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Synthesis of New Ligands Based on Camphoric Acid

Doctoral Thesis

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Synthesis of New Ligands Based on Camphoric Acid

(Synthese neuer Liganden basierend auf Camphersäure)

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Dedicated to

My Dear Mom and Loving Husband

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Abstract

This PhD thesis is divided into three chapters: *Introduction, Results and Discussion* and *Experimental Part*.

First part of chapter one is a review of compounds incorporating diamine moieties. Nowadays, it is one of the most investigated area of studies in several fields. Their uses in medicine and in chemistry will be discussed. However, attention will be refunded mainly on the use of diamines in organic synthesis as chiral auxiliaries, as chiral ligands in asymmetric synthesis or as organocatalysts. Additionally, the selected methods for their preparation will be given.

In the second part of chapter one, the research area of the phosphorus-heteroatom heterocyclic compounds will be the main focus. This part of chapter one will present the cyclisation process of chiral diamines around the phosphorus atom. The cyclisation step affords heterocycles containing a trivalent or pentavalent stereogenic phosphorus atom. Finally, the application of these compounds in catalyzed transition metal transformations will be discussed.

The investigation, presented in terms of the current thesis in chapter two, covers the preparation of various diamine ligands based on camphoric acid. The chiral diamine ligands with nitrogen atoms containing the same or different substituents will be described and their application in to the nitroaldol reaction presented which provides an easy access to chiral β-nitroalcohols in high enantioselectivity up to 84% and excellent yield in up to 93%. The further transformations of the secondary chiral diamines into heterocycles containing phosphorus atom in quantitative yields in up to 97% without any purification and their application as ligands or as versatile chiral shift reagents will be also discussed in the second chapter.

Lastly, the third chapter is the collection of experimental procedures and data of the presented work.

Kurzzusammenfassung

Die vorgelegte Doktorarbeit ist in drei Hauptkapitel gegliedert: *Einleitung*, *Ergebnisse und Diskussion* und *Experimenteller Teil*.

Der erste Teil der Einleitung gibt einen Überblick über Verbindungen mit einer Diamin-Komponente, die in den unterschiedlichsten Bereichen intensiv untersucht werden. Dabei wird deren Verwendung in der Medizin und Chemie diskutiert. Hauptsächlich werden sie jedoch als chirale Auxiliare in der organischen Synthese, als chirale Liganden in der asymmetrischen Synthese und als Organokatalysatoren eingesetzt. Zusätzlich werden ausgewählte Synthesemöglichkeiten der Diamin-Verbindungen aufgeführt.

In dem zweiten Teil der Einleitung liegt der Fokus auf dem Forschungsfeld der Phosphor-basierten heterozyklischen Verbindungen. Dieser Teil beschreibt die Zyklisierung von chiralen Diamin-Verbindungen zu Phosphor-basierten Heterozyklen mit einem drei- oder fünfbindigen stereogenen Phosphoratom. Abschließend wird die Anwendung dieser Verbindungen in übergangsmetall-katalytischen Reaktionen diskutiert.

Die Synthese und darauffolgende Untersuchung unterschiedlicher Diamin-Verbindungen basierend auf Camphersäure werden im zweiten Kapitel dargestellt. Dabei werden die chiralen Diamin-Liganden, deren Stickstoffatome entweder gleiche oder unterschiedliche Substituenten tragen, beschrieben und deren Anwendung in der Nitroaldol-Reaktion vorgestellt. Über diese Reaktion können, chirale-*ß*-Nitroalkohole mit hoher Enantioselektivität von bis zu 84% und hervorragenden Ausbeuten von bis zu 93% unter Verwendung der neuen Liganden erhalten werden. Anschließend wird die Umsetzung der hierbei dargestellten chiralen sekundären Diamin-Verbindungen zu Phosphor-basierten Heterozyklen beschrieben, die mit einer Ausbeute von bis zu 97% ohne weitere Aufreinigung erhalten werden Zudem werden sie als Liganden und als vielseitig einsetzbare chirale Shift-Reagenzien diskutiert und untersucht.

Abschließend sind im letzten Kapitel die Synthesen und experimentellen Daten der im Rahmen dieser Arbeit dargestellten Verbindungen aufgeführt.

Abbreviations

δ	Chemical shift
°C	Temperature in degree centigrade
Ac	Acetyl
AD-H	Amylose *tris*(3,5-dimethylphenylcarbamate) high performance
AS-H	Amylose *tris*[(*S*)-*α*-methylbenzylcarbamate] high performance
aq.	Aqueous
Ar	Aryl
BINAP	2,2'-*Bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
bp	Boiling point
br	Broad
br s	Broad singlet
BSA	*Bis*(trimethylsilyl)acetamide
Bu	Butyl
c	Concentration
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
cm	Centimeter
d	doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane

DCM	Dichloromethane
dd	doublet doublet
ddd	doublet doublet doublet
DIAPHOX	Diaminophosphine oxide
dr	diastereomeric ratio
EDTA	Ethylenediaminetetraacetic acid
ee	enantiomeric excess
eq	Equivalent
ESI	Electron spray ionisation
et al.	*et alii* (‘and others’)
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FCC	Flash column chromatography
g	Gram
h	Hour
HASPO	Heteroatom-substituted secondary phosphine oxide
HPLC	High pressure liquid chromatograpy
HRMS	High resolution mass spectroscopy
Hz	Hertz
i	*iso*
***i*PrOH**	Isopropanol

IR	Infrared
J	Coupling constant
m	Multiplet
M	Molar (mol/L)
m/z	Mass to charge ratio
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
MHz	Megahertz
min	Minute(s)
mmol	Millimole
mol	Mole
mp.	Melting point
MS	Mass spectroscopy
Naphth	Naphthyl
NMR	Nuclear magnetic reasonance
o	*ortho*
p	*para*
Ph	Phenyl
ppm	Parts per million
q	Quartet
R	Alkyl
rt	Room temperature (25°C)

SPO	Secondary phosphine oxide
t	triplet
TEA	Triethylamine
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
Ts	*para*-Toluene sulfonate

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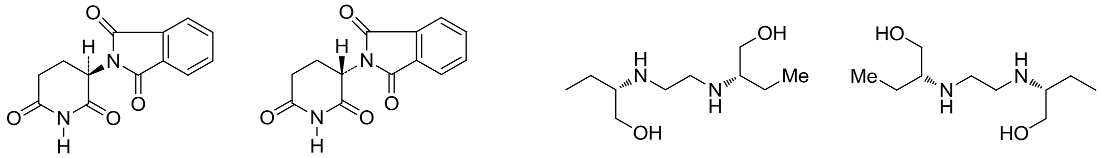
1. Introduction

1. Introduction

The phenomenon of chirality, common in nature, is an inseparable feature of various levels of matter. Chirality plays a huge role in many areas such as biology and material science.[1] Chiral recognition and differentiation of the enatiomers are indeed a fundamental goal in chemistry. This point affects the climax of many branches of chemistry and industry, in particular pharmacy.[2] Chiral separation of isomers in medicine and pharmacy plays a key role. One of the enantiomers may not have therapeutic properties, while the second enantiomer may be inactive, and in the worst case, one may be toxic.[3] One of the example of the importance of separation of two isomers and the relation between molecular chirality and pharmacological activity is the tragedies of the thalidomide babies in the 1960s, when the drug was used for a treatment of nausea in pregnant women.[4] In the case of thalidomide, (*S*)-enantiomer **1** demonstrate teratogenic and induces fetal malformations, while (*R*)-enantiomer **2** posse's desirable sedative properties.[5] Unfortunately, later tests showed that (*R*)-(+)-thalidomide **2** can racemize in the liver. Thus, another example of the significance of separation of two isomers is ethambutol. The (*S*,*S*)-enantiomer **3** is a frontline antituberculous drug, while (*R*,*R*)-enantiomer **4** can cause blindness[6] (Figure 1).



1 (*S*)-(-)-Thalidomide **2** (*R*)-(+)-Thalidomide **3** (*S*,*S*)-Ethambutol **4** (*R*,*R*)-Ethambutol

Figure 1. The Absolute Configuration of Thalidomide and Ethambutol.

Despite many accidences associated with racemates until 1992, the Food and Drug Administration in the U.S. introduced clear rules called "racemic switches" in order to syntheses single enantiomers.[1] Since that time, progress in the separation of enantiomers is impressive. Nowadays it has been an essential challenge for chemists in academia and industry. Racemates have large importance not only in medicine but also in such areas like cosmetics and food industry. One essential example is limonene of which the (*R*)-enantiomer **5** smells like orange and the (*S*)-enantiomer **6** smells like lemon.[7,8] The same situation is with the (*S*)-enantiomer **7** of the amino acid asparagines which is responsible for a sweet taste while the (*R*)-enantiomer **8** is responsible for a bitter taste (Figure 2).[9]

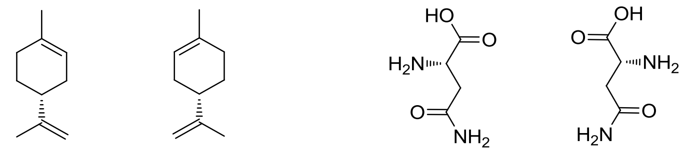

5 (*R*)-Limonene **6** (*S*)-Limonene **7** (*S*)-Asparagine **8** (*R*)-Asparagine

Figure 2. Examples of Enantiomers.

1.1. Chiral Diamines

Chiral diamines contain in their structure two amino groups, which can be attached to different atoms in a chain of carbon atoms. Since many years chiral diamine derivatives are investigated by many research groups. Some examples of them which are the most widely used and reported are presented in Figure 3.[10]

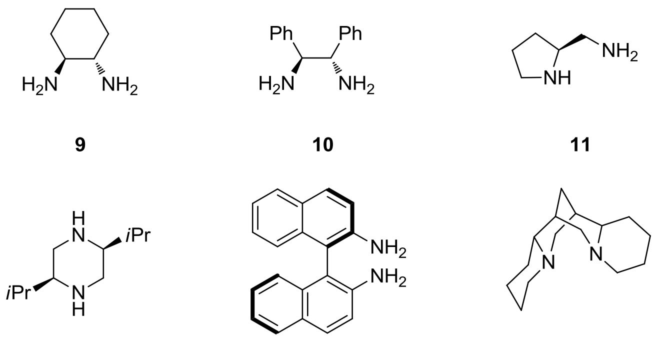

9 **10** **11** **12** **13** **14**

Figure 3. Examples of Chiral Diamines.

Since enantiopure diamines are constituents of many natural products[11] they play an important role in various areas of science such as pharmaceutical or medicinal chemistry.[12] Also chiral diamines found huge interest in stereoselective organic synthesis[13] where they can be successful used as chiral catalysts, chiral reagents and chiral ligands. Taking into account the wide use of these compounds it is not a surprise that development of novel synthetic methodologies to obtain enantiopure diamines has been a subject of intense research.[14]

1.1.1. Diamines in Natural Products[13]

Nowadays many natural products are known where we can find diamino moieties in their structures. One of the best examples are peptides which contain *n*, *n*+1 diamino carboxylic acid **15**,[15] like diaminopropanoic acid which is part of the composition of antibiotics such as edeines and tuberactomycin derivatives. 2,3-Diamino carboxylic acid is a part of well known antibiotics, like penicillin **16**[16] discovered by Alexander Fleming in 1929[17] and cephalosporin **17**[18] found by Giuseppe Brotzu in 1948. The vitamin H also called biotin or coenzyme R **18**[19] contains a 1,2-diamino unit (Figure 4).[13]

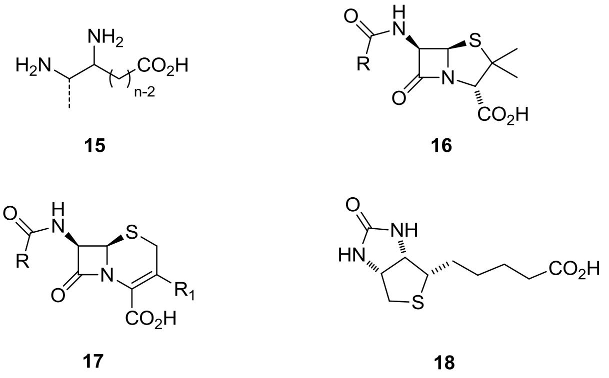
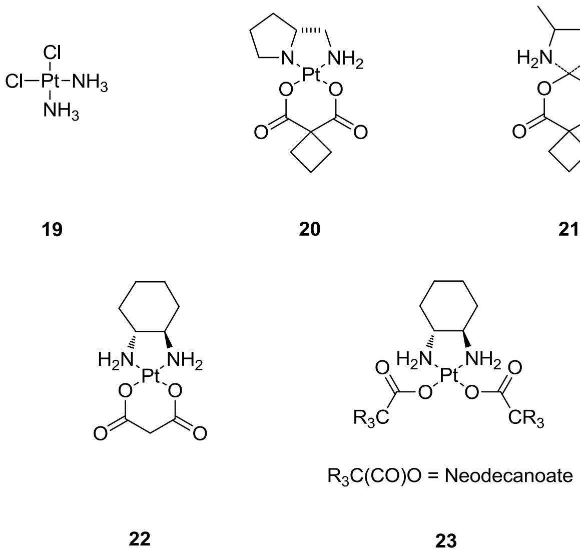


Figure 4. Natural Products Containing Diamino Moieties.

1.1.2. Diamines in Medicinal Chemistry

Diamines are an essential part of biologically active compounds. Chiral diamines such as 1,4-diamines have found application as intermediates in the synthesis of potent HIV protease inhibitors. However, 1,2-diamines play a key role in applications in medicinal chemistry. These compounds have been reported for instance against, antiarrhythmics, antidepressant agents antipsychotics, analgesics, antianxiety agents, antiparasitic agents and anticancer drugs.[13] Cisplatin **19** is one of the most well-known cancer drugs. In the mid 1960s Rosenberg discovered antitumoral properties of cisplatin, which started a new beginning of the synthesis of novel diamine-platinum complexes like DWA 2114R **20**, NK 121 **21**, oxaliplatin **22** and NDDP **23** (Figure 5). 1,2-Diaminoplatinum complexes are used in antitumor chemotherapy because they have high antitumoral activity and less toxicity.[13]



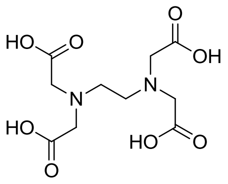
19 **20** **21**

22 **23**

$R_3C(CO)O$ = Neodecanoate

Figure 5. Diamine – Platinum Complexes.

EDTA **24** is another example of a compound which posses in its structure a 1,2-diamine moiety (Figure 6).[20] From a medical point view, EDTA has the ability to chelate metal ions to generate stable complexes which can be used in the field of nuclear medicine.[21]



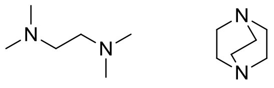
24

Figure 6. Structure of EDTA.

1.1.3. Diamines in Organic Chemistry

Organic chemistry is an area where chiral diamines are widely used as auxiliaries or ligands in stereoselective synthesis. Diamines also have found applications as novel reagents for enantioselective synthesis.

One of the types of important diamines which are often used in organic transformations is TMEDA **25**. It plays a key role as a ligand which is able to generate stable complexes with many metal halides.[22] Next interesting example is DABCO **26**. This compound can be a Lewis base catalyst for polyurethane for the Baylis-Hillman reaction, or it can be used as a Brønsted base (Figure 7).[23]

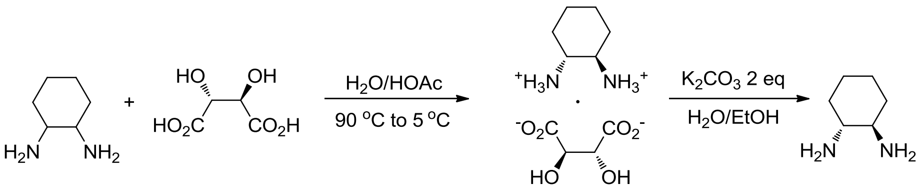


25 **26**

Figure 7. TMEDA and DABCO as Examples of Diamines in Organic Chemistry.

1.1.3.1. Resolution of Racemates and Determination of Enantiomeric Excess[13]

Resolution is one of the oldest methods used for the separation of racemic compounds into their enantiomerically pure forms.[24,25] The most common example of a resolution of *trans*-1,2-cyclohexadiamine **9** by crystallization was described by Larrow and Jacobsen which is illustrated in Scheme 1.[26]



rac- **27** **28** **29** Yield = 40% - 42% **9** > 98%

Scheme 1. Resolution of *rac*-27.

The (*R,R*)-1,2-cyclohexadiamine **9** and (*R,R*)-1,2-diphenylethylenediamine **10** were used to resolve binaphthol atropisomers **30** (Figure 8).[13]

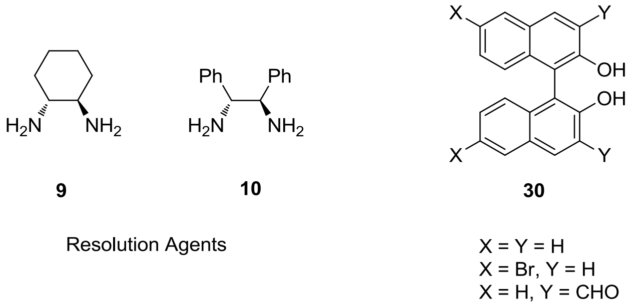
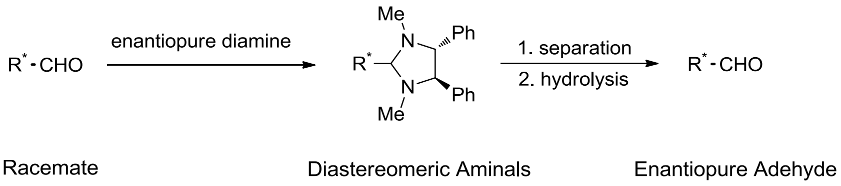


Figure 8. 1,2-Diamines Used to Resolve Atropisomeric Binaphthols.[13]

Diamines have found also application as resolving agents for chiral aldehydes. Mangeney, Alexacis and *co*-workers proved that the enantiopure aldehydes can be determined by NMR or isolated by chromatographic methods after converting them into diastereomeric imidazolidines (aminals) by condensation with *N,N*'-dimethyl-1,2-diphenylethylene diamine (DMPEDA)[27] which was the most efficient diamine in this case (Scheme 2).[28]

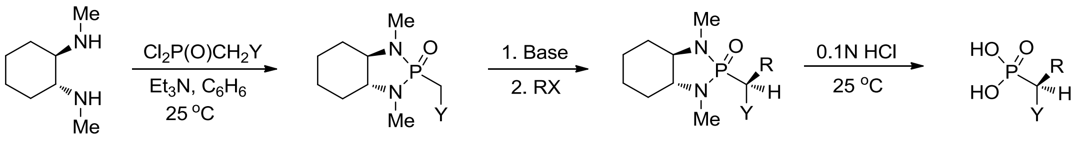


Scheme 2. 1,2-Diamines as Resolving Agents for Aldehydes.

1.1.3.2. Diamines as Chiral Auxiliaries

Chiral auxiliaries are enantiomerically pure compounds that are connected to a substrate in order to control the stereochemical course of a reaction.[29] Especially for asymmetric transformations the use of chiral auxiliaries is a flexible and well-established method.[30] Several examples of chiral auxiliaries based on diamines have found their way in highly stereoselective synthesis.[13]

Chiral bicyclic phosphonamides **31** were reported from diaminocyclohexane as chiral auxiliaries by Hanessian's group,[31,32] and also inspired by the work of Blazis *et al.*[33] The process is shown in Scheme 3. The anion derived from **31**, which was prepared from (*R*,*R*)-1,2-*bis*-*N*-methylamino-cyclohexane **32** with a base such as *n*-BuLi or LDA, was treated by an alkyl halide and after hydrolysis of the resulting product **33** the corresponding *α*-substituted phosphonic acids **34** were obtained in excellent yields.[32]



(*R*,*R*)-**32**

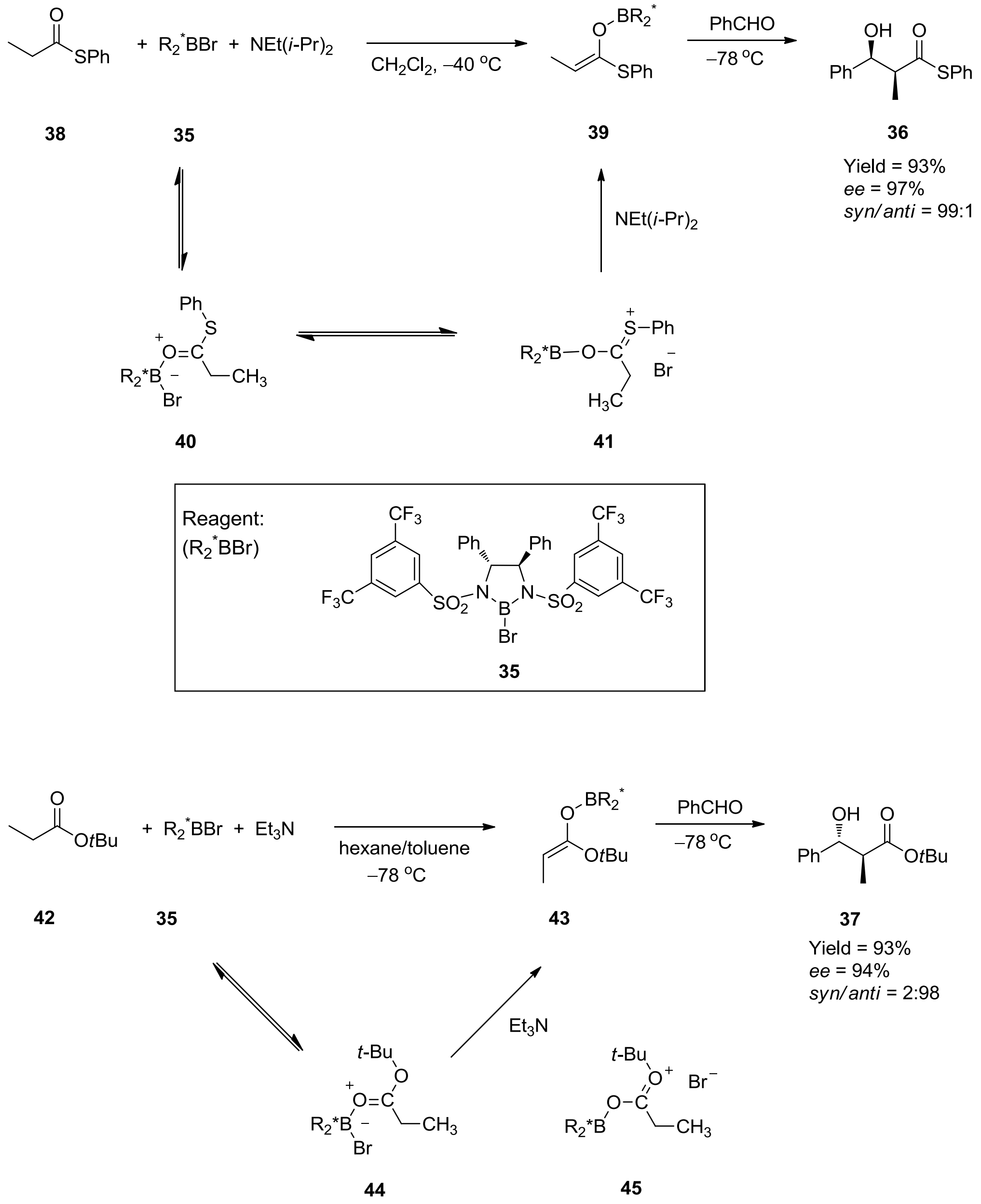
31
Y= Me, Ph, Cl, N_3

33

34
Y= Me, Ph, Cl, NH_2
Yield: 88% - 98%

Scheme 3. Chiral Bicyclic Phosphonamides Prepared from a *C*$_2$ Symmetrical Diamine.

Corey described the boron-containing chiral auxiliaries, derived from 1,2-diphenylethylenediamine[13] **35** which was applied in an enantioselective aldol reactions as presented in Scheme 4 for the synthesis of *syn* aldol product **36** and the *anti* aldol product **37** with excellent diastereoselectivity and enantioselectivity.[34] The investigation shows that the difference in stereochemistry of enolate construction from 1,2-diphenylethylenediamine **35** as a function of ester formation can be due to a fundamental mechanistic dichotomy. The initial complex of **35** with *S*-phenyl thiopropionate **40** may undergo sulfur-promoted dissociation of bromide ion in CH_2Cl_2 to generate ion pair **41** more rapidly than direct deprotonation by the hindered base diisopropylethylamine (DPEA). Deprotonation of **41** in the conformation shown would then favor the "cisoid" enolate **39**. The less polar solvent should slow the dissociation of **40** to ion pair **41** while the sterically smaller TEA (triethylamine) is supposed to accelerate the direct deprotonation of **40** to generate the transoid enolate. In contrast, the bulky *tert*-butyl group prefers an out-of-plane orientation which disfavors ionization to **45** that's why the complex of **35** and *tert*-butyl propionate **42** should lose bromide ion slowly compared to deprotonation by TEA, to generate the transoid enolate.[35]

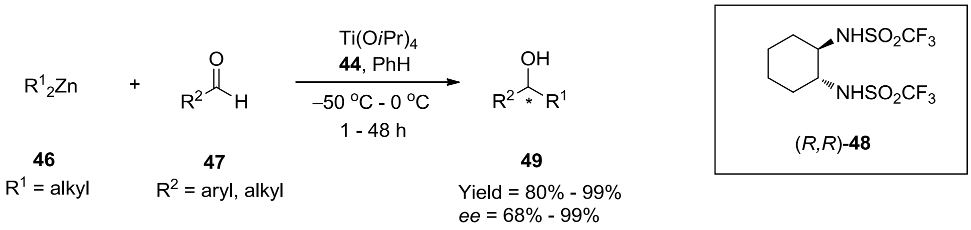


Scheme 4. Enantioselective *Syn* or *Anti* Aldol Reactions of Boron Enolates Derived from a C_2-Symmetric Diazaborolidine.

1.1.3.3. Diamines as Ligands in Asymmetric Synthesis

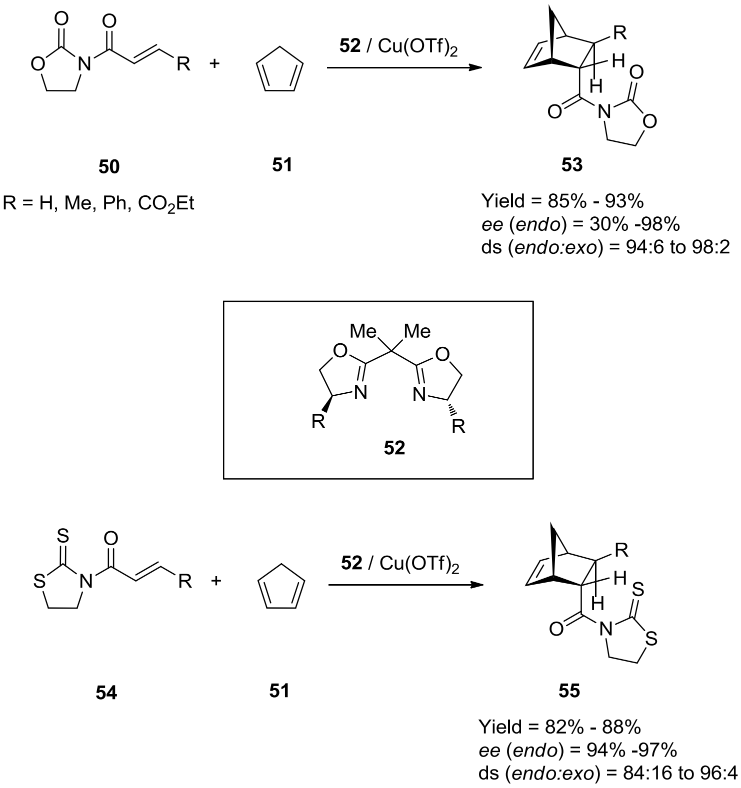
Asymmetric synthesis is one of the most developing areas in organic chemistry. Therefore, it is very important nowadays to design external chiral ligands.[36] One of them are diamines which play a huge role as ligands for organometallic catalysis.

The group of Knochel reported a successful example of the addition of dialkylzinc **46** to aldehydes **47** in the presence of the diamine **48** linked chiral Ti(IV) complex as the catalyst[37] which affords functionalized secondary alcohols **49** with high enantioselectivity (Scheme 5).[38-40]



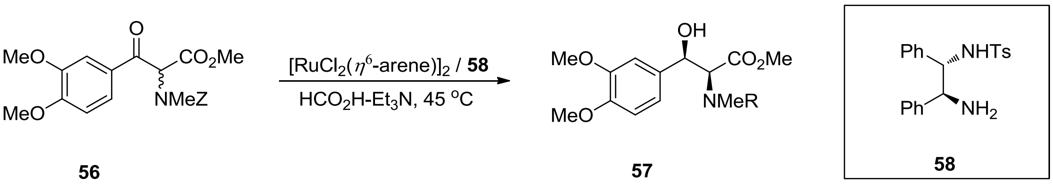
Scheme 5. Enantioselective Addition of Dialkyzinc to Aldehydes in the Presence of 1,2-Diamine.

Evans *et al.* described the influence of C_2-symmetric *bis*(oxazoline)copper complexes from diamine as catalysts for the Diels-Alder reactions. Cycloadducts synthesized from a diene and an oxazolidinone were achieved in excellent yields and enantioselectivities (Scheme 6).[41] In addition, Corey has proved that the same ligands linked with Mg(II)[42] and Fe(III)[43] complexes as chiral Lewis acid catalysts showed the successful application in the Diels-Alder reaction of unsubstituted acrylimides.[41]



Scheme 6. Enantioselective Diels-Alder Reaction.

Chiral diamines found also applications in the catalytic transfer hydrogenation using formic acid as hydrogen source which is a well known, inexpensive reducing agent.[44] Noyori were successful in the asymmetric reduction of racemic *threo*-*β*-hydroxy-*α*-amino acids **56** applying this hydride donor to furnish *threo*-**57** isomer in 94% *ee* using a chiral rhodium catalysts and vicinal diamine **58** as ligand (Scheme 7).[45] More recently, followed by Nyori's work, Miostkowski and *co*-workers proved that introducing a better electron-withdrawing perfluorobutylsulfonate group on the TsDPEN (*N*-tosyl-1,2-diphenylethylenediamine) ligand increases the catalyst activity and stereoselectivity up to > 99% *ee* in transfer hydrogenations *via* dynamic resolution.[46]

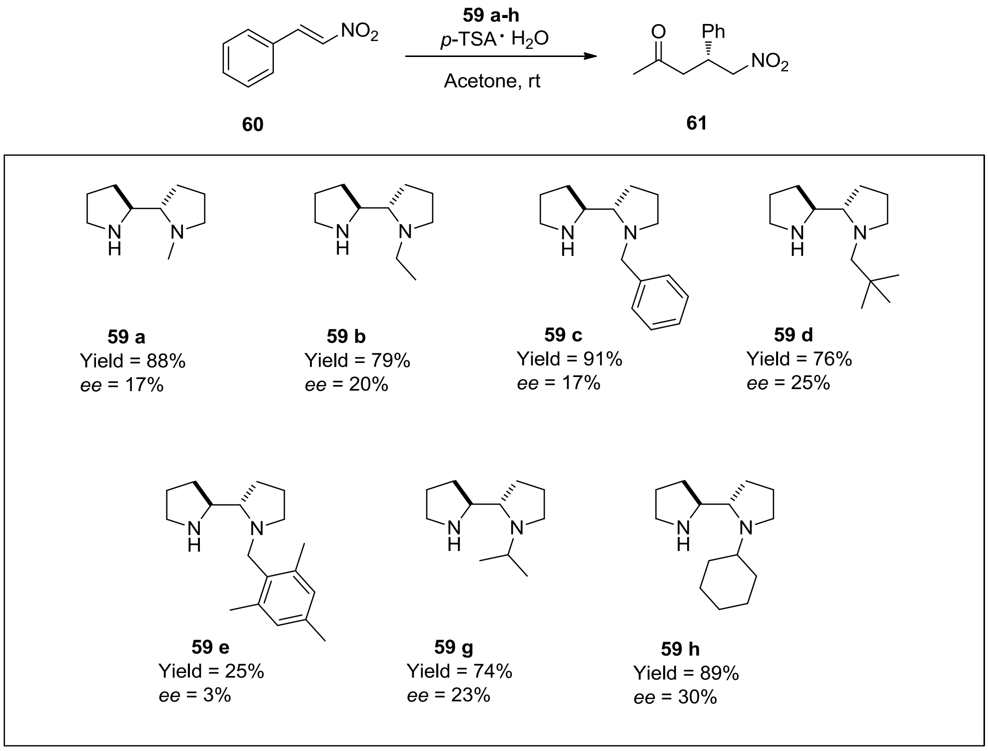


Scheme 7. Asymmetric Transfer Hydrogenation Using Chiral Ru-Diamine Complex as a Catalyst.

1.1.3.4. Diamines as Organocatalysts

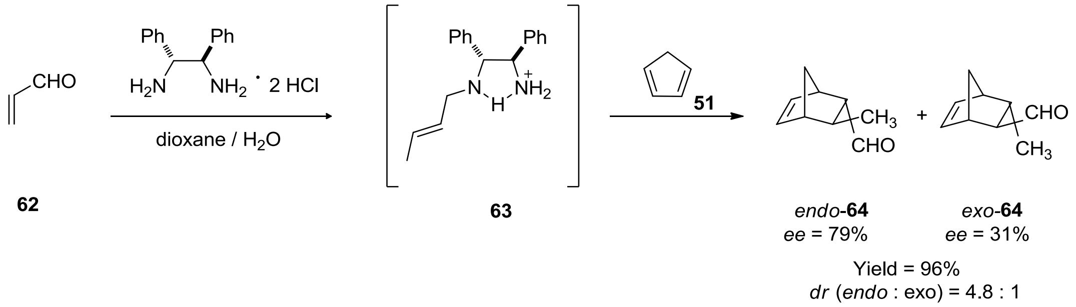
The phrase organocatalyst is a connection between two words: "organic" and "catalyst". In connection with the use of L-proline as organocatalysts for the intramolecular aldol reaction by two independent pharmaceutical companies Hoffman-La Roche[47] and Schering AG[48] in the early 1970s[49], proline started to be a good asymmetric catalyst. There are many reasons why it has become a significant, chiral molecule in asymmetric catalysis. First of all, proline is available in both enantiomeric forms. From the chemistry side, proline is bifunctional, which means in proline's structure is a carboxylic acid and amine portion, which can both act as an acid or base and also can facilitate chemical transformations in concert, similar to enzymatic catalysis.[49] Surprisingly, this idea was not exploited until lately.[50] In 2000 a breakthrough for organocatalytic reactions was achevied. MacMillan proposed the concept of organocatalysis which defines itself as the acceleration of chemical reactions with a substoichiometric amount of an organic molecule which does not include a metal atom in the catalytic active center.[51] The field of asymmetric organocatalysis is a rapidly progressing area and catalysts have been used in many different reactions such as the Michael reaction,[52] aldol condensation,[53] and others.

Nowadays, many groups are focused on proline-derived diamines. Alexakis *et al.* described the 2,2'-bipyrrolidine derivatives **59 a-h** which can be compared to L-proline due to its pyrrolidine backbone[50] as an organocatalysts for the asymmetric addition of ketones to nitroolefins **60** (Scheme 8).[54] Change of the additive from *p*-TSA·H_2O to HCl in MeOH and from acetone to cyclohexane afforded much higher enantioselectivities in up to 81% *ee*.[54]



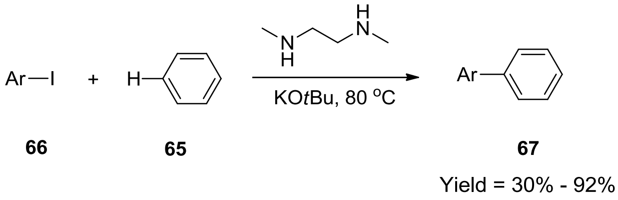
Scheme 8. Asymmetric Michael Addition of Ketones to Nitroolefins.

The group of Deok-Chan Ha reported a successful example of a bisammonium salt of mono-*N*-alkylated chiral 1,2-diamino-1,1-diphenylethane (DPEN) in the Diels-Alder reaction between cyclopentadiene **51** and crotonaldehyde **62** (Scheme 9). It is the first case where a chiral 1,2-diamine formed an imine intermediate **3** which is activated for the cycloaddition by an internal ammonium Brønsted acid in wet solvent. Interesting is that solvents having more than 10% (by volume) of water indicated a decreased *endo/exo* selectivity and *endo*-enantioselectivity.[55]



Scheme 9. Diels-Alder Reaction.

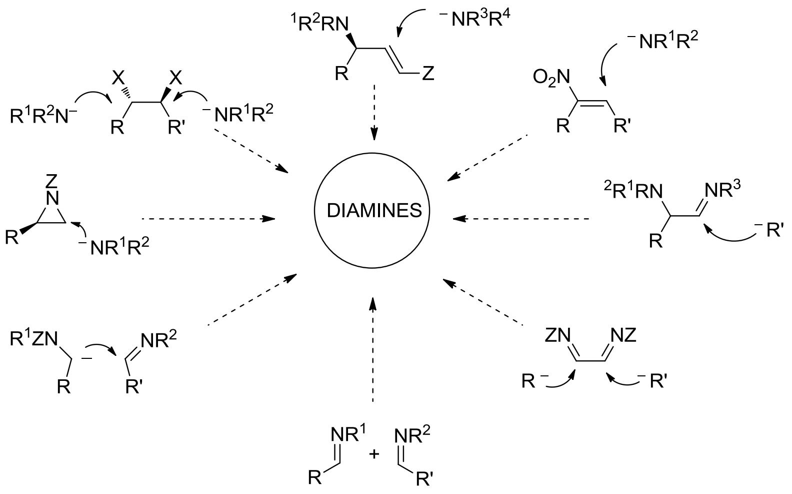
DMEDA was examined by Lei and *co*-workers as catalyst to promote the direct C-H arylation of unactivated benzene **65** with aryl iodides **66** in the presence of potassium *tert*-butoxide (Scheme 10). The novel method is believed to involve an aryl radical anion as an intermediate. This discovery suggests an option toward establishing a new horizon for the direct C-H/cross-coupling reactions.[56]



Scheme 10. DMEDA-Catalyzed C-H Arylation.

1.1.4. Methods of Diamine Syntheses

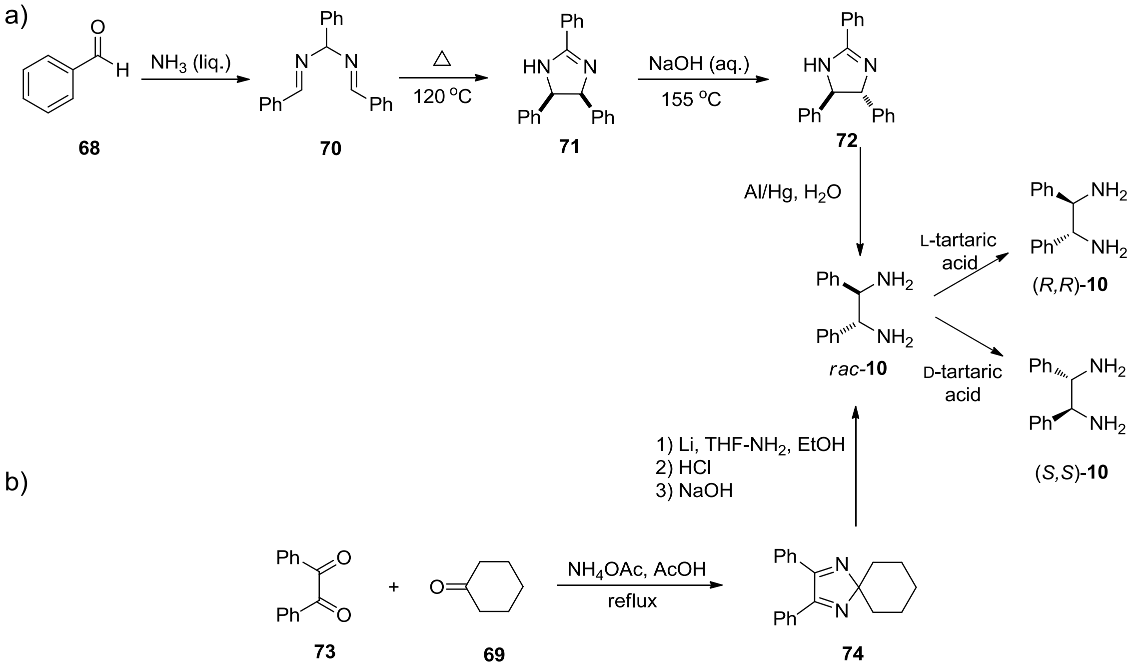
Due to the huge interests in the use of diamines in many areas of chemistry, many researchers have been developed novel and effective methods for their preparation. Recently, several ways have been described using different compounds as a starting material, such as double substitution of diols, reduction and addition of organometallic reagents to diimines, reductive coupling of imines and *N*-sulfinylimines, and diaza-Cope rearrangement[57] (Scheme 11).[13]



Scheme 11. Routes for the Synthesis of Diamines.

1.1.4.1. Synthesis of DPEN

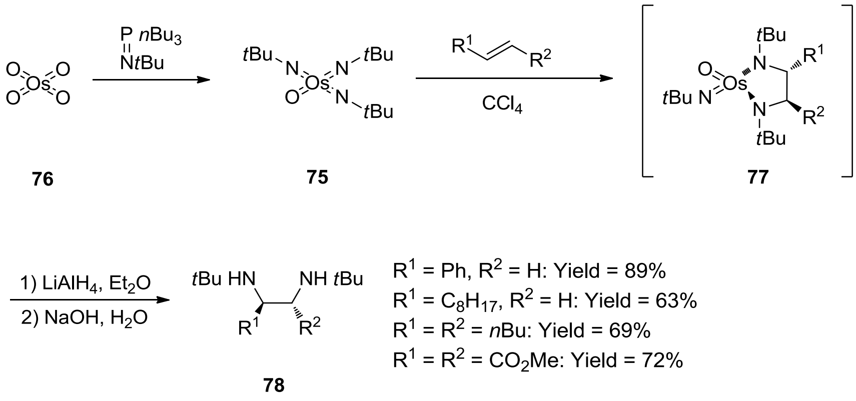
DPEN (1,2-diphenylethylenediamine) is one of the most recognized and common used substance as a diamine moiety. Racemic DPEN **10** can be synthesized in two ways. It can be obtained through the hydrolysis of isoamirine synthesized from ammonia and benzaldehyde **68** (Scheme 12a)[58] or from the reduction of the intermediate imidazole generated by the reductive ammination of cyclohexanone **69** and benzyl (Scheme 12b).[59] The enantiomerically pure form of (*S*,*S*)-**10** and (*R*,*R*)-**10** can be obtained by the resolution of the racemic product with L- or D-tartaric acid.[60]



Scheme 12. Synthesis of DPEN.

1.1.4.2. The Development of Diamination of Alkenes

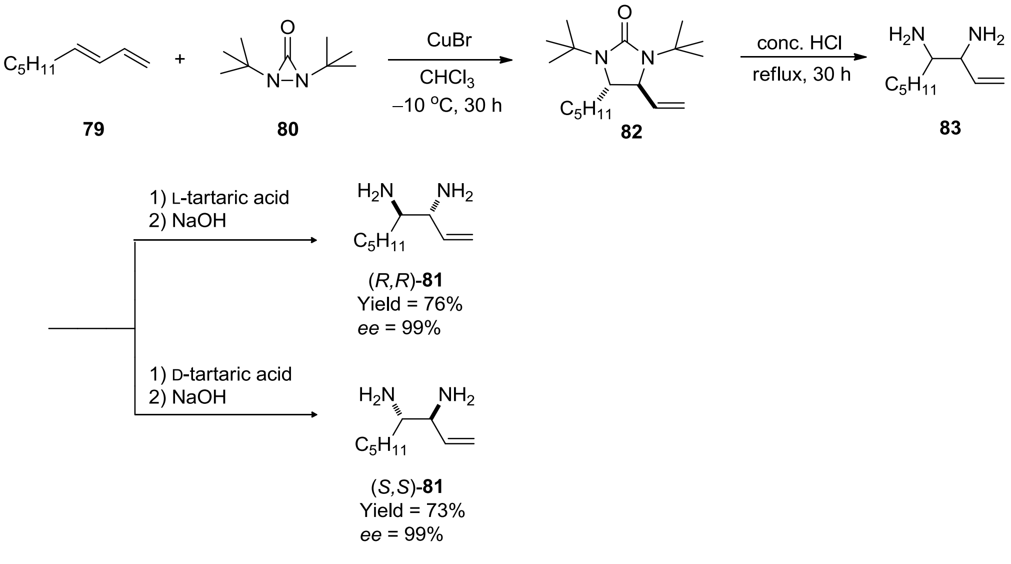
Sharpless *et al*. have reported the diamination of monosubstituted and disubstituted *E*-olefins through a stereospecific *cis* addition in the presence of the triimidoosmium complex **77** (Scheme 13).[61] Although the desire products were obtained in good yields, the reaction is only possible with *E*-alkenes. In addition, complex **75** has to be synthesized from OsO_4, which is expensive and has to be used in stoichiometric amounts.[13]



R^1 = Ph, R^2 = H: Yield = 89%
R^1 = C_8H_{17}, R^2 = H: Yield = 63%
R^1 = R^2 = *n*Bu: Yield = 69%
R^1 = R^2 = CO_2Me: Yield = 72%

Scheme 13. Asymmetric Diamination of Alkenes in the Presence of the Triimidoosmium Complex.

Nowadays, the diamination is an established method. Shi and *co*-workers proposed the regioselective diamination of dienes. They suggested in their report that conjugated dienes **79** can be regioselectively diaminated by Cu(I) as a catalyst and di-*tert*-butyldiazaridone **80** as a nitrogen source. The desired chiral diamines (*R,R*)-**81** and (*S,S*)-**81** were obtained *via* the diamination at the internal double bond and the resolution of the racemic diamine with L- and D-tartaric acid in the last step, with high regio- and diastereoselectivity in good yield (Scheme 14).[62] The CuBr as the catalyst provided a higher regioselectivity than CuCl.[63,64]

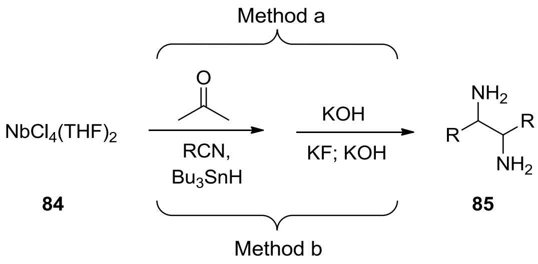


Scheme 14. CuBr-Catalyzed Regioselective Diamination.

1.1.4.3. Diamines from Imines

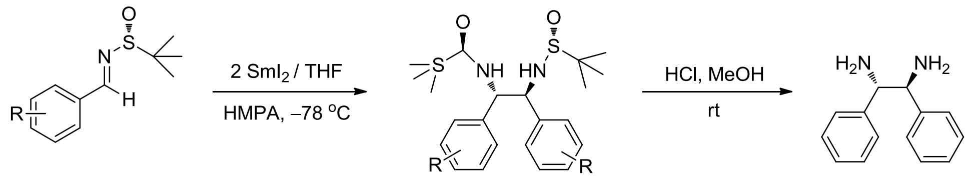
The reductive coupling of imines is a straightforward method for generating vicinal diamines.[65] In principle, the reductive coupling leads to variable proportions of *anti*- and *syn*-diamines.[13]

Pederson and Roskamp researched a convenient method for the preparation of unsubstituted vicinal diamines from *N*-(trimethylsilyl) imines with d^1 niobium reagent ($NbCl_4(THF)_2$) **84** (Scheme 15). The presented process is able to give the desired diamines with good yields and diastereoselectivities. The dialkyl products show however lower results[66] and the resolution of racemic diamines can require the use of complicated methods.[67]



Scheme 15. Vicinal Diamines by Pederson.

More recently, Xu *et al.*[65] have investigated a practical way for the preparation of diamines by the reductive homocoupling of aromatic *N*-*tert*-butanesulfinyl imines in the presence of SmI_2 and HMPA (Scheme 16). The authors were able to prepare enantimerically enriched C_2-symmetrical diamines in excellent yields and diastereoselectivities. However, the electron-donating substituted imines were relatively less reactive and gave a lower yield of homocoupling products.[65]



86

R = H, F, Cl, Br, Me,
OAc, OMe

87

88

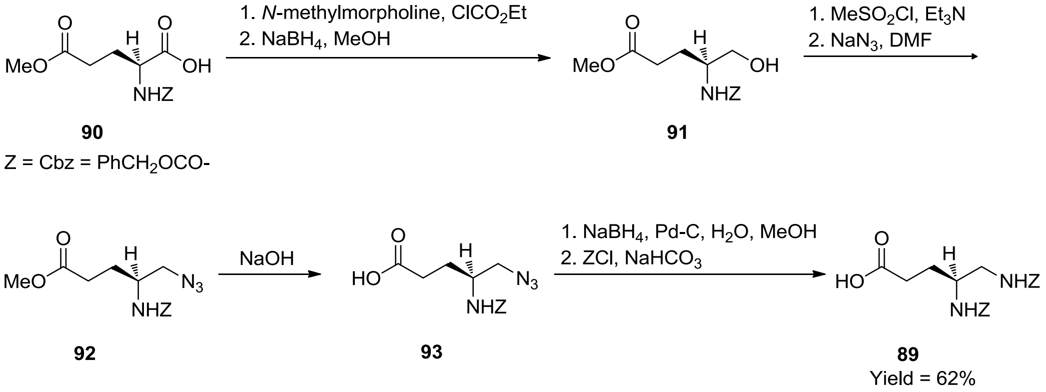
Yield = 25% - 99%

Scheme 16. Preparation of Diamine by Reductive Homocupling.

1.1.4.4. Diamines from *β*-Amino Alcohols

Taking into account the development of effective methods for the preparation of diamines, amines substituted at the *β*-position by a hydroxyl group are widely used as starting material. Many optically active *β*-amino alcohols can be synthesized from natural compounds from the chiral pool such as alkylated amino acids through reduction.[13,68]

Kokotos and *co*-workers have developed the method to reach diamine **89** with 62% yield using L-glutamic acid **90** by reduction of the amino acid, replacement of the hydroxyl group by an azido group and selective reduction (Scheme 17). The presented procedure reported for the conversion of glutamic acid into diamine is free of racemization.[69]



90

Z = Cbz = PhCH$_2$OCO-

91

92

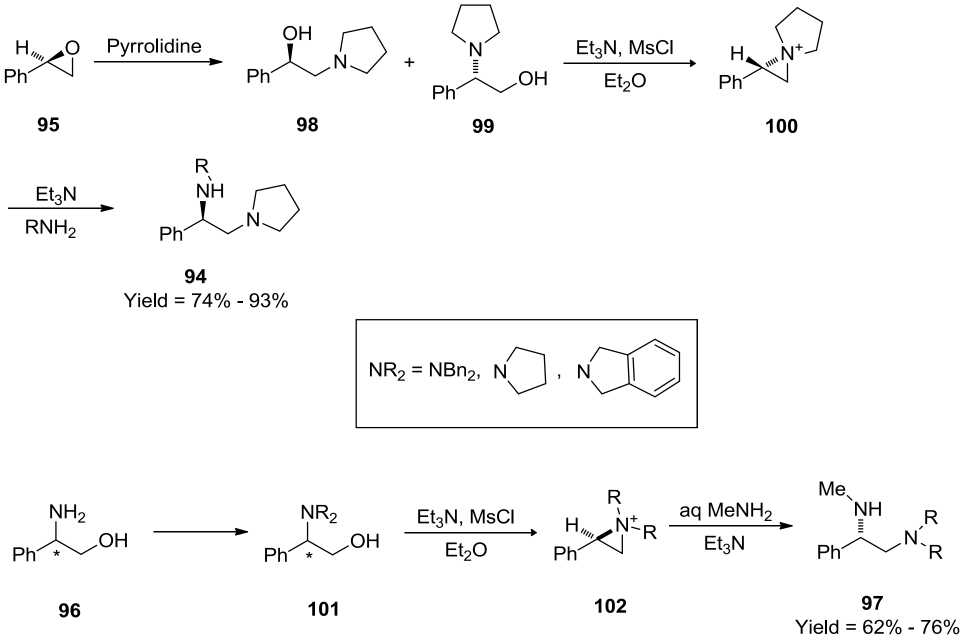
93

89

Yield = 62%

Scheme 17. Diamines from Amino Acids.

Syntheses of chiral diamines have been reported by O’Brien *et al.*[70-72] They proposed a one-pot method to obtain homochiral diamines **94** from commercially available (*R*)-styrene oxide **95** in high yields. Unfortunately, the reaction was only possible when reactive amines such as pyrrolidine and piperidine were used in the first step. Hence, in further work they investigated new strategies where they used phenylglycinol **96** which is available in two enantiomeric forms as a precursor to diamines **97** (Scheme 18).[13,70]



Scheme 18. Preparation of Diamines from (*R*)-Styrene Oxide or (*R*)-Phenylglycinol

1.1.5. Summary

Compounds incorporating diamino moiety in their structures play significant roles in synthesis. The diamines can be derived from natural products or from synthesis. This fact let to use diamines in many scientific fields. Taking into account their biological properties some of them found applications as medicinal agents. Moreover, chiral diamine derivatives are useful compounds in organic synthesis. They are ideally suited as chiral auxiliaries or as ligands especially in catalytic asymmetric reactions. Additionally, there are many different routes for the synthesis of diamines. However, few examples are of broad scope. Most of them are able to form specific classes of primary, secondary, and tertiary diamines or *syn*, *anti* products. Others are suited for the preparation of C_2-symmetrical desired diamines. These days the challenge is to develop new ways to prepare chiral diamines selectively either from the chiral pool and *via* asymmetric catalysis.

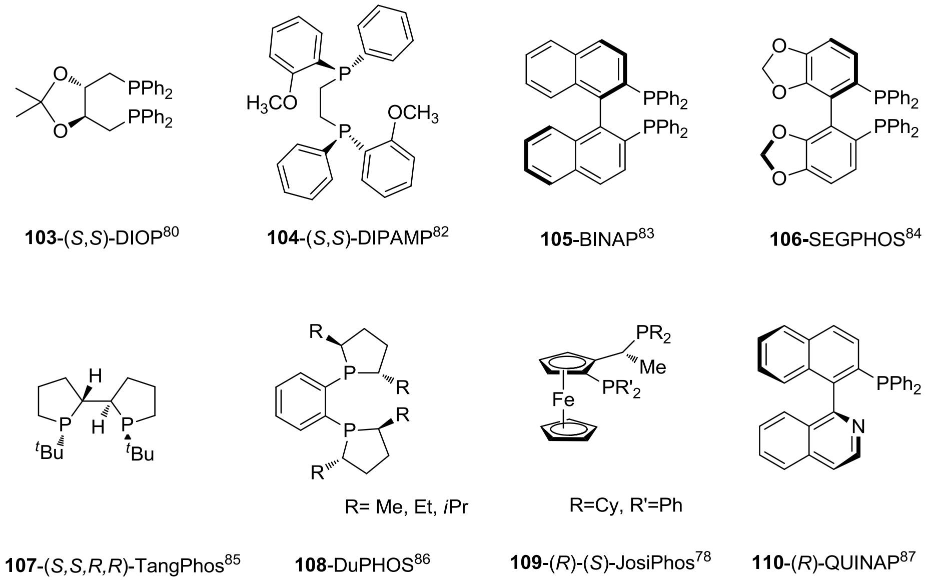
1.2. Organophosphorus Compounds

Arabian alchemists have discovered phosphorus in the 12th century nonetheless the whole success of the discovery of the element belongs to a German physician and alchemist who first isolated it in 1669 by distillation from urine. Nowadays phosphorus has found huge interest in many areas of research. Especially the development of organophosphorus compounds has found huge attention this days.[73]

Since the early 1970s, chiral ligands and their application to several transition metal-catalyzed asymmetric transformations has been the subject of attention for several research groups.[74] Desirable ligands, from a practical view, should be air-stable, easily accessible and inexpensive. On the other hand, from a functional view a new ligand should give the desired product in a highly regio- and enantioselective manner. There are many examples of organophosphorus compounds which have found huge applications, for example in agriculture, medicine or organic synthesis like the Mitsunobu, Wittig and Staudinger reaction and as ligands in catalysis or as organocatalysts.[75] They play an important role in the growth, reproduction and sustenance of life. For example, esters and thioesters of phosphoric acid are used as pesticides. Phosphate esters are known as precursors in the *bio*-synthesis of many macro molecules. Diazophospholes, diazophosphirinanes and certain phosphinyl carbamates have applications in the field of medicine and chemistry. Some of them have demonstrated to possess antitumor, antiviral, bactericidal and anti-carcinogenic activity.[76] Organophosphorus combinations are very important chiral auxiliaries in synthesizing many organic compounds.[77] Those compounds are also applied as chiral or achiral ligands to the nowadays rapidly growing field of transition metal-catalyzed transformations.[78]

1.2.1. Phosphines

Since phosphines and derivatives are known to be excellent ligand precursors, they have found huge applications as stable ligands in numerous transition-metal-catalyzed asymmetric reactions.[79] Significantly, ligands play an important role in activating the transition metal as an efficient catalyst. Despite the variety of ligands available, the large number of phosphine ligands with different functions and structural forms nowadays are the most essential type of ligands in transition-metal catalyzed transformations.[80] The most common and useful phosphines are presented in Figure 9.[78,81-87]



103-(*S*,*S*)-DIOP[80] **104**-(*S*,*S*)-DIPAMP[82] **105**-BINAP[83] **106**-SEGPHOS[84]

R= Me, Et, *i*Pr

R=Cy, R'=Ph

107-(*S*,*S*,*R*,*R*)-TangPhos[85] **108**-DuPHOS[86] **109**-(*R*)-(*S*)-JosiPhos[78] **110**-(*R*)-QUINAP[87]

Figure 9. Examples of the Most Used Phosphines.

