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„Evaluation of Synthetic Concepts to Access Chiral Bisheteroaryls“

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Christina MARK

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The most exciting phrase to hear in science,
the one that heralds new discoveries,
is not 'Eureka!' (I found it!) but
'That's funny ...'

(Isaac Asimov)

Acknowledgement

To Michael Widhalm, my supervisor, who gave me the chance to work on this interesting topic and who offered always a helping hand. Thanks for all the support, discussions, critics and encouragement during my work, it made me learning a lot.

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Thanks!

I Content

1. Introduction

1.1. Chirality

The shape of objects can be described through their symmetry properties expressed by the presence or absence of symmetry elements like mirror planes (σ), inversion centers (i), rotational axes (C_n) and rotational-reflexion axes (S_n). Applying any of these symmetry operations to an object will transform it into a position undistinguishable from the original one. The higher the number of such possible transformations, the higher the symmetry. Objects where none of those elements or only rotational axes are present are called chiral[i]. Thus, these objects and their mirror image cannot be longer superposed onto each other.[1]

The same consideration will be valid on a molecular level, where chiral molecules are existing in two forms with identical physical properties, but they behave as (non-superposable) image and mirror image. Such pairs of molecules are then called enantiomers (figure 1), the only difference they show are their 'chiroptical properties'. The best known is their different optical rotation, this means that they are rotating the plane of linearly polarized light about the same number of degree as light travels through them, but in different direction. If it rotates the light clockwise, the enantiomer is given the prefix (+), its mirror image with counter-clockwise rotation the prefix (-) respectively. When enantiomers are present in equal amounts, the mixture is termed 'racemic'. A racemic mixture is optically inactive and differs usually from enantiopure compounds by physical properties.

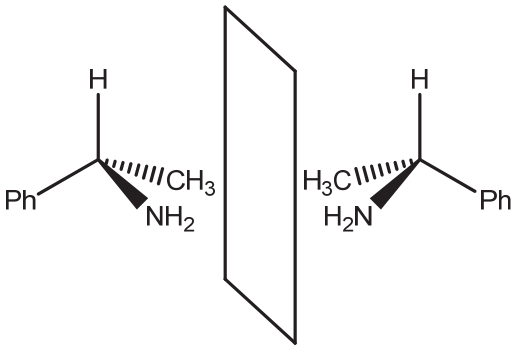


Figure 1 Two enantiomers and their mirror plane

[i] The word 'chiral' originates from the greek word *cheir* (χειρ), which means hand. Chirality therefore refers to the handedness of objects, like right and left hand which cannot be superposed onto each other.

1.1.1. Relevance of Chiral Compounds

As a consequence of the high complexity of biomolecules chirality is omnipresent. Not only macromolecules but also smaller building blocks like carbohydrates and amino acids are chiral. Thus their reactivity and conformation is controlled by chiral recognition. All 21 proteinogenic amino acids despite glycine are chiral and typically present in nature only as single enantiomers. Proteins, consisting of these amino acids, are therefore also single enantiomers with defined shape through inter- and intramolecular interaction.

Besides, the same holds true for carbohydrates and also for the plenitude of smaller biomolecules like hormones, neurotransmitters, flavors and pheromones, chemical factors initiating and controlling social and biological responses in many species (figure 2).

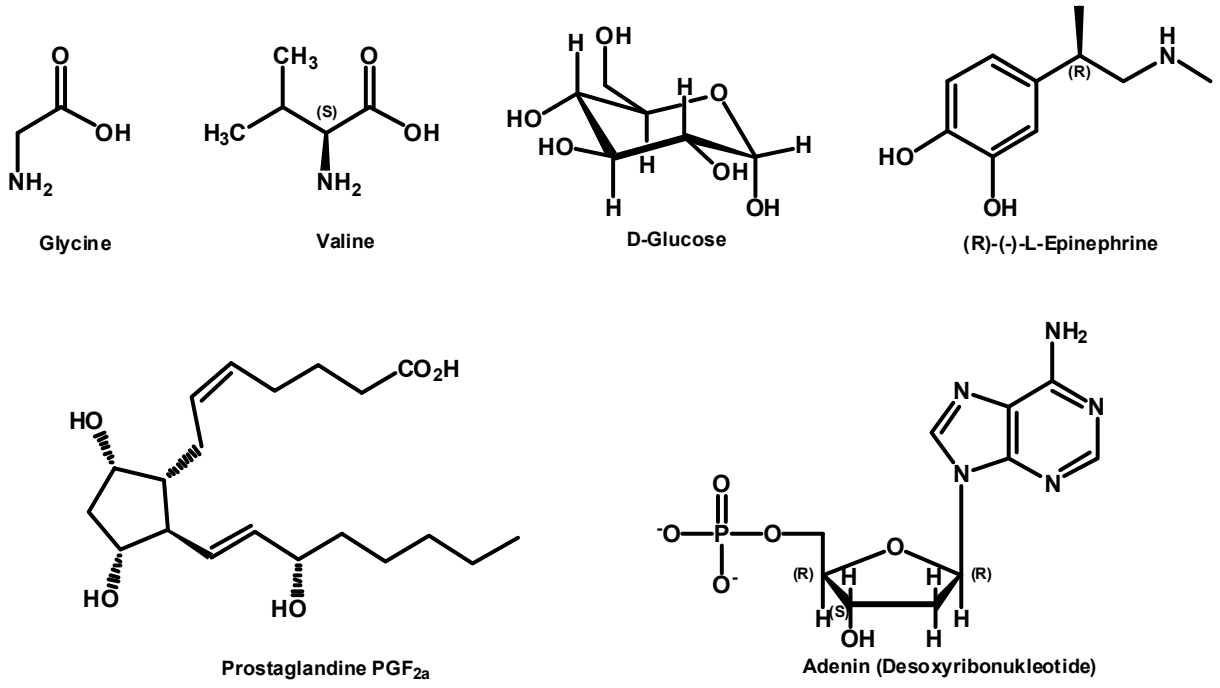


Figure 2 Naturally occurring chiral products and Glycine

Another essential feature of enantiomeric species is their different response (reactivity) to the two enantiomers of another chiral molecule. This enantioselective interaction results in exceptional stereocontrol during biosynthesis and biological processes, particularly obvious in the different interaction with receptors. One well known example is the smell of limonene. Due to the chirality of our nasal receptors, we are able to distinguish between the two enantiomers by smell; the one is lemon the other orange.

But also in the pharmaceutical industry the chirality of drugs became more and more important. After the tragedy caused by Thalidomide[2] in the 1950's, scientists recognized the importance of chirality. The sedative drug was used as a racemic mixture to cure sleeping disorders and was also given to pregnant women. Unfortunately one enantiomer of the drug turned out to be teratogenic. Thus it led to deformities and malformations. Many affected newborns died within their first year of life. Upon this catastrophe the way was clear for enantiomerically pure drugs.

While the synthesis of racemic compounds is usually easier and cheaper, the access to enantiopure products is often complex. Therefore several sophisticated strategies for the synthesis of non-racemic compounds have been developed.

1.1.2. Synthesis of Enantiopure Compounds from Natural Products

There are three basic strategies to access chiral molecules. The first and cheapest one is the transformation of naturally occurring enantiopure compounds. Since many precursors like amino acids or carbohydrates are available in large quantities from the chiral pool, these are straightforwardly usable as enantiomerically pure starting materials or building blocks. Therefore there are two main synthetic ways. The first is that the natural product itself is modified. The second possibility is to use an enantiopure compound as a synthon to build a completely different compound. It is also used that before tagging the chiral part, the natural products are altered in side chains or substituents. One well known example is the use of proline[3,4] and proline-derivatives as chiral precursors. The emerging molecules are often applied as chiral catalysts (figure 3).

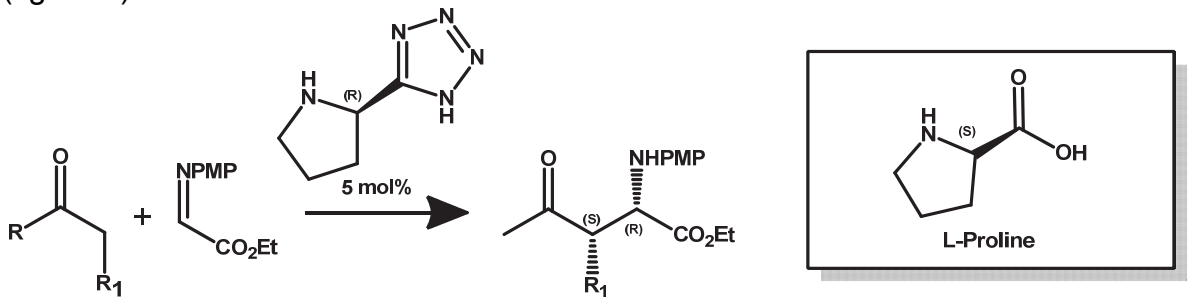


Figure 3 The amino acid proline and one example for an asymmetric aldol type reaction with a proline-derived-organocatalyst[4]

However, the drawbacks of this method are e.g. that nature usually provides only one enantiomer of a molecule. Furthermore, the chiral pool offers only a limited number of chiral structures, useful as starting materials for organic synthesis.

1.1.3. Optical Resolution

Another possibility to get enantiopure compounds is to synthesize racemic products and subsequently carry out an optical resolution. While the synthesis of racemates is often comparably easy and quick, much empirical work is needed to separate the enantiomers efficiently. This is especially challenging for industrial use, where it has to be performed in kilo-gram scales.

In this method, the enantiomers are converted into diastereomers by reaction with an enantiomerically pure auxiliary. The resulting diastereomers may be covalent or ionic species or even clathrates. They differ by their physical properties (solubility, melting point, ...) and are typically separated by chromatography or fractional crystallization. In figure 4 an optical resolution process is outlined.

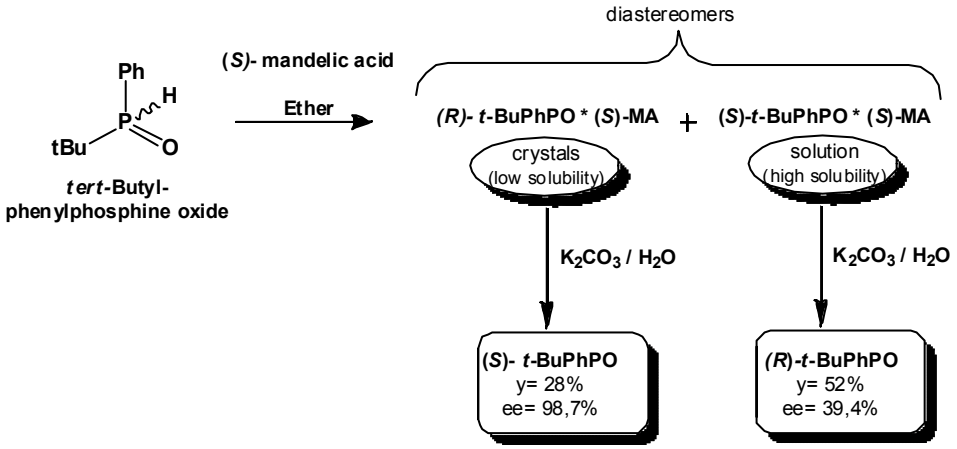


Figure 4 An exemplarily resolution of *tert*-butylphenylphosphine oxide with (*S*)- mandelic acid[5]

Obvious disadvantages of this method are the need of an equimolar amount of the enantiopure compound, which has to be recycled, and a maximum yield of 50% of the desired enantiomer. Furthermore, to obtain the desired molecule, the auxiliary has to be cleaved and separated after resolution. This causes definitely some yield loss.

More attractive are chromatographic resolution processes of racemic mixtures using chiral phases.[6] In favorite cases is separation possible by spontaneous crystallization of one enantiomer from an oversaturated solution after adding a seeding crystal.[7]

1.1.4. Asymmetric Synthesis

The third strategy to get enantiopure (or enantioenriched) compounds is the asymmetric synthesis. In the last decades this method has become one of the most powerful and

straightforward techniques to produce non-racemic molecules from achiral starting materials.

During the generation of a new chiral center in the target molecule its configuration will be controlled by any interacting chiral, non-racemic entity. This may be either a chiral reagent, a chiral auxiliary or a chiral catalyst. In rare examples also the use of a chiral solvent may cause some degree of asymmetric induction. In all cases, it is the aim to traverse diastereomorphous transition states of highly different energy to produce selectively or even exclusively only one enantiomer of the desired product.

According to the role of the auxiliary, asymmetric synthesis may be divided into three sections.

- The *auxiliary-controlled method* is based on a homo-chiral moiety, temporarily covalently linked to a prochiral group. Once the diastereomerically controlled reaction has been performed, the auxiliary is cleaved leaving eventually an enantiopure product. Suitable auxiliaries can be often derived from the chiral pool, early reports dating back to E.J.Corey (1978, 8-phenylmenthol) and B.M. Trost (1980, mandelic acid). Examples are given in figure 5.

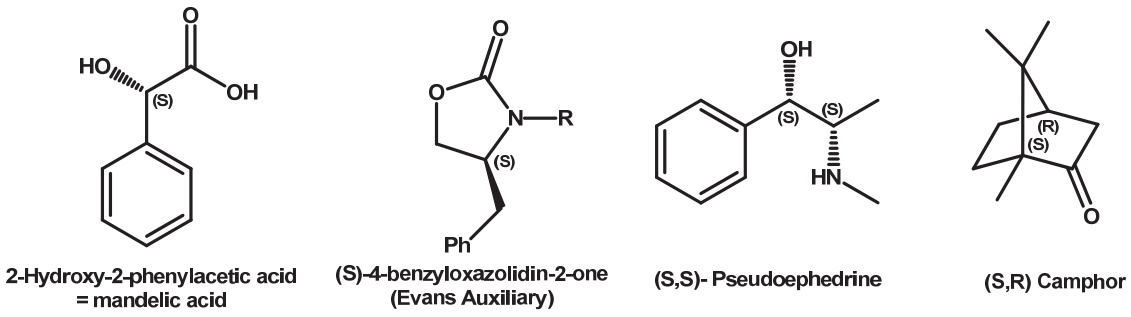
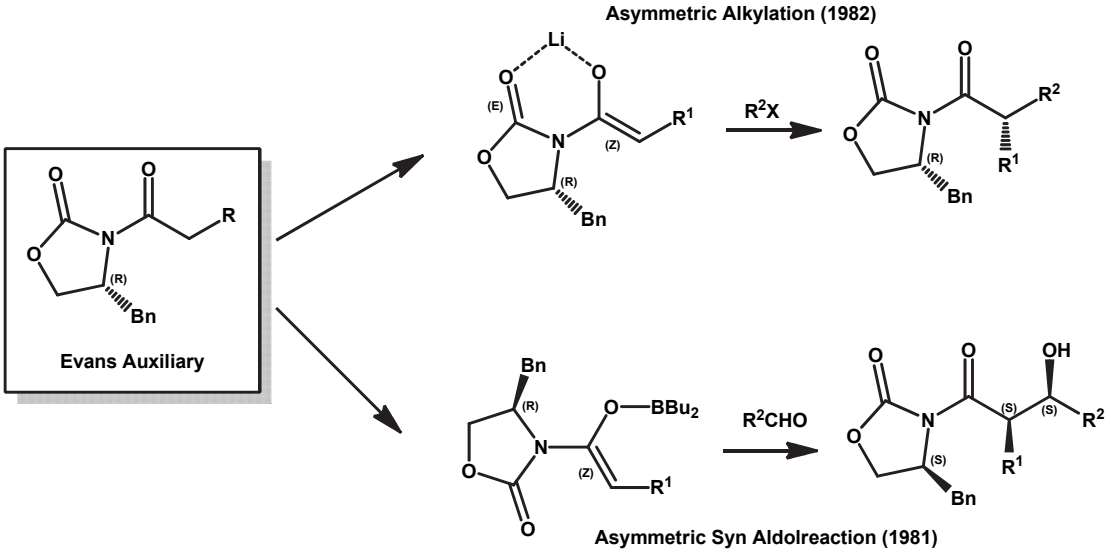


Figure 5 Common chiral auxiliaries

Over the last two decades, the use of *N*-acyloxazolidinone-auxiliaries became increasingly important for a large number of reactions. The most famous example is the Evans Auxiliary, first published in 1981.[8] The key steps of the Evans asymmetric alkylation and Evans asymmetric *syn*-aldol reaction are shown in scheme 1.



Scheme 1 The asymmetric induction from the chiral Evans Auxiliary

Negative aspects of this approach (in addition to those mentioned above) are the need of two extra steps within the synthesis – the addition *and* cleavage of the auxiliary. Although the selectivity is often high, these processes are time-consuming and suffer sometimes from moderate yields.

- The second approach is the *reagent-controlled asymmetric synthesis*. Herein the chiral information is transferred from an enantiopure reagent. The reagent must be selective in terms of functional group specificity and enantioselectivity.
  Some well-known examples are Brown's or Roush's allylations/crotylations, or α-hydroxylation of ketones via Davis' oxaziridine[9]. Examples for these chiral reagents are given in figure 6.
  Using this strategy only a single step is needed, a significant advantage compared to the first approach. On the other side, the preparation of chiral reagents is expensive, especially on industrial scales. To recover the valuable auxiliary recycling processes have to be established for large scale application, but can usually be omitted in research laboratories.

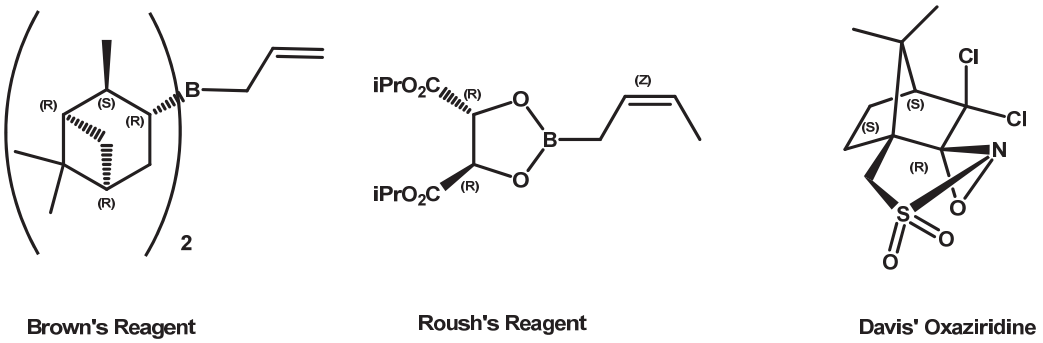


Figure 6 Common chiral reagents

- The third and highly popular method is the *asymmetric catalysis*. A catalyst is a substance that accelerates the reaction without affecting the equilibrium, which means without changing the overall standard Gibbs energy differences in the reaction. Catalysis can be classified as *homogeneous catalysis*, in which only one phase is involved or *heterogeneous catalysis*, in which the reaction occurs on the surface between phases.[10] Since catalysts are running through the catalytic cycle, they are typically present in a reaction in far smaller amount compared to the reactants and chiral information present in tiny amounts is multiplied in the chirality of the products.

  Features and various types of asymmetric catalysis are described in detail in the chapter 1.2.

1.2. Asymmetric Catalysis - Ligand Tuning

In principle, the asymmetric catalysis can be divided into three main fields:

- Enzymatic catalysis
- Organocatalysis
- Transition-metal-catalysis

In *enzyme-catalyzed asymmetric transformations*, the chirality is induced into the substrate by the complex three-dimensional architecture of enzymes. They are usually very specific to certain substrates and to the reactions they catalyze. Responsible for this specificity are complementary charge, shape and hydrophobic/hydrophilic characters of the enzymes and substrates, respectively. This specificity has been described by the Nobel laureate Emil Fisher (in 1894); he suggested the “Lock and Key”

model, where enzyme and substrate are possessing specific complementary (geometric) shape, fitting exactly and exclusively to each other.[11]
However, this early model can only explain the specificity, but fails to elucidate possible transition states and their relative stability.

Therefore the improved model of “induced fit” was developed in 1958. D. Koshland proposed that the area surrounding the active site (catalytic center) is constantly reshaped through hydrophilic/hydrophobic inter- and intramolecular interactions until the substrate-enzyme-complex has reached the final shape and charge distribution. It’s also possible that the conformation of the substrate itself is slightly altered while binding to the enzyme. Induced fit may enhance the fidelity of molecular recognition in the presence of competition and noise via the ‘conformational proofreading mechanism’.[12,13] Enzymes can be used directly or immobilized on polymers, and are frequently used in industrial processes, where extremely high selectivity is needed.

The second area of asymmetric catalysis is the *Organocatalysis*. The reaction rate is hereby increased by an organic catalyst (=organocatalyst), a small organic molecule, thus no metal atoms are involved.[14] The first demonstration of organocatalysis dates back to 1971.[15] They typically proceed under Lewis or Brønsted acid or base catalysis, where enamine and iminium salts are common intermediates. Often proline derivatives are used as catalysts, especially well-suited for Michael or aldol-type reactions. An example thereof is outlined in figure 7.

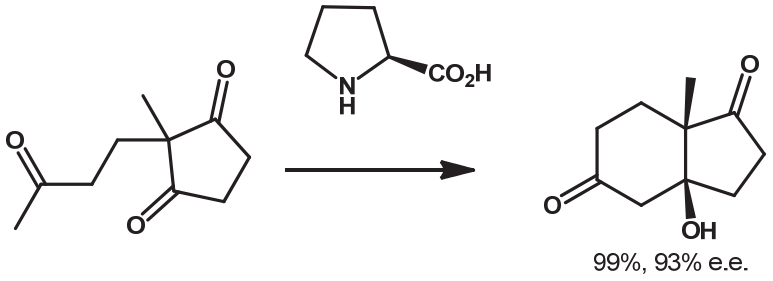


Figure 7 Hajos–Parrish–Eder–Sauer–Wiechert reaction: a proline catalyzed aldol reaction to obtain steroid-precursors[16]

The advantages of this type of catalysis compared to metal-catalyzed reactions are the lower costs (no expensive metal-precursors are needed), the easier purification-procedures and often the tolerance of air and water.

The third type are *transition-metal-catalyzed asymmetric transformations*, based on enantiopure transition-metal complexes, usually generated through chelation of a transition metal at low oxidation state with a chiral ligand. Requirements to be fulfilled by the chiral complex are kinetic stability, sufficient reactivity and chemoselectivity. Many successful examples have been reported and in favorite cases complete stereocontrol at a catalyst load of below 0.01% has been achieved. These low concentrations sufficient for catalysis are making them particularly attractive for industrial application, especially since many transition metals (and complexes) are expensive and highly toxic; a serious problem when it comes to preparation of pharmaceuticals where metal residues must be kept below ppm.

Historically, the development of the first catalysis was in the year 1834, where Michael Faraday cleared the way for novel reactions.

But it took more than 130 years to combine the ideas of asymmetric induction and transition metal catalyzed reactions. The breakthrough was reached by W. Knowles in 1968 when he replaced the achiral triphenylphosphine ligands in a Rh(I)complex (Wilkinson catalyst) by chiral phosphine ligands as shown in figure 8.[17]

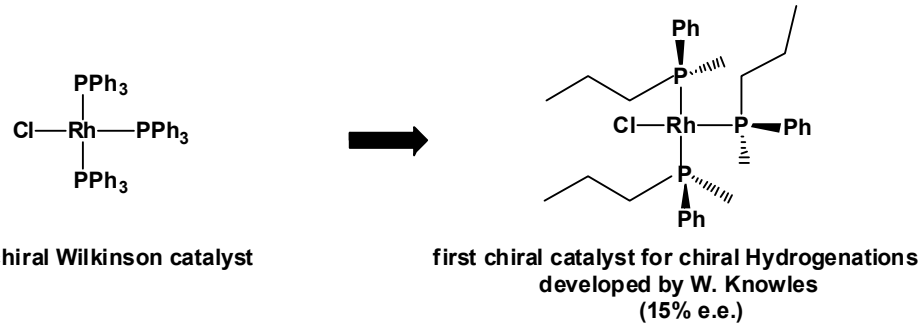
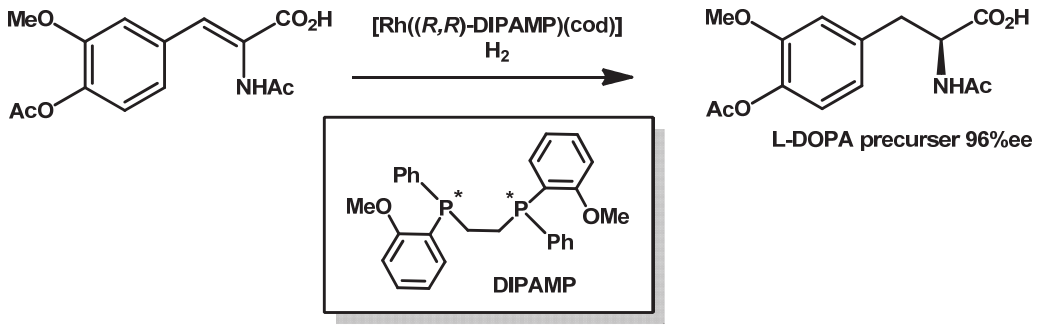


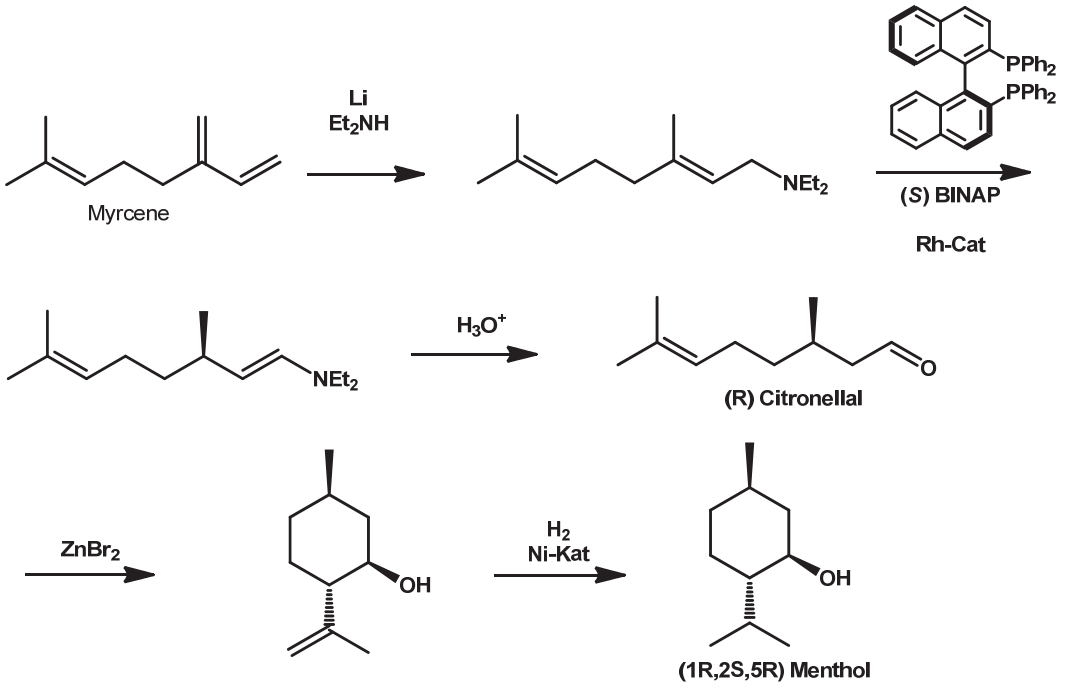
Figure 8 The first chiral catalyst emerging from the Wilkinson Catalyst

With the development of further chiral catalysts, the group around W. Knowles (Monsanto) presented the first effective asymmetric hydrogenation process leading to L-DOPA, a drug to cure Parkinson's disease (scheme 2).[18]



Scheme 2 The asymmetric hydrogenation as a key step in the L-DOPA synthesis

Independently R. Nojori designed in the same period Rh and Ru based catalysts. He discovered the family of the versatile 2,2'-bis(diarylphosphino)-1,1'-binaphthyl (BINAP)-ligands.[19] Complexes of these ligands are particularly useful for the hydrogenation of various olefins and ketones or isomerization reactions. A highlight is the enantioselective isomerization of (*E*)-*N,N*-diethyl-3,7-dimethylocta-2,6-dien-1-amine as outlined in scheme 3. Based on this step, an industrial process for the synthesis of (*1R, 2S, 5R*)-menthol from myrcene has been established (Takasago, capacity 3000t/a).



Scheme 3 The industrial synthesis of Menthol.

