Chiral Oxazolines - Their Legacy as Key Players in the Renaissance of Asymmetric Synthesis

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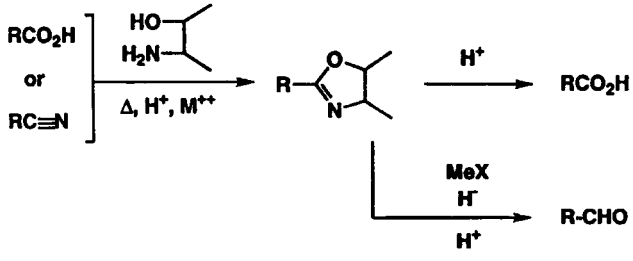
The oxazoline ring system, first described in 1884, has enjoyed a remarkable resurgence in its synthetic utility. No less than five reviews have appeared extolling the virtues of this simple ring system [1-5] both with regard to its synthetic access and its remarkable utility in general synthetic methods. In general, the heterocyclic ring is accessed by a cyclodehydration of carboxylic acids or nitriles with a variety of amino alcohols (Scheme 1). Once

Scheme 1

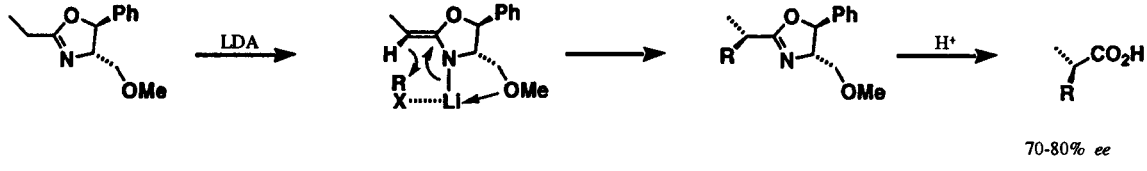


prepared, the ring may be cleaved under a variety of conditions to carboxylic acids or reductively cleaved to aldehydes. The use as a protecting group for carboxylic acids against hydride and Grignard reagents also remains one of the highlights of oxazoline utility in synthesis. Furthermore, the behavior of the oxazolines in *ortho*-directing metalation on aromatic rings also ranks it as among the best functional groups in this regard.

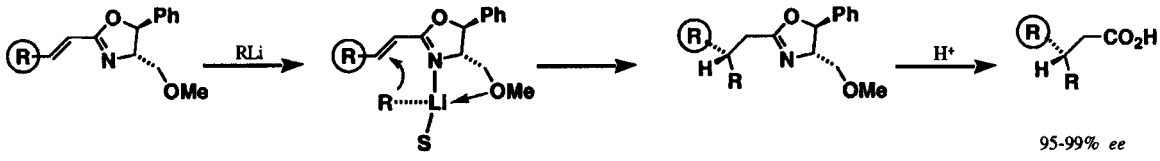
The present lecture will, however, deal only with the use of chiral oxazolines, generated from available chiral, non-racemic, amino alcohols and their powerful contributions to the present day surge in activity involving asymmetric reactions. The first report of a chiral oxazoline appeared from our laboratories in 1974 [6] where they were transformed into chiral carbanions and alkylated by various alkyl halides and then hydrolyzed to α-substituted propionic acids in 70-80% enantiomeric excess (Scheme 2). Not only was this a novel and unprecedented efficiency level for asymmetric C-C bond forming reactions, it also introduced the importance of lithium-oxygen chelation to reduce the rigidity of the transition states, allowing higher stereoselectivity to occur.

Following the chiral enolate-like oxazoline alkylation, we also showed that organolithium reagents could add, with high diastereoselectivity, to α,β-unsaturated oxazolines [7]. The latter, upon acidic hydrolysis, unmasked the carboxylic acid affording β-substituted alkanoic acids in 98-99% *ee* - an efficiency level for C-C bond asymmetric syntheses unprecedented at that time (Scheme 3). Here again, chelation of the organolithium reagent to the methoxy-containing oxazoline was deemed critical to the level of stereoselectivity achieved. These chelation proposals were supported by studies we carried out comparing chelating and non-chelating reactants (Scheme 4). We studied oxazoline anion alkylations using methoxyl *vs.* methyl substituents and the level of diastereoselective alkylation was dramatically different (10-13% *vs.* 75-80% *ee*). Unfortunately, we were unable to increase the asymmetric efficiency in the azaenolate alkylation above ~80% *ee* due to the presence of 5-7% of the *E*-azenolate which were alkylating to give the other diastereomer (and ultimately, the other enantiomer) of the oxazoline. Our operational mechanism for this pioneering asymmetric alkylation, shown in Scheme 4, placed the incoming electrophile (usually bromide or iodide) in a pre-complexing mode to the lithium cation, thus delivering the alkyl group to the enolate carbon from the same side of the molecule. This work is more fully discussed in a chapter written earlier [8]. Similar discussions on the early synthetic uses of chiral oxazolines may be found in the 1983 review [8]. Suffice it to say, this early work (1974-1976) prompted a torrent of activity in the synthetic community wherein enolates attached to ligand-furnishing chiral auxiliaries showed that a variety of α-alkyl carboxylic acids, aldehydes and ketones, were indeed feasible (Scheme 5). Several of these systems proved to be considerably more efficient than the oxazolines

