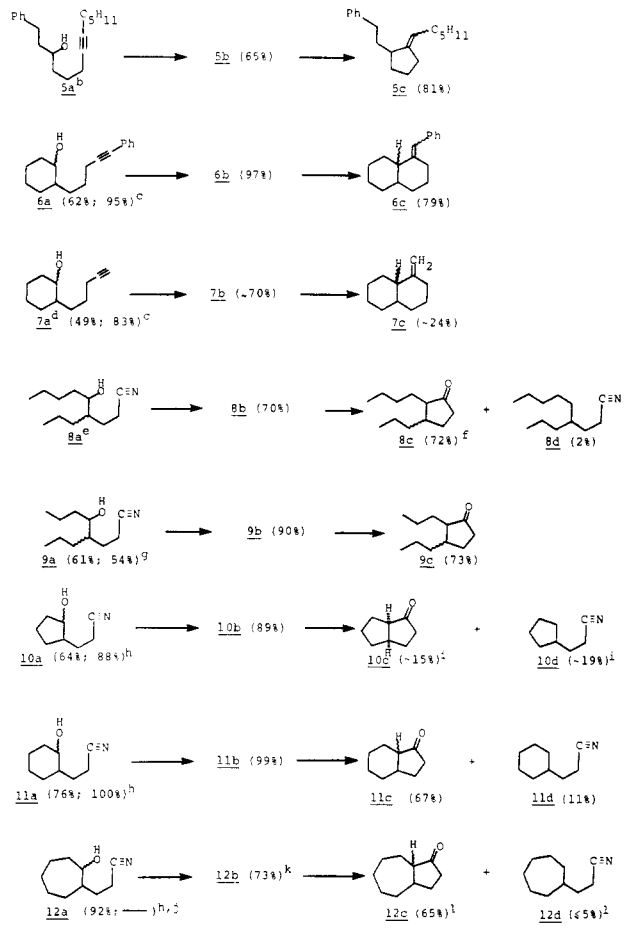
Scheme II[a]



[a] Yields refer to isolated material unless otherwise stated. The intermediate compounds **5b-12b** are the thiocarbonylimidazolides (cf. Scheme 1) corresponding to the alcohols **5a-12a**. Stereochemistries for **5c-9c, 11c** and **12c** were not established. [b] Prepared by Grignard reaction ($PhCH_2CH_2Br/Mg$) with undec-6-ynal [Svirskaya, P. I.; Leznoff, C. C.; Weatherston, J.; Laing, J. E. *J. Chem. Eng. Data* **1979**, *24*, 152.] Yield from undec-6-ynol, 59%. [c] First yield refers to alkylation of *N*-cyclohexylidenecyclohexanamine; second yield to carbonyl reduction ($LiAlH_4$). [d] Prepared by route analogoue to that used (see text) for **6a**. [e] The preparation of **8a** from the pyrrolidine enamine of 5-nonanone proceeded in poor yield: acyclic hydroxynitriles are better made from olefins: see ref 12 and Scheme II, **9a**. [f] >95% of one isomer. **8c** and **8d** were not separated; combined yield 74%; individual yields calculated by GLC. [g] First yield refers to hydroxymercuration product from (*Z*)-oct-4-ene (see ref 12); second yield refers to alkylation with acrylonitrile. [h] First yield refers to alkylation using a pyrrolidine enamine (cf. eq 2); second yield refers to carbonyl reduction ($NaBH_4$; THF or, for **8a**, 95% EtOH). [i] **10c** and **10d** were not separated: combined yield 39%; individual yields calculated by GLC. [j] The keto nitrile was processed directly to thiocarbonylimidazolide without purification of the intermediate alcohol. [k] Overall yield from keto nitrile. [l] **12c** and **12d** were not separated: combined yield 77%; individual yields calculated by GLC.

lenes (such as **6a**) are easily made by enolate alkylation (eq 1). Suitable hydroxy nitriles are readily accessible by the method of eq 2 and are also available[12] from olefins (eq 3; Scheme II, **9a**), so that the cyclization process constitutes a method for the potentially valuable transformation summarized in eq 4 ($n \geq 1$).

