DISSERTATION

ASYMMETRIC CONJUGATE ADDITIONS TO PYRIDINE AND QUINOLINE

Submitted by

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY DAVID G. WETTLAUFER ENTITLED "ASYMMETRIC CONJUGATE ADDITIONS TO PYRIDINE AND QUINOLINE" BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Adviser

Department Head

ABSTRACT

ASYMMETRIC CONJUGATE ADDITIONS TO PYRIDINE AND QUINOLINE

Extensive studies have investigated the stereochemical and mechanistic aspects of NADH (nicotinamide adenine dinucleotide)mimics. With potential use in mind, chiral 4-methyl and 4-phenyl-1,4-dihydropyridines were synthesized by alkylation of 3-oxazolinylpyridine. (This oxazoline and the oxazolinylquinoline below were derived from (1S,2S)-1-phenyl-2-amino-3-methoxypropanol). Addition of excess methyllithium gave the dihydropyridines, isolated as the methyl urethanes, in 85-90% de and 79-81% yield. This high stereoselectivity was found to be independent of temperature and concentration. The oxazoline was readily removed to the aldehyde in 60% yield *via* quaternization with methyl fluorosulfonate followed by reduction and hydrolysis. Phenyllithium addition gave the addition products in 84% de and 94% yield.

Chiral 4-methyl-1,4-dihydropyridines were also synthesized by alkylation of 3-imino pyridines with excess methyl cuprates. These imines were prepared from 3-pyridinecarboxaldehyde condensed with phenylalaninol, phenylalaninol methyl ether, (S)-ethylvalinate, and (S)-t-butylvalinate. The highest stereoselectivity was realized upon alkylation of the t-butylvalinate imine to give the dihydropyridines as the methyl urethanes in 56% de. Mild acid hydrolysis yielded N-carbomethoxy-3-formyl-4-methyl-1,4-dihydropyridines in 82% yield.

ACKNOWLEDGEMENTS

The author would like to thank Professor A. I. Meyers for the support and the opportunity to do exciting research in his group. His never-ending enthusiasm was refreshing and an inspiration throughout my graduate career.

Several people who helped with various aspects of my reserch I would also like to thank. These include Susie Miller and Don Dick for their guiding hand in the operation of the high-field NMR instruments. The extensive rotational barrier experiments and data manipulation would not have been possible without the generous assistance by Jeff Sullivan and Professor Jack Norton. Similarly, the electrochemistry became reality with the help of Jody Redepenning. Valuble discussions with (and valuble reagents from) members of the Meyers' group are also greatly appreciated.

Thanks also goes to Rosalie Jaramillo for typing this dissertation and to Dianne Lindermann and Cathy Highsmith for their structure drawing.

My good friends P. Floyd, D. Straits, C. B. Potts, and, of course, Sally, must also be acknowledged.

Finally, my sincere thanks to my family for helping me through the highs and lows of my educational process and life in general, and for teaching me how to work.

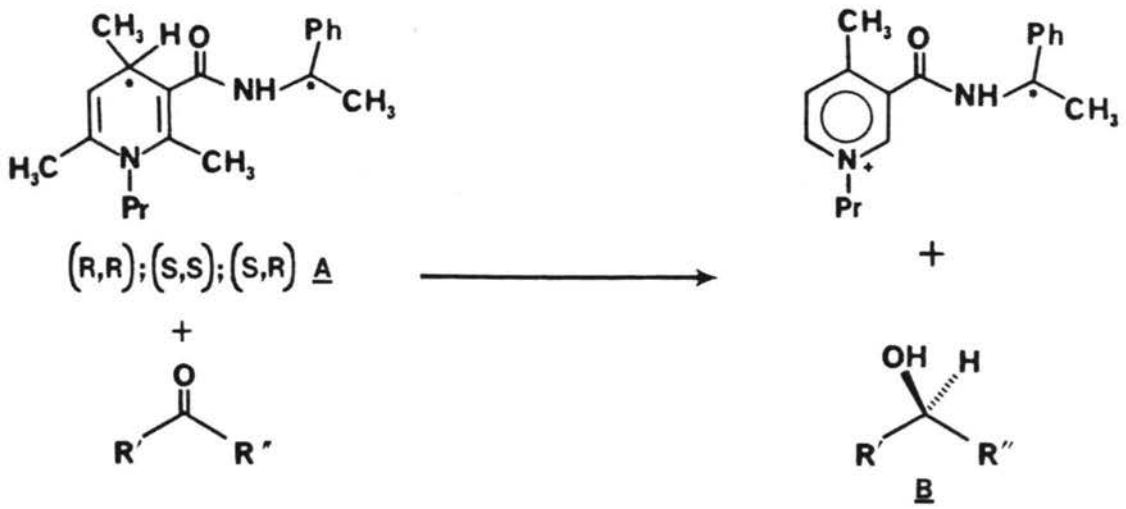
TO MY PARENTS

PREFACE

Significant progress has been made in the past ten years towards the development of methodology for various asymmetric synthetic processes. These include oxidations, reductions, and the formation of carbon-carbon bonds. With this arsenal of techniques in hand, chemists have undertaken the stereospecific synthesis of numerous complex natural products. Organic chemists have also been interested in the study of natural chemical processes, including reductions of imines of keto acids to amino acids by NADH (nicotinamide adenine dinucleotide). This has been studied using laboratory model systems or NADH mimics.

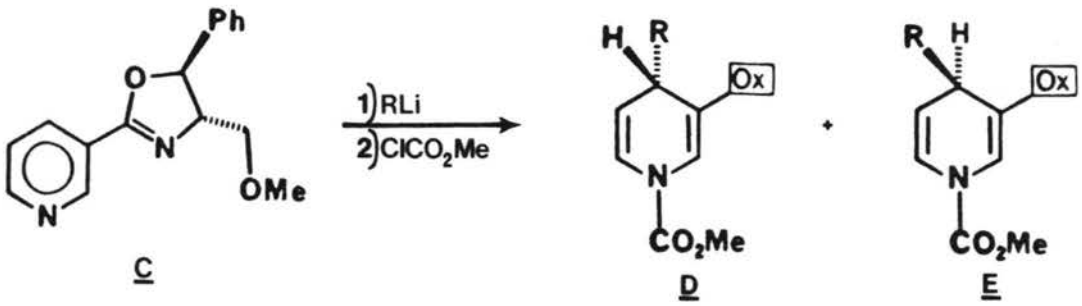
In nature, the NADH coenzyme reduces functionalities such as aldehydes, carboxylic acids, olefins, and imines to name a few. Alternatively, the oxidized NADH (NAD^+) participates as a coenzyme for oxidation processes, regenerating the NADH. Investigators have used the NADH mimics with attention directed towards the role of the metal ion present during the reduction process, the mechanism of reduction, and the stereospecificity.

Dihydropyridine A, containing two stereocenters, has been studied in other laboratories for the reduction of various carbonyl substrates. The absolute configuration of the resulting alcohols B (formed in >90% ee) was found to depend only on the configuration at C-4, and independent of the amide moiety configuration. It should be noted however, that the diastereomerically pure dihydropyridines A were

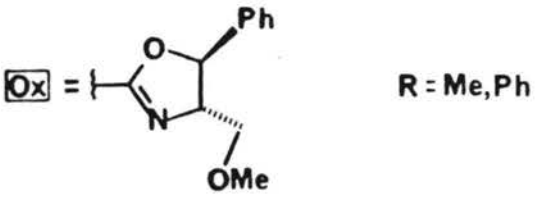


prepared by a fractional recrystallization from an equal mixture of two diastereomers. Because of the high stereospecificity exhibited by A and an interest by the Meyers' group in NADH mimics, a project was initiated to investigate the stereospecific synthesis of chiral 1,4-dihydropyridines. The first portion of this dissertation describes their synthesis via two routes.

Methodology developed by a former postdoctoral fellow in our group, N. R. Natale, was used by this author for the synthesis of diastereomeric dihydropyridines D and E, by the addition of methyllithium and phenyllithium to oxazolinylpyridine C. Consistantly high stereoselectivity occurred with addition of methyllithium (85-90% de) over a -40°C to -100°C temperature range. Concentration also had no effect, 0.10M to 0.01M, resulting in ∿90% de. Slightly lower asymmetric induction (84% de) was observed for the addition of phenyllithium. The formation of the major diastereomers (4S) was rationalized in terms of a tightly coordinated pre-addition complex formed from the oxazolinylpyridine and the organolithium.

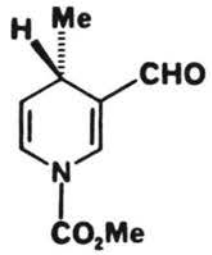


C D E



R = Me,Ph

The oxazoline moiety was easily removed from D (and E) (R=Me) by quaternization, reduction, and hydrolysis to give aldehyde F. The

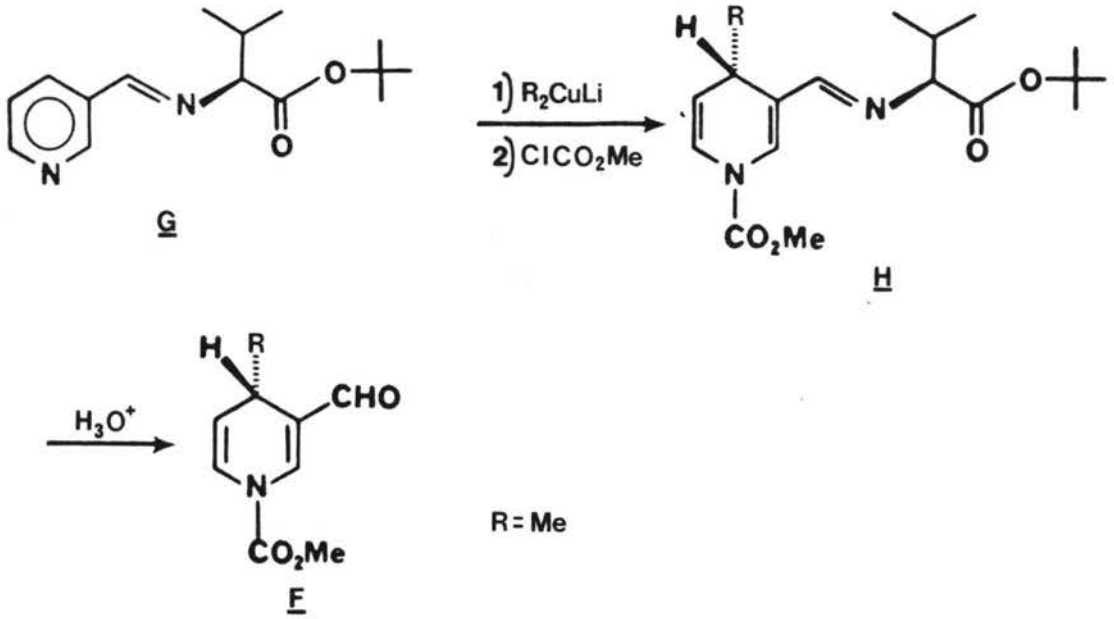


F

enantiomeric excess was determined by reduction of the aldehyde and preparation of the Mosher ester. Analysis by ^{19}F and ^{1}H NMR indicated 82% ee, slightly lower than the oxazoline precursor (88% de).

In a similar fashion, chiral 1,4-dihydropyridines were synthesized by conjugate addition to a series of imino pyridines, derived from 3-pyridine carboxaldehyde and various chiral amines. (It should be noted that this investigation was undertaken before the methodology for facile oxazoline had been realized. It was postulated that the intermediate imino-1,4-dihydropyridines could be hydrolyzed under mild

acid conditions to liberate the enantiomeric dihydropyridines). The highest stereoselectivity was observed for the addition of lithium dimethylcuprate to imine G, formed from t-butylvalinate. The diastereomeric ratio of the dihydropyridine H was found to be 22:78 as determined by HPLC. Mild acid hydrolysis gave the enantiomerically

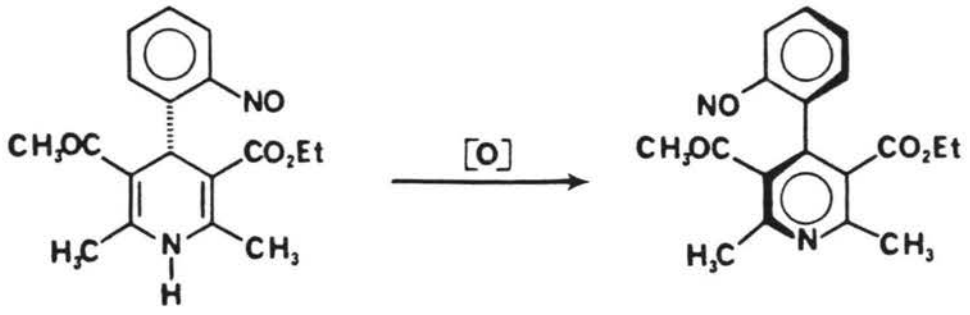


G H F

enriched aldehyde F, with the newly created center of the (S)-configuration. This stereochemistry was rationalized in terms of conjugate addition of the cuprate to a complex formed from the imine and lithium iodide.

The latter portion of the dissertation is concerned with asymmetric synthesis via a self-immolative process. Examples in which one stereocenter, or element of chirality, is destroyed with concomitant formation of another have appeared in the literature and include a hetero-ene reaction, and the formation of allenes and olefins. Another type was proposed by Berson and Brown in 1955, in

which the sp^3 center (central chiral element) of dihydropyridine I was destroyed during the formation of biaryl J (axial chiral element), via

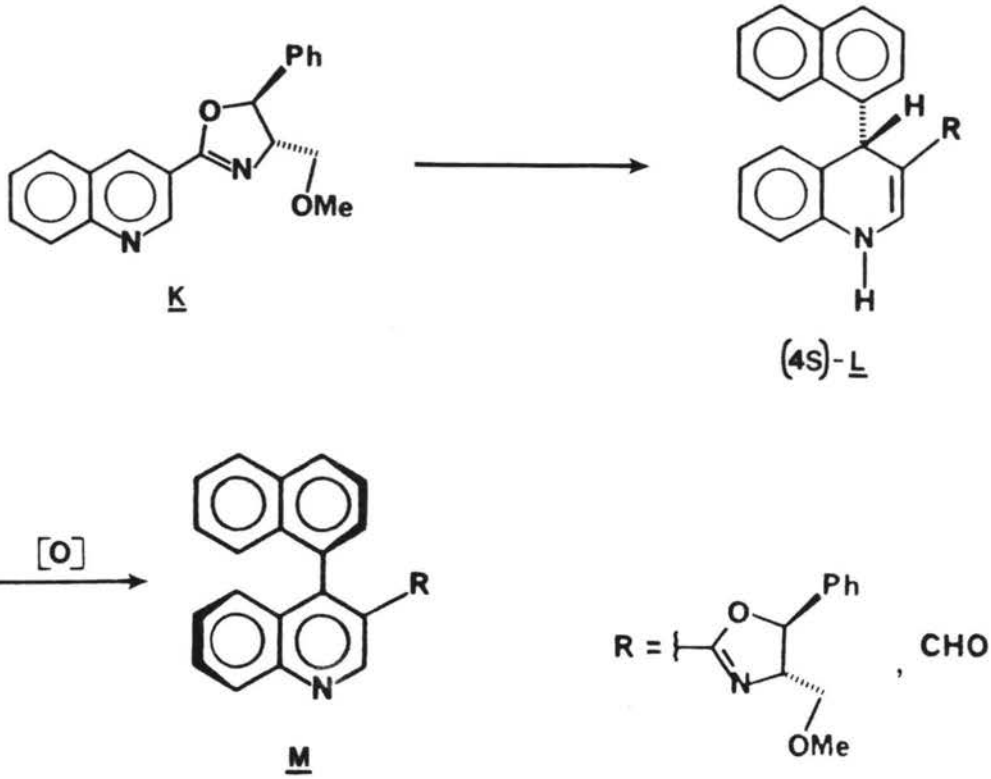


I J

oxidation. Because the aryl group in I was free to rotate, diastereomeric transition states were proposed during the oxidation process. Thus, enantiomerically enriched biaryl would result upon complete reaction, in the absence of any additional stereocenters capable of exerting a stereochemical bias during the transformation. Due to lack of sufficiently enantiomerically enriched I, the proposal could not be conclusively verified, nor has it been since investigated or shown to occur until now, albeit on a slightly different system.

Dihydroquinoline L (R=[OX]) (76% de) was synthesized by addition of 1-naphthyllithium to oxazolinylquinoline K. Virtually complete conservation of chirality occurred upon oxidation with DDQ to biaryl M (R=[OX]) (78% de), albeit in the presence of external stereocenters, namely the oxazoline. Similar results were obtained for the oxidation of K (R=CHO) (75% ee) to give M (R=CHO in 80% ee). With this high degree of conservation of chirality, and establishing the free rotation of the naphthyl group by low temperature ^1H NMR (rotational barrier = $\Delta G^{\dagger}_{298} = 11.2 \pm 0.2$ kcal mol^{-1}, for the 7'-methoxy-L, R=CHO) complete verification of the Berson proposal had been realized. Most

importantly, this was accomplished with no external stereocenters present in the molecule (R=CHO).



Addition of 1-naphthylmagnesium bromide to oxazolinylquinoline K in toluene led to the antipodal addition adduct. Based on a solvent effect study, this reversal in stereoselectivity was attributed to addition of an aggregated Grignard reagent, in contrast to a monomeric naphthyllithium. Pre-addition complexes were proposed to rationalize the observed stereochemistry.

As previously mentioned, the oxidation to the biaryls was done with DDQ. Subsequent investigation of smaller reducing agents including aqueous $KMnO_4$ and PDC led to considerable loss of chirality. Thus, it was apparent that the proper choice of reducing agents was essential for the transfer of stereocenters. Treatment of the lithium

derivative of the dihydroquinolines, with DDQ led to near random oxidation and greatly diminished chirality.

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CHAPTER I

INTRODUCTION

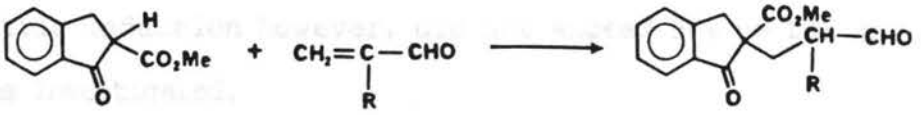
Since the first reported asymmetric synthesis via conjugate addition (Michael addition) in 1962, several types of reactions have been developed utilizing different functionalities in the construction of centers of asymmetry. Overall, the highest selectivity has been realized by the addition of an achiral nucleophile to a chiral substrate, such as chiral α,β-unsaturated esters, sulfoxides, oxazolines, and aryl oxazoline compounds. Considerable attention has also been directed towards the use of nucleophiles incorporating a chiral ligand, such as chiral heterocuprates and chiral bases, so as to impart asymmetry into the reaction. Finally, nucleophiles which are inherently chiral due to an attached asymmetric center, such as chiral enolates and azaenolates, have undergone conjugate addition. Subsequent manipulations removed the asymmetric moiety to give the desired product.

This section will survey, in detail, the addition of chiral nucleophiles to achiral substrates, followed by achiral nucleophiles to chiral acceptors. Special attention, where possible, will be directed at proposed transition states and internal chelation.

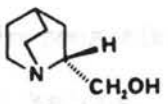
A. Achiral Acceptors

1. Chiral Catalysts

The first report of the use of a chiral catalyst in a Michael addition was reported by Langstrom and Bergson[1] in 1973. Conjugate addition of methyl-2-carboxy-1-indanone 1 to acrolein and -isopropylacrolein, catalyzed by optically active (R)-(+)-2-(hydroxymethyl)-quinuclidine 2, led to the Michael adduct 3 in quantitative yields. Although the enantiomeric excess (ee) could not be determined on the optically active products, it nonetheless served to open the door to further investigations of this type of reaction.



1 R: Me, i-Pr 3



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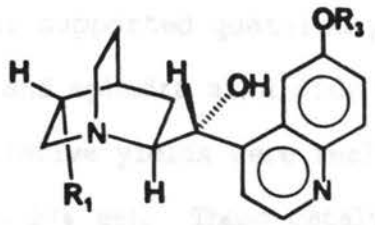
A similar study reported by Wynberg[2] described the conjugate addition of 1 to methyl vinyl ketone. The catalyst, (-)-quinine afforded the corresponding Michael adduct in 68% ee in 89% yield. The use of carbon tetrachloride, in place of toluene, further increased the ee to 76%.[3] Addition of ethanol (2%), to the carbon tetrachloride reaction mixture resulted in a large decrease in selectivity to 33% ee. It was concluded that an apolar solvent favored the formation of a tight ion pair between the protonated catalyst and the enolate ion. Addition of ethanol caused partial destruction of the hydrogen bonding

between the hydroxyl group and the catalyst 4 and the enone, which was postulated to be important for high selectivity.



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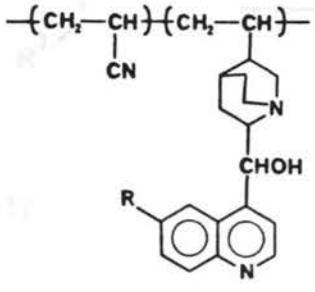
Several other reports have appeared in the literature in which various other cinchona alkaloid derivatives,[4] ephedrine salts,[5] and brucine,[6] were used as catalysts for the Michael additions. The asymmetric induction however, did not exceed 50% ee for any of the examples investigated.

The use of polymer supported catalysts has also been extended to asymmetric conjugate addition processes.[7] A copolymer derived from acrylonitrile and various cinchona alkaloids, 5, catalyzed the addition of indanone to methyl vinyl ketone. Chemical yields were generally



5 R=H, OMe

90%, with up to 42% ee realized. The polymer, recovered after use by filtration of the reaction mixture, was found to retain nearly all of its activity. Additions utilizing the non-polymer bound alkaloids gave

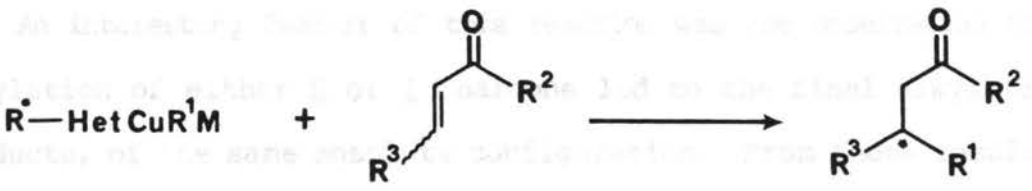
higher stereoselectivity (up to 57% ee), however they were not as easily isolated for reuse.

Similarly, polymer supported quaternary ammonium salts derived from several cinchona and ephedra alkaloids have also been used as catalysts.[8] Near quantitative yields were realized, albeit with lower stereoselectivity (up to 27% ee). These catalysts were also found to be more fragile, and hence more difficult to recycle.

2. Chiral Organometallics

An area of asymmetric conjugate addition which has received considerable attention over the past few years relies on the use of chiral heterocuprate reagents. Overall, the process may be summarized by Scheme 1. Several laboratories have investigated the effect of

Scheme 1

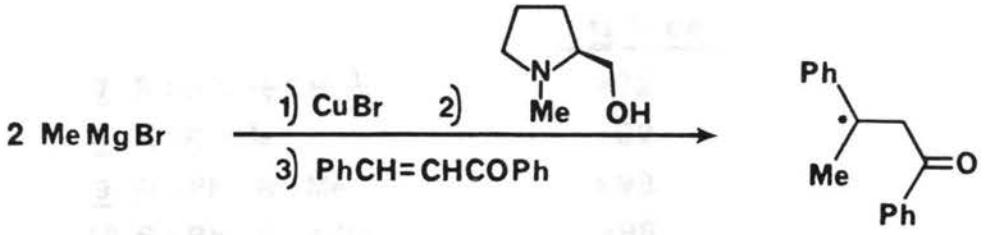


R• = chiral moiety
Het = N, O, S
M = $Mg^{+}Br$, Li^{+}
R^1, R^2, R^3 = alkyl, aryl

various coordinated chiral amines,[9] with generally low stereoselectivity (<1-23% ee). In a similar fashion, chiral thiolates and alcoholates[10] have been utilized with only slightly greater success (up to 34% ee). Many of these alkylations however, were plagued by a

central problem. Higher ee's were frequently accompanied by low chemical yields, and vice versa, making their synthetic utility questionable.

In 1980, Mukaiyama[11] reported the conjugate addition of a chiral heterocuprate which overcame the problem of low ee's and low yields. Treatment of chalcone with the cuprate derived from (S)-1-methyl-2-hydroxymethylpyrrolidine, cuprous bromide, and methylmagnesium bromide, led to addition product 6 in 68% ee and 71% yield.



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An interesting feature of this reaction was the observation that alkylation of either E or Z chalcone led to the final alkylation products, of the same absolute configuration. From these results, Mukaiyama suggested that both reactions proceeded through the same radical anion intermediate, which was generated by initial one electron transfer from the cuprate to the substrate.

Further investigation of this same reaction in another laboratory[12] further improved the asymmetric induction. Upon dilution of the reaction mixture, up to 88% ee was realized in 80% yield.

Chiral cuprates have also been reported where the chiral ligand was transferred to a series of prochiral receptors.[13] Treatment of the enones 7-10 with the homo or heterocuprate of (S)-2-(1-dimethylamino)

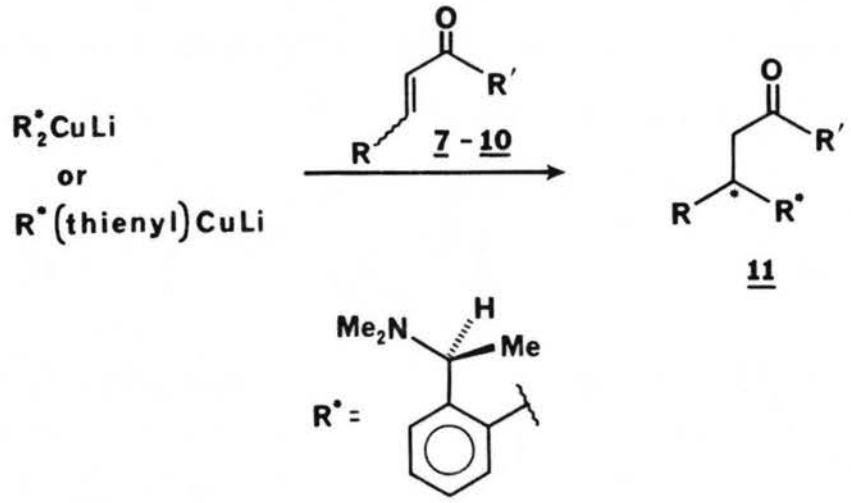


TABLE 1

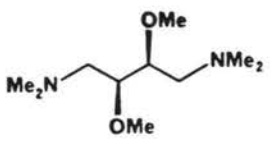
		11 % ee
7	R = R′ = $-(CH_2)_3-$	>92
8	R = R′ = Me	82
9	R = Ph, R′ = Me	>98
10	R = Ph, R′ = t-Bu	>98

phenyllithium, led to the corresponding addition product 11. The reactions were generally characterized by excellent stereoselectivity in 42-87% chemical yield (Table 1).

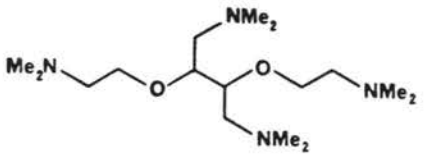
Treatment of enone 10 with the chiral phenyllithium (R*Li) gave a mixture of 1,2 and 1,4 addition products, the latter being formed in a diastereomeric excess (de) of 94%. Interestingly, the absolute configuration of the major diastereomer was opposite to that formed in the cuprate additions.

Chiral ligands of another sort were reported in 1979 by Seebach.[14] The use of ligating cosolvents DDB 12 and DEB 13 (both derived from tartaric acid) in association with various achiral aliphatic cuprates,

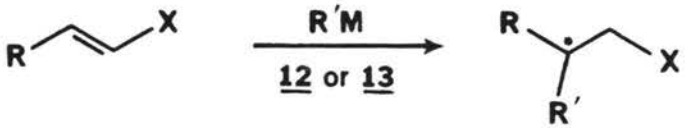
organozinc, and organolithium compounds underwent conjugate addition to 14. Yields of 15 varied (39-84%) with a wide range of ee's. The most



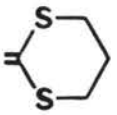
(S,S) - 12



(S,S) or (R,R) - 13



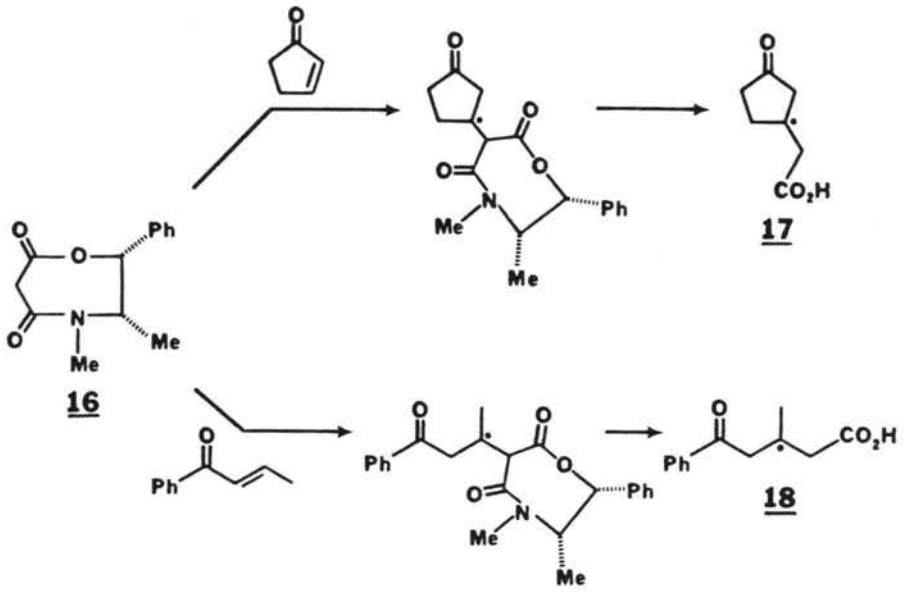
14 15

X = COR, NO_2, CH= 

effective influence was exhibited for the addition of butyllithium to 1-nitropropene. DDB complexation resulted in 28% ee with DEB complexation giving 58% ee, presumably due to the increased number of heteroatoms available for complexation.

3. Resonance Stabilized Carbanions

In 1978, it was reported that the enolate of oxazepine dione 16 underwent addition to 2-cyclopentenone to give, after hydrolysis, ketoacid 17.[15] Depending on the base employed, the stereoselectivity varied greatly (from 7% ee with $NiCl_2$/t-BuOK, to 76% ee with dicyclohexyl-18-C-6/t-BuOK). Similar results were realized for the addition to 1-phenyl-2-butenone, (0% ee with t-BuOK, and 55% ee with 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU)), to give 18.



Oxazepine dione 16 was also added to 1-nitrocyclohexene, under basic conditions, to give addition product 19 in 67-98% yield, as a mixture of cis-trans isomers.[16] Further transformations gave hydroxy acid 20 and lactone 21. Interestingly, the addition of a crown ether to the reaction mixture, increased as well as reversed, the stereoselectivity (Table 2). The exact role of the crown ether was not known, but was thought to form a bulky complex which somehow controlled the stereoselective approach of the nucleophile.

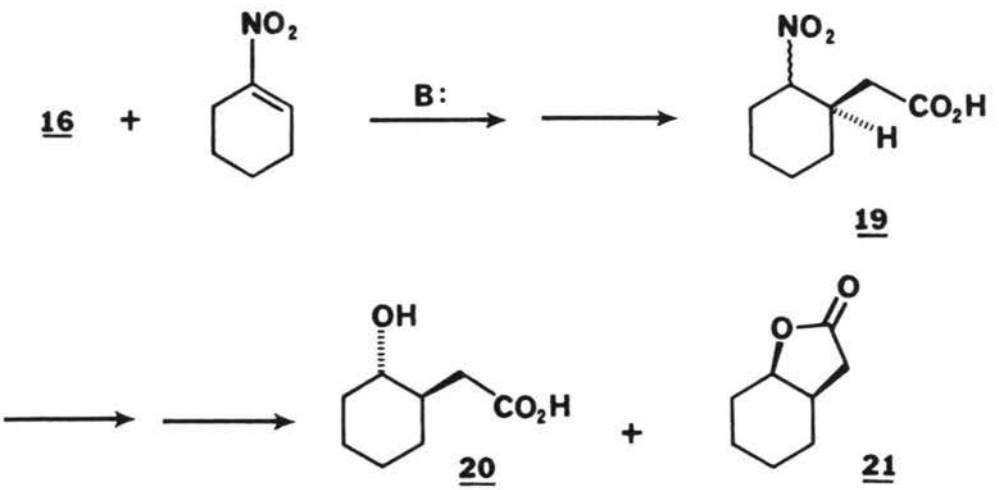
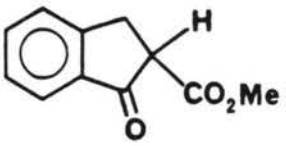


TABLE 2

Entry	Base	Additive	% ee (21)	Abs. Confign. (21) (C-1)
1	t-BuOK		26	S
2	t-BuOK	dicyclohexyl 18-C-6	75	R
3	CsF		38	S
4	CsF	dicyclohexyl 18-C-6	71	R

A rather novel approach to asymmetric conjugate addition of an enolate was reported in 1981 by Cram.[17] The potassium enolates of 22, 23, and 24, complexed to the chiral crown ethers 25 and 26, were added to methyl vinyl ketone and methyl acrylate. The resulting Michael adducts were formed in 60-99% ee and usually >80% yield. The observed stereochemistry of the resulting products was rationalized by the steric interactions of the incoming electrophile and the naphthalene rings. For example, in the reaction of the potassio anion of 23 with



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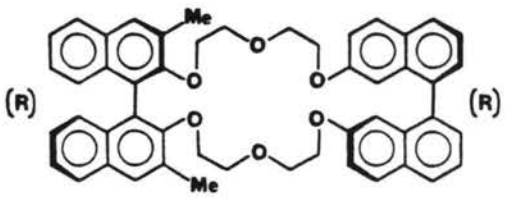

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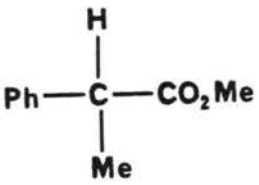

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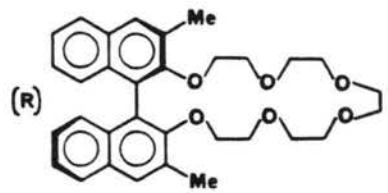

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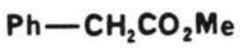

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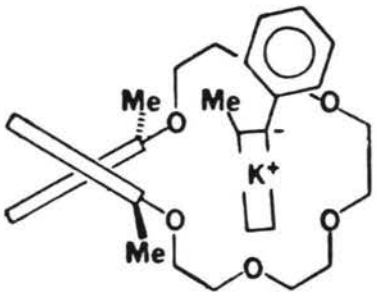
methyl acrylate, the anion would be situated such that steric interactions between the naphthalene rings and the phenyl ring were minimized (27). The rectangle embracing K^+ symbolyzes the plane of the ion pair. Subsequent reaction with methyl acrylate, from the topside (28), resulted in the addition product 29, with the (S)-configuration.



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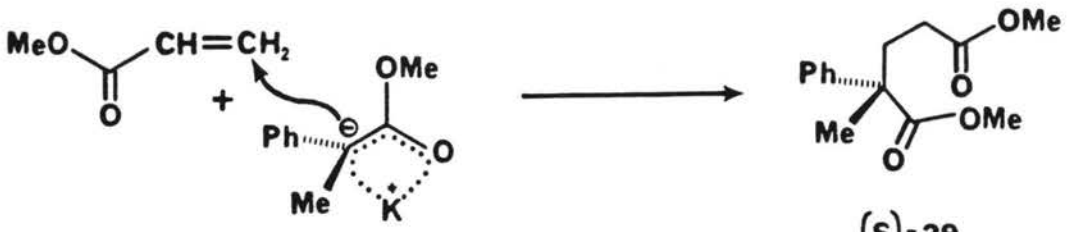
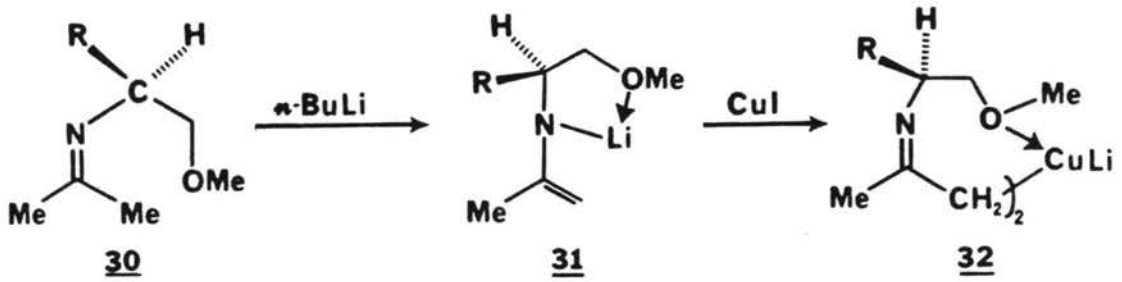


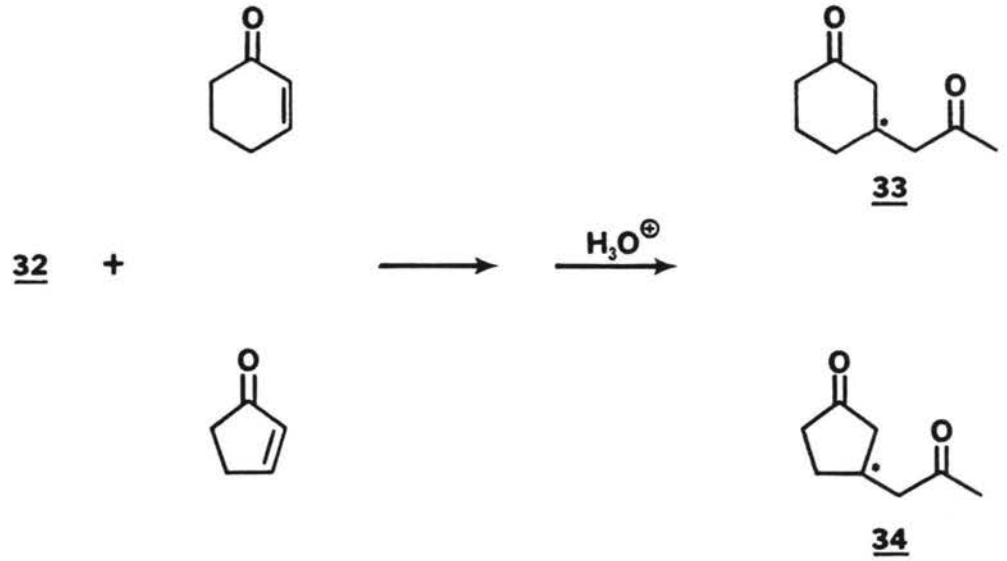
(R) Host 28 (S)-29

In 1982, chiral copper azaenolates, derived from acetone and chiral amino alcohols, were found to add in a Michael fashion to enones.[18] Thus, deprotonation of imine 30 followed by addition of cuprous iodide formed the homocuprate 32, via 31. Addition to 2-cyclohexenone and 2-cyclopentenone gave, after hydrolysis, the alkylation products 33 in 27-44% ee (30-46% yield) and 34 in 16-75% ee (54-89% yield) respectively. The stereoselectivity of the alkylation generally improved with increasing size of the chiral auxiliary (i.e., R = CH_2Ph < i-Pr < t-Bu). Furthermore, either enantiomer could be

prepared by the use of the appropriate enantiomer of the chiral auxiliary.

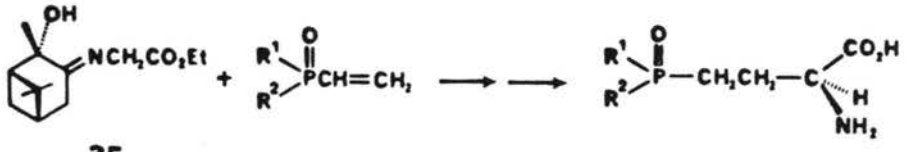


30 31 32



R = CH_2Ph, *i*-Pr, *t*-Bu

More recently, the chiral imine 35, derived from glycine ethyl ester and (1S,2S,5S)-2-hydroxypinan-3-one, after treatment with base, underwent addition to vinyl phosphinate 36.[19] The resulting (+)-



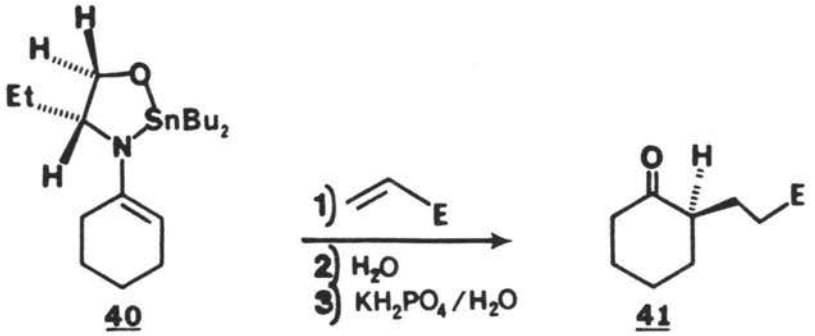
35

36 (R^1 = Me, R^2 = OH)
38 (R^1 = R^2 = OEt)

37 (R^1 = Me, R^2 = OH)
39 (R^1 = R^2 = OH)

phosphinotricine (37), which exhibits herbicidal activity, was formed in 85% ee and 66% yield. Similarly, addition to 38 led to antiviral (+)-2-amino-4-phosphonobutyric acid 39, in 54% ee and 68% yield.

Chiral organotin azaenolates are also known to add to acrylates and acrylonitrile.[20] Tin enamine 40, when treated with various Michael

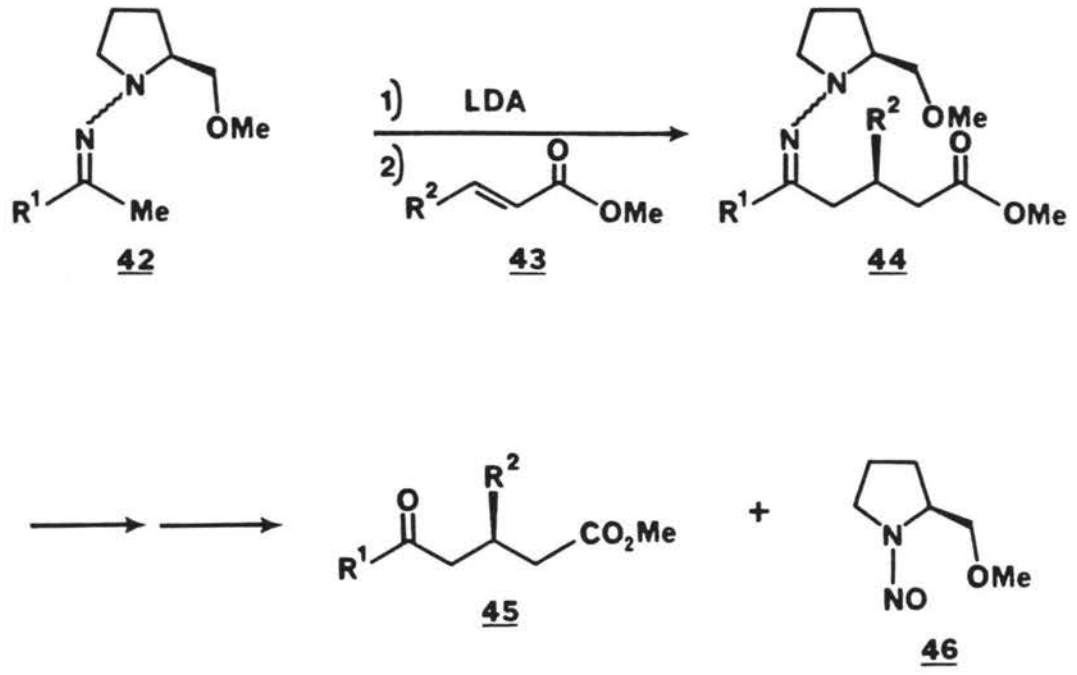


40 41

E = CO_2Me, CO_2Et, CN

acceptors, gave optically active addition products, 41. The highest stereoselectivity was observed for addition to methyl acrylate to give 41 (E = CO_2Me) in 86% ee (after correction for the optical purity of the starting material) in 63% yield.

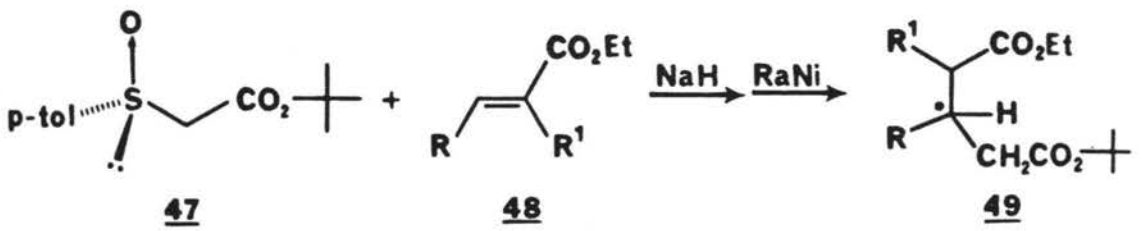
The use of chiral hydrazones as masked enolates has been extensively studied by Enders.[21] In 1983, he reported the asymmetric conjugate addition to acrylic esters. Deprotonation of hydrazone 42, followed by addition to acrylate 43, gave imino ester 44. Removal of the chiral auxiliary afforded δ-keto ester 45 and nitrosamine 46, which was recycled. The alkylations proceeded with high enantioselectivity (≥96%) and 49–61% yield. Here again, either enantiomer could be formed preferentially by proper choice of the (R) or (S) chiral auxiliary.



R^1, R^2= alkyl, Ph

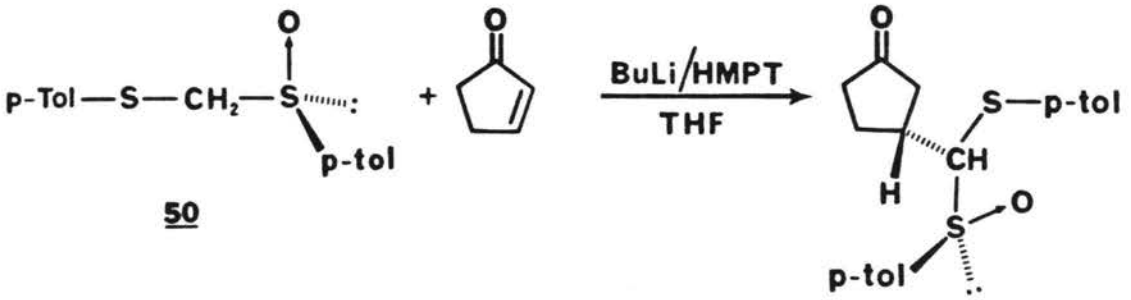
The chiral delocalized carbanions mentioned thus far have all possessed the element of chirality at a carbon atom. Another class of stabilized carbanions, where this is in fact not the case, is chiral sulfoxides.

The first report of the conjugate addition by a chiral sulfoxide appeared in 1979.[22] The anion derived from α-sulfinyl ester 47, on addition to acrylate 48 gave, after desulfurization, the diesters 49 in up to 24% ee and 70% yield.

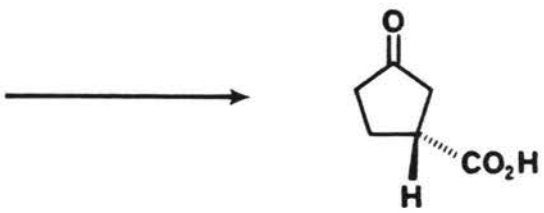


R = Me, Ph ; R^1 = H, CO_2Et

Two years later, Colombo[23] described the addition of a similar sulfoxide 50 to 2-cyclopentenone, producing 51. Reductive cleavage led

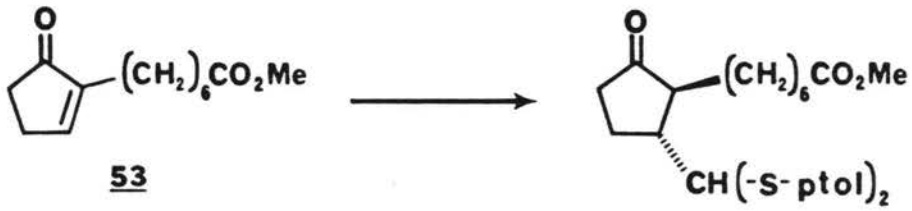


50 51



52

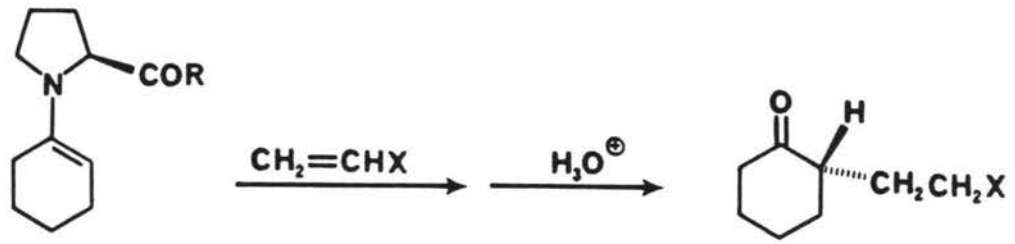
to the chiral keto-acid 52 in 38% ee (32.5% overall yield from the enone). This methodology was used for the stereoselective synthesis of cyclopentanone 54,[24] an intermediate in prostaglandin synthesis. Thus, 2-substituted-2-cyclopentenone 53 was alkylated with sulfoxide 50. Sulfoxide reduction gave 54 which was obtained in 59% yield as a single diastereomer.



