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Perspective

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Quinap and Congeners: Atropos PN ligands for Asymmetric Catalysis

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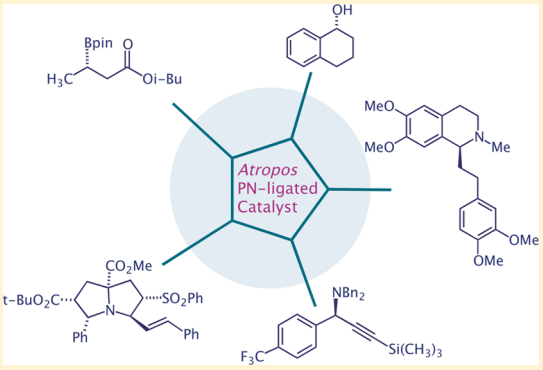
ABSTRACT: Among the range of P,N-chelating ligands that have been employed in asymmetric catalysis, those relying on atropisomerism for the stability of individual enantiomers form a definable class. These APN (*atropos* P,N) ligands require a specific type of biaryl, with one component carrying a pendant phosphine unit, most commonly diaryl substituted, and the other bearing an sp^2-nitrogen adjacent to the biaryl link. When substituents in the biaryl inhibit rotation about the linking bond, stable nonracemizing six-membered ring chelates can be formed. This Perspective relates the background to the initial synthesis in 1993 of Quinap, the original member of the series, and initial observations on its effectiveness in asymmetric catalysis. The current state of play in development of syntheses of this and other members of the APN ligand family is assessed, and their applications in asymmetric catalysis are presented. These include hydroboration and diboration of alkenes, 1,3-dipolar cycloadditions, alkynylation of iminium salts in a three-component (A^3) condensation, and conjugate additions of Cu acetylides.



SYNTHETIC ROUTES TO APN LIGANDS

The development of ruthenium catalysts by Noyori and co-workers in the mid-1980s extended the reaction scope of asymmetric hydrogenation immensely. Together with parallel work on the isomerization of tertiary allylic amines to enantiomerically pure enamines through rhodium catalysis, this brought their atropisomeric Binap ligand to high prominence.[1] Around the same time, Hayashi, Kumada, and co-workers had successfully demonstrated the utility of ferrocene-based P−N ligands in diverse areas of asymmetric catalysis, in particular for C−C and C−heteroatom couplings.[2] These precedents provided the incentive for synthesizing a P−N analogue of Binap, and the close structural relationship of this ligand (named Quinap by analogy to Binap) made it the focus of our efforts. The parent heterocycle lacking the PPh_2 group is known[3] and racemizes readily below ambient temperature, although the steric bulk of the PPh_2 group was expected to provide an effective barrier in the desired ligand. It was rapidly discovered that the conceptually simple route by direct metalation was not successful but that access to a related ligand by a lithiation route could be achieved readily.[4] Unfortunately, the latter proved stereochemically labile, sufficiently so to preclude resolution.

In late 1991, David Hulmes was starting his doctorate in Oxford and accepted the original challenge of the synthesis and resolution of Quinap, now using a Suzuki coupling for the key C−C bond-forming step. This worked remarkably well on a 0.25 molar scale, and the remaining steps to synthesize the racemic ligand were achieved by conventional chemistry. Resolution proved difficult until the palladium complex derived from (*R*)- or (*S*)-1′-(dimethylamino)-1-ethylnaphthalene was used, when two very easily separated diastereomeric salts were formed.[5] This procedure did not work with the simpler (*R*)- or (*S*)-1′-(dimethylamino)-1-ethylbenzene complexes and depends critically on the enforced rigid conformation of the Pd complexes where the C-methyl of the side-chain is locked in an axial position.[6] The two diastereomeric complexes possess distinct geometries, as confirmed by X-ray, and this distinction leads to remarkably distinct solubilities. Initially, the resolution was carried out by fractional crystallization of the diastereomeric complexes. Later, and more economically, the method of half-equivalents was used, in effect a thermodynamic resolution in which the more stable of the two Pd complexes was separated by crystallization of the enantiomerically pure free ligand. This route can now be used to synthesize 20 g of each hand of ligand routinely according to Scheme 1.[7]

Essentially the same general method was used to prepare analogues of Quinap where the phosphine unit is modified.[8] The synthesis is robust but suffers from two inherent disadvantages: the resolution step requires a stoichiometric palladium complex (which can in principle be recycled) and the phosphine is introduced prior to this resolution step, limiting the ease of access to ligand diversity that is desirable for modern industrial application.

These limitations have encouraged alternative synthetic routes, both to related motifs (vide infra) and to Quinap itself. A potentially productive strategy was opened up through the

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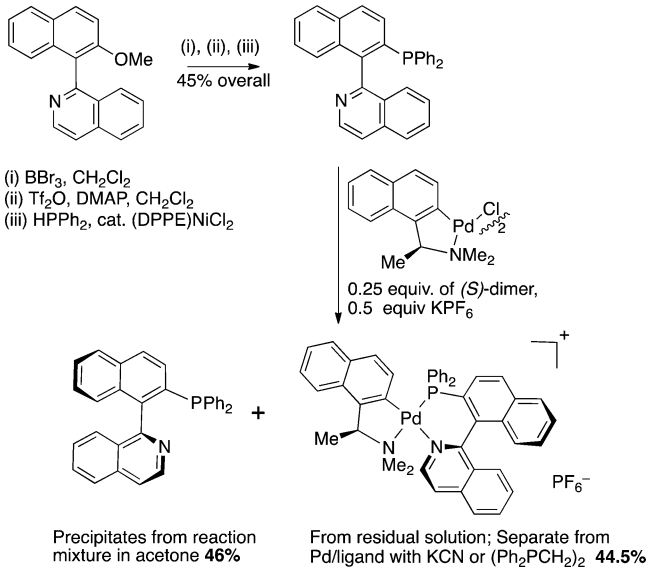
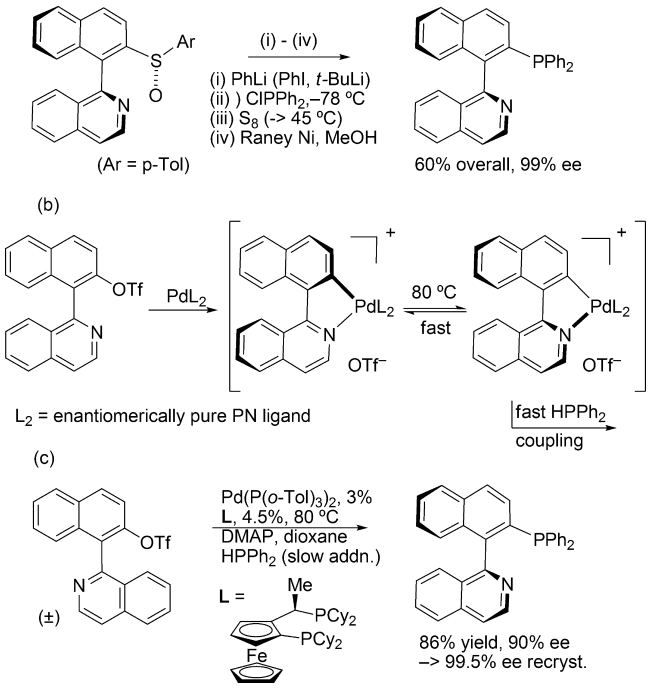
Scheme 1. Synthesis and Resolution of Quinap, from ref 7



