MASTERARBEIT

Titel der Masterarbeit

„Novel binaphthyl auxiliaries and their application in asymmetric intermolecular bromofunctionalization of olefins"

verfasst von

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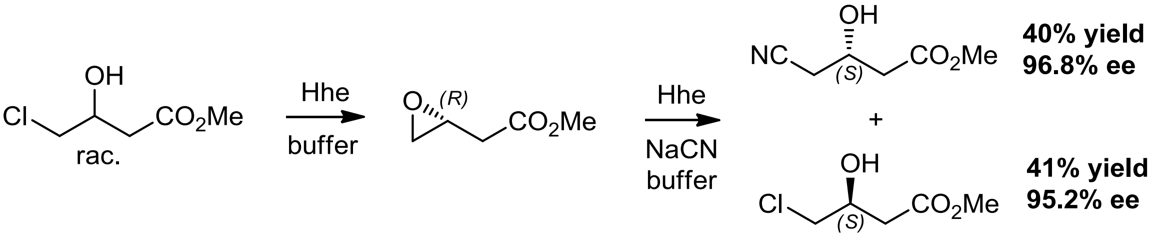
Content

1 Introduction

1.1 A short introduction in organocatalysis

Catalysis is a big deal in organic synthesis. The reasons are quite obvious considering the benefits that catalysis has to offer. Catalysts enhance the rate of chemical reactions by treading new reaction pathways. Additionally, these new pathways can enable otherwise impossible transformations by lowering of the energy levels of the transition states. Lowering of these “activation barriers” enables reactions to perform at lower temperature or shorter reaction times, meaning that a significant amount of energy can be saved through the use of catalysts, especially in the large scale processes of chemical industry. The most important feature of catalysts is the talent to control the selectivity of chemical reactions, especially the control of stereoselectivity in organic transformations. Since many natural products and drugs are enantiomerically pure compounds it is the most reasonable approach to produce an excess of the biologically active stereoisomer in order to avoid complex optical resolution procedures and considerable amount of waste.

Nature also utilizes catalytic systems in form of enzymes, the role models amongst the catalysts. Besides the fact that they are essential for life, they are already heavily applied in organic transformations. Halohydrin dehalogenases (Hhe) is one example of these highly efficient biocatalysts. Hhe catalyzes the transformation of vicinal halohydrins to epoxides in a highly stereoselective manner. Furthermore, they can be used for epoxide ring opening with different nucleophiles. For example, this allows the stereoselective one pot transformation of racemic halohydrins to precious chiral building blocks via kinetic resolution (Scheme 1).[1]



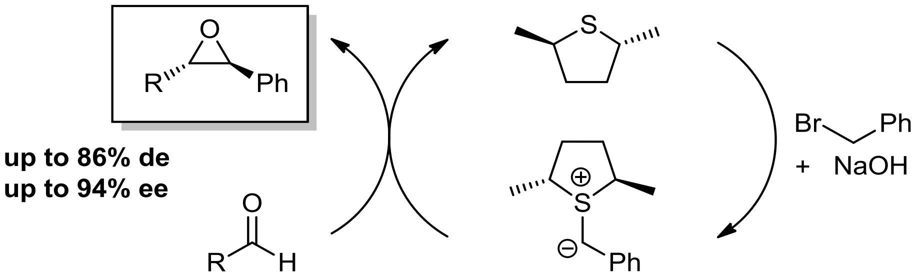
Scheme 1: Kinetic resolution of methyl 4-chloro-3-hydroxybutanoate methylester

The highly stereoselective transformations of enzymes are based on the localization of the catalytic center in “pockets”, which allows only substrates of suitable geometries to approach, but the number of matching substrates is rather limited because of that.

Metalloenzymes are the natural analogs of transition metal catalysts, the predominant catalyst-family in homogenous catalysis over the last decades. This field of research is well developed, with many reactions having high turnover frequencies and excellent stereoselectivity due to tailor-made chiral ligands. Anyway, residues of these catalysts in pharmaceuticals can be problematic, due to the high toxicity of a number of transition metals. Also, these catalysts can be highly sensitive to oxygen and moisture, which can make the performance of these reactions sophisticated and time consuming.

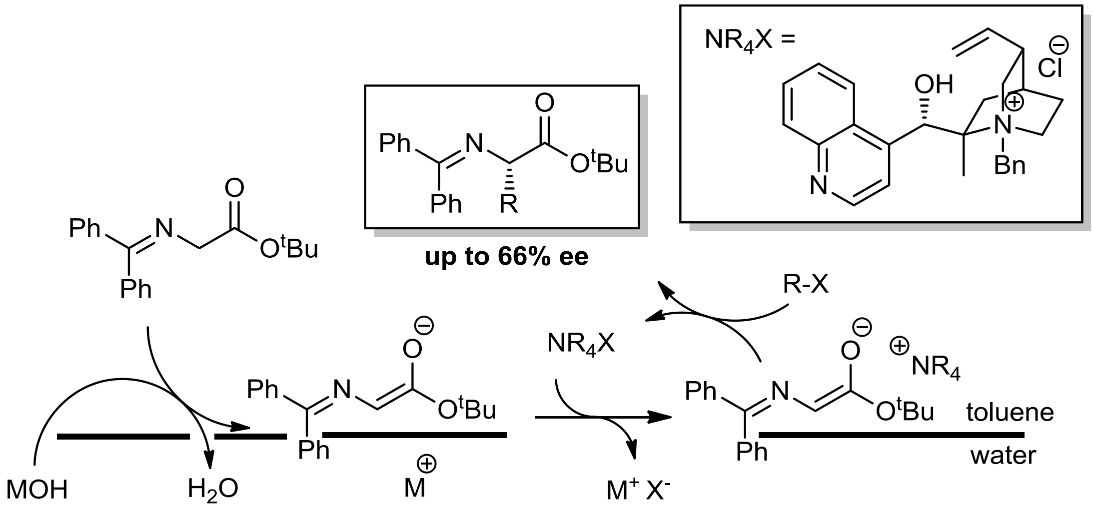
A complementary and rather young class of catalysts does not suffer the disadvantages mentioned above. In organocatalysis, chemical transformations get promoted by organic molecules. Organocatalysts are non-sensitive molecules with less toxicity then transition metal catalysts. Nature offers many optically pure compounds which can act as catalysts, such as alkaloids, sugars, and amino acids. Many natural products have been successfully applied in organocatalysis without further derivatization. They have also been utilized as backbones for semi-synthetic catalysts providing a chiral environment necessary for asymmetric transformations. Unfortunately, the chiral pool offers, for the majority of natural products, only one of two enantiomers. Few exceptions exist, for instance, some cinchona alkaloids. Concluding from this, the advantage of fully synthetic catalysts is obvious. Chiral synthetic backbones, which are often obtained through optical resolution by means of natural products as resolving agents, give access to both enantiomers of the catalyst, and therefore allow approach to both enantiomers of products, too.

There are different ways how organocatalysts can promote reactions. Seayad *et al.* categorized organocatalysts into roughly four main groups based on their mode of activation, using the terms Lewis base-, Lewis acid-, Brønsted base-, and Brønsted acid-catalysis.[2] Probably, the most frequent activation mode is Lewis-base catalysis. Lewis bases, simplified, activate electrophilic substrates by nucleophilic addition to give reactive intermediates. An interesting example is the use of a catalytic amount of chiral thioethers in the asymmetric epoxidation of carbonyl groups via a highly reactive sulfur-ylide intermediate (Scheme 2).[3]



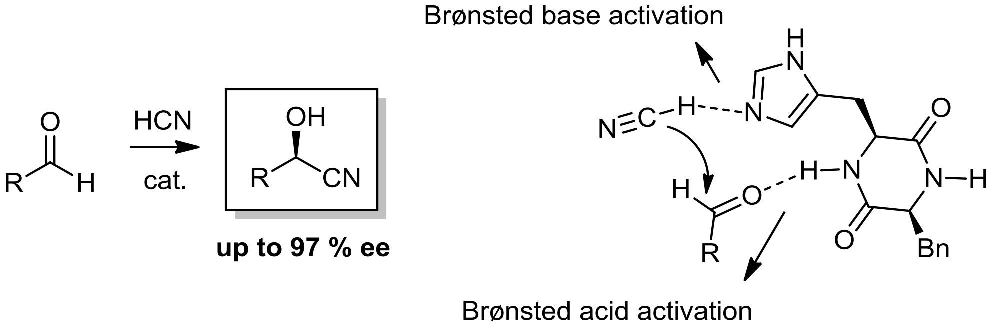
Scheme 2: Asymmetric catalytic epoxidation via sulfur-ylide catalysis

Another type of organocatalysis is phase transfer catalysis (PTC), which can be considered Lewis-acid-catalysis. The general concept follows the transfer of a polar substrate into an anpolar organic phase carried out by a lipophilic catalyst. This enhances the reactivity of the "naked" polar substrate, due to a reduced degree of solvation. An example of this is a pioneer work from 1989 dealing with the asymmetric alkylation of *N,O*-protected glycine catalyzed by cinchona alkaloid derived chiral ammonium salts (Scheme 3).[4]



Scheme 3: Mechanism of phase transfer catalysis in the asymmetric α-alkylation of *N,O*-protected glycine

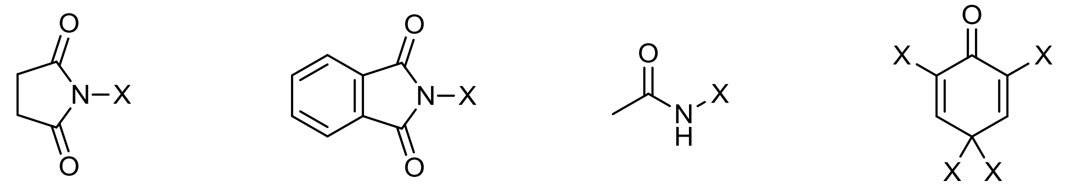
The mode of activation in Brønsted base/acid-catalysis is based on hydrogen bond formation between catalyst and substrate. Brønsted base catalysts are often amines, whose lone pairs are able to activate acidic substrates via partial deprotonation, which results in an increased nucleophilicity. Brønsted acid catalysts, on the other hand, use acidic groups for partial protonation of electrophilic groups, like carbonyl groups, to enhance their electrophilicity. A demonstrative example using both activation modes is the enantioselective addition of hydrogen cyanide to aldehydes developed by Tanaka *et al.* with the use of a cyclic dipeptide (Scheme 4).[5]



Scheme 4: Enantioselective synthesis of cyanohydrins using a dual Brønsted base/acid mechanism

1.2 Bromofunctionalization of olefins

A possible way of the introduction of functional groups in olefins is the addition of halides. Using X_2 (X = Br, Cl) in aprotic solvents in the presence of olefins, fast formation of dihalide will occur. X^+ will add to the double bond forming a cationic intermediate, which can be attacked by X^-. However, with the addition of Br_2, even the formation of Br_3^- is possible.[6] In protic solvents like alcohols, acids, or aqueous DMSO, the solvent itself can compete with X^- to give haloethers, haloesters or halohydrins. The formation of these bifunctional products can be increased by use of X^+-sources (X = Cl, Br, I) instead of molecular halides. A large number of X^+-sources, especially *N*-halo-reagents, have been developed.[7] Popular examples are *N*-haloimides, *N*-haloamides[8] and 2,4,4,6-tetrahalo-2,5-cyclohexadienones[9] (Scheme 5).



N-Halo-succinimide (X = Cl, Br, I)

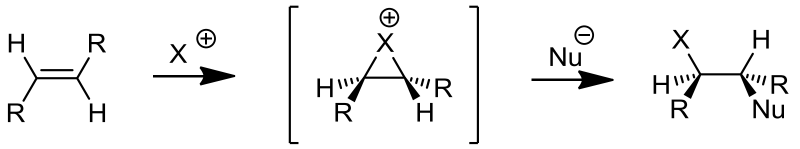
N-Halo-phthalimide (X = Cl, Br, I)

N-Halo-acetamide (X = Cl, Br, I)

2,4,4,6-Tetrahalo-2,5-cyclohexadienone (X = Cl, Br)

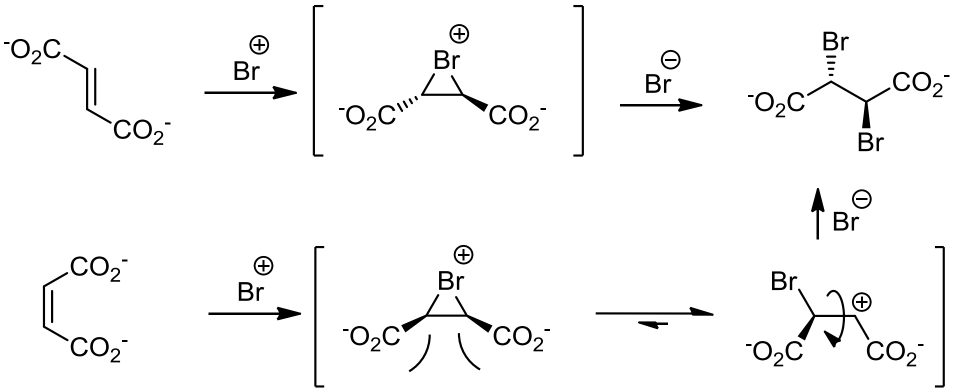
Scheme 5: Selection of popular X^+-sources

The formation of bridged halonium ions between olefins and X^+ (X = Cl, Br, I) was first proposed in 1937 by Roberts *et al.*[10] This widely accepted mechanism, with formation of a 3-membered ring containing the halide atom as intermediate through addition of "X^+" to the double bond can be found in every organic chemistry textbook. The most attractive feature of these intermediates is the possible ring opening with various nucleophiles, giving difunctionalized molecules (Scheme 6).



Scheme 6: Formation of halonium ions and diastereoselective S_N2 ring opening

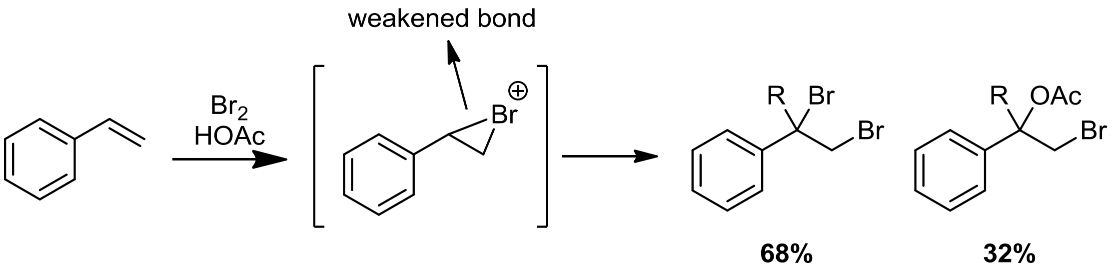
The suggestion of the existence of an equilibrium between the cyclic halonium ion and an acyclic carbenium intermediate was described based on known observations of the addition of bromine or chlorine to unsaturated dicarboxylates. In the case of the trans-substituted olefins, the bridged intermediate with hindered rotation is the predominant species, based on the observed high selectivity of trans-addition to fumarate ions. On the other hand, the strong electronic repulsion in maleate ions led mostly to cis-addition, which is explained by the predominance of an acyclic carbenium intermediate, where rotation is possible (Scheme 7).



Scheme 7: Release of electronic repulsion via an acyclic carbenium intermediate

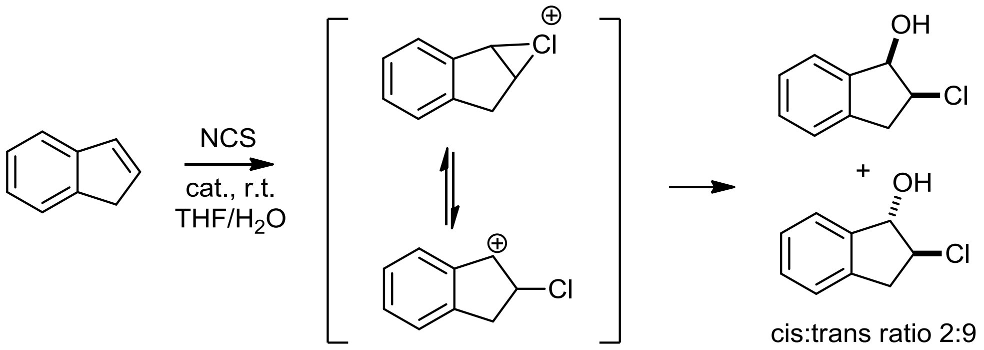
The diastereoselectivity and regioselectivity of the nucleophilic attack strongly depends on the substrate and, as a consequence, on the character of the preferred intermediate after X^+-addition to the olefin.[6] Considering the borderline cases, bridged halonium intermediates undergo S_N2-fashioned ring opening, giving only trans-adducts, while the symmetric distribution of positive charge in the 3-membered ring yields a mixture of regioisomers. The carbenium intermediate, on the other hand, reacts with high regioselectivity, as a result of localization of the positive charge on carbon, but with low diastereoselectivity, since the nucleophilic attack is possible from both sides, following an S_N1-like-mechanism.

In most cases, however, the intermediate can be found mostly in between these two borderline cases, particularly when substituents are present which can stabilize partially positive charge on carbon. This stabilization, often caused by hyperconjugation or aromatic delocalization, increases the bond length between carbon and halide, which results in a weakened bond. In extreme cases, this weakened bond undergoes a ring opening to form carbenium ions. This effect is generally stronger with chloronium ions than with bromonium ions because of the higher ring strain, due to shorter C-Cl-bonds.[11] A demonstrative example regarding high regioselectivity caused by this stabilization is the addition of Br_2 to styrol in acetic acid (Scheme 8). The acetic acid is competing with the bromide ion as a nucleophile, giving some of the bromoacetate as by-product as well. Due to the strong stabilization of the positive charge in the benzylic position, only the formation of the 1-acetoxy-2-bromide as by-product occurs.[12]



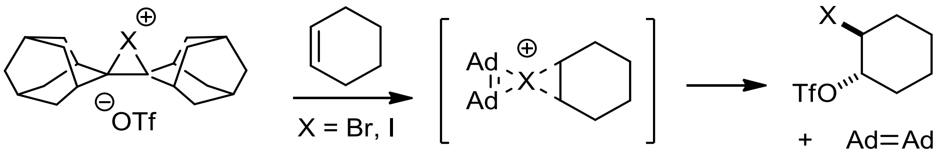
Scheme 8: Regioselective formation of 1-acetoxy-2-bromine adduct as by-product.

The preference of formation of a carbenium intermediate due to strong stabilization of positive charge in benzylic positions leads to a loss of diastereoselectivity in the thiourea-accelerated chlorohydroxylation of indene yielding a diastereomeric mixture (Scheme 9).[13]



Scheme 9: Chlorohydroxylation of indene yielding a diastereomeric mixture of products caused by an acyclic carbenium intermediate.

Despite these substrate-dependent deviations of regio- and diastereoselectivity, asymmetric variants for bromofunctionalizations are desired and one of the remaining challenges in organic synthesis. But there is one phenomenon about this, on first glimpse, easy manageable reaction which makes it more complicated and difficult than expected. An obvious approach to an asymmetric variant may be the enantiofacial addition of X^+ to one of the two possible faces of prochiral olefins. Once the chiral halonium ion is established, regioselective and S_N2-fashioned ring opening should lead to one single diastereomer. But Brown *et al.* [14] discovered a possible diffusion-controlled “olefin-to-olefin transfer” of X$^+$, which means that temporarily formed chiral halonium ions are not necessarily stable intermediates and that X$^+$ can switch in between olefins in a reversible manner. This phenomenon was discovered with halonium ions of adamantylideneadamantane, where X$^+$ can undergo an olefin-to-olefin transfer to cyclohexene to give its saturated functionalized analog (Scheme 10).[15]



Scheme 10: Olefin-to-olefin transfer to cyclohexene via a 3-membered transition state

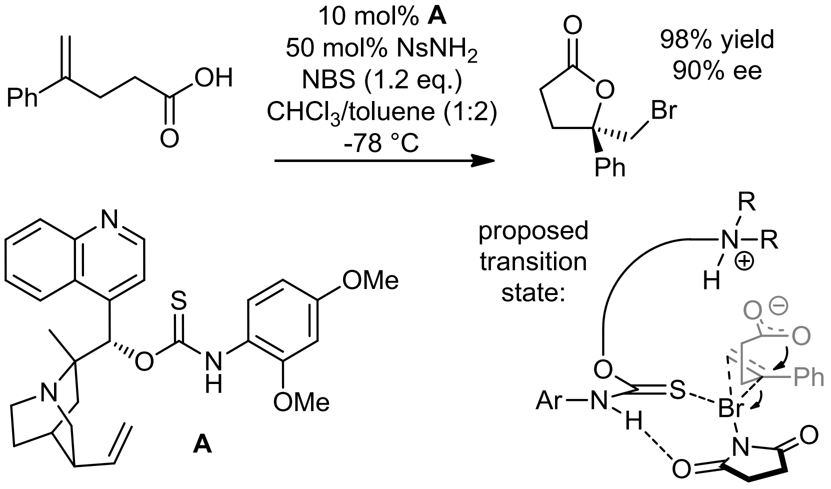
Concluding from this, it suggests itself that, in asymmetric catalyzed bromofunctionalisations, the halide atoms could switch to a congenerous olefin right after the enantiofacial addition, resulting in the racemization of these intermediates, which makes an enantioselective reaction difficult.

1.3 Organocatalytic bromofunctionalization of olefins

Especially in recent years, the interest and effort towards asymmetric bromofunctionalization has grown immensely.[16,17,18,19] Although a number of successful asymmetric intramolecular versions have been developed, intermolecular reactions are still in its infancy yet.

1.3.1 Intramolecular bromofunctionalization of olefins

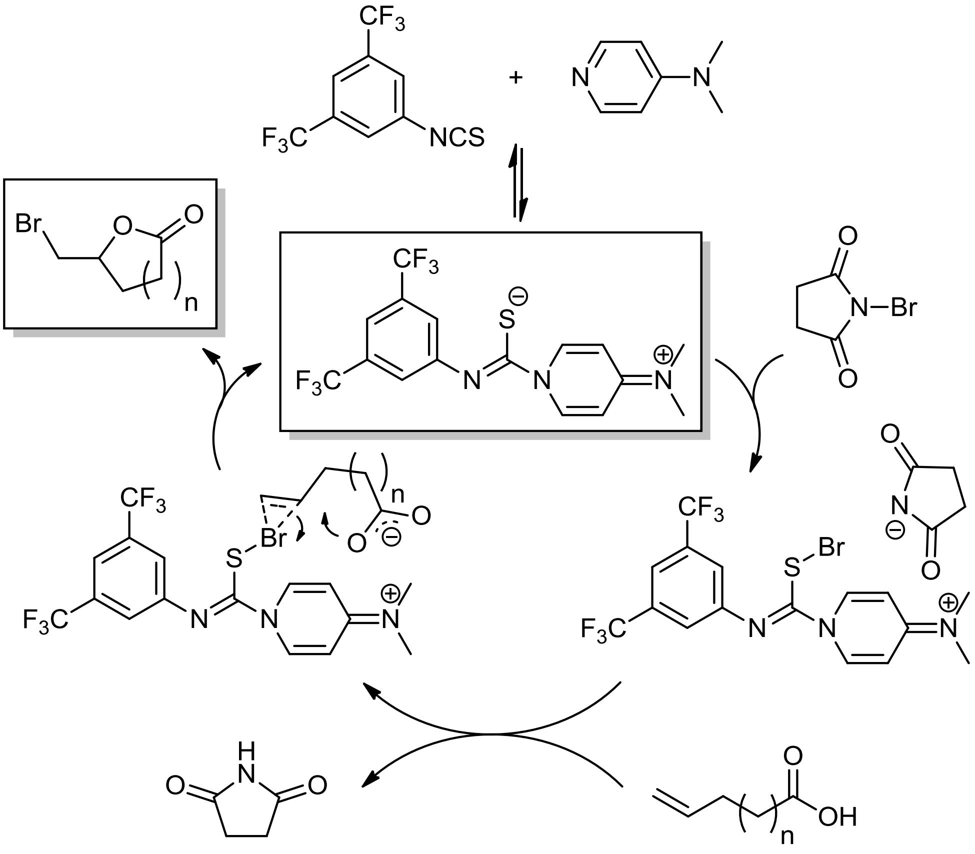
A very popular motif in intramolecular asymmetric variants is the thiocarbamate-moiety, which was extensively applied in halolactonization. An example may be given in Scheme 11 in the highly asymmetric formation of *γ*-lactones using bifunctional chinchonine derived catalysts.[20,21] The proposed mechanism postulates an activation of NBS by the nucleophilic sulfur of the thiocarbamate unit and an assisting deprotonation of the nucleophile by a tertiary amine. The relatively apolar solvent mixture $CHCl_3$/toluene (1:2) was found to enhance the enantiomeric excess by suppressing the non-catalyzed reaction. Furthermore, the use of the acidic additive *p*-nitrobenzene sulfonylamide ($NsNH_2$) was used successfully for additional hydrogen bond activation of NBS to cause an increase in electrophilicity.



Scheme 11: Example and mechanism of bifunctional thiocarbamate catalysis

Thiocarbamate catalysts were also applied in several other reactions like intramolecular bromoaminations[22] or bromoetherifications[23] and several other catalytic systems have found application in these useful transformations.

There is one catalyst in particular that is worth mentioning because of the simple beauty of its proposed mechanism, despite its use in non-enantioselective bromolactonization. The *in situ* formation of a zwitterionic catalyst at low temperatures in a mixture of 3,5-bis(trifluoromethyl)phenylisothiocyanate and DMAP gave up to 9-membered bromolactones in good to excellent yields with high regioselectivity. The proposed mechanism follows the formation of a rare S-Br σ-bond in the reactive intermediate instead of activation of the carbonyl groups in NBS, presenting a rather unusual way of increasing the electrophilicity of Br^+ (Scheme 12).

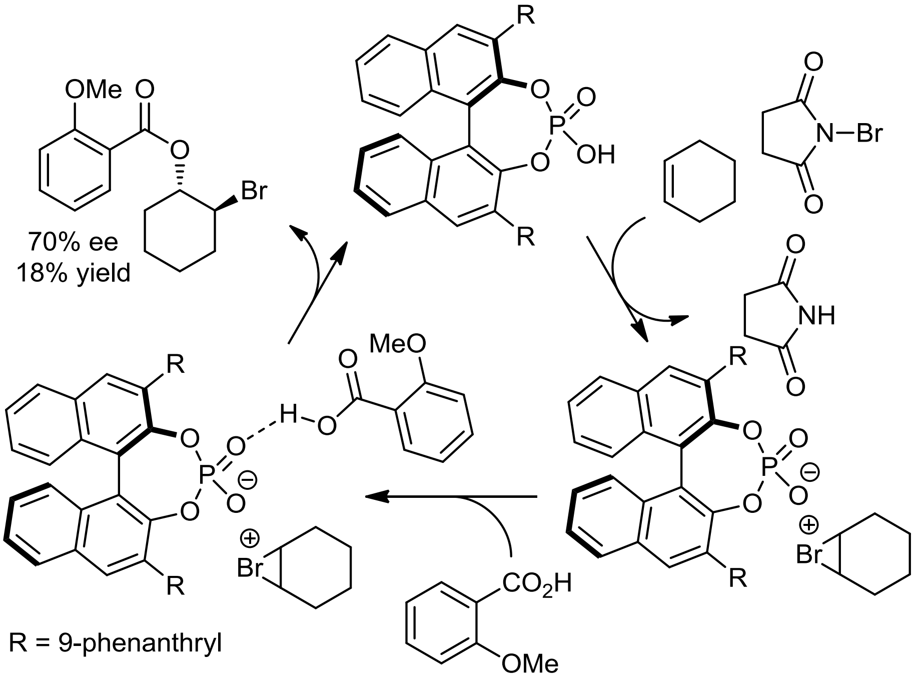


Scheme 12: Mechanism of a zwitterion-catalyzed bromolactonisation

1.3.2 Intermolecular bromofunctionalization of olefins

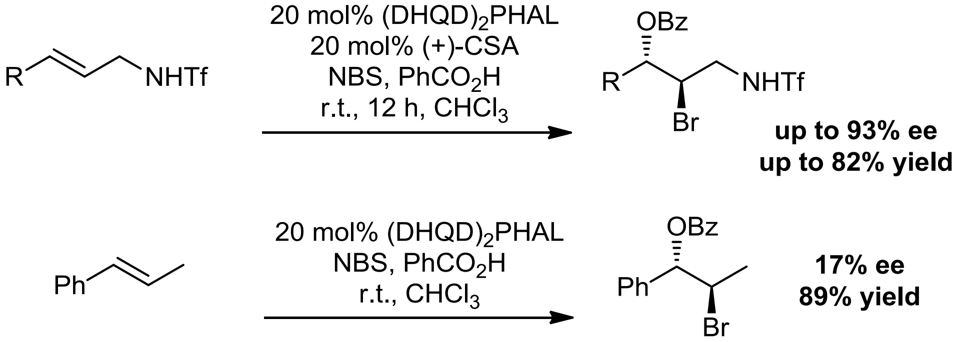
So far, the majority of publications dealing with asymmetric halofunctionalization are concerned with intramolecular reactions, but the number of attempts towards enantioselective intermolecular halofunctionalization remains pretty low.

In 2012, Li *et al.* managed to perform asymmetric intermolecular bromoesterification with a BINOL-derived phosphoric acid.[24] Screening with different carboxylic acids gave ee´s up to 70%, but with disappointingly low yields. The proposed reaction mechanism follows an ion pair intermediate, and the low yields are explained by possible self-bromoesterification of the catalyst with the olefin (Scheme 13).



Scheme 13: Proposed mechanism of phosphoric acid-catalyzed intermolecular asymmetric bromoesterification

In 2013, Zhang *et al.* reported the asymmetric bromoesterification of allylic sulfonamides using $(DHQD)_2PHAL$ as commercially available catalyst.[25] Benzoic acid proved to be the best nucleophile and in coherence to most of the other catalytic systems for this kind of reaction, NBS proved to be the best Br^+-source in terms of yield and enantiomeric excess. With (+)-camphorsulfonic acid as acidic additive, high enantiomeric excess with good yields were obtained for a broad range of substrates. An exchange of the alkaloid derived catalyst with DABCO showed only low enantiomeric excess meaning that the presence of $(DHQD)_2PHAL$ is essential for the high enantioselectivity, and not the presence of (+)-CSA. An even more interesting result from this work is an attempt for the asymmetric bromoesterification of *trans*-β-methylstyrene, because efforts towards non-functionalized olefins are barely known, with exception of the transformation shown before (Scheme 14). The low selectivity of the olefin might be explained by the absence of functional groups and therefore a reduced capability for interaction with the catalyst via hydrogen bond formation.

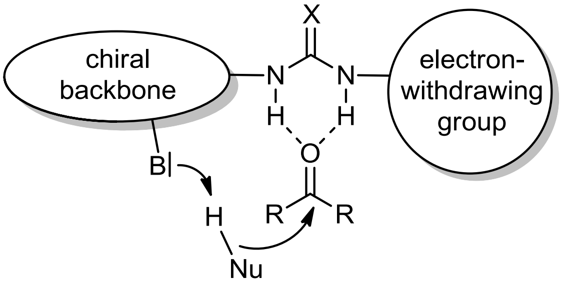


Scheme 14: Asymmetric intermolecular bromoesterification of allylic sulfonamides and *trans*-β-methylstyrene.

