solution of piperidine (9.7 g, 0.114 mol) in dry toluene (50 mL). The mixture was stirred for 3 h and washed with water (3 × 50 mL). Drying over $MgSO_4$, evaporation of the solvent, and crystallization of the residue from Et_2O afforded **29** in 85% yield; mp 91 °C; ^1H NMR ($CDCl_3$) δ 7.55 (m, 5 H, C_6H_5); IR 1630, 1485, 1470, 1450, 1340, 1180 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.8; H, 6.85; N, 6.25.

Diphenyl[2-(piperidinosulfonyl)phenyl]methanol (30). Lithiation of **29** with LDA was carried out at 0 °C followed by reaction with benzophenone at −70 °C. Unreacted starting materials were removed by steam distillation. Flash chromatography of the dried product over silica gel (Et_2O/hexane, 15/75) yielded **30** (55%); mp 160 °C; ^1H NMR ($CDCl_3$) δ 6.85 (s, 1 H, OH), 7.25 (m, 12 H, $C_6H_5 + H_4 + H_5$), 7.90 (m, 1 H, H_3); IR 3370, 1595, 1580, 1540, 1490, 1445, 1430, 1405, 1330, 1145 cm^{-1}. Anal. Calcd for $C_{24}H_{25}NO_3S$: C, 70.71; H, 6.19; N, 3.44. Found: C, 70.7; H, 6.31; N, 3.36.

Registry No. **1a**, 106762-43-0; **1b**, 106762-44-1; **1c**, 106762-45-2; **2a**, 715-07-1; **2b**, 715-08-2; **2c**, 106762-42-9; **4a**, 106762-58-7; **4b**, 106762-59-8; **4c**, 106762-60-1; **5**, 33486-07-6; **6a**, 106762-46-3; **6b**, 106762-47-4; **6c**, 106762-48-5; **7**, 106762-66-7; **8**, 106762-61-2; **9**, 106762-62-3; **10**, 106762-63-4; **11**, 106762-64-5; **12**, 106762-65-6; **13**, 106762-67-8; **14**, 106762-51-0; **15**, 106762-53-2; **16**, 106762-49-6; **17**, 106762-54-3; **18**, 106762-55-4; **19**, 106762-56-5; **20**, 106762-57-6; **21**, 106762-52-1; **22**, 106762-50-9; **23**, 106762-69-0; **24**, 106762-70-3; **25**, 106762-68-9; **26**, 106762-72-5; **27**, 106762-73-6; **28**, 106762-71-4; **29**, 5033-23-8; **30**, 106762-74-7; $C_6H_5OC_6H_5$, 119-61-9; C_6H_5CHO, 100-52-7; I_2, 7553-56-2; $C_2H_5COC_2H_5$, 96-22-0; 2,4-$Cl_2C_6H_3CHO$, 874-42-0; H_3CCHO, 75-07-0; $(CH_3)_2NCHO$, 68-12-2; CO_2, 124-38-9; $C_6H_2SO_2Cl$, 98-09-9; piperidine, 110-89-4; morpholine, 110-91-8; pyrrolidine, 123-75-1; 4-(piperidinosulfonyl)pyridine oxide, 719-09-5; 4-(morpholinosulfonyl)pyridine oxide, 884-96-8; 4-(pyrrolidinosulfonyl)pyridine oxide, 106762-41-8; 2-pyridinethione, 2637-34-5.

Supplementary Material Available: Experimental procedures and complete ^1H NMR and IR spectral data for compounds 1, 2, 4, and **6**–**30** (16 pages). Ordering information is given on any current masthead page.

