Synthesis and Diels-Alder Reactions of *N*-Carbalkoxydihydropyridines. Substituent Effects on the Regiochemistry of Reduction of *N*-Carbalkoxypyridinium Ions

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A number of 3-substituted pyridines have been subjected to reduction by various hydride-transfer reducing agents in the presence of ethyl and benzyl chloroformate (Fowler reduction). In reductions by sodium borohydride, substituents which act as electron donors exhibit regiochemical control to the extent of 90% or more, favoring hydride addition at the 2-position. Substituents shown to follow this pattern were methyl, ethyl, methoxy, methylthio, bromo, and chloro. More bulky donor substituents such as trimethylsilyl, trimethylstannyl, and tributylstannyl also favor 1,2-reduction but the ratio is not as high. Acceptor substituents such as carbomethoxy and cyano are not strongly regiodirective under similar reaction conditions. The directive effect is relatively insensitive to the steric effects in the reducing agent, although the trimethylsilyl and trialkylstannyl groups do give increased amounts of 1,6-dihydropyridine with reducing agents such as potassium triisopropoxyborohydride, diisobutylaluminum hydride, and sodium tri-*sec*-butylborohydride. Representative dihydropyridines have been shown to react with methyl acrylate, and the effect of the dihydropyridine substituents on the regiochemistry and stereochemistry of the Diels-Alder reaction has been determined. The origin of the substituent effect on the reduction reaction is discussed on the basis of CNDO calculations on models of the reactant pyridinium ions and product dihydropyridines.

Dihydropyridines and dihydropyridine equivalents have been of wide interest in the synthesis of nitrogen-containing compounds and natural products.[1] One of the most useful approaches to these intermediates is that developed by Fowler, involving sodium borohydride reduction of *N*-carbalkoxypyridinium ions formed in situ from a pyridine and a chloroformate ester.[2] It is well-established that 3-alkylpyridines are selectively reduced at C-2, giving 3-alkyl-1,2-dihydropyridines under these conditions.[3] 5-Alkyl-1,2-dihydropyridines, which would result from hydride addition at C-6, are potentially valuable synthetic intermediates but only less direct methods have been developed to obtain these compounds.[4]

We were interested in several aspects of this problem: (1) What is the basis for the regiochemical control exerted by the 3-alkyl group? (2) What regiochemical control is exerted by other types of substituents? (3) Can a change in the reducing agent, for example, enhanced steric demand, change the regioselectivity? To develop this information, we have reduced a range of substituted pyridines under the Fowler conditions using sodium borohydride and under modified conditions with related reducing agents, specifically, potassium triisopropoxyborohydride, K(*i*-PrO)$_3$BH, lithium tri-*tert*-butoxyaluminum hydride, Li(*t*-BuO)$_3$AlH, sodium tri-*sec*-butylborohydride, Na(*sec*-Bu)$_3$BH, and diisobutylaluminum hydride, (*i*-Bu)$_2$AlH. A previous study of the effect of a change of reducing agent has shown that the use of a reductant prepared from lithium tri-*tert*-butoxyaluminum hydride and cuprous bromide leads to predominantly 1,4-reduction.[5] In order to assess the stability and reactivity of the substituted dihydropyridines, we have carried out Diels-Alder reactions with representative compounds using methyl acrylate as the dienophile.

Table I. NMR Assignments for Dihydropyridines

	proton at position[a]			
	2	4	5	6
A. 1,2-Dihydropyridines in $CDCl_3$ at 25 °C				
CH_3	4.2 s	5.55 m	5.07 t	(6.6)
CH_3CH_2	4.2 s	5.52 d	5.07 t	(6.5)
Cl	4.4 m	5.92 d	5.07 t	(7.7)
CH_3O	4.3 s	4.92 d	5.18 t	(6.5)
CH_3S	4.3 s	5.58 d	5.20 t	(6.7)
$(CH_3)_3Si$	4.3 m	6.14 d	5.28 t	(6.8)
$(CH_3)_3Sn$	4.5 s	5.97 m	5.15 d of d	(6.7)
$(C_4H_9)_3Sn$	4.5 s	5.8 m	5.18 t	(6.7)
CN	4.5	*b*	*b*	*b*
B. 1,6-Dihydropyridines in $CDCl_3$ at 25 °C				
$(CH_3)_3Si$	6.80 s	5.48 d of t	5.88 d	4.3 m
$(CH_3)_3Sn$	(6.7)	(5.5)	5.87 d of m	4.3 m
$(C_4H_9)_3Sn$	(6.7)	5.6 m	5.85 d of m	4.3 m
C. 1,2-Dihydropyridines in MeSO-d_6				
CH_3[c]	4.07 s	5.54 m	5.11 d of d	6.50 d
CH_3O[c]	4.11 s	5.02 d	5.18 t	6.37 d
$(CH_3)_3Si$[c]	4.18 s	6.02 d	5.20 d of d	6.62 d
CH_3O_2C[d]	4.6 s	6.3 d of d	5.8 m	6.97 d
D. 1,6-Dihydropyridines in Me_2SO-d_6				
$(CH_3)_3Si$[c]	6.62	5.49 d of t	5.78 d	4.14 m
CH_3O_2C[d]	7.65	6.15	5.60	4.32 m

[a] Peak positions in parentheses are broadened by rotational effects of the alkoxycarbonyl group. [b] All vinyl peaks are severely broadened. [c] At 80 °C. [d] At 20 °C.

Results

A. Identification and Analysis of Product Mixtures. The mixtures of dihydropyridines from reduction of 3-substituted pyridines can, in general, consist of the 1,2-, 1,4-, and 1,6-reduction products. Analysis was carried out by examination of the NMR spectra of the mixtures.

(1) For reviews and summaries, see: Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. Husson, H.-P. *Bull Soc. Chim. Belg.* **1982**, *91*, 985. Imanishi, T. *Yakugaku Zasshi* **1984**, *104*, 549. Wenkert, E. *Acc. Chem. Res.* **1968**, *1*, 78.

(2) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321.

(3) (a) Beeken, P.; Bonfiglio, J. N.; Hasan, I.; Piwinski, J. J.; Weinstein, B.; Zollo, K. A.; Fowler, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 6677. (b) Casini, A.; DiRienzo, B.; Micheletti Moracci, F.; Tortorella, S.; Liberatore, F.; Arnone, A. *Tetrahedron Lett.* **1978**, 2139. (c) Kutney, J. P.; Greenhouse, R.; Ridaura, V. E. *J. Am. Chem. Soc.* **1974**, *96*, 7364. (d) Wenkert, E.; Broquet, C. *Synth. Commun.* **1979**, *9*, 689.

(4) Raucher, S.; Lawrence, R. F. *Tetrahedron Lett.* **1983**, *24*, 2927. Marazano, C.; Le Goff, M.-T.; Fourrey, J.-L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 389. Wyle, M. J.; Fowler, F. W. *J. Org. Chem.* **1984**, *49*, 4025.

