Non-Symmetrically Substituted 1,1′-Binaphthyls in Enantioselective Catalysis[⊥]

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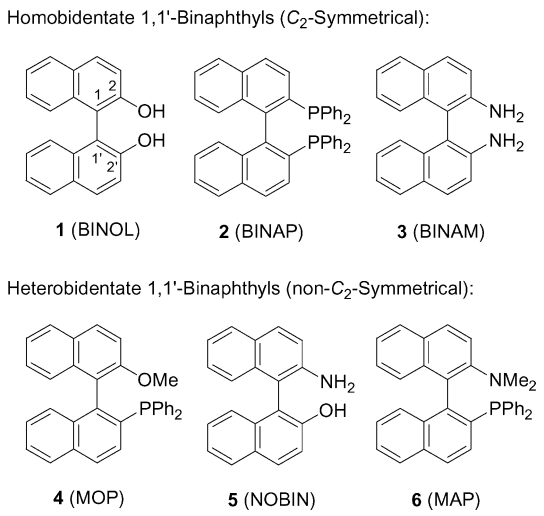
I. Introduction

Axial chirality[1] was predicted by van't Hoff in his historical paper,[1,2] which laid the foundations of stereochemistry.[3] BINOL (**1**), one of the best known representatives of axially chiral molecules (Chart 1),

Chart 1



was first prepared as a racemate in 1873,[4] and later as an optically active compound,[5,6] whose absolute configuration was determined in 1971.[5] In 1979, Noyori showed BINOL (**1**) to be a superb chiral ligand in the stoichiometric reduction of ketones with $LiAlH_4$, giving the corresponding alcohols in ≤99% ee.[7] Soon afterward, Noyori demonstrated that BINAP (**2**) can serve as a chiral version of Ph_3P in Ru- and Rh-catalyzed asymmetric hydrogenations and allylic hydrogen shifts,[8,9] which opened the gates for the advent of 2,2′-di-substituted 1,1′-binaphthyls as chiral ligands in transition metal-catalyzed asymmetric reactions.

The unparalleled success of BINAP (**2**) and related diphosphines stimulated intensive research worldwide, which gradually led to the creation of the cult of C_2-symmetrical homo-bi-dentate ligands. As a result, numerous BINAP analogues and other binaphthyl derivatives (e.g., **3**) have been synthesized since the mid-1980s and tested as chiral ligands in a variety of transition metal-catalyzed reactions,[9,10]

[⊥] Dedicated to Dr. Vladimír Hanuš on the occasion of his 80th birthday.

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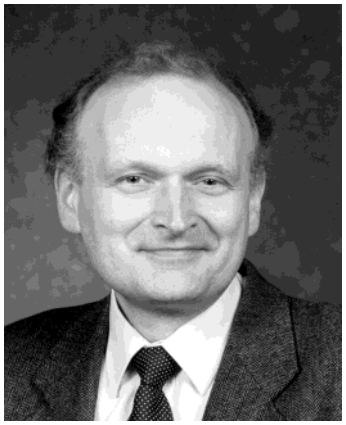
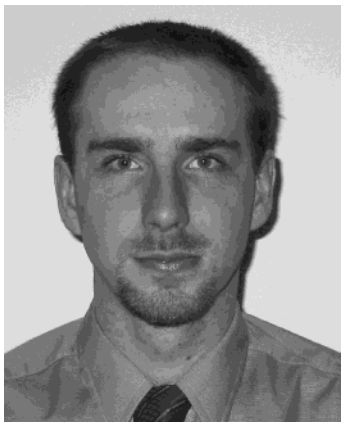


Pavel Kočovský was born in 1951 in Rychnov nad Kněžnou, Czechoslovakia (now Czech Republic), and, in the same year, the family moved to Prague, where he was raised and educated. He received an M.Sc. (first class) in 1974 from the Technical University, Prague, where he did his diploma work with Prof. O. Červinka in the area of asymmetric reactions. He obtained a Ph.D. in 1977 from the Czechoslovak Academy of Sciences, Institute of Organic Chemistry and Biochemistry, Prague, where he worked on steroid chemistry under the guidance of Dr. V. Černý and Prof. F. Šorm. He was then appointed to his first academic position at the same Institute, and stayed for another 12years. During this period, he also taught various advanced courses at Charles University, Prague. In 1983, he obtained permission to temporarily leave Czechoslovakia and joined Prof. J. E. McMurry at Cornell University, Ithaca, NY, as a research associate (1983–84). He returned to his position in Prague in 1984 and later spent a sabbatical year with Prof. J.-E. Bäckvall at the University of Uppsala, Sweden (1989–1990). In January 1991, he emigrated to the U.K. and started a new academic career, first at the University of Leicester, where he spent almost nine years, obtained a D.Sc. (1993), and rose in the ranks to full professor. In 1999 he moved to the University of Glasgow as the Sir William Ramsay Professor of Chemistry. His research interests span organic and organometallic stereochemistry, asymmetric catalysis, reaction mechanisms, organic synthesis, and electrochemical sensors for chiral molecules.



Stěpán Vyskočil was born in 1971 in Poříčí nad Sázavou, a small town near Prague, Czechoslovakia (now Czech Republic). He received an M.Sc. (first class) in 1994 from Charles University, Prague, where he did his diploma work with Dr. M. Smrčina in the area of chiral binaphthyls and won the Rhône-Poulenc Prize for the best diploma thesis of the year. He then joined the graduate school of Charles University, worked under the supervision by Dr. M. Smrčina and Prof. P. Kočovský, and spent a year at the University of Leicester, U.K. (with Prof. Kočovský), as part of his training. He obtained his Ph.D. in 1999 and was subsequently appointed assistant professor at Charles University, Prague. He spent a year at the University of Glasgow with Prof. P. Kočovský as a NATO Fellow (2000–2001), resumed his position in Prague, and in 2002 joined Prof. K. C. Nicolaou at the Scripps Research Institute, La Jolla, CA, as a research associate. In 2002 he became a recipient of the Alfred Bader Award for his work in binaphthyl chemistry. His research is focused on transition metal-catalyzed asymmetric reactions, development of new chiral ligands, and, more recently, total synthesis of natural products.

Martin Smrčina was born in 1961 in Ústí nad Labem, Czechoslovakia (now Czech Republic), and, when he was seven years old, the family moved to Prague, where he was raised and educated. He received an M.Sc. (first class) in 1985 from Charles University, Prague, where he did his diploma work with Prof. M. Procházka. He then joined the graduate school of Charles University and worked independently in the area of chiral binaphthyls, with occasional guidance (rather than supervision) by Dr. V. Hanuš and Dr. P. Kočovský. He received a Ph.D. in 1992 and was immediately appointed assistant professor at Charles University. He then did postdoctoral work with Prof. J. E. McMurry at Cornell University, Ithaca, NY (1993–1995), and returned to Prague to resume his position. In 1995 he received the Alfred Bader Award for his achievements in the chemistry of binaphthyls. In 1996, he emigrated to the United States and worked first as a research associate at the National Cancer Institute, Frederick, MD. In 1997 he moved to Aventis (formerly Selectide), Tucson, AZ, where he is now a group leader. His research interests include combinatorial chemistry, asymmetric reactions, reaction mechanisms, and mass spectrometry.

some of which attained incredibly high efficiency in terms of enantioselectivity, catalyst loading, and turnovers.[8h,j]

Despite the general inclination of the chemical community toward the central dogma of homo-bi-dentate C_2-symmetrical ligands, such as binaphthyls **1**−**3**, several groups contemplated a different approach, namely the development of potentially hetero-bi-dentate binaphthyls (i.e., with non-identical coordinating groups), lacking the notorious C_2 symmetry. First, Hayashi synthesized the C_1-symmetrical methoxyphosphine MOP (**4**)[11] in 1991, and his efforts were paralleled by the present authors, who introduced the amino phenol NOBIN (**5**) in 1991[12−15] and the amino phosphine MAP (**6**) in 1998.[16]

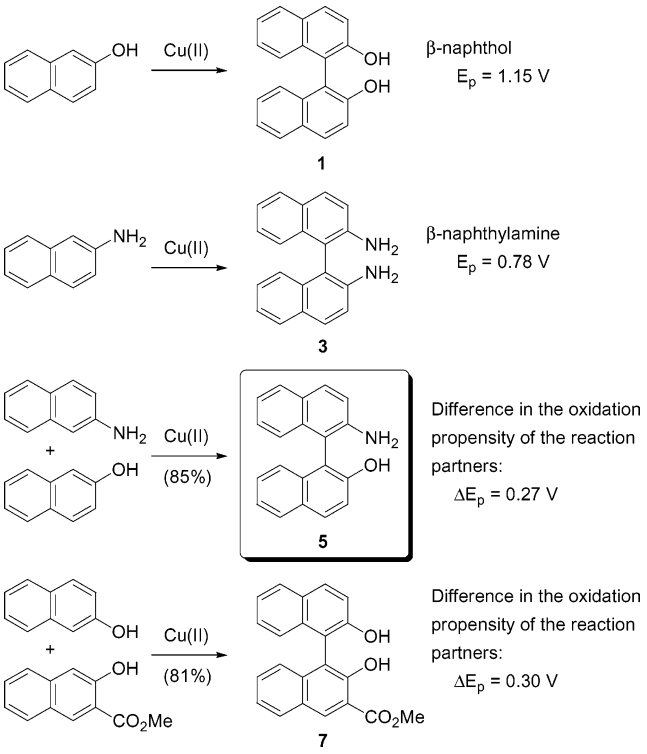
This review deals with 1,1′-binaphthyls having non-identical substituents in positions 2,2′, 8,8′, and 2,8′. Those with identical 2,2′-substituents and an additional group in the 3-position are not covered. Analogous non-binaphthyls, e.g., biphenyls and phenylnaphthyl derivatives, are mentioned only if they are closely related to their binaphthyl relatives. However, heterocyclic analogues of 1,1′-binaphthyls, in which one of the 2-substituents is replaced by heterocyclic nitrogen (as in QUINAP), are fully covered here. The literature coverage ends at the end of 2002; several more recent references were added just prior to publication.

II. General Strategies for the Synthesis of Non-Symmetrically Substituted 1,1′-Binaphthyls

A. Oxidative Cross-Coupling

The synthesis of BINOL (**1**) is straightforward, since mild oxidizing agents, such as Cu(II),[6,14,17] Fe-

Scheme 1

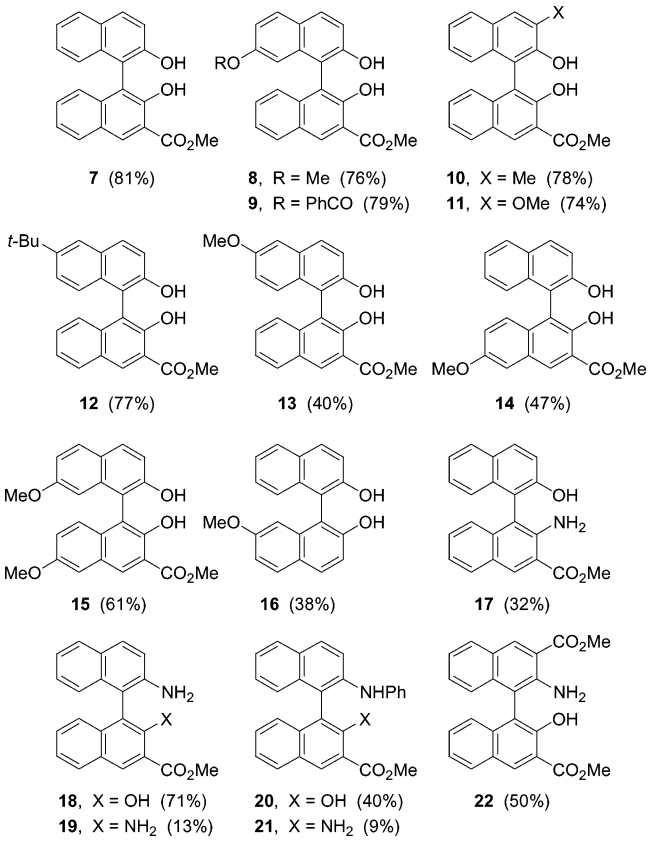


(III),[18] and Mn(III),[19] effect high-yielding, stoichiometric oxidative coupling of β-naphthol (Scheme 1). Similar coupling of β-naphthylamine leads to BINAM (**3**).[12,13] More recently, catalytic coupling reactions with Cu,[20] V,[21] and Ru[22] complexes have also been developed with oxygen as the terminal oxidant. In 1991, we reported that equimolar mixtures of β-naphthol and β-naphthylamine undergo a very selective cross-coupling to afford NOBIN (**5**); under optimized conditions ($CuCl_2$, *t*-$BuNH_2$, MeOH, room temperature, 48 h), the formation of homo-coupled products (i.e., **1** and **3**) is reduced to 2−3% each, while NOBIN (**5**) can be isolated in up to 85% yield.[12−15] At the time of this observation, only two other examples of preferred cross-coupling had been known, namely the synthesis of **7**[23] (81%)[14,24] from its components (Scheme 1) and the coupling of 9-phenanthrol with 3-(methoxy)methyleneoxy-2-naphthol, which afforded the cross-coupled product in 67% yield.[25]

Further investigation led us to the formulation of a model hypothesis, according to which the cross-coupling is favored for those coupling partners which have sufficiently different redox potentials (Scheme 1).[15] In this instance (i.e., if $\Delta E_p \geq 0.25$ V), one partner is preferentially oxidized and the intermediate thus generated is captured by the species with higher redox potential;[15] this condition is met, for instance, in the coupling that leads to binaphthyls **5**, **7**−**12**, **14**, **15**, **18**, and **22** (Chart 2).[15,23d] On the other hand, when the redox potentials of the individual partners are similar, as in the case of the attempted synthesis of **13**, **16**, **17**, and **19**−**21**, mixtures are formed.[15,23d,26,27]

When complexes of Cu(II) with chiral amines, such as phenethylamine or sparteine, were used as oxidants, the unsymmetrically substituted binaphthyls

Chart 2. Products of Selective Oxidative Cross-Coupling



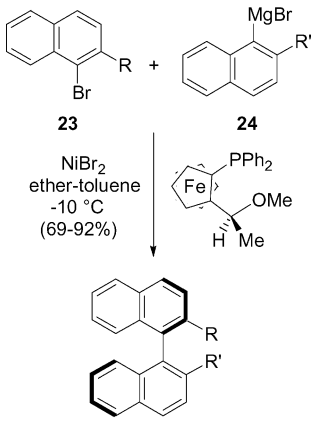
were obtained in enantiomerically enriched forms, showing that Cu must be coordinated to at least one reactive species during the reaction.[13,14] It is noteworthy that three different mechanisms for enantioselection have been found to operate in these oxidative couplings: (a) asymmetric transformation of the second kind,[28] identified for the formation of BINOL (**1**) (with ≤100% ee);[6,14,29] (b) stereoselective crystallization of the Cu−amine−product complex from the reaction mixture, typical for NOBIN (**5**) (with 46% ee);[13,14] and (c) genuine asymmetric coupling, as in the case of **7** (71% ee).[14]

An improved, practical synthesis of NOBIN (**5**) via stoichiometric oxidative cross-coupling with $FeCl_3$ in a heterogeneous system was reported by Ding:[30] according to his protocol, a two-component molecular crystal, obtained by co-crystallization of β-naphthol and β-naphthylamine from MeOH−Me_2CO (1:1),[31] was added as a solid to an aqueous solution of $FeCl_3$, and the resulting heterogeneous mixture was stirred at 55 °C for 6 h. Although both the starting materials and the product are only sparingly soluble, even in boiling water, the coupling did indeed occur (70%), which led Ding to the conclusion that the selective cross-coupling originated from the orientation of the partner molecules in the molecular crystal.[30,31] The latter hypothesis was challenged by us since we had found that, in the liquid−liquid-phase system (CH_2Cl_2−water), where molecular pre-orientation was excluded, $FeCl_3$ exhibited similar selectivity (at room temperature) as in the solid−liquid system (at 55 °C).[32]

B. Metal-Mediated Cross-Coupling

The nickel-catalyzed coupling of aryl halides with aryl Grignard reagents (Kumada coupling) is an obvious choice for the synthesis of the cross-coupled 1,1′-binaphthyls.[33] Thus, for example, the reaction of substituted 1-bromonaphthalenes (**23**) with 2-methyl-1-naphthylmagnesium bromide (**24**, R = Me), catalyzed by nickel, afforded the corresponding cross-coupled products **25** in high yields (Scheme 2). The

Scheme 2

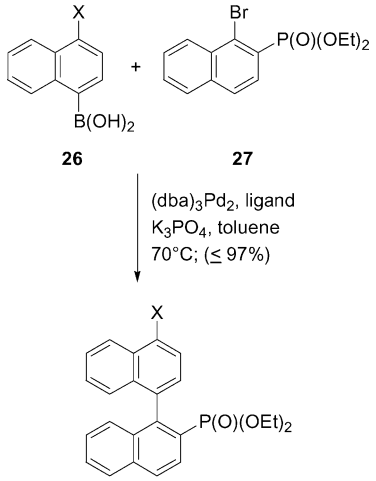


25a, R, R' = Me (95% ee)
25b, R = Me, R' = H (83% ee)
25c, R = Et, R' = H (77% ee)

latter reactions can also be carried out in an asymmetric version using chiral ferrocene phosphines as ligands. With (*S*,*R*)-PPFOMe, the unsymmetrically substituted binaphthyls **25b** and **25c** were obtained with 83 and 77% ee, respectively. Better results were arrived at in the case of C_2-symmetrical products (e.g., **25a**, up to 95% ee).[34]

More recently, Suzuki−Miyaura coupling (Scheme 3) has been developed as an alternative method for

Scheme 3

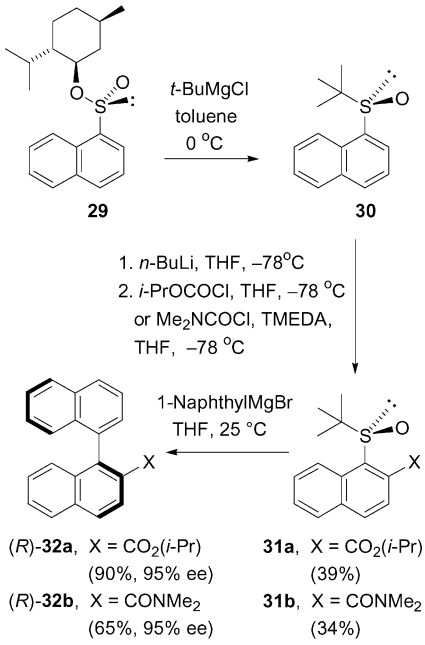


28a, X = H
28b, X = OMe

the synthesis of cross-coupled 1,1′-binaphthyls, such as **28**.[35,36] Its asymmetric version will be discussed in connection with the application of MAP ligands[35,36] (see section III.D). In the (racemic) synthesis of 2,8′-di-substituted 1,1′-binaphthyls, Suzuki−Miyaura coupling was employed as a key step (vide infra).[37]

A different approach relies on the chemistry of chiral sulfoxides (Scheme 4). Here, enantiopure sul-

Scheme 4



(*R*)-**32a**, X = CO_2(*i*-Pr) (90%, 95% ee)
(*R*)-**32b**, X = $CONMe_2$ (65%, 95% ee)
31a, X = CO_2(*i*-Pr) (39%)
31b, X = $CONMe_2$ (34%)

foxide **30**, prepared from menthyl sulfinate **29** on reaction with *t*-BuMgCl, was first *o*-lithiated with *n*-BuLi, and the intermediate organometallic species was quenched with either *i*-PrOCOCl or Me_2NCOCl to afford carboxylic derivatives **31a**,**b**. In the crucial step, the latter sulfoxides were reacted with α-naphthylmagnesium bromide to afford binaphthyls **32a**,**b** (both in 95% ee).[38]

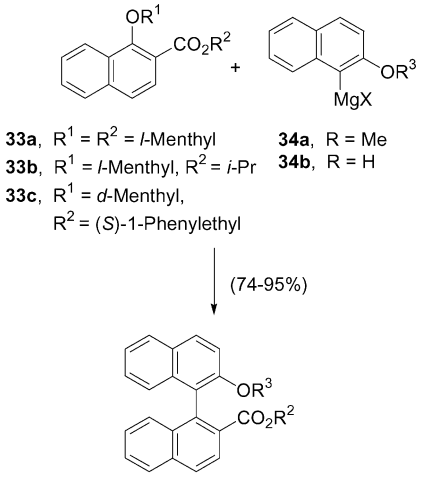
C. Synthesis via Nucleophilic Aromatic Substitution

Nucleophilic aromatic substitution of the alkoxy group in 1-alkoxy-2-naphthoic acid derivatives **33** with Grignard reagents **34** constitutes a general method for the preparation of substituted 1,1′-binaphthyl-2-carboxylic acid derivatives **35** (Scheme 5).[39−43] High levels of asymmetric induction (≤98% de) were obtained when chiral alkoxy substituents in **33** (e.g., menthyloxy) were used as chiral auxiliaries.[39] By contrast, chiral alkyl esters[39] or oxazolines[41] exhibited only moderate stereoselectivities. A similar strategy has been employed in the synthesis of biphenyl derivatives.[44] Substituted 2-sulfonyl-1,1′-binaphthyls were also prepared by this method, starting from 2-sulfonyl-1-methoxynaphthalenes.[45]

D. Selective Modification of the Substituents in the Symmetrically Substituted 1,1′-Binaphthyls

Substituent modification in the symmetrically substituted 2,2′-bifunctional 1,1′-binaphthyls usually leads to a mixture of mono- and bis-modified products. Thus, acylation of BINOL (**1**) can be controlled to give preferentially the mono-acyl derivatives[46] **36**

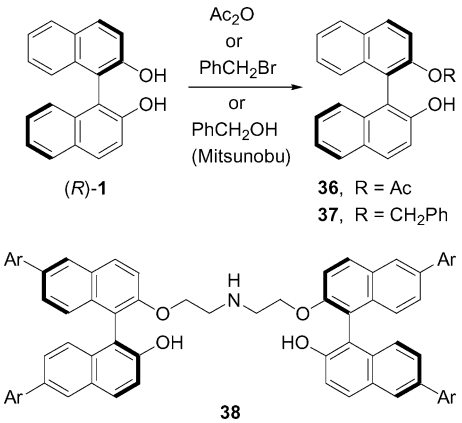
Scheme 5



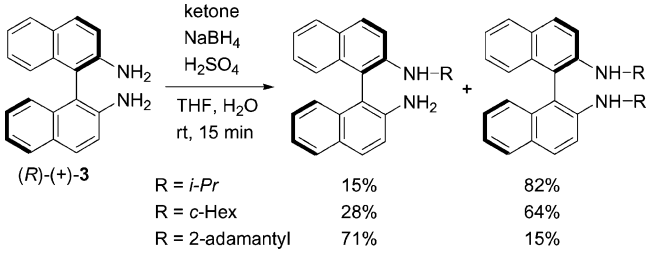
(86%)[46g,h] (Scheme 6).[46] Bulky acylating agents exhibit a slightly higher preference for the formation of mono-esters.[46] Benzylation of BINOL (**1**) with benzyl bromide has been shown to give the mono-substituted derivative **37** in 66% yield,[47] whereas Mitsunobu reaction with benzyl alcohol furnished the same product in 84% yield;[48] no di-substituted product was detected in the latter case.[48a] In several instances, when bulky substituents were being introduced, almost exclusive formation of the mono-substituted derivative was observed.[48] Non-symmetrical crown ethers and other derivatives have been synthesized by mono-alkylation, followed by further functional group manipulation.[48b−e] Dimeric derivatives **38** have been developed as fluorescent sensors for mandelic acid.[48e]

In the reductive alkylation of BINAM (**3**) with ketones, the ratios of mono- and di-substituted derivatives increases with the increasing bulk of the incoming substituent (Scheme 7). Thus, for example, with acetone, cyclohexanone, and 2-adamantone, the corresponding mono-substituted products were obtained in 15, 28, and 71% yield, respectively (under the conditions maximizing the yield of the bis-alkylated product).[49,50]

Scheme 6



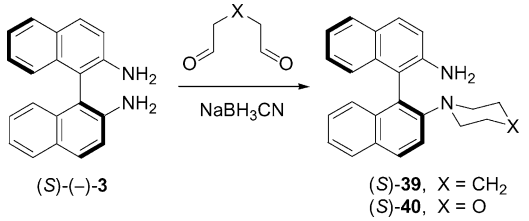
Scheme 7[a]



[a] Ketone = acetone, cyclohexanone, or 2-adamantanone.

