, a monomeric diamine−lithium adduct. For an analysis of stereoselectivity in asymmetric deprotonation based on a monomeric sparteine·alkyllithium complexes, see: (a) Wiberg, K. B.; Bailey, W. F. *J. Am. Chem. Soc.* **2001**, *123*, 8231−8238. (b) Wiberg, K. B.; Bailey, W. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2127−2129. (c) Wiberg, K. B.; Bailey, W. F. *Tetrahedron Lett.* **2000**, *41*, 9365−9368.

(20) For example, the NMR spectra of the *N*,*N*′-di-*n*-butyl derivative of **1** in d_8-toluene indicated the presence of the N-out form. Upon the addition of *n*-BuLi in hexanes, the spectra did not indicate a change to the N-in conformer.

indirectly controls the stereochemical environment. The incorporation of conformational design into chiral ligands will be beneficial to the development of optimum polydentate ligands.[21]

Conclusion

In summary, chiral 2,6- and 3,7-substituted-1,5-diaza-*cis*-decalins with designed conformational preferences were synthesized in optically pure form starting from 1,5-diaza-*cis*-decalin. The nature of preferred conformations present in solution was discerned from the coupling constants of the angular protons H-10/H-9 with the adjacent H-4/H-8 protons. Compounds **4**, **5**, **6**, **9**, and **10** populated predominantly the N-in conformation. Since the N-in form of the 1,5-diaza-*cis*-decalins orients the two nitrogens in a manner that allows ready chelation of a metal, these compounds are predisposed to more effectively bind weakly coordinating species such as alkyllithiums. With these compounds, the consequences of substitution on the stereochemical course of asymmetric lithiation−substitution reactions can be assessed since the rigid 1,5-diaza-*cis*-decalin framework allows useful structure−activity data to be collected and compared. Further work to determine the stereochemical control features in these reactions is underway. Investigation of other applications of these novel chiral 1,5-diaza-*cis*-decalins is also in progress.

Experimental Section[22]

(2*S*,6*S*,9*R*,10*R*)-1,2,5,6-Tetramethyl-1,5-diaza-*cis*-decalin (5). A mixture of **4**[8] (0.698 g, 4.15 mmol), formaldehyde (6 mL, 37% w/w solution), and formic acid (3 mL, 88% w/w aq solution) was heated at 75 °C in an oil bath for 41 h, and then ice water was added. The solution was adjusted to pH >14 with 50% aq NaOH and extracted with CH_2Cl_2. The extract was dried (K_2CO_3) and concentrated, and the residue was chromatographed (basic Al_2O_3; 3% MeOH/CH_2Cl_2) to afford 0.696 g (85%) of **5**. Further purification could be accomplished by Kugelrohr distillation at 60−70 °C (≤1 mmHg) to give pure **5** (0.488 g, 60%) as a colorless liquid. R_f = 0.68 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ +39.6 (*c* 2.43, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12 (s, 6H), 2.05 (dq, J = 12.4, 3.1 Hz, 2H), 2.04 (deformed dd, J = 2.6, 1.8 Hz, 2H), 1.98 (dqd, J = 12.3, 6.2, 2.9 Hz, 2H), 1.70 (tdd, J = 13.1, 11.0, 2.9 Hz, 2H), 1.32 (tt, J = 13.9, 3.3 Hz, 2H), 1.25 (dq, J = 12.6, 3.1 Hz, 2H), 1.12 (d, J = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.8, 60.6, 37.8, 29.7, 28.7, 21.4; IR (film) 2963, 2772 cm^{-1}; HRMS (ES) calcd for $C_{12}H_{24}N_2Na$ (MNa^+) 219.1837, found 219.1844.

(9*R*,10*R*)-1,5-Di-*tert*-butoxycarbonyl-2,6-bis[(trifluoromethylsulfonyl)oxy]-1,4,5,8,9,10-hexahydro-1,5-naphthridine (14). To a solution of **13**[8] (0.919 g, 2.49 mmol) in THF (20 mL) at −78 °C was added 7.5 mL (7.5 mmol, 3.0 equiv) of a 1.0 M LiHMDS solution by syringe pump at 0.2 mL/min rate. After an additional 6 h, *N*-(5-chloro-2-pyridyl)triflimide[23] (3.02 g, 3 equiv) in THF was added. The resulting mixture was stirred overnight, with the temperature slowly rising to ambient. The reaction mixture was quenched with saturated brine. The organic layer was diluted with Et_2O, and the aqueous phase was extracted twice with Et_2O. The combined organic extracts were dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography (SiO_2; 5% EtOAc/hexane) affording **14** (1.458 g, 93%). R_f = 0.43 (20% EtOAc/hexane); mp 181−183 °C; $[\alpha]_D^{20}$ −121.8 (*c* 1.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 (t, J = 3.9 Hz, 2H), 4.65 (deformed t, J = 7.0 Hz, 2H), 2.53 (ddd, J = 18.9, 7.5, 3.8 Hz, 2H), 2.42 (ddd, J = 18.9, 10.2, 4.0 Hz, 2H), 1.51 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 136.8, 119.6, 117.1, 104.0, 84.2, 49.4, 27.9, 22.3; IR (film) 1727, 1683, 1213 cm^{-1}; MS (ES) *m*/*z* 655.1 (MNa^+). Anal. Calcd for $C_{20}H_{26}F_6N_2O_{10}S_2$: C, 37.98; H, 4.14; N, 4.43. Found: C, 37.67; H, 4.08; N, 4.30.

