CAMPHOR-DERIVED HETEROCYCLES
SYNTHESES AND POTENTIAL APPLICATIONS

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Abstract. *Syntheses and applications of camphor-derived heterocycles are described. Heterocycles are arranged in five distinct groups: fused camphor-derived heterocycles, spiro camphor-derived heterocycles, camphor substituted heterocycles, ring expanded camphor-derived heterocycles, and tethered camphor-derived heterocycles. The respective literature covers a period from 2000 to 2015 non-comprehensively.*

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1. Introduction

Camphor (**1**) is one of nature's privileged scaffolds. It is readily available in both enantiomeric forms. In addition, several of its simple derivatives are also commercially available like camphorsulfonic acid (**2**) or ketopinic acid (**3**), but can also easily be prepared from camphor (**1**) (Figure 1).[1-3] Camphor undergoes a wide variety of chemical transformations which, at first glance, functionalize inactivated positions, thus enabling the preparation of structurally and functionally very diverse products.[4,5] All of the above makes camphor a very desirable starting material for the preparation of a wide variety of products ranging from natural products[4,5] to chiral auxiliaries,[6,7] ligands in asymmetric synthesis,[8-12] organocatalysts, NMR shift reagents,[13] *etc.* including numerous examples of heterocyclic derivatives.

Figure 1
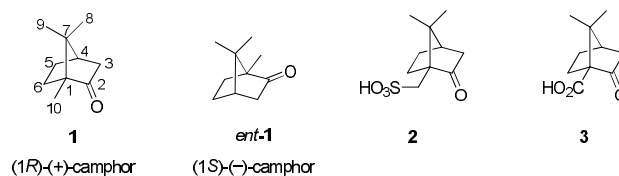
In spite of the very diverse reactivity of camphor, most transformations of camphor take place at the *C*2, *C*3, and *C*10 positions of camphor skeleton, thus leaving a large chemical space for further transformations.

Herein, selected camphor-derived heterocycles are presented, their synthesis and applications. Compounds have been divided according to their structure in five distinct groups: *i*) camphor-derived heterocycles, *ii*) spiro camphor-derived heterocycles, *iii*) camphor substituted heterocycles, *iv*) ring expanded camphor-derived heterocycles, and *v*) tethered camphor-derived heterocycles. The respective literature covers a period from 2000 to 2015 and is by no means comprehensive. It reflects author's selection and covers only a fraction of the existing camphor-derived heterocycles.

2. Fused camphor-derived heterocycles

Camphor-derived chiral [1,2,4]triazolo[4,3-*a*]tetrahydroquinoline *N*-heterocyclic carbene precursors **8** have been prepared in 4 steps starting from camphor-pyridone **4**[14]. Treatment of **4** with triflic anhydride in the presence of a base gave pyridyl triflate **5**, which was coupled with *N*-Boc aryl hydrazines **6** using either Pd(OAc)$_2$/tBu$_3$P or [Pd(η-C$_3$H$_5$)Cl]$_2$/SIPr catalytic systems to give diaryl hydrazines **7**. Finally, Boc-deprotection followed by TOF/NH$_4$PF$_6$ cyclization gave NHC-precursors **8** (Scheme 1).[15]
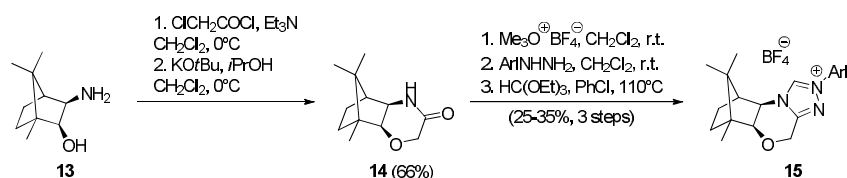

Scheme 1
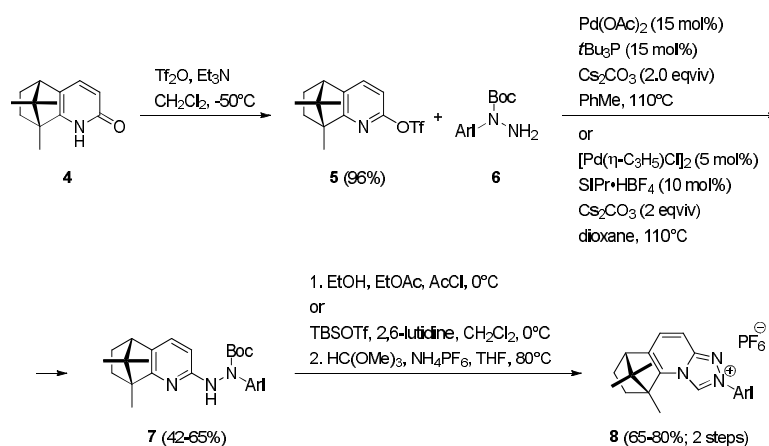
Camphor derived *N*-heterocyclic carbene precursor **12** was prepared from diimine **9**[16] via reduction with NaCNBH$_3$ which furnished chromatographically separable diamines **10** and **11**. *Cis*-diamine **11** was successfully transformed into imidazolium salt **12** (Scheme 2).[17]

Triazolium salts **15** have been prepared from *exo*-amino alcohol **13**[18] in five steps. Treatment of **13** with chloroacetyl chloride followed by base catalyzed (KOtBu) cyclization gave lactam **14**. Finally, applying the three step procedure developed by Rovis and co-workers[19] furnished the desired triazolium salts **15** (Scheme 3).[20] Camphor-derived triazolium salts **15** have been used, very successfully, as organocatalysts in the intramolecular crossed aldehyde-ketone benzoin reactions,[20] in promoting asymmetric intramolecular Michael additions,[21] for the enantioselective Michael addition reactions of different dicarbonyl compounds

to *α,β*-unsaturated aldehydes using redox oxidation in the construction of 3,4-dihydro-*α*-pyrones,[22] for enantioselective intramolecular Stetter reactions,[23] for the aldehyde-ketone benzoin reactions with *N*-tethered substrates,[24] and for the de-symmetrization of cyclohexadienones via intramolecular Stetter reaction[25] in the construction of tricyclic carbocycles.
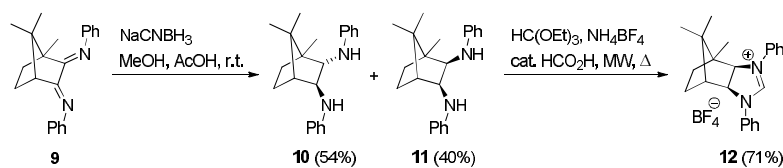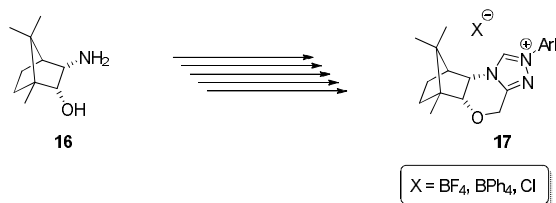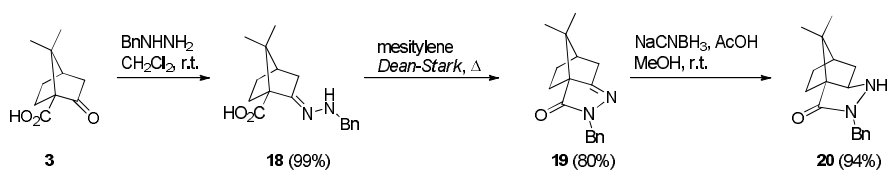

Scheme 2

Scheme 3

Starting from (–)-3-*endo*-aminoborneol **16**,[26] Rafinski and Kozakiewicz reported the preparation of diastereomeric *endo-N*-heterocyclic carbene precursors **17**, following the same synthetic protocol as described above (Scheme 4, see Scheme 3). Catalysts of type **17** have been most successfully employed in the enantioselective preparation of chromanones bearing quaternary substituted stereocentres in excellent yields and up to 96% ee.[27]


X = BF₄, BPh₄, Cl

Scheme 4

In 2005, Ogilvie *at al.* reported the preparation of camphor-derived organocatalyst **20**. (*S*)-(+)-Ketopinic acid (**3**) was condensed with benzylhydrazine into hydrazone **18** (Scheme 5).
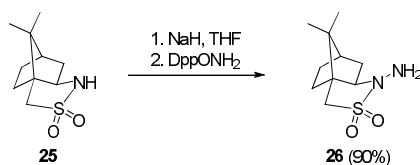

Scheme 5

The following cyclocondensation using *Dean-Stark* conditions gave cyclic hydrazone **19**. Finally, compound **19** was reduced using NaCNBH$_3$ to furnish hydrazide **20** (Scheme 5). Other substituted hydrazide organocatalysts have been prepared in a similar fashion.[28] Organocatalyst **20** has been used in asymmetric Diels-Alder reaction between cyclopentadiene and various α,β-unsaturated enals.[28]

In 2008, Lee and co-workers reported the preparation of camphor sulfonyl hydrazines **24**. They were prepared in three steps from (+)-camphor sulfonyl chloride (**21**). Compound **21** was cyclized with hydrazine monohydrate into hydrazone **22**. The following alkylations under phase transfer conditions gave compounds **23**. Finally, NaCNBH$_3$ reduction of **23** yielded sulfonyl hydrazines **24** (Scheme 6).[29] Using similar reaction strategy, Langlois and co-workers also reported the preparation of camphor-derived sulfonyl hydrazines.[30] Catalysts of type **24** have been used in the asymmetric Diels-Alder cycloaddition of cyclopentadinene to various α,β-unsaturated enals,[29] in enantioselective Aza-Michael additions to α,β-unsaturated aldehydes,[31] and in the asymmetric *Friedel-Crafts* alkylations[32] of *N*-benzyl indole with α,β-unsaturated aldehydes.
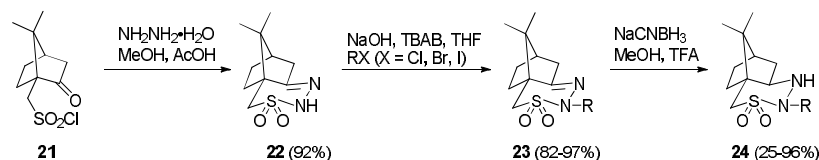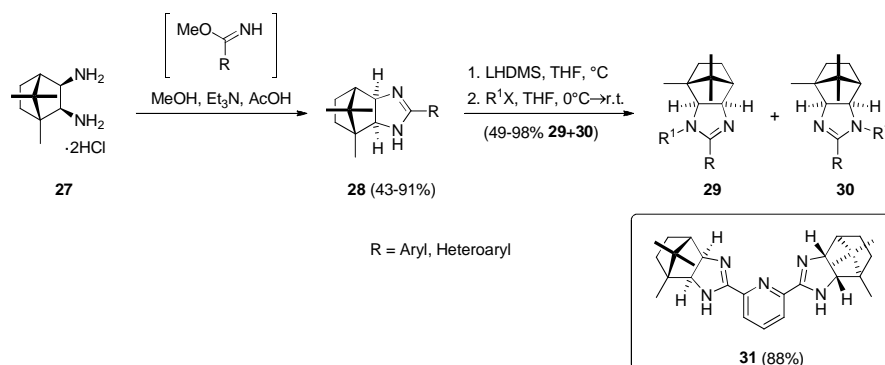

Scheme 6

In 2009, Lee and co-workers prepared the second generation camphor sulfonyl hydrazine **26**. Oppolzer's sultam **25**[6] was transformed into primary sulfonyl hydrazine **26** using electrophilic amination with DppONH$_2$ (Scheme 7).[33] Hydrazine **26** catalyzed asymmetric Diels-Alder reactions between unsaturated ketones and different dienes.[33]
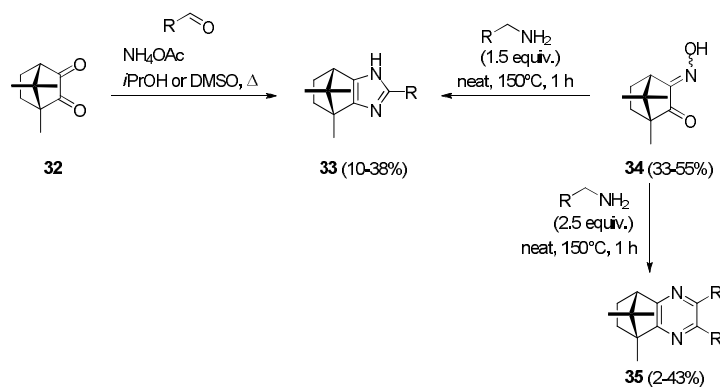

Scheme 7

Camphor-annelated imidazolines **29-31** were prepared in two steps from (1*R*,2*S*,3*R*)-camphordiamine **27**.[34] Treatment of **27** with imidates (pre-formed from nitriles via *Pinner* reaction) gave unsubstituted imidazolines **28**. The following reaction with different electrophiles yielded separable regioisomeric products **29** and **30** (**30** as the major isomer). Similarly, reaction of **27** with pyridine-2,6-dicarbonitrile yielded bidentate ligand **31** (Scheme 8). Disubstituted camphor-annelated imidazolines **29-31** were applied in the Cu(II)-catalyzed asymmetric Henry reaction, furnishing the corresponding nitroaldol product with enantioselectivities up to 67% ee. The stereoselectively of the product (*R vs. S*) was controlled by the regioisomer of the applied ligand.[35,36]

Annelated camphor-imidazoles **33** were prepared either by treatment of camphorquinone (**32**)[37] with an aldehyde in the presence of ammonium acetate or from camphor oxime **34**[37,38] in the reaction with excess amine (1.5 equiv.).[39] Interestingly, reaction between camphor oxime **34** and 2.5 equivalents of arylmethanamine, under the same reaction conditions, lead to the formation of camphor-fused pyrazines **35** in 10-51% yield.[40] Camphor-imidazoles **33** were used as ligands in the Cu(II)-catalyzed asymmetric Henry reaction with enantioselectivities of the product reaching up to 29% ee (Scheme 9).[39]