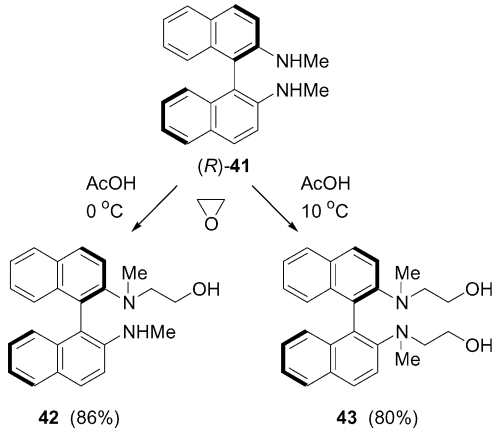
Reductive alkylation of BINAM (**3**) with glutaraldehyde or 3-oxapentadienal and $NaBH_3CN$ has been reported to afford mainly the mono-functionalized products **39** and **40**, respectively (Scheme 8).[51] On the other hand, with an excess of glutaric dialdehyde and $NaBH_4$, the corresponding di-functionalized product was obtained (98%).[49] The C_1-symmetrical diamines **39** and **40** were employed in a stoichiometric synthesis of mevalonic acid (58% ee).[51]

Scheme 8



Reaction of the secondary bis-amine **41** with ethylene oxide can be directed toward mono- or bis-substituted product **42** and **43**, respectively, by controlling the reaction temperature (Scheme 9).[52]

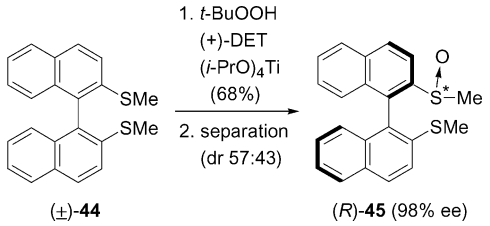
Scheme 9



Asymmetric oxidation of racemic bis-thioether **44** with *t*-BuOOH, (+)-diethyl tartrate, and $(i\text{-PrO})_4Ti$ afforded a 57:43 mixture of diastereoisomeric mono-sulfoxides **45** (68%), ≥98% ee each, separated by chromatography (Scheme 10).[53]

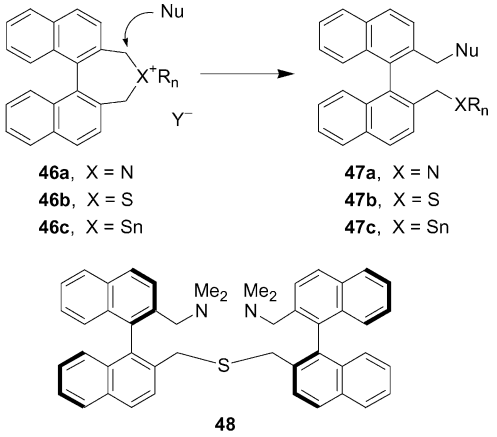
Selective ring-opening of the C_2-symmetrical azepinium ions **46a** and their S and Sn analogues **46b** and **46c** with nucleophiles (Scheme 11) constitutes a general method for the synthesis of binaphthyls **47a−c**, with the heteroatom insulated from the aromatic ring by a methylene group.[54−58] This high-yielding ring-opening with various nucleophiles is

Scheme 10



(±)-**44** (*R*)-**45** (98% ee)

Scheme 11[a]



46a, X = N **47a**, X = N
46b, X = S **47b**, X = S
46c, X = Sn **47c**, X = Sn

48

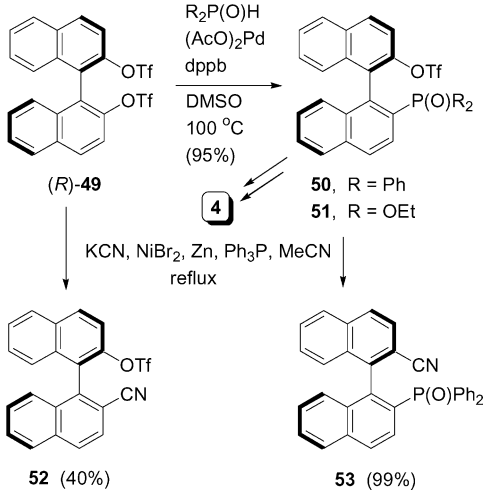
[a] Nu = HNR′R″, N_3^-, Ph_3P, BuS^-, $PhSe^-$, AcO^-, CN^-.

general and paves the way to a variety of hetero-disubstituted binaphthyls **47**. In the case of cyclic sulfide **46b**, attack at the external alkyl may prevail, depending on various factors.[57] Interestingly, reaction of dimethylammonium bromide **46a** ($X^+R_n = N^+Me_2$) with Na_2S afforded sulfide **48** rather than the expected mercaptane.[56]

E. Selective Replacement of the Substituents in the Symmetrically Substituted 1,1′-Binaphthyls

Morgans has reported on the selective mono-phosphinylation of BINOL bis-triflate (−)-**49** that afforded phosphine oxide **50** (65%), contaminated by the corresponding product of reduction (20%).[59] The latter reduction was considerably suppressed (to 11%) in the case of the analogous phosphate **51**, which was obtained in 77% yield (Scheme 12). This protocol was further improved by Hayashi,[11] who changed the

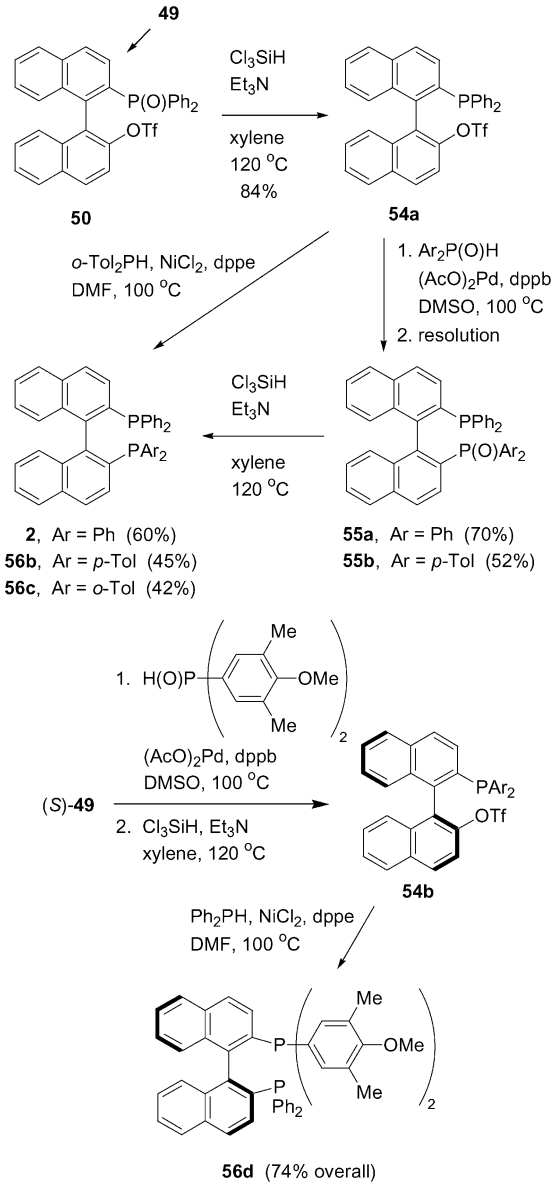
Scheme 12



(*R*)-**49** **50**, R = Ph
51, R = OEt

52 (40%) **53** (99%)

Scheme 13



56d (74% overall)

ligand (from dppp to dppb), increased the reaction temperature (from 80 to 100 °C), and obtained **50** in 95% yield. Phosphine oxide **50** was then used as a key intermediate in the synthesis of a series of MOP ligands (**4**), which involved reduction with Cl_3SiH (see section II.J.2). By contrast, Ni-catalyzed coupling of bis-triflate **49** with Ar_2PH[60a,b] or Ph_2PCl[60c] occurs at both positions, giving BINAP and its congeners.[60]

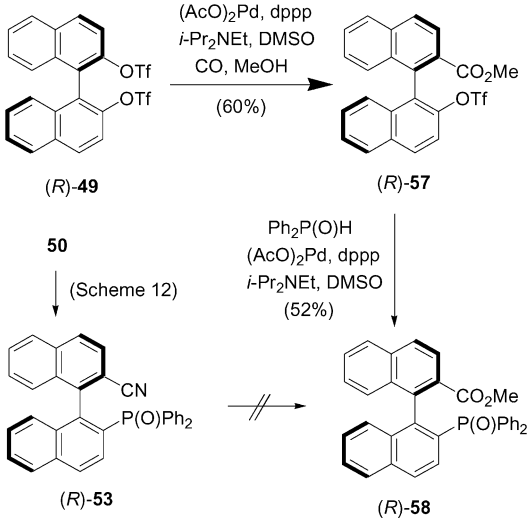
Mono-phosphination has also been reported for the di-triflate of 8,8′-dihydroxy-1,1′-binaphthyl to produce the 8,8′-isomer of MOP (see section II.I).[61] Cyanation of (−)-**49** afforded a mixture of mono-nitrile **52** (40%) and the corresponding bis-nitrile (10%).[59] The phosphinoxy triflate **50** underwent cyanation to provide phosphinoxy nitrile **53**.[62] All these transformations apparently proceeded without racemization.

The selectivity of phosphination of BINOL bis-triflate (**49**) has been utilized in the synthesis of analogues of BINAP (**2**) with two different phosphine groups (Scheme 13).[63] Thus, phosphinoxy triflate (±)-**50** was reduced to afford phosphine **54a**, whose

coupling with diarylphosphine oxide under harsher conditions produced racemic BINAPO (**55a**). The latter racemate was resolved via stoichiometric cyclopalladation with (*S*)-1′-(*N*,*N*-dimethylamino)-1-ethylnaphthalene; crystallographic analysis of this complex revealed the absolute configuration. Reaction of the enantiopure (*S*)-**54a** with di-*p*-tolylphosphine oxide led to the BINAPO analogue (*S*)-**55b**, whose reduction produced another analogue of BINAP, namely (*S*)-**56b** (BINAPP′). A similar diphosphine bearing a P(*o*-Tol)$_2$ group, (*S*)-**56c**, was obtained directly from triflate (*S*)-**54a** on Ni-catalyzed coupling with (*o*-Tol)$_2$PH (42%).[63] Finally, the methoxydimethyl analogue **56d** was synthesized using a reversed strategy: the bis(3,5-dimethyl-4-methoxy)-phosphino group was introduced first by phosphinylation of triflate **49**, followed by reduction of the resulting phosphine oxide, giving phosphino triflate **54b**, that was in turn phosphinated to give the desired ligand **56d**.[60d]

Carbonylation of triflate **49** is similarly selective, giving methyl ester **57** as the mono-carbonylation product in 60% yield (Scheme 14).[64] However, when

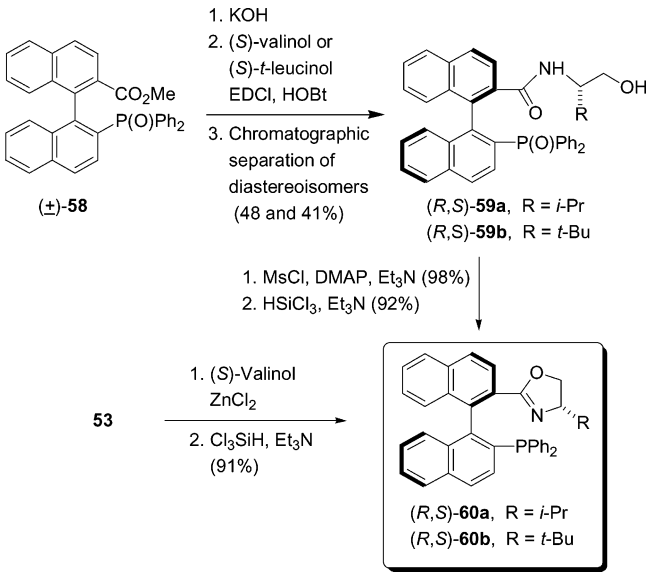
Scheme 14



the solvents and reagents were meticulously purified, mainly bis-carbonylation was observed (57%), with **57** being formed as a minor product (9%).[65] Alternative approaches to these binaphthyls rely on the side-chain oxidation of 2-methyl-1,1′-binaphthyls,[33] or on nucleophilic aromatic substitution (see section II.C). While sterically bulkier phosphinoxy triflate **50** is inert to carbonylation,[62] it can be converted into nitrile **53** (99%) on a Ni-catalyzed reaction with KCN, as shown above (Scheme 12); however, the latter nitrile resisted all attempts at hydrolysis.[62] The 2′-phosphineoxide-2-carboxylate **58** was then prepared by phosphinylation of triflate **57** in 52% yield (Scheme 14).[62]

Hydrolysis of racemic ester **58**, followed by condensation with (*S*)-valinol, gave a mixture of diastereoisomeric amides (48 and 41%, respectively) that was separated using flash chromatography (Scheme 15). Transformation of the enantiomerically pure amide (*R*,*S*)-**59a** into the corresponding oxazolidine (98%), followed by reduction with trichlorosilane,

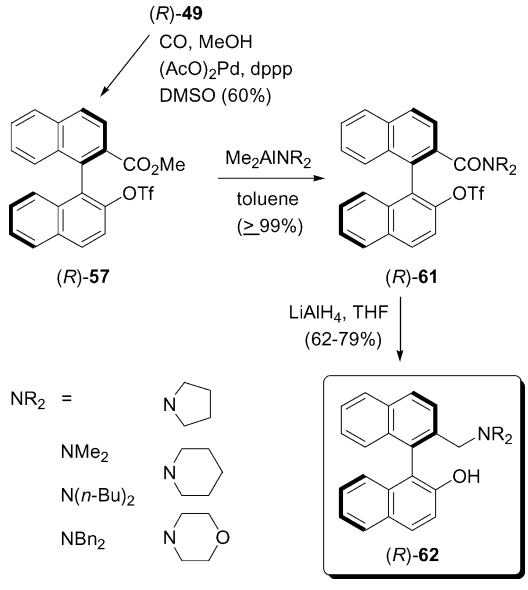
Scheme 15



furnished the phosphinoxazolidine derivative (*R*,*S*)-**60a** (92%).[66] The analogous *tert*-butyl derivative (*R*,*S*)-**60b** was synthesized in a similar manner.[66b] An alternative synthesis of **60a** relies on the $ZnCl_2$-mediated reaction of nitrile **53** with (*S*)-valinol, followed by reduction of the resulting oxazoline−phosphine oxide with Cl_3SiH (91% yield).[67]

N-Alkylated homologues of NOBIN **62** have been synthesized from ester-triflate **57**, which in turn was obtained by mono-carbonylation of bis-triflate **49** (Scheme 16). Reaction of ester **57** with a series of

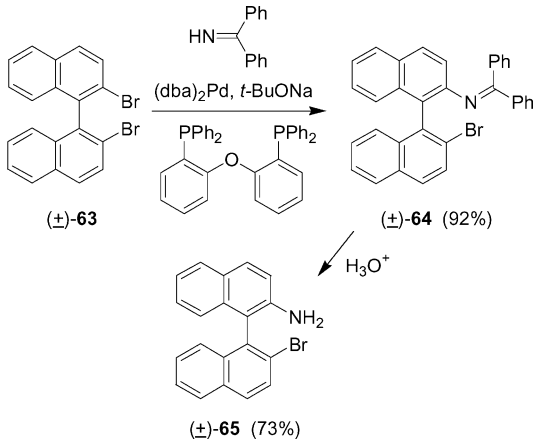
Scheme 16



amidation reagents Me_2AlNR_2 gave the corresponding amides **61**; subsequent standard amide reduction with $LiAlH_4$ afforded the required series of NOBIN homologues **62**.[68]

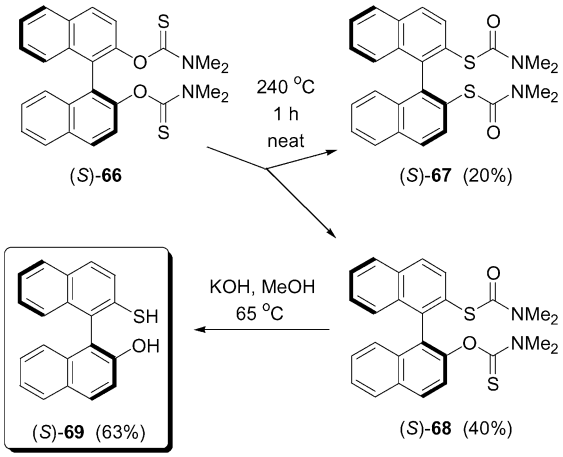
Another selective mono-functionalization (Scheme 17) was reported for the Buchwald amination of dibromide **63** with benzophenone imine, which afforded imine **64** (92%). Hydrolysis of the latter compound produced bromoamine **65**.[69]

Scheme 17



The Newman−Kwart rearrangement of the bis-(dimethylthiocarbamoyl) derivative of BINOL (**66**) has been reported to give the mono-rearranged product **68** in 40% yield under optimized conditions (Scheme 18), which was then hydrolyzed to afford

Scheme 18



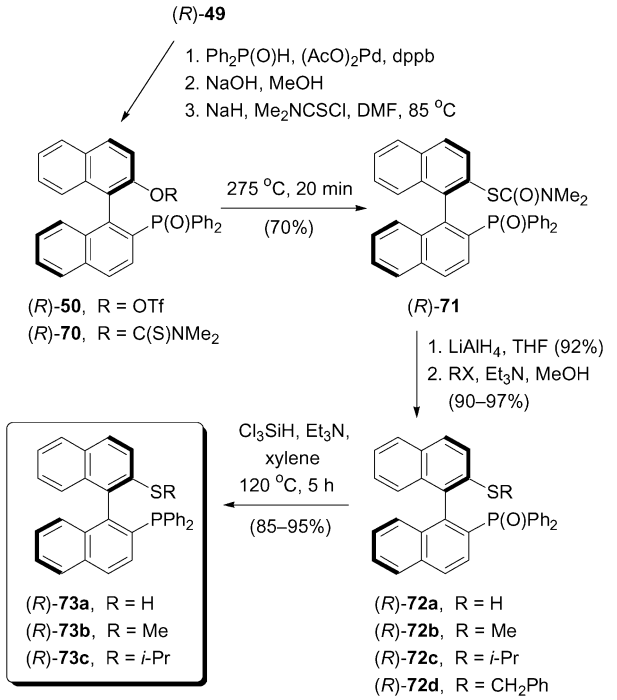
hydroxy thiol **69**.[70,71] Harsher conditions of the initial rearrangement led to **67** as the major product.[70,71] Interestingly, no racemization has been reported, despite the high temperature used. Alkylation of **69**, followed by oxidation with MCPBA, afforded the corresponding sulfoxides.[70a]

The Newman−Kwart rearrangement has also been employed as the key step in the synthesis of thiophosphines **73a**−**c**, which can be regarded as thioanalogues of MOP (Scheme 19).[72]

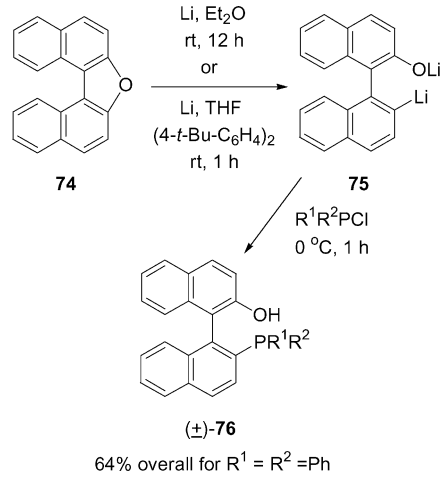
Selective ring-opening of dinaphthofuran **74** with lithium under electron-transfer conditions has been reported as an alternative approach to 2,2′-nonsymmetrically substituted 1,1′-binaphthyls from a symmetrical precursor (Scheme 20). The intermediate lithio derivative **75** was quenched with various phosphine chlorides to provide several hydroxyphosphines (±)-**76**.[73]

An analogous application of dinaphthothiophene **77** required the Ni-catalyzed ring-opening with a Grignard reagent and led to a series of thiols **80** (Scheme 21). With phosphinoxazoline **81** as chiral ligand, the products were obtained with ≤95% ee; other chiral ligands were less successful.[74]

Scheme 19



Scheme 20[a]



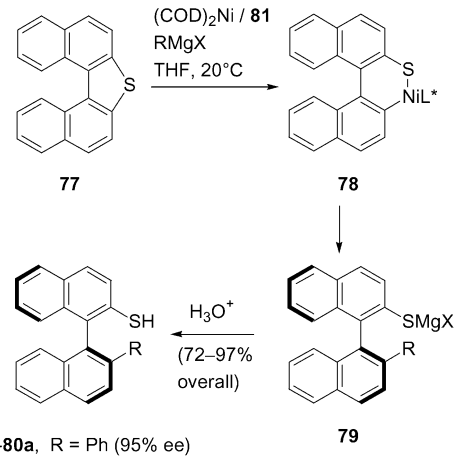
[a] R[1] = Ph; R[2] = Ph, Me, *i*-Pr, *t*-Bu.

