Chiral 2,2′-Bipyridines, 1,10-Phenanthrolines, and 2,2′:6′,2″-Terpyridines: Syntheses and Applications in Asymmetric Homogeneous Catalysis

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1. Introduction

Although chiral phosphines have enjoyed a long-time popularity in the design of enantioselective catalytic systems, there has been a recent renaissance in the use of nitrogen ligands for this same purpose.[1] This renaissance partly arises from several distinct advantages presented by nitrogen-containing ligands. First, they can often be employed in catalytic processes where the use of phosphines may be incompatible with the reaction conditions. Second, many nitrogen ligands are now available in enantiomerically pure form. Third, ligands that bind through nitrogen are known to coordinate with a wide variety of metal ions, and considerable progress has been made in understanding the role which these ligands play in affecting catalytic processes.

In this context, the most important nitrogen-containing ligands are those that involve the pyridine ring.[2−8] Three classes of ligand stand out in that regard and are the topic of this review: 2,2′-bipyridines (bpys), 1,10-phenanthrolines (phens), and 2,2′:6′,2″-terpyridines (tpys). Synthetic approaches to these ligands have been readily adapted to provide chiral derivatives, and these chiral ligands are finding widespread application in asymmetric catalysis. Furthermore, it will be seen that many ligands that are prepared as racemic mixtures, if they were to be resolved, might be of considerable utility as chiral auxiliaries.

This article is organized in two sections. The first section is dedicated to the synthetic procedures used to prepare chiral pyridine-containing ligands with particular attention to those ligands that have found application as chiral auxiliaries in asymmetric processes. The second section is devoted to a discussion of the enantioselective processes that utilize such ligands.

2. Syntheses

2.1. 2,2′-Bipyridines

2.1.1. 2,2′-Bipyridines with Central Chirality

The first preparation of a chiral, nonracemic bpy was reported in 1984 by Botteghi's group as part of a study aimed at the preparation of the four regioisomeric monoalkyl-substituted bpys. This group prepared the 4- and 6-substituted bpys **4** and **9** (Schemes 1 and 2)[9] followed by the other two regioisomers **22** and **26** (Schemes 5 and 6).[10] All these ligands share the *sec*-butyl group as a common substituent and the optically active (*S*)-2-methylbutanol (**1**) as the starting material.

The preparation of the bpy **4** starts from the monoprotected 1,5-dialdehyde **2**, which was treated with 2-pyridyllithium at −70 °C to give the corresponding carbinol (Scheme 1). This carbinol was not isolated, but directly oxidized with activated manganese dioxide (MnO_2) at room temperature to the ketone **3** (50%), which underwent aza-anellation in the presence of hydroxylamine hydrochloride (NH_2-OH−HCl) in dry acetic acid to afford 4-*sec*-butylbpy (**4**) in 40% yield.

The synthesis of the 6-*sec*-butylbpy (**9**) (Scheme 2) is based on the cobalt(I)-catalyzed cyclotrimerization reaction of nitrile **8** with acetylene.[11] This reaction represents a straightforward approach for the construction of a bipyridine from a 2-cyanopyridine with

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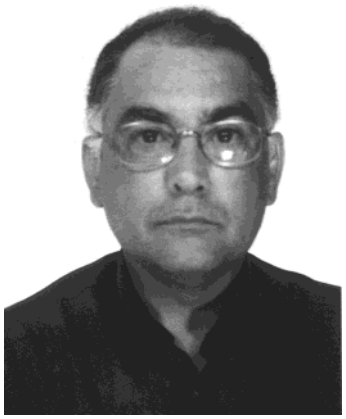
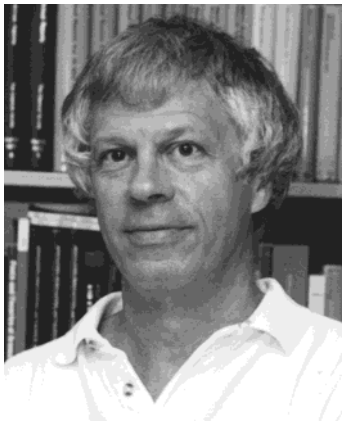


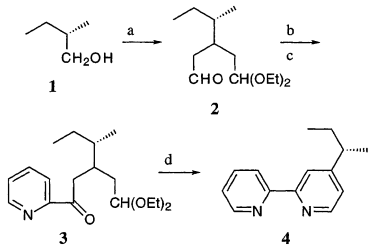
Giorgio Chelucci was born in Cagliari (Sardegna, Italy) and studied Chemistry at the University of Sassari (Sardegna), where he received his Laurea degree in 1978. After 5 years of postdoctoral work he became a Researcher in the Department of Organic Chemistry at the University of Sassari. Since 1994, he has been an Assistant Professor of Organic Chemistry at the Faculty of Science of the University of Sassari. His research centers on the synthesis of chiral heterocycles based on the pyridine framework (bipyridines, phenanthrolines, terpyridines, pyridylphosphines, etc.) and their utilization as ligands for asymmetric catalytic reactions (allylic alkylations, cyclopropanations, allylic oxidations, etc.).



Randy Thummel was born in New York City and raised in Montclair, NJ. He received his B.S. degree in Chemistry from Brown University and his Ph.D. degree from the University of California at Santa Barbara, working with Professor Bruce Rickborn studying base-promoted epoxide rearrangements. He then spent two years as an N.I.H. postdoctoral fellow with Professor Paul Gassman at the Ohio State University. In 1973, he accepted a faculty position in the Chemistry Department at the University of Houston, where he is currently Professor of Organic Chemistry. Thummel's early research interests included the study of benzocyclobutenes and other small ring-fused aromatic systems. More recently, he has become involved in the design, synthesis, and coordination chemistry of novel ligand systems involving pyridine and pyrrole.

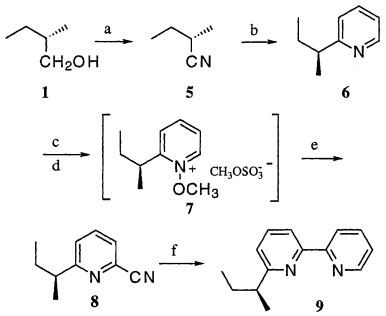
a stereogenic center bonded to the 6-position, starting from a chiral nonracemic compound.[12] In fact, not only bpy **9**, but also the pyridine **6** was prepared by this method, starting from nitrile **5**, which is available from (*S*)-2-methylbutanol (**1**) by several different methods.[13] Compound **8** was prepared by the regioselective introduction of the cyano group into the 6-position of the pyridine ring by treatment of the *N*-oxide of **6** with dimethyl sulfate followed by reaction of the unisolated pyridinium salt **7** with potassium cyanide (51%). The final cyclization reaction with acetylene was carried out by using (*p*-cyclopentadienyl)cobalt 1,5-cyclooctadiene [CpCo(COD)] as the catalytic precursor and toluene as the solvent to give the 6-*sec*-butylbpy (**9**) in 80% yield.

Scheme 1[a]



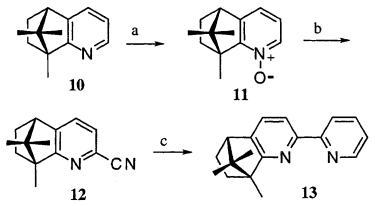
[a] Legend: (a) Several steps; (b) 2-PyLi, Et_2O, −70 °C; (c) MnO_2, Et_2O, 50%; (d) $NH_2OH-HCl$, CH_3COOH, reflux, 6 h, 40%.

Scheme 2[a]



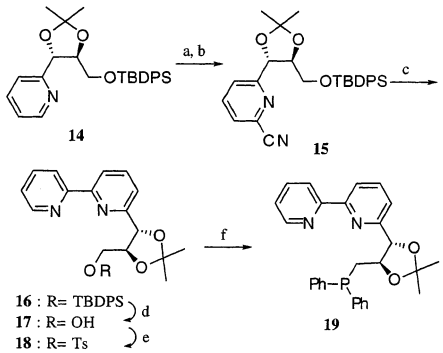
[a] Legend: (a) several steps; (b) CpCo(COD), acetylene, 8 atm, 140 °C, 95%; (c) *m*-CPBA, $CHCl_3$, 0 °C to room temperature, 3 h, 85%; (d) $(CH_3O)_2SO_2$, 80 °C, 2 h; (e) KCN, H_2O, 51%; (f) CpCo(COD), toluene, acetylene, 13 atm, 120 °C, 20 h, 80%.

Scheme 3[a]



[a] Legend: (a) *m*-CPBA, $CHCl_3$, 0 °C to room temperature, 3 h, 92%; (b) $(CH_3O)_2SO_2$, 80 °C, 2 h; then KCN, H_2O, 12 h, 35%; (c) CpCo(COD), toluene, acetylene, 12 atm, 130 °C, 68%.

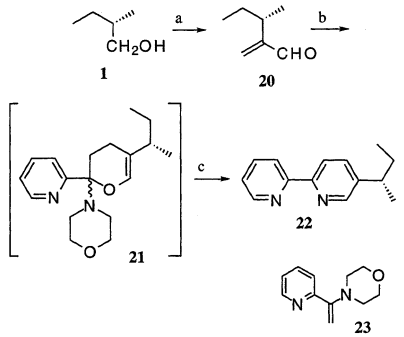
Scheme 4[a]



[a] Legend: (a) *m*-CPBA, $CHCl_3$, 24 h; (b) $(CH_3)_2NCOCl$, $(CH_3)_3SiCn$, CH_2Cl_2, room temperature, 6 days, 83%; (c) CpCo(COD), acetylene, toluene, 120 °C, 13 atm, 86%; (d) Bu_4NF, THF, 97%; (e) TsCl, Et_3N, DMPA, CH_2Cl_2, 75%; (f) Ph_3P, Na/K, dioxane, 67%.

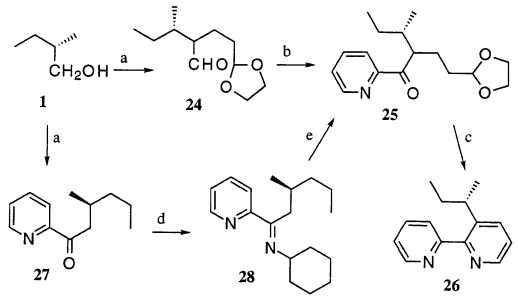
The sequence of cyanation-cyclotrimerization not only represents a general approach to obtain simple 6-substituted bpys but also more complex derivatives. In Scheme 3 is outlined the synthesis of bpy **13** in which the chiral auxiliary, (+)-camphor, is present in the form of a cycloalkeno-condensed substituent.[14]

Scheme 5[a]



[a] Legend: (a) several steps; (b) **23**, benzene; (c) $NH_2OH-HCl$, CH_3COOH, reflux, 60%.

Scheme 6[a]



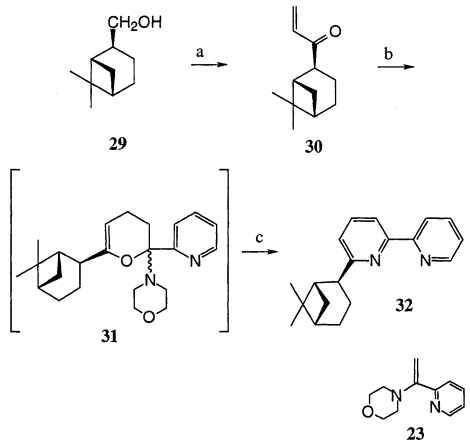
[a] Legend: (a) several steps; (b) 2-PyLi, Et_2O, −60 °C; then MnO_2, Et_2O, 5 days, 60%; (c) $NH_2OH-HCl$, CH_3COOH, 115 °C, 2 h, 61%; (d) $C_6H_{11}NH_2$, benzene, 3.5 h, 83%; (e) $LiNEt_2$, HMPTA/THF, −60 °C, then BED, THF; finally 10% tartaric acid, 0 °C, 5 h, 62%.

Another representative example is found in the reaction sequence that affords the bpy-phosphine **19** (Scheme 4).[15] In this case, the introduction of the cyano group onto pyridine **14** occurs in a regiospecific manner by treatment of its *N*-oxide derivative with trimethylsilylcarbonitrile and dimethylcarbamyl chloride in CH_2Cl_2 for 6 days (83% yield based on **14**).[16] Cyclotrimerization of **15** with acetylene in the presence of CpCo(COD) afforded the bpy **16** in 86% yield. Nucleophilic displacement of the tosyl group of **18**, obtained from **16** in the usual manner, using Na/K diphenylphosphide, gave **19** in low yield (15%) after three chromatographic separations.

The 5-*sec*-butylbpy (**22**) (Scheme 5) was obtained by cycloaddition of the morpholino-enamine of 2-acetylpyridine (**23**) with (*S*)-2-*sec*-butylacrolein (**20**) followed by aza-annelation of the crude intermediate dihydropyran **21** with $NH_2OH-HCl$ in acetic acid (60% overall yield).[10]

The synthesis of the 3-*sec*-butylbpy (**26**) is based on the cyclization of the monoprotected 1,5-dicarbonyl compound **25**, which was prepared by following two different pathways starting from the chiral alcohol **1**.[10] In one approach, the aldehyde **24** was transformed into **25** by treatment with 2-pyridyllithium followed by oxidation of the intermediate crude carbinol with activated MnO_2 (60% overall yield). In the other approach, the ketone **27** was converted into the cyclohexylimine derivative **28** and then alkylated with 1-bromo-3,3-ethylenedioxypropane (BED) to give, after selective hydrolysis of the primary alkylation product, the compound **25** in 50% overall yield.

Scheme 7[a]



[a] Legend: (a) several steps; (b) **23**, benzene, reflux; (c) $NH_2OH-HCl$, AcOH, reflux, 25% overall.

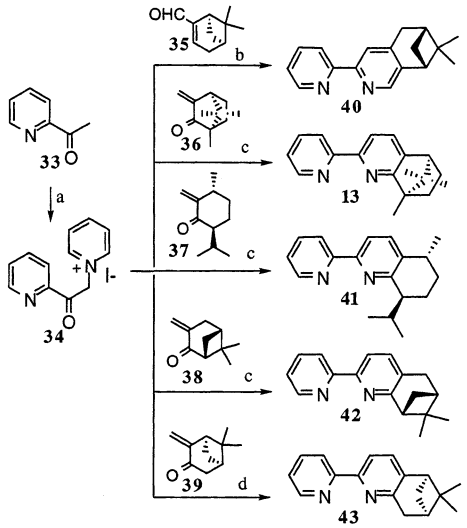
Substituted bpys that have found application in metal-catalyzed asymmetric reactions often bear a stereogenic center at the 6- or 6,6′-positions of the bpy framework. Such substitution should markedly affect the steric interaction between the ligand and the substrate, both of which are coordinated to the metal. Thus, stereoselectivity is expected to improve, as the chiral portion of the ligand gets closer to the metal center. Many efforts have been focused on the preparation of such ligands. To obtain 6-substituted bpys, the method of choice, starting from a chiral, nonracemic compound, is the cobalt(I)-catalyzed cyclotrimerization of nitriles with acetylene. However, a possibly easier entry to such compounds would involve the reaction of an α,β-unsaturated carbonyl compound with a 2-acetylpyridine derivative. The main limitation of this procedure is that the configuration of the stereocenter on the carbonyl function must be stable. This circumstance occurs with diastereomers.

For example, condensation of the morpholine enamine of 2-acetylpyridine **(23)** with the vinyl ketone **30**, followed by reaction with $NH_2OH-HCl$ in dry acetic acid gives the intermediate **31**, which affords the bpy **32** in 25% overall yield as a single diastereomer (Scheme 7).[17]

A more general approach to [4,5]- and [5,6]-cycloalkeno-fused bpys involves the Kröhnke-type cyclization of 2-acetylpyridinepyridinium iodide (**34**), prepared by reaction of 2-acetylpyridine **(33)** with iodine in pyridine,[18] with an α,β-unsaturated carbonyl compound.[19] Following this protocol, von Zelewsky and co-workers condensed **34** with (−)-myrtenal (**35**) and (+)-pinocarvone ((+)-**39**) to obtain the bpys **40** and **43**, respectively[20] (Scheme 8). Similarly, other groups prepared the bpys **13**,[21] **41**,[21] and **42**[22] (Scheme 8). The Kröhnke-type cyclization of a pyridinium salt and an α,β-unsaturated ketone has been also used to synthesized the bpy **47** with two methyl groups at the 3- and 3′-positions of the heterocycle (Scheme 9).[21]

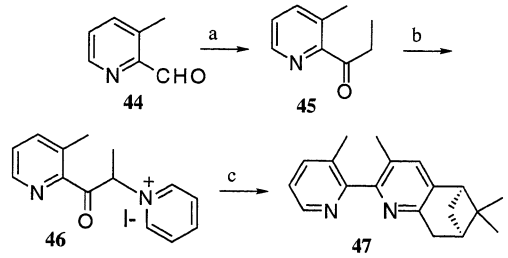
Bpys **40** and **43** are interesting molecules because they can easily be transformed into other chiral bpys (Schemes 10 and 11). In fact, these ligands have the useful property that the α-methylene proton is removable by strong base (lithium diisopropylamide,

Scheme 8[a]



[a] Legend: (a) I_2, pyridine; (b) **35**, NH_4OAc, $HCONH_2$, 100 °C, 12 h, 55%; (c) **36** or **37** or **38**, AcOH, $AcONH_4$, 100 °C, 3 h; (d) **39**, NH_4OAc, $HCONH_2$, 70 °C, 6 h, 75%.

Scheme 9[a]

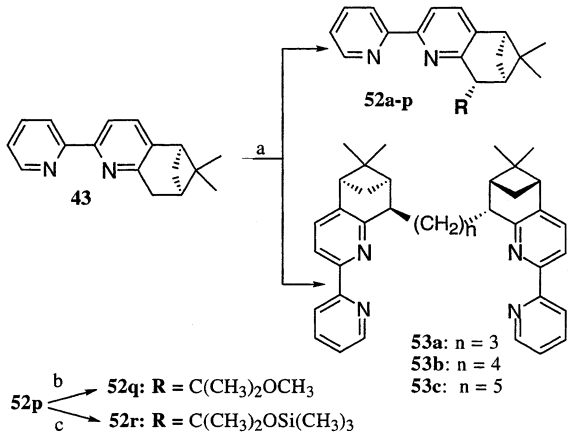


[a] Legend: (a) EtMgBr, Et_2O, −78 °C; then Swern oxidation; (b) I_2, pyridine, 100 °C; (c) (+)-**39**, NH_4OAc, HOAc, 100 °C.

LDA). The resulting anion can subsequently undergo stereospecific substitution or addition reactions in high yield. The substituent adds to the sterically less hindered side (*trans* to the dimethyl bridge) creating a new, well-defined stereocenter.

Thus, starting from **40** and **43** von Zelewsky and co-workers prepared a number of chiral bpy derivatives that they call "CHIRAGEN" ligands (CHIRAGEN = chirality generating). Some examples are reported in Schemes 10 and 11.[20,23] These CHIRAGEN ligands prove to be useful in the stereoselective self-assembly of large supramolecular coordinating species.[24]

Scheme 11[a]



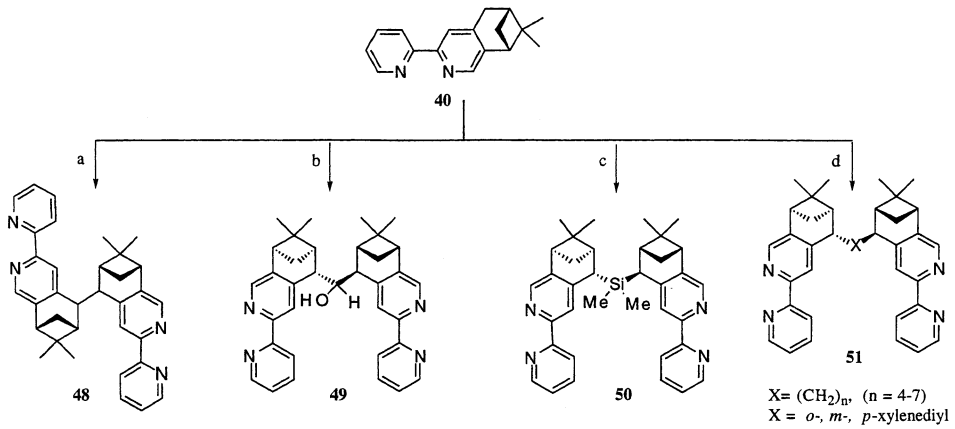
R= **a**: CH_3, **b**: CH_2CH_3, **c**: $CH_2CH_2CH_3$, **d**: $CH_2(CH_2)_2CH_3$, **e**: $CH_2(CH_2)_3CH_3$, **f**: CH_2-C_6H_5, **g**: $CH(CH_3)_2$, **h**: $CH(C_2H_5)_2$, **i**: $CH_2CH(CH_3)_2$, **l**: $CH_2CH_2CH(CH_3)_2$, **m**: $CH_2(CH_2)_2CH(CH_3)_2$, **n**: $C(CH_3)$(2-naphthyl)OH, **o**: C(Aryl')(Aryl")OH, **p**: $C(CH_3)_2OH$

[a] Legend: (a) LDA, THF, 2 h at −40 °C, then RI or RBr or $I(CH_2)_nI$ or CH_3CO(2-naphthyl) or Aryl'COAryl" or CH_3COCH_3; (b) NaH, THF, then CH_3I; (c) imidazole, DMF, $ClSi(CH_3)_3$.

Other ligands that may be used as chiral controllers for asymmetric catalysis are derivatives of bpy **43**. By treating the anion of **43** with different electrophiles, a number of new bpys have been obtained[21,24−26] (Scheme 11). These compounds are interesting because the rigidity of the [5,6]-fused pineno-ring forces the substituents to be directed toward the metal center so that high asymmetric induction is expected.

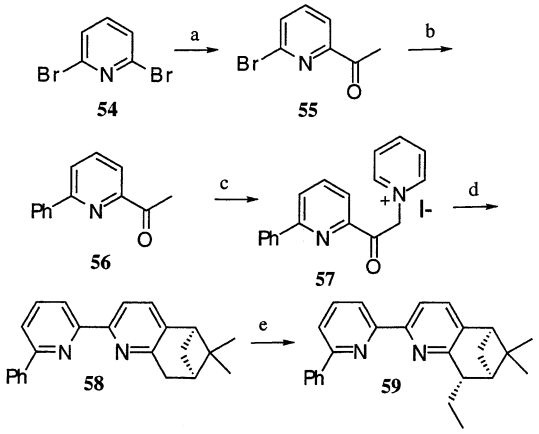
The synthesis of a C_1-symmetric bpy, with a pinene fused to one pyridine ring and a phenyl group attached at the 6′-position of the other pyridine ring, has been recently reported by von Zelewsky and coworkers (Scheme 12).[27] Their synthesis starts from 2-acetyl-6-phenylpyridine (**56**), which was prepared in 53% overall yield by the reaction of the monolithium salt of 2,6-dibromopyridine (**54**) with dimethylacetamide followed by cross-coupling of **55** with phenylboronic acid in the presence of $Pd(PPh_3)_4$

Scheme 10[a]



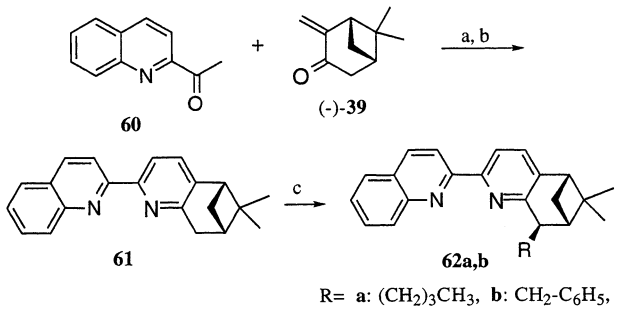
[a] Legend: (a) LDA, THF, 2 h at − 40 °C then I_2, THF; (b) LDA, THF, 2 h at −40 °C then HCOOEt; (c) LDA, THF, 2 h at −40 °C then $SiMe_2Cl_2$, THF.

Scheme 12[a]



[a] Legend: (a) BuLi, Et_2O, −60 °C, then $MeCONMe_2$, 58%; (b) $PhB(OH)_2$, xylene, $Pd(PPh_3)_4$, Na_2CO_3, 91%; (c) I_2, pyridine, 100%; (d) (+)-**39**, NH_4OAc, AcOH, 110 °C, 16 h, 55%; e: LDA, THF, −40 °C, then EtI.

Scheme 13[a]



[a] Legend: (a) LDA, THF, −78 °C, 2 h; then **39** from −78 °C to slowly room temperature; (b) AcOH, NH_4OAc, THF, reflux, 2 h; (d) LDA, THF, −40 °C, 2 h; then $CH_3(CH_2)_2CH_2I$ or $C_6H_5CH_2I$.

and Na_2CO_3. Compound **56** was then converted to the Kröhnke salt **57**, which, by condensation with (+)-pinocarvone ((+)-**39**) and subsequent aza-annelation, yielded the bpy **58** in 40% yield. The corresponding ethyl derivative **59** was also prepared by alkylation of **58** using LDA and ethyl iodide.

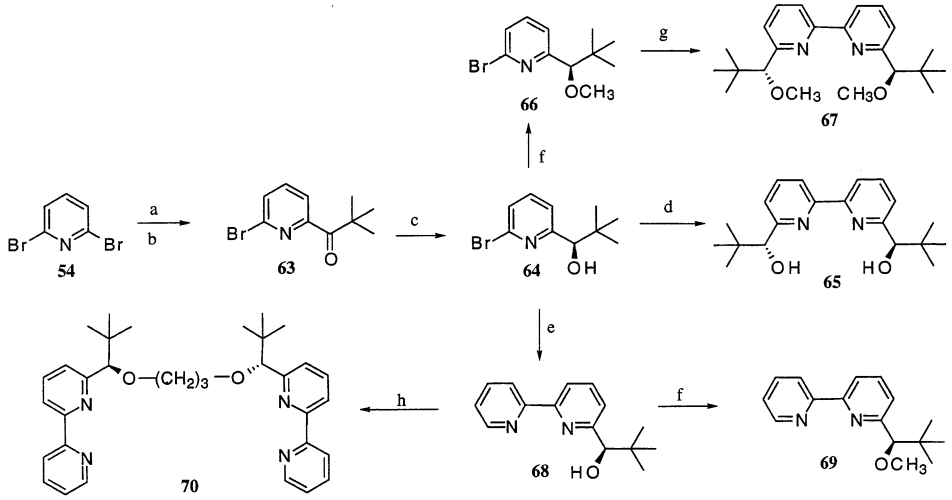
We have recently employed a different approach for the synthesis of compounds **62a**,**b** where a 2-quinolinyl ring has been substituted for a pyridine (Scheme 13).[28] In this case, the key quinolinylpyridine **61** was obtained by conjugate addition of the lithium enolate of 2-acetylquinoline (**60**) to (−)-pinocarvone ((−)-**39**) followed by aza-annelation of nonisolated 1,5-dicarbonyl intermediate using ammonium acetate and acetic acid. The alkylation of **61** with butyl or benzyl iodide completes the synthesis.

The presence of a C_2-symmetry axis within a chiral auxiliary can dramatically reduce the number of possible competing diastereomeric transition states.[29] For this purpose, several different bpys have been prepared with this topological property. Three general approaches have been successfully employed for the synthesis of a C_2-symmetric bpy: (i) the metal-mediated homocoupling of a 2-halopyridine bearing a chiral substituent; (ii) the construction of a second pyridine ring bearing a chiral group to elaborate an existing pyridine which bears the same chiral group; (iii) the incorporation of chiral substituents onto a functionalized bpy.

Following the first approach, the 2-halopyridines, used for the homocoupling, have been prepared in two ways. The first way involves the monolithiation of 2,6-dibromopyridine followed by treatment with an appropriate chiral derivative. The second approach involves constructing a pyridine derivative containing both the chirogenic element and a functional group which may be converted into a 2-chloro or 2-bromo derivative.

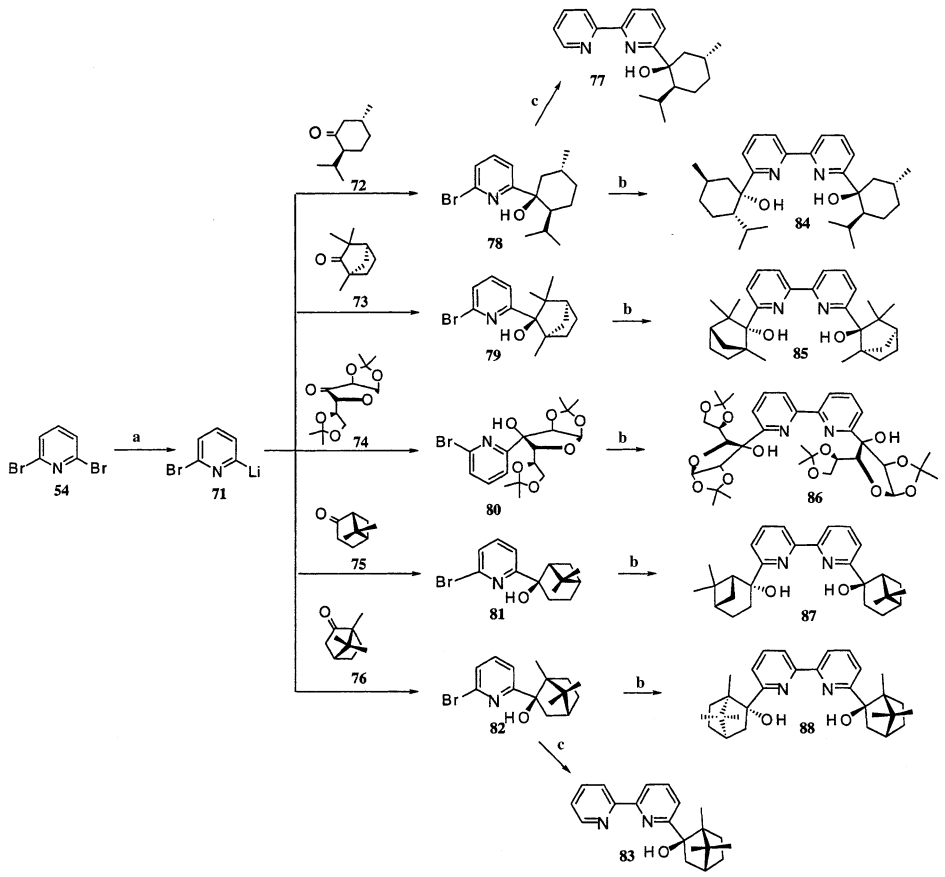
In 1990, Bolm et al. reported the synthesis of bpy **65**, as the first example of a chiral bpy with C_2-symmetry, by a nickel(0)/triphenylphosphine mediated reaction[30] of bromopyridine **64** (55%, Scheme 14).[31] In this case, the optically active alcohol **64** was accessible in a two-step reaction from 2,6-dibromopyridine (**54**) through condensation of its monolithium salt, generated by treatment with *n*-butyllithium at −90 °C, with methyl 2,2-dimethylpropionate, fol-

Scheme 14[a]



[a] Legend: (a) BuLi, THF, −78 °C; (b) *t*-$BuCO_2CH_3$, −78 °C to room temperature, 3.5 h, 80%; (c) (−)-*β*-chlorodiisopinocampheylborane, neat, room temperature, 2 days; then iminodiethanol, Et_2O, 3 h, 59%; (d) $NiCl_2 \cdot 6H_2O$, Zn, PPh_3, DMF, 72 °C, 3.5 h, 55%; (e) Py−ZnCl (53%) or Py−$SnBu_3$ (50%), $Pd(PPh_3)_4$; (f) NaH, THF, MeI; (g) $NiCl_2 \cdot 6H_2O$, Zn, PPh_3, DMF, 72 °C, 2 h, 50%; (h) NaH, THF, 1,3-dibromopropane, 13%.

Scheme 15[a]



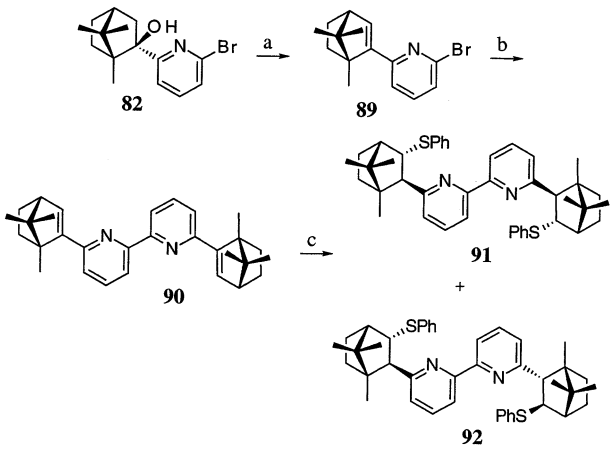
[a] Legend: (a) *n*-BuLi, Et_2O, −78 to −40 °C then **72**−**76**; (b) $NiCl_2 \cdot 6H_2O$, PPh_3, Zn, DMF; (c) $Pd(PPh_3)_4$, 2-ClZnPy.

lowed by asymmetric reduction of the prochiral ketone **63** with (−)-*β*-chlorodiisopinocamphenylborane.[32] Moreover, the heterocoupling[33] of **64** with 2-pyridylzinc chloride [2-pyZnCl] or 2-pyridyl-tri-*n*-butylstannane [2-py$SnBu_3$] in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] provides the bpy **68** with C_1-symmetry in about 50% yield. Treatment with NaH/MeI converted the optically active alcohol **69** into the methoxy derivative **66** (84%), which was homocoupled in the usual way to give the bpy **67** (50%).[31] The bpy **68**, by treatment with NaH and then MeI or 1,3-dibromopropane, also afforded the bpy **69** and the C_2-symmetric compound **70**,[21] respectively (Scheme 14).

