SYNTHESIS OF BIFUNCTIONAL 2-AMINODMAP/PROLINAMIDE ORGANOCATALYSTS AND THEIR USE IN ASYMMETRIC MICHAEL REACTION TO AFFORD WARFARIN

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Approval of the thesis:

SYNTHESIS OF BIFUNCTIONAL 2-AMINODMAP/PROLINAMIDE ORGANOCATALYSTS AND THEIR USE IN ASYMMETRIC MICHAEL REACTION TO AFFORD WARFARIN

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ABSTRACT

SYNTHESIS OF BIFUNCTIONAL 2-AMINODMAP/PROLINAMIDE ORGANOCATALYSTS AND THEIR USE IN ASYMMETRIC MICHAEL REACTION TO AFFORD WARFARIN

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January 2012, 70 pages

In the first part of this thesis, the construction of the novel bifunctional proline-(1*R*,2*R*)-2-aminoDMAP organocatalyst backbone is described. Target compound has both Lewis base and Brønsted acid catalaphoric sites. The Lewis base site is synthesized via selective mono-*N*-pyridilization of trans-(1*R*,2*R*)-cyclohexane-1,2-diamine by Cu catalysis and Brønsted acid site is subsequently introduced by anchoring L-proline unit. In the second part, catalytic activities of organocatalysts are tested in asymmetric Michael addition reaction between a cyclic 1,3-dicarbonyl compound 4-hydroxycoumarin and various α,β-unsaturated ketones to afford optically active warfarin as anticoagulants, in one step. Reaction parameters such as solvent, temperature, equivalency, and cocatalyst were screened. Enantiomeric excess value (*ee*) up to 72% is attained.

Keywords: warfarin, organocatalysis, bifunctional organocatalyst, asymmetric synthesis.

ÖZ

BİFONKSİYONEL 2-AMİNODMAP/PROLİNAMİT ORGANOKATALİZÖRLERİN SENTEZİ VE ASİMETRİK MİCHAEL TİPİ KATILMA İLE WARFARİN ELDESİ

Akkoca, Hasan Ufuk
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli
Ocak 2012, 70 sayfa

Çalışmanın birinci kısmında, özgün bifonksiyonel prolin-(1*R*,2*R*)-2-aminoDMAP organokatalizör iskeletinin oluşturulması açıklanmaktadır. Hedef organokatalizör, Lewis baz ve Brønsted asit katalaforik birimlerinin her ikisinede sahiptir. Lewis baz birimi trans-(1*R*,2*R*)-siklohekzan-1,2-diamin'in Cu katalizörlüğünde seçici mono-*N*-piridilizasyonu ile sentezlenmekte ve sonrasında Brønsted asit birimi L-prolin'in takılmasıyla oluşturulmaktadır. İkinci kısımda, organokatalizörlerin katalitik aktiviteleri, halkalı 1,3-dikarbonil bileşiği olan 4-hidroksikumarin ve çeşitli α,β-doymamış ketonlar arasında yapılan asimetrik Michael katılma tepkimesiyle test edilmektedir. Bu test reaksiyonları sonucu optikçe aktif antikoagülan özelliğine sahip warfarin tek basamakta elde edilmektedir. Çözücü, sıcaklık, eşdeğerlik, kokatalizör gibi tepkime parametreleri test edilmiş, %72 enantiyomerik değere ulaşılmıştır.

Anahtar kelimeler: warfarin, organokataliz, bifonksiyonel organokatalizör, asimetrik sentez.

To my family and lovely sweetheart…

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LIST OF ABBREVIATIONS

DCM: Dichloromethane

TFA: Trifluoroaceticacid

DMAP: Dimethylaminopyridine

LDA: Lithium diisopropylamide

TMSCl: Trimethylsilyl chloride

TADDOLS: α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol

NOBIN: 2-Amino-2′-hydroxy-1,1′-binaphthalene

DMSO: Dimethyl sulfoxide

BTF: Benzotrifluoride

THF: Tetrahydrofuran

NMR: Nuclear magnetic resonance

IR: Infrared

J: Coupling constant

Hz: Hertz

ppm: Parts per million

mg: miligram

mmol: milimole

CHAPTER 1

INTRODUCTION

1.1 Importance of Warfarin

Organic chemistry has the unique role in the development and maintenance of the societies. Since, it's involved in food, textile, cosmetics and pharmaceutics field. There is no doubt that pharmaceutics is one of the most important field for human beings' life. Organic chemistry should be understood very well by pharmacists for selection and usage of a drug in body. Because human body consists of many types of organic compounds as well as drugs. The reaction of living systems with a drug may result undesirable outcomes such as poisoning, paralysis and death. Therefore, the functions, structures and metabolic activities of organic compounds are very important for their selection and usage obtaining high efficiency results in human beings' healthiness. The main subject of this thesis focuses on the asymmetric synthesis of one of these organic compounds named as warfarin (Figure 1).

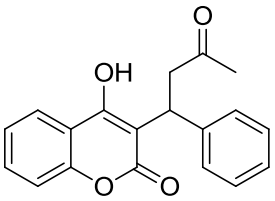


Figure 1. Warfarin

Initially, warfarin was used as a rat poison in 1940s [1]. A couple of years later, scientists found that it was efficient for the treatment of thrombosis. So it was called as anticoagulant. Vitamin K, one of the fat soluble vitamins causes blood coagulation and participates in metabolic activities of bone and tissues. Two kinds of Vitamin K as Vitamin K_1 (phylloquinone) and Vitamin K_2 (menaquinone) are found in nature (Figure 2). Many sources are available for Vitamin K. For example, spinach, cabbage and broccoli are the main sources for Vitamin K_1, whereas, meat

and egg are the main sources for Vitamin K_2 [2]. Infants should get enough Vitamin K in daily diets. Otherwise, the deficiency problems would seem. The symptoms of deficiency are anemia, bruising and bleeding problems in nose [3]. In addition, the lower amount of Vitamin K_2 causes an osteoporosis and heart attack problems [4]

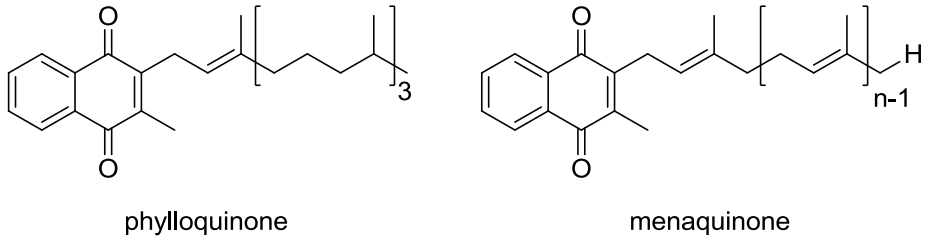


Figure 2. Vitamin K_1 and Vitamin K_2

As mentioned above, since blood coagulation activity of Vitamin K causes some diseases such as embolism and thrombosis [5]. Coumarins are generally used as an antagonist for Vitamin K. Among the coumarin derivatives (Figure 3), warfarin is widely used as medicine [2] which inhibits the Vitamin K epoxide reductase and this situation disrupted blood-clotting proteins to synthesize Vitamin K [6]; therefore, blood coagulation is diminished. In addition, there is an obvious difference in metabolic activities of two enantiomeric form of Warfarin. (*S*)-Enantiomer is 2-5 times more active than (*R*)-enantiomer [7-8]. Due to this fact, asymmetric synthesis of warfarin has been targeting by many research groups applying different methods.

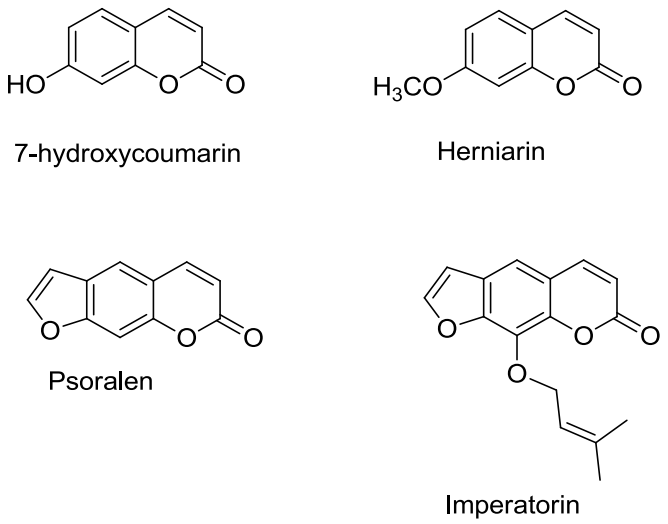
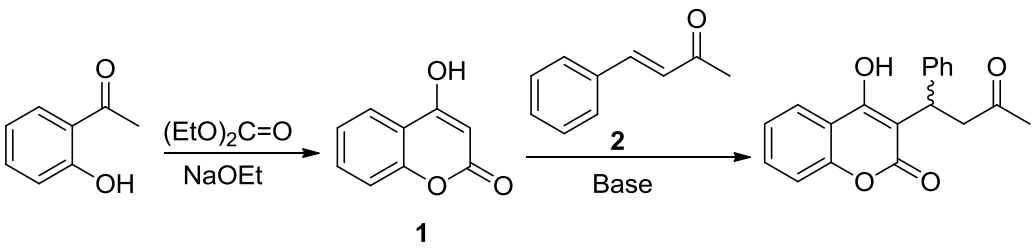


Figure 3. Structures of Vitamin K antagonists

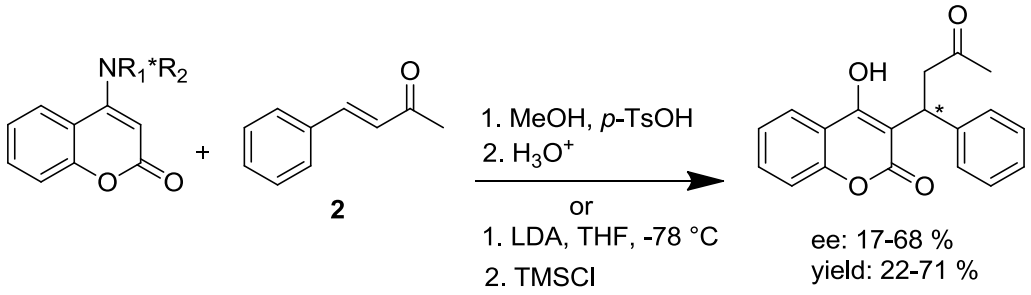
1.2 Synthetic History of Warfarin

In history, first synthesis of warfarin in racemic form was achieved by Karl Paul Link and his lab mates in Wisconsin Alumni Research Foundation (WARF) in 1933 [9] as shown in Scheme 1. The common name warfarin aroused from the abbreviation of this foundation. In their synthetic route 4-hydroxycoumarin (**1**) was synthesized from acetylphenol, and then it underwent Michael type addition reaction with benzylideneacetone (**2**) in the presence of base.



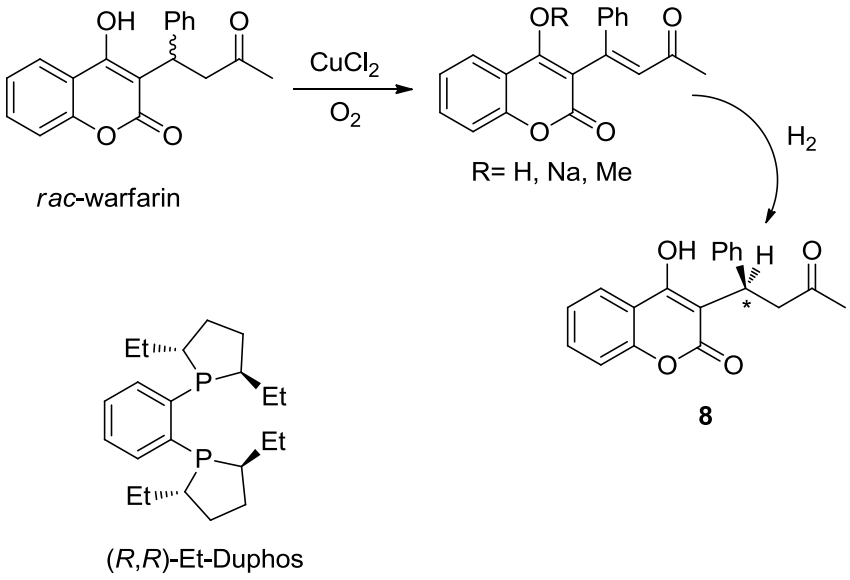
Scheme 1. First warfarin synthesis

In an asymmetric manner, various chiral enamines derived from 4-hydroxycoumarin (**1**) were treated with benzylideneacetone (**2**) in the presence of LDA and Lewis acids to synthesize enantiomerically enriched warfarin [10] as shown in Scheme 2.



Scheme 2. Enantioselective warfarin synthesis

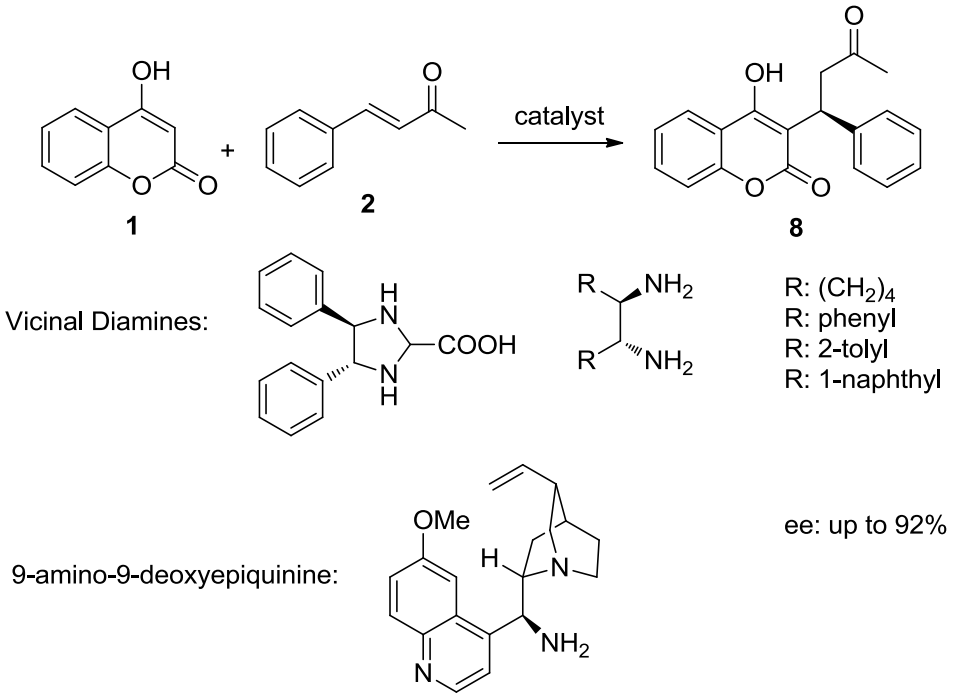
Alternatively, enantioriched warfarin was synthesized from racemic warfarin by an oxidation procedure and then subsequent asymmetric hydrogenation [11-12] (Scheme 3). In this reaction, the DuPhos catalyst which is the most common commercial product was used. Its name aroused from DuPont Company and the compound class of phospholanes group.



Scheme 3. Enantioriched warfarin synthesis

In recent years, many types of catalysts have been tried on synthesis of warfarin. One of them was the chiral vicinal diamines using as a catalyst for the stereoselective coupling of 4-hydroxycoumarin (**1**) and benzylideneacetone (**2**) [13] (Scheme 4). In other study, 9-amino-9-deoxyepiquinine was used as an

organocatalyst in the enantioselective Michael addition reaction 4-hydroxycoumarin (**1**) and benzylideneacetone (**2**) to synthesize enantiomerically enriched warfarin [14] (Scheme 4).



Scheme 4. Synthesis of optically active warfarin

1.3 Organocatalysis

Organocatalyst is an organic molecule that generally composes of carbon, nitrogen, oxygen, phosphorous and sulphur atoms, not including metal atoms. They are used to speed up the chemical reactions with less than stoichiometric amounts. Moreover, they generally do not have high molecular weight. The interest toward the organocatalysis has been increasing as the years passed. According to Table 1 [15], the number of publications on the topic of organocatalysis has increased clearly. As shown in the table, there is no sharp ascension between the 1980-2000 years. However, the sharp ascension is seen markedly after 2000. The reason of this is the more advantages [16] of them over the other catalyst systems, such as;

- Lasting and strong
- Readily available
- No toxicity
- Low- priced
- Inert toward moisture and O_2
- No transition metals included

Table 1. Number of publications on topic of organocatalysis

Number of publications	Year
~15	1980-1984
~20	1984-1988
~25	1988-1992
~35	1992-1996
~40	1996-2000
~150	2000-2004
~1200	2004- 2008

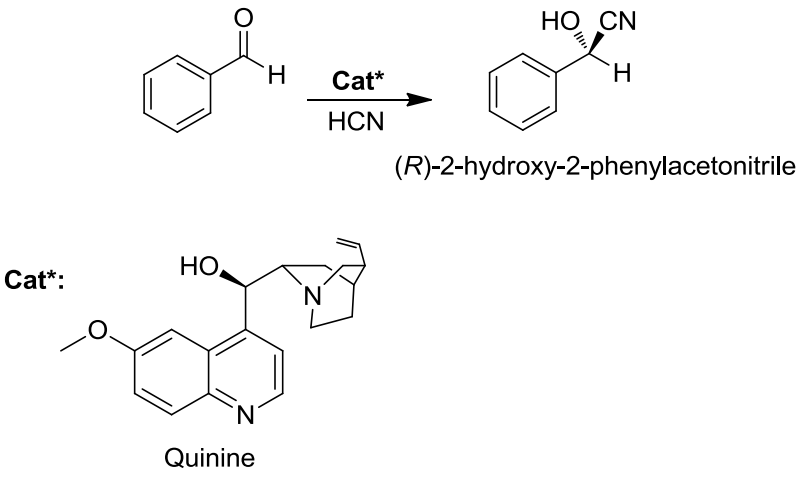
1.3.1 Asymmetric Organocatalysis

Formation of paramount of an enantiomer is called asymmetric synthesis. Asymmetric synthesis plays an important role in particular pharmaceutics area, because different biological effects and metabolic activities are observed for each enantiomer or diastereomer of a compound. For instance, (*S*)-warfarin is metabolized faster in men body than women body [7].

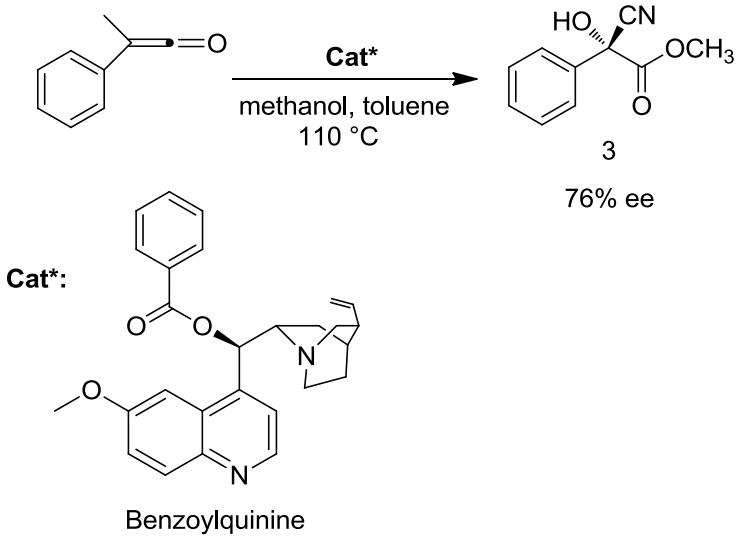
1.3.2 Historical Background of Asymmetric Organocatalysis

The first experiment in asymmetric organocatalysis was shown in 1912. Bredig and Fiske demonstrated that the alkaloids quinine speeded up the reaction of benzaldehyde with HCN resulted in the optically active products [17]. After this work, no related studies have been observed until 1960s. Pracejeus demonstrated that

alkaloids speeded up the reaction between methanol and phenyl (methyl) ketene to afford enantiomerically enriched (*R*)-methyl 2-phenylpropanoate (**3**) having (76% ee) as shown in Scheme 6 [18].

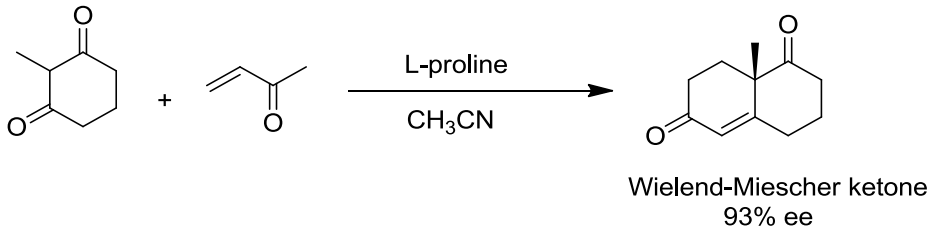


Scheme 5. Reaction between benzaldehyde with HCN



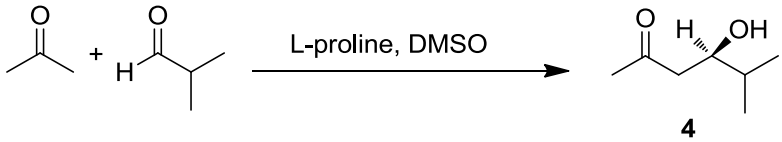
Scheme 6. Reaction between methanol and phenylmethylketene

Later, Pracejeus and his co-workers extended the scope of organocatalysis to the asymmetric synthesis of natural product precursor known as Wieland-Miescher ketone in 1971. In his work, L-proline was used as organocatalyst to afford Wieland Miescher ketone in 93% ee. [19] (Scheme 7).



Scheme 7. The Hajos-Parrish-Eder-Sauer-Wiechert reaction

Studies were increasing on this topic by using L-proline as organocatalyst. As shown in Scheme 8, the aldol reaction of acetone and isobutyraldehyde afforded (*R*)-4-hydroxy-5-methylhexan-2-one (**4**) with 96% ee [20-21].



Scheme 8. Aldol reaction with using proline as a catalyst

In the last decade, various organacatalysts have been developing exponentially and applying to various kinds of asymmetric reactions. Figure 4 shows the major class of organocatalysts.

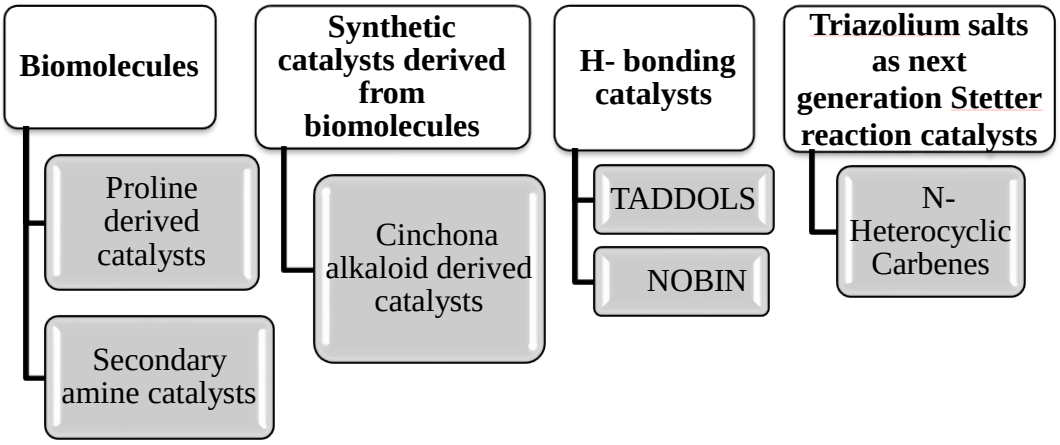


Figure 4. Organocatalysts using in asymmetric synthesis

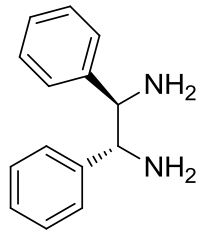
1.3.3 Types of Organocatalysts and Cocatalysts Using in the Synthesis of Warfarin

Since, the most preferred organocatalysts to accelerate the Michael type addition reaction used in the synthesis warfarin in the literature are primary and secondary amine type organocatalysts, herein a brief introduction is given for this class of organocatalysts.

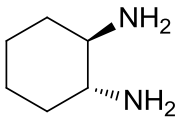
1.3.3.1 Primary and Secondary Amine Organocatalysts

Using primary amines to accelerate the organic reactions began at the beginning of 1900s with the Knoevenagel condensation [22]. In 1950s, Stork and his co-workers introduced the using of enamines [23]. Later, in 1970s as mentioned above proline has been studied as an organocatalyst in the Hajos–Parrish–Eder–Sauer–Wiechert reactions. After the 2000, parallel to the increasing demand on organocatalyst in asymmetric synthesis, the usage of primary and secondary amines as an organocatalyst become widespread. Some examples to common primary and secondary amines are being shown in Figure 5.

