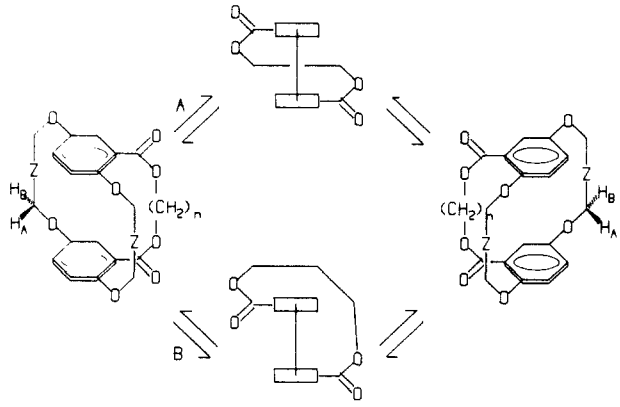
Scheme I[a]



[a] A, donut-hole, mechanism; B, jump rope mechanism. **2**·*n*, Z = —C≡C—C≡C—, *n* = 3-11; **2**·11′, $(CH_2)_n$ = —$(CH_2)_5CMe_2(CH_2)_5$—; **3**·*n*, Z = "bd$(CH_2)_4$—, *n* = 3-11.

Table I. Stereodynamics of **2**·*n* and **3**·*n*

	RT^a	T_c^b	$\Delta G^{\ddagger}_{298}$, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$
2·3	slow	>>180	21.4	14.2	-24
2·4	slow				
2·6	slow	>180	~20-21		
2·7	slow	~160	19.2	16.4	-12.7
2·8	slow	103			
2·9	slow	+73	16.5	13.6	-9.6
2·10	int.	+12	13.8	15.0	+4.0
2·11	fast	-43	10.4	13.8	+11.5
2·11′	fast	-35			
3·3	slow	>>180	>26		
3·7	slow	>>160	>23.3		
3·8	slow	~110			
3·9	int.	+16			
3·10	fast	-24	12.8	9.4	-11.4
3·11	fast	<<-50			

[a] Behavior on NMR time scale (room temperature, 270 MHz). [b] Coalescence temperature (°C), 270 MHz.

Cyclophanes were synthesized[5,6] from $Br(CH_2)_nBr$.[7] Inversion rates were measured by line-shape analysis of the interconverting OCH_2 AB quartets[8] or by the Forsén-Hoffman saturation-transfer technique.[9] Results for series **2**·*n* and **3**·*n* are shown in Table I.

When *n* is less than ~8, ring-inversion barriers are *much* greater for **2**·*n* and **3**·*n* than for the corresponding **1**. A $\Delta G^{\ddagger}_{298}$ of 17 kcal/mol for **1a**·3 (*N*-propyl ester)[3a] may be compared with $\Delta G^{\ddagger}_{298} \geq 21$ kcal/mol for **2**·3 and >26 kcal/mol (minimum estimate) for **3**·3. These results are consistent only with a donut-hole process.

For large *n* ($n \geq 9$), the barriers are much *smaller* for **2**·*n* and **3**·*n* than for **1**·*n*. We assign the jump rope mechanism here: (a) For large *n* the donut-hole barrier should be *no less* for **2**·*n* and **3**·*n* than for **1**·*n*. The jump rope process, however, passes the unsubstituted side of the arene through the cavity; this has a very low barrier. (b) The compact cyclophanes have *lower* barriers than the rigid cyclophanes (e.g., **3**·10 vs. **2**·10). The jump rope mechanism predicts this, as the diester passes around the exterior of the cyclophane; the donut-hole mechanism predicts the opposite.[3a] (c) Geminal dimethylation of the middle of the chain of **2**·11 (to give **2**·11′) does not increase the barrier: the quaternary carbon must not be passing through the cavity.[3a,10]

Registry No. **2**·3, 84198-45-8; **2**·4, 102073-04-1; **2**·6, 102073-05-2; **2**·7, 102073-06-3; **2**·8, 102073-07-4; **2**·9, 102073-08-5; **2**·10, 102073-09-6; **2**·11, 102073-10-9; **2**·11′, 102073-11-0; **3**·3, 84198-46-9; **3**·7, 102073-12-1; **3**·8, 102073-13-2; **3**·9, 102073-14-3; **3**·10, 102073-15-4; **3**·11, 102073-16-5.

