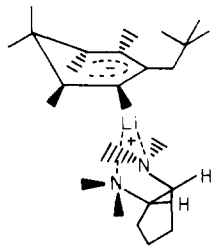

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complex with a tight ion paired salt, and demonstrates that exchange of cis diamine between its bound and free states is slow relative to the NMR time scale.

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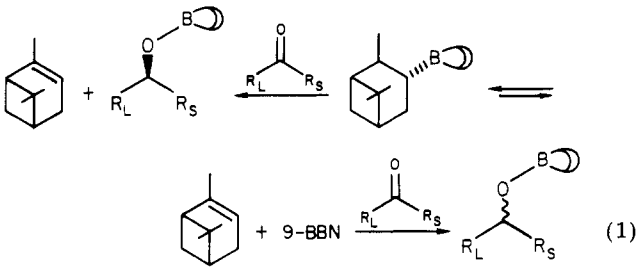
Asymmetric Reduction of Prochiral Ketones with *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane in Efficiencies Approaching 100%. Simultaneous Rate Enhancement and Side Reaction Suppression via the Use of Elevated Pressures

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

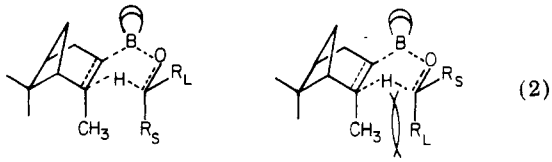


(1)

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



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(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.

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Table I. Reductions of Prochiral Ketones with Neat *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane at 6000 atm (92% ee (+)-α-Pinene)

ketone	reaction time, days: 6000 atm[a]	reaction time, days: 1 atm[b]	%ee[c]: 6000 atm	%ee[c]: (corrected[d])	%ee[c]: 1 atm	isolated yield	abs config[e]
acetophenone	1	7[4a]	92	(100)	78[4a]	80	*S*
acetophenone	1		98.4[f]			83	*S*
3-acetylpyridine	1.5[g]	2	92	(100)	90	67	*S*
2,2-dimethyl-5-(trimethylsilyl)-4-pentyn-3-one	2.5[h]	NR[i]	92	(100)	*i*		(*R*)[j]
3-methyl-2-butanone	1	14[4a]	83	(90)	57[4a]	47	*S*
α-tetralone	3	29	82	(89)	52	43	*S*
cyclopropyl methyl ketone	5.5	NR[i]	69	(75)	*i*	65	(*S*)[j]
trans-4-phenyl-3-buten-2-one	<1	3	65	(71)	58		*S*
2-octanone	<1	7[4a]	58	(63)	44[4a]	63	*S*

[a] Reaction carried to >97% completion. [b] Reaction typically carried to 60–75% completion except as noted in ref 4a. [c] %ee determined by proton chiral shift study at 200 MHz with $Eu(hfc)_3$. [d] Corrected for 92% ee (+)-α-pinene. [e] Determined by sign of rotation. [f] 98.5% ee (+)-α-pinene was used. [g] 1.0 mL of THF added per 10.0 mmol of borane. [h] Reaction was 83% complete. [i] Reaction at 1 atm too slow to be useful. [j] Configuration based on proposed mechanism.

selectivity is largely due to a 1,3-diaxial repulsion of the 3-methyl group of the pinane skeleton and the larger group of the approaching ketone. In all cases thus far observed, this model predicts the proper stereochemistry of the product alcohols. From the data in Table I and other data,[2-4] one may group the substituents according to steric bulk into categories of very small (acetylene, nitrile, hydrogen), small (methyl, carbomethoxy), medium (*n*-alkyl, vinyl), medium-large (trifluoromethyl), large (aryl, isopropyl), and very large (*tert*-butyl). Ketones containing substituents from the same or two adjacent categories will be reduced with low selectivity while ketones with substituents from two nonadjacent categories will provide alcohols in higher ee's.