Primary amine organocatalyst

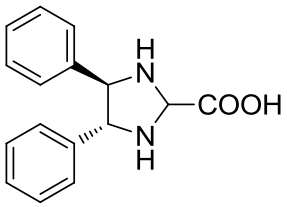


(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine

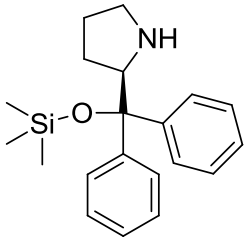


(1*R*,2*R*)-cyclohexane-1,2-diamine

Secondary amine organocatalyst



(4*R*,5*R*)-4,5-diphenylimidazolidine-2-carboxylic acid



(*R*)-2-(diphenyl(trimethylsilyloxy)methyl) pyrrolidine

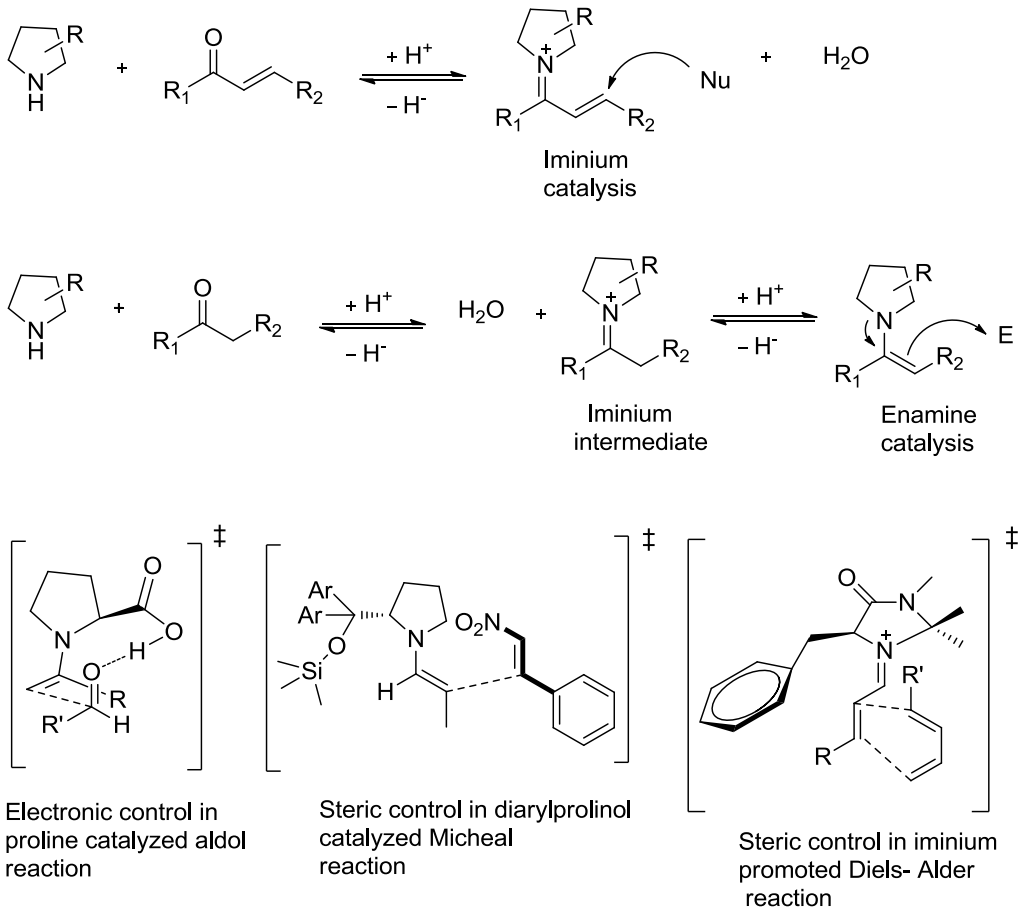
Figure 5. Examples to primary and secondary amine organocatalysts

Knoevenagel, Michael and aldol reactions catalysed by primary and secondary amines, iminium and enamine type intermediate formations strongly favour the enantioface discrimination [24-25-26]. Enamine formation favours the reaction between the nucleophile and electrophile [27]. Since, enamine activates the HOMO of nucleophile. On the other hand, iminium intermediate decreases the energy level of LUMO of electrophile that's why nucleophile easily undergoes the reaction with electrophile. Iminium and enamine activation of α,β-unsaturated ketone and saturated ketone, respectively is shown in Scheme 9 [24].

When investigating the transition states, there are two possible ways to take control on the stereoselectivity of the reaction;

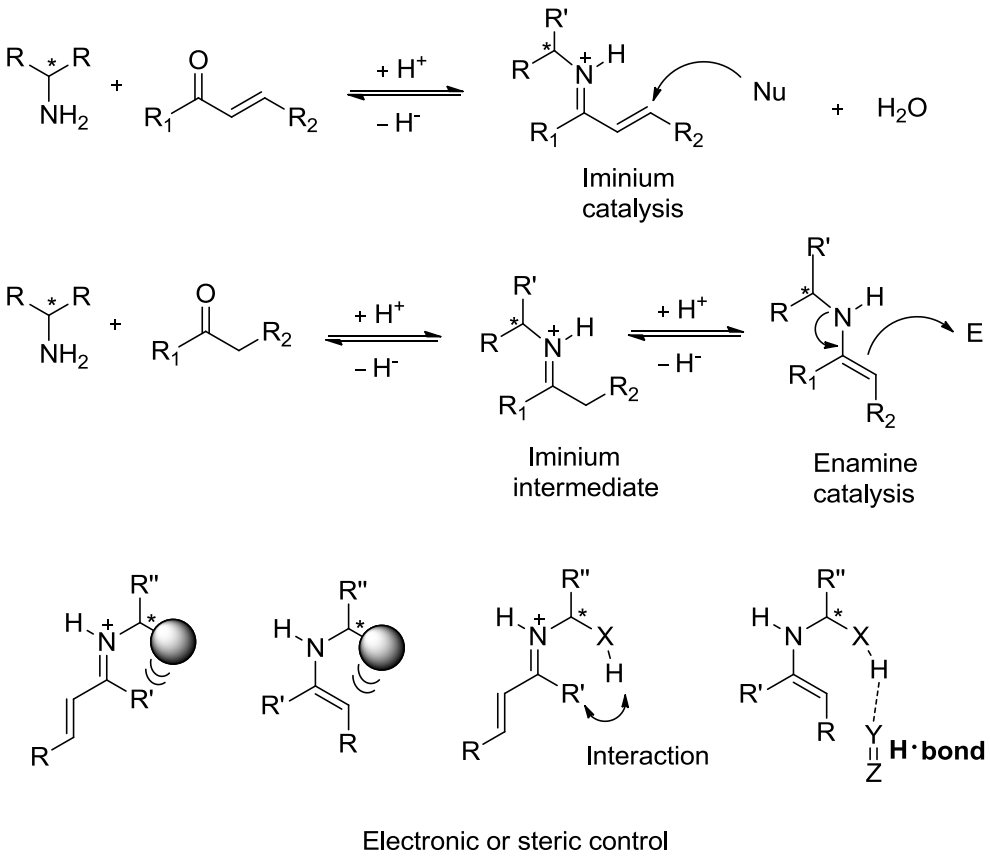
- Electronic (generally H-bonding) interaction
- Steric interaction

Examples to possible transition state models having control on the stereoselectivity are shown in Scheme 9.



Scheme 9. Secondary amines in iminium and enamine catalysis

Literature results show that primary amine catalysts have advantageous over secondary amine catalysts [28-29]; especially in ketone substrates [30], the active catalytic intermediate is formed easily because of availability of hydrogen on nitrogen instead of alkyl group. Moreover, the stereoselectivity of the reaction and also enamine formation could easily be controlled by the presence of N-H group. Examples to iminium and enamine intermediate formations from primary amine are demonstrated in Scheme 10 [24]. An iminium intermediate formation from primary amine and carbonyl compound should be done in acidic medium. Indeed to get enamine, the acidic medium assists the transformation of iminium intermediate to enamine. Scheme 10 also shows the electronic and steric control effects in same proposed transition state models.



Scheme 10. Primary amines as iminium and enamine forms

As mentioned before, in electronic or steric control of the asymmetric reactions, the chiral stages should be determined very accurately to get active chiral induction. There are some examples of the chiral primary amine organocatalysts in Figure 6 [24]. In literature, primary amine based organocatalysts are classified as;

- Natural primary amino acids and their derivatives
- Primary amines derived from various chiral diamines
- Catalysts based on Cinchona alkaloids
- Primary amine catalysts containing chiral counter ions.

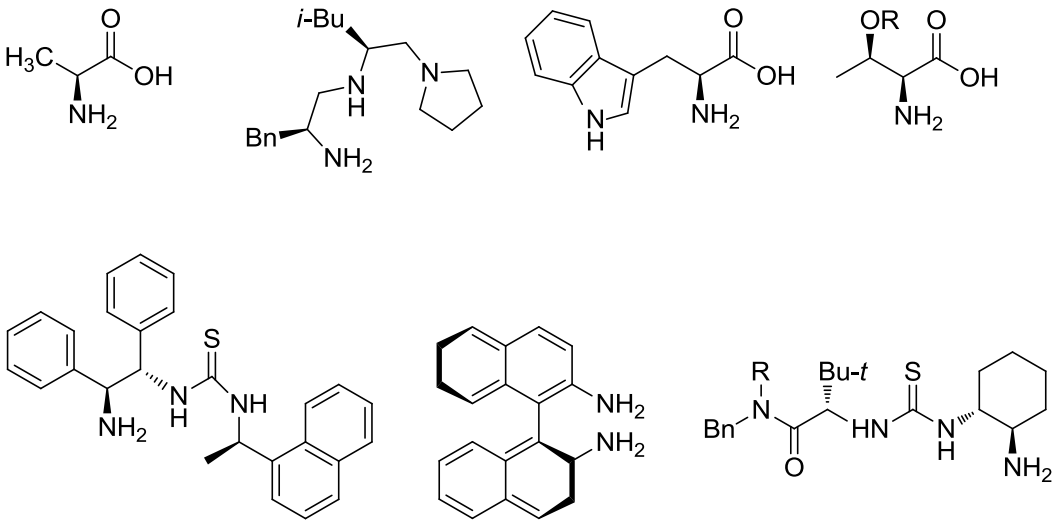


Figure 6. Some examples of selected chiral primary amine organocatalysts

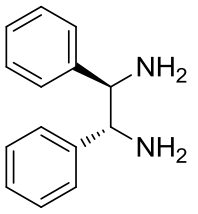
1.3.3.2 Types of Cocatalysts Using in the Synthesis of Warfarin

Cocatalysts are chemical compounds that increase the rate in catalysis occurring cooperatively. Many functional groups are treated as cocatalysts to enhance catalytic activity in the synthesis of warfarin. Thus, carboxylic acid group is the best candidate as a cocatalyst. Because, it provides two advantageous properties as;

- Improvement of the stereoselectivity
- Enhancement of the catalytic activity

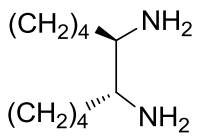
However, sometimes it may not improve the catalytic activity and stereoselectivity of a reaction. An example to this case is given in Figure 7. In (*1R,2R*)-1,2-diphenylethane-1,2-diaminephenyl (**5**), due to high ‘‘s’’ character of phenyl substituents, the elecetronegativity is high [31-32]. Thus, they can pull the free electrons of nitrogen, and also they cause the decreasing of basicity. For this reason, compound **5** using as organocatalyst in warfarin synthesis requires a cocatalyst. On the other hand, in (*1R,2R*)-1,2-dibutylethane-1,2-diamine (**6**), butyl substituents have low electronegativity due to their sp^3 hybridizations [33]. They could not pull the

free electrons of nitrogen as well as the phenyl substituents. As a result, there is no need a cocatalyst in the synthesis of warfarin using **6** as organocatalyst [13].



(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine

5



(1*R*,2*R*)-1,2-dibutylethane-1,2-diamine

6

Figure 7. Cocatalyst requirement comparison

1.3.4 Bifunctional Organocatalysis

With a sharp increasing demand on the organocatalysis in catalytic asymmetric synthesis, many organocatalysts have been exploring and utilizing in a various kinds of asymmetric reactions. Among them, bifunctional organocatalysts have been an important role in last decades. Since, their usage provides a wide range of asymmetric transformations and excellent stereoselectivity. Bifunctional organocatalysts present various opportunities to new asymmetric bond formations between carbon-carbon and carbon-hetero atom by the dual activation of nucleophilic reagent and electrophilic substrate toward each other with acid-base interactions [34]. As shown in Figure 8, the electrostatic attraction between hydrogen bond and electrophile decreases the electron density of this species which enables it against the nucleophilic attack. As a result, this ternary complex provides high enantioselectivity with low catalyst loading in a reasonable reaction time [35].

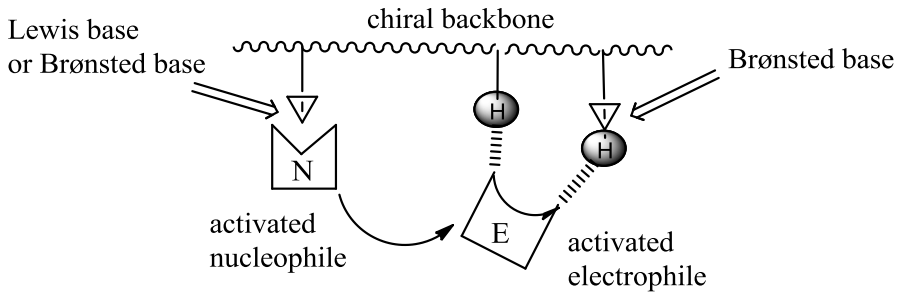
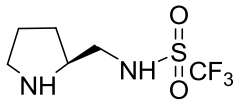
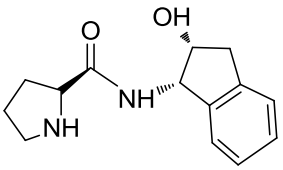


Figure 8. Activation of nucleophile and electrophile in metal complex catalysis and organocatalysis.

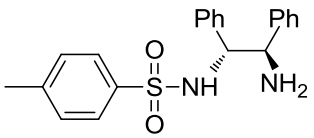
In asymmetric reactions, proline and its analogues, ammonium salts of diamine, cinchona alkaloids and derivatives, thiourea derivatives, phosphoric acid derivatives, H-bonding phase-transfer catalysts as well as peptides have potential to use as a bifunctional organocatalyst [35-36]. Figure 9 depicts some examples to bifunctional organocatalyst using in Michael type addition reaction.



(*S*)-1,1,1-trifluoro-*N*-(pyrrolidin-2-ylmethyl)methanesulfonamide



(*R*)-*N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)pyrrolidine-2-carboxamide

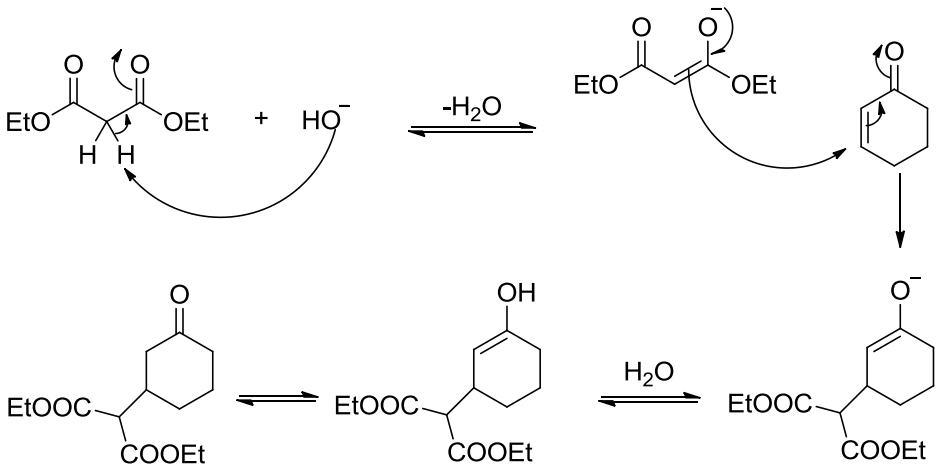


N-((1*R*,2*R*)-2-amino-1,2-diphenylethyl)-4-methylbenzenesulfonamide

Figure 9. Examples to bifunctional organocatalysts

1.4 Asymmetric Michael Addition Reaction

A well-known method in the synthesis of warfarin is Michael type addition reaction taking place between the α,β-unsaturated carbonyl and β-dicarbonyl compound having active methylene unit [37]. Firstly, one of the active methylene protons is detached from β-dicarbonyl system and enolate is formed. That enolate is added to β carbon of an α,β-unsaturated carbonyl compound. Generally, bases are used to detach a proton from carbonyl group. A general mechanism of Michael type using β-dicarbonyl nucleophile is depicted in Scheme 11.



Scheme 11. Michael addition reaction

1.5 Aim of the work

After all the advantages of organocatalysts were invented, their usage has been dispersing in many areas. Among those, medicine is the most important field. High catalytic activities of organocatalysts enable many developments in the reaction parameters; such as short reaction time, high purity and low-cost area.

In this work, the aim was to develop a novel bifunctional organocatalyst system to be used in the asymmetric synthesis of warfarin. In the bifunctional organocatalyst design, we have chosen (*1R,2R*)-2-cyclohexane-1,2-diamine (**7**) as a chiral ligand which is very well known and widely used in asymmetric reactions.

In our research group Tanyeli *et al* achieved synthesis of (*1R,2R*)-2-aminocyclohexyl-dimethylpyridine-2,4-diamine (**8**) named as (1*R,2R)*-2-AminoDMAP *via* selective mono-*N*-pyridilization of (*1R,2R*)-cyclohexane-1,2-diamine (**7**) as shown in Figure 9. DMAP part of compound **8** has Lewis base character. In the construction of H-bond donor functionality, we planned to introduce L-proline unit. The rational bifunctional organocatalyst design is shown in Figure 10 as a retrosynthetic approach. After the synthesis of bifunctional proline-(1*R*,2*R*)-2-AminoDMAP **9** organocatalyst, catalytic activities of **8** and **9** are going to be tested in the asymmetric synthesis of warfarin. For this purpose, benzylideneacetone (**2**) and 4-hydroxycoumarin (**1**) will be used as Michael acceptor and as a nucleophile, respectively (Scheme 12). Moreover, many parameters are going to be tried to find the best result. These parameters are;

- Solvent screening
- Organocatalyst concentration
- Equivalence of reagents
- Temperature
- Cocatalyst

We also planned to test the catalytic activities of **9** on various Michael acceptors depicted in Figure 11.

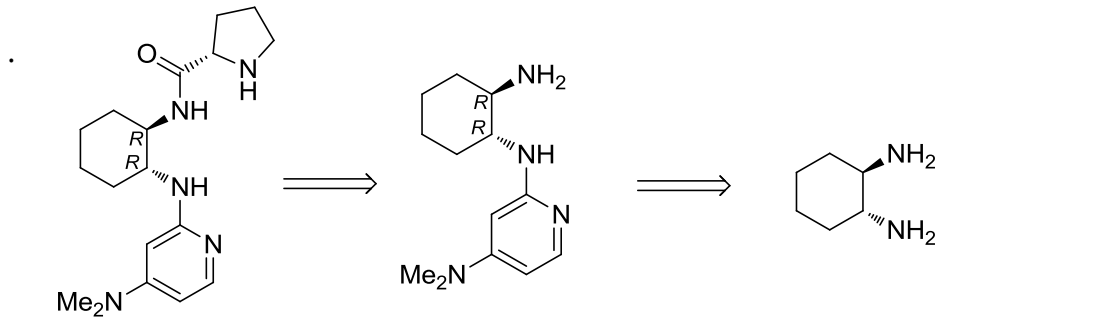


Figure 10. Retrostynthetic bifunctional organocatalyst design

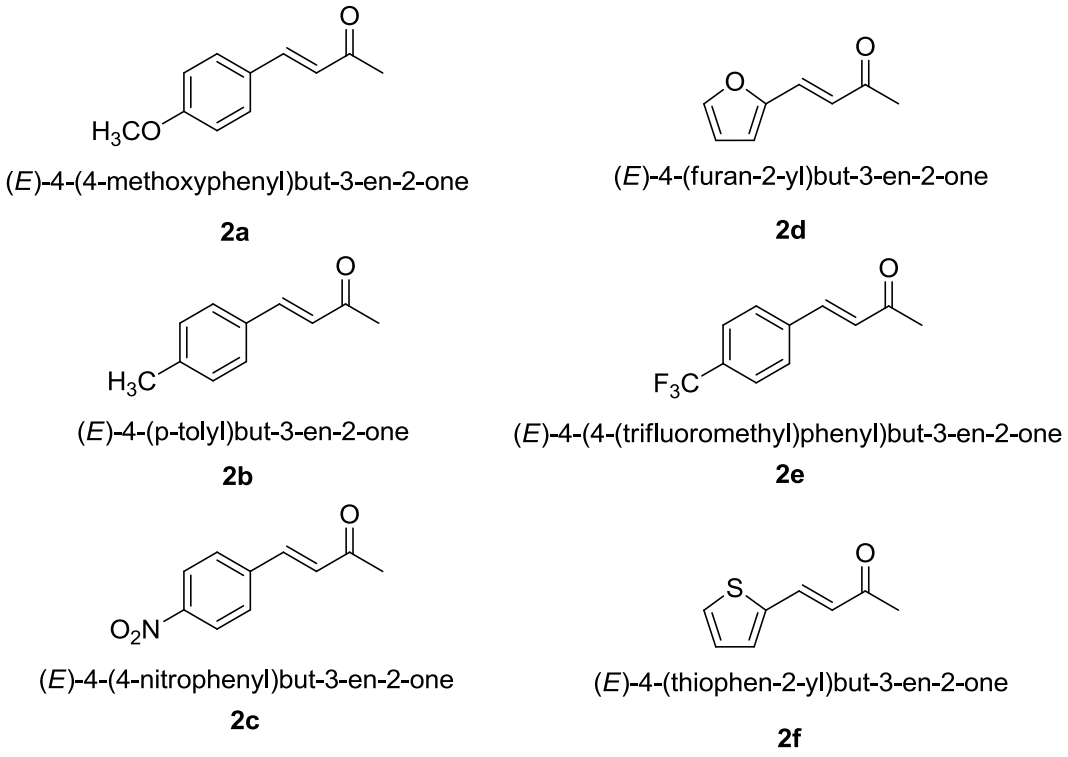
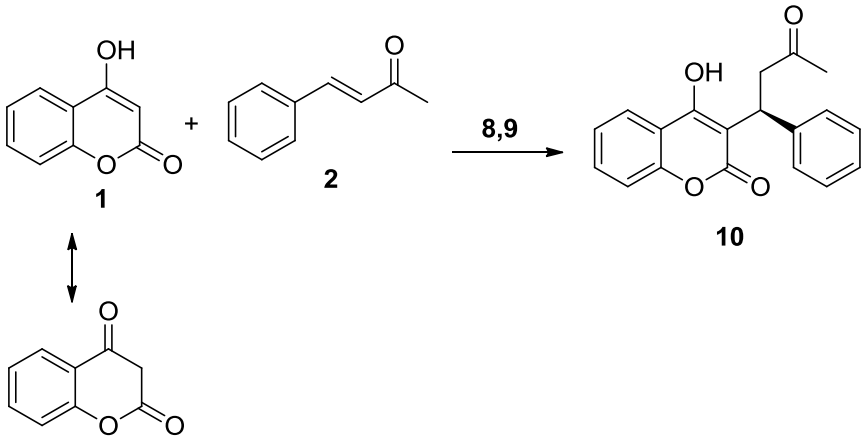


Figure 11. Michael acceptors



Scheme 12. Warfarin synthesis via asymmetric Michael reaction

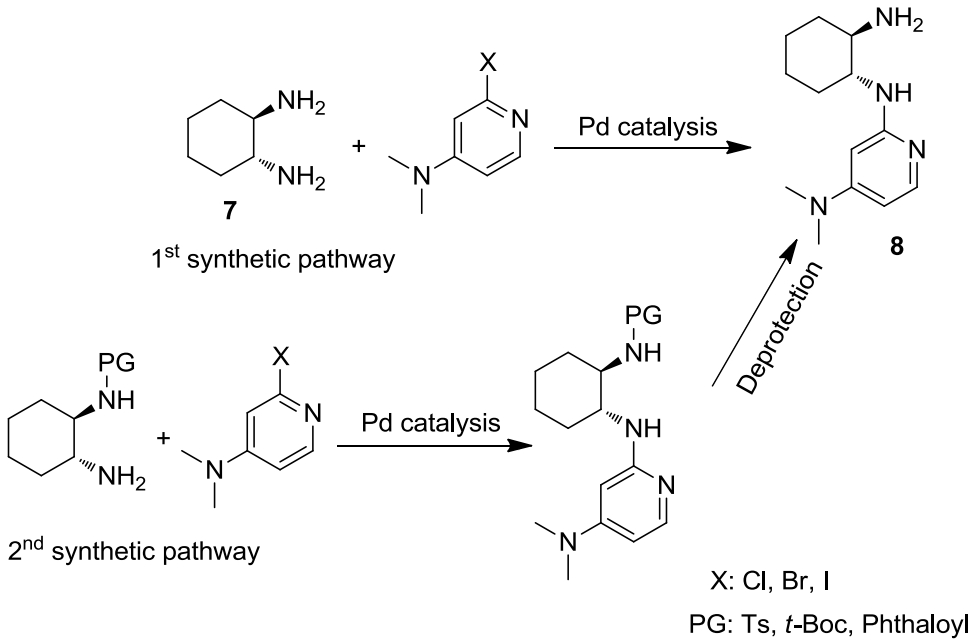
CHAPTER 2

RESULT AND DISCUSSION

2.1 Synthesis of Organocatalysts

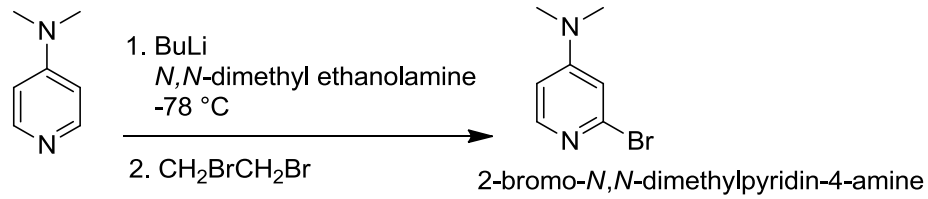
2.1.1 Synthesis of (1*R,2R)*-2-AminoDMAP 8

In our research group, two synthetic pathways were devised for the synthesis of (1*R,2R)*-2-AminoDMAP **8** (Scheme 13)**.** The first one comprised the direct palladium catalysed Buchwold-Hartwig *N*-arylation of the diamine with 2-haloDMAP [38-39]. At the same time, alternatively the mono protecting group approach was applied to synthesize target compound **8**. In this approach, diamine **7** was selectively protected by ts, *t*-Boc and phthaloyl units and subsequent Pd-catalyst pyridilization followed by deprotection to afford compound **8**. However, the conversion was considerably lower in both synthetic pathways.