The chiral key step is the isomerization, using $[Rh\text{-}(S)\text{-}BINAP(cod)]^{+}X^{-}$

1.2.1. Origin of Enantioselectivity and Choice of Proper Ligands

The observed asymmetric induction originates from stereocontrol by a chiral ligand in the configuration determining step. A catalytic cycle is schematically drawn in figure 9. Only small amounts of a highly effective chiral catalyst is needed to produce a chiral compound AB in large amounts out of an achiral and a prochiral moiety A and B.[18]

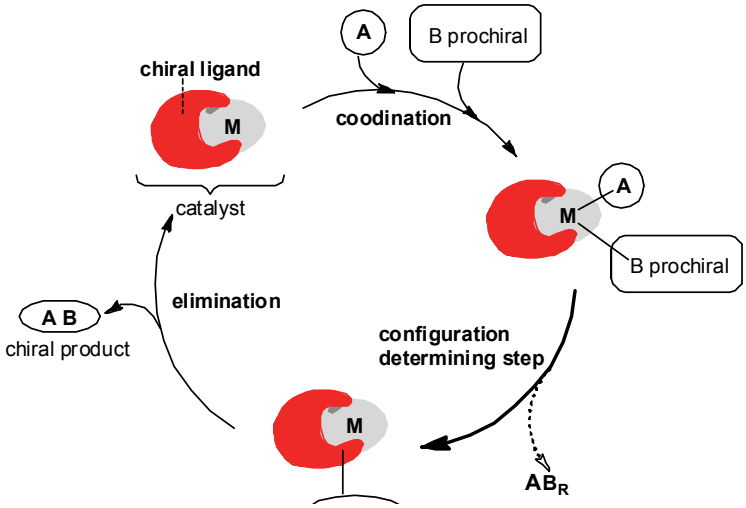


Figure 9 The schematical principle of asymmetric catalysis with a chiral catalyst. M= metal; A = reactant; B=prochiral substrate[20]

In addition to high levels of stereocontrol and chemoselectivity an ideal catalytic system will display high turnover numbers (high stability) and turnover frequencies (reactivity). To ensure solubility in the reaction medium, the molecular weight should not exceed 1000 dalton. Due to the broad range of metal centers and almost limitless structural variation of the organic ligands, the prospects of organometallic catalysis are endless.

While general steps operating in a catalytic cycle are usually well defined, including the configuration determining step, the details of geometry and consequences on the outcome of reactions are less well understood. Common interpretations of observed enantioselectivities are based on the assumption of different energy content and different reactivities of diastereomeric intermediates. Often simply two diastereomeric substrate complexes arising from different coordination modes are postulated as unequivocal precursors of either R- or S-configurated products. Distinct differences in their reactivity should be responsible for the enantiomeric access. Although this model could reasonably explain experimental results in many cases, it is an oversimplification since it will not taking into account a conformative mobility of catalysts. A more realistic

picture should therefore consider the coexistence of various conformations of the species involved. As a consequence a manifold of catalytic cycles will run in parallel and not only two but groups of diastereomeric intermediates differing in concentration and reactivity will contribute to either predominance of R- or S-configured products. This merging process typically tends to blur structural and energetic differences and results in erosion of enantioselectivity.

Therefore, beyond high reactivity and chemoselectivity (functional group tolerance), all attempts in catalyst design focus on opening only a single reaction channel to the desired enantiomer.

This is achieved by (a) using conformationally stable ligands (best bidentate) to yield (b) stable chelates and (c) use two-fold coordinating substrates. Moreover, working with C_2-symmetrical bidentate ligands will reduce the number of possible substrate complexation modes by a factor two. An example for a chelate complex from a C_2-symmetric bidentate ligand is given in figure 10.

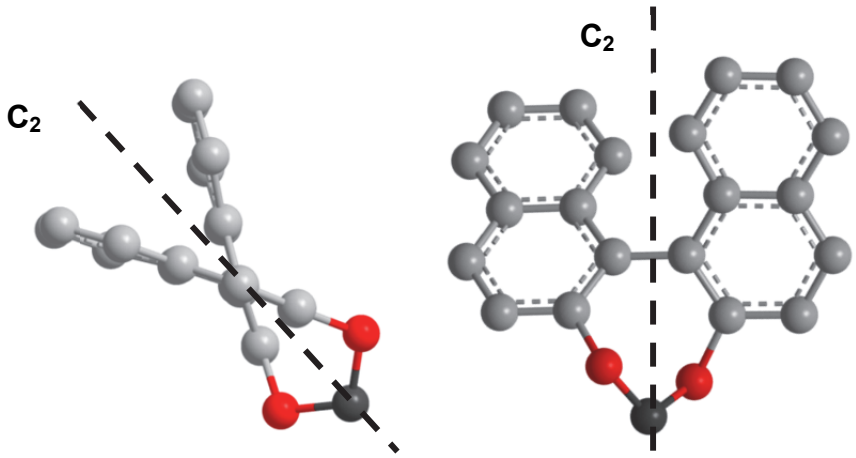


Figure 10 A 3D model showing the Metal - BINAM bonding with formation of a 7-membered ring

On the other hand, if the rigidity of a ligand is too high no stable chelate can be formed or the coordination of the substrate might be hampered. As a consequence the reaction will become slow and side reactions will spiral out of control. The metals used in these organometallic complexes are typically transition metals. These tend to form easily complexes of variable geometry depending on electronic and steric properties of the ligand and oxidation state.

Also for this reason some conformational freedom is needed to accommodate geometric changes during the catalytic cycle. Finally, as a general rule, catalysts existing in only one predominating conformation will be a good choice while strictly rigid complexes will give poor catalysts.

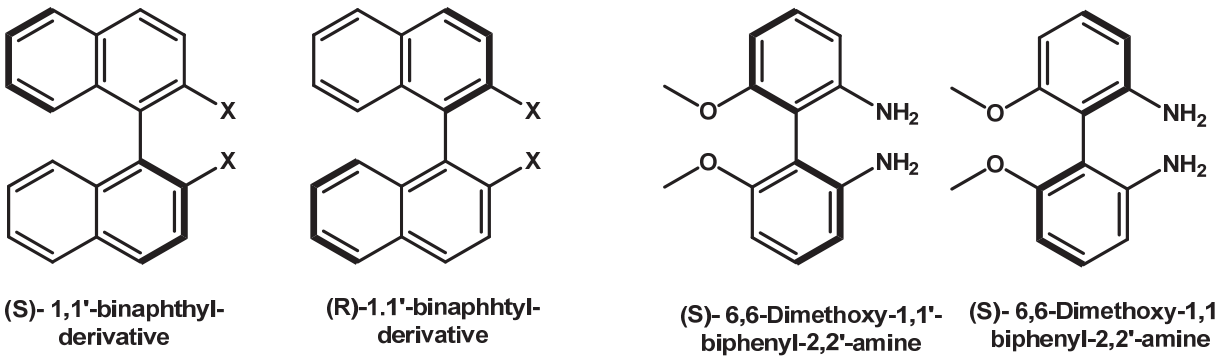
As a consequence of the frequently observed high substrate specificity, so-called “tailor-made” catalysts became more and more favored, when ligands were designed according to structure requirements of the substrate of interest.

1.3. 2,2’-substituted 1,1’-Binaphthyls – Functional and Flexible Ligands

A very important class of chiral ligands is found in atropisomeric biaryls, particularly 1,1’-binaphthyl-derivatives. In the previous chapters some examples for the application in asymmetric catalysis have been already shown.

1.3.1. About 1,1’-Binaphthyls

Many biaryl compounds display atropisomerism, such as 1,1’-binaphthyls. When the hindrance to rotate around the 1,1’-axis is sufficient, these compounds can be resolved into enantiomers. This form of chirality is called ‘axial chirality’. In figure 11 the two rotamers of 1,1’-binaphtyls and respectively of 1,1’-biphenyl-derivatives are shown.



(S)- 1,1'-binaphthyl-derivative | (R)-1.1'-binaphhtyl-derivative | (S)- 6,6-Dimethoxy-1,1'-biphenyl-2,2'-amine | (S)- 6,6-Dimethoxy-1,1'-biphenyl-2,2'-amine

Figure 11 The enantiomers of two versatile biaryl-compounds. The assignment of descriptors R and S is dependent on the priority of substituents X. (X ≠ H, alkyl)

As illustrated in figure 11, the absolute stereochemistry of the unsubstituted biaryls is only dependent on the relative orientation of the aryl moieties in the space. Potential racemization of unsubstituted 1,1'-binaphthyls arises by rotation around the 1,1'-axis. The rotational barrier is 23.5 kcal/mol with a racemization half-life of 14.5 minutes at 50 °C (figure 12).[21]

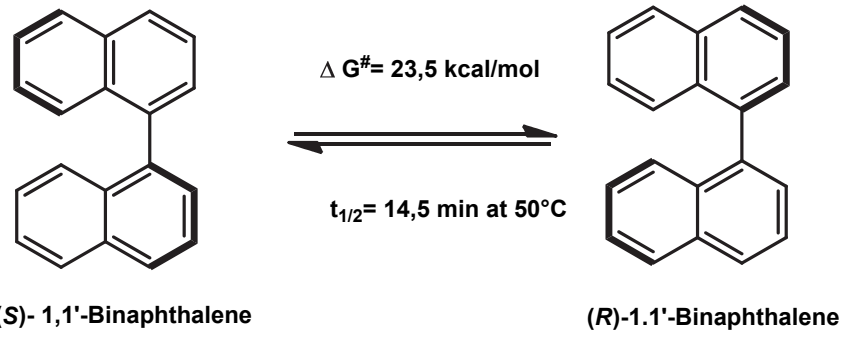
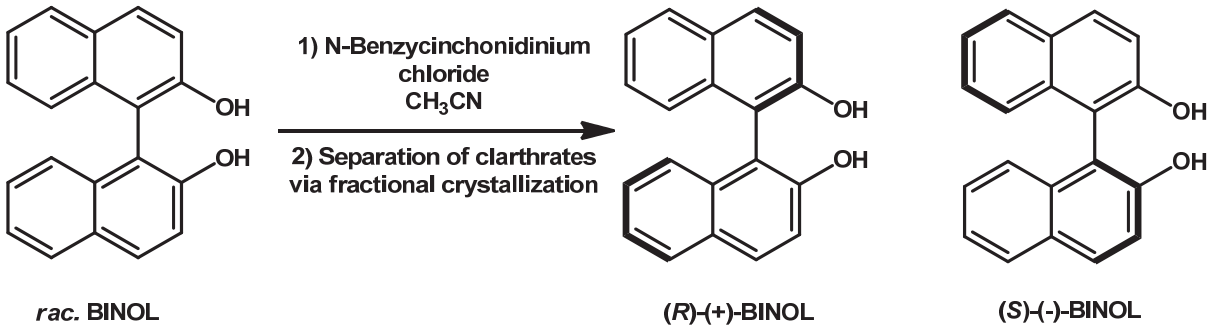


Figure 12 The racemization of 1,1'-binaphthalene

Since 2,2'-substituted 1,1'-binaphthyls are very stable compounds, these can hardly be racemized. One example is (*S*)-1,1'-binaphthyl-2,2'-dicarboxylic acid, which doesn't show any racemization even at 175°C (DMF). If the substitution pattern is symmetric, the molecules are C_2-symmetric. Consequently the number of involved diastereomeric transition states is reduced to one half. Due to these outstanding properties the 2,2'-substituted binaphthyls are frequently used as stable ligands to transfer chiral information in catalytic processes.

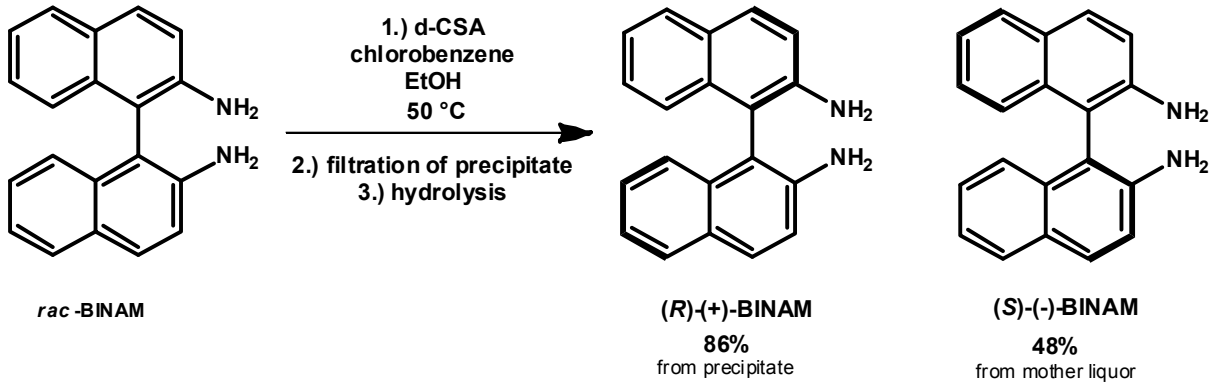
To obtain non-racemic 2,2'-substituted binaphthyls a large variety of methods is available, as summarized by M. Putala in his review.[22] To these belong e.g. enantioselective oxidative coupling of 2-substituted naphthalenes, and kinetic or (conventional) optical resolution of racemic 1,1'-binaphthyls.[23]

The commonly used strategy to obtain non-racemic 1,1'-binaphthyls is certainly optical resolution. As outlined in scheme 4, 1,1'-binaphthalene-2,2'-diol (BINOL) is treated with *N*-benzylcinchonidinium chloride to give diastereomeric clathrates, which differ by their solubility. After separation by fractional crystallization and separate cleavage of the N-benzylcinchonidinium chloride from each fraction, R and S- BINOL are isolated.[24]



Scheme 4 Optical resolution of BINOL

In scheme 5 a typical procedure for the optical resolution of 2,2‘-diamino-1,1‘-binaphthalene (DABN, BINAM) is shown.[25] The resolving agent used is d-camphorsulfonic acid (d-CSA). The resulting diastereomeric salts can be separated by their different solubility. After cleavage of d-CSA optically pure BINAM is obtained.



Scheme 5 Optical resolution of DABN

1.3.2. Synthesis of racemic 2,2’-substituted Binaphthyls

BINOL, BINAM and only a few other non-racemic 2,2’-substituted 1,1’binaphthyls (e.g. di-acid, di-methyl) are used as starting materials. Although exchange of the substituents in the 2 and 2’ position is problematic (risk of racemization), in the other positions it is still possible to introduce substituents.

The electrophilic aromatic substitution is one example thereof, it occurs preferentially in the 6 and 6’ positions of any activated 1,1’-binaphthyl. Hence this behavior can be used to prepare a variety of poly-functionalized chiral catalysts or the products are useful for various technical applications such as nonlinear optics material.[26]

Also substitution in other positions is possible, e.g. twofold orthometallation of N- or O-substituted binaphthyls allows the introduction of substituents in 3,3' position resulting in C_2-symmetric 2,2'3,3'-tetrasubstituted binaphthyl moieties. These substitution patterns are of high interest in chiral catalysis since they can enhance the stereoinduction. The most frequently used substrate for direct ortho-metallations is protected BINOL; possible 3,3' substituents are halides, trimethylsilanes (TMS) or boronic acid.[27] Further exchange of these substituents can be used to obtain a broad range of functionalized binaphthyl-derivatives. One example is the ipso substitution of the TMS groups, leading to halides. Furthermore the aryl boronic acid can easily be oxidized, resulting in hydroxy substituents.[28] Moreover, halides or boronic acids can be used in various cross-coupling reactions to introduce alkyl, alkenyl, allyl, amino or aryl moieties. [29, 30, 31]

1.4. Aim and Scope of the Thesis

The goal of the present work was to investigate synthetic paths to bis(azaheteroaryls) **A** and **B** with C_2 symmetry and enhanced steric interaction close to N-functionalities (outlined in figure 13). These compounds might be well suited as bidentate ligands or organo-catalysts, either efficiently surrounding a (transition) metal substrate complex or forming transient diastereomeric intermediates with reagent or (prochiral) substrate. From such base structure several ligands with tunable steric and electronic properties will be accessible by varying R^1 or ring size. Moreover, the electron density at N may be changed through introduction of substituents R^2, preferably in pos. 6 and 6'. Preliminary experiments provided the fully aromatic compounds **C** and **D** in moderate yield.[31] Problematic seemed the cleavage of the N-PG (mesyl) of **D**, which remained unsuccessful so far. Therefore it was the aim to elucidate suitable N- protective groups, easily to introduce *and* to remove.

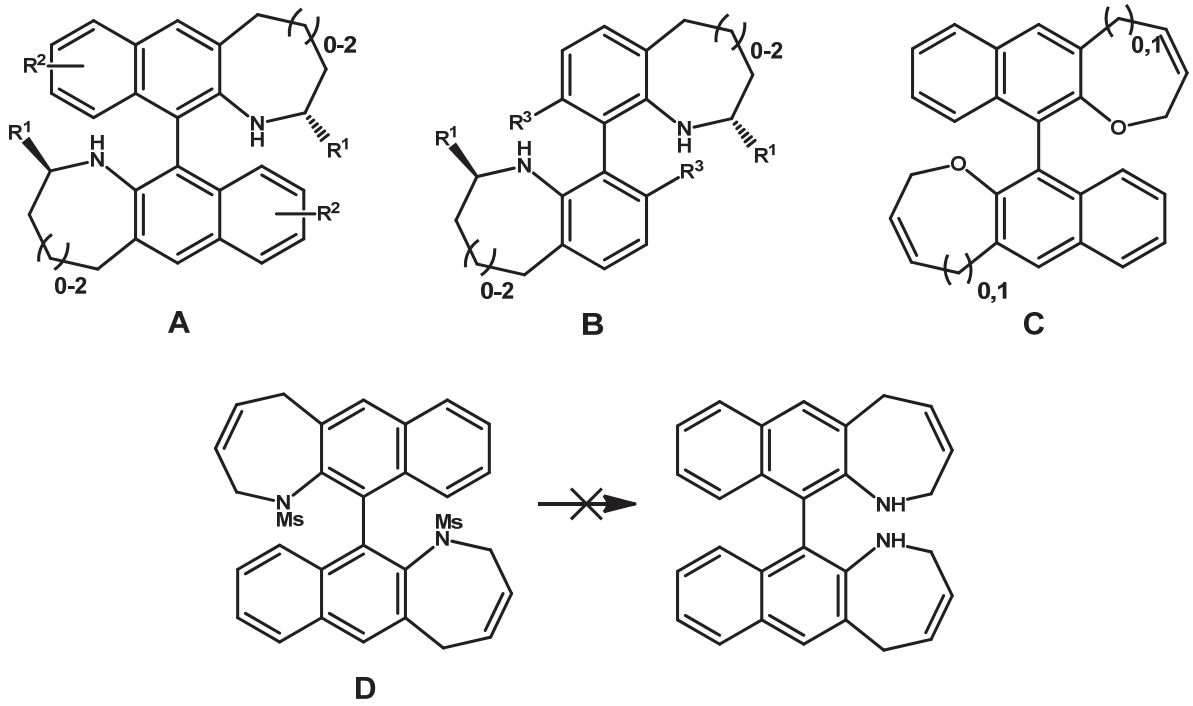


Figure 13 Bisazaheteroaryls with C_2- symmetry as target structures, R^1, R^2 = H, alkyl, phenyl

2. Results and Discussion

In principle two strategies have been considered, (a) elaboration of a naphthalene condensed aza-cycle followed by oxidative homocoupling or (b) starting from a 2,2'-substituted 1,1'-binaphthyl precursor. In the first case success of coupling two o,o'-substituted moieties seemed rather difficult, besides an optical resolution procedure has to be worked out. More promising looked an approach from 2,2'-diamino-1,1'-binaphthyl (BINAM). This starting material was chosen since it can be conveniently prepared as a racemate from 2-naphthol and hydrazine.[32] As mentioned before, subsequent optical resolution with CSA yielded optically pure BINAM on a multi-gram scale. [25]

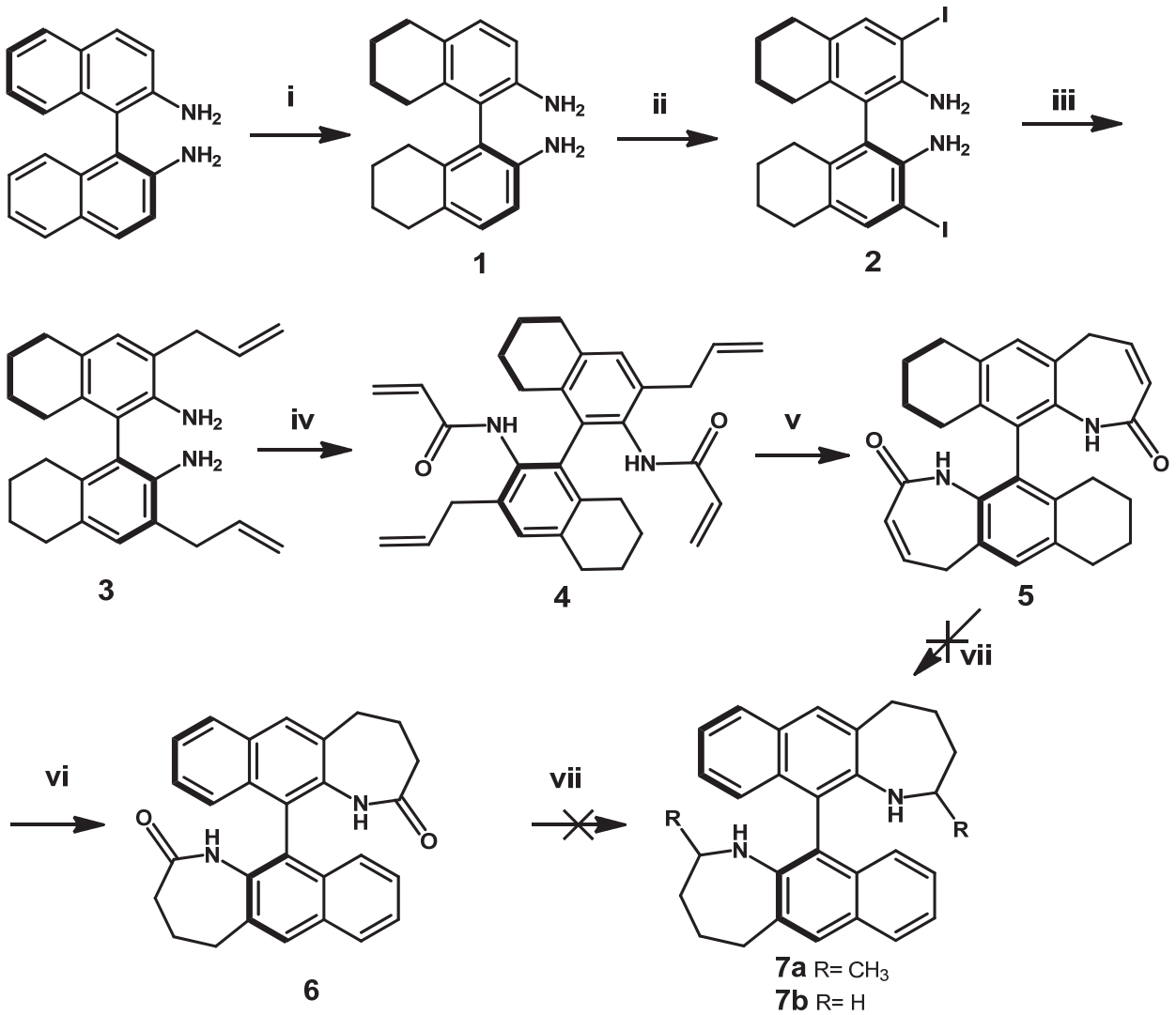
Although it can be expected that N-bound electrophilic entities could be cyclized in the activated position 3 and 3', intermediates with I or Br in 3 and 3' were preferred since analog synthesis worked well yielding **C** and **D** from N,N',C,C'- and O,O',C,C'-tetraallyl precursors, respectively in 25% and 18% overall yield. In both cases RCM reactions with Grubbs I catalysts were used.[33]

It was planned to investigate methods to simultaneously introduce 5-7 membered azacycles by bridging position 2 and 3, as well as 2' and 3'. Already at the start of the investigation it was obvious that main challenges would be (a) the severe steric hindrance in 2 and 2' and (b) the choice of a cyclisation method not requiring N-protection or – if necessary – to use a (non-bulky) protective group (PG) easy to introduce but also to remove at a later stage, and not suppressing the cyclisation step from steric reasons. Moreover (c) R^1 should be introduced diastereoselectively.

The first synthetic attempt to reach a chiral bis(heteroaryl) is shown in scheme 6. The synthesis starts from the commercially available (S)-[1,1'-binaphthalene]-2,2'-diamine (=(S)-BINAM). Many syntheses for heterocycles are starting with (Aza-)Claisen-rearrangements of *N*-allyl aryl amines, either thermic or Lewis acid catalyzed,[34] and subsequent *N*-allylations, followed by ring closing metathesis (RCM).[35] [36]

Since Aza-Claisen-rearrangements could not be performed under mild conditions and ortho-metallation of BINAM didn't lead to the desired 3,3'-substituted binaphthyl, an alternative method had to be found to obtain o-halo-amino aryls, ideal starting units.

These could be reached by iodination of **1** with benzyltrimethylammonium dichloroiodate,[37] followed by Stille coupling.[38] Next, the resulting allyl amine **3** should be protected; therefore at first it was chosen to introduce the PG and the functional allyl moiety necessary for RCM in a single step. This was done by reaction of **3** with acryloyl chloride to give **4**. Subsequent ring closing metathesis was expected to afford the amide protected bisheterocycle **5,** reduction of the amide functionality or Petasis-methenylation followed by reduction should finally yield the target structures **7a** and **7b,** respectively**.**



Scheme 6: **i)** Ra-Nickel, iPrOH, KOH 1% H_2O, 85°C; **ii)** $BnMe_3NICl_2$, $CaCO_3$, DCM, MeOH; **iii)** Allyl tributylstannane, $Pd(PPh_3)_4$, toluene; **iv)** Acryloyl chloride, Sm, ACN; **v)** Grubbs 2°Generation Catalyst, DCM; **vi)** H_2, Pd/C,EtOH, DCM or BH_3*THF; **vii)** Petasis reagent, toluene then reduction

In order to prevent iodination in 6,6'-position, partial hydrogenation of the naphthyl system is required.[39] This was performed using a slightly modified procedure from H. Guo yielding **1** in 77% yield.[40] As already published procedures for re-aromatization of **2** from Kano et al. couldn't be reproduced, it was decided to perform the synthesis with

the partially hydrogenated system. Moreover, it was the aim to find other possible intermediates were re-aromatization would be possible. More detailed information is given in a later section of this chapter (p.35).

Subsequent reaction of the 3,3'-allyl amine **3** with acryloyl chloride using a samarium-mediated protocol gave **4** in 61% yield. The advantages of this method are mild conditions (at RT, in neutral medium), and high yields.[41] The benefits of introducing acryloyl chloride as PG *and* reactive species are not only fewer reaction steps, but also less steric hindrance in the already crowded molecule. Thus a stable secondary diamide is obtained after RCM.

As catalysts for metathesis were explored *Grubbs 1st and 2nd Generation Catalysts* as well as 2,6-diisopropyl-phenylimidoneophyliden-molybdenum(VI)-dimethoxyethan adduct (Schrock type catalyst)[42]. In table 1 the isolated yields and conditions are outlined.

Table 1 RCM Conditions

Catalyst	Grubbs 1st Gen.	Grubbs 2nd Gen.	Schrock-type Cat.
mol %[ii]	10	10	20
reaction time[iii]	36 h	24 h	48 h
temperature	RT or 40°C	RT	RT
isolated yield	51%	quantitative (97%)	n.r.

Best results were reached with *Grubbs 2nd Generation Catalyst* at RT with typical catalyst loads of 10 mol%[ii]. Using *Grubbs 1st Generation Catalyst*, only moderate yields were obtained, whereas performing RCM with the Schrock-type catalyst didn't show any conversion; thus starting material was quantitatively recovered.