(9*R*,10*R*)-1,5-Di-*tert*-butoxycarbonyl-2,6-diphenyl-1,4,5,8,9,10-hexahydro-1,5-naphthridine (15). To a solution of **14** (1.000 g, 1.58 mmol) in THF (50 mL) were added, under a nitrogen atmosphere, phenylboronic acid (0.58 g, 4.75 mmol, 3.0 equiv), 2 M Na_2CO_3 (35 mL), and $(Ph_3P)_2PdCl_2$ (0.111 g, 0.16 mmol, 0.1 equiv). The mixture was stirred for 5.5 h at 50 °C. Saturated brine was then added, the mixture was extracted three times with Et_2O, and the combined extracts were dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (SiO_2; 5% EtOAc/hexane) affording **15** (0.749 g, 97%). R_f = 0.40 (20% EtOAc/hexane); mp 208−210 °C; $[\alpha]_D^{20}$ −352.2 (*c* 1.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24−7.32 (m, 10H), 5.26 (t, J = 3.8 Hz, 2H), 4.93 (deformed t, J = 7.0 Hz, 2H), 2.66 (ddd, J = 18.8, 7.6, 3.6 Hz, 2H), 2.35 (ddd, J = 18.9, 10.0, 4.0 Hz, 2H), 1.09 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 141.1, 135.7, 128.0, 127.0, 125.3, 112.7, 81.0, 48.6, 27.7, 24.6; IR (film) 1699, 1646, 1344 cm^{-1}; HRMS (ES) calcd for $C_{30}H_{36}N_2O_4Na$ (MNa^+) 511.2573, found 511.2556. Anal. Calcd for $C_{30}H_{36}N_2O_4$: C, 73.74; H, 7.42; N, 5.73. Found: C, 73.37; H, 7.36; N, 5.25.

(9*R*,10*R*)-2,6-Diphenyl-3,4,7,8,9,10-hexahydro-1,5-naphthridine (16). A solution of **15** (0.709 g, 1.45 mmol) and TFA (4 mL) in CH_2Cl_2 (24 mL) was stirred at room temperature for 27 h, and then the volatiles were removed in vacuo. The residue was treated with 5% NaOH and extracted twice with CH_2Cl_2. The combined organic layers were dried over K_2CO_3. Filtration and concentration yielded bisimine **16** (0.421 g), which was used in the next step without further purification. An analytical sample was purified by chromatography (basic Al_2O_3; 2% MeOH/CH_2Cl_2). R_f = 0.86 (10% MeOH/CH_2Cl_2); mp 151−153 °C; $[\alpha]_D^{20}$ −99.2 (*c* 0.34, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75−7.77 (m, 4H), 7.33−7.37 (m, 6H), 4.01 (br s, 2H), 2.69−2.73 (m, 2H), 2.50−2.57 (m, 2H), 2.28−2.32 (m, 2H), 2.15−2.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 139.7, 129.7, 128.2, 126.1, 53.5, 25.7, 23.6; IR (film) 1632 cm^{-1}; MS (ES) *m*/*z* 289.2 (MH^+). Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 82.84; H, 6.82; N, 9.30.

(2*R*,6*R*,9*R*,10*R*)-2,6-Diphenyl-1,5-diaza-*cis*-decalin (6). A mixture of **16** and 5% Rh/Al_2O_3 (0.147 g) in MeOH (9 mL) and HOAc (1 mL) was placed under 40 psi H_2 at room temperature. After 48 h, the mixture was diluted with CH_2Cl_2 and washed with 30% NaOH. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over K_2CO_3. After the solvent was evaporated under reduced pressure, the residue was chromatographed (SiO_2; 2% MeOH/$CHCl_3$) to give 43% of **6** (0.180 g) in two steps from **15**. R_f = 0.42 (20% MeOH/$CHCl_3$); $[\alpha]_D^{20}$ −1.34 (*c* 1.19, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 7.1 Hz, 4H), 7.35 (t, J = 7.6 Hz, 4H), 7.26 (t, J = 7.3 Hz, 2H), 3.75 (dd, J = 11.2, 2.8 Hz, 2H), 2.97 (dd, J = 2.5, 2.3 Hz, 2H), 1.89−1.92 (m, 4H), 1.74−1.88 (m, 2H), 1.74 (br s, 2H), 1.63 (dq, J = 12.8, 3.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 128.4, 127.0, 126.5, 61.9, 53.3, 31.6, 29.0; IR (film) 3424, 2922, 698 cm^{-1}; HRMS (CI) calcd for $C_{20}H_{24}N_2$ (M^+) 292.1939, found 292.1945.