Scheme 8

Scheme 9

Reaction of (+)-3-methylenecamphor (**36**)[41] with 2,6-bis(pyridinioacetyl)pyridine iodide (**37**) furnished ligand **38**. Treatment of **38** with RhCl$_3$·3H$_2$O gave rhodium complex **39** (Scheme 10). Rhodium complex **39** was assessed as chiral catalyst in the enantioselective cyclopropanations of styrene with diazoacetates giving the corresponding products in enantioselectivities up to 32% ee.[42]

Chiral C_2-symmetric 1,10-phenanthroline **43** was prepared in 5 steps from (+)-3-methylenecamphor (**36**)[41]. Michael-aza-annulation-aromatization of **36** with **40** afforded pyridine **41**. The following cleavage of benzyl ether and Swern oxidation yielded ketone **42**. Finally, the second Michael-aza-annulation-

aromatization of **42** with **36** and the following dehydrogenation furnished 1,10-phenanthroline **43** (Scheme 11).[43]
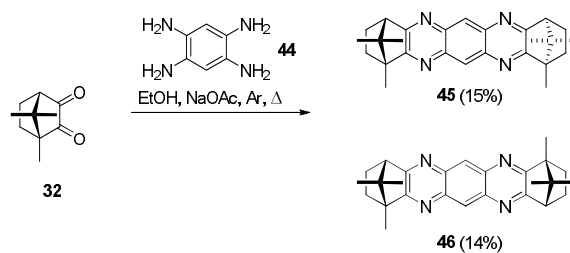

Scheme 10

Scheme 11
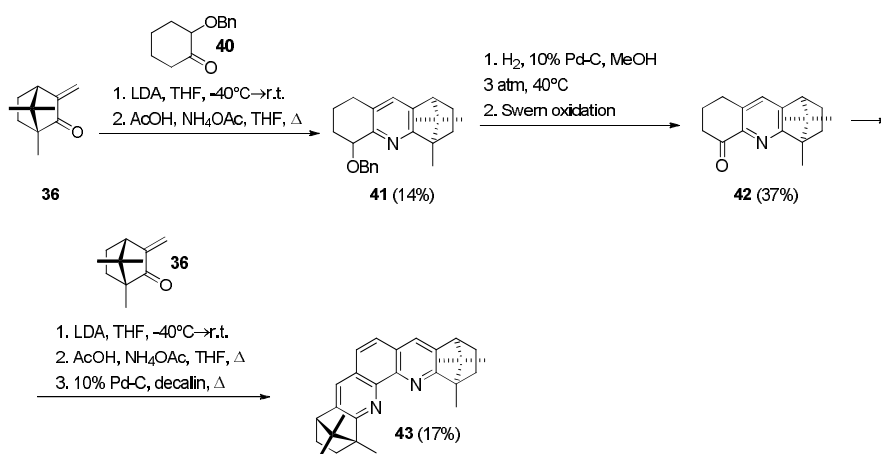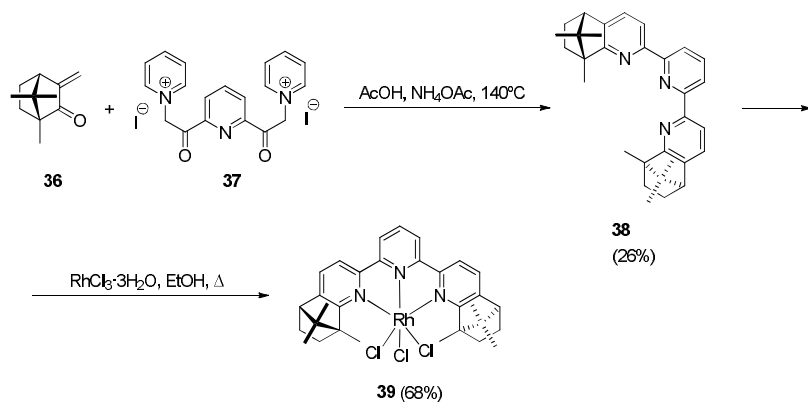
Condensation of camphorquinone (**32**) with 1,2,4,5-tetraaminobenzene (**44**) yielded a separable mixture of pyrazine derivatives **45** and **46** in a 1:1 ratio. Compounds **45** and **46** have been used as heterocyclic ligands for the construction of coordination polymers (Scheme 12).[44]

The preparation of ligand **50** started from 3-formylcamphor **47**[45]. Condensation of **47** with guanidine yielded pyrimidine **48**[46]. Diazotation of **48** and treatment of the resulting pyrimidinone with POCl$_3$ gave chloro-pyrimidine **49**. Finally, nickel-mediated coupling of **49** furnished bis-pyrimidine **50**. Ligand **50** was used for the preparation of Pd, Mo, and Ru complexes **51** (Scheme 13).[47]

Starting from camphorpirazole **52**[48], heteroscorpionate ligand **54** has been prepared in a one-pot two-step synthesis. Treatment of **52** with sodium hydride and thionyl chloride furnished sulfinylbis(camphorpyrazole) **53**, which was, without isolation, upon the addition of pyridine and

salicylaldehide transformed into ligand **54** in 60% yield. Other ligands of type **54** have been prepared in a similar manner. A two-step synthesis of **54** via carbonylbis(camphorpyrazole) was also developed. Alkylation of **52** with CH_2Cl_2 followed by deprotonation and alkylation with CO_2 gave bis(camphorpyrazol-1-yl)acetic acid **55** (Scheme 14). C_2 symmetrical ligands **54** and **55** were used in the preparation of zinc, rhenium, and rhodium complexes.[49-51]

Scheme 12
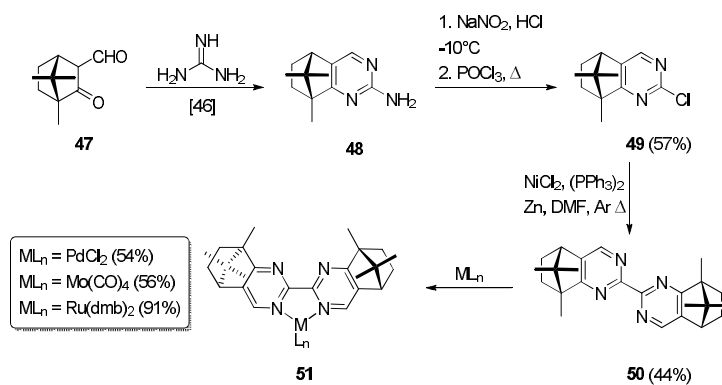
Scheme 13
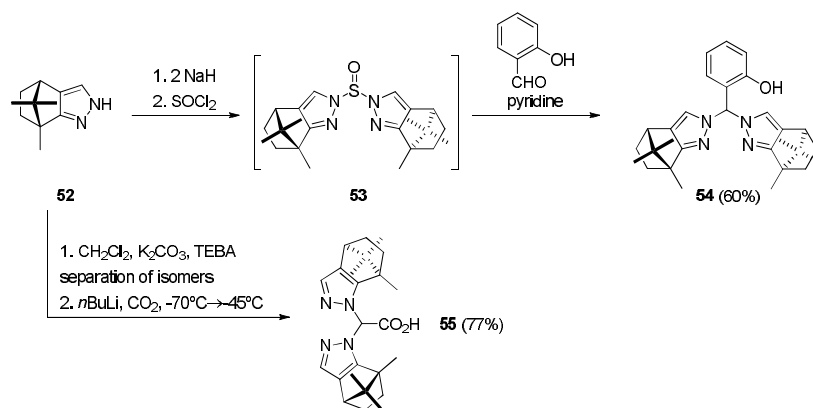
Scheme 14

Monophosphine ligand **60** has been prepared from camphor (**1**) in 5 steps. Reaction of enolate of **1** with dichlorophenylphosphine gave diketophosphine **56**. The following LiAlH₄ reductio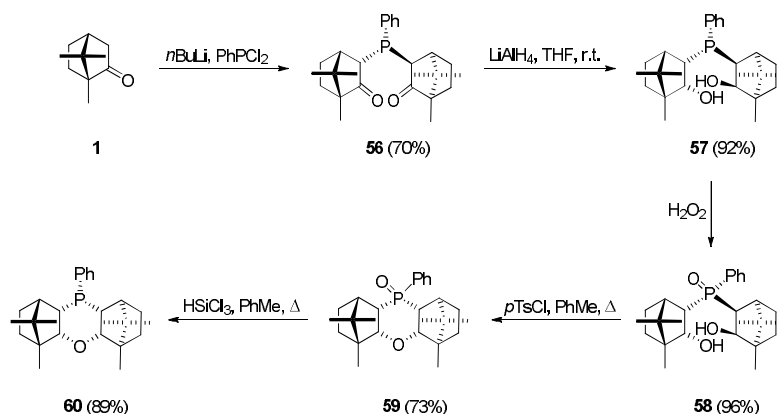n of **56** furnished the all *endo*-compound **57**. Treatment of **57** with H₂O₂ gave oxide **58**, which was cyclized in the presence of *p*TsCl into compound **59**. Final reduction with trichlorosilane gave ligand **60** (Scheme 15). Coordination chemistry of **60** with palladium was examined.[52]
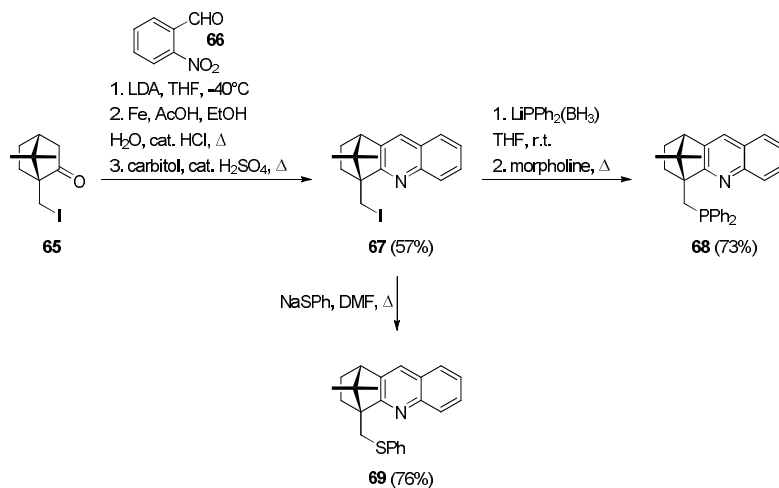

Scheme 15

Camphor-derived phosphine ligands **64** have been prepared from *β*-diketones **61**.[53] Cyclocondensation of **61** with (2-bromo-6-methoxyphenyl)hydrazine (**62**) gave pyrazoles **63**. The following lithiation of pyrazoles **63** at low temperature and quenching with chlorophosphines gave the final *P,N*-ligands **64** (Scheme 16). Iridium complexes derived from ligands **64** have been applied in the asymmetric hydrogenation of *trans-α*-methylstilbene giving the corresponding products with the highest enantiomeric excess of 85%.[54]
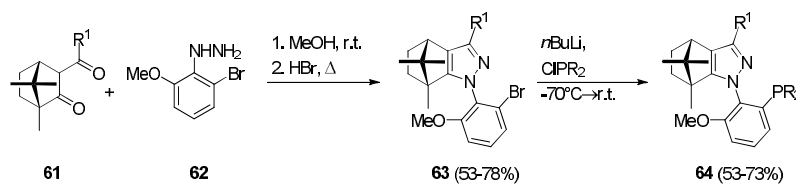
Scheme 16

A five step procedure starting from 10-iodocamphor (**65**)[55] gave *P,N*-ligand **68**. Thus, condensation of **65** with 2-nitrobenzaldehyde (**66**) followed by reduction of the nitro group and cyclocondensation gave tetrahydroacridine **67**. Nucleophilic substitution of iodine of **67** with sodium diphenylphosphine–borane followed by deprotection gave *P,N*-ligand **68**. On the other hand, reaction of **67** with sodium benzenethiolate furnished *S,N*-ligand **69** (Scheme 17). Ligands **68** and **69** have been applied in the palladium catalyzed enantioselective allylic substitution, yielding the respective products in up to 44% ee.[56]

Scheme 17

Tricyclic imino-lactones **74** and **75** have been prepared in three steps from camphorquinone (**32**). Reduction of **32** with NaBH$_4$ gave an inseparable mixture of *exo*-hydroxy-ketones **70** and **71**. The following esterification with *N*-Cbz-glycine gave inseparable mixture of esters **72** and **73**. The final catalytic hydrogenation-cyclization furnished easily separable imino-lactones **74** and **75** (Scheme 18).[57] Compounds **74** and **75** have been used as chiral auxiliaries in the formation of *α*-amino acids,[58,59] *α,α*-disubstituted *α*-amino acids,[57] and enantiopure 3-aryl-2,3-diaminopropanoic acids[60] in good yields and excellent diastereoselectivities (d.r. ≥98%). Synthesis of 3,4-diepipolyoxamic acid and the isomer of polyoxamic acid has been realized via the diastereoselective aldol reaction of camphor-based tricyclic iminolactones.[61]
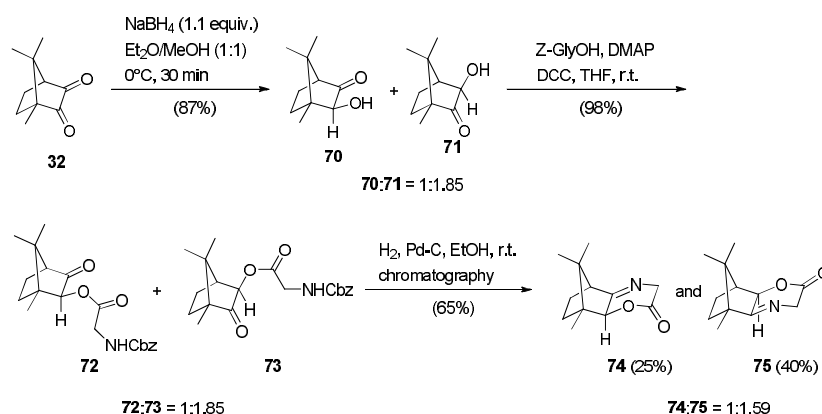
Scheme 18

Camphor-derived, geometrically fixed nitrones **77** and **79** were used in 1,3-dipolar cycloadditions with various alkenes, giving the respective cycloadducts in high yields and with excellent stereoselectivity.