A general mechanism for ring closing metathesis is shown in figure 14, early mechanistic insights dating back to Y. Chauvin.[43] The driving force of the reaction is the removal of ethen and/or the release of steric strain. In order to generate a free

[ii] The molar percentage of catalyst used refers to both functionalities in the molecules, thus 10 mol% means 5 mol% for each reacting group.
[iii] The reaction time refers to the time the reaction mixture was stirred after complete addition of the catalyst.

coordination site at the metal-complex, the dissociation of one $P(Cy)_3$ ligand is required. Key-intermediates are the two metallacyclobutanes. [44]

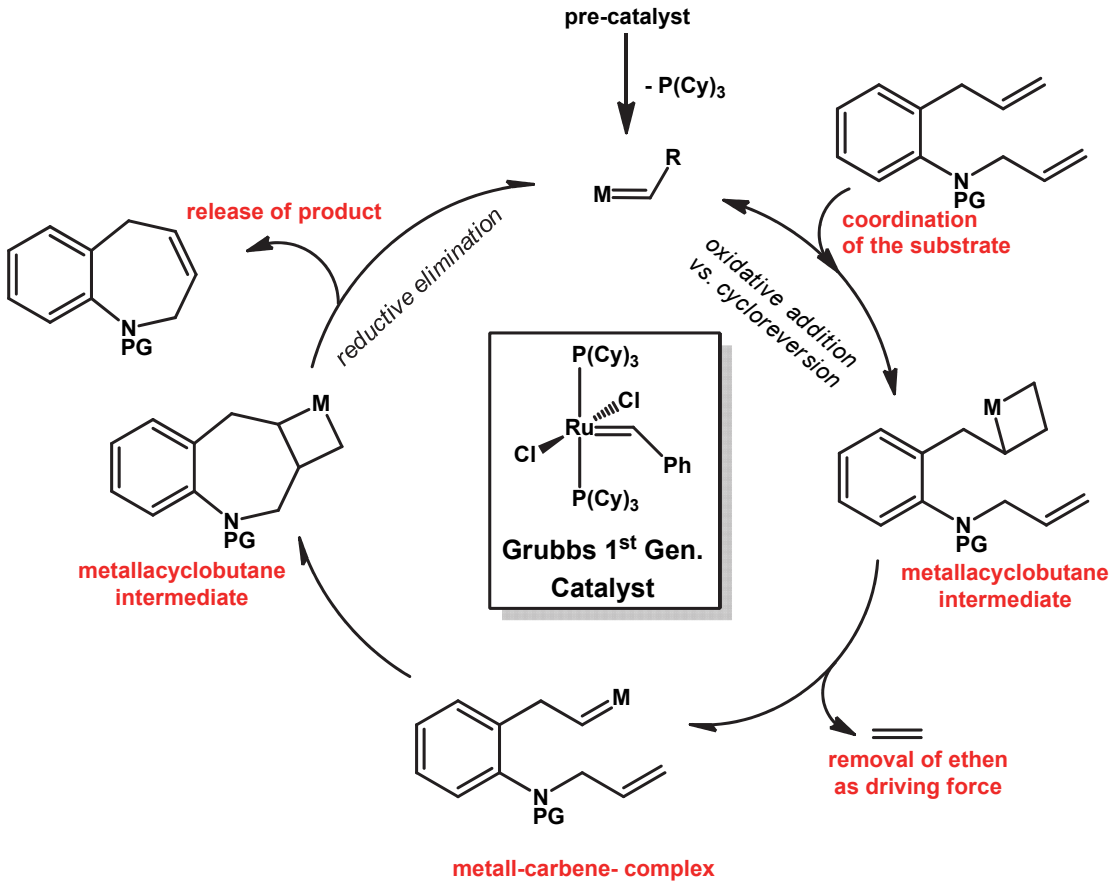


Figure 14 The schematic Chauvin-mechanism of ring closing metathesis; PG= protective group

The three used catalysts differ in activity, stability and expense. E.g. the Schrock type catalysts are usually more active and converting also sterically demanding substrates, while the Grubbs catalysts typically show more functional group tolerance. The 2nd Generation Grubbs Catalyst is more stable and active than the cheaper 1st Generation catalyst.

The resulting secondary amide **5** turned out to be very stable, but not useful as chiral ligand for Michael or aldol reactions, demanding higher basicity. Therefore a strategy for removal of the carbonyl function had to be developed. Since reduction with various reagents (as depicted in table 2) didn't lead to the desired amide, methenylation of the carbonyl function was tried next.

Table 2 Reduction attempts

Reducing agent	LAH	$LAH/AlCl_3$	$LAH/AlCl_3$	BH_3*THF
equivalents	10	4.3/1.43	8.6/2.86	7
reaction time	3 h	3 h	3 h	4 h
temperature	0 °C to RT	0°C	0 °C	0 °C to RT
isolated yield	decomposition	**5**	mixture DB and/or CO reduced	**6** (95%)

Therefore Petasis reagent, dimethyl titanocene, was used, but didn't show any effect, even though elevated temperatures were used and the Petasis reagent prepared freshly.[45] [46] In case that it would have worked, subsequent reduction of the *exo*-methylene group would be required to obtain a reasonable ligand **7a**. This could be performed by hydrogenation with palladium on activated charcoal.

A similar reduction protocol was performed to obtain **6** quantitatively. As shown in table 2 also the reduction with BH_3*THF lead to the saturated lactame **6**, but not to the expected reduction of the CO bond.

Since the strategy above seemed to provide some obstacles difficult to overcome, a new approach had to be developed. Since amides as PG seem to be necessary for RCM, other useful *N*-protective groups forming amides had to be explored.

The next attempt was to synthesize a product without amide functionality within the ring, but with a reasonable '*exo-cyclic*' *N*-protective group. First PG tried to introduce into the allyl amine **3** was the acetyl group. In scheme 7 the synthesis of **11** is outlined; the allyl amine **3** was prepared as shown in scheme 6. The RCM precursor **10** could be obtained in two different ways; either first *N*-allylation with subsequent protection with acetyl chloride or *vice versa*. It turned out that starting with the acetylation step followed by allylation gave slightly better overall yields (yield of two steps: i+iii: 25% vs. ii+iv: 27%). It should be mentioned that the allylation of **3** could be performed with 79% yield, but subsequent protection was incomplete (only 32% yield).

Optimized acetylation of **3** was carried out using a similar protocol as mentioned above for acryloyl chloride, yielding **9** in 65% yield.[39] If standard procedures (acetic anhydride in pyridine at elevated temperatures) were applied, also trifold substitution was observed.[47] Subsequent allylation of **9** was carried out under various conditions (reported in table 3). Best suited was a mixture of allyl bromide and potassium hydroxide in DMSO, where 41 % of **10** were obtained.

Table 3 Allylation of **9** with allyl bromide

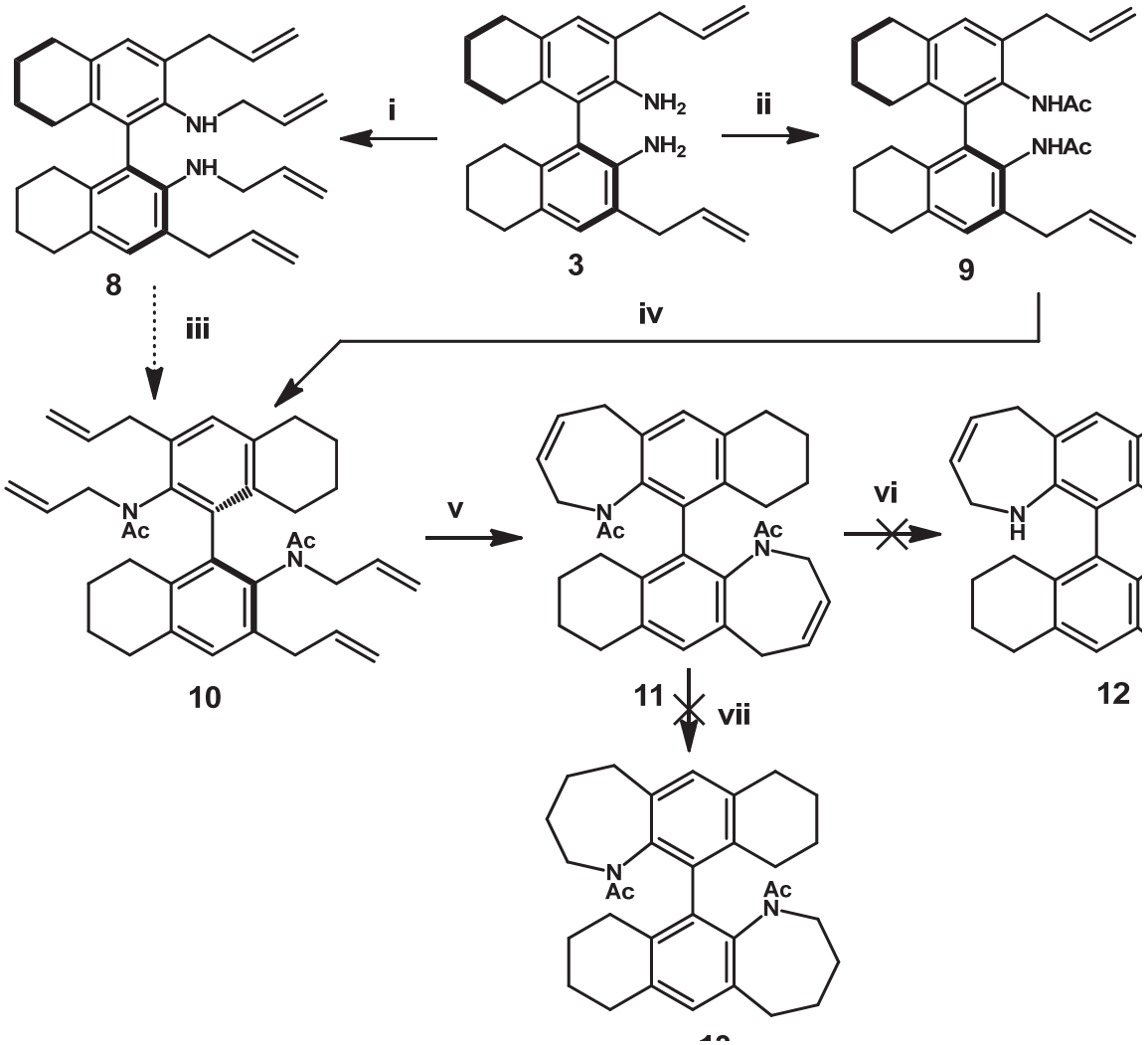
base	K_2CO_3	NEt_3	KOH	KOH	KOH+ TBAB
solvent	ACN	ACN	DMSO	DMSO	DMSO
reaction time	40 h	36 h	24 h	36 h	72 h
temperature	60°C	65°C	RT	RT	RT
isolated yield of **10**	10%	0%[iv]	32%	41%	38 %

RCM of acetyl protected tetra-allyl **10** was performed in dichloromethane at RT using *Grubbs 1st Generation Catalyst* resulting in the tertiary amide **11** in 59 % yield. Moreover, removal of the PG after cyclisation was investigated using standard protocols (table 4), but without success. Also hydrogenation of **11** didn't give the desired product, *viz*. decomposition occurred. To summarize it should be mentioned that both pathways in general are suffering from poor yields due to the high sterically hindrance in the substrate.

Table 4 Attempts of cleavage of acetyl groups of **11**

reducing reagent	$LiEt_3BH$	$LiEt_3BH$	KOH
solvent	THF	THF	$MeOH/H_2O$
conditions	0 °C; 24 h	RT; 24 h	RT; 16 h
yield of **12**	n.r.	n.r	n.r

[iv] Starting material was recovered quantitatively



Scheme 7 Synthesis of a bis(heteroaryl) with an acetyl as PG. i) Allyl bromide, K_2CO_3, ACN; ii) Sm, acetyl chloride, ACN; iii) Sm, acetyl chloride, ACN; iv) Allyl bromide, DMSO, KOH; v) Grubbs 1st Generation Catalyst, DCM, RT; vi) vide table 4; vii) H_2, Pd/C, EtOH/DCM.

Hence other protective groups need to be found, easily to tag on before RCM *and* to remove afterwards. Moreover, these PGs had to be small; so at first transformation of **8** and the *N,N'*-diallyl-precursor into the hydrochlorides **14** and **15** was attempted. Although the hydrochloride was formed, it was not reactive in ring closing metathesis; only starting material was quantitatively recovered after treatment with *Grubbs 1st* or *2nd Generation Catalyst*, respectively.

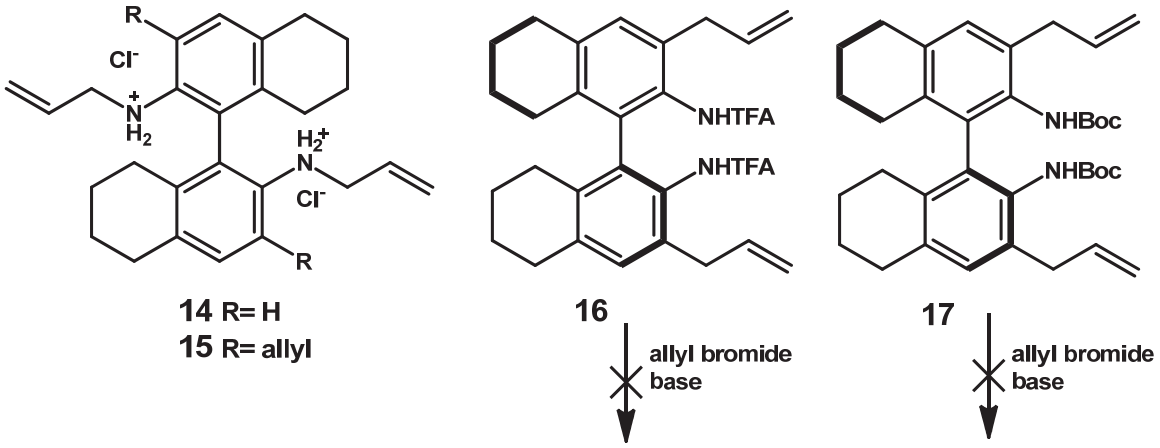


Figure 15 N-protected precursors

The next protective group investigated was trifluoro acetyl (TFA). Due to the easy cleavage, it seemed to be an attractive *N*-PG. The synthesis of TFA-protected allyl amine **16** proceeded quite smoothly from **3**; almost quantitative yield (88%) was reached. Unexpectedly, subsequent allylation only resulted in recovery of starting material.

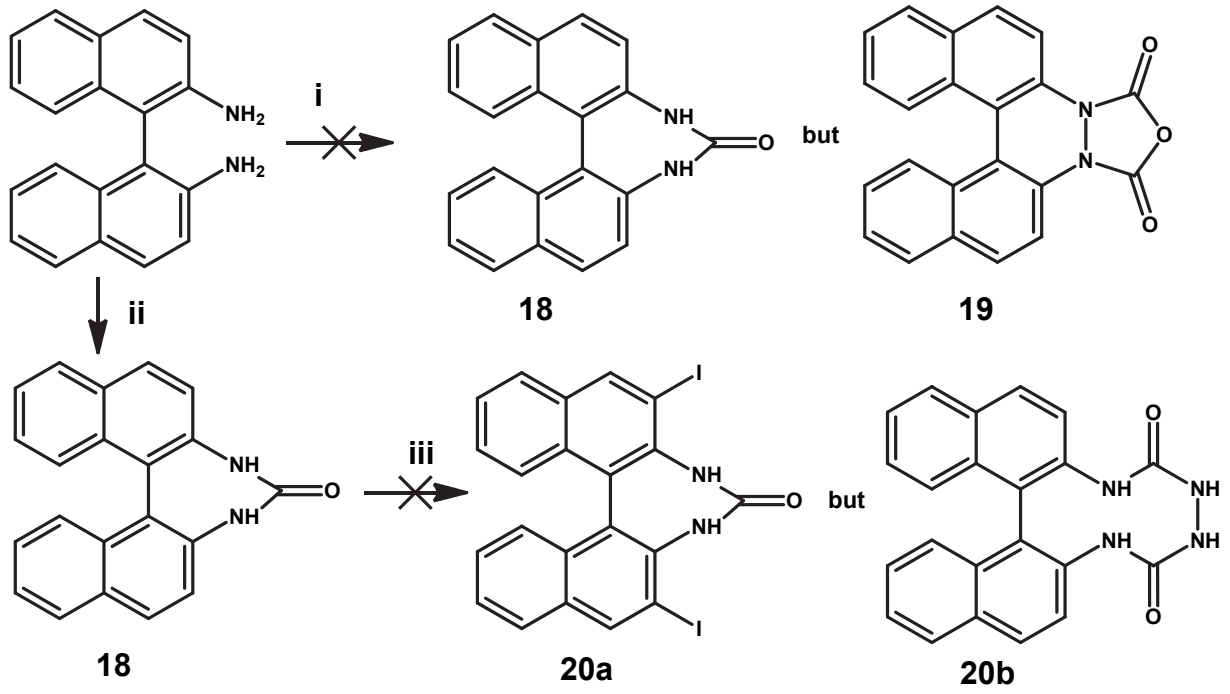
Next it was tried to use the common N-protective group Boc; easily introduced by reaction of **3** with the anhydride Boc_2O in presence of a base, to give **17**.[48] Though this group is tolerant towards most nucleophiles and bases, it is too bulky to allow the allylation of **17**. It seems that the molecule is too sterically crowded to allow any further reaction on the protected nitrogen atoms, only acetyl was 'slim' enough to permit allylation (but in moderate yields).

A further attempt to access a suitable *N*-protected intermediate was the synthesis of urea- derivatives (scheme 3). Reaction of BINAM with diphosgene only showed the formation of **19** in 19% yield instead of the desired product **18**, but altered conditions using urea in acetic acid/ *i*-PrOH led to the *N,N'*-bridged moiety **18**.

Since the urea derivative **18** is fully aromatic, it seemed reasonable to perform direct ortho-lithiation *and* omitting the hydrogenation step with Raney-Ni. As reported in the literature, ortho-lithiation of boc-protected BINAM could be achieved (symmetrically and unsymmetrically).[49]

Nonetheless, using similar conditions as published in ref. [49], namely ortho-lithiation of **18** with *n*-BuLi and TMEDA in diethyl ether at 0 °C and quenching with 1,2-diiodo-ethane, led only to recovery of substrate **18** and small amounts of side product **20b**. As the (fully aromatic) ortho-halo key-intermediate **20a** could not be obtained, this synthetic

path was abandoned and novel strategies for the synthesis of bis(heteroaryls) had to be developed.



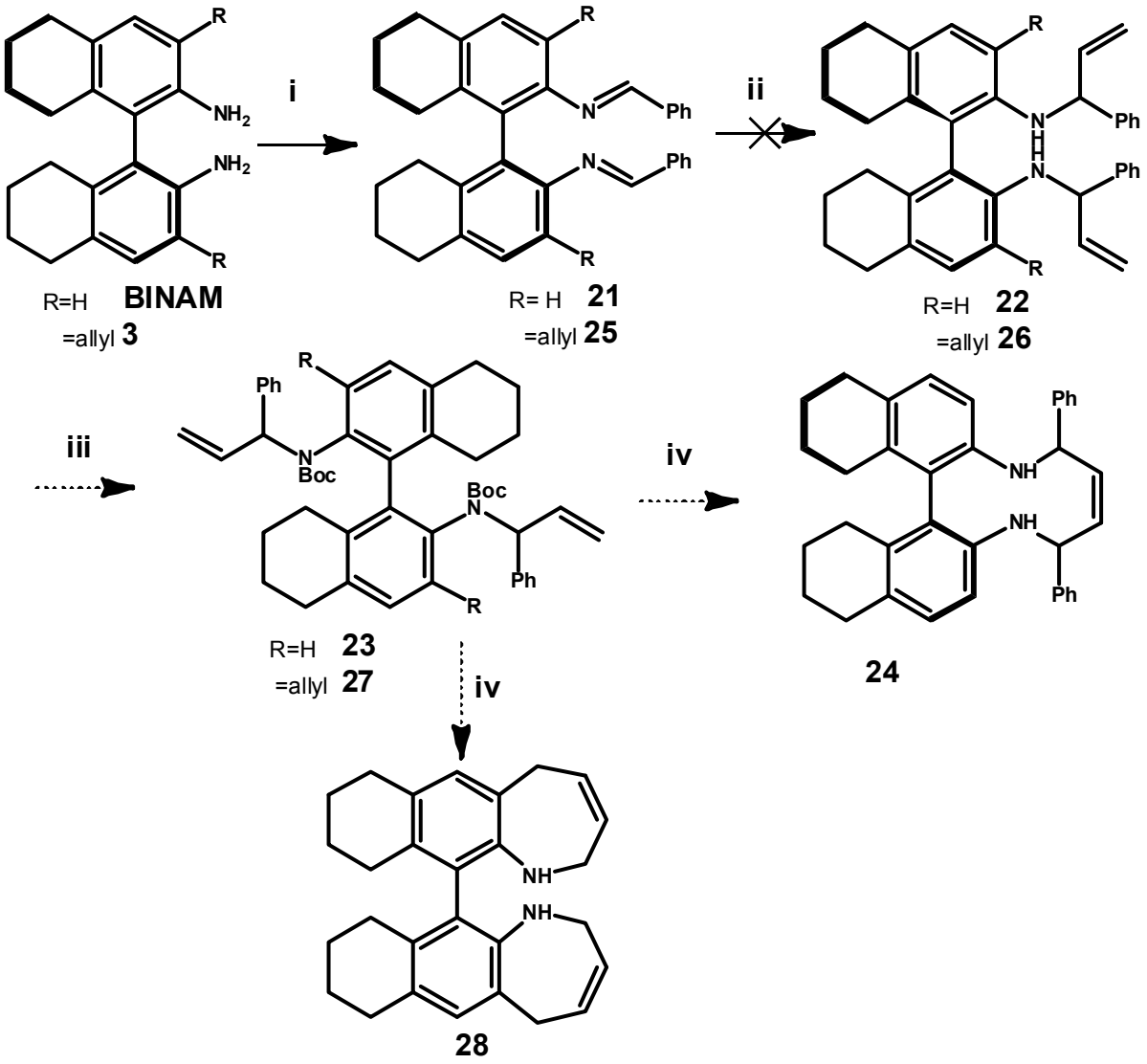
Scheme 8 i) diphosgene, NEt_3, DCM, ii) Urea, i-PrOH, AcOH;
ii) 1.) BuLi, TMEDA, ether; 2.) 1,2-Diiodo-ethane -78°C

In parallel to reactions mentioned before, it was also tried to introduce further substituents in the system, such as α-branchings. The first approach was to introduce a phenyl substituent followed by cyclisation in 2,2'-position (scheme 9). Starting from BINAM, a condensation with benzaldehyde should give the Schiff base **21**. From here the introduction of a vinyl group, using a Grignard reaction, seemed straight forward.

Subsequent *N*-protection with Boc_2O would be required to block the free NH-group in **22** and **26**. As demonstrated by R. Varala and co-workers under solvent-free conditions, catalytic amounts of iodine (10 mol%) reduced the reaction time needed for Boc protection in various cases .[50] The resulting amide **23** could then be cyclized via RCM using Grubbs 1st Generation Catalyst and finally subjected to Pd/C O_2 to cleave the Boc-PG leading to **24**.

The formation of the Schiff base **21** proceeded quantitatively. Although Grignard reaction took place, as confirmed by TLC, no products could be isolated after chromatography; but the imine **21** turned out to be very labile , hydrolysis occured

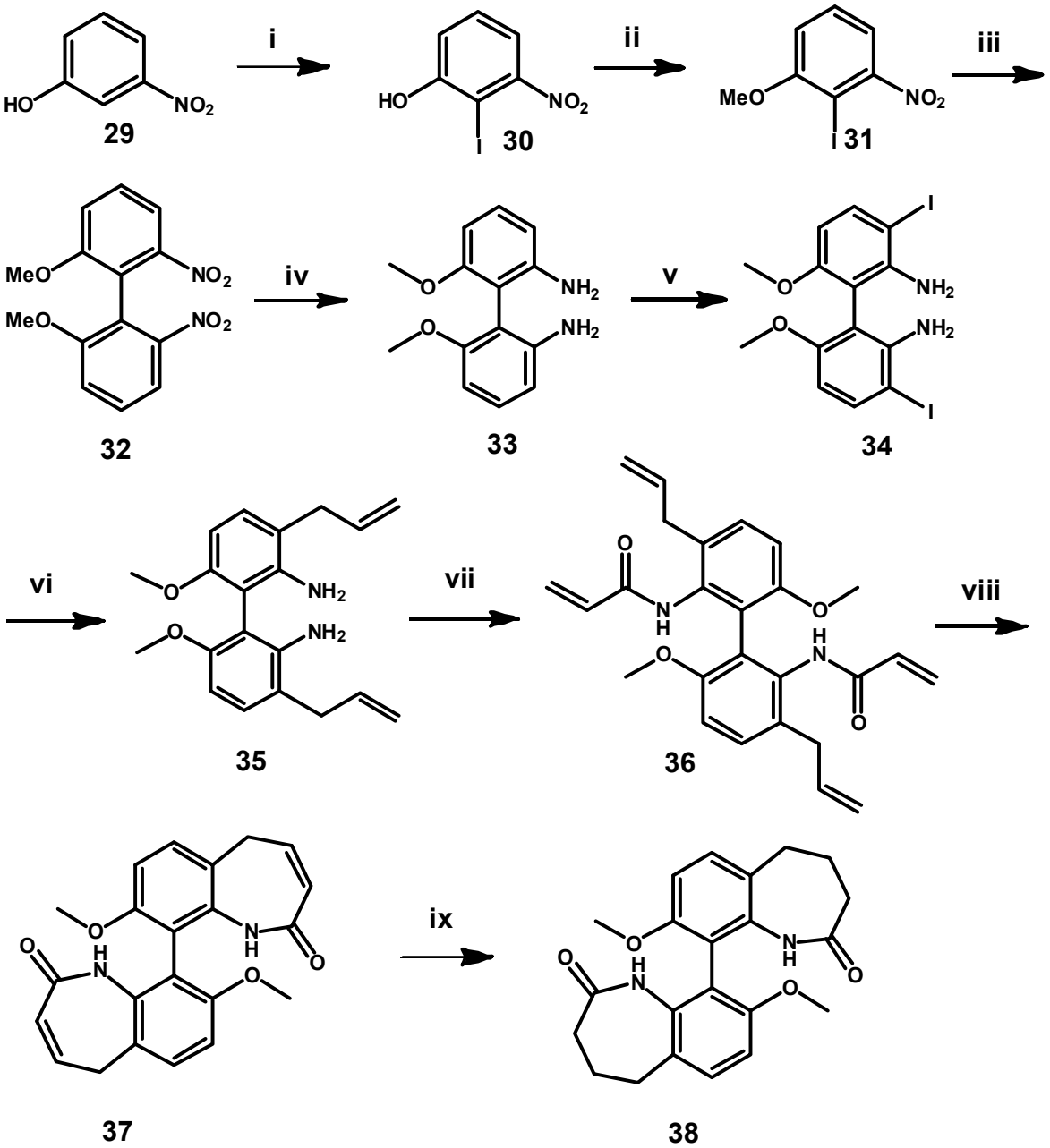
easily, eventually also promoted by hν (a sample after 12 h exposure to light it was completely reconverted into benzaldehyde and BINAM).



Scheme 9 An alternative strategy to obtain a bridged moiety
i) PhCHO, $MgSO_4$, MS 4 Å, ether/DCM, reflux **ii)** VinylMgBr, THF, -78°C to RT **iii)** Boc_2O, I_2, THF, **iv)** Grubbs 1st Gen. Catalyst, DCM; then Pd/C O_2, THF, reflux

The same sequence was also applied to 3,3'-diallylamine **3.** The synthetic steps similar as before are outlined in scheme 9. As before, condensation with benzaldehyde to the imine **25** proceeded in quantitative yield. Unfortunately the subsequent Grignard-reaction with the vinyl magnesium bromide didn't lead to any product; hence only starting material could be isolated. RCM of **27** was planned to give the 2,3- and 2'3'-dicyclized product, which should be deprotected to give **28**.

Since the already mentioned strategies didn't lead to the target molecule with a free NH group, other starting materials were considered. So it was tried to perform a synthesis based on a biphenyl skeleton, with the aim to reduce the sterical crowdedness, enhance the reactivity and facilitate the addition *and* cleavage of any PG. An appropriate biphenyl system had to be generated first, as starting unit 3-nitrophenol (**29**) was chosen (scheme 10).



Scheme 10 i) Raney-Nickel, iPrOH, KOH 1% H_2O, 85°C; **ii)** MeI, acetone, **iii)** Cu, DMF, 175°C; **iv)** Hydrazine-hydrate, $FeCl_3$*$6H_2O$; **v)** $BnMe_3NICl_2$, $CaCO_3$, DCM, MeOH; **vi)** Allyltributylstannane, $Pd(PPh_3)_4$, toluene; **vii)** Acryloyl chloride, Sm, ACN; **viii)** Grubbs 2°Generation Catalyst, DCM; **ix)** H_2, Pd/C, EtOH, DCM

The synthesis of **33** was performed according to a modified procedure of J. Jiang.[51] The initial step was the iodination of **29**, proceeding via mercury acetate intermediate to yield 52% of **30**. Subsequent methylation of **30** with MeI leads to the methoxy compound **31** in almost quantitative yield (97%). Ullmann coupling[52] of **31** gives the 2,2'-dimethoxy-6,6'-dinitro-1,1'-biphenyl (**32**) in 67% yield, and after reduction of the nitro functionality with hydrazine hydrate / $FeCl_3$ (cat.) the key product **33** was obtained (81% yield).[53]

Although the Ullmann coupling requires harsh conditions (excess of Cu, DMF, elevated temperatures) it is still a versatile protocol for aryl-aryl homo-coupling (especially on industrial scales), even if the functional group tolerance is moderate (necessity of PG) and electron withdrawing groups are required. However, also other methods for coupling the two moieties could be used, e.g. the plenitude of palladium catalyzed cross-couplings proceeding at milder conditions, but since the racemic resolution of the target molecule anyway has to be carried out later, Ullmann coupling was preferred

To introduce any alkyl or allyl-substituents in 3,3'-positions the ortho halo-amine was needed as precursor. while the regiochemistry of iodination of **33** with benzyl trimethylammonium dichloroiodate could not be predicted, it was quite surprising that under mild conditions almost exclusively the desired 3,3'-iodo-product **34** was obtained.[35] In table 4 the used conditions and reagents are outlined. Best results were obtained at -30 °C with $BnMe_3NICl_2$ (a typical procedure is given in detail in the experimental section).