The development of novel chiral ligands containing heterodonor atoms with nitrogen and phosphorus functional moieties (P,N-ligands) are widely investigated in metal-catalyzed asymmetric reactions.[88] The P,N-ligands are extremely attractive compounds because they can stabilize metal ions in a variety of oxidation states and geometries.[89] These hemilabile ligands in their structure have the well balanced combination of hard and soft donor atoms which is resulting unsymmetrical coordination to transition metals.[87] Another advantage of this class of ligands is that they can display different coordination modes compared with P,P- and N,N- ligands.[89] The π-acceptor character of the phosphorous ligand can stabilize a metal center in a low oxidation state, while the metals more susceptible to oxidative addition reactions.[90] Furthemore, their chelating effect confers stability to the catalyst in the absence of substrates.[89]

1.2.2. Phosphorus-Heteroatom Heterocyclic Compounds

In the late years of the 19th century phosphorus-containing heterocycles were synthesized for the first time. Although phosphorus heterocyclic compounds have been studied for many years, it is only since the middle of the 20th century that researchers have realized the importance of these compounds especially in biological areas. This fact started the development of new varies of functionalized phosphorus-containing heterocycles, especially structures containing phosphorus-heteroatom bonds,[91] which can be abbreviated as SPO (secondary phosphine oxides) or according to the suggestion of Ackermann HASPO (heteroatom-substituted phosphine oxides).[92] First heterocyclic compounds having both phosphorus and nitrogen atoms were prepared by Liebig and Wöhler.[93]

Enantiopure or enantioenriched heterocycles containing a trivalent or pentavalent P-stereogenic phosphorus atom can be easily generate by cyclisation of diamines, amino alcohols or diols around phosphorus moieties. Another advantage of this class of compounds is that they can be prepared in an inexpensive easy way in high yields and optical purities. Phosphorus-heteroatom heterocycles are extremely attractive compounds because in contrast to the classic phosphines they presented marked stability towards moisture and air. In addition, they can be used as organocatalysts or as ligands in transition metal transformations (Figure 10).[94]

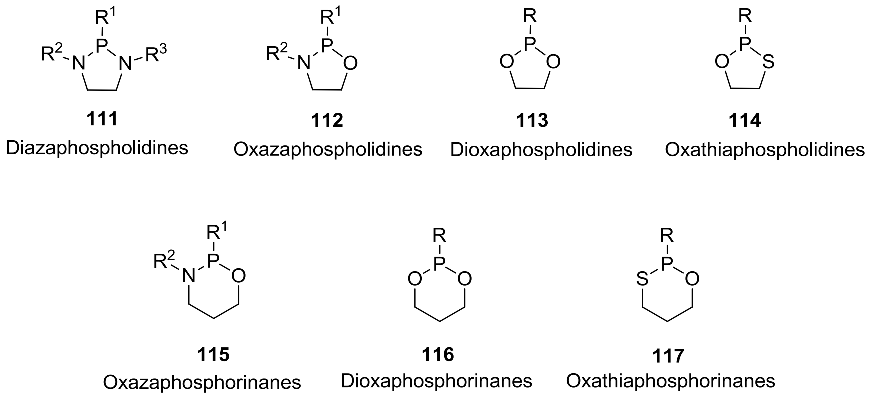
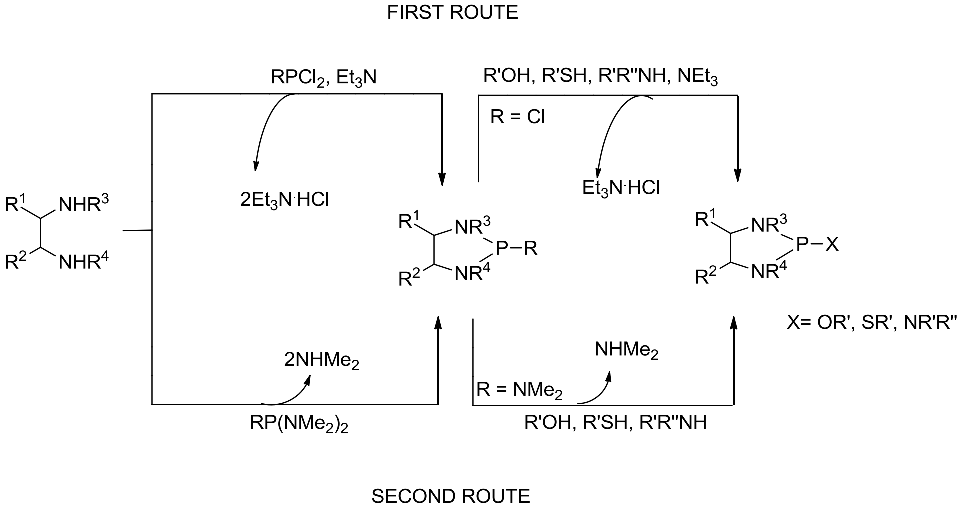


Figure 10. Phosphorus-Heteroatom Heterocycles.

1.2.2.1. Diazophospholidines

1.2.2.1.1. Phosphorus Tertiary Diazophospholidines

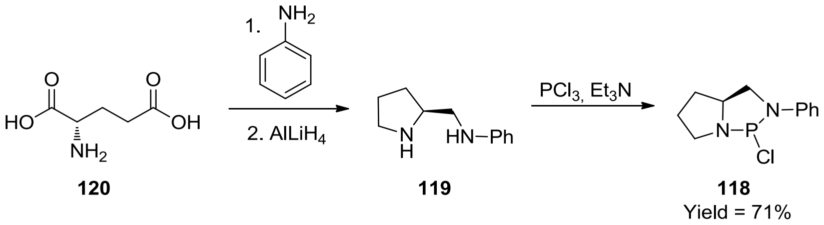
Five-membered ring diazophospholidines called also diaminophosphines which contain in their structure N,P,N atoms are nowadays very desired compounds in chemistry. These stable P-compounds can be easily synthesized in two possible pathways which are depending on the phosphorus precursors. The procedures are based on the displacement of two leaving groups (chlorine or dimethylamino groups) *via* a chiral secondary diamine (Scheme 19).



Scheme 19. Possible Pathways to Obtain P-Diazophospholidines.

The first route described in Scheme 19 shows the preparation of P(III) diazophospholidines with phosphorus trichloride or a dichlorophosphine in benzene or toluene at low temperature in the presence of a triethylamine as a base[95] followed by the filtration of the resulting $Et_3N{\cdot}HCl$.[96]

Many examples of diazophospholidines were achieved through the first route. Bondarev *et al*. proposed the preparation of chlorodiaminophospane **118** which marked the beginning of a series of desired derivatives of phosphoprus triamides. The compound **118** contains a chiral P atom and was achieved as an *anti* isomer through the diastereoselective phosphorylation of (*S*)-2-(anilinomethyl)pyrrolidine **119**. The latter was easily prepared from L-glutamic acid **120** (Scheme 20).[97,98]



Scheme 20. Preparaton of Chlorodiaminophospane.

Further research has been performed by Leitner, Franciò and *co*-workers. They obtained compound **118** as a mixture of the two diastereoisomers in which the *syn* diastereomer predominates.[94,99] Additionally, they noted that the presence of a base accelerates the epimerization process. In further studies they obtained novel ligands in good to excellent yields and with high diastereomeric purities by treating the diastereomeric mixture **118** with various secondary amines (Figure 11).[99]

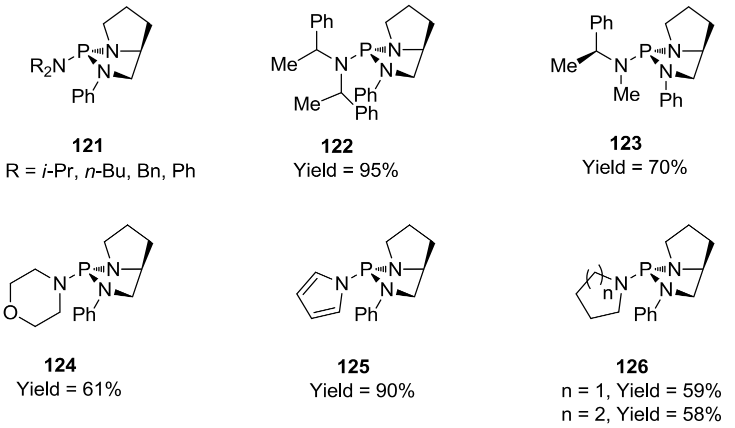


Figure 11.

Gavrilov's group following the first procedure afforded many various ligands. One group of novel P,N-ligands were synthesized through a one step phosphorylation of amino alcohols[100] or terpene alcohols[101] with chlorodiaminophospane **118** (Figure 12).

The synthesis of stable compounds was highly stereoselective, yielding only epimers with exocyclic substituents at the phosphorus atom in a pseudo-equatorial location.[100]

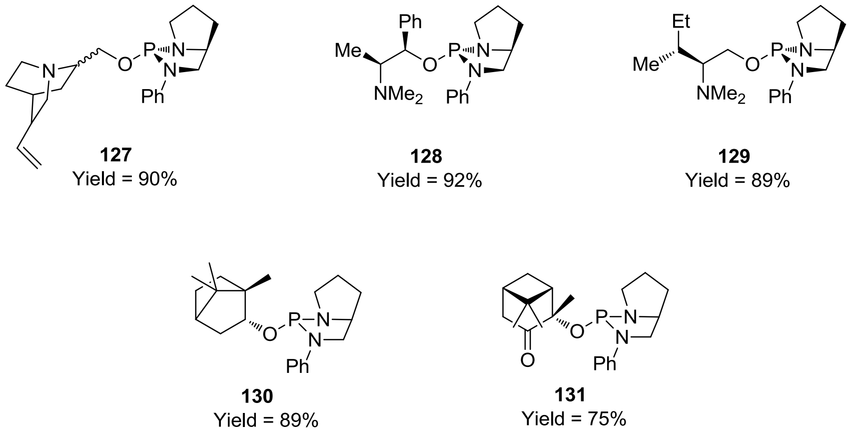

127 Yield = 90%
128 Yield = 92%
129 Yield = 89%
130 Yield = 89%
131 Yield = 75%

Figure 12.

Inspired from previously synthesized BINAP **105**, they also discovered very promissing phosphite-type ligands with P*-stereogenic phosphoramidites derived from *ortho*-substituted BINOL (Figure 13).[102,103]

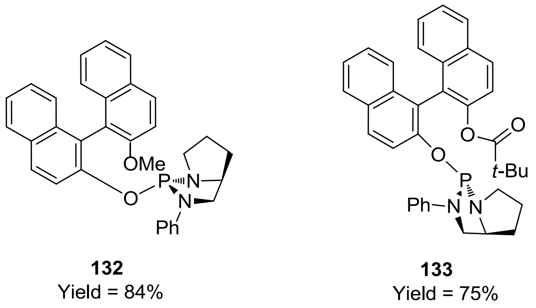
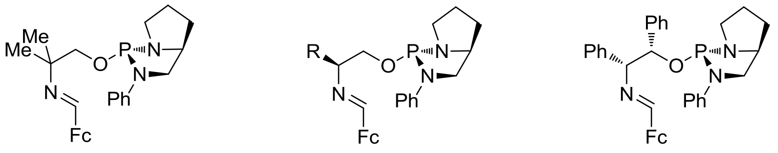

132 Yield = 84%
133 Yield = 75%

Figure 13.

Tsarev *et al.* proposed the synthesis of novel P,N-bidentate diamidophosphites possesing a P*-stereocentre and a distant ferrocenylimino group (Figure 14).[104] Chiral ligands containing in their structure ferrocene and its derivatives have been the subject of increasing attention in organometallic chemistry.[105] This sandwich structure has perfect properties such as: thermal stability or high tolerance to moisture and many kinds of reagents.[106,107,108]



134
Yield = 92%

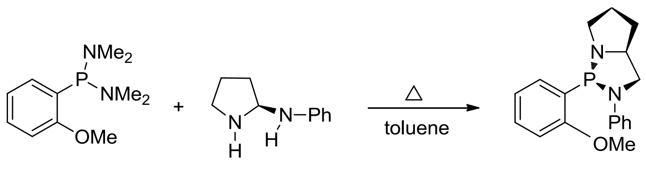
135
R = (*S*)-*s*-Bu, Yield = 90%
R = *t*-Bu, Yield = 91%

136
Yield = 85%

Figure 14.

A second route has been performed through the reaction between the diamine and *bis*(dimethylamino)phosphines or *tris*(dimethylamino)phosphine (HMPT) in toluene at reflux to obtain usually the pure *anti* diastereoisomer (Scheme 19, Second Route).[109] In contrast to the first pathway, no base is required in the second case. Although the second pathway is limited to thermally stable compounds,[94] excellent results were obtained.

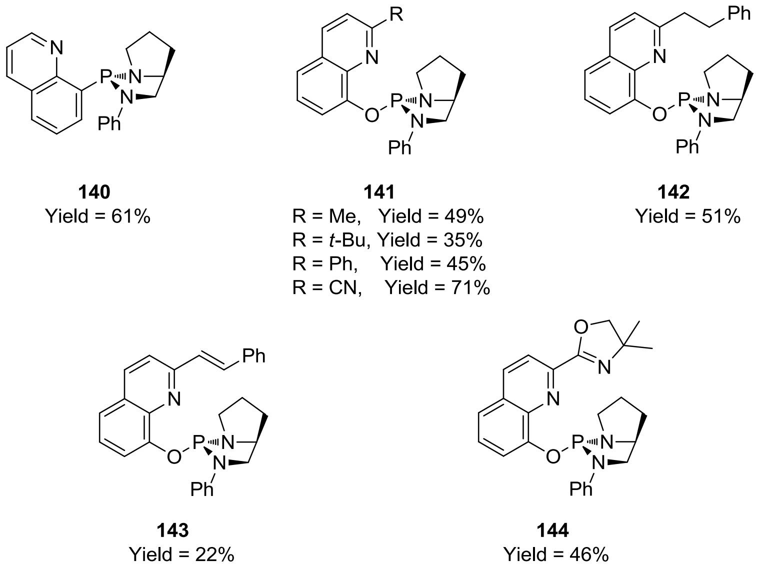
An example for the preparation of ligand (SEMI-EPHOS) **137** by the second route was presented by Buono and *co*-workers[110] following the initial work of Wills.[111] They obtained SEMI-EPHOS ligand **137** as a single isomer in 69% yield (Scheme 21).[110,111]



138 **139** **137**
Yield = 69%

Scheme 21. Preparation of SEMI-EPHOS Ligand.

An important class of unsymmetrical P,N-ligands was proposed by Buono *et al*. The corresponding chiral quinoline-phosphine ligands **140** (QUIPHOS) were prepared, respectively by the exchange reaction between *tris*(dimethylamino)phosphine and a chiral auxiliary (Figure 15) in good to excellent yields.[112,113]



140
Yield = 61%

141
R = Me, Yield = 49%
R = *t*-Bu, Yield = 35%
R = Ph, Yield = 45%
R = CN, Yield = 71%

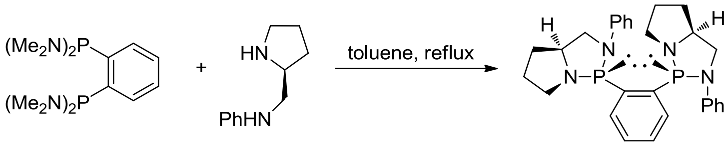
142
Yield = 51%

143
Yield = 22%

144
Yield = 46%

Figure 15.

Very interesting are diphosphorus ligands, which can be prepared in both ways. ESPHOS **145** can be synthesized in 76% yield as a single diastereoisomer (Scheme 22). Unfortunately, ESPHOS ligand **145** was not as effective as SEMI-ESPHOS **137** for the catalysis of asymmetric allylic substitution reactions.[111]



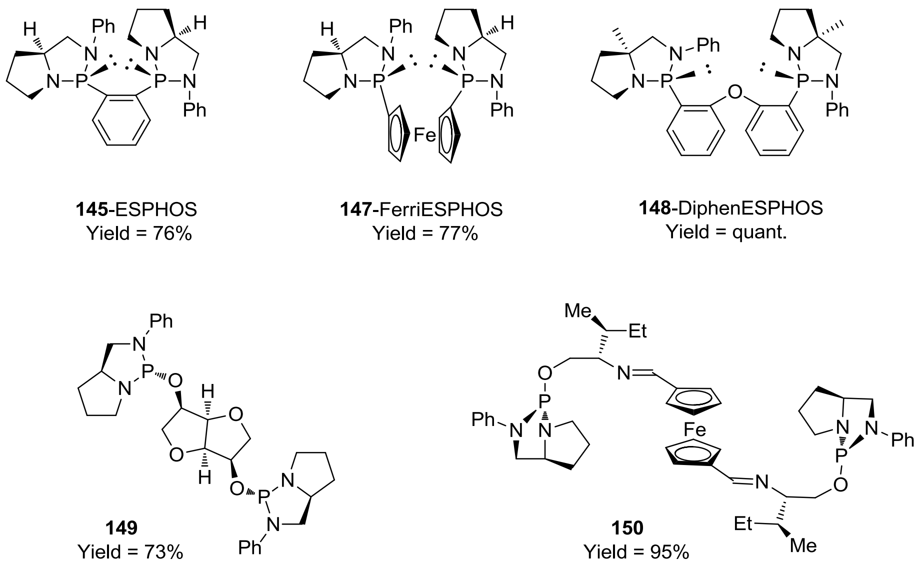
146

139

145
Yield = 76%

Scheme 22. The Synthesis of ESPHOS.

In the literature only a few examples of similar bi- or polyphosphorus ligands are known which are shown below (Figure 16).[94]



145-ESPHOS
Yield = 76%

147-FerriESPHOS
Yield = 77%

148-DiphenESPHOS
Yield = quant.

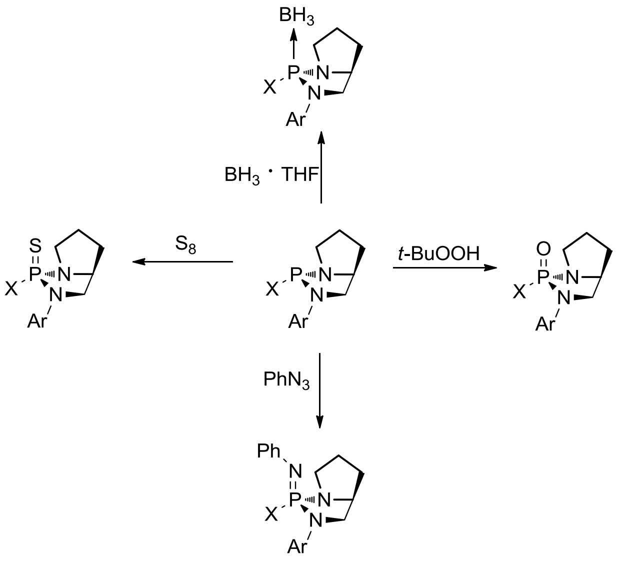
149
Yield = 73%

150
Yield = 95%

Figure 16.

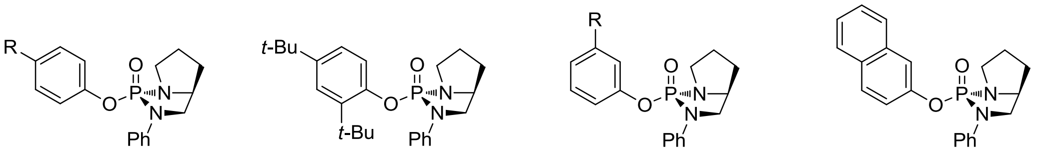
1.2.2.1.2. P(V) Diazaphospholidines

Diazophospholidines have found huge attention these days as ligands in transition metal-catalyzed transformations. Some of them play also a key role as precursors to generate novel diazophospholidine boranes, and few classes of P(V) compounds such as oxides, sulfides or iminophosphines (Scheme 23). An important fact is that most of the reactions have been found to proceed with complete retention of configuration at the phosphorus atom.[94]



Scheme 23. Preparation of Diazaphospholidine Derivatives.[94]

Buono *et al.* proposed the preparation of a series of diazophospholidine derivatives from the P(III) precursors (Figure 17). They obtained the desired products in good yields ranging from 63% to 87%. Additionally, the corresponding diazophospholidine derivatives were achieved as one diastereomer, which was characterized as the theromodynamic *anti* diastereomer.[114,115]

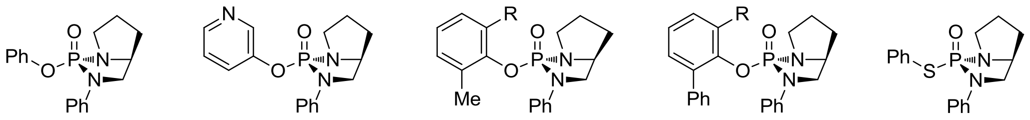


151
R = OMe, Yield = 84%
R = F, Yield = 83%
R = Cl, Yield = 81%

152
Yield = 63%

153
R = OMe, Yield = 75%
R = F, Yield = 75%
R = Cl, Yield = 70%
R = *t*-Bu, Yield = 63%

154
Yield = 77%



155
Yield = 87%

156
Yield = 63%

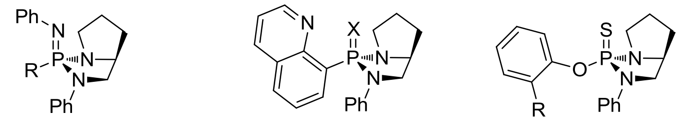
157
R = H, Yield = 55%
R = $SiEt_3$, Yield = 55%

158
R = H, Yield = 70%
R = $SiEt_3$, Yield = 63%

159
Yield = 65%

Figure 17.

Besides P(V) oxides achieved from P(III) precursors also the design of sulfides and iminophosphines has been the subject of attention from a number of researchers (Figure 18).[113,115,116]



160[116]
R = NMe_2, Yield = 48%
R = Ph, Yield = 61%

161[113]
R = O, Yield = 100%
R = S, Yield = 95%
R = NPh, Yield = 85%

162[115]
R = H, Yield = 78%
R = Br, Yield = 69%

Figure 18.

More recently, chiral P-stereogenic phosphorus ligands have been developed owing to the application of borane as a protecting group.[117] The diazaphospholidine-borane complexes were prepared in diastereomerically pure form in good to excellent yields (Figure 19).[117,118]

163[117]

X = lone pair, R = H, Yield = 94%
R = F, Yield = 95%
R = Me, Yield = 91%
R = *t*-Bu, Yield = 85%
R = Ph, Yield = 85%
R = OMe, Yield = 96%

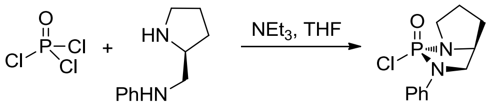
X = BH_3, R = H, Yield = 90%
R = F, Yield = 83%
R = Me, Yield = 85%
R = *t*-Bu, Yield = 85%
R = Ph, Yield = 85%
R = OMe, Yield = 92%

164[118]

R^1 = H, R^2 = H, Yield = 86%
R^2 = Me, Yield = 71%
R^2 = Ph, Yield = 76%
R^2 = Cl, Yield = 76%
R^1 = Me, R^2 = H, Yield = 76%

Figure 19.

The phosphine oxide ligands prepared from P(V) precursors by a version of the first strategy obtain the diazophospholidines with low stereoselectivity which is equal to the prior formation of the corresponding P(III) products (Scheme 24).[94]

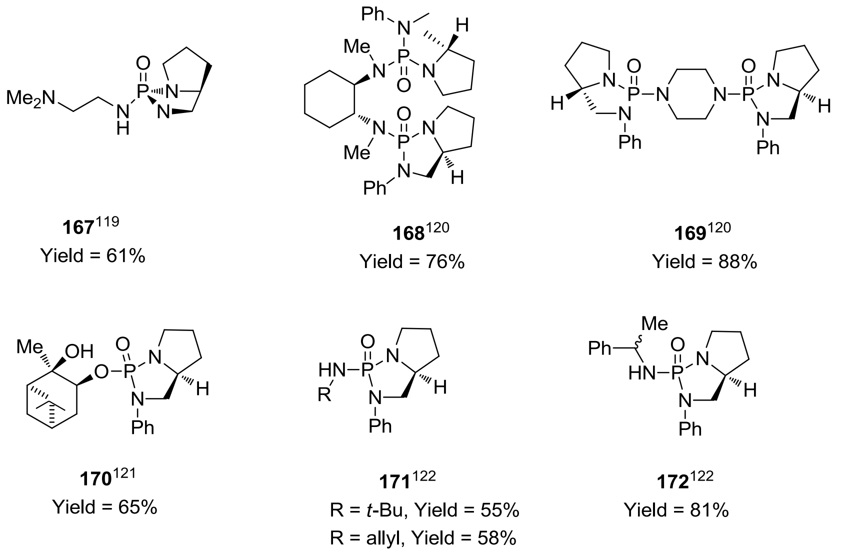


165 **139** **166**

Yield = 76%

Scheme 24. Preparation of 166.

An exception is the relatively stereoselective reaction of the chloro derivative **166** at 0 °C. This concept was used by Fiaud *et.al.*[119] Their pioneering work was followed by Basavaiahand and *co*-workers who yielded a series of diazaphospholidine oxides from chloro derivative **166** with alcohols and amines (Figure 20).[119-122]



167[119]
Yield = 61%

168[120]
Yield = 76%

169[120]
Yield = 88%

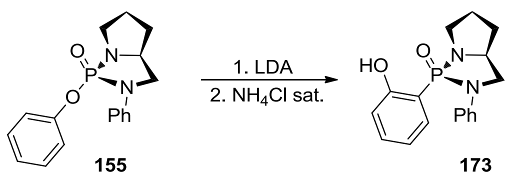
170[121]
Yield = 65%

171[122]
R = *t*-Bu, Yield = 55%
R = allyl, Yield = 58%

172[122]
Yield = 81%

Figure 20.

The synthesis of a new class of chiral *o*-hydroxyaryl phosphine oxides by the rearrangement of a P-O to a P-C bond with a bifunctional feature, a basic (P=O) and an acid side (OH), has been reported by Buono and *co*-workers.[123] Due to the work of Melvin *et al.* lithium diisopropylamide (LDA) has been the most common base used in the rearrangement of arylphosphate to *o*-hydroxyarylphosphonate and derivatives which resulted in good yields and total diastereoselectivity. Only a few examples of this reaction with lower selectivity are mentioned with butyllithium. Buono *et al.* achieved the *o*-hydroxyphenyl diazaphospholidine oxide **173** in 94% yield through the treatment of compound **155** with LDA followed by an aqueous work-up (Scheme 25).[115]

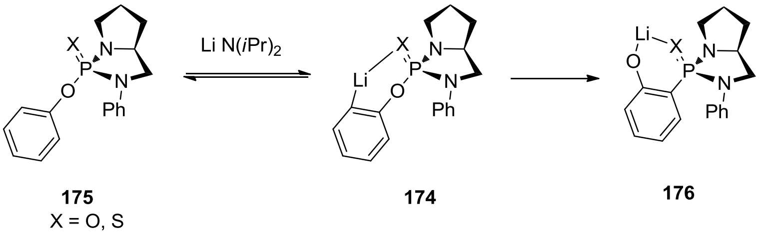


155

173
Yield = 94%

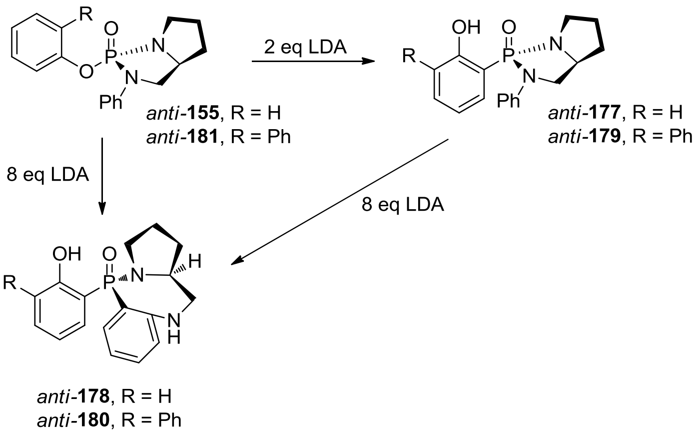
Scheme 25. Preparation of Hydroxyphenyl Diazaphospholidine Oxide 173 with LDA.

The diazaphospholidine oxide group has played an excellent role as an activator for the direct metallation of the *ortho* position in aromatic system generating the stabilised carboanion **174**. Additionally, the driving force of anionic [1,3] rearrangement is the formation of the stable chelate complex in which both oxygen atoms can interact with the lithium atom (Scheme 26).[115]



Scheme 26. Metalation of the *ortho* Position.

Buono *et al.* presented in further work a new general procedure for the first ring-expansion reaction of diazophospholidine oxides involving a stereospecific migration of P from N to C.[94,124] The *anti*-**177** compound can be synthesized in 94% yield in the presence of 2 eq. of LDA. However, the synthesis of the product **178** was readily achieved with 8 equivalents of LDA in 89% yield. This compound is a product of two diasereoselective 1,3-migration rearrangements (first P-O to P-C_{sp}^2 followed by P-N to P-C_{sp}^2).[94,124] Additionally, treatment of *anti*-**177** with 8 equivalents of LDA led to the diastereoselective generation of the corresponding *anti*-**178**.[124] This fact shows that P-N to P-C only exists once the P-O to P-C_{sp}^2 step has been completed (Scheme 27).[94,124]

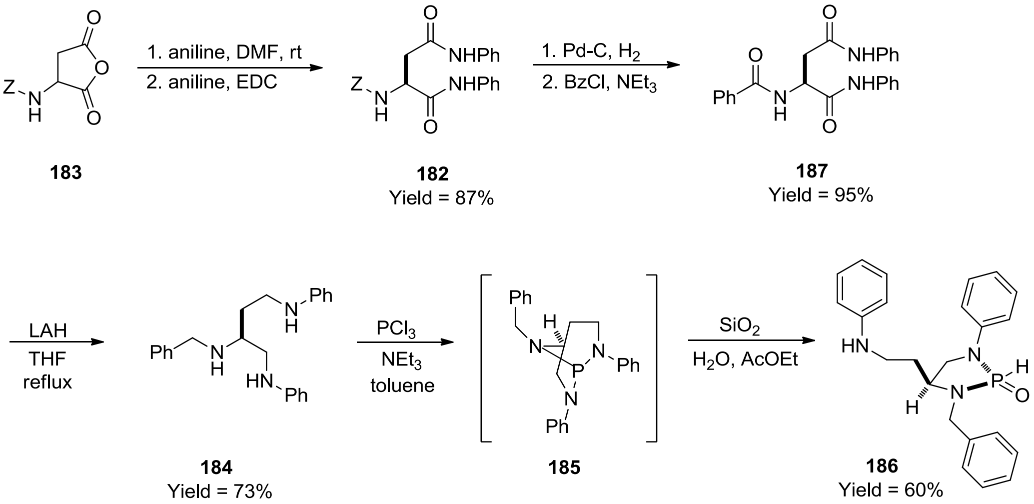


Scheme 27. P–O to P–C and P–N to P–C Rearrangements in a Diazaphospholidine Oxide.[94]

1.2.2.1.3. P(V) Secondary Diazaphospholidines

One relevant class of P-stereogenic diaminophosphine oxides was discovered by Hamada, Nemoto and *co*-workers. They synthesized a new class of P-chirogenic phosphine oxides based on a chiral asymmetric diamine framework, called P-chirogenic diaminophosphine oxides: DIAPHOXs.[74]

These chiral ligands with a stereogenic center on a phosphorus atom[125] have been prepared from commercially available acid anhydride **182**, which can be synthesized from (*S*)-aspartic acid **183**[126] which was easily converted to triamine **184** over four steps.[127] The triamine was reacted with phosphorus trichloride to obtain triaminophosphine **185**[127] which was converted into DIAPHOX **186** by an S_N2-type hydrolysis[128] upon purification by silica with wet ethyl acetate in 60% yield (Scheme 28).[126,129]



183

182
Yield = 87%

187
Yield = 95%

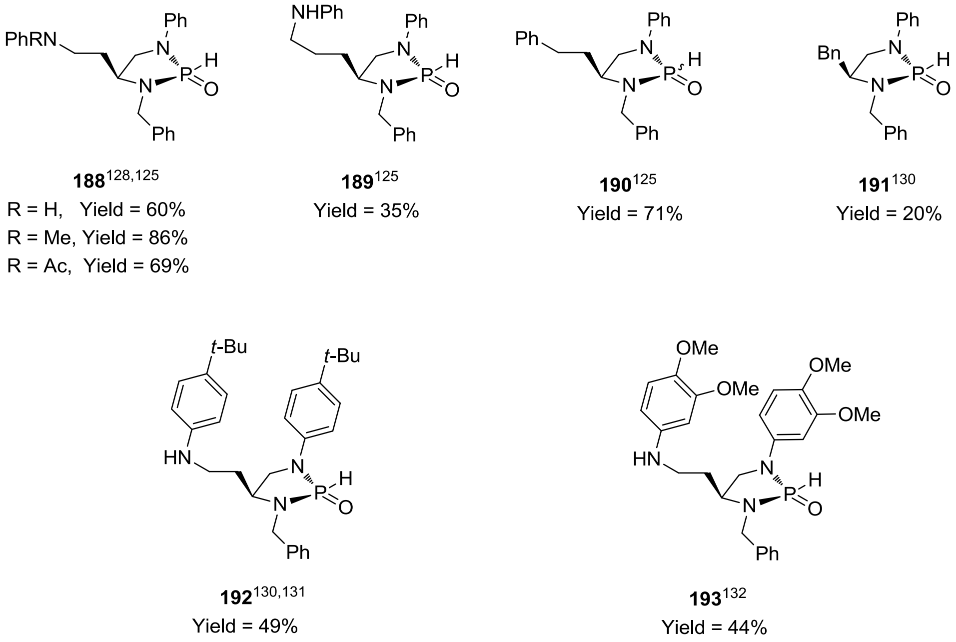
184
Yield = 73%

185

186
Yield = 60%

Scheme 28. Preparation of Ph-DIAPHOX.

The analogues of DIAPHOXs which are shown below were prepared *via* the same synthetic route as compound **186** (Figure 21).[125,128,130-132]



188[128,125]
R = H, Yield = 60%
R = Me, Yield = 86%
R = Ac, Yield = 69%

189[125]
Yield = 35%

190[125]
Yield = 71%

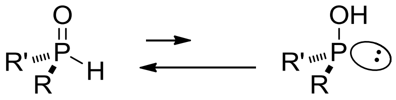
191[130]
Yield = 20%

192[130,131]
Yield = 49%

193[132]
Yield = 44%

Figure 21. DIAPHOX Ligands.

DIAPHOXs are a class of ligands which are air- and moisture-stable pentavalent phosphorus compounds. The chiral diaminophosphine oxides exist in equilibrium between pentavalent forms (RR'P(=O)H) and trivalent tautomeric forms (RR'POH) (Scheme 29).[125] In this process, the secondary phosphine oxides are activated by a BSA-induced tautomerization, resulting in a trivalent diamidophosphite form.[133,134] The interesting phenomenon is that the P(V)-P(III) equilibrium does not affect the stereochemistry around the phosphorus center.[126] This effect allows for the application of the DIAPHOXs analogues as ligands in many reactions such as Pt-catalyzed hydrolysis or Pt-catalyzed hydroformylation but the most popular are Pd and Ir enantioselective allylic substitution reactions. Additionally, it has to be mentioned that tautomeric phosphinous acid coordinates to the metal center through a phosphorus atom.[125]

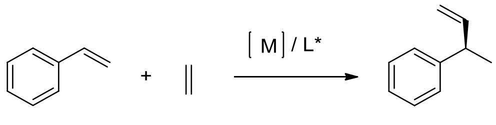


Scheme 29. Equilibrium between P(V) and P(III).

1.2.3. Phosphorus-Nitrogen Atom Heterocyclic Compounds as Ligands for Asymmetric Reactions

1.2.3.1. Asymmetric Hydrovinylation

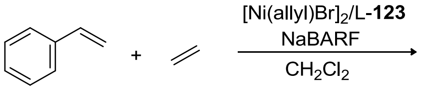
The concept of hydrovinylation defines itself as the addition of ethylene across a double bond or as a *co*-dimerisation of ethylene and an activated alkene (Scheme 30).[135] The hydrovinylation reaction was first discovered in 1965 by Alderson and *co*-workers by using hydrated ruthenium and rhodium salts under high ethane pressure with a range of substrates. Iron, cobalt, nickel, and palladium have been also used, but nowadays studies have focused especially on nickel and palladium.[136]



194 **196** **195**

Scheme 30.

Followed by the early studies of Wilke *et al.*,[137] Franciò, Leitner and *co*-workers investigated the reaction of 1,3-cyclooctadiene **194** with ethane **195** by using [Ni(allyl)Br]$_2$ with NaBARF as an activator in combination with the chiral monodentate phosphines derived from monoterpenes and resulting the product **194** in 77% yield and 63% *ee* (Scheme 31).[99]



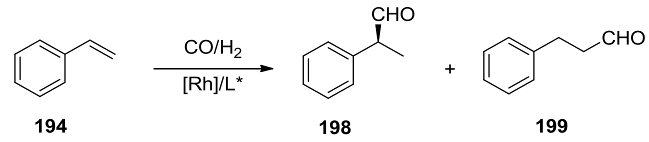
194 **196** **197**

Yield = 77%
ee = 63%

Scheme 31.

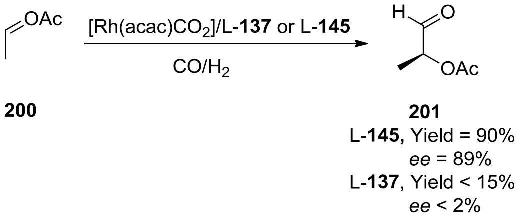
1.2.3.2. Asymmetric Hydroformylation

The hydroformylation reaction has been known for more than 70 years and is one of the most essential industrial processes for the production of aldehydes from C-C double bonds (Scheme 32).[138] Hydroformylation is based on the application of a transition metal, which provides the formation of metal-carbonyl species. The resultting complex can be modified by the ligand and the structure $H_xM_y(CO)_zL_n$ can be obtained.[139] Several metals like cobalt, rhodium or platinum were applied as a catalyst in hydroformylations but the most attention was paid to ruthenium.[94]



Scheme 32.

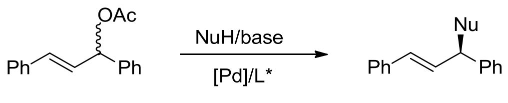
Phosphorus compounds are one of the most widely accepted ligands which are able to form the complex and coordinate to hydroformylation reactions. Cole-Hamilton *et al.* reported the application of ESPHOS **145** and SEMI-ESPHOS **137** in the asymmetric hydroformylation of vinyl acetate **200** (Scheme 33). They showed that bidentate C_2-symmetric ESPHOS ligand **145** obtained better results than the monodentate analogue SEMI-ESPHOS **137**.[140]



Scheme 33. Asymmetric Hydroformylation of Vinyl Acetate.

1.2.3.3. Allylic Substitution

The allylic substitution is one of the most powerful methods for introducing chirality on an allylic carbon, catalyzed by a transition metal complex (Scheme 34).[141] The allylic substitution can be used to create C-C, C-N or C=O bond formation with transition metals mainly including palladium, iridium and ruthenium and involving electrophilic π-allylmetal intermediates.[142]

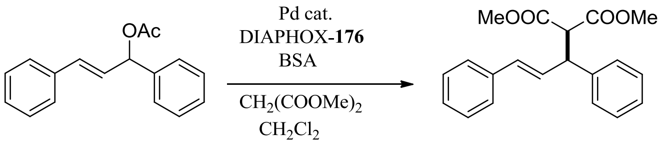


202 **203**

Scheme 34. Allylic Substitution.

Recently, a few groups proved that diazaphospholidines with two different donor atoms (P, N) are brilliant ligands for these allylic transformations. One of the reasons is that this kind of ligand is able to impart an electronic distortion upon the allyl moiety of the palladium complex and the nucleophilic attack is predicted to occur *trans* to the better π–acceptor.[143]

One of the most investigated HASPO ligand for Pd-catalyzed asymmetric allylic substitution reactions with carbon nucleophiles is DIAPHOX. Nemoto, Hamada and *co*-workers obtained the desired product **205** in 94% yield and an excellent *ee* of 99% from 1,3-diphenylallyl acetate **202** with dimethyl malonate (Scheme 35). This type of reaction is one of the most important benchmark-system to examine the ability of novel chiral ligands.[144]



202 **204**

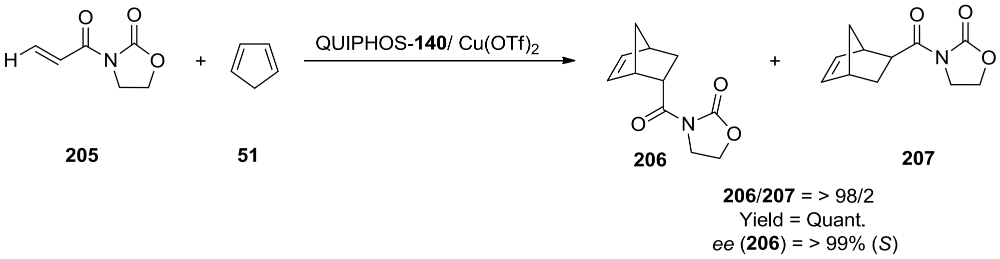
Yield = 94%, *ee = 99%*

Scheme 35. Asymmetric Allylic Alkylation using DIAPHOX as a Ligand.

1.2.3.4. Diels-Alder Reaction

The formation of a cyclic adducts from two unsaturated molecules plays an important role in organic chemistry. From the cycloaddition reactions one of the most important and well-known reaction is the Diels-Alder reaction (4+2 cycloaddition), which can be catalyzed by chiral Lewis acids.[94] Also P-ligands found applications in such reactions.

Buono *et al*. employed the QUIPHOS **140** in the Cu-catalyzed enantioselective 4+2 cycloaddition of *N*-acrylamide dienophiles **205** and cyclopentadiene **51** (Scheme 36). They obtained two isomers with very high *endo/exo* ratios and excellent yields and enantioselectivities if the reagents were mixed at −78 °C and slowly warmed to room temperature.[94,145]



Scheme 36. Catalytic Diels-Alder Reaction.

1.2.4. Summary

Phosphorus compositions play an essential role in chemistry and especially in organic chemistry where the attention is devoted to organophosphorus compounds. This stems from the fact that phosphorus has the ability to form bonds with many other elements. Phosphorus compounds have found applications in many areas of life, such as agriculture, medicine or organic synthesis.

Due to the interest in organophosphorus compounds, phosphorus derivatives have been investigated by many researchers. There are many examples of the phosphorus compositions which are subsequently examined. One of the most desired and investigated groups of organophosphorus compounds are phosphines. This large group can be synthesized by many methods. General preparations of phosphines are multi-step processes which involve tetra- or pentacoordinated intermediates. From phosphine derivatitives P-heterocycles are not less interesting compounds especially when phosphorus-heteroatom heterocycles are concerned. Nowadays, the most important direct precursors of free phosphines are phosphine oxides and phosphine boranes. For many years chiral phosphines are one of the most widely accepted ligands which are able to generate complexes that are successfully applied in transition metal-catalyzed asymmetric processes.

2. Results and Discussion

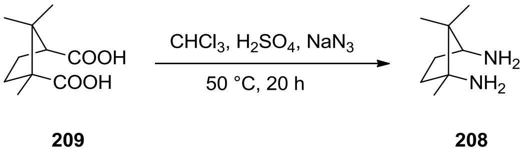
2.1. Aim of the Work

The aim of the work was the development of novel chiral ligands which are the essential part of asymmetric catalysis. One important class of chiral ligands are diamines, which have attracted substantial attention over the last years. Hence, a good amount of chiral diamine ligands has been discovered. One significant starting material from the chiral pool is camphor and several diamine ligands have been prepared from camphor and the number of chiral 1,3-diamines are limited. However, ligands from camphoric acid are still rare. Therefore, the preparation of a new class of ligands from camphoric acid, a cheap, common chiral building block derived from camphor is desirable.

The purpose of this work was the preparation of novel ligands and their application in asymmetric transformations. This includes the investigation of primary and secondary 1,3-diamine ligands which found application in the asymmetric Henry or nitroaldol reaction. The later is one of the most useful methods for the formation of C-C bonds in organic synthesis. Later on, special attention should be paid to the HASPO (heteroatom-substituted secondary phosphine oxide) ligands which exist in equilibrium between pentavalents form [RR'P(O)H] and trivalent tautomeric forms (RR'POH). They were synthesized from the new chiral diamines derived from camphoric acid.

2.1.1. Synthesis of Camphoric 1,3-Diamine

The rigid camphoric 1,3-diamine **208** was synthesized from (+)-camphoric acid **209**, a cheap, common chiral building block derived from camphor[146,147] *via* a Schmidt reaction.[148,149] To a reaction mixture of (+)-(1*R*,3*S*)-camphoric acid **209** in concentrated sulfuric acid and ethanol free chloroform was added sodium azide. The reaction was carried out for 20 h at 50 °C. The desired product **208** was obtained as a white solid in 71% yield (Scheme 37).

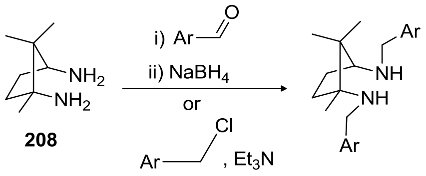


Scheme 37.

The camphor diamine **208** was used in the next steps as a starting material for the preparation of a new class of diamine ligands which have been applied to the asymmetric nitroaldol Henry reaction and also for synthesizing HASPO (heteroatom-substituted secondary phosphine oxide) ligands. From diamine **208** two types of ligands can be prepared. One class of ligands in the structure includes both nitrogen atoms with the same substituent while the second class contains only one aryl substituted nitrogen atom. These two different types of diamine ligands are designed to induce different chirality in asymmetric reactions. From later research can be deduced that ligands include nitrogen atoms with different substituted aryl groups in the structure provides higher enantiomeric excess while secondary diamines with the same substituent affords lower enantioselectivities.

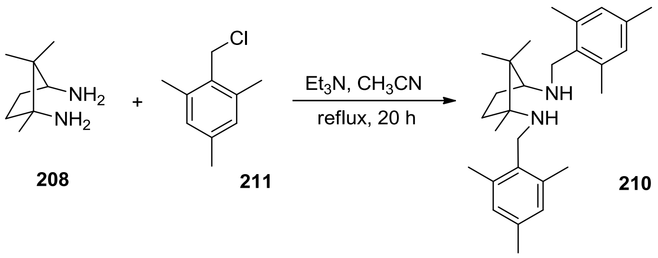
2.1.2. Preparation of Diamine Ligands with the Same Substituent on Both Nitrogen Atoms

Enantiopure diamines with two secondary amine groups were prepared through an alkylation by treating the camphor diamine **208** with arylmethylene chloride or with an aldehyde, followed by the reduction of the corresponding imine (Scheme 38).[150]



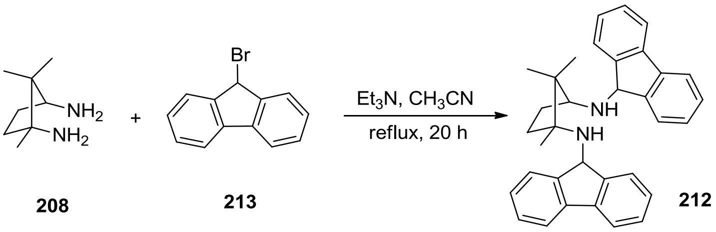
Scheme 38.

Following the first strategy, the enantiopure diamine **210** was performed under dry conditions with diamine **208** and 2,4,6-trimethylbenzylchloride **211** in the presence of the triethylamine in acetonitrile under reflux. The corresponding product **210** was obtained as colorless oil in 57% yield (Scheme 39).



Scheme 39.

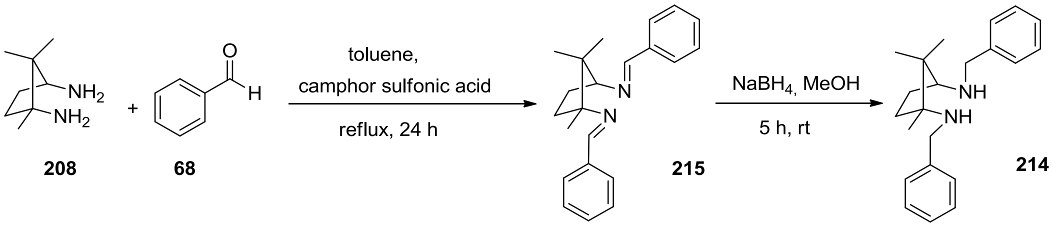
Similarly, product **212** was prepared by the reaction of diamine **208** and 9-bromofluorene **213** under reflux in acetonitrile. The desired compound **212** was purified by flash column chromatography to afford a yellow solid in 59 % yield (Scheme 40).



Scheme 40.

In both cases the products were obtained as disubstitued compounds. Monosubstitued product was not observed despite the reactions were performed with the use of 1 equiv. of aryl halide.

Furthemore, as shown below the diamine **214** formation was performed in two steps. First benzaldehyde **68** and camphor diamine **208** were refluxed in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid, followed by the reduction of imine **215** which is an efficient method for the preparation of diamine **214** in 75 % yield (Scheme 41).

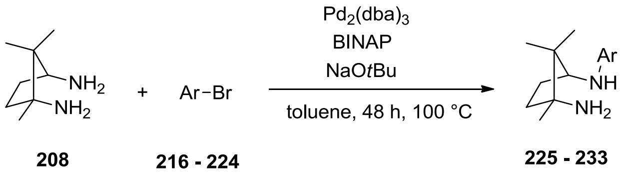


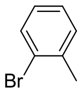
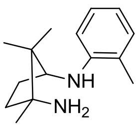
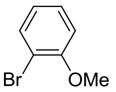
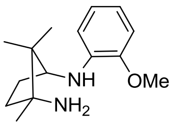
Scheme 41.

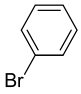
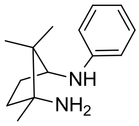
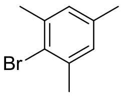
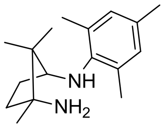
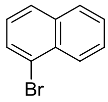
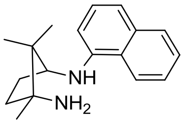
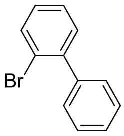
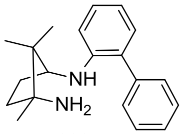
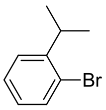
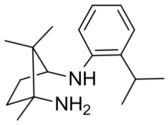
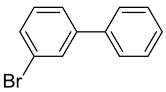
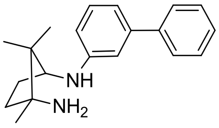
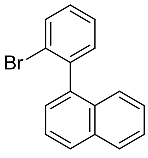
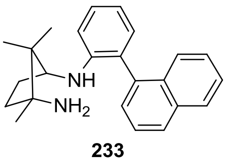
2.1.3. Selective Monoalkylation

Enantiopure diamines with a primary amine function were prepared *via* a monoalkylation reaction by treating the diamine **208** with an aryl halide **216-224** in the presence of $Pd_2(dba)_3$, BINAP and NaO*t*Bu according to a modified procedure reported by Dorta.[151] After purification by acid base extraction treatment products **225-233** were obtained in good to excellent yields. The results are summarized in Table 1.[152-154]

Tabele 1. Monoalkylation Reaction by Treating Diamine 208 with Aryl Halide *via* a Buchwald-Hartwig Amination.



Entry	Arene	Product	Yield [%]
1	 **216**	 **225**	82
2	 **217**	 **226**	99

3	 **218**	 **227**	60
4	 **219**	 **228**	97
5	 **220**	 **229**	64
6	 **221**	 **230**	73
7	 **222**	 **231**	49
8	 **223**	 **232**	48
9	 **224**	 **233**	33

The results which are summarized in Table 1 show that the reaction accepted arenes with various substitution patterns. For example the 2-bromoanisole **217** (Table 1, Entry 2) gave a brilliant yield of 99%. Also the most sterically hindered 2-bromomesitylene **219** (Table 1, Entry 4) resulted excellent yield of 97%, while 1-bromo-2-isopropylbenzene **222** (Table 1, Entry 7) gave less than 50% yields. Bromobiphenyls such as 2-bromo-1,1’-biphenyl **221** (Table 1, Entry 6) and 3-bromobiphenyl **223** (Table 1, Entry 8) resulted in an yield of 73% and 48% respectively. On the other hand due to the axial chirality of 1-(2-bromophenyl)naphthalene the product **233** (Table 1, Entry 9) was obtained as a mixture of diastereomers in 33%.[152] The resulted product **233** of two diastereomers which does not possess a stereogenic center could not be separate by column chromatography.[152]

Additionally, it is remarkable that the arylation is highly selective despite the high reaction temperature. In all cases the other possible regioisomers were not observed. This fact results from sterical hindrance around tertiary carbon. Only the desired monoalkylated products which were identified by ^{1}H-, ^{13}C-NMR and 2D spectra-HMBC were present.[152] As an example the HMBC spectrum for **232** proved that the proton at the C(1)-atom appears at 3.75 ppm and coupled with the quaternary aromatic carbon at 149.04 ppm. A coupling of this aromatic carbon with the protons of the methyl group attached to the C(3) atom was not observed, which excludes the other regioisomers (Figure 22).

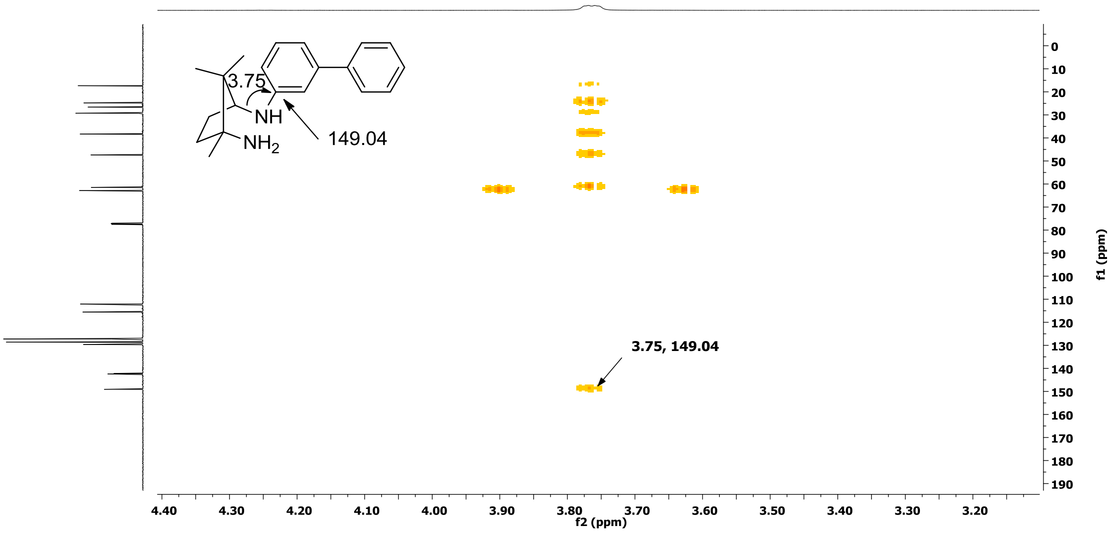
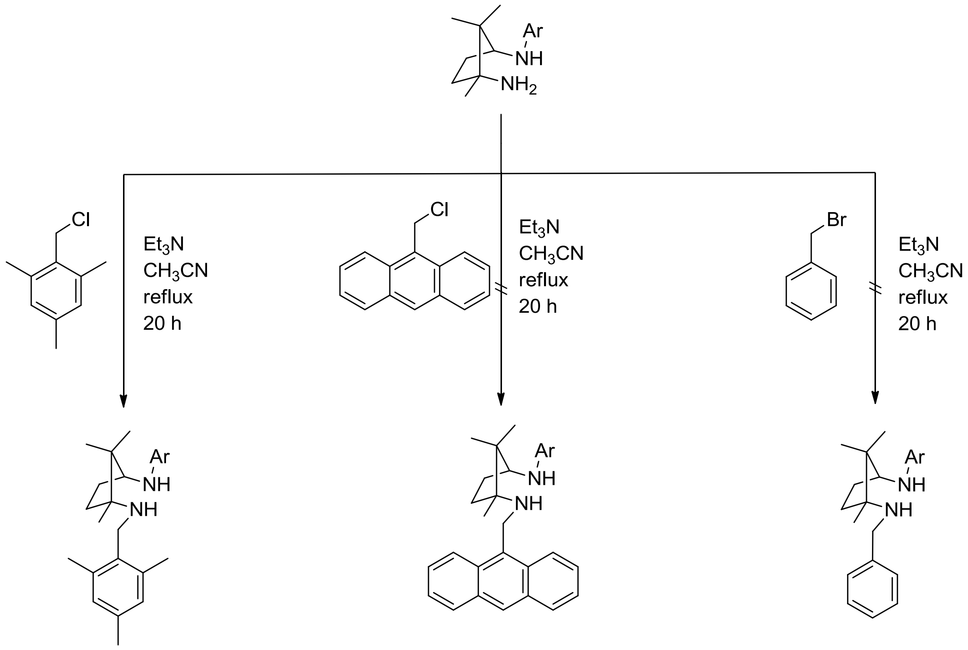


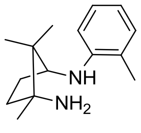
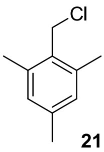
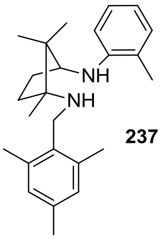
Figure 22.

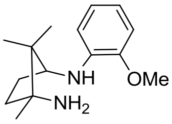
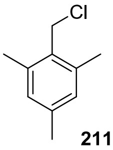
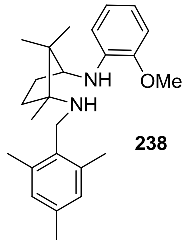
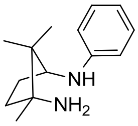
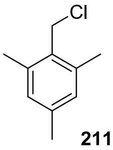
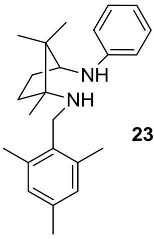
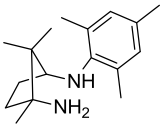
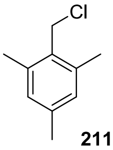
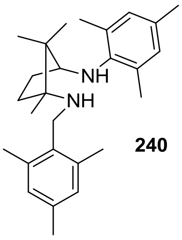
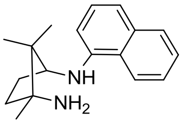
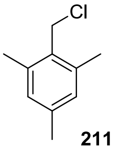
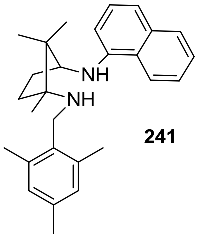
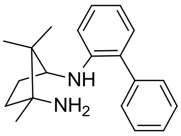
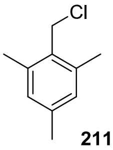
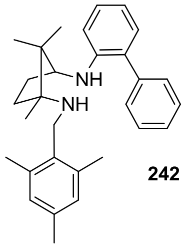
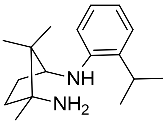
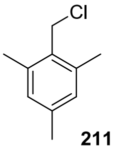
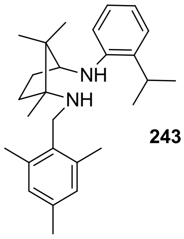
2.1.4. Alkylation of Monosubtituted Diamines

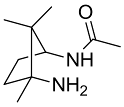
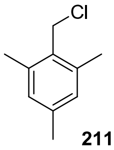
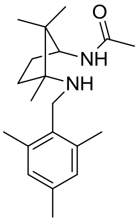
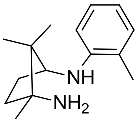
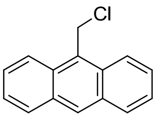
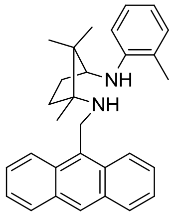
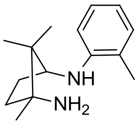
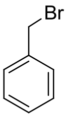
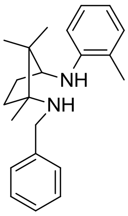
A series of enantiopure secondary diamines with two different substituted nitrogen atoms were synthesized *via* an alkylation of monosubstituted diamine by aryl halides such as mesitylmethylene chloride **211**,[155] 9-(chloromethyl)anthracene **234** or benzyl bromide **235** in the presence of the triethylamine in acetonitrile under reflux. The corresponding results are summarized in Table 2.