An easier entry to bpy alcohols involves trapping 6-bromo-2-pyridyllithium (**71**) with optically active, naturally occurring ketones (Scheme 15). Thus, the bpy alcohols **84**, **85**, **87**, **88**,[34] and **86**[35] were obtained as single diastereomers in 43−58% yield based on **54**, depending only slightly on the nature of the ketone. Furthermore, the C_1-symmetric bpys **77** and **83**[34] were prepared by Pd(0)-catalyzed cross-coupling of **78** and **82** with 2-pyZnCl.

The hydroxyl group of pyridyl alcohols such as **78**−**82** can be transformed into other functional groups to provide different bpy derivatives. An example of this strategy, reported in Scheme 16, is the synthesis of bpy thioethers **91** and **92** derived from (+)-camphor.[36] Bromopyridine **82** was dehydrated with thionyl chloride in pyridine to give the alkene **89**, which was homocoupled in the presence of Ni(0) to give bpy **90** in 82% yield. Addition of thiophenol to

Scheme 16[a]

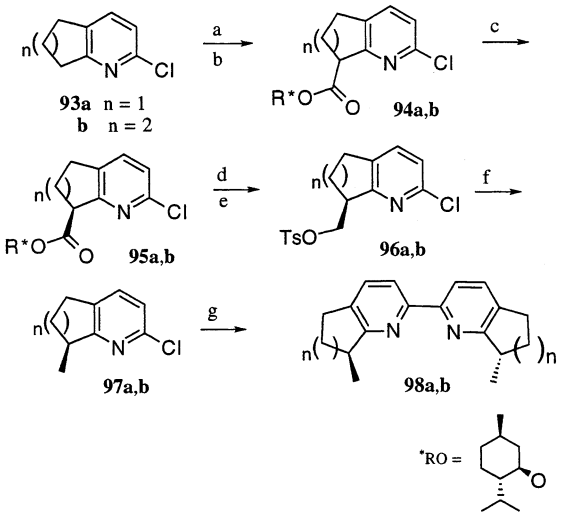


[a] Legend: (a) $SOCl_2$, pyridine, 0 °C then 1 h at room temperature; (b) $NiCl_2 \cdot 6H_2O$, Zn, PPh_3, DMF; (c) PhSH, AcOH, reflux, 3 h.

the double bonds of bpy **90** occurred, and a 9:2 mixture of C_2-symmetric bpy **91** and C_1-symmetric bpy **92** was obtained. From this mixture, only the more abundant ligand **91** was recovered in 66% yield.

In a series of papers, Katsuki et al. reported the synthesis of a number of chiral, C_2-symmetric 5,6-cycloalkeno-fused bpys with a stereogenic center bonded to the α-position of the cycloalkene ring. This work was prompted by the belief that the stereoselectivity of a process increases as the substituent on the stereogenic carbon is directed more toward the bound metal ion.

Scheme 17[a]



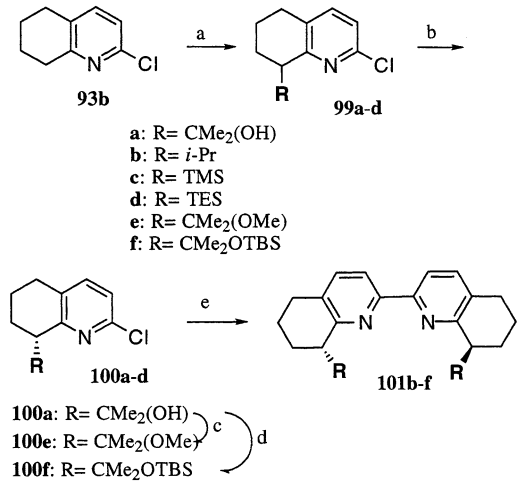
[a] Legend: (a) LDA, −78 °C; (b) (−)-menthyl chloroformate, −78 °C; (c) chromatographic separation; (d) AlH_3; (e) TsCl, NEt_3, DMAP; (f) $LiBEt_3H$; (g) $NiCl_2$, PPh_3, Zn.

As a first example, they reported the preparation of the enantiomerically pure methyl substituted bpys **98a,b** (Scheme 15).[37] Their synthesis of these compounds starts from 6-chloro-2,3-cyclopenteno- and 6-chloro-2,3-cyclohexenopyridines (**93a**,**b**), which were successively treated with LDA and (−)-menthyl chloroformate at −78 °C to give the respective carbonates **94a,b** as mixtures of diastereomers. From these mixtures, the more polar diastereomers with the S-configuration (**95a,b**) were separated by chromatography on silica gel and then converted to the toluenesulfonates (*S*)-**96a**,**b** by reduction with AlH_3 followed by tosylation of the resulting alcohol. The toluene sulfonylmethoxymethyl group in (*S*)-**96a**,**b** was converted into a methyl group by $LiBEt_3H$ reduction to give (*S*)-**97a**,**b**. These compounds were then subjected to a Ni(0)-mediated homocoupling reaction to give the desired chiral bpys (*S*,*S*)-**98a** and (*S*,*S*)-**98b** in 33 and 47% overall yields from **93a** and **93b**, respectively. The less polar isomers (*R*)-**95a,b** were converted into the corresponding bpys (*R*,*R*)-**98a**,**b** in a similar manner.

To explore the potential of ligands bearing a substituent larger than a methyl group, Katsuki et al. synthesized the series **101b**−**f** (Scheme 18).[38] These bpys were prepared starting from the 2-chloro-5,6,7,8-tetrahydroquinoline (**93b**), which was treated with LDA followed by the appropriate electrophile to give a C8-substituted tetrahydroquinoline **99a**−**d**. All attempts to resolve these compounds with the aid of various optically active acids were unsuccessful. The enantiomers were ultimately separated by HPLC using an optically active column (Daicel Chiracel, OF) and the ligand, which eluted first, was used for the next reaction. Tetrahydroquinolines **100b**−**f** were homocoupled in the presence of Ni(0) to give bpys **101b**−**f** and a trace amount (<5%) of the corresponding *meso*-isomers, which were readily removed by column chromatography.

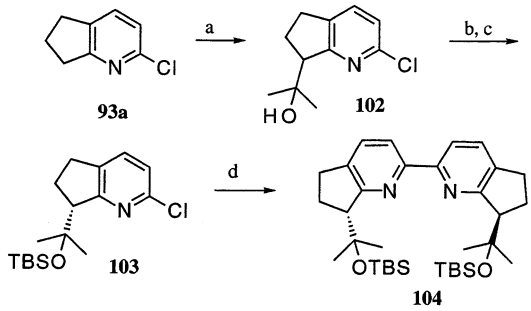
In a later paper, the same group reported the preparation of bpy **104**, starting from 2-chloro-6,7-dihydro-5H-1-pyridine (**93a**) following the sequence in Scheme 19.[39]

Scheme 18[a]



[a] Legend: (a) LDA, −78 °C, then acetone (60%) or *i*-PrI (58%) or TMSCI (58%) or TESCl (25%); (b) resolution by chiral HPLC (Daicel Chiralcel, OF) (16−43%); (c) BuLi, then MeOTf, 58%; (d) TBDSOTf, 2,6-lutidine; (e) $NiCl_2$, PPh_3, Zn, 46−66%;

Scheme 19[a]

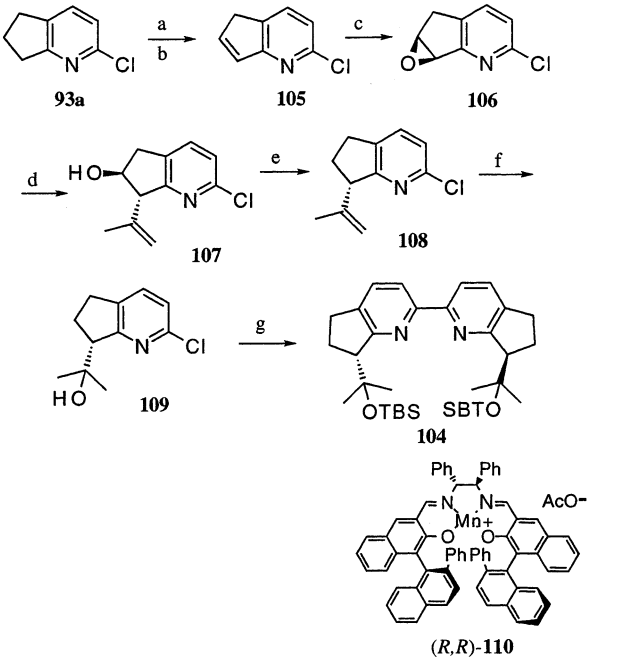


[a] Legend: (a) LDA, −78 °, then acetone, 61%; (b) TBDSOTf, 2, 6-lutidine, 90%; (c) resolution by chiral HPLC (Daicel Chiralcel, OF); (d) $NiCl_2$, PPh_3, Zn, 91%.

The synthesis of **101b**−**f** and **104** is rather difficult because resolution of the intermediate tetrahydroquinolines **99** and **102** could be achieved only with aid of HPLC using an optically active column, thus providing only a small amount of these ligands. Hoping to obtain these ligands in larger quantities, Katsuki and co-workers examined alternative synthetic methods. Schemes 20 and 21 depict a different route to bpy **104**[40] and the synthesis of the new bpy **115**,[40] respectively. Both syntheses employ the asymmetric epoxidation of an alkene catalyzed by a chiral Mn-salen complex as a key step.[41]

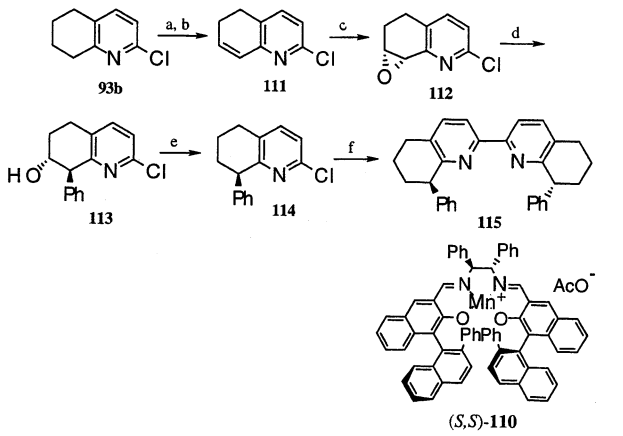
The synthesis of **104** starts with **93a**, which was successively treated with LDA and diphenyldiselenide. The resulting selenide was oxidized with H_2O_2 to give the alkene **105** (Scheme 20). Asymmetric epoxidation of **105** with the catalyst **(*R*,*R*)-110** proceeded smoothly with 96% ee to give the epoxide **106**. Treatment of this epoxide with a higher order cuprate provided the alcohol **107** as a single isomer (90%). No regiomeric epoxide-opening was detected. The absolute configuration was determined to be 6S,7S consistent with the empirical rule on enantioface selectivity in the Mn-salen catalyzed epoxidation.[40b] Reaction of **107** with phenyl chlorothionoformate in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMPA), followed by treatment of the resulting

Scheme 20[a]



[a] Legend: (a) LDA then PhSeSePh; (b) H_2O_2, $NaHCO_3$, 53%; (c) NaClO, 4-phenylpyridine-*N*-oxide, (*R*,*R*)-**110**, 89%; (d) $(CH_3C(CH_2)CH_2)_2Cu(CN)Li_2$, 90%; (e) PhOC(S)Cl, DMPA then *n*-Bu_3SnH, BEt_3, 45%; (f) *m*-CPBA then $LiBEt_3H$, 57%; (g) TBDMSOTf, 2,6-lutidine, 91% then $NiCl_2$, Ph_3, Zn, 91%.

Scheme 21[a]

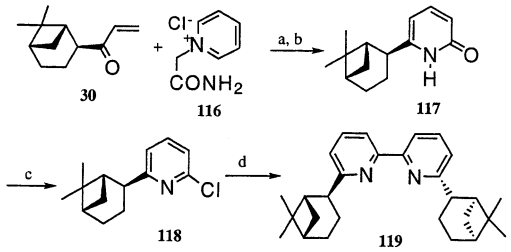


[a] Legend: (a) LDA then PhSeSePH; (b) *m*-CPBA then toluene reflux, 57%; (c) $NaClO_4$, 4-phenylpyridine *N*-oxide, (*S*,*S*)-**110**, 77%; (d) $Ph_2Cu(CN)Li_2$, $BF_3{\cdot}OEt_2$, 84%; (e) PhOC(S)Cl, DMPA then *n*-Bu_3SnH, BEt_3, 44%; (f) $NiCl_2$, PPh_3, Zn, 61%.

thiocarbonate with tri-*n*-butyltin hydride in the presence of triethylborane gave **108** (45%). Compound **108** was converted into bpy **104** by the sequence: (i) epoxidation of **108** with *m*-chloroperbenzoic acid, (ii) reduction of the epoxide with super hydride to give the alcohol **109**, (iii) protection of the hydroxy group as a TBS ether, and finally, (iv) Ni(0)-catalyzed coupling of the TBS ether (91%). After separation of *meso*-**104**, the resulting **(*R*,*R*)-104** was calculated to have 99.9% ee.[40]

For the synthesis of the phenyl substituted bpy **115**,[40] the chiral epoxide was prepared in 96% ee starting from **93b** and following the sequence reported in Scheme 21. Treatment of the epoxide **112** with a higher order cuprate in the presence of BF_3-Et_2O provided the alcohol **113** as a single isomer

Scheme 22[a]



[a] Legend: (a) MeOH, reflux, 12 h; (b) neat, 200 °C, 10 min, 35%; (c) $POCl_3$, DMF, 110 °C, 1.5 h, 70%; (d) $NiCl_2{\cdot}6H_2O$, PPh_3, Zn, NaI, DMF, 70 °C, 3 h, 60%.

(84%) whose absolute configuration was determined to be 7R,8R. This alcohol was reduced to give the phenyltetrahydroquinoline **114**, which was finally subjected to Ni-catalyzed coupling to afford **115** in 99.9% ee and 61% yield.

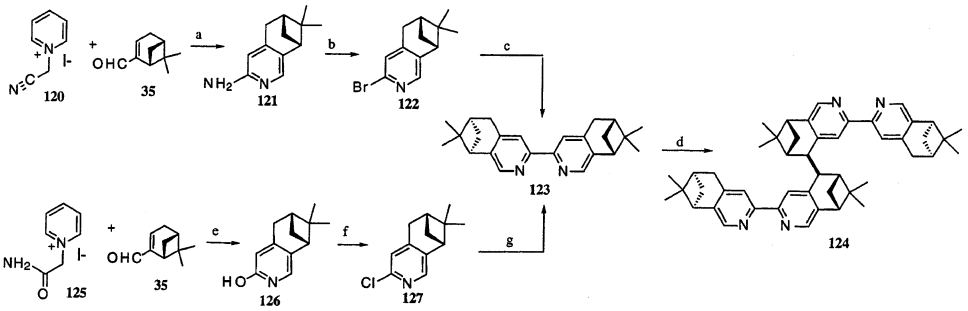
In the syntheses examined thus far, the halogen required for the homocoupling of 2-halopyridines was part of the initial pyridine ring, and the chiral substituent was then incorporated into the heterocycle. There are some cases, however, in which the pyridine is built up in such a way as to contain both the chiral substituent and a chloro or bromo group or a functional group that may be easily converted into a halo-derivative. Some examples are reported in Schemes 22−25.

Scheme 22 shows the reaction sequence leading to the C_2-symmetric bpy **119**,[42] which bears the 2,2-dimethylnorpinen-2-yl unit as a pendant chiral auxiliary. The key intermediate, pyridinone **117**, was obtained in 35% yield by heating the vinyl ketone **30** with *N*-(carbamylmethyl)pyridinium chloride (**116**), followed by thermal decomposition of the primary reaction adduct at about 200 °C. It is noteworthy that, despite the proximity of the stereocenter to the heterocyclic ring, no epimerization occurs even under the drastic cyclization conditions. Pyridinone **117** was converted to the corresponding chloropyridine **118** by reaction with phosphorus oxychloride in DMF (71%). Homocoupling of the chloropyridine **118** by a Ni(0)-triphenylphosphine-mediated reaction afforded bpy **119** in 60% yield.

For the synthesis of the bpy **123**,[23] two similar routes have been followed (Scheme 23). The key step in both routes was a Kröhnke-type cyclization using the (cyanomethyl)pyridinium salt **120** or the (carbamylmethyl)pyridinium salt **125** and (−)-myrtenal (**35**) to give the pyridylamine **121** (38%) or the alcohol **126** (15%), respectively. The amine **121** was then converted to the bromo-derivative **122** via a Sandmeyer-type synthesis (28%), and the alcohol **126** was converted to the chloro-derivative **127** by treatment with $POCl_3-PCl_5$ (40%). Final coupling of either **122** or **127** with Ni(0) produced the di-(pineno-fused) bpy **123** in 76 and 58% yields, respectively. The bpy **123** was coupled using one equivalent of LDA followed by oxidation with iodine to give the bis-bpy **124** with 10 stereocenters (67%).[26]

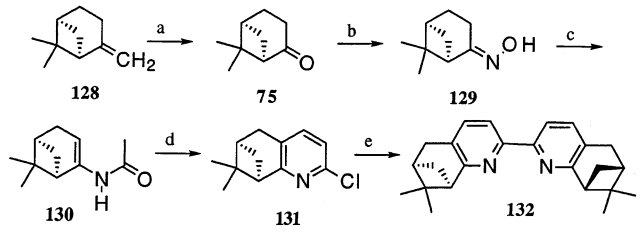
The symmetric ligand **132** was synthesized via annulation of a pyridine building block originating from the chiral pool (Scheme 24).[43] (+)-Nopinone (**75**), prepared from (−)-β-pinene (**128**), was converted to

Scheme 23[a]



[a] Legend: (a) EtOH/AcOH, $AcONH_4$, reflux, 6 h, 38%; (b) $NaNO_2$, HBr, 0 °C then CuBr, HBr, 70 °C, 3 h, 28%; (c) $Zn(Ni(PPh_3)_4Cl_2)$, DMF, 76%; (d) LDA, THF, −40 °C then I_2, THF, 67%; (e) piperidine, MeOH, reflux, 2 h; (f) $POCl_3$, DMF, reflux, 12 h, 73%; (g) $NiCl_2 \cdot 6H_2O$, PPh_3, Zn, DMF, 60 °C, 2 h, 58%.

Scheme 24[a]



[a] Legend: (a) O_3, CH_2Cl_2, −30 °C; (b) $NH_2OH-HCl$, Pyridine, EtOH; (c) Fe, Ac_2O, toluene, AcOH, 0 °C, 10 min, 90%; (d) DMF, $POCl_3$, 0−5 °C, 1 h, 70%; (e) $NiCl_2 \cdot 6H_2O$, Ph_3P, Zn, DMF, 60 °C, 18 h, 50%.

the oxime **129**, which was reduced with powdered iron in the presence of acetic anhydride to give the enamide **130** in 90% yield. Under Vilsmeier−Haack conditions, compound **130** afforded the choropyridine derivative **131** in 70% yield, and stoichiometric Ni(0)-coupling furnished the desired bpy **132** (50%).

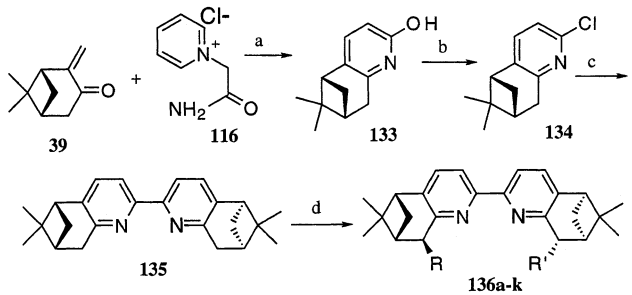
The C_2-symmetric bpy **135** was prepared from **39** via condensation with the Kröhnke salt **116**, followed by ring closure with concomitant aromatization to afford the α-hydroxypyridine **133** in 39% yield. Treatment with $POCl_3-PCl_5$ converted this compound into the α-chloropyridine **134** (40%), and a Ni(0)-mediated dimerization gave **135** (90%).[22]

Von Zelewsky's group has more recently reported the preparation of a number of derivatives of bpy **135** using LDA as a base and up to three equivalents of the appropriate alkyl iodide to yield either a C_1- or C_2-symmetric bpy **136a**−**k**, depending upon the number of equivalents of LDA that are employed (Scheme 25).[27]

Metal-mediated homocoupling of 2-halopyridines is the only route that has been followed to obtain C_2-symmetric bpys. The difficulties associated with the preparation of 2-halopyridines have recently led us to introduce a new procedure for obtaining such ligands. Our strategy involves the sequential construction of the two pyridine rings as illustrated by the synthesis of the pineno-fused bpy **132** from (+)-nopinone (Scheme 26).[44]

The starting pyridine **138** was obtained by the conjugate addition of the lithium enolate of the benzyl ketone **137** to (1*R*,5*R*)-3-methylenenopinone (**38**) followed by aza-annelation with ammonium acetate of the unisolated 1,5-dicarbonyl intermediate (23% overall yield). Catalytic hydrogenolysis of the benzyl derivative **138** gave the carbinol **139** (92%), which

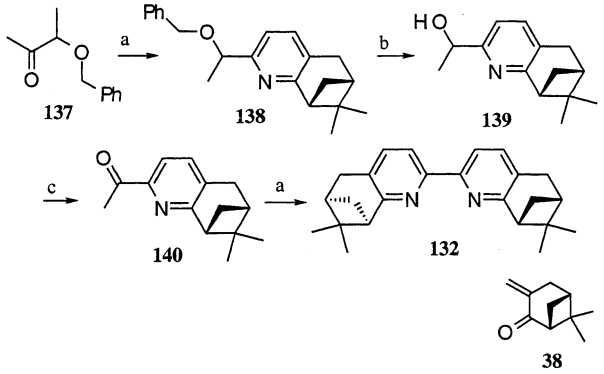
Scheme 25[a]



a: R=R'= Me **g**: R=H, R'= Me
b: R=R'= Et **h**: R=H, R'= Et
c: R=R'= Pr **i**: R=H, R'=*i*-Pr
d: R=R'= *i*-Pr **j**: R=H, R'= Bn
e: R=R'= Bn **k**: R=H, R'= TMS
f: R=R'= TMS

[a] Legend: (a) Piperidine, MeOH, reflux, 3 h, then 200 °C, 1 h, 39%; (b) $POCl_3$, PCl_5, reflux, 12 h, 40%; (c) $NiCl_2 \cdot 6H_2O$, Ph_3P, Zn, DMF, 60 °C, 2 h, 90%; (d) LDA, THF, 2 h at −40 °C, then room temperature.

Scheme 26[a]

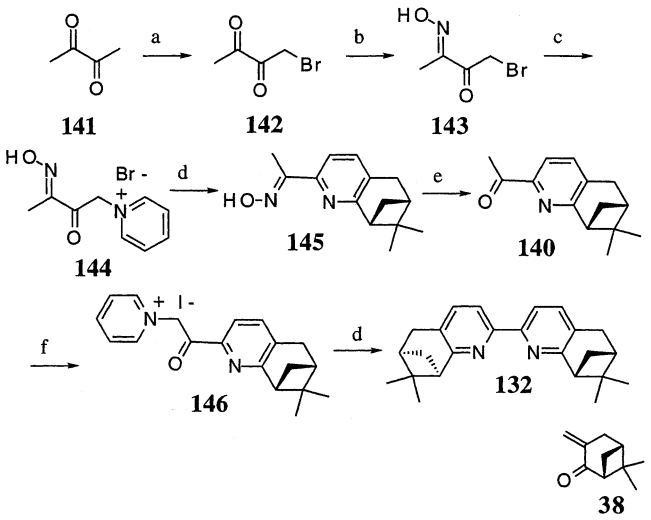


[a] Legend: (a) LDA, THF, −78 °C, 2 h then 38, THF, −78 °C; (b) H_2, Pd/C (3 atm), MeOH; (c) Swern oxidation.

was then oxidized under Swern conditions to ketone **140** (93%). From this key intermediate, the bpy **132** was prepared by building the second pyridine ring in a manner similar to that used to prepare **138** from **137** (35% overall yield).

An alternative route to the bpy **132** that avoids the homocoupling of 2-halopyridines has very recently been reported by von Zelewsky's group.[45] In this approach, the key intermediate **140** was prepared in several steps starting from 2,3-butanedione **141** (Scheme 27). This compound was transformed into the bromoketone **142**, which, after protection of one

Scheme 27[a]

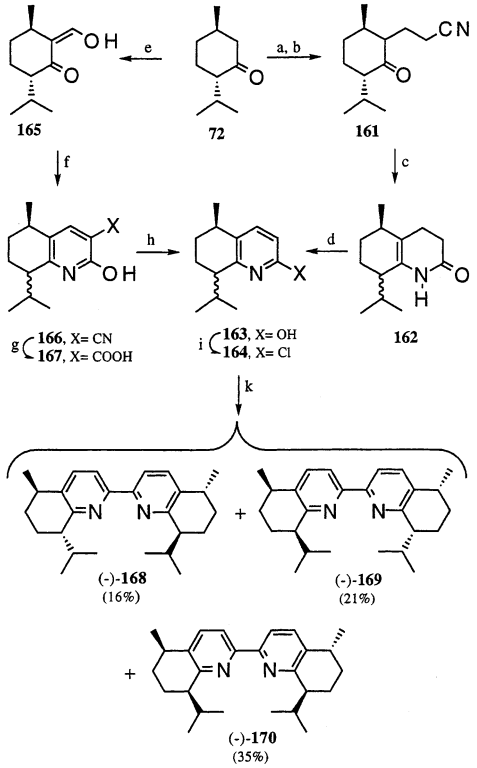


[a] Legend: (a) Br_2, 0 °C; (b) $NH_2OH-HCl$, H_2O, Na_2CO_3, 0 °C; (c) pyridine, Et_2O, room temperature; (d) **38**, NH_4OAc, AcOH, 100 °C, 15 h; (e) aq HCl, reflux, 8 h; (f) pyridine, I_2, reflux, 3 h.

acetyl group as its oxime, allowed the other to be converted to the pyridine ring **145**[46] by a Kröhnke-type reaction with (1*R*,5*R*)-3-methylenenopinone (**38**). Hydrolysis of the oxime afforded **140**, which by iodination in pyridine afforded the pyridinium salt **146**. This compound was finally converted into the bpy **132** by aza-annelation with **38** under the usual conditions.

A similar strategy has been followed to prepare the bpy **159** (Scheme 28).[47] The synthesis of this compound starts from (*R*)-3-methylcyclohexanone **147** obtained from (+)-(*R*)-pulegone. Compound **147**, by treatment with benzaldehyde and NaOH, afforded the benzylidene ketone **148** (70%), which by hydrogenation with 10% Pd on charcoal at room temperature provided a mixture of diastereomeric benzyl derivatives **149** (92%). The corresponding dimethylhydrazone **150** was deprotonated with LDA and quenched with 2-(2-bromoethyl)dioxolane (BED) to give the alkylation product **151** which, without isolation, was converted into the tetrahydroquinoline **152** by heating in glacial acetic acid[48] (40% based on **149**). Oxidation of **152** with 3-chloroperbenzoic acid yielded the *N*-oxide, which, by treatment with acetic anhydride at 110−140 °C, gave a mixture of benzylidene derivatives **154** and **155** in 90% yield. These two compounds were not separated, but directly ozonized to give the ketone **156** in 30% yield. Starting from this key intermediate, the bpy **159** was prepared by building up the second pyridine ring, following the sequence used to prepare **152** from **149**.

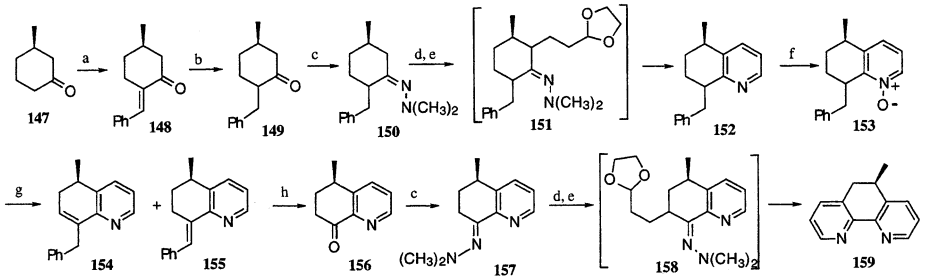
Scheme 29[a]



[a] Legend: (a) Piperdine, TsOH, 24 h, 42%; (b) acrylonitrile, EtOH, reflux, then AcOH, AcONa, dioxane, H_2O, reflux, 2 h, 94%; (c) KOH, *t*-BuOH, reflux, 1 h; (d) H_2SO_4, room temperature, 12 h, 74% or SO_2Cl_2, 100 °C, 30 min, 45%; (e) HCO_2Et, MeONa, toluene, room temperature, 48 h, 75%; (f) α-cyanoacetamide, EtOH, H_2O, reflux, 12 h, 54%; (g) conc HCl, reflux, 6 h, 81%; (h) heat to mp, <1 h, 95%; (i) PCl_5, $POCl_3$, $PhNMe_2$, reflux, 12 h, 88%; (k) $(Ph_3P)_2NiCl_2$, Zn, Ph_3P, DMF, 80 °C, 7 h, then chromatographic separation.

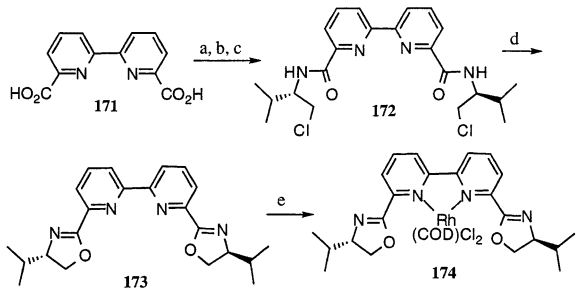
Two alternative routes to the synthesis of some bpys derived from (−)-menthone (**72**) have been recently reported by Kocovsky (Scheme 29).[22] In one approach, **72** was converted into the ketonitrile **161** via formation of the enamine (42%) and subsequent treatment with acrylonitrile (94%). Cyclization of **161** was effected by powdered KOH to produce **162** (75%), which was aromatized with H_2SO_4 (74%) or SO_2Cl_2 (45%) to give the α-hydroxypyridine **163** as a 1:1 mixture of epimers. The second route involved the Claisen condensation of **72** with HCO_2Et (75%) followed by condensation with α-cyanoacetamide, where spontaneous cyclization furnished the hy-

Scheme 28[a]



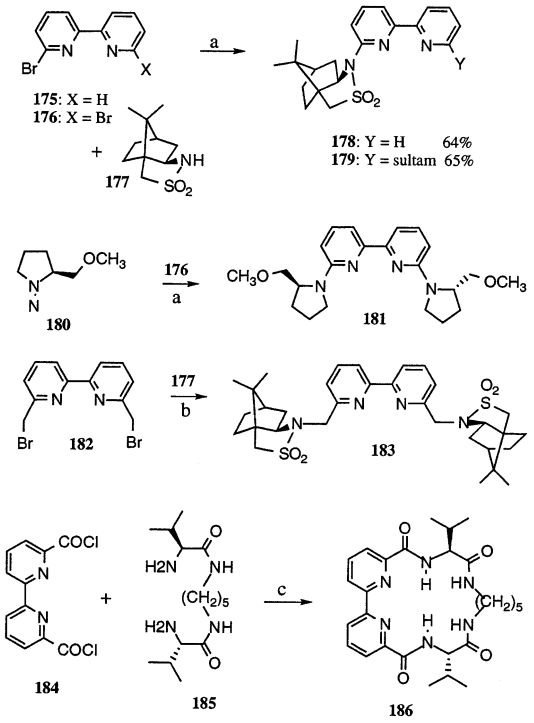
[a] Legend: (a) C_6H_5CHO, NaOH; (b) H_2, Pd/C; (c) $(CH_3)_2N-NH_2$; (d) LDA, THF, HMPT; (e) BED; (f) m-CPBA, $CHCl_3$; (g) Ac_2O, 110−140 °C; (h) O_3, MeOH then $(CH_3)_2S$.

Scheme 30[a]



[a] Legend: (a) $SOCl_2$, reflux, 13 h; (b) (*S*)-valinol, Et_3N, $CHCl_3$, room temperature, 1 day; (c) $SOCl_2$, 3 h, 69%; (d) NaOH, MeOH/H_2O, 40 °C, 37 h, 80%; (e) $Rh(COD)Cl_2$, THF, CCl_4, room temperature, 1 day, 61%.

Scheme 31[a]



[a] Legend: (a) Cu_2O, collidine, reflux; (b) KH, 18-crown-6, THF, reflux, 20−30%; (c) CH_2Cl_2 ($c < 10^{-3}$ M), Et_3N, 67%.

droxy-nitrile **166** as a 1:1 mixture of epimers (54%). This mixture was hydrolyzed with concentrated HCl (85%), and the resulting acid **167** was thermally decarboxylated to give the α-hydroxypyridine **163** (95%). This compound was converted to the chloro-derivative **164** (PCl_5, $POCl_3$, 88%) and Ni(0)-catalyzed dimerization then produced a mixture of (−)-**168** (16%), (−)-**169** (21%), and (−)-**170** (35%), which were easily separated by flash chromatography. Interestingly, isomer **170** can be equilibrated (BuLi, THF, −78 °C, 1 h, followed by acid quench) to produce a 1:1:1 mixture of the three diastereoisomers.