Nitrone **77** was prepared by catalytic hydrogenation of **75**,[57] followed by MCPBA oxidation of amino lactone **76**. On the other hand, the preparation of nitrone **79** proceeded via 3-(hydroxylamino)isoborneol hydrochloride **78**, which was cyclized into nitrone **79** in a one-pot procedure with glyoxylic acid and DCC (Scheme 19).[62]
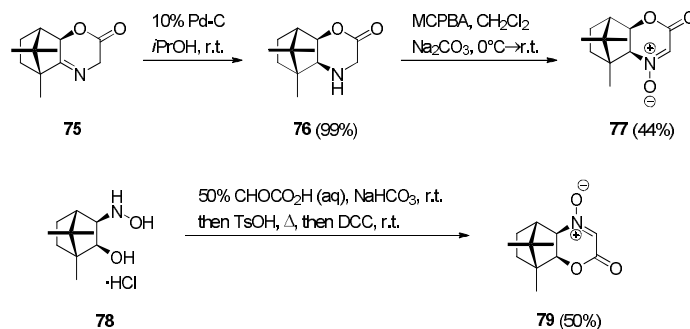
Scheme 19

Cycloadditions between camphor-derived oxazoline-*N*-oxides **80**, obtained *in situ* from (+)-3-(hydroxylamino)isoborneol hydrochloride,[62] and Pt(II)-coordinated nitriles **81** furnished diastereomerically pure platinum(II) complexes **82** (X-ray structure) in 66-90% isolated yields. Treatment of complexes **82** with excess NaCN liberated the final products **83** (Scheme 20).[63]
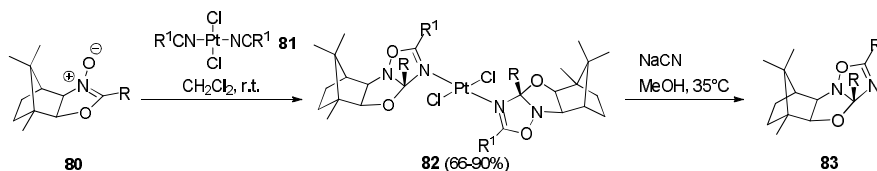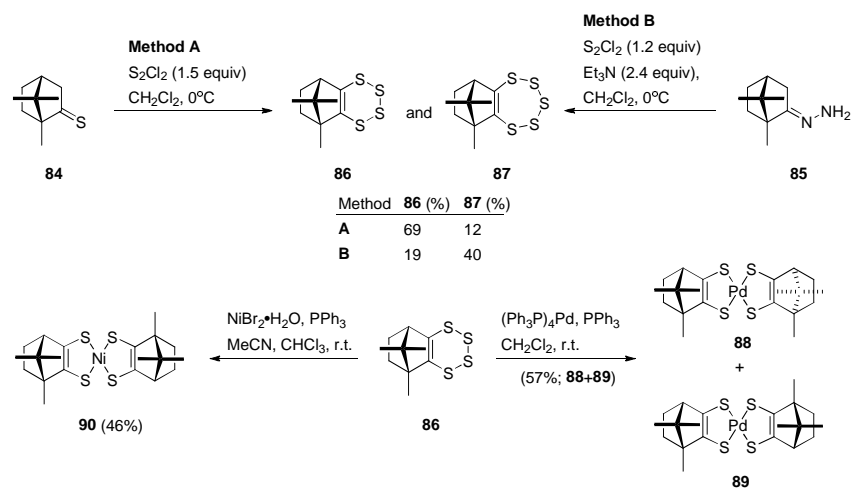

Scheme 20

Six- and seven-membered tricyclic polysulfanes **86** and **87** have been prepared either by treatment of thiocamphor (**84**) or camphor hydrazone **85** with disulfur dichloride. The two methods gave different ratios of polysulfanes **86** and **87**. Oxidations and reductions of polysulfanes **86** and **87** have been studied. In addition, treatment of **86** with (Ph₃P)₂PdCl₂ or NiBr₂ in the presence of PPh₃ furnished complexes **88**/**89** and **90**, respectively (Scheme 21).[64,65]

The base catalyzed reaction of camphor (**1**) with isatin (**91**) gave the condensation product **92** in 60% yield. Treatment of **92** with urea, thiourea, ethylenediamine, *o*-phenylenediamine, and 2-aminopyridine in refluxing EtOH gave, as the major product, the corresponding spiro heterocycles **93-97** (Scheme 22). The relative stereochemistry of the products **93-97** is unfortunately not defined.[66]

Two different two-step synthetic routes have been used for the preparation of 3-cyanopyridine-2(1*H*)-ones and their thione analogues **102**. First, reaction of camphor (**1**) with cyanothioacetamide and malononitrile furnished the starting condensation products **98** and **99**, respectively. Next, treatment of **98**

with arylmethylidenemalononitriles **100** in boiling ethanol, containing catalytic amounts of piperidine, yielded pyridin-2(1*H*)-thione derivatives **102**. Similarly, reactions of **99** with arylmethylidene(cyano)(thio)acetamides **101** furnished the same pyridin-2(1*H*)-thione derivatives and their oxa analogues **102** (Scheme 23).[67]

Scheme 21
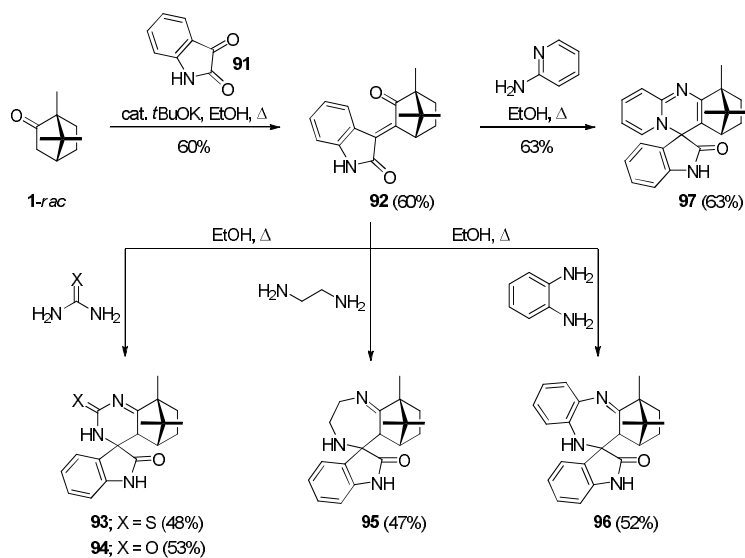
Scheme 22
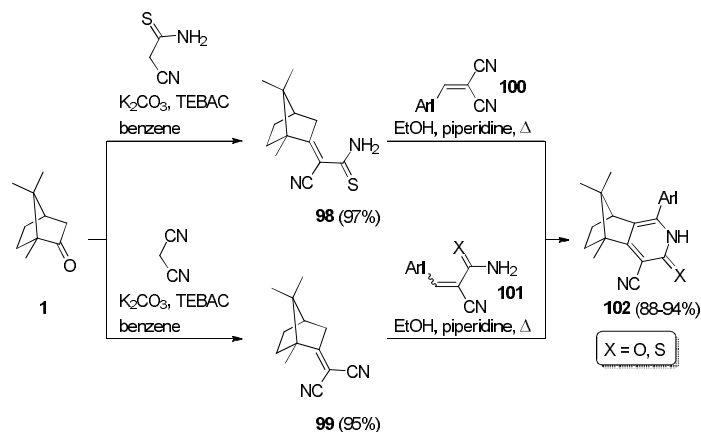
Scheme 23

Reaction of hydroxymethylene camphor **47**[41] with excess phosphonium salt **103** and trimethylamine gave an (*E/Z*)-mixture of amides **104**. Thermal cyclization of **104** in a mixture of ammonium acetate in acetic acid yielded pyridone **4** (Scheme 24).[14]
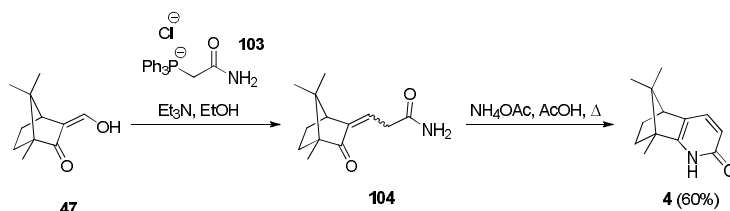
Scheme 24

Camphor-derived 1,3-oxathianes of *α,β*-unsaturated aldehydes **105**[68] furnished with dichloroketene, prepared *in situ* under elimination conditions from dichloroacetyl chloride, macrocyclic thiolatones **106** in good yields (67-96%) and with complete stereocontrol. The reductive, *in situ* preparation of dichloroketene from trichloroacetly chlorid in the presence of Lewis acid furnished [1,3]-rearrangement product **107** (Scheme 25).[69]
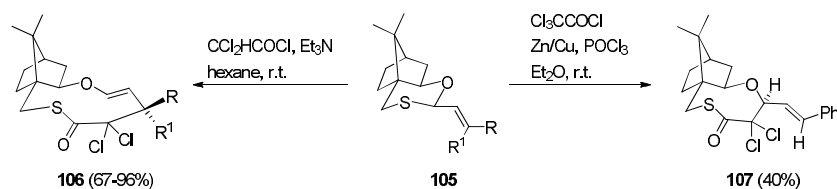
Scheme 25

While studying the origin of carboxylate migration selectivity in $Rh_2(II)$-catalyzed *N*-heterocycle formation from trisubstituted styryl azides, Driver and co-workers prepared a series of fused camphor-indole products **111** in two steps starting from camphor derived triflate **108**. Coupling of **108** with 2-azidoarylboronic pinacolate esters **109** gave trisubstituted styryl azides **110**.[70] The following $Rh_2(II)$-catalyzed tandem reaction sequence yielded regioselectively indoles **111** (Scheme 26).[71]
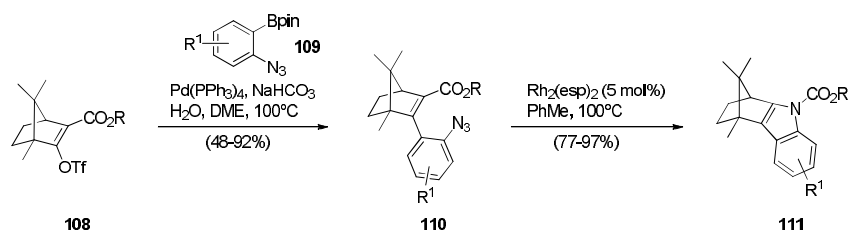
Scheme 26

3. Spiro camphor-derived heterocycles

Synthesis of spirocyclic camphor-derived triazolium salts **115** commenced from camphor **1**. Stereoselective addition of TMSCN to **1** yielded cyanohydrin **112**.[72] The following LiALH$_4$ reduction furnished amino-alcohol **113**, which was converted into lactam **114** in a two-step procedure via alkylation with chloroacetyl chlorid and base catalyzed cyclization. Lactam **114** was converted into triazolium salts **115** applying the three-step procedure developed by Rovis and co-workers (Scheme 27).[19] Catalysts of type **115** have been employed in the catalytic asymmetric benzoin condensation giving the respective products in moderate enantiomeric excesses.[73]
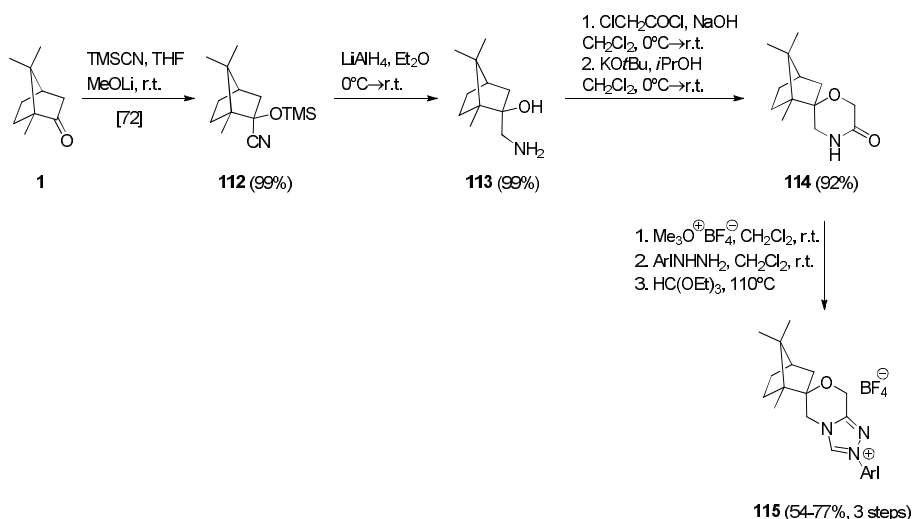
Scheme 27

α-Alkylidene-(+)-camphor derivatives **116** have been used as dipolarophiles in 1,3-dipolar cycloadditions to stable substituted-benzonitrile *N*-oxides **117**. The corresponding spiro-cycloadducts **118** and **118'** were formed in 4-60% yields and in 66-100% de (Scheme 28).[74]
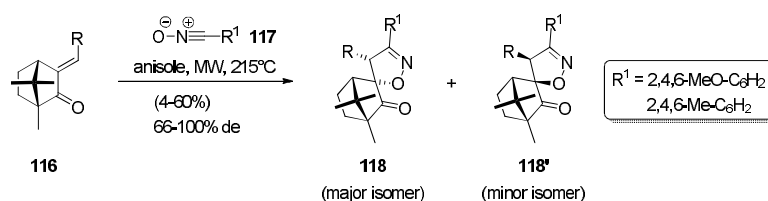
Scheme 28