Tabele 2. Alkylation Reaction of Monosubstituted Diamines.



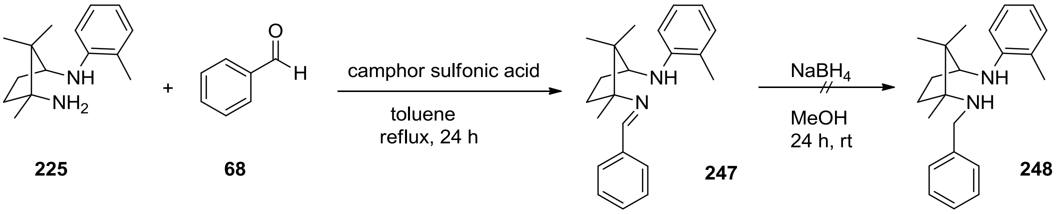
Entry	Arene	Alkyl halide	Product	Yield [%]
1	 **225**	 **211**	 **237**	64

2	 **226**	 **211**	 **238**	71
3	 **227**	 **211**	 **239**	62
4	 **228**	 **211**	 **240**	61
5	 **229**	 **211**	 **241**	54
6	 **230**	 **211**	 **242**	57
7	 **231**	 **211**	 **243**	51

8	 **236**	 **211**	 **244**	57
9	 **225**	 **234**	 **245**	0
10	 **225**	 **235**	 **246**	0

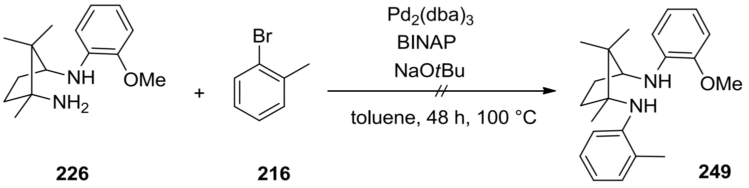
The results are summarized in Table 2 and present those products with mesitylmethylene chloride **211** and diamines **225-231** or acetylated diamine **236** gave yields between 50-70 %. The TLC plate and NMR spectra of the crude products showed that starting material did not react completely despite the lengthening of the reaction time to 48 hours. An attempt was made for secondary diamines by alkylation of monosubstituted diamine **225** with 9-(chloromethyl)anthracene **224** (Table 2, Entry 9) and benzyl bromide **235** (Table 2, Entry 10), but expected products were not isolated.

Additionally, the secondary diamine formations **248** was attempted to be performed in two steps. First benzaldehyde **68** and monosubstituted diamine **225** were refluxed in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid, followed by the reduction of product **247** in methanol (Scheme 42). No product was achieved.



Scheme 42.

Furthemore, the preparation of secondary diamine **249** was also tried by Buchwald-Hartwig amination. Enantiopure diamines with a secondary amine function was prepared *via* a monoalkylation reaction by treating the diamine **226** with an aryl halide **216** in the presence of $Pd_2(dba)_3$, BINAP and NaO*t*Bu (Scheme 43). No product was obtained.



Scheme 43.

2.2. Application of Primary and Secondary Diamines to the Henry Reaction

2.2.1. Nitroaldol Henry Reaction

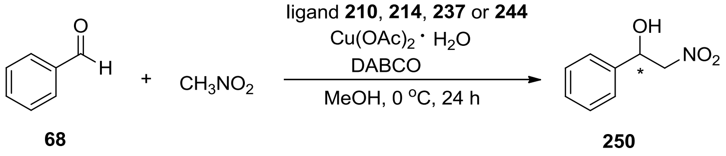
The addition reaction between a nitroalkane and a carbonyl compound in the presence of a chiral metal complex and addivites, was discovered by Louis Henry in 1895.[156,157] The asymmetric Henry or nitroaldol reaction is one of the most useful methods for the formation of C-C bonds in organic synthesis.[158] The nitroaldol reaction provides an easy access to chiral *β*-nitroalcohols, which can be converted into chiral buildings blocks, such as 1,2-aminoalcohols, *α*-hydroxy acids, 1,2-diamines and other precursors of biologically active compounds.[157,159,160]

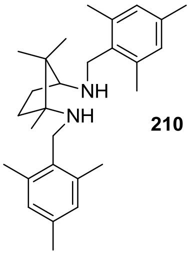
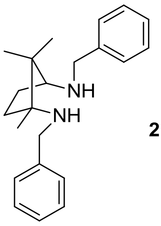
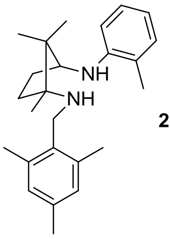
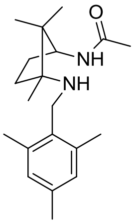
The Henry reaction has found huge applications in synthesis of natural products, polyaminoalcohols, polihydroxylated amides and especially in pharmaceutical industries,[161] for example: HIV protease inhibitors, antifungal or antibacterial peptides and *α*/*β*-adrenergic agonists or antagonists.[162] Even though the applications are very important, the asymmetric nitroaldol reaction was unknown to the world until 1992, when Shibasaki *et al.* reported the first example of a highly asymmetric addition of nitroalkene and aldehyde catalyzed by a bimetallic complex of lanthanum(III), lithium and 1,1'-bi-2-naphthol (BINOL).[157,163] Also Trost and *co*-workers discovered new chiral dinuclear zinc semi-aza-crown complexes, which are found to be successful catalysts for inducing high enantioselectivity in the addition of nitromethane to various aldehydes.[164]

Since this time, many chiral metal complexes have been developed for nitroaldol reactions, for example copper complexes (Jørgensen *et al.*),[157] which have low-toxicity and perfect chelating properties.[165] Among the ligands which have been used in Cu(II)-catalyzed asymmetric Henry reaction are *N*,*N*-donor ligands, such as *bis*-oxazolines, *bis*-pyridines, *bis*-imine, and chiral diamines.[165,166] Also many other efficient metal-based catalysts like Zn triflate-chiral amino alcohol complexes[167] or salen-cobalt complexes[168] have found applications for this reaction.[164]

In the present work the potential of various diamine ligands was explored in the copper-catalyzed asymmetric Henry reaction. First, 10 mol% secondary ligand (**210**, **214**, **237**, **244**) with 10 mol% $Cu(OAc)_2 \cdot H_2O$ was applied as a catalyst by using benzaldehyde **68** and 10 equiv. of nitromethane in the presence of 3 mol% DABCO **252** as a base in methanol at 0 °C. The results are summarized in Table 3.

Table 3. The Nitroaldol Reaction with Secondary Diamine Ligands.

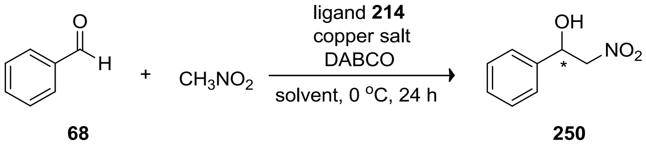


Entry	Ligand	Yield [%]	*ee* [%]	Config.
1	 **210**	26	11	*R*
2	 **214**	57	7	*R*
3	 **237**	4	*Rac*	–
4	 **244**	3	*Rac*	–

From Table 3 it can be concluded that the best results were obtained with ligand **214** (Table 3, Entry 2), which resulted 57% yield and 7% *ee*. Ligand **210** (Table 3, Entry 1) increased the enantioselectivity up to 11% but the yield decreased. In the other two cases the products were obtained as racemates.

Due to the best result which gave ligand **214**, a series of experiments were prepared in order to further optimize the reaction conditions with various influences like impact of copper salts, bases, solvents and temperature. The results are summarized in Table 4.

Table 4. Henry Reaction with Ligand 214 under Different Reaction Conditions.



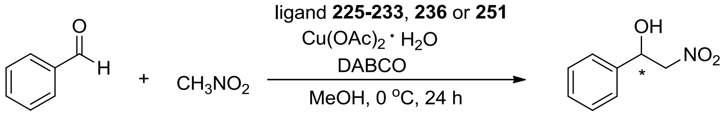
Entry	Solvent	Copper Salt	T [°C]	Yield [%]	*ee* [%]
1	MeOH	$Cu(OAc)_2{\cdot}H_2O$	0	57	7
2	EtOH	$Cu(OAc)_2{\cdot}H_2O$	0	57	6
3	*i*-PrOH	$Cu(OAc)_2{\cdot}H_2O$	0	45	7
4[a]	MeOH	$Cu(OAc)_2{\cdot}H_2O$	0	55	*rac*
5	MeOH	$Cu(OAc)_2{\cdot}H_2O$	rt	77	3
6	MeOH	CuCl	0	74	6
7	MeOH	$CuCl_2$	0	50	4
8	MeOH	$Cu(OTf)_2$	0	0	–
9	EtOH	$Cu(OTf)_2$	0	4	2
10	*i*-PrOH	$Cu(OTf)_2$	0	0	–
11	THF	$Cu(OTf)_2$	0	0	–

[a] 3 mol% Et_3N

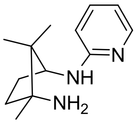
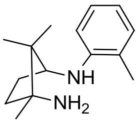
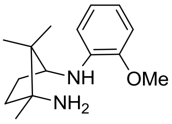
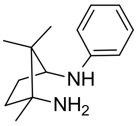
From Table 4 can be concluded that changing the solvent did not increased the yield and enantioselectivity either. Different copper salts were also investigated. Copper(I) chloride (Table 4, Entry 6) and copper(II) chloride (Table 4, Entry 7) gave yields around 50-70% but no improvement in *ee* was observed, while copper trifluoromethansulfonate (Table 4, Entries 8-11) decreased the yields to 0%. Additionally at room temperature (Table 4, Entry 5) a yield of 77% was obtained.

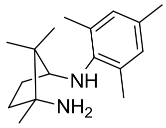
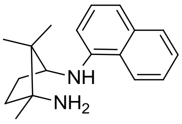
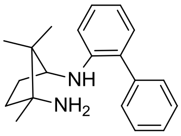
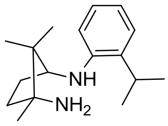
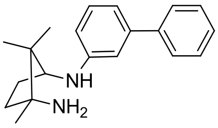
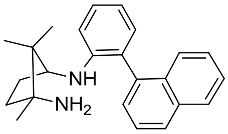
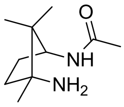
Following the general procedure, different diamine ligands were applied under the same conditions. A complex formed with 10 mol% ligand (**225-233** and **236** or **251**) and 10 mol% $Cu(OAc)_2 \cdot H_2O$ was estimated as a catalyst by using benzaldehyde **68** as a model substrate and 10 equiv. of nitromethane as reagent in the presence of 3 mol% DABCO **252** as a base in methanol at 0 °C. The results are summarized in Table 5.

Tabele 5. Henry Reaction with the Monosubstituted Diamine Ligands.



68 **250**

Entry	Ligand	Yield [%]	*ee* [%]	Config.
1	 **251**	18	4	*S*
2	 **225**	82	45	*S*
3	 **226**	60	38	*S*
4	 **227**	78	31	*S*

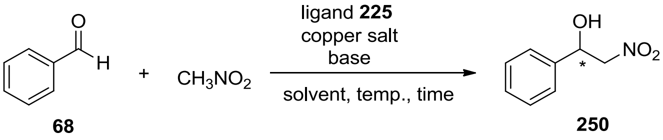
5	 **228**	34	47	*S*
6	 **229**	41	37	*S*
7	 **230**	56	69	*S*
8	 **231**	64	45	*S*
9	 **232**	32	30	*S*
10	 **233**	84	48	*S*
11	 **236**	6	*Rac*	-

The highest *ee* of 69% gave ligand **230** (Table 5, Entry 7), while the best yield of 82% was obtained with ligand **225** (Table 5, Entry 2). On the other hand, diamine **251** with heteroaromatic substituent was also tested. The ligand **251** (Table 5, Entry 1) resulted 18% yield and 4% *ee*. Acetylated diamine **236** (Table 5, Entry 11) obtained the nitroaldol product as a racemate with 6% yield. It is a significant fact that in general a sterically demanding substituent at one *ortho* position of the arene ring increases the enantiomeric excess. On the other hand, if an arene substituent is too large, the yield reduces.

Diamines with a primary amine group afford the *S* enantiomer with good results, while diamines with two secondary amine functions provided the *R* enantiomer, although in low enantioselectivities.

A series of experiments were performed in order to further optimize the reaction conditions with ligand **225** with various influences of copper salts, bases, solvents, reaction time and temperature. The results are summarized in Table 6.

Tabele 6. The Nitroaldol Reaction with Ligand 225 under Different Reaction Conditions.



Entry	Solvent	Copper Salt	T [°C]	Yield [%]	*ee* [%]
1	MeOH	$Cu(OAc)_2 \cdot H_2O$	0	82	45
2	EtOH	$Cu(OAc)_2 \cdot H_2O$	0	53	49
3	*i*PrOH	$Cu(OAc)_2 \cdot H_2O$	0	47	46
4	MeOH	CuCl	0	65	34
5[a]	MeOH	$Cu(OAc)_2 \cdot H_2O$	0	69	47
6[b]	MeOH	$Cu(OAc)_2 \cdot H_2O$	0	75	41
7[c]	MeOH	$Cu(OAc)_2 \cdot H_2O$	0	60	47
8	MeOH	-	0	68	*rac*
9	MeOH	$Cu(OAc)_2 \cdot H_2O$	rt	63	38

10	MeOH	-	0	59	*rac*
11	MeOH	$Cu(OAc)_2{\cdot}H_2O$	–25	39	53
12[d]	MeOH	$Cu(OAc)_2{\cdot}H_2O$	–25	42	54
13	THF	$Cu(OAc)_2{\cdot}H_2O$	–25	11	73
14	H_2O	$Cu(OAc)_2{\cdot}H_2O$	rt	21	31
15	THF	CuCl	0	56	36
16	MeOH	$CuCl_2$	0	60	16
17	MeOH	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	0	92	52
18	THF	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	0	26	72
19	CH_2Cl_2	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	0	9	56
20	MeOH	$Cu[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2$	0	93	77
21[e]	MeOH	$Cu(OAc)_2{\cdot}H_2O$	0	69	46

---

[a] 3 mol% Et_3N

[b] 15 mol% diamine **225**

[c] $Cu(OAc)_2{\cdot}H_2O$ 15 mol%

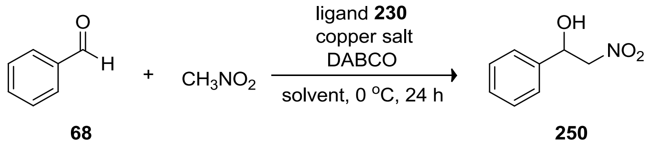
[d] Reaction time 48 h

[e] 200 equiv. $MeNO_2$

From Table 6 can be concluded that methanol is the most appropriate solvent. Two others alcohols like ethanol (Table 6, Entry 2) and *iso*-propanol (Table 6, Entry 3) were tested, which resulted lower yields. Different copper salts were also investigated. Copper(I) chloride (Table 6, Entry 14) and copper(II) chloride (Table 6, Entry 16) gave yields around 60% but did not improve the *ee*. Longer reaction time and lower temperature did not result satisfactory yields and *ee*'s. Also water (Table 6, Entry 14) did not give better yield and *ee*. However, using THF (Table 6, Entry 13) increased significantly the *ee* but reduced the yield. Additionally, the influence of a variety of carboxylate counter-anions was examined. By comparing the results copper(II)-2-ethylhexanoate (Table 6, Entry 20) with a racemic chiral stereocenter resulted an excellent yield of 93% and enantiomeric excess of 77%, while copper(II) cyclohexanebutyrate decreased the *ee* (Table 6, Entry 17). Interestingly, the racemic stereocenter could form two diastereomeric complexes in the present case where one carboxylate ligand is replaced with the diamine ligand.

Also ligand **230** was tested under different conditions (Table 7). Nevertheless, the obtained enantioselectivities were higher and the yields decreased compared to ligand **225**.

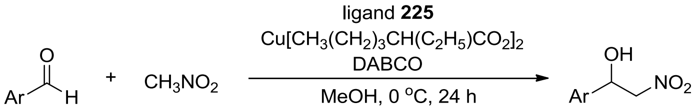
Tabele 7. The Copper Catalyzed Henry Reaction with Ligand 230 under Different Reaction Conditions.



Entry	Solvent	Copper Salt	Yield [%]	*ee* [%]
1	MeOH	$Cu(OAc)_2 \cdot H_2O$	56	69
2	THF	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	21	84
3	MeOH	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	74	72
4	CH_2Cl_2	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	5	76
5	MeOH	$Cu[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2$	59	74

Following the results obtained with ligand **225** the reactions of nitromethane with electron-rich and electron-poor benzaldehydes were investigated (Table 8).

Tabele 8. The Nitroaldol Reaction with Various Aldehydes.

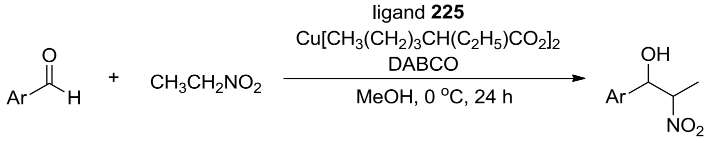


Entry	**Ar**	**T [°C]**	**Product**	**Yield [%]**	***ee* [%]**
1	Ph	0	**250**	93	77
2	3-Cl-C_6H_4	0	**253**	65	63
3	2-NO_2-C_6H_4	0	**254**	68	82
4	3-NO_2-C_6H_4	0	**255**	57	59
5	2-MeO-C_6H_4	0	**256**	65	83

It can be seen from the table that aldehydes in the *ortho* position are obtaining the best enantiomeric excess in up to 83% (Table 8, Entry 5) but unfortunately the yield is reduced.

Ultimately, the electronic effect on benzaldehyde with nitroethane was then explored. The results are summarized in Table 9.

Tabele 9. The Henry Reaction with Nitroethane and Various Aldehydes.



Entry	Ar	T [°C]	Product	Yield [%]	*ee* [%] *syn/anti*	*dr* *syn/anti*
1	Ph	0	**257**	41	58/27	28/72
2	2-NO_2-C_6H_4	0	**258**	73	57/53	62/38
3	2-MeO-C_6H_4	0	**259**	30	63/39	47/53

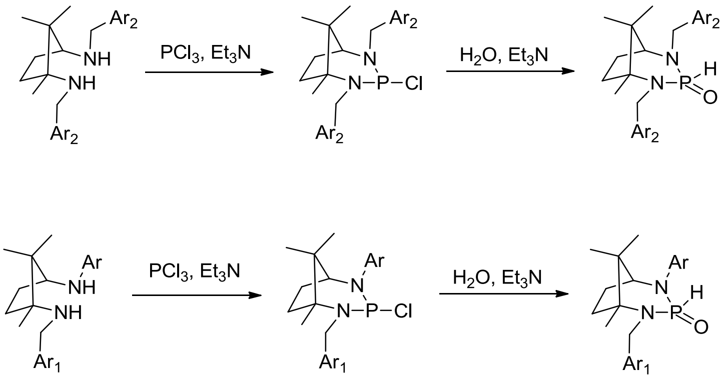
The resulting *syn*/*anti* selectivities of diastereoisomers were determined by ^{1}H-NMR. Benzaldehyde obtained the product **257** with nitroethanol in 41% yield and 58% *ee* of *syn* diastereomer and 27% *ee* of *anti* diastereomer (Table 9, Entry 1). By comparing the results between *ortho*-nitrobenzaldehyde (Table 9, Entry 2) and *ortho*-methoxybenzaldehyde (Table 9, Entry 3), the first one provided significantly higher yield 73% with 57% *ee* of *syn* diastereomer and 53% *ee* of *anti* diastereomer than the second aldehyde.

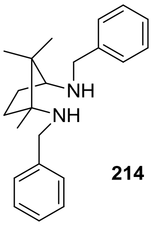
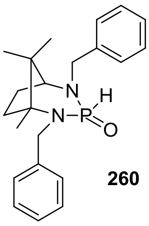
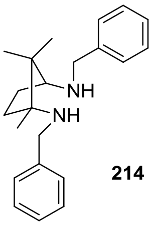
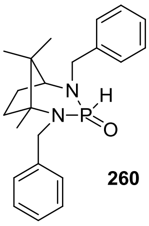
2.3. Cyclization of Diamines with Phosphorus Trichloride

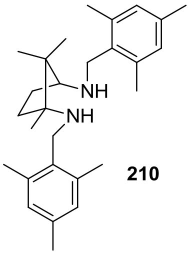
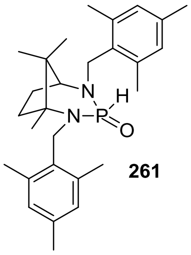
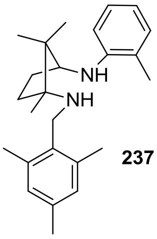
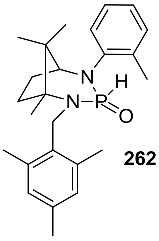
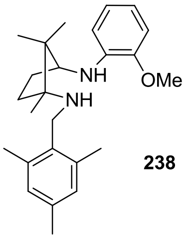
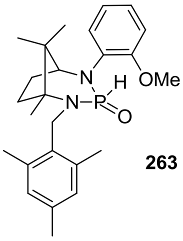
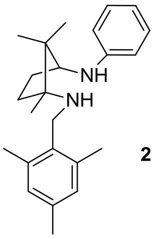
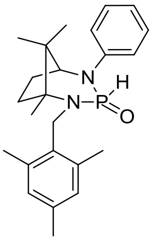
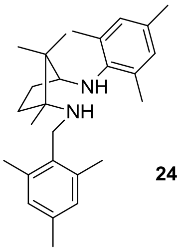
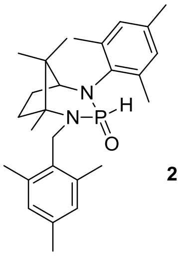
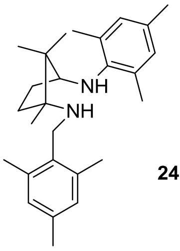
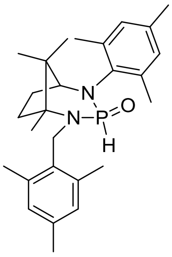
Heteroatom-substituted phosphine oxides are simply accessible from diamines.[169] A new class of chiral HASPO (heteroatom-substituted secondary phosphine oxide) ligands[155,170] for transition-metal-catalyzed reactions was prepared in two steps from the new diamines, by treating the secondary diamine with PCl_3 and Et_3N at –60 °C. The temperature was slowly raised to room temperature in toluene. After filtration through

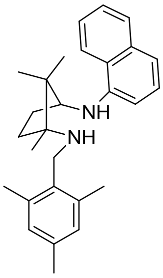
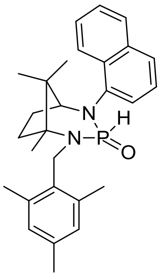
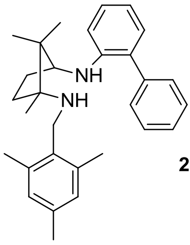
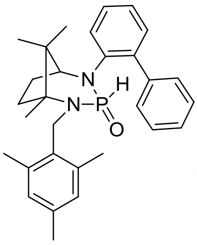
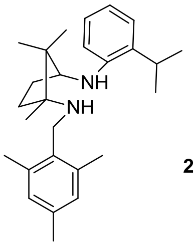
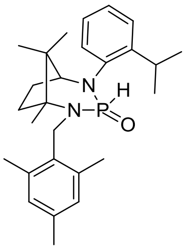
$MgSO_4$, the heterocyclic chloride derivative was obtained. In the second step, H_2O and Et_3N were added to the chloride derivative at –60 °C. The temperature was slowly raised to room temperature in toluene. After filtration through $MgSO_4$ the desire product was obtained.[96,77] The presence of Et_3N as a base was required because of the formation of HCl.[102] The desired products were characterized by mass spectrometry and multinuclear NMR spectroscopy. ^{31}P-NMR chemical shifts were respectively in the same range as those reported for analogous ligands.[96,97] The results with selected ^{31}P-NMR data are shown in Table 10.

Table 10. Heteroatom-Substituted Phosphines.



Entry	Diamine	Product	Yield [%]	^{31}P, δ [ppm]
1	 **214**	 **260**	94	10.1
2*	 **214**	 **260**	85	10.1

3	 **210**	 **261**	73	9.6
4	 **237**	 **262**	89	3.9
5	 **238**	 **263**	97	3.9
6	 **239**	 **264**	89	3.9
7	 **240**	 **265a**	37	1.9
8	 **240**	 **265b**	15	–4.2

9	 **241**	 **266**	85	4.9
10	 **242**	 **267**	97	5.4
11	 **243**	 **268**	86	5.4

From Table 10 it is possible to conclude that excellent yields can be obtained. The products were obtained as one diastereoisomer. It is remarkable that the reactions carried out on a larger scale gave cleaner desired products which did not need any purification. Only one product obtained from diamine **240** was achieved as two diatereoisomers **265a** (Table 10, Entry 7) and **265b** (Table 10, Entry 8) which were separated by column chromatography (Figure 23). The reason of the formation of two diastereoisomers can be due to the structure of the corresponding ligand, which is steric hinderance. Followed by the Ackerman suggestion,[169] the HASPO ligand **260** was also prepared in CH_2Cl_2 but the yield was lower than in toluene.

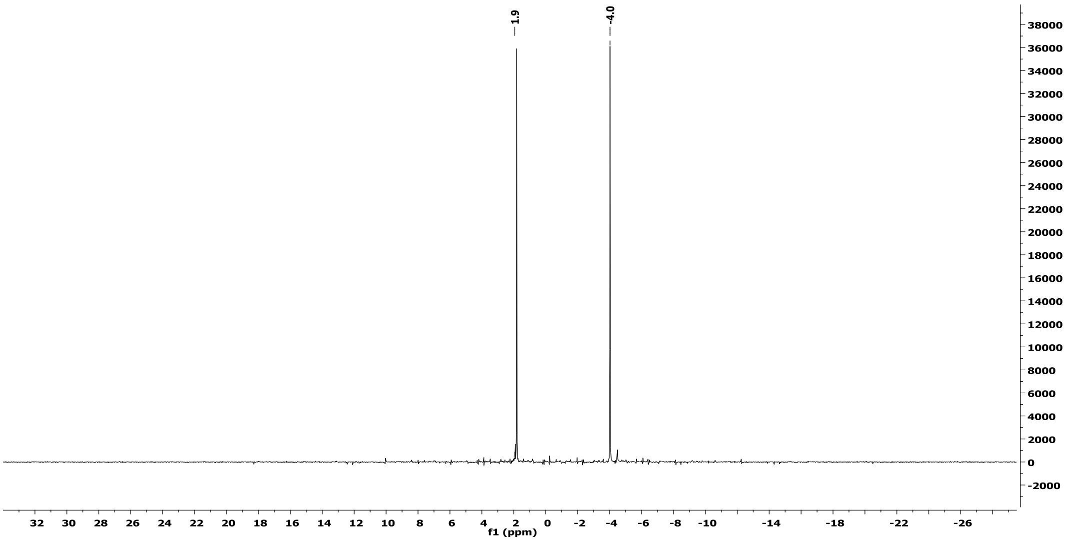
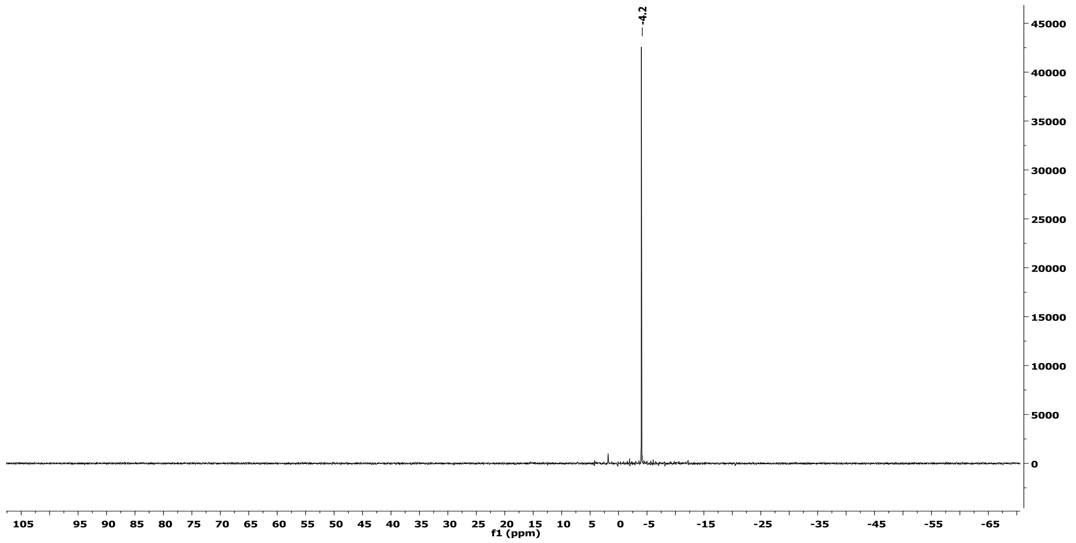


Figure 23.

The absolute configuration of the HASPO ligands was established by NOESY-NMR spectra. It can be assume that the HASPO ligands containing the same substituent on the nitrogen atoms have *S* configuration on the phosphorus atom while ligands with two different substituents on the nitrogen atoms show *R* configuration on the phosphorus atom.[171]

Furthermore, ^{31}P-NMR resonances for the HAPSO ligands were in the range of δ = 1.9-10 ppm whereas, the ligand (*S*)-**265** appeared at δ = –4.2 ppm (Figure 24). Additionally, the ^{1}H-NMR spectra of the HASPO ligands present some interesting characteristics. The proton attached to the phosphorus appeared as a characteristic doublet with a coupling between $J_{P\text{-}H}$ = 617.0-649.9 Hz. Additionally, NOESY-NMR studies revealed that the P-H bond in the ligands is on the same side as the Me_2C bridge (Figure 25). The exception is with one of the two diastereoisomers **265**. In this case the P-H bond of ligand **265b** is on the other side as the Me_2C bridge (Figure 26).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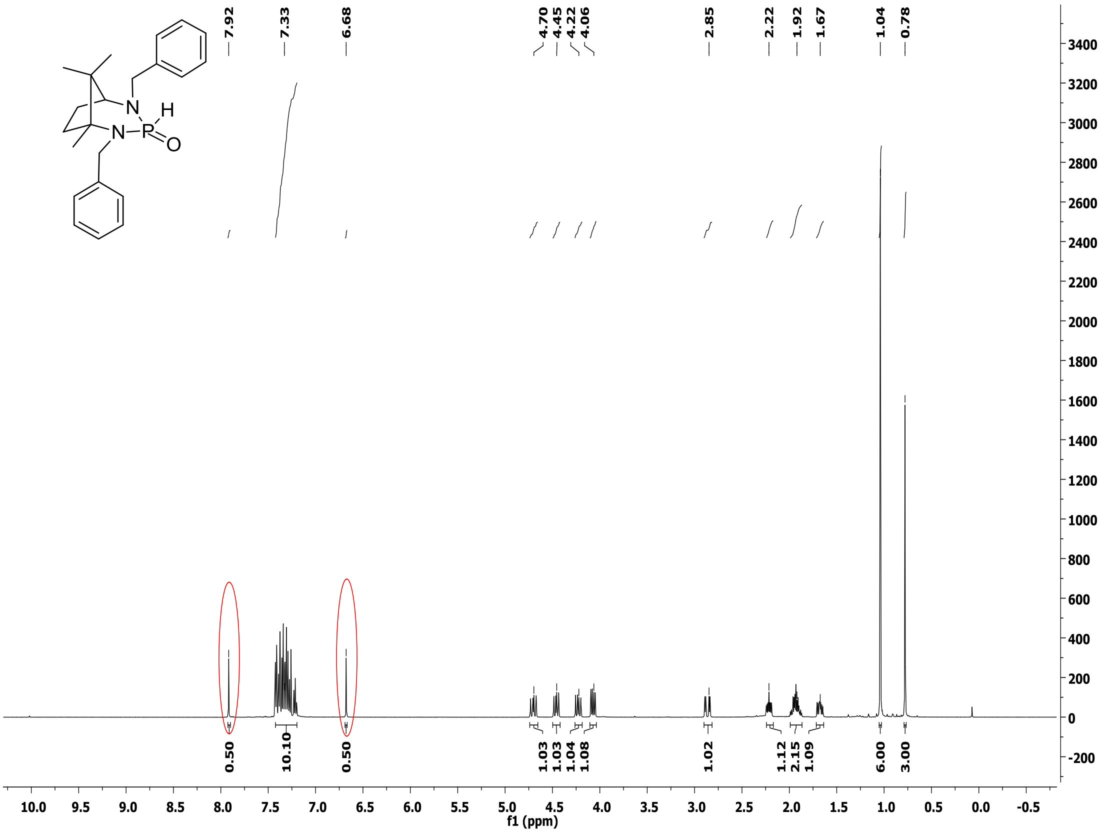
40000
35000
30000
25000
20000
15000
10000
5000
0
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-15
-25
-35
-45
-55
-65
f1 (ppm)

Figure 24.


N
H
N
P
O
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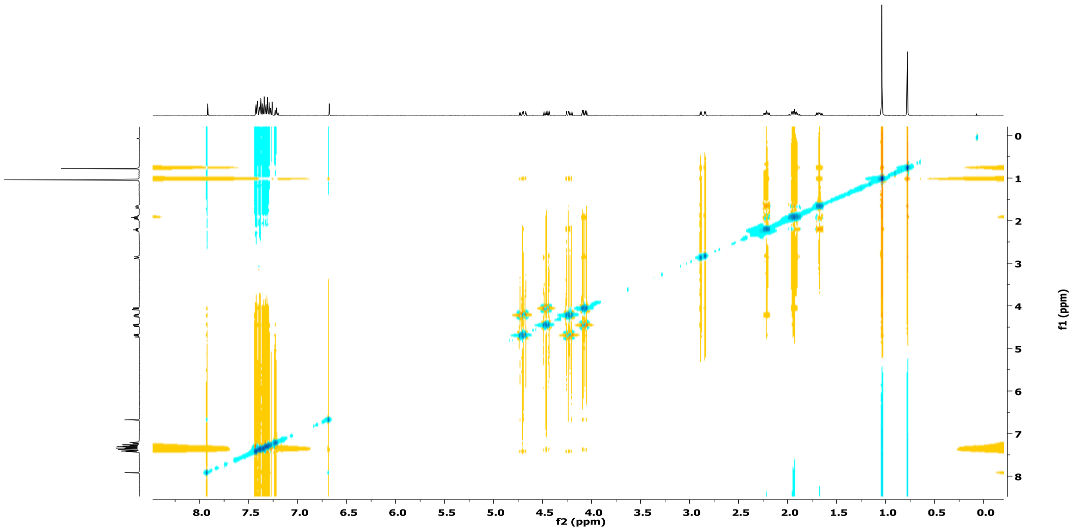
4.70
4.45
4.22
4.06
2.85
2.22
1.92
1.67
1.04
0.78
0.50
10.10
0.50
1.03
1.03
1.04
1.08
1.02
1.12
2.15
1.09
6.00
3.00
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


f2 (ppm)
f1 (ppm)
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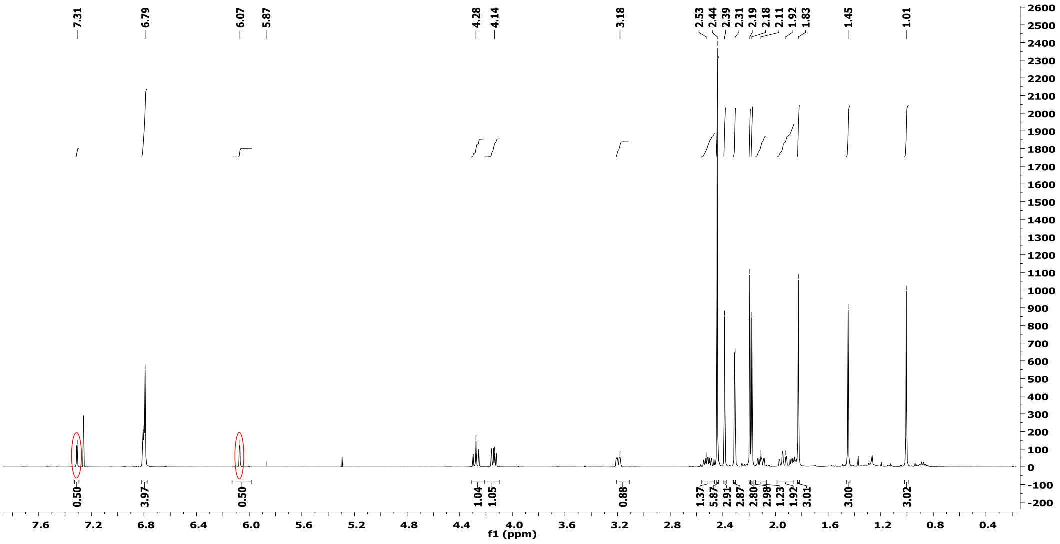
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

Figure 25.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6.79
6.07
5.87
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4.14
3.18
2.53
2.44
2.39
2.31
2.19
2.18
2.11
1.92
1.83
1.45
1.01
0.50
3.97
0.50
1.04
1.05
0.88
1.37
5.87
2.91
2.87
2.80
2.98
1.23
1.92
3.01
3.00
3.02
f1 (ppm)

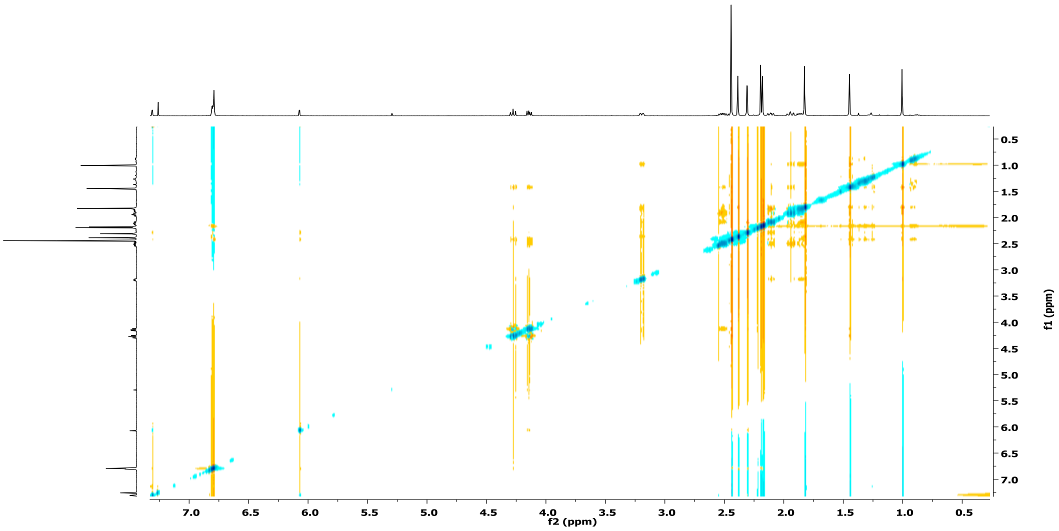
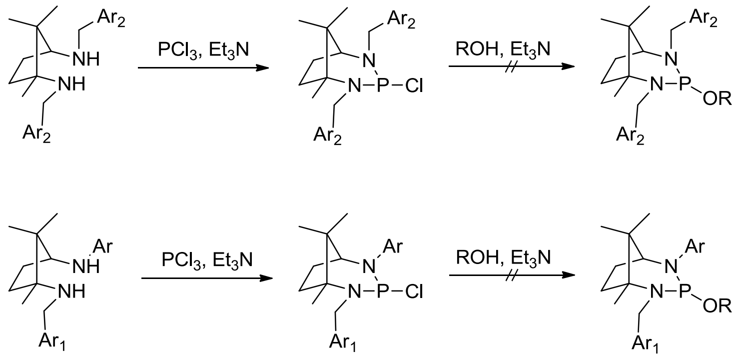
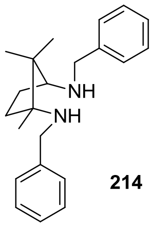
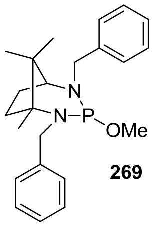
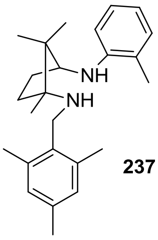
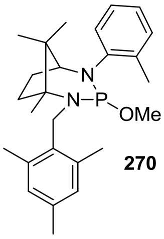
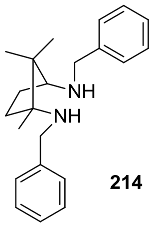
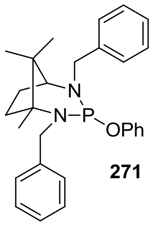
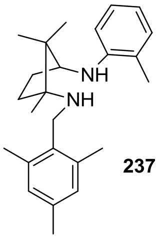
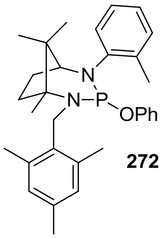


Figure 26.

The preparation of trivalent phosphorus compounds was also tested. Unfortunately, subsequent treatment of chlorodiaminophosphites with sodium methanolate, sodium phenoxide or commercially available alcohols such as methanol and phenol did not result the corresponding products (Table 11). Probably the products were not stable because of their sensitivity to oxygen and moisture.[172]

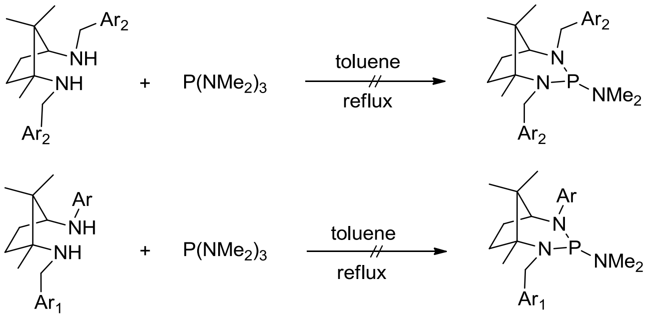
Table 11. The Preparation of Trivalent Phosphorus Compounds.

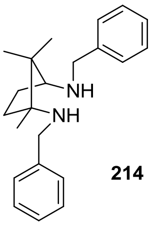
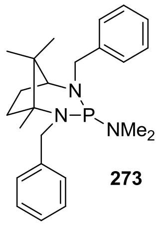
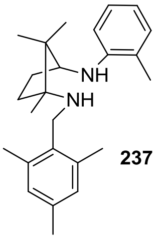
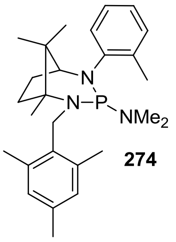


Entry	Diamine	ROX	Product	Yield [%]
1	 **214**	MeOH	 **269**	0
2		NaOMe		0
3	 **237**	MeOH	 **270**	0
4		NaOMe		0
5	 **214**	PhOH	 **271**	0
6		NaOPh		0
7	 **237**	PhOH	 **272**	0
8		NaOPh		0

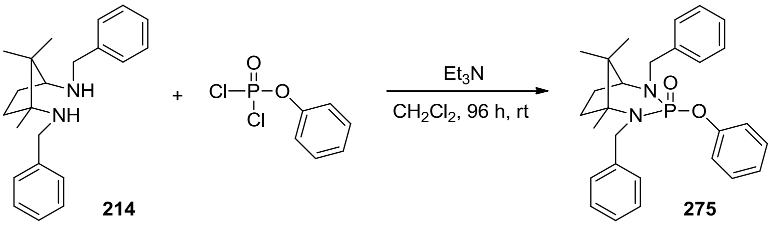
Moreover, it was attempted to prepare trivalent phosphorus derivatives from hexamethylphosphorus triamide and chiral diamines.[109,173,174] Although the reactions were carried out under reflux for 5 days, no product was achieved (Table 12).[170]

Table 12. The Preparation of Trivalent Phosphorus Compounds from Hexamethylphosphorus Triamide.



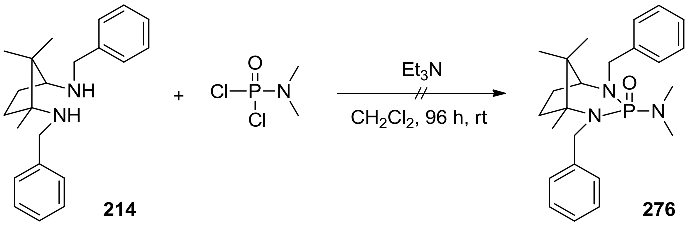
Entry	Diamine	Product	Yield [%]
1	 **214**	 **273**	0
2	 **237**	 **274**	0

On the other hand, another group of organophosphorus compounds was synthesized. The product **275** was obtained as a pair of diastereomers from secondary diamine **214** with *o*-phenyl phosphorodichloridate in the presence of Et_3N in CH_2Cl_2 (Scheme 44). The two diastereomers were separated by column chromatography resulted compound **275a** in 27% yield and compound **275b** in 43% yield. The absolute configuration of the P*-stereocentre in the structure of **275** diastereomers were compared with the literature.[175-177]



Scheme 44.

Also *N*,*N*-dimethylphosphoramic dichloride was tested with diamine **214** in the presence of Et$_3$N in CH$_2$Cl$_2$ (Scheme 45). No product was achieved.



Scheme 45.

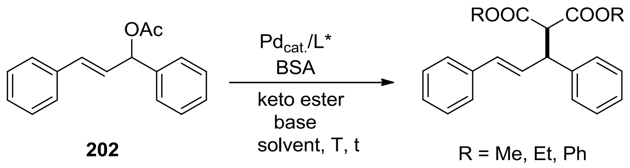
2.4. Metal-Catalyzed Asymmetric Transformations

2.4.1. Pd-Catalyzed Asymmetric Allylic Substitution Reactions Using Carbon Nucleophiles

2.4.1.1. Asymmetric Allylic Alkylation of 1,3-Diphenylallyl Acetate

Recently, special attention has been devoted to studies included the investigation of the chiral ligands with a stereogenic center on the phosphorus atom, followed by the formation of an effective asymmetric environment around a central metal.[94]

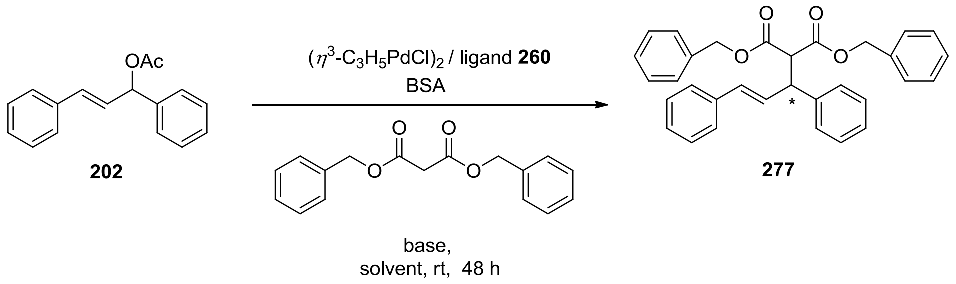
Thus, chiral HASPO ligands were applied to some important type of reactions. First the asymmetric allylic alkylation was investigated. The Pd-catalyzed asymmetric allylic alkylation of (*E*)-1,3-diphenylallyl acetate **202** with the stabilized carbanion derived from keto ester in the presence of *N*,*O*-*bis*(trimethylsilyl)acetamide (BSA) is one of the most important benchmark-systems to examine the ability of novel chiral ligands (Scheme 46).[144]



Scheme 46.

First, the HASPO ligand **258** with the same substituent on both nitrogen atoms and dibenzyl malonate with (*E*)-1,3-diphenylallyl acetate **202** were tested in the presence of BSA and an additive (Table 13).

Table 13. Asymmetric Allylic Alkylation of 1,3-Diphenylallyl Acetate with Dibenzyl Malonate.



Entry	Additive	Solvent	Yield [%]
1	$Zn(OAc)_2$	Toluene	0
2[a]	NaOAc	Toluene	0
3[b]	NaH	Toluene	0
3	KOAc	Toluene	4
4	KOAc	THF	0

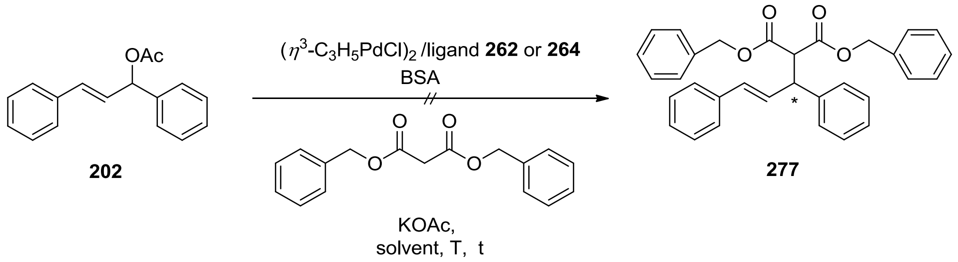
[a] After 24 h $AgBF_4$ was added and the reaction was carried out further 24h

[b] Without BSA and KOAc

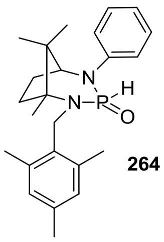
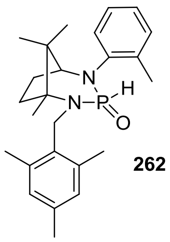
From the Table 13 it can be concluded that the influence of different additives such as NaOAc, KOAc, $Zn(OAc)_2$ was tested. The potassium salts are obviously better than sodium salts, and sodium salts are stronger bases than zinc salts. Additionally, no reaction occurs when a strong base such as sodium hydride (Table 13, Entry 2) was used. The desired product did not give satisfactory results. The product **277** was obtained in the presence of KOAc below 5% yield (Table 13, Entry 3). In other cases the product was not achieved. Moreover, using THF did not give the product (Table 13, Entry 4).

The same reaction was investigated with HASPO ligands **262** or **264** containing in the structure two different substituted nitrogen atoms. Following the best result from the table above KOAc was applied as an additive. During the reaction different conditions were optimized which are presented in Table 14. No yield was obtained.

Table 14. Asymmetric Allylic Alkylation of 1,3-Diphenylallyl Acetate with Dibenzyl Malonate under Different Reaction Conditions.



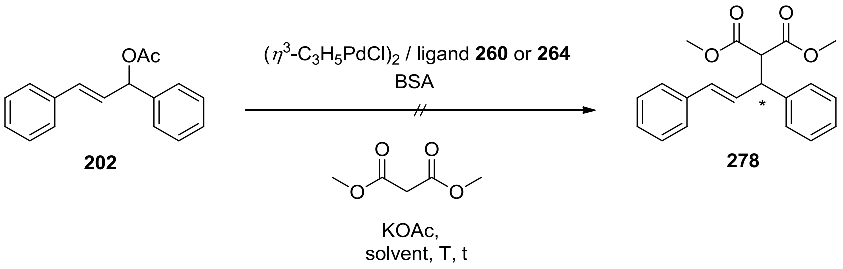
202 **277**

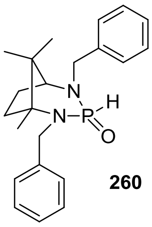
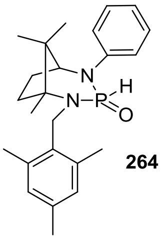
Entry	Ligand	Solvent	T [°C]	t [h]	Yield
1	 **264**	Toluene	rt	48	0
2			40	24	
3			100	24	
4[a]	 **262**	Toluene	rt	120	0
5[b]		Toluene	rt	120	0
6[c]		Toluene	rt	48	0
7		CH_3CN	rt	48	0

[a] After 96 h 0.1 equiv. of pyridine was added
[b] After 96 h 0.1 equiv. of Et_3N was added
[c] 0.1 equiv. of Pd cat. was used

Subsequently, the novel HASPO ligands **260** or **264** were also applied to the original reaction between (*E*)-1,3-diphenylallyl acetate **202** and dimethyl malonate as the *C*-nucleophile.[171] As seen from Table 15, similar to the reaction of 1,3-Diphenylallyl acetate with dibenzyl malonate no product was observed.

Table 15. Asymmetric Allylic Alkylation of 1,3-Diphenylallyl Acetate with Dimethyl Malonate.

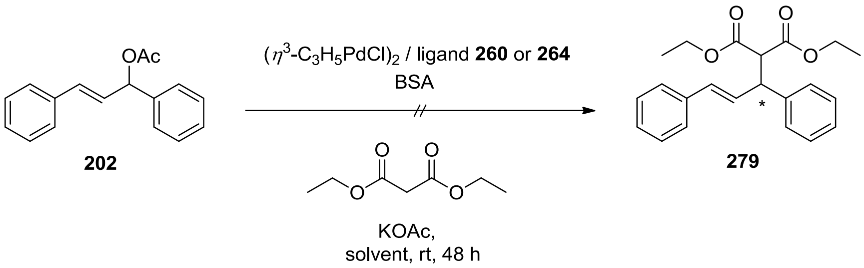


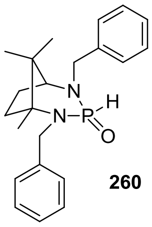
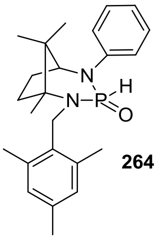
Entry	Ligand	Solvent	T [^oC]	t [h]	Yield [%]
1	 260	Toluene	rt	48	0
2		THF	rt	48	0
3	 264	Toluene	rt → 40	40 → 24	0
4[a]		CH_2Cl_2	rt	48	0

[a] Instead of $Pd_{cat.}$, $Ir_{cat.}$ was used and $NaPF_6$ was added

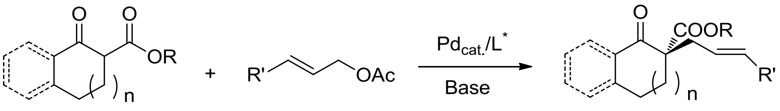
Consequently, analogous reactions were performed with diethyl malonate as the *C*-nucleophile. No product was achieved (Table 16).

Table 16. Asymmetric Allylic Alkylation of 1,3-Diphenylallyl Acetate with Diethyl Malonate.



Entry	Ligand	Solvent	Yield
1	 **260**	Toluene	0
2		THF	0
3	 **264**	Toluene	0

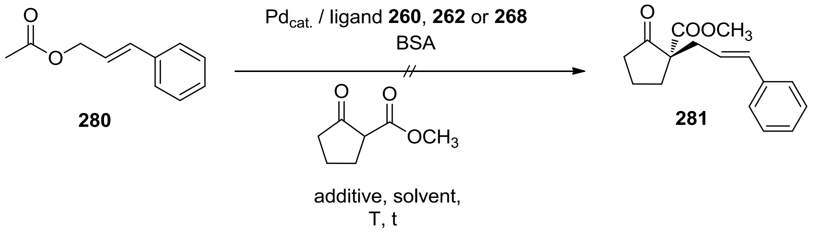
Similarly as in the substitution reaction, using the substrate with a phenyl group also HASPO ligands were investigated in the Pd-catalyzed construction of quaternary stereocenters (Scheme 47).[94]

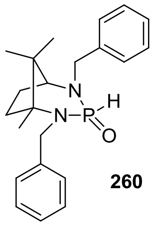


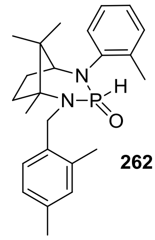
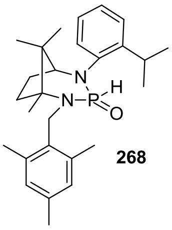
Scheme 47.

The HASPO ligands **260**, **264** or **268** and methyl 2-oxocyclopentanecarboxylate with cinnamyl acetate **280** were applied in the presence of BSA and an additive. The desired product was not achieved although the reactions were carried out under different conditions with various influences like impact of palladium catalysts, bases as additives, solvents, temperatures and reaction times. The results are presented in Table 17.

Table 17. Asymmetric Allylic Alkylation of Cinnamyl Acetate with Methyl 2-Oxocyclopentanecarboxylate.



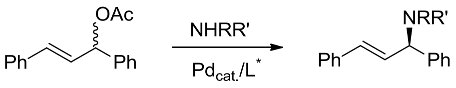
Entry	Ligand	Additive	Pd$_{cat.}$	Solvent	T [°C]	t [h]	Yield [%]
1		$Zn(OAc)_2$	$(\eta^3\text{-}C_3H_5\text{-}PdCl)_2$	Toluene	rt	20	0
2		$Zn(OAc)_2$	$(\eta^3\text{-}C_3H_5\text{-}PdCl)_2$	Toluene	40	18	0
3		$Zn(OAc)_2$	$(\eta^3\text{-}C_3H_5\text{-}PdCl)_2$	Toluene	rt	48	0
4[a]	 260	$Zn(OAc)_2$	$(\eta^3\text{-}C_3H_5\text{-}PdCl)_2$	Toluene	rt	72	0
5		NaOAc	$(\eta^3\text{-}C_3H_5\text{-}PdCl)_2$	Toluene	rt	72	0
6		$Zn(OAc)_2$	$Pd_2(dba)_3$	Toluene	rt	72	0
7		NaOAc	$Pd_2(dba)_3$	Toluene	rt	72	0
8		KOAc	$(\eta^3\text{-}C_3H_5\text{-}PdCl)_2$	CH_2Cl_2	rt	72	0

9	 **262**	$Zn(OAc)_2$	$(\eta^3\text{-}C_3H_5\text{-}PdCl)_2$	Toluene	Rt	48	0
10	 **268**	$Zn(OAc)_2$	$(\eta^3\text{-}C_3H_5\text{-}PdCl)_2$	Toluene	rt → 40	24 → 18	0

[a] Without BSA, *n*-BuLi and TMSCl were used

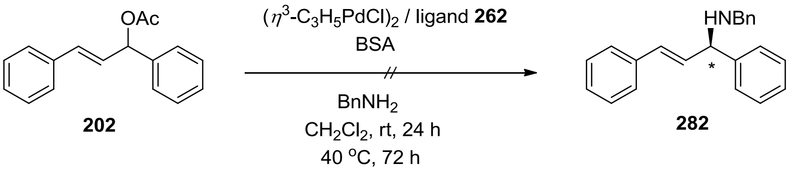
2.4.1.2. Other Nucleophiles

P-stereogenic ligands can react in Ir- or Pd-catalyzed allylic substitutions with non-carbon nucleophiles. A transition-metal-catalyzed asymmetric allylic amination is a powerful method for the formation C-N of bonds (Scheme 48).[94]



Scheme 48.