Although the most interesting ligands for asymmetric catalysis are bpys with a stereocenter bonded to the heterocyclic ring, some interesting bpys without this topological property have been reported and several representative examples are illustrated in Schemes 30 and 31. The synthesis of bpy **173** (bpymox) begins with 2,2′-bipyridine-6,6′-dicarboxylic acid (**171**), which was converted to the diamide **172** through a standard sequence of chlorination with $SOCl_2$, amidation with (*S*)-valinol, and a second chlorination with $SOCl_2$ (69% overall yield) (Scheme 30).[49] In the presence of aqueous NaOH, cyclization of **172** gave **173** in 80% yield. The corresponding bpymox−rhodium(III) trichloride complex **174** was then obtained by an oxidation procedure using [Rh(I)(cyclooctene)$_2$Cl]$_2$ in CCl_4 (61%).

Scheme 31 illustrates the synthesis of some bpys, which are potential ligands for asymmetric catalysis. Kandzia et al. have reported a short and efficient route to bpy camphor sultam-based ligands.[50] Bpys **178** and **179** were prepared by substitution of the bromo group of 6-bromo-2,2′-bipyridine (**175**) and 6,6′-dibromo-2,2′-bipyridine (**176**) with the camphorsultam **177** using a copper oxide catalyst in refluxing collidine. Following this procedure, the bpy **181** was also obtained from **176** and (*S*)-2(methoxymethyl)-pyrrolidine (**180**) in 20−30% yield. The same group described the synthesis of the sultam-bpy-derivative **183** using the bis-bromomethyl substituted bpy **182** as a precursor and the potassium salt of sultam as the nucleophile (68%).

Hamilton et al. prepared the chiral bpy macrocycle **186** and the corresponding Fe(III) complex (Scheme 31, bottom). Ligand **186** was obtained by high-dilution coupling of the diamine **185** with 6,6′-bis-(chlorocarbonyl)-2,2′-bpy (**184**) in 67% yield.[51]

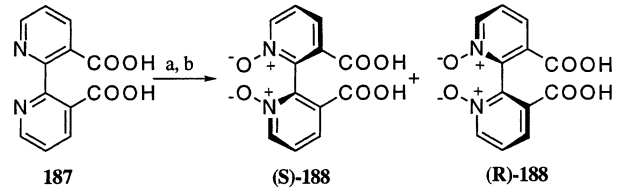
2.1.2. 2,2′-Bipyridines with Axial Chirality

Although the presence of a chiral center in a molecule is a sufficient condition for the existence of chirality, chiral molecules without a center of chirality exist. Molecules whose chirality results from restricted rotation about a single bond, defined as the axis of chirality, are designated as molecules with axial chirality (atropoisomers) and those whose chirality stems from the arrangement of out-the-plane groups with respect to a reference plane, called the chiral plane, are designated as molecules with planar chirality. Representative examples of chiral ligands of the former type are those based on 1,1′-binaphthalene,[52] such as BINOL[53] and BINAP[54] and of the latter type are those based on ferrocene derivatives.[55] Recently, some examples of bpy derivatives with axial and planar chirality have been reported.

Three approaches have been used to incorporate the bpy framework into an atropoisomeric system. The easiest method is to introduce a substituent in all four positions (3,3′ and 1,1′) adjacent to the central connecting bond. This strategy has been followed by the groups of Tichy[56] and Nakajima[57] for the preparation of the enantiomerically pure bpy **188** and biquinoline **191**. The former was obtained by hydrogen peroxide oxidation of 2,2′-bipyridine-3,3′-dicarboxylic acid (**187**) followed by resolution via crystallization of corresponding brucine salt **189** (Scheme 32).[56] The latter, prepared by *m*-CPBA oxidation of 3,3′-dimethyl-2,2′-biquinoline (**190**), was resolved via a hydrogen-bonded complex with (*S*)- or (*R*)-binaphthol **192** (Scheme 33).[57]

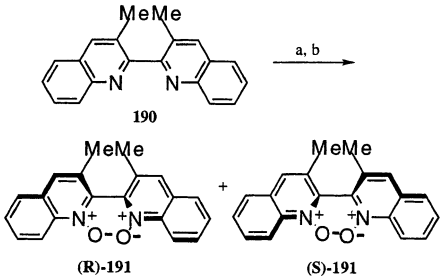
A further example is afforded by 1,1′-biisoquinoline-*N*,*N*′-dioxide (**194**) whose atropoisomers were obtained optically pure by preparative high performance liquid chromatography (HPLC) using a chiral column (Scheme 34).[58]

Scheme 32[a]



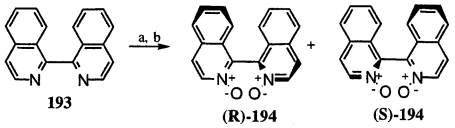
[a] Legend: (a) H_2O_2, AcOH, 92%; (b) brucine dihydrate, then fractional crystallization.

Scheme 33[a]



[a] Legend: (a) *m*-CPBA; (b) (*S*)- or (*R*)-binaphthol (**192**), then crystallization and chromatography.

Scheme 34[a]



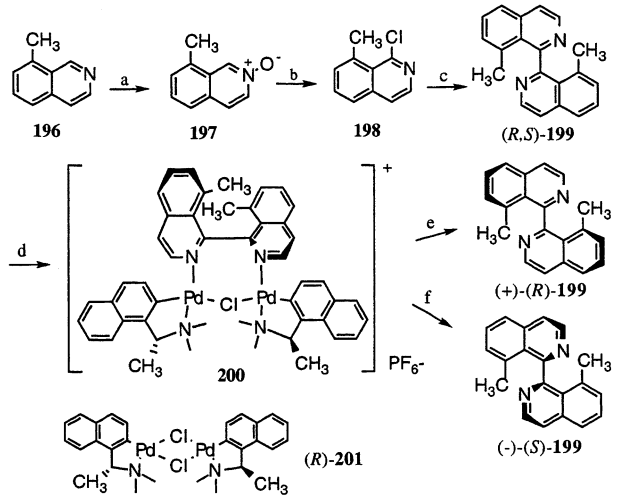
[a] Legend: (a) H_2O_2, AcOH, 80%; (b) enantiomeric separation by chiral HPLC.

A second method to obtain an axially chiral bpy is to introduce a bulky substituent on the 3- and 3′-positions of the heterocycle to offset the small steric requirement of the nitrogen lone-pairs. A good example is 1,1′-biisoquinoline (**193**), but attempts to achieve its resolution have thus far failed.[59] However, substitution at the 8- and 8′-positions with a bulky substituent made enantiomeric separation possible. Thus, the 8,8′-dimethyl-1,1′-biisoquinoline (**199**), prepared independently by us[60] and Hirao[61] using Ni(0)-catalyzed homocoupling of 1-chloro-8-methylisoquinoline (**198**, Scheme 35), was resolved into its enantiomers by chiral HPLC[61] or by separating the chiral dinuclear palladium complexes (**200**).[60] However, enantiomerically pure **199** underwent gradual racemization at ambient temperature (half-life in $CHCl_3$ at 20 °C was estimated to be 4 h), making it unsuitable for asymmetric catalysis. Unexpectedly, the ethyl and isopropyl analogues of **199**, prepared in hopes of increasing the resistance to rotation about the 1,1′-bond, were found to racemize more quickly than **199**.[62]

The third method to induce atropisomerim in the bpy system is to hinder rotation about the chiral axis by using a bridging unit between the 3- and 3′-positions of the heterocycle. Only two examples of such a system have been described.

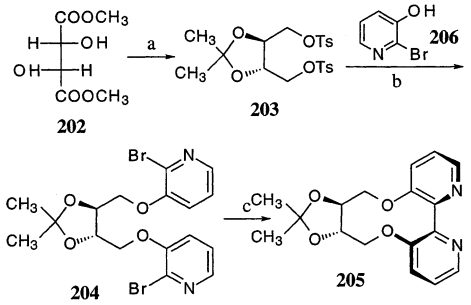
Botteghi et al. reported the synthesis of bpy **205** whose atropisomerism is imposed by a side-chain derived from tartaric acid (Scheme 36).[63] Nucleophilic substitution of 2-bromo-3-hydroxypyridine (**206**) on the readily available ditosylate **203** afforded the

Scheme 35[a]



[a] Legend: (a) H_2O_2, AcOH, 16 h, 95%; (b) $POCl_3$, $CHCl_3$, 2 h, reflux, 41%; (c) $NiCl_2$, PPh_3, Zn, DMF, 50 °C, 5 h, 56%; (d) (*R*)-**201**, MeOH, KPF_6, room temperature, 16 h; (e) 1,2-bis(diphenylphosphino)ethane, $CHCl_3$, 15 min; (f) from the mother liquors.

Scheme 36[a]



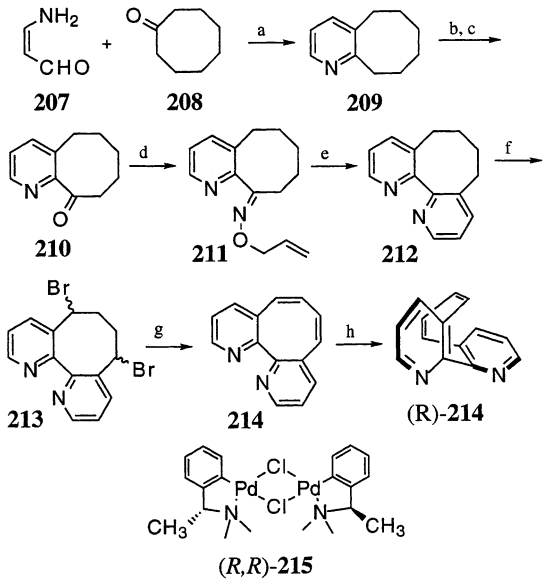
[a] Legend: (a) several steps; (b) NaOH, H_2O, 1 h, 25 °C, 95%; (c) $NiCl_2$, PPh_3, Zn, DMF, 20 h, 50 °C, 38%.

intermediate bpy **204** in 95% yield. Cyclization with a Ni(0)-triphenylphosphine complex gave **205** in 38% yield.

Wong et al. described the preparation and resolution of the diazabiaryl **214** where the chirality results from fusion of a cyclooctatetraene nucleus.[64] Compound **214** was synthesized as outlined in Scheme 37. Condensation of *β*-aminoacrolein (**207**) and cyclooctanone (**208**) in the presence of ammoniun acetate and triethylamine gave the pyridine **209** in 25% yield. The pyridyl ketone **210** was obtained by ozonolysis (40%) of the corresponding benzylidene derivative obtained by the condensation of **209** with benzaldehyde (83%). The second pyridine ring was constructed by sealed tube pyrolysis of the *O*-allyloxime **211** (52% overall). *N*-Bromosuccinimide converted bpy **212** into a mixture of dibromides **213** (65%), which was then dehydrobrominated with alcoholic KOH to afford **214** in 70% yield. Resolution was effected by treatment of **214** with the chiral palladium complex (*R*,*R*)-**215** to provide only one diastereomeric complex with (*R*,*R*,*R*) stereochemistry.

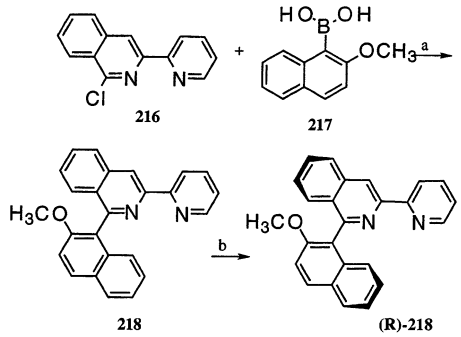
Although stable atropisomers of bpys are difficult to obtain where the chiral axis connects the 2- and 2′-positions, other bpys with this topological characteristic have been recently described where the chiral axis involves a 6- or 6,6′-substituent(s). Brunner described the synthesis of the bpy **218** (Scheme 38)

Scheme 37[a]



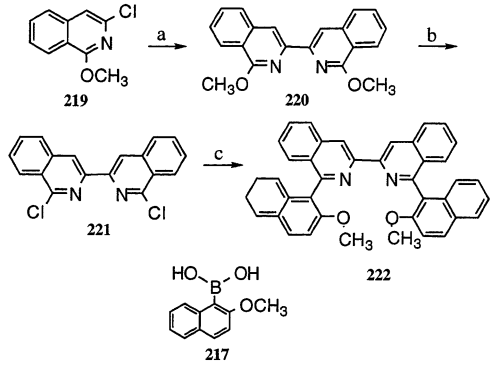
[a] Legend: (a) NH_4OAc, Et_3N, 120 °C, 25%; (b) PhCHO, Ac_2, reflux, 83%; (c) O_3, CH_2Cl_2, −40 °C, then, Me_2S, 40%; (d) $CH_2{=}CHCH_2ONH_2{-}HCl$, NaOAc, Na_2CO_3, EtOH, reflux, 87%; (e) sealed tube, 180 °C, 52 h, 60%; (f) NBS, CCl_4, reflux, 65%; (g) KOH, EtOH, reflux, 70%; (h) (*R*,*R*)-**215**, MeOH, $NaClO_4$, −3 °C.

Scheme 38[a]



[a] Legend: (a) $(PPh_3)_4Pd$ (3 mol %)/2 M aq Na_2CO_3/ethylene glycol dimethyl ether, reflux, 16 h, 71%; (b) HCl, then (−)-3-bromocamphor-8-sulphonic acid ammonium salt, MeOH, then crystallization from CH_2Cl_2/petroleum ether at −25 °C.

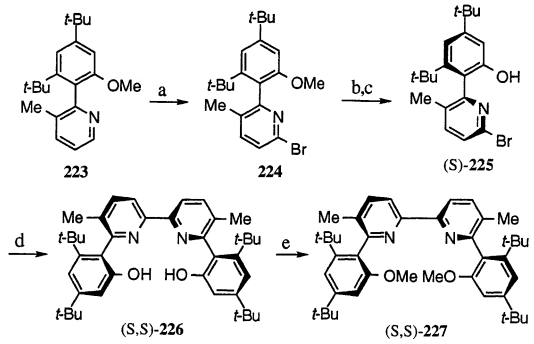
Scheme 39[a]



[a] Legend: (a) NaH/*t*-BuOH/Ph_3P/anhyd $Ni(OAc)_2$/ethylene glycol dimethyl ether, 3.5 h, 67%; (b) $POCl_3$, reflux, 36 h, 91%; (c) **217**, $(PPh_3)_4Pd$ (6 mol %)/2 M aq Na_2CO_3/ethylene glycol dimethyl ether, reflux, 36 h, 42%.

and the corresponding C_1-symmetric ligand **222** (Scheme 39), although so far only the former has been obtained enantiomerically pure.[65] Racemic **218** was obtained by Suzuki coupling of the chloro derivative

Scheme 40[a]



[a] Legend: (a) *t*-BuLi, THF, −78 °C, 1 h; then $BrCH_2CH_2Br$, THF, −78 °C, 4 h, 71%; (b) 48% HBr, AcOH, 120 °C, 8 h, 95%; (c) enantiomeric separation by chiral HPLC; (d) 30% $NiCl_2(Ph_3P)_2$, Zn, Et_4NI, THF, 60 °C, 8 h, 89%; (e) NaOH, MeOH, room temperature, 1 h, Me_2SO_4, 40 °C, 2 h, 90%.

216 and the boronic acid **217** using 3 mol % of tetrakis(triphenylphosphine)palladium(0) as the catalyst (71%). Bpy **218** was resolved via diastereomeric salt formation with (−)-3-bromocamphor-8-sulfonic acid, and the absolute configuration was determined by X-ray analysis.

For the synthesis of **222**[65] Ni(0)-catalyzed reductive homocoupling of 1-chloro-3-methoxyisoquinoline (**219**) afforded the C_2-symmetric 1,1′-dimethoxy-3,3′-biisoquinoline (**220**) (67%) (Scheme 39). Refluxing **220** in $POCl_3$ resulted in substitution of the two methoxy groups by chlorine to give **221** (91%). Double Suzuki coupling of **221** with **217** using 6 mol % of the Pd-catalyst, yielded **222** as a mixture of diastereomers which differ in the orientation of their naphthyl substituents. This diastereomeric mixture has not yet been separated.

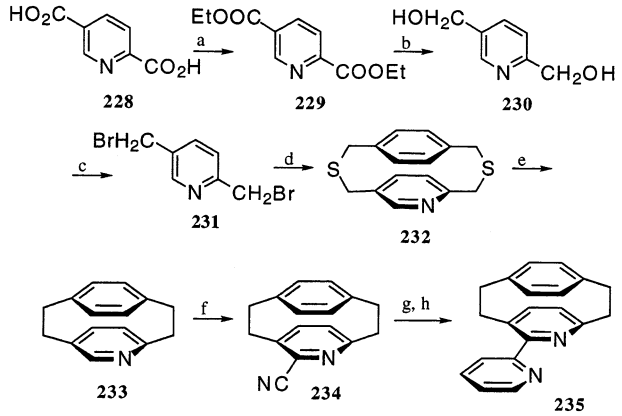
Chan has described the synthesis of the optically active atropisomeric bpys (*S*,*S*)-**226** and (*S*,*S*)-**227** (Scheme 40).[66] A bromo-group was introduced at the *ortho*-position of the pyridyl group of **223** by lithiation with *tert*-butyllithium and quenching with 1,2-dibromoethane (71%). Demethylation of 2-bromopyridylanisole **224** with 48% HBr/HOAC gave **225** (95%), which was subsequently separated into enantiomers by chiral HPLC. Ni(0)-catalyzed homocoupling of (*S*)-**225** gave (*S*,*S*)-**226** without any racemization (89%). Methylation of the chiral tetradentate ligand (*S*,*S*)-**226** gave the chiral bpy (*S*,*S*)-**227** (90%).

2.1.3. 2,2′-Bipyridines with Planar Chirality

Although bpys with central chirality are fairly numerous, only recently have some examples of chiral nonracemic bpy with planar chirality been reported. Both bpys **235** (Scheme 41) and **241** (Scheme 42) have been reported by Vögtle.[67]

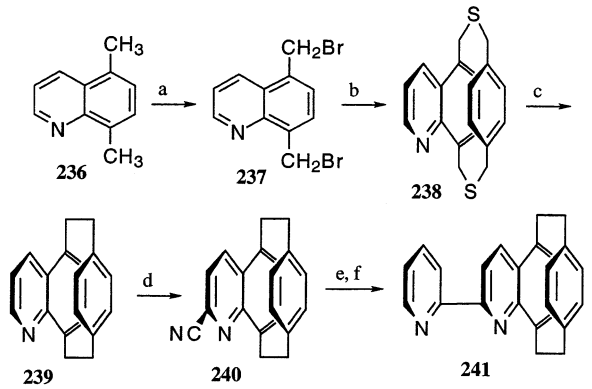
The synthesis of the bpy **235** started from 2,5-pyridinedicarboxylic acid (**228**), which was converted, via the acid chloride, into the diethyl ester **229** (82%) (Scheme 41). This diester was reduced with sodium borohydride/calcium chloride in ethanol to give the diol **230** (67%), which was converted to dibromide **231**. Under high dilution, and taking advantage of a cesium template effect,[68] **231** was coupled with 1,4-bis(sulfanylmethyl)benzene to give **232** (62%). Irradiation with UV light then generated the [2.2]-

Scheme 41[a]



[a] Legend: (a) $SOCl_2$, reflux, 8 h, then EtOH, reflux, 2 h, 82%; (b) $NaBH_4$, $CaCl_2$, EtOH, room temperature, 16 h, 67%; (c) HBr/AcOH, room temperature, 6 days, 30%; (d) sol. A: **231** in EtOH, sol B: 1,4-bis(sulfanylmethyl)benzene, KOt-Bu, EtOH, 85%; Cs_2CO_3, reflux, 16 h, 62%; (e) $P(OMe)_3$, *hν* (Hg, 180 W), room temperature, 18 h, 84%; (f) *m*-CPBA, CH_2Cl_2, room temperature, 20 h, then Me_2NCOCl, Me_3SiCN, CH_2Cl_2, room temperature, 16 h, 75%; (g) CpCo(COD), acetylene, toluene, 120 °C, 20 h, 23%; (h) enantiomeric separation by HPLC.

Scheme 42[a]

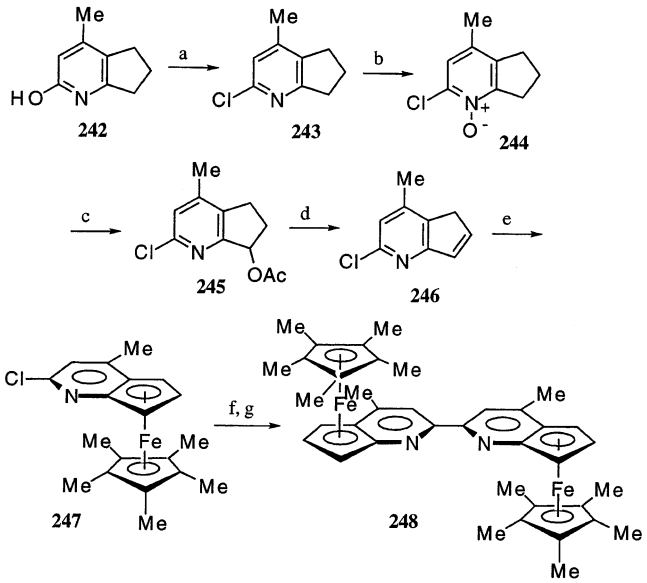


[a] Legend: (a) NBS, CCl_4, reflux, 7 h, 38%; (b) sol. A: **238** in EtOH, sol B: 1,4-bis(sulfanylmethyl)benzene, KO*t*-Bu, EtOH; Cs_2CO_3, reflux, 16 h, 40%; (c) $P(OMe)_3$, *hν* (Hg, 180 W), room temperature, 18 h, 71%; (d) *m*-CPBA, CH_2Cl_2, room temperature, 20 h, then Me_2NCOCl, Me_3SiCN, CH_2Cl_2, room temperature, 16 h, 70%; (e) CpCo(COD), acetylene, toluene, 120 °C, 20 h, 36%; (f) enantiomeric separation by chiral HPLC.

cyclophane **233** (84%). The *N*-oxide of **233** was converted into the nitrile **234** using trimethylsilyl cyanide (75%). Finally, Co(I)-catalyzed cocyclotrimerization of acetylene with **234** afforded the bpy **235** in 23% yield. Resolution of **235** was accomplished by chiral HPLC, and the absolute configuration was assigned by the comparison of experimental and theoretical CD spectra.

The synthesis of **241**[69] followed a procedure analogous to that used for the preparation of bpy **235** (Scheme 41). Dibromide **237** was obtained from 5,8-dimethylquinoline (**236**) via NBS-bromination (38%) (Scheme 42). Cyclization of **237** with 1,4-bis(sulfanylmethyl)benzene (34%) followed by irradiation gave the quinoline intermediate **239** (71%). Introduction of the pyridine ring into structure **239** was accomplished using the protocol of cyanation followed by cyclization with acetylene (25% overall). Finally, the resolution of **241** was achieved by chiral HPLC.

Scheme 43[a]



[a] Legend: (a) $POCl_3$, 74%; (b) H_2O_2, AcOH, 88%; (c) Ac_2O, 58%; (d) H_2SO_4, 79%; (e) BuLi, then $(Cp^*FeCl)_n$, 58%; (f) 30% $NiBr_2(Ph_3P)_2$, Zn, Et_4NI, 58%; (g) enantiomeric separation by chiral HPLC.

An interesting C_2-symmetric chiral bpy **248** has been reported by Fu's group (Scheme 43).[70] Their synthesis begins with the pyridine derivative **242**, which was converted into the chloride **243** with $POCl_3$ (74%). Oxidation of **243** with H_2O_2 in acetic acid yielded the *N*-oxide, which upon treatment with acetic anhydride gave the acetate **245** in 58% yield. Elimination with H_2SO_4 then furnished the pyridine **246** (79%). The cyclopentadiene ring of **246** was complexed with iron through the reaction of its lithium salt with $(Cp^*FeCl)_n$ (59%), and the resulting ferrocene derivative was reductively coupled using $NiBr_2(PPh_3)_2$/Zn/Et_4NI, to provide racemic **248** as a single diastereomer in 58% yield. Finally, the enantiomers of **248** were separated by chiral HPLC, and the absolute configuration of the purified enantiomers was established through X-ray crystallography.

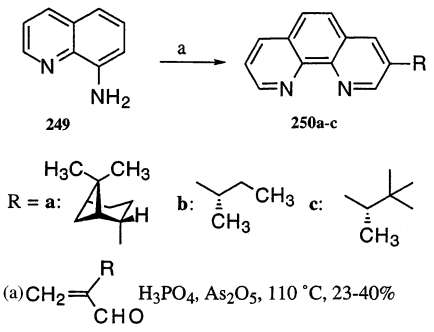
2.2. 1,10-Phenanthrolines

Chiral 1,10-phenanthrolines (phens) can be roughly grouped into two categories: those in which the chiral auxiliary is appended to the phen nucleus, generally at the 2- or 3-position and those in which the auxiliary is fused to the phen nucleus either at the 2,3- or 3,4-position. The latter class of phens is conformationally less mobile and hence their interaction with a substrate can be more easily evaluated.

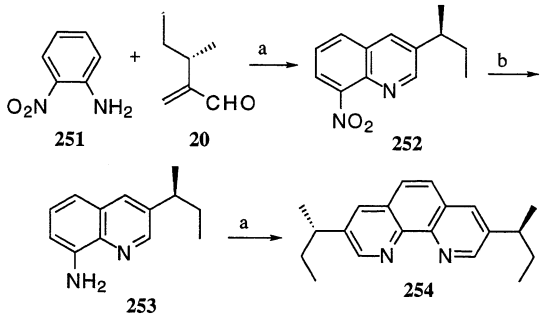
A general approach to 3-mono- or 3,8-disubstituted phens involves the reaction of aminobenzene derivatives and 2-substituted propenals by a modified Doebner-Miller reaction.[71] As outlined in Scheme 44, 3-monosubstituted phens **250a**−**c** were obtained by heating 8-aminoquinoline (**249**) with 2-substituted propenals in the presence of 85% phosphoric acid and arsenic acid (23−40% yield).[70−74]

For the synthesis of the C_2-symmetric 3,8-disubstituted phen **254**, two consecutive Doebner-Miller

Scheme 44[a]

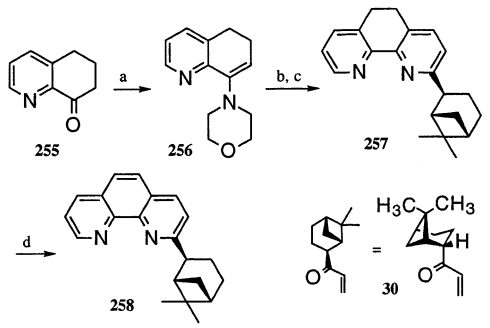


Scheme 45[a]



[a] Legend: (a) **20**, H_3PO_4, As_2O_5, 110 °C, 20 h; (b) H_2, Pd/C, 3 h, 89%.

Scheme 46[a]



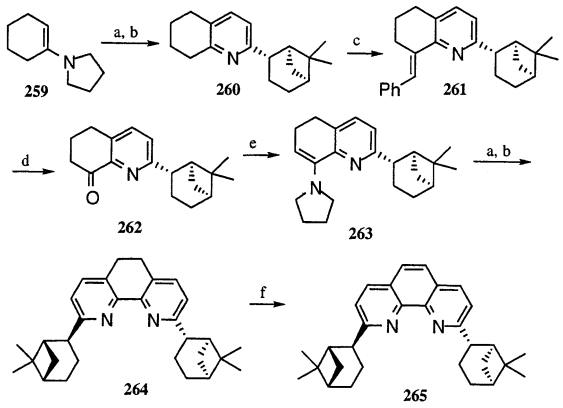
[a] Legend: (a) morpholine, benzene, TsOH, 24 h, 81%; (b) **30**, benzene, reflux, 70 h; (c) AcOH, $NH_2OH-HCl$, 115 °C, 5 h, 43%; (d) 10% Pd/C, xylene, reflux, 4 h, 90%.

reactions were employed (Scheme 45). The prerequisite 3-substituted-8-aminoquinoline (**253**) was obtained in two steps by the condensation of 2-nitroaniline (**251**) with (*S*)-3-methyl-2-methylenepentanal (**20**) followed by hydrogenantion of the 8-nitroquinoline to provide **253** (10% overall yield).[74]

An approach to 2-mono- or 2,9-disubstituted phens involves the reaction of enamines with alkyl vinyl ketones followed by aza-annelation of the unisolated 1,5-dicarbonyl intermediate (Schemes 46 and 47).[42] For the preparation of phen **258** (Scheme 46), the morpholine enamine **256** of 8-quinolone (**255**) was treated with the norpinalylvinyl ketone **30**, and the crude product was cyclized with hydroxylammonium chloride. Conversion of **257** into **258** was accomplished in high yield by dehydrogenation with palladium on charcoal in boiling xylene.[42]

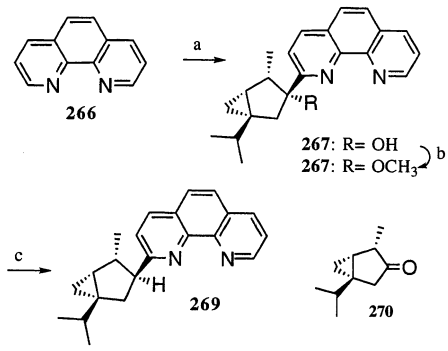
Synthesis of the corresponding C_2-symmetric phen **265** required more steps (Scheme 47).[42] The reaction of ketone **30** with the pyrrolidine enamine of cyclohexanone (**259**) followed by treatment with hydroxy-

Scheme 47[a]



[a] Legend: (a) **30**, benzene, reflux, 3 h; (b) $NH_2OH-HCl$, reflux, 5 h; (c) PhCHO, Ac_2O, 170 °C; (d) O_3, $MeOH/CH_2Cl_2$, −35 °C; (e) pyrrolidine, toluene; (f) Pd/C, xylene, reflux.

Scheme 48[a]



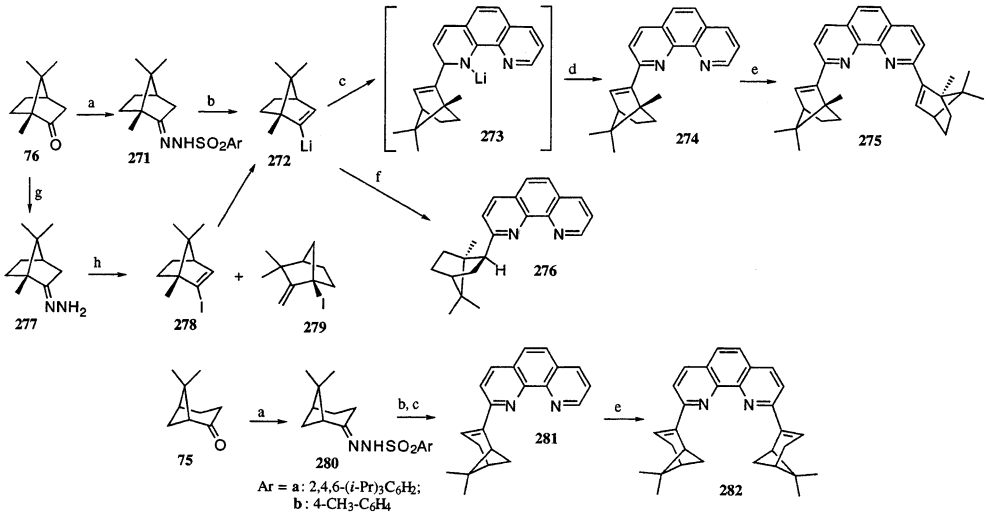
[a] Legend: (a) **270** (1 eq), SmI_2 (2 eq), THF, 25 °C, 45%; (b) NaH, CH_3I, THF, 25 °C, 75%; (c) SmI_2, 68%.

lammonium chloride provided the tetrahydroquinoline **260** in 51% yield. The intermediate 8-quinolone **262** was prepared by a two-step route that involved the treatment of **260** with benzaldehyde in acetic anhydride to form the 8-benzylidene derivative **261** (82% yield) followed by its ozonolysis. For the construction of the second pyridine ring, the same hetero-annelation reaction used for **260** was employed. Dihydrophenanthroline **264** was prepared in 21% overall yield and then converted into the phen **265** by dehydrogenation with palladium on charcoal in refluxing xylene (85%).

Two other strategies to prepare 2-substituted and 2,9-disubstituted phens have been reported. Helquist et al. discovered that the phen group undergoes samarium iodide promoted coupling with ketones to produce 2-(1-hydroxyalkyl)phens.[75] O-methylation of these derivatives provided the corresponding 2-(1-methoxyalkyl)-1,10-phens, which were demethoxylated to afford 2-alkylphens. This process has been applied to the chiral ketone (−)-thujone (**270**) to give the corresponding phen **269** as a single stereoisomer in 23% overall yield from **266** (Scheme 48).

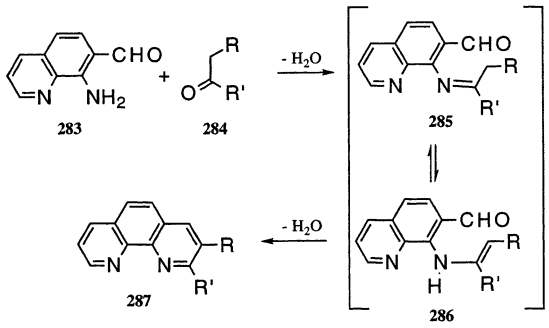
Åkermark and co-workers reported the preparation of terpene-based phen derivatives by the addition of an alkyllithium reagent to the 2- or 2,9-position of the phen nucleus followed by rearomatization of the primary reaction adduct (Scheme 49).[76] Using (1*R*)-camphor **76** as a starting material, the alkenyllithium derivative **272** was prepared from 2,4,6-

Scheme 49[a]



[a] Legend: (a) H_2NNHSO_2-C_6H_2(i-Pr)$_3$ or H_2NNHSO_2-$C_6H_2CH_3$, HCl; (b) *s*-BuLi, hexane/TMEDA, −55 °C; (c) phen (0.5 mol %), hexane, −78 °C, 12 h; (d) DDQ, DME, −50 °C, then NH_4Cl, 52% overall; (e) **271**, hexane/TMEDA, −78 °C, then DDQ, 25 °C, 4 h, 17% overall; (f) phen (0.5 mol %), hexane, 25 °C, 60 h, 52%; (g) H_2NNH_2, EtOH, reflux, 95%; (h) I_2, Et_3N, ether, 72% of a 1:1 mixture of **278**/**279**.