Acid catalyzed condensations of (1*S*)-(+)-camphorquinone (*ent*-**32**) with anilines yielded keto-imines **119** as mixtures of the major (3*E*)- and the minor (3*Z*)-isomer. Carbocyclic 1,3-dipolar cycloadditions of the *in situ* formed trimethylenemethane (TMM)[75,76] to 3-imino-ketones **119** yielded separable mixtures of the major spiro-furans **120** and the minor spiro-pyrrolidines **121**. Cycloaddition of TMM to (1*S*)-(+)-camohorquinone (*ent*-**32**) furnished inseparable mixture of regioisomeric furans **122** and **122'** in a 1:1 ratio. Hydrolysis of imine **120** (Arl=Ph) gave ketone **122**. LiAlH₄ reduction of imines **120** furnished, selectively, the *exo*-amines **123**, while sequential reduction of spiro-ketone **121** (R=4-O₂N-C₆H₄) furnished isoborneol derivative **124** in 76% de and in 20% yields (Scheme 29).[77]
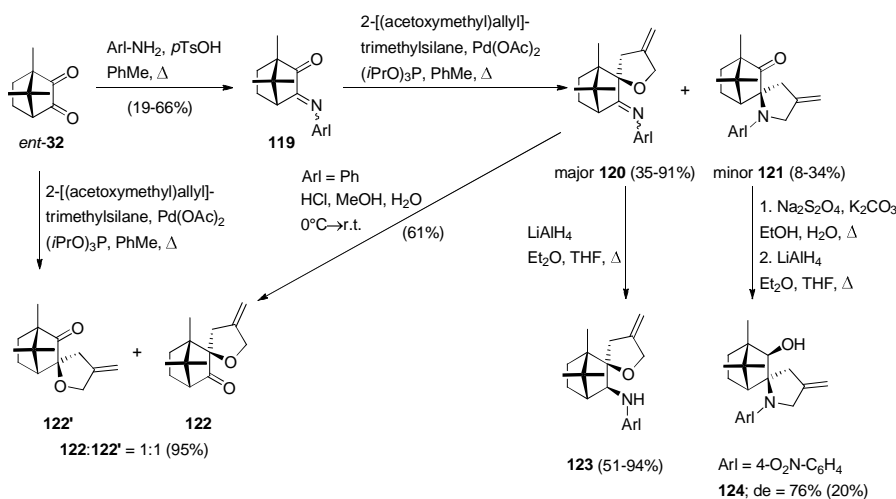
Scheme 29

Inverse electron-demand [4+2] cycloadditions of spiro-furanone **122** and spiro-furanone imines **120**[77] to tetrazines **125**[78-80] yielded, stereoselectively, the corresponding dispiro-cycloadducts **126** and **127** in 84-98% de. In contrast, cycloadditions of tetrazine **125** to spiro-pyrrolidinone **121** and spiro-amine **123**[77]

furnished the corresponding dispiro-heterocycles **128** and **129** with moderate selectivity 50% and 62% de, respectively (Scheme 30).[81]
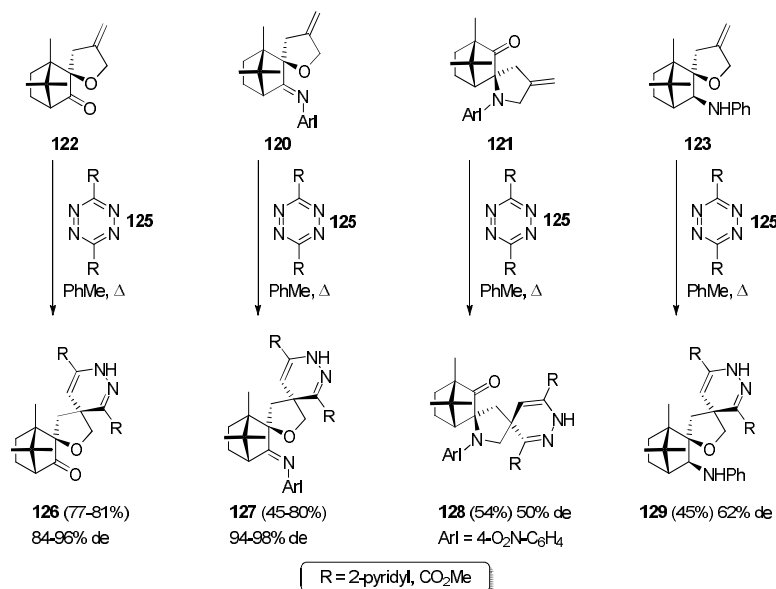
Scheme 30

Acid catalyzed condensation of diamine **130**[77] with camphorquinone (*ent*-**32**) gave condensation products **131**, **132**, and **133** in a ratio of 26:44:30, respectively. Chromatographic purification of the reaction mixture gave pure compound **131** and mixture of compounds **132** and **133**. Cycloaddition of TMM[75,76] to **131** gave the desired bis-spirofurane **134**, while the same cycloaddition to a mixture of compounds **132** and **133** yielded product **134** (from **132**) and the unreacted *endo*-amine **133** (Scheme 31). NaCNBH$_3$ reduction of **134** gave bis-*exo*-diamine **135**. Catalytic hydrogenation of **135**, after chromatographic purification, gave diamine **136**. Thermal cyclization of **135** and **136** with HC(OEt)$_3$ in the presence of NH$_4$BF$_4$ and formic acid yielded camphor-derived *N*-heterocyclic carbene precursors **137** and **138**, respectively (Scheme 32).[82]

Camphor-derived spirocyclic cyclopentapyrans **141** and **142** have been prepared in a highly stereoselective manner by intramolecular *Pauson-Khand* reaction of the corresponding enynes **139** and **140**. The starting enynes **139** and **140** have been synthesized in two steps from camphor via *endo*-selective addition of a suitable Grignard reagent, followed by *O*-alkylation reactions (Scheme 33).[83]

Camphor-derived thiadiazoline **144** was prepared in two steps from camphor (**1**) by first forming the corresponding thiosemicarbazone **143**, followed by cyclization in a mixture of pyridine and acetic anhydride into spiro-heterocycle **144** (Scheme 34).[84,85]

130

pTsOH (cat)
PhMe, Δ
ent-32

131 (31%) + **132** + **133**

132+133 (36%)

2-[(acetoxymethyl)allyl]-trimethylsilane
Pd(OAc)₂, (iPrO)₃P, PhMe, Δ

134 (69%)

134 (32%) + **133** (22%)

Scheme 31

134

NaCNBH₃, MeOH
AcOH, r.t.

135 (88%)

H₂, 10% Pd-C
EtOH, then CC

136 (44%)

HC(OEt)₃, HCO₂H
NH₄BF₄, 120°C

HC(OEt)₃, HCO₂H
NH₄BF₄, 120°C

137 (61%)

138 (42%)
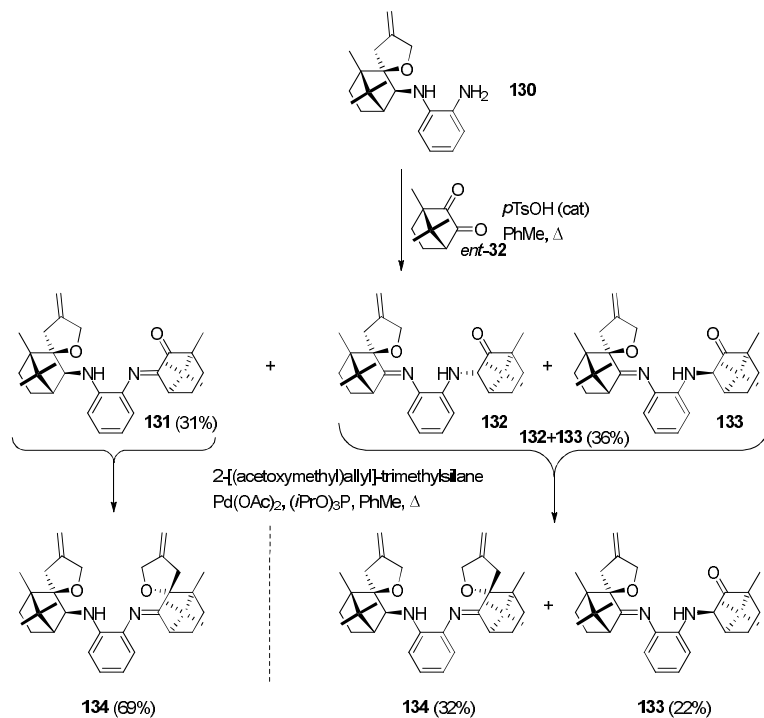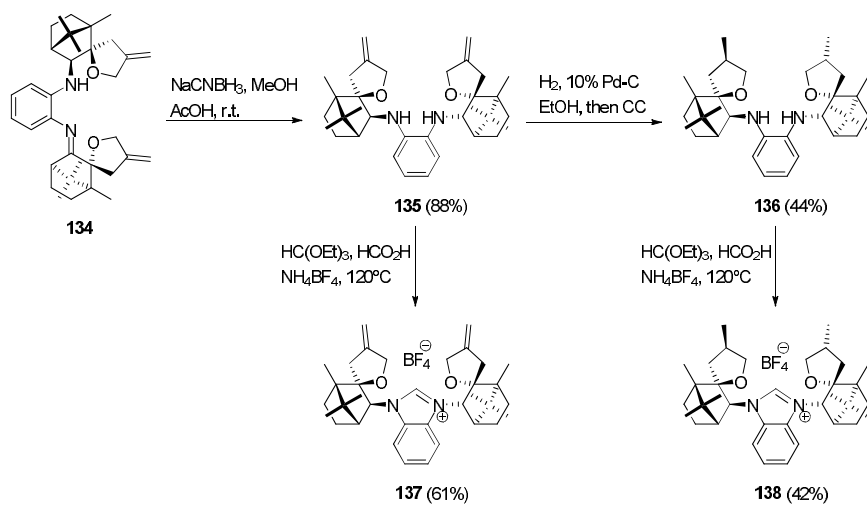
Scheme 32

Scheme 33

Scheme 34
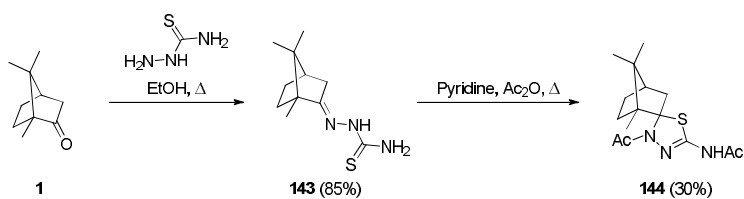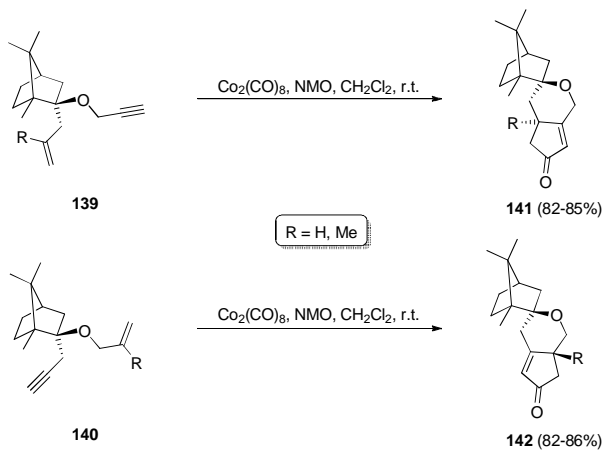
4. Camphor substituted heterocycles

Camphor-derived amido-functionalized *N*-heterocyclic carbene nickel complex **148** has been prepared in three steps from (*R*)-(–)-isobornylamine (**145**). Reaction of **145** with glyoxal, formaldehyde, and NH₄Cl in the presence of H₃PO₄ at elevated temperature yielded isobornylimidazole **146**. Alkylation of **146** with 2-chloro-*N*-phenylacetamide furnished imidazolium salt **147**, which was treated with NiCl₂·6H₂O in the presence of K₂CO₃ to yield nickel carbene complex **148** with *cis*-geometry as confirmed by single crystal X-ray analysis (Scheme 35).

Scheme 35
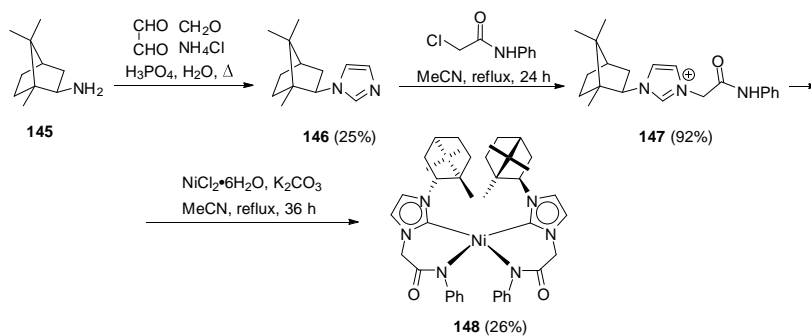
The **148** catalyzed Michael addition of ethyl 2-cyanopropanoate to methyl vinyl ketone gave the desired product in 92% yield though without any chiral induction.[86]

N-heterocyclic carbene precursor **152** was prepared in three steps from (+)-bornylamine (**149**). Reaction of **149** with glyoxal gave diimine **150**, which upon reduction with NaBH(OAc)$_3$ yielded diamine **151**. Final cyclization of **151** with trimethyl orthoformate in the presence of ammonium tetrafluoroborate furnished carbene precursor **152** (Scheme 36). Ligand **152** was used in the Pd-catalyzed synthesis of oxindoles via amide *α*-arylation.[87]
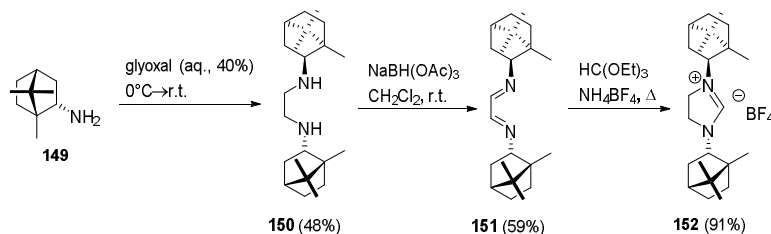
Scheme 36