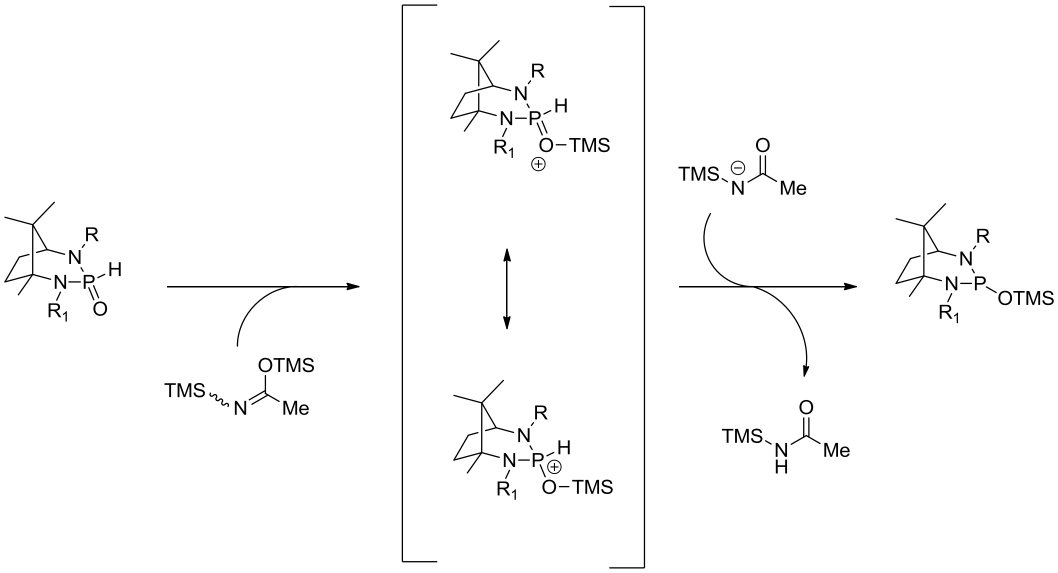
The HASPO ligand **262** and (*E*)-1,3-diphenylallyl acetate **202** with benzylamine were tested in the presence of BSA. The desired product was not observed (Scheme 49).



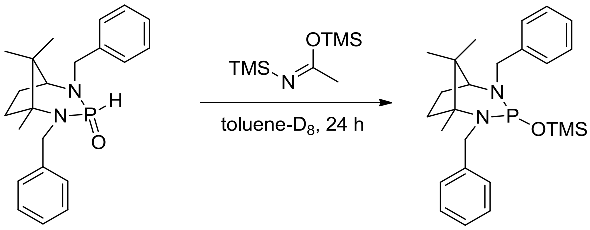
Scheme 49.

2.4.1.3. Preparation of Trivalent Phosphorus Ligands from Pentavalent Phosphorus Species

During the preliminary studies on a new series of HASPO ligands, the pentavalent phosphorus species were activated in situ by *N,O-bis*(trimethylsilyl)acetamide (BSA) to induced P(V) - P(III) tautomerization (a commonly used abbreviations for valency) to afford trivalent phosphorus compounds, which play a role as the actual ligand (Scheme 50).[131,144] The generation of a trivalent phosphorus compounds were monitored by ^{31}P-NMR spectroscopy. The principal investigation was performed with symmetric secondary P-ligand **260** and BSA in a ratio of 1:4 in toluene-D_8. The experiment was controlled at different times, however the best result was obtained after 24 h. ^{31}P-NMR showed that pentavalent ligand **260** (chemical shift: 8.1 ppm, toluene-D_8) reacted with BSA to provide the formation of a trivalent phosphorus species (chemical shift: 117.4 ppm, toluene-D_8) (Figure 27).



Scheme 50. Reaction Mechanism of BSA-Induced P(V)-P(III) Transformation of HASPO Ligand 260.



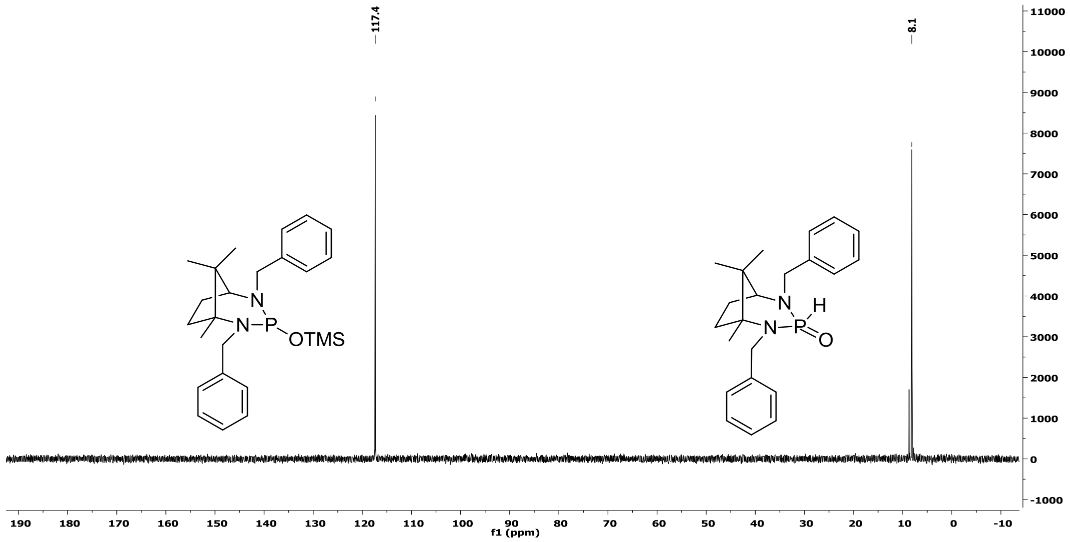
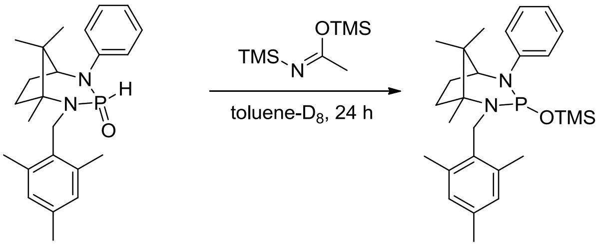


Figure 27. ^{31}P-NMR of BSA and Ligand 260 after 24 h.

Further investigation revealed that when asymmetric HASPO ligand **264**, with a chemical shift of 2.40 ppm was reacted with BSA in toluene-D$_8$, the generation of the trivalent phosphorus species, with a chemical shifted 104.9 ppm, was observed similar to the case of symmetric HASPO ligand **260** (Figure 28).



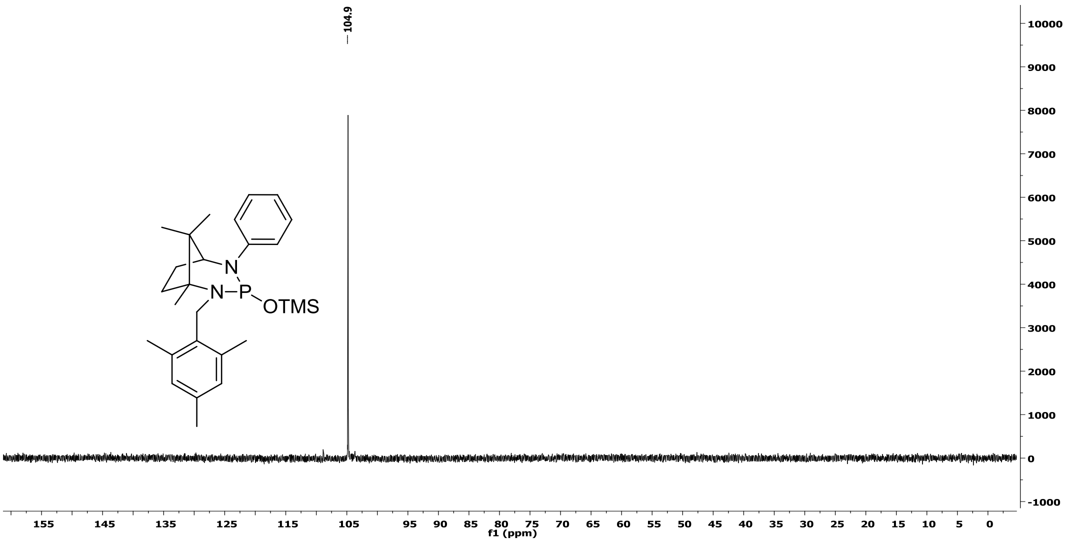
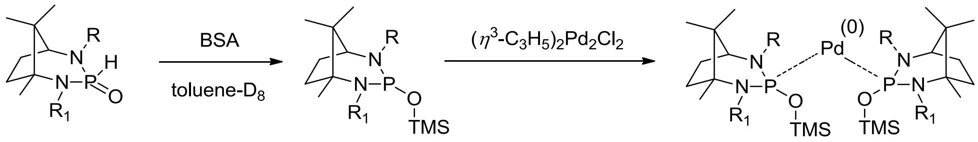


Figure 28. ^{31}P-NMR of BSA and Ligand 264 after 24 h.

2.4.1.4. Preparation of Allylic Palladium(II) Complexes with Trivalent Phosphorus Ligands

Following the Nemoto, Hamada and *co*-workers investigations, the neutral palladium complexes were prepared with the new corresponding ligand with the well known bridged chloride complex[178] (η^3-C_3H_5)$_2$$Pd_2Cl_2$ in dry toluene in a ratio: ligand : BSA : $Pd_{cat.}$ = 1:4:1. To obtain information about the formation of the Pd complex (Scheme 51), an experiment was also examined by ^{31}P-NMR.



Scheme 51. Preparation of Pd-Ligand Complex.

First the Pd-complex was achieved with trivalent phosphorus compound which contains in the structure two nitrogen atoms with the same substituents. ^{31}P-NMR suggests that complex Pd-**260** was formed, but the reagents did not react completely. The resulting

^{31}P-NMR spectra showed two sharp signals, with approximately the same ratio 1:1, from the two rotamers.[178] For the complex Pd-**260** spin system at 102.9 and 102.5 ppm appeared with Δδ= 79.3 Hz (Figure 29).

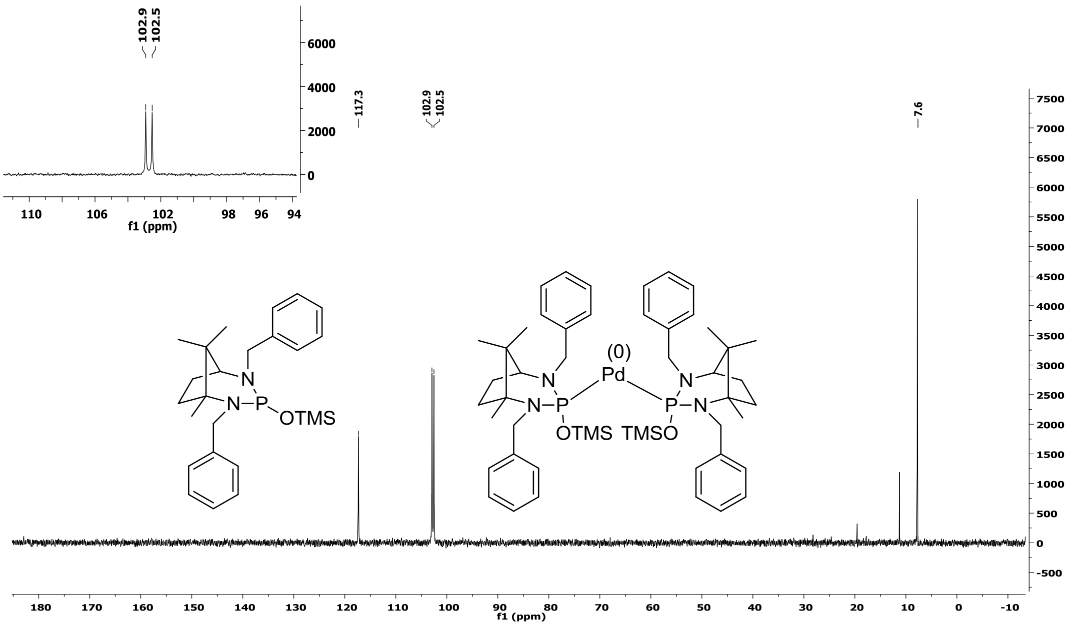


Figure 29. ^{31}P-NMR of Pd-260 Complex.

Further examination was carried out under the same conditions with asymmetric trivalent ligand **264**. ^{31}P-NMR spectra showed that change of the substituent from the ligand containing the same substituent on both nitrogen atoms to the compound which has in the structure nitrogen atoms with different substituted aryl groups has a huge influence on the formation of rotamers. In this case the asymmetric chiral trivalent ligand led to some discrimination between the two rotamers. The ratio of the desired rotamers obtained from the ^{31}P-NMR spectra was 1:2. For this complex spin system at 92.4 and 91.8 ppm appeared with Δδ= 116.7 Hz (Figure 30). Additionally, the experiment was prepared with other catalysts such as $Pd_2(dba)_3$, $Pd(OAc)_2$ and CuCl. No stable complex was achieved.

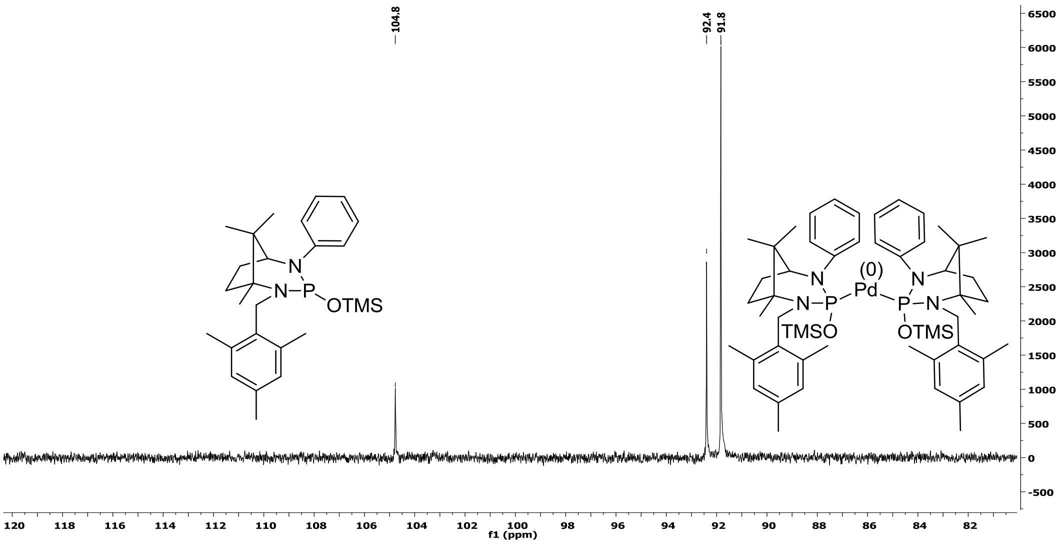
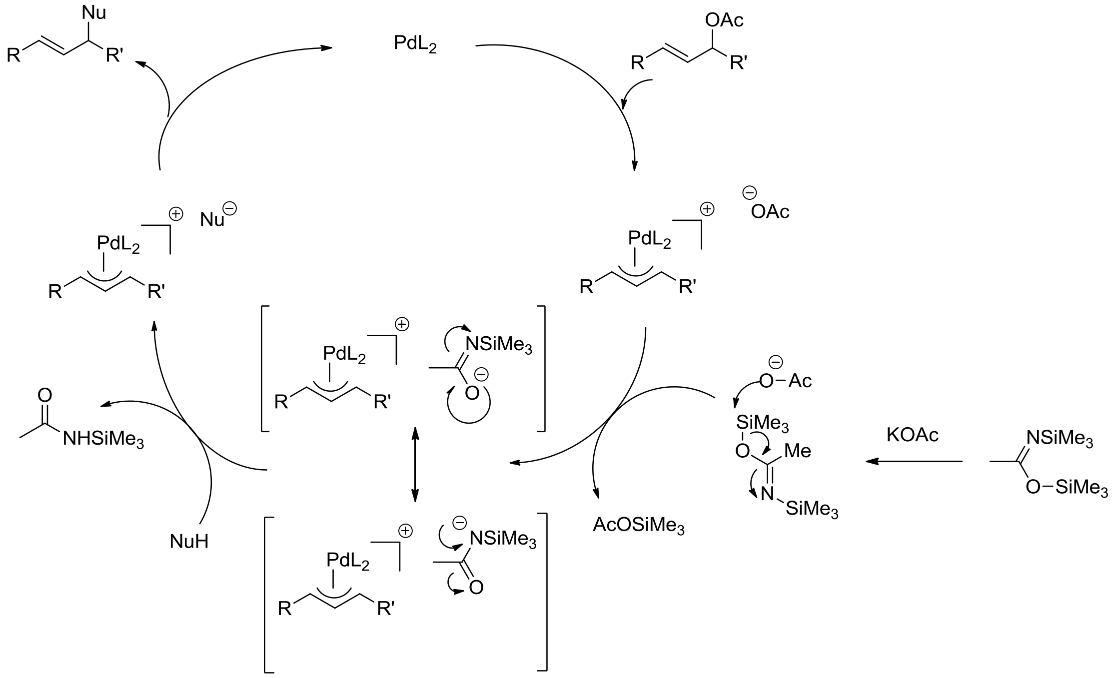


Figure 30. ^{31}P-NMR of Pd-264 Complex.

Detailed investigations into the reaction mechanism of complex Pd-**264** did not give the satisfactory answer for the question why the final product could not be obtained. There are two possibilities to explain this fact. One option could be the high stability of the complex and the second option is that the corresponding complex can not be recycled after the reaction. The whole general reaction mechanism procedure (Scheme 52)[179] was repeated in a NMR tube in dry conditions and every step of the reaction was controlled by ^{31}P-NMR. The cycle begins by generation of trivalent ligand **264** by BSA and in the next step formation of the complex Pd(0)-**264** (Scheme 51). Oxidative addition of Pd(0) to form the π-allyl species with 1,3-diphenylallyl acetate **202** then occurs with ionization of a leaving group center, providing the key η^3-π-allyl-Pd^{2+} complex. This intermediate has been observed spectroscopically and the ^{31}P-NMR study permitted to prove that the signals did not change which means that the complex is very stable (Figure 31). Nucleophilic addition to the reaction mixture showed on ^{31}P-NMR that the signals did not change prior to the addidion of diphenylallyl acetate (Figure 32). Additionally, the use of potassium acetate as an added catalyst has advantages in the reactions which involve a wide range of carbon nucleophiles because if BSA does not convert the dibenzyl malonate into its related silyl ketene acetal then it can be suggested that the catalytic activity of the potassium acetate serves to initiate the formation of a dibenzyl malonate nucleophile.[180] Following the ^{31}P-NMR spectrum after addition of KOAc as an additive it is possible to conclud that the complex is very stable and it does not react with other reagents resulting the desired product, or the product is generated in small quantities what can be concluded from new signals at 96.2 and 95.3 Hz (Figure 33). Summarizing, the whole experiment proved that the complex Pd-**264** was not an active catalyst for the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylallyl acetate **202** with dibenzyl malonate.



Scheme 52. Mechanism of Asymmetric Allylic Substitution.

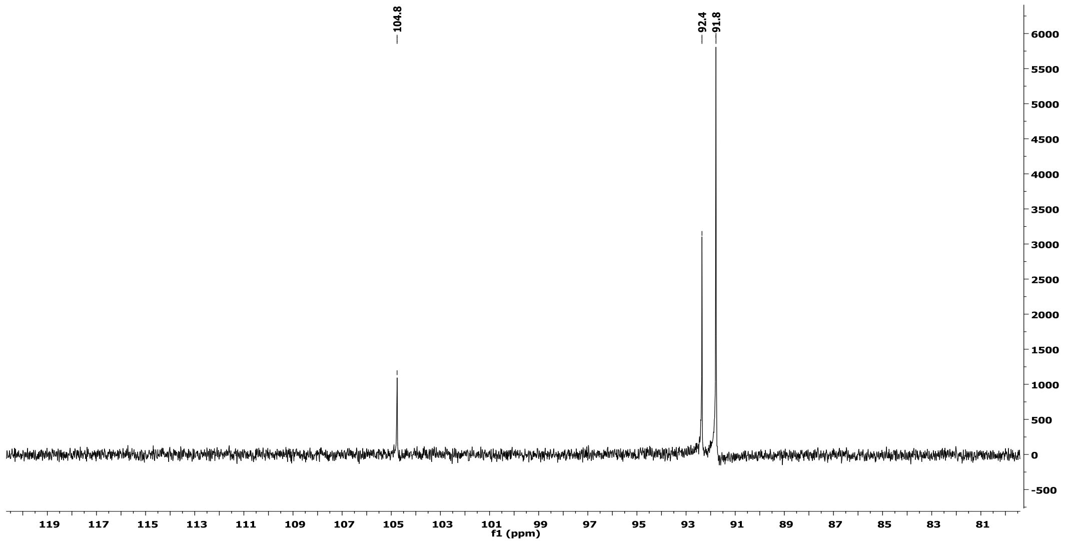


Figure 31. ^{31}P-NMR of BSA + Pd-264 Complex + 1,3-Diphenylallyl Acetate.

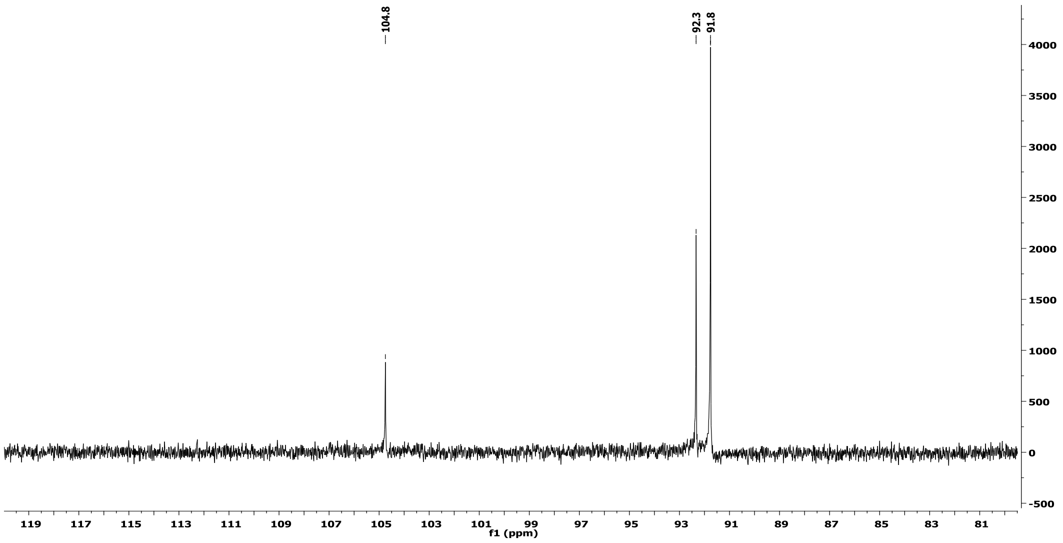


Figure 32. ^{31}**P-NMR of BSA+Pd-264 Complex + 1,3-Diphenylallyl Acetate + Dibenzyl Malonate.**

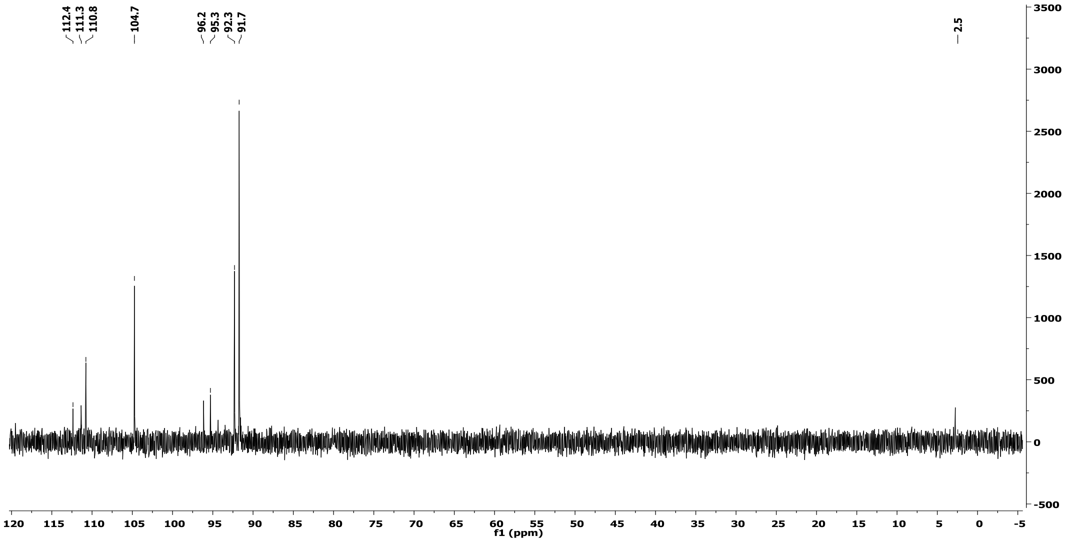


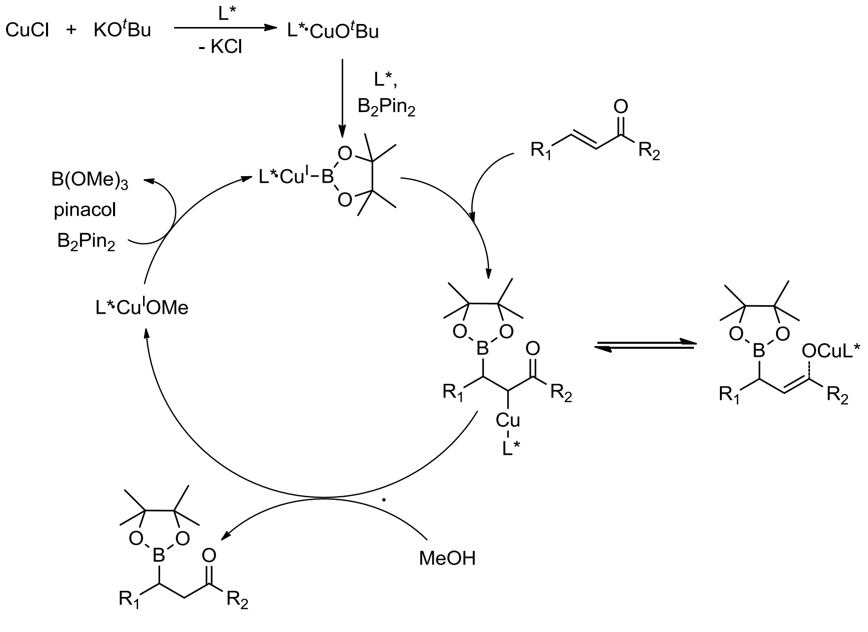
Figure 33. ^{31}**P-NMR of BSA + Pd-264 Complex + 1,3-Diphenylallyl Acetate + Dibenzyl Malonate +KOAc.**

2.4.2. Copper-Catalyzed Conjugated Borylation Reactions

In organic synthesis one of the most significant chiral building blocks are enantioenriched chiral organoboron compounds.[181] Several transition metals catalyze the *β*-boration, but the most convenient and efficient metal to mediate the chemoselective formation of *β*-borated esters, ketones, nitriles, and amides is copper.[182] The first application of a copper(I) salt modified with chiral diphosphines to *α,β*-unsaturated carbonyl compounds was investigated by Yun and *co*-workers.[182]

2.4.2.1. Borylation of a C-C Double Bond Catalyzed by Chiral HASPO-Copper(I) Complex

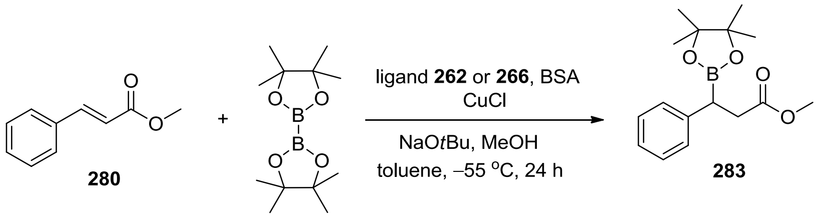
The mechanism for the conjugate boration of enones shows that the protonated product and a copper alkoxide are achieved *via* an intermediate copper enolate that undergoes protolytic cleavage by an alcohol. Additionally, the copper alkoxide reacts with diboron to regenerate the active copper boryl complex (Scheme 53).[183]

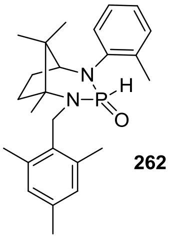
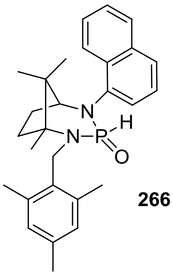


Scheme 53. Mechanism of Borylation of a C-C Double Bond

Following the previous studies, the HASPO ligands **262** or **266** were applied to the enantioselective *β*-boration of enolate. A pentavalent ligand (0.11 equiv.) was transformed by BSA (0.09 equiv.) to the trivalent phosphorus compound in toluene. A complex of trivalent ligand with CuCl (0.1 equiv.) was estimated as a catalyst by using methyl cinnamate **280** (1 equiv.) as a model substrate and adding *bis*(pinacolato)diboron (1.1 equiv.) in the presence of NaO*t*Bu (0.3 equiv.) as a base and MeOH (2 equiv.) as a proton source in toluene at –55 °C. The results are summarized in Table 18.

Table 18. Borylation of a C-C Double Bond in the Presence of BSA.

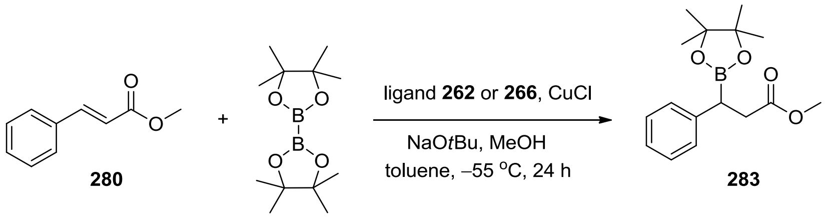


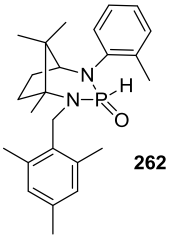
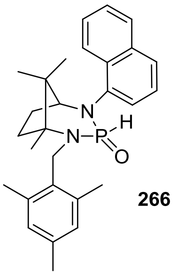
Entry	Ligand	Yield [%]	*ee* [%]
1	 **262**	51	*Rac*
2	 **266**	37	*Rac*

From the Table 18 it can be concluded that HASPO ligand **262** (Table 18, Entry 1) gave higher yield than HASPO ligand **266** (Table 18, Entry 2). Unfortunately both of them obtained the desired product as racemate.

Also ligands **262** and **266** were tested under different conditions, specifically without BSA (Table 19). Nevertheless resulted yields decreased compare to results from Table 18 and similarly as in the above case the desire product was obtained as a racemates.

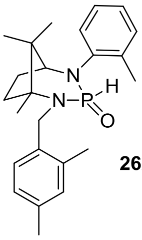
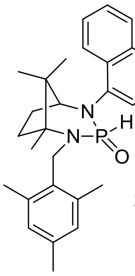
Table 19. Borylation of a C-C Double Bond without Tautomerisation of HASPO Ligands.



Entry	Ligand	Yield [%]	*ee* [%]
1	 **262**	18	*Rac*
2	 **266**	11	*Rac*

A series of experiments were performed in order to further optimize the reaction conditions with HASPO ligands and the impact of copper salt and BSA. No product was obtained. The results are summarized in Table 20.

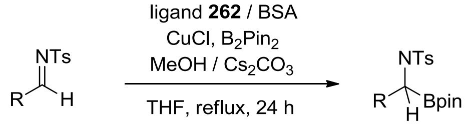
Table 20. Borylation of a C-C Double Bond with the impact of BSA and CuCl.

Entry	Ligand	CuCl [mol%]	BSA [mol%]	Yield [%]	*ee* [%]
1	 **262**	0	9	0	–
		0	0	0	–
2	 **266**	0	9	0	–
		0	0	0	_

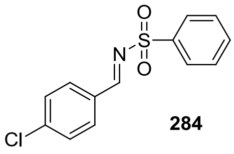
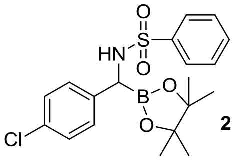
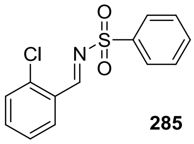
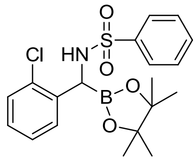
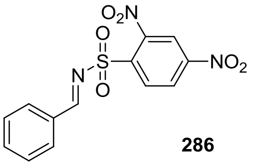
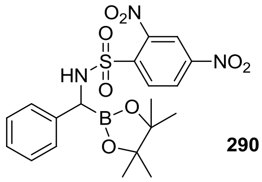
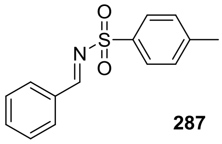
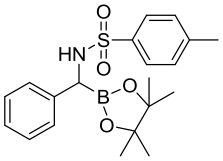
2.4.2.2. Asymmetric Synthesis of α-Amino Boronate Esters

The HASPO ligands were applied to the asymmetric synthesis of α-amino boronate esters *via* organocatalytic pinacolboryl addition to tosyldimines.[184] A pentavalent ligand **262** (0.04 equiv.) was transformed by BSA (0.09 equiv.) to trivalent ligand in THF. A complex of trivalent ligand with CuCl (0.04 equiv.) was estimated as a catalyst by using tosylaldimines **284-287** (1 equiv.) as a model substrate and *bis*(pinacolato)diboron (1.2 equiv.) in the presence of Cs_2CO_3 (0.15 equiv.) and MeOH (2.5 equiv.) as a proton source in THF at 70 ^{o}C. A series of experiments were performed in order to further optimize reaction conditions with HASPO ligand **262** with various influences of copper salt and BSA. No products were obtained. The results are summarized in Table 21.[170]

Table 21. Asymmetric Synthesis of α-Amino Boronate Esters in Various Reaction Conditions.



284-287 **288-291**

Entry	Tosylaldimines	CuCl [mol%]	BSA [mol%]	Product	Yield [%]
1	 **284**	4	9	 **288**	0
		0	9		0
		4	0		0
		0	0		0
2	 **285**	4	9	 **289**	0
		0	9		0
		4	0		0
		0	0		0
3	 **286**	4	9	 **290**	0
		0	9		0
		4	0		0
		0	0		0
4	 **287**	4	9	 **291**	0
		0	9		0
		4	0		0
		0	0		0

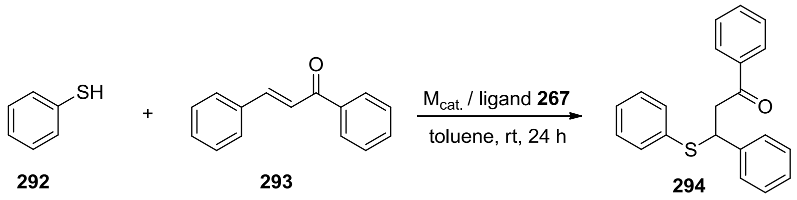
2.4.3. Michael Addition

The Michael addition also called conjugated addition reaction is an addition of a nucleophile to a *α,β*-unsaturated carbonyl compound in the presence of a transition metal to avoid direct attack on the carbonyl group of the Michael acceptor.[185]

2.4.3.1. Michael Addition of Thiophenol

The HASPO ligand **267** (0.05 equiv.) and the catalyst (0.08 equiv.) were applied to the Michael addition with thiophenol **292** (1 equiv.) and chalcone **293** (1 equiv.) in toluene. A series of experiments were performed in order to further optimize reaction conditions with HASPO ligands with various influences of impact of catalysts. The results are summarized in Table 22.[170]

Table 22. Michael Addition Reaction with Different Reaction Conditions.

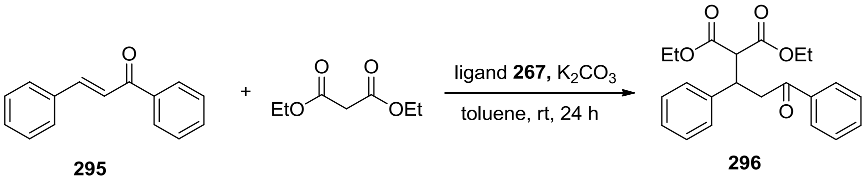


Entry	$M_{cat.}$	Yield [%]	*ee* [%]
1	$Sc(SO_3CF_3)_3$	91	*rac*
2	$Y(SO_3CF_3)_3$	32	6
3	$HoCl_3$	49	9
4	–	61	*rac*

From the Table 22 it can be concluded that scandium(III) trifluoromethanesulfonate gave the corresponding product **294** as a racemate in excellent 91% yield (Table 22, Entry 1). Holium(III) chloride resulted the product **294** in 9% enantioselectivity while the yield decreased to 49% (Table 22, Entry 3).

2.4.3.2. Michael Addition of Carbonyl Compound

The HASPO ligand **267** (0.18 equiv.) and K_2CO_3 (3 equiv.) were applied to the Michael addition with diethyl malonate (1.5 equiv.) and chalcone **290** (1 equiv.) in toluene (Scheme 54). No corresponding product was obtained.[170]



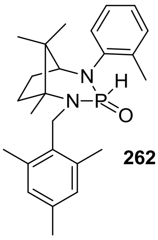
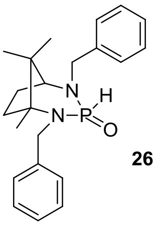
Scheme 54.

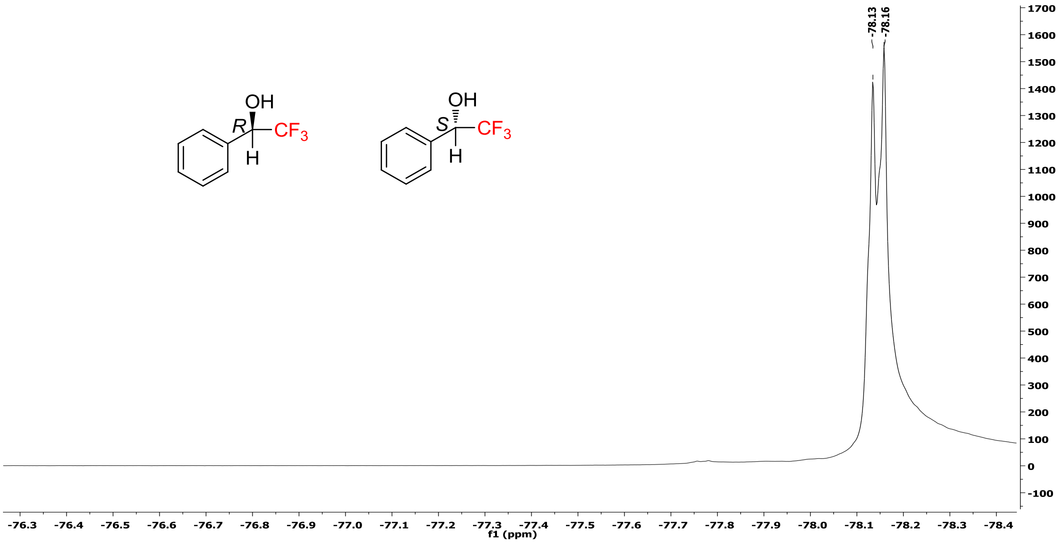
2.5. Chiral HASPO Ligands as Chiral Shift Reagents

Nowadays it is very important to find efficient methods for the easy and fast measurement of the enantiomeric excess of chiral compounds.[186] The application of chiral shift reagent, also called chiral solvating reagent for NMR spectroscopy is one of the most useful method to achieve determination of the enantiomeric excesses of chiral organic molecules. The advantage of this convenient method is an easy performance without using any chiral derivatization of the analyte.[187] Many different kinds of shift reagents, such as lanthanide complexes, crown ethers, cyclodextrins, porphyrins, macrocycles, and others have been investigated by many researchers.[188]

The novel chiral HASPO ligands were evaluated as chiral resolving agents in dry toluene. The chiral shift experiments were carried out by measuring the ^{1}H-NMR and ^{19}F-NMR spectra of a mixture of HASPO ligand **262** with two different substituted nitrogen atoms or HASPO ligand **258** with the same substituted nitrogen atoms with α-(trifluoromethyl)benzyl alcohol in a ratio 1:1 in toluene at room temperature. Table 23 shows the splitting with HASPO ligands **262** and **260** did not change for the CF_3 group. In both cases, the signals shifted properly.

Table 23. Resolution of *α*-(Trifluoromethyl)benzyl Alcohol in the Presence of HASPO Ligands (^{19}F-NMR).

Entry	Ligand	*δ* (ppm)	^{19}F Δ *δ* (Hz)
1	-	–78.16/–78.13	0
2	 **262**	–77.89/–77.86	7
3	 **260**	–77.73/–77.70	0



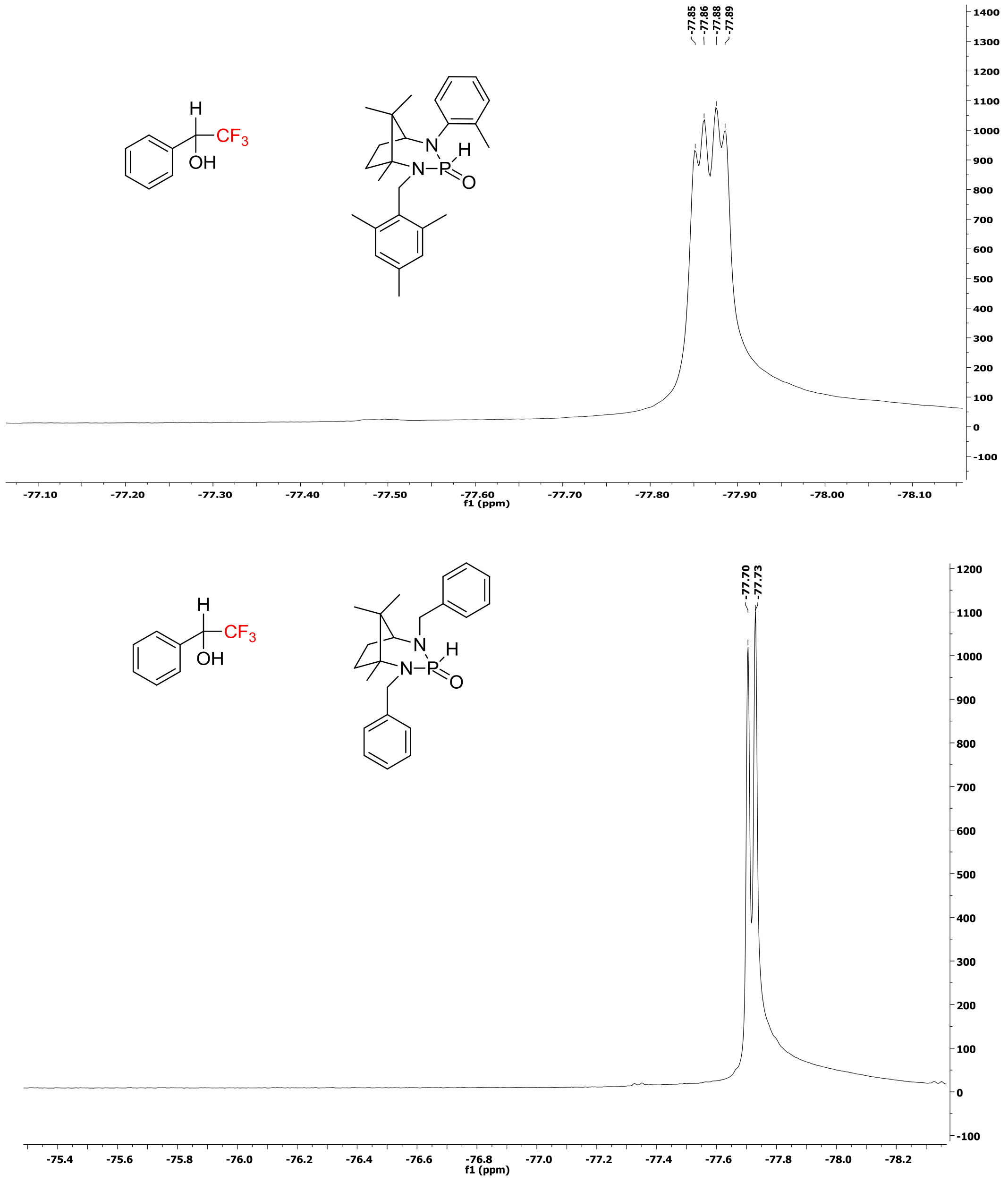
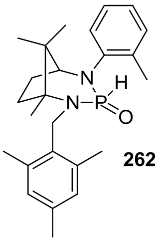
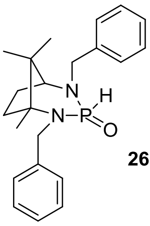
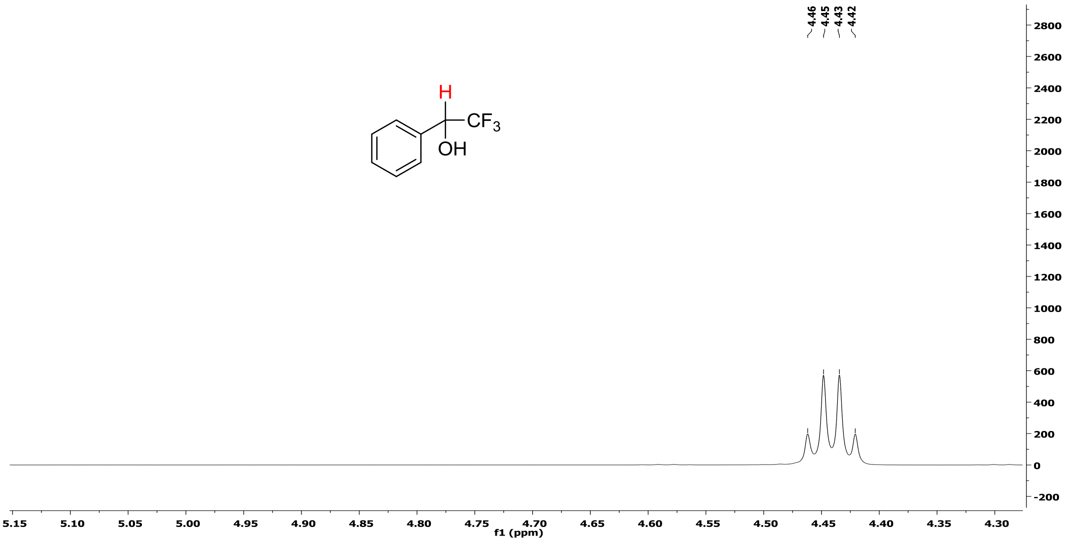


Figure 34.

The ^{1}H-NMR spectra were also recorded for the mixture of compounds which are mentioned above. The results are presented in Table 24. The HASPO ligand **260** interacted with the methine proton of α-trifluoromethyl benzyl alcohol and showed a splitting of 7 Hz, while no stereodiscrimination for the CF_3 group was observed from the more symmetrical ligand **260**.

Table 24. Resolution of Alcohol in the Presence of HASPO Ligands (^{1}H-NMR).

Entry	Ligand	δ (ppm)	^{1}H Δ δ (Hz)
1	-	4.45/4.42	0
2	 **262**	4.63/4.61	7
3	 **260**	4.91/4.88	0



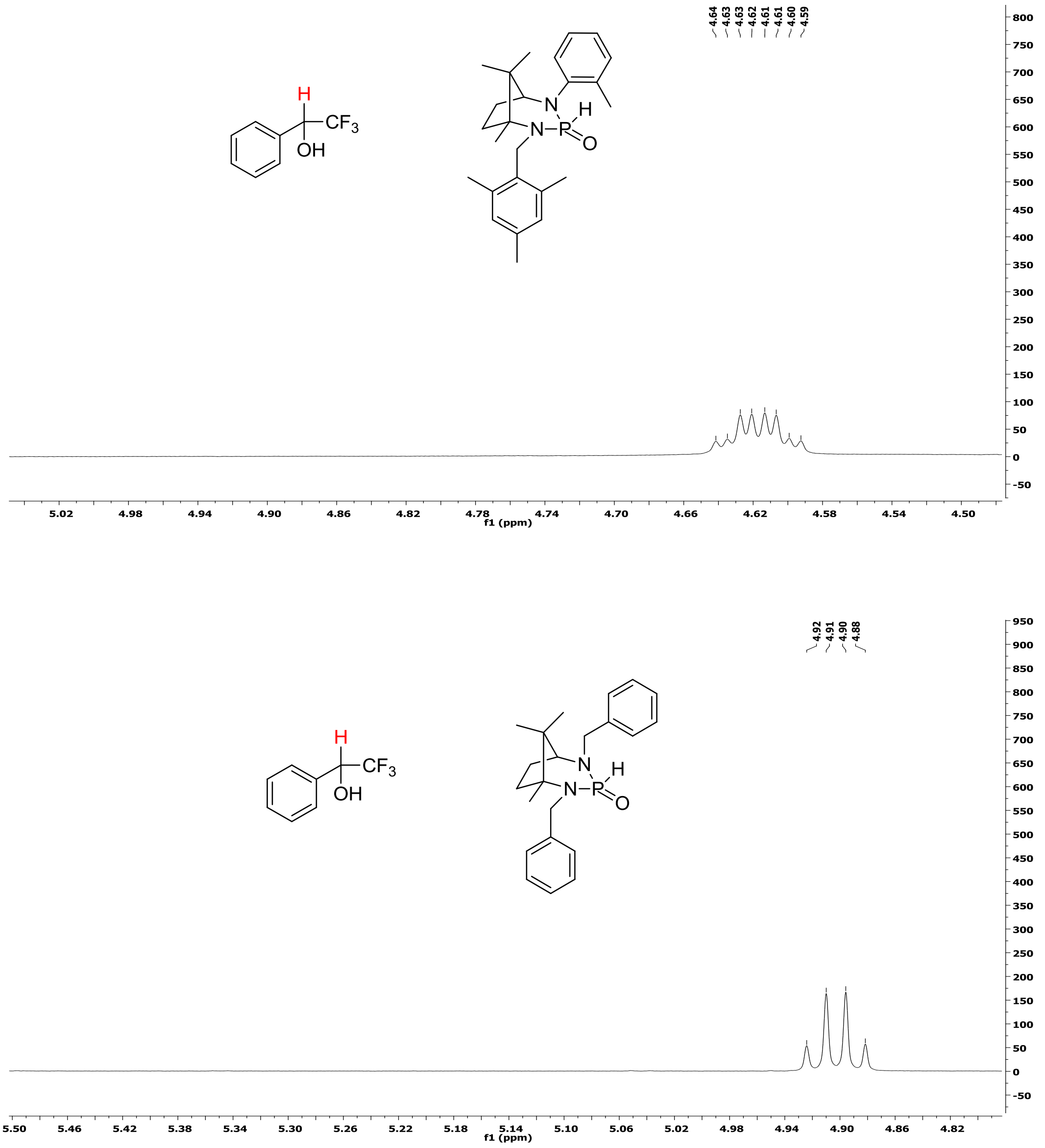
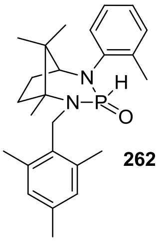
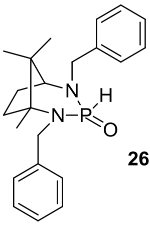
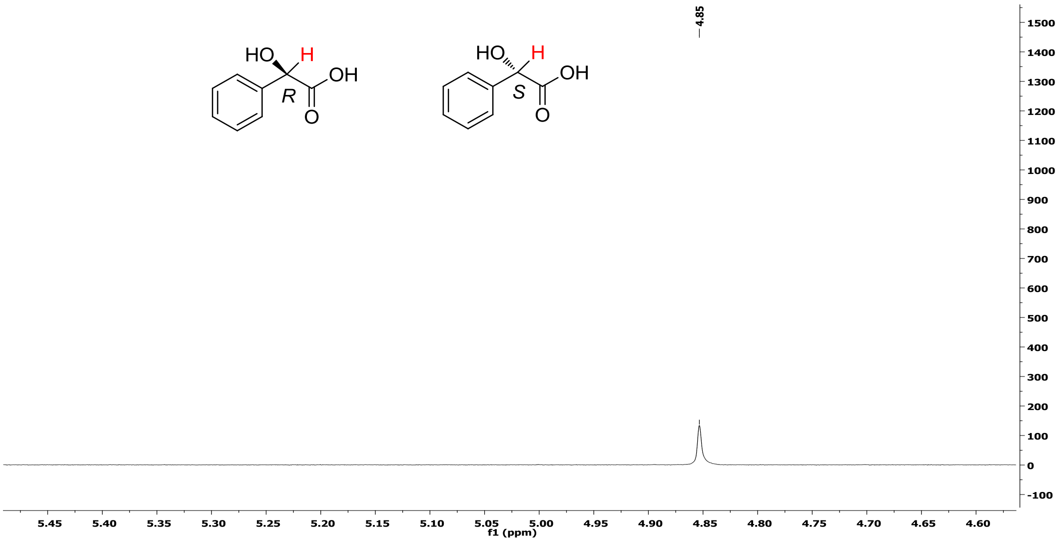


Figure 35.

The mandelic acid interacted with HASPO ligands **260** and **262**, and the signals shifted from singlet to doublet. Additionaly, the proton attached to the chiral center of mandelic acid interacted with ligand **262** showed a baseline separation of 6 Hz (Table 25).

Table 25. Resolution of Carboxylic Acid in the Presence of HASPO Ligands (^{1}H-NMR).

Entry	Ligand	δ (ppm)	^{1}H $\Delta\delta$ (Hz)
1	-	4.85	0
2	 **262**	5.12/5.10	6
3	 **260**	5.24/5.24	1



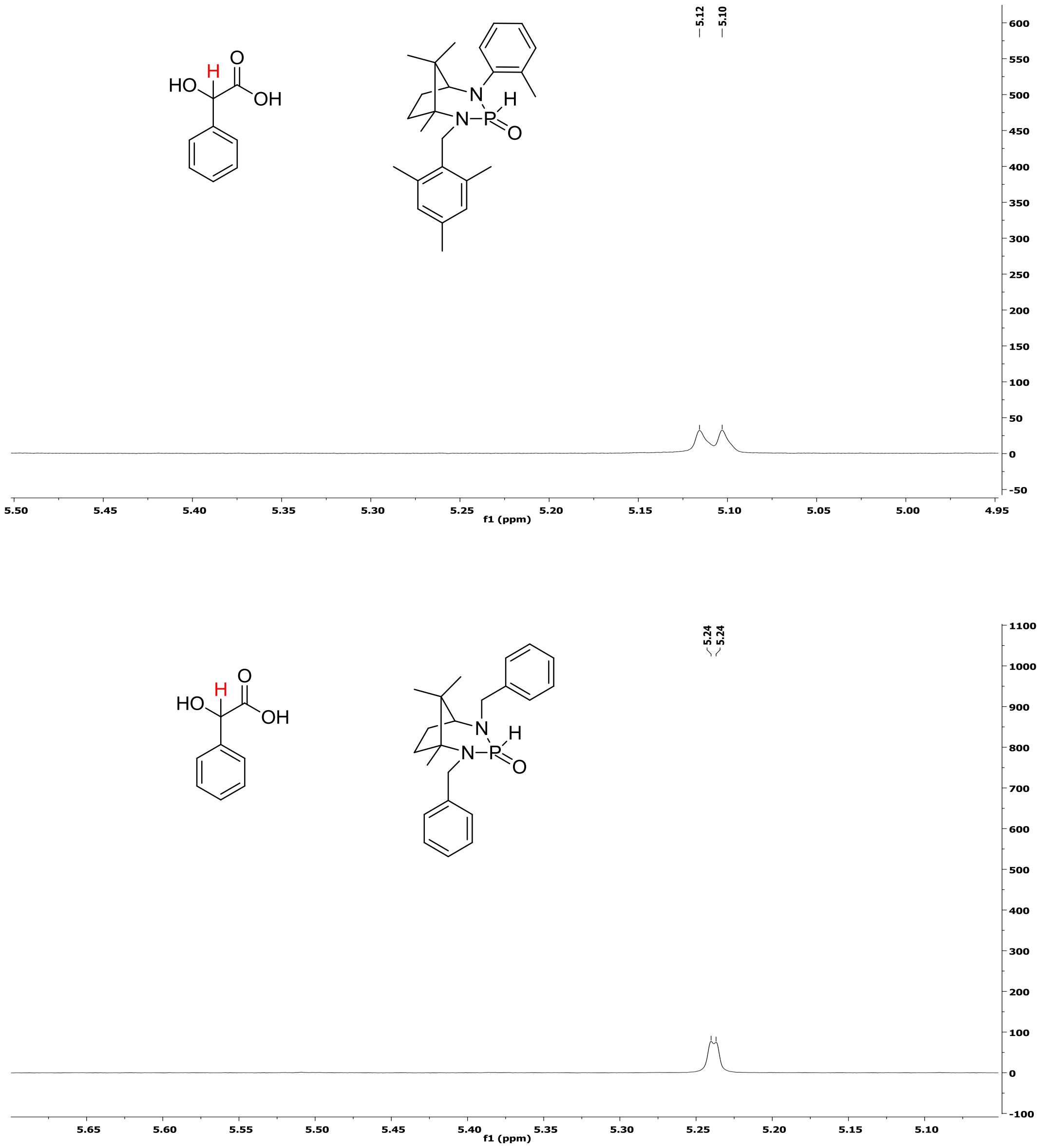
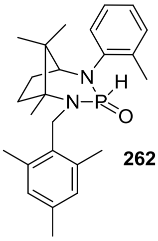
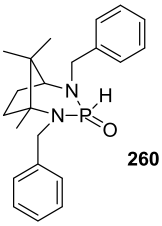
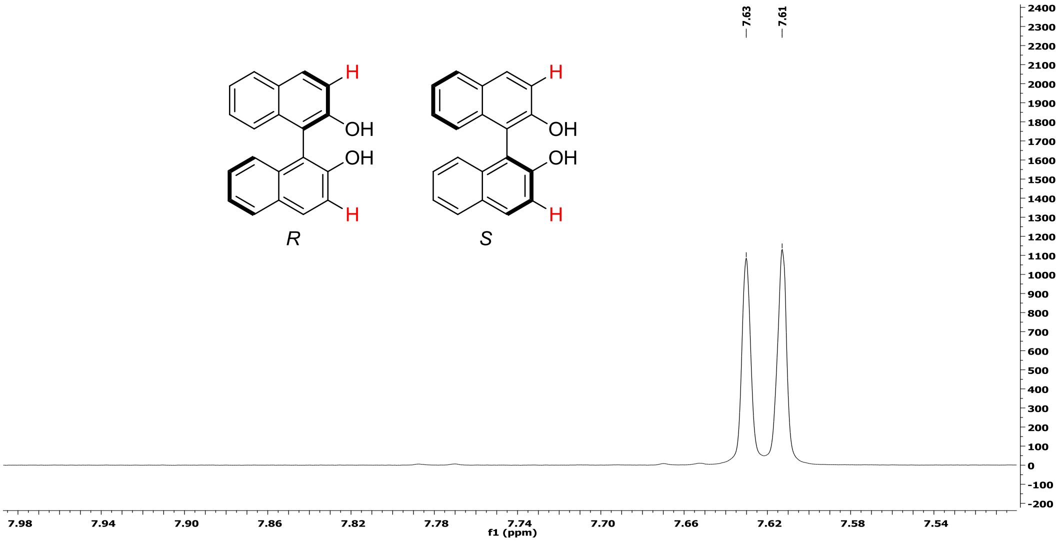


Figure 36.