(5) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1984**, *49*, 3392.

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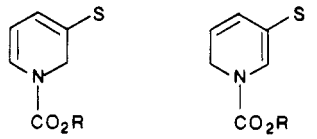
Table II. Ratio of 1,2-, 1,4-, and 1,6-Reduction Products

3-substitutent	$NaBH_4$	$K(i\text{-}PrO)_3BH$	$Li(t\text{-}BuO)_3AlH$	$(i\text{-}Bu)_2AlH$	$Na(sec\text{-}Bu)_3BH$
CH_3	95:5:0	95:5:0[b]	95:5:0[b]	95:5:0[c,d]	60:20:20[b,c]
CH_3CH_2	95:5:0	95:5:0[b]	90:5:5[b]	75:15:10[b,c]	45:20:35[a,b,c]
CH_3O	100:0:0	100:0:0[b]	100:0:0[b]		
CH_3S	100:0:0	100:0:0[b]	100:0:0[b]		
Cl	85:15:0				
Br	90:10:0				
$(CH_3)_3Si$	65:0:35	35:0:65[b]	25:0:75[b]	33:0:67[c,d]	0:0:100[b,c]
	40:30:30[b]			33:33:33[b,c]	
$(CH_3)_3Sn$	50:25:25	20:0:80[b]	20:0:80[b]		
$(C_4H_9)_3Sn$	70:15:15	25:0:75[b]	10:0:90[b]		
CH_3O_2C	50:15:35	50:10:40[b,c]			
NC	15:55:30[c]	*e*	*e*		

[a] Ratios are calculated from the NMR integration. In the case of minor products (5% or less) the peaks are recognized but integration is not quantitative. [b] In THF. [c] Inverse mode of addition. [d] In CH_2Cl_2. [e] Procedure is unsuccessful because only very limited reduction occurs.

In many cases the spectra are broad near room temperature because of effects of the carbamate rotational barrier. In these cases spectra were recorded at elevated temperature. Spectral assignments are given in Table I for the 1,2- and (when formed in sufficient amount) 1,6-dihydropyridines. The 1,4-reduction products were usually minor but could be recognized and estimated by a characteristic finely coupled multiplet near 3.0 ppm due to the 4-methylene group.



1 1,2-product 2 1,6-product

B. Variation of Reaction Conditions. In the original Fowler procedure, the pyridine to be reduced and sodium borohydride are mixed in methanol at −78 °C. The chloroformate ester is then added and a vigorous reaction ensues. We made two general types of variations of the reaction conditions. Certain of the reducing agents studied, e.g., $(i\text{-}Bu)_2AlH$ and $Li(t\text{-}BuO)_3AlH$ are incompatible with hydroxylic solvents. For these reducing agents, either THF or dichloromethane was used as the solvent. Some variation of product ratios was observed with use of aprotic solvents as can be noted from the results in Table II. In particular, it was found that use of THF as the solvent increases the amount of 1,4-reduction product. For example, Fowler reduction of 3-(trimethylsilyl)pyridine in THF results in approximately equal amounts of 1,2-, 1,4-, and 1,6-reduction product whereas in methanol, the ratio of 1,2- and 1,6-dihydropyridines is 2:1 and little 1,4-product is seen. Reduction of 3-(trimethylsilyl)pyridine in THF solvent by $(i\text{-}Bu)_2AlH$ led to a mixture of all three regioisomers in nearly equal amounts. However, when the reaction was run in methylene chloride only the 1,2- and 1,6-isomers were obtained.

We obtained relatively low yields of reduction products from the pyridines with electron-attracting 3-substituents under the normal Fowler conditions and also with the other reducing agents. 3-Cyanopyridine provides a specific example. Repeated attempts to use the regular methodology on this compound met with negligible yields of reduction product; the pyridine was recovered unchanged. Reduction by sodium borohydride occurred when an inverse method of addition was used. While methyl nicotinate is reduced under the usual Fowler conditions, it was found that the yields could be improved by adding the chloroformate component first and then adding the reducing agent. Neither 3-nitropyridine nor 3-(methylsulfonyl)pyridine could be satisfactorily reduced by using any of the methods. It appears that the cause of the low reactivity is the weak nucleophilicity of these pyridines. A low concentration of the *N*-(alkoxycarbonyl)pyridinium ion would favor the competing reduction of the alkyl chloroformate. The improved yield obtained by adding the reducing agent to a mixture of the pyridine and alkyl chloroformate may result from an increased concentration of the reactive *N*-acylpyridinium species. Clearly, these inverse addition conditions may not be appropriate in hydroxylic solvents with more nucleophilic pyridines, since formation of carbonate esters by nucleophilic catalysis could occur.

Table III. Other Examples of Reduction of 3-Substituted Pyridines

3-substituent	ROCCl	reductant	1,2:1,4:1,6 ratio	ref
CH_3CH_2	C_2H_5	$NaBH_4$	90:0:10	3a
$CH_3(-OCH_2CH_2O-)C$	$PhCH_2$	$NaAlH_2(OCH_2CH_2OCH_3)_2$	22[a]:78	9a
CH_3O_2C	Cl_3CCH_2	$NaBH_4$	50:0:50	9b

[a] 1,2 and 1,4 combined.

The inverse-addition mode is required for use of certain reducing agents regardless of the substitution of the pyridine ring. Both $(i\text{-}Bu)_2AlH$ and $Na(sec\text{-}Bu)_3BH$ gave poor yields with the normal mode of addition for all pyridines studied. When the order of addition was reversed, satisfactory yields were obtained. It is possible that these reagents can successfully compete with the pyridine for the chloroformate. The reactions carried out by the inverse addition mode are noted in Table II.

One type of reducing agent of interest was the Selectrides,[6] since they are well-known to be influenced by the steric effects of the trialkyl substitution. Reductions with $Na(sec\text{-}Bu)_3BH$ (N-Selectride) were carried out in THF by inverse addition. Normal hydrolytic and extractive workup left large quantities of alkylboranes or alkylborane complexes in the product mixture. After briefly investigating morpholine oxide treatment as a means of decomposing these boranes,[7] we found that the *N*-(ethoxycarbonyl)dihydropyridines could survive room-temperature oxidation with the more economical alkaline hydrogen peroxide solutions which are generally useful in borane oxidations. Isolated yields of the *N*-(alkoxycarbonyl)dihydropyridine derivatives from 3-methyl- and 3-(trimethylsilyl)pyridine were 50-70% under these conditions.

C. Regioselectivity. The ratio of the 1,2-, 1,4-, and 1,6-dihydro isomers formed in the reduction can usually

(6) Selectride is a registered trademark of Aldrich Chemical Company for salts of trialkylborohydrides. We used N-Selectride, sodium tri-*sec*-butylborohydride.

(7) Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Org. Chem.* **1975**, *40*, 1776.

