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Chiral Oxazolines and Their Legacy in Asymmetric Carbon−Carbon Bond-Forming Reactions*

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The studies performed with chiral oxazolines as vehicles for a number of C−C bond-forming reactions are traced back to the early 1970s. The main source of chirality in these studies was derived from chiral, nonracemic amino alcohols which, themselves, were prepared from amino acids. The formation of chiral oxazolines from these materials provided interesting and useful starting materials for these studies.The factors responsible for high optical yields during that era were attributed to rigidity or precomplexation of the reactants, thus providing a more well-defined topography during the reaction course. A number of C−C bond reaction types are described including alkylations, additions, and organometallic reactions. The ee's of many of the products arrived at are well above 90%. This level of ee was virtually unprecedented in the early to mid 1970s. In addition to the synthetic emphasis, several mechanistic questions, arising in other areas, were also undertaken due to the accessibility of the appropriate requisite chiral materials.

Introduction and Some Historical Perspective

The formation of C−C bonds—the basic building blocks of molecules—is the most important chemical process in the chemical sciences. This is also true for the biological and material sciences. If one agrees with this premise, then it follows that *asymmetric* C−C bond formation is even more important. That is, the formation of a C−C bond with simultaneous creation of absolute stereochemistry. Today, we reap the rewards from the efforts of so many organic chemists who have opened these routes to form virtually every type of asymmetric C−C bond.

However, this was not always so. Until the early 1970s, there were almost no useful asymmetric C−C bond-forming methods leading to enantiomerically pure compounds, and the field of "asymmetric reactions" was relegated mainly to mechanistic studies.

In this paper, the reader will be exposed to some early studies which paved the way for many of today's asymmetric C−C bond formations. One of these studies was performed in the author's laboratory at Colorado State University between 1972 and 1975 and centered around a simple heterocycle namely the oxazoline, **1**. If either of the 4- and 5-carbon positions contain a substituent then the molecule is potentially a chiral nonracemic oxazoline. It is the chemistry surrounding this small molecule, first appearing in the chemical literature in 1884, that is the subject of this report.

1, R = alkyl, aryl

1

Early attempts to reach enantiomerically pure compounds go back to Emil Fischer in 1894 and othrs between 1900 and 1933. There were extensive controversies over this subject, which is outside the scope of this report. However, we would be remiss in not mentioning the extraordinary efforts of Markwald, Mackenzie, Prelog, Cram, Horeau, Mosher, Doering, Yamada, Walborsky, Berson, Mislow, and Wynberg, who, before 1960, were the true "fortrekkers" that bore the fruits we enjoy today from asymmetric syntheses. Their efforts as well as many early studies and controversies are described in the excellent monograph by Mosher and Morrison[1] published in 1971.

Beginning in the 1960s and 1970s, there were remarkable advances in asymmetric reductions of olefins, namely stereoselective C−H bond-forming reactions,[2−4] as well as C=N reductions to chiral amino acids.[5]

In 1967−1970, we began a study on the general use of heterocycles as useful vehicles in a variety of C−C bond-forming reactions (Scheme 1). We felt strongly that there may be a wealth of information both in the literature and also to be obtained by experiment which would bear this

* This article is dedicated to the memory of Kenji Koga (Tokyo), Wolfgang Oppolzer (Geneva), and Ulrich Schoellkopf (Gottingen) who were among the early pioneers in the renaissance of asymmetric syntheses.

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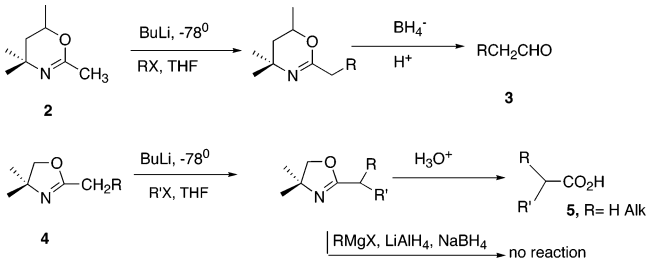

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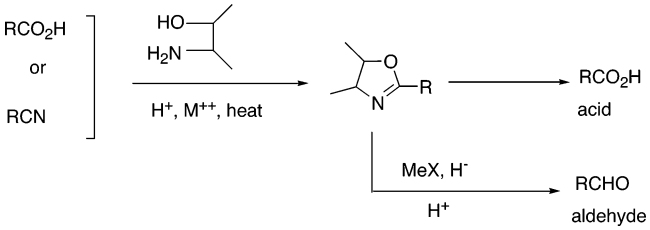


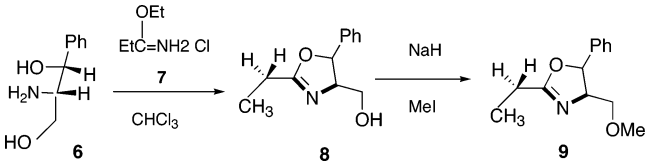
out.[6] We first looked at dihydro-1,3-oxazines **2** as a potential functionalized carbanion which led to an efficient route to a variety of aldehydes **3** by a two-carbon extension of alkyl halides.[7]

We also studied the analogous five-membered ring system, oxazolines **4**, and found that they, too, could act as functionalized carbanions and lead to a number of α,α-disubstitued carboxylic acids **5**.[8] In addition it was also observed that the oxazoline ring **4** was completely inert to hydride reagents, unlike its oxazine analogue above, as well as Grignard reagents, making it a new and versatile protecting group[9] for carboxylic acids.

Based on the above results, namely that functionalized carbanions derived from **2** and **4** can be efficiently generated and alkylated to produce racemic products in good yields, we turned to the chiral variant of these systems. In the hope that alkylation of a chiral, nonracemic oxazoline might also produce a chiral, nonracemic α,α-disubstituted carboxylic acid such as **5**, we searched for a facile route to chiral oxazolines. Since the synthesis of 2-oxazolines had been known since 1884, we were able to find a number of routes to this system, most of which involved 2-amino alcohols and carboxylic acid derivatives (Scheme 2). From these early studies we found, or have written, seven reviews on oxazolines between 1949 and 2004,[10] which attests to their extensively rich chemistry. It is interesting that the early reviews on oxazolines (1949, 1966, 1971) focused mainly on their preparation, polymerization, and spectroscopic properties. Hardly any mention was made that they were nascent aldehydes or carboxylic acids.

One of the earliest experiments involving chiral oxazolines was performed in our laboratory in 1972 and involved the use of a chiral amino alcohol **6**, which we obtained as a generous gift from Parke Davis (Scheme 3). One of the resolved enantiomers of this compound was required in the manufacture of the antibiotic "Chloramphenicol", whereas the other was deemed "useless" and stored away in large quantities. Using the method of condensing imidates **7** with amino alcohols, we prepared the chiral 2-ethyloxazoline **8** in good yields[11] from the "useless" enantiomer of **6**. The free hydroxyl in **8** was

SCHEME 3



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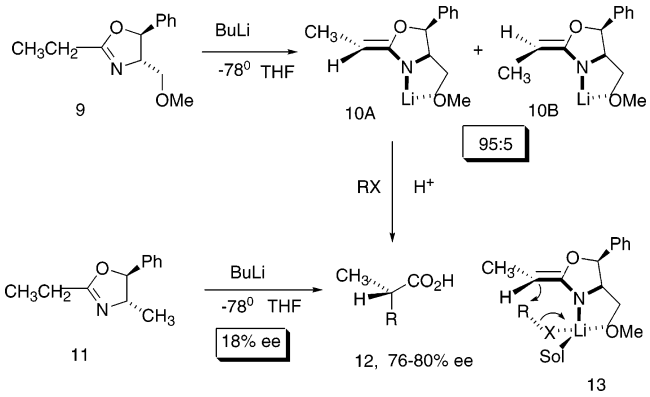
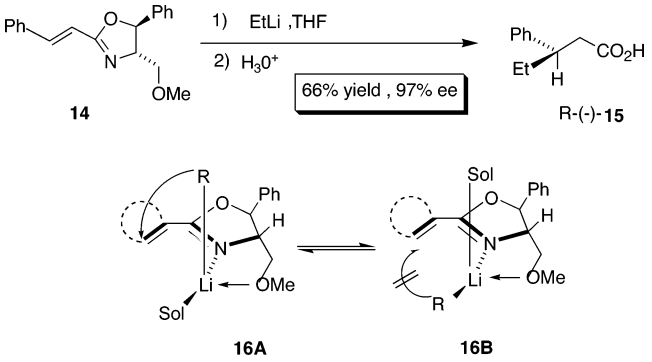


transformed into its methyl ether **9** to avoid using excess butyllithium in the subsequent carbanion formation. The stage was now set to see if we could generate the α-carbanion, alkylate with an alkyl halide, and thereby provide the two diastereomers, hopefully, in a highly biased ratio (Scheme 4).

If the bias was sufficiently high then hydrolysis of the alkylated oxazoline would provide the α-substituted propionic acid **12** in high enantiomeric purity, assuming no racemization occurred during the acidic hydrolysis. In the actual experiment,1.1 equiv of *n*-BuLi was added to a THF solution of the chiral oxazoline **9** at −78 °C, and after several minutes the alkyl halide was introduced and the solution allowed to warm. Isolation of the crude alkylated oxazolines was immediately followed by acidic hydrolysis (aq HCl) to yield the α-substituted propionic acid **12** in 75−80% optical purity, when compared to the literature value for $[\alpha]_D$ (Scheme 4). Based upon the optical purity of **12** there was probably a significant proportion of one of the azaenolates (**10A** or **10B)** formed during the deprotonation step. At the time the experiment was performed there was no information available to us regarding the ratio of azaenolates(**10A**, **10B**) formed. Subsequently, we prepared the ^{13}C-methyl analogue of **9** such that the methyl groups in **10A**, **10B** were 40% enriched in ^{13}C, and an NMR assessment[12a,b] of the THF solution of the azaenolates **10** indicated a ratio of 95:5.