Table 5 Halogenation of **33**

reagent	$BnMe_3NICl_2$	$BnMe_3NICl_2$	NBS
solvent	DCM	DCM	THF
reaction time	3 h	3 h	1 min
temperature	0 °C	-30 °C to 0°C	0 °C
isolated yield of **34**	59%	68%	mixture
undesired products	Poly iodination	**33** & tetra-iodide	Poly bromination and oxidation to NO_2

This new compound **34** turned out to be a versatile molecule with three different functional groups, opening a variety of possible new synthetic pathways. Not only further synthetic modifications of the hydroxyl group including eventually allylation followed by Claisen-rearrangement or introduction and/or alterations of substituents on the two amino groups can be done, but also the replacement of the halide by alkenyl- or aryl-groups in various cross-coupling reactions can be readily carried out.

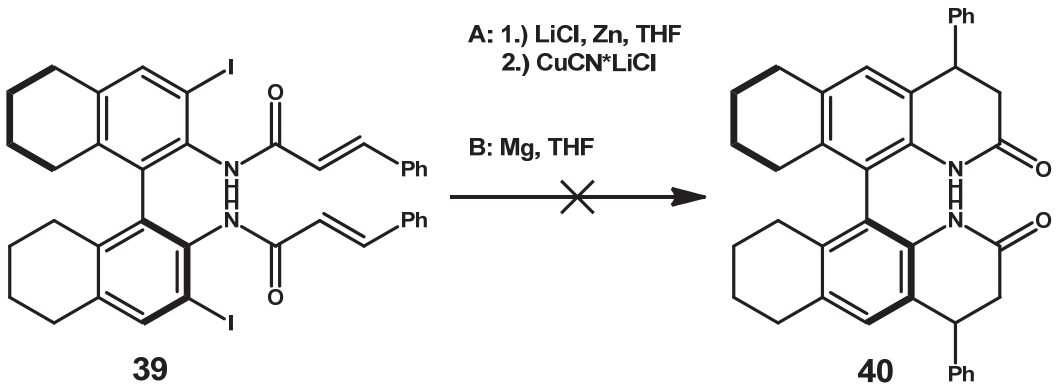
Therefore it was next attempted to introduce allyl groups in 3,3'-positions by Stille-coupling of **34** with allyltributylstannane.[36] This cross-coupling proceeded quite smoothly with 72% yield; and the resulting allyl-amine **35** could be subjected to acylation. Since the synthesis of the acetyl-protected (S)-octahydro-[binaphtho[2,3-b]azepine] gave only poor yields, it was tried to perform the better-working acryloylation of the biphenyl-analogue as in scheme 1 step iv.[39] Hereby, in contrary to the expectation, only moderate yields of **36** were observed (37% yield).
Next ring closing metathesis was performed using Grubbs 2nd Generation Catalyst, but unexpectedly, it led only to 28% of **37**. The hydrogenation of the olefinic double bond in the seven-membered ring was carried out under the same conditions as mentioned in scheme 1 (palladium on activated charcoal with a hydrogen pressure of 4 bar, 15 h at RT). The resulting 8,8'-dimethoxy-4,4',5,5'-tetrahydro-1H,1'H-[9,9'-dibenzo[b]azepine]-2,2'(3H,3'H)-dione **38** was obtained in quantitative yield and characterized by two dimensional NMR and MS.

So far all strategies to obtain the desired bis(heteroaryls) were based on ring closing metathesis, but, as recognizable from the previous results, these approaches didn't result in target molecules since amide functionalities colud neither be reduced nor cleaved to give secondary amines. Consequently other tactics had to be developed. At first other metal-mediated reactions to obtain a N-heterocycle with sufficient basicity of the NH_2-group were investigated.

The first attempt was to use copper/zinc reagents for transmetallation. Such functional zinc reagents can be generated easily[54] and transmetallation into the corresponding organocopper species can be done smoothly with of CuCN.[55] Several reports from Knochel et al. confirmed the formation of organocopper reagents, from complex salts CuCN* LiX with organozinc compounds.[56] Many examples of efficient coupling

reactions were published in these papers, so it was obvious to try an intramolecular variation using a binaphthyl derivative.

As outlined in scheme 6, as starting material (2E,2'E)-*N,N'*-(3,3'-diiodo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(3-phenylacrylamide) (**39**) was used.



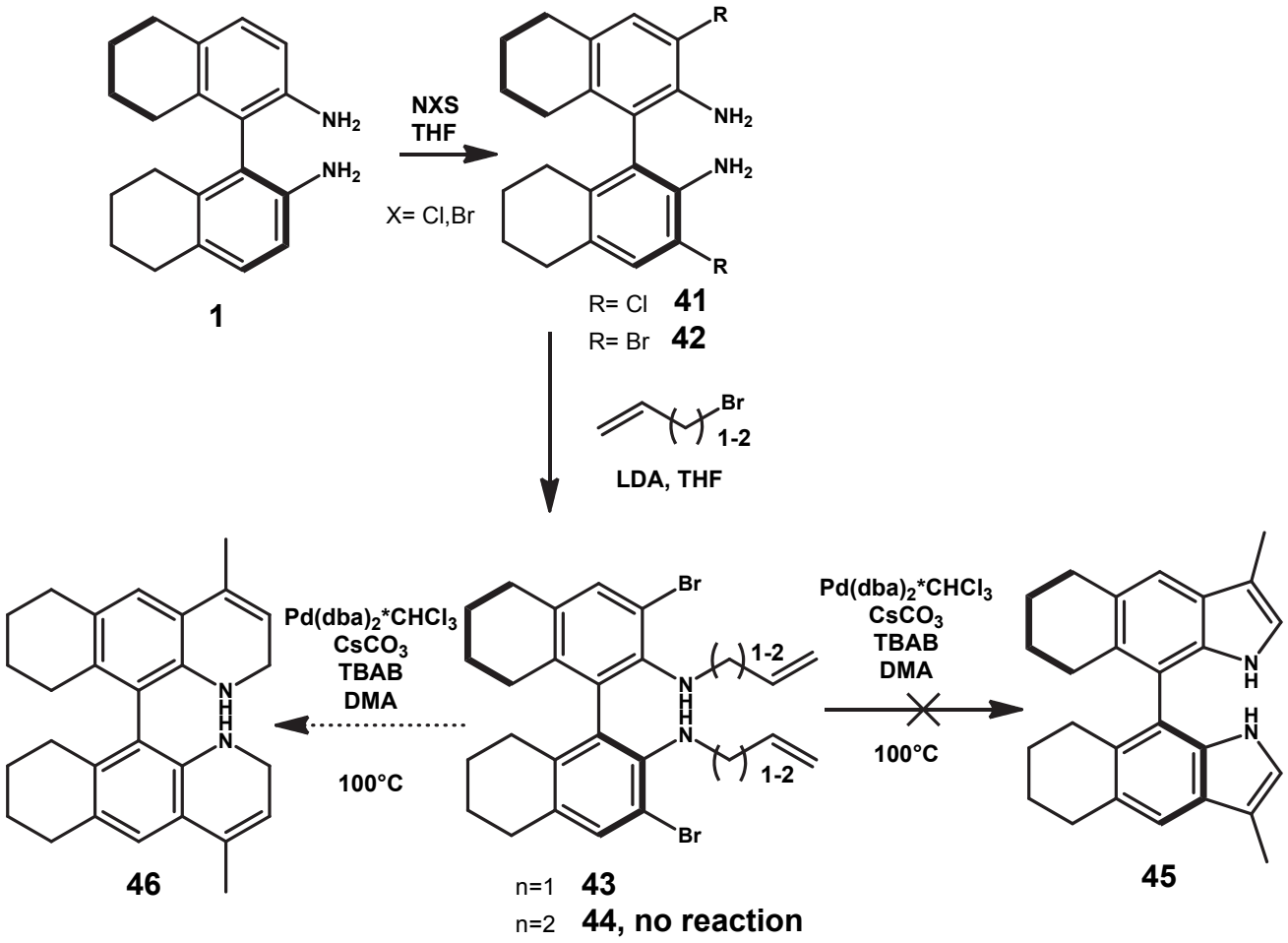
Scheme 11 Cu/Zn mediated transmetallation

In the first step of the pathway A the organozinc species should be generated, then transmetallation to the more reactive organocopper species should proceed. This active species should then react with the enone-moiety to give the cyclized product **40**. Unfortunately only starting material (90%) was isolated after 36 h reaction time; it should be mentioned that all reported reaction were intermolecular reactions, and not intramolecular as depicted above.

As the copper mediated reactions didn't give any positive results, the next attempt was to use magnesium (pathway B in scheme 6). Intermediary a Grignard reagent should be formed in 3,3'-position, then an intramolecular cyclisation should occur yielding **40**. Regrettably after usual work-up no conversion was noticeable, thus only starting material could be isolated.

Consequently further strategies had to be developed, and at next a Heck-type reaction was intended resulting in five- or six-membered heterocycles **43** and **44** (scheme 12). A similar cyclization method was published by M. Weinrich, starting from 2-chloraniline;[57] this reaction can either be carried out as an one pot reaction, or over 2 steps (allylation followed by Heck reaction); both pathways are starting from the ortho-halo-compound. Therefore **1** has to be halogenated; but the known iodo-compound **2** seems to be too sterically demanding, no substituent can be introduced at the nitrogen atom. So it was thought to synthesize the chloro- or bromo-species **41** and **42**, using NCS and NBS,

respectively.[35] The bromination of **1** was already published by Kano et al, but so far no reports concerning the chloro-species **41** were available. Therefore it was tried to subject **1** to similar conditions as appropriate for bromination; NCS in THF was used yielding 7.5% of **41,** the rest was mono- and poly-chlorinated species. Although the chlorines seem to be more reactive in the Heck-coupling sequence, the quantitative yield of the bromination reactions made **42** more attractive to work with.

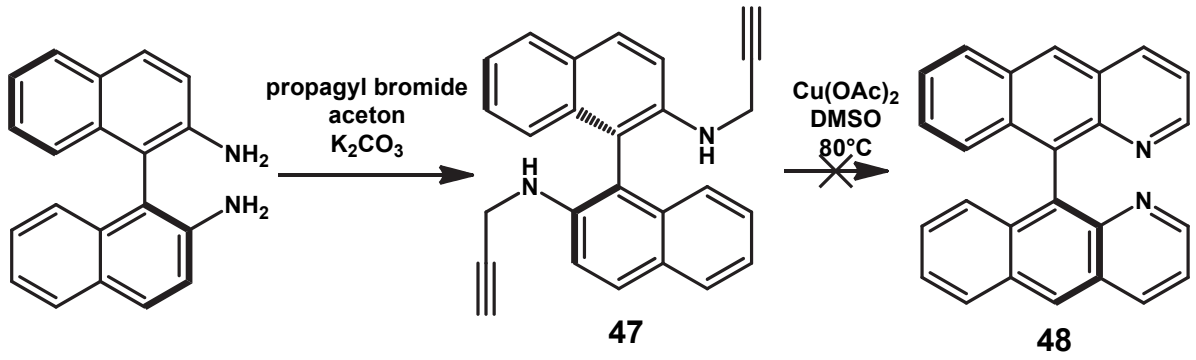


Scheme 12 Heck-coupling reaction to obtain a 5- and 6-membered heterocycle

Subsequent allylation of 3,3'-dibromo-1,1'-binaphthalene-2,2'-diamine **42** with allyl bromide in THF gave **43** in 71% yield, but Heck-reaction didn't proceed. This could be eventually due to a higher ring strain in the 5-membered ring **45**, so it was tried to substitute **42** with 1-bromo-4-butene to obtain a six-membered heterocylce **46**, but the butenylation didn't give **44** but only starting material, even when the conditions were varied [A: THF, LDA (0°C to RT); B: toluene, KI, Cs_2CO_3, 80°C].

The next strategy was to perform a 6-*endo*-dig cycloisomerization, similar to those published by Majumdar et al.[58] Therefore (S)-BINAM was reacted with propargyl bromide in presence of anhyd. potassium carbonate; as outlined in scheme 13. After 8 h reflux in acetone and aqueous work-up 21% of the desired dialkyne **47** could be isolated; the byproduct formed was *(S)-N,N'*-tetra(prop-2-yn-1-yl)-[1,1'-binaphthalene]-2,2'-diamine.

Copper(II)acetate-mediated cycloisomerization in DMSO at 65°C for 24 h failed; only starting material was isolated. In further experiments the cycloisomerization-catalyst should be altered. For $AgSbF_6$ a higher reactivity is expected.[56]



Scheme 13 Attempted copper catalyzed-cycloisomerization reaction

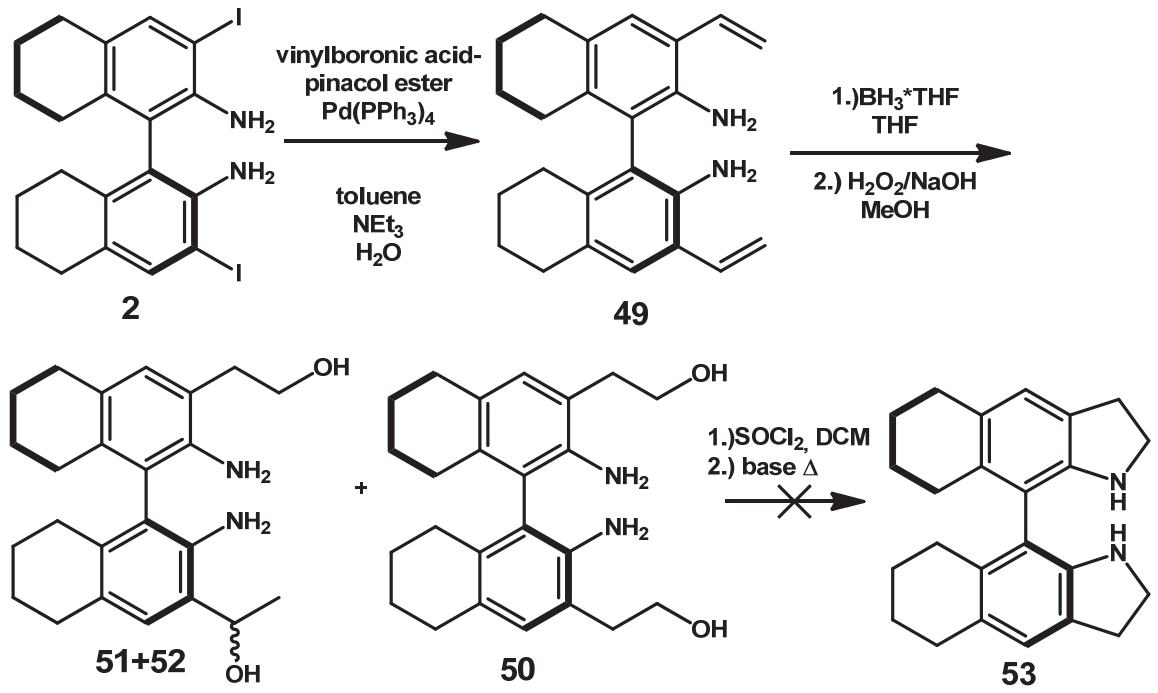
A difficult attempt was to perform the cyclization without metal-catalysis; the first strategy was to prepare an amino alcohol as precursor for an intramolecular alkylation (scheme 14). Diiodide **2** was subjected to a Suzuki-Miyaura coupling reaction[59], using vinylboronic acid pinacol ester, $Pd(PPh_3)_4$ and NEt_3 in refluxing toluene, yielding the vinyl amine **49** (66%). Hydroboration of the vinyl amine **49** with BH_3*THF afforded the primary alcohol **50**. Unfortunately also side products were formed, namely the two non-symmetric diastereomeric regioisomers of **51** and **52**. To prevent their formation, a sterically more demanding borane should be used, such as 9-borabicyclononane (9-BBN).

From the resulting amino alcohol **50** the bisindole **53** should be accessible via a chlorination / cyclodehydration sequence (scheme 14) according to Xu et al.[60] This can be realized in a one pot reaction using thionyl chloride with subsequent pH adjustment (from acidic to basic) during aqueous work up. The formation of by-products due to the competition between O- and N-sulfination can be suppressed by protonation of the NH_2

group. According to Xu, quantitative formation of the chlorides takes place and after work up with aqueous base the cyclized product can be isolated, often in excellent yield.

So it seemed a promising strategy also to be tried with substrate **50**, but unfortunately when employing the same conditions (DME, NaOH), after 8 h 98% substrate was isolated; clearly indicating that the formation of the chloride couldn't be perceived.

So the solvent and the base were changed to dichloromethane with triethylamine and catalytic amounts of KI was added. But also this attempt didn't give the desired dodecahydro-bibenzo[f]indole **53**, but a complex mixture was obtained.

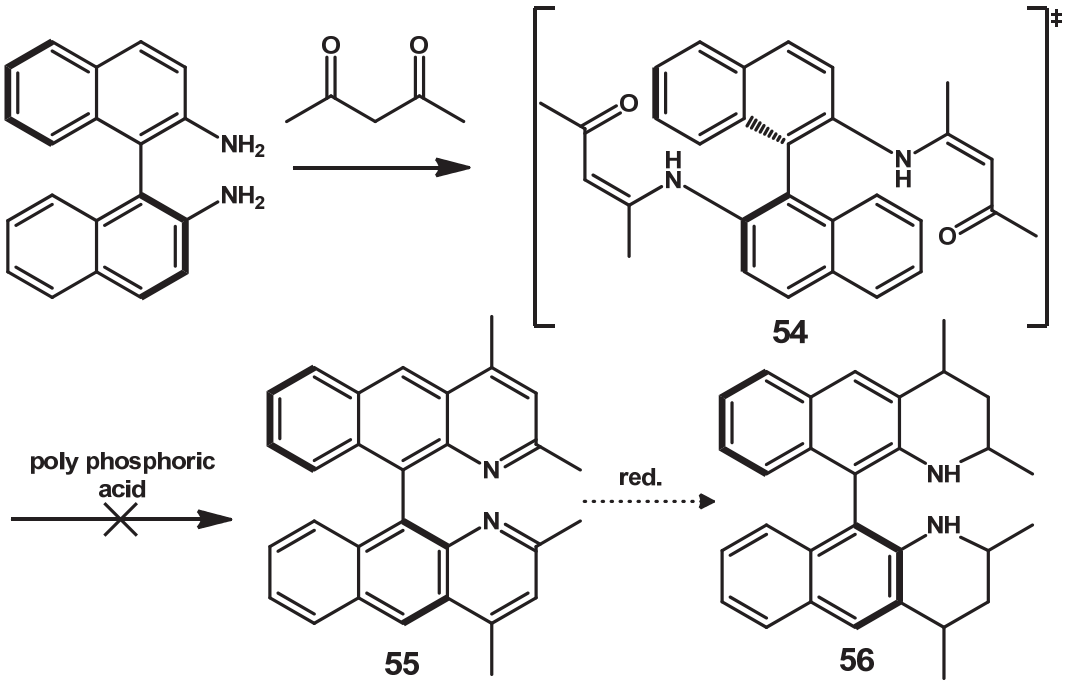


Scheme 14 Cyclodehydration of amino alcohol **50** with $SOCl_2$

Since also the cyclodehydration didn't work, it was tried to perform a very deep-rooted synthesis, the Combes' quinoline synthesis. Hereby a condensation of unsubstituted amino-aryls with β-diketons formes an imine as intermediate, acid catalyzed cyclization yields substituted quinoline derivatives.[61] This resulting bibenzo[f]quinoline would have to be partially reduced (Birch?) to give free NH-groups necessary for catalytic activity.

As depicted in scheme 15, (S)-BINAM was condensed solvent free with excess acetyl acetone to the imine **54**. Immediate addition of poly-phosphoric acid and heating to 65°C should give the desired tetramethyl-bibenzo[f]quinoline-derivative **55**.

Disappointingly, after work up with aqueous base, only polymers of acetyl acetone could be identified by NMR, thus no product was detected.

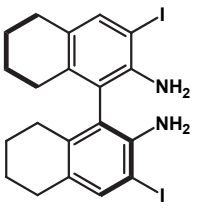
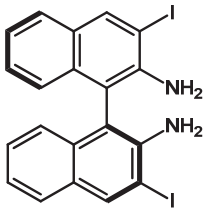
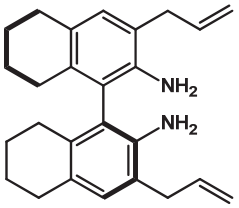
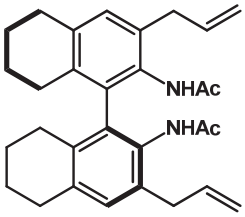
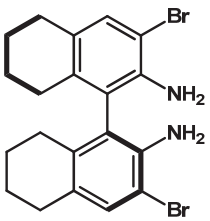
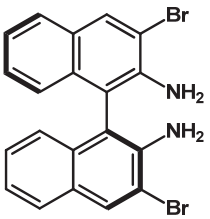


Scheme 15 combes quinoline synthesis

Another obstacle to overcome was that in order to obtain exclusively ortho-halo-binaphthyls, the second phenyl rings always had to be reduced. But it would be of interest to recover the fully aromatic binaphthyl core in the final product, so rearomatisation was examined on various intermediates.

Earlier reports from T. Kano claimed that the H_8-ortho-halo substituted compounds like **2** are easily rearomatized using DDQ in refluxing benzene.[35] But reproducing these yields proved to be rather difficult, reproducibly only 40% of **57** have been obtained (5 attempts under different conditions). Hence it was thought that the free NH_2 might interact with the quinone, forming adducts or NH-bonds. So rearomatisation was tried on other intermediates such as **3** and **9**; in table 5 the results are summarized.

Table 6 Attempts of re-aromatization

entry	substrate	product	yield
1	 **2**	 **57**	40%[v]
2	 **3**	-	0%
3	 **9**	-	0%
4	 **42**	 **58**	32%[vi]

From these results it is evident that only halides can be re-aromatized albeit in low yield; all other intermediates investigated yielded only decomposition. Therefore a metal catalyzed oxidative aromatization method has been chosen.

Finally a protocol published by J. Bercaw was applied using oxygen in presence of a palladium catalyst to aromatize cycloolefins. [61,62,63] Treatment of the ortho-iodo intermediate **2** with O2 in acetone with $Pd(CF_3CO_2)_2$ didn't give any aromatization; only substrate could be recovered. Possibly coordination to the metal center is hampered due to the crowdedness of the substrate, or the NH-groups are interfering in the reaction (in Bercaw's paper only unsubstituted cyclic olefins were used).

[v] compared to published 72% yield
[vi] done in our group (compared to 74% published by Kano)

3. Conclusion

As outlined in the Results and Discussion section, the synthesis of bisheteroaryls via ring-annelation to already existing biaryls turned out to be a difficult task, especially the synthesis of free NH-group bearing heterocycles with sufficient basicity could not be achieved. The central problem seems the severe steric hindrance arising in synthesizing and modifying the 2,2',3,3'-tetrasubstituted biaryls-unit.

Nevertheless 19 interesting new biaryls could be synthesized, among these five amide-protected bisheteroaryls. A polyfunctional molecule was accessible in the iodo-biphenyl-species **34,** a versatile precursor for many different synthetic applications when three different functionalities (OMe, I and NH_2). Further developments in this direction should also cover the development of an optical resolution procedure, best before reduction to the amine **33**.

Introduction of substituents in 3,3'-positions of the H_8-BINAM worked well, giving reproducible high yields. Also substitution of the NH_2-group with one substituent gave good results, but introduction of further *N*-substituents into the Ar-NHR provided - if working at all - only poor yields. The twofold ortho substitution seems to hinder further substitution of the Ar-NHR-moiety. Despite acetyl no proper protective group could be found. Moreover cleavage of N-Acetyl or reduction of the bislactame after RCM failed.

From these results it turned out that next synthetic strategies should focus on a *de-novo* synthesis of the bisheteroaryl-skeleton *via* homo-coupling methods; thus the complete heterocycle should be built up before. As a consequence new optical resolution methods need to be established and the proper coupling conditions have to be developed. This approach would also avoid any problem with the re-aromatization. On the other hand also Friedländer-type cyclization reactions could provide a new strategy to obtain novel bisazaheteroaryls with sufficient basicity for applications in asymmetric catalysis.

4. Experimental

The ^{1}H-NMR and ^{13}C-NMR Spectra were measured on a Bruker AVIII400 NMR spectrometer at 400 or 100 MHz respectively. Chemical shifts δ are given in ppm relatively to the residual peaks of the deuterated solvent used. Spectra measured in $CDCl_3$ are referenced to 7.24 ppm (^{1}H) and 77.00 ppm (^{13}C). Coupling patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and b (broad). The ^{13}C spectra were recorded in a j-modulated mode. Signals are assigned as C, CH, CH_2 and CH_3. Coupling constants *J* are given in Hz.

ESI-MS Spectra were recorded at the Mass Spectrometry Center of the University of Vienna. HRMS was measured on an ESI-Qq aoTOF mass spectrometer (Bruker).

Melting points were measured on a Kofler hot stage equipped with microscope.

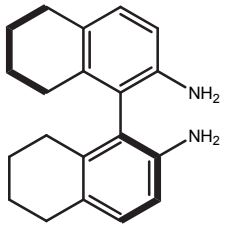
Inert reaction conditions were achieved by using oven-dried (140°C, overnight) glasswares, reactions were performed under dry argon atmosphere with degassed solvents (three freeze-pump-thaw cycles) or reaction mixtures, respectively, and performing the reactions under argon.

Furthermore the solvents and reagents were, if possible, distilled freshly. Thus CH_2Cl_2, toluene and ACN were distilled from CaH_2, ether from $LiAlH_4$ and THF from Na/benzophenone.

2,6-Diisopropyl-phenylimidoneophyliden-molybdenum(VI)-dimethoxyethan adduct and palladium trifluoroacetate were obtained from Strem Chemicals. The 1,1'-binaphthalene-2,2'-diamine was used in enantiopure form, prepared previously according to standard procedures.[25,32] All other reagents were analytical grade and purchased from Sigma Aldrich.

All experiments were monitored by analytical thin layer chromatography (TLC). Medium pressure chromatography was performed on a Biotage Isolera Flash Purification System; the flowrate was adjusted according to the used cartridges.

4.1. (*S*)- 5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (**1**)



1

(S)-BINAM (1.137 g; 4 mmol) was dissolved in *i*-PrOH (400 mL) and Raney-Nickel (8 g) and water (400 mL) were added. After heating the mixture to 85 °C, the aqueous potassium hydroxide (1%, 800 mL) was added dropwise over 10 h. The mixture was allowed to reflux for another 36 h, then cooled to RT. The slurry was filtered from the Raney-Nickel using a 'Büchner-funnel' and the filtrate was concentrated by distillation at atmospheric pressure. After complete removal of *i*-PrOH the crude product was repeatedly extracted with DCM (400, 200, 100, 100, 100 mL). The combined organic layers dried over Na_2SO_4 and the solvents were removed under reduced pressure.

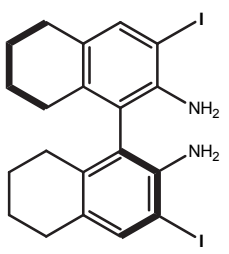
The crude product was purified via MPLC using a gradient (EE/PE 5/95 to 40/60) to give *(S)*-**1**.

Yield: 901 mg (77%)

Spectroscopical Data: (matched literature)

^{1}H-NMR ($CDCl_3$): δ 6.91 (d, *J* = 8.0 Hz, 2H); 6.61 (d, *J* =8.1 Hz, 2H); 3.30 (bs, 4H); 2.71 (pt, *J* = 6.0 Hz, 4H); 2.31-2.13 (m, 4H); 1.75-1.60 (m, 8H) ppm.

4.2. (S)-3,3'-diiodo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (**2**)



2

Diamine *(S)*-**1** (597 mg; 2.04 mmol) was placed in a Schlenk tube and dissolved and degassed in DCM (15 mL). $CaCO_3$ (613 mg; 6.13 mmol) as well as MeOH (4 mL) were added. The mixture was cooled to -30 °C and to this was dropwise added under argon via Teflon tube a solution of the benzyltrimethylammonium dichloroiodate (1.422 g; 4.08 mmol) degassed in DCM (10 mL).

After 2 h at -30 °C the mixture was allowed to warm up to RT and stirred at this temperature for 0.5 h. The reaction was subsequently quenched with sat. $NaHCO_3$-solution (10 mL) and washed with $NaHSO_3$-solution (10%, 2x10 mL). The product was extracted with DCM (4x10 mL) and the combined organic layers dried over Na_2SO_4. The solvents were removed under reduced pressure to afford the crude product, which was purified via MPLC (PE/EE 95/5) giving (S)-**2**.

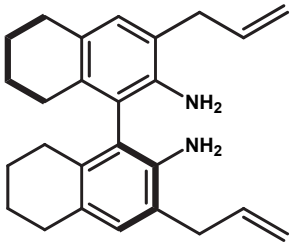
Yield: 966 mg (87%)

Spectroscopical Data: (matched literature)

^{1}H-NMR ($CDCl_3$): δ 7.41 (s, 2H); 3.69 (bs, 4H); 2.66 (t, *J* = 6.1 Hz; 4H); 2.22-2.01 (m, 4H); 1.70-1.57 (m, 4H)

^{13}C-NMR ($CDCl_3$): δ 141.7 (C); 138.8 (CH); 136.7 (C); 129.9 (C); 121.9 (C); 81.5(C); 28.9 (CH_2); 26.8 (CH_2); 23.1 (CH_2); 22.9 (CH_2) ppm.