1.4 (Thio)ureas in hydrogen bond donor catalysis

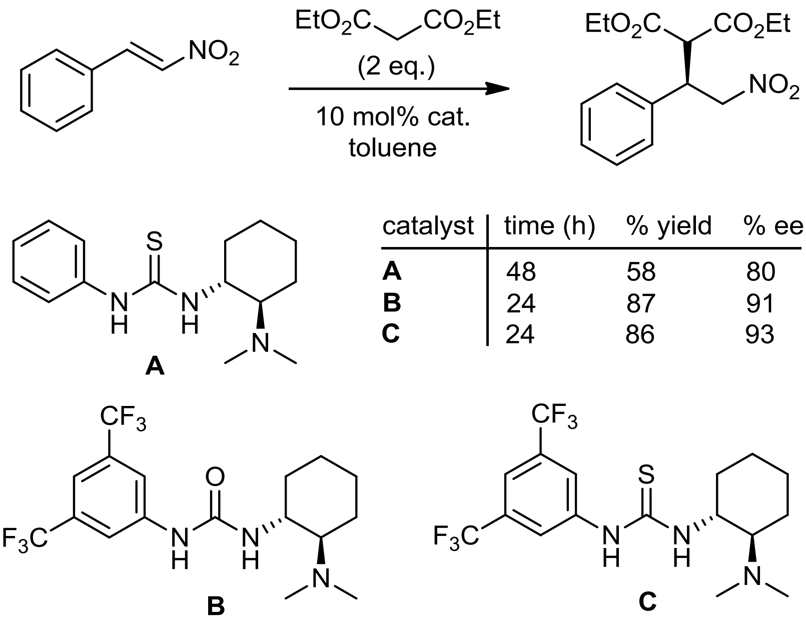
As shown in Scheme 4, functional groups containing acidic protons can be used to coordinate, and therefore activate, electrophilic substrates. These so called hydrogen-bond-donor (HBD) catalysts have grown into a big and very effective family of organocatalysts.[26] Using chiral backbones, it is possible to control the stereoselectivity, and the reactivity can be adjusted by various electron-withdrawing groups influencing the pK_a of the catalyst.

Ureas and thioureas are able to catalyze a broad range of reactions and are an important moiety in HBD-catalysis, due to their ability of double activation. They are often used in combination with Lewis- or Brønsted bases, giving bifunctional catalysts, which can activate electrophiles as well as nucleophiles.[27,28] A common structural design for efficient thiourea catalysts including the simplified dual activation mode is shown in Scheme 15.



Scheme 15: Structural design of effective bifunctional thiourea-catalysts

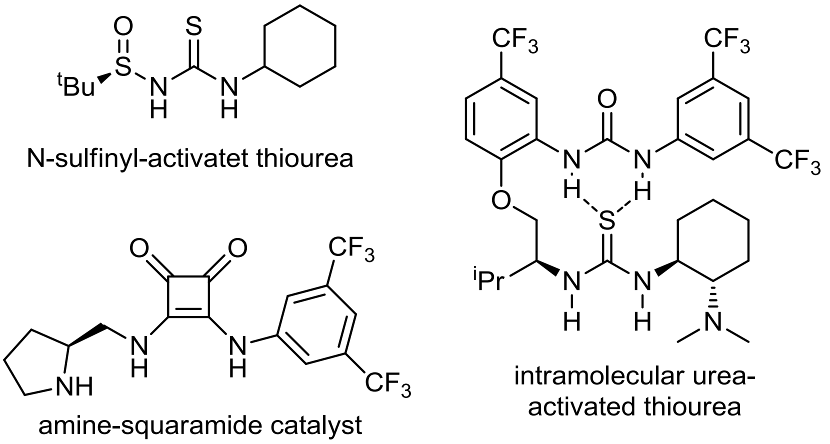
The influence of electron withdrawing groups can be significant in terms of yield and enantioselectivity. A nonambiguous example is the asymmetric Michael addition, optimized by using different *N*-aryl-groups by Takemoto *et al.* (Scheme 16).[29] The 3,5-bis(trifluoromethyl)aryl-group increases the enantioselectivity and reaction rate significantly, and is generally an often used component in this class of organocatalysts. Even more interesting is the similar yield and enantiomeric excess obtained from the thiourea and its urea-analog.



catalyst	time (h)	% yield	% ee
A	48	58	80
B	24	87	91
C	24	86	93

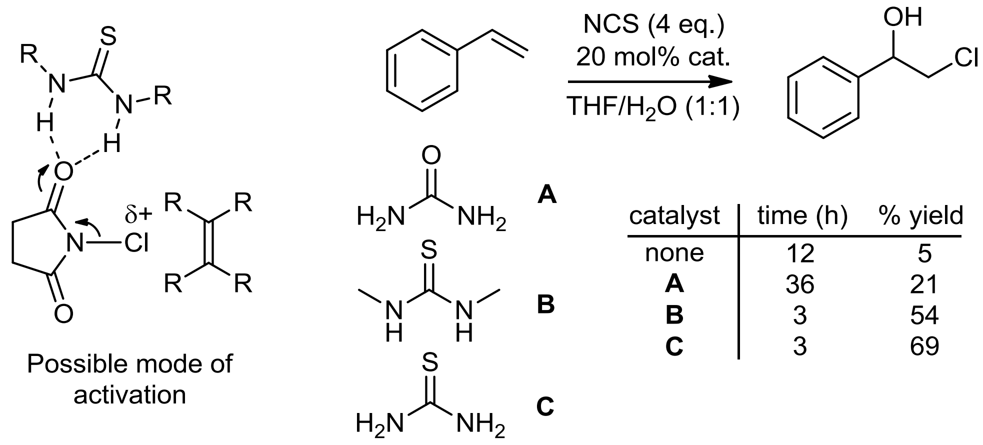
Scheme 16: Variation of (thio)urea and *N*-arylsubstituents

Many other possibilities exist to increase the reactivity of the (thio)urea-moiety. Scheme 17 shows two rather exotic examples of increasing the acidity. To begin with, the use of *N*-sulfinylsubstituents,[30] which activate the thiourea moiety and provide a chiral environment simultaneously, was successful. Furthermore, intramolecular urea activation[31] is possible as well. Alternative hydrogen bond donors to (thio)ureas are squaramide catalysts,[32] which can perform better in terms of yield and enantioselectivity in certain cases.



Scheme 17: Modes of acidification of thioureas and squaramides as alternative HBD-catalysts

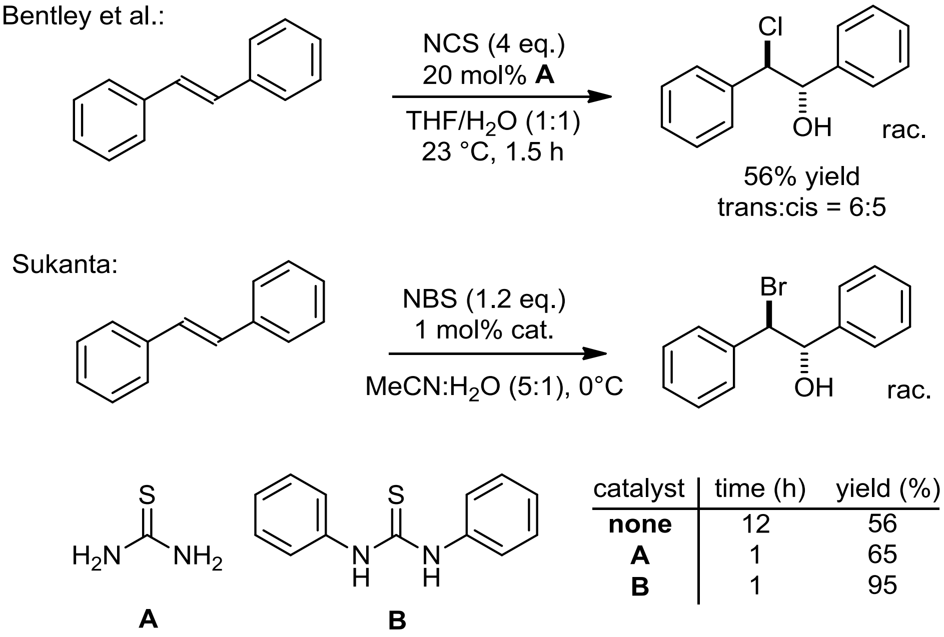
In 2007, Bentley *et al.* reported the thiourea promoted synthesis of chlorohydrins[13] and chloroethers.[33] Inspired of the capability of (thio)ureas to activate carbonyl groups via hydrogen bond formation and, as a result the increased electrophilicity of the halide in NCS, they succeeded, and thiourea proved to be the most active species (Scheme 18).



catalyst	time (h)	% yield
none	12	5
A	36	21
B	3	54
C	3	69

Scheme 18: Thiourea-accelerated chlorohydroxylation of styrene

In 2010, the successful *N,N'*-diarylthiourea-catalyzed bromohydroxylation of olefins was reported.[34] Compared with the moderate diastereoselectivity of chlorohydroxylation of Bentley et al. (*vida supra*), bromohydroxylation showed no formation of cis-adducts. With aqueous acetonitrile as the best solvent, the bromohydrin of *trans*-stilbene was achieved in high yields without the expected formation of dibromide as byproduct (Scheme 19).

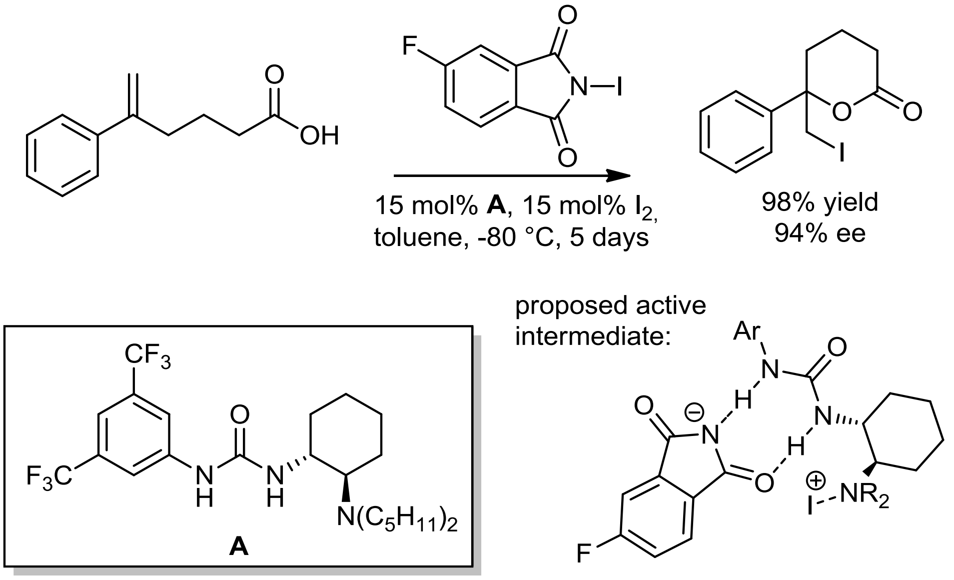


catalyst	time (h)	yield (%)
none	12	56
A	1	65
B	1	95

Scheme 19: Thiourea catalyzed halohydroxylation of *trans*-stilbene

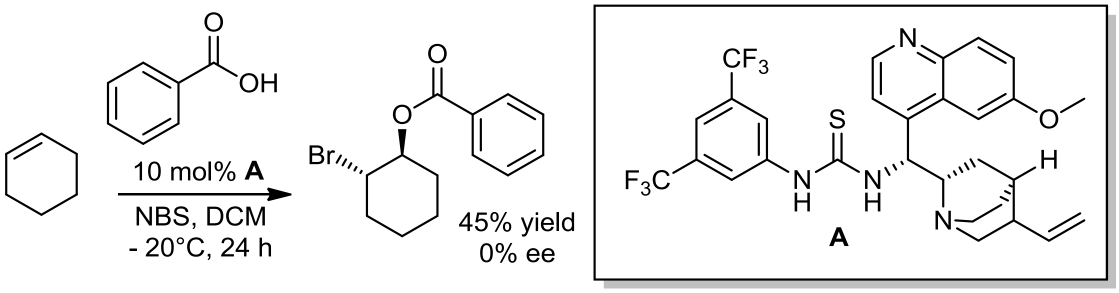
Bromomethoxylation of stilbene with methanol as solvent gave, under the same conditions, the *trans*-adduct in a yield of 95%.

Although Bentley *et al.* mentioned the ongoing development of an enantioselective variant in their summary, no corresponding paper has been published from this group yet. Also, in 2010, Veitch *et al.* reported an aminourea-catalyzed asymmetric intramolecular iodolactonization.[35] The structural design equates the general structure for effective bifunctional (thio)urea-catalysts shown in Scheme 15. As I^+-source, *N*-iodo-4-fluorophthalimide was found to be the best reagent. The addition of a catalytic amount of I_2 increased the reactivity of the I^+ source via temporary formation of a *N*-triiodide-species. Instead of mere activation of the carbonyl groups of the imide, the proposed mechanism contains the stabilization of I^+ via Lewis-base-coordination donated by a tertiary amine. The remaining phthalimide-anion is aligned via double hydrogen-bond formation and assists the deprotonation of the nucleophile (Scheme 20).



Scheme 20: Aminourea-catalyzed iodolactonization

Li *et al.* reported in 2012 the first asymmetric intermolecular bromoesterification promoted by a group of different chiral Brønsted acids containing acidic N-H groups.[36] All of them showed good to moderate yield, but the obtained enantiomeric excess were low to zero. Amongst them was one chinchona-derived thiourea catalyst, constructed similarly to the structural design shown in Scheme 15. Unfortunately, this catalyst yielded a racemic mixture (Scheme 21).



Scheme 21: Unsuccessful attempt for asymmetric thiourea-catalyzed intermolecular bromoesterification

2 Results and discussion

2.1 Scope of this work

As already mentioned in the introduction, no practical protocols for asymmetric intermolecular bromofunctionalizations seem having been developed to date. Therefore, the motivation for this work was to design thiourea catalysts and auxiliaries useful for application in these desirable transformations. As there are marginal reports on this field of research, it was concluded that the application of conventional ligands might not be promising, as more reports about this topic would be expected otherwise. The novel ligands should contain combined active functionalities in order to give potentially new approaches to solve this remaining challenge in organic synthesis.

The classic reactions, bromohydroxylation and bromoalkoxylation, were chosen, since no reports could be found addressing these intermolecular transformations. As the solvent (water or alcohol) is usually used in large excess, difficulties in terms of regioselectivity can be expected due to a high degree of solvation through the nucleophile.

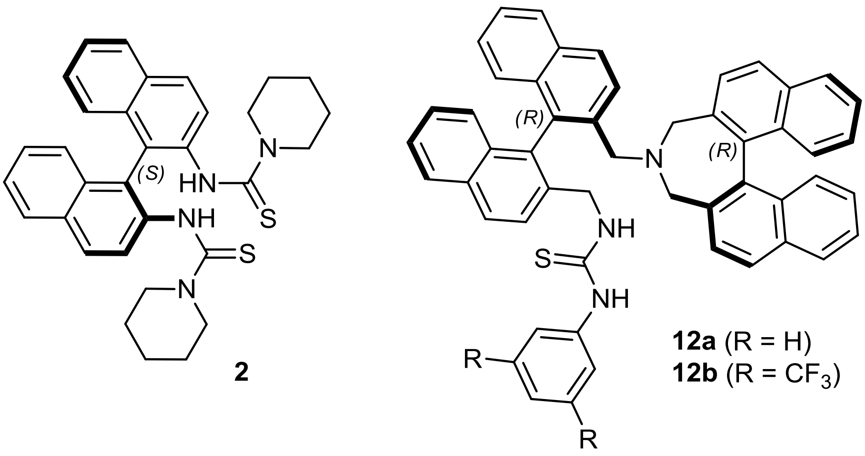
In the catalytic attempts, prochiral *trans*-stilbene was used as substrate because of its bulky structure. The majority of unsaturated compounds applied successfully in asymmetric halofunctionalization are, so far, compounds, which are designed for this particular transformation, meaning that there is often no commercially availability and, to some extent, considerable effort necessary to obtain the substrates. In this work, the substrate is a simple and cheap olefin, which means that a successful asymmetric transformation would be, simultaneously, a tremendous rise in value. Regardless, difficulties towards high enantiomeric excess can be expected, since there are no functional groups in the substrate and, therefore, only weak interaction possible with the catalyst. However, there can still be interaction between the catalyst and the X^+-source, the halonium-ion intermediate or the solvent which acts as nucleophile.

Additionally, a convenient and short route to a new auxiliary has been developed. *N*-Binaphthimide is an axially chiral imide which can be used in Gabriel synthesis for introduction of a primary-amine functionality into alkyl halides. Simultaneously, it should act as a bulky chiral protection group to perform asymmetric diastereoselective transformations on the prochiral starting material. According to the topic of this work, the asymmetric and highly dia- and regioselective bromomethoxylation of ethyl 4-bromocrotonate was successfully performed.

2.2 Catalytic experiments towards the bromohydroxylation and bromoalkoxylation of *trans*-stilbene

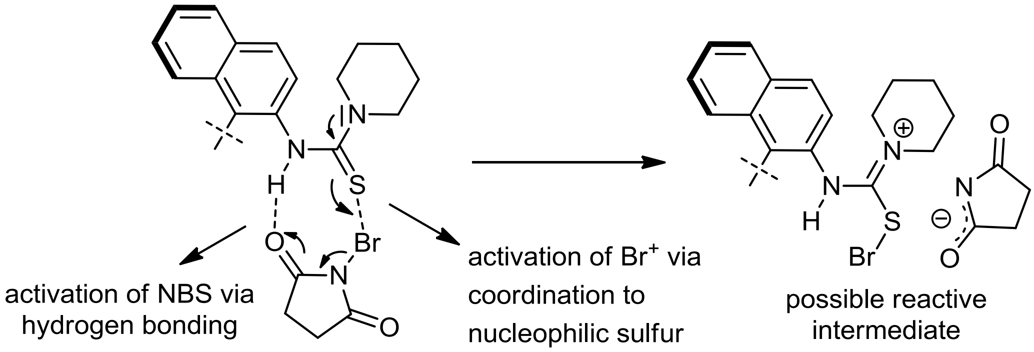
Two structurally diverse catalysts, shown in Scheme 22, were synthesized and applied in the bromohydroxylation or bromoethoxylation of *trans*-stilbene. Since there is minimal interaction expected between the catalyst and the olefin, the formation of a proper pocket seemed to be necessary to induce chirality, which results in the necessity of rather big structures with bulky components. For the chiral backbone, the binaphthyl-unit was chosen, due to its reliable capability of asymmetric induction.[37] Furthermore, a catalyst is required which forms the most reactive intermediate with NBS in order to suppress any background reaction.

Although suggested mechanisms are often based on speculation, there should be an idea as to why the desired structure could be a potentially good catalyst for the desired transformation. Rational arguments will be given based on facts known from the literature.



Scheme 22: Novel thiourea-derived catalysts

Catalyst **2** shows a very rare combination of a thiourea moiety with a tertiary amine. Two facts known from the literature gave reason to try this structure as a potential catalyst. Proposed mechanisms (compare Scheme 11 and 12) often describe a dual activation mode of NBS through the catalysts, as shown in Scheme 23 (left structure). To begin with, acidic N-H protons from thiourea can activate NBS via formation of hydrogen bonds to its carbonyl groups. Since each thiourea unit of structure **2** has only one acidic proton, which is located near the chiral BINOL-backbone, it should cause a strong draw of NBS into the chiral pocket, amplified by twofold activation due to the presence of two thiourea units. Additionally, the widely accepted idea of an interaction between the lone pairs of sulfur to Br^+ could be intensified by the electron-pushing tertiary amine. The cooperation of these effects might lead to the formation of an intermediate with a fragile and therefore highly reactive S-Br σ-bond shown in Scheme 23 (right structure). Furthermore, the bulky aliphatic ring of the piperidine-unit might lead to an extension of the asymmetric environment and an establishment of the desired pocket.

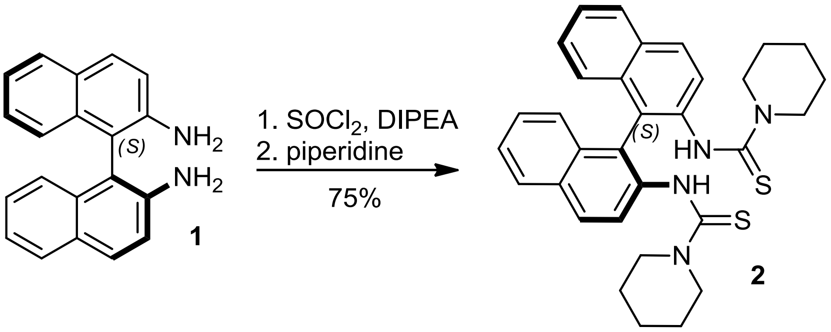


Scheme 23: Possible activation mode of catalyst 2

Structures **12a** and **12b**, on the other hand, contain next to a common thiourea moiety, a rare tertiary amine, comparable to tribenzylamine. Tribenzylamine is known for its extraordinarily low basicity in aqueous solution compared with other trialkylamines, which is caused by a solvation effect and not due to the low electron density of the amine.[38] This similarity should suppress possible deprotonation of benzylic protons in the product, which would result in epimerization. In addition to that, common tertiary amines could also lead to elimination of HBr. This tertiary amine might lead to a different kind of behavior in terms of mechanism and activation of Br^+.

2.2.1 Synthesis of the catalysts

Binaphthyl **2** was prepared in a one pot procedure (Scheme 24). *(S)*-DABN was dissolved in DCM and added drop-wise into a solution of thiophosgene in DCM. This order seemed to be critical to provide excess of thiophosgene during the addition, in order to suppress intramolecular thiourea formation or bis-DABN thiourea products. The reaction was completed by addition of DIPEA followed by an excess of piperidine, giving **2** in a yield of 75%.



Scheme 24: Synthetic approach to structure 2

Addition of a large excess of piperidine was crucial in order to obtain **2**, otherwise no product would be isolated due to various side reactions. The structure of **2** was confirmed by X-ray crystallography (Figure 1).

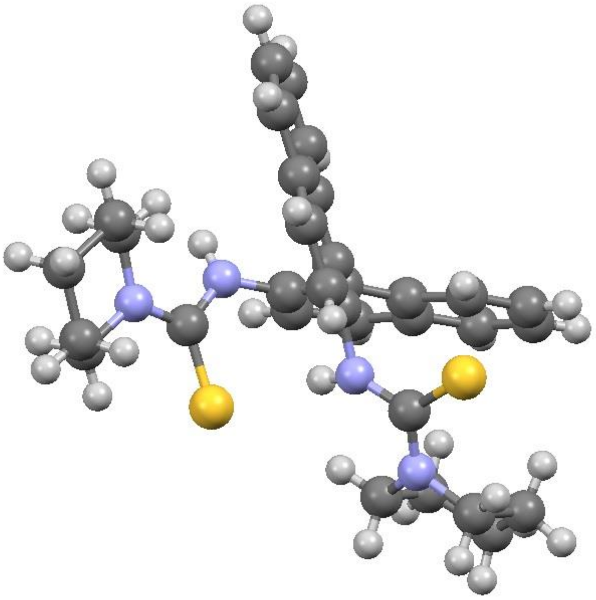
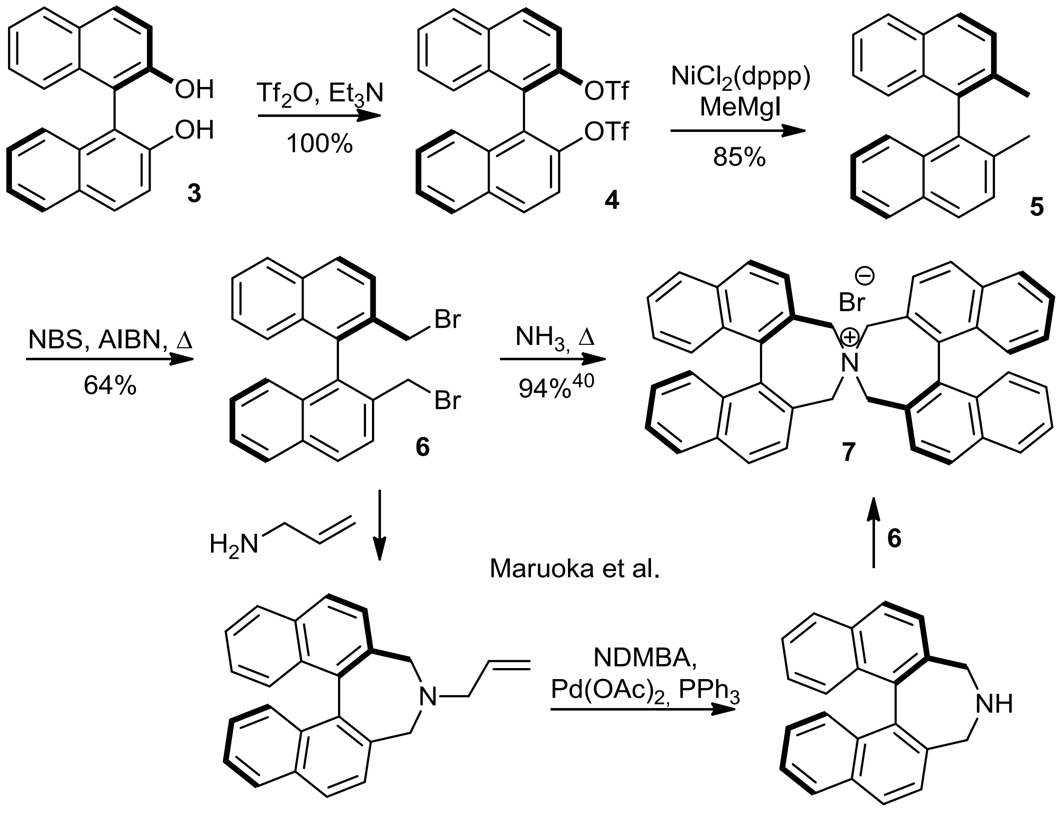


Figure 1: X-ray structure analysis of 2

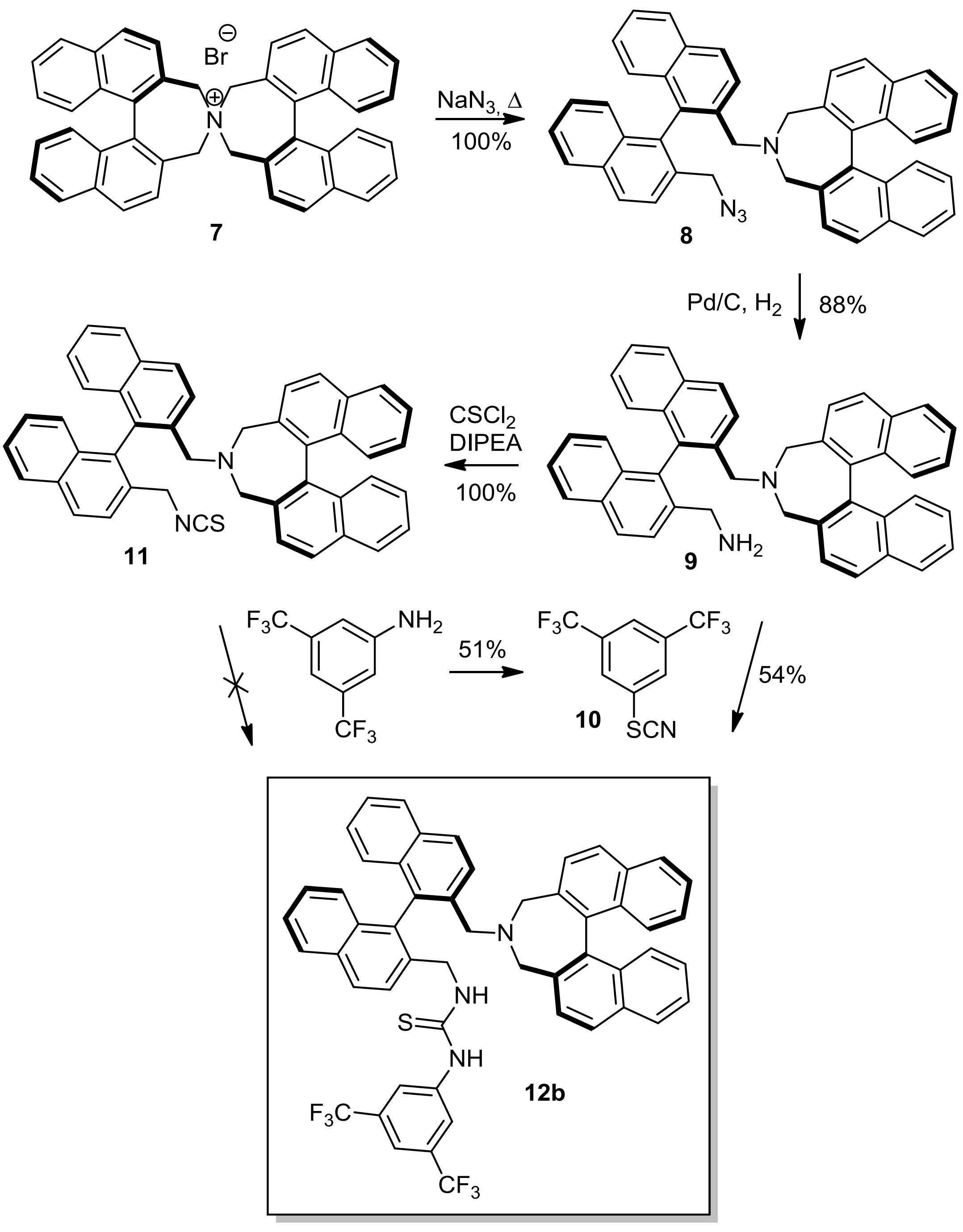
Structure **12** is derived from *N*-spiro-ammonium salt **7**, which is already known as a highly efficient phase transfer catalyst, developed by Maruoka *et al.* (Scheme 25).[39] The synthetic approach to structure **7** follows the literature procedure to yield dibromide **6**. Maruoka´s approach from **6** to **7** is a 3-step procedure, starting with condensation of the dibromide with allylbromide to form the azepine. Rh- or Pd-mediated cleavage of the allylgroup was followed by condensation with **6** to give the ammonium salt in a total yield of 71%. However, a different procedure, developed by Widhalm,[40] gave **7** in excellent yield in a single step.



Scheme 25: Modified synthetic approach to phase transfer catalyst 7 and original approach by Marouka *et al.*.

The synthesis of **12b** started with the preparation of optically pure BINOL. Oxidative coupling of 2-naphthole with $FeCl_3$ in aqueous solution gave racemic BINOL in a yield of 75%.[47] Optical resolution of BINOL was achieved by means of *N*-benzylcinchonidiniumchloride through the preferred formation of an inclusion complex with *(R)*-BINOL[48]. This clathrate can be separated due to its precipitation in acetonitrile. Several steps of recrystallization gave 79% of *(R)*-**3** and 84% of *(S)*-**3** with 100% enantiomeric excess for both enantiomers, determined by HPLC-analysis. The following steps were carried out according to the literature.[39] Conversion of *(R)*-BINOL with triflic anhydride to its corresponding triflate gave **4** in quantitative yield, and Kumada-coupling with freshly prepared MeMgI, catalyzed with $NiCl_2$(dppp), gave the dimethylated species **5** in a yield of 85%. Monobromination of the methyl groups by NBS, initiated by AIBN, afforded dibromide **6** in 64% yield. According to Widhalm´s procedure, the dibromide was reacted with aqueous ammonia by heating in an autoclave for 28 h at 70-80 °C, to give the pure ammonium bromide **7** in 94% yield, without necessity for further purification.