Scheme 2. Key Steps in New Syntheses of Quinap (a) from ref 10; (b) DKR of the Reactive Cationic Intermediate (ref 14); (c) from ref 12



initial results of Baker, Sargent, and co-workers.[9] They demonstrated that the (*S*)-sulfoxide (Scheme 2) will couple with arylmagnesium reagents through sulfoxide displacement, partially retaining the configuration at the new interaryl bond. Unfortunately, there is substantial loss of enantiomeric purity that limits the utility of this approach. Knochel's approach also involved the same sulfoxide intermediate but avoided this problem.[10] The precursor was formed in one step by Negishi coupling of two arene precursors and then converted into a diastereomeric mixture of sulfoxides with the enantiomerically pure sulfinate, which were separated by chromatography. Further phosphinylation and reduction of the individual isomers followed by reduction gave both hands of enantiomerically pure Quinap via a short efficient process. Thermal equilibration of the diastereomeric sulfoxide intermediates was demonstrated to be biased in favor of the $(R)(R)_{ax}$ over the $(R)(S)_{ax}$ isomer, simplifying the separation process and hence giving access to one pure hand of the final ligand.[11]

A key paper was published in late 2013.[12] In principle, the synthesis of Quinap involves the construction of just two bonds, the first to couple the two aryl fragments and the second to introduce the phosphine, and then finally the ligand resolution stage. The basic framework was already readily accessible on a large scale. Stoltz, Virgil, and co-workers conceived the possibility of a dynamic kinetic resolution during C−P bond-formation, thereby combining key steps. This could be achieved starting from either the bromide or triflate precursor. This group had already demonstrated the feasibility of catalytic phosphinylation in the series.[13] Conditions were first found for Pd-catalyzed phosphinylation from the bromide with efficient kinetic resolution to give both phosphine product and recovered ArBr in high enantiomeric purity. The ensuing formation of product by phosphinylation of recovered bromide proved more challenging, since loss of enantiomeric purity occurred unless the opposite hand of the asymmetric catalyst to the one used in the first stage was employed. Initial attempts at DKR with the more stereolabile triflate or tosylate were not so successful; these reactants racemized at 80 °C over several hours, while the bromide was stable under these conditions. The breakthrough came when it was realized that the cationic oxidative addition intermediate shown in Scheme 2b stereomutated rapidly once formed, and this encouraged slow addition of $HPPh_2$ so that the intermediate had a better chance to equilibrate before reacting to form the product. The optimized procedure for the step is shown in Scheme 2c.

An explanation for the configurational lability of the palladium intermediate lies in concurrent work by Fernandez, Lassaletta, and co-workers.[14] Their objective was similar, aimed at a general asymmetric synthesis of atropisomeric heterocycles by DKR. In the course of this work, they secured an X-ray structure corresponding to the Pd intermediate shown in Scheme 2b, with a different ligand. The N−Pd−C chelate ring is distorted by angular constraints such that the C−Pd vector and the N−Pd vector are bent away from coplanarity with their arenes, by 26° and 32° respectively. There are two independent conformations that arise through strain in the Pd-coordinated intermediate and their interconversion effects interconversion of the $(R)_{ax}$ and $(S)_{ax}$ atropisomers.

All the syntheses described thus far are based on a 6-ring heterocyclic component. In the one attempt made to incorporate an indole unit bearing the PPh_2 group in the ligand, the product proved too stereolabile for catalytic applications.[15] Recent work by Aponick and co-workers has provided an elegant alternative by effectively freezing racemization about the biaryl linkage (Scheme 3). The basic idea involved incorporation of an imidazole where the nonligating nitrogen carried a $CH_2C_6F_5$ group that was anticipated to engage in π,π-interaction with the electron-rich naphthalene. This made a sufficient enhancement to the stability of enantiopure complexes of the ligand that they were highly effective in asymmetric catalysis. Furthermore, the palladacycle intermediate analogous to the Quinap resolution complex racemized under forcing conditions, permitting isolation of the thermodynamically preferred diastereomer in 81% yield.[16]

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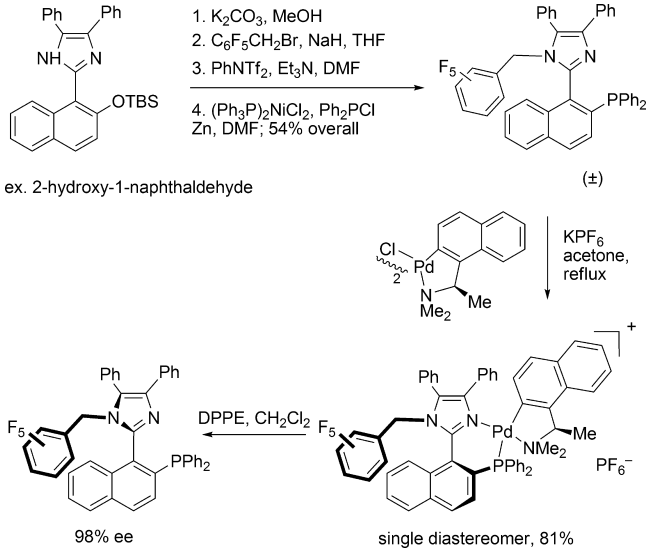
Scheme 3. Synthesis of a Ligand from Aponick's Group Where Atropisomer Interconversion Is Inhibited by π-Stacking