53 54

4. Chiral Enamines

The use of chiral enamines as nucleophiles in Michael additions was first reported by Yamada[25] in 1969. Enamine 55, derived from various esters of proline and cyclohexanone, underwent addition to acrylonitrile and methyl acrylate followed by hydrolysis of the

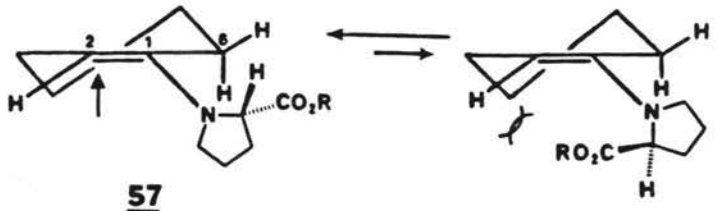


55 56

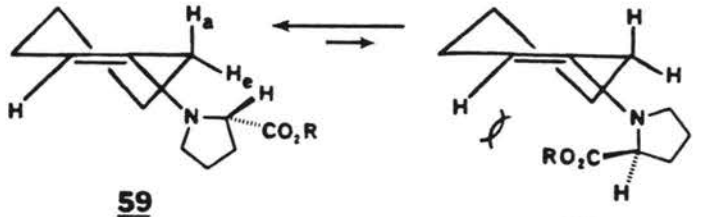
R = Me, Et, t-Bu X = CN, CO_2Me

intermediate adducts to give chiral α-substituted cyclohexanones 56. Stereoselectivity increased with size of the chiral auxiliary (R = Me < Et < t-Bu), forming 56 (X = CO_2Me) in 15, 21, and 59% ee respectively, and 17-38% yield. Additions to acrylonitrile showed a similar trend with increasing optical rotation for the resulting product 56 (X = CN), in 34-41% yield.

The mechanism postulated for the observed stereochemistry, was based on the preference of conformer 57. Conformers 58 and 60 were assumed to be less favorable due to interactions of the ester moiety and the C-2 proton. Similarly, the interaction of the ester moiety and the C-6 quasi-equatorial proton, in conformer 59 was determined also to be less favorable. Hence, 57 appeared to be the most stable, and was assumed to undergo axial attack of the electrophile to yield the observed stereochemistry.

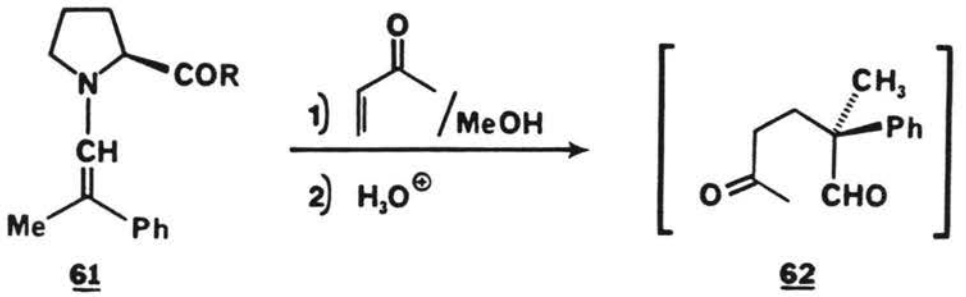


57 ⇌ 58

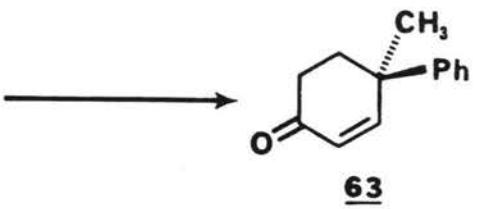


59 ⇌ 60

Simultaneously, Yamada[26] reported the addition of chiral enamine 61, derived from 2-phenylpropionaldehyde and various proline derivatives, to methyl vinyl ketone. The resulting keto aldehyde 62 was cyclized to 63 in an overall yield of 43-53%. The



61 → 62



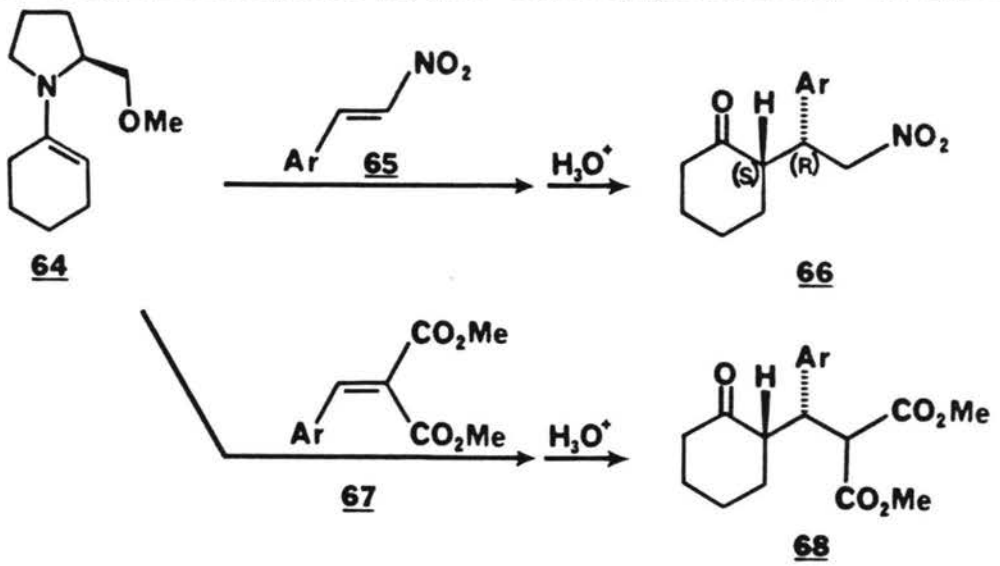
63

R= O-*t*-Bu, NR_2

stereoselectivity exhibited in the synthesis of 63 varied considerably. In direct contrast to the cyclohexanone series (vide supra), alkylation of 61 (R = t-Bu), gave only 6% ee. The highest induction was realized for 61 (R = NR_2, R = $-(CH_2)_4-$) which resulted in 49% ee. Various other aldehyde enamines were investigated, all of which formed the corresponding optically active 4,4-disubstituted-2-cyclohexenones.

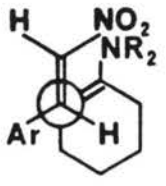
Subsequent reports reinvestigated this aldehydo enamine chemistry,[27] and determined the absolute configuration of 4-methyl-4-phenyl-2-cyclohexenone.[28] Further, the asymmetric syntheses of mesembrine[29] and podocarpic acid[30] were completed using this enamine chemistry. In all of the above reports however, there was no improvement in asymmetric induction.

In 1982, Seebach[31] reported the first in a series of papers in which two chiral enamines underwent conjugate addition to various Michael acceptors. In contrast to the previous work, diastereomeric products resulted after hydrolysis. Thus, addition of enamine 64, derived from (S)-2-methoxymethylpyrrolidine and cyclohexanone, to various 2-arylnitroethylenes 65 gave addition products 66. Of the four

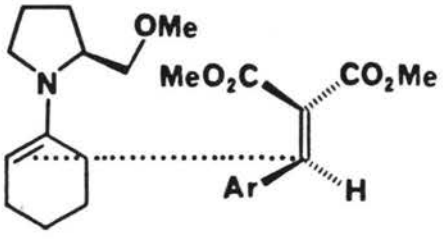


possible diastereomers, only one (66) was generally formed in yields of >70%. Hydrolysis of the crude primary addition products furnished the alkylated cyclohexanones in >90% ee. Similarly, enamine 64 was added to several methyl-α-(methoxycarbonyl)cinnamates 67.[32] The resulting cyclohexanones 68 were formed with high stereoselectivity (88->95% de, 80-95% ee) in 35-76% yield.

The observed stereochemistry for 66 and 68 was rationalized by approach of the acceptor to the enamine as shown in 69 and 70 respectively. In both cases, the aryl group was anti to the enamine, so as to minimize steric interactions.

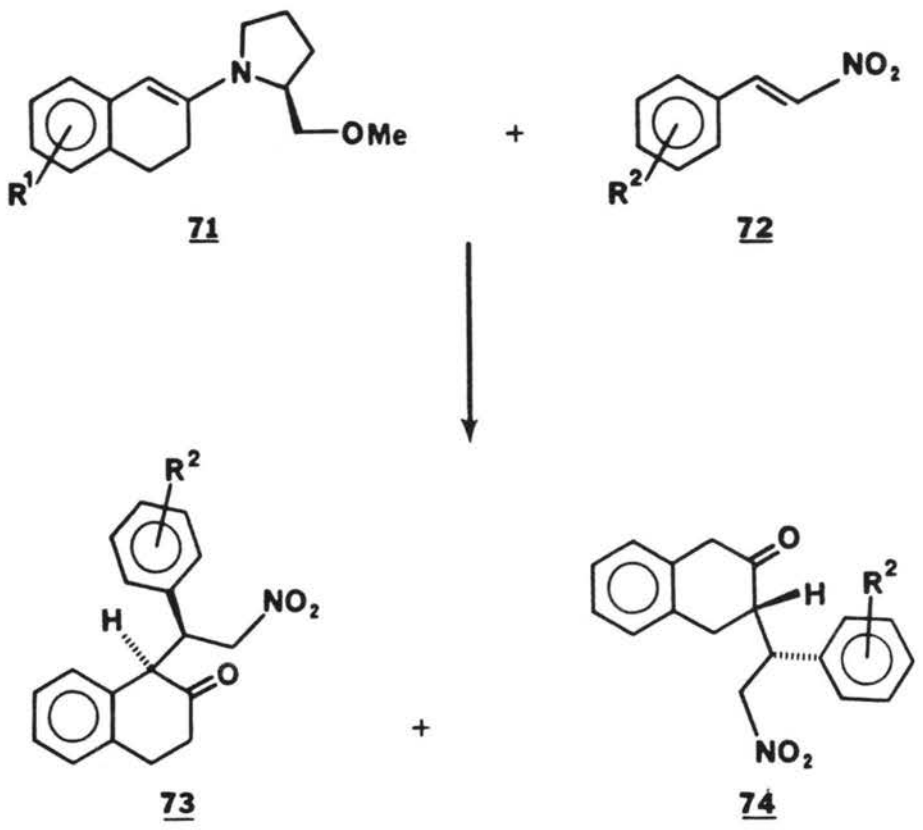


69



70

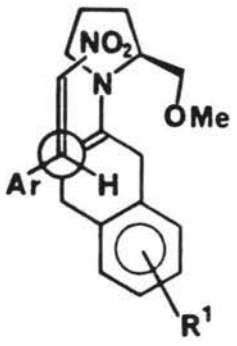
Enamine 71, derived from various β-tetralones and (S)-2-methoxymethyl pyrrolidine, was added to several ω-nitrostyrenes 72.[33] Hydrolysis of the intermediate products led to mixtures of β-tetralones 73 and 74, with ratios varying from 1:5 - 1:20. The desired product 74 was recovered in 35-55% yield, and found to be >90% diastereomerically pure (75-99% ee).



71 + 72

73 + 74

Likewise, the observed stereochemistry of the addition products was rationalized by the approach of the acceptor to the enamine as depicted in 75, with the aryl group anti to the enamine.



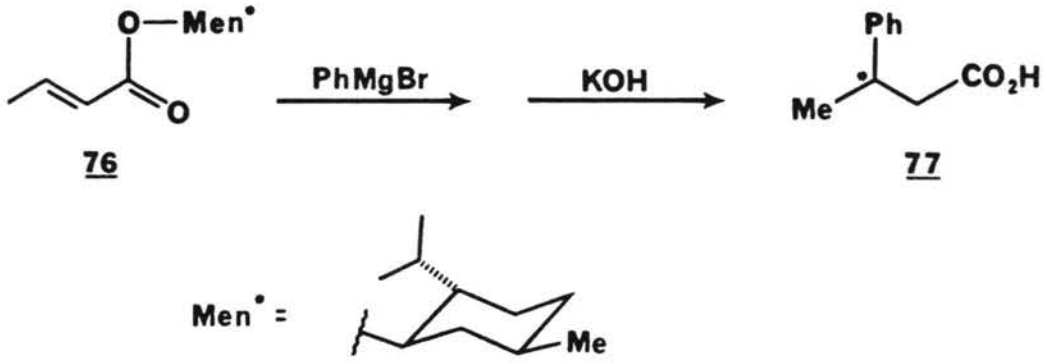
75

B. Chiral Acceptors

1. Addition to Chiral Acrylates

In 1962, Inouye and Walborsky[34] reported the first conjugate addition to an α,β-unsaturated ester containing a chiral moiety. Thus,

menthyl crotonate 76 was treated with phenylmagnesium bromide, and after hydrolysis gave (S)-(+)-3-phenylbutanoic acid 77, in 6.7% ee and

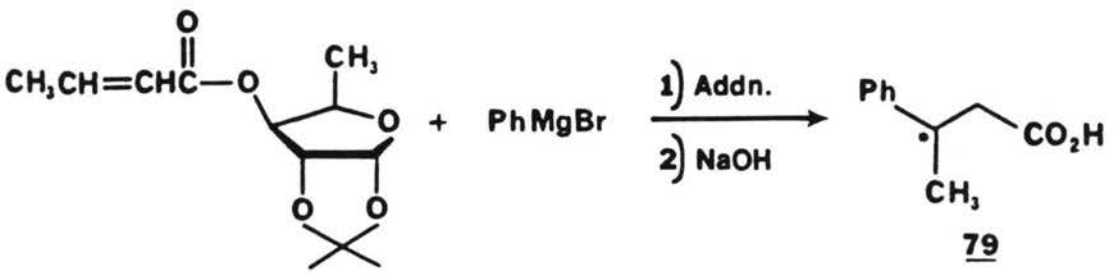


76 77

Men• =

53% yield. Of particular interest however, was the fact that addition of cuprous chloride to the reaction mixture favored the formation of the antipode, (R)-(-)-3-phenylbutanoic acid, in 10.2% ee and 64% yield.

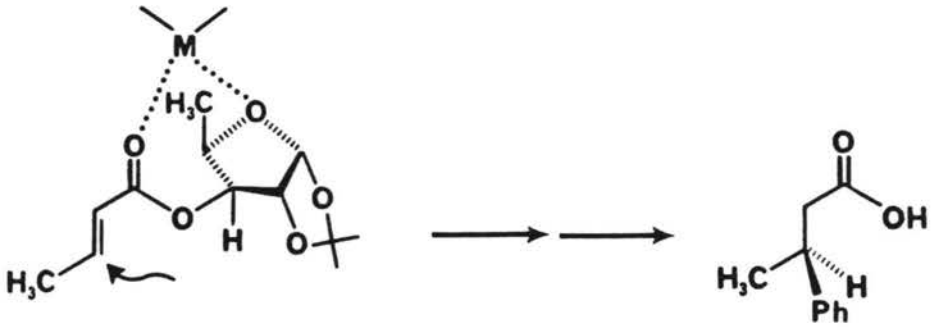
A similar phenomenon was observed in the addition to 3-O-crotonyl-1,2-O-isopropylidene-5-deoxy-D-xylose 78 by phenylmagnesium bromide.[35] Addition in the absence of cuprous chloride led to the formation of



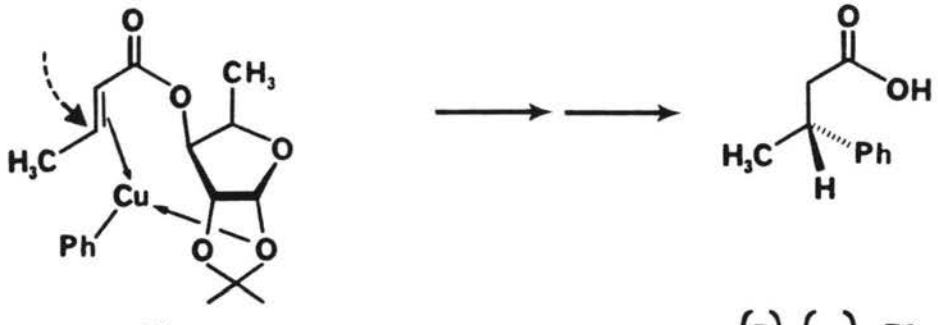
78 79

(+)-3-phenylbutanoic acid 79 in 16% ee and 32% yield. Alternatively, the antipode predominated in better yield (61%) and significantly higher optical yield (58%) upon addition of catalytic cuprous chloride.

Formation of (S)-79 was rationalized in terms of addition from the β-face of 80, due to steric interactions exerted by the methyl group on the chiral auxiliary. Addition of cuprous chloride resulted in



80 (S)-(+)-79

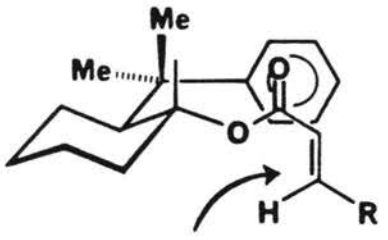


81 (R)-(−)-79

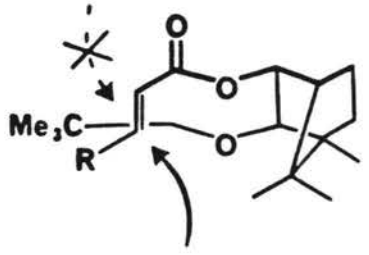
formation of phenyl copper, which was believed to form a complex between the olefin and the C-2 oxygen on the furan (81). As a result, β-face addition was restricted, causing addition from the backside to give (R)-79. Several other sugar derivatives were investigated and resulted in enantioselectivities up to 74% ee in 42-58% yield. Addition of cuprous chloride in these examples, however, did little to reverse the observed stereochemistry.

Menthyl acrylates in addition to several other acrylates, have been used as acceptors for chiral cuprates[36] and an enamine.[37] The yields of the resulting addition products however, reached only 31% at best, with up to 49% ee realized.

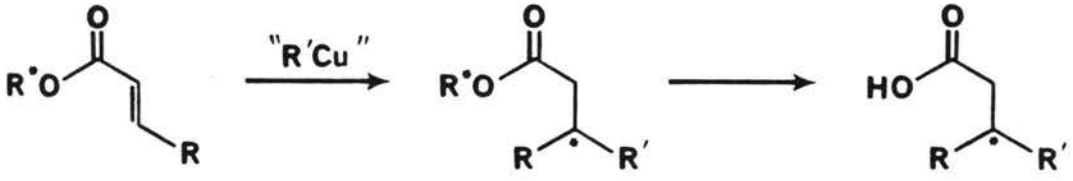
Oppolzer and coworkers[38] reported the very highly stereoselective addition of cuprates to acrylates, derived from (-)-8-phenylmenthol and (S)-(-)-camphor, 82 and 83 respectively. Upon treatment with various cuprates, the resulting ester 84 was hydrolyzed to the chiral



82



83

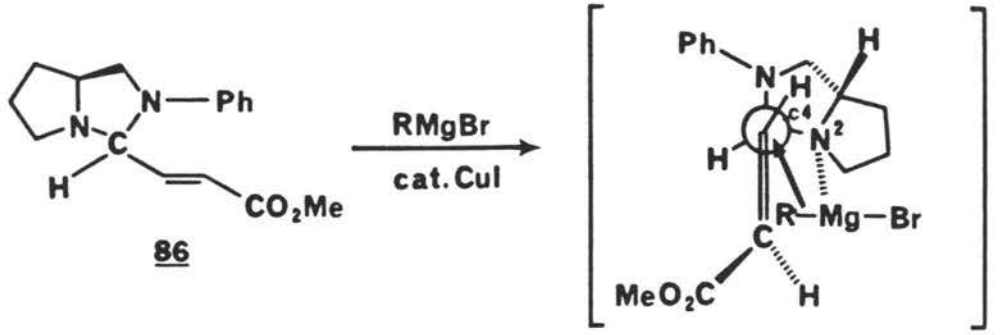


82,83 84 85

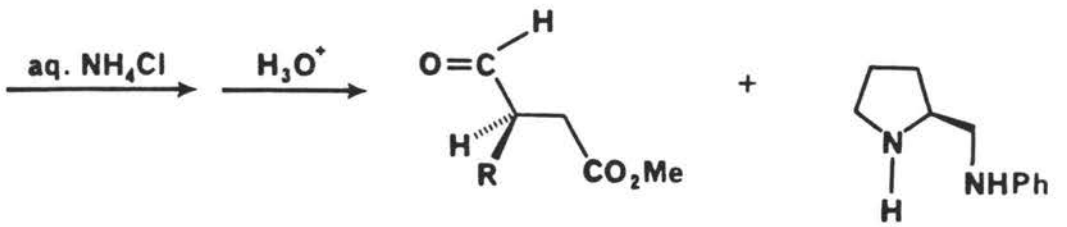
β-substituted alkanoic acid 85. Enantiomeric excesses ranged from 24->99% (most were >80% ee) depending on the nature of the cuprate. The chemical yields were generally >80%. This high selectivity was attributed to the antiplanar C=C/C=O disposition in the enolate, thus blocking one side of the olefin to attack (82 and 83). By altering the order of introduction of the substituents, or by using either enantiomer of 83, either enantiomer of acid 85 could be formed preferentially.

Another form of a chiral acrylate is one in which the center of asymmetry is attached at the β-terminus of the olefin. In 1979, Mukiayama[39] reported the copper(I) catalyzed conjugate addition of a

series of aliphatic and benzyl Grignard reagents to chiral aminal 86, derived from fumaraldehydic acid methyl ester and



86 87

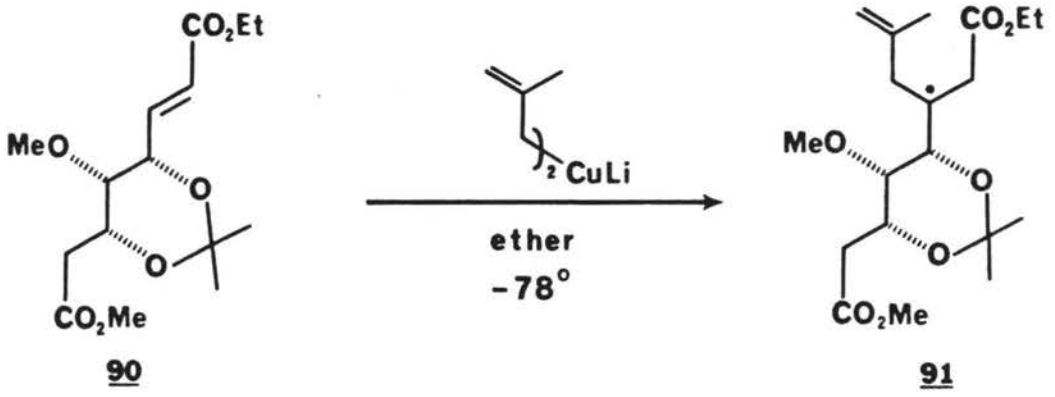


88 89

(S)-2-(anilinomethyl)-pyrrolidine. The resulting -formyl esters 88 were formed in 38-83% yield. Enantiomeric excesses were consistently high, (except for R = $PhCH_2$-; 35% ee), with 85-93% being the norm for the other examples. Formation of the product, determined to be of the (R) configuration, was rationalized in terms of precomplexation and addition to conformer 87. This was believed to be the preferred conformation, since the double bond, which underwent addition would be flanked by the two smallest groups attached at C-4 (the proton and the N-2 of the pyrrolidine ring).

In 1979, a series of papers describing asymmetric natural product synthesis based on this methodology began to appear. These utilized addition to acrylates containing several asymmetric centers, in which the one nearest to the site of reaction resided at the γ-carbon.

Nicolaou[40] accomplished a synthesis of a portion of the ring present in carbomycins A and B, and Leucomycin A_3. The transformation of interest was the conjugate addition of lithium di-2-methallyl



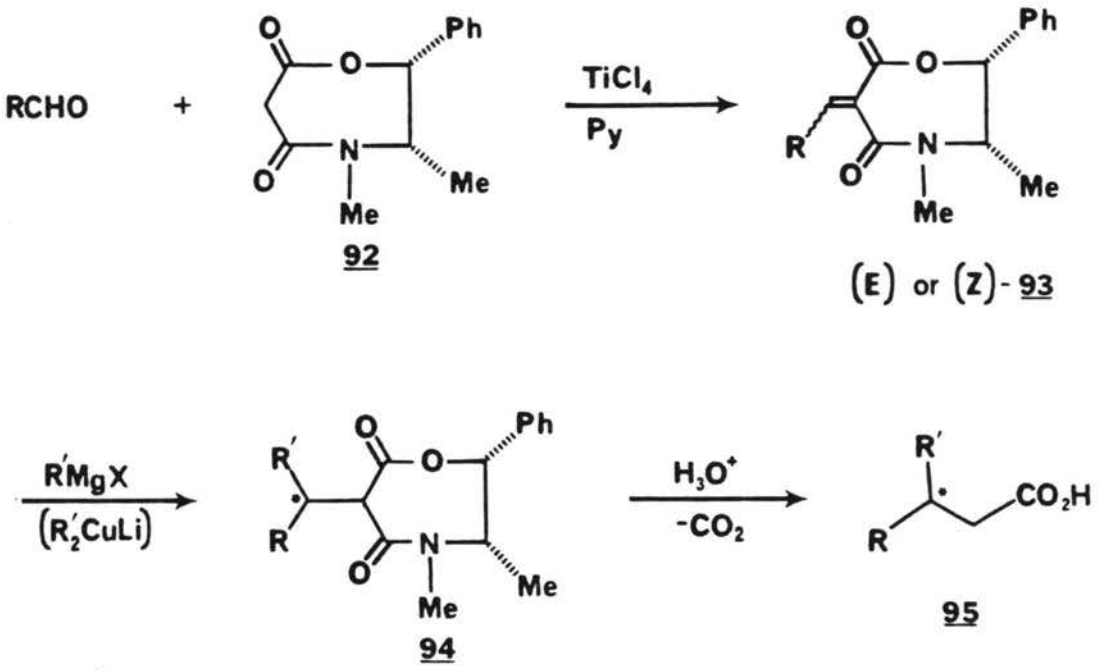
90 91

cuprate to acrylate 90, derived from D-glucose. The resulting product 91, was formed in excellent diastereoselectivity (90%) in 85% yield. Completion of carbomycin B and leucomycin A_3 was reported in 1981,[41] which utilized the same cuprate on a slightly different acrylate.

Workers in other laboratories have also used this approach towards elaboration of chiral acrylates. Natural product targets again included carbomycin B and leucomycin A_3,[42] tylonolide,[43] O-mycinosyltylonolide,[44] and olivin.[45] All of which exhibited generally high stereoselectivity and high yields.

Similar to the conjugate addition to chiral acrylates, the corresponding α,β-unsaturated amides have also been investigated. The condensation of an aldehyde with the 6-unsubstituted oxazepine dione 92 was reported in 1978.[46] The resulting alkylidene 93 reacted in a Michael fashion with various Grignard reagents and homocuprates. Hydrolysis of the alkylation product 94 gave, after decarboxylation, β -

substituted alkanoic acids 95 in 56-99% ee (generally >80% ee) and 55-94% yield.

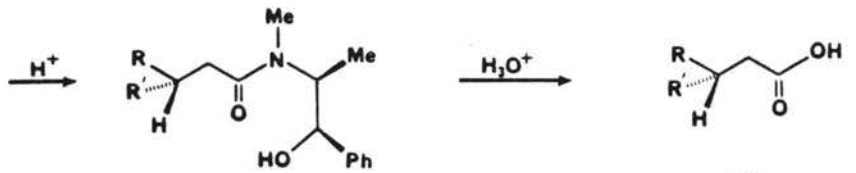


The versatility of the reaction was shown by the fact that either enantiomer could be formed selectively with the proper choice of alkylidene. Thus, addition of Grignard reagents to the Z olefin resulted in alkanoic acids of the (R) configuration, while the E olefin gave the corresponding (S)-acids. This selectivity however, was not characteristic of the homocuprate additions. Alkylation of either the E or Z olefin resulted in formation of the (S) product for both cases, implying a radical anion intermediate. In all of the above Grignard reagent additions, the observed stereochemistry of the products was rationalized by approach of the nucleophile from the less hindered topside of the alkylidene 93.

Another highly stereospecific route to chiral β-substituted alkanoic acids was reported in 1981.[47] Addition of excess Grignard

reagent to eneamide 96, resulted initially in deprotonation, followed by formation of a rigid internal chelate complex 97. Because of these strong interactions, subsequent addition of the nucleophile to the less hindered bottom side gave the substituted acid 99 in 79-99% ee and >85% yield.

96 97

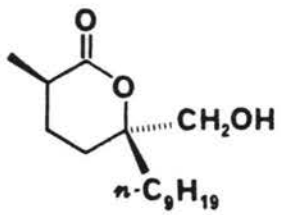


98 99

R,R' = alkyl, aryl

Support for the hypothesis that formation of the rigid chelate complex was important prior to alkylation was accumulated by a solvent study. Alkylation in highly coordinating solvents such as THF or dimethyl ether resulted in 22 and 19% ee respectively, significantly lower than the 85% ee observed for diethyl ether. These results were attributed to competative complexation with the metal salts, and deterioration of the asymmetric synthesis through disruption of the strong internal chelate.

A recent report by Eliel and Kogure[48] describes the asymmetric synthesis of (-)-magyngolide 100, utilizing this methodology.

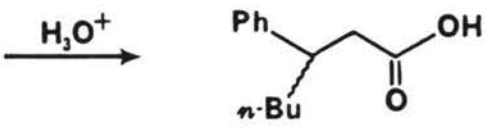


100

Conjugate addition to 96 gave 98 (R = Me, R' = Ph) in 97% de (after recrystallization) and 70% yield. Further transformations led to 100 in 97.4% de.

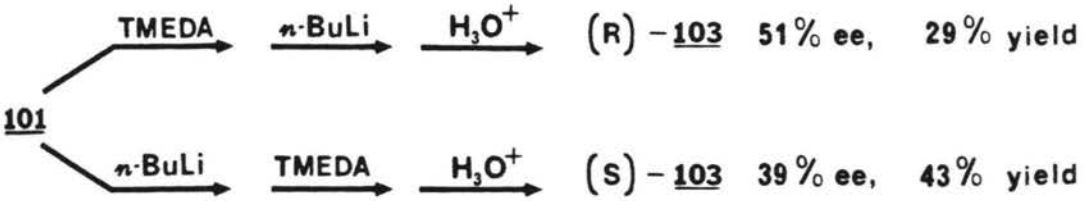
Soai and coworkers[49] reported an interesting phenomenon for the conjugate addition of butyllithium to the eneamide 101, derived from proline. By reversing the order of addition of the reagents to the

101 102



103

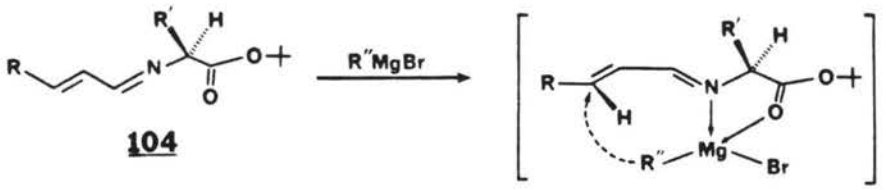
Scheme 2



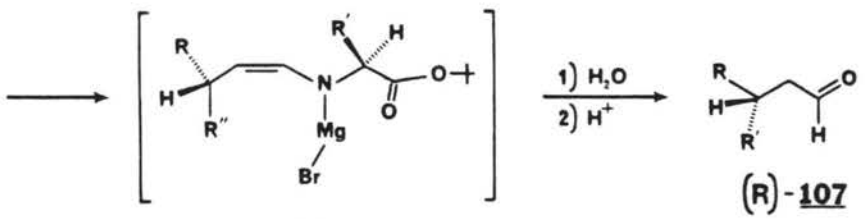
reaction mixture, the observed stereochemistry of the resulting acid 103 was reversed. The results are summarized in Scheme 2. The explanation of these interesting results are yet unknown and further work by the authors is in progress.

2. α,β-Unsaturated Aldehyde Derivatives

Koga and coworkers[50] examined the use of chiral α,β - unsaturated aldimines as Michael acceptors. Addition of phenyl and several aliphatic Grignard reagents to aldimine 104, derived from an aldehyde and a chiral amino ester, led to alkylated aldehyde 107.



104 105



106 (R)-107

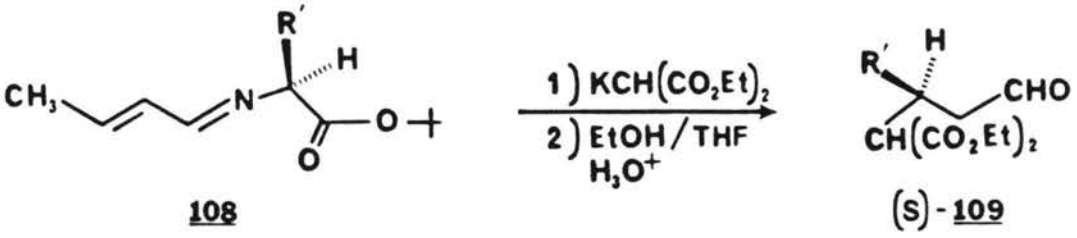
R = Me, Ph; R' = i-Pr, t-Bu

Reduction of the aldehyde, provided the primary alcohol which was used for the determination of optical purity and yield. For all cases examined, >90% ee was realized for the addition to 104 (R' = t-Bu) in 40-56% overall yield. Lower asymmetric induction (63% ee, 41% yield) was obtained for the alkylation of 104 (R' = i-Pr) with phenylmagnesium bromide. It should be noted that the amino ester (R' = t-Bu) is not

from a naturally occurring amino acid and its availability is based on resolution.

The observed absolute configuration of the products, (R), was rationalized by initial chelation between the magnesium and the lone pairs on the nitrogen and carbonyl to form complex 105. With the remainder of the molecule in an (S)-cis conformation, subsequent addition, to the less hindered bottom side gave 106, the precursor to 107.

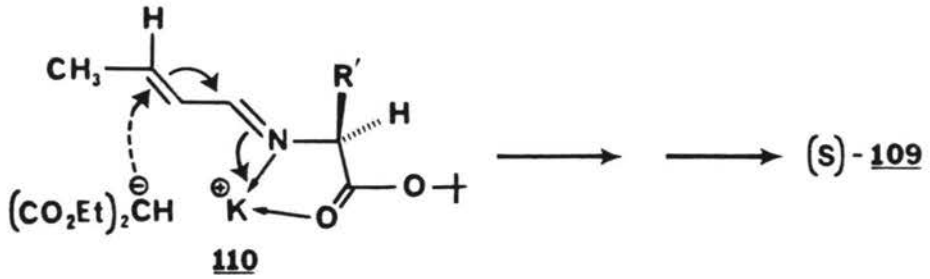
Subsequent investigation of this chiral aldimine chemistry involved the conjugate addition of diethyl potassiomalonate.[51] Treatment of 108 with the malonate anion gave, after hydrolysis, 109 in



108 (S)-109

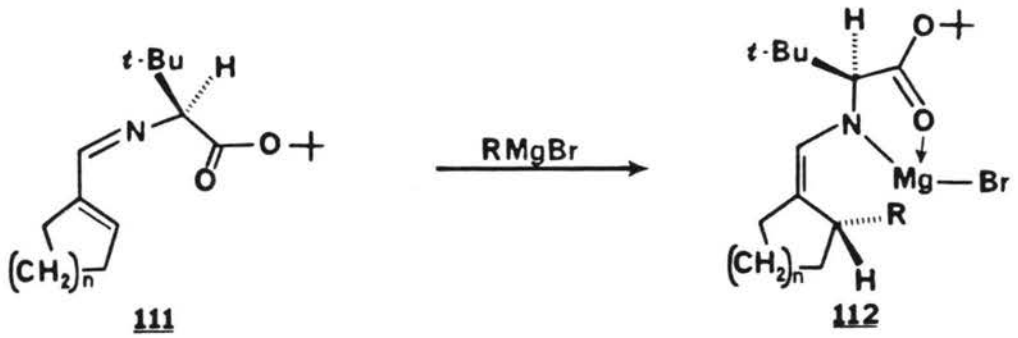
R = i-Bu, i-Pr, t-Bu

86% ee (for R' = t-Bu) and 48% yield. Interestingly, the sense of addition was opposite to that reported for the addition of Grignard reagents (vide supra). This stereochemical outcome was rationalized by complexation of the potassium to the imine nitrogen and carbonyl, followed by addition to the less hindered backside of the (S)-trans conformer 110.

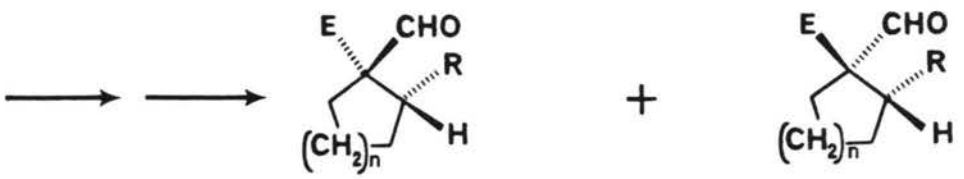


110

A further extension of work used cyclic aldimines 111.[52] Treatment with excess Grignard reagent led to addition, producing the intermediate 112. Depending on the reaction conditions, the product obtained was either the cis or trans aldehyde 113 or 114. Yields were generally 50–65% in usually >90% ee.



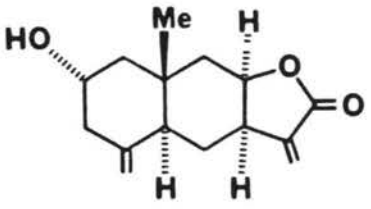
111 112



trans - 113 cis - 114

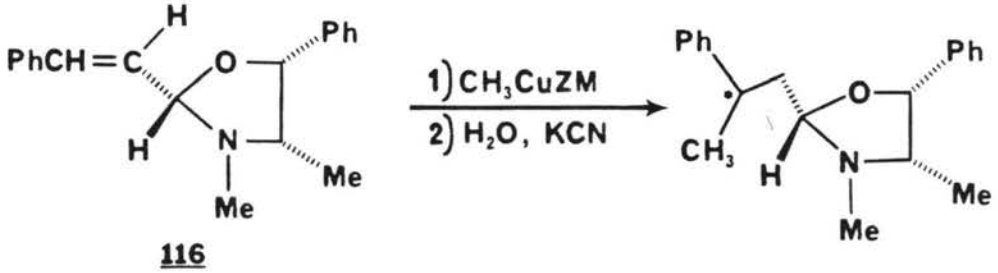
n = 1,2; R = Ph, vinyl; E = aliphatic, benzyl

Subsequent use of this methodology resulted in the asymmetric total synthesis of optically pure (+)-ivalin 115,[53] an antileukemic sesquiterpene.



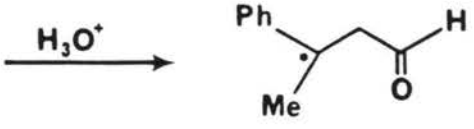
115

Another interesting route to chiral β-substituted aldehydes employed the conjugate addition of methyl cuprate reagents to eneoxazolidine 116, derived from cinnamaldehyde and ephedrine.[54]



116

M = Li, MgBr
Z = I, Me



117

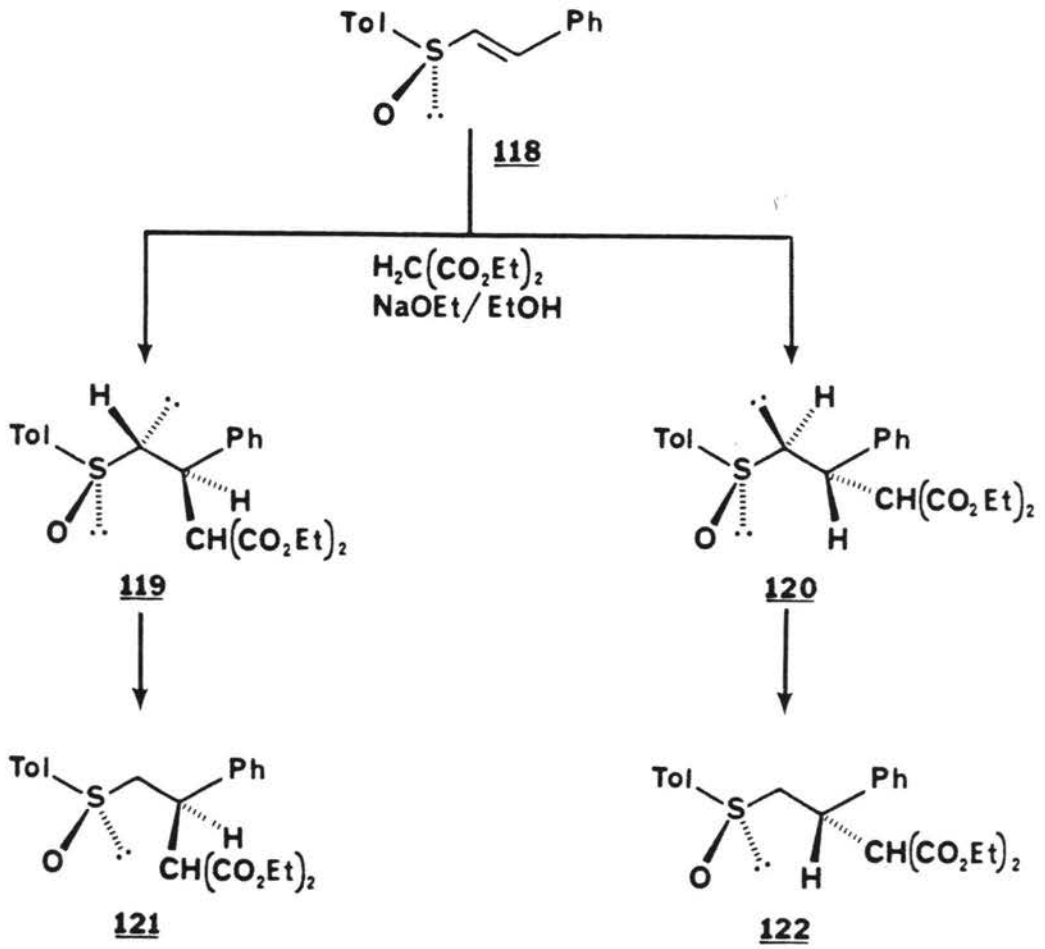
Considering the experimental parameters examined, the most striking feature was the pronounced solvent effect. Ethereal solvents resulted in formation of (S)-117 (up to 49% ee), while utilization of a

non-coordinating solvent gave predominantly the enantiomeric product (up to 80% ee). This dichotomy in selectivity was considered to be the result of differing aggregation of and coordination by the cuprate reagents.

Similar results for alkylations of 116, in ethereal solvents, were also reported by Normant and coworkers.[55]

3. α,β-Unsaturated Chiral Sulfoxides

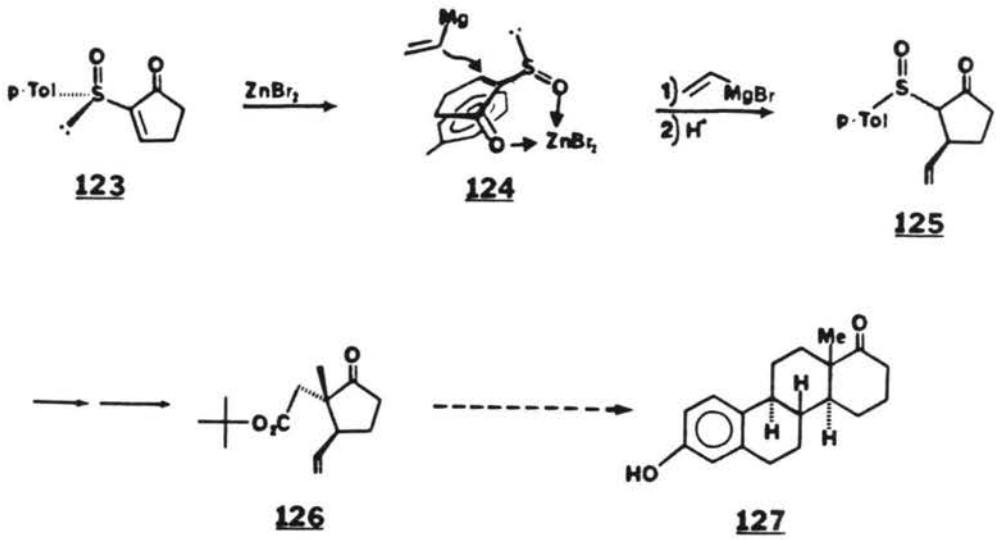
In 1973, Tsuchihashi and coworkers reported asymmetric conjugate addition of malonate anion to the chiral sulfoxide 118.[56] The resulting mixture (80:20) of diastereomers was formed in 80% yield with 121 predominating.



Of particular interest however, was a later report[57] in which diastereomer 122 could be predominantly formed (60% de). This was accomplished by generation of the lithio anion of diethylmalonate in THF-hexane (3:2), followed by addition of sulfoxide 118. A yield of 63% was realized.

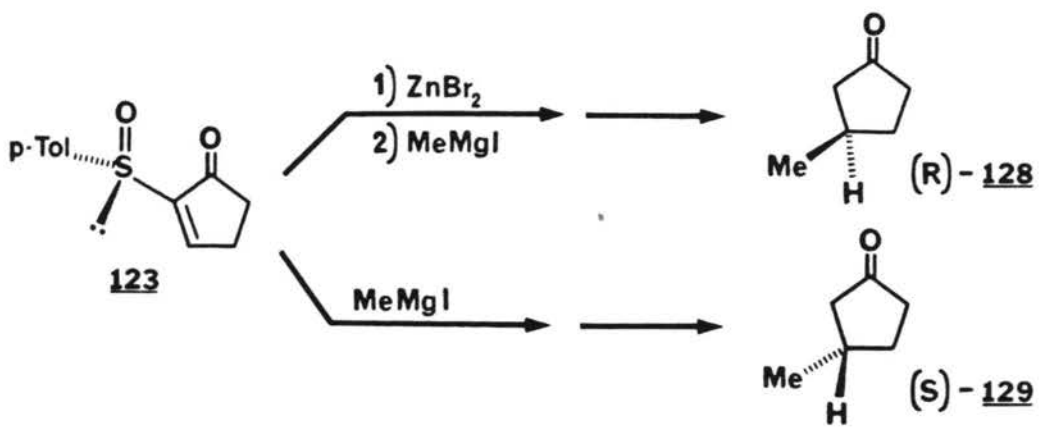
The observed stereochemical outcome was thought to result from the stability of the intermediate carbanionic addition adducts 119 and 120. In a polar protic solvent (ethanol), carbanion 119 would be favored due to the trans relationship of the carbanion to the sulfinyl oxygen, thus leading to 121. Alternatively, the more stable conformer in THF-hexane is 120. Preferred because the carbanion is gauche to the sulfinyl oxygen and able to form a chelate between the cation and the oxygen, resulting in 122.

Employing a chiral vinyl sulfoxide in a cyclic system for the stereoselective synthesis of substituted cyclopentanones was reported by Posner and coworkers[58] in 1981. Virtually complete asymmetric induction was achieved for the conjugate addition of vinylmagnesium

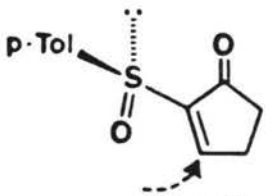


bromide to enantiomerically pure (S)-(+)-(p-tolylsulfinyl)-2-cyclopentenone 123, forming 3-vinylcyclopentanone 125. Further transformations led to the trisubstituted cyclopentanone 126, as a single diastereomer in an overall yield of 30% from 123. This constituted a formal total synthesis of natural estrone (127). Crucial to the high stereoselectivity was the precoordination of the substrate with zinc bromide. The proposed chelate model 124, involved complexation to the sulfinyl and ketone oxygens, thus limiting access to the electrophilic olefin to the side opposite the eclipsing p-tolyl group. Without zinc bromide, alkylation, (in the presence of catalytic copper bromide), under the same conditions resulted in a decrease in asymmetric induction (80% ee).

Either enantiomer of 3-methylcyclopentanone could be formed preferentially from a common precursor 123, by simple modification of the alkylation procedure. Thus, precomplexation with zinc bromide, followed by addition of methylmagnesium iodide gave mainly (R)-128 in 87% ee and 89% yield. Alternatively, in the absence of zinc bromide, the antipode (S)-129 predominated in 72% ee and 76% yield.

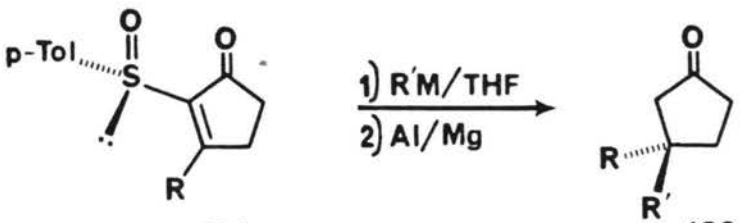


This result was rationalized by addition of the nucleophile to the enone primarily in conformation 130, in which the sulfoxide and carbonyl dipoles are anti-periplanar. Attack from the less hindered bottomside led to the observed stereochemistry. Further examples of this reversed stereoselectivity for both cyclopentenone and cyclohexenone ring systems was recently reported.[59] Up to >98% ee was observed for a wide range of nucleophiles.



130

An extension of this methodology gave a stereoselective synthesis of quaternary carbons.[60] Beginning with 131, additions by a series of



131 132

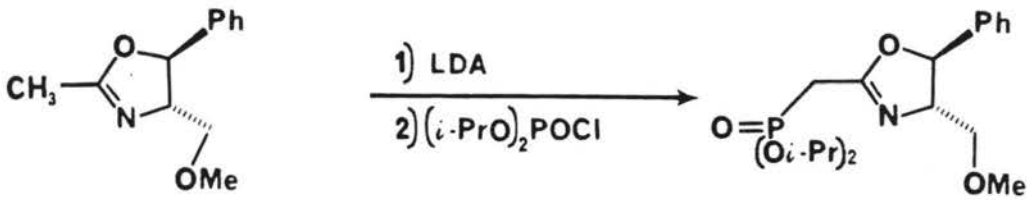
R = p-Tol, Me

of organometallic reagents led to the 3,3-disubstituted cyclopentanone 132, after reductive cleavage of the sulfinyl group. Asymmetric induction was generally >75% ee with yields of 53-79%. The observed stereochemistry followed that of the already familiar chelate model 124.

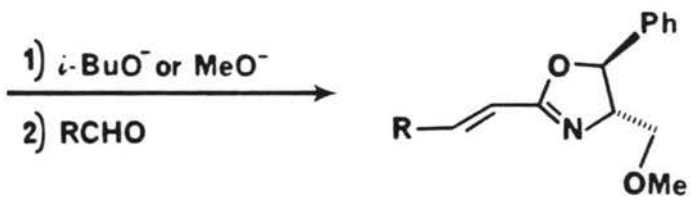
4, Substituted Vinyl Oxazolines

A route to chiral β-substituted alkanoic acids which enjoyed very high stereoselectivity, as well as a reusable chiral auxiliary, employed substituted vinyl oxazolines. The first, in a series of reports by Meyers[61,62] investigating this methodology, appeared in 1975.