Notes

Iminium Ion Mediated Cyclizations of 4-Aryl-1,4-dihydropyridines. Regio- and Stereoselectivity in Intermolecular Reactions

George D. Hartman,* Brian T. Phillips, and Wasyl Halczenko

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

James P. Springer and Jordan Hirshfield

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

Received July 18, 1986

We have recently reported the generation of iminium ions from 4-aryl-1,4-dihydropyridines and the intramolecular trapping of these electrophilic intermediates with carbon–carbon double bonds[1] and reactive heterocycles.[2,3] We have also noted other cyclization modes for 1,4-dihydropyridines that either compete with iminium ion formation[4] or utilize the iminium species at a secondary stage in the cyclization.[5] We now report that the iminium ion derived from dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1**; Scheme I) can be generated under conditions of Lewis acid catalysis and efficiently trapped in an intermolecular sense by allyltrimethylsilane and styrene. The resulting products are formal $\pi_{4s} + \pi_{2s}$ cycloadducts derived from an inverse-electron-demand Diels–Alder reaction and are formed both regio- and stereoselectivity, reflecting endo addition of the dienophile to the electron-deficient iminium diene system.

Formal $\pi_{4s} + \pi_{2s}$ cycloaddition reactions between dienophiles and 2-aza dienes have been extensively studied.[6,7] This work has shown that both normal- and inverse-electron-demand Diels–Alder type reactions depend upon the electronic nature of substituents on the aza diene. In the case of inverse-electron-demand processes, the utilization of Lewis acid catalysis to render the diene more electron deficient has resulted in successful cyclization under mild conditions.[8-12]

Unlike the examples described above that relate to reaction of a 2-aza diene in which the nitrogen is either neutral or formally charged by virtue of complexation[11] with a Lewis acid, our published results[1-5] have described 2-aza diene systems that are positively charged from covalent binding of nitrogen to a proton or alkyl group. In this respect our work is perhaps more closely aligned mechanistically with that of Bradsher and co-workers,[13] who have demonstrated facile cationic polar cycloaddition between acridizinium salts and vinyl ethers, and that of Stevens et al.[14] and Franck et al.[15] It was therefore the

(1) The following library of crystallographic programs was used: MULTAN 80 [P. Main et al. University of York, York, England, 1980]; ORTEP-II [C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, TN, 1970]; SDP Plus V1.1 [Y. Okaya et al., B. A. Frenz and Associates, College Station, TX, 1984]. Hartman, G. D.; Halczenko, W.; Phillips, B. T. *J. Org. Chem.* **1985**, *50*, 2427.

(2) Hartman, G. D.; Halczenko, W.; Phillips, B. T. *J. Org. Chem.* **1986**, *51*, 142.

(3) Hartman, G. D.; Halczenko, W.; Phillips, B. T.; Pitzenberger, S. M.; Springer, J. P.; Hirshfield, J. *J. Org. Chem.* **1986**, *51*, 2202.

(4) Hartman, G. D.; Halczenko, W.; Cochran, D. W. *Can. J. Chem.* **1986**, *64*, 556.

(5) Hartman, G. D.; Phillips, B. T.; Halczenko, W. *J. Org. Chem.* **1985**, *50*, 2423.

(6) For an excellent review, see Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.