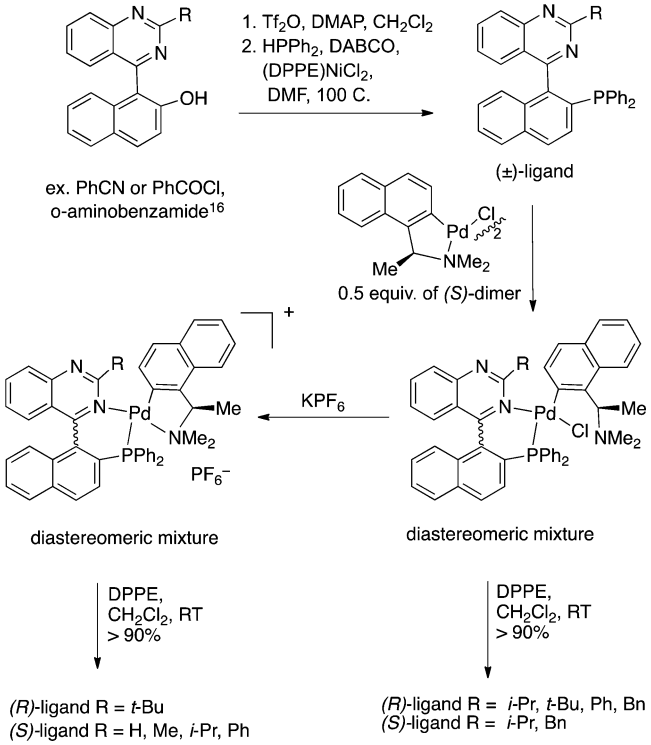


The late resolution step exposes a limitation inherent in the synthesis of Quinap, since the main potential for structural modification is through varying substituents at phosphorus. In the related quinazoline-based ligands, the substituent at the 2-position flanked by the two heteroatoms is easy to vary and such variation will change the electronic and steric environment of catalysis. This was a logical road to follow, and the synthesis by Guiry and co-workers proved straightforward; the R-group in the ligand was formally derived from RCOCl or RCN, introduced at an early stage[17,18] (Scheme 4). After the aryl components were coupled, the synthesis and resolution proceeded smoothly for an extensive series of ligands, for which 2-R was varied. In this way, a wide variety of side chains was introduced. Two pathways were developed for the resolution step, depending on the solubility properties of the intermediates. Either the neutral PdCl complex diastereomers arising directly from the ligand/palladacycle addition step or the corresponding PF_6 salts formed by addition of KPF_6 were subjected to fractional crystallization, depending on the ease of separation in each case.

More recent work has considerably extended the range of available ligands in the Quinazolinap family, improved the ease of synthesis of a key precursor,[19] and enabled the introduction of functional side chains at the position flanked by the two nitrogen atoms.[20−23]

An alternative approach that provides late-stage flexibility arises from Carreira's work (Scheme 5).[24] Here, the heterocyclic moiety is based on phthalazin-4-one, and the site of variation arises naturally from the synthesis, since the enolic 4-position can be substituted with *N*- or *O*-alkyl groups. Introduction of a resolved stereogenic center through this substituent transforms the racemic ligand precursor into a pair of diastereomers that can be separated by chromatography or crystallization. 7-OMe-substitution in the naphthalene moiety provides a parallel set of ligands. The diastereoisomeric mixture of ligands prior to separation may be directly useful in catalysis under conditions where a nonlinear effect can operate (vide infra).

Scheme 4. Synthesis of Enantiomerically Pure Quinazolinap Ligands with Resolution through Neutral and/or Cationic Palladium Complexes



In summary, these developments have made a range of *atropos* P−N ligands (APN) accessible with the promise of more variants in the near future through recent advances in methodology.

■ CATALYSIS WITH APN LIGANDS: INITIAL WORK

With sufficient quantities of resolved Quinap in hand in 1993 (Scheme 1), attention turned to its application in catalytic asymmetric synthesis. Of various reactions subjected to a preliminary screen, only hydroboration and allylic alkylation showed promise, and initial work focused on these two areas. For allylic alkylation, a Pd−Quinap complex was an effective catalyst for the reaction between malonate and *rac*-1,3-diphenylallyl acetate (Scheme 6). Since the reaction involves a concurrent DKR of the substrate, some optimization was needed to obtain the final ee of 98%. NMR studies showed that two diastereomers of the intermediate 1,3-diphenylallyl−Pd complex were present in solution, and their relative configurations could be determined by NOE. This led to a model for the origin of enantioselectivity in which the nucleophile attacks *trans*-to phosphorus with a late transition state.[25] Similar conclusions on the mechanism of allylic alkylation had been deduced by Helmchen and co-workers on the basis of the X-ray structures of intermediates and later endorsed through the observation of reactive intermediates by NMR.[26,27] In 1993, three groups, including his, had published the first papers on catalysis using Phox ligands almost concurrently, with emphasis on their application in allylic alkylation, where they excelled.[28−30] In view of this, the Oxford work on allylic alkylation was not substantially extended.