The requisite vinyl oxazoline 135, for the conjugate addition, was prepared by the use of a Wadsworth-Emmons olefination. Deprotonation of 2-methyl oxazoline 133, followed by addition of diisopropyl phosphonochloridate, gave phosphonate 134. Subsequent deprotonation and reaction with a suitable aldehyde led to the desired vinyl oxazoline 135, with near exclusive formation of the (E) isomer.



133 134

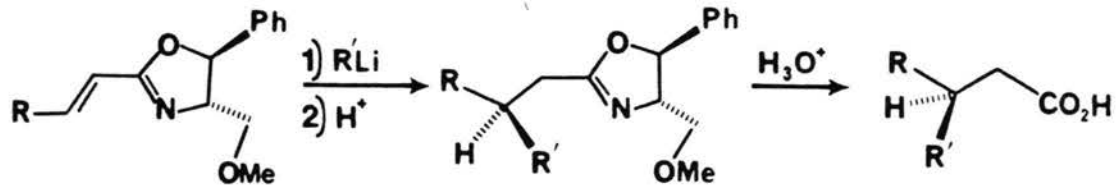


135

R= alkyl, aryl

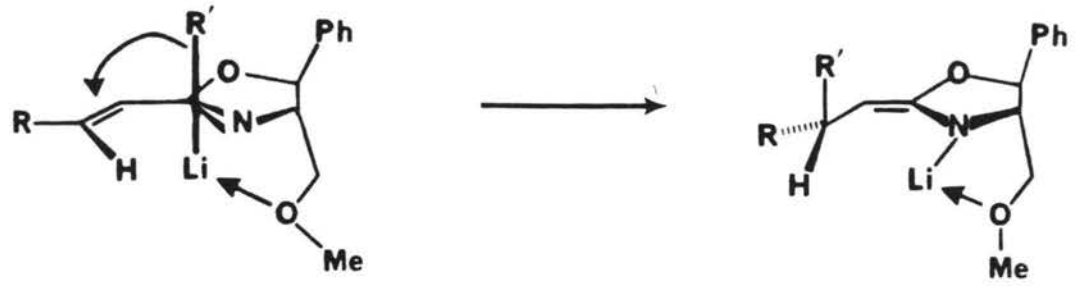
Addition of phenyllithium and related alkyl derivatives gave oxazoline 136. Hydrolytic removal of the oxazoline yielded chiral β -

substituted acids 137 in >90% ee (50-80% yield) for all the cases examined.



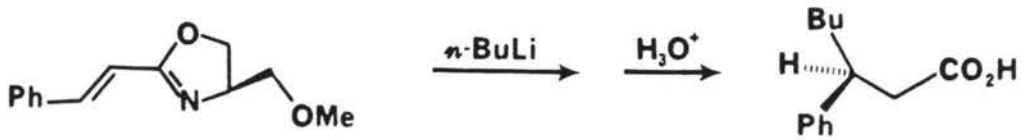
135 136 137

Mechanistically, the observed stereochemistry of the products was thought to be a result of initial complexation of the organolithium reagent to the nitrogen and the methoxy group of the oxazoline to form complex 138. Topside addition to the π-system afforded lithio oxazoline 139, which upon quench gave 136. Because of the stereospecificity of the alkylation, either enantiomer of the resulting acid could be formed preferentially by reversing the order in which the substituents were introduced.



138 **139**

An experiment which supported the idea that formation of the initial complex **138** was indeed important for high stereoselectivity was realized by alkylation of vinyl oxazoline **140**, derived from serine.[62,63] Addition of n-butyllithium gave (S)-3-phenylheptanoic acid **141**, in 96% ee (after correction for the optical purity of the



(R)-**140** (S)-**141**

starting material). Taking into account the absolute configuration at C-4 on **140**, (R), and on oxazoline **135**, (S), the nucleophile added in the same sense for both cases, i.e., (R)-**140** gave the (S) acid and (S)-**135** gave the (R) acid. Thus, it was considered reasonable that the

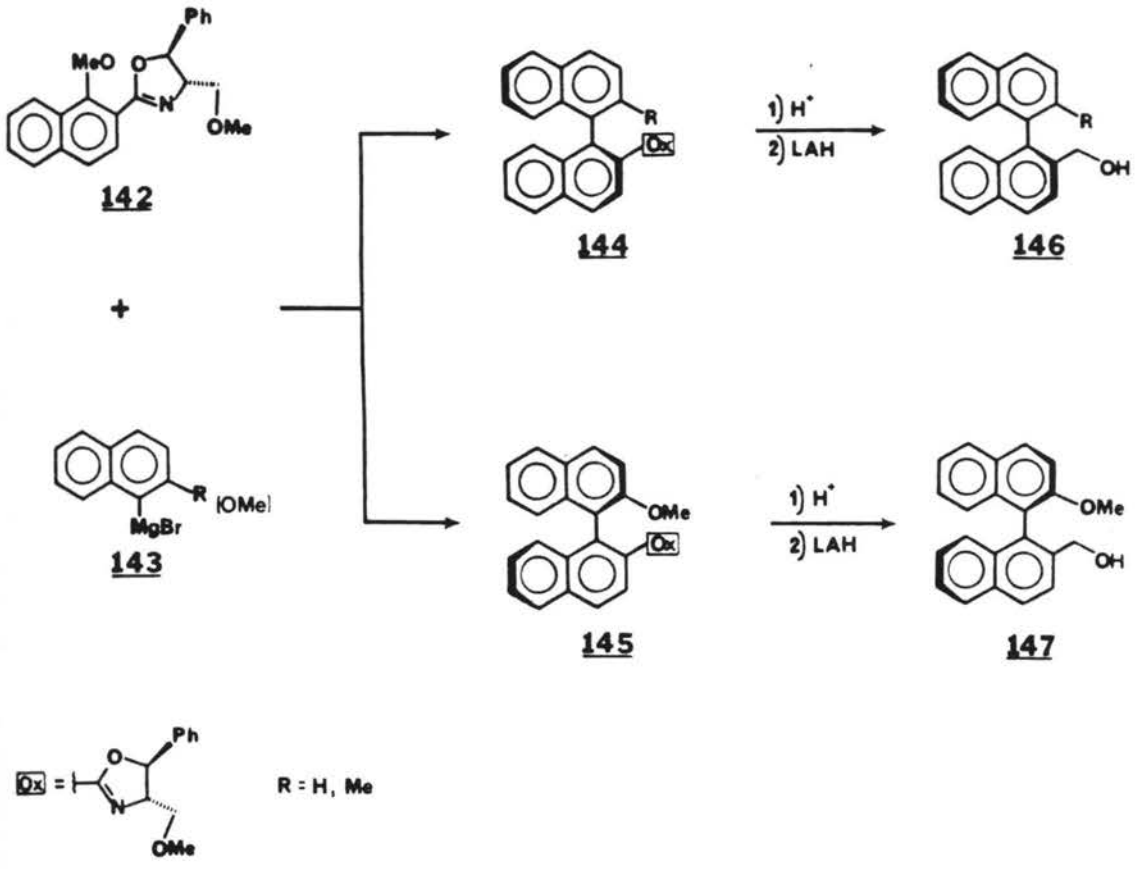
organolithium reagent added as shown (138 → 139 → 136), and that the phenyl group had no effect on the stereochemical outcome.

This methodology was subsequently used in the synthetic approaches to carbomycins[64] and also for the asymmetric total synthesis of (+)-arturmerone.[65]

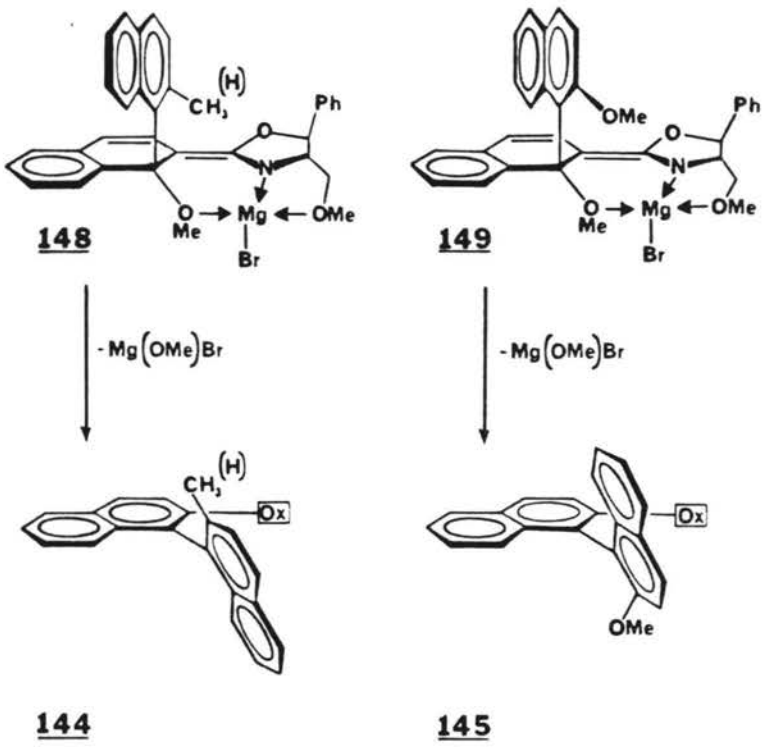
5. Aromatic Oxazolines

Recently, two variations of asymmetric conjugate addition have appeared in the literature. First, aryl oxazolines have undergone nucleophilic aromatic substitution to form biaryl compounds, which were chiral by virtue of axial asymmetry. Secondly, conjugate addition reactions have occurred, whereby aromaticity was lost in the formation of dihydronaphthalene compounds.

In 1982, Meyers and Lutomski[66] reported the synthesis of chiral substituted binaphthyls 146 and 147 via nucleophilic aromatic substitution. Alkylation of chiral oxazolinylnaphthylene 142 with naphthalene Grignard reagents 143 led to the diastereomeric binaphthyls 144 and 145, in 52-83% de and 68-80% yield. Treatment with acid, followed by LAH reduction gave the binaphthyl alcohols, formed with enantiomeric enrichment (87.4-96% ee and 29-46% overall yield).



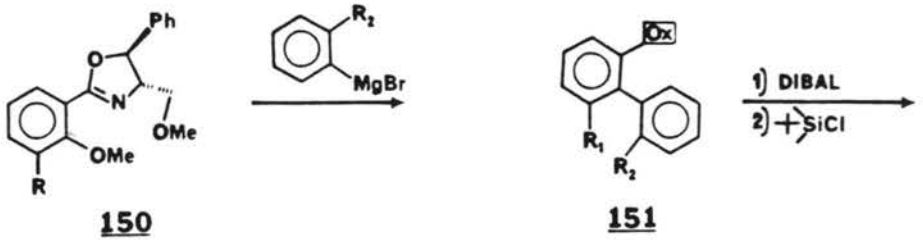
The preliminary rationalization of the observed stereochemistry for 144 was considered to be the result of addition of the Grignard reagent to form dihydronaphthalene intermediate 148, in which the unsubstituted naphthalene ring was at a maximum distance from the phenyl ring. Subsequent elimination of Mg(OMe)Br afforded biaryl 144. The precursor to 145 was postulated to be dihydronaphthalene 149, in which chelation of the methoxy group overrode the steric effects. Elimination of Mg(OMe)Br then gave the binaphthyl.



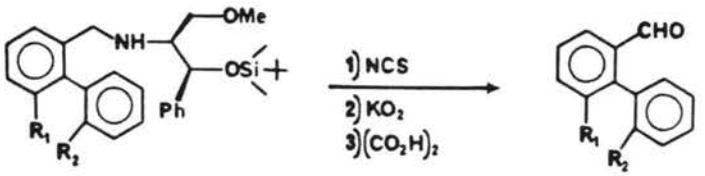
In a similar fashion, binaphthyls were formed utilizing 2-achiral oxazolinylnaphthalene which was also substituted at the 1-position with various chiral ethers.[67] Upon displacement with 1-naphthyllithium and 2-methoxynaphthylmagensium bromide, binaphthyls were realized in 10-94% ee and 7-80% yield.

Chiral biphenyls have also been synthesized via this same methodology.[68] Addition of various ortho-substituted phenyl Grignard reagents to 150 resulted in biphenyl 151, via nucleophilic aromatic substitution. Good to excellent yields were realized (59-95%), as well as a wide range of de's (Table 3). Interestingly, on addition of the corresponding aryllithium reagents, the resulting biphenyls exhibited little or no diastereoselectivity. This was attributed to lack of a rigid complex formation prior to displacement, or very rapid reaction,

devoid of any selectivity. Further studies are obviously necessary to establish this point.



150 **151**



152 **153**

R_1 = MeO, Me

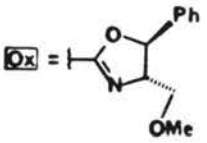


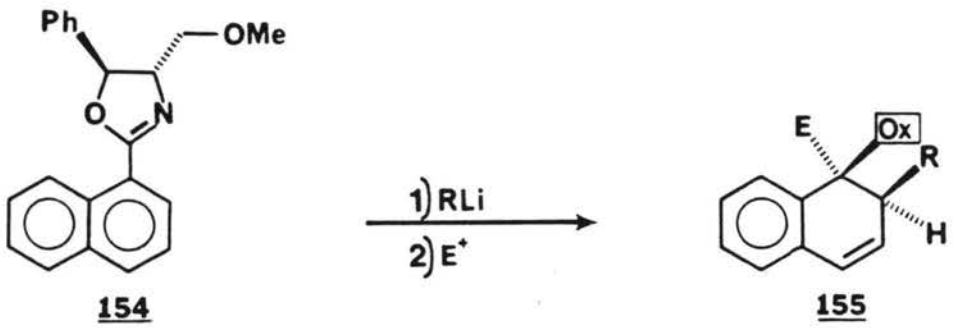
TABLE 3

#	R_1	R_2	% de (151)	% ee (153)
1	Me	Me	36	36
2	Me	OMe	92	0
3	OMe	Me	60	60
4	OMe	OMe	0	0
5	OMe	CH_2OSiMe_2t-Bu	58	52
6	Me	CH_2OCH_2OMe	68	64

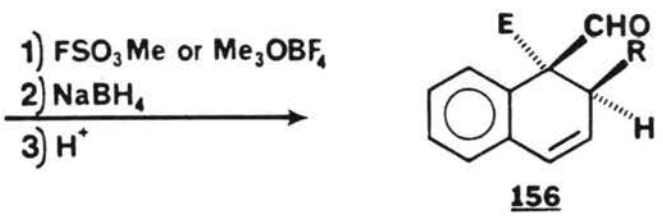
Enantiomeric biphenyls were obtained by reductive cleavage of the oxazoline, which after further transformation, afforded the desired aldehydes **153**. Under these mild conditions, synthetically useful

yields resulted (56-72%), as well as the preservation of the axial chirality in most cases (Table 3).

In a rather novel reaction, chiral 1,2-dihydronaphthalenes 155 were synthesized from oxazolinylnaphthalene 154.[69] Treatment with a series of organolithium reagents, followed by quenching with an electrophile, gave only the trans orientation (of R and E) in the resulting dihydronaphthalene 155. The diastereomeric ratios therefore,



154 155



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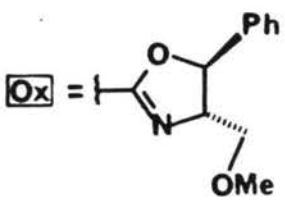
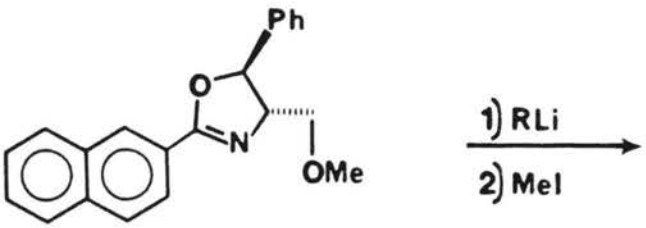


TABLE 4

RLi	Et	% de (155)
n-BuLi	$ClCO_2Me$	88
PhLi	MeI	66
MeLi	PhSSPh	72
TMSLi	MeI	20

reflected the facial selectivity of the initial attack of the incoming nucleophile (predominantly from the β-face), (Table 4), with yields of 56-99%). This was consistant with the precomplexation-addition mechanism for the addition to the substituted vinyl oxazoline (vide supra). Subsequent removal of the oxazoline, via quaternization, reduction, and hydrolysis, yielded the corresponding aldehydes 156 in 69-88% yield.

In a similar fashion, dihydronaphthalenes were formed from the isomeric oxazolinylnaphthalene 157.[70] Alkylation with a series of organolithium reagents and quenching with methyl iodide afforded the



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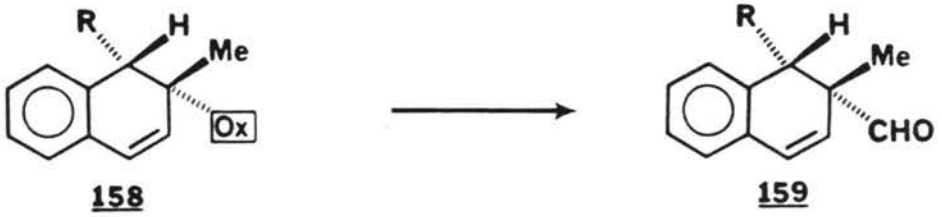
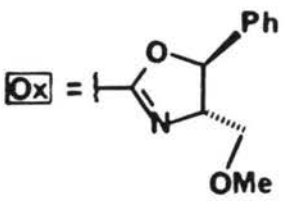


158 159



intermediate dihydronaphthalene 158, in 49-96% de and 67-89% yield. Removal of the oxazoline, via quaternization, generated the aldehyde 159 in 65-81% yield. These alkylations also exhibited the same sense of diastereoselectivity as that of the substituted vinyl oxazoline system (vide supra).

The preceding survey of asymmetric conjugate additions represents the major contributions from a number of laboratories mainly over the past 15 years. The following section will describe the author's results on conjugate additions on pyridines and quinoline to furnish chiral dihydropyridines and dihydroquinolines.

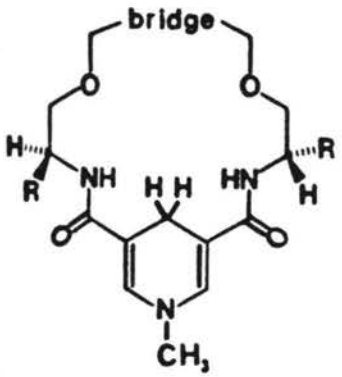
CHAPTER II

RESULTS AND DISCUSSION

Since the first reported asymmetric reduction of a prochiral substrate by a so-called NADH (nicotinamide adenine dinucleotide) mimic in 1975,[71] numerous other reports have appeared in the literature. These have focused on both the stereochemical and mechanistic aspects of this intriguing reaction, which was recently reviewed by Inouye.[72] For the sake of brevity, only a portion of the work from three laboratories will be examined.

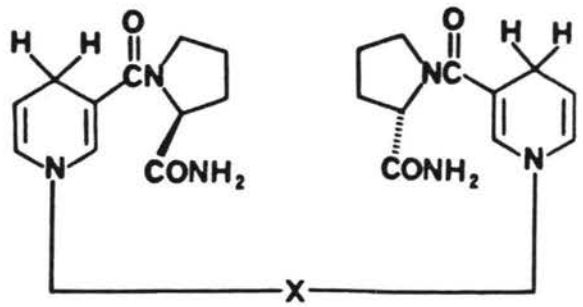
Significant contributions has been made by Kellogg[73] and Inouye[74] utilizing the macrocyclic dihydropyridine 160 and the bis-dihydropyridine 161, respectively. Both led to the stereospecific reduction of carbonyl compounds with enantiomeric excess reaching ≥90% (Scheme 3). Common to each of the reagents was the centers of asymmetry, outside the dihydropyridine nucleus, which contained two transferrable hydrides located at C-4.

Scheme 3



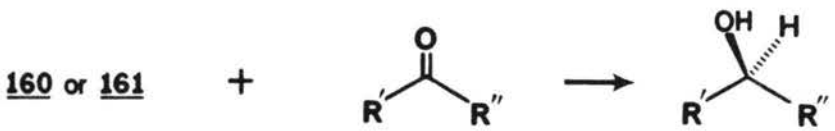
160

R = i-Pr, benzyl
bridge = alkyl

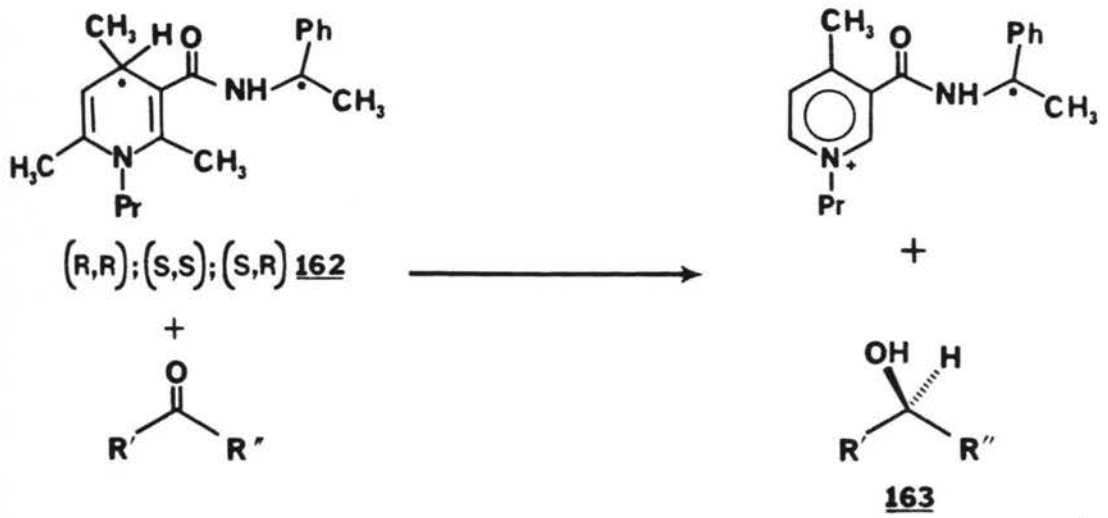


161

X = alkyl, aryl



Comparable asymmetric induction (up to 99% ee) was realized by Ohno and coworkers[75] using dihydropyridine 162. In contrast to the work by Kellogg and Inouye (vide supra), the dihydropyridine contained



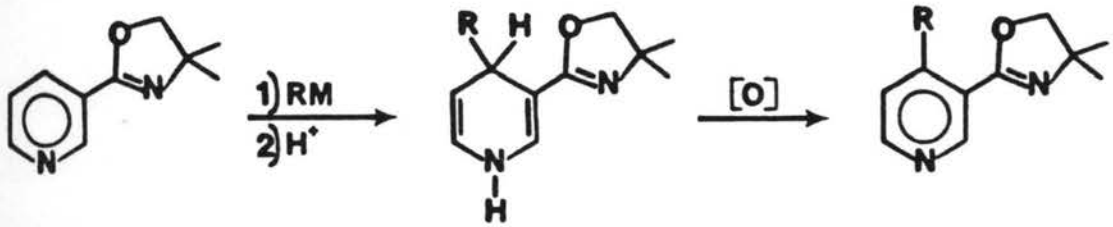
163

an asymmtric center at C-4, in addition to an asymmetric amide moiety attached at C-3. For a series of reductions, the absolute

configuration of the resulting alcohol 163 was dependent only on the configuration at C-4, and not the asymmetric side chain. A disadvantage of this method however, was the required fractional recrystallization of 162, from an equal mixture of two diastereomers.

Because of the interest in NADH mimics and the high stereoselectivity exhibited by the dihydropyridine of type 162, it was desirable that methodology for their asymmetric synthesis be developed. The preparation of chiral 1,4-dihydropyridines will be discussed in the first portion of this dissertation, following a brief review of pertinant work for the synthesis of achiral analogs.

In 1978, Meyers and Gabel[76] reported the synthesis of 3-oxazolinyl-1,4-dihydropyridines 165, by alkylation of oxazolinyl-

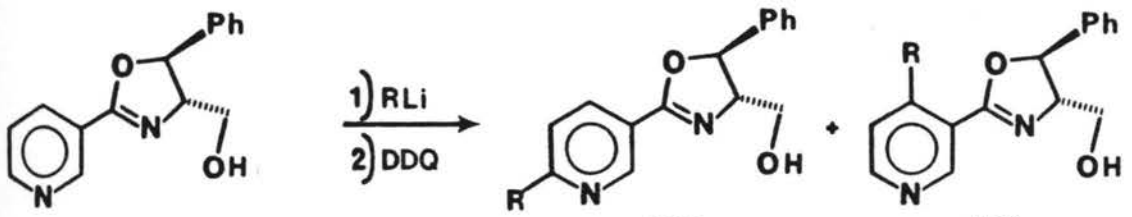


164 165 166

pyridine 164, with several organometallic reagents (in near quantitative yields). Subsequent oxidation led to the disubstituted pyridines 166 in 45-100% yield. The only exception was the addition of t-butyllithium, which afforded 6-t-butyl-3-oxazolinylpyridine (59%) via the corresponding dihydro compound.

This methodology was recently reinvestigated in another laboratory.[77] Depending on reaction conditions, substantial amounts of 1,2-dihydropyridines were formed. (The synthesis, by various routes, and use of dihydropyridines was recently reviewed[78]).

Incorporation of the chiral oxazoline moiety saw the preferential synthesis of either 3,4-disubstituted or 3,6-disubstituted pyridines.[79] Thus, alkylation of oxazolinylpyridine 167 with a series of



167

R=Me,Bu,Ph

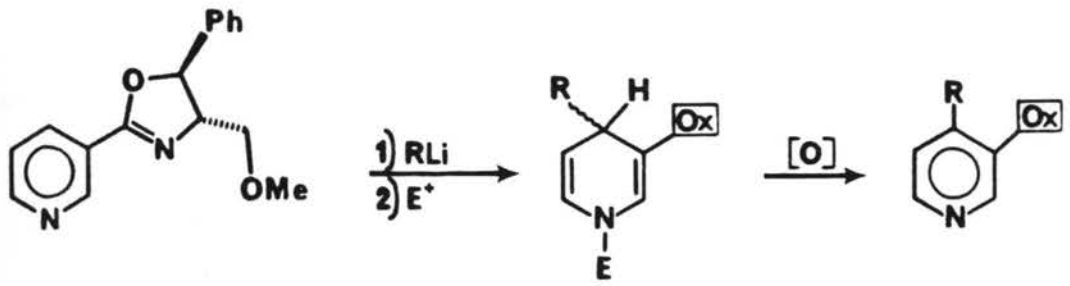
168

169

organolithium reagents, followed by oxidation resulted in the pyridines 168 and 169. Variation of the reaction conditions allowed for the formation of 168 in up to 95% selectivity (60-95% yield).

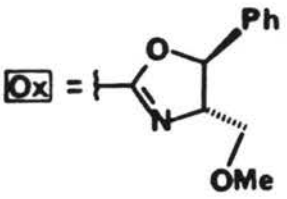
Alternatively, use of the methylated oxazolinylpyridine 170 resulted in near exclusive formation (>99%) of the 3,4-disubstituted pyridine 172 after oxidation. Trapping of the intermediate lithio dihydropyridine with t-butyl chloroformate afforded 171 (R = n-Bu, E = CO_2t-Bu) with a diastereomeric ratio of 89:11 (by LISR) in quantitative yield.

This approach to chiral 1,4-dihydropyridines will be further expanded in the following pages.



170 171 172

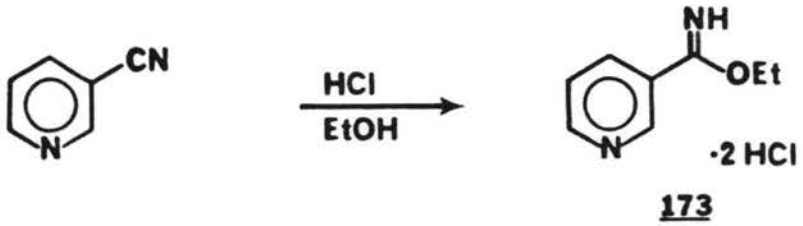
R = Me, *n*-Bu, Ph
E = H, CO_2, *t*-Bu



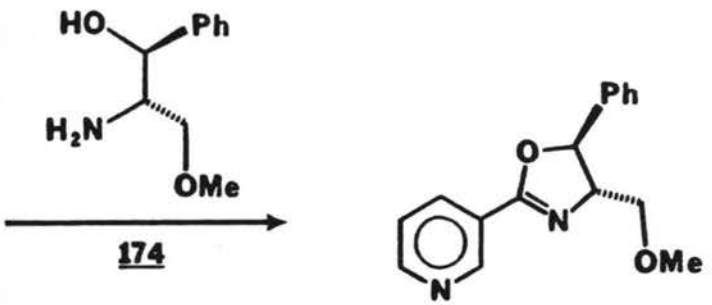
A. Synthesis of Chiral 1,4-Dihydropyridines via an Oxazoline

The requisite oxazolinylpyridine 175 was prepared as outlined in Scheme 4. Treatment of 3-cyanopyridine with dry HCl and ethanol gave imidate 173 in 92% yield as a dihydrochloride salt. The oxazoline was formed by warming a solution of the imidate, triethylamine, and (1S,2S)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol 174. Kugelrohr distillation afforded 175 as a clear vicous oil in 51% yield.

Scheme 4



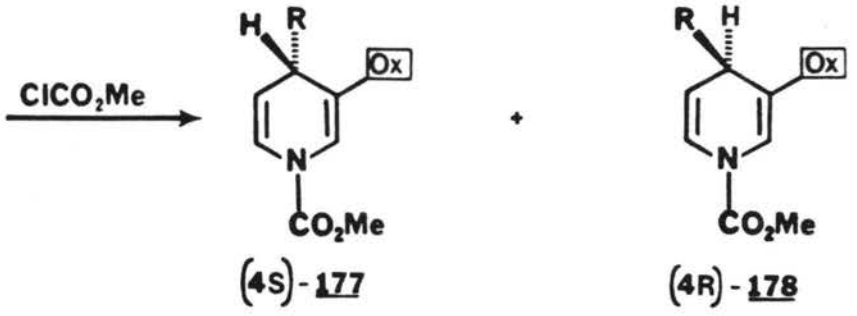
173



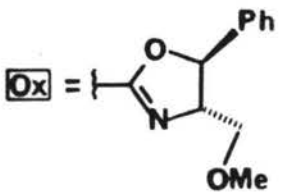
174 175

Alkylation with methyllithium and phenyllithium in THF gave the intermediate lithio anion 176. Subsequent quenching with methyl

175 176



(4S)-177 (4R)-178



R = Me, Ph

chloroformate resulted in the formation of urethanes 177 and 178. (The determination of the absolute configuration of the major diastereomer 177 will be discussed shortly). The results of these alkylations, including a temperature and concentration effect study for the addition of methyllithium, are shown in Table 5.

The diastereomeric ratios were determined for the reaction mixtures after extractive isolation. So as to avoid a resolution, an aliquot was eluted through a small plug of silica gel or florisil with copius amounts of ethylacetate. All of the ratios were found to be

TABLE 5

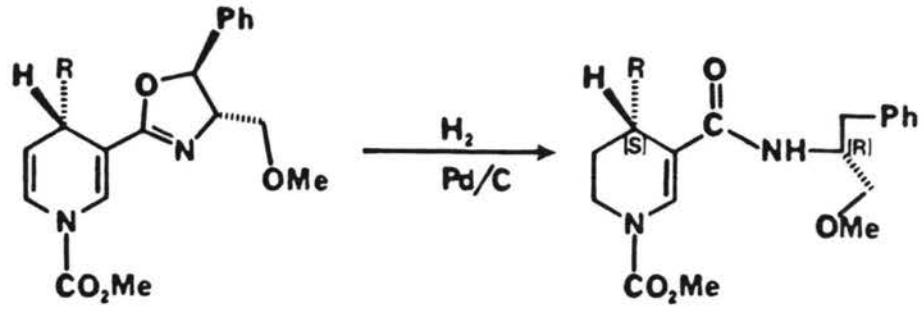
RM[a]	Addition Temperature (°C)	Concentration (M)	Ratio[b] (177:178) (S,S,S):(R,S,S)	% Yield
CH_3Li	- 40	0.01	93:7	79
CH_3Li	- 78	0.01	94:6	79
CH_3Li	-100	0.01	95:5	81
CH_3Li	- 78	0.10	93:7	81
PhLi	- 78	0.01	92:8	94

[a] Inverse Addition: RM was added to a chilled THF solution of the oxazolinylpyridine.

[b] Determined by HPLC. Diastereomeric dihydropyridines 177 & 178 ($R=CH_3$) were found to have the same extinction coefficients by N. R. Natale.[80]

consistantly high as indicated by HPLC, with good to excellent yields after purification.

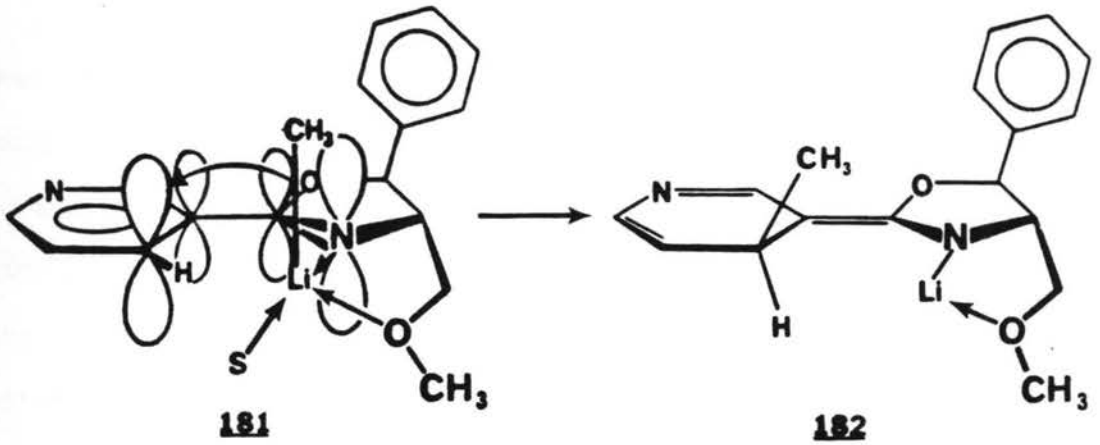
Because the product dihydropyridines were previously unknown compounds, it was necessary to determine the absolute configuration of the newly formed center. Hydrogenolysis of a pure diastereomer of 4-



177 (R=Me) 180

methyl-1,4-dihydropyridine 177 (R = Me) by N. R. Natale led to the crystalline amide 180. The X-ray structure indicated the carbon at C-4 was of the (S)-configuration.

Mechanistically, shown here for the addition of methyllithium, the observed stereochemistry may be rationalized by formation of preaddition complex 181, where the methyllithium bond is coplaner with



181 182

S = Solvent

the π-system. (This type of precomplex was invoked for the stereospecific conjugate addition to substituted vinyl oxazoline compounds).[62] Subsequent conjugate addition, from the topside, resulted in intermediate 182, with the observed stereochemistry of the final product. The alternative configuration would require the solvent molecule and the methyl group be interchanged. The result would be a near orthogonal arrangement of the π-system with the methyllithium bond, less suitable for addition. That no difference in diastereoselectivity was observed for the addition of methyllithium over the range of temperatures and concentrations implied that all of the reactions proceeded through the same, highly coordinated, precomplex 181. The analogous precomplex was also formed for the phenyllithium addition.

Alkylations of 175 by N. R. Natale,[81] using a series of other nucleophiles followed by quenching with methyl chloroformate gave urethanes 177 and 178 are shown in Table 6. The results were also characterized by excellent diastereoselectivity and good to excellent yields.

A very significant problem associated with some of the oxazoline chemistry was the removal of the chiral auxiliary after use. Normal hydrolysis generally required strong acid at elevated temperatures, not suitable for the preservation of the dihydropyridine. Quaternization, which had been used for the removal of achiral oxazolines,[82] met with limited success for the chiral analog.[80] More recently, facile quaternization was realized by the use of strong methylating agents such as methyl fluorosulfonate ("magic methyl") and trimethyloxonium tetrafluoroborate,[69] which led to the removal of the oxazoline moiety

TABLE 6

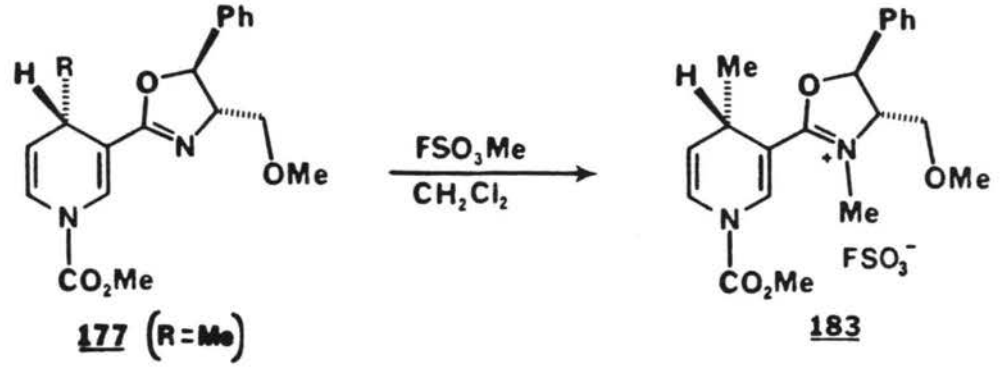
RM[a]	Addition Temperature (°C)	Ratio[b]: (177;178) (S,S,S):(R,S,S)	% Yield
MeMgCl	0	91:9	88
n-BuLi	-78	97:3	95
n-BuMgCl	0	95:5	98
EtMgBr	0	92:8	63

[a] Inverse Addition: RM added to a chilled THF solution of the oxazolinylpyridine.

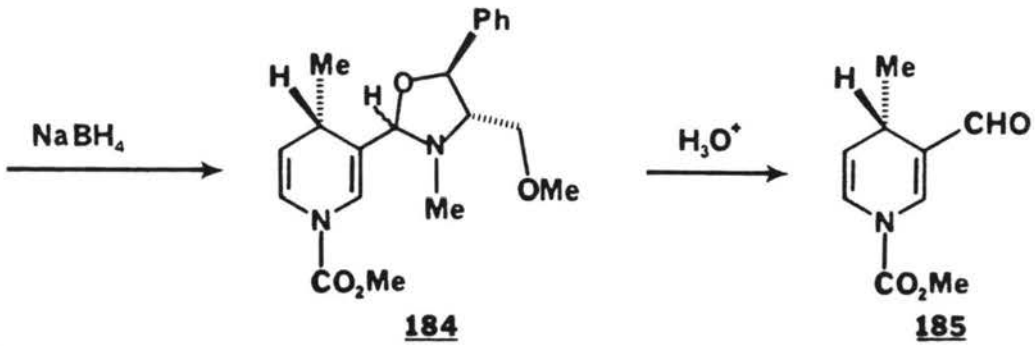
[b] Determined by HPLC.

from dihydronaphthalenes. This procedure was applied to a 3-oxazolinyl-1,4-dihydropyridine 177 (R=Me).

Treatment of 4-methyl-1,4-dihydropyridine 177 (R=Me) (94:6 ratio) with methyl fluorosulfonate resulted in a rapid color change from light



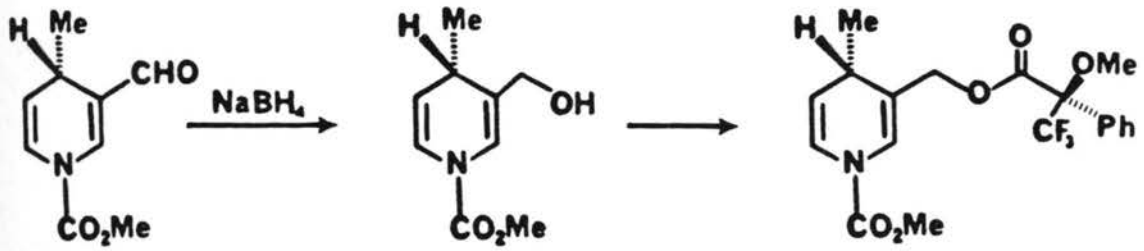
177 (R=Me) 183



184 185

yellow to green. Upon stirring overnight, the intermediate oxazolinium salt 183 was reduced with $NaBH_4$ to give oxazolidine 184. Acidic hydrolysis gave aldehyde 185 as an oil in 60% overall yield after purification ($[\alpha]_D$ +144).

The enantiomeric excess was determined by reduction of 185 to alcohol 186. The hydroxyl group was acylated with (+)-methoxyphenyl-trifluoromethylacetyl chloride[83] (derived from the corresponding acid, "Mosher's acid"). The resulting ester 187 was analyzed by ^1H NMR (270 MHz) and found to have a ratio of 91:9. This corresponded reasonably well with the 94:6 ratio of the starting oxazoline 177 (R=Me).



185 186 187

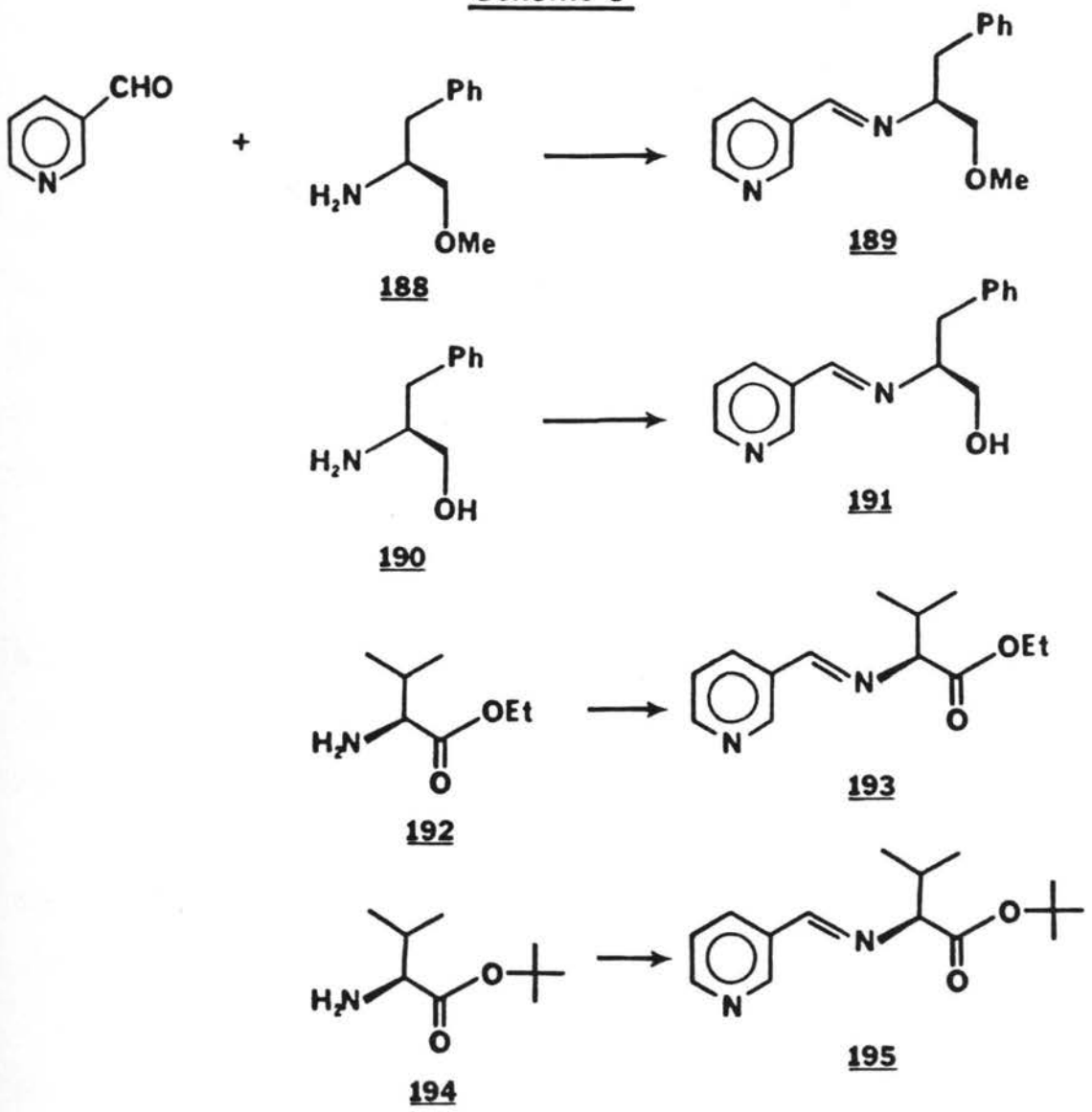
B. Synthesis of Chiral 1,4-Dihydropyridines via Imines

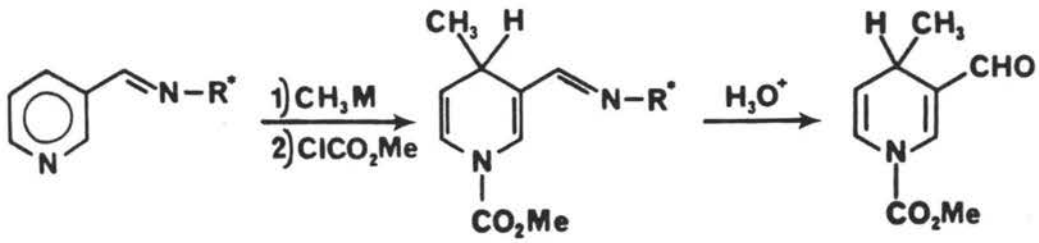
At the outset of this project methodology for the mild removal of the oxazoline moiety from the dihydropyridines had not yet been realized. It was reasoned that use of an asymmetric imine moiety as the chiral auxiliary could lead to a stereoselective alkylation. Subsequent mild acid hydrolysis would then give enantiomerically enriched dihydropyridines. This portion of the dissertation will focus on studies to this end.

The imino pyridines investigated were formed by condensation of 3-pyridinecarboxaldehyde and a chiral amine, derived from phenylalanine or valine in 53-94% (Scheme 5).

The alkylations were carried out using only methyl-substituted organometallic reagents. The reason being, a more simplified ^{1}H NMR spectra, and if high asymmetric induction could be realized for the smaller methyl group, better optical yields should be realized with larger nucleophiles. Typically, upon alkylation the resulting anion was quenched with methyl chloroformate and the urethanes 196 were isolated by extraction. The diastereomeric excesses were determined by ^{1}H NMR (integrations of the methyl doublets, $\sim\delta$1.2) or by HPLC. Periodically, the imino 1,4-dihydropyridines were easily hydrolyzed at

Scheme 5





196 185

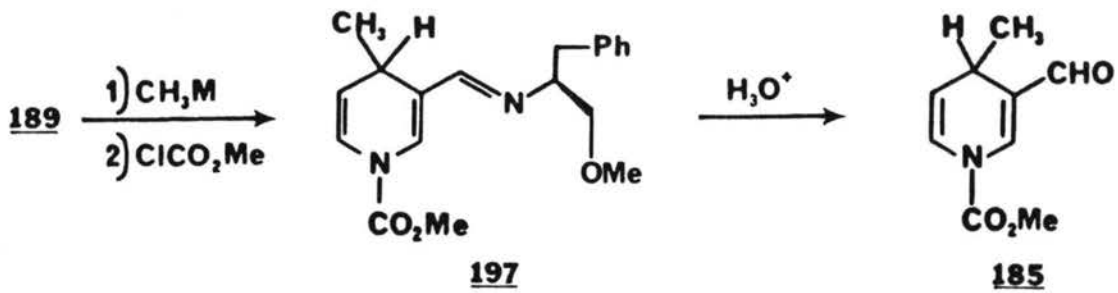
room temperature using either an aqueous sodium acetate buffer or aqueous oxalic acid, with a cosolvent. Following extractive isolation, the aldehyde 185 was found to be of high purity, and could be further purified by chromatography. Below is described the alkylation of the imino pyridines.

1. Alkylation of Imino Pyridine 189

Imine 189, derived from phenylalaninol methyl ether, which was used very successfully in the asymmetric alkylation of ketimines and aldimines,[84] was treated with several organometallic reagents as shown in Table 7.

Addition of methyllithium and the methyl Grignard reagents formed complex mixtures, presumably of various regioisomers resulting from unbiased addition to the pyridine ring. In contrast, cuprate reagents formed 1,4-dihydropyridines exclusively. The homocuprate, however, showed no stereoselectivity. This may have been due to its symmetrical nature with no stereodifferentiating effect exhibited by the chiral auxiliary. Alternatively, the mixed cuprate gave a 16% de, possibly as a result of the dissymmetry of the cuprate reagent and/or the ability of the chiral auxiliary to form diastereomeric transition states.

TABLE 7[a]



CH_3M[b]	Diastereomeric Ratio[c] (197)	% Yield (185)
CH_3Li	complex mixture	
CH_3MgBr[d]	complex mixture	
$(CH_3)_2CuLi$[e]	1:1	
$CH_3CuCNLi$	42:58	88[f]

[a]The typical reaction was done at 0.01M in THF at -78° (-20° for Grignard reagent addition) for 3-5 hours, followed by quenching with methyl chloroformate, and extractive isolation. [b]1.1 to 2.0 eq. [c]Determined by ^1H NMR. [d]Similar results were observed for the addition of CH_3MgCl and CH_3MgI. [e]Similar results were observed in ether. [f]Unpurified yield, found to be >95% pure by ^1H NMR as a mixture of enantiomers.

Hydrolysis of the product gave the desired aldehyde 185, as a somewhat unstable oil, in 88% crude yield.

2. Alkylation of Imino Pyridine 191

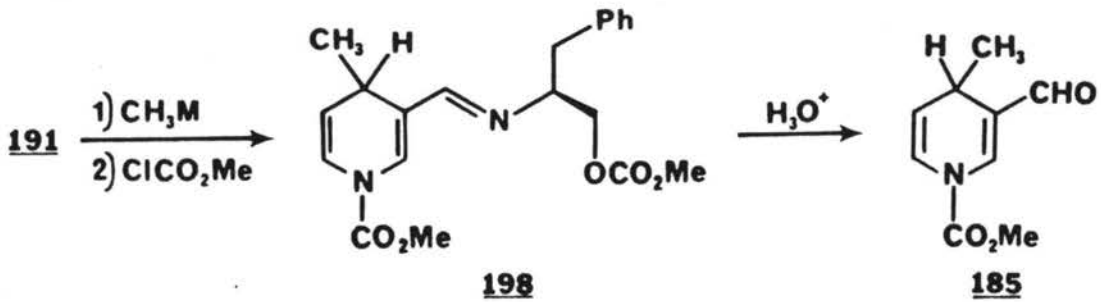
Because of the regioselectivity problems associated with the alkylation of imine 189, imine 191, derived from phenylalaninol was prepared. It was postulated that the free deprotonated hydroxyl group could better serve as a ligand, forming a more rigid chelate to aid in the overall selectivity. The results are summarized in Table 8.