Another metalation strategy relied on borane−BINAPO complex **82** and quenching the intermediate organolithium **83** with Sn and Si electrophiles and subsequent decomplexation to obtain phosphines **85** (Scheme 22).[75]

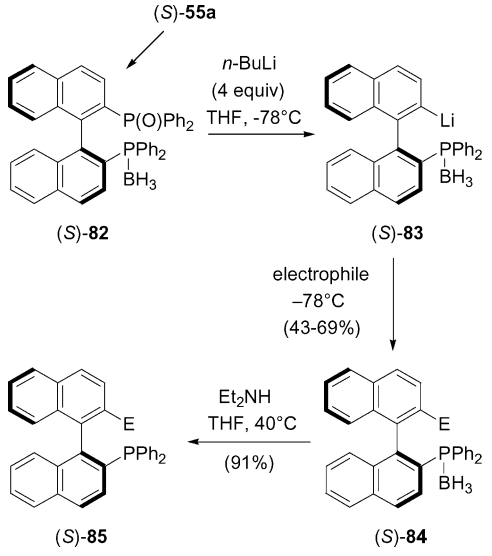
F. Other Substituent Manipulations

Further substituent manipulation can be utilized for the conversion of C_1-symmetrical 1,1′-binaphthyls into other derivatives. Thus, for instance, the selenium binaphthyl derivative **87**[76] was prepared from mono-amine **86** (Scheme 23), which in turn was obtained from the mono-acetamide of BINAM (**3**) by the sequence of diazotation of the free amino group, reduction with H_3PO_2, and amide hydrolysis.[77] Diazotation of **86**, followed by the Sandmeyer reaction with potassium selenocyanate,[78] then afforded **87**,[76] whose treatment with NaOH produced diselenide **88**.[76] This series is (*R*)-configured, but the enantiopu-

Scheme 21

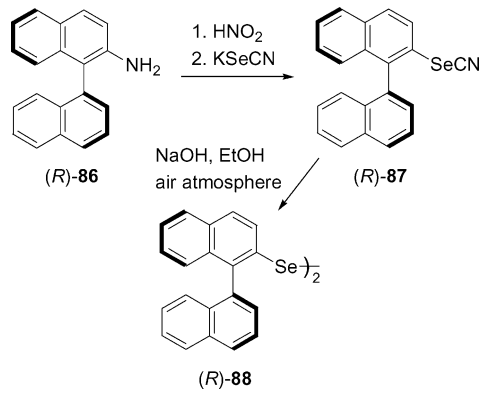


Scheme 22[a]



[a] E = $SnMe_3$, $SiMe_3$, $SiMe_2H$.

Scheme 23

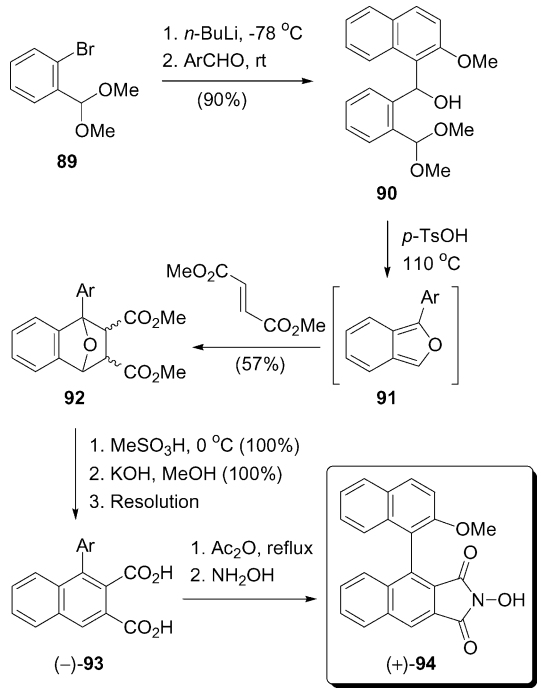


rity has not been discussed by the authors.[76] In view of the generally rather low barrier to racemization of 2-mono-substituted 1,1′-binaphthyls,[37] in conjunction with our experience of racemization of binaphthylamines during diazotation,[37,79] we feel that this issue should have been discussed in detail.

G. De Novo Synthesis of an Aromatic Ring of the 1,1′-Binaphthyl Skeleton

An interesting approach to the synthesis of non-symmetrically substituted 1,1′-binaphthyls is based on the de novo construction of an aromatic ring; this strategy was employed in the preparation of *N*-hydroxy imide **94** (Scheme 24). Here, the bottom

Scheme 24

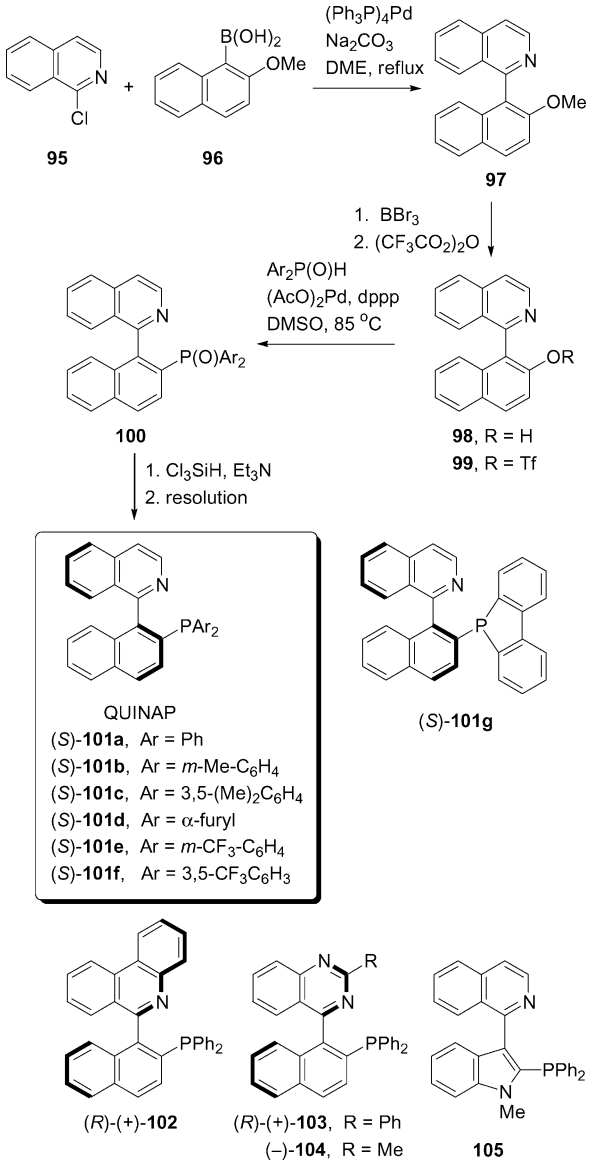


naphthalene system was constructed by the Diels–Alder addition of dimethyl fumarate to intermediate **91** (generated in situ by acid-catalyzed pyrrolysis of hydroxy acetal **90**), followed by the acid-catalyzed aromatization of the resulting adduct **92**. Free diacid **93** was resolved by crystallization with brucine from acetone; although the (−)-enantiomer obtained is depicted in the original paper to have (*R*)-configuration, the authors seem to have not established this in an unequivocal manner. Diacid (−)-**93** was then converted into *N*-hydroxy imide (+)-**94** via the reaction of the corresponding anhydride with hydroxylamine.[80]

H. Synthesis of Heterocyclic Analogues of 1,1′-Binaphthyls

In 1993, Brown introduced QUINAP (**101a**) as a hetero-bi-dentate aza-binaphthyl analogue of BINAP (Scheme 25).[81] Its synthesis commenced with the Suzuki–Miyaura coupling of α-chloroisoquinoline (**95**) with boronic acid **96**,[81] which in turn was obtained from (2-methoxy-1-naphthyl)magnesium bromide.[82] The resulting azabinaphthyl derivative **97** was depro-

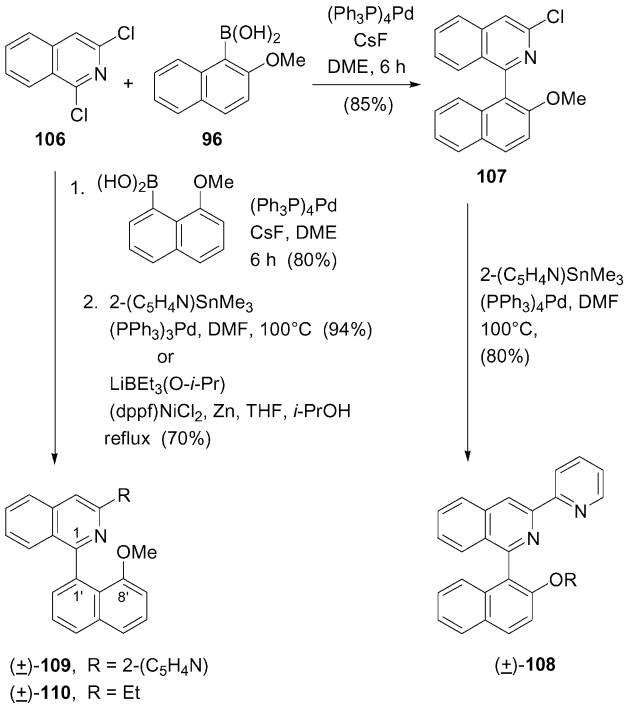
Scheme 25



tected, and the resulting phenol **98** was converted into triflate **99**, whose coupling with $Ph_2P(O)H$[59] afforded phosphinoxide **100**. Standard reduction of the latter derivative with Cl_3SiH[83] gave rise to the new *P,N*-ligand (±)-**101a** that was christened QUINAP.[81] QUINAP was resolved via the diastereoisomeric, cyclopalladated complexes with $PdCl_2$ and (*R*)-(+)-dimethyl[1-(1-naphthyl)ethyl]amine,[81,84] and the absolute configuration was established by X-ray analysis of the latter Pd complex.[81] Synthesis a series of QUINAP analogues with different aryl/heteroaryl groups adjacent to phosphorus **101b**−**g**[81c,86] and of the phenanthridine analogue PHENAP (**102**)[85] followed shortly.

A similar strategy was employed by Guiry in the synthesis of 2-phenyl- and 2-methyl-quinazolinap **103** and **104**; the absolute configuration of the former ligand was established by X-ray crystallography of its Pd complex (similarly to QUINAP), whereas the configuration of the latter was proposed by analogy.[87] While these ligands are configurationally stable, the indole-type analogue **105** proved to have a racemization barrier too low for the purpose of asymmetric catalysis.[88]

Scheme 26

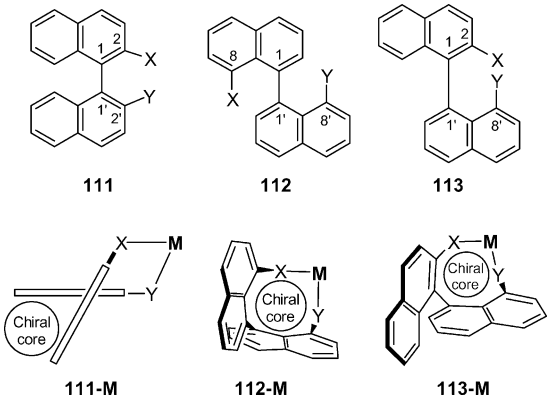


Woodward has synthesized 3-substituted analogues of QUINAP, e.g., **108** (Scheme 26), by a selective Suzuki−Miyaura coupling of 1,3-dichloroquinoline (**106**) with boronic acid **96**, followed by a Pd-catalyzed coupling of the intermediate **107** thus formed with the corresponding tin reagent. A similar strategy was employed in the synthesis of the 8-isomers **109** and **110** and a series of analogues.[89]

I. Synthesis of 1,1′-Binaphthyls with Substituents in the 8,8′- and 2,8′-Positions

The synthesis of 2,2′-substituted 1,1′-binaphthyls (**111**; Chart 3) has been the main focus in the

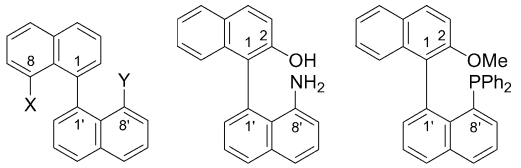
Chart 3. 2,2′-Di-substituted, 8,8′-Di-substituted, and 2,8′-Di-substituted 1,1′-Binaphthyls



development of chiral ligands for asymmetric catalysis. However, this molecular architecture fails to offer a direct communication between the binaphthyl system and the reaction center (Chart 3; **111-M**), and so the enantioselection must originate from additional effects (for exceptions, see section III.D). Thus, with BINAP (**2**), the binaphthyl moiety serves merely as a chiral scaffold, which dictates the orien-

tation of the Ph groups adjacent to the phosphorus atoms.[9] By contrast, the 8,8′- and 2,8′-di-substituted 1,1′-binaphthyls **112** and **113** would offer a direct interaction of the chiral core of the binaphthyl skeleton with the reactants (**112-M** and **113-M**).

Chart 4

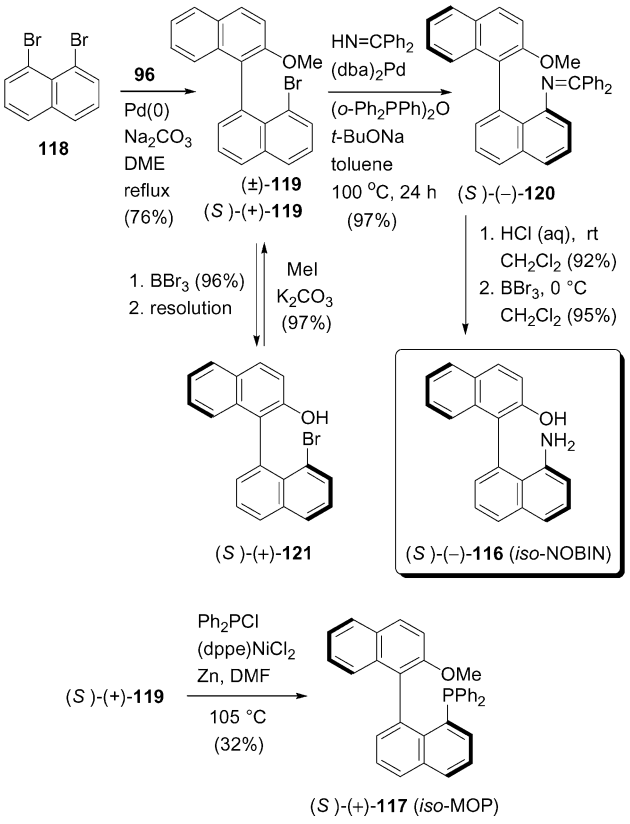


114a, X = OH, Y = $OCONMe_2$ **116** **117**
114b, X = OH, Y = $OCONEt_2$
114c, X = OH, Y = $OCON(i\text{-}Pr)_2$
115, X = OMe, Y = PPh_2

Representatives of the 8,8′-pattern (Chart 4),[90] e.g., the mono-functionalized isomer of BINOL (**114a**−**c**)[91] and the positional isomer of MOP (**115**),[61,92] have been synthesized by Meyers and Fuji but shown to have a racemization barrier rather lower than that of their 2,2′-ancestors.[61,90−92] The 2,8′-di-substituted pattern has recently been synthesized by us, in particular, *iso*-NOBIN (**116**) and *iso*-MOP (**117**).[37] In contrast to the 8,8′-system, these derivatives proved to be configurationally as stable as the classical 2,2′-substituted 1,1′-binaphthyls and, therefore, suitable for asymmetric catalysis.[37]

iso-NOBIN (**116**) was synthesized as follows (Scheme 27):[37] Suzuki−Miyaura coupling of boronic acid **96** with 1,8-dibromonaphthalene (**118**), which in turn was obtained via Sandmeyer chemistry from the commercially available diamine, afforded racemic

Scheme 27



methoxy bromide (±)-**119** (76%). While resolution of the latter derivative into enantiomers proved inefficient, the corresponding phenol (±)-**121**, obtained by BBr_3-mediated deprotection of (±)-**119**, was successfully resolved[37] by co-crystallization with benzylcinchonidinium chloride.[93] The absolute configuration was established by X-ray crystallography as (*S*)-(+)-**121**. Methylation of (*S*)-(+)-**121** afforded (*S*)-(+)-**119**, which was converted into imine (*S*)-(−)-**120** (97%) by Buchwald amination.[94,95] Deprotection of the latter imine by sequential treatment with Lewis and Brønsted acids afforded *iso*-NOBIN (*S*)-(−)-**116** in good overall yield.[37]

iso-MOP (*S*)-(+)-**117** was prepared from bromide (*S*)-(+)-**119** by Ni-catalyzed coupling[60c] with Ph_2PCl, although in a low yield (32%).[37]

J. Synthesis of Selected 2,2′-Di-substituted 1,1′-Binaphthyls

1. Synthesis of NOBIN and Its Congeners

Racemic (±)-**5** (NOBIN) was first prepared in one step by the convenient oxidative cross-coupling of a 1:1 mixture of β-naphthol with β-naphthylamine in up to 85% yield, as discussed earlier (Scheme 1).[12,15] Our original method, employing the Cu(II)-mediated coupling in solution (eq 1),[12] was later improved by Ding in the form of an Fe(III)-mediated coupling in a quasi-solid state (vide supra).[30,32]

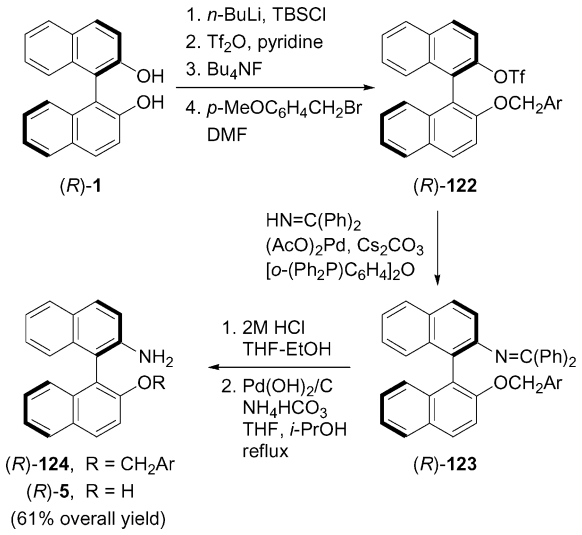
When carried out in the presence of a chiral amine, such as α-methylbenzylamine or sparteine, the Cu(II) coupling affords NOBIN in up to 46% ee as a result of enantioselective crystallization from the reaction mixture;[13,14] the latter product can be purified by crystallization to ∼100% ee.[14] Resolution of the racemate has been attained by crystallization with (1*S*)-(+)-10-camphorsulfonic acid from a 10:1 mixture of chlorobenzene and ethanol,[96] which gives (*S*)-(−)-NOBIN;[96−99] kinetic resolution of the corresponding imine by reaction with various chiral amino alcohols appears to be rather inefficient.[100] Racemic NOBIN has been found to be much less soluble than the pure enantiomers,[100,101] which reflects the stability of the crystal lattice (note that racemic NOBIN melts by 68 °C higher than the pure enantiomer![13]). Therefore, partially resolved NOBIN can be substantially enriched by extraction into pentane in a Soxhlet extractor[100] or by chromatography on an ordinary silica gel column.[101] The most reliable procedure for resolution employs the co-crystallization of (±)-NOBIN with 0.5 equiv of *N*-benzylcinchonidinium chloride from acetone, which gives (*R*)-(+)-NOBIN.[102]

The absolute configuration of **5** was determined by CD spectroscopy via comparison with the spectra of **1** and **3**.[13] This assignment was confirmed by chemical correlation (vide infra) and by crystallographic analysis of the inclusion complex of **5** with *N*-benzylcinchonidinium chloride.[102]

The synthesis of NOBIN via the direct, one-step cross-coupling of the respective components is very simple and efficient; however, its large-scale utilization is precluded by the reputation of β-naphthylamine as a carcinogenic agent. Therefore, Buchwald

developed an alternative route, starting with (*R*)-**1** (BINOL), which involves the Buchwald amination of the protected mono-triflate (*R*)-**122** as the key step (Scheme 28).[103] Although it is environmentally

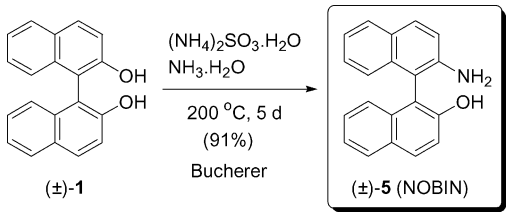
Scheme 28



friendly, and although no racemization was observed, this protocol lacks the advantage of simplicity, as it requires seven steps from (*R*)-**1**. Since enantiomerically pure NOBIN was obtained from BINOL of the known configuration, this synthesis further confirms the absolute configuration of NOBIN.

Zhang has most recently reported on the Bucherer reaction carried out with BINOL (**1**), which under rather harsh conditions gives NOBIN (**5**) in one step (Scheme 29); no bis-amination was observed.[104] Un-

Scheme 29

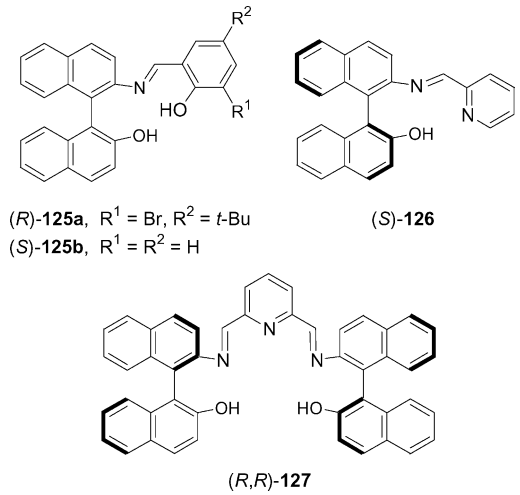


der these conditions, enantiopure BINOL (and most likely NOBIN as well) would racemize, so that this protocol can only produce racemic NOBIN.[104] However, in view of the recently published, very efficient resolution of NOBIN[102] (vide supra), this can hardly be regarded as a disadvantage, since resolution has to be carried out at some stage anyway, either with BINOL or for NOBIN. Therefore, the Zhang method appears to be ideal for the synthesis of NOBIN on a large scale, and we believe that this important improvement will lead to a wider application of NOBIN in asymmetric catalysis.