It was further found that there was little or no equilibration of the two intermediate Li salts (**10A**, **10B**) between −78 and −30 °C. Thus, the ratio of azaenolates **10** was kinetically determined during the deprotonation step. In addition to the largely selective deprotonation, the entry of the alkyl halide was assumed to proceed predominantly from the underside face of both azaenolates generally leading to a 9:1 selectivity(80% de) for the overall two-step process. The assignment of **10A** as the major azaenolate was based upon the fact that the (*S*) acids **12** were obtained as the major enantiomer, and this can only occur if alkylation of **10A** took place from the

SCHEME 5



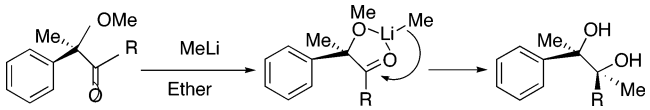
Li-chelated face as shown in **13**. Deprotonation to give **10A** demonstrated that *Z*-enolates were the major species formed with LDA and seemed to be in agreement with other carbanion work at the time.[13]

These results clearly indicated that there are two stereoselective steps (deprotonation, alkylation) that must take place with considerable bias in order for the final chiral acid to have been enantiomerically enriched to 80%. In other words, even if the deprotonation step proceeded to give the *Z*-enolate **10A** in 99% selectivity, the asymmetric route to the carboxylic acid would still be poor if the alkylation step was nonselective. Fortunately, in the cases cited here, both steps proceed with at least 9:1 selectivity.

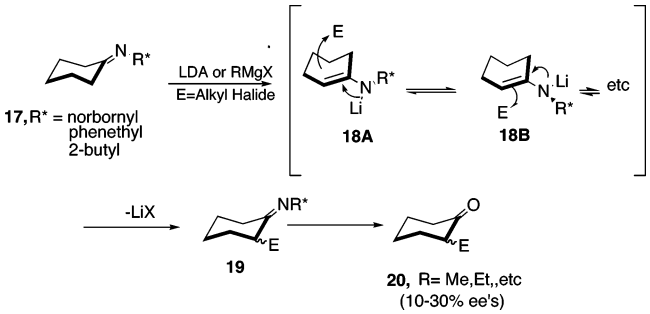
The unexpectedly good asymmetric induction obtained in the above process was seen as being influenced by the rigid chelated anion shown in **10A**. We felt that the lithium ion was "locked" in a position below the plane of the oxazoline enolate, thus allowing the subsequent alkylation step to occur from the underside.What followed was an assist to the entry of the alkyl halide by first coordination of the halogen lone pairs with the electrophilic Li ion (**13**). By displacement of one of the solvent molecules by the halide, the alkyl group would then be attacked by the azaenolate "π bond" (**13**). To confirm or deny that chelation was significant in the stereoselective alkylation step, we carried out the same process with the oxazoline **11**, incapable of chelation with the lithium ion. Deprotonation and alkylation of **11** under identical conditions followed by hydrolysis gave the same carboxylic acid **12** in only 18% enantiomeric excess.[11] As an interesting side note to this chelation notion, we were able to *solublize 1.0 equiv of LiCl in THF, which contained the oxazoline* ***9****, further supporting the strong tendency of lithium ion for the bidentate ligand present in* ***9****.*

Asymmetric addition to electrophilic olefins had been reported in the 1960s and early 1970s, but the stereochemical results were very poor (ee < 10%)[14]. In 1974–5, we reported[15] that the chiral oxazoline **14**, prepared from a Horner–Emmons elaboration of the then commercially available 2-methyl derivative with benzaldehyde, underwent remarkably high stereoselective 1,4-addition when treated with various organolithium reagents at −78 °C in THF (Scheme 5). After hydrolysis to remove the oxazoline, the β,β-disubstituted propionic acid **15** was obtained as nearly the pure enantiomer.[15] It is noteworthy to mention that this level (>97% ee) of asymmetric conjugate addition had not yet been seen in organic synthesis.

SCHEME 6. Cram's Cyclic Model[17]



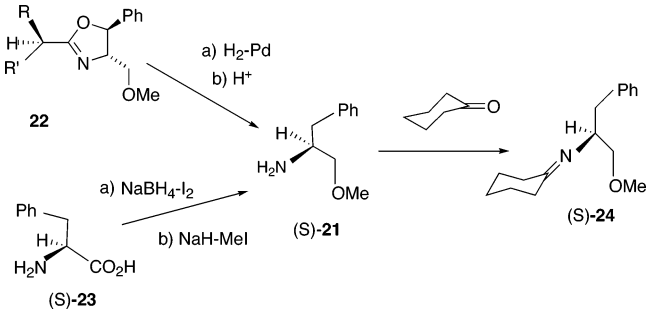
SCHEME 7



The highly efficient stereochemical 1,4-addition to **14** was seen as another example of the influence that rigidity (topography) has on the addition process. Since the absolute stereochemistry of the 3-phenyl-3-alkyl-substituted acids **15** were known[16] to be R, the mode of addition of the organolithium may be written as approach from the β-face of the π bond as shown in **16A**. If chelation by the nitrogen and methoxyl group is presumed to be important for the organolithium to position itself, then the orbital alignments are also important. In **16A**, the apical R group is aligned to the π orbitals of the double bond whereas if the solvent and R groups exchange positions on the lithium, then the orbitals are not aligned, as in **16B**. It is assumed that addition can only occur when the orbitals are aligned as in **16A**, and this would then lead to the R configuration at the stereogenic center.[15]

The rigid chelates that are discussed above and their seemingly significant contribution to stereoselectivity is not a new concept in controlling stereochemical outcomes. In the 1950s and 1960s, Cram and co-workers[17] showed that additions to carbonyls containing a proximal ligand substituent gave stereochemical results consistent with a "cyclic model". In other words, a chelated, rigid precursor directing the facial addition to a carbonyl (Scheme 6). Having confidence in the "chelated models", which appeared to give superior asymmetric alkylations, we contemplated other alkylations where this model would serve to enhance enantiomer purity. The literature was not without attempts[1] to reach enantiomerically pure compounds, but in 1974 there were very few C–C bond-forming reactions which gave ee's above 20%. Noteworthy among those early efforts were the studies of Horeau[18] who showed that imines **17**, derived from chiral amines and cyclohexanone, could be metalated in the Stork[19] manner and then alkylated to to give the imine **19** (Scheme 7). After hydrolysis, the alkylated cyclohexanone **20** was isolated in 10–30% ee's. In 1974, Yamada[20] also examined the closely related metalated cyclohexanone imines containing chiral carbons and observed asymmetric alkylation to the 2-alkylcyclohexanones **20** in 25–35% ee. Based on our earlier observations in the chiral

SCHEME 8



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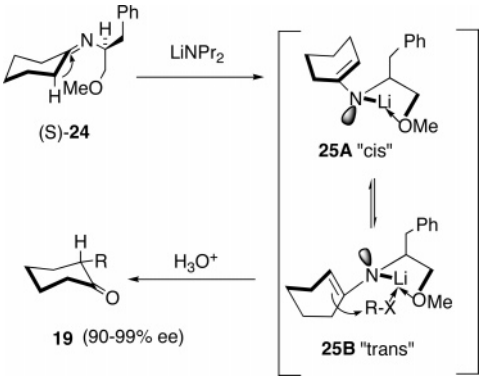


oxazolines we felt that the amines, utilized in the imine **17** by Horeau and Yamada above, were responsible for the poor enantioselectivity in the final cyclohexanones **20**. If one examines the metalated enamines **18A**, **18B** there are too many degrees of freedom for the lithium ion to occupy a specific position. In other words there are too many conformations wherein the nitrogen−lithium "bond" and the π bond in the cyclohexenyl moiety may properly overlap. This would allow the electrophile (E) to enter with comparable ease from either face (**18A**, **18B**) of the cyclohexenyl π bond leading to poor stereoselectivity.

It seemed reasonable to us at the time that the presence was required of some substituent on the chiral amine which could serve to "rigidify" the metalated enamines **18A**, **18B** and therefore limit the $\pi-\pi$ overlap options of the nitrogen and olefin as well as the approach of the electrophile. As a result, this may serve to increase the stereoselectivity of the alkylation.

The problem then arose as to accessibility of a chiral amine possessing a suitably positioned ligand. We felt that any of the chiral alkylated oxazolines **22** could serve as a suitable precursor to the requisite methoxy amine **21** which,when treated with a ketone, can provide the imine **24** containing the ligand we sought (Scheme 8). This was accomplished by catalytic reduction of the purified oxazoline **22**, which gave the reductively cleaved amide and immediate acidic hydrolysis of the latter led to the desired methoxy amine **21**. The latter was >98% ee based on the ee of the starting oxazoline **22**. It became obvious that the methoxy amine **21** could also have been readily obtained by reduction of (*S*)-phenylalanine **23** and etherified with base and methyl iodide. However, in 1975 there were too many questions regarding racemization during the reduction of amino acids to their corresponding alcohols[21] and we did not wish to risk preparing the chiral methoxy amine in less than complete enantiomeric purity. As events later showed,[22] there was little risk, indeed, of racemization of amino acids using various hydride reagents contrary to the many literature reports at the time. The amino alcohols from amino acids using various hydride sources were examined as their Mosher amides and the ^{19}F NMR spectra taken to show the % ee. All exhibited greater than 98% ee precluding any racemization during the reduction step.