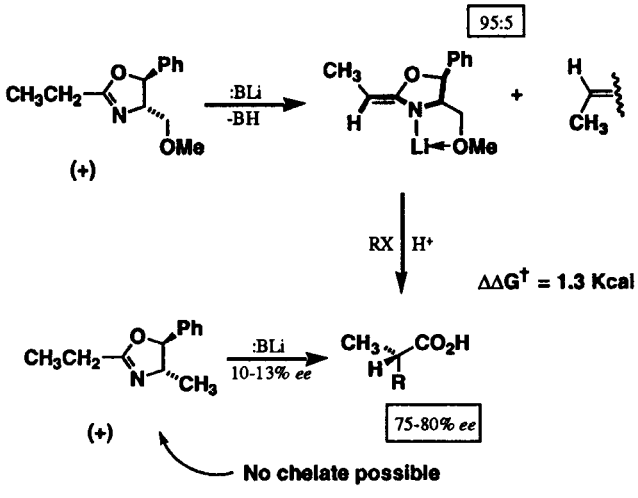
Scheme 2



Scheme 3



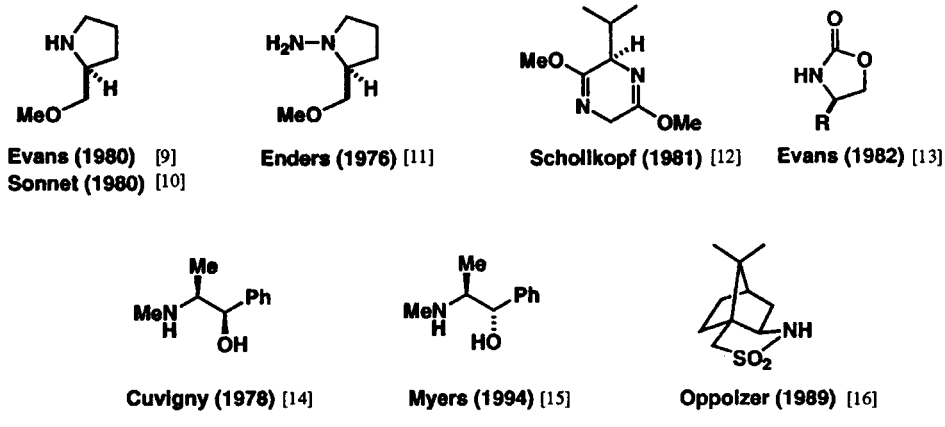
Scheme 4



In recent years (1989 to the present) the chiral oxazolines have taken on a slightly different role - namely that of ligands for a variety of chiral reactions. In our 1994 review [5c] we added more to this aspect of oxazoline utility. However, a short summary is given in Scheme 6 to depict the various types of chiral oxazolines presently in service as catalyst ligands [17-26]. It is unlikely that one can pick up any journal today without seeing some work using chiral oxazolines, as ligands, vehicles, or auxiliaries.

We now describe some of our recent studies involving chiral oxazolines which utilize the naphthalene system containing either chiral or achiral oxazolines. We showed some time ago that alkyl and aryl lithium reagents add in a very high diastereoselective manner to the naphthalene ring followed by trapping the intermediate azaenolate with alkyl halides (*e.g.* Mel) [27]. This allowed introduc-

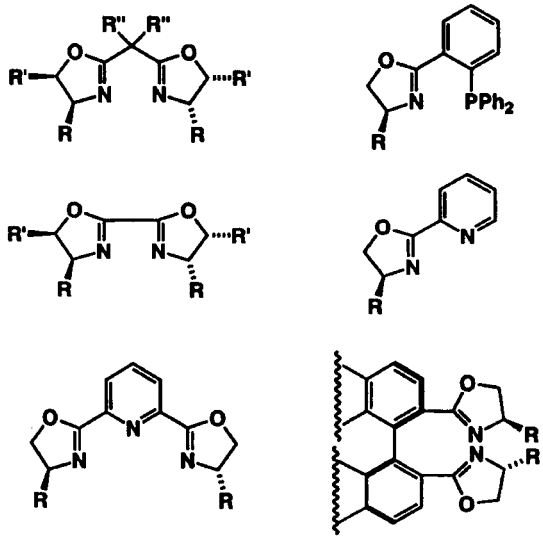
Scheme 5
Chelate-Driven Chiral Enolate Auxiliaries



above and are today's standard reagents and reactants for highly enantioselective routes to chiral compounds [9-16]. It should be noted, however, that the chiral oxazolines set the parameters, or "raised the stakes" so to speak, for what we now enjoy in efficient asymmetric syntheses.

tion of two clean stereogenic centers into the aromatic system in a single pot reaction (Scheme 7). Furthermore, once in hand, these doubly substituted dihydronaphthalenes were routinely transformed into the tetralin aldehydes with or without a quaternary carbon [27,28]. The latter

Scheme 6
Chiral Oxazolines as Modern Catalyst Ligands
(1989-present)



Carsten Bolm [17]
Henri Brunner [18]
E. J. Corey [19]
David Evans [20]
Günter Helmchen [21]

Jean-Marie Lehn [22]
Satoru Masamune [23]
Hisao Nishiyama [24]
Andreas Pfaltz [25]
Tamio Hayashi [26]

were formed by using a proton quench, in place of an alkyl halide. Interestingly, this allowed epimerization to occur to the *trans*-1,2-substituents so two complementary stereochemical products could be accessed - one in which the entering organolithium group was *cis* to the aldehyde (or acid) whereas the other led to the organolithium group and formyl group being *trans*-disposed (Scheme 8).

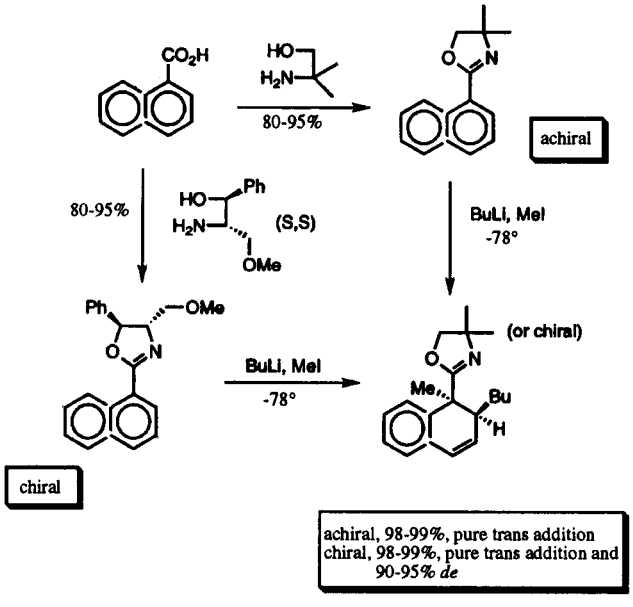
In passing, it is important to cite the work of Kündig [29] who, through clever use of chromium carbonyl adducts, has also shown that organolithium and alkyl halides can be introduced into the aromatic nucleus containing a chiral oxazoline. The advantage here is that without the π-arene chromium species, nucleophilic addition to the benzene would not be possible.