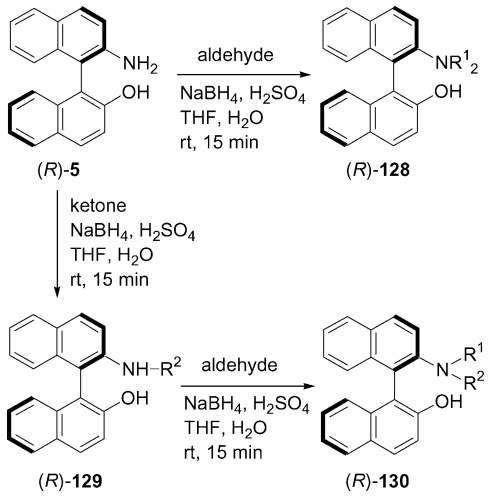
NOBIN (**5**) readily forms imines with a variety of aldehydes.[49] Some of them, e.g., **125** and its congeners,[99,105] **126**[106] and **127**[107] (Chart 5), have been employed as chiral ligands in asymmetric synthesis (vide infra).

The imine formation has been utilized in reductive amination to produce various *N*-alkylated NOBIN analogues (Scheme 30).[49] Generally, aldehydes, such

Chart 5



Scheme 30



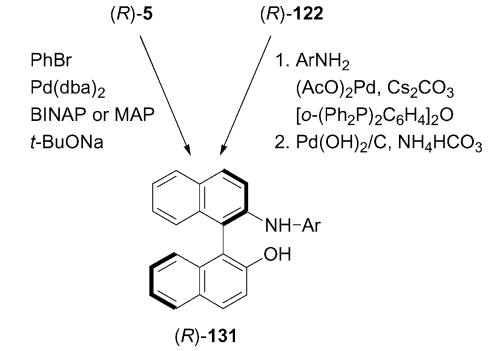
as formaldehyde and acetaldehyde, react in the presence of $NaBH_4$ and H_2SO_4 to produce tertiary amines **128** with two identical *N*-alkyl groups, whereas ketones, e.g., acetone, cyclohexanone, and 2-adamantanone, afford secondary amines **129**. The latter amines can be submitted to second reductive alkylation with aldehydes, to give tertiary amines **130** with non-identical *N*-alkyl groups.[49] Reaction of NOBIN with ethylene oxide gives the corresponding ethanolamine derivative **129** ($R_2 = CH_2CH_2OH$) as the product of *N*-mono-functionalization.[79]

N-Arylation of NOBIN **5** has been attained using the Hartwig−Buchwald methodology (**5** → **131**; Scheme 31).[108] Alternatively, *N*-aryl derivatives **131** can also be prepared by amination of the protected mono-triflate **122** derived from BINOL (Scheme 28) with various aromatic and heteroaromatic amines.[103]

An interesting carbene ligand, **133**, has been synthesized from NOBIN in three steps by Hoveyda (Scheme 32) and utilized in asymmetric metathesis reactions (vide infra).[109]

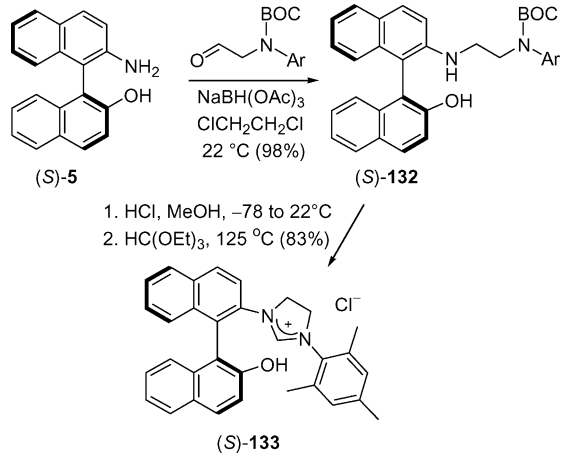
O-Methyl-NOBIN **135a** and its methyl analogue **135b** have been prepared from methoxy acids **134a** and **134b**, respectively, by Curtius rearrangement (Scheme 33).[110] Employing the Newman−Kwart rearrangement, dimethyl-NOBIN (**136**) has been converted into the corresponding amino thiol **137**; other

Scheme 31[a]

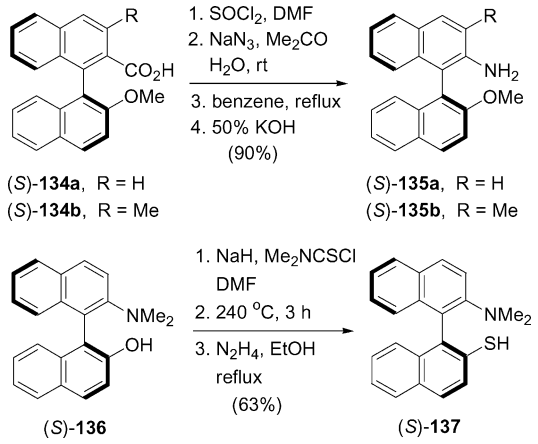


[a] Ar = Ph, *o*-MeO-C_6H_4, *o*-(MeO_2C)-C_6H_4.

Scheme 32



Scheme 33

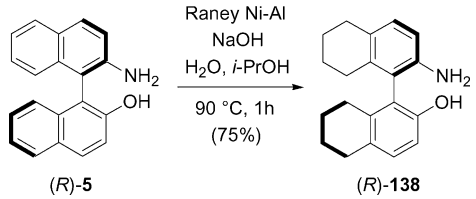


derivatives of thio-NOBIN have been prepared in a similar way.[71] All reactions shown in Scheme 33 proceed without racemization.[71,110]

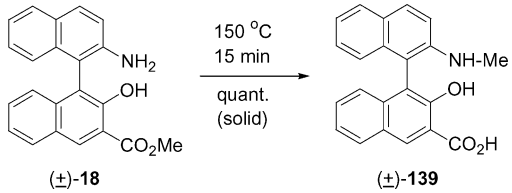
5,5′,6,6′,7,7′,8,8′-Octahydro-NOBIN **138** (H_8-NOBIN) has been prepared by Ding via partial reduction of NOBIN with Ni−Al alloy in a dilute aqueous alkaline solution (Scheme 34)[111,112] and utilized as a starting material for the synthesis of the corresponding aminophosphine (vide infra).[111] No loss of stereochemical integrity had been observed; the absolute configuration of **138** follows from the absolute configuration of the starting NOBIN.[111]

Finally, an interesting rearrangement was reported for the NOBIN derivative **18** (Scheme 35), prepared by the Cu(II)-mediated coupling of 2-aminonaphthalene with 3-methoxycarbonyl-2-naphthol. Heating of (±)-**18** in the solid state triggers $B_{AL}2$ intermolecular migration of the ester CH_3 group to nitrogen, giving methylamino acid (±)-**139**.[113] This rearrangement represents the first example of a $B_{AL}2$ reaction in the solid state. Enantiopure **18** is much less prone to this reaction.[101]

Scheme 34



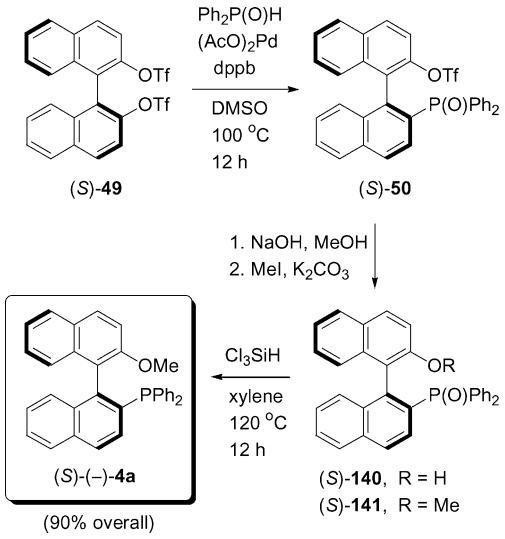
Scheme 35



2. Synthesis of MOP and Its Congeners

Being inspired by Morgans's earlier report on the selective mono-phosphinylation of BINOL bis-triflate **49**,[59] Hayashi employed the resulting phosphine oxide triflate **50** in the preparation of MOP ligands **4** (Scheme 36).[11] The synthesis involved hydrolysis

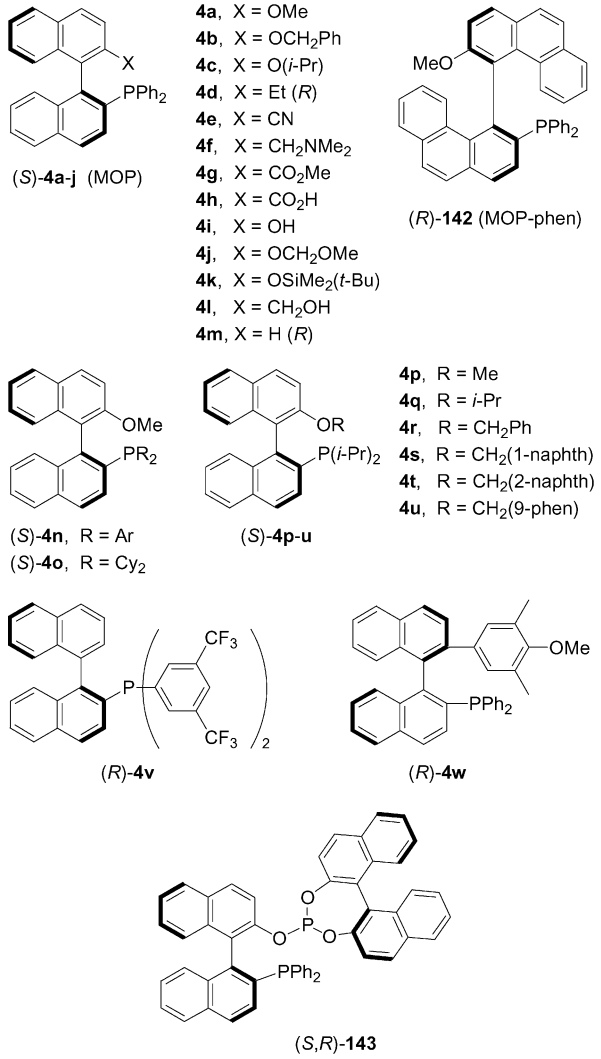
Scheme 36



of the triflate group (**50** → **140**), followed by methylation (**140** → **141**) and the subsequent reduction of phosphinoxide **141** to MeO-MOP (**4a**). The optimized overall yield, starting from (*S*)-BINOL (**1**), was ~90% with no deterioration of the stereochemical integrity.[11]

Similar processes involving *O*-alkylation have led to benzyl and isopropyl derivatives **4b**,**c** (Chart 6).[10,11] Kumada coupling of triflate **50** with EtMgBr, catalyzed by Pd(0), provided ethyl derivative **4d**,[62a] while Pd-catalyzed cyanation with KCN led to phosphinonitrile **4e**[62a] (see also Scheme 12). Reduction of the

Chart 6. MOP-Type Ligands

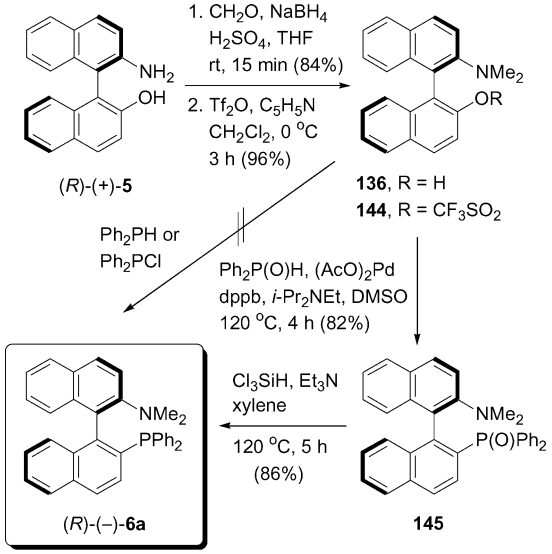


latter nitrile with diborane, followed by Eschweiler–Clarke methylation (CH_2O, HCO_2H), afforded aminophosphine **4f** (a homologue of MAP).[62] The carboxy derivatives **4g** and **4h** were prepared from BINOL bis-triflate (**49**) via Pd-catalyzed mono-carbonylation[62] (see also Scheme 14) and the homologue **4l** by the $LiAlH_4$ reduction of ester **4g**.[62a] The MOP derivative **4m**,[62a] lacking the 2-substituent, has been prepared from mono-deoxy-BINOL[77] in the same manner as **4a**, with retention of the original configuration of BINOL.[62a] The phenanthryl analogue (*R*)-(+)-**142** was synthesized from (*R*)-(−)-3,3′-dihydroxy-4,4′-biphenanthryl, again via the same sequence as **4a**.[114] Further variation has led to the diarylphosphines **4n** (Ar = various mono- and 3,5-di-substituted benzene rings)[11b] and the cyclohexyl analogue **4o**.[115] *O*-Alkylation of free hydroxyl in the $(i\text{-Pr})_2P$ analogue of **4i** (obtained by hydrolysis of the corresponding triflate) has led to a series with P(isopropyl)$_2$ derivatives **4p**–**u**.[115] Variation of the precursors allowed the synthesis of mono-phosphines **4v**[62b,c] and **4w**,[62d] where the original OMe group is replaced by hydrogen and an electron-rich aromatic ring, respectively. Finally, further derivatization of the free hydroxy group in **4i** produced the phosphine–phosphite analogue **143** with two binaphthyl units.[116]

3. Synthesis of MAP and Its Congeners

(*R*)-MAP (**6a**) was first synthesized by us in 1998 from (*R*)-dimethyl-NOBIN (*R*)-**136** (Scheme 37) via

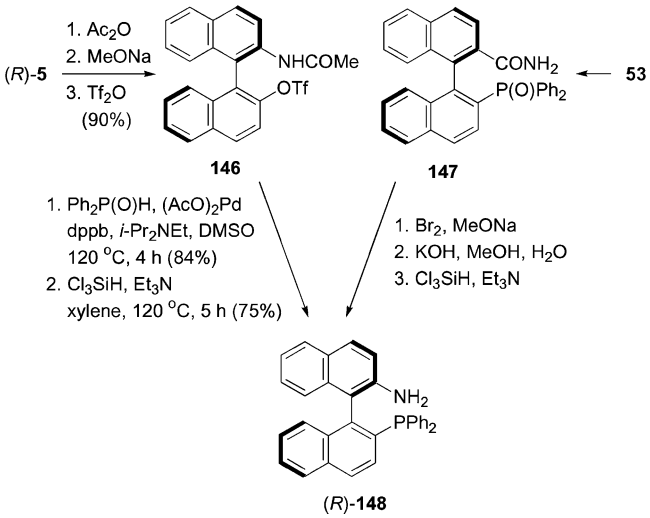
Scheme 37



the Pd(0)-catalyzed coupling of its triflate **144** with $Ph_2P(O)H$, followed by reduction of the resulting phosphine oxide **145** with Cl_3SiH.[16,108] A practically identical procedure was reported more than a year later for (*S*)-MAP.[102] Direct coupling of the triflate **144** with Ph_2PH was unsuccessful,[16] while the Ni(0)-catalyzed coupling with Ph_2PCl (**144** → **6a**) proved capricious, giving 0–30% of MAP.[79] Like with MOP, the MAP synthesis gives an enantiopure product.[16]

Des-methyl-MAP (**148**) was synthesized by an analogous procedure (Scheme 38),[16,117] starting with

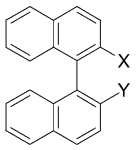
Scheme 38



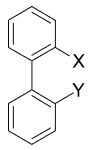
NOBIN acetamide, which in turn was prepared from NOBIN via *N*,*O*-bis-acetylation, followed by the selective Zemplén hydrolysis of the ester group.[71] Triflate **146** was then submitted to the standard sequence, affording **148**.[16,117] A different approach to the same product relies on the Hofmann rearrangement of amide **147** (obtained by partial hydrolysis of the corresponding nitrile **53**[62]), followed by reduction of the P–O bond.[118]

Further analogues of MAP with various *N*,*N*-dialkyl and *P*,*P*-dialkyl/diaryl groups and binaphthyl, biphenyl, or other biaryl skeletons have been described by Buchwald (some of them in an enantiopure form), namely, **6b**−**k**, **149a**−**j**, **150**−**152** (Chart 7).[69,117,119−130] The homologous MAP **6l** was obtained via the $LiAlH_4$ reduction of the corresponding nitrile **53** (Scheme 12); Eschweiler−Clarke methylation of the latter amine led to dimethylamino phosphine **6m**.[62a] Mono-*N*-alkylated aminophosphines **6n**,**o** and their analogues with two non-identical *N*-alkyl groups, **6p**,**q**, were prepared from the respective NOBIN precursors, which in turn were obtained by stepwise reductive alkylation, as shown in Scheme 30.[16] This series continues with ligands having a partly hydrogenated skeleton (**153**)[111,125] or an asymmetric center at phosphorus (**154**) (Chart 8).[127] All their syntheses utilized either the triflate coupling (as in Schemes 37 and 38)[16] or the lithiation of the corresponding bromide[69] with *t*-BuLi, followed by quenching with R_2PCl.[118,119] The latter protocol was employed for the racemic series. Pyridine-type amides **155** (Chart 8) were synthesized from **148** using standard methodology for amidation.[117]

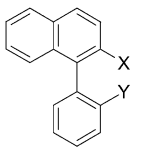
Chart 7. MAP-Type Ligands[a]



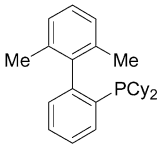
6a, X = NMe_2, Y = PPh_2
6b, X = NMe_2, Y = PCy_2
6c, X = NMe_2, Y = P(*i*-Pr)$_2$
6d, X = NMe_2, Y = P(*t*-Bu)$_2$
6e, X = H, Y = PCy_2
6f, X = H, Y = P(*t*-Bu)$_2$
6g, X = Me, Y = PCy_2
6h, X = Bu, Y = PCy_2
6i, X = Ph, Y = P(*t*-Bu)$_2$
6j, X = $SiMe_3$, Y = PCy_2
6k, X = $SiMe_3$, Y = P(*t*-Bu)$_2$
6l, X = CH_2NH_2, Y = PPh_2
6m, X = CH_2NMe_2, Y = PPh_2
6n, X = NH(*i*-Pr), Y = PPh_2
6o, X = NHCy, Y = PPh_2
6p, X = NMe(*i*-Pr), Y = PPh_2
6q, X = NMeCy, Y = PPh_2
148, X = NH_2, Y = PPh_2



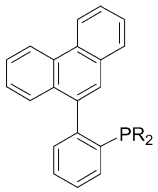
149a, X = NMe_2, Y = PPh_2
149b, X = NMe_2, Y = PCy_2
149c, X = NMe_2, Y = P(*i*-Pr)$_2$
149d, X = NMe_2, Y = P(*t*-Bu)$_2$
149e, X = H, Y = PCy_2
149f, X = H, Y = P(*t*-Bu)$_2$
149g, X = Me, Y = PCy_2
149h, X = *i*-Pr, Y = PCy_2
149i, X = Ph, Y = P(*t*-Bu)$_2$
149j, X = *i*-Pr, Y = P(*t*-Bu)$_2$



150a, X = H, Y = PCy_2
150b, X = H, Y = P(*t*-Bu)$_2$
150c, X = *i*-Pr, Y = P(*t*-Bu)$_2$



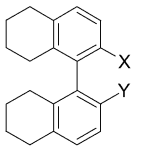
151



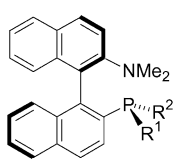
152a, R = *t*-Bu
152b, R = Cy

[a] Cy = cyclohexyl.