Satisfied that the methoxy amine **21**, derived from the oxazoline **22**, was enantiomerically pure, the cyclohexyl imine **24** was subjected to the metalation−alkylation conditions of Horeau[18] or Yamada[20] and produced the 2-ethylcyclohexanone **19** in 98% ee after hydrolysis (Scheme 9). Additional alkyl groups that were stereoselectively placed on cyclohexanone were methyl, ethyl, *n*-propyl, allyl, and benzyl.[23] The rigid lithio enamine **25** was expected to have only two major options for its conformation, **25A** and **25B**, and the latter was assumed to be the more favored of the two. The *trans*-1,2-substitution seemed to us to be the least strained and encumbered species unlike the *cis* version **25B**. If this was indeed the case, then the electrophilic entry into the lithium enamine would be limited to **B** and a high degree of diastereoselectivity should result. That this was actually the case was observed when the 2-alkyl cyclohexanones **19** were all obtained in excess of 90% ee. A number of other ketones were examined as well as other electrophiles in a more complete study[24] and the ee values ranged from 80 to 99%, values never before seen at that time in an asymmetric alkylation. There were several poorer values (ca. 20% ee) encountered in certain cases where the 2-alkylated ketones were prone to facile racemization. In addition, macrocyclic ketones (C_{12-15}) were examined and their respective lithio azaenolates were found to equilibrate into *E*- and *Z*-forms (analogous to **25A**, **25B**) at various temperatures. In this manner, after alkylation and hydrolysis, we we able to prepare either enantiomer of the 2-alkyl macrocyclic ketones.[25]

With these additional examples supporting the need for chelation and rigidity on the reacting azaenolates, the evidence for their significance had now become rather convincing. A flurry of reports subsequently appeared in the literature from many outstanding laboratories which described further examples of asymmetric C−C bond-forming reactions, seemingly dependent upon the rigid nature (via chelation) of the intermediates (Figure 1). There were reports of α-alkylation of carboxylic acids, aldehydes, and ketones using chiral auxiliaries equipped with a suitable ligand to complex to the metal ion of the resulting enolate.

The chelating presence in the enolate or aza enolate moiety is summarized in a general manner (Scheme 10). The proton abstraction from the chiral starting material **26** is accompanied by a rigid intermediate **27** due to the ligand. Electrophilic entry is guided by the position of the Li ion in **27**, which provides the new product **28** as a diastereomeric mixture in varying ratios. Hydrolysis of the latter produces the enantiomerically enriched acid **30** and recovered amine **29**, which can then be reacylated to **26** repeating the process.

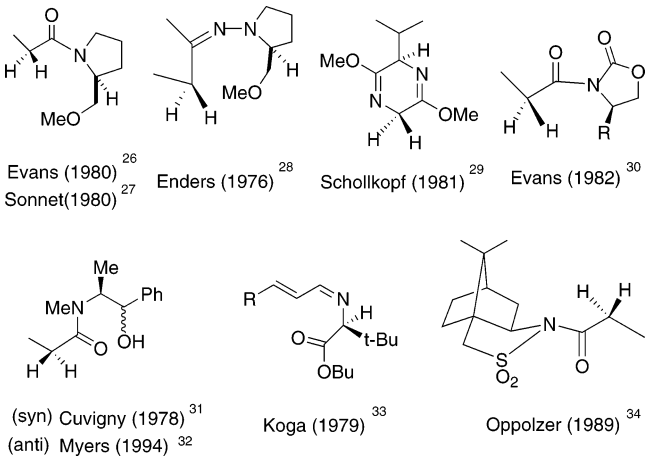
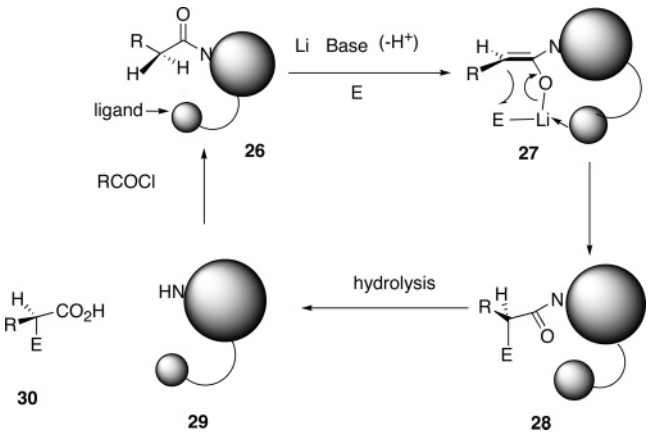


FIGURE 1. Chelating chiral auxiliaries.

SCHEME 10



As might be expected, several of these systems subsequently investigated (Figure 1) were shown to be considerable more efficient than the chiral oxazolines above, particularly the Evans entry.[30] Nevertheless, the chiral oxazolines above,set the parameters or "raised the stakes", so to speak, for what is now a very successful and productive area of synthesis. Some of the more prominent chiral auxiliaries that made significant synthetic history are shown in Figure 1. These systems were responsible for some of the most exciting events in organic synthesis during the 20th century.

In 1989, chiral oxazolines began to take on an additional role in organic synthesis. Due to the important need to seek out useful and more cost-effective asymmetric C−C bond forming reactions, the oxazolines have served exceedingly well as chiral ligands for a variety of metal catalysts. Some of the early ligands **31**−**36** utilized for this purpose are displayed in Figure 2. It is noteworthy to point out that some ligands possess one or two oxazoline rings while others are a mix of an oxazoline and nitrogen or phosphorus ligands. Many further variations were yet to come.

The research laboratories responsible for the early utilization of **31**−**36** are those of Bolm,[35] Brunner,[36] Corey,[37] Evans,[38] Helmchen,[39] Lehn,[40]Masamune,[41] Nishiyama,[42] Pfaltz,[43] and Hayashi.[44] For a more recent discussion on scores of additional chiral oxazolines as

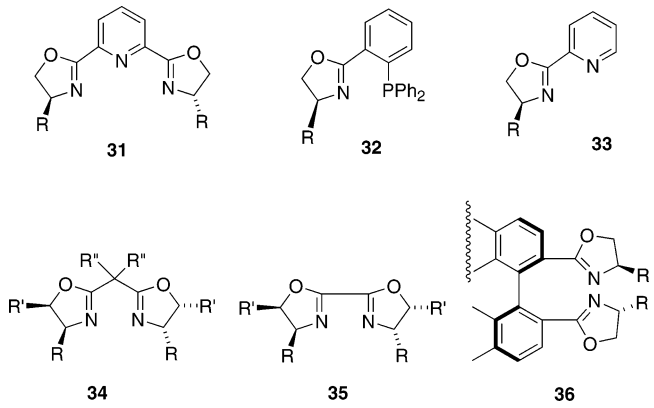
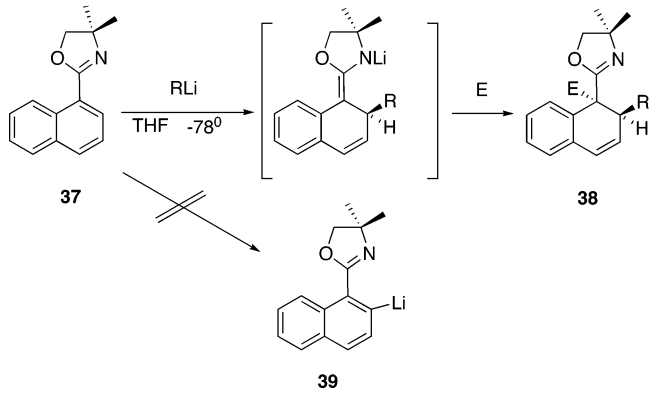


FIGURE 2. Chiral oxazoline ligands for asymmetric catalysts.

SCHEME 11

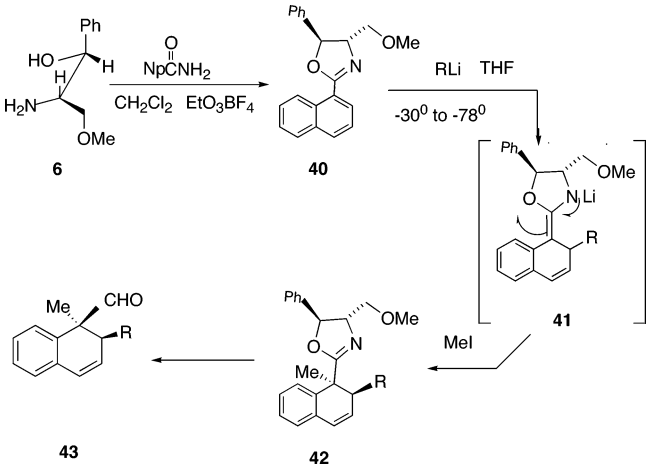


ligands for various metal catalysts, the recent reviews on mono-[10g] and bis-oxazolines[45] should be consulted.

The overwhelming success of chiral oxazolines as ligands in the catalytic arena must not be construed as suggesting that their role as chiral auxiliaries has been diminished. Furthermore, several works on the extensive continued use of chiral auxiliaries in a wide variety of C−C bond-forming reactions have appeared.[46,47] In fact, there are as many success stories using oxazolines as an auxiliary as there are as a chiral ligand.[10g] It seems appropriate at this point to briefly relate some of the subsequent studies we performed on asymmetric C−C bond-forming reactions using chiral oxazolines as auxiliaries.

In the early 1980s, we examined the asymmetric addition of organometallics to naphthalenes after first observing that simple organolithium reagents added conjugatively to achiral naphthyloxazolines **37** followed by electrophilic trapping to give the doubly alkylated product **38** in good yield (Scheme 11). This unanticipated event was observed as we were looking to assess the ortho metalation[48] of naphthyloxazolines (to **39**) as had been reported by others[49] in related systems. The addition of organometallics into the naphthalene pi system to give tandem 1,2-addition products similar to **38** had been observed earlier, with generally poor success, on several occasions. However, the effect of the oxazoline substituent on this reaction was considerably more effective[51] than earlier efforts and, once again, opened up the question regarding an asymmetric variant to this process (Scheme 12). The chiral amino alcohol **6**, mentioned above, was

SCHEME 12



again used to prepare the corresponding chiral naphthyl oxazoline **40** and this was subjected to addition of various alkyl lithium reagents. Addition produced the intermediate azaenolate **41** which was trapped by various electrophilic reagents(e.g., MeI) at low temperatures furnishing the doubly alkylated dihydronaphthalene **42** in >95:5 diastereoisomeric ratios.[52] The products were exclusively trans substituted (R and Me) and none of the cis isomers were detected. The high ratios obtained reflected the initial entry of the organolithium to the naphthalene **40**, predominantly from either the α or β face. That β-face entry was the major course of addition was confirmed by the hydrolysis of **42** to the 1,1,2-trisubstituted dihydronaphthalene **43** which showed that the separated 95:5 mixture of diastereomers **42** was indeed enantiomers and not diastereomers. X-ray structures were also obtained to confirm absolute configurations.

