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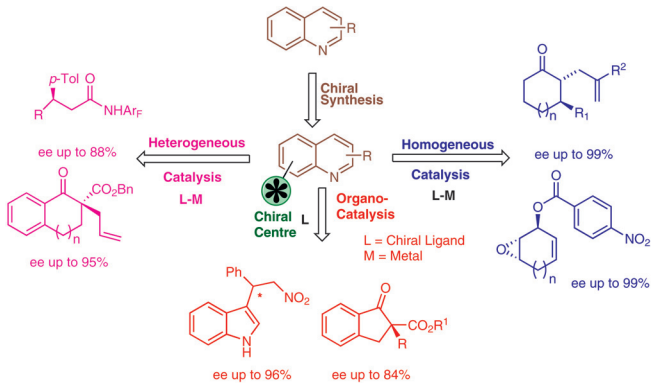
Synthesis and Applications of Asymmetric Catalysis Using Chiral Ligands Containing Quinoline Motifs

Vasudevan Dhayalan[*a]
Rambabu Dandela[b]
K. Bavya Devi[c]
Ragupathy Dhanusuraman[a]

[a] Department of Chemistry, National Institute of Technology Puducherry, Karaikal, 609609, Union Territory Puducherry, India
dhaya.chem@nitpy.ac.in
orgdhaya@gmail.com
[b] Department of Industrial and Engineering Chemistry, Institute of Chemical Technology, Indian oil Odisha Campus, Kharagpur extension Centre, Mouza, Samantpuri, Bhubaneswar-751013, Odisha, India
[c] Department of Chemistry, Thassim Beevi Adbul Kader College for Women, Kilakarai, Ramanathapuram, Tamilnadu, India

Dedicated to Professor Benjamin List



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Abstract In the past decade, asymmetric synthesis of chiral ligands containing quinoline motifs, a family of natural products displaying a broad range of structural diversity and their metal complexes, have become the most significant methodology for the generation of enantiomerically pure compounds of biological and pharmaceutical interest. This review provides comprehensive insight on the plethora of nitrogen-based chiral ligands containing quinoline motifs and organocatalysts used in asymmetric synthesis. However, it is confined to the synthesis of quinoline-based chiral ligands and metal complexes, and their applications in asymmetric synthesis as homogeneous and heterogeneous catalysts.

Key words chiral ligands, catalysis, asymmetric synthesis, nitrogen heterocycles, quinoline motifs, organometallics

1 Introduction

Quinoline, which is now one of the most important heterocyclic compounds, displaying a wide range of applications in pharmaceutical industries and organic synthesis, was first discovered by German chemist Friedlieb Ferdinand Runge in 1834, as a hygroscopic colorless liquid obtained by the distillation of coal tar.[1] The Friedländer annulation remains one of the simplest and most straightforward methods used in organic synthesis to access highly functionalized polysubstituted quinolines. This transformation is generally accomplished through the condensation of 2-aminoarylaldehydes or ketones with a ketone containing an active methylene group in the presence of acid or base.[2–4] Later, numerous methods were developed for the preparation of highly substituted quinoline and its derivatives.[5–11] Moreover, many quinoline derivatives exhibiting significant biological activities have been isolated from plants or systematically designed and synthesized.[12,13]

Quinolines and their derivatives have been labeled as 'privileged scaffolds' owing to their prevalent existence in natural and synthetic molecules that exhibit notable applications in pharmacological, agrochemical, and electronic industries (Figure 1).[14–24]

Biographical Sketches

Dr. Vasudevan Dhayalan obtained his MSc in organic chemistry (2005) and his PhD in organic chemistry (2011) at the University of Madras, Chennai, India. Then he received postdoctoral research experience with Prof. Masahiko Hayashi, Kobe University, Kobe, Japan, Prof. Paul Knochel, Ludwig-Maximilians-University, Munich, Germany, and Prof. Anat Milo, Ben-Gurion University of the Negev, Beer Sheva, Israel. He is a recipient of a PBC Outstanding Postdoctoral Research Fellowship. Recently, he was awarded a Ramanujan Fellowship from the Science and Engineering Research Board (SERB), India. Currently, he is working as a Ramanujan Fellow (Assistant Professor) at the National Institute of Technology Puducherry, Karaikal, India.

Dr. Rambabu Dandela obtained his MSc (organic chemistry) from Kakatiya University (2002–2004) and then worked as a research chemist at Matrix Laboratories, Hyderabad (2004–2008). He obtained his PhD from Dr. Reddy's Institute of Life Sciences, University of Hyderabad campus, in 2013.Then he moved to Ben-Gurion University of the Negev as a PBC Outstanding Postdoctoral Research Fellow to work with Prof. Michael M. Meijer (2013–2017) where he was involved in the development of novel chemical probes for the study of quorum sensing processes in bacteria. In early 2017 he joined the CSIR-National Chemical Laboratory, Pune as a Ramanujan Faculty Fellow. In 2018, he became an Assistant Professor of Chemistry at the Institute of Chemical Technology, Indian Oil Odisha Campus, Bhubaneswar. His research interests lie at the interface of chemistry and biology with particular focus on structure-based drug design, bacterial signaling and polymorphism in pharmaceutical solids.

Dr. K. Bavya Devi is currently working as an Assistant Professor in the Department of Chemistry and Research Head at Thassim Beevi Abdul Kader College for Women, Kilakarai, Ramnad, Tamil Nadu. She received her MSc in chemistry from the University of Madras, India, in 2008. After that, she obtained her PhD in the Department of Chemistry, Anna University Chennai and carried out her research collaboratively with the Bhabha Atomic Research Centre (BARC) Mumbai. Dr. Bavya has received eight best paper awards in both national and international conferences. She was awarded a National Doctoral Fellowship (NDF) by the All India Council of Technical Education, New Delhi, India. Later, she joined Professor Mangal Roy's group as a post-doctoral researcher in the Department of Metallurgical and Materials Engineering at the Indian Institute of Technology Kharagpur, India, in 2015. Her research interests are primarily focused on the development of new degradable materials that support bone regeneration.

Dr. Ragupathy Dhanusuraman received an MSc degree in chemistry from Bharathiar University, Coimbatore, India (2005). He completed his PhD in the Department of Chemistry, Kyungpook National University, South Korea (2010). Currently, he is working as an Assistant Professor in the Department of Chemistry, National Institute of Technology Puducherry, Karaikal, India. His research interests include organic polymers and the development of new nanomaterials for energy and electro-analytical applications.

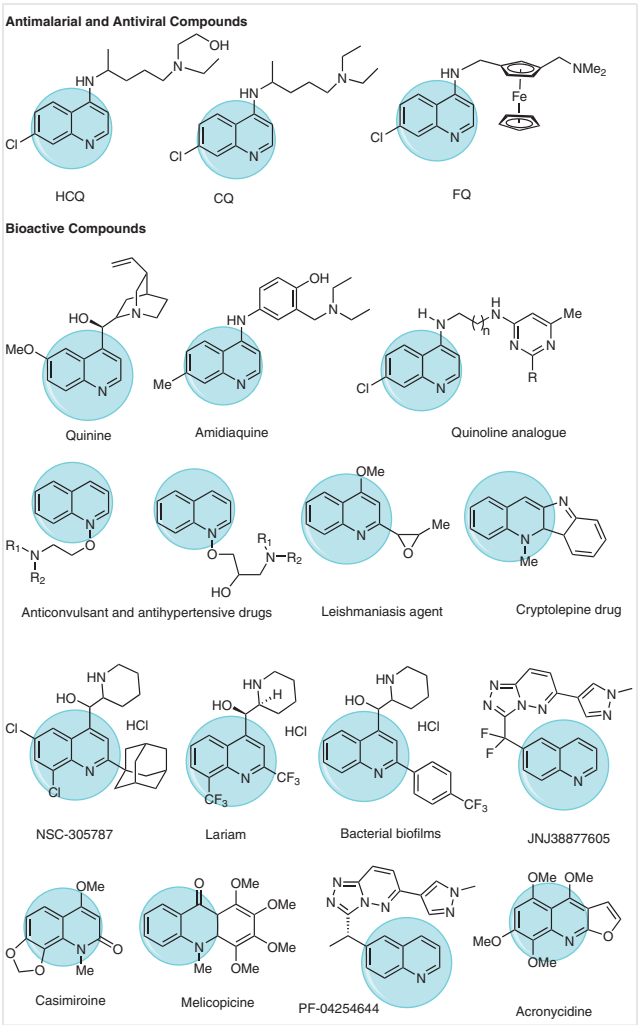


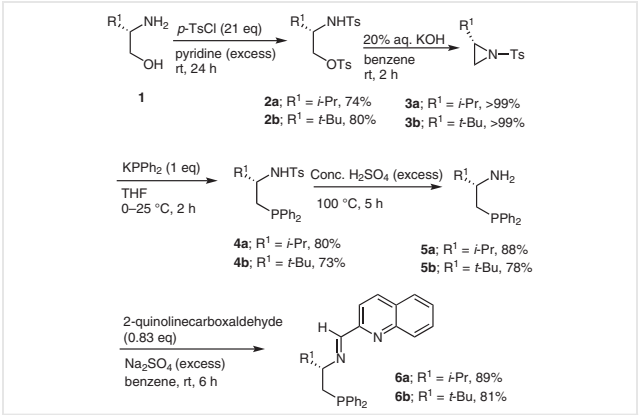
Figure 1 Examples of biologically active quinolines

Furthermore, quinoline analogues display antimalarial,[25–27] anti-inflammatory, antitumor, antibacterial, antiviral,[28] anticonvulsant,[29] and cardiovascular[30] activities.[31] Numerous studies on enantioselective catalysis have focused on the development of novel chiral ligands for use in organo- and transition-metal-catalyzed asymmetric reactions.[32–41] Recently, Benjamin List and David MacMillan have clearly demonstrated the significance of organocatalyst in asymmetric synthesis.[41] Given the broad structural diversity of bicyclic nitrogen heterocycles, these recent Nobel Laureates have demonstrated the ability of these compounds to catalyze a range of chemical transformations. The ease with which many such quinoline (benzo[*b*]pyridine) ring systems can be synthetically modified within chiral scaffolds[42–67] can lead to the discovery of new enantioselective processes for the synthesis of highly challenging chiral products with interesting applications in biology.

2 Synthesis of Chiral Ligands Containing Quinoline Motifs

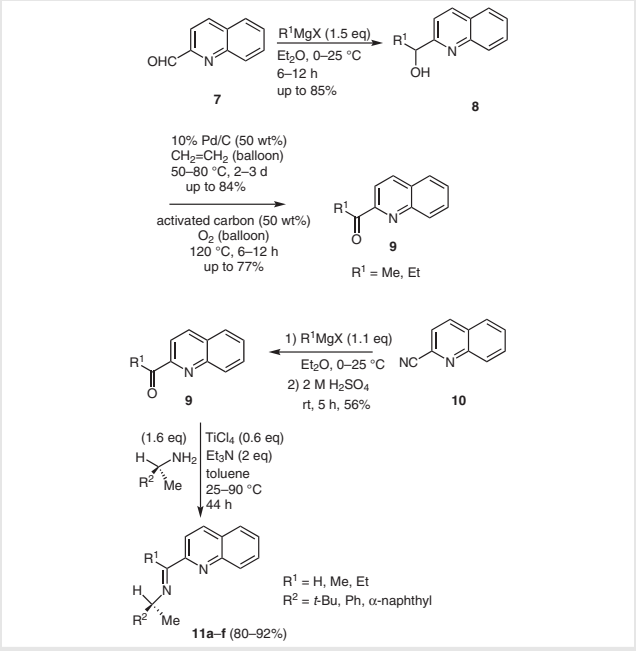
2.1 Synthesis of Schiff Base Type Chiral Ligands

In 2008, Hayashi and co-workers reported the preparation of the N,N,P-ligands. The N,N,P-tridentate Schiff base ligands **6a**,**b** were prepared from chiral amino alcohols **1** in five steps with high yields (Scheme 1). The synthetic pathway started from chiral amino alcohols **1**, NH and OH-tosylation of which, followed by treatment with potassium hydroxide (KOH) gave the anticipated substituted aziridines **3a**,**b**. The obtained amine-protected aziridines **3** were treated with $KPPh_2$ to afford the corresponding N-tosylated amino phosphines **4**. Simple condensation of 2-quinolinecarboxaldehyde with these N-H free amino phosphines **5** gave the expected N,N,P-tridentate chiral Schiff bases **6a**,**b** in good yields. These N,N,P-tridentate Schiff base ligands were used quinoline-based asymmetric catalysts in organic synthesis, such as 1,4-addition of R_2Zn to α,β-unsaturated ketones.

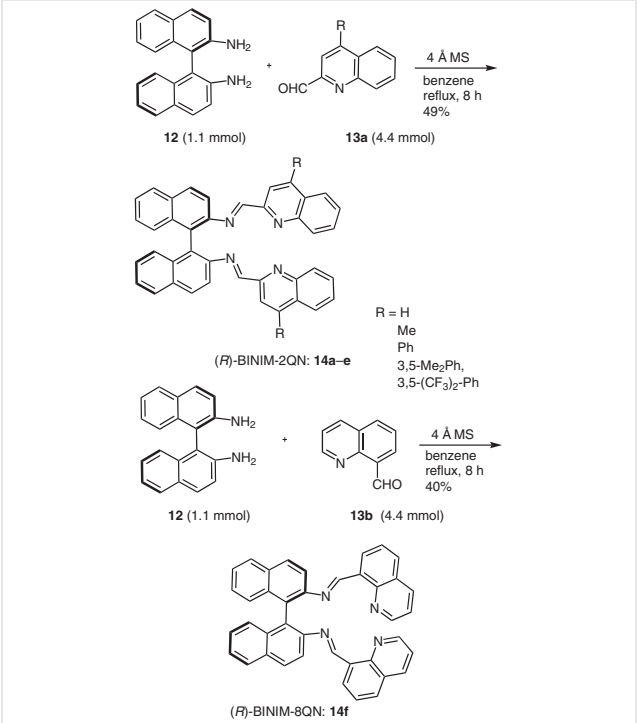


Scheme 1 Synthesis of chiral N,N,P-tridentate Schiff base ligands[68]

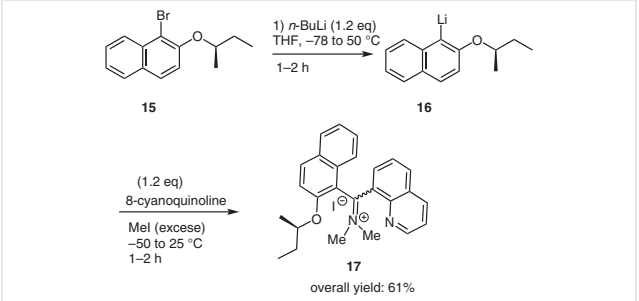
In the same year, Hayashi and co-workers reported the preparation of a library of chiral Schiff base ligands **11a–f** (Scheme 2). Chiral imines were readily prepared by condensation of aldehydes **7** or ketones **9** with chiral amines. The keto-imine chiral Schiff bases, **11a–f** were prepared by two different methods. In method 1, the addition of a Grignard reagent[69a] to 2-quinolylaldehyde **7** produced the desired alcohol **8** in good yields; the obtained secondary alcohol was then effectively converted into the corresponding ketones **9** via a radical oxidation process. In method 2, treatment of 2-quinoline cyanide **10** with a Grignard reagent furnished the required ketones **9**. Finally, condensation of ketones **9** with chiral amino alcohols in the presence of $TiCl_4$ and Et_3N gave the corresponding chiral ligands **11a–f** (Scheme 2). These N,N-bidentate Schiff base ligands were applied to the allylic oxidation of olefins.



Scheme 2 Synthesis of chiral keto-imine N,N-bidentate Schiff base ligands[69b,c]



Scheme 3 Synthesis of binaphthyldiimine chiral Schiff base ligands[70]



Scheme 4 Synthesis of a keto-imine chiral Schiff base ligand[71]

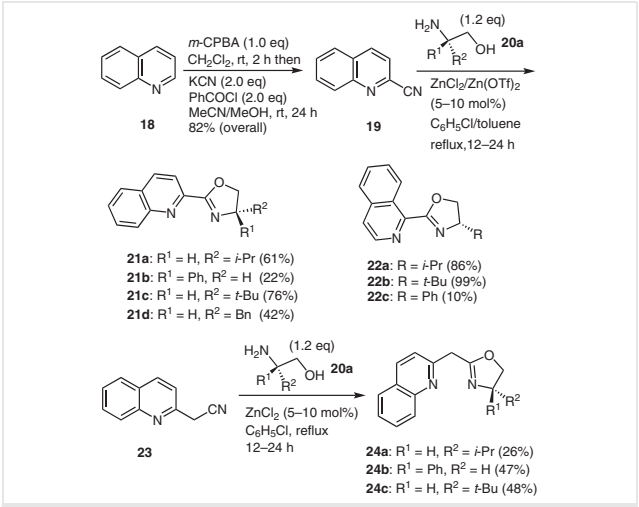
In 2004, Suga and co-workers investigated the synthesis of diamine type chiral Schiff base ligands **14a–f**. Aldimine type chiral Schiff bases were synthesized by simple condensation of substituted 2/8-quinolylaldehyde **13a**,**b** with chiral 1,1′-binaphthyldiamine **12** in benzene under reflux (Scheme 3). These binaphthyldiimine Schiff base ligands were found to be widely applicable to various 1,3-dipolar cycloaddition reactions and Diels–Alder reactions.