(4)

Reactions corresponding to eq 1 and Scheme I but involving hydroxy *olefins* are also feasible[8,15] and we have studied several examples. In such trigonal cyclizations functionality is destroyed; in contrast, the 5- and 6-exodigonal ring closures (Scheme I) provide compounds readily convertible into cyclic ketones and offer, therefore, numerous possibilities for further manipulations based on carbonyl chemistry.[16]

Acknowledgment of financial support is made to the Natural Sciences and Engineering Research Council of Canada and to the Alberta Heritage Foundation for Medical Research. We also thank NSERC for a Postgraduate Scholarship (to P.L.B.).[17]

Registry No. **5a**, 88854-20-0; **5b**, 88854-21-1; **5c**, 88854-22-2; **6a**, 88854-23-3; **6b**, 88854-24-4; **6c**, 88854-25-5; **7a**, 88854-26-6; **7b**, 88854-27-7; **7c**, 57662-70-1; **8a**, 88854-28-8; **8b**, 88854-29-9; **8c**, 88854-30-2; **9a**, 88854-31-3; **9b**, 88854-32-4; **9c**, 88854-33-5; **10a**, 88904-01-2; **10b**, 88867-01-0; **10c**, 32405-37-1; **10d**, 1123-04-2; **11a**, 21197-34-2; **11b**, 88854-34-6; **11c**, 29927-85-3; **11d**, 41010-09-7; **12a**, 88854-35-7; **12b**, 88854-36-8; **12c**, 10407-30-4; **12d**, 4448-80-0; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; 1-(1-pyrrolidinyl)cyclopentene, 7148-07-4; 1-(1-pyrrolidinyl)cyclohexene, 1125-99-1; 1-(1-pyrrolidinyl)-cycloheptene, 14092-11-6; *N*-cyclohexylidenecyclohexanamine, 10468-40-3; 1-phenyl-5-iodopent-1-yne, 34886-50-5; thiocarbonyldiimidazole, 6160-65-2.

Supplementary Material Available: Experimental and spectroscopic details for compounds **9a-c** (3 pages). Ordering information is given on any current masthead page.

(15) Cf. Beckwith, A. L. J.; Phillipou, G, Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811.
(16) Roberts, B. P.; Winter, J. N. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1353. Griller, D.; Schmid, P.; Ingold, K. U. *Can. J. Chem.* **1979**, *57*, 831.
(17) This work was reported at the Fourth International Conference on the Organic Chemistry of Selenium and Tellurium (Birmingham, U.K., July 25, 1983) and at the International Symposium on Heteroatoms for Organic Synthesis (Montreal, August 14, 1983).
(18) In part.

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Efficient One-Step Synthesis of a Cis Vicinal Tertiary Diamine and Its Complexation to a Lithium Carbanion Salt

Summary: *cis*-*N,N,N′,N′*-Tetramethyl-1,2-diaminopentane, obtained by reductive ($NaBH_4$) amination of 2-(dimethylamino)cyclopentanone, forms a 1:1 complex with the tight ion pair of a peralkylcyclohexadienyllithium salt.

Sir: The unique efficacy of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), compared to ethers, tertiary amines, and even 1,3-tertiary diamines, in catalyzing the metalation and addition reactions of alkyllithium compound[1] has been ascribed to its predilection to form five-membered bidentate chelates with lithium.[2]

One might imagine that a truly cis vicinal tertiary diamine would form strong complexes with organolithium compounds and spectacularly increase their reactivities.

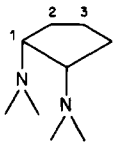
(1) Langer, A. W. *Trans. N.Y. Acad. Sci., Ser II* **1965**, *27*, 741.
(2) Zerger, R. P.; Stucky, G. D. *J. Chem. Soc., Chem. Commun.* **1973**, 44-45. Thoennes, D.; Weiss, E. *Chem. Ber.* **1978**, *111*, 3157.