Parallel work on the asymmetric hydroboration/oxidation of arylalkenes with catecholborane and Rh−Quinap catalysts proved to be successful, however. Enantiomer excesses were

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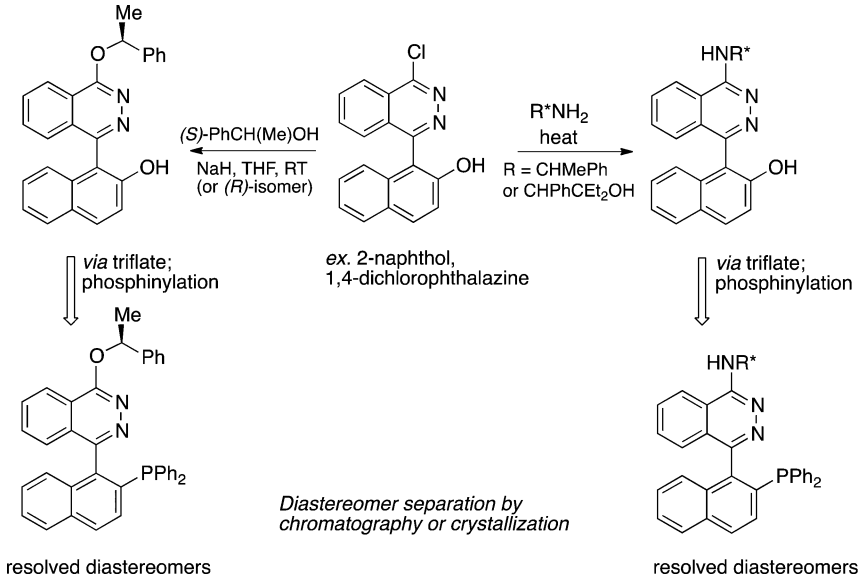
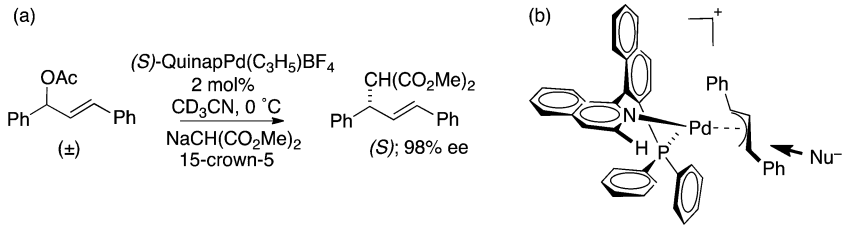
Scheme 5. Routes to PINAP Ligands That Avoid a Resolution Step through Incorporation of an Enantiomerically Pure Side Chain



Scheme 6. (a) Asymmetric Allylic Alkylation Employing (*S*)-Quinap; (b) Model for the C−C Bond-Forming Step with the Preferred Diastereomer

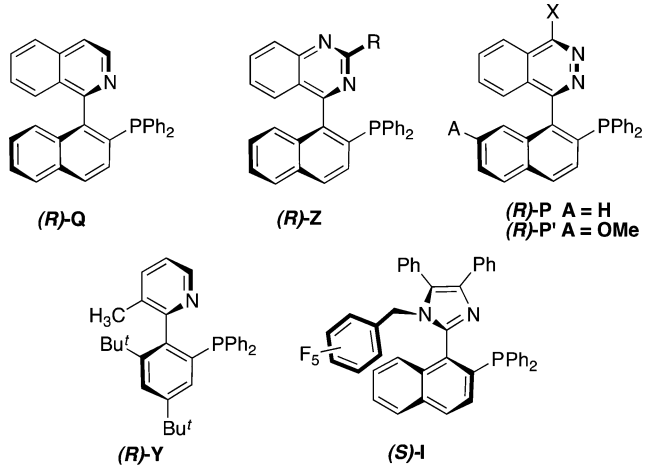


comparable to the best in the literature that had been achieved with Rh−Binap,[31] with two advantages. The reactions with Quinap were best conducted at rt rather than the low temperatures required with Binap, and a far wider range of alkenes could be reacted in acceptable (>90%) ee, as discussed in more detail below.[32]

■ CATALYSIS WITH APN LIGANDS: STATUS QUO

In the following sections we summarize the contributions of this class of ligands to asymmetric catalysis. The content is selective rather than exhaustive; thus, the cited procedure should be the best in the literature for the particular class of reaction, or at least comparable with the best, and the ee needs to be at a useful level, normally ≥90%. The ligands are represented as **Q** (Quinap), **Z** (Quinazolinap), and **P** (Pinap) with suffixes to identify the variable side chain in the latter two; all are available as both atropisomers. The 2-phenylpyridine-derived ligand from Chan's group, **Y** (Pyphos, (*R*)-enantiomer),[33] is included in the hydroboration section; Aponick's imidazole-based ligand **I** ((*S*)-enantiomer) is included in the section concerned with asymmetric alkynylation, where excellent results have been obtained.

A. Hydroboration of Arylalkenes. All early work in the field using Quinap as ligand followed the original experiments of Mannig and Nöth, where catecholborane (CB) was used as reagent. In asymmetric hydroboration, the broader applicability of the ligand family over Binap was apparent in the extension to nonterminal and cyclic arylalkenes, as exemplified in



Scheme 7. All prototypical APN ligands are comparably successful in the reaction, and in many cases, the tunability of the Quinazolinap family provides the most effective examples. The regiochemistry of reaction is normally strongly biassed toward boration of the benzylic position.

For *rac*-1-substituted 1,2-dihydronaphthalenes, good levels of kinetic resolution in hydroboration/oxidation were observed using Quinap enabling both the alkene reactant and the secondary alcohol product to be produced in high enantiomer excess.[34] For nonsymmetrical stilbenes of either (*E*)- or (*Z*)-configuration, electronic effects drive boron substitution adjacent to the more electron-poor ring. The regioselectivity