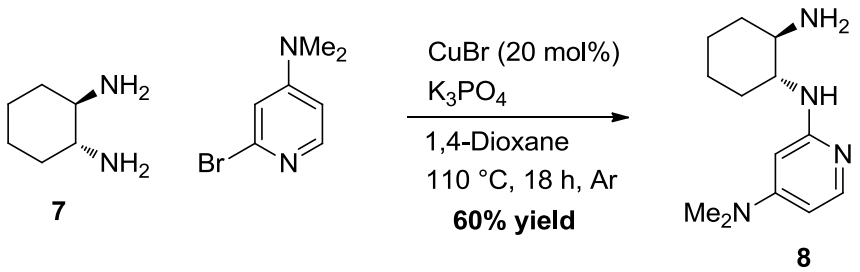


Scheme 13. Synthetic pathways for (1*R,2R)*-2-AminoDMAP **8**

Realizing unsatisfactory result with palladium chemistry, our group turned our attention to copper catalyst modified Ullmann coupling reaction and got satisfactory results. In the synthetic pathway, 2-bromo-*N*,*N*-dimethylpyridin-4-amine known as 2-BromoDMAP was synthesized via direct α-lithiation of 4-DMAP by using ligand *N*,*N*-dimethyl ethanolamine, BuLi as a base and dibromoethane as an electrophile at -78 °C under argon atmosphere by applying literature procedure (Scheme 14) [40]. Compound diamine **7** and 2-BromoDMAP underwent the coupling reaction in the presence of CuBr (20 mol %) and K_3PO_4 as base in 1,4-dioxane at 110 °C to afford (1*R*,*2R)*-2-AminoDMAP **8** in 60% chemical yield (Scheme 15) [41]. In this thesis, the same procedure was performed by using 2-bromo-*N*,*N*-dimethylpyridin-4-amine as DMAP moiety with $CuBr_2$ as copper catalyst in mono-*N*-pyridilization of (1*R*,2*R*)-cyclohexane-1,2-diamine (**7**). ^1H and ^{13}C NMR spectra of the final product were in complete accordance with that of literature [41].



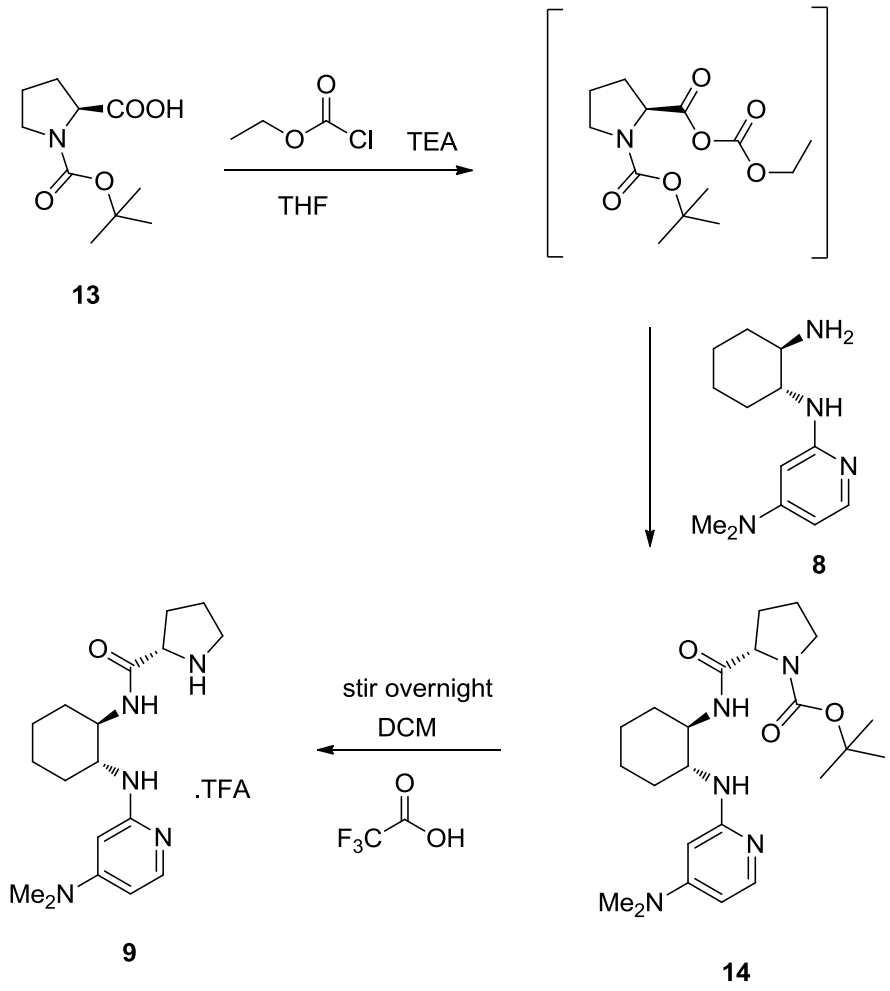
Scheme 14. 2-BromoDMAP synthesis



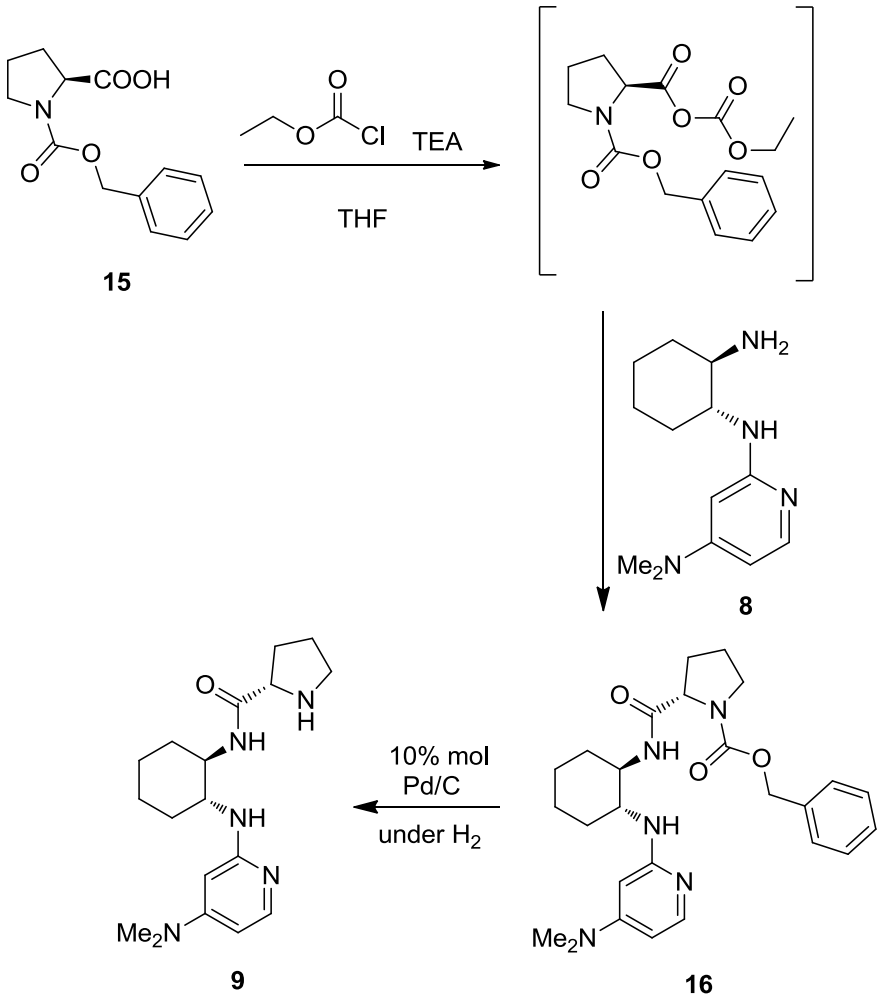
Scheme 15. (1*R*,*2R)*-2-AminoDMAP **8** synthesis

2.1.2 Synthesis of Proline-(1*R*,2*R*)-2-aminoDMAP 9 Bifunctional Organocatalyst

As mentioned above in ‘‘aim of the work’’ part of the thesis, main objective was to construct the novel bifunctional organocatalyst system having both Lewis base and H-bond donor units. So far, the Lewis base catalophic unit was constructed on the chiral backbone. We have chosen L-proline (**12**) unit as H-bond donor. For this purpose, L-proline (**12)** unit was protected with di-*tert*-butyl dicarbonate (Boc_2O) to prevent some possible side reactions. *T*-Boc protected L-proline (**13**) was *in situ* carbomylated with ethylcholoroformate under basic condition to activate the carboxylic acid unit and subsequently was reacted with (1*R,2R)*-2-AminoDMAP **8** to afford *t*-Boc protected (*S*)-*N*-((1*R*,2*R*)-2-((4-(dimethylamino)pyridin-2-yl)amino)cyclohexyl)pyrrolidine-2-carboxamide (**14**) with 75% yield (Scheme 16). The removal of *t*-Boc unit was performed with TFA in DCM [42-43]. Unfortunately, complete deprotection could not be accomplished. Therefore, we decided to change protecting group with the Carboxybenzyl unit known as Cbz group which is also one of the common protecting groups preventing side reactions. Cbz protected proline (**15**) was synthesized by the reaction of proline with benzyl chloroformate in the presence of a base [26]. By following the same procedure given in Scheme 16, Cbz protected proline-(1*R*,2*R*)-2-aminoDMAP **16** was obtained with 85 % (Scheme 17). The removal of Cbz unit was achieved by Pd(c) catalysed hydrogenation resulted in our target bifunctional organocatalyst **9** with 80 % yield [44].



Scheme 16. First synthetic pathway of proline-(1*R*,2*R*)-2-aminoDMAP **9**



Scheme 17. Second synthetic pathway of proline-(1*R*,2*R*)-2-aminoDMAP **9**

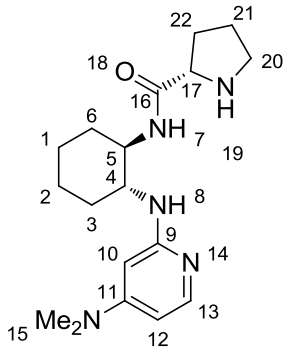


Figure 12. Proline-(1*R*,2*R*)-2-aminoDMAP **9**

The structure elucidation of bifunctional organocatalyst **9** as shown in Figure 12 was done by ^{1}H, ^{13}C NMR and also with full NMR analysis including DEPT, COSY, HSQC and HMBC. ^{13}C NMR shows that seventeen signals as expected. In ^{1}H NMR, signal of amide protons is observed at 7.87 ppm as broad doublet (J= 8.4 Hz). HSQC spectrum supports this observation (Figure 15). Moreover, the characteristic amide carbonyl unit resonates at 174.6 ppm in ^{13}C NMR. The amine protons in proline unit and DMAP attached one are observed at 2.04 and 4.61 ppm as doublet and broad singlet, respectively. DMAP unit protons are observed at 7.66 ppm as doublet (J= 6.2 Hz) for H_{13}, 5.90 ppm as doublet of doublets (J= 2.3 *and* 6.3 Hz) for H_{12}, and 5.45 ppm as broad singlet for H_{10}, respectively. HSQC results also confirm these observations. In COSY spectrum (Figure 13), the cross signals between 7.66 and 5.90 ppm indicates that the neighbouring positions of these protons H_{13} proton should resonate at relatively lower field due to the inductive effect of DMAP ring nitrogen. The signals of protons of ^{13}C, DEPT 90 and DEPT 135 help us to identify the exact position of carbon signals. From DEPT 90 spectrum (Figure 14), the signals observed at 59.6, 53.3 and 52.6 ppm belong to methine carbons C_4, C_5, C_{17}, respectively. The methine group of proline unit (H_{17}) is observed at 3.55 ppm. The other methine groups H_4 and H_5 are observed at 3.62 and 3.80 ppm, respectively in ^{1}H NMR. Their exact positions are proved by the HMBC spectrum (Figure 16). H_4 has attraction with a quaternary carbon (C_9) of DMAP and H_{17} has attraction with the carbonyl compound. DEPT 135 spectrum (Figure 14) shows the methylene carbon of proline unit next to the nitrogen (C_{20}) at 45.9 ppm. The diastereotopic methylene

protons (H_{20}) shift to low field due to the inductive effect of nitrogen atom resonated at 2.75-2.49 ppm as doublet of doublets (AB system). Methyl protons are resonated at 2.86 ppm as singlet. In HMBC spectrum, interaction between the characteristic methyl protons and the quaternary carbon of pyridine (C_{11}) indicates the exact position of C_{15} at 38.3 ppm. HRMS analysis verified the closed formula of bifunctional organocatalyst **25** as $C_{18}H_{29}N_5O$.

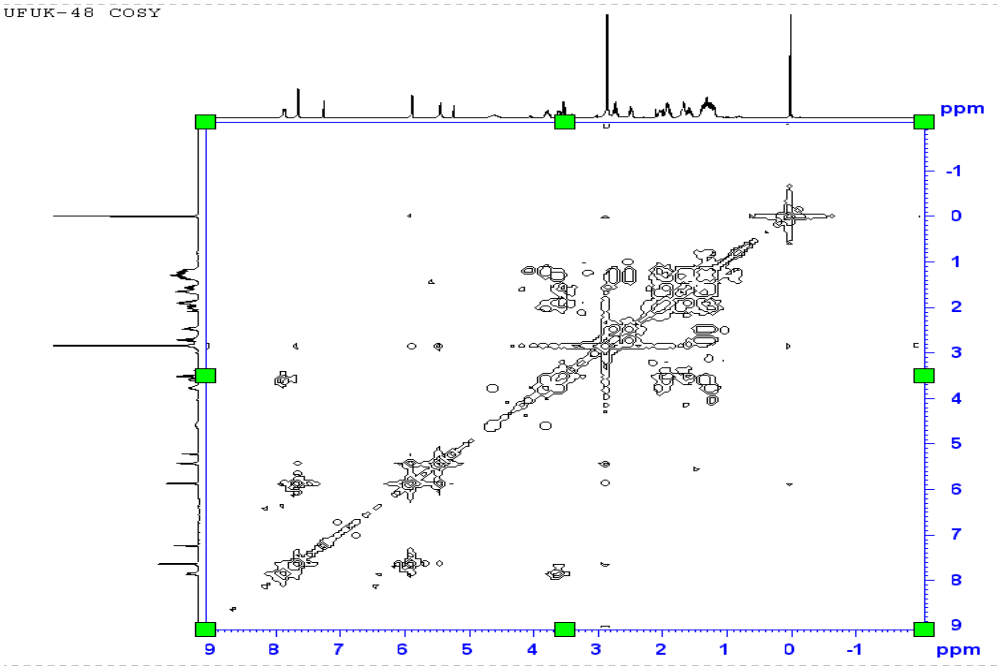


Figure 13. COSY NMR spectrum of organocatalyst **9**

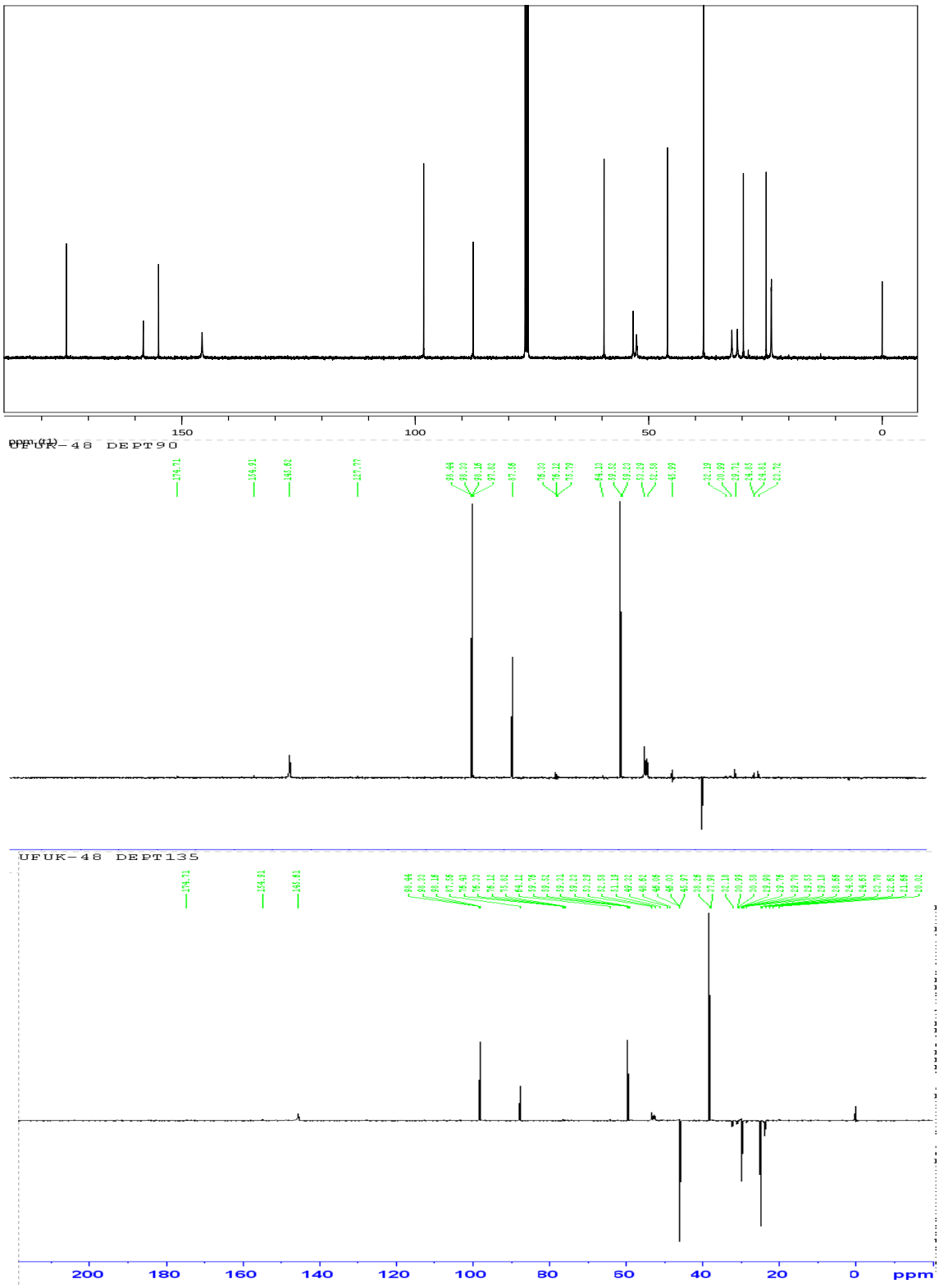


Figure 14. ^{13}C, DEPT-90 and DEPT-135 NMR spectrum of organocatalyst **9**

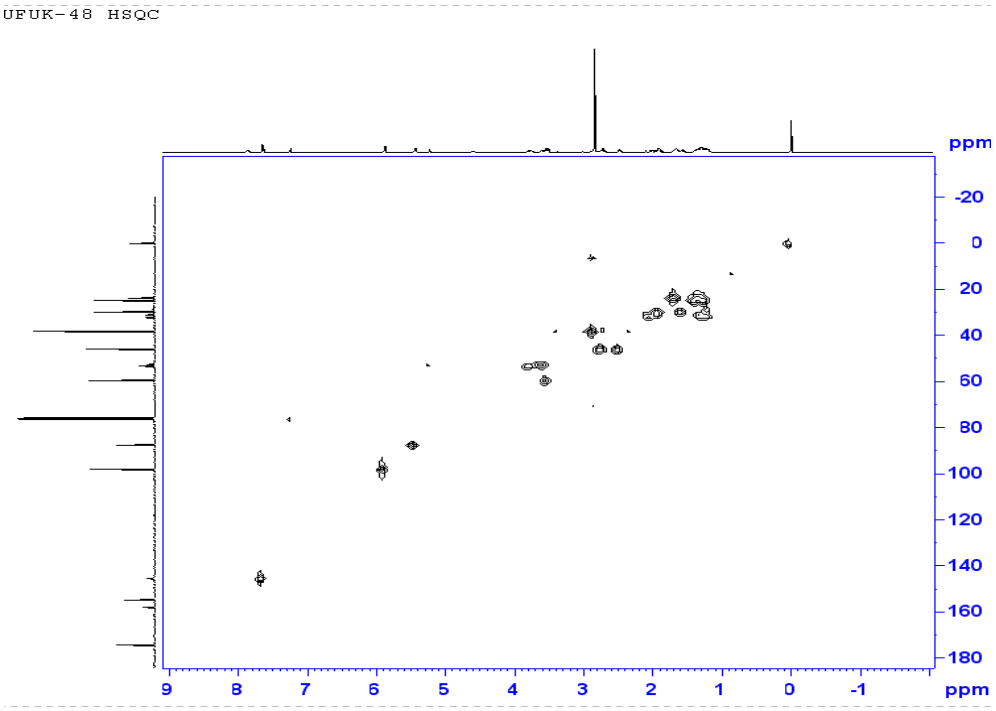


Figure 15. HSQC NMR spectrum of organocatalyst **9**

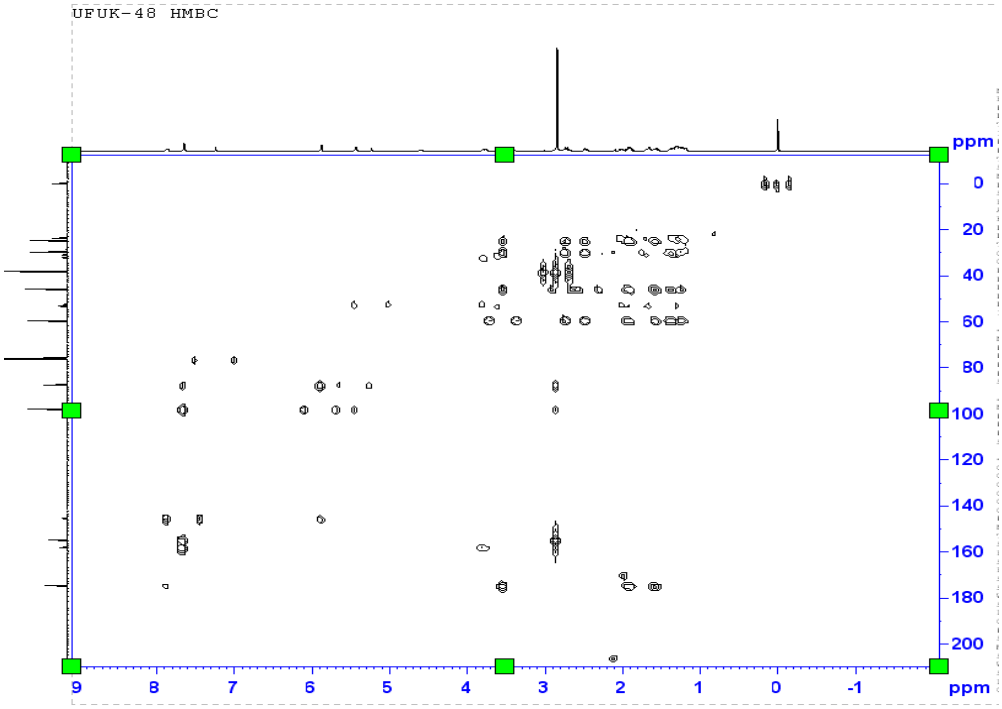
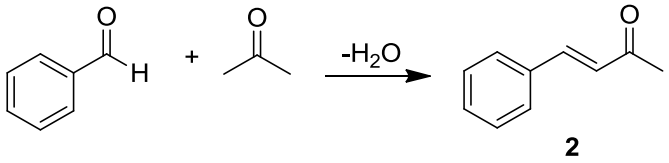


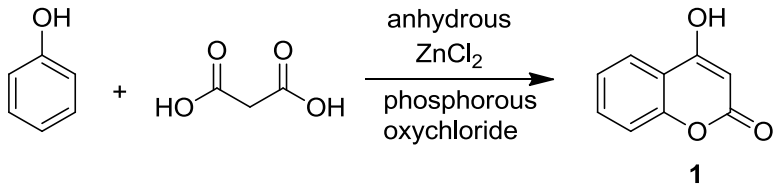
Figure 16. HMBC NMR spectrum of organocatalyst **9**

2.2 Asymmetric Synthesis of Warfarin

This part of thesis involves the application of (1*R*,*2R)*-2-AminoDMAP **8** and proline-(1*R*,2*R*)-2-aminoDMAP **9** as bifunctional organocatalysts in asymmetric synthesis of warfarin. Benzylideneacetone (**2**) was used as Michael acceptors synthesized by Claisen-Schmidt condensation between benzaldehyde and acetone as shown in Scheme 18 [45]. 4-Hydroxycoumarin (**1**) synthesized from phenol and malonic acid in the presence of anhydrous zinc chloride and phosphorous oxychloride (Scheme 18) [46], was used as a nucleophile. In asymmetric synthesis of warfarin, various parameters such as solvent screening, organocatalyst concentration equivalence of reagents, temperature and cocatalyst screening were tried to optimize the reaction condition as given below.