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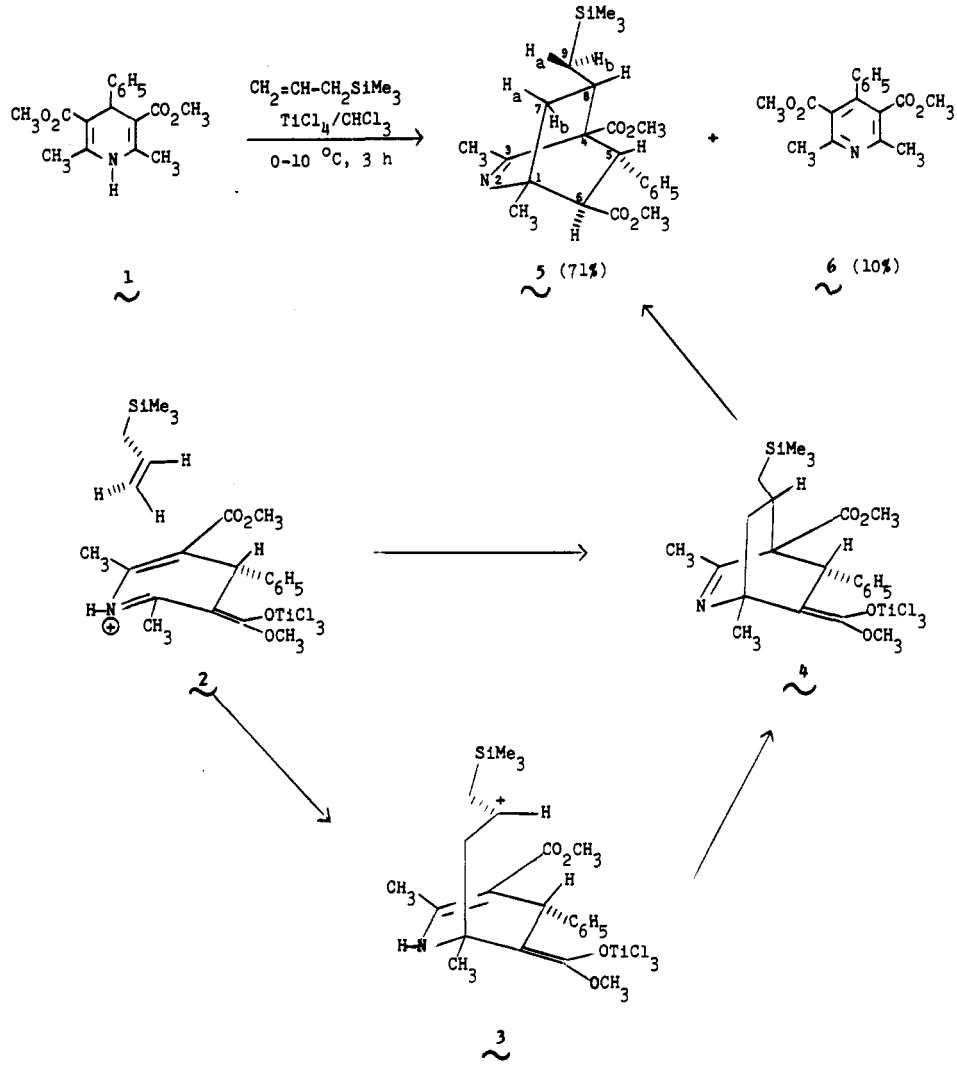
(14) Stevens, R. V.; Pruitt, J. P. *J. Chem. Soc., Chem. Commun.* **1983**, 1425.

(15) Franck, R. W.; Gupta, R. B. *Tetrahedron Lett.* **1985**, 293.

0022-3263/87/1952-1136$01.50/0

Scheme I



intent of the present work to probe the feasibility of intermolecular $\pi_{4s} + \pi_{2s}$ cyclization reactions involving the dihydropyridine iminium species and to relate observations of dienophilic reactivity and adduct stereochemistry to points of mechanism.

Results

In anticipation of possible marginal reactivity of the dihydropyridine iminium ion toward unactivated olefins, we chose to initiate cyclization studies with the highly reactive olefin allyltrimethylsilane. This compound has been used extensively as the nucleophilic partner in both addition[16] and cycloaddition[17] reactions. Treatment of dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1**)[18] in chloroform at 0–10 °C for 3 h with 3 equiv of titanium tetrachloride and 20 equiv of allyltrimethylsilane resulted in a product mixture containing one major and one minor component, in addition to starting material, which were isolated by flash chromatography. The major product, formed in 71% yield, was dimethyl 1α,3-dimethyl-5β-phenyl-8-[(trimethylsilyl)methyl]-2-azabicyclo[2.2.2]oct-2-ene-4,6α-dicarboxylate (**5**), derived formally from cycloaddition of the carbon–carbon double bond of allyltrimethylsilane across the 2,5-positions of **1** (Scheme I). The minor component was found to be dimethyl 2,6-dimethyl-4-phenyl-1,3-pyridinedicarboxylate (**6**) and was isolated in 10% yield. The structure of **5** was proven by single-crystal X-ray analysis and was consistent with 300-MHz ^{1}H NMR spectral data. On the basis of difference NOE and spin correlation (COSY) experiments, all protons attached to the bicyclic framework in **5** have been assigned as described in the Experimental Section.

