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Tesi di Laurea

Novel cinchona alkaloids
derivatives and their application
as PTCs

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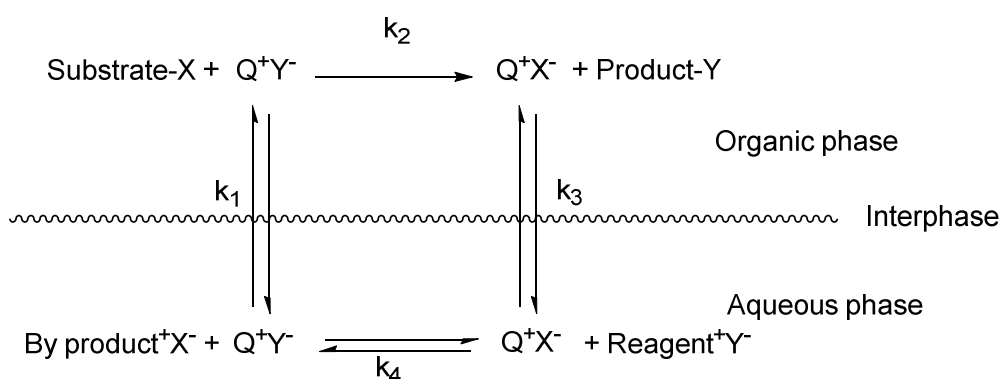
1 Theoretical section

1.1 Introduction

The term "Phase transfer catalysis" (PTC) was introduced for the first time in 1971 by Stark to explain the critical role of tetraalkylammonium or phosphonium salts (Q^+X^-) in the reactions between two substances located in different immiscible phases [1-2-3]. Although the catalytic activity of quaternary onium salts was already known, the foundations of PTC were laid by Starks, together with M. Makosza and A. Brändstrom in 1960s [2]. In particular the phase transfer catalyst (PTCs) helps the migration of a molecule or ion from one phase to another and in doing so can greatly accelerate the rate of heterogeneous reaction processes [4-5].

Quaternary ammonium salts are commonly used as PTCs but also phosphonium salts, crown ethers, cryptands as well [6].

The simplest example of this process is referred as normal biphasic phase-transfer reaction (**Scheme 1**). The catalyst (Q^+X^-), dissolved in aqueous phase, undergoes anion exchange with the aqueous anion of the reactant (Y^-). The ion pairs formed (Q^+Y^-), can cross the inter phase due to its lipophilic nature and diffuses into the organic phase. The anion can thus react with the organic reagent giving the product and the initial catalyst, that can return in the aqueous phase and the cycle continues [7].



Scheme 1. General mechanism of trans-phase catalyst

The transfer of the target molecule from one phase to another depends on the characteristic and nature of the PTCs employed. However, other mechanisms are possible and the ionic exchange can take place also in the interfacial region or in the organic phase [8].

One of the most documented example is the cyanation of 1-chlorooctane (**1**). The reaction with aqueous sodium cyanide leads to zero yield even after several days. However with the presence of small amount of hexadecyltributylphosphonium bromide (**3**), a rapid formation of 1-cyanoctane (**2**) is observed.

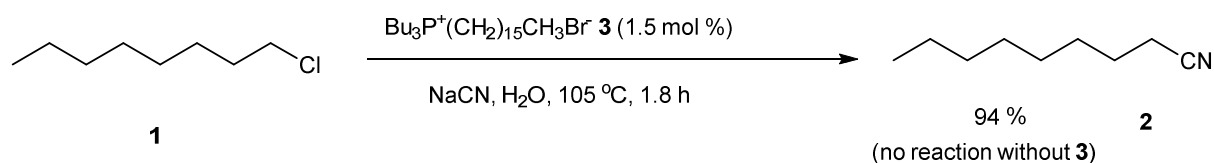


Fig. 2. Cyanation of 1-chlorooctane using a quaternary phosphonium salt as PTCs

The enhanced reactivity of **1** is particularly due to the formation of a quaternary phosphonium cyanide, which increases the solubility of the anion in the organic phase and thus its nucleophilicity [9].

Generally speaking, phase transfer catalysis presents some advantages over conventional homogeneous reaction, and have been recognized as a practical methodology in organic synthesis [9]. In particular the reactivity of the reagent anion (Y^-) in the organic phase is usually enhanced since the Q^+Y^- ion pair tends to have greater charge separation and reduced hydration compared to aqueous solutions of the precursor salt (Reagent^+Y^-). Consequently intrinsic reaction rate (k_2) tends to be higher than those obtained in homogeneous media [10]. This means lower reaction temperature, and high selectivity and yield are observed since the final product is protected in the organic phase from solvolysis reactions or the presence of base if it is base sensitive [3]. No polar anhydrous solvents are required and sometimes no organic solvents are used as the reagent can be use itself as phase. In most of cases biphasic condition simplifies the separation of the product from by-product. Moreover the quaternary salt is usually inexpensive, readily available and biodegradable [7].

The concept of ion pairs, as distinct chemical entities, was introduced in 1926 by Bjerrum [11]. The interactions between the cation catalyst and the anion can be described by Coloumb's law, in which the magnitude of the electrostatic interaction is inversely related to the distance between the ions and the dielectric constant of the media. Ions pair can be classified into three different types: contact, solvent-shared and solvent-separated. The first type is preferred in low dielectric constant solvents and no solvent molecules are present between the two ions [12].

In addition when a chiral phase transfer catalyst is employed with prochiral reagent, reactions may proceed stereoselectively giving optical active compound [13]. In the last 25 years, many effort have been done in the development of asymmetric catalysis using chiral PTCs, although this field has progressed rather slowly [2-14].

In particular *Cinchona* alkaloids, natural products found in the bark of trees of the genus *Cinchona* [15], although they played a long history in medicine as antimalarial drugs and in food and beverage industry as a bitter additive, nowadays have found several applications in organic chemistry especially in asymmetric catalysis [16]. As shown in **fig.3**, Quinine (**QN**), quinidine (**QD**), cinchonine (**CN**), cinchonidine (**CD**), the best known cinchona alkaloids, have five stereocenter C-3, C-4, N-1, C-8 and C-9. They occur in pairs with different configuration only at N-1, C-8 and C-9. They are related as diastereomeric pairs, but often are referred as pseudoenantiomers. In all cinchona alkaloids, the configuration at C-3 and C-4 is identical [17].

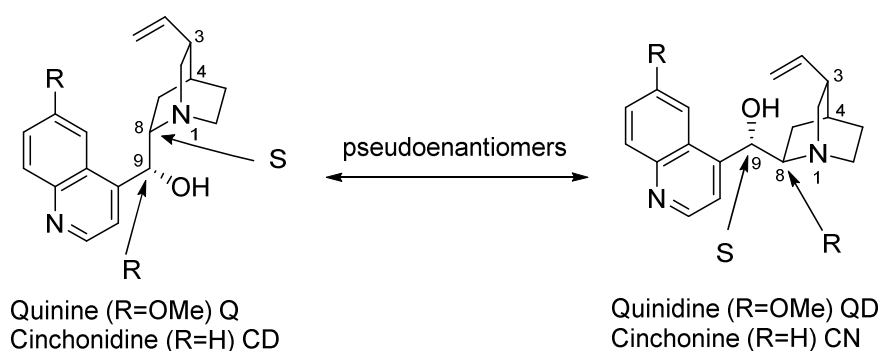


Fig. 3. Representative cinchona alkaloids

Easy commercially available, inexpensive and obtainable in diastereomeric pairs, *Cinchona* alkaloids are privileged chiral inducers and they have been used extensively in designing chiral PTCs [13]. The reason of their useful utility is due to their chiral skeleton and structure that is easy tunable for different type of reactions [18]. As reported in **fig. 4**, the basic structure of the *Cinchona* alkaloids consists of two rigid ring moiety: an aromatic quinoline and an aliphatic quinuclidine ring, linked by two carbon-carbon single bonds. The quinuclidine nitrogen is nucleophilic and it is responsible for the basic character of cinchona alkaloids. It can act as a ligand or nucleophilic unit in metal-catalyzed or organocatalytic reactions and can be quaternarized to obtain a large number of quaternary ammonium salts that can be used as efficient phase-transfer catalyst [17].

In addition the secondary 9-hydroxy group can serve as an acid site or in hydrogen bond donor, providing an enzyme like interactions [17-18].

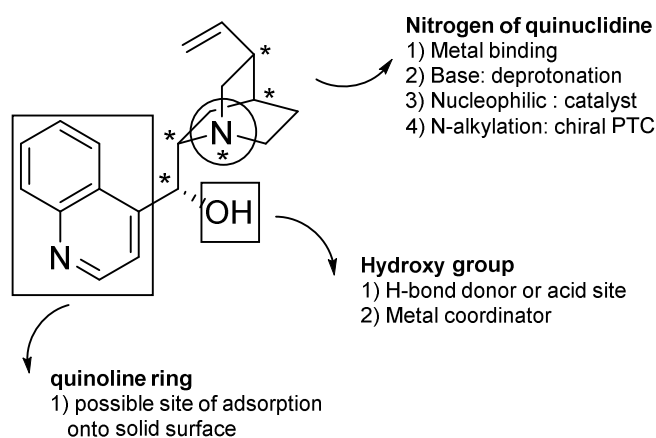


Fig. 4. Active sites in cinchonidine

Asymmetric phase-transfer catalysis is characterized by the presence of biphasic system, composed of an organic phase, containing an acid methylene compound and an electrophile, and an aqueous or solid phase of inorganic base [2-9]. Basically, asymmetric induction is due to the formation of anionic nucleophile which coordinates to the chiral phase-transfer catalyst. In doing this, the nucleophile is located in a chiral environment by which the transition states, in the reaction between the nucleophile and a given electrophile, is differentiate in diastereoselective manner. However different types of mechanisms are possible and this generally depends on the particular reaction taken in consideration.

The first example of using *Cinchona* alkaloids in asymmetric PTCs dates from 1984. A Merck research group conducted the first enantioselective methylation of phenylindanone derivative **4** using N-(p-(trifluoromethyl)benzyl)cinchonidinium bromide (**5**) as catalyst under phase transfer conditions (Fig. 5) [19]. In toluene and 50 % aqueous NaOH, the alkylated product (**6**) is obtained in excellent yield and selectivity of 95 % and 92 %, respectively.

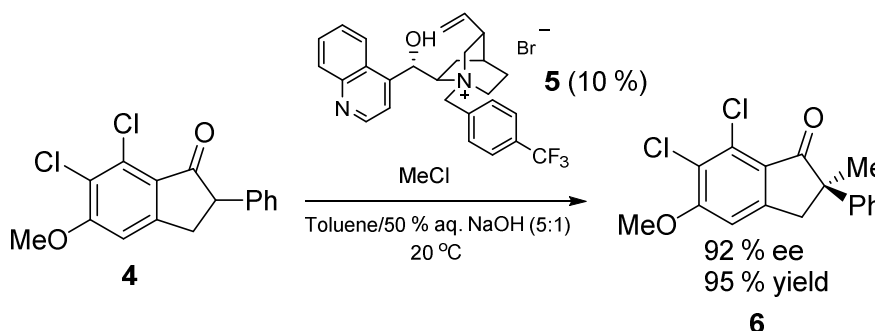
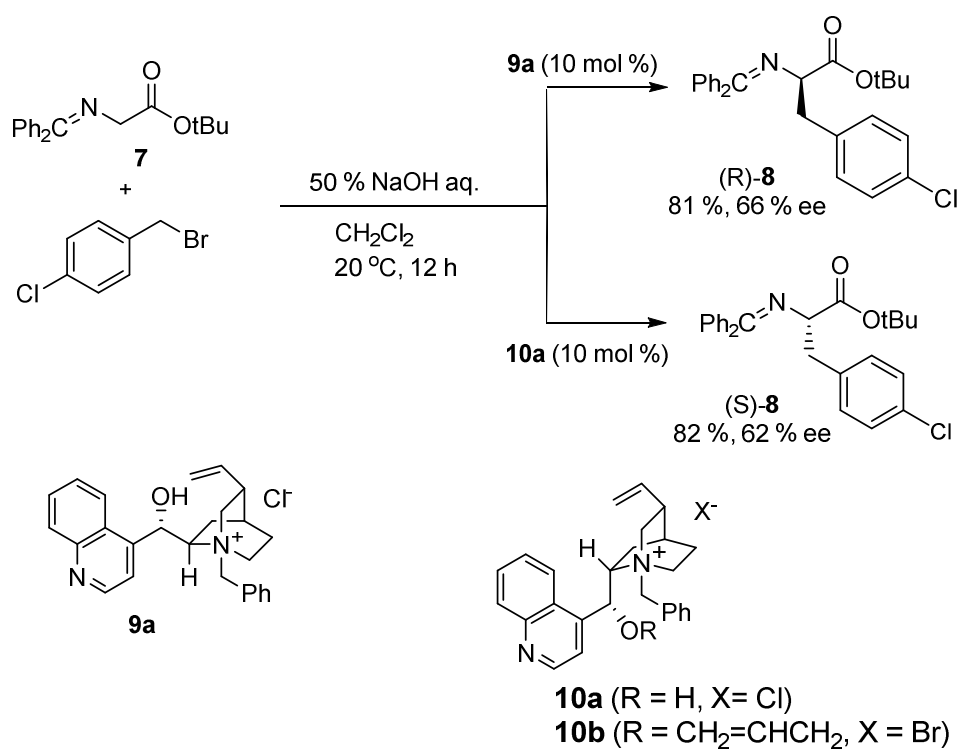


Fig. 5. Methylation of Phenylindanone derivate using PTCs catalyst

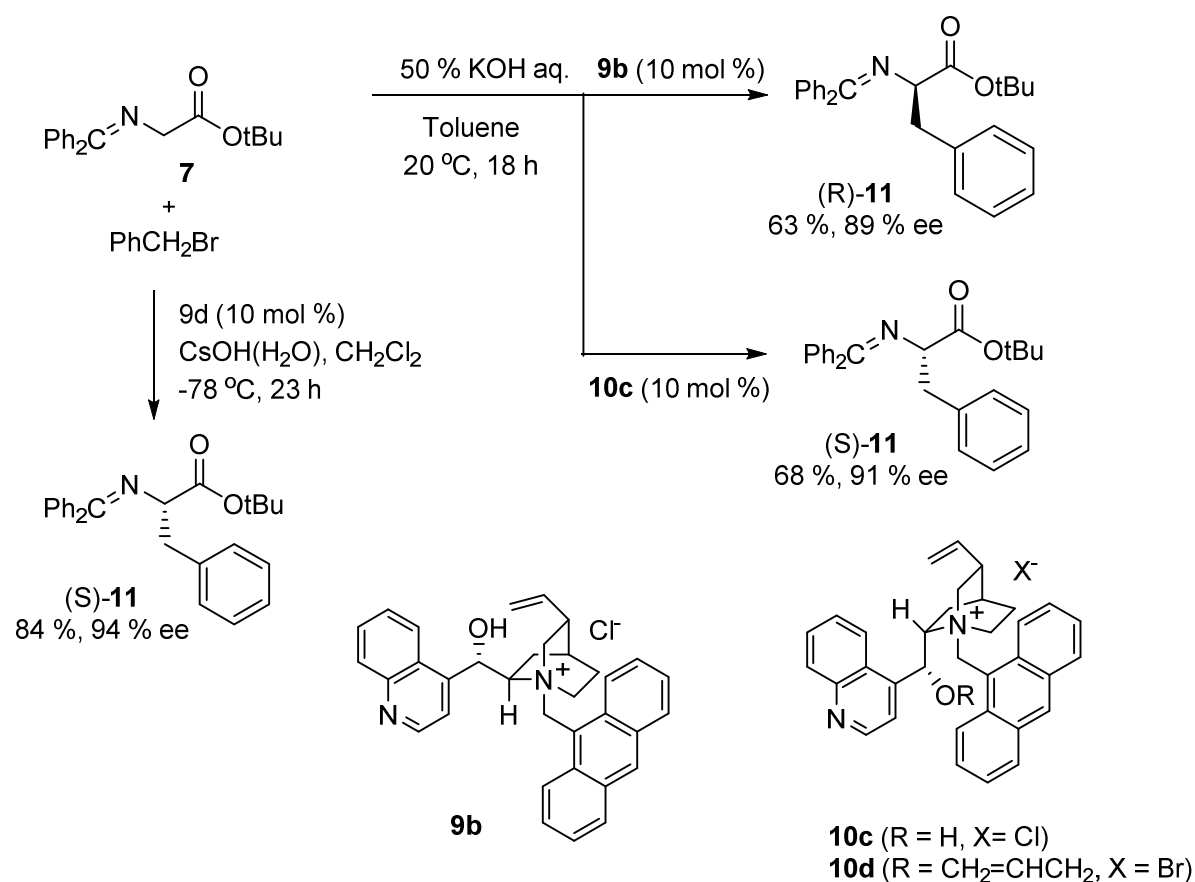
Since the first pioneering studies, many effort were done in the development and consequently in the applications of various *Cinchona* derived chiral PTCs. One of the most interesting reactions studied, which has been useful in the synthesis of aliphatic α -amino acids, is the asymmetric alkylation of glycinate Schiff base (**7**) [13]. The first employment of *Cinchona* derived PTCs to the asymmetric synthesis of α -amino acids was done by the research group of O'Donnel in 1989. They used N-benzylcinchoninium chloride (**9a**) as catalyst in asymmetric alkylation of **7** to give the product (*R*)-**8** in moderate enantiomeric excess (**Scheme 2**).



Scheme 2. Asymmetric alkylation of glycinate Schiff base with PTCs developed by O'Donnel

By simply switching to the cinchonidine-derivative (**10a**), the product could be obtained with the opposite configuration (*S*) but with similar degree of selectivity. Further optimization with the O-alkylated catalyst **10b** (second generation) has led to an improvement in enantioselectivity up to 81 % e.e [20-21]. The study of activity-structure relationship has been crucial in the development of new class of cinchona PTCs derivatives. In 1997 Lygo accomplished higher enantioselectivity by introduction of bulkier 9-Anthracenylmethyl group at quinoline nitrogen (**9b** and **10c**, **Scheme 3**) [22]. Corey at the same time prepared

O-allyl-N-anthracenylmethylcinchonidinium salt **10d** (**Scheme 3**) employing CsOH·(H₂O) as base at lower temperature and achieving results very similar to Lygo's [23].



Scheme 3. Alkylation of glycinate Schiff base with Lygo's and Corey's catalysts

The enantioselectivity of the alkylation of glycine derivative (**7**) using N-anthracenylmethyl ammonium salt (**10c** and **10d**) as catalyst, has been elucidated by the presence of an imaginary tetrahedron composed of four carbon atoms adjacent to the bridgehead nitrogen. It is believed that three of the faces of the tetrahedron are blocked by the quinuclidine, quinoline, and anthracenylmethyl groups (**Fig. 6**). The remaining face is sufficiently opened to allow close contact between the enolate anion and catalyst cation [23].