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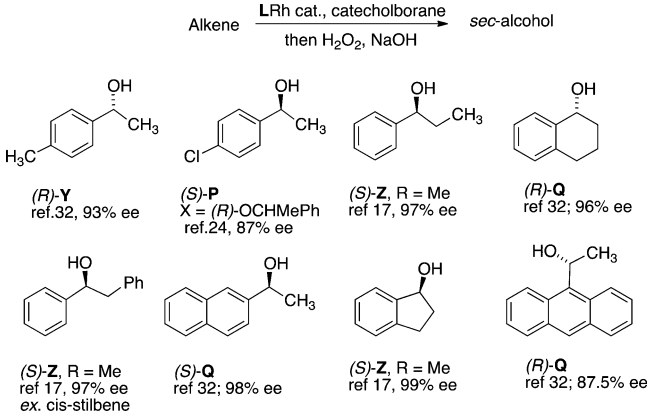
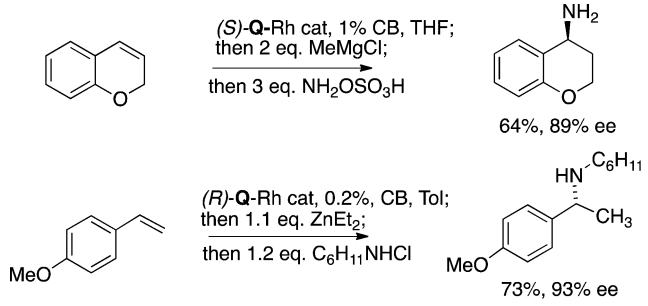
Scheme 7. Examples of Catalytic Hydroboration/Oxidation of Arylalkenes, Where the Major Product Shown Is Obtained in High ee; $(S)_{ax}$ Ligand Correlates with (*S*)-Alcohol in All Cases



Scheme 8. Examples of Asymmetric Hydroboration/Amination with Quinap as Ligand Leading to (a) Primary or (b) Secondary Amines (CB = Catecholborane)



is more marked for Quinap–Rh catalysis than for a simple diphosphine catalyst based on dppb and in favorable cases leads to a predominance of a single product in high ee.[35] The robust nature of the cationic Quinap–Rh complex involved in hydroboration is underscored by the use of a Montmorillonite MK10-supported version, where the clay support is the source of the counteranion. This heterogeneous catalyst operates through four to five successive cycles with minimal decline in product enantioselectivity following H_2O_2 oxidation, equal to the homogeneous catalyst. There is an initial cycle in which the supported catalyst is primed, for which the product has a lower ee.[36]

Unlike trialkylboranes, boronate esters cannot be converted directly into amines by established synthetic protocols. A simple method was discovered for achieving this desirable transformation that involved prior in situ alkylation of the ester with 2 equiv of MeMgCl or Et_2Zn; the former was developed later and is preferred for primary amine synthesis. Conventional electrophilic aminating agents—HO_3SNH_2 for primary amines and R′NHCl for secondary amines—can then be used on the resulting R_3B compound. There is a very strong preference for migration of the benzylic fragment rather than the Me or Et moiety to nitrogen. The multistep procedure is advantageously carried out in a single pot. The level of enantioselection is comparable to that observed in H_2O_2 oxidations; for secondary amines, the yields were also comparable and for primary amines somewhat lower (Scheme 8).[37]

The mechanism of asymmetric hydroboration using Quinap, in comparison with related ligands, has been addressed in a detailed QM/MM computational study.[38] In parallel NMR studies it was shown that a Rh hydride adduct with two cis P–H couplings was formed on addition of catecholborane to (Binap)Rh(COD)·BF_4 in the presence of excess styrene. Hydridic species were not observed in the corresponding experiment with the Quinap–Rh complex. Computational analysis indicated a 5-coordinate adduct as the key intermediate in catalytic hydroboration with axial-H and the alkene trans-N, with an important stabilizing π–π interaction between ligand and alkene. A careful comparison was made between pinacolborane (PB) and catecholborane (CB) as reagents and for Quinap-Rh vs Binap-Rh at rt.[39−41] Under these defined conditions Quinap–Rh was the superior ligand and CB the superior reagent, save with the electron-deficient 4-fluorostyrene. An important observation was made concerning catalyst delivery; availability of chloride ion through deliberate addition of $R_4N{\cdot}Cl$ to the cationic complex, or using free ligand plus $[(COD)RhCl]_2$, consistently enhances the ee.

B. Catalysis with Diboron Reagents. Diboration of alkynes and alkenes using dicatechol–diborane has been known since 1993,[42,43] but the major breakthrough for asymmetric catalysis came from Morken's group. They showed that alkenes reacted with this reagent at ambient temperature using ligated Rh(I) catalysts of which Quinap proved the most effective, and in many cases high ee's of the *syn*-addition product of consistent configuration were obtained in an efficient reaction after oxidation to the corresponding diol.[44,45] The catalytic reaction was particularly efficient for *trans*-disubstituted alkenes, and for the given examples the ee was ≥97% and isolated yields were 48–77% (Scheme 9a). *Cis*-disubstituted alkenes were reduced with poorer stereocontrol, and the product configuration varied with alkene structure. Competing hydroboration was observed with vinylarenes as reactant.[46] High enantiomeric purity was obtained for the diol products from the limited number of trisubstituted alkenes tested, less so for 1,1-disubstituted cases. For monosubstituted alkenes, an adjacent tertiary center was required for effective levels of enantiomeric purity in the resulting diol. In this last case, the two new C–B bonds in the initial product possessed distinct reactivity, with the terminal C–B preferentially replaced. This was demonstrated by homologation with $TMSCHN_2$ prior to oxidation[47] and by Suzuki coupling with aryl electrophiles (Scheme 9b).[48,49] Both of these reactions occurred regiospecifically at the terminal site. The reaction mechanism for the diboration was inferred to involve a straightforward oxidative addition of the B–B bond to rhodium followed by two successive insertion steps; this may possibly be worth reexamining in the light of more recent studies on metal-free nucleophile catalyzed addition of dipinacoldiborane to simple alkenes, where one boron is activated first, in a pathway that is in accord with parallel computational studies.[50]

Enantioselective β-boration of unsaturated carbonyl compounds through copper catalysis using dipinacoldiborane ($B_2(pin_2)$) has been established, and a useful variant involves Cu–Quinap or Cu–Quinazolinap catalysis. The reaction proceeds smoothly in high yield with ee's of up to 79%. The X-ray structure of a dimeric P-bound Cu–Quinazolinap complex was obtained (cf. ref 59).[51]