Scheme 18. Synthesis of benzylideneacetone (**2**)

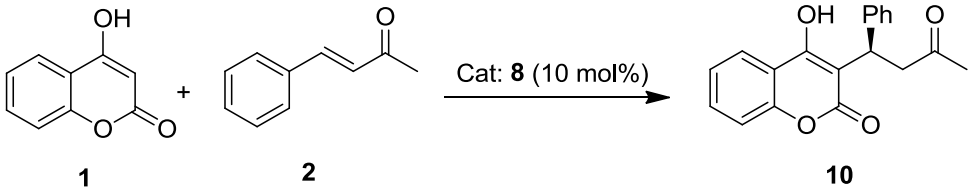


Scheme 19. Synthesis of 4-hydroxycoumarin (**1**)

In the first part, (1*R*,*2R)*-2-AminoDMAP **8** was used as bifunctional organocatalyst and the asymmetric trails were carried out in various solvent systems at ambient temperatures. The results are shown in Table 2. Moderate results were obtained using DCM and DCM-water (entries 1,4-6). as solvent systems. However, no conversion was observed by using DMSO, THF and toluene (entries 7-9). Water and TFA were used as additives with different ratios in some experiments.

Since, they could participate the iminium activation. Using 5 eq. water (entry 4) increases the enantiomeric excess and chemical yield, and decreases the reaction time with respect to entry 1. By increasing the amount of water up to 20 eq., the enantiomeric excess value decreased. On the other hand, no conversion was observed by using TFA (entries 2-3).

Table 2. Solvent screening studies with organocatalyst **8**[a]



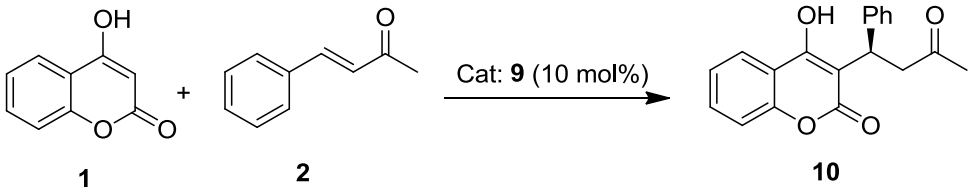
1 **2** **10**

Entry	Solvent	*t* [h]	yield [%]	*ee* [%]
1	DCM	120	70	22
2	DCM, 20% TFA	-	-	-
3	DCM, 40% TFA	-	-	-
4	DCM, 5 eq. Water	96	74	28
5	DCM, 10 eq. Water	96	77	23
6	DCM, 20 eq. Water	96	82	19
7	DMSO	-	-	-
8	THF	-	-	-
9	Toluene	-	-	-

[a] Reaction conditions: **8** (20 mol%), **1** (0.1 mmol), **2** (0.15 mmol), 2 mL solvent were stirred at ambient temperature for the time indicated. The crude mixture was then purified by column chromatography.

Due to the low ee values obtained by organocatalyst **8**, we turned our attention to proline-(1*R*,2*R*)-2-aminoDMAP **9**. Solvent screening results shown in Table 2 directed us to use DCM solvent systems. The results are summarized in Table 3. The first experiment (entry 1) was carried out in DCM without any additive and fortunately, after 96 h (*R*)-Warfarin (**10**) was isolated in 75% chemical yield with almost three fold increasing in ee as 64% comparing with the result obtained with organocatalyst **8** (22% ee). This promising result prompted us to search the effect of additives on enantioselectivity. For this purpose, 20% TFA was used as additive (entry 2), no conversion was observed. Instead of TFA, 5 eq. water was used (entry 3). Slight decreasing was observed in chemical yield and ee as 68% and 60%, respectively. We also checked the effect of concentration on enantioselectivity by decreasing the amount of solvent (entry 4). The reaction was stopped after 32 hours. The sharp decreasing was obtained in both chemical yield and ee value as 52% and 44%, respectively. By adding 5 eq. of water to the medium given in entry 4, slight decreasing in chemical yield and increasing in ee as 48% and 55%, respectively was observed.

Table 3. Solvent screening studies with organocatalyst **9**[a]



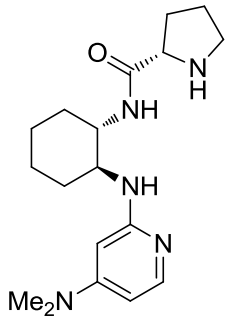
1 **2** **10**

Entry	Solvent	*t* [h]	yield [%]	*ee* [%]
1	2 mL DCM	96	75	64
2	2 mL DCM, 20% TFA	-	-	-
3	2 mL DCM, 5 eq. Water	96	68	60
4	1 mL DCM	32	52	44
5	1 mL DCM, 5 eq. water	32	48	55

[a] Reaction conditions: **9** (20 mol%), **1** (0.1 mmol), **2** (0.15 mmol), given amount of solvent were stirred at ambient temperature for the time indicated. The crude mixture was then purified by column chromatography.

At this point, since our catalyst system **9** consists of two different chiral ligand sources as (1*R*,2*R*)-cyclohexane-1,2-diamine (**7**) and L-proline (**12**), this combination may show mismatching properties. In order to be sure whether mismatching is present or not, the diastereomeric form of bifunctional organocatalyst **9** was synthesized with the synthetic pathway as depicted in Scheme 17 by replacing (1*R*,2*R*)-cyclohexane-1,2-diamine (**7**) with (1*S*,2*S*)-cyclohexane-1,2-diamine (**17**). The results obtained by using bifunctional organocatalyst (*S*)-*N*-((1*S*,2*S*)-2-((4-(dimethylamino)pyridin-2-yl)amino)-cyclohexyl)pyrrolidin2-carboxamide (**18)** (Figure 17) are given in Table 4.

In the first experiment, the asymmetric reaction was carried out just in 2 mL of DCM and stopped after 96 h (entry 1). By comparing the results obtained with organocatalyst **9**, increasing the chemical yield from 75% to 81%, whereas, sharp decreasing in enantioselectivity from 64% to 23% were observed. Further trials were performed in the presence of 3,5-Dinitrobenzoic acid used as additive (entry 2) in polar aprotic solvent DMSO (entry 3) and in polar protic MeOH (entry 4). In all three cases, very good chemical yields varied between 91-94% but very low enantioselectivities were obtained. These results show that no mismatching property is present in the structure of bifunctional organocatalyst (*S*)-*N*-((1*R*,2*R*)-2-((4-(dimethylamino)pyridin-2-yl)amino)-cyclohexyl)pyrrolidine-2-carboxamide (**9**).



18

Figure 17. Proline-(1*S*,2*S*)-2-aminoDMAP **18**

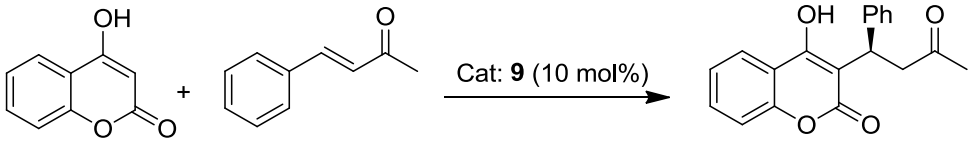
Table 4. Solvent screening studies with organocatalyst **18**[a]

Entry	Solvent	*t* [h]	yield[%]	*ee* [%]
1	DCM	96	81	23
2	DCM, 3,5-Dinitro benzoic acid	96	91	21
3	DMSO	96	91	7
4	MeOH	96	94	1

[a] Reaction conditions: **18** (20 mol%), **1** (0.1 mmol), **2** (0.15 mmol), 2 mL solvent were stirred at ambient temperature for the time indicated. The crude mixture was then purified by column chromatography.

Optimization studies continued with the screening of various equivalences of 4-hydroxycoumarin (**1**) and benzylideneacetone (**2**) in DCM (1 mL) at ambient temperature. All reactions were performed with 10 mol% of organocatalyst **9**. By comparing the results given in Table 5, the best condition was obtained with 0.1 mmol of 4-hydroxycoumarin (**1**) and 0.3 mmol benzylideneacetone (**2**) (entry 4). The reaction was completed after 26 h with quite high chemical yield (90%) and 64% ee. This equivalence ratio drastically decreases the reaction time comparing with the former results. This promising finding directed us to recheck the effect of solvent on the chemical yield and enantioselectivity. All the results are summarized in Table 6. Among the solvents, DCM, $CHCl_3$, 1,2-dichloroethane (entries 1, 8 and 15 respectively) gave the best results in terms of enantioselectivity. However, DCM was chosen as the solvent for further screening studies due to easily availability and low cost.

Table 5. Reactant equivalence screening studies[a]

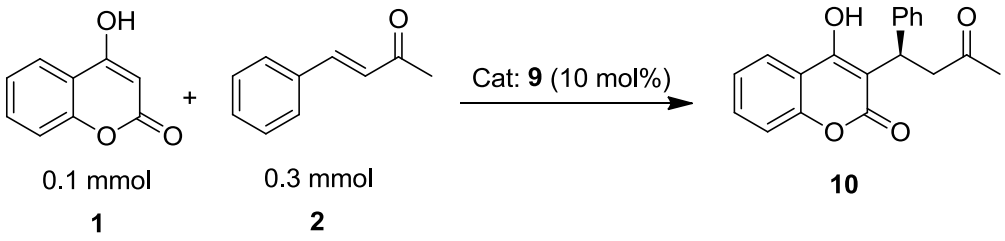


1 **2** **10**

Entry	1 [mmol]	2 [mmol]	*t* [h]	yield [%]	*ee* [%]
1	0.3	0.1	135	91	65
2	0.1	0.15	48	92	61
3	0.15	0.1	135	91	63
4	0.1	0.3	26	90	64

[a] Reaction conditions: **9** (10 mol%), given amounts of reactants, 1 mL DCM were stirred at ambient temperature for the time indicated. The crude mixture was then purified by column chromatography.

Table 6. Solvent screening studies[a]



Entry	Solvent	*t* [h]	yield [%]	*ee* [%]
1	DCM	26	90	64
2	EtOAc	23	92	57
3	Acetone	260	70	33
4	MeOH	140	91	22
5	H_2O	40	65	38
6	Toluene	27	64	52
7	THF	27	65	47
8	$CHCl_3$	27	80	62
9	1,2-dibromoethane	96	75	39
10	DMSO	35	65	25
11	DMF	27	80	23.5
12	Benzene	27	75	40
13	BTF	27	92	45
14	Chlorobenzene	27	90	61
15	1,2-dichloroethane	26	90	63.5

[a] Reaction conditions: **9** (10 mol%), **1** (0.1 mmol), **2** (0.3 mmol), 1 mL solvent were stirred at ambient temperature for the time indicated. The crude mixture was then purified by column chromatography.

The next attempt in the screening studies was the temperature parameter the optimum temperature was found as 10 °C. Under this condition, (*R*)-Warfarin (**10**) was isolated with 85% chemical yield and 70% ee after 48 h. (Table 7, entry 3).

Table 7. Temperature screening studies[a]

Entry	Temp [°C]	*t* [h]	yield [%]	ee [%]
1	R T	26	90	64
2	15	42	86	65
3	10	48	85	70
4	5	90	82	67
5	0	120	78	68

[a] Reaction conditions: **9** (10 mol%), **1** (0.1 mmol), **2** (0.3 mmol), 1 mL DCM were stirred at given temperature for the time indicated. The crude mixture was then purified by column chromatography.

In the optimization studies, we also screened the effect of cocatalyst as acid donor source. For this purpose, 3,5-Dinitrobenzoic acid was chosen as the model cocatalyst to find out best cocatalyst equivalency which was found as 10 mol% (Table 8, entry 2). Different cocatalysts were screened with 10 mol% equivalency as shown in Table 9. β-naphtol afforded the best result in terms of chemical yield and enantioselectivity as 94% and 64.5%, respectively (entry 6).

Table 8. Cocatalyst equivalency screening with 3,5-dinitrobenzoic acid[a]

Entry	Eq. [%]	*t* [h]	yield [%]	ee [%]
1	5	60	80	59
2	10	64	84	60
3	15	96	85	54

[a] Reaction conditions: **9** (10 mol%), **1** (0.1 mmol), **2** (0.3 mmol), given amount of 3,5-dinitrobenzoic acid, 1 mL DCM were stirred at ambient temperature for the time indicated. The crude mixture was then purified by column chromatography.

Table 9. Cocatalyst screening studies[a]

Entry	Cocatalyst	*t* [h]	yield [%]	ee [%]
1	3,5-Dinitrobenzoic acid	60	84	60
2	TFA	53	75	61
3	Benzoic acid	48	88	62
4	Picric acid	40	96	57.5
5	α- naphtol	40	93	60
6	β- naphtol	40	94	64.5
7	phenol	40	91	63
8	Acetic acid	-	-	-
9	(*R*)-Binaphtol	70	82	61

[a] Reaction conditions: **9** (10 mol%), **1** (0.1 mmol), **2** (0.3 mmol), 10% eq. cocatalyst, 1 mL DCM were stirred at ambient temperature for the time indicated. The crude mixture was then purified by column chromatography.

The evolution of results obtained so far showed that the best condition comprises 10 mol% organocatalyst loading, 4-hydroxycoumarin (**1**): benzylideneacetone (**2**) ratio as 1:3, 10% equivalency of β-naphtol as cocatalyst in DCM at 10 °C. Further screening studies on cocatalyst equivalency and temperature parameter have been carrying out with β-naphtol cocatalyst as H-donor source. The results are shown in Table 10. First, the amount of cocatalyst was drastically decreased to 2.5% eq. and the reactions were performed at 10 °C and RT, respectively (entries 1 and 2). (*R*)-Warfarin (**10**) was isolated with 74% chemical yield and 69.5% ee value, whereas, ee value was measured as 63.5% in entry 2. Although, almost 5% increasing in ee value was observed in entry 1 by comparing with the result given in Table 9, entry 6, lowering the cocatalyst caused sharp decreasing in terms of chemical yield (74% vs 94%). The second set of trials was performed with 5% eq. of cocatalyst (entries 3-4). (*R*)-Warfarin (**10**) was isolated 85% chemical yield having 68% ee.

Doing the same comparison with the result given in Table 9, entry 6, no promising results were obtained. In the final set trials, cocatalyst was used as 10% eq. and the reactions were conducted at 10 °C, 15 °C and RT, respectively (entries 5-7). Among these, the best result was obtained in terms of ee as 72%.

Table 10. Cocatalyst and temperature screening studies on asymmetric warfarin synthesis[a]

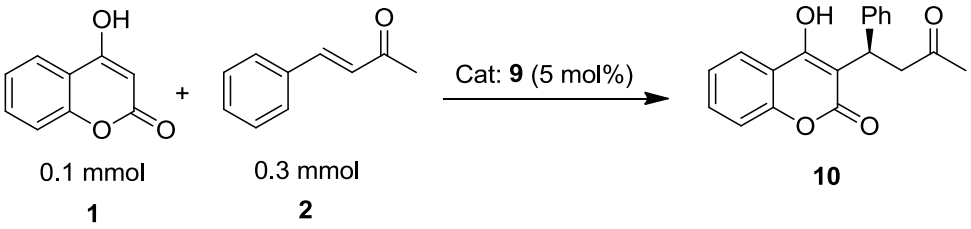
Entry	Cocatalyst eq. [%]	Temp [°C]	*t* [h]	yield [%]	ee [%]
1	2.5	10	46	74	69.5
2	2.5	RT	28	78	63.5
3	5	10	50	75	65
4	5	RT	30	85	68
5	10	10	55	80	72
6	10	15	45	88	67
7	10	RT	40	94	64

[a] Reaction conditions: **9** (10 mol%), **1** (0.1 mmol), **2** (0.3 mmol), given amount of β-naphtol, 1 mL DCM were stirred at given temperature for the time indicated. The crude mixture was then purified by column chromatography.

The last part of studies involved the 5 mol% (*S*)-*N*-((1*R*,2*R*)-2-((4-(dimethylamino)pyridin-2-yl)amino)cyclohexyl)pyrrolidine-2-carboxamide (**9**) trials in the asymmetric warfarin synthesis. The results are summarized in Table 11. In entries 1 and 2, the reactions were carried out at 10 °C and RT without any cocatalyst and 70% and 64.5% ee values were measured. In the presence of various amounts of cocatalyst β-naphtol, 2.5-10% eq, the ee values of (*R*)-Warfarin (**10**) were measured as 65%, 63% and 71.5%, respectively (entries 3-5). The best ee value was indicated as 71.5% among the all screening results. Further studies done with various Michael acceptors synthesized by Claisen-Schmidt condensation [45] were performed by using the best condition mentioned above.

The results are shown in Table 12. Complete conversions were obtained in all trials. Among them, the best result using (*E*)-4-(furan-2-yl)but-3-en-2-one as Michael acceptor was obtained in terms of ee as 69% (entry 3).

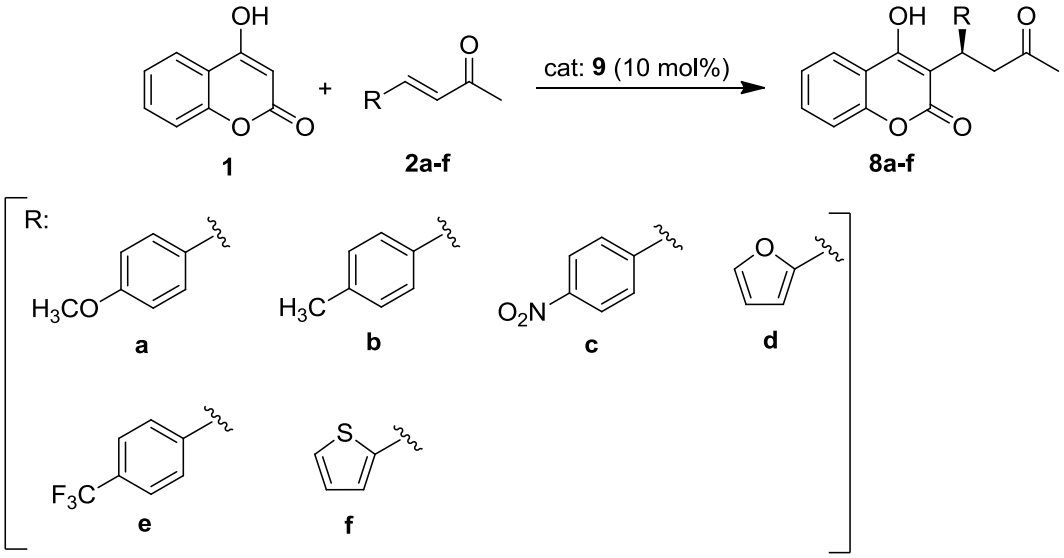
Table 11. Cocatalyst and temperature screening studies with diluted organocatalyst **7**[a]



Entry	Cocatalyst	Temp [°C]	*t* [h]	yield [%]	ee [%]
1	-	10	96	75	70
2	-	RT	60	80	64.5
3	2.5% β-naphtol	RT	45	86	65
4	5% β-naphtol	10	86	88	63
5	10% β-naphtol	10	90	78	71.5
6	10% β-naphtol	RT	50	90	67

[a] Reaction conditions: **9** (10 mol%), **1** (0.1 mmol), **2** (0.3 mmol), given amount of β-naphtol, 1 mL DCM were stirred at given temperature for the time indicated. The crude mixture was then purified by column chromatography.

Table 12. Michael acceptor screening studies[a]



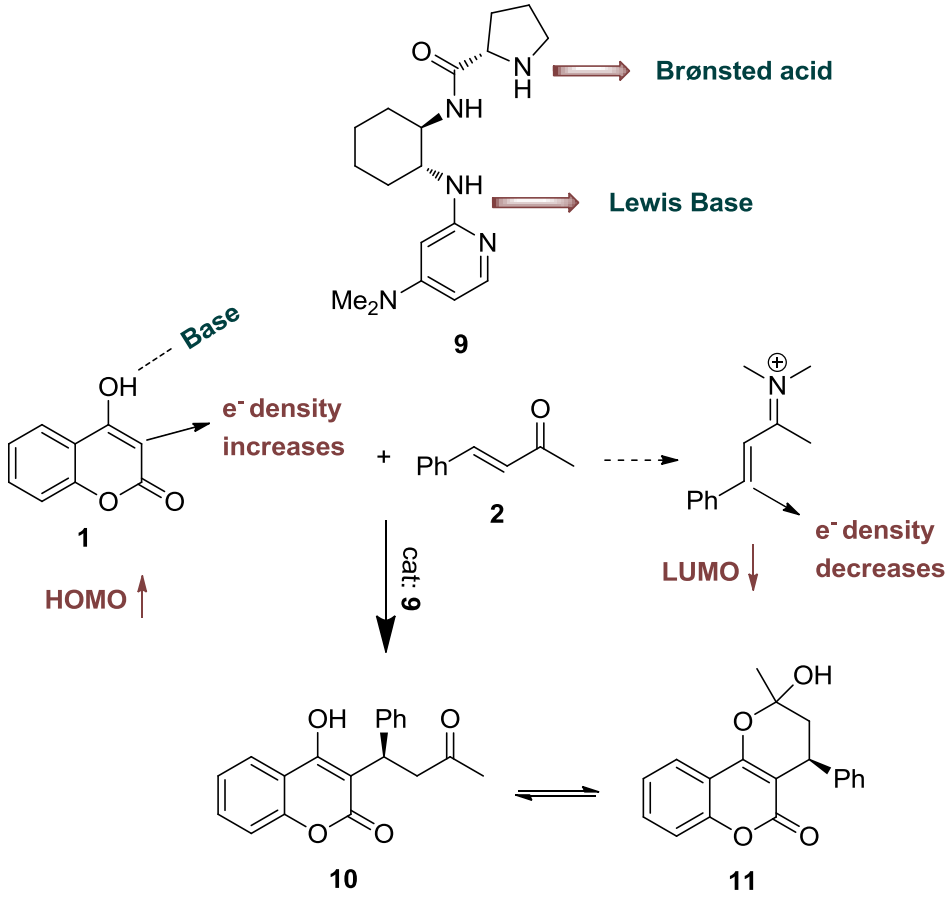
Entry	Michael acceptors	products	*t* [h]	ee [%]
1	2a	8a	68	63.5
2	2b	8b	89	58.5
3	2c	8c	117	60
4	2d	8d	135	69
5	2e	8e	86	63
6	2f	8f	65	58

[a] Reaction conditions: **9** (10 mol%), **1** (0.1 mmol), **2** (0.3 mmol), 10% eq. of β-naphtol, 1 mL DCM were stirred at 10°C for the time indicated. The crude mixture was then purified by column chromatography.