Scheme 50

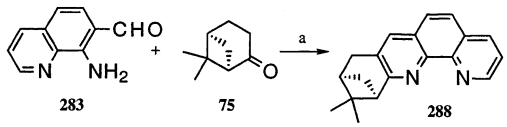


triisopropylbenzenesulfonyl-hydrazide (**271**) by a Shapiro reaction or from the iodide **278** by a lithium/iodide exchange reaction. Addition of **272** to phen at −78 °C followed by DDQ-induced rearomatization at −50 °C gave the phen **274** in 52% yield. If the addition was carried out at 25 °C, the phen **276** was obtained in 50% yield as a single stereoisomer by double bond migration and rearomatization of the intermediate adduct **273**. Addition of the bornenyllithium **272** to the monosubstituted phen **274** followed by rearomatization gave the bis(bornenyl)phen **275** in 15% yield. Likewise, phens **281** and **282** were obtained when (1*R*)-nopinone (**75**) was used as a starting material (Scheme 49, bottom).

The most straightforward synthetic approach to fused phen derivatives is the classical Friedländer reaction where an *ortho*-aminoaldehyde such as 8-aminoquinoline-7-carbaldehyde (**283**) condenses in a two-step fashion with an enolizable ketone such as **284** (Scheme 50).[77] In the first, step the aminoaldehyde **283** acts as a *nucleophile* to initially form an imine **285** by condensation with the ketone partner **284**. Isomerization of **285** to an enamine **286**, followed by intramolecular cyclocondensation with the aldehyde group, leads to the final phen product.

The Friedländer approach to obtain chiral phens was first employed by Thummel and co-workers who used both enantiomers of nopinone as a chiral starting ketone (Scheme 51). Thus, the aldehyde **283** was condensed with (+)-nopinone **75** in the presence of saturated ethanolic KOH to give the corresponding phen **288** in 40−58% yield.[78] The enantiomeric phen was prepared from (−)-nopinone in an analogous fashion.

Scheme 51[a]



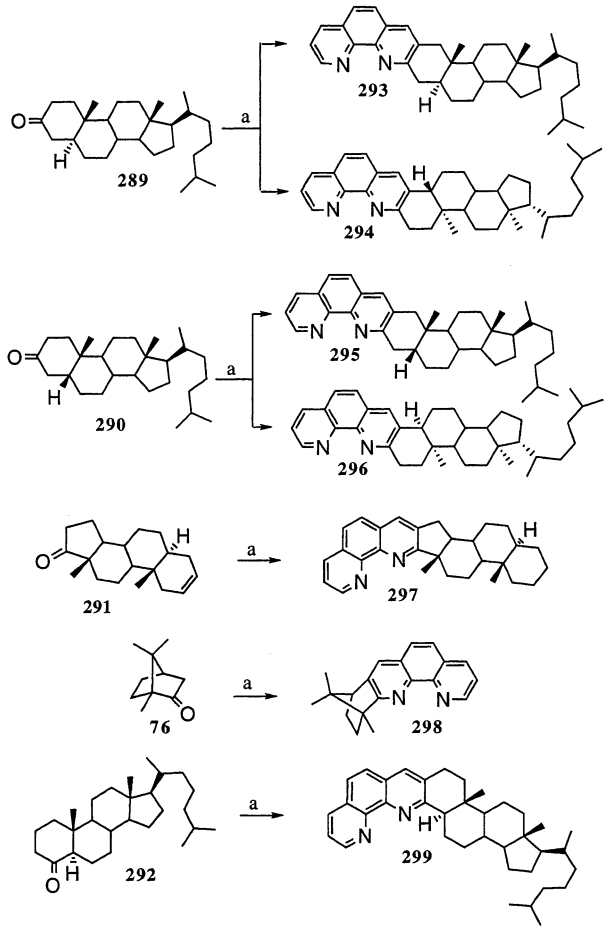
[a] Legend: (a) KOH, EtOH, reflux, 17 h, 40−58%.

More recently, the Friedländer condensation has been used for the preparation of (2,3-*b*)-cycloalkeno-fused phens using a number of ketones (**76**, **289**−**292**) from the chiral pool (Scheme 52).[79,80] This study pointed out that with ketones where enol formation is subject to kinetic and thermodynamic control, the ratio of isomeric phens can be regulated, to a large extent, by choosing the appropriate reaction temperature.

Moreover, under appropriate conditions, the Friedländer condensation is well suited to the production of chiral 3-alkylphens from chiral monosubstituted acetaldehydes (Scheme 53).[79]

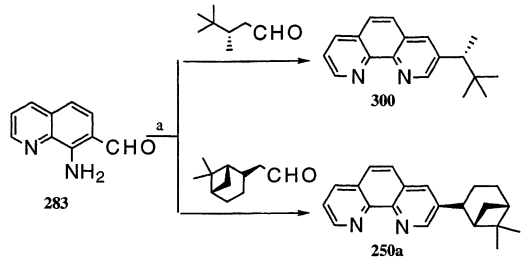
The Friedländer reaction works well for unencumbered ketones but only poorly, or not at all, when the ketone is sterically hindered as in the case of camphor (5%) or 3-pinanone (16%). We have developed a general alternative to the Friedländer approach in the case of such hindered ketone partners.[81] This approach has been applied to the preparation of 1,7,7-trimethyl[2.2.1]bicyclohepteno-[2,3-*b*]-1,10-phenanthroline (**298**) from the hindered ketone (+)-camphor (Scheme 54). It is interesting that this approach essentially reverses the order of the two steps in the Friedländer condensation. In the initial step, the enolate anion (generated by LDA) of the carbonyl partner **76** attacks 8-nitroquinoline-7-carbaldehyde (**303**), which now acts as an *electrophile*. The nitro

Scheme 52[a]



[a] Legend: (a) **283**, *t*-BuOK, 2-methoxyethanol, reflux, 12 h.

Scheme 53[a]

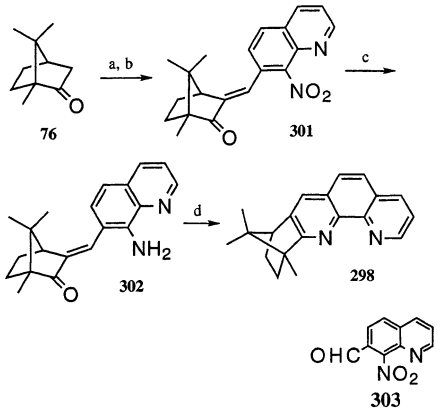


[a] Legend: (a) KOH, EtOH, 25−35 °C, 120 h, 55−77%.

group, which has been used to increase the electrophilic activity of the aldehyde moiety, is then reduced to an amine (83%) by refluxing with powdered iron in acetic acid/ethanol/water (2:2:1). Subsequently, intramolecular condensation with the carbonyl group is accomplished by refluxing a degassed carbitol solution of **302** in the presence of a small amount of sulfuric acid (51% overall yield from **76**). In this manner, steric problems associated with the hindered carbonyl group of camphor are obviated.

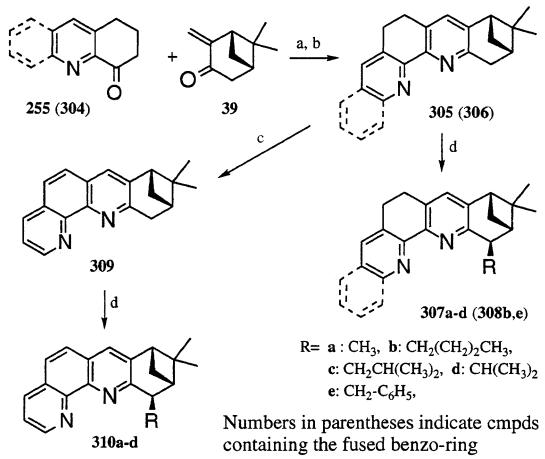
Another general approach to (2,3-*b*)-cycloalkeno-fused phens and their corresponding C_2-symmetric analogues has been reported by our group.[82,83] The pineno-fused dihydrophenathroline **305** and the corresponding benzo-fused **306** were prepared by conjugate addition of the lithium enolate of tetrahydroquinolone **255** and of the 4-oxotetrahydroacridine **304** with (−)-pinocarvone (**39**) followed by aza-annelation

Scheme 54[a]



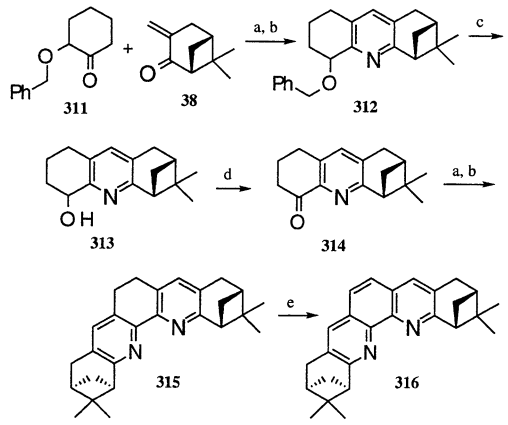
[a] Legend: (a) LDA, THF, −78 °C, 2 h, 87%; (b) **303**, THF/HMPA (1:1), −78 °C to room temperature, 83%; (c) Fe, CH_3COOH, HCl; (d) carbitol, reflux, 4 h, 71%.

Scheme 55[a]



[a] Legend: (a) LDA, THF, −78 °C, 2 h; then **39** from −78 °C slowly to room temperature; (b) AcOH, $AcONH_4$, THF, reflux, 2 h; (c) 10% Pd/C, decalin, reflux, 3 h; (d) LDA, THF, −40 °C, 2 h; then CH_3I or $CH_3(CH_2)_3I$ or $(CH_3)_2CHCH_2I$ or $(CH_3)_2CHI$ or $C_6H_5CH_2I$.

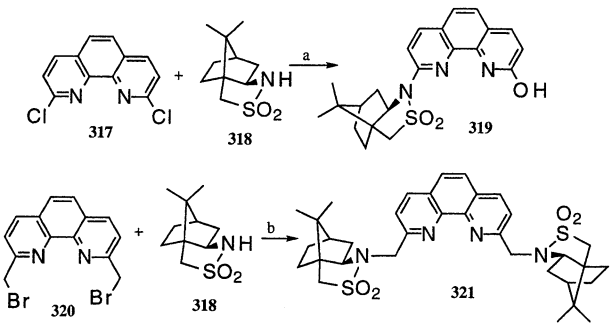
Scheme 56[a]



[a] Legend: (a) LDA, THF, −78 °C, 2 h; then **38** from −78 °C slowly to room temperature; (b) AcOH, $AcONH_4$, THF, reflux, 2 h; (c) Pd/C, MeOH, 3 atm; (d) Swern oxidation; (e) 10% Pd/C, decalin, reflux, 3 h.

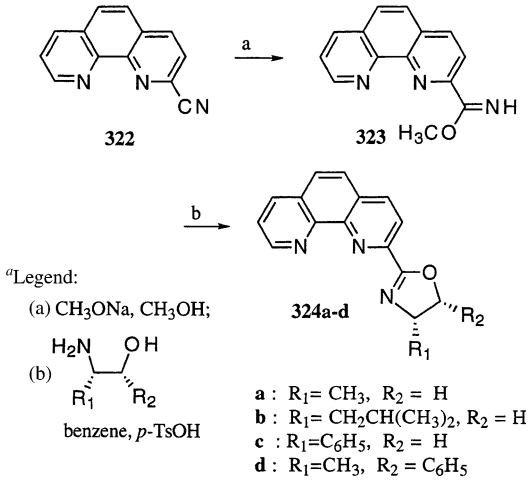
of the unisolated 1,5-dicarbonyl intermediate with ammonium acetate (Scheme 55).[83] Both 5,6-dihydrophens **305** and **306** have been subsequently alkylated with a variety of alkyl iodides to give the chiral ligands **307a**−**d**[83] and **308b**,**e**,[83] respectively.

Scheme 57[a]



[a] Legend: (a) Cu_2O, collidine, reflux, 30%; (b) KH, 18-crown-6, THF, reflux, 60%.

Scheme 58[a]



The dihydrophen **305** was heated under reflux in a decalin solution with 10% palladium on charcoal to give phen **309** (90% yield). Finally, the red solution of lithiated phen **309** was quenched with an appropriate alkyl iodide to give ligands **310a**−**d** in 35−67% yield.[82]

For the synthesis of the C_2-symmetric phen **316**,[84] the conjugate addition of the lithium enolate of the benzyl ketone **311** with **38** followed by aza-annelation afforded the pyridine **312** (Scheme 56). Catalytic hydrogenolysis of this benzyl derivative (Pd/C at 3 atm) gave the carbinol **313**, which was oxidized under Swern conditions to ketone **314** (93%). Starting from this key intermediate, the dihydrophen **315** was prepared by building up the second pyridine ring in a manner similar to that used to prepare **312** from **311**. Dehydrogenation by using 10% palladium on carbon completes the synthesis of **316**.

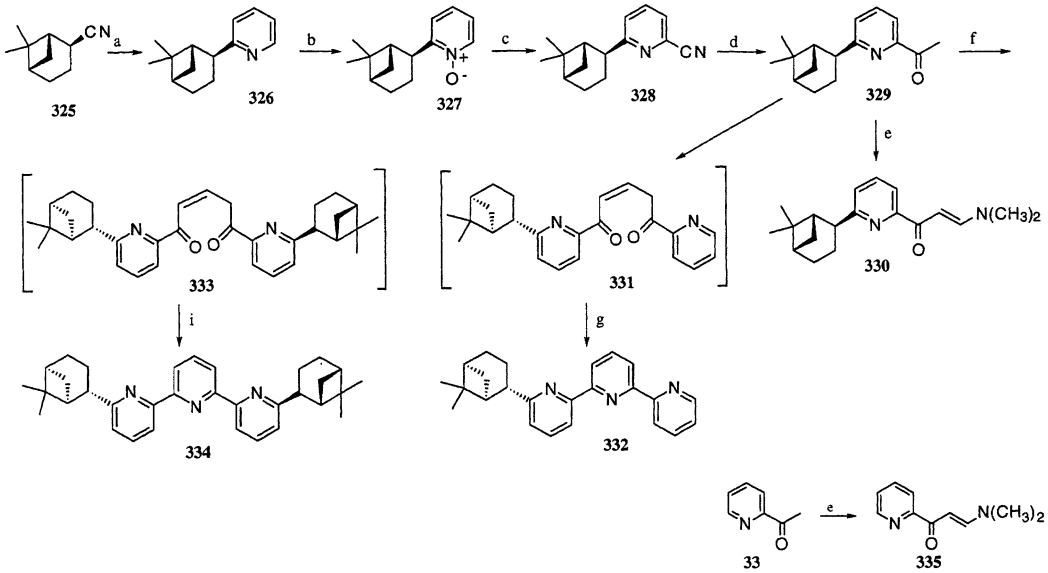
Kandzia et al. prepared several phen camphor sultam-based ligands.[85] Thus, phens **319** and **321** were prepared by direct substitution of the chloro group of 6,6′-dichloro-2,2′-phen (**317**) and the bromo group of the bis-bromomethyl substituted phen **320**, respectively, with the camphor sultam group. The former reaction was carried out in refluxing collidine using a copper oxide catalyst (30%), while in the latter reaction, the potassium salt of sultam was used as the nucleophile (60%).

Gladiali et al. synthesized a short set of potentially terdentate phen derivatives (**324a**−**d**).[86] These ligands were prepared from readily available 2-cyanophenanthroline (**322**) by condensation of the relevant methoxyimidate **322** with a suitable optically active β-amino alcohol.

2.3. 2,2′:6′,2″-Terpyridines

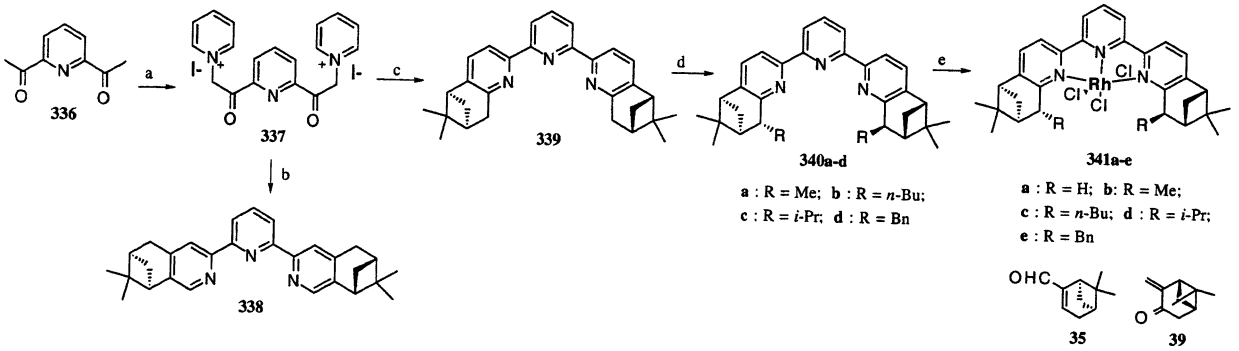
Substituted derivatives of 2,2′:6′,2"-terpyridine (tpy) are interesting ligands whose rich coordination chemistry affords compounds of use in supramolecular chemistry,[87] molecular biology,[88] photochemistry,[89] and potential pharmaceutical applications.[90] Despite the many possible applications for this ligand, only a few chiral tpys and their application in asymmetric catalysis have been recently reported.

Scheme 59[a]



[a] Legend: (a) CpCo(COD), acetylene, 8 atm, 140 °C, 95%; (b) *m*-CPBA, CH_2Cl_2, >95%; (c) $(CH_3)_3SiCN$, $(CH_3)_2NCOCl$, CH_2Cl_2, room temperature, 5 days, 95%; (d) CH_3MgBr, Et_2O, 32%; (e) $(CH_3)_2NCH(OCH_3)_2$, toluene, reflux, 24 h, 86%; (f) *t*-BuOK, room temperature, 2 h; then, **335**, room temperature, 15 h; (g) NH_4OAc, AcOH, 5 h, 45%; (h) *t*-BuOK, room temperature, 2 h; then **330**, room temperature, 15 h; (i) NH_4OAc, AcOH, 5 h, 47%.

Scheme 60[a]



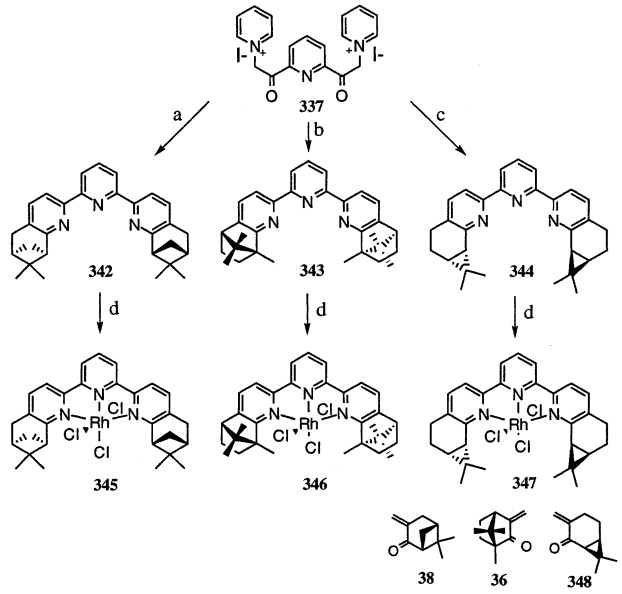
[a] Legend: (a) I_2, pyridine, 100 °C; (b) **35**, AcOH, $AcONH_4$, H_2NCHO, 100 °C, 12 h, 36%; (c) **39**, AcOH, $AcONH_4$, reflux, 12 h, 70%; (d) LDA, THF, −40 °C, 2 h; then RI; (e) $RhCl_3 \cdot H_2O$, EtOH, reflux, 4 h, 85−91%.

The synthesis of a chiral, nonracemic tpy was first carried out in our laboratory.[91] We prepared the tpy **332** and the corresponding C_2-symmetric tpy **334** having the 2,2-dimethylnorpinen-2-yl group as the chiral auxiliary. According to Scheme 59, *m*-CPBA oxidation of pyridine **327**, readily accessible in good yield from the Co(I)-catalyzed cyclotrimerization of the cyanopyridine **325** with acetylene, converted it in almost quantitative yield to the corresponding *N*-oxide **327**. Nitrile **328**, obtained by treatment of **327** with trimethylsilylcyanide and dimethylcarbamoyl chloride at room temperature for 5 days (95%), was converted into ketone **329** by reaction with methylmagnesium iodide (32%). Both enaminones **330** and **335** were obtained in high yield (86%) by the reaction of *N*,*N*-dimethylformamide dimethylacetal with the pyridyl ketone **329** and 2-acetylpyridine **33**, respectively. In the final step of this synthesis, the potassium enolate of **329** was condensed with the enaminones **300** or **335** to give the unisolated 1,5-enediones **333** and **331**, respectively. Cyclization with ammonium acetate of the unisolated **333** and **331** gave the tpys **334** and **332** in about 46% overall yield for the two steps.

Recently, von Zelewsky's group has reported the synthesis of the pineno-fused tpys **338** and **339**.[92] Next, we[93] and Kwong's group[94] prepared the alkylated derivatives of **303**. From 2,6-diacetylpyridine (**336**) and iodine in pyridine, 2,6-bis(pyridinioacetyl)-pyridine diiodide **337** was prepared. The reaction of (−)-myrtenal (**35**) and (−)-pinocarvone (**39**) with **337**, following the Kröhnke methodology, provided **338** and **339** (36 and 70% yield) (Scheme 60). Finally, the alkylated ligands **340a**−**d** were prepared by treatment of dilithiated **339** with the appropriate alkyl iodide. Rh(tpy)Cl_3 complexes **341a**−**e** were prepared in high yield by refluxing a methanolic solution of **339** and **340a**−**d** with $RhCl_3 \cdot 3H_2O$ (85−91%).

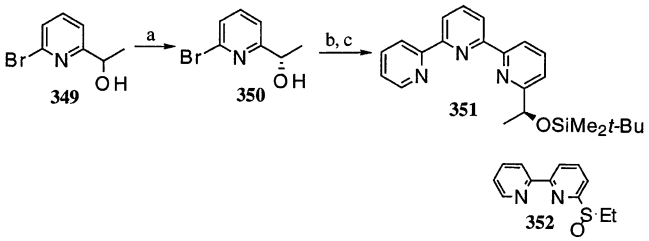
In hopes of increasing the scope of chiral tpy ligands in asymmetric reactions, we further reported the synthesis of the chiral tpys **342**−**344**, bearing a stereogenic center on the 6- and 6″-positions of the two distal pyridine rings.[95] These new ligands were obtained in the normal way by the reaction of Kröhnke salt **337** with the α,*β*-methylene ketones **38**, **36**, and **345**, which were prepared from (−)-*β*-pinene, (+)-camphor, and (+)-2-carene, respectively.[96] The rhodium(III) complexes **345**−**347** were synthesized in the usual way (Scheme 61).

Scheme 61[a]



[a] Legend: (a) **38**, AcOH, $AcONH_4$, reflux, 12 h, 16%; (b) **36**, AcOH, $AcONH_4$, reflux, 12 h, 21%; (c) **348**, AcOH, $AcONH_4$, reflux, 12 h, 26%; (d) $RhCl_3 \cdot H_2O$, EtOH, reflux, 4 h, 60−68%.

Scheme 62[a]



[a] Legend: (a) Lipase, vinyl acetate, diisopropyl ether, molecular sieves 4A, 49%; (b) Me_2t-BuSiOTf, 2,6-lutidine, CH_2Cl_2, 95%; (c) BuLi, THF:Et_2O:hexane (1:2:1), −78 °C then **351**, 65%.

Uenishi et al. reported the synthesis of the optically pure tpy **351**.[97] This synthesis was based on a kinetic resolution of the racemic pyridylethanol **349**, which was performed by Candida Antarctica lipase with vinyl acetate in diisopropyl ether (Scheme 62). The bromopyridine **350**, after silylation, was treated with butyllithium and the resulting lithio-pyridine was treated with ethyl bipyridyl sulfoxide **352** to give **351** in 65% yield.

3. Applications in Asymmetric Homogeneous Catalysis

3.1. Cyclopropanation Reactions

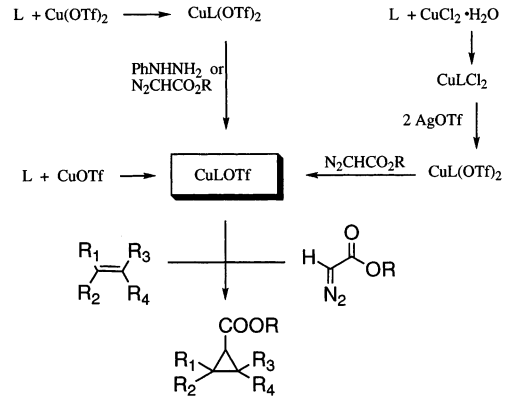
The synthesis of optically active cyclopropane derivatives by the stereoselective addition of a carbenoid reagent to an alkene is an important reaction from an historical as well as a practical point of view.[98] The vast majority of successful catalysts for this reaction are complexes of ruthenium, rhodium, and especially copper derivatives of nitrogen ligands with which excellent control of both diastereo- and enantioselectivity has been observed.[1a] While cyclopropanation reactions employing bpy and phen ligands have been carried out using only copper complexes, those with tpy ligands have also been carried out with rhodium and ruthenium complexes.

Three methods have been employed to carry out catalytic cyclopropanations using copper catalysts (Scheme 63). The most straightforward method is a one-pot synthesis using Cu(I)-trifluoromethanesulfonate [$Cu(OTf)(C_6H_6)_{0.5}$]. The second method uses the more stable $Cu(OTf)_2$ as the copper source and then transforms the resulting Cu(II)−ligand complex into the corresponding active species by reduction using either phenylhydrazine or a slight excess of the diazo ester. In the third method, a Cu(II)−dichloro complex is first synthesized and then converted into its ditriflate by treatment with silver triflate. The catalytically active Cu(I) species is finally obtained in situ by treatment with a diazo ester.

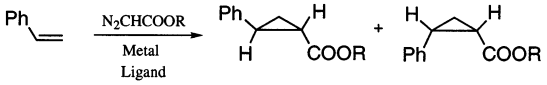
The reaction of styrene with ethyl or *t*-butyl diazoacetate is widely used as a model to evaluate the ability of new ligands to provide asymmetric cyclopropanation (Scheme 64). Tables 1, 3, and 4 report the results obtained in this reaction by using bpys, phens, and tpys.

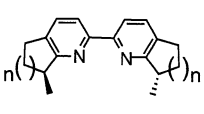
Initial data showing the high potential of various bpys as chiral controllers for asymmetric catalytic cyclopropanation have been reported by Katsuki and co-workers who examined the reaction of styrene with *t*-butyl diazoacetate in the presence of a Cu(I) complex of a C_2-symmetric bpy **98a**,**b**.[37] With these ligands, enantioselectivity of 72% ee for **98a** and 77% ee for **98b** was achieved, notwithstanding that both ligands carried only methyl substituents on the stereogenic carbons.

Scheme 63

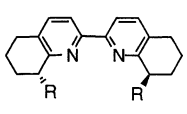


Scheme 64

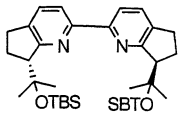




98a: n = 1
b: n = 2



101b: R = *i*-Pr;
c: R = TMS
d: R = TES
e: R = $CMe_2(OMe)$
f: R = CMe_2OTBS



104

Encouraged by these results, Katsuki synthesized several new optically active 2,2′-bi-tetrahydroquinolines bearing bulkier substituents on the C8(8′)-carbons. As expected, the reaction of styrene with *t*-butyl diazoacetate in the presence of the **101c**, bearing the bulky trimethylsilyl group, proceeded with high enantioselectivity for both *cis*- and *trans*-cyclopropane formation (92 and 98% ee, respectively). However, the use of ligand **101d**, bearing the even bulkier triethylsilyl group, gave poor results.[38] Reasonable asymmetric induction was found with ligand **104** (94% ee for the *trans*-isomer).[39]

Next Katsuki examined the cyclopropanation of various alkenes using the best performing ligand **101c**. The reaction of monosubstituted alkenes gave high enantioselectivity of >83% ee. Styrene derivatives bearing an electron-withdrawing group showed higher enantioselectivity than those with an electron-donating group, suggesting the participation of an electrophilic copper-carbene species. Cyclopropanation of *cis*-*β*-methylstyrene afforded very high *trans*-selectivity (>99:1), but the enantioselectivity was decreased to some extent. Differing from other substrates, *trans*-*β*-methylstyrene showed *cis*-selectivity, and the enantiomeric excess of the *trans*-isomer was poor but that of the major *cis*-isomer was excellent (>99% ee).[38]

To clarify the origin of this unusual *cis*-selectivity, Katsuki examined the cyclopropanation of several *E*-olefins in the presence of ligands **101c**,**d**,**e**.[101] Among these ligands, the bpy **101c** afforded the best *cis*-selectivity and enantioselectivity. For instance, the cyclopropanation of *trans*-*β*-methylstyrene and *trans*-anethole with *t*-butyl diazoacetate proceeds with moderate *cis*-selectivity to give the corresponding *cis*-cyclopropanecarboxylates with excellent enantiomeric excess (>99% ee). This result differs from the same reaction with the copper complex of structurally similar bisoxazolines. Katsuki explained the reaction using Pfaltz's model (vide infra).[103] The facial approach of the *trans*-*β*-methylstyrene resembles styrene but the conformational orientation is different.

Although the bpys prepared by Katsuki afforded good results in asymmetric cyclopropanation, their use is limited because only small amounts of these ligands are available. In fact, their preparation requires a rather elaborate synthesis or the separation of a racemic mixture by preparative chiral HPLC. With the aim of obtaining similar ligands more easily, several research groups have prepared

a series of bpys from terpenes and examined the corresponding copper complexes in asymmetric cyclopropanation. Thus, while C_1-symmetric bpys were used by von Zelewsky[27] (bpys **52a**,**b**,**g**, **59**, and **136g**−**k**) and our group[99] (bpys **52a**,**f**), C_2-symmetric bpys were employed by Kocovsky[22] (bpys **132** and **168**) and von Zelewsky[27] (bpys **132** and **136a**−**f**).

Catalytic cyclopropanation with copper complexes of **52a**,**b**,**f**,**g** showed increasing ee with increasing steric demand of the alkyl group. The best result was obtained with the ligand **52f** bearing the benzyl substituent. The introduction of a substituent on the pyridine ring not containing the chiral auxiliary was detrimental for stereoselectivity of the reaction. Thus, ligand **59** afforded poor results (up to 17% ee) compared with the corresponding **52b** (up to 55% ee). In contrast with these results, the monosubstituted bis-pineno-[5,6]-bpys **136a**−**f** showed better enantioselectivity compared to ligands **52a**,**b**,**f**,**g** with small substituents (methyl and ethyl), while worse enantioselectivity was observed with bulky substituents (*i*-propyl, benzyl). Also with the C_2-symmetric bpys **136a**−**f** the best enantioselectivity (up to 84% ee) was obtained with small substituents, whereas the more bulky substituents reduced the ee significantly or showed no ee at all.

These results differ from those obtained by Katsuki, who demonstrated that ligands **101** produce the best results with the bulky trimethylsilyl group. Probably, when ligands bear sterically demanding substituents at the C8(8′)-positions, the bridge dimethyl groups interact in the catalytic process. This situation does not occur in the case of ligand **168** (67% ee for the *trans*-cyclopropane) bearing methyl groups on the C5(5′)-positions which afforded results similar to Katsuki's ligand **101b** (77% ee for the *trans*-cyclopropane).