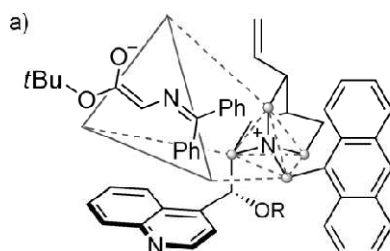


Fig. 6. Model for explaining the origin of enantioselectivity in cinchona derived PTCs.

However application of cinchona alkaloids as PTCs has not regarded only asymmetric alkylation. In the last few years cinchona alkaloids quaternary ammonium salts have been proved to be active catalysts in a huge amount of asymmetric transformation including the Michael additions, aldol reactions, Darzens reactions, epoxidation of enones and etc. [9].

Furthermore the design of chiral *Cinchona* PTCs derivatives has interested not only their monomeric forms. The group of Jew and Park reported dimeric (and also trimeric) catalysts with a spacer group between the *Cinchona* alkaloids units (**Fig. 7**) [13].

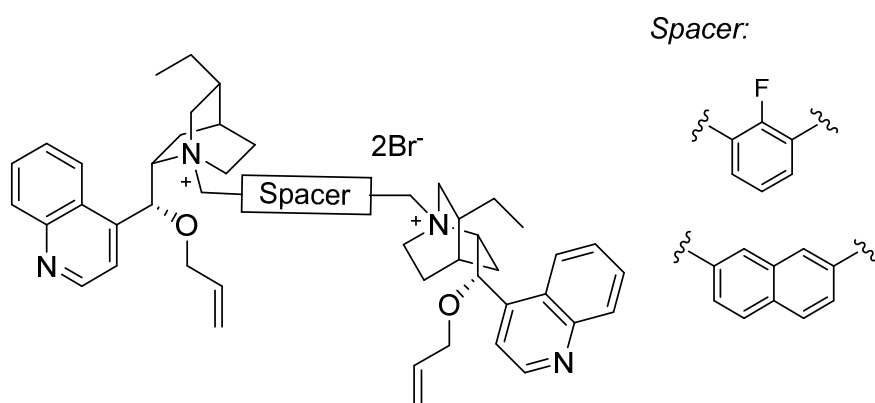


Fig. 7. Jew and Park phase-transfer catalysts

Several groups have developed polymer-bound phase-transfer catalysts. Advantages for such resin-bound catalysts include simplified product purification and catalyst recovery by filtration. Merrifield- and PEG-bound catalysts derived from Cinchonidine (**CD**) are reported in **fig. 8** [24-25].

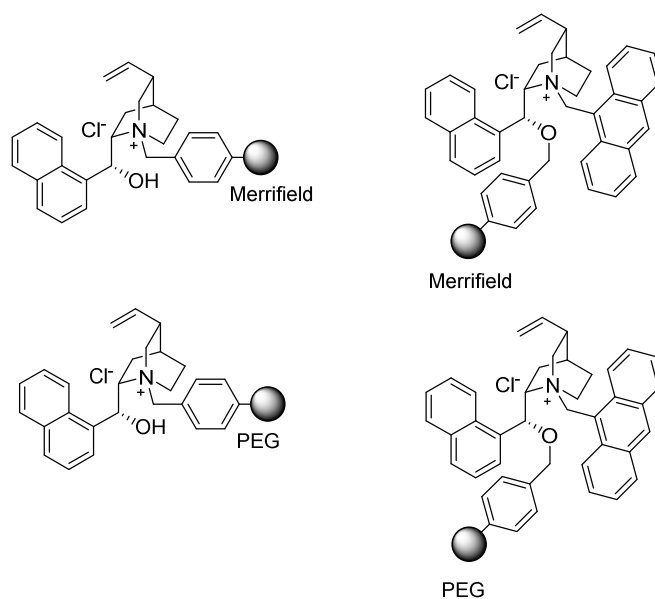


Fig. 8. Polymer-bound *Cinchona*-derived phase-transfer catalysts

1.2 Aim and Motivation

Structure modifications of cinchona alkaloids has been a major field of work in the research group of Prof. L. Hintermann. Recently, L. Hintermann and coworkers have reported a nucleophilic addition of Grignard reagents to the quinoline ring of cinchona alkaloids [26]. Based on this simple modification of the cinchona core, the first goal of this work was focused on the synthesis of new chiral quaternary ammonium salts (**14a** and **14b**) based on cinchona aminal cores derived from cinchonidine **12a** and dihydrocinchonidine **12b** (Fig. 9).

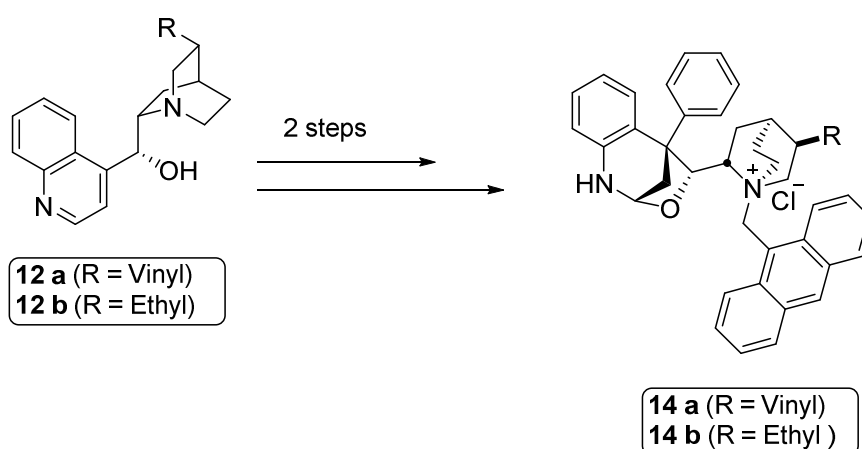


Fig. 9. Novel quaternary ammonium salts derived from cinchonidine and dihydrocinchonidine

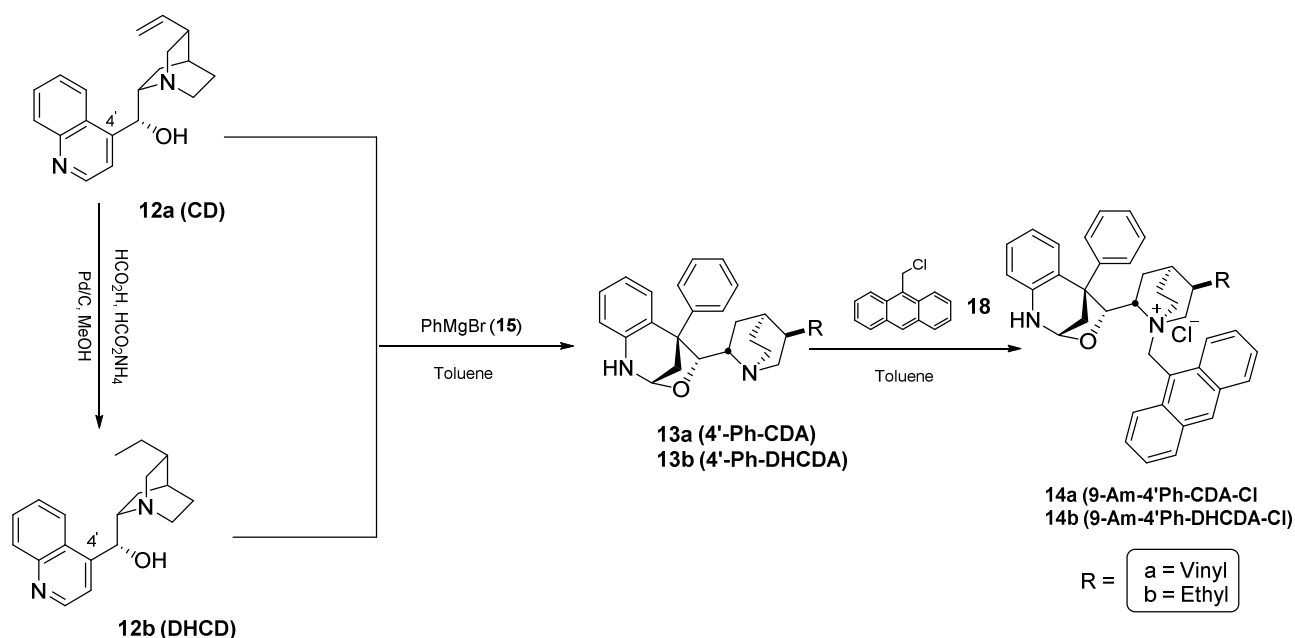
In the first part of this thesis, the synthesis and characterization of the quaternary salts **14** are presented. Since they are new compounds, nothing is known about their catalytic activity as PTCs. The following second part of the thesis describes tests of **14** as possible chiral catalysts under typical asymmetric phase-transfer conditions. In particular, asymmetric alkylation of glycine Schiff base, epoxidation of chalcone, Michael addition of dibenzyl malonate to chalcone and cyclization of 2'-hydroxychalcone to flavanone were investigated and will be discussed in detail in the catalysis chapter.

1. 3 Results and discussion

1.3.1 Synthesis of novel cinchona alkaloids derivatives

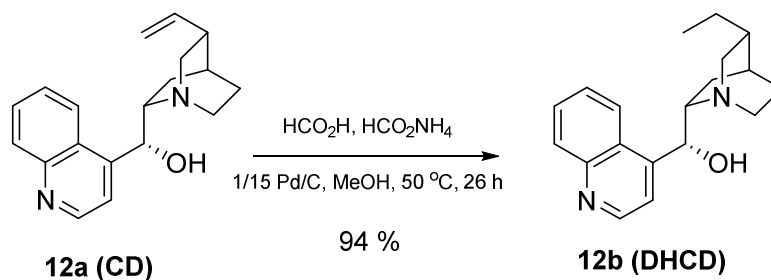
Cinchona alkaloids are well known to catalyze a huge number of reactions, above all in the field of asymmetric organocatalysis. This is due to their particular easy tunable structure that allow them to be applied in enantioselective reactions. Basic diversifications of cinchona alkaloid's structure to the corresponding quaternary salt have involved especially the hydroxy group at C-9 and quinuclidine nitrogen [27].

In this work we synthesized novel cinchona derivatives with modification of the quinoline moiety and introduction of the N-anthracenylmethyl (9-Am) function. In **Scheme 4** is reported the general synthesis of **9-Am-4'-Ph-CDA-Cl (14a)** and **9-Am-4'-Ph-DHCDA-Cl (14b)** in two steps. The proposed synthesis starts from **CD (12a)** and **DHCD (12b)**, followed by nucleophilic addition of Grignard reagent (**15**) to the quinoline C-4 carbon, to give the corresponding **4'-Ph-CDA (13a)** and **4'-Ph-DHCDA (13b)** [23]. Finally these compounds gave the N-alkylation with 9-anthracenylmethylchloride, thus forming the final products **14a** and **14b**.



Scheme 4. General pathway for the synthesis of **9-Am-4'-Ph-CDA-Cl (14a)** and **9-Am-4'-Ph-DHCDA-Cl (14b)**.

The synthesis of **14a** and **14b** started from **12a** and **12b**, being cheap starting materials. In particular dihydrocinchonidine (**12b**) was obtained from cinchonidine (**12a**) by hydrogenation of the vinyl to an ethyl group over palladium on carbon using an excess of formic acid and ammonium formate (**Scheme 5**).



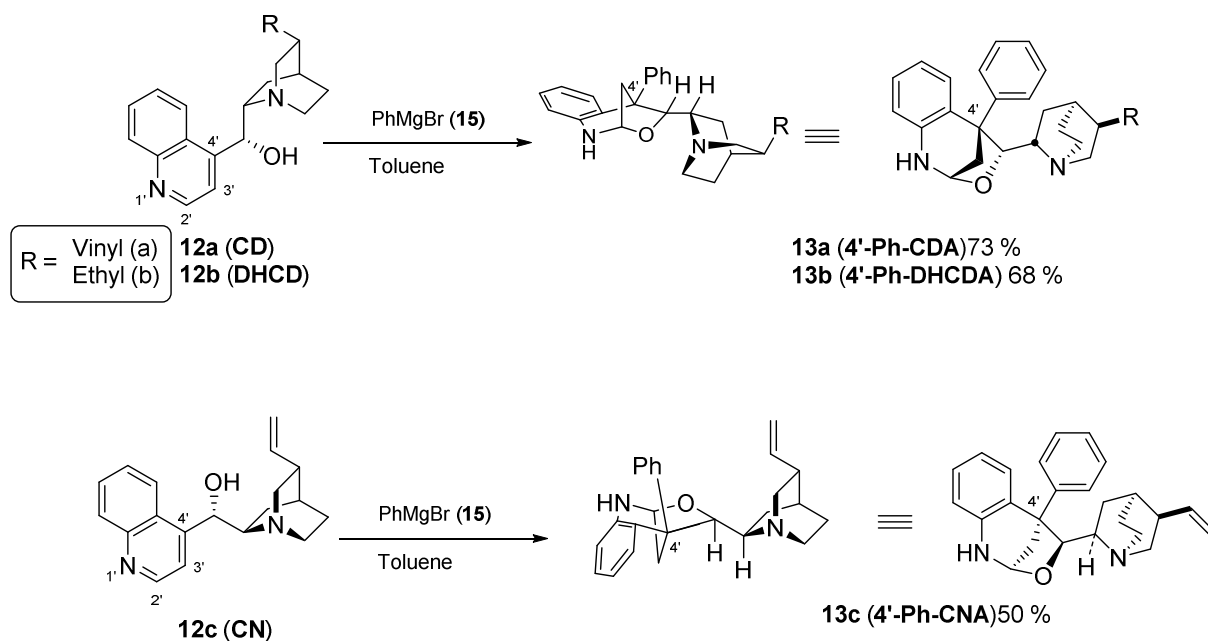
Scheme 5. Transformation of Vinyl to Ethyl group by transfer hydrogenation.

The synthesis was performed following the procedure of Emma Wu¹ and L. Hintermann as recently reported [28].

¹ I am thankful to M. Sc. Emma Wu for preparing dihydrocinchonidine.

1.3.2 Synthesis of 4'-Ph-CDA and 4'-Ph-DHCDA

In the first step, the 1,4 nucleophilic addition of Grignard reagent, derived from bromobenzene (**15**), occurred at the C4'-position of the quinoline moiety of cinchona alkaloids (**12a**, **12b**, **12c**, **Scheme 6**). The reaction proceeded with loss of heteroaromaticity and formation of bicyclic N,O-acetals (**13a**, **13b**, **13c**).



Scheme 6. Synthesis of aminals from CD, DHCD and CN

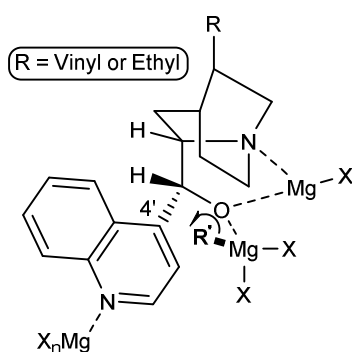


Fig. 10. Possible direct transfer of an R group from RMgX to quinoline ring

The Grignard reagent adds to less accessible 4'-position rather than the 2'-position, and single diastereomers are isolated from all reactions. The two bridgehead carbons cannot be inverted independently. Both observation are explained by assuming a group transfer R' from R'MgX to the quinoline unit within a chelate (**Fig. 10**). Moreover, toluene seems not to break up this type of aggregates which is a key factor for obtaining good results [26].

All reactions were carried out in toluene with an excess of Grignard reagent (**Table 1**). The reason (**Fig. 10**) is due to major consumption of the Grignard, which reacts not only with the hydroxy group, but also coordinates to quinoline nitrogen. Highly concentrated solutions of PhMgBr were preferred in order to obtain the products in acceptable yields in a gram scale (entry 1, 3). In small scale (entry 2, 4, 5), it was observed that lower concentration of Grignard reagent (**15**) led to a significant loss of yield due to a major dilution of the nucleophile. This probably was caused by lower activity or decomposition of the Grignard reagent. In the case of **DHCD** (entry 3, 4) and **CN** (entry 5, 6) the reactions were performed overnight with more equivalents of Grignard reagent and lower temperature than entry **1** and **2**.

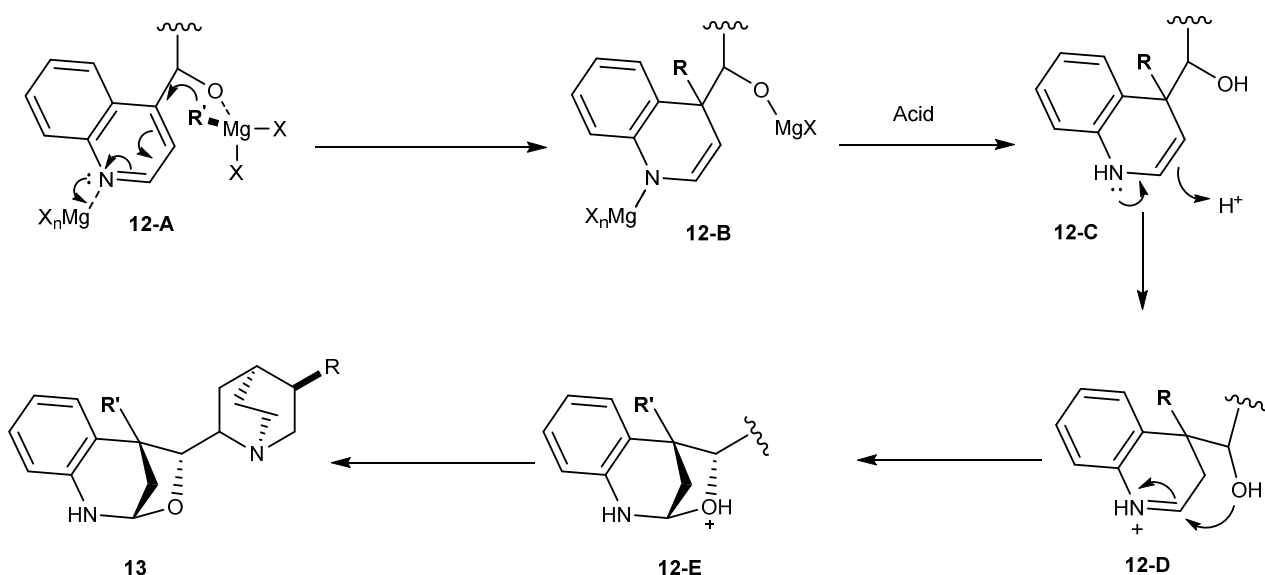
Entry	Substrate	Scale (g)	Toluene (mL)	PhMgBr conc. (eq.)	Temp. (°C)	Time (h)	Product	Yield (%)
1	CD (12a)	5	50	1.8 M (3)	70	2	13a	71
2	CD (12a)	0.1	1	1 M (3)	70	2	13a	40
3	DHCD (12b)	5	50	1.8 M (5)	50	18	13b	68
4	DHCD (12b)	0.1	1	1 M (5)	50	18	13b	35
5	CN (12c)	0.1	1	1 M (5)	50	18	13c	48

Table 1. Reaction conditions for amination synthesis in **Scheme 6**.