(10) Financial support by the National Science Foundation is acknowledged.

(5) (a) Jarvi, E. T.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 657-662. (b) Brown, A. B.; Haller, K. J.; Whitlock, H. W., Jr. *Tetrahedron Lett.* **1982**, *23*, 3311-3314.

(6) (a) Jarvi, E. T.; Whitlock, H. W. *J. Am. Chem. Soc.* **1982**, *104*, 7196-7204. (b) Miller, S. P.; Whitlock, H. W., Jr. *Ibid.* **1984**, *106*, 1492-1493.

(7) (1) 2-Hydroxy-5-(propargyloxy)benzoic acid, Et_3N, DMF; (2) $Cu(OAc)_2$, pyridine, 40 °C; (3) $HC{\equiv}CCH_2Br$, K_2CO_3, DMF; (4) $Cu(OAc)_2$, pyridine, 40 °C (to give **2**·*n*); (5) H_2, Rh/Al_2O_3, EtOAc (giving **3**·*n*).

(8) Binsch, G. In *Dynamic Nuclear Magnetic Resonance Spectroscopy*; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; pp 45-81.

(9) Led, J. J.; Gesmar, H. *J. Magn. Reson.* **1982**, *49*, 444-463.

A Rationally Designed, Chiral Lewis Acid for the Asymmetric Induction of Some Diels-Alder Reactions

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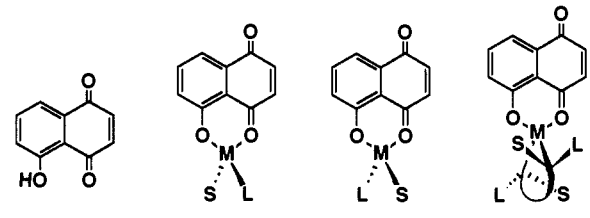
Received February 18, 1986

Development of methods for the asymmetric induction of Diels-Alder reactions is of considerable current interest.[1] The use of chiral auxiliaries to this end has provided some notable solutions to specific problems, but the need to invest separate reaction steps in the incorporation and subsequent jettisoning of the auxiliary is a generally inherent limitation. Chiral Lewis acids, were they available, would offer an attractive alternative, particularly if three results attended their use: predictable absolute chirality of product, high levels of enantiomeric excess (ee), and compatibility with varied substrate structures. To date, there have been only a few reports[2] of attempts to employ chiral Lewis acids in Diels-Alder reactions, and none satisfies any of the above criteria. We now describe a system which does.

peri-Hydroxyquinones such as juglone (**1**) are attractive candidates for the use of chiral Lewis acids because the hydroxy group can serve as a second ligand to the Lewis acid, thereby greatly diminishing conformational mobility in the complex. Thus in the generalized complex **2**, if L is sufficiently large to block attack of a diene on the top face of the quinone while S is sufficiently small to still permit approach of the diene on the bottom face, asymmetric induction should result. The utility of **2** appears severely compromised, however, because it must be prepared without simultaneous generation of its enantiomer (**3**). But this apparent difficulty can be circumvented by incorporating both S and L into a single, bidentate ligand possessing C_2 symmetry,[3]



1 2 3 4

S=small group, L=large group, M=metal

(1) For recent reviews, see: (a) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3B, pp 455-501. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876-889.

(2) Guseinov, M. M.; Akhmedov, I. M.; Mamedov, E. G. *Azerb. Khim. Zh.* **1976**, 46-48; *Chem. Abstr.* **1976**, *85*, 176925z. Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437-438. Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716-3717; **1983**, *105*, 6968-6969. Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451-3454.

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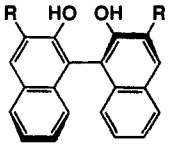
in which event *only one* complex (e.g., **4**) can be formed.