Furthermore, the asymmetric naphthalene additions were also successful in the isomeric 2-naphthyloxazolines **44** and gave the trisubstituted dihydronaphthalenes **45** in generally good yields and high diastereomeric ratios (Scheme 13). The purification, hydrolysis, and removal of the oxazoline chiral auxiliary led to a series of chiral aldehydes **46** in 99+% ee. In this fashion, several aromatic lignans (e.g., phyltetralin, **47**,[52a] and podophyllotoxin **47A**)[52b] were prepared from the appropriately substituted naphthalenes **48** in high ee's.

It is interesting to note that, in the synthesis of (+) **47**, the absolute configuration at the 1-(α-aryl) position is that of the natural lignan but in the other example shown, i.e., **46**, the absolute configuration of the 1-R-substituent is reversed to the β-face. Furthermore, the oxazolines **44** and **48** also have opposite senses of stereochemistry at C-4 and C-5 because they are derived from different amino acids.[52] This is an important point to be made at this juncture of the discussion. The stereochemistry at the methoxymethyl groups (C-4) in the oxazolines are the major factors responsible for the stereochemical outcome of the alkyllithium addition. We found, after numerous experiments, that the stereochemistry and size (Ph, Me, H) of the substituent at C-5 on the oxazoline had very little effect on the stereochemical addition to the naphthalene π system. This and other aspects of the mechanism and stereochemical rational have been discussed earlier.[52]

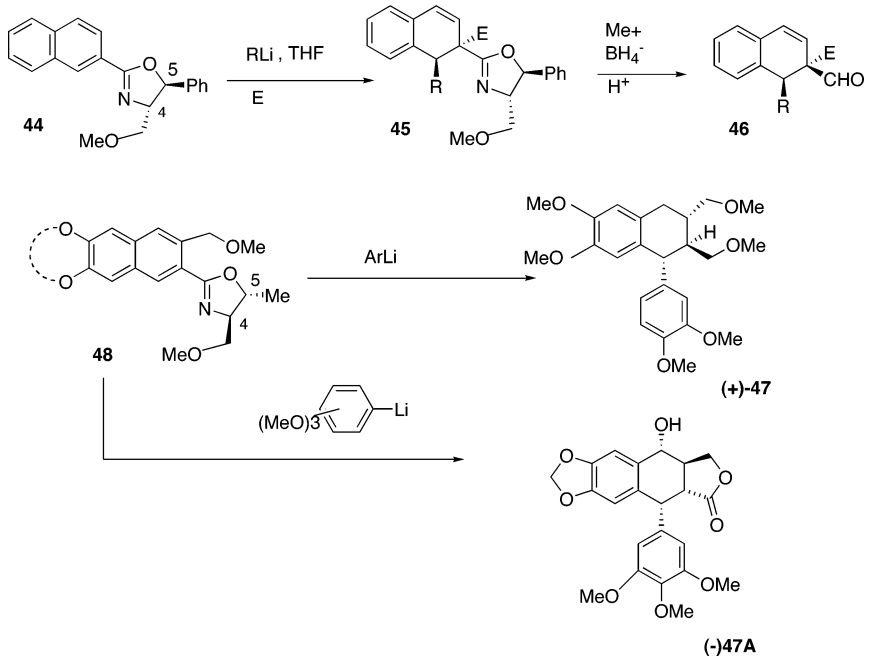
The mechanistic steps leading to the absolute configurations obtained are essentially the same as those discussed above with regard to the α,β-unsaturated oxazolines **16A**, **16B** (Scheme 5).

We found many years later, while continuing to probe the versatility of chiral oxazolines, that equally high diastereoselectivity can still be achieved in the absence of the chelating property of the methoxymethyl group.[53] When amino alcohol **49**, derived from (S)-*tert*-leucine, was converted into the corresponding α,β-unsaturated oxazoline **50**, additions with alkyl and aryllithiums gave very high diastereoselectivities (>95%) of the adducts **51**. These products were readily transformed into the β,β-substituted propionaldehydes **52** which were all obtained in 94−98% ee.[53] In some cases errors were found in the literature concerning the absolute configuration asignments, and these were subsequently corrected.[53] The absolute configuration of these aldehydic products were shown to be the same as those obtained using the chiral methoxmethyl oxazolines **14** and **40**. We reasoned that the organolithium reagent was complexing to, rather than chelated by, the substituents on the oxazoline ring **53**. This complex would be favored as a result of the rich pi orbital density on the O−C=N portion of the oxazoline and may undergo a HOMO driven 1,5-shift to place the organic residue (R) on the β -face of the olefinic carbon, as shown in **51**. Furthermore, the bulky *tert*-butyl group in **53** could prevent the Li complex from forming on the "underside" (α-face) of the oxazoline. This would still have the same orbital requirements for overlap with the π system and cause the R-group to enter from the "top face" (β-face) of the olefinic bond. On the other hand, a complex **54** similar to that proposed earlier for the methoxy oxazolines can also precede addition. Both models would have the same orbital geometry requirements for addition. ***Therefore, the methoxymethyl or other ligands may not always be necessary for high stereochemical selectivity in chiral oxazolines***. We have not yet found any evidence to support which of the two (**53**, **54**) may be operating (Scheme 14).

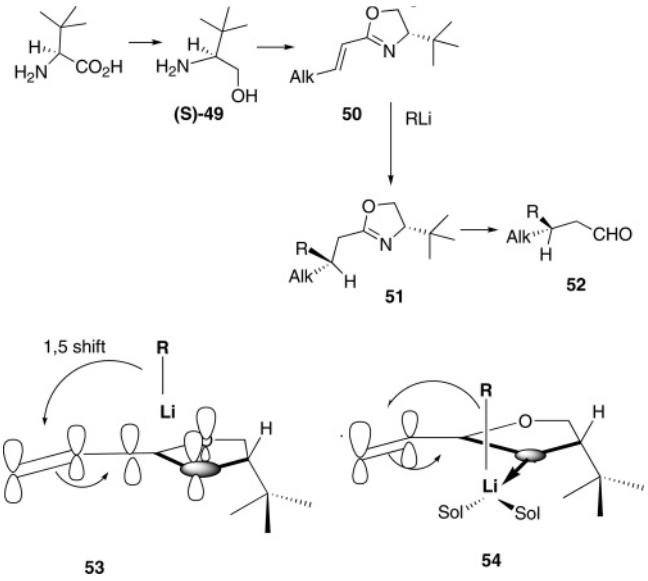
In addition to the asymmetric alkylations and additions, described above, the oxazolines had exhibited another unusual behavior in nucleophilic aromatic substitution. In 1975, we observed a facile displacement of methoxy groups from aromatic nuclei when they were situated ortho to the oxazoline ring (Scheme 15). Thus, when the 2-(2-methoxyphenyl) oxazoline **55** was treated with simple organolithium or Grignard reagents at temperatures from −50 to +25 °C there occurred a rapid displacement furnishing the *o*-alkyl derivative **56**.[54] This facile displacement was found to proceed with polymethoxy substitutions as well; however, only the *o*-methoxyl group was displaced. We later found that *o*-fluoride can also be displaced in this process.[55]

When we subsequently learned that other electron-withdrawing groups (e.g., CN, $CONR_2$, CO_2R, N=N, SO_2NR_2) had been reported[56] to be poor activating groups in this displacement relative to the oxazoline, our thoughts turned to the asymmetric version of this process. The question was raised—Could chiral biaryls be obtained if there was a suitable chiral oxazoline involved? This question was soon answered when we prepared the chiral aromatic methoxy phenyl oxazoline **57** and subjected it

SCHEME 13

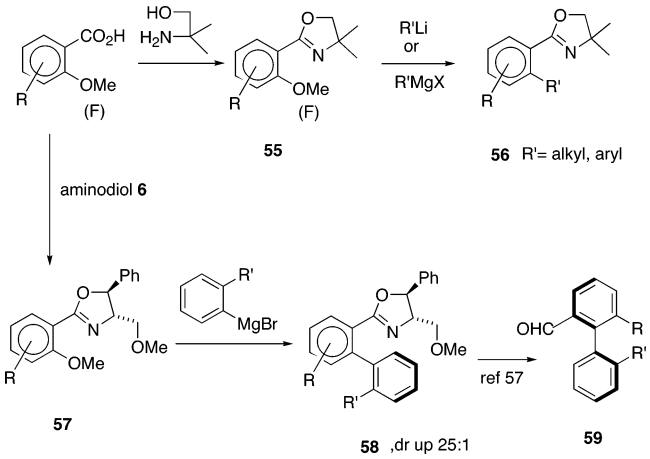


SCHEME 14



to the same nucleophilic substitution conditions (Scheme 15).[57] Diastereomeric ratios of biphenyls **58**, ranging from 1:1 to 25:1 were obtained. These ratios were dependent on the nature of the substituents present on both the aryl Grignard and the aryl oxazoline. If the substituents were "small" (methoxy, H) then atropisomerization occurred greatly reducing the diastereomeric ratios of the isolated products. If the substituents were "large or space filling" (CH_3, CH_2R) then the rotation about the biaryl axis was hindered and the ratios reflected the kinetic products formed. When we removed the oxazoline moiety in **58**, under various conditions, we were unable to inhibit the racemization of the biphenyl products completely and the ee's of the biphenyls **59** suffered significant losses after isolation and purification. In fact, almost total loss of enantiomeric purity was noted[57] in some cases. The steric requirements to totally inhibit atropisomerization must

SCHEME 15

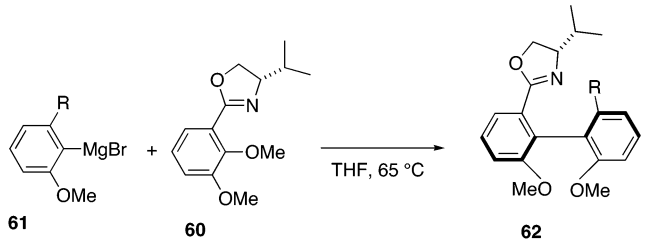


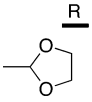
be satisfied in order to preserve absolute stereochemical integrity.[57] Substituents bearing sp^3 bonding were more effective than those with sp^2.