However, in all cases it was observed by following the reactions by TLC that conversions were not complete, even if the reaction times were prolonged. Nucleophilic addition of PhMgBr with **CN (12c)** in small scale (entry **5**) was also investigated: NMR analysis of the final product showed at least 5 % of *dihydro* compound derived from a **DHCN** impurity in the starting material (**CN**). For this reason *Cinchonine* was not used in the next step of the synthesis.

Plausible mechanism for aminal formation

Another important feature is how and when the N,O acetals (**13**) is formed after nucleophilic addition of Grignard. A plausible mechanism for the reaction is depicted in **Scheme 7**. As previously described, the addition of Grignard reagent forms a chelate (**12-A**) that transfers R' group to C4'-position of quinoline ring, giving the enamine salt (**12-B**). The salt is destroyed by acidification during the workup: probably nitrogen and oxygen are protonated giving intermediate **12-C** that rearranges into an iminium ion structure (**12-D**). Subsequently, N,O acetal **13** is generated by intramolecular nucleophilic attack of the hydroxy group to the electrophile carbon in 2'-position of the iminium ion forming an oxonium ion **12-E** with loss of proton giving the aminal **13**.



Scheme 7. Plausible mechanism for N,O acetal **13** formation.

The basification with an excess of base, during the work up, is also important for shifting the acid/base equilibrium to the free aminal base (**13**).

In **fig. 11**, the $^1\text{H-NMR}$ spectra of **CDA (13a)** and **DHCDA (13b)** are compared. Both spectra present the aromatic protons signals between $\delta = 6.0 - 7.5$ ppm belonging to the Aryl and Phenyl groups. At higher field no significant differences are observed and from $\delta = 1.2 - 3.5$ ppm the signals are similar for both compounds. However the doublet of doublets of doublets at $\delta = 5.61$ ppm (1 H, $-\text{CH}_{\text{vinyl}}^-$) and the multiplet at $\delta = 4.87 - 4.93$ ppm (2 H, $-\text{CH}_2_{\text{vinyl}}^-$) are characteristic of the vinyl group in **13a**. Instead in the dihydro compound **13b**, these signals are not present and, as expected, the ethyl group gives a triplet at $\delta = 0.75$ ppm (3H, $-\text{CH}_3_{\text{ethyl}}^-$) and a quintet (doublet of quartets) at $\delta = 1.09$ ppm (2 H, $-\text{CH}_2_{\text{ethyl}}^-$).

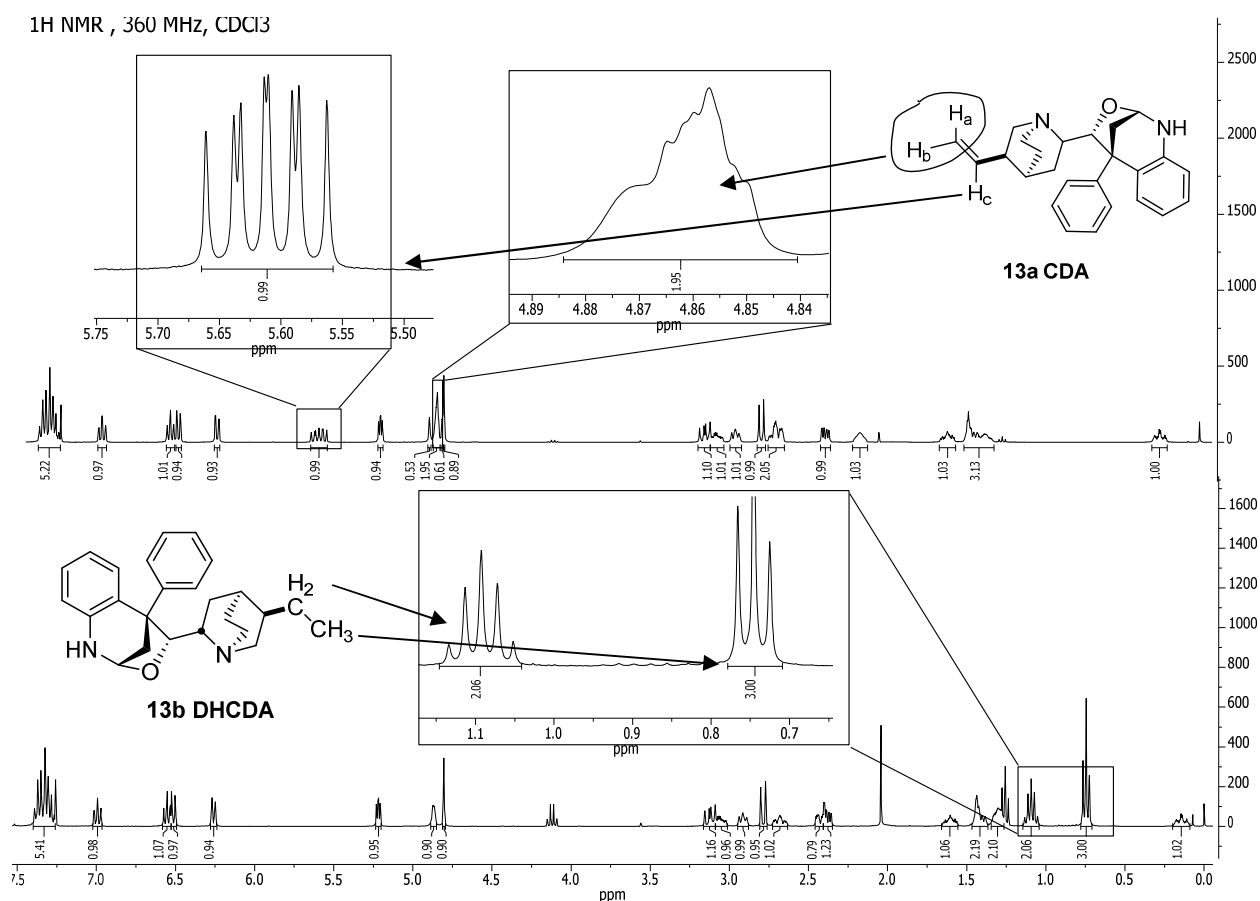
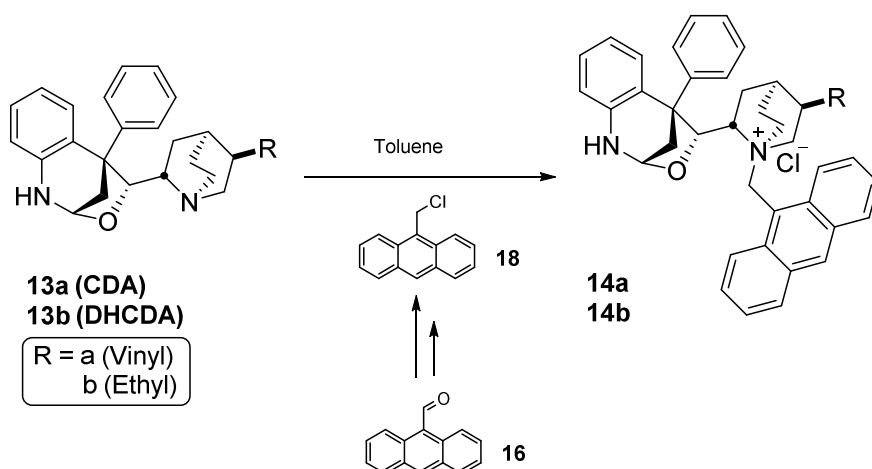


Fig. 11. $^1\text{H-NMR}$ of **CDA (13a)** and **DHCDA (13b)**.

1.3.3 Synthesis of 9-Am-4'-Ph-CDA-Cl and 9-Am-4'-Ph-DHCDA-Cl

The following step is the N-alkylation of amins **13a** and **13b** with 9-chloromethylanthracene (**18**). The latter was synthesized from 9-anthracenaldehyde (**16**) by reduction with NaBH₄ in methanol (85% yield), followed by chlorination with thionylchloride [29-30]. Comparing the reactivity of cinchona alkaloids, it was supposed that N-alkylation of **4'-Ph-CDA** (**13a**) and **4'-Ph-DHCDA** (**13b**) could occur at the most nucleophilic quinuclidine nitrogen, giving the quaternary ammonium salts **14a** and **14b** (Scheme 8).



Scheme 8. N-Alkylation of cinchona amins (**13a** and **13b**) with 9-Anthracenylmethylchloride (**18**)

In the ¹H-NMR spectrum of the *dihydro*- derivative (**Fig. 12**) are clearly present two coupled doublets at $\delta = 5.4$ ppm (2 H, -CH₂ methylenic-), corresponding to the diastereotopic methylenic protons of the *9-anthracenylmethyl* unit bonded to nitrogen. This is confirmed by COSY spectrum (**Fig. 13**) where the coupling between two methylenic protons is present. Moreover in HSQC spectrum (**Fig. 14**) is clearly showed that these two protons belonged to the same carbon at $\delta = 45.5$ ppm, which is consistent with a benzylic position.

¹H NMR 500 MHz CDCl₃

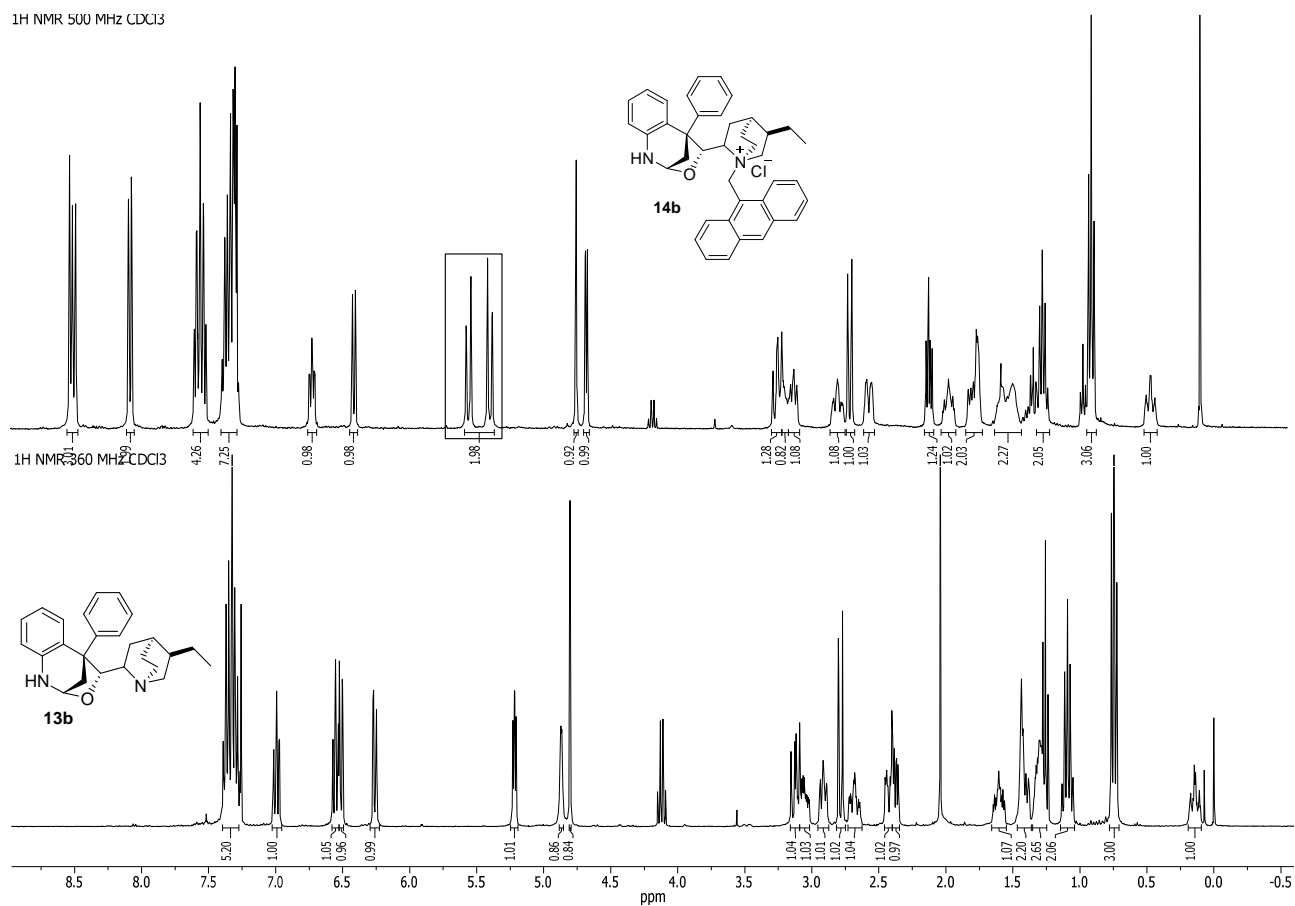


Fig. 12: ¹H-NMR spectrum of 9-Am-4'-Ph-DHCDA-Cl (14b).

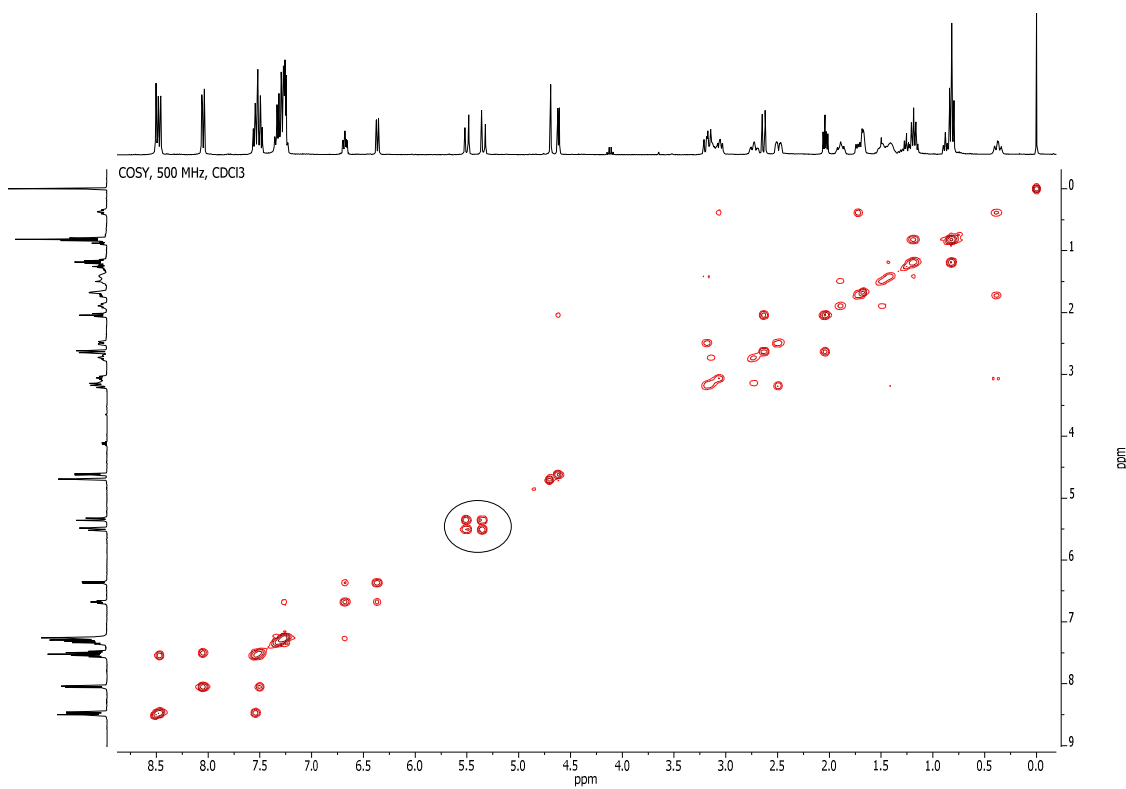


Fig. 13. COSY spectrum of 9-Am-4'-Ph-DHCDA-Cl (14b)

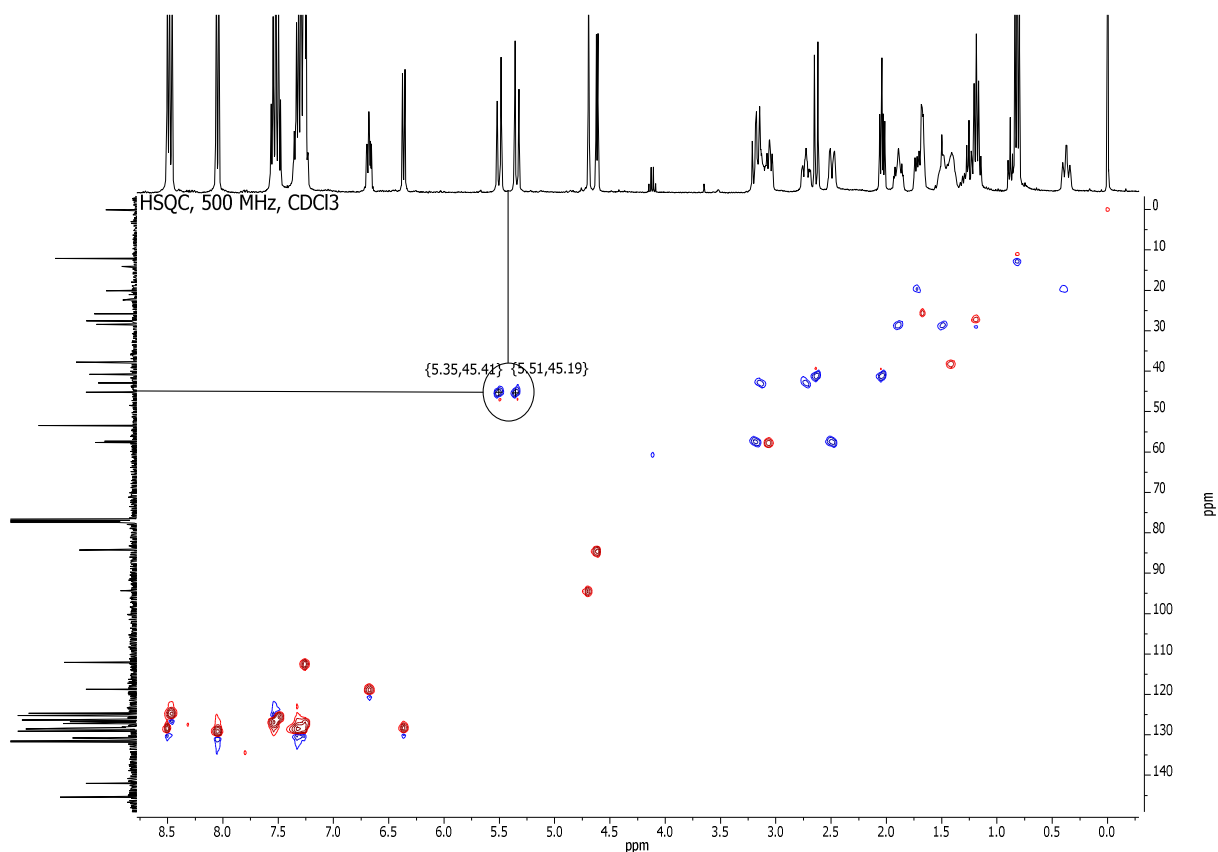


Fig. 14. HSQC spectrum of **9-Am-4'-Ph-DHCDA-Cl (14b)**.