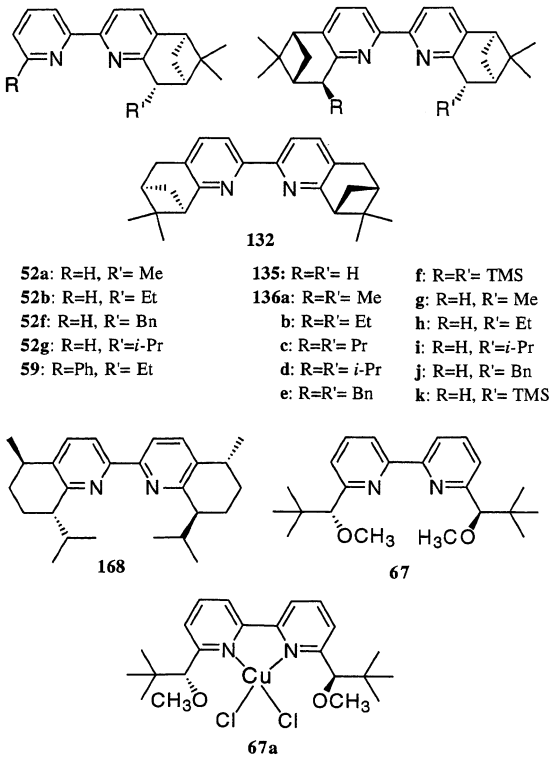


Table 1. Enantioselective Cyclopropanation of Styrene with Diazoacetates and Copper−2,2′-Bipyridine Complexes[a]

ligand	diazo-acetate	method[b]	yield (%)	*trans*:*cis* (ratio)	ee *trans* (%)	ee *cis* (%)	ref
32	Et	A	54	58:42	20	8	12
43	Et	A	74	70:30	0	20	99
52a	Et	A	66	58:42	20	11	99
52b	Et	A	83	63:37	55	45	27
52f	*t*-Bu	A	55	77:23	64	68	99
52g	Et	A	39	63:37	58	51	27
59	Et	C	86	63:37	17	9	27
67	Et	A	50	80:20	89	74	100
67	Et	C	52	80:20	91	82	100
67	*t*-Bu	A	75	90:10	92	71	100
98a	*t*-Bu	A	81	67:33	77	73	37
98b	*t*-Bu	A	72	72:28	72	67	37
101b	*t*-Bu	A	64	75:25	77		38
101c	*t*-Bu	A	75	86:14	92	98	38
101d	*t*-Bu	A	75	57:43	66		38
101e	*t*-Bu	A	53	66:34	83		38
101f	*t*-Bu	A	85	81:19	92		39
104	*t*-Bu	A	76	81:19	94		39
119	Et	A	13	69:31	8	15	12
132	Et	A	74	64:36	8	6	27
132	Et	A	95	65:35	10	15	22
132	*t*-Bu	A	95	84:16	67	69	22
135	Et	A	80	67:33	4	3	27
136a	Et	A	93	62:38	79	78	27
136b	Et	A	94	73:27	84	83	27
136d	Et	A	78	67:33	<2	<1	27
136e	Et	A	79	55:45	18	40	27
136g	Et	A	78	60:40	54	48	27
136h	Et	A	78	67:33	71	64	27
136i	Et	A	91	60:40	42	43	27
136j	Et	A	85	64:36	60	50	27
168	Et	A	85	72:28	72	70	22
168	*t*-Bu	A	61	83:17	16	16	22
227	Et	A	89	86:14	80		66
227	Et	B	95	86:14	86		66
235	Et	A	72	65:35	10	23	67
241	Et	A	55	67:33	26	26	69
248	Ar[c]	A	55	93:7	87		70

[a] Only representative examples are reported. For further examples, see the references cited in the table. [b] Method A: $[Cu(OTf)(C_6H_6)_{0.5}]$. Method B: $Cu(OTf)_2$ and then reduction with phenylhydrazine or a slight excess of the diazo ester. Method C: $CuLCl_2$ and then 2AgOTf, followed by reduction with the diazo ester. [c] Ar = 2,6-di-*tert*-butyl-4-methylphenyl

Kwong et al. reported the synthesis of the Cu(II) complex $[Cu(\mathbf{67})Cl_2]$ (**67a**), its crystal structure, and the use of this complex and the parent ligand **67** in the cyclopropanation of a number of alkenes (Table 2).[100] They showed that the complex **67a** is not an active catalyst, but that the corresponding triflate complex, formed by treating **67a** with silver triflate, was active. The cyclopropanation of various alkenes by ethyl diazoacetate in the presence of 1 mol % of the copper catalyst gave ethyl cyclopropanecarboxylates with enantioselectivities up to 92% ee for the *trans*- and up to 84% ee for the *cis*-isomer. When the catalyst was generated by stirring free **67** with Cu(II) triflate for 2 h, a slight decrease in enantioselectivity was observed. Styrene derivatives with electron-withdrawing groups showed higher enantioselectivity and greater *trans*:*cis* selectivity than those with electron-donating groups. These results differ from Katsuki's chiral ligand **101c** for which styrene derivatives having electron-withdrawing groups showed higher enantioselectiviy but lower *trans*:*cis* ratios than those with electron-donating groups. This ob-

Table 2. Enantioselective Cyclopropanation of Different Olefins with Diazoacetates and Copper−2,2′-Bipyridine Complexes[a]

ligand	substrate	diazoacetate	method[b]	yield (%)	*trans*:*cis* (ratio)	ee *trans* (%)	ee *cis* (%)	ref
227	*p*-methoxystyrene	Et	A or B	81	86:14	73		66
227	*p*-methylstyrene	Et	A or B	86	85:15	76		66
227	*p*-chlorostyrene	Et	A or B	78	86:14	84		66
67	*p*-methoxystyrene	Et	C	60	75:25	77	63	100
67	*p*-methylstyrene	Et	C	86	80:20	88	83	100
67	*p*-chlorostyrene	Et	C	61	86:14	89	84	100
67	1-hexene	Et	C	42	73:27	76	83	100
136b	*a*-methylstyrene	Et	A	64	66:34	79	75	27
136b	*trans*-*β*-methylstyrene	Et	A	75	55:45	11	46	27
101c	*p*-methoxystyrene	*t*-Bu	A	73	90:10	83	>99	38
101c	*p*-chlorostyrene	*t*-Bu	A	72	82:18	95	98	38
101c	*cis*-*β*-methylstyrene	*t*-Bu	A	94	>99:1	73		38
101c	*trans*-*β*-methylstyrene	*t*-Bu	A	54	40:60	24	>99	38
101c	1-octene	*t*-Bu	A	65	85:15	91		38
101c	*trans*-anethole	*t*-Bu	A	45	45:55	33	>99	102
101c	*trans*-2-octene	*t*-Bu	A	67	50:50	69	75	102
248	*p*-methoxystyrene	Ar[c]	A	71	95:5	75		70
248	*p*-(CF_3)styrene	Ar[c]	A	83	96:4	94		70
248	1-heptene	Ar[c]	A	78	94:6	78		70

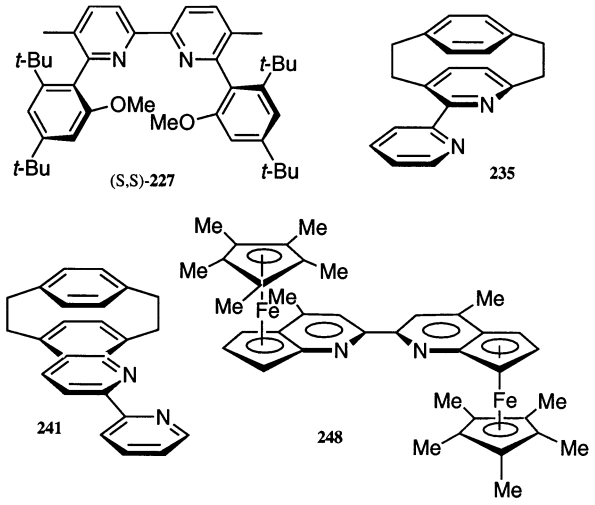
[a] Only representative examples are reported. For further examples, see the references cited in the table. [b] Method A: [$Cu(OTf)(C_6H_6)_{0.5}$]. Method B: $Cu(OTf)_2$ and then reduction with phenylhydrazine or a slight excess of the diazo ester. Method C: $CuLCl_2$ and then 2AgOTf, followed by reduction with the diazo ester. [c] Ar = 2,6-di-*tert*-butyl-4-methylphenyl.

servation has been ascribed to the unusual bulkiness of **67**.

Vögtle et al. described the application of the new planar chiral bpys **235**[67] and **241**[69] in the cyclopropanation of styrene with ethyl diazoacetate. They used $Cu(OTf)_2$ as the copper source and reduced the resulting Cu(II) complex to the Cu(I) complex with phenylhydrazine. Although the results obtained with these ligands were rather disappointing (up to 26% ee), probably due to lack of C_2-symmetry, they again demonstrate that planar chirality is an interesting option for the design of new chiral ligands.

This topological property is also present in Fu's planar chiral bpy **248**.[70] This C_2-symmetric ligand, with 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate as the carbene source, was able to cyclopropanate a variety of alkenes with high stereoselectivity (Tables 1 and 2). For instance, treatment of styrene with 1% CuOTf, 1.2% of **248** and 2 equiv of the diazo ester in CH_2Cl_2 at room temperature furnished the *trans*-cyclopropane in good diastereomeric and enantiomeric excess (94% de, 87% ee). It is worth noting that, in contrast to many reported Cu(I)-catalyzed cyclopropanations, wherein the diazo-ester is the limiting reagent, the conditions employed by Fu have the alkene as the limiting species. For styrene derivatives, he found that, whereas the nature of the aromatic ring has only a modest effect on *trans*:*cis* diastereoselectivity, it exerts a significant impact on enantioselectivity (Table 2). Alkyl-substituted alkenes and vinylsilanes underwent cyclopropanation with excellent diastereoselectivity and good enantioselectivity.

Chan et al. prepared the optically active atropoisomeric bpy **227** and used both its Cu(I)- and Cu(II)-triflate in the cyclopropanation of styrene and *para*-substituted styrene derivatives.[66] Both complexes gave cyclopropanes with similar ee values (up to 86% ee) and high *trans*/*cis* ratios. They found that the enantioselectivity depended on the electronic nature of the *para*-substituent and followed a linear free

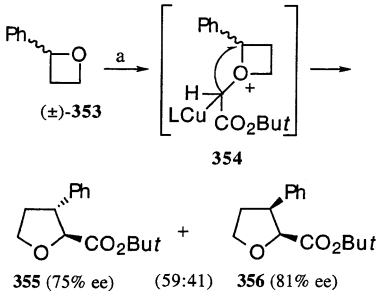


energy relationship. The most electron-poor alkene gave the highest enantioselectivity (Table 2).

Following their successful studies on copper-catalyzed asymmetric cyclopropanations, Katsuki et al. next examined various ligands in the Cu-catalyzed enantiospecific ring expansion of oxetane. This reaction provides a useful entry to the asymmetric synthesis of tetrahydrofuran and *γ*-butyrolactone derivatives. Initially they investigated carbene insertion into the C−O bond of racemic phenyloxetane **353** using *t*-butyl diazoacetate in the presence of the Cu(I) complex of bpy **104** (Scheme 65).[39,104] The reaction was considered to proceed through the copper complexed oxonium salt **354**, and provided *trans*- and *cis*-*tert*-butyl-3-phenyltetrahydrofuran-2-carboxylates **355** (75% ee) and **356** (81% ee). Next the asymmetric insertion reaction of (*R*)- and (*S*)-**353** was examined. The reaction of (*R*)-**353** gave the *trans*-isomer preferentially (92% ee) and (*S*)-**353** gave the *cis*-isomer preferentially (93% ee).

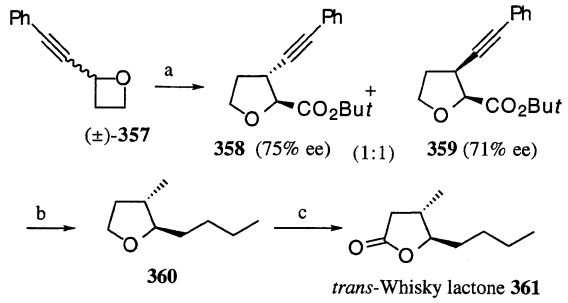
These interesting results prompted Katsuki's group to explore the possibility of applying their methodology to the synthesis of several natural products. They

Scheme 65[a]



[a] Legend: (a) CuOTf-**104**, $N_2CHCO_2Bu^t$.

Scheme 66[a]



[a] Legend: (a) CuOTf-**104**, $N_2CHCO_2Bu^t$; (b) several steps; (c) $ZnCr_2O_7$.

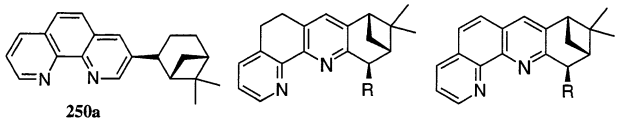
Table 3. Enantioselective Cyclopropanation of Styrene with Diazoacetates and Copper(I)−1,10-Phenanthroline Complexes

ligand	diazo-acetate	yield (%)	*trans*:*cis* (ratio)	% ee (*trans*)	% ee (*cis*)	ref
250a	Et	50	68:32	4	1	101
305	Et	65	64:36		3	99
307a	Et	63	68:32	24	19	99
307e	Et	67	60:40	47	37	99
307e	*t*-Bu	61	70:30	65	64	99
309	Et	64	68:32	3	2	99
310a	Et	57	64:36	30	22	99
310e	Et	51	60:40	32	12	99
310e	*t*-Bu	58	78:22	66	38	99

described the enantioselective synthesis of *trans*-Whisky lactone **361** using the ring expansion of (±)-2-(phenylethynyl)oxetane (**357**) as a key step (Scheme 66).[40] The reaction of racemic **357** with *t*-butyl diazoacetate in the presence of the Cu(I) complex of bpy **104** afforded a 1:1 mixture of *trans*- and *cis*-isomers **358** and **359** with 75 and 71% ee, respectively. This mixture was subjected to several transformations to give the tetrahydrofuran **360**, which, by oxidatation with $ZnCr_2O_7$, afforded *trans*-Whisky lactone **361**.

Katsuki's group extended this methodology to the synthesis of (−)-avenaciolide (**367**) and (−)-isoavenaciolide (**369**), two natural products having a condensed bis-lactone structure (Scheme 67).[40,105] Their synthesis started from the optically active oxetane **362**, which was subjected to ring expansion with *t*-butyl diazoacetate in the presence of the Cu(I) complex of bpy **104**. The reaction proceeded with good stereoselectivity to give a mixture of *cis*-**363** (72% ee) and *trans*-**364** in a ratio of 85:15, which was separated by chromatography. The *cis*-isomer was hydrogenated to afford the alkene **365**, which was used as a starting material for the synthesis of both **367** and **369**.

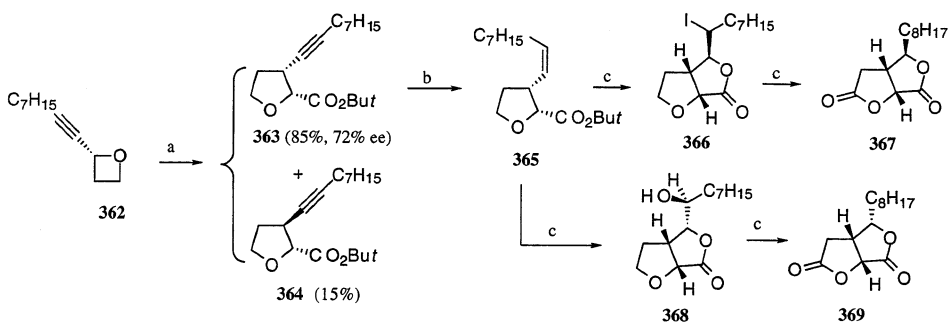
While it has been repeatedly shown that C_2-symmetric bpys are capable of providing high ee's in the enantioselective cyclopropanation of alkenes with diazoesters, there are no data on the use of C_2-symmetric phens in this reaction.



In 1995 we reported, in an isolated experiment, the use of phen **250a**, which afforded very low ee in the Cu(I)-catalyzed cyclopropanation of styrene with ethyl diazoacetate (Table 3).[101] More recently, the efficiency of phens **309**, **310a**,**e** and of their 5,6-dihydro derivatives **305**, **307a**,**e** have been examined in this reaction.[99] Enantioselectivity was negligible with unsubstituted ligands **305** and **309** but increased substantially when the hydrogen at C11 was substituted by a methyl or a benzyl group (up to 47% ee for the *trans*- and up to 37% for the *cis*-cyclopropane). A further increase in stereoselectivity was obtained when *tert*-butyl diazoacetate was used in the place of the ethyl ester (up to 66% ee for the trans and up to 64% for the *cis*-cyclopropane).

The tpys **332** and **334** have been evaluated as chiral controllers in the Cu(I)-catalyzed cyclopropanation of styrene with ethyl diazoacetate.[101] It was found that the 6,6-dimethylnorpinen-2-yl group was unable to provide satisfactory enantioselectivity (up to 5% ee) (Table 4). This disappointing result was ascribed to the conformational mobility of this group which can minimize the steric interaction between the stereogenic centers on the ligand and the sub-

Scheme 67[a]



[a] Legend: (a) CuOTf-**104**, $N_2CHCO_2Bu^t$, chlorobenzene, 0° C, 69%; (b) Ra-Ni, H_2, EtOH; (c) several steps.

Table 4. Enantioselective Cyclopropanation of Styrenes with Diazoacetates and Copper−2,2′:6′,2″-Terpyridine Complexes[a]

ligand	substrate	diazoacetate	method[b]	yield (%)	*trans*:*cis* (ratio)	ee *trans* (%)	ee *cis* (%)	ref
334	styrene	Et	A	60	78:22	4	5	101
332	styrene	Et	A	62	64:36	2	2	101
338	styrene	Et	A	97	70:30	3	17	94
339	styrene	Et	A	98	78:22	30	29	94
340a	styrene	Et	A	87	64:36	75	84	94
340b	styrene	Et	A	98	68:32	86	90	94
340b[c]	styrene	Et	A	96	69:31	90	94	94
340b	styrene	*t*-Bu	A	91	77:23	85	90	94
340c	styrene	Et	A	98	59:41	40	51	94
340d	styrene	Et	A	97	61:39	72	75	94
340b	*p*-chlorostyrene	*t*-Bu	A	90	78:22	83	82	94
340b	*p*-methoxystyrene	*t*-Bu	A	88	81:19	86	87	94
342	styrene	Et	A	78	72:28	22	20	95
343	styrene	Et	A	73	75:25	32	34	95
344	styrene	Et	A	33	67:33	7	4	95
342	styrene	Et	B	73	64:36	20	18	95
343	styrene	Et	B	71	67:33	18	16	95
344	styrene	Et	B	22	70:30	6	4	95

[a] Only representative examples are reported. For further examples, see the references cited in the table. [b] Method A: $[Cu(OTf)(C_6H_6)_{0.5}]$. Method B: $Cu(OTf)_2$ and then reduction with a slight excess of the diazo ester. [c] Reaction was carried out at 0 °C.

strate which lead to formation of the enantioselective transition state.

Recently, the use of more effective tpy ligands, bearing substituents on the rigid asymmetric framework, has been independently studied by Kwong[94] and our group.[93] Both groups reported the use of tpys **339**, **340a**−**d**, which incorporate the 6,6-dimethylnorpinene ring fused at the 5,6 (and 5′,6′) position of the two distill pyridine rings. While Kwong used Cu(II) complexes of these ligands, we examined their Rh(III) and Ru(II) complexes.

Kwong carried out the cyclopropanation of alkenes with Cu(II) tpy complexes generated from **338, 339**, **340a**−**d** and $Cu(OTf)_2$.[94] These catalysts were activated by stirring with a few equivalents of alkyl diazoacetates for 30 min at room temperature. All the copper−tpy complexes were found to be active catalysts and the yields of isolated cyclopropyl esters were excellent (87−98%). The best enantioselection was achieved with ethyl diazoacete and the *n*-butyl-substituted ligand **304b**, where enantiomeric excesses of 86% ee (90% ee at 0 °C) for the *trans*- and 90% ee (94% ee at 0 °C) for the *cis*-isomer were obtained. Variation of the diazo ester structure had a great effect on the *trans*/*cis* diastereoselectivity. As the size of the ester group was enlarged, the *trans*:*cis* ratio increased, but the enantioselectivity for both the *trans*- and *cis*-isomers decreased. Moreover, Kwong examined the relative reaction rates in the competitive cyclopropanation of EDA with substituted styrenes. The reaction was enhanced by electron-donating groups but retarded by electron withdrawing groups.

We prepared the Ru(II)−tpy complexes of **339**, **340a**−**d** in situ by adding two equivalents of the ligand to the $[RuCl_2(p\text{-cymene})]_2$ complex. These tpys provided effective Ru(II) catalysts but evidenced negligible enantioselectivities.[93]

More interesting results were discovered when the Rh(III)-catalyzed cyclopropanation reaction of styrene was investigated.[93] In this case, the active catalyst was obtained by treatment of the $Rh(tpy)Cl_3$ complex (tpy = **341a**−**e**) with two equivalents of silver triflate. The cyclopropanes were obtained in moderate yield as a mixture of *trans* and *cis* isomers in a ratio that varied appreciably with the nature of the substituents present on tetrahydroquinoline rings (Table 5). Enantioselectivities were also moderate, with the best result being obtained with the tpy **341b** (59% ee).

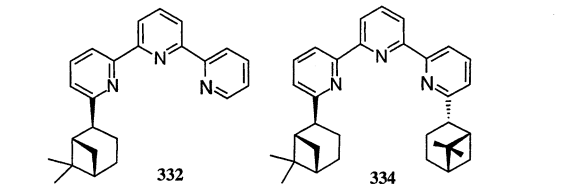
Table 5. Enantioselective Cyclopropanation of Styrene with Ethyl Diazoacetate and Rh(III)−2,2′:6′,2″-Terpyridine Complexes

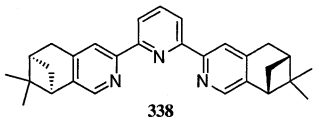
ligand	yield (%)	*trans*:*cis* (ratio)	ee trans (%)	ee cis (%)	ref
341a	75	46:54	7	0	93
341b	68	34:66	49	59	93
341c	64	46:54	37	45	93
341d	57	71:29	39	33	93
341e	53	57:43	35	25	93
345	73	71:29	10	12	95
346	71	46:54	8	32	95
347	78	37:63	52	64	95
347[a]	78	52:48	40	12	95

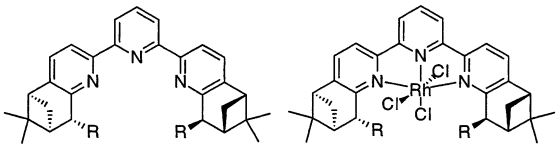
[a] *t*-Butyl diazoacetate was used.

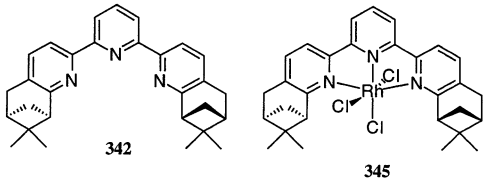
Recently, we reported a study on the catalytic activity of the three Rh(III) complexes of **345**−**347**.[95] The Cu(II)- and Cu(I)-catalyzed cyclopropanation of styrene with diazoacetates were rather disappointing both in diastereoselectivity and enantioselectivity (up to 34% ee). Better results were obtained with the corresponding Rh(III) complexes, with the best result being obtained with the complexed ligand **347**. In this case, 54% ee for the *trans*- and 64% ee for the *cis*-isomer were obtained with ethyl diazoacetate. Unexpectedly, the use of the *tert*-butyl diazoacetate with this same ligand reduced both the *trans*−*cis* diastereoselectivity and the enantioselectivity (40% ee for the *trans*- and 12% ee for the *cis*-cyclopropane).

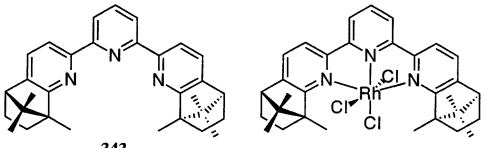
The asymmetric induction observed with both C_2-symmetric bpys and tpys has been explained by a

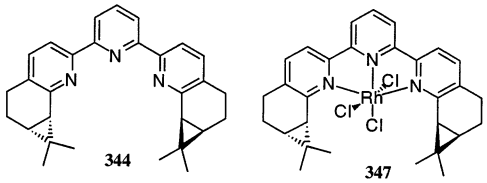






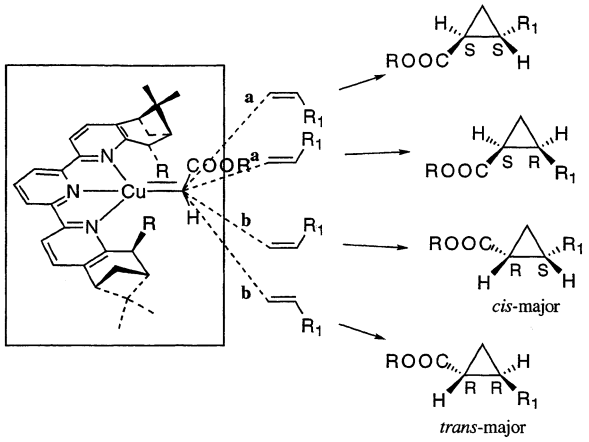




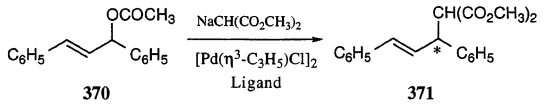


model that is in agreement with one previously proposed by Pfaltz for other *N*,*N*-bidentate ligands.[103] Scheme 68 shows an example for ligand **340**. In the proposed mechanism, the electrophilic copper car-

Scheme 68



Scheme 69



benoid atom is attacked by the more nucleophilic end of the alkene with concomitant pyramidalization of the involved centers. Approach by path **b** is more favorable than approach by path **a** wherein the carbenoid ester group is directed toward the R-substituent of the tpy ligand which is positioned above the plane bisecting the carbenoid ester group, causing steric repulsion as the reaction proceeds. This model also accounts for the *trans*:*cis* selectivity. If pathway **b** is followed, there are two possible approaches of the alkene to the carbenoid center. The approach in which the R_1 group on the alkene is transoid to the ester group is favored due to the lack steric interaction between these two groups. A repulsive interaction results when the alkene approaches the carbenoid in a cisoid orientation. In conclusion, pathway **b** leading preferentially to the *trans*-(1*R*)- and *cis*-(1*R*)-cyclopropyl esters, is in accord with experimental findings.

3.2. Allylic Substitution Reactions

Enantioselective reactions based on palladium catalyzed allylic substitutions are currently an area of active research interest.[106] In this context, a number of nitrogen-containing ligands are now achieving high levels of stereocontrol.[1,106]

Allylic substitutions have generally been carried out using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as a procatalyst and sodium dimethyl malonate as the nucleophile in a tetrahydrofuran solution. An alternative condition for generation of the nucleophile entails in situ treatment of dimethyl malonate with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in methylene chloride at room or reflux temperature (Trost procedure).[107] The alkylation of 1,3-diphenylprop-2-enyl acetate (**370**) with dimethyl malonate has been used as a model reaction to compare the ability of new ligands to provide asymmetric induction in palladium-catalyzed allylic substitutions (Scheme 69). Tables 6 and 8 report the results obtained in this reaction by using bpys and phens.

We have recently evaluated the potential utility of a variety of chiral bpy, phen, and tpy ligands as chiral controllers for enantioselective palladium catalyzed allylic substitutions.[108] Preliminary investigations indicated that palladium catalysts based on the C_1-symmetric bpys **9**, **32**, and **372** showed some reasonable activity while a catalyst based on the C_2-symmetric bpy **119**, closely related with **32**, showed both poor catalytic activity and stereoselectivity. The best enantioselectivity (32% ee) was obtained with ligand **32**, while for **119** there was no enantioselectivity.

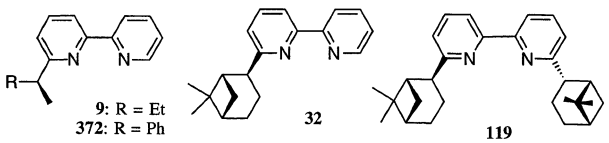


Table 6. Allylic Alkylation of 1,3-Diphenylprop-2-enyl Acetate with Dimethyl Malonate Catalyzed by Palladium(0) Complexes with 2,2′-Bipyridines[a]

ligand	reaction time (h)	yield (%)	ee (%)	conf	ref
32	7[b]	72	32	*R*	108
119	72[b]	46	0		108
43	3	93	11	*R*	25
52a	12	95	74	*R*	25
52d	32	88	85	*R*	6
52f	48	94	89	*R*	25
52g	12	91	79	*R*	25
52q	3	77	16	*R*	25
52r	288	68	26	*S*	25
62	60	77	14	*S*	83
62	84	86	6	*R*	83
42		60	26	*S*	22
132		28	20	*S*	22
91	168	76	48	*R*	36

[a] Only representative examples are reported. For further examples, see the references cited in the table. [b] Reaction carried out at 40 °C.

Table 7. Allylic Alkylation of Different Allylic Acetates and Nucleophiles Catalyzed by Palladium(0) Complexes with 2,2′-Bipyridines 274, 276, and 281[76]

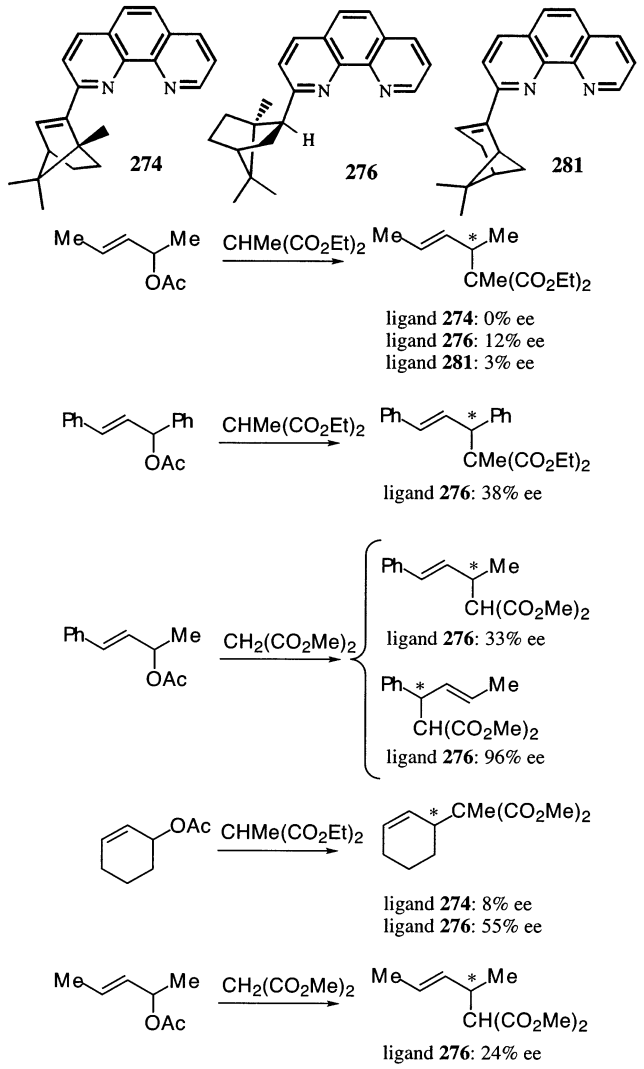


Table 8. Allylic Alkylation of 1,3-Diphenylprop-2-enyl Acetate with Dimethyl Malonate Catalyzed by Palladium(0) Complexes with 1,10-Phenanthrolines[a]

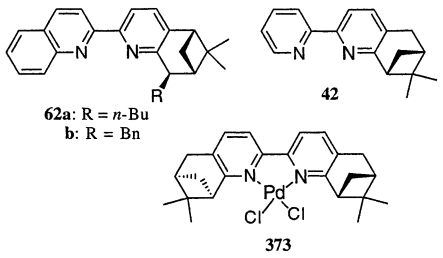
ligand	reaction time (min)	yield (%)	% ee	conf	ref
309	30	93	4	*R*	82
310a	35	95	78	*R*	82
310b	25	93	84	*R*	82
310c	45	91	70	*R*	82
310e	25	88	34	*R*	82
305	15	87	3	*R*	83
307a	35	92	70	*R*	83
307b	90	96	72	*R*	83
307c	140	98	81	*R*	83
307e	8	95	40	*R*	83
308b	55	87	6	*R*	83
308e	75	89	23	*R*	83
293	30	90	22	*S*	80
295	75	88	4	*S*	80
297	95	90	54	*S*	80
298	180	89	86	*S*	80
299	60	92	96	*R*	80
276		80	92	*R*	76

[a] Only representative examples are reported. For further examples, see the references cited in the table.

These preliminary results prompted us to prepare and evaluate C_1-symmetric bpys in which the substituents on the stereocenter bonded to the heterocyclic ring are arranged as part of the chiral backbone so as to provide a more rigid array of the ligand around the metal center.[25]

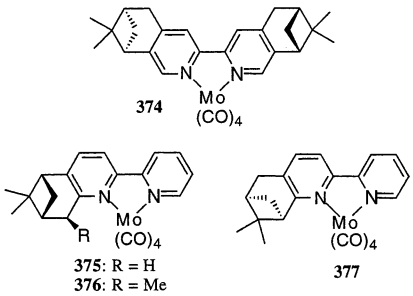
The ligands **43**, **52a**,**d**,**f**,**g**,**q**,**r** provided effective palladium catalysts, giving high yields of dimethyl 1,3-diphenylprop-2-enylmalonate (**371**). The best stereoselectivity (89% ee) was obtained with the 8-benzyl-substituted ligand **52f**. Unexpectedly, the bpy **52q**, bearing the crowded $C(CH_3)_2OCH_3$ group, gave a stereoselectivity and reaction rate similar to that of the unsubstituted bpy **43**. With bpy **52r**, bearing the very sterically demanding $C(CH_3)_2OSi(CH_3)_3$ group, a dramatic drop in catalytic activity and an inversion of the stereochemical outcome was observed. The data with **52r** appear to indicate that, in this case, the stereochemistry of the transition state might be different from what is observed for other similar ligands.[107]

To study the effect on the catalytic activity and stereoselectivity of a substituent on the pyridine ring not containing the chiral backbone, the bpys **62a,b** were synthesized.[83] These systems possess a benzo ring fused to the achiral pyridine ring. This modification resulted in a drastic reduction of the reaction rate and stereoselectivity. Moreover, in the case of the *n*-butyl derivative **62a**, a reaction product with the unexpected (*S*)-configuration prevailed.