Many years later,[58] we returned to the chiral biphenyl problems and utilized the valine derived oxazolines **60** and found that we were able to achieve more success with these systems (Scheme 16). First, we opted to prepare biphenyls that possessed four ortho substituents to minimize the atropisomerization (racemization) of the final chiral nonracemic biphenyls. Employing 2,6-disubstituted aryl Grignards **61**, we treated chiral oxazoline **60** (derived from 2,3-dimethoxybenzoic acid) in THF at 25 °C and found the reaction to be extremely slow, undoubtedly due to the four ortho substituents that would have to deal with each other as the transition state is approached. The reactions were then conducted at reflux (65 °C) which led to a significant rate enhancement producing the diastereomeric biphenyls **62** in 67−90% yields.

The seemingly erratic ratios of diastereomers listed in Scheme 16 were readily explained by considering the

SCHEME 16

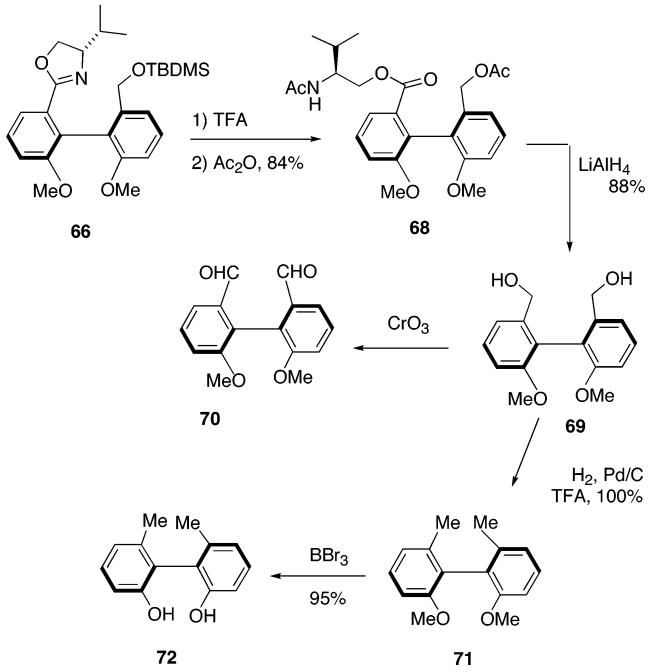


R	% yield	S : R
	90	20 : 80
CH_3	79	90 : 10
$CH_2OTBDMS$	73	93 : 7
CH_2OCH_3	75	40 : 60

substituents present during the aryl-aryl coupling. The highest stereoselectivity shown for **62** occurred when the substituent R on the Grignard is methyl and TBDMSoxy methyl, whereas the poorest selectivity arises when dioxolanyl and the methoxymethyl were the substituents on the Grignard. There were 10 examples reported of this coupling including some utilizing the analogous *tert*-butyl oxazoline, derived from *tert*-leucine. The results were generally similar[58] to that shown for the isopropyloxazoline **60**. The most significant aspect of the oxazoline mediated aryl aryl coupling is the high levels of stereoselectivity observed and this may be partially due to the severe steric requirements to afford tetrasubstituted biphenyls. One must contemplate the transition state characteristics of these aryl couplings and these have been described in the paper published in 2004.[58] Interestingly, the chelation−complexation aspects of the two reactants seem to have played a major role in this study. The essential mechanistic proposals are described in Scheme 17.

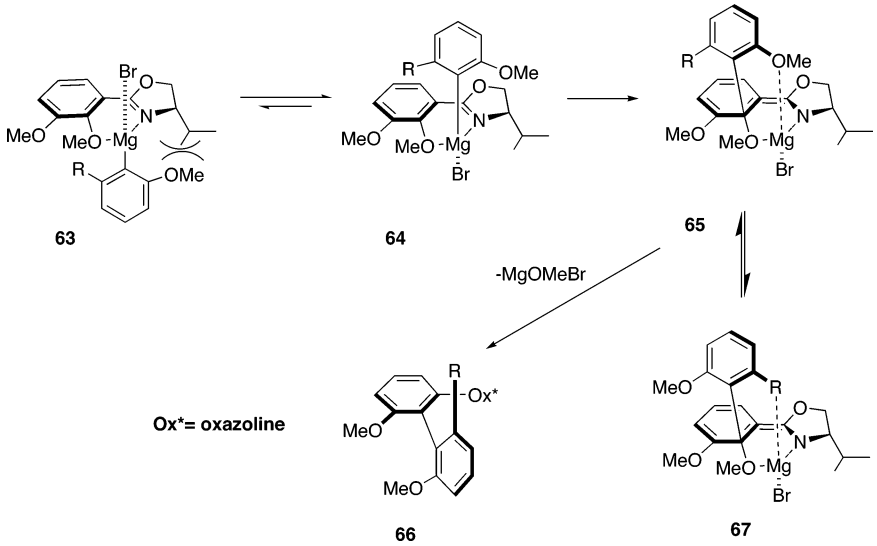
The approach of the Grignard to oxazoline can take place from either the α or β face to give **63** or **64**. The latter appears to be more accessible due to the large

SCHEME 18



isopropyl (or *tert*-butyl) group present on the oxazoline ring. The β entry (**64**) also allows for the formation of a clean, unencumbered chelate aligning the orbitals for transfer to the aromatic ring in **65**. Another important aspect of the addition is the presence of a ligand on the Grignard which may also complex to the magnesium, seen in **65**. Intermediate **65** now becomes a sigma complex which opens the possibility of the aromatic ring rotating about the sigma bond to provide an alternate conformation **67**. The stereochemistry of the final biaryl product should depend on which conformation is prevalent, **65** or **67**. As it happened, the major product was **66**, which must have arisen from conformation **65** as the sigma complex. This is further supported by the good stereoselectivity obtained from the Grignard containing R = Me or the rather bulky TBDMSoxymethyl (Scheme 16). These substituents were not able to compete with

SCHEME 17



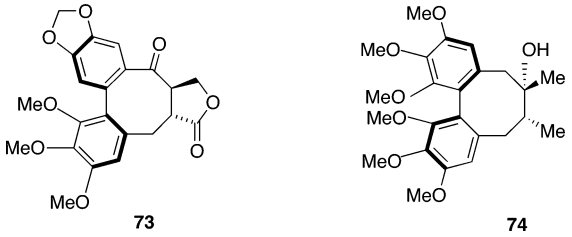
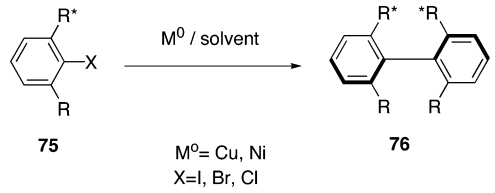


FIGURE 3. Natural products obtained via oxazoline aryl−aryl coupling.

SCHEME 19



the methoxyl for the magnesium complex causing conformation **67** to be less favored. On the other hand when R = 1,3-dioxanyl or methoxymethyl (Scheme 16) then the conformer **65** and **67** will be equally favorable and the biaryl products will form in smaller ratios.

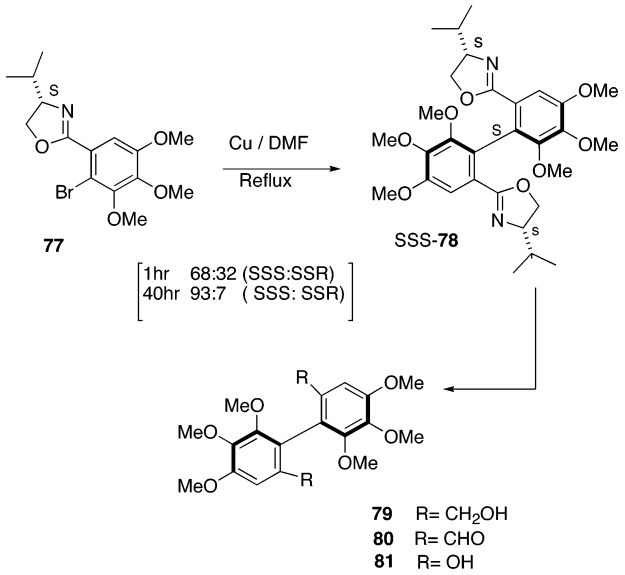
This type of asymmetric biaryl coupling was also capable of producing enantiomerically pure biaryls which were both functionally useful and stable to racemization (Scheme 18)

Thus, by removing the chiral auxiliary and the silyl ether in **66** in a two-step, one-pot procedure,[58] the bis ester **68** was reached which was readily reduced to the bis carbinol **69**. The latter was totally stable to racemization and could be transformed into the stable bismethyl biaryl **71** by hydrogenolysis. Ether cleavage of **71** gave the bis phenol **72** which was also quite stable ($t_{1/2}$ 140 °C for 9 h). The biphenyls **69**−**72** were all obtained in >99% ee after simple chromatography of the 93:7 mixture present in the starting material, **66**. As expected, the "volume-rich" sp^3 substituents are best at inhibiting bond rotation(atropisomerism), whereas sp^2 substituents such as those present in the bis-formyl biphenyl **70** are able to "slide past" each other and undergo racemization. The latter was completely racemized after 24 h at 90 °C, conditions that did not affect the biphenyls **69**, **71**, and **72**.[58]