However the N-alkylations were performed in toluene in a gram scale under optimized conditions as reported in **Table 2**.

Table 2. Optimized conditions for the synthesis of the N-alkylation (**Scheme8**).

Entry	SM ^(a)	Scale (g)	9-Am-Cl (eq.)	Product	Temperature (°C)	Toluene (mL)	Time (h)	Yield (%)
1	13a	1	1.5	14a	110	10	18	51
2	13b	1	1.8	14b	110	10	18	48

(a) starting material

The reactions proceeded smoothly with an excess of alkylating agent in moderate yield (entry 1, 2). Low yield were justified by a difficult purification of final product by column chromatography on silica gel. In all cases the conversions were not completed and, following the reactions by TLC, starting materials were still present. This was probably due to slow decomposition of 9-Am-Cl (**18**) to hydrogen chloride and formation of the corresponding salt

of **13a** or **13b**. For this reason higher temperature were avoided and the reactions were carried out at 110 °C.

In her PhD research, H. Wu optimized the condition for entry **2**: she found that the best results were achieved using 1.8 equivalents of **18**. Moreover, improvement in final yield was obtained adding K₂CO₃ in small quantities in order to limit salt formation [31].

However the optimization for entry **1** (**Table 2**) was not yet tested and therefore it was done during this work (**Table 3**).

Table 3. Optimized reaction condition for the alkylation of aminal **13a** to **14a** (**Scheme 8**). Reactions were carried out in toluene (1 mL), **13a** (0,17 mmol) at 110 °C for 24 h.

Entry	9-Am-Cl (eq.)	P/SM ratio ^(a)
1	1.2	70/30
2	1.5	80/20
3	1.8	80/20

(a) Product to starting material ratio.

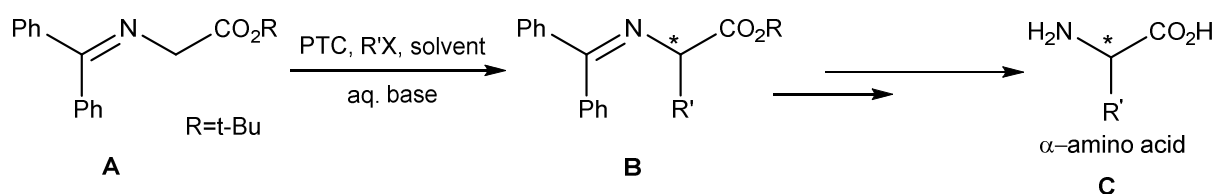
For cinchonidine aminal **13a**, it was observed that using 1.5 equivalents of **18** (entry 2), instead of 1.2 equivalents (entry 1), the ratio product/starting-material was higher. Moreover no changes were detected using more equivalents of 9-Anthracenylmethylchloride (entry 3).

1.3.4 Catalytic test

The second goal of this work was to verify the catalytic activity of the synthesized compounds **14**. In particular, some model reactions were chosen to test the activity of new ammonium salts as chiral inducers under phase-transfer conditions.

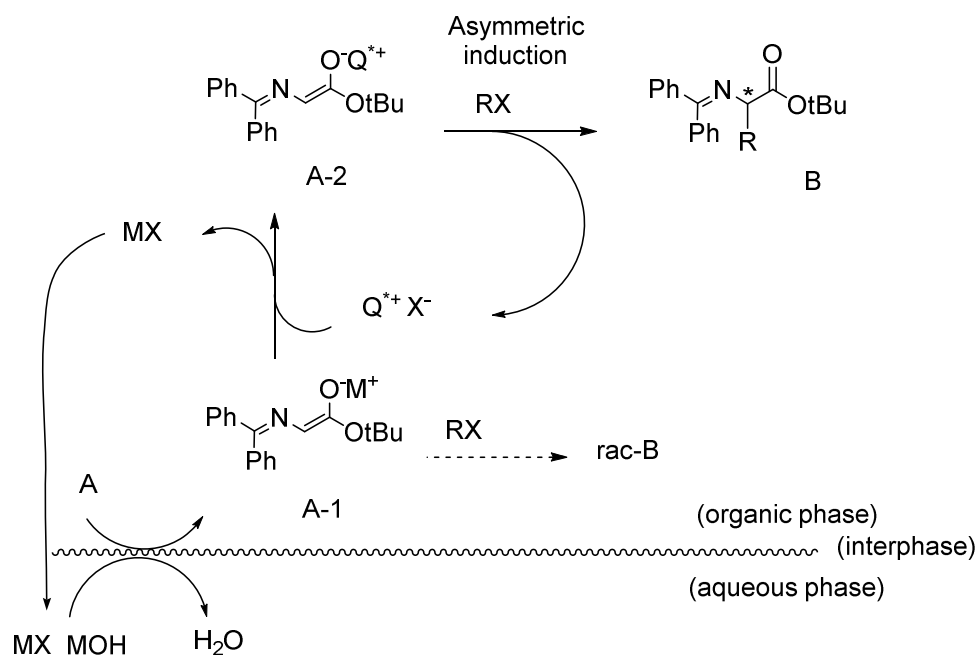
1.3.4.1 Asymmetric alkylation of N-(diphenylmethylene)glycine tert-butyl ester

Preparation of amino acid in their chiral form remains an ongoing challenge for organic chemistry [32]. Amino acids need to be prepared in a well defined stereochemistry since they are used for their biological activity or as a building blocks for peptide synthesis [33]. To date, one of the most successful uses of cinchona-PTCs has been the preparation of non-natural α -amino acid derivatives (**Scheme 10**) [34]. Enantioselective monoalkylation under catalytic phase transfer conditions of benzophenone imine of glycine ester (**A**), as a key substrate, has been recognized as an excellent method for the synthesis of a wide range of optically active α -amino acid (**C**) with high chemical yield and enantioselectivity [2].



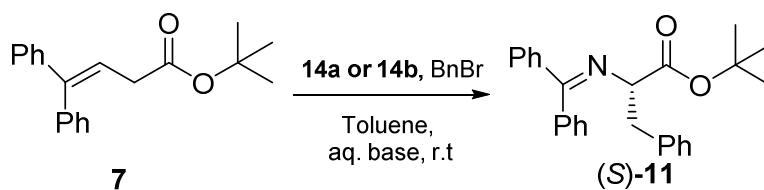
Scheme 10. General synthesis of optical α -amino acids via asymmetric phase-transfer catalytic alkylation of benzophenone imine glycine ester (**A**)

As depicted in **Scheme 11**, in the first step glycine Schiff base (**A**) is deprotonated at the interface of two phases by the presence of inorganic base (MOH) [35]. The metal enolate (**A-1**), which is consequently formed, stays at the interface due to its polar character. Ion-exchange with the catalyst generates a chiral onium enolate (**A-2**) which is lipophilic enough to migrate into the organic phase where it reacts with the alkyl halide to give optically active monoalkylated product **B** with regeneration of the catalyst [9].



Scheme 11. Mechanism of Asymmetric Alkylation of **A** under phase transfer conditions.

As a first approach it was decided to test the supposed quaternary ammonium salts **14a** and **14b**, in the asymmetric phase-transfer alkylation of glycine Schiff base (**7**) with benzyl bromide as alkylating agent (**Scheme 12**). The first experiment was performed in toluene, aq. 50 % KOH and 10 % mmol of catalysts. The final product (**11**) was obtained after 24 h (after complete conversion as indicated by TLC analysis) at 25 °C in moderate yield and e.e. % (**Table 4**).



Scheme 12. Asymmetric alkylation of **7** under phase-transfer conditions using **14a** and **14b** (or the nitrogen aminal alkylated)

Table 4. Asymmetric alkylation of **7**. Run conditions: toluene (1 mL) 0.17 mmol of **7**, 1.2 eq. of benzyl bromide and 50 % aq. KOH (1.8 mmol) at r.t for the given time.

Entry	Catalyst (10 mol-%)	Time (h)	Yield ^(a) (%)	ee (%) ^(b)
1	14a	24	58	50 (S)
2	14b	24	55	62 (S)

(a) after purification on silica gel column.

(b) Enantiopurity was determined by chiral HPLC. Absolute configuration was compared with data reported in literature [36].

As it shown in **Table 4** (entry 1), compound **14b**, derived from dihydrocinchonidine aminal, gave the best result in term of enantioselectivity compared to the corresponding cinchonidine aminal derived salt. As reported by Lygo, shifting from vinyl to ethyl group substituent might destabilize one of the possible ion-pairing arrangements leading to slight increase of selectivity [10].

It was therefore investigated the effect of solvent, temperature and base on the enantioselectivity. In order to have reproducible conditions, all reactions were performed in a 10 mL vial with Teflon cup, in air, with magnetic stirring. High stirring rate does not appear to influence the enantioselectivity but it does effect the rate of reaction and substantially decreased reaction time can be achieved [37]. Moreover other alkylating agents as other possible electrophiles were investigated.

Effect of base

The effect of inorganic base on chemical yield and enantioselectivity was investigated. As shown in **Table 5**, values of 62 % and 50 % ee were achieved respectively with catalysts **14b** and **14a** when 50 % aqueous KOH was employed (entry 1, 2). With 50 % aqueous NaOH (entry 3, 4), the chemical yield and enantioselectivity were lower and the reactions proceeded faster. Low yield could be explained by a major decomposition of the substrate (**7**) or benzylated imine (**11**) under strong basic conditions. As reported by Lygo, lower % ee was due to an increasing rate of uncatalyzed reactions when sodium hydroxide was used as the base [22]. This was confirmed by TLC, following the product formation in the uncatalyzed reaction.

Table 5. Asymmetric alkylation of **7**. Run conditions: toluene (1 mL), 0.17 mmol of **7**, 1.2 eq. of benzyl bromide, 50 % aq. base at r.t for the given time.

Entry	Catalyst (10 mol-%)	50 % aq. Base	Time (h)	yield^(a) (%)	ee^(b) (%)
1	14a	KOH	24	58	50 (<i>S</i>)
2	14b	KOH	24	55	62 (<i>S</i>)
3	14a	NaOH	12	30	39 (<i>S</i>)
4	14b	NaOH	12	28	53 (<i>S</i>)

(a) after purification on silica gel column.

(b) Enantiopurity was determined by chiral HPLC. Absolute configuration was compared with data reported in literature [36].

Effect of solvent and temperature

Different solvents were used for the alkylation of **7** (Table 6). Catalyst **14b** was more active than **14a**. In particular the solvent influenced the selectivity, and the enantioselectivity decreased with the increasing of solvent polarity. Toluene (entry 1, 2) presented a similar selectivity to MTBE (entry 5, 6) while in dichloromethane (entry 7, 8) the % ee was shown to decrease. This effect can be explained with the concept of ions pair between the quaternary ammonium salt (Q^+) and the enolate (**A-2**, see Scheme 11). Higher selectivity is generally observed in non polar solvent in which stronger interaction are favored providing thus a major influence of the catalyst's chiral environment [12]. However no changing in absolute configuration of **11** was observed with solvent polarity meaning that the reaction pathway remained the same.

Table 6. Asymmetric alkylation of **7**. Run conditions: solvent (1 mL), 0.17 mmol of **7**, 1.2 eq. of benzyl bromide, 50 % aq. KOH (1.8 mmol) at the given temperature for 24 h.

Entry	Solvent	catalyst (10 % mmol.)	Temperature (°C)	Yield ^(a) (%)	ee ^(b) (%)
1		14a	25	58	50 (S)
2	Toluene $\epsilon=2.4$	14b	25	55	62 (S)
3		14a	35	63	44 (S)
4		14b	35	70	58 (S)
5	MTBE $\epsilon=2.6$	14a	25	66	50 (S)
6		14b	25	71	55 (S)
7	CH ₂ Cl ₂ $\epsilon=8.9$	14b	25	68	31 (S)
8		14a	25	85	30 (S)

(a) after purification on silica gel column.

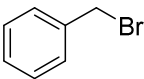
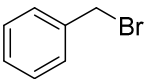
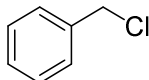
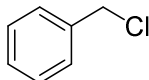
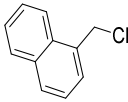
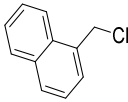
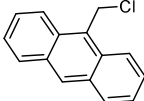
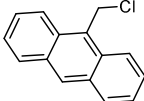
(b) Enantiopurity was determined by chiral HPLC. Absolute configuration was compared with data reported in literature [36].

Toluene is however preferred because it is less volatile than MTBE, while dichloromethane gives less % ee than toluene [22]. Furthermore, when the reaction is performed in toluene at 35 °C, the % ee decreases while the yield increases as a consequence of higher reaction rate (entry 3, 4).

Nature of electrophile

Once the optimal reaction conditions had been found, other alkylating agents were chosen as electrophiles. As reported in **Table 7** (entry 1,2), only benzyl bromide reacted with substrate (**7**). On the contrary, benzyl chloride, 1-chloromethylnaphtalene and 9-anthracenylmethylchloride did not react at all (entry 5-8). This suggested that active electrophiles were needed.

Table 7. Asymmetric alkylation of **7**. Run conditions: toluene (1 mL) 0.17 mmol of **7**, 1.2 eq. of alkylating agent, 50 % aq. KOH (1.8 mmol) at r.t for 24 h.

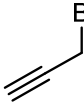
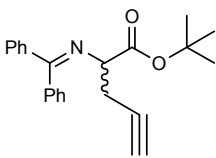

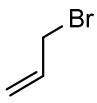
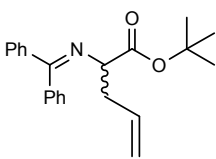

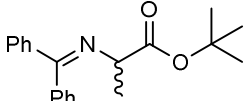
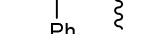
Entry	Alkylating agent	cat. (10 % mmol.)	Yield ^(a) (%)	ee ^(b) (%)
1		14a	58	50 (S)
2		14b	55	62 (S)
3		14a	0	-
4		14b	0	-
5		14a	0	-
6		14b	0	-
7		14a	0	-
8		14b	0	-

(a) after purification on silica gel column.

(b) Enantiopurity was calculated with chiral HPLC. Absolute configuration was compared with data reported in literature [36].

Moreover other alkyl halides were investigated as possible electrophiles. Methyl iodide was the most active electrophile as denotes the short reaction time (**Table 8**, entry 5, 6). However the yield was lower (entry 5, 6) in comparison with propargyl or allyl bromide (entry 1, 2 and 3, 4). Loss of product during work up occurred due to the polar nature of methylated product [21]. Although for entry **1** and **2** was not possible to determine the e.e % with chiral HPLC, in the other cases racemic mixtures were isolated (entry 3, 4 and 5, 6). The lack of asymmetric induction was probably a consequence of higher rate of background reactions with these electrophiles compared to the rate of ions' pair formation.

Table 8. Asymmetric alkylation of **7**. Run conditions: toluene (1 mL) with 0.17 mmol of **7**, 1.2 eq. of alkylating agent, 50 % aq. KOH at r.t and for the desired time.

Entry	Alkylating agent	cat. (10 % mmol.)	Time (h)	Product	Yield ^(a) (%)	ee ^(b) (%)
1		14a	24		51	n.d ^(c)
2		14b	24		65	n.d ^(c)
3		14a	24		76	Racemic
4		14b	24		88	Racemic
5	CH ₃ I	14a	5		30	Racemic
6		14b	5		26	Racemic

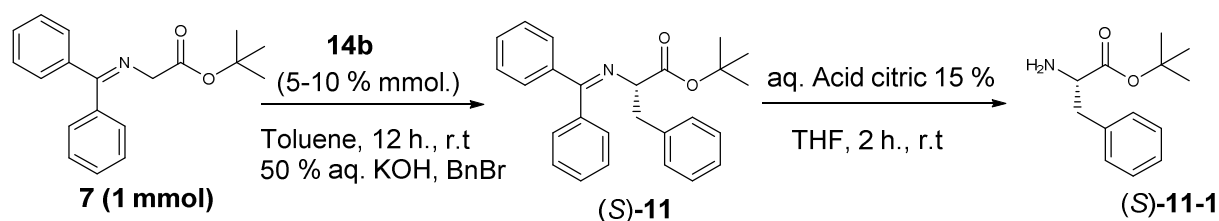
(a) after purification on silica gel column

(b) Enantiopurity was calculated with chiral HPLC.

(c) not determined.

Scale up of reaction

As a last stage we decided to investigate the alkylation of **7** with benzyl bromide in a 1.0 mmol scale using catalyst **14b** under the optimized reaction conditions (**scheme 13**). Different catalyst loading were employed in order to observe the effect of catalyst amount. The imine **11** was then hydrolyzed to the corresponding α -amino acid ester **11-1**.



Scheme 13. Scale up of asymmetric alkylation of **16** to **21**

As reported below in **table 9**, different amount of catalyst had no effect on enantioselectivity and the ee-value is in according to those obtained at smaller scale (see **Table 4**, entry 2). Using 10 mol-% of the catalyst **14b** (entry 2), the reaction was complete after 14 h affording **11-1** with 63 % yield. However upon reducing the catalyst loading from 10 to 5 mol-%, a decrease of the reaction rate was observed since the conversion was not complete after 24 h (entry 1). For this reason entry 1 gave **11-1** in lower yield.