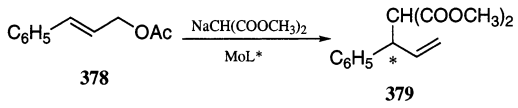
Kocovsky's group recently examined the palladium complexes derived from bpys **132** and **42**.[22] While the C_2-symmetric complex **373** gave (*S*)-**371** in low yield (28%) and with only 20% ee, the complex involving

42 proved to be a better catalyst, affording the reaction product in 60% yield and with 26% ee. These data confirm previous findings which indicated that the introduction of a second substituent in the 6′-position to give a C_2-symmetric bpy caused a drop of both catalytic activity and enantioselectivity.[107]



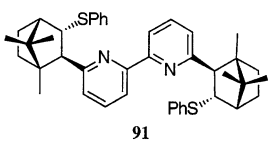
Kocovsky's group also prepared the (bpy)$Mo^0(CO)_4$ complexes **374**−**377** from the corresponding bpys.[22] The effectiveness of these complexes was evaluated, not only in the alkylation of **370** but also in the reaction of cinnamyl acetate (**378**) with the sodium salt of dimethyl malonate (Scheme 70).

Scheme 70



The active Mo(0)-species were obtained by the oxidative addition of $SnCl_4$ in CH_2Cl_2 to the complexes **374**−**377**. The precipitated orange-yellow precatalyst (bpy)$Mo^{II}(CO)_3(SnCl_3)Cl$ was then reduced in situ with excess of NaH. With **374**, cinnamyl acetate afforded (*R*)-**379** in 43% yield with good regioselectivity (78:22 favoring the branched product **379**) but with low enantioselectivty (12% ee). With **370**, the reaction produced (*R*)-**371** in 22% yield and 10% ee. Complex **375** catalyzed the transformation of **378** into (*S*)-**379** in 52% yield (quantitative conversion) with good regioselectivity (86:14) but low enantioselectivity (22% ee). On the other hand, the more sterically encumbered methyl analogue **376** proved to be inert to both **378** and **370**. Finally, complex **377** produced (*S*)-**379** in 33% yield (at ∼50% conversion) with good regioselectivity (87:13) but poor enantioselectivity (∼8% ee).

In a study involving the synthesis and application of pyridine-thioethers derived from (+)-camphor, we examined the diastereomerically pure bpy-thioether **91** in the palladium catalyzed allylic substitution of **370** with dimethyl malonate.[36] This ligand was not able to provide a reactive palladium catalyst since it required 7 days for the complete consumption of **370**. Furthermore, it afforded only poor enantioselectivity (48% ee).



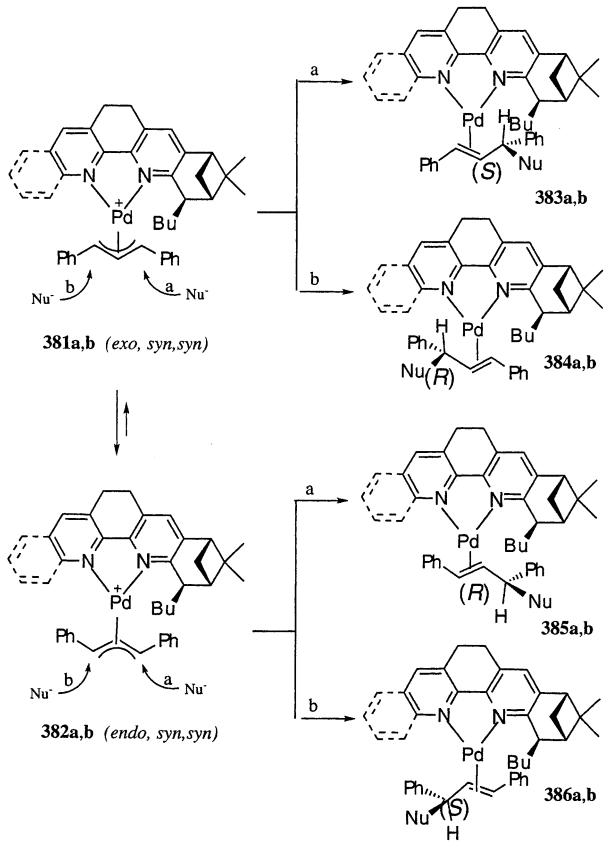
Bolm et al. investigated the ability to control the enantioselective catalyzed allylic alkylation of **370** with dimethyl malonate using a series of chiral sulfoximine/Pd complexes.[109] In this context, the sulfoximine−bpy **380** afforded **371** with a moderate yield (56%) and low enantiomeric excess (13%).

The first application of chiral phens to asymmetric palladium-catalyzed allylation was described by Norrby et al.[76] They used molecular mechanics calculations to probe the conformational properties of a number of substituted phens and their η^3-allyl−palladium complexes. Special attention was focused on chiral phens bearing terpene-derived alkyl (**276**) or alkenyl (**274**, **281**) groups. Upon the basis of these calculations, predictions were then made regarding the suitability of these ligands for use in the asymmetric palladium-catalyzed substitution reaction of allylic acetates. Subsequent experiments gave results, which were in good agreement with the calculated predictions. Table 7 describes the results obtained in the allylic alkylation of different allylic acetates and nucleophiles with these ligands. The highest levels of asymmetric induction were predicted and obtained with the 2-(2-bornyl)phen ligand **276** with which an enantioselectivity of 92% was obtained in the reaction with dimethyl malonate and the 1,3-diphenylallyl-system. Moreover, in the case of the 1,3-methylphenylallyl system, the major pathway involved reaction at the methyl-substituted terminus (68% yield), which gave an ee of 33%, whereas reaction at the phenyl-substituted terminus (17% yield) afforded an ee of 96%.

The chiral C_1-symmetric phens **309**, **310a**−**c**,**e**[82] and their 5,6-dihydro derivatives **305**, **307a**−**c**,**e** were evaluated in the palladium catalyzed allylic substitution of **370** with dimethyl malonate.[83] This study showed that phens and dihydrophens possess similar catalytic activity and stereoselectivity. The best enantiomeric excess was obtained with the *n*-butyl substituted phen **310b** (84% ee).

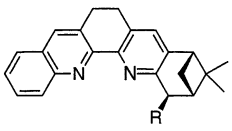
Comparison of the series of bpy, phen, and dihydrophen in the palladium catalyzed allylic substitution showed that bpys provided less effective catalysts than the related phens and dihydrophens. Whereas bpys required several hours to completely consume **370**, phens and dihydrophens needed only few minutes. This trend was independent of the substituent. The greatest differences were found with catalysts derived from ligands bearing the benzyl substituent. For example, **307e** and **310e** were more reactive than **52f**, affording the alkylation product in 8 and 25 min, respectively, whereas with **52f** the reaction required 48 h. Concerning the stereoselectivity of the reaction, there are not significant differences among the three kinds of ligands except in the case of the benzyl substituent in which the stereodifferentiating ability of bpy **52f** was much better (89% ee) than that of the

Scheme 71[a]



[a] Legend: (a) Ligand **307b**; (b) ligand **308b**; the dotted lines represent the fused benzo-ring in **308b**.

related phen **310e** (36% ee) or dihydrophen **307e** (40% ee). Particularly disappointing results were obtained with dihydrobenzophens **308b**,**e** where enantioselectivities (6 and 23% ee, respectively) were lower than their unsubstituted counterparts **307** (72 and 40% ee, respectively).



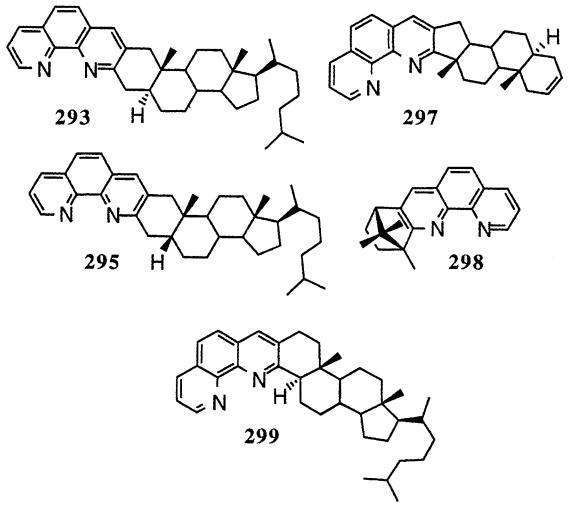
308b: R = *n*-Bu
e: R = Bn

This stereochemical outcome has been explained using arguments based on both early and late transition states. In Scheme 71 are depicted the two diastereomeric Pd(η^3-1,3-diphenylallyl) complexes, **381a**,**b** (*exo*, *syn*, *syn*) and **382a**,**b** (*endo*, *syn*, *syn*), derived from ligands **307b** or **308b**, which are postulated as the intermediates on which the nucleophilic attack occurs. On the basis of the assumption of an early transition state which dictates that the more abundant isomer (**381a**,**b**) is the more reactive one,[110] and in conjunction with the configuration of the substitution products, nucleophilic attacks occurs preferentially at the carbon *trans* to the tetrahydroquinoline ring of the *exo* isomer (path b in **308**). The prediction of an early transition state is thus favored by the increase in enantioselectivity, which occurs in parallel with stabilization of the more abundant isomer. This stabilization is provided by the presence of alkyl groups at the 11-position of the tetrahydroquinoline.

However, benzo-fusion on the pyridine ring not containing the chiral backbone reduced the enantioselectivity. This result could be explained by invoking a late transition state resulting from increased steric interactions during formation of the Pd(0)−olefin complex.[111] According to this explanation, the nucleophile would push the allylic phenyl group toward the chirogenic group on the tetrahydroquinoline ring. Thus, attack would be favored at that position of the allylic termini which avoids an unfavorable steric interaction between the proximal phenyl group of the diphenylallyl moiety and the chirogenic element on the tetrahydroquinoline ring. Therefore, with ligands such as **307b**, nucleophilic attack will occur preferentially on the carbon *trans* to the tetrahydroquinoline ring of the *exo* isomer (**381a** to **384a**). However with ligand **308b**, the nucleophilic attack on the carbon *trans* to the tetrahydroquinoline ring of the *exo* isomer (from **381b** to **384b**) involves steric interaction between the benzo-fused ring and the phenyl group at the emerging stereocenter. Thus, nucleophilic attack at this position is diminished and only slightly favored with respect to *cis* attack (**381b** to **383b**), causing a considerable reduction in enantioselectivity. Both the prediction of an early and a late transition state leads to the conclusion that the preferred product arises from the more abundant *exo*-isomer but only arguments based on a late transition state explain the stereochemical outcome obtained with ligand **308**.

A variety of chiral C_1-symmetric phens (**293**, **295**, **297**, and **298**), especially those with an incorporated steroid moiety, have been examined in palladium catalyzed allylic substitution.[80] These phens provided effective catalysts (Table 8) affording total conversion of the starting material in less than 75 min to give high yields of dimethyl 1,3-diphenylprop-2-enylmalonate **371**. When the allylic substitutions were carried out employing the Trost procedure (BSA/KOAc), the best enantioselectivity was obtained with the 5α-cholestan[4,3-*b*]-phen **299** (94% ee). The enantiomeric excess was increased to 96% when a different method, which involves the use of BSA as a base in association with an appropriate tetraalkylammomium fluoride,[112] was followed for generation of the malonate anion with a bulky counterion.

There has been only one report on the use of chiral tpy ligands in asymmetric allylic alkylation. The tpys **334** and **332** showed moderate catalytic activity (48 and 7 h for total conversion) and enantioselectivity (38 and 40% ee).[108] The monosubstituted tpy **332** showed a comparable reactivity and enantioselectivity with respect to the related bpy whereas the disubstituted C_2-symmetric tpy **334** was less reactive than **332** but more reactive than the C_2-symmetric bpy **119**. This stereochemical outcome was rather surprising in light of a recent study demonstrating that, in solution, tpy−allyl-palladium(II) complexes are in dynamic equilibrium between η^1- and η^3-allyl isomeric forms. In the former case, the tpy behaves as a terdentate ligand whereas in the latter it coordinates palladium in a bidentate fashion.[113] Thus,



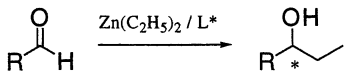
ligand **337** could form two η^3-allyl complexes depending on whether the central pyridine coordinates palladium together with the substituted or unsubstituted pyridine. On the other hand, the C_2-symmetric ligand **334** can form only one palladium η^3-allyl complex. Both ligands **332** and **334** show the same enantioselectivity but they provide different catalytic species.

3.3. Addition of Organometallic Reagents to Aldehydes

One of the most studied processes in the field of carbon−carbon bond forming reactions is the nucleophilic addition of organometallic reagents to carbonyl substrates.[114] Modification of the organometallic reagent by chiral, nonracemic auxiliaries offers a good opportunity to create optically active alcohols and a catalytic version of this process provides maximum synthetic efficiency.

Organozinc reagents have been used for the catalytic, enantioselective alkylation of aldehydes leading to a diverse array of secondary alcohols.[115] Chiral pyridine-containing ligands have found application in this process, affording high asymmetric induction.[2−6] The general procedure for this reaction is presented in Scheme 72, in which commercially available diethylzinc is usually used in large excess, generally in a 3−5-fold molar excess as compared to the substrate. In Table 9 are described the results obtained in the enantioselective addition of diethylzinc to different aldehydes catalyzed by bpys.

Scheme 72



In 1990 Bolm et al. used the C_2-symmetric chiral bpys **65** and **67** to catalyze the asymmetric addition of diethylzinc to a variety of aldehydes.[31a] While the presence of only 5 mol % of **65** provided alcohols in good yields and high enantiomeric excess (up to 92% ee), the corresponding methylated compound **67** showed only slight catalytic activity and led to products with much lower enantiomeric excesses (28% ee). With **65**, *para*-substituted aromatic aldehydes gave alcohols in high enantiomeric excess (up to 88% ee). Asymmetric induction was lower for aliphatic aldehydes (70% ee) and α,β-unsaturated

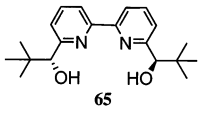
Table 9. Enantioselective Addition of Diethylzinc to Different Aldehydes Catalyzed by 2,2-Bipyridines[a]

R	ligand	solvent	temp (°C)	time (h)	yield (%)	ee (%)	ref
Ph	**65**	toluene	−25	48	94	92	31a
Ph	**67**	toluene	0	52	93	28	31a
Ph	**65**	hexane	0	3	92	88	31a
p-ClC_6H_4	**65**	toluene	0	3	65	90	31a
p-$MeOC_6H_4$	**65**	toluene	0	9.5	96	80	31a
n-C_6H_{13}	**65**	toluene	0	3	75	70	31a
CH_2=CH−$(CH_2)_2$−	**65**	hexane	0	3	76	36	116
Ph-CH=CH−	**65**	toluene	0	3	75	70	116
	65	toluene	0	3	88	24	116
Ph	**68**	toluene	0	3	80	78	116
Ph	**84**	toluene	0	3	77	85	117
Ph	**85**	toluene	22	0.5	82	77	117
Ph	**87**	toluene	22	0.5	86	79	117
Ph	**88**	toluene	0	1	86	95	117
p-ClC_6H_4	**88**	toluene	0	7	68	54	117
n-C_6H_{13}	**88**	toluene	0	6	66	80	117
Ph-CH=CH−	**88**	toluene	0	2.5	54	44	117
n-C_6H_{13}	**88**	toluene	0	6	74	47	117
1-naphthyl	**88**	toluene	0	7	52	20	117
2-naphthyl	**88**	toluene	0	7.5	67	68	117
Ph	**77**	toluene	0	1		21	117
Ph	**83**	toluene	0	3		65	117
Ph	**48n**	toluene−hexane	0	1	99	86	26
Ph	**48o**	toluene−hexane	0	1	100	79	26
Ph	**48p**	toluene−hexane	0	1	100	73	26
Ph	($S_{C'}$)-**52s**	toluene−hexane	0	1	100	82	26
Ph	($R_{C'}$)-**52s**	toluene−hexane	0	1	99	47	26
Ph	($S_{C'}$)-**52t**	toluene−hexane	0	1	100	78	26
Ph	($R_{C'}$)-**52t**	toluene−hexane	0	1	100	52	26
Ph	**19**	toluene−hexane	25	22	84	2	120

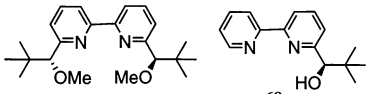
[a] Only representative examples are reported. For further examples, see the references cited in the table.

aldehydes, such as cinnamaldehyde or 3-phenylpropenal, were alkylated with moderate enantioselectivity. Lowering of the reaction temperature and the use of hexane or a hexane/toluene mixture in place of the more polar acetonitrile solvent led to an increase in asymmetric induction with benzaldehyde. On the other hand, doubling the amount of catalyst to 10 mol % had little effect on the enantioselectivity.

To examine the features controlling the stereochemical outcome and reaction rate, a number of pyridine derivatives were synthesized and tested.[116] Among these new ligands, the C_1-symmetric bpy **68** showed catalytic activity similar to **65** but lower enantioselectivity (78% ee).



65

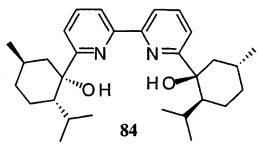


67 **68**

Kwong et al. prepared a series of C_2-symmetric bpys (**84**, **85**, **87**, **88**) from naturally occurring ketones and tested their effectiveness as catalysts for the addition of diethylzinc to benzaldehyde.[117] In all cases, the yields of 1-phenyl-1-propanol were good and the enantioselectivities obtained were high (77−95% ee). Temperature and solvent had a significant effect on both the rate and enantioselectivity. Lowering the temperature from 22 to 0 °C led to slightly slower reactions but to an increase in asymmetric induction from 81 to 85% ee for **84** and from 92 to 95% ee for **88**. Toluene, hexane, and THF gave similar results, while CH_2Cl_2 and acetonitrile lowered enantioselectivity as well as the rate. Nevertheless, the observed reaction rates were still very fast when compared with previously reported pyridyl alcohol-type ligands.[5,7−9] Using bpy **88** as the best ligand, other aldehydes were examined. In all cases, chemical yields of the alcohol products were good but enantioselectivities were all lower than benzaldehyde and the reactions required more time for completion.

Since Bolm et al. showed that it not essential to have C_2-symmetry to achieve high enantioselectivity in the alkylation of aldehydes,[116] Kwong compared the C_1-symmetric bpys **77** and **83** with the corresponding C_2-symmetric bpys **84** and **88**. Both **77** and **83** were also active in catalyzing the ethylation of benzaldehyde and complete conversions were achieved in 1 and 3 h, respectively. However, these ligands gave enantioselectivities (21 and 65% ee, respectively) which were much lower than those obtained with the related C_2-symmetric ligands. Moreover, **77** gave an alcohol having the opposite configuration to that obtained with **84**, indicating that a different mechanism may be operating for these ligands.

Von Zelewsky et al. prepared a number of bpy alcohols (**52o**,**n**,**p**,**s**,**t**) from (−)-α-pinene and studied their catalytic activity in the reaction of diethylzinc with benzaldehyde.[26] All the studied ligands induced formation of the *R*-enantiomer of 1-phenyl-1-propanol with good enantiomeric excess. The chirality at the



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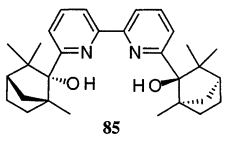

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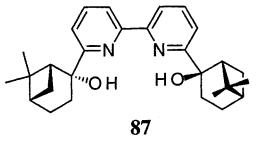

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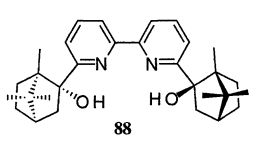

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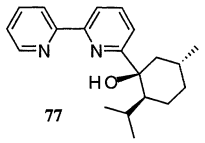
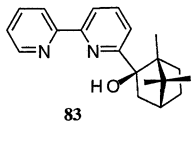
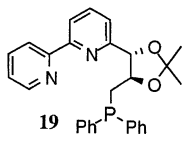


77



83

stereocenter involving the C′-hydroxy group was not a criterion for high enantioselectivity. The most important factor in this regard appeared to be due to configuration at C8. In fact, ligands **52o** and **52p**, where C′ is not a stereogenic center, afforded high enantiomeric excesses. This observation was corroborated by the fact that the two epimeric pairs ($S_{C'}$)-**52s**/($R_{C'}$)-**52s** and ($S_{C'}$)-**52t**/($R_{C'}$)-**52t**, which differ only in the absolute configuration at C′, gave the same enantiomer for the addition product, however with very different efficiencies. The epimers having the *S*-configuration at C′ were the most effective ligands.



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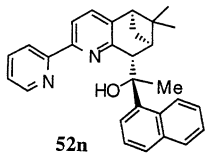
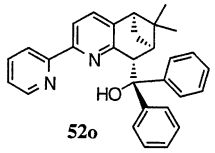
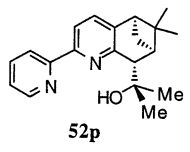


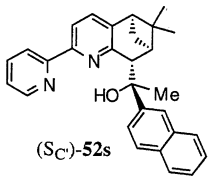
52n



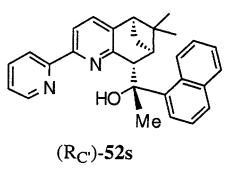
52o



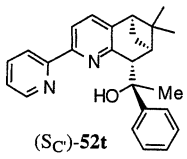
52p



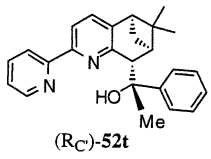
($S_{C'}$)-**52s**



($R_{C'}$)-**52s**



($S_{C'}$)-**52t**



($R_{C'}$)-**52t**

All bpys examined thus far contain an hydroxy group in their backbone. In fact, the presence of a protic functional group, which may form a covalent bond with the dialkylzinc reagent, appears to be essential for effective catalysis.[115] An indirect confirmation of this observation is afforded by bpy **19**, which gave 1-phenyl-1-propanol in good yield but with no enantioselectivity.[15]

Kwong et al. reported the synthesis and spectroscopic characterization of the zinc complex **387**

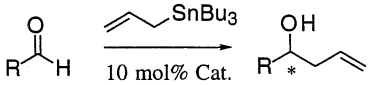
Table 10. Enantioselective Allylation by Allyl Tri-*n*-butyltin of Different Aldehydes Catalyzed by 387[a]

R	time (h)	yield (%)	ee (%)
Ph	21	92	39
p-$MeOC_6H_4$	22	90	38
p-BrC_6H_4	15	82	40
p-$NO_2C_6H_4$	70	82	40
Ph-CH=CH−	16	98	36
2-naphthyl	25	83	38
n-C_7H_{15}	30	82	56
2-furyl	46	85	53
5-Me-2-furyl	46	91	59
2-thiophenyl	29	92	41

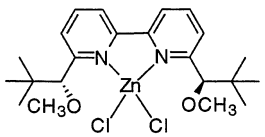
[a] All reactions were carried out in CH_2Cl_2 at room temperature and 10 mol % of **387**.

derived from bpy **67** and its use as a catalyst for the allylic addition reaction[120] of different aldehydes with allyl tri-*n*-butyltin (Scheme 73 and Table 10).[121]

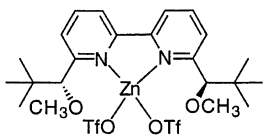
Scheme 73



The zinc dichloride complex **387** was not an active catalyst for allylation of benzaldehyde; however, the corresponding triflate complex **388**, generated in situ by treating **387** with silver triflate, served as an active catalyst. The effects of both temperature and counterion on the enantioselectivity and yield of the zinc complex were investigated. Lowering the temperature reduced the yield but slightly increased the enantioselectivity (from 39% ee at 25 °C to 46% ee at −40 °C). Counterions such as ClO_4^-, PF_6^-, BF_4^- etc., slowed the reaction rate and lowered the enantioselectivity when compared with the triflate. The utility of the zinc complex **387** as a catalyst for the asymmetric allylation of various aldehydes was then examined. All these reactions gave excellent yields and moderate enantioselectivities for aromatic, aliphatic, and heterocyclic aldehydes. The enantioselectivities were found to be independent of the electronic property of a substituent (withdrawing or donating) on the aromatic aldehyde. Better enantioselectivities were found with straight chain and heterocyclic aldehydes.



387

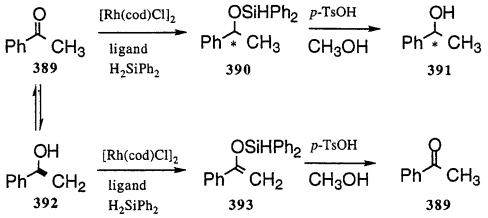


388

3.4. Hydrosilylation Reactions

The transition-metal catalyzed addition of a Si−H bond across a C=O double bond, followed by hydrolysis of the resulting silyl derivative, is equivalent to the reduction of the carbonyl group to the corresponding alcohol.[122,123] The hydrosilylation of acetophenone with diphenylsilane is considered a model reaction for the reduction of prochiral ketones (Scheme 74). There is a competing side-reaction in the catalytic hydrosilylation of carbonyl compounds, which

Scheme 74



represents a major drawback. Carbonyl compounds are often enolizable and the transition metal catalyst may also catalyze the hydrosilylation of the corresponding enol. Subsequent hydrolysis converts the silylenol ether to the starting carbonyl compound so that the conversion to the alcohol seems incomplete, although hydrosilylation of the carbonyl compound as its enol may have been quantitative.

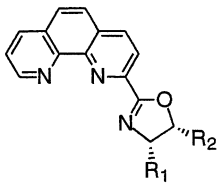
Table 1 reports representative results obtained in the asymmetric hydrosilylation of acetophenone using bpy and phen ligands. For the enantioselective hydrosilylation of prochiral ketones with transition metal complexes, it was found that nitrogen ligands were more effective than phosphorus ligands which had been so successful in similar enantioselective hydrogenations.[1,123]

In a study to determine the catalytic activity and enantioselective behavior of 16 optically active nitrogen ligands, Botteghi and Brunner evaluated the bpys **13**, **22**, **32,** and **372** in the rhodium-catalyzed hydrosilylation of acetophenone with diphenylsilane.[124] The rhodium(I) complexes, prepared by using $[Rh(cod)Cl]_2$ as the procatalyst, displayed remarkable catalytic activity but only bpy **32** showed any satisfactory stereo-differentiating ability (72% ee).

Next these workers evaluated ligands **119**, **264**, and **265** that are the C_2-symmetric analogues of **32**, **257**, and **258**, respectively.[99] The catalysts originating from these ligands were reasonably active, but provided a racemic product. It could not be ascertained if this observation should be ascribed to the C_2-symmetry or to poor binding resulting from the presence of two bulky substituents close to the donor centers.

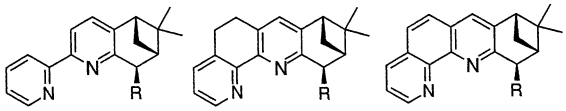
Gladiali et al. investigated the rhodium catalyzed asymmetric hydrosilylation of acetophenone with diphenylsilane in the presence of phens **250a**,**b**, **254**, **257**, **258**, and potentially terdentate phen derivatives **324a**−**d**.[86] The in situ catalysts obtained from the former set of ligands and $[Rh(cod)Cl]_2$ were very effective, and complete hydrosilylation was observed in 12 h at room temperature even at the relatively high substrate-to-catalyst ratio of 400:1. The reaction was chemoselective, and no trace of enol silyl ether could be detected in the reaction mixture, providing 1-phenylethanol in almost quantitative yield. For this series of phens, the enantioselectivity increased dramatically as the chiral auxiliary is moved closer to the nitrogen. Whereas 2-substituted phens **257** and **258** gave moderately high enantioselectivities (70 and 76% ee, respectively), the 3-substituted phens **250a**,**b** and **254** afforded not higher than 6% ee. On the other hand, catalysts prepared from the oxazolinyl derivatives **324a**−**d** displayed good catalytic

activity and chemoselectivity, but the asymmetric inductions were only modest (up to 20% ee).



324a: $R_1 = CH_3$, $R_2 = H$
b: $R_1 = CH_2CH(CH_3)_2$, $R_2 = H$
c: $R_1 = C_6H_5$, $R_2 = H$
d: $R_1 = CH_3$, $R_2 = C_6H_5$

We evaluated a homogeneous series of bpys (**43**, **52a**,**f**), 5,6-dihydrophens (**305**, **307a**,**e**) and phens (**309**, **310a**,**e**) in the enantioselective hydrosilylation of acetophenone with diphenylsilane.[99] High conversion levels and satisfactory yields were obtained with all ligands after 24 h at room temperature but, in most cases, the reaction was completely devoid of enantioselectivity. A modest but definite enantiomeric excess was obtained with only the unsubstituted cycloalkeno-condensed derivatives **(43**, **305**, **309)**, with a decreasing trend in going from bpy **43** to phen **305**. Moreover, phen **309** induced a switch in the chirality of the reaction product as compared to bpy **43** and dihydro-phen **305**. The introduction of an alkyl substituent onto the carbon adjacent to the heterocyclic ring resulted in the reduction of both the chemical yield and the stereoselectivity of the reaction. This was a disappointing result because an enantioselectivity higher than one observed with the unsubstituted counterparts was expected in view of the close proximity of one chirogenic element to the metal center. During the preparation of the Rh(I)-ligand adducts in situ, the color of the solution changed from yellow to orange with ligands **43**, **305**, and **309**, while the solution remained yellow with the substituted ligands, indicating that these latter ligands may not bind readily to rhodium.

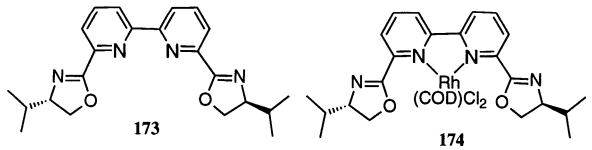


43: R = H
52a: R = CH_3
f: R = CH_2-C_6H_5

305: R = H
307a: R = CH_3
e: R = CH_2-C_6H_5

309: R = H
310a: R = CH_3
e: R = CH_2-C_6H_5

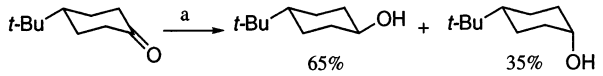
Nishiyama et al. examined the 6,6′-bis(oxazolinyl)-bpy **173** (bipymox) and its rhodium(III) complex **174** in the asymmetric hydrosilylation of ketones.[49] Although bipymox could coordinate in a terdentate fashion, the bidentate bipymox−rhodium complex **174** was formed preferentially.



173 **174**

The combination of $Rh(cot)_2Cl$ and **174** catalyzed the reduction of acetophenone with diphenysilane to give the alcohol with 41% ee. The addition of $AgBF_4$ increased the enantioselectivity to 70%. However, the product selectivities were not as high (57−68%) due to the formation of the silyl enol ether as a byproduct (32−39%). In contrast, the use of the complex **174** as a catalyst drastically increased the selectivity (up to 98%) as well as the enantioselectivity (up to 90%) especially upon the addition of excess ligand and $AgBF_4$. Other ketones were also subjected to hydrosilylation using the complex **174** as a catalyst: 1-tetralone (97% yield, 86% ee), 1-acetylnaphthalene (89% yield, 92% ee), and 4-phenyl-2-butanone (78% yield, 72% ee). For the hydrosilylation of 4-*tert*-butylcyclohexanone, the *tran*/*cis* ratio of 4-*tert*-butylcyclohexanols was 65:35 (Scheme 75). This selectivity was similar to that obtained with other bpy-oxazoline based ligands.[126]

Scheme 75[a]



[a] Legend: (a) Rh(**173**)Cl_3, $AgBF_4$, Ph_2SiH_2, THF, 87%.

Tpy liands were also used in the rhodium-catalyzed enantioselective hydrosilylation of acetophenone. We evaluated the tpys **332** and **334**, having C_1 and C_2-symmetries, respectively, in the Rh(I)-catalyzed hydrosilylation of acetophenone with diphenylsilane.[99] These tridentate ligands led to low conversions and low reaction rates. The enantiomeric excess did not exceed 14% even upon changing the solvent from methylene chloride to tetrachloromethane or by the addition of silver tetrafluoroborate, which only increased the amount of the enol ether **393**. These disappointing results were ascribed to the conformational mobility of the 6,6-dimethylnorpinan-2-yl group which minimizes the steric interaction between the stereogenic centers on the ligand, the substrate and the reagent leading to the enantioselective transition state.

On this basis, we evaluated the tpys **339**−**340a**−**d** incorporating the 6,6-dimethylnorpinane framework in the form of a cycloalkeno-condensed substituent in the rhodium(I)-catalyzed hydrosilylation of acetophenone with diphenylsilane.[93] These ligands were expected to be more effective chiral controllers because the asymmetric substituents are directed toward the metal ion upon complex formation. With these rhodium(I)-tpy catalysts, moderate levels of conversion were obtained (45−59%). Only tpys **339** and **340a** gave in low yield (29 and 18%, respectively) the desired silylalkyl ethers **390**. The resulting carbinols, however, did not show significant enantioexcesses (7% and 13% ee, respectively). Surprisingly, the tpys **340b**,**d** afforded the silyl enol ether **393** as the sole product. Apparently, increasing the size of the substituent on the tetrahydroquinoline ring favors the formation of **393** over **390**.

The disappointing results obtained with Rh(I)-catalysts prompted us to examine the ability of the Rh(III) complexes of these ligands.[93] This study was inspired by the work of Mukayama et al. who showed that trivalent rhodium complexes, derived from terdentate C_2-symmetrical bis(oxazolinyl)pyridines and $RhCl_3$, with the aid of $AgBF_4$, are effective chiral catalysts for the hydrosilylation of ketones.[127] The

Rh(**339**, **340a**−**d**)Cl_3 complexes in the presence of $AgBF_4$ were evaluated in the hydrosilylation of acetophenone with diphenylsilane. High conversion levels (65−95%) and satisfactory yields (55−71%) were obtained, but the derived carbinols showed very low enantio-excesses (2−6% ee).