0022-3263/84/1949-1314$01.50/0

Table I. ^{13}C NMR (75.47 MHz) Shifts (ppm/Me_4Si) of Ligands Free and with Salt 8, in Cyclopentane, 24 °C (concn, M)

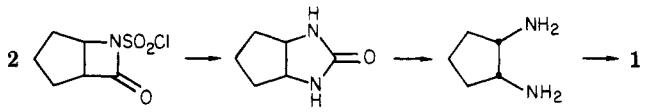
	NMP			1			
sample	CH_3	1	2	CH_3	1	2	3
NMP (0.6)	42.28	56.84	24.94				
NMP (1.2) 8 (0.6)	42.38	56.96	24.64				
1 (0.6)				44.50	69.09	27.18	23.11
NMP (1.2) 1 (0.7) 8 (0.6)	42.28	56.84	24.94	45.11 44.50	70.39 69.10	25.78 27.18	22.43 23.11

Such ligands have not been tried out. They are not commercially available nor are there simple, efficient, inexpensive ways to make them. Therefore this report addresses the synthesis of *cis-N,N,N',N'*-tetramethyl-1,2-diaminocyclopentane (1) and the structure of its complex with a lithium carbanion salt.



1

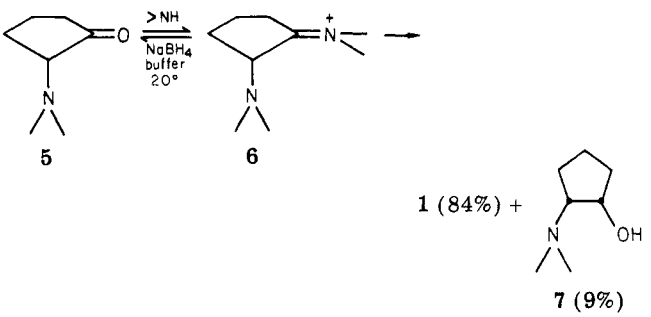
Compound 1 has now been prepared by two routes: Curtius rearrangement[3] (triethylammonium azide/CH_2Cl_2/0 °C, then refluxing xylene) of the cycloadduct[4] 2 of CSI and cyclopentene gives cyclic urea 3, which after



3 4

hydrolysis to cis diamine 4[5] and alkylation yielded 1 in 8% yield (seven steps) based on cyclopentene: bp 40 °C (0.8 torr), picrate mp 195–197 °C; ^{13}C NMR, Table I; ^1H NMR (CCl_4) δ 1.7 (CH_2), 2.3 (CH_3), 2.6 (CH).

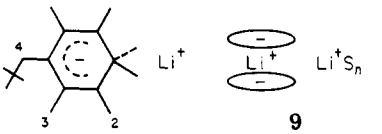
A more efficient route to 1 is the slow addition at 0 °C of $NaBH_4$ (44 mmol in 40 mL of water) to a mixture of 2-(dimethylamino)cyclopentanone (5) (30 mmol), excess dimethylamine (363 mmol), sodium acetate (18.3 mmol), acetic acid (245 mmol), THF (50 mL), and methanol (20 mL), resulting in 3.6 g (84% based on amino ketone) of a compound identical with 1 (NMR, IR, MS, mixed picrates), described above, and 9% of *cis*-2-(dimethylamino)cyclopentanol (7).



5 6 1 (84%) + 7 (9%)

A key feature of the reductive amination procedure is that slow addition of $NaBH_4$ allows time to reestablish the equilibrium concentration of iminium ion 6; faster addition gives relatively more of 7. Also the trans (to CH_3N) addition of hydride to 6 must be favored due to crowding around the two nitrogens.

Finally we have investigated the interaction of 1 with an ion-paired salt, 8, formed by the addition of *tert*-butyllithium to 1,1,2,3,5,6-hexamethyl-4-methylenecyclohexa-2,5-diene.[6] We reported how 8 forms just two kinds of ion pairs identified by their NMR spectra since exchange of ions among ion pairs is slow relative to the NMR time scale.[7] With ethers, 8 forms a dimeric loose ion pair 9 with ^7Li shifts at 0 and −8 ppm (relative to external LiCl in methanol) while in the presence of tertiary amines only monomeric tight ion pairs (TIP) are formed, with ^7Li resonance at ca. −4 ppm.