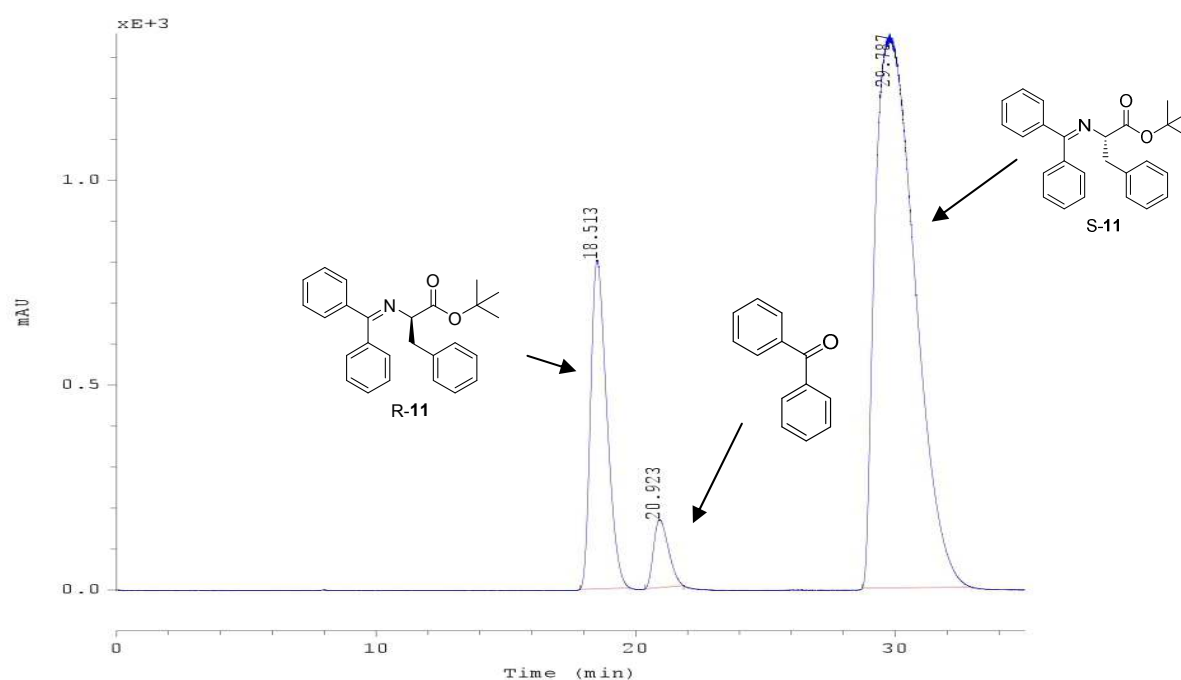
Table 9. Asymmetric alkylation of **7**. Run conditions: toluene (1 mL) with 1 mmol of **7**, 1.2 eq. of BnBr, 50 % aq. KOH at r.t and for the desired time.

Entry	Catalyst loading (14b) (mmol %)	Time (h)	ee (%) ^(a) (11)	% yield ^(b) (11-1)
1	5	24	61 (S)	50
2	10	14	60 (S)	63

(a) E nantiopurity of **11** was determined by chiral HPLC. Absolute configuration was compared with data reported in literature [36].

(b) isolated yield of **11-1**.

In **fig. 15** is reported the HPLC traces analysis of the imine **11** (entry 2) after purification *via* column chromatography on silica gel. At 20.9 min. there is the peak of benzophenone. ¹H-NMR analysis also confirmed the presence of this impurity that was at least around 3 mol-%. This is explained because the product **11** was sensitive to hydrolysis on acid silica gel. However, benzophenone was subsequently removed during the hydrolysis of the imine **11** to the free α -amino acid ester (**11-1**).

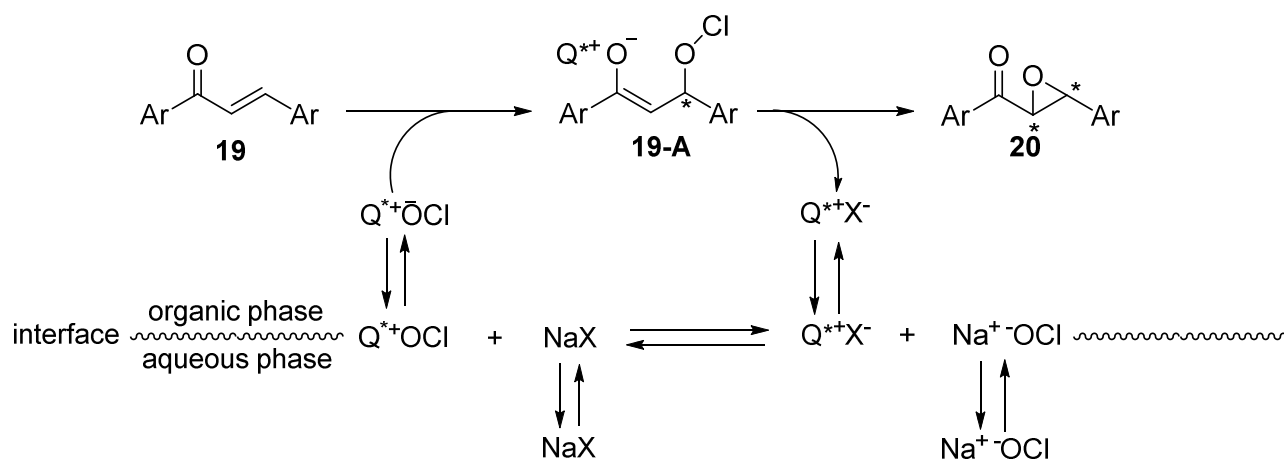


Entry	Ret. Time (min)	Area (mAU*min)	Product
1	18.513	578.113	R-11
2	20.923	110.28	benzophenone
3	29.789	2391.66	S-11

Fig. 15. Chiral HPLC traces analysis of alkylated imine ester (**11**) after purification on column chromatography.

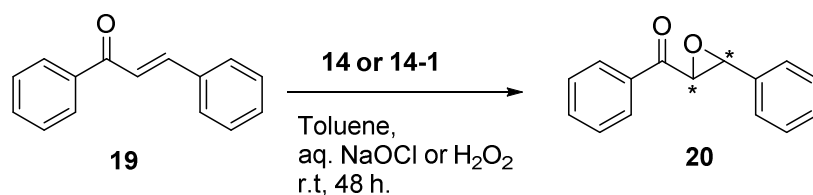
1.3.4.2 Asymmetric epoxidation of trans chalcone

The asymmetric epoxidation of electron-deficient olefins has been regarded as one of the most representative asymmetric PTC reactions [2]. Asymmetric epoxidation of chalcone derivatives can be achieved with aqueous NaOCl or H₂O₂ as cheap oxidant using cinchona derived PTCs [35,36]. The mechanism of asymmetric epoxidation of α,β -unsaturated ketone, using sodium hypochlorite, is illustrated in **Scheme 14** [39]. An extraction mechanism is thought to be operative. Hypochlorite is extracted as an onium salt into the organic phase, and the onium hypochlorite then reacts with the ketone (**19**) while recognizing its enantiotopic face to provide the optically enriched α,β -epoxy ketone (**20**) [9].



Scheme 14. Mechanism of Asymmetric epoxidation of α,β -unsaturated ketone

Epoxydation of *trans*-chalcone (**Scheme 15**) was performed in toluene employing catalysts **14** and aqueous oxygen peroxide or sodium hypochlorite as oxidant. As shown in **Table 10**, no conversion of *trans*-chalcone to the corresponding epoxide was observed when sodium hypochlorite was employed (entry 3 and 4). However switching from sodium hypochlorite to oxygen peroxide, only little conversion was achieved (entries 1 and 2). In this case both catalysts did not exhibit any asymmetric induction and no e.e % values were detected.



Scheme 15. Asymmetric epoxidation of *trans*-chalcone

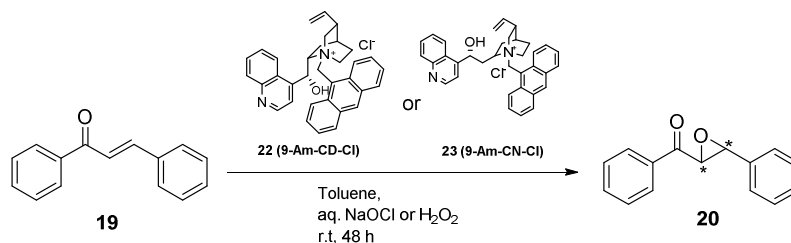
Table 10. Asymmetric epoxidation of **19**. Run conditions: toluene (1 mL), 0,17 mmol of **19** at r.t for 48 h.

Entry	Catalyst (10 mol-%)	Oxidant	Conversion ^(a) (19)	ee % (20)
1	14a	aq. H ₂ O ₂ 15% ^(b)	13,5	-
2	14b	aq. H ₂ O ₂ 15% ^(b)	14,5	-
3	14a	aq. 14 % NaClO ^(c)	no	-
4	14b	aq. 14 % NaClO ^(c)	no	-

(a) calculated with HPLC. Selectivity was 95-98 %.

(b) 5 eq.; (c) 2 eq.

It was then decided to try the asymmetric epoxidation with 9-Am-CD-Cl (**22**) and 9-Am-CN-Cl (**23**) as catalysts in the same conditions like in literature (**Scheme 16**) [37].



Scheme 16. Asymmetric epoxidation of *trans*-chalcone using **22** and **23** as catalysts

Table 11. Asymmetric epoxidation of **19**. Run conditions: toluene (1 mL), 0,17 mmol of **19** at r.t for 48 h.

Entry	Catalyst (10 % mmol)	Oxidant	Conversion ^(a) (19)	ee % (20)
1	22	aq. H ₂ O ₂ 15% ^(b)	87,5	17,3
2	22	aq. 14 % NaClO ^(c)	65,7	38,25
3	23	aq. H ₂ O ₂ 15% ^(b)	99,3	14,3
4	23	aq. 14 % NaClO ^(c)	97,5	32

(a) calculated with HPLC. Selectivity was 95-98 %.

(b) 5 eq.; (c) 2 eq.

The results obtained in **Table 11** were in according to Lygo. As reported, catalysts **22** and **23** were active in the asymmetric epoxidation of *trans*-chalcone, although the % ee were low.

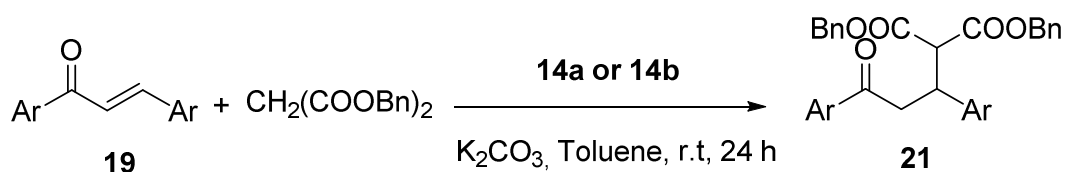
As a matter of fact, the particular structure of our catalysts seems to be a limitation for this type of reaction.

1.3.4.3 Other reactions

Michael addition of dibenzyl malonate to *trans*-chalcone

The formation of carbon-carbon bonds by conjugated addition of appropriate carboanionic reagents to α,β -unsaturated carbonyl compound is one of the most useful methods of remote functionalization in organic synthesis [40]. Asymmetric Michael addition of malonates to chalcone have been appeared in literature with limited successful examples [38]. The mechanism is initially similar to alkylation of glycine Schiff base. In the presence of inorganic base, the malonate is deprotonated, followed by extraction of the carbanion as onium salt from the interfacial area into the organic phase. Thus nucleophilic addition to α - β unsaturated carbonyl compounds can occur giving the Michael adducts.

The reaction was performed in toluene and solid potassium carbonate as base at room temperature for 24 h (Table 12) with catalyst **14a** and **14b** (scheme 17) as reported in literature [42].



Scheme 17. Asymmetric Michael addition of dibenzylmalonate to *trans*-chalcone (**26**)

Dibenzyl malonate was chosen as Michael donor. However after one day, conversions were not complete and isolated yield (entry 1 and 2) were lower than that obtained in the absence of catalyst (entry 3). This could be due to the solubility of the dibenzylmalonate potassium salt in the organic phase.

Table 12. Run conditions: toluene (2 mL), 0.48 mmol of **19**, 1.5 eq. of dibenzylmalonate, 0,16 g of K_2CO_3 at r.t for 24 h. Entry 2 was performed with 0.96 mmol of **19** and 0,32 g of K_2CO_3 .

Entry	Catalyst (10 mol-%)	Yield (%) ^(a)	ee %
1	14a	43	n.d
2	14b	35	n.d
3	-	51	n.d

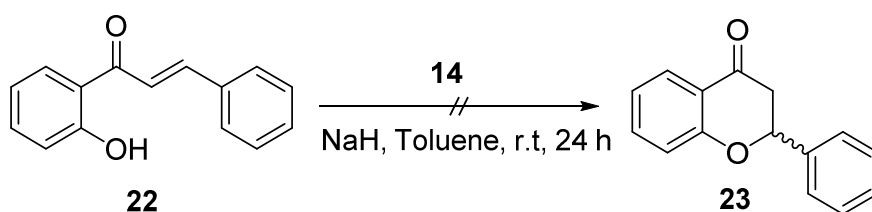
(a) isolated yield.

In these reactions the enantiomeric excess were not determined, as it was impossible to separate the two enantiomers with available chiral HPLC type columns (chiralcel OD and OJ).

Cyclization of 2'-hydroxychalcone to flavanone

Following previous studies of L. Hintermann, the asymmetric catalytic cyclization of 2'-hydroxychalcone to flavanone was also investigated. The mechanism involves the formation of ion pairs. The presence of a base is fundamental in order to deprotonate the 2'-hydroxychalcone (**22**) and give the corresponding salt. Ion exchange between the catalyst and chalconate anion gives an ion-pair. The chiral cation induces an asymmetric intramolecular conjugate addition within the chalconate anion (oxa-Michael cyclization) [43].

Using catalysts **14**, the reaction was carried out in toluene with co-catalytic sodium hydride. However no product formation was detected after 24 h.



Scheme 18. Asymmetric cyclization of **22** to flavanone **23**

The lack of reactivity of both catalysts could be explained in term of hydrogen bonding between the catalyst and chalconate anion. In fact it was believed that the presence of free hydroxyl group was important to achieve some catalytic activity.

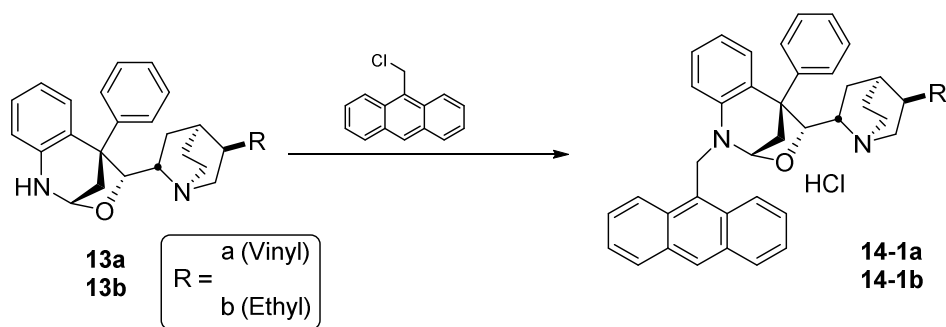
1.4 Summary and Conclusion

In conclusion, starting from cinchona alkaloids cinchonidine and dihydrocinchonidine, two novel chiral quaternary ammonium salts were synthesized in two steps. In particular the basic structure of the alkaloids were modified with introduction of phenyl group in 4'-position of quinoline ring to give cinchona aminal bases. Further N-alkylation with 9-Anthracenylmethylchloride was achieved.

The catalytic activity of the new salts was tested in different types of reactions under asymmetric phase transfer conditions. Enantioselectivities up to 60 % ee were obtained in the alkylation of glycine Schiff base with benzyl bromide in toluene when **9-Am-4'-DHCDA-Cl (14b)** was used as catalyst. The selectivity was retained when the reaction was scaled up to the 1 mmol scale. Catalytic activity was shown to be influenced by the nature of the leaving group of alkylating agent. However, with active electrophile asymmetric induction was not detected, as a consequence of the higher rate of the background reaction. The new compounds were also tested with other reactions like Michael addition of dibenzyl malonate to *trans*-chalcone, epoxidation of *trans*-chalcone and cyclization of 2'-hydroxychalcone to flavanone. In those cases no chiral induction could be observed, too.

Structure hypothesis

All the results relating catalytic activity of the novel cinchona derivatives do not agree with previous results of other cinchona derivatives [2]. These experimental findings suggest a poor involvement of **14a** and **14b** in the catalytic process except for asymmetric alkylation of **7** with benzyl bromide. The question is: did we synthesize the quaternary ammonium salts? During the large part of the period of thesis, we thought that N-alkylation could occur at the quinuclidine nitrogen. The idea was that the aminals **13a** and **13b** reacted with 9-chloromethylantracene at the same position of the *Cinchona* alkaloids giving the corresponding quaternary ammonium salts. The reactivity of several substrates and in different reactions suggest that N-alkylation at the aminal nitrogen might be possible as shown in **Scheme 19**.



Scheme 19. N-alkylation at the aminal nitrogen

In fact it is likely that **14-1a** and **14-1b** are not quaternary ammonium salts but the corresponding chlorhydrates, which became a tertiary amine under basic conditions.

On the other hand, the reactivity of benzyl bromide with glycine Schiff base (**7**) in which it is observed a good asymmetric induction, could be explained by the *in situ* formation of a quaternary ammonium salt, which induces the formation of the final chiral alkylated product (**11**). The function of the likely **14-1a**, **14-1b** is actually that of homogeneous catalyst precursor giving, in the presence of benzyl bromide **14-2a** or **14-2b**, the PTC catalysts reported in **Fig. 15**.

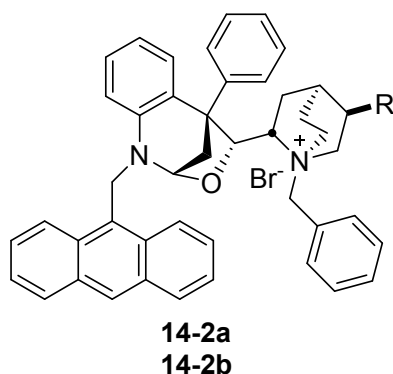


Fig. 15. Possible formation of quaternary ammonium salt *in situ* during asymmetric alkylation of glycine Schiff base (**7**).

The reactivity of the modified cinchonans is in agreement with the possible alkylation at the aminal nitrogen taking also into consideration the $^1\text{H-NMR}$ spectrum of **14b** (**Fig.12**). As a matter of fact, the two methylenic protons gave higher chemical shift ($\delta=5.41$ ppm) than those obtained with 9-anthracenylmethyl-cinchonidinium chloride ($\delta=4.94$ ppm), thus

suggesting the structure **14-1a** and **14-1b** as possible. However, this is only a conjecture, which will be demonstrated by further investigations.