3.5. Transfer Hydrogenation Reactions

Transfer hydrogenation (H-transfer) from a donor to an acceptor molecule provides an important method of reducing multiple bonds and can be catalyzed by homogeneous systems.[128] Unlike asymmetric hydrogenation with molecular hydrogen, the best catalysts often use nitrogen donors as the auxiliary ligands. In fact, although phosphorus ligands are useful and have found several applications in this field, remarkable successes have been realized with chiral nitrogen ligands,[1a] which should be considered the ligands of choice in the design of high efficiency H-transfer catalysts.

Transfer hydrogenation from 2-propanol to prochiral ketones catalyzed by optically active transition metal complexes represents a method for asymmetric alcohol synthesis (Scheme 76). Acetophenone is used as a model substrate for prochiral ketones, and in Table 12 representative results are collected for the asymmetric transfer hydrogenantion of acetophenone using bpy and phen ligands.

The catalytic activity of rhodium(I) and iridium(I) complexes with bpys and phens is well documented.

Table 11. Enantioselective Hydrosilylation of Acetophenone with Diphenylsilane[a]

ligand	catalyst	enolether (%)	yield (%)	ee (%)	conf	ref
13	$[Rh(cod)Cl]_2$			6	*R*	124
22	$[Rh(cod)Cl]_2$			0		124
32	$[Rh(cod)Cl]_2$		86	72	*R*	124
372	$[Rh(cod)Cl]_2$		66	1	*R*	124
43	$[Rh(cod)Cl]_2$	2	88	32	*R*	99
***ent*-43**	$[Rh(cod)Cl]_2$	1.5	87	34	*S*	125
52a	$[Rh(cod)Cl]_2$	25	63	2	*S*	99
52f	$[Rh(cod)Cl]_2$	26	61	3	*S*	99
305	$[Rh(cod)Cl]_2$	36	56	21	*R*	99
307a	$[Rh(cod)Cl]_2$	27	61	1	*S*	99
307e	$[Rh(cod)Cl]_2$	32	49	0		99
309	$[Rh(cod)Cl]_2$	19	73	10	*S*	99
310a	$[Rh(cod)Cl]_2$	22	55	0		99
310e	$[Rh(cod)Cl]_2$	25	61	1	*R*	99
173	$Rh(cot)_2Cl/AgBF_4$	39	57	70	*S*	49
173	$RhCl_3$(**173**)	2	98	90	*S*	49
332	$[Rh(cod)Cl]_2$	31	51	6	*S*	99
334	$[Rh(cod)Cl]_2/AgBF_4$	49	37	14	*S*	99
119	$[Rh(cod)Cl]_2$	30	70	1	*S*	99
264	$[Rh(cod)Cl]_2$	27	69	2	*S*	99
265	$[Rh(cod)Cl]_2$	33	63	1	*S*	99
250a	$[Rh(cod)Cl]_2$	100	0	6	*R*	86
257	$[Rh(cod)Cl]_2$	100	0	70	*R*	86
258	$[Rh(cod)Cl]_2$	100	0	76	*R*	86
324c	$[Rh(cod)Cl]_2$			20	*S*	86

[a] Only representative examples are reported. For further examples, see the references cited in the table.

Scheme 76

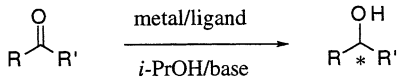


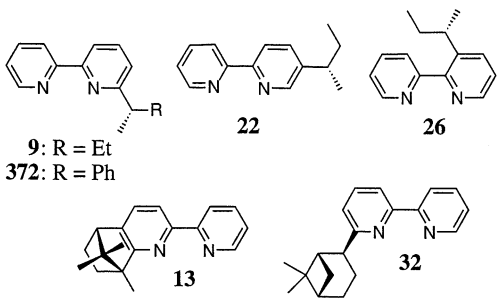
Table 12. Asymmetric Transfer Hydrogenation of Acetophenone[a]

ligand	metal	H-donor	base	temp (°C)	ee (%)	conf.	ref
9	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	83	7.2	*R*	17
32	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	83	14.8	*R*	17
22	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	83	2.5	*R*	17
26	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	83	1.1	*R*	17
372	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	83	4.1	*R*	17
13	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	83	9.4	*S*	14
235	$[Ir(cod)Cl]_2$	*i*-PrOH	NaO*i*-Pr	25	31	*S*	67
241	$[Ir(cod)Cl]_2$	*i*-PrOH	NaO*i*-Pr	80	23	*R*	69
250a	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	83	24	*R*	73
250b	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	60	31.5	*R*	72
250c	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	60	63	*R*	74
254	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	60	0	*R*	74
257	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	83	14	*R*	73
258	$[Rh(cod)Cl]_2$	*i*-PrOH	KOH	83	15.4	*R*	73

[a] Only representative examples are reported. For further examples, see the references cited in the table.

They are among the most active catalysts in the H-transfer to ketones with 2-propanol. Turnover frequencies higher than 10,000 cycles/h have been recorded in the reduction of acetophenone with Rh(I)−bpy complexes. Even more active are Ir(I)−phen complexes which are capable of reducing acetophenone in less than one minute at substrate-to-metal ratios as high as 50,000:1.[129]

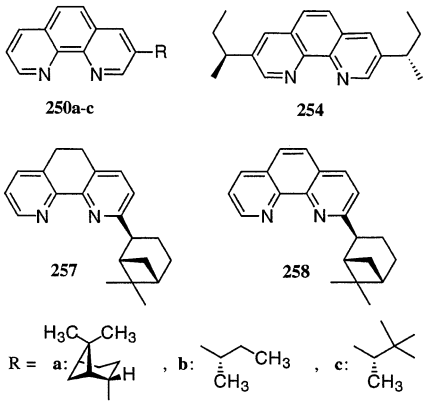
Gladiali et al.[17] first applied chiral bpys to the H-transfer enantio-differentiating reduction of acetophenone using 2-propanol as a hydrogen donor, potassium hydroxide as the base, and $[Rh(cod)Cl]_2$ as the catalyst precursor. They examined two kinds of bpys: the homogeneous series of **9**, **22**, and **26** bearing the (+)-*sec*-butyl group in the 6, 5, and 3 positions of the heterocycle, respectively, and the heterogeneously 6-substituted bpys **9**, **372**, and **32**. The position and the structure of the chiral alkyl substituent were found to strongly influence the stereoselectivity. For ligands bearing the same substituent, the highest stereodifferentiation was observed when the chiral group is closest to the nitrogen (i.e., **9** is better than **22** and **26**), while among 6-alkylbpys the bulkiest substituent was also the most effective (i.e., **32** is better than **9** and **372**). The authors also investigated the dependence of base concentration and ligand/metal ratio on the catalytic activity and stereoselectivity of the reaction. Usually, considerable ligand excess was required for a satisfactory reaction rate. Under optimal conditions, the enantiomeric excesses obtained in these experiments were rather low, reaching about 15% ee in the case of bpy **32**.



Following these results, the same authors next evaluated bpy **13**, characterized by the presence of a

more demanding substituent on the bpy ring.[14] However, the greater rigidity of the alkyl substituent unfavorably affected the ligand coordination to the rhodium(I)-procatalyst. The bulky substituent close to one pyridine differentiates the coordinating ability of the two pyridines in the molecule and may even favor monodentate coordination of the bpy. Therefore, the authors concluded that more than one catalytically active species is present in solution and that the low stereoselectivity (9.4% ee at best) is the consequence of a delicate balance between the concentration and the activity of the different rhodium complexes involved in the process.

Vögtle et al. reported the iridium-catalyzed transfer hydrogenation of acetophenene with 2-propanol using the planar chiral bpys **235**[67] and **241**.[69] The [Ir(**235**)] complex showed good catalytic activity, and the reaction could be carried out at room temperature in contrast to many other ligands.[128] However, the observed stereoselectivity was low (31% ee). On the other hand, the [Ir(**241**)] complex was practically inactive toward transfer hydrogenation when the reaction was performed at room temperature. When the reaction was carried out at 80 °C, it was considerably accelerated but must be stopped early to produce some enantiomeric excess (23% ee at best).



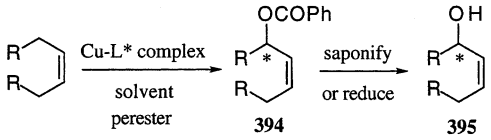
Another class of pyridine-based chiral ligand has been tested to extend the scope of the rhodium-catalyzed transfer hydrogenation of ketones. Gladiali et al. examined the efficiency of a number of chiral phens. In a preliminary study, they found that the 3-*sec*-butylphen (**250b**) afforded a remarkable enhancement of asymmetric induction with respect to the structurally related 3-*sec*-butylbpy (**22**) (31.5 vs 2.5% ee).[72] Next, they examined the phens **250a**, **258**, and the 5,6-dihydrophen **257** having the 2,2-dimethylnorpinan-2-yl group as the common chiral auxiliary.[73] The prominent features of these new ligands are high catalytic activity, up to 500 cycles-per-hour, and complete selectivity in reduction. However, the highest stereoselectivity recorded with these ligands (24% ee with **250a**) was lower than the best case observed with the 3-*sec*-butylphen **250b**. Moreover, ligands **257** and **258** displayed almost identical stereo-differentiating efficiencies and showed no improvement over the corresponding bpy **32**. The data obtained from this study appeared to indicate that 3-substituted phens are more effective than the corresponding 2-substituted ones. This is rather surprising in view of the greater distance between the stereocenter and the reactive site.

To confirm this trend and to improve the enantioselectivity of this catalytic system, Gladiali synthesized the phen **250c** bearing the 1,2,2-trimethylpropyl group, a very sterically demanding substituent, and the C_2-symmetric phen **254**.[74] Surprisingly, the C_2-symmetry of **254** gave a catalytic system of poor activity and devoid of enantio-differentiation. On the other hand, the phen **250c** displayed an extremely high catalytic activity with turnover rates up to 10,000 cycles/h and an asymmetric induction of 63% ee.

3.6. Allylic Oxidation Reactions

The allylic oxidation of alkenes with peresters in the presence of copper salts to give allylic esters (known as the Kharasch-Sosnovsky reaction)[130] represents an allylic alcohol synthesis since the allylic esters easily can be converted into allylic alcohols by saponification or reduction methods (Scheme 77). Copper complexes of chiral nitrogen-containing ligands are the catalysts of choice for the enantioselective version of such a reaction.[131,132]

Scheme 77



In this context, both bpys and phens recently have been used. Kocovsky et al. reported that the Cu(I) complex of the chiral C_2-symmetric bpy **132** is a very effective catalyst in this process.[43] The conditions followed by Kocovsky entail the initial reaction of the ligand with $Cu(OTf)_2$ to give a Cu(II) complex which is then reduced in situ with phenylhydrazine to the corresponding Cu(I) species. The oxidation reactions then were carried out with *tert*-butyl peroxybenzoate in the presence of the alkene and 1 mol % of the catalyst. Although the enantioselectivities do not exceed 76% ee, only a short reaction time ($\leq$ 30 min at room temperature) is needed for consumption of the starting material. The reaction time is significantly shorter than with most of the catalysts reported to date, which often require several days for completion. By contrast, the complex of the chiral C_2-symmetric bpys **168** and **169** turned out to be less stable to the oxidation of Cu(II) and gave less encouraging results (Table 13).[22] The results obtained with ligand **132** have been attributed to the stabilization of a Cu geometry halfway between square planar [favored by Cu(II)] and tetrahedral [favored by Cu(I)].

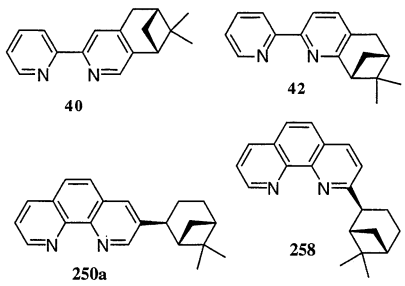
Our preliminary investigation on the use of bpy- and phen-based ligands in this process has indicated that the presence of C_2-symmetry is not an essential feature to obtain a catalytically active copper complex. However, the ligands provide effective catalysts only when they bear a substituent close to the reactive site. For example, whereas the bpy **40** and phen **250a** failed to convert cyclohexene into the corresponding allylic benzoate, their isomers **42** and

Table 13. Asymmetric Allylic Oxidation of Cycloalkenes Catalyzed by Cu(I) Complexes of 2,2′-Bipyridines and 1,10-Phenanthrolines[a]

alkene	ligand	temp (°C)	time (h)	yield (%)	ee (%)	ref
cyclopentene	**132**	20	0.5	85	48	43
cyclopentene	**132**	0	12	80	59	43
cyclopentene	**316**	25	0.5	67	57	134
cyclohexene	**40**	25	3.5	79	7	133
cyclohexene	**42**	25				133
cyclohexene	**132**	20	0.5	96	49	43
cyclohexene	**132**	−20	48	56	60	43
cyclohexene	**168**	20	24	74	19	22
cyclohexene	**169**	20	24	70	11	22
cyclohexene	**254a**	25	24	trace		133
cyclohexene	**258**	25	24	75	8	133
cyclohexene	**297**	25	0.25	87	30	133
cyclohexene	**298**	25	60	85	8	133
cyclohexene	**299**	25	0.5	82	21	133
cyclohexene	**316**	25	0.5	85	47	134
cycloheptene	**132**	20	0.5	88	62	43
cycloheptene	**132**	0	5	66	75	43
cycloheptene	**316**	25	0.5	91	76	134

[a] The reactions were carried out at room temperature in Me_2CO in the presence of the catalyst (1 mol %), generated in situ by reduction of $Cu(OTf)_2$−L* complex with $PhNHNH_2$.

258 were successful for this conversion in about 3.5 and 24 h, respectively.[133]



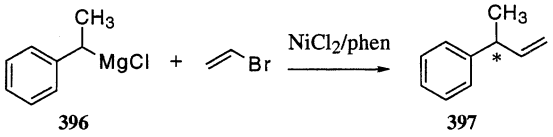
Results obtained with copper(I)−phen complexes have shown that phens are also good catalysts in the asymmetric copper(I)-catalyzed allylic oxidation of cyclohexene. In the case of phen **297**, the reaction rate was the shortest to date for this kind of transformation. The stereochemical outcome with C_1-symmetric phens such as **297** and **299** (30 and 21% ee with cyclohexene) suggests that the presence of C_2-symmetry is a necessary feature to obtain an effective enantioselective catalytic system.

We have recently confirmed this suggestion by preparing the C_2-symmetric phen **316**. With this ligand, the oxidations of cyclopentene, cyclohexene, and cycloheptene were complete within <30 min at room temperature, giving the corresponding benzoate esters in good yields.[134] The enantioselectivity depended on the structure of the cycloalkene. For the oxidation of cyclopentene and cyclohexene the selectivity was modest (57 and 47% ee, respectively), while cycloheptene was somewhat higher (76% ee).

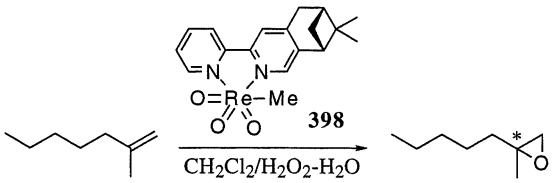
3.7. Other Processes

Gladiali et al. studied the efficiency of phens **250**, **257**, and **258** in the nickel catalyzed cross-coupling of Grignard reagents.[86] They treated α-methylbenzylmagnesium chloride (**396**) with vinyl bromide at

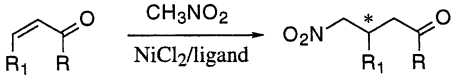
Scheme 78



Scheme 79



Scheme 80



399: $R = R_1 = C_6H_5$
400: $R = CH_3$, $R_1 = C_6H_5$
401: $R\text{-}R_1 = -(CH_2)_3-$

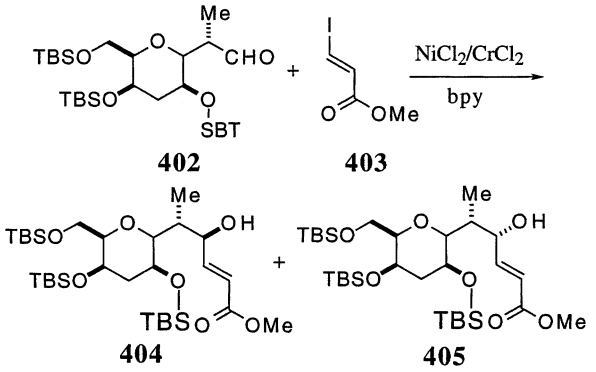
0 °C in the presence of a 1:1 $NiCl_2$/phen catalyst prepared in situ (Scheme 78).[135] The chemical yields were consistently less than 20% and enantioselectivities of 2.7, 8.5, and 4.3% were observed with ligands **250**, **257**, and **258**, respectively. It was concluded that these phens were not well suited for catalysis of the cross-coupling process.

Rudler et al. studied the epoxidation of olefins and found that methoxytrioxorhenium (MTO) catalyzes the selective epoxidation of alkenes in the biphasic medium $CH_2Cl_2/H_2O_2-H_2O$.[136] They observed that especially sensitive epoxides, which could not be obtained by the use of other reagents, can be isolated in high yield by the addition of bpy to this reaction mixture. Starting from this observation, and with the intent of making the epoxidation enantioselective, they synthesized the optically active bpy−MTO complex **398**, starting from an equimolecular amount of MTO and the chiral (−)-(4,5)-pinenobpy **40**. The chiral complex **398** was tested in the epoxidation of 2-methyl-1-heptene. Although epoxidation took place, no enantioselectivty was observed (Scheme 79).

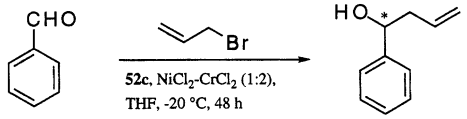
Botteghi and co-workers assessed nickel(II) complexes of a number of chiral bpys (**9**, **22**, **32**) and phens (**250a**,**b**) in the enantioselective Michael addition of nitromethane to α,β-unsaturated ketones (Scheme 80).[137] The catalytic precursors, prepared in situ by the reaction between an equimolar amount of $Ni(acac)_2$ and the ligand in toluene, were used for the conjugate addition of nitromethane to chalcone (**399**), benzalacetone (**400**), and 2-cyclohexenone (**401**). Whereas 6-substituted bpys **9** and **32** suppress the reaction, indicating that a 6-substituent inhibits the formation of the catalytically active species; other ligands, where the chiral group is far from the nitrogen, gave fairly good yields of product. However, no asymmetric induction was observed.

In a study of the Ni(II)/$CrCl_2$-mediated reaction of aldehydes with alkenyl iodides, Kishi's group found that the coupling took place smoothly in the presence of modified bpys.[21] Whereas no reaction was observed by using bpys unsubstituted at the 6- and 6′-posi-

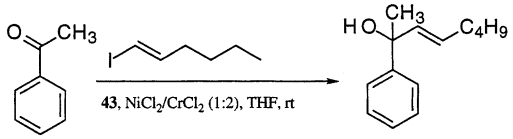
Scheme 81



Scheme 82



Scheme 83



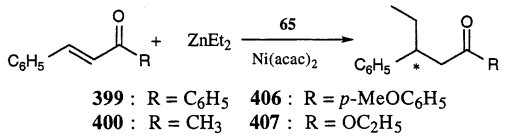
tions, the reaction proceeded smoothly in the presence of bpys with a 6-substituent. In addition, homocoupling of alkenyl halides was effectively suppressed in the presence of these bpys. Kishi prepared a variety of chiral bpys (**13**, **40**, **41**, **43**, **52a**−**l**, **47**, **53a**−**c**, **67**, **69**, and **70**) and tested their ability to induce stereoselectivity in the asymmetric coupling process shown in Scheme 81. The most effective ligand was identified as **52c**, providing the two diastereomers **404** and **405** in a 4.1:1 ratio when the coupling was carried out at room temperature. The asymmetric induction reached an 8−10:1 ratio when the reaction was carried out at −20 °C.

Finally, the same group used the bpy **52c** to induce stereoselectivity in the Ni(II)/$CrCl_2$-mediated reaction of simple aldehydes with halides (Scheme 82).[21] Thus benzaldehyde was coupled with 1-iodo-1-hexene, 3-iodo-acrylic acid methyl ester, and 3-bromopropene. The highest enantiomeric ratio (6.7:1) was obtained with 3-bromopropene when the reaction was carried out at −20 °C (Scheme 82).

Later, Chen reported the Ni(II)/$CrCl_2$-mediated reaction of ketones with unsaturated halides in the presence of bpy **43** at room temperature (Scheme 83).[138] The coupling of cyclohexanone, 2-hexanone, and acetophenone with alkenyl, alkynyl, and aryl bromides, iodides, or triflates afforded the corresponding allylic, propargylic, and benzylic alcohols, respectively, in fairly good yields. Scheme 83 illustrates the general procedure to synthesize 2-phenyl-3-octen-2-ol; however, no data have been reported about asymmetric induction.

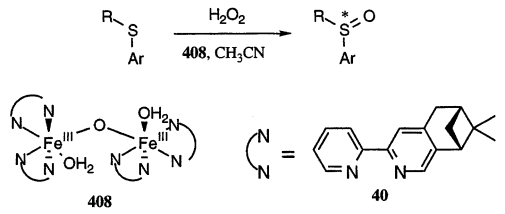
Bolm et al. used the C_2-symmetric bpy **65** as a ligand for the nickel-catalyzed enantioselective conjugate ethyl transfer from diethyl zinc to aryl substituted enones (Scheme 84).[139] High yields of optically active β-substituted ketones were obtained with good asymmetric induction which was found to be highly dependent on the nickel-to-ligand ratio, the solvent, and the temperature. In the conjugate addition to chalcone (**399**), an enantiomeric excess of 72% was obtained, carrying out the reaction at −30 °C in acetonitrile and by using 1 mol % of $Ni(acac)_2$ and 20% of **65**. Conjugate addition to 4-methoxy chalcone (**406**) afforded the product with an enantiomeric excess of 74%. Methyl substituted ketone **400** gave the expected product in good yield but essentially racemic (2% ee). Ethyl cinnamate (**407**) did not react with diethyl zinc under $Ni(acac)_2$ catalysis. Attempts to use $Co(acac)_2$ or $Pd(PPh_3)_4$ instead of $Ni(acac)_2$ resulted in the formation of complex product mixtures. $Cu(OAc)_2$ did not affect ethyl transfer.

Scheme 84



399 : R = C_6H_5 **406** : R = *p*-$MeOC_6H_5$
400 : R = CH_3 **407** : R = OC_2H_5

Scheme 85



Fontecave's group investigated the catalytic properties of the diiron complex **408**, containing the chiral bpy **40**, in the stereoselective oxidation of sulfides (Scheme 85).[140] Complex **408** efficiently catalyzed the hydrogen peroxide oxidation of aryl sulfides to the corresponding sulfoxides with yields ranging from 45 to 90% based on the oxidant. Furthermore, the reactions produced a mixture of sulfoxide enantiomers with significant enantiomeric excesses. The largest ee (40%) was found in the case of *p*-bromophenyl methyl sulfide. Optimal ee's were obtained in polar solvents and at low temperature (below 0 °C) and when the excess of the oxidant was limited. The observation of (i) saturation kinetics with respect to both sulfide and H_2O_2 concentration, (ii) a linear Hammett correlation of the V_{max} values with σ_p values for a series of *p*-substituted aryl methyl sulfides, (iii) iron−peroxo complexes, characterized by light absorption and resonance Raman spectroscopy, during reaction of complex **408** with H_2O_2, and (iv) saturation kinetics with respect to sulfide during the oxidation by iron−peroxo complexes, led the authors to propose that the iron−peroxo moiety is the actual oxygen atom donor, thus explaining the enantioselective control of the catalytic reaction. These data demonstrate that oxidations by non-heme diiron complexes can proceed through metal-based pathways and thus can be made stereoselective.

Nakajima et al. described the enantioselective allylation of aldehydes with allylchlorosilanes, a reaction that utilizes the C_2-symmetric 2,2′-biquino-

Scheme 86

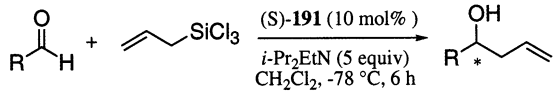
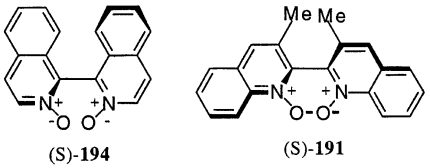


Table 14. Enantioselective Allylation of Different Aldehydes (RCHO) with Allyltrichlorosilane Catalyzed by (*S*)-191

R	yield (%)	ee (%)	conf.
Ph	85	88	*R*
4-$MeOC_6H_4$	91	92	*R*
4-$CF_3C_6H_4$	71	71	*R*
2-MeC_6H_4	70	90	*R*
1-naphthyl	68	88	*R*
(*E*)-$C_7H_{15}CH$=CH	74	81	*R*
(*E*)-Ph-CH=CH-	87	80	*R*
$Ph(CH_2)_2$	30	7	*S*
cyclohexyl	27	28	*S*

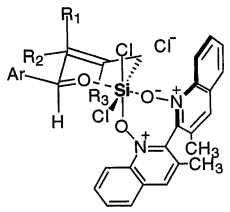
line *N*,*N*′-dioxide (*S*)-**191** and 1,1′-biisoquinoline *N*,*N*′-dioxide (*S*)-**194** as catalysts (Scheme 86).[141]



(S)-**194** (S)-**191**

They examined the addition of allyltrichlorosilane to benzaldehyde using 10 mol % of (*S*)-**194**, which afforded (23 °C, 2 h) the corresponding allylic alcohol in 82% yield and 52% ee. An improved yield (90%) and enantioselectivity (71% ee) was found using (*S*)-**191**, wherein the *N*-oxide moieties were embedded within a chiral pocket created by the benzo-rings of the biaryl species. After considerable experimentation, they found that the reaction was accelerated (23 °C, 10 min) with no loss of enantioselectivity (90% yield, 71% ee) by the addition of five equivalents of diisopropylamine. The increased reaction rate made it possible to conduct the reaction at −78 °C, thereby enhancing the enantioselectivity up to 88% ee. The results for a variety of aldehydes with allyltrichlorosilane in the presence of (*S*)-**191** are summarized in Table 14.

To establish the mechanistic profile of the amine *N*-oxide-promoted process, they then examined the allylation of benzaldehyde with (*E*)- and (*Z*)-crotyltrichlorosilanes. Their results suggested that the allylations proceeded via a cyclic chairlike transition state **409**, involving hypervalent silicates with an *N*-oxide moiety occupying an axial position.



409

Next, Nakajima et al. developed a modification of the *N*-oxide-catalyzed enantioselective addition of allyltrichlorosilanes to aldehydes, which entails the one-pot preparation of optically active homoallylic alcohols from allyl halides.[142] According to this method, allyltrichlorosilanes were generated in situ from allyl halides and trichlorosilane in the presence of cuprus chloride and tertiary amine. Without isolation of the allyltrichlorosilanes, benzaldehyde and (*S*)-**191** were introduced into the same flask, producing the corresponding homoallylic alcohols with good to high enantioselectivities.

Scheme 87

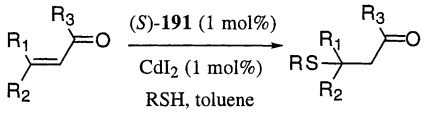


Table 15. Enantioselective Conjugate Addition of Thiols (RSH) to 2-Cyclohexen-1-one Catalyzed by (*S*)-191−CdI_2 Complex

R	time (h)	yield (%)	ee (%)
Ph	6	96	78
2-MeC_6H_4	24	28	29
2,6-$Me_2C_6H_3$	48	8	33
4-MeC_6H_4	12	74	29
4-*t*-BuC_6H_4	12	78	40
4-ClC_6H_4	3	98	24
4-$MeOC_6H_4$	6	91	58
$PhCH_2$	12	48	40

The same workers have also reported the enantioselective conjugate addition of thiols to cyclic enones and enals catalyzed by the chiral 2,2′-biquinoline *N*,*N*′-dioxide (*S*)-**191**−cadmium iodide complex (Scheme 87).[143] They examined the conjugate addition of thiophenol to 2-cyclohexen-1-one using various metal salts (CuCl, $ZnCl_2$, $PdCl_2$, AgCl, $SnCl_2$, HgCl, $BiCl_3$, $CdCl_2$, CBr_2, CdI_2) in the presence of (*S*)-**191**. Among the metal chlorides surveyed, cadmium chloride yielded the corresponding sulfides quantitatively with 30% ee. Further investigation revealed that an equimolecular amount cadmium iodide (1% mol) and (*S*)-**191** (1% mol) in toluene are sufficient for optimum enantioselectivity. Table 15 summarizes the conjugate addition of various thiols to 2-cyclohexen-1-one under optimized conditions.

The scope of the acceptor in the conjugate addition was also investigated. A slight modification of the substrate strongly influenced the enantioselectivity, such that 2-cyclohepten-1-one gave 61% ee, comparable to that of 2-cyclohexen-1-one (78% ee), while 2-cyclopenten-1-one gave only 21% ee. The introduction of a substituent onto the 3- or 4-position of 2-cyclohexenone resulted in a decline in both chemical yield and enantioselectivity, probably for steric reasons.

It was further discovered that, while the addition of thiophenol to conjugate acyclic ketones was unsuccessful, the addition to conjugate acyclic aldehydes afforded the corresponding sulfides in high yields and with enantioselectivities up to 70% ee. The mild reaction conditions allow the enantioselective conjugate addition of thiols to enals, a reaction not previously reported due the lability of the aldehydes.

Nakajima et al., continuing their program of developing *N*-oxide-mediated conjugate addition reactions, have very recently reported the Michael addi-

Scheme 88

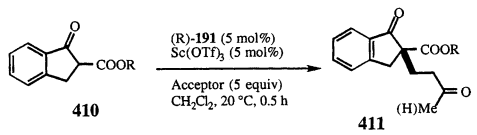


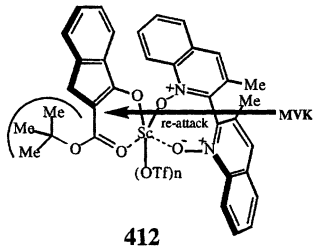
Table 16. Enantioselective Michael Addition of *β*-Keto Ester 410 to Methyl Vinyl Ketone Catalyzed by 191−Sc(OTf)$_3$ Complex.

donor	R	acceptor	adduct	yield (%)	ee (%)
410a	Me	CH_2=CHCOMe	**411a**	98	39
410b	CH_2Ph	CH_2=CHCOMe	**411b**	85	38
410c	*i*-Pr	CH_2=CHCOMe	**411c**	94	47
410d	CH(*i*-Pr)$_2$	CH_2=CHCOMe	**411d**	98	69
410e	*t*-Bu	CH_2=CHCOMe	**411e**	93	80
410e	*t*-Bu	CH_2=CHCHO	**411e**	73	75

tion of *β*-keto esters to methyl vinyl ketone exploiting the (*R*)-**191**-scandium trifluoromethanesulfonate complex as a catalyst (Scheme 88).[144]

They initially investigated the Michael addition of dimethyl malonate to cyclohexenone employing (*R*)-**191**−cadmium iodide complex. However, no Michael adduct was obtained with this cadmium complex. On the other hand, the Michael addition of methyl 1-oxoindan-2-carboxylate (**410a**) to methyl vinyl ketone with the **191**−CdI_2 complex proceeded smoothly, but the observed enantiomeric excess of the adduct was low (75% yield, 13% ee). After screening a number of complexes prepared in situ from (*R*)-**191** and various metal salts, they found that 5 mol % of the 1:1 complex of (*R*)-**191** and scandium trifluoromethanesulfonate in dichloromethane at room-temperature catalyzed the Michael addition to generate the adduct **411a** in quantitative yield with moderate enantioselectivity (Table 16).

After examining various Michael acceptors and donors that afforded unsatisfactory results, Nakajima et al. investigated the enantioselective Michael addition of different *β*-keto esters **410** to methyl vinyl ketone catalyzed by the **191**−Sc(OTf)$_3$ complex. As shown in Table 16, the bulkiness of the ester substituent was found to have a pronounced effect on the observed enantioselectivity which increases with the bulkiness of the ester. The stereochemical results may be explained by the transition-state model **412**. The bulky *tert*-butyl ester moiety would prefer to be located on the *si*-face of the keto-ester plane to avoid steric repulsion with the quinoline moiety, which leads to preferential attack of the methyl vinyl ketone at the *re*-face.



