CHIRAL 2-AMINODMAP/SULFONAMIDES AND SQUARAMIDES AS BIFUNCTIONAL ACID/BASE ORGANOCATALYSTS IN ASYMMETRIC CATALYSIS

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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ABSTRACT

CHIRAL 2-AMINODMAP/SULFONAMIDES AND SQUARAMIDES AS BIFUNCTIONAL ACID/BASE ORGANOCATALYSTS IN ASYMMETRIC CATALYSIS

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July 2011, 154 pages

Synthesis and evaluation of catalytic performances of novel bifunctional 2-aminoDMAP-Thiourea/ Sulfonamide/ Squaramide organocatalysts derived from *trans*-(*R,R*)-cyclohexane-1,2-diamine forms the main goal of this thesis. For this purpose, direct selective mono-*N*-pyridilization of *trans*-(*R,R*)-cyclohexane-1,2-diamine *via* Pd and Cu catalysis is described successfully first. Facile preparation of chiral 2-aminoDMAP core catalaphore led to the development of various 2-aminoDMAP- Thiourea/ Sulfonamides/ Squaramides as bifunctional acid/base organocatalyst libraries (most in two-steps overall) which showed good results in asymmetric conjugate addition of 1,3-dicarbonyls to *trans*-(β)-nitrostyrene. Enantiomeric excesses (*ee*) up to 93% were attained.

Keywords: Asymmetric Catalysis, Organocatalysis, Bifunctional Acid/Base Catalysis, Chiral DMAP.

ÖZ

KİRAL 2-AMİNODMAP/SULFONAMİT VE SKUARAMİT BİFONKSİYONEL ASİT/BAZ ORGANOKATALİZÖRLERİN GELİŞTİRİLMESİ VE ASİMETRİK KATALİZ UYGULAMALARI

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Temmuz 2011, 154 sayfa

trans-(*R,R*)-Siklohegzan-1,2-diamin'den türetilmiş özgün bifonksiyonel 2-aminoDMAP-Tiyoüre/ Sülfonamit/ Skuaramit organokatalizörlerin sentezi ve katalitik performanslarının değerlendirilmesi bu tezin temel amacını oluşturmaktadır. Bu amaçla, ilk olarak *trans*-(*R,R*)-siklohegzan-1,2-diamin'in Pd ve Cu katalizi yoluyla direkt olarak seçici mono-*N*-piridilizasyonu başarıyla gerçekleştirilmiştir. Bu yolla; kolayca elde edilen 2-aminoDMAP çekirdek katalafor, çoğunluğu toplamda iki sentetik basamakta sentezlenen çeşitli bifonksiyonel asit/baz tipi DMAP-Tiyoüre/ Sülfonamit/ Skuaramit organokatalizör kütüphanesinin geliştirilmesine olanak sağlamıştır. Elde edilen katalizörlerin, 1,3-dikarbonil bileşiklerinin *trans*-(*β*)-nitrostiren'e asimetrik konjuge katılma tepkimelerini %93 enantiyomerik zenginlikle (*ee*) katalizlediği görülmüştür.

Anahtar kelimeler: Asimetrik Kataliz, Organokataliz, Bifonksiyonel Asit/Baz Katalizi, Kiral DMAP.

To my dear family

and my beloved Burçin

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SCHEMES

LIST OF ABBREVIATIONS

A	:	Acid
AO	:	Asymmetric organocatalysis
B	:	Base
BAM	:	Bis-amidine
BINAM	:	1,1'-binaphthyl-2,2'-di-amine
BINAP	:	2,2'-bis(Diphenylphosphino)-1,1'-binaphthyl
Boc	:	*tert*-Butoxycarbonyl
BTF	:	Benzotrifluoride
Cbz	:	Carboxybenzyl
DBP	:	3,5-Di-*tert*-butylphenyl
DCM	:	Dichloromethane
DMAP	:	4-Dimethylaminopyridine
DMF	:	*N*,*N*-Dimethylformamide
DMSO	:	Dimethyl sulfoxide
dppe	:	1,2-Bis(diphenylphosphino)ethane
dppp	:	1,3-Bis(diphenylphosphino)propane
dr	:	Diastereomeric ratio
ee	:	Enantiomeric excess
ESI	:	Electrospray Ionization
HOMO	:	Highest Occupied Molecular Orbital
HPLC	:	High Performance Liquid Chromatography

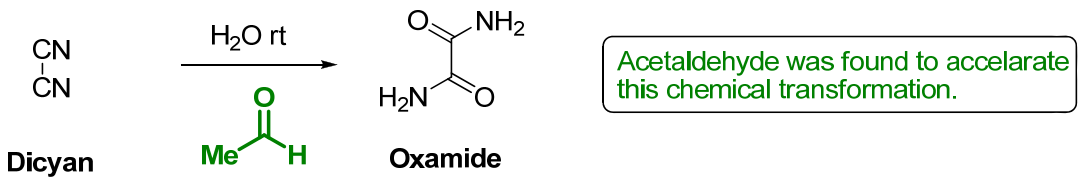
HRMS	:	High Resolution Mass Spectrometry
IR	:	InfraRed
LUMO	:	Lowest Unoccupied Molecular Orbital
MeCN	:	Acetonitrile
MS	:	Molecular Sieve
NMR	:	Nuclear Magnetic Resonance
ppm	:	Parts per million
PPY	:	4-Pyrrolidinopyridine
PTC	:	Phase Transfer Catalysis/Catalyst
PTSA	:	*p*-Toluenesulfonic acid
SOMO	:	Singly Occupied Molecular Orbital
TEA	:	Triethyl amine
THF	:	Tetrahydrofuran
TLC	:	Thin Layer Chromatography
TRADAP	:	(trialkyldiamino)pyridine
Ts	:	Tosyl
TS	:	Transition State

CHAPTER 1

INTRODUCTION

1.1 Organocatalysis

The term, "*organocatalysis*" introduced by MacMillan in 1998 from the fundamental concepts of chemistry (concatenation of the terms *organic* + *catalysis*), describes the acceleration of chemical reaction by the use of substoichiometric quantity of an organic compound. Such a small organic compound, he termed also as "*organocatalyst*", comprises (mainly) carbon (C), hydrogen (H), nitrogen (N), oxygen (O), sulfur (S) and phosphorus (P). Organocatalysts do not contain transition metals in their active sites.[1] Although the field took its name only recently, about a decade ago, the history dates back to the work of German chemist Justus von Liebig appeared in 1860 (German title: *Ueber die Bildung des Oxamids aus Cyan*) where he reported the synthesis of oxamide from dicyan and water representing the first organocatalytic reaction (Scheme 1).[2] It will require more than a century for chemical community to capture the attention of this fruitful field of catalysis serving diverse opportunities in chemical synthesis particularly in asymmetric synthesis.



Scheme 1. Justus von Liebig's oxamide synthesis

1.1.1 Asymmetric Organocatalysis

The first asymmetric reaction was discovered by Louis Pasteur in 1858 where he carried out a decarboxylative kinetic resolution utilizing the microorganism *Penicillium glauca*. He observed that this organism destroyed (*d*)-enantiomer of a racemic solution of ammonium tartarate more rapidly.[3] That is why enzymes were the first to be considered as a catalyst for accelerating organic reactions.[4] In fact, it was long believed that an enantiomerically enriched product could be obtained in a catalytic reaction only by utilizing either enzymes or chiral ligand complexes of transition metals. To illustrate, in their excellent book *Classics in Total Synthesis*, Sorensen and Nicolaou defined asymmetric catalysis by stating that "In a catalytic asymmetric reaction, a small amount of an enantiomerically pure catalyst, either an enzyme or a synthetic, soluble transition metal complex, is used to produce large quantities of an optically active compound from a precursor that may be chiral or achiral."[5,2b] Only a few years after the publication of this book, this view has been significantly altered by booming papers of List *et al.*[6] and MacMillan *et al.*[7] on asymmetric organocatalysis (AO), even though it has had long standing history.

1.1.2 Historical Development

The first example of an asymmetric organocatalytic reaction reported in the literature was the enantioselective synthesis of mandelonitrile, a compound of cyanohydrin class, from benzaldehyde and HCN employing quinine and quinidine (pseudo-enantiomers of each) alkaloids as the chiral catalysts. The milestones in the historical developments of asymmetric organocatalysis from this infancy are summarized in Figure 1 (For the work of Takemoto published in 2003 please see page 17-19. It is presented there to serve a better organization for this thesis.).

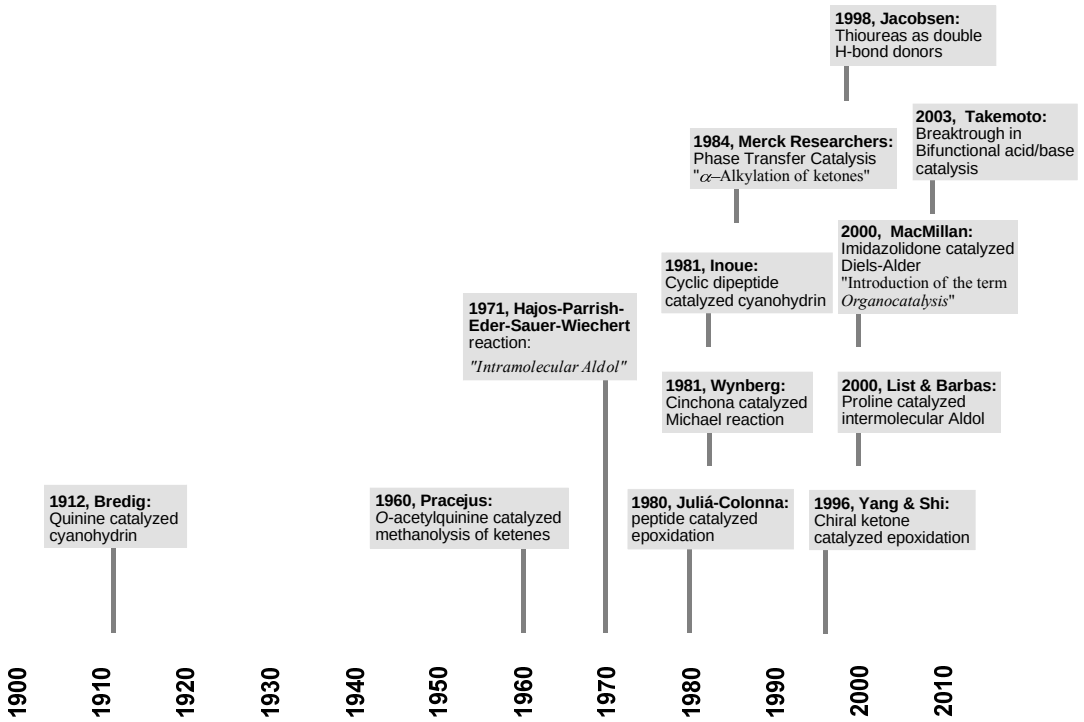
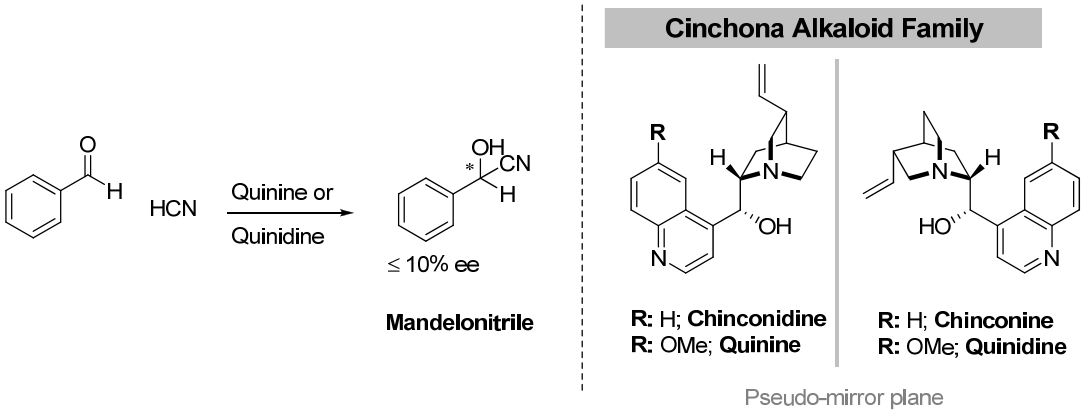


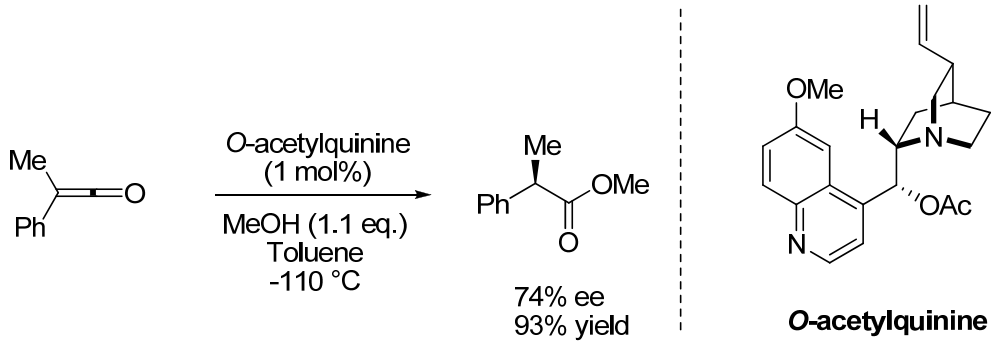
Figure 1. Milestones in the historical developments of asymmetric organocatalysis

In this pioneering investigation done by Bredig and Fiske in 1912, they reported that the enantiomeric excesses (*ee*) up to 10% were achieved at most (Scheme 2).[8]



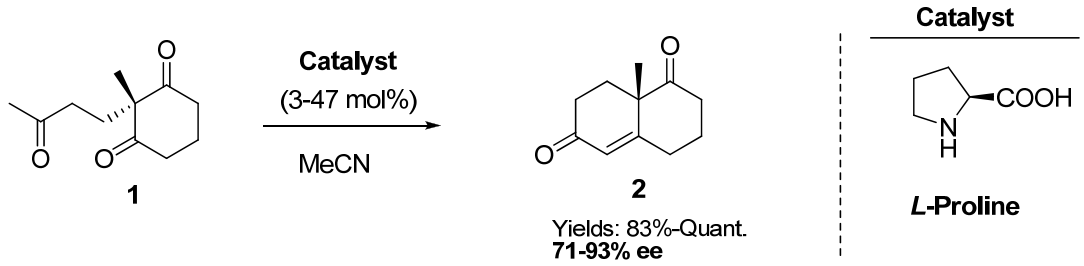
Scheme 2. The first example of asymmetric organocatalysis (AO) - Bredig's work

It took about a half century that a purely organic compound catalyzed reaction to appear again in the chemical literature (Figure 1). This time again, it was a member of cinchona alkaloid as catalyst tested by Pracejus *et al*. in the methanolysis of phenylmethylketene in 1960.[9] They have achieved 74 % *ee* at -110 °C when only 1 mol% *O*-acetyl-quinine (hydroxyl-acetylated quinine derivative) was applied as the catalyst (Scheme 3).



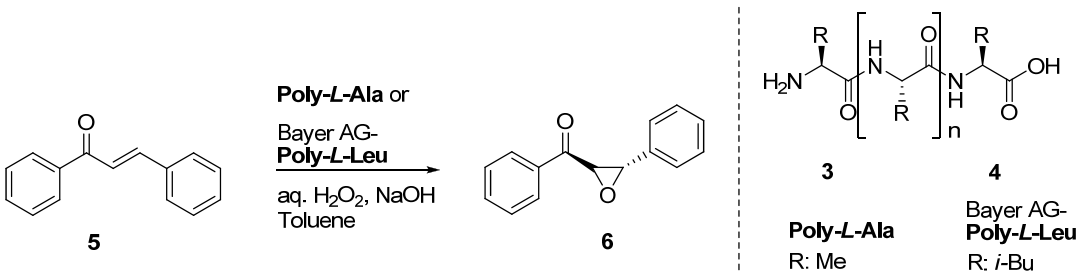
Scheme 3. The first successful example of AO - Pracejus's work.

The year 1971 came up with a breaktrough in an enantioselective organocatalytic reaction but this time the actors were pharmaceutical company employees. Namely; Hajos and Parrish of Hoffmann-La Roche and Eder, Sauer and Wiechert of Shering independently discovered that the triketone **1** could be cyclized in an intramolecular aldol reaction by the structurally very simple amino acid (*S*)-Proline as the catalyst to afford the highly enantioenriched Wieland-Miescher enone **2** which is an important precursor for stereoid synthesis.[10] This reaction is recognized later as the Hajos-Parrish-Eder-Sauer-Wiechert reaction.



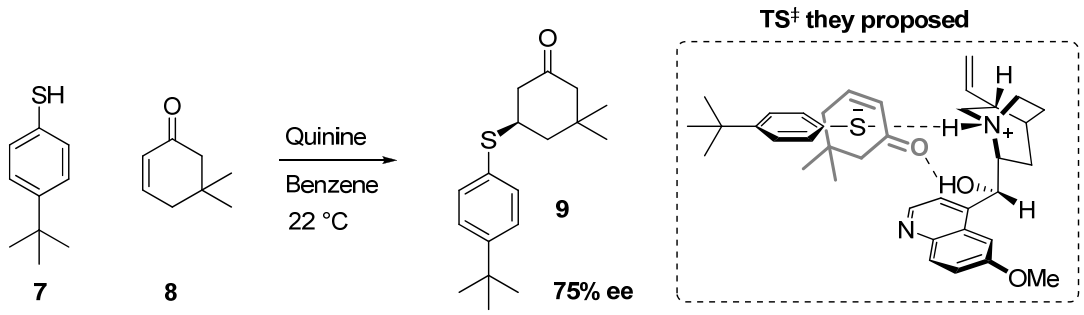
Scheme 4. The Hajos-Parrish-Eder-Sauer-Wiechert reaction

Another striking discovery in this area of research appeared in chalcone epoxidation in 1980. Juliá and Colonna *et al*. reported that an alanine-derived poly-amino acid macromolecule **3** can catalyze epoxidation of chalcones in enantioselectivities up to 95%.[11] Although Juliá's work noticed the attention of chemical industry since using cheap oxidant (H_2O_2) and base (NaOH) and avoiding transition metals, this protocol had some drawbacks for industrial applications such as long reaction times (5 day), employing large excesses of catalyst as much as 200% (w/w) and requiring preactivation of catalyst for 6h were needed. Interestingly, Bayer AG researchers developed the Poly-Leu **4** after a straightforward screening of amino acids and this catalyst was found to be much more active than Poly-Ala **3** (3h of reaction time, none of necessity for preactivation of catalyst) in transformation of chalcone **5** to epoxide **6** (Scheme 5).[1]



Scheme 5. Juliá-Colonna epoxidation-Bayer AG's application

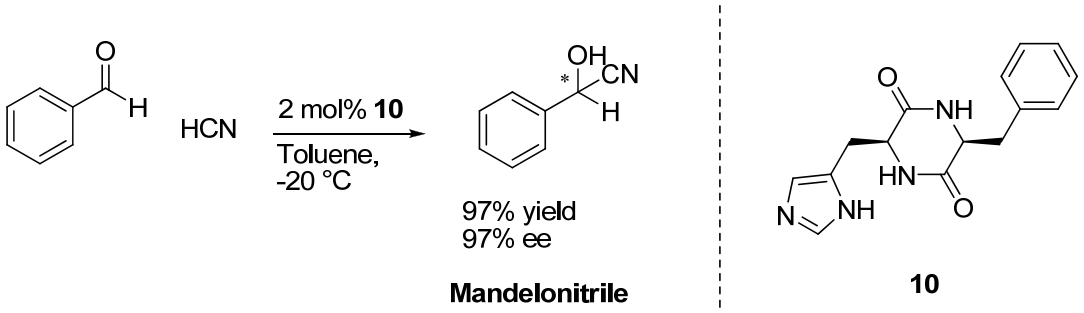
Chincona alkaloids emerged again by Wynberg *et al*. presenting chincona alkaloid catalyzed reaction series where quinuclidine N atom of the catalyst acting as both nucleophile and base in the early 1980s. Among them, the most notable came in 1981 where they reported that cinchona alkaloids were efficient (albeit only moderately selective, 75% *ee*) bifunctional organocatalysts for the conjugate addition of thiophenol **7** to cyclohexanone **8** to afford Michael addition product **9**, and proposed a mode of catalysts action after doing some systematic mechanistic studies (Scheme 6).