Both ligands were tested also with BINOL which interacted with both compounds. Ligand **260** and the aromatic –CH showed a baseline separation of 18 Hz, while ligand **262** showed 9 Hz. However, in both cases impurities are visible on NMR spectra (Table 26).

Table 26. Resolution of BINOL in the Presence of HASPO Ligands (^{1}H-NMR).

Entry	Ligand	δ (ppm)	^{1}H Δ δ (Hz)
1	-	7.63/7.61	0
2	 **262**	7.66/7.64	9
3	 **260**	7.69/7.66	18



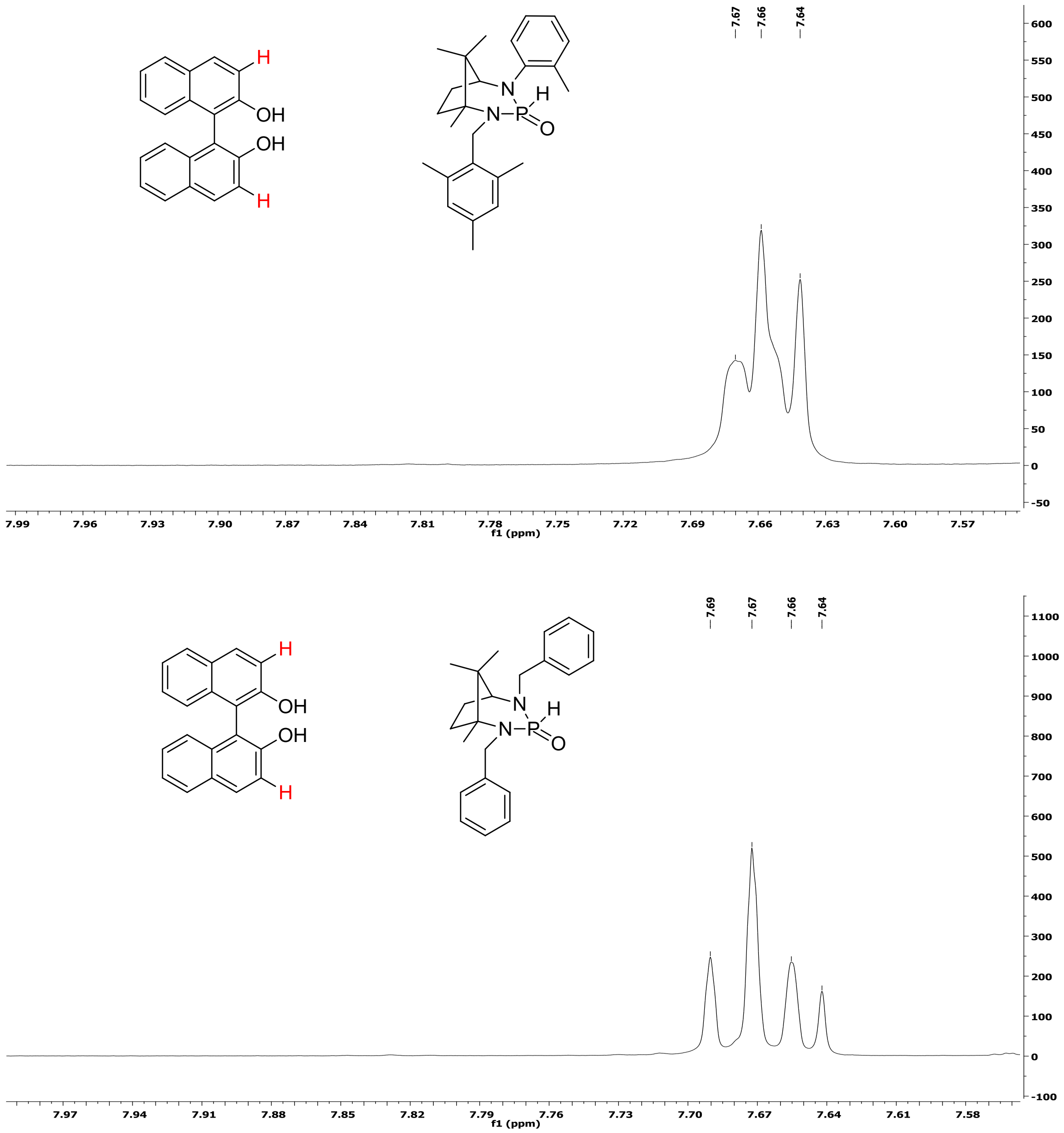
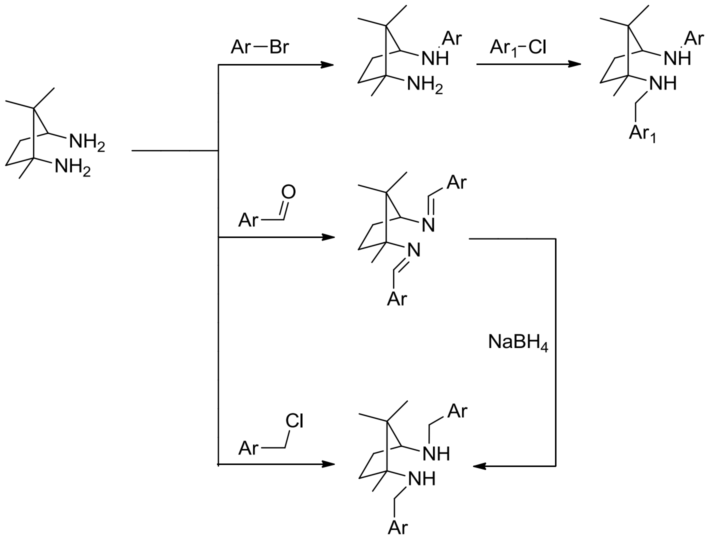


Figure 37.

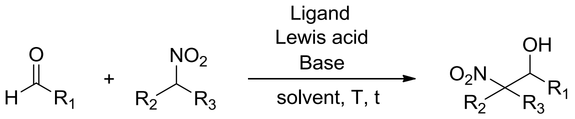
2.6. Summary and Future Work

The presented investigation began with the preparation of novel chiral diamines ligands followed by heteroatom-substituted secondary phosphine oxides based on camphoric acid. Two different types of diamines were prepared starting with a Schmidt reaction from camphoric acid. One of them with the same substituted nitrogen atoms were synthesized through alkylation by treating the diamine with arylmethylene chloride or with an aldehyde, followed by the reduction of the corresponding imine. The enantiopure diamines with a primary amine function were prepared *via* a Buchwald-Hartwig amination, followed by the alkylation of the monosubstituted diamines with arylmethylene chloride in the second step.



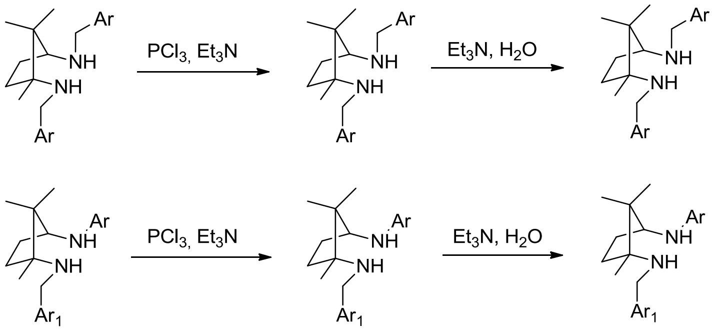
Scheme 54.

The new diamine ligands were successfully applied in the copper catalyzed asymmetric Henry reaction. The chiral nitroaldol products were obtained in good yields and enantioselectivities.[152]



Scheme 55.

Also a new class of chiral HASPO (heteroatom-substituted secondary phosphine oxide) ligands for transition-metal-catalyzed transformations was prepared from cheap camphor, by treating the secondary diamine with PCl_3 and Et_3N, followed by H_2O which provided the desired HASPO ligands. Preliminary experiments using HASPO ligands based on camphoric acid indicated that trivalent phosphorus compounds are formed in the presence of BSA, which can be converted to HASPO complexes with palladium. The experiments were supported by ^{31}P-NMR in toluene-D_8.



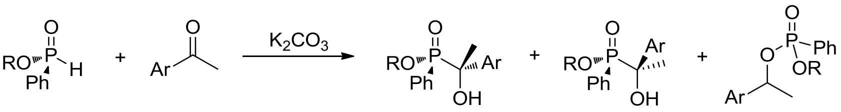
Scheme 56.

In the last section of this chapter, the HASPO ligands were presented as chiral shift reagents. The phosphorus compounds proved to be a versatile chiral discriminating agent for different types of racemic compounds such as alcohols, an acid or naphthol.

Several parts of the thesis have been published.[189,190]

In the future the synthesized of novel HASPO ligands can be explored in several other reactions such as the alkylative ring-opening with a palladium-catalyzed C-C bond formation, the Heck reaction, the enantioselective hydrovinylation of alkenes or the hydroformylation processes for the production of aldehydes from C-C double bonds. On the other hand, the allylpalladium chloride dimer is one of the most important catalyst used in organic synthesis, but the allylic substitution can be investigated with other allyl palladium complexes with larger ligands such as (2-methylallyl)palladium(II) chloride dimer or (2-butenyl)chloropalladium dimer.

Another excellent application of the HASPO compounds would be the addition HASPO ligands to aromatic methyl ketones and asymmetric ketones. The hydrophosphorylation gives in the presence of potassium carbonate P,C-stereogenic tertiary α-hydroxyl phosphinates (Scheme 57).[191]



Scheme 57.

3. Experimental

3.1. General Experimental

All reactions were conducted in vacuum flame-dried glassware under an atmosphere of dry argon. Catalytic reactions were carried out using Schlenk line techniques.

Organic Compounds

All reagents which are not described below were purchased from commercial sources such as ACROS ORGANICS, SIGMA ALDRICH, MERCK AG, FLUKA AG, LANCASTER, and ALFA AESAR. In addition, compounds which are shown in Table 27 were prepared by Sobia Tabassum,[153] Amélie Blanrue[192] and Andreas Winkel[193] under the supervision of Prof. Wilhelm.

Table 27.

Entry	Compound
1[a]	(1*R*,3*S*)-1,2,2-Trimethyl-*N*^{3}-(pyridin-2-yl)cyclopentane-1,3-diamine **251**
2[a]	*N*-((1*R*,3*S*)-3-Amino-2,2,3-trimethylcyclopentyl)acetamide **236**
3[b]	2,2,2-Trifluoro-1-phenylethanol
4[c]	(*E*)-*N*-(4-Chlorobenzylidene)benzenesulfonamide **284**
5[c]	(*E*)-*N*-(2-chlorobenzylidene)benzenesulfonamide **285**
6[c]	(*E*)-*N*-benzylidene-2,4-dinitrobenzenesulfonamide **286**
7[c]	(*E*)-*N*-benzylidene-4-methylbenzenesulfonamide **287**

[a] Compound was prepared by Dr. Sobia Tabassum.[153]
[b] Compound was prepared by Dr. Andreas Winkel.[193]
[c] Compound was prepared by Dr. Amélie Blanrue.[192]

Solvents

The solvents were dried according to the general, common procedures. THF and diethyl ether were distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. CH_2Cl_2 was distilled from calcium hydride. Anhydrous methanol, ethanol and acetonitrile were purchased from SIGMA ALDRICH and used without any purification.

Chromatography

Reactions were monitored by TLC with MERCK Silica gel 60 F254 plates. Flash column chromatography was performed on Silica gel 60 (230 – 400 mesh) from MERCK.

HPLC Analysis

Enantiomeric excess was determined on a Merck Hitachi HPLC system with the L-7200 autosampler using a Daicel CHIRALPACK OD-H, a Daicel CHIRALPACK AD-H and Daicel CHIRALPACK AS-H column. *i*-Propanol and *n*-hexane were used as mobile phase.

NMR

Nuclear magnetic resonance data were recorded on a BRUKER Advance 500 (^{1}H-NMR: 500 MHz, ^{13}C-NMR: 126 MHz, ^{15}N-NMR: 51 MHz) and on a BRUKER Advance 300 (^{31}P-NMR: 202 MHz, ^{19}F-NMR: 125 MHz). The measurements of the substances were performed in deuterated chloroform (99.8%, DEUTERO) or deuterated toluene (99.5% DEUTERO). NMR chemical shifts δ are reported in parts per million (ppm) and are referenced to the residual solvent signal as the internal standard: $CDCl_3$: 7.26 (^{1}H) and 77.0 (^{13}C). The coupling constants J are given in Hertz (Hz). Following symbols are used to analyze the spectra: br- broad, s- singlet, d- doublet, t- triplet, q- quartet, m- multiplet.

Melting points

Melting points were taken on a Dr Tottoli apparatus from BÜCHI and are uncorrected.

Infrared spectra

Infrared IR data were recorded on a FT-IR spectrometer Vertex from BRUKER. The absorption of solids was measured by KBr pellets. The absorption of liquids or oils was measured by using thin films between NaCl plates. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}).

LR-MS

Mass spectra were recorded with a Hewlett Packard 5989B at 70 eV. Analytical data are given as relative mass (*m/z*) and the brackets indicate the intensity in percent (%) related to the basic peak.

HR-MS

High resolution mass spectra were recorded on a Waters Quadrupole-ToF Synapt 2G.

Elemental analysis

Elemental analysis were carried out with a vario MICROcube analysator from ELEMENTAR.

Optical rotations

Optical rotations were measured using a 1 dm path length (c is given as g/100 mL) on a PERKIN-ELMER 241 MC polarimeter in the reported solvent.

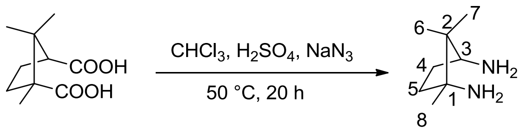
Specification of configuration

The configuration of HASPO ligands was compared to the general rules followed by IUPAC recommendations and matched up to ChemDraw.

3.2. Experimental Procedures for the Preparation of Diamines

3.2.1. Synthesis of Camphor Diamine

3.2.1.1. (1*R*,3*S*)-1,2,2-Trimethylcyclopentane-1,3-diamine (208)



209 **208**

To a stirred solution of concentrated sulfuric acid (50 mL) and ethanol-free chloroform (300 mL) was added (+)-(1*R*,3*S*)-camphoric acid **209** (20.00 g, 0.12 mol, 1 equiv.) at 50 ^{o}C. Sodium azide (19.50 g, 0.30 mol. 3 equiv.) was added in small amounts over a period of 2h. The resulting mixture was stirred at 50 ^{o}C for 18h. The reaction mixture was cooled to room temperature, poured into water (500 mL) and extracted with chloroform (2 x 500 mL). The aqueous layer was strongly basified with 12N sodium hydroxide and extracted with chloroform (2 x 500 mL). After drying over anhydrous sodium sulfate and removal of the solvent, the product was dissolved in diethyl ether (100 mL). The solution was filtered and the solvent removed in vacuo to give the product **208** as a white solid (10.10 g, 71.00 mmol, 71 %). The spectroscopic properties concur with published data.[148]

Mp: 131 ^{o}C; Lit.: 128 ^{o}C.[148]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.84 (dd, *J* = 8.6, 7.0 Hz, 1H, *H*-3), 1.89 (dddd, *J* = 13.9, 9.7, 8.6, 5.4 Hz, 1H, *H*-4), 1.44 – 1.62 (m, 2H, *H*-5), 1.4 (s, 4H, *H*-N^2, *H*-N^1), 1.08 – 1.29 (m, 1H, *H*-4),), 0.88 (s, 3H, *H*-8), 0.64 (d, *J* =4.5 Hz, 6H, *H*-7, *H*-6) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 60.9 (*C*-1), 60.8 (*C*-3), 46.2 (*C*-2), 38.2 (*C*-5), 30.2 (*C*-4), 25.8 (*C*-8), 22.3 (*C*-6), 16.2 (*C*-7) ppm.

^{15}N-NMR (51 MHz, $CDCl_3$): δ = 47.2 (bs, 1N, N^1), 31.3 (bs, 1N, N^2) ppm.

IR (ATR): ν = 3390, 2964, 1571, 1469, 1370, 1322, 689, 590 cm^{-1}.

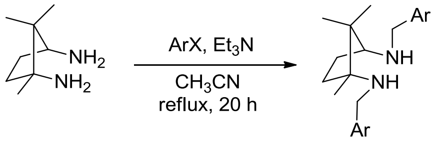
MS (ESI, + 3 kV): *m/z* (%) = 143 (M+1, 100%).

HRMS (ESI): Calc. for $C_8H_{19}N_2$: 143.1548, found: 143.1545.

$[\alpha]^{20}_D$ = +28 (c = 0.48, EtOH); Lit.: $[\alpha]^{25}_D$ = +30 (c = 1, EtOH).[194]

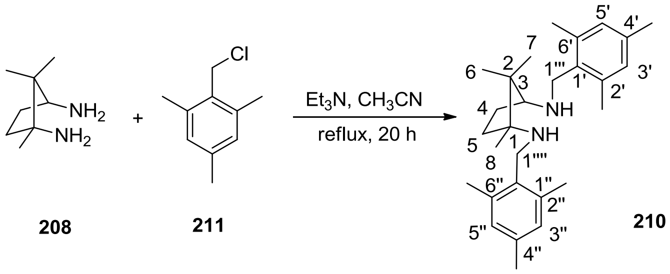
3.2.2. Alkylation of Camphor Diamine with Arylmethylene Halide

General Procedure



Arylmethylene halide (2 equiv.) was added to a stirring solution of 1,2,2-trimethylcyclopentane-1,3-diamine **208** (1 equiv.) and triethylamine (2 equiv.) in dry acetonitrile at room temperature. The mixture was heated at reflux for 20 h. Triethylamine hydrochloride was filtered off and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel with CH_2Cl_2 as an eluent and the product was eluted with CH_2Cl_2/EtOAc, 90:10.

3.2.2.1. (1*R*,3*S*)-1,2,2-Trimethyl-*N*^{1},*N*^{3}-*bis*(2,4,6-trimethylbenzyl) cyclopentane-1,3-diamine (210)



Prepared from 2,4,6-trimethylbenzylchloride **211** (0.71 g, 4.23 mmol), 1,2,2-trimethylcyclopentane-1,3-diamine **208** (0.30 g, 2.09 mmol) and triethylamine (0.55 mL, 4.30 mmol) in dry acetonitrile (20 mL). After work up, the product was further purified *via* column chromatography (CH$_2$Cl$_2$/EtOAc, 90:10) and diamine **210** was obtained as colorless oil (0.46 g, 1.14 mmol, 57%).

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 6.89 (d, *J* = 12 Hz, 4H, *H*-3’, *H*-5’, *H*-3’’, *H*-5’’), 3.86 (d, *J* = 11.4 Hz, 1H, *H*-1’’’), 3.82 – 3.79 (m, 1H, *H*-1’’’’), 3.71 – 3.67 (m, 1H, *H*-1’’’’), 3.64 – 3.60 (m, 1H, *H*-1’’’), 2.97 – 2.92 (m, 1H, *H*-3), 2.43 (s, 6H, 6’-C*H*$_3$, 6’’-C*H*$_3$), 2.40 (s, 6H, 2’-C*H*$_3$, 2’’-C*H*$_3$), 2.32 (s, 6H, 4’-C*H*$_3$, 4’’-C*H*$_3$), 2.22 – 2.11 (m, 2H, *H*-4, *H*-5), 1.76 (m, 1H, *H*-5), 1.60 – 1.50 (m, 1H, *H*-4), 1.28 (s, 3H, *H*-8), 1.02 (s, 3H, *H*-7), 0.92 (s, 3H, *H*-6) ppm.

^{13}C-NMR (50 MHz, CDCl$_3$): δ = 137.1 (*C*-1’, *C*-1’’), 136.2 (*C*-4’), 136.1 (*C*-4’’), 134.7 (*C*-2’, *C*-6’), 134.5 (*C*-2’’, *C*-6’’), 128.9 (*C*-3’, *C*-5’, *C*-3’’, *C*-5’’), 68.1 (*C*-3), 64.4 (*C*-2), 47.5 (*C*-1’’’), 40.9 (*C*-1’’’’), 34.1 (*C*-4), 28.9 (*C*-5), 23.9 (*C*-7), 21.0 (4’-*C*H$_3$, 4’’-*C*H$_3$), 20.6 (*C*-8)19.5 (2’-*C*H$_3$, 2’’-*C*H$_3$, 6’-*C*H$_3$, 6’’-*C*H$_3$) 16.8 (*C*-6) ppm.

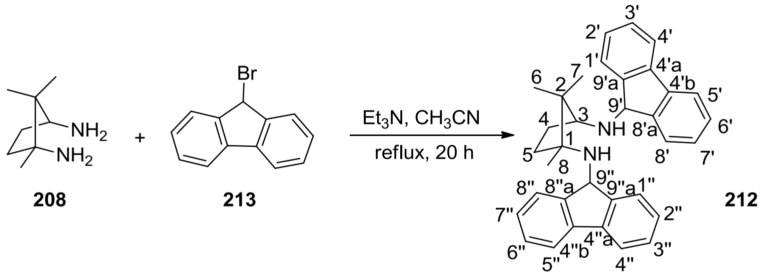
IR (ATR): ν = 2953, 2918, 2862, 1715, 1610, 1444, 1369, 1107, 848, 798, 714 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 407 ([M+H]$^+$, 100%).

HRMS (ESI): Calc. for C$_{28}$H$_{43}$N$_2$: 407.43426, found: 407.3431.

[α]$^{20}_{D}$ = +33 (c = 0.45, EtOH).

3.2.2.2. (1*R*,3*S*)-*N*^{1},*N*^{3}-Di(9H-fluoren-9-yl)-1,2,2-trimethylcyclopentane-1,3-diamine (212)



Prepared from 9-bromofluorene **213** (1.03 g, 4.20 mmol), 1,2,2-trimethylcyclopentane-1,3-diamine **208** (0.30 g, 2.10 mmol) and triethylamine (0.58 mL, 4.20 mmol) in dry acetonitrile (20 mL). After work up, the product was further purified *via* column chromatography (CH_2Cl_2/EtOAc, 90:10) and the diamine **212** was obtained as a yellow solid **(**0.60 g, 1.25 mmol, 59%).

Mp: 162 ^oC.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.77 – 7.63 (m, 8H, *H*-1’, *H*-2’, *H*-3’, *H*-4’, *H*-5’,*H*-6’, *H*-7’, *H*-8’), 7.44 – 7.24 (M, 8H, *H*-1’’, *H*-2’’, *H*-3’’, *H*-4’’, *H*-5’’,*H*-6’’, *H*-7’’, *H*-8’’), 4.97 (s, 1H, *H*-9’), 4.89 (s, 1H, *H*-9’’), 3.08 (s, 1H, *H*-3), 2.30 – 1.87 (m, 4H, *H*-4, *H*-5), 1.31 (s, 3H, *H*-8), 1.01 (s, 3H, *H*-7), 0.98 (s, 3H, *H*-6) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 149.5 (*C*-9’a), 149.2 (*C*-9’’a), 147.3 (*C*-8’a), 146.3 (*C*-8’’a), 140.6 (*C*-4’a), 140.5 (*C*-4’b), 140.2 (*C*-4’’a), 140.1 (*C*-4’’b), 127.9 (*C*-1’), 127.9 (*C*-8’), 127.7 (*C*-1’’), 127.6 (*C*-8’’), 127.5 (*C*-2’), 127.4 (*C*-7’), 127.3 (*C*-2’’), 126.9 (*C*-7’’), 125.5 (*C*-3’), 125.5 (*C*-6’), 125.1 (*C*-3’’), 125.0 (*C*-6’’), 119.9 (*C*-4’), 119.8 (*C*-5’), 119.7 (*C*-4’’), 119.6 (*C*-5’’), 64.8 (*C*-1), 63.9 (*C*-3), 62.4 (*C*-9’), 59.7 (*C*-9’’), 48.3 (*C*-2), 36.8 (*C*-5), 30.0 (*C*-4), 24.0 (*C*-8), 23.5 (*C*-6), 17.1 (*C*-7) ppm.

IR (ATR): ν = 3348, 3044, 2963, 1448, 1265, 1066, 797, 727 cm^{-1}.

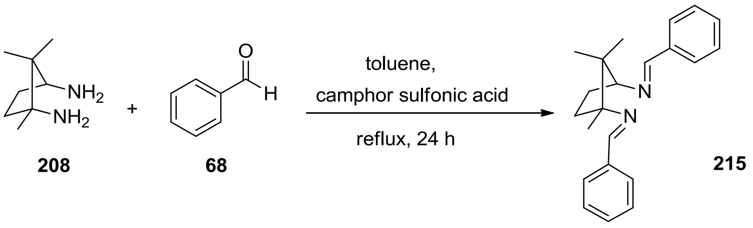
MS (ESI, + 3 kV): *m/z* (%) = 471 (M+1, 100%).

HRMS (ESI): Calc. for $C_{34}H_{34}N_2$: 471.2800, found: 471.2806.

[α]^{20}$_D$ = −19 (c = 0.65, EtOH).

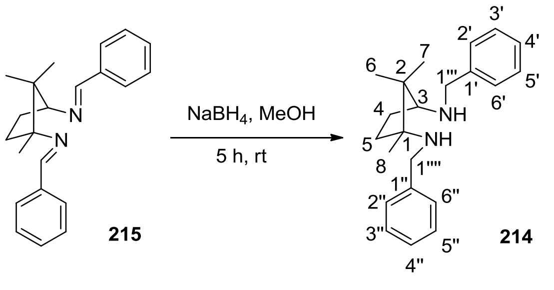
3.2.3. Alkylation of Camphor Diamine with Aldehyde

3.2.3.1. (1*R*,3*S*,N^1*E*,N^3*E*)-N^1,N^3-Dibenzylidene-1,2,2-trimethylcyclopentane -1,3-diamine (215)



Benzaldehyde **68** (1.42 mL, 14.00 mmol) in toluene (5 mL) was added drop wise to a solution of 1,2,2-trimethylcyclopentane-1,3-diamine **208** (1.00 g, 7.00 mmol), *p*-toluenosulfonic acid (70.00 mg) and toluene (15 mL) at room temperature. The resuling mixture was heated at reflux overnight on a Dean Stark under a stream of argon. After removal of the solvent, the crude product **215** was obtained as brown oil which was reduced in the next step.

3.2.3.2. (1*R*,3*S*)-N^1,N^3-Dibenzyl-1,2,2-trimethylcyclopentane-1,3-diamine (214)



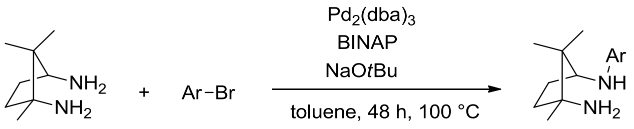
To a solution of N^1,N^3-dibenzylidene-1,2,2-trimethylcyclopentane-1,3-diamine **215** (1.85 g, 5.82 mmol) in dry methanol (20 mL) was carefully added sodium borohydride (0.81 g, 21.43 mmol) under a stream of argon. The resulting mixture was stirred at room temperature for 5 h. Water (25 mL) was added and methanol was evaporated. Ethyl acetate (20 mL) was added and the organic phase was washed with 2N hydrochloric acid (3 x 50 mL). The aqueous phase was basified with 12N sodium hydroxide and extracted with methylene chloride (3 x 50 mL). The combined organic layers were dried (Na_2SO_4). The solvent was evaporated to give a diamine **214** as yellow oil (1.38 g, 4.37 mmol, 75%). Spectral data were consistent with literature values.[176]

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.28 – 7.36 (m, 10H, *H*-1', *H*-2', *H*-3', *H*-4', *H*-5' *H*-6', *H*-1'', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 3.66 – 3.92 (m, 4H, *H*-1''', *H*-1''''), 2.88 (dd, *J* = 8.2, 6.1 Hz, 1H, *H*-3), 2.04 (m, 1H, H-4), 1.90 (m, 1H, *H*-5), 1.64 (m, 1H, *H*-4), 1.46 (m, 1H, *H*-5), 1.14 (s, 3H, *H*-8), 1.02 (s, 3H, *H*-6), 0.99 (s, 3H, *H*-7) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 142.1 (*C*-1'), 141.3 (*C*-1''), 128.3 (*C*-2', *C*-6', *C*-2'', *C*-6''), 128.2 (*C*-2'', *C*-6''), 128.1 (*C*-3', *C*-5'), 128.0 (*C*-3'', *C*-5''), 126.7 (*C*-4'), 126.6 (*C*-4''), 66.7 (*C*-1), 64.6 (*C*-3), 52.6 (*C*-1'''), 47.6 (*C*-1''''), 47.3 (*C*-2), 34.2 (*C*-4), 28.5 (*C*-5), 24.4 (*C*-8), 20.7 (*C*-6), 17.0 (*C*-7) ppm.

3.2.4. Regioselective Arylation of Camphor Diamine

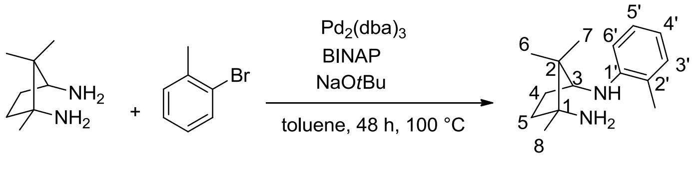
General Procedure



In a dried Schlenk-tube $Pd_2(dba)_3$ (2-4 mol%), (±)-BINAP (6-9 mol%) and NaO*t*Bu (3 equiv.) were dissolved in toluene under a nitrogen atmosphere and stirred for 20 min. Camphor diamine **208** (1 equiv.) and a bromoaryl **216-224** (1 equiv.) were added and the solution was stirred for 48 h at 100 °C. The solution was filtered through a plug of silica and the plug was eluted with additional toluene. Thereafter, the plug was eluted with CH_2Cl_2/MeOH (9:1) until all the product was removed from the silica plug. The solvent was evaporated under reduced pressure and the crude product was dissolved in CH_2Cl_2. The organic phase was extracted with 12 M HCl. The aqueous phase was separated and washed 3x with CH_2Cl_2. Thereafter, the aqueous phase was cooled to

0 °C and 12 M NaOH was slowly added until the solution had a pH of 14. The basic solution was extracted 5x with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed. The crude product was dissolved in pentane and the solution was filtered to remove insoluble impurities.

3.2.4.1. (1*R*,3*S*)-1,2,2-Trimethyl-*N*^{3}-(*o*-tolyl)cyclopentane-1,3-diamine (225)



208 **216** **225**

Prepared from $Pd_2(dba)_3$ (0.80 g, 0.87 mmol, 4 mol%), (±)-BINAP (1.20 g, 1.93 mmol, 9 mol%), NaO*t*Bu (6.10 g, 63.48 mmol), diamine **208** (3.00 g, 21.09 mmol), 2-bromotoluene **216** (2.50 mL, 20.79 mmol) in toluene (360 mL). After work up, the product **225** was obtained as a yellow solid (4.00 g, 17.21 mmol, 82%).

Mp: 95 °C.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.10 – 7.05 (m, 1H, *H*-4'), 7.03 (dd, *J* = 7.3, 0.6 Hz, 1H, *H*-6'), 6.61 – 6.55 (m, 2H, *H*-5', *H*-3'), 5.11 (s, 1H, *H*-N^3), 3.68 (d, *J* = 4.5 Hz, 1H, *H*-3), 2.28 – 2.18 (m, 1H, *H*-4), 2.13 (s, 3H, 2'-C*H*$_3$), 1.86 – 1.77 (m, 1H, *H*-5), 1.69 – 1.56 (m, 2H, *H*-5, *H*-4), 1.18 (s, 3H, *H*-8), 1.02 (s, 3H, *H*-7), 0.98 (s, 3H, *H*-6) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 146.6 (*C*-1'), 130.1 (*C*-6'), 126.9 (*C*-4'), 122.3 (*C*-2'), 115.7 (*C*-3'), 109.6 (*C*-5'), 62.6 (*C*-3), 61.7 (*C*-1), 47.2 (*C*-2), 38.2 (*C*-5), 29.4 (*C*-4), 26.5 (*C*-8), 25.0 (*C*-6), 17.9 (2'-*C*H$_3$), 17.3 (*C*-7) ppm.

^{15}N-NMR (51 MHz, $CDCl_3$) δ = 82.4 (bs, 1N, *N*^{2}), 52.1 (bs, 1N, *N*^{1}) ppm.

IR (ATR) ν = 3288, 2967, 1602, 1580, 1502, 1448, 1386, 1364, 1314, 1262, 1227, 1144, 1049, 980, 953, 909, 856, 745, 715, 654 cm^{-1}.

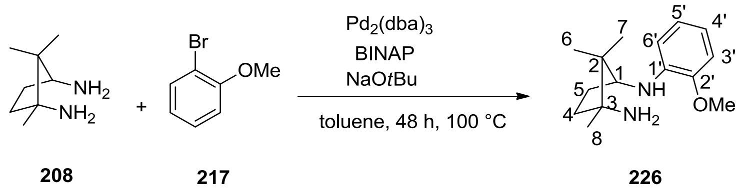
MS (EI, 70 eV): m/z (%) = 248 (16) [M]$^+$, 216 (10), 123 (100), 108 (15), 70 (10).

HRMS (ESI): Calcd. for $C_{15}H_{25}N_2$: 233.2018 $[M+H]^+$, found: 233.2017.

Anal. Calc. for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06; found: C, 77.43; H, 10.31; N, 12.00.

$[\alpha]^{20}_{D}$ = +112 (c = 6, $CHCl_3$).

3.2.4.2. (1*S*,3*R*)-*N*^{1}-(2-Methoxyphenyl)-2,2,3-trimethylcyclo-pentane-1,3-diamine (226)



Prepared from $Pd_2(dba)_3$ (0.80 g, 0.87 mmol, 4 mol%), (±)-BINAP (1.20 g, 1.93 mmol, 9 mol%), NaO*t*Bu (6.11 g, 63.48 mmol), diamine **208** (3.00 g, 21.09 mmol), 2-bromoanisole **217** (2.60 mL, 20.88 mmol) in toluene (360 mL). After work up, the product **226** was obtained as a yellow solid (5.20 g, 20.94 mmol, 99%).

Mp: 65 °C.

^{1}H-N.MR (500 MHz, $CDCl_3$) δ = 6.85 (ddd, *J* = 7.7, 6.1, 1.4 Hz, 1H, *H*-5’), 6.77 (dd, *J* = 7.9, 1.3 Hz, 1H, *H*-3’), 6.66 – 6.59 (m, 2H, *H*-6’, *H*-4’), 4.96 (bs, 1H, *H*-*N*^{1}), 3.85 (s, 3H, 2’-OC*H*$_3$), 3.73 – 3.66 (m, 1H, *H*-1), 2.24 (dddd, *J* = 13.6, 10.3, 8.5, 4.9 Hz, 1H, *H*-5), 1.76 (ddd, *J* = 13.2, 10.3, 6.1 Hz, 1H, *H*-4), 1.66 (ddd, *J* = 13.3, 11.0, 4.9 Hz, 1H, *H*-4), 1.54 (ddt, *J* = 13.7, 11.0, 6.0 Hz, 1H, *H*-5), 1.15 (s, 3H, *H*-8), 0.97 (s, 3H, *H*-6), 0.96 (s, 3H, *H*-7) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 146.9 (*C*-2’), 138.7 (*C*-1’), 121.3 (*C*-5’), 115.5 (*C*-4’), 110.0 (*C*-6’), 109.8 (*C*-3’), 61.8 (*C*-1), 61.0 (*C*-3), 55.6 (2’-O*C*H$_3$), 47.1 (*C*-2), 38.3 (*C*-4), 29.3 (*C*-5), 26.3 (*C*-8), 23.7 (*C*-6), 17.2 (*C*-7) ppm.

^{15}N-NMR (51 MHz, $CDCl_3$) δ = 70.5 (bs, 1N, *N*^{1}), 47.7 (bs, 1N, *N*^{2}) ppm.

IR (KBr) ν = 3435, 3062, 2961, 2869, 2284, 1601, 1515, 1454, 1428, 1368, 1341, 1311, 1223, 1179, 1119, 1026, 879, 839, 737, 551 cm^{-1}.

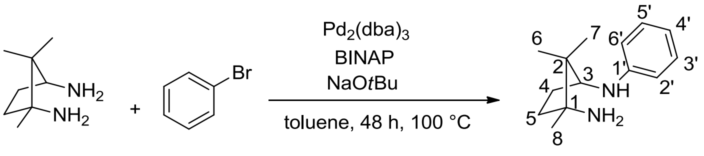
MS (EI, 70 eV): m/z (%) = 248 (16) $[M]^+$, 216 (10), 123 (100), 108 (15), 70 (10).

HRMS (ESI): Calcd. for $C_{13}H_{25}N_2O$: 249.1967 $[M+H]^+$, found: 249.1976.

Anal. Calc. for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28; found: C, 72.41; H, 9.71; N, 11.21.

$[\alpha]^{20}_D$ = +51 (c = 2.7, $CHCl_3$).

3.2.4.3. (1*R*,3*S*)-1,2,2-Trimethyl-*N*³-phenylcyclopentane-1,3-diamine (227)



208 **218** **227**

Prepared from $Pd_2(dba)_3$ (0.30 g, 0.33 mmol, 2.5 mol%), (±)-BINAP (0.52 g, 0.80 mmol, 6 mol%), NaO*t*Bu (1.70 g, 17.69 mmol), diamine **208** (2.50 g, 17.57 mmol), bromobenzene **218** (1.80 mL, 17.14 mmol) in toluene (180 mL). After work up, the product **227** was obtained as brown oil (2.30 g, 10.53 mmol, 60%).

¹H-NMR (500 MHz, $CDCl_3$) δ = 7.15 (dd, *J* = 8.6 Hz, *H*-6’, *H*-2’), 6.62 (m, 3H, *H*-3’, *H*-4’, *H*-5’), 5.2 – 4.7 (s (br), 1H, *H*-N^1), 3.65 (m, 1H, *H*-3), 2.21 (m, 1H, *H*-4), 1.77 (m, 1H, *H*-5), 1.59 (m, 2H, *H*-5, *H*-4), 1.38-1.20 (s (br), 2H, *H*-N^3), 1.14 (s, 3H, *H*-8), 0.96 (s, 3H, *H*-7), 0.95 (s, 3H, *H*-6) ppm.

¹³C-NMR (126 MHz, $CDCl_3$) δ = 148.7 (*C*-1’), 129.2 (*C*-6’, *C*-2’), 116.3 (*C*-4’), 113.1 (*C*-5’, *C*-33), 62.6 (*C*-3), 61.3 (*C*-1), 47.2 (*C*-2), 38.2 (*C*-5), 29.1 (*C*-4), 26.5 (*C*-8), 24.5 (*C*-6), 17.2 (*C*-7) ppm.

¹⁵N-NMR (51 MHz, $CDCl_3$) δ = 83.8 (bs, 1N, N^2), 51.0 (bs, 1N, N^1) ppm.

IR (ATR) ν = 3401, 3360, 3300, 3083, 3052, 3020, 2959, 2867, 1909, 1595, 1500, 1468, 1312, 854, 742, 690, 502 cm^{-1}.

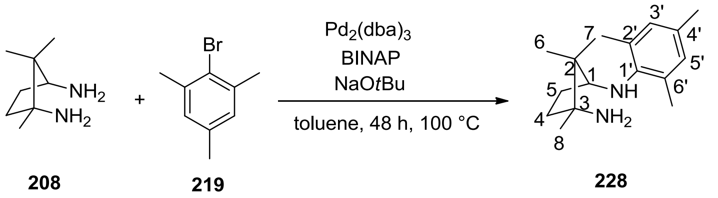
MS (EI, 70 eV): m/z (%) = 218 (85) [M]$^+$, 201 (27), 186 (77), 132 (40), 126 (97), 119 (72), 109 (68), 93 (100), 77 (32), 70 (72), 57 (65), 41 (30).

HRMS (ESI): Calcd. for $C_{14}H_{23}N_2$: 219.1861 [M+H]$^+$, found: 219.1854.

Anal. Calc. for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83; found: C, 76.86; H, 10.11; N, 12.69

$[\alpha]^{20}_D$ = +112.2 (c = 1.05, CH_2Cl_2).

3.2.4.4. (1*S*,3*R*)-*N*^{1}-Mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (228)



Prepared from $Pd_2(dba)_3$ (0.80 g, 0.87 mmol, 4 mol%), (±)-BINAP (1.20 g, 1.93 mmol, 9 mol%), NaO*t*Bu (6.11 g, 63.48 mmol), diamine **208** (3.00 g, 21.09 mmol), 2-bromo-1,3,5-trimethyl-benzol **219** (3.20 mL, 20.90 mmol) in toluene (360 mL). The product **228** was obtained as yellow oil (5.30 g, 20.35 mmol, 97%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 6.78 (s, 2H, *H*-5', *H*-3'), 4.21 (bs, 1H, *H*-N^1), 3.42 (dd, *J* = 7.7, 4.9 Hz, 1H, *H*-1), 2.25 (s, 6H, 6'-C*H*$_3$, 2'-C*H*$_3$), 2.21 (s, 3H, 4'-C*H*$_3$), 1.90 – 1.81 (m, 1H, *H*-5), 1.75 – 1.60 (m, 2H, *H*-4), 1.54 – 1.45 (m, 1H, *H*-5), 1.12 (s, 3H, *H*-8), 1.09 (s, 3H, *H*-7), 0.94 (s, 3H, *H*-6) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 143.5 (*C*-1'), 129.7 (*C*-6', *C*-2'), 129.6 (*C*-5', *C*-3'), 128.7 (*C*-4'), 66.4 (*C*-1), 61.2 (*C*-3), 47.0 (*C*-2), 38.2 (*C*-4), 28.6 (*C*-5), 26.8 (*C*-8), 23.9 (*C*-6), 20.5 (*C*-4'), 19.4 (*C*-6', *C*-2'), 17.1 (*C*-7) ppm.

^{15}N-NMR (51 MHz, $CDCl_3$) δ = 68.8 (bs, 1N, *N*^{1}), 50.6 (bs, 1N, *N*^{2}) ppm.

IR (ATR) ν = 3319, 2961, 2866, 1584, 1481, 1386, 1370, 1300, 1237, 1156, 1137, 1110, 1059, 1026, 927, 890, 851, 810, 763 cm^{-1}.

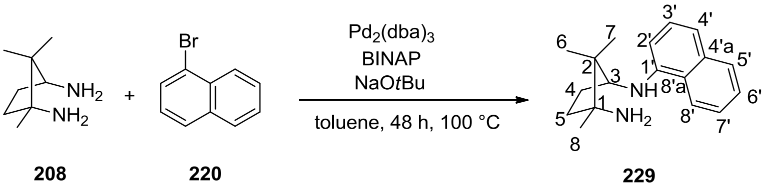
MS (EI, 70 eV): m/z (%) = 260 (24) [M]$^+$, 228 (22), 161 (8), 146 (21), 135 (100), 120 (8), 86 (9), 70 (46), 57 (30), 41 (11).

HRMS (EI): Calcd. for $C_{17}H_{28}N_2$: 260.2247 [M]$^+$, found: 260.2248.

Anal. Calc. for $C_{17}H_{28}N_2$: C, 78.41; H, 10.84; N, 10.76; found: C, 78.39; H, 10.80; N, 10.75.

$[\alpha]^{20}_D$ = +79 (c = 4.3, $CHCl_3$).

3.2.4.5. (1*R*,3*S*)-1,2,2-Trimethyl-*N*^{3}-(naphthalen-1-yl)cyclo-pentane-1,3-diamine (229)



Prepared from $Pd_2(dba)_3$ (0.51 g, 0.55 mmol, 4 mol%), (±)-BINAP (0.50 g, 0.80 mmol, 6 mol%), NaO*t*Bu (4.10 g, 42.66 mmol), diamine **208** (2.00 g, 14.06 mmol), 1-bromonaphthalene **220** (1.90 mL, 13.58 mmol) in toluene (180 mL). After work up, the product **229** was further purified *via* column chromatography (CH_2Cl_2/MeOH, 99:1) on neutral aluminum oxide and obtained as a white solid (2.41 g, 8.94 mmol, 64%).

Mp: 126 °C.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.0 Hz, 1H, *H*-8’), 7.81 – 7.74 (m, 1H, *H*-5’), 7.46 – 7.37 (m, 2H, *H*-7’, H-6’), 7.34 (t, *J* = 7.9 Hz, 1H, *H*-3’), 7.15 (d, *J* = 8.2 Hz, 1H, *H*-4’), 6.64 – 6.48 (m, 2H, *H*-N^3, *H*-2’), 3.84 (d, *J* = 5.0 Hz, 1H, *H*-3), 2.37 – 2.25 (m, 1H, *H*-4), 1.93 – 1.85 (m, 1H, *H*-5), 1.85 – 1.76 (m, 1H, *H*-4), 1.75 – 1.66 (m, 1H, *H*-5), 1.23 (s, 3H, *H*-8), 1.13 (s, 3H, *H*-7), 1.05 (s, 3H, *H*-6) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 144.1 (*C*-1’), 134.7 (*C*-4’a), 128.5 (*C*-5’), 126.8 (*C*-3’), 125.5 (*C*-6’), 124.2 (*C*-7’), 124.0 (*C*-8’a), 120.9 (*C*-8’), 115.7 (*C*-4’), 103.6 (*C*-2’), 63.3 (*C*-3), 62.2 (*C*-1), 47.5 (*C*-2), 38.2 (*C*-5), 29.2 (*C*-4), 26.4 (*C*-8), 25.7 (*C*-6), 17.4 (*C*-7) ppm.

^{15}N-NMR (51 MHz, $CDCl_3$) δ = 83.6 (bs, 1N, N^2), 54.4 (bs, 1N, N^1) ppm.

IR (ATR) ν = 1258, 1227, 1153, 1028, 633, 574, 517 cm^{-1}.

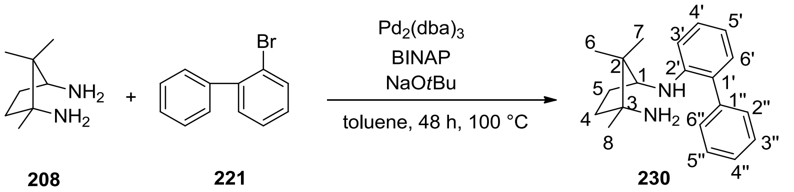
MS (EI, 70 eV): m/z (%) = 268 (34), 157 (36), 143 (100), 112 (49), 97 (44), 95 (24), 83 (66), 71 (53), 70 (58), 69 (58), 57 (84), 55 (63), 44 (42), 43 (57), 41 (56).

HRMS (ESI): Calcd. for $C_{18}H_{24}N_2Na$: 291.1837 [M+H+Na]$^+$, found: 291.1829.

Anal. Calc. for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44; found: C, 80.55; H, 9.13; N, 10.43.

[α]$^{20}_{D}$ = +137 (c = 2.1, $CHCl_3$).

3.2.4.6. (1*S*,3*R*)-*N*^{1}-([1,1'-Biphenyl]-2-yl)-2,2,3-trimethylcyclo-pentane-1,3-diamine (230)



Prepared from $Pd_2(dba)_3$ (0.83 g, 0.87 mmol, 4 mol%), (±)-BINAP (1.21 g, 1.93 mmol, 9 mol%), NaO*t*Bu (6.20 g, 64.52 mmol), diamine **208** (3.10 g, 21.79 mmol), 2-bromo-1,1´-biphenyl **221** (3.70 mL, 20.26 mmol) in toluene (360 mL). After work up, the product **230** was obtained as yellow oil (4.72 g, 15.96 mmol, 73%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.47 – 7.38 (m, 4H, *H*-6’’, *H*-5’’, *H*-3’’, *H*-2’’), 7.34 – 7.29 (m, 1H, *H*-4’’), 7.19 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H, *H*-6’), 7.08 (dd, *J* = 7.6, 1.7 Hz, 1H, *H*-4’), 6.72 – 6.67 (m, 2H, *H*-5’, *H*-3’), 4.90 (s, 1H, *H*-N^1), 3.64 (s, 1H, *H*-1), 2.19 (tdt, *J* = 10.6, 8.2, 5.4 Hz, 1H, *H*-5), 1.72 (ddd, *J* = 13.4, 10.5, 6.0 Hz, 1H, *H*-4), 1.61 –

1.52 (m, 1H, *H*-4), 1.49 – 1.38 (*H*-5), 1.11 (s, 3H, *H*-8), 0.91 (s, 3H, *H*-7), 0.78 (s, 3H, *H*-6) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 145.5 (*C*-2'), 140.0 (*C*-1''), 130.3 (*C*-4'), 129.5 (*C*-5'', *C*-3''), 128.6 (*C*-6'), 128.6 (*C*-6'', *C*-2''), 127.9 (*C*-1'), 126.9 (*C*-4''), 116.0 (*C*-5'), 110.5 (*C*-3'), 62.2 (*C*-1), 61.2 (*C*-3), 47.1 (*C*-2), 37.9 (*C*-4), 29.0 (*C*-5), 26.1 (*C*-8), 23.8 (*C*-7), 17.2 (*C*-6) ppm.

^{15}N-NMR (51 MHz, $CDCl_3$) δ = 79.6 (bs, 1N, N^1), 50.4 (bs, 1N, N^2) ppm.

IR (ATR) ν = 3296, 3057, 2959, 2867, 1597, 1576, 1506, 1489, 1462, 1436, 1387, 1368, 1319, 1283, 1161, 1144, 1063, 1007, 994, 927, 879, 841, 769, 734, 701, 615 cm^{-1}.

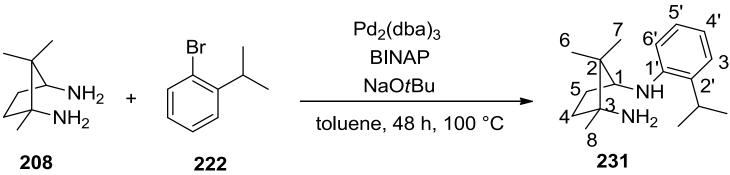
MS (EI, 70 eV): m/z (%) = 294 (9) $[M]^+$, 258 (34), 248 (15), 216 (12), 169 (99), 123 (100), 110 (70), 70 (58), 57 (65).

HRMS (ESI): Calcd. for $C_{20}H_{27}N_2$: 295.2174 $[M+H]^+$, found: 295.2162.

Anal. Calc. for $C_{20}H_{26}N_2$: C, 81.59; H, 8.90; N, 9.51; found: C, 80.95; H, 8.98; N, 9.43.

$[\alpha]^{20}_D$ = +44 (c = 7, $CHCl_3$).

3.2.4.7. (1*S*,3*R*)-*N*^{1}-(2-Isopropylphenyl)-2,2,3-trimethylcyclopentane-1,3-diamine (231)



Prepared from $Pd_2(dba)_3$ (0.50 g, 0.55 mmol, 4 mol%), (±)-BINAP (0.81 g, 1.29 mmol, 9 mol%), NaO*t*Bu (4.10 g, 42.66 mmol), diamine **208** (2.00 g, 14.06 mmol), 1-bromo-2-isopropylbenzene **222** (2.20 mL, 14.37 mmol) in toluene (350 mL). After work up, the product **231** was obtained as brown oil (1.80 g, 6.91 mmol, 49%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.13 – 7.03 (m, 2H, *H*-5’, *H*-3’), 6.67 – 6.59 (m, 2H, *H*-6’, *H*-4’), 5.41 (s, 1H, *H*-N^1), 3.66 (s, 1H, *H*-1), 2.92 – 2.87 (m, 1H, 2’-C*H*$(CH_3)_2$), 2.25 – 2.17 (m, 1H, *H*-5), 1.84 – 1.78 (m, 1H, *H*-4), 1.64 – 1.56 (m, 2H, *H*-5, *H*-4), 1.25 (t, *J* = 7.1 Hz, 6H, 2’-CH(C*H*)$_3$), 1.16 (s, 3H, *H*-8), 1.02 (s, 3H, *H*-7), 0.97 (s, 3H, *H*-6) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 145.3 (*C*-1’), 132.5 (*C*-2’), 126.6 (*C*-4’), 124.9 (*C*-6’), 115.9 (*C*-3’), 110.1 (*C*-5’), 62.8 (*C*-3), 61.5 (*C*-1), 47.3 (*C*-2), 38.5 (*C*-5), 29.3 (2’-*C*H$(CH_3)_2$), 27.5 (*C*-4), 26.8 (2’-CH*C*H$_3$), 25.1 (2’-CH*C*H$_3$), 22.5 (*C*-8), 22.1 (*C*-7), 17.3 (*C*-6) ppm.

^{15}N-NMR (51 MHz, $CDCl_3$) δ = 80.6 (br, 1N, *N*^{1}), 51.1 (br, 1N, *N*^{2}) ppm.

IR (ATR) ν = 3306, 2957, 2870, 1602, 1579, 1509, 1451, 1364, 1258, 1056, 886, 735 cm^{-1}.

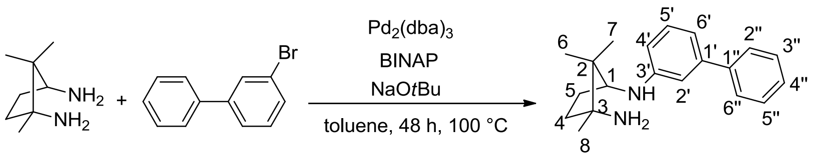
MS (EI, 70 eV): m/z (%) = 261 (6) [M]$^+$, 260 (26), 243 (5), 228 (16), 201 (2), 200 (6), 186 (3), 161 (4), 146 (24), 135 (100), 120 (57), 110 (71), 93 (11), 71 (15), 70 (43), 57 (56), 42 (22).

HRMS (ESI): Calcd. for $C_{17}H_{29}N_2$: 261.2331 [M+H]$^+$, found: 261.2324.

Anal. Calc. for $C_{17}H_{28}N_2$: C, 78.41; H, 10.84; N, 10.76; found: C, 78.38; H, 10.34; N, 10.90.

$[\alpha]^{20}_D$ = +172 (c = 0.55, CH_2Cl_2).

3.2.4.8. (1*S*,3*R*)-*N*^{1}-([1,1'-Biphenyl]-3-yl)-2,2,3-trimethylcyclopentane-1,3-diamine (232)



208 **223** **232**

Prepared from $Pd_2(dba)_3$ (0.08 g, 0.09 mmol, 4 mol%), (±)-BINAP (0.10 g, 0.16 mmol, 9 mol%), NaO*t*Bu (0.62 g, 6.24 mmol), diamine **208** (0.32 g, 2.11 mmol), 3-bromobiphenyl **223** (0.40 mL, 2.40 mmol) in toluene (60 mL). After work up, the product **232** was obtained as yellow oil (0.33 g, 1.02 mmol, 48%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.67 – 7.64 (m, 2H, *H*-6'', *H*-5''), 7.50 – 7.45 (m, 2H, *H*-2'', *H*-3''), 7.40 – 7.36 (m, 1H, *H*-4''), 7.29 – 7.25 (m, 1H, *H*-6'), 6.93 (ddd, *J* = 7.5, 1.6, 0.9 Hz, 1H, *H*-5'), 6.90 – 6.87 (m, 1H, *H*-4'), 6.66 (ddd, *J* = 8.1, 2.4, 0.8 Hz, 1H, *H*-2'), 5.19 (br s, 1H, *H*-N^3), 3.76 (d, *J* = 4.6 Hz, 1H, *H*-1), 2.32 – 2.25 (m, 1H, *H*-5), 1.87 – 1.80 (m, 1H, *H*-4), 1.71 – 1.63 (m, 2H, *H*-5, *H*-4), 1.19 (s, 3H, *H*-8), 1.04 (s, 3H, *H*-7), 1.02 (s, 3H, *H*-6) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 149.1 (*C*-3'), 142.4 (*C*-1''), 142.2 (*C*-5'), 129.6 (*C*-5'', *C*-3''), 128.6 (*C*-6'), 127.3 (*C*-6'', *C*-2''), 127.1(*C*-1'), 115.6 (*C*-4''), 112.2 (*C*-5'), 112.1 (*C*-4'), 62.8 (*C*-1), 61.4 (*C*-3), 47.4 (*C*-2), 38.3 (*C*-4), 29.3 (*C*-5), 26.6 (C-8), 24.8 (C-7), 17.3 (C-6) ppm.

^{15}N-NMR (51 MHz, $CDCl_3$) δ = 84.1 (bs, 1N, N^1), 51.1 (bs, 1N, N^2) ppm.

IR (ATR) ν = 3286, 3051, 2940, 2866, 1577, 1523, 1480, 1466, 1425, 1374, 1346, 1253, 1161, 1140, 1076, 1011, 927, 899, 845, 759, 713, 616 cm^{-1}.