The recent addition of lithium amides to napththyl oxazolines described by our group opens another versatile pathway to chiral, non-racemic functionalized amines or amino acids [30] (Scheme 10). The initially reversible addition is trapped with various electrophiles to provide the 2-aminodihydronaphthalenes in exceedingly high diastereoselectivity (Scheme 10). The only limitation noted is when the substituents on the lithio amide were larger than diethyl. The steric crowding reverses the adduct to starting material. The further utility of this asymmetric addition was demonstrated by transforming the amino adducts to a primary amino group and thus to a new class of chiral β-amino acid derivatives (Scheme 11). Since lithium amide would not add to the naphthalene, due mainly to insolubility in tetrahydrofuran (THF) or ether solvents, we designed a surrogate amino group which was introduced in the form of a piperidine derivative [30].

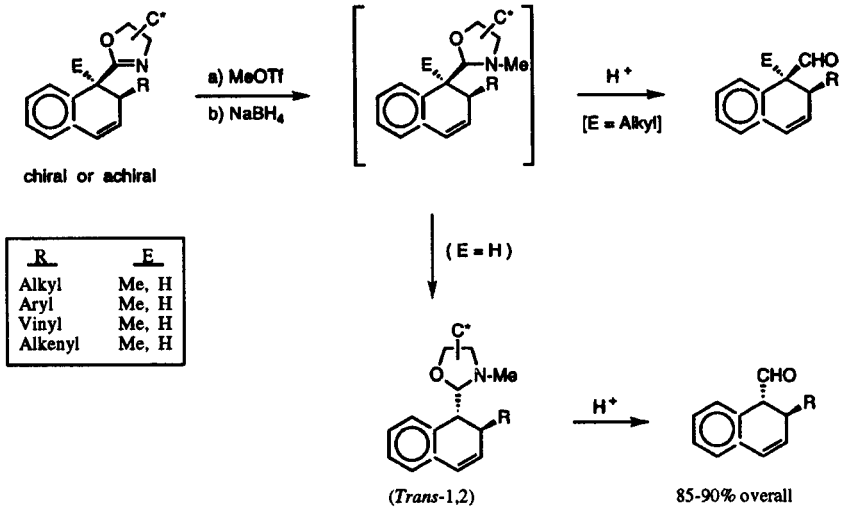
A number of studies utilizing oxazoline-containing naphthalene rings are currently in progress and should provide some useful synthetic results for future discussion.

Another area which we have currently been intrigued with is a revisit to the very old Ullmann reaction, first reported in 1904 [31]. The process involved a copper-mediated coupling of aryl halides to biaryls. The asymmetric variant, using appropriate ortho substituents and chiral controller groups, would indeed be a valuable process (Scheme 12). A number of attempts over the years have been employed to effect an asymmetric Ullmann coupling for binaphthyls, but have met with little success (Scheme 13) [32]. We recently described a facile Ullmann coupling (Scheme 14) utilizing 1-bromo-2-carboxynaphthalene which was transformed into the 1-bromo-2-oxazolines. Three different amino alcohols were employed derived from phenylglycine, valine, and *tert*-leucine, respectively. Upon heating in pyridine at 100-110°, the copper-mediated reactions proceeded well and only in the case of *tert*-leucine derived oxazoline was there a signifi-