Scheme 6. Wynberg's proposal for the bifunctional activation mode of Quinine

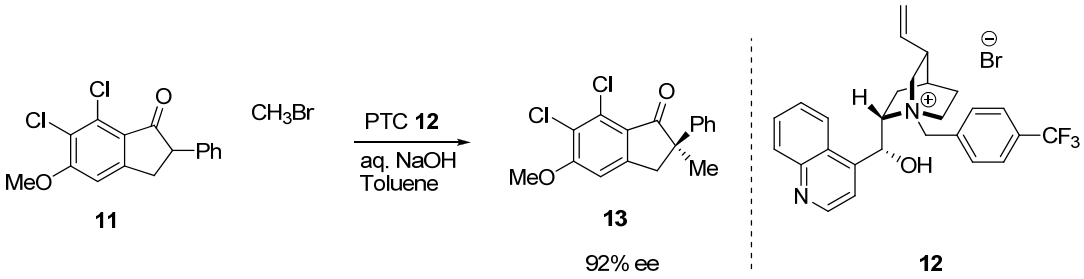
To my best knowledge, this work was the first example of an organocatalyzed reaction studied in detail both mechanistically and presenting the future challenges and perspectives for such organic transformations. In that paper's "Conclusion and Prospects" part they stated their perspective as the following. "…This study…shows the advantages of bifunctional (or polyfunctional) catalysis in the preparation of enantiomers by catalytic chiral synthesis. A great number of reactions can be catalyzed bifunctionally. *The scope of the utility of hydroxy amines can perhaps be extended by constructing a catalyst containing a stronger base or a better hydrogen bond donor.*"[12] However their critical work will not be noticed until the report of Takemoto *et al*. in 2003, which is considered as the first highly enantioselective bifunctional acid/base catalysis using tertiary amine-thiourea catalyst.[13]

Again in 1981, a sparking catalysis example was reported on a cyclic dipeptide **10** organic catalyst derived from readily available *L*-histidine and *L*-phenylalanine by Inoue and co-workers. Both enantioselectivity and simplicity of the reaction protocol was quite impressive (Scheme 7). Their dipeptide catalyst **10** has been shown to effectively catalyzing the formation of the cyanohydrin type mandelonitrile from benzaldehyde and HCN highly enantioselectively (97%) as opposed to the first organocatalytic attempt done by Bredig.[14]



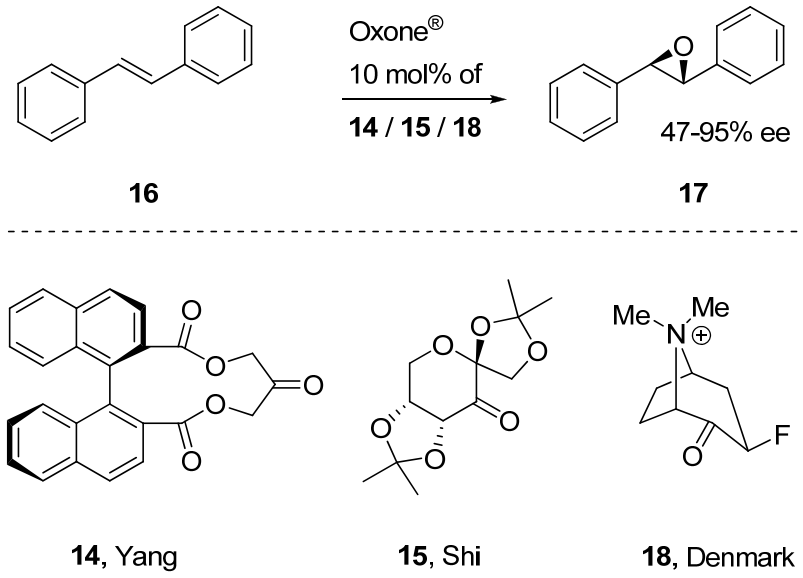
Scheme 7. Cyclic dipeptide **10** catalzed cyanohydrin formation by Inoue *et al.*

One of the most important works in asymmetric organocatalysis accomplished by the researchers at Merck in 1984, was rendering asymmetric α-alkylation of an achiral ketone **11** possible. Researchers applied a chiral phase-transfer-catalyst (PTC) **12**, a quaternary ammonium salt of cinchonidine, thereby succeeded the first asymmetric PTC reaction to produce α-methylated ketone **13** in high yield and enantioselectivity (Scheme 8)[15].



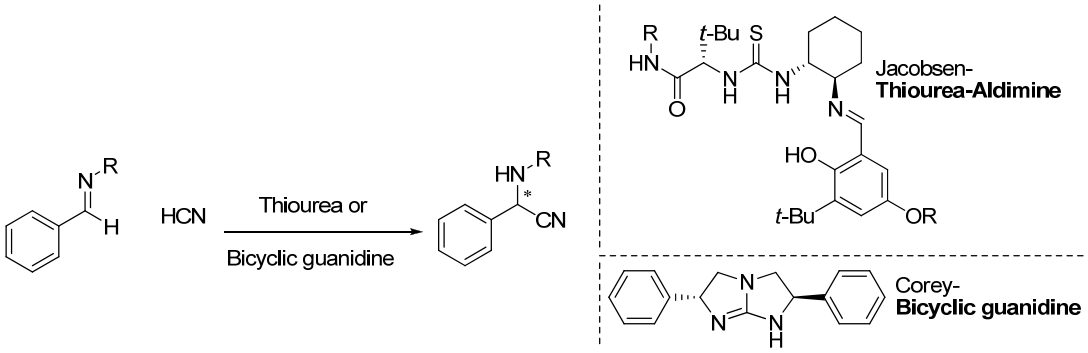
Scheme 8. Asymmetric PTC strategy for α-alkylation of ketones-Researchers at Merck

The year 1996 has witnessed two conspicuous catalytic epoxidations employing chiral ketones **14** and **15** as the chirality inducing small organic molecules developed respectively by Yang and Shi for the conversion of *trans*-stilbene **16** to obtain epoxide **17** utilizing oxone® as the oxidant. One year after their publication, Denmark also reported another chiral ketone **18** bearing a quaternary ammonium unit for the same purposes (Scheme 9).[16]



Scheme 9. Chiral ketones as organocatalyst-Yang, Shi and Denmark

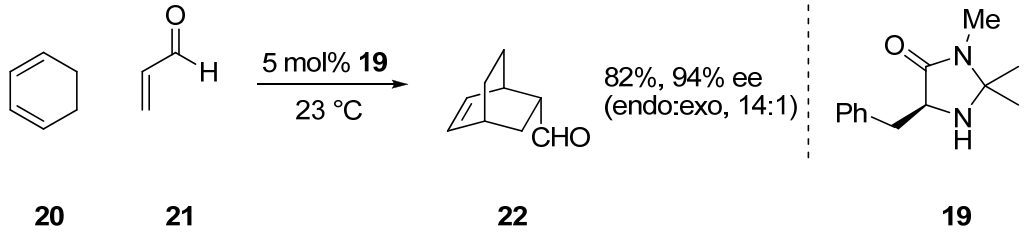
Following these works, two interesting papers were published in years 1998 and 1999 respectively by Jacobsen and Corey, describing the utility of thioureas-Schiff base hybrid (Jacobsen) and bicyclic guanidines (Corey) as well-defined hydrogen-bond donor chiral organocatalysts for the activation of imine electrophiles in asymmetric Strecker reaction shown in Scheme 10.[17]



Scheme 10. Jacobsen's thiourea-aldimine and Corey's bicyclic guanidine catalysts

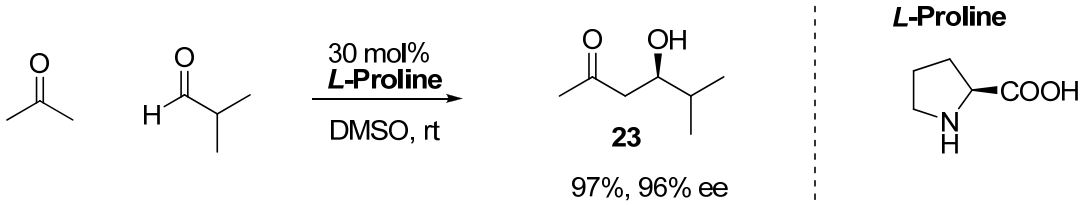
Although few in number, very impressive and cutting-edge works described in asymmetric small purely organic molecule catalyzed reactions appeared during the 20th century. However none of the aforementioned organocatalytic works has drawn the attention of chemical society as that of MacMillan[7] and List & Barbas[6] published

at the same year, in 2000. Their seminal works sparked asymmetric synthesis chemists to go for "organocatalysis rush", resultantly causing an exponentially increasing number of publications in this hot field of research during the last decade. As shown in Scheme 11, in their paper, MacMillan presented a readily available phenylalanine-derived imidazolidone **19** catalyzed asymmetric Diels-Alder reaction of *α,β*-unsaturated aldehydes (94% *ee*) and more significantly introduced the terms "organocatalyst" and "organocatalysis" for the first time.[7] Following this paper, wherein their imidazolidone **19** catalyzed Diels-Alder reaction of cyclohexa-1,3-diene **20** and acrolein **21** with 94% *ee* and quite good 14 to 1 endo/exo isomeric ratio of bicyclic adduct **22**, they showed that such secondary amine catalysts can successfully catalyze at least 50 new asymmetric organic reactions up to now.



Scheme 11. MacMillan's imidazolidone organocatalyzed Diels-Alder reaction

Other breakthrough work published at the turn of the millennium by List and Barbas, presented natural cyclic amino acid (*S*)-Proline as a very effective catalyst mimicking aldolase enzyme and catalyzing the first intermolecular asymmetric organocatalytic direct aldol reaction.[6] They proposed the mode of activation as enamine catalysis for the aldol reaction of acetone and isobutyraldehyde for the highly enantioselective formation of aldol product **23** (Scheme 12). After their pioneering work, many chemists worldwide investigated the catalytic potential of (*S*)-Proline in wide array of reactions.[18]



Scheme 12. (*S*)-Proline catalyzed direct intermolecular aldol reaction by List and Barbas

1.1.3 Classification of Asymmetric Organocatalysis

The classification of organocatalysis is somehow immature. Unavailability of sufficient mechanistic works in particular kinetic data in this field might have been the reason. Books or reviews written in this field use an approach generally according to the reactions catalyzed or type of organocatalyst used. To our best knowledge, the best conceptualizations were done by Berkessel[1], List[19] and Macmillan[20]. In his brilliant book, Berkessel categorized them according to the type of bonding presumed in transition state interaction of the substrate with the catalyst. He classified them broadly into two as "covalent catalysis" and "non-covalent catalysis". Next elements could be the nature of the catalaphoric unit, whether acid or base in broad terms. List categorized them in such a manner into four as seen in Figure 2, where principal active site being either Lewis acid, Lewis base, Brønsted acid or Brønsted base.

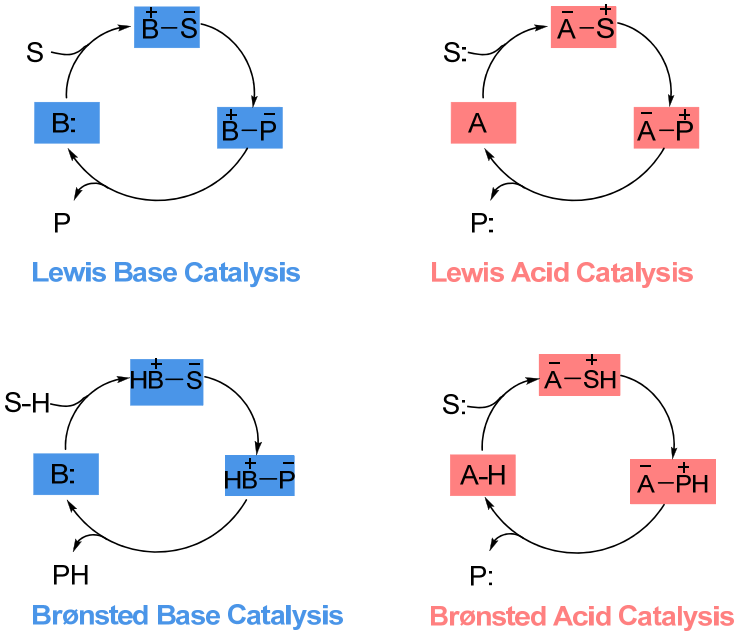


Figure 2. Classification of organocatalytic cycles according to nature of catalaphore

Although the devised catalytic cycles are very helpful for giving the field a logical structure, this approach is insufficient somewhat to consider a quick grasping of the underlying mechanism of any reaction by such catalytic reactions. In 2008, Macmillan reported his insights on the advent of the field, organocatalysis.[20] In that report, he focused on the significance of organization of the field and in this respect discussed the advantages of regarding generic mode of activation of catalytic systems. Some of the perspectives presented there are as follow. *"A generic activation mode describes a reactive species that can participate in many reaction types with consistently high enantioselectivity (as opposed to one or two unique transformations). ... The value of generic activation modes is that, after they have been established, it is relatively straightforward to use them as a platform for designing new enantioselective reactions."* A notable observation stated in the same article is that the most of 130 organocatalytic reactions published during the period 1998-2008 fitting directly on only five or six activation modes shown in Figure 3. Therefore, it is quite rational to think on those well-established activation modes in designing both new organocatalytic reactions and new organocatalysts. However, focusing on new activation modes would have a greater impact on catalysis in a broader aspect. [20]

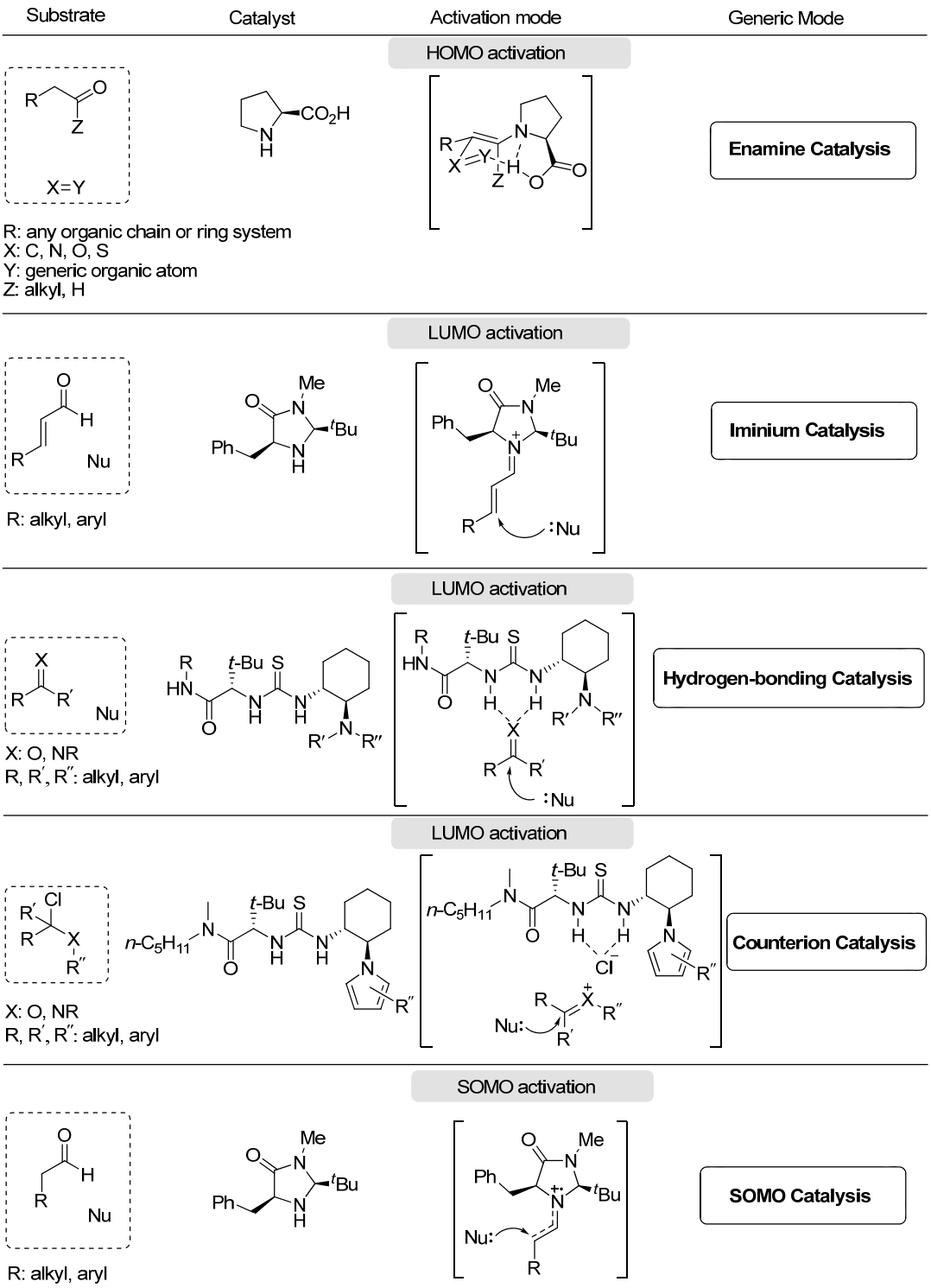


Figure 3. Commonly encountered generic modes of activation in organocatalysis

The most frequently encountered generic modes of activation in asymmetric organocatalysis are that of "enamine" and "iminium" catalysis. The next frequent is being "hydrogen-bonding catalysis". Hydrogen-bonding catalysis is giving birth to a

highly emerging mode of activation. More explicitly, it is acquiring a new name, "bifunctional organocatalysis" sometimes called "multifunctional organocatalysis" as the work in such catalytic processes increase day by day.[20,13a]

1.1.4 General Acid/Base Catalysis-Bifunctional Organocatalysis

"*Catalysis* by acids or bases in solution is said to be general when it is possible to detect catalysis brought about by species other than the ions formed from the solvent itself (e.g. when water is the solvent, by species other than H^+ and OH^- ions)" by definition according to IUPAC Compendium of Chemical Terminology.[21] General acid/base catalysis is encountered in many protein enzymes as a way to increase the rate of biological transformations.[22] The classical example is the enzyme *α-chymotrypsin*, a serine protease, having general acid/base (and covalent) catalysis for protein hydrolysis. This enzyme comprises aspartic acid, histidine and serine residues, called *catalytic triad*, as catalytically functioning active site for peptide hydrolysis. Serine residue is a hydroxyl group which is widely accepted as a poor nucleophile. However, carboxylate group of aspartic acid partially removing the proton of imidazole unit of histidine which in turn becomes sufficiently basic to deprotonate the hydroxyl proton of serine residue thereby rendering that hydroxyl group nucleophilic enough to attack the amide's carbonyl carbon (Figure 4). This scenario is supported by the hydrogen-bonding network observed in X-ray crystal structure of *α-chymotrypsin*.[22c]

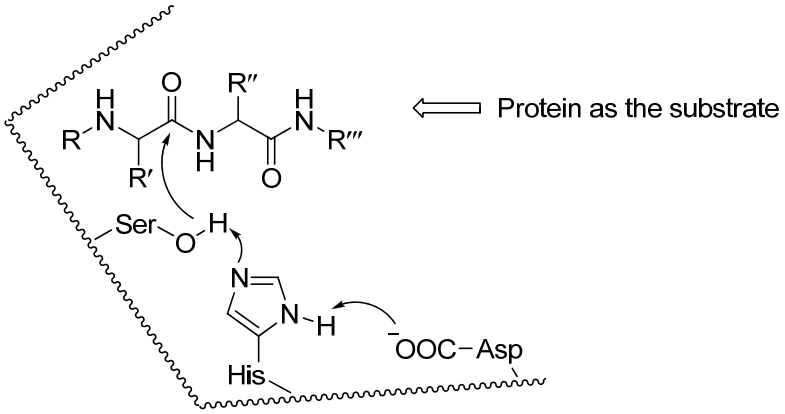


Figure 4. Catalytic triad of *α*-chymotrypsin.

