Synthesis and application in asymmetric catalysis of camphor-based pyridine ligands

Giorgio Chelucci

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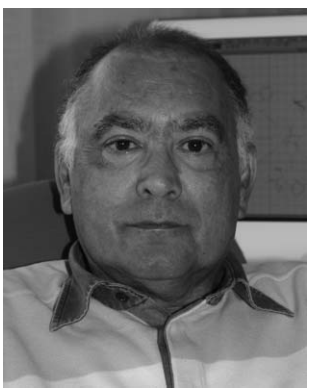
This *tutorial review* deals with the synthesis and application in asymmetric catalysis of camphor-based pyridine ligands. These ligands can be roughly divided into two groups: those in which the camphor is annulated in the 2,3-positions to the β-face of the pyridine ring and those in which the pyridine is contained as a pendant on the C2 or C3 of the camphor framework. Camphor-based pyridine ligands can also contain other donor centers located on the pyridine ring or camphor skeleton. Some of these ligands have provided interesting enantioselectivities in several asymmetric reactions, such as S_N2' reactions, allylic oxidations, carbonyl additions with organozinc reagents and hydrogenations. This review contains a lot of chemistry on ligand synthesis and readers will find it of value and also perhaps an inspiration for the development of more active and improved versions.

1 Introduction

Chiral non-racemic monoterpenes derived from naturally occurring compounds have been widely used as chiral building blocks for the preparation of auxiliaries for asymmetric synthesis and ligands for asymmetric catalysis.[1] Amongst monoterpenes a prominent position is occupied by optically active camphor, the framework of which has been incorporated into a variety of chiral ligands having homo or heterodonor atoms.[2] In the middle of this type of ligand many examples enclose pyridine N-donors that have been for a long time the target of the our research. In this review we outline the progress made by our group and others in the synthesis of camphor-based pyridine ligands and in the application of their metal complexes in catalytic asymmetric synthesis.

Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy. E-mail: chelucci@uniss.it; Fax: +39-079-229559; Tel: +39-079-229539



Giorgio Chelucci

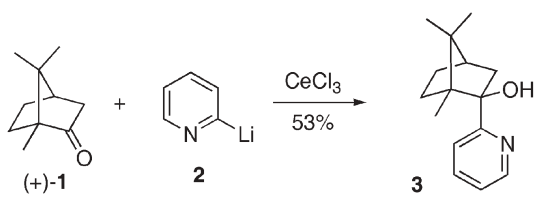
Giorgio Chelucci was born in Cagliari (Sardegna, Italy) and studied Chemistry at the University of Sassari (Sardegna), where he received his laurea degree in 1978. After five years of postdoctoral work he became a Researcher in the Department of Organic Chemistry at the University of Sassari. Since 1994, he has been a Lecturer at the Faculty of Science of the University of Sassari. His research centers on the design, synthesis and application in asymmetric catalysis of chiral ligands with particular interest toward those based on the pyridine framework.

These ligands can be roughly divided into two groups: those in which the camphor is annulated in the 2,3-positions to the β-face of the pyridine ring and those in which the pyridine is contained as a pendant on the C2 or C3 of camphor framework. These ligands can also contain other donor centers located on the pyridine ring or camphor skeleton.

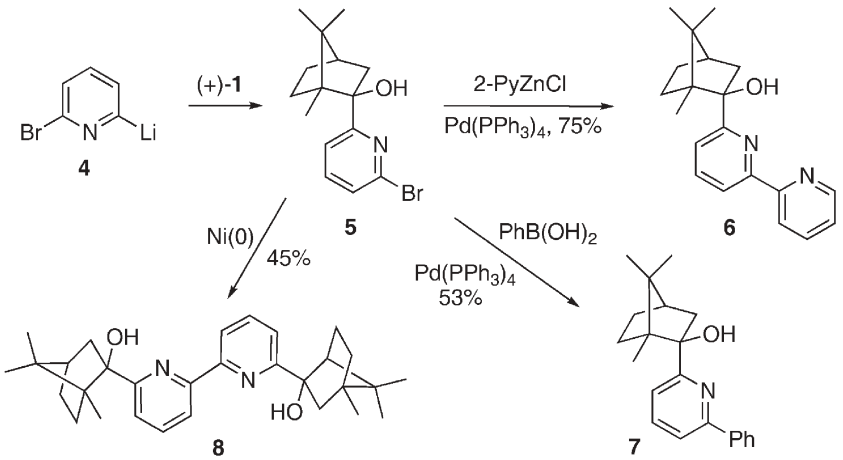
2 Pyridines contained as a pendant on the C2 or C3 of camphor

The simplest way to obtain camphor-based pyridines is the addition of pyridyllithium derivatives to camphor **1**. We reported the first example of a pyridyl carbinol from (+)-**1** by this approach (Scheme 1). However, the low thermal stability of 2-pyridyllithium and the low reactivity of the camphor-carbonyl that is inclined to give enolization or reduction rather than addition, afforded the alcohol **3** in only 12% yield as sole *endo* isomer.[3] Interestingly, the yield of the addition was greatly improved (53%) when the highly active anhydrous $CeCl_3$ was used to activate the carbonyl group.[4]

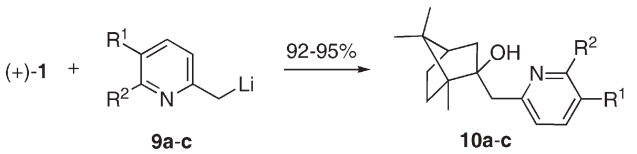
Kwong *et al.* reported the synthesis of a number of 2,2′-bipyridine alcohols from (+)-**1** (Scheme 2).[5] The synthesis of ligands **6–8** started from the pyridyl-carbinol **5** which was obtained by reaction of the 2-lithio-6-bromopyridine **4** with (+)-**1**. Coupling of **5** with 2-pyridylzinc chloride using a catalytic amount of $Pd(PPh_3)_4$ afforded the 2,2′-bipyridine **6**. The 6-phenylpyridine **7** was prepared by palladium(0)-catalyzed cross-coupling of **5** with phenylboronic acid. Finally, the



Scheme 1



Scheme 2



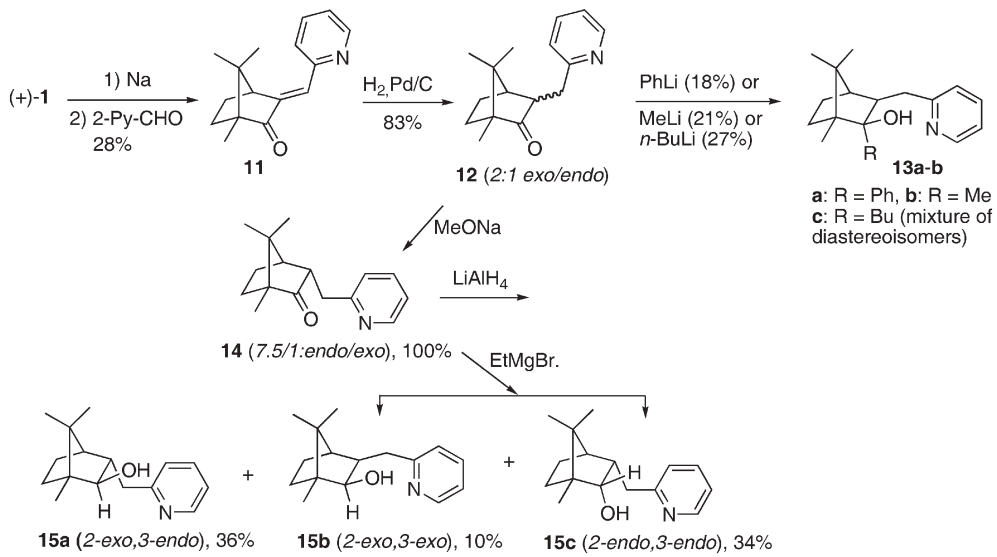
a: R^1 = H, R^2 = H; **b**: R^1 = H, R^2 = CH_3; **c**: R^1-R^2 = CH=CH-CH=CH

Scheme 3

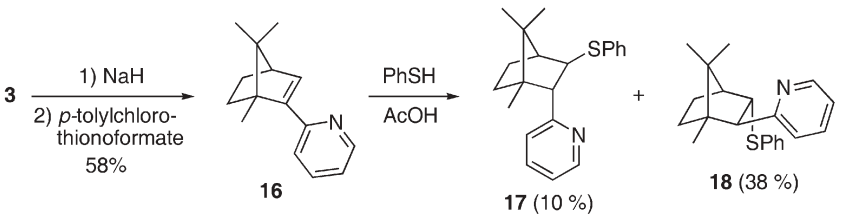
C_2-symmetric 2,2′-bipyridine **8** was obtained by nickel(0)-mediated homocoupling of **5**.