Table IV. Chemical Shifts and Coupling Constants for Diels–Alder Adducts in Me_2SO-d_6 at 110 °C

adduct[a]	1	3	4	5	6	7	8
3bX	4.81 m	2.70, 3.03	1.15	1.38, 1.76	2.53 m	6.40	6.12
		J_{gem} = 10				J = 7, 5	J = 7
3bN	4.87 m	2.60, 3.00	1.13	1.5, 1.65	3.03[b]	6.20	6.10
		J_{gem} = 10		J_{gem} = 13		J = 6, 8	J = 8
3cX	4.83 m	2.61, 3.02	1.61 q	1.44, 1.81	2.56 m	6.48	6.25
		J_{gem} = 10	0.94 t	J_{gem} = 13		J = 8, 7	J = 8
3cN	4.91 m	2.68, 2.99	1.57 q	1.58,[b] 1.68	3.07 m	6.30	6.24
		J_{gem} = 10	0.95 t	J_{gem} = 13		J = 8, 6	J = 8
4cX	4.69 m	(2.83),[b] 3.19	2.73 m	1.51, 1.92	2.54 m	2.18 q	5.99 d
		J_{gem} = 10		J_{gem} = 13		1.02 t	
4cN	4.80 m	2.78,[b] 3.15	2.77[b]	1.68, 1.83	3.05 m	2.07 q	6.00 d
		J_{gem} = 10		J_{gem} = 13		0.95 t	J = 6
4fX	4.92 s	2.82,[b] 3.21	2.8,[b]	1.50, 1.95[c]	2.37[d]	~0.5	6.72
		J_{gem} = 10		J_{gem} = 13			J = 6
4fN	5.05 m	2.78, 3.17[e]	2.83 m	1.7, 1.8	3.07 m	~0.3	6.76
		J_{gem} = 10					J = 6
5dX	4.62 m	2.78[f]	3.38 s	2.86 m[g]	1.72, 2.00[h]	6.42	6.64
		J_{gem} = 10			J_{gem} = 13	J = 9, 6	J = 9
5dN	4.62 m	2.92, 3.28	3.34 s	3.02[i]	1.49, 2.17[j]	6.39	6.32
		J_{gem} = 10			J_{gem} = 13	J = 9, 6	J = 9
5eX	4.63 m	2.84[k]	3.38 s	~2.9[l]	1.74, 2.02[m]	6.45	6.65
		J_{gem} = 10				J = 9, 6	J = 9
5eN	4.66 m	2.92,[n]	3.35 s	3.05[n]	1.52, 2.20[o]	6.41	6.34
		J_{gem} = 10				J = 9, 6	J = 9

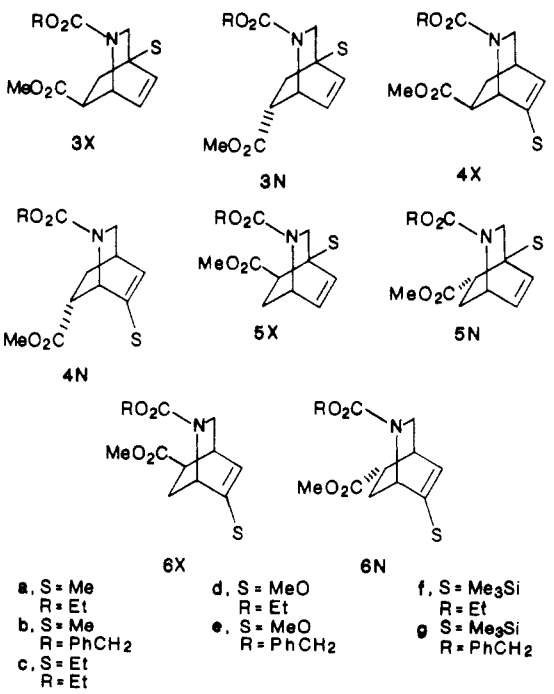
[a] 2-Azabicyclo[2.2.2]oct-7-ene numbering. The carbomethoxy group is at 5 or 6. [b] Overlaps another signal. [c] Additional couplings of 10, 2.5, and 2.5 Hz in 1.50 signal; additional couplings of 5 and 2 Hz in 1.95 signal. [d] Additional couplings of 10.5, 5, and 2 Hz. [e] Additional coupling of ~2 and ~1 Hz in 2.78 signal; additional coupling of ~1 Hz in 3.17 signal. [f] Other signal obscured by HOD; additional 1.5-Hz coupling in signal at 2.78. [g] Additional coupling of 10.5, 5, and 1.5 Hz. [h] Additional couplings of 10.5 and 2.5 Hz in 1.72 signal; additional couplings of 5 and 2 Hz in 2.00 signal. [i] Additional couplings of 10 and 5 Hz. [j] Additional couplings of 5 and 2 Hz in signal at 1.49; additional couplings of 10 and 3 Hz in signal at 2.17. [k] Other signal obscured by HOD; additional 1.5 Hz coupling in signal at 2.84. [l] Partially obscured by HOD. [m] Additional couplings of 10 and 2 Hz in signal at 1.74; additional coupling of 5 and 2Hz in signal at 2.02. [n] Additional couplings of 10 and 5 Hz. [o] Additional couplings of 5 and 2 Hz in signal at 1.52; additional couplings of 10 and 3 Hz in signal at 2.20.

be estimated to within ±5% by integration of the NMR spectra of the mixture obtained by reduction. The results obtained in this manner are given in Table II. There is some data, although not precisely comparable because of variation in reaction conditions, which can be found in the literature. This is summarized in Table III.

The trends in the data for sodium borohydride reduction can be summarized as follows: Sterically nondemanding donor substituents (alkyl, alkoxy, alkylthio, chloro, bromo) exert an effective regiocontrol, favoring reduction at C-2 by 9:1 or more. This control is not overcome by use of more bulky reductants such as K(i-OPr)$_3$BH or Li(t-BuO)$_3$AlH. Branched substituents $(CH_3)_3Si$ and $(C_4H_9)_3Sn$ exert a weaker C-2 selectivity and the ratio is more sensitive to steric factors in the reductant. Acceptor substituents (CO_2CH_3, CN) are only weakly regiodirective with sodium borohydride as the reducing agent.

D. Diels–Alder Reactions. Our interest in the Diels–Alder reactions was primarily to determine which substituent patterns on the dihydropyridines were consistent with preparative utility. The Diels–Alder reactivity of the parent 1-carbalkoxy-1,2-dihydropyridines has been repeatedly demonstrated[8] but much less is known about substituted cases.[9] Since mixtures of regioisomeric dihydropyridines cannot be easily separated, in those cases where two dihydropyridines are formed, two families of

Scheme I



adducts are possible. In the case of the unsubstituted dihydropyridine, the nitrogen atom controls the regiochemistry of the Diels–Alder addition.[10] Since this orientational effect is opposed by a donor substituent at C-3 in a 1,2-dihydropyridine, regiochemical control cannot be assumed. Finally, each combination permits an endo–exo stereoisomeric pair. Thus a total of eight isomers is con-

(8) Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L. *J. Org. Chem.* **1979**, *44*, 124. Sliwa, H.; Le Bot, Y. *Tetrahedron Lett.* **1977**, 4129. Wender, P. A.; Schaus, J. M.; Torney, D. C. *Tetrahedron Lett.* **1979**, 2485. Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1980**, *45*, 3382. Krow, G. R.; Carey, J. T.; Cannon, K. C.; Henz, K. J. *Tetrahedron Lett.* **1982**, *23*, 2527; Marazano, C.; Fourrey, J.-L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 37. Knaus, E. E.; Avasthi, K.; Giam, C. S. *Can. J. Chem.* **1980**, *58*, 2447.