4.3. (S)-3,3'-diallyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (**3**)



3

Diiodide *(S)*-**2** (870 mg; 1.6 mmol) was dissolved in toluene and degassed. Then palladium tetrakistriphenylphosphine (185 mg; 0.160 mmol) and allyl tributylstannane (1.088 g; 3.50 mmol) were added subsequently. The mixture was heated to 85 °C and stirred at this temperature for 20 h, then cooled to RT and quenched with water. The mixture was extracted with EE (3x10 mL), the combined organic extracts washed with brine and dried over Na_2SO_4. The solvents were evaporated under reduced pressure to give crude (*S*)-**3**.

Finally the crude product was purified via MPLC using a gradient (EE/PE 5/95 to 50/50).

Yield: 396 mg (66%)

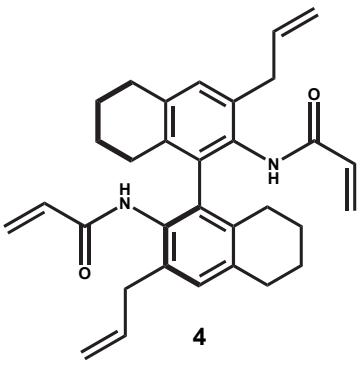
Spectroscopical Data:

^{1}H-NMR ($CDCl_3$): δ 6.79 (s, 2H); 5.96 (m, 2H); 5.08 (m, 4H); 3.32 (bs, 4H); 3.28 (bd, *J* = 6.2 Hz; 4H); 2.69 (m, 4H); 2.22-2.04 (m, 4H); 1.73-1.60 (m, 8H) ppm.

^{13}C-NMR ($CDCl_3$): δ 140.1 (C); 136.39 (CH); 134.3 (C); 129.9 (CH); 127.5 (C); 122.7 (C), 121.9 (C); 115.9 (CH_2); 36.6 (CH_2); 29.3 (CH_2); 26.9 (CH_2); 23.5 (CH_2); 23.3 (CH_2) ppm.

HRMS (ESI): calcd. for $C_{26}H_{33}N_2$ 373.2644 ([M+H]), found 373.2644 ([M+H]).

4.4. (*S*)-*N,N'*-(3,3'-diallyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)diacrylamide (**4**)



4

Diamine *(S)*-**3** (300 mg; 0.81 mmol) was dissolved and degassed in DCM (0.5 mL) / acetonitrile (2 mL), and Samarium (254 mg; 1.69 mmol) as well as acryloyl chloride (219 mg; 2.42 mmol) were added. The mixture was stirred at RT for 16 h, then filtered and quenched with 1N hydrochloric acid (2 mL). After neutralization with sat. $NaHCO_3$ solution (5 mL), the product was extracted with EE (3x10 mL). The combined organic layers were dried over Na_2SO_4 and the solvents removed under reduced pressure. The crude product was purified via MPLC (EE/PE 10/90).

Yield: 202 mg (52%) off-white powder

Spectroscopical Data:

mp= 183.6- 185.6 °C

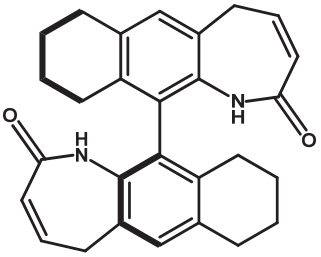
^{1}H-NMR ($CDCl_3$): δ 6.95 (s, 2H); 5.98 (m, 4H); 5.96-5.82 (m, 2H); 5.51 (dd, *J* = 11.3, 6.0 Hz, 2H); 4.99 (dm, *J* = 9.9, 2H); 4.92 (dm, *J* = 17.0, 2H); 3.28 (m, 4H); 2.74 (pt, *J* = 6.0 Hz, 4H); 2.24-1.94 (bm, 4H); 1.75-1.54 (bm, 8H) ppm.[vii]

^{13}C-NMR ($CDCl_3$): δ 137.1 (CH); 136.9 (C); 131.1 (CH); 129.9 (CH); 126.6 (CH_2); 115.4 (CH_2); 36.5 (CH_2); 29.7 (CH_2); 27.2 (CH_2); 23.1 (CH_2); 22.9 (CH_2) ppm.[viii]

HRMS (ESI): calcd. for $C_{32}H_{36}O_2N_2Na$ 503.2674 ([M+Na]) found 503.2664 ([M+Na])

[vii] NH could not be observed
[viii] five quaternary carbon could not be detected

4.5. (*S*)-1H,1'H-[11,11'-binaphtho[2,3-b]azepine]-2,2'(5H,5'H)-dione (**5**)



5

Diamide *(S)*-**4** (42 mg; 0.90 mmol) was dissolved and degassed in DCM (0.5 mL). Grubbs 2nd Generation Catalyst[ix] (7 mg; 0.01 mmol) was likewise dissolved and degassed in DCM (1.5 mL) and was then added slowly at RT via syringe pump (350 µL/h). Upon complete addition of the catalyst, the mixture was allowed to stir at RT for 24 h. To decompose the catalyst, the solution was stirred for 1 h under air. It was filtered over celite and the filtrate evaporated. The crude product was purified via column chromatography (PE/EE 50/50, then EE + 1% EtOH).

Yield: 36 mg (97%)

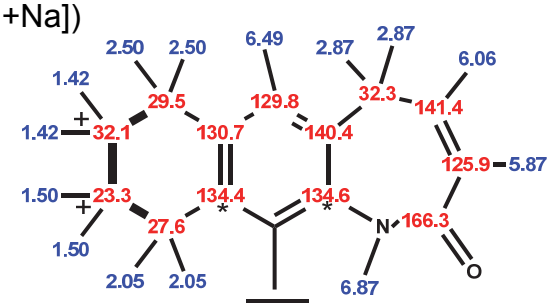
Spectroscopical Data:

^{1}H-NMR (toluene-d_8): δ 6.87 (s, 2H); 6.49 (s, 2H); 6.06 (m, 2H); 5.87 (dd, *J* = 10.9, 2.1 Hz, 2H); 2.87 (m, 4H); 2.49 (m, 4H); 2.06-2.00 (m, 4H); 1.55-1.35 (m, 8H) ppm.

^{13}C-NMR ($CDCl_3$): δ 167.4 (C); 142.1 (CH); 135.4 (C); 134.5 (C); 132.1 (C); 129.9 (CH); 129.7 (CH); 126.3 (C); 124.9 (C); 32.2 (CH_2); 29.3 (CH_2); 27.2 (CH_2); 22.9 (CH_2); 22.6 (CH_2) ppm.

HRMS (ESI): calcd. for $C_{28}H_{28}O_2N_2Na$ 447.2048 ([M+Na]) found 447.2043 ([M+Na])

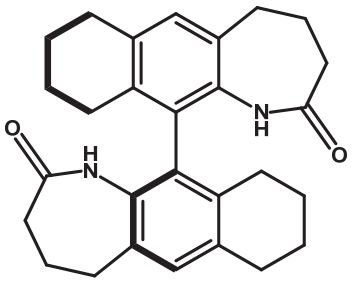
Partial assignment of NMR shifts based on 2D NMR (toluene)



\+ interchangeable
* interchangeable

[ix] The same procedure was carried out with Grubbs 1st Generation Catalyst and the Schrock-type Catalyst; results of these reaction are mentioned in table 1 in the Results & Discussions section

4.6. *(S)*-4,4',5,5'-tetrahydro-1H,1'H-[11,11'-binaphtho[2,3-b]azepine]-2,2'(3H,3'H)-dione (**6**)



6

Bislactame *(S)*-**5** (40 mg; 0.09 mmol) was dissolved in DCM (0.5 mL) and transferred into a pressure tube. To this EtOH (2,5 mL) and Pd/C (10 mg) were added, the tube then flushed with hydrogen and subsequently filled with 5 bar H_2. The mixture was stirred vigorously at RT for 18 h. To remove catalyst residues the reaction mixture was filtered over celite and the solvents removed under reduced pressure. The product was purified via chromatography over silica gel (PE/EE 50/50, then EE).

Yield: 38 mg (95%)

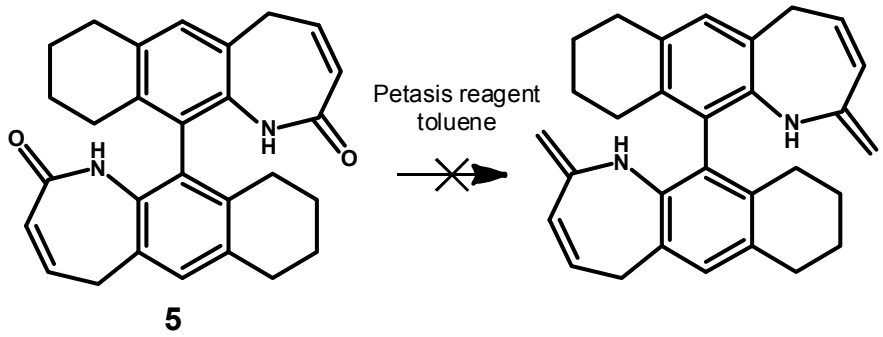
Spectroscopical Data:

^{1}H-NMR ($CDCl_3$): δ 6.91 (s, 2H); 6.25 (bs, 2H); 2.83-2.55 (m, 4H); 2.72 (pt, *J* = 6.2 Hz, 4H); 2.29-1.92 (m, 12H); 1.71-1.57 (m, 8H) ppm.

^{13}C-NMR ($CDCl_3$): δ 174.4 (C); 135.6 (C); 134.0 (C); 132.8 (C); 132.0 (C); 130.6 (CH); 128.3 (C); 32.36 (CH_2); 30.2 (CH_2); 29.4 (CH_2); 28.3 (CH_2); 27.2 (CH_2); 23.0 (CH_2); 22.7 (CH_2) ppm.

HRMS (ESI): calcd. for $C_{28}H_{32}O_2N_2Na$ 451.2361 ([M+Na]) found 451.2348 ([M+Na])

4.7. Attempt of Methenylation of (*S*)-**5**

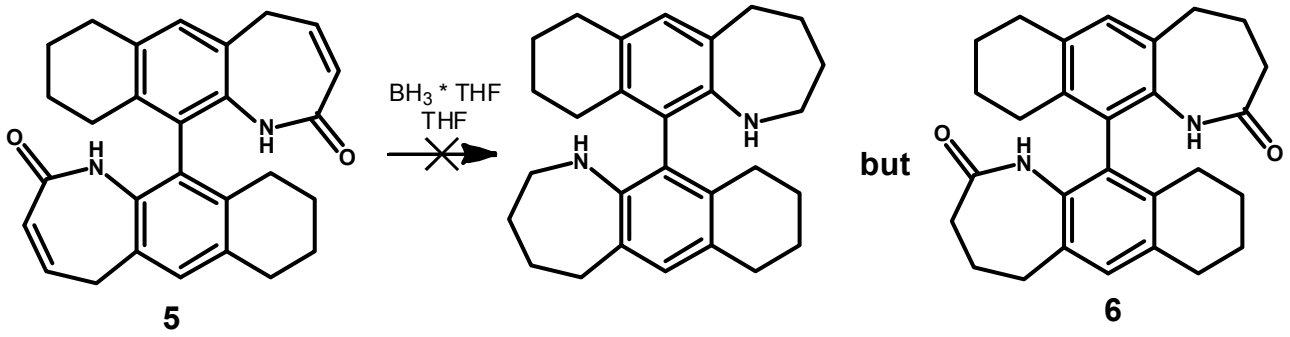


5

Bislactame (S)-**5** (50 mg; 0.12 mmol) was placed in a Schlenk-tube, dissolved and degassed in toluene (1 mL). To this solution the Petasis reagent (1.44 mL; 0.72 mmol; 0.5 M in THF) was added slowly at RT under argon. The reaction mixture was stirred at RT for 12 h, and then heated to 60 °C for 24 h. Thus it was quenched with hydrochloric acid (1N, 2 mL) and the product extracted with EE (3 x 7 mL). The combined organic layers were dried over Na_2SO_4, the solvents removed under reduced pressure and the crude product subjected to chromatography (EE).

Yield: quantitatively starting material

4.8. Attempt of Reduction of the carbonyl function of (*S*)-**5**



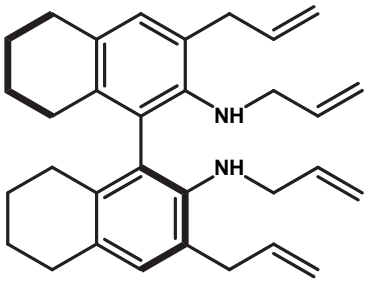
5 **6**

Bislactame (S)-**5** (18 mg; 0.042 mmol) was dissolved in THF (1.5 mL) and degassed. The solution was cooled to 0 °C and BH_3* THF (300 µL; 0.296 mmol; 1 M in THF) was added. The mixture was allowed to warm up to RT, then stirred for 4 h. Upon the consumption of the starting material, the reaction was quenched with water (1 mL), then sodium hydroxide solution (15%, 3 mL) and water (5 mL) were added. The product was extracted with EE (3x10 mL) and the combined organic layers dried over Na_2SO_4. The solvents were evaporated and the crude product purified via MPLC (gradient from PE/EE 50/50 to pure EE).

Yield: 17 mg (*S*)-**6** (95%)

Spectroscopical Data: vide 4.6

4.9. *(S)-N,N'*,3,3'-tetraallyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (**8**)



8

Diamine (S)-**3** (200 mg; 0.54 mmol) was dissolved in acetonitrile (1,5 mL) and degassed. Under argon allyl bromide and potassium carbonate were added successively and the mixture was stirred at 65 °C for 20 h. The reaction was quenched at 0 °C with water and the product was extracted with EE (3x10 mL). The combined organic layers were subsequently dried over $MgSO_4$ und the solvents evaporated. The crude product was purified via chromatography (PE/EE 95/5).

Yield: 192 mg (79%)

Spectroscopical Data:

According to ^{1}H and ^{13}C NMR, it seems like in minimum 2 rotamers being present (one thereof with C_1-symmetry). In ^{13}C-spectra most of the shifts seemed to be doubled. Similar behaviour was reported for a mesyl derivative by Pluempanupat (*vide JOC, 2011, 76, 3222-3230*).

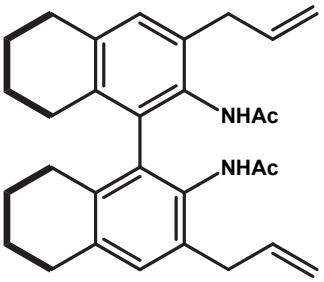
^{1}H-NMR ($CDCl_3$): δ 6.85 (s, 1H); 6.74 (s, 1H); 6.08-5.83 (m, 2H); 5.76-5.58 (m, 1H); 5.09-4.82 (m, 6H); 3.35 -3.27 (m, 4H); 3.22 (d, *J* = 6.0 Hz, 4H); 2.79 (b, 1H); 2.71-2.57 (m, 4H); 2.18-1.92 (m, 4H); 1.69-1.52 (m, 8H) ppm.[x]

^{13}C-NMR ($CDCl_3$): δ 143.1; 140.0; 137.8; 136.8; 136.4; 134.2; 134.1; 131.3; 130.6; 130.6; 130.1; 129.9; 129.5; 128.8; 128.1; 127.4; 126.5; 123.2; 121.8; 115.9; 115.8; 115.7; 115.4; 52.4; 36.6; 36.0; 29.7; 29.5; 29.4; 29.3; 29.3; 27.5; 27.4; 26.9; 26.9; 26.4; 26.3; 23.5; 23.5; 23.3; 23.2 ppm.[xi]

HRMS (ESI): calcd. for $C_{34}H_{44}N_3Na$ 517.3433 ([M+Na+H+ACN]) found 517.3170 ([M+Na+ H+ACN])

[x] Due to dynamic phenomena, H-shifts could not be fully assigned.
[xi] Due to dynamic phenomena and partially doubled C-shifts, no C-assignments are given.

4.10. *(S)-N,N'*-(3,3'-diallyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)diacetamide (**9**)



9

Diamide (S)-**3** (191 mg; 0.51 mmol) was dissolved in DCM (0.5 mL), ACN (2 mL) was added and the solution degassed. Samarium (170 mg; 1.13 mmol) and acetyl chloride (122 mg; 1.54 mmol) were added successively and the mixture was stirred for 24 h. Thus it was filtered and to quench to the filtrate was added 1N hydrochloric acid (2 mL). After neutralization with saturated $NaHCO_3$, the product was extracted with EE and the combined organic layers dried over Na_2SO_4. The solvents were removed under reduced pressure and the product purified by chromatography (PE/EE 70/30).

Yield: 151 mg (65 %)

Spectroscopical Data:

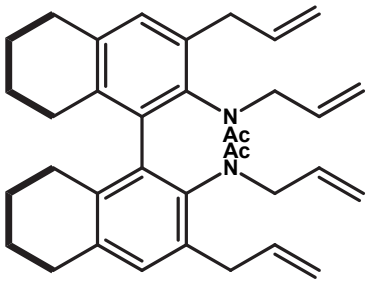
^{1}H-NMR ($CDCl_3$): δ 6.95 (s, 2H); 5.93 (m, 2H); 5.03 (dm, *J* = 10.0 Hz, 2H); 4.97 (dm, *J* = 17.0 Hz, 2H); 3.29 (m, 4H); 2.75 (m, 4H); 2.20-1.93 (m, 4H); 1.79 (s, 6H); 1.73-1.53 (m, 8H) ppm.[xii]

^{13}C-NMR ($CDCl_3$): δ 172.9 (C); 137.2 (CH); 129.9 (CH); 127.4 (C); 115.5 (CH_2); 36.5 (CH_2); 29.7 (CH_2); 27.2 (CH_2); 23.2 (CH_2); 23.0 (CH_3); 22.9 (CH_2) ppm.[xiii]

HRMS (ESI) calcd. for $C_{30}H_{36}N_2O_2Na$ 479.2674 ([M+Na]) found 479.2653 ([M+Na])

[xii] NH-groups could not be detected
[xiii] 3 quaternary carbons could not be observed

4.11. *(S)-N,N'*-(3,3'-diallyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(*N*-allylacetamide) (**10**) from (*S*)-**8**



10

(S)-**8** (190 mg; 0.42 mmol) was dissolved in DCM (2.5 mL), ACN (2.5mL) added and degassed. At RT samarium (127 mg; 0.84 mmol) and acetyl chloride (100 mg; 1.26 mmol) were added respectively. The mixture was stirred for 20 h at RT, then filtered over cotton wool and to the filtrate HCl (2N, 2 mL) was added. After neutralization with sat. $NaHCO_3$ (5 mL), the mixture was extracted with EE (3 x 7 mL), the combined organic layers dried over Na_2SO_4 and the solvents removed under reduced pressure. The crude product was purified via chromatography (PE/EE 70/30 + 1% NEt_3).

Yield: 74 mg (32 %)

Spectroscopical Data:

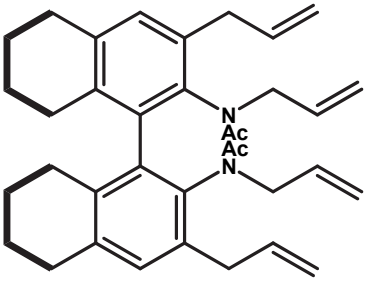
^{1}H-NMR ($CDCl_3$): δ 7.05 (s, 2H); 5.87-5.65 (m, 4H); 5.17-5.08 (m, 4H); 5.02-4.90 (m, 4H); 4.34 (dd, *J* = 14.4, 5.6 Hz, 2H); 3.24-3.12 (m, 6H); 2.85-2.71 (m, 4H); 2.01-1.96 (m, 4H); 1.86-1.51 (m, 8H); 1.72 (s, 6H) ppm.

^{13}C-NMR ($CDCl_3$): δ 164.3 (C); 138.1 (C); 136.7 (CH); 135.5 (C); 133.1 (CH); 130.9 (CH); 118.0 (CH_2); 117.1 (CH_2); 49.8 (CH_2); 35.3 (CH_2); 29.6 (CH_2); 27.6 (CH_2); 22.9 (CH_2); 22.7 (CH_2); 21.9 (CH_3) ppm.[xiv]

HRMS (ESI) calcd. for $C_{36}H_{44}N_2O_2Na$ 559.3300 ([M+Na]) found 559.3310 ([M+Na])

[xiv] 3 quaternary carbons were not detectable

4.12. *(S)-N,N'*-(3,3'-diallyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(*N*-allylacetamide) (**10**) from (*S*)-**9**



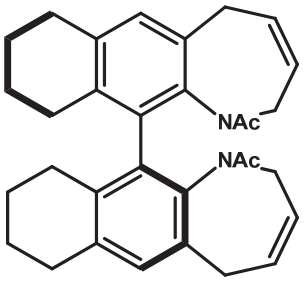
10

(S) -**9** (190 mg; 0.42 mmol) was dissolved in dichloromethane (2,5 ml), ACN (2,5mL) added and degassed. At RT samarium (127 mg; 0.84 mmol) and acetyl chloride (100 mg; 1.26 mmol) were added in sequence. The mixture was stirred for 20 h at RT, filtered over cotton and to the filtrate HCl (2N, 2 mL) was added. After neutralization with sat. $NaHCO_3$ (5 mL), the mixture was extracted with EE (3x10 mL), the combined organic layers dried over Na_2SO_4 and the solvents removed under reduced pressure. The crude product was purified via chromatography (PE/EE 70/30 + 1% NEt_3 long column).

Yield: 92 mg (41%)

Spectroscopical Data: vide 4.11

4.13. *(S)*-1,1'-(7,7',8,8',9,9',10,10'-octahydro-1H,1'H-[11,11'-binaphtho[2,3-b]azepine]-1,1'(2H,2'H,5H,5'H)-diyl)diethanone (**11**)



11

Tetraallyl compound (S) -**10** (51 mg; 0.95 mmol) was dissolved and degassed in DCM (2 mL). To this a solution of Grubbs 1st Generation Catalyst (degassed) in DCM (1 mL) was added dropwise at RT via Teflon tube. The reaction mixture was stirred for 24 h at RT, followed by stirring under air for 30 min. Thus it was filtered over celite and the filtrate concentrated *in vacuo*. The crude product was purified via chromatography (PE/EE 50/50 then pure EE).

Yield: 27 mg (59%)

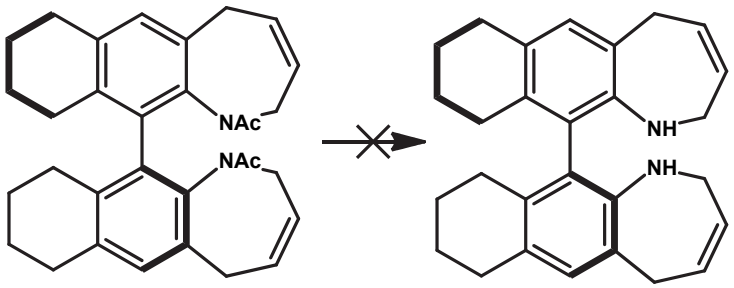
Spectroscopical Data:

^{1}H-NMR ($CDCl_3$): δ 6.93 (s, 2H); 5.83-5.74 (m, 2H); 5.40-5.32 (m, 2H); 4.93-4.83 (m, 2H); 3.66-3.54 (m, 2H); 3.24-3.14 (m, 2H); 2.91 (qd, *J* = 17.0, 8.8 Hz, 2H); 2.78 (t, *J* = 6.1 Hz, 4H); 1.93-1.83 (m, 3H); 1.80 (s, 6H); 1.79-1.70 (m, 3H); 1.69-1.53 (m, *6*H) ppm.

^{13}C-NMR ($CDCl_3$): δ 173.4 (C); 140.1 (C); 138.3 (C); 137.5 (C); 136.4 (C); 135.4 (C); 129.3 (CH); 126.3 (CH); 126.1 (CH); 43.8 (CH_2); 31.4 (CH_2); 29.8 (CH_2); 27.2 (CH_2); 22.9 (CH_2); 22.7 (CH_2); 21.8 (CH_3) ppm.

HRMS (ESI): calcd. for $C_{32}H_{36}N_2O_2Na$ 503.2674 ([M+Na]) found 503.2669 ([M+Na])

4.14. Attempts to remove the acetyl-group from (*S*)-**11**



11 **12**

- With superhydride ($LiEt_3BH$)

Diamide (*S*)-**11** (6 mg; 0.01 mmol) was dissolved in THF (0.5 mL) and degassed. Under argon $LiEt_3BH$ (1M in THF, 125 µL; 0.13 mmol) was added and the mixture stirred at RT for 24h. The reaction was quenched with 2N HCl (1.5 mL), neutralized with saturated $NaHCO_3$-solution (5 mL) and extracted with EE (3x5 mL). The combined organic layers were dried over Na_2SO_4 and solvents were removed under reduced pressure.

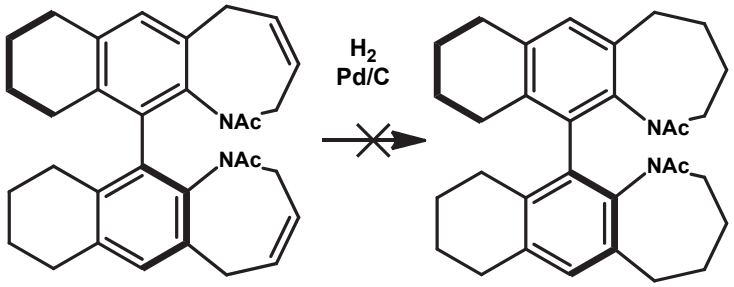
→ no reaction

- With KOH/ MeOH

To (*S*)-**11** (5 mg; 0.01 mmol) was added a mixture of KOH (1 small pellet) in MeOH (1.5 mL), then water (1.5 mL) was dropped in quickly. The inhomogeneous mixture was stirred at RT for 16 h, then extracted with ether (3x3 mL). After drying over Na_2SO_4 the solvents were evaporated.

→ no reaction

4.15. Attempted reduction of *(S)*-**11**



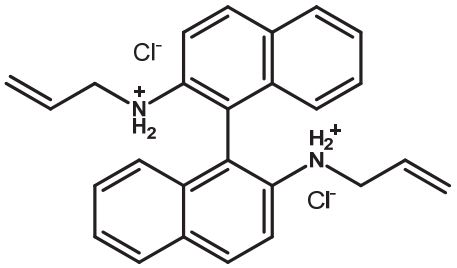
11 **13**

Diamide (*S*)-**11** (27 mg, 0.05 mmol) was dissolved in DCM (0.5 mL) and placed in a pressure tube. Then ethanol (2.5 mL) and palladium on activated charcoal (10 mg) were added and the tube sealed. After 10 times flushing with hydrogen, the tube was filled with 4 bar H_2 and vigorously stirred at RT for 18 h. The slurry was filtered over celite and the solvents removed under reduced pressure.

Yield: (decomposition)

4.16. (*S*)-*N,N'*-diallyl-[1,1'-binaphthalene]-2,2'-diamine hydrochloride (**14**) and cyclization attempts

- With 6N HCl in toluene



14

(S)-N,N'-diallyl-[1,1'-binaphthalene]-2,2'-diamine (20 mg, 0.05 mmol) was dissolved in toluene and 6N hydrochloric acid was added (0.5 mL). After stirring the mixture for 15 minutes at RT precipitation of the hydrochloride occurred and all volatiles were evaporated. The resulting crude **14** was then dissolved in THF (2 mL) and degassed. To this solution Grubbs 2nd Generation catalyst (5 mg, 0.01 mmol, in 1 mL toluene) was added via Teflon tube and the solution heated to 60 °C for 14 h. The reaction was quenched at 0 °C with 1N KOH (2 mL), filtered over celite, the filtrate evaporated and analyzed by ^{1}H-NMR.

Yield: (only starting material)

- With AcOH

(S)-N,N'-diallyl-[1,1'-binaphthalene]-2,2'-diamine (20 mg, 0.05 mmol) was dissolved in acetic acid and degassed. Under argon the Grubbs 2nd Generation Catalyst was added and the mixture stirred for 3 h at RT. The reaction was quenched at 0 °C with 1N NaOH-solution (2 mL), filtered over celite and the solvents removed under reduced pressure.