Scheme 7

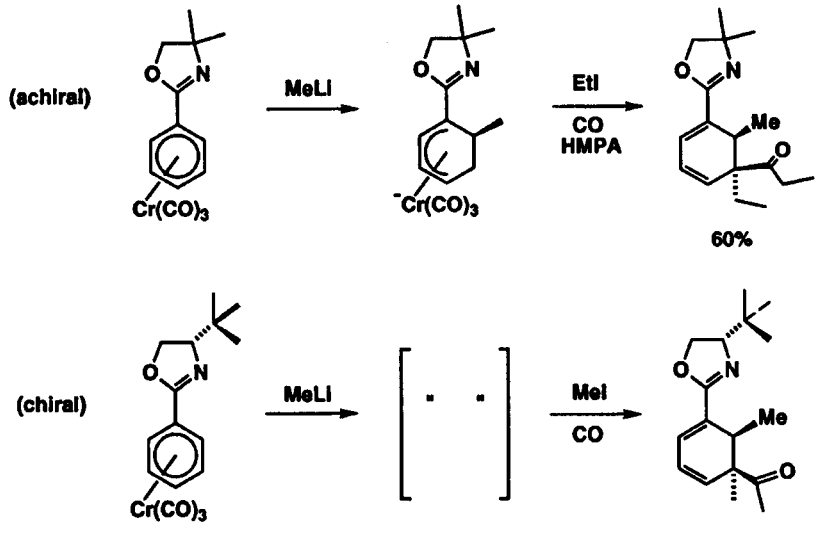


Scheme 8



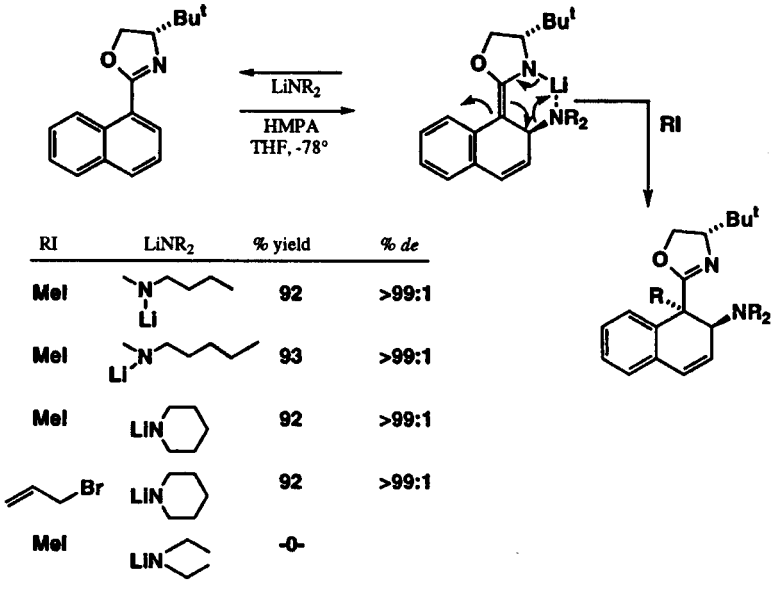
R	E
Alkyl	Me, H
Aryl	Me, H
Vinyl	Me, H
Alkenyl	Me, H

Scheme 9



HMPA = Hexamethylphosphoric triamide.

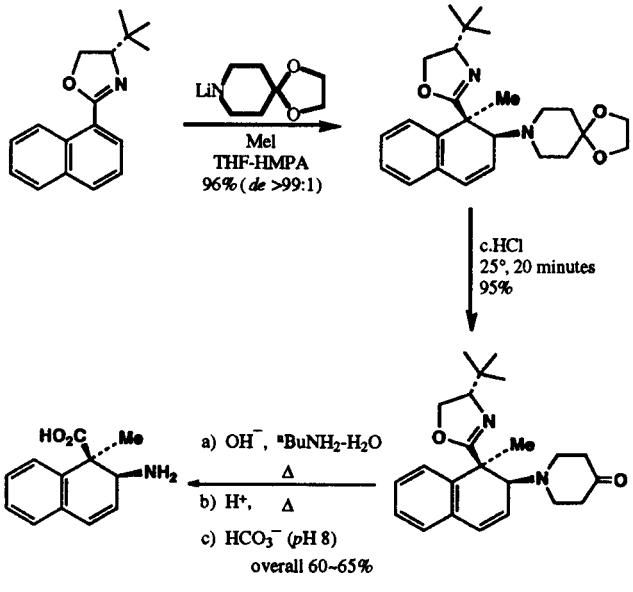
Scheme 10



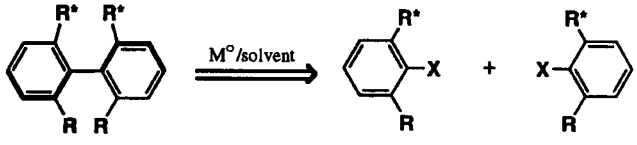
RI	$LiNR_2$	% yield	% *de*
MeI		92	>99:1
MeI		93	>99:1
MeI		92	>99:1
		92	>99:1
MeI		-0-	

HMPA = Hexamethylphosphoric triamide; THF = Tetrahydrofuran.

Scheme 11



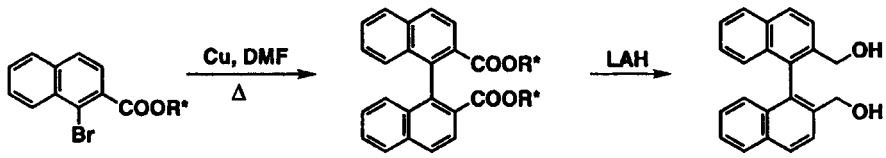
Scheme 12



R* = Chiral controller
X = I, Br, *etc.*
M° = Cu, Ni, ...

HMPA = Hexamethylphosphoric triamide; THF = Tetrahydrofuran.

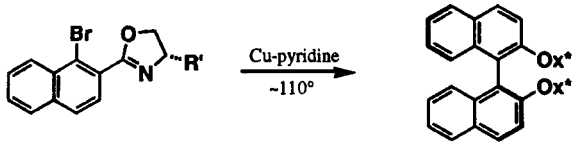
Scheme 13



R*	% ee
l-menthol	13.0
(-)-cholesterol	5.3
(-)-1-phenylethanol	7.5
(-)-2-octanol	1.8

DMF = Dimethylformamide; LAH = Lithium aluminum hydride.

Scheme 14

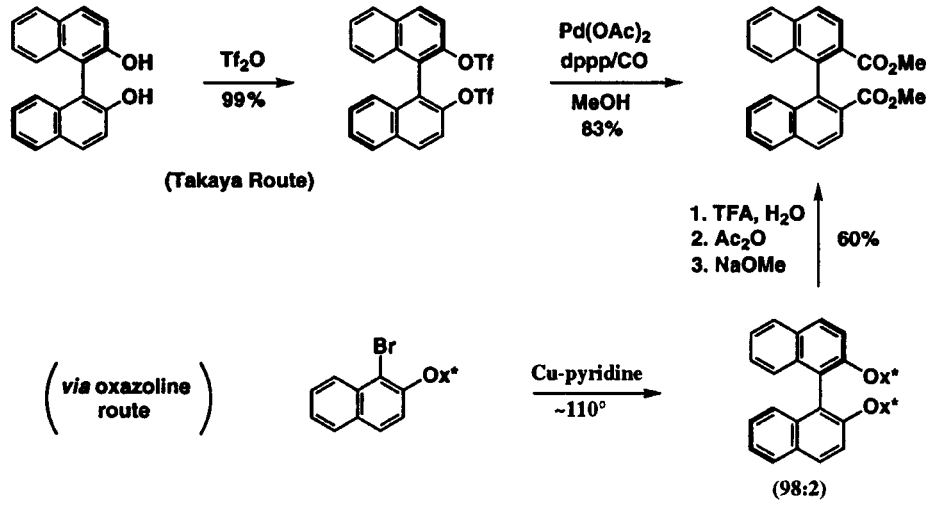


R'	Diastereomeric Ratio S:R
Ph	2:1
i-Pr	4:1
t-Bu	30:1

cant diastereoselectivity observed (Scheme 14) [33]. Similarly, use of benzene substituted bromooxazolines gave good ratios of biphenyls after prolonged heating [34].