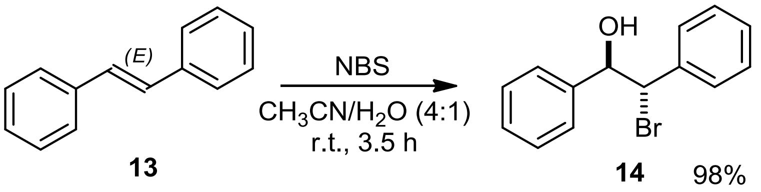
The synthetic approach to structure **12b** is shown in Scheme 26. Opening of one azepine ring of ammonium salt **7** was achieved by nucleophilic substitution. Stirring the mixture with sodium azide in DMF at 110 °C for 12 h provided azide **8** in quantitative yield, and reduction with Pd/C under H_2-atmosphere overnight gave the corresponding amine **9** in 88% yield. In order to achieve structure **12b**, the pathway via isothiocyanate **11** was chosen first. **11** was easily obtained by drop-wise addition of **9** to a solution of thionylchloride in DCM, followed by addition of DIPEA to give the isothiocyanate in quantitative yield. However, the formation of thiourea **12b** via nucleophilic addition of 3,5-bis(trifluoromethyl)aniline to **11** in DCM was not successful, most likely due to the low nucleophilicity of the aniline. Concluding from this, a different approach was chosen. Isothiocyanate **10** was prepared by treatment of 3,5-bis(trifluoromethyl)aniline with thiophosgene and DIPEA, to give **10** in 51% yield. Combination of amine **9** and isothiocyanate **10** yielded the desired thiourea **12b** in 54% yield.



Scheme 26: Synthetic approach to thiourea 12b

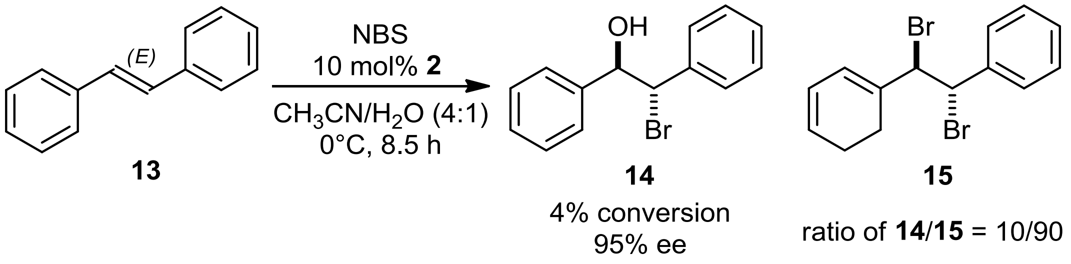
2.2.2 Catalytic experiments

To begin with, non-catalyzed bromohydroxylation and bromomethoxylation of *trans*-stilbene **13** were carried out, in order to characterize racemic products and to find a method for determination of enantiomeric excess. In the case of bromohydroxylation, a good separation was discovered using chiral HPLC. Unfortunately, no separation conditions could be found for the corresponding methoxybromide. The bromohydroxylation was carried out in a mixture of acetonitrile/water (4:1) with 1.2 equivalents of *N*-bromosuccinimide (Scheme 27). After stirring for 3.5 h at room temperature, stilbene was converted to **14** with 98% yield. It is worth to note that no formation of dibromide was observed.



Scheme 27: Bromohydroxylation of *trans*-stilbene

Catalyst **2** showed unexpected behavior in the attempts towards bromohydroxylation of **13**. Addition of NBS to a solution of structure **2** in an acetonitrile/water mixture showed a fast change of color to dark red, with formation of considerable amounts of dibromide **15**, as determined in the ^{1}H-NMR spectra of the crude mixture. This result is quite confusing, since the tremendous excess of nucleophile in the solution should give the bromohydrin as the major product. The reaction was repeated under a variety of conditions, but barely any experiments gave detectable amounts of the desired bromohydrin **14**. This result indicates an unusual mode of activation of NBS. A radical pathway might be operative, explaining the preferred formation of dibromide. Additionally, an unwanted reaction between the catalyst and NBS cannot be excluded, since the catalyst was not found in the reaction mixture. Despite poor yields, one experiment giving detectable amounts of product is described below. (Scheme 28)



Scheme 28: Bromohydroxylation of *trans*-stilbene with catalyst 2

The reaction was carried out in a mixture of CH_3CN/water (4:1) at 0 °C. *N*-bromosuccinimide was added in 10 portions over a period of 7.5 h in order to keep the concentration of the bromination agent low, and stirring for an additional hour gave the desired bromohydrin in 4% conversion. Surprisingly, the enantiomeric excess seemed to have 95%, which is extraordinarily high (Figure 2). Unfortunately, the bromohydrin/dibromide ratio was 10/90, as determined in the ^{1}H-NMR spectra from the crude mixture.

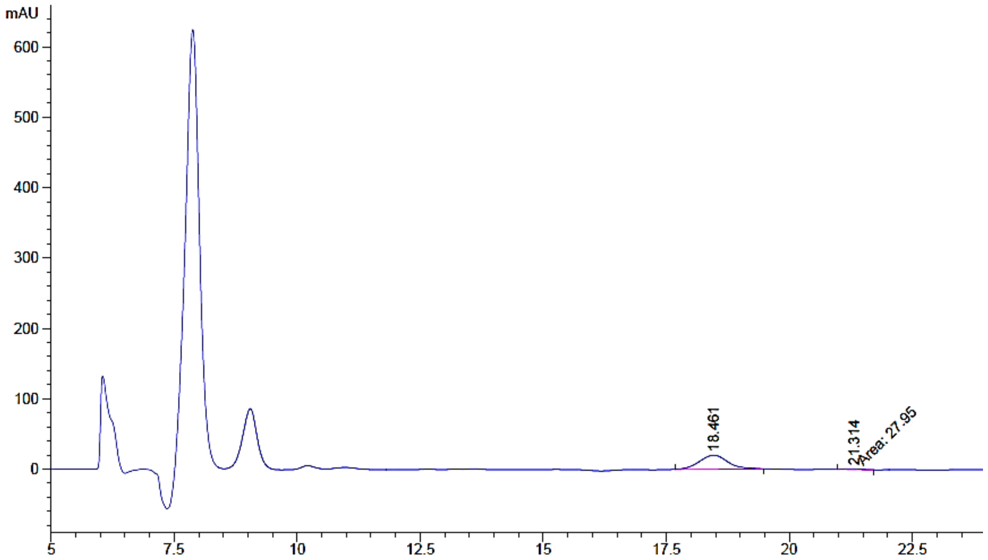
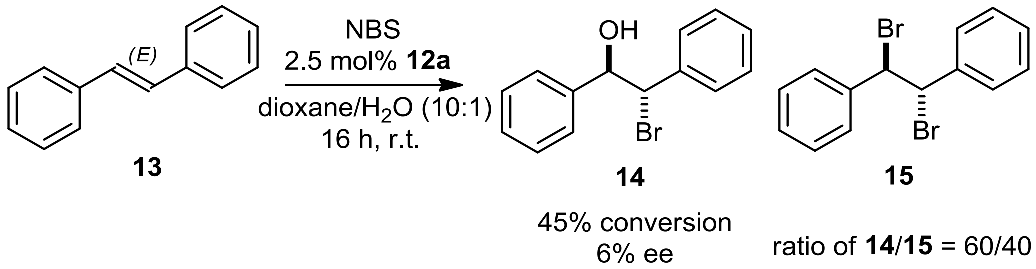


Figure 2: HPLC analysis of bromohydrin catalyzed with 2. Retention times of the bromohydrin: 18.461 min (major) and 21.314 (minor)

Despite the high enantiomeric excess, it was impractical to continue experimentations with structure **2**, due to the preference for the formation of dibromide.

The unexpected behavior of compound **2** might be due to the strong nucleophilicity of the sulfur. Therefore, structures of type **12** have been applied, since a weak nucleophilicity is expected from the common thiourea moiety and from the tertiary amine, due to its similarity to tribenzylamine. To begin with, an attempt with auxiliary **12a** was made. **12a** was supposed to be, in general, a mild catalyst, since it showed no catalytic activity in test reactions like Aldol reaction or Michael addition. Tetranaphthyl **12a** was applied in the bromohydroxylation of *trans*-stilbene.

The reaction was carried out in a less polar mixture of dioxane/water (10:1), since **12a** proved to be insoluble in an acetonitrile/water mixture, especially at low temperatures. Under these conditions, bromohydrin **14** was obtained. After stirring for 16 h at room temperature, with a catalyst loading of 2.5 mol%, 45% conversion was observed (Scheme 29).



Scheme 29: Bromohydroxylation of *trans*-stilbene with catalyst 12a

The bromohydrin/dibromide ratio was found to be 60/40, determined by the ^{1}H-NMR spectra of the crude mixture. An enantiomeric excess of 6% was determined via HPLC analysis (Figure 3).

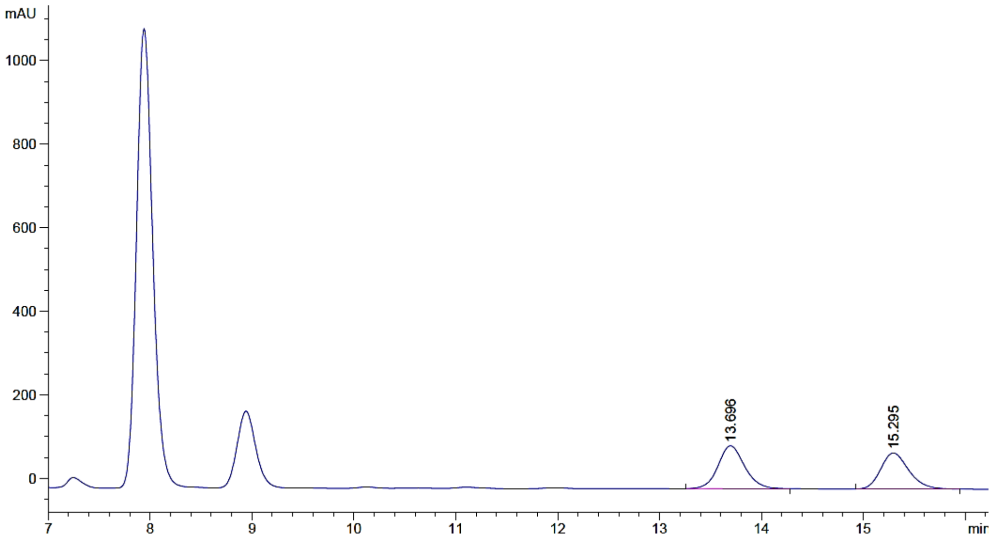
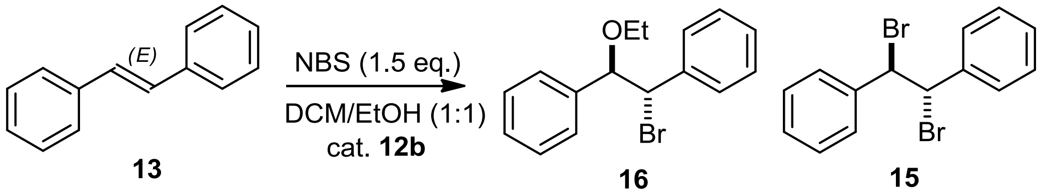


Figure 3: HPLC analysis of bromohydroxylation catalyzed with 12a. Retention times: 13.696 min (major) and 15.295 (minor)

Since only a small amount of **12a** was available, further investigations were abandoned.

The promising result with catalyst **12a** regarding the relatively high conversion justified the synthesis of **12b**. The attachment of an electron withdrawing group to the thiourea moiety was chosen in order to increase its Brønsted-acid reactivity. Additionally, a change of solvents, and as a result, a different reaction type, was necessary in order to suppress the non-catalyzed reaction. This conclusion was based on experiments of non-catalyzed bromohydroxylation and bromoalkoxylation, which seem to be rather slow at temperatures below 0 °C. The solvent was altered to a dichloromethane/ethanol mixture instead of dioxane/water. This change was necessary in order to decrease the reaction temperature, since the high melting points of these solvents do not allow reactions below 0 °C.

Compared to previous results, this reaction seemed to work promisingly at the first glimpse. Addition of NBS to a solution of 10 mol% **12b** in a 1:1 mixture of DCM/EtOH showed a sudden color change to intensely bright yellow. Of course, no conclusion can be made based on the colors of reaction mixtures, but it at least demonstrated a possible interaction between NBS and the otherwise nearly colorless catalyst. The expected products of bromoethoxylation of **13** are shown in Scheme 30.



Scheme 30: Expected products for bromoethoxylation of *trans*-stilbene

Conditions for the determination of the enantiomeric excess were found by GC by measurement of a racemic sample of **16**. As in the case of the corresponding methoxybromide, no separation of **16** via HPLC was possible.

Table 1: Results of asymmetric bromoethoxylation of *trans*-stilbene with catalyst 12b shown in Scheme 30:

Catalyst loading	T (°C)	t (h)	Conversion in %	ee in %	Ratio of **16/15**
-	0	24	20	-	100/0
10 mol%	0	24	100	5	72/28
10 mol%	-30	24	**86**	**25**	**89/11**

Results are given in Table 1. At 0 °C, the non-catalyzed reaction gave only 20% conversion after stirring for 1 day. This reaction was rather slow, but, as in case of the bromohydroxylation shown in Scheme 27, no formation of dibromide was observed.

The presence of **12b**, on the other hand, led, after stirring for 1 day at 0 °C, to complete conversion. Concluding from this, the catalyst seems to accelerate the reaction significantly. In accordance with the catalytic attempts mentioned above, thiourea **12b** led also to 28% dibromide as by-product, which is quite an improvement, compared to former experiments. GC analysis showed a low enantiomeric excess of 5% with a catalyst loading of 10 mol%. Next, the reaction was carried out at -30 °C under the same conditions. After 1 day, a conversion of 86% was detected by the ^{1}H-NMR-spectra of the crude mixture, which was quite satisfying in view of the low temperature. Fortunately, the dibromide formation seems to decrease at low temperature, with the ethoxybromide to dibromide ratio increasing to 89/11. In terms of asymmetric induction, an improvement of enantiomeric excess to 25% (Figure 4) was found, which makes this catalyst a promising candidate for this kind of transformation.

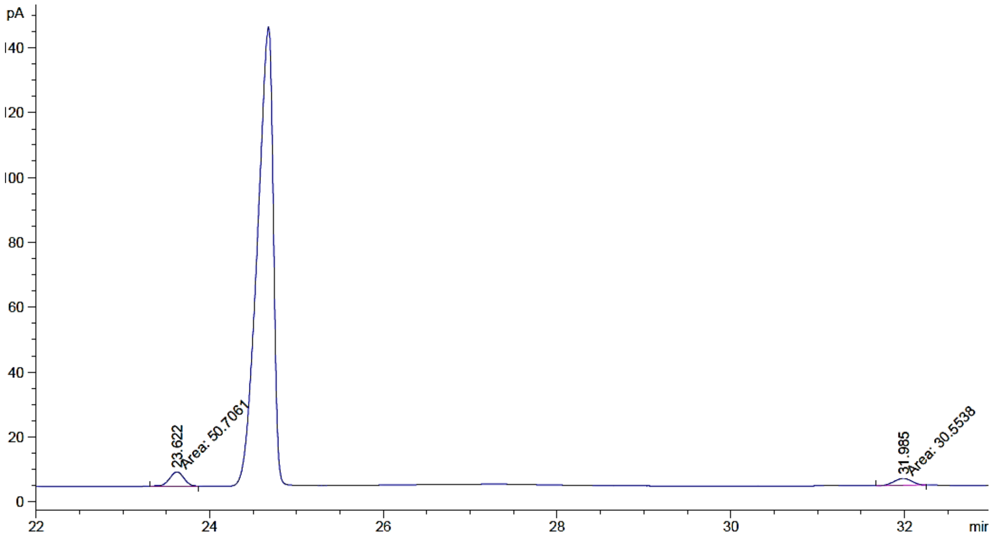


Figure 4: GC-analysis of the bromoethoxylation of *trans*-stilbene with catalyst 12b at -30 °C. Retention time: major (23.622) and minor (31.985) including a tremendous peak for trans-stilbene due to its high response factor.

Unfortunately, purification of the product via chromatography on silica gel remained unsuccessful. Product **16**, dibromide **15** and *trans*-stilbene are highly apolar and, therefore, elute together at the very beginning.

2.2.3 Conclusion

Compared to the non-catalyzed reactions, all catalytic attempts showed significant formation of dibromide as side-product. When **2** was applied as catalyst, the dibromide was even obtained as the major product. This unexpected fact showed that it is not straight forward to find catalysts with high chemoselectivity towards the formation of the desired products, and cannot be extrapolated from the non-catalyzed transformations. Therefore, to find a chemoselective catalyst is a quest on its own, which makes the aim for enantioselectivity the second priority. It should be mentioned that at least high diastereoselectivity was observed, since no *cis*-adducts have been found. In general, low temperatures seem to be necessary to obtain significant ee´s, since it is important to suppress the non-catalyzed pathway, which is sluggish at temperatures below 0°C. This makes the use of water as a nucleophile critical and, therefore, limits the access to bromohydrins by means of this method.

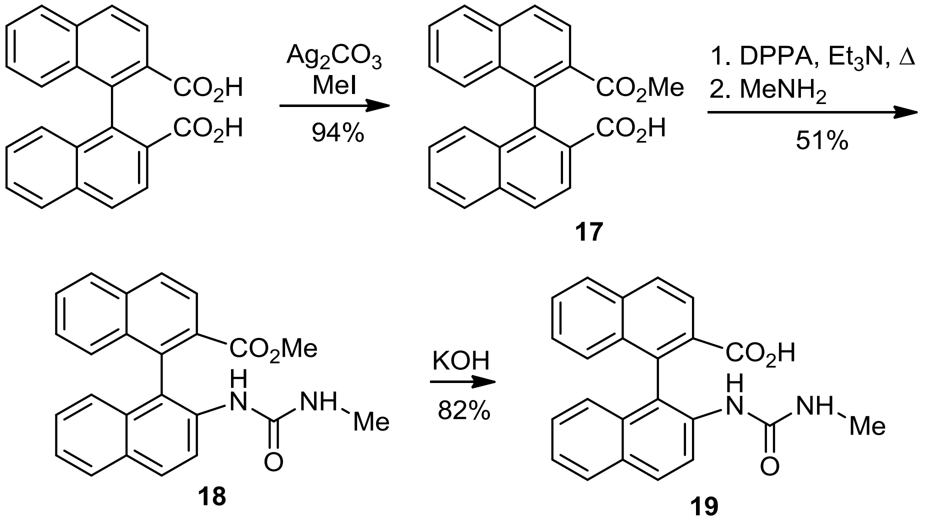
Promising is structure **12b**, as it accelerates the bromoethoxylation of trans-stilbene significantly. With a decrease in temperature, the formation of dibromide, fortunately, also decreased, and the enantiomeric excess increased as expected. Since no information about thiourea-catalyzed intermolecular asymmetric bromoalkoxylation of non-functionalized olefins was found in the literature, the results of the experiments with **12b** are quite satisfying. It shows high conversion, even at low temperatures, and good chemoselectivity towards formation of the ethoxybromide. Additionally, an enantiomeric excess of 25% confirms the capability of asymmetric induction of this catalyst.

In order to make this reaction practically useful in organic synthesis, the extension to other nucleophiles is a priority objective. Beyond this, screening of different olefins and variation of the temperature will be necessary to show scope and limitations of this catalytic system.

2.3 Synthesis of non-thiourea ligands

Aside from thiourea catalysts, other novel BINOL-derived Brønsted acids were prepared in order to find alternative catalytically active moieties for bromofunctionalization-reactions. The synthetic approach towards these structures was first developed with achiral starting material, in order to optimize the synthesis with cheap precursors. The structures are derived from binaphthyl-dicarboxylic acid.

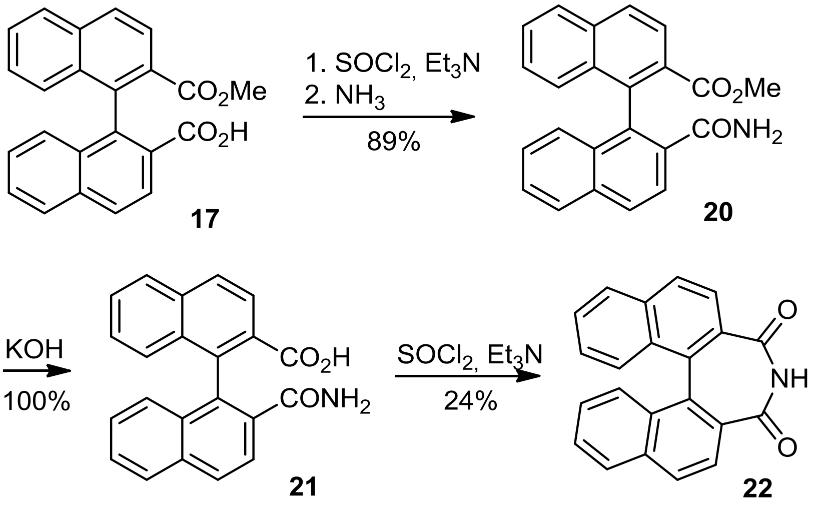
In order to gain bifunctional compounds, a desymmetrization step is necessary. This was achieved by monoesterification of the binaphthyl dicarboxylic acid with freshly prepared silver(I)carbonate and methyl iodide.[41] Monoester **17** was obtained in nearly quantitative yield, with a monoester/diester ratio of 94/6. The crude monoester was used without further purification, since an attempt to purify by flash chromatography on silica led to quantitative saponification and recovering of the starting material. The synthesis of urea **19** was developed (Scheme 31), since the combination of a urea-moiety with a carboxylic acid seemed to be interesting. Especially in terms of intramolecular hydrogen bonding, compared to the urea-activated thiourea shown in Scheme 17, internal activation of the carboxylic acid through the urea moiety should significantly increase the acidity of the carboxylic acid.



Scheme 31: Synthetic approach to racemic bifunctional Brønsted-acid 19

Therefore **17** was converted to the urea via Curtius-rearrangement with DPPA and methylamine to give **18**. Simple saponification of the methyl ester with KOH gave the corresponding carboxylic acid **19**, which was isolated as a yellow solid. However, **19** was insoluble in all common solvents, which made a proper characterization by NMR-spectroscopy and, more important, application in homogenous catalysis, impossible. The structure was confirmed by mass spectroscopy, but was not applied in any transformations.

A very versatile functionality in bromofunctionalization could be the imide moiety, since it holds a relatively acidic proton due to two electron-withdrawing carbonyl groups. Additionally, imides are strongly linked to halofunctionalization, since *N*-halosuccinimides and *N*-halophthalimides are popular X^+-sources. A major drawback of asymmetric halofunctionalization via hydrogen bond donor catalysis is that these reagents do not necessarily require activation through a catalyst to undergo reactions with olefins. In order to obtain reasonable asymmetric induction, the occurrence of this non-catalyzed pathway, which forms the racemic product, must be prevented. A possible, but non-catalytic, approach to solve this problem could be the use of a chiral X^+-source. This makes binaphthimide **22** an obvious candidate. Surprisingly, this molecule was not found in the literature, which gave reasonable doubts concerning the stability of this compound. In order to test formation and stability of this 7-membered ring, a synthetic route towards the racemic compound from already prepared monoester **17** was developed (Scheme 32).



Scheme 32: Synthetic approach to racemic binaphthimide 22

Treatment of monoester **17** with thionylchloride and reaction of the acid chloride with ammonia gave amide ester **20**, which was converted quantitatively by saponification with KOH into amide acid **21** (Figure 5).

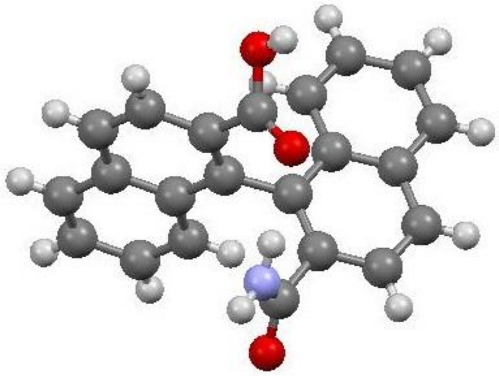


Figure 5: X-ray structure analysis of amide acid 21

Ring closure of **21** was quite difficult since high temperatures or the coupling agent DCC did not result in the formation of the 7-membered ring. The condensation was finally achieved in a poor yield of 24% with thionylchloride to give the strongly fluorescing binaphthimide **22**, whose structure was also confirmed by X-ray-crystallography (Figure 6).

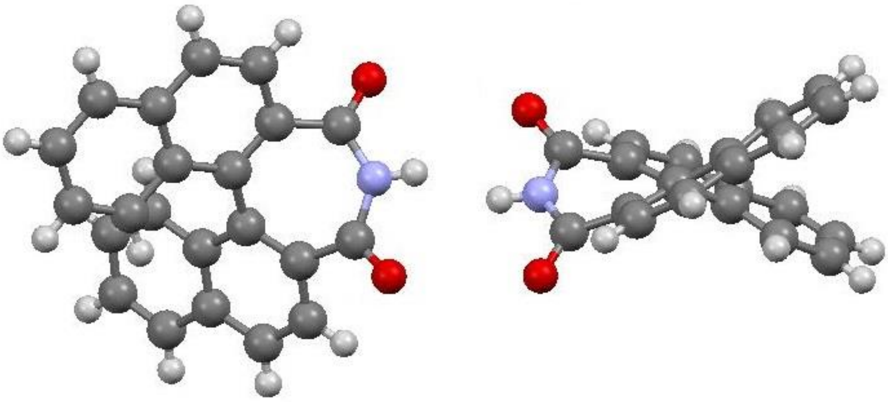


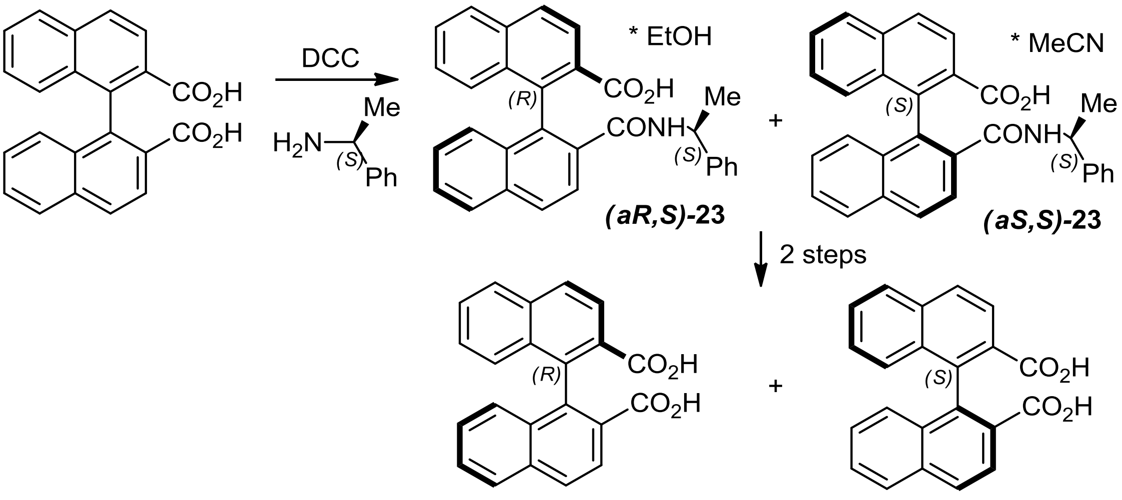
Figure 6: X-ray structure analysis of binaphthimide 22. Note the pronounced overlap of the naphthylgroups observable in the left structure.

Several attempts towards *N*-bromination of **22**, in order to prepare a chiral NBS-analog, failed. Concluding from this, a different chemical behavior also in other transformations, compared to common imides, was expected. Despite the fact that the viability of **22** was confirmed, it was still unknown whether this compound racemizes easily. The 7-membered ring flattens the molecule compared to acyclic binaphthylderivates, but it also leads to distortion of the binaphthyl skeleton, which should inhibit the racemization through rotation. In order to conduct further investigations, the development of an efficient synthetic route towards the enantiopure compound was required.

2.4 Non-catalytic bromomethoxylation of ethyl-crotonate with binaphthimide

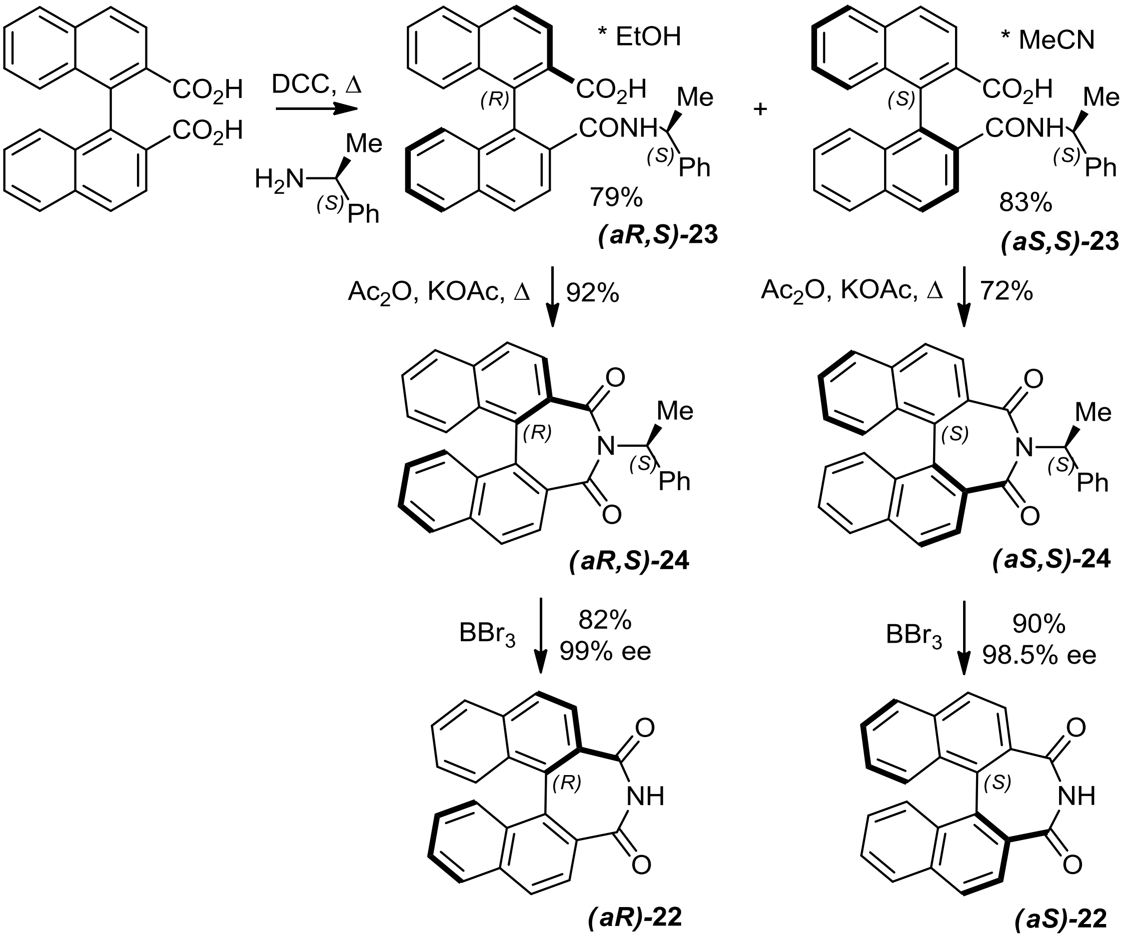
2.4.1 Synthesis of enantiopure binaphthimide

In order to prepare enantiopure **22**, a completely different approach compared to the racemic synthesis was chosen. Since the optical resolution of binaphthyl dicarboxylic acid via *(S)*-1-phenylethylamine takes already 3 steps, according to the method developed by Oi *et al.*[42] (Scheme 33), the synthesis of enantiopure **22** via the pathway shown in Scheme 32 would be too time consuming. Furthermore, this pathway should not be preferred, since the ring closure in the last step has a pretty low yield. The preparation of a fully synthetic auxiliary should be short and efficient, otherwise it is not reasonable. Additionally, it would be favorable if the nitrogen from *(S)*-1-phenylethylamine stays in the molecule in order to form the imide.