(9) (a) Natsume, M.; Utsunomiya, I. *Chem. Pharm. Bull.* **1984**, *32*, 2477. (b) Kunng, F.-A.; Gu, J.-M.; Chao, S.; Chen, Y.; Mariano, P. S. *J. Org. Chem.* **1983**, *48*, 4262. (c) Krow, G. R.; Cannon, K. C.; Carey, J. T.; Lee, Y. B.; Szcepanski, S. W.; Ramjit, H. G. *J. Heterocycl. Chem.* **1985**, *22*, 131. Dubey, S. K.; Knaus, E. E. *J. Org. Chem.* **1985**, *50*, 2080.

(10) Overman, L. E.; Taylor, G. F.; Houk, K. N.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1978**, *100*, 3182. Mariano, P. S.; Dunaway-Mariano, D.; Huessmann, P. L.; Beamer, R. L. *Tetrahedron Lett.* **1977**, 4299.

ceivable starting from a dihydropyridine mixture. These are designated as 3X,3N-6X,6N; X denotes exo and N denotes endo stereochemistry of the carbomethoxy substituent (Scheme I). We focused attention on the Diels–Alder adducts from the 3-methyl, 3-methoxy, and 3-(trimethylsilyl)pyridine reduction products. Both *N*-carbethoxy- and *N*-carbobenzyloxydihydropyridines were examined. Each of the dihydropyridines gave rise to predominantly two adducts which are exo, endo stereoisomers. In order to permit structural assignments, small samples of the isomeric products were separated by HPLC. The 360-MHz spectra of the adducts were used for structural assignment. At 20 °C the 360-MHz spectra are doubled as the result of the carbamate rotational barrier. Well-resolved, time-averaged spectra were obtained at 110 °C in Me_2SO-d_6. The chemical shifts and coupling constants for the Diels–Alder adducts are given in Table IV. The structural assignments based on these spectra are described in the following paragraphs.

a. Diels–Alder Adducts of 1-Carbethoxy-1,2-dihydro-3-methylpyridine. Diels–Alder addition in a sealed tube at 120 °C, followed by chromatography, gave a mixture of adducts in 70% yield. The spectrum of the mixture was consistent with the presence of two major products **3aX** and **3aN** (ratio ~4:6). These were not separable by HPLC on a C-18 reversed-phase column. Treatment under conditions expected to epimerize the carboxylate substituent gave a slight enhancement of the minor isomer (~1:1 after epimerization). The most pronounced differences in the two spectra is the downfield shift (6.4 ppm) of the C-7 vinyl proton in the minor isomer. The other features of the spectrum of the mixture are closely analogous to those obtained from the carbobenzyloxy analogues described in **b**.

b. Diels–Alder Adducts of 1-Carbobenzyloxy-1,2-dihydro-3-methylpyridine. The adduct mixture was obtained after chromatography in 60% yield. In the carbobenzyloxy case the two isomers were separable by preparative HPLC. The exo isomer (**3bX**) showed the more downfield position for the C-7 vinyl proton (6.4 vs. 6.2 in **3bN**). The C-1 bridgehead protons were also slightly different: 4.81 in **3bX** and 4.87 in **3bN**. Confirmation of the exo vs. endo assignment was achieved by hydrolyzing each ester and subjecting each carboxylic acid to iodolactonization conditions. Only **3bN** gave a cyclized product.

c. Diels–Alder Adducts of 1-Carbethoxy-1,2-dihydro-3-ethylpyridine and 1-Carbethoxy-1,6-dihydro-3-ethylpyridine. Reduction of 3-ethylpyridine by N-Selectride in THF in the presence of ethyl chloroformate gave a mixture of 1,2-, 1,4-, and 1,6-reduction product. Diels–Alder reaction of the mixture with methyl acrylate was done at 120 °C for 48 h and gave a 65% yield of isomeric adducts. After partial separation by column chromatography, preparative HPLC gave each of the four adducts with <20% contamination by other isomers. Two were identified as **3cX** and **3cN** by the appearance of two vinyl protons and the stereochemical assignment was made by comparison with **3bX** and **3bN**. The other two isomers revealed single vinyl protons as doublets. Stereochemical assignments were made by comparison with **4fX** and **4fN**. The pairs of spectra were similar, including the fact that the methoxy group is split to a doublet in **4cX** at room temperature but not in **4cN**.

d. Diels–Alder Adducts of 1-Carbethoxy-1,2-dihydro-3-methoxypyridine. The Diels–Alder reaction was carried out at 120 °C. Chromatography of the reaction mixture gave a mixture of adducts in 25% yield. Most features could be attributed to two isomeric adducts in a 2:1 ratio which accounted for at least 85% of the material. An additional ester methoxy peak at 3.53 ppm suggested the presence of a third minor isomer. The two major products were separable by HPLC on a C-18 column. The NMR spectra permitted assignment of the two compounds as **5dX** and **5dN**. Both are 4-methoxy-2-azabicyclo-[2.2.2]oct-7-ene-2,5-dicarboxylate esters *resulting from methoxy-directed regioselective cycloaddition.* The trace product may possess the alternative regiochemistry but there was insufficient material to definitely determine its structure. In **5dX** the vinyl protons appear at 6.42 (C-7) and 6.64 (C-8). Both signals of the C-6 methylene AB quartet show coupling to the C-1 bridgehead proton. This establishes the regiochemistry of the product. The stereochemical assignment is made on the basis of a W-type coupling in the C-5 proton.[11] In **5dN** the vinyl protons are at higher field; (C-7 at 6.39; C-8 at 6.32). Both the C-6 protons are coupled to the C-1 proton and in this case the exo-C-5 proton shows no long range W coupling.

e. Diels–Alder Adducts of 1-Carbobenzyloxy-1,2-dihydro-3-methoxypyridine. The mixture of adducts was obtained in 37% yield and two principal products were separated by HPLC. The spectrum of **5eX** was similar to that of **5dX**, although the C-5 multiplet was obscured by HOD in this case. The spectrum of the second isomer **5eN** was closely analogous to that of **5dN**. The C-3 methylene AB quartet was partially obscured by HOD but the absence of any long-range W-coupling in the C-5 proton was confirmatory of the stereochemistry.[11] As in the case of **5dX** and **5dN** there was a significant upfield shift of the C-7 vinyl proton in **5eN** to 6.34, compared to 6.65 in **5eX**.