Inspired by the efficient and selective nature of enzymes, recent years have witnessed an explosively emerging use of acid/base catalysis cooperatively for the dual activation of both electrophiles and nucleophiles in a variety of asymmetric organocatalytic reactions. Such catalytic processes are called "bifunctional organocatalysis" involving a basic unit for the highest-occupied molecular orbital (HOMO) activation (increase) of pro-nucleophiles and an acidic moiety for the lowest-unoccupied molecular orbital (LUMO) activation (decrease) of pro-electrophiles thereby causing a decrease in activation energy which renders reactions possible.[13b,20] The most commonly encountered and emerging case of bifunctional organocatalysis involves the use of *tert*-amines as the base and double hydrogen-bond donor (e.g. most frequently urea or thiourea as a well-established donor) as the acidifying moiety anchored on a chiral scaffold (Figure 5). [13b]

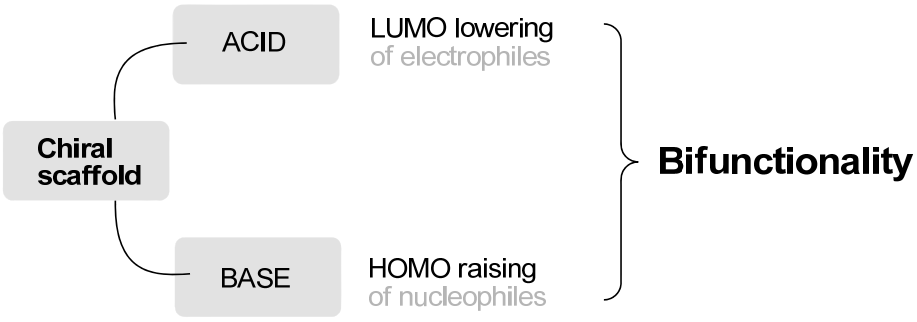


Figure 5. Bifunctionality of a chiral *tert*-amine/thiourea organocatalyst

1.1.4.1 The Emergence of Highly Enantioselective Acid/Base Organocatalysis

Most organic reactions comprise an electrophile and a nucleophile counterpart and, therefore these reactions can be promoted either by acid or base catalyst or more effectively by a combination of both, an acid/base catalyst, causing dual activation of electrophile and nucleophile simultaneously. Arguably, the most structurally simple bifunctional acid/base catalysts are natural amino acids. Figure 6 demonstrates an (*S*)-Proline catalyzed direct aldol reaction performed by List *et al.*[6] and proposed transition state structure.[13b]

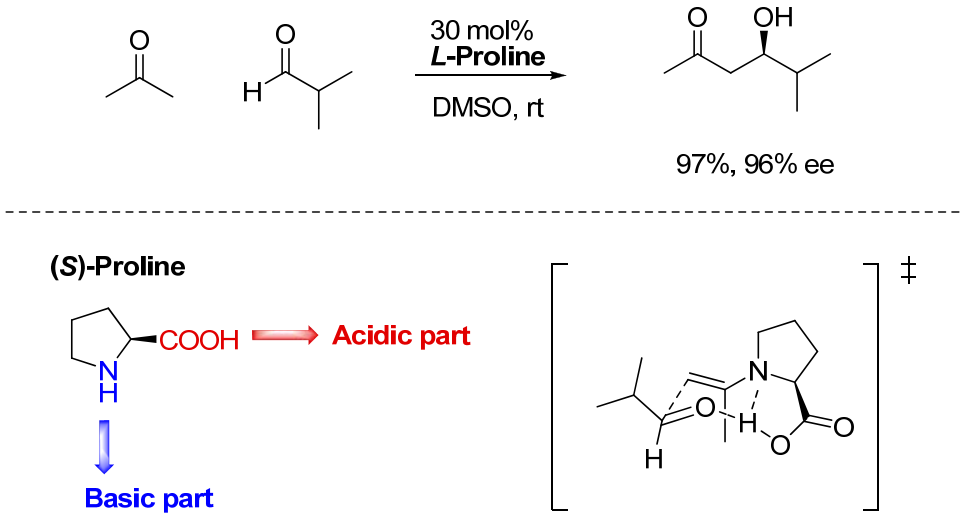
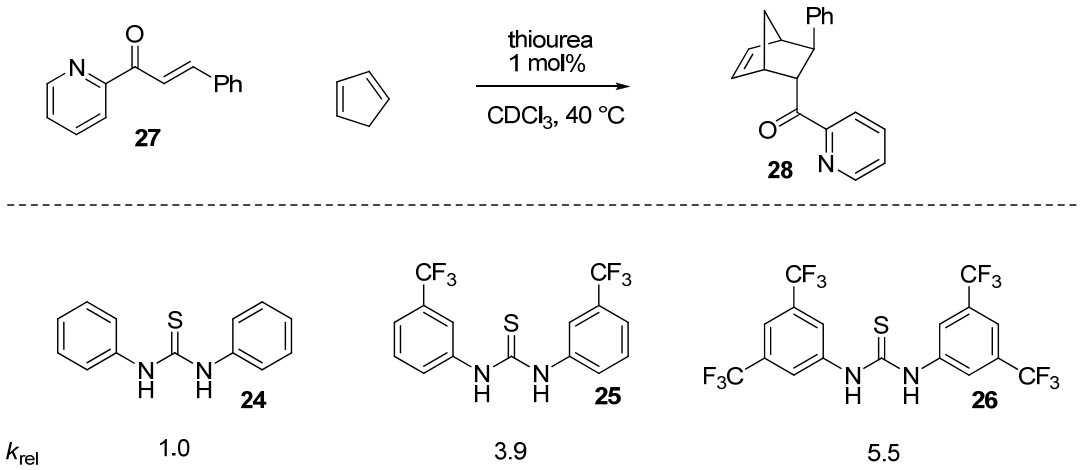


Figure 6. Bifunctionality of (*S*)-Proline in direct aldol reaction

Bifunctionality of the catalyst can easily be recognized after the analysis of TS of this reaction. TS of this aldol involves a six membered cyclic structure assisted by the carboxylate proton which serves as the acid activation of reacting aldehyde. Secondary nitrogen in proline acts as a base however restricting the substrates to enolazible and more explicitly enamine forming substrates such as aldehydes or ketones. However, bifunctional acid/base catalysis can be applied to a diverse array of nucleophiles and electrophiles as the substrates.[13b] The first mechanistic study in asymmetric bifunctional acid/base organocatalysis dates back to Wynberg's works reported in 1980. In this pioneering study, after a systematic screening of various natural cinchona alkaloid derivatives for conjugate addition of thiols to cyclic enones, it was shown that the presence of hydroxyl proton is a prerequisite for the double activation, acting as acid. Although catalytic efficiency of natural alkaloids was superior in asymmetry induction compared to the esters variants modified on hydroxyl group, enantioselectivity was moderate (75% *ee* at most).[12] The development of highly stereoselective stood as an unmet challenge for about three decades.

A breakthrough in this field came in 2003 with the seminal work of Takemoto and coworkers where authors reported the first truly stereoselective bifunctional acid/base organocatalysis.[13a] They have designed a tertiary amine/thiourea catalyst

initially tested for conjugate addition of malonates to nitroolefins. They were inspired by the Schreiner's work for their catalyst design.[23] Schreiner *et al*. reported that symmetric thioureas (**24**, **25** and **26**) shown in Scheme 13 can catalyze the Diels-Alder reactions of chalcone **27** and cyclopentadiene to afford the bicyclic adduct **28**.[24] They have observed that the increase in acidity of thiourea caused increase in rate accelerations.



Scheme 13. Schreiner's thiourea catalyzed Diels-Alder reactions

Inspired by Schreiner's thiourea catalysts, Takemoto *et al*. designed and developed various novel bifunctional organocatalysts possessing a thiourea moiety and an amino group. Authors discussed the rational design of their thiourea catalysts in their account published in 2008 (Figure 7).[23]

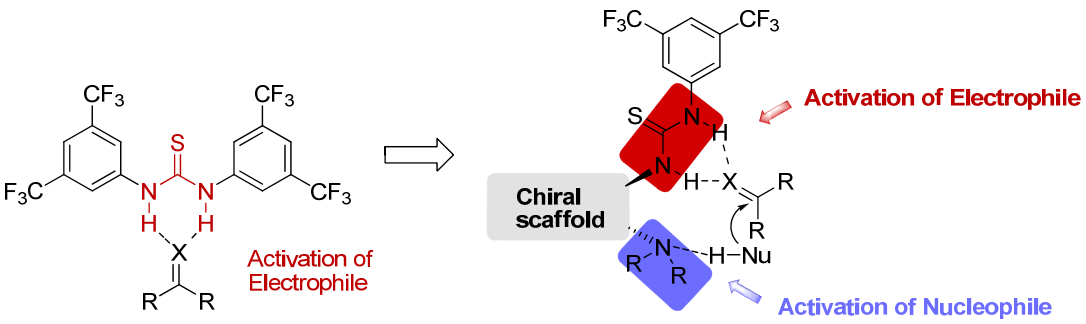
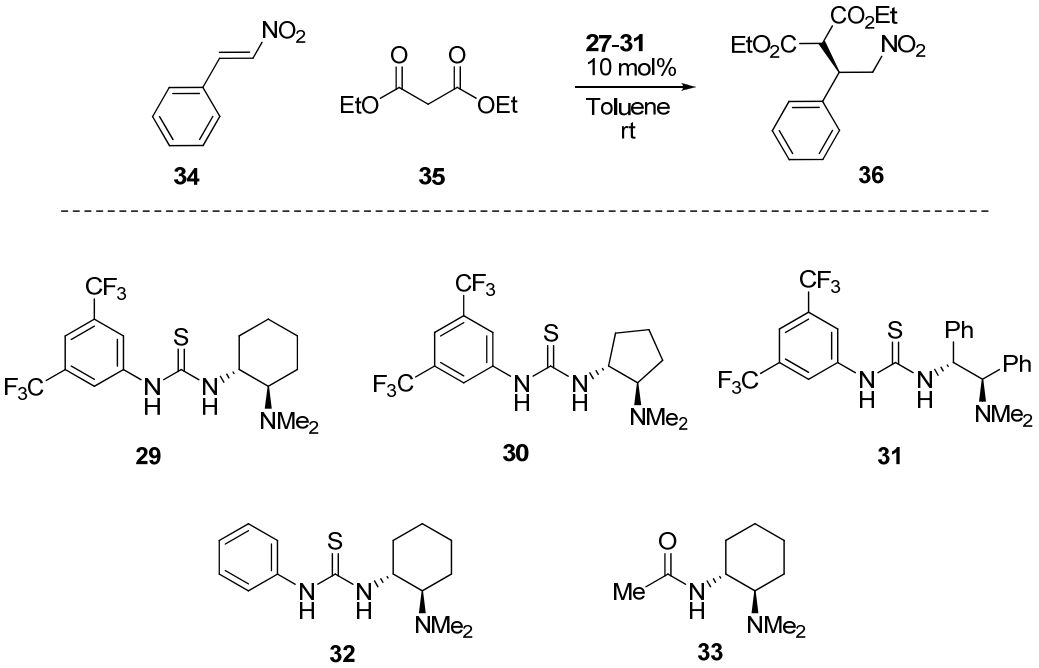


Figure 7. Takemoto's design of bifunctional *tert*-amine/thiourea catalysts

They have designed various bifunctional catalysts derived from chiral vicinal diamines **29-33** and investigated their catalytic activities in asymmetric conjugate addition of diethylmalonate **35** to *trans*-(*β*)-nitrostyrene **34** yielding Michael adduct **36** (Scheme 14 and Table 1).[23]



Scheme 14. Takemoto's bifunctional *tert*-amine/thiourea catalysts in asymmetric conjugate addition

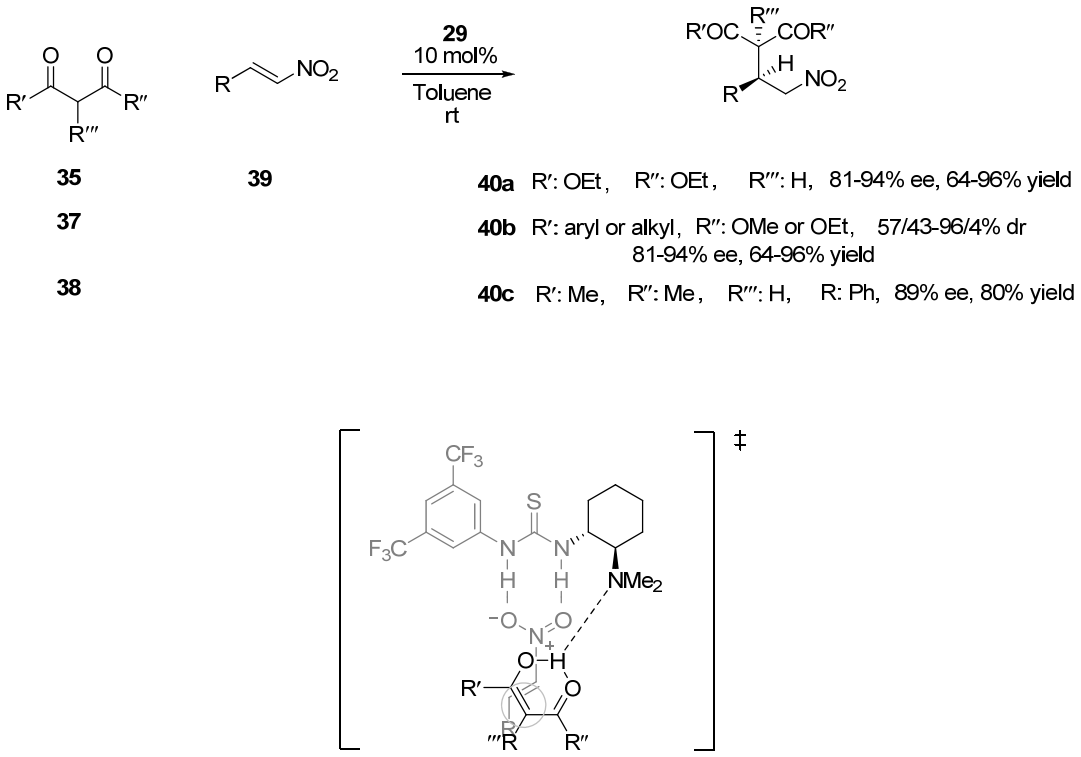
Table 1. Michael Addition of diethylmalonate **35** to *trans*-(*β*)-nitrostyrene **34** catalyzed by **29**-**33**[a]

Entry	Thiourea	Time (h)	Yield (%)	*ee* (%)
1	**29**	24	86	93
2	**30**	48	56	84
3	**31**	48	52	64
4	**32**	48	58	80
5	**33**	24	14	35

[a]Reactions were carried with 2 equiv. of diethyl malonate.

Nitrostyrenes were used as the substrate in their catalyst evaluations since it was known that the thioureas were shown to exhibit eight-membered hydrogen bonding with nitro group of nitrobenzene by co-crystallization experiments. To understand the effect of mono hydrogen-bond donor on reactivity and selectivity in catalysis, they prepared the amide **33** and subjected to the Michael reaction shown in Scheme 14. Among the thiourea catalysts **29**-**31**, catalyst **29** was the best in terms of chemical yield and enantioselectivity (entries 1-3). Further modification on acidity showed that bis-trifluoromethyl substituted catalyst **27** giving better results considering both yields and *ee*'s (entries 1 and 4). Using mono hydrogen-bond donor amide catalyst **33** gave frustrating results in terms of reactivity and selectivity (entries 1 and 5). With these results in hand, they concluded that both rigidity of the chiral diamine scaffold and dual synergistic function of two N–H bonds as the double hydrogen-bond donor and the tertiary amino group in the catalyst were crucial for the highly enantioselective Michael reaction (entries 1–5).[13a,20]

After their initial ground-breaking report in 2003, they published the next work in 2005 fully accounting the substrate scope of the bifunctional catalyst **29**. They showed that the scope of the substrates could be extended to *β*-ketoesters (**37**) and *β*-diketones (**38**) presenting more or less the same catalytic performances with various nitrostyrenes (**39**) yielding higly stereoselective conjugate adducts **40a-c**. In that work, they have also presented a transition state model to rationalize the sense of stereoselectivity (Scheme 15).[25]

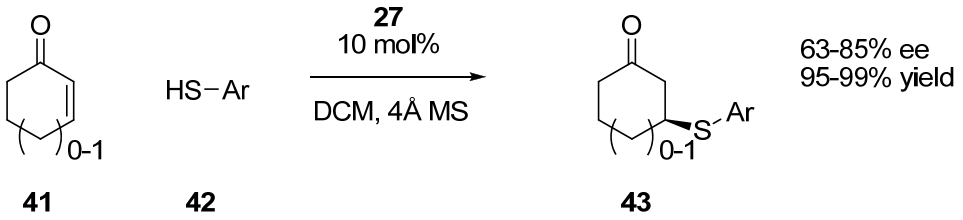


Scheme 15. Substrate scope and TS model of bifunctional *tert*-amine/thiourea catalyst **29**

Their thiourea and pendant tertiary amino group bearing bifunctional catalysts were found to significantly accelerate several nucleophilic addition reactions of active methylene compounds to electron-deficient alkenes. Following their seminal work, they employed structurally diverse electrophile partners bearing nitro,[25] imide[26], and imine[27] to such acid/base catalysis reactions. It was concluded that the double hydrogen-bonding activation of electrophiles by the thiourea moiety and simultaneous deprotonation of nucleophiles by the basic dimethylamino group of catalyst **29** proved to play a crucial role for enhancing both reaction rate and enantioselectivity.

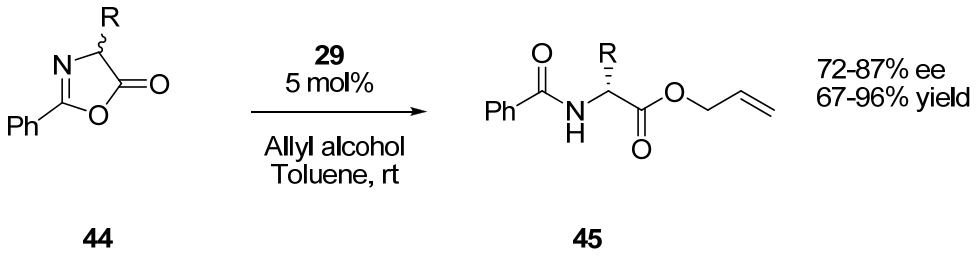
1.1.4.2 Conjugate Addition of 1,3-Dicarbonyls to *trans*-(*β*)-Nitroolefins

Following Takemoto's pioneering study, there has been great interest in designing novel acid/base bifunctional chiral catalysts for synthetically useful such organic transformations.[13b,23] Chen and coworkers demonstrated that using Takemoto's catalyst **29** they can effectively promote the addition of aryl thiols **42** to cyclic enones **41** to furnish *β*-thiolated ketones **43** in moderate to good *ee*'s as shown in Scheme 16.[28]



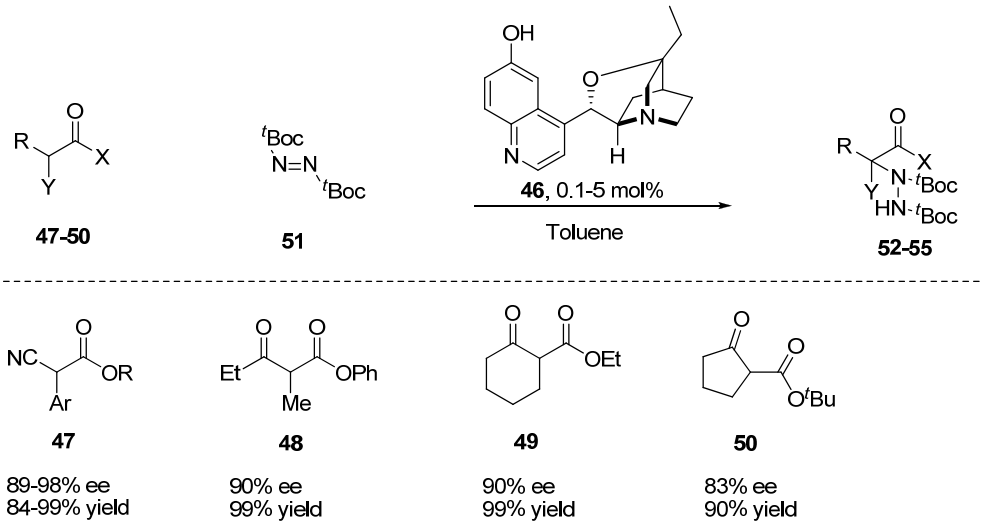
Scheme 16. Catalyst **29** catalyzing Michael additions of thiols by Chen

Again in 2005, Berkessel *et al*. reported the use of catalyst **29** in dynamic kinetic resolution of azalactone **44** by utilizing allyl alcohol to yield *α*-aminoacid derivatives **45**, thereby expanding the scope of Takemoto's catalyst further (Scheme 17).[29] By this work, Berkessel showed again a bifunctional mode of Takemoto's catalyst, however more interestingly Lewis basic dimethylamino group of the catalyst as a nucleophile and thereby raised the potential of this catalyst which could act as acyl transfer agent.