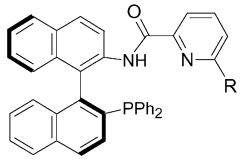
Chart 8



(*R*)-**153a**, X = NMe_2, Y = PPh_2
(*R*)-**153b**, X = NMe_2, Y = *p*-Me-C_6H_4
(*R*)-**153c**, X = NMe_2, Y = *m*-Me-C_6H_4
(*R*)-**153d**, X = NMe_2, Y = *p*-Me-C_6H_4
(*R*)-**153e**, X = NMe_2, Y = *p*-(*t*-Bu)-C_6H_4
(*R*)-**153f**, X = NMe_2, Y = 3,5-$Me_2C_6H_4$
(±)-**153b**, X = NMe_2, Y = P(*t*-Bu)$_2$
(±)-**153c**, X = H, Y = P(*t*-Bu)$_2$



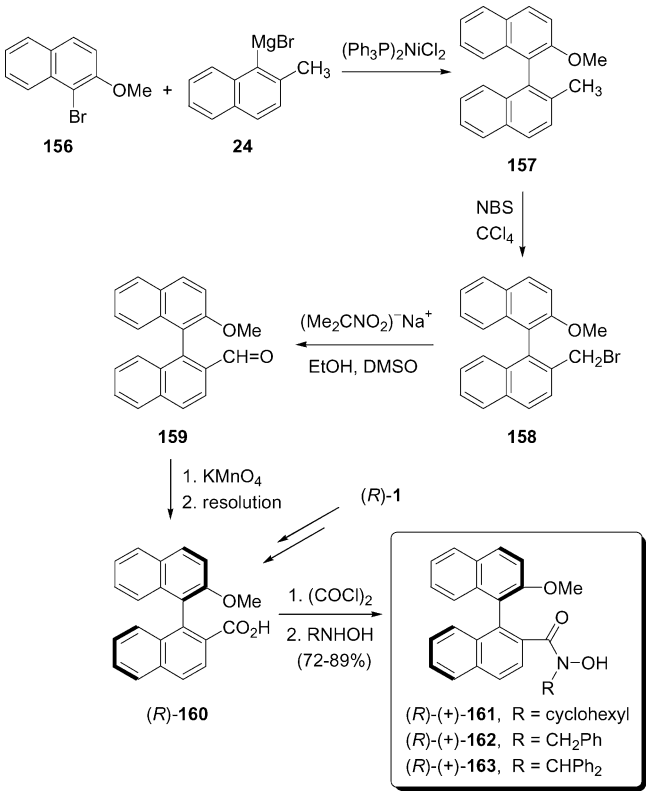
(*R*)-**154a**, R^1 = *t*-Bu, R^2 = Ph
(*R*)-**154b**, R^1 = Ph, R^2 = *t*-Bu



(*S*)-(+)-**155a**, R = H
(*S*)-(+)-**155b**, R = Me

ment in section II will be mentioned where relevant in section III. A few selected examples are shown below. Thus, for instance, hydroxamic acids **161**−**163** have been synthesized as follows (Scheme 39):[33,131,132] Kumada coupling of bromide **156** with Grignard reagent **24** afforded binaphthyl derivative **157**, whose methyl group was functionalized by bromination. The resulting benzylic bromide **158** was then oxidized in two steps to afford carboxylic acid **160**,[33] that was resolved into enantiomers via diastereoisomeric esters with menthol.[131] The latter methoxy acid was alternatively prepared from (*R*)-BINOL in sev-

Scheme 39



4. Synthesis of Other C_1-Symmetrical 1,1′-Binaphthyls

Further substituent variation has led to a number of 1,1′-binaphthyls with non-identical 2,2′-substituents. Those that are closely related to the derivatives mentioned above but did not merit a specific com-

eral steps.[33,131] The enantiopure acid **160** was then converted into hydroxamic acids **161**−**163** via the corresponding chloride.[132]

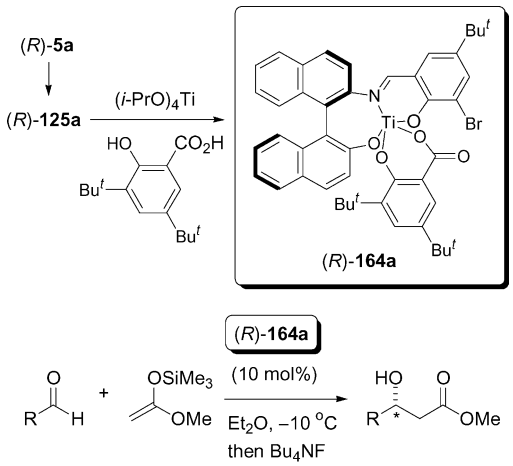
III. Application of Non-Symmetrically Substituted 1,1′-Binaphthyls in Asymmetric Catalysis

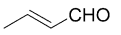
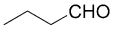
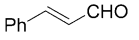
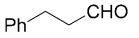
Most of the binaphthyls dealt with in the previous section have been used in asymmetric catalysis, either as chiral ligands coordinated to a metal or as metal-free organocatalysts. Representative examples of these reactions are highlighted in this section. On the other hand, stoichiometric reactions are not covered unless there is a close connection to a catalytic process.

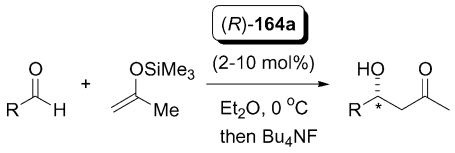
A. NOBIN and Its Congeners in Metal-Catalyzed Reactions

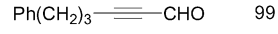
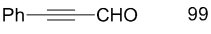
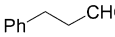
The first application of NOBIN came from Carreira, who took advantage of its propensity to form imines (Scheme 40).[105a−d] Thus, the tridentate imine **125a** (Carreira ligand) was converted into the Ti(IV) complex **164a** (Carreira catalysts) and shown to catalyze Mukaiyama aldol condensation with very high enantioselectivities (≤97% ee), even for silyl enol ethers unsubstituted in the α-position,[105] which represented a breakthrough in this chemistry. Methoxypropene has been found to react with similar efficiency.[105]

Scheme 40

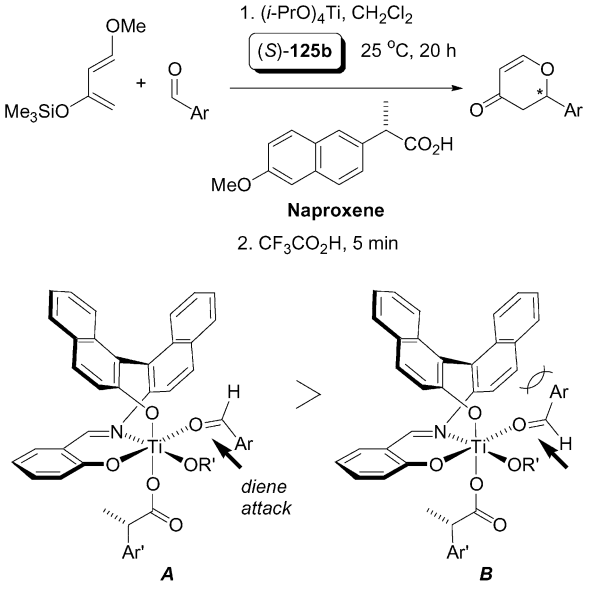


Aldehyde	yield (%)	ee (%)
	92	97
	88	95
	93	97
	89	94
$C_6H_{11}CHO$	94	95
PhCHO	93	96



aldehyde	yield (%)	ee (%)
	99	98
	85	93
	99	91
	98	90
PhCHO	83	66
c-$C_6H_{11}CHO$	79	75

Scheme 41

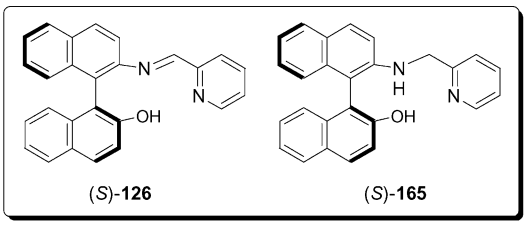


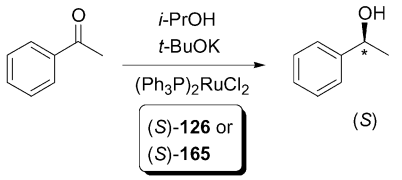
Ar	yield (%)	ee (%)
Ph	99	97
4-Cl-C_6H_4	99	97
4-Br-C_6H_4	98	95
4-(NO_2)-C_6H_4	91	83
3-Br-C_6H_4	83	86
3-Me-C_6H_4	81	96
3-MeO-C_6H_4	96	92
2-MeO-C_6H_4	99	82
2-furyl	90	75
trans-cinnamyl	96	83
phenethyl	83	75

The titanium(IV) complexes of ligand (*S*)-**125b** and its congeners have been employed in a systematic study of the effect of various carboxylic acids as additives on the catalytic activity in the hetero-Diels−Alder addition of the Danishefsky diene to various aldehydes (Scheme 41). Of 36 carboxylic acids (both chiral and non-chiral), (*S*)-naproxen was identified as most efficient. In its presence, the reaction rate was increased by an order of magnitude, and the addition product was obtained in >99% yield and 97% ee. The stereochemical outcome was rationalized by assuming that transition state **A** is less congested than **B**.[105f]

Imine **126** and the product of its reduction, **165**, both derived from NOBIN and α-picolinic aldehyde, proved to be efficient ligands in the ruthenium-catalyzed Meerwein−Pondorf−Verley-type reduction of acetophenone (Scheme 42):[106] thus, the use of both **126** and **165** led to the corresponding alcohol in 98% and 97% ee, respectively, whereas imines derived

Scheme 42





ligand	ratio[a]	temp (°C)	yield (%)	ee (%)
(*S*)-**126**	1 / 1.1 / 2.1 / 200	28	23	~ 97
(*S*)-**126**	1 / 1.1 / 2.1 / 100	28	94	96
(*S*)-**126**	1 / 1.1 / 2.1 / 50	28	87	96
(*S*)-**126**	1 / 1.1 / 2.5 / 50	28	96	95
(*S*)-**126**	1 / 1.1 / 2.1 / 200	50	97	~ 91
(*S*)-**126**	1 / 1.1 / 2.1 / 200	83[b]	94	52
(*S*)-**126**	1 / 1.1 / 1.6 / 200	28	31	98
(*S*)-**126**	1 / 1.1 / 3.1 / 200	28	38	98
(*S*)-**126**	1 / 1.1 / 2.1 / 100	50	98	~ 86
(*S*)-**165**	1 / 1.1 / 3.2 / 200	28	86	96
(*S*)-**165**	1 / 1.1 / 3.2 / 100	28	94	97

[a]Ratio metal / ligand / base / substrate. [b]1 h.

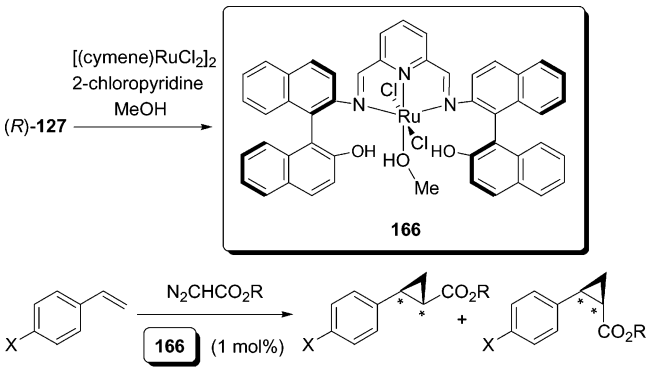
from other aldehydes, such as *o*-hydroxybenzaldehyde, were much less successful.

The ruthenium bis-imine complex **166** (Scheme 43) has been designed as a cyclopropanation catalysts for styrene, its para-substituted derivatives, and their β-naphthyl analogues.[107] The highest trans/cis ratio (9:1) and enantioselectivity (96% ee) were attained for unsubstituted styrene (X = H; Scheme 43); the cis byproduct was, as a rule, less enantiomerically enriched. α-Methylstyrene, on the other hand, gave a ~1:1 trans/cis mixture but with 93% ee for both isomers.[107]

Imines **167**, **168**, and **170**−**172**, all derived from *O*-methyl-NOBIN **135a**, and imine **169**, prepared from aldehyde **160** (as shown in Scheme 39) via Wittig-type extension, have been employed by Knölker as a chiral iron carbonyl-transferring catalyst (Scheme 44). Thus, a thermal reaction of $Fe(CO)_5$ with a mixture of the respective imine **167**−**172** and cyclohexadiene has led to the preferential formation of one enantiomer of the diene complex.[110c] While this system exhibits low enantioselectivity (≤34% ee) and the yields obtained with **171** and **172** are extremely low (≤6%), switching to the analogous camphor-derived azadienes as catalysts resulted in a modest improvement (≤62% ee).[110c,133]

Dimethyl-NOBIN (**136**), prepared from NOBIN by reductive alkylation, as described above (Scheme 30), has been found to catalyze diethylzinc addition to aromatic aldehydes (Scheme 45).[49] Apparently, the

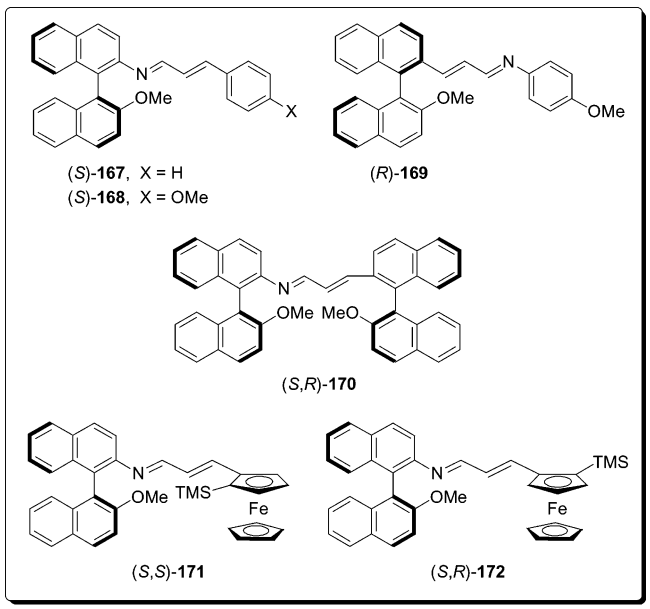
Scheme 43[a]

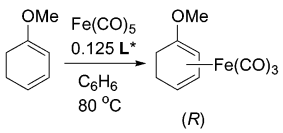


R (X = H)	solvent	ratio *trans* : *cis*	ee (%) *trans*	ee (%) *cis*
Et	CH_2Cl_2	90 : 10	97	90
Et	$(CH_2Cl)_2$	88 : 12	96	87
Et	toluene	89 : 11	95	85
Et	THF	83 : 17	64	5
Me	CH_2Cl_2	85 : 15	88	56
i-Pr	CH_2Cl_2	95 : 5	90	63
t-Bu	CH_2Cl_2	97 : 3	86	54
(–)-menthyl	CH_2Cl_2	95 : 5	58	44
(+)-menthyl	CH_2Cl_2	96 : 4	85	4

[a] X = H, Cl, MeO

Scheme 44

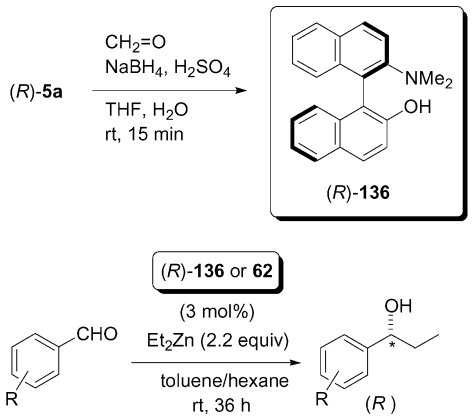




L*	time (h)	yield (%)	ee (%)
167	41	87	25 (*R*)
168	16	20	28 (*R*)
169	16	20	6 (*R*)
170	44	20	16 (*S*)
171	16	6	34 (*R*)
172	16	2	14 (*S*)

ligand works as a phenolate, since the in situ deprotonation of **136** prior to the addition of the reaction components leads to an increase of the enantioselectivity by 20%. Interestingly, analogues of **136** with bulkier *N*-alkyls (Scheme 30) are less efficient.[49]

Scheme 45



R	Ligand (*R*)-**136** yield (%)	ee (%)	Ligand (*R*)-**62**[68,b] yield (%)	ee (%)
H	89	68	89	94
H	96[a]	88	–	–
4-MeO	95[a]	75	97	94
2-MeO	93[a]	62	–	–
4-Cl	93[a]	83	97	95
3-Cl	–	–	95	96
2-Cl	93[a]	79	97	93
4-F	94[a]	79	–	–
4-Me	96[a]	82	–	–
2-Me	81[a]	81	–	–
1-naphthyl	87[a]	79	92	96
2-naphthyl	89[a]	83	95	96

[a] In the presence of *n*-BuLi (5 mol%). [b] At 0 °C.

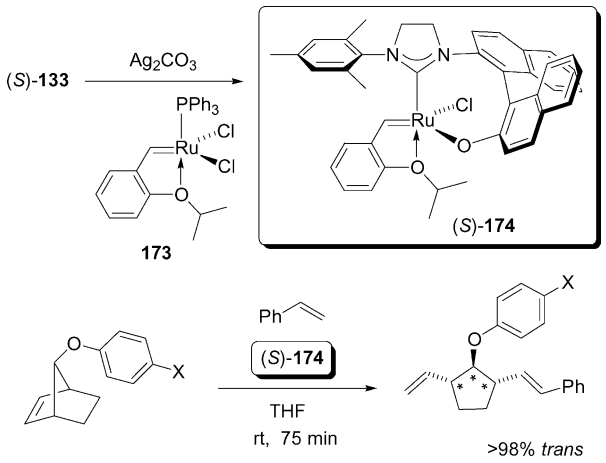
NOBIN homologues (*R*)-**62** (Scheme 16) exhibited similar enantioselectivities: the pyrrolidine derivative (**62**, NR_2 = pyrrolidyl) gave the highest ee [95% ee of the (*R*)-enantiomer].[68] On the other hand, the ethanolamine-type diamine (*R*)-**42** was less selective [51% ee of the (*R*)-enantiomer].[52]

Hoveyda has developed a robust, easy-to-handle ruthenium complex, **174**, as a new catalyst for ring-opening cross-metathesis, derived from ligand (*S*)-**133** and Ru chelate **173** (Scheme 46).[109] Norbornene substrates react with styrene to afford the product with three chiral centers with excellent stereocontrol (≤96% ee, >98% trans selectivity) and good yield (76%); most of the catalyst can be recycled. Neither an inert atmosphere nor degassing of the solvent was required, which demonstrates the stability of the catalyst; however, without these usual precautions, higher catalyst loading was required (5 mol %) and the yield dropped to 66%.[109]

B. NOBIN and Its Congeners as Metal-Free Organocatalysts

Asymmetric enolate alkylation constitutes a powerful method for the construction of a chiral carbon. In addition to various protocols requiring a chiral auxiliary or stoichiometric use of a chiral base, phase-transfer catalysis represents a promising technology. To date, most of the established chiral phase-transfer catalysts are based on the classical concept of tetraalkylammonium salts (e.g., derived from quinine alkaloids) that operate in a two-phase liquid−liquid system, with aqueous potassium hydroxide and an organic solution of the substrates.[134] NOBIN (**5a**) and its congeners could certainly be quaternized at the nitrogen and the resulting ammonium salts used as phase-transfer catalysts. However, this molecule also offers an attractive alternative, owing to the presence of the phenolic hydroxyl, which can be deprotonated. In fact, β-naphthol itself can be employed as a phase-transfer catalyst in alkylations,[135] so that its chiral version, such as NOBIN, has an interesting potential.

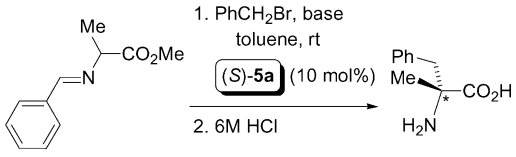
Scheme 46



X	cat (mol%)	yield (%)	ee (%)
CF_3	5	66	96
OMe	0.5	76	95

Indeed, alkylation of the alanine-derived imine **175** with benzyl bromide (Scheme 47), carried out under

Scheme 47



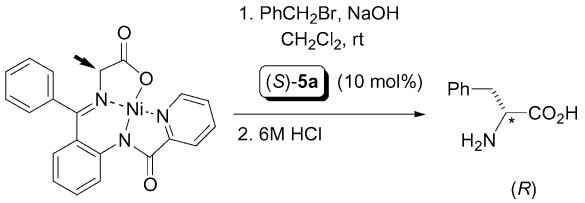
175

base	yield (%)	ee (%)
NaOH	90	62
KOH	90	43
NaH	60	68

solid−liquid phase-transfer conditions (toluene solution and solid NaOH) in the presence of NOBIN (**5a**) as catalyst, followed by imine hydrolysis, afforded α-methylphenylalanine of 62% ee.[136] Other good S_N2 electrophiles (e.g., allyl and methyl halides) reacted with similar efficiency.[136]

The glycine-derived Ni(II) complex **176**, whose planarity is imposed by the preferred square-planar geometry of the nickel(II), has been utilized as a second-generation starting material for asymmetric, phase-transfer alkylation (Scheme 48).[137] In the presence of NOBIN (**5a**) as catalyst, alkylation with benzylic and allylic halides occurred with a remarkably high enantioselectivity (≤98.5% ee); phenyl alanine, DOPA, and other amino acids were thus obtained in ∼90% yield.[137] Alkylation with *iso*-

Scheme 48



solvent	base	time (min)	yield (%)	ee (%)
toluene	NaOH (s)	45	50	89
CH_2Cl_2	NaOH (s)	8	90	97
MeCN	NaOH (s)	20	80	17
$(CH_2Cl)_2$	NaOH (s)	5	70	97
$(CH_2Cl)_2$[a]	NaOH (s)	5	86	93
CH_2Cl_2	KOH (s)	7	80	16
CH_2Cl_2	CsOH (s)	15	25	10
CH_2Cl_2	NaOH (aq)	60	5	55
CH_2Cl_2	NaH (s)	11	50	97

[a] Carried out at 70 °C

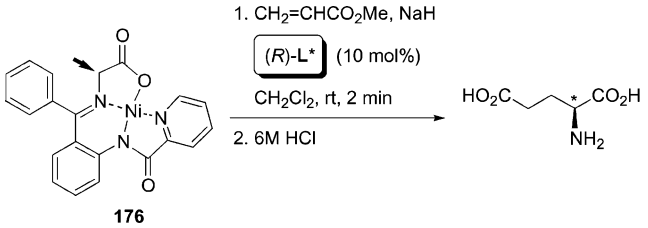
NOBIN (**116**) as catalyst proceeded with slightly lower enantioselectivity (87% ee for phenyl alanine).[135] Only mono-alkylation has been observed in these instances, presumably owing to the inability of the mono-alkylated Ni complex to undergo further enolization and alkylation due to the possible clash of the first alkyl substituent with the phenyl of the scaffold during the process of second enolization. The alkylation exhibits a strong non-linear effect (NOBIN of only 40% ee still gives a practically enantiopure product) and specificity to sodium cation (LiOH, KOH, and CsOH give much slower reaction and low enantioselectivity).[137] This behavior suggests that the chiral cavity, created by the enolate and the chiral catalyst, is sized just for Na^+. The non-linear effect can be rationalized by the strong attractive interaction of (+)-NOBIN with (−)-NOBIN (as in the solid state; vide supra), leaving enantiopure NOBIN free to catalyze the alkylation. In light of further experiments, the latter rationalization appears more likely than the alternative mechanism involving more than one NOBIN molecule in the catalytic process.[135]

The above alkylation (Schemes 47 and 48) may seem rather limited by the S_N2 mechanism that allows only the most reactive electrophiles to be used. Nucleophilic addition of complex **176** to simple Michael precursors, such as methyl acrylate (Scheme 49),[135] represents further extension of this phase-transfer methodology.[37,134] Although NOBIN (**5a**) and *iso*-NOBIN (**116**) failed abysmally in terms of asymmetric induction (26% and 22% ee, respectively), *N*-acetyl NOBIN (**177**) gave a promising result (55% ee). Amides **178** and **179**, derived from *iso*-NOBIN, have been found to exhibit high enantioselectivity, with pivalamide **179** giving the corresponding glutamic acid in 96% ee in a remarkably fast reaction.[135]

C. MOP Ligands in Transition Metal-Catalyzed Reactions

The MOP ligands have been developed by Hayashi with the aim to generate catalysts for those reactions,