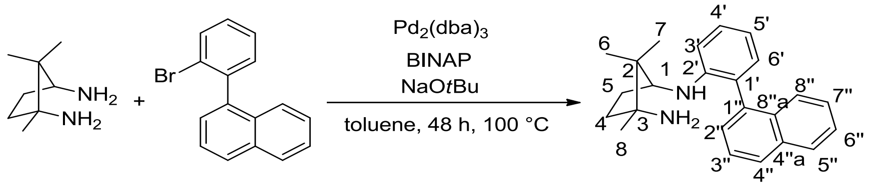
MS (EI, 70 eV): m/z (%) = 294 (15) $[M]^+$, 277 (4), 262 (9), 250 (3), 234 (8), 208 (4), 195 (8), 194 (4), 170 (17), 169 (100), 155 (13), 152 (6), 126 (11), 93 (5), 70 (5), 41 (4).

HRMS (ESI): Calcd. for $C_{20}H_{27}N_2$: 295.2174 $[M+H]^+$, found: 295.2172.

Anal. Calc. for $C_{20}H_{28}N_2$: C, 81.59; H, 8.90; N, 9.51; found: C, 80.70; H, 9.17; N, 9.52.

$[\alpha]^{20}_D$ = +88 (c = 0.49, CH_2Cl_2).

3.2.4.9. 1,2,2-Trimethyl-N^3-(2-(naphthalen-1-yl)phenyl)cyclopentane-1,3-diamine (233)



208 **224** **233**

Prepared from Pd$_2$(dba)$_3$ (0.03 g, 0.03 mmol, 4 mol%), (±)-BINAP (0.04 g, 0.06 mmol, 9 mol%), NaO*t*Bu (0.2 g, 2.08 mmol), diamine **208** (0.10 g, 0.71 mmol), 1-(2-bromophenyl)naphthalene **224** (0.20 mg, 0.70 mmol) in toluene (100 mL). After work up, the product **233** was obtained as a mixture of diastereoisomers with an axis of chirality (*P*, *M*) as a yellow solid (0.08 g, 0.23 mmol, 33%).

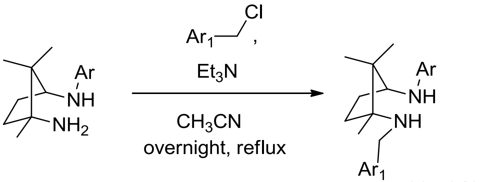
^{1}**H-NMR** (500 MHz, CDCl$_3$) δ = 7.86 (dd, *J* = 16.7, 8.1 Hz, 4H, *H*-8’’$_{\mathrm{D1}}$, *H*-8’’$_{\mathrm{D2}}$, *H*-2’’$_{\mathrm{D1}}$, *H*-2’’$_{\mathrm{D2}}$), 7.72 – 7.62 (m, 2H, *H*-5’’$_{\mathrm{D1}}$, *H*-5’’$_{\mathrm{D2}}$), 7.58 – 7.28 (m, 10H, *H*-4’’$_{\mathrm{D1}}$, *H*-4’’$_{\mathrm{D2}}$, *H*-3’’$_{\mathrm{D1}}$, *H*-3’’$_{\mathrm{D2}}$, *H*-6’$_{\mathrm{D1}}$, *H*-6’$_{\mathrm{D2}}$, *H*-6’’$_{\mathrm{D1}}$, *H*-6’’$_{\mathrm{D2}}$, *H*-7’’’$_{\mathrm{D1}}$, *H*-7’’$_{\mathrm{D2}}$), 7.15 (dt, *J* = 7.5, 1.7 Hz, 2H, *H*-4’$_{\mathrm{D1}}$, *H*-4’$_{\mathrm{D2}}$), 6.79 – 6.74 (m, 4H, *H*-5’$_{\mathrm{D1}}$, *H*-5’$_{\mathrm{D2}}$, *H*-3’$_{\mathrm{D1}}$, *H*-3’$_{\mathrm{D2}}$) 4.67 (d, *J* = 9.1 Hz, 1H, *H*-N$^1_{\mathrm{D1}}$), 4.50 (d, *J* = 9.1 Hz, 1H, *H*-N$^1_{\mathrm{D2}}$), 3.81 – 3.48 (m, 2H, *H*-1$_{\mathrm{D1}}$, *H*-1$_{\mathrm{D2}}$), 2.24 – 1.90 (m, 2H, *H*-5$_{\mathrm{D1}}$, *H*-5$_{\mathrm{D2}}$), 1.67 – 1.55 (m, 2H, *H*-4$_{\mathrm{D1}}$, *H*-4$_{\mathrm{D2}}$), 1.42 – 1.20 (m, 4H, *H*-5$_{\mathrm{D1}}$, *H*-5$_{\mathrm{D2}}$, *H*-4$_{\mathrm{D1}}$, *H*-4$_{\mathrm{D2}}$), 0.96 (s, 3H, C*H*$_3$, *H*-8$_{\mathrm{D1}}$), 0.94 (s, 3H, C*H*$_3$, *H*-8$_{\mathrm{D2}}$), 0.82 (s, 3H, C*H*$_3$, *H*-7$_{\mathrm{D1}}$), 0.78 (s, 3H, C*H*$_3$, *H*-7$_{\mathrm{D2}}$), 0.53 (s, 3H, C*H*$_3$, *H*-6$_{\mathrm{D1}}$), 0.37 (s, 3H, C*H*$_3$, *H*-6$_{\mathrm{D2}}$) ppm.

^{13}**C-NMR** (126 MHz, CDCl$_3$) δ = 146.6 (*C*-2’$_{\mathrm{D1}}$), 146.4 (*C*-2’$_{\mathrm{D2}}$), 137.7 (*C*-1’’$_{\mathrm{D1}}$, *C*-1’’$_{\mathrm{D2}}$), 133.9 (*C*-4’’a$_{\mathrm{D1}}$), 133.7 (*C*-4’’a$_{\mathrm{D2}}$), 132.3 (*C*-8’’a$_{\mathrm{D1}}$), 132.1 (*C*-8’’a$_{\mathrm{D2}}$), 130.8 (*C*-4’a$_{\mathrm{D1}}$, *C*-4’a$_{\mathrm{D2}}$), 128.8 (*C*-5’’$_{\mathrm{D1}}$, *C*-5’’$_{\mathrm{D2}}$), 128.1 (*C*-8’’$_{\mathrm{D1}}$), 128.1 (*C*-8’’$_{\mathrm{D2}}$), 127.8 (*C*-4’’$_{\mathrm{D1}}$), 127.8 (*C*-4’’$_{\mathrm{D2}}$), 127.7 (*C*-6’’$_{\mathrm{D1}}$), 127.6 (*C*-6’’$_{\mathrm{D2}}$), 126.9 (*C*-7’’$_{\mathrm{D1}}$, *C*-7’’$_{\mathrm{D2}}$), 126.4 (*C*-3’’$_{\mathrm{D1}}$, *C*-3’’$_{\mathrm{D2}}$), 126.1 (*C*-2’’$_{\mathrm{D1}}$, *C*-2’’$_{\mathrm{D2}}$), 125.9 (*C*-6’$_{\mathrm{D1}}$), 125.8 (*C*-6’$_{\mathrm{D2}}$), 125.8 (*C*-5’$_{\mathrm{D1}}$, *C*-5’$_{\mathrm{D2}}$), 115.7 (*C*-1’$_{\mathrm{D1}}$), 115.6 (*C*-1’$_{\mathrm{D2}}$), 110.2 (*C*-3’$_{\mathrm{D1}}$), 110.1 (*C*-3’$_{\mathrm{D2}}$), 62.4 (*C*-1$_{\mathrm{D1}}$), 62.2 (*C*-1$_{\mathrm{D2}}$), 60.7 (*C*-3$_{\mathrm{D1}}$), 60.6 (*C*-3$_{\mathrm{D2}}$), 46.9 (*C*-2$_{\mathrm{D1}}$, *C*-2$_{\mathrm{D2}}$), 38.2 (*C*-4$_{\mathrm{D1}}$, *C*-4$_{\mathrm{D2}}$), 29.1 (*C*-5$_{\mathrm{D1}}$), 28.8 (*C*-5$_{\mathrm{D2}}$), 26.3 (*C*-8$_{\mathrm{D1}}$), 26.2 (*C*-8$_{\mathrm{D2}}$), 24.2 (*C*-6$_{\mathrm{D1}}$), 23.9 (*C*-6$_{\mathrm{D2}}$), 16.8 (*C*-7$_{\mathrm{D1}}$), 16.7 (*C*-7$_{\mathrm{D2}}$) ppm.

3.2.5. Alkylation of Monosubtituted Diamines

3.2.5.1. Alkylation by Arylmethylene Chloride or Benzyl Bromide

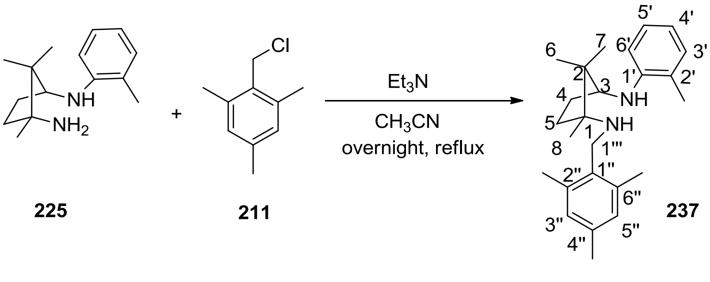
General Procedure



225-231 **237-242**

To the stirred mixture of monosubtituted diamine **225-231** (1 equiv.) and triethylamine (1.2 equiv.) in acetonitrile at room temperature was added arylmethylene chloride or benzyl bromide (1.1 equiv.). The resulting solution was refluxed overnight. After refluxing, the reaction mixture was cooled down, filtered and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash column chromatography.

3.2.5.1.1. (1*R*,3*S*)-1,2,2-Trimethyl-N^3-(*o*-tolyl)-N^1-(2,4,6-trimethylbenzyl) cyclopentane-1,3-diamine (237)



225 **211** **237**

Prepared from monosubstituted diamine **225** (0.30 g, 1.29 mmol), triethylamine (0.22 mL, 1.55 mmol) and 2,4,6-trimethylbenzylchloride **211** (0.24 g, 1.42 mmol) in acetonitrile (10 mL). The crude product was purified *via* column chromatography (CH_2Cl_2/MeOH, 95:5) and the secondary diamine **237** was obtained as colorless oil (0.30 g, 0.82 mmol, 64%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.18 – 7.14 (m, 1H, *H*-5'), 7.06 (dd, *J* = 7.2, 0.6 Hz, 1H, *H*-6'), 6.96 (s, 2H, *H*-3'', *H*-5''), 6.69 (d, *J* = 7.9 Hz, 1H, *H*-3'), 6.65 (td, *J* = 7.3, 1.0 Hz, 1H, *H*-4'), 4.97 (s, 1H, *H*-N^1), 3.86 (d, *J* = 10.7 Hz, 1H, *H*-1'''), 3.82 – 3.77 (m, 1H, *H*-3), 3.74 (d, *J* = 10.7 Hz, 1H, *H*-1'''), 2.46 (s, 6H, 2''-CH_3, 6''-CH_3), 2.39 (s, 3H, 4''-CH_3), 2.28 – 2.18 (m, 2H, *H*-4), 1.90 (s, 3H, 2'-CH_3), 1.80 – 1.71 (m, 2H, *H*-5), 1.36 (s, 3H, *H*-8), 1.14 (s, 3H, *H*-6), 1.02 (s, 3H, *H*-7) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 146.6 (*C*-1'), 136.8 (*C*-2'', *C*-6''), 136.4 (*C*-4''), 134.1 (*C*-1''), 130.2 (*C*-6'), 129.2 (*C*-3'', *C*-5''), 126.9 (*C*-5'), 122.2 (*C*-2'), 115.6 (*C*-4'), 109.5 (*C*-3'), 65.5 (*C*-1), 62.1 (*C*-3), 48.8 (*C*-2), 40.2 (*C*-1'''), 32.5 (*C*-4), 30.6 (*C*-5), 25.9 (*C*-6), 21.0 (4''-CH_3), 19.6 (2''-CH_3, 6''-CH_3), 19.0 (*C*-8), 17.5 (*C*-2'), 17.0 (*C*-7) ppm.

^{15}N-NMR (51 MHz, $CDCl_3$) δ = 83.8 (1N, N^2), 53.5 (1N, N^1) ppm.

IR (ATR) ν = 3360, 2958, 2914, 2865, 1601, 1576, 1507, 1477, 1448, 1384, 1370, 1316, 1257, 1217, 1158, 1070, 1051, 850, 742, 713 cm^{-1}.

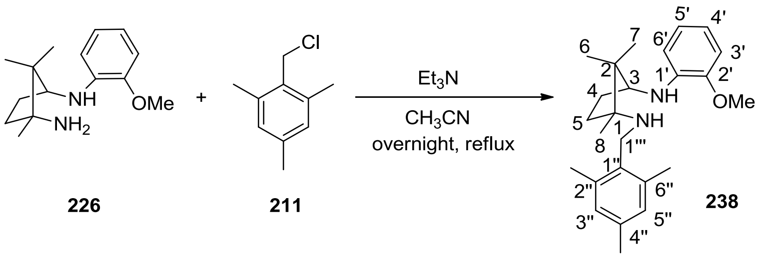
MS (ESI, + 3 kV): *m/z* (%) = 365 ($[M+H]^+$, 100%).

HRMS (ESI): Calc. for $C_{25}H_{37}N_2$: 365.2956, found: 365.2957.

Anal. Calc. for $C_{25}H_{36}N_2$: C, 82.36; H, 9.95; N, 7.68; found: C, 82.13; H, 9.91; N, 7.36.

$[\alpha]^{20}_D$ = +24 (c = 0.5, CH_2Cl_2).

3.2.5.1.2. (1*R*,3*S*)-*N*^{3}-(2-Methoxyphenyl)-1,2,2-trimethyl-*N*^{1}-(2,4,6-trimethylbenzyl)cyclopentane-1,3-diamine (238)



Prepared from monosubstituted diamine **226** (0.30 mg, 1.21 mmol), triethylamine (0.20 mL, 1.45 mmol, 1.2 equiv.) and 2,4,6-trimethylbenzylchloride **211** (0.22 g, 1.33 mmol) in acetonitrile (10 mL). The crude product was purified *via* column chromatography (CH_2Cl_2/MeOH, 95:5) and the secondary diamine **238** was obtained as yellow oil (0.32 g, 0.85 mmol, 71%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 6.95 (s, 2H, *H*-3'', *H*-5''), 6.91 – 6.87 (m, 1H, *H*-5'), 6.77 (dd, *J* = 7.9, 1.3 Hz, 1H, *H*-6'), 6.69 (dd, *J* = 8.0, 1.2 Hz, 1H, *H*-3'), 6.63 (td, *J* = 7.7, 1.5 Hz, 1H, *H*-4'), 3.84 (d, *J* = 10.6 Hz, 1H, *H*-1'''), 3.76 (dd, *J* = 8.4, 4.5 Hz, 1H, *H*-3), 3.72 (s, 3H, 2''-OC*H*$_3$), 3.70 (s, 1H, *H*-1''') 2.46 (s, 6H, 2''-C*H*$_3$, 6''-C*H*$_3$), 2.36 (s, 3H, 4''-C*H*$_3$), 2.20 – 2.11 (m, 2H, *H*-4), 1.76 – 1.64 (m, 2H, *H*-5), 1.33 (s, 3H, *H*-8), 1.09 (s, 3H, *H*-6), 0.97 (s, 3H, *H*-7) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 146.9 (*C*-2'), 138.8 (*C*-1'), 137.2 (*C*-2'', *C*-6''), 136.3 (*C*-4''), 134.3 (*C*-1''), 129.0 (*C*-3'', *C*-5''), 121.2 (*C*-5'), 115.1 (*C*-4'), 109.5 (*C*-6', *C*-3'), 65.0 (*C*-1), 61.9 (*C*-3), 55.2 (2'-O*C*H$_3$), 48.6 (*C*-2), 40.5 (*C*-1'''), 32.8 (*C*-4), 30.3 (*C*-5), 25.5 (*C*-6), 21.0 (4''-*C*H$_3$), 20.2 (*C*-8), 19.5 (2''-*C*H$_3$), 19.4 (6''-*C*H$_3$), 17.0 (*C*-7) ppm.

^{15}N-NMR (51 MHz, $CDCl_3$) δ = 74.1 (bs, 1N, *N*^{1}), 53.5 (bs, 1N, *N*^{2}) ppm.

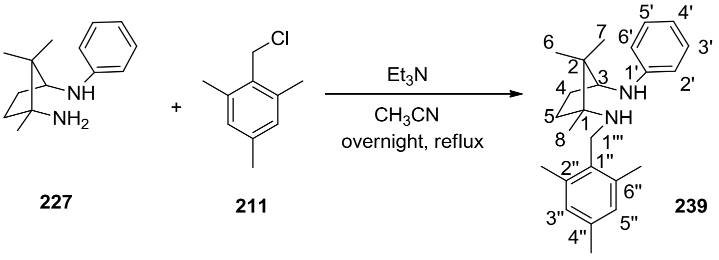
IR (ATR) ν = 3424, 2958, 2865, 1596, 1517, 1453, 1370, 1336, 1252, 1223, 1174, 1110, 1027, 850, 732 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 381 ([M+H]$^+$, 100%).

HRMS (ESI): Calc. for $C_{25}H_{37}N_2$: 381.2913, found: 381.2906.

[α]^{20}$_D$ = +12 (c = 0.49, CH_2Cl_2).

3.2.5.1.3. (1*R*,3*S*)-1,2,2-Trimethyl-*N*^{3}-phenyl-*N*^{1}-(2,4,6-trimethylbenzyl) cyclopentane-1,3-diamine (239)



Prepared from monosubstituted diamine **227** (0.30 g, 1.37 mmol), triethylamine (0.23 mL, 1.65 mmol) and 2,4,6-trimethylbenzylchloride **211** (0.26 g, 1.51 mmol) in acetonitrile (10 mL). The crude product was purified *via* column chromatography (CH_2Cl_2/MeOH, 95:5) and the secondary diamine **239** was obtained as yellow oil (0.30 g, 0.85 mmol, 62%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.27 – 7.23 (m, 2H, *H*-3’, *H*-5’), 7.03 (s, 2H, *H*-3’’, *H*-5’’), 6.75 – 6.71 (m, 1H, *H*-4’), 6.64 (dd, *J* = 8.6, 0.9 Hz, 2H, *H*-2’, *H*-6’), 3.88 (d, *J* = 10.6 Hz, 1H, *H*-1’’’), 3.78 – 3.74 (m, 2H, *H*-1’’’, *H*-3), 2.52 (s, 6H, 2’’-C*H*$_3$, 6’’-C*H*$_3$), 2.43 (s, 3H, 4’’-C*H*$_3$), 2.30 – 2.21 (m, 2H, *H*-4), 1.81 – 1.72 (m, 2H, *H*-5), 1.38 (s, 3H, *H*-8), 1.14 (s, 3H, *H*-6), 1.05 (s, 3H, *H*-7) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 148.7 (*C*-1’), 137.1 (2’-*C*H$_3$, 6’’-*C*H$_3$’), 136.6 (*C*-1’’), 134.1 (*C*-4’’), 129.3 (*C*-3’’, *C*-5’’), 129.2 (*C*-3’, *C*-5’), 116.2 (*C*-4’), 113.0 (*C*-2’, *C*-6’), 65.5 (*C*-1), 62.7 (*C*-3), 48.7 (*C*-2), 40.6 (*C*-1’’’), 32.3 (*C*-4), 30.1 (*C*-5), 26.1 (*C*-6), 21.1 (4’’-*C*H$_3$), 19.6 (2’’-*C*H$_3$, 6’’-*C*H$_3$), 19.4 (*C*-8), 17.1 (*C*-7) ppm.

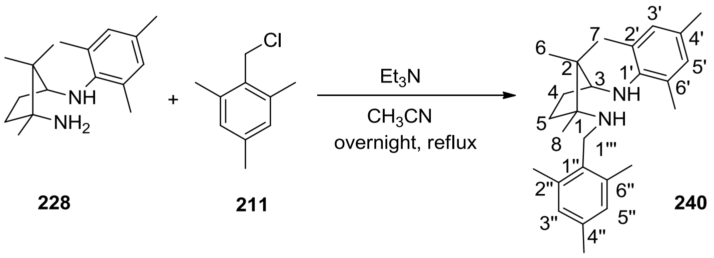
IR (ATR) ν = 3409, 2963, 2865, 1601, 1502, 1384, 1370, 1316, 1257, 1076, 850, 742, 688 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 351 ($[M+H]^+$, 100%).

HRMS (ESI): Calc. for $C_{24}H_{35}N_2$: 351.2808, found: 351.2800.

$[\alpha]^{20}_{D}$ = +71 (c = 0.5, CH_2Cl_2).

3.2.5.1.4. (1*R*,3*S*)-*N*^{3}-Mesityl-1,2,2-trimethyl-*N*^{1}-(2,4,6-trimethylbenzyl) cyclopentane-1,3-diamine (240)



Prepared from monosubstituted diamine **228** (0.30 g, 1.15 mmol), triethylamine (0.19 mL, 1.38 mmol) and 2,4,6-trimethylbenzylchloride **211** (0.21 g, 1.27 mmol) in acetonitrile (10 mL). The crude product was purified *via* column chromatography (CH_2Cl_2/MeOH, 95:5) and the secondary diamine **240** was obtained as colorless oil (0.28 g, 0.11 mmol, 61%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 6.94 (s, 2H, *H*-3'', *H*-5''), 6.84 (s, 2H, *H*-3', *H*-5'), 3.89 (d, *J* = 10.9 Hz, 1H, *H*-1'''), 3.75 (d, *J* = 10.9 Hz, 1H, *H*-1'''), 3.58 (dd, *J* = 8.1, 6.3 Hz, 1H, *H*-3), 2.48 (s, 6H, 2''-C*H*$_3$, 6''-C*H*$_3$), 2.36 (s, 3H, 4''-C*H*$_3$), 2.29 (s, 3H, 4'-C*H*$_3$), 2.28 (s, 6H, 2'-C*H*$_3$, 6'-C*H*$_3$), 2.18 – 2.01 (m, 2H, *H*-4, *H*-5), 1.67 (dqd, *J* = 12.0, 10.1, 5.8 Hz, 2H, *H*-4, *H*-5), 1.32 (s, 3H, *H*-8), 1.12 (s, 3H, *H*-6), 1.10 (s, 3H, *H*-7) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 143.8 (*C*-1'), 136.9 (*C*-1''), 136.3 (*C*-2'', *C*-6''), 134.5 (*C*-4''), 129.8 (*C*-3', *C*-5'), 129.3 (*C*-4'), 129.1 (*C*-3'', *C*-5''), 127.7 (*C*-2', *C*-6'), 65.8 (*C*-3), 64.4 (*C*-1), 48.1 (*C*-2), 40.9 (*C*-1'''), 34.0 (*C*-5), 30.0 (*C*-4), 23.8 (*C*-7), 21.0 (4'- *C*H$_3$), 20.6 (4''- *C*H$_3$), 20.5 (*C*-8), 19.6 (2'-*C*H$_3$, 6'-*C*H$_3$), 19.5 (2''- *C*H$_3$, 6''- *C*H$_3$), 16.9 (*C*-6) ppm.

^{15}N-NMR (51 MHz, $CDCl_3$) δ = 67.46 (1N, *N*^{2}), 54.62 (1N, *N*^{1}) ppm.

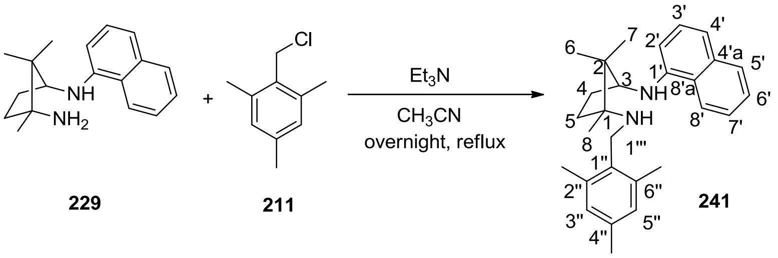
IR (ATR) ν = 3379, 2962, 2864, 1610, 1583, 1477, 1368, 1297, 1226, 1156, 1121, 1085, 1023, 1004, 846, 737, 717, 686, 564 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 393 ($[M+H]^+$, 100%).

HRMS (ESI): Calc. for $C_{27}H_{41}N_2$: 393.3268, found: 393.3270.

$[\alpha]^{20}_{D}$ = −1 (c = 0.48, CH_2Cl_2).

3.2.5.1.5. (1*R*,3*S*)-1,2,2-Trimethyl-*N*^{3}-(naphthalen-1-yl)-*N*^{1}-(2,4,6-trimethylbenzyl)cyclopentane-1,3-diamine (241)



Prepared from monosubstituted diamine **229** (0.30 g, 1.12 mmol), triethylamine (0.19 mL, 1.34 mmol) and 2,4,6-trimethylbenzylchloride **211** (0.21 g, 1.23 mmol) in acetonitrile (10 mL). The crude product was purified *via* column chromatography (CH_2Cl_2/MeOH, 95:5) and the secondary diamine **241** was obtained as brown oil (0.24 g, 0.61 mmol, 54%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 8.0 Hz, 1H, *H*-8’), 7.48 – 7.43 (m, 1H, *H*-5’), 7.39 (dd, *J* = 9.9, 5.9 Hz, 1H, *H*-4’), 7.29 (d, *J* = 8.4 Hz, 1H, *H*-7’), 7.18 (d, *J* = 8.1 Hz, 1H, *H*-6’), 7.11 (t, *J* = 7.5 Hz, 1H, *H*-3’), 7.01 (s, 2H, *H*-3’’, *H*-5’’), 6.64 (d, *J* = 7.6 Hz, 1H, *H*-2’), 3.91 (d, *J* = 10.6 Hz, 2H, *H*-1’’’), 3.79 (d, *J* = 10.8 Hz, 1H, *H*-3), 2.48 (s, 3H, 4’’-C*H*$_3$), 2.41 (d, *J* = 6.4 Hz, 6H, 2’’-C*H*$_3$, 6’’-C*H*$_3$), 2.23-2.09 (m, 2H, *H*-4), 1.91 – 1.75 (m, 2H, *H*-5), 1.40 (s, 3H, *H*-8), 1.18 (s, 3H, *H*-7), 1.09 (s, 3H, *H*-6) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 143.9 (*C*-1’), 137.6 (*C*-4’’), 136.8 (*C*-1’’), 136.5 (*C*-2’’), 134.8 (*C*-6’’), 134.0 (*C*-4’a), 129.5 (*C*-5’), 128.8 (*C*-3’’, *C*-5’’), 128.3 (*C*-3’), 126.9 (*C*-6’), 125.5 (*C*-7’), 123.9 (*C*-8’), 121.1 (*C*-8’a), 115.4 (*C*-4’), 103.0 (*C*-2’), 66.0 (*C*-1), 62.9 (*C*-3), 49.2 (*C*-2), 40.0 (*C*-1’’), 31.9 (*C*-5), 30.2 (*C*-4), 26.5 (4’’-*C*H$_3$), 21.1 (*C*-11), 20.0 (2’’-*C*H$_3$) , 19.7 (6’’-*C*H$_3$), 18.8 (*C*-7), 17.0 (*C*-6) ppm.

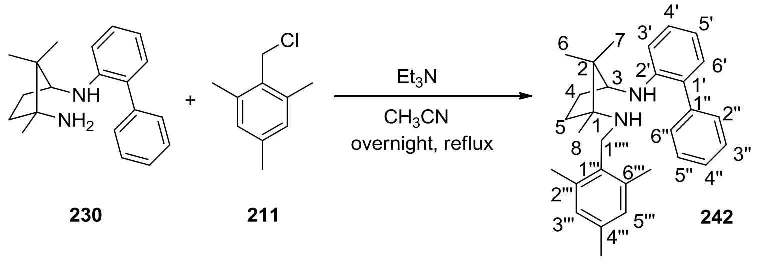
IR (ATR) ν = 3326, 2958, 2867, 1579, 1524, 1482, 1405, 1385, 1371, 1230, 1074, 849, 764, 720 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 400 ([M+H]$^+$, 10%).

HRMS (ESI): Calc. for $C_{28}H_{37}N_2$: 400.2878, found: 400.3000.

[α]$^{20}_{D}$ = −12 (c = 0.47, CH_2Cl_2).

3.2.5.1.6. (1*R*,3*S*)-*N*^{3}-([1,1'-Biphenyl]-2-yl)-1,2,2-trimethyl-*N*^{1}-(2,4,6-trimethylbenzyl)cyclopentane-1,3-diamine (242)



Prepared from monosubstituted diamine **230** (0.30 g, 1.02 mmol), triethylamine (0.17 mL, 1.22 mmol) and 2,4,6-trimethylbenzylchloride **211** (0.19 g, 1.12 mmol) in acetonitrile (10 mL). The crude product was purified *via* column chromatography (CH_2Cl_2/MeOH, 95:5) and the secondary diamine **242** was obtained as yellow oil (0.25 g, 0.58 mmol, 57%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.46 – 7.43 (m, 2H, *H*-6’, *H*-4’’), 7.36 – 7.28 (m, 4H, *H*-3’’, *H*-5’’, *H*-3’, *H*-4’), 7.17 (dd, *J* = 7.4, 1.6 Hz, 1H, *H*-5’), 6.91 (s, 2H, *H*-3’’’, *H*-5’’’), 6.81 (ddd, *J* = 8.4, 6.2, 2.6 Hz, 2H, *H*-2’’, *H*-6’’), 4.49 (br s, 1H, *H*-N^3), 3.79 (d, *J* = 10.7 Hz, 2H, *H*-1’’’’), 3.62 (d, *J* = 10.7 Hz, 1H, *H*-3), 2.39 (s, 3H, 4’’’-CH_3), 2.35 (s, 6H, 2’’’-CH_3, 6’’’-CH_3), 2.18 – 2.11 (m, 1H, *H*-4), 2.07 – 1.99 (m, 1H, *H*-5), 1.73 (ddd, *J* = 13.4, 9.7, 7.4 Hz, 1H, *H*-5), 1.56 – 1.47 (m, 1H, *H*-4), 1.33 (s, 3H, *H*-8), 1.08 (s, 3H, *H*-7), 0.85 (s, 3H, *H*-6) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 145.5 (*C*-2’), 139.8 (*C*-1’’), 137.1 (*C*-4’’’), 136.2 (*C*-2’’’, *C*-6’’’), 134.2 (*C*-3’’, *C*-5’’), 130.5 (*C*-4’), 129.3 (*C*-2’’, *C*-6’’), 129.1 (*C*-4’’), 128.7 (*C*-3’’’, *C*-5’’’), 127.8 (*C*-6’), 127.0 (*C*-5’), 116.2 (*C*-1’), 110.7 (*C*-3’), 64.4 (*C*-1), 62.0 (*C*-3), 48.2 (*C*-2), 40.7 (*C*-1’’’’), 33.4 (*C*-5), 30.1 (*C*-4), 24.8 (4’’’-CH_3), 21.0 (*C*-8), 19.9 (2’’’-CH_3, 6’’’-CH_3), 19.5 (*C*-7), 16.9 (*C*-6) ppm.

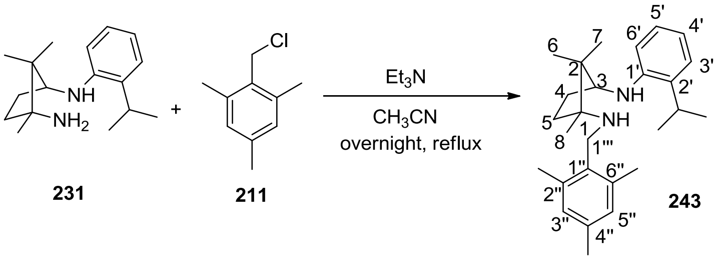
IR (ATR) ν = 3424, 2958, 2860, 1600, 1578, 1508, 1435, 1317, 849, 768, 739, 702 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 427 ($[M+H]^+$, 100%).

HRMS (ESI): Calc. for $C_{30}H_{39}N_2$: 427.3116, found: 427.3113.

$[\alpha]^{20}_D$ = –50 (c = 0.48, CH_2Cl_2).

3.2.5.1.7. (1*R*,3*S*)-*N*



Prepared from monosubstituted diamine **231** (0.30 g, 1.15 mmol), triethylamine (0.19 mL, 1.40 mmol) and 2,4,6-trimethylbenzylchloride **211** (0.21 g, 1.27 mmol) in acetonitrile (10 mL). The crude product was purified *via* column chromatography (CH_2Cl_2/MeOH, 95:5) and the secondary diamine **243** was obtained as yellow oil (0.23 g, 0.59 mmol, 51%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.15 – 7.09 (m, 2H, *H*-3’, H-5’), 6.95 (s, 2H, H-3’’, H-5’’), 6.69 (dd, *J* = 7.8, 5.1 Hz, 2H, *H*-4’, H-6’), 5.20 (br s, 1H, N^3*H*), 3.92 – 3.63 (m, 4H, *H*-1’’’, *H*-3, 2’-C*H*), 2.44 (s, 6H, 2’’-CH_3, 6’’-CH_3), 2.38 (s, 3H, 4’’-CH_3), 2.23 (ddd, *J* = 18.2, 13.7, 10.5 Hz, 2H, *H*-5), 1.78 – 1.68 (m, 2H, *H*-4), 1.35 (s, 3H, *H*-8), 1.16 (d, *J* = 6.7 Hz, 3H, 2’-C-CH_3), 1.13 (s, *J* = 5.9 Hz, 3H, 2’-C-CH_3), 1.01 (s, 3H, *H*-7), 0.93 (s, 3H, *H*-6) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 146.3 (*C*-1’), 136.6 (*C*-4’’), 136.3 (*C*-2’’), 134.1 (*C*-6’’’), 132.1 (*C*-2’’), 129.2 (*C*-3’’), 126.6 (*C*-5’’), 125.5 (*C*-3’), 124.9 (*C*-5’), 115.7 (*C*-4’), 109.7 (*C*-6’), 65.5 (*C*-1), 62.2 (*C*-3), 49.0 (*C*-2), 40.2 (*C*-1’’’), 32.5 (*C*-5), 30.6 (2’-

*C*H), 27.3 (2’-CH-*C*H$_3$), 26.0 (2’-CH-*C*H$_3$), 22.1 (4’’-*C*H$_3$), 21.9 (*C*-8), 21.0 (2’’-*C*H$_3$), 19.5 (6’’-*C*H$_3$), 18.8 (*C*-6), 17.1 (*C*-7) ppm.

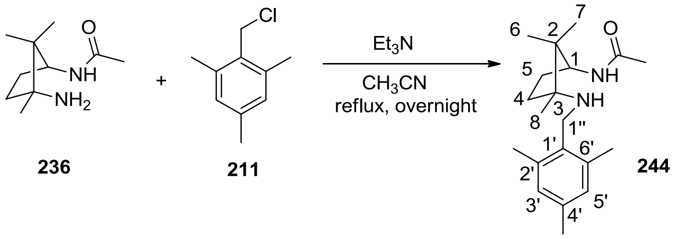
IR (ATR) ν = 3370, 2963, 2870, 1601, 1579, 1508, 1453, 1386, 1369, 1312, 1258, 1219, 1160, 1084, 1037, 850, 739 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 393 ([M+H]$^+$, 100%).

HRMS (ESI): Calc. for $C_{27}H_{41}N_2$: 393.3280, found: 393.3270.

$[\alpha]^{20}_{D}$ = –16 (c = 0.48, CH_2Cl_2).

3.2.5.1.8. *N*-((1*S*,3*R*)-2,2,3-Trimethyl-3-((2,4,6-trimethylbenzyl)amino) cyclopentyl)acetamide (244)



Prepared from monosubstituted diamine **236** (0.30 g, 1.60 mmol), triethylamine (0.27 mL, 1.95 mmol) and 2,4,6-trimethylbenzylchloride **211** (0.30 g, 1.79 mmol) in acetonitrile (10 mL). The crude product was purified *via* column chromatography (CH_2Cl_2/MeOH, 95:5) and the secondary diamine **244** was obtained as brown oil (0.29 g, 0.92 mmol, 57%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 6.87 (s, 2H, *H*-3’, *H*-5’), 4.21 – 3.92 (m, 1H, *H*-1), 3.66 (m, 2H, *H*-1’’), 2.36 (s, 6H, 2’-C*H*$_3$, 6’-C*H*$_3$), 2.27 (s, 3H, 4’-C*H*$_3$), 2.16 – 2.01 (m, 2H, *H*-4), 1.80 (s, 3H, C-O-C*H*$_3$), 1.62 – 1.44 (m, 2H, *H*-5), 1.21 (s, 3H, *H*-8), 0.95 (s, 3H, *H*-6), 0.80 (s, 3H, *H*-7) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 168.1 (*C*-O-CH$_3$), 136.6 (*C*-4’), 133.5 (*C*-1’, *C*-2’, *C*-6’), 129.2 (*C*-3’, *C*-5’), 66.0 (*C*-3), 58.7 (*C*-1), 48.2 (*C*-2), 40.2 (*C*-1’’), 31.5 (*C*-4), 30.4

(C-O-*C*H_3), 25.2 (*C*-5), 23.5 (4’-*C*H_3), 20.9 (*C*-8), 19.6 (2’-*C*H_3, 6’-*C*H_3), 18.4 (*C*-6), 16.1 (*C*-7) ppm.

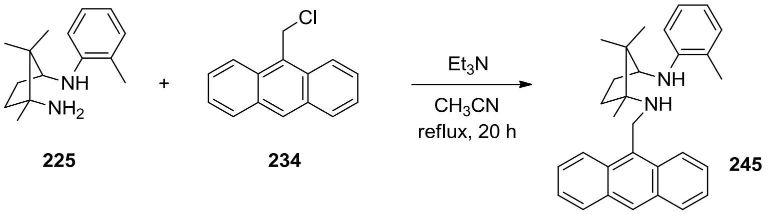
IR (ATR) ν = 3298, 2961, 1646, 1443, 1369, 1295, 1129, 907, 846, 731 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 317 ($[M+H]^+$, 100%).

HRMS (ESI): Calc. for $C_{20}H_{33}N_2O$: 317.2593, found: 317.2591.

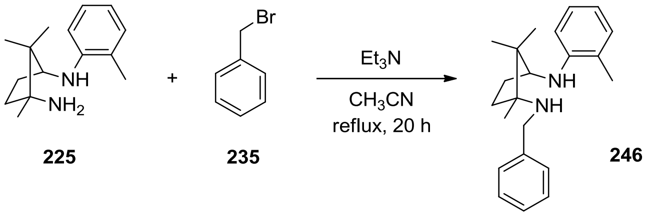
$[\alpha]^{20}_D$ = −1 (c = 0.45, EtOH).

3.2.5.1.9. (1*R*,3*S*)-*N*^{1}-(Anthracen-9-ylmethyl)-1,2,2-trimethyl-*N*^{3}-(*o*-tolyl) cyclopentane-1,3-diamine (245)



Prepared from 9-(chloromethyl)anthracene **234** (0.21 g, 0.94 mmol), diamine **225** (0.20 g, 0.86 mmol) and triethylamine (0.14 mL, 1.03 mmol) in dry acetonitrile (20 mL). The corresponding product was not obtained.

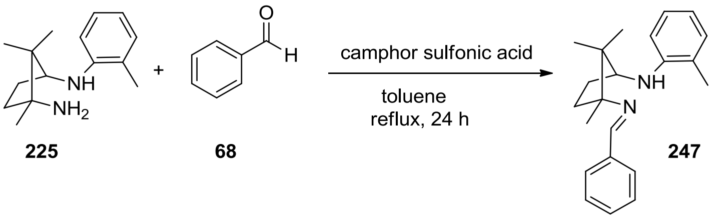
3.2.5.1.10. (1*R*,3*S*)-*N*^{1}-Benzyl-1,2,2-trimethyl-*N*^{3}-(*o*-tolyl)cyclopentane-1,3-diamine (246)



Prepared from benzyl bromide **235** (0.11 mL, 0.94 mmol), diamine **225** (0.20 g, 0.86 mmol) and triethylamine (0.14 mL, 1.03 mmol) in dry acetonitrile (20 mL). The corresponding product was not obtained.

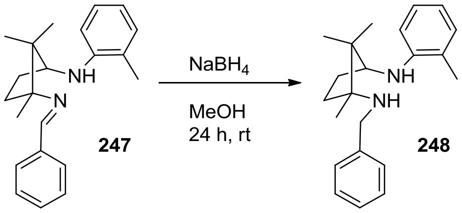
3.2.5.2. Alkylation with Benzaldehyde

3.2.5.2.1. (1*R*,3*S*,*E*)-*N*^{1}-Benzylidene-1,2,2-trimethyl-*N*^{3}-(*o*-tolyl) cyclopentane-1,3-diamine (247)



Benzaldehyde **68** (0.20 mL, 1.94 mmol, 1.5 equiv.) in toluene (5 mL) was added dropwise to a solution of diamine **225** (0.30 g, 1.29 mmol, 1 equiv.), *p*-toluenosulfonic acid (5 mg) and toluene (20 mL) at room temperature. The resuling mixture was heated at reflux overnight on a Dean Stark under a stream of argon. After removal of the solvent, the crude product **247** was reduced in the next step.

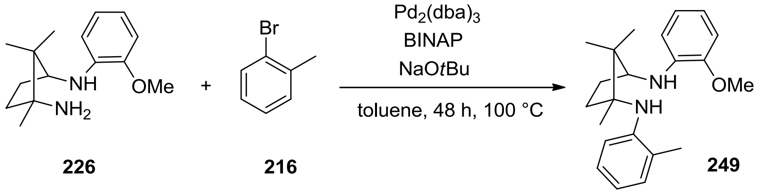
3.2.5.2.2. (1*R*,3*S*)-*N*^{1}-Benzyl-1,2,2-trimethyl-*N*^{3}-(*o*-tolyl)cyclopentane-1,3-diamine (248)



To a solution of diamine **247** (0.41 g) in dry methanol (20 mL) was carefully added sodium borohydride (1.95 g) under a stream of argon. The resulting mixture was stirred at room temperature for 5 h. Water (25 mL) was added and the mixture was extracted with methylene chloride (3 x 50 mL). The combined organic layers were dried (Na_2SO_4). The solvent was evaporated. No product was obtained.

3.2.5.3. Alkylation with Aryl Halide

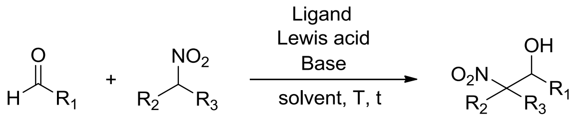
3.2.5.3.1. (1*R*,3*S*)-*N*^{3}-(2-Methoxyphenyl)-1,2,2-trimethyl-*N*^{1}-(*o*-tolyl) cyclopentane-1,3-diamine (249)



In a dried Schlenk-tube $Pd_2(dba)_3$ (0.07 g, 0.08 mmol, 0.04 equiv.), (±)-BINAP (0.11 g, 0.18 mmol, 0.09 equiv.) and NaO*t*Bu (0.58 g, 6.04 mmol, 3 equiv.) were dissolved in toluene (200 mL) under a nitrogen atmosphere and stirred for 20 min. Diamine **226** (0.50 g, 2.01 mmol, 1 equiv.) and 2-bromotoluene **216** (0.48 mL, 4.03 mmol, 1 equiv.) were added and the solution was stirred for 48 h at 100 °C. After work up, no product was obtained.

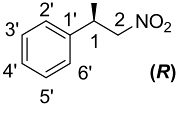
3.3. Application of Diamines as Ligands in the Henry Reaction

General Procedure



The appropriate ligand (1-1.5equiv.) and Lewis acid (0-1.5equiv.) were dissolved in a solvent (1 mL) and the mixture was stirred for 1 h at room temperature under an argon atmosphere. A solution of aldehyde (10 equiv.) and base (0.2 equiv.) in a solvent (0.5 mL) was added and the reaction mixture was stirred at various temperatures over 15 min. A nitroalkane (100-200 equiv.) was added and the solution was stirred for the specific time at various temperatures. The resulting mixture was filtered through a silica gel column (10 cm^3) with EtOAc (100 mL) to remove the catalyst. The solvent was removed under reduced pressure at < 30 °C and the crude product was purified by a silica gel flash column chromatography to give the corresponding *β*-nitro alcohol. The enantiomeric excess was determined by chiral HPLC analysis. Spectral data were consistent with literature values and the absolute configuration was assigned by comparison with literature values (For yields and enantiomeric excess see Table 3-9).

3.3.1. (*R*)-2-Nitro-1-phenylethanol (*R*-250)



(*R*)-250

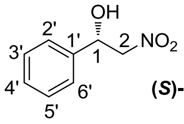
Prepared from ligand **214** (20.00 mg, 0.06 mmol), $Cu(OAc)_2 \cdot H_2O$ (12.00 mg, 0.06 mmol), benzaldehyde **68** (0.63 mL, 0.62 mmol, 10 equiv), DABCO (14.00 mg, 0.01 mmol) and CH_3NO_2 (3.35 mL, 6.24 mmol) in ethanol (15 mL). The crude product was purified *via* column chromatography (*n*-hexane/EtOAc, 8:2) to give colorless oil (150.00 mg, 0.90 mmol, 57%). Spectral data were consistent with literature values.[195]

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.48 – 7.31 (m, *H*-2’, *H*-3’,*H*-4’, *H*-5’, *H*-6’), 5.46 (dd, *J* = 9.6, 3.0 Hz, 1H, *H*-2), 4.61 (dd, *J* = 13.4, 9.6 Hz, 1H, *H*-2), 4.51 (dd, *J* = 13.4, 3.0 Hz, 1H, *H*-1), 2.84 (s, 1H, O*H*) ppm.

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 138.1 (*C*-1’), 129.1 (*C*-3’, *C*-5’), 129.0 (*C*-2’, C-6’), 125.9 (*C*-4’), 81.0 (*C*-2), 71.1 (*C*-1) ppm.

HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85/15 *v*/*v*, 1 mL/min, 25 ^{o}C, UV = 250 nm): t_{majorr}= 11.79 min, t_{minor}= 14.11 min; 7% *ee*.[195]

3.3.2. (*S*)-2-Nitro-1-phenylethanol (*S*-250)



(*S*)-250

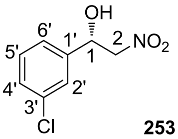
Prepared from ligand **225** (20.00 mg, 0.09 mmol), [CH$_3$(CH$_2$)$_3$CH(C$_2$H$_5$)CO$_2$]$_2$Cu (30.00 mg, 0.09 mmol), benzaldehyde **68** (0.09 mL, 0.90 mmol), DABCO (2.00 mg, 0.02 mmol) and CH$_3$NO$_2$ (0.46 mL, 8.60 mmol) in methanol (1.5 mL). The crude product was purified *via* column chromatography (*n*-hexane/EtOAc, 8:2) to give colorless oil (133.00 mg, 0.80 mmol, 93%). Spectral data were consistent with literature values.[196,197]

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.57 – 7.20 (m, 5H, *H*-2’, *H*-3’, *H*-4’, *H*-5’, *H*-6’), 5.41 (dt, *J* = 9.5, 3.3 Hz, 1H, *H*-2), 4.57 (ddd, *J* = 13.2, 9.6, 2.3 Hz, 1H, *H*-2), 4.49 (dd, *J* = 13.2, 3.1 Hz, 1H, *H*-1), 3.18 (s, 1H, O*H*) ppm.

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 138.3 (*C*-1’), 129.0 (*C*-3’, *C*-5’), 128.9 (*C*-2’, *C*-6’), 126.0 (*C*-4’), 81.2 (*C*-2), 71.0 (*C*-1) ppm.

HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85/15 *v*/*v*, 1 mL/min, 25 ^{o}C, UV = 250 nm): t_{minor}= 11.76 min, t_{major}= 14.05 min; 77% *ee*.[196]

3.3.3. (*S*)-1-(3-Chlorophenyl)-2-nitroethanol (253)



253

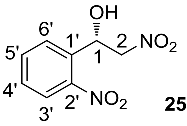
Prepared from ligand **225** (20.00 mg, 0.09 mmol), $[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2Cu$ (30.00 mg, 0.09 mmol), 3-chlorobenzaldehyde (0.10 mL, 0.90 mmol), DABCO (2.00 mg, 0.02 mmol) and CH_3NO_2 (0.46 mL, 8.60 mmol) in methanol (1.5 mL). The crude product was purified *via* column chromatography (*n*-hexane/EtOAc, 8:2) to give yellow oil (113.00 mg, 0.56 mmol, 65%). Spectral data were consistent with literature values.[196]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.42 – 7.39 (m, 1H, *H*-2’), 7.35 – 7.30 (m, 2H, *H*-4’, *H*-6’), 7.29 – 7.24 (m, 1H, H-5’), 5.43 (dd, *J* = 9.3, 3.1 Hz, 1H, *H*-2), 4.67 – 4.43 (m, 2H, *H*-1, *H*-2), 3.18 (s, 1H, O*H*) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 140.0 (*C*-1’), 134.6 (*C*-3’), 130.3 (*C*-5’), 128.9 (*C*-2), 126.1 (*C*-4’), 124.1 (*C*-2’, *C*-6’), 70.3 (*C*-1) ppm.

HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 1 mL/min, 25 °C, UV = 250 nm): t_{minor}= 11.44 min, t_{major}= 13.97 min; 63% *ee*.[196]

3.3.4. (*S*)-2-Nitro-1-(2-nitrophenyl)ethanol (254)



254

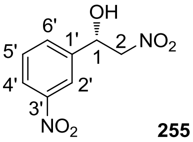
Prepared from ligand **225** (20.00 mg, 0.09 mmol), $[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2Cu$ (30.00 mg, 0.09 mmol), 2-nitrobenzaldehyde (130.00 mg, 0.90 mmol), DABCO (2.00 mg, 0.02 mmol) and CH_3NO_2 (0.46 mL, 8.6 mmol) in methanol (1.5 mL). The crude product was purified *via* column chromatography (*n*-hexane/EtOAc, 7:3) to give an orange solid (123.00 mg, 0.58 mmol, 68%). Spectral data were consistent with literature values.[198]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 8.2, 1.2 Hz, 1H, *H*-3'), 7.93 (dd, *J* = 7.9, 1.1, 1H, *H*-5'), 7.74 (td, *J* = 7.7,1.2 Hz, 1H, *H*-4'), 7.54 (dd, *J* = 11.4, 4.2 Hz, 1H, *H*-6'), 6.02 (d, *J* = 8.9 Hz, 1H, *H*-2), 4.88 – 4.78 (m, 1H, *H*-2), 4.60 – 4.49 (m, 1H, *H*-1), 3.42 (s, 1H, O*H*) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 147.1 (*C*-6'), 134.4 (*C*-5'), 134.1 (*C*-2'), 129.7 (*C*-1'), 128.7 (*C*-4'), 125.0 (*C*-2), 66.6 (*C*-1) ppm.

HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 1 mL/min, 25 °C, UV = 250 nm): t_{minor}= 13.36 min, t_{major}= 14.61 min; 82% *ee*.[198]

3.3.5. (*S*)-2-Nitro-1-(3-nitrophenyl)ethanol (255)



255

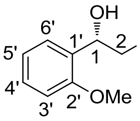
Prepared from ligand **215** (20.00 mg, 0.09 mmol), $[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2Cu$ (30.00 mg, 0.09 mmol), 3-nitrobenzaldehyde (130.00 mg, 0.90 mmol), DABCO (2.00 mg, 0.02 mmol) and CH_3NO_2 (0.46 mL, 8.6 mmol) in methanol (1.5 mL). The crude product was purified *via* column chromatography (*n*-hexane/EtOAc, 8:2) to give a yellow solid (105.00 mg, 0.49 mmol, 57%). Spectral data were consistent with literature values.[198]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.32 (t, *J* = 1.8, 1H, *H*-2'), 8.22 (ddd, *J* = 8.2, 2.2, 0.9 Hz, 1H, *H*-4'), 7.78 – 7.75 (m, 1H, *H*-6'), 7.61 (dd, *J* = 10.5, 5.4 Hz, 1H, *H*-5'), 5.59 (dt, *J* = 15.1, 7.5 Hz, 1H, *H*-2), 4.66 – 4.56 (m, 2H, *H*-1, *H*-2), 3.33 (s br, 1H, O*H*) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.5 (*C*-3'), 140.0 (*C*-1'), 132.1 (*C*-6'), 129.8 (*C*-5'), 123.8 (*C*-2), 121.0 (*C*-2', *C*-4'), 69.7 (*C*-1) ppm.

HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 1 mL/min, 25 °C, UV = 250 nm): t_{minor}= 20.56 min, t_{major}= 22.72 min; 59% *ee*.[198]

3.3.6. (*S*)-1-(2-Methoxyphenyl)-2-nitroethanol (256)



256

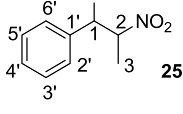
Prepared from ligand **225** (20.00 mg, 0.09 mmol), $[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2Cu$ (30.00 mg, 0.09 mmol), 2-methoxybenzaldehyde (117.00 mg, 0.90 mmol), DABCO (2.00 mg, 0.02 mmol) and CH_3NO_2 (0.46 mL, 8.60 mmol) in methanol (1.5 mL). The crude product was purified *via* column chromatography (*n*-hexane/EtOAc, 8:2) to give yellow oil (110.00 mg, 0.56 mmol, 65%). Spectral data were consistent with literature values.[196]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.42 (dd, *J* = 7.5, 1.4 Hz, 1H, *H*-6'), 7.35 – 7.30 (m, 1H, *H*-4'), 7.00 (td, *J* = 7.5, 0.9 Hz, 1H, *H*-5'), 6.90 (d, *J* = 7.7 Hz, 1H, *H*-3'), 5.60 (dd, *J* = 9.2, 2.9 Hz, 1H, *H*-2), 4.64 (dd, *J* = 13.0, 3.2 Hz, 1H, *H*-2), 4.55 (dd, *J* = 13.0, 9.3 Hz, 1H, *H*-1), 3.87 (s, 3H, O-C*H*$_3$), 3.30 (s br, 1H, O*H*) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 155.9 (*C*-2'), 129.8 (*C*-2), 127.0 (*C*-4), 126.1 (*C*-1'), 121.0 (*C*-6'), 110.6 (*C*-5', *C*-3'), 67.8 (*C*-1), 55.2 (O-*C*H$_3$) ppm.

HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 1 mL/min, 25 °C, UV = 250 nm): t_{minor}= 10.32 min, t_{major}= 11.55 min; 83% *ee*.[196]

3.3.7. 2-Nitro-1-phenylpropan-1-ol (257)



257

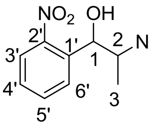
Prepared from ligand **225** (20.00 mg, 0.09 mmol), $[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2Cu$ (30.00 mg, 0.09 mmol), benzaldehyde (0.09 mL, 0.90 mmol), DABCO (2.00 mg, 0.02 mmol) and $C_2H_5NO_2$ (0.61 mL, 8.6 mmol) in methanol (1.5 mL). The crude product was purified *via* column chromatography (*n*-hexane/EtOAc, 8:2) to give a colorless oil (63.00 mg, 0.35 mmol, 41% as a mixture of diastereoisomers), dr (*anti*/*syn*) = 72:28 determined by ^{1}H NMR analysis. Spectral data were consistent with literature values.[199]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.51 – 7.20 (m, 8.5H) (*syn*/*anti*), 5.38 (t, *J* = 3.6 Hz, 0.7H) (*anti*), 5.02 (dd, *J* = 9.0, 3.9 Hz, 1H) (*syn*), 4.76 – 4.64 (m, 1.7H) (*syn/anti*), 2.72 (d, *J* = 3.6 Hz, 0.7H) (*anti*), 2.70 (d, *J* = 4.0 Hz, 1H) (*syn*), 1.51 (d, *J* = 6.8 Hz, 2.3H) (*anti*), 1.32 (d, *J* = 6.8 Hz, 3H) (*syn*) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 138.6 (*anti*), 138.4 (*syn*), 129.2 (*syn*), 129.0 (*anti*), 128.7 (*anti*), 128.5 (*syn*), 127.0 (*syn*), 126.0 (*anti*), 88.4 (*syn*), 87.6 (*anti*), 76.3 (*syn*), 74.0 (*anti*), 16.4 (*syn*), 11.9 (*anti*) ppm.

HPLC (combination of Chiralpak AD-H column + Chiralpak AS-H column, *n*-hexane/*i*-PrOH, 95/5 *v*/*v*, 0.5 mL/min, 25 °C, UV = 250 nm): t_{major}= 26.77 min, t_{minor}= 30.69 min for *anti*-isomer, t_{major}= 33.33 min, t_{minor}= 41.55 min for *syn*-isomer; 27% *ee* for *anti*-isomer, 58% *ee* for *syn*-isomer.[199]

3.3.8. 2-Nitro-1-(2-nitrophenyl)propan-1-ol (258)



258

Prepared from ligand **225** (20.00 mg, 0.09 mmol), $[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2Cu$ (30.00 mg, 0.09 mmol), 2-nitrobenzaldehyde (130.00 mg, 0.90 mmol), DABCO (2.00 mg, 0.02 mmol) and $C_2H_5NO_2$ (0.61 mL, 8.6 mmol) in methanol (1.5 mL). The crude product was purified *via* column chromatography (*n*-hexane/EtOAc, 8:2) to give a brown oil (142.00 mg, 0.63 mmol, 73% as a mixture of diastereoisomers), dr (*anti*/*syn*)

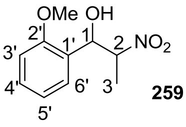
= 38:62 determined by ^{1}H NMR analysis. Spectral data were consistent with literature values.[200]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 8.2, 1.1 Hz, 1H) (*anti*), 7.99 (d, *J* = 8.2 Hz, 0.6 H) (*syn*), 7.91 (d, *J* = 7.8, 1H) (*anti*), 7.76 – 7.68 (m, 2.2 H) (*syn*/*anti*), 7.57 – 7.50 (m, 1.6H) (*syn*/*anti*), 6.08 (d, *J* = 2.1 Hz, 1H) (*anti*), 5.70 (d, *J* = 6.6, 0.6H) (*syn*), 5.15 – 4.90 (m, 1.6H) (*syn*/*anti*), 3.18 (d, *J* = 31.5 Hz, 1.5H) (*syn*/*anti*), 1.55 – 1.51 (m, 5H) (*syn*/*anti*) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.1 (*syn*), 147.2 (*anti*), 134.2 (*syn*), 134.1 (*anti*), 134.1 (*anti*), 134.0 (*syn*), 129.7 (*syn*), 129.5 (*anti*), 129.3 (*anti*), 128.9 (*syn*), 125.2 (*anti*), 125.0 (*syn*), 87.6 (*syn*), 84.5 (*anti*), 70.6 (*syn*), 69.4 (*anti*), 16.1 (*anti*), 11.9 (*syn*) ppm.