Six-membered camphor-derived NHCs **157a-c** were prepared in 3 steps from (*R*)-(+)-bornylamine (**149**). Reaction of **149** with 1-bromo-3-propanol **153** yielded aminoalcohols **154a,b**, which upon treatment with thionyl chloride furnished corresponding chloride salts **155a,b**. Finally, reaction of aminoalkyl chlorides **155a,b** with palladium(II) isonitrile **156** in the presence of base gave bornyl-derived Pd-isonitrile complexes **157a,b**. The cyclododecanone derivative **157c** was prepared in a similar manner (Scheme 37). Compounds **157a-c** have been applied as catalysts in the asymmetric, intramolecular *α*-arylation of amides. The corresponding oxindole products were formed in good yields and enantioselectivities up to 72% ee.[88]
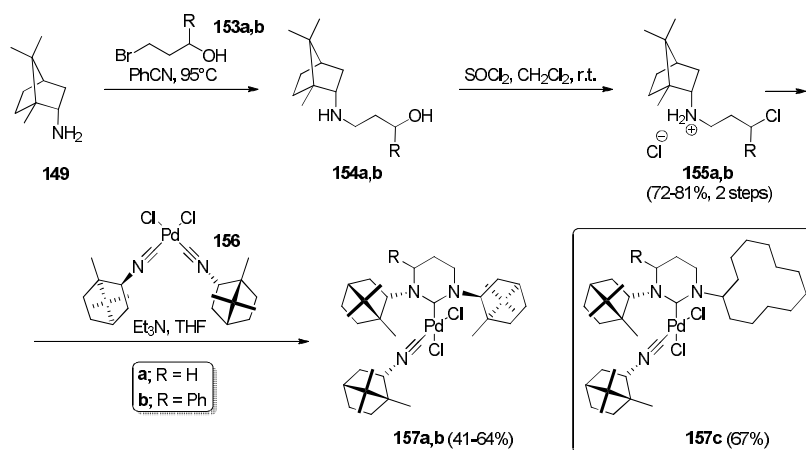
Shema 37

Chiral *P,N*-ligands **161** and **162** have been prepared from camphor-derived triflate **158**.[89] Negishi cross-coupling reactions of **158** with 2-pyridylzinc bromide and 2-quinolylzinc bromide furnished compounds **159** and **160**, respectively. The following phosphine oxide addition to **159** *i.e.* **160** and finally reduction with HSiCl$_3$ and Et$_3$N furnished the respective ligands **161** and **162** (Scheme 38).[90]
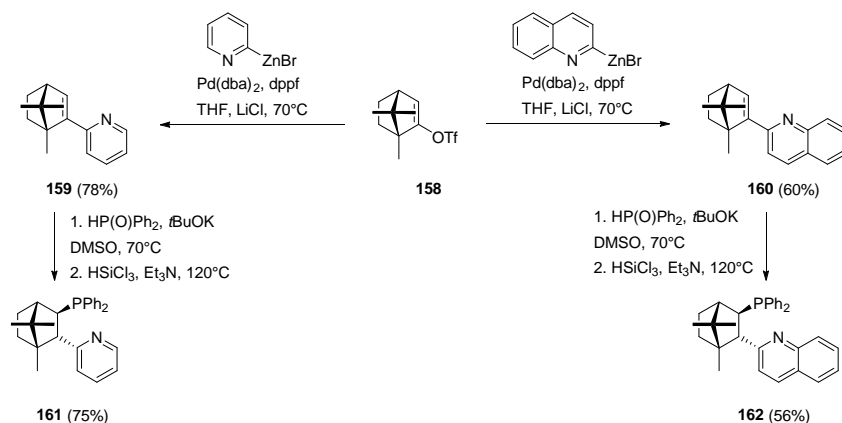
Scheme 38

Compounds **161** and **162** have been employed as ligands in Ir-catalyzed asymmetric hydrogenation reactions of (*E*)-1,2-diphenylpropene and (*Z*)-α-(acetamido)cinnamate, furnishing the corresponding products in high enantioselectivities.[90]

Chiral *P,N*-ligands **167** have been prepared from ketopinic acid (**3**). The starting acid **3** was esterified and then converted to vinyl triflate **163**. Pd-catalyzed coupling of triflate **163** with diphenylphosphine was followed by protection of phosphine as its sulfide **164**. Ester hydrolysis and amidation gave amides **165**. Finally, sequential cyclisation furnished the corresponding phosphine-oxazoline sulfides **166**. The free phosphine ligands **167** are readily generated by reduction of **166** with Raney nickel prior to use (Scheme 39).
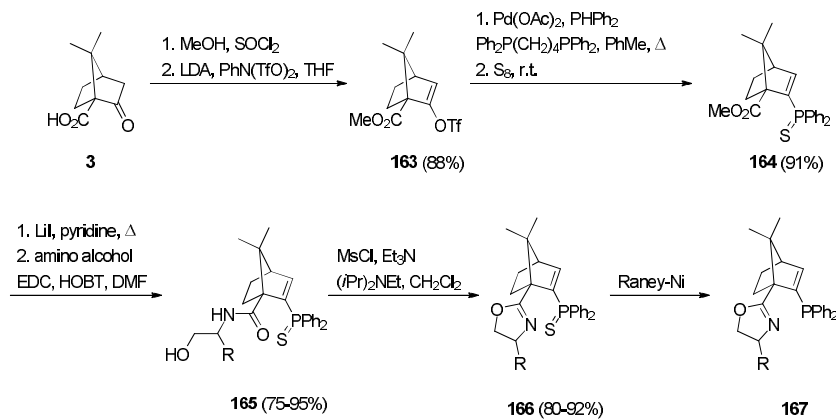
Scheme 39

Ligands **167** were used in the palladium-catalyzed asymmetric Heck reaction between aryl or alkenyl triflates and cyclic alkenes. Arylation and alkenylation of 1,2-dihydrofuran, cyclopentane, and 4,7-dihydro-1,3-dioxepin gave the corresponding products in good to excellent enantioselectivities.[91]

Enaminone **168**[92] was prepared by treatment of camphor (**1**) with *Bredereck's* reagent in refluxing DMF. Acid catalyzed reactions of **168** with hydrazinoazines **169** afforded (*E/Z*)-enehydrazines **170**, which are, in solution, in equilibrium with *endo/exo*-hydrazones **171'**. The substitution products **170/171'** could either be isolated or directly *in situ* oxidized with Br₂ into triazoloazines **172** in 37-79% yield and in 68-94% de. *Dimroth* rearrangement of the *endo*-1,2,4-triazolo[4,3-*a*]pyrimidine **173** furnished 1,2,4-triazolo[1,5-*a*]pyrimidine **174** in 55% yield and 92% de (Scheme 40).[93]
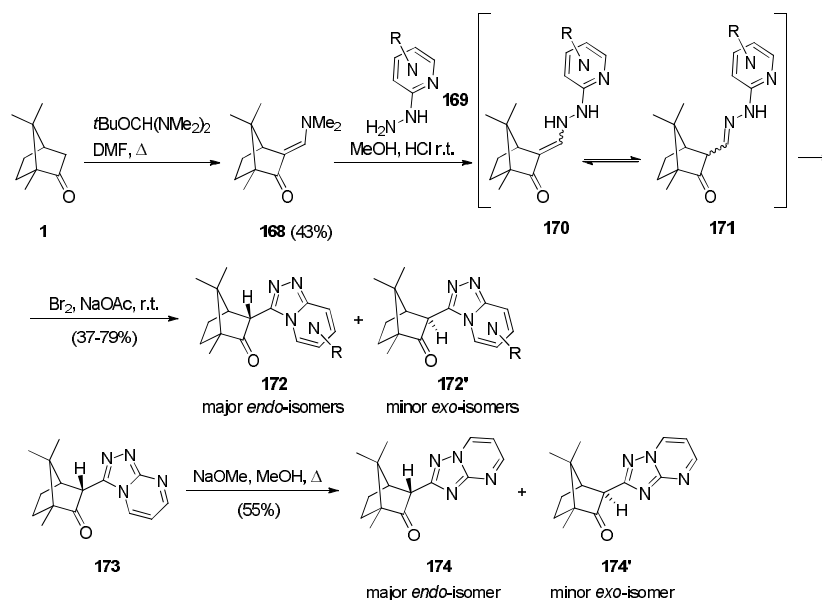
Scheme 40

Catalytic hydrogenation of 1,2,4-triazolo[4,3-*x*]azines **172**[93] takes place at the azine part yielding, in most cases, 5,6,7,8-tetrahydro analogues **175**. Treatment of **172** with borane dimethyl sulfide gave stable complexes with borane **176**. In order to achieve reduction of the keto group, compounds **172** were first activated with boron trifluoride etherate and then treated with borane dimethyl sulfide to yield, stereoselectively, isoborneol derivatives **177**. Reaction of **177** with borane dimethyl sulfide furnished the corresponding complexes with borane **178** (Scheme 41).[94]

Thermal reactions of pyrazolidinones **179** with dimethyl acetylenedicarboxylate (DMAD) proceeded via azomethine imine intermediates **180**, yielding a mixture of all four possible diasteromeric products, the major 3-*endo*-diastereomers **181a,b** and the minor 3-*exo*-diastereomers **182a,b**, which could only partially be separated by column chromatography (Scheme 42).[95]
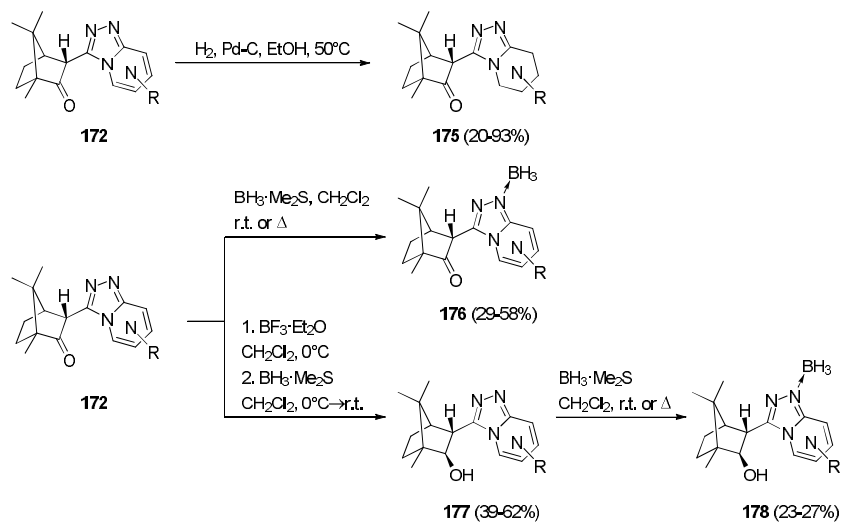
Scheme 41
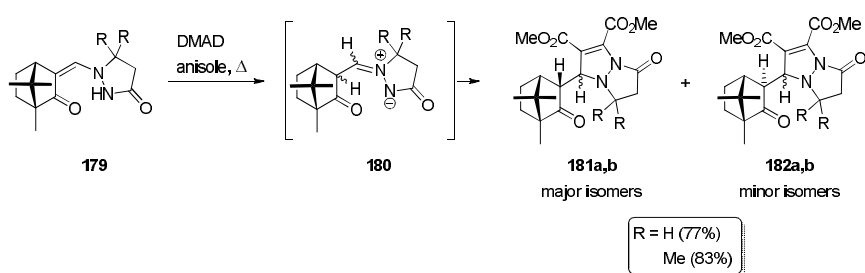
Scheme 42

Pyrrolidine, piperidine, and morpholine substituted camphor-derived organocatalysts **185** and **186** have been prepared in three steps from bromo oxime **183** (Scheme 43).

Scheme 43

Treatment of α-bromo nitroimine **183**[96] with cyclic secondary amine in the presence of hydroxyl amine afforded amino oximes **184**.[97] The following diastereoselective reduction with sodium in *n*PrOH and reaction with isothiocyanate gave 2-*endo*-3-*exo*-catalysts **185a-d**, while reduction with Raney-Nickel and subsequent thiourea formation gave, 2,3-*exo*-catalysts **186a-d**, selectively. Compounds **185a-c** and **186a-c** have been used as organocatalysts in Michael addition of dimethyl malonate to *trans*-β-nitrostirene, giving the respective product in up to 35% ee.[98]

In a similar fashion, 8-pyrrolidine-substituted thiourea bifunctional organocatalysts **189** and **190** were prepared. 8-Bromocamphor **187**[99] was subjected to nucleophilic substitution with pyrrolidine followed by oxime formation to give **188**. Oxime **188** was selectively reduced using sodium in *n*PrOH or Raney-Nickel followed by thiourea formation to furnish the desired *endo*-**189** and *exo*-**190** catalysts, respectively (Scheme 44). Compounds **189** and **190** have been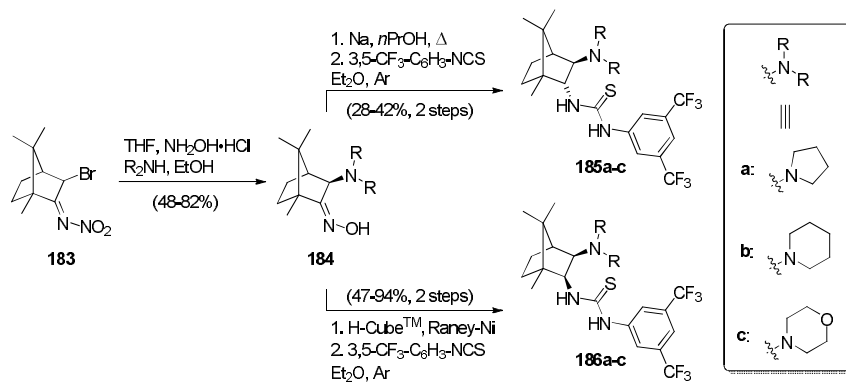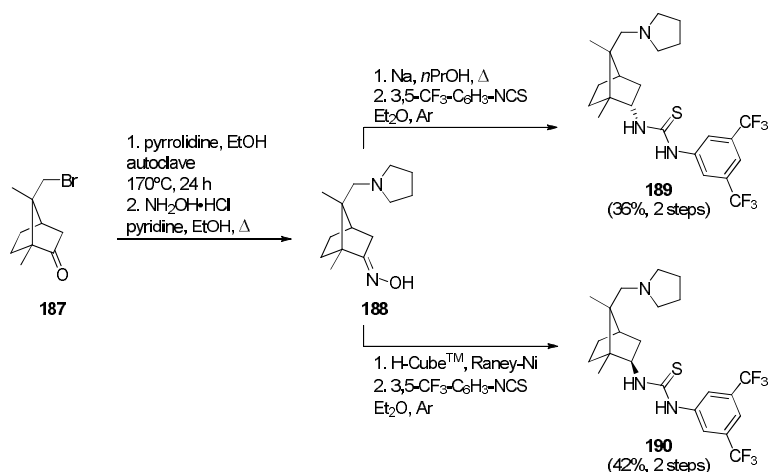 used as organocatalysts in Michael addition of dimethyl malonate to *trans*-β-nitrostirene, yielding the respective product in up to 14% ee.[98]