(3*R*,7*R*,9*R*,10*R*)-*N*,*N*′-Di-*tert*-butoxycarbonyl-2,6-dioxo-3,7-dimethyl-1,5-diaza-*cis*-decalin (20). To a solution of **13**[8] (1.605 g, 4.35 mmol) in THF (60 mL) at −78 °C was added 9.2 mL (9.2 mmol, 2.1 equiv) of a 1.0 M LiHMDS solution by syringe pump at 0.12 mL/min rate. After an additional 6.5 h, MeI (2.2 mL, 8 equiv) was added. The resulting mixture was stirred overnight, with the temperature slowly rising to ambient. The reaction mixture was quenched with saturated brine and extracted three times with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated, and

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(22) See Supporting Information for the General Procedures section.

(23) (a) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1997**, *74*, 77−83. (b) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

the residue was chromatographed (SiO_2; 20% EtOAc/hexane) to afford **20** (0.842 g, 49%). R_f = 0.39 (50% EtOAc/hexane); mp 92−93 °C; $[\alpha]_D^{20}$ −95.3 (*c* 1.60, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55−4.59 (m, 2H), 2.68−2.75 (m, 2H), 2.12−2.18 (m, 2H), 1.96 (ddd, *J* = 14.0, 7.4, 4.8 Hz, 2H), 1.53 (s, 18H), 1.30 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 152.5, 83.9, 51.8, 35.3, 32.4, 27.9, 17.5; IR (film) 1769, 1720, 1251, 1151 cm^{-1}; MS (ES) *m*/*z* 419.2 (MNa^+). Anal. Calcd for $C_{20}H_{32}N_2O_6$: C, 60.59; H, 8.13; N, 7.06. Found: C, 60.39; H, 8.38; N, 7.02.

(3*R*,7*R*,9*R*,10*R*)-2,6-Dioxo-3,7-dimethyl-1,5-diaza-*cis*-decalin (21). A solution of **20** (0.842 g, 2.12 mmol) and TFA (5 mL) in CH_2Cl_2 (30 mL) was stirred at room temperature for 16 h, and then the volatiles were removed in vacuo. MeOH was added to the residue and then was removed under reduced pressure affording **21** (0.420 g, 100%) as a white solid. R_f = 0 (EtOAc); mp > 280 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (br s, 2H), 3.90 (s, 2H), 2.54−2.62 (m, 2H), 2.00 (ddd, *J* = 14.4, 5.4, 2.2 Hz, 2H), 1.78 (deformed t, *J* = 13.7 Hz, 2H), 1.25 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 49.5, 35.0, 29.5, 15.9; IR (film) 3188, 1651, 1622 cm^{-1}. Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.03; H, 8.53; N, 14.08.

(3*R*,7*R*,9*R*,10*R*)-3,7-Dimethyl-1,5-diaza-*cis*-decalin (9). A mixture of **21** (0.417 g, 2.12 mmol) and $LiAlH_4$ (2 g, 20 equiv) in THF (60 mL) was heated at reflux for 53 h, and then the mixture was cooled in ice−water. Excess $Na_2SO_4 \cdot 10H_2O$ was added. The resulting mixture was diluted with Et_2O and filtered through filter paper, and the solid was washed with Et_2O. The filtrate was concentrated under reduced pressure yielding **9** (0.360 g, 100%) as a waxy solid. R_f = 0.56 (Al_2O_3; 10% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ +31.4 (*c* 2.53, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.00 (ddd, *J* = 12.3, 3.9, 2.4 Hz, 2H), 2.63 (dd, *J* = 2.6, 2.2 Hz, 2H), 2.20 (dd, *J* = 11.9, 11.3 Hz, 2H), 1.81 (br s, 2H), 1.69−1.78 (m, 2H), 1.23−1.30 (m, 2H), 0.77 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.0, 53.9, 39.9, 26.3, 19.4; IR (film) 3285, 2949, 2924, 1651, 1456 cm^{-1}; HRMS (ES) calcd for $C_{10}H_{21}N_2$ (MH^+) 169.1705, found 169.1706.