Scheme 33: 3-Step optical resolution of binaphthyl dicarboxylic acid by Oi et al.[42]

A reasonable synthesis of optically pure **22** was developed, which is shown in Scheme 34. The binaphthimide was prepared simply in 3 steps, including optical resolution, starting with racemic binaphthyl dicarboxylic acid. The first step is adapted from the optical resolution of binaphthyl dicarboxylic acid, the monoamide formation with *(S)*-1-phenylethylamine, yielding 79% of clathrate ***(aR,S)*-23** and 83% of clathrate ***(aS,S)*-23**. Ring closure of **23** was achieved in good yield in acetic anhydride at 100 °C in the presence of potassium acetate. The *N*-alkyl group originating from *(S)*-1-phenylethylamine significantly increases the nucleophilicity from the nitrogen in order to give the imide **24**, as the ring closure of the unsubstituted amide **21** did not afford **22** under similar conditions. Removal of the alkyl group in **24** was attempted with Pd/C under H_2-atmosphere, but without any product isolated. Boron tribromide, on the other hand, was the reagent of choice, giving enantiopure imide **22** in high yield. It is important to note that residues of BBr_3 should be completely removed *in vacuo* before quenching of the reaction mixture, since nucleophilic ring opening of **22** was observed with incomplete BBr_3 removal followed by quenching with a methanol/water mixture.



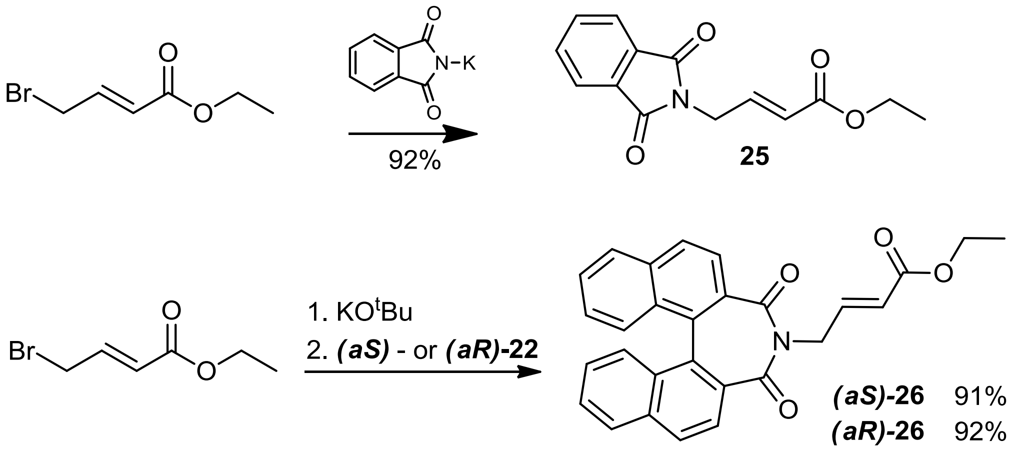
Scheme 34: Synthetic pathway to optically pure binaphthimide 22

The optical purity was determined after the last step by chiral HPLC, giving ***(aR)*-22** with 99% ee in an overall yield of 60% and ***(aS)*-22** with 98.5% ee in an overall yield of 54% over 3 steps.

2.4.2 Application of binaphthimide in asymmetric bromomethoxylation

A prominent application of imides is the Gabriel synthesis, which results the introduction of nitrogen in molecules by substitution of halides by imides. The common reagent for this transformation is potassium phthalimide salt. An advantage of this method is that the nitrogen is introduced already with a proper protection group attached, since phthalimides need relatively strong bases like potassium hydroxide or hydrazine to be cleaved, in order to gain the corresponding primary amine.

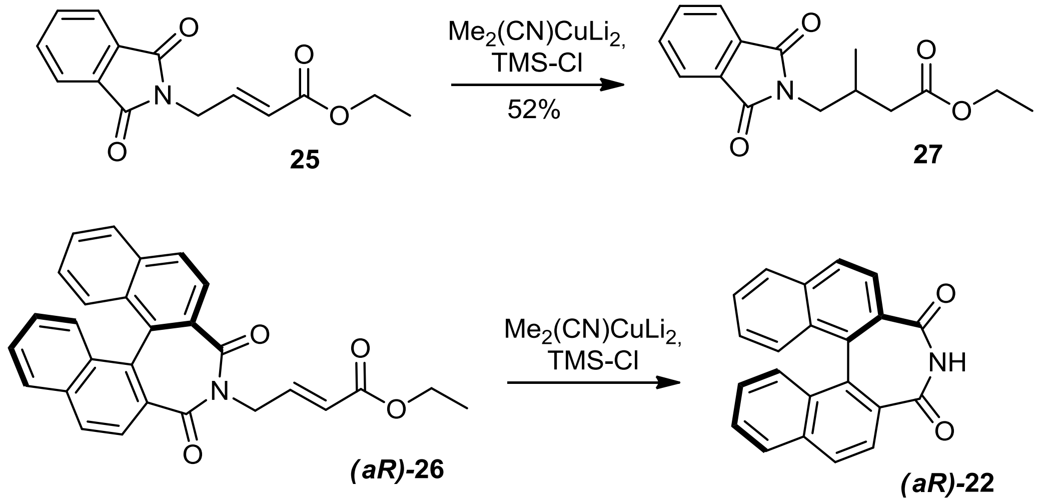
With this in mind, use of **22** in the Gabriel synthesis was its most obvious application. Since binaphthimide **22** is axially chiral, its binaphthyl skeleton can act as an *N*-protection group and chiral auxiliary at the same time. Additionally, binaphthimide is a strongly fluorescing molecule, which makes compounds attached to this functionality easily detectable. Ethyl 4-bromocrotonate was chosen as the prochiral substrate and it was coupled with **22** and phthalimide in order to have the opportunity to compare the results with **26** to its achiral analog **25** (Scheme 35).



Scheme 35: Coupling of phthalimide potassium salt and binaphthimide 22 with ethyl 4-bromocrotonate.

Coupling of ethyl 4-bromocrotonate with phthalimide potassium salt to give **25** was carried out according to a literature procedure[43] with 92% yield. In situ formation of the potassium salt of **22** with a potassium hydroxide solution in ethanol followed by addition of ethyl 4-bromocrotonate gave **26** in only 74% yield. Since DMF proved to be a good solvent for the synthesis of **25**, an improved procedure for the preparation of **26** was developed. Therefore, binaphthimide **22** was dissolved in DMF and freshly purified potassium *tert*-butoxide was added. The resulting suspension was poured on neat bromocrotonate in order to obtain **26** in more than 90% yield. It is worth mentioning that both steps, the deprotonation and the substitution, are completed within minutes, which makes this coupling procedure pretty convenient.

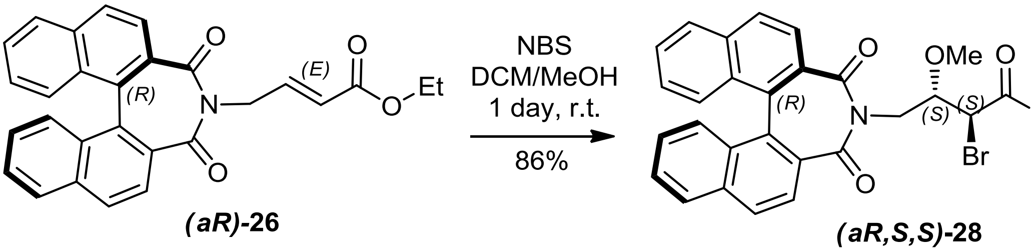
A useful transformation of compounds **25** and **26** would be the 1,4-addition of organocuprates with the aim to obtain the corresponding GABA-analogs after cleavage of the protection groups. To begin with, addition of methyl cuprates was performed on achiral **25** first, in order to find the best reaction conditions with the cheaper compound first. The reaction was carried out with the lower-order cuprate $(Me)_2CuLi$ in the presence of TMS-Cl in the first place, which gave only traces of the methylated product.[44] Quite an improvement was found by the use of the higher-order cuprate $(Me)_2Cu(CN)Li_2$. Under similar conditions, compound **27** was isolated in 52% yield (Scheme 36).



Scheme 36: β-Methylation of 25 and unsuccessful reaction of *(aR)*-26 under the same conditions

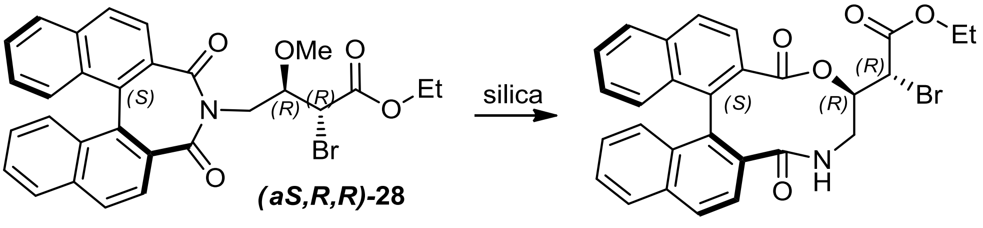
The chiral crotonate **26** showed completely different reactivity to its achiral counterpart **25**. Instead of the expected 1,4-addition under similar conditions applied in the formation of **27**, no methylated product of **26** was obtained. The reaction conditions caused cleavage of the imide and the unsubstituted binaphthimide **22** was isolated in quantitative yield. It is worth to note that **22** seemed to form a complex with copper(I) and was only found after aqueous workup of the reaction mixture and decomposition of its precipitate.

Compound **26** was applied afterwards in asymmetric bromomethoxylation. The reaction was carried out with NBS in a mixture of DCM/MeOH at 0 °C, and after 24 h a low conversion of only 4% was detected in the ^1H-NMR-spectra of the crude reaction mixture. Performance of the reaction at room temperature on the contrary gave complete conversion, meaning a drastic increase in the reaction rate. The ^{1}H-NMR-spectra showed a very clean reaction mixture containing only two out of eight possible isomers in the ratio of 86/14. The two diastereomers are separable by flash chromatography to give as the major component presumably ***(aR,S,S)*-28**, which was obtained in a yield of 86% (Scheme 37).



Scheme 37: Highly regioselective and diastereoselective methoxybromination of ethylcrotonate with use of binaphthimide 22 as an auxiliary

The configuration of the main product was concluded from the X-ray structure of a rearrangement product (Figure 7). ***(aS)*-26** was reacted with NBS at the same conditions as shown in Scheme 37, yielding the corresponding enantiomer of ***(aR,S,S)*-28** with a similar diastereomeric ratio of 84/16, determined from the ^{1}H-NMR-spectra of the reaction mixture. In order to prepare the crude product for purification by chromatography, silica gel was added to the solution and evaporated to dryness. While common liquid application of the product on the column did not harm the product, the acidic environment on the dry silica gel led quantitatively to an unusual ring expansion to form a 10-membered ring, which was isolated as the main component and not observed in the crude product (Scheme 38).



Scheme 38: Silica gel initiated ring expansion of *(aS,R,R)*-28

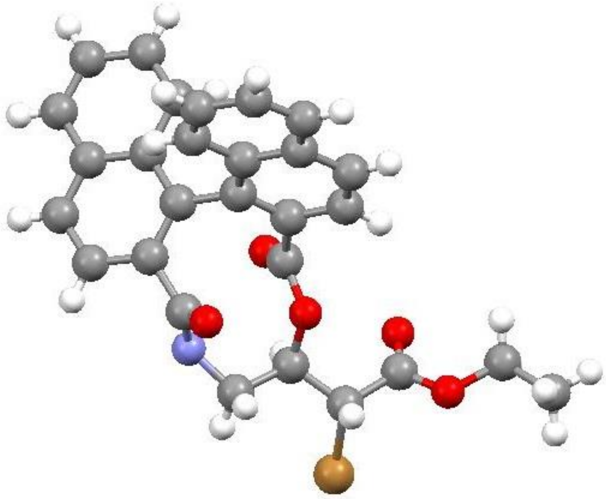


Figure 7: X-ray structure of silica gel initiated ring expansion product originating from *(aS,R,R)*-28

Since it is assumed that the α-bromine is not involved in the unknown mechanism of the ring expansion and therefore keeps its chirality, α-configuration of original and the rearranged product will be identical.

2.4.3 Conclusion

With binaphthimide **22**, a fluorescing and therefore easily detectable auxiliary has been developed. It can be prepared in 3 steps starting from achiral binaphthyl dicarboxylic acid in high yield and can be coupled with alkyl halides in a short and convenient procedure. It shows very strong asymmetric induction in the highly regio- and diastereoselective methoxybromination of ethyl-crotonate, yielding only two out of eight possible isomers in a diastereoselective ratio of 86/14, which was obtained without comprehensive optimization of the reaction. Additionally, possible separation of the diastereomers by flash chromatography on silica gel gives the diastereomerically pure compounds. Especially with the ring expansion shown in Scheme 38 in mind, the unusual and different chemical behavior of binaphthimide compared to its achiral analogs might become interesting concerning new and rare transformations. Anyway, in order to make its behavior predictable, more experiments are still necessary to explore its capabilities and to broaden the field of application. Additionally, a mild and selective procedure to cleave the auxiliary from the product is still required. The observed quantitative cleavage of binaphthimide from the crotonate in the presence of organocuprates might be one solution, since it offers the possibility to recover the precious auxiliary after a successful transformation.

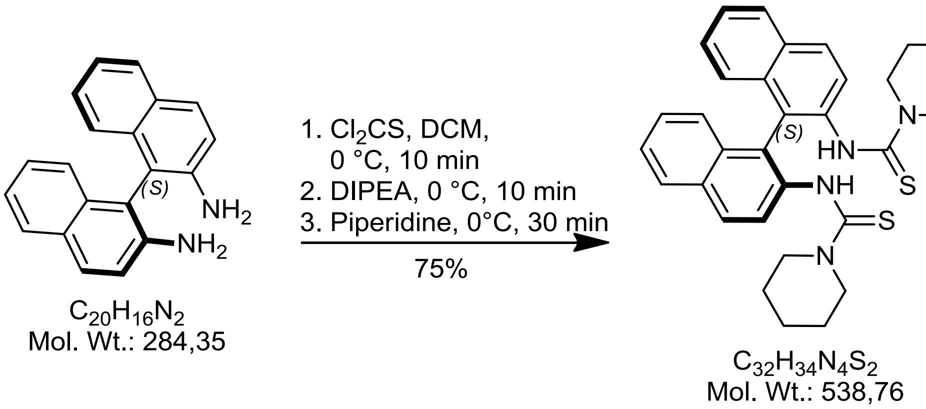
3 Experimental section

Melting points were measured with a Kofler melting point apparatus, uncorrected. Optical rotations were determined with a Perkin Elmer polarimeter 341 in a 1 dm thermostated cell. NMR-spectra were measured on a Bruker AVIII400 spektrometer at 400.27 MHz (^{1}H) and 100.66 MHz (^{13}C). NMR-spectra were measured with $CDCl_3$, chemical shifts δ are stated in ppm and relative to solvent residual signals at 7.26 (^{1}H) and 77.16 (^{13}C) ppm. ^{13}C-NMR spectra were recorded in a *J*-modulated mode, signals are assigned as C, CH, CH_2, CH_3. Coupling patterns in ^{1}H-NMR spectra are designated according to standard abbreviations using s (singulett), d (duplett), t (triplett), q (quartett), m (multiplett) and b (broad). HRMS was measured with an ESI TOF mass spectrometer (Bruker Maxis). Purification by chromatography was performed with a Biotage Isolera One flash purification system and SiO_2 - cartridges. Enantiomeric excess was determined via chiral HPLC using Agilent Technologies 1200 series or chiral GC using Agilent Technologies 7683 B Series Injector.

Heptane, dichloromethane and ethylacetate were distilled before use. Absolute solvents were gained by distillation with sodium benzophenone ketyl for tetrahydrofurane, CaH_2 for dichloromethane and LAH for diethylether. Dimethylformamide, thionylchloride, diisopropylethylamine, piperidine and Et_3N were purified by distillation, in case of Et_3N in the presence with CaH_2. Purification of potassium tert-butoxide was performed by dissolving KO^{t}Bu in anhydrous THF, followed by filtration under argon atmosphere over celite in dry glassware in order to remove the insoluble decomposition products potassiumhydroxide and potassiumcarbonate, followed by removal of the solvent on the pump. MeMgI was prepared according to standart procedures. The starting materials were prepared via a procedure by Kanoh et al.[45] for binaphthyl dicarboxylic acid and Miyano et al.[46] for *(S)*-DABN. Other solvents and reagents were used in analytical grade and applied without further purification.

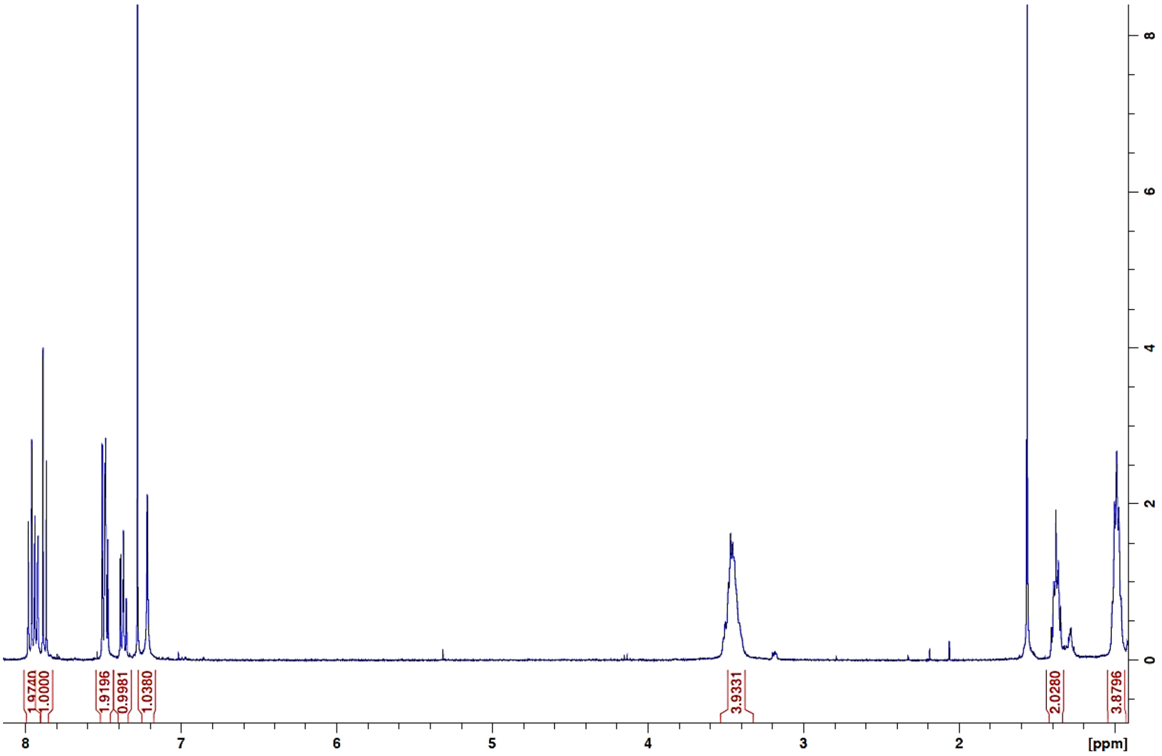
3.1 Procedures for the synthesis of thiourea ligands and related experiments

(S)-N,N'-([1,1'-Binaphthalene]-2,2'-diyl)bis(piperidine-1-carbothioamide) (2)

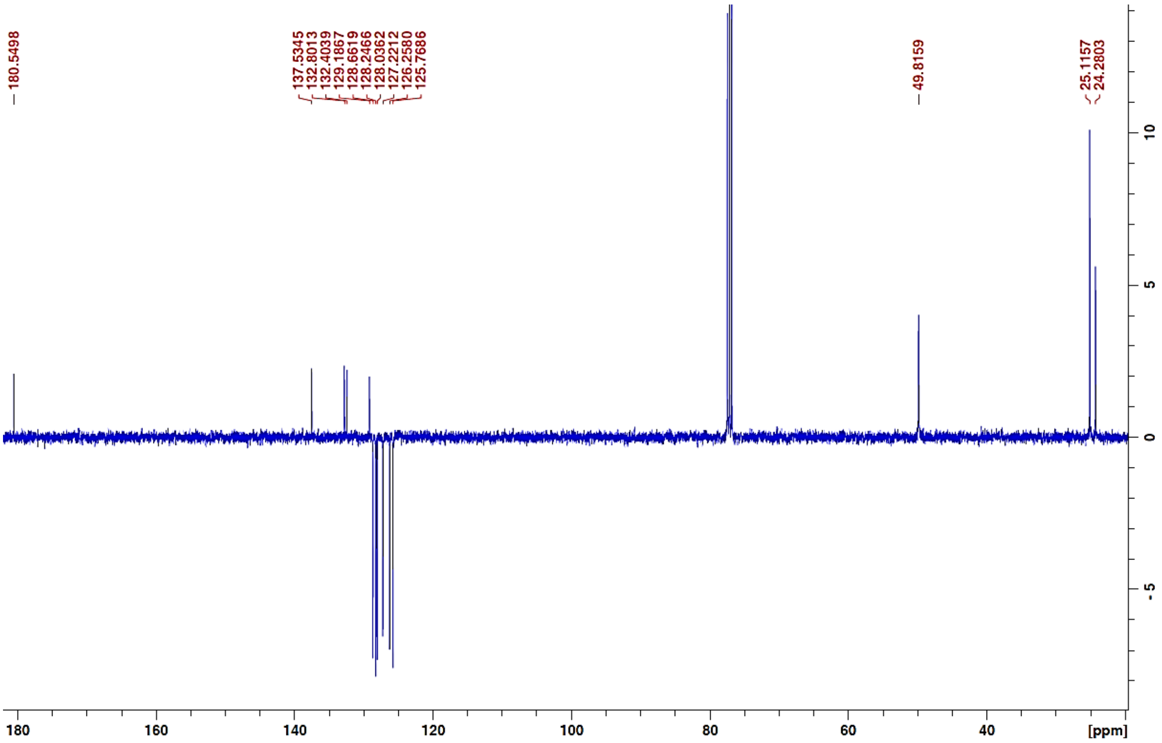


Procedure: To a solution of thiophosgene (0.11 mL, 1.41 mmol) in dry DCM (3 mL) was added a suspension of *(S)*-DABN (100 mg, 0.35 mmol) in dry DCM (7 mL) dropwise at 0 °C over a period of 30 min. After stirring for 10 min, DIPEA (0.18 mL, 1.41 mmol) was added and the mixture was stirred for another 10 min. Piperidine (1.1 mL) was added and the solution was stirred still at 0 °C for 30 min. The mixture was concentrated on the oil pump and flash chromatography with gradient elution (5-40% EtOAc in heptane) gave 141 mg (75%) of pure **2** as yellow solid. ^{1}H-NMR δ = 7.95 (2H, bd, *J* = 8.8 Hz, ArH), 7.93-7.89 (2H, m, ArH), 7.86 (2H, d, *J* = 8.8 Hz, ArH), 7.49-7.44 (4H, m, ArH), 7.38-7.33 (2H, m, ArH), 7.19 (2H, s, NH), 3.51-3.36 (8H, m, CH_2), 1.39-1.32 (4H, m, CH_2), 1.01-0.92 (8H, m, CH_2) ppm. ^{13}C-NMR δ = 180.5 (C), 137.5 (C), 132.8 (C), 132.4 (C), 129.2 (C), 128.7 (CH), 128.2 (CH), 128.0 (CH), 127.2 (CH), 126.3 (CH), 125.8 (CH), 49.8 (CH_2), 25.1 (CH_2), 24.3 (CH_2) ppm. HRMS: m/z calcd for $C_{32}H_{34}N_4S_2 + Na^+$: 561.2123; found: 561.2120.

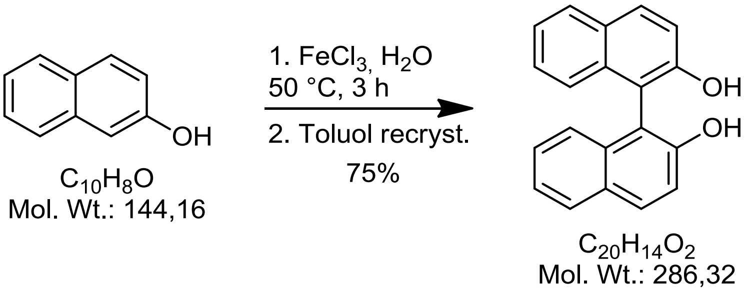
^{1}H-NMR:



^{13}C-NMR:

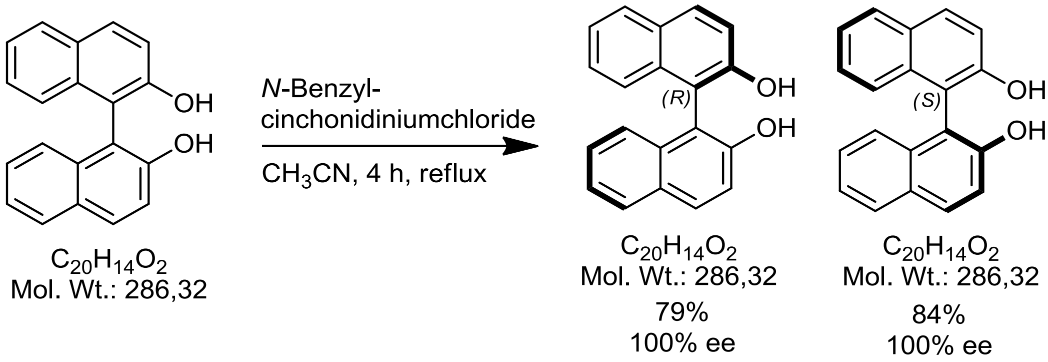


[1,1']Binaphthalenyl-2,2'-diol



Procedure:[47] 2-Naphthol (69.14 g, 0.48 mol) and $FeCl_3 \cdot 6\ H_2O$ (259.2 g, 0.96 mmol) were suspended in distilled water (1.2 L) and stirred for 3 h at 50 °C and additional 3 h at room temperature. The formed dark green solid was collected and recrystallized from toluene (1 L). The precipitate was washed with cold toluene (4 x 40 mL) and dried *in vacuo* to give 51.43 g (75%) of racemic BINOL as bright brown solid. M.p.: 215-217 °C (Lit. 216-218 °C). ^{1}H-NMR δ = 7.99 (2H, d, *J* = 9.0 Hz, ArH), 7.90 (2H, d, *J* = 8.1 Hz, ArH), 7.42-7.35 (4H, m, ArH), 7.34-7.28 (2H, m, ArH), 7.16 (2H, d, *J* = 8.5 Hz, ArH), 5.03 (2H, s, OH) ppm.

Optical resolution of [1,1']binaphthalenyl-2,2'-diol (3)

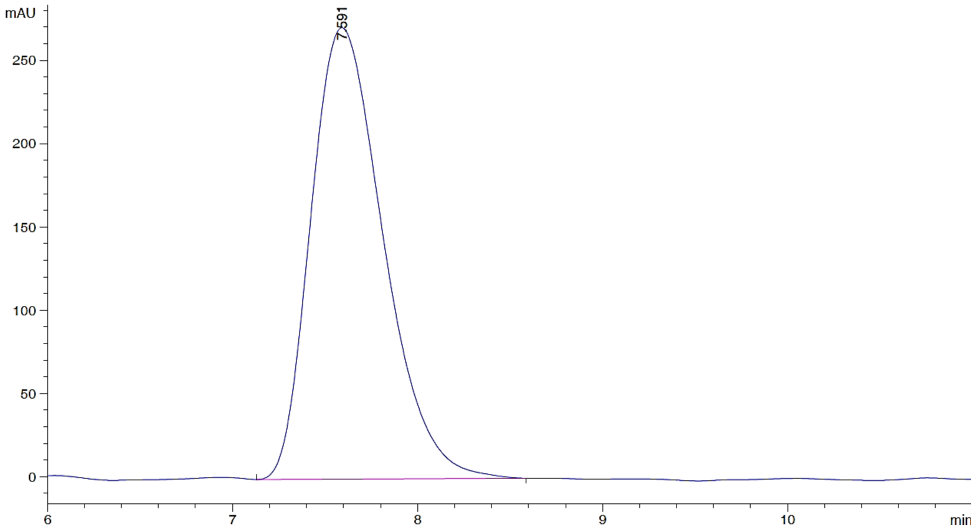


Procedure:[48] BINOL (36.46 g, 127.3 mmol) and *N*-benzylcinchonidiniumchloride (29.48 g, 70.1 mmol) were suspended in acetonitrile (475 mL) and refluxed for 4 h. After stirring overnight at room temperature, the mixture was stirred 2 h at 0 °C. The white solid was collected by filtration, suspended in MeOH (160 mL) and refluxed for 20 h. The complex, containing the *(R)*-enantiomer, was collected by filtration, washed with MeOH (40 mL) and stirred for 30 min in a mixture of EtOAc (450 mL) and 1 M HCl (250 mL). The organic layer was separated and washed with 1 N HCl (250 mL) and brine (200 mL). Drying with $MgSO_4$, filtration and concentration under reduced pressure yielded a white solid. Recrystallization from benzene (180 mL) gave 14.47 g (79%, 100% ee) of *(R)*-BINOL as colorless crystals.

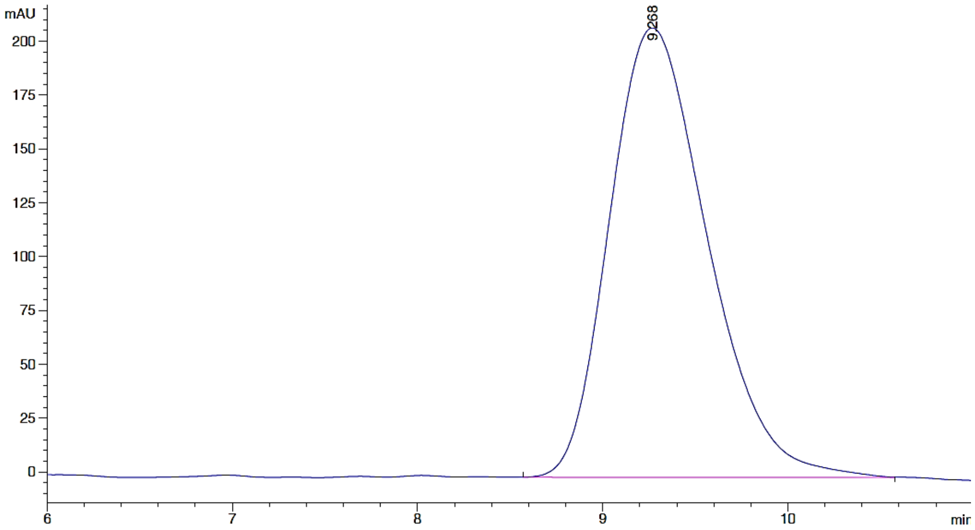
The mother liquor was concentrated in vacuo and the residue was diluted with EtOAc (450 mL). The organic layer was washed with 1 M HCl (2 x 160 mL) and brine (160 mL). Drying with $MgSO_4$, filtration and concentration *in vacuo* led to a bright brown solid. Recrystallization in benzene (180 mL) gave 15.36 g (84%, 100% ee) of *(S)*-BINOL as colorless crystals.

The enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel OJ column, 25 °C, hexane/iPrOH = 7:3, flow rate = 1 mL/min, retention time: 7.6 min (R) and 9.3 min (S).