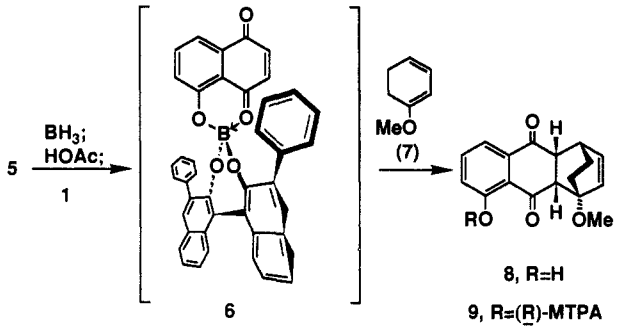
In the specific, reaction of **1** via a complex we propose to be **6** (prepared from (*S*)-**5**[4] as indicated[5]) with 1-methoxycyclo-



(S)-5, R=phenyl

(S)-10, R=Me

hexa-1,3-diene (**7**) proceeds rapidly[5,6] (−78 °C, <2 min) and regiospecifically[7a,b] to give the adduct **8** in high chemical yield with >98% ee as determined by ^{19}F NMR spectroscopy of the (*R*)-α-methoxy-α-(trifluoromethyl)phenyl acetate derivative[8] **9**. The chiral ligand (**5**) is recovered in full.



6

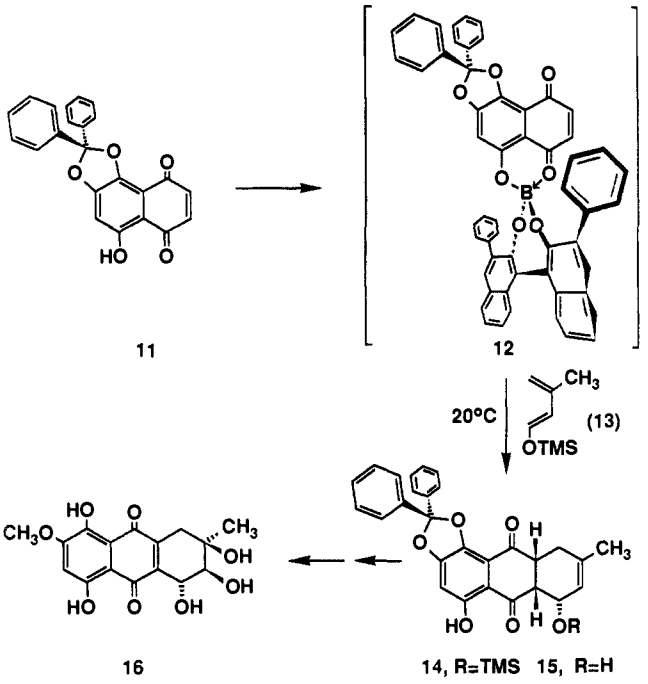
8, R=H

9, R=(R)-MTPA

It has not yet been possible to obtain direct (e.g., X-ray) evidence demonstrating the intermediacy of **6**, but its existence is supported by the three experiments described below.

First, one would predict that replacement of the two phenyl substituents in **6** by (smaller) methyls would cause the Diels–Alder reaction to proceed with poorer ee. This prediction is borne out: replacement of **5** by **10**[9] in eq 1 gives under otherwise identical conditions the same enantiomer of **8** but in only 70% (vs. >98%) ee.

Second, asymmetric induction should not be restricted to the specific case in eq 1; i.e., it should also be achievable with other dienes and other *peri*-hydroxyquinones. In both of the other reactions we have examined to date (eq 2 and 3), this expectation is realized. Thus, use of the same type of chiral Lewis acid complex (**12**) in the reaction of **11**[10] with **13** (eq 2) gives **14** regiospecifically in high (>90%)[11] ee [the degree of asymmetric



11

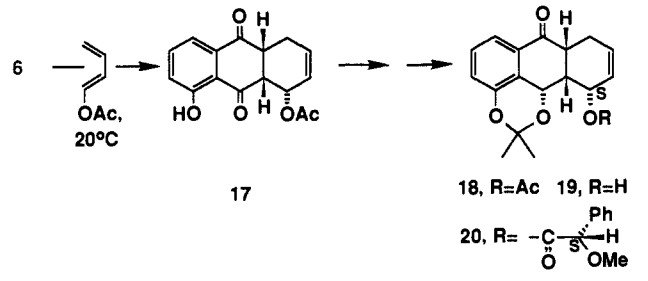
12

16

14, R=TMS 15, R=H

induction was determined by conversion of **14** to (−)-bostrycin (**16**)[12] using a sequence previously developed[10] for the synthesis of (±)-bostrycin; the overall yield of (−)-**16** from **11** is 51%].