8 9

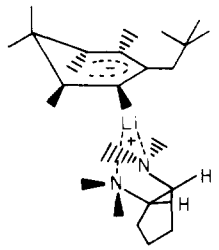
The ^{13}C NMR spectrum of 0.6 M 8 in cyclopentane containing *N*-methylpyrrolidine (NMP), 1.2 M, shows that some NMP is bonded to Li^+ since the ligand shifts are different from those for free NMP, see Table I. Addition of diamine 1, 0.7 M, to the latter solution replaces lithium-bound NMP with bound 1; the NMP shifts are now identical with those for free NMP while diamine gives rise to *two spectra* one with shifts the same as free diamine and one for bound diamine. Intensities of resonances due to free ligand increased correspondingly on addition of a second equivalent of 1. From the ratio of the two sets of resonances of 1, one can infer that one molecule of diamine is bound to each lithium. This is one of the very few cases where ligand exchange is slow relative to the NMR time scale.

The complexation of 1 with 8 produces significant downfield shifts, relative to the NMP complex, for the ring ^{13}C methyl and CH_2 resonances in the anion,[8] as well as the *N*-methyls and tertiary carbons of 1, see Table I. Most likely this is the result of steric compression between the methyls of the anion and ligand in a TIP.[9] This is also confirmed by the ^7Li shift of ca. −3.5 ppm, close to the Li^+ shift for all TIP complexes of tertiary amines with 1.

On the basis of the above results we would like to propose that the complex of 8 with 1 is best described by 10.

In summary, this communication reports how reductive amination of a 2-amino ketone efficiently produces a cis tertiary diamine (1),[10] establishes the structure of its

(3) Typical conditions: Fliri, A.; Hohenlohe-Oehringen, K. *Chem. Ber.* **1980**, *113*, 607–613.
(4) Bestian, H.; Biener, H.; Clauss, K.; Heyn, H. *Liebigs Ann. Chem.* **1968**, *718*, 94–100.
(5) All new compounds gave NMR spectral and elemental analytical data in accord with the assigned structures.
(6) Hallden-Abberton, M. P.; Engelman, C.; Fraenkel, G. *J. Org. Chem.* **1981**, *46*, 538.
(7) Fraenkel, G.; Hallden-Abberton, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 5657–5664.
(8) In the order 2-methyl, 3-methyl, and 4-methylene, ^{13}C NMR shifts in 11 are with NMP (1 equiv), 13.44, 16.80, and 41.51 ppm, with 1 equiv of NMP and 1 equiv of 1, 14.47, 17.53, and 43.18 ppm, respectively.
(9) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; pp 179–180.
(10) Stereospecific cis tertiary amination can be accomplished via aminopalladatian: Bäckvall, J. *Tetrahedron Lett.* **1978**, 163–166.



10

complex with a tight ion paired salt, and demonstrates that exchange of cis diamine between its bound and free states is slow relative to the NMR time scale.

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Registry No. 1, 89121-43-7; 1·xpicrate, 89121-44-8; 2, 68703-21-9; 3, 5587-80-4; 4, 40535-45-3; 5, 55154-09-1; 7, 57070-96-9; 8, 79376-82-2; 10, 89121-45-9.

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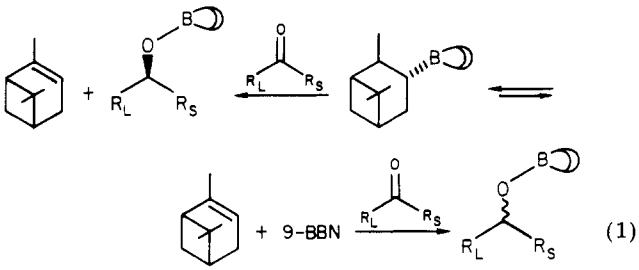
Asymmetric Reduction of Prochiral Ketones with *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane in Efficiencies Approaching 100%. Simultaneous Rate Enhancement and Side Reaction Suppression via the Use of Elevated Pressures

Summary: Elevated pressures (up to 6000 atm) significantly accelerate the asymmetric reduction of prochiral ketones with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane while suppressing the competing dehydroboration–reduction process. In selected cases enantiomeric efficiencies approaching 100% may now be achieved.

Sir: *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane, Aldrich)[1] is a very effective asymmetric reducing agent for 1-deuterio aldehydes[2] and α,β-acetylenic ketones.[3] Unfortunately, prochiral ketones of moderate steric bulk are only reduced slowly, and often several days or weeks are required for the reaction to reach completion.[4] Additionally, as the rate of reduction slows, the enantiomeric purity of the product alcohol diminishes through the intervention of a side reaction. We herein report that elevated pressures completely suppress the dissociative side reaction while enhancing the rate of the desired reaction. Enantiomeric efficiencies approaching 100% may thus be obtained.