f. Diels–Alder Adducts of 1-Carbethoxy-1,2-dihydro-3-(trimethylsilyl)pyridine and 1-Carbethoxy-1,6-dihydro-3-(trimethylsilyl)pyridine. The ability to control the regiochemistry of the reduction to favor either 1,2- or the 1,6-isomer permitted synthesis of adducts of both types **3** and **4** in the trimethylsilyl case. The adduct mixture from nearly pure 1-carbethoxy-3-(trimethylsilyl)-1,6-dihydropyridine was obtained in 60% yield and consisted of two main components. The appearance of two vinyl hydrogen signals as doublets at 6.72 and 6.76 ppm in the approximate ratio ~2.5:1 confirmed that the major adducts were both vinylsilanes of structure **4**, as was to be expected for the 1,6-dihydro isomer. The C-1 bridgehead protons (4.92, 5.05) and ester methoxy (3.62, 3.57) also appeared in ~2.5:1 ratios. The anticipated regiochemistry was confirmed by the absence of C-1–C-7 proton–proton coupling. The two isomers were separated by HPLC. The isomer with the following chemical shifts was assigned as the exo isomer **4fX**. C-8 vinyl: 6.72 d; C-1 4.92 s; and OMe 3.62. The isomer with peaks C-8 vinyl, 6.76 d; C-1 5.05 s; and OMe 3.57 was assigned as **4fN**. The main basis for this assignment was the fact that the methoxy peak of **4fX** was temperature-dependent, being split to peaks of nearly equal intensity at 20 °C. From this observation it was surmised that the carbomethoxy group was in close proximity to the carbamate substituent and therefore exo.

Since sodium borohydride reduction gives a substantial amount of 1,6- as well as the dominant 1,2-dihydro product, the Diels–Alder mixture contains the previously described 1,6-adducts. Features due to the adducts **3fX** and **3fN** from the 1,2-dihydropyridine can be recognized by elimination of the peaks due to the 1,6-adduct. The peaks in the vinyl region could be assigned to two compounds, each having one doublet (J = 7.6 Hz; these doublets are

(11) Krow, G. R.; Rodebaugh, R. *Org. Magn. Reson.* **1973**, *5*, 73.

Table V. Yields of Diels–Alder Adducts from Dihydropyridines and Methyl Acrylate[a]

3-substituent	RO_2C	yield of adduct mixture,[a] %
CH_3	Et	70[b]
CH_3	$PhCH_2$	60[b]
CH_3CH_2	Et	65[b]
CH_3O	Et	25[b]
CH_3O	$PhCH^2$	37[b]
CH_3S	Et	74[c]
CH_3S	$PhCH_2$	67[c]
Cl	$PhCH_2$	56[c]
Me_3Si	Et	60[b]
Me_3Sn	Et	51[c]
Bu_3Sn	Et	72[c]
CH_3O_2C	Et	45[c]

[a] Yields are for adduct mixtures purified by chromatography. [b] See text for isomer composition. [c] Expected to contain a mixture of regioisomers and stereoisomers.

nearly coincident at 6.04) and a doublet of doublets (J = 7.6, 6.5 Hz) at 6.37 (major) and 6.57 (minor). Also distinct from the 1,6-dihydro adduct was the ethoxy methylene which appear at 3.93 (major isomer). Overlap in the upfield region of the spectra prevents further by assignment of the spectrum or the stereochemistry of the two isomers.

g. Other Substituents. Isomer separation and complete spectral analysis was not undertaken in the other cases. Diels–Alder reactions were observed, however, and ambient temperature NMR spectra of the adduct mixtures were recorded. The yields for the mixtures of isomeric adducts are included in Table V. Regioisomeric and stereoisomeric adducts must be assumed to be present and the NMR spectra of the mixtures are consistent with this expectation.

Discussion

A. Substituent Effects. We would first like to place this work in the broader context of nucleophilic addition to pyridine rings. The tendency for pyridines with donor substituents to undergo addition at C-2 appears to be quite general. We have compiled some examples from the literature in Table VI. There is less information about systems with acceptor substituents, but in cases where data is available the acceptor substituents appear to result in reduced regioselectivity, as we observed in the case of hydride reduction.

It has long been known that 3-alkyl substituents lead to preferential addition of alkyllithium reagents to C-2 (entry A, Table VI).[12] Data on cases with acceptor substituents are sparse, but in the case of nicotinonitrile, reaction with butyllithium occurs with about a 3:1 preference for C-6 over C-2.[12b] Amination also favors C-2 in the case of 3-methylpyridine.[13a] 3-Aminopyridine and 3-(dimethylamino)pyridine undergo exclusive C-2 amination.[13b,c]

The most extensive set of data for substituent effects on nucleophilic addition involves cyanation of pyridine N-oxides (entry C, Table VI). This reaction has been carried out in two ways. Fife and co-workers treated

Table VI. Other Examples of Nucleophilic Addition Processes in 3-Substituted Pyridines Showing Preferential C-2 Addition for Donor Substituents

	3-substituent	2:6 ratio	ref
A. Addition of Organolithium Reagents to Neutral Pyridines			
MeLi	CH_3	84:16	12a
PhLi	CH_3	95:5	12a
i-PrLi	CH_3	20:80	12a
n-BuLi	CN	27:73	12b
t-BuLi	CN	37:63	12b
B. Amination of Neutral Pyridines			
	CH_3	90:10	13a
	H_2N	large	13b
	$(CH_3)_2N$	large	13c
C. Cyanation of Pyridine N-Oxides by $(Me_3)_3SiCN/(Me)_2NCOCl$			
	CH_3	90:10	14a
	CH_3O	98:2	14a
	Cl	89:11	14a
	CO_2CH_3	40:60	14a
	CN	55:45	14a
D. Alkaline Ferricyanide Oxidation of N-Methylpyridinium Ions to 2-Pyridones			
	CH_3	97:3	15
	CO_2CH_3	0:100	15
	CN	83:17	15

pyridine N-oxide and trimethylsilyl cyanide with an acylating agent, preferably dimethylcarbamoyl chloride.[14a] At room temperature, cyanation occurs with elimination of the acylated N-oxide substituent. The trend of substituent effects is closely parallel to that which we have observed. Under more vigorous conditions the acylating reagent is unnecessary as the N-oxide apparently undergoes silylation prior to elimination.[14b] The substituent orientation trend is similar; alkoxy, halogen, and dimethylamino are 2-directive but carbethoxy and cyano are not strongly directive. Under the more vigorous conditions, however, alkyl groups are only weakly 2-directive.

Oxidative conversion of pyridinium ions to pyridones by ferricyanide is a related reaction involving hydroxide ion addition. The methyl substituent is 2-directing. Two withdrawing substituents (CO_2CH_3, CN) are not consistent in this case.[15] The latter is completely 6-directing whereas the former is 2-directing.