CHAPTER 3

CONCLUSION

In this study, bifunctional (1*R*,2*R*)-2-AminoDMAP **8** organocatalyst was synthesized by Tanyeli *et al*. via selective mono-*N*-pyridilization of trans-(1*R*,2*R*)-cyclohexane-1,2-diamine (**7**) by Cu catalysis and showed moderate results (28% ee) in asymmetric warfarin synthesis via Michael addition reaction. The novel bifunctional proline-(1*R*,2*R*)-2-aminoDMAP **9** organocatalyst having both Lewis base and H-bond donor units was synthesized.



Scheme 20. Iminium and enamine catalysis in asymmetric synthesis of warfarin

In asymmetric synthesis of warfarin, enamine activates the HOMO of 4-hydroxycoumarin (**1**) and iminium intermediate decreases the energy level LUMO of benzylideneacetone (**2**). So that 4-hydroxycoumarin (**1**) easily underwent the Michael addition reaction with benzylideneacetone (**2**) (Scheme 20). Enantiomeric excesses (ee) up to 72% were attained for this asymmetric reaction at 55 h. Same experiment was performed by Jorgensen *et al*. utilizing their organocatalyst under identical conditions and got up to 85% ee at 160 h. In his study, warfarin was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form **11** in solution [47]. Furthermore, various asymmetric warfarin derivatives were synthesized via Michael addition reaction with different α,β-unsaturated ketones as Michael acceptor and showed promising results varied between 58-69% ee.

APPENDIX A

EXPERIMENTAL

In this work, we required some instruments and materials that given below, for the purification and characterization studies.

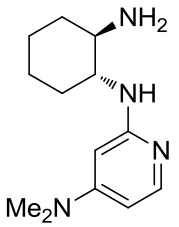
Bruker DPX 400 spectrometer was used to record ^{1}H-NMR and ^{13}C-NMR spectra in $CDCl_3$ (triplet centered at 77.0 ppm at 100 MHz) Chemical shifts are represented as ppm and tetramethylsilane as an internal standard is in downfield. Spin multiplicities are expressed as; s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad).

Rudolph Research Analytical Autopol III, automatic polarimeter was used for measuring Optical rotations. And Mel-Temp 1002D for determining melting points. ThermoFinnigan Spectra System instrument was used for HPLC measurements Separations were performed with Chiralcel AD analytical column (250 x 4.60 mm) with hexane/2-propyl alcohol/TFA (70:30:0.1) as eluent.

Flash column chromatography was fulfilled by employing thick-walled glass columns with a flash grade silicagel (Merck Silica Gel 60, particle size: 0.040-0.063 mm, 230-400 mesh ASTM). UV-light visualizes reactions with helping thin layer chromatography that employs pre-coated silica gel plates (Merck Silica Gel PF-254). In addition, generally EtOAc/hexane and DCM/MeOH solvent systems are performed in TLC and flash column chromatography. Finally, magnesium sulphate and sodium sulphate were used to dry the extracts, after rotary evaporator is used to concentrate the solutions.

Only characterization data of novel compounds are given in experimental section and related literature is cited.

4.1. Synthesis of N^2-((1*R*,2*R*)-2-aminocyclohexyl)-N^4,N^4-dimethylpyridine-2,4-diamine (8)



8

To a resealable dry Schlenk tube, CuBr (200.8 mg, 1.4 mmol) and K_3PO_4 (2.97 g, 14 mmol) was added, evacuated and backfilled with argon twice. 4-BromoDMAP (1.4 g, 7 mmol), (*1R,2R*)-cyclohexane-1,2-diamine (**7**) (960 mg, 8.4 mmol) and dioxane, distilled over Na-benzophenone under argon atmosphere (7.0 mL) was added under Schlenk line. The mixture was stirred at 110 ^oC. After 18 hours, the green-brown heterogeneous mixture was cooled to room temperature. Then it was washed with DCM twice (2x30 mL), filtered and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel by using successively DCM saturated with NH_3, DCM saturated with NH_3/MeOH (95:5) solvent systems. The brownish solid product was obtained (60% yield).

Mp: 138-140 ^oC

$[\alpha]_D^{31}$ -55 ° (*c* 0.25, CH_2Cl_2)

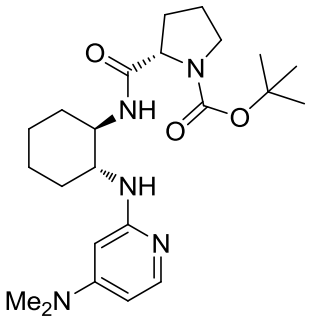
^1H NMR (400 MHz, $CDCl_3$) δ 1.09 - 0.93 (m, 1H), 1.09 - 1.43 (m, 4H), 1.65 (dd, *J* = 2.5, 10.0 Hz, 2H), 1.75 (bs, 2H), 1.85 – 1.95 (m, 1H) 1.97 - 2.07 (m, 1H), 2.41 (dt, *J* = 4.1, 10.4 Hz, 1H), 2.87 (s, 6H), 3.24 (dq, *J* = 4.0, 9.6 Hz, 1H), 4.15 (d, *J* = 9.5 Hz, 1H), 5.53 (d, *J* = 2.2 Hz, 1H), 5.91 (dd, *J* = 2.3, 6.1 Hz, 1H), 7.69 (d, *J* = 6.1 Hz, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.1, 25.4, 32.9, 34.9, 39.2, 56.3, 58.4, 87.8, 99.2, 148.0, 156.1, 160.1.

IR (neat) 3321, 3254, 2922, 2854, 1599, 1527,I 1495, 1444, 265, 1145, 979, 964, 804.

HRMS (ESI) calculated for $C_{13}H_{22}N_4$ $[M + H]^+$ 235.1923, found 235.1918.

4.2. Synthesis of (*S*)-tert-butyl 2-(((1*R*,2*R*)-2-((4-(dimethylamino)pyridin-2-yl)amino)cyclohexyl)carbamoyl)pyrrolidine-1-carboxylate (14)



14

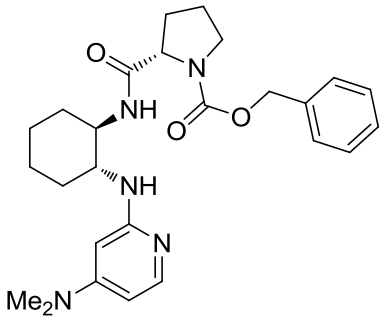
To a 100 mL flask, t-Boc protected proline **13** (210 mg, 1 mmol) within 10 mL THF was added at 0 ^oC. Then successively triethylamine (92 μL, 1 mmol) and ethyl choloroformate (135 μL, 1 mmol) was added. After 90 minutes, (1*R*,2*R*)-2-aminoDMAP **8** (234 mg, 1 mmol) was added within 3 mL THF. 30 minutes later the combined organic phase was washed with a saturated aqueous $NaHCO_3$ (10 mL). EtOAc (3x30 mL) was utilized to extract the aqueous phase. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel by successively EtOAc, EtOAc/TEA (99:1), EtOAc/TEA (98:2) solvent systems. Brownish solid product was obtained (75% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 1.08 – 1.34 (m, 6H), 1.40 (s, 9H), 1.69 (bs, 2H), 1.86 – 2.03 (m, 2H), 2.16 (d, 1H), 2.85 (s, 6H), 2.96 (dd, *J* = 13.6, 24.0 Hz, 1H), 3.16 (bs, 1H), 3.47 (bs, 1H), 3.82 (bs, 1H), 3.94 - 4.09 (m, 2H), 5.39 (s, 1H), 5.85 – 5.94 (m, 1H), 7.54 (bs, 1H), 7.72 (bs, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.4, 24.8, 25.6, 28.6, 31.4, 32.4, 33.7, 39.3, 47.1, 53.3, 56.9, 61.4, 80.0, 88, 8, 96.3, 99.8, 145.1, 155.9, 159.9, 172.69.

HRMS (ESI) calculated for $C_{23}H_{38}N_5O_3$ $[M + H]^+$ 432.2975, found 432.2963.

4.3. Synthesis of (*S*)-benzyl 2-(((1*R*,2*R*)-2-((4-(dimethylamino)pyridin-2-yl)amino)cyclohexyl)carbamoyl)pyrrolidine-1-carboxylate (**16**)



16

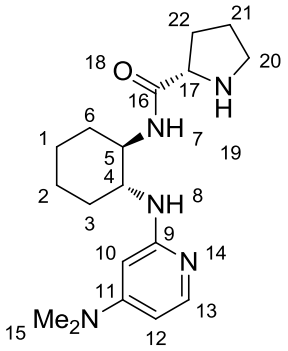
To a 100 mL flask, compound **15** (311.4 mg, 1.25 mmol) within 10 mL THF was added at 0 ^{o}C. Then successively triethylamine (118 μL, 1.25 mmol) and ethyl choloroformate (174.4 μL, 1.25 mmol) was added. After 2h, (1*R*,2*R*)-2-aminoDMAP **8** (234 mg, 1 mmol) was added within 5 mL THF. 45 minutes later the mixture was washed with saturated $NaHCO_3$ (15 mL). EtOAc (3x30 mL) was utilized to extract the aqueous phase. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using successively EtOAc, EtOAc/TEA (99:1), EtOAc/TEA (98:2) solvent systems. White solid product was obtained (85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (bs, 1H), 1.17 – 1.30 (m, 4H), 1.58 (d, *J* = 48.9 Hz, 3H), 1.81 (s, 1H), 1.92 – 2.01 (m, 4H), 2.81 (s, 6H), 3.07 (s, 1H), 3.29 (dd, *J* = 22.6, 44.4 Hz, 2H), 3.76 (s, 1H), 3.99 – 4.29 (m, 2H), 4.89 – 5.22 (m, 2H), 5.40 (d, *J* = 29.8 Hz, 1H), 5.79 – 5.96 (m, 1H), 7.23 – 7.33 (m, 5H), 7.57 (s, 1H), 7.69 (dd, *J* = 5.7 - 10.1 Hz, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.1, 23.3, 23.5, 24.3, 32.5, 38.1, 52.0, 57.3, 60.1, 62.3, 65.8, 98.4, 98.9, 102.8, 126.8, 127.4, 135.6, 146.2, 146.7, 154.7, 158.7, 171.4.

HRMS (ESI) calculated for $C_{26}H_{35}N_5O_3$ $[M + H]^+$ 466.2818, found 466.2831.

4.4. Synthesis of (*S*)-N-((1*R*,2*R*)-2-((4-(dimethylamino)pyridin-2-yl)amino) cyclohexyl) pyrrolidine-2-carboxamide (**9**)



9

To a 25 mL flask, evacuated and backfilled with argon twice, compound **15** (318 mg, 0.677 mmol) was added within 10 mL MeOH. Then 10% Pd/C (72 mg, 0.0677 mmol) was added to the flask, flushed with H_2 gas to replace with argon. Then the mixture was stirred at overnight. In filtration process, the celite was used to remove Pd/C from the solution, and MeOH was used to wash the solution then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel by using successively DCM, DCM/DCM-MeOH-NH_3 (90:9:1) (50:50), DCM-MeOH-NH_3 (90:9:1) solvent systems. White solid product was obtained (80% yield).

Mp: 112-114 °C

$[\alpha]_D^{31}$ -10.5 ° (*c* 0.25, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 – 1.17 (m, 7H), 169 – 1.53 (m, 3H), 1.95 – 1.86 (m, 2H), 2.02 (d, *J* = 12.9 Hz, 1H, H_{19}), 2.47 (dt, *J*AB = 6.4, 10.1 Hz, 1H, H_{20}), 2.72 (dt, *J*AB = 10.1, 6.7 Hz, 1H, H_{20}), 2.84 (s, 6H, H_{15}), 3.53 (dd, *J* = 5.3, 9.2 Hz, 1H, H_{17}), 3.60 (ddd, *J* = 4.9, 9.9, 14.8 Hz, 1H, H_4), 3.79 (ddd, *J* = 4.0, 10.5, 18.7 Hz, 1H, H_5), 4.61 (bs, 1H, H_8), 5.45 (s, 1H, H_{10}), 5.90 (dd, *J* = 2.3, 6.2 Hz, 1H, H_{12}), 7.65 (d, *J* = 6.2 Hz, 1H H_{13}), 7.88 (d, *J* = 8.4 Hz, 1H, H_7)

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.7, 24.8, 28.6, 29.7, 31.0, 32.1, 38.2, 45.9, 52.9, 53.3, 59.5, 87.5, 98.1, 145.6, 154.9, 158.2, 174.6.

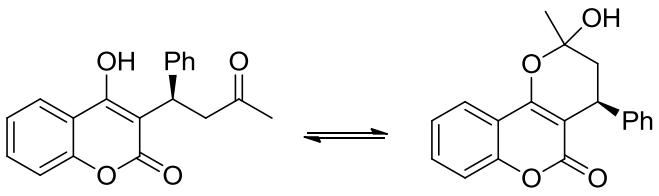
IR (neat) 3284, 2925, 2853, 1603, 1523, 1290, 1164.

HRMS (ESI) calculated for $C_{18}H_{30}N_5O$ $[M + H]^+$ 332.2455, found 332.2450.

4.5. General procedure for the synthesis of Michael acceptors [45]

To a 100 mL flask, a solution of the aldehyde (50 mmol) within 10 mL acetone (137.5 mmol) and 5 mL H_2O was added. Then 2.5 mL of aqueous NaOH (10%) was added dropwise within 30 min at 0°C. The reaction mixture was stirred at room temperature until complete disappearance of the starting material. Then aqueous HCl (1 N) was added, adjusted the pH to 4, and extracted by DCM. The combined organic phase was washed successively with a saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel by using EtOAc/hexane solvent systems. Spectroscopic data of Michael acceptors synthesized in this part, (*E*)-4-phenylbut-3-en-2-one (**2**) [45], (*E*)-4-(4-methoxyphenyl)but-3-en-2-one (**2a**) [45], (*E*)-4-(p-tolyl)but-3-en-2-one (**2b**) [45], (*E*)-4-(4-nitrophenyl)but-3-en-2-one (**2c**) [48], (*E*)-4-(furan-2-yl)but-3-en-2-one (**2d**) [45], (*E*)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one (**2e**) [49] and (*E*)-4-(thiophen-2-yl)but-3-en-2-one (**2f**) [45] are all in accordance with the literature as given above.

4.6. General procedure for asymmetric synthesis of warfarin via Michael addition reaction



To a dry Schlenk tube, a solution of 4-hydroxycoumarin (**1**) (16.2 mg, 0.1 mmol), α,β-unsaturated ketone **2-2f** (0.3 mmol), within 1 mL DCM, bifunctional organocatalyst **8-9** (0.02-0.01 mmol) was added. The reaction mixture stirred at 10 °C about 55-137 h. The reaction was monitored on TLC and residue was purified by column chromatography on silica gel by using EtOAc/hexane (1:5) solvent systems. White solid product (88% yield) was obtained. The enantiomeric excess value of the product was obtained by HPLC analysis using with Chiralcel AD column, *n*-hexane/*i*- PrOH/TFA 70:30:0.1, flow rate 1 mL min^{-1}, λ=254 nm, t_R =4.5 min. and t_S = 8.5 min. The spectroscopic data are in accordance with the literature values [47].

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 6H), 1.63 (s, 6H), 1.87 - 1.98 (m, 4H), 2.22 (d, *J* = 5.8 Hz, 2H), 2.30 –2.49 (m, 12H), 3.21 (d, *J* = 5.8 Hz, 2H), 3.45 (s, 3H), 3.74 – 3.83 (m, 1H), 4.09 (dd, *J* = 6.8, 11.4 Hz, 4H), 4.20 (dd, *J* = 3.3 - 6.8 Hz, 3H), 4.63 (d, *J* = 10.0 Hz, 1H), 7.15 –7.25 (m, 45H), 7.39 –7.52 (m, 6H), 7.73 (d, *J* = 6.7 Hz, 3H), 7.82 (d, *J* = 7.9 Hz, 3H), 7.87 (d, *J* = 7.9 Hz, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 26.6, 27.1, 29.0, 29.9, 33.1, 33.9, 34.3, 39.0, 41.5, 44.2, 98.0, 99.5, 103.1, 114.5, 114.8, 115.6, 121.7, 122.0, 122.6, 122.8, 122.9, 125.4, 125.9, 126.0, 126.1, 126.9, 127.1, 127.6, 128.2, 130.5, 131.0, 140.4, 142.1, 151.9, 152.0, 157.8, 158.6, 161.1, 211.6.