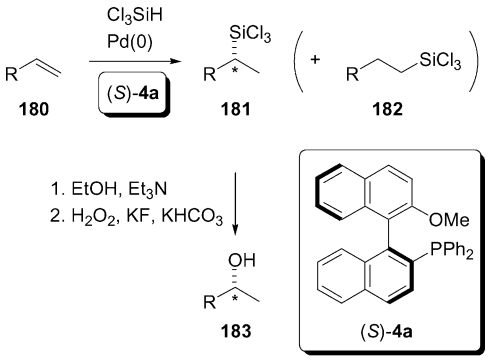
Scheme 49



L*	yield (%)	ee (%)	L*	yield (%)	ee (%)
5, R = H	40	26	**116**, R = H	50	13
177, R = COMe	50	55	**178**, R = COMe	70	92
			179, R = CO(*t*-Bu)	80	96

where chelating diphosphines and related ligands were inefficient because of their low activity or selectivity. The most fruitful application of **4a** and its congeners has been found in the Pd-catalyzed hydrosilylation (Scheme 50).[11] Here, bi-dentate phos-

Scheme 50



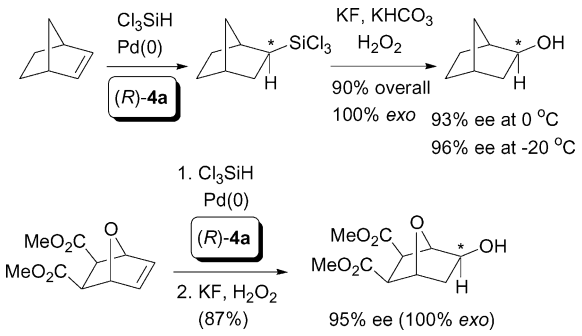
R	**181** : **182**	**183** yield (%)	**183** ee (%)
n-Bu	89 : 11	70	94 (*R*)
n-C_6H_{13}	93 : 7	71	95 (*R*)
n-$C_{10}H_{21}$	94 : 6	75	95 (*R*)
$PhCH_2CH_2$	81 : 19	68	97 (*S*)
c-C_6H_{11}	66 : 34	45	96 (*R*)

phines, such as BINAP, were known to prevent the reaction, while the mono-dentate ones (e.g., Ph_3P) reacted sluggishly, giving mainly the terminal products **182** in the case of terminal olefins **180**.[11] With (*S*)-**4a**, Hayashi has demonstrated reversion of regioselectivity for terminal olefins **180**, which now produced mainly the branched (i.e., chiral) isomer **181**, with high enantioselectivities in favor of the (*R*)-product (92−97% ee after oxidation to the secondary alcohols **183**); the formation of the opposite enantiomer in one case has not been rationalized. These reactions typically occur at 0 °C with 0.1 mol % of the catalyst. The resulting silanes were then oxidized

to produce the corresponding secondary alcohols with retention of configuration. All these reactions are characterized by low catalyst loading (0.1−0.01 mol %).[11,138]

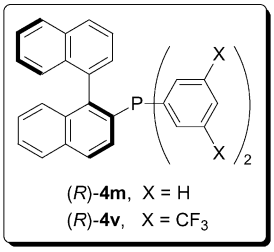
Good asymmetric induction and high exo-selectivity (Scheme 51) have also been found for bicyclo-[2.2.1]heptene derivatives (92−96% ee).[11,139]

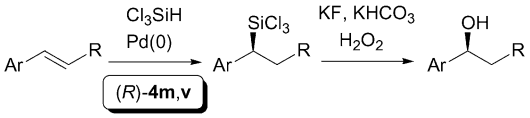
Scheme 51



While MeO-MOP (**4a**) exhibited high enantioselectivities in the hydrosilylation of terminal olefins (Scheme 50), it proved to be considerably less efficient with styrenes.[140] Hayashi has identified the desmethoxy analogue H-MOP (**4m**) as the ligand of choice here (Scheme 52), as the enantiopurity of the

Scheme 52





		(*R*)-**4m**[a]		(*R*)-**4v**	
Ar	R	yield (%)	ee (%)	yield (%)	ee (%)
Ph	H	100	93	93	97
p-MeC_6H_4	H	94	89	90	95
p-$CF_3C_6H_4$	H	98	96	–	–
o-ClC_6H_4	H	–	–	88	91
m-ClC_6H_4	H	68	95	93	96
p-ClC_6H_4	H	80	94	92	98
Ph	Me	95	89	81	98
Ph	*n*-Bu	89	92	–	–

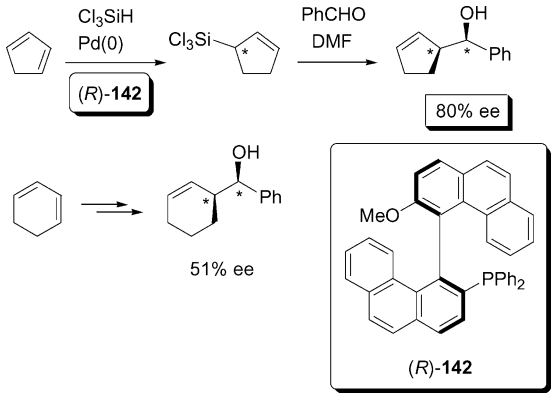
[a] The opposite enantiomer was, in fact, used in ref 141.

benzylic silanes formed in its presence was again in the high range (≤93% ee).[141] Further improvement (≤98% ee) was attained with **4v**.[62b] On the other hand, most of the remaining MOP-type ligands (Chart 6) exhibited much lower levels of asymmetric induction. The results for hydrosilylation of unsubstituted styrenes were as follows: MeO-MOP (**4a**), 14% ee (*R*); Et-MOP (**4d**), 18% ee (*R*); CN-MOP (**4e**), 26% ee (*R*); CO_2Me-MOP (**4g**), 30% ee (*S*); HO-MOP (**4i**), 34% ee (*S*).[140,141]

The success of the mono-denate MOP ligands in hydrosilylation has been attributed to the formation of the square-planar palladium(II) intermediate (MOP)Pd(H)$SiCl_3$(CH_2═CHR) that accommodates both reactants, which is precluded in the case of bi-dentate ligands.[11] The preferential formation of the branched isomer **181** from terminal olefins **180** (Scheme 50) is unique in the transition metal-catalyzed hydrosilylation. Isotopic labeling has indicated that the catalytic cycle includes both (MOP)Pd(silyl)(1-alkyl) and (MOP)Pd(silyl)(2-alkyl) intermediates, which exist in an equilibrium; MOP has been shown to accelerate reductive elimination from the latter intermediate, which results in the predominant formation of 2-silylalkane.[62b]

MOP-phen (**142**) turned out to be the champion ligand for the silylation of simple cyclic dienes (Scheme 53).[11c] Thus, at 20 °C, cyclopentadiene

Scheme 53

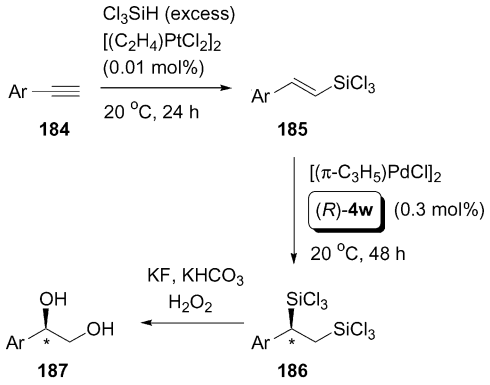


underwent a 1,4-addition to afford the corresponding silane in quantitative yield. The subsequent SE′ reaction with benzaldehyde gave rise to the corresponding homoallylic alcohol, which proved to be of 80% ee. Cyclohexadiene gave lower enantioselectivity (51%).[11c] Other MOP-type ligands (Chart 6) exhibited much lower levels; the results for hydrosilylation of cyclopentadiene were as follows: MeO-MOP (**4a**), 39% ee; Et-MOP (**4d**), 43% ee; H-MOP (**4m**), 28% ee.[11c]

Hydrosilylation of aryl acetylenes (Scheme 54) with 2 equiv of Cl_3SiH, catalyzed by the Pd complex of the **4v** group, afforded bis-silylated product **186** (33%).[62c] This reaction has been substantially improved by adopting a two-step protocol, according to which the first silylation (**184** → **185**) was catalyzed by a platinum complex, while the second silylation was catalyzed by Pd/**4v**. The final diol **187** was obtained in 85% overall yield and was of 95% ee (for Ar = Ph).[62c]

A palladium−**4a** complex has been shown to catalyze 1,4-hydroboration of 1,3-enynes, such as **188**, with catecholborane; the resulting axially chiral allenyl borane **189** was of at least 61% ee (Scheme 55).[142] Again, the use of mono-dentate phosphine was essential, since bi-dentate phosphines promote exclusive 1,2-addition that gives 1,3-dienylboranes. The reaction of **189** with benzaldehyde gave predominantly the syn product **190a** in 34% ee, whereas the

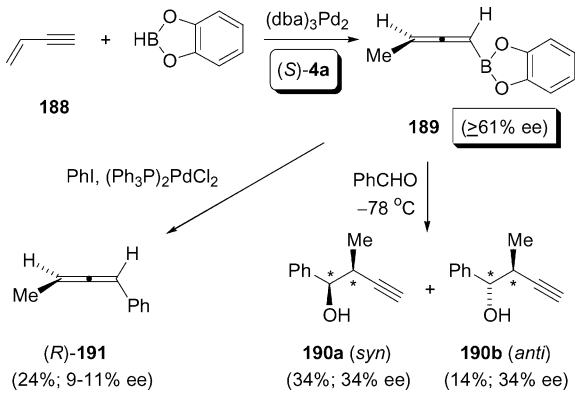
Scheme 54



(*R*)-**187**

Ar	yield (%)	ee (%)
Ph	75	95
4-MeC_6H_4	83	95
4-ClC_6H_4	75	94
4-$CF_3C_6H_4$	50	96
3-$NO_2C_6H_4$	67	98

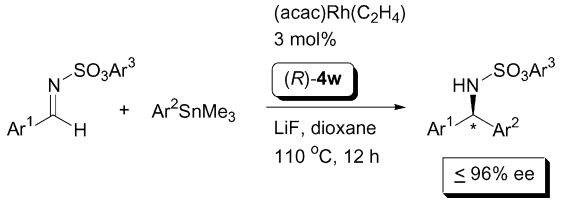
Scheme 55



Pd-catalyzed coupling with PhI afforded the almost racemic allene derivative **191**.

Rhodium-catalyzed asymmetric arylation of imines by organostannanes (Scheme 56) has been reported

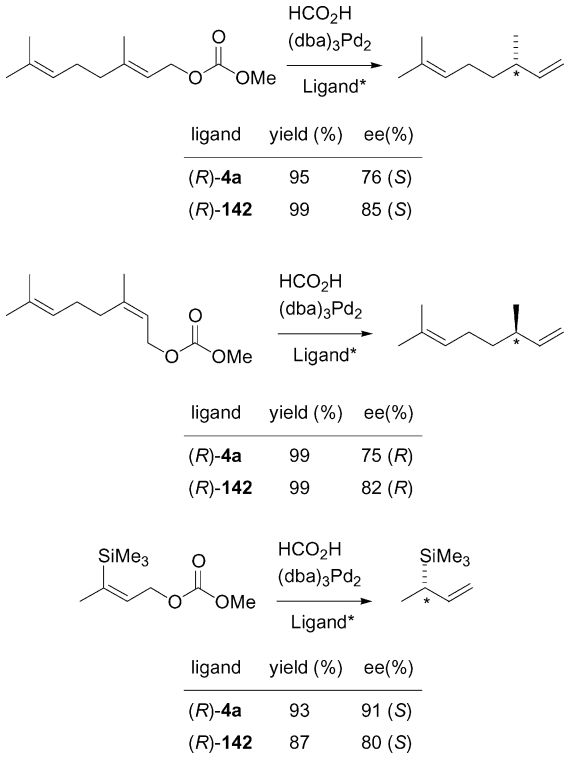
Scheme 56



to occur in the presence of MOP ligand **4w** (Chart 6) with up to 96% ee; **4a** was only slightly less efficient.[62d]

Palladium-catalyzed reduction of allylic carbonates, such as geranyl carbonate, with HCO_2H and Proton Sponge in the presence of MOP-phen (**142**) gave (*S*)-3,3-dimethyl-1,6-octadiene of 85% ee (Scheme 57).[143] Interestingly, neryl carbonate [the (*Z*)-isomer] gave the product of essentially the same enantiomeric purity (82% ee), but of the opposite absolute configuration. The MOP ligand **4a** was found to be slightly less effective.[143] Analogous reduction of vinylsilane carbonates led to allylsilanes with up to 91% ee.[144]

Scheme 57



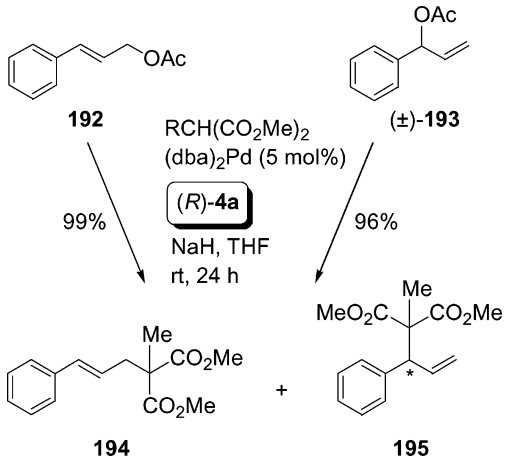
ligand	yield (%)	ee(%)
(*R*)-**4a**	95	76 (*S*)
(*R*)-**142**	99	85 (*S*)

ligand	yield (%)	ee(%)
(*R*)-**4a**	99	75 (*R*)
(*R*)-**142**	99	82 (*R*)

ligand	yield (%)	ee(%)
(*R*)-**4a**	93	91 (*S*)
(*R*)-**142**	87	80 (*S*)

MOP ligands have also been employed in Pd-catalyzed allylic substitution,[145−149] and Hayashi has demonstrated an interesting "memory effect" (Scheme 58).[147−150] He has shown that, whereas cinnamyl

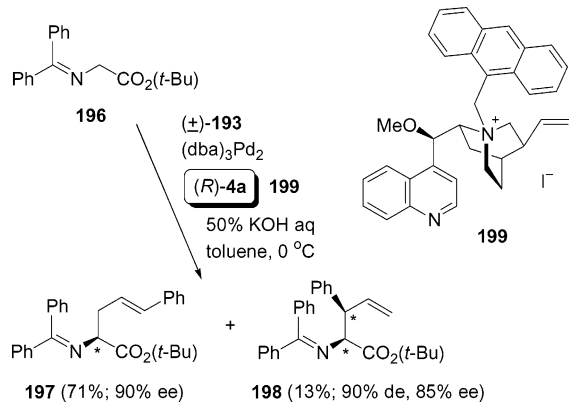
Scheme 58



acetate **192** reacted with $NaCMe(CO_2Me)_2$ in the presence of the complex of Pd(0) and MOP **4a** (in THF at 20 °C) to give a 79:21 mixture of the regioisomers **194** and **195**, isocinnamyl acetate **193** gave a reversed ratio (23:77).[148] Apparently, in this instance, the nucleophile tends to preferentially attack the carbon that originally carried the leaving group. In an earlier preliminary communication,[149] he reported 68−86% ee for the resulting branched isomer **195**, whereas his subsequent full paper[148] lacked this information. We have further investigated this behavior both with MOP and MAP ligands, and these issues are discussed in section III.D, together with MAP effects.[145−147]

An interesting dual asymmetric catalysis was reported for the allylation of glycine-derived imine **196** with isocinnamyl acetate (±)-**193** (Scheme 59),

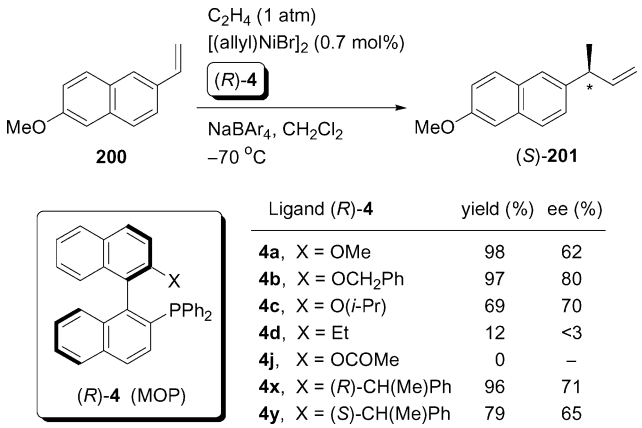
Scheme 59



employing **199** as the chiral phase-transfer catalyst, responsible for enolization of **196**, and MOP **4a**/Pd, which activated the allylic partner (±)-**193**. However, in this case, the memory effect was essentially absent, since the branched product **198** was formed in a mere 13% yield, whereas the linear isomer **197** predominated (71%),[151] which is in stark contrast to the reaction of (±)-**193** with malonate nucleophiles (vide supra). Furthermore, MOP had practically no influence on the stereochemical course of the reaction, as revealed by control experiments carried out in the presence of $(PhO)_3P$; **4a** only improved the yield.[151]

Vinylation of styrene-type molecules, such as the naproxene precursor **200**, has been attained with Ni−MOP catalysts (Scheme 60) by RajanBabu.[152] Here,

Scheme 60

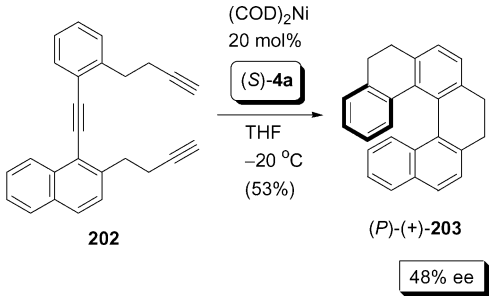


Ligand (*R*)-**4**	yield (%)	ee (%)
4a, X = OMe	98	62
4b, X = OCH_2Ph	97	80
4c, X = O(*i*-Pr)	69	70
4d, X = Et	12	<3
4j, X = OCOMe	0	–
4x, X = (*R*)-CH(Me)Ph	96	71
4y, X = (*S*)-CH(Me)Ph	79	65

the most successful ligands **4** were those with X = O-alkyl (**4a**−**c**); with the ethyl derivative **4d**, a practically racemic product was obtained, whereas no reaction occurred in the presence of the MOM-ether **4j**, BINAP (**2**), or BINAPO (**55a**) ligands, suggesting that a weak interaction of the metal with the OR group is crucial for the reaction to occur effectively. The nature of the anion (in particular, BAr_4^-) has also been shown to play an important role.[152]

Among other applications of MOP ligands, namely (*S*)-**4m**, was the ring-opening of thiophene binaphthyl **77** (Scheme 21). In this case, the enantioselectivity of the resulting thiol (*R*)-**80** was 68% ee, while the phosphinoxazoline **81** gave 95% ee (vide supra).[74] MOP ligands **4p**−**u** served in the asymmetric Pd-catalyzed arylation of ketone enolates;[115] this chemistry is dealt with in section III.D in connection with MAP ligands. Finally, MeO-MOP (*S*)-**4a** was employed by Starý as a chiral ligand in the Ni-catalyzed asymmetric cyclotrimerization of triyne **202** to produce tetrahydrohexahelicene (+)-**203** (Scheme 61).

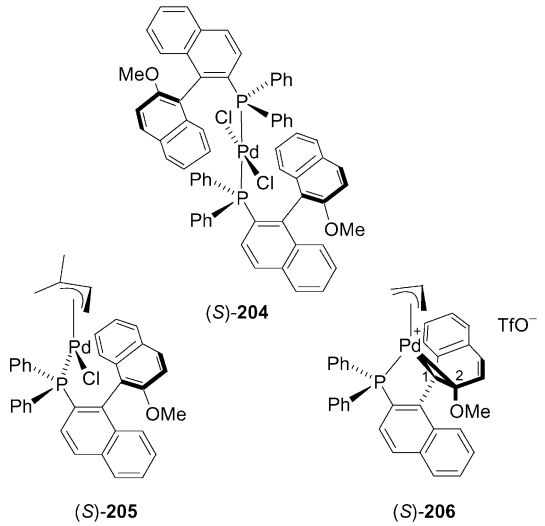
Scheme 61



Although the enantioselectivity obtained (48% ee) may not seem high, it is, in fact, by far the highest one reported to date. This asymmetric cyclotrimerization reaction represents the most successful catalytic translation of axial chirality into helicity reported to date.[153]

The actual structure of the MOP−Pd complex represents an interesting issue. Hayashi has reported compelling crystallographic evidence for the mono-coordination of Pd by MOP. According to the X-ray analysis, the $(\mathbf{4a})_2PdCl_2$ complex **204**, which was formed by mixing the ligand with $PdCl_2$, exhibits square-planar geometry with trans configuration at Pd (Chart 9).[138,154] Similarly, the η^3-prenyl complex

Chart 9



of Pd−MOP **205** also proved to be mono-dentate.[142] However, replacing the strongly coordinating Cl ligand with a weakly coordinating triflate, as in the η^3-allyl complex **206**, has been shown by us (by both NMR and X-ray analysis) to result in a different type of complex, in which Pd is chelated between phosphorus and the $C_1{=}C_2$ bond of the naphthalene ring

in η^2-fashion (**206**).[145−147] The formation of the latter complex can be understood by inspecting the crystallographic structures of **205**. Here, the palladium is actually positioned right above the C_1═C_2 bond, so that as soon the chloride is removed, the resulting vacancy at Pd is filled by coordination to the electron-rich naphthalene ring. Similar η^2-coordination has been reported for the Ru complex of BINAP (**2**)[155] and BINAPO (**55a**),[156] whereas η^6-coordination has been detected for the Ru complexes of mono-phosphine **4m** and several other methoxyphenyl analogues of MOP (**4a**).[157] This issue will be discussed in detail in connection with a similar behavior of MAP (section III. D).