The yield of **5** from treatment of **1** with allyltrimethylsilane was extremely sensitive to the Lewis acid catalyst employed. The utilization of up to 20 equiv of titanium tetrachloride did not significantly improve the yield of **5** or the ratio **5**/**6**. The utilization of other catalysts including trimethylsilyl trifluoromethanesulfonate, gaseous hydrogen chloride, and aluminum chloride, all of which had been successful in the earlier intramolecular cyclizations,[1-5] gave product mixtures containing negligible amounts of **5** and increased quantities of the aromatized product **6**.

The mechanism for formation of cycloadduct **5** most likely involves Lewis acid complexation (Scheme I) on the ester function to afford the iminium species **2**. This intermediate then undergoes regio- and stereoselective endo attack by the olefinic unit of allyltrimethylsilane, thus establishing the anti relationship between the (trimethylsilyl)methyl group and the phenyl ring at C-4. The

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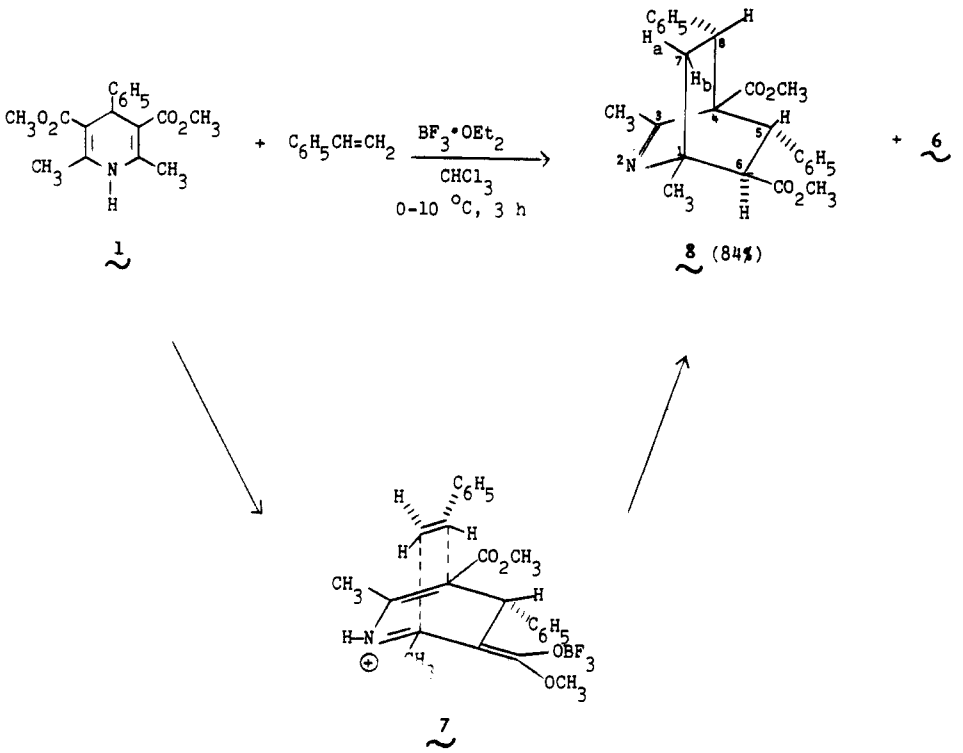
(17) (a) Hartman, G. D.; Traylor, T. G. *Tetrahedron Lett.* **1975**, 939. (b) Brady, W. T.; Cheng, T. C. *J. Org. Chem.* **1977**, *42*, 732. (c) Hoffmann, H. M. R.; Ismail, Z. M.; Weber, A. *Tetrahedron Lett.* **1981**, 1953. (d) Ismail, Z. M.; Hoffmann, H. M. R. *Angew. Chem.* **1982**, *94*, 862.
(18) Loev, B.; Goodman, M. M.; Snador, K. M.; Tedeschi, R.; Macko, E. *J. Med. Chem.* **1974**, *17*, 956.