Eddine and co-workers demonstrated the preparation of iminium salt **17** via halogen–metal exchange reaction of (*R*)-2-(*sec*-butoxy)bromonaphthalene (**15**) with *n*-BuLi at low temperature to furnish the aryl lithium species **16**, which, upon subsequent nucleophilic addition to 8-cyanoquinoline followed by quenching with methyl iodide (Scheme 4), furnished the corresponding chiral *N*-methyl-1-(8-quinolinyl)-1-(2-(*R*)-*sec*-butoxynaphthyl)-methylenimime ligand **17** (Scheme 4). These keto-imine type chiral Schiff base ligands were examined in effective phase-transfer catalyzed asymmetric alkylation reactions.

2.2 Synthesis of Oxazolinyl-Type Chiral Ligands

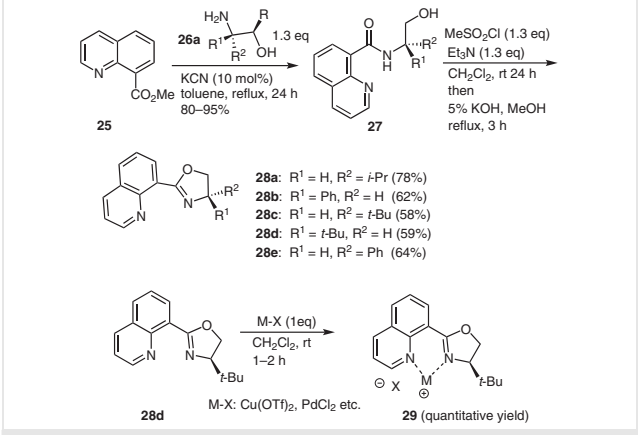
In 1999, Chelucci and co-workers designed a simple synthesis of chiral oxazolinylquinoline type ligands **21** and **22**. Oxidation of quinoline **18** with 3-chloroperbenzoic acid (*m*-CPBA) in DCM for 2 h and then treatment of the obtained *N*-oxide with 2.0 equivalents of KCN and PhCOCl in CH_3CN/MeOH at room temperature for 24 h, produced the corresponding compound **19**. Subsequent treatment with 2-cyanoquinoline **19** and chlorobenzene under reflux with the addition of a suitable chiral amino alcohol **20a** in the presence of $ZnCl_2$ produced the corresponding oxazolinylquinoline type chiral ligands **21** and **22** in yields of 10–99% (Scheme 5). In a similar manner, chiral quinoline ligands **24a–c** were synthesized from 2-cyanomethylquinoline **23** and the corresponding amino alcohol **20a**, mediated by $ZnCl_2$ under reflux conditions (Scheme 5).

Chelucci (2000) and co-workers expanded the library of quinoline ligands, by synthesizing chiral oxazolines **28a–e**, employing an amide–mesylate–oxazoline reaction sequence (Scheme 6). Thus, 8-quinolyl carboxylic ester **25** was heated in toluene under reflux with chiral amino alcohol **26a** in the presence of potassium cyanide to afford the corresponding amide derivates **27** in quantitative yields. Finally, the quinolyloxazolines **28a–e** were obtained by the reaction of amino alcohol **27** with methane sulfonyl chlo-



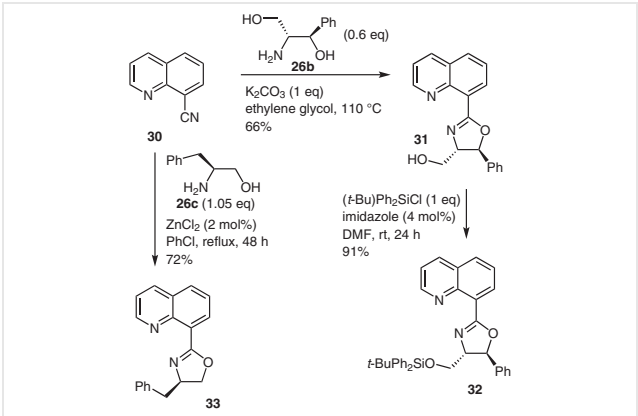
Scheme 5 Synthesis of N,N-chiral 2-quinolyloxazoline ligands[72]

ride ($MeSO_2Cl$) and Et_3N in DCM solvent. The obtained chiral ligands **28a–e** were air-sensitive and, upon standing at 25 °C, underwent a ring opening reaction to furnish the amide by-products. The chiral ligand **28d** was treated with metal salts such as $Cu(OTf)_2$ or $PdCl_2$ to give the corresponding oxazoline transition-metal complexes **29**. These chiral quinolyloxazoline ligands were studied in Friedel–Crafts alkylation, cyclopropanation of olefins, cascade intramolecular cyclization reactions, dialkoxylation of 2-alkenes, intramolecular aerobic oxidative amination, and allylic alkylation.



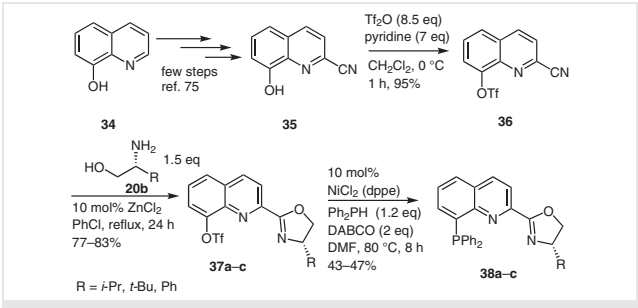
Scheme 6 Synthesis of N,N-chiral 8-quinolyloxazoline ligands[72b,73]

Muller and co-workers (2000) reported an innovative synthesis of oxazolinyl ligands **31** containing a hydroxyl group and silyl group **32** (Scheme 7). The central chiral ligand was prepared by one-pot cyclization of 8-cyanoquinoline and chiral amino benzyl alcohol **26b** at 110 °C in the presence of ethylene glycol. The obtained oxazolinyl-OH ligand **31** was protected using TBDPSCl in the presence of imidazole at room temperature for 24 h. Likewise, the benzyl protected oxazolinyl ligand **33** was prepared.



Scheme 7 Synthesis of silyl protected chiral oxazolinyl ligands[74]

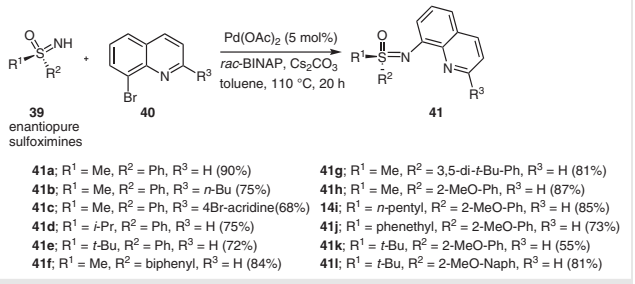
Ahn and co-workers (1999) designed and synthesized 8-diarylphosphino-2-oxazolinylquinoline type chiral ligands **38a–c** starting from **35**. 2-Cyano-8-hydroxyquinoline precursor **35**, synthesized from 8-hydroxyquinoline **34** according to the literature,[75] was used for the preparation of the target chiral ligands. The authors reported that $ZnCl_2$-catalyzed oxazolinyl ring formation furnished better yields when the quinoline-alcohol group was converted into the corresponding aryl triflate **36**; otherwise, in the presence of the quinoline free OH group, oxazolinyl ligand derivatives **37** were obtained in lower yields. The condensation of L-valinol **20b** and aryl cyanide **36** in the presence of $ZnCl_2$ (10 mol%) with PhCl as a solvent, afforded the resulting oxazolines **37a–c** in good yields. Introduction of the diphenylphosphino group (PPh_2) was accomplished by Ni-catalyzed C–P coupling. Thus, reaction of the oxazoline derivatives **37** with diphenylphosphine in the presence of $NiCl_2$(dppe) (10 mol%) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 2 equiv) in DMF at 80 °C afforded the subsequent N,N,P-ligands **38a–c** in moderate isolated yields. When the coupling reaction was carried out at 100 °C or above, as previously reported, the reaction yield was diminished (Scheme 8).



Scheme 8 Synthesis of N,N,P-chiral 2-oxazolinylquinoline ligands[75]

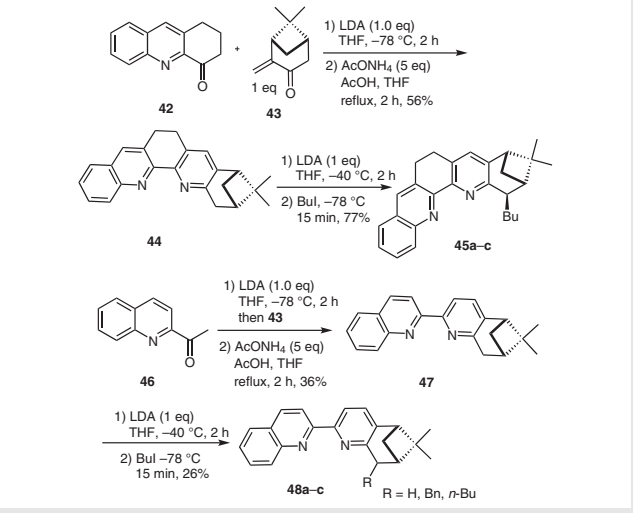
2.3 Synthesis of Chiral N,N-Type Ligands

Bolm and co-workers prepared a wide range of quinoline-based C_1-symmetric chiral monosulfoximine derivatives **41a–l**, in which the second donor nitrogen atom is in a quinolinyl aromatic ring, by $Pd(OAc)_2$-catalyzed N-arylation of optically pure sulfoximines **39** with the corresponding 8-bromoquinoline derivatives **40**. The chiral sulfoximine substrate scope is summarized in Scheme 9.



Scheme 9 Synthesis of monosulfoximine chiral ligands[76]

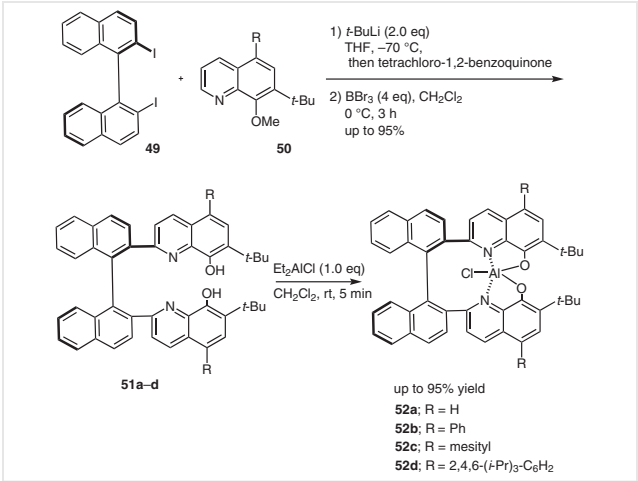
Several N,N-bidentate type chiral quinoline derivatives have been prepared from the corresponding ketones, as reported by Chelucci and co-workers in 2000. Chiral ligands **45a–c** were prepared by the reaction of quinoline ketone **42** with vinyl ketone **43** (Scheme 10) to produce the desired chiral quinoline intermediate **44**, which was subsequently deprotonated with LDA at –78 °C and then treated with alkyl or benzyl iodide to give the corresponding alkylated ligands **45a–c**.



Scheme 10 Synthesis of chiral N,N-bidentate quinoline ligands[77]

Quinoline analogues **48a–c** were successfully synthesized from methyl ketones **46** under similar reaction conditions (Scheme 10) using LDA and alkyl halides.

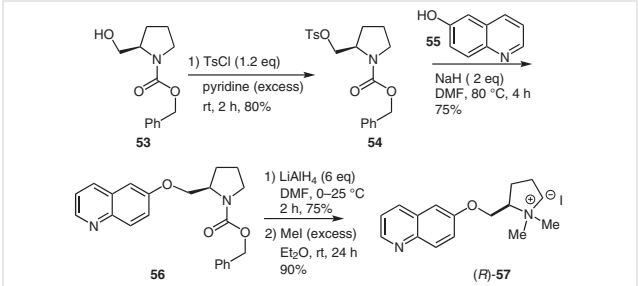
A new class of chiral ligands containing the quinoline moiety **51a–d** was developed by Yamamoto and co-workers in 2004. The coupling reaction of bis-aryl iodo compound **49** with quinoline derivatives **50** in the presence of LDA and BBr_3 furnished the required bis quinoline compounds **51a–d** (Scheme 11). Chiral ligands **51a–d** were then treated with Et_2AlCl or $CrCl_2$ to give the corresponding tethered bis(8-quinolinato) (TBOx) aluminum complexes **52a–d** in good yields. These *N,N*-quinoline ligands were applied in pinacol couplings, the Pudovik reaction, hydrogenation of ketones and allylic alkylations.



Scheme 11 Synthesis of N,N,O-chiral bis-quinoline ligands[78]

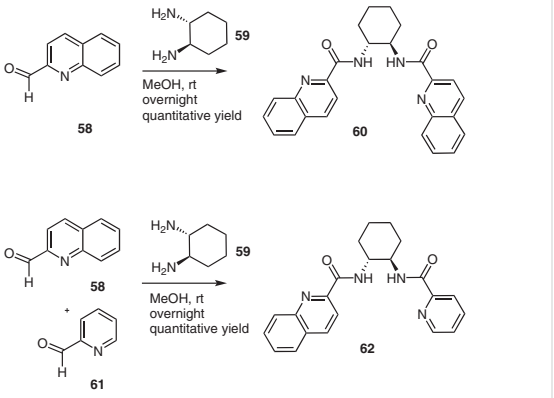
2.4 Synthesis of Amine-Based Chiral Ligands

In 2007, Romanelli and co-workers reported a series of quinoline ligands **57** prepared by the alkylation of alcohol **53** in the presence of TsCl (1.2 equiv) and pyridine at room temperature. Subsequent alkylation of 6-hydroxyquinoline **55** with Ts-ester **54** in the presence NaH (2 equiv) in DMF at 80 ° for 4 h was followed by reduction with LAH and then MeI was added to furnish the required chiral amine salt (*R*)-**57** in high yield (Scheme 12).



Scheme 12 Synthesis of chiral quinoline with amine salt **57**[79]

Kwong et al. introduced a novel synthesis of bisamide ligand-containing quinolines, whose asymmetric synthesis started from condensation of cyclohexyl diamine **59** with heterocyclic aldehydes **58** and **61** to give amide-based unsymmetrical ligands **62** and symmetrical ligands **60** in good yields (Scheme 13).

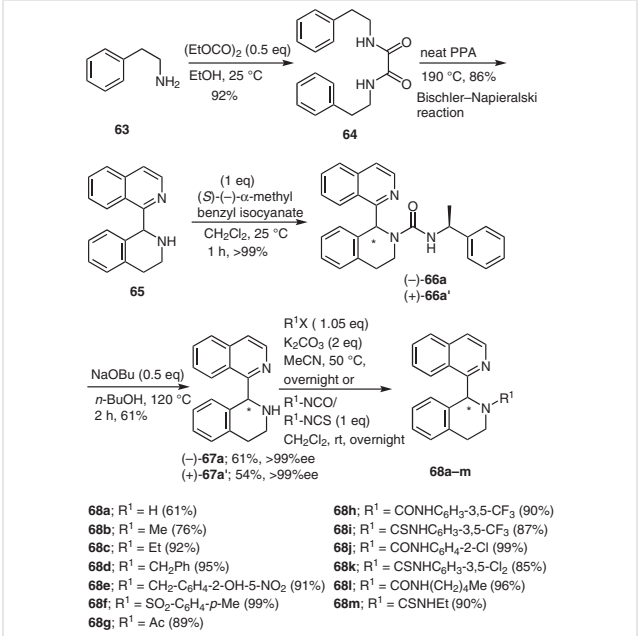


Scheme 13 Synthesis of amide-type chiral ligands[80]

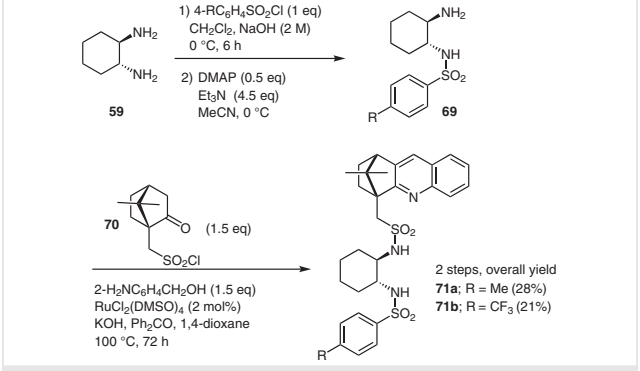
Judeh and co-workers described a series of quinoline ligand derivatives **68a–m**, whose synthesis starts from simple condensation of phenylethylamine **63** with diethyl oxalate in ethanol to give compound **64** in high yield (Scheme 14). Then, *rac*-**65** was synthesized under double Bischler–Napieralski conditions. Bis-amide **64** was then reacted with polyphosphoric acid (PPA) at 190 °C for 12 h to furnished the target compound *rac*-**65** in 86% yield. Reaction of compound **65** with a stoichiometric amount of enantiopure (*S*)-(–)-α-methylbenzyl isocyanate furnished the diastereomeric urea analogues **66a** and **66a′** in excellent yield. When a solution of **66a** or **66a′** was treated with *n*-BuONa in warm *n*-BuOH (Scheme 14), the cleaved products (+)-**67a** and (–)-**67a′**, were obtained in up to 61% yield and 99% ee. Fortunately, one of the products could be recrystallized from ethanol and gave a very high enantiomeric excess >99%.