Scheme 44

Camphor-derived bicyclic sulfides **195** and **196** have been prepared in 4 steps from camphorsulfonyl chloride (**21**) in 48% and 24% overall yields, respectively. Treatment of **21** with PPh$_3$ followed by reaction with phenacyl chloride furnished compound **191**. Thioaldehyde **192** was photochemically generated from **191** and *in situ* trapped in a highly selective [4+2] cycloaddition reaction with cyclopentadiene *i.e.* cyclohexadiene to form adducts **193** and **194**, respectively. Finally, catalytic hydrogenation of **193** and **194** gave respective sulfides **195** and **196** (Scheme 45). Sulfides **195** and **196** have been employed in highly stereoselective catalytic asymmetric epoxidations and aziridinations.[100,101]

Amino alcohols **199** were prepared by cycloalkylation of amino ketone **197**[102] with various dibromides to give ketones **198**. The following NaBH$_4$/CeCl$_3$ reduction of **198** furnished *exo*-alcohols **199** (Scheme 46). Ligands **199** were applied in the asymmetric diethylzinc addition to aldehydes, giving the corresponding products in excellent chemical yields and in up to 94% ee.[103]
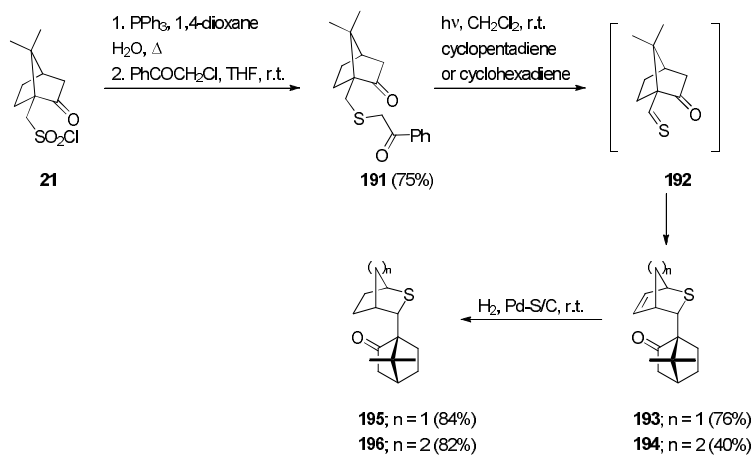
Scheme 45
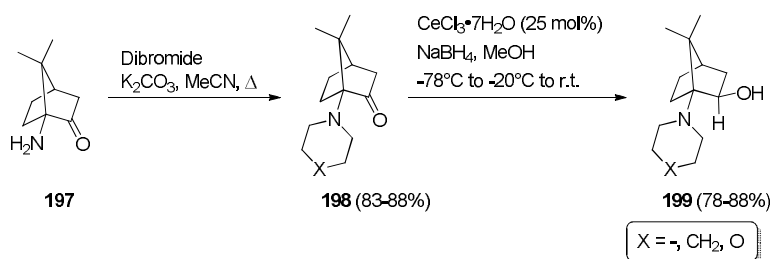
Scheme 46

1,3-Dipolar cycloaddition of nitrile oxides to acetylene **200**[104] yielded isoxazoles **201**. Dehydration of **201** furnished separable mixture of respective alkenes **202** and ring rearrangement products **203** (Scheme 47).[105]
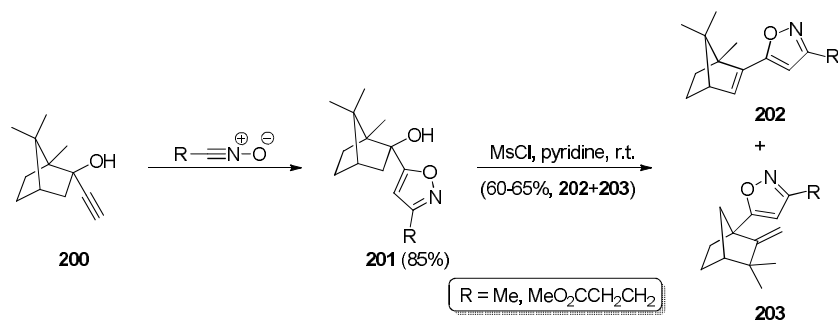
Scheme 47

5. Ring expanded camphor-derived heterocycles

C_1 Symmetric camphor-based amidinium salts **207** have been prepared in three steps from diamine **204**, which was prepared from (+)-camphoric acid.[106,107] Regioselective Buchwald-Hartwig amination of **204** gave **205**,[108] followed by cyclization with trimethyl orthoformate into **206**. The final alkylation of **206** with benzylic halide derivatives furnished amidinium salts **207** (Scheme 48).[109] Previously, Wilhelm and co-workers prepared enantiopure carbene precursors of type **207** from **204** via double alkylation (or double reductive alkylation) followed by cyclization for the construction of symmetricaly substituted products of type **207**. On the other hand, sequential regioselective alkylation-cyclization-alkylation was used for the preparation of unsymmetrical representatives of type **207**.[110] Ligands **207** have been used in the copper-catalyzed bis(pinacolato)diboron addition to methyl cinnamate, giving the corresponding product in up to 82% ee.[109] The highly nucleophilic carbenes generated from **207** were able to catalyze a formal [2+2] reaction of ketenes with aldehydes. The corresponding (*S*)-*β*-lactones were formed in good chemical yields and enantioselectivities up to 92% ee.[110] Di-benzyl- and di(pyridine-2-ylmethyl)-substituted azolium precursors of type **207** have been used for the preparation of the corresponding NHCs containing metal complexes.[111] Diphosphine containing ligand of type **207** has been used for the preparation of various Pd, Pt, Rh, and Ag complexes and their reactivity in the Suzuki-type reactions has been studied.[112]
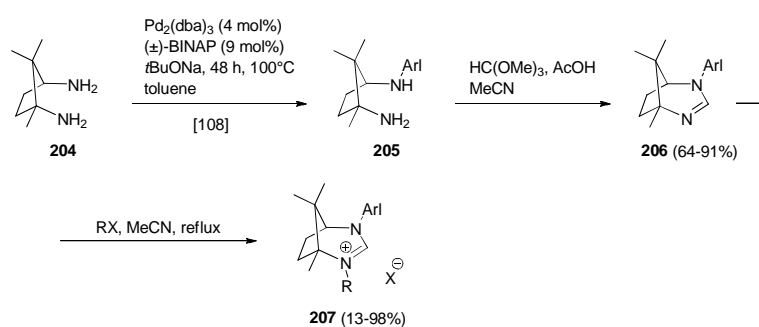
Scheme 48

Ring-expanded *N,S*-chiral ligands **211** have been prepared from (1*S*)-1-(mercaptomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**208**).[113,114] Thus, alkylations of thiole **208** in the presence of NaH gave thioethers **209**. Treatment of **209** with hydroxylamine furnished oximes **210**. Reactions of **210** with DIBAL initiated *Beckmann* rearrangement followed by *in situ* reduction of the amide to give the final amines **211** (Scheme 49). Compounds **211** have been evaluated as ligands in the Ir-catalyzed transfer hydrogenation of acetophenone, giving the corresponding products in up to 60% ee.[115]

Starting from enaminone **168**,[116] the ring-expanded amines **215** have been prepared in four steps. Addition of Grignard reagents to enaminone **168** yielded arylidene compounds **212**, which upon catalytic hydrogenation furnished epimeric mixtures of ketones **213**. Treatment of **213** with hydroxylamine-*O*-sulfonic acid yielded Beckmann rearrangement products **214**. Final reduction of amides **214** furnished the 4-*endo*-substituted amines **215** as confirmed by single crystal X-ray analysis (Sheme 50).[17]

Scheme 49

208 → NaH, THF, RX, 0°C → **209** (80-91%) → NH$_2$OH·HCl, EtOH, pyridine, Δ → **210** (88-94%)

DIBAL-H, Et$_2$O, r.t.→Δ → **211** (45-51%)

Scheme 50

168 → ArIMgBr, THF, 0°C→r.t. → **212** (28-86%) → Pd–C, H$_2$, EtOH, r.t. → **213** (44-87%) →
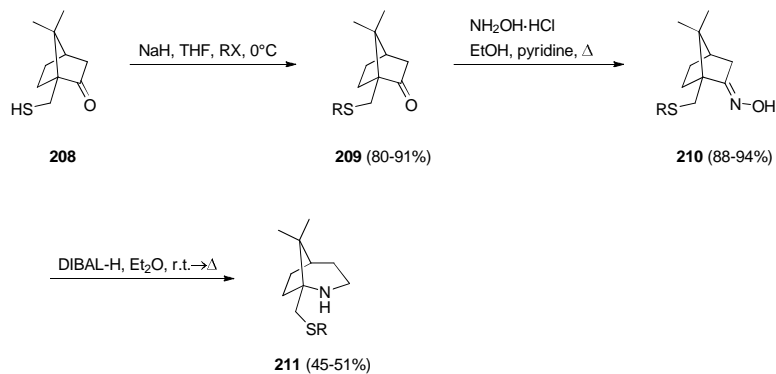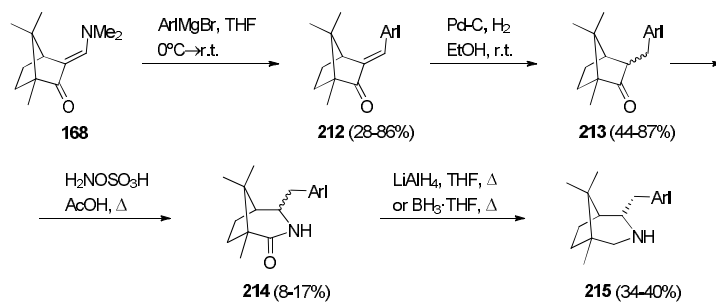
H$_2$NOSO$_3$H, AcOH, Δ → **214** (8-17%) → LiAlH$_4$, THF, Δ or BH$_3$·THF, Δ → **215** (34-40%)

Enamino lactone **218** was prepared in two steps from camphor (**1**). Baeyer-Villiger oxidation of ketone **1** furnished a mixture of isomeric oxabicyclo[3.2.1]octanones **216** and **217** (Scheme 51).[117]

1 → AcOOH, AcOH, NaOAc, r.t. [117] → **216** + **217** → tBuOCH(NMe$_2$)$_2$, decalin, Δ → **218** (43%)

218 → R-NH$_2$•HCl or R-NH$_2$, H$_2$SO$_4$, MeOH or nPrOH, r.t. or Δ → (Z)-**219** and/or (E)-**219** (29–87% E+Z)

220 (87%)
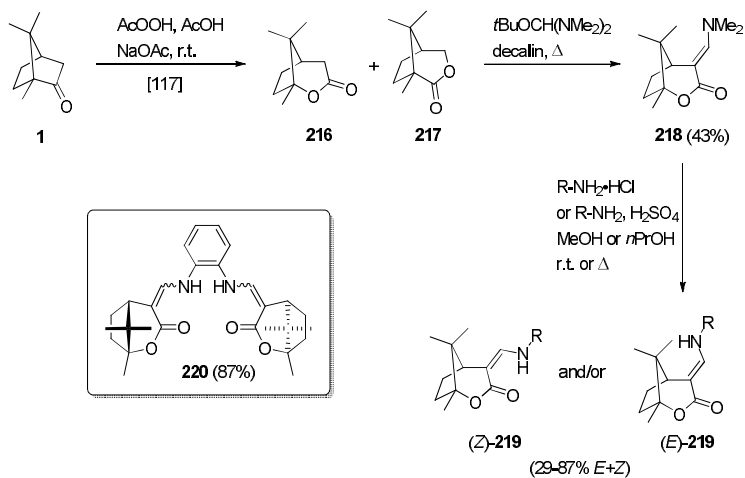
Scheme 51

Treatment of this mixture with Bredereck's reagent furnished, after chromatographic separation, enaminone **218**. Compound **218** served as a starting point for the preparation of a large number of its derivatives. Thus, acid catalyzed treatment of enaminone **218** with a variety of amines (primary (hetero)aromatic and aliphatic amines including optically active α-amino acid esters) yielded the corresponding dimethylamino substitution products **219**, usually as a separable mixture of the (*E*)- and the (*Z*)-isomers. The configurations around the exocyclic C=C double bond depend upon the type of amine used. Benzene-1,2-diamine substitution product **220** was used for the preparation of palladium(II), copper(II), and nickel(II) coordination compounds (Scheme 51).[118]

Acid catalyzed reaction of enamino lactone **218** with potassium cyanide and 2-methylindole yielded the corresponding dimethylamino substitution products **221** and **222**, respectively. Similarly, dimethylamino substitution products **223** have been formed, exclusively, upon treatment of enaminone **218** with excess Grignard reagents (Scheme 52).[119]
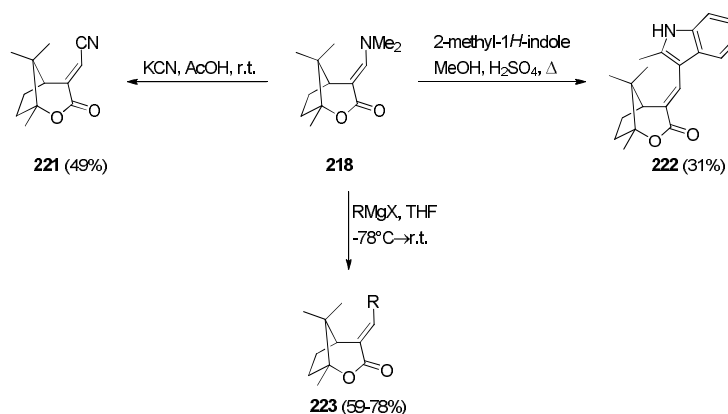
Scheme 52