Third, if complexes such as **6** and **12** are operative, then the absolute stereochemistry of the adducts **8** and **14** should be as shown. It has not been possible so far to determine the absolute stereochemistries of **8** and **14**,[13] but the absolute stereochemistry of the adduct (**17**, >98% ee) produced regiospecifically in eq 3



17

18, R=Ac 19, R=H

20, R=

(note the successful use of yet another diene) has been established as that shown by conversion[14] to **18** (68% overall yield from **1**) and then[15] to **20**, whose absolute structure is known.[14a] Racemic **17** has played a prominent role in the synthesis of tetracycline-type substances.[14b,16]

(3) For a review of chiral organic molecules with high symmetry, see: Nakazaki, M. *Top. Stereochem.* **1984**, *15*, 199–251.

(4) Lingenfelter, D. S.; Helgeson, R. C.; Cram, D. J. *J. Org. Chem.* **1981**, *46*, 393–406.

(5) **Representative Procedure.** To a stirred mixture of 100 mg (0.23 mmol) of (*S*)-**5** and 0.23 mmol of BH_3·THF in 5 mL of dry THF under Ar was added, at 20 °C, 0.23 mmol of dry AcOH[7a] (AcOH accelerates the otherwise very slow[7c] reaction between **5** and BH_3·THF). After 10 min, volatiles were removed under high vacuum. The colorless residue was dissolved in 5 mL of THF, a (orange) solution of 0.115 mmol of **1** in 2 mL of THF was added, and the resulting deep red solution was cooled to −78 °C. Addition of 30 μL of 70%-pure **7** (Aldrich) caused immediate decolorization. After 2 min, 200 μL of H_2O was added [TLC (silica, 4:1 petroleum ether/EtOAc) showed the presence of only **5** and **8**] and the mixture was warmed to 20 °C. Purification by partition between EtOAc and H_2O followed by preparatory TLC gave **8**, mp 114 °C, with partial decomposition beginning at 100 °C, $[\alpha]^{22}_D$ −125.3° (*c* 0.85, CH_2Cl_2), in 70–90% yield (**8** is somewhat unstable to chromatography), and quantitative recovery of pure (*S*)-**5**.

(6) The reaction of **1** and **7** without complex or catalyst is less than half complete after 48 h at −78 °C (Boudet, B., unpublished observation).

(7) Compare, inter alia: (a) Kelly, T. R.; Montury, M. *Tetrahedron Lett.* **1978**, 4311–4314. (b) Kelly, T. R.; Ananthasubramanian, L.; Borah, K.; Gillard, J. W.; Goerner, R. N., Jr.; King, P. F.; Lyding, J. M.; Tsang,; W.-G.; Vaya, J. *Tetrahedron* **1984**, *40*, 4569–4577. (c) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 1637–1646.

(8) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.

(9) Prepared in 85% yield by bis ortholithiation (see ref 4) of (*S*)-2,2′-dimethoxy-1,1′-binaphthyl and methylation (CH_3I, 24 h). For an alternate preparation, see: Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domier, L. A.; Moreau, P. M.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930–1946.

(10) Kelly, T. R.; Saha, J. K.; Whittle, R. R. *J. Org. Chem.* **1985**, *50*, 3679–3685.

(11) Because of the intense color of bostrycin, only very dilute solutions (*c* ~0.01, 1.0-dm cells) could be used for determining optical rotations. The synthetic and natural[12] samples of **16** have identical rotations, $[\alpha]^{22}_D$ −295° (*c* 0.012, Me_2SO), but the accuracy of the measurement is ±10%. A value of $[\alpha]^{22}_D$ −81° (*c* 1.19, Me_2SO, cell length unspecified) has been reported: Stevens, K. L.; Badar-ud-Din; Ahmad, A.; Ahmad, M. *Phytochemistry* **1979**, *18*, 1579–1580.

(12) Noda, T.; Take, T.; Watanabe, T.; Abe, J. *Tetrahedron* **1970**, *26*, 1339–1346. We thank Dr. Noda for an authentic sample.

(13) The absolute stereochemistry of natural bostrycin has not been rigorously established.[11]

(14) (a) Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595–7596. (b) Trost, B. M.; Caldwell, G. C.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252–3265. We thank Drs. O'Krongly and Caldwell for providing additional details.

(15) Conversion of **19** to **20** used "Method 3" in: Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christry, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.*, in press. We thank Prof. Trost for a preprint.