The acquisition of the binaphthyl oxazolines in high diastereoselectivity now opened a route to a host of chiral binaphthyls - a class of chiral materials which has found so much utility in today's chemical studies [35]. For example, we were able to transform the binaphthyl oxazolines, more recently prepared in 49:1 ratio, to the chiral binaphthoic diester (Scheme 15) in 60% overall yield. This route to these important compounds compares favorably with the route using optically pure binaphthol described by Takaya [36].

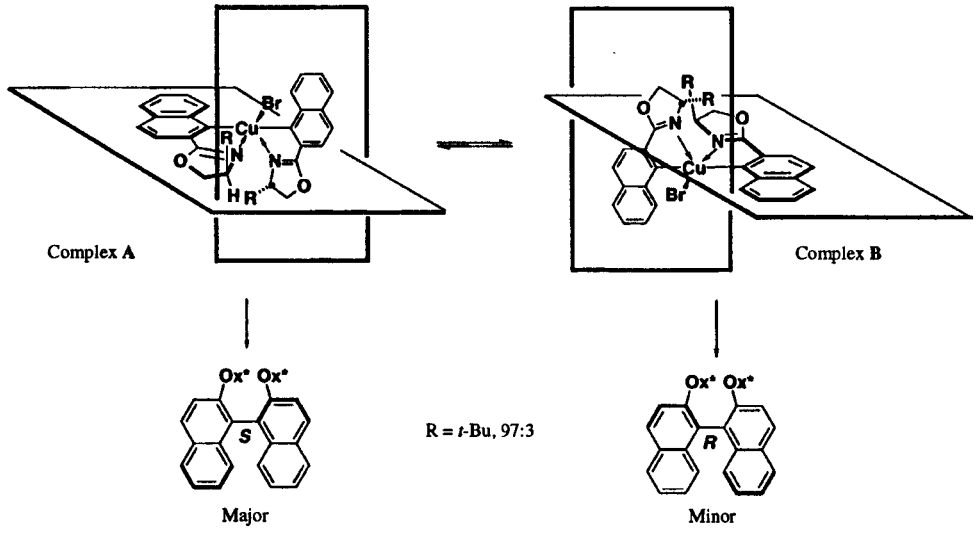
Scheme 15



TFA = Trifluoracetic acid.

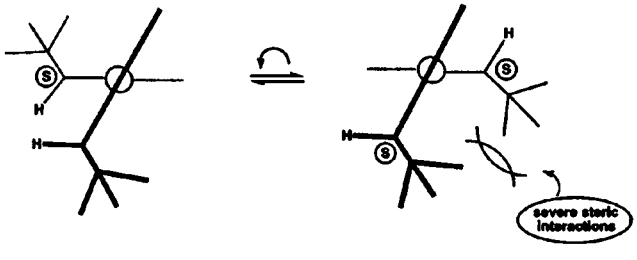
The fact that the major diastereomer in the binaphthyl coupling was *S* at the biaryl axis is consistent with our conception of the transition states during the Ullmann coupling (Scheme 16). We propose that a copper(III) species holding the two naphthalene rings prior to reductive coupling is situated such that the substituents on the oxazoline rings are anti-periplanar to each other (Complex **A** in Scheme 16 *vs.* Complex **B**). In Complex **B** the two "R" groups on the oxazoline ring are rather close and as shown earlier, the larger the R group (Ph *vs.* *i*-Pr *vs.* *t*-Bu) the higher the stereoselectivity. Another, simplied version of Scheme 16 is shown in Scheme 17 where the *t*-butyl groups on the left-hand structure are at a maximum distance while they are seriously close to each other in the right-hand structure.

Scheme 16

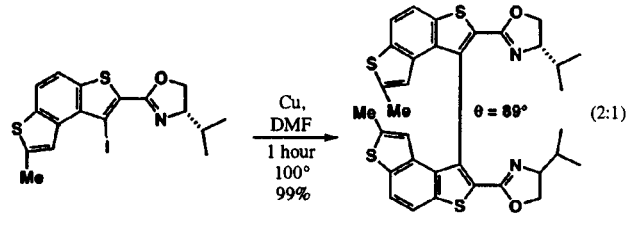


Recently, Tanaka utilized the oxazoline-mediated Ullmann coupling to prepare the bis-(bisthienyl benzene) as an optically active biaryl system (Scheme 18) [37]. Unfortunately, the use of the valine oxazoline rather than the *t*-butyl, produced the biaryl system in only a 2:1 ratio.

Scheme 17



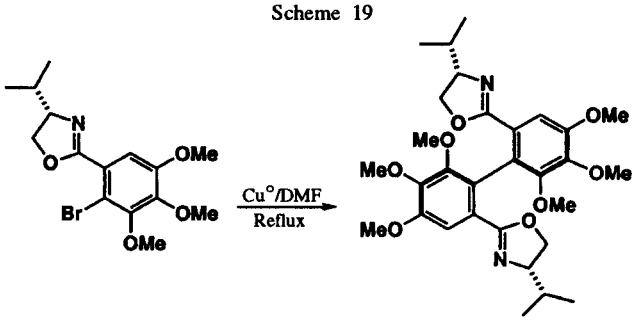
Scheme 18



It is also interesting to note that the X-ray structure of the bis-(bisthienyl benzene) showed the angle between the aryl portion to be almost 90°. This is consistent with the angle between 1,1-binaphthyls, shown by Miyano [38] to be 89°.