There are other types of nucleophilic additions to pyridinium species which occur preferentially 1,4.[16] We have not considered substituent directing effects for these reactions.

Several factors have previously been considered as influencing the regioselectivity of nucleophilic additions to 3-substituted pyridines. Abramovitch and co-workers emphasized London (attractive) forces as the basis of the directing effect observed for addition of organolithium reagents to 3-alkylpyridines.[12] Directive effects on the 2-amination of 3-(dimethylamino)pyridine and cyanation of pyridine N-oxides by trimethylsilyl cyanide have been explained on the basis of lone-pair coordination with the approaching reagent.[13,14b] In the language of the qualitative molecular orbital theory these are "secondary orbital

(12) (a) Abramovitch, R. A.; Poulton, G. A.; *J. Chem. Soc. B* **1969**, 901. Abramovitch, R. A.; Giam, C. S. *Can. J. Chem.* **1964**, *42*, 1627. See also: Abramovitch, R. A.; Helmer, F.; Liveris, M. *J. Org. Chem.* **1969**, *34*, 1730. Abramovitch, R. A.; Helmer, F.; and Liveris, M. *J. Chem. Soc. B* **1968**, 492. (b) El Din, M. G.; Knaus, E. E.; Giam, C. S. *Can. J. Chem.* **1982**, *60*, 1821.

(13) (a) Abramovitch, R. A.; Helmer, F.; Saha, J. G. *Can. J. Chem.* **1965**, *43*, 725. (b) Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry*, 1984; Vol. 2, pp 236–237. Pozharskii, A. F.; Kuz'menko, V. V.; Azimov, V. A.; Yakhontov, L. N. *Khim. Geterotsikl. Soedin.* **1973**, 1232; *Chem. Abstr.* **1974**, *80*, 3412y.

(14) (a) Fife, W. K. *Heterocycles* **1984**, *22*, 2375. Fife, W. K.; Boyer, B. D. *Heterocycles* **1984**, *22*, 1121. Fife, W. K. *J. Org. Chem.* **1983**, *48*, 1375. (b) Sakamoto, T.; Kaneda, S.; Nishimura, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 565. Vorbruggen, H.; Krolikiewicz, K. *Synthesis* **1983**, 316.

(15) Abramovitch, R. A.; Vinutha, A. R. *J. Chem. Soc. B* **1971**, 131.

(16) Akiba, K.; Nishihara, Y.; Wada, M. *Tetrahedron Lett.* **1983**, *24*, 5269. Akiba, K.; Iseki, Y.; Wada, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1994. Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1984**, *25*, 3297. Comins, D. L.; Stroud, E. D.; Herrick, J. J. *Heterocycles* **1984**, *22*, 151.

(17) Ohno, A.; Ushida, S.; Oka, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 506.

Table VII. Total π-Density for Substituted Pyridines and Pyridinium Ions

3-substituent	N	2	3	4	5	6
			A. Pyridines			
H	1.06	0.97	1.02	0.96	1.02	0.97
CH_3O	1.03	1.04	0.97	1.02	0.99	1.01
CH_3	1.03	1.02	0.97	1.00	0.99	1.00
CH=O	1.08	0.91	1.03	0.88	1.13	0.92
CN	1.06	0.97	1.01	0.96	1.02	0.96
			B. *N*-Methylpyridinium Ions			
H	1.30	0.92	0.99	0.87	0.99	0.92
CH_3O	1.31	1.01	0.94	0.89	0.98	0.96
CH_3	1.30	0.99	0.93	0.87	0.98	0.95
CH=O	1.34	0.94	1.00	0.78	1.00	0.91
CN	1.32	0.94	0.98	0.85	0.99	0.93
			C. *N*-(Methoxycarbonyl)pyridinium Ions			
CH_3O	1.33	0.96	0.94	0.88	0.98	0.93
CH=O	1.36	0.84	1.00	0.76	1.01	0.87

Table VIII. Energies and Orbital Coefficients for Two π-LLUMO Orbitals

3-substituent	E	N	2	3	4	5	6
				A. *N*-Methylpyridinium Ions			
H	−0.089	0.00	−0.48	+0.51	0.00	−0.51	+0.48
	−0.170	−0.54	+0.44	+0.11	−0.54	+0.11	+0.44
CH_3O	−0.070	+0.01	+0.44	−0.53	+0.01	+0.52	−0.47
	−0.172	+0.52	−0.45	−0.10	+0.52	−0.13	−0.43
CH_3	−0.070	0.00	+0.46	−0.12	+0.02	−0.51	−0.44
	−0.165	+0.52	−0.43	−0.12	+0.53	−0.13	−0.44
CH=O	−0.129	−0.20	+0.62	−0.32	−0.04	+0.35	−0.23
	−0.165	+0.46	−0.27	−0.19	+0.56	+0.02	−0.52
CN	−0.115	+0.09	−0.53	+0.48	−0.01	−0.44	+0.39
	−0.178	−0.51	+0.39	+0.15	−0.54	+0.08	+0.47
				B. *N*-(Methoxycarbonyl)pyridinium Ions			
CH_3O	−0.085	−0.01	+0.50	−0.54	−0.17	+0.53	−0.39
	−0.202	−0.44	+0.34	+0.14	−0.47	+0.04	+0.57
CH=O	−0.136	−0.12	+0.60	−0.35	+0.03	+0.33	−0.28
	−0.182	−0.40	+0.33	+0.15	−0.55	+0.03	+0.50

effects" which ordinarily are dominant only when more direct regioselective influences are noncommittal. Since the regiodirective effect of donor substituents at the 3-position appears to be operative over a range of nucleophilic addition reactions, we wished to consider general structural features of the pyridine and pyridinium rings which might account for the observed regiochemistry. We explored the following mechanisms for regioselection, which ordinarily would take precedence over secondary orbital effects.

(1) Substituents can affect the total charges on the ring positions. If nucleophilic addition is a hard acid–hard base reaction, the total charges should dictate the position of attack.

(2) Substituents also influence the forms of molecular orbitals on the substrate. If nucleophilic addition is a soft acid–soft base reaction, the amplitudes of the pyridinium LUMO(s) at the ring positions should dictate the position of attack.

(3) Substituents affect the relative stability of the dihydropyridine products. If the transition states are late in the reaction path, the preferred product regiochemistry will reflect the stability of the products.

Total charges, molecular orbital energies and forms, and relative product stability can all be estimated within one computational scheme, approximate MO calculation. We chose CNDO-parametrized calculations[18] because (1) they are simple and fast enough to deal with the many structures of the relatively large systems in question and (2) they provide accurate charge distributions, qualitatively valid orbital forms, and reliable relative energies among systems with closely similar bonding. We took the essential precaution of energy-optimizing all structures' geometries by the gradient descent method[19] so that departures from conventional model geometries would not confound the energy comparisons.