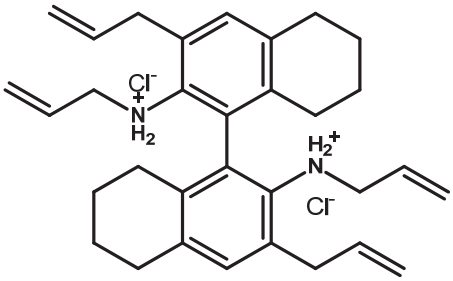
Yield: (only starting material detected by ^{1}H-NMR)

- With 1N HCl in ether

(S)-N,N'-diallyl-[1,1'-binaphthalene]-2,2'-diamine (8 mg, 0.02 mmol) was dissolved in DCM (0.5 mL) and the hydrochloric acid (1M in ether, 80 µL, 0.08 mmol) was added. The mixture was stirred for 30 min at RT (precipitation of the hydrochloride), then diluted with 2 mL DCM. To this solution Grubbs 2nd Generation catalyst (2 mg, 0.01 mmol) was added and the mixture stirred at RT for 72 h. The reaction was quenched at 0 °C with 1N KOH (2 mL), filtered over celite and the filtrate evaporated

Yield: (only starting material detected by ^{1}H-NMR)

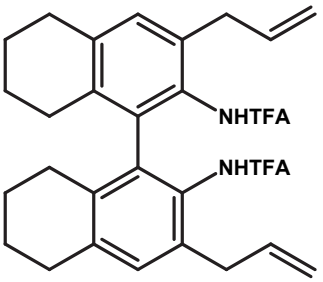
4.17. (*S)-N,N'*,3,3'-tetraallyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diaminium chloride (**15**)



15

Tetraallyl compound (S)-**8** (26 mg, 0.06 mmol) was dissolved in DCM (1.5 mL) and HCl (1M in ether, 2 mL) was added. The mixture was stirred at RT for 2 h, then evaporated. It was subsequently dissolved in dichloromethane (1.5 mL) and degassed. Likewise the Grubbs 2nd Generation Catalyst was degassed in DCM (1.5 mL) and dropped into the substrate solution at RT via Teflon tube. The reaction was stirred for 48 h at RT, followed by stirring for 1 h under air. The reaction mixture was neutralized with 1N NaOH (3 mL) and extracted with DCM (3x7 mL). Thus the combined organic layers was dried over Na_2SO_4, and then concentrated *in vacuo*. ^{1}H-NMR-Analysis showed only starting material being present.

4.18. (*S*)-*N,N'*-(3,3'-diallyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(2,2,2-trifluoroacetamide) (**16**)



16

Diallylamine (S)-**3** (25 mg, 0.07 mmol) was dissolved in THF (1 mL) and degassed. Sodium carbonate (14 mg, 0.14 mmol) and triethylamine were added and cooled to 0 °C. A solution of trifluoroacetic acid anhydride (44 mg, 0.21 mmol) degassed in THF (1 mL) was dropped into the substrate solution via Teflon tube. It was allowed to warm up to RT and stirred for 17 h. The reaction was quenched at 0 °C with sat. $NaHCO_3$-solution (5 mL) and extracted with EE (3x5 mL). The organic layers were combined and dried over Na_2SO_4. Subsequent removal of the solvents under reduced pressure gave the crude product, which was purified via MPLC (gradient from PE/EE 95/5 to 60/40).

Yield: 35 mg (88%)

Spectroscopical Data:

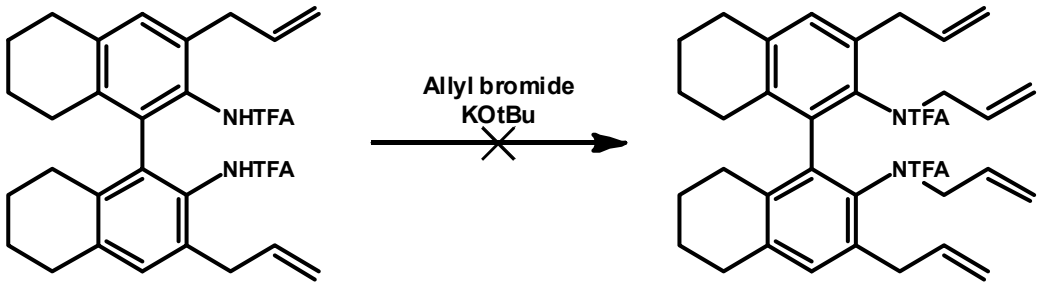
^{1}H-NMR ($CDCl_3$): δ 7.94 (bs, 2H); 7.01 (s, 2H); 5.92-5.77 (m, 2H); 5.06 (qd, *J* = 10.1, 1.5 Hz, 2H); 4.96 (qd, *J* = 17.1, 1.6 Hz, 2H); 3.34-3.17 (m, 4H); 2.84-2.69 (m, 4H); 2.20-1.93 (m, 4H); 1.77-1.55 (m, 8H) ppm.

^{13}C-NMR ($CDCl_3$): δ 176.6 (C); 139.7 (C); 136.0 (CH); 134.7 (C); 130.9 (CH); 126.9 (C); 123.7 (C); 116.2 (CH_2); 60.4 (CF_3); 36.3 (CH_2); 29.7 (CH_2); 27.2 (CH_2); 22.9 (CH_2); 22.6 (CH_2) ppm.[xv]

HRMS (ESI): calcd. for $C_{30}H_{30}F_6N_2O_2Na$ 587.2109 ([M+Na]) found 587.2130 ([M+Na]), for $C_{30}H_{30}F_6N_2O_2K$ 603.1849 ([M+K]) found 603.1863 ([M+K]).

[xv] One quaternary carbon could not be detected

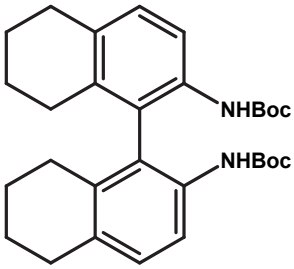
4.19. Attempt of Allylation of (*S*)-*N,N'*-(3,3'-diallyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(2,2,2-trifluoroacetamide)



16

Bistrifluoroacetate (*S*)-**16** (35 mg, 0.06 mmol) was dissolved and degassed in THF (1.5 mL), and potassium *tert*-butylate (15 mg, 0.14 mmol) and allyl bromide (22 µL, 0.25 mmol) were added successively at RT. The mixture was stirred for 18 h and further 2 equivalents of the base were added. After another 6 h, the reaction was cooled to 0 °C and quenched with sat. $NaHCO_3$ solution (5 mL). The product was extracted with EE (3x7 mL) and the combined organic layers dried over Na_2SO_4. The solvents were removed under reduced pressure and the crude material purified via MPLC (gradient from PE/EE 95/5 to 60/40). Exclusively starting material was recovered.

4.20. (*S*)-di-*tert*-butyl (3,3'-diallyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)dicarbamate (**17**)



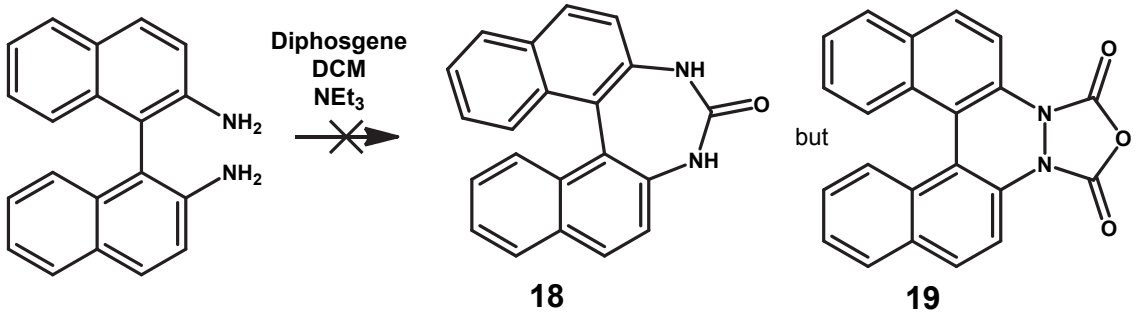
17

Diamine (*S*)-**3** (100 mg, 0.27 mmol) was suspended in ether (2 mL) and degassed, then triethylamine was added (75 µL, 0.54 mmol). Boc-anhydride (165 mg, 0.76 mmol) was dissolved in ether (2 mL) and dropped under argon via Teflon tube into the to 0 °C cooled substrate solution. After 10 min, it was allowed to warm to RT and stirred for another 4.5 h. The reaction mixture was diluted with ether and filtered over celite. The filtrate was concentrated in vacuo to give crude (*S*)-17.

During purification via chromatography (PE/EE 80/20) the slightly acidic conditions on silica gel cleaved the PG, thus only substrate could be isolated. [xvi]

[xvi] Care should be taken to avoid the use of 'acidic' solvents such as $CDCl_3$ containing traces of phosgene and HCl.

4.21. Attempt of synthesis of (*R*)-3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-one (**18**) using diphosgene



18 **19**

(R)-BINAM (100 mg; 0.35 mmol) was dissolved in dichloromethane (3 mL) and degassed. Triethylamine (106 mg, 1.05 mmol) and DMAP (~1 mg) were added successively. The reaction mixture cooled to 0 °C and diphosgene (152 mg, 0.77 mmol) was added carefully. The mixture was stirred for 2 h, quenched with water (4 mL) at 0 °C and extracted with DCM (3x7 mL). The organic layers were combined, dried over magnesium sulfate and then the filtrate concentrated *in vacuo.* The residue was re-dissolved in toluene (3 mL), filtered over celite and the solvent evaporated. The crude product was purified via chromatography (PE/EE, 95/5)

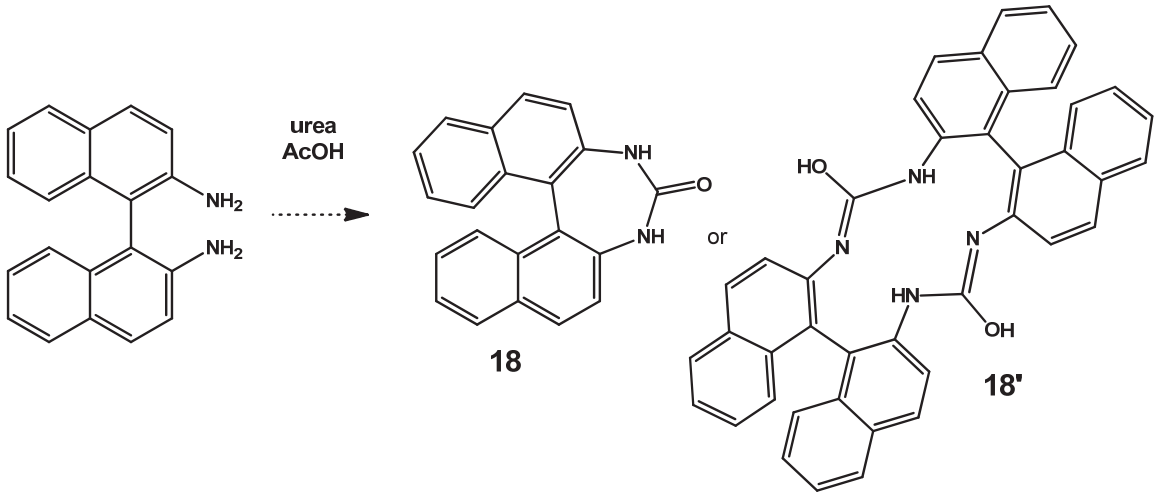
Yield: 24 mg *(R)*-**19** (19%)

Spectroscopical Data:

^{1}H-NMR ($CDCl_3$): δ 7.99 (d, *J* = 8.7 Hz, 2H); 7.93 (d, *J* = 8.2 Hz, 2H); 7.50-7.44 (m, 2H); 7.39 (d, *J* = 8.7 Hz, 2H); 7.34-7.29 (m, 2H); 7.12-7.07 (m, 2H) ppm.

MS (ESI): calcd. for $C_{22}H_{12}N_2O_3K$ 391.05 ([M+K]) found 391.0 ([M+K]), for $C_{23}H_{16}N_2O_4K$ 423.07 ([M+K+MeOH]) found 423.1 ([M+K+MeOH]).

4.22. Attempt of synthesis of (*R*)-3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-one (**18**) using Urea



(R)- BINAM (100 mg; 0.35 mmol) was dissolved in acetic acid (1.5 mL) and urea (42 mg, 0.7 mmol) added. The mixture was refluxed for 3 h, then diluted with *i*-propanol (5 mL) and allowed to cool to RT. The solvents were removed under reduced pressure and the crude mixture purified via chromatography (PE/EE 80/20 +1% NEt_3).

Yield: 41 mg (38%)

Spectroscopical Data:

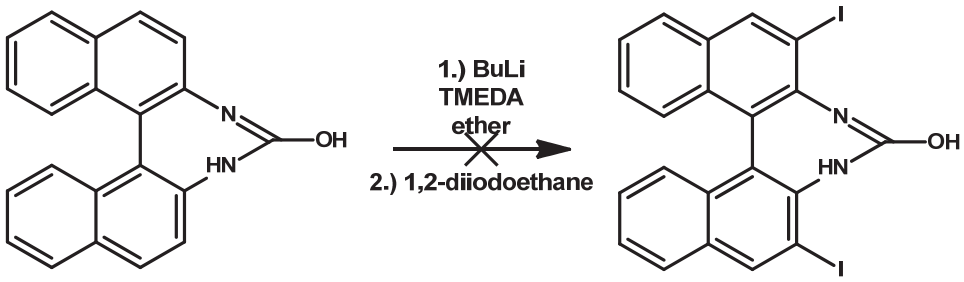
^{1}H-NMR ($CDCl_3$): δ 8.61 (bd, *J* = 9.0 Hz, 1H); 7.98 (d, *J* = 9.0 Hz, 1H); 7.89 (d, *J* = 8.1 Hz, 1H); 7.84 (d, *J* = 8.8 Hz, 1H); 7.81-7.78 (m, 1H); 7.39 (t, *J* = 7.4 Hz, 1H); 7.25 (t, *J* = 7.0 Hz, 2H); 7.18 (t, *J* = 8.3 Hz, 1H); 7.13 (d, *J* = 8.8 Hz, 1H); 7.00 (bs, 1H); 6.90 (d, *J* = 8.5 Hz, 1H) ppm.[xvii]

^{13}C-NMR ($CDCl_3$): δ 142.8 (C); 135.1 (C); 133.6 (C); 132.4 (C); 131.3 (C); 130.3 (CH); 129.2 (CH); 128.2 (CH); 128.2 (CH); 127.3 (CH); 126.8 (CH); 125.4 (CH); 125.1 (CH); 123.6 (CH); 122.7 (CH); 120.9 (CH); 118.0 (CH); ppm.[xviii]

MS (ESI): calcd. for $C_{21}H_{14}N_2OK$ 349.07 ([M+K]) found 349.2 ([M+K]).

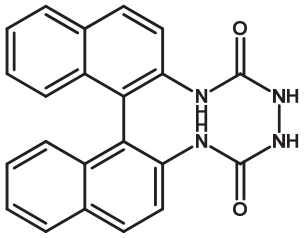
[xvii] Current spectroscopical data are not in full agreement with structure 18, a dimeric structure cannot be excluded.
[xviii] All CH signals were doubled, C only occurring once.

4.23. Attempt of synthesis of (*R*)- 2,6-diiodo-3H-dinaphtho[2,1-d:1',2'-f] [1,3]diazepin-4-ol (**20**)



18/ 18' **20**

The binaphthyl 18/18' (41 mg) was dissolved in ether (1 mL) and degassed. To this was dropped a solution of BuLi (1.6M, 0.4 mL, 0.64 mmol) and TMEDA (97 µL; 0.64 mmol) in ether (1 mL) at 0 °C. The solution was stirred for 3 h at RT, then cooled to -78 °C and 1,2-diiodoethane (180 mg; 0.64 mmol) was added. The reaction was allowed to warm to RT overnight, then quenched with sat. $NaHCO_3$- (5 mL) and 10%- $NaHSO_3$-solution (10 mL). Then it was extracted with EE (4x5 mL), the combined organic layers dried over Na_2SO_4 and the solvents evaporated. The crude product was purified via chromatography (PE/EE 50/50).



product 20b

Yield: 65% starting material and
9 mg of 20b

Spectroscopical Data (product 20b):

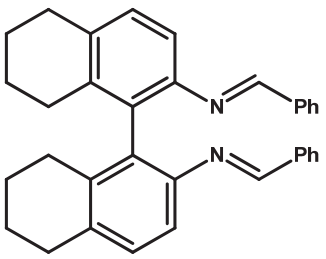
^{1}H-NMR ($CDCl_3$): δ 8.34 (d, *J* = 9.0 Hz, 2H); 8.03 (d, *J* = 9.0 Hz, 2H); 7.93 (d, *J* = 8.1 Hz, 2H); 7.44 (t, *J* = 7.5 Hz, 2H); 7.26 (t, *J* = 7.7 Hz, 2H); 7.01 (d, *J* = 8.5 Hz, 2H); 6.88 (bs, 2H) ppm.[xix]

^{13}C-NMR ($CDCl_3$): δ 169.3 (C); 134.9 (C); 132.4 (C); 131.4 (C); 129.8 (CH); 128.3 (CH); 127.2 (CH); 125.7 (CH); 125.3 (CH); 122.5 (CH) ppm.[xx]

HRMS (ESI): calcd. for $C_{22}H_{16}N_4O_2Na$ 391.1171 ([M+Na]) found 391.1431 ([M+Na]).

[xix] 2H from NH could not be detected.
[xx] One quaternary carbon could not be detected.

4.24. *(S)-N,N'*-dibenzylidene-[1,1'-binaphthalene]-2,2'-diamine (**21**)



21

Diamine (S)-**1** (150 mg; 0.51 mmol) was dissolved in DCM (1 mL) and ether (3 mL) and degassed. To the solution magnesium sulfate (1.24 g, 10.3 mmol) and molecular sieve (4Å, 700 mg) were added, and benzaldehyde (156µL, 1.54 mmol) dropped in at RT. The mixture was refluxed for 48 h, cooled to RT and the crude product extracted with EE (3x10 mL). Removal of solvents left the crude product which was not further purified due to its expected sensitivity.

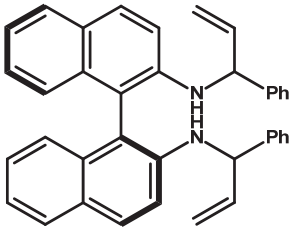
Yield: 239 mg (quantitative)

Spectroscopical Data:

^{1}H-NMR ($CDCl_3$): δ 8.14 (s, 2H); 7.51-7.46 (m, 4H); 7.36-7.26 (m, 6H); 7.01 (d, *J* = 8.0 Hz, 2H); 6.74 (d, *J* = 8.0 Hz, 2H); 2.80-2.74 (m, 4H); 2.45-2.16 (d, 4H); 1.79-1.62 (m, 8H) ppm.

HRMS (ESI): calcd. for $C_{34}H_{32}N_2Na$ 491.2463 ([M+Na]) found 491.2465 ([M+Na]), for $C_{34}H_{32}N_2K$ 507.2203 ([M+K]) found 507.2204 ([M+K]).

4.25. *(S)-N,N'*-bis(1-phenylallyl)-[1,1'-binaphthalene]-2,2'-diamine (**22**)

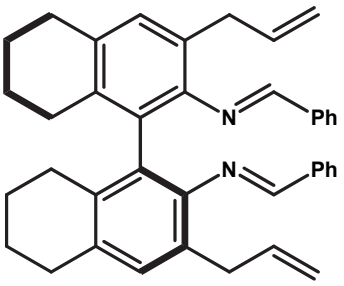


22

Imine (S)-**21** (239 mg, 0.51 mmol) was dissolved in THF (2 mL), degassed and cooled to -78°C. Vinyl magnesium bromide solution (1M in THF, 1.53 mL, 1.53 mmol) was added slowly and the reaction allowed to warm up to -20°C within 5 h. The reaction was stirred at -20 °C for 30 h, quenched with sat. ammonium chloride solution (5 mL), extracted with EE (3x10 mL). The comined organic layers were dried over $NaSO_4$, the solvents evaporated and the crude product was purified via chromatography (PE/EE 95/5).[36]

Yield: Although TLC, run before work-up, indicated the absence of starting material, no product could be isolated from the chromatography fractions. Exclusively fractions containing benzaldehyde and diamine **1** were obtained.

4.26. *(S)-N,N'*-3,3'-diallyl-*N,N'*-dibenzylidene-[1,1'-binaphthalene]-2,2'-diamine (**25**)



25

Diamine (*S*)-**3** (200 mg; 0.54 mmol) was dissolved in ether (3 mL) and degassed. Dry $MgSO_4$ (1.3 g; 10 mmol) and molecular sieve (4A, 500 mg) were added in sequence under argon and finally benzaldehyde (171 mg; 1.61 mmol) dropped in. The mixture was refluxed for 48 h, cooled to RT and extracted with EE (3x10 mL). The combined organic layers were concentrated to give crude **25**. Due to the expected sensitivity of the imine, no further purification was performed.

Yield: (almost) quantitative (only a weak spot (PhCHO) was detected on TLC, EE/PE, 15/85)

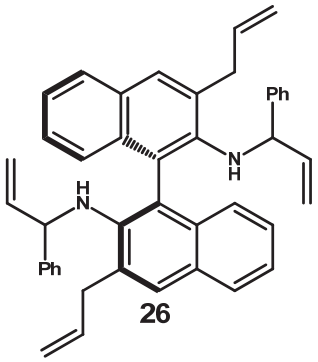
Spectroscopical Data:

^{1}H-NMR ($CDCl_3$): δ 7.65-7.59 (m, 2H); 7.49-7.44 (m, 2H); 7.38-7.26 (m, 6H); 6.94 (s, 1H); 6.59 (s, 1H); 6.00-5.87 (m, 1H); 5.87-5.73 (m, 1H): 5.0-4.7 (bm, 4H); 3.22-3.17 (m, 2H); 3.25-3.09 (m, 2H); 2.77 (m, 2H); 2.73-2.45 (m, 4H); 2.36-2.09 (m, 4H); 1.78-1.55 (bm, 8H) ppm.[xxi]

^{13}C-NMR ($CDCl_3$): δ 161.0 (CH); 151.2 (C); 132.8 (C); 130.6 (CH); 129.3 (CH); 129.0 (CH); 128.4 (CH); 128.3 (CH); 128.1 (CH); 114.9 (CH_2); 35.9 (CH_2); 29.6 (CH_2); 27.8 (CH_2); 23.4 (CH_2); 23.2 (CH_2) ppm.[xxii]

[xxi] Due to dynamic phenomena, full assignment of H-shifts cannot be given.
[xxii] 4 quaternary carbon could not be detected.

4.27. *(S)*-3,3'-diallyl-*N,N'*-bis(1-phenylallyl)-[1,1'-binaphthalene]-2,2'-diamine (**26**)

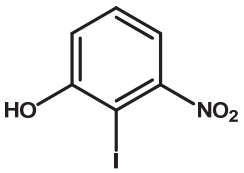


26

Crude Diamine (*S*)-**25** (220 mg, 0.4 mmol) was dissolved in THF (2 mL) and degassed. The solution was cooled to -78 °C and vinyl magnesium bromide (1M in THF, 1.2 mL, 1.2 mmol) added via Teflon tube. The reaction was allowed to warm to -20 °C within 2 h, and stirring was continued for 28 h at the same temperature. The reaction was quenched with water, the product extracted with EE (3x10 mL) and dried over Na_2SO_4. After removal of solvents the residue was subjected to chromatography (PE/EE 95/5) affording exclusively precursor **3** in high yield.

Yield: (Diamine **3**)

4.28. 2-iodo-3-nitrophenol (**30**)



30

After dissolving 3-nitrophenol (**9**) (13.91 g; 100 mmol) in water (150 mL), sodium hydroxide (3 g, 75 mmol) was added. Mmercury(II)acetate (31.87 g, 100 mmol) was dissolved in water (150 mL) and acetic acid (3 mL) added. This solution was dropped slowly to the substrate solution, after complete addition the mixture was heated to 100 °C and refluxed for 1 h. The reaction was allowed to cool to RT and the mercury-intermediate isolated by suction filtration. The yellow crude solid was dried under air and directly used for the next step.

The yellow residue was suspended in 10% aqueous KI-solution (200 mL), and to this a 20% aqueous KI_3-solution (200 mL) was added dropwise. After the complete addition, the mixture was stirred for 3 h. The product was extracted with DCM (4 x 200 mL) and the combined organic layers were washed with saturated $NaHSO_3$-solution (100 mL) and water (100 mL). The combined organic extracts were dried over Na_2SO_4 and the crude product was obtained by removal of the solvents. The crude **30** was purified by recrystallization from water (or DCM).[51]

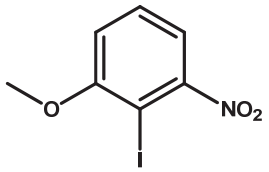
Yield: 13.88 g (52%)

yellow needles

Spectroscopical Data: (matched literature)

^{1}H-NMR ($CDCl_3$): δ 7.42 (dd, J = 8.0, 1.6 Hz, 1H); 7.35 (t, J = 8.1 Hz, 1H); 7.21 (dd, J = 8.1, 1.6 Hz, 1H); 5.94 (bs, 1H) ppm.

4.29. 2-iodo-1-methoxy-3-nitrobenzene (**31**)



31

The 2-iodo-3-nitrophenol **30** (13.88 g; 52 mmol) was dissolved in acetone p.a. (100 mL) and potassium carbonate was added (14.37 g; 104 mmol). At RT methyliodide (11.07 g; 78 mmol) was dropped in within 30 min, and the mixture stirred for 6 h. Upon the complete consumption of the starting material, the solvent was evaporated and the residue extracted with EE (100 mL). The EE-extract was concentrated *in vacuo* and the crude product purified by chromatography (PE/EE 70/30). [51]

Yield: 12.30 g + 1.77g from less pure fraction (in total 97%)

bright yellow crystals

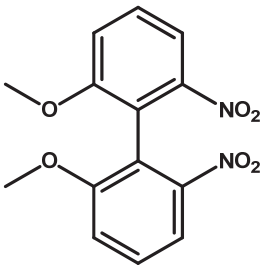
Spectroscopical Data: (matched literature)

^{1}H-NMR ($CDCl_3$): δ 7.40 (t, *J* = 8.2 Hz, 1H); 7.27 (dd, *J* = 8.2, 1.3 Hz, 1H); 6.96 (dd, *J* = 8.2, 1.3 Hz, 1H); 3.94 (s, 3H) ppm.

^{13}C-NMR ($CDCl_3$): δ 130.0 (CH); 116.8 (CH); 113.4 (CH); 57.2 (C) ppm[xxiii].

[xxiii] 2 quaternary carbon were not detectable

4.30. 2,2'-dimethoxy-6,6'-dinitro-1,1'-biphenyl (**32**)



32

After degassing **31** (9.1 g; 33 mmol) in DMF (60 mL) activated copper[64] (6.75 g; 106 mmol) was added and the heterogeneous mixture heated to 150 °C. After 3 h at this temperature, another portion of activated copper (6.75 g; 106 mmol) was added, and heating continued for further 3 h. The mixture was allowed to cool to RT, and poured into water (250 mL). The residue was repeatedly extracted with EE (in total 700 mL) and the combined organic layers were dried over Na_2SO_4. The solvents were removed to give crude **32** in sufficient purity for the next reaction step. [51]

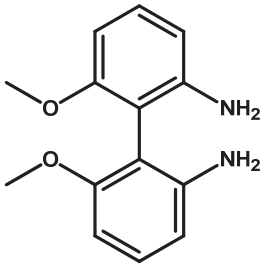
Yield: 3.357 g (67%)

green-yellow crystals

Spectroscopical Data: (matched literature)

^{1}H-NMR ($CDCl_3$): δ 7.72 (dd, *J* = 8.3, 1.0 Hz, 2H); 7.47 (t, *J* = 8.3, 2H); 7.16 (dd, *J* = 8.3, 1.0 Hz, 2H); 3.69 (s, 6H) ppm.

4.31. 2,2'-dimethoxy-6,6'-diamino-1,1'-biphenyl (**33**)



33

To a suspension of **32** (3.55 g; 11.7 mmol) in methanol p.a. (50 mL), was successively added activated carbon (1 g) and ferric(III)chloride hexahydrate (60 mg, 0.22 mmol). The mixture was refluxed for 30 min, then cooled to RT and hydrazine hydrate (4.67 g; 935 mmol) dropped in slowly. The mixture was refluxed for further 5 h, cooled to RT and filtered over celite. The filtrate was concentrated in vacuo and the resulting residue diluted with water (35 mL) and extracted with ether (3x 50 mL). The organic layers were combined and dried over Na_2SO_4. After removal of the solvents the crude product was purified via MPLC (gradient PE/EE 80/20 to pure EE). [51]

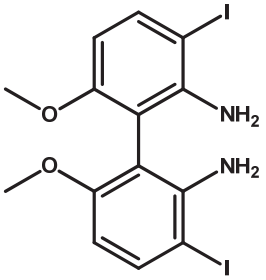
Yield: 2.311 g (81%)

white crystals

Spectroscopical Data: (matched literature)

^{1}H-NMR ($CDCl_3$): δ 7.12 (t, J = 8.1 Hz, 2H); 6.44 (dd, J = 8.1, 0.9 Hz, 2H); 6.41 (dd, J = 8.3, 0.8 Hz, 2H); 3.69 (s, 6H); 3.55 (b, 4H) ppm.