1.5 Outlook

Obtaining X-ray quality crystals will be important in order to understand the structure of new compounds and the reactivity of the aminals. In particular more extensive investigations will be done in the N-alkylation of *Cinchona* aminals with other alkylating agents. The bulky 9-anthracenylmethyl function can be replaced by less steric hindered benzyl group. In addition, varying the bulkiness of the group in 4'-position of the aminal system using different types of Grignard reagents would be also of interest.

Further investigations and applications can be extended to the synthesis optimization of quaternary salts derived from other cinchona alkaloids like cinchonine, quinine, quinidine and the relative dihydro-compounds.

2 Experimental section

2.1 Preface

2.1.1 Materials and synthesis

All materials were obtained from VWR, SIGMA-ALDRICH, FLUKA, GRÜSSING, ALFA-AESAR AND MERCK, and if not otherwise mentioned, were used without further purification. All air or moisture-sensitive manipulations were carried out using standard SCHLENK technique with argon 4.6 as inert gas. Organic solvent, e.g. pentane, hexane, EtOAc, CH₂Cl₂, EtOH, were freshly distilled, prior to use. Toluene were filtered under Aluminium oxide and stored under molecular sieve (3 Å). 1,4-Dioxane was first pre-treated with KOH and FeSO₄ to remove peroxide and then distilled under argon atmosphere with sodium and benzophenone to dryness. The trace water content of organic solvents was determined by coulometric Karl Fischer titration.

2.1.2 Analysis

Nuclear magnetic resonance spectroscopy (NMR)

^1H , ^{13}C measurements were recorded on a BRUKER AV500 (500 MHz), AV360 (360 MHz) or AV250 (250 MHz) spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane SiMe_4 as internal standard. Data are presented as follows: chemical shift, multiplicity (s=singlet, d=doublet, dd=doublet of doublet, ddd=doublet of doublets of doublets t=triplet, td=triplet of doublets, q=quartet, m=multiplet, br=broad), coupling constant is given in Hertz (Hz), and signal area integration in natural numbers.

Gas chromatography-mass spectrometry (GC-MS)

GC-MS analysis was performed on a THERMO FISCHER SCIENTIFIC device. GC system: trace GC Ultra, column: TG-SQG (length 15 m., inner diameter 0.25 mm, 0.25 mm film), carrier gas: helium, measurement conditions 40-30-300 °C (start gradient-end), MS-system: ISQ, method of ionization: EI (70 eV).

High-performance liquid chromatography (HPLC)

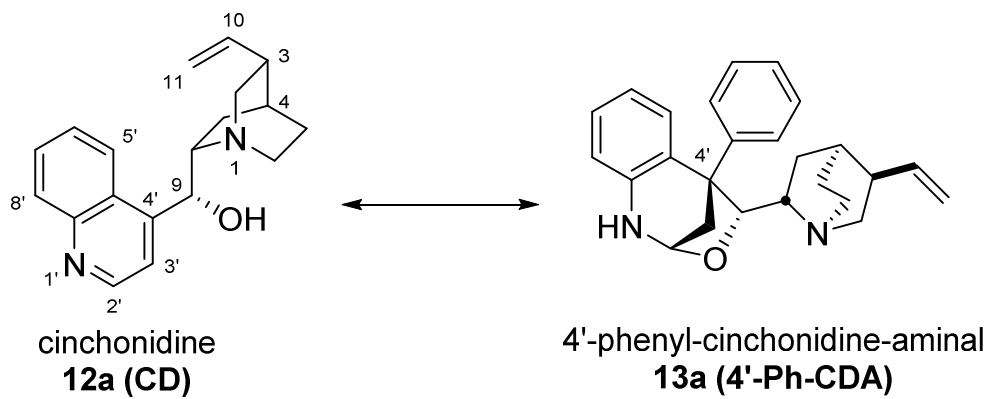
Chiral-HPLC analysis were performed on a KNAUER device with Smartline Autosampler 3800, Smartline manager 5000 as well as Smartline Pump 1000 and WellChrom Diode Array Detector K-2800. Column: ChiralCell OD (250 x 4.6 mm) Chiral Technologies.

Thin layer chromatography (TLC)

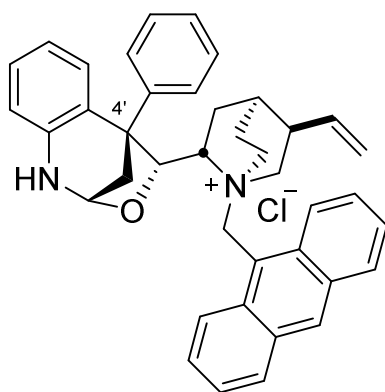
TLC was performed using MERCK plates with fluorescent indicator (Glass, pore size 60 Å, F254). Spots were detected by exposure to UV-Light with a wavelength of 254 nm [UV] and by dyeing with Mostain-solution and a subsequent thermal treatment. Preparation of Mostain: 10 g ammonium heptamolybdate tetrahydrate and 0.2 g $\text{Ce}(\text{SO}_4)_2 \cdot 4 \text{H}_2\text{O}$ were dissolved in 200 ml of H_2O and 12 ml concentrated sulfuric acid was added with stirring.

2.2 Nomenclature

For convenience base alkaloids are named as follows: Cinchonidine (**CD**), dihydrocinchonidine (**DHCD**) and cinchonine (**CN**). For the alkaloids resulting in the addition of Phenyl Magnesium bromide, nomenclature is based on the sites of substitution of the alkaloids, e.g:



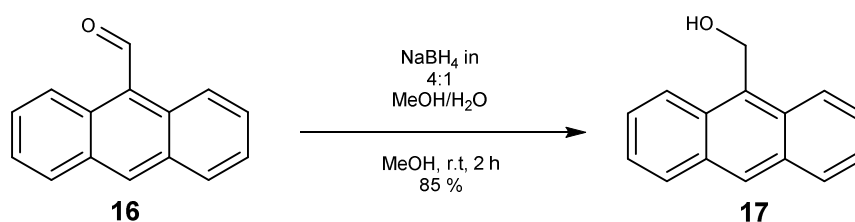
while for the ammonium salts derived from the aminals, supposing alkylation at quinuclidine nitrogen, as follow, e.g:



N-(9-Anthracenylmethyl)-4'-Phenyl-cinchonidinium-aminal-chloride
14a (9-Am-4'-Ph-CDA-Cl)

2.3 Synthesis

9-Antracenemethanol (**17**) ^[27]

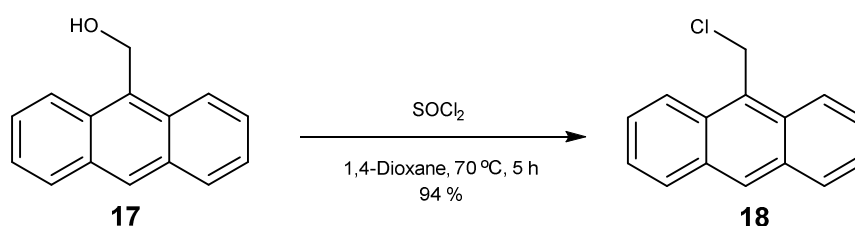


Sodiumborohydride (8,72 g, 230,5 mmol) in 20 mL of water and 80 mL of Methanol was added, during a period of ca. 30 min., to a slurry of **14** (30 g, 145 mmol) in 150 mL of methanol at r.t. The mixture was stirred at r.t for 2 h. **TLC**: EtOAc/Hexane = 1:2, R_f:0,33 [UV]. During addition of NaBH₄ solvent evaporated. It was necessary to add new fresh methanol to the mixture.

Work up:

HCl (2M) was added to the slurry drop by drop till no hydrogen evolution was observed. Water was added (150 ml) and then the precipitate was filtered, washed with water (100 mLx3). The solid was then dried under vacuum. The raw material was not pure as it could contain starting material. After purification by recrystallization from hot EtOAc (150 mL), filtration and washing with pentane, 25.5 g (85 %) of yellowish crystals were obtained. **Mp** 160,4-162,1 °C. **¹H NMR**, δ (250 MHz, CDCl₃): 8.34 (s, 1H), 8.25 (d, J=8,30, 2H), 7.92 (d, J=7,98, 2H), 7.50-7.35 (m, 4H), 5.45 (s, 2H), 2.01 (s, 1H) ppm. **¹³C NMR**, δ (63 MHz, CDCl₃): 131.54, 131.02, 130.24, 129.14, 128.37, 126.45, 125.1, 123.9, 57.4 ppm. **GC-MS** (EI); calcd. for C₁₅H₁₂O: 208,09; found: m/z (rel. int. %) = 208.06 (50) M⁺, 209.09 (8,4) M⁺+1, 180.06 (14,5), 179.04 (100), 178.06 (38).

9-Chloromethylantracene (**18**) [28]

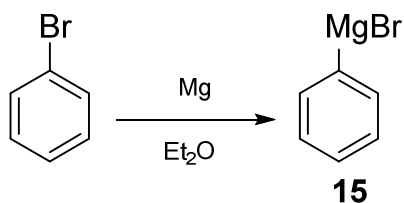


In a 500 ml round bottom flask, 9-anthracenemethanol (24,46 g, 117,46 mmol) was dissolved in 195 mL of dry 1,4-dioxane with magnetic stirring. SOCl_2 (10 ml, 137,85 mmol) was added with syringe to the solution and heated up to 70 °C for 5 h. **TLC:** EtOAc/Hexane = 1:2, R_f : 0,33 (referred to starting material).

Work up:

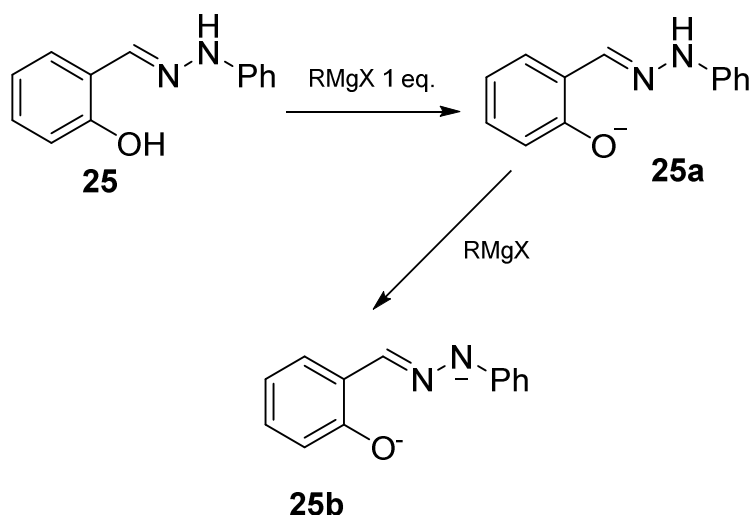
Solid NaHCO_3 (10 g) was added slowly to the solution (sodium bicarbonate reacted with acid chloride by developing CO_2) with stirring until no more acid was present (checked by pH strips). The mixture was filtered on celite and the solvent was removed under reduced pressure. The solid was dissolved in a small amount of CH_2Cl_2 and hexane. The solvent was then evaporated to a small volume and let to stand to r.t over a night. 23.92 g (93.6 %) of long yellow needles were obtained. **TLC:** EtOAc/Hexane = 1:2, R_f : n.d . **Mp:** 139,4-140.7. **$^1\text{H NMR}$,** δ (250 MHz, CDCl_3): 8.40 (s, 1H), 8.26 (d, $J=8,30$ Hz, 2H), 7.96 (d, $J=8,01$ 2H), 7.56 (t, $J=7,60$ 2H), 7.45 (t, $J=7,50$ 2H), 5.54 (s, 2H) ppm. **$^{13}\text{C NMR}$,** δ (63 MHz, CDCl_3): 131.45, 129.96, 129.28, 129.24, 127.67, 126.89, 125.21, 123.40, 38.97 ppm. **GC-MS** (EI); calcd. for $\text{C}_{15}\text{H}_{11}\text{Cl}$: 226.05; found: m/z (rel. int.) = 226.02 (24) M^+ , 206.94 (12), 191.01 (100).

Phenylmagnesium bromide (15)



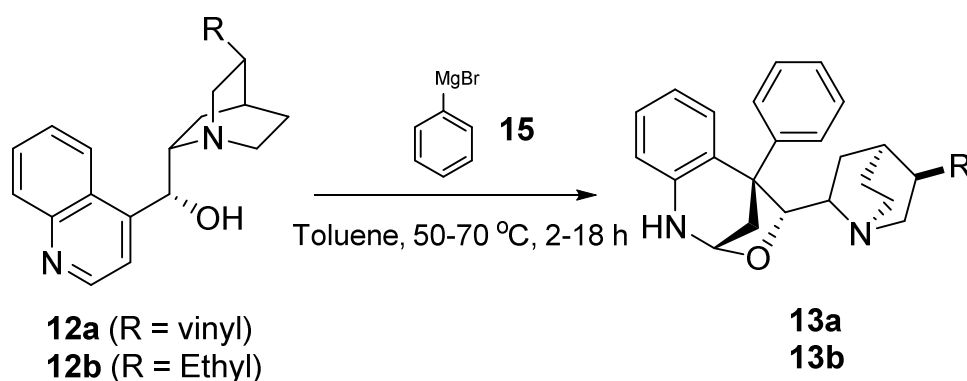
Bromobenzene (4,63 g, 3,1 ml, 29,4 mmol) in 14 ml of diethyl ether was added dropwise to magnesium turnings (1,07 g, 44,03 mmol) in 4 ml of diethyl ether. It was cooled with an ice bath if the reaction becomes too vigorous. After the addition of bromobenzene, the reaction mixture was refluxed gently for 40' to 60 min.

Titration of Grignard reagent:



In a Schlenk tube, an accurately weighed sample of **25** (typically between 60.0 and 80.0 mg) is dissolved in 1 mL of freshly distilled THF and stirred at room temperature under argon while the organometallic reagent is added slowly by means of a gastight syringe. A yellow color (the monoanion, **25a**) forms initially, the end point being indicated by a change in this color to bright golden orange.

General procedure for alkylation of cinchona alkaloids with Grignard reagent (GP1)

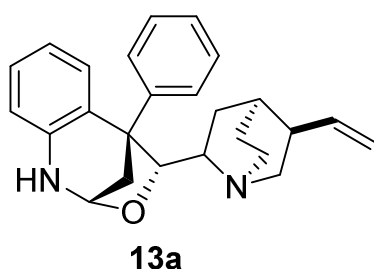


12a or 12b (17 mmol) was suspended in dry toluene (50 mL). The system was heated up to 50-70 °C. The Grignard reagent (**15**) was added as a concentrated solution in diethyl ether (1,8 M, 51 to 85 mmol, 3 to 5 eq.) and homogeneous solution was stirred at 50-70 °C for 2-18 h. **TLC**: EtOAc:MeOH:NEt₃= 25:1:1 [UV, molybdate staining gives reddish spot].

Work up:

After cooling, the mixture was quenched with toluene (50 mL) and carefully addition of NH₄Cl aq. (60 mL). The system was acidified with 2 M HCl (100 mL) to give homogeneous solution. Aqueous 25 % ammonia was added (60 mL). The aqueous phase was then extracted with EtOAc (3 x 100 mL). The collected organic phase was washed with NH₄Cl aq. (80 mL) and water (80 mL), then dried over MgSO₄, filtered and evaporated under reduced pressure to obtain **13a** or **13b** yellow resin. The crude material was purified by chromatographic column (CC: EtOAc:MeOH:NEt₃=50:1:1).

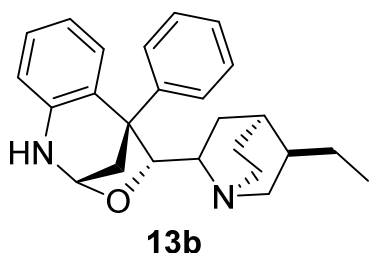
4'-Phenyl-cinchonidine-aminal (**13a**)



Prepared according to **GP1** from 5 g (17 mmol) of **CD (12a)** and PhMgBr (1,82 M, 28 ml, 50,95 mmol, 3 eq.) for 2 h at 70 °C. After purification by column chromatography and evaporation of the solvent, **13a** was obtained as a colorless resin (4,5 g, 12,1 mmol, 71 %). **TLC**: R_f:0,2. **M_p**:135-140 °C. ¹H NMR δ (360 MHz, CDCl₃): 0.16-0.34 (m, 1H), 1.31-1.53 (m, 3H), 1.54-1.68 (m, 1H), 2.10-2.23 (m, 1H), 2.38 (ddd, J = 10.9, 5.04, 1.4, 1H), 2.64-2.75

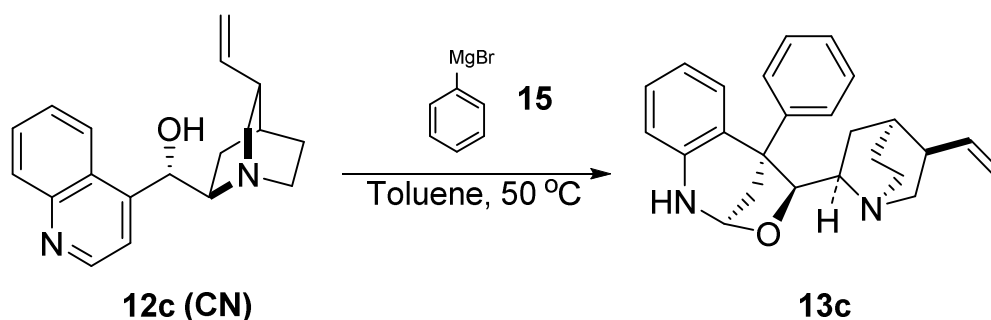
(m, 2H), 2.79 (d, J = 10.9 1H), 2.91-3.01 (m, 1H), 3.01-3.09 (m, 1H), 3.15 (dd, J = 13.65, 10.14 1H), 4.83 (s, 1H), 4.84-4.87 (m, 1H), 4.87-4.93 (m, 2H, vinyl), 4.93 (NH hidden), 5.21 (dd, J = 4.70, 3.83 1H), 5.61 (ddd, J = 17.1, 9.6 8.2 1H, vinyl), 6.26 (dd, J = 7.6, 1.2 1H, Arl), 6.50 (dd, J = 7.9, 0.9 1H, Arl), 6.57 (td, J = 7.6, 1.1, 1, 1H, Arl), 6.99 (td, J = 7.5, 1.3, 1, 1H, Arl), 7.29-7.41 (m, 5H, Arl). $^{13}\text{C NMR } \delta$ (91 MHz, CDCl_3): 19.2, 27.36, 27.74, 40.54, 40.57, 42.78, 52.85, 55.89, 57.73, 83.26, 94.26, 94.71, 113.79, 114.57, 119.02, 126.79, 127.9, 128.12, 128.3, 128.58, 129.9, 141.64, 142.14, 142.64 ppm. **GC-MS** (EI); calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}$: 372.22; found: m/z (rel. int. %) = 372.16 (6), 206.03 (52), 166.09 (22,5), 136.17 (100), 130 (24).