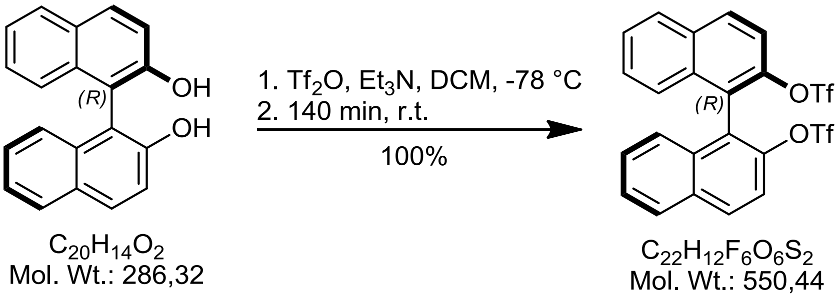
(R)-BINOL:



(S)-BINOL:

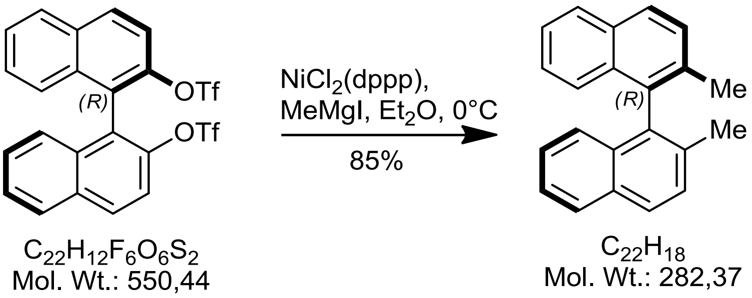


(R)-[1,1'-Binaphthalene]-2,2'-diyl bis(trifluoromethanesulfonate) (4)



Procedure:[39] *(R)*-BINOL (4.614 g, 16.11 mmol) was dissolved in dry DCM (40 mL) and Et_3N (6.70 mL, 48.34 mmol) was added under argon atmosphere. After cooling to -78 °C, triflic anhydride (5.96 mL, 35.45 mmol) was added, and the solution was stirred for 140 min at room temperature. The mixture was poured into 1 N HCl (100 mL) (cooled down to 0 °C) and extracted with heptane (2x 50 mL). After washing with $NaHCO_3$ sat. and brine, the organic phase was dried with $MgSO_4$ and removal of the solvent gave crude **4** in quantitative yield as an orange solid, which was used without further purification. ^{1}H-NMR δ = 8.16 (2H, d, *J* = 9.1 Hz, ArH), 8.03 (2H, d, *J* = 8.2 Hz, ArH), 7.66-7.58 (4H, m, ArH), 7.46-7.40 (2H, m, ArH), 7.29-7.26 (2H, m, ArH) ppm.

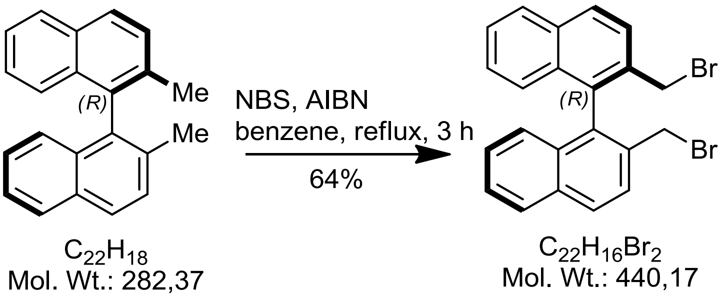
(R)-2,2'-Dimethyl-1,1'-binaphthalene (5)



Procedure:[39] To a degassed solution of crude triflate **4** (17.39 g, 31.59 mmol) and $NiCl_2$(dppp) (513 mg, 0.95 mmol) in dry ether (30 mL) was added a 1 M solution of MeMgI (126 mL, 126 mmol) at 0 °C. After stirring at room temperature overnight, there was no conversion (by TLC). The same amount of $NiCl_2$(dppp) was added again and the solution was stirred overnight again at room temperature. The reaction mixture was poured in ice cooled 1 M HCl and ether (300 mL) was added. After separation, the aqueous phase was extracted with ether (300 mL) and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was filtered over silica with EtOAc/heptane (1:100) to give 7.59 g (85%) of

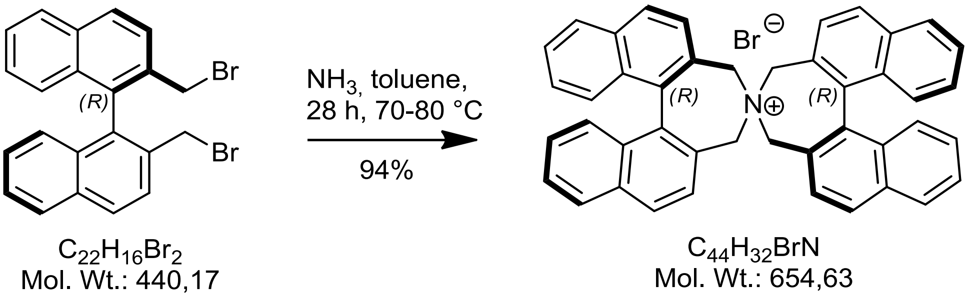
5. ^{1}H-NMR δ = 7.93-7.88 (4H, m, ArH), 7.53 (2H, d, *J* = 8.4 Hz, ArH), 7.41 (2H, ddd, *J* = 8.0, 6.8, 1.2 Hz, ArH), 7.22 (2H, ddd, *J* = 8.3, 6.8, 1.3 Hz, ArH), 7.08-7.04 (2H, m, ArH), 2.05 (6H, s, CH_3) ppm.

(R)-2,2'-Bis(bromomethyl)-1,1'-binaphthalene (6)



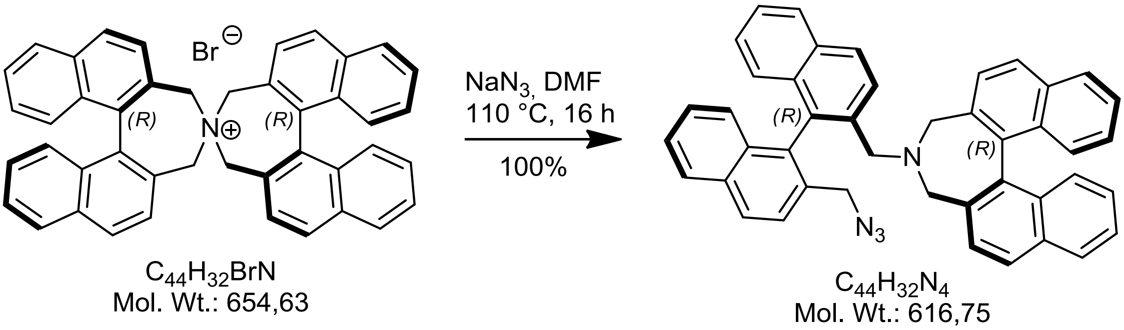
Procedure:[39] To a solution of **5** (7.59 g, 26.9 mmol) in benzene p.a. (140 mL) was added NBS (10.52 g, 59.1 mmol) and AIBN (441 mg, 2.7 mmol) and the mixture was refluxed for 3 h. After cooling down to room temperature, the suspension was poured into water and extracted with EtOAc (2x 100 mL). The combined organic phases were dried with $MgSO_4$ and the bulk of solvent was removed under reduced pressure. The concentration was kept in the refrigerator overnight to give 5.485 g of dibromide as yellow crystals. After removal of the solvent from the mother liquor, recrystallization of the residue with DCM/heptane followed by flash chromatography with EtOAc/PE (60:40) yielded another 2.080 g of pure **6** to give a total yield of 64%. ^{1}H-NMR δ = 8.04 (2H, d, *J* = 8.5 Hz, ArH), 7.95 (2H, d, *J* = 8.2 Hz, ArH), 7.77 (2H, d, *J* = 8.6 Hz, ArH), 7.51 (2H, ddd, *J* = 8.1, 6.8, 1.2 Hz, ArH), 7.29 (2H, ddd, *J* = 8.4, 6.8, 1.3 Hz, ArH), 7.11-7.08 (2H, m, ArH), 4.28 (4H, s, CH_2) ppm.

(11c*R*,11c'*R*)-3,3',5,5'-Tetrahydro-4,4'-spirobi[dinaphtho[2,1-c:1',2'-e]azepin]-4-ium bromide (7)



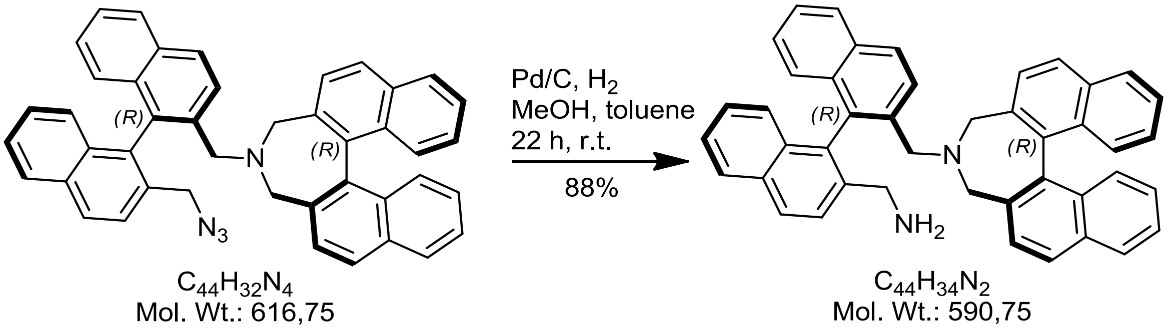
Procedure:[40] Dibromide **6** (3.375 g, 7.67 mmol), toluene (40 mL) and NH_3 (25% in water) (40 mL) were combined in an autoclave and stirred for 28 h at 70-80 °C. The resulting white ammonium salt was filtered off and rinsed with a small amount of ether to give 2.35 g (94%) of **7** as a white solid. ^{1}H-NMR δ = 8.39 (4H, d, *J* = 8.4 Hz, ArH), 8.19 (4H, d, *J* = 8.4 Hz, ArH), 8.13 (4H, bd, *J* = 8.2 Hz, ArH), 7.65 (4H, ddd, *J* = 8.0, 6.6, 1.3 Hz, ArH), 7.48-7.77 (4H, m, ArH), 7.43-7.38 (4H, m, ArH), 4.55 (4H, d, *J* = 13.2 Hz, CH_2), 3.96 (4H, d, *J* = 13.2 Hz, CH_2) ppm.

4-(((*R*)-2'-(Azidomethyl)-[1,1'-binaphthalen]-2-yl)methyl)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepine (8)



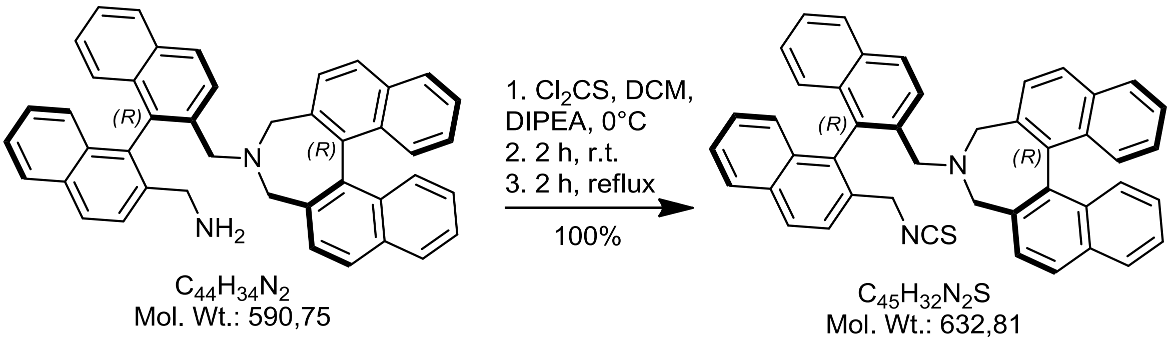
Procedure:[40] A degassed suspension of NaN_3 (332 mg, 5.11 mmol) and **7** (1.115 g, 1.70 mmol) in DMF (22 mL) was stirred at 110 °C for 16 h. After cooling to room temperature, the solution was diluted with EtOAc (80 mL) and washed with water and brine. The organic layer was dried with K_2CO_3 to give the crude azide. Filtration over a short column of silica and elution with EtOAc gave pure **8** in quantitative yield as white foam. ^{1}H-NMR δ = 8.10 (1H, bd, *J* = 8.5 Hz, ArH), 8.09-8.01 (3H, m, ArH), 7.98 (1H, bd, *J* = 8.1 Hz, ArH), 7.90 (2H, bd, *J* = 8.2 Hz, ArH), 7.76 (2H, d, *J* = 8.2 Hz, ArH), 7.75 (1H, d, *J* = 8.5 Hz, ArH), 7.59 (1H, ddd, *J* = 8.0, 6.8, 1.2 Hz, ArH), 7.49 (1H, ddd, *J* = 8.0, 6.8, 1.2 Hz, ArH), 7.43 (2H, ddd, *J* = 8.0, 7.7, 1.1 Hz, ArH), 7.40-7.35 (3H, m, ArH), 7.32-7.27 (1H, m, ArH), 7.24-7.19 (3H, m, ArH), 7.18-7.14 (1H, m, ArH), 7.10 (2H, d, *J* = 8.2 Hz, ArH), 4.07 (1H, d, *J* = 14.0 Hz, CH_2), 4.03 (1H, d, *J* = 14.0 Hz, CH_2), 3.34 (2H, d, *J* = 12.2 Hz, CH_2), 3.28 (1H, d, *J* = 14.4 Hz, CH_2), 3.17 (1H, d, *J* = 14.4 Hz, CH_2), 3.00 (2H, d, *J* = 12.1 Hz, CH_2) ppm.

((1'*R*)-2'-((3*H*-Dinaphtho[2,1-c:1',2'-e]azepin-4(5*H*)-yl)methyl)-[1,1'-binaphthalen]-2-yl)methanamine (9)



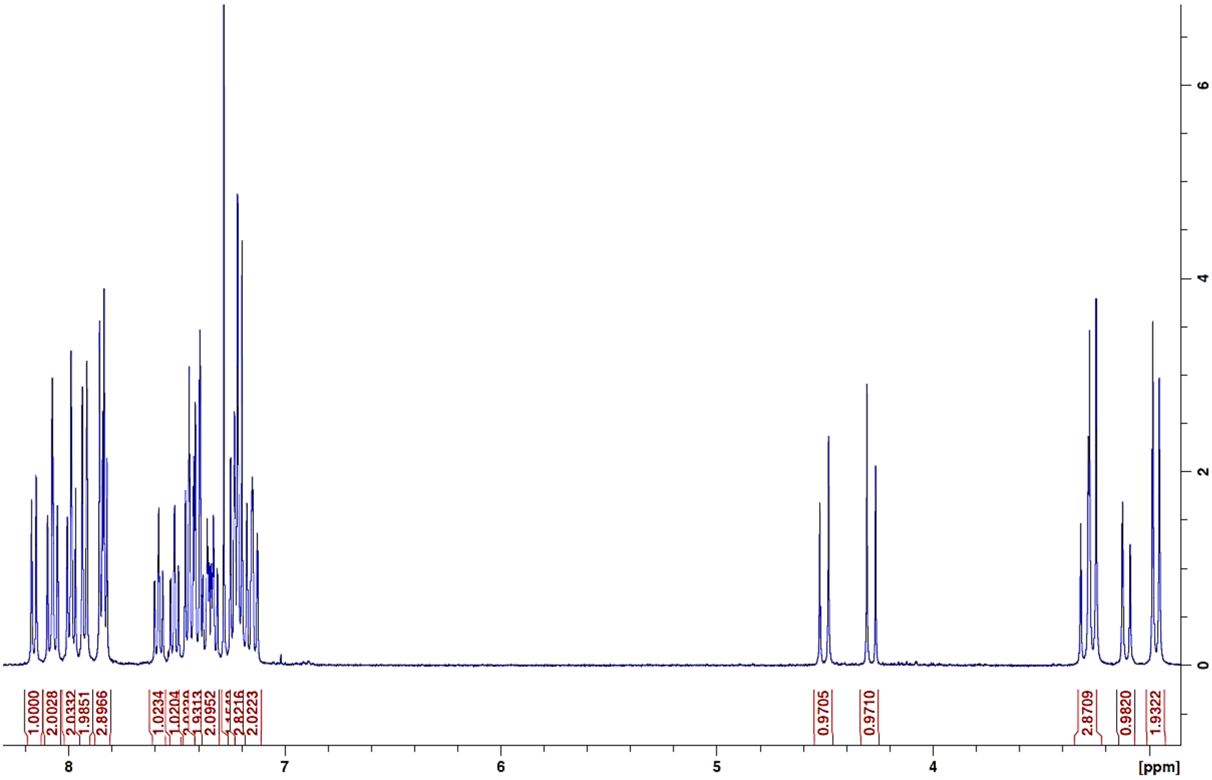
Procedure:[40] Azide **8** (2.210 g, 3.58 mmol) and Pd/C (10%) (264 mg, 0.25 mmol) was suspended in MeOH p.a. (50 mL) and toluene p.a. (50 mL) and stirred for 22 h under an H_2-atmosphere at room temperature. After removal of the catalyst by filtration and evaporation of the solvent, the crude product was purified by flash chromatography with gradient elution (0-15% MeOH in DCM) to yield 1.86 g (88%) of amine **9** as yellow oil. ^{1}H-NMR δ = 8.68 (1H, bd, *J* = 8.5 Hz, ArH), 8.34 (1H, d, *J* = 8.6 Hz, ArH), 8.08 (2H, d, *J* = 8.4 Hz, ArH), 8.07 (2H, d, *J* = 8.3 Hz, ArH), 7.95 (1H, bd, *J* = 8.2 Hz, ArH), 7.90 (1H, d, *J* = 8.4 Hz, ArH), 7.86 (2H, bd, *J* = 8.2 Hz, ArH), 7.68 (2H, d, *J* = 8.2 Hz, ArH), 7.56-7.51 (1H, m, ArH), 7.50-7.45 (1H, m, ArH), 7.41-7.33 (4H, m, ArH), 7.30-7.23 (2H, m, ArH), 7.22-7.17 (2H, m, ArH), 7.10 (1H, d, *J* = 8.5 Hz, ArH), 6.98 (1H, d, *J* = 8.5 Hz, ArH), 3.77 (1H, d, *J* = 13.0 Hz, CH_2), 3.38-3.28 (3H, m, CH_2), 3.25 (1H, d, *J* = 13.0 Hz, CH_2), 3.00-2.92 (3H, m, CH_2) ppm.

4-(((*R*)-2'-(Isothiocyanatomethyl)-[1,1'-binaphthalen]-2-yl)methyl)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepine (11)

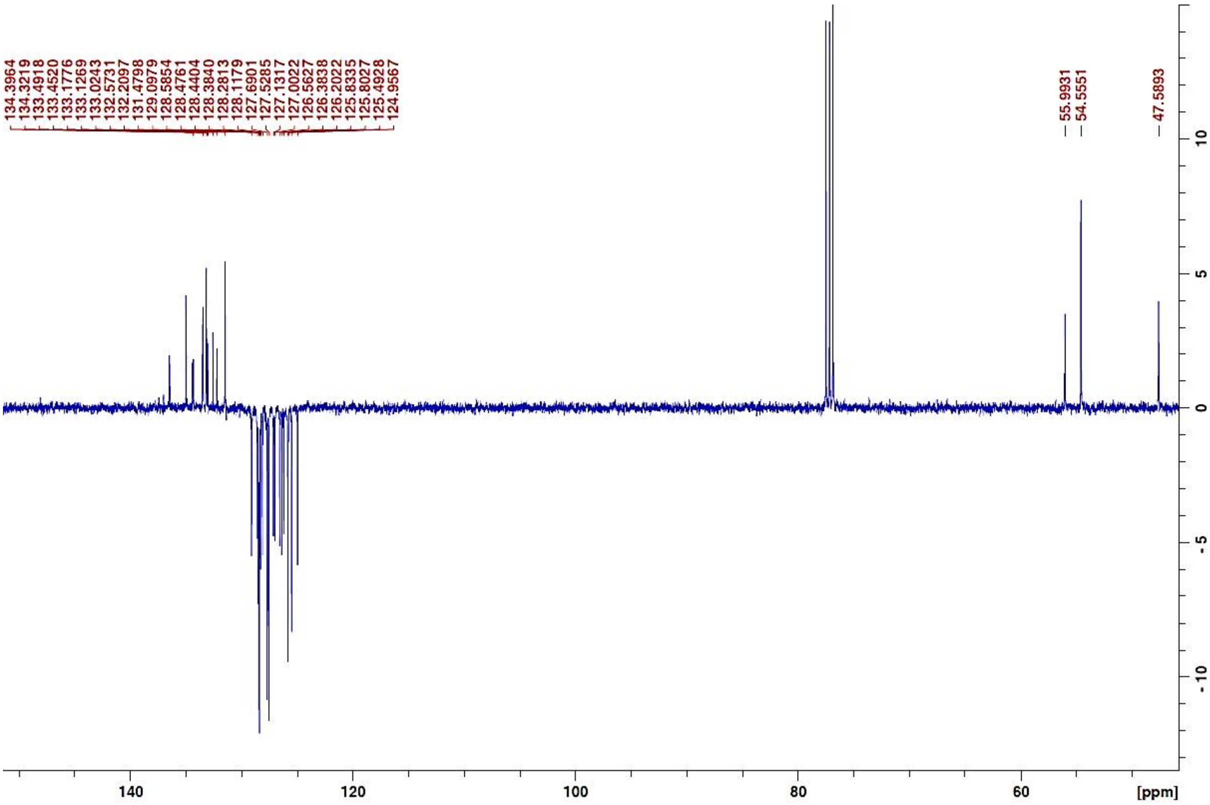


Procedure: Diamine **9** (85 mg, 0.14 mmol) was dissolved on DCM (4 mL) and added drop-wise to a solution of thiophosgene (19.0 mg, 0.16 mmol) and DIPEA (0.10 mL, 0.58 mmol) in DCM (4 mL) at 0 °C and then stirred for 30 min. After stirring for 2 h at room temperature followed by refluxing for 2 h, the solvent was removed under reduced pressure and the residue was redissolved in DCM. The solution was washed with water and brine and purification by flash chromatography with gradient elution (1-20% EtOAc in PE) yielded isothiocyanate **11** in quantitative yield. ^{1}H-NMR δ = 8.14 (1H, d, *J* = 8.6 Hz, ArH), 8.08-8.02 (2H, m, ArH), 7.99-7.94 (2H, m, ArH), 7.91 (2H, bd, *J* = 8.2 Hz, ArH), 7.83 (2H, d, *J* = 8.2 Hz, ArH), 7.81 (1H, d, *J* = 8.6 Hz, ArH), 7.56 (1H, ddd, *J* = 8.0, 6.8, 1.1 Hz, ArH), 7.49 (1H, ddd, *J* = 8.0, 6.8, 1.1 Hz, ArH), 7.42 (2H, ddd, *J* = 8.0, 6.7, 1.1 Hz, ArH), 7.38 (2H, bd, *J* = 8.6 Hz, ArH), 7.34 (1H, ddd, *J* = 8.4, 6.9, 1.3 Hz, ArH), 7.31 (1H, ddd, *J* = 8.2, 6.8, 1.3 Hz, ArH), 7.21 (2H, ddd, *J* = 8.2, 6.7, 1.3 Hz, ArH), 7.19 (2H, d, *J* = 7.2 Hz, ArH), 7.16-7.10 (2H, m, ArH), 4.48 (1H, d, *J* = 16.2 Hz, CH_2), 4.26 (1H, d, *J* = 16.2 Hz, CH_2), 3.28 (1H, d, *J* = 14.0 Hz, CH_2), 3.24 (2H, d, *J* = 12.2 Hz, CH_2), 3.08 (1H, d, *J* = 14.0 Hz, CH_2), 2.95 (2H, d, *J* = 12.2 Hz, CH_2) ppm. ^{13}C-NMR δ = 136.5 (C), 135.0 (C), 134.4 (C), 134.3 (C), 133.5 (C), 133.4 (C), 133.2 (C), 133.1 (C), 133.0 (C), 132.6 (C), 132.2 (C), 131.5 (C), 129.1 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 127.0 (CH), 126.6 (CH), 126.4 (CH), 126.2 (CH), 125.8 (CH), 125.8 (CH), 125.5 (CH), 125.0 (CH), 56.0 (CH_2), 54.6 (CH_2), 47.6 (CH_2) ppm. HRMS: m/z calcd for $C_{45}H_{32}N_2S + H^+$: 633.2364; found: 633.2372.

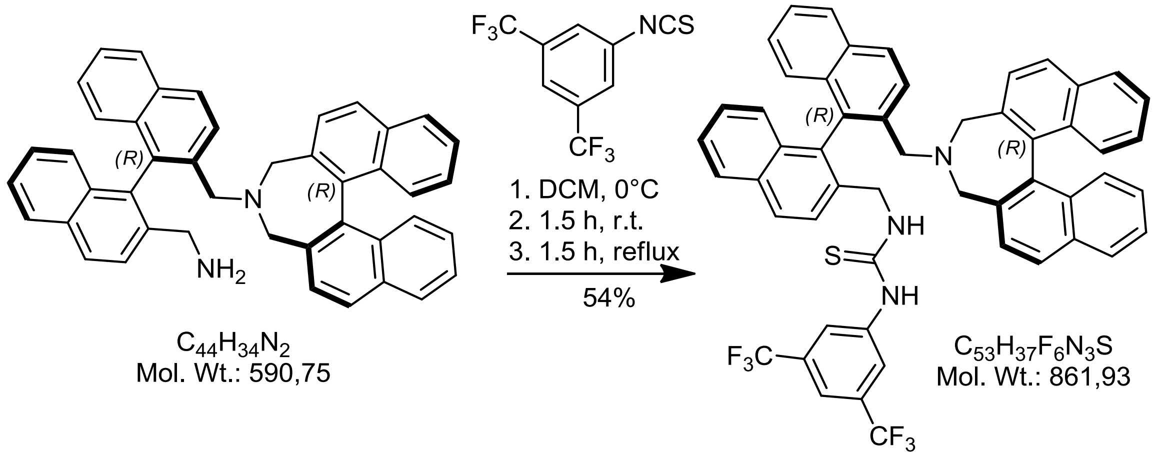
^{1}H-NMR:



^{13}C-NMR:



1-(((1'*R*)-2'-((3*H*-Dinaphtho[2,1-c:1',2'-e]azepin-4(5*H*)-yl)methyl)-[1,1'-binaphthalen]-2-yl)methyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (12b)

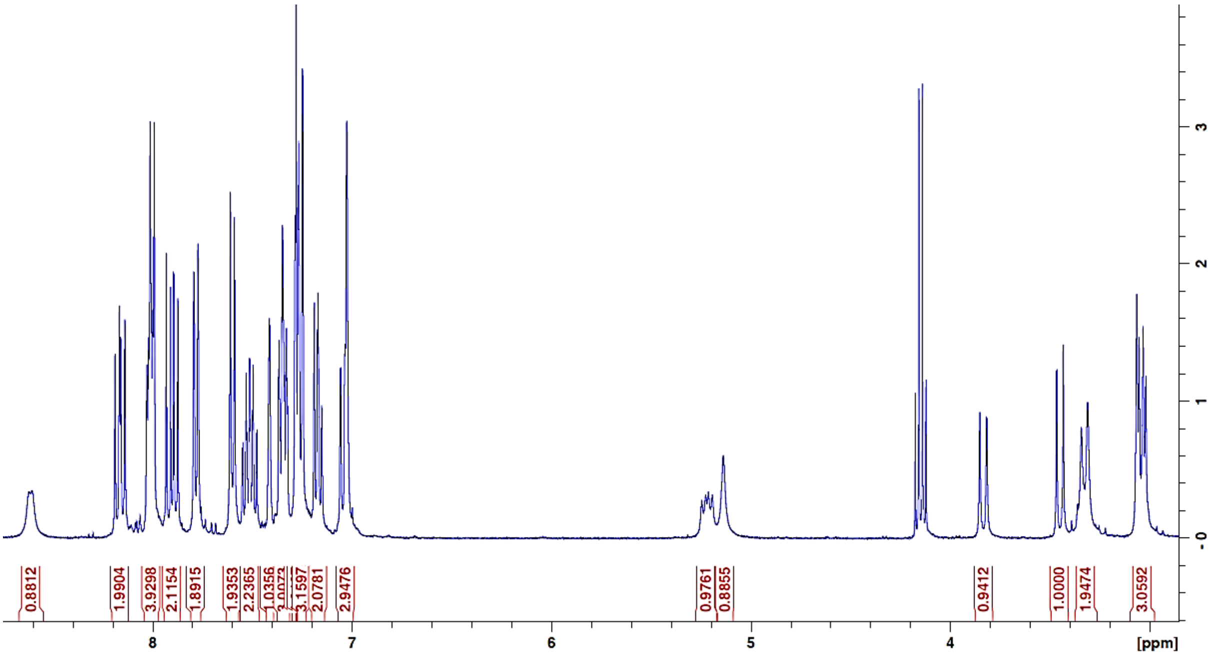


Procedure: Preparation of isothiocyanate 10: Thiophosgene (0.67 mL, 8.73 mmol) and DIPEA (2.97 mL, 17.46 mmol) were dissolved in DCM (20 mL). 3,5-Bis(trifluoromethyl)aniline (2.00 g, 8.73 mmol) was dissolved in DCM (20 mL) and added drop-wise to the thiophosgene solution over a period of 50 min at 0 °C. The mixture was stirred at room temperature overnight and then refluxed for 1 h. After low conversion by TLC, thiophosgene (0.54 mL, 6.98 mmol) and the same amount of DIPEA as before was added and the solution was refluxed for another hour. The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc and washed with water. After removal of the solvent, purification by flash chromatography with gradient elution (5-20% EtOAc in PE) gave 1.21 g (51%) of the isothiocyanate.