As briefly mentioned above, the biphenyl series was also shown to be accessible in the non-racemic form using aryloxazolines. Thus, as seen in Scheme 19, the bromo-aromatic containing oxazoline, when heated with copper in

Scheme 19

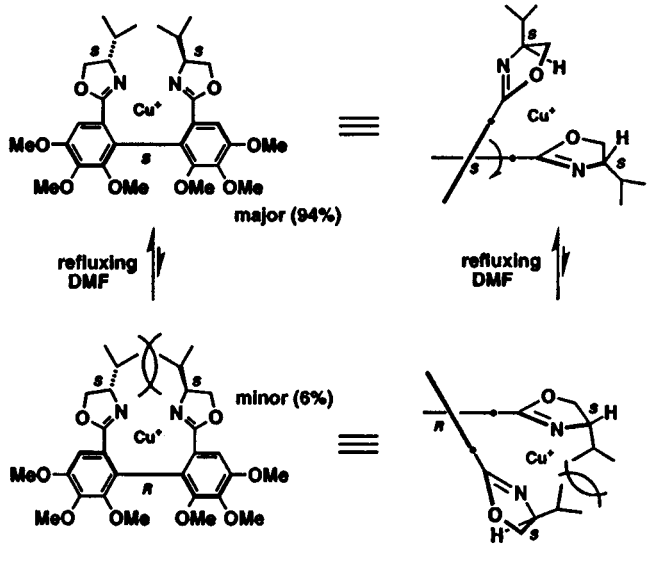


dimethylformamide (DMF), led to the biphenyl system in 88% *de* (94:6). Of interest was the fact the isopropyl (not *t*-butyl) oxazoline was employed and that the longer the reaction was allowed to proceed the higher the diastereoselectivity of the biphenyl [39].

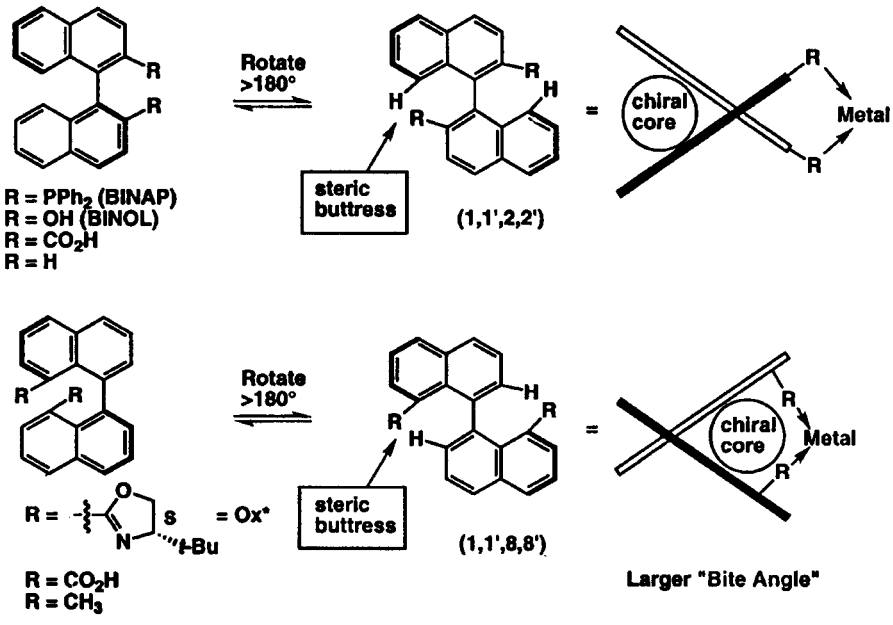
In a remarkable series of experiments, it was found that if the reaction was discontinued after a few minutes, the biphenyl yield was satisfactory, but the ratio of diastereomers was only 1.5:1. As the reaction was allowed to continue, with the copper present, the ratio reached 94:6 after 72 hours (Scheme 20). We attribute this change in ratios to the ability of the copper salts to hold the oxazolines as a chelated species thus bringing either conformation of the chelate into play. The one where the isopropyl groups are farthest apart becomes the major diastereomer. Obviously, this rotation about the copper can only occur at elevated temperatures (130-150°) so, once the system is cooled and the copper removed (aqueous ammonia), the configuration of the biphenyl remains fixed.

We have also examined the isomeric binaphthyl system continuing the 1,8 substitution pattern. Since so much work has appeared in the literature on the 1,2-system (BINOL), we felt some studies on the 1,8 might be warranted (Scheme 21). A closer examination of each of these two systems indicates that the 1,8 (more specifically the 1,1',8,8') has a larger bite angle to accommodate larger metals or larger ligands. Surprisingly, the literature on these 1,8-binaphthols is truly sparse and the fact that any have been prepared in optically active form is limited to one study [40]. The Harris group, some thirty years ago, studied the racemization of resolved optically active 1,1',8,8'-binaphthyls (Scheme 22). As seen, the racemization rates are quite high for the sp^2-substituted systems, but a bit more reasonable for methyl substituents. Why the racemization (or more accurately, the atropisomerization) should be so much more facile in this binaphthyl system than in the more commonly studied 1,1',2,2'-derivative (BINOL) is not clear. A study was recently published by Fuji [41] who compared the racemization rates of the 1,1',8,8' (left side, Scheme 23) to the 1,1',2,2' isomer (right side, Scheme 23) and showed clearly the vast difference in ease of atropisomerism. He suggests that there is distortion from planarity in the 1,1',8,8'-system of about 10° compared to an absence of this effect in the 1,1',2,2'-system. This, he states, allows the rings to rotate around the central axis so that the $POPh_2$ and MeO substituents can "gear" past each other. Further work will be necessary to better understand this dichotomy of behavior.