Cycloadditions of stable 2,4,6-trimethoxybenzonitrile oxide (**117**) to the exocyclic C=C double bond of α-alkylidene-(+)-camphor derivatives **223** furnished a mixture of diastereomeric spiro-lactones **224** and **224'** in 8-49% yield. The same cycloaddition of **117** to cyanomethylidene compound **221** furnished stereoselectively spiro-product **225** and 1,2,4-oxadiazole **226** in a combined yield of 46% (Scheme 53).[74]

Acid catalyzed reaction of enaminone **218**[118] with hydrazinoazines **169** yielded the corresponding substitution products as mixtures of the (*E*)- and the (*Z*)-enehydrazines **227**, which, in solution, are in equilibrium with the *exo*- and the *endo*-hydrazones **228**. Oxidation of the **227/228** mixture with lead tetraacetate furnished diazenes **229** and [1,2,4]triazolo[4,3-*x*]azines **230**. The selectivity of oxidations is dependent on and correlates with the ratio of isomeric intermediates (*E*)-**227**/(*Z*)-**227**:*exo*-**228**/*endo*-**228**. Enehydrazines (*E*)-**227** and (*Z*)-**227** are oxidized into diazenes (*E*)-**229** and (*Z*)-**229**, respectively, while hydrazones *exo*-**228** and *endo*-**228** are oxidized into [1,2,4]triazolo[4,3-*x*]azines *exo*-**230** and *endo*-**230**, respectively (Scheme 54).[120]

Scheme 53

(63-91% for **227**+**228**)

(10-84% for (E/Z)-**229**; 4-52% for *endo*/*exo*-**230**)
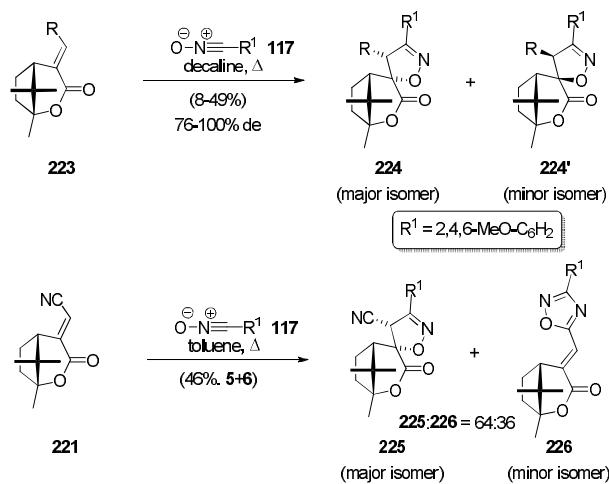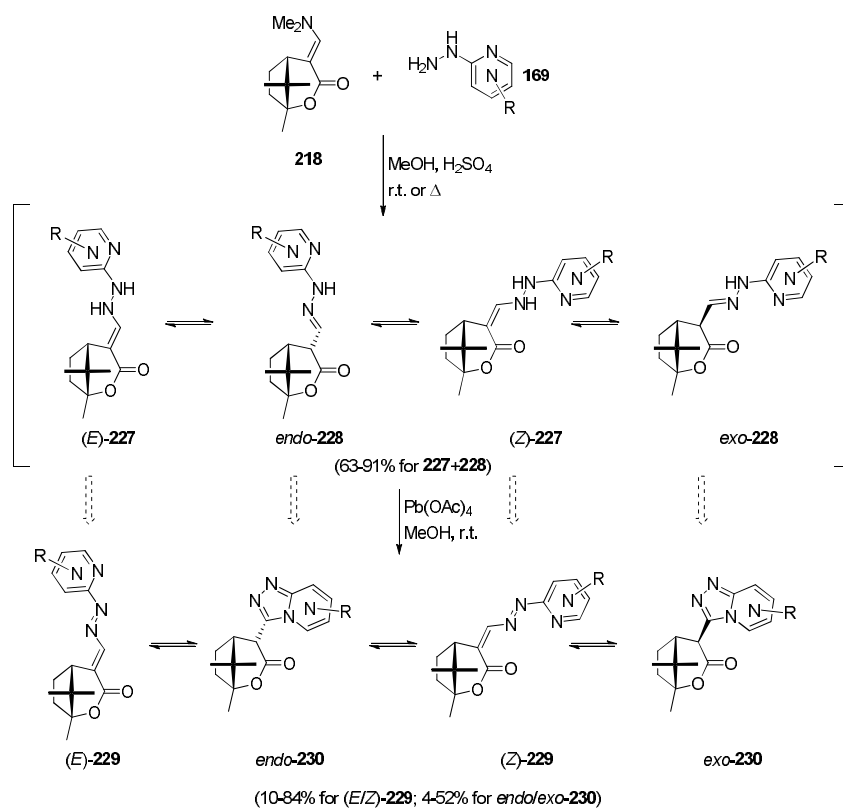
Scheme 54

Treatment of *endo*-[1,2,4]triazolo[4,3-*b*]pyridazines **230**[120] with borane dimethyl sulfide afforded borane complexes **231**, with borane coordinated at the *1* position of the [1,2,4]triazolo[4,3-*b*]pyridazines system (Scheme 55).[94]
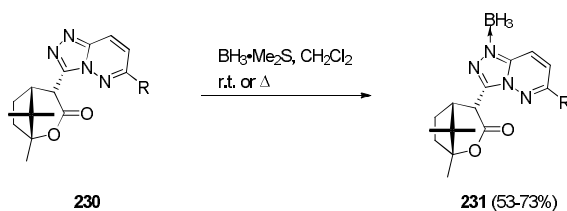
Scheme 55

Nitrosation of enaminone **218**[118] with NaNO$_2$-HCl yielded oxime **232**. Catalytic hydrogenation of **232** in EtOH furnished amine **233** in full conversion and 50% d.e., followed by trapping of **233** with pyrazolone-derived bis-enaminone **234**[121] into pyrazolo[4,3-*c*]pyridine **235**. Catalytic hydrogenation of **232** in a mixture of AcOH:Ac$_2$O=1:1 gave diethylamine **236** as a single stereoisomer. Reactions of **232** with Grignard reagents furnished separable mixtures of dialkylamines **237** and *α*-keto-oximes **238**. Treatment of **218** with XeF$_2$ yielded, after chromatographic purification, fluoroaldehyde **239** in 20% yields as a single diastereomer (Scheme 56).[122,123]
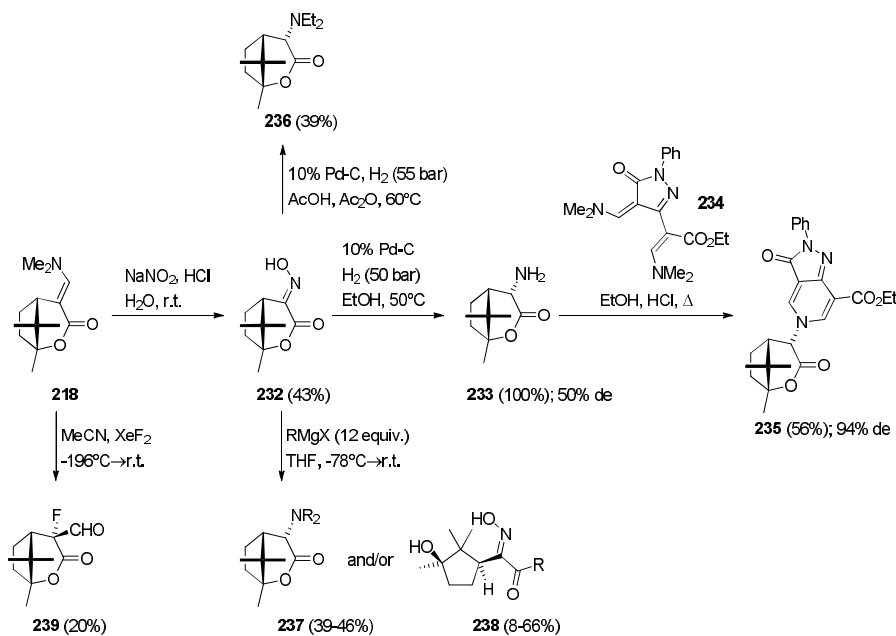
Scheme 56

Starting from 9-hydroxycamphor (**240**),[124] the ring expansion products **245a,b**-**247a,b** were prepared in 4-7 steps. Oxidation of **240** followed by de-carbonylation of aldehyde **241** furnished a mixture of α- and β-santenones **242a,b**. Treatment of **242a,b** with SeO_2 gave a mixture of α-diketones **243a,b**. The ensuing hydrogen peroxide oxidation of **243a,b** yielded easily separable acid **244** and anhydride **245a**. Acid **244** was converted to anhydride **245b**. **245a** and **245b** were separately converted to imides **246a** and **246b** and dithioimides **247a** and **247b**, respectively (Scheme 57). Structure and chiroptical spectra of the bicyclic products have been studied.[125]
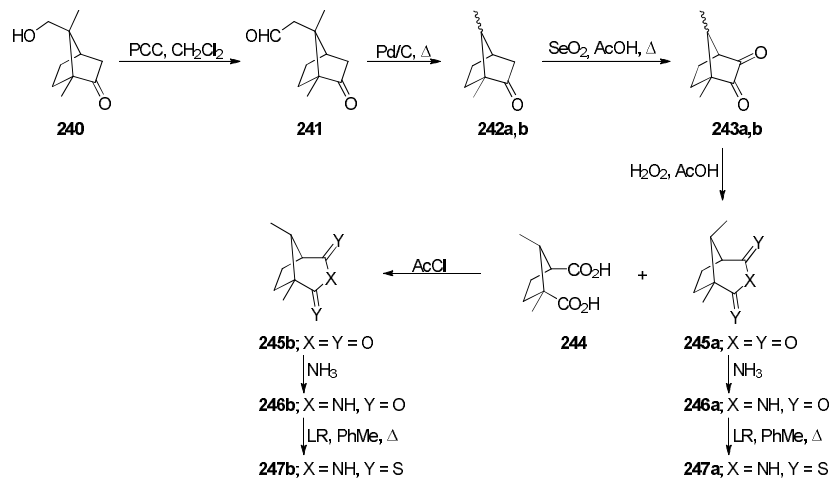
Scheme 57

6. Tethered camphor-derived heterocycles

Mannich reaction of isatin **91** with camphor **1** in the presence of HCl yielded isatin derivative **248**, which exhibits significant anticancer activity against NCI's human cancer cell lines with GI_{50} values between 1.53 and 26.9 μM (Scheme 58).[126]
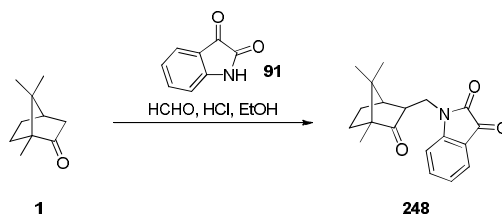
Scheme 58

New camphor-derived sulfonamides **251** and **252** were prepared *via* condensation of (1*S*)- and (1*R*)-(–)-10-camphorsulfonyl chloride (**21**) and (*ent*-**21**), respectively, with aromatic sulfonamides containing amino group **249** and heterocyclic sulfonamide possessing imino moiety **250** (Scheme 59). The new sulfonamides

251 and **252** selectively inhibited the mitochondrial isozymes hCA VA and VB over the cytosolic, off-target ones hCA I and II, with inhibition constants in the low nanomolar range (5.9-68.6 nM).[127]
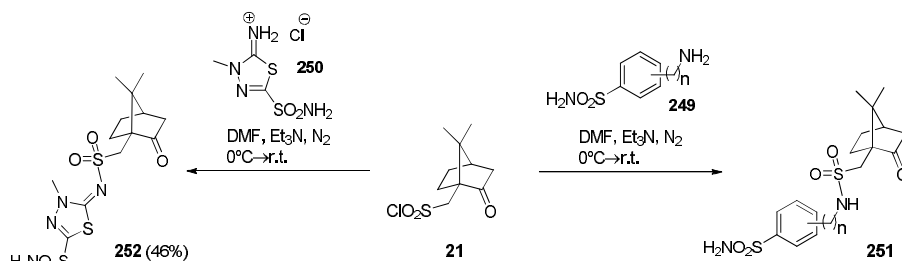
Scheme 59

Reaction of binaphthyl-derived amine **253**[128] with camphor **1** yielded imine **254**, which upon NaBH$_4$-NiCl$_2$ reduction furnished diamine **255** (Scheme 60). *N*,*N*-ligand **255** was evaluated in the asymmetric allylic alkylation of *rac*-1-acetoxy-1,3-diphenylpropene with dimethyl malonate. The corresponding product was formed in quantitative yields and enantioselectivity exceeding 99% ee.[129]
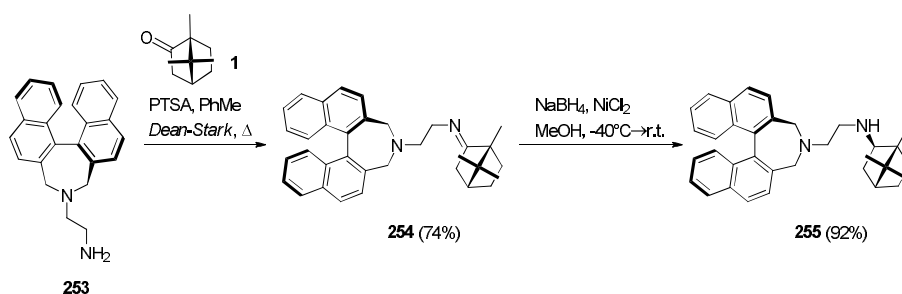
Scheme 60

Iminopyridine ligands **258** were prepared by BF$_3$·Et$_2$O catalyzed condensation between camphor or its *C*10-modified ketones **1**, **2**, **3**, **256** and 2-picolylamine (**257**). Reduction of camphor-derived imino-pyridine **258a** with NaBH$_4$-NiCl$_2$ gave isobornylamine **259**, exclusively (Scheme 61).[130,131] Compounds **258** have been applied as ligands in copper(II) catalyzed enantioselective Henry reaction between nitromethane and aldehydes, giving the corresponding products in up to 84% ee.[130] Application of amino-pyridine ligand **259** in the same reaction turned out to be superior, giving the corresponding products in high yields, moderate to good diastereoselectivities and excellent enantioselectivities (up to 98% ee).[131,132]

A large group of tethered camphor-derived heterocycles represent compounds where chiral pyrrolidine and camphor unit are connected through a suitable linker. The pyrrolidine unit is connected to the *C*1 or the *C*10 atom of the camphor framework via amide, sulfonamide, sulfonate, sulfide, sulfone and amine linker. In addition, the two chiral units are occasionally connected through an additional spacer like 1,2-diaminobenzene (Figure 2).
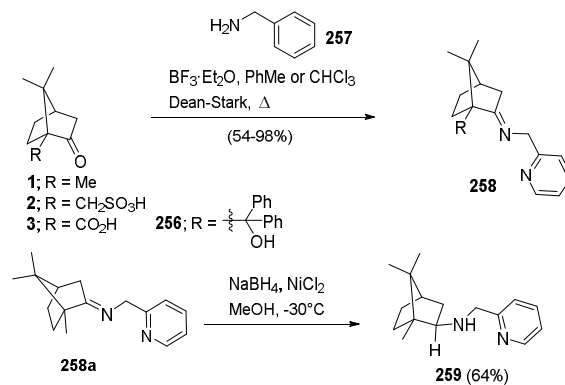
Scheme 61
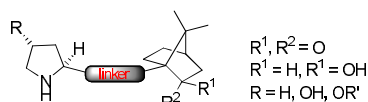
Figure 2

In Figure 3 all the proline- and camphor-derived building blocks, used for the assembly of tethered camphor-derived heterocycles, are presented.