Similar to the alkylation of imine 189, methyllithium and methylmagnesium bromide in ether and DME gave a complex mixture of products. In contrast however, treatment with methylmagnesium bromide in THF gave exclusively 1,4-dihydropyridines, as a racemic mixture, indicating that a stronger chelate was formed, although with a lack of stereodifferentiation. The cuprate also gave the desired products in racemic form. Hydrolysis of the homocuprate reaction mixture afforded aldehyde 185 in 94% crude yield.

3. Alkylation of Imino Pyridine 193

An alternative approach was the use of imines prepared from esters of valine. Imine 193, derived from (S)-ethylvalinate, was alkylated with the organometallic reagents as shown in Table 9. Significant improvement for the asymmetric induction (up to 38% de) was realized with the cuprate addition. These reactions showed little, if any, temperature dependence, with higher selectivity observed in THF compared with ether. An interesting feature of the valine imine was the increased stability to chromatography, specifically HPLC, employed to determine the diastereomeric excesses.

TABLE 8[a]

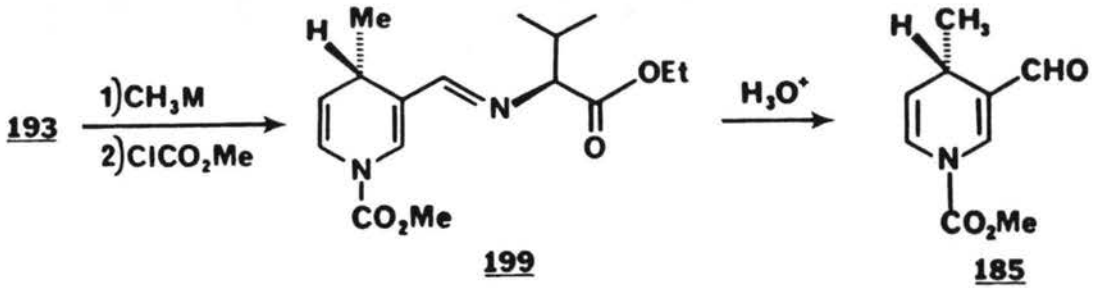


198 185

CH_3M[b]	Diastereomeric Ratio[c] (198)	% Yield (185)
CH_3Li	complex mixture	
CH_3MgBr[d]	1:1	
$(CH_3)_2CuLi$	1:1	94[e]
$CH_3CuCNLi$	1:1	

a) Reaction conditions, see Footnote a of Table 7 (p. 60). b) 2.2-3.0 eq. c) Determined by ^1H NMR. d) Additions in ether and DME gave complex mixtures. e) Unpurified yield, found to be >95% pure by ^1H NMR as a mixture of enantiomers.

TABLE 9[a]



199 185

CH_3M[b]	Diastereomeric Ratio[c] (199)	% Yield (185)
$(CH_3)_2CuLi$[d]	34:66	97[e]
$(CH_3)_2CuLi$[f]	31:69	
CH_3MgBr	complex mixture	

a) Reaction conditions, see Footnote a, Table 7 (p. 60). b) 1.1-2.0 eq. c) Determined by HPLC. d) Alkylation in ether gave a ratio of 41:59. e) Purified yield, $[\alpha]_D^{24}$ +66.5. f) Alkylation temperature was -100°C.

Upon hydrolysis, aldehyde 185 was recovered in 97% yield after chromatography. The rotation, +66.5°, indicated that the absolute configuration of the newly formed center, at C-4, was of the (S)-configuration. This was determined by comparison with authentic material of known configuration, from the alkylation of oxazolinyl-pyridine 175 (vide supra). Mechanistic rationalization of the observed stereochemistry will be discussed on page 66.

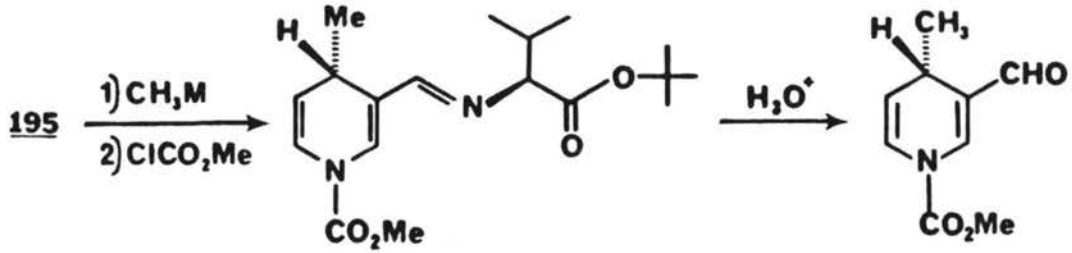
4. Alkylation of Imino Pyridine 195

Imine 195, prepared from (S)-t-butylvalinate, was alkylated using the optimum conditions observed from imine 193. Additionally, the imino pyridine was precomplexed with magnesium dibromide etherate,[85] in an attempt to form a more rigid complex. Finally, addition of a chiral mixed cuprate, derived from N-methylprolinol[86] was also investigated. The results for these reactions are shown on Table 10.

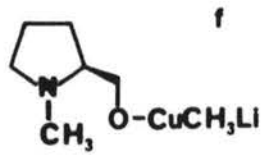
It was apparent that increasing the bulkiness of the chiral auxiliary had a definite effect on the asymmetric induction, up to 56% de. Addition of magnesium dibromide resulted in no change in the stereoselectivity. Similar results were obtained for the addition of the chiral mixed cuprate. (It should be noted however, that the reaction was performed at -78° instead of -100°. Thus, it is conceivable that the stereoselectivity could be further increased with further cooling, though probably not significantly based on a slight increase for the alkylation of imine 193 at -78° and -100°).

Hydrolysis of the product imine gave aldehyde 185 in 82% yield after purification. This lower yield reflected the prolonged hydrolysis period required for complete reaction, resulting in partial

TABLE 10[a]



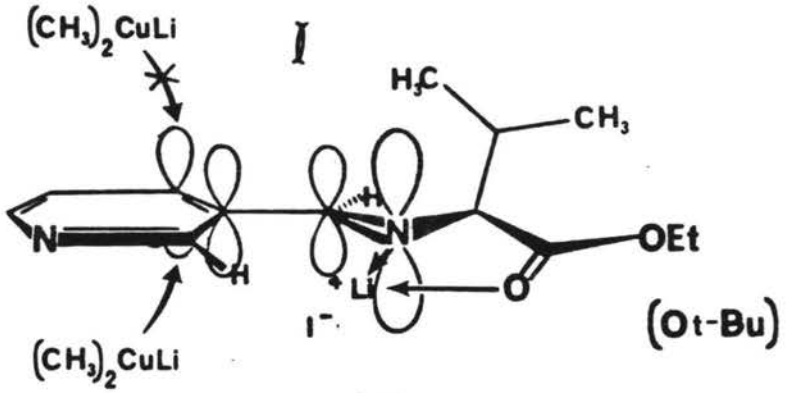
200 185

CH_3M[b]	Reaction Temperature	Diastereomeric Ratio[c] (200)	% Yield (185)
$(CH_3)_2CuLi$	-100	22:78	82[d]
$(CH_3)_2CuLi$ ($MgBr_2$ precomplex)	-105	24:76	
 [f]	- 78	23:76[f]	

a) Reaction conditions, see Footnote a, Table 7 (p. 60). b) 2.0-2.1 eq. c) Determined by HPLC (waters μ-porasil). d) Purified yield, $[\alpha]_D^{24}$ +98 (c 0.7, C_6H_6). e) See Reference 11. f) Determined by HPLC (Universal Scientific Spherosorb, 10 μ).

loss of the aldehyde through decomposition. The absolute configuration was also found to be (S), by correlation of the rotation. Similarly, the mode of addition was analagous to imine 193 to be discussed below.

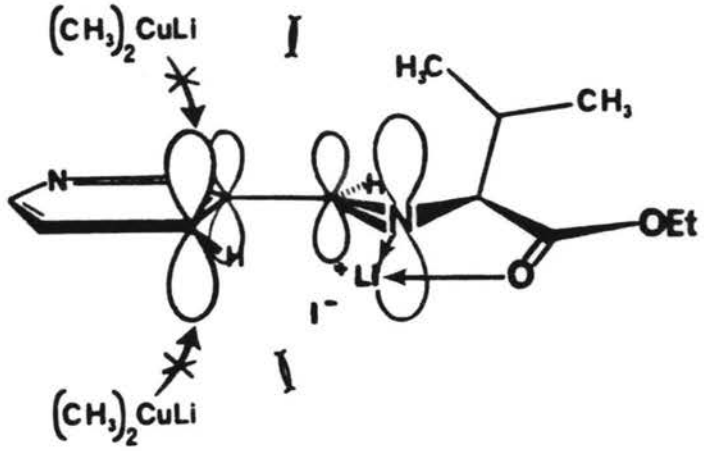
The stereochemistry observed for the alkylation of imines 193 and 195 may be rationalized in terms of a bimolecular reaction between precomplex 201 (formed from the imine and lithium iodide, a byproduct of cuprate formation) and lithium dimethyl cuprate. Conjugate addition to the transoid imino pyridine from the less hindered bottomside, would



201

result in the observed stereochemistry. An alternative conformation, in which the pyridine ring has been rotated 180°, is shown in 202. The required attack from the top face of the molecule would be less desirable due to steric interaction with the isopropyl group. Similarly, approach from the bottomside, which would result in the wrong stereochemistry, would also be unfavorable due to the steric interaction with the lithium iodide precomplex. This appears to be a less stringent steric requirement, and could be a reasonable competitive pathway for the addition. If so, this would explain the

diastereomeric excesses not exceeding 38% (and 56% de for the alkylation of imine 195).



202

Considering the progress made in the synthesis of chiral 1,4-dihydropyridines via the imine route (up to 56% de), there is still substantial room for improvement. One would have to consider however, the benefits of further study since very high stereoselectivity was realized (up to 94% de) using the oxazoline chiral auxiliary, which can now be easily removed. Another lucrative characteristic of the oxazoline moiety was the capacity to add organolithium and Grignard reagents, instead of being restricted only to cuprate reagents. Clearly, further imine alkylations would be justified only from the standpoint of ease with which the imine may be formed and hydrolyzed, in far fewer steps than the corresponding oxazoline compounds.

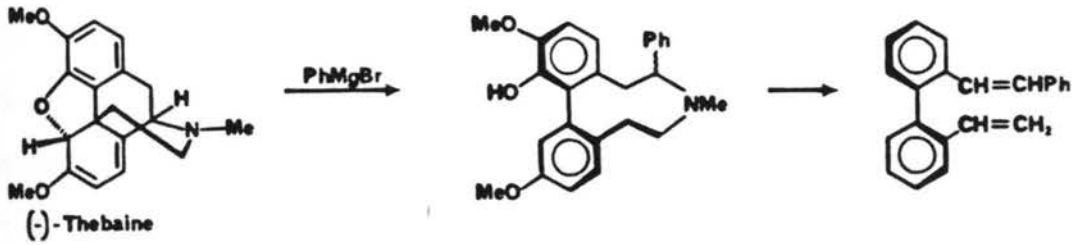
C. Conservation of Chirality

The methodology discussed for the synthesis of chiral 1,4-dihydropyridines focused on the creaction of a new stereochemical

center (an element of chirality or stereogenic unit)[87] in the presence of an already existing stereocenter namely that present in the oxazoline or the imine. An approach to asymmetric synthesis which has received considerably less attention, is the formation of a new stereogenic unit with simultaneous destruction of another. These processes are known as "self-immolative"[88] and occur with some degree of conservation of chirality. (It should be noted that "chirality" is a molecular term. A molecule is chiral or chirotopic by virtue of its topology or molecular geometry and not due to a center or point in the molecule).

Examples in which an sp^3 center (central chiral element) is converted to an sp^2 center (axial chiral element), and vice versa,[89] include a hetero-ene reaction,[90] and the formation of allenes[91] and olefins.[92] Self-immolative processes where a central chiral element is converted to another central chiral element have also been observed.[93]

In 1955, Berson and Brown[94] proposed an experiment, a self-immolative process, where destruction of a central chiral element would result in simultaneous formation of an element of chirality of the biphenyl type, with conservation of chirality. This investigation was prompted by the observation that such a process occurred when thebaine 203 was treated with phenylmagnesium bromide. Rearrangement and aromatization gave biphenyl 204, epimeric at the benzyl position.[95] A subsequent investigation[96] converted 204 to the enantiomeric biphenyl 205.

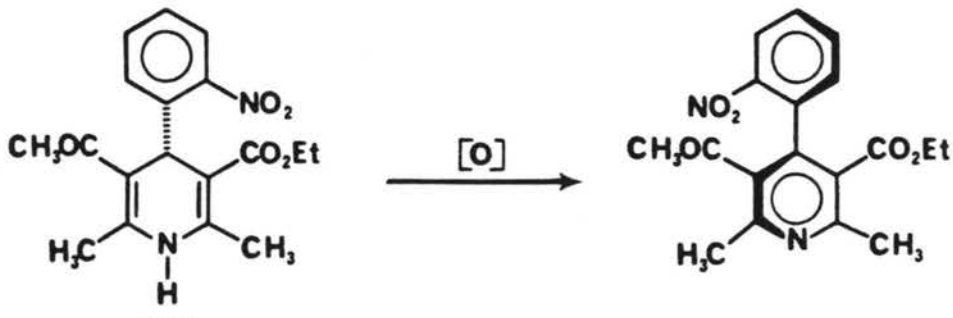


(-)-Thebaine

203 **204** **205**

The precursor 203 however, was a special case due to the three stereocenters present in the molecule. Thus, the conservation of chirality could have been, in addition to the center which was destroyed, a function of the other two centers exerting an influence on the stereochemical outcome.

Berson, realizing this complexity, sought to simplify the problem by use of 4-(2-nitrophenyl)-1,4-dihydropyridine 206. During the self-

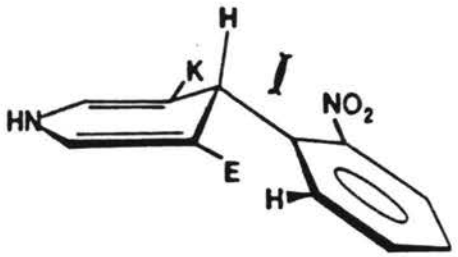


206 **207**

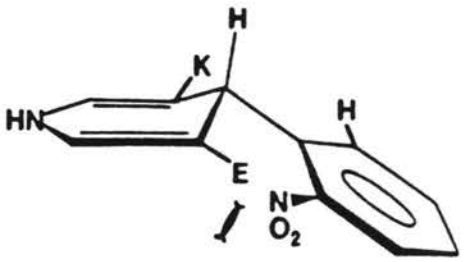
immolative process (by oxidation), the only stereocenter present in the molecule was the one destroyed in the formation of biphenyl 207.

An important feature of the dihydropyridine was the free rotation around the C-4 and aryl bond. During oxidation, when the C-4 proton bond was not completely broken and full aromaticity had not been

reached, a given enantiomer should have given rise to two diastereomeric transition states. These are shown as 208 and 209, in which the nitro group interacts differently with the ring substituents imparting an energy bias and predominatly one axial enantiomer would prevail upon complete oxidation.



208



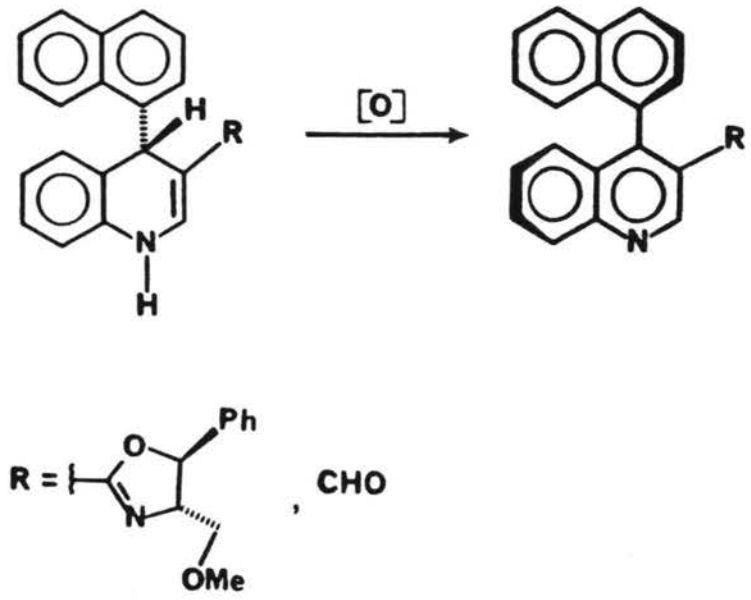
209

K = $COCH_3$
E = CO_2Et

Due to the experimental difficulties, namely obtaining suitable enantiomerically enriched dihydropyridine 206, the proposal could not be conclusively verified, nor was it investigated and successfully shown to occur until now.

This portion of the dissertation will focus on results which verify that the Berson proposal does occur, albeit on a naphthylquinoline system rather than an arylpyridine system (Scheme 6). Discussion of mechanistic aspects of this process, as well as related studies will also be presented.

Scheme 6

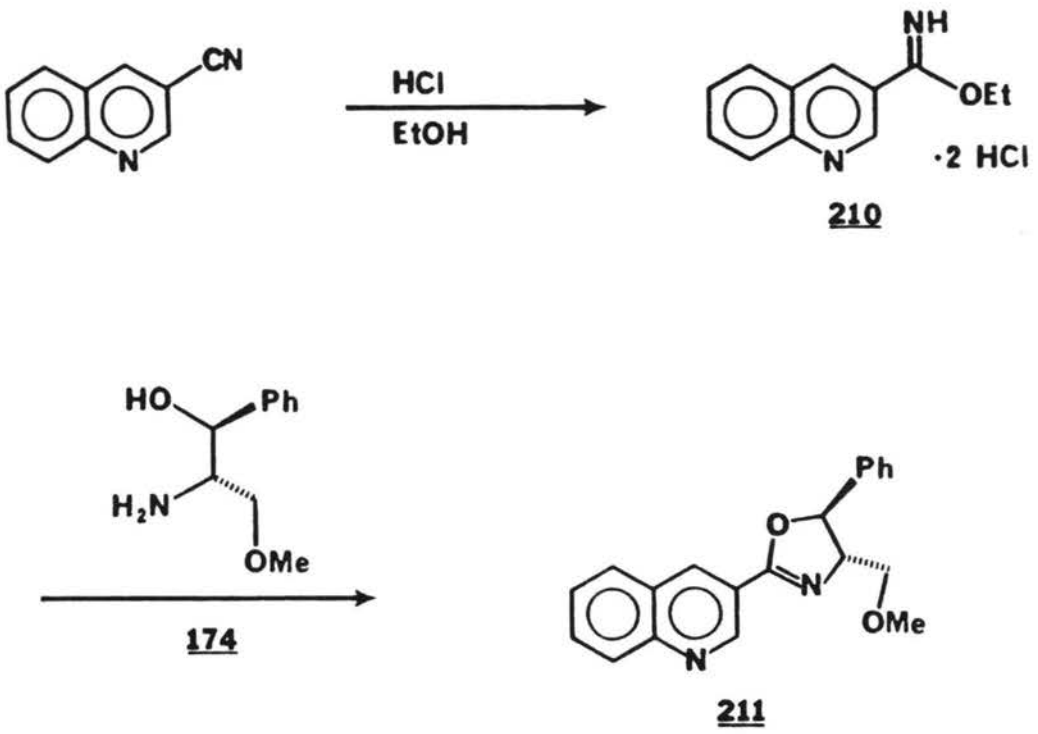


, CHO

1. Verification of the Berson Proposal (Alkylation with 1-Naphthyllithium)

The synthesis of the requisite starting material, oxazolinylquinoline 211 is shown in Scheme 7. Ethyl imidate 210 was prepared in 95% yield by treatment of 3-quinolinecarbonitrile with dry HCl and ethanol. The oxazoline was formed by heating a mixture of the imidate, triethylamine, and (1S,2S)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol 174 in 1,2-dichloroethane. Recovery of the crude product by extraction, and purification, afforded the oxazolinylquinoline 211 as a viscous light yellow oil in 82.5% yield.

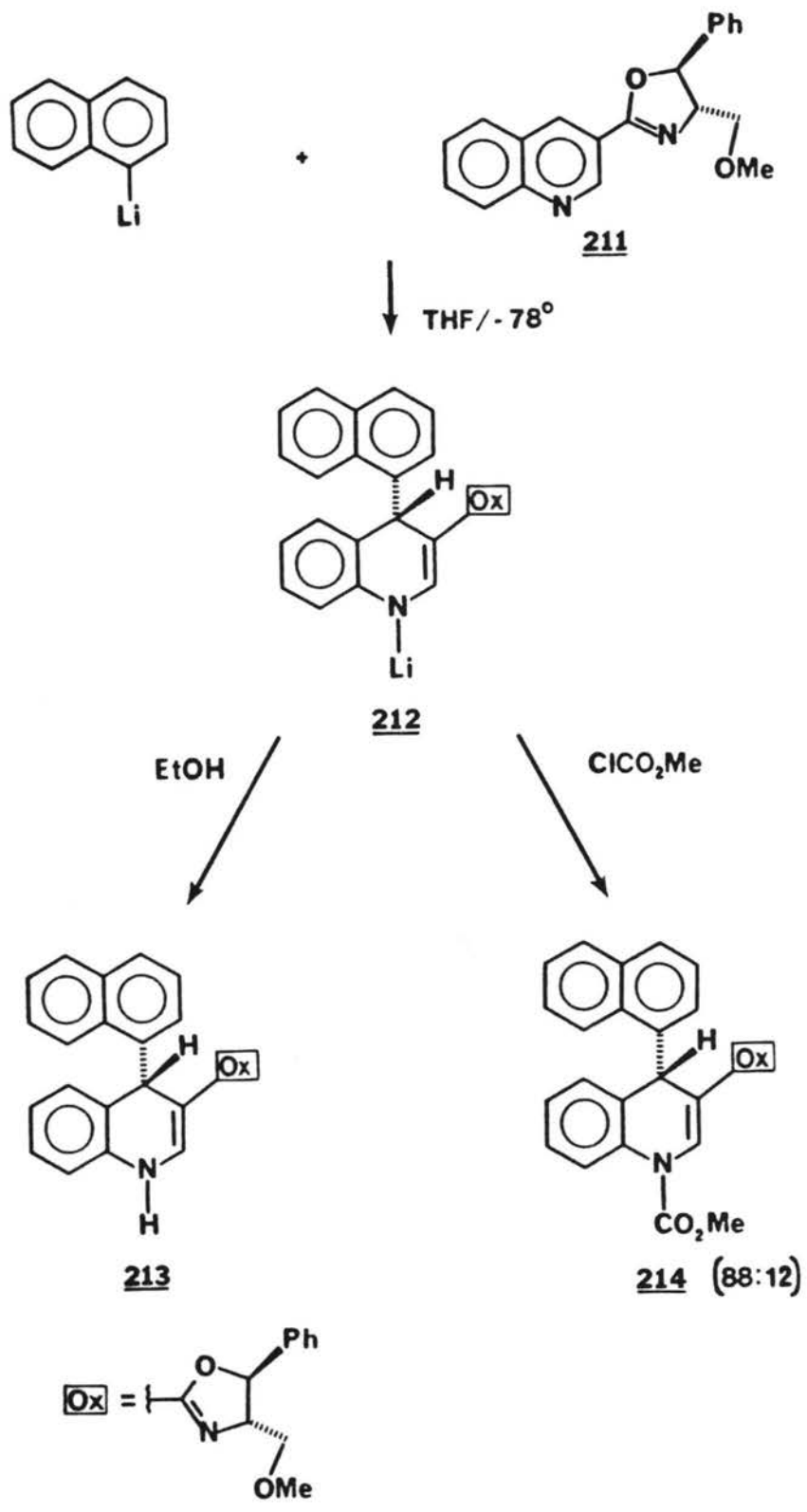
Scheme 7

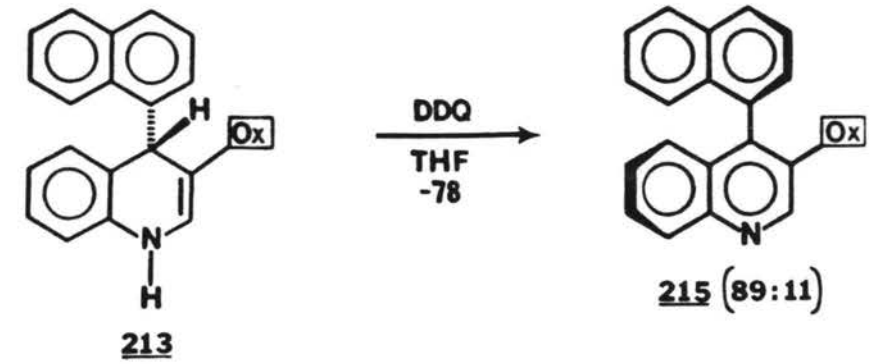


Alkylation with 1-naphthyllithium in THF is summarized in Scheme 8. Upon complete reaction, the bulk of the lithio anion 212 solution (99% by volume) was transferred out of the flask and quenched with ethanol to give 213. The remaining 212 was quenched with methyl chloroformate forming urethane 214. This urethane served as an analytical sample for the determination of the diastereomeric excess before oxidation. Analysis by HPLC indicated a ratio of 88:12.

The N-H dihydroquinoline 213 was oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give naphthylquinoline 215 in 87% yield. Analysis by HPLC indicated a diastereomeric ratio of 89:11, in excellent agreement with that of the precursor 213 (determined as urethane 214). The oxazoline was removed from 215 by acid hydrolysis

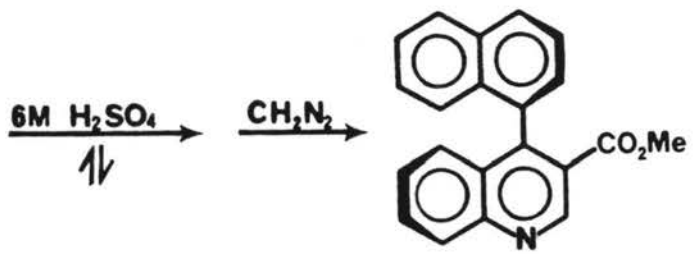
Scheme 8


Li
Ph
O
N
OMe
N
211
THF/-78°
H
Ox
N
Li
212
EtOH
ClCO2Me
H
Ox
N
H
213
H
Ox
N
CO2Me
214 (88:12)
Ox =
O
Ph
N
OMe

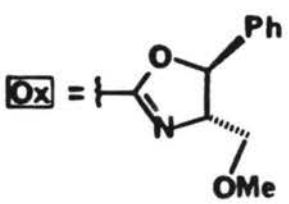


213

215 (89:11)



216

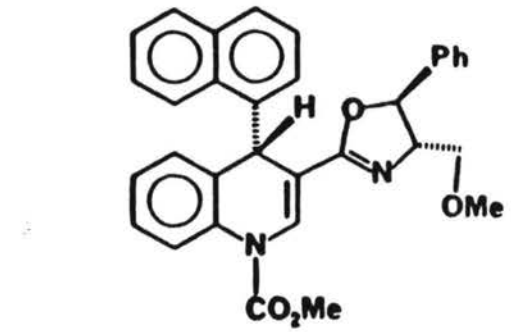


and the resulting carboxyl group esterified with diazomethane to give ester 216 in 84% yield ($[\alpha]_D$ -9.8°). Spectra of the diastereomeric urethanes 214 and biaryls 215 are shown in Figures 1 and 2 respectively.

From the results obtained from this series of experiments, support for the Berson proposal had been realized, since the ratio before oxidation (88:12) agreed very well with that of the oxidized product 215 (89:11). However, one could argue, as in the thebaine oxidation, that the high conservation of chirality in going from 213 to 216 was a direct result of the additional stereocenters present in the oxazoline moiety. It was therefore necessary to perform the oxidation without any external stereochemical environment.

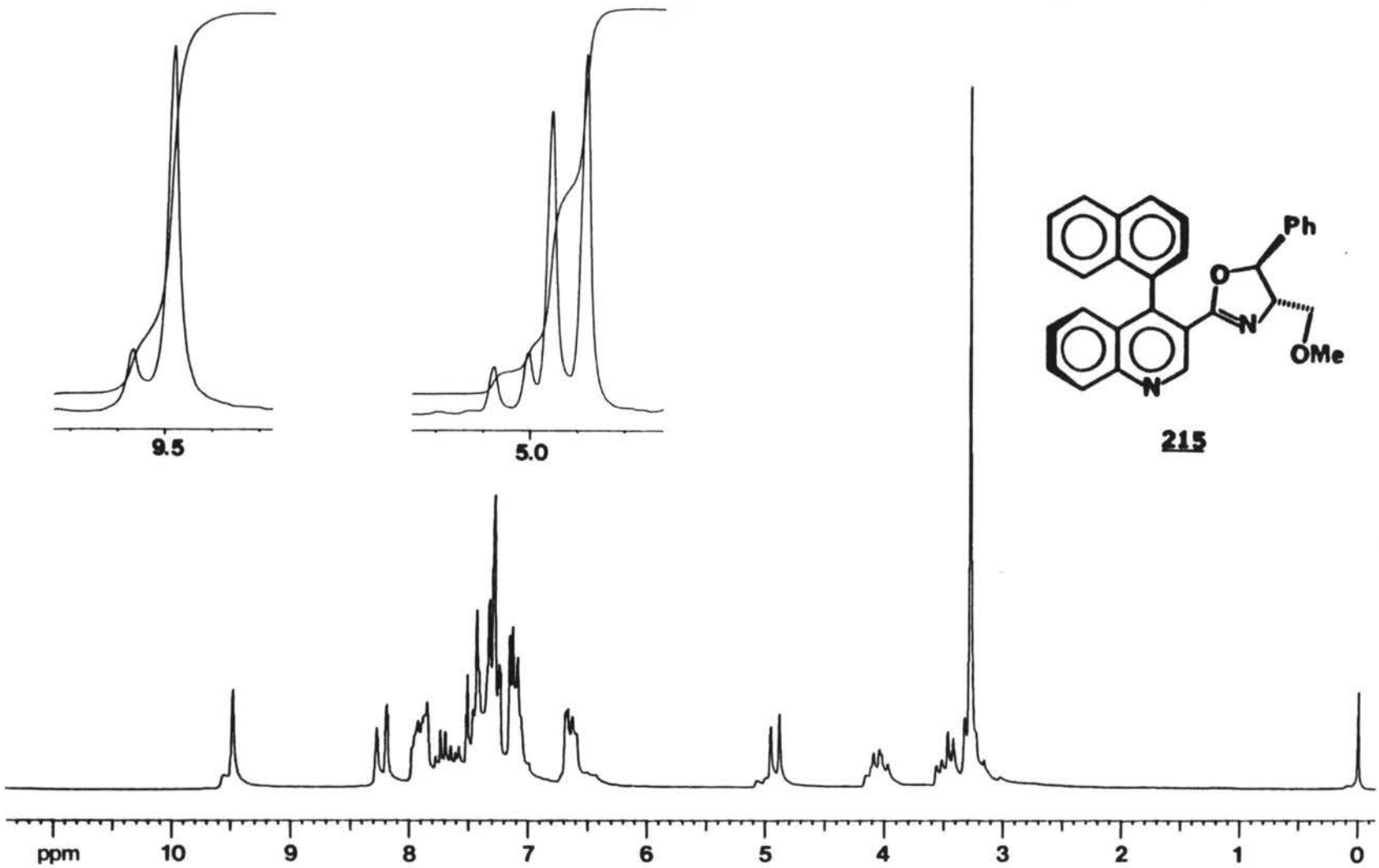
The 4-naphthyl-1,4-dihydroquinoline 214 (87.5:12.5 ratio) was quaternized with methylfluorosulfonate ("magic methyl") to form the oxazolinium salt 217, which was reduced ($NaBH_4$) to the corresponding oxazolidine without isolation (Scheme 9). Hydrolysis with aqueous oxalic acid on silica gel gave aldehyde 218 in 96% overall yield from 214. (Previous attempts at the hydrolysis employing other aqueous acids, with a two phase solvent system, failed to give the desired aldehyde). The urethane was cleaved under basic conditions to the N-H dihydroquinoline 219, the required precursor for the oxidation to 216.

Treatment with DDQ (-78°C) afforded the biaryl 220 in 90% yield. Since this naphthylquinoline was previously unknown, it was necessary to correlate it with a previously prepared compound. The aldehyde was converted to the well characterized ester 216 in 71% yield by oxidation with silver oxide and esterification.



214

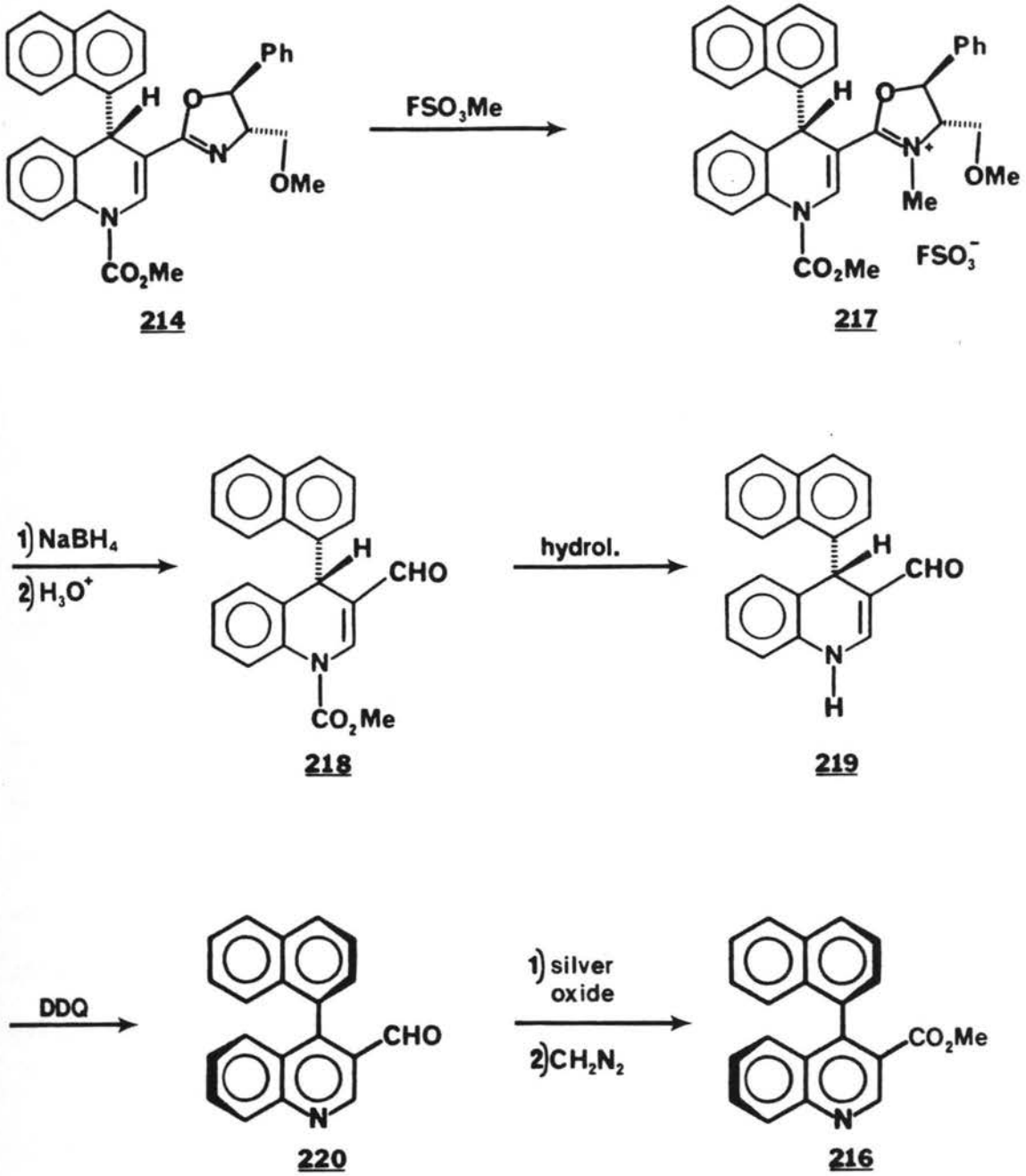
Fig.1



215

Fig. 2

Scheme 9


Ph
H
O
N
OMe
N
CO2Me
214
FSO3Me
Ph
H
O
N+
OMe
Me
N
CO2Me
FSO3-
217
1) NaBH4
2) H3O+
H
CHO
N
CO2Me
218
hydrol.
H
CHO
N
H
219
DDQ
CHO
N
220
1) silver oxide
2) CH2N2
CO2Me
N
216

The enantiomeric excess of ester 216 ($[\alpha]_D$ -10.6) was determined by comparison of the rotation with that observed for a pure enantiomer, $[\alpha]_D$ +13.2. (This pure enantiomer, of opposite configuration, was prepared by enrichment of (R)-4-naphthyl-3-oxazolinylquinoline 224 (vide infra). Subsequent recrystallization gave a single diastereomer which was hydrolyzed and esterified). This comparison indicated 80% ee (90:10 ratio) in excellent agreement with the initial ratio of 87.5:12.5. With these results, the Berson proposal was shown to occur with >95% conservation of chirality, and in the absence of any external stereochemical elements.

Complete confirmation of the Berson proposal however, had not been realized. Of central importance was establihsing free rotation in 4-naphthyl-1,4-dihydroquinoline 219. A conformationally locked naphthyl group would be characterized by two stereochemical elements, the configuration of the newly created center and the rotational isomer form. The oxidation of such a species would remove the central chiral element replacing it with an axial chiral element, with no change in the rotational isomer form. This type of process would not give rise to diastereomeric transition states, necessary for the true confirmation of the Berson proposal. ^1H NMR studies determined free rotation did occur, with a rotational barrier of 11.2 kcal mol^{-1}. Details of this study follow in p. 91.

2. Alkylation with 1-Naphthylmagnesium Bromide

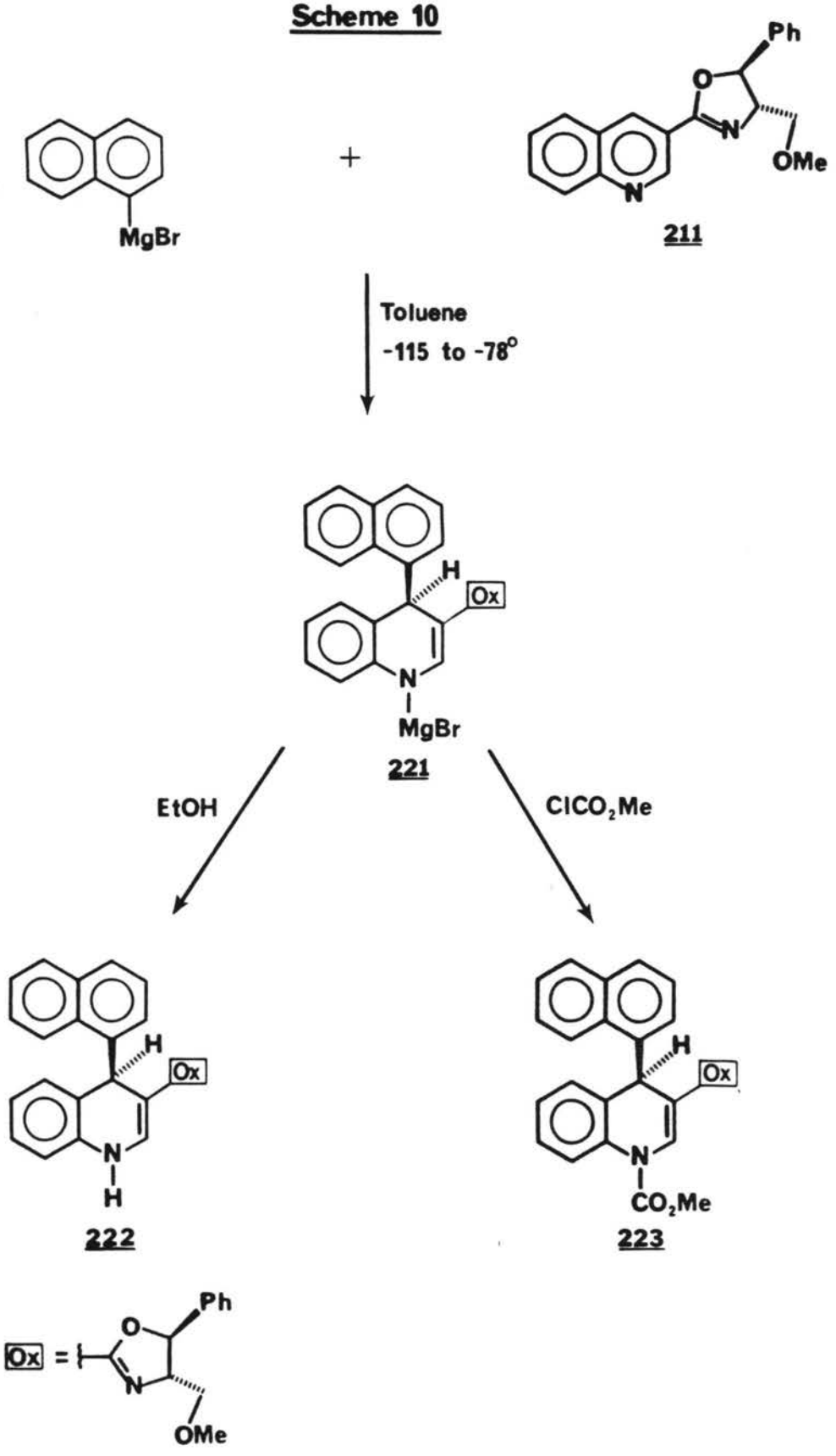
Alkylation of oxazolinylquinoline 211 in toluene with 1-naphthylmagnesium bromide proved to be a more challenging aspect of this chemistry. A significant problem dealt with at the beginning was very erratic optical yields for the products. This was found to be a

function of solvent composition in the stock Grignard reagent. Large amounts of THF (20-30% by volume) could not be tolerated for high asymmetric induction, though smaller amounts of up to ~5% had no effect. Several different mixtures were investigated, of which 55:45 (V/V) ether/benzene was found to be optimal, and gave reproducible results. The reaction sequence is summarized in Scheme 10.

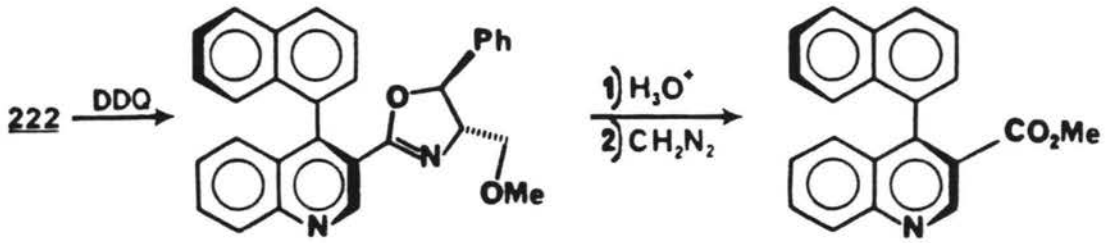
Upon complete reaction, the bulk of the magnesio anion 221 solution (98% by volume) was transferred out of the flask and quenched with ethanol to give 222. The remaining anion solution was allowed to warm to room temperature, at which time THF and more Grignard reagent were added. The reaction was quenched with methyl chloroformate to give 223. This elaborate urethane formation sequence was necessary due to the tendency to get competing C and N acylation. Quenching at room temperature with THF as a cosolvent was found to alleviate this problem. However, because only ~0.06 mmol of the anion was present, traces of moisture or HCl (from the methyl chloroformate) would easily lead to a resolution. This problem was eliminated with the addition of extra Grignard reagent, which insured a proton-free environment. Analysis by HPLC of urethane 223 indicated a ratio of 14:86 with the epimeric dihydroquinoline (compared to naphthyllithium addition) predominating.

Oxidation of N-H dihydroquinoline 222 with DDQ gave the biaryl 224 in 79% yield with a ratio of 12:88. Comparison with the ratio before oxidation (14:88) indicated a very high degree of conservation of chirality. Hydrolytic oxazoline removal and esterification gave ester 225 ($[\alpha]_D$ +9.55) in 91% yield, which proved to be the epimeric product from 1-naphthyllithium addition. Spectra of the diastereomeric

Scheme 10



urethanes 223 and oxidized products 224 are shown in Figures 3 and 4 respectively.



224 225

3. Determination of Absolute Configurations and the Rotational Barrier

Since the 4-naphthyl-1,4-dihydroquinolines and the 4-naphthylquinolines were previously unknown compounds, determination of the absolute configurations by X-ray analysis was necessary for each. The dihydro analog was prepared by quenching intermediate 221, from Grignard reagent addition, with di-t-butyldicarbonate. Chromatographic enrichment of the major diastereomer followed by recrystallization gave the crystalline compound (R)-226. The absolute configuration of the newly formed center was found to be (R) (Figure 5).

Likewise, the naphthylquinoline (R)-224 was prepared by quenching anion 221 and oxidation by DDQ. The major diastereomer was enriched by chromatography, recrystallized, and subjected to X-ray analysis. The absolute configuration of biaryl (R)-224 was also found to be (R) (Figure 6).