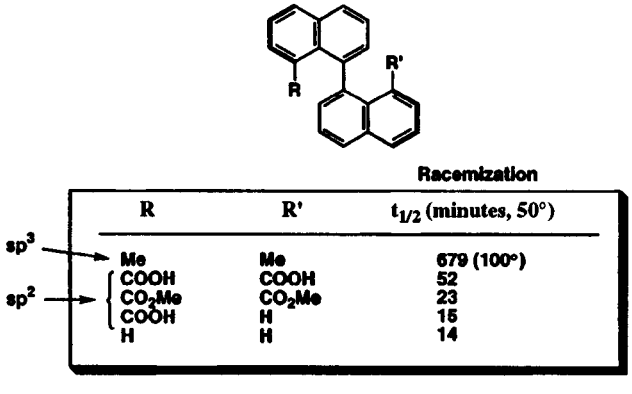
Scheme 20



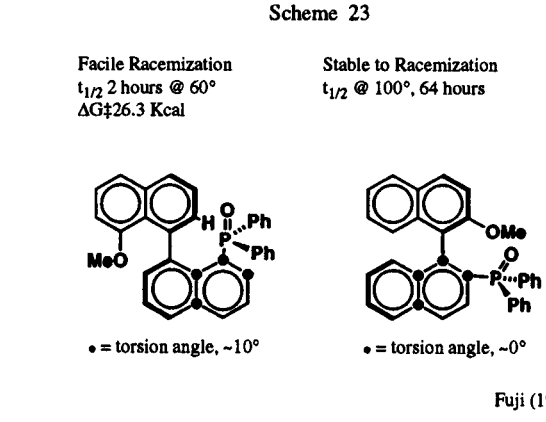
Scheme 21



Scheme 22

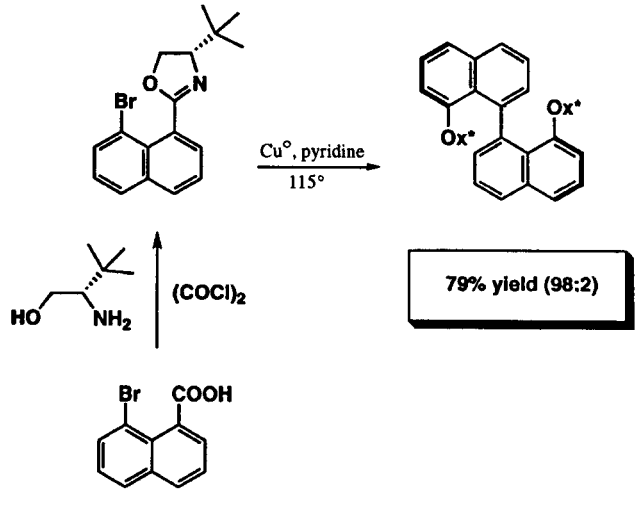


Scheme 23



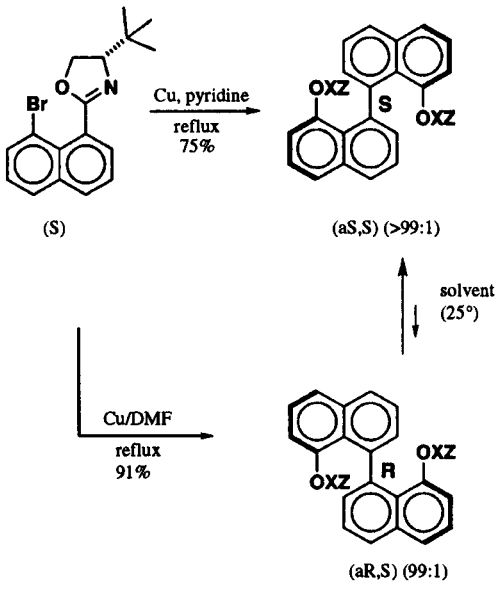
We performed the Ullmann reaction on the 1-oxazolinyl-8-bromonaphthalene and obtained a good yield [42] of the binaphthyl in a 98:2 diastereomeric ratio (Scheme 24). Of even further interest was the fact that we could, depending on the coupling conditions, prepare either

Scheme 24



atropisomer [43]. For example, if the Ullmann conditions were copper powder in pyridine, we would get the *S*-atropisomer whereas the *R*-atropisomer was obtained if dimethylformamide (DMF) was the solvent (Scheme 25). This is easily verified by nmr and ultimately X-ray structural determination. What was surprising is that even though each atropisomer in Scheme 25 could be made exclusively after removal of the copper salt (aqueous ammonia),

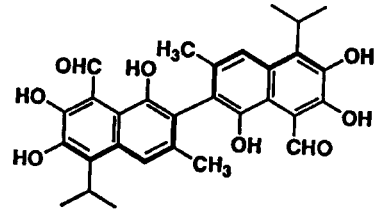
Scheme 25



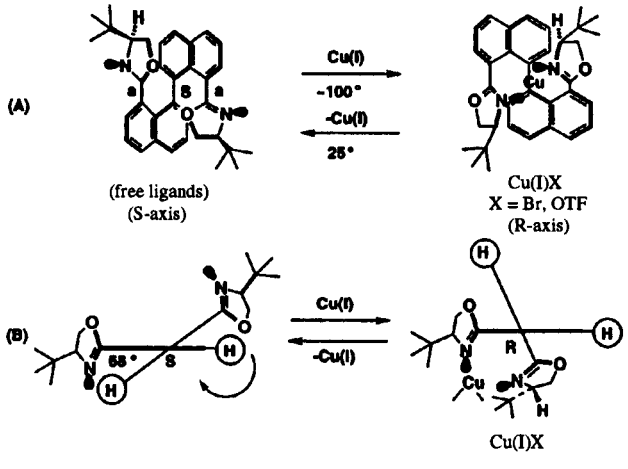
allowing it to sit neat showed each atropisomer to be stable (particularly at 0-5°). However, if *R*-atropisomer was dissolved in most solvents, it slowly and steadily transformed itself into the *S*-atropisomer. Thus, we feel the *R*-atropisomer with the *tert*-butyl groups on the oxazoline is thermodynamically less favored and reverts to the more stable *S*-atropisomer [43] in solution. If copper triflate is added to the more stable *S*-atropisomer and heated to ~100° it will clearly be transformed into the copper complex of the less stable *R*-atropisomer. This may be due to the strength of the copper-nitrogen coordination which overrides the *tert*-butyl-*tert*-butyl interaction (Scheme 26, simple line drawings, B). Recently [43] we also showed that the binaphthyl oxazolines, as copper chelates, can serve as useful catalysts in the cyclopropanation of styrenes with diazoacetic esters. Thus, the copper complex of the *S*-atropisomer in Scheme 26 is a poor and disorganized catalyst whereas the copper complex of the *R*-atropisomer in Scheme 26 is an efficient catalyst for this process.