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APPENDIX B

SUPPORTING INFORMATION

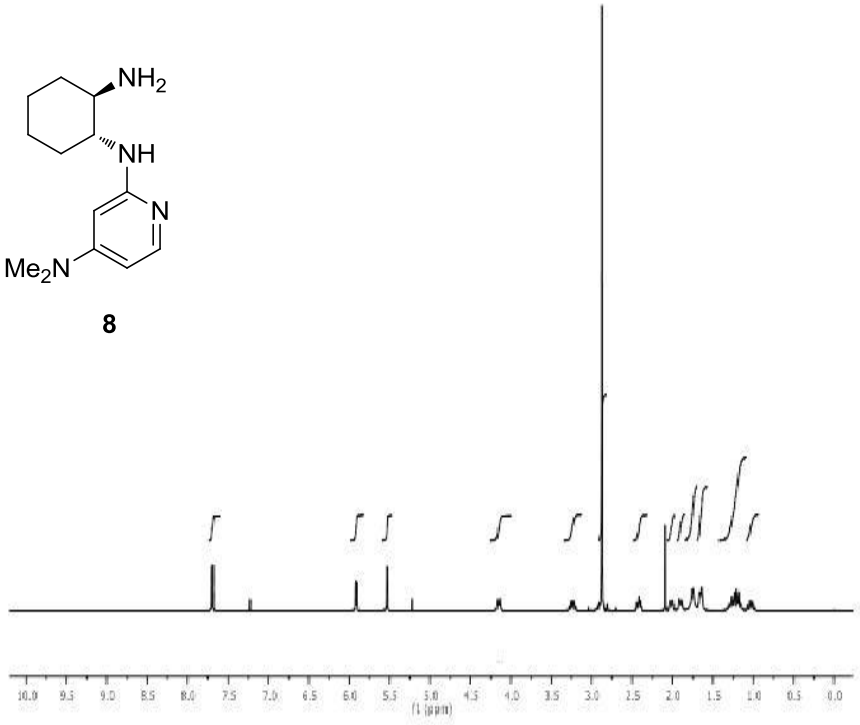

Figure A1. ^{1}H NMR spectrum of compound **8**

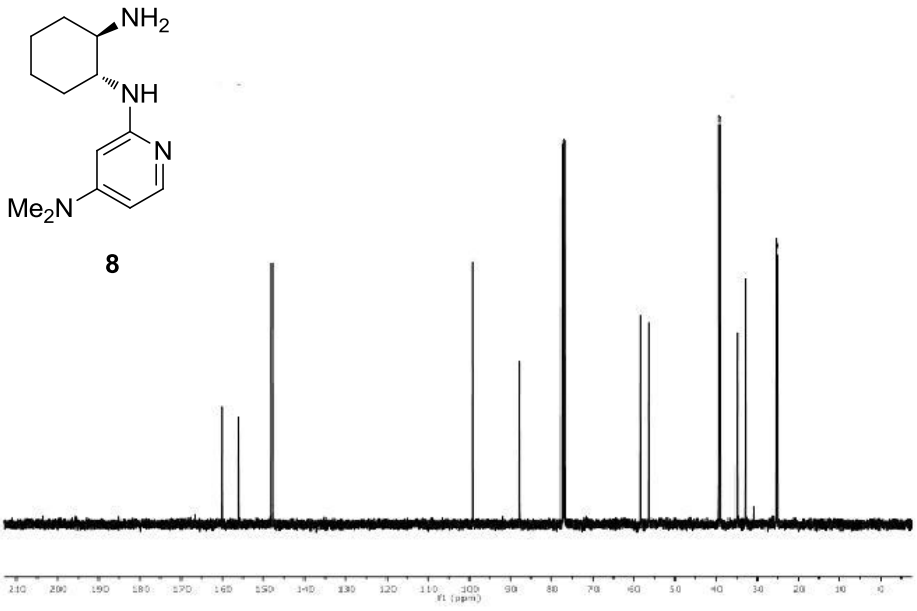

Figure A2. ^{13}C NMR spectrum of compound **8**

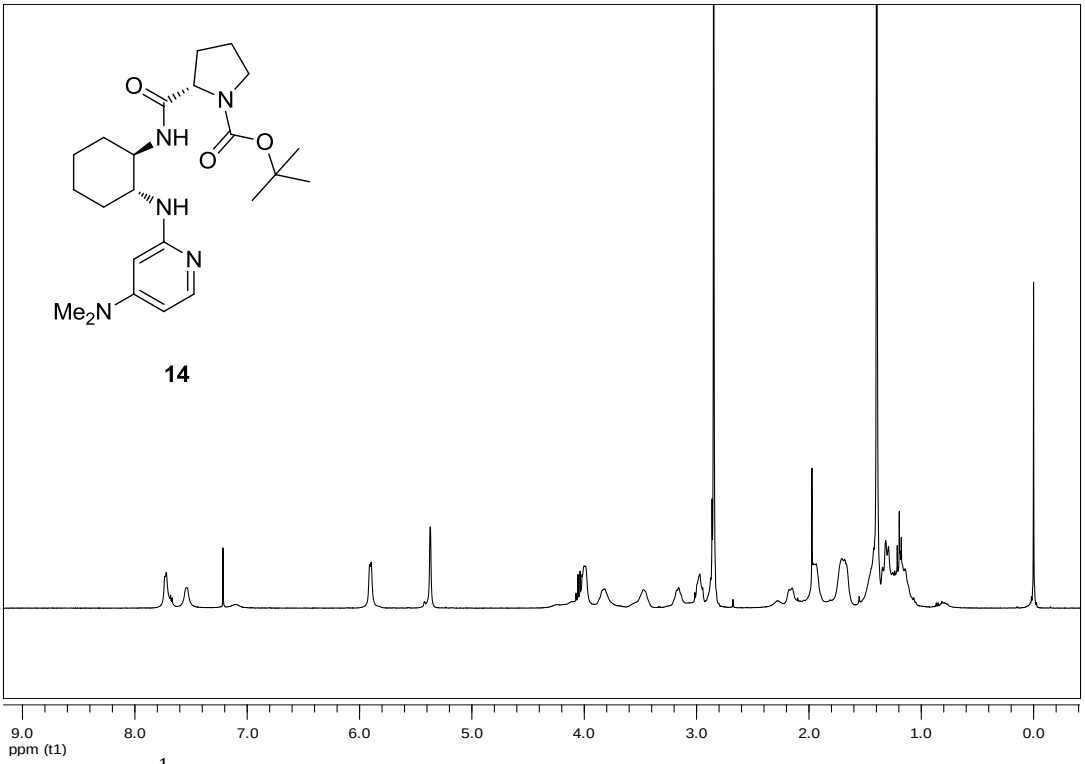

Figure A3. ^{1}H NMR spectrum of compound **14**

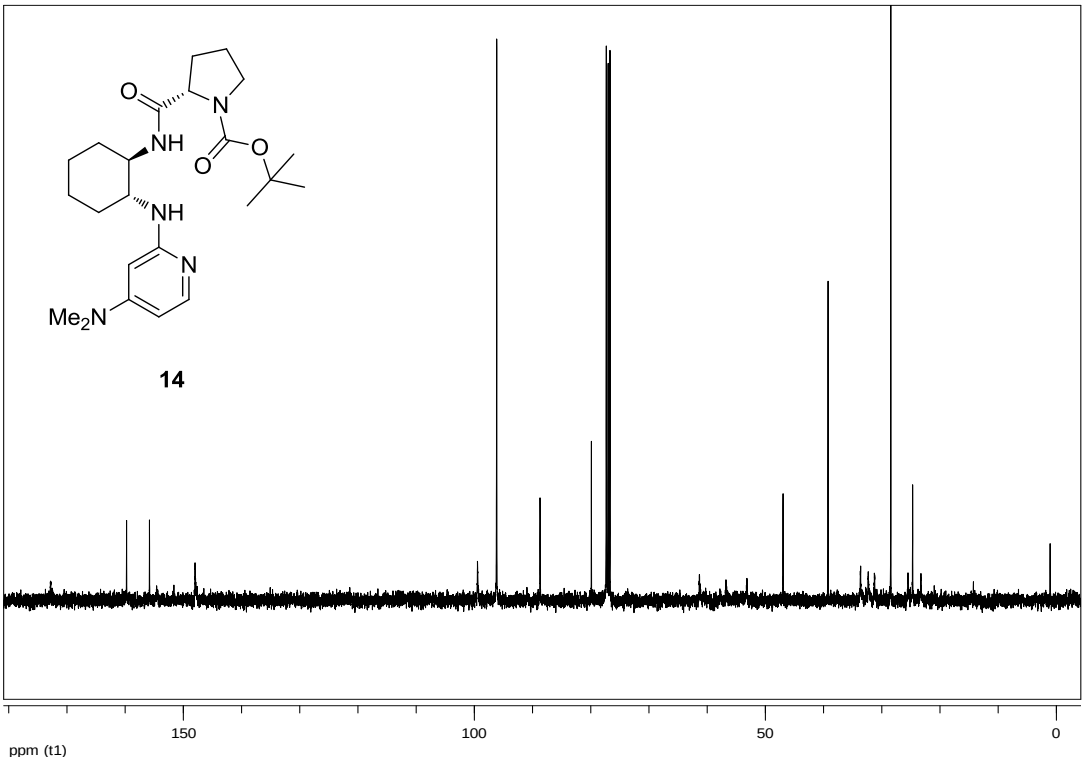

Figure A4. ^{13}C NMR spectrum of compound **14**

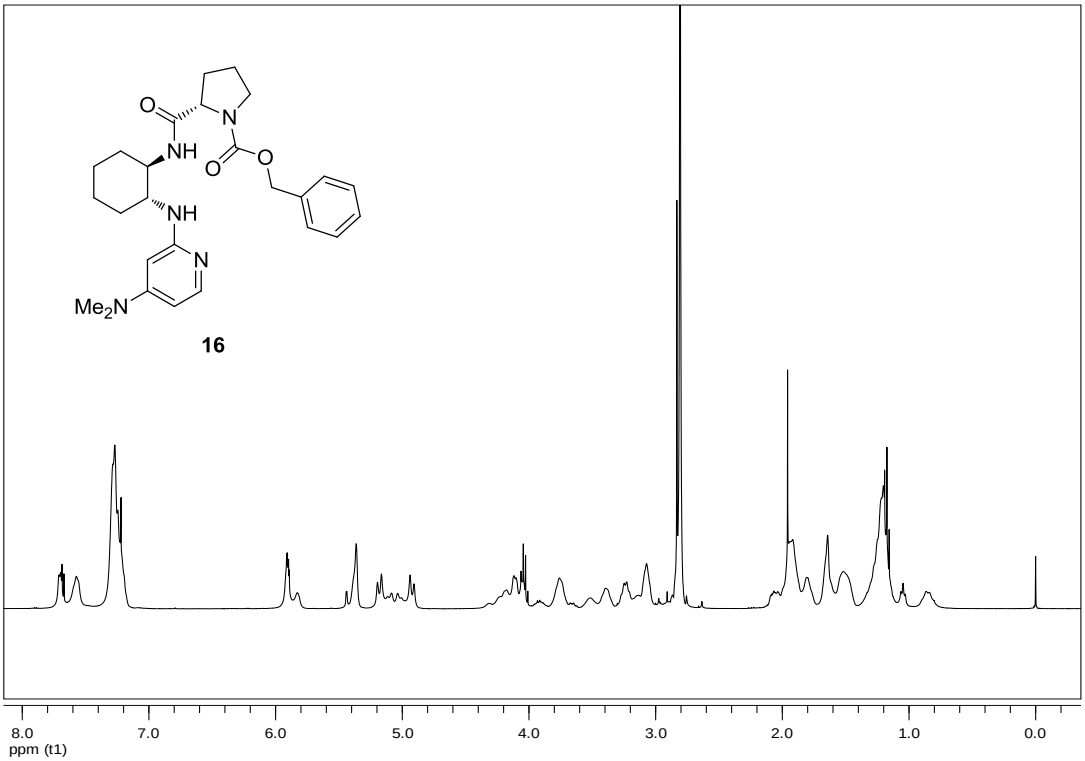

Figure A5. ^{1}H NMR spectrum of compound **16**

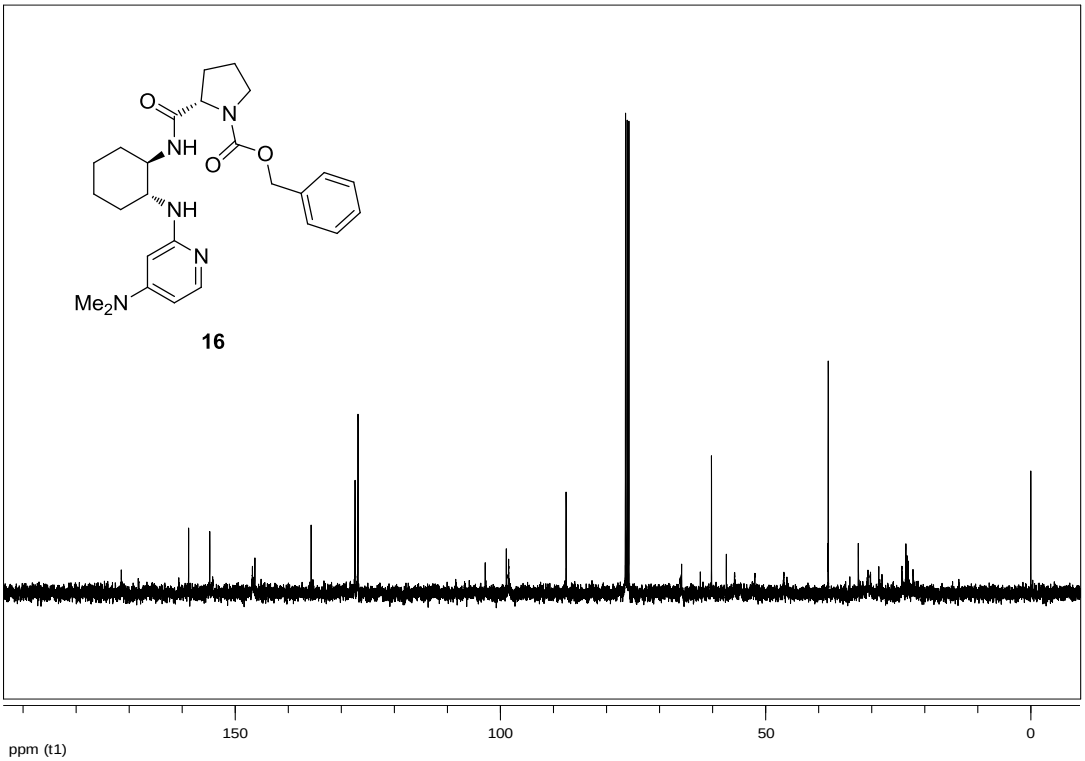

Figure A6. ^{13}C NMR spectrum of compound **16**

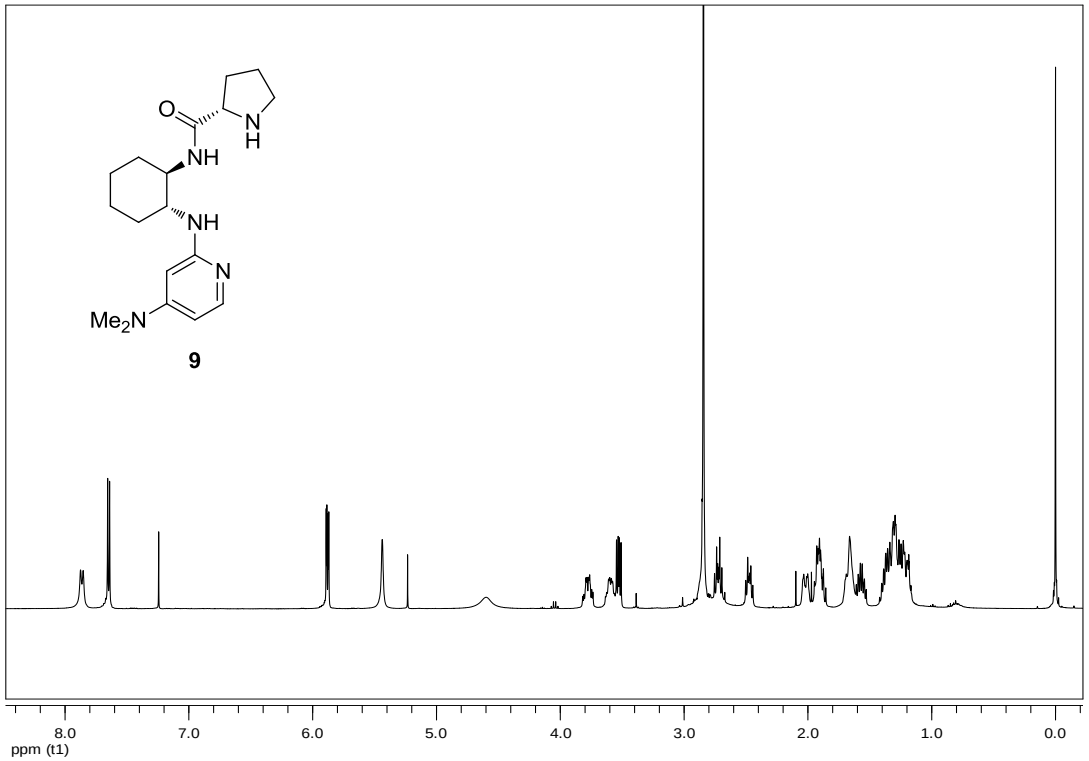

Figure A7. ^{1}H NMR spectrum of compound **9**

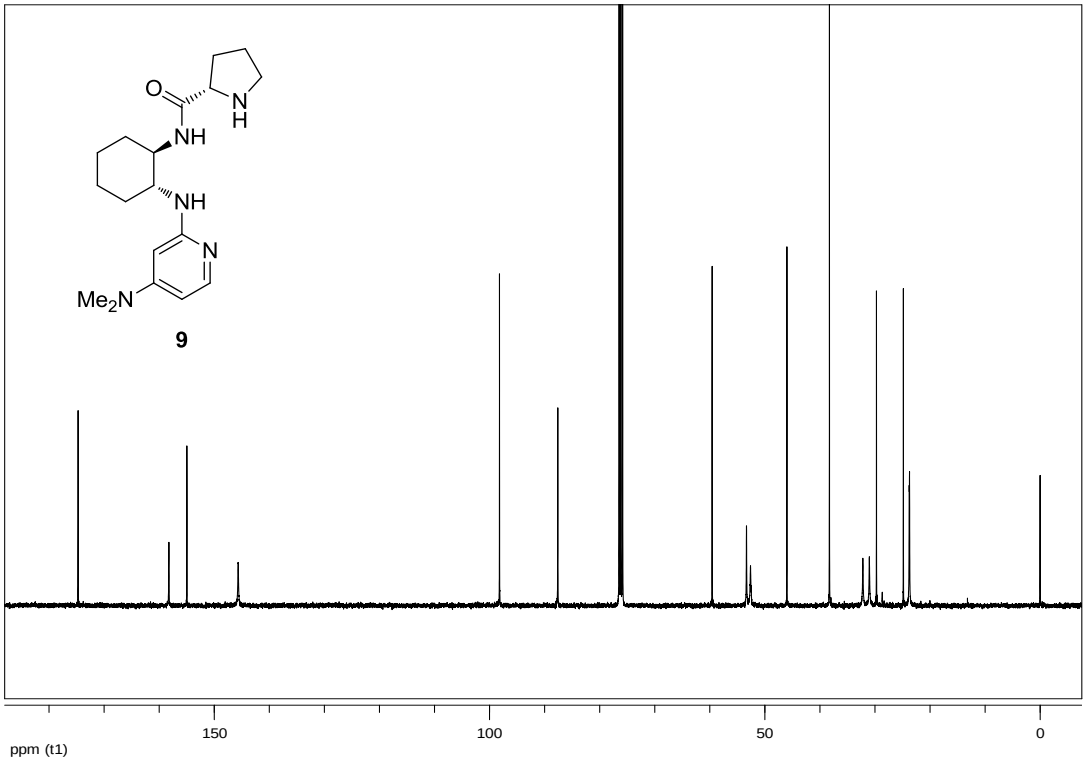

Figure A8. ^{13}C NMR spectrum of compound **9**

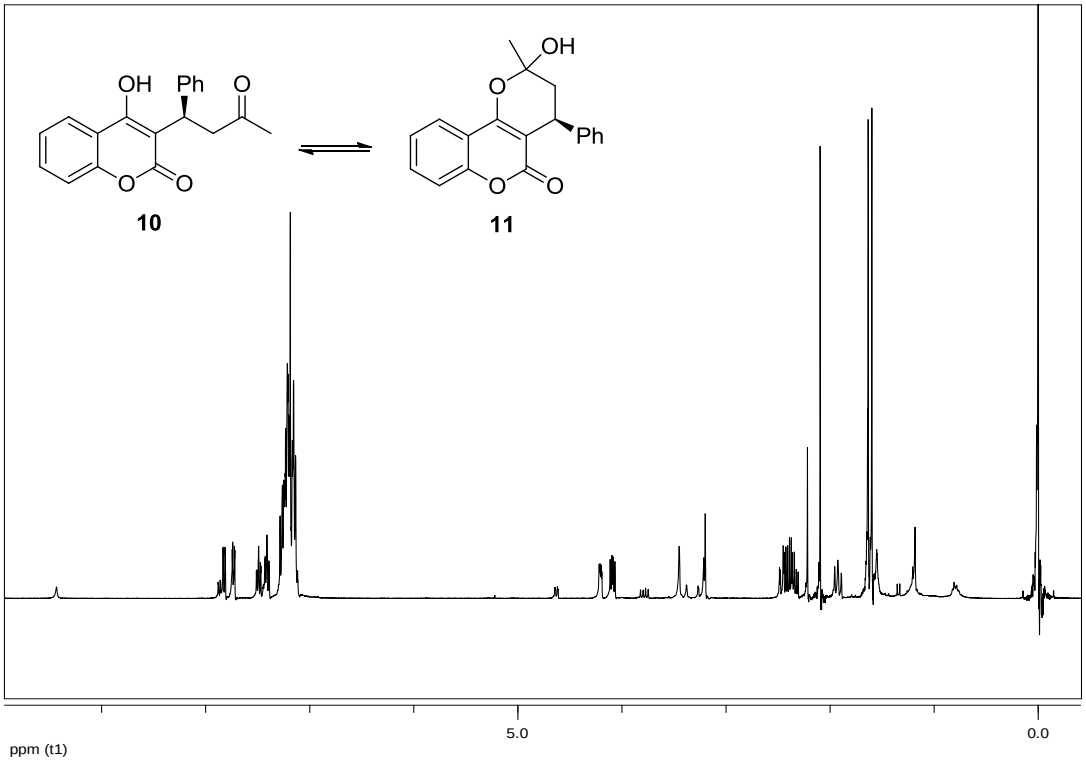

Figure A9. ^{1}H NMR spectrum of compound **10**

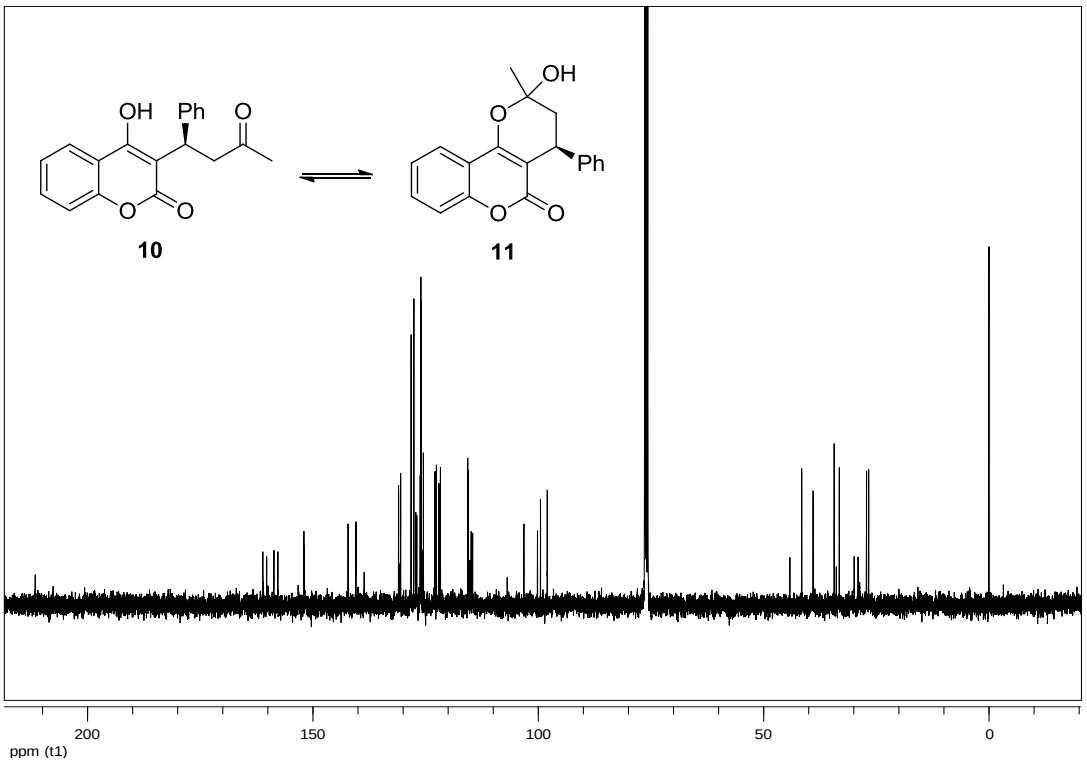

Figure A10. ^{13}C NMR spectrum of compound **10**

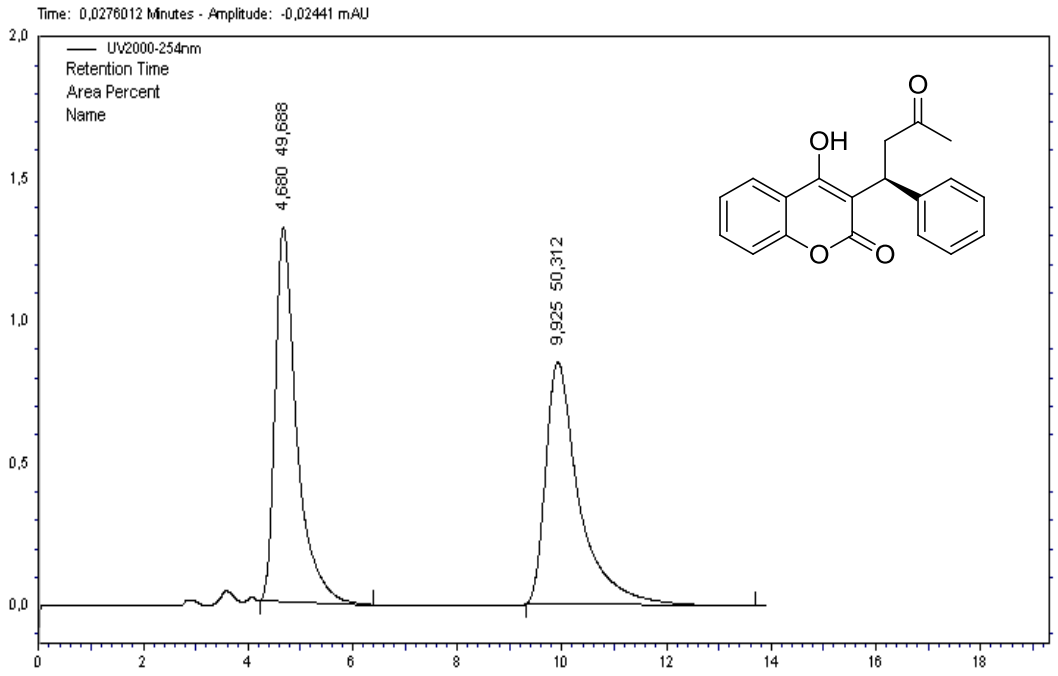

Figure A11. HPLC chromatogram of *rac*-**1**

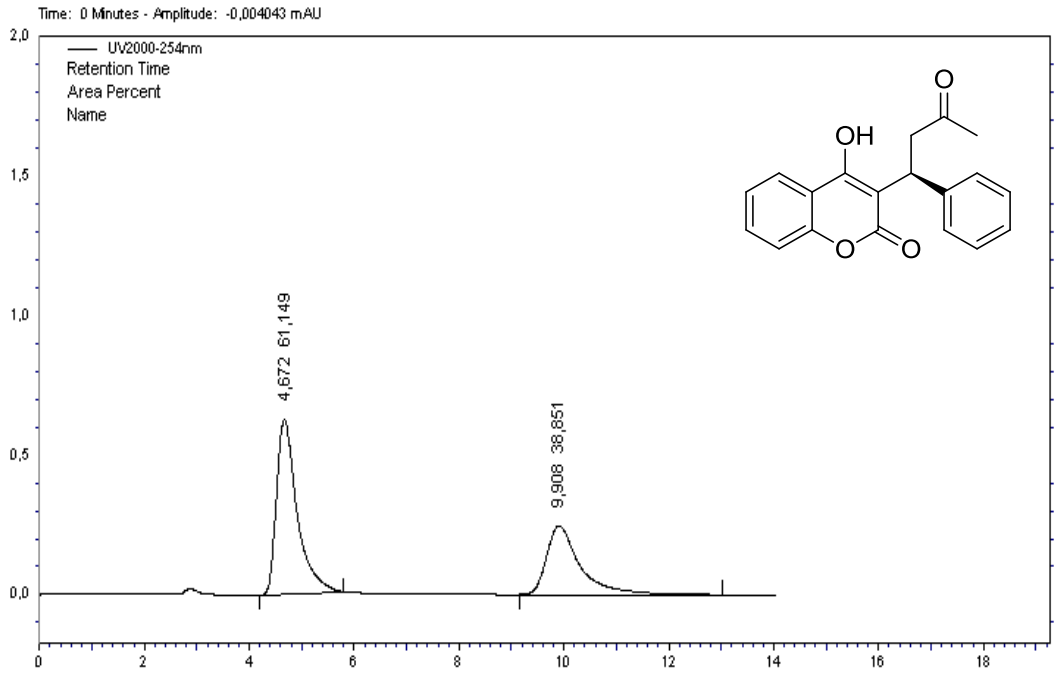

Figure A12. HPLC chromatogram of entry 1 in Table 2 (22% ee)

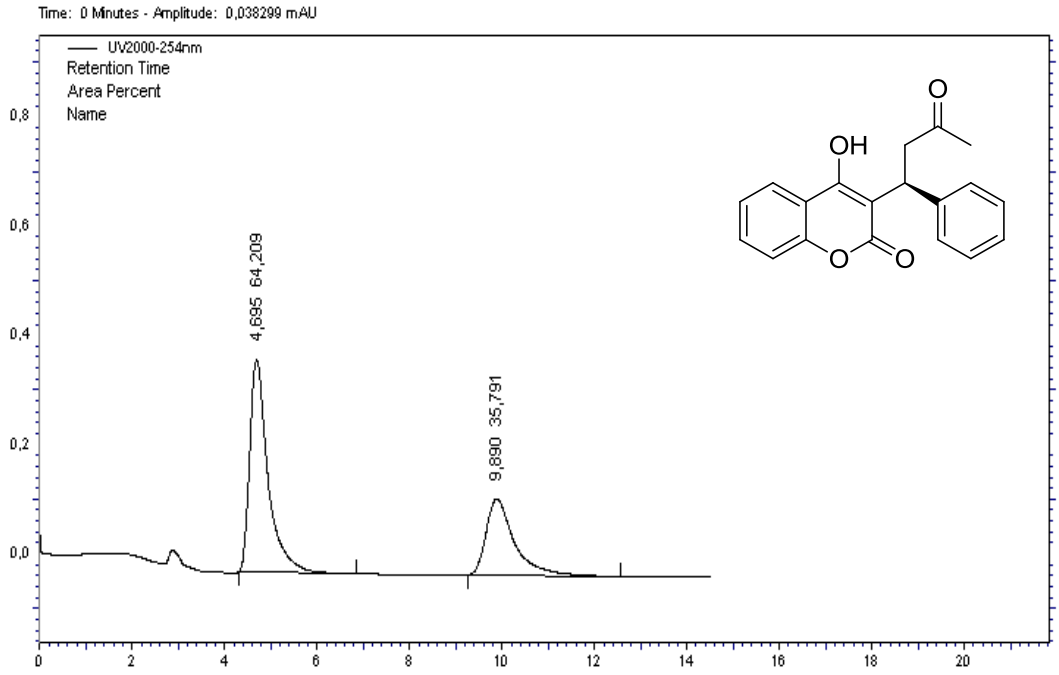

Figure A13. HPLC chromatogram of entry 4 in Table 2 (28% ee)