Chan *et al.* synthesized easily a number of chiral β-amino alcohols containing a pyridine[6] or quinoline[7] ring (Scheme 3). Camphor was reacted with 2-picolyllithium **9a**, 2-lithiomethyl-6-methylpyridine **9b** or 2-quinolylmethyllithium **9c** to produce carbinols **10a**, **10b** or **10c**, respectively, in nearly quantitative yields as single diastereomers (Scheme 3).

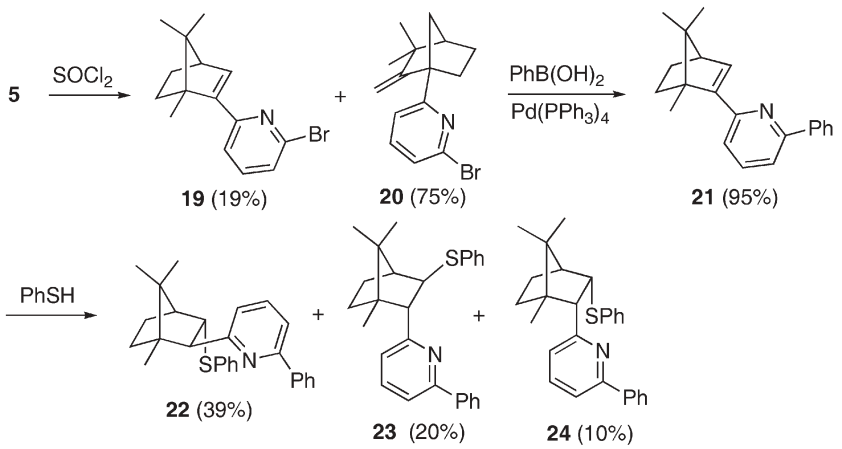
In the α- and β-hydroxyalkyl pyridines reported so far, both hydroxy group and pyridine substituent are located on the C2 of camphor. Nevalainen *et al.*[8] reported γ-hydroxyalkyl pyridines in which the heterocycle is present as a pendant on the C3 of the terpene. The introduction of a pyridylmethyl group on the α-position of the carbonyl group of (+)-**1** was obtained by treatment of the sodium enolate of (+)-**1** with pyridine-2-carbaldehyde to give the enone **11** which by hydrogenation on Pd/C in ethanol yielded the ketone **12** as a 2 : 1 *exo* : *endo* mixture of diastereoisomers (Scheme 4). That mixture was isomerized by treatment with sodium methoxyde in methanol to give the *endo* diastereomer **14** as the more abundant epimer. Reduction of the ketone **14** (7.5 : 1 *endo* : *exo* diastereomeric mixture) with $LiAlH_4$ afforded the alcohol **15** as a *ca*. 1 : 1 mixture of *trans*- and *cis*-isomers **15a** and **15b,c**, respectively. The small size of hydride allows both the *endo* and *exo* diastereomers to be formed, whereas the addition of more bulky nucleophiles such as PhLi or MeLi to ketone *exo*-**12** occurred in polar solvents at the less hindered *endo* side affording **13a** and **13b**, respectively. In contrast to those results, the addition of BuLi to a 2 : 1 *exo* : *endo* mixture of **12** in hexane provided an inseparable mixture of diastereomeric alcohols **13c**. Probably, the *exo* attack was in that case possible



Scheme 4



Scheme 5



Scheme 6

as a result of the increased nucleophilicity of the BuLi in an apolar solvent. When the ketone **14** (7.5 : 1 *endo* : *exo* diastereomeric mixture) was treated with EtMgBr in THF no ethyl addition product was formed, but *cis*-**15b,c** was obtained as a 1 : 6 mixture of 2-*exo*,3-*exo* : 2-*endo*,3-*endo* alcohols. Interestingly, EtMgBr was a more facially selective reducing agent than $LiAlH_4$ for the preparation of 2-*endo*, 3-*endo*-**15a** *via* reduction of **12**.

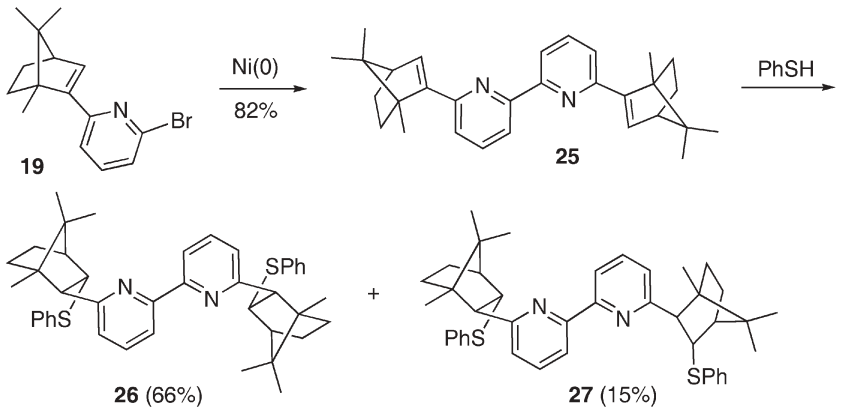
Investigating new pyridine and 2,2′-bipyridine thioethers from (+)-camphor, we prepared initially the simpler exponents **17** or **18** (Scheme 5).[9] Thus, when the alkene **16**, obtained by dehydration of the alcohol **3** with NaH in benzene followed by *p*-tolylchlorothionoformate, was treated with thiophenol in boiling acetic acid the desired Michael addition occurred to give a mixture of diastereomeric thioethers **17** and **18** in about a 1 : 4 ratio.

Unexpected difficulties were encountered extending this approach to analogue compounds with a phenyl group on the 6 position of the pyridine ring (Scheme 6).[9] Indeed, the dehydration of the tertiary alcohol **5** to the corresponding alkene **19** in the usual way failed, as did other methods tried to avoid the formation of ionic intermediates that can cause skeletal rearrangements or fragmentations. After several attempts, we found the alkene **19** can be obtained in 19% yield by treatment of **5** with the $SOCl_2$ in pyridine, though it was not possible to avoid the formation of a relevant amount of the rearranged compound **20**. The bromopyridine **19** was then cross-coupled with phenylboronic acid in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give the pyridine **21** in satisfactory yield (95%). Finally, the reaction of **21** with thiophenol in boiling acetic acid afforded the *trans* isomeric thioethers **22** and **23** with the unexpected *cis* isomer **24** in about a 4 : 2 : 1 ratio, respectively.

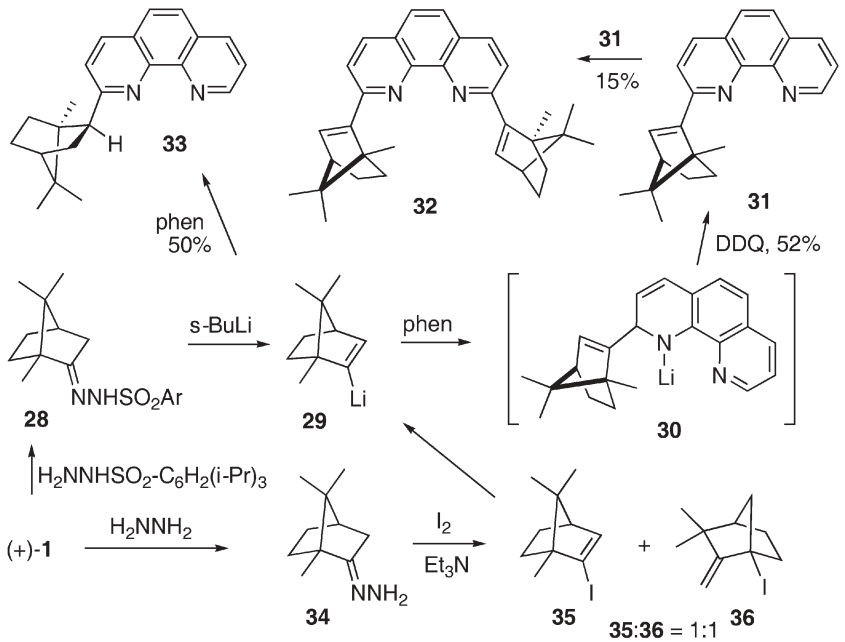
The bromopyridine **19** was homocoupled in the presence of nickel(0) to give the bipyridine **25** (82% yield) (Scheme 7). The debrominated derivative of **19** was the major by-product of the coupling reaction, but the use of a carefully degassed DMF solution could substantially reduce its formation. Addition of thiophenol to the double bonds of the bipyridine **25** occurred and a mixture of bipyridine **27** and its C_2-symmetric counterpart **26** in about a 9 : 2 ratio was obtained in 66% yield.