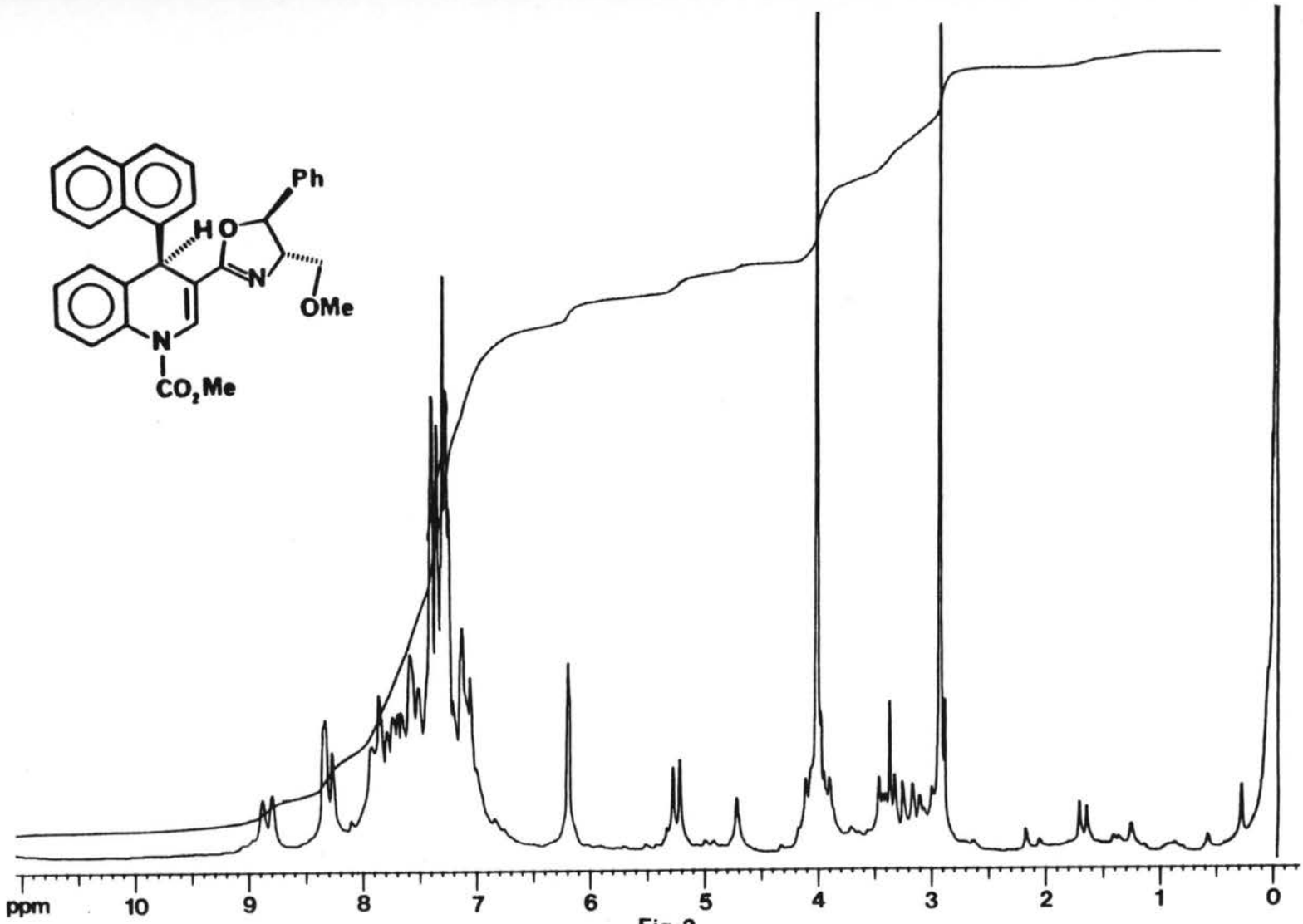


Fig.3

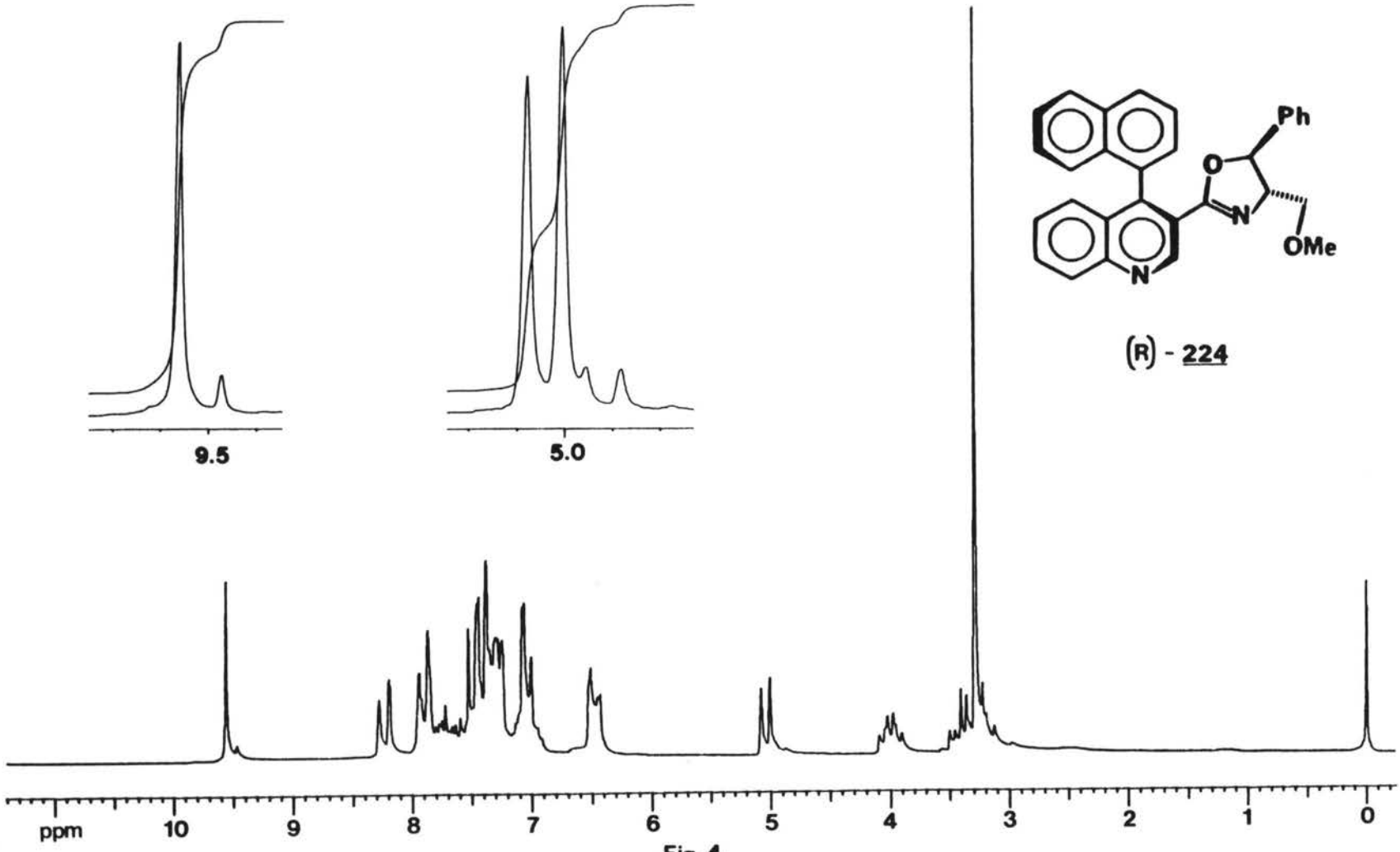
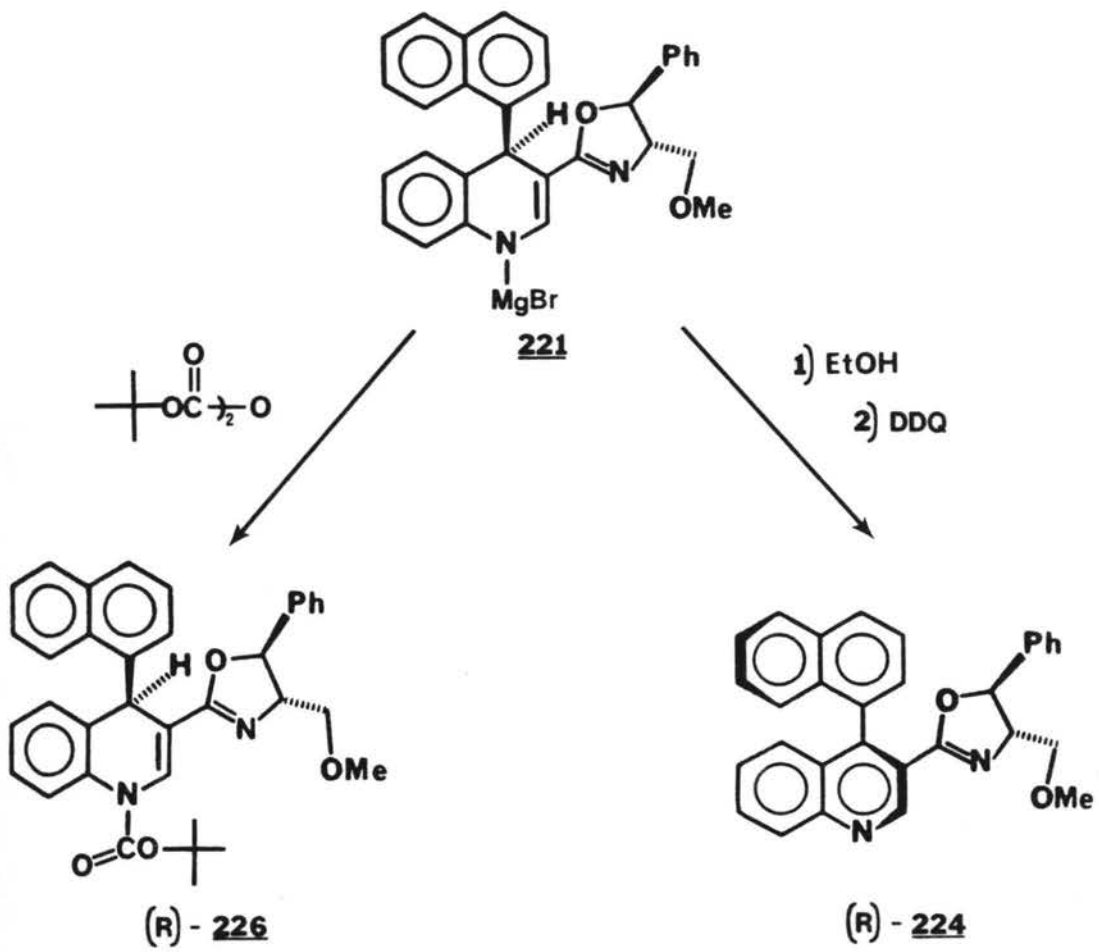
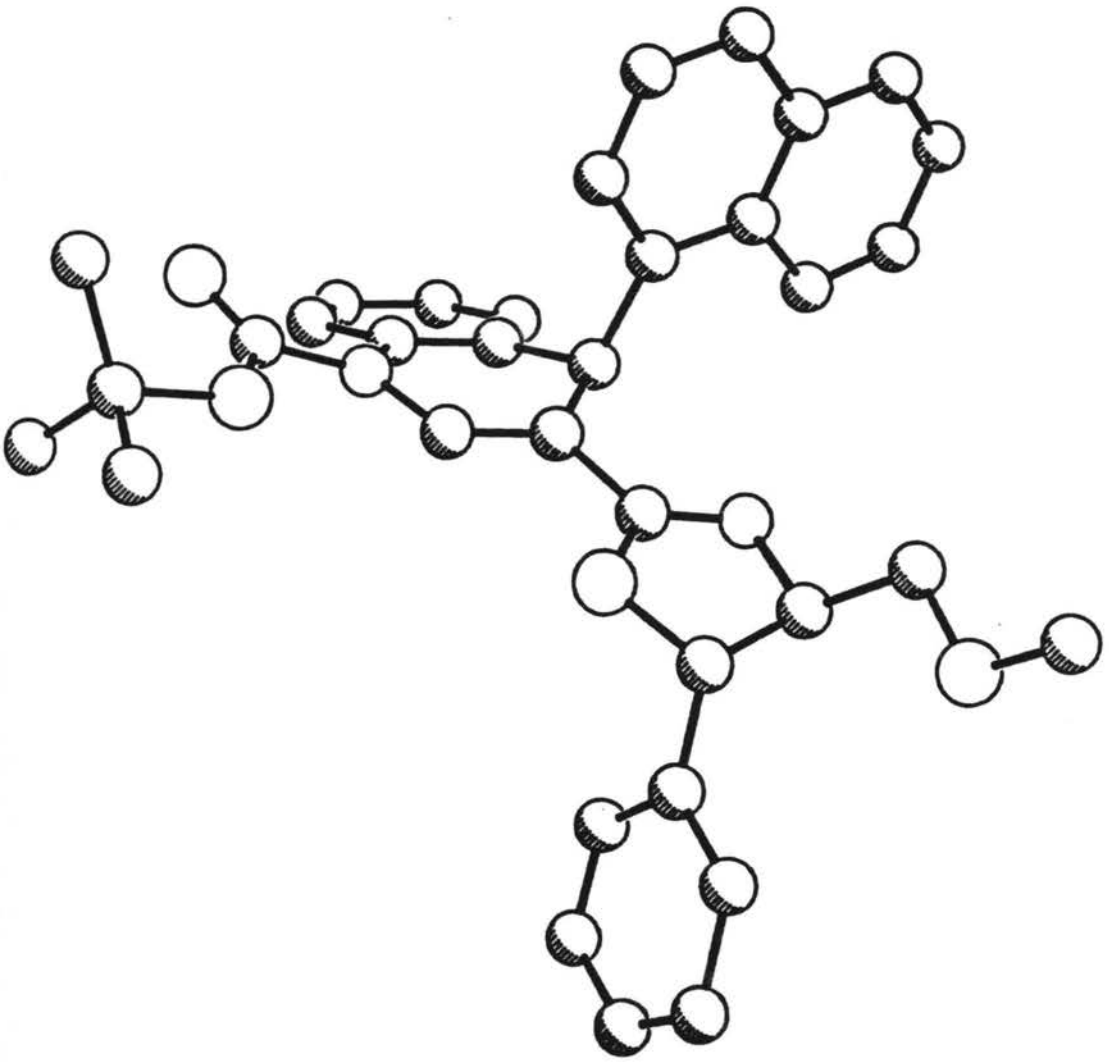


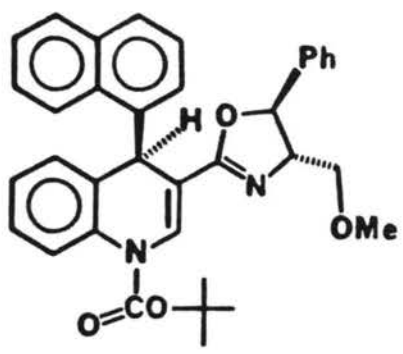
Fig. 4



(R) - 226 (R) - 224

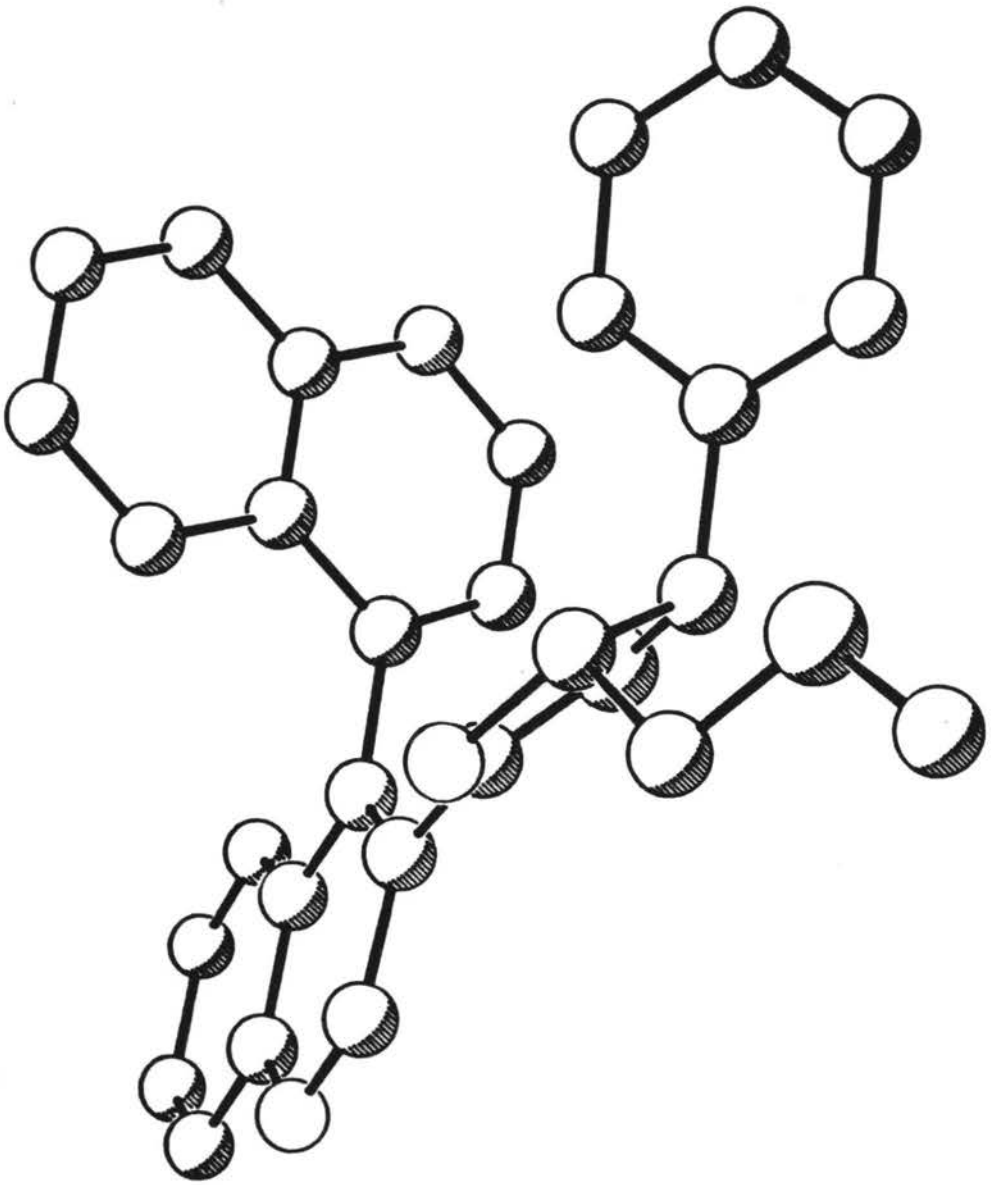
As alluded to earlier, key to the confirmation of the Berson proposal was the establishing of free rotation in the dihydroquinolines. The structures determined by X-ray were further evidence that such a process did occur. Dihydroquinoline (R)-226 showed the unsubstituted naphthalene ring situated synperiplaner[97] (sp-rotamer, shown as the N-H-dihydroquinoline sp-222) to the hydrogen at C-4, thus able to minimize steric interactions with the dihydroquinoline nucleus. That the absolute configuration of the naphthylquinoline (R)-224 was (R), implied rotation of the naphthyl

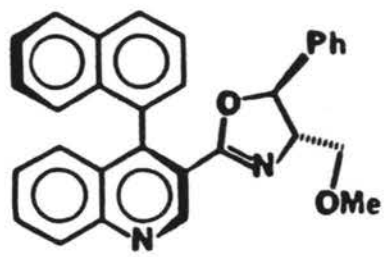




(R) - **226**

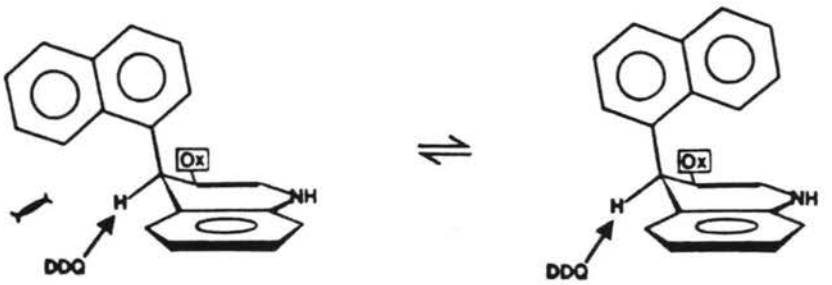
Fig. 5



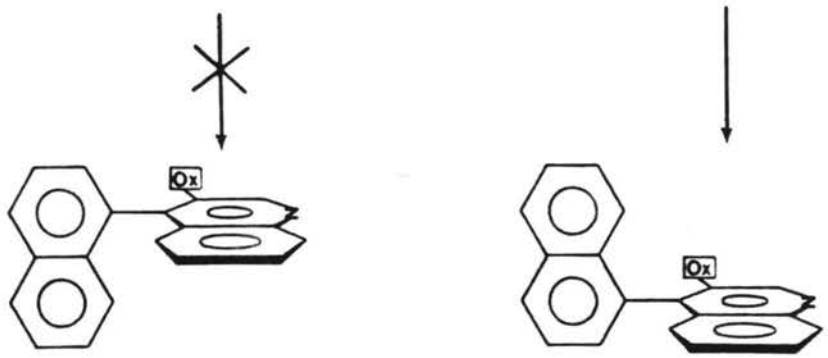


(R) - 224

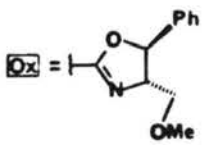
Fig. 6



(4R) - sp - 222 ⇌ (4R) - ap - 222

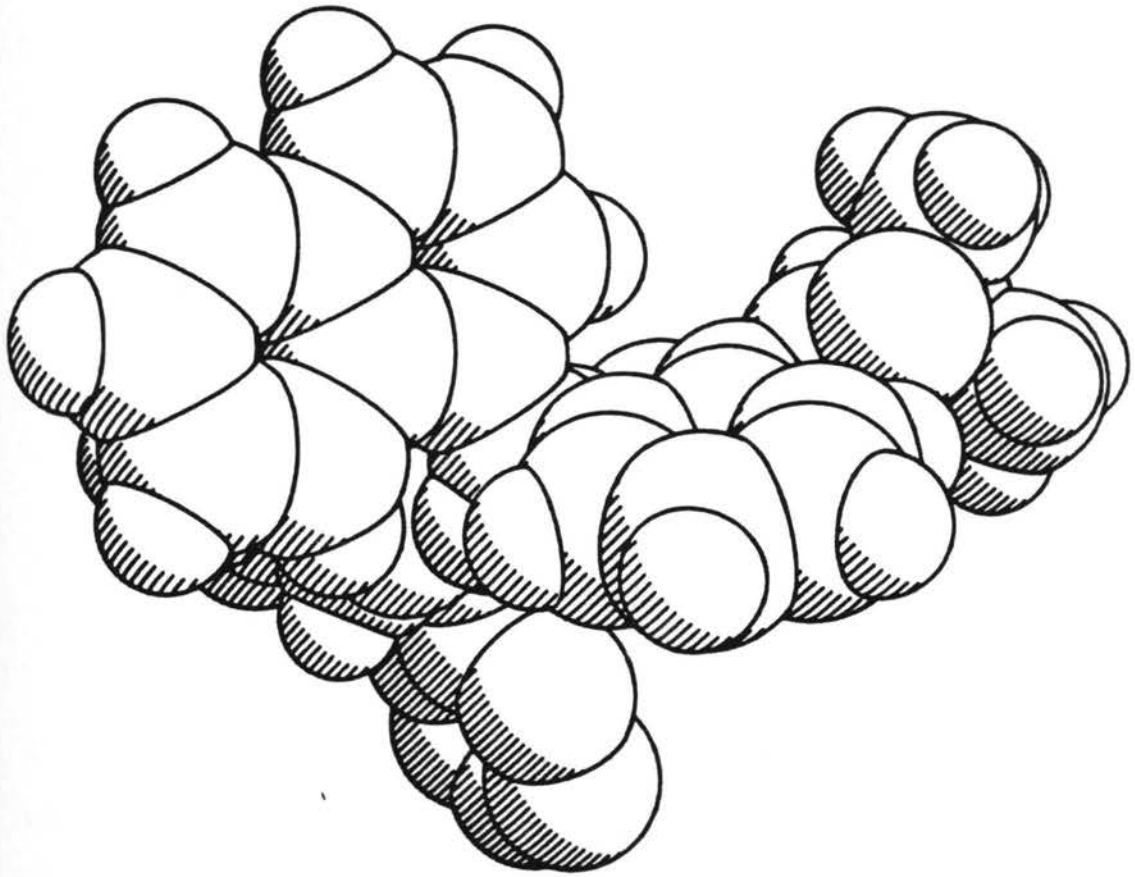


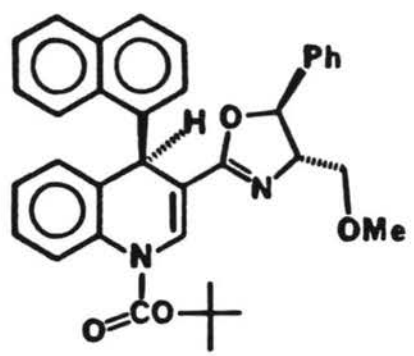
(S) - 215 (R) - 224



group to the anti periplaner rotamer ap-222 before oxidation. (Likewise, Dreiding models and a space filling drawing (Figure 7) favored free rotation, while space filling models showed hindered rotation).

Literature precedence supported the facile interchange between sp-222 and ap-222. Free rotation had been observed in 9-arylxanthyl[98] and 9-arylthioxanthyl[99] systems, exhibiting rotational barriers of 9.4 to 12.8 kcal mol^{-1}. Higher values (17.6 kcal mol^{-1}) had also been reported,[100] however, at these free rotation at room temperature was not possible. In addition, 9-arylfluorenes[101] had been studied and



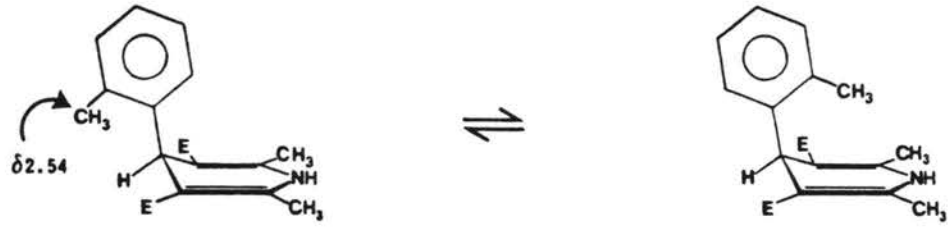


(R) - 226

Fig. 7

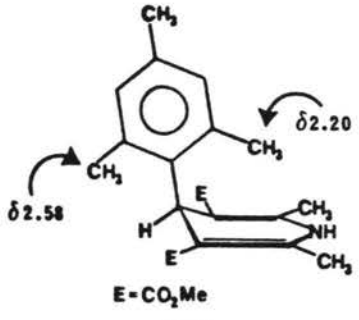
were generally characterized by higher barriers of rotation (16-35 kcal mol^{-1}).

Recent interest in the use of 4-aryl-1,4-dihydropyridines as calcium antagonists[102] prompted an investigation by a German group to establish which rotamer, sp-227 or ap-227, was favored.[103] The rotational barrier of the 4-mesityl analog (more closely related to 1,4-dihydroquinolines) was also determined.



sp - 227 ⇌ ap - 227

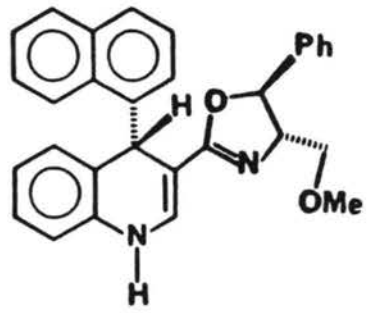
Analysis by ^1H NMR of 227 found the chemical shift of the 2'-methyl group (δ 2.54) to be independent of temperature. That sp-227 was the more favored rotamer was established by comparison of the chemical shifts exhibited by 4-mesityl-1,4-dihydropyridine 228. The ^1H spectrum displayed a broad singlet for the two ortho methyl groups at



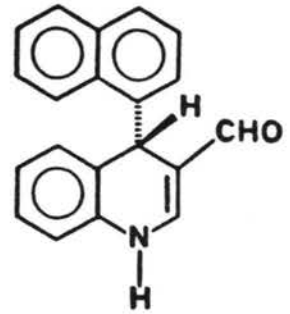
228

room temperature (δ 2.39). Upon cooling, coalescence was reached at -18°, with two separate peaks observed at -50° (the rotational barrier was calculated to be 12.2 kcal mol^{-1}). The chemical shifts were δ 2.58 and δ 2.20 for the synperiplaner (deshielded) methyl group and the antiperiplaner methyl groups respectively. The former agreed well with δ 2.54 from 227. By this comparison, it was concluded that the thermodynamically more favored rotamer was sp-227. Additional evidence from an NOE experiment on 227, and the knowledge that the sp-form was adopted preferentially on similar (2'-nitro and 2',4'-dinitro)-1,4-dihydropyridines in the crystalline state,[104] further supported the preference of sp-227.

Logically, the next step was to determine if free rotation was occurring in the dihydroquinoline system and if so, determine the rotational barrier. The approach was to observe the particular sample by ^1H NMR while cooling to various temperatures. The first two compounds investigated were oxazolinyldihydroquinoline 213 and aldehydo dihydroquinoline 219. The oxazoline spectra showed line shape



213



219

changes and possible freezing out of rotational isomers. Conclusive results however, could not be made due to the complexity of the spectra. The aldehyde spectra were much simpler, with line shape

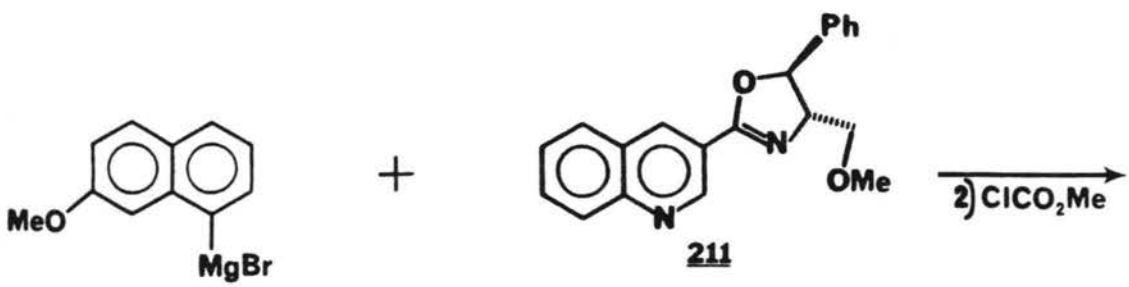
changes also occurring upon cooling. Here again, no rotamers were conclusively frozen out. Two features of the spectra did however, become important in the following experiment. The C-4 chemical shift varied from δ6.03 at room temperature to δ6.14 at -65°. The line shape changed upon cooling, becoming broader down to -45° (probably near the coalescence temperature) with slight sharpening at the low temperature limit. Similarly, the aldehyde proton chemical shift varied from δ 9.13 to δ9.15 upon cooling, with only slight broadening of the peak. This indicated that the aldehyde moiety failed to freeze out.

Successful rotation experiments were realized by the use of aldehyde 231, prepared by alkylation of oxazolinylquinoline 211 with 7-methoxynaphthylmagnesium bromide (Scheme 11). The resulting oxazoline 229 was cleaved, via quaternization to the corresponding aldehyde 230. Hydrolysis of the urethane gave the requisite aldehyde 231.

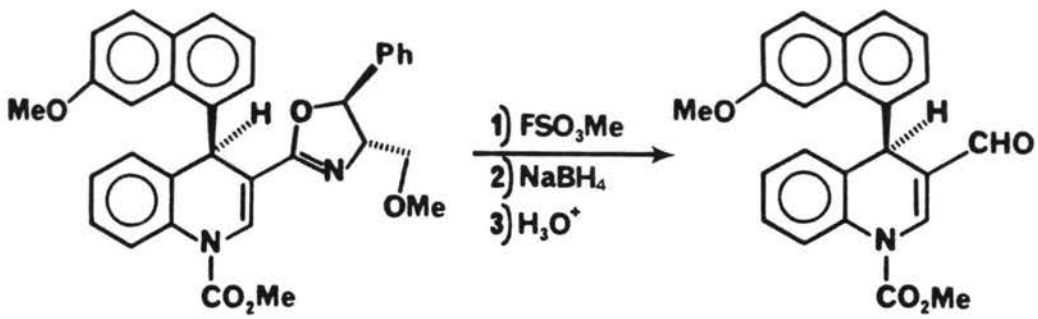
Spectra were taken at room temperautre and at 5 to 10° increments down to -70° at 100 MHz and 200 MHz. Another spectrum was taken upon warming to ambient temperature, to insure total reversibility, and upon final warming to $+40^{\circ}$.

The spectrum at room temperature contained sharp singlets for the aldehyde, C-4 proton, and the methoxy group at δ9.11, 5.93, and 3.93 respectively. Upon cooling, line broadening occurred with the C-4 proton and the methoxyl group signals eventually splitting into two singlets in approximately a 2:1 ratio (below the coalescence temperature, T_c, which was -43° at 200 MHz and -54° at 100 MHz). The aldehyde signal broadened, but failed to freeze out into two fully recognizable signals, similar to aldehyde 219 (vide supra). Thus, the observed changes in the spectra were not a result of restricted

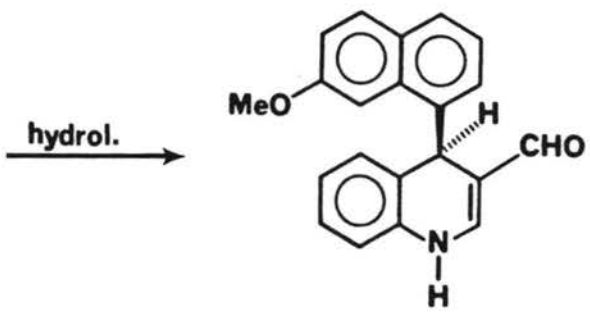
Scheme 11



211



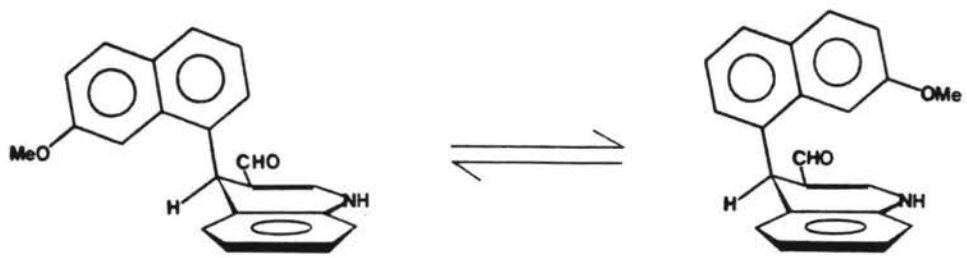
229 230



231

aldehyde rotation. Since the C-4 proton peaks were cleaner and better resolved than those of the methoxy group, they were used for measurements. Spectra taken at +25° and -63° are shown in Figures 8 and 9 respectively.

The chemical shifts, at the low temperature limit, of the two singlets resulting from the C-4 proton occurred at δ 6.03 (0.68H) and δ 5.69 (0.32H). The former chemical shift was very similar to the C-4 proton chemical shift over the temperature range of +25° to -65° (δ 6.03 to δ 6.14) of aldehyde 219 (p. 92). Following the rationale



sp-231 ap-231

of Goldman and Geiger, for the thermodynamically more favored sp-rotamer of dihydropyridine 227 (p. 90) in preference to the ap-rotamer, sp-231 would appear to be the more stable rotamer for the dihydroquinoline system. The NMR data supports this notion (with the similarity of chemical shift for the major rotamer and the chemical shift over the temperature range for aldehyde 219), as does the X-ray structure for dihydroquinoline (R)-226 (p. 86), which is also the sp-rotamer.

Several methods were used to calculate the rotational barrier: 1) as a function of the coalescence temperature (T_c),[105] 2) by the Eyring equation using rate constants derived from the computer simulation[106]

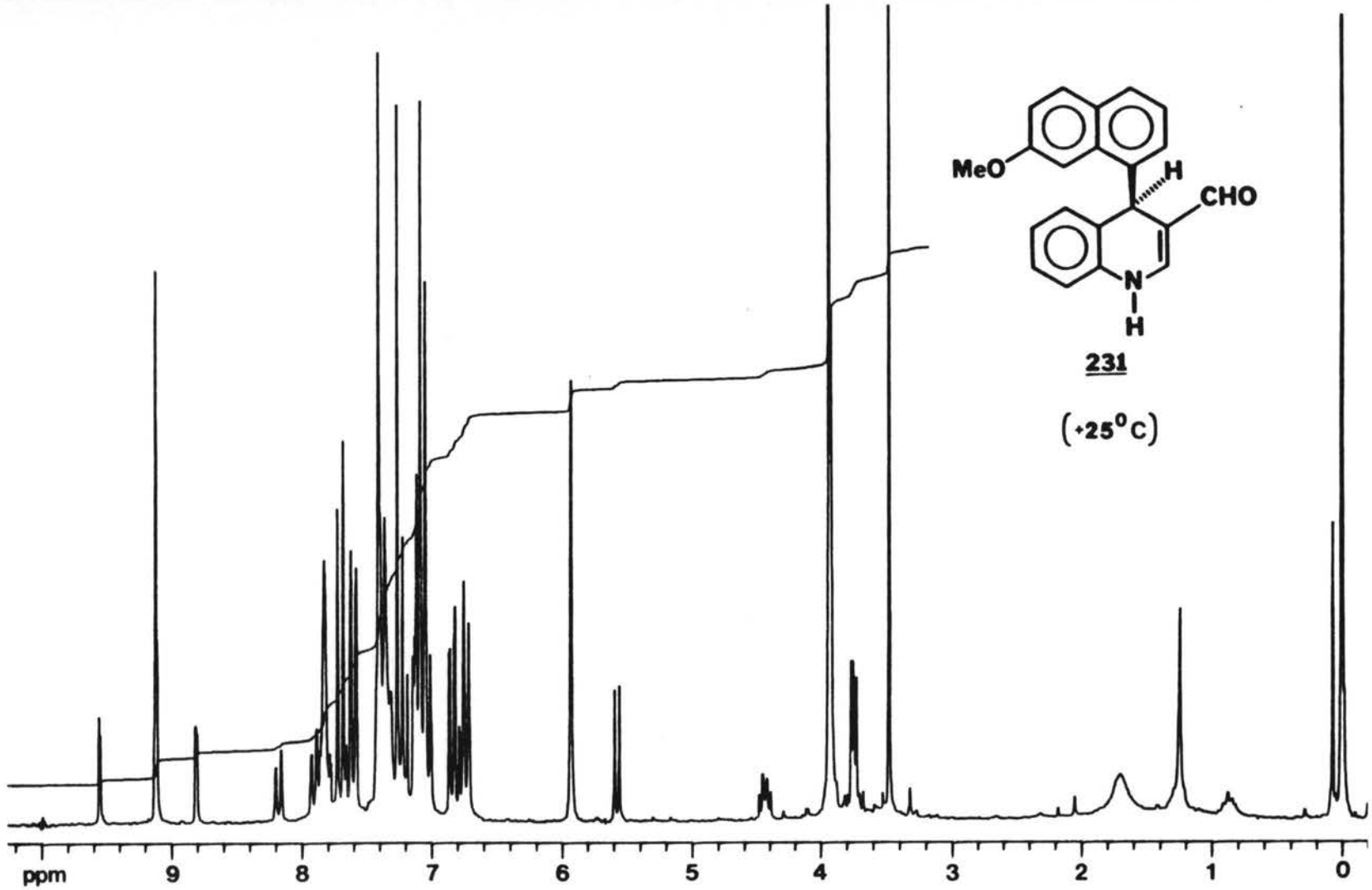


Fig. 8

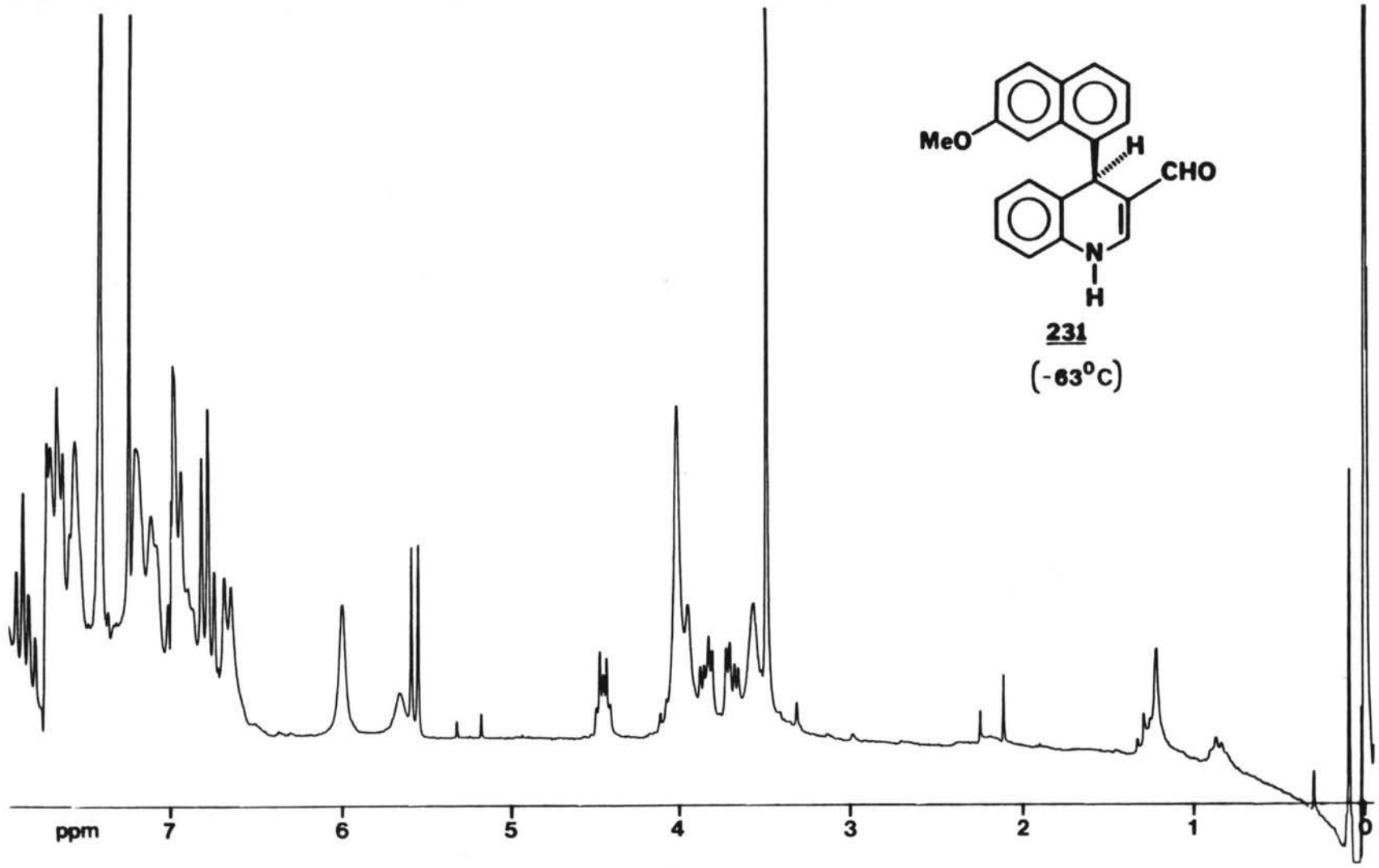


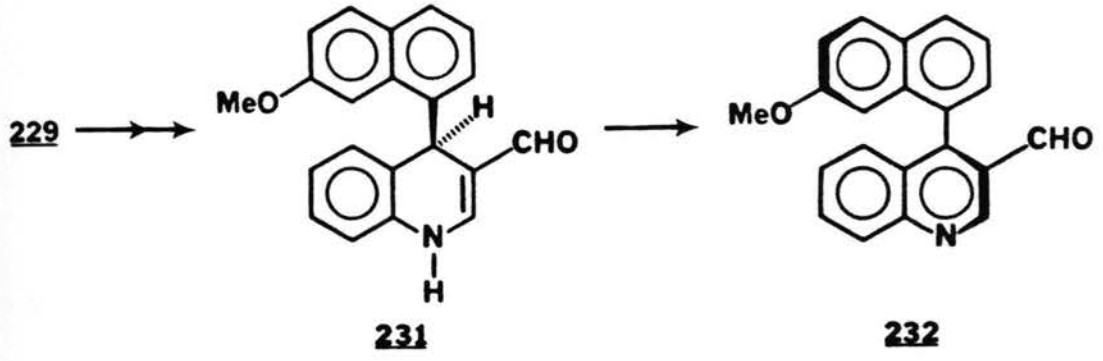
Fig. 9

of spectra (as shown in Figure 10), 3) by the Gibbs free energy of activation equation, also using the simulated spectra for rates.

The Eyring plot (Figure 11) was used to extract data for the calculation of the rotation barrier. The calculated values are shown in Table 11.

The values obtained for the rotational barrier vary over the range of 10.8 to 11.5 kcal mol^{-1}. The average, 11.2 kcal, was also calculated by the Eyring equation, with a standard deviation of 0.7 kcal and correlates well with other systems investigated in the literature. The variation of the activation energies was the result of inaccuracies in the determination of any one (or combination) of several experimental parameters. These included the chemical shifts, relative populations, and the coalescence temperature, all of which inherently have some error in their measurement.

Having already synthesized 7'-methoxynaphthyldihydroquinoline 229 (25:75 ratio), another check of the Berson proposal was straightforward. The absolute configuration of the dihydro compounds (229-231) was assigned by analogy to those prepared by 1-naphthyl-



231 232

magnesium bromide addition. Following oxazoline removal and urethane hydrolysis, aldehyde 231 was oxidized with DDQ. The absolute

Observed (200 MHz)

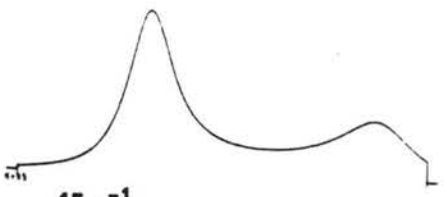
T= -48° C

-58°

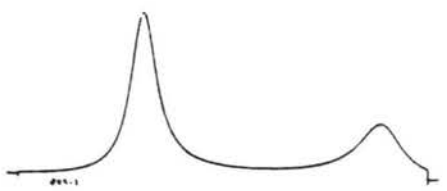
-63°

Computer Simulated

k = 125 s^{-1}



45 s^{-1}



24 s^{-1}

T_c(200 MHz) = -43°

T_c(100 MHz) = -54°

Fig. 10

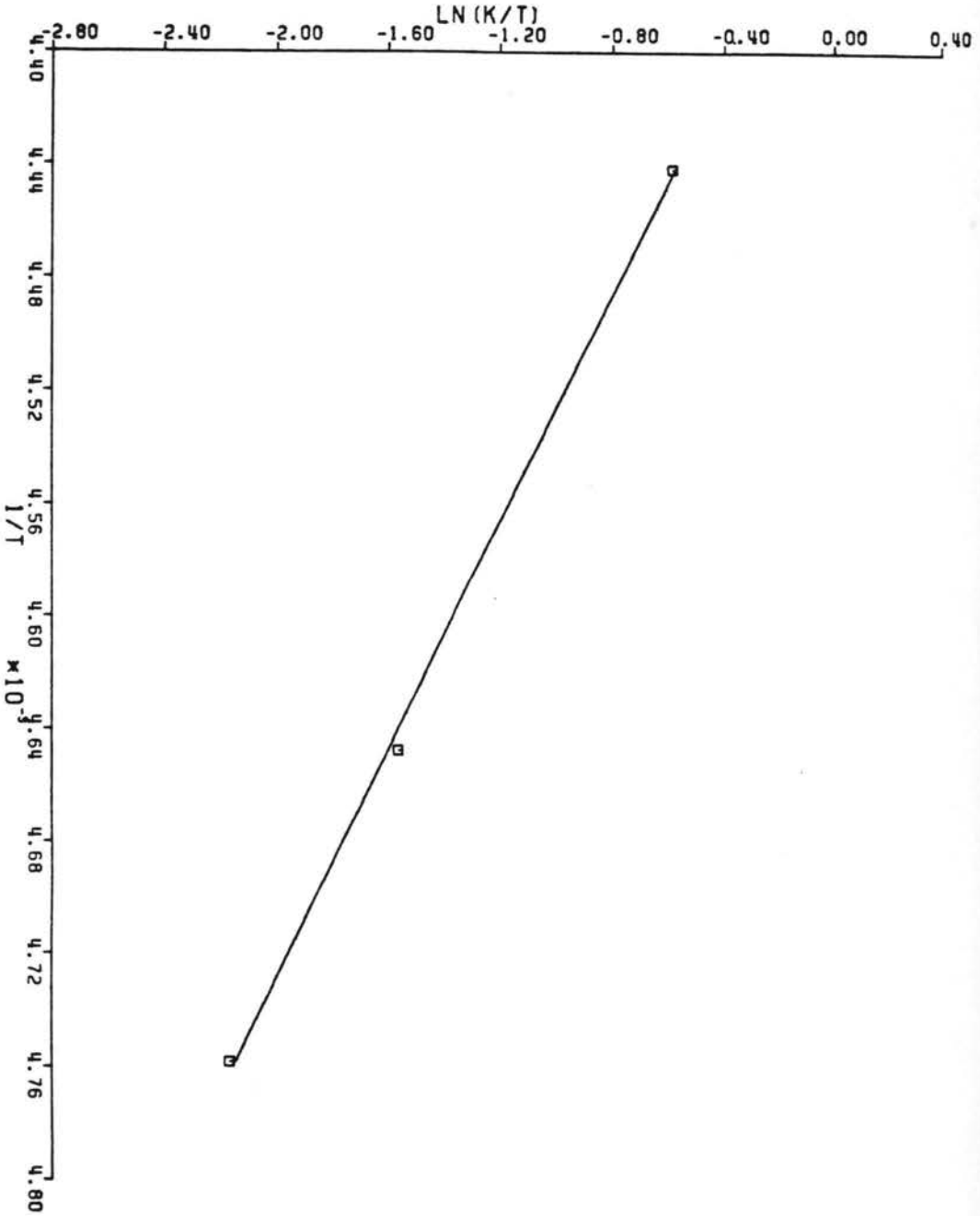
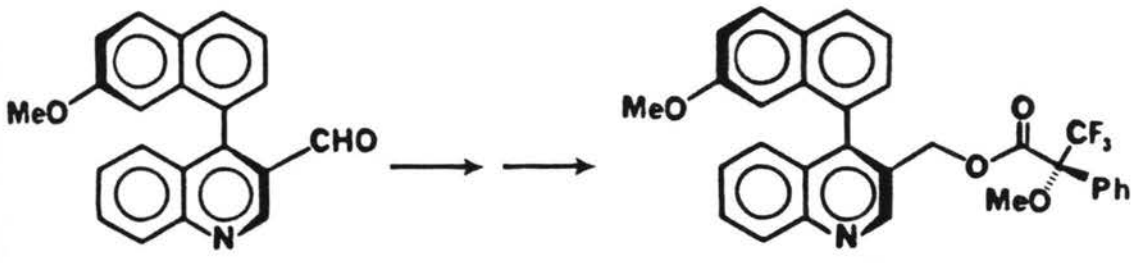


Fig.11

TABLE 11

Method of Calculation	$\Delta G^{\dagger}$ (kcal mol^{-1})
Coalescence Temperature (100 MHz)	$\Delta G^{\dagger}_{219} = 11.2$
Coalescence Temperature (200 MHz)	$\Delta G^{\dagger}_{230} = 11.5$
Eyring equation	$\Delta G^{\dagger}_{298} = 11.2 \pm 0.2$
Gibbs free energy of activation equation	$\Delta G^{\dagger} = 10.8$

configuration of the resulting biaryl 232 was verified by comparison of its circular dichroism (CD) curve with that of aldehyde 220, from the addition of 1-naphthyllithium (Figure 12). The enantiomeric excess of 232 was determined by reduction of the aldehyde and preparation of the Mosher ester 233. Analysis by ^{1}H and ^{19}F NMR indicated ratios of 73:27 and 75:25 respectively. Here again, the Berson proposal was verified with virtually complete conservation of chirality, and no external stereochemical centers.

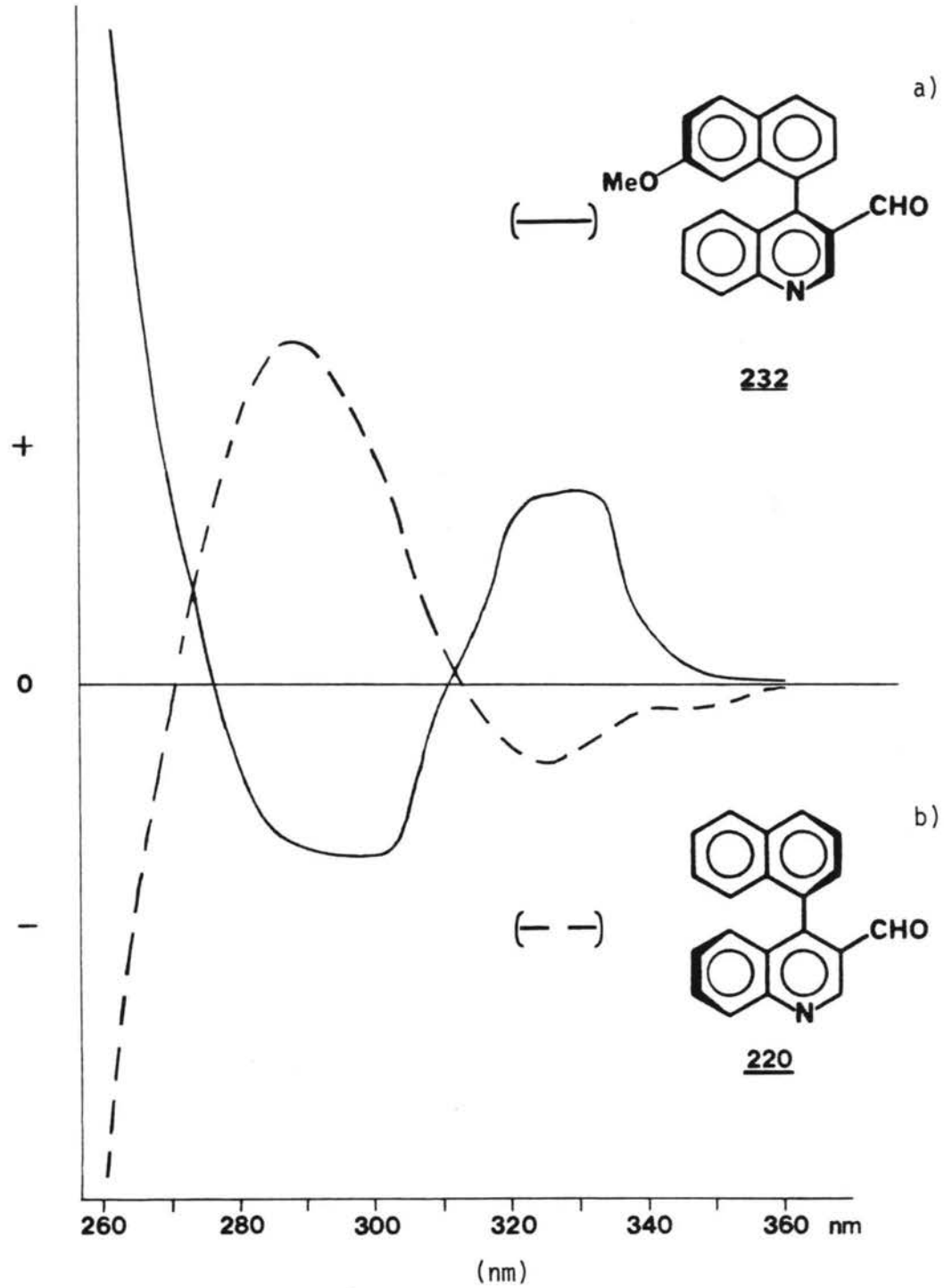


232 233

4. Mechanism of Addition; Li^{+} vs $Mg^{+}Br$

The unusual stereoselectivity of 1-naphthylmagnesium bromide (the absolute configuration of the newly formed center was (R)) in comparison with 1-naphthyllithium which gave the (S)-configuration was unprecedented for conjugate additions to oxazoline compounds. Mechanistic information accounting for these marked differences in reactivity was desirable from the standpoint of proposing pre-addition complexes.