4'-Phenyl-Dihydrocinchonidine-aminal (**13b**)



Prepared according to **GP1**, from 5 g (17mmol) of **DHCD (12b)** and PhMgBr (1,82 M, 46,6 mL, 84,81 mmol, 5 eq.) at 50°C for 18 h. After purification by column chromatography, evaporation of the solvent, **13b** was obtained as a colorless resin (4,3 g, 11,5 mmol, 68 %). **TLC**: R_f :0,2. **M_p**: 113-117 $^\circ\text{C}$. $^1\text{H NMR } \delta$ (360 MHz, CDCl_3) : 0.07-0.21 (m, 1H), 0.75 (t, 3H), 1.09 (q, 2H), 1.25-1.35 (m, 2H), 1.37-1.56 (m, 2H), 1.56-1.65 (m, 1H), 2.35-2.40 (m, 1H), 2.41-2.46 (m, 1H), 2.63-2.73 (m, 1H), 2.79 (d, 1H), 2.88-2.95 (m, 1H), 3.02-3.09 (m, 1H), 3.12 (dd, 1H), 4.8 (s, 1H), 4.87 (s, 1H), 5.22 (dd, 1H), 6.26 (dd, 1H Arl), 6.51 (dd, 1H), 6.56 (td, 1H), 6.99 (td, 1H), 7.27-7.40 (m, 5H). $^{13}\text{C NMR } \delta$ (91 MHz, CDCl_3) : 12, 19.1, 25.6, 27.5, 28.1, 37.7, 40.6, 42.9, 52.9, 57.4, 57.5, 83.2, 95.1, 114.6, 118.9, 126.7, 127.9, 128, 128.3, 128.5, 130, 141.7, 142.7 ppm. **GC-MS** (EI); calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}$: 374,24; found: m/z (rel. int. %) = 374.16 (8) M^+ , 206.20 (100), 166.23 (84), 130.03 (54).

4'-Phenyl-cinchonine-aminal (13c)



Small scale:

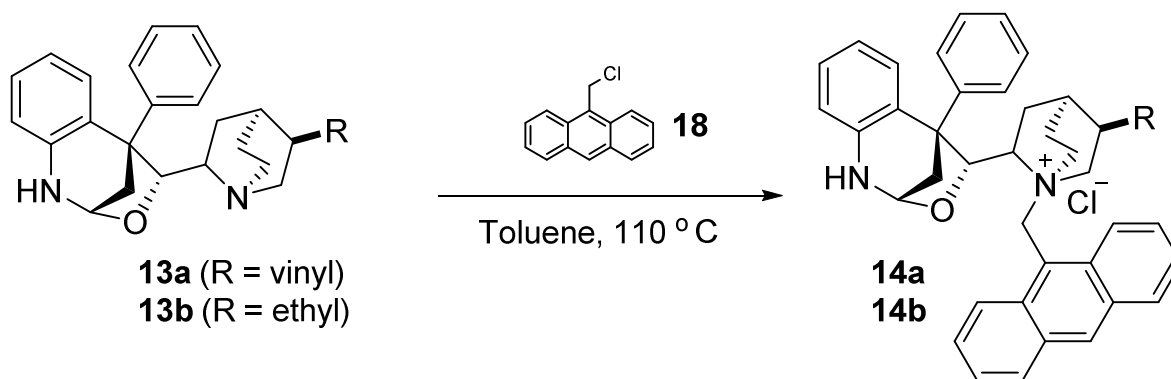
CN (100 mg, 0,34 mmol) was suspended in dry toluene (1 mL). The system was heated up to 50 °C. PhMgBr was added as a solution in diethyl ether (1 M, 1,4 ml, 1,7 mmol, 5 eq.). After addition a homogeneous solution was formed. The mixture was stirred at 50 °C for 18 h. **TLC**: EtOAc:MeOH:NEt₃= 25:1:1, R_f: 0,22.

Work up:

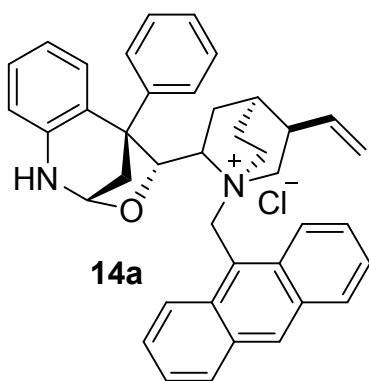
After cooling , the mixture was quenched with toluene (1,5 ml) and carefully addition of NH₄Cl aq. (1 ml). The system was acidified with 2 M HCl (2 ml) to give homogeneous solution. Ammonia 25 % was added (1,5 ml). the aqueous phase was then extracted with EtOAc (4 mLx3). Collected organic phase is washed with NH₄Cl aq. (1ml) and water (1 ml), then dried over MgSO₄, filtered and dried under reduced pressure to obtain yellow oil. The crude material was purified by chromatographic column [CC: EtOAc:MeOH:NEt₃=50:1:1] to give **13c** as tan powder (73 mg, 58 % yield). **¹H NMR** δ (360 MHz, CDCl₃) : -0,16-0,03 (m, 1H), 1,33-1,51 (m, 3H), 1,85 (ddt, J = 13.3, 7.8, 2.2, 1H), 2,14 (q, J = 8.9, 1H), 2,38 (ddd, J = 10.8, 4.9, 1.4, 1H), 2,78 (d, J = 10.9, 1H), 2,79-2,99 (m, 5H), 4,86 (s, 1H), 4,86 (NH covered), 4,93-5,05 (m, 2H, vinyl), 5,23 (dd, J = 4.8, 3.7, 1, 1H), 6,09 (ddd, J = 17.1, 10.2, 8.4, 1H, vinyl), 6,26 (dd, J = 7.6, 1.3, 1, 1H, ArI), 6,50-6,60 (m, 2H, ArI), 6,99 (td, J = 7.8, 1.5, 1, 1H), 7,27-7,41 (m, 5H, ArI). **¹³C NMR** δ (91 MHz, CDCl₃) : 19.9, 27.1, 28.3, 40.6, 40.9, 48.8, 49.5, 52.9, 57.5, 83.1, 95.1, 113.9, 114.7, 118.8, 126.8, 127.97, 128, 128.3, 128.5, 130, 141.6, 141.7, 142.7 ppm. **GC-MS** (EI); calcd. for C₂₅H₂₈N₂O: 372.22; found: m/z (rel. int. %) = 372.16 (8) M⁺, 206.20 (100), 166.23 (84), 130.03 (54).

General procedure for N-alkylation of cinchona aminsals (GP2)

A mixture of **13a** or **13b** (2,7 mmol) and **18** (1.5 to 1.8 eq.) in Toluene (10 ml) was stirred at 115 °C for 18 h. The solvent was then removed to give **14a** or **14b** a yellow oil. After purification by column chromatography (CC:EtOAc:MeOH:NEt₃=50:1:1), the fractions were evaporated. **TLC**: EtOAc:MeOH:NEt₃= 25:1:1 (R_f not easy to determine as the spot on silica gel shows strong tailing).



N-9-(Anthracenylmethyl)-4'-phenyl-cinchonidinium-aminal Chloride (**14a**).

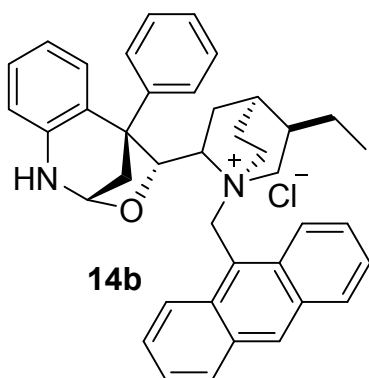


14a

Prepared according to **GP2** from **13a** (1 g, 2,7 mmol) and 9-anthracenylmethylchloride (1,5 eq.) The crude material was purified by CC to give **14a** as yellow powder (0,82g, 1,37 mmol, 51 % yield). ¹H NMR, δ (500 MHz, CDCl₃): 0.44-0.52 (m, 1H), 1.51-1.69 (m, 1H), 1.69-1.72 (m, 1H), 1.72-1.77(m, 1H), 1.84-1.91 (m, 1H), 2.04 (q, 1H), 2.21-2.30 (m, 1H), 2.64 (d, 1H), 2.70-2.78 (m, 2H), 3.05-3.12 (m, 1H), 3.12-3.17 (m, 1H), 3.20 (dd, 1H), 4.62 (d, 1H), 4.70 (s, 1H), 4.90-4.95 (m, 1H), 4.96 (dt, 1H), 5.41 (dd, 2H), 5.70 (ddd, 1H), 6.37 (dd, 1H), 6.68 (td, 1H), 7.26-7.240(m, 7H), 7.51-7.60 (m, 4H), 8.08 (d, 2H), 8.49 (d, 2H), 8.54 (s, 1H). ¹³C NMR, (63 MHz, CDCl₃): 145.37, 142.13, 141.96, 131.73, 131.51, 130.72, 129.15, 128.60, 128.53, 128.35, 128.23, 127.16, 126.77, 126.37, 125.24, 124.62, 118.82, 114.01,

112.07, 94.17, 84.27, 57.82, 55.90, 53.47, 45.13, 42.77, 40.77, 40.59, 27.89, 27.68, 20.48 ppm. **MS (ESI)**: calcd. for $C_{40}H_{39}N_2O^+$: 563.31; found: 563,29.

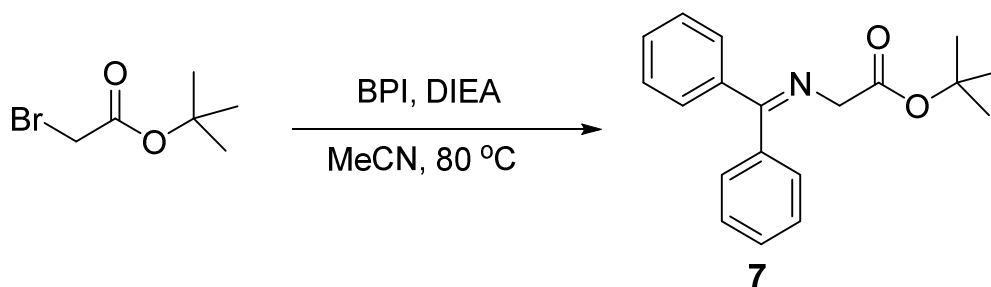
N-9(Anthracenylmethyl)-4'-phenyl-dihydrocinchonidinium-aminal Chloride (14b)



Prepared according to **GP2** from **13b** (1 g, 2,7 mmol) and 9-Anthracenylmethylchloride (1,8 eq.) The crude material was purified by CC to give **14b** as yellow powder (0,78 g, 1,3 mmol, 48 % yield). (0,8 g, 48 % yield). CC:[EtOAc:MeOH:NEt₃=50:1:1]

Mp, ¹H NMR δ (500 MHz, CDCl₃) : 0.33-0.40 (m, 1H), 0.815 (t, 3H), 1.22 (q, 2H), 1.37-1.44 (m, 1H), 1.45-1.53 (m, 1H), 1.68-1.80 (m, 2H), 1.87-1.98 (m, 1H), 2.04-2.11 (m, 1H), 2.49 (dq, 1H), 2.635 (d, 1H), 2.69-2.76 (m, 1H), 3.03-3.08 (m, 1H), 3.10-3.15 (m, 1H), 3.15-3.21 (dd, 1H), 4.614 (d, 1H), 4.69 (s, 1H), 5.425 (dd, 2H), 6.365 (dd, 1H), 6.68 (td, 1H), 7.20-7.40 (m, 7H), 7.48-7.56 (m, 4H), 8.045 (d, 2H), 8.47 (d, 2H), 8.50 (s, 1H). ¹³C NMR, δ (63 MHz, CDCl₃): 145.50, 141.95, 131.69, 131.47, 130.76, 129.09, 128.54, 128.41, 128.28, 128.16, 127.14, 126.69, 126.31, 125.19, 124.60, 118.72, 112.07, 94.33, 84.19, 57.58, 57.31, 53.40, 45.13, 42.89, 40.73, 37.71, 28.34, 27.52, 25.73, 20.04, 12.10. **MS (ESI)**; calcd. for $C_{40}H_{41}O^+$:563.32; found:565.30.

N-(Diphenylmethylene)glycine tert-butyl ester (7)^[41]



A solution of tert-butyl 2-bromoacetate (2,3 ml, 3 g, 15,37 mmol) in acetonitrile (20 mL) was treated with BPI (2,5 mL, 2,7 g, 14,9 mmol) and DIEA (2,6 mL, 1,9 g, 14,9 mmol), and the mixture was heated at reflux for 12 hours. After the system was cooled to room

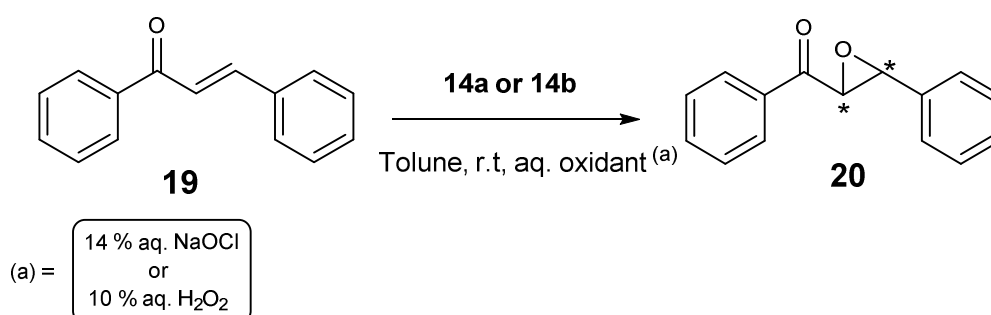
temperature, acetonitrile was removed in vacuo. The solid was dissolved in CH₂Cl₂ (30 mL) and washed with water (2x40 mL). The organic phase was dried with MgSO₄, filtered and the solvent removed in vacuo. The crude was recrystallized from Hexane to give **7** as white-off powder. After filtration, from the mother liquor is possible to obtain other product. Final yield 70 %.

¹H NMR δ (360 MHz, CDCl₃): 1.46 (s, 9H), 1.88 (s, 2H), 7.16-7.20 (m, 2H), 7.30-7.42 (m, 3H), 7.43-7.49 (m, 3H), 7.64-7.68 ppm (m, 2H). ¹³C NMR δ (91 MHz, CDCl₃): 28.11, 56.33, 128.01, 128.59, 128.73, 130.34, 136.18, 139.39, 169.83, 171.48.

2.3 Catalysis

The general procedure, analytical method and HPLC run conditions for catalytic asymmetric reactions are given below. All non racemic materials were compared with racemic compounds prepared using N-tetrabutylammonium iodide (TBAI) as phase transfer catalyst.

General procedure for asymmetric epoxidation of trans-chalcone (GP3)



To a solution of **19** (0,17 mmol) and the catalyst (0,017 mmol, 10 %) in toluene (1mL) was added aqueous oxidant (2 eq. of aq. NaOCl or 5 eq. of aq. H₂O₂) and the mixture was stirred for 48 hours at room temperature. **TLC**: Hexane:EtOAc = 9:1, R_f:0,17. Water was then added (2 mL) and the aqueous layer extracted with EtOAc (2x2 mL). The organic phase was then dried over MgSO₄, filtered and concentrated in vacuo to give yellow oil. The enantioselectivity was determined by chiral HPLC analysis of the crude product (DAICEL Chiralcel OD, hexane:isopropanol = 98:2, 20 °C, flow rate = 0,8 mL/min, λ = 254 nm, R_t: 20 min. and 21.56 min.

Procedure for racemic epoxidation of (19)

In according to **GP3**, the racemic mixture was obtained using 0,34 mmol of **19**, TBAI (0,034 mmol., 10 mmol. %), and 0,4 ml NaClO (2 eq.) as oxidant.

Preparation of HPLC samples:

All the samples for HPLC analysis were prepared by weighing: the crude product was dissolved in 10 mL of EtOAc and then 0,2 mL of the solution was diluted to 1 mL with the eluent in a small vial. Conversion of trans calchone to the corresponding epoxide was determined by comparison the area value of the same compound with that obtained from calibration curve (**fig. 14**) made from standard solutions.

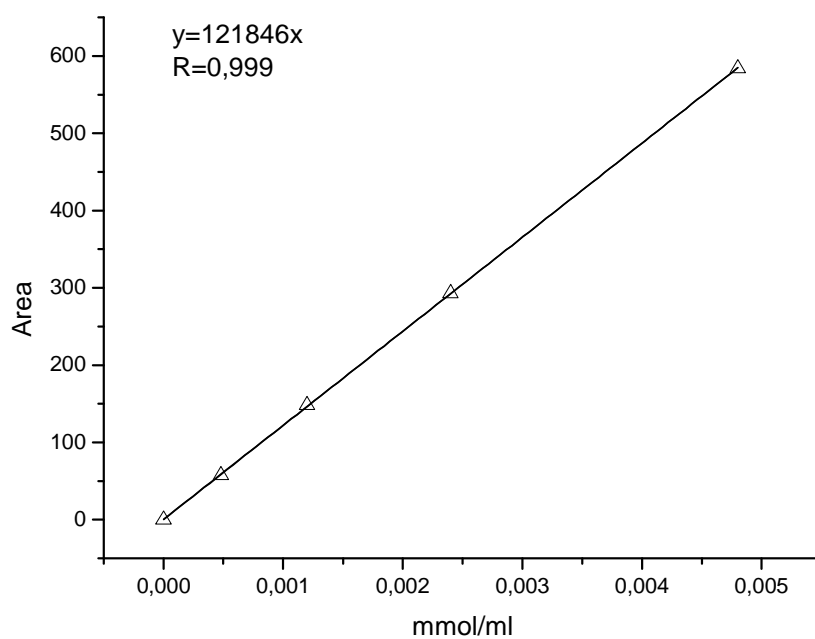
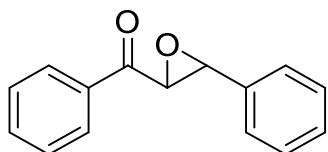


Fig. 14. Calibration curve of **19**.