Scheme II



final product **5** is generated by protonation of the titanium-complexed enolate **4** from the α face to provide the thermodynamic product.

A stepwise addition process would involve the intermediacy of cation **3** which, since no products derived from simple allyl transfer[16] were seen, would be required to undergo internal attack by the crotonate in preference to either bond rotation or loss of the trimethylsilyl cation.[17a] This analysis does not rule out a more synchronous[19] bond formation scheme as might be formally described by a $\pi_{4s} + \pi_{2s}$ Diels–Alder reaction. The endo geometry of the product does not establish a point of distinction between these mechanistic possibilities because both steric and secondary overlap arguments would predict in the same direction.

Our next concern was the exploitation of the cycloaddition process with olefins that were not highly activated. We, therefore, chose to study styrene, and the results are shown in Scheme II. Treatment of **1** in chloroform at 0–10 °C with 3 equiv of boron trifluoride etherate and 20 equiv of styrene resulted in the disappearance of starting material after 3 h and the formation of a major and a minor component. These were isolated by flash chromatography, and the major product was shown to be dimethyl 1α,3-dimethyl-5β-phenyl-8-phenyl-2-azabicyclo-[2.2.2]oct-2-ene-4,6α-dicarboxylate (**8**; Scheme II), which was isolated in 84% yield. The minor component was pyridine **6** and the ratio of **8**/**6** was 7/1, as determined by proton NMR analysis of the crude product mixture. The structure of **8** was determined by analysis of its 300-MHz ^{1}H NMR spectrum, and the use of difference NOE measurements and spin correlation studies allowed the assignment of all protons attached directly to the bicyclic framework. Cyclization to **8** also occurred when titanium tetrachloride was employed as catalyst; however, the reaction time was longer and the yield was lower.

As was observed in the previous case, styrene underwent efficient cycloaddition to the protonated 2-aza diene portion of the dihydropyridine iminium species. Again, no evidence of regio- or diastereomers was present indicating that, as was found with allyltrimethylsilane, cycloaddition proceeded regiospecifically to form the endo adduct and that the final product **8** was derived by protonation of the boron enolate from the α face. Qualitatively, the reactions involving allyltrimethylsilane/$TiCl_4$ and styrene/BF_3·OEt_2 appeared to proceed at comparable rates at 0–10 °C.

The present work has several features worthy of note. These results demonstrate that dihydropyridine iminium ions can be generated under conditions of mild Lewis acid catalysis and that these reactive electrophiles take part in intermolecular inverse-electron-demand Diels–Alder reactions with olefins. Although only two olefins were studied herein, the strong implication of the success with styrene is that many other simple aryl- and alkyl-substituted olefins would suffice. In this respect, the present work contrasts with that of Mariano and co-workers[11] who found that enamines and enol ethers were required for cyclization with the boron trifluoride complexes 1-phenyl-2-aza-1,3-pentanediene system. Finally, the efficient formation of cycloadducts in both regio- and stereoselective fashion allows the prediction of relative configuration at all newly created stereocenters in the bicyclic framework. This methodology should therefore have application in preparing molecules for studies of geometrical features important in the biological activity of dihydropyridines,[20] as well as in the construction of intermediates for natural product synthesis.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. NMR spectra were recorded on an EM-390 or a Nicolet NT-360 spectrometer with Me_4Si as an internal standard. Mass spectra were obtained on a LKB-9000S mass spectrometer at 70 eV. Allyltrimethylsilane and styrene were obtained from Aldrich and distilled before use. Boron trifluoride

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etherate and titanium tetrachloride were obtained from Aldrich and were used without purification.