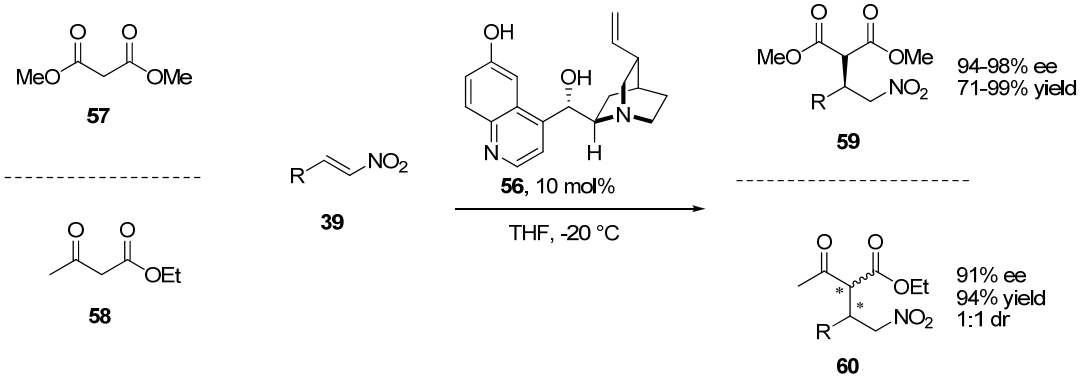
Scheme 17. Berkessel's dynamic kinetic resolution with the catalyst **29**

One year after the report of Takemoto's seminal paper, cinchona alkaloid derived catalyst have emerged as highly stereoselective bifunctional acid/base organocatalysts independently by the Jørgensen *et al*. and Deng *et al*. Jørgensen and coworkers reported an *β*-isocupreidine catalyst **46** promoted *α*-amination of unsymmetrical 1,3-dicarbonyls **47-50** with di-tert-butyl azodicarboxylate **51** to form various *α*-aminoacid analogues **52-55** (Scheme 18).[30]



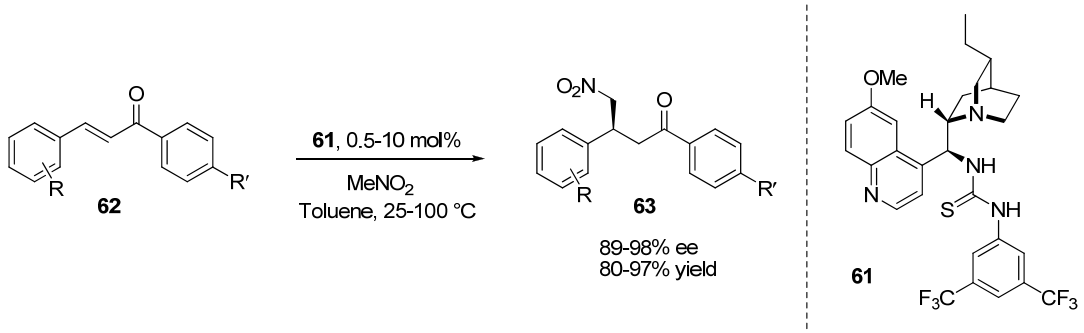
Scheme 18. Jørgensen's *α*-amination of unsymmetrical 1,3-dicarbonyls

n that same year, Deng and coworkers designed structurally similiar catalyst **56** derived from chincona alkaloids functioning very effectively in the 1,4-addition of dimethyl malonate **57** and ethyl acetoacetate **58** to various nitroolefins **39** forming enantiomerically highly pure adduct series **59** and **60** (Scheme 19).[31]



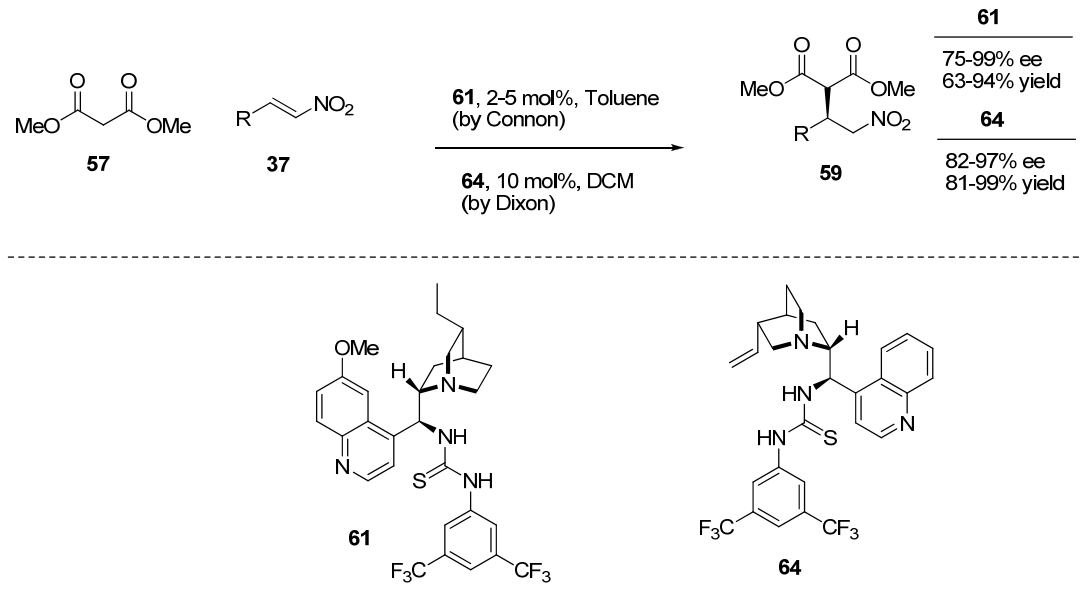
Scheme 19. Deng's catalyst promoted Michael reaction.

Thioureas appeared again in 2005, this time derived from cinchona alkaloids as bifunctional acid/base catalysts. Scheme 20 demonstrates a report by Soós *et al*. presenting a highly enantioselective conjugate addition of nitromethane to chalcones **62** using bifunctional cinchona organocatalyst **61** to produce *γ*-nitro ketones **63**.[32]



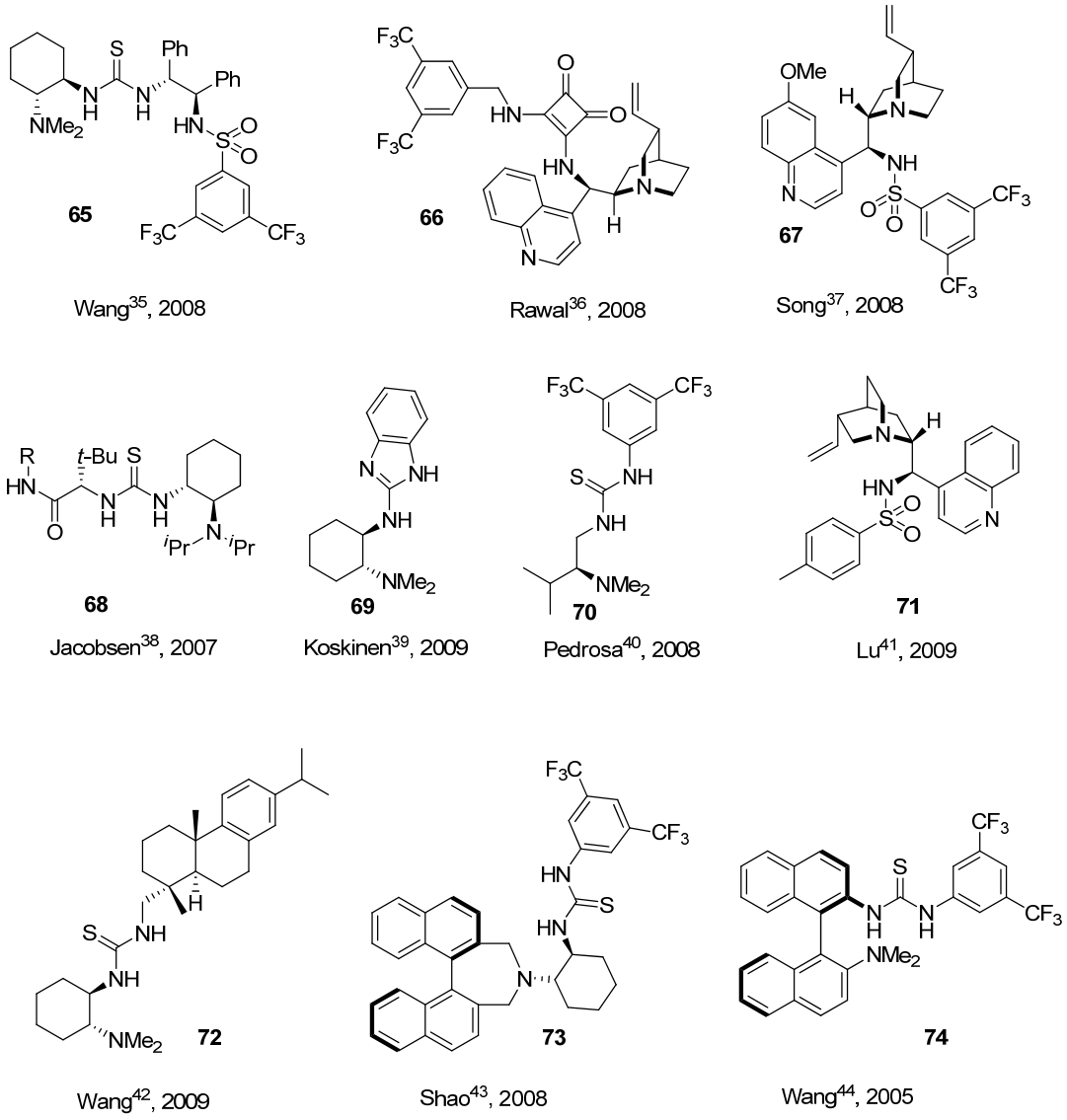
Scheme 20. Conjugate addition of nitromethane to chalcones by Soós *et al*.

The same catalyst **61** was shown to effectively catalyze conjugate addition of dimethyl malonate **57** to various nitroolefins **39** by Connon *et al*. to obtain *γ*-nitro carboxylates **59** in very high enantioselectivities and yields.[33] Independently in 2005 Dixon and coworkers has published a similar thiourea catalyst **64** promoting the same reaction with comparable results.[34]



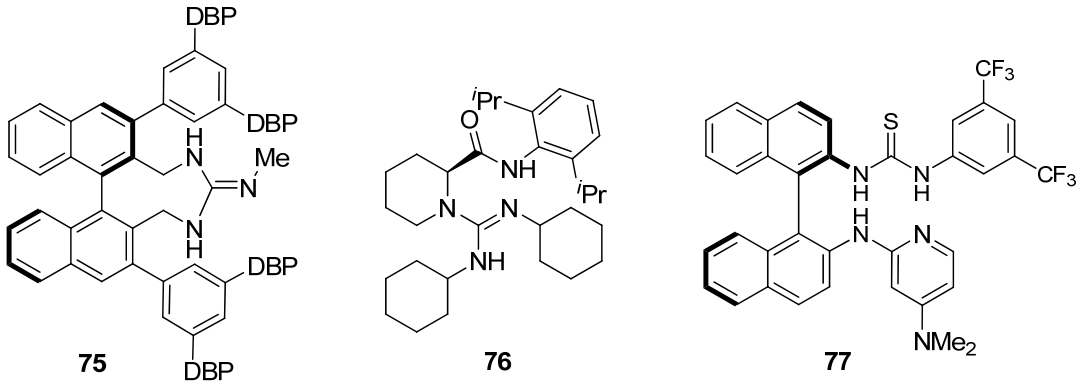
Scheme 21. Connon's and Dixon's thiourea catalysts **61** and **64**

Following these early examples of bifunctional acid/base organocatalysts, there has been great interest in designing novel chiral catalysts (e.g. **65**-**74**) for synthetically useful such organic transformations.[35-44] Most of the aforementioned designs particularly focused on the introduction of new reactivity on the acidifying moiety where thioureas being the most popular choice. In some brilliant designs, the utility of thioureas bearing an additional proton donor **65** by Wang,[35] squaramides **66** by Rawal,[36] and sulfonamides **67** by Song[37] in conjuction with a tertiary amine most allowed the emergence of higly effective protocols applying as low as 0.5 mol% catalyst loadings for such highly stereoselective reactions (Scheme 22).[38,39,40,41,42,43,44]



Scheme 22. A literature selection of bifunctional acid/base organocatalysts

Scheme 22 shows a selection of literature concerning the development of novel bifunctional acid/base organocatalysts. A careful look at these catalyst shown in Scheme 22 would reveal the fact that all were designed in the pursuit of novel acidifying moieties without arguing. However, very little attention has been paid to replace the commonly used trialkylamines as bases with their more active surrogates such as guanidines, amidines, imidazoles, 4-dimethylaminopyridine (DMAP) *etc.* Terada and co-workers have reported a higly active axially chiral C_2-symmetric guanidine as a super-base catalyst **75** that can successfully catalyze the Michael addition of malonates (the least reactive member of 1,3-dicarbonyls) to nitrostyrenes with catalyst loadings low as to 2 mol%.[45] As a second interesting example, Feng *et al*. developed an amide/guanidine bifunctional organocatalyst **76** for the asymmetric Michael addition of *β*-ketoesters to nitroolefins. Catalyst **76** demonstrated very high enantio- and diastereoselectivities (up to >99:1 d.r. and 97% *ee*) and yields (up to 99%) for a wide range of substrates.[46] Direct Michael addition of nitroalkanes to nitroalkenes remained complicated by further reaction of the initial product, causing oligomer formations till the work of Wulff *et al*. They overcame this problem by designing a BINAM incorporating a thiourea **77** to activate the nitroalkene and a basic DMAP unit for deprotonation of nitroalkane and for binding the resulting nitronate anion *via* double hydrogen bonds. Resultantly, 1,3-dinitro compounds were furnished in both high yield and enantioselectivity, without competing oligomerization.[47] Wulff's work described shortly here will be re-evaluated in forthcoming pages, since it is closely related to our work.



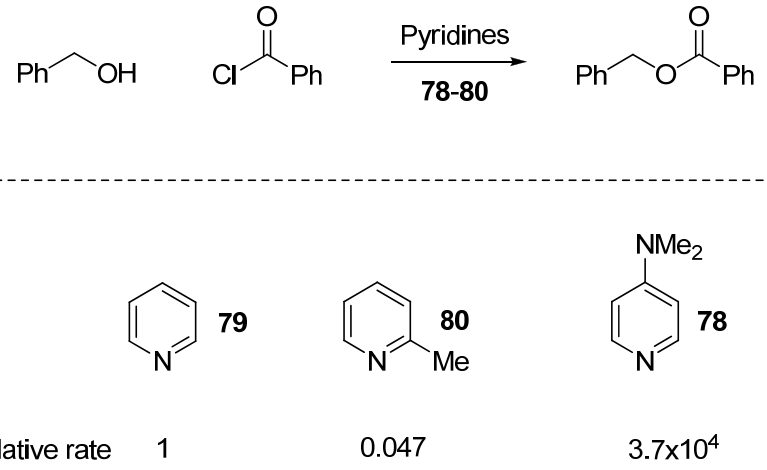
Terada, 2006; [45] Feng, 2009; [46] Wulff, 2008; [47]

DBP = 3,5-di-tert-butylphenyl.

Scheme 23. Novel basic motifs in bifunctional acid/base organocatalysis

1.1.5 Chiral DMAP Analogues in Asymmetric Catalysis

4-Dimethylaminopyridine (DMAP) **78** has broad utilty as a nucleophile catalyst in organic chemistry. It offers unique reactivity and versatility as Lewis base catalysts in a wide array of organic reactions where some prominent examples include; esterification of sterically hindered alcohols, addition of alcohols to ketenes and Steglich rearrangement.[48] It was first used in organic chemistry by Litvinenko and Kirichenko in 1967.[49] They discovered that DMAP provides a 10^4-fold rate enhancement (versus pyridine) in the benzoylation of 3-chloroaniline. Soon after their report, Steglich and Höfle described the use of DMAP as a catalyst for the esterification of a sterically bulky alcohol, 1-methylcyclohexanol.[50] In a work of Litvinenko and Kirichenko, it is demonstrated that substituting dimethyl amino group to the *para* position of pyridine increases the rate of benzoylation of benzyl alcohol to a 10^4 fold versus pyridine **79** itself. Another interesting point of their work was the utility of α-picoline (2-methylpyridine) **80** where deleterious effect of methyl group was observed (Scheme 24).[51]



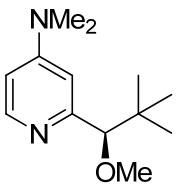
Scheme 24. Comparison of nucleophilicity of substituted pyridines

Their work is an important reference for the chemists who would design a chiral DMAP variant. In asymmetric catalyst design, it is widely accepted that generally the proximity of the chiral element (stereogenic center, axis, plane *etc*.) to the catalyst active site (catalaphore) has crucial effect in asymmetry induction. In fact,

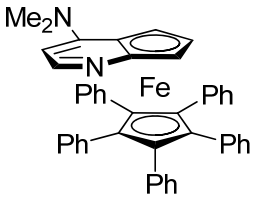
incorporating an effective chiral element in the 2nd position of DMAP would have deleterious effect in availability of pyridinic nitrogen's lone pair electrons. That is to say, such a design most likely would erode nucleophilicity considering Litvinenko's work given in Scheme 24.[52] In his excellent review on chiral DMAPs in asymmetric catalysis Wurz questions this stuation as the following: "*In a nutshell, it is this sensitivity of pyridine-based nucleophilic catalysts to substitution at the 2- position that has provided the central challenge in the design of a chiral DMAP derivative: how can one best project an effective chiral environment without paying an unacceptable cost with respect to reactivity?*."[52]

1.1.5.1 Chiral DMAP Synthesis and Applications: Challenges on Design and Synthesis

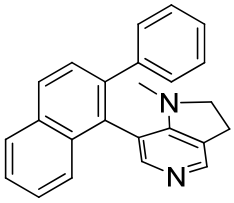
Although numerous chiral variants have been reported to date, due to synthetic challenges for the facile construction of DMAP unit and its highly symmetrical nature (two symmetry plane), synthetic protocols often require multiple steps whereby more practical and rational designs still remain elusive. Scheme 25 shows some successful chiral DMAP analogues **81-85** reported in the literature.[53,54,55,56,57] Examples are selected on the incorporating chirality elements.



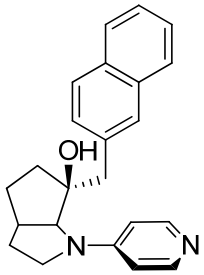
Vedejs[53]
Chiral DMAP-Reagent, **81**



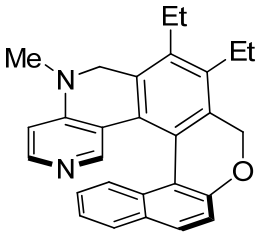
Fu[54]
Planar chiral DMAP, **82**



Spivey[55]
Atropoisomeric chiral DMAP, **83**



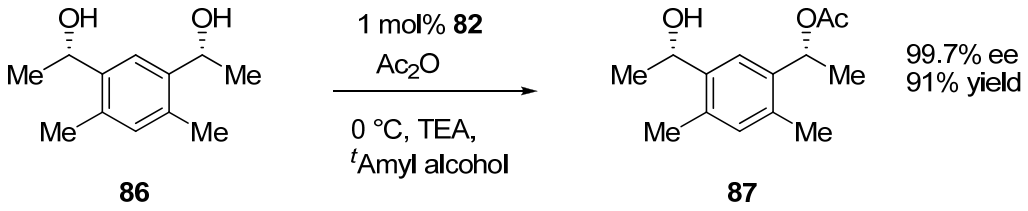
Fuji[56]
Chiral DMAP, **84**



Carbery[57]
Helicenoidal Chiral DMAP, **85**

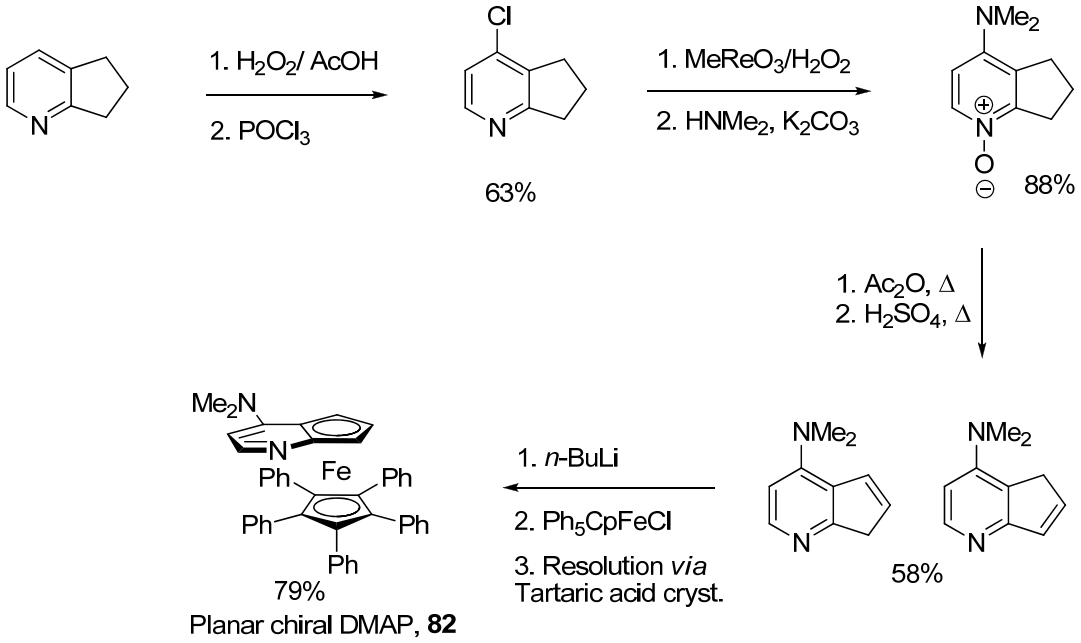
Scheme 25. Literature selection of chiral DMAP analogues

Of the 5 chiral DMAP analogues shown in Scheme 25, Vedejs' choice **81** is the first example appeared in literature. Although synthetically simplest of those (prepared in 3 steps), this compound however fails to act as a catalyst rather used as a chiral reagent due to the connectivity of the chirality inducing moiety incorporating through the α position of the pyridine. Although Fu's planar chiral DMAP **82** blocks also the α position of the DMAP unit by being fused to a ferrocene unit, it is the best of all 5 in terms of catalytic performances and competing with enzymes considering the selectivities achieved. This spectacular catalyst **82** catalyzes following acylative desymmetrization of *meso*-diol **86** using acetic anhydride as the cheap acyl source to yield stereoselectively mono-acylated product **87** with 99.7 % *ee* using 1 mol % catalyst loading (Scheme 26).[58] Higher reaction rates obtained with Fu's planar chiral DMAP **82** compared to that of Vedejs' chiral DMAP **81**, may be attributed to the electron rich ferrocene unit further activating the pyridine ring electronically thereby overcoming the deleterious effect of the steric bulkiness in catalyst **82**.