(16) (a) Stork, G.; Hagedorn, A. A., III *J. Am. Chem. Soc.* **1978**, *100*, 3609–3510. (b) Kolosov, M. N.; Popravko, S. A.; Shemyakin, M. M. *Justus Leibigs Ann. Chem.* **1963**, *668*, 86–91. Gurevich, A. I.; Karapetyan, M. G.; Kolosov, M. N.; Korobko, V. G.; Onoprienko, V. V.; Popravko, S. A.; Shemyakin, M. M. *Tetrahedron Lett.* **1967**, 131–134. (c) See also: Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554–3572. (d) Inhoffen, H. H.; Muxfeldt, H.; Schaefer, H.; Kramer, H. *Croat. Chem. Acta* **1957**, *29*, 329–345.

We submit that the foregoing results demonstrate the viability of the overall design strategy inherent in **4**. Further studies are in progress.[17]

Acknowledgment. Support of this project by Grant CA-17631 from the National Cancer Institute is gratefully apppreciated. We thank Drs. B. Boudet, J. Steele, P. King, and Z.-H. Chen for their contributions to earlier parts of this work, Dr. D. A. Evans and K. Chapman (Harvard University) for a helpful discussion, and Dr. G. R. Weisman (University of New Hampshire) for a valuable suggestion.

(17) Other[5,11] $[\alpha]^{22}_D$'s (in CH_2Cl_2) and mp's of stable solids: **9**, +93.7° (*c* 0.30); **15**, +160.4° (*c* 1.0); **18** [mp 215-217 °C (lit.[14b] mp for (±)-**18**: 212-213 °C)], +344° (*c* 1.0); **19** (mp 132-133 °C), +333° (*c* 1.0). All compounds gave spectra consistent with the structures assigned.

Reactions of Allylsilanes with Simple Iminium Salts in Water: A Facile Route to Piperidines via an Aminomethano Desilylation-Cyclization Process

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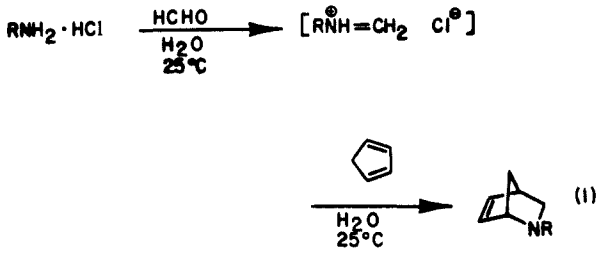
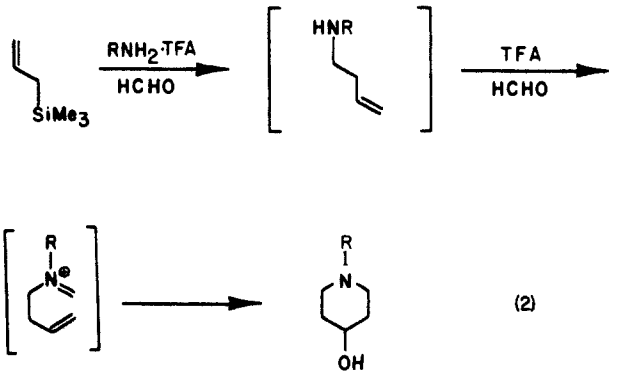
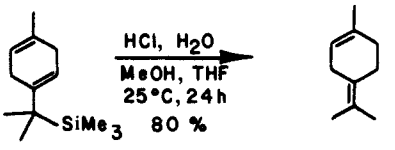
We recently demonstrated that simple iminium salts generated in aqueous medium are sufficiently reactive to undergo [4 + 2] cyclocondensation with unactivated dienes (cf. eq 1).[1] In con-



nection with an ongoing project it was of interest to determine if iminium ion chemistry could be extended to allylsilanes in water.[2] The well-documented reactivity of allylsilanes toward electrophiles[3-5] suggested that treatment of allyltrimethylsilane with an *N*-alkyliminium ion under Mannich-like conditions should provide access to homoallylamines via an aminomethano desilylation process. It was anticipated that subsequent reaction of the homoallylamine with formaldehyde would lead exclusively to 4-substituted *N*-alkylpiperidines via an intramolecular olefin-iminium ion cyclization[6] (eq 2). Of particular concern was the fact