C. 1,3-Dipolar Cycloadditions. Catalysis of dipolar cycloadditions is prominent in the literature, and Schreiber's

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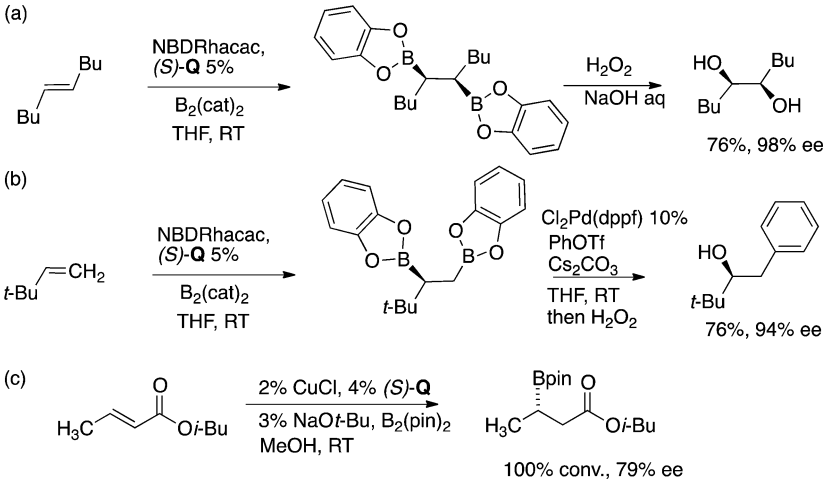
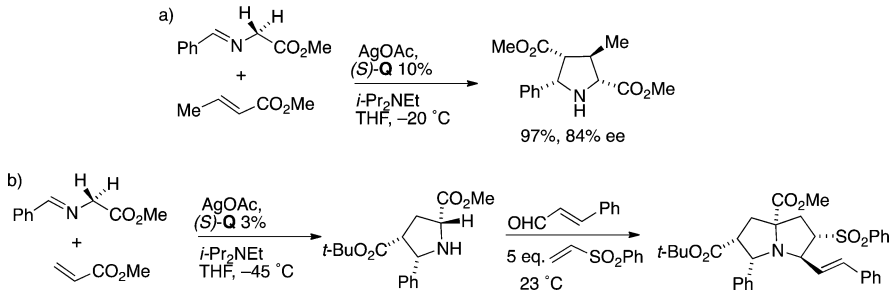
Scheme 9. (a) Example of Diboration of *trans*-Alkenes with $B_2(cat)_2$; (b) of Diboration Followed by Suzuki Coupling; (c) of Conjugate Addition Leading to β-Boration with $B_2(pin)_2$



Scheme 10. (a) Single and (b) Double Ag/Quinap-Catalyzed [3 + 2] Cycloadditions of Azomethine Ylides

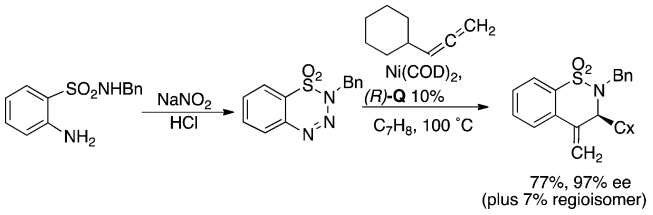


work provides an early example where Quinap was the preferred ligand.[52] Silver complex catalysis (AgOAc/(*S*)-Quinap) of the reaction of azomethine ylides with electron-poor alkenes at or below −20 °C gives a pyrrolidine product with up to four new stereogenic centers. The basic catalytic reaction had already been discovered,[53] but this paper extended the scope and selectivity and permitted a polystyrene bead-based variant for diversity studies. For the reaction with simple glycine-derived ylids and *tert*-butyl acrylate, a single diastereomer was formed in high ee. Azomethine ylids derived from α-substituted amino-acids gave products with a single quaternary center in ca. 80% ee. Using *tert*-butyl crotonate gave a product with controlled configuration at four ring centers, but now the ee was closer to 80% (Scheme 10a).

Enantioselective synthesis of pyrrolizidines through a double dipolar cycloaddition was developed by Reisman and co-workers, when cinnamaldehydes were used as the precursor of the azomethine ylide.[54] The second stage occurs when the initial pyrrolidine product formed by [3 + 2] cycloaddition reacts with a second aldehyde to form the iminium salt precursor of a new azomethine ylide. Conditions were found to optimize the two-step process in a single pot. Once achieved, this was extended to a range of related reactions varying the initial arylaldehyde, with cinnamaldehyde being used in the second step. This second step needs more forcing conditions than the first, and hence a different dipolarophile can be used. In this way, starting with (*R*)- or (*S*)-Quinap as the sole catalytic source of chirality, control of the stereochemistry of pyrrolizidines with five stereogenic centers (six centers if a prostereogenic dipolarophile is used) can be achieved on a gram scale (Scheme 10b).

Quinap was also the preferred ligand for a distinct type of cycloaddition.[55] The aminosulfonamide-derived heterocycle shown in Scheme 11 reacted under ligated Ni catalysis to give the corresponding cyclic sulfonamide in 86−97% ee and good regioselectivity, using cyclohexylallene as the reactant. The reaction is reasonably considered to involve the formation of a 5-membered nickelacycle with extrusion of N_2, followed by allene insertion preferentially at the more substituted double bond and then reclosure of the cycle through intramolecular capture of the sulfonamide. Variations of the reactant structure with substituents on the allene smaller than cyclohexyl were effective but gave somewhat lower enantiomeric purity in the product.