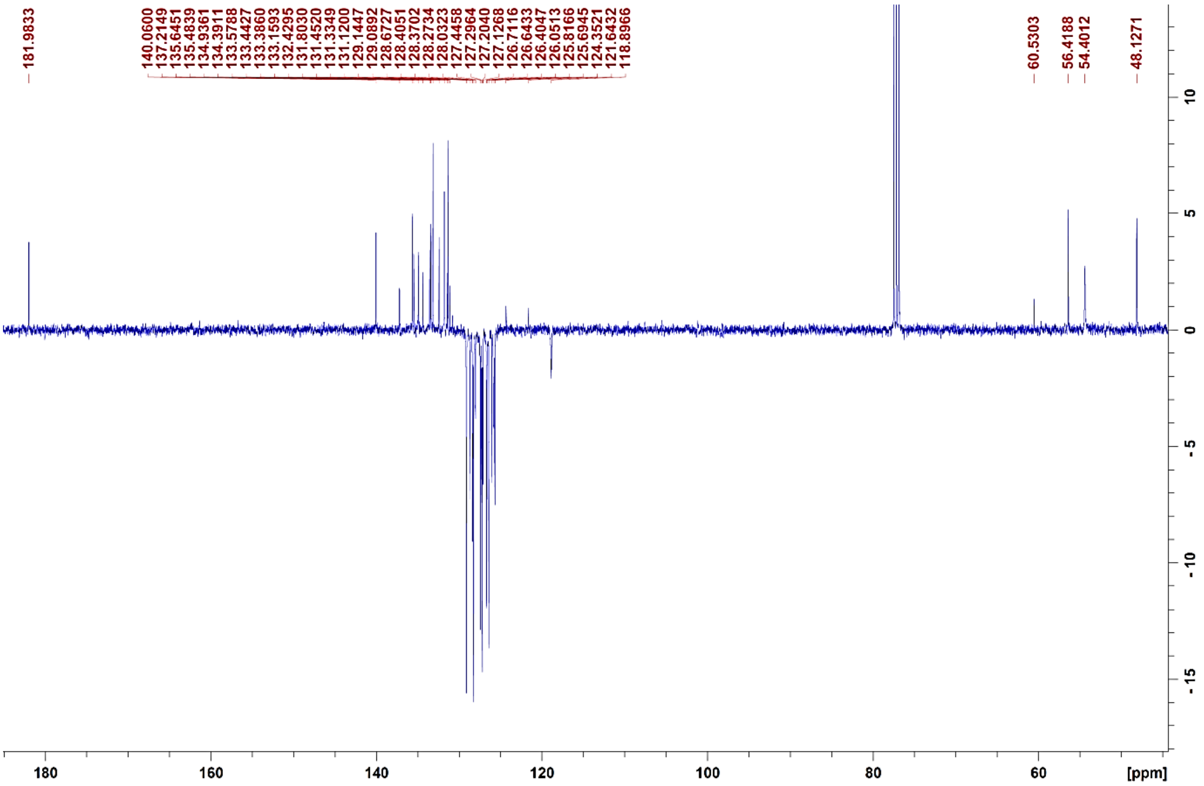
Preparation of thiourea 12b: Isothiocyanate **10** (1.21 g, 4.45 mmol) and amine **9** (1.750 g, 2.96 mmol) was dissolved in DCM (150 mL), stirred for 1.5 h at room temperature and refluxed for another 1.5 h. The solvent was removed *in vacuo* and flash purification with gradient elution (5-50% EtOAc in PE) yielded 1.38 g (54%) of **12b** as a bright brown foam. ^{1}H-NMR δ = 8.59 (1H, d, *J* = 7.8 Hz, NH), 8.16 (1H, d, *J* = 8.5 Hz, ArH), 8.13 (1H, d, *J* = 8.4 Hz, ArH), 8.02-7.96 (4H, m, ArH), 7.90 (1H, d, *J* = 8.5 Hz, ArH), 7.86 (1H, d, *J* = 8.4 Hz, ArH), 7.76 (2H, bd, *J* = 8.2 Hz, ArH), 7.58 (2H, d, *J* = 8.2 Hz, ArH), 7.53-7.45 (2H, m, ArH), 7.39 (1H, bs, ArH), 7.35-7.29 (3H, m, ArH), 7.28-7.22 (4H, m, ArH), 7.15 (2H, ddd, *J* = 8.0, 6.7, 1.2 Hz, ArH), 7.04-6.99 (3H, m, ArH), 5.20 (1H, dd, J = 13.7, 7.8 Hz, CH_2), 5.12 (1H, s, NH), 3.81 (1H, d, *J* = 13.7 Hz, CH_2), 3.43 (1H, d, *J* = 13.2 Hz, CH_2), 3.31 (2H, bd, *J* = 12.5 Hz, CH_2), 3.03 (2H, bd, *J* = 12.5 Hz, CH_2), 3.01 (1H, d, *J* = 13.2 Hz, CH_2) ppm. ^{13}C-NMR δ = 182.0 (C), 140.1 (C), 137.2 (C), 135.6 (C), 135.5 (C), 134.9 (C), 134.4 (C), 133.6 (C), 133.4 (C), 133.4 (C), 133.2 (C), 132.4 (C), 131.8 (C), 131.4 (C), 131.3 (C), 131.1 (C), 129.1 (CH), 129.1 (CH), 128.7 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.4 (CH), 127.3

(CH), 127.2 (CH), 127.1 (CH), 126.7 (CH), 126.6 (CH), 126.4 (CH), 126.0 (CH), 125.8 (CH), 125.7 (CH), 123.0 (CF_3), 118.9 (CH), 56.4 (CH_2), 54.4 (CH_2), 48.1 (CH_2) ppm. HRMS: m/z calcd for $C_{53}H_{37}F_6N_3S + H^+$: 862.2691; found: 862.2711.

^{1}H-NMR:

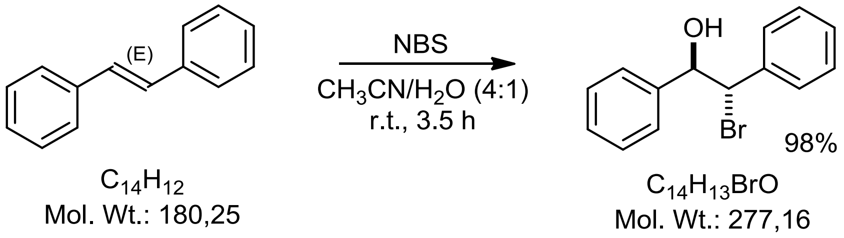


^{13}C-NMR:



General procedures for the bromofunctionalization of *trans*-stilbene 13:

2-Bromo-1,2-diphenylethanol (14)



Procedure: To a stirred solution of *trans*-stilbene (100 mg, 0.55 mmol) in CH_3CN (2 mL) and H_2O (0.5 mL) was added NBS (118.6 mg, 0.67 mmol). The solution was stirred for 3.5 h at room temperature. After complete conversion by TLC, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography with gradient elution (10-15% EtOAc in PE) to give 150 mg (98%) of racemic **14**. ^{1}H-NMR δ = 7.41-7.36 (2H, m, ArH), 7.35-7.27 (8H, m, ArH), 5.21 (1H, bd, *J* = 6.7 Hz, CH), 5.10 (1H, d, *J* = 6.7 Hz, CH), 2.40 (1H, bs, OH) ppm.

The catalytic reactions were performed with the same procedure but variation of temperature and reaction time. Due to low conversion and low absorbance of the product, purification by flash chromatography was avoided. Instead, the crude product was dissolved in DCM and filtered over a short column of aluminium oxide in order to remove polar compounds.

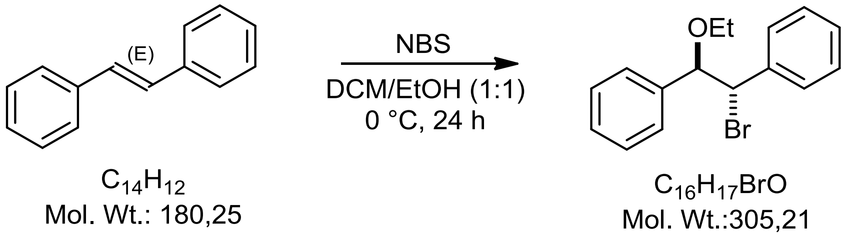
HPLC analysis of **14:**

Daicel Chiralcel IA column (250 mm), 25 °C, hexane/iPrOH = 9:1, flow rate = 0.5 mL/min, 230 nm. Retention times: 18.4 min and 21.3 min.

or

Daicel Chiralcel IA column (250 mm), 25 °C, hexane/iPrOH = 4:1, flow rate = 0.5 mL/min, 230 nm. Retention times: 13.8 min and 15.4 min.

(1-Bromo-2-ethoxyethane-1,2-diyl)dibenzene (16):



Procedure: To a stirred solution of *trans*-stilbene (100 mg, 0.55 mmol) in DCM (2 mL) and EtOH (2 mL) was added NBS (148 mg, 0.83 mmol). The solution was stirred for 24 h at 0 °C. The solvent was removed under reduced pressure and the crude product was dissolved in DCM and filtered over a short column of aluminiumoxide to remove polar compounds. ^{1}H-NMR δ = 7.39-7.21 (10H, m, ArH), 5.02 (1H, d, *J* = 6.8 Hz, CH), 4.74 (1H, d, *J* = 6.8 Hz, CH), 3.40 (1H, dq, *J* = 7.0, 9.4 Hz, CH_2), 3.31 (1H, dq, *J* = 7.0, 9.4 Hz, CH_2), 1.06 (3H, t, *J* = 7.0 Hz, CH_3) ppm.

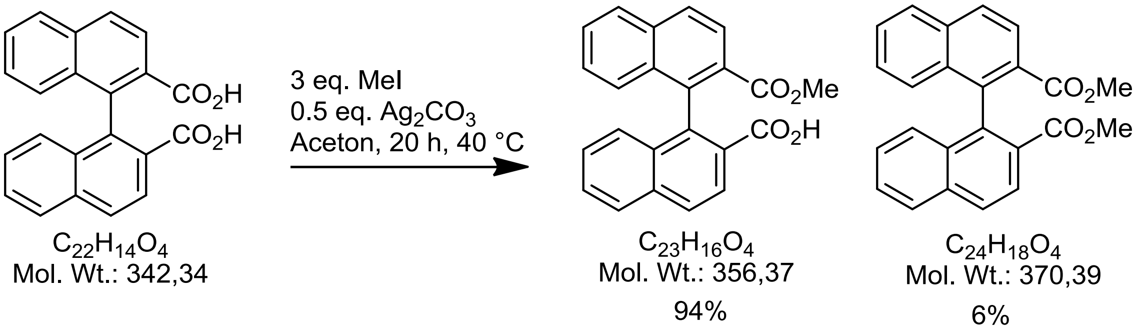
The catalytic reactions were performed with the same procedure but variation of temperature.

GC-analysis of **16**:

SUPELCO, BetaDEX 110 (30 m), 170 °C isothermal, carrier gas He, 15.3 psi. Retention times: 23.6 min and 32.0 min.

3.2 Procedures for the synthesis of non-thiourea ligands

2'-(Methoxycarbonyl)-[1,1'-binaphthalene]-2-carboxylic acid (17)



Procedure:

Preparation of Ag_2CO_3: A filtered solution of Na_2CO_3 (10.44 g, 98.7 mmol) in water (200 mL) was added to a stirred solution of $AgNO_3$ (16.77 g, 98.7 mmol) in water (50 mL) in an erlenmeyer flask. The resulting yellow precipitate was filtered off, rinsed with EtOH (20 mL) and Et_2O (20 mL) and dried on the pump to give 13.543 g (99%) of air-sensitive silver(I)carbonate.

Preparation of monoester 17:[41] Binaphthyl-dicarboxylic acid (3.00 g, 8.7 mmol) and freshly prepared Ag_2CO_3 (1.21 g, 4.38 mmol) were suspended in acetone p.a (120 mL) in an argon atmosphere. After dropwise addition of MeI (1.64 mL, 26.3 mmol), the mixture was stirred for 20 h at 40 °C. The solution was quenched with 2 M HCl (160 mL) and extracted with EtOAc (2x 160 mL). The combined organic phases were washed with water, dried with $MgSO_4$ and removal of the solvent *in vacuo* gave 3.03 g of crude product with a monoester/diester-ratio of 94/6, determined by ^{1}H-NMR. The product was used without further purification.[a] ^{1}H-NMR δ = 8.14 (2H, dd, *J* = 8.7, 7.1 Hz, ArH), 8.04 (2H, bd, *J* = 8.7 Hz, ArH), 7.96 (2H, bd, *J* = 8.2 Hz, ArH), 7.57-7.51 (2H, m, ArH), 7.29-7.23 (2H, m, ArH), 7.07 (1H, bd, *J* = 8.7 Hz, ArH), 7.02 (1H, bd, *J* = 8.5 Hz, ArH), 3.57 (3H, s, CH_3) ppm.

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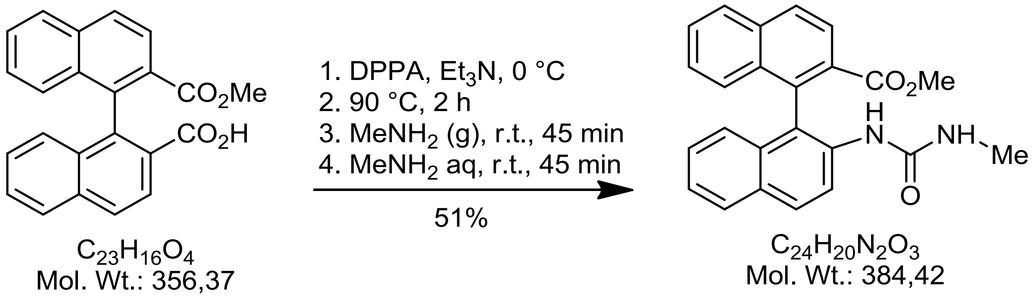
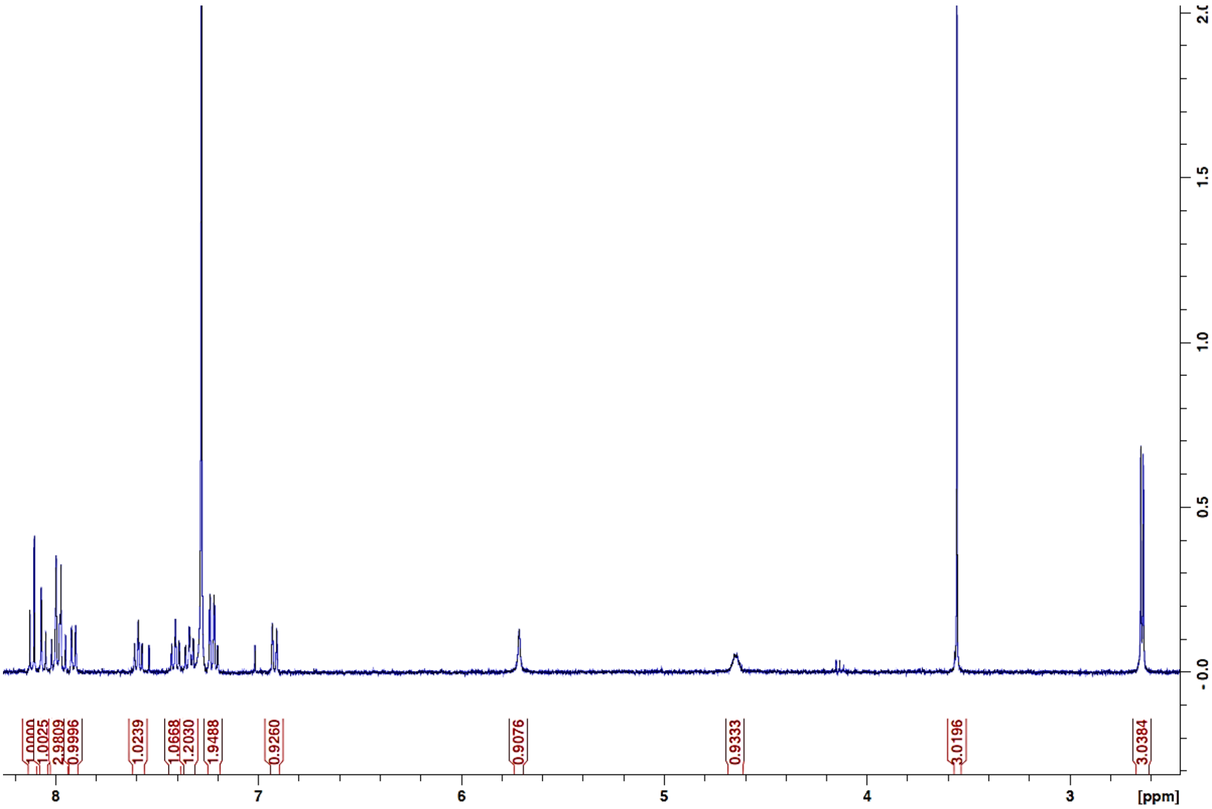
[a] Monoester **17** is quite sensitive to acidic conditions. Purification by flash chromatography on silica led to quantitative saponification on the column.

Methyl 2'-(3-methylureido)-[1,1'-binaphthalene]-2-carboxylate (18)

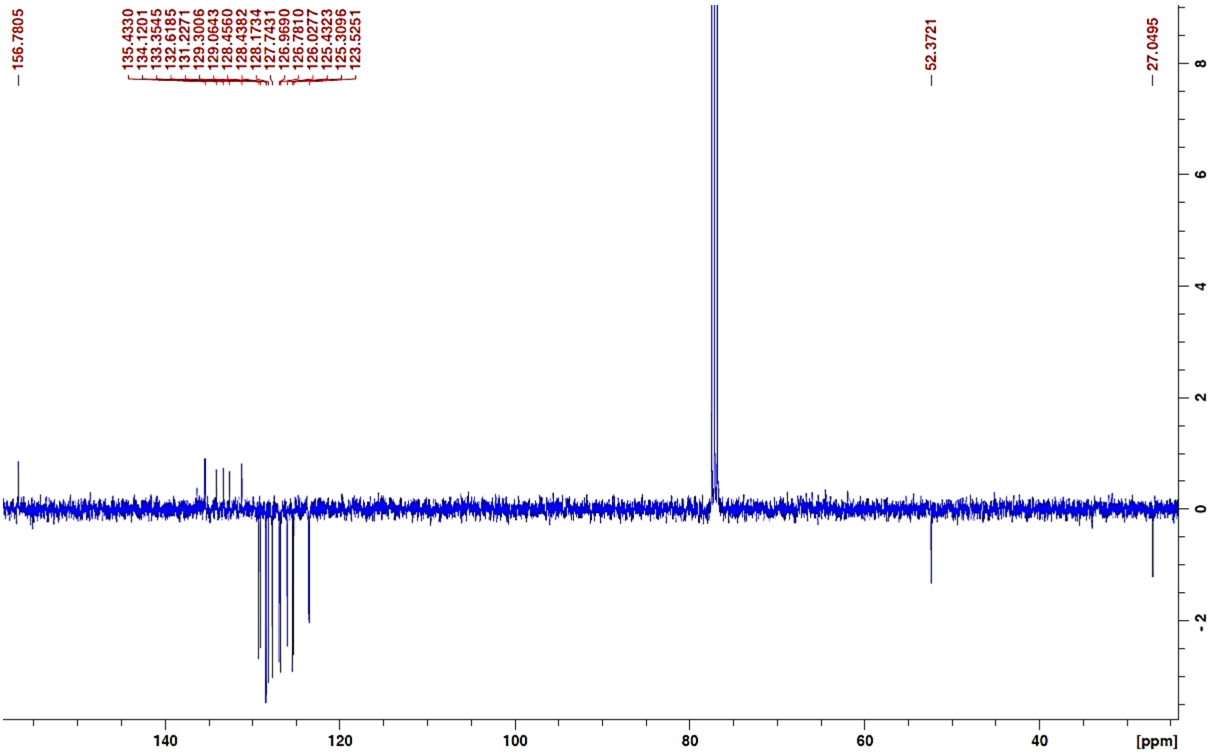


Procedure: To a degassed solution of crude monoester **17** (92%) (700 mg, 1.96 mmol) in toluene (24 mL) was added dropwise DPPA (0.42 mL, 1.95 mmol) and TEA (0.82 mL, 5.89 mmol) at 0 °C. The mixture was stirred for 2 h at 90 °C and allowed to cool to room temperature. Gaseous $MeNH_2$ was bubbled through the stirred solution for 45 min (1 bubble per sec) while a white precipitate occurred. $MeNH_2$ aq. (40%) (0.43 mL) was added and stirring for another 45 min at room temperature the mixture was quenched with 2 M HCl and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the yellow residue by flash chromatography with gradient elution (30-100% EtOAc in PE) gave 356 mg (51%) of urea **18**. M.p.: 230-233 °C. ^{1}H-NMR δ = 8.09 (1H, d, *J* = 8.7 Hz, ArH), 8.04 (1H, bd, *J* = 8.6 Hz, ArH), 8.00-7.92 (3H, m, ArH), 7.89 (1H, bd, *J* = 8.2 Hz, ArH), 7.57 (1H, ddd, *J* = 8.1, 6.8, 1.2 Hz, ArH), 7.39 (1H, ddd, *J* = 8.1, 6.8, 1.1 Hz, ArH), 7.32 (1H, ddd, *J* = 8.4, 6.8, 1.2 Hz, ArH), 7.23-7.17 (2H, m, ArH), 6.90 (1H, bd, *J* = 8.4 Hz, ArH), 5.69 (1H, s, NH), 4.63 (1H, d, *J* = 4.8 Hz, NH), 3.54 (3H, s, CH_3), 2.62 (3H, d, *J* = 4.8 Hz, CH_3) ppm. ^{13}C-NMR δ = 156.8 (C), 135.4 (C), 134.1 (C), 133.4 (C), 132.6 (C), 131.2 (C), 129.3 (CH), 129.1 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 127.7 (CH), 127.0 (CH), 126.8 (CH), 126.0 (CH), 125.4 (CH), 125.3 (CH), 123.5 (CH), 52.4 (CH_3), 27.0 (CH_3) ppm. HRMS: m/z calcd for $C_{24}H_{20}N_2O_3 + Na^+$: 407.1367; found: 407.1354.

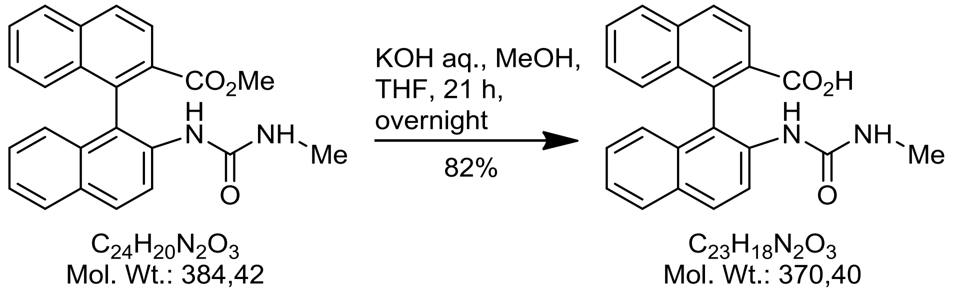
^{1}H-NMR:



^{13}C-NMR:

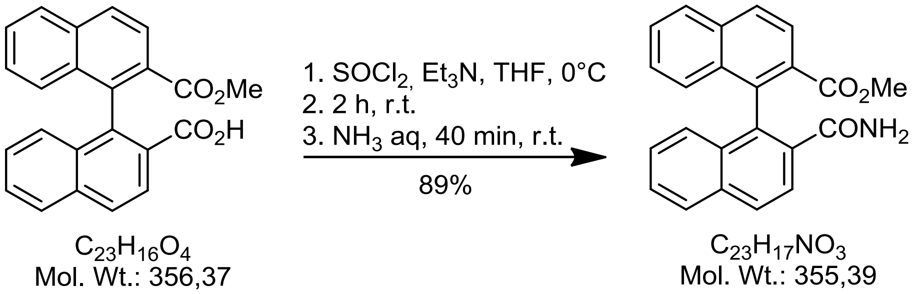


2'-(3-Methylureido)-[1,1'-binaphthalene]-2-carboxylic acid (19)



Procedure: Monoester **18** (63.0 mg, 0.16 mmol) was dissolved in THF (2 mL) in a round bottom flask. A solution of KOH (64.4 mg, 1.15 mmol), dissolved in MeOH (1 mL) and water (1 mL), was added and the mixture was stirred for 21 h at room temperature. After addition of 1 N HCl (1.2 mL), the yellow precipitate was collected by filtration and rinsed with EtOH and Et_2O to give 38 mg (82%) of the dicarboxylic acid. Unfortunately, compound **19** was insoluble in all common solvents, therefore characterization via NMR was not possible. HRMS: m/z calcd for $C_{23}H_{18}N_2O_3$ + Na^+: 393.1215; found: 393.1207.

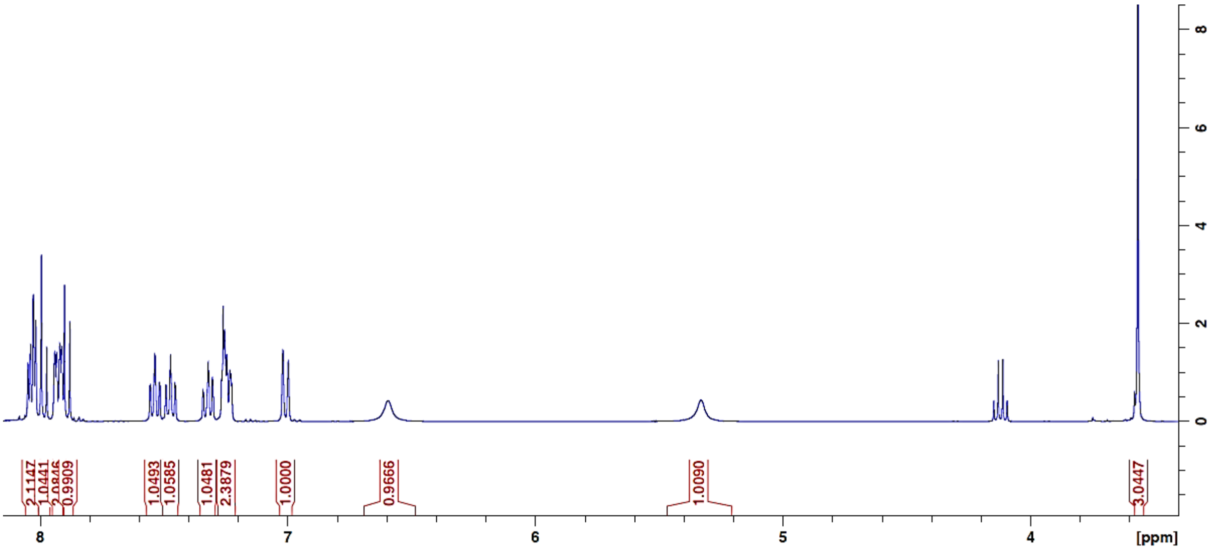
Methyl 2'-carbamoyl-[1,1'-binaphthalene]-2-carboxylate (20)



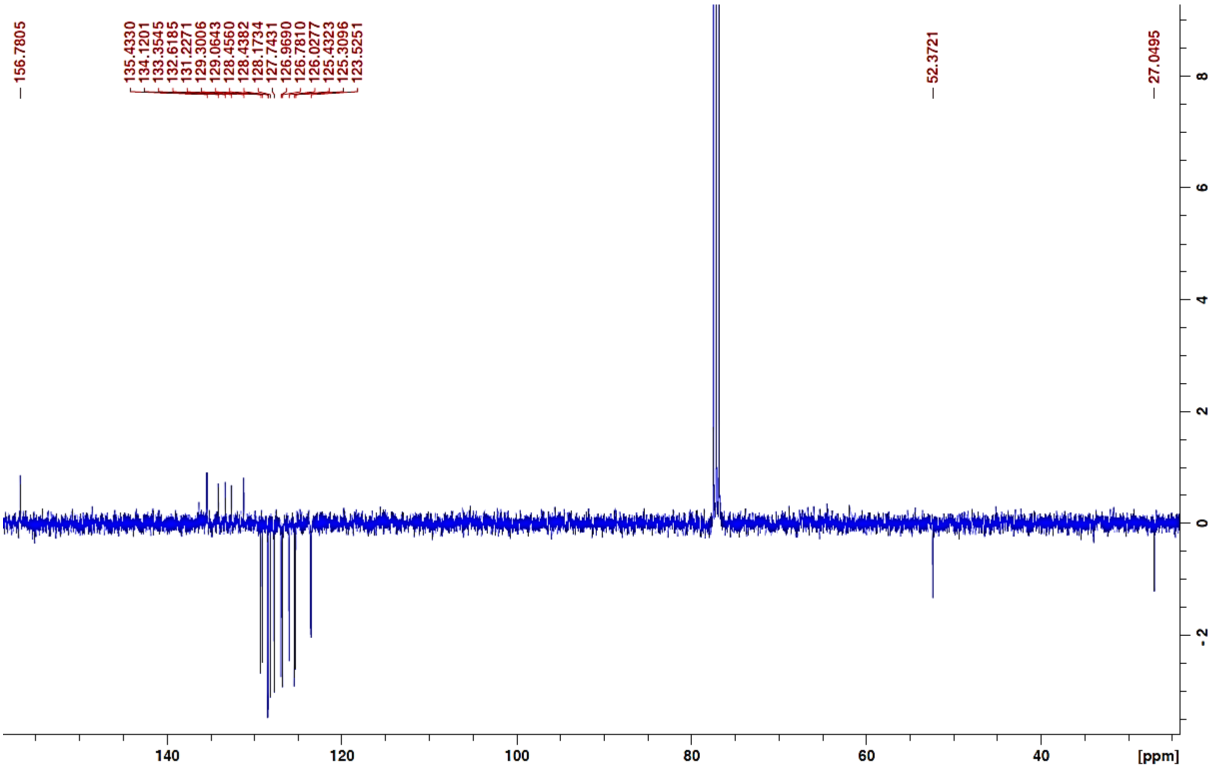
Procedure: To a solution of monoester **17** (92%) (1.00 g, 2.8 mmol) in THF (70 mL) was added $SOCl_2$ (0.24 mL, 3.4 mmol) and Et_3N (1.56 mL, 11.2 mmol) at 0 °C in an argon atmosphere and stirred for 15 min. The mixture was stirred for 2 h at room temperature. NH_3 aq. (25%) (2 mL) was added and the solution was stirred for another 40 min. The solvent was removed *in vacuo* and purification by flash chromatography with gradient elution (20-80% EtOAc in PE) gave 812 mg (89%) of amidoester **20** as white solid. M.p.: 166-168 °C. ^{1}H-NMR δ = 8.04 (1H, bd, *J* = 8.6 Hz, ArH), 8.03 (1H, bd, *J* = 8.5 Hz, ArH), 7.98 (1H, d, *J* = 8.6 Hz, ArH), 7.93 (1H, bd, *J* = 8.2 Hz, ArH), 7.92 (1H, bd, *J* = 8.2 Hz, ArH), 7.89 (1H, d, *J* = 8.5 Hz, ArH), 7.54 (1H, ddd, *J* = 8.0, 6.8, 1.1 Hz, ArH), 7.47 (1H, ddd, *J* = 8.0, 6.9, 1.0 Hz, ArH), 7.32 (1H, ddd, *J* = 8.4, 6.8, 1.2 Hz, ArH), 7.27-7.22 (2H, m, ArH), 7.01 (1H, bd, *J* = 8.6 Hz, ArH), 6.59 (1H, s, NH), 5.33 (1H, s, NH), 3.57 (3H, s, CH_3) ppm. ^{13}C-NMR δ = 171.5 (C), 169.3 (C), 137.8 (C), 135.2 (C), 134.2 (C), 134.2 (C), 133.3

(C), 132.9 (C), 132.2 (C), 129.2 (C), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 127.1 (CH), 127.0 (CH), 126.3 (CH), 124.9 (CH), 124.8 (CH), 52.6 (CH_3) ppm. HRMS: m/z calcd for $C_{23}H_{17}NO_3 + H^+$: 356.1287; found: 356.1271.

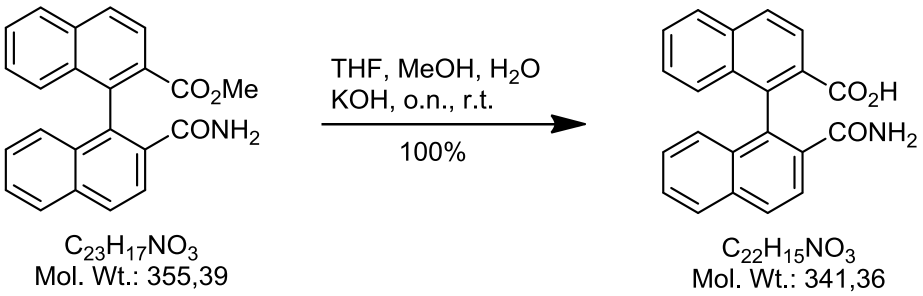
^{1}H-NMR:



^{13}C-NMR:



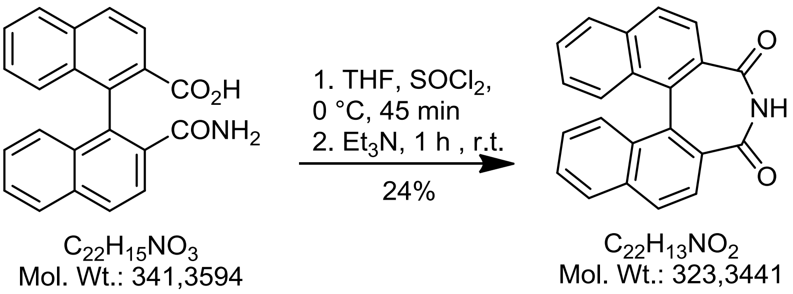
2'-Carbamoyl-[1,1'-binaphthalene]-2-carboxylic acid (21)



Procedure: To a solution of amide **20** (200 mg, 0.56 mmol) in THF (6 mL) was added a solution of KOH (221 mg, 3.94 mmol) in MeOH (3 mL) and water (3 mL) and stirred overnight. The mixture was acidified with 1 N HCl and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine and dried with $MgSO_4$ to give **21** in quantitative yield. ^{1}H-NMR δ = 8.06 (2H, bt, *J* = 8.7 Hz, ArH), 7.97-7.92 (2H, m, ArH), 7.89 (1H, d, *J* = 8.5 Hz, ArH), 7.74 (1H, d, *J* = 8.5 Hz, ArH), 7.55-7-48 (2H, m, ArH), 7.31 (1H, ddd, *J* = 8.5, 6.8, 1.3 Hz, ArH), 7.29-7.24 (1H, m, ArH), 7.09-7.04 (1H, m, ArH), 6.97-6.94 (1H, m, ArH), 6.17 (1H, s, NH), 5.63 (1H, s, NH) ppm.