Dimethyl 1α,3-Dimethyl-5β-phenyl-8-[(trimethylsilyl)-methyl]-2-azabicyclo[2.2.2]oct-2-ene-4,6α-dicarboxylate (5). To a solution of 3.0 g (0.01 mol) of 1 and 22.8 g (0.2 mol) of allyltrimethylsilane in 75 mL of chloroform cooled to 0–10 °C under nitrogen was added dropwise via syringe 5.7 g (0.03 mol) of titanium tetrachloride over 20 min. The reaction mixture was then stirred at 0–10 °C for 3 h during which time the color darkened and some precipitate became apparent. The reaction mixture was then poured onto ice, and this neutralized with saturated sodium bicarbonate solution. This was extracted with 3 × 75 mL of chloroform, and the combined organics were washed with brine and dried over sodium sulfate. Solvent removal on the rotary evaporator afforded a yellow oil that was purified by flash chromatography on silica gel (230–400 mesh), eluting with 2% methanol/chloroform. Eluting from the column were 2.95 g (71%) of **5** [R_f 0.5, white, crystalline solid, mp 152–155 °C] and 0.29 g (10%) of **6** [R_f 0.4, mp 131–133 °C]: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.078 (9 H, s), 0.27 (1 H, dd, J = 13.9, 12.7 Hz, H_{9a}), 0.47 (1 H, dd, J = 14.0, 1.5 Hz, H_{9b}), 0.83 (1 H, br dd, J = 13.0, 3.4 Hz, H_{7a}), 1.56 (3 H, s), 2.46 (1 H, dd, J = 13.1, 9.4 Hz, H_{7b}), 2.55 (3 H, s, allylic CH_3), 2.60 (1 H, r d, J = 6.9 Hz, H_6), 2.76 (1 H, m, H_8), 3.58 (3 H, s, CO_2CH_3), 3.74 (1 H, d, J = 7 Hz, H_5), 3.74 (3 H, s, CO_2CH_3), 7.0–7.35 (5 H, m, aromatic); mass spectrum, m/e 415 (M^+), 400, 384, 374, 356, 342, 314, 302, 270, 261, 242, 238. Anal. Calcd for $C_{23}H_{33}NO_4Si$: C, 66.46; H, 8.00; N, 3.37. Found: C, 66.43; H, 8.23; N, 3.59.

Dimethyl 1α,3-Dimethyl-5β,8-diphenyl-2-azabicyclo-[2.2.2]oct-2-ene-4,6α-dicarboxylate (8). To a solution of 1.0 g (3.3 mmol) of 1 and 6.86 g (66 mmol) of styrene dissolved in 60 mL of chloroform and cooled to 0–10 °C under nitrogen was added 10 mmol of boron trifluoride etherate via syringe over 20 min. The resulting clear, yellow solution was stirred at 0–10 °C for 3 h, and the reaction mixture was then quenched by pouring on ice. This was neutralized with saturated sodium bicarbonate solution, and the aqueous phase was extracted with 3 × 75 mL portions of chloroform. The combined organic extracts were washed with brine and dried over sodium sulfate, and the solvent was stripped on the rotary evaporator to give a yellow oil. This material was purified by flash chromatography on silica gel (230–400 mesh), eluting with 10% isopropyl alcohol/hexane. The desired cycloadduct 8 was eluted from the column, R_f 0.5, to afford after solvent removal a white, crystalline solid: mp 138–139 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.49 (1 H, ddd, J = 13.8, 6.1, 2.0 Hz, H_{7a}), 1.59 (3 H, s, CH_3), 2.30 (3 H, s, allylic CH_3), 2.62 (1 H, dd, J = 13.8, 10.1 Hz, H_{7b}), 2.66 (1 H, dd, J = 6.8, 1.9 Hz, H_6), 3.36 (3 H, s, CO_2CH_3), 3.70 (3 H, s, CO_2CH_3), 3.78 (1 H, dd, J = 10.1, 6.1 Hz, H_8), 3.88 (1 H, d, J = 6.8 Hz, H_5), 7.10 (3 H, m), 7.2 (7 H, m); mass spectrum, m/e 405 (M^+). Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 74.40; H, 6.81; N, 3.33.