Scheme 11. Catalytic Asymmetric Nitrogen Extrusion and Allene Cycloaddition



D. Asymmetric Alkynylation of Iminium ions. In 2002, Knochel's group developed an asymmetric synthesis of propargylamines.[56,57] Their first reports involved direct reaction of a preformed tertiary enamine with a terminal

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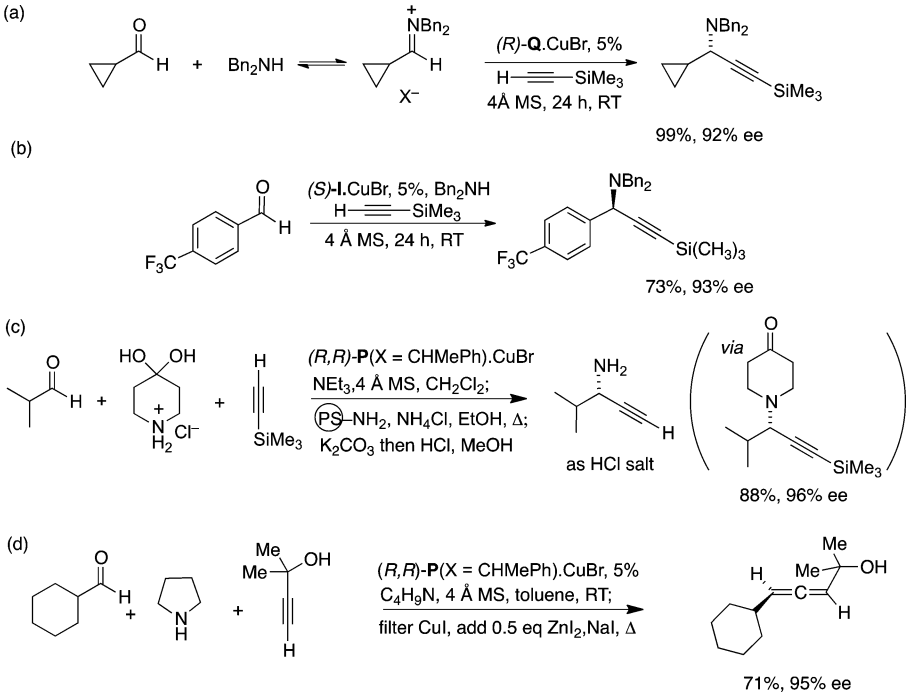
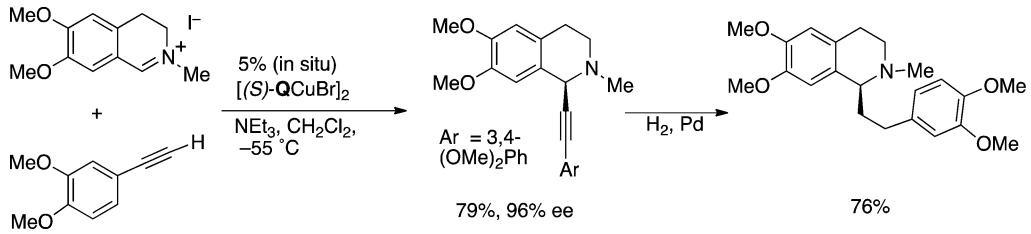
Scheme 12. Examples of the Three-Component Condensation Route (A^3) to Enantiopure Amines: (a) ref 59, (b) ref 16, (c) ref 64, (d) ref 65



Scheme 13. Asymmetric Catalytic Synthesis by Iminium/Alkyne Coupling



alkyne catalyzed by CuBr/Quinap at ambient temperature and gave the desired products in good yields with ee's varying from 54 to 90%. Subsequently, a more powerful adaptation utilized a three-component coupling between aldehyde, secondary amine, and alkyne, which gives good yields and ee's for dibenzylamines with a wide range of aldehydes and alkynes but is somewhat less effective for diallylamines (Scheme 12a).[58,59] With scalemic ligand, a striking positive nonlinear effect is observed. In line with this observation, the X-ray structure of the Cu complex formed between Quinap and CuBr is dimeric, with strong P−Cu bonding but a much weaker P−N association. The synthetic potential of this procedure has been demonstrated in several ways, summarized in the ensuing full paper (ref 59). The best results were obtained with silylalkynes that gave consistently high ee's, and this observation allowed an extension to a simple synthesis of the neurotoxin (*S*)-coniine. More generally, desilylation afforded terminal alkynes that could be further functionalized; reduction of the alkyne and debenzylation could be carried out sequentially, giving access to a variety of enantiomerically enriched primary amines.[60] The terminal alkyne moiety provides a template for the modular synthesis of enantiomerically pure 4-aminoalkyl-substituted pyrimidines[61] and for regiospecific click reactions with triazoles.[62] In the three-component condensation step, highest ee's were obtained with *N*-(mesitylmethyl)benzylamine.[63] Aponick's ligand gives good results for difficult aromatic aldehydes, exemplified by Scheme 12b. An alternative and effective route to primary amines involves piperidin-4-one as the amine reactant. In this case, a double-retro-Michael addition can be conducted in the workup stage to remove the five-carbon unit of the ring, giving the desired primary amine with concurrent desilylation under the reaction conditions (Scheme 12c).[64] Starting from a tertiary acetylenic alcohol as the alkyne component and pyrrolidine as the secondary amine and conducting the three-component condensation in the normal manner, addition of a half-equivalent of ZnI_2/NaI to the reaction mixture and heating after completion provides a stereospecific synthesis of trisubstituted allenes (Scheme 12d).[65]

A closely related CuX/Quinap-catalyzed reaction works well for the catalytic alkynylation of *N*-alkylated dihydroisoquinolines using excess alkyne at −55 °C, as shown by Schreiber and co-workers. Except for the case of MeOCCH, product ee values are ≥94%. The procedure is exemplified in Scheme 13 with an enantioselective synthesis of homolaudanosine, a neuroactive alkaloid. With the parent isoquinoline, alkynylation works at −20 °C, albeit with lower yield and ee.[66] The procedure has been utilized by Waldmann's group in developing analogues of noscapine as potential anticancer drugs that inhibit tubulin polymerization, and several hits were

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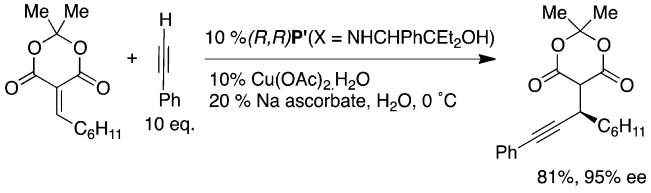
discovered in testing the products through a HeLa cell line assay.[67] In other examples, Carreira's Pinap ligand family has proved more effective than Quinap for heterocyclic condensation reactions, giving higher ee values in challenging cases.[68]