HPLC (combination of Chiralpak AD-H column + Chiralpak AS-H column, *n*-hexane/*i*-PrOH, 95/5 *v*/*v*, 0.5 mL/min, 25 °C, UV = 250 nm): t_{major}= 59.65 min, t_{minor}= 63.41 min for *anti*-isomer, t_{minor}= 74.88 min, t_{major}= 81.81 min for *syn*-isomer; 53% *ee* for *anti*-isomer, 57% *ee* for *syn*-isomer.[200]

3.3.9. 1-(2-Methoxyphenyl)-2-nitropropan-1-ol (259)



259

Prepared from ligand **257** (20.00 mg, 0.09 mmol), $[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2Cu$ (30.00 mg, 0.09 mmol), 2-methoxybenzaldehyde (117.00 mg, 0.90 mmol), DABCO (2.00 mg, 0.02 mmol) and $C_2H_5NO_2$ (0.61 mL, 8.6 mmol) in methanol (1.5 mL). The crude product was purified *via* column chromatography (*n*-hexane/EtOAc, 8:2) to give a white solid (55.00 mg, 0.26 mmol, 30% as a mixture of diastereoisomers), dr (*anti*/*syn*) = 53:47 determined by ^{1}H NMR analysis. Spectral data were consistent with literature values.[199]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.43 (dd, *J* = 7.6, 1.1 Hz, 1H) (*anti*), 7.36 – 7.26 (m, 2H) (*syn*/*anti*), 7.05 – 6.97 (m, 2H) (*anti*), 6.95 – 6.87 (m, 1.5H) (*syn*), 5.54(dd, *J* = 5.2, 4.1 Hz, 1H) (*anti*), 5.15 (t, *J* = 8.7 Hz, 0.5H) (*syn*), 5.01 (dq, *J* = 8.9, 6.8 Hz, 0.5H) (*syn*), 4.89 (qd, *J* = 6.9, 3.8 Hz, 1H) (*anti*), 3.95 – 3.86 (m, 5.5H) (*syn*/*anti*), 3.23 (d, *J* = 8.5Hz, 0.5H) (*syn*), 3.03 (d, *J*=5.5 Hz, 1H) (*anti*), 1.49 (d, *J* = 6.9 Hz, 3H) (*anti*), 1.33 (d, *J* = 6.8Hz, 1.5H) (*syn*) ppm.

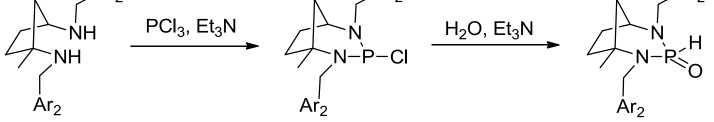
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 156.5 (*syn*), 155.9 (*anti*), 135.8 (*syn*), 130.1 (*syn*), 129.5 (*anti*), 129.0 (*syn*), 128.6 (*syn*), 127.7 (*anti*), 126.3 (*anti*), 121.3 (*syn*), 121.0 (*syn*), 120.7 (*anti*), 111.7 (*syn*), 111.0 (*syn*), 110.4 (*anti*), 87.6 (*syn*), 85.1 (*anti*), 74.0 (*syn*), 70.6 (*anti*), 55.2 (*anti*), 16.5 (*syn*), 12.5 (*anti*) ppm.

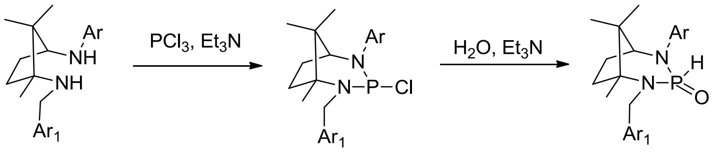
HPLC (combination of Chiralpak AD-H column + Chiralpak AS-H column, *n*-hexane/*i*-PrOH, 95/5 *v*/*v*, 0.5 mL/min, 25 ^{o}C, UV = 250 nm): t_{major}= 27.41 min, t_{minor}= 38.45 min for *anti*-isomer, t_{major}= 46.67 min, t_{minor}= 68.00 min for *syn*-isomer; 39% *ee* for *anti*-isomer, 63% *ee* for *syn*-isomer.[199]

3.4. Preparation of Chiral Phosphorus Ligands

3.4.1. Preparation of Pentavalent HASPO Ligands from Chloro-Derivatives

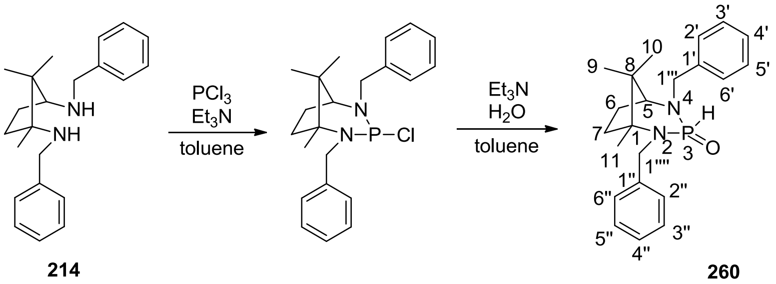
General Procedure





Solution of the suitable diamine (1 equiv.) in toluene was added to the mixture of phosphorus trichloride (1.1 equiv.) and triethylamine (2.5 equiv.) in toluene at −60 °C over 30 min. The solution was warmed to room temperature. After 2 h, the mixture was filtered through $MgSO_4$ and the filtrate was again cooled to −60 °C. Triethylamine (1.1 equiv.) and water (1 equiv.) were added and the cooling bath was removed. After 1 h, the reaction mixture was filtered again through $MgSO_4$ and the filtrate was concentrated under reduced pressure. The method of filtration for each compounds are given below.

3.4.1.1. (1*R*,3*S*,5*S*)-2,4-Dibenzyl-1,8,8-trimethyl-2,4-diaza-3-phosphabicyclo[3.2.1] octane 3-oxide (260)



Prepared from diamine **214** (0.60 g, 1.86 mmol), phosphorus trichloride (0.18 mL, 2.05 mmol) and triethylamine (0.66 mL, 4.65 mmol) in toluene (10 mL) and water (34.00 µL, 1.86 mmol), triethylamine (0.28 mL, 2.05 mmol) after filtration. After evaporation product **260** was obtained as a yellow solid (0.68 g, 1.75 mmol, 94%).

Mp: 118.3 °C.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.44 – 7.13 (m, 10H, *H*-2’, *H*-3’, *H*-4’, *H*-5’, *H*-6’, *H*-2’’, *H*-3’’, *H*-4’’, *H*-5’’, *H*-6’’), 7.30 (d, *J* = 619.9 Hz, 1H, P-*H*), 4.69 (dd, *J* = 12.4, 4.9 Hz, 1H, *H*-1’’’), 4.47 (dd, *J* = 15.4, 10.3 Hz, 1H, *H*-1’’’’), 4.23 (dd, *J* = 17.3, 10.5 Hz, 1H, *H*-1’’’’), 4.08 (dd, *J* = 15.4, 7.3 Hz, 1H, *H*-1’’’), 2.86 (dd, *J* = 15.6, 6.7 Hz, 1H, *H*-5), 2.22 (ddd, *J* = 13.9, 10.1, 5.8 Hz, 1H, *H*-6), 1.99 – 1.86 (m, 2H, *H*-6, *H*-7), 1.68 (ddd, *J* = 13.8, 11.0, 5.5 Hz, 1H, *H*-7), 1.04 (s, 6H, *H*-11, *H*-9), 0.78 (s, 3H, *H*-10) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 141.2 (*C*-1’), 138.1 (*C*-1’’), 128.6 (*C*-3’, *C*-5’), 128.5 (*C*-3’’, *C*-5’’), 128.4 (*C*-2’, *C*-6’), 127.4 (*C*-2’’, *C*-6’’), 127.0 (*C*-4’), 126.7 (*C*-4’’), 71.4 (*C*-1’’’), 67.7 (*C*-1’’’’), 50.1 (*C*-1), 47.3 (*C*-5), 45.6 (*C*-8), 36.6 (*C*-7), 29.2 (*C*-6), 24.4 (*C*-9), 19.5 (*C*-11), 18.4 (*C*-10) ppm.

^{31}P-NMR (202 MHz, $CDCl_3$) δ = 10.1 ppm.

IR (ATR) ν = 3429, 3056, 3022, 2949, 2336, 1604, 1493, 1453, 1373, 1201, 1113, 1092, 1066, 1027, 908, 876, 739, 698, 520, 481, 454 cm^{-1}.

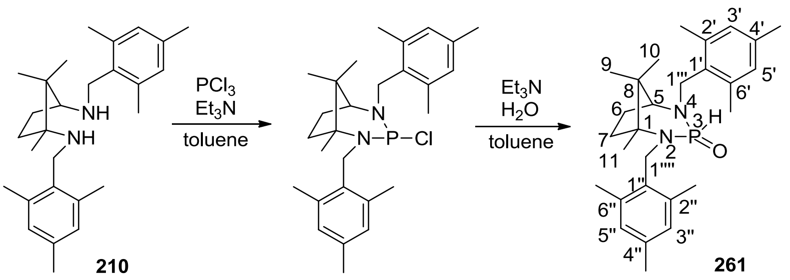
MS (ESI, + 3 kV): *m/z* (%) = 391 [M+Na]$^+$, 100%).

HRMS (ESI): Calc. for $C_{22}H_{29}N_2ONaP$: 391.1930, found: 391.1915.

Anal. Calc. for $C_{22}H_{29}N_2OP$: C, 71.72; H, 7.93; N, 7.60; found: C, 71.27; H, 8.12; N, 7.60.

$[\alpha]^{20}_D$ = +19 (c = 0.60, EtOH).

3.4.1.2. (1*R*,3*S*,5*S*)-1,8,8-Trimethyl-2,4-*bis*(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (261)



Prepared from diamine **210** (0.20 g, 0.49 mmol), phosphorus trichloride (0.05 mL, 0.54 mmol) and triethylamine (0.17 mL, 1.23 mmol) in toluene (10 mL) and water (8.90 µL, 0.49 mmol), triethylamine (0.08 mL, 0.54 mmol) after filtration. After evaporation product **261** was obtained as a yellow solid (0.16 g, 0.35 mmol, 73%).

Mp: 99.7 °C.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 6.83 (d, J = 7.4 Hz, 4H, *H*-3’, *H*-5’, *H*-3’’, *H*-5’’), 6.32 (d, J = 629.4 Hz, 1H, P-*H*), 4.28 (dd, J = 11.5, 3.0 Hz, 1H, *H*-1’’’), 4.11 (dt, J = 21.3, 9.4 Hz, 2H, *H*-1’’’, *H*-1’’’’), 3.96 (dd, J = 14.2, 7.4 Hz, 1H, *H*-1’’’’), 2.59 – 2.50 (m, 1H, *H*-5), 2.46 (s, 6H, 4’-CH_3, 4’’-CH_3), 2.34 (m, 1H, *H*-7), 2.25 (d, J = 3.1 Hz, 12H, 2’-CH_3, 6’-CH_3, 2’’-CH_3, 6’’-CH_3), 2.00 – 1.81 (m, 3H, *H*-6, *H*-7, *H*-6), 1.32 (s, 3H, *H*-9), 0.92 (s, 3H, *H*-11), 0.80 (s, 3H, *H*-10) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 139.1 (*C*-4’), 138.2 (*C*-4’’), 137.5 (*C*-1’), 136.9 (*C*-1’’), 130.1 (*C*-2’), 130.0 (*C*-2’’), 129.1 (*C*-3’, *C*-5’ *C*-3’’, *C*-5’’), 128.6 (*C*-6’), 128.5 (*C*-6’’), 69.7 (*C*-1), 65.2 (*C*-5), 47.1 (*C*-8), 43.1 (*C*-1’’’), 42.3 (*C*-1’’’’), 35.4 (*C*-7), 28.0 (*C*-6), 24.9 (*C*-10), 21.0 (4’-*C*H_3), 20.9 (4’’-*C*H_3), 20.4 (2’-*C*H_3), 20.0 (2’’-*C*H_3), 18.9 (6’-*C*H_3, 6’’-*C*H_3), 18.0 (*C*-9), 17.9 (*C*-11) ppm.

^{31}P-NMR (202 MHz, $CDCl_3$) δ = 9.6 ppm.

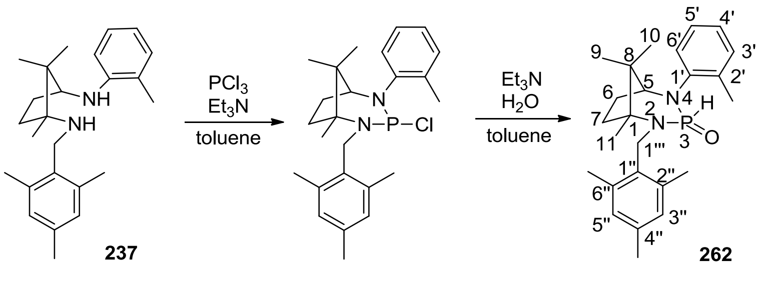
IR (ATR) ν = 2949, 2379, 1610, 1468, 1370, 1305, 1257, 1194, 1164, 1115, 1017, 894, 841, 747, 531 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 453 ($[M+H]^+$, 100%); 453 ($[M+Na]^+$, 100%).

HRMS (ESI): Calc. for $C_{28}H_{42}N_2OP$: 453.3032, found: 453.3035; $C_{28}H_{41}N_2ONaP$: 475.2853, found: 475.2854.

$[\alpha]^{20}_{D}$ = –12 (c = 0.50, EtOH).

3.4.1.3. (1*R*,3*R*,5*S*)-1,8,8-Trimethyl-4-(*o*-tolyl)-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (262)



Prepared from diamine **237** (0.26 g, 0.72 mmol), phosphorus trichloride (0.07 mL, 0.79 mmol), triethylamine (0.25 mL, 1.80 mmol) in toluene (10 mL) and water

(13.00 µL, 0.72 mmol) and triethylamine (0.11 mL, 0.79 mmol) after filtration. After evaporation product **262** was obtained as a white solid (0.26 g, 0.64 mmol, 89%).

Mp: 170.5 °C.

^{1}H-NMR (500 MHz, CDCl$_3$) δ = 7.15 – 7.04 (m, 3H, *H*-4', *H*-5', *H*-6'), 6.31 (d, *J* = 637.2 Hz, P-*H*), 6.91 (s, 1H, *H*-3'), 6.79 (s, 2H, *H*-3'', *H*-5''), 4.33 (dd, *J* = 11.7, 3.3 Hz, 1H, *H*-1'''), 4.21 – 4.10 (m, 1H, *H*-1'''), 3.08 (dd, *J* = 20.4, 5.5 Hz, 1H, *H*-5), 2.72 (ddd, *J* = 14.2, 9.7, 4.9 Hz, 1H, *H*-6), 2.59 (ddd, *J* = 14.0, 9.7, 4.1 Hz, 1H, *H*-7), 2.48 (s, 6H, 2''-C*H*$_3$, 6''-C*H*$_3$), 2.31 (s, 3H, 2'-C*H*$_3$), 2.20 (s, 3H, 4''-C*H*$_3$), 2.15–1.91 (m, 2H, *H*-6, *H*-7), 1.42 (s, 3H, *H*-9), 1.37 (s, 3H, *H*-11), 0.97 (s, 3H, *H*-10) ppm.

^{13}C-NMR (126 MHz, CDCl$_3$) δ = 141.8 (*C*-1'), 139.0 (*C*-2'), 137.4 (*C*-4''), 131.1 (*C*-3'), 129.1 (*C*-3'', *C*-5''), 128.7 (*C*-1'') , 128.6 (*C*-2'', *C*-6''), 126.9 (*C*-4', *C*-5'), 126.7 (*C*-6'), 73.4 (*C*-11), 70.2 (*C*-5), 47.4 (*C*-8), 42.2 (*C*-1'''), 35.4 (*C*-7), 30.0 (*C*-6), 24.9 (4''-*C*H$_3$), 20.9 (6''-*C*H$_3$), 20.5 (4''-*C*H$_3$), 20.2 (*C*-11), 19.4 (2'-*C*H$_3$), 18.2 (*C*-9), 18.1 (*C*-10) ppm.

^{31}P-NMR (202 MHz, CDCl$_3$) δ = 3.9 ppm

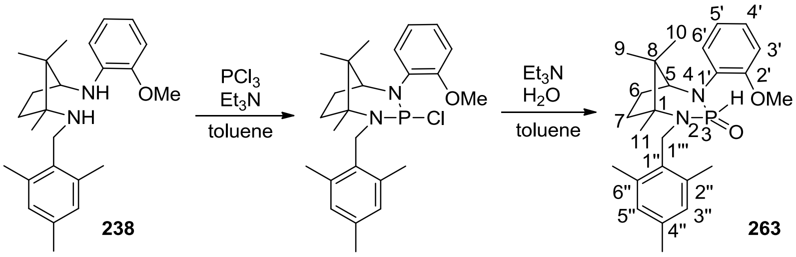
IR (ATR) ν = 3414, 2953, 2409, 1610, 1488, 1458, 1389, 1345, 1207, 1192, 1154, 1110, 1080, 1018, 976, 890, 852, 759, 724, 544, 454 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 411 ([M+H]$^+$, 58%); 453 ([M+Na]$^+$, 100%).

HRMS (ESI): Calc. for $C_{25}H_{42}N_2OP$: 453.3032, found: 453.3035; $C_{28}H_{41}N_2ONaP$: 475.2853, found: 475.2854.

$[\alpha]^{20}_D$ = +73 (c = 0.52, EtOH).

3.4.1.4. (1*R*,3*R*,5*S*)-4-(2-Methoxyphenyl)-1,8,8-trimethyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (263)



Prepared from diamine **238** (0.15 g, 0.39 mmol), phosphorus trichloride (0.04 mL, 0.43 mmol), triethylamine (0.14 mL, 0.98 mmol) in toluene (10 mL) and water (7.00 µL, 0.39 mmol) and triethylamine (0.06 mL, 0.43 mmol) after filtration. After evaporation product **263** was obtained as yellow oil (0.16 g, 0.38 mmol, 97%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 6.86 (s, 2H, 2’’-C*H*$_3$, 6’’-C*H*$_3$), 6.80 (m, 1H, *H*-3’), 6.69 (d, *J* = 7.7 Hz, 1H, *H*-6’), 6.60 (dd, *J* = 7.9, 1.2 Hz, 1H, *H*-4’), 6.55 (d, *J* = 7.1 Hz, 1H, *H*-5’), 6.36 (d, *J* = 645.2 Hz, 1H, P*H*), 3.81 – 3.58 (m, 5H, *H*-1’’’, 2’-O-C*H*$_3$), 2.52 – 2.44 (m, 1H, *H*-5), 2.38 (s, 6H, 2’’-C*H*$_3$, 6’’-C*H*$_3$), 2.28 (s, 3H, 4’’-C*H*$_3$), 2.09 (dd, *J* = 25.7, 12.1 Hz, 2H, *H*-7, *H*-6), 1.62 (dd, *J* = 19.9, 10.9 Hz, 2H, *H*-7, *H*-6), 1.25 (s, 3H, *H*-9), 1.01 (s, 3H, *H*-11), 0.89 (s, 3H, *H*-10) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 146.8 (*C*-2’), 138.9 (*C*-4’’), 137.2 (*C*-1’’), 136.1 (*C*-2’’, *C*-6’’), 134.3(*C*-1’), 128.9 (*C*-3’’), 128.1 (*C*-5’’), 125.3 (*C*-5’), 121.3 (*C*-4’), 115 (*C*-6’), 109.4 (*C*-2’), 64.9, (*C*-1), 61.8 (*C*-5), 55.1 (2’-O*C*H$_3$), 48.6 (*C*-8), 40.5 (*C*-1’’’), 32.8 (*C*-7), 30.2 (*C*-6), 25.4 (4’’-*C*H$_3$), 20.9 (2’’-*C*H$_3$, 6’’-*C*H$_3$), 19.5 (*C*-9), 19.3 (*C*-10), 16.9 (*C*-11) ppm.

^{31}P-NMR (202 MHz, $CDCl_3$) δ = 3.9 ppm.

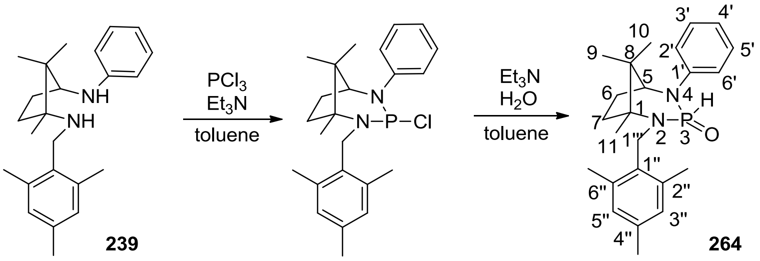
IR (ATR) ν = 3424, 2958, 1599, 1515, 1455, 1371, 1224, 1113, 1029, 909, 850, 730 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 427 ([M+H]$^+$, 62%); 449 ([M+Na]$^+$, 100%).

HRMS (ESI): Calc. for $C_{25}H_{36}N_2O_2P$: 427.2514, found: 427.2525; $C_{25}H_{35}N_2O_2NaP$: 449.2334, found: 449.2343.

$[\alpha]^{20}_{D}$ = +11 (c = 0.45, EtOH).

3.4.1.5. (1*R*,3*R*,5*S*)-1,8,8-Trimethyl-4-phenyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (264)



Prepared from diamine **239** (0.27 g, 0.76 mmol), phosphorus trichloride (0.07 mL, 0.84 mmol), triethylamine (0.27 mL, 1.91 mmol) in toluene (10 mL) and water (14.00 µL, 0.76 mmol) and triethylamine (0.12 mL, 0.84 mmol) after filtration. After evaporation product **264** was obtained as a white solid (0.27 g, 0.68 mmol, 89%).

Mp: 154.3 °C.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.28 – 7.18 (m, 4H, *H*-2', *H*-6', *H*-3'', *H*-5''), 6.84 (s, 2H, *H*-3', *H*-5'), 6.37 (d, *J* = 649.9, 1H, P-*H*), 4.34 (dd, *J* = 11.7, 2.9 Hz, 1H, *H*-1'''), 4.23 – 4.11 (m, 1H, *H*-1'''), 3.63 (dd, *J* = 18.6, 6.0 Hz, 1H, *H*-5), 2.73 – 2.64 (m, 1H, *H*-6), 2.49 (s, 6H, 2''-C*H*3, 6''-C*H*3), 2.45 – 2.36 (m, 2H, *H*-7), 2.25 (s, 3H, 4''-C*H*3), 1.95 – 1.87 (m, 1H, *H*-6), 1.44 (s, 3H, *H*-9), 1.24 (s, 3H, *H*-11), 1.06 (s, 3H, *H*-10) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 146.1 (*C*-1'), 139.1 (*C*-4''), 137.5 (*C*-1''), 129.3 (*C*-3'), 129.1 (*C*-5'), 128.3 (*C*-3'', *C*-5''), 125.4 (*C*-2'', *C*-6''), 123.4 (*C*-4'), 122.2 (*C*-2'', *C*-6''), 71.5 (*C*-5), 70.7 (*C*-1), 46.9 (*C*-8), 42.4 (*C*-1'''), 35.4 (*C*-7), 30.5 (*C*-6), 24.7 (4''-*C*H3), 21.0 (2''-*C*H3), 20.5 (6''-*C*H3), 19.4 (*C*-11), 18.0 (*C*-9, *C*-10) ppm.

^{31}P-NMR (202 MHz, $CDCl_3$) δ = 3.9 ppm.

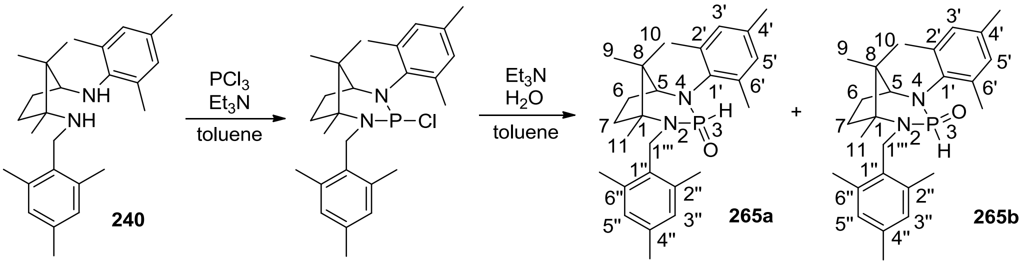
IR (ATR) ν = 3424, 2943, 2375, 1595, 1493, 1464, 1391, 1360, 1278, 1249, 1224, 1205, 1154, 1114, 1087, 1058, 1016, 963, 889, 850, 747, 693, 524, 464 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 397 ([M+H]$^+$, 50%); 419 ([M+Na]$^+$, 100%).

HRMS (ESI): Calc. for $C_{24}H_{34}N_2OP$: 397.2409, found: 397.2408; $C_{24}H_{33}N_2ONaP$: 419.2228, found: 419.2232.

[α]^{20}$_D$ = +39 (c = 0.46, EtOH).

3.4.1.6. 4-Mesityl-1,8,8-trimethyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (265a/ 265b)



Prepared from diamine **240** (0.35 g, 0.89 mmol), phosphorus trichloride (0.09 mL, 0.98 mmol), triethylamine (0.31 mL, 2.23 mmol) in toluene (10 mL) and water (16.00 µL, 0.89 mmol) and triethylamine (0.14 mL, 0.98 mmol) after filtration. After evaporation product **265** was obtained as a yellow solid of two diastereoisomers which were separated by column chromatography (*n*-hexane/EtOAc, 7:3).

3.4.1.6.1. (1*R*,3*R*,5*S*)-4-Mesityl-1,8,8-trimethyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octan-3-ol (265a)

The product was obtained as a yellow solid (0.14g, 0.33 mmol, 37%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 6.79 (t, *J* = 20.3 Hz, 4H, *H*-3’, *H*-5’, *H*-3’’, *H*-5’’), 6.62 (d, *J* = 627.9 Hz, 1H, P-*H*), 4.49 (dd, *J* = 12.8, 5.9 Hz, 1H, *H*-1’’’), 4.29 – 4.12 (m, 1H, *H*-1’’’), 3.09 (dd, *J* = 17.9, 5.0 Hz, 1H, *H*-5), 2.67 – 2.60 (m, 2H, *H*-6, *H*-7), 2.54

(s, 3H, 4'-C*H*$_3$), 2.47 (s, 6H, 2'-C*H*$_3$, 6'-C*H*$_3$), 2.26 (s, 3H, 4''-C*H*$_3$), 2.20 (d, *J* = 9.3 Hz, 6H, 2''-C*H*$_3$, 6''-C*H*$_3$), 2.09 – 2.01 (m, 1H, *H*-6), 1.91 – 1.85 (m, 1H, *H*-7), 1.37 (s, 3H, *H*-9), 1.29 (m, 3H, *H*-11), 0.94 (s, 3H, *H*-10) ppm.

^{13}C-NMR (126 MHz, CDCl$_3$) δ = 139.7 (*C*-1'), 138.3 (*C*-4''), 137.6 (*C*-1''), 137.1 (*C*-6''), 136.9 (*C*-1''), 136.6 (*C*-6'), 130.8 (*C*-3', *C*-5'), 130.5 (*C*-4'), 129.9 (*C*-3''), 129.2 (*C*-5''), 73.4 (*C*-5), 70.6 (*C*-1), 48.5 (*C*-8), 42.3 (*C*-1''), 35.8 (*C*-6), 30.6 (*C*-7), 25.9 (4'-*C*H$_3$), 22.1 (4''-*C*H$_3$), 21.5 (*C*-9), 20.9 (2''-*C*H$_3$), 20.7 (6''-*C*H$_3$), 20.7 (6'-*C*H$_3$), 20.6 (2'-*C*H$_3$), 18.9 (*C*-11), 18.8 (*C*-10) ppm.

^{31}P-NMR (202 MHz, CDCl$_3$) δ = 1.9 ppm.

IR (ATR) ν = 3424, 2924, 2345, 2212, 1605, 1468, 1341, 1212, 1144, 1081, 1031, 968, 850, 728, 565 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 439 ([M+H]$^+$, 100%).

HRMS (ESI): Calc. for $C_{27}H_{40}N_2OP$: 439.2878, found: 439.2874.

[α]$^{20}_{D}$ = +54 (c = 0.56, EtOH).

3.4.1.6.2. (1*R*,3*S*,5*S*)-4-Mesityl-1,8,8-trimethyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octan-3-ol (265b)

The product was obtained as a white solid (0.06 g, 0.14 mmol, 15%).

^{1}H-NMR (500 MHz, CDCl$_3$) δ = 6.79 (m, 4H, *H*-3, *H*-5, *H*-3'', *H*-5''), 6.69 (d, *J* = 617.0 Hz, 1H, P-*H*), 4.28 (t, *J* = 10.7 Hz, 1H, *H*-1'''), 4.14 (dd, *J* = 11.1, 7.1 Hz, 1H, *H*-1'''), 3.19 (ddd, *J* = 11.2, 3.5, 1.9 Hz, 1H, *H*-5), 2.58 – 2.45 (m, 1H, *H*-6), 2.44 (s, 6H, 2'-C*H*$_3$, 6'-C*H*$_3$), 2.39 (s, 3H, 4'-C*H*$_3$), 2.31 (s, 3H, 4''-C*H*$_3$), 2.19 (s, 3H, 2''-C*H*$_3$), 2.18 (s, 3H, 6''-C*H*$_3$), 2.13 – 2.08 (m, 1H, *H*-7), 1.98 – 1.85 (m, 2H, *H*-6, *H*-7), 1.83 (s, 1H, *H*-10), 1.45 (s, 1H, *H*-9), 1.01 (s, 1H, *H*-11) ppm.

^{13}C-NMR (126 MHz, CDCl$_3$) δ = 139.9 (*C*-1'), 139.1 (*C*-4''), 137.9 (*C*-1''), 136.9 (*C*-2''), 136.7 (*C*-6''), 136.4 (*C*-4'), 130.3 (*C*-3'), 129.7 (*C*-5'), 129.0 (*C*-3'', *C*-5''), 127.8 (*C*-2'), 127.7 (*C*-6'), 73.2 (*C*-5), 70.0 (*C*-1), 48.5 (*C*-8), 43.3 (*C*-1''), 36.9 (*C*-6), 30.3

(*C*-7), 26.9 (4’-*C*H$_3$), 21.0 (4’’-*C*H$_3$), 20.7 (*C*-11), 20.4 (2’’-*C*H$_3$), 20.0 (6’’-*C*H$_3$), 19.9 (6’-*C*H$_3$), 19.6 (2’-*C*H$_3$), 18.6 (*C*-9), 18.5 (*C*-10) ppm.

^{31}P-NMR (202 MHz, CDCl$_3$) δ = –4.2 ppm.

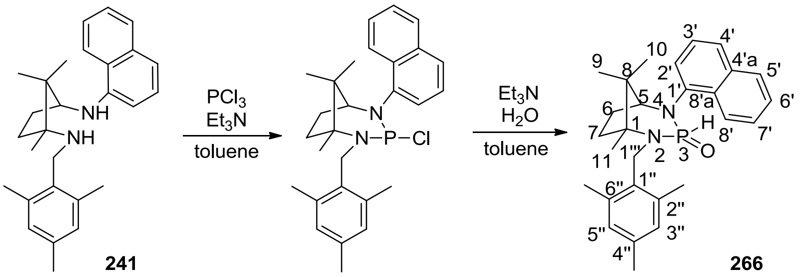
IR (ATR) ν = 3424, 2924, 2345, 2212, 1605, 1468, 1341, 1212, 1144, 1081, 1031, 968, 850, 728, 565 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 439 ([M+H]$^+$, 100%).

HRMS (ESI): Calc. for $C_{27}H_{40}N_2OP$: 439.2878, found: 439.2872.

[α]$^{20}_{D}$ = +40 (c = 0.57, EtOH).

3.4.1.7. (1*R*,3*R*,5*S*)-1,8,8-Trimethyl-4-(naphthalen-1-yl)-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (266)



Prepared from diamine **241** (0.17 g, 0.42 mmol), phosphorus trichloride (0.04 mL, 0.46 mmol), triethylamine (0.15 mL, 1.05 mmol) in toluene (10 mL) and water (7.60 µL, 0.42 mmol) and triethylamine (0.06 mL, 0.46 mmol) after filtration. After evaporation product **266** was obtained as brown oil (0.16 g, 0.36 mmol, 85 %).

^{1}H-NMR (500 MHz, CDCl$_3$) δ = 8.29 (s, 1H, *H*-8’), 8.01 (s, 1H, *H*-5’), 7.83 (d, *J* = 8.1 Hz, 1H, *H*-6’), 7.73 (d, *J* = 6.6 Hz, 1H, *H*-7’), 7.48 (m, 1H, *H*-4’), 7.31 – 7.26 (m, 1H, *H*-3’), 7.22 – 7.19 (m, 1H, *H*-2’), 6.81 (s, 2H, *H*- 3’’, *H*-5’’), 6.38 (d, *J* = 644.7 Hz, 1H, P-*H*), 4.41 (d, *J* = 10.4 Hz, 1H, *H*-1’’’), 4.29 – 4.20 (m, 1H, *H*-1’’’), 3.27 (d, *J* = 19.6 Hz, 1H, *H*-5), 2.55 (s, 6H, 2’-C*H*$_3$, 6’-C*H*$_3$), 2.20 (s, 3H, 4’-C*H*$_3$), 2.01 (m, 4H, *H*-6, *H*-7), 1.66 (s, 3H, *H*-9), 1.50 (s, 3H, *H*-11), 1.01 (s, 3H, *H*-10) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) *δ* = 139.1 (*C*-1’), 138.8 (*C*-4’’), 137.2 (*C*-1’’), 135.0 (*C*-2’’, *C*-6’’), 131.9 (*C*-4’a, *C*-8’a), 129.1 (*C*-5’), 128.8 (*C*-3’’, *C*-5’’), 128.5 (*C*-3’), 127.2 (*C*-6’), 126.1 (*C*-7’), 125.0 (*C*-8’), 125.7 (*C*-4’), 122.9 (*C*-2’), 73.9 (*C*-5), 70.2 (*C*-1), 53.4 (*C*-8), 42.7 (*C*-1’’’), 36.0 (*C*-7), 29.7 (*C*-6), 24.9 (4’-CH_3), 20.9 (*C*-11), 20.5 (2’-CH_3, 6’-CH_3), 18.3 (*C*-9), 18.1 (*C*-10) ppm.

^{31}P-NMR (202 MHz, $CDCl_3$) *δ* = 4.9 ppm.

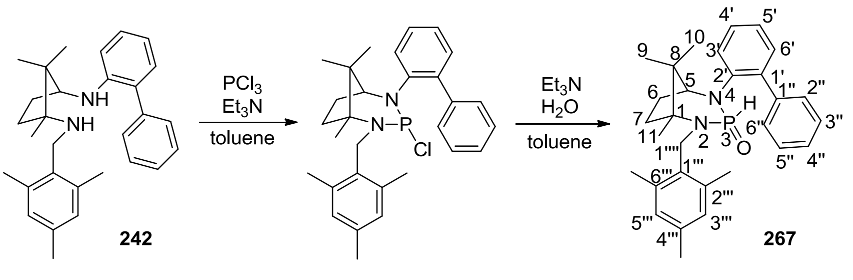
IR (ATR) *ν* = 3429, 2949, 2390, 2218, 1725, 1610, 1592, 1573, 1464, 1392, 1267, 1197, 1150, 1113, 1079, 1052, 1014, 950, 885, 848, 796, 775, 726, 641, 571, 546, 519, 461, 429 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 447 ([M+H]$^+$, 81%); 469 ([M+Na]$^+$, 100%).

HRMS (ESI): Calc. for $C_{28}H_{36}N_2OP$: 447.2565, found: 447.2574; $C_{28}H_{35}N_2ONaP$: 469.2385, found: 469.2388.

[α]$^{20}_{D}$ = +48 (c = 0.45, EtOH).

3.4.1.8. (1*R*,3*R*,5*S*)-4-([1,1'-Biphenyl]-2-yl)-1,8,8-trimethyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (267)



Prepared from diamine **242** (0.15 g, 0.35 mmol), phosphorus trichloride (0.03 mL, 0.39 mmol), triethylamine (0.12 mL, 0.88 mmol) in toluene (10 mL) and water (6.00 µL, 0.35 mmol) and triethylamine (0.05 mL, 0.39 mmol) after filtration. After evaporation product **267** was obtained as a yellow solid (0.16 g, 0.34 mmol, 97%).

Mp: 139.1 °C.

^{1}**H-NMR** (500 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 8.0 Hz, 1H, *H*-6'), 7.39 – 7.33 (m, 2H, *H*-3'', *H*-5''), 7.29 – 7.24 (m, 3H, *H*-2'', *H*-4'', *H*-3''), 7.21 – 7.16 (m, 3H, *H*-3', *H*-4', *H*-5'), 6.81 (s, 2H, *H*-3''', *H*-5'''), 6.23 (d, *J* = 642.7 Hz, 1H, P-*H*), 4.26 (dd, *J* = 11.7, 3.7 Hz, 1H, *H*-1''''), 4.06 (dd, *J* = 20.8, 11.7 Hz, 1H, *H*-1''''), 3.03 – 2.95 (m, 1H, *H*-5), 2.59 (ddd, *J* = 14.0, 9.7, 4.4 Hz, 1H, *H*-6), 2.40 (s, 6H, 2'''-CH_3, 6'''-CH_3), 2.26 (s, 3H, 4'''-CH_3), 2.21 – 2.13 (m, 1H, *H*-7), 1.85 (dddd, *J* = 15.9, 13.5, 11.9, 4.5 Hz, 2H, *H*-6, *H*-7), 1.28 (s, 3H, *H*-9), 0.77 (s, 3H, *H*-11), 0.61 (s, 3H, *H*-10) ppm.

^{13}**C-NMR** (126 MHz, $CDCl_3$) δ = 141.5 (*C*-2'), 141.3 (*C*-1''), 140.8 (*C*-4'''), 139.0 (*C*-1'''), 137.9 (*C*-2'''), 137.4 (*C*-6'''), 131.6 (*C*-3''), 130.4 (*C*-5''), 129.8 (*C*-4'), 129.1 (*C*-2'), 129.1 (*C*-6'), 128.5 (*C*-3'''), 128.3 (*C*-5'''), 128.2 (*C*-4''), 127.9 (*C*-6'), 127.1 (*C*-5'), 126.0 (*C*-1'), 125.3 (*C*-3'), 74.0 (*C*-1), 70.0 (*C*-1''''), 47.3 (*C*-5), 42.5 (*C*-8), 35.7 (*C*-7), 29.3 (4'''-CH_3), 24.7 (*C*-6), 21.5 (*C*-11), 21.0 (2'''-CH_3), 20.5 (6'''-CH_3), 18.5 (*C*-9), 18.0 (*C*-10) ppm.

^{31}**P-NMR** (202 MHz, $CDCl_3$) δ = 5.4 ppm.

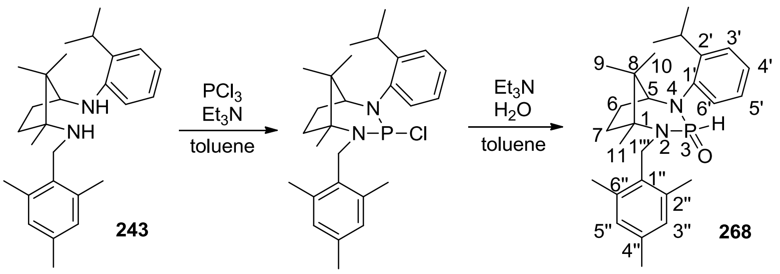
IR (ATR) ν = 3444, 2933, 2399, 1473, 1345, 1193, 1153, 1108, 1077, 1018, 976, 894, 850, 762, 749, 703, 559, 528 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 472 ($[M+H]^+$, 24%); 495 ($[M+Na]^+$, 52%).

HRMS (ESI): Calc. for $C_{30}H_{38}N_2OP$: 473.2722, found: 473.2737; $C_{30}H_{37}N_2ONaP$: 495.2541, found: 495.2559.

$[\alpha]^{20}_{D}$ = +41 (c = 0.45, EtOH).

3.4.1.9. (1*R*,3*R*,5*S*)-4-(2-Isopropylphenyl)-1,8,8-trimethyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (268)



Prepared from diamine **243** (0.15 g, 0.37 mmol), phosphorus trichloride (0.04 mL, 0.41 mmol), triethylamine (0.13 mL, 0.93 mmol) in toluene (10 mL) and water (6.70 µL, 0.37 mmol) and triethylamine (0.06 mL, 0.41 mmol) after filtration. After evaporation product **268** was obtained as a brown solid (0.14 g, 0.32 mmol, 86%).

Mp: 157.2 °C.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.23 – 7.04 (m, 3H, *H*-3’, *H*-4’, *H*-5’), 6.81 (d, *J* = 33.2 Hz, 3H, *H*-6’, *H*-3’’, *H*-5’’), 6.23 (d, *J* = 638.8 Hz, 1H, P*H*), 4.40 – 4.06 (m, 2H, *H*-1’’’), 3.45 (s, 1H, 2’-C*H*), 3.07 (dd, *J* = 20.7, 5.3 Hz, 1H, *H*-5), 2.81 – 2.53 (m, 2H, *H*-7), 2.47 (s, 6H, 2’’-CH_3, 6’’-CH_3), 2.19 (s, 3H, 4’’-CH_3), 1.96 (dd, *J* = 43.6, 32.4 Hz, 2H, *H*-6), 1.47 – 1.32 (m, 6H, *H*-9, *H*-11), 1.31 – 1.13 (m, 6H, 2 x 2’-CH-CH_3), 0.97 (s, 3H, *H*-10) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 147.6 (*C*-1’), 139.9 (*C*-4’’), 138.9 (*C*-1’’), 137.5 (*C*-2’’, *C*-6’’), 132.2 (*C*-3’’, *C*-5’’), 129.1 (*C*-6’), 128.5 (*C*-2’), 127.4 (*C*-4’), 126.5 (*C*-3’), 126.3 (*C*-5’), 74.5 (*C*-5), 70.0 (*C*-1), 53.4 (2’-*C*), 47.8 (*C*-8), 42.6 (*C*-1’’’), 35.7 (*C*-6), 29.9 (*C*-7), 26.6 (2’-C-*C*H_3), 25.0 (2’-C-*C*H_3), 24.5 (4’’-*C*H_3), 23.9 (*C*-9), 20.9 (2’’-*C*H_3), 20.5 (6’’-*C*H_3), 19.7 (*C*-10), 18.2 (*C*-11) ppm.

^{31}P-NMR (202 MHz, $CDCl_3$) δ = 5.4 ppm.

IR (ATR) ν = 3438, 2958, 2384, 1612, 1582, 1483, 1443, 1387, 1349, 1308, 1217, 1151, 1112, 1079, 1055, 1016, 973, 890, 848, 754, 688, 548, 526, 506, 473, 446, 407 cm^{-1}.

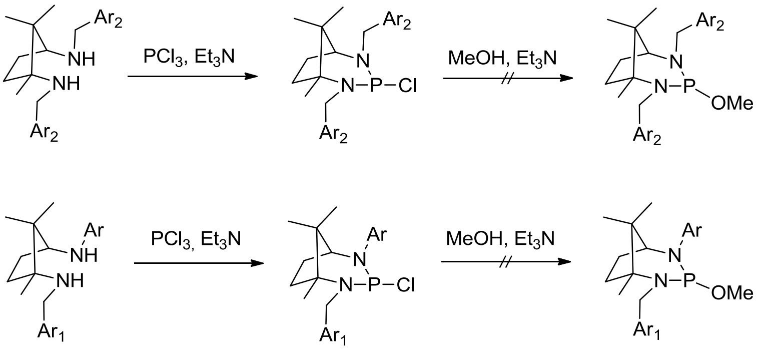
MS (ESI, + 3 kV): *m/z* (%) = 439 ($[M+H]^+$, 63%); 461 ($[M+Na]^+$, 100%).

HRMS (ESI): Calc. for $C_{27}H_{40}N_2OP$: 439.2878, found: 439.2880; $C_{27}H_{39}N_2ONaP$: 461.2698, found: 461.2700.

$[\alpha]^{20}_D$ = +51 (c = 0.46, EtOH).

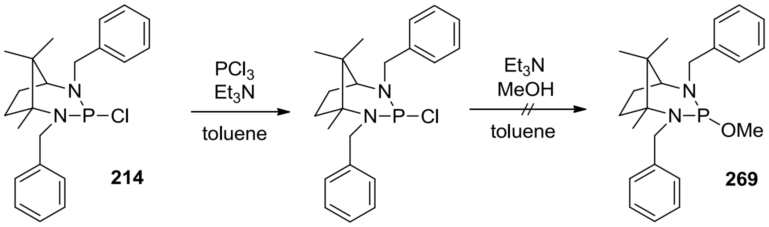
3.4.2. Preparation of Trivalent Ligands from Chloro-Derivatives

General Procedure



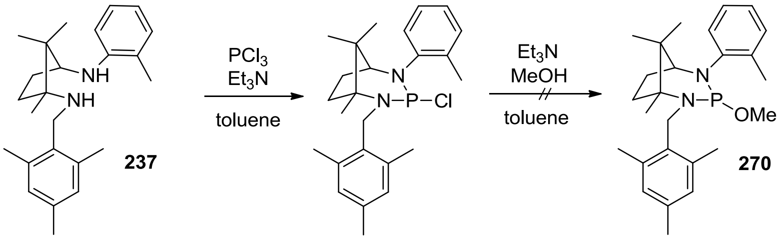
Solution of the suitable diamine (1 equiv.) in toluene was added to the mixture of phosphorus trichloride (1.1 equiv.) and triethylamine (2.5 equiv.) in toluene at –60 °C over 30 min. The solution was warmed to room temperature. After 2 h, the mixture was filtered through $MgSO_4$ and the filtrate was again cooled to –60 °C. Triethylamine (1.1 equiv.) and alcohol (1 equiv.) were added and the cooling bath was removed. After 1 h, the reaction mixture was filtered again through $MgSO_4$ and the filtrate was concentrated under reduced pressure.

3.4.2.1. (1*R*,3*S*,5*S*)-2,4-Dibenzyl-3-methoxy-1,8,8-trimethyl-2,4-diaza-3-phosphabicyclo[3.2.1]octane (269)



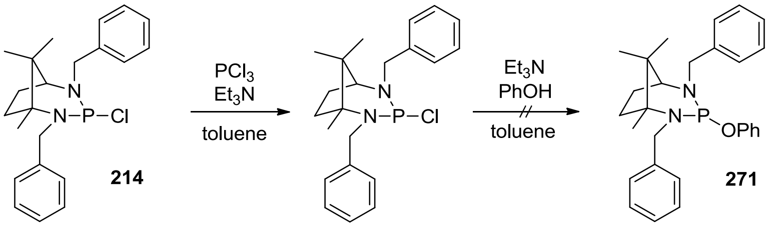
The general procedure was followed for diamine **214** (0.60 g, 1.86 mmol), phosphorus trichloride (0.18 mL, 2.05 mmol) and triethylamine (0.66 mL, 4.65 mmol) in toluene (10 mL), methanol (75.00 µL, 1.86 mmol) and triethylamine (0.28 mL, 2.05 mmol) after filtration. No product was obtained.

3.4.2.2. (1*R*,3*R*,5*S*)-3-Methoxy-1,8,8-trimethyl-4-(*o*-tolyl)-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane (270)



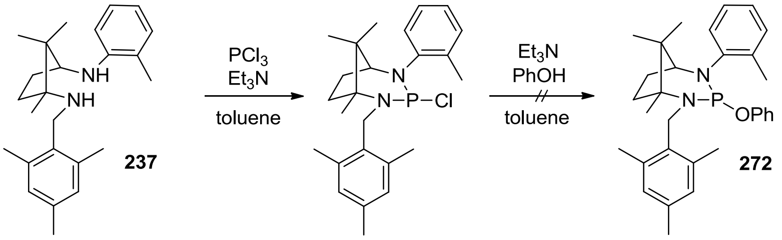
The general procedure was followed for diamine **237** (0.26 g, 0.72 mmol), phosphorus trichloride (0.07 mL, 0.79 mmol) and triethylamine (0.25 mL, 1.80 mmol) in toluene (10 mL), methanol (29.00 µL, 0.72 mmol) and triethylamine (0.11 mL, 0.79 mmol) after filtration. No product was obtained.

3.4.2.3. (1*R*,3*S*,5*S*)-2,4-Dibenzyl-1,8,8-trimethyl-3-phenoxy-2,4-diaza-3-phosphabicyclo[3.2.1]octane (271)



The general procedure was followed for diamine **214** (0.60 g, 1.86 mmol), phosphorus trichloride (0.18 mL, 2.05 mmol) and triethylamine (0.66 mL, 4.65 mmol) in toluene (10 mL), phenol (0.18 g, 1.86 mmol) and triethylamine (0.28 mL, 2.05 mmol) after filtration. No product was obtained.

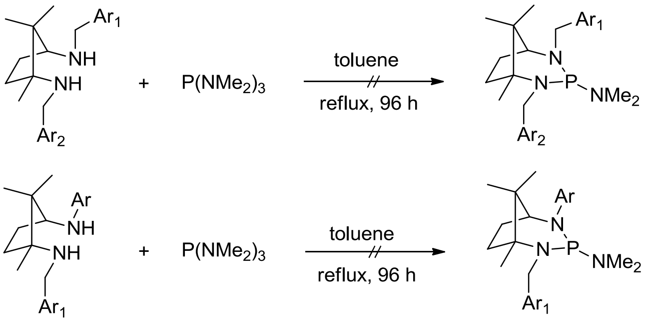
3.4.2.4. (1*R*,3*R*,5*S*)-1,8,8-Trimethyl-3-phenoxy-4-(*o*-tolyl)-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane (272)



The general procedure was followed for diamine **237** (0.26 g, 0.72 mmol), phosphorus trichloride (0.07 mL, 0.79 mmol) and triethylamine (0.25 mL, 1.80 mmol) in toluene (10 mL), phenol (0.08 g, 0.72 mmol) and triethylamine (0.11 mL, 0.79 mmol) after filtration. No product was obtained.

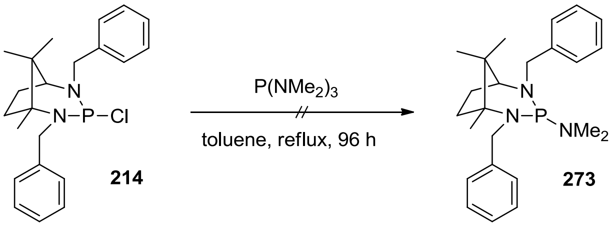
3.4.3. Preparation of Trivalent Phosphorus Derivatives from Hexamethylphosphorus Triamide

General Procedure



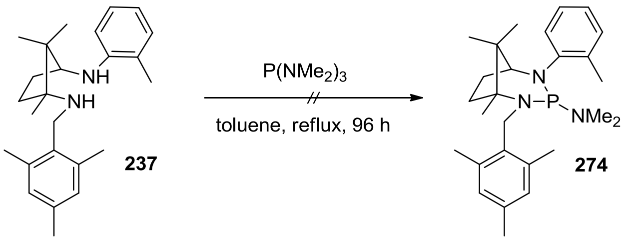
A solution of the suitable diamine (1 equiv.) in toluene was added to the mixture of hexamethylphosphorus triamide (1.3 equiv.) in toluene. The solution was refluxed over 96 h.

3.4.3.1. (1*R*,3*S*,5*S*)-2,4-Dibenzyl-*N*,*N*,1,8,8-pentamethyl-2,4-diaza-3-phosphabicyclo[3.2.1]octan-3-amine (273)



Prepared from diamine **214** (150.00 mg, 0.45 mmol) and hexamethylphosphorus triamide (0.11 mL, 0.59 mmol) in toluene (5 mL). The desired product was not obtained.

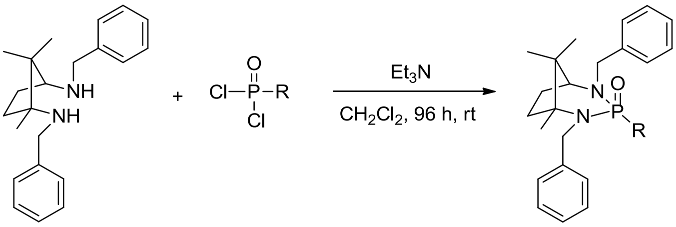
3.4.3.2. (1*R*,3*R*,5*S*)-*N*,*N*,1,8,8-Pentamethyl-4-(*o*-tolyl)-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octan-3-amine (274)



Prepared from diamine **237** (150.00 mg, 0.41 mmol) and hexamethylphosphorus triamide (0.10 mL, 0.54 mmol) in toluene (5 mL). The desired product was not obtained.

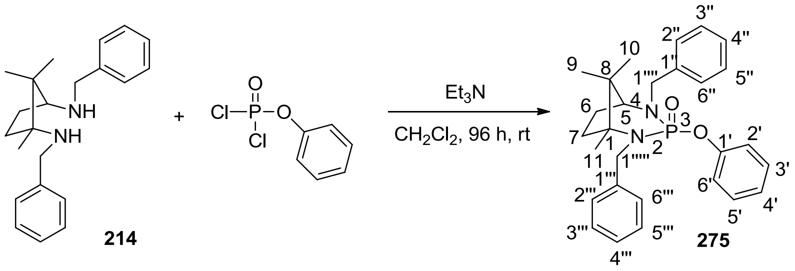
3.4.4. Preparation of Pentavalent Phosphorus Oxide

General Procedure



A solution of the suitable diamine (1 equiv.) in dichloromethane was added dropwise to the mixture of phosphorus compound (1.2 equiv.) and triethylamine (2.4 equiv.) in dichloromethane at 0 ^{o}C. The reaction mixture was warmed to room temperature and stirred for 96 h. The solution was washed with distilled water and brine. The organic phase was separated and dried over $MgSO_4$. The solvent was evaporated and the crude product was separated by column chromatography. The method of isolation for each compounds are given below.

3.4.4.1. 2,4-Dibenzyl-1,8,8-trimethyl-3-phenoxy-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (275)



Prepared from diamine **214** (0.35 g, 1.09 mmol), phenyl dichlorophosphate (0.31 mL, 1.31 mmol) and triethylamine (0.37 mL, 2.62 mmol) in dichloromethane (10 mL). After evaporation product **268** was obtained as two diastereoisomers which were separated by column chromatography (*n*-hexane/EtOAc, 5:5). The spectroscopic properties concur with published data.[176]

3.4.4.1.1. (1*R*,3*S*,5*S*)-2,4-Dibenzyl-1,8,8-trimethyl-3-phenoxy-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (275a)

The product was obtained as a white solid (0.13 g, 0.28 mmol, 27 %).

Mp: 124.3 °C.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.43 – 7.06 (m, 15H, *H*-1’, *H*-2’, *H*-3’, *H*-4’, *H*-5’, *H*-1’’, *H*-2’’, *H*-3’’, *H*-4’’, *H*-5’’, *H*-1’’’, *H*-2’’’, *H*-3’’’, *H*-4’’’, *H*-5’’’"), 4.55 (dd, *J* = 17.0, 12.6 Hz, 1H, *H*-1’’’’), 4.36 (dd, *J* = 15.1, 8.7 Hz, 1H, H-1’’’’’), 4.15 (ddd, *J* = 15.2, 13.0, 6.3 Hz, 2H, *H*-1’’’’, *H*-1’’’’’), 2.93 – 2.86 (m, 1H, *H*-5), 2.61 (ddd, *J* = 14.1, 9.7, 4.7 Hz, 1H, *H*-6), 2.27 (ddd, *J* = 14.1, 9.7, 4.5 Hz, 1H, *H*-7), 2.03 – 1.97 (m, 1H, *H*-6), 1.85 – 1.78 (m, 1H, *H*-7), 1.19 (s, 3H, *H*-11), 0.95 (s, 3H, *H*-9), 0.76 (s, 3H, *H*-10) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 153.2 (*C*-1’), 141.9 (*C*-1’’), 138.1 (*C*-1’’’), 129.5 (*C*-*C*-3’, *C*-5’), 128.6 (*C*-3’’, *C*-5’’), 128.3 (*C*-3’’’, *C*-5’’’), 128.2 (*C*-2’’, C-6’’), 127.2 (*C*-C-2’’’, C-6’’’), 127.1 (*C*-4’’), 126.4 (*C*-4’’’), 123.7 (*C*-4’), 120.4 (*C*-2’, *C*-6’), 72.4 (*C*-1’’’’’), 67.8 (*C*-1’’’’), 51.2 (*C*-1), 47.2 (*C*-5), 46.7 (*C*-8), 27.8 (*C*-7), 24.0 (*C*-6), 19.1 (*C*-11), 19.0 (*C*-9), 18.3 (*C*-10) ppm.

^{31}**P-NMR** (202 MHz, $CDCl_3$) δ = 12.0 ppm.

IR (ATR) ν = 3061, 2938, 1595, 1488, 1452, 1375, 1242, 1203, 1100, 1065, 870, 767, 723, 688, 511 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 461 ([M+H]$^+$, 11%); 483 ([M+Na]$^+$, 100%).

HRMS (ESI): Calc. for $C_{28}H_{34}N_2O_2P$: 461.2358, found: 461.2359; $C_{28}H_{33}N_2O_2NaP$: 483.2177, found: 483.2175.

[α]^{20}$_D$ = +3 (c = 0.49, EtOH).

3.4.4.1.2. (1*R*,3*R*,5*S*)-2,4-Dibenzyl-1,8,8-trimethyl-3-phenoxy-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (275b)

The product was obtained as colorless liquid (0.22 g, 0.48 mmol, 43%).