Scheme 26. Desymmetrization of a meso-diol with Fu's planar chiral DMAP **82**

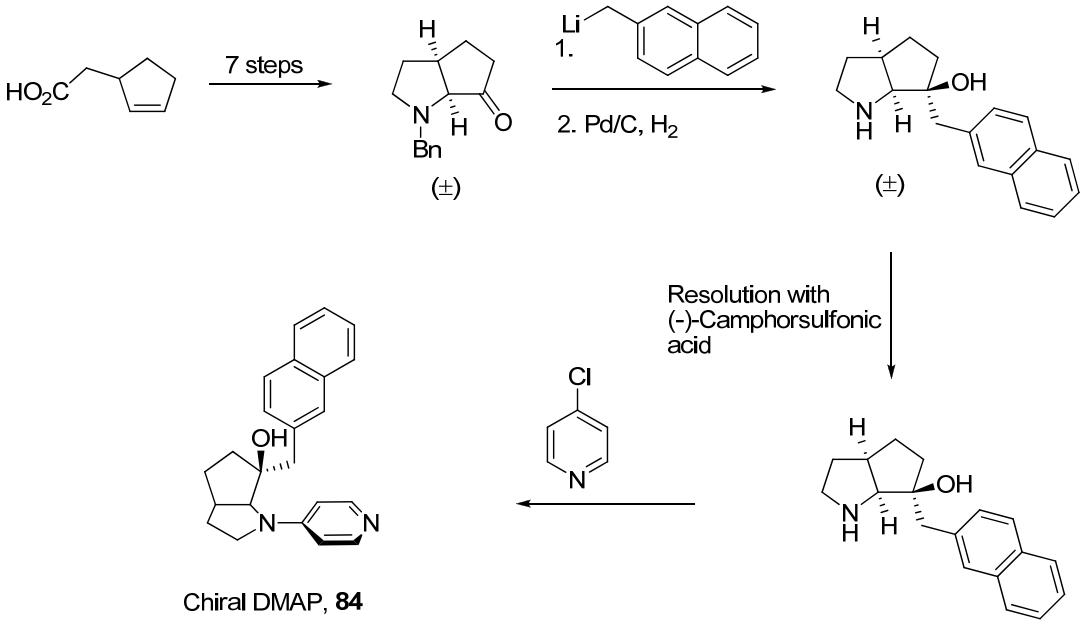
Although having exceptional selectivity, initial synthesis of planar chiral DMAP **82** involved numerous steps and semi-preparative chiral HPLC separations. Later in 2007, they published an improved synthesis of this catalyst. This time, they managed to synthesize racemic catalyst in 7 synthetic step in an overall yield of 25 % which was then resolved *via* two crystallizations with the tartaric acid with yields, 28% for (-)-enantiomer and 44% for (+)-enantiomer with >99% *ee* for each (Scheme 27).[59]



Scheme 27. Eight step synthesis of Fu's planar chiral DMAP **82**

Like Fu's planar chiral DMAP **82**; atropoisomeric chiral DMAP analogue **83** developed by Spivey involves multistep synthesis and resolution (7 synthetic steps)

and Fuji's chiral DMAP derivative **84** acting *via* "induced fit" mechanism comprises 11 synthetic steps (Scheme 28).

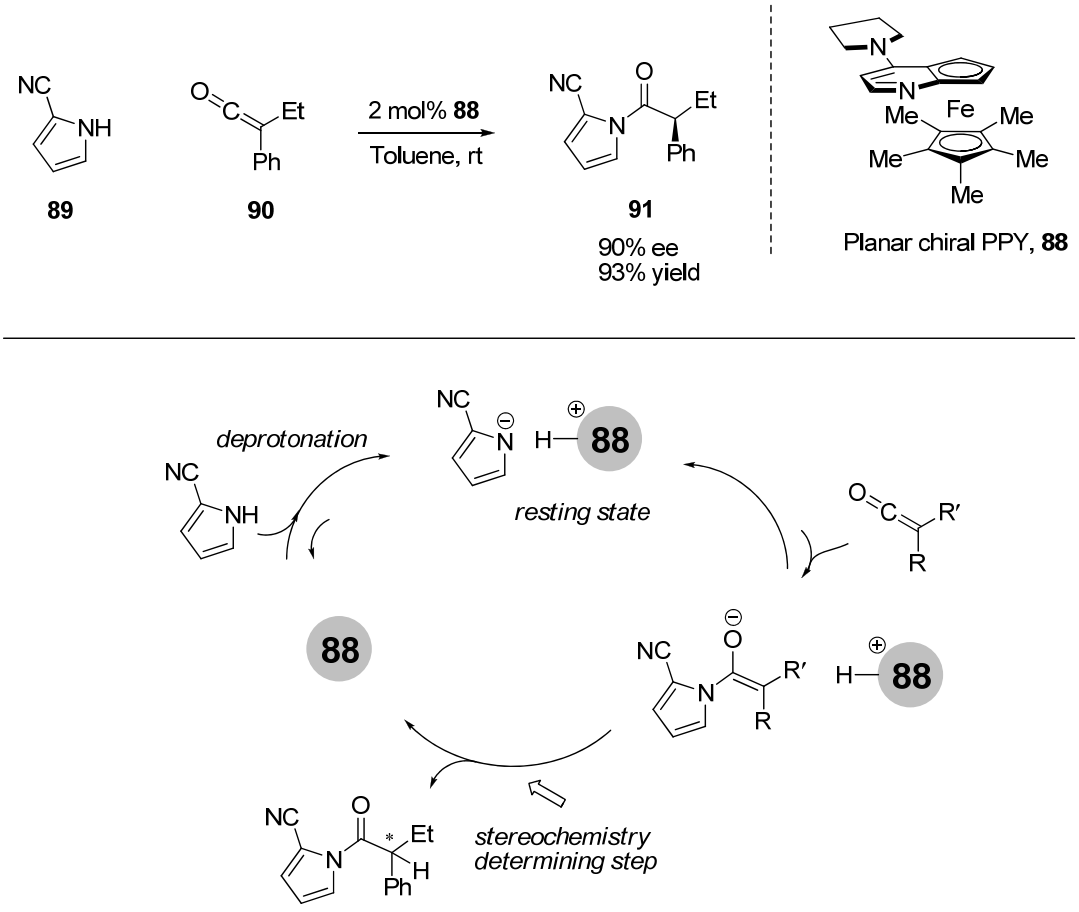


Scheme 28. Fuji's 11 step synthesis of chiral DMAP **84**

Even the most recently published example **85**, a helicenoidal DMAP having chiral plane, designed and prepared by Carbery *et al*. in 2011 required 7 steps. All these five chiral DMAP analogues demonstrated in Scheme 25 serve as excellent nucleophilic organocatalysts furnishing impressive enantioselectivities in kinetic resolution (KR) of *sec*-alcohols whereas in economical point of view, their multistep synthesis (7 to 11) makes them irrational for both academic and industrial research. Therefore more practical designs still remain elusive and challenging.

1.1.5.2 Chiral DMAP Analogues as Brønsted Base Organocatalysts in Asymmetric Catalysis

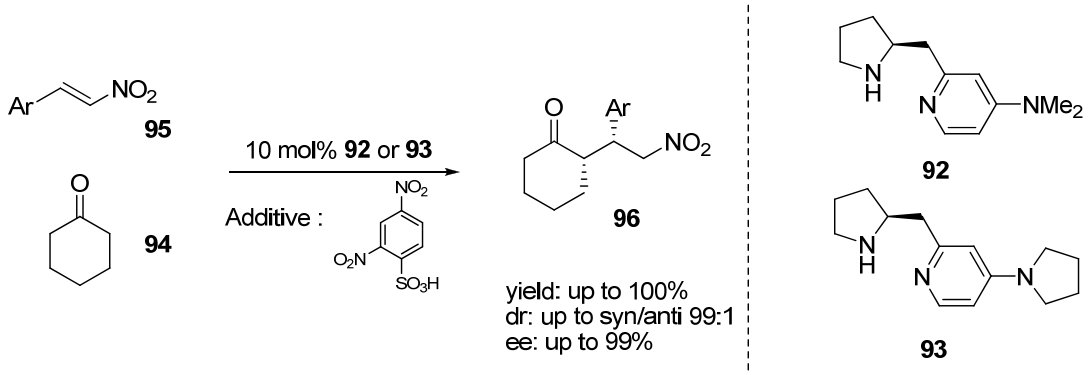
The catalytic role of chiral DMAPs has resided mainly in their nucleophilic character particularly for KR of *sec*-alcohols, until a planar chiral 4-dialkylaminopyridine **88** developed by Fu and coworkers has been shown to effectively catalyze the addition nitrogen nucleophiles to prochiral ketenes where DMAP unit acting as a Brønsted base.[60] In their pioneering investigation, 2-cyanopyrrole **89** was successfully added to the ketene **90** producing *N*-acylpyrrole **91** in high enantiomeric excess (90%) employing 2 mol% commercially available 4-(pyrrolidino)pyridine (PPY) derivative **88** (a DMAP analogue) as shown in Scheme 29.



Scheme 29. Fu's planar-chiral PPY **88** catalyzed pyrrole addition to ketenes

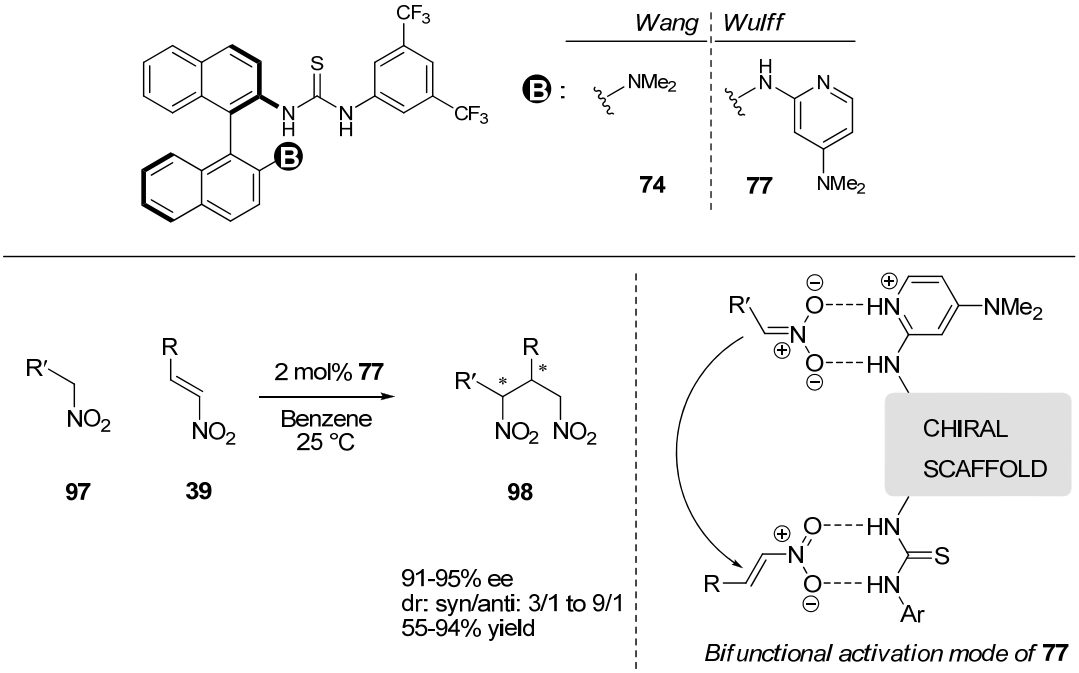
Such additions proceeded swiftly when pyrroles having acidic N-H protons and examination of various ketenes yielded *N*-acylpyrrole derivatives in very good *ee*s (81-98%). Hodous and Fu investigated the origin of stereoselection by performing several experiments such as kinetic experiments, primary kinetic isotope labeling studies *etc*. They proposed that Brønsted base catalyst **88** deprotonates the pyrrole **89**. Resultantly formed ion-pair was presumed to be the resting state of the catalyst being a chiral conjugate Brønsted acid. Addition of deprotonated pyrrole to the ketene generating the enolate/conjugate-acid led to the stereochemistry determining step, which could be the enantioselective protonation of the achiral enolate by conjugate Brønsted acid thereby leaving the base free for further catalytic functioning (Scheme 29).

In 2004, bis-Lewis basic Pyrrolidine/DMAP hybrids **92** and **93** developed by in three steps by Kotsuki group. These hybrid catalysts were shown to effectively catalyze Michael addition reaction involving ketones and nitroolefins where DMAP unit acted as a conjugate base.[61] They anticipated that the incorporation of this base should facilitate enamine formation *via* α-hydrogen abstraction from the cyclohexanone **94**. Additionally, the resulting pyridinium ring should shield one side of an enamine double bond, which would direct nitroolefin acceptors **95** approach to generate the desired Michael adducts **96** stereoselectively. Their work describes the second example of DMAP derivative's utility as Brønsted base catalysts performing asymmetric Michael addition reactions with very high enantio- and diastereo-selectivities in almost quantitative yields (Scheme 30).



Scheme 30. Kotsuki's Pyrrolidine/DMAP hybrids **92** and **93** catalyzed Michael reactions

More interestingly, in a recent work of Wulff, *via* the modification of dimethyl amine with the superior basic unit 2-aminoDMAP on Wang's catalyst **74** [44], it was demonstrated that their bifunctional DMAP/Thiourea catalyst **77** derived from (*R*)-1,1'-binaphthyl-2,2'-diamine ((*R*)-BINAM) was found to exhibit unique properties over the Wang's catalyst in conjugate addition reactions of nitroalkanes **97** to nitroolefins **39** (Scheme 31).[47]

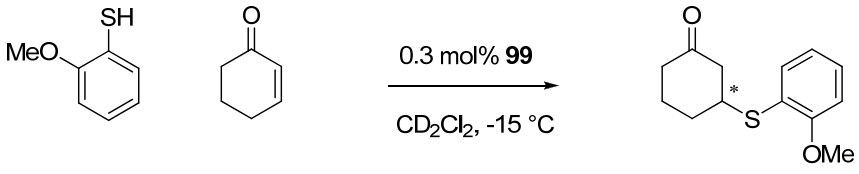


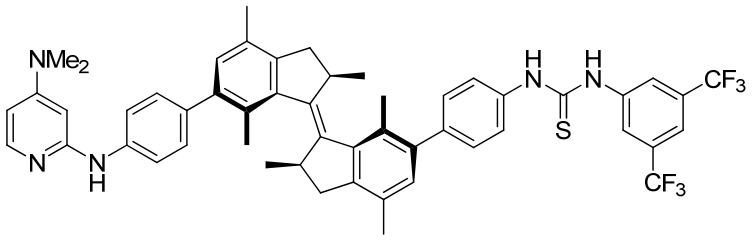
Scheme 31. Wulff's modification on Wang's catalyst and application in conjugate addition reaction

In their highly impressive work, it was shown that using bifunctional DMAP/Thiourea catalyst **77**, various 1,3-dinitro compounds **98** could be afforded with very high enantioselectivities (91-95% *ee*) without observing any oligomerization which is a common case decreasing the product yields. Comparing their results with that of Wang, they concluded that incorporating a superior base (DMAP) could do faster deprotonation therefore yielding higher reaction rates. In addition, after deprotonation, double coordination of the nitronate anion presumed to form leading a stronger coordination thereby bringing the nitronate in closer proximity to the chiral pocket. They reasoned that activation of nitroolefins **39** by hydrogen bond donor thiourea moiety together with such interaction (DMAP-

nitroalkane) would cause more effective asymmetry induction resultantly yielding higher enantioselectivities in their case. Although authors Rabalakos and Wulff chosen to call the basic unit as "DMAP", to me it would be more convenient to call such a catalaphoric unit as "2-aminoDMAP" considering the activation mode they proposed for which enabling double coordination to the nitronate in its protonated form.

A molecular motor acting as a multifunctional chiral catalyst bearing 2-aminoDMAP and thiourea combination as the catalytic functioning entities has been reported very recently by Feringa group.[62] This second example of 2-aminoDMAP catalyst developed by Wang and Feringa in 2011 introduced a conceptually new approach in which the structure of this single catalyst **99** can be manipulated by readily available physical stimuli (light and heat) transforming it to the structures (*P,P*)-*trans* → (*M,M*)-*cis* → (*P,P*)-*cis* → (*M,M*)-*trans*. Generating full rotary cycle around C-C double bond by aforementioned physical stimuli, catalysts are formed that provide either sluggishly racemic (*R,S*) with (*P,P*)-*trans* or preferentially the *S* (employing (*M,M*)-*cis*) or the *R* enantiomer (employing (*P,P*)-*cis*) of the chiral product 3-(2-methoxyphenylthio)cyclohexanone of the conjugate addition of 2-methoxybenzenethiol to cyclohex-2-enone (Scheme 32). This catalytic machine demonstrates how sequentially changing molecular tasks can be achieved and with no doubt will influence the future of asymmetric catalysis deeply.





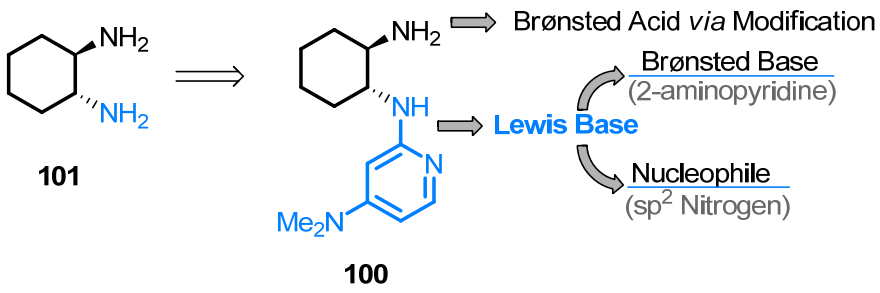
(2*R*,2'*R*)-(*P,P*)-*trans* **99**

Scheme 32. Feringa's molecular motor catalyst, a DMAP/Thiourea

1.1.6 Aim of the Work

A great number of chiral DMAP analogues have shown superiority as chiral nucleophilic catalysts over their less reactive surrogates such as *tert*-amines, phosphines *etc.* since past decade. However most of the effectively functioning ones suffer generally from involving multistep synthetic protocols (7-11 steps). Additionally, the use of relatively unexplored Lewis basic 2-aminoDMAP entities serving unique opportunities particularly in bifunctional acid/base organocatalysis prompted us to work on this highly emerging field of catalysis.

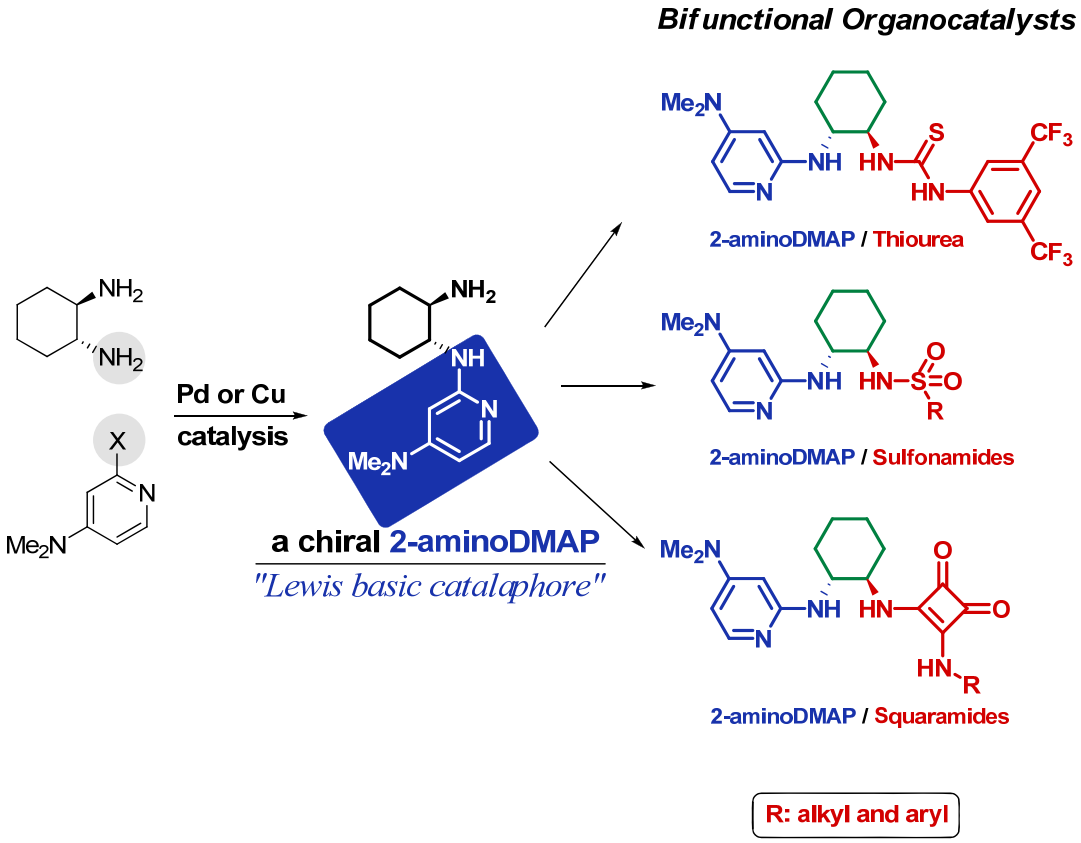
In this respect, we have anticipated that the chiral 2-aminoDMAP **100** derived from the *trans*-cyclohexane-1,2-diamine **101** could serve as a versatile Lewis basic catalaphore and introducing various Brønsted acid entities *via* modification of remaining primary amine might led to discovery of new reactivities in context of bifunctional acid/base catalyst (Scheme 33). In principle, it was thought that this 2-*N*-alkylamino and 4-dimethylamino bisubstituted chiral pyridine **100** might act as both Brønsted base and nucleophile, due to two electron-donor nitrogens on the pyridine ring rendering it highly electron-rich which may amplify the scope of the reactions to be catalyzed asymmetrically.