E. Conjugate Addition. Carreira's group carried out asymmetric additions of alkynes to alkylidene derivatives of Meldrum's acid, catalyzed by ligated copper complexes. The process is expected to be mechanistically similar to the A^3 three-component addition of alkynes, but the electrophilic component is now the alkene.[69,70] The malonate unit of Meldrum's acid in the reaction product can be removed by hydrolysis or aminolysis with concurrent decarboxylation, leaving a carboxylic acid derivative with a resolved chiral β-carbon atom. In initial screening, Quinap was the only ligand that gave significant ee's, but insufficient for synthetic use. Involvement of the Pinap ligand family with variable substitution patterns allowed the discovery of conditions where the reaction proceeded with >90% ee (Scheme 14). The

Scheme 14. Example of Enantioselective Copper-Catalyzed Conjugate Addition to Meldrum's Acid Derivatives



procedure for ligand synthesis described previously (Scheme 5) gives initially a pair of diastereomers—opposite atropisomers, but with the same hand of enantiomer for the substituent at C4 of the phthalazine. This mixture can be used in catalysis without chromatographic separation, and in specific cases a product with high ee arises.[71] There is a strong nonlinear effect based on the dimer reservoir effect under these conditions that causes the major part of the less abundant diastereomer to be associated as dimeric Cu complexes (cf. ref 59).[72] A similar strong nonlinear effect was found in A^3 coupling, related to Knochel's observations.

CONCLUSIONS

The original synthesis of Quinap was primarily intended for development of asymmetric cross-coupling, for which it proved to be ineffective. Nevertheless, the ligand family has provided an excellent return on the original synthetic efforts, through applications in diverse areas of catalysis.[73] Notably, the applications to rhodium-catalyzed asymmetric hydroboration and diboration remain competitive methodologies, many years after the original discoveries.

The individual character of the ligands can be assessed through X-ray structure analysis of their complexes, together with comparison to both Binap and Phox complexes. This approach reveals information on the relative rigidity of the chelate ring in different series and other conformational differences. The 6-membered chelate ring is formed at the expense of strain, manifested in the deviation from ideality seen in the direction of the N-metal vector; the metal is distorted out of the plane of the isoquinoline ring by 0.5−1.0 Å. This distortion limits the conformational flexibility of the chelate ring of Quinap-type ligands, as evaluated by comparing the range of endocyclic torsion angles about the P−M bond of the chelate, Quinap being the least flexible of the three series. (Figure 1). This is an advantage if the desired catalytic reaction has a strong "lock and key" component, less so if "induced fit" of catalyst and reactants is important.[74]

Ligand development for asymmetric catalysis serves two purposes; it enables the improvement of existing reactions and also the discovery of new ones. The original synthesis of Quinap encouraged advances in both of these areas. Continued progress most likely depends on the emerging ability to develop rapid access to variations on the original structure by enhanced synthetic/enantioselective approaches. In particular, the recent DKR approach for the phosphination step should permit straightforward syntheses of structurally varied phosphines.

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Notes

The authors declare no competing financial interest.

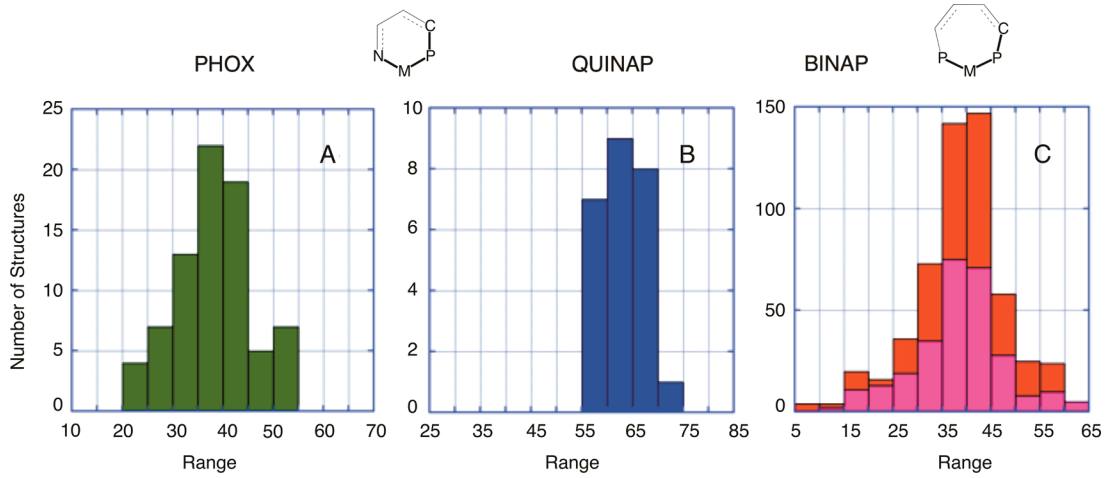

Figure 1. Variation in torsion angles about the M−P bond in P−N chelate complexes showing the narrower range involved with APN ligands. Shading in the Binap case C shows the two different torsions measured there. The information was obtained from the CSD database using Conquest software.[75]

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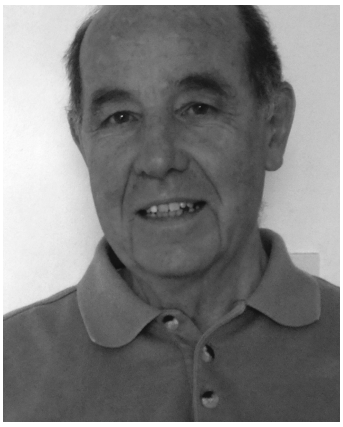
Biography



John Brown is a Manchester graduate who conducted his Ph.D. with Professor Arthur Birch on metal−ammonia reductions. This was followed by postdoctoral work with Professor Ronald Breslow at Columbia. After spells in Canberra, Bristol, and then Warwick (1966−1974) he moved to Oxford and has been Emeritus since 2008. His main research was and is catalysis by transition-metal complexes with emphasis on understanding their mechanisms and contributing to synthesis, particularly asymmetric synthesis. He was the recipient of the RSC Robert Robinson award for 2013.

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