Various alkyl groups were introduced by reaction of (+)-**67** with alkyl halides in the presence of K_2CO_3 with CH_3CN as a solvent at 50 °C. Likewise, compound (+)-**67** reacted with 1 equivalent of isocyanates and thioisocyanates in DCM at room temperature to give the target products **68a–m** in excellent yields (Scheme 14).

Yus and co-workers studied a practical method for the preparation of camphor sulfonamide-based quinoline ligands **71a**,**b**. Their synthesis started from cyclohexyldiamine **59** by reaction with arylsulfonyl chloride in two steps, followed by treatment with camphor sulfonyl methyl chloride **70**. Friedlander annulation in the presence of ruthenium chloride as a catalyst then furnished the expected camphor sulfonamide-based quinoline ligands **71a**,**b** in moderate yields (Scheme 15).



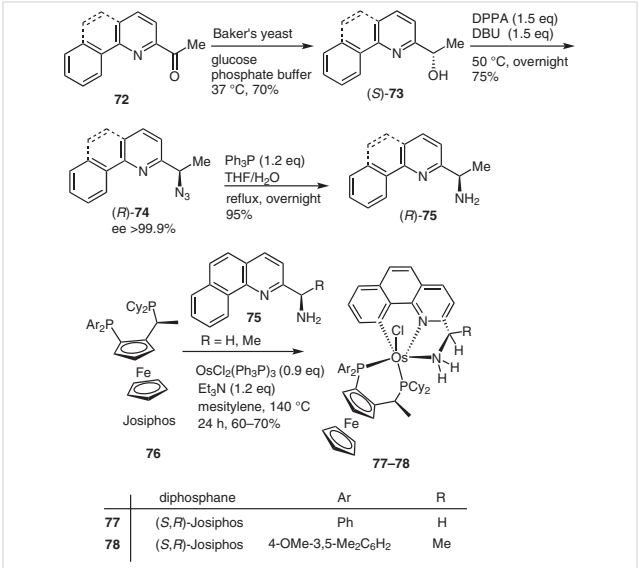
Scheme 14 Synthesis of chiral isoquinoline amine ligands[81]



Scheme 15 Synthesis of camphor sulfonamide-based quinoline ligands[82]

Felluga et al. efficiently synthesized the enantiopure amine-based ligands **75**. Baker's yeast mediated reduction of methyl ketone **72** afforded alcohol (*S*)-**73**. However, the required chiral alcohol (*S*)-**73** could also be obtained by a kinetic resolution approach. Thus, azide precursors (*R*)-**74** were obtained in good yield from the benzyl alcohol in the presence of DPPA/DBU and reduction with triphenylphosphine (Ph_3P) led to the desired amine ligands **75** with high enantioselectivity (Scheme 16).

Osmium metal complexes **77** and **78** were prepared by treatment of $[OsCl_2(PPh_3)_3]$ with (*S*,*R*)-Josiphos (1.2 equiv) in mesitylene at 110 °C for 2 h to give an uncharacterized mixture of products, which was then reacted with 2-aminomethylbenzo[*h*]quinoline **75** (1.4 equiv) in the presence of triethylamine (Et_3N) at 140 °C for 24 h to furnish the cor-



Scheme 16 Synthesis of chiral benzo[*h*]quinoline ligands and their osmium complexes[83]

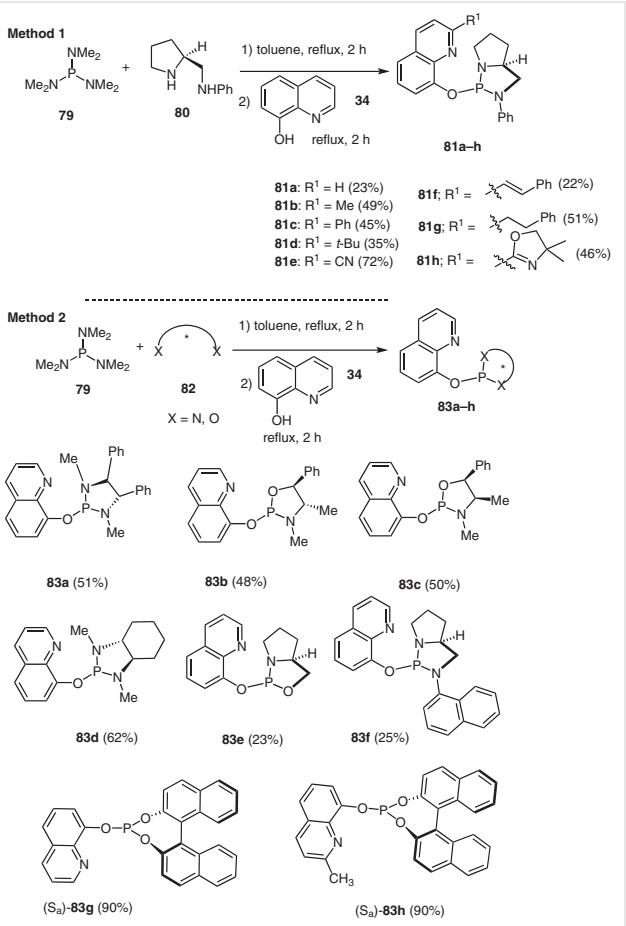
responding coordination metal complexes **77** and **78** in good yields (Scheme 16). These amine-based ligands were studied in catalytic applications such as 1,2-addition of organozinc reagents to substituted aldehydes, 1,4-addition of Grignard reagents (R^1MgX) to cyclic enones, allylic alkylations, and C–H bond arylation reactions

2.5 Synthesis of P,N-Type Chiral Ligands

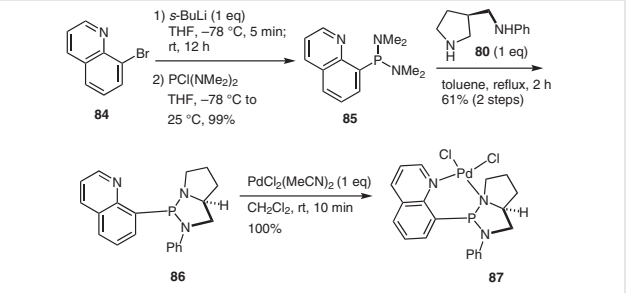
The efficient synthesis of QUIPHOS type chiral ligands **81a–h** by the reaction of phosphane **79** and pyrrolidine **80** followed by addition of hydroxyquinoline **34** (method 1, Scheme 17) afforded the desired ligands **81a–h** in moderate to good yields, as reported by Buono and co-workers. Applying a similar reaction protocol led to a wide range of P,N-quinoline–phosphine ligand derivatives **83a–h**; selected examples are shown in method 2, Scheme 17.

Quinoline-based chiral Pd complex **87** was effectively prepared via halogen–metal (Li–Br) exchange of heterocyclic bromo compound **84** and *s*-BuLi, followed by quenching with $PCl(NMe_2)_2$ to give quinoline–phosphine ligand **85**. Reaction of P,N-ligand **85** with chiral amine **80** produced the corresponding chiral ligand **86** and this was treated with $[PdCl_2(CH_3CN)_2]$ in DCM to produce the desired *N,N,P*-Pd complex **87** in excellent yield (Scheme 18).

The phosphonito, nitrogen ligand (*R*)-**90** has been synthesized in a one-pot, two-step process (Scheme 19). *trans*-Metalation of 8-bromoquinoline **84** with *n*-butyllithium (*n*-BuLi) and subsequent treatment with $PCl(NEt_2)_2$ to form

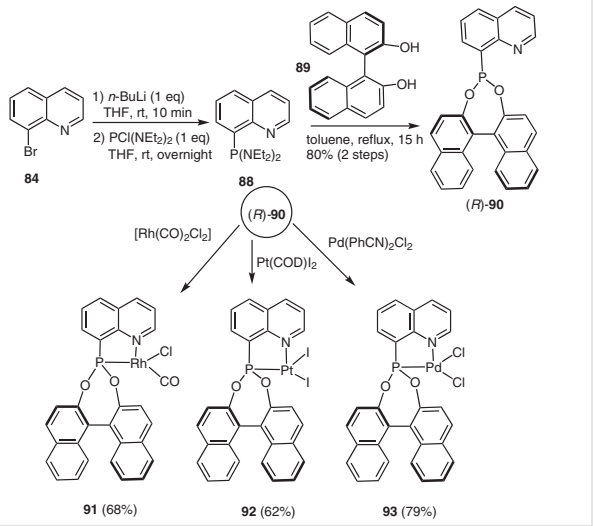


Scheme 17 Synthesis of chiral N,P,O-quinoline–phosphine ligands[84]



Scheme 18 Synthesis of N,N,P-chiral quinoline–phosphine ligand **86** and its Pd complex[85]

phosphine compound **88**, followed by the reaction with (*R*)-binaphthol **89** in toluene at reflux, furnished P,N-ligand (*R*)-**90** in good yield. This ligand was reacted with Pd, Pt and Rh complexes to furnish the desired metal complexes **91–93** in good yields.



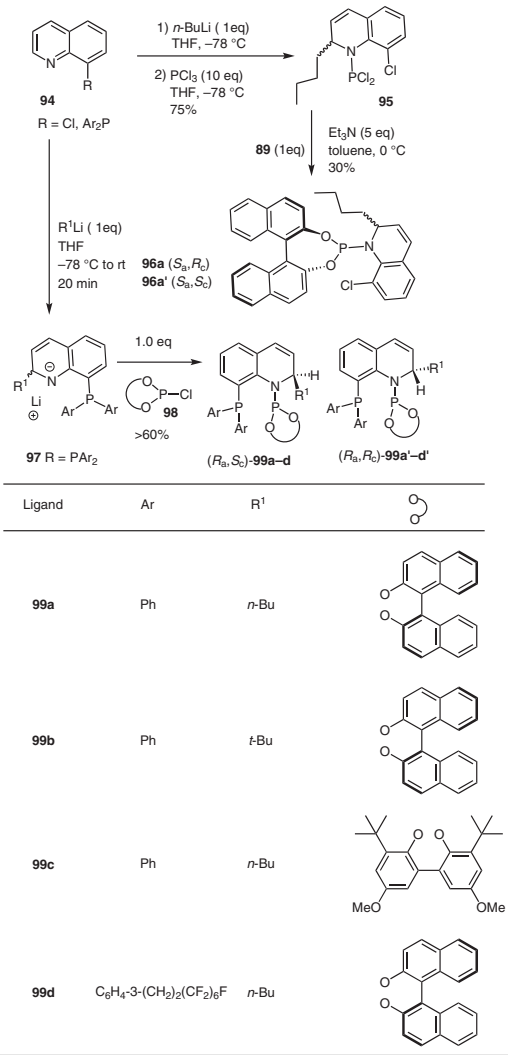
Scheme 19 Synthesis of N,P,O-chiral quinoline–phosphine ligand (*R*)-**90** and its Pd, Pt, Rh complexes[86]

In 2000, Faraone and Leitner introduced the enantioselective synthesis of phosphane/phosphoramidite ligands **96a** and **96a′** in a one-pot procedure from readily available 8-biarylphosphinoquinoline **94** by nucleophilic addition of organometallic lithium reagents and direct quenching with PCl_3 to obtain P,N-ligand **95**, followed by addition to chiral 1,1′-bi-2-naphthol **89** in the presence of Et_3N. Under the same reaction conditions, a 1:1 mixture of diastereomers containing 2-substituted quinoline ligands **99a–d** and **99a′–d′** was obtained from phosphinoquinoline **94**. Selected examples are illustrated in Scheme 20.

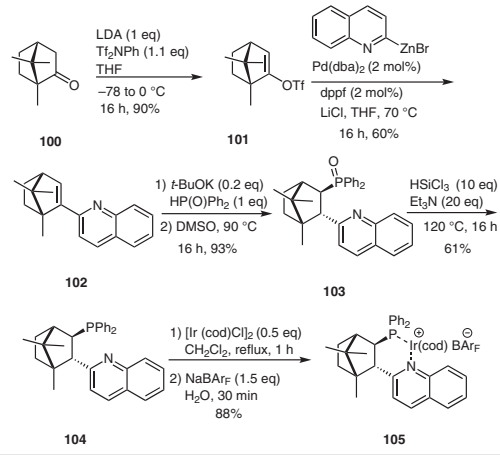
Knochel and co-workers examined the synthesis of P,N-ligands **104** from commercially available starting materials. Treatment of (+)-camphor **100** with Tf_2NPh in THF at 0 °C produced the desired compound **101** in 90% yield (Scheme 21). The chiral camphor triflate **101** efficiently underwent a Pd-catalyzed Negishi cross-coupling reaction with the quinoline organozinc reagent,[88a–d] affording the desired 2-alkenylquinoline **102** in acceptable yield. Subsequent hydrophosphination with $Ph_2P(O)H$, in the presence of a catalytic amount of *t*-BuOK (20 mol%) in DMSO provided phosphine oxide **103** (Scheme 21). Reduction of compound **103** was accomplished in the presence of $HSiCl_3$ and Et_3N in toluene at reflux, to generate the chiral aminophosphine **104** in good yield.

Chiral Ir complex **105** was synthesized by reaction of $[Ir(cod)Cl]_2$ and P,N-ligand **104** in DCM at reflux. After treatment with $NaBAr_F$ in a biphasic DCM–H_2O system, the subsequent orange colored salt **105** was obtained after chromatographic purification. The iridium chiral metal complexes were stable towards moisture and oxygen.

Jiang et al. have designed and synthesized a series of phosphine–quinoline ligands. Their synthetic protocol began from optically pure paracyclophane **106**. Hence, treat-

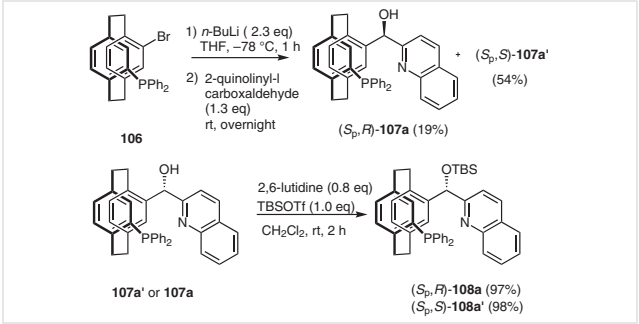


Scheme 20 Synthesis of chiral phosphane/phosphoramidite ligands[87]



Scheme 21 Synthesis of a chiral *P,N*-quinolinyl ligand and its Ir complexes[88e,f]

ment of (R_p)-**106** with *n*-butyllithium (*n*-BuLi) followed by successive addition to 2-quinolinylcarboxaldehyde, produced two diastereoisomers, (S_p,*S*)-**107a'** and (S_p,*R*)-**107a** that could be readily separated by flash column chromatography (Scheme 22). Modifying (*Sp*,*S*)-**107a'** and (*Sp*,*R*)-**107a** by silylation in the presence of TBSOTf and lutidine as a base produced (*Sp*,*S*)-**108a'** in 98% yield and (*Sp*,*R*)-**108a** in 97% yield, respectively.