Two competing reaction pathways are believed to be involved in the reduction of ketones by Alpine-Borane: a bimolecular β-hydride elimination process leading to optically active product[5] and a dehydroboration–reduction sequence yielding racemic product[6] (eq 1). We felt that

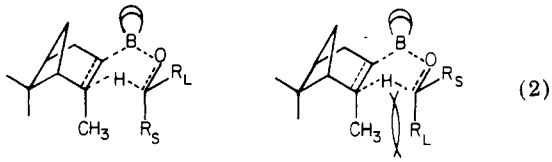


(1)

the bimolecular process should be favorably influenced by pressure while the undesired dissociation process should be suppressed. Indeed at 2000 atm[7] and 25 °C, the desired asymmetric reductions are accelerated approximately 3-fold. Additionally, the undersired side reaction leading to racemic product is completely suppressed, thereby providing a significant increase in the enantiomeric purity. A further increase in pressure to 6000 atm provides an approximately 15-fold acceleration in rate over the corresponding reactions at 1 atm.[8] Thus, acetophenone is reduced in 3 days with an enantiomeric efficiency of >98% at 2000 atm and is completely reduced in less than 24 h at 6000 atm.

In order to delineate the scope of the reduction, a variety of ketones were examined (Table I). The enantioselectivities are largely determined by the steric size of the groups flanking the carbonyl. Acetophenone and 3-acetylpyridine are reduced with virtually complete selectivity as is the fairly bulky 2,2-dimethyl-5-(trimethylsilyl)-4-pentyn-3-one. The aliphatic ketone 3-methyl-2-butanone is reduced in over 90% efficiency. Surprisingly, even 2-octanone, in which the steric differences between the methyl and the *n*-alkyl group are slight, is reduced with better than 60% efficiency. These last two cases are particularly noteworthy since reductions of aliphatic ketones remain among the most difficult processes in asymmetric synthesis. In several cases, the enantiomeric purity of the product is limited by the purity of the α-pinene. Since optically enriched α-pinene is available,[9] this problem is overcome.

We postulate that the reductions are taking place via a cyclic "boat-like" transition state (eq 2) and that the



favored disfavored

(2)

(1) *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane is commericially available from Aldrich Chemical Co. under the trademark Alpine-Borane as a 0.5 M solution in THF. For the preparation of this reagent see ref 2.

(2) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.

(3) (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (b) Midland, M. M.; Graham, R. S. *Org. Synth.*, submitted for publication.

(4) (a) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606. (b) Brown, H. C.; Pai, G. G. *Ibid.* **1983**, *48*, 1784.

(5) Midland, M. M.; Zderic, S. A. *J. Am. Chem. Soc.* **1982**, *104*, 525.

(6) Midland, M. M.; Petre, J. E.; Zderic, S. A.; Kazubski, A. *J. Am. Chem. Soc.* **1982**, *104*, 528.

(7) Lockyer, G. D., Jr., Owen, D.; Crew, D.; Neuman, R. C., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7303. Lockyer, G. D. Ph.D. Dissertation, University of California, Riverside, 1975. This apparatus consisted of a manually operated hydraulic pump, pressure gauge, valve, and reaction vessel. Also see: Rogers, V. E.; Angell, C. A. *J. Chem. Ed.* **1983**, *60*, 602.

(8) Neuman, R. C., Jr.; Behar, J. V. *J. Am. Chem. Soc.* **1969**, *91*, 6024. Le Noble, W. J. *Ibid.* **1963**, *85*, 1470. This high-pressure vessel has internal dimensions of 1 in. in diameter and 9 in. in depth.

(9) (+)-α-Pinene of 92% ee was purified to 98.5% ee: Brown, H. C.; Jadhav, P. K.; Desai, M. C. *J. Org. Chem.* **1982**, *47*, 4583. Optically enriched α-pinene is now available from Aldrich Chemical Co.

0022-3263/84/1949-1316$01.50/0