X-ray Crystal Structure Analysis of 5. Suitable crystals of **5** ($C_{23}H_{33}NO_4Si$) for X-ray diffraction studies formed from a neat oil with space group symmetry of $P2_1/C$ and cell constants of a = 10.668 (1) Å, b = 26.569 (5) Å, c = 9.274 (1) Å, and β = 114.70 (1)° for Z = 4 and a calculated density of 1.15 g/cm^3. Of the 3211 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 2791 were observed [$I > 3\sigma(I)$]. The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by full-matrix least-squares techniques.[1] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/[\sigma(F_o)]^2$ was minimized to give an unweighted residual of 0.062. No abnormally short intermolecular contacts were noted. Tables I containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 1 (supplementary material) is a computer-generated perspective drawing of **5** from the final X-ray coordinates showing the relative stereochemistry.

Acknowledgment. We thank Dr. S. M. Pitzenberger for his analysis of NMR spectra, J. P. Moreau for elemental analysis, Dr. H. Ramjit for mass spectral determinations, and M. Banker for typing the manuscript. We also thank Dr. J. J. Baldwin for help and encouragement throughout the course of this work.

Registry No. 1, 70677-78-0; (±)-**5**, 105335-61-3; **6**, 77234-00-5; (±)-**8**, 105335-62-4; $H_2C{=}CHCH_2SiMe_3$, 762-72-1; $C_6H_5CH{=}CH_2$, 100-42-5.

Supplementary Material Available: ORTEP of **5** and listings of crystallographic data including atomic positional and thermal parameters, bond distances, and bond angles (5 pages). Ordering information is given on any current masthead page.

Homogeneous and Heterogeneous Catalytic Asymmetric Reactions. 1. Asymmetric Hydrogenation of the Prochiral C=C Bond on a Modified Raney Ni Catalyst

M. Bartók,* Gy. Wittmann, Gy. Göndös, and G. V. Smith†

Department of Organic Chemistry, József Attila University, Szeged, Hungary

Received January 30, 1985

The catalyst TA–MRNi (Raney Ni catalyst modified with (*R,R*)-tartaric acid) has been in use for the asymmetric hydrogenation of prochiral ketones since 1962.[1] An optical yield of 80–90% has been achieved in the case of prochiral ketones on the catalyst TA–NaBR–MRNi.[2] The efforts to carry out the enantioselective hydrogenation of the prochiral C=C bond on modified MRNi have proved practically ineffective.[3-5]

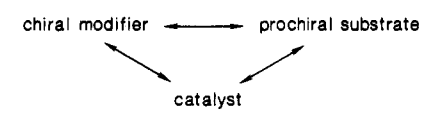
The literature data lead to the conclusion that there is a considerable difference between organic compounds containing C=O and C=C bonds as concerns enantioselective hydrogenation. The monographs referred to[4,5] did not pay any special attention to this difference.

In our opinion, the failure of C=C compounds to display enantioselectivity can be explained in that the examined substrates, in the absence of an appropriate binding site, could not form a complex with the catalyst or with the chiral group of the modifier. Setting out from this starting point, after a number of efforts, we selected the sodium salts of prochiral C=C containing carboxylic acids as model compounds for a study of enantioselective hydrogenation.

Results and Discussion

Some characteristic data relating to our experimental results are listed in Table I. It may be seen that an outstandingly high enantioselectivity was observed with sodium (*E*)-α-phenylcinnamate (1). The enantioselectivity was considerably lower for the *Z* isomer and for the free acids. We interpret these experimental results as follows.

The accepted view concerning the mechanism of action of the catalyst in question is that the occurrence of enantioselectivity demands the formation of a mixed ligand complex on the surface of the catalyst:[4,5,7]



The enantioselectivity is governed by the strength of the interactions between the components of this complex. The steric structure of the product formed during hydrogenation is determined by the adsorption of the substrate. The

† Department of Chemistry and Biochemistry, Southern Illinois University, Carbondale, IL 62901.

0022-3263/87/1952-1139$01.50/0