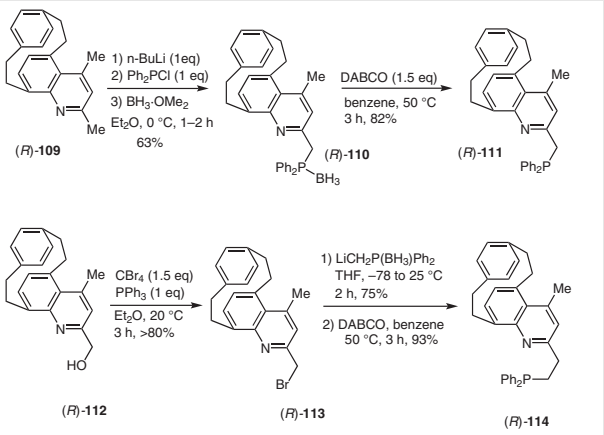


Scheme 22 Synthesis of chiral phosphino-quinoline paracyclophane P,N-ligands[89]

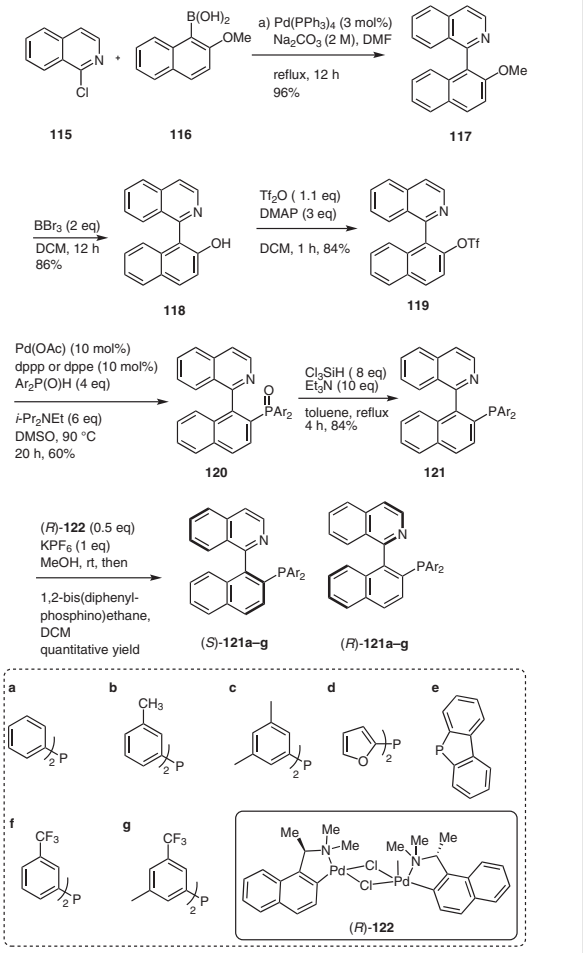
Ruzzicon et al. investigated the valuable synthesis of P,N-bidentate planar chiral ligands **111** and **114**. Deprotonation of methyl compound **109** with *n*-BuLi at 0 °C, involved the 2-methyl quinoline, giving the 2-methyllithium intermediate, exclusively. The borane complex (*R*)-**110** was achieved in high yield, by the reaction of Ph_2PCl with $BH_3{\cdot}OMe_2$ (Scheme 23). The subsequent air-stable borane complex (*R*)-**110** was treated with DABCO, to obtain the expected phosphine (*R*)-**111**. On the other hand, bromo-compound **113** was prepared from alcohol **112** by treating with CBr_4 and PPh_3 in Et_2O at 25 °C and successfully underwent nucleophilic substitution with lithium (diphenylphosphine)methylborane complex, followed by treatment with DABCO, providing the corresponding P,N-chiral ligand (*R*)-**114** in 70% overall yield (Scheme 23).

Brown et al. focused on the synthesis of chiral ligands **121a–g** (QUINAP). Boronic acid **116** underwent smooth cross-coupling with aryl chloride **115** in the presence of 3 mol% $Pd(PPh_3)_4$ and Na_2CO_3 in DME to give carbon–carbon coupled product **117** in 96% yield. Cleavage of the methyl group from aryl methyl ether **117** with boron tribromide (BBr_3) gave the required phenol analogue **118**, which was further converted into the triflate **119** (Scheme 24). Finally, palladium-catalyzed cross-coupling of triflate **119** with diphenylphosphine oxide gave the phosphine oxide **120**. Subsequently, compound **120** was reduced to the phosphine ligand **121** with $HSiCl_3$ and Et_3N in 84% yield.

Finally, the racemic ligand **121** was reacted with the chiral palladacycle **122** to form diastereomers, from which the desired enantiopure *R* or *S* ligands **121a–g** were obtained in good yields after fractional recrystallization and ligand decomplexation (Scheme 24).



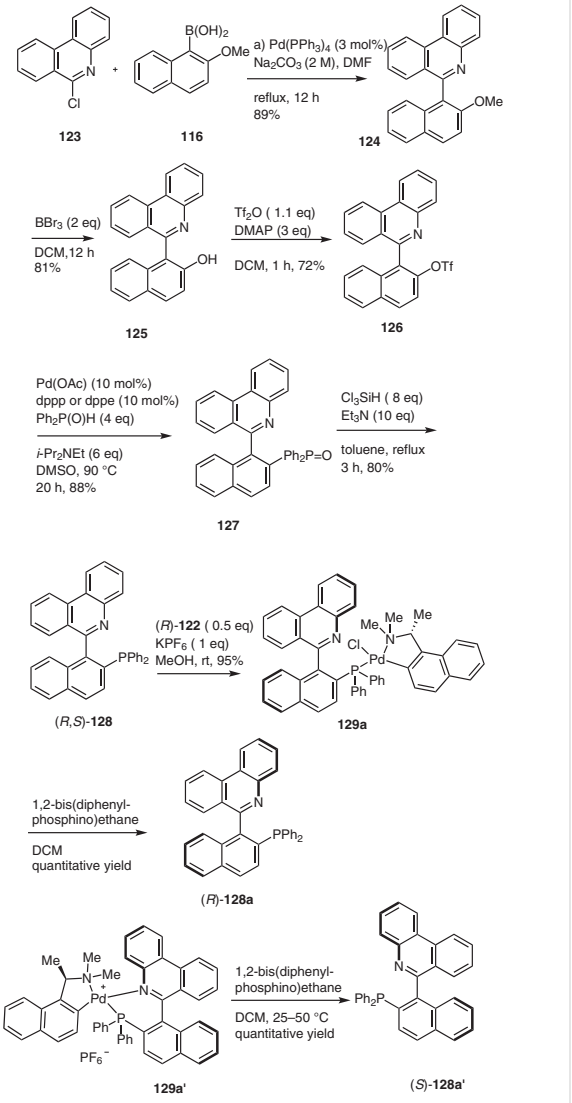
Scheme 23 Synthesis of P,N-planar chiral ligands[90]



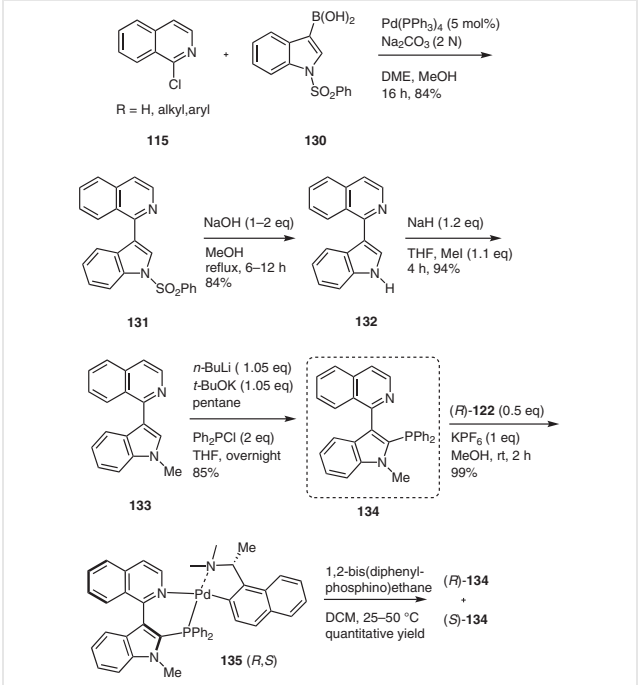
Scheme 24 Synthesis of *P*,*N*-isoquinoline chiral ligand[91,75]

Furthermore, the same group developed a method for the preparation of benzo ring fused isoquinoline and indole-based chiral P,N-ligands **128** and **134** (Scheme 25 and Scheme 26).

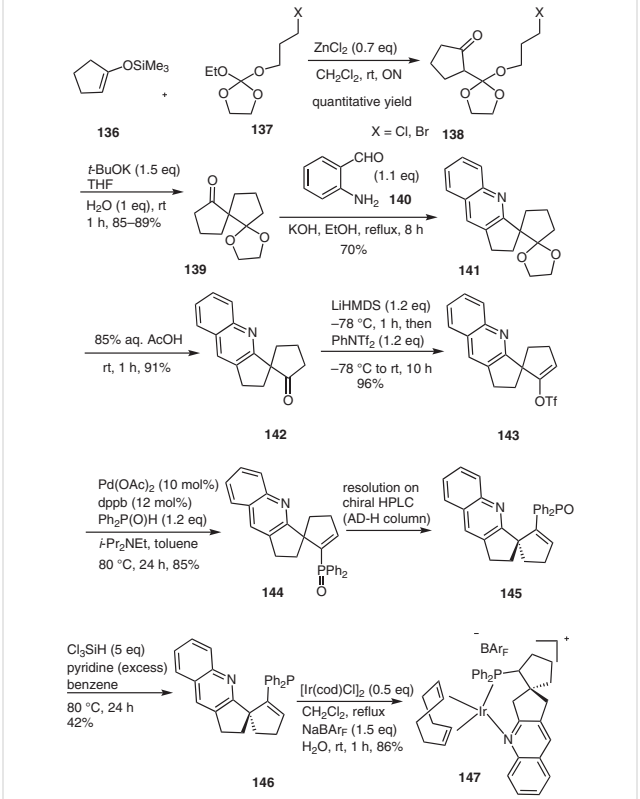
Ding and co-workers have synthesized *spiro*-based P,N-ligand **146** through a sequence of reactions as shown in Scheme 27. Nucleophilic addition of compound **136**, to a ketal derivative **137** generated a protected spiro-diketone **138**. Then Friedländer condensation of **139** with 2-amino benzaldehyde **140** in the presence of KOH and EtOH furnished the polycyclic quinoline **141** in 70% yield. Selective deprotection of compound **141** in aq. TFA at room temperature for 1 h furnished the corresponding *spiro*-ketone **142**



Scheme 25 Synthesis of *P,N*-benzo ring-fused isoquinoline chiral ligand[91]



Scheme 26 Synthesis of chiral P,N-ligands with an indole unit[91]



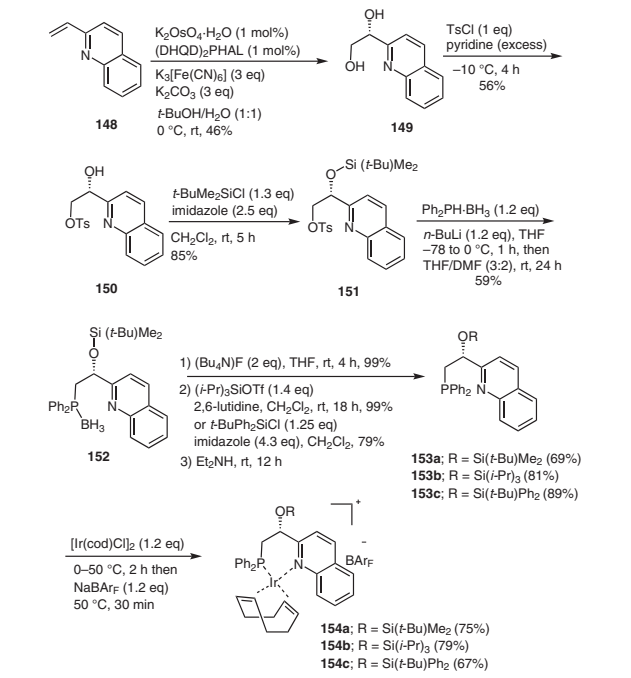
Scheme 27 Synthesis of chiral P,N-ligands with a *spiro*-skeleton[92]

in excellent yield. Subsequent treatment of *spiro*-compound **142** with LiHMDS, followed by addition of $PhNTf_2$, gave enol triflate **143** in 96% yield. Next, the coupling reaction of compound **143** with $Ph_2P(O)H$ in the presence of Pd catalyst afforded racemic phosphine oxide **144** in 85% yield, which was readily resolved by chiral HPLC to give both enantiomers in enantiomerically pure form.

The resulting chiral phosphine oxide **145** was simply reduced with $HSiCl_3$ in the presence of pyridine, affording the required chiral nitrogen ligand (S)-**146** in moderate yield (Scheme 27). The reaction of nitrogen based P,N-ligand **146** with $[Ir(cod)\text{-}Cl]_2$ in DCM followed by addition of NaBArF after counter-anion exchange gave the corresponding desired Ir metal complex (+)-**147** in 87% yield.

Multi-step synthesis of silyl substituted chiral quinolinyl phosphane ligands **153a–c** has been achieved by Pfaltz and co-workers. In the initial step, hydroxylation of compound **148** using a metal catalyst gave the corresponding 1,2-diol **149** in moderate yield and high enantiomeric excess on a gram scale (46% yield, 94% ee). Selective tosylation of the primary alcohol **149** in the presence of TsCl with pyridine, followed by silylation of benzyl alcohol **150** using TBDMSCl and imidazole generated enantiomerically pure compound **151** after recrystallization.

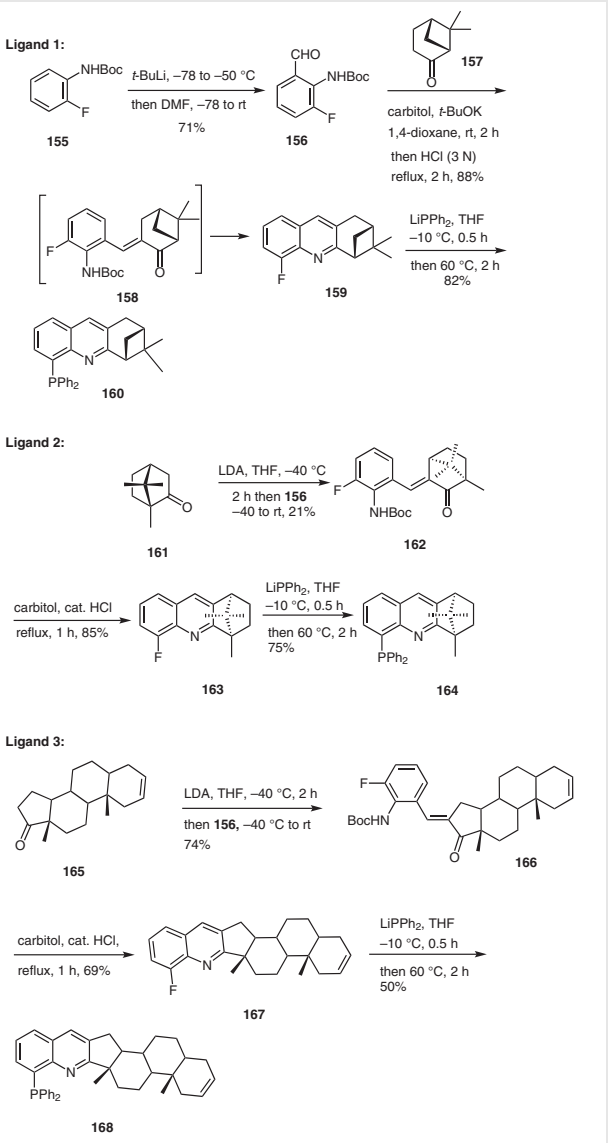
Next, sulfonate **151** was treated with $LiPPh_2{\cdot}BH_3$ at –78 °C to furnish the phosphine-protected ligand **152** in good yield (Scheme 28). Finally, the P–B bond was successfully cleaved using diethylamine to afford the desired P,N-ligands **153a–c** in good yield.



Scheme 28 Synthesis of silyl substituted chiral quinolinyl phosphane ligands and their Ir complexes[80,93]

Additionally, Ir-based transition-metal complexes **154a–c** were produced from *N*-heteroaryl phosphane derivatives **153a–c**. Warming a DCM solution of the requisite organocatalysts **153** in the presence of $[Ir(cod)Cl]_2$ (0.5 equiv) for 2 h at 30–40 °C followed by counter-ion exchange with NaBArF (1.6 equiv), provided the metal complexes as orange solids. These types of metal complexes are generally stable to air and moisture, and are simply purified by flash column chromatography on silica gel (Scheme 28).

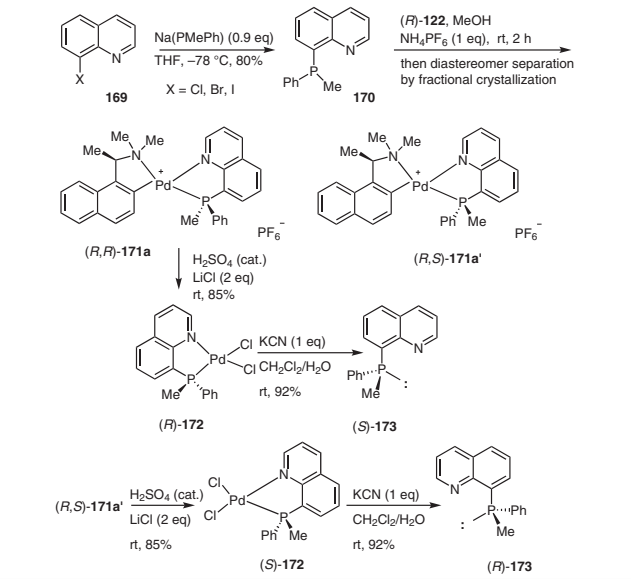
Chelucci et al. reported a new class of bidentate ligands **160**, **164** and **168** that were synthesized from the corresponding starting materials (+)-nopinone, (+)-camphor and 5-androst-2-en-17-one. The direct lithiation of compound **155** with *t*-BuLi at low temperature and then quenching with electrophile DMF affording coupled aldehyde **156**. The



Scheme 29 Synthesis of quinoline based P,N-chelating ligands[94]

N-Boc aldehyde **156** thus obtained reacts with acyclic ketone **157** in the presence of *t*-BuOK at 25 °C, leading to **159** in good yield (Scheme 29). Finally, treatment of compound **159** with $LiPPh_2$ gave the desired acridine **160** in 82% yield. The same group used similar reaction conditions to prepare additional quinoline-based P,N-chelating chiral ligands **164** and **168** in good yields (Scheme 29).