4.32. 3,3'-diiodo-6,6'-dimethoxy-[1,1'-biphenyl]-2,2'-diamine (**34**)



34

To a degassed solution of **33** (360 mg, 1.47 mmol) in dichloromethane (10 mL), calcium carbonate (441 mg, 4.41 mmol) and methanol (2.87 mL) were added. The mixture was cooled to -30 °C and a solution of the benzyltrimethylammonium dichloroiodate (1.024 g; 2.94 mmol) in DCM (15 mL) dropped in via Teflon canula. After 3 h at -30 °C the mixture was allowed to warm to RT and stirred at this temperature for 30 min. The reaction was quenched with $NaHCO_3$ (20 mL) and treated with $NaHSO_3$ (40 mL) to decompose excess reagent. The product was extracted with ether (3x20 mL) and the combined organic layers were dried over Na_2SO_4. After removal of the solvents by evaporation, the crude product was purified via chromatography (PE/EE 95/5).

Yield: 496 mg (68%)

colorless needles , mp: 132.5- 134.5 °C

Spectroscopical Data:

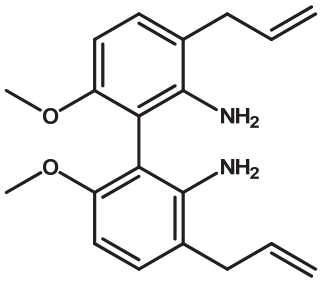
^{1}H-NMR ($CDCl_3$): δ 7.60 (d, *J* = 8.8 Hz, 2H); 6.23 (d, *J* = 8.8 Hz, 2H); 3.95 (bs, 4H); 3.67 (s, 6H) ppm.

^{13}C-NMR ($CDCl_3$): δ 158.7 (C); 145.58(C); 138.9 (CH); 103.6 (CH); 74.5 (C); 56.1 (CH_3) ppm.[xxiv]

HRMS (ESI): calcd. for $C_{14}H_{14}N_2O_2I_2H$ 496.9223 ([M+H]) found 496.9216 ([M+H]).

[xxiv] One quaternary carbon could not be observed

4.33. 3,3'-diallyl-6,6'-dimethoxy-[1,1'-biphenyl]-2,2'-diamine (**35**)



35

To a degassed solution of **34** (680 mg; 1.37 mmol) in toluene (10 mL) were added palladium tetrakistriphenylphosphine (158 mg, 0.14 mmol) and allyl tributylstannane (1.59 g; 4.8 mmol). The resulting mixture was heated to 100 °C and stirred at this temperature for 22 h. The mixture was cooled to RT and subsequently quenched with water. The product was extracted with ether (3x10 mL) and the combined organic layers were dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded crude **35**, which was further purified by MPLC (PE/EE 90/10).

Yield: 322 mg (70%)

bright yellow oil

Spectroscopical Data:

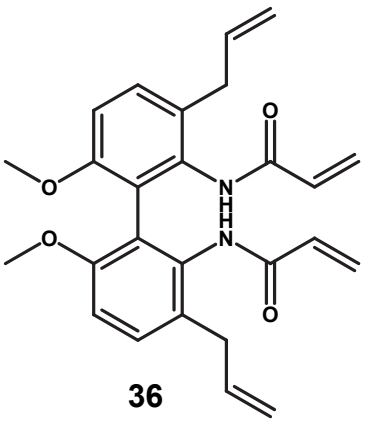
^{1}H-NMR ($CDCl_3$): δ 7.01 (d, *J* = 8.3 Hz, 2H); 6.40 (d, *J* = 8.3 Hz, 2H); 6.03-5.90 (m, 2H); 5.10 (m, 2H); 5.06 (m, 2H); 3.66 (s, 6H); 3.56 (bs, 4H), 3.28 (m, 4H) ppm.

^{13}C-NMR ($CDCl_3$): 136.9 (CH); 130.2 (CH); 117.5 (C); 116.3 (CH_2); 110.2 (C); 101.8 (CH); 56.3 (CH_3); 36.7 (CH_2) ppm.[xxv]

HRMS (ESI): calcd. for $C_{20}H_{24}O_2N_2H$ 325.1916 ([M+H]) found 325.1921 ([M+H]).

[xxv] 2 quaternary carbon could not be detected.

4.34. *N,N'*-(3,3'-diallyl-6,6'-dimethoxy-[1,1'-biphenyl]-2,2'-diyl)diacrylamide (**36**)



36

A solution of **35** (310 mg, 0.96 mmol) in acetonitrile (3.5 mL) was degassed; then samarium (301 mg; 2 mmol) and acryloyl chloride (260 mg; 2.87 mmol) were added successively. The mixture was stirred at RT for 18 h, quenched with 2N hydrochloric acid (3 mL) and neutralized with saturated $NaHCO_3$. The product was extracted with EE (3x10 mL) and the combined organic layers dried over Na_2SO_4. The solvents were removed under reduced pressure and the crude product purified via MPLC (gradient PE/EE 5/95 to pure EE).

Yield: 151 mg (37%)

yellow oil

Spectroscopical Data:

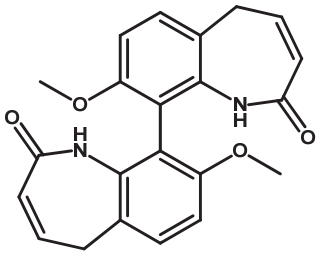
^{1}H-NMR ($CDCl_3$): δ 7.19 (d, *J* = 8.5 Hz, 2H); 6.84 (d, *J* = 8.5 Hz, 2H); 6.00-5.84(m, 6H); 5.50 (dm, 3.2 Hz, 2H); 5.00 (m, 2H); 4.93 (m, 2H); 3.62 (s, 6H); 3.40-3.25 (m, 4H); 1.83 (m, 2H) ppm.

^{13}C-NMR ($CDCl_3$): δ 137.2 (CH); 130.9 (CH); 130.0 (CH); 126.4 (CH_2); 116.3 (C); 115.3 (CH_2); 110.4 (CH); 109.2 (C); 56.1 (CH_3); 36.0 (CH_2) ppm.[xxvi]

HRMS (ESI): calcd. for $C_{26}H_{28}O_4N_2Na$ 455.1947 ([M+Na]) found 455.1949 ([M+Na]).

[xxvi] 3 quaternary carbon could not be detected.

4.35. 8,8'-dimethoxy-1H,1'H-[9,9'-bibenzo[b]azepine]-2,2'(5H,5'H)-dione (**37**)



37

Biphenyl **36** (151 mg, 0.35 mmol) was dissolved in dichloromethane (1 mL) and degassed. To this was added via syringe pump (400 µl/h) a solution of *Grubbs 2nd Generation Catalyst* (30 mg; 0.035 mmol) in DCM (2.5 mL). After complete addition of the catalyst, the reaction was stirred at RT for another 12 h. Thus it was filtered over celite and the filtrate evaporated. The crude product was purified via chromatography (PE/EE 50/50 to pure EE +1% EtOH).

Yield: 35 mg (27 %)

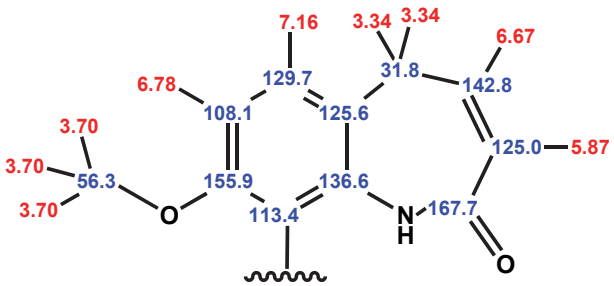
dark grey semi-solid material

Spectroscopical Data:

^{1}H-NMR ($CDCl_3$): δ 7.17 (bs, 2H); 7.15 (d, *J* = 8.6 Hz, 2H); 6.77 (d, *J* = 8.6 Hz, 2H); 6.70-6.61 (m, 2H); 5.86 (d, *J* = 2.2 Hz, 2H); 3.69 (s, 6H); 3.39-3.27 (m, 4H) ppm.

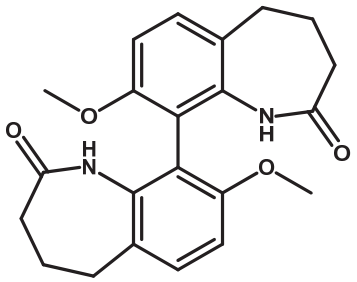
^{13}C-NMR ($CDCl_3$): δ 167.7 (C); 155.9 (C); 142.5 (CH); 136.5 (C); 129.5 (CH); 125.5 (C); 124.8 (CH); 113.5 (C); 107.9 (CH); 56.1 (CH_3); 31.8 (CH_2) ppm.

HRMS (ESI): calcd. for $C_{22}H_{20}O_4N_2Na$ 399.1321 ([M+Na]) found 399.1317 ([M+Na]), for $C_{22}H_{20}O_4N_2K$ 415.1060 ([M+K]) found 415.1060 ([M+K]).



Structure assignment by 2D-NMR

4.36. 8,8'-dimethoxy-4,4',5,5'-tetrahydro-1H,1'H-[9,9'-bibenzo[b]azepine]-2,2'(3H,3'H)-dione (**38**)



38

A solution of **37** (20 mg, 0.053 mmol) in dichloromethane (0.5 mL) was placed into a pressure tube and diluted with ethanol (2 mL). To this palladium on activated charcoal (10 mg) was added and the tube sealed. The system was flushed with hydrogen, then filled with 4 bar H_2 and stirred vigorously for 18 h. The mixture was filtered over celite, the filtrate evaporated and the crude product purified via chromatography (PE/EE 50/50 to EE +1% EtOH).

Yield: 19 mg (95 %)

grey semi-solid

Spectroscopical Data:

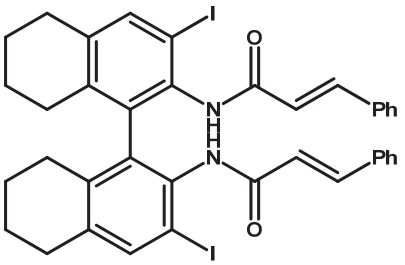
^{1}H-NMR ($CDCl_3$): δ 7.20 (d, *J* = 8.5 Hz, 2H); 6.77 (d, *J* = 8.5 Hz, 2H); 6.69 (b, 2H); 3.71 (s, 6H); 2.83-2.70 (m, 4H); 2.38-2.10 (m, 8H) ppm.

^{13}C-NMR ($CDCl_3$): δ 174.87 (C); 155.9 (C); 138.0 (C); 130.3 (CH); 127.6 (C); 108.3 (CH); 55.9 (CH_3); 32.4 (CH_2); 29.8 (CH_2); 28.4 (CH_2) ppm.[xxvii]

HRMS (ESI): calcd. for $C_{22}H_{24}O_4N_2Na$ 403.1634 ([M+Na]) found 403.1641 ([M+Na]).

[xxvii] One quaternary carbon could not be detected.

4.37. *N,N'*-(3,3'-diiodo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(3-phenylacrylamide) (**39**)



39

A solution of (*S*)-**2** (100 mg, 0.18 mmol) in EE p.a. (1.5 mL) was degassed and cooled to 0 °C. To this TEA (55 µL, 0.39 mmol) and cinnamoyl chloride (65 mg, 0.39 mmol) were added. After 10 min at 0 °C the mixture was allowed to warm up to RT and stirred there for 6 h. Another equivalent of base and reagent were added and the mixture was heated to 45 °C and stirred for 5 h. Subsequently it was cooled to RT and quenched with water (2 mL). The product was extracted with ethyl acetate (3x7 mL) and the combined organic layers dried over $MgSO_4$. The solvents were evaporated and the crude product purified via chromatography (DCM).

Yield: 100 mg (70 %)

bright yellow oil

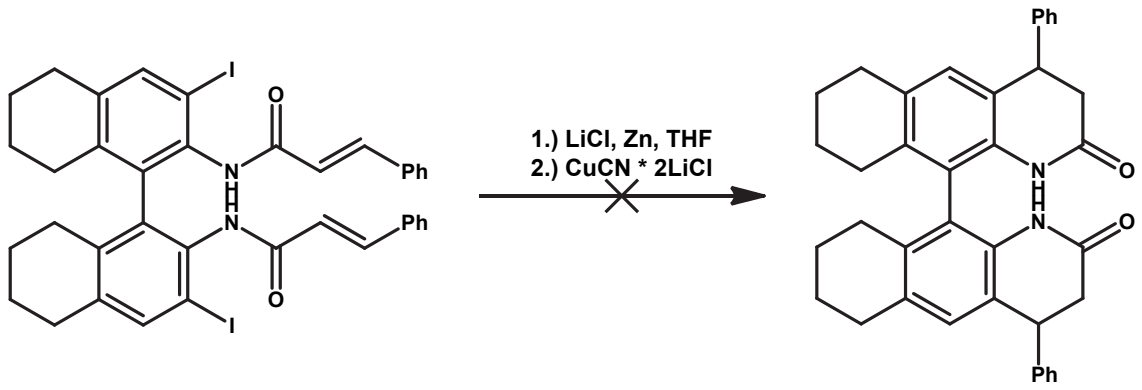
Spectroscopical Data:

^{1}H-NMR ($CDCl_3$): δ 7.62 (s, 2H); 7.55 (bd, *J* = 16.1 Hz, 2H); 7.51-7.45 (m, 4H); 7.38-7.29 (m, 6H); 6.37 (d, *J* = 16.1 Hz, 2H); 2.81-2.63 (m, 4H); 2.55 (bm, 2H); 1.98 (bm, 2H); 1.76-1.54 (m, 8H) ppm.

^{13}C-NMR ($CDCl_3$): decomposition before analysis

HRMS (ESI): calcd. for $C_{38}H_{35}O_2N_2I_2$ 805.0788 ([M]) found 805.0779 ([M]).

4.38. Attempt of copper mediated cyclisation of (*S*)-**39**

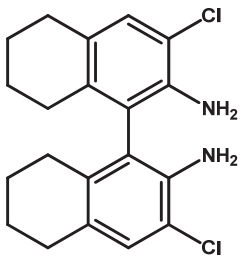


39 **40**

A solution of **39** (100 mg, 0.16 mmol) in THF (1.5 mL) was degassed in separate Schlenk tube. Lithium chloride (7 mg, 0.16 mmol) was dried at 150 °C at 1 mbar for 10 min, then zinc dust was added and dried likewise. The solids were allowed to cool to RT, then THF (1 mL) and 1,2-dibromoethane (1 µL) was added and heated for 1 min to 65 °C. At RT TMS-Cl (0.25 mg, 0.023 mmol (diluted with THF to 0.23mM)) in THF was added and the inhomogeneous mixture stirred for 15 min. To this the substrate solution was added and stirred at RT for 24 h. Subsequently a solution of LiCl (10 mg, 0.24 mmol) and CuCN (11 mg, 0.12 mmol) in THF (1 mL) was added and the mixture stirred for another 12 h. Thus the reaction was quenched with water (4 mL) and extracted with DCM (4x5 mL). The combined organic layers were dried over Na_2SO_4 and the solvents evaporated.[56]

^{1}H-NMR of the residue indicated only the presence of starting material.

4.39. (*S*)-3,3'-dichloro-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (**41**)



41

A solution of **1** (90 mg, 0.37 mmol) in dichloromethane (2 mL) was degassed and cooled to 0 °C. *N*-chlorosuccinimide (99 mg, 0.74 mmol) was added and the mixture stirred for 1 min. It was quenched with sat. $NaHCO_3$-solution (10 mL) and 10%-Na_2SO_3-solution (10 mL) and extracted with EE (3x20 mL). The organic layers were combined and dried over Na_2SO_4, then evaporated. The crude product was purified via MPLC (gradient PE/EE 98/2 to PE/EE 60/40).

Yield: 10 mg (8 %) (*S*)-**41**

rest poly chlorinated substances

yellow oil

Spectroscopical Data:

^{1}H-NMR ($CDCl_3$): δ 7.02 (s, 2H), δ 3.66 (bs, 4H), due to dynamic phenomena only multiplets in the following range can be given: 2.73-2.62 (m, ~4H); 2.27-2.03 (m, ~4H); 1.77-1.57 (m, ~8H)

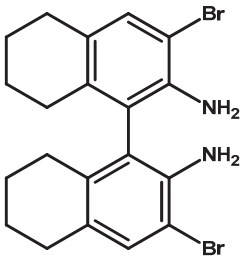
^{13}C-NMR ($CDCl_3$): δ 129.1 (CH), δ 29.1 (CH_2), δ 26.7 (CH_2), δ 23.2 (CH_2), δ 23.0 (CH_2) ppm.[xxviii]

HRMS (ESI): calcd. for $C_{20}H_{23}Cl_2N_2$ 361.1238 ([M+H]) found 361.1228 ([M+H]), for $C_{20}H_{22}Cl_2N_2Na$ 383.1058 ([M+Na]) found 383.2248 ([M+Na]) .

[xxviii] Quaternary carbons could not be detected.

4.40. (*S*)-3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (**42**)

A solution of **1** (70 mg, 0.24 mmol) in dichloromethane (1.5 mL) was degassed and cooled to 0 °C. N-bromosuccinimide was (85 mg, 0.48 mmol) was added and the mixture stirred for 1 min. Then it was quenched with sat. $NaHCO_3$-solution (5 mL), treated with 10% Na_2SO_3-solution (10 mL) and extracted with EE (3x5 mL). The organic layers were combined and dried over Na_2SO_4, then evaporated. The crude product was not further purified.



42

Yield: quantitative 107 mg (99%)

orange oil

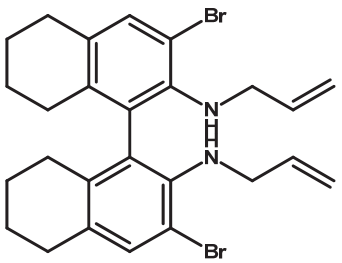
Spectroscopical Data:

^{1}H-NMR ($CDCl_3$): δ 7.19 (s, 2H); 3.70 (bs, 4H); 2.71-2.64 (m, 4H); 2.23-2.03 (m, 4H); 1.73-1.58 (m, 8H) ppm.

^{13}C-NMR ($CDCl_3$): δ 139.2 (C); 135.7 (C); 132.3 (CH); 129.0 (C); 122.4 (C); 107.0 (C); 29.0 (CH_2); 26.7 (CH_2); 23.1 (CH_2); 23.0 (CH_2) ppm.

HRMS (ESI): calcd. for $C_{20}H_{22}Br_2N_2Na$ 473.0027 ([M+Na]) found 473.0032 ([M+Na]).

4.41. (*S*)-*N,N'*-diallyl-3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (**43**)



43

After dissolving (S)-**42** (107 mg, 0.24 mmol) in THF (2 mL), the solution was degassed and cooled to -78 °C. To this LDA (1.8M in THF, 294 µL, 0.53 mmol) was added and the mixture was stirred for 30 min. Then allyl bromide (83 µL, 0.96 mmol) was added, the solution allowed to reach RT and stirring continued for 12 h. It was subsequently quenched with saturated $NaHCO_3$ solution (5 mL) and extracted with EE (3x5 mL). The combined organic layers were dried over Na_2SO_4, the solvents removed and the crude product purified via MPLC (gradient PE/EE 98/2 to 50/50).

Yield: 91 mg (71%)

orange oil

Spectroscopical Data:

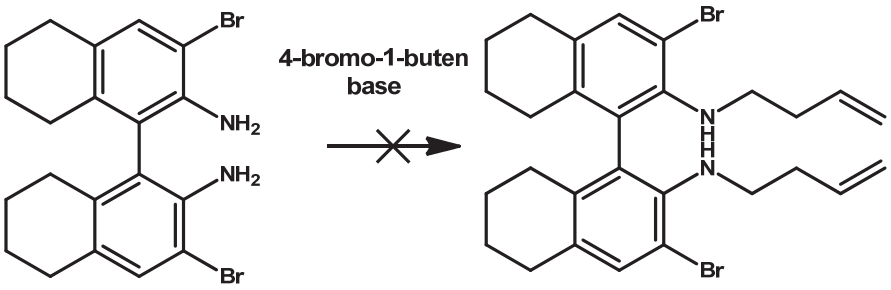
^{1}H-NMR ($CDCl_3$): δ 7.27 (s, 2H); 5.80-5.65 (m, 2H); 5.02 (m, 2H); 4.96 (m, 2H); 3.55-3.40 (bm, 4H); 3.25 (bs, 2H); 2.74-2.66 (m, 4H); 2.27-1.91 (m, 4H); 1.73-1.55 (bm, 8H) ppm.

^{13}C-NMR ($CDCl_3$): δ 144.3 (C); 136.2 (CH); 136.0 (C); 133.7 (CH); 129.2 (C); 115.9 (CH_2); 112.8 (C); 50.5 (CH_2); 29.1 (CH_2); 27.5 (CH_2); 23.0 (CH_2); 22.8 (CH_2) ppm.[xxix]

HRMS (ESI): calcd. for $C_{26}H_{30}Br_2N_2Na$ 553.0653 ([M+Na]) found 553.0632 ([M+Na], for $C_{26}H_{30}Br_2N_2K$ 569.0397 ([M+K]) found 569.0392 ([M+K]).

[xxix] One quaternary carbon could not be detected.

4.42. Attempt of butenylation of (*S*)-**42**



42 **44**

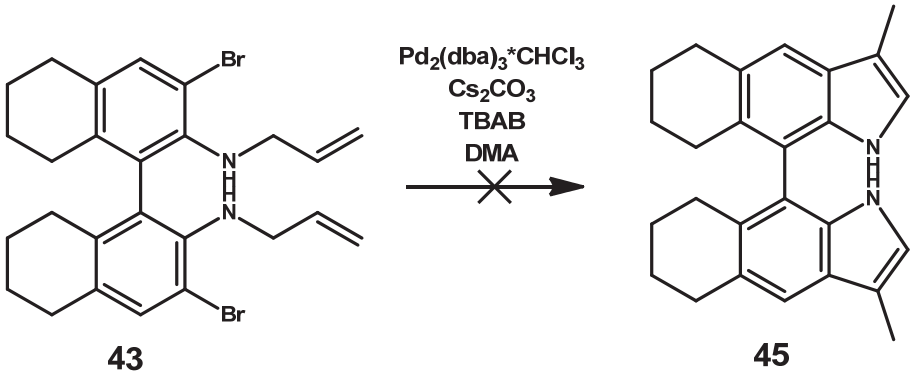
- with 4-bromo-1-buten / LDA / THF

A solution of (*S*)-**42** (100 mg, 0.22 mmol) in THF (2 mL) was degassed and cooled to -78 °C. To this LDA (1.8M in THF, 269 µL, 0.484 mmol) was added and the solution stirred for 2 h. 4-Bromo-1-butene (67 µL, 0.66 mmol) was added subsequently and the reaction allowed to come to RT and stirred for 12 h. The reaction was quenched with sat. $NaHCO_3$-solution (10 mL) and extracted with EE (3x5 mL). The combined organic layers were dried over Na_2SO_4 and the solvents evaporated. The crude product was subjected to chromatography (PE/EE 95/5), but only starting material recovered.

- With 4-bromo-1-buten / LDA / THF

To a degassed solution of (S)-**42** (100 mg, 0.22 mmol) in toluene (2 mL) were added Cs_2CO_3 (287 mg; 0.88 mmol) and KI (73 mg, 0.44 mmol). To this 4-bromo-1-butene (67 µL, 0.66 mmol) was added and the slurry heated to 80 °C. After 24 h reflux, the reaction was quenched at RT with sat. $NaHCO_3$-solution (10 mL) and extracted with EE (3x5 mL). The combined organic layers were dried over Na_2SO_4 and the solvents evaporated. The crude product mixture chromatographed (PE/EE, 95/5) yielding only starting material.

4.43. Attempted Heck-reaction to cyclize (*S*)- **43**

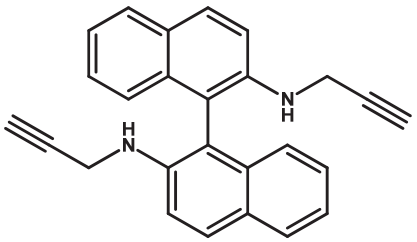


43 **45**

Dibromide (S)-**43** (91 mg, 0.17 mmol) was dissolved in DMA and degassed. To this solution caesium carbonate (168 mg, 0.52 mmol), TBAB (111 mg, 0.34 mmol) and $Pd_2(dba)_3$*$CHCl_3$ (9 mg, 0.01 mmol) were added successively and the reaction mixture heated to 100 °C. Thus it was stirred for 36 h, quenched at RT with saturated ammonium chloride solution (5 mL) and extracted with DCM (3x8 mL). The combined organic layers were dried over K_2CO_3 and the solvents removed under reduced pressure.

NMR analysis indicated only presence of unreacted substrate.

4.44. Propargylation of *(S)*-BINAM



47

(S)-BINAM (100 mg, 0.35 mmol) was dissolved in acetone (1.5 mL) and degassed. To this solution potassium carbonate (145 mg, 1.05 mmol) and propargyl bromide (104 mg, 0.88 mmol) were added successively and the mixture refluxed. After 8 h the reaction was quenched with sat. $NaHCO_3$ (5 mL) and the product was extracted with EE (3x5 mL). The combined organic layers were dried over Na_2SO_4, the solvents evaporated and the crude mixture purified via chromatography (PE/EE 90/10).[58]

Yield: 26 mg (21%)

yellow oil

Spectroscopical Data:

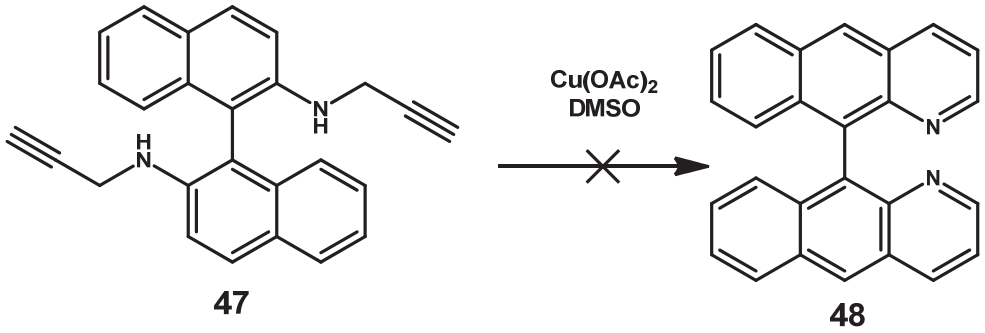
^{1}H-NMR ($CDCl_3$): δ 7.94 (d, *J* = 8.3 Hz, 2H); 7.80 (d, *J* = 7.6 Hz, 2H); 7.35 (d, *J* = 9.1 Hz, 2H); 7.22 (ddd, *J* = 9.3, 8.1, 1.4 Hz, 2H); 7.15 (ddd, *J* = 8.3, 6.7, 1.4 Hz, 2H); 6.98 (bd, *J* = 8.4 Hz, 2H); 3.96 (dd, *J* = 18.0, 2.4 Hz, 2H); 3.93 (bs, 2H); 3.89 (dd, *J* = 18.0, 2.4 Hz, 2H); 2.06 (m, 2H) ppm.

^{13}C-NMR ($CDCl_3$): δ 133.7 (C); 129.8 (CH); 128.4 (C); 128.1 (CH); 126.8 (CH); 124.1 (CH); 122.7 (CH); 116.4 (C); 114.5 (CH); 70.9 (CH); 33.7 (CH_2) ppm.[xxx]

HRMS (ESI): calcd. for $C_{26}H_{20}N_2Na$ 383.1524 ([M+Na]) found 383.1518 ([M+Na]).

[xxx] 2 quaternary carbon could not be observed

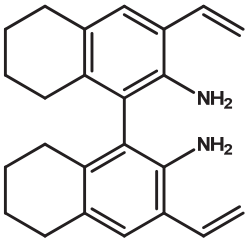
4.45. Attempt of copper mediated cyclization of (*S*)- **47**



47 **48**

After dissolving (*S*)-**47** (20 mg, 0.05 mmol) in DMSO (1 mL), the solution was degassed. To this copper(II)acetate (2 mg, 0.02 mmol) was added and the reaction mixture was heated to 65 °C for 24 h. Quenching with water (3 mL) was followed by extraction with DCM (5x10 mL). The organic layers were combined and dried over Na_2SO_4, the solvents removed under reduced pressure. Analysis of the residue by ^{1}H-NMR indicated only starting material being present.

4.46. (*S*)-3,3'-divinyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine



49

Diiodide (*S*)-**2** (150 mg, 0.276 mmol) and $Pd(PPh_3)_4$ (32 mg, 0.03 mmol) were dissolved under argon in toluene (5 mL) and water (400 µL). Triethylamine (168 mg, 1.66 mmol) and vinyl boronic acid pinacol ester (128 mg, 0.83 mmol) were added subsequently. The mixture was stirred at 80 °C for 16 h. The solvents were evaporated and the crude product purified via MPLC (gradient PE/EE 95/5 to pure EE).