Åkermark and co-workers reported the preparation of chiral phenanthrolines bearing the framework of camphor as chiral pendant by the addition of an alkyllithium reagent to the 2- or 2,9-positions of the phenanthroline nucleus followed by rearomatization of the primary reaction adduct (Scheme 8).[10] Using (+)-**1**, the alkenyllithium derivative **29** was prepared from 2,4,6-triisopropylbenzenesulfonyl-hydrazide **28** by a Shapiro reaction or from the iodide **35** by lithium/iodide exchange. Addition of **29** to phenanthroline at −78 °C followed by DDQ-induced rearomatization at −50 °C gave the phenanthroline **31** in 52% yield. When the addition was carried out at 25 °C, the phenanthroline **33** was obtained in 50% yield as a single stereoisomer by double bond migration and rearomatization of the intermediate adduct **30**. Addition of the bornenyllithium **29** to **31**, followed by rearomatization gave the bis(bornenyl)phenanthroline **32** in 15% yield.

Knochel *et al.*[11] reported the synthesis of the chiral N,P-ligands **42–44** from monoterpenes (Scheme 9). The synthesis started from camphor triflate **37** which was prepared in 90% yield by treatment of the lithium enolate of (+)-**1** with *N*-phenyltrifluoromethanesulfonamide (Tf_2NPh) in THF at



Scheme 7



Scheme 8

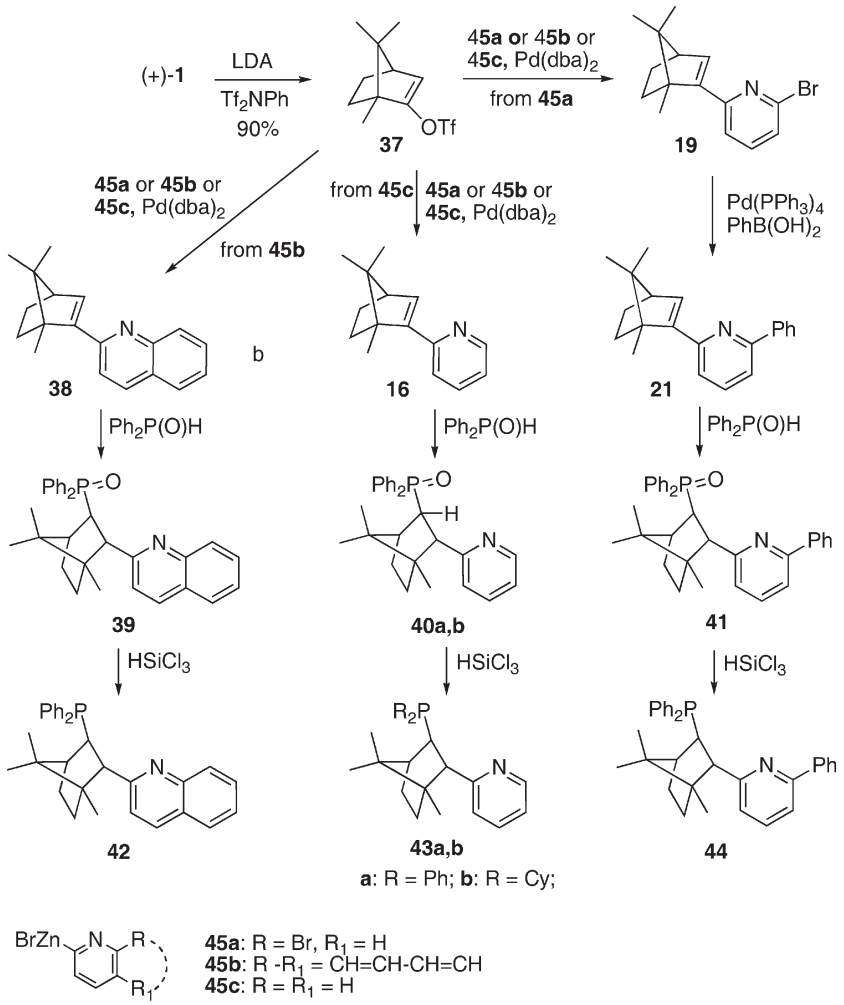
0 °C. Triflate **37** underwent smooth Negishi cross-coupling with the zinc-derivatives **45a–c** to give the 2-alkenyl pyridines **19**, **38** and **16** in good yields. This synthesis approach is more convenient than that previously reported (see Schemes 5 and 6). The bromopyridine **19** was then coupled with phenylboronic acid in the presence of $Pd(PPh_3)_4$ to afford **21** in 35% overall yield from **37**. The treatment of 2-alkenyl pyridines **38**,**16** and **21** with diphenylphosphane, dicyclohexylphosphane or diphenylphosphane oxide in dimethyl sulfoxide or *N*-methylpyrrolidinone in the presence of a catalytic amount of *t*-BuOK provided the phosphane oxides **39**,**40** and **41** (55–93% yields). Finally, the phosphane oxides were reduced with $HSiCl_3/Et_3N$ in toluene to give the desired N,P-ligands **42**,**43** and **44**.

3 Pyridines annulated in the 2,3-positions to camphor

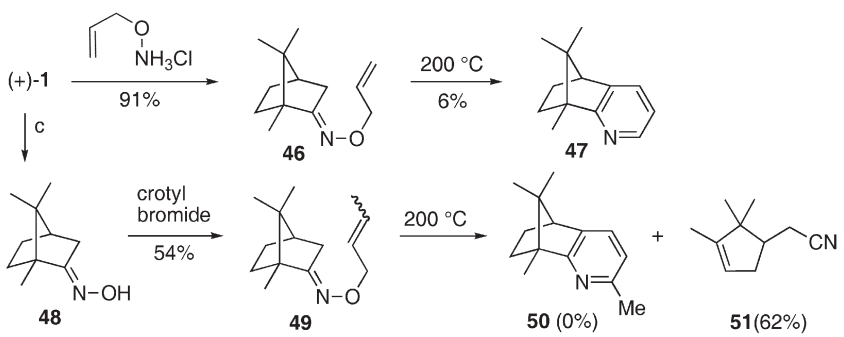
Chiral pyridines in which (+)-**1** is present in the form of a cycloalkeno-condensed substituent are interesting starting points for the synthesis of more complex ligands and well suited substrates for the study of the chirooptical properties of the pyridine chromophore. In fact, the stiffening of the chiral array determined in the molecule by the ring constraint cuts down drastically the number of possible conformers that may contribute to the optical activity, resulting in an enhancement of the dissymmetric factor and allowing a more reliable attribution of the circular dichroism bands observed.

The synthesis of the simplest type of these heterocycles, namely the pyridine **47** and the 6-methyl analogue **50** (Scheme 10), was initially attempted by us *via* thermolysis of (+)-camphor oxime *o*-allyl ethers **46** and **49**.[12,13] These ethers were prepared by reaction of (+)-**1** with *o*-allylhydroxylamine hydrochloride (91% yield) or by treatment of the (+)-camphor oxime **48** with crotyl bromide (54% yield), respectively. Heating at 200 °C a benzene solution of **46** in a sealed tube for 46 h afforded **47** in a very poor yield (6%), whereas **49** failed to give **50** and only the cyanoolefin **51** was obtained in 62% yield.