The generally accepted idea for this variation in reactivity, rested on the premise that the Grignard reagent existed in a more highly aggregated state during the reaction. Alternatively, 1-naphthyllithium was regarded as a monomeric unit during reaction (based



a) Prepared by addition of 7-methoxynaphthylmagnesium bromide.

b) Prepared by addition of 1-naphthyllithium (known absolute configuration).

Fig.12

on the absolute configuration of the products, and previous oxazoline compound alkylations.[62,81]

Detailed studies regarding the aggregate structure of 1-naphthylmagnesium bromide and 1-naphthyllithium are lacking in the literature. However, an estimate may be made by comparison with the corresponding phenyl compounds. Phenylmagnesium bromide was found to be monomeric in THF over a wide range of concentrations, and monomeric to aggregated (1 to 3.5 PhMgBr per aggregate) in ether; the degree of which was a function of concentration.[107] Phenyllithium was determined to be dimeric in THF, with a small degree of dissociation to the monomeric form.[108] Thus, adapting the aggregating state for the Grignard reagent, and a dimeric 1-naphthyllithium in equilibrium with the monomeric form (thought to be the reactive species) one would expect greatly differing oxazoline complexes prior to addition.

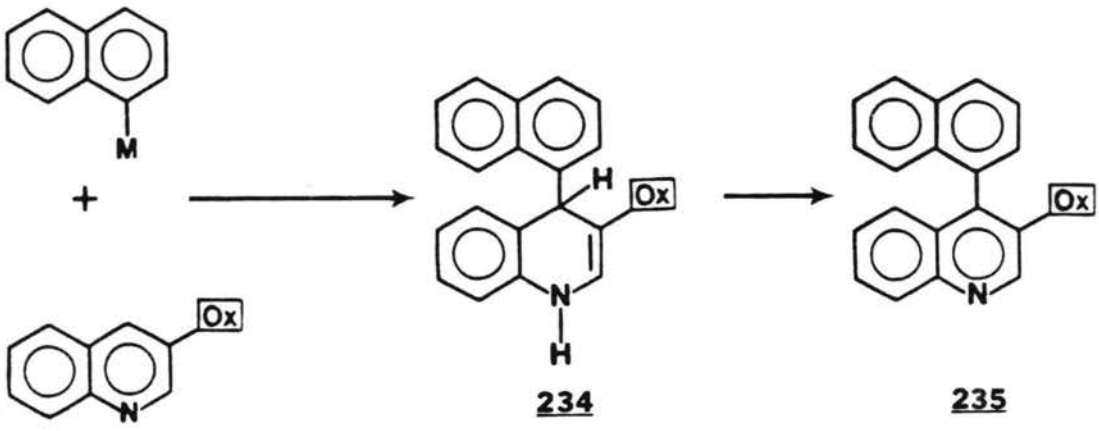
A series of experiments were performed which investigated various complexing agents and solvents. Possible effects of the Schlenk equilibrium have been neglected, since a rigorous investigation of this sort was beyond the scope of this study. From the results, conclusions will be drawn regarding possible pre-addition complex structures.

The alkylations were carried out under the conditions shown, forming N-H dihydroquinoline 234. Since the oxidation process had already been found to occur with near quantitative conservation of chirality, biaryl 235 was used to ascertain the diastereomeric excess. The resulting ratio would presumably be a direct result of the addition of monomeric vs aggregated organometallic reagent. The results are shown in Table 12.

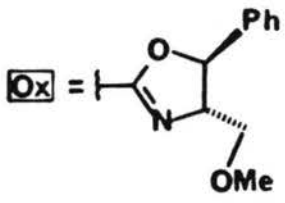
TABLE 12[a]

Expr. #	Solvent	Complexing Agent	Ratio[b] for 235 (S,S,S):(R,S,S)	% Yield
1	toluene[c]		8:92	91
2	toluene[d]		8:92	95
3	toluene[c,e]		25.5:74.5	93
4	ether[c]		25:75	91
5	THF[c]		61:39	93:5
6	DME[c]		88.5:11.5	93
7	toluene[d]	1 eq TMEDA[f]	45:55	92
8	toluene[d]	4 eq TMEDA[g]	75:25	70[h]
9	toluene[c]	NEt_3[i]	17:83	92
10	DME[c]	NEt_3[i]	84:16	82[j]

a) See the experimental section for reaction conditions (p. 165). b) Determine by HPLC. c) Inverse Addition: The Grignard reagent was added to the oxazolinylquinoline. d) Normal Addition: The oxazolinylquinoline was added to the Grignard reagent. e) The reaction temperature was +24°. f) TMEDA (N,N,N',N'-tetramethylethylenediamine), 1 eq relative to the Grignard reagent. g) 4 eq TMEDA relative to the Grignard reagent. h) Reacted for 3 days at room temperature, also isolated 7% starting material for a total mass recovery of 77%. i) 1-Naphthylmagnesium bromide-triethylamine complex, stock solution prepared in toluene. j) Isolated 8% starting material for a total mass recovery of 90%.



M = MgBr
= MgBr·NEt$_3$

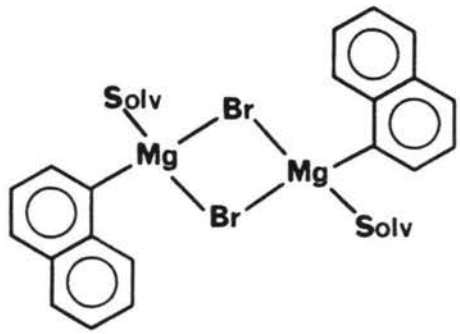


All of the reactions were characterized by good to excellent yields. The basis of comparison for the reactions (experiments 1 and 2) indicated there was no difference between normal and inverse addition, both giving identical ratios of 8:92. A moderate temperature dependence was also observed (experiment 3) with the reaction performed at +24°, lowering the stereoselectivity to 25.5:74.5.

Support for the hypothesis of an aggregated Grignard reagent was gathered on changing from toluene (non-coordinating) to donor solvents. With increasing coordination ability, ether < THF < DME, the stereoselectivity decreased and was completely reversed with ratios of 25:75, 61:39, and 88.5:11.5 respectively. This significant solvent effect was also observed using 1-naphthylmagnesium bromide-triethylamine complex (experiments 9 and 10), in which the highly

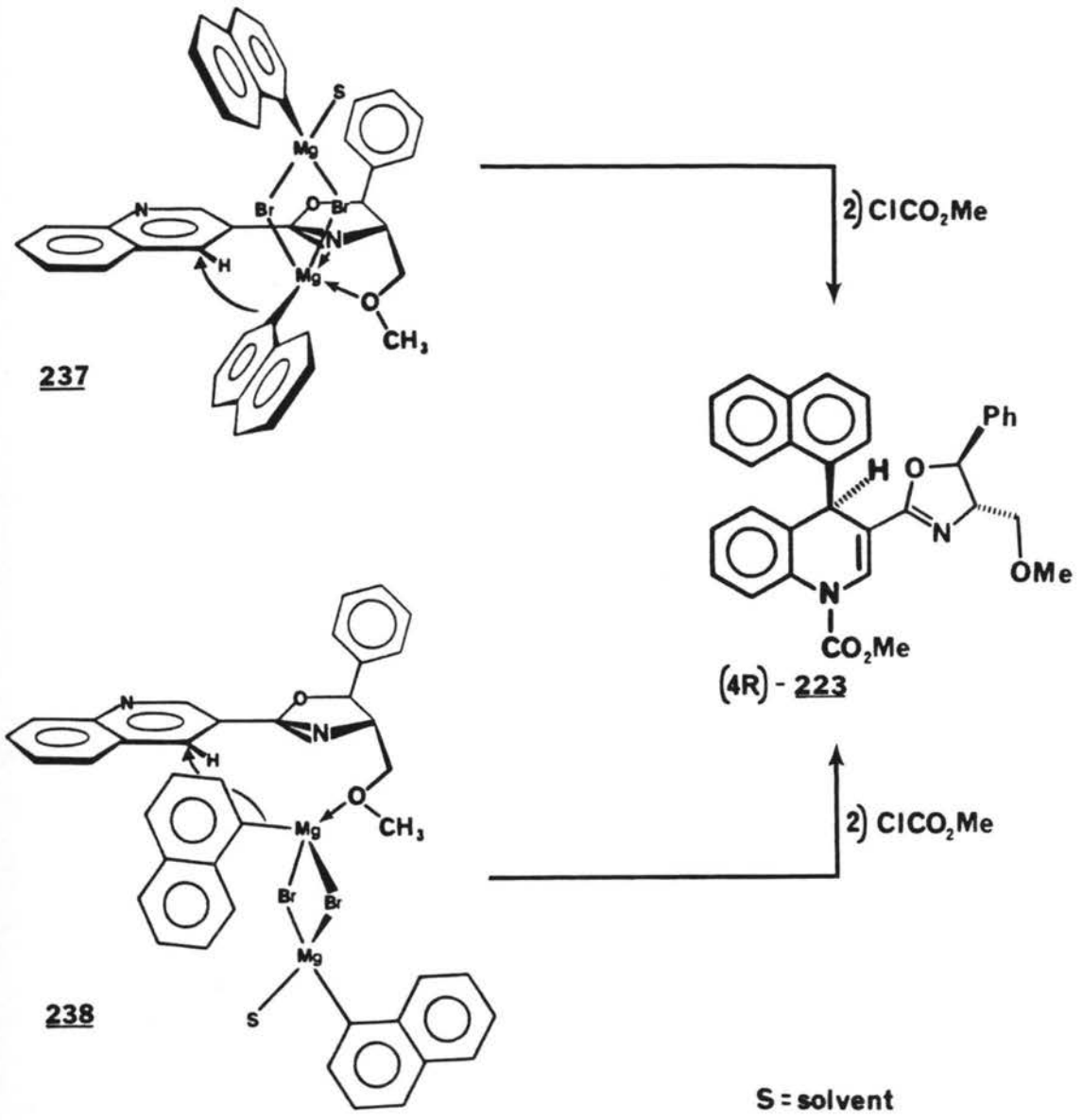
coordinating DME also reversed the stereoselectivity. Additional evidence for the aggregated Grignard reagent arose from the addition of TMEDA (experients 7 and 8), in which the stereoselectivity was similarly decreased and completely reversed (with a large excess of TMEDA), paralleling the DME results. That 1 equivalent of TMEDA resulted in a near racemic mixture suggests competing reaction pathways, ie., complexed monomeric vs. aggregated reagent. (Methylmagnesium bromide, precomplexed to TMEDA, gave the reversed stereoselectivity compared to uncomplexed reagent in the addition to 2-benzoyloxazoline).[109]

These results are best summarized and explained by analysis of the "extreme reactions" - toluene vs DME (or 4 equivalent TMEDA). In the non-coordinating environment of toluene, the Grignard reagent may be envisioned as existing, and reacting, as an aggregate 236 (shown here as a dimer). The observed stereochemistry may be rationalized in terms



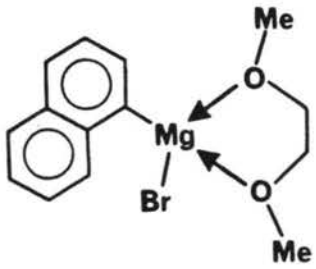
236

of two possible pre-addition complexes 237 and 238. In precomplex 237, the upper naphthyl group was assumed to be out of proximity for addition to the quinoline ring, leaving the lower group for addition. This resulted in the observed stereochemistry shown in 223. Alternatively, the lower naphthyl group of 238 was too distant for addition, allowing the upper group to undergo reaction, also leading to

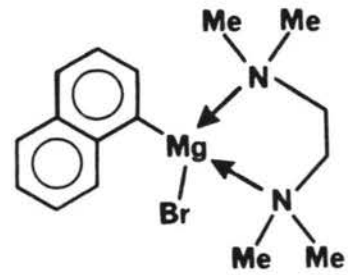


223. It must be noted that, the oxazoline is potentially a bidentate ligand, analogous to DME or TMEDA. Based on the formation of 223, this does not appear to be the case.

The alkylations carried out in DME or with TMEDA present, may be envisioned as proceeding through the monomeric-complexed Grignard reagent as shown in 239 and 240. (Similar complexes have been observed



239



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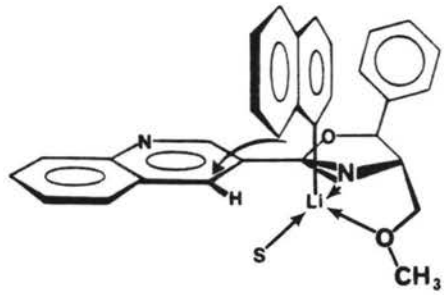
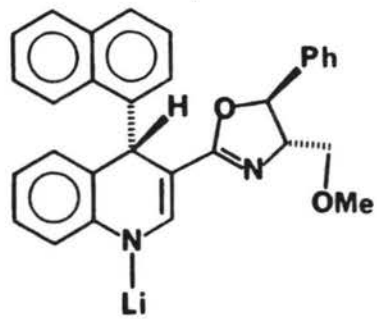


241

$ClCO_2Me$



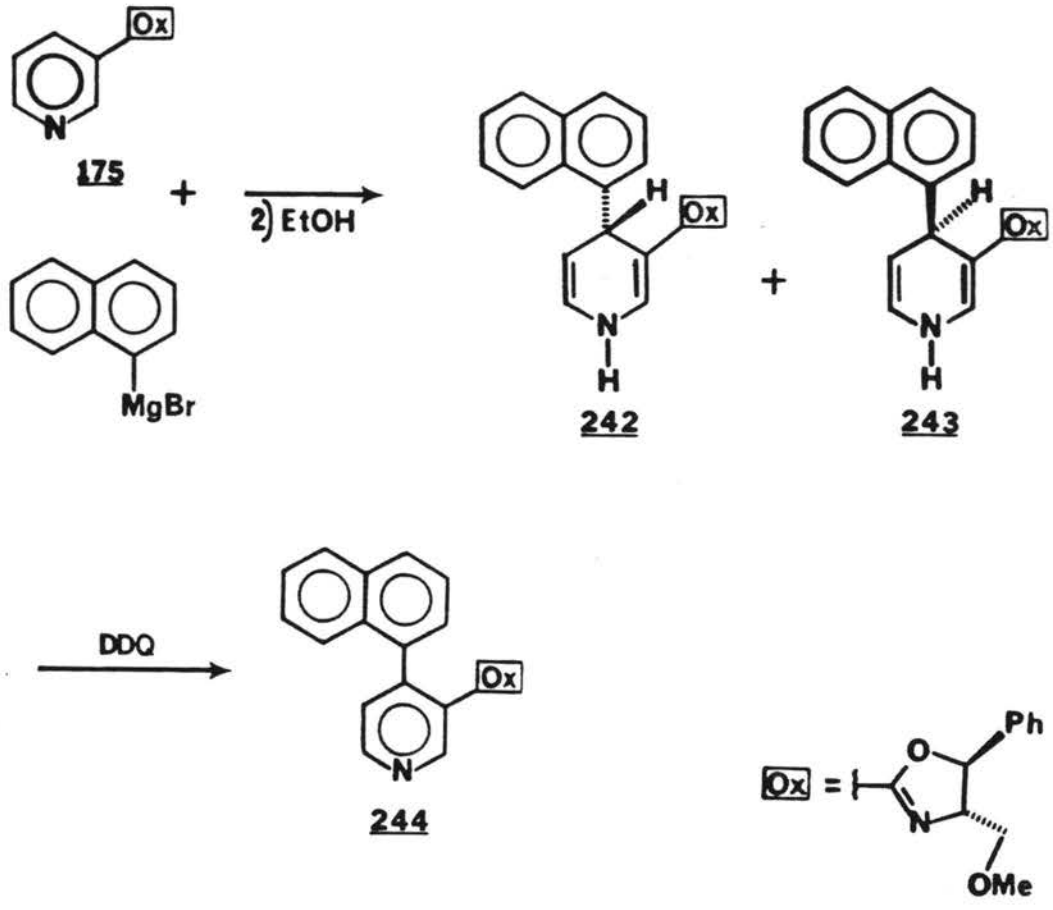
(4S) - 214

S = solvent
E^+ = electrophile

for TMEDA and DME with dimethyl magnesium and diphenyl magnesium,[110] as well as formation of a 1:1 complex with N,N,N',N'-tetraethylethylenediamine with p-fluorophenylmagnesium bromide).[111] The naphthyllithium addition also occurred with the same observed stereochemistry. Thus, it may be assumed that all three of these reactions proceeded via the same type of precomplex, ie., the "more universal" oxazoline intermediate 241 (shown for the addition of 1-naphthyllithium) leading to 214. For these alkylations, the oxazoline competed favorably with the DME and TMEDA in complexing ability, allowing for 241 to form. Here again, as with the addition to oxazolinylpyridine 181 (p. 53), topside addition is favored due to the coplanar arrangement of the π-system and the lithium-naphthyl bond.

Besides gaining information regarding the mechanism of this unique stereoselectivity, the methodology now allowed for the stereoselective synthesis of either diastereomer of biaryl 235 from the same starting materials, by varying only the solvent. Either diastereomer of the dihydroquinolines 234, the precursor to the biaryl, could potentially be isolated with proper choice of electrophile.

These solvent effects were also extended to the alkylation of oxazolinylpyridine 175. Alkylation in benzene resulted in the formation of 242 and 243 in a diastereomeric ratio of 20:80 respectively by ^{1}H NMR. Reversed stereoselectivity was observed for the alkylation in DME with a ratio of 90:10. The absolute configurations were assigned based on previous alkylations. The dihydropyridines were oxidized to the biaryl 244 but, due to free rotation in 244, no enantiomers could be isolated.

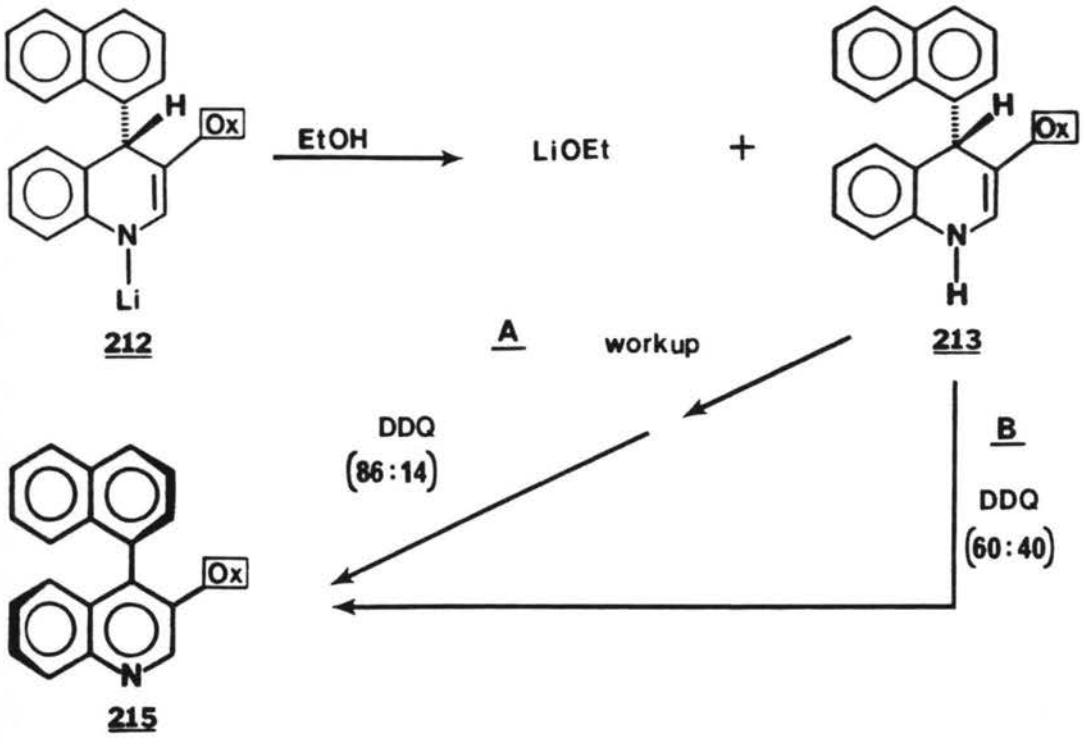


5. Anionic Oxidations

In an effort to shorten the synthetic scheme for the transfer of stereocenters from sp^3 to axial, an attempt was made at direct oxidation of 213 without prior isolation. The two procedures are sumzarized in Scheme 12.

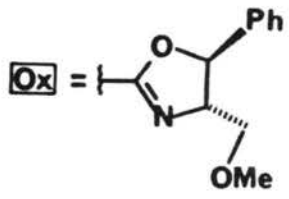
Thus, quenching with ethanol, followed by immediate cooling to -78° and addition of DDQ, gave the biaryls 235 in a 60:40 ratio (procedure B) (considerably different from the 86:14 ratio obtained from the normal procedure A). The lack of chirality in the product was attributed to the presence of lithium ethoxide, a byproduct from the ethanol quench. On the assumption that ethoxide was altering the final product ratio, a study was initiated in which the oxidation was done on

Scheme 12



A = Normal Route, $T_0 = -78^0C$

B = Shortened Route, $T_0 = -78^0C$



the lithio dihydroquinoline 212 under several conditions. The results are shown in Table 13.

The basis of comparison for the anionic oxidation was established by several experiments (1, 2, 3, and 5), where it was shown there was essentially no temperature dependence (-78° to $+40^{\circ}$) and no solvent effect (THF or toluene). A series of oxidations done in THF under anionic conditions (experiment 4) resulted in an essentially constant ratio over a 100° temperature range. It should be pointed out however, the stereoeselectivity had been reversed, with the (R,S,S) diastereomer predominanting. Similarly, this trend continued for a series of anionic oxidations in benzene and toluene. The ratios increased, with decreasing temperature (experiments 6, 7, and 8) resulting in the (R,S,S) diastereomer formed in 26% de (88% yield) at the low temperature limit.

The highly stereospecific nature of the oxidations by DDQ was seen in the temperature independence exhibited. Having already established free rotation around the naphthyl-C-4 bond, and the observed stereochemistry of the diastereomers subjected to X-ray analysis (vide supra), the observed stereochemistry was rationalized (alluded to earlier) as shown in Scheme 13. The N-H dihydroquinoline may be envisioned as existing in two rotamers, sp-213 and ap-213. Upon approach of the DDQ, sp-213 was less favored due to steric interaction with the incoming DDQ, which overrode the repulsion between the naphthyl group and the π-system of the dihydroquinoline. The more favorable ap-213 was subsequently oxidized to biaryl 215 with the observed stereochemistry.

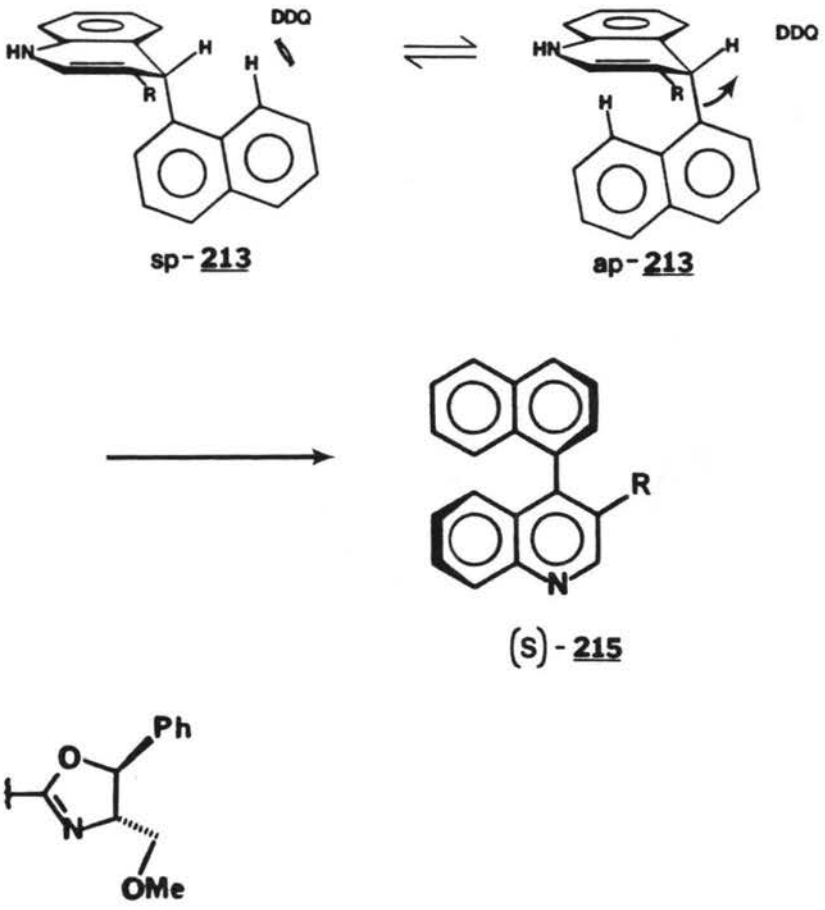
TABLE 13[a]

235

Expt. #	Solvent	Base[b]	Temperature (°C)	Ratio[c] (235) (S,S,S):(R,S,S)
1	THF		-78	84:16
2	THF		+25	87.5:12.5
3	THF		+40	87.5:12.5
4	THF	LDA	0, -78, -100	43.5:57.5± 3[d]
5	toluene		-78	85:15
6	benzene	LDA	+5	46:54
7	toluene	LDA	-78	41:59
8	toluene	LDA	-100	37:65[e]

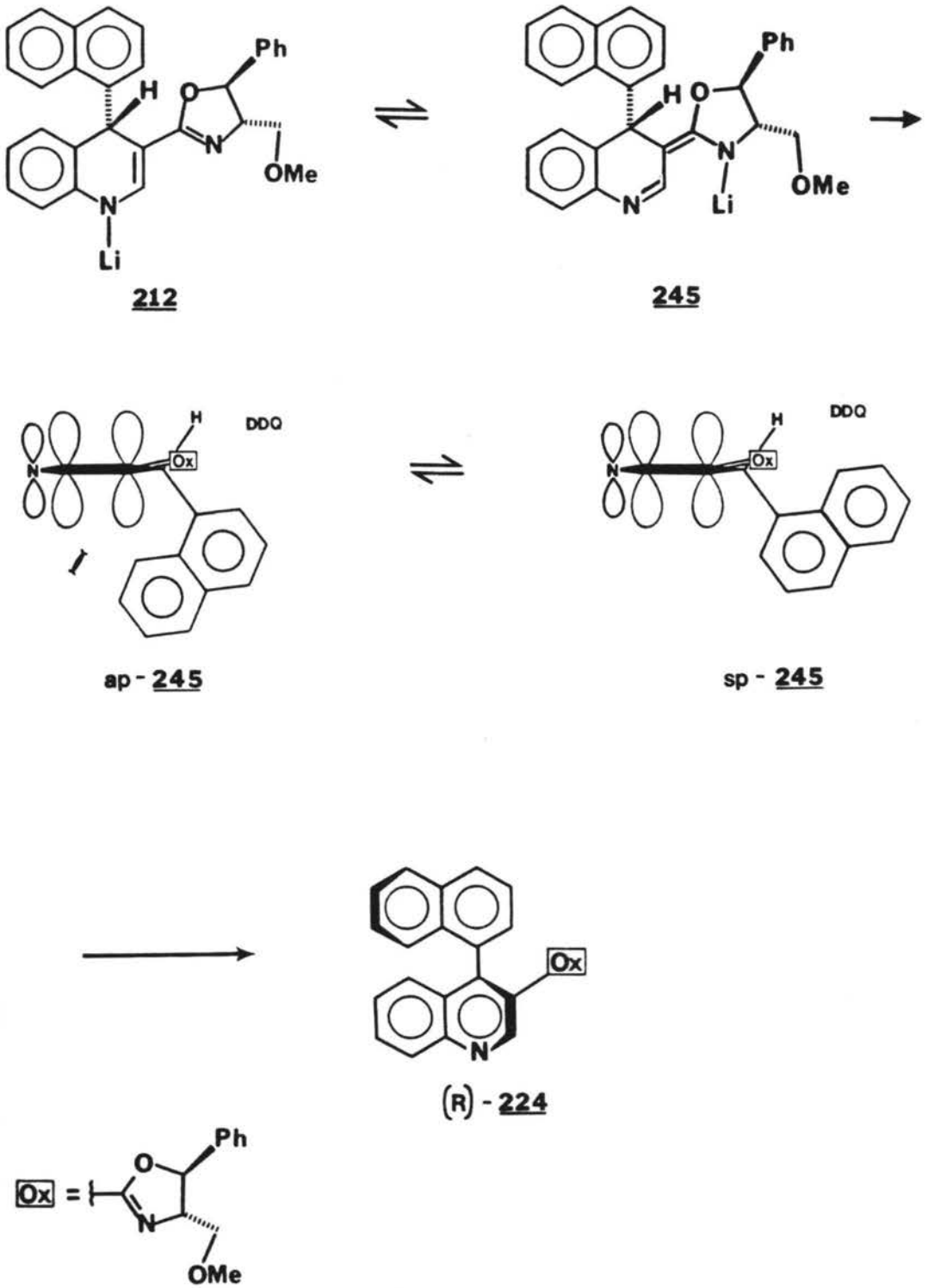
a) The oxidations were done at the indicated temperature with 1.1 eq DDQ and allowed to warm to room temperature. The products were then isolated. b) Excess base (1.2-2.0 eq) was used, the dihydroquinoline was deprotonated at the reaction temperature for 15 min, followed by addition of DDQ. The remainder of the procedure was as in (a). c) Determined by HPLC. d) The range of temperatures gave random ratios as indicated. e) The biaryls were produced in 88% yield. Other yields were not determined since it had already been well established, in previous experiments, the oxidation occurred in high yield.

Scheme 13



Deprotonation with LDA resulted in formation of 212 (Scheme 14), which could have existed in equilibrium with 245. Oxidation of the former would have been expected to exhibit similar stereospecificity as the N-H dihydroquinoline ap-213. Alternatively, due to delocalization of the anion (in 245), the conformation of the dihydroquinoline would have been more planar as shown in ap-245 and sp-245. Here again, subtle differences in the steric interactions dictated the outcome of the oxidation. In contrast to the oxidation of ap-213, the undesirable interactions depicted in ap-245 were alleviated by rotation to rotamer

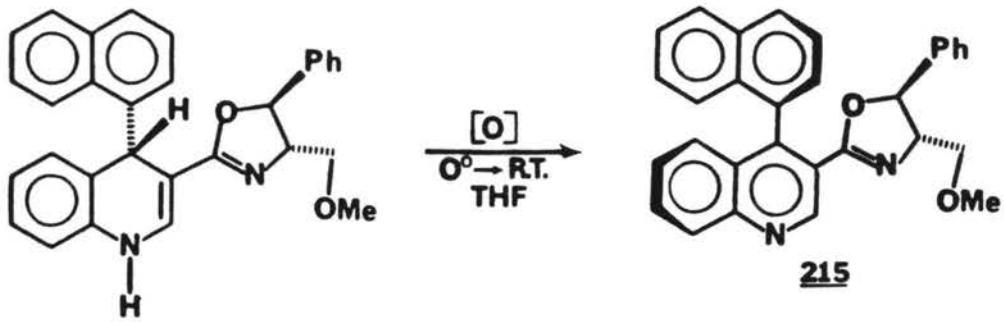
Scheme 14



sp-245, which was subsequently oxidized to (R)-224. Since complete conservation of chirality did not occur, this implies oxidation of both 212 and 245 occurred in an almost random fashion.

A short investigation probing the stereospecificity of other oxidizing agents with various bulk was also undertaken as shown in Scheme 15. In contrast to the DDQ reactions, PDC (pyridinium

Scheme 15

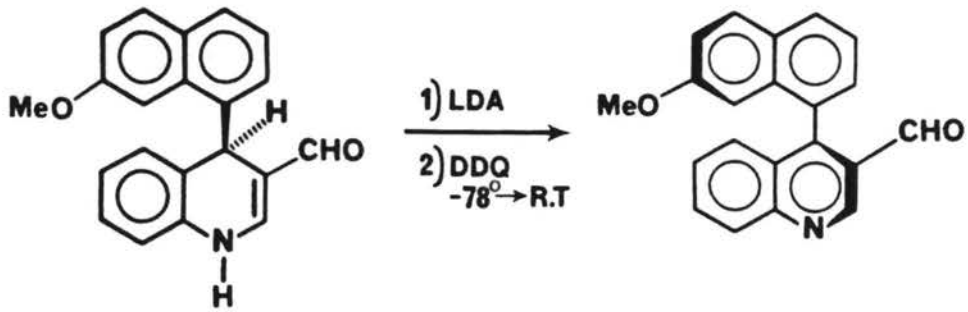


215

Exp. ※	oxidizing agent	Ratio (HPLC) (S,S,S) : (R,S,S)
1	DDQ	84:16
2	PDC	74:26
3	aq. $KMnO_4$	65:35

dichromate) and aqueous $KMnO_4$ reactions did not occur with complete conservation of chirality. A possible explanation is the size of the reagents, and hence less steric interaction with the dihydroquinoline during the oxidation process. Other oxidants were also investigated including I_2, MnO_2, O_2, and DMSO/TMEDA (Swern), but failed to react. It may be concluded that the initial choice of DDQ as the oxidizing agent was the correct one.

The oxidation experiments described thus far have examined oxazolinyldihydroquinolines. The study was further extended to the anoinic oxidation of aldehydo dihydroquinoline 231, which formed biaryl 220 ($[\alpha]_D$ +23). The enantiomeric excess was determined by reduction of the aldehyde followed by preparation of the Mosher ester 233 (as on p. 101). Analysis by ^1H NMR indicated a ratio of 59:41, with only moderate preservation of chirality from the starting ratio of 75:25.

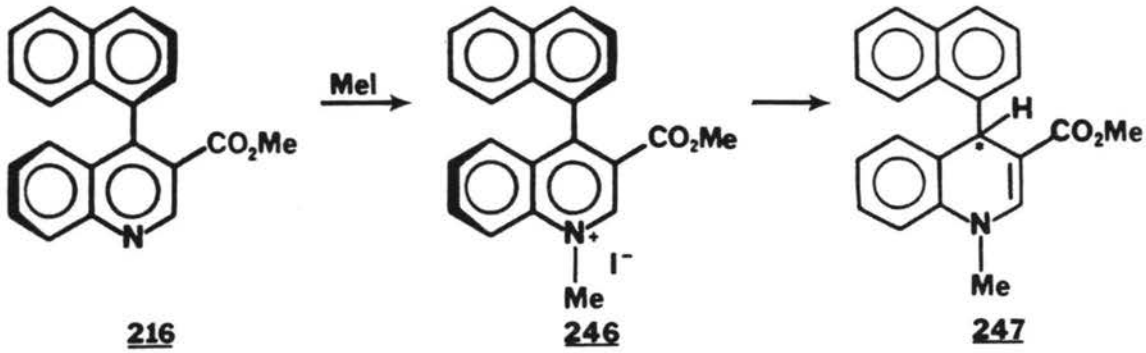


231 220

Here again, the deprotonated dihyroquinoline was sensitive to various steric interactions similar to that of lithio dihydroquinoline 212, but to a lesser degree.

6. Conservation of Chirality, $sp^2 \rightarrow sp^3$

As indicated at the outset of the Results and Discussion section, self-immolative processes have been observed for the conversion of an axial chiral element to a central chiral element, with conservation of chirality. Various attempts to reduce methiodide 246, prepared by quaternization of 216 with methyl iodide, using several



216 246 247

hydride reagents failed to give substantial amounts of 1,4-dihydroquinoline 247. Most reactions were characterized by complex mixtures or mainly the isomeric 1,2-dihydroquinoline, with only trace amounts of 247 rarely seen by ^{1}H NMR. These results were attributed to the inaccesibility of the C-4 position due to steric bulk.

The most logical step was to use the smallest reducing agent possible, an electron. Several attempts were made usingdissolving metal reductions, but were quickly abandoned due to complex mixtures of products. Apparently, 246 was prone to several electron transfer processes, and hence the reduction potential had to be well tuned.

Electrochemistry, capable of exact potentials and bulk electrolysis, was investigated. Cyclic voltammetry determined the reduction potentials for the two electron process (Figure 13). The potentials observed were -0.7 and -1.9V vs SCE, for the first and second electrons respectively. These values compared well with the potentials for the reduction of quinoline methiodide (-0.86 and -1.98V dihydroquinoline 247 in 23% yield. The product however, was found to be optically inactive.

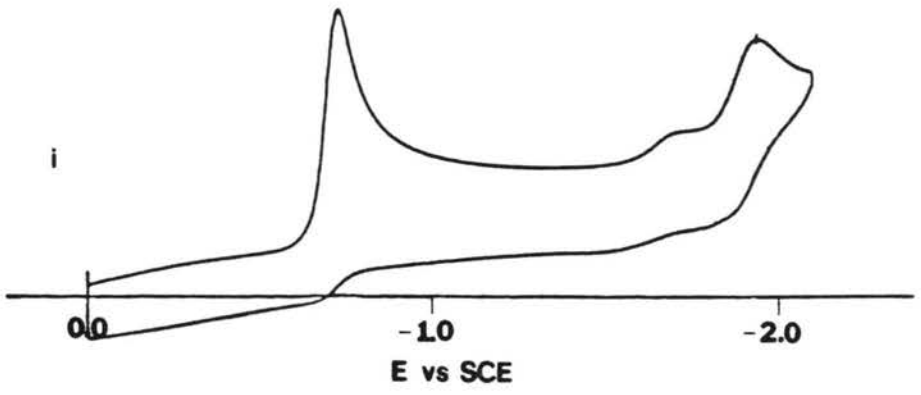


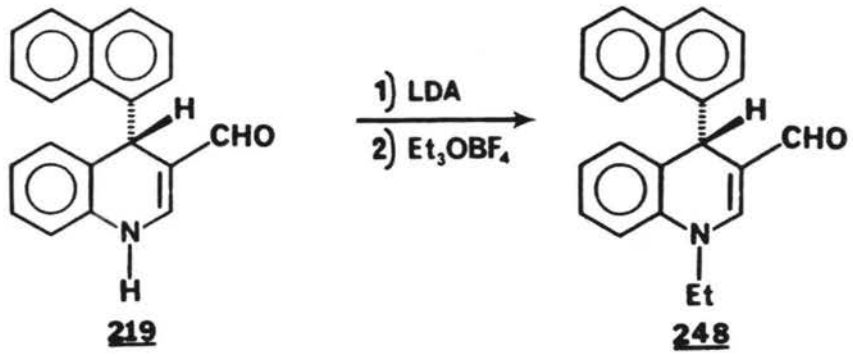
Fig.13

At the extremes, larger hydride sources failed to give the desired product while the electron, from the electrolysis, failed to give any stereochemical bias to the reduction process.

7. A Possible Extension of This Chemistry

Dihydroquinoline compounds have been used as NADH mimics for the reduction of carbonyl compounds,[113] just as the dihydropyridines (vide supra). A possible extension of the methodology described on the previous pages is the use of a 4-naphthyldihydroquinoline as an NADH mimic. Of principle importance is the synthesis of an N-alkyl derivative, which is sufficiently electron rich to transfer the hydride.

N-Ethyl-1,4-dihyroquinoline 248 was prepared by deprotonation of 219 with LDA and quenching with triethyloxonium tetrafluoroborate, to give 248 in 59% yield. The Meerwein salt was necessary for alkylation due to the "hardness" of the anion. (Attempts at alkylating the corresponding oxazolinyldihydroquinoline failed with methyl iodide.



219 248

Similar results were observed for the alkylation of magnesio dihydropyridines, [114] which also required the Meerwein salt). The product is reasonably stable and can be handled in the open atmosphere for short periods of time.

Preliminary attempts to reduce a carbonyl substrate netted inconclusive results (possible detection of a product by GC, but could not be verified). However, based on these results, and the observation that 248 was instantly oxidized by DDQ at -78° (not characteristic of the N-H precursor 219), given time and more experiments, a successful reduction could possibly be realized.

CHAPTER III

EXPERIMENTAL

A. General Information

1. Physical Data

All melting points were determined on a Buchi or Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 4240 or Beckman Acculab 3 spectrophotometer, and are reported in wave numbers (cm^{-1}). Ultraviolet (UV) spectra were recorded on a Varian Techtron Model 635 or Cary 118CX with the wavelength (λ) in nm and the molar extinction coefficient (ε) of the absorption maxima are reported in the form λ_{max} (ε_{max}). Optical rotations were measured on a Perkin-Elmer 241 or a Rudolph Research Autopol III polarimeter at wavelength 589 nm (sodium D line) using a 1.0 decimeter cell with a volumn of 1 ml. Specific rotations, $[\alpha]_D$, are reported in degrees per decimeter at the specified temperature and the concentration (c) given in grams per 100 ml in the specified solvent. Circular dichroism curves were obtained on a JASCO J-41C spectropolarimeter.

All proton magnetic resonance (^{1}H-NMR) spectra were measured at 100 MHz on a JEOL JNM FX100 instrument, unless otherwise indicated. Other spectrometers used for proton spectra included: Varian T60 (60 MHz), Varian EM360A (60 MHz), Bruker WP-200SV (200 MHz, 5 mm probe), and Bruker WP-270SY (270 MHz, 5 mm probe). Spectra were taken in the

solvents indicated for each sample and the chemical shifts are reported in δ; parts per million (ppm) downfield from the internal standard tetramethylsilane (TMS). Coupling constants are reported in Hertz (Hz) and the data are reported in the form: chemical shift (multiplicity, coupling constants, number of protons). Carbon-13 magnetic resonance (^{13}C-NMR) spectra were measured at 25 MHz on a JEOL JNM FX100 spectrometer, and all spectra were decoupled. Diastereomeric proton and carbon chemical shifts are underlined. Fluorine-19 magnetic resonance (^{19}F NMR) spectra were measured at 188 MHz on the Bruker WP-200SY (5 mm probe) spectrometer. Spectra were taken in $CDCl_3$ and the chemical shifts are reported in δ, in parts per million (ppm) upfield from the external standard ($CFCl_3$ in CH_2Cl_2, 0 ppm).

Mass spectra were obtained from a V.G. Micromass Ltd. 16F spectrometer. Elemental analysis was performed by MicAnal, Tucson, Arizona.

2. Removal of Solvents

Concentrated (or concentration) refers to solvent removal under the vacuum achieved by a water aspirator attached to a Buchi rotary-evaporator. Residual solvent was removed at reduced pressure (0.3-0.1 mm) using a vacuum pump.

3. Chromatography

Analytical thin layer chromatography (tlc) was performed on aluminum backed 0.2 mm silica gel plates containing 254 nm indicator (E. Merck). Spots were visualized under UV light, and/or by staining with Dragendorff's Reagent.[115] All preparative thin layer

chromatography (ptlc), unless otherwise noted, were done on 2 mm plates made from a pH 7 aqueous phosphate buffer slurry of EM Silica Gel 60 PF-254. The plates were dried at room temperature (R.T.) at least 5 days before use. Other ptlc separations were performed on glass backed 0.25 mm silica gel plates containing 254 nm indicator (E. Merck). Column chromatography, flash chromatography, and medium pressure liquid chromatography (MPLC)[116] were performed with silica Woelm, 32-63 silica gel. Flash chromatography (tlc silica gel) used silica gel 60H (E. Merck) in which the compounds were presorbed on the silica gel and eluted under pressure. Preparative HPLC was done with a Waters Prep 500 using commercially available silica gel columns (Waters, Prep Pak). Radial chromatography was done on 1-4 mm silica gel plates (EM Silica Gel 60 PF-254 containing gypsum) using a Harrison Research Chromatotrom 7924. Other column chromatography sorbents included florisil (Fisher, 60-100 mesh) and aluminum oxide (Baker, pH 6.4, powder).

Analytical HPLC was perfomred on a Waters instrument with an ultraviolet detector (λ = 254 nm) and a Hewlett Packard recorder (model 3390A). Two columns were used: normal phase refers to a Waters μ-porasil, 3.9 mm x 30 cm column; reverse phase refers to an Altex (Beckman) Ultrasphere, 5μ, 4.6 mm x 25 cm, C-18 bonded column.

4. Solvents and Reagents

In all cases (except extraction ether) reagent grade solvents were distilled prior to use. Reaction solvents and reagents were dried as follows.

For reactions requiring dry solvents, tetrahydrofuran (THF), ether, and benzene were distilled from sodium-benzophenone ketyl under

argon or nitrogen (recycling stills). Similarly, toluene, dimethoxyethane (DME) and xylenes were distilled from sodium-benzophenone ketyl and stored over 3Å sieves. Dry methylene chloride and 1,2-dichloroethane were distilled from P_2O_5 under argon and stored over 3A sieves. Diisopropylamine and N,N,N',N'-tetramethylethylenediamine (TMEDA) were distilled from calcium hydride and stored over 3Å sieves. Methyl chloroformate was purified by purging with argon (until HCl could not be detected) followed by distillation and storage over potassium carbonate or calcium hydride.

All organic intermediates were purchased from Aldrich Chemical Company, Milwaukee, Wisconson. The 1S,2S-(+)-1-phenyl-2-amino-1,3-propanediol was obtained from Warner Lambert, Pharmaceutical Research Division, Ann Arbor, Michigan. All organolithium reagents, Grignard reagents, and inorganic reagents were purchased from Alfa Ventron, Danvers, Massachusettes, unless otherwise noted. Titration of the organometallic reagents was periodically done using diphenylacetic acid or s-butanol and 1,10-phenanthroline.[117]

5. General Experimental Considerations

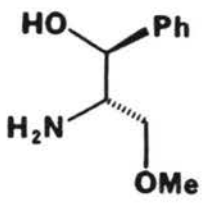
The argon used for the reactions was dried by passing through a concentrated sulfuric acid bubbler followed by a column of potassium hydroxide.

All glassware (for reactions requiring a dry set-up) was flame dried or oven dried (135°C). The warm flask was then fitted with a magnetic stirrer bar, septum, and argon inlet. The apparatus was allowed to cool while purging with argon.

The following low temperature baths were used: 0° (ice water), -15° to -20° (ice, methanol), -20° to -78° (aqueous ethanol, dry ice), -78° (acetone, dry ice), -110° to -115° (methanol, liquid nitrogen).

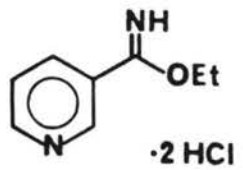
B. Synthesis of Chiral 1,4-Dihydropyridines via an Oxazoline

1. (+)-(1S-2S)-1-Phenyl-2-amino-3-methoxy-1-propanol 174



Prepared as described previously,[118] (79%). Mp 49-51°C (lit. 48.5-50°C); $[\alpha]_D$ +25.7° (c, 10.4, $CHCl_3$), lit. $[\alpha]_D$ +24.4 (c, 10.6, $CHCl_3$).

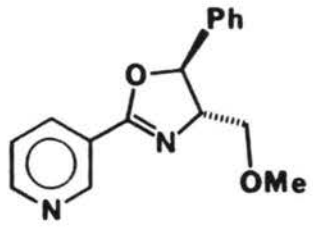
2. Ethyl-(3-pyridyl)-imidate Dihydrochloride 173



To an oven dried 1L 3-necked flask fitted with a magnetic stirrer bar, septum, reflux condensor, pressure equilizing addition funnel and argon inlet was added absolute EtOH (80 ml, 1.37 mol) and $CHCl_3$ (100 ml). Upon cooling to 0°, acetyl chloride (80 ml, 1.13 mmol, Fisher) was added dropwise, followed by addition, via cannula, of a solution consisting of 3-cyanopyridine (10.4 g, 100 mmol) and $CHCl_3$ (300 ml). The resulting solution was allowed to warm to room temperature overnight (25 hr), at which time dry ether (225 ml) was added and the mixture was placed in the freezer (-15°C) overnight (16 hr). The precipitated imidate was recovered by filtration through a sintered glass funnel and washed with dry ether. Residual HCl was removed under aspirator vacuum (1-2 days) to afford 20.5 g (92%) of a

finely divided white powder. Mp 230-232°C (lit.[119] 233°). IR(KBr) cm^{-1}: 3200-2400 (br), 1610 (br).

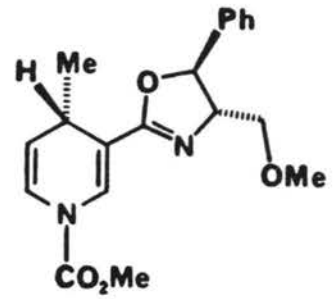
3. 2-(3'-Pyridyl)-4S-methoxymethyl-5S-phenyl-Δ^2-oxazoline 175



To an oven dried 500 ml round bottomed flask fitted with magnetic stirrer bar, reflux condensor, and argon inlet was added dry 1,2-dichloroethane (300 ml), and pyridyl-imidate 173 (10.5 g, 47 mmol). The resulting suspension was treated with dry triethylamine (6 ml, 43 mmol) and amino alcohol 174 (8.33 g, 46 mmol). The reaction mixture was heated to reflux (24 hr), cooled to room temperature, and poured into water (100 ml). Upon separation of the layers, the organic layer was washed with water (4 x 75 ml) and the aqueous layers were back extracted with $CHCl_3$ (3 x 75 ml). The combined organic layers were washed with brine (3 x 100 ml) and dried (K_2CO_3). Filtration and concentration gave the crude yellow-brown oxazoline, which upon Kugelrohr distillation under reduced pressure afforded 6.3 g (51%) of a light orange oil. Bp 147-149°C (0.013 mm Hg), $[\alpha]_D$ +42.9° (c 7.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 9.22(d, J=2Hz, 1H), 8.67(dd, J=5Hz, J=2Hz, 1H), 8.26(dt, J=8Hz, J=2Hz, 1H), 7.48-7.10(m, 1H), 7.34(s, 5H), 5.48(d, J=7Hz, 1H), 4.53-4.16(m, 1H), 3.83-3.25(m, 2H), 3.42(s, 3H); IR(film) cm^{-1}: 1665, 1593, 1570.