Yield: 63 mg (66%)

yellow oil

Spectroscopical Data:

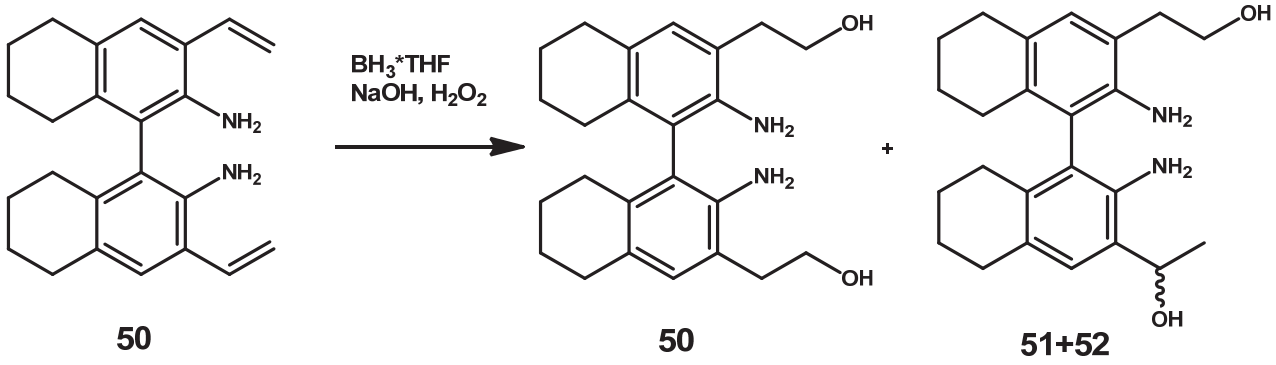
^{1}H-NMR ($CDCl_3$): δ 7.06 (s, 2H); 6.76 (dd, *J* = 17.3, 11.1 Hz, 2H); 5.60 (dd, *J* = 17.3, 1.5 Hz, 2H); 5.23 (dd, *J* = 11.1, 1.5 Hz, 2H); 3.66 (b, 4H); 2.76-2.65 (m, 4H); 2.28-2.05 (m, 4H); 1.77-1.58 (m, 8H) ppm.

^{13}C-NMR ($CDCl_3$): δ 139.1 (C); 136.3 (C); 133.1 (CH); 127.8 (C); 127.1 (CH); 122.5 (C); 114.5 (CH_2); 29.4 (CH_2); 27.1 (CH_2); 23.4 (CH_2); 23.3 (CH_2)[xxxi] ppm.

HRMS (ESI): calcd. for $C_{24}H_{29}N_2$ 345.2331 ([M+H]) found 345.2328 ([M+H]).

[xxxi] One quaternary carbon could not be observed.

4.47. Hydroboration of *(S)*-**49**



50 **50** **51+52**

A solution of (S)-**49** (60 mg, 0.17 mmol) in THF (2 mL) was degassed and cooled to -30 °C. The borane-THF-complex (1M in THF; 837 µL, 0.84 mmol) was added and the mixture allowed to warm up to -20 °C and stirred for 20 h. It was cooled subsequently to -78 °C and hydrogen peroxide (30%, 100 µL, 0.84 mmol), methanol (5 mL) and NaOH (aq. 3N, 280 µL, 0.84 mmol) added. The mixture was allowed to warm up to -20 °C and stirred for 2 h. It was successively quenched with water (5 mL) and sat. $NaHCO_3$-solution (5 mL) and extracted with EE (3x7 mL). The organic layers were combined, dried over Na_2SO_4 and the solvents evaporated. The crude product mixture was purified via MPLC (gradient PE/EE 50/50 to EE+ 3 % EtOH).

Yield: 28 mg (44%) colorless oil

[+12 mg of 1st (**51**) and 23 mg of 2nd asymmetric diasteromer (**52**)]

Spectroscopical Data of 50:

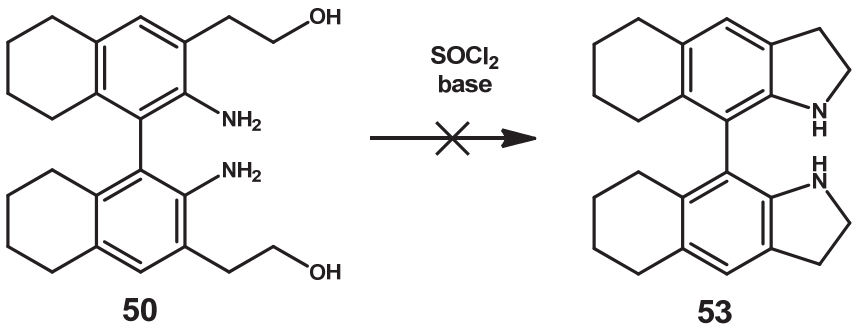
^{1}H-NMR ($CDCl_3$): δ 6.81 (s, 2H); 3.94-3.85 (m, 4H); 2.78 (m, 4H); 2.69 (m, 4H); 2.13 (bm, 8H); 1.66 (bm, ~8H) ppm.[xxxii]

^{13}C-NMR ($CDCl_3$): δ 140.2 (C); 134.6 (C); 130.4 (CH); 128.1 (C); 123.2 (C); 122.1 (C); 63.4 (CH_2); 34.9 (CH_2); 29.3 (CH_2); 26.9 (CH_2); 23.5 (CH_2); 23.3 (CH_2) ppm.

HRMS (ESI): calcd. for $C_{24}H_{32}N_2O_2Na$ 403.2361 ([M+Na]) found 403.2369 ([M+Na]).

[xxxii] OH could not be assigned. The substance was purified twice by chromatography, but due to the pronounced polarity no higher degree of purity could be reached.

4.48. Attempt of cyclization of *(S)*-**50**



50 **53**

- With NaOH as base

Thionyl chloride (154µL, 0.16 mmol) was dissolved in degassed DCM (1 mL) and a solution of *(S)*-**50** (20 mg, 0.05 mmol), dissolved and degassed in DCM (2.5 mL), was subsurface-added dropwise via Teflon tube. The mixture was stirred 8 h at RT, then cooled to 0 °C and quenched with 5N NaOH-solution (530 µL, 2.65 mmol). The two-phase system was stirred vigorously for 30 min, then the layers were separated, extracted with DCM (3x5 mL) and the organic phase was washed with water and brine. The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure.[62]

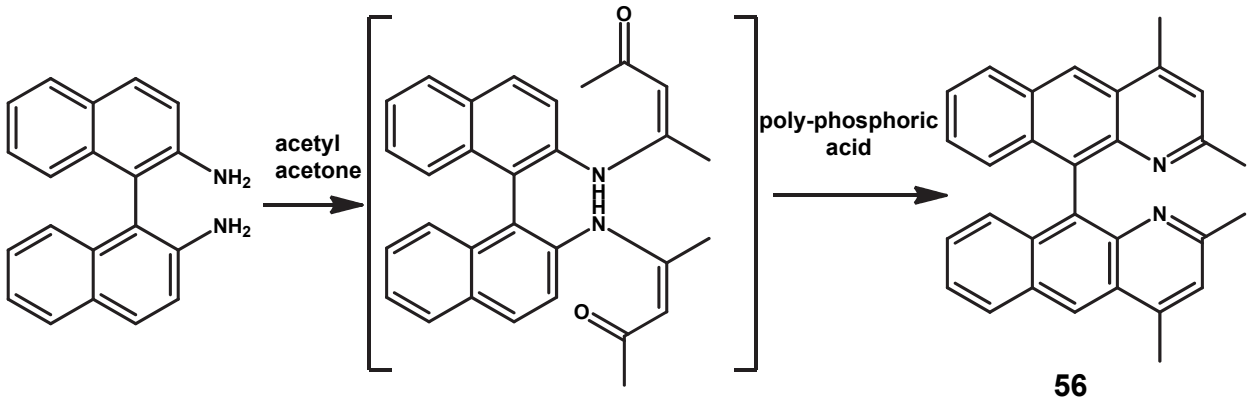
Yield: 5% conversion (NMR), rest: starting material

- With KI and triethylamine as base

Thionyl chloride (154µL, 0.16 mmol) was dissolved in degassed DCM (1 mL) and to this a degassed solution of *(S)*-**50** (20 mg, 0.05 mmol) in DCM (2.5 mL) was subsurface-added dropwise via Teflon tube. The mixture was stirred 8 h at RT, then cooled to 0 °C and treated with TEA (330 µL, 2.83 mmol). After stirring the reaction vigorously for 20 min and heating to 45 °C for 8 h, the gelatinous residue was diluted with DCM water (5 mL) was added. The crude mixture was extracted with DCM (3x5 mL) and the organic phase washed with water and brine. The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure.

Yield: complex mixture, not separable

4.49. Attempted Combes quinoline synthesis



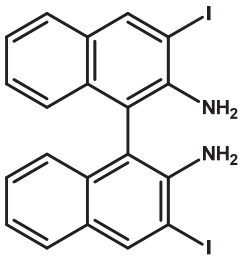
56

(S)-BINAM (100 mg, 0.36 mmol) was placed in a Schlenk tube and acetyl acetone (400 µL, 3.91 mmol) added. The mixture was stirred for 6 h at RT, then polyphosphoric acid (excess) added and the sticky residue refluxed for 16 h. The reaction was quenched, neutralized with $NaHCO_3$ (25 mL) and extracted with DCM (3x5 mL). The combined organic layers were dried over Na_2SO_4 and the filtrate concentrated *in vacuo*. The crude mixture was purified via MPLC (gradient PE/EE 95/5 to PE/EE 20/80).

Yield: complex mixture, only polymerized acetyl acetone derivatives were detected.

4.50. Re-aromatization of *(S)*-**2**

- With DDQ in toluene



57

Diiodide (**S**)-2 (100 mg, 0.18 mmol) was dissolved in toluene (2 mL) and degassed. Then a solution of DDQ (209 mg, 0.92 mmol) in degassed toluene (2 mL) was dropped in via Teflon tube at RT, and heated to 100 °C for 5 min. The mixture was allowed to cool to RT and filtered over celite. The crude filtrate was directly loaded on the column and purified (PE/EE 95/5). [xxxiii]

Yield: 39 mg (40%)

off-white foam

Spectroscopical Data: (matched literature)

^{1}H-NMR ($CDCl_3$): δ 8.41 (s, 2H); 7.70-7.64 (m, 2H); 7.32-7.16 (m, 4H); 6.97-6.90 (m, 2H); 4.08 (bs, 4H) ppm.

- With $Pd(OCOCF_3)_2$ and oxygen

Diiodide *(S)*-**2** (100 mg, 0.18 mmol) was dissolved in acetone (2 mL), degassed and placed in a pressure tube. Palladium trifluoroacetate (7 mg, 0.02 mmol) was added and the tube sealed. The system was flushed with oxygen, the filled with 2 bar O_2. The mixture was stirred vigorously at RT for 16 h, then filtered over celite and washed with acetone. The filtrate was evaporated. NMR Analysis of the residue showed only starting material.

[xxxiii] 3,3‘ Dibromo compound **42** was rearomatized in our group using a similar protocol as given for the diiodo moiety **2.**

5. References

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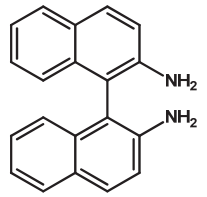
6. Appendix

6.1. Structure Index



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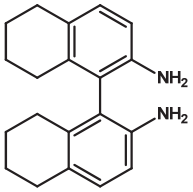

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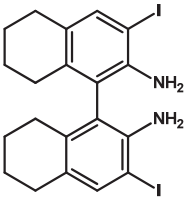

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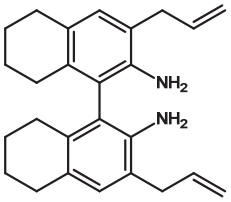

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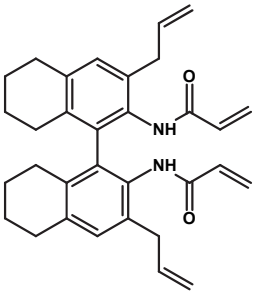

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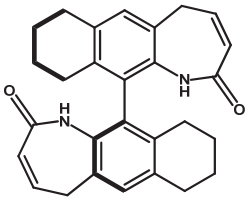

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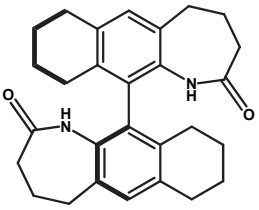

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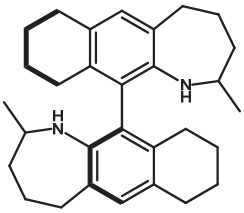

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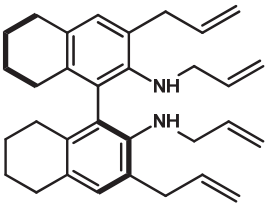

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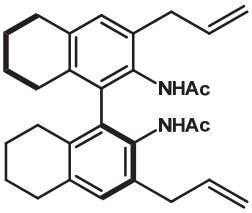

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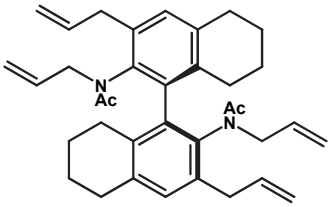

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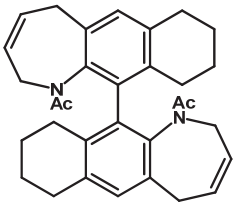

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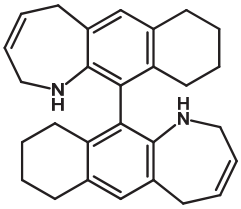

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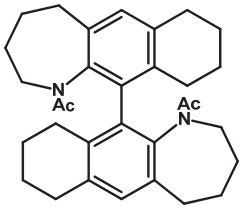

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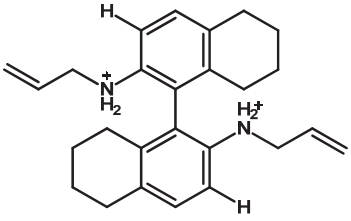

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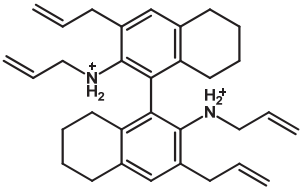

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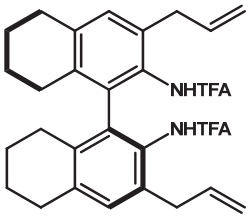

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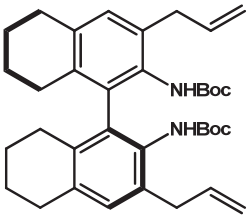

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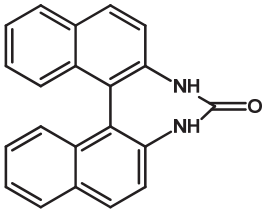

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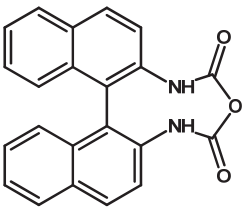

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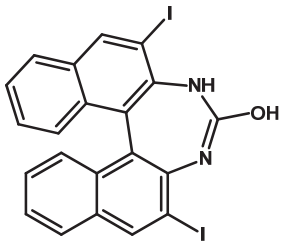

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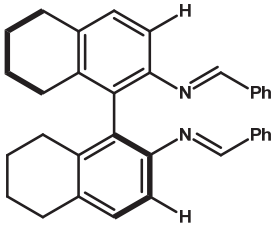

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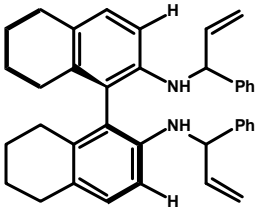

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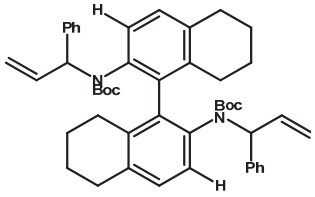

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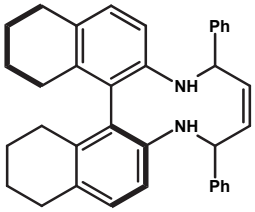

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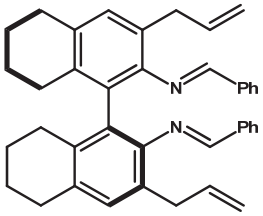

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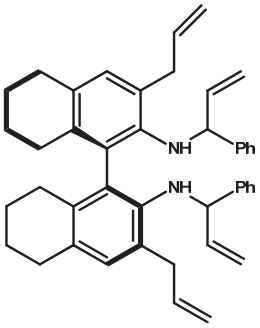

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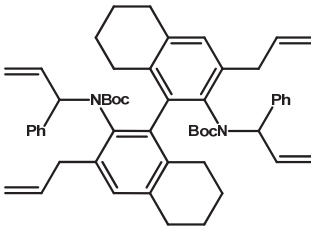

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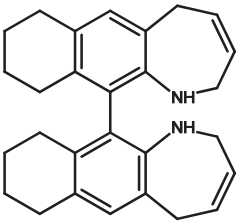

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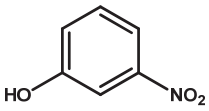

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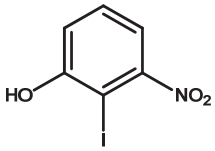

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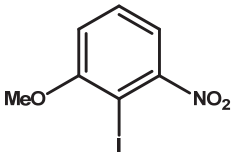

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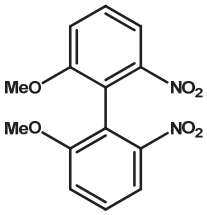

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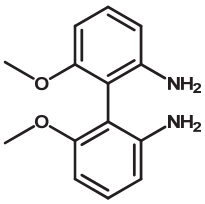

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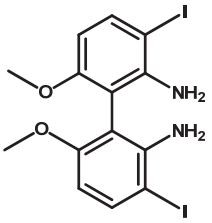

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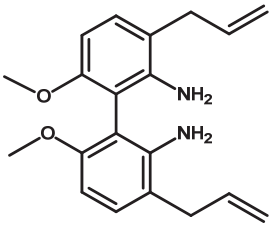

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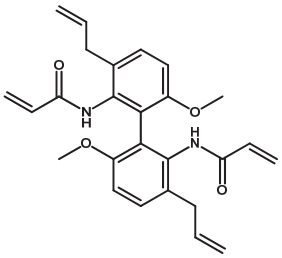

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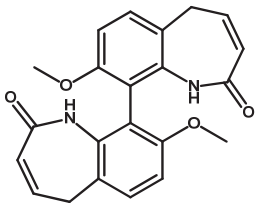

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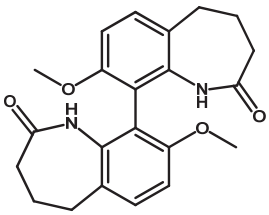

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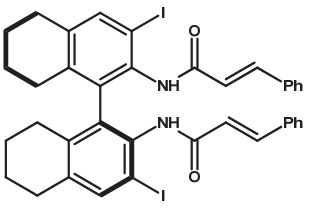

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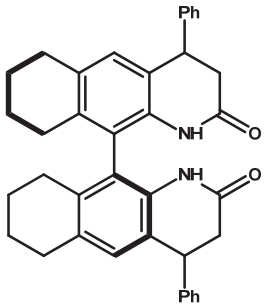

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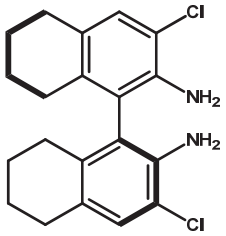

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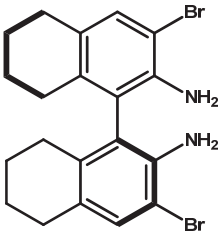

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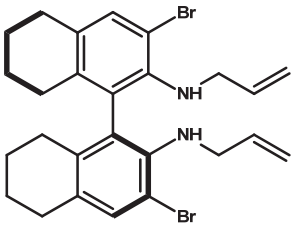

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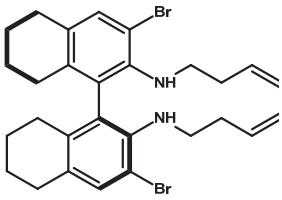

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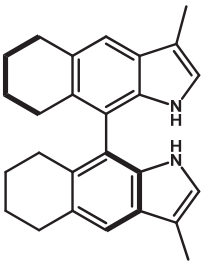

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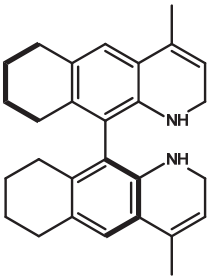

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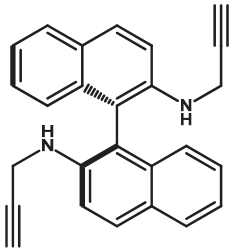

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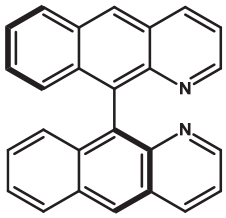

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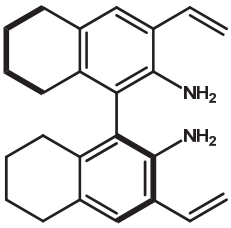

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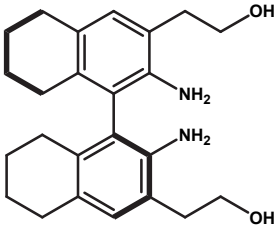

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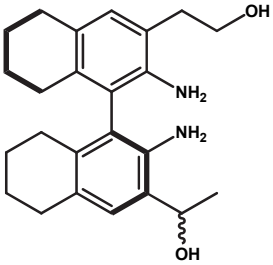

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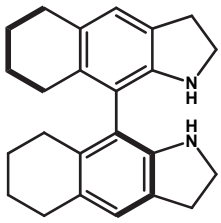

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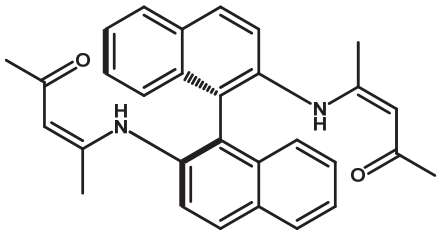

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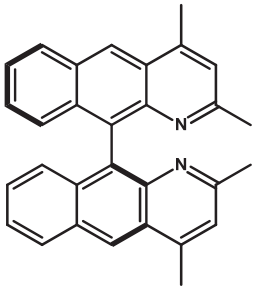

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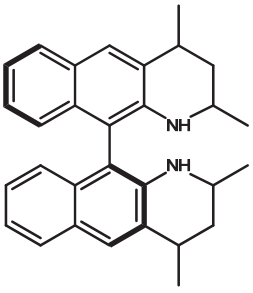

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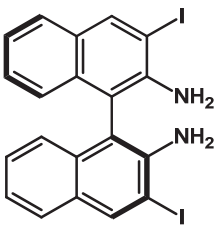

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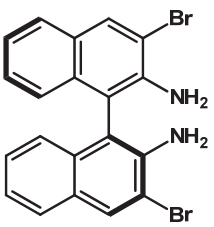

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6.2. Abbreviations

AcOH	acetic acid
ACN	acetonitrile
9-BBN	9-borabicyclononane
BINAM	1,1‘-binaphthalene-2,2‘-diamine
BINAP	2,2’-bis(diarylphosphino)-1,1’-binaphthyl
BINOL	1,1’-binaphthalene-2,2’-diol
Boc	*tert*-butyloxycarbonyl
n-BuLi	*n*-butyl lithium
d-CSA	*d*-camphor sulfonic acid
DABN	1,1‘-binaphthalene-2,2‘-diamine
DB	double bond
dba	dibenzylidenacetone
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EE	ethyl acetate
ESI	electron spray ionization
EtOH	ethanol
L-DOPA	*L*-3,4-dihydroxyphenylalanin
Grubbs 1st Generation Catalyst	benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium

Grubbs 2nd Generation Catalyst	benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinyliden]dichloro(tricyclohexylphosphine) ruthenium
HRMS	high resolution mass spectroscopy
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
$LiEt_3BH$	lithium triethylborohydride (=super hydride)
MeOH	methanol
MPLC	medium pressure chromatography
MS	molecular sieve
MS	mass spectroscopy
NBS	*N*-bromo succinimide
NCS	*N*-chloro succinimide
NEt_3	triethylamine
n.r.	no reaction
Pd/C	palladium on activated charcoal
PE	petrolether / hexane
PG	protective group
Raney-Ni	Raney-nickel
RCM	ring closing metathesis
RT	room temperature
TBAB	tetrabutylammonium bromide
TFA	trifluoroacetate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylendiamine
TMS	trimethylsilane
Petasis reagent	dimethyl titanocene dichloride

6.3. German Abstract

Verschiedene Syntheseansätze zu Bisazaheteroarylen wurden untersucht, wobei vorwiegend Ringschlussmetathese (RCM) zur Anwendung kam. Als Vorstufen wurden ausgehend von 2,2‘-Diamino-1,1‘-binaphthyl verschiedene -3,3‘-Dihalogenverbindungen hergestellt. Mittels Stille- oder Suzuki-Cross-Kupplung wurden in 3,3‘-Position geeignete Olefinsubstituenten eingeführt. Danach wurden endständigen Olefinsubstituenten an die beiden Stickstoffatome geknüpft. Um geeignete Substrate für die RCM zu erhalten, mussten N-Schutzgruppen gefunden werden, da freie NH-Gruppen bei der Grubbs-Katalysator-vermittelten RCM stören. Die Suche stellte sich als äußerst schwierig dar, da die sterischen Ansprüche des Aromaten die Einführung von zwei Substituenten an den sp^3-Stickstoff nur in wenigen Fällen (sehr kleine PG) zulassen. Unter anderem wurden untersucht: Acetyl, Boc, Trifluoroacetyl und *N*-Hydrochloride. Darüber hinaus wurden die Amidfunktion auch als Teil des Ringsystems eingeführt. Schließlich konnten zyklisierte Produkte sowohl von N-Acetyl als auch von N-Acryloyl-Vorstufen in guten Ausbeuten erhalten werden. Es zeigte sich aber, dass die Abspaltung der Schutzgruppe, bzw. die Reduktion des Bislactams trotz vielfacher Variation der Reaktionsbedingungen nicht erreicht werden konnte oder zur Zersetzung führte.

Um einerseits die Probleme des schwierigen synthetischen Zugangs zu den Vorstufen zu umgehen, und andereseits die sterische Hinderung zu reduzieren, wurden alternative Synthesewege untersucht, darunter Heck-Kupplungen, Combes Quinoline Synthesen und andere, nicht auf Metathese-beruhende Herstellungsmethoden. Diese lieferten zwar interessante Syntheseintermediate (als polyfunktionelle, flexible Bausteine für zukünftige Synthesen), aber die gewünschten 2,3- und 2‘,3‘-zyklisierten Binaphthylderivate mit freier NH-Funktionalität konnten nicht erhalten werden.

Um die hohen sterischen Anforderungen, die typisch für das Binaphthyl-Systems sind, zu reduzieren, wurde die Grundstruktur geändert und weitere Versuche an analogen Biphenyl-Verbindungen durchgeführt. Da bei vorausgehenden Zyklisierungen die endozyklische Amidfunktionalität besonders gut zugänglich war, wurde die Acryloyl-Gruppe auch in die analoge Biphenyl-Verbindung eingeführt. Anschließende RCM lieferte den Biphenyl-gestützten Heterozyklus in guter

Ausbeute. Die Abspaltung der Schutzgruppe war jedoch auch in diesem Fall unter üblichen Bedingungen nicht möglich.

Als allgemein interessantes Syntheseintermediat wurde 2,2‘-Diamino-3,3‘-diiodo-6,6’-dimethoxy-1,1’-biphenyl in guter Ausbeute synthetisiert und charakterisiert. Dieses stellt eine wichtige Schlüsselverbindung für eine Vielzahl potentieller Synthesewege dar, da die Variation/Substitution aller 3 funktionellen Gruppen getrennt voneinander erfolgen kann.

Für zukünftige Syntheseplanungen sollte eine *de-novo* Kupplung von zwei bereits funktionalisierten Naphthyleinheiten mit freier NH-Funktionalität in Erwägung gezogen werden. Ebenso könnten Friedländer-Synthesen angewendet werden, um Bisheteroaryle mit ausreichender *N*-Basizität zu erzeugen, geeignet für den Einsatz in der Organokatalyse.

Zusammenfassend wurden in dieser Arbeit 19 neue Verbindungen synthetisiert und charakterisiert, darunter 5 atropisomere zyklische Amide.

6.4. Curriculum Vitae (german)

Angaben zur Person:

Christina MARK

Einsiedlergasse 23/10 ; 1050 Wien

Geb. am 18.Juni 1988 in Kirchdorf/Krems

Mail: Christina.Mark@gmx.at

Schulbildung:

1995-1999	Volksschule Windischgarsten
1999-2006	AHS Stiftsgymnasium Admont
2006	Matura mit ausgezeichnetem Erfolg abgeschlossen

Studium:

2006-2009	Bakkalaureatsstudium der Chemie
SS 2009	Bakkalaureatsarbeit unter AO. Univ.-Prof. Mag. Dr. Markus Galanski
2009-2011	Masterstudium der Chemie
SS 2011	Masterarbeit unter AO. Univ.-Prof. Mag. Dr. Michael Widhalm

Wissenschaftliche Arbeitserfahrung:

Feb. 2009-	Tutorin am Institut für Organische Chemie der Universität
Okt. 2010	Wien