Scheme 33. Catalysts design rationale

For this purpose, we are initially aiming "direct access" to the chiral 2-aminoDMAP **100** in one step *via* selective mono-*N*-heteroarylation of the C_2-symmetric vicinal diamine **101**. Arguably the most frequently addressed vicinal chiral diamine, **101** has proven its broad utility in a diverse array of catalyst systems (from

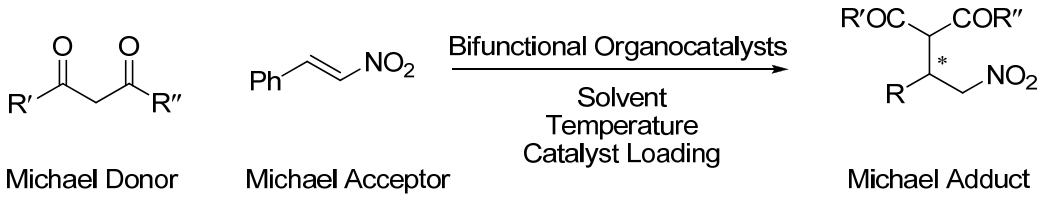
salen type transition metal complexes to bifunctional acid/base organocatalysts) as a "*privileged*" chiral catalyst backbone.[63] Our recent SciFinder® search clearly shows that the diamine **101** is 26.5 fold more demanding than the next frequently encountered diamine BINAM. Therefore it was chosen as the chiraphoric core unit for our entire catalyst library.



Scheme 34. Synthetic strategy for our catalyst library

In this context, synthesis and evaluation of catalytic performances of novel bifunctional 2-aminoDMAP-Thiourea/ Sulfonamide/ Squaramide organocatalysts derived from *trans*-(*R,R*)-cyclohexane-1,2-diamine forms the main goal of this thesis. Direct selective mono-*N*-pyridilization of diamine **100** *via* Pd and Cu catalysis is going to be described successfully for the first time. Facile preparation of chiral 2-aminoDMAP core catalaphore might lead to the development of various 2-aminoDMAP- Thiourea/ Sulfonamides/ Squaramides as novel bifunctional acid/base organocatalyst libraries (most in two-steps overall). Developed catalysts are anticipated to show unique reactivities due to superior basicity of 2-aminoDMAP

compared to the commonly employed trialkylamines as base in such acid/base catalysts. Catalytic performances of synthesized bifunctional organocatalysts are planned to be evaluated in asymmetric conjugate addition of 1,3-dicarbonyls (Michael donors) to *trans*-(*β*)-nitrostyrene (Michael acceptor) outlined in Scheme 35. After systematic structural elaborations in search for optium catalysts incorporating the most compatible acidic moieties for asymmetric conjugate additions; best functioning ones are planned to screen further for solvent, temperature and catalyst loading effects.



Scheme 35. Evaluation of catalytic performances of bifunctional organocatalysts in asymmetric conjugate addition reactions

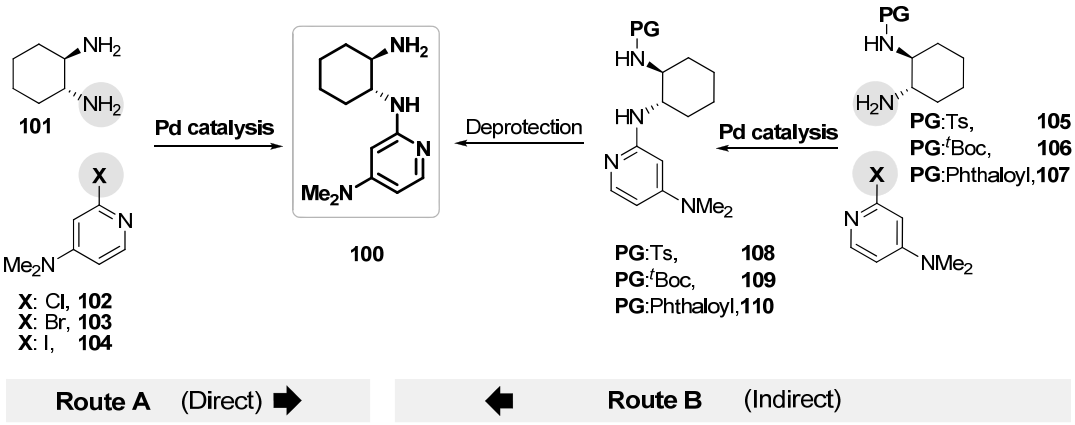
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Palladium and Catalyzed C-N Coupling Reactions

2.1.1 Palladium Catalyzed C-N Coupling Reactions for the Synthesis of Chiral 2-aminoDMAP 100

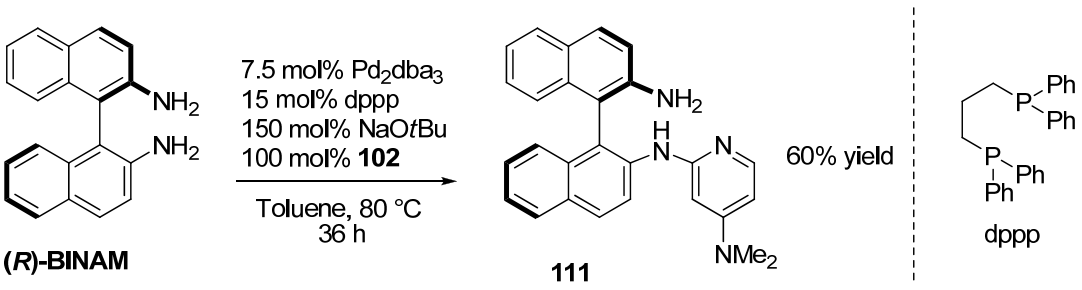
In order to establish the Lewis basic core catalaphore **100** of our entire target catalysts, two synthetic routes (A and B) shown in Scheme 36 were devised. Our initial efforts were the direct palladium catalyzed Buchwald-Hartwig *N*-arylation of the diamine **101** with 2-haloDMAPs **102** and **103** (Route A). Such coupling reactions targeting C-N bond forming processes through palladium catalysis were discovered independently by Buchwald and Hartwig in 1995.[64] The second alternative route B was also devised in case route A would fail. Route B comprises the use of selectively mono-protected diamine derivatives (**105-107**) to obtain protected intermediate structures **108-110** which could furnish chiral 2-aminoDMAP **100** upon deprotection under appropriate conditions. Both of these two routes involve the palladium catalyzed nucleophilic aromatic substitution of electrophilic 2-haloDMAPs (**102** and **103**) with nitrogen nucleophiles either **101** or **105-107** as the key step for success.



Scheme 36. Synthetic routes A and B for the synthesis of 2-aminoDMAP **100** *via* Pd catalysis

2.1.2 Direct C-N Coupling Reactions *via* Palladium Catalyzed Synthesis of Chiral 2-aminoDMAP 100

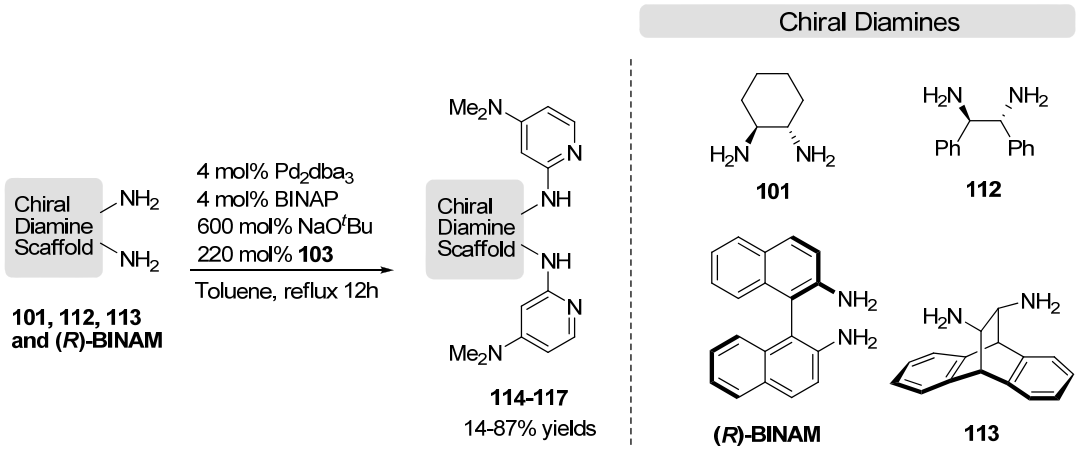
The first example of 2-aminoDMAP skeleton was developed by Rabalakos and Wulff in 2008. They employed a protocol shown in Scheme 37 to obtain their bifunctional DMAP/Thiourea **77** catalyst precursor **111** in 60% yield using equivalent amounts of (*R*)-BINAM and 2-chloroDMAP **102** as the reacting partners.[47]



Scheme 37. Wulff's selective mono-pyridilization of (*R*)-BINAM

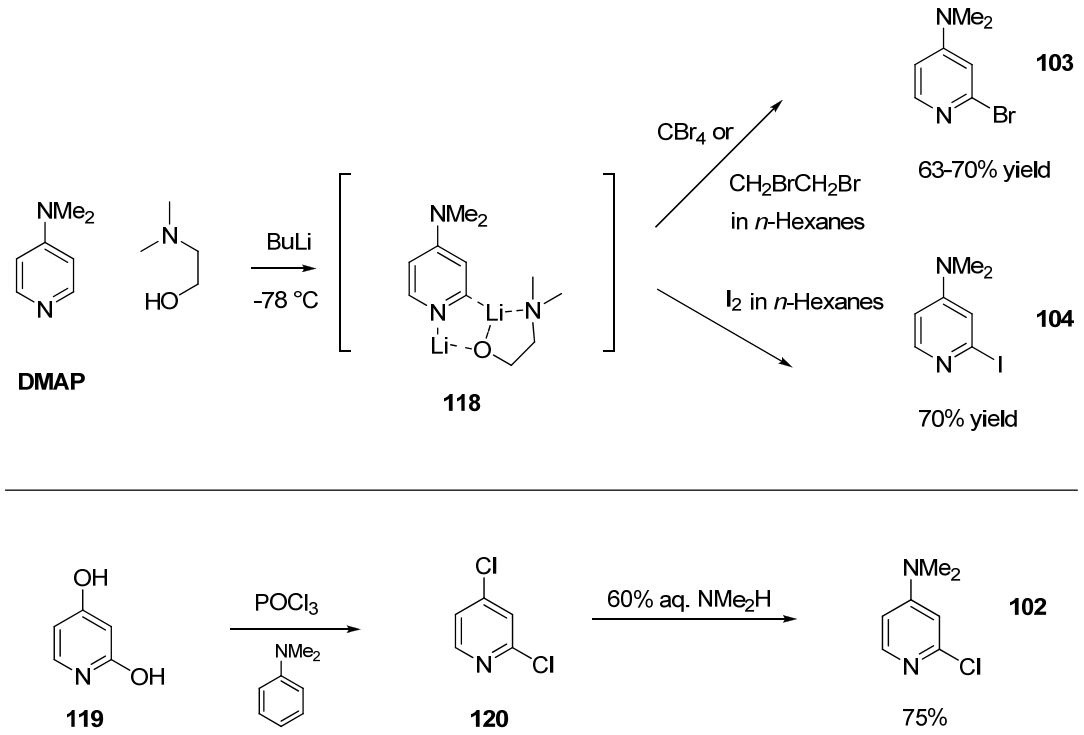
Tanyeli and Yazıcıoğlu prepared various C_2-symmetric (trialkyldiamino)pyridines (TRADAPs) **114-117** by subjecting four chiral diamines

(**101**, **112**, **113** and **(*R*)-BINAM**) with two equivalent 2-bromoDMAP **103** to palladium catalysis. Notably, their target TRADAP catalysts were obtained in one step and utilized in KR of alcohols producing enantioselectivities up to 76%.[65]



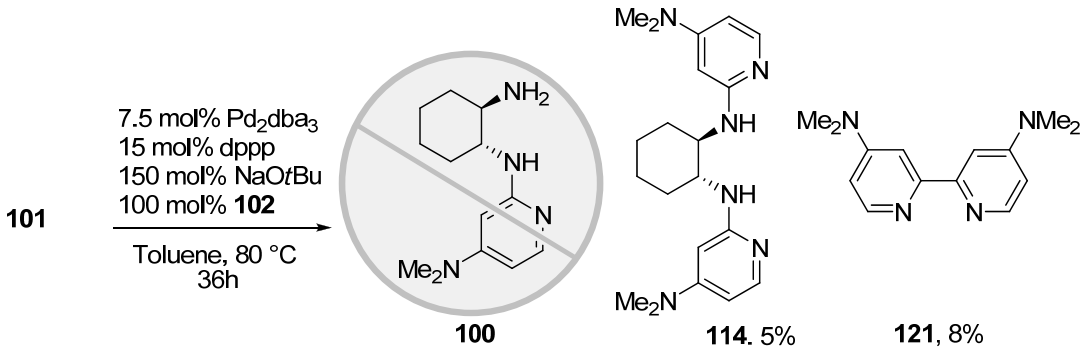
Scheme 38. C_2-symmetric TRADAPs by Tanyeli and Yazıcıoğlu

In this respect, three 2-haloDMAP derivatives **102-104** were prepared according to Scheme 39 using published procedures. In this process, the reactive intermediate **118** presumed to form by direct α-lithiation of DMAP *via* chelating ligand *N,N*-dimethyl ethanolamine and the base *n*-BuLi. Adding appropriate electrophile to this intermediate provided a convenient access to the desired α-substituted DMAP derivatives in good yields. Both CBr_4 and CH_2BrCH_2Br were used to obtain **103** however product obtained somewhat in lower yields in our hand (63-70%) than that of literature.[66] The 2-iodo derivative was problematic because of low solubility of iodine in *n*-hexanes and compound **104** was prepared with at most 70% yield opposed to 90% yield claimed in the paper.[66] Different synthetic pathway was used for the synthesis of compound **102** due to the unavailability of the electrophilic chlorinating agent in our laboratory. 2,4-Dihydroxy pyridine (**119**) was used as the starting material. It was converted first to 2,4-dichloro pyridine (**120**) quantitatively upon reacting with phosphoryl chloride and *N,N*-dimethyl aniline under refluxing conditions using a patent procedure.[67] Treating compound **120** with 60% aqueous dimethylamine solution afforded the target **102** in 75% yield following a published method (Scheme 39).[68]



Scheme 39. Synthesis of 2-haloDMAP derivatives **102-104**

Keeping the works of Rabalakos[47] and Yazıcıoğlu[65] as a reference point for our palladium catalyzed C-N bond forming investigations, we initially explored the possibility of Pd-catalyzed Buchwald-Hartwig *N*-arylation of the diamine **101** with 2-haloDMAPs **102-103**. Of the various conditions investigated, first was the Wulff's coupling protocol applied just by replacing diamine **101**, however formation of 4,4'-bis(dimethylamino)-2,2'-bipyridine[69] **121** was observed presumably by the reductive homo-pyridyl coupling in 8% yield as the major product. Additionally, 5% C_2-symmetric bisDMAP[65] coupled product **114** was isolated. Wulff's protocol shown to be incompatible using the diamine **101** as the substrate since no trace of formation of target **100** was observed at the end of 36h of stirring at 80 °C (Scheme 40 and entry 1 of Table 2).



Scheme 40. Application of Wulff's protocol

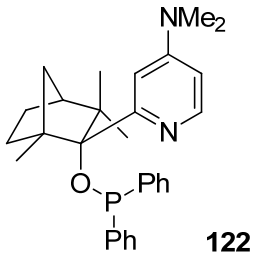
Table 2. Direct C-N bond forming trials to access compound **100**

Entry	Pd Complex	Ligand	Base	2-haloDMAP	Substrate	Product	Yield (%)[a]
1	Pd_2dba_3	dppp	NaO^tBu	**102**	**101**	**114**	5
2[b]	Pd_2dba_3	BINAP	NaO^tBu	**102**	**101**	**114**	9
3[b]	Pd_2dba_3	BINAP	NaO^tBu	**103**	**101**	**114**	27

[a]Refer to isolated yields on column chromatography. [b] Refluxed for 60 h under Ar atm.

Changing the ligand in such transition metal catalyzed transformations may change the fate of the reaction. In this respect, dppp was replaced by a well established ligand BINAP keeping the others same and this time reaction again gave **114** with a little higher yield despite refluxing 60 h (entry 2). Nature of electrophile has considerable effect on such C-N coupling reactions.[70] Yazıcıoğlu succeeded to anchor double DMAP unit to diamine **101** employing 2-bromoDMAP **103** as the electrophile.[65] In the light of these, we subjected 2-bromoDMAP **103** instead of 2-chloro derivative **102** (entry 3), but compound **114** was the only product again, however in considerably higher isolated yield (27%) when unprotected diamine **101** was employed. With these results presented in Table 2 in hand, it was thought that the formed **100** would act as a ligand excluding the bisphosphine ligands (dppe and BINAP) thereby coordinating to the palladium. In proximity of the metal Pd, the acidity of the protons of free NH_2 may increase due to coordination and ligand **100** may be arylated further to generate undesired product **114**. Compounds containing

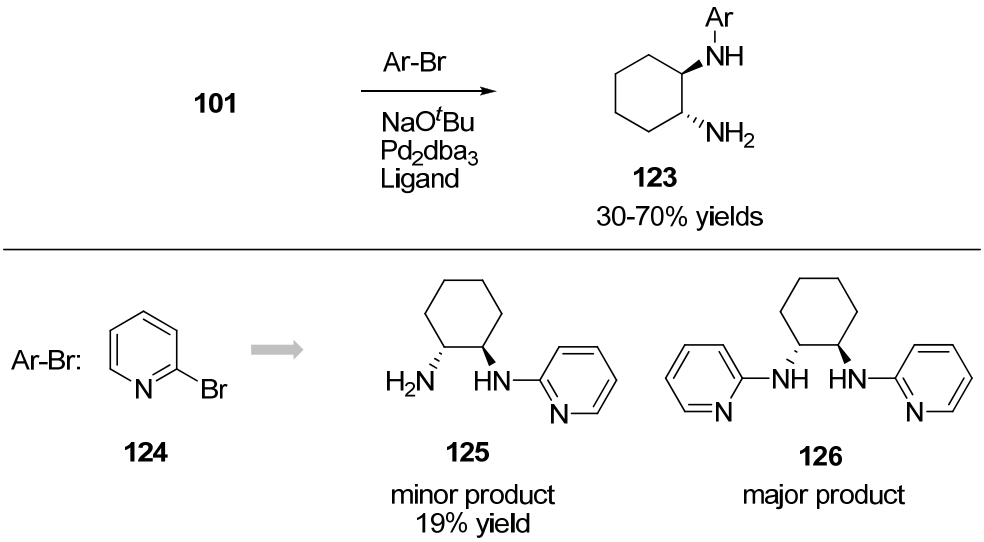
DMAP unit and phosphinite group **122** are known in the literature to act as ligands in Pd catalyzed asymmetric allylic substitution reactions (Figure 8).[71]



122

Figure 8. Fenchone derived DMAP/phosphinite ligand **122** for Pd catalyzed allylic substitution

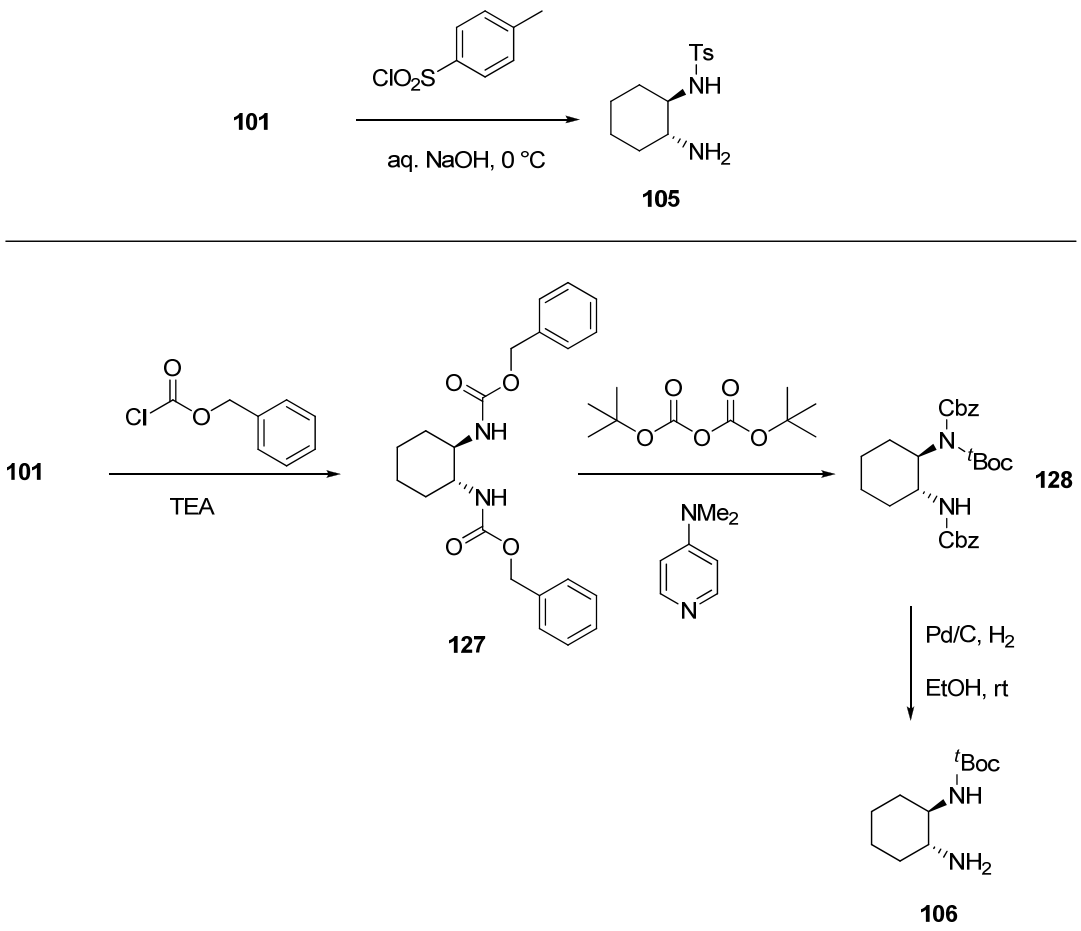
A similar observation was reported by Frost *et al*. in 1998.[72] They efficiently desymmetrized the diamine **101** using various arylbromides as the electrophiles. Although the reaction shown in Scheme 41 proceeded smoothly for several arylbromides affording 30-70% yield of products **123**; using 2-bromopyridine (**124**) as the aryl halide, reaction produced only 19% yield of mono-*N*-pyridylated product **125** and major being the bis-heteroarylated product **126**. Their findings also support our scenario accounting for our unsatisfactory attempts for direct C-N bond forming reactions outlined in Table 2 and Scheme 40.