This unsatisfactory result incited us to examine an alternative procedure that afforded a valuable result for **47**, but not for **50** (Scheme 11). Thus, lithiated dimethylhydrazone **52** was quenched with 2-(2-bromoethyl)-[1,3]dioxolane to give



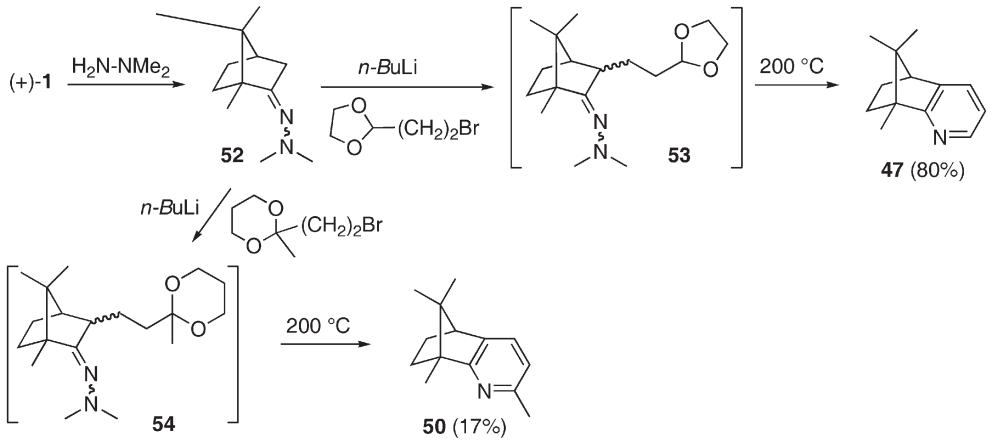
Scheme 9



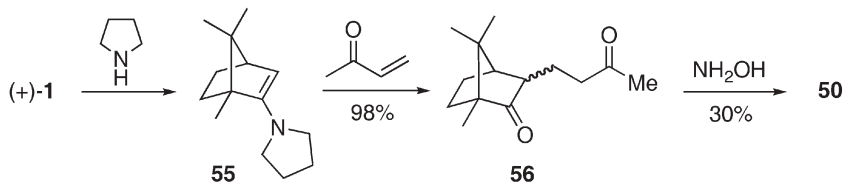
Scheme 10

the alkylation product **53** that was not isolated, but directly converted in the tetrahydroquinoline **47** by heating in carbitol (80% yield). The application of this protocol to the preparation of its 2-methyl analogue, but using 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane as the electrophile, gave **50** in much lower yield (17%) (Scheme 11).[14]

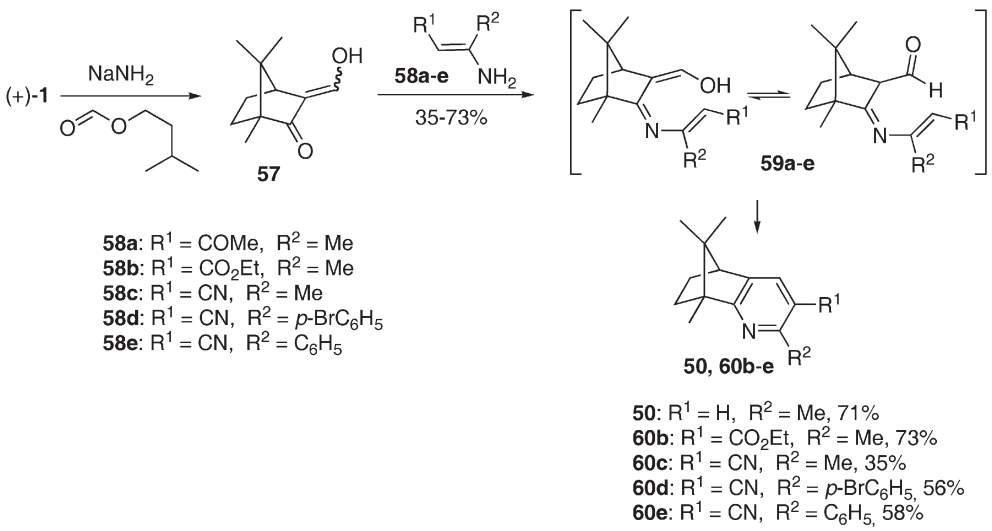
A more convenient approach to **50** was obtained *via* camphor pyrrolidine enamine **55** that by treatment with methyl vinyl ketone afforded the 1,5-diketone **56** in 98% yield (Scheme 12).[13] Annulation and aromatization of **56** with hydroxylamine hydrochloride in EtOH gave the desired pyridine **50** in moderate yield (30%).



Scheme 11



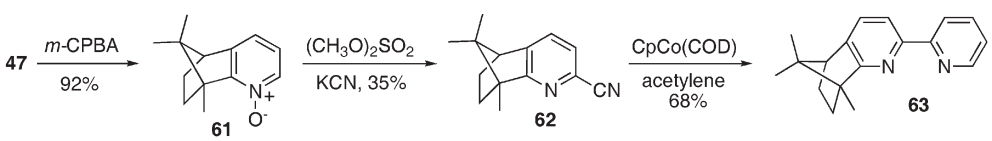
Scheme 12



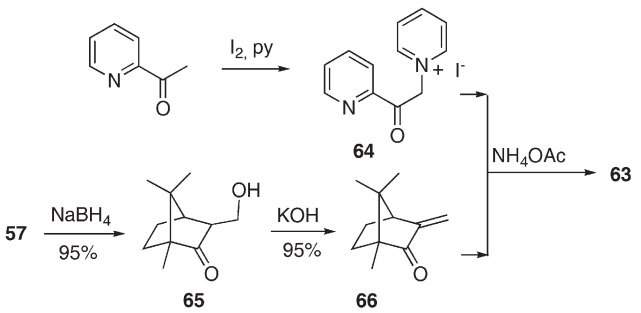
Scheme 13

An interesting synthesis of **50** and other analogue pyridines has been very recently reported (Scheme 13).[15] Pyridines **50** and **60b–e** were prepared *via* annulation of (+)-β-hydroxymethylenecamphor **57** with the enamines **58a–e** derived from active methylene compounds. The reaction presumably proceeds *via* the formation of imines **59a–e** followed by cyclization reaction to give **50** and **60b–e** in fairly good yields (35–73%). In the case of the enamine **58a** the unexpected deacetylation product **50** was obtained in 71% yield.

Starting from the pyridine **47**, we carried out the synthesis of bipyridine **63** by the cyanation–cyclotrimerization sequence (Scheme 14).[16] Accordingly, the nitrile **62** was prepared by regioselective introduction of the cyano group in the 6-position of the pyridine ring of **47** by treatment of the corresponding



Scheme 14



Scheme 15

N-oxide **61** with $(CH_3O)_2SO_2$ followed by reaction of the unisolated intermediate pyridinium salt with KCN (35% yield). The final cyclotrimerization of nitrile **62** with acetylene, carried out by using (π-cyclopentadienyl)cobalt 1,5-cyclooctadiene [CpCo(COD)] as the catalytic precursor and toluene as the solvent at 130 °C, gave the bipyridine **63** in 68% yield.

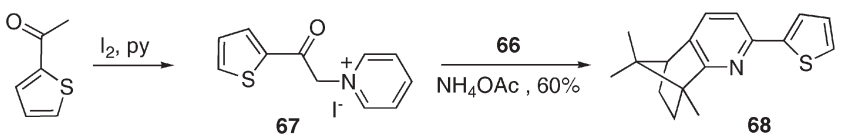
A more direct access to bipyridine **63** was obtained by Kishi *et al.*[17] who used the Kröhnke-type cyclization[18] of 2-acetylpyridinepyridinium iodide **64**, prepared by reaction of 2-acetylpyridine with iodine in pyridine, with 2-methylenecamphor **66**, in turn easily accessible from (+)-**1** (Scheme 15).

This strategy was next extended to obtain a number of camphor-based pyridine ligands. Thus, the thienylpyridine **68**[19] (60% yield) and the 2-(2-phelylthiophenyl)-5,6,7,8-tetrahydroquinoline **70**[20] (24% yield) were obtained by reaction of **66** with the pyridinium salts **67** and **69**, respectively (Scheme 16 and 17).

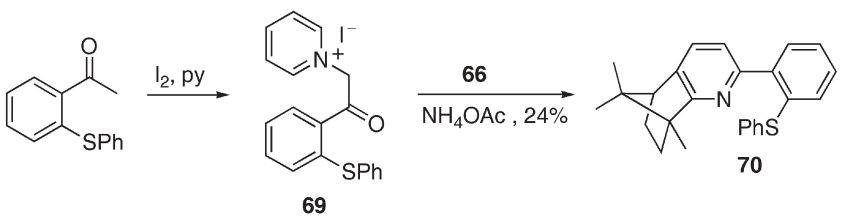
We also followed the same tactic for the synthesis of the N,P-ligand **75** (Scheme 18).[21] Thus, condensation of the pyridinium salt **71** derived from 2-methoxyacetophenone with **66** gave the methoxyquinoline **72** which was demethylated with boron tribromide (85% yield) to give the phenol **73**. This was converted in the trifluoromethansulfonate **74** with $(CF_3SO_2)_2O$ in pyridine (79% yield). Further treatment of **74** with diphenylphosphine in the presence of 10 mol% of $NiCl_2$(dppe) and two equivalent of 1,4-diazabicyclo[2.2.2]octane (DABCO) in DMF at 100 °C gave the expected phosphinoquinoline ligand **75** (19% yield) with two main by-products, namely the *P*-oxide and the phenyl derivative derived from the reduction of the trifluoromethansulfonate group.