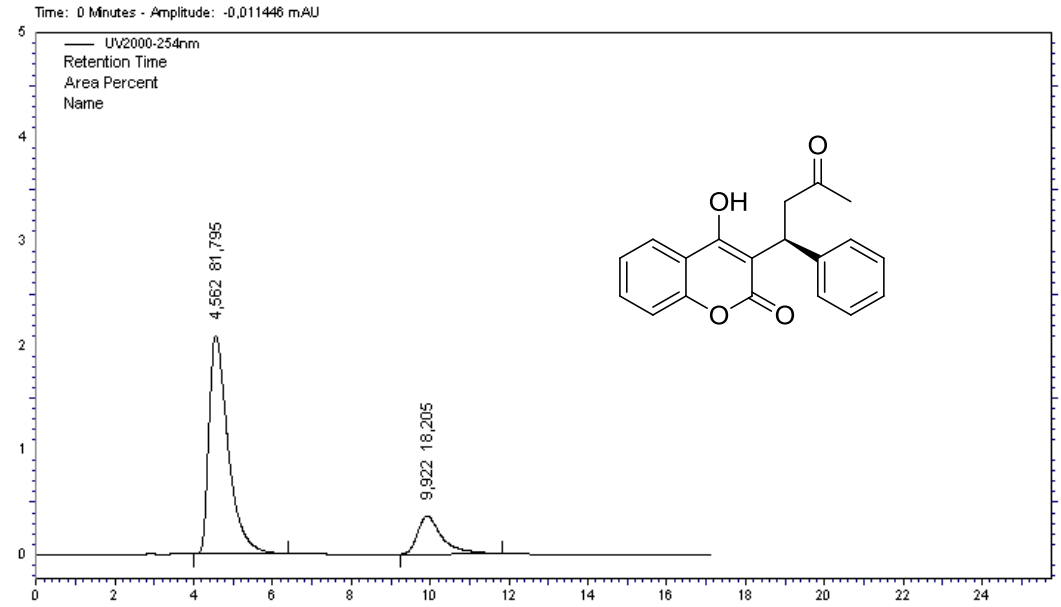

Figure A14. HPLC chromatogram of entry 1 in Table 3 (64% ee)

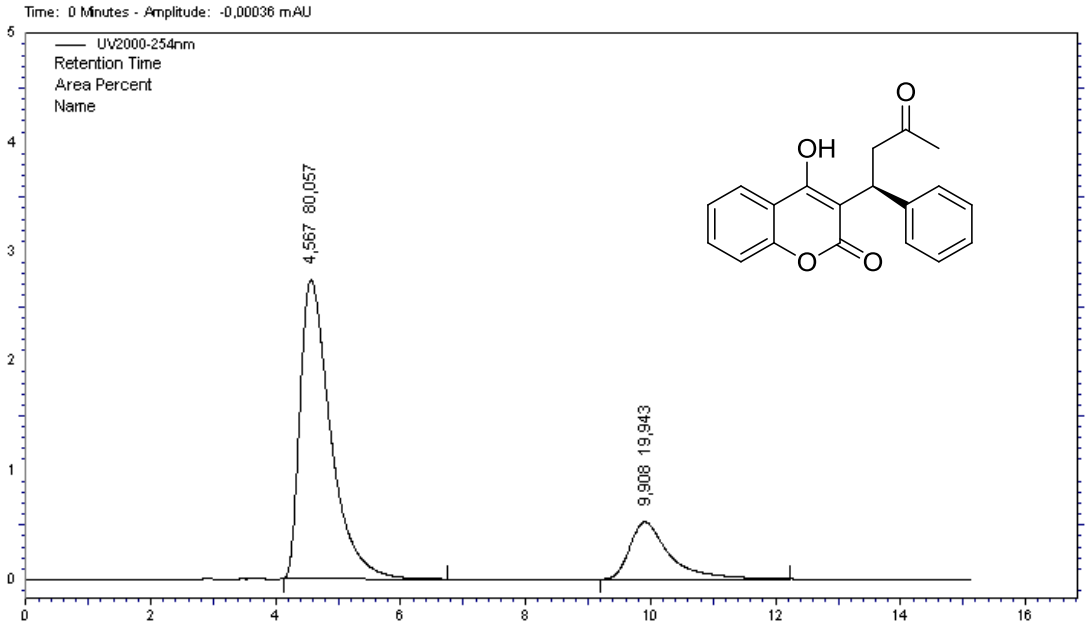

Figure A15. HPLC chromatogram of entry 3 in Table 3 (60% ee)

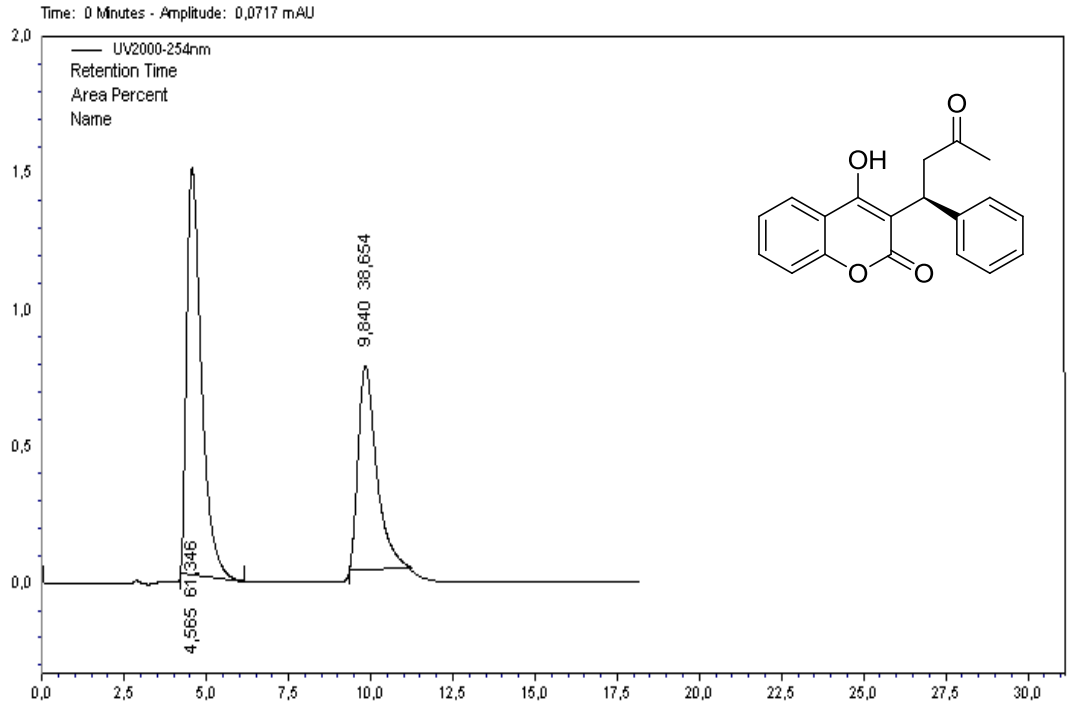

Figure A16. HPLC chromatogram of entry 1 in Table 4 (23% ee)

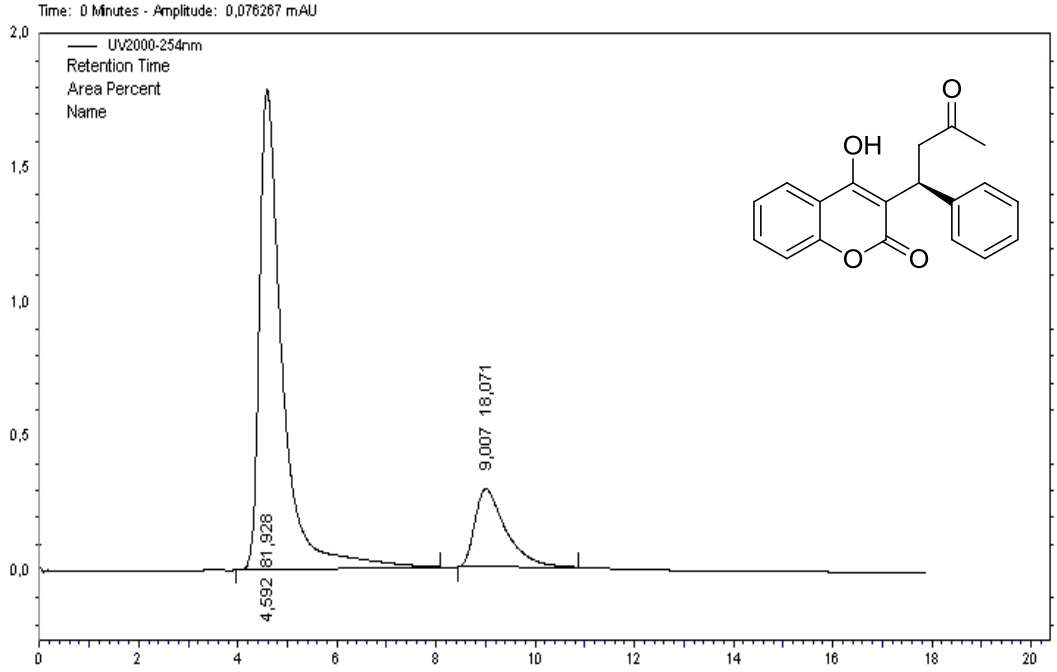

Figure A17. HPLC chromatogram of entry 4 in Table 5 (64% ee)

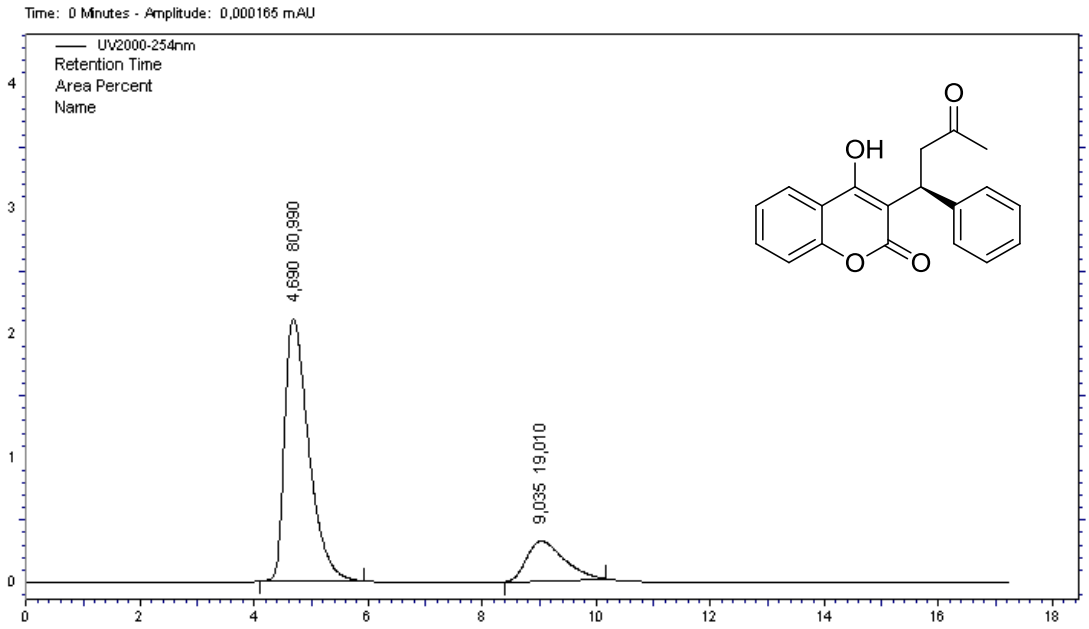

Figure A18. HPLC chromatogram of entry 8 in Table 6 (62% ee)

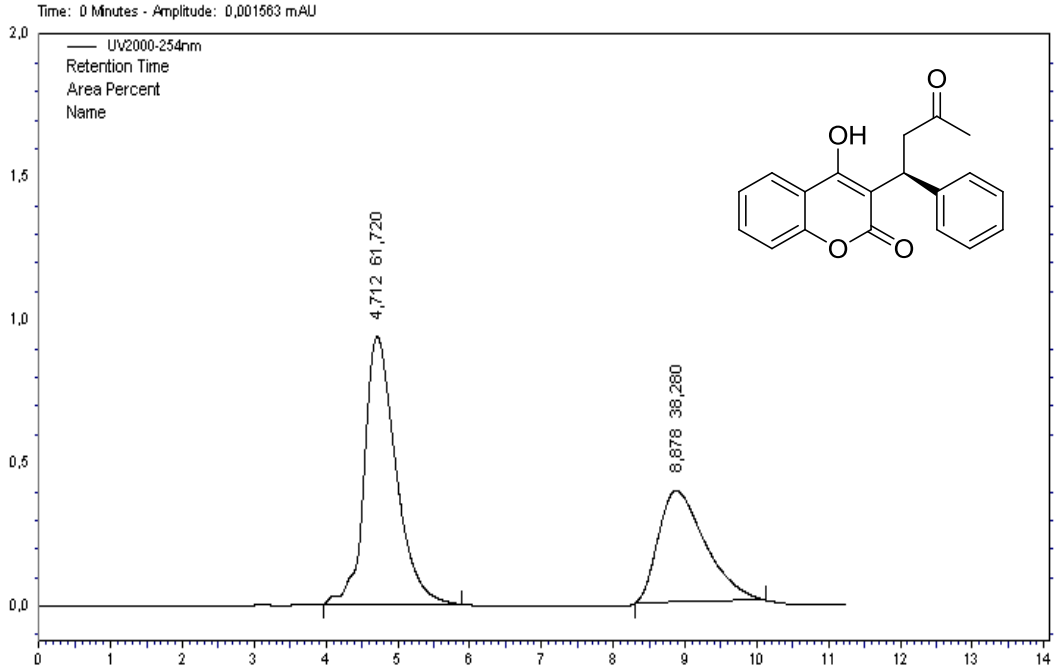

Figure A19. HPLC chromatogram of entry 11 in Table 6 (23.5% ee)

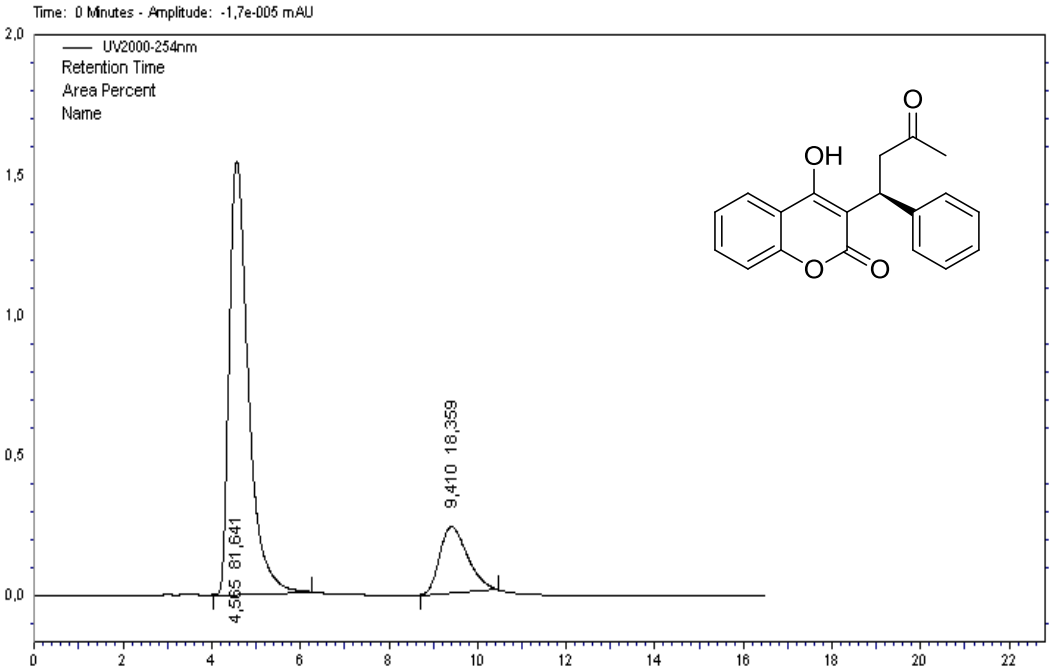

Figure A20. HPLC chromatogram of entry 15 in Table 6 (63.5% ee)

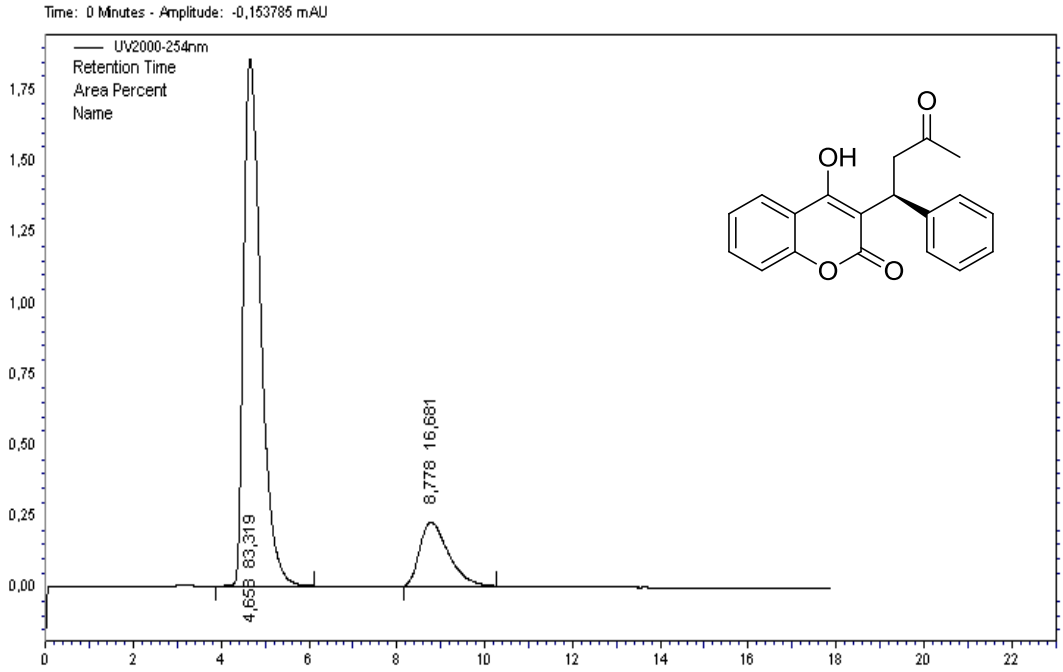

Figure A21. HPLC chromatogram of entry 3 in Table 7 (66.5% ee)

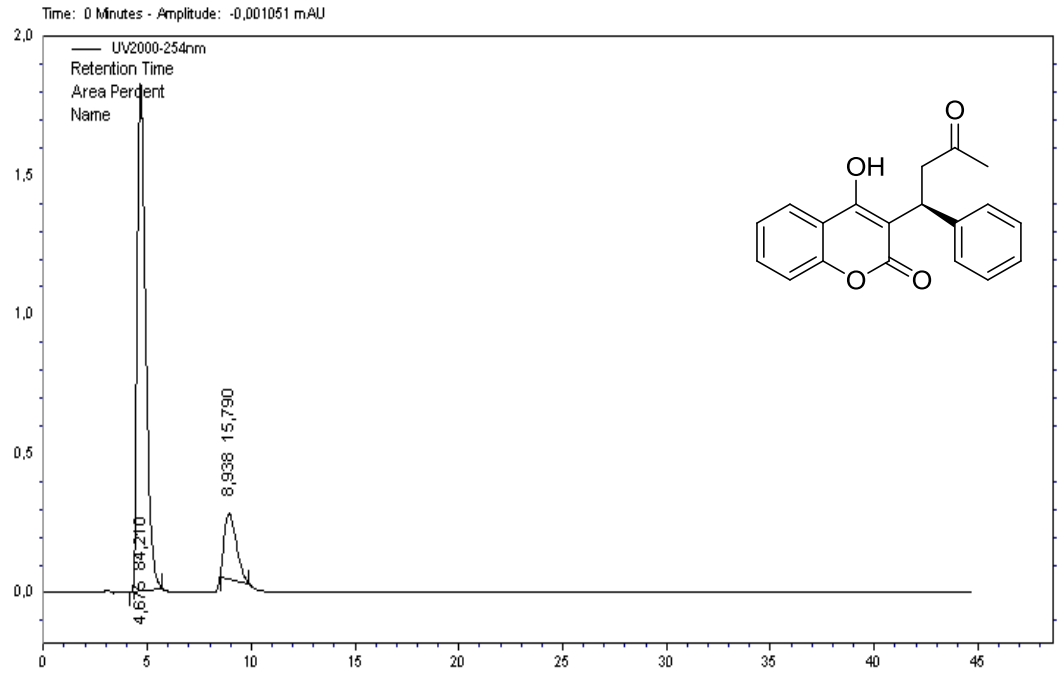

Figure A22. HPLC chromatogram of entry 5 in Table 7 (68.5% ee)

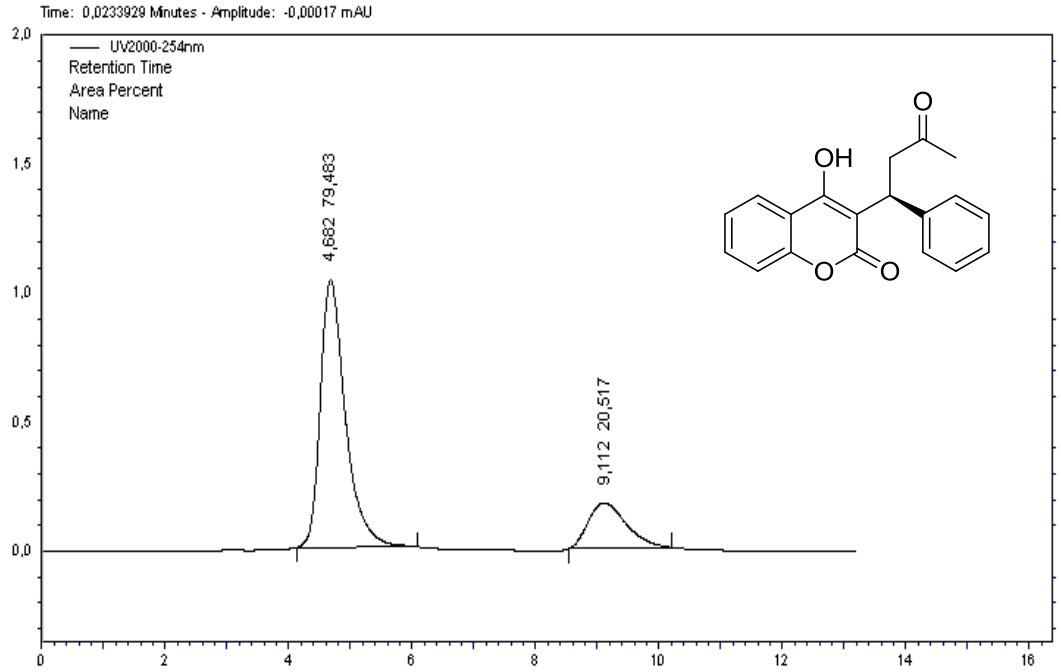

Figure A23. HPLC chromatogram of entry 2 in Table 8 (59% ee)

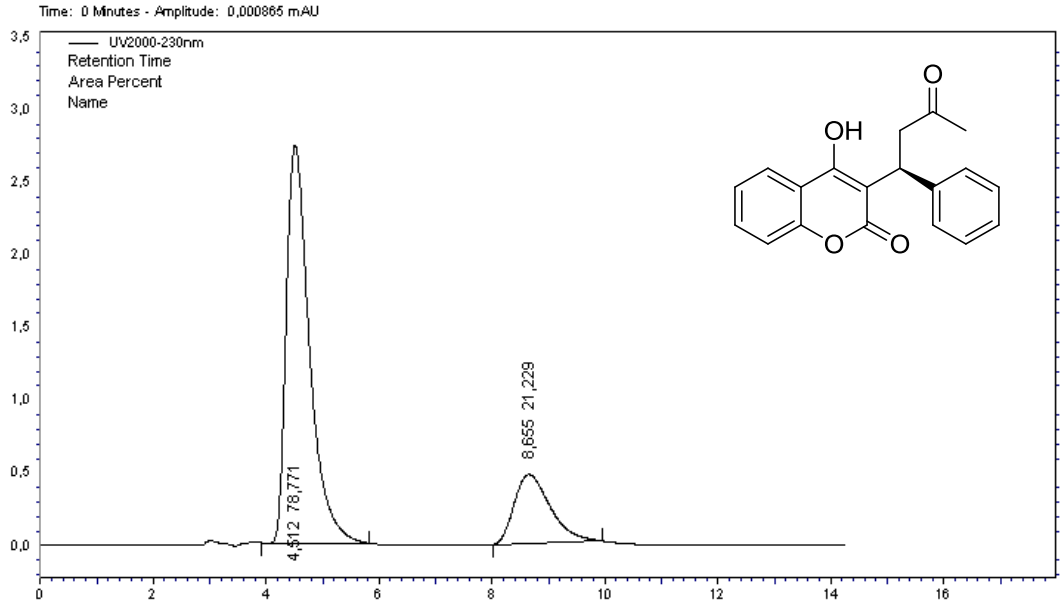

Figure A24. HPLC chromatogram of entry 4 in Table 9 (57.5% ee)