Scheme 41. Pd catalyzed mono-*N*-arylation by Frost and co-workers

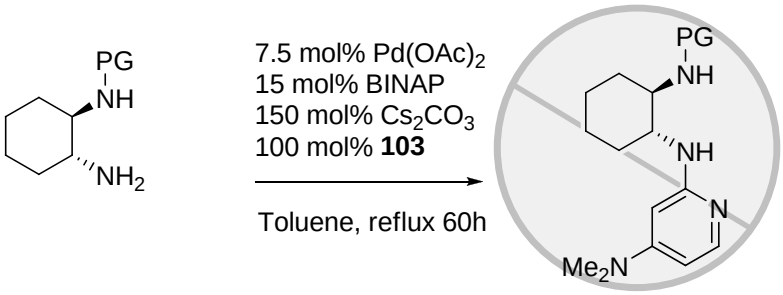
2.1.3 Palladium Catalyzed C-N Coupling Reactions for the Indirect Synthesis of Chiral 2-aminoDMAP 100

Realizing unsatisfactory results with palladium chemistry in direct C-N coupling trials (Route A), we have turned our attention to the route B involving protection of the substrate (Scheme 36). It is anticipated that protection of one of the equally reactive amine functional groups may lead to convenient substrates to access mono DMAP coupled products. For this purpose, mono-*N*-tosyl and mono-*N*-^{t}Boc protected substrates **105** and **106**, respectively were prepared according to published methods depicted in Scheme 41. Synthesis of mono-tosylamide **105** was straightforward. Diamine **101** was treated with one equivalent *p*-toluenesulfonyl chloride in aqueous alkaline medium to yield the product **105** in quite good yield and purity. Characterization of the compound done with ^{1}H NMR and ^{13}C NMR and was in complete agreement with the literature.[73] However, synthesis of mono-*N*-^{t}Boc derivative **106** required protecting strategy due to the higher reactivity of di-*tert*-butyl carbonate. Compound **101** was first doubly carbamoylated with benzyl chloroformate under basic condition to give bis-Cbz **127** which was further selectively mono-carbamoylated with di-*tert*-butyl carbonate employing DMAP as the nucleophile to get compound **128**. Cbz groups were removed by Pd on activated carbon catalyzed hydrogenation to produce target compound **106** in overall 3 steps. ^{1}H NMR and ^{13}C NMR spectra of the final product were in complete accordance with that of literature. Although authors claimed the production of compound **128** in 89% yield in overall 3 steps, experiments produced conflicting results in our hand (at most 40% yield was observed).[74]



Scheme 42. Synthesis of mono-*N*-tosyl **127** and mono-*N*-^{t}Boc **128** protected substrates

Prepared substrates (**105** and **106**) were subjected to a well-established palladium catalyzed carbon-nitrogen bond forming reaction protocol comprising $Pd(OAc)_2$ as the Pd source, Cs_2CO_3 as the relatively soluble inorganic base (in organic solvents) and bis-phosphine ligand BINAP (see Scheme 45). Employing substrates **105** and **106** produced neither of C-N coupled products **108** and **109**. Instead, uncharacterized products were observed in each case and no reasonable explanation could be made for these failing experiments (Scheme 43).

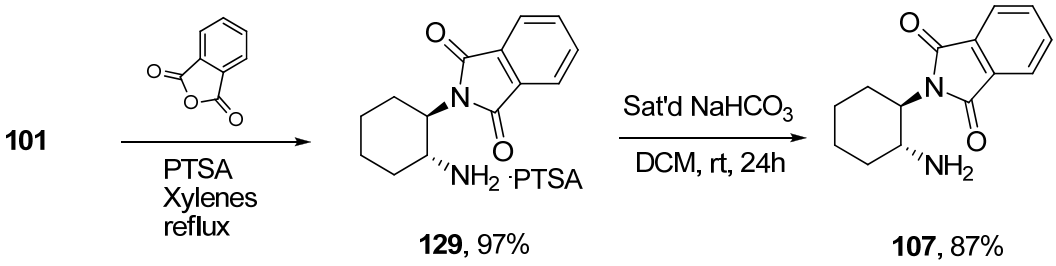


105, PG: Ts
106, PG: ^{t}Boc

108, PG: Ts
109, PG: ^{t}Boc

Scheme 43. Unsuccessful trials with mono-*N*-tosyl **105** and mono-*N*-^{t}Boc **106** protected substrates

As a second strategy for the coupling reactions targeting compound **100**, we devised a more robust phthaloyl protecting group. In order to realize this purpose, mono-*N*-phthaloyl protected diamine **107** was synthesized employing a reported procedure outlined in Scheme 44.[75] One equivalent PTSA monohydrate was first azeotropically dried using a Deanstark trap *via* refluxing xylenes. After the addition of our chiral backbone and phthalic anhydride, refluxed mixture of these formed solid acid-base salt **129**, which was further reacted with sat'd $NaHCO_3$ to furnish the substrate **107** in high yield.

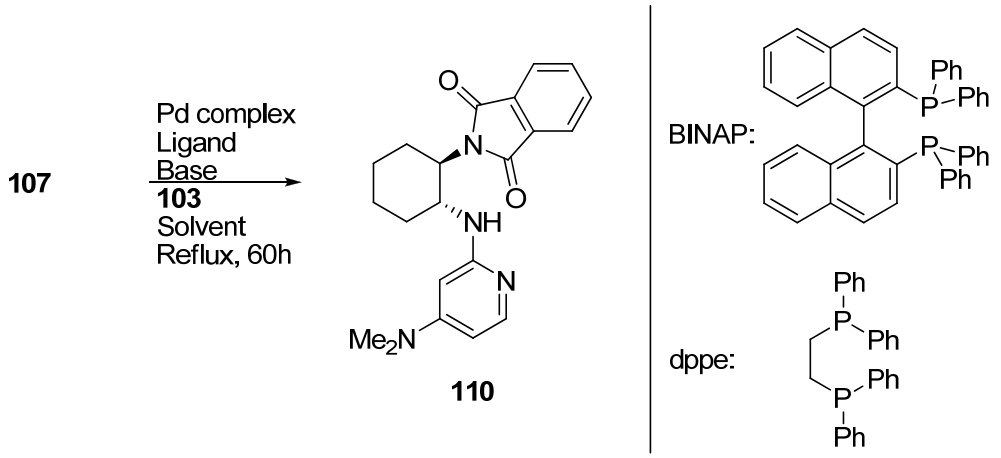


129, 97%

107, 87%

Scheme 44. Synthesis of mono-*N*-phthaloyl protected diamine **107**

Obtained mono-*N*-phthaloyl protected diamine **107** was subjected to the Buchwald-Hartwig coupling conditions presented by Scheme 45 and Table 3.



Scheme 45. C-N coupling reactions of mono-*N*-phthaloyl protected diamine **110**

To our delight we could manage to isolate coupled product **110**. Subjecting Pd_2dba_3 as palladium source and sodium *tert*-butoxide as base, coupled product was obtained in 14% yield (Table 3, entry 1). Employing the palladium source $Pd(OAc)_2$ in place of Pd_2dba_3 and using Cs_2CO_3 as the base, yield of **110** further increased to 15% yield (entry 2). When ligand dppe (diphenylphosphino ethane) was utilized in place of BINAP, no appreciable amount of product formation was observed (entry 3). Xylenes were replaced by toluene to serve as solvent having higher boiling point, however no trace of target **110** formation was observed at the end of 60h of refluxing (entry 4). Due to their facile air oxidation of bis-phosphine ligands all reactions were carried out under argon atmosphere and toluene was dried and deoxygenated *via* distilling over sodium benzophenone ketyl radical.

Table 3. C-N coupling reactions of mono-*N*-phthaloyl protected diamine trials to access compound **110**

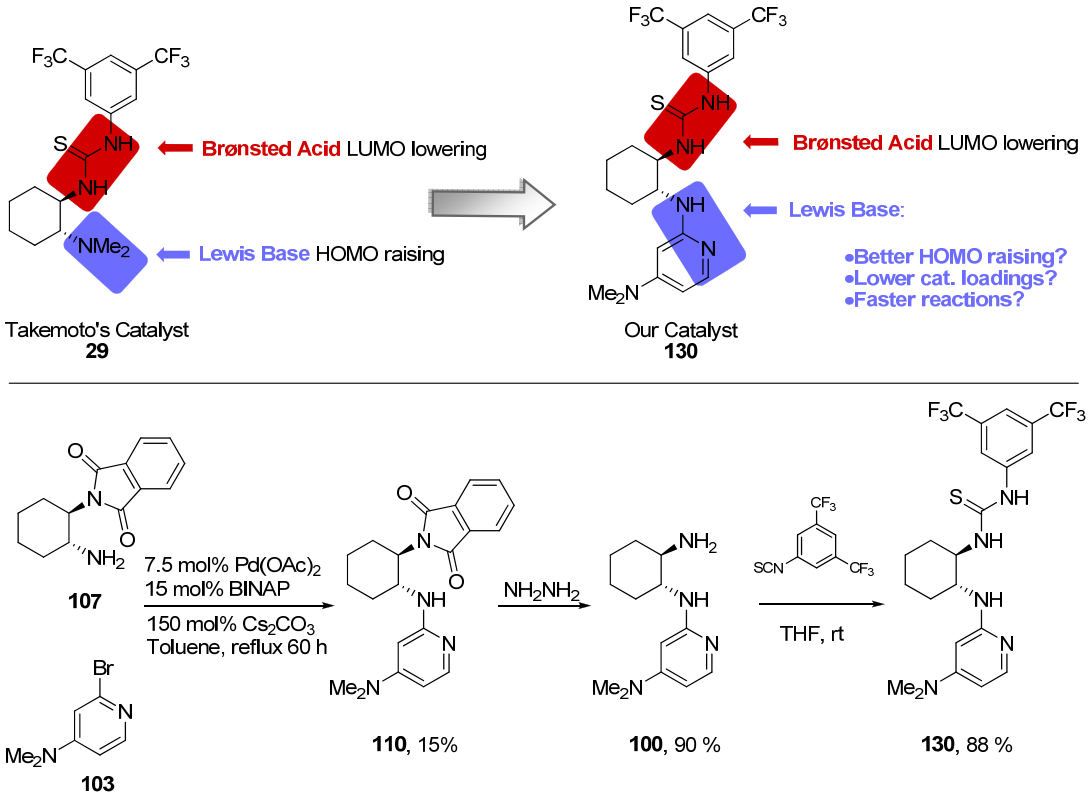
Entry	Pd Complex	Ligand	Base	Solvent	Substrate	Product	Yield (%)
1	Pd_2dba_3	BINAP	NaO^tBu	Toluene	**107**	**110**	14
2	$Pd(OAc)_2$	BINAP	Cs_2CO_3	Toluene	**107**	**110**	15
3	$Pd(OAc)_2$	dppe	Cs_2CO_3	Toluene	**107**	**110**	-
4	$Pd(OAc)_2$	BINAP	Cs_2CO_3	Xylenes	**107**	**110**	2

Characterization of the DMAP coupled product **110** was done primarily by ^{1}H NMR and ^{13}C NMR spectra and HRMS. By ^{1}H NMR and ^{13}C NMR spectroscopy, characteristic aromatic protons both on phthaloyl group and DMAP unit and dimethyl amino group were located intuitively. HRMS analysis verified the closed formula of the compound **110** as $C_{21}H_{24}N_4O_2$.

2.2 Synthesis of 2-aminoDMAP/Thiourea Organocatalyst and Application in Michael Reaction

Although having a C-N coupling protocol producing the compound **110** at most in 15% yield in hand, it was questioned whether it is worthwhile to further work on the yield improvement studies for compound **110**. To overcome this dichotomy, it was thought that the answer lied in the synthesis and evaluation of catalytic performance of a bifunctional catalyst derived from **100**. To evaluate catalytic potential of this new Lewis basic catalaphoric unit in asymmetric reactions, 2-aminoDMAP/thiourea organocatalyst **130** was designed to compare the results with Takemoto's established *tert*-amine/thiourea catalyst **29**[13a] and developed according to the Scheme 46. Structurally, our catalyst is very similar to the Takemoto's catalyst. Both incorporate the same thiourea group which may activate electrophile *via* LUMO lowering. Both have the chiral vicinal diamine **101** as the chirality transferring unit. However ours differs in having a superior basic moiety.[47] Considering its higher basicity, would it possibly serve better HOMO raising for better nucleophile activation? Resultantly, may it possibly lead to lower catalyst loadings considering "green chemistry" and economy together with timesaving? With such questions in mind, the synthesis of catalyst **130** was put in action. The amine **107** and 2-bromoDMAP **103** was subjected to our optimized Pd-catalyzed C-N coupling reaction to access 15% yield of **110**. Deprotection of the phthaloyl group with hydrazine hydrate was straightforward to produce precatalyst **100** in 90% chemical yield. Installation of thiourea unit swiftly took place in one hour by simply mixing

compound **100** and commercially available 3,5-bis(trifluoromethyl)benzene isothiocyanate in THF at room temperature.

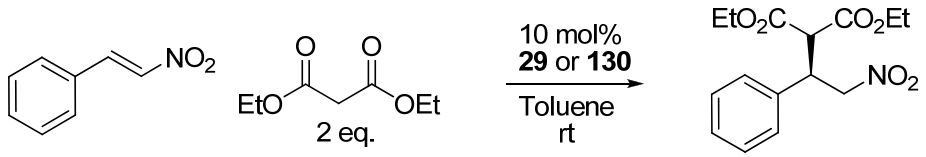


Scheme 46. Synthesis of 2-aminoDMAP/Thiourea organocatalyst **130**

Characterization of the bifunctional organocatalyst **130** made by ^{1}H NMR and ^{13}C NMR spectroscopy and characteristic protons and carbons were in agreement with the structure. It was further verified by HRMS analysis revealing the closed molecular formula of the compound as $C_{22}H_{25}F_6N_5S$.

Our initial investigation was to test the catalytic activity of obtained catalyst **125** in asymmetric conjugate addition of diethyl malonate **35** to *trans*-(*β*)-nitrostyrene. Scheme 47 depicts the experiment performed by us and shows also the results reported by Takemoto *et al.*[13a] utilizing their catalyst **29** in the same reaction under identical conditions. Takemoto[13a] and many others[39-44] employed generally at least 10 mol% bifunctional organocatalyst for a reasonable reaction rate. Considering the basic motifs of such catalysts incorporating a tertiary amine, it is reasonable to attribute this

fact to the insufficient basicity of such systems for the deprotonation of malonates (least reactive member of 1,3-dicarbonyls family). Therefore it is not surprising to see some protocols employing very concentrated conditions (13 molar) for such addition reaction and though completing reactions in long reaction times (4 to 6 days).[76] Bearing in mind low reactivity of malonates, it was quite encouraging to observe that the reaction proceeded faster (4h vs. 24h) and furnishing higher isolated of 1,4-addition product **36**. These findings proved the accelerative effect of incorporated base (aminoDMAP moiety). Although the enantioselectivity accessed was disappointing (42%) considering the double coordination capacity of 2-aminoDMAP group which was anticipated to bring the malonate pro-nucleophile to the close proximity of chiral environment. Being aware of the literature reports claiming catalyst aggregation for those including the thiourea unit[37,77] and forming *trans*/*cis* rotamers based on the HNCS angle;[39,78] it was supposed that the low selectivity encountered here may stem from the same reason, primarily due to catalyst aggregation.



34 **35** **36**

	Takemoto's Catalyst **29**	Our Catalyst **130**
time	24 h	4 h
yield	86 %	92 %
ee	93 %	42 %

Scheme 47. Catalytic activities of **130** vs. **29** in conjugate addition reaction

As a next step in our catalytic investigations, we decreased the catalyst loading to 2 mol% and various solvents were screened to understand catalyst behavior. In this respect, we carried out reaction in toluene employing lower catalyst loadings (Table 4, entries 1 and 2). Fortunately enantioselectivity was improved to 54% using 4 mol% catalyst and further improved (57%) by lowering the loading to 2 mol%. Even though

reactions were sluggish (90 h for 82% yield) at 2 mol% loading, it was choosen as the optimal amount for further screened solvents due to yielding higher *ee*. In entry 3, acetic acid was used as the additive however it decreased the catalytic activity of **130** in terms of both selectivity and yields. Using more polar solvents (benzene, chloroform and tetrahydrofuran) lowered selectivities inversely proportional to their polarities (entries 4-6). Our next choice was hydrocarbon type solvents (entries 7-11). Of the solvents examined, cyclohexane provided the best level of enantiocontrol (61% *ee*) in 73% yield in 21h (entry 7). Unfortunately no trace of **36** was detected at lower catalyst usage (1 mol% and 0.5 mol%) even after running reactions for 4 days.

Table 4. Solvent and catalyst loading investigations

Entry	Solvent	Cat. Loading (%)	Time (h)	Yield (%)	*ee* (%)
1	Toluene	4 mol	28	87	54
2	Toluene	2mol	90	nd	57
3 [a]	Toluene	2 mol	144	55	52
4	Benzene	2 mol	96	56	40
5	$CHCl_3$	2 mol	48	60	25
6	THF	2 mol	96	41	9
7	Cyclohexane	2 mol	21	73	61
8	*n*-Hexane	2 mol	21	78	40
9	*n*-Pentane	2 mol	48	66	18
10	*n*-Heptane	2 mol	48	66	40
11	Cyclohexane	1 mol	96	-	nd
12	Cyclohexane	0.5 mol	96	-	nd

[a] 2 mol% acetic acid was used as the additive.

Characterization of the 1,4-addition adduct **36** done by ^{1}H NMR and ^{13}C NMR spectra and were in complete accordance with those of literature.[13b] Absolute configuration of the chiral adduct was assigned as *R*, *via* comparison of the retention time of the major product (*via* HPLC) with that of literature.[13b] In order to understand

the origin of selectivity in the Michael addition of 1,3-dicarbonyl compound **35** to nitroolefin **34** catalyzed by bifunctional organocatalyst **130** we proposed a transition-state (TS) model similar to that by Takemoto *et al*. due to the high degree of resemblance of catalysts **130** and **29** (incorporating the same chiraphoric and acidic unit). As in the case of catalyst **29**, thiourea unit of **130** presumed to be responsible for acceptor alkene activation through double hydrogen bonding with the nitro group. However for nucleophile activation we propose two fused six membered hydrogen bond networks formed between 2-aminoDMAP unit and the dicarbonyl after the partial deprotonation as depicted in Figure 9.