As a final note to our recent studies with chiral oxazolines, we utilized the asymmetric Ullmann coupling in the the total synthesis [44] of *S*-gossypol, a male spermatogenic agent (Scheme 27). Although synthesis of gossypol in racemic form had been reported some 40 years ago [45], there was no asymmetric route yet reported. From the pentasubstituted benzene in Scheme 28 we elaborated, *via* a Stobbe condensation, to the naphthalene which was transformed into the chiral oxazoline and then brominated to prepare it for the asymmetric Ullmann coupling. The coupling was performed using copper powder in dimethylformamide (DMF) for 30 minutes at reflux to give the biaryl as a 17:1 mixture of atropisomers with the major one possessing the *S*-axis. The latter, after purification, was subjected to a short sequence of oxazoline removal to the primary alcohol (Scheme 29), followed by hydrogenolysis to the requisite methyl group and cleavage of eight methyl groups. The product was identical to natural gossypol and chiral hplc confirmed its enantiomeric purity as >99%.

Scheme 27
(*S*)-Gossypol

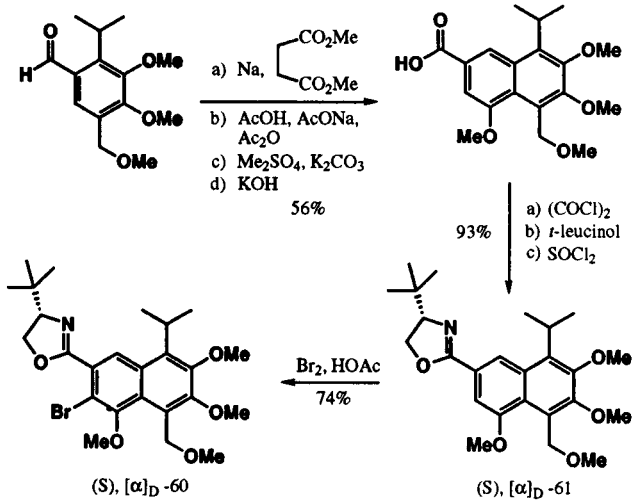


Scheme 26

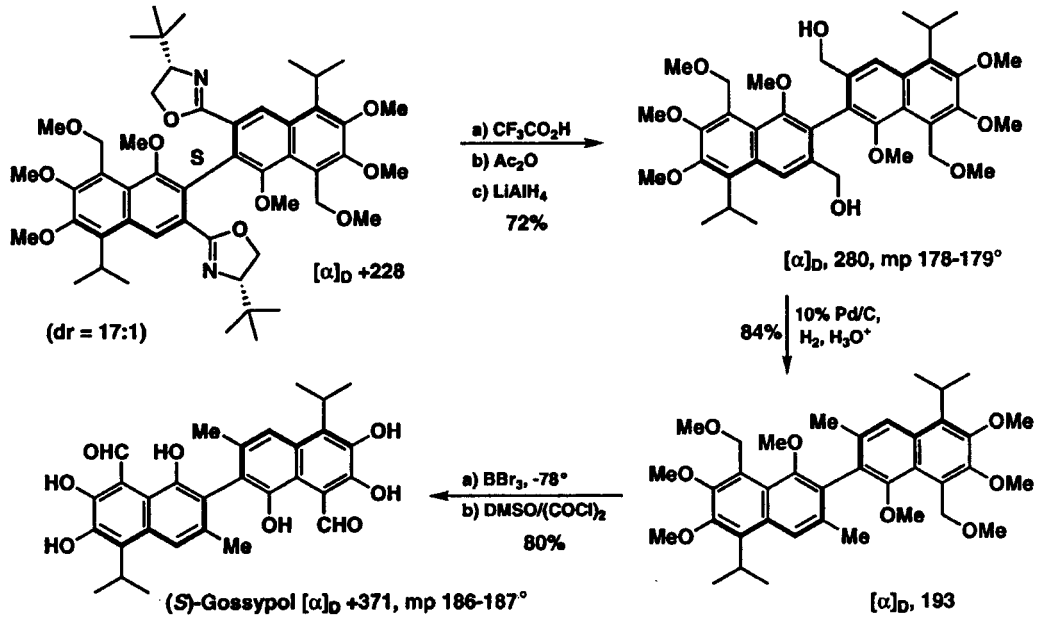


(A) aS-Binaphthyl oxazoline without Cu complex and aR-'configuration' with Cu-inserted. (B) Same, but simplified line schematic.

Scheme 28



Scheme 29



DMSO = Dimethyl sulfoxide.

In summary, the chiral oxazoline continues to be an extremely versatile synthetic player in reaching a wide variety of chiral compounds. Whether it serves as a chiral auxiliary, a catalyst ligand, or an intermediate, it has grown from its inauspicious beginnings in the last century to a major part of synthetic chemistry. Who would have thought when we first began to use oxazolines in 1969 [5a] as acetic or benzoic acid equivalents, that its use would have grown to these levels.

It only remains to express my sincere gratitude to the scores of graduate and postdoctoral students who have worked diligently on the oxazoline problem since our initial efforts in 1969. Their names appear throughout the reviews [5a-c] and those who worked beyond the reviews are clearly noted in the references cited herein. None of our work would have been possible without the generous and unbroken funding that began in 1969 and continues today. The major funds came in the early period from the National Science Foundation and later from the National Institutes of Health. A number of postdoctoral fellows received funding in the form of NIH fellowships as well as from foreign sources (CNR, CNRS, SERC, DFG, JPS). To these agencies and to all those who contributed to the success of this program, I am eternally grateful.

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