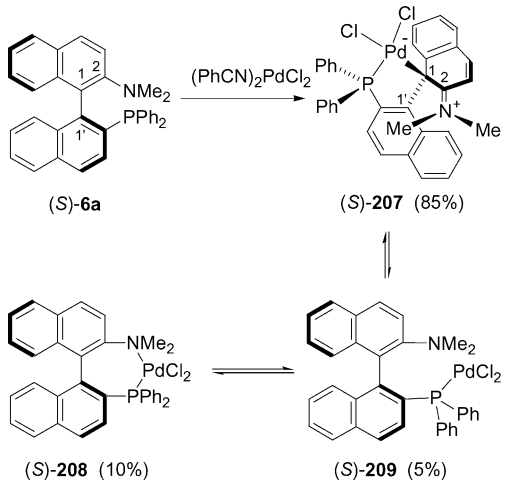
D. MAP Ligands in Transition Metal-Catalyzed Reactions

The synthesis of MAP (**6a**) by our group was inspired partly by the success of *P*,*N*-ligands, such as phosphinoxazolines, in transition metal-catalyzed allylic substitution[158] (a reaction of our continued interest[159]), and partly by the attractive opportunity to apply this ligand in Hartwig−Buchwald amination and related reactions.[94b,160] Thus, we reasoned that, in the electronically dissymmetric complex Pd-**6a**, Pd would be coordinated strongly to P but weakly to N,[16,108] which might enhance its reactivity. Apparently, the same idea occurred to Buchwald, who initially synthesized the biphenyl analogue of MAP **149b**,[120] to be followed by an impressive series of both biphenyl and binaphthyl analogues (Charts 7 and 8), in some of which the donation to Pd was further increased by switching from the PPh_2 group to the even more donating P(cyclohexyl)$_2$ or P(*t*-Bu)$_2$.[130,161]

Initial experiments with MAP-type ligands **6** and **149** indeed confirmed a substantial acceleration of the Hartwig−Buchwald amination of ArX (X = Cl, Br, I, OTf) with a variety of amines,[16,69,108,120] the Suzuki−Miyaura coupling,[36,128,145] and the formation of aryl ethers,[69,125,126] suggesting that the initial ideas were viable. Buchwald has shown that, in most of these cases, the MAP catalysts worked very well, even in the instance of sterically very hindered reaction partners and with less reactive substrates, such as aryl chlorides.[127]

To gain more insight into the behavior of the MAP−Pd system, we have elucidated the mode of coordination of **6a** to $PdCl_2$ (Scheme 62).[145] ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy indeed confirmed the presence of the expected *P*,*N*-chelate **208** in the solution, but only as a minor component (∼10%). In this equilibrium, another minor species was identified as the *P*-mono-coordinated complex **209** (∼5%), which was still in line with the initial hypothesis. However, rather surprisingly, this mixture was dominated by **207** (∼85%), a five-membered palladacycle with an unusual *P*,*C* *σ*-coordination. Crystallization of the **6a**/$PdCl_2$ mixture afforded **207** as a single product, whose structure was confirmed by X-ray crystallography.[145] Its formation can be understood in terms of the enamine-like behavior of the aminonaphthalene moiety in **6a**, which can encourage an electrophilic attack at the ipso-carbon;[145] furthermore, formation of a five-membered palladacycle, as

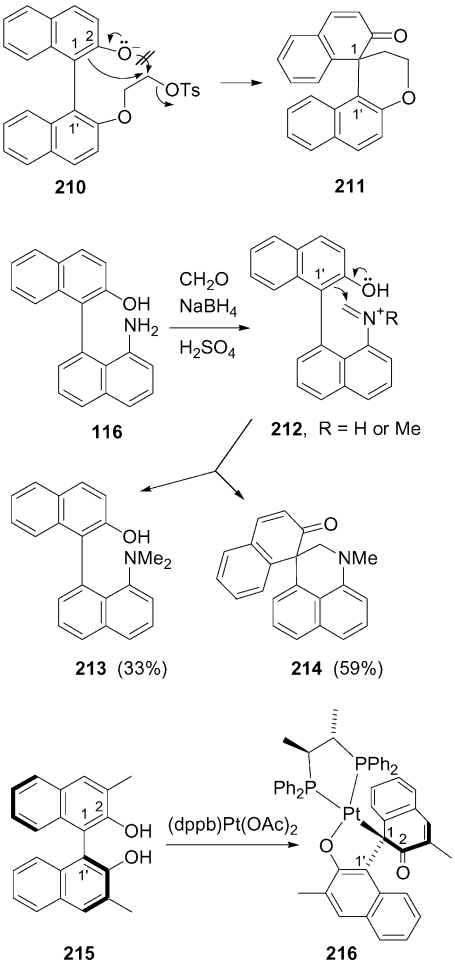
Scheme 62



in **207**, should be thermodynamically favored over that of the seven-membered chelate **208**,[162] which apparently contributes to the overall outcome.

The ipso-attack by an electrophilic species has been observed in several other instances (Scheme 63).

Scheme 63

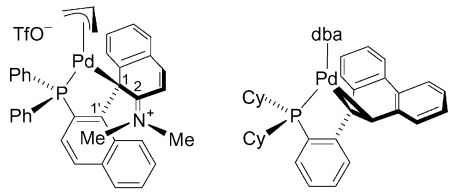


Thus, Wenkert[163] and Cram[5b] observed an intramolecular *C*-alkylation (rather than *O*-alkylation) in an attempt to close a crown ether (**210** → **211**), and we have reported the formation of spirocycle **214** (59%) in the reductive alkylation of *iso*-NOBIN (**116**) with

formaldehyde, whereas the desired dimethyl derivative **213** was obtained as a minor product.[37] The *C*-coordination of Pt(II) to Me_2BINOL (**215** → **216**), reported by Gagné,[164] is also in line with these observations.[165]

There is an interesting difference in the coordination mode of MOP and MAP ligands to Pd. While MOP prefers clear η^2-binding (**206**), the geometry of the MAP−$PdCl_2$ complex suggests η^1-coordination (**207**).[145] The π-allyl complex **217**, derived from MAP (Chart 10), resembles **207**, but the position of Pd has

Chart 10



(*S*)-**217** **218**

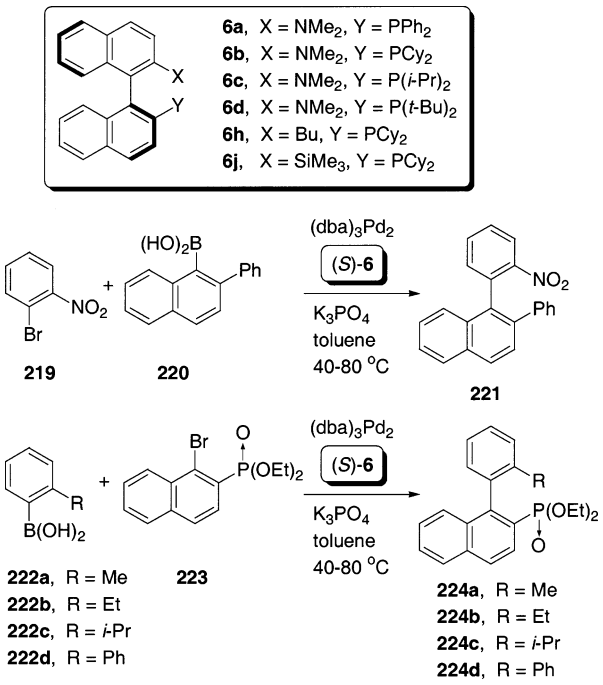
moved slightly, as shown by X-ray crystallography.[145] This effect is best observed by looking at the bonding angle Pd−C(1)−C(2) in each of these complexes: 104° (**207**), 94° (**217**), and 78° (**206**).[145] Note that each of these complexes contains Pd(II). Recently, Buchwald reported a crystallographic characterization of the Pd(0) complex **218**, which exhibits η^2-coordination, similar to that of MOP.[128] It may be speculated that this additional donation renders the Pd very electron-rich, which may lead to the stabilization of intermediates in the catalytic cycle. However, the actual role of this coordination in coupling reactions remains to be established.

Since the binaphthyl ligands **6** are inherently chiral, their application in the Hartwig−Buchwald amination of racemic substrates should, in principle, be amenable to kinetic resolution. However, to date, the experiments were only of very limited success; thus, *N*-arylation of racemic NOBIN (±)-**5** with bromobenzene, catalyzed by (*R*)-**6a**/Pd, gave a racemic product, while BINAP (*S*)-**2** exhibited a modest preference for the (*R*)-product (27% ee at 35% conversion). On the other hand, MOP (**4a**) proved unsuccessful again.[108]

More promising is the Suzuki−Miyaura coupling: First, in 2000, Cammidge demonstrated the principle, using a ferrocene-derived *P*,*N*-ligand (85% ee) or BINAP (25% ee),[166] as the first examples of asymmetric Suzuki−Miyaura coupling. These efforts were shortly followed by Buchwald's more thorough study, in which he employed MAP-type ligands **6a**−**d**,**h**,**j** and a broader range of substrates (Scheme 64).[36]

Asymmetric, Pd-catalyzed α-arylation of ketones was first attained by Buchwald, who initially used BINAP (**2**) as the ligand (Scheme 65).[119a] Thus, ketone **225a**, whose α′-position was protected by a removable group, was selectively alkylated at the α-position, also carrying another alkyl group (to prevent eventual racemization of the product via enolization). The arylation products were obtained in up to 98% ee.[119a] However, this method had several disadvantages: (1) high reaction temperatures (100 °C); (2) high catalyst loading [10−20 mol % of Pd and

Scheme 64



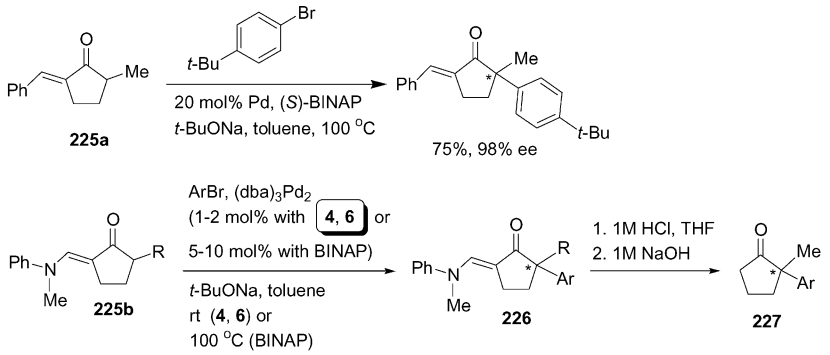
catalyst	conversion (%) / ee (%)				
(mol%)	**221**	**224a**	**224b**	**224c**	**224d**
6a (5)	67 / 38	76 / 75	–	–	–
6b (1-3)	81 / 73	100 / 87[a]	94 / 92	89 / 85	74 / 74
6c (1)	92 / 65	61 / 86	–	–	–
6d (1)	–	73 / 81[b]	–	–	–
6h (1)	100 / 32	100 / 54	–	–	–
6j (1)	60 / 62	100 / 23	–	–	–

[a]98% yield. [b]A 1:1 mixture of the desired and dehalogenated product.

12−24 mol % of (*S*)-BINAP]; and (3) difficulties associated with removal of the benzylidene protecting group.[119a] Buchwald then showed that switching to an *N*-methylanilinomethylene blocking group in **225b**, which can be readily installed and removed, had a beneficial effect upon the catalytic efficiency (Scheme 65),[115] but the arylations using (*S*)-BINAP still required high catalyst loading (5−10 mol %) and high temperature (100 °C); very good enantioselectivities were observed (up to 93% ee, Scheme 65).[115] The MAP ligands **6b**, **6c**, **6h**, and **6j** exhibited significantly higher reactivity, so the reactions could be carried out at room temperature and lower catalyst loading was required. However, these benefits are offset by lower enantioselectivities (39−70% ee).[115] The best results were finally obtained using MOP-related ligands **4q**, **4r**, and **4s**. These catalysts gave results better than or comparable to those obtained using (*S*)-BINAP (up to 94% ee), and the reactions now occurred at room temperature and required relatively low catalyst loading.[115] Interestingly, (*S*)-configured MOP and MAP ligands induce the formation of (*S*)-**226**, whereas (*S*)-BINAP gives predominantly (*R*)-**226**.[115] Deprotection of the α-position has been exemplified in one representative case (**226** → **227**).[115]

Buchwald has also developed arylation of esters using racemic **6d**, **149b**, and **149d**;[124] similar results

Scheme 65[a]



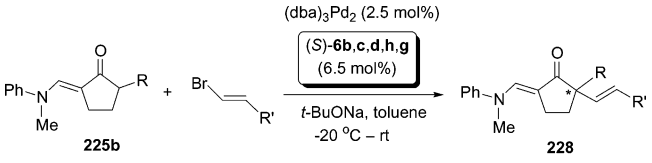
R	ligand	yield (%) / ee (%)					
		4-*t*-BuC_6H_4	2-MeC_6H_4	3-MeC_6H_4	4-MeC_6H_4	3-MeOC_6H_4	4-MeOC_6H_4
Me	(*S*)-**2**	65 / 88 (*S*)	45 / 8 (*S*)	70 / 80 (*S*)	65 / 63 (*S*)	87 / 85 (*S*)	74 / 57 (*S*)
Me	(*S*)-**6b**	99 / 67 (*R*)	–	–	–	–	–
Me	(*R*)-**6c**	80 / 70 (*S*)	–	–	–	–	–
Me	(*R*)-**6h**	78 / 60 (*S*)	–	–	–	–	–
Me	(*R*)-**6j**	66 / 39 (*S*)	–	–	–	–	–
Me	(*S*)-**4q**	87 / 86 (*R*)	40 / 42 (*R*)	72 / 87 (*R*)	70 / 86 (*R*)	79 / 80 (*R*)	77 / 83 (*R*)
Me	(*S*)-**4r**	79 / 88 (*R*)	53 / 23 (*R*)	82 / 89 (*R*)	83 / 87 (*R*)	81 / 84 (*R*)	82 / 87 (*R*)
Me	(*S*)-**4s**	84 / 93 (*R*)	44 / 22 (*R*)	85 / 94 (*R*)	84 / 93 (*R*)	80 / 89 (*R*)	80 / 94 (*R*)
n-Pr	(*S*)-**2**	–	–	74 / 91 (*S*)	–	–	–
n-Pr	(*S*)-**4s**	–	–	85 / 88 (*R*)	–	–	–
n-C_5H_{11}	(*S*)-**2**	–	–	75 / 93 (*S*)	–	–	–
n-C_5H_{11}	(*S*)-**4s**	–	–	86 / 91 (*R*)	–	–	–

[a] R = Me, Pr, C_5H_{11}; **2** = BINAP; for **4** and **6**, see Charts 6 and 7.

were reported by Hartwig, who employed carbene ligands.[167] Arylation of amides with MOP ligand **4a** gave racemic products, whereas ≤61% ee was attained with ferrocene-based diphosphine ligands and up to 76% ee using carbene ligands.[168b]

MAP ligands proved indispensable in the asymmetric vinylation of ketones,[123] as shown by Buchwald (Scheme 66). Thus, ketone **225b** has been

Scheme 66

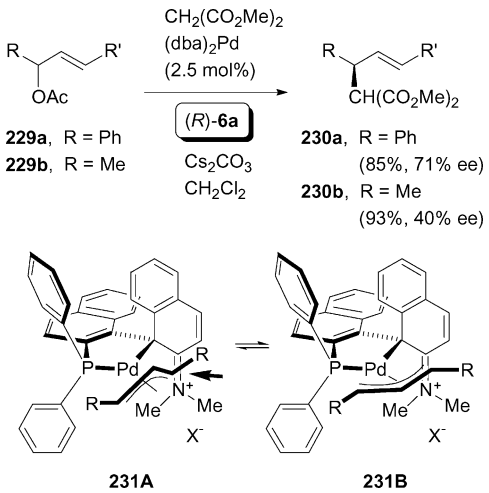


R	R'	yield (%) / ee (%)					
		6a	**6b**	**6c**	**6g**	**6h**	**6j**
Me	Me	40 / 56	98 / 94 (*S*)	<10 / –	93 / 80	90 / 82	60 / 35
Me	H	–	94 / 92 (*S*)	–	–	–	–
Me	Ph	–	92 / 89 (+)	–	–	–	–
n-Pr	H	–	86 / 90 (+)	–	–	–	–
n-C_5H_{11}	H	–	84 / 92 (–)	–	–	–	–

vinylated in an enantioselective fashion with 1-bromo-1-propene and its congeners in the presence of various Pd−MAP catalysts with up to 96% ee (at −20 °C to room temperature).[123] The best results were obtained using complex Pd/**6b**. Similar results were reported for MAP ligands **154** having an additional chiral center at phosphorus; a synergy effect was observed for the (*R*,*R*)-diastereoisomer **154b** (96%, 89% ee), while the (*R*,*S*)-diastereoisomer **154a** gave **228** in only 34% ee (91% yield).[127]

In the Pd-catalyzed allylic substitution, (*R*)-**6a** exhibited modest enantioselectivity in the reaction of 1,3-diphenylprop-2-en-1-yl acetate (±)-**229** with dimethyl malonate nucleophiles (Scheme 67). The

Scheme 67



results were fairly dependent on the method of malonate activation and the solvent (from 53% ee with NaH in THF to 71% ee with Cs_2CO_3 in CH_2Cl_2).[16] Lower enantioselectivity was observed with pent-3-en-2-yl acetate (40% ee).

Both NMR and crystallographic studies, carried out for the unsubstituted allyl complexes **206** and **217**, have indicated the presence of two rotamers in ∼3:2 to ∼1:1 ratios, which are in an equilibrium via an η^1-allyl intermediate. Furthermore, both in the solid

state and in solution, the allyl unit is coordinated in a slightly distorted η^3-fashion, so that the bond between Pd and the carbon terminus of the allyl unit trans-disposed to phosphorus is longer (and therefore weaker) than that of the other terminus, trans-related to the ipso-carbon (Figure 1). Accordingly, the

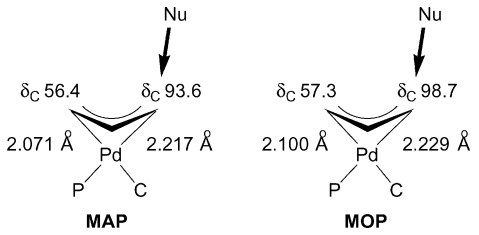
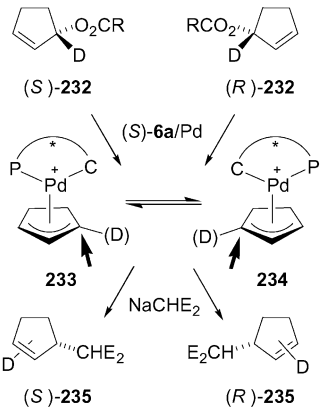


Figure 1. Bond lengths and ^{13}C chemical shifts in the palladium η^3-complexes of MAP and MOP, both suggesting a preferential attack at the carbon trans-related to phosphorus via palladium.

carbon trans to phosphorus has more π-character, as indicated by the respective chemical shifts in the ^{13}C NMR spectra (Figure 1). These parameters predict the preferential attack by the nucleophile at the terminus trans to the phosphorus. By analogy, allylic substrates **229** can be anticipated to form diastereoisomeric η^3-complexes **231A** and **231B**, of which the former will give rise to the predominant enantiomer of the product by the nucleophilic attack at the carbon trans-positioned to the phosphorus, as indicated by the arrow in Scheme 67.[145−147]

Further experiments, carried out by Lloyd-Jones in collaboration with our group, have demonstrated that the Pd-catalyzed allylic substitution with MAP ligand is dramatically affected by the memory effect.[150,169] Thus, the reaction of (±)-[1-2H]-cyclopent-2-enyl pivalate (±)-**232** with $NaCH(CO_2Me)_2$ and (*S*)-**6a**/Pd (5 mol %) in THF (Scheme 68) was found to

Scheme 68[a]



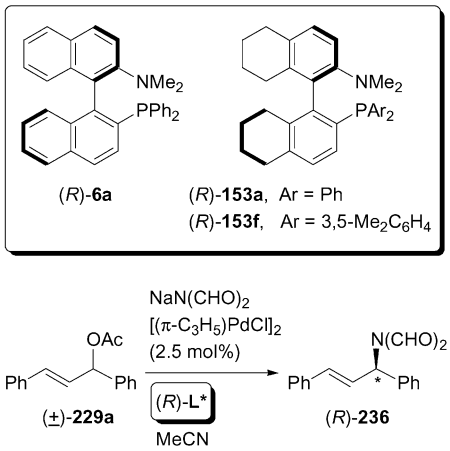
Solvent	Nucleophilic attack at (±)-**232** (S)-**232** (α/γ)	(R)-**232** (α/γ)	ee (%)
THF	46 : 4	42 : 8	8
CH_2Cl_2	38 : 12	12 : 38	52

[a] R = *t*-Bu; E = CO_2Me.

proceed with 88% regiochemical retention, i.e., via the nucleophilic attack at the carbon that originally carried the leaving group, namely 46:4 from the (*S*)-enantiomer and 42:8 from the (*R*)-enantiomer, showing that little equilibration of the intermediate η^3-complexes **233** and **234** could occur.[170] The resulting (global) ee is then very low (8% in this instance).[145−147] This powerful effect proved to be attenuated by the solvent, e.g., by switching from THF to CH_2Cl_2, which slows the nucleophilic attack, allowing the equilibration **233** ⇄ **234**, which leads to an overall increase of the global ee to 52% (Scheme 68). Similarly, addition of Cl^- (5 mol %) has also been found to minimize the memory effect, which can be understood in terms of accelerated collapse of an ion-paired[171] intermediate $[\eta^3$-(*c*-C_5H_7)-PdL$]^+$ $[O_2C$-*t*-Bu$]^-$ (L = **6a** in *P*,*C*-mode) and chloride-catalyzed diastereoisomer equilibration.[146,147] Nearly identical results were observed with the MOP catalyst (*S*)-**4a**/Pd.[145−147] Lloyd-Jones then developed a model of stereoconvergence and global ee in order to quantitatively analyze the magnitude of the memory effect.[147]

Ding has demonstrated that application of (*R*)-H_8-MAP derivatives **153a**−**f** as chiral ligands to allylic substitution with malonate nucleophiles resulted in the improvement of the enantioselectivity (86% ee with **153a** and ≤ 91% ee with **153f** vs 71% ee with **6a**) in toluene.[111] It is possible that the benzene analogues **153** have lower propensity to act as *P*,*C*-ligands (note that, in this case, it would lead to a total loss of aromaticity), which may shut off the memory effect associated with the *P*,*C*-coordination and thus lead to higher enantiomeric excess of the final product. The same ligands have also been applied to the allylic substitution with a nitrogen nucleophile, namely sodium salt of diformylamide (Scheme 69).[172] Although the enantioselectivity improved from **6** to **153f**, the actual yield was low (14% with **6** and 4% with **153f**). BINAP (**2**) proved superior, giving both high yield and good enantioselectivity. Further im-