The Kröhnke methodology was useful for the synthesis of the C_2-symmetric terpyridine **76** that was obtained in one step by reaction of **66** with 2,6-bis(pyridinioacetyl)pyridine iodide (26% yield) (Scheme 19).[22]

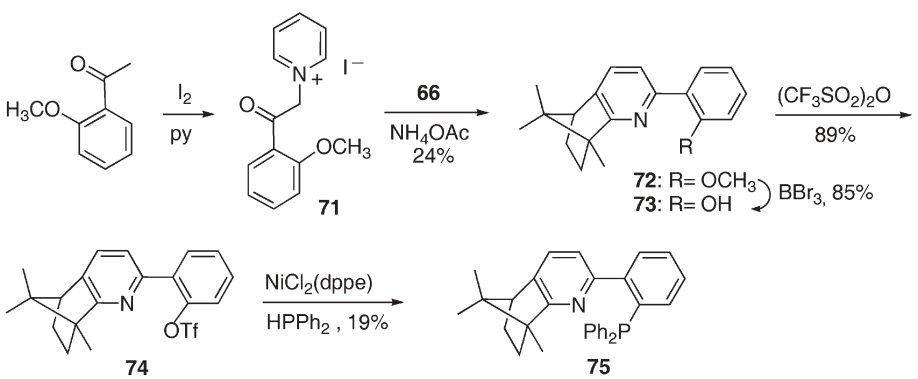
The most straightforward synthetic approach to fused phenanthroline derivatives is the classical Friedländer reaction where an *ortho*-aminoaldehyde condenses in a two-step fashion with an enolizable ketone.[23] However, when (+)-camphor was allowed to react with aminoaldehyde **77** the phenanthroline **78** was produced in only 5% yield.[24] To overcome this drawback we developed a general alternative to



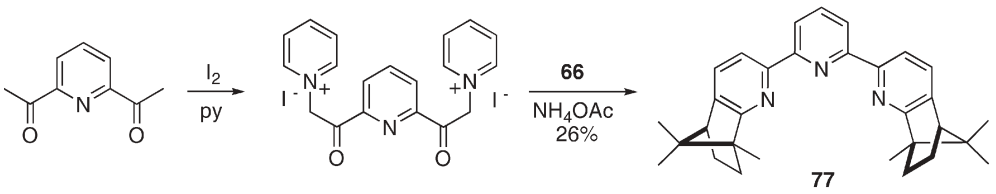
Scheme 16



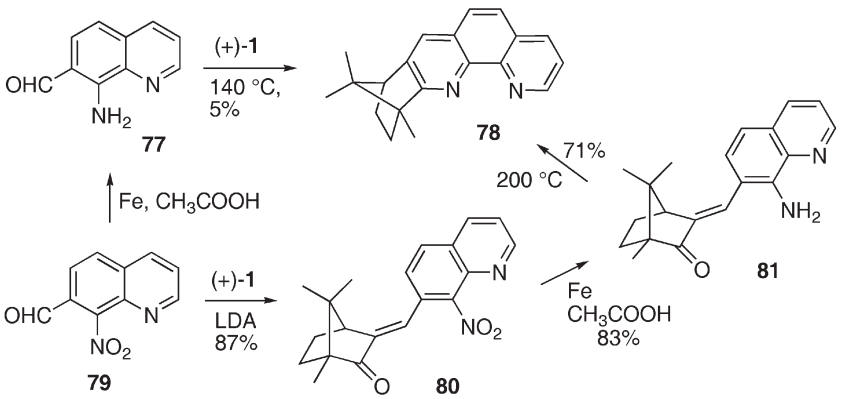
Scheme 17



Scheme 18



Scheme 19

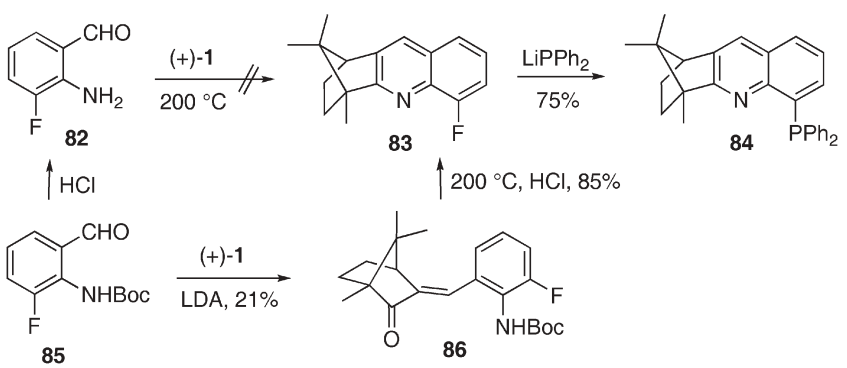


Scheme 20

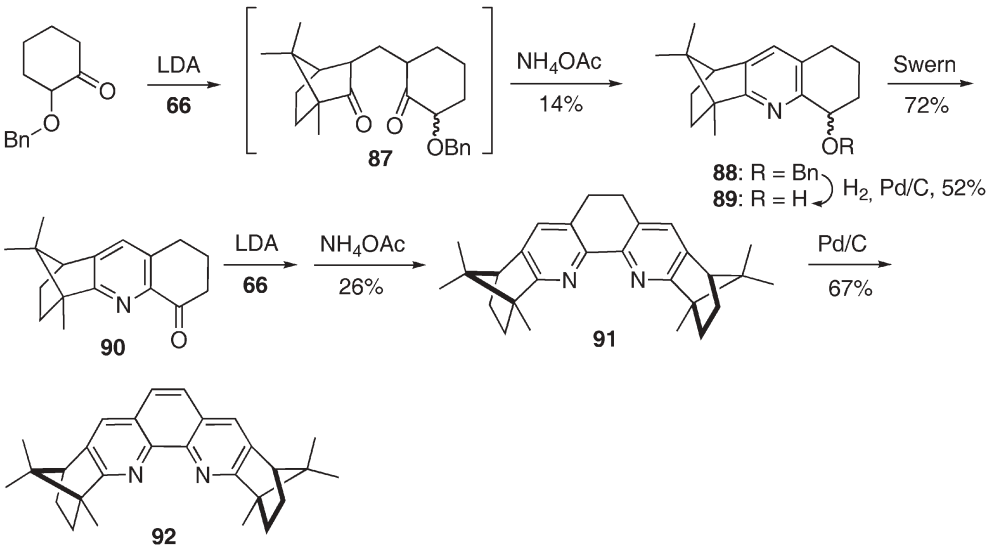
the Friedländer reaction useful in the case of hindered ketones[25] (Scheme 20). This approach essentially reverses the order of the two steps in the Friedländer condensation. In the initial step, the enolate anion of (+)-**1** attacks the nitroaldehyde **79** to give the condensed product **80**, the nitro group of which was then reduced to the amine **81** (83% yield) by refluxing with powdered iron in acetic acid/ethanol/water (2 : 2 : 1). Subsequent intramolecular condensation, accomplished by refluxing **81** in a degassed carbitol solution, afforded the phenanthroline **78** in 51% overall yield from (+)-**1**.

We could also verify the resistance of camphor to undergo the Friedländer reaction when (+)-**1** was condensed with the fluoro-*ortho*-aminoaldehyde **82** in an initial attempt to obtain the fluoroacridine **83**, key intermediate in the synthesis of the diphenylphosphinoacridine **84** (Scheme 21). In that circumstance we were able to overcome this unsuccess by condensing (+)-**1** with the *N*-Boc aldehyde **85** (21% yield) and then heating the resulting product **83** under reflux in a carbitol solution for one hour.[26] In this way the removal of the *N*-protecting group, azaannulation and aromatization steps occurred in sequence giving the fluoroacridine **86** in high yield (85%). Treatment of **83** with lithium diphenylphosphide gave the N,P-ligand **84** in good yield (75%).

Having accomplished the preparation of **78**, we also developed the synthesis of the related C_2-symmetric phenanthroline **92** (Scheme 22).[27] The lithium enolate of racemic 2-benzyloxycyclohexanone was treated with (+)-**1** to give, by conjugate addition the 1,5-dicarbonyl intermediate **87**, which was not isolated, but subjected to azaannulation–aromatization. Thus, the pyridine **88** was obtained in 14% overall yield as a 52 : 48 mixture of epimers at the C5. Catalytic hydrogenolysis (Pd/C at 3 atm) of benzyloxy derivatives **88** gave the corresponding mixture of carbinols **89** (92% yield) that was oxidized under Swern conditions to ketone **90** (72% yield). Starting from this key intermediate, the 5,6-dihydrophenanthroline **91** was prepared by building up the second pyridine ring in a similar manner to that used to prepare **88** (26% overall yield). The synthesis of **92** was finally accomplished by



Scheme 21



Scheme 22

refluxing a decaline solution of **91** in the presence of a catalytic amount of palladium on charcoal (67% yield).