Wild and co-workers introduced an efficient method for the preparation of (*R* or *S*)-carbene ligands **173** (Scheme 30). The reaction of halogenated quinoline **169** with Na(PMePh) in THF furnished the desired compound **170** in very good yield. This racemic product was resolved by crystallization of a pair of internally diastereoisomeric Pd(II) complexes (*R*,*R*)- and (*R*,*S*)-**171a**,**a′** derived from the chelating ligand (*R*)-**122**. The resulting tertiary phosphine (*R*)- and (*S*)-**172** was accessed by treatment with H_2SO_4 and LiCl (Scheme 30). Finally square-planar palladium complexes (*R*)- and (*S*)-**172** were successfully converted into the optically pure enantiomers (*S*)- and (*R*)-**173** with aq. KCN and DCM/H_2O in a biphasic reaction medium.

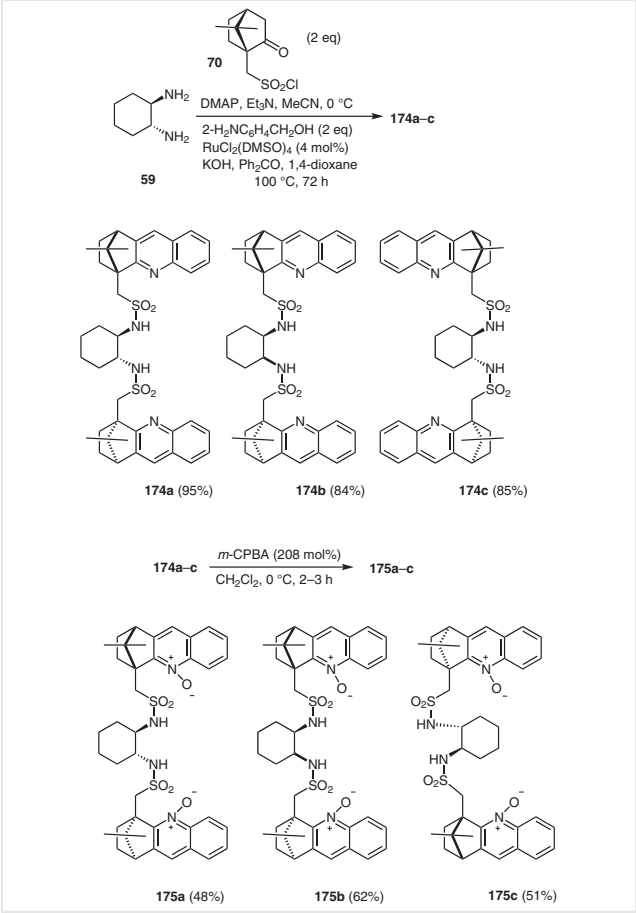


Scheme 30 Synthesis of chiral P,N-carbene ligands[75,95]

These quinoline-based P,N-ligands were broadly applied as asymmetric catalysts in cyclopropanation of olefins, Heck reactions, hydrogenation of olefins, ketones and imines, hydroformylation, allylic alkylation, and oxidative hydroboration.

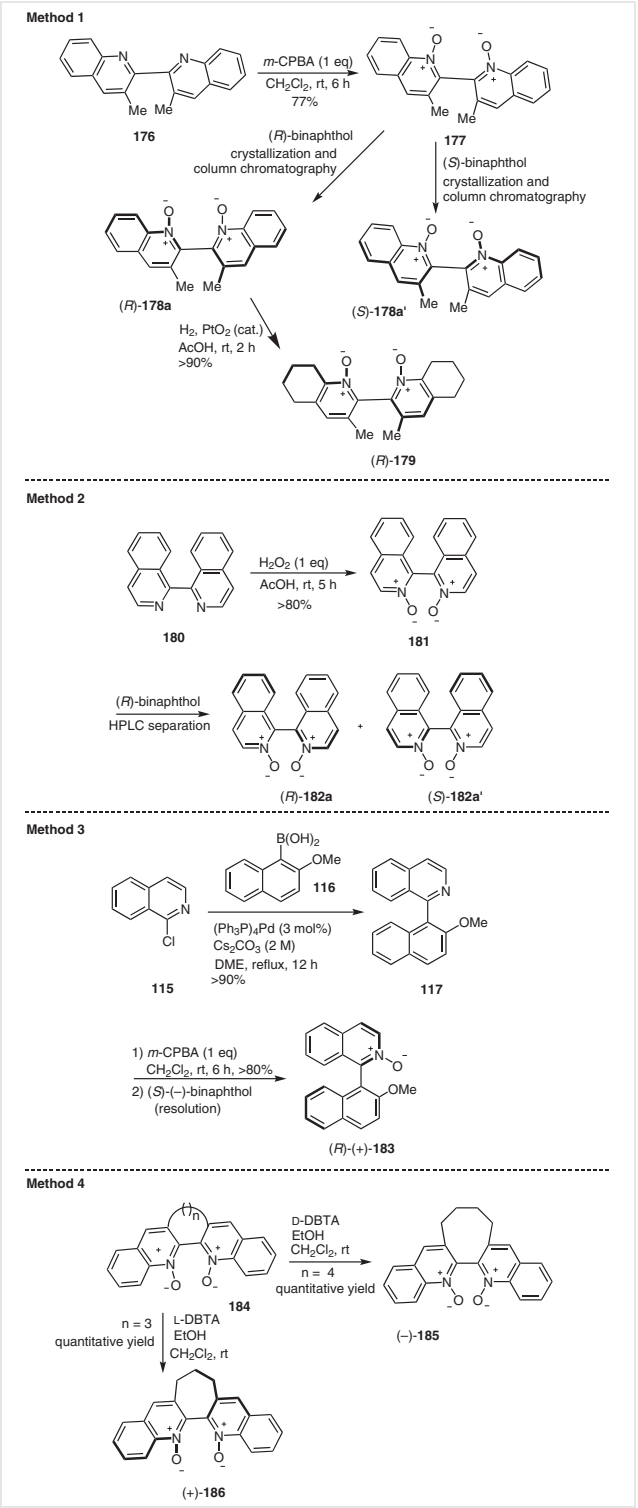
2.6 Synthesis of Chiral *N*-Oxide and Nitrogen Ligands

Martinez et al. developed an efficient method for the preparation of camphor sulfonamide-based quinoline chiral ligands and their *N*-oxide derivatives. These chiral amine ligands **174a–c** (C_2-symmetry) were prepared by the addition of camphorsulfonyl chloride **70** to 1,2-cyclohexanodiamine **59** and, without additional purification, the resulting intermediates were treated with an aminobenzyl alcohol (Scheme 31) to afford the desired camphor sulfonamide-based quinoline ligands **174a–c** in high yields. The quinoline *N*-dioxide ligands **175a–c** were simply synthesized from the corresponding ligands **174a–c** (C_2-symmetry) by oxidation with *m*CPBA in DCM at 0 °C. The resulting amine type *N*-dioxide ligands **175a–c** were formed in reasonable yields and were typically stable enough to be purified by flash column chromatography.



Scheme 31 Synthesis of camphorsulfonamide-based quinoline *N*,*N*′-dioxide ligands[82]

Nakajima et al. successfully developed a protocol for the synthesis of C_2-symmetric 2,2′-biquinoline *N*,*N*′-dioxide (*R* or *S*)-**178** and 1,1′-biisoquinoline *N*,*N*′-dioxide (*R* or *S*)-**182** (Scheme 32). The racemic compound **177** was prepared by *m*CPBA oxidation of 3,3′- dimethyl-2,2′-biquinoline **176**, and the product was resolved through a hydrogen-bonding complex with (*S*)- or (*R*)-binaphthol to afford desired chiral compounds (*R*)-**178a** and (*S*)-**178a′** (Scheme 32). The enantiomerically pure ligand 1,1′-biisoquinoline *N*,*N*′-dioxide



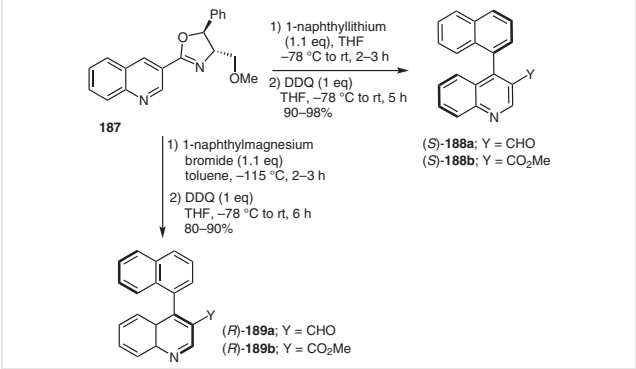
Scheme 32 Synthesis of bis-quinoline-based chiral *N*,*N*′-dioxide ligands[96]

(*S*)-**182** was prepared by preparative chiral HPLC from racemic compound **181**, which was in turn synthesized by N-oxidation of 1,10-bisisoquinoline **180** using H_2O_2.

The racemic compound **117** was prepared from 1-chloro isoquinoline **115** via Suzuki cross-coupling reaction in the presence of boronic acid **116**. Racemic **117** was further reacted with *m*CPBA, and was resolved via a complex with (*S*)-binaphthol to give the required chiral compounds (*R*)-**183**.

The ligands (–)-**185** and (+)-**186** were obtained by resolution of *rac*-**184** with D and L-dibenzoyltartaric acid, respectively. The absolute configuration of chiral ligand (*S*)-**186** was determined by single-crystal X-ray analysis (Scheme 32). Quinoline-based *N*-oxide ligands were studied in various asymmetric catalytic reactions such as 1,4-addition and Michael addition reactions, allylation of aromatic and heteroaromatic aldehydes, and Strecker reactions.

Finally, in this section, Meyers et al. established the synthesis of chiral naphthylquinoline ligands **188** and **189**. Addition of naphthyllithium (1.1 equiv) to quinoline oxazoline **187** in THF at –78 °C for 2–3 h followed by oxidation with dichlorodicyanoquinone (DDQ) in THF at –78 °C gave 1-naphthyl-4-quinoline (*S*)-**188a**,**b** in good yield. A similar process using **187** and arylmagnesium reagents[97a] followed by oxidation with DDQ (THF, –78 °C) gave the biaryl compounds (*R*)-**189a**,**b** in high yields (Scheme 33).



Scheme 33 Synthesis of chiral naphthylquinoline ligands[97b,c]

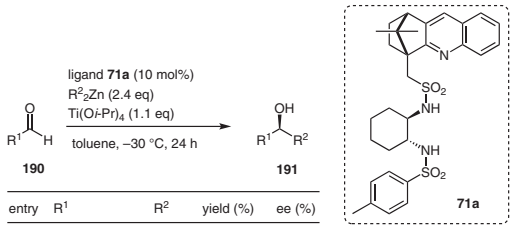
3 Homogeneous Catalytic Asymmetric Reactions

3.1 Asymmetric Carbon–Carbon Bond-Formation Reactions

Catalytic asymmetric C–C bond-forming reactions provide one of the most efficient methods to synthesize chiral molecules, and a range of pyridine and quinoline-based chiral catalysts have been developed in the past two decades, finding a wide range of applications.[14–31]

3.1.1 Asymmetric Addition of Dialkylzinc to Aldehydes

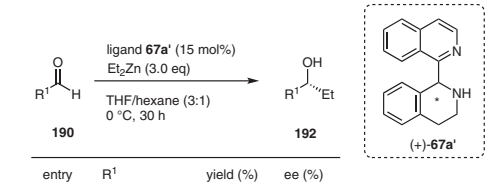
In 2008 Cozzi, Yus, Ramón and co-workers described the preparation of camphor sulfonamide-based quinoline ligands. This type of chiral quinoline ligands has been used for the synthesis of trisubstituted chiral alcohols. The enantioselective 1,2-addition of organozinc reagents to substituted aldehydes **190**, provides alcohols **191** with high enantioselectivities (up to 96% ee) with either aromatic or aliphatic substrates (Scheme 34). These reactions were carried out using 10 mol% chiral amine ligand **71a** organozinc reagent (2.4 equiv) and 1.1 equivalents of $Ti(O\text{-}i\text{-}Pr)_4$.



entry	R^1	R^2	yield (%)	ee (%)
1	Ph	Et	>95	92 (*S*)
2	Ph	Me	94	80 (*S*)
3	4-ClC_6H_4	Et	89	90 (*S*)
4	4-$CF_3C_6H_4$	Et	>95	87 (*S*)
5	4-$OMeC_6H_4$	Et	>95	89 (*S*)
6	1-naphthyl	Et	>95	96 (*S*)
7	$PhCH_2CH_2$	Et	86	93 (*S*)

Scheme 34 Enantioselective addition of dialkylzinc reagents to aldehydes[82]

In 2010, Judeh and co-workers synthesized constrained chiral C_1-symmetric 1,10-bisisoquinoline ligands. The consequences of their geometrical conformations were found to have a significant effect on the catalytic asymmetric addition of diethylzinc to aromatic aldehydes **190**. To study the reaction scope and limitations of ligand (+)-**67a′**, several aromatic aldehydes having electron-donating and electron-withdrawing substituents were examined under the optimized reaction conditions. In general, this protocol produced excellent yields and high enantioselectivities of the secondary alcohols **192** (Scheme 35).



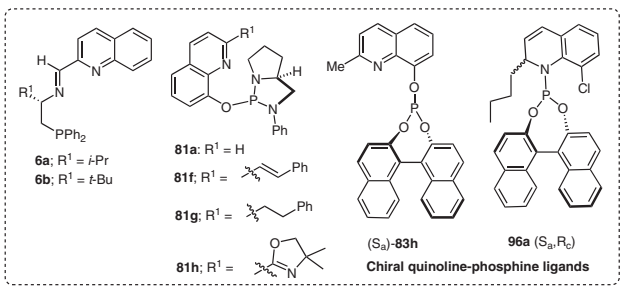
entry	R^1	yield (%)	ee (%)
1	Ph	96	85
2	3-IC_6H_4	89	80
3	2,6-$Cl_2C_6H_3$	99	87
4	2-naphthyl	73	81

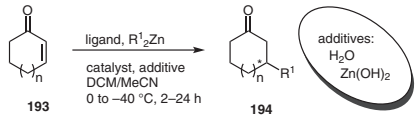
Scheme 35 Enantioselective addition of diethylzinc to aldehydes[81]

3.1.2 Asymmetric 1,4-Additions of Dialkylzincs to Enones

Buono and co-workers investigated the use of a copper catalyst involving QUIPHOS **81a–h** as a chiral ligand. This system was applied to the 1,4-addition of Et_2Zn to α,β-unsaturated cyclic ketones. Notably, additives such as water or zinc hydroxide had a significant effect, leading to an improved enantiomeric excess from 7 to 61% *ee* in this enantioselective 1,4-addition system (Scheme 36).

Faraone and co-workers examined the Cu(II)-catalyzed asymmetric 1,4-addition of diethylzinc to 2-cyclohexen-1-one, in the presence of a catalytic amount of chiral ligands **96a** and **83h** with appropriate metal salts. The 1,4-adducts were formed with enantioselectivities up to 70% ee with BINAPHOSHQUIN **96a** (Scheme 36).