(3*R*,7*R*,9*R*,10*R*)-1,3,5,7-Tetramethyl-1,5-diaza-*cis*-decalin (10). A mixture of **9** (0.357 g, 2.12 mmol), formaldehyde (10 mL, 37% w/w aq solution), and formic acid (5 mL, 88% w/w aq solution) was heated at 85 °C in an oil bath for 36 h. The cooled solution was adjusted to pH >14 with 30% aq NaOH and extracted three times with CH_2Cl_2. The extract was dried (K_2CO_3) and concentrated, and the residue was chromatographed (basic Al_2O_3; 2% MeOH/CH_2Cl_2) to afford **10** (0.341 g, 82%) as a solid. R_f = 0.76 (10% MeOH/CH_2Cl_2); mp 52−63 °C (hexane); $[\alpha]_D^{20}$ −26.7 (*c* 1.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (ddd, *J* = 10.9, 3.2, 2.4 Hz, 2H), 2.15 (s, 6H), 2.02−2.07 (m, 4H), 1.86 (deformed dd, *J* = 2.4, 1.8 Hz, 2H), 1.62 (dd, *J* = 11.0, 10.9 Hz, 2H), 0.92 (td, *J* = 13.6, 2.6 Hz, 2H), 0.79 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 65.8, 63.3, 42.7, 37.0, 25.5, 19.6; IR (film) 2944, 2776, 1453 cm^{-1}; HRMS (ES) calcd for $C_{12}H_{25}N_2$ (MH^+) 197.2018, found 197.2026.

Typical Procedure for Asymmetric Lithiation−Substitution of *N*,*N*-Diisopropyl-*o*-ethylbenzamide. To a solution of **10** (0.262 g, 1.34 mmol, 1.5 equiv) in MTBE (13 mL)/ pentane (13 mL) at −78 °C was added *s*-BuLi (1.05 mL, 1.23 M in cyclohexane, 1.30 mmol, 1.5 equiv). The reaction mixture was stirred for 40 min at −78 °C and then added to a precooled solution of *N*,*N*-diisopropyl-*o*-ethylbenzamide (0.200 g, 0.857 mmol, 1.0 equiv) in MTBE (13 mL)/pentane (13 mL) at −78 °C. The resulting purple reaction mixture was stirred for 6 h at −78 °C, and then 0.3 mL (4.0 equiv) of allyl bromide was added. The resulting mixture was stirred overnight, with the temperature slowly rising to ambient. The reaction mixture was quenched with MeOH (0.5 mL). After 0.5 h, the reaction mixture was diluted with 5% H_3PO_4 and extracted three times with Et_2O. The combined Et_2O extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography (SiO_2; 10% EtOAc/hexane) to give alkylated product (0.169 g, 72%). The analytical data were identical to those reported by Beak.[17] The enantiomeric purity was determined by HPLC using a Pirkle Covalent (*R*,*R*)-β-GEM 1 column (25 cm × 4.6 mm) with 1% *i*-PrOH/hexane at 1 mL/min: t_R (*R*) = 10.9 min, t_R (*S*) = 11.7 min.

The combined aqueous layers were adjusted to pH > 14 with 30% NaOH and then extracted three times with CH_2Cl_2, dried (K_2CO_3), and concentrated in vacuo. The residue was chromatographed (basic Al_2O_3; 3% MeOH/CH_2Cl_2) to afford 0.237 g (90%) of **10**, identical spectral data and rotation with the sample above.

Typical Procedure for Asymmetric Lithiation−Substitution of *N*-Boc-Pyrrolidine. To a solution of **10** (0.289 g, 1.47 mmol, 1.3 equiv) in Et_2O (10 mL) at −78 °C was added *s*-BuLi (1.14 mL, 1.29 M in cyclohexane, 1.47 mmol, 1.3 equiv). The reaction mixture was stirred for 25 min, and then a solution of *N*-Boc-pyrrolidine (0.188 g, 1.10 mmol, 1.0 equiv) in Et_2O (10 mL) was added by cannula. The reaction was allowed to stir for 6 h, TMSCl (0.3 mL, 2 equiv) was added, and the reaction was allowed to warm slowly to room-temperature overnight. The reaction was quenched by addition of 5% H_3PO_4, extracted with Et_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (SiO_2; 2−3% EtOAc/hexane) to afford 0.079 g (30%) of product. The analytical data were identical to those reported by Beak.[16] The enantiomeric purity was determined by GC using a chiral capillary Supelco β-Dex 120 column (30 m × 0.25 mm) at 95 °C and 30 psi: t_R (*S*) = 43.0 min, t_R (*R*) = 44.2 min.

Diamine **10** was recovered in 88% yield from the aqueous phase as described above.

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Supporting Information Available: Detailed experimental procedures and characterization data of compounds **18**, **19**, **7**, and **8** are provided as well as copies of the ^{1}H NMR and ^{13}C NMR spectra for compounds **3**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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