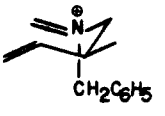


that the acidic conditions (pH 3-4) required to generate iminium ions in aqueous medium would not be compatible with the initial aminomethano desilylation process. It is well established that allylsilanes readily undergo protodesilylation in acidic media.[3] For example exposure of (dihydrobenzyl)silane **1** to hydrochloric acid in aqueous methanol-tetrahydrofuran at ambient temperature for 20 h gives rise to an 80% yield of terpinoline (**2**).[7]



1 2

In order to probe the chemistry depicted in eq 2, a heterogeneous mixture of allyltrimethylsilane, *N*-benzylammonium trifluoroacetate, and 37% aqueous formaldehyde in water was stirred at 35 °C. After 24 h, an 81% yield of *N*-benzyl-4-hydroxypiperidine was isolated (Table I). Use of tetrahydrofuran as a cosolvent resulted in a reduced reaction rate and an increase in the amount of undesired side products. Somewhat surprising was the fact that the corresponding 4-chloropiperidine derivative could be obtained (entry 2) by employing the hydrochloride salt of benzylamine in the presence of lithium chloride. In general, the aminomethano desilylation-cyclization process proceeds smoothly with terminal allylsilanes (entries 4-8). Entries 7 and 8 are of particular interest since they demonstrate the potential for internal participation by a nucleophile during the cyclization process. Crotyltrimethylsilane (entry 3) reacts under the general reaction conditions providing as the sole product a 3,4-trans-disubstituted piperidine which undoubtedly arises from a concerted olefin-iminium ion cyclization of intermediate **3**. Also noteworthy is the fact that substrates



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possessing free hydroxyl groups exhibited greatly accelerated reaction rates relative to those lacking a polar functional group. Table I also reveals that cyclic allylsilanes could be efficiently converted into bicyclic amines (entries 9-11) giving rise to only cis-fused products in the case of entries 9 and 10.

Our studies suggest that the cyclization step is very rapid relative to homoallylamine formation since only traces of the intermediate homoallylamine were ever observed even when only 1 equiv of formaldehyde was used. However, exclusive homoallylamine

(1) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.

(2) The reaction of iminium ions with olefins (e.g., α-methylstyrene, β-pinene) has been reported to give rise to aminomethylated products in poor yield; see: (a) Hennion, G. F.; Price, C. C.; Wolff, C. V. *J. Am. Chem. Soc.* **1955**, *77*, 4633. (b) Schmidle, C. J.; Mansfield, R. C. *J. Am. Chem. Soc.* **1955**, *77*, 4636, 5698, 5754. (c) Bohme, H.; Fresenius, W. *Arch. Pharm. (Weinheim, Ger.)* **1972**, *305*, 601, 610. (d) Manninen, K.; Haaple, J. *Acta Chem. Scand., Ser. B* **1974**, *B28*, 433.

(3) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83. For some recent examples of allylsilane additions to *N*-acyliminium ions, see: (a) Kozikowski, A. P.; Pyeong-uk, P. *J. Org. Chem.* **1984**, *49*, 1674. (b) Gramain, J.-C.; Remuson, R. *Tetrahedron Lett.* **1985**, 327. (c) Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Ibid.* **1985**, 3155. (d) Shono, T.; Matsumura, Y.; Uchida, K.; Kobayashi, H. *J. Org. Chem.* **1985**, *50*, 3243.

(4) For an example of an iminium ion-vinylsilane cyclization, see: Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.

(5) A photochemically initiated reaction of allylsilanes with iminium ions has recently been reported (Ahmed-Schofield, R.; Mariano, P. S. *J. Org. Chem.* **1985**, *50*, 5667).

(6) For examples of intramolecular olefin-iminium ion cyclizations, see: Grewe, V. R.; Hamann, R.; Jacobsen, G.; Nolte, E.; Riecke, K. *Liebigs. Ann. Chem.* **1953**, *581*, 85. Bohlmann, F.; Winterfeldt, E. *Chem. Ber.* **1960**, *93*, 1956. Cope, A. C.; Burrows, W. D. *J. Org. Chem.* **1966**, *31*, 3099. Wilcock, J. D.; Winterfeldt, E. *Chem. Ber.* **1974**, *107*, 975.

(7) Coughlin, D. J.; Salomon, R. G. *J. Org. Chem.* **1979**, *44*, 3784.

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