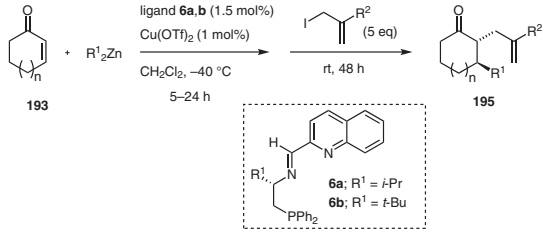
entry	n	ligand (mol%)	Cu cat. (mol%)	R^1	yield (%)	ee (%)
1	1	**6a** (2.5)	$Cu(OTf)_2$ (0.2)	Et	66[a]	99 (*S*)
2	1	**6b** (2.5)	$Cu(OTf)_2$ (1.0)	Et	99[a]	99 (*S*)
3	2	**6a** (0.25)	$Cu(OTf)_2$ (0.1)	Me	44[a]	88 (*S*)
4	2	**6b** (0.25)	$Cu(OTf)_2$ (0.1)	Me	32[a]	83 (*S*)
5	1	**81a** (1.0)	CuI (0.5 mol%)	Et	76	61 (*R*)
6	1	**81f** (1.0)	CuI (0.5 mol%)	Et	100	50 (*R*)
7	1	**81g** (1.0)	CuI (0.5 mol%)	Et	100	51 (*R*)
8	1	**81h** (1.0)	CuI (0.5 mol%)	Et	96	55 (*R*)
9	1	**83h** (0.03)	$Cu(OTf)_2$ (0.03)	Et	95[a]	51 (*S*)
10	1	**96a** (0.03)	$Cu(OTf)_2$ (0.03)	Et	96[a]	70 (*S*)

Scheme 36 Enantioselective 1,4-addition of dialkylzinc to cyclic enones[68,84,98]

Later, Hayashi and co-workers developed mild and effective methods for the synthesis of chiral alcohols with excellent enantioselectivity. The copper-catalyzed enantioselective conjugate 1,4-addition of dialkylzinc reagents to α,β-unsaturated cyclic ketones **193** with catalytic amounts (0.2 mol%) of $Cu(OTf)_2$ and 0.25 mol% of one of the N,N,P-tridentate Schiff base ligands **6a**,**b** gave cyclic ketone adducts **194** in up to 99% ee in good yield (Scheme 36). The impact on the enantioselectivity and reactivity of many other vari-

ables, such as the nature of the metal catalyst, ligands, and ligand/catalyst loading involved were also examined in detail and the results obtained are summarized in Scheme 36.

Moreover, Hayashi and co-workers further expanded the scope of the 1,4-addition reaction to access disubstituted ketones via copper-catalyzed 1,4-addition of dialkylzincs to α,β-unsaturated ketones. The reactive zinc enolate intermediates were trapped efficiently with reactive allyl iodides to afford the corresponding disubstituted ketones **195** with excellent diastereo- and enantioselectivity. The desired 1,4-addition reactions were performed using 1 mol% $Cu(OTf)_2$ and 1.5 mol% Schiff base ligand **6a**,**b**. The results obtained are summarized in Scheme 37.

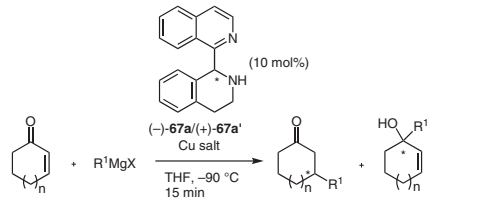


entry	n	ligand	R^1	R^2	yield (%)	*trans*/*cis*	ee *trans* (%)
1	1	**6a**	Et	H	76	95:5	99
2	1	**6a**	Me	H	71	93:7	99
3	1	**6a**	Et	Me	85	97:3	99
4	1	**6a**	Me	Me	83	96:4	99
5	0	**6b**	Et	H	44	95:5	97

Scheme 37 Enantioselective 1,4-addition followed by trapping of zinc enolate by allyl iodides[68b]

3.1.3 Asymmetric Conjugate Addition of Grignard Reagents to Enones

Highly constrained C_1-1,10-bisisoquinoline chiral ligands (+)/(–)-**67** were examined in the enantioselective 1,4-addition of Grignard reagents (R^1MgX) to cyclic enones **193**. The desired 1,4-adducts **194** were obtained in very good yields but with low enantioselectivity (up to 35% ee) (Scheme 38).

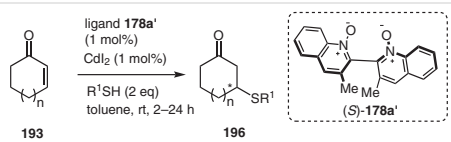


entry	n	ligand (mol%)	Cu cat. (mol%)	R^1	1,4 adduct/ 1,2 adduct	ee 1,4-adduct (%)
1	1	(–)-**67a** (10)	$CuCl_2$ (10)	*n*-Bu	100/0	35 (*S*)
2	0	(+)-**67a'** (15)	$Cu(OTf)_2$ (15)	*i*-Pr	97/3	30 (*R*)

Scheme 38 Grignard reagent conjugate addition to cyclic enones in the presence of copper salts and chiral ligands[99]

3.1.4 Asymmetric Conjugate 1,4-Addition of Thiols to Cyclic Enones

Nakajima and co-workers examined the enantioselective conjugate nucleophilic 1,4-addition of thiols to enones under mild reaction condition, leading to the corresponding sulfides **196** with moderate enantioselectivities (up to 78% ee). This protocol provided the first example of using a cadmium complex in an asymmetric thiol 1,4-addition reaction (Scheme 39).

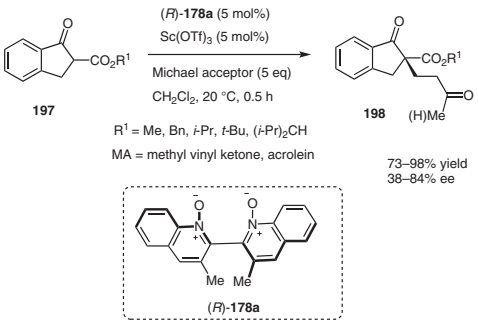


entry	n	R^1	time (h)	yield (%)	ee (%)
1	2	Ph	24	68	61
2	1	Ph	6	96	78 (*S*)
3	1	4-$OMeC_6H_4$	6	91	58 (*S*)

Scheme 39 Enantioselective conjugate 1,4-addition of thiols to enones[96c,d]

3.1.5 Asymmetric Michael Addition Reaction

In 2003, Nakajima et al. studied the catalytic, enantioselective Michael addition of β-keto esters to α,β-unsaturated carbonyl compounds using a chiral biquinoline *N*,*N*′-dioxide–$Sc(OTf)_3$ (*R*)-**178a** complex as catalyst. The Michael adducts **198** were produced in good yields with moderate enantioselectivities (up to 84% ee) (Scheme 40). Electron-donating indanone substrates **197** were tested using 5 mol% quinoline *N*,*N*′-dioxide ligand–$Sc(OTf)_3$.

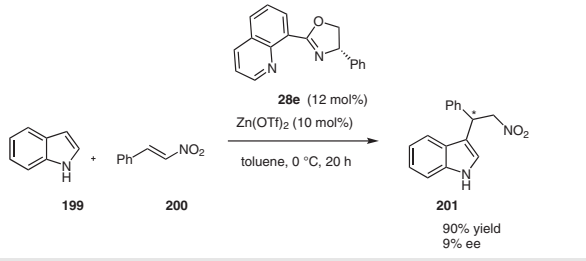


Scheme 40 Enantioselective Michael addition of β-keto esters to methyl vinyl ketone (MVK)[96e,100]

3.1.6 Asymmetric Friedel–Crafts Alkylation

Zhou and co-workers (2006) investigated an efficient asymmetric Friedel–Crafts alkylation of free N–H indoles **199** with nitro compound **200** catalyzed by $Zn(OTf)_2$-oxazoline complexes **28e**. The nitroindole **201** was prepared in

good yield, but very low enantioselectivities (up to 9% ee) were observed in the presence of 12 mol% chiral ligand **28e** and 10 mol% $Zn(OTf)_2$ at 0 °C for 20 h (Scheme 41).

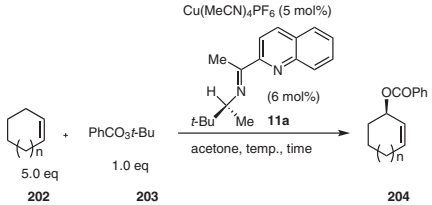


Scheme 41 Asymmetric catalytic Friedel–Crafts alkylation of indole with *trans*-β-nitrostyrene[101]

3.2 Asymmetric Allylic Reactions

3.2.1 Asymmetric Allylic Oxidation

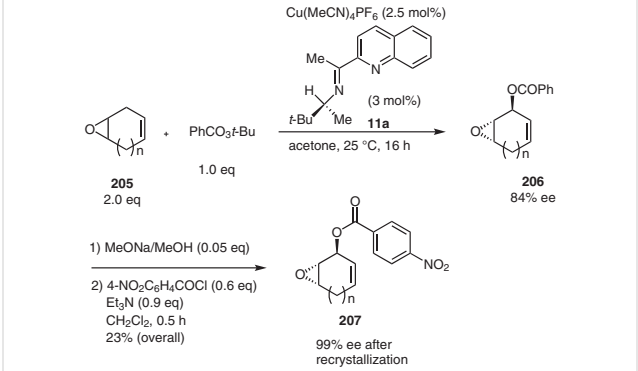
In 2008 Hayashi and co-workers studied the copper (I)-catalyzed enantioselective allylic oxidation of several cyclic olefins with *tert*-butyl perbenzoate ($PhCO_3Bu^t$) enabled by N,N-bidentate Schiff base ligands **11a**, which were effective in conferring high reactivity and moderate-to-good enantioselectivity (up to 84% ee). The authors examined the allylic oxidation of numerous cyclic olefins **202** using a $Cu(CH_3CN)_4PF_6$ and Schiff base ligand system. The results, summarized in Scheme 42, were obtained using a catalytic amount of chiral N,N-bidentate ligand **11a**.



entry	n	temp. (°C)	time (h)	yield (%)	ee (%)
1	0	0	48	70	51 (*R*)
2	1	0	48	89	51 (*R*)
3	2	0	48	51	84 (*R*)
4	3	20	72	41	70 (*R*)

Scheme 42 Enantioselective allylic oxidation of cyclic olefins[69]

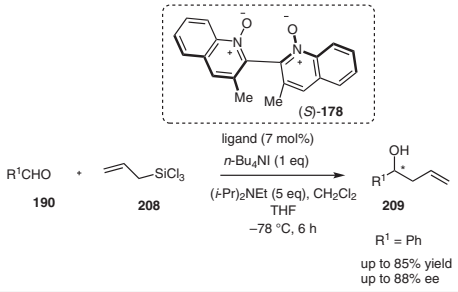
Later, in 2009, Hayashi and co-workers developed an enantioselective desymmetrization by allylic oxidation of 4,5-epoxycyclohex-1-ene **205** in the presence of 3 mol% of chiral N,N-bidentate Schiff base ligand **11a** and 2.5 mol% of $Cu(CH_3CN)_4PF_6$ to afford phenyl epoxide **206** in 84% ee, which was improved to >99% ee after derivatization with 4-nitro benzoyl chloride and recrystallization to give the corresponding nitroaryl epoxide derivatives **207** (Scheme 43).



Scheme 43 Enantioselective allylic oxidation of 4,5-epoxycyclohex-1-ene[102]

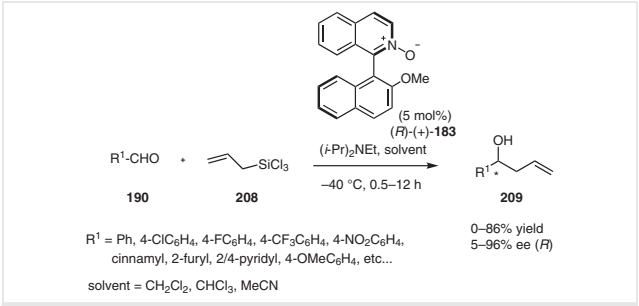
3.2.2 Asymmetric Allylation of Aldehydes with Allylchlorosilanes

In 2002, Malkov, Koćovský and co-workers developed the Sakurai–Hosomi-type allylation of aromatic aldehydes **190** catalyzed by C_2-symmetric 2,2′-biquinoline *N*,*N*′-dioxide (*S*)-**178**, leading to the corresponding chiral alcohol **209** in good enantioselectivities (up to 88% ee) and 85% reaction yield (Scheme 44)



Scheme 44 Sakurai–Hosomi-type allylation of aromatic and heteroaromatic aldehydes[103]

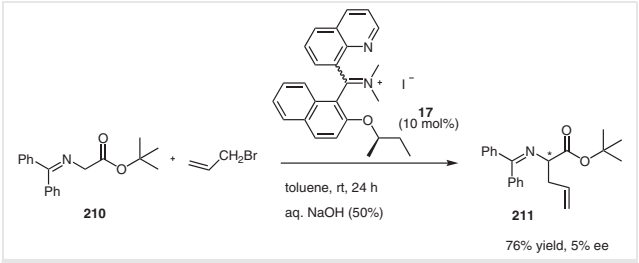
Later, the same group (2003) revealed that the addition of allyltrichlorosilane **208** to aromatic aldehyde **190** in the presence of quinoline *N*-oxide ligand (*R*)-**183** (5 mol%) at –40 °C in DCM for 0.5–12 h, produced the corresponding alcohol derivatives **209** with 5–96% ee and good yields. The aldehyde substrate scope is summarized in Scheme 45.



Scheme 45 Allylation of aldehydes catalyzed by quinoline *N*-oxide ligand[80,96f]

3.2.3 Asymmetric Phase-Transfer Allylic Alkylation

Later, in 2008, Eddine and co-workers reported the phase-transfer-catalyzed asymmetric alkylation of ester **210** with allyl bromide in the presence of 10 mol% of chiral N,N-bidentate Schiff base salt **17** with the use of NaOH, affording the desired compound **211** in good yield and very low enantioselectivity (Scheme 46).



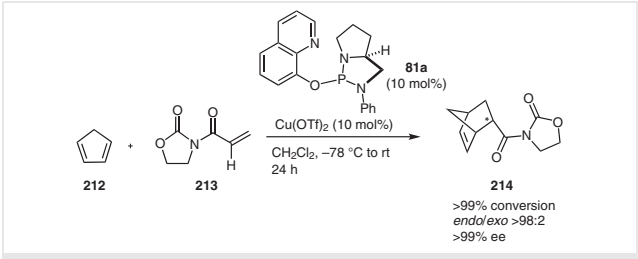
Scheme 46 Allylation of keto-imine under phase-transfer conditions[71]

3.3 Asymmetric Cycloadditions

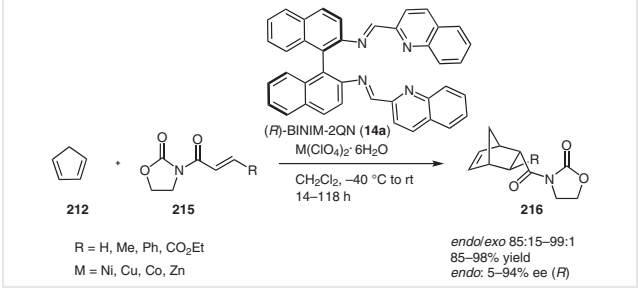
3.3.1 Asymmetric Diels–Alder Reactions

Buono and co-workers (1998) reported the asymmetric Diels–Alder reaction catalyzed by copper-phosphene complexes. The nitrogen-based copper(II) catalyst was prepared by mixing $Cu(OTf)_2$ and chiral quinolinephosphine ligand **81a** in DCM and further used in the Diels–Alder reaction of 3-acryloyloxazolidin-2-one **213** with cyclopentadiene **212**, leading to the corresponding amide product **214** in excellent yields and remarkable enantioselectivities (up to 99%) (Scheme 47).

Subsequently, in 2004, Suga et al. developed an efficient method for Ni(II)-catalyzed asymmetric Diels–Alder reactions of cyclopentadiene **212** and 3-alkenoyl-2-oxazolidinones **215** in the presence of the ligand BINIM-2QN **14a** (Scheme 48). Even loadings down to 1 mol% Ni(II) catalyst promoted Diels–Alder reactions with high conversions and enantioselectivities (*endo*-addition with up to 94% ee).



Scheme 47 Copper-catalyzed asymmetric Diels–Alder reactions of cyclopentadiene with *N*-acyl oxazolidinones[104]

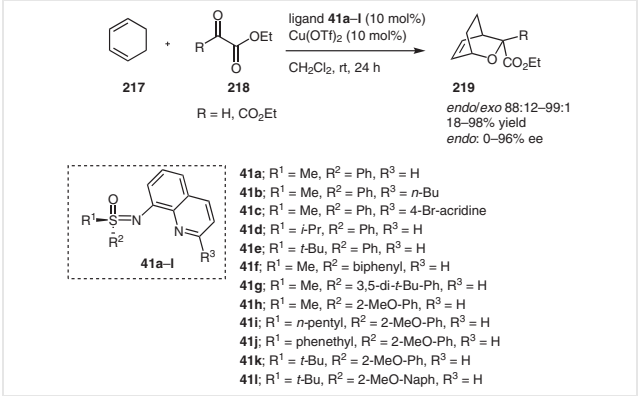


Scheme 48 BINIM-2QN catalyzed asymmetric Diels–Alder reactions of cyclopentadiene with 3-acryloyl-2-oxazolidinone[70a]

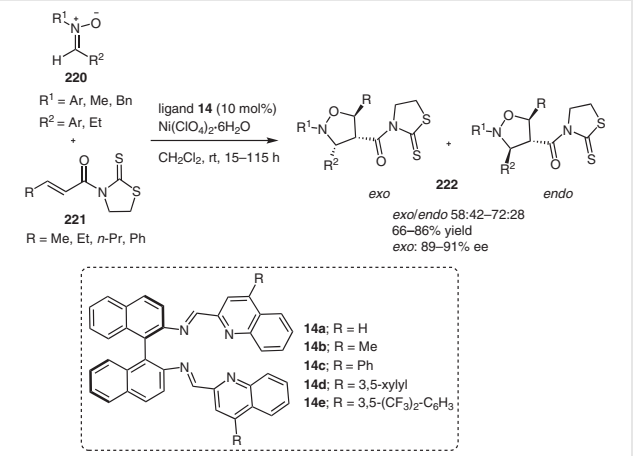
3.3.2 Asymmetric Hetero-Diels–Alder Reactions

Bolm et al. studied the first example of a copper-catalyzed hetero-Diels–Alder reaction of cyclohexa-1,3-diene (**217**) and keto ester **218** in the presence of 10 mol% $Cu(OTf)_2$ and C_1-symmetric sulfoximine ligands **41a–l**, leading to cycloadducts in good yields and high enantioselectivities (up to 96% ee) as shown in Scheme 49.