Anal.[120] Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01. Found: C, 71.35; H, 6.101.

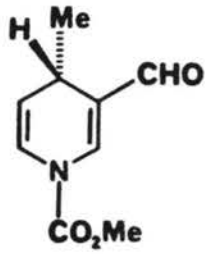
4. N-Carbomethoxy-4S-methyl-3-oxazolinyl-1,4-dihydropyridine 177 (R=Me)



To a solution of oxazolinylpyridine 175 (0.299 g, 1.12 mmol) and THF (70 ml) cooled to -78°C was added dropwise, methyllithium (1.4M, 2.4 ml, 2.36 mmol). Stirring was continued for 6.5 hr, at which time the bright yellow solution was placed in a 0°C bath for 2 min. The flask was recooled to -78°C and the reaction quenched with methyl chloroformate (0.52 ml, 6.72 mmol).

The reaction mixture was concentrated, slurried in CH_2Cl_2 (60 ml), and washed with dilute aqueous bicarbonate (3 x 50 ml) and brine. Drying (K_2CO_3), filtration, and concentration gave the crude dihydropyridine. Purification on radial chromatography (silica gel, 20% EtOAc/hex) afforded 0.231 g (62%) of the product. Analysis by HPLC (normal phase, 30% EtOAc/hex, 4 ml/min) indicated a diastereomeric ratio of 6:94. ^{1}H NMR ($CDCl_3$, 60 MHz): δ 7.73(br s, 1H), 7.38(s, 5H), 6.80(br d, J=8Hz, 1H), 5.35(d, J=6Hz, 1H), 5.10(dd, J=8Hz, J=5Hz, 1H), 4.45-3.97(m, 1H), 3.83(s, 3H), 3.60-3.30(m, 3H), 3.43(s, 3H), 1.25(d, J=7Hz, 3H), (diastereomeric proton signals were not detected in the spectrum); ^{13}C NMR (C_6D_6): δ 162.9, 151.3, 140.8, 128.4, 128.1, 127.7, 125.2, 120.6, 113.1, 110.4, 82.6, 74.6, 74.2, 59.1, 53.6, 27.8, 23.6; IR(film) cm^{-1}: 1720, 1672, 1622, 1430, 1330; MS[120] (70 ev) m/e: 342, 327, 311, 295, 283.

5. N-Carboxymethyl-3-formyl-4S-methyl-1,4-dihydropyridine 185



Dihydropyridine 177 (R=Me) (0.103 g, 0.30 mmol) was quaternized with methyl fluorosulfonate (0.049 ml, 0.06 mmol, 12 hr) according to the procedure described for the synthesis of 218 (p. 149).

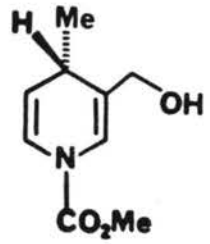
Similarly, reduction with $NaBH_4$ was done according to the procedure. Hydrolysis of the resulting oxazolidine to the aldehyde was performed using a mixture of CH_2Cl_2 (20 ml) and 10% aqueous oxalic acid (10 ml) for 12 hr with rapid stirring. The mixture was diluted with ether (30 ml) and the layers were separated. The organic layer was washed with dil. NH_4Cl/H_2O (3 x 40 ml) and brine. Drying (K_2CO_3) followed by filtration and concentration yielded the aldehyde.

Purification via radial chromatography (silica gel, 10% THF/hex) afforded 0.041 g (76%) of the desired aldehyde as a yellow oil. $[\alpha]_D^{23.5}$ +83.6° (c 0.51, $CHCl_3$). Analysis by tlc (50% THF/hex) indicated the yellow color was contamination. Repurification by ptlc (50% ether/pentane) separated the yellow color and gave the near colorless aldehyde (0.027 g, 60% overall yield from the oxazoline). $[\alpha]_D$ +143.9° (c 0.62, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 9.35(s, 1H), 7.60(br s, 1H), 6.74(br d, J=8Hz, 1H), 5.14(dd, J=8Hz, J=4Hz, 1H), 3.91(s, 3H), 3.50-3.08(m, 1H), 1.16(d, J=7Hz, 3H); ^1H NMR (C_6D_6): δ 9.04(s, 1H), 7.16(br s, 1H), 6.49(br s, 1H), 4.62(dd, J=8Hz, J=4Hz, 1H), 3.38-3.08(m, 1H), 3.32(s, 3H), 1.11(d, J=7Hz, 3H); ^{13}C NMR (C_6D_6): δ 189.8,

150.9, 140.1, 124.8, 120.9, 114.6, 53.7, 26.2, 23.0; IR(film) cm^{-1}: 1743, 1677, 1618, 1348, 1318.

Anal. Calcd, for $C_9H_{11}NO_3$: C, 59.66; H, 6.12. Found: C, 60.20; H, 6.32.

6. N-Carboxymethyl-3-hydroxymethyl-4S-methyl-1,4-dihydropyridine 186



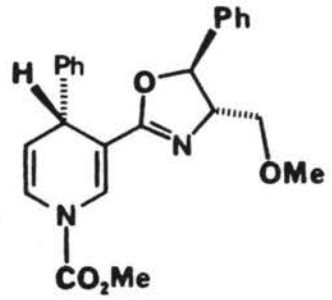
Aldehyde 185 (9.7 mg, 0.05 mmol) was reduced with $NaBH_4$ according to the procedure for naphthylquinoline 232 (p. 162). Purification by ptlc (0.25 mm, 70% ether/pentane, R_f = 0.3) afforded 6.2 mg (63%) of the desired alcohol. ^1H NMR ($CDCl_3$): 6.97-6.43(br s, 2H), 4.87(br s, 1H), 4.33-3.89(m, 2H), 3.80(s, 3H), 3.27-2.91(m, 1H), 1.40(br s, 1H), 1.15(d, J=7Hz, 3H). The alcohol was esterified directly.

7. Mosher Ester of Alcohol 186

Alcohol 186 (6.2 mg, 0.034 mmol) was esterified with (+)- -methoxy- -(trifluoromethyl)phenylacetyl chloride according to the procedure for preparation of ester 233 (p. 162). Upon aqueous extractive isolation, the ester was immediately analyzed by NMR without purification (potentially unstable). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.63-7.30(m, 5H), 7.08-6.57(m, 2H), 5.05-4.77(m, 2H), 4.68(d, J=12Hz, 0.90H), 4.64(d, J=12Hz, 0.10H), 3.81(s, 3H), 3.57(s, 1.5H), 3.56(s, 1.5H), 3.03-2.84(m, 1H), 1.07(d, J=7Hz, 3H); ^{19}F NMR ($CDCl_3$, 188 MHz): -72.9, -73.0(0.00ppm set with a standard of $CFCl_3$ in CH_2Cl_2), relative

areas of the peaks 9:91 respectively; IR(film) cm^{-1}: 1735, 1722(sh), 1697, 1688(sh), 1440, 1340.

8. N-Carbomethoxy-3-oxazolinyl-4S-phenyl-1,4-dihydropyridine 177 (R=Ph)

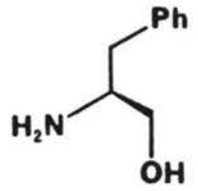


To a solution of oxazolinylpyridine 175 (0.65 g, 2.42 mmol) and THF (250 ml) cooled to -78°C, was added phenyllithium[121] (0.90M, 3.3 ml, 3.0 mmol). Stirring was continued for 3 hr and the reaction was quenched with methyl chloroformate (0.27 ml, 3.5 mmol).

The reaction mixture was concentrated, slurried in saturated aqueous bicarbonate (150 ml), and extracted with $CHCl_3$ (4 x 50 ml). Drying (K_2CO_3) followed by filtration and concentration gave the dihydropyridine. The diastereomeric ratio was determined by HPLC (normal phase, 10% THF/hex, 2 ml/min) and found to be 12:88. Purification by HPLC (Waters Prep 500, 10% THF/hex) afforded 0.70 (71%) of the pure dihydropyridine. ^1H NMR ($CDCl_3$): δ 7.80 (br s, 1H), 7.57-6.67(m, 11H), 5.47-4.96(m, 2H), 4.59(br d, J=5Hz, 1H), 4.30-2.98(m, 3H), 3.80(s, 3H), 3.32(s, 3H), (Diastereomeric proton signals were not detected in the spectrum); IR(film) cm^{-1}: 1730, 1680, 1580, 1555, 1490, 1120; Ms[120] (70 ev) m/e (% R.I.): 404(46), 359(100), 345(45), 327(34), 256(24), 182(24), 119(63), 91(82).

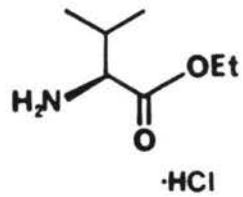
C. Synthesis of Chiral 1,4-Dihydropyridines via Imines

1. (S)-Phenylalaninol 190



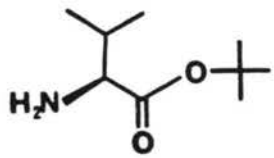
Amino alcohol 190 was prepared according to the procedure by Yamada.[122] Mp 88.5-90°C (lit. 91-93°C); $[\alpha]_D^{24}$ =23.7 (c 1.05, EtOH), lit. $[\alpha]_D^{25}$ -25.6 (c 1.037, EtOH).

2. (S)-Ethylvalinate hydrochloride 192



Amino ester 192 was prepared according to the procedure by Yamada.[123] Mp 102-103°C (lit. 93-96°C), $[\alpha]_D^{24}$ +6.70° (c 2.0, H_2O), lit. $[\alpha]_D$ 6.74 (c 5.407, H_2O). Yield 86%.

3. (S)-t-Butylvalinate 194



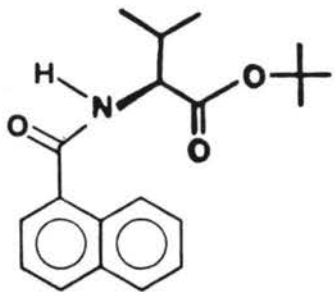
Amino ester 194 was prepared as reported previously,[124] using diglyme as a cosolvent. Note: A more convenient procedure,[125] used for the synthesis of d,l-t-butylvalinate, utilized dioxane as a cosolvent with equally good results.

The ester was isolated from an ether solution by precipitation as the hydrochloride. Filtration followed by rinsing with ether gave the finely divided white powder (55%). Mp 146-147°C (lit.[124] 147-149°C).

The hydrochloride was neutralized and the amino ester purified by Kugelrohr distillation. $[\alpha]_D$ +23.8 (neat), lit.[125] $[\alpha]_D$ +25.5 (neat).

The rotation exhibited by the amino ester (+23.8°) was low (1.7°) compared with the literature value. It was therefore necessary to establish the absolute purity by some other means. Below is described the synthesis of the 1-naphthamide, which was subjected to HPLC analysis on a chiral covalently bonded column.[126]

4. (S)-t-Butylvalinate Naphthamide



To a flame dried round bottomed flask fitted with magnetic stirrer bar, septum, and argon inlet was added amino ester 194 (0.040 g, 0.19 mmol), dry CH_2Cl_2 (3 ml), and Et_3N (0.070 ml, 0.50 mmol). Upon cooling to 0°, α-naphthoyl chloride[127] (0.10 ml, 0.67 mmol) was added and the solution stirred 2.6 hr. The reaction mixture was diluted with CH_2Cl_2 (5 ml) and washed with sat. aqueous bicarbonate (3 x 5 ml). Drying (K_2CO_3) followed by filtration and concentration gave the naphthamide which was purified by radial chromatography (silica gel, 10% EtOAc/50%, CH_2Cl_2/40% hex).

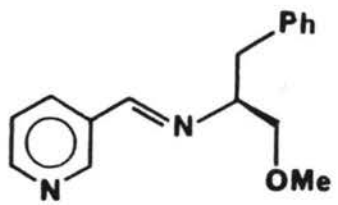
HPLC analysis (10% i-PrOH/hex, 2 ml/min) gave only a single peak (retention time: 11.75 min). Verification of 100% enantiomeric purity was realized by analysis of dl-t-butylvalinate naphthamide, which gave two peaks, of near baseline separation (retention times: 11.60 and 13.56 min).

It may be concluded from the above data that an optical rotation is useful for approximate optical purity however, the absolute purity should be determined by some other means.

5. General Procedure Synthesis of Imines 189 to 195 of 3-Pyridinecarbox-aldehyde

To a flask fitted with a magnetic stirrer bar, Dean-Stark trap, and reflux condensor was added a 0.37-0.55 M solution of the amine in toluene (1.1 eq of triethylamine was also added if the amine was the hydrochloride). 3-Pyridinecarboxaldehyde was added and the mixture was heated at reflux for 4 hr - 2 days (until the starting material was consumed, as indicated by TLC). Upon cooling, the reaction mixture was further dried (Na_2SO_4 or K_2CO_3). Filtration and concentration gave the imine which was purified by Kugelrohr distillation and recrystallization, if necessary. The individual imines prepared by this route are described on the following pages.

6. (S)-N-(3-Pyridylmethyliden)-1-phenyl-2-amino-methoxypropane 189

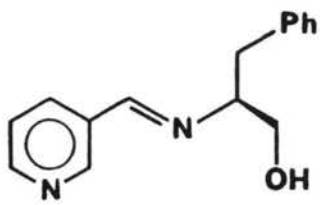


Following the procedure above, (S)-1-phenyl-2-amino-methoxypropane[128] (27.4 g, 1.66 mmol) and 3-pyridinecarboxaldehyde (14.8 ml, 157 mmol) were heated in refluxing toluene for 2 days. Kugelrohr distillation afforded the crude imine which was recrystallized, from pentane, to give 21.2 g (53% after one crop) as a highly crystalline white product. Bp 98-99°C (0.015 mm Hg); mp 43.5-44.5; $[\alpha]_D$ -226° (c

6.1, $CHCl_3$); $[\alpha]_D$ -199° (c 6.0, C_6H_6). ^1H NMR ($CDCl_3$): δ 8.75(d, J=2Hz, 1H), 8.58(dd, J=5Hz, J=2Hz, 1H), 8.12-7.87(m, 2H), 7.40-6.98(m, 6H), 3.73-3.45(m, 3H), 3.34(s, 3H), 3.13-2.66(m, 2H); ^{13}C NMR ($CDCl_3$): 158.3, 151.0, 149.9, 138.2, 134.4, 131.4, 129.5, 128.0, 126.0, 123.2, 75.6, 72.4, 59.0, 39.2; IR(melt) cm^{-1}: 1655.

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13. Found: C, 75.51; H, 6.94.

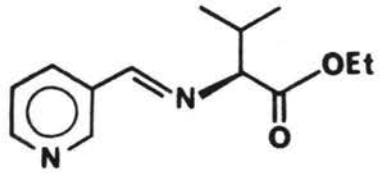
7. (S)-N-(3-Pyridylmethyliden)phenylalaninol 191



Following the procedure above, (S)-phenylalaninol[190] (6.7 g, 44.4 mmol) and 3-pyridinecarboxaldehyde (6.4 ml, 67.8 mmol) were heated in refluxing toluene for 4 hr. Kugelrohr distillation afforded 8.9 g (83%) of the imine. Further purification, by recrystallization from ether, gave 8.25 g (77% after 2 crops) of the highly crystalline product. Bp 153-155°C (0.05 mm Hg); mp 64-66°C; $[\alpha]_D^{24}$ -267° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.64(d, J=1Hz, 1H), 8.46(dd, J=5Hz, J=1Hz, 1H), 7.93-7.63(m, 2H), 7.31-6.82(m, 6H), 4.49(br s, 1H), 3.97-3.27(m, 3H), 3.10-3.53(m, 2H); ^{13}C NMR ($CDCl_3$): δ 158.5, 150.5, 149.3, 138.1, 134.5, 131.1, 129.3, 127.9, 125.9, 123.2, 74.8, 65.3, 38.8; IR(film) cm^{-1}: 1647, 1420. (Traces of the isomeric oxazolidine could be detected in the ^1H and ^{13}C NMR spectra).

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71. Found: C, 75.00; H, 6.77.

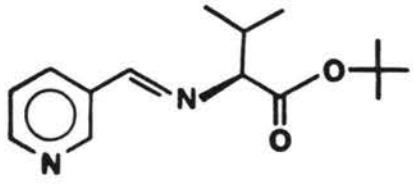
8. (S)-N-(3-Pyridylmethyliden)ethylvalinate 193



Following the procedure above, (S)-ethylvalinate hydrochloride (2.0 g, 11.0 mmol), Et_3N (1.69 ml, 12.1 mmol), and 3-pyridinecarboxaldehyde (1.07 ml, 11.3 mmol) were heated in refluxing toluene for 4 hr. Kugelrohr distillation afforded 2.19 g (85%) of the pure imine, as a clear free-flowing liquid. Bp 68-71°C (0.05 mm Hg); $[\alpha]_D^{24}$ -107.7° (c 3.25, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.92(d, J=2Hz, 1H), 8.65(dd, J=5Hz, J=2Hz, 1H), 8.40-8.01(m, 2H), 7.34(dd, J=8Hz, J=5Hz, 1H), 4.22(q, J=7Hz, 2H), 3.72(d, J=7Hz, 1H), 2.61-2.11(m, 1H), 1.29(t, J=7Hz, 3H), 0.98(d, J=7Hz, 3H), 0.96(d, J=7Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 170.7, 159.7, 151.1, 149.9, 134.2, 130.8, 123.0, 79.5, 60.3, 31.3, 19.1, 18.2, 13.9; IR(film) cm^{-1}: 1748, 1658.

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74. Found: C, 66.57, H, 7.51.

9. (S)-N-(3-Pyridylmethyliden)-t-butylvalinate 195



Following the procedure above, (S)-t-butylvalinate (0.68 g, 3.9 mmol) and 3-pyridinecarboxaldehyde (0.39 ml, 4.14 mmol) were heated in refluxing toluene for 4 hr. Kugelrohr distillation afforded 0.97

g (94%) of the imine. Bp 75-78°C (0.03 mm Hg); $[\alpha]_D^{24}$ -85.5° (c 1.5, $CHCl_3$).

A small amount was recrystallized from pentane. Mp 54.5-55.5°C; $[\alpha]_D^{24}$ -86.1 (c 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.90(d, J=2Hz, 1H), 8.65(dd, J=5Hz, J=2Hz, 1H), 8.34-8.05(m, 2H), 7.34(dd, J=8Hz, J=5Hz, 1H), 3.60(d, J=7Hz, 1H), 2.55-2.14(m, 1H), 1.49(s, 9H), 0.98(d, J=7Hz, 3H), 0.96(d, J=7Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 170.4, 159.6, 151.4, 150.2, 134.6, 131.2, 123.3, 81.0, 80.4, 31.6, 28.0, 19.4, 18.4; IR(melt) cm^{-1}: 1738, 1645.

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45. Found: C, 68.94, H, 8.56.

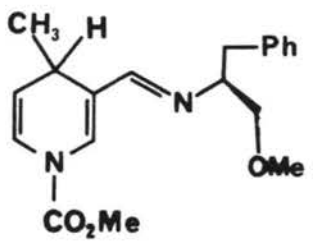
10. Lithium Dimethylcuprate

To a 0.11 M suspension of cuprous iodide (Fisher) and THF cooled to 0°C was added dropwise methyllithium (1.90 eq). The grey suspension turned to a yellow suspension midway through the methyllithium addition, becoming a clear peach-color upon complete addition. After stirring 20 min at 0°C, the cuprate was ready for use.

11. Lithium Cyanomethylcuprate

A procedure similar to the report by Marino and Abe[129] was followed. To a suspension of cuprous cyanide (Baker) and THF cooled to -78°C was added dropwise methyllithium (0.90 eq). After stirring for 1 hr at -78°C, the blue green mixed cuprate was ready for use.

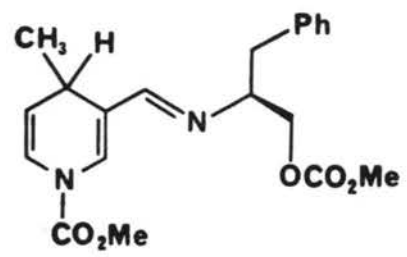
12. Alkylation of Imino Pyridine 189 with Lithium Cyanomethylcuprate



To a solution of lithium cyanomethyl cuprate (0.57 mmol) cooled to -100°C was added dropwise, via a pressure equilizing addition funnel, a solution of pyridiyl imine 189 (0.120 g, 0.47 mmol) and THF (30 ml). Upon complete addition, the mixture was warmed to -78°C. Stirring was continued for 3.3 hr and the reaction quenched with methyl chloroformate (0.066 ml, 0.85 mmol). The reaction mixture was concentrated, slurried in CH_2Cl_2 (30 ml), washed with 5% aqueous ammonium hydroxide (4 x 30 ml) until the blue copper color was no longer extracted, and then brine. Drying (K_2CO_3), filtration, and concentration gave the crude dihydropyridine 197. The diastereomeric ratio was found to be 1:1 by ^1H NMR (60 MHz). ^1H NMR ($CDCl_3$, 60 MHz): 7.38(br s, 1H), 7.27-6.40(m, 7H), 5.0(dd, J=8Hz, J=4Hz, 1H), 3.95-3.05(m, 4H), 3.76(s, 3H), 3.31(s, 3H), 3.02-2.64(m, 2H), 1.21(d, J=7Hz, 1.5H), 1.17(d, J=7Hz, 1.5H); IR(film) cm^{-1}: 1681, 1671(sh), 1664(sh), 1646, 1639(sh).

The crude methylated imine was hydrolyzed according to the procedure on p. 140, utilizing chloroform and aqueous oxalic acid. The racemic aldehyde 185 was recovered (0.075 g, 88%) and found to be >95% pure by ^1H NMR.

13. Alkylation of Imino Pyridine 191 with Lithium Dimethylcuprate

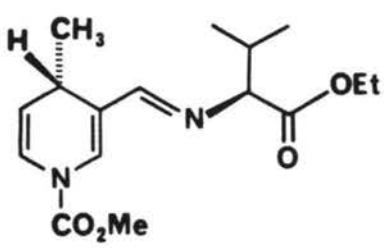


To a solution of pyridyl imine 191 (0.250 g, 0.104 mmol) and THF (50 ml) cooled to -78°C, was added via cannula lithium dimethylcuprate (2.3 mmol, precooled to -78°C). Stirring was continued for 3 hr, at which which time the dianion was quenched with methyl chloroformate (0.42 ml, 5.5 mmol).

The dihydropyridine was isolated by extraction as described for dihydropyridine 197 (p. 137). Analysis by ^{1}H NMR indicated 1:1 mixture. ^{1}H NMR ($CDCl_3$, 100 MHz): δ 7.31(s, 1H), 7.25-6.40(m, 7H), 4.98(dd, J=7Hz, J=3Hz, 1H), 4.37-4.00(m, 2H), 3.90-3.13(m, 2H), 3.73(s, 3H), 3.64(s, 3H), 3.03-2.60(m, 2H), 1.15(d, J=7Hz, 1.5Hz), 1.13(d, J=7Hz, 1.5H); IR(film) cm^{-1}: 1745, 1733(sh), 1718(sh), 1678, 1623.

The reaction mixture was hydrolyzed according to the procedure on p. 140, using an ether-pentane and aqueous oxalic acid mixture. The racemic aldehyde 185 was recovered (0.177 g, 94%) as a yellow oil and found to be >95% pure by ^{1}H NMR.

14. Alkylation of Imino Pyridine 193 with Lithium Dimethylcuprate



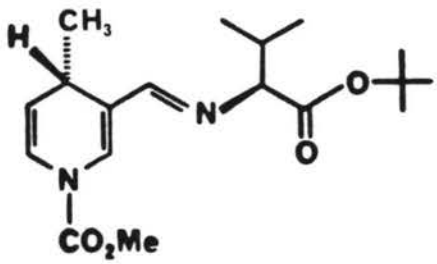
To a solution of pyridiyl imine 193 (0.087 g, 0.37 mmol) and THF (35 ml) cooled to -78°C, was added via cannula, lithium dimethylcuprate (0.74 mmol, precooled to -78°C). Stirring was continued at -78°C for

5 hr at which time the reaction was quenched with methyl chloroformate (0.172 ml, 2.22 mmol). The addition product was isolated as described for dihydropyridine 197 (p. 137). The diastereomeric ratio was found to be 34:66 as determined by HPLC (normal phase, 10% THF/hex, 1 ml/min). ^{1}H NMR ($CDCl_3$, 60 MHz): δ 7.70(br s, 1H), 7.17(d, J=2Hz, 1H), 6.73(br d, J=8Hz, 1H), 5.08(dd, J=8Hz, J=5Hz, 1H), 4.20(q, J=7Hz, 2H), 3.87(s, 3H), 3.72-3.32(m, 2H), 2.70-2.03(m, 1H), 1.48-0.73(m, 12H), (Diastereotopic proton signals were not detected in the spectrum); IR(film) cm^{-1}: 1745, 1695, 1638, 1458, 1363, 1338, 1226.

The imine was hydrolyzed (4 hr) using a CH_2Cl_2 and aqueous oxalic acid mixture according to the procedure on p. 140. Following trituration with pentane, the crude aldehyde 185 was recovered. $[\alpha]_D^{25}$ +60 (c 1.0, C_6H_6).

Purification via column chromatography (florisil, 0-75% ether/pentane) afforded the purified aldehyde (0.066 g, 97%). $[\alpha]_D^{24}$ +66.5° (c 1.2, C_6H_6).

15. Alkylation of Imino Pyridine 195 with Lithium Dimethyl Cuprate



To a solution of pyridyl imine 195 (0.061 g, 0.23 mmol) and THF (21 ml) cooled to -78°C, was added via cannula, lithium dimethylcuprate (0.465 mmol, precooled to -78°C). Stirring was continued for 4 hr, at which time the reaction was quenched with methyl chloroformate (0.108 ml, 1.4 mmol). The addition product was isolated as described for

dihydropyridine 197 (p. 137). The diastereomeric ratio was found to be 22:78 as determined by HPLC (normal phase, 4.8% THF/hex, 1 ml/min). ^{1}H NMR ($CDCl_3$): δ 7.70(s, 1H), 7.14(br s, 1H), 6.73(br d, J=8Hz, 1H), 5.08(dd, J=8Hz, J=5Hz, 1H), 3.93-3.20(m, 2H), 3.85(s, 3H), 2.21-1.73(m, 1H), 1.45(s, 9H), 1.17(br d, J=7Hz, 3H), 0.90(br d, J=6Hz, 6H), (Diastereomeric proton signals were not detected in the spectrum); ^{13}C NMR ($CDCl_3$): δ 171.1, 161.6(4S), 161.1(4R), 151.4, 130.7, 122.8, 120.6, 113.9, 80.8(4R), 80.6(4S), 80.0, 53.7, 31.7(4S, 0.725C), 31.3(4R, 0.275C), 28.1, 27.1(4R), 27.0(4S), 22.9(4S), 22.7(4R), 19.7, 18.4; IR(film) cm^{-1}: 1735, 1720(sh), 1700(sh), 1680, 1620, 1440.

The imine was hydrolyzed (9 hr) using a CH_2Cl_2 and aqueous oxalic acid mixture according to the procedure on p. 140. Purification by column chromatography (florisil, 0-90% ether/pentane) afforded 0.034 g (82%) of aldehyde 185. $[\ ]_D^{24}$ +98° (c 0.7, C_6H_6).

16. Imine Hydrolysis Procedures

a. Aqueous Oxalic Acid

The pH 1 stock solution was prepared from two parts saturated aqueous oxalic acid and one part water. It should be noted that saturated aqueous oxalic acid was ineffective towards hydrolysis.

To a round bottomed flask was added the imine, as an ether/pentane (70/30 by volume, 25 ml) solution and aqueous oxalic acid (25 ml). (CH_2Cl_2 or chloroform may be used as a cosolvent instead of ether/pentane). The mixture was stirred rapidly at room temperature until complete reaction was realized (minutes to hours, as determined by tlc). The yellow layers were separated and the aqueous layer was extracted with ether (3 x 25 ml). The combined organic layers were

washed with 5% aqueous HCl (2 x 25 ml) and dried (K_2CO_3). Filtration and concentration gave the yellow aldehyde.

b. Aqueous Acetic Acid - Sodium Acetate

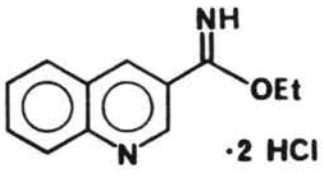
A procedure similar to the report by Schlessinger and coworkers[130] was used. The pH 5 stock solution was prepared from glacial acetic acid (50 ml), water (50 ml), and anhydrous sodium acetate (5.2 g).

To a round bottomed flask was added a CH_2Cl_2 or chloroform (25 ml) solution of the imine and aqueous acetate (25 ml). The mixture was stirred rapidly at room temperature until complete reaction was realized (minutes to hours, as determined by tlc). The layers were separated and the organic layer was washed with brine (3 x 25 ml) and dried (K_2CO_3). Filtration and concentration gave the desired aldehyde.

D. Conservation of Chirality

1. Starting Materials

a. Ethyl-(3-quinolinyl)-imidate Dihydrochloride 210



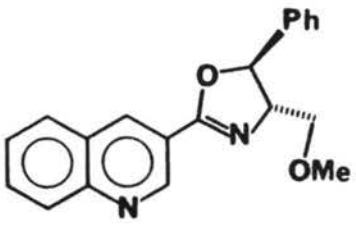
To an oven dried 1L 3-necked flask fitted with magnetic stirrer bar, pressure equilizing addition funnel, reflux condensor, septum, and argon inlet was added absolute EtOH (21.8 ml, 37.4 mmol) and $CHCl_3$ (220 ml). Upon cooling to 0°C, acetyl chloride (19.0 ml, 267 mmol) was added dropwise, followed by addition, via cannula, of a solution consisting of 3-quinolinecarbonitrile (4.12 g, 26.7 mmol) and $CHCl_3$ (220 ml). During addition, the flask was allowed to warm to room temperature and

the imidate began to precipitate from solution. Stirring was continued at room temperature overnight (16 h), and the mixture was concentrated. The product was slurried in ether and collected in a sintered glass funnel and washed with ether (250 ml). Residual HCl was removed under reduced pressure (aspirator vacuum for 24 h, in the presence of a beaker of NaOH pellets) to afford 6.9 g (95%) of the light brown powder, mp 175-178°C.

A satisfactory analysis could not be obtained for this compound.

A small portion was hydrolyzed (5% aqueous HCl) to the corresponding ester for characterization. ^{1}H NMR ($CDCl_3$): δ 9.47(br s, 1H), 8.90(br s, 1H), 8.40-7.37(m, 4H), 4.48(q, J=8Hz, 2H), 1.47(t, J=7Hz, 3H); IR(film) cm^{-1}: 1730, 1725(sh), 1635.

b. 2-(3'-Quinolinyl)-4S-methoxymethyl-5S-phenyl-Δ^2-oxazoline 211



To an oven dried 1L round bottomed flask fitted with magnetic stirrer bar, reflux condensor, septum, and argon inlet was added imidate 210 (6.14 g, 22.5 mmol) and dry 1,2-dichloroethane (425 ml). The resulting slurry was treated with Et_3N (3.1 ml, 22.5 mmol) and amino alcohol 174 (4.2 g, 23.2 mmol) followed by heating at reflux overnight (16 h). Upon cooling to room temperature, the organic layer was washed with water (4 x 150 ml). The combined aqueous layers were back extracted with CH_2Cl_2 (3 x 150 ml), and the combined organic layers

were washed with brine and dried (K_2CO_3). Filtration and concentration gave the desired oxazoline as a heavy oil.

The crude oxazoline was purified by medium pressure liquid chromatograph (MPLC) or normal gravity column chromatography (silica gel, 20% pentane/ether). Concentration of the pure fractions (as indicated by tlc) gave the dark yellow starting material. Upon dissolving in pentane, the yellow impurity remained as an insoluble film. Concentration of the pentane soluble portion, followed by warming at 70°C under reduced pressure (0.005 mm Hg, 3h) afforded 7.7 g (82.5%) of the desired light yellow oxazolinylquinoline. $[\alpha]_D^{24}$ +124.0° (c, 9.75, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 9.54(d, J=2Hz, 1H), 8.77(br d, J=2Hz, 1H), 8.27-7.11(m, 9H), 5.56(d, J=7Hz, 1H), 4.43(m, 1H), 3.88-3.50(m, 2H), 3.45(s, 3H); ^{13}C NMR ($CDCl_3$): δ 161.9, 149.3, 148.8, 140.1, 136.2, 130.8, 129.2, 128.6, 128.4, 128.1, 127.1, 126.7, 125.4, 120.4, 83.5, 75.1, 73.9, 59.3; IR(film) cm^{-1}: 1650, 1625, 1608, 1575, 1498, 1125.

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70. Found: C, 75.26; H, 5.59.

c. 1-Bromonaphthalene

1-Bromonaphthalene contains a small amount (<5%) of the isomeric 2-bromonaphthalene. This was removed by recrystallization from absolute EtOH (-20° to -5°C) as previously described.[131] The white crystals were recovered by rapid filtration through a chilled sintered glass funnel. Residual EtOH was removed by dissolving the bromide in CH_2Cl_2 and washing with water (3x). The organic layer was

further washed with brine and dried (K_2CO_3). Filtration, concentration, and distillation gave the purified bromide. Purity was determined by close inspection of a ^{13}C NMR spectrum ($CDCl_3$), which indicated the presence or absence of the 2-bromo isomer between δ128.9-129.3.

d. 1-Naphthyllithium

To a solution of 1-bromonaphthalene (0.096 ml, 0.69 mmol) and THF (5 ml) cooled to -78°C, was added dropwise s-butyllithium (1.14M, 0.5 ml, 0.57 mmol). The resulting cloudy light yellow solution was warmed to -45°C. This temperature was maintained for 30 min, at which time the naphthyllithium was ready for use.

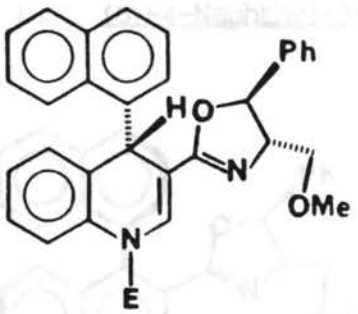
e. 1-Naphthylmagnesium Bromide

To a 100 ml 3-necked flask fitted with magnetic stirrer bar, pressure equilizing addition funnel, reflux condensor, septum, and argon inlet was added magnesium turnings (1.19 g, 49.1 mmol). The entire apparatus was flame dried while purging with argon. Upon cooling to room temperature, ether (5 ml) and 1-bromonaphthalene (0.5 ml, 3.6 mmol) were added. After a few minutes (sometimes with slight warming), the reaction began and the solution became brown accompanied by some slight cloudiness. Dropwise addition of a solution, consisting of 1-bromonaphthalene (6.0 ml, 43.1 mmol) and ether (25 ml), followed at a rate so as to maintain a gentle reflux. After addition of 5 ml of this bromide solution, benzene (5 ml) was added. (If the brown Grignard reagent precipitated before this time, then benzene was added). Addition of the bromide was completed and stirring was

continued an additional 4 hr at room temperature. The Grignard reagent was further diluted with benzene (20 ml) and transferred, via cannula, to an oven dried bottle covered with a double septum and stored at room temperature. The titration procedure was as described by Watson and Eastham[117] using s-butanol in benzene.

2. Alkylation with 1-Naphthyllithium

a. 4S-Naphthyl-3-oxazolinyl-1,4-dihydroquinoline 213 and 214



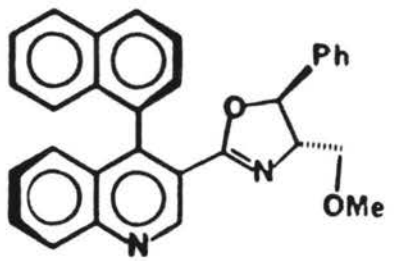
E = H 213
CO_2Me 214

To a solution of oxazolinylquinoline211 (0.091 g, 0.29 mmol) and THF (22.6 ml) cooled to -78°C was added, via cannula, 1-naphthyllithium (0.57 mmol, precooled to -78°C). The resulting yellow solution was stirred until complete disappearance of the starting material (2 hr), as determined by tlc (50% THF/hex). The bulk of the solution (99% by volume) was quenched by transferring, via cannula, to a graduated cylinder containing EtOH (0.3 ml), and allowing to warm to room temperature. The remaining portion of the reaction mixture (<1 ml) was quenched with methyl chloroformate (1 drop, stored over CaH_2) and stirred for an additional 3 hr, while warming to room temperature. The chloroformate mixture was concentrated, slurried in CH_2Cl_2 (10 ml) and washed with dilute aqueous bicarbonate (3 x 10 ml) and brine. Drying (K_2CO_3), followed by filtration and concentration gave urethane 214. The analytical sample was prepurified by column chromatography (small plug of silica gel, 40 ml EtOAc) and subjected to

analysis by HPLC (reverse phase, 90% MeOH/H_2O, 1 ml/min) for the determination of the diastereomeric ratio (88:12).

The ethanol quenched dihydroquinoline solution was concentrated, slurried in CH_2Cl_2 (40 ml), and washed with dilute aqueous bicarbonate (3 x 40 ml) and brine. Drying (K_2CO_3), followed by filtration and concentration gave the N-H dihydroquinoline 213 suitable for oxidation in the next experiment.

b. (S)-4-Naphthyl-3-oxazolinylquinoline 215

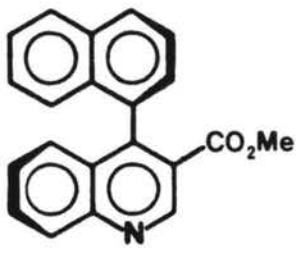


To a dry flask was added dihyroquinoline 213 as a dried CH_2Cl_2 solution (5-10 ml). Upon concentration , the flask was flushed with argon and THF (10 ml) was added. The solution was cooled to -78°C and treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.068 g, 0.30 mmol). The resulting dark green solution became red while warming slowly to room temperature (3 hr).

The mixture was diluted with CH_2Cl_2 (50 ml) and washed with saturated aqueous bicarbonate (3 x 30 ml) until the aqueous layer was no longer colored and then brine. Drying (K_2CO_3), followed by filtration and concentration gave the oxidized product. Analysis by HPLC (reverse phase, 82% MeOH/H_2O, 1 ml/min) indicated a diastereomeric ratio of 89:11. Purification via radial chromotraphy (silica gel, EtOAc) afforded 0.111 g (87%) of naphthylquinoline 215 as a foam. ^1H NMR ($CDCl_3$): δ 9.58(s, 0.17H), 9.49(s, 0.83H), 8.24(br d, J=8Hz, 1H), 8.04-6.93(m, 13H), 6.75-6.63(m, 2H), 5.04(d, J=7Hz, 0.14H), 4.92(d,

J=7Hz, 0.86H), 4.20-3.88(m, 1H), 3.60-2.97(m, 2H), 3.28(s, 3H); ^{13}C NMR ($CDCl_3$): δ 162.9, 150.2, 148.6, 146.9, 139.8, 133.7, 133.0, 131.9, 130.4, 129.4, 128.4, 128.1, 127.9, 127.4, 127.3, 127.0, 126.2, 125.7, 124.8, 121.7, 83.8, 74.2, 59.1. IR and elemental analysis were obtained from the single diastereomer 224 (p. 156) used for X-ray analysis.

c. (S)-3-Carbomethoxy-4-naphthylquinoline 216

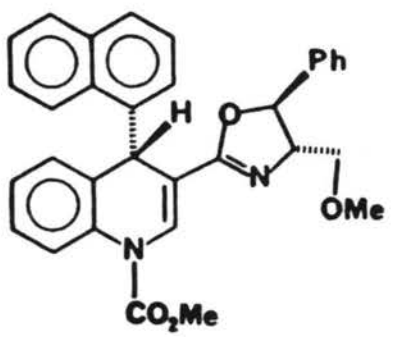


To a 25 ml round bottomed flask fitted with magnetic stirrer bar and reflux condensor was added oxazolinylquinoline 215 (0.111 g, 0.25 mmol) and 6M aqueous H_2SO_4 (5 ml). The flask was placed in an oil bath, preheated to 150°C, which resulted in a vigorous reflux. (A vigorous reflux was required so as to hasten the reaction, thus minimizing decomposition and possible resolution). Heating of the resulting yellow orange solution was continued until the high R_f material was no longer visible (6.6 hr), as indicated by tlc. Neutralization of an aliquot with aqueous bicarbonate and elution with 10% Et_3N/EtOAc, acid has R_f = 0. Upon cooling to 0°C, the mixture was adjusted to pH 4 with 40% aqueous sodium hydroxide. The insoluble product was extracted with CH_2Cl_2 (3 x 50 ml), and the combined organic layers were washed with brine and dried (Na_2SO_4). Filtration and concentration gave the acid, which was esterified directly as described below.

Esterification by Diazomethane. To a scratch-free 250 ml flask was added an ether solution (200 ml) of the acid. Diazomethane (4.29 mmol, 15 eq) was bubbled into the mixture to furnish a clear light green solution, which was further diluted with ether to 250 ml and stirred overnight (16 hr). Drying (K_2CO_3), filtration, and concentration gave the crude ester. Purification by radial chromatography (silica gel, 0-10% EtOAc/hex), followed by trituration with pentane afforded 0.069 g (89% from the oxazoline) of the light brown naphthylquinoline 216. Mp 101-102.5°C; $[\alpha]_D^{22}$ -9.8° (1.12, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 9.50(s, 1H), 8.33-6.96(m, 11H), 3.48(s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.7, 150.0, 148.9, 133.9, 132.9, 131.6, 130.9, 129.3, 128.3, 128.1, 127.5, 127.1, 126.2, 126.1, 125.8, 125.1, 124.8, 123.4, 52.0; IR(film) cm^{-1}: 1730, 1713, 1568, 1221.

Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.48; H, 4.84; N, 4.47. Found: C, 80.23; H, 4.93; N, 4.29.

d. N-Carbomethoxy-4S-naphthyl-3-oxazolinyl-1,4-dihydroquinoline 214

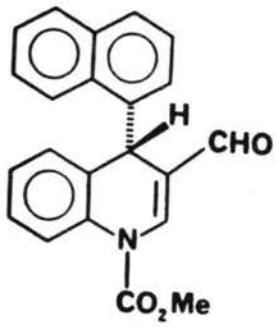


Oxazolinylquinoline 211 (1.034 g, 3.25 mmol) was alkylated with 1-naphthyllithium (4.9 mmol) as desdribed on p. 145. After 3 hr at -78°C, the reaction was quenched with methyl chloroformate (0.75 ml, 9.75 mmol). Purification by column chromatography (silica gel, 0-40% THF/hex) afforded 1.39 (85%) of the urethane. HPLC analysis (reverse

phase, 90% MeOH/H_2O, 1 ml/min) indicated a diastereomeric ratio of 87.5:12.5. ^1H NMR ($CDCl_3$): δ 8.74(br d, J=8Hz, 1H), 8.31-8.04(m, 2H), 7.90-6.72(m, 14H), 6.14(s, 1H), 5.21(d, J=7Hz, 0.86H), 5.18(d, J=7Hz, 0.14H), 4.10-2.55(m, 3H), 3.78(s, 3H), 3.23(s, 2.5H), 2.82(s, 0.5H); ^{13}C NMR ($CDCl_3$): δ 162.4, 152.4, 141.0, 140.8, 140.5, 134.2, 133.9, 131.2, 130.7, 128.6, 128.4, 127.7, 127.1, 126.6, 125.8, 125.7, 125.4, 125.2, 125.1, 124.3, 120.8, 112.8, 83.4(4S), 83.0(4R), 75.0(4R), 74.5(4S), 74.1, 59.1, 53.8, 38.5; IR(film) cm^{-1}: 1740, 1672, 1630, 1130.

Anal. Calcd for $C_{32}H_{28}N_2O_4$: C, 76.16; H, 5.61; N, 5.55. Found: C, 76.09; H, 5.71; N, 5.43.

e. N-Carbomethoxy-3-formyl-4S-naphthyl-1,4-dihydroquinoline 218



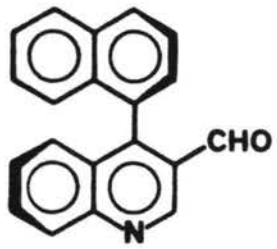
To a solution of 4-naphthyldihydroquinoline 214 (0.193 g, 0.38 mmol, diastereomeric ratio of 87.5:12.5) and dry CH_2Cl_2 (10 ml) was added dropwise, methyl fluorosulfonate ("Magic Methyl") (0.064 ml, 0.079 mmol). Stirring was continued at room temperature overnight (17.5 hr), at which time the resulting yellow solution was cooled to 0°C and treated with a suspension of $NaBH_4$ (0.045 g, 1.20 mmol) in THF (1 ml) and MeOH (0.5 ml). (Flask must be sufficiently vented to accommodate vigorous gas evolution). The grey suspension was allowed to warm slowly to room temperature. After 4 hr, the reaction was quenched with

water (1 ml) and saturated aqueous ammonium chloride (1 ml). Upon further dilution with ether (25 ml) and water (1 ml), the layers were separated. The aqueous layer was extracted with ether (20 ml), and the combined organic layers were washed with brine and dried (K_2CO_3). Filtration and concentration gave the crude oxazolidine which was immediately hydrolyzed.

Hydrolysis. To a stirred slurry of silica gel 137 (6 g, Silica Woelm, 32-63μ), CH_2Cl_2 (20 ml) and aqueous oxalic acid (24 drops, used for imine hydrolysis p. 140) was added a CH_2Cl_2 solution (15 ml) of the oxazolidine at room temperature. After complete reaction (<1 hr, by tlc, 50% THF/hex) the slurry was filtered through a sintered glass funnel, and the silica gel was washed with CH_2Cl_2 (150 ml). Concentration gave the aldehyde which was purified via radial chromatography (silica gel, 0-30% THF/hex) affording 0.125 g (96%) of the purified compound as a foam. $[\alpha]_D^{23}$ +150° (c 0.96, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 9.40(s, 1H), 8.67(br d, J=8.5Hz, 1H), 8.31-8.00(m, 2H), 7.87-6.78(m, 9H), 5.96(s, 1H), 4.04(s, 3H); ^{13}C NMR ($CDCl_3$): δ 189.0, 152.0, 143.0, 140.9, 134.0, 133.9, 130.7, 130.4, 129.4, 128.6, 127.4, 127.0, 126.3, 126.2, 126.0, 125.8, 125.5, 123.7, 120.6, 54.5, 35.6; IR(film) cm^{-1}: 1745, 1678, 1650, 1582, 1340, 1230.

Anal. Calcd for $C_{22}H_{17}NO_3$: C, 76.94; H, 5.00; N, 4.08. Found: C, 76.50; H, 5.21; N, 4.00.

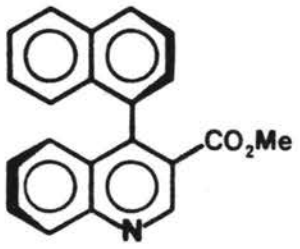
f. (S)-4-Naphthyl-3-quinolinecarboxaldehyde 220



To a solution of dihydroquinoline 218 (0.121 g, 0.35 mmol), THF (11.4 ml), absolute EtOH (7.5 ml) was added aqueous 20% potassium hydroxide (1.5 ml). Stirring was continued at room temperature for 15 min, at which time tlc (50% THF/hex) indicated complete removal of the urethane. Upon dilution with CH_2Cl_2 (40 ml), the organic layer was washed with dil. aqueous bicarbonate (3 x 40 ml) and brine. Drying (K_2CO_3), filtration, and concentration gave the desired N-H dihydroquinoline.

Oxidation with DDQ was performed according to the procedure outlined for the synthesis of naphthylquinoline 215 (p. 146). Purification via radial chromatography (silica gel, 10% THF/hex) gave 0.089 g (90%) of the aldehyde. Mp 128-130°C; $[\alpha]_D^{24.5}$ -93.3° (c 0.98, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 9.72(s, 1H), 9.53(s, 1H), 8.36-6.92(m, 11H); ^{13}C NMR ($CDCl_3$): δ 190.7, 151.7, 150.1, 148.0, 133.3, 132.4, 131.9, 130.2, 129.9, 129.5, 128.4, 127.4, 127.3, 127.2, 126.5, 125.4, 124.8; IR(film) cm^{-1}: 1685, 1612, 1570; UV(EtOH) nm max: 272(sh), 282(ε = 10,250 M^{-1} cm^{-1}), 289(sh), 316(sh), 338; CD(EtOH, 282 nm): negative Cotton effect at 325 nm, positive Cotton effect at 288 nm. No analysis was obtained for this compound since it was oxidized to the acid and esterified with diazomethane in the folloiwng experiment. The resulting ester was compared with authentic material, which was fully characterized.

g. (S)-3-Carbomethoxy-4-naphthylquinoline 216

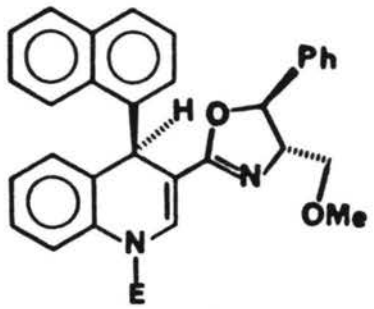


To a slurry of aldehyde 220 (0.084 g, 0.29 mmol), water (9 ml), and dioxane (1.6 ml), was added a solution consisting of $AgNO_3$ (0.100 g, 0.59 mmol) and water (1.5 ml). Upon warming in a 65°C oil bath, aqueous 40% NaOH (0.35 ml) was added. Additional 40% NaOH (0.35 ml) was added after 5 min and 10 min, as well as 2.5 hr and 3.2 hr (0.05 ml both times). On complete reaction (3.5 hr, as indicated by tlc, 10% Et_3N/EtOAc), the mixture was filtered and the solids were washed with dilute aqueous NaOH and CH_2Cl_2. The aqueous layer was acidified to pH 4 (6M aqueous H_2SO_4), and extracted with CH_2Cl_2 (3 x 40 ml). The combined organic layers were washed with brine and dried (Na_2SO_4). Filtration and concentration gave the desired acid.