The asymmetric methoxyl displacements shown above have also been used to achieve the total synthesis of several biaryl natural products including (−) steganone **73**[59] and (−) schizandrin **74**.[60] In all cases, the aryl−aryl coupling took place in the presence of the chiral oxazoline in greater than 95% diastereomeric excess (Figure 3)

In addition to the mixed aryl couplings shown above, the chiral oxazoline has further demonstrated its prowess in *homo* aryl couplings. These processes, known as Ullmann reactions,[61] have been known for well over 100 years (Scheme 19). They involve the metal-mediated oxidative coupling of aryl halides, usually at very high temperatures, affording symmetrical biaryls. Since its earliest appearance, the Ullmann reaction has been exhaustively studied and vast improvements have been made in the efficiency of the process.[61] There have been a number of attempts to intermolecularly prepare chiral

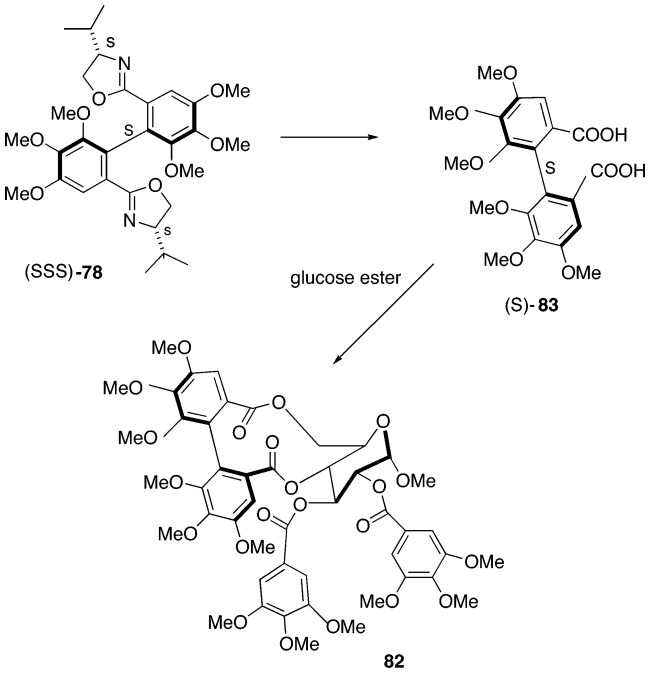
SCHEME 20



non- racemic biaryls using various chiral environments but none have produced meaningful levels of enantiomeric products.[62]

It was our intention to revisit some of these attempts to reach chiral biaryls, suitably substituted, so they would not racemize under the reaction conditions. We sought to study the "asymmetric Ullman" by employing a chiral controller, e.g., R* = oxazoline, and introducing at least three ortho substituents so the biphenyl obtained[21] would be able to retain, through its steric bulk, whatever stereoselectivity was kinetically formed. With these parameters in mind we prepared the aryloxazoline **77**,[63] and using copper as the mediator/catalyst, heated a solution in dimethylformamide(DMF) at 110 °C for 24h (Scheme 20). We obtained the biphenyl as a 94:6 mixture of SS**S** and SS**R** diastereomers **78** in 60% yield (the bold S and R refer to the chiral axis). This was a very pleasing result and showed for the first time that the *intermolecular* Ullmann reaction could be modified to efficiently produce chiral biphenyls.[63] The reasons for the high stereochemical bias in **78** were not immediately understood until we examined the Ullmann coupling further. We subsequently found that the product ratio in **78** was the result of a *thermodynamic resolution*, a process referred to by Izumi[64] as a "first-order asymmetric transformation". We observed that after periodic monitoring of the reaction, there was a steady increase in the diastereoselectivity over time reaching an equilibrium value of 93:7 after 40 h. Interestingly, the ratio of diastereomers in **78** was 62:38 after only I h of heating indicating there was already some bias toward one stereoisomer in the early phase of the reaction. Similar results were also obtained using the *tert*-butyl oxazoline derived from *tert*-leucine (Scheme 14). The high cost and minor stereochemical differences observed using the *tert*-butyl oxazoline did not warrant further studies with the leucine derivative. However, this was not always the case (see Scheme 22). Additional studies on the asymmetric Ullmann reaction are described in a recent report.[58] We demonstrated that the biphenyl oxazolines **78** were readily converted into several generally useful functional groups producing the enantiomerically pure biphenyls

SCHEME 21



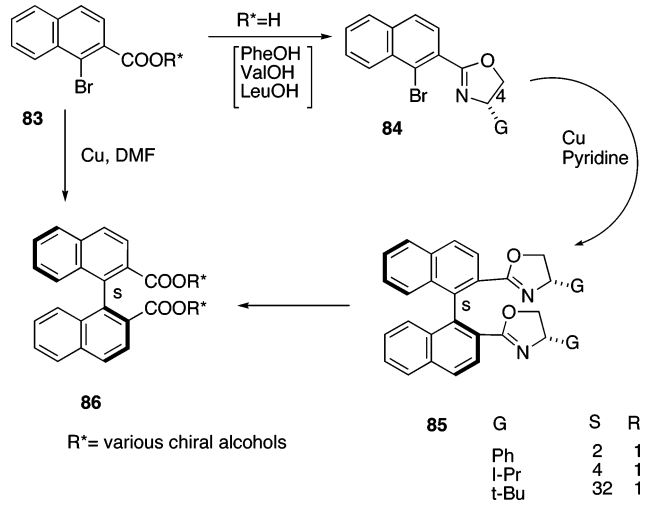
79−**81**.[58] It is noteworthy that all three of the latter biphenyls were stable to racemization[58] for weeks at room temperature but racemized to varying degrees after heating above 75−95 °C.

This asymmetric Ullmann method was utilized in the total asymmetric synthesis of the galloyl esters of glucose,namely the ellagitannins,[65] which contain a chiral biphenyl moiety encapsulated in a glucose core, **82**. The synthetic route (Scheme 21) started with the chiral biphenyl oxazoline **78**, which was hydrolyzed to the biphenic acid **83** and subsequently coupled with the bis-galloyl ester of glucose to afford permethyl tellimagrandin, **82** in 38% yield and enantiomerically pure by comparison with an authentic sample.[65]

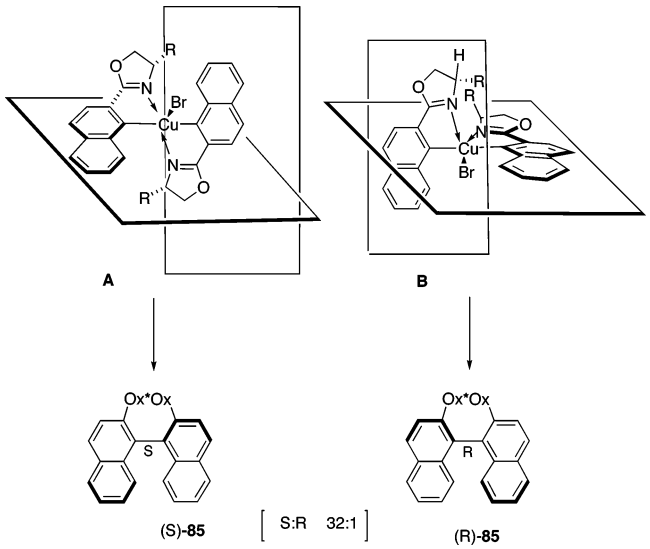
As studies progressed during this period, the oxazoline route to chiral binaphthyls appeared to be not far removed from the biphenyl studies described above. The attempts by others to carry out intermolecular asymmetric Ullmann couplings on naphthyl halides using chiral control elements (chiral esters of halonaphthoic acids **86**) have already been mentioned.[62]

Using the naphthylbromo acid **83**, we prepared the chiral naphthyl oxazolines **84** by treating it with phenylglcinol, valinol, or *tert*-leucinol, each representing an incremental increase in steric bulk. Heating a solution in pyridine, containing powdered copper, at reflux for 24 h gave the bis-naphthyloxazolines **85** in 75, 60, and 79% yields, respectively.[66] However, more importantly, the diastereomeric ratios of the binaphthyl products increased from 2:1 to 32:1 as the bulk of the C-4 substituent increased in size (Scheme 22). Comparing these results to the earlier studies by Miyano,[62] wherein the chiral esters in **83** gave only 2−13% diastereomeric excess, use of the chiral oxazoline seemed to be a major step forward. The bis-naphthyloxazoline **85** was subsequently transformed into several generally useful binaphthyls including the dimethyl ester **86** (R* = Me). Comparing all the properties of the previously prepared ester[67] with that

SCHEME 22



SCHEME 23



from the oxazoline coupling confirmed that the absolute configuration at the axis was *S*. We have proposed that the highly stereoselective cuprate coupling proceeds via an initially formed Cu(III) intermediate where the *tert*-butyl groups position themselves as far as possible from each other (Scheme 23). One can envision the two possible transition states, **A** and **B**, wherein the copper assumes a linear Cu(III) state which has been suggested as the transient intermediate prior to aryl−aryl coupling.[68] In structure **B**, the two oxazoline rings are brought into close proximity by the copper and it's ligands as are the C-4 substituents groups. This suggests that the larger the oxazoline ring substituent, the more steric interaction would result. Thus, the *tert*-butyl groups in **B** are in a more crowded environment than the isopropyl or phenyl. In structure **A**, the rings are further apart and the oxazoline ring substituents reside in a more unencumbered environment. As a result, the transition state derived from **A** would be lower in energy and the stereochemistry observed in the product is consistent with this model,namely that **S-85** was formed in a 32:1 ratio over **R-85**. These steric differences in the transition state, when nitrogen coordination was absent, were

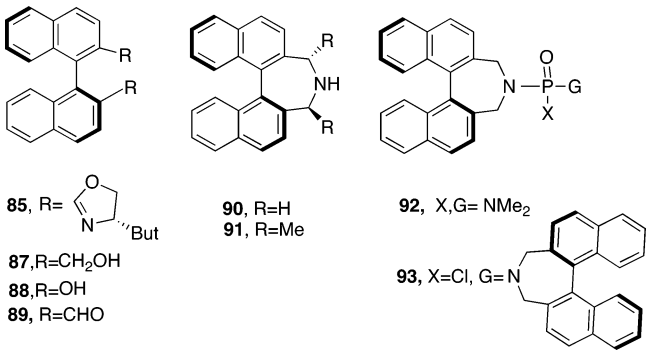


FIGURE 4. Figure 4. Chiral binaphthyl systems from naphthyloxazolines.