Asymmetric cycloaddition of nitrones **220** and 3-(2-alkenoyl)-2-thiazolidinethiones **221** using chiral binaphthyldiimine–Ni(II) complexes **14a–e** to afford products in high *exo*-diastereoselectivities and enantioselectivities was reported by Suga et al. in 2005 (Scheme 50).



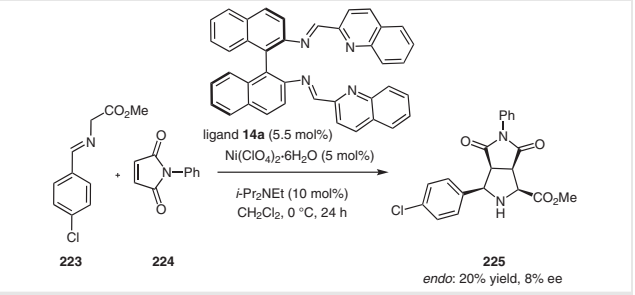
Scheme 49 Enantioselective hetero-Diels–Alder reactions catalyzed by monosulfoximine ligands[76]



Scheme 50 Asymmetric cycloaddition reactions catalyzed by chiral BINIM–Ni(II) complexes[70b]

3.3.3 Asymmetric 1,3-Dipolar Cycloaddition Reactions

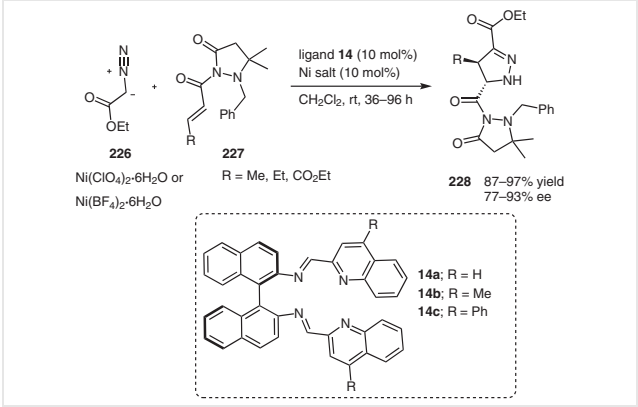
Shi and co-workers reported chiral binaphthalenediimine-Ni(II) complex **14a** as an active catalyst in the 1,3-dipolar cycloaddition reactions of azomethine ylides **223** and 1-phenyl-1*H*-pyrrole-2,5-dione **224** to give the corresponding adducts **225** in very low yields and poor enantiomeric excesses (up to 8%) in Scheme 51.



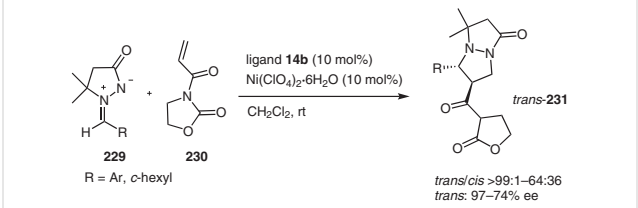
Scheme 51 Enantioselective 1,3-dipolar cycloadditions catalyzed by $Ni(ClO_4)_2{\cdot}6H_2O$ and chiral ligands[70c]

Furthermore, in 2011, Suga et al. demonstrated that BINIM–Ni(II) catalysts **14a–c** were efficient for enantioselective 1,3-dipolar cycloaddition reactions between ethyl diazoacetate **226** and 3-acryloyl-2-oxazolidinones **227** to produce the corresponding adducts **228** in high yields and enantiomeric excesses (up to 93%) as shown in Scheme 52.

The same group had previously reported in 2007 the first example of highly enantioselective 1,3-dipolar cycloaddition reactions between azomethine imines **229** and 3-acryloyl-2-oxazolidinone **230** using 10 mol% of chiral BINIM–Ni(II) complex **14b** (Scheme 53).



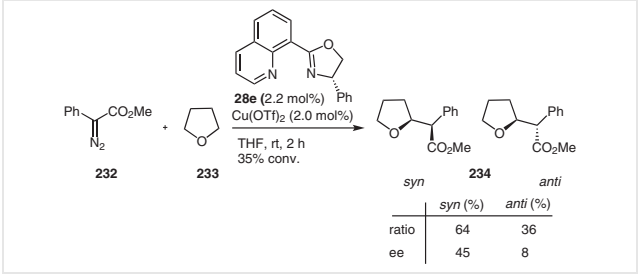
Scheme 52 Reactions of ethyl diazoacetate with 2-(2-alkenoyl)-3-pyrazolidinones catalyzed by (*R*)-BINIM–Ni(II) complexes[105]



Scheme 53 Cycloaddition reactions of azomethine imines with 3-acryloyl-2-oxazolidinone[70d]

3.4 Asymmetric Carbene Insertions

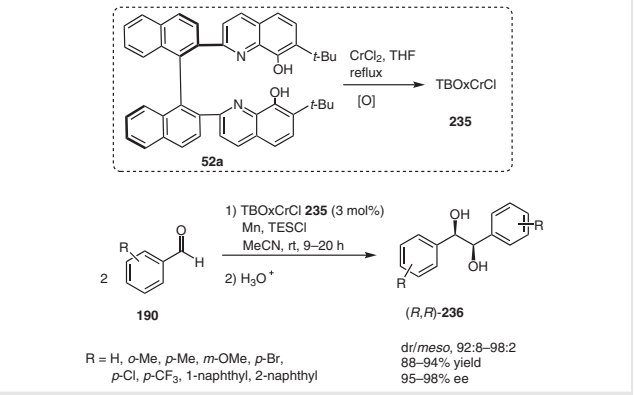
A simple and efficient method for Cu-catalyzed enantioselective C–H carbene insertion between methyl phenyldiazoacetate and THF in the presence of 2.2 mol% of chiral N,N-bidentate Schiff-base ligand **28e** and 2.0 mol% of copper catalyst to afford the corresponding *syn*-product **234** in 45% ee, was reported by Fraile et al. in 2007. Copper salts such as $Cu(OTf)_2$, $CuBr_2$, $Cu(OAc)_2$, CuCl, and $CuSbF_6$ were examined to optimize the reaction and copper triflate furnished better results (Scheme 54).



Scheme 54 Reaction between methyl phenyldiazoacetate and THF catalyzed by oxazole-copper complexes[106]

3.5 Asymmetric Pinacol Couplings

In 2004, Yamamoto and co-workers introduced a new class of chiral tetradentate ligand, TBOx **52a**, as a catalyst for pinacol coupling. Chromium complex TBOxCrCl **235** was shown to be an efficient catalyst for the asymmetric pinacol coupling reactions of both functionalized aromatic and aliphatic aldehydes **190**. With aromatic substrates, the catalyst system was shown to be quite insensitive to changes in steric effects on the substrates as well as to the presence of electron-donating and electron-withdrawing substituents on the aromatic ring, providing high enantiomeric excesses (up to 98%, Scheme 55).



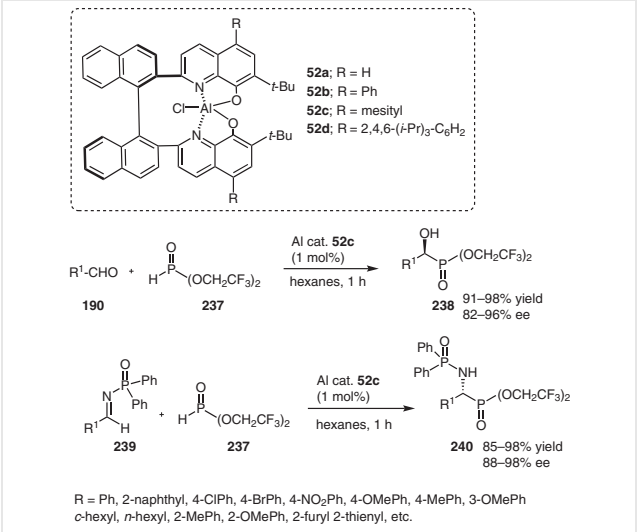
Scheme 55 Pinacol coupling reaction of aromatic aldehydes[78a]

3.6 Asymmetric Pudovik Reactions

The same group in 2008 developed the catalytic enantioselective Pudovik reaction of aldehydes **190** and aldimines **239** with tethered bis(8-quinolinato) (TBOx) aluminum complexes **52a–d**. α-Hydroxy- and α-aminophosphonates **238** and **240** were prepared in high yields and enantioselectivities (96–98% ee) using a low catalyst loading (1 mol%). This was a significant improvement over other catalysts in that they generally required higher catalyst loadings, typically >5 mol% and extended reaction times. The chiral ligand could be easily recovered in high purity after simple purification without loss in either reactivity or selectivity (Scheme 56).

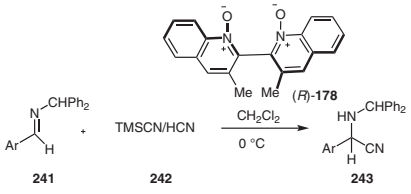
3.7 Asymmetric Strecker Reactions

Feng and co-workers (2003) investigated enantioselective Strecker reactions with trimethylsilyl cyanide (TMSCN) **242** and aryl imines **241** catalyzed by chiral *N*,*N*′-dioxide ligand **178**. These chiral quinoline *N*,*N*-dioxide Lewis base promoters were effectively applied to the chiral synthesis of α-amino aryl nitrile analogues **243** with high enantio-



Scheme 56 Catalytic enantioselective Pudovik reaction of aldehydes/aldimines with tethered bis(8-quinolinato) (TBOx) aluminum complexes[78b]

selectivities (up to 95% ee). Enantiomerically pure products (up to 99% *ee*) were subsequently obtained by recrystallization (Scheme 57).

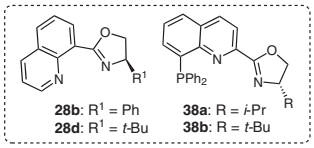


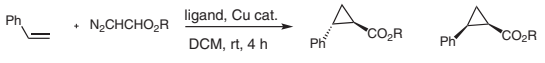
entry	Ar	time (h)	yield (%)	ee (%)
1	2-ClC$_6$H$_4$	96	96	95
2	2-NO$_2$C$_6$H$_4$	96	85	89
3	3-NO$_2$C$_6$H$_4$	96	87	88
4	3-NO$_2$C$_6$H$_4$	96	63	73 (*S*)
5	4-ClC$_6$H$_4$	57	93	68 (*S*)

Scheme 57 Enantioselective Strecker reactions between aldimines and TMSCN[96g,h]

4 Heterogeneous Catalytic Asymmetric Reactions

Fraile, Mayoral and co-workers reported quinoline-based oxazoline ligands, a class of C_1-symmetric chiral ligands, in the enantioselective cyclopropanation of styrene (**244**) with ethyl diazoacetate **245** in DCM at 25 °C, which proceeded with excellent *cis*-selectivity (up to 65%). This result may be synthetically of interest, given that *cis*-cyclopropanes are generally difficult to obtain. The substrate scope is summarized in Scheme 58.



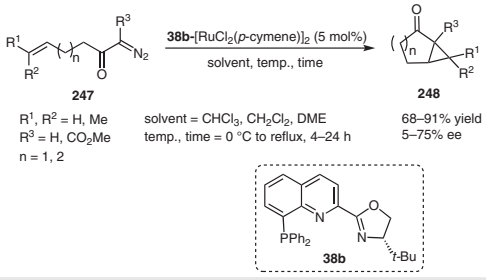


entry	R	catalyst	yield (%)	*trans*/*cis*	*trans* ee (%)	*cis* ee (%)
1	Et	**28d**-Cu(OTf)$_2$	65	68:32	48	28
2	Et	**28b**-Cu(Laponite)	67	14:86	39	30
3	Me	**38b**-[RuCl$_2$(*p*-cymene)]$_2$	81	89:11	28	65
4	Et	**38a**-[RuCl$_2$(*p*-cymene)]$_2$	59	62:38	4	7

Scheme 58 Cyclopropanation reaction between styrene and diazoacetate esters[107]

4.1 Asymmetric Cyclopropanation of Olefins

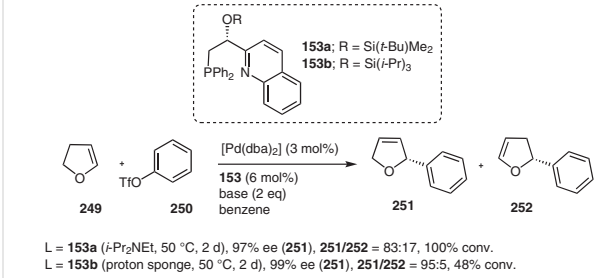
In 1998, Ahn and co-workers studied the Ru(II)-catalyzed intramolecular cyclopropanation of diazo-alkenes **247**. The catalytic chiral system demonstrated good reactivity and stability, and produced high yields with moderate enantioselectivities (Scheme 59).



Scheme 59 Ru(II)-catalyzed asymmetric intramolecular cyclopropanations using a chiral diphenylphosphino(oxazolinyl)quinoline ligand[75a]

4.2 Asymmetric Heck Reactions

In 2004 Pfaltz and co-workers described the generality and utility of ligands **153a**,**b** in palladium-catalyzed enantioselective Heck reactions. The results are summarized in Scheme 60.

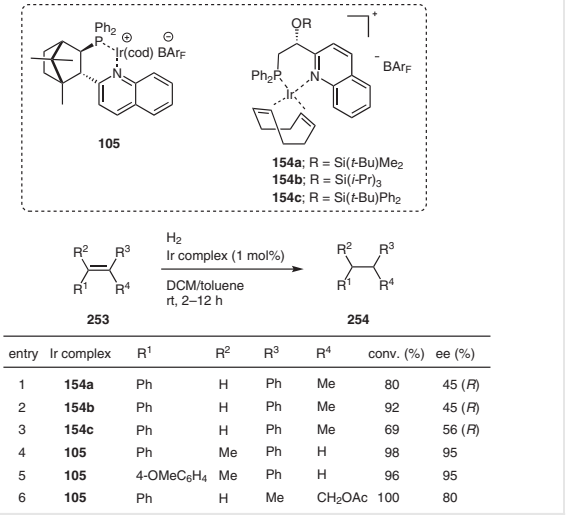


Scheme 60 Enantioselective Heck reaction using chiral quinolyl phosphane ligands[93]

4.3 Asymmetric Hydrogenations

4.3.1 Asymmetric Hydrogenation of Alkenes

P,N-Chiral iridium complexes **154a–c** were efficiently applied to asymmetric hydrogenation of di-substituted alkenes **253** (Scheme 61, entries 1–3), resulting in up to 56% ee, as reported by Pfaltz and co-workers in 2004. The reactivities of the metal complexes are summarized in Scheme 61. In general, phosphinites were excellent in terms of both enantioselectivity and reactivity. Additionally, in 2003, Knochel and co-workers demonstrated that ligand **105** mediated Ir-catalyzed asymmetric hydrogenation reactions of tri-substituted alkenes (Scheme 61, entries 4–6) leading to hydrogenated products with high enantioselectivity (up to 95% ee).



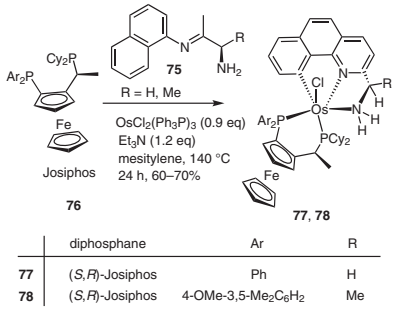
entry	Ir complex	R^1	R^2	R^3	R^4	conv. (%)	ee (%)
1	**154a**	Ph	H	Ph	Me	80	45 (*R*)
2	**154b**	Ph	H	Ph	Me	92	45 (*R*)
3	**154c**	Ph	H	Ph	Me	69	56 (*R*)
4	**105**	Ph	Me	Ph	H	98	95
5	**105**	4-OMeC$_6$H$_4$	Me	Ph	H	96	95
6	**105**	Ph	H	Me	CH_2OAc	100	80

Scheme 61 Iridium-catalyzed hydrogenation of alkenes[88,93]

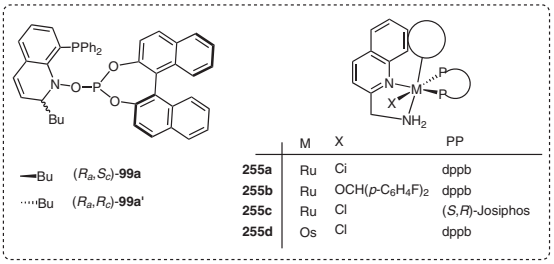
4.3.2 Asymmetric Hydrogenation of Ketones

In 2005, Leitner and co-workers developed a highly enantioselective ruthenium-catalyzed hydrogenation of aromatic ketones with (R_a,S_c)-QUINAPHOS **99a** in the presence of substituted and non-substituted diamines as co-catalysts. The hydrogenation results obtained are summarized in Scheme 62.