Proline derived building blocks

R = H, OH, OBn, OTBDPS   [134, 135]   [136]   [137]

R = H, OH, OTBDPS

Camphor derived building blocks

[102]   [3]   [2]   [113, 114]
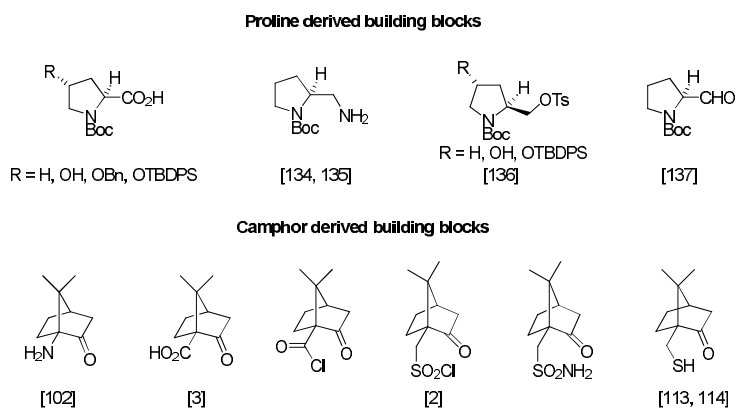
Figure 3

Syntheses of the respective camphor-pyrrolidine heterocycles are omitted, only the final compounds, with the respective references, are depicted (Figures 4,5). The first reference refers to the original literature where the synthesis of the heterocycle was described, all other references refer to the applications of the respective heterocycle as organocatalyst in catalytic asymmetric transformations. Heterocycles in Figures 4,5 have been used in the C-C and C-N bond forming reactions *i.e.* Michael additions and aldol reactions. For a detailed review on tethered camphor-pyrrolidine-derived heterocycles and their application in asymmetric organocatalysis see reference.[133]

Camphor-pyrrolidine derived organocatalysts

R = H, OH, OTBDPS
[138]

[139, 140]

[141]

[142]

R = Bn, (naphthalen-1-yl)methyl
[142, 143]

[144, 145]

[146, 140]

[146]
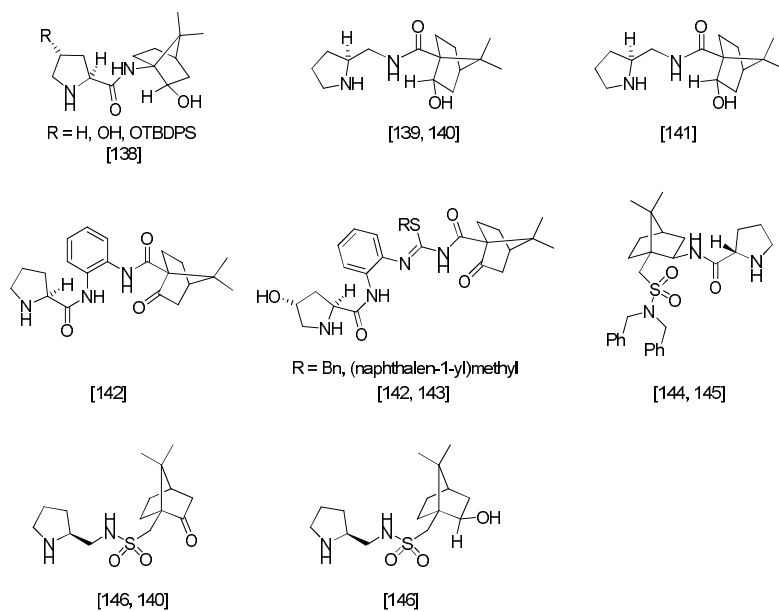
Figure 4

Camphor-pyrrolidine derived organocatalysts

[146]

[142]

[147]

[141, 148]

R = H, OH, OTBDPS
[141, 148, 149, 150]

[141, 148]

R = H, OH, OTBDPS
[141, 148, 151]

[152]

[153]
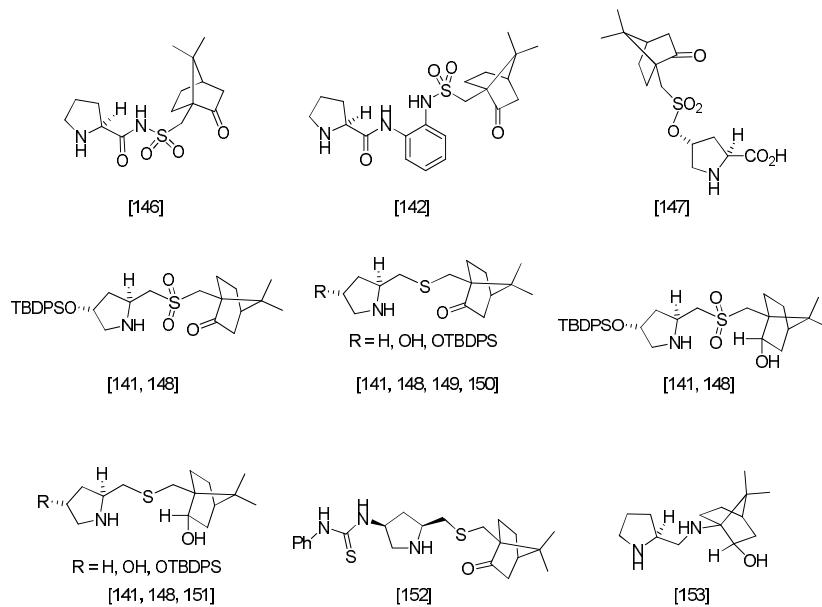
Figure 5

Primary-secondary diamines have been prepared from tryptophan-derivatives **260** and *exo*-(–)-bornylamine **145**[154] in three steps. First, Cbz protected *α*-amino acids **260** were coupled with *exo*-(–)-bornylamine **145** using DCC to give amides **261**. The following hydrogenolitic Cbz-deprotection yielded amino-amides **262**, which were, in the final step, reduced to the primary-secondary diamines **263a,b** using LiAlH$_4$ (Scheme 62).[155] Compounds **263a,b** have been used as organocatalysts in the addition of ethyl nitroacetate to various enones giving the corresponding products in high yields and enantioselectivities up to 95% ee.[156]
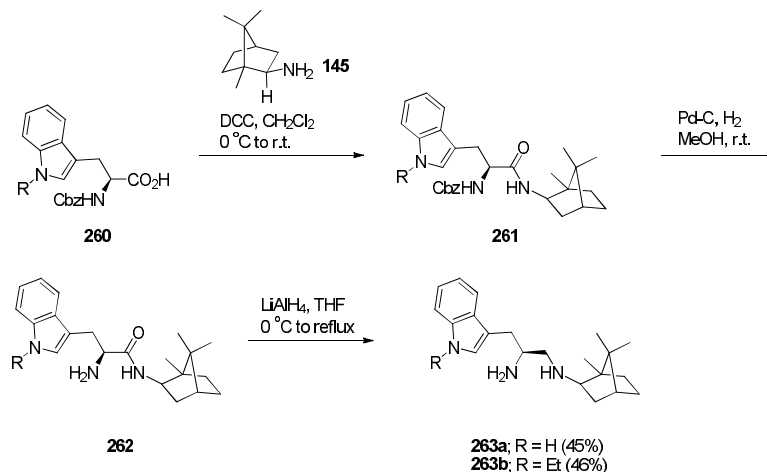
Scheme 62

Catalytic hydrogenation of Cbz-protected oxazoline-derivative **264**, prepared in three steps from serine methyl ester hydrochloride, followed by coupling with (1*S*)-(+)-10-camphorsulfonyl chloride (**21**) in the presence of base gave camphor-derived oxazoline **265** (Scheme 63). Compound **265** has been applied as organocatalyst in the enantioselective hetero Diels-Alder reaction of aldehydes to electron rich dienes yielding pyranones in enantioselectivities up to 92% ee.[157]
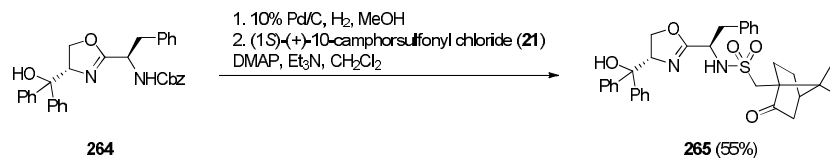
Scheme 63

Reaction of camphor-10-sulfonyl chloride *ent*-**21** with *endo*-amine **266** in the presence of a base gave sulfonamide **267**, which upon oxidation with monoperoxyphthalic acid yielded tricyclic compound **268** (Scheme 64).[158,159]

Scheme 64
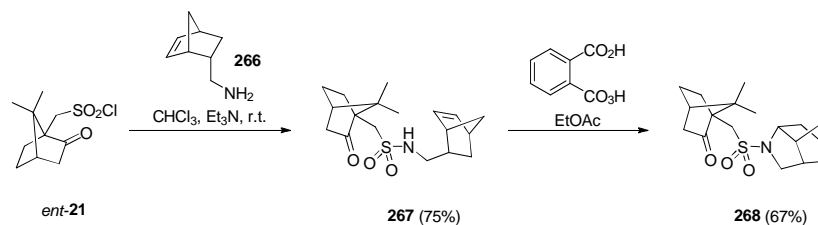
Starting from camphor-derived enaminone **168**,[93] the corresponding substitution products **269**[45] and **270** were prepared upon acid catalyzed treatment with potassium cyanide and 2-methyl-1*H*-indole, respectively. Cycloaddition of nitrile oxide **117** to cyanomethylidene-derivative **269** gave 1,2,4-oxadiazole **271**, exclusively, while catalytic hydrogenation of compound **270** furnished the corresponding *exo*-indole-derivative **272** as the sole stereoisomer (Scheme 65).[74]
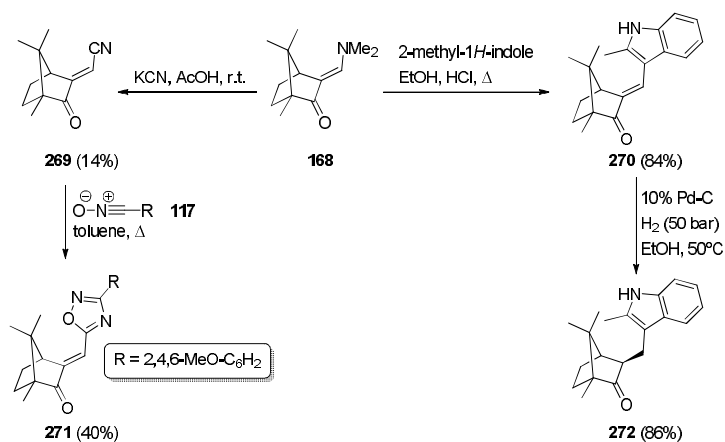
Scheme 65

Acid catalyzed reactions of enamino-ketone **168**[93] with pyrazolidin-3-ones **273** gave the corresponding dimethylamino-substitution products **179** in 40-80% yields. Products **179** were obtained as the (*Z*)-isomers, exclusively (Scheme 66).[95]

Scheme 66
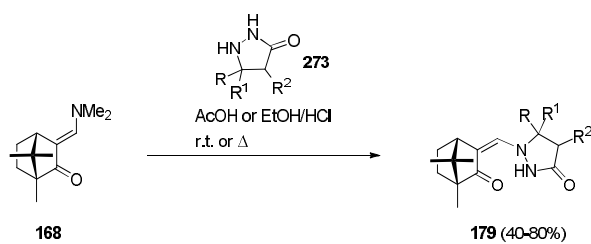
7. Conclusions and outlooks

Camphor and its simple *C*10, *C*2, and *C*3 functionalized, commercially available derivatives provide the base for the construction of a large number of more complex derivatives. Motifs for their preparation are diverse, ranging from reactivity/methodology driven research to the ever more applicable aspects of these compounds. In this context, camphor-derived heterocycles have found application as ligands in metal catalyzed asymmetric transformations and coordination chemistry, as organocatalysts, chiral synthons, and biologically active compounds. There is no doubt, the future will bring further development of heterocycles derived from camphor and their applications in diverse fields of catalysis, material science etc., the progress lies in the hands of researchers, their inspiration and imagination.

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