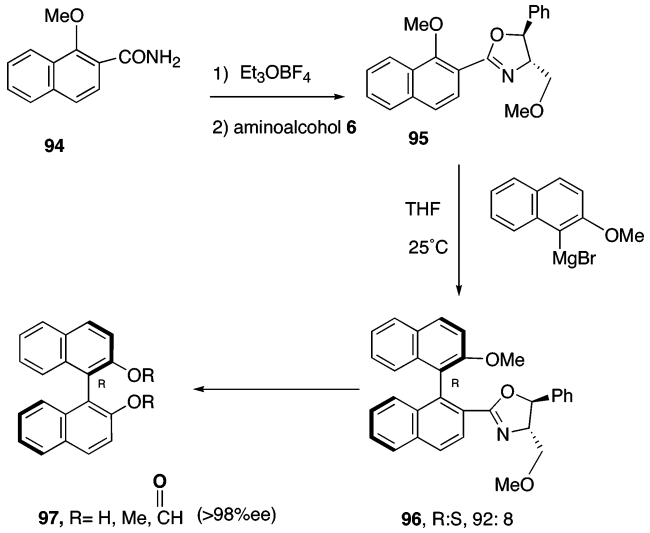
probably not operating in the naphthoic esters **83** mentioned previously.

The dimethyl ester **86** (R* = Me), which was readily prepared in >98% ee via the oxazoline route has been utilized by others in various ways such as a chiral stationary phase,[68] as a chiral host for inclusion of chiral alcohols,[69] and chiral ligands for Pd-catalyzed reactions.[70] We have also converted the bis-oxazolines **85** into carbinols **87**, diols **88**, aldehydes **89**, as well as chiral azepines **90** and their C_2-symmetric dimethyl derivatives **91** (Figure 4)[71,72] The latter have shown considerable utility as chiral bases in a variety of asymmetric transformations.[71] We also prepared two "chiral HMPA" derivatives **92**, **93** of the binaphthyl **90,** which was studied with regard to its chiroptical properties.[72] Unfortunately, circumstances prevailed at that time which precluded any further studies using these systems.

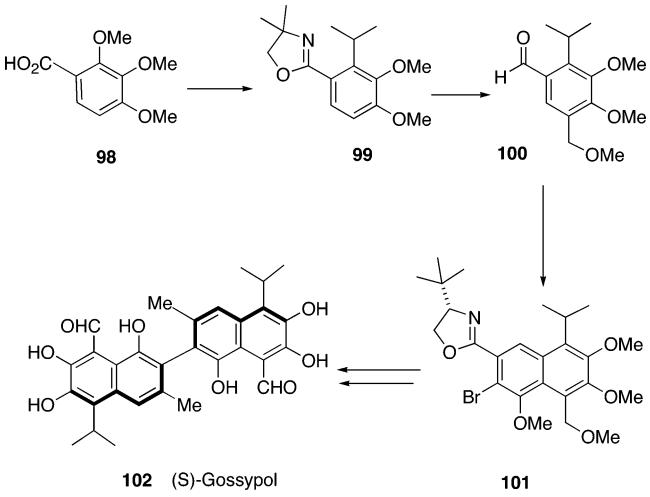
Before leaving the subject of chiral binaphthyls we need to mention work done in our laboratory in the early 1980s which involved reaching chiral binaphthyls.[71] This work was inspired by the extraordinary findings by Cram[73] and Noyori[74] regarding the remarkable properties of these substances as selective hosts for amino acids and as a chiral ligand for asymmetric hydrogenations and isomerizations. During that period we had been studying some of the early asymmetric additions to chiral olefinic oxazolines (Scheme 5) and nucleophilic aromatic displacements of methoxyl in aryloxazolines (Scheme 15). On the basis of these studies, it did not require a huge leap forward to see if we would be able to connect two different binaphthyl systems enantioselectivity. *At that time there were no viable asymmetric routes to binaphthyls*, and all attempts at this goal led to the binaphthyls in 12−16% ee.[75,76] Their acquisition at that time arose mainly from resolution of racemic materials and use of enantiomerically pure binaphthyl precursors.[77] If we were successful, then there would be a direct route to these valuable aromatic systems from achiral precursors.

Employing a series of 1,2-disubstituted naphthalenes, we were ultimately successful in reaching our goal (Scheme 24).[71] Thus, the methoxynaphthylcarboxyl amide **94** was transformed[52] into the chiral oxazoline **95**. The appropriate naphthyl Grignard was added to a THF solution of **95** at room temperature for 15 h, and the resulting binaphthyl oxazoline **96** was obtained in 70−80% yield as a 92:8 mixture of diastereomers. The latter was converted to binaphthyl systems **97** by hydrolysis and removal of the oxazoline auxiliary.[71] The various

SCHEME 24



SCHEME 25



derivatives of chiral binaphthyls formed by this route were the first to be reported as being available from nonenantiomeric binaphthyl starting materials. In collaboration with Cram, who also utilized oxazolines as a route to enantiomeric binaphthyls, the absolute configurations were confirmed via CD studies.[78]

As a further demonstration of the use of chiral oxazolines in the asymmetric synthesis of natural products we were able to prepare (*S*)-gossypol **102** in enantiomerically pure form for the first time.[79] This polyhydroxy binaphthyl system, first synthesized formally in 1957, has been of interest recently as an anti-fertility agent in men and male animals and has shown HIV and anticancer properties as well. Its structure was elucidated in a massive effort by Roger Adams and his students, reported in 1938, a period when there was absolutely no spectroscopic assistance other than some crude UV absorption for the aromatic rings.[80] The final structure relied only on chemical degradations, derivatives, combustion analysis, and synthetic correlations all of which led to the correct structure. Our route to, and the first asymmetric synthesis of, (*S*)-gossypol **102** (Scheme 25) hinged on an efficient combination of achiral and chiral oxazoline methodology utilizing the aromatic displacements (Scheme

15, **55**−**56)** and the asymmetric Ullmann coupling (Scheme 22, **84**−**85**).[79] As outlined briefly below, the trimethoxybenzoic acid **98** was converted to the simple achiral oxazoline, and the *o*-methoxy group was replaced with isopropyl to form the oxazoline **99** which was reductively hydrolyzed to the tetrasubstituted benzaldehyde **100** via the chemistry in Scheme 15. Regioselective introduction of the hydroxymethyl group[81] followed by oxazoline removal gave the tetrasubstituted benzaldehyde **100**. The latter was subjected to a Stobbe condensation[82] to provide the homologated naphthoic acid which was once again converted to the corresponding chiral naphthyloxazoline **101**. An asymmetric Ullmann coupling, using copper−DMF, gave the corresponding binaphthyl derivative in a 17:1 ratio of diastereomers which was then transformed in four steps to (*S*)-gossypol **102**.

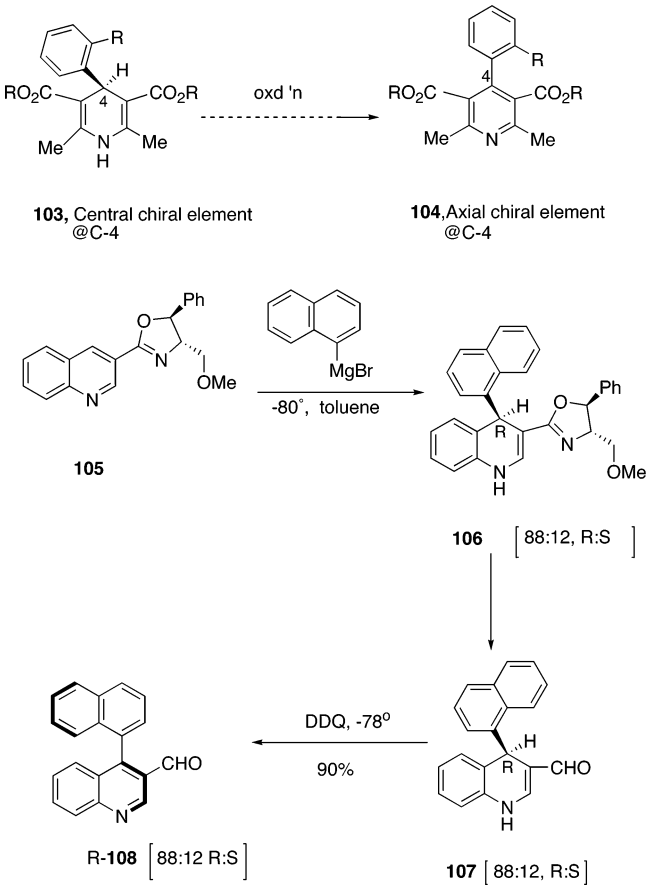
The above discussions have readily demonstrated that the chiral and achiral oxazolines were quite valuable vehicles for a variety of different C−C bond-forming reactions. However, there were occasions where we felt the need to approach other stereochemical problems and the chiral oxazolines proved to be very helpful in reaching their solutions. One such case came to our attention in the early 1980s when we came upon Berson's important question concerning "asymmetric transfer".[83] That is to say, the complete transformation of a carbon center of stereochemistry to an axial center (biphenyl link) of stereochemistry within the same molecule. This is termed as a "self-immolative" process.[84] The experiments attempted by Berson to demonstrate the feasibility of this process was severely limited by the difficulty in obtaining enantiomerically enriched starting material and biaryl products (Scheme 26).