Table VII shows that total π charges predict no discrimination between 2- and 6-attack by any nucleophile on substituted pyridiniums. Neither donor nor acceptor substituents cause major differentiation between C-2 and C-6 in *N*-methylpyridinium ions. In the 1-carbomethoxypyridinium ion there is a distortion of total charge but in the direction opposite from the experimentally observed regiochemistry.

Table VIII contains the amplitudes at ring positions of the two low-lying unoccupied MOs (LLUMOs) of several pyridinium ions. Though the frontier MO analysis stresses the properties of the lowest unoccupied MO, this represents only the first in a series of influences. In ions it is often a poor approximation to retain only the first term in the series. Often two or more vacant MOs are comparably accessible in energy. (In the table the lower lying MO has the more negative energy value *E*.) Among the *N*-methylpyridinium ions, the donor substituents do polarize both LLUMOs, but only to a small extent, and in opposite directions! In the *N*-carbomethoxypyridiniums the LLUMOs are lower in energy and more profoundly polarized but once again in opposite directions. In every

(18) Pople, J. A.; Beveridge, D. L. *Approximate Molecular Orbital Theory*; McGraw-Hill: New York, 1970.

(19) McIver, J. W., Jr.; Komornicki, A. *Chem. Phys. Lett.* **1976**, *10*, 303.

Table IX. Total Energies for 1,2- and 1,6-Dihydro-1-carbomethoxypyridines[a]

3-substituent	isomer	total energy (au)	Δ
CH_3O	1,2-syn	−10.6027	0.0105
CH_3O	1,6-syn	−10.5922	
CH_3O	1,2-anti	−10.5965	0.0041
CH_3O	1,6-anti	−10.5924	
CH_3	1,2-syn	−10.2381	0.0035
CH_3	1,6-syn	−10.2346	
CH_3	1,2-anti	−10.2394	0.0016
CH_3	1,6-anti	−10.2378	
CH=O	1,2-syn	−10.1807	−0.0020
CH=O	1,6-syn	−10.1827	
CH=O	1,2-anti	−10.1771	−0.0011
CH=O	1,6-anti	−10.1782	

[a] Syn refers to the conformation in which the carbonyl group is rotated toward the C-2 or C-6 CH_2 group.

case the influence exerted by the lowest UMO is canceled in major part by the influence of the next UMO. No clear prediction can be made on the basis of the frontier orbitals.

Preliminary calculations on the approach of BH_4^- to pyridinium species showed no hint of regioselectivity in early stages of the reaction, which is just what the noncommittal results of the analysis of total π-charges and LLUMOs would suggest. There is of course a strong driving force toward products, but it is mainly the electrostatic force between the oppositely charged reactants.

Table IX shows the relative energies of several reduction products. Energies for the 1,2- and 1,6-dihydro isomers of 3-methoxy-, 3-methyl-, and 3-formyl-1-carbomethoxypyridine were computed for individually optimized geometries for both syn and anti isomers. (We designate as syn the form in which the carbomethoxy carbonyl group is directed toward the ring CH_2 fragment.) For donor substituents, the 1,2-isomer is weakly but unambiguously favored. The preference is stronger for the methoxy-substituted system (6 kcal, syn; 2.5 kcal, anti) than for the methyl-substituted system (2 kcal, syn; 1 kcal, anti). For the acceptor substituent, the 1,6-isomer is weakly favored.

The preference for the 1,2-reduction product when a donor substituent is located at the 3-position can be understood with the help of a very simple Huckel model. If (for example) methoxy contributes two electrons and a sp^2 center to the butadiene-like π-system of the reduced pyridine ring, we have something like the normal pentadienyl anion π-system in the 1,2-product and an isopentadienyl anion in the 1,6-product. The two systems have Huckel energies of 5.646 and 5.226 β units, respectively. Incorporation of the N center and assumption of different α values to reflect the electronegativity of N and O reduces the difference in stability but does not change the result; the normal π-system is always more stabilized than the iso π-system.

Neither charge densities nor LUMO amplitudes and energies account for the preference for 1,2-reduction over 1,6-reduction. Product stabilities, however, do reflect this preference. Direct MO calculations thus can rationalize the directive effects of donor substituents and the lack of direction by acceptor substituents *if it can be assumed* that the reaction transition state(s) possess a product-like character which reflects the stability difference induced in the products by these substituents. Rings with donor substituents would be expected to be less reactive and therefore have more *product-like transition states* than rings with acceptor substituents. This would amplify the importance of stability effects for the donor substituents.

B. Synthetic Aspects. The Fowler reduction has been a valuable approach to 1,2-dihydropyridines for synthetic purposes. This work extends the reduction to a number of new and possibly useful substituted dihydropyridines. It further demonstrates some potential for regiochemical control by use of substituted hydride-transfer agents. While methyl and ethyl groups retain a preference for 1,2-reduction, branched substituents, in particular the trimethylsilyl group, open the possibility for regiochemical control favoring the 1,6-reduction product. Finally, the relative resistance of the *N*-carbethoxydihydropyridines to alkaline hydrogen peroxide may portend use of these intermediates under other conditions where oxidation might have been anticipated. While the compounds are quite sensitive to molecular oxygen, it appears that they may have substantial stability in the presence of other types of oxidants.

Experimental Section

A. Pyridines. The following literature preparations were employed: 3-methoxypyridine;[20] 3-(methylthio)pyridine;[21] 3-(trimethylsilyl)pyridine, 3-(trimethylstannyl)pyridine, and 3-(tributylstannyl)pyridine.[22] 3-(Methylsulfonyl)pyridine was prepared in 50% yield by oxidation of 3-(methylthio)pyridine with 3 equiv of "oxone".[23] The other pyridines were from commercial sources.

B. Reduction Procedures. All reductions were done under a nitrogen atmosphere. Tetrahydrofuran was distilled from benzophenone sodium. Methylene chloride was distilled from phosphorus pentoxide. Methanol was "absolute" reagent grade material used without further purification.

1. Inverse Addition Modification Applicable to Methyl Nicotinate and 3-Cyanopyridine. (a) Methyl Nicotinate. A solution of methyl nicotinate (0.31 g, 2.25 mmol) in 15 mL of absolute methanol was stirred at −40 °C under an N_2 atmosphere and 2.5 mmol (1.1 equiv) of ethyl chloroformate in 5 mL of ether was slowly added dropwise. After stirring this mixture together for 30 min, there was slowly added 2 equiv of a commercial solution of $K(i\text{-}PrO)_3BH$. The mixture was stirred at −40 °C for 1 h and then allowed to come to room temperature. The reaction mixture was poured into 30 mL of ice water and the product was extracted into 3 × 30 mL of ether. The ether was dried ($MgSO_4$) and concentrated in vacuo to deliver the product.