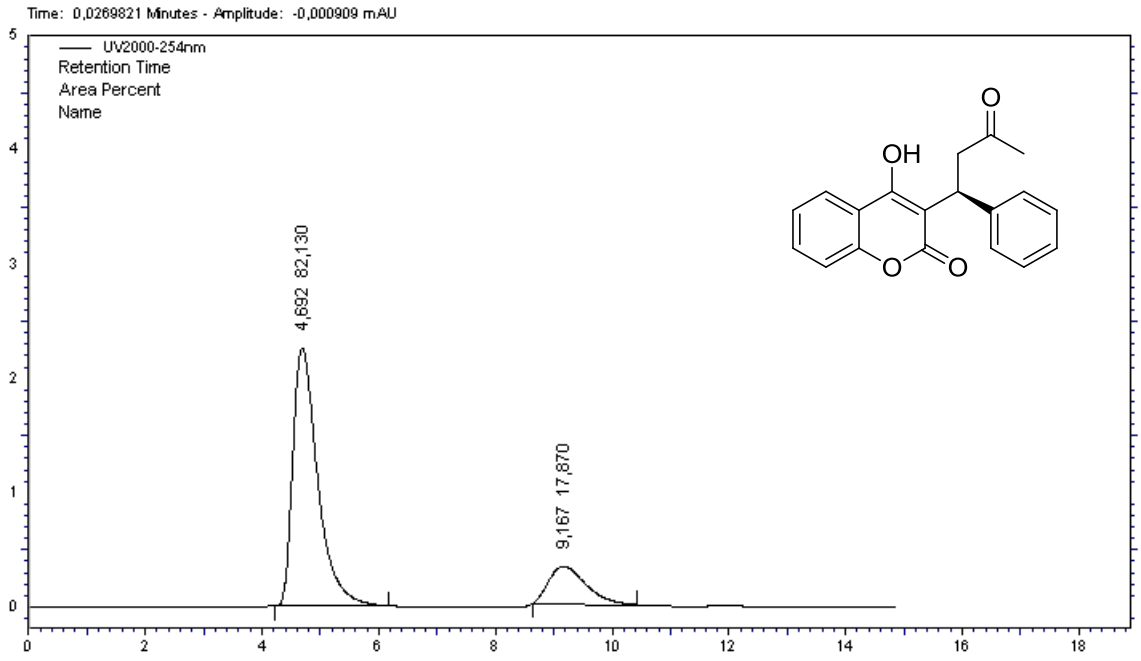

Figure A25. HPLC chromatogram of entry 6 in Table 9 (64.5% ee)

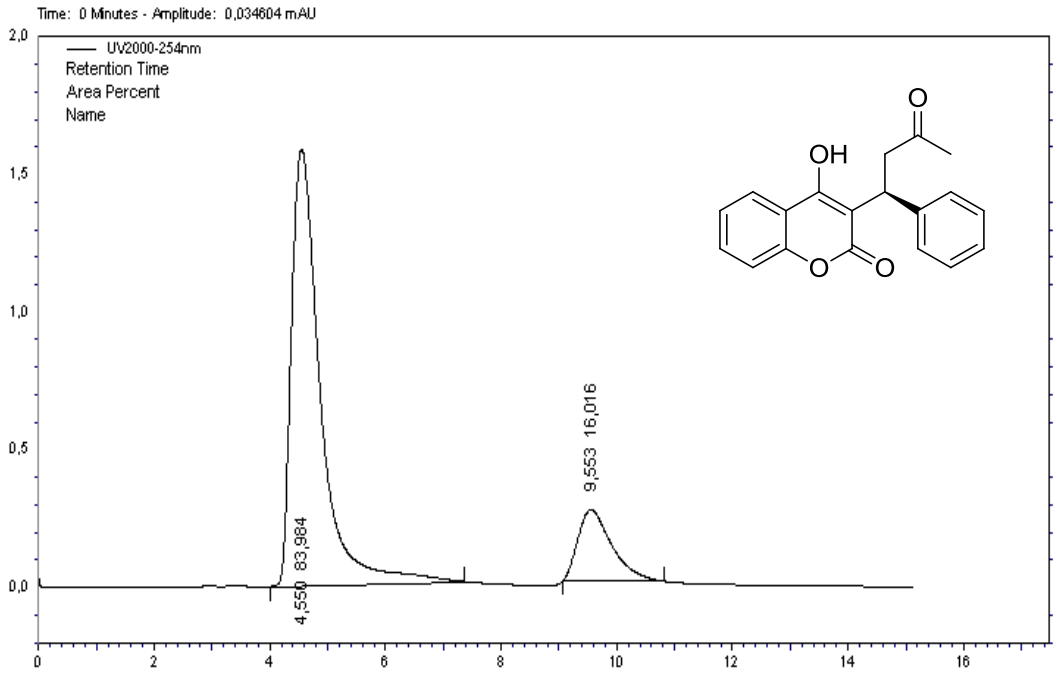

Figure A26. HPLC chromatogram of entry 4 in Table 10 (68% ee)

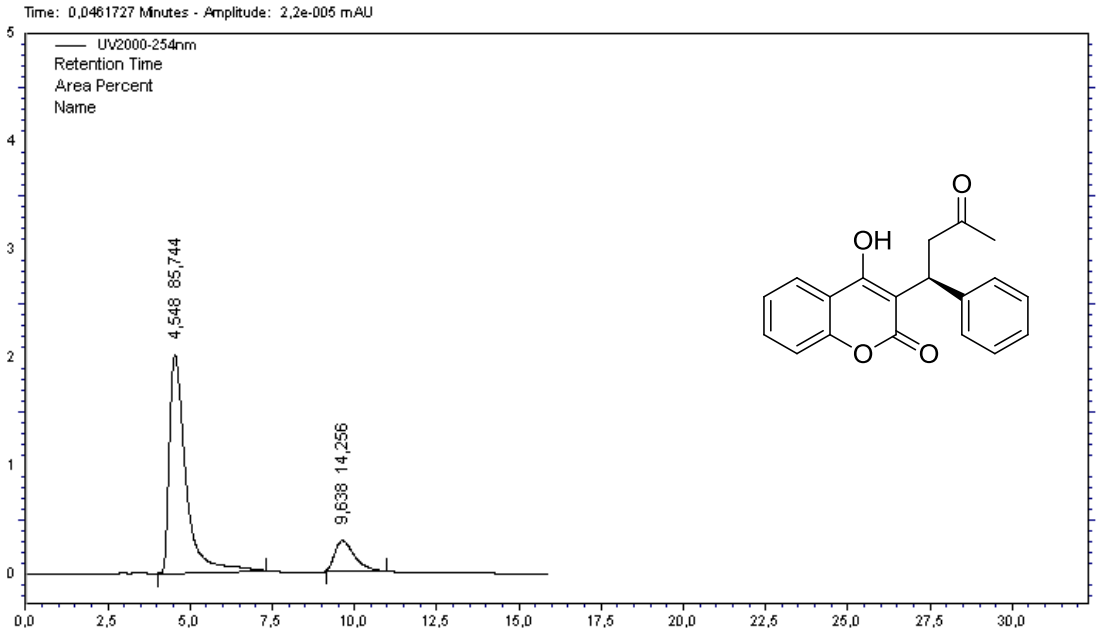

Figure A27. HPLC chromatogram of entry 5 in Table 10 (72% ee)

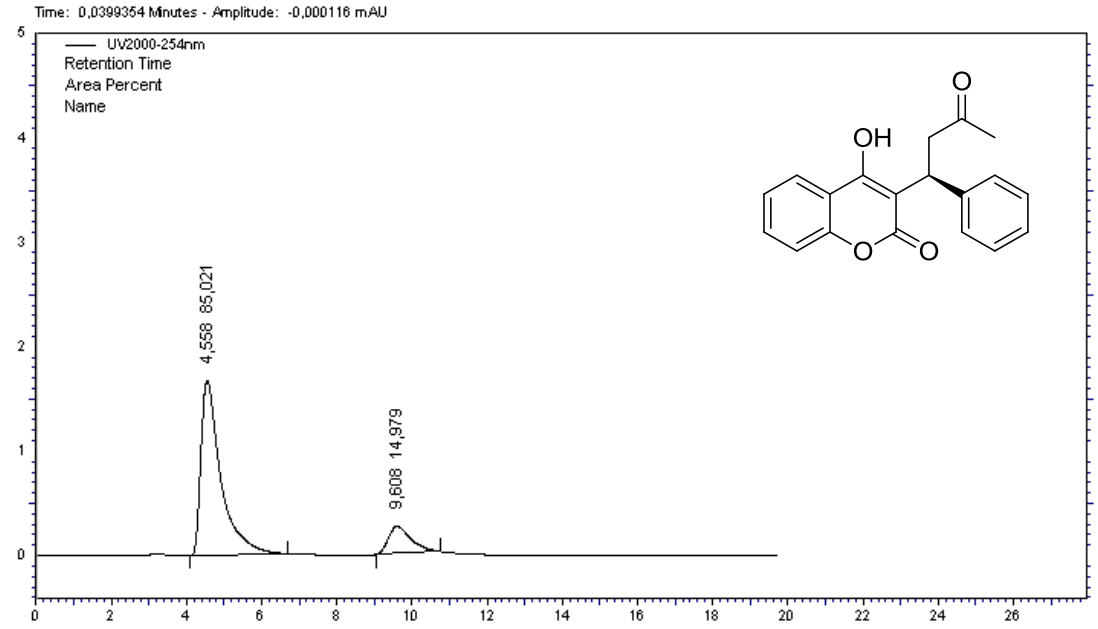

Figure A28. HPLC chromatogram of entry 1 in Table 11 (70% ee)

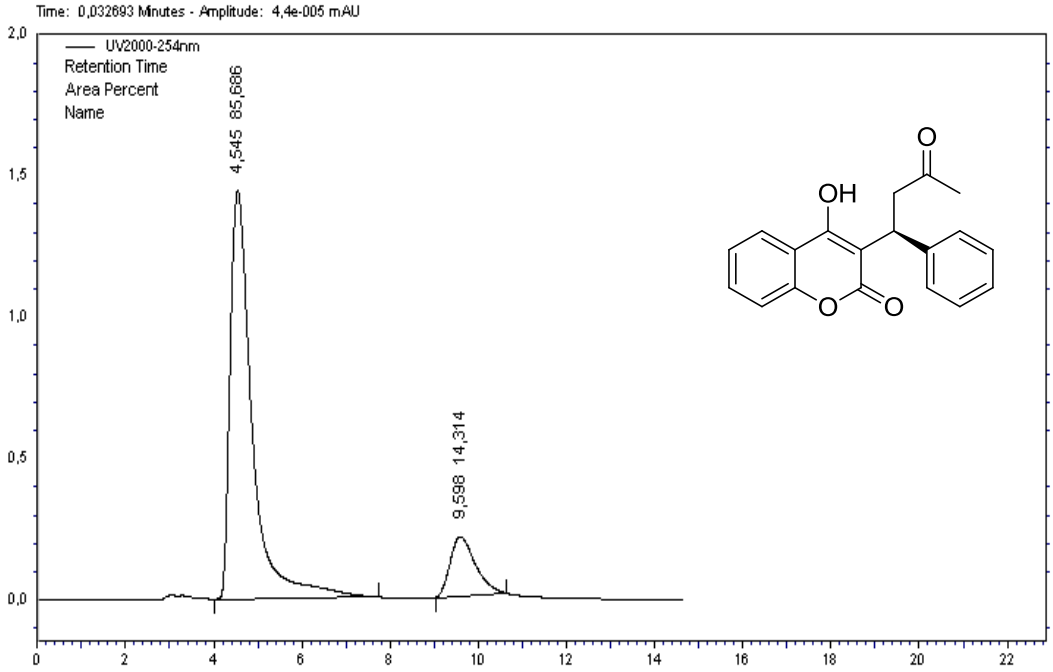

Figure A29. HPLC chromatogram of entry 5 in Table 11 (71.5% ee)

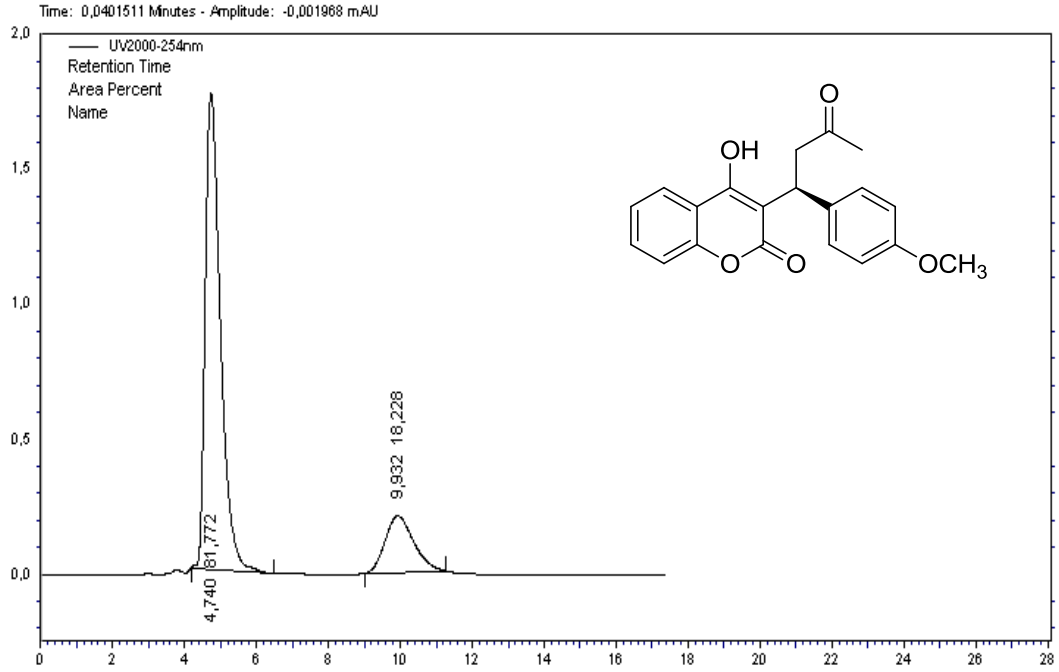

Figure A30. HPLC chromatogram of compound **10a** (63.5% ee)

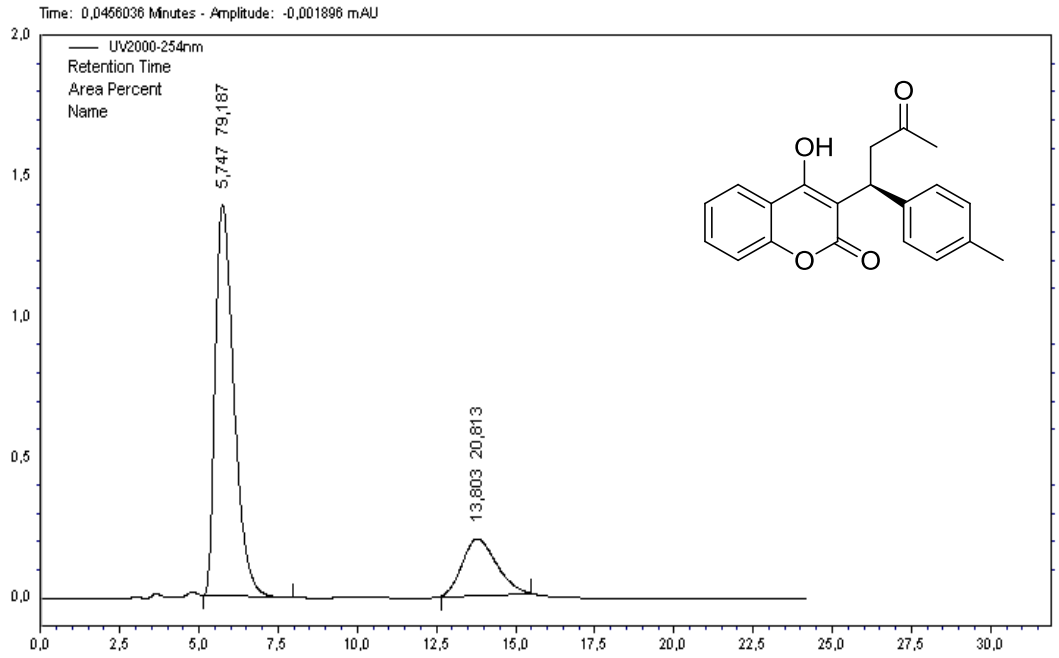

Figure A31. HPLC chromatogram of compound **10b** (59.5% ee)

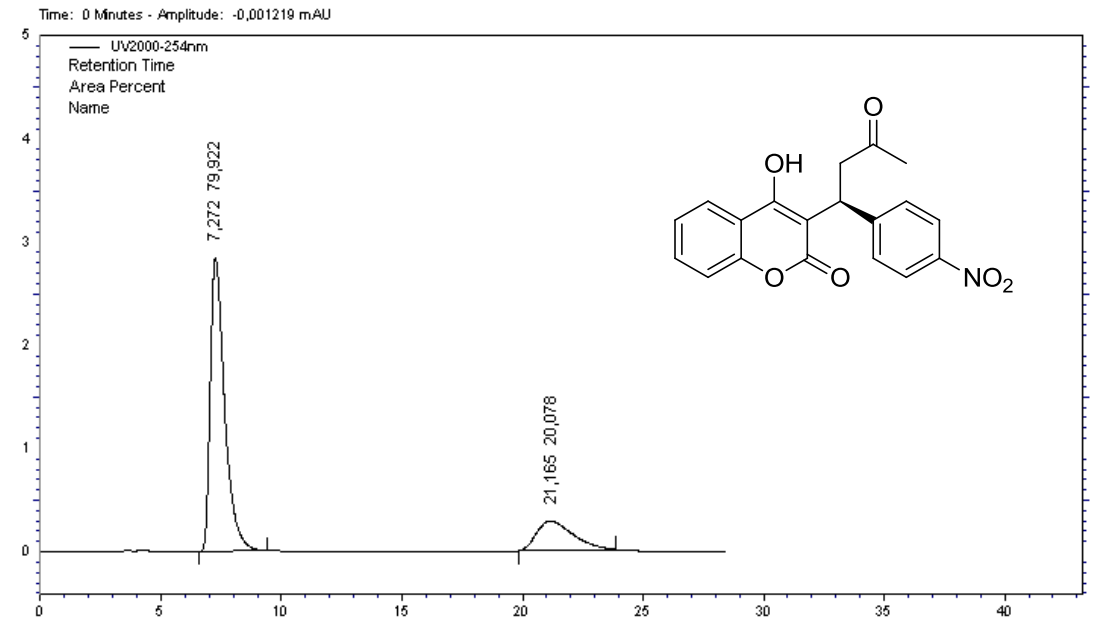

Figure A32. HPLC chromatogram of compound **10c** (60% ee)

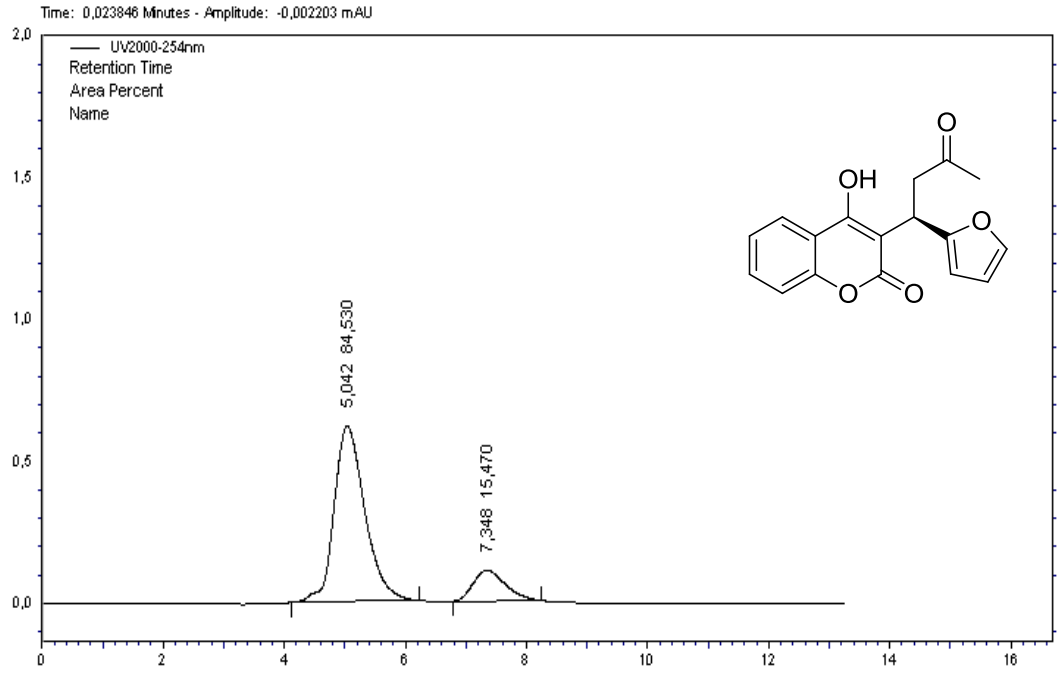

Figure A33. HPLC chromatogram of compound **10d** (69% ee)

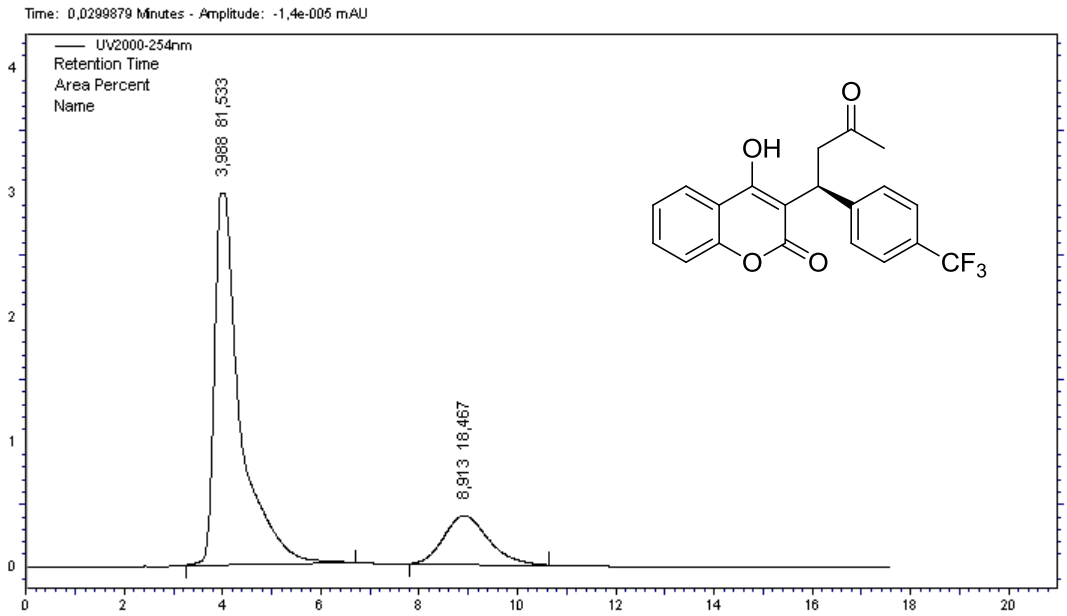

Figure A34. HPLC chromatogram of compound **10e** (63% ee)

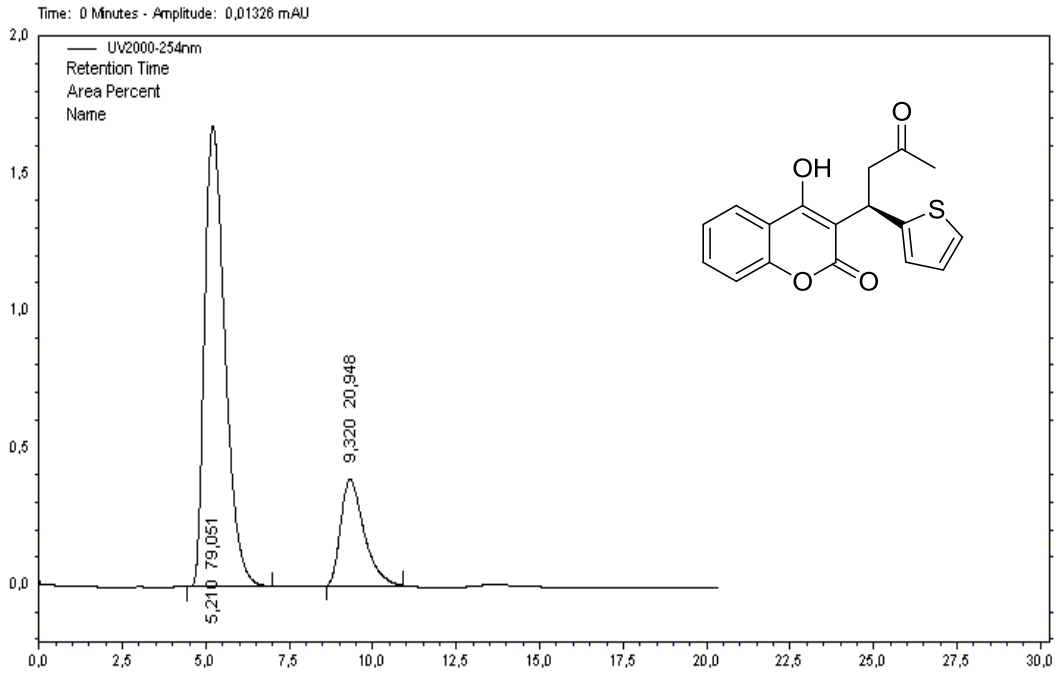

Figure A35. HPLC chromatogram of compound **10f** (58% ee)