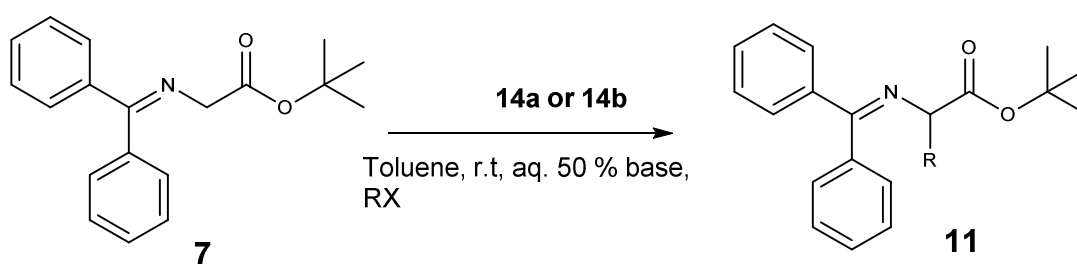
Product:

Trans-2,3-epoxy.1,3-diphenylpropan-1-one (20)



$^1\text{H NMR}$ δ (360 MHz, CDCl_3): 4.1 (d, $J = 1.9$, 1H), 4.30 (d, $J = 1.9$, 1H), 7.37-7.44 (m, 5H), 7.46-7.53 (m, 2H), 7.59-7.67 ppm (m, 1H). $^{13}\text{C NMR}$ δ (91 MHz, CDCl_3): 59.38, 61.02, 125.78, 128.34, 128.77, 128.87, 129.05, 133.98, 135.47, 193.06 ppm.

General procedure for asymmetric alkylation of N-(diphenylmethylene)glycine tert-butyl ester (GP4)



In a 10 ml vial with teflon cup to a mixture of **7** (50 mg, 0,17 mmol) and **14a** or **14b** (0,017 mmol, 10 %) in toluene (1 mL), the alkylating agent (0,2 mmol, 1,2 eq.) and the base (0,2 mL) were added with vigorous stirring (1200 rpm). The reaction mixture was kept at 25 °C for 18-24 h. **TLC**: Hexane:MTBE: NEt_3 = 15:1:1%. EtOAc was added (1x2 mL) and organic layer separated and washed with water (2x2 mL), dried over MgSO_4 , filtered and concentrated in vacuo. The crude was purified by column chromatographic (Hexane:MTBE: NEt_3 = 15:1:1%) and obtained as a colourless oil after evaporation of the solvent. TLC of final product revealed the presence of side product (benzophenone R_f :0,31). The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD).

Procedure for racemic alkylation of 7

In accordance to **GP4**, the racemic mixture was obtained using N-(diphenylmethylene)glycine tert-butyl ester (100 mg, 0.34 mmol), TBAI (10 mmol %), alkylating agent (0.4 mmol, 1.2 eq.) and 50 % aq. KOH (0.4 ml). The reaction was kept at 25 °C for 24 h.

Preparation of HPLC samples:

All the samples for HPLC were prepared by weighing: the product after purification on silica gel, was dissolved in 10 mL of eluent, then 0.2 mL of the solution was taken and diluted to 1 mL in a small vial. Final yield was calculated with HPLC with external standard calibration curve (**fig.15**), made from benzophenone solutions.

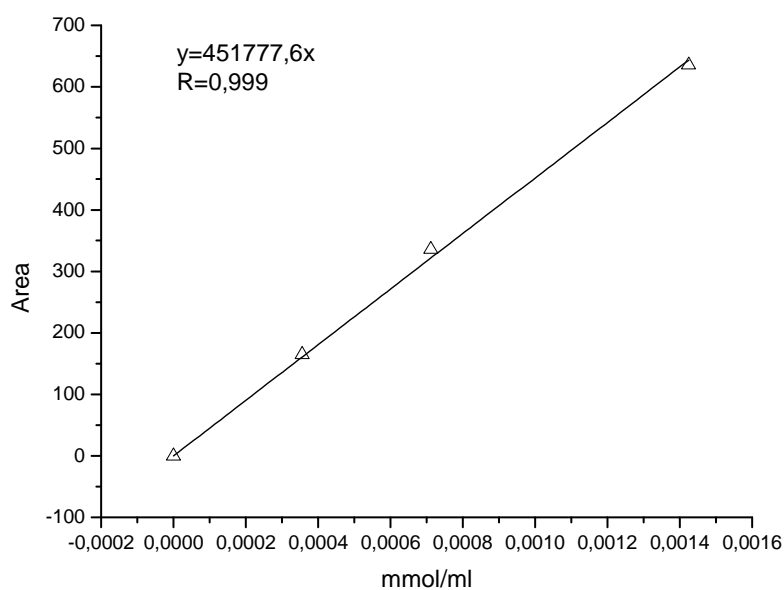


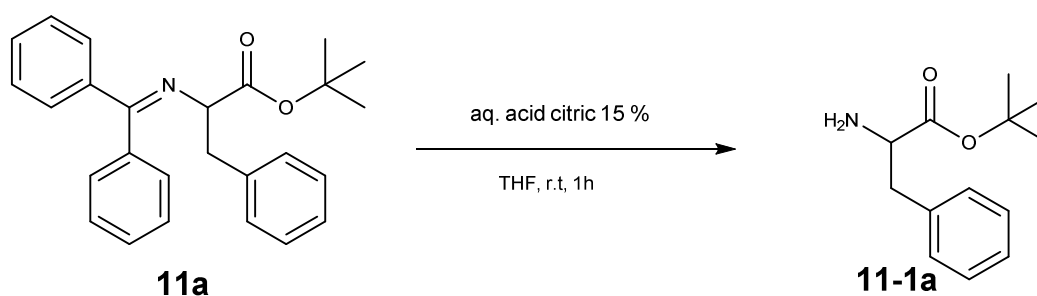
Fig. 15. Calibration curve of benzophenone

Scale up of asymmetric benzylation and of N-(diphenylmethylene)glycine tert-butyl ester (GP5a)

In a shlenk tube under argon, to a mixture of **7** (0.300 g, 1,015 mmol) and **14b** (5 to 10 % mmol.) in Toluene (6 ml) was added benzyl bromide (0,216 g, 1.2 mmol, 1.2 eq.) and 50 % aq. KOH (1.2 ml, 10,7 mmol). The biphasic system was kept at 25 °C for 24 h with stirring. **TLC**: Hexane:MTBE:NEt₃ = 15:1:1%. EtOAc (10 mL) was added and organic layer separated and washed with water (2x8 mL), dried over MgSO₄, filtered and the solvent removed in vacuo. The residue obtained was purified by chromatography on silica gel (Hexane:MTBE:NEt₃ = 15:1:1%) and the fractions evaporated to give **11a** as pale yellow oil.

The enantioselectivity was determined by chiral HPLC analysis of the crude product (DAICEL Chiralcel OD, hexane:isopropanol = 99.5:0.5, 20 °C, flow rate = 0,5 mL/min, λ = 254 nm)

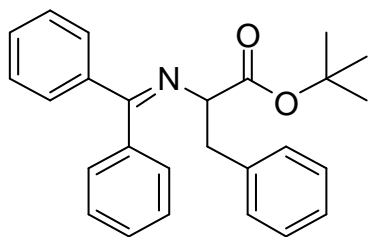
Hydrolysis of N-(diphenylmethylene)glycine tert-butyl ester-phenylalaninate (GP5b)



11a was dissolved in THF (5 mL) and 15% aq citric acid (1.5 mL) was added. Then the product was stirred vigorously at r.t. for 1 h, and then diluted with H₂O (5 mL). The mixture was extracted with Et₂O (2 × 5 mL) to remove benzophenone and the aqueous layer was basified with K₂CO₃. Extraction with EtOAc (3 × 5 mL) followed by drying (MgSO₄) and concentration under reduced pressure gave **11-1a** as a colourless oil.

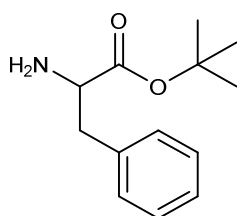
Product:

tert-Butyl-N-(diphenylmethylene)-phenylalaninate (**11a**)



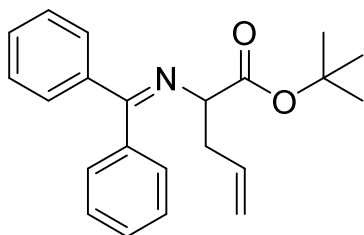
Alkylation of imine **7** with benzyl bromide, according to the general procedures, gave tert-butyl N-(diphenylmethylene)phenylalaninate (**11a**) as a pale yellow oil which was further chromatographed on silica gel. R_f:0,22. ¹H NMR δ (360 MHz, CDCl₃): 1.44 (s, 9H), 3.12-3.29 (m, 2H), 4.1 (dd, J = 5.0, 9.1 Hz, 1 H), 6.6 (d, 2H), 7.03-7.08 (m, 2H), 7.12-7.21 (m, 3H), 7.25-7.39 (m, 6H), 7.55-7.6 ppm (m, 2H). ¹³C NMR δ (91 MHz, CDCl₃): 28.07, 39.61, 67.95, 81.13, 126.16, 127.68, 127.94, 128.05, 128.09, 128.19, 128.73, 129.89, 130.08, 136.39, 138.38, 139.59, 170.28, 170.84 ppm. R_t HPLC (DAICEL ChiralCel,99.5:0.5, hexane/isopropanol, 254 nm, 0.5 ml/min, 20 °C): 18.5 min. (*R*-enantiomer), 29.8 min. (*S*-enantiomer).

tert-Butyl-phenylalaninate (**11-1a**)



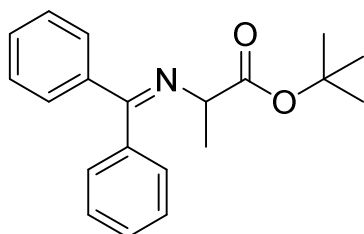
Synthesized according to **GP5b**. ¹H NMR δ (360 MHz, CDCl₃):1.35 (s, 9H), 1.43 (s, br., 2H, NH₂), 2.75 (dd, J= 7.7, 13.5, 1H), 3.0 (dd, J = 7.6, 13.5), 3.5 (dd, J= 5.7, 7.7, 1H), 7.12-7.26 (m, 5H). ¹³C NMR δ (91 MHz, CDCl₃):28.00, 41.3, 56.32, 81.1, 126.65, 128.4, 129.39, 137.57, 174.32 ppm.

tert-Butyl 2-[(diphenylmethylene)amino]pent-4-enoate (11b)



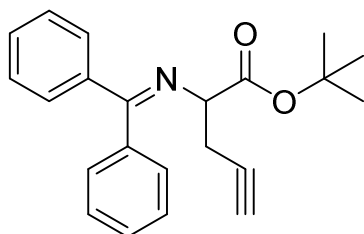
Alkylation of imine **7** with allylbromide, according to the general procedure **GP4**, gave crude tert-butyl 2-[(diphenylmethylene)amino]pent-4-enoate as a pale yellow oil which was further chromatographed on silica gel. R_f:0,22. ¹H NMR δ (360 MHz, CDCl₃): 1,44 (s, 9H), 2.55-2.71 (m, 2H), 4.01 (dd, J = 4.5, 9.0 Hz, 1H), 4.99-5.10 (m, 2H), 5.66-5.79 (m, 1H), 7.15-7.20 (m, 2H), 7.28-7.38 (m, 3H), 7.40-7.47 (m, 3H), 7.62-7.67 ppm (m, 2H). ¹³C NMR δ (91 MHz, CDCl₃): 28.09, 38.15, 65.85, 117.25, 127.95, 127.97, 128.27, 128.38, 128.50, 128.81, 130.05, 130.16, 134.74, 136.68, 139.73, 170.08, 170.86 ppm. R_t HPLC (DAICEL ChiralCel, 99.5:0.5, hexane/isopropanol, 254 nm, 0.5 ml/min, 20 °C): 9.6 min. and 10.8 min.

tert-Butyl alaninate (11c)



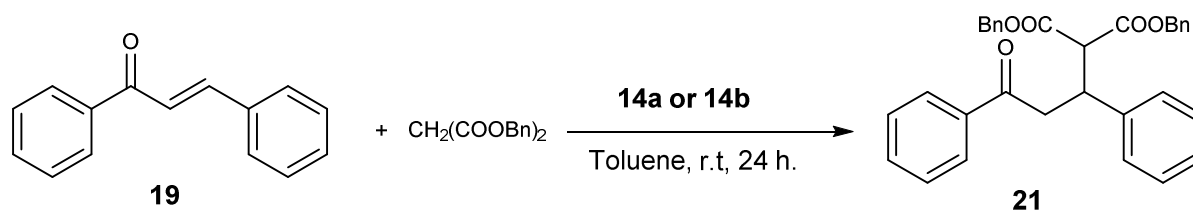
Alkylation of imine **7** with methyl iodide, according to the general procedure, gave crude tert-butyl N-(diphenylmethylene)alaninate as a pale yellow oil which was further chromatographed on silica gel. R_f : 0,22. ¹H NMR δ (360 MHz, CDCl₃): 1.4 (d, J = 9.4, 3H), 1.44 (s, 9H), 4.03 (q, J = 13.9, 1H), 7.16-7.21 (m, 2H), 7.29-7.41 (m, 3H), 7.42-7.48 (m, 3H), 7.62-7.66 ppm (m, 2H). ¹³C NMR δ (91 MHz, CDCl₃):19.16, 28.06, 61.29, 80.74, 127.72, 128, 128.28, 128.49, 128.73, 130.06, 130.14, 132.42, 136.56, 139.71, 169.29, 172.02 ppm. R_t HPLC (DAICEL ChiralCel,99.5:0.5, hexane/isopropanol, 254 nm, 0.5 ml/min, 20 °C) 13.0 min. and 14.6 min.

tert-Butyl-2-(diphenylmethyleneamino)pent-4-ynoate (**11d**)



Alkylation of imine **7** with propargyl bromide, according to the general procedure **GP4**, gave crude tert-Butyl-2-(diphenylmethyleneamino)pent-4-ynoate as a pale yellow oil which was further chromatographed on silica gel. Rf :0,22. $^1\text{H NMR}$ δ (360 MHz, CDCl_3): 1.45 (s, 9H), 1.95 (t, $J = 2.6$ Hz, 1H), 2.71-2.86 (m, 2H), 4.17 (dd, $J = 5.3, 8.5$ Hz, 1H), 7.24-7.28 (m, 2H), 7.295-7.40 (m, 3H), 7.42-7.47 (m, 3H), 7.635-7.68 ppm (m, 2H). $^{13}\text{C NMR}$ δ (91 MHz, CDCl_3): 23.37, 28.03, 64.79, 70.08, 76.70, 77.06, 77.41, 81.25, 81.60, 128.02, 128.26, 128.36, 128.63, 128.97, 130.05, 130.35, 132.41, 136.27, 139.63, 169.55, 171.41 ppm. Rt HPLC (DAICEL ChiralCel,99.5:0.5, hexane/isopropanol, 254 nm, 0.5 ml/min, 20 °C): n.d.

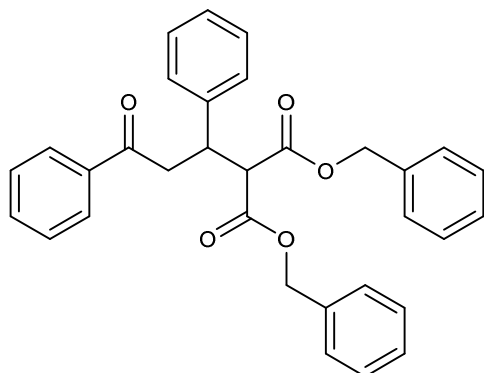
General procedure for Michael addition of dibenzylmalonate to trans-chalcone (**GP6**)



To a mixture of **19** (0.45 mmol), K_2CO_3 (0,16 g, 2.0 mmol, 4.45 eq.), catalyst (0,03 mmol, 10 mmol. %) in Toluene (2 mL), dibenzylmalonate (0,11 mL, 0,45 mmol, 1.43 eq.) was added. The reaction was stirred at room temperature for 24 h. **TLC** : EtOAc:Hex = 1:5, $R_f = 0,32$. The mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 10 mL). The organic layers were combined, dried over MgSO_4 , filtered, concentrated and evaporated in vacuo. The crude material was purified by column chromatography (CC: EtOAc:Hex = 1:5).

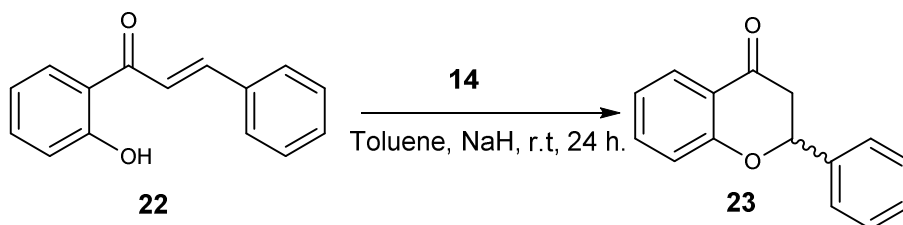
Product:

2-(3-Oxo-1,3-diphenylpropyl)dibenzylmalonate (**21**)



NMR δ (360 MHz, CDCl_3): 3.45-3.5 (m, 2H), 3.98 (d, $J = 9.6$ Hz, 1H), 4.21-4.30 (m, 1H), 4.935 (s, 2H), 5.15-5.20 (m, 2H), 7.07-7.85 ppm (m, 20 H). **^{13}C NMR** δ (91 MHz, CDCl_3): 40.76, 41.58, 42.26, 57.53, 67.12, 67.32, 127.16, 128.04, 128.14, 128.20, 128.29, 128.38, 128.42, 128.48, 128.55, 128.58, 132.99, 135.04, 135.13, 136.72, 140.3, 167.47, 167.98, 197.33 ppm.

General procedure for cyclization of 2'-hydroxychalcone to flavanone (GP7)



In a dried shlenck tube to a solution of **22** (0,100 g, 0,45 mmol) in toluene (3 mL) was added solid NaH (60 % in oil, 10 %). The catalyst **14** was added as solid (0,045 mmol). The reaction was stirred at room temperature for 24 h. TLC: samples quenched with 0.5 mL of HCl (2M) and diluted with 1 mL of MTBE; MTBE:Hex:NEt₃ = 15:1:1%.

3 List of abbreviations

Aq.	aqueous
Ar	Aryl
Bn	Benzyl
^t Bu	tertiary butyl
BPI	Benzophenone imine
DIPEA	diisopropylethylamin
EI	electronionization
MS (ESI)	mass spectroscopy (electrospray ionization)
Eq.	Equivalent
EtOAc	Ethylacetate
EtOH	Ethanol
GC	Gas chromatography
H (s)	hour(s)
HPLC	High performance chromatography
MeCN	Acetonitrile
MeOH	Methanol
Min.	minute(s)
MS	Mass spectrometry
MTBE	Methyl tert-butylether
TBAI	Tetrabutylammonium iodide
THF	tetrahydrofuran
TLC	thin layer chromatography
r.t	room temperature
R _t	retention time

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