The pyridine ligands examined until now contain another donor centre on the pyridine ring or on the C2 and/or C3 of the terpene skeleton. We are now investigating camphor-based pyridine ligands containing an additional ligand on the 10-methyl group of the camphor backbone in order to obtain ligands of the type **93** (Fig. 1). As a part of this project we have now prepared the 4-(diphenylphosphanylmethyl)- and 4-(phenylthiomethyl)-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine **94** and **95**, respectively.[28]

For the synthesis of **94** and **95** we have experimented several strategies, the most effective of which is described in Scheme 23. The 10-iodocamphor **96**[29] was deprotonated by lithium diisopropylamide (LDA, −40 °C, 2 h) and then condensed with 2-nitrobenzaldehyde to give the crossed-aldol product **97** as a single geometric isomer (72% yield). The nitro group of **97** was then reduced by refluxing with powdered iron in acetic acid/ethanol/water (2 : 2 : 1) to the corresponding amine **98** (87% yield) that gave the camphor-fused quinoline **99** in 89% yield by heating in carbitol solution. Treatment of **99** with sodium diphenylphosphide-borane gave the phosphine-borane **100** (76% yield) from which the phosphine **94** was finally obtained by removal of the BH_3-protecting group with an excess of morpholine (96% yield).

The iodo-compound **99** was also converted in good yield (76%) in the phenylthiomethyl-acridine **95** by treatment with sodium benzenethiolate in *N,N*-dimethylformamide.

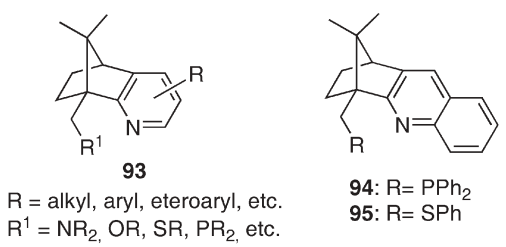


Fig. 1 Camphor-based pyridine ligands with an additional ligand on the 10-methyl group of the camphor backbone.

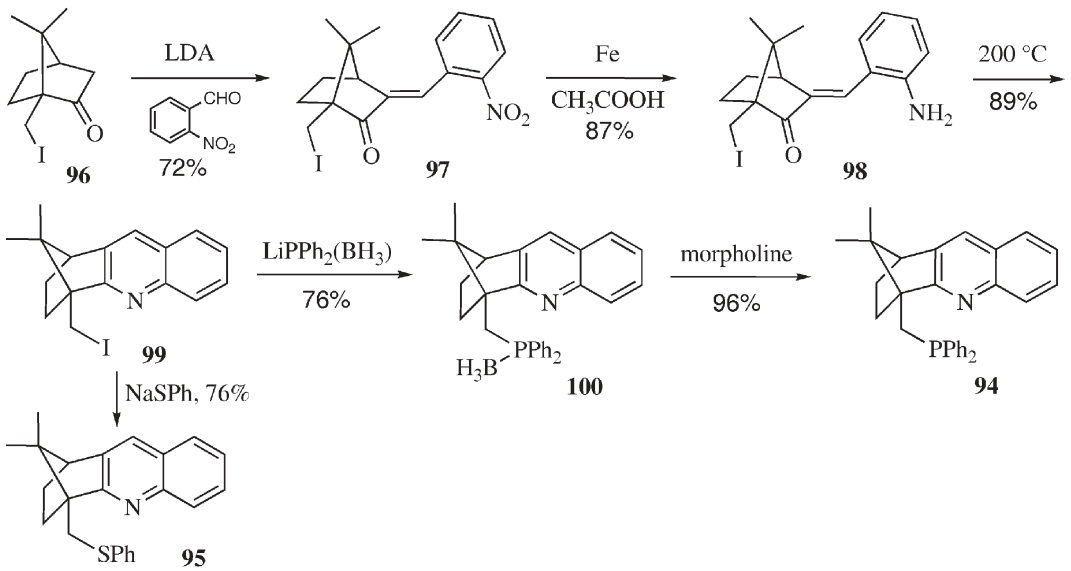
4 Catalysis

4.1 Allylic substitution

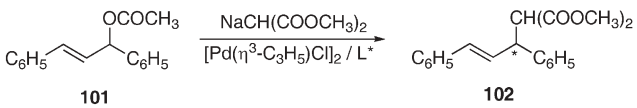
A number of nitrogen-containing ligands have achieved high levels of stereocontrol in the enantioselective reactions based on palladium-catalyzed allylic substitutions.[30] The alkylation of 1,3-diphenylprop-2-enyl acetate **101** with dimethyl malonate (Scheme 24) has been used as a model to compare a variety of camphor-based pyridine ligands (Table 1).[31]

We examined in this process the diastereomerically pure pyridine-thioethers **17**,**18**,**22**,**24**,**26** that however did not give reactive palladium catalyst[9] (Table 1). Ligands **17** and **18** afforded **102** in low ee (30 and 26%, respectively) and with opposite configuration, indicating that they behave as pseudoenantiomers. A dramatic effect on both stereoselectivty and catalytic activity was observed by the presence of a phenyl group in the 6-position of the pyridine ring. Thus, the ligand **22** gave a 77% ee, but providing a less effective palladium catalyst than related ligand **18**. The *trans* isomer **24** was very ineffective regarding both catalytic activity and stereoselectivity. Finally, the bipyridine **26** showed comparable reactivity, but poorer enantioselectivity (48% ee) with respect to the related ligand **22**.

Norrby *et al.* described the first application of chiral phenanthrolines to asymmetric palladium-catalyzed allylation.[10] They used molecular mechanics calculations to probe the conformational properties of a number of substituted phenanthrolines and their η^3-allyl-palladium complexes. Special attention was focused on chiral phenanthrolines **31** and **33** bearing an alkenyl or alkyl group, respectively. Based upon these calculations, predictions were then made regarding the suitability of these ligands for use in asymmetric palladium-catalyzed substitutions of allylic acetates. Subsequent experiments gave results that were in good agreement with the calculated predictions (Table 2). The highest levels of asymmetric induction were predicted and obtained with the 2-(2-bornyl)phenanthroline **33** with which an ee of 92% was obtained in the reaction with dimethyl malonate and the 1,3-diphenylallyl system. Moreover,



Scheme 23



Scheme 24

Table 1 Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate catalyzed by palladium(0)-complexes

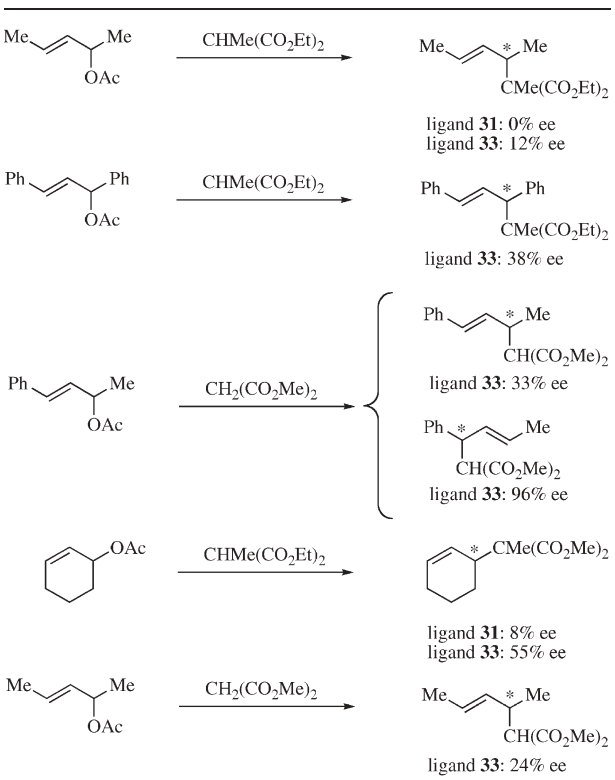
Ligand	React. time (h)	Yield (%)	ee (%)	Conf.	Ref.
17	106	84	30	S	9
18	101	85	26	R	9
22	168	—	76	R	9
24	168	—	3	S	9
26	168	76	48	R	9
33	—	80	92	R	10
70	168	65	20	S	20
75	12	96	50	S	21
78	180	89	86	S	32
84	1	96	69	S	26

in the case of the 1,3-methylphenylallyl system, the major pathway involved reaction at the methyl-substituted terminus giving the alkylated product in 68% yield and 33% of ee, whereas the minor product, derived from reaction at the phenyl-substituted terminus (17% yield), showed 96% of ee.