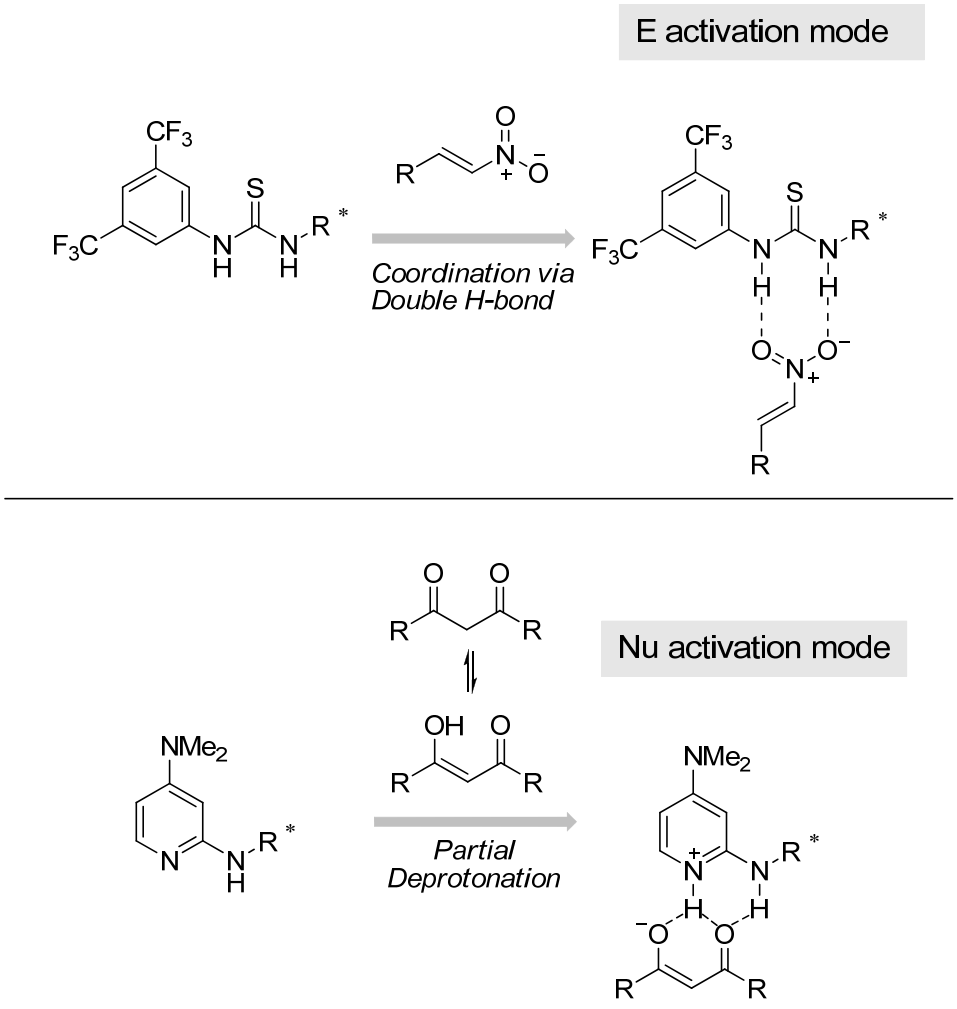


Figure 9. Proposed nucleophile and electrophile activation modes by active catalytic units of **130**

Based on the proposed activation modes presented in Figure 9, a plausible transition state model was devised in Figure 10 to account for the sense of enantioselectivity brought by catalyst **130**.

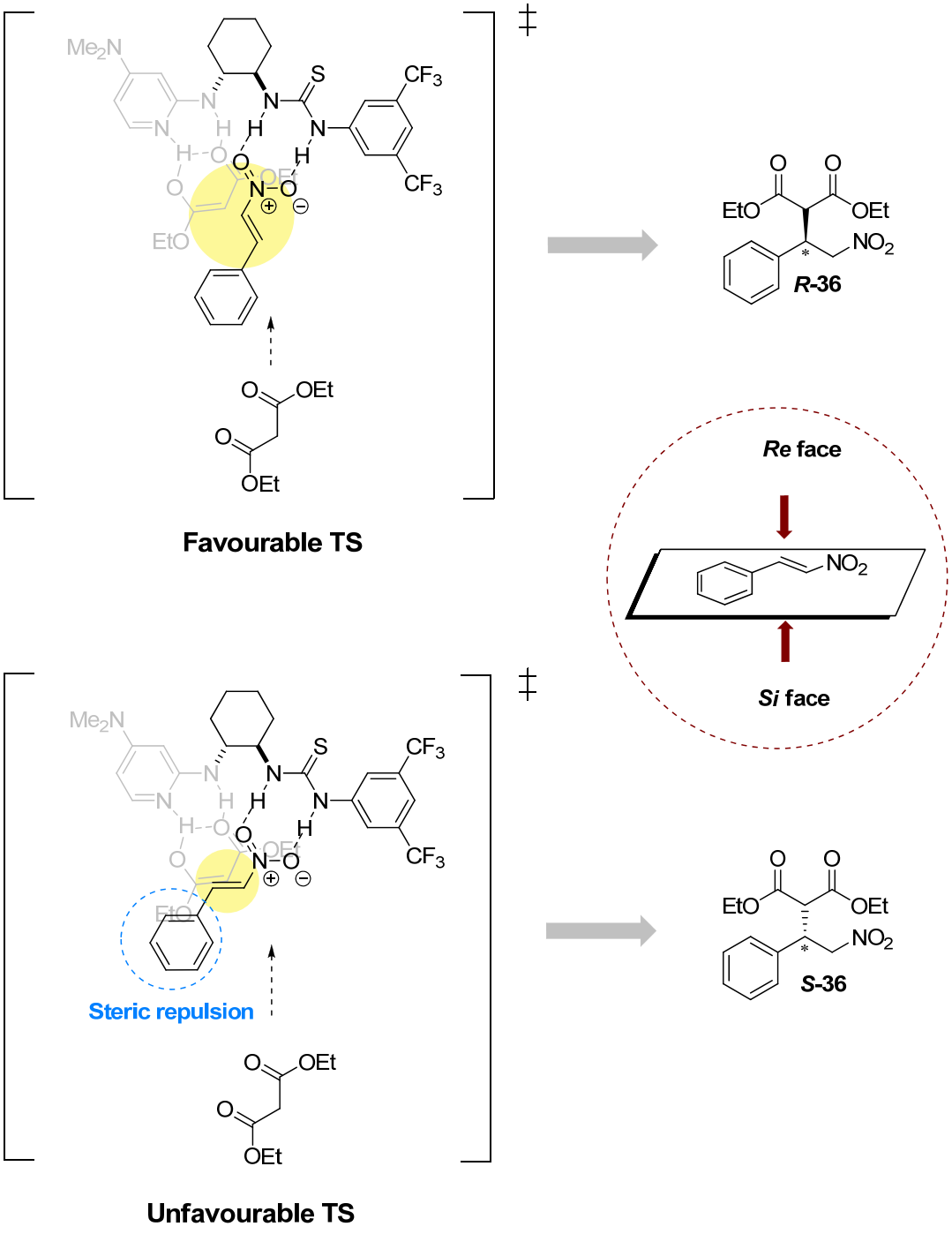


Figure 10. Proposed Transition State model explaining the sense of enantioselection

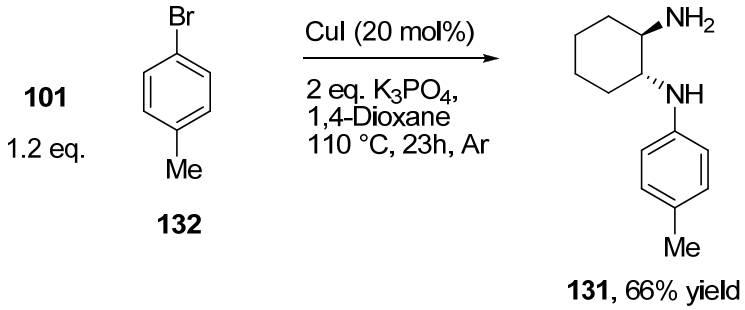
A quick glimpse of TS drawn at the bottom of the Figure 10 envisages the steric repulsion between ethoxy group of diethyl malonate and benzene ring of nitroalkene causing unfavourable interactions. Here the reacting prochiral face of the nitroolefin is the *Si*-face having sp^2-hybridized C center leading to the formation of (*S*)-configurated product (*S*)-**36** according to the Cahn-Ingold-Prelog nomenclature system.[79] TS drawn at the top of the Figure 10 avoids such repulsions therefore expected to have lower energy. In this TS model, delivery of the enolate from the *Re*-face of the nitrostyrene would provide (*R*)-**36** as the major enantiomer (Figure 10).

Although lower selectivities were observed with catalyst **130** when compared with that of Takemoto **29**; considering the reaction rates, **130** promotes Michael addition reaction faster as a proof of claim. To us, the tricky point is to explore better acidic functional group compatible with the core **100**. By performing these catalytic asymmetric reactions, we were convinced to investigate a more facile and higher yielding synthesis of our catalyst core unit **100** for further structural elaborations.

2.3 Copper-Catalyzed Modified Ullmann C-N Coupling Reactions

Realizing unsatisfactory results with palladium chemistry, we have turned our attention to copper-catalyzed Ullmann coupling reaction. Classical Ullmann condensation has been valuable method for the coupling of aryl halides with amines typically requiring the use of elemental copper metal and temperatures generally about 150-200 °C.[80] The use of catalytic copper to replace expensive palladium comprising the use of accompanying air sensitive bisphosphine ligands is an attractive research goal for many groups.[81] In this context, Buchwald and coworkers successfully accomplished *N*-arylation of either aryl iodides or bromides with π-excessive nitrogen heterocycles (pyrroles, pyrazoles, imidazoles, and indoles) and diverse range of amides in 2001.[82] In their report, coupling reactions were successfully promoted in good yield with ligands **101** and its bis-*N*,*N*'-methylated

derivative using CuI precatalyst. To our interest, in a miscellaneous screening of varied nucleophiles for Cu-catalyzed C-N bond forming reactions, Buchwald *et al.* observed a selective mono-*N*-arylated product **131** in moderate yield when using the ligand **101** in excess of stoichiometric amount as the nucleophile and *p*-bromotoluene (**132**) as the electrophile (Scheme 48).

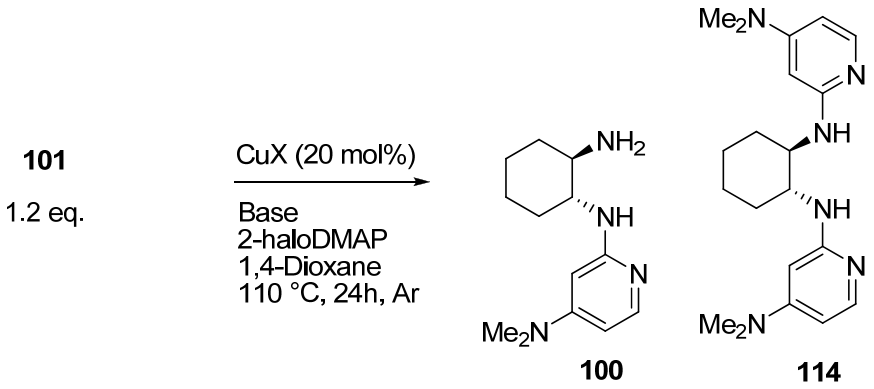


Scheme 48. Cu-catalyzed selective mono-*N*-arylation of diamine **101**

2.3.1 Synthesis of Chiral 2-aminoDMAP (100) *via* Cu-Catalysis

Motivated by their work, we have initiated our copper catalysis studies by applying their protocol as a starting point (Table 5). To our delight, employing their reaction protocol aiming our precatalyst structure **100** depicted in Scheme 49 produced our target compound selectively in 56% yield and 16% yield of C_2-symmetric bisDMAP coupled product **114** as the minor side product. Additionally, formation of trace amounts of 4,4'-bis(dimethylamino)-2,2'-bipyridine **121** was observed in all reactions outlined in Table 5. As an initial investigation, the effect of base on yields was explored (entries 1-5). Of the commonly employed inorganic bases (K_3PO_4, K_2CO_3, Cs_2CO_3, NaO^{t}Bu and KO^{t}Bu) for such transformations, K_3PO_4 and Cs_2CO_3 furnished **100** in comparably higher yields (56% and 53% respectively; entries 1-5). Although the best selectivity (4.5, **100** over **114**) was obtained when using sodium *tert*-butoxide as the base, the worst yield of **100** was obtained (entry 4). Due to its much lower price and relatively higher reactivity, tribasic potassium

phosphate was chosen as the base for further screening studies. The effect of nature of the electrophile (2-haloDMAP **102** and **104**) was also investigated as the next. Reactions carrried out with **102** and 1**04** showed the incompatibility of chloride and iodide halogens as leaving group for the selective and high yielding formation of compound **100**. More explicitly, 2-chloroDMAP **102** was ineffective electrophile in terms of giving sluggish reactions which produced 17% yield of target chiral 2-aminoDMAP compound (entry 6).



Scheme 49. Cu-Catalyzed selective mono-*N*-pyridilization of **101**

In the case of employing 2-iodoDMAP **104** to this C-N coupling reaction, selectivity was lowered considerably (26% vs. 32%) however it proved to be highly reactive substrate for this transformation (entry 7). Due to high reactivity of **104**, reactions were carried out at lower temperatures (50 °C and room temperature) also but fate did not change, more or less the same selectivity was attained within 48h of reaction time. Uncontrolled reactivity of the **104** again directed us to the bromo derivative serving optimal reactivity for our purpose. The effect of copper source was also inquired as the final works to optimize the yield of **100** (entries 8 and 9). Copper (I) salts were screened only, since they generally proved to provide slightly higher rates compared to those of Cu(0) and Cu(II) in literature.[83] Although all copper (I) species furnished product in high yield (56% to 60%), copper (I) bromide gave the best result.

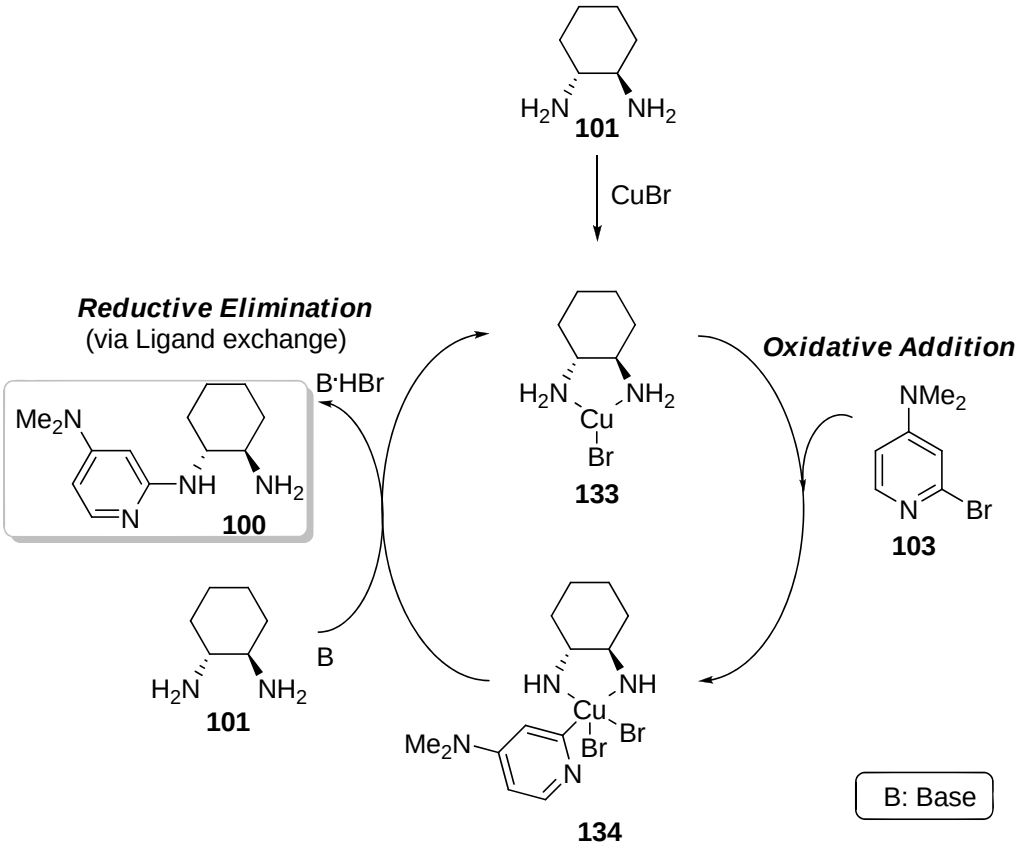
Table 5. Optimization studies for Cu-catalyzed selective direct mono-*N*-pyridilyzation reaction[a]

Entry	Base	2-HaloDMAP	CuX	Yields (%) [b]	
				100	**114**
1	K_3PO_4	**103**	CuI	56	16
2	K_2CO_3	**103**	CuI	40	23
3	Cs_2CO_3	**103**	CuI	53	16
4	NaO^tBu	**103**	CuI	9	2
5	KO^tBu	**103**	CuI	27	4
6	K_3PO_4	**102**	CuI	17	4
7	K_3PO_4	**104**	CuI	26	32
8	K_3PO_4	**103**	CuBr	60	6
9	K_3PO_4	**103**	CuCl	58	8

[a]Reaction conditions: **101** (1.2 mmol), 2-haloDMAP (1.0 mmol), Base (2.0 mmol), 20 mol% CuX, 1mL 1,4-Dioxane were stirred 24 h under Ar atm at 110 °C. [b]Isolated yields after column chromatography.

Semi-optimization of the C-N bond forming reaction by the works presented in Table 5, compound **100** was isolated in quite good yield (60%) considering its highly polar nature (4 basic nitrogens in small organic portion). Scheme 50 presents the possible scenario for the formation of products **100** and **114** based on the similar works published in the literature.[82,84] Scenario is presumed to start with the chelation of the diamine **101** with the copper (I) bromide to form activated copper complex **133** and subsequent oxidative addition of 2-BromoDMAP **103** is thought to generate unstable pentacoordinate reactive intermediate **134**. In the presence of base, intermediate **134** is speculated to reductively eliminate to afford **100**, which is exchanged with the sterically less demanding diamine ligand **101**. Then the catalytically active copper species **133** would be ready to operate in the forthcoming cycle.

Furthermore, a possible formulation for the cycle operating to yield C_2-symmetric bisDMAP coupled product **114** would be as follow. Apart from the catalytic cycle shown in Scheme 50, it is presumed that another catalytic cycle operating may be the one in which competitive ligation of the product **100** and diamine **101** to the copper ending up in favor of **100**. Upon oxidative addition of 2-bromoDMAP followed by base promoted reductive elimination may thereby furnish the side product **114**.

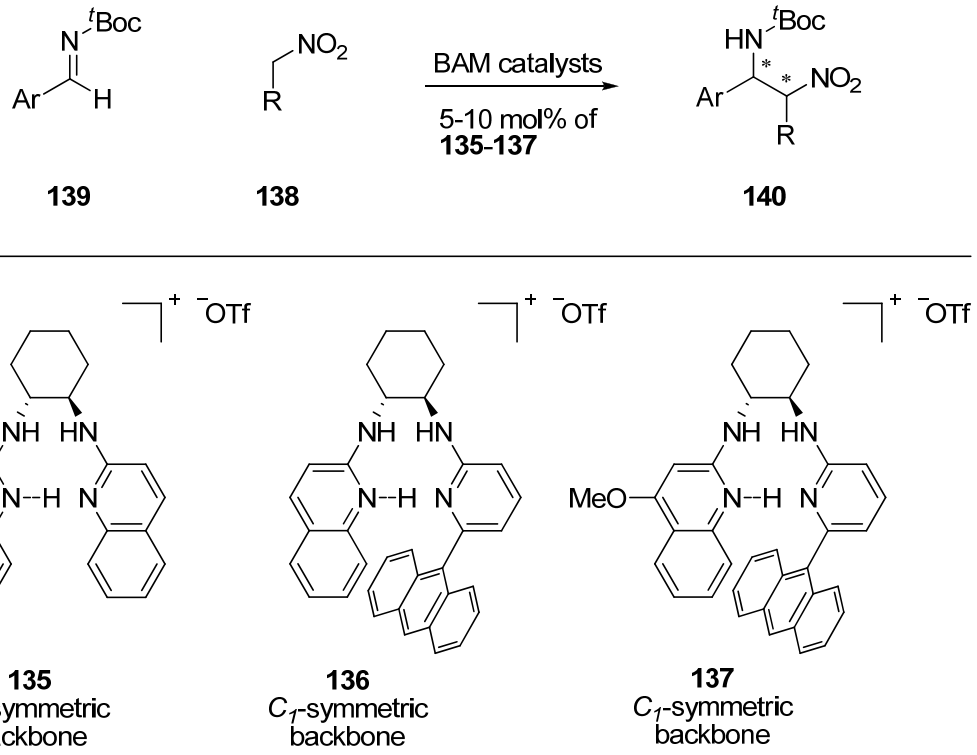


Scheme 50. Proposed operating catalytic cycle producing compound **100**

We claim here that the method we developed is the first successful direct selective mono-*N*-pyridilative/hetero-arylative desymmetrization of *trans*-(*R,R*)-cyclohexane-1,2-diamine **101**. It is especially important to note that the synthesis of compound **100** was achieved also utilizing palladium catalysis, however yielding at most 11 % over 4 consecutive synthetic steps, a process which took at least 5 days. Additionally remarkable is that palladium protocol involves the use of high-priced and air sensitive bis-phosphine ligands. This copper catalyzed protocol avoids the utility of such expensive ligands. The reacting diamine substrate **101** itself acts as the ligand in these transformations. Comparing the Sigma-Aldrich price of palladium and copper complexes it is seen that copper salts are at least 100 fold cheaper (price of 1 Kg of CuBr: 168 Euro, price of 5 g of $Pd(OAc)_2$: 227.50 Euro). Such economic factor would be of great importance in case of commercialization of the protocols for industrial applications regarding research costs.

2.3.2 Application to a Formal Synthesis of Johnston's C_1-symmetric BAM Catalyst