The enantiopure compound is already published by Oi *et al.*[42]

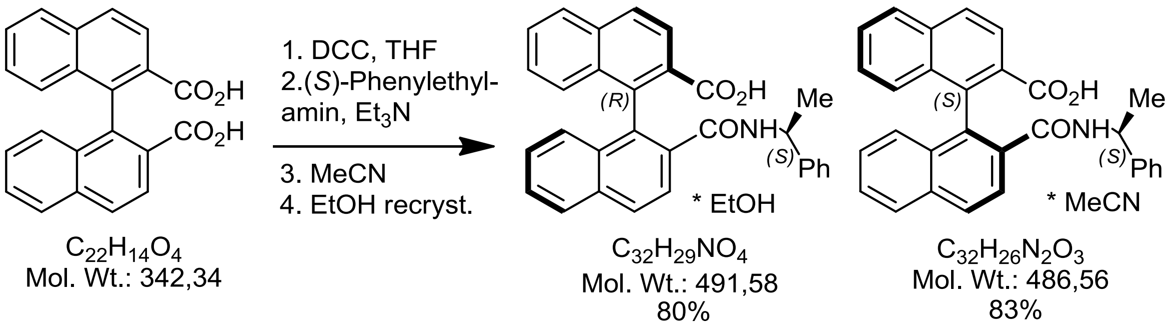
3*H*-Dinaphtho[2,1-c:1',2'-e]azepine-3,5(4*H*)-dione (22)



Procedure: To a solution of amide **21** (80 mg, 0.23 mmol) in THF (15 mL) was added $SOCl_2$ (22 µL, 0.30 mmol) at 0 °C and the mixture was stirred at room temperature. After 45 min, Et_3N (0.13 mL, 0.94 mmol) was added and stirred for another 60 min. Due to low conversion by TLC, the same amount of $SOCl_2$ as before was added added and the solution was stirred for 10 min at room temperature and 1 h at 55 °C. Due to lack of further conversion by TLC, the mixture was quenched with water (20 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash chromatography with gradient elution (10-30% EtOAc in PE) yielded 18 mg (24%) of strongly fluorescing imide **22** as white solid. For characterization data see procedures for the enantiopure compound below.

3.3 Procedures for the synthesis of enantiopure binaphthimide and related experiments

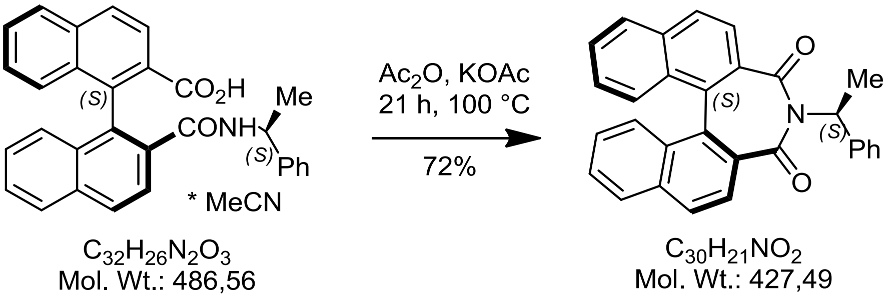
(*R*)-2'-(((*S*)-1-Phenylethyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid ((a*R,S*)-23)
(*S*)-2'-(((*S*)-1-Phenylethyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid ((a*S,S*)-23)



Procedure:[42] Binaphthyldicarboxylic acid (5.00 g, 14.6 mmol) was dissolved in dry THF (50 mL) in a round bottom flask, equipped with an addition funnel. After setting up an argon atmosphere, DCC (3.01 g, 14.6 mmol) was dissolved in dry THF (33 mL), and the solution was added dropwise over 1 h at room temperature. The mixture was stirred for another 2 h and refluxed for 4 h. *(S)*-Phenethylamine (2.26 mL, 2.14 g, 17.5 mmol) and triethylamine (1.67 mL, 1.48 g, 14.6 mmol) were added to the hot solution, the mixture was refluxed for another 2.5 h and then allowed to cool to room temperature overnight. The formed urea was filtered off via celite, the filter cake was rinsed with small portions of THF and the filtrate was concentrated under reduced pressure. The residue was redissolved in chloroform (66 mL) and washed with HCl conc. (2 x 66 mL) and water (4 x 66 mL). The organic phase was dried with $MgSO_4$ and treated with activated charcoal. After filtration, the solvent was removed and the residue was dissolved in acetonitrile (333 mL). 233 mL of the solvent was removed by distillation under atmospheric pressure and the solution was kept in the refrigerator for 72 h. The precipitate was filtered off to give 2.950 g (83%) of ***(aS,S)*-23** as an off white acetonitrile-clathrate. ^{1}H-NMR δ = 8.05 (2H, bt, *J* = 9.0 Hz, ArH), 7.96 (2H, bq, *J* = 8.3 Hz, ArH), 7.87 (1H, d, *J* = 8.5 Hz, ArH), 7.63 (1H, d, *J* = 8.5 Hz, ArH), 7.57-7.51 (2H, m, ArH), 7.36-7.25 (5H, m, ArH), 7.17-7.13 (1H, m, ArH), 7.08-7.04 (2H, m, ArH), 7.03-6.99 (1H, m, ArH), 6.33 (1H, bd, *J* = 8.3 Hz, NH), 4.96-4.87 (1H, m, CH), 0.92 (3H, d, *J* = 6.9 Hz, CH_3) ppm.

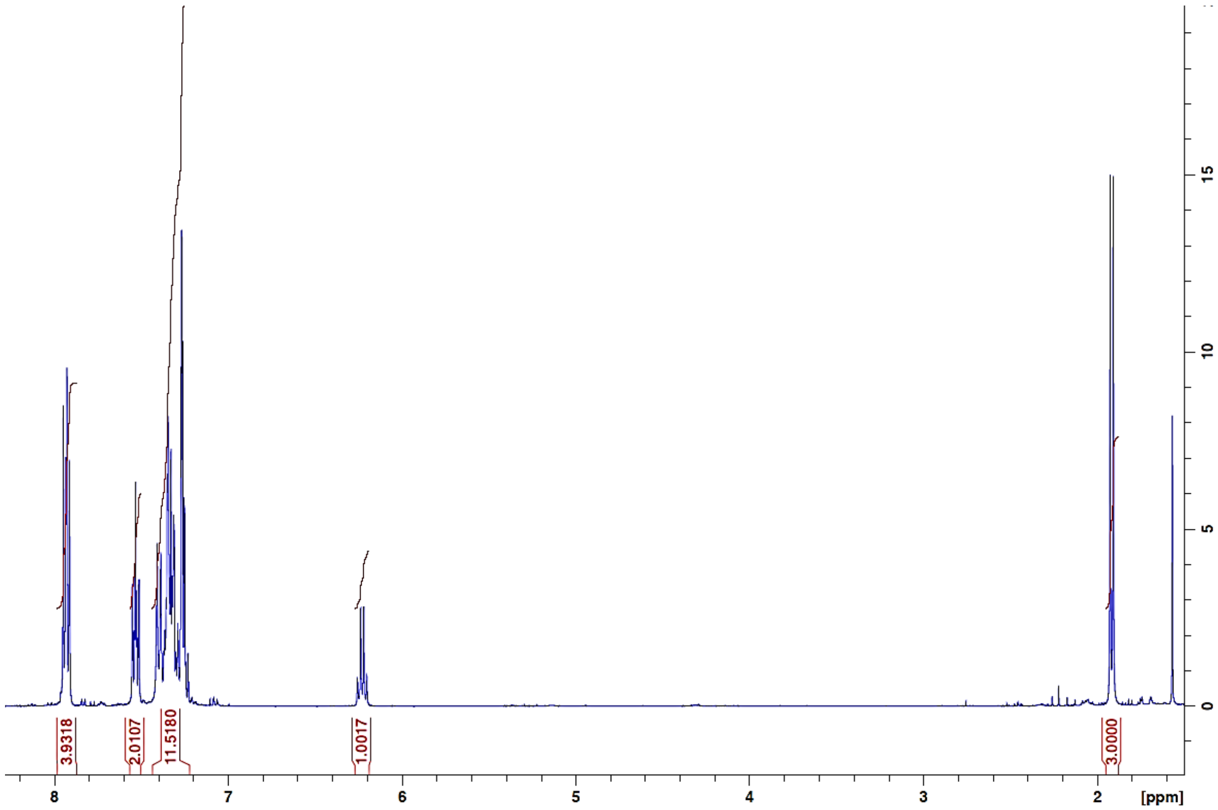
The mother liquor was concentrated under reduced pressure and the solid residue was dissolved in EtOH abs. (86 mL). After removal of 50 mL of the solvent at atmospheric pressure, the suspension (some precipitation already occurred during the distillation) was kept in the refrigerator overnight. The white precipitate was isolated by filtration and redissolved in EtOH abs. (83 mL). As before, 50 mL of the solvent was distilled off under reduced pressure and the solution was stored in the refrigerator overnight to give 2.840 g (80%) of **(a*R,S*)-23** as an ethanol-clathrate as white needles. ^{1}H-NMR δ = 8.08 (1H, bd, *J* = 8.5 Hz, ArH), 8.04 (1H, bd, *J* = 8.6 Hz, ArH), 7.99 (1H, bd, *J* = 8.3 Hz, ArH), 7.95 (1H, d, *J* = 8.3, ArH), 7.84 (1H, d, *J* = 8.5 Hz, ArH), 7.69, (1H, d, *J* = 8.5 Hz, ArH), 7.58-7.51 (2H, m, ArH), 7.36-7.31 (1H, m, ArH), 7.27-7.21 (1H, m, ArH), 7.16-7.13 (1H, m, ArH), 7.10-7.06 (1H, m, ArH), 6.98-6.93 (3H, m, ArH), 6.60 (2H, m, ArH), 6.36 (1H, bd, *J* = 7.7 Hz, NH), 5.01-4.92 (1H, m, CH), 1.41 (3H, d, *J* = 6.9 Hz, CH_3) ppm.

4-((*S*)-1-Phenylethyl)-3*H*-dinaphtho[2,1-c:1',2'-e]azepine-3,5(4*H*)-dione ((a*S,S*)-24)

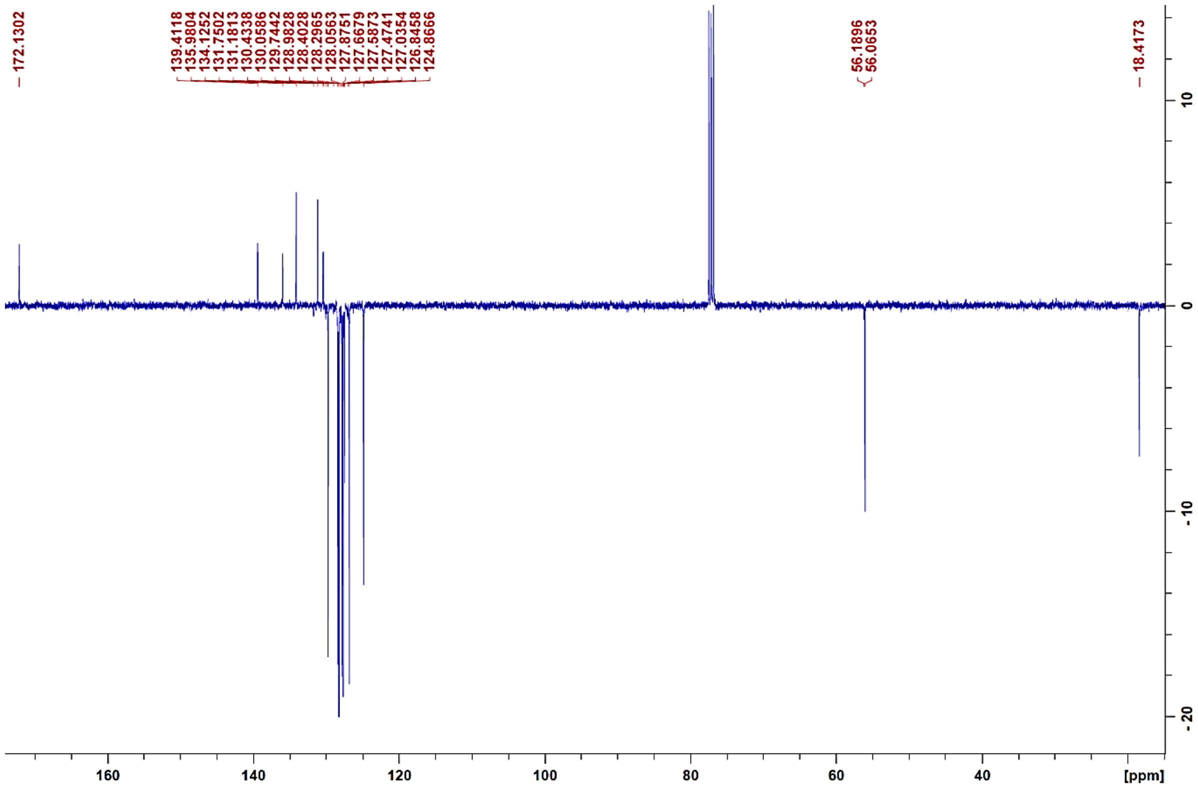


Procedure: Acetonitrile-clathrate (2.457 g, 5.06 mmol) and KOAc (1.110 g, 11.27 mmol) were suspended in Ac_2O (100 mL), and the mixture was stirred for 21 h at 100 °C. After removal of excess of anhydride under reduced pressure, the residue was dissolved in EtOAc/heptane (1:1) and filtered over a short column of silica to give 3.301 g of the crude *N*-alkylimide. The product was purified by flash chromatography on silica with gradient elution (5-15% EtOAc in heptane) to yield 1.558 g (72%) of ***(aS,S)*-24** as a white solid. M.p.: 217-219 °C. ^{1}H-NMR δ = 7.94 (2H, d, *J* = 8.5 Hz, ArH), 7.92 (2H, bd, *J* = 8.2 Hz, ArH), 7.53 (2H, ddd, *J* = 8.1, 5.9, 2.1 Hz, ArH), 7.40 (2H, bd, *J* = 8.5 Hz, ArH), 7.38-7.22 (9H, m, ArH), 6.23 (1H, d, *J* = 7.1 Hz, CH), 1.92 (3H, d, *J* = 7.1 Hz, CH_3) ppm. ^{13}C-NMR δ = 172.1 (C), 139.4 (C), 136.0 (C), 134.1 (C), 131.2 (C), 130.4 (C), 129.7 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 126.8 (CH), 124.9 (CH), 56.1 (CH), 18.4 (CH_3) ppm. $[\alpha]_D^{20}$ = -318 (c = 1.0, $CHCl_3$). HRMS: m/z calcd for $C_{30}H_{21}NO_2 + Na^+$: 450.1470; found: 450.1473.

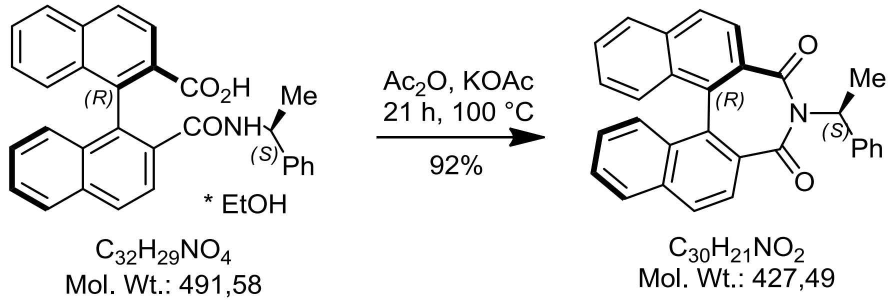
^{1}H-NMR:



^{13}C-NMR:

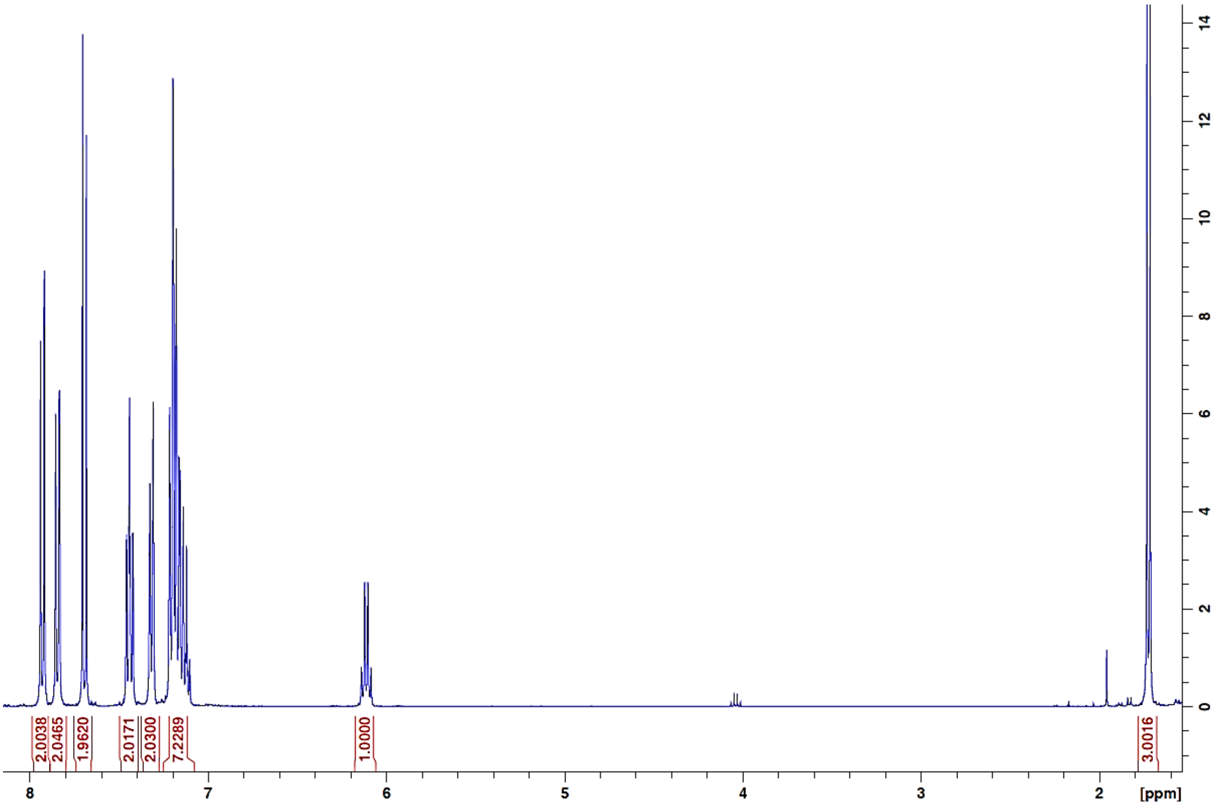


(*R*)-4-((*S*)-1-Phenylethyl)-3*H*-dinaphtho[2,1-c:1',2'-e]azepine-3,5(4*H*)-dione ((a*R,S*)-24)

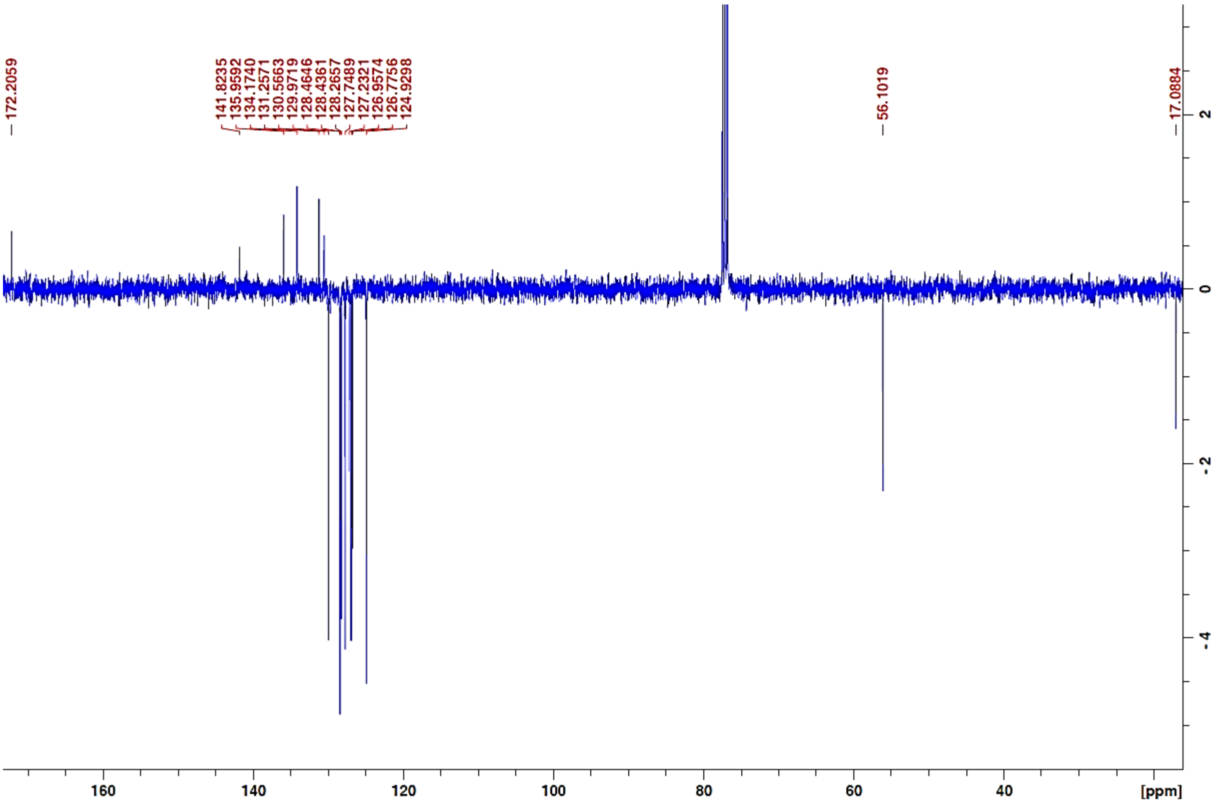


The same procedure for the preparation of **(a*S,S*)-24** gave the (a*R,S*)-imide as white foam in a yield of 92%. ^{1}H-NMR δ = 8.01 (2H, d, *J* = 8.6 Hz, ArH), 7.93 (2H, bd, *J* = 8.3 Hz, ArH), 7.78 (2H, d, *J* = 8.6 Hz, ArH), 7.52 (2H, ddd, *J* = 8.1, 6.4, 1.5 Hz, ArH), 7.42-7.38 (2H, m, ArH), 7.31-7.17 (7H, m, ArH), 6.19 (1H, p, *J* = 7.1 Hz, CH), 1.80 (3H, d, *J* = 7.1 Hz, CH_3) ppm. ^{13}C-NMR δ = 172.3 (C), 141.9 (C), 135.96 (C), 134.3 (C), 131.4 (C), 130.6 (C), 130.0 (CH), 128.5 (CH), 128.4 (CH), 128.3 (C), 127.7 (CH), 127.2 (CH), 126.9 (CH), 126.8 (CH), 124.9 (CH), 56.1 (CH), 17.1 (CH_3) ppm. $[\alpha]_D^{20}$ = +244 (c = 1.0, $CHCl_3$). HRMS: m/z calcd for $C_{30}H_{21}NO_2$ + Na^+: 450.1470; found: 450.1473.

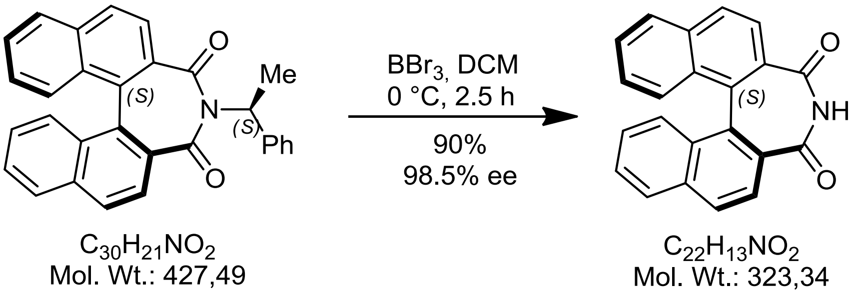
^{1}H-NMR:



^{13}C-NMR:



(*S*)-3*H*-Dinaphtho[2,1-c:1',2'-e]azepine-3,5(4*H*)-dione ((a*S*)-22)

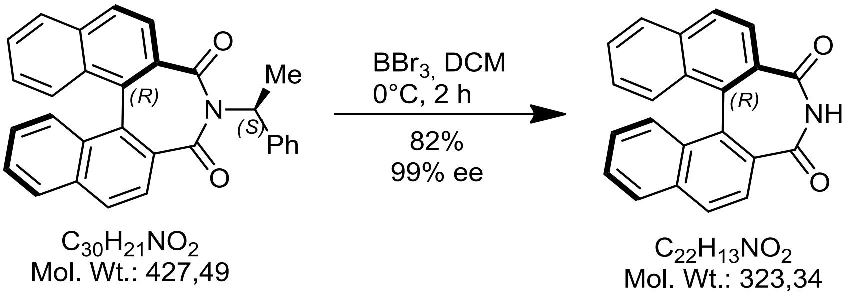


Procedure: *N*-Alkylimide (1.47 g, 3.4 mmol) was dissolved in freshly distilled DCM (60 mL) in a round bottom flask under argon and the solution was cooled to 0 °C. A solution of BBr_3 (1.64 mL, 17.3 mmol) in DCM (40 mL) was added dropwise over a period of 20 min, and the solution was stirred for another 2.5 h at 0 °C. After removal of the solvent, the residue was dissolved in DCM (100 mL) and to the dark red solution was added carefully water (70 mL) to quench excess of BBr_3. After separation, the organic phase was dried with $MgSO_4$ and evaporation of the solvent gave crude *(S)*-imide as yellow oil. Purification by flash chromatography with gradient elution (0-50 % EtOAc in heptane) yielded 1.01 g (90%, 98.5% ee) of **(a*S*)-22** as bright yellow solid. M.p.: 158-

164 °C. ^{1}H-NMR δ = 8.25 (1H, bs, NH), 8.06 (4H, s, ArH), 7.95 (2H, bd, *J* = 8.3 Hz, ArH), 7.54 (2H, dt, *J* = 6.9, 0.9 Hz, ArH), 7.20 (2H, dt, *J* = 6.9, 1.2 Hz, ArH), 7.06 (2H, d, *J* = 8.7 Hz, ArH) ppm. ^{13}C-NMR δ = 168.9 (C), 134.8 (C), 132.6 (C), 132.5 (C), 132.1 (C), 129.8 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 126.9 (CH), 125.6 (CH) ppm. $[\alpha]_D^{20}$ = -178 (c = 1.0, $CHCl_3$). HRMS: m/z calcd for $C_{22}H_{13}NO_2 + Na^+$: 346.0844; found: 346.0839.

The enantiomeric excess was determined by HPLC analysis (see below).

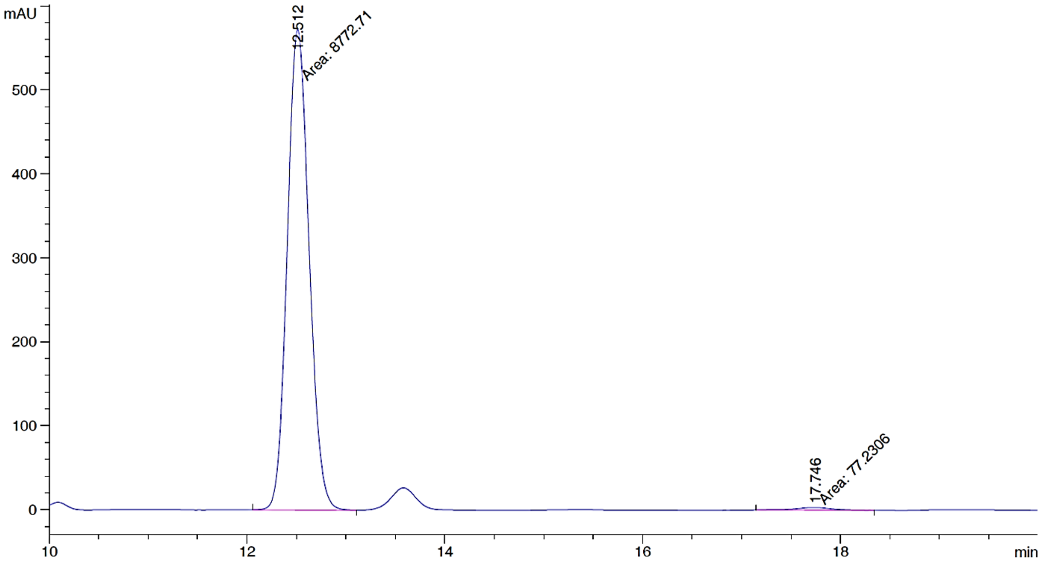
(*R*)-3*H*-Dinaphtho[2,1-c:1',2'-e]azepine-3,5(4*H*)-dione ((a*R*)-22)



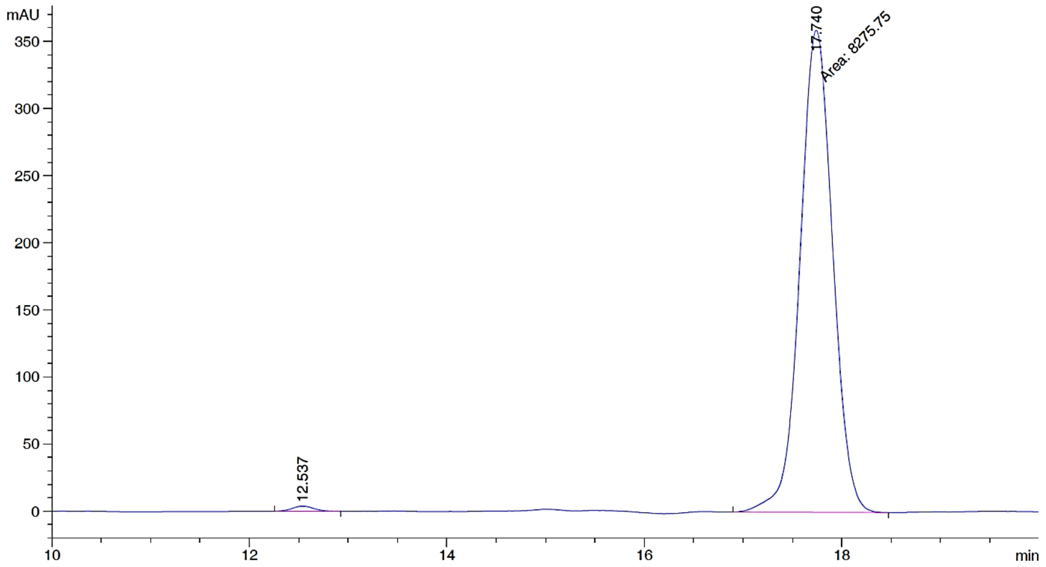
Procedure similar with the *(S)*-enantiomer with exception of stirring for 2 h at 0°C yielded **(a*R*)-22** in 82% yield (99% ee). $[\alpha]_D^{20}$ = +179 (c = 1.0, $CHCl_3$).

The enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel AD-H column, 25 °C, hexane/iPrOH = 1:1, flow rate = 0.5 mL/min, 280 nm. Retention times: 12.5 min *(S)* and 17.7 min *(R)*.

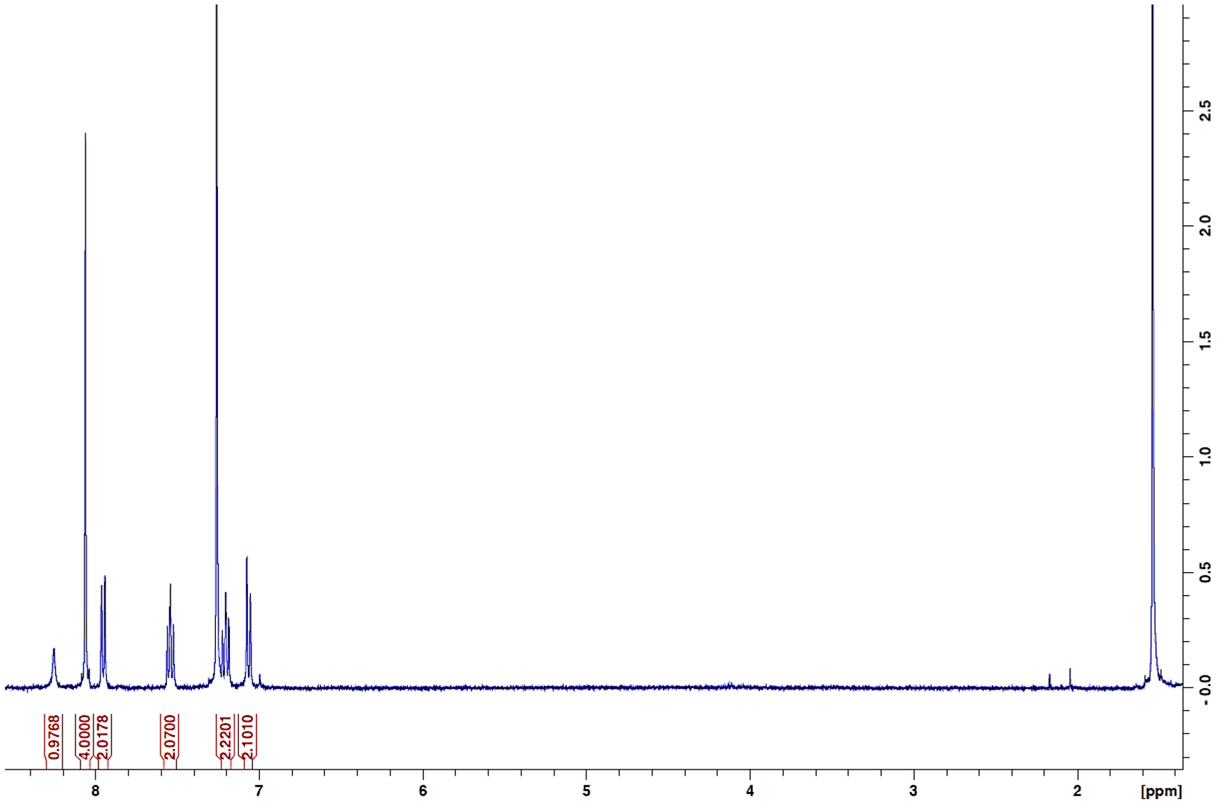
HPLC-analysis of *(S)*-Enantiomer:



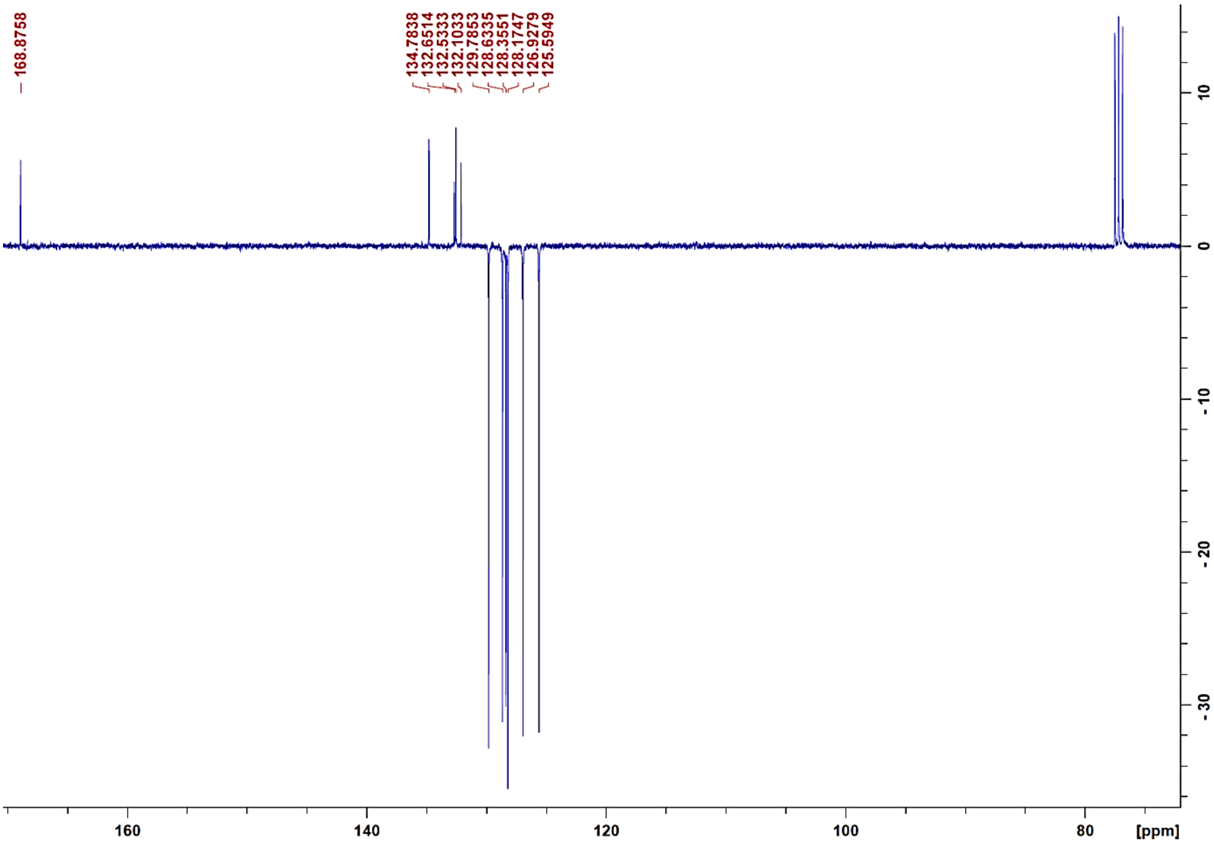
HPLC-analysis of *(R)*-Enantiomer:



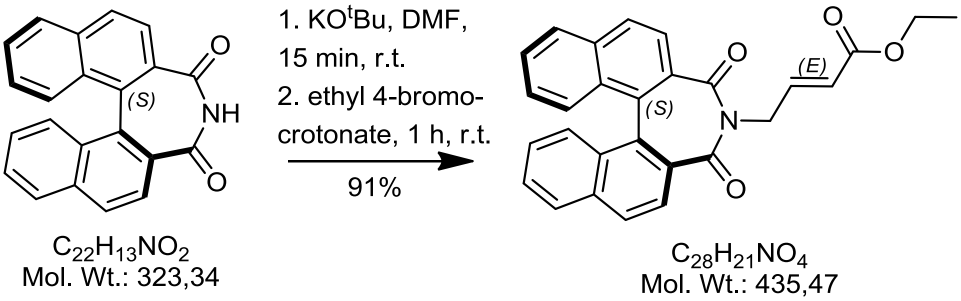
^{1}H-NMR:



^{13}C-NMR:



(*S,E*)-Ethyl 4-(3,5-dioxo-3*H*-dinaphtho[2,1-c:1',2'-e]azepin-4(5*H*)-yl)but-2-enoate ((a*S*)-26)



Procedure: To a stirred solution of *(S)*-Imide (355.0 mg, 1.10 mmol) in DMF (7 mL) was added KO^{t}Bu (184.8 mg, 1.65 mmol) at room temperature. After 15 min, the suspension was poured into a round bottom flask containing ethyl 4-bromocrotonate (75% purity, 423.9 mg, 1.65 mmol[b]). After completing the transfer by afterwashing with DMF (2 mL),

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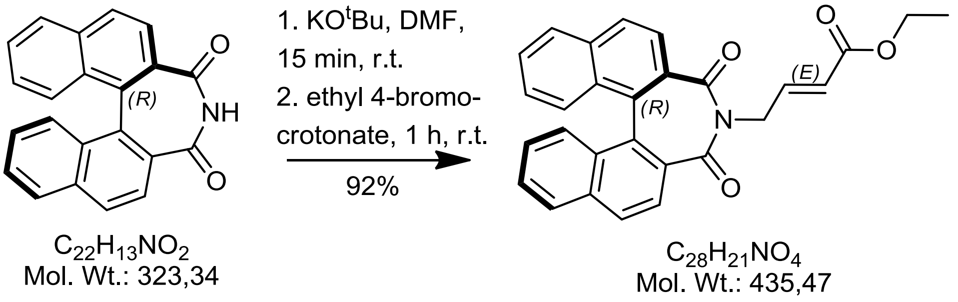
[b] With consideration of 75% purity of the reagent (technical grade).

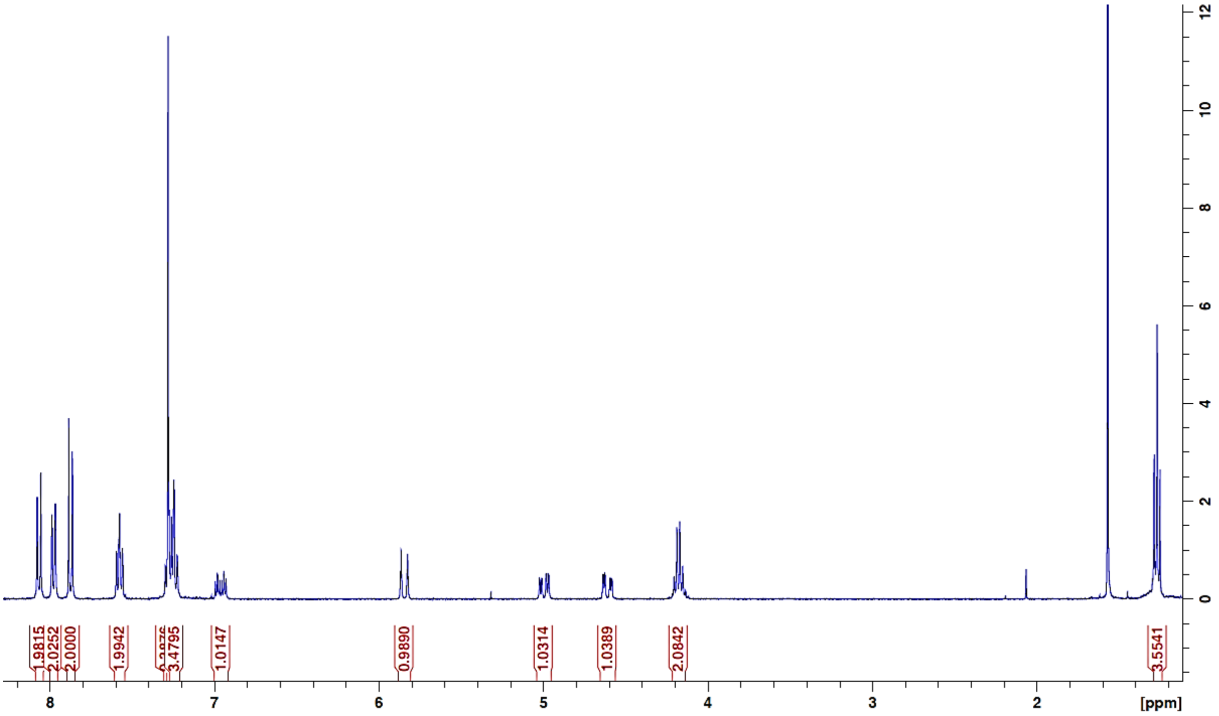
the mixture was stirred for 1 h. The reaction mixture was diluted with DCM and washed with a mixture of brine and water (1:1) and the aqueous phase was extracted with DCM. The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The crude enoate was purified by flash chromatography on silica with gradient elution (5-30% EtOAc in heptane) to give 435 mg (91%) of **(a*S*)-26** as bright yellow foam. ^{1}H-NMR δ = 8.04 (2H, d, *J* = 8.6 Hz, ArH), 7.95 (2H, d, *J* = 8.2 Hz, ArH), 7.85 (2H, d, *J* = 8.6 Hz, ArH), 7.55 (2H, ddd, *J* = 8.2, 6.5, 1.4 Hz, ArH), 7.29-7.19 (4H, m, ArH), 6.94 (1H, ddd, *J* = 15.7 Hz, 5.9, 4.6 Hz, CH), 5.86-5.78 (1H, m, CH), 4.97 (1H, ddd, *J* = 16.3, 5.0, 1.6 Hz, CH_2), 4.59 (1H, ddd, *J* = 16.3, 4.6, 1.8 Hz, CH_2), 4.16 (2H, qd, *J* = 7.2, 1.3 Hz, CH_2), 1.35 (3H, t, *J* = 7.2 Hz, CH_3) ppm. ^{13}C-NMR δ = 171.6 (C), 165.9 (C), 141.9 (CH), 143.4 (C), 143.2 (C), 131.6 (C), 131.2 (C), 130.0 (CH), 128.4 (CH), 128.4 (CH), 128.0 (CH), 127.0 (CH), 125.5 (CH), 123.1 (CH), 60.6 (CH_2), 47.3 (CH_2), 14.3 (CH_3) ppm. $[\alpha]_D^{20}$ = -214 (c = 1.0, $CHCl_3$). HRMS: m/z calcd for $C_{28}H_{21}NO_4 + Na^+$: 458.1368; found: 458.1368.

(*R,E*)-Ethyl 4-(3,5-dioxo-3*H*-dinaphtho[2,1-c:1',2'-e]azepin-4(5*H*)-yl)but-2-enoate ((a*R*)-26)

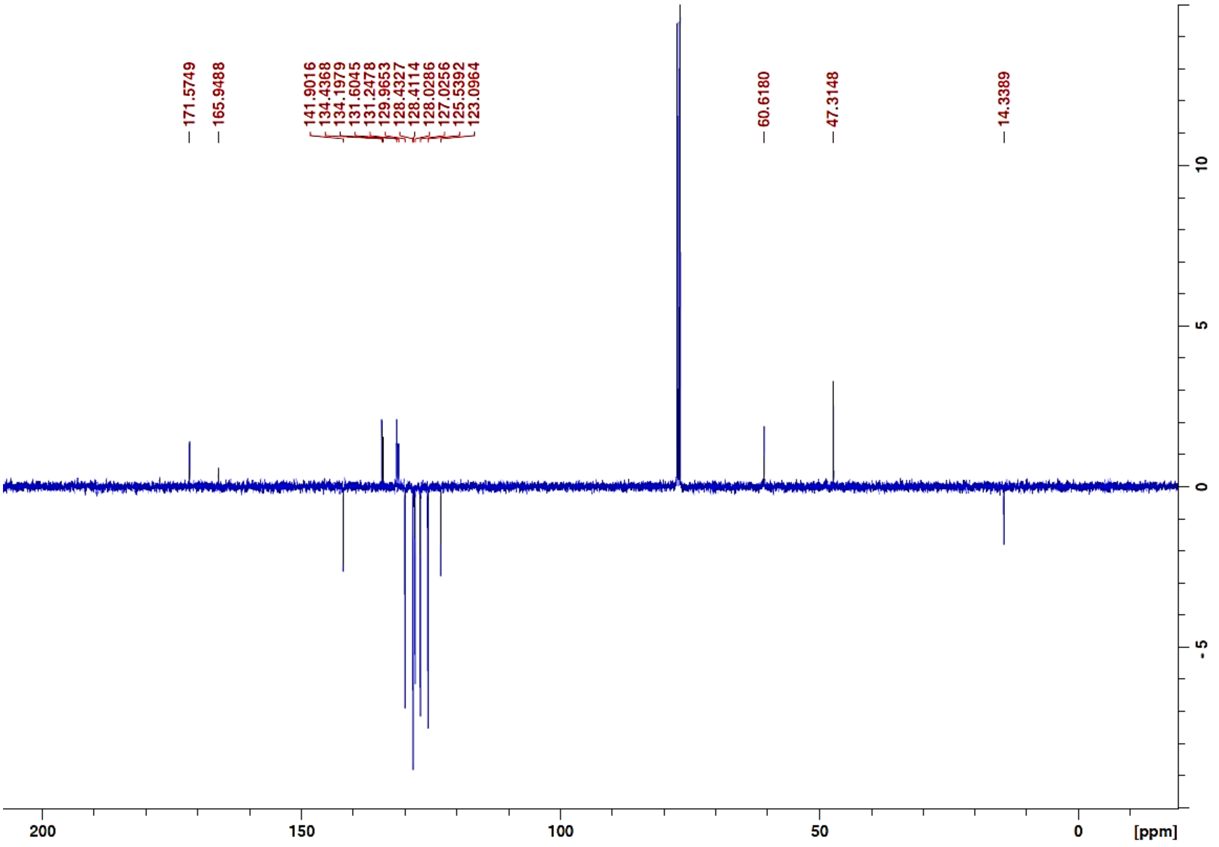


The same procedure for the preparation of the *(S)*-enantiomer gave **(a*R*)-26** in a yield of 92%. $[\alpha]_D^{20}$ = +233 (c = 1.0, $CHCl_3$).

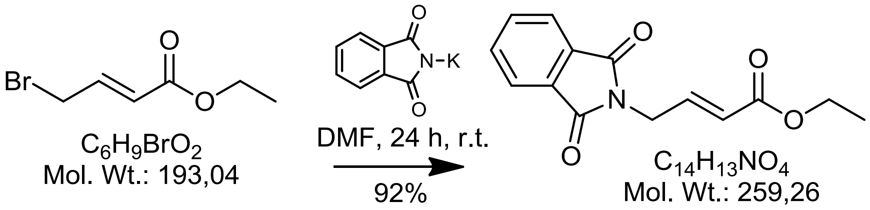
^{1}H-NMR:



^{13}C-NMR:



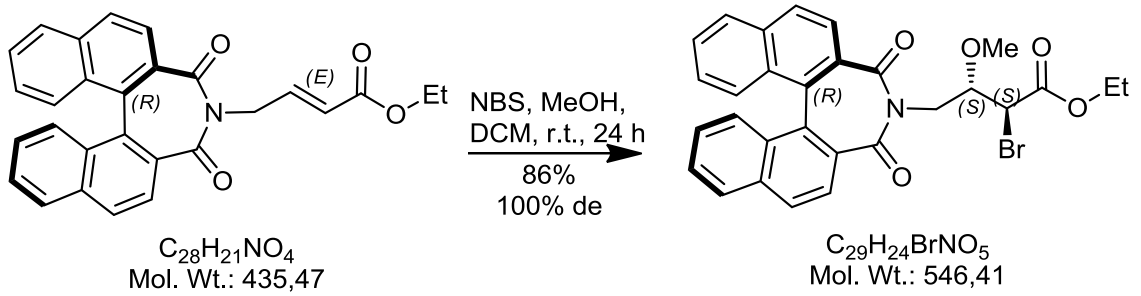
(*E*)-Ethyl 4-(1,3-dioxoisoindolin-2-yl)but-2-enoate (25)



Procedure:[49] To a solution of ethyl 4-bromocrotonate (75% purity, 500 mg, 1.9 mmol[c]) in DMF (5 mL) was added potassium phthalimide (480 mg, 2.6 mmol) at 0 °C and stirred for 1 h and additional 24 h at room temperature. The solution was diluted with $CHCl_3$ (30 mL) and extracted with water (2 x 30 mL). After extraction of the aqueous phase with $CHCl_3$ (30 mL), the combined organic layers were washed with brine, dried with $MgSO_4$ and concentration in vacuo gave a white residue. Purification by flash chromatography with gradient elution (10-40% EtOAc in PE) gave 464 mg (92%) of **25** as white solid. ^{1}H-NMR δ = 7.88 (2H, dd, *J* = 5.4, 3.0 Hz, ArH), 7.75 (2H, dd, *J* = 5.5, 3.0 Hz, ArH), 6.92 (1H, dt, *J* = 15.7, 5.3 Hz, CH), 5.90 (1H, dt, *J* = 15.7, 1.8 Hz, CH), 4.44 (2H, dd, *J* = 5.3, 1.8 Hz, CH_2), 4.17 (2H, q, *J* = 7.1 Hz, CH_2), 1.26 (3H, t, *J* = 7.1 Hz, CH_3) ppm;

General procedure for diastereoselective bromomethoxylation of (a*S*)-26 or (a*R*)-26:

(2*S*,3*S*)-Ethyl-2-bromo-4-((*R*)-3,5-dioxo-3*H*-dinaphtho[2,1-c:1',2'-e]azepin-4(5*H*)-yl)-3-methoxybutanoate ((a*R*)-28)



Procedure: *N*-Alkylimide **(a*R*)-26** (283 mg, 0.65 mmol) was dissolved in DCM (3 mL) and diluted with MeOH abs. (10 mL). *N*-Bromosuccinimide (173 mg, 0.97 mmol) was added und the mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure and a full conversion was determined via ^{1}H-NMR of the crude product. Purification via flash chromatography with gradient elution (10-20% EtOAc in

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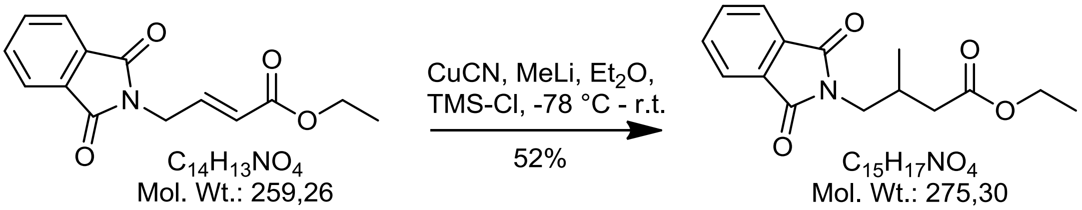
[c] With consideration of 75% pureness of the reagent (technical grade).

heptane) gave 305 mg (86%) of diastereomerically pure **(a*R,S,S*)-28** as a white solid. ^{1}H-NMR δ = 8.03 (2H, t, *J* = 8.5 Hz, ArH), 7.99 (2H, s, ArH), 7.94 (1H, bd, *J* = 8.4 Hz, ArH), 7.91 (1H, bd, *J* = 8.2 Hz, ArH), 7.52-7.47 (1H, m, ArH), 7.45 (1H, ddd, *J* = 8.1, 6.7, 1.2 Hz, ArH), 7.21-7.14 (3H, m, ArH), 7.08 (1H, bd, *J* = 8.6 Hz, ArH), 5.01-4.94 (1H, m, CH), 4.46 (1H, d, *J* = 7.9 Hz, CH), 4.42-4.38 (1H, m, CH_2), 4.38 (2H, q, *J* = 7.2 Hz, CH_2), 3.69 (1H, dd, *J* = 9.0, 11.8 Hz, CH_2), 2.86 (3H, s, CH_3) 1.40 (3H, t, *J* = 7.2 Hz, CH_3) ppm. HRMS: m/z calcd for $C_{29}H_{24}BrNO_5$ + Na^+: 568.0731; found: 568.0735.

Ethyl 4-(1,3-dioxoisoindolin-2-yl)-3-methylbutanoate (27)



Procedure: To a degassed suspension of CuCN (82.9 mg, 0.9 mmol) in Et_2O (2 mL) was added 1.6 M MeLi in Et_2O (1.58 mL) at -78 °C and the mixture was stirred for 30 min. TMSCl (80 µL, 67 mg, 0.6 mmol) and a degassed solution of **25** (80 mg, 0.3 mmol) in Et_2O (5 mL) was added and the mixture was stirred at a temperature raising from -78 to -5 °C within 135 min, while a yellow precipitate occurred. After stirring for 1 h at room temperature, the suspension was quenched with a saturated solution of NH_4Cl with pH 8 (adjusted via NH_4OH, 10 mL) and extracted with ether (2 x 10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash chromatography with gradient elution (30-50% EtOAc in PE) gave 44 mg (52%) of **27** as a white solid. ^{1}H-NMR δ = 7.69-7.63 (2H, m, ArH), 7.57 (1H, td, *J* = 7.5, 1.1 Hz, ArH), 7.48 (1H, td, *J* = 7.5, 1.1 Hz, ArH), 4.41-4.27 (2H, m, CH_2), 4.12 (1H, bs, CH_2), 3.64 (1H, dd, *J* = 11.1, 8.6 Hz, CH_2), 3.47-3.34 (1H, m, CH), 3.24 (1H, dd, *J* = 11.1, 8.7 Hz, CH_2), 2.31 (1H, bd, *J* = 11.1 Hz, CH_2), 1.38 (3H, t, *J* = 7.1 Hz, CH_3), 1.19 (3H, d, *J* = 6.7 Hz, CH_3) ppm. HRMS: m/z calcd for $C_{15}H_{17}NO_4$ + Na^+: 298.1055; found: 298.1051.

4 Appendix

4.1 Abbreviations

AIBN	Azobisisobutyronitrile
BINOL	1,1'-Bi-2-naphthol
CSA	Camphorsulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DABN	2,2'-Diamino-1,1'-binaphthalene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
$(DHQD)_2PHAL$	Hydroquinidine-1,4-phthalazinediyl diether
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridin
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
dppp	1,3-Bis(diphenylphosphino)propane
ee	Enantiomeric excess
GC	Gas chromatography
HPLC	High-performance liquid chromatography
LAH	Lithium aluminium hydride
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NDMBA	*N,N′*-Dimethylbarbituric acid
NMR	Nuclear magnetic resonance
PE	Petroleum ether
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride

4.2 Curriculum Vitae

Name: **Martin Berger BSc**

Education

10/2012 - present	M.Sc. student (major chemistry), Supervisor: Ao. Prof. Dr. Michael Widhalm, Institute of Chemical Catalysis, University of Vienna
10/2009 - 10/2012	B.Sc. (major chemistry), University of Vienna
10/2007 - 06/2009	School leaving examination (BFI / HTL Waidhofen a.d. Ybbs / HTL Krems)
07/2000 - 07/2003	Professional education in carpentry

Working experience

01/2014 - 02/2014	Project co-worker (FWF project) in the group of Ao. Prof. Dr. Walter Weissensteiner
07/2013 - 08/2013	Project co-worker (FWF project) in the group of Ao. Prof. Dr. Walter Weissensteiner
10/2012 - 07/2014	Tutor at the Institute of Organic Chemistry, University of Vienna
06/2006 - 06/2009	Technician at Wittur GmbH, Scheibbs
06/2005 - 05/2006	Paramedic at Austrian Red Cross
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4.3 Abstract

Bromofunctionalizations of olefins are useful transformations in organic synthesis. The interest in asymmetric intramolecular bromofunctionalization of olefins, like bromolactonisation or bromoetherification, has grown immensely during the last years and a large number of enantioselective organocatalysts has been developed. Intermolecular variants on the other hand turned out to be more sophisticated and the number of catalytic systems, which have been successfully applied so far, is rather limited. While some examples for functionalized olefinsubstrates exist, non-functionalized olefins proved to be difficult to apply in this transformation. Therefore, sterically crowded binaphthyl thiourea catalysts have been synthesized and applied in the bromohydroxylation and bromoethoxylation of *trans*-stilbene in combination with *N*-bromosuccinimide as efficient Br^+-source. Since low temperatures are required in order to suppress the non-catalyzed reaction, only bromoethoxylation was practicable. A bifunctional thiourea catalyst, containing a tertiary amine with weak nucleophilicity and two chiral binaphthyl units, showed significant increase of the reaction rate, compared to the non-catalyzed reaction, and high chemoselectivity towards the desired ethoxybromide. An enantiomeric excess of 25% and high conversion have been achieved. Since it is already known that this kind of transformation can be accelerated through the activation of *N*-bromosuccinimide via thioureas, this work shows that there is also some asymmetric induction possible by use of bulky catalysts. Furthermore, a non-catalytic approach concerning this topic has been worked out by application of a new chiral biaryl auxiliary. Binaphthimide is a strongly fluorescing, and therefore easily detectable, axially chiral imide. A 3-step procedure for the preparation of enantiopure binaphthimide has been developed starting from achiral binaphthyl dicarboxylic acid. The auxiliary can be easily attached to alkyl halides. It was coupled with ethyl 4-bromocrotonate and the reaction of choice was bromomethoxylation of the enoate. The auxiliary showed 100% regioselectivity and high diastereoselectivity, since only two diastereomers in a ratio of 86/14 have been obtained.

4.4 German abstract

Bromofunktionalisierungen von Olefinen sind nützliche Reaktion in der organischen Synthese. Asymmetrische Varianten sind von großem Interesse, was die mittlerweile große Zahl an Publikationen zu intramolekularen Halozyklisierungen und dabei angewandten Organokatalysatoren belegt. Der Zugang zu asymmetrischen intermolekularen Halofunktionalisierungen hat sich jedoch als schwierig herausgestellt und die Zahl an Arbeiten zu diesem Thema ist stark begrenzt. Besonders schwierig scheint es bei Olefinen ohne weiteren Funktionalitäten zu sein. Es wurde versucht, das Problem mit sterisch besonders anspruchsvollen Binaphthylthioharnstoffen als Katalysatoren zu lösen, welche in der Bromohydroxylierung und Bromoethoxidierung von *trans*-Stilben in Kombination mit *N*-Bromsuccinimid als effiziente Br^+-Quelle angewendet wurden, wobei sich nur die Bromoethoxidierung als anwendbar erwiesen hat. Ein bifunktionalisierter Thioharnstoff, welcher neben einem schwach nukleophilen tertiären Amin auch zwei chirale Binaphthylgerüste enthält, zeigte eine deutliche Zunahme der Reaktionsgeschwindigkeit im Vergleich zur nicht katalysierten Reaktion und hohe Chemoselektivität für das gewünschte Produkt. Es konnte ein Enantiomerenüberschuss von 25% bei hohem Umsatz erzielt werden. Nachdem schon bekannt war, dass Thioharnstoffe diese Reaktion durch Aktivierung von *N*-Bromsuccinimid beschleunigen, konnte hiermit gezeigt werden, dass auch eine asymmetrische Induktion durch Anwendung sperriger Katalysatoren möglich ist. Des Weiteren wurde auch eine nicht-katalytische Variante durch Einsatz eines neuen chiralen Biarylauxiliares realisiert. *N*-Binaphthimid ist ein stark fluoreszierendes und daher leicht detektierbares axial-chirales Imid und wurde in 3 Stufen enantiomerenrein aus racemischer Binaphthyldicarbonsäure hergestellt. Es kann leicht an Alkylhalogenide gekoppelt werden und zeigte in der asymmetrischen Bromomethoxylierung von Ethylcrotonat 100% Regioselektivität und hohe Diastereoselektivität, da nur 2 Diastereomere in einem Verhältnis von 86/14 erhalten wurden.

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