Some 25 years later, as we were engaged in the chiral oxazoline work, we felt we could contribute to the answer Berson sought in his studies on the simple dihydropyridine−pyridine system **103** and **104** (Scheme 26).[85] The goal was to assess whether the stereochemistry could be preserved by transferring the asymmetric central carbon at C-4 in **103** to an asymmetric axial biphenyl **104**. The ortho substituents present were to inhibit bond rotation in the biaryl axis,once formed, so optical activity could be measured. We turned to the related dihydroquinoline−naphthalene system **107** and **108** as a source of enantiomerically enriched starting material and product which should also serve to answer the "asymmetry transfer" question—Can this central-to-axis process occur with complete conservation of chirality? The well-known high barrier to rotation in the binaphthyl series was considered sufficient to preserve the enantiomeric purity of the biaryl product.[85]

By starting with the quinoline oxazoline **105**, we were able to add the naphthyl Grignard (or the lithium) to give the adduct **106** as an 88:12 mixture of diastereomers (Scheme 26). We also noticed large solvent effects that affected the ratio of stereoisomers in **106** and either *S* or *R* at C-4 could be obtained as the major product.[85]

A sample of **106** was converted to the *N*-carbomethoxy derivative and analyzed by HPLC to give the ratio stated. After removal of the chiral oxazoline in **106** so that the only remaining stereogenic element was the C-4 naphthyl group, we obtained the aldehyde **107** as the same ratio of enantiomers (88:12). Treatment with DDQ at −78 °C

SCHEME 26



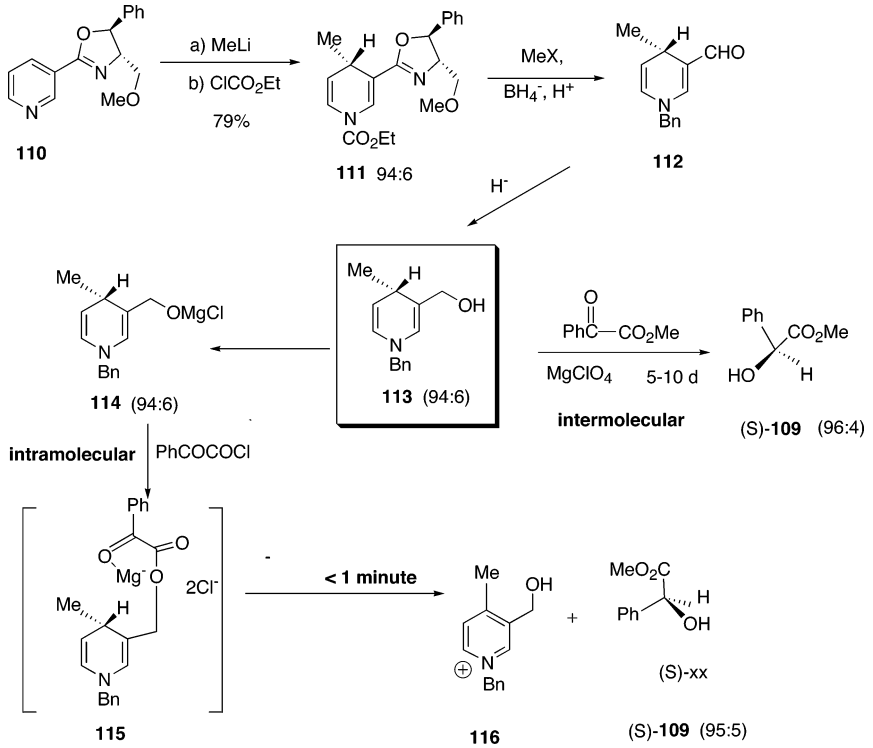
destroyed the central asymmetric center in **107** and also provided the biaryl system **108** which had not lost any of its enantiomeric integrity. Thus, it seemed that the Berson prediction of "asymmetry transfer" was indeed valid.

There was, however, one more question to be answered—Is the naphthyl substituent in **107** hindered to free rotation? If so, *then there are two stereogenic centers* in **107** and the "asymmetry transfer" would not be valid in this case. We, therefore, performed a number of rotational barrier experiments[86] at all temperatures between +45 and −80 °C and found that there was indeed free rotation with a ΔG =11.2 kcal/mol. Thus, at the temperatures of oxidation, the naphthalene ring in **107** was freely rotating and did not constitute another stereogenic center. We therefore were able to show that the Berson prediction[83] was correct and conservation of chirality ("asymmetry transfer") between central and axial chirality occurred in a manner that precluded any detectable racemization.

Additions to heterocyclic systems, i.e., **105**, were not uncommon in our studies, and other polycyclic materials containing a heteroatom were prepared using this asymmetric addition. For example, a route to pyrrolophenathridine alkaloids[87] wa also reported as well as additions to pyridine systems affording dihydropyridines.[88]

One such study we considered of interest was the acquisition of a chiral NADH mimic[89] **113** which exhibited remarkable reducing properties, much like the natural coenzyme in the NAD−NADH$^+$ system. We were interested in both the inter- and intramolecular hydride

SCHEME 27



transfer and studied the reduction of α-keto esters-(methylbenzoyl formate) to the mandelate ester **109**. There were a number of reports[90] describing efforts to mimic the NADH reductions and the work of Ohno in particular should be cited.[91] The latter studied the chiral 4-methyldihydropyridines, obtained by resolution, as coenzyme mimics and found that the major factor involved in the stereochemistry of carbonyl reduction was the stereochemistry of hydrogen at C-4. We were again interested in the "self-immolation" of stereocenters; a process which, at the time, was still very rare.[90]

With the oxazoline chemistry at our disposal for reaching chiral dihydropyridines[88] we sought to study the NADH system and determine whether self-immolation would occur while simultaneously reducing carbonyls as in the NAD−NADH$^+$ process.

That both goals were reached[92] was very pleasing, and the studies are outlined in Scheme 27. To reach the pivotal compound **113**, we once again called upon the addition of organometallics to the aryl oxazolines as described above. By treating the oxazoline **110** with MeLi and trapping the intermediate as its carbamate, we were able to obtain the dihydropyridine **111** as a 94:6 mixture of diastereomers.The absolute configuration at C-4 in **111** was confirmed by X-ray studies to be *S*. Interestingly, although at first glance the stereochemical addition to the pyridine ring in **111** appears to have been reversed from earlier studies of this type, the stereochemistry was still consistent with the mechanistic proposals offered earlier in Scheme 5. The presence of nitrogen in the pyridine ring affects the 1,4-addition such that the ring must be rotated to add to the 4-position. It should also be said that in Scheme 27 we found similar solvent affects which can produce either stereochemistry at the C-4 as had been observed in quinoline oxazoline **105**. However, no such solvent studies were made for the pyridine **110** in Scheme 27.

The dihydropyridine **111** was transformed into aldehyde **112** by the usual reductive cleavage and carbamate exchange with benzyl bromide. The latter was found to be a very poor reducing agent due to the electron deficiency incurred by the 3-formyl group. Reduction to the carbinol **113** now presented us with an unstable product whose half-life, through air oxidation, was less than 1 h. Thus, the experiment would have to be done quickly in order to study the redox system. When benzoylformic ester was added to **113** containing varying amounts of $MgClO_4$ under a sealed atmosphere the mandelate ester **109** was obtained in 94% yield and 92%ee as the *S*-enantiomer. Other derivatives of **113** were also examined[89] and gave ee's in the range of 92−95% of reduced material. The major drawback found in this study, which was also the problem observed by many others,[90] was the slow reaction rate (5−10 days!) to reach completion. However, the self-immolation question was answered when complete (or nearly so) transfer of chirality was observed in going from the central stereochemistry in the dihydropyridine **113** to the mandelate **109**. **Yet, this can hardly be called a NAD−NADH$^+$ mimic since the natural enzyme/coenzyme is exceedly rapid and these systems were so slow.**

We considered that some "organizational" problem had to be addressed[92] in order to reach the proposed crucial "ternary complex" involving the (a) carbonyl, (b) the dihydropyridine, and (c) the magnesium ion (similar to **115**). To force three molecules into a specific arrangement would be rather difficult—the entropy change alone will be very large. We thought that by first preparing the magnesium alkoxide **114** and then adding the acid chloride of the ketoester we would have a situation

whereby all three necessary components would be present in the solvent shell (e.g., **115)** and this may lead to the rapid stereochemical reduction we sought. *This was exactly what happened*.[92] The mandelate **109** was obtained after methanolysis of the pyridinium salt **116** in 65% yield. The reaction was complete in seconds as the ketoacid chloride was added to a THF solution of the magnesium alkoxide. Thus, we had demonstrated again that chiral molecules available from the oxazolines can be made useful in studies other than synthetic.

There are many other studies on the chiral oxazolines that space will not allow to discuss, but I wish to direct the reader to the reviews mentioned above and in particular, the most recent one which has appeared in 2004 in the *Chemistry of Heterocycles*, Vol. 60, mentioned earlier.[10s]

As there have been so many reports on oxazolines in asymmetric synthesis from many laboratories around the world, I apologize to those who were not included in the paper and in no way should this be taken to diminish their contributions.

The preceding discussion relating to the use of chiral oxazolines has occupied about a third my laboratory for more than 30 years and involved 100 co-workers (36 Ph.D. students and 64 Postdoctorals.) Although there have been another 200+ co-workers working on other projects since 1959, the oxazoline work remains among my most joyous memories. Whether these oxazoline studies will prove to be of some worth to organic and medicinal chemistry in future years, only time can relate. In any case, the time spent with students uncovering all the mysteries of this and other chemical problems was pure pleasure and something I shall always treasure.

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