Scheme 69



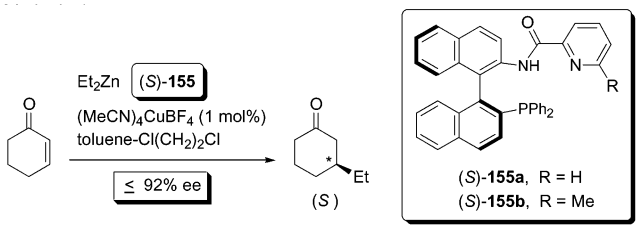
Ligand	solvent	temp (°C)	yield (%)	ee (%)
(*R*)-**6**	MeCN	20	14	46 (*R*)
(*R*)-**153a**	MeCN	20	7	61 (*R*)
(*R*)-**153f**	MeCN	20	4	69 (*R*)
(*S*)-**2**	MeCN	20	59	87 (*S*)
(*S*)-**2**	$Cl(CH_2)_2Cl$	0	43	94 (*S*)
(*S*)-**2**[a]	$Cl(CH_2)_2Cl$	0	99	95 (*S*)

[a] 1 equivalent of Et_3N was added.

provement was attained with BINAP (**2**) by changing the solvent to dichloroethane.[172]

MAP-type picolinic amides **155a**,**b** have been employed by Zhang as chiral ligands in the copper-catalyzed 1,4-addition of Et_2Zn to cyclohexenone. While **155a** gave 91% ee, its methyl analogue **155b** exhibited marginally higher enantioselectivity (92% ee) (Scheme 70).[117]

Scheme 70



ligand	Cu precursor	ligand/Cu ratio	solvent	temp (°C)	yield (%)	ee (%)
(*S*)-**155a**	$Cu(MeCN)_4BF_4$	2.5:1	a	0	82	82
(*S*)-**155a**	$Cu(MeCN)_4BF_4$	2.5:1	b	0	76	70
(*S*)-**155b**	$Cu(MeCN)_4BF_4$	2.5:1	b	−20	98	92
(*S*)-**155a**	$Cu(OTf)_2$.benzene	2.5:1	a	0	100	82
(*S*)-**155a**	$Cu(OTf)_2$.benzene	5:1	a	−20	76	91
(*S*)-**155b**	$Cu(OTf)_2$.benzene	2.5:1	a	−20	100	89

a: toluene b: toluene:dichloroethane 2:1

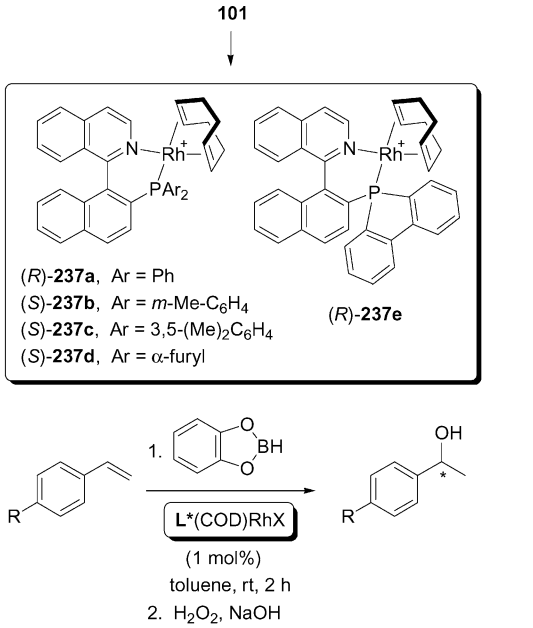
E. QUINAP and Its Congeners in Transition Metal-Catalyzed Reactions

Brown has developed asymmetric, rhodium-catalyzed hydroboration of substituted styrenes with QUINAP (**101a**−**g**)[81a,c] and PHENAP (**102**)[85b] as chiral ligands (Scheme 71).[87f] The catalysts **237** were pre-formed from $(COD)RhIBF_4$ or (COD)RhI(acac)/Me_3SiOTf and the respective ligand in THF; the individual reactions were carried out in CH_2Cl_2 at room temperature. The regiochemistry of the reaction was very much in favor of the formation of the branched (i.e., chiral) alcohol (≥88%). The enantioselectivity (≤97% ee) proved to be moderately sensitive to the ligand structure: the diarylphosphino complexes (e.g., **237a**) gave the best results with electron-rich styrenes, while difurylphosphino complex **237d** was identified as the champion ligand for electron-poor substrates. The styrenes may carry (*E*)- or (*Z*)- substituents but not α-substituents.[81c] Excellent regioselectivities and high enantioselectivites were obtained for cyclic olefins, such as indene.[81c] Generally, lower enantioselectivities were observed for PHENAP (**102**).[85b] X-ray crystallography, in conjunction with molecular modeling, has been employed to rationalize the various stereochemical outcomes.[81c]

Guiry has extended these Rh-catalyzed hydroboration studies by application of quinazolinap **103**: styrene and its para-substituted derivatives (X−$C_6H_4CH{=}CH_2$) gave ∼4:1 regioselectivity in favor of the branched isomer with 79, 81, and 49% ee, respectively, for X = H, MeO, and Cl. Indene, as a representative of cyclic olefins, exhibited both higher regioselectivity (98:2) and higher enantioselectivity (84%).[87b] Further improvements (up to the level of QUINAP) will be published in due course.

Hydroboration/amination represents another fruitful application of the Rh−QUINAP catalyst **237a**

Scheme 71[a]



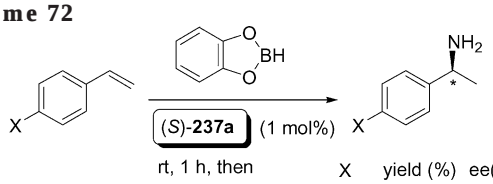
R	catalyst	yield (%) / ee (%)	R	catalyst	yield (%) / ee (%)
Me	(*R*)-**237a**	75 / 89 (*R*)	Cl	(*R*)-**237a**	82 / 78 (*R*)
Me	(*S*)-**237b**	79 / 88 (*S*)	Cl	(*S*)-**237b**	72 / 65 (*S*)
Me	(*S*)-**237c**	77 / 79 (*S*)	Cl	(*S*)-**237c**	77 / 54 (*S*)
Me	(*S*)-**237d**	79 / 88 (*S*)	Cl	(*S*)-**237d**	78 / 82 (*S*)
Me	(*R*)-**237e**	76 / 71 (*R*)	F	(*R*)-**237a**	77 / 80 (*R*)
EtO	(*R*)-**237a**	82 / 94 (*R*)	F	(*S*)-**237b**	77 / 70 (*S*)
EtO	(*S*)-**237b**	80 / 87 (*S*)	F	(*S*)-**237c**	72 / 65 (*S*)
EtO	(*S*)-**237c**	73 / 70 (*S*)	F	(*S*)-**237d**	77 / 75 (*S*)
EtO	(*S*)-**237d**	72 / 78 (*S*)	F	(*R*)-**237e**	71 / 70 (*R*)
EtO	(*R*)-**237e**	77 / 68 (*R*)	CF_3	(*R*)-**237a**	81 / 45 (*R*)
Me_2N	(*R*)-**237a**	55 / 62 (*R*)	CF_3	(*S*)-**237b**	84 / 23 (*S*)
Me_2N	(*S*)-**237d**	67 / 79 (*S*)			

[a] X = BF_4, CF_3SO_3.

(Scheme 72).[173] The regioselectivities reported are excellent and enantioselectivities high (77−98% ee).

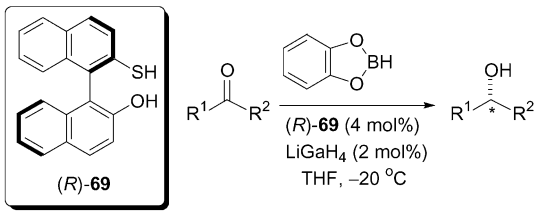
Both Brown[174] and Guiry[175] have also studied the ever popular Pd-catalyzed allylic substitution. With 1,3-diphenylpropenyl acetate (**229a**) and malonate nucleophile, QUINAP (**101a**) gave 98% ee with sodiomalonate and 76% ee under base-free conditions (using the BSA method); methylcyclohexenyl carbonate afforded the substitution product in 67% ee.[174a] PHENAP (**102**) exhibited 95% ee in the case of 1,3-diphenylpropenyl acetate (**229a**), while methylcyclohexenyl carbonate furnished a racemic product.[174b] The intermediate η^3-complexes were extensively studied by a combination of ^1H NMR spectroscopy and

Scheme 72

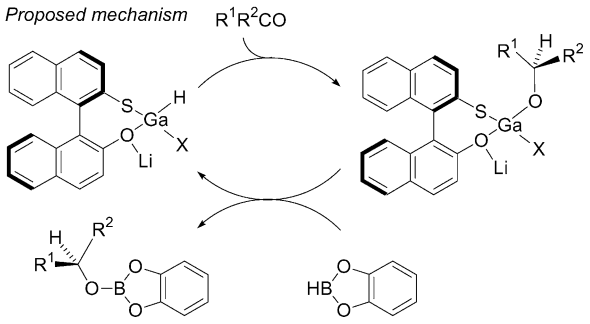


X	yield (%)	ee(%)
H	54	87
MeO	56	98

Scheme 73



R^1	R^2	temp (°C)	time (h)	yield (%)	ee (%)
Ph	Me	-25	18	90	90
Ph	Et	-25	18	96	93
Ph	*n*-Bu	-25	18	80	92
Ph	*i*-Pr	-15	60	65	24
Ph	*i*-Bu	-15	60	65	92
4-Br-Ph	Me	-25	18	80	87
4-Me-Ph	Me	-25	18	95	87
Ph	CH_2Br	-25	18	60	70
Ph	CH_2Ph	-20	19	88	68
2-furyl	*n*-C_6H_{13}	-25	18	76	81
1-naphthyl	Me	-20	20	82	59
2-naphthyl	Me	-20	20	83	73
Ph	C≡CH	-15	60	50	0
PhCh=CH	Me	-25	18	70	75
EtC≡C	Me	-25	18	60	63
HC≡C	*n*-C_5H_{11}	-25	18	88	22
HC≡C	*n*-C_5H_{11}	-25	18	50	12
i-Pr	Me	-20	18	81	69
i-Bu	Me	-20	18	93	46
c-C_6H_{11}	Me	-20	18	72	72
t-Bu	Me	-20	18	76	79



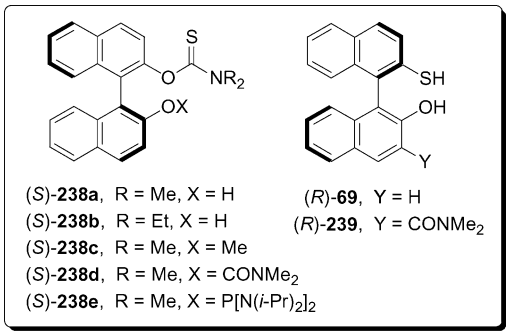
X-ray crystallography, and predictions were made as to the stereochemical outcome.[174] Quinazolinaps (**103** and **104**) exhibited rather low enantioselectivites (≤36 and 88% ee, respectively with BSA), but, interestingly, the product had the opposite absolute configuration to that formed in the case of QUINAP and PHENAP.[175]

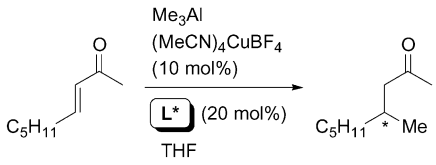
F. Thio Ligands in Transition Metal-Catalyzed Reactions

As discussed in the historical introduction, in 1979 Noyori developed a stoichiometric method for the asymmetric reduction of ketones, using BINOL-$LiAlH_4$, with the enantioselectivity of ≤99%, then unheard of.[7,176] It took two decades before that protocol was transformed into a catalytic process. Thus, Woodward has shown that an in situ-generated complex of mono-thio-BINOL **69** (4 mol %) with $LiGaH_4$ (2 mol %), which in turn was prepared fresh from $GaCl_3$ and LiH, can act as a catalyst in the reduction of ketones with catecholboranes as the terminal reducing agents (Scheme 73).[177] Aryl/*n*-alkyl ketones (e.g., with R_1 = Ar, Het; R_2 = Me, Et, *n*-Bu) are reduced in 90−93% ee, whereas branched ketones (R_2 = *i*-Pr, cyclohexyl, *t*-Bu) give 60−72% ee. Detailed NMR studies have improved the insight into the mechanism, suggesting that dimeric species are involved.[177]

Thiourea derivatives of BINOL, **238a**−**e**, have been employed as chiral ligands by Woodward in the copper-catalyzed 1,4-addition of Me_3Al, MeMgBr, and Et_2Zn to α,β-unsaturated ketones (Scheme 74);[178] the

Scheme 74





L*	conversion	yield (%)	ee (%)
(*S*)-**238a**	96	80	50
(*S*)-**238b**	93	75	40
(*S*)-**238c**	69	31	12
(*S*)-**238d**	46	23	15
(*S*)-**238e**	90	63	8

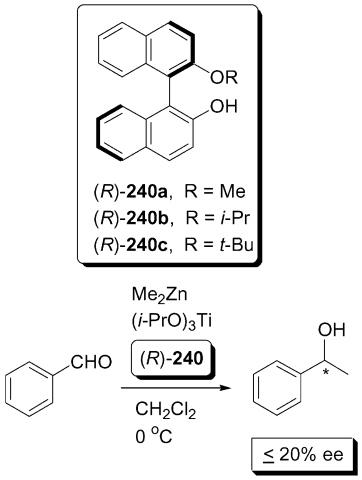
highest enantioselectivity (50% ee) was observed for **238a** with 20 mol % of the ligand present. Other ligands, such as **69** and **239**, exhibited generally lower enantioselectivities.[70c,179]

G. Miscellaneous Non-Symmetrically Substituted 1,1′-Binaphthyls as Chiral Ligands

Mono-functionalized BINOLs (*R*)-**240a**−**c** catalyze dialkylzinc addition to aromatic aldehydes with modest enantioselectivity (Scheme 75).[180] Mechanistic and crystallographic studies revealed the existence of several di- and tri-nuclear species and the absence of a non-linear effect. Moreover, the reactive species in the stoichiometric and catalytic reaction turned out to be different. The role of Me_2Zn appears to be to transfer the methyl first to Ti rather than directly to the aldehyde. A mechanism has been proposed that involves (L*)Ti(O-*i*-Pr)$_2$(aldehyde)·MeTi(O-*i*-Pr)$_3$ intermediate.[180]

The Lewis acidic species, generated from the ruthenium complexes of BINAPO (*S*)-**55a** and Tol-BINAPO (*S*)-**55b**, respectively, by treatment with $AgSbF_6$, have been shown by Faller to catalyze

Scheme 75

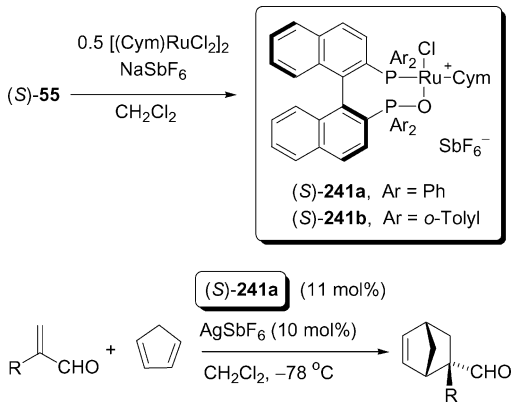


BINOL (**1**) is superior to **240a-c**.

Diels−Alder cycloaddition of cyclopentadiene to substituted acroleins (Scheme 76) with high diastereoselectivity (≤99%) and enantioselectivity (≤99% ee). By contrast, when parent diphosphines, i.e., BINAP (*S*)-**2** and the corresponding tolyl analogue, were employed as ligands, the opposite enantiomer of the product was obtained with much lower enantioselectivity (19−50% ee). The superior performance of **55a** and **55b** has been attributed to the electronic dissymmetry at the Ru center rather than to effects that may arise from the differences in chelate ring size.[181] The mechanism presented by Faller does not take into account the possible η^2-coordination of Ru to **55a**, demonstrated for a similar system at about the same time as his report.[155]

Conjugate addition of various aromatic boronic acid derivatives (Scheme 77) can be catalyzed by Pd complexes of BINAP (**2**) and its congeners. With the C_1-symmetrical analogue (*R*)-**56d**, the corresponding product was obtained in 54% yield and with 96% ee. BINAP (**2**) reacted with similar efficiency.[60b]

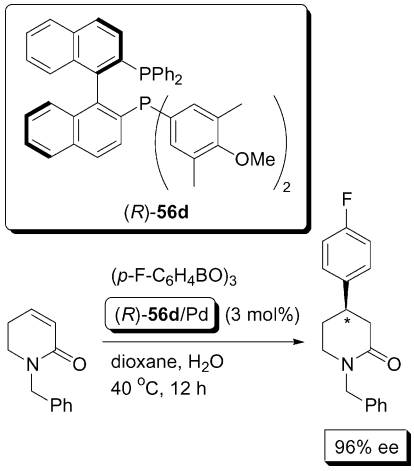
Scheme 76[a]



R	temp (°C)	de (%)	ee(%)
Me	-78	93	99
Me	-24	99	94
Et	-78	99	95
Et	-24	99	93
Br	-78	96	76
Br	-24	88	50

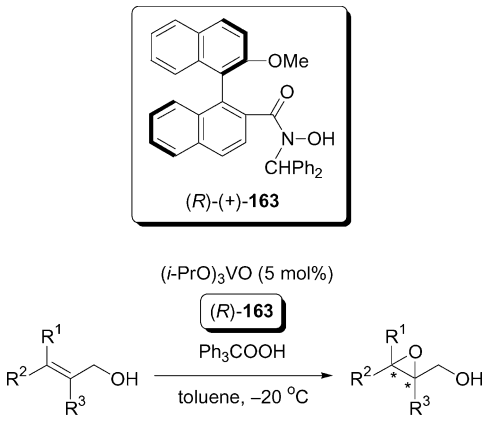
[a] Cym = *p*-cymene.

Scheme 77



Hydroxamic acids (*R*)-**161**−**163** have been utilized as chiral ligands in the vanadium-catalyzed epoxidation of allylic alcohols (Scheme 78) by H. Yama-

Scheme 78



Alkene	yield (%)	ee (%)
Ph, OH	14	71 (*S*,*S*)
Ph, OH	70	78 (*S*,*S*)
Ph, OH	96	91 (*S*,*S*)
Ph, OH	53	39 (*S*)
Ph, OH	19	38 (*S*,*R*)
OH	61	87 (*S*,*S*)
OH	59	94 (*S*,*S*)
geraniol	80	66 (*S*,*S*)
nerol	87	41 (*S*,*R*)
OH	16	40 (*S*)

moto;[132] ligand (*R*)-**163** has been found to give the highest enantioselectivities.

Hydroxy imide (+)-**94** served as chiral catalyst in the oxygen-mediated oxidation of substituted indenes to the corresponding indenones; however, the enantioselectivity was extremely low (~2% ee). Marginally better results were obtained in the attempted kinetic resolution by oxidation of racemic dioxolenes (≤12% ee).[80]

Combination of a binaphthyl skeleton with the well-established oxazoline moiety represents another appealing option in asymmetric catalysis. Ligands (*S*,*S*)-**60a**, (*R*,*S*)-**60a**, and (*R*,*S*)-**60b** (Scheme 15) have been employed in the Pd-catalyzed allylic substitution, again using 1,3-diphenylpropenyl acetate (**229a**) and dimethyl malonate in the presence of BSA.[66] While (*S*,*S*)-**60a** catalyzed the formation of the (*S*)-product in 85% ee,[66a] (*R*,*S*)-**60b** gave the (*R*)-product of 96% ee,[66b] demonstrating that the chiral axis of the binaphthyl scaffold plays the decisive role in determining the stereochemical outcome.

IV. Conclusions

In this review, we have shown various aspects of 1,1′-binaphthyl chemistry, in particular the synthesis of C_1-symmetrical derivatives and their application in asymmetric catalysis. The success of MOP (**4**), NOBIN (**5**), MAP (**6**), QUINAP (**101a**), and their congeners in the past decade demonstrates that hetero-bi-dentate C_1-symmetrical ligands represent a valuable addition to the existing C_2-symmetrical realm and that they can serve very well in the areas in which their better known C_2-symmetrical relatives, such as BINOL (**1**) or BINAP (**2**), may fail. It also shows that new methodology opens new horizons, which is best illustrated with the example of NOBIN (**5**): although the original synthesis in 1991−2 was straightforward (Scheme 1), it was not applicable on a large scale, owing to the toxicity of one of the crucial components; as a result, the catalytic applications were sparse. With the arrival of the new, benign synthesis a decade later (Scheme 29), its applications are growing.[182]

Aside from the development of highly efficient catalytic methodology based on these ligands at the center, new structural and mechanistic phenomena have also arisen, such as the unusual *P*,*C* σ-coordination (e.g., Scheme 62), which contributes to the wealth of our knowledge of the fascinating behavior of transition metals.

While the use of C_1-symmetrical binaphthyls in asymmetric catalysis is likely to rapidly grow further, applications will undoubtedly be sought in other areas as well, such as in the stereocontrolled polymerization and in the development of new chiral sensors. The present authors wish all those who will pursue these goals the best of luck and feel proud for being part of some of the early developments.

V. Acknowledgments

We thank the many students, co-workers, colleagues, and external collaborators who participated in various parts of the projects which constitute our contribution to the binaphthyl chemistry as highlighted in this review, and whose names appear in the reference section. In particular, we are indebted to Drs. Vladimír Hanuš, Miroslav Lorenc, Jana Poláková, Jana Polívková, Stanislav Jaracz, Luděk Meca, Iva Tišlerová, Miroslav Polášek, Ivana Císařová (all in Prague), Vratislav Langer (Göteborg), Robin D. Brooks, Russel M. J. Stead, Andrew P. Abbott, Thomas A. Claxton (all in Leicester), Steve Lockhart, Lenka Dufková, and Radim Hrdina (all in Glasgow). Particularly fruitful was the collaboration with Dr. Guy C. Lloyd-Jones (Bristol) and Prof. Yuri N. Belokon (Moscow) and their research groups. We also thank GAČR, EPSRC, NATO, Charles University, University of Leicester, University of Glasgow, Merck Sharp & Dohme, GlaxoSmithKline, and Dr. Alfred Bader for support.

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(27) Among the byproducts are the corresponding dibenzocarbazoles (refs 15 and 26).
(28) For definition, see ref 1, pp 316, 364, and 1193.
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