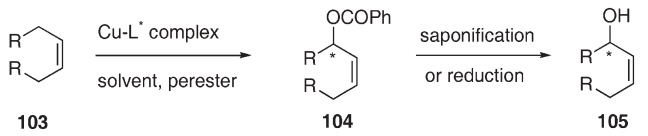
We assessed in this process a variety of chiral C_1-symmetric phenanthrolines, obtaining enantiomeric excesses up to 96%. Among them, the phenanthroline **78** afforded total conversion of the starting material in less than 3 hours to give **102** in good yield (89%) and stereoselectivity (86% ee).[32]

We recently examined the structurally analogue N,S- and N,P-ligands **70**[20] and **75**[21] that differ from one another in the phenylthio and diphenylphosphino group. The Pd-complex involving **75** proved the better catalyst, affording **102** in 96% yield in 12 hours and with 50% ee, whereas **70** gave both low conversion (33% after 7 days) and ee (20%).

Table 2 Allylic alkylation of different allylic acetates and nucleophiles catalyzed by palladium(0) complexes with 1,10-phenathrolines **31** and **33**



Next, we improved both catalytic activity and stereoselectivity using the N,P-ligand **84**[26] obtained by structural modification of the ligand **75**. In fact, in ligand **84** the 2-diphenylphosphinophenyl group is bonded to the 2-position of the tetrahydroquinoline ring, whereas in the ligand **75** the phenyl group of the 2-diphenylphosphinophenyl substituent is now annulated to the pyridine ring of the tetrahydroquinoline.



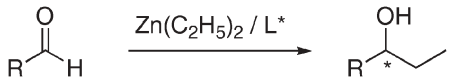
Scheme 25

This structural modification makes the two nitrogen and phosphorus donor atoms to be arranged in a rigid backbone in such a way as to provide a more rigid array of the ligand around the metal centre. Last but not least, the ligand **75** forms a six-membered metal chelate while the new ligand **84** forms a five-membered chelate ring. As a consequence, ligand **84** gave both a better catalytic activity (reaction time: 1 *versus* 10 h) and stereoselectivity (50 *versus* 69% ee).

4.2 Allylic oxidation

Copper complexes of chiral nitrogen-containing ligands are the catalysts of choice for the enantioselective allylic oxidation of olefins with peresters (Scheme 25).[33]

In this contest, Kocovsky and ourselves found that copper(I)-complexes of bipyridines[34] and phenanthrolines[27b,35] are good catalysts in asymmetric copper(I)-catalyzed allylic oxidation of cyclopentene, cyclohexene and cycloheptene providing very short reaction times ($\leqslant$30 min at room temperature) and good stereoselectivities (up to 76% ee) for this process. The phenanthroline **78** provided a reactive catalyst that required less than 60 minutes for complete oxidation of cyclohexene, but showed low stereodifferentiating ability (8% ee).[27b] A much better stereochemical result in the allylic oxidation of cyclohexene was obtained with the catalysts formed *in situ* from the C_1- and C_2-symmetric bipyridines **6** and **8** with $[Cu(CH_3CN)_4]PF_6$, CuOTf or CuBr giving the cyclohexe-2-enyl benzoate in moderate yield (43 and 63%, respectively) and ee (65 and 58%, respectively).[36] These catalysts were also examined in the allylic oxidation of cyclopentene and cyclooctene giving enantiomeric excesses up to 70% ee.[36]



Scheme 26

4.3 Addition of organozinc reagents to aldehydes

Chiral pyridine-containing ligands have found application in the catalytic enantioselective addition of organozinc reagents to aldehydes leading to a diverse array of secondary alcohols with high stereoselectivities.[37] In Table 3 are described the results obtained in the enantioselective addition of diethylzinc to different aldehydes catalyzed by pyridine-carbinols based on camphor.

We firstly checked pyridine-carbinols derived from monoterpenes as enantioselective catalysts in the addition of diethylzinc to aldehydes. Among them the alcohol **3** appeared to be in all cases the most effective ligand, though the enantioselectivity did not exceed 44% ee.[3] In that study we pointed out that a predictable improvement of the stereodifferentiating ability of 2-pyridyl-carbinols could be obtained by introduction of a suitable substituent on the 6-position of the pyridine ring.

Kwong *et al.* next confirmed these expectations preparing the pyridyl and phenyl substituted pyridyl alcohols **6** and **7**, respectively.[5] Both these ligands were very active in catalyzing the ethylation of benzaldehyde giving enantioselectivities (up to 78% ee) which were much higher than those obtained with **3**. A further increasing of the stereoselectivity was obtained with the C_2-symmetric bipyridine diol **8** (95% ee).[5] Using this ligand

Table 3 Enantioselective addition of diethylzinc to different aldehydes

R	Ligand	Solvent	Temp (°C)	Time (h)	Yield (%)	ee (%)	Ref.
Ph	**3**	hexane–ether	25	20	93	44 (*R*)	3
3-Phenypropanal	**3**	hexane–ether	25	20	87	38 (*R*)	3
3-Phenypropynal	**3**	hexane–ether	25	20	92	21 (*R*)	3
Ph	**6**	toluene	0	3	—	78	5
Ph	**7**	toluene	0	3	—	65	5
Ph	**8**	toluene	0	1	86	95	5
p-ClC_6H_4	**8**	toluene	0	7	68	54	5
n-C_6H_{13}	**8**	toluene	0	6	66	80	5
Ph–CH=CH–	**8**	toluene	0	2.5	54	44	5
n-C_6H_{13}	**8**	toluene	0	6	74	47	5
1-Naphthyl	**8**	toluene	0	7	52	20	5
2-Naphthyl	**8**	toluene	0	7.5	67	68	5
Ph	**10a**	toluene–hexane	0	—	91	38	6
Ph	**10b**	toluene–hexane	0	—	93	75	6
Ph	**10c**	toluene–hexane	0	4	96	83	7
p-ClC_6H_4	**10c**	toluene–hexane	0	4	90	76	7
p-$MeOC_6H_4$	**10c**	toluene–hexane	0	4	89	91	7
Ph–CH=CH–	**10c**	toluene–hexane	0	2.5	92	74	7
1-Naphthyl	**10c**	toluene–hexane	0	4	94	89	7
2-Naphthyl	**10c**	toluene–hexane	0	4	90	79	7
C_6H_5	**10c**	toluene–hexane	0	4	74	43	7
Ph	**15b**	toluene	212	4	96	52	8
Ph	**15c**	toluene–hexane	22	4	96	89	8
p-ClC_6H_4	**15c**	toluene–hexane	22	8	92	87	8
p-$MeOC_6H_4$	**15c**	toluene–hexane	22	4	90	78	8

other aldehydes were examined (Table 3), but enantioselectivities were in all cases lower than with benzaldehyde. Interestingly, the absolute configuration of the major product obtained with the C_1-symmetric ligand **6** was opposite to that obtained with the C_2-symmetric ligand **8**, suggesting that the transition states of the reactions promoted by complexes of **6** and **8** are different.

Recently Xu *et al.* assessed in this process a number of β-hydroxyalkyl pyridines and in particular the ligands **10a–c**[6,7] derived from camphor (Table 3). The presence of a methylene spacer between the pyridine and the C–OH did not increase the stereodifferentiating ability of the ligand **10a** with respect to the simpler pyridine **3** (38% *versus* 44% ee). Also in this case the asymmetric induction was greatly increased by introducing a substituent on the 6-position of the pyridine ring of **10a**. Thus, ligands **10b**[6] and **10c**[7] bearing a 6-methyl group and a benzo-fused ring on the pyridine gave the 1-phenylpropanol in 75 and 83% enantiomeric excess, respectively. With **10c** being the best ligand, the ethylation to both aromatic and aliphatic aldehydes was also examined (Table 3). The best result was obtained with the *p*-methoxybenzaldehyde (91% ee).

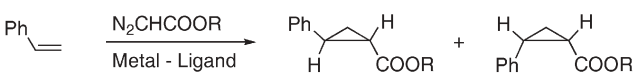
Nevalainen *et al.*[8] used the pyridylalcohols **15b** and **15c** that are very different from the previous ones since the pyridine is now present as a pendant on the C3 of the camphor. These isomeric ligands exhibited a different behavior concerning both catalytic activity and stereoselectivity (Table 3). The *trans*-isomer **15c** showed a better performance than the *cis*-isomer **15b** providing (*S*)-1-phenylpropanol in 96% yield and 89% ee, whereas the **15b** gave the opposite enantiomer in 84% yield and 52% ee.