The use of high pressure allows one to achieve reductions of moderately bulky ketones such as 2,2-dimethyl-5-(trimethylsilyl)-4-pentyn-3-one, cyclopropyl methyl ketone, and α-tetralone. These ketones are reduced only sluggishly or not at all at atmospheric pressure. Only 3,3-dimethyl-2-butanone failed to react at high pressure (9 days, 6000 atm). This compound is slowly reduced at atmospheric pressure (70% in 40 days)[4a] to racemic product, presumably by the dissociative process. Our results thus indicate that even at 2000 atm the dehydroboration process is essentially stopped.

In a typical procedure, Alpine-Borane is first formed as a 0.5 M THF solution.[1,3] The solvent is then removed under reduced pressure at 30 °C;[4] 0.5 equiv of a prochiral ketone is then added, and the mixture is transfered to a disposable syringe and placed in the high-pressure apparatus. After the reaction is deemed complete (>97% reduction), the sample is quenched with an aldehyde (i.e., 1.0 equiv of propionaldehyde, room temperature 1 h). The chiral alcohol product is isolated after either oxidative workup[3b] (1 equiv of 3 N NaOH followed by 3 equiv of 30% hydrogen peroxide, 40–50 °C in THF for 2 h) or ethanolamine complexation of the borane[2] (1.1 equiv of ethanolamine in ether, 0 °C) followed by chromatography and/or Kügelrohr distillation.

Our results thus indicate that pressures as low as 2000 atm can provide the rather unique ability to accelerate a desired process while stopping an undersired reaction. Increases of pressure above 2000 atm serve to further accelerate the rate of reduction. As the wide variety of ketones studied indicate, good to excellent enantiomeric excesses may be obtained with Alpine-Borane if the steric differences between the two substituents of the prochiral ketone are large enough. The enantiomeric alcohols should be readily available through the use of (−)-α-pinene or nopol.[10] We are currently exploring further applications of this novel use of high-pressure chemistry.

Acknowledgment. We thank the National Institutes of Health (GM-24517) for support of this work and Professor R. C. Neuman for helpful discussions and for the use of the high-pressure apparatus.

Registry No. $Me_3SiC{\equiv}CC(O)C(CH_3)_3$, 53723-94-7; (*S*)-$PhCH(OH)CH_3$, 1445-91-6; (*R*)-$Me_3SiC{\equiv}CCH(OH)C(CH_3)$, 89017-38-9; acetophenone, 98-86-2; 3-acetylpyridine, 350-03-8; 3-methyl-2-butanone, 563-80-4; α-tetralone, 529-34-0; cyclopropyl methyl ketone, 765-43-5; *trans*-4-phenyl-3-buten-2-one, 1896-62-4; 2-octanone, 111-13-7; *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane, 64106-79-2; (*S*)-3-(1-hydroxyethyl)pyridine, 5096-11-7; (*S*)-3-methyl-2-butanol, 1517-66-4; (*S*)-α-tetralol, 53732-47-1; (*S*)-1-cyclopropylethanol, 55637-37-1; (*S*)-*trans*-4-phenyl-3-buten-2-ol, 81176-43-4; (*S*)-2-octanol, 6169-06-8.

(10) Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2814.

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Silicon in Organic Synthesis. 23. Chloro[(trimethylsilyl)methyl]ketene as a Useful Intermediate for the Elaboration of α-Methylenecyclobutanones and -cyclopentanones[1]

Summary: The title ketene, which is readily available by dehydrohalogention of the α-chloro acid chloride, adds to cyclopentadiene, vinyl ethers, and silyl enol ethers to give cyclobutanones with complete stereocontrol (and regiocontrol where relevant). These products enter regiospecifically into ring expansion with diazomethane. Both sets of molecules experience desilylative elimination with introduction of an α-methylene group on reaction with fluoride ion in an anhydrous dipolar solvent at room temperature.

Sir: Although methyleneketene ($CH_2{=}C{=}C{=}O$) could well service several synthetic objectives, the elusiveness and instability of this substance[2] preclude its widespread

(1) Part 22: DeLucca, G.; Paquette, L. A. *Tetrahedron Lett.* **1983**, *24*, 4931.

0022-3263/84/1949-1317$01.50/0