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Kwong et al. have recently reported the use of a series of C_1- and C_2-symmetric bpys (**77**, **83** and **84**, **85**, **87**, **88**, respectively) in the copper-catalyzed

Table 17. Asymmetric Reactions Catalyzed by Metal Complexes with Chiral Ligands[a]

type of donor	class of ligands	addition of organometallic reagents to aldehydes[b] ee (%) (ref)	allylic substitution[c] ee (%) (ref)	allylic oxidation[d] ee (%) (ref)	cyclopropanation[e] ee (%) (ref)	hydrosilylation[f] ee (%) (ref)	transfer hydrogenation[g] ee (%) (ref)
N−N	bipyridines	95 (117)	89 (25)	65 (144)	98 (38)	90 (49)	23 (69)
N−N	phenanthrolines		96 (80)	47 (134)	65 (99)	76 (86)	63 (74)
N−N	bis(oxazolines)		97 (146)	77 (147)	98 (148)	65 (149)	91 (150)
N−N	diamines	95 (151)	99 (152)		98 (153)	85 (154)	98 (155)
N−N	aminopyridines	100 (6f)	64 (108)		9 (101)		59 (156)
N−N	oxazolinylpyridines		93 (4a)		60 (157)	89 (158)	
N−N−N	terpyridines		40 (108)		94 (94)	14 (99)	
N−N−N	bis(oxazolinyl)-pyridines		26 (159)	81 (160)	97 (161)	94 (162)	
N−N−N	bis(oxazolinyl-methyl)amines					98 (163)	
N−N−N−N	bis(oxazolinyl-pyridines)		>98 (164)			50 (165)	
N−N−N−N	tris(oxazolinyl-methyl)amines			82 (166)			
N−P	phosphinooxazolines		99 (167)			94 (168)	94 (169)
N−P	ferrocenylphosphino-oxazolines		91 (170)			91 (171)	94 (172)
N−P	aminophosphines	21 (15)	96 (173)			53 (174)	
P−P	DIOP		0 (175)			58 (176)	4 (177)
P−P	(*R*)-PROPHOS						52 (178)
P−P	BINAP		34 (179)				30 (178)
P−P	CHIRAPHOS		22 (180)				24 (181)
P−P	glucophinite					65 (182)	
P−N−P	bis(phosphino)amines		75 (183)			28 (184)	79 (185)
P−P−P	PIGIPHOS						72 (186)
P−N−N−P	bis(aminophosphines)		77 (187)				97 (188)

[a] The data refer to a reaction model typical for each reaction. [b] The data refer to the addition of diethylzinc to benzaldehyde. [c] The data refer to the allylic substitution of 1,3-diphenyl-2-enyl acetate with dimethyl malonate. [d] The data refer to the allylic oxidation of cyclohexene. [e] The data refer to the cyclopropanation of styrene. [f] The data refer to the hydrosilylation of acetophenone. [g] The data refer to the transfer hydrogenation of acetophenone.

asymmetric allylic oxidation of cyclic alkenes with *tert*-butyl perbenzoate.[145] At first, they examined the allylic oxidation of cyclohexene using bpy−$CuPF_6$ complexes and found that these are active catalysts affording the cyclohex-2-yl benzoate in isolated yields ranging from moderate to good and enantiomeric excesses up to 65%. The best ligands were **83** and **88** which afforded 65 and 52% ee, respectively.

To increase both the conversion and the enantioselectivity, they attempted to optimize the reaction conditions by varying the copper salt ($[Cu(CH_3CN)_4]PF_6$, $[Cu(CH_3CN)_4]ClO_4$, CuOTf, CuCl, CuBr). Different trends were observed using ligands **83** and **88**. The highest enantioselectivity (65%) was still observed with $[Cu(CH_3CN)_4]PF_6$ in the case of **83**, whereas with **88** the best result (58% ee) was achieved with CuOTf.

Finally they examined the allylic oxidation of cyclopentene, cycloheptene and cyclooctene using ligands **83** and **88** in combination with different copper salts. The best enantioselectivities were obtained in all cases with the bpy **88** which gave 61, 61, and 70% ee, respectively.

4. Conclusions

This report outlines the synthesis of a wide range of chiral bpy, phen, and tpy ligands and their utility in various enantioselective processes. In Table 17 we have collected the best results obtained by these ligands in the six asymmetric catalytic organic transformations in which they have found widest application. Moreover, to evaluate the scope and performance of these pyridine derivatives, we have also summarized similar data for a series of the most common other homo- and heterodonor ligands. Ligands that have been used in a single process have not been considered.

Examination of Table 17 shows that while nitrogen-containing ligands are useful in a wide range of processes, affording very good enantioselectivities, phosphorus-based ligands are less well represented. It is not surprising that phosphorus-based ligands are not employed in catalytic processes where their use is incompatible with the operative conditions (i.e., oxidation). It should be noted, however, that in transformations where they are compatible, they generally afford lower enantioselectivities than nitrogen-based ligands (P−N ligands, such as phosphinooxazolines, are an exception). Due to their ability to give complexes with a large variety of metals, chiral bpy, phen, and tpy ligands rival not only chiral phosphines, but also other nitrogen ligands as stereocontrollers in many asymmetric reactions. Moreover, chiral pyridine derivatives are usually more chemically stable and easier to recover than chiral phosphine and amine derivatives.

It should be noted that, although the synthesis of chiral bpys and phens dates back to 1984 and 1987, respectively, only recently have efficient methods for their preparation been reported. Thus, with new C_2-symmetric bpys, high efficiency in catalytic processes such as cyclopropanation or allylic oxidation has been achieved. On the other hand, the synthesis of C_2-symmetric phens and tpys has been undertaken only recently and their widescale utility as chiral controllers in asymmetric catalysis is yet to be demonstrated. It is tempting to predict that many processes involving a high degree of stereocontrol will become available as an increasing number of chiral bpys, phens, and tpys become available.

5. References

(1) (a) Fache, F.; Schulz, E.; Tammasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159. (b) Tonks, L.; Williams, J. M. J. *Contemp. Org. Synth.* **1997**, *4*, 353. (c) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497. For recent overviews on bisoxazolines, see (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (e) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(2) Chelucci, G. *Gazz. Chim. Ital.* **1992**, *122*, 89.

(3) For hydroxyalkylpyridines, see (a) Chelucci, G.; Craba, S.; Saba, A.; Soccolini, F.; Sotgiu, G. *J. Mol. Catal. A* **2000**, *164*, 179. (b) Zhang, H.; Chan, K. S. *J. Chem. Soc., Perkin Trans.* **1999**, 381. (c) Kang, J.; Kim, H. Y.; Kim, J. H. *Tetrahedron: Asymmetry* **1999**, *10*, 3203. (d) Kotsuki, H.; Hayakawa, H.; Tateishi, H.; Wakao, M.; Shiro, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3203. (e) Williams, D. R.; Fromhold, M. G. *Synlett* **1997**, 523. (f) Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002. (g) Malfait, S.; Pelinski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1996**, *7*, 653. (h) Collomb, P.; von Zelewsky, A. *Tetrahedron: Asymmetry* **1995**, *6*, 2903. (i) Macedo, E.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 549. (j) Ishizaki, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1901. (k) Bolm, C. *Tetrahedron: Asymmetry* **1991**, *2*, 701.

(4) For pyridyloxazolines, see (a) Chelucci, G.; Pinna, G. A.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **2000**, *11*, 4027. (b) Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 543. (c) Chelucci, G.; Deriu, S. P.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 1457. (d) Franco, D.; Panyella, D.; Rocamora, M.; Gomez, M.; Clinet, J. C.; Muller, G.; Duñach, E. *Tetrahedron Lett.* **1999**, *40*, 5685. (e) Ghosh, A. K.; Mathivan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (f) Brenberg, U.; Rahm, F.; Moberg, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3437. (g) Nordstrom, K.; Macedo, E.; Moberg, C. *J. Org. Chem.* **1997**, *62*, 1604.

(5) For pyridine-thioethers and thiols, see (a) Koning, B.; Meetsma, A.; Kellogg, R. M. *J. Org. Chem.* **1998**, *63*, 5533. (b) Chelucci, G.; Berta, D.; Fabbri, D.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3537. (c) Chelucci, G.; Culeddu, N.; Fabbri, D.; Pinna, G. A.; Saba, A.; Ulgheri, F. *Tetrahedron: Asymmetry* **1998**, *9*, 1933. (d) Chelucci, G.; Berta, D.; Saba, A. *Tetrahedron* **1997**, *53*, 3843. (e) de Vries, A. H. M.; Hof, R. P.; Staal, D.; Kellogg, R. M.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *10*, 1539. (f) Chelucci, G.; Cabras, M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 965.

(6) For aminopyridines, see (a) Fiore, K.; Martelli, G.; Monari, M.; Savoia, D. *Tetrahedron: Asymmetry* **1999**, *10*, 4803. (b) Warnmark, K.; Stranne, R.; Cernerud, M.; Terrien, I.; Rahm, F.; Nordstrom, K.; Moberg. *Acta Chem. Scand.* **1998**, *52*, 961. (c) Alvaro, G.; Martelli, G.; Savoia, D. *J. Chem. Soc., Perkin, Trans. 1* **1998**, 775. (d) Sweet, J. A.; Cavallari, J. M.; Price, W. A.; Ziller, J. W.; McGrath, D. V. *Tetrahedron: Asymmetry* **1997**, *8*, 207. (e) Chelucci, G.; Cabras, M. A.; Saba, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1973. (f) Chelucci, G.; Conti, S.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1991**, *47*, 8251.

(7) For phosphinopyridines, see (a) Newkome, G. R. *Chem. Rev.* **1993**, *93*, 2067. (b) Malkov, A. V.; Bella, M.; Stará, I. G.; Kocovsky, P. *Tetrahedron Lett.* **2001**, *42*, 3045. (c) Brunel, J. M.; Tenaglia, A.; Buono, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3585. (d) Arena, C. G.; Drommi, D.; Faraone, F. *Tetrahedron: Asymmetry* **2000**, *11*, 4753. (e) Ito, K.; Kashiwagi, R.; Iwasaki, K.; Katsuki, T. *Synlett* **1999**, *10*, 1563. (f) Son, S. U.; Jang, U.-Y.; Han, J. W.; Lee, I. S.; Chung, Y. K. *Tetrahedron: Asymmetry* **1999**, *10*, 347. (g) Valk, J. M.; Whitlock, G. A.; Layzell, T. P.; Brown, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2593. (h) Arena, C. G.; Nicolò, F.; Drommi, D.; Bruno, G.; Faraone, F. *J. Chem. Soc., Chem. Commun.* **1994**, 2251. (i) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743.

(8) For terdentate phosphinopyridines, see (a) Zhu, G.; Terry, M.; Zhang, X. *J. Organomet. Chem.* **1997**, *547*, 97. (b) Jiang, Q.; Plew, D. V.; Murtuza, S.; Zhang, X. *Tetrahedron Lett.* **1996**, *37*, 797. (c) Sablong, R.; Osborn, J. A. *Tetrahedron Lett.* **1996**, *37*, 4937. (d) Yang, H.; Alvarez-Gressier, M.; Lugan, N.; Mathieu, R. *Organometallics* **1997**, *16*, 1401.

(9) Botteghi, C.; Caccia, G.; Chelucci, G.; Soccolini, F. *J. Org. Chem.* **1984**, *49*, 4290.

(10) Chelucci, G.; Soccolini, F.; Botteghi, C. *Synth. Commun.* **1985**, *15*, 807.

(11) Bönnemann, H.; Bogdanovich, B.; Brignkmann, R.; He, D.; Spliethoff, B.; *Angew. Chem.* **1983**, *95*, 749; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 728.
(12) For a review on the synthesis of chiral pyridines by this method, see Chelucci, G. *Tetrahedron: Asymmetry* **1995**, *6*, 811.
(13) Botteghi, C.; Chelucci, G.; Marchetti, M. *Synth. Commun.* **1982**, *12*, 25.
(14) Gladiali, S.; Chelucci, G.; Soccolini, F.; Delogu, G. *Appl. Organomet. Chem.* **1988**, *2*, 227.
(15) Chelucci, G.; Cabras, M. A.; Botteghi, C.; Basoli, C.; Marchetti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 855.
(16) For an review on regiospecific cyanation of pyridine, see Five, W. K. *Heterocycles* **1984**, *22*, 2375.
(17) Botteghi, C.; Chelucci, G.; Chessa, G.; Delogu, G.; Gladiali, S.; Soccolini, F. *J. Organomet. Chem.* **1986**, *304*, 217.
(18) Kröhnke, F. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 386, and references therein.
(19) Kröhnke, F. *Synthesis* **1976**, 1.
(20) Hayoz, P.; von Zelewsky, A. *Tetrahedron Lett.* **1992**, *33*, 5165.
(21) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386.
(22) Malkov, A. V.; Baxandale, I. R.; Bella, M.; Langer, V.; Fawcett, J.; Russell, D. R.; Mansfield, D. J.; Valko, M.; Kocovsky, P. *Organometallics* **2001**, *20*, 673.
(23) (a) Fletcher, N. C.; Keene, F. R.; Ziegler, M.; Stoeckli-Evans, H.; Viebrock, H.; von Zelewsky, A. *Helv. Chim. Acta* **1996**, *79*, 1192. (b) Mürner, H.; von Zelewsky, A.; Stoeckli-Evans, H. *Inorg. Chem.* **1996**, *35*, 3931. Hayoz, P.; von Zelewsky, A.; Stoeckli-Evans, H. *J. Am. Chem. Soc.* **1993**, *115*, 5111.
(24) (a) Mamula, O.; Monlien, F. J.; Porquet, A.; Hopfgartner, G.; Merbach, A. E.; von Zelewsky, A. *Chem. Eur. J.* **2001**, *7*, 533. (b) Bark, T.; von Zelewsky, A. *Chimia* **2000**, *54*, 589. (c) von Zelewsky, A.; Mamula, O. *J. Chem. Soc., Dalton Trans.* **2000**, 219. Mamula, O.; von Zelewsky, A.; Bark, T.; Stoeckli-Evans, H.; Neels, A.; Bernardinelli, G. *Chem. Eur. J.* **2000**, *6*, 3575. (d) Riklin, M.; von Zelewsky, A.; Bashall, A.; McPartlin, M.; Baysal, A.; Connor, J. A.; Wallis, J. D.. *Helv. Chim. Acta* **1999**, *82*, 1666. (e) von Zelewsky, A. *Coord. Chem. Rev.* **1999**, *190−192*, 811−825. (f) Knof, U.; von Zelewsky, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 303.
(25) Chelucci, G.; Pinna, G. A.; Saba, A. *Tetrahedron: Asymmetry*, **1998**, *9*, 531.
(26) Collomb, P.; von Zelewsky, A. *Tetrahedron: Asymmetry* **1998**, *9*, 3911.
(27) Lötscher, D.; Rupprecht, S.; Stoeckli-Evans, E.; von Zelewsky, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4341.
(28) Chelucci, G.; Saba, A.; Sanna, G.; Soccolini, F. *Tetrahedron: Asymmetry* **2000**, *11*, 3427.
(29) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
(30) Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* **1984**, 736.
(31) (a) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205. (b) Bolm, C.; Ewald, M. *Tetrahedron Lett.* **1990**, 5011. (c) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem Ber.* **1992**, *125*, 1169.
(32) (a) Brown, H.; Chandrasekharan, J.; Ramachandran, P. V. *J. Org. Chem.* **1986**, *51*, 3394. (b) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H.; *J. Org. Chem.* **1985**, *50*, 5446.
(33) (a) Stille, J. K.; *Angew. Chem.* **1986**, *98*, 504; *Angew. Chem., Int. Ed.* **1986**, *25*, 508. (b) Negishi, E. I. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237. (d) Alves, T.; de Oliveira, A. B.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 2135.
(34) Kwong, H.-L.; Lee, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3791.
(35) Peterson, M. A.; Dalley, N. K. *Synth. Commun.* **1996**, *26*, 2223.
(36) Chelucci, G.; Culeddu, N.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3537.
(37) Ito, K.; Tabuchi, S.; Katsuki, T. *Synlett* **1992**, 575.
(38) Ito, K.; Katsuki, T. *Tetrahedron Lett.***1993**, *34*, 575
(39) Ito, K.; Katsuki, T. *Chem. Lett.* **1994**, 1857.
(40) Ito, K.; Yoshitake, M.; Katsuki, T. *Tetrahedron* **1996**, *52*, 3905.
(41) (a) Sasaki, H.; Irie, R.; Katsuki, T. *Synlett* **1994**, 356. (b) Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K. Katsuki, T. *Tetrahedron* **1994**, *50*, 11827. (c) Fukuda, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 197.
(42) Chelucci, G.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1992**, *48*, 3653.
(43) Malkov, A. V.; Bella, M.; Langer, V.; Kocovsky, P. *Org. Lett.* **2000**, *2*, 3047.
(44) Chelucci, G.; Saba, A. *Synth. Comm.* **2001**, *31*, 3161.
(45) Kolp, B.; Abeln, D.; Fletcher, N. C.; Stoeckli-Evans, H.; von Zelewsky, A. *Eur. J. Inorg. Chem.* **2001**, *1207*.
(46) Motson, G. R.; Mamula, O.; Jeffery, J. C.; McCleverty, J. A.; Ward, M. D.; von Zelewsky, A. *J. Chem. Soc., Dalton Trans.* **2001**, 1389.
(47) Bertucci, C.; Uccello-Barretta, G.; Chelucci, G.; Botteghi, C. *Gazz. Chim. Ital.* **1990**, *120*, 263.
(48) (a) Chelucci, G.; Gladiali, S.; Marchetti, M. *J. Heterocycl. Chem.* **1988**, *25*, 1761. (b) Chelucci, G.; Delogu, G.; Gladiali, S.; F. Soccolini, F. *J. Heterocycl. Chem.* **1986**, *23*, 1395.
(49) Nishiyama, H.; Yamaguchi, S.; Park, S.; B. Itoh, K. *Tetrahedron: Asymmetry* **1993**, *4*, 143.
(50) Kandzia, C.; Steckhan, E.; Knoch, F. *Tetrahedron: Asymmetry* **1993**, *4*, 39.
(51) Hopkins, R. B.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 171.
(52) Rosini, C.; Franzini, I.; Raffaelli, A.; Salvadori, P. *Synthesis* **1993**, 503.
(53) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187. Pu, L. *Chem. Rev.* **1998**, *98*, 2405.
(54) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
(55) For reviews, see *Ferrocenes, Homogeneous Catalysis, Organic Synthesis, Materials Science*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, 1995.
(56) Tichy, M.; Závada, J.; Podlaha, J,; Vojtísek, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1279.
(57) Nakajima, M.; Sakaki, Y.; Shiro, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **1997**, *8*, 341.
(58) Fujii, M.; Honda, A. *Chem. Express* **1992**, *7*, 329.
(59) Crawford, M.; Smyth, F. B. *J. Chem. Soc.* **1954**, 3464.
(60) Chelucci, G.; Cabras, M. A.; Saba, A.; Sechi, A. *Tetrahedron: Asymmetry* **1996**, *7*, 1027.
(61) Hirao, K.; Tsuchiya, R.; Yano, Y.; Tsue, H. *Heterocycles* **1996**, *42*, 415.
(62) Tsue, H.; Fujinami, H.; Itakura, T.; Tsuchiya, R.; Kobayashi, K.; Takahashi, H.; Hirao, K. *Chem. Lett.* **1999**, 17.
(63) Botteghi, C.; Schionato, A.; De Lucchi, O. *Synth. Commun.* **1991**, *21*, 1819.
(64) Wang, X. C.; Cui, Y. X.; Mak, T. C.; Wong, H. N. C. *J. Chem. Soc., Chem. Commun.* **1990**, 167. Wang, X. C.; Wong, H. N. C. *Tetrahedron* **1995**, *51*, 6941.
(65) Brunner, H.; Olschewski, G.; Nuber, B. *Synthesis* **1999**, 429.
(66) Wong, H. L.; Tian, Y.; Chan, K. S. *Tetrahedron Lett.* **2000**, *41*, 7723.
(67) Wörsdörfer, U.; Vögtle, F.; Nieger, M.; Waletzke, M.; Grimme, S.; Glorius, F.; Phaltz, A. *Synthesis* **1999**, 597.
(68) Ostrowicki, A.; Koepp, E.; Vögtle, F. *Top. Curr. Chem.* **1991**, *161*, 37.
(69) Wörsdörfer, U.; Vögtle, F.; Glorius, F.; Phaltz, A. *J. Prakt. Chem.* **1999**, 445.
(70) Rios, R.; Liang, J.; Lo M. M.-C.; Fu, G. C. *J.C.S. Chem. Commun.* **2000**, 377.
(71) (a) Manske, R. H.; Kulka, M. *Org. React.* **1953**, *7*, 59. For other recent papers on this subject, see (b) Matsugi, M.; Tabusa, F.; Minamikawa, J.-I. *Tetrahedron Lett.* **2000**, *41*, 8523. (c) Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Lett.* **2000**, *41*, 531.
(72) Gladiali, S.; Chelucci, G.; Chessa, G.; Delogu, G.; Soccolini, F. *J. Organomet. Chem.* **1987**, *327*, C 15.
(73) Gladiali, S.; Chelucci, G.; Soccolini, F.; Delogu, G.; Chessa, G. *J. Organomet. Chem.* **1989**, *370*, 285
(74) Gladiali, S.; Pinna, L.; Delogu, G.; De Martin, S.; Zassinovich, G.; Mestroni, G. *Tetrahedron: Asymmetry* **1990**, *1*, 635.
(75) O'Neill, D.; Helquist, P. Org. *Lett.* **1999**, *1*, 1659.
(76) Pea-Cabrera, E.; Norrby, P.-A.; Sjgren, M.; Vitagliano, A.; De Felice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Åkermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299.
(77) Thummel, R. P. *Synlett* **1992**, 1.
(78) Riesgo, E. C.; Credi, A.; De Cola, L.; Thummel, R. P. *Inorg. Chem.* **1998**, *37*, 2145.
(79) Gladiali, S.; Chelucci, G.; Madadu, M. T.; Gastaut, M. G.; Thummel, R. P. *J. Org. Chem.* **2001**, *66*, 400.
(80) Chelucci, G.; Pinna, G. A.; Saba, A.; Sanna, G. *J. Mol. Catal. A* **2000**, *159*, 423.
(81) Chelucci, G.; Thummel, R. P. *Synth. Commun.* **1999**, *29*, 1665.
(82) Chelucci, G.; Saba, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2575.
(83) Chelucci, G.; Saba, A.; Sanna, G.; Soccolini, F. *Tetrahedron: Asymmetry* **2000**, *11*, 3427.
(84) Chelucci, G.; Loriga, G.; Murineddu, G.; Pinna, G. A. Manuscript in preparation.
(85) Kandzia, C.; Steckhan, E.; Knoch, F. *Tetrahedron: Asymmetry* **1993**, *4*, 39.
(86) Gladiali, S.; Pinna, L.; Delogu, G.; Graf, E.; Brunner, H. *Tetrahedron: Asymmetry* **1990**, *1*, 937.
(87) Constable, E. C. *Macromol. Symp.* **1995**, *98*, 503. Sauvage, J. P.; Collin J. P.; Chambron, J. C.; Guillerez, S.; Coudret, C.; Balzani, V.; Barigelletti, F.; De Cola, L.; Flamigni, L. *Chem. Rev.* **1994**, *94*, 993.
(88) Trawick, B. N.; Daniher, A. T.; Bashkin J. K. *Chem Rev.* **1998**, *98*, 939; McCoubrey A.; Latham, H. C.; Cook P. R.; Rodger A.; Lowe G. *FEBS Lett.* **1996**, *380*, 73.
(89) Harriman, A.; Ziessel R. *Coord. Chem. Rev.* **1998**, *171*, 331.
(90) Brothers, H. M.; Kostic, N. M. *Inorg. Chem.* **1988**, *27*, 1761.
(91) Chelucci, G. *Synth. Commun.* **1993**, *23*, 1897.
(92) Ziegler, M.; Monney, V.; Stoeckli-Evans, H.; von Zelewsky, A.; Sasaki, I.; Dupic, G.; Daran, J.-C.; Balavoine, G. G. A. *J. Chem. Soc., Dalton Trans.* **1999**, 667.

(93) Chelucci, G.; Saba, A.; Vignola, D.; Solinas, C. *Tetrahedron* **2001**, *57*, 1099.
(94) Kwong, H.-L.; Lee, W. S. *Tetrahedron: Asymmetry* **2000**, *11*, 2299.
(95) Chelucci, G.; Saba, A.; Soccolini, F.; Vignola, D. *J. Mol. Catal. A* **2001**, in press.
(96) Gianini, M.; von Zelewsky, A. *Synthesis* **1996**, 702.
(97) Uenishi, J.; Nishiwaki, K.; Hata, S.; Nakamura, K. *Tetrahedron Lett.* **1994**, *43*, 7973.
(98) For recent reviews on cyclopropanation, see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; J. Wiley: New York, 1998. Singh, V. K.; DattaGupta, A.; Sekar, G. *Synthesis* **1997**, 137.
(99) Chelucci, G.; Gladiali, S.; Sanna, M. G.; Brunner, H. *Tetrahedron: Asymmetry* **2000**, *11*, 3419.
(100) Kwong, H.-L.; Lee, W.-S.; Ng, H.-F.; Chiu, W.-H.; Wong, W.-T. *J. Chem. Soc., Dalton Trans.* **1998**, 1043.
(101) Chelucci, G.; Cabras, M. A.; Saba, A. *J. Mol. Catal. A* **1995**, *95*, L7.
(102) Ito, K.; Katsuki, T. *Synlett* **1993**, 638.
(103) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553.
(104) Ito, K.; Yoshitake, M.; Katsuki, T. *Heterocycles* **1996**, *42*, 305.
(105) Ito, K.; Fukuda, T.; Katsuki, T. *Heterocycles* **1997**, *46*, 401.
(106) For recent reviews on allylic substitution reactions, see (a) Helmchen, G. *J. Organomet. Chem.* **1999**, 576, 203. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, 96, 395. (c) Reiser, O. *Angew. Chem.* **1993**, *105*, 576; *Angew. Chem., Int. Ed. Engl.* **1993,** *32*, 547. (d) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, Ed.; VCH: Weinheim, **1993**. (e) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry*, **1992**, 3, 1089. (f) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron: Asymmetry* **1995**, 2535.
(107) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
(108) Chelucci, G.; Caria, V.; Saba, A. *J. Mol. Catal.* **1998**, *130*, 51.
(109) Bolm, C.; Kaufmann, D.; Zehnder, M.; Neuburger, M. *Tetrahedron Lett.* **1996**, *37*, 3985.
(110) Bosnich, B.; Mackenzie, P. B. *Pure Appl. Chem.* **1982**, *54*, 189.
(111) Brown, J. M.; Hulmes, D. I.; Guiry, P. I. *Tetrahedron* **1994**, *50*, 4493.
(112) Gilbertson, S. R.; Chang, C.-W. T. *J. Org. Chem.* **1998**, *63*, 8424.
(113) Ramdeehul, S.; Barloy, J. A.; Osborn, L.; De Cian, A.; Fischer, J. *Organometallics* **1986**, *15*, 5442.
(114) For a review, see Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.
(115) For a review, see Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
(116) Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191.
(117) Kwong, H.-L.; Lee, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3791.
(118) Chelucci, G.; Soccolini, F. *Tetrahedron: Asymmetry* **1992**, *3*, 1235.
(119) Genov, M.; Kostova, K.; Dimitrov, V. *Tetrahedron: Asymmetry* **1997**, *8*, 1869.
(120) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Trost, B. M., Fleming, L., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 11, p 1, and references therein.
(121) Kwong, H.-L.; Lau, K. M.; Lee, W.-S.; Wong, W.-T. *New J. Chem.* **1999**, *23*, 629.
(122) Brunner, H. In *Hydrosilylations of Carbonyl Compounds Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, Chapter 21, pp 131−140.
(123) Brunner, H.; Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; p 303.
(124) Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Kürzinger, A.; Obermann, U. *J. Organomet. Chem.* **1989**, *370*, 17.
(125) Brunner, H.; Störicko, R.; Nuber, B. *Tetrahedron: Asymmetry* **1998**, *9*, 407.126.
(126) Nishiyama, H.; Park, S. B.; Itoh, K. *Tetrahedron: Asymmetry* **1992**, *3*, 1209.
(127) Nishiyama, H.; Kondo, M.; Nakamura, T. *Organometallics* **1991**, *10*, 500.
(128) (a) Gladiali, S.; Mestroni, G. *Transfer hydrogenation in Comprensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, Chapter 21, pp 97−119. (b) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051.
(129) (a) Spogliarich, R.; Mestroni, M.; Graziani, M. *J. Mol. Catal.* **1984,** *22*, 309. (b) Mestroni, M.; Zassinovich, G.; Camus, A.; Martinelli, F. *J. Organomet. Chem.* **1980**, *198*, 87.
(130) For a review for the Kharasch reaction, see: Rawlinson, D. J.; Sosnovsky, G. *Synthesis* **1972**, 1.
(131) (a) Katsuki, T. *Asymmetric C−H Oxidation in Comprensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, **1999**; Vol. 2, Chapter 21, pp 791−802. (b) Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567.
(132) For recent reports, see (a) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3941. (b) Andrus, M. B.; Asgari, D. *Terahedron* **2000**, *56*, 5775.
(133) Chelucci, G.; Iuliano A.; Muroni, D.; Saba, A. Submitted for publication.
(134) Chelucci, G.; Loriga, G.; Murineddu, G.; Pinna, G. A. Submitted for publication.
(135) Brunner, H.; Lautenschlager, H.-J.; König, W. A.; Krebber, R. *Chem. Ber.* **1990**, *123*, 847.
(136) Rudler, H.; Gregorio, J. R.; Denise, B.; Brégeault, J.-M.; Deloffre, A. *J. Mol. Catal.* A **1998**, *133*, 255.
(137) Schionato, A.; Paganelli, S.; Botteghi, C.; Chelucci, G. *J. Mol. Catal.* **1989**, *50*, 11.
(138) Chen, C. *Synlett* **1998**, 1311.
(139) Bolm, C.; Ewald, M. *Tetrahedron Lett.* **1990**, *35*, 5011.
(140) (a) Duboc-Toia, C.; Ménage, S.; Ho, R. Y. N.; Que, L., Jr.; Lambeaux, C.; Fontecave, M. *Inorg. Chem.* **1999**, *38*, 1261. (b) Duboc-Toia, C.; Ménage, S.; Lambeaux, C.; Fontecave, M. *Tetrahedron Lett.* **1997**, *38*, 3727.
(141) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419.
(142) Nakajima, M.; Saito, M.; Y.; Hashimoto, S. *Chem. Pharm. Bull.* **2000**, *48*, 306.
(143) (a) Saito, M.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **2000**, 1851. (b) Saito, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2000**, *56*, 9589.
(144) Nakajima, M.; Yamaguchi, Y.; Hashimoto, S. *Chem. Commun.* **2001**, 1596.
(145) Lee, W.-S.; Kwong, H.-L.; Chan, H.-L.; Choi, W.-W.; Ng, L.-Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1007.
(146) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.
(147) Andrus, M. B.; Argade, A. B.; Chen. X.; Pamment, M. G. *Tetrahedron Lett.* **1995**, *36*, 2945.
(148) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* ***1991***, *113*, 726.
(149) Imai, H.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 2453.
(150) Muller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232.
(151) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895.
(152) Andersson, P. G.; Harden, A.; Tanner, D.; Norby, P. O. *Chem. Eur. J.* **1995**, *1*, 12
(153) Suga, H.; Fudo, T.; Ibata, T. *Synlett* **1998**, 933.
(154) Brunner, H.; Henrichs, C. *Tetrahedron: Asymmetry* **1995**, 6, 653.
(155) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.
(156) Mizushima, E.; Ohi, H.; Yamaguchi, M.; Yamagishi, T. *J. Mol. Catal.* **1999**, *149*, 43.
(157) Chelucci, G.; Sanna, M. G.; Gladiali, S. *Tetrahedron* **2000**, 56, 2889.
(158) Nishibayashi, Y.; Singh, J. D.; Segawa, K.; Fukuzawa, S.-I.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1375.
(159) Chelucci, G.; Deriu, S.; Pinna, G. A.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3803.
(160) Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831. Sekar, G.; Datta Gupta, A.; Singh, V. K. *J. Org. Chem.* **1998**, *63*, 2961.
(161) Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247.
(162) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500.
(163) Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817.
(164) Chelucci, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2667.
(165) Lee, S.-G.; Lim, C. W.; Song, C. E.; Kim, I.; Jun, C.-H. *Tetrahedron: Asymmetry* **1997**, *8*, 2927.
(166) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3941.
(167) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566.
(168) Sudo, A.; Yoshida, H.; Saigo, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3205.
(169) Langer, T.; Helmchen, G. *Tetrahedron Lett.* **1996**, *37*, 1381.
(170) Zhang, W.; Yoneda, Y.-I.; Kida, T.; Nakatsuji, Y. Ikeda, I. *Tetrahedron: Asymmetry* **1998**, *9*, 3371.
(171) Nischibayashi, Y.; Segawa, K.; Takada, H.; Ohe, K.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1996**, 847.
(172) Sammakia, T.; Strangeland, E. L. *J. Org. Chem.* **1997**, *62*, 6104.
(173) Wimmer, P.; Widhalm, M. *Tetrahedron: Asymmetry* **1995**, *6*, 657.
(174) Brunner, H.; Rahman, A. F. M. M. *Chem. Ber.* **1984**, *117*, 710.
(175) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191.
(176) Dumont, W.; Poulin, J. C.; Dang, T.-P.; Kagan, H. B. *J. Am. Chem. Soc.* **1973**, *95*, 8295.
(177) Bianchi, M.; Matteoli, U.; Menchi, G.; Frediani, P.; Piacenti, F.; Botteghi, C. *J. Organomet. Chem.* **1980**, 198.
(178) Genet, J.-P.; Ratavelomanana-Vidal, V.; Pinel, C. *Synlett* **1993**, *16*, 478.
(179) Yamaguchi, M.; Shima, T.; Yamagishi, T.; Hida, M. *Tetrahedron Lett.* **1990**, *31*, 5049.
(180) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033.

(181) Spogliarich, R.; Zassinovich, G.; Kasplar, J.; Graziani, M. *J. Mol. Catal.* **1982**, *16*, 359.
(182) Johnson, T.; Klein, K.; Thomen, S. *J. Mol. Catal.* **1981**, *12*, 37.
(183) Zhu, G.; Terry, M.; Zhang, X. *Tetrahedron Lett.* **1996**, *37*, 4475.
(184) Hayaschi, T.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1974**, *15*, 4405.
(185) Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 215.
(186) Barbaro, P.; Bianchini, C.; Togni, A. *Organometallics* **1997**, *16*, 3004.
(187) Wimmer, P.; Widhalm, M.; Klintschar, G. *J. Organomet. Chem.* **1996,** *523*, 167.
(188) Gao, J.-X.; Ikariya, T.; Noyori, R. *Organometallics* **1996**, *15*, 1087.

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