4.4 Transfer hydrogenation

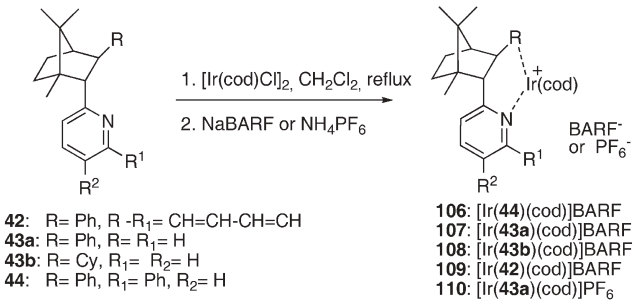
Our group applied chiral bipyridines to the H-transfer enantiodifferentiating reduction[38] of acetophenone using 2-propanol as a hydrogen donor, potassium hydroxide as the base and $[Rh(cod)Cl]_2$ as the catalyst precursor. Among these bipyridines we also evaluated **63**, which afforded low stereoselectivity (10% ee at best).[16] This unsatisfactory result was explained considering that the great rigidity of the alkyl substituent unfavorably affects the ligand coordination to the rhodium(I)-procatalyst. Moreover, the large demanding substituent close to one pyridine differentiates the coordinating ability of the two pyridines in the molecule and may even favor monodentate coordination of **63**. Therefore, we concluded that more than one catalytically active species is present in solution and that the low stereoselectivity is the consequence of a delicate balance between the concentration and the activity of the different rhodium complexes involved in the process.

4.5 Cyclopropanation

The vast majority of successful catalysts for stereoselective addition of a carbenoid reagent to an alkene (Scheme 27) are complexes of ruthenium, rhodium and especially copper



Scheme 27



Scheme 28

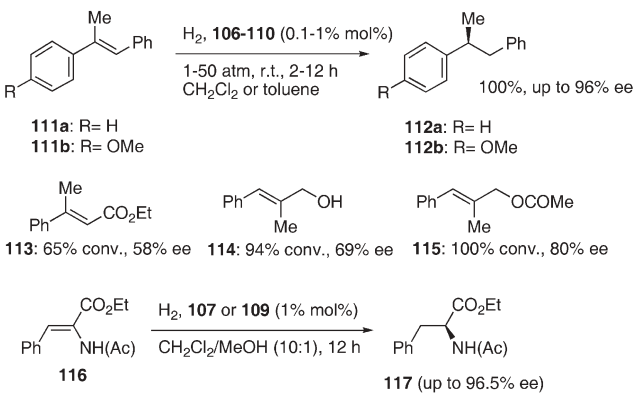
derivatives of nitrogen ligands with which excellent control of both diastereo- and enantioselectivity has been observed.[39]

Though cyclopropanation reactions employing copper complexes of bipyridines and phenanthrolines afforded good results, no camphor-derivative of these heterocycles has been applied in this reaction. On the other hand, the copper and rhodium complexes of the terpyridine **76** were examined in the cyclopropanation of styrene with diazoacetates.[22] These catalysts proved to be poorly suitable chiral controllers in this reaction, affording at best 32% and 34% ee for the *trans*- and *cis*-cyclopropane, respectively.

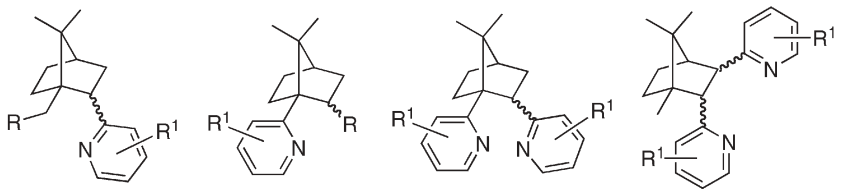
4.6 Hydrogenation

Particularly high enantioselectivity in the asymmetric hydrogenations[40] was displayed by the Ir-complexes **106–110**[11] derived from the N,P-ligands **44**, **43a,b** and **42** (Scheme 28).

The Ir-catalyzed hydrogenation of (*E*)-1,2-diphenylpropene **111a** and 2-(4-methoxyphenyl)-1-phenylpropene **111b** (Scheme 29) was performed at room temperature in the presence of complexes **106–110** (0.1–1 mol%) to give high yield and enantioselectivity (up to 96% ee) of the reduced product. Other substrates **112–115** (Scheme 29) were hydrogenated (1 mol%, H_2 (50 bar)) in the presence of the best performing catalyst **109**, giving moderate to good enantioselectivities (58–80% ee). Finally, the Ir-complexes **107** and **109** were assessed in the hydrogenation of the unsaturated enamide **116** (Scheme 29). Under optimized conditions (1 mol%, CH_2Cl_2/MeOH (10 : 1), H_2 (50 bar), 50 °C, 12 h) ligand **107** provided the alanine derivative **117** in 100% conversion and excellent ee (96.5%).

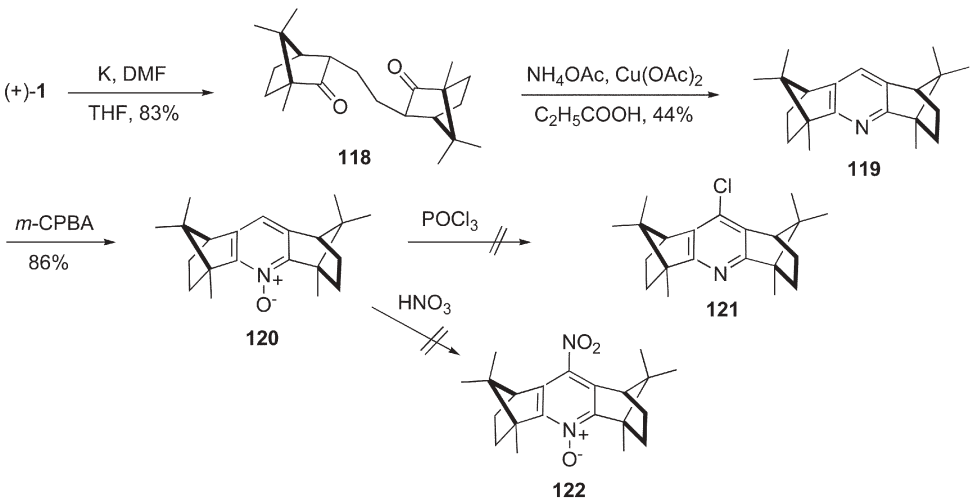


Scheme 29



R = NR_2, OR, SR, PR_2, etc.; R^1 = alkyl, aryl, eteroaryl, etc.;

Fig. 2 Potential available new camphor-based pyridine ligands.



Scheme 30

5 Conclusions and prospects

In this review we have outlined the progress made by ourselves and by other groups in the synthesis of camphor-based pyridine ligands and in the application of their metal complexes in catalytic asymmetric synthesis. Though a variety of these ligands are now available, the reports on their applications in enantioselective processes are rather limited, in the spite of very good stereoselectivities achieved in some cases. Thus, new opportunities are yet to be explored. Moreover, many structural modifications are still possible because their synthesis has been until now limited to those containing an additional donor centre on the pyridine ring or the C2 and/or the C3 of the terpene skeleton. In this connection, we have just demonstrated the possibility of obtaining bidentate pyridine ligands with a donor centre on the 10-methyl group of the camphor backbone. The methodologies reported in this paper suggest the possibility of designing new camphor-based pyridine ligands such as those illustrated in Fig. 2. It is hoped that this review will stimulate further research so that new camphor-based pyridine ligands can be prepared and their metal complexes applied in catalytic asymmetric synthesis.

6 Note added in proof

Kotsuki *et al.* reported the synthesis of the C_2-symmetric pyridine **119** in which (+)-**1** is presented in the form of a cycloalkeno-condensed substituent on both b and e faces of the pyridine ring (Scheme 30).[41] Camphor was treated with potassium metal and DMF in THF to give the 1,5-diketone **118** (83% yield) as a sole *endo–endo* isomer. Subsequent heating of **118** in propionic acid with NH_4OAc and $Cu(OAc)_2$ afforded **119** in moderate yield (44%). Since **119** showed no remarkable nucleophilic reactivity, in order to enhance its coordinating ability, the insertion of an electron-donating group at the 9-position of the heterocyclic ring was attempted. Thus, the corresponding *N*-oxide **120** was prepared and subjected to chlorination and nitration. Unfortunately, no expected product was observed due to the serious decomposition of **120** (Scheme 30).

Acknowledgements

Most of the work described in this review has been carried out in the laboratory of the author. The contribution of many dedicated co-workers, whose names are cited in the references, is gratefully acknowledged.

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