^{1}**H-NMR** (500 MHz, $CDCl_3$) δ = 7.55 – 6.96 (m, 15H, *H*-1’, *H*-2’, *H*-3’, *H*-4’, *H*-5’, *H*-1’’, *H*-2’’, *H*-3’’, *H*-4’’, *H*-5’’, *H*-1’’’, *H*-2’’’, *H*-3’’’, *H*-4’’’, *H*-5’’'), 4.87 – 4.81 (m, 1H, *H*-1’’’’), 4.57 (dd, *J* = 15.7, 10.0 Hz, 1H, *H*-1’’’’’), 4.22 – 4.14 (m, 1H, *H*-1’’’’’), 3.98 (dd, *J* = 15.7, 4.2 Hz, 1H, *H*-1’’’’), 2.91 (dd, *J* = 27.3, 5.4 Hz, 1H, *H*-5), 2.43 (ddd, *J* = 13.9, 9.7, 4.4 Hz, 1H, *H*-6), 2.19 (ddd, *J* = 14.3, 9.7, 4.7 Hz, 1H, *H*-7), 1.98 – 1.91 (m, 1H, *H*-7), 1.74 (ddd, *J* = 13.7, 12.0, 4.7 Hz, 1H, *H*-6), 1.44 (s, 3H, *H*-9), 1.00 (s, 3H, *H*-10), 0.80 (s, 3H, *H*-11) ppm.

^{13}**C-NMR** (126 MHz, $CDCl_3$) δ = 152.9 (*C*-1’), 141.7 (*C*-1’’’), 138.1 (*C*-1’’), 129.3 (*C*-3’, *C*-5’), 128.5 (*C*-3’’’, *C*-5’’’), 128.4 (*C*-3’’, *C*-5’’), 128.3 (*C*-2’’’, *C*-6’’’), 127.4 (*C*-2’’, *C*-6’’), 126.9 (*C*-4’’), 126.5 (*C*-4’’’), 123.9 (*C*-4’), 120.8(*C*-2’, *C*-6’) , 72.7 (*C*-1’’’’), 67.9 (*C*-1’’’’’), 49.6 (*C*-1), 47.2 (*C*-5), 46.0 (*C*-8), 36.5 (*C*-7), 28.3 (*C*-6), 24.8 (*C*-11), 19.0 (*C*-10), 18.9 (*C*-9) ppm.

^{31}**P-NMR** (202 MHz, $CDCl_3$) δ = 14.4 ppm.

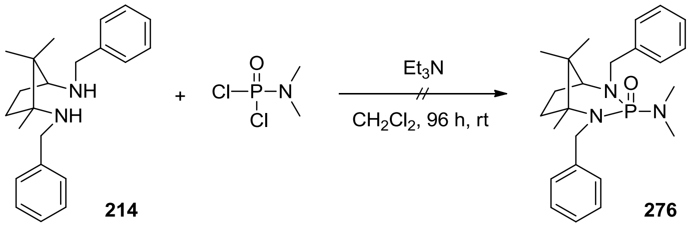
IR (ATR) ν = 2938, 1587, 1484, 1448, 1369, 1198, 1203, 1086, 1058, 907, 870, 753, 726, 689 cm^{-1}.

MS (ESI, + 3 kV): *m/z* (%) = 461 ([M+H]$^+$, 71%); 483 ([M+Na]$^+$, 100%).

HRMS (ESI): Calc. for $C_{28}H_{34}N_2O_2P$: 461.2358, found: 461.2361; $C_{28}H_{33}N_2O_2NaP$: 483.2177, found: 483.2177.

[α]^{20}$_D$ = +37 (c = 0.54, EtOH).

3.4.4.2. (1*S*,3*R*,5*S*)-2,4-Dibenzyl-3-(dimethylamino)-1,8,8-trimethyl-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (276)

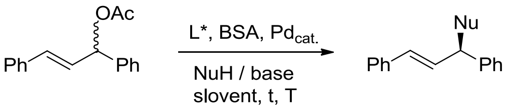


Diamine **214** (0.35 g, 1.09 mmol), dimethylphosphoramidic dichloride (0.21 g, 1.31 mmol) and triethylamine (0.37 mL, 2.62 mmol) were placed in dichloromethane (10 mL). No product was obtained.

3.5. Allylic Substitution

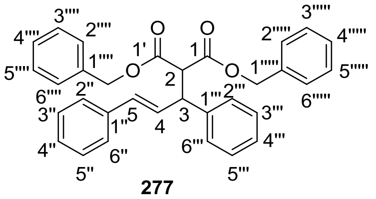
3.5.1. Pd-Catalyzed Asymmetric Allylic Alkylation with Carbon Nucleophiles

General Procedure



The appropriate ligand (0.1 equiv.) and BSA (4 equiv.) were dissolved in a solvent (1 mL) and the mixture was stirred for 24 h at room temperature under an argon atmosphere. Pd$_{cat.}$ (0.025 equiv.) was added and the mixture was stirred for 40 min. A solution of diphenylallyl acetate (1 equiv.), keto ester (1.5 equiv.) and base (0.1 equiv.) in a solvent (0.5 mL) was added and the reaction mixture was stirred at various temperatures for 24h. The solvent was removed under reduced pressure and the crude product was purified by a silica gel flash column chromatography to give the corresponding product. Spectral data were consistent with literature values and the absolute configuration was assigned by comparison to literature values (For optimal conditions see Table 13-17).

3.5.1.1. (*E*)-Dibenyl 2-(1,3-diphenylallyl)malonate (277)



277

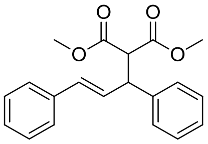
Prepared according to the general procedure from ligand **260** (12.00 mg, 0.03 mmol), BSA (0.31 mL, 1.27 mmol), $(\eta^3\text{-}C_3H_5)_2Pd_2Cl_2$ (2.90 mg, $7.93\cdot10^{-3}$ mmol), (±)-*trans*-

1,3-diphenylallyl acetate **202** (80 mg, 0.32 mmol), dibenzyl malonate (0.12 mL, 0.48 mmol) and KOAc (3.11 mg, 0.03 mmol) in toluene (1 mL). The crude product was purified *via* column chromatography (*n*-hexane/EtOAc, 90:10) and obtained as colorless oil (5.60 mg, 0.01 mmol, 4%). Spectral data were consistent with literature values.[201]

^{1}H-NMR (500 MHz, CDCl$_3$) δ = 7.43 – 7.01 (m, 20H, *H*-2’’, *H*-3’’, *H*-4’’, *H*-5’’ *H*-6’’, *H*-2’’’, *H*-3’’’, *H*-4’’’, *H*-5’’’ *H*-6’’’, *H*-2’’’’, *H*-3’’’’, *H*-4’’’’, *H*-5’’’’ *H*-6’’’’, *H*-2’’’’’, *H*-3’’’’’, *H*-4’’’’’, *H*-5’’’’’ *H*-6’’’’’), 6.41 (d, *J* = 15.8 Hz, 1H, *H*-4), 6.31 (dd, *J* = 15.7, 8.4 Hz, 1H, *H*-5), 5.11 (m, 2H, 1’-O-C*H*$_2$), 4.90 (m, 2H, 1-O-C*H*$_2$), 4.29 (m, 1H, *H*-3), 4.05 (d, *J* = 10.8 Hz, 1H, *H*-2) ppm.

^{13}C-NMR (126 MHz, CDCl$_3$) δ = 167.6 (*C*-1), 167.2 (*C*-1’), 140.1 (*C*-1’’’), 136.8 (*C*-1’’), 135.2 (*C*-1’’’’, *C*-1’’’’’), 135.0 (*C*-3’’’’), 131.9 (*C*-5), 129.0 (*C*-5’’’’), 128.8 (*C*-3’’’’’, *C*-5’’’’’), 128.5 (*C*-3’’*C*-5’’), 128.4 (*C*-3’’’, *C*-5’’’), 128.3 (*C*-2’’, *C*-6’’), 128.2 (*C*-4’’), 128.1 (*C*-2’’’, *C*-6’’’), 127.5 (*C*-4’’’’, *C*-4’’’’’), 127.4 (*C*-2’’’’, *C*-6’’’’), 127.2 (*C*-2’’’’’, *C*-6’’’’’), 126.5 (*C*-4’’’), 67.4 (1-O-*C*H$_2$), 67.1 (1’-O-*C*H$_2$), 57.8 (*C*-2), 49.0 (*C*-3) ppm.

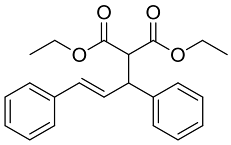
3.5.1.2. (*E*)-Dimethyl 2-(1,3-diphenylallyl)malonate (278)



278

The general procedure was followed for ligand **260** (12.00 mg, 0.03 mmol), BSA (0.31 mL, 1.27 mmol), (η^3-C$_3$H$_5$)$_2$Pd$_2$Cl$_2$ (2.90 mg, 7.93·10^{-3} mmol), (±)-*trans*-1,3-diphenylallyl acetate **202** (80 mg, 0.32 mmol), dimethyl malonate (0.05 mL, 0.48 mmol) and KOAc (3.11 mg, 0.03 mmol) in toluene (1 mL). The product was not obtained.

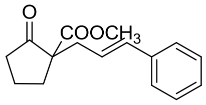
3.5.1.3. (*E*)-Diethyl 2-(1,3-diphenylallyl)malonate (279)



279

The general procedure was followed for ligand **260** (12.00 mg, 0.03 mmol), BSA (0.31 mL, 1.27 mmol), (η^3-C_3H_5)$_2$$Pd_2Cl_2$ (2.90 mg, $7.93\cdot10^{-3}$ mmol), (±)-*trans*-1,3-diphenylallyl acetate **202** (80 mg, 0.32 mmol), diethyl malonate (0.07 mL, 0.48 mmol) and KOAc (3.11 mg, 0.03 mmol) in toluene (1 mL). The product was not obtained.

3.5.1.4. Methyl 1-cinnamyl-2-oxocyclopentanecarboxylate (281)

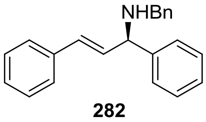


281

The general procedure was followed for ligand **260** (10.00 mg, 0.03 mmol), BSA (0.28 mL, 1.14 mmol), (η^3-C_3H_5)$_2$$Pd_2Cl_2$ (2.60 mg, $7.10\cdot10^{-3}$ mmol), cinnamyl acetate **280** (0.05 mL, 0.28 mmol), methyl 2-oxocyclopentanecarboxylate (0.05 mL, 0.43 mmol) and Zn(OAc)$_2$ (5.21 mg, 0.03 mmol) in toluene (1 mL). The corresponding product was not obtained.

3.5.2. Pd-Catalyzed Allylic Substitution with Non-Carbon Nucleophile

3.5.2.1. (*R*,*E*)-*N*-Benzyl-1,3-diphenylprop-2-en-1-amine (282)



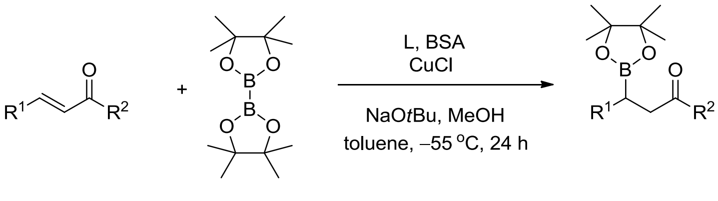
282

The general procedure was followed for ligand **262** (5.00 mg, 1.22·10^{-4} mmol, 0.04 equiv.), BSA (0.23 mL, 0.01 mmol, 3 equiv.), (η^3-$C_3H_5)_2Pd_2Cl_2$ (1.10 mg, 3.05·10^{-3} mmol, 0.01 equiv.), (±)-*trans*-1,3-diphenylallyl acetate **202** (75 mg, 0.31 mmol, 1 equiv.) and benzylamine (0.10 mL, 0.91 mmol, 3 equiv.) in methyl chloride (1 mL). The corresponding product was not obtained.

3.6. The Construction of Chiral Organoboranes

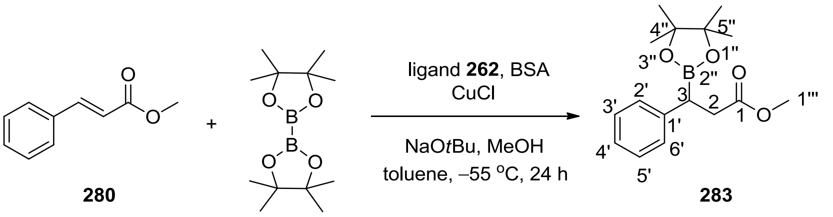
3.6.1. Copper-Catalyzed Asymmetric Hydroboration

General Procedure



The HASPO ligand (0.11 equiv.) and BSA (0.09 equiv.) were dissolved in toluene (1 mL) and the mixture was stirred for 24 h at room temperature under an argon atmosphere. CuCl (0.1 equiv.) was added and the mixture was stirred 10 min. A solution of methyl cinnamate (1 equiv.), Bin_2Pin_2 (1.1 equiv.) and NaO*t*Bu (.3 equiv.) in toluene (1 mL) was added and the reaction mixture was stirred at –55 °C 10 min. MeOH (2 equiv.) was added and the reaction mixture was stirred at –55 °C 24 h. The solvent was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography. The enantiomeric excess was determined by chiral HPLC analysis. Spectra data were consistent with literature values (For yields and enantiomeric excess see Table 18-20).

3.6.1.1. Methyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) propanoate (283)



Prepared from HASPO ligand **262** (10 mg, $2.44 \cdot 10^{-2}$ mmol), BSA (5µL, 0.02 mmol), CuCl (2.19 mg, $2.21 \cdot 10^{-2}$ mmol) methyl cinnamate **280** (36 mg, 0.22 mmol), Bin_2Pin_2 (62 mg, 0.24 mmol), NaO*t*Bu (6.38 mg, $6.64 \cdot 10^{-2}$ mmol, 0.3 equiv.) and MeOH (18 µL, 0.44 mmol) in toluene. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc, 95:5). The corresponding product **283** was obtained as colorless oil (0.025 g, 0.09 mmol, 51%). Spectra data were consistent with literature values.[202]

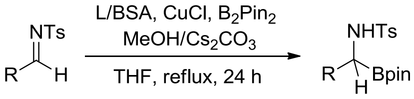
^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.27 – 7.20 (m, 4H, *H*-6‘, *H*-5‘, *H*-3‘, *H*-2‘), 7.17 – 7.13 (m, 1H, *H*-4‘), 3.61 (s, 3H, *H*-1‘‘‘), 2.89 (dd, *J* = 16.2, 10.0 Hz, 1H, *H*-2), 2.74 (dd, *J* = 10.0, 6.1 Hz, 1H, *H*-3), 2.66 (dd, *J* = 16.2, 6.0 Hz, 1H, *H*-2), 1.22 (s, 6H, 5‘‘-C*H*$_3$, 4‘‘-C*H*$_3$), 1.17 (s, 6H, 5‘‘-C*H*$_3$, 4‘‘-C*H*$_3$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 173.8 (*C*-1), 141.4 (*C*-1‘), 128.5 (*C*-5‘, *C*-3‘), 128.2 (*C*-6‘, *C*-2‘), 125.7 (*C*-4‘), 83.3 (*C*-5‘‘, *C*-4‘‘), 51.3 (*C*-1‘‘‘), 36.8 (*C*-2, C-3), 24.6 (5‘‘-*C*H$_3$, 4‘‘-*C*H$_3$), 24.3 (5‘‘-*C*H$_3$, 4‘‘-*C*H$_3$) ppm.

HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 90/10 *v*/*v*, 1 mL/min, 25 ^{o}C, UV = 250 nm): t_{majorr}= 9.25 min, t_{minor}= 13.79 min; 0% *ee*.

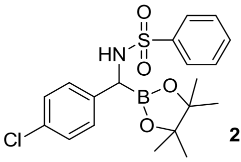
3.6.2. Organocatalytic Pinacolboryl Addition to Tosylaldimines

General Procedure



The HASPO ligand (0.03 equiv.) and BSA (0.09 equiv.) were dissolved in THF (1 mL) and the mixture was stirred for 24 h at room temperature under an argon atmosphere. Tosylaldimines ((1 equiv.), CuCl (0.04 equiv.), Bin_2Pin_2 (1.2 equiv.) and Cs_2CO_3 (0.15 equiv.) were added and the reaction was stirred at room temperature for 10 min. MeOH (2.5 equiv.) was added and the reaction mixture was stirred at reflux for 24 h. (For optimal conditions see Table 21).

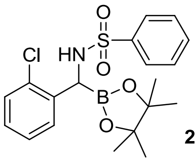
3.6.2.1. *N*-((4-Chlorophenyl)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methyl) benzenesulfonamide (288)



288

The general procedure was followed for ligand **262** (4.11 mg, 0.01 mmol) BSA (7.70 µL, 0.03 mmol), CuCl (1.39 mg, $1.40^{.}10^{-2}$ mmol), B_2Pin_2 (106.65 mg, 0.42 mmol), (*E*)-*N*-(4-chlorobenzylidene) benzenesulfonamide **284** (98.00 mg, 0.35 mmol), Cs_2CO_3 (17.10 mg, 0.05 mmol) and MeOH (0.04 mL, 0.88 mmol) in THF (1 mL). The corresponding product was not obtained.

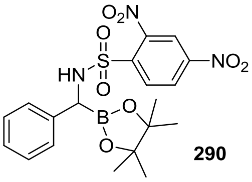
3.6.2.2. *N*-((2-Chlorophenyl)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methyl) benzenesulfonamide (289)



289

The general procedure was followed for ligand **262** (4.11 mg, 0.01 mmol) BSA (7.70 μL, 0.03 mmol), CuCl (1.39 mg, $1.40\cdot10^{-2}$ mmol), B_2Pin_2 (106.65 mg, 0.42 mmol), (*E*)-*N*-(2-chlorobenzylidene) benzenesulfonamide **285** (98.00 mg, 0.35 mmol), Cs_2CO_3 (17.10 mg, 0.05 mmol) and MeOH (0.04 mL, 0.88 mmol) in THF (1 mL). The corresponding product was not obtained.

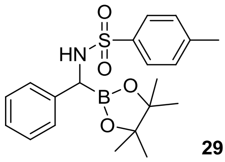
3.6.2.3. 2,4-Dinitro-*N*-(phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methyl) benzenesulfonamide (290)



290

The general procedure was followed for ligand **262** (4.06 mg, $9.90\cdot10^{-3}$ mmol), BSA (7.26 μL, 0.03 mmol), CuCl (0.99 mg, 0.01 mmol), B_2Pin_2 (100.00 mg, 0.40 mmol), (*E*)-*N*-benzylidene-2,4-dinitrobenzenesulfonamide **286** (111.00 mg, 0.33 mmol), Cs_2CO_3 (16.12 mg, 0.05 mmol) and MeOH (0.03 mL, 0.83 mmol) in THF (1 mL). The corresponding product was not obtained.

3.6.2.4. 4-Methyl-*N*-(phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methyl)benzenesulfonamide (291)



291

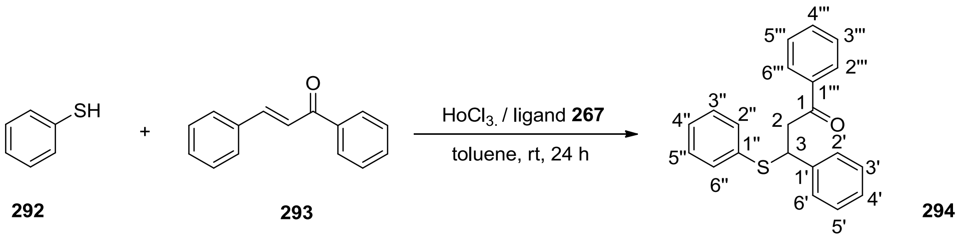
The general procedure was followed for ligand **262** (4.11 mg, 0.01 mmol), BSA (9.42 μL, 0.04 mmol), CuCl (0.99 mg, 0.01 mmol), B_2Pin_2 (131.03 mg, 0.52 mmol), (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide **287** (111.00 mg, 0.43 mmol), Cs_2CO_3 (19.55 mg, 0.06 mmol) and MeOH (0.04 mL, 1.08 mmol) in THF (1 mL). The corresponding product was not obtained.

3.7. Michael Addition

General Procedure

The appropriate ligand (0.05 equiv.) and catalyst (0.08 equiv.) were dissolved in toluene (2 mL). The Michael donor (1 equiv.) and chalcone (1 equiv.) were added and the reaction mixture was stirred at room temperature over 24 h. The solvent was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography to give the corresponding product. The enantiomeric excess was determined by chiral HPLC analysis. Spectra data were consistent with literature values (For yields and enantiomeric excess see Table 22).

3.7.1. 1,3-Diphenyl-3-(phenylthio)propan-1-one (294)



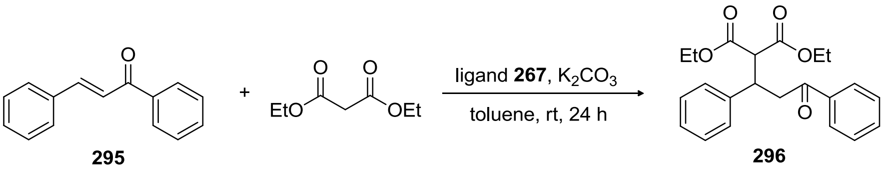
Prepared according to the general procedure from ligand **267** (10.00 mg, 0.02 mmol), $HoCl_3$ (8.14 mg, 0.03 mmol), (*E*)-*N*-benzylidene-tiophenol **292** (46.00 mg, 0.42 mmol) and chalcone **293** (87.00 mg, 0.42 mmol) in toluene (1 mL). The crude product was purified *via* column chromatography (Petrolether/EtOAc, 10:1) to give a while solid (65.00 mg, 0.21 mmol, 49%). Spectral data were consistent with literature values.[203]

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.90 – 7.86 (m, 2H, *H*-2''', *H*-6'''), 7.56 – 7.51 (m, 1H, *H*-4'''), 7.41 – 7.45 (m, 2H, *H*-3''', *H*-5'''), 7.32 – 7.35 (m, 4H, *H*-2', *H*-6', *H*-2'', *H*-6''), 7.17 – 7.27 (m, 6H, H-3', H-4', H-5', H-3'', H-4'', H-5''), 4.97 (dd, *J* = 8.1, 6.0 Hz, 1H, H-2), 3.63 (ddd, *J* = 23.1, 17.1, 7.1 Hz, 2H, *H*-3) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 197.0 (*C*-1), 141.2 (*C*-1'), 136.8 (*C*-1''), 134.3 (*C*-1'''), 133.2 (*C*-4'''), 132.8 (*C*-2'', *C*-6''), 128.9 (*C*-3'', *C*-5''), 128.6 (*C*-3', *C*-5'), 128.4 (*C*-3''', *C*-5'''), 128.1 (*C*-2''', *C*-6'''), 127.8 (*C*-2', *C*-6'), 127.5 (*C*-4'), 127.4 (*C*-4''), 48.3 (*C*-2), 44.5 (*C*-3) ppm.

HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 50:50 *v*/*v*, 1 mL/min, 25 °C, UV = 250 nm): t_{minor}= 8.37 min, t_{major}= 9.23 min; 9% *ee*.

3.7.2. Diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate (296)



The general procedure was followed for ligand **267** (10.00 mg, 0.02 mmol), K_2CO_3 (49.00 mg, 0.35 mmol), diethyl malonate (28.00 mg, 0.17 mmol) and chalcone **295** (24.00 mg, 0.12 mmol) in toluene (1 mL). The corresponding product was not obtained.

3.8. HASPO Ligands as Chiral Shift Reagents

3.8.1. NMR Experiments with HASPO Ligands and Racemic Compounds

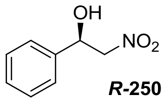
The HASPO ligand (1 equiv.) and the corresponding racemic compound (1 equiv.) were dissolved in deuterated toluene and the ^{1}H-NMR and ^{19}F-NMR spectra were recorded at room temperature. For results see Table 23-26.

4. Appendix

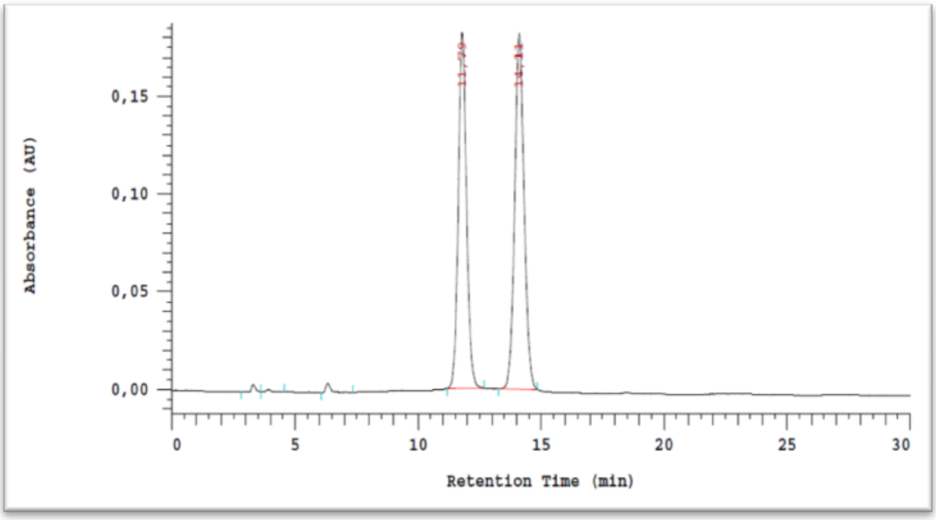
4. Appendix

HPLC- Chromatograms:

(*R*)-2-Nitro-1-phenylethanol

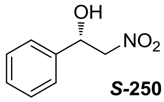


***R*-250**

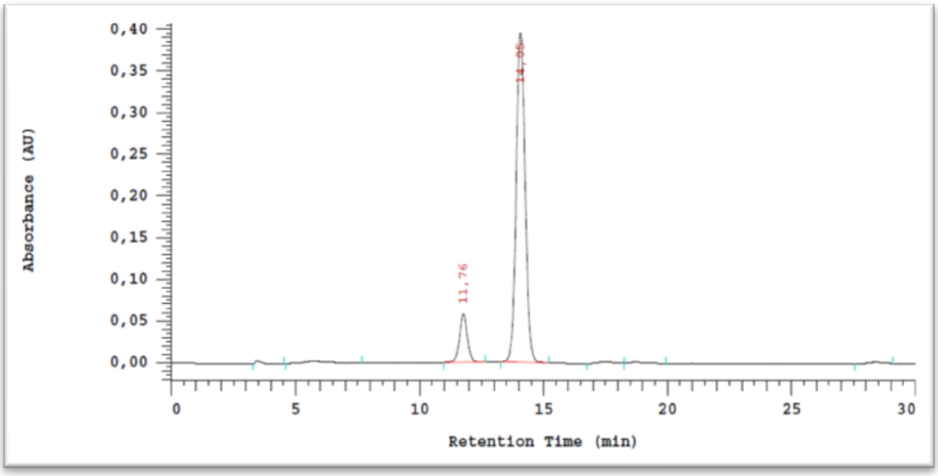


No.	Retention time (t_R) [min]	Area	Concentration [%]
1	11.79	2103392	46.280
2	14.11	2441529	53.720
		4544921	100.000

(*S*)-2-Nitro-1-phenylethanol

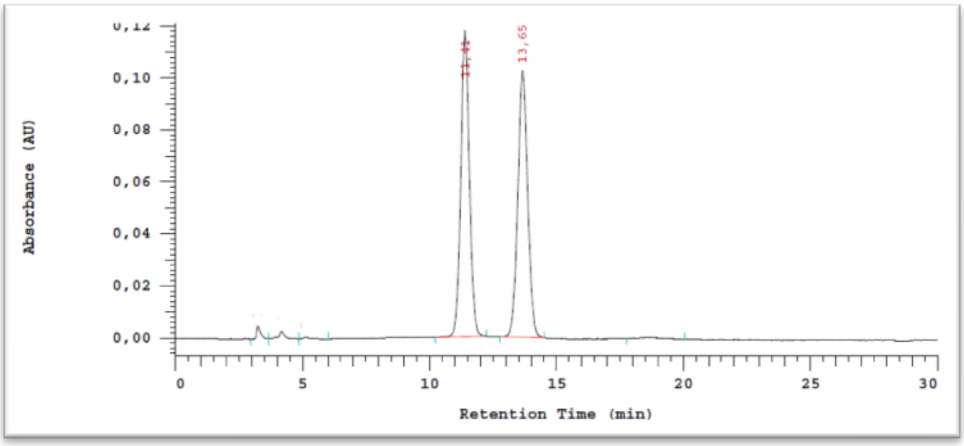


***S*-250**



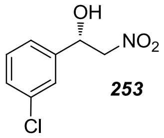
No.	Retention time (t_R) [min]	Area	Concentration [%]
1	11.76	642200	11.314
2	14.05	5034138	88.686
		5676338	100.000

rac-2-Nitro-1-phenylethanol



No.	Retention time (t_R) [min]	Area	Concentration [%]
1	11.41	1380064	49.921
2	13.65	1384459	50.079
		2764523	100.000

(*S*)-Nitro-1-(3-Chlorophenyl)-2-nitroethanol



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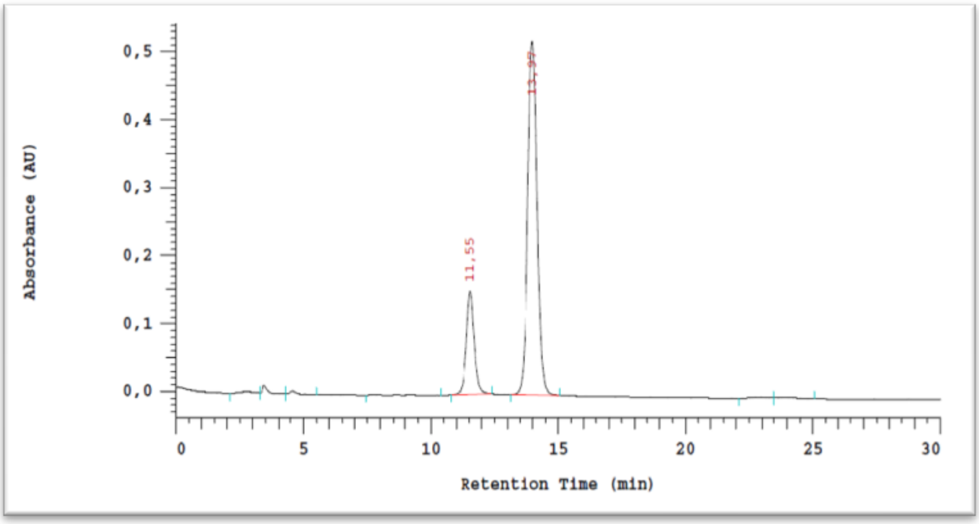
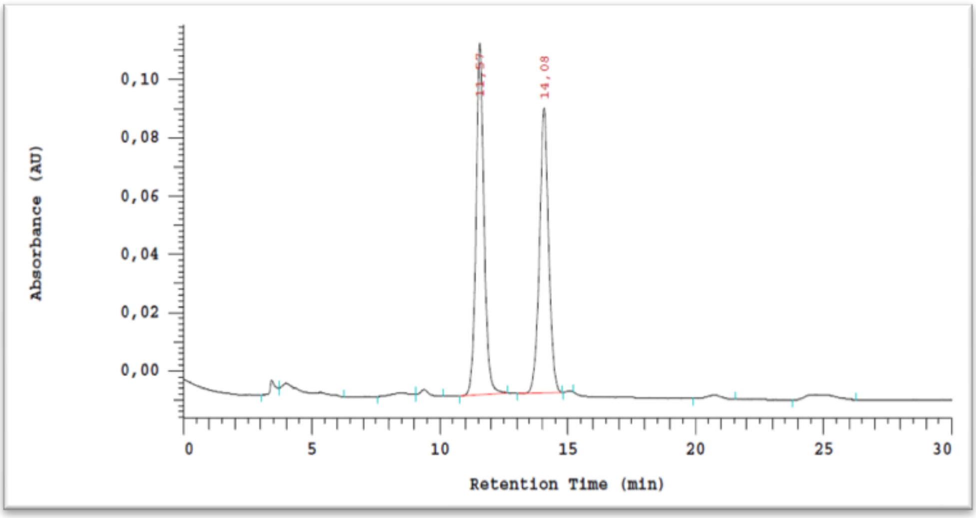


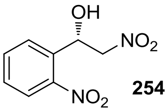
No.	Retention time (t_R) [min]	Area	Concentration [%]
1	11.55	1651660	19.285
2	13.97	6912896	80.715
		8564556	100.000

rac-Nitro-1-(3-Chlorophenyl)-2-nitroethanol



No.	Retention time (t_R) [min]	Area	Concentration [%]
1	11.57	1308219	51.116
2	14.08	1251098	48.884
		2559317	100.000

(*S*)-2-Nitro-1-(2-nitrophenyl)ethanol



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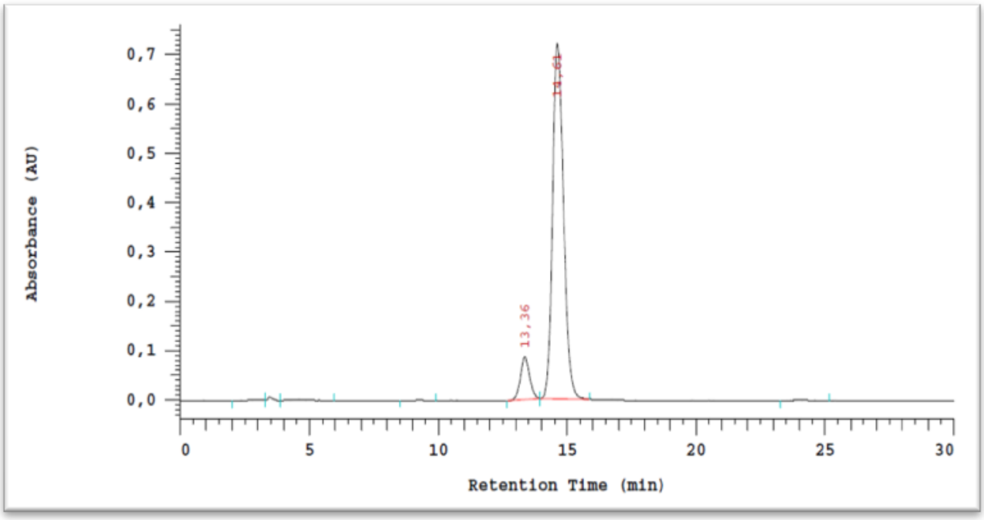
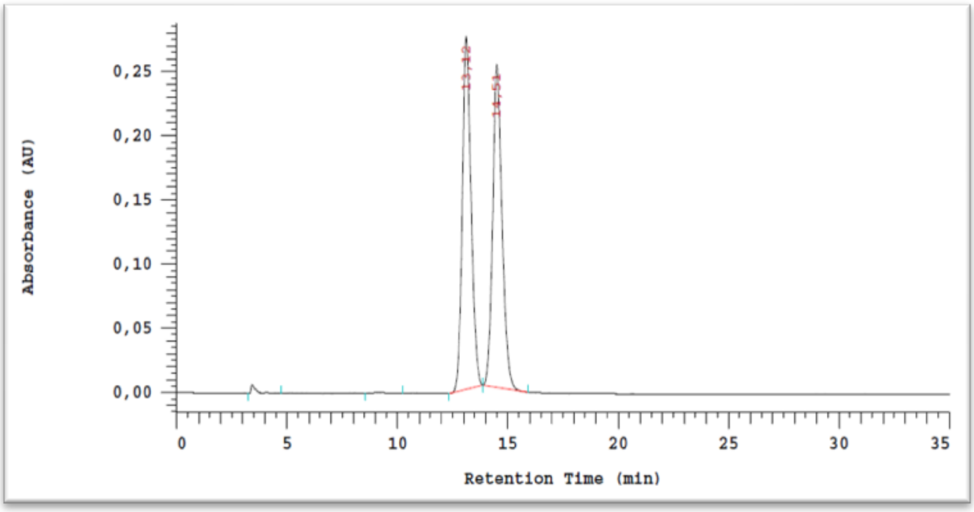


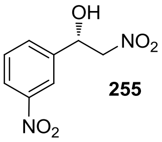
No.	Retention time (t_R) [min]	Area	Concentration [%]
1	13.36	1056635	9.037
2	14.61	10635950	90.963
		11692585	100.000

rac-2-Nitro-1-(2-nitrophenyl)ethanol



No.	Retention time (t_R) [min]	Area	Concentration [%]
1	13.12	3717980	49.935
2	14.51	3727693	50.065
		7445673	100.000

(*S*)-2-Nitro-1-(3-nitrophenyl)ethanol



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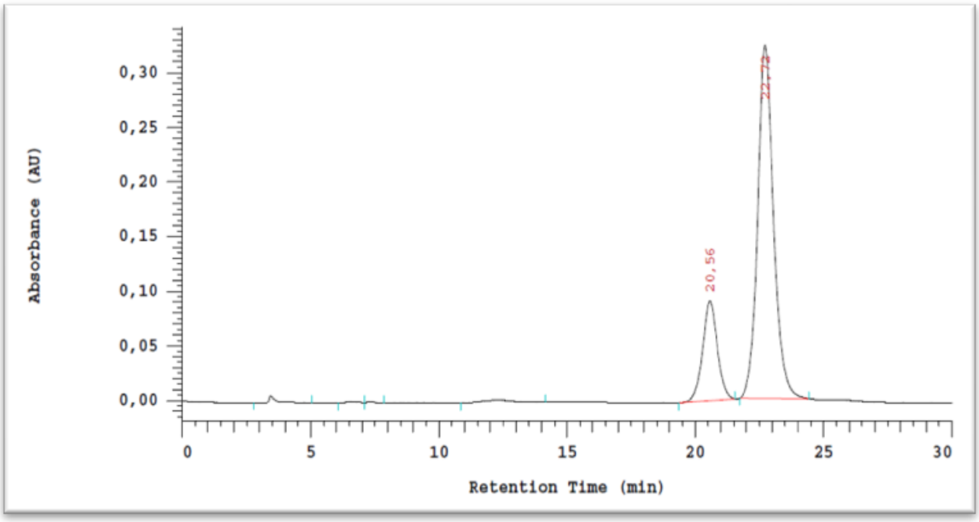
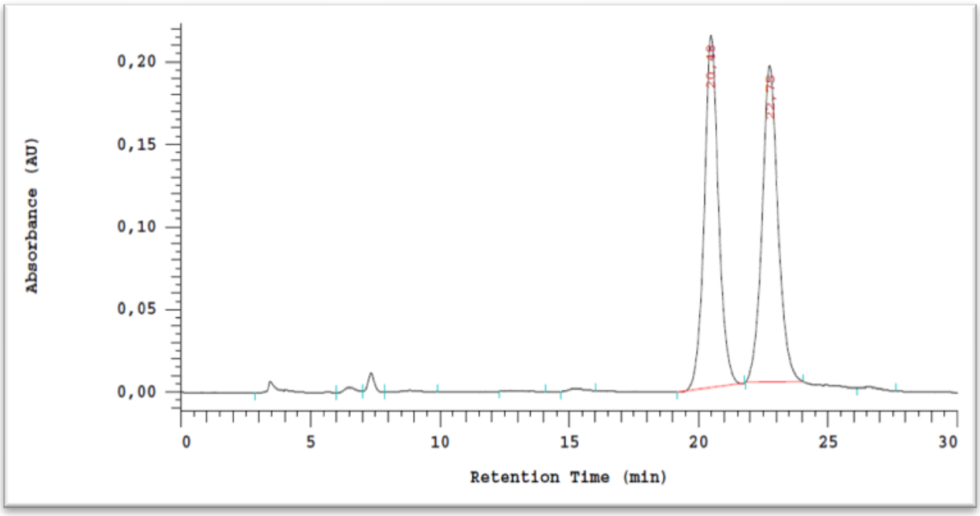


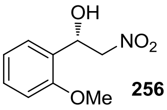
No.	Retention time (t_R) [min]	Area	Concentration [%]
1	20.56	1816018	20.766
2	22.72	6929058	79.234
		8745076	100.000

rac-2-Nitro-1-(3-nitrophenyl)ethanol

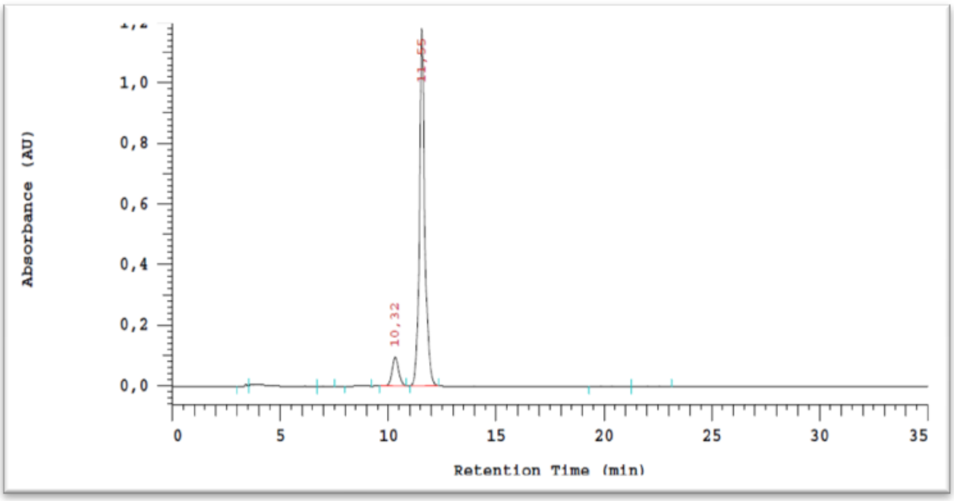


No.	Retention time (t_R) [min]	Area	Concentration [%]
1	20.48	4101677	50.106
2	22.75	4084300	49.894
		8185977	100.000

(*S*)-1-(2-Methoxyphenyl)-2-nitroethanol

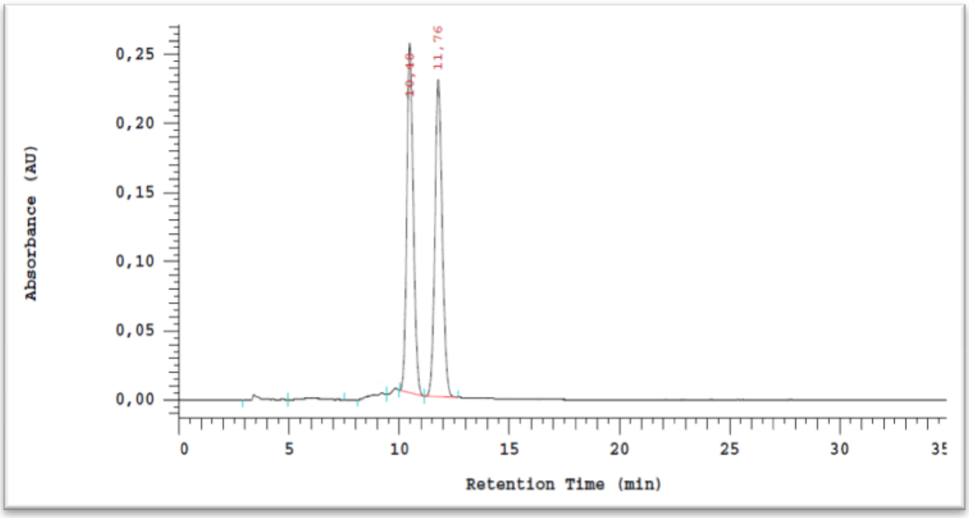


256



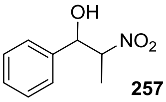
No.	Retention time (t_R) [min]	Area	Concentration [%]
1	10.32	989689	8.768
2	11.55	10298249	91.232
		11287938	100.000

rac-1-(2-Methoxyphenyl)-2-nitroethanol

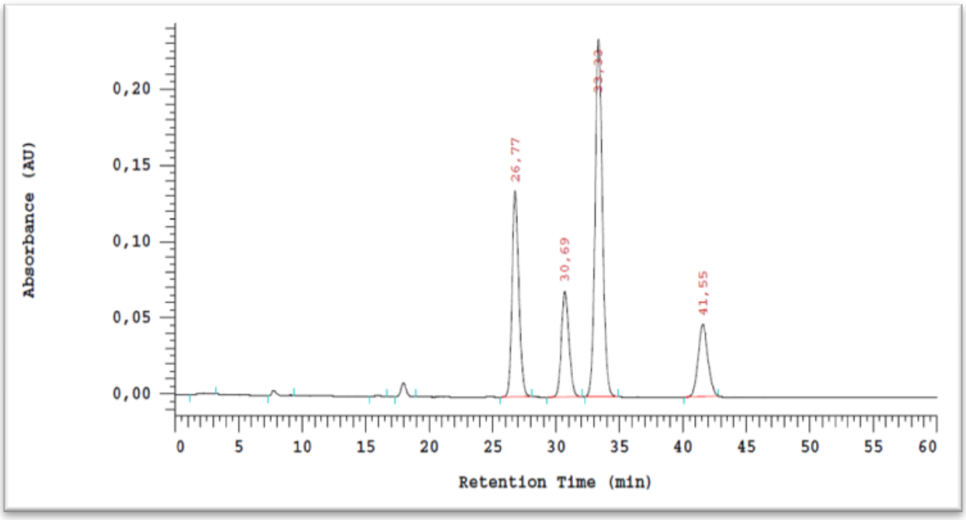


No.	Retention time (t_R) [min]	Area	Concentration [%]
1	10.48	2590044	49.390
2	11.76	2654049	50.610
		5244093	100.000

2-Nitro-1-phenylpropan-1-ol

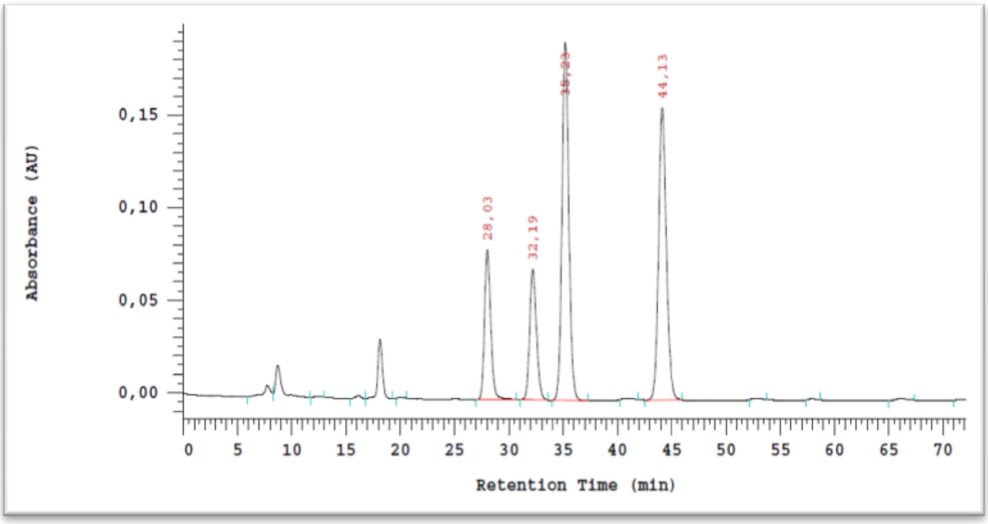


257



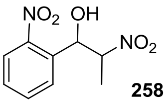
No.	Retention time (t_R) [min]	Area	Concentration [%]
1	26.77	2488446	25.005
2	30.69	1428573	14.355
3	33.33	4754230	47.773
4	41.55	1280500	12.867
		9951749	100.000

rac-2-Nitro-1-phenylpropan-1-ol

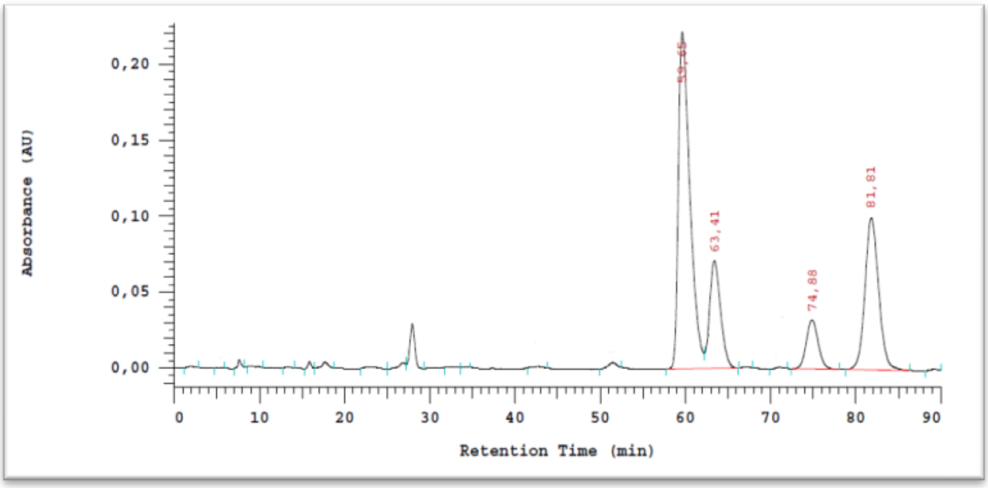


No.	Retention time (t_R) [min]	Area	Concentration [%]
1	28.03	1607321	14.293
2	32.19	1526350	13.573
3	35.23	4181356	37.183
4	44.13	3930324	34.951
		11245351	100.000

2-Nitro-1-(2-nitrophenyl)propan-1-ol

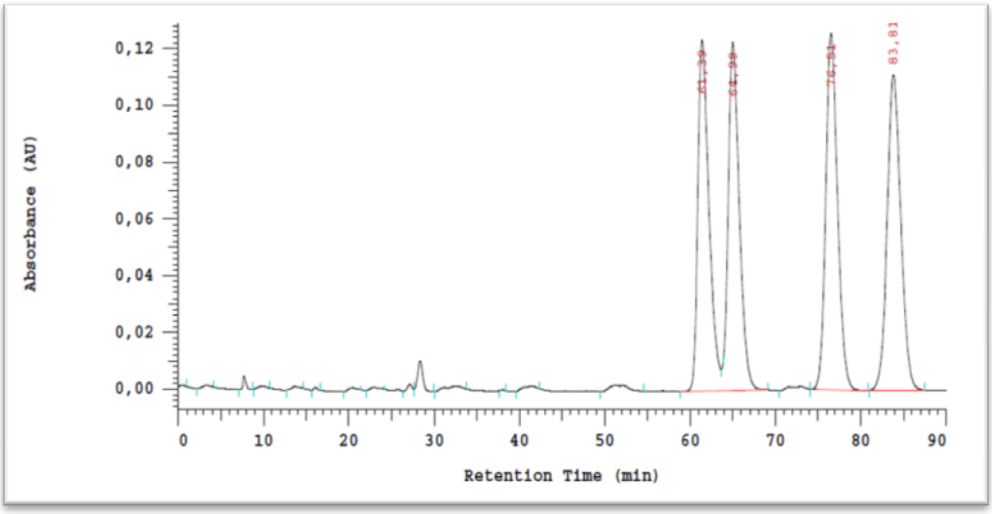


258



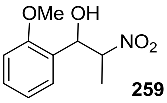
No.	Retention time (t_R) [min]	Area	Concentration [%]
1	59.65	10341972	50.021
2	63.41	3203503	15.494
3	74.88	1551729	7.505
4	81.81	5577920	26.979
		20675124	100.000

rac-2-Nitro-1-(2-nitrophenyl)propan-1-ol

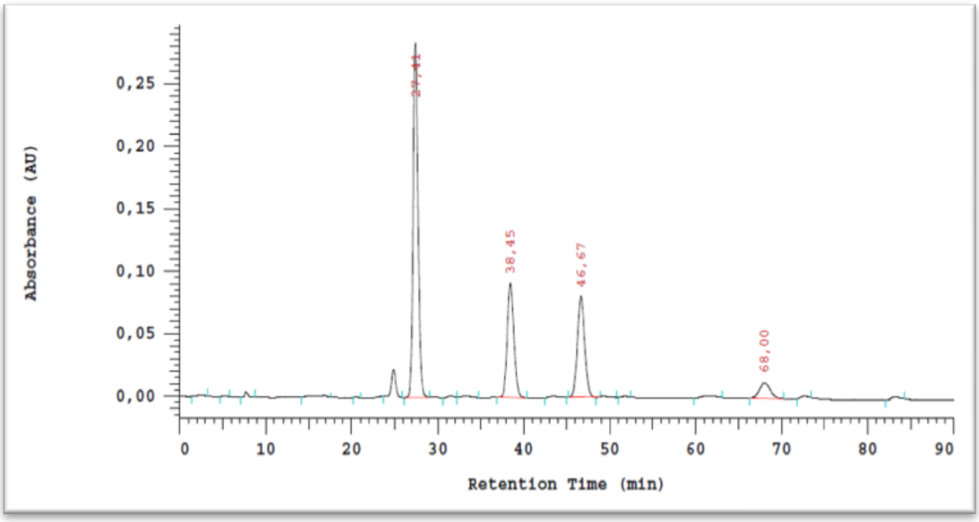


No.	Retention time (t_R) [min]	Area	Concentration [%]
1	61.39	5649298	24.282
2	64.99	5543324	23.826
3	76.51	5977812	25.694
4	83.81	6095182	26.198
		23265616	100.000

1-(2-Methoxyphenyl)-2-nitropropan-1-ol

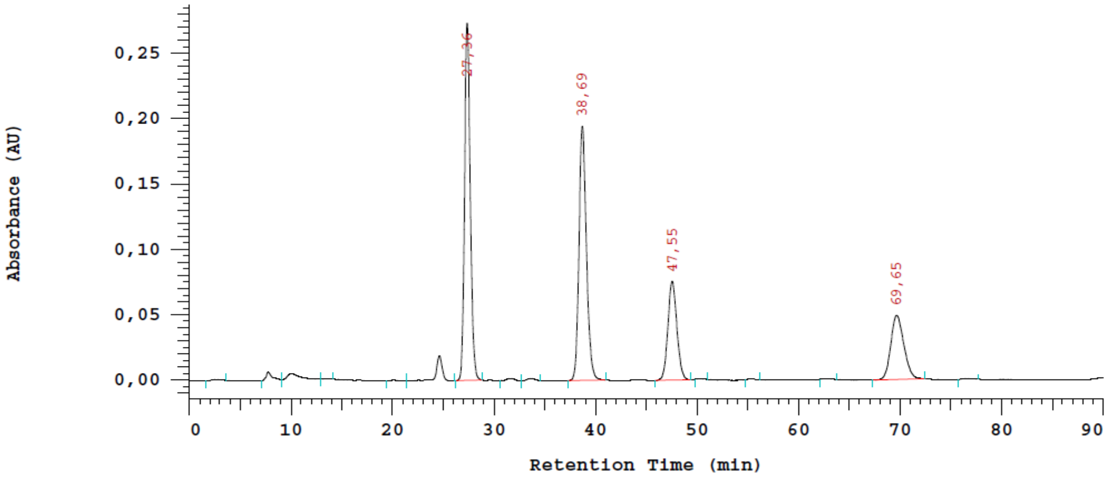


259



No.	Retention time (t_R) [min]	Area	Concentration [%]
1	27.41	5519955	50.869
2	38.45	2422516	22.325
3	46.67	2368883	21.830
4	68.00	539973	4.976
		10851327	100.000

rac-1-(2-Methoxyphenyl)-2-nitropropan-1-ol



No.	Retention time (t_R) [min]	Area	Concentration [%]
1	27.36	5298323	36.077
2	38.69	4895988	33.337
3	47.55	2308814	15.721
4	69.65	2183132	14.865
		14686257	100.000

5. Literature

5. Literature

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6. Curriculum Vitae

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B.Sc. *Chemistry* 2006-2009	**Nicolaus Copernicus University, Toruń, Poland** ***Topic: Synthesis of Optically Active Selenides*** Supervisor: Dr. Jacek Ścianowski

Publications

- **Highly Regioselective Synthesis of Chiral Diamines *via* a Buchwald-Hartwig Amination from Camphoric Acid and their Application in the Henry Reaction**
  M. Uzarewicz-Baig, M. Koppenwallner, S. Tabassum and R. Wilhelm
  Appl. Organomet. Chem. 2014, 28, 552-558.

- **Synthesis of New Camphor-Based Carbene Ligands and Their Application in a Copper Catalysed Michael Addition with B_2Pin_2**
  M. Koppenwallner, E. Rais, M. Uzarewicz-Baig, S. Tabassum, M. A. Gilani and R. Wilhelm
  Synthesis 2015, DOI: 10.1055/s-0034-1379877.

- *M. Uzarewicz-Baig, R. Wilhelm*
  Eur. J. Org. Chem. 2015, manuscript in preparation.

- **Terpene Selenides- Synthesis and Applications in Asymmetric Epoxidation**
  A. Banach, J. Ścianowski, M. Uzarewicz-Baig, A. Wojtczak
  2015, manuscript in preparation.

Symposia Attended

➢ Posters

- **Synthesis and Application of New HASPO Ligands Based on Camphoric Acid**
  M. Uzarewicz-Baig and R. Wilhelm
  20th International Conference on Phosphorus Chemistry, Dublin, Ireland June/July 28-02, 2014.
- **Synthesis of Chiral Diamines Based on Camphor *via* a Buchwald-Hartwig Amination and their application as ligands in the Henry Reaction**
  M. Uzarewicz-Baig and R. Wilhelm
  5th Münster Symposium on Cooperative Effects in Chemistry, Münster, Germany, May 9th, 2014.
- **Novel Amine Ligands Derived from Camphor for the Asymmetric Henry Reaction**
  M. Uzarewicz and R. Wilhelm
  XIV European Symposium on Organic Reactivity, Prague, Czech Republic, September 1-6, 2013.
- **Syntheses and Reactions of Optically Active Selenides and Tellurides from the *p*-Menthane Group**

  J. Ścianowski, Z. Rafiński, A. Banach, M. Uzarewicz

  54th PTChem and SITPChem Meeting, Poland, Lublin, September 18-22, 2011.
- **Syntheses and Reactions of Optically Active Selenides Derivatives Terpenes**
  A. Banach, J. Ścianowski, M. Uzarewicz, Z. Rafiński
  5th Copernican Doctoral Seminar, Poland Thorn, June 16-18, 2011.
- **Syntheses and Reactions of Optically Active Selenides of Derivatives Terpenes**
  J. Ścianowski, Z. Rafiński, A. Banach, M. Uzarewicz
  9th National Symposium on Organic Chemistry, Poland, Warsaw, April 6-9, 2011.

➢ Oral presentations

- **Novel Diamine Ligands Derived from Camphor for Asymmetric Catalysis**
  M. Uzarewicz and R. Wilhem
  11th YoungChem 2013 International Congress of Young Chemists, Poznań, Poland, October 09-13, 2013.

Technical Skills

Gas Chromatography (GC), Liquid Chromatography (HPLC, TLC, GPC), Atomic Absorption Spectrophotometry (AAS), Multi-nuclear NMR spectroscopy, FT-IR spectroscopy, Mass spectrometry, Sampling and Preparation of Samples: Distillation, Digestion, Extraction (LLE, SPE, SFE), Filtration, Membrane Processes, Air-Free Technique: Schlenk Line.