Esterification with diazomethane (2.95 mmol, 10 eq) as described on p.147 gave, after purification via radial chromatography (silica, 0-15% EtOAc/hex, with one recycle), the purified ester (0.065 g, 71%). $[\alpha]_D^{22}$ -10.6° (c 1.0, $CHCl_3$). The ester was identified by NMR to the same compound which was fully characterized formed via acidic hydrolysis of the oxazolinyl biaryl and esterification (p. 147).

3. Alkylation with 1-Naphthylmagnesium Bromide

a. (4R)-Naphthyl-3-oxazolinyl-1,4-dihydroquinolines 222 and 223

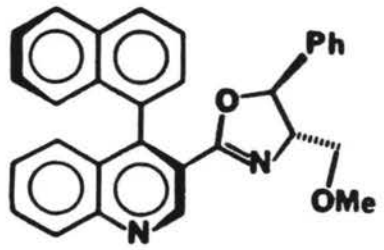


E = H 222
CO_2Me 223

To a solution of oxazolinylquinoline 211 (0.096 g, 0.30 mmol) and toluene (22.1 ml) cooled to -115°C was added dropwise, 1-naphthylmagnesium bromide (0.42 M, 1.1 ml, 0.46 mmol). The resulting yellow-brown solution was allowed to warm slowly to -105°C, and finally warmed to -85°C with stirring. After 17 hr, additional Grignard reagent (1.1 ml) was added, as well as after 43 hr (1.1 ml). Stirring was continued 5 hr, and the mixture was allowed to warm to 0°C over 5 hr. The orange solution was cooled to -78°C and stirred overnight (14 hr). On warming to room temperature, the bulk of the reaction mixture (98% by volume) was quenched by transferring, via cannula, to a graduated cylinder containing EtOH (0.3 ml). The remaining protion (<0.5 ml) was diluted with THF (0.3 ml) and 1-naphthylmagnesium bromide (0.1 ml) was added (to consume any moisture or HCl from the methyl chloroformate). The anion was quenched with methyl chloroformate (0.2 ml, stored over CaH_2). Stirring was continued for 3 hr, and urethane 223 was isolated according to the procedure on p. 145. Analysis by HPLC (reverse phase, 90% MeOH/H_2O) indicated a disastereomeric ratio of 14:86.

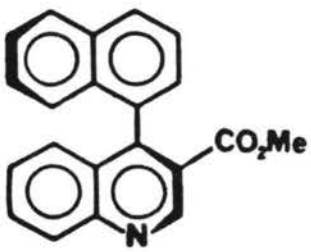
Similarly, the N-H dihydroquinoline 222 was recovered by extraction according to the procedure on p. 145.

b. (R)-4-Naphthyl-3-oxazolinylquinoline 224



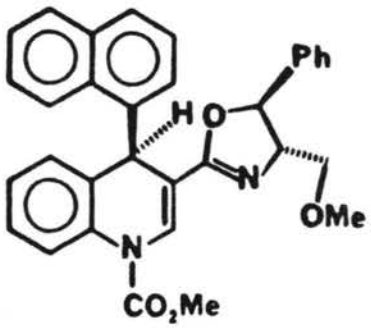
Dihydroquinoline 222 was oxidized with DDQ following the procedure for the synthesis of 215 (p. 146). Following purification, 0.106 g (79%) was recovered with a diastereomeric ratio of 12:88. ^{1}H NMR ($CDCl_3$): δ 9.56(s, 0.89H), 9.47(s, 0.11H), 8.24(br d, J=8Hz, 1H), 8.02-6.87(m, 13H), 6.71-6.34(m, 2H), 5.04(d, J=7Hz, 0.90H), 4.92(d, J=7Hz, 0.10H), 4.14-3.85(m, 1H), 3.60-3.07(m, 2H), 3.29(s, 3H); ^{13}C NMR ($CDCl_3$): 162.9, 150.4, 148.7, 146.9, 139.8, 133.6, 133.2, 131.8, 130.5, 129.5, 128.3, 128.1, 127.3, 127.1, 126.4, 125.8, 125.3, 124.6, 121.3, 83.8, 74.2, 74.0, 59.1. IR and analysis were obtained for the single diastereomer 224 (p. 156) used for X-ray analysis.

c. (R)-3-Carbomethoxy-4-naphthylquinoline 225



Oxazolinylquinoline 224 (0.106 g, 0.29 mmol) was hydrolyzed (6 hr) to the corresponding acid according to the procedure on p. 147. Esterification and purification gave 0.068 g (91%) of ester 225. $[\alpha]_D^{22}$ +9.55° (c 1.1, $CHCl_3$), identical by ^{1}H NMR to fully characterized (S)-3-carbomethoxy-4-naphthylquinoline 216 (p. 147).

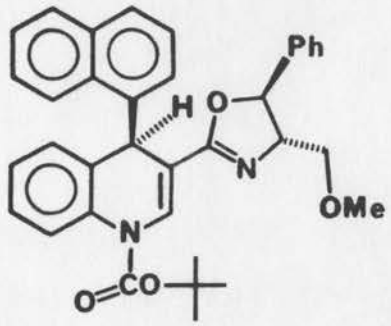
d. N-Carbomethoxy-4R-naphthyl-3-oxazolinyl-1,4-dihydroquinoline 223



Oxazolinylquinoline 211 (0.139 g, 0.44 mmol) was alkylated with 1-naphthylmagnesium bromide (0.37M, 2.4 ml, 0.88 mmol) as described on p. 152. After stirring 5 hr at -78°C, the reaction mixture was allowed to warm to room temperature (2 hr), at which time methyl chloroformate (0.14 ml, 1.76 mmol) was added. Purification by radial chromatography (silica gel, 25% THF/hex) afforded 0.131 g (59%) of the urethane. HPLC analysis (reverse phase, 90% MeOH/H_2O, 1 ml/min) indicated a diastereomeric ratio of 21:79. ^1H NMR ($CDCl_3$): δ 8.75(br d, J=8Hz, 1H), 8.35-8.05(m, 2H), 7.92-6.75(m, 14H), 6.14(s, 1H), 5.21(d, J=7Hz, 0.28H), 5.18(d, J=7Hz, 0.72H), 4.17-3.79(m, 1H), 3.93(s, 3H), 3.53-2.74(m, 2H), 3.13(s, 0.9H), 2.89(s, 2.1H); ^{13}C NMR ($CDCl_3$): δ 162.4, 152.4, 141.5, 141.0, 140.7, 140.5, 134.2, 133.9, 133.7, 131.3, 131.0, 130.8, 130.6, 128.7, 128.3, 127.7, 127.0, 126.6, 125.7, 125.6, 125.5, 125.4, 125.2, 125.0, 124.3, 120.8, 112.8, 83.3(4S, 0.21C), 83.0(4R, 0.79C), 74.8, 74.4, 74.0, 59.1(4S), 58.9(4R), 53.8, 38.2. These data were identical to the antipodal product 214 (p. 148) which was fully characterized.

4. Samples for X-Ray Analysis

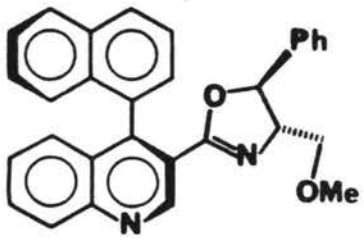
a. N-Carbo-t-butoxy-4R-naphthyl-3-oxazolinyl-1,4-dihydroquinoline 226



Following the procedure for the alkylation of oxazolinylquinoline 211 with 1-naphthylmagnesium bromide on p. 152, the desired t-butyl urethane was obtained by quenching the anion with excess di-t-butyldicarbonate (Aldrich). The products (diastereomeric urethanes and N-H dihydroquinolines) from two alkylations were combined. The major diastereomer was enriched by fractionating the band from purification via radial chromatography (silica gel, 20% EtOAc/hex). Concentration, followed by trituration with pentane, gave the solidified product. Recrystallization from pentane/CH_2Cl_2 afforded highly crystalline 26, suitable for use. Mp 148.5-151.5°C; $[\alpha]_D^{22}$ -91.4° (c 1.12, $CHCL_3$). ^1H NMR ($CDCl_3$): δ 8.74(br d, J=7Hz, 1H), 8.26-6.77(m, 16H), 6.11(s, 1H), 5.19(d, J=6Hz, 1H), 4.18-3.87(m, 1H), 3.56-2.71(m, 2H), 2.95(s, 3H), 1.64(s, 9H); ^{13}C NMR ($CDCl_3$): δ 162.6, 150.9, 141.5, 141.0, 134.7, 133.9, 132.2, 131.0, 128.7, 128.4, 127.7, 127.0, 126.4, 125.7, 125.2, 125.0, 124.5, 121.3, 112.4, 96.3, 83.7, 83.0, 75.0, 74.2, 59.0, 38.8, 28.4; IR(film) cm^{-1}: 1727, 1663, 1488, 1344, 1150, 1123.

Anal. Calcd for $C_{35}H_{34}N_2O_4$: C, 76.89; H, 6.28. Found: C, 77.04; H, 6.26.

b. (R)-4-Naphthyl-3-oxazolinylquinoline 224

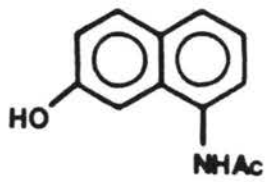


Biaryl 224 was prepared according to the procedure on p.152 to 153. Several reaction mixtures were combined and the major diastereomer was enriched by flash column chromatography (tlc silica gel, 0-20% EtOAc/hex). Concentration, followed by trituration with pentane, gave the solidified product which was recrystallized from pentane/CH_2Cl_2. Mp 203-206°C; $[\alpha]_D^{22}$ -51.3° (c 1.11, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 9.55(s, 1H), 8.36-6.29(m, 16H), 5.04(d, J=7Hz, 1H), 4.12-3.81(m, 1H), 3.54-3.03(m, 2H), 3.30(s, 3H); ^{13}C NMR ($CDCl_3$): δ 163.0, 150.5, 148.8, 146.9, 139.8, 133.7, 133.3, 131.9, 130.5, 129.5, 128.4, 128.1, 127.4, 127.2, 126.4, 125.9, 125.4, 124.7, 121.4, 83.9, 74.3, 74.1, 59.2,; IR(film) cm^{-1}: 1648, 1611, 1571, 1500, 1266, 1228.

Anal. Calcd for $C_{30}H_{24}N_2O_2$: C, 81.05; H, 5.45. Found: C, 80.84; H, 5.46.

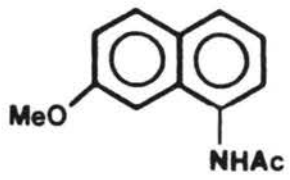
5. Hindered Rotation Experiment

a. 1-Acetylamino-7-naphthol



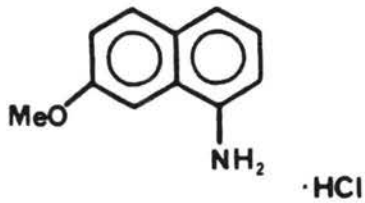
1-Acetylamino-7-naphthol was prepared from 1-amino-7-naphthol (Aldrich, sublimed and recrystallized from ethanol before use) according to the procedure by Kehrmann and Engelke.[133] Yield: 72%. Mp 167-169°C (lit.[134] 164-165°C).

b. 1-Acetylamino-7-methoxynaphthalene



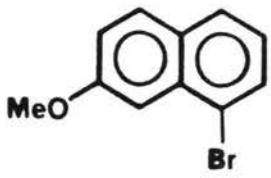
1-Acetylamino-7-naphthol (13.7 g, 68 mmol) was methylated according to the procedure by Fierz-David and coworkers.[134] The resulting product was used without purification.

c. 1-Amino-7-methoxynaphthalene·HCl



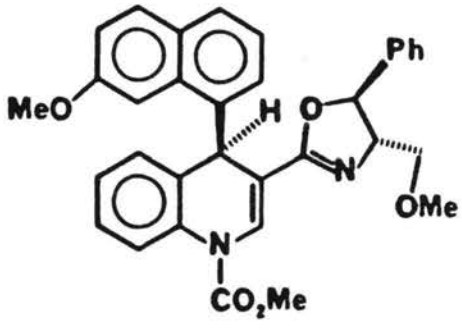
A procedure similar to a report by Fiertz-David and coworkers[134] was used. To a flask fitted with a reflux condensor was added 1-acetylamino-7-methoxynaphthalene (68 mmol theoretically) and 10% HCl (200 ml). The resulting slurry was treated with conc. HCl (57 ml) and warmed at reflux for 4 hr, until the precipitate was no longer present. Upon cooling to room temperature, concentrated HCl (37 ml) was added and the solution cooled to 0°C to precipitate the product. Filtration, washing with water, followed by drying at reduced pressure gave 9.4 g (64%) of the amine hydrochloride as a light grey solid. Mp 180-185°C (dec) (lit.[135] 185-190°C).

d. 1-Bromo-7-methoxynaphthalene



The bromide was prepared according to the procedure of LaBudde and Heidelberger,[135] except that additional 1M H_2SO_4 (100 ml total) was used. Purification gave 0.58 g (8.8%) the olive green crystalline bromide. Mp 61-63°C (lit.[136] 64-67°C).

e. N-Carbomethoxy-4-(7-methoxynaphthyl)-3-oxazolinyl-1,4-dihydroquinoline 229



A procedure similar to the report (for the preparation of 2-methoxy-naphthylmagnesium bromide) by K. Lutomski[136] was used. An apparatus consisting of a 25 ml round bottom flask fitted with magnetic stirrer bar, reflux condensor, septum, and containing magnesium turnings (0.080 g, 3.25 mmol) was flame dried while purging with argon. Upon cooling to room temperature, THF (7.4 ml) and 1-bromo-7-methoxynaphthalene (0.70 g, 2.95 mmol) were added. The reaction mixture was warmed at 42°C for 6 hr, during which time the solution became grey green in color with blackened magnesium. Stirring was continued at room temperature overnight (14 hr), and the Grignard reagent was used directly.

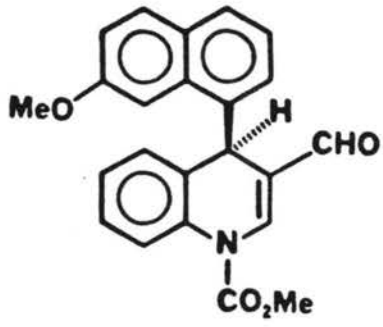
To a solution of oxazolinylquinoline 211 (0.290 g, 0.91 mmol) and benzene (50 ml) cooled to 0°C, was added dropwise 7-methoxy-1-

naphthylmagnesium bromide (theoretically 2.95 mmol). Stirring was continued for 6 hr, and the lime green solution was quenched with methyl chloroformate (0.31 ml, 4.0 mmol).

The reaction mixture was concentrated, slurried in CH_2Cl_2 (50 ml), and washed with dilute aqueous bicarbonate (3 x 50 ml) and brine. Drying (K_2CO_3) followed by filtration and concentration gave the urethane. Purification (flash chromatography on silica gel, 0-40% THF/hex) afforded 0.257 g (53%) of the desired product as a foam. The diastereomeric ratio, determined by HPLC (reverse phase, 90% MeOH/H_2O 1ml/min) was 22:78. ^1H NMR ($CDCl_3$): δ 8.38-6.79(m, 16H), 6.00(s, 1H), 5.19(br d, J=7Hz, 1H), 4.18-2.73(m, 3H), 3.98(s, 3H), 3.94(s, 3H), 3.35(s, 0.74H), 2.97(s, 2.3H); ^1H NMR (C_6D_6): δ 8.67-8.11(m, 3H), 7.70-6.54(m, 13H), 6.28(br s, 1H), 5.28(d, J=7Hz, 0.25H), 5.18(d, J=7Hz, 0.75H), 4.30-2.52(m, 3H), 3.72(br s, 3H), 3.36(br s, 3H), 3.01(s, 0.75H), 2.70(s, 2.25H); ^{13}C NMR (C_6D_6): δ 162.8, 162.6, 158.5, 158.3, 152.6, 141.8, 141.4, 141.1, 134.9, 132.8, 132.0, 131.7, 131.2, 130.3, 130.1, 129.7, 129.4, 127.6, 127.5, 126.0, 125.7, 123.9, 121.4, 118.5, 113.1, 104.1, 84.0, 83.7, 75.9, 75.3, 74.6, 58.8, 55.1, 53.6, 39.9; IR(film) cm^{-1}: 1738, 1670, 1628, 1602, 1513, 1488, 1438, 1350, 1245, 1225.

Anal. Calcd for $C_{33}H_{30}N_2O_5$: C, 74.14; H, 5.66; N, 5.24. Found: C, 73.81; H, 5.51; N, 4.94.

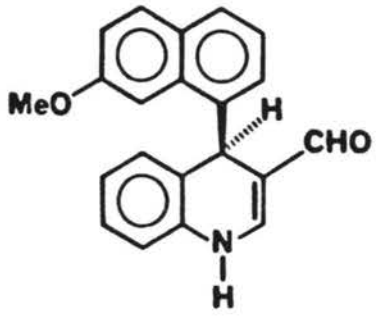
f. N-Carbomethoxy-3-formyl-4-(7-methoxynaphthyl)-1,4-dihydroquinoline 230



Dihydroquinoline 229 (0.199 g, 0.37 mmol) was quaternized with methyl fluorosulfonate (0.090 ml, 1.11 mmol, 18 hr) and reduced according to the procedure described for 218 (p. 149). Purification by radial chromatography (silica gel, 0-30% THF/hex) gave 0.128 g (92%) of the aldehyde as a foam. $[\alpha]_D$ -28.0° (c 0.3, C_6H_6). ^1H NMR ($CDCl_3$): δ 9.42(s, 1H), 8.35-7.83(m, 3H), 7.80-7.45(m, 2H), 7.38-6.85(m, 6H), 5.85(s, 1H), 4.04(s, 3H), 4.02(s, 3H); ^1H NMR (C_6D_6): δ 9.05(s, 1H), 8.50-8.30(m, 1H), 8.22(d, J=2Hz, 1H), 7.60-6.58(m, 9H), 5.93(s, 1H), 3.82(s, 3H), 3.34(s, 3H); ^{13}C NMR (C_6D_6): δ 188.6, 158.7, 152.0, 142.7, 140.0, 135.2, 132.7, 131.0, 130.5, 130.1, 130.0, 127.7, 127.5, 127.2, 126.5, 126.0, 123.6, 120.9, 118.9, 103.5, 55.3, 53.8, 37.4; IR(film) cm^{-1}: 1747, 1678, 1652, 1626, 1488, 1438, 1338, 1245, 1222; MS (70 ev), m/e (% R.I.): 373(21), 313(100), 281(58), 270(68), 254(35), 253(39), 216(35).

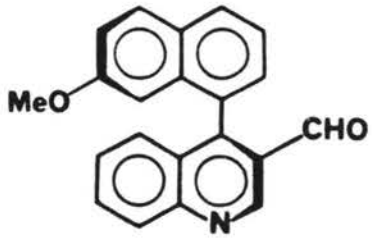
Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13. Found: C, 73.20; H, 5.21.

g. 3-Formyl-4-(7-methoxynaphthyl)-1,4-dihydroquinoline 231



Urethane 230 (0.100 g, 0.27 mmol) was hydrolyzed according to the procedure on p. 150. The resulting N-H dihydroquinoline was oxidized without purification. ^{1}H NMR ($CDCl_3$): δ 8.90(br s, 1H), 8.41(br s, 1H), 7.93-6.37(m, 11H), 5.89(br s, 1H), 3.80(br s, 3H); ^{13}C NMR ($CDCl_3$): δ 188.2, 157.5, 146.5, 142.6, 134.7, 131.7, 130.1, 129.4, 128.6, 127.9, 127.6, 127.1, 126.7, 126.1, 124.1, 123.2, 117.7, 115.9, 115.7, 102.9, 55.1, 37.2; IR(film) cm^{-1}: 3260, 1625, 1605, 1585, 1510, 1485, 1250. No analysis was performed on this compound due to instability, it was immediately subjected to the oxidation step.

h. (R)-3-Formyl-4-(7-methxoynaphthyl)quinoline 232

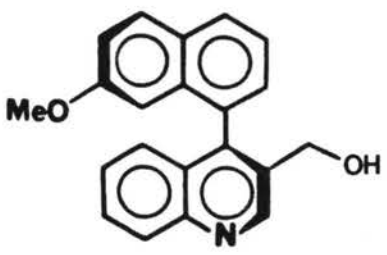


The N-H dihydroquinoline 231 (0.27 mmol) was subjected to oxidation by DDQ as described in p. 146. Purification by radial chromatography (silica gel, 30% THF,hex) afforded 0.065 g (78%) of the desired product as a foam. $[\alpha]_D$ +78.2 (0.11, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.75(s, 1H), 9.52(s, 1H), 8.25(br d, J=8.5Hz, 1H), 8.10-7.70(m, 3H), 7.62-7.36(m, 4H), 7.19(dd, J=9Hz, J=2Hz, 1H), 6.41(d, J=2Hz, 1H), 3.51(s, 3H); ^{1}H NMR (C_6D_6): δ 9.79(br s, 2H), 8.38-8.17(m, 1H), 7.77-6.78(m, 8H), 6.51(d, J=2Hz, 1H), 2.88(s, 3H); ^{13}C NMR (C_6D_6): 190.4, 159.2, 151.7, 150.9, 148.6, 134.1, 132.0, 130.6, 130.4, 129.4,

129.2, 127.6, 127.5, 126.8, 122.9, 119.9, 103.9, 54.7; IR(film) cm^{-1}: 2835, 1691, 1626, 1575, 1500, 1268(sh), 1260, 1235; UV (EtOH) nm max: 277, 287(ε = 10,250 M^{-1} cm^{-1}), 317, 333; CD (EtOH, 282 nm): positive Cotton effect at 327 nm(br), negative Cotton effect at 284 nm(br).

Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.82; N, 4.47. Found: C, 79.95; H, 4.70; N, 4.46.

i. Reduction of Aldehyde 232



A solution of aldehyde 232 (5.8 mg, 0.018 mmol), THF (1 ml) and absolute EtOH (0.2 ml) was cooled to 0°C. Sodium borohydride (1.7 mg, 0.045 mmol) was added and the solution stirred for 30 min. The reaction was quenched with sat. aqueous ammonium chloride (1 ml) and further diluted with CH_2Cl_2 (3 ml) and ether (3 ml). The layers were separated and the organic layer was washed with brine and dried (K_2CO_3). Purification by ptlc (0.25 mm silica gel, ether) afforded, after trituration with pentane, 3.6 mg (62%, R_f = 0.25) of the desired alcohol. ^1H NMR ($CDCl_3$): δ 9.21(br s, 1H), 8.19(br d, J=9Hz, 1H), 8.06-7.02(m, 8H), 6.39(d, J=2Hz, 1H), 5.54(s, 2H), 3.50(s, 3H), 1.85(br s, 1H). The alcohol was immediately esterified.

j. Preparation of Mosher Ester 233

To a solution of the above alcohol (3.6 mg, 0.011 mmol) and dry CH_2Cl_2 (1 ml) was added 4-(dimethylamino)pyridine (0.2 mg) and

(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl[83] chloride (0.017 ml). Stirring was continued at room temperature for 1 hr, and Et_3N (0.020 ml, 1.43 mmol) was added over the next 4 hr. The reaction was complete (by tlc, 50% THF/hex) after an additional 5 min and was quenched with water (1 drop) and sat. bicarbonate (1 drop). The mixture was stored in the refrigerator (-10°C) overnight. Drying (Na_2SO_4, K_2CO_3), followed by filtration and concentration gave the Mosher ester which was immediately analyzed by NMR without purification.

^1H NMR ($CDCl_3$, 200 MHz): Diastereotopic protons were detected at δ9.08 and δ 9.05 with relative areas of 27:73 respectively.

^{19}F NMR ($CDCl_3$, 188 MHz): Diastereotopic fluorine signals were detected at δ-63.7 and δ-63.8 (0.00 ppm set with a standard of $CFCl_3$ in CH_2Cl_2) with relative areas of 25:75 (respectively.

The ester was repurified (ptlc, 0.25 mm silica gel, 50% THF/hex) for reporting of entire proton spectrum. ^1H NMR ($CDCl_3$, 270 MHz): 9.07(s, 0.27H), 9.04(s, 0.73H), 8.20(d, J=8Hz, 1H), 7.99-7.82(m, 2H), 7.77-7.65(m, 1H), 7.52-7.00(m, 10H), 6.31(d, J=2Hz, 1H), 5.43-4.98(m, 2H), 3.53-3.17(m, 6H); IR(film) cm^{-1}: 1750, 1740(sh), 1626.

k. N-H Dihydroquinoline 231 for the NMR Experiment

Urethane230 (0.011 g, 0.03 mmol) was cleaved according to the procedure described for the cleavage of urethane218 (p. 150). Following extractive isolation the N-H dihydroquinoline was used directly for the NMR experiment. The sample was dissolved in $CDCl_3$ (0.7 ml) and spectra were taken at room temperature and at 5 to 10° increments down to -70°C. Upon warming to room temperature, the

spectrum returned to its original form, ie., sharp lines, indicating total reversibility and free rotation.

6. Organometallic Experiments

a. 1-Naphthmagnesium Bromide - Triethylamine Complex

A procedure similar to the report by Ashby and Reed[138] was followed. A 3-necked flask was fitted with a pressure equalizing addition funnel, magnetic stirrer bar, septum, and reflux condensor. Magnesium shot (0.41 g, 16.9 mmol, Ventron) was added and the entire apparatus was flame dried while purging with argon. Upon cooling to room temperature, benzene (2 ml) and triethylamine (2.0 ml, 14.4 mmol) were added to the flask. The addition funnel was charged with 1-bromonaphthalene (2.0 ml, 14.4 mmol) and benzene (16 ml). A portion of the bromide-benzene solution (2 ml) was added. The reaction was initiated by addition of activated magnesium turnings (0.1 g, activated in a solution of THF and 1,2-dibromoethane) while warming at 45-50°C. The remainder of the bromide solution was added dropwise, during which time the reaction became cloudy dark brown. Addition of toluene (3 ml) improved the solubility slightly. Heating was continued overnight (14 hr). The resulting mixture contained a yellow-green suspension which was not dissolved upon addition of toluene (3 ml).

The Grignard reagent was titrated according to the procedure of Watson and Eastham[117] using s-butanol in THF. The endpoint observed was not sharp (plum to light plum in color) however, an approximate concentration was calculated. (The resulting concentration (0.25M) indicated that the formation could have been incomplete, suggesting that heating should have been continued an additional 12-24 hr).

b. General Alkylation Procedure (Inverse Addition)

To a solution of oxazolinylquinoline 211 (0.103 g, 0.32 mmol) and toluene (31 ml) cooled to -78°C was added dropwise 1-naphthylmagnesium bromide (0.65M, 1.49 ml, 0.97 mmol). Stirring was continued for 4h at -78°C followed by slow warming to -10°C, at which time no starting material could be detected (tlc, 50% THF/hex). For several examples, the reaction mixtures were allowed to warm to room temperature and stirring was continued for up to 3 days before quenching. The reaction was quenched with 95% EtOH (0.5 ml), concentrated, and slurried in CH_2Cl_2 (40 ml). The organic layer was washed with dilute aqueous bicarbonate (3 x 40 ml), brine, and dried (K_2CO_3). Filtration and concentration gave the N-H dihydroquinoline for oxidation.

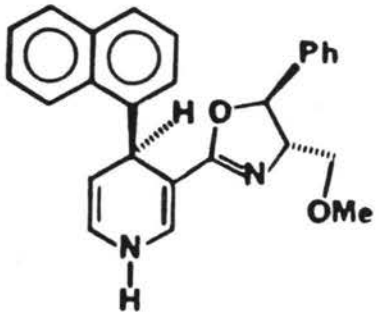
The oxidation and purification procedures were as described for the synthesis of naphthylquinoline 215 (p. 146), affording 0.129 g (91%) of the biaryl 224. The diastereomeric ratio was found to be 8:92 by HPLC (reverse phase, 82% MeOH/H_2O, 1 ml/min).

c. Normal Addition

All of the reaction conditions remained unchanged except for the mode of addition. To 1-naphthylmagnesium bromide (0.65M, 1.50 ml, 1.02 mmol) cooled to -78°C, was added via cannula, a solution (precooled to -78°C) of oxazolinylquinoline 211 (0.109 g, 0.34 mmol) and toluene (30 ml). The resulting mixture was stirred for 4 hr at -78°C, allowed to warm to room temperature overnight (12 hr) and quenched with 95% EtOH (0.5 ml). Following extractive isolation of the N-H dihydroquinoline, oxidation, and purification (as described for the inverse addition procedure, p. 165) gave 0.143 g (95%) of the naphthylquinoline 224.

The diastereomeric ratio was found to be 8:92 by HPLC (reverse phase, 82% MeOH/H_2O, 1 ml/min).

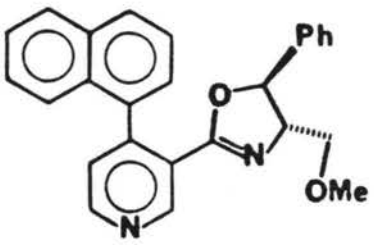
d. (4R)-Naphthyl-3-oxazolinyl-1,4-dihydropyridine 243 (in Benzene)



To a solution of oxazolinylpyridine 175 (0.131 g, 0.49 mmol) and benzene (50 ml) cooled to 0°C, was added dropwise 1-naphthylmagnesium bromide (0.6M, 1.63 ml, 0.98 mmol). The resulting lime green solution was allowed to warm slowly to room temperature over 2 hr. Upon complete reaction (tlc, 50% THF/hex), 95% EtOH (0.5 ml) was added. The 4-naphthyldihydropyridine was isolated by extraction as described for dihydroquinoline 213 (p. 145). Due to inherent instability, the dihydropyridine was analyzed by NMR without purification.

^1H NMR ($CDCl_3$, 270 MHz): Close inspection of the spectrum indicated diastereotopic proton signals at δ 3.18 and δ 2.98 with relative areas of 20:80 respectively. IR(film) cm^{-1}: 3422, 1673, 1616, 1593, 1573. The compound was oxidized to the corresponding naphthylpyridine for complete characterization.

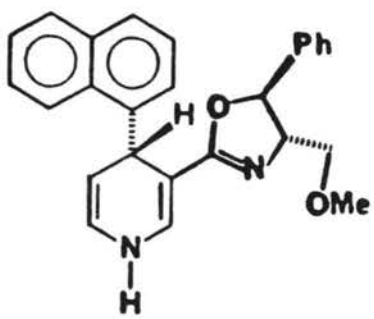
e. 4-Naphthyl-3-oxazolinylpyridine 244



Dihydropyridine 243 (0.49 mmol) was oxidized according to the procdure on p. 146. Extraction and purification (ptlc, ether) afforded 0.172 g (89%) of the naphthylpyridine as a foam. ^{1}H NMR ($CDCl_3$): δ 9.23(br s, 1H), 8.75(br d, J=5Hz, 1H), 7.97-7.70(m, 2H), 7.63-6.90(m, 9H), 6.83-6.48(m, 2H), 5.03(d, J=7Hz, 0.54H), 4.81(d, J=7Hz, 0.46H), 4.13-3.77(m, 1H), 3.57-2.90(m, 2H), 3.26(s, 1.4H), 3.21(s, 1.6H); ^{13}C NMR ($CDCl_3$): δ 162.6, 162.4, 151.3, 151.0, 150.4, 148.1, 139.6, 136.3, 136.1, 133.1, 130.8, 128.3, 128.1, 127.5, 126.3, 126.2, 126.0, 125.8, 125.6, 125.2, 124.8, 83.9, 74.5, 74.3, 74.0, 73.6, 59.0; IR(film) cm^{-1}: 1650, 1586, 1260.

Anal. Calcd for $C_{26}H_{22}N_2O_2$: C, 79.17, H, 5.62. Found: C, 78.90, H, 5.77.

f. (4S)-Naphthyl-3-oxazolinyl-1,4-dihydropyridine 242 (in Dimethoxyethane)



To a solution of oxazolinylpyridine 175 (0.031 g, 0.12 mmol) and dry DME (12 ml) cooled to -78°C was added dropwise 1-naphthylmagnesium bromide (0.70M, 0.50 ml, 0.25 mmol). The reaction mixture was allowed to warm slowly to room temperature overnight (10 hr). Upon quenching with 95%

EtOH (0.5 ml), the dihydropyridine was isolated by extraction as described for dihydroquinoline 213 (p. 145). The products were analyzed by NMR without purification, due to instability.

^{1}H NMR ($CDCl_3$): Close inspection of the spectrum indicated diastereotopic proton signals at δ3.18 and δ3.00 with relative areas of 90:10 respectively. The product was oxidized to the corresponding naphthylpyridine for characterization.

g. 4-Naphthyl-3-oxazolinylpyridine 244

4-Naphthyldihydropyridine 243 (0.12 mmol) was oxidized according to the procedure for the synthesis of naphthylquinoline 215 (p. 146). Purification by ptlc (50% THF/hex, eluted 3x) afforded 0.101 g (86%) of naphthylpyridine 244, identical by ^{1}H NMR to authentic material derived from the oxidation of dihydropyridine 242 (p. 167). Thus, no elemental analysis was obtained.

7. Anionic Oxidations

a. Lithium Diisopropylamide

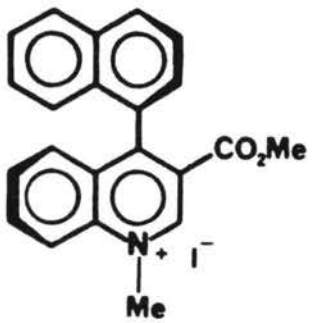
To a flame dried 3-necked flask fitted with magnetic stirrer bar, septum, and argon inlet was added THF (15 ml) and diisopropylamine (0.70 ml, 5.0 mmol). The solution was cooled to -78°C, at which time n-butyllithium (2.27M, 2.1 ml, 4.77 mmol) was added. The ice bath was removed and the flask allowed to warm to 25°C for 15 min. The mixture was cooled back to -78°C and was ready for use.

b. General Procedure for Oxidation of the Anionic Dihydroquinlines

To a 0.01-0.03M solution of the N-H dihydroquinoline 213 in toluene cooled to -78°C, was added methyllithium (1.2-2.0 eq). Stirring was continued for 15 min at which time DDQ (1.1 eq) was added. The resulting mixture was allowed to warm slowly to room temperature overnight (14 hr). The oxidized products were isolated, purified, and analyzed according to the procedure for 215 (p. 146).

8. Conservation of Chirality ($sp^2 \rightarrow sp^3$)

a. (S)-N-Methyl-3-carbomethoxy-4-naphthylquinolinium Iodide 246



To a flame dried 10 ml round bottomed blask fitted with magnetic stirrer bar, condensor, and septum was added methyl iodide (5 ml) and naphthylquinoline 216 (0.153 g, 0.49 mmol, 70% ee). The mixture was heated in a 40°C oil bath for 28 hr, during which time a precipitate formed. Upon concentration, the methiodide was slurried in ether and filtered. The yellow precipitate was washed with dry ether (50 ml). Residual solvent was removed under reduced presure to afford 0.192 g (86%) of the desired quaternary salt. Mp 155-158°C (dec); $[\alpha]_D$ +20.6° (c 0.34, $CHCl_3$). ^1H NMR (d_6 DMSO): 10.14(s, 1H), 8.70(br d, J=9Hz, 1H), 8.50-7.03(m, 10H),4.84(s, 3H), 3.89(s, 3H); ^{13}C NMR (d_6 DMSO): δ 162.1, 157.7, 150.3, 138.9, 136.7, 132.4, 131.0, 130.7, 129.4, 129.1, 128.2, 126.8, 126.2, 125.0, 124.7, 124.4, 119.5, 52.9, 45.6; IR(DMSO film) cm^{-1}: 2255, 1750, 1710.

Anal. Calcd for $C_{22}H_{18}NO_2I$: C, 58.00; H, 4.00. Found: C, 58.74; H, 4.01.

The methiodide (0.030 g, 0.07 mmol) was dissolved in absolute EtOH (15 ml) and precipitated as the perchlorate salt with sodium perchlorate (0.020 g, 0.16 mmol, 2 ml EtOH). Recrystallization from absolute EtOH gave light green crystals which may have crystallized with 1 eq EtOH. Mp 286-288°C (dec).

Anal. Calcd for $C_{24}H_{24}ClNO$: C, 60.82; H, 5.11. Found: C, 60.49; H, 3.99.

b. Electrolysis Experiment

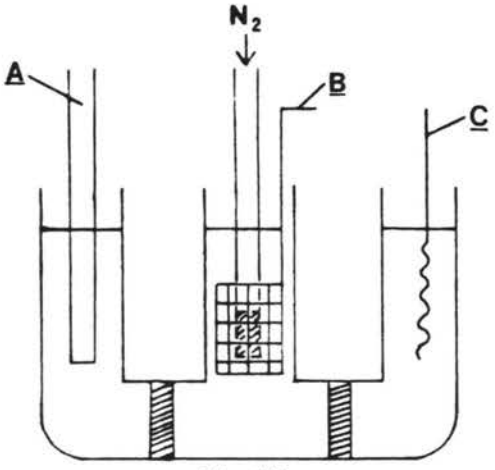


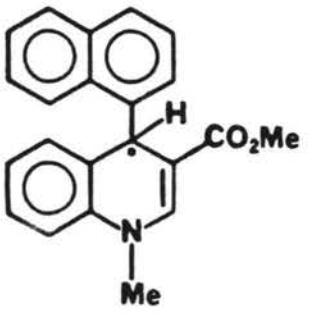
Fig. 14

A: Standard. Calomal Electrode (SCE) (reference)

B: Pt mesh working electrode (cathode)

C: Pt wire auxiliary electrode (anode)

c. 3-Carbomethoxy-N-methyl-4-naphthyl-1,4-dihydroquinoline 247



All fittings shown in figure 14 (except SCE) were thoroughly dried at 110° before use.

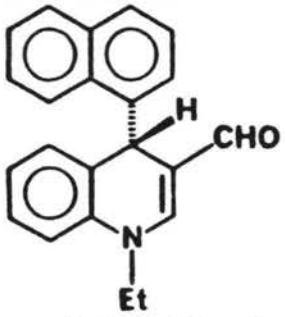
To the 3-compartment cell was added a solution of dry DMF and Bu_4NPF_6 (0.1 M). The working electrode compartment (with a volume of 8 ml) was deoxygenated by purging with nitrogen for several minutes at which time methiodide 246 (0.025 g, 0.05 mmol) and phenol (0.015 g, 0.11 mmol) were added to form a yellow solution. Stepping the working electrode potential from 0.0V to -2.1V vs SCE (Model 173 Potentiostate/Galvanostat, Princeton Applied Research) began the reduction process. The nitrogen purge was continued so as to mix the solution and maintain an oxygen-free mixture. As the reaction proceeded, the solution became dark orange in color. The electrolysis was stopped at 15.3 coulombs (10.6 coulombs theoretical) at which time the reduction current had fallen to nearly zero.

The DMF solution was poured into water (50 ml), and the products extracted with ether (3 x 30 ml). The combined organic layers were washed with water (2 x 30 ml) and brine. Drying (K_2CO_3), filtration, and concentration at room temperature gave the product mixture. Purification by column chromatography (neutral alumina, pentane to ether to CH_2Cl_2) afforded 0.004 g (23%) of the desired 1,4-dihydroquinoline 247 as a light green foam. $[\alpha]_D$ 0.00° (c 0.4, $CDCl_3$).

^{1}H NMR ($CDCl_3$): δ 8.60(br d, J=8Hz, 1H), 7.95-7.58(m, 11H), 6.06(s, 1H), 3.48(s, 3H), 3.42(s, 3H).

9. A Possible Extension of this Chemistry

a. 3-Formyl-N-ethyl-4S-naphthyl-1,4-dihydroquinoline



Urethane 218 (0.069 g, 0.20 mmol) was cleaved to the N-H dihydroquinoline 219 by the procedure described on p. 150.

To a flame dried 25 ml round bottomed flask was added the unpurified dihydroquinoline 219 as a dry CH_2Cl_2 solution (10 ml). Upon careful concentration, the flask was fitted with a magnetic stirrer bar, septum, and flushed with argon. THF (4 ml) was added and the solution was cooled to -78°C. Freshly prepared lithium diisopropylamide (0.27M in THF, 1.12 ml, 0.30 mmol) was added dropwise and the flask allowed to warm slowly to 0°C (2 hr). The resulting clear light brown solution was cooled to -15°C, and the temperature maintained between -10° to -15°C an additional 0.75 hr. On cooling to -78°C, the red-brown anion was treated with a freshly prepared stock solution of triethyloxonium tetrafluoroborate (~0.8M, 0.42 ml, 0.33 mmol). (Prepared from Et_3OBF_4 (0.547 g, 2.50 mmol) and dry CH_2Cl_2 (3 ml)). A granular precipitate formed, which gradually dissolved upon slow warming of the reaction mixture to room temperature (1.5 hr).

The mixture was concentrated at room temperature and slurried in ether (40 ml) and CH_2Cl_2, a sufficient amount to completely dissolve the products. The organic layer was washed with 5% aqueous ammonium

chloride (3 x 40 ml) and brine. Drying (K_2CO_3), filtration, and concentration gave the crude product as a dark red oil. Purification by flash column chromatography (neutral alumina, pentane followed by CH_2Cl_2) afforded 0.038 g (59%) of the viscous light yellow oil. (The crude product may be prepurified by elution through a small plug of florasil with 50% THF/hex). R_f (silica gel, 50% THF/hex) was 0.35. $[\alpha]_D$ -32.9° (c 0.17, EtOH). ^1H NMR ($CDCl_3$): δ 9.13(s, 1H), 8.57(br d, J=8Hz, 1H), 8.23-6.40(m, 11H), 6.01(s, 1H), 4.17-3.59(m, 2H), 1.51(t, J=7Hz, 3H); ^1H NMR (C_6D_6): δ 9.16(s, 1H), 8.79(br d, J=8Hz, 1H), 7.79-6.06(m, 12H), 3.27-2.59(m, 2H), 0.81(t, J=7Hz, 3H); ^{13}C NMR (C_6D_6): 186.7, 148.3, 145.4, 136.2, 134.5, 131.4, 131.0, 128.3, 127.5, 127.3, 126.2, 125.8, 125.6, 124.9, 124.0, 117.5, 113.3, 46.0, 37.2, 13.5; IR(film) cm^{-1}: 1626, 1620; UV (EtOH) nm max: 223, 287, 352; MS (70 ev) m/e (% R.I.): 313(19), 283(62), 282(61), 255(37), 254(81), 253(27), 186(100); the calculated molecular weight was 313.42 g mol^{-1}.

Anal. A satisfactory analysis on this compound could not be obtained due to instability.

CHAPTER IV

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CHAPTER V

APPENDIX

A. X-Ray Structure Determination of (R)-226

A crystal of compound (R)-226 ($C_{35}H_{34}N_2O_4$) was centered on the Nicolet R3m/E diffractometer at -130°C. The compound crystallized in the space group $P2_1$, with a = 10.751(3) Å, b = 9.264(3) Å, c = 14.611(3) Å, β = 101.39(2)°, and Z = 2. A unique data set containing 2143 observed ($I > 2\alpha(I)$) reflections was collected using $\theta/2\theta$ scans ($4.0° < 2\theta < 50°$) and MoK_α radiation. Least squares refinement of the structural model (anisotropic thermal parameters for non-hydrogen atoms and hydrogen atoms in idealized positions) converged at R = 0.091, R_w = 0.096, and GOF = 2.97. These relatively high residual indices are at least partly due to the considerable librational motion of the atoms of the phenyl ring attached to the oxazoline ring. Table 14 contains final atomic coordinates and equivalent isotropic thermal parameters.

Table 14

(Atom Coordinates ($x10^4$) and Temperature Factors ($\mathring{A}^2 \times 10^3$))

Atom	X	Y	Z	U
N(2)	970(b)	7873(8)	1145(5)	32(2)*
C(2)	1513(7)	8919(9)	623(6)	26(3)*
C(3)	2983(8)	8595(9)	826(6)	27(3)*
O(4)	3062(5)	7451(7)	1541(4)	31(2)*
C(5)	1880(7)	7154(10)	1606(6)	30(3)*
C(6)	1453(7)	3241(9)	3062(5)	23(2)*
C(7)	357(7)	3950(9)	2597(6)	26(3)
C(8)	-777(8)	3189(10)	2401(6)	29(3)*
C(9)	-838(9)	1748(10)	2602(7)	40(3)*
C(10)	246(8)	1045(10)	3049(6)	30(3)*
C(11)	1360(8)	1765(9)	3269(5)	25(3)*
C(12)	1710(7)	5941(9)	2247(6)	24(3)*
C(13)	397(8)	5533(9)	2338(6)	29(3)*
C(14)	2740(7)	5226(9)	2697(6)	26(3)*
N(1)	2645(6)	3986(7)	3217(4)	25(2)*
C(16)	3701(7)	3486(9)	3888(5)	24(2)*
O(2)	4732(5)	4183(6)	3798(4)	28(2)*
O(1)	3604(5)	2589(7)	4457(4)	34(2)*
C(17)	6016(8)	3838(10)	5394(6)	38(3)*
C(18)	5996(7)	3716(9)	4368(6)	26(3)*
C(19)	6899(8)	4772(10)	4031(8)	37(3)*
C(22)	1847(10)	12794(11)	469(7)	45(4)*

Table 14 (Continued)

Atom	X	Y	Z	U
C(4)	1211(9)	10447(11)	797(7)	41(3)*
C(25)	-89(8)	6485(10)	3038(6)	28(3)*
C(26)	617(7)	6681(9)	3934(6)	29(3)*
C(27)	214(7)	7473(10)	4612(6)	30(3)*
C(28)	-965(8)	8058(10)	4462(6)	29(3)*
C(29)	-1747(7)	7928(9)	3558(6)	25(2)*
C(30)	-2996(8)	8490(9)	3400(6)	29(3)*
C(31)	-3802(8)	8290(11)	2548(7)	41(3)*
C(32)	-3395(8)	7506(12)	1845(7)	46(3)*
C(33)	-2204(9)	6971(11)	1969(6)	37(3)*
C(34)	-1356(7)	7105(9)	2860(6)	26(2)*
O(3)	1833(6)	11337(7)	244(4)	43(2)*
C(39)	6266(8)	2180(9)	4083(7)	30(3)*
C(36)	4108(11)	9208(18)	-419(9)	72(5)*
C(37)	4601(17)	8764(37)	-1223(18)	131(12)*
C(38)	4621(20)	7475(45)	-1467(12)	129(12)*
C(20)	3518(8)	8153(11)	17(6)	36(3)*
C(21)	3985(14)	6338(28)	-1092(15)	118(9)*
C(35)	3455(12)	6738(15)	-298(10)	80(5)*

*Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

B. X-Ray Structure Determination of (R)-224

A crystal of compound (R)-224 ($C_{30}H_{24}N_2O_2$) was centered on the Nicolet R3m/E diffractometer at -130°C. The compound crystallized in the space group $P2_12_12_1$, with a = 9.470(3) Å, b = 13.909(4) Å, c = 17.366(5) Å, and Z = 4. A unique data set containing 2326 observed ($I > 2\alpha(I)$) reflections was collected using $\theta/2\theta$ scans ($3.5^\circ < 2\theta < 50^\circ$) and MoK_α radiation. Least squares refinement of the structural model (which included anisotropic thermal parameters for all non-hydrogen atoms and hydrogen atoms in idealized positions) converged at R = 0.045, R_w = 0.042, and GOF = 1.04. Table 15 contains final atomic coordinates and equivalent isotropic thermal parameters.

Table 15

(Atom Coordinates ($\times 10^4$) and Temperature Factors ($\mathring{A}^2 \times 10^3$))

Atom	X	Y	Z	U
C(1)	7068(4)	1902(3)	1521(2)	34(1)*
C(2)	6413(3)	1034(3)	1517(2)	32(1)*
C(3)	4954(3)	949(2)	1678(2)	23(1)*
C(4)	4253(4)	47(2)	1685(2)	28(1)*
C(5)	2843(4)	-4(2)	1844(2)	28(1)*
C(6)	2062(3)	831(2)	1989(2)	24(1)*
C(7)	2690(3)	1722(2)	1995(2)	19(1)*
C(8)	4171(3)	1802(2)	1851(2)	19(1)*
C(9)	4898(3)	2695(2)	1866(2)	23(1)*
C(10)	6313(4)	2744(3)	1706(2)	32(1)*
C(11)	1837(3)	2607(2)	2142(2)	20(1)*
C(12)	1002(3)	3016(2)	1542(2)	21(1)*
C(13)	861(3)	2595(2)	804(2)	23(1)*
C(15)	-685(4)	3873(2)	408(2)	32(1)*
C(16)	-572(3)	4310(2)	1107(2)	30(1)*
C(17)	276(3)	3887(2)	1688(2)	22(1)*
N(2)	356(3)	4365(2)	2381(2)	27(1)*
C(19)	1114(3)	3961(2)	2920(2)	24(1)*
C(20)	1871(3)	3081(2)	2839(2)	20(1)*
C(21)	2638(3)	2748(2)	3529(2)	20(1)*
N(1)	3357(3)	3297(2)	3953(1)	24(1)*
O(2)	2513(2)	1801(1)	3716(1)	25(1)*

Table 15 (Continued)

Atom	X	Y	X	U
C(24)	3224(3)	1692(2)	4457(2)	23(1)*
C(25)	4276(3)	885(2)	4433(2)	22(1)*
C(26)	5075(4)	709(2)	3779(2)	25(1)*
C(27)	6148(4)	26(2)	3792(2)	32(1)*
C(28)	6408(4)	-492(2)	4466(2)	33(1)*
C(30)	4531(4)	353(2)	5095(2)	27(1)*
C(31)	3872(3)	2704(2)	4595(2)	23(1)*
C(32)	3457(4)	3152(2)	5351(2)	30(1)*
O(1)	3929(3)	2532(2)	5952(1)	33(1)*
C(34)	3513(4)	2881(3)	6688(2)	41(1)*
C(14)	24(3)	3010(2)	253(2)	29(1)*
C(29)	5591(4)	-324(2)	5109(2)	32(1)*

*Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.