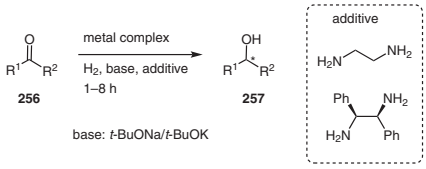
Later, in 2010, Baratta et al. employed ruthenium metal complexes (MC) **255a–d** and osmium complexes **77** and **78** in the presence of *t*-BuOK, to catalyze chemoselective asymmetric hydrogenation (5 atm H_2) of aromatic and aliphatic ketones to give the desired chiral alcohols in high conversions and good selectivities (Scheme 62).



	diphosphane	Ar	R
77	(*S*,*R*)-Josiphos	Ph	H
78	(*S*,*R*)-Josiphos	4-OMe-3,5-Me$_2$C$_6$H$_2$	Me



	M	X	PP
255a	Ru	Cl	dppb
255b	Ru	OCH(*p*-C$_6$H$_4$F)$_2$	dppb
255c	Ru	Cl	(*S*,*R*)-Josiphos
255d	Os	Cl	dppb



entry	M complex	R^1	R^2	conv. (%)	ee (%)
1	**99a**/[RuCl$_2$(C$_6$H$_6$)]$_2$	Ph	Me	99	94 (*R*)
2	**99a**/[RuCl$_2$(C$_6$H$_6$)]$_2$	4-FC$_6$H$_4$	Me	99	94 (*R*)
3	**99a**/[RuCl$_2$(C$_6$H$_6$)]$_2$	4-OMeC$_6$H$_4$	Me	99	94 (*R*)
4	**99a'**/[RuCl$_2$(C$_6$H$_6$)]$_2$	Ph	Me	45	65 (*S*)
5	**255c**	3-OMeC$_6$H$_4$	Me	99	94 (*S*)
6	**255c**	Ph	Et	97	99 (*S*)
7	**77**	Ph	Me	99	86 (*S*)
8	**78**	Ph	Me	97	92 (*S*)

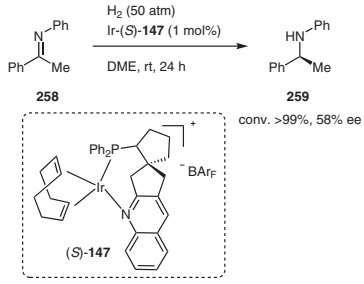
Scheme 62 Asymmetric hydrogenation of ketones in the presence of chiral metal complexes[83a,b,108]

4.3.3 Asymmetric Hydrogenation of Imines

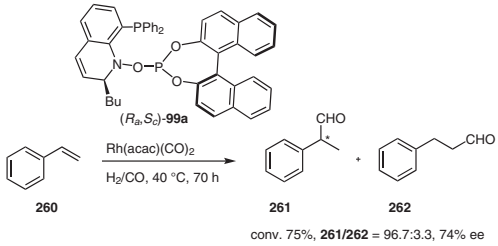
In 2010, Ding and co-workers reported a chiral ligand bearing a *spiro*-scaffold-based Ir-complex **147** and successfully applied it in the enantioselective hydrogenation of aryl-imine **258**, furnishing the corresponding chiral amine with enantioselectivities up to 58% ee (Scheme 63).

4.4 Asymmetric Hydroformylation of Styrene

Rh-catalyzed asymmetric hydroformylation of styrene **260** in the presence of P,N-chiral quinoline ligand **99a** was reported by Leitner and co-workers in 2007. The P,N-chiral Rh complexes were applied to asymmetric hydroformylations of mono-substituted alkenes to give the corresponding product **261** with up to 74% enantiomeric excess, with a linear aldehyde by-product **262** also being observed (Scheme 64).



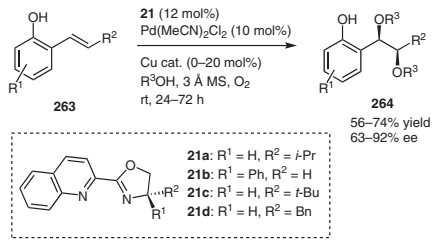
Scheme 63 Asymmetric hydrogenation of imines catalyzed by chiral iridium complex[92b]



Scheme 64 Rhodium-catalyzed hydroformylation of styrene[87b]

4.5 Asymmetric Dialkoxylation of 2-Propenylphenols

Sigman and co-workers (2007) successfully developed a direct O_2-coupled Pd(II)-catalyzed enantioselective dialkoxylation of 2-alkenylphenols by using quinoline oxazoline ligands **21a–d** (Scheme 65). Pd(II)-catalyzed enantioselective dialkoxylation of 2-alkenylphenols **263**, at room temperature for 24–72 h furnished the desired phenol **264** with enantioselectivities up to 92% ee.

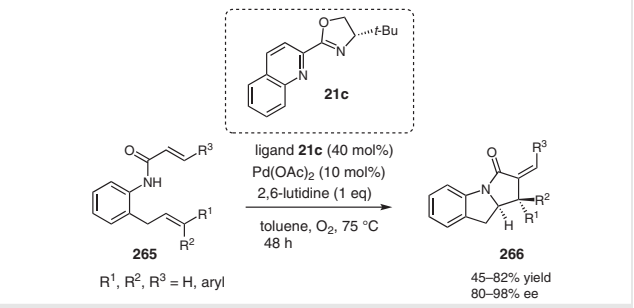


Scheme 65 Scope of Pd(II)-catalyzed enantioselective dialkoxylation[109]

4.6 Asymmetric Cascade Cyclizations

In 2009 Yang and co-workers reported the structurally tunable and an air-stable oxazoline **21c**-Pd catalyst system for the highly enantioselective oxidative cascade intramolecular cyclization reaction of a variety of substituted bis-

olefins **265**, with excellent enantioselectivities (up to 98% ee), good yields and high diastereoselectivities (dr >24:1) (Scheme 66).



Scheme 66 Pd(II)-catalyzed enantioselective cascade cyclization[72c]

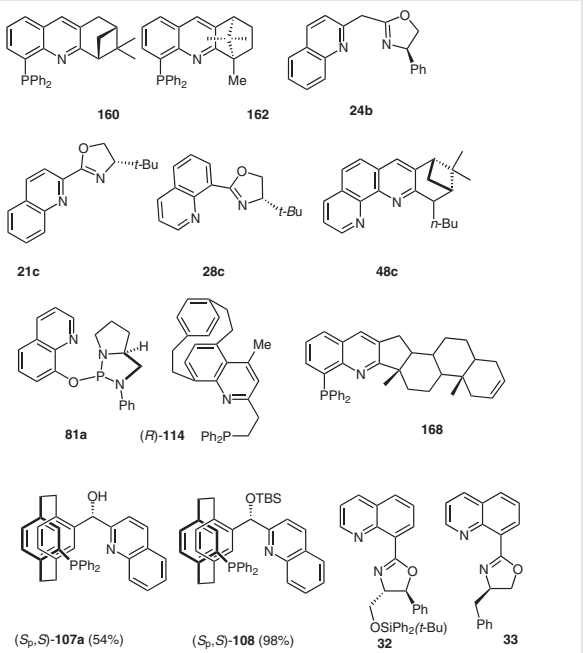
4.7 Asymmetric Allylic Alkylations

Several chiral phosphine-quinoline ligand analogues were found to be good candidates for Pd-catalyzed asymmetric allylic alkylation reactions, as reported by Jiang et al. in 2008. Catalytic allylic alkylation has been demonstrated to be a powerful tool for stereoselective carbon–carbon bond-formation reactions in the presence of palladium-nitrogen ligand systems. Among many quinoline-based ligands designed for this chiral reaction, chiral bi- and tridentate type P,N-ligands have played a significant role owing to their electronic and steric parameters. The reactions were carried out using 1.0–6.4 mol% Pd catalyst and 2.5–12.8 mol% chiral quinoline ligand. The results from a range of ligands are summarized in Scheme 67. Other protocols have been successfully examined for allylic alkylation reactions using various phosphine-quinoline based chiral ligands as outlined in Scheme 67.[72,74,77,84,89,90,94,110]

Trost and co-workers (2002) investigated Mo-catalyzed enantioselective allylic alkylations with sodium dimethyl malonate in the presence of diamide or amine type ligands **62**. Allylic alkylation of ester **270** with sodium dimethyl malonate **271** furnished the corresponding chiral product **272** in low yields but high enantioselectivities (up to 98%) (Scheme 68).

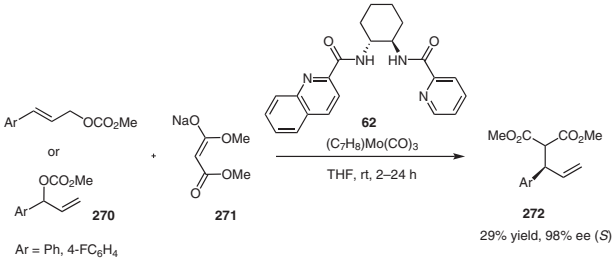
4.8 Asymmetric Alkylation of β-Keto Esters

Buono and co-workers studied the use of the palladium catalyst QUIPHOS **81a** as a chiral ligand in the enantioselective alkylation of β-keto esters **273** with allyl substrate **274**, leading to chiral products with high enantioselectivity (up to 95% ee) depending on the nature of the substrates and specific reaction conditions. In particular, solvents such as THF led to poor enantioselectivity (5–30% ee); whereas the alkylation reaction performed with a five-membered-ring keto ester in DCM at –10 °C gave the desired product **275** in 75% yield and high enantiomeric excess (95% ee) (Scheme 69).

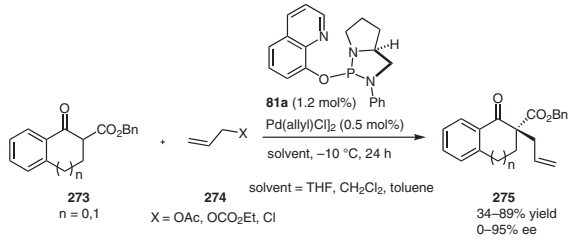


entry	ligand (mol%)	Pd cat. (mol%)	additive	yield (%)	ee (%)
1	**160–168** (10)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5)	BSA	90–95	69–74 (*S*)
2	**24b** (10)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5)	BSA	88	78 (*S*)
3	**21c** (10)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5)	BSA	93	92 (*S*)
4	**28c** (10)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5)	BSA	94	77 (*S*)
5	**48c** (10)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5)	BSA	93	84 (*R*)
6	**81a**	$[Pd(\pi\text{-allyl})Cl]_2$	–	>90	85
7	**114** (5)	$[Pd(\pi\text{-allyl})Cl]_2$ (1.0)	BSA	60[a]	58 (*S*)
8	**107** (6.0)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.0)	BSA	98	96 (*R*)
9	**108** (6.0)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.0)	BSA	67	96 (*R*)
10	**32** (2.5)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.0)	BSA	85	65 (*S*)
11	**33** (2.5)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.0)	BSA	98	69 (*R*)

Scheme 67 Asymmetric allylic alkylation (AAA) of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[72a,b,74,77a,b,84c,89,90,94a,b,110]



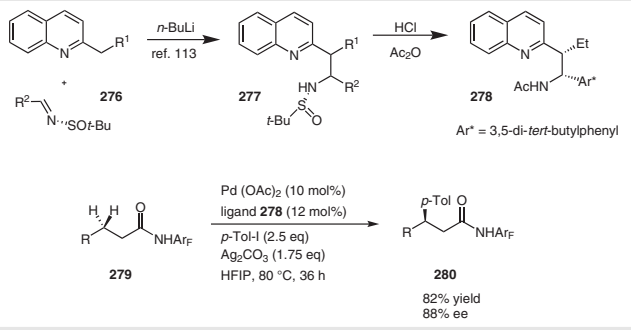
Scheme 68 Mo-catalyzed asymmetric allylic alkylation with sodium dimethyl malonate[111]



Scheme 69 Palladium-catalyzed asymmetric allylic alkylation of β-keto esters[112]

4.9 Asymmetric C–H Bond Arylation Reactions

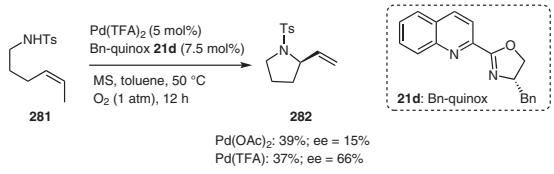
In 2019, Yu, Bertrand and co-workers studied the C–C bond coupling reaction reactivity and selectivity of quinoline-based amine ligands **278** in palladium-catalyzed β-C(sp^3)–H bond asymmetric arylation reactions. They disclosed the ligand synthesis, isolation, and detailed characterization of APAPy (acetyl-protected aminoethylpyridine) and APAQ (acetyl-protected aminoalkyl quinoline) ligands (Scheme 70).[113]



Scheme 70 Palladium catalyzed C–H bond arylation reactions[113]

4.10 Intramolecular Aerobic Oxidative Amination of Alkenes

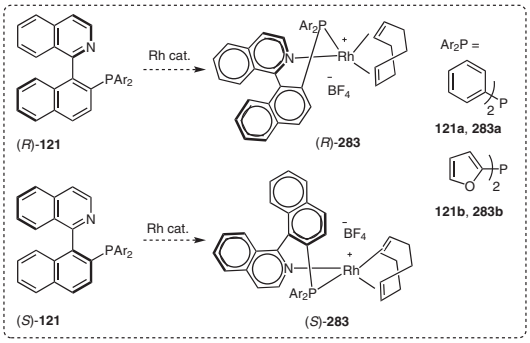
Stahl and co-workers (2011) described the enantioselective aerobic oxidative amination of cyclic alkenes **281** in the presence of chiral quinoline-oxazoline ligand **21d**. The intramolecular addition of alkenes with a protected amine in the presence of Pd catalyst 5 mol% and chiral quinoline-oxazoline ligands **21d** (7.5 mol%) gave the corresponding product in low yield but with up to 66% enantiomeric excess (Scheme 71).



Scheme 71 Enantioselective oxidative amination employing a quinoline oxazoline ligand[114]

4.11 Asymmetric Oxidative Hydroboration of Alkenes

Brown and co-workers systematically studied the asymmetric hydroboration/oxidation of vinyl-arenes **284** at ambient temperature in the presence of rhodium complexes of 1,1′-(2-diarylphosphino-1-naphthyl)isoquinolines. Vinylarene substrates **284** bearing electron-withdrawing or -donating groups on the aryl ring led to the desired alcohol **286** with enantioselectivities up to 94% ee in the most favorable cases. The enantioselectivity of this specific conversion is moderately sensitive to the structure of the phosphorus type ligand, with the difurylphosphino ligand **121b** furnishing excellent results using an electron-deficient styrene **284**. Diphenylphosphino-ligand **121a** showed the best results using an electron-donating alkene substrate (Scheme 72).[75,91]



entry	Ar	ligand	yield (%)	ee (%)
1	2,4-$Me_2C_6H_3$	(*R*)-**121a**	78	94 (*R*)
2	4-$OEtC_6H_4$	(*R*)-**121a**	82	94 (*R*)
3	3-ClC_6H_4	(*S*)-**121b**	75	89 (*S*)
4	2-naphthyl	(*R*)-**121a**	80	89 (*R*)
5	Ph	(*S*)-**121a**	71	91 (*S*)
6	Ph	(*R*)-**121a**	70	67 (*R*)

Scheme 72 Enantioselective oxidative hydroboration of electron-rich and electron-deficient vinylarenes[75b,91b,c]

5 Conclusions

This review compiles the advancement in the synthesis of chiral ligands containing quinoline motifs and their catalytic asymmetric reactions. The potential of chiral quinolines and their metal complexes has been demonstrated in numerous catalytic asymmetric reactions such as the addition of dialkylzinc to aldehydes and enones, addition of Grignard reagents to enones, Michael addition reactions, Friedel–Crafts alkylations, aldol lactonizations, allylic oxidations, Diels–Alder reactions, Pudovik reactions, pinacol coupling reactions, Strecker reactions, cyclopropanations of olefins, Heck reactions, hydrogenation reactions, cascade cyclizations, allylic alkylations, C–H bond arylation reactions, and oxidative hydroborations. We believe that this review will direct researchers to develop further methodologies for the synthesis of chiral quinoline-based ligands and to explore their new applications in asymmetric catalysis.

Conflict of Interest

The authors declare no conflict of interest.

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