(b) 3-Cyanopyridine. A solution of 3-cyanopyridine (0.48 g, 4.6 mmol) in 20 mL of absolute methanol was stirred at −40 °C, and 1.1 equiv of ethyl chloroformate in 5 mL of ether was slowly added. After stirring this mixture for 30 min, it was treated with 1.1 equiv of sodium borohydride added in portions, and the reaction mixture was stirred 1 h at −40 °C before being allowed to come to room temperature. The product was worked up and extracted as described for methyl nicotinate.

2. General Procedure for Reduction by Potassium Triisopropoxyborohydride. A solution of 5.0 mmol of the substituted pyridine and 10.5 mmol of $K(i\text{-}PrO)_3BH$ (as a 1.0 M solution, Aldrich) in 20 mL of THF was stirred at −78 °C and a solution of alkyl chloroformate (5.5 mmol in 5 mL of ether) was added over a 10-min period. The mixture was stirred for 1 h at −78 °C, allowed to come to room temperature, and stirred for an additional hour. The reduction product was isolated by being poured into 30 mL of ice water and then extracting with ether. The ether extract was dried over $MgSO_4$ and evaporated in vacuo to provide the product.

3. General Procedure for Reduction by Lithium Tri-*tert*-butoxyaluminum Hydride. A mixture of 5.0 mmol of the substituted pyridine and 10.5 mmol (2.1 equiv) of $Li(t\text{-}BuO)_3AlH$ in 25 mL of THF was stirred at −78 °C and a solution of 5.5 mmol (1.1 equiv) of alkyl chloroformate in 5 mL of ether (or THF) was slowly added. The reaction mixture was stirred at −78 °C for an hour after the addition and then allowed to slowly come to room

(20) Finkentey, C.; Langhals, E.; Langhals, H. *Chem. Ber.* **1983**, *116*, 2394.
(21) Jacob, P., III; Shulgin, A. T. *Synth. Commun.* **1981**, *11*, 957.
(22) Fischer, A.; Morgan, M. W.; Eaborn, C. *J. Organomet. Chem.* **1977**, *136*, 323.
(23) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

temperature and stirred for an additional hour. The mixture was then poured into 30 mL of ice water at which point a thick slurry formed. This mixture was extracted with 3 × 30 mL of ether and the ether extracts were dried and concentrated to furnish the product.

4. General Procedure for Reduction by Diisobutylaluminum Hydride. A solution of 5.0 mmol of the substituted pyridine in 10 mL of CH_2Cl_2 was stirred at −78 °C and 1.1 equiv of alkyl chloroformate was added as a CH_2Cl_2 solution. This mixture was stirred at −78 °C for 30 min and 2.1 equiv of $(i\text{-Bu})_2AlH$ (as a 25% by wt solution in toluene) was then added via syringe over a period of 10 min. The reaction mixture was stirred at −78 °C for 1 h, allowed to come to room temperature, and stirred for an additional 30 min. Ether, 20 mL, was added, followed by the slow dropwise addition of 10 mL of 3% HCl. After stirring for 5 min, the initially formed precipitate had redissolved. The layers were separated and the aqueous layer was washed with several portions of ether. The ether was dried and evaporated to provide the dihydropyridine.

5. General Procedure for Reduction by Sodium Tri-*sec*-butylborohydride. A solution of 5.0 mmol of the 3-substituted pyridine was stirred in 15 mL of THF at −78 °C. The alkyl chloroformate, 1.1 equiv, dissolved in 5 mL of THF was added slowly over the course of 15 min and the resulting slurry was stirred at −78 °C for 30 min. A 1.0 M solution of $Na(sec\text{-Bu})_3BH$,[6] 2.1 equiv, was slowly added via syringe, and the mixture was stirred at −78 °C for an additional hour. After being allowed to slowly warm up to room temperature, a mixture of 4 mL of 30% H_2O_2 and 6 mL of 10% NaOH was *very slowly and carefully* added. (The initial reaction is vigorous and exothermic.) After the addition was complete, the mixture was stirred overnight at room temperature with the nitrogen atmosphere being maintained. The reaction mixture was then poured into 50 mL of ice water and extracted with 3 × 40 mL of ethyl ether. The ether extracts were dried over $MgSO_4$ and concentrated in vacuo to deliver the dihydropyridines as oils in yields of 50–70%.

C. Diels–Alder Reactions. The dihydropyridines were placed in glass tubes with 5 equiv of methyl acrylate, frozen, and sealed under a nitrogen atmosphere. The tubes were heated to 120 °C for 48 h. After cooling, the tubes were opened and the contents removed and held under 0.1 mmHg vacuum overnight to remove excess methyl acrylate. The crude adduct mixtures were dissolved in a minimum amount of ethyl acetate and passed through a flash chromatography column eluting with a mixture of 1:1 hexane/ethyl acetate. The collected fractions were checked by TLC and the appropriate tubes combined to furnish the adducts.

D. Iodolactonization of 3bN. The separated diastereomeric adducts **3bX** (12 mg) and **3bN** (20 mg) were saponified by stirring in MeOH (3 mL) to which 2 mL of 20% NaOH was added. After 3 h, TLC indicated complete hydrolysis. The solutions were made slightly acidic (pH 5) with 10% HCl and extracted with CH_2Cl_2. Removal of the solvent in each case gave the acid. The acid from **3bN**, 11.7 mg, was stirred in 2 mL of 0.5 M $NaHCO_3$ solution and a solution of 0.0285 g of iodine and 0.045 g of potassium iodide in 3 mL of H_2O was added. The mixture was allowed to stand in the dark overnight and was then shaken with 0.6 M sodium thiosulfate solution and chloroform. The chloroform layer was dried over sodium sulfate and evaporated in vacuo to provide 11.3 mg of material. The acid from **3bX**, 3.0 mg, was stirred in 1 mL of 0.5 M $NaHCO_3$, and 0.0098 g of iodine and 0.013 g of KI in 2 mL of H_2O were added. After standing in the dark overnight, it was worked up with sodium thiosulfate and extracted with chloroform as in the previous case. Evaporation of the solvent furnished 3.3 mg of material. The product from each diastereomer was compared against an iodolactonization run in a similar manner on an unseparated mixture of **3bN** and **3bX**. TLC of the two reaction products against this iodolactone showed that diastereomer **3bN** gave a matching spot while diastereomer **3bX** gave no corresponding spot. The high-field NMR of the product from **3bN** was consistent with the expected iodolactone structure. None of this material was present in the product from diastereomer **3bX**. NMR of iodolactone: (360 MHz NMR) (2-azabicyclo-[2.2.2]octane-6-carboxylate numbering) δ 7.4, aromatic; 5.2, benzyl and C-7; 4.93 and 4.76 triplets, rotational doubling, C-1; 4.16 d C-8; 3.67, d of t, and 3.08, d of d, C-3 CH_2, J_{gem} = 11 Hz; 2.89 m, C-6; 2.27, d of d and 1.89, d of m C-5 CH_2, J_{gem} = 14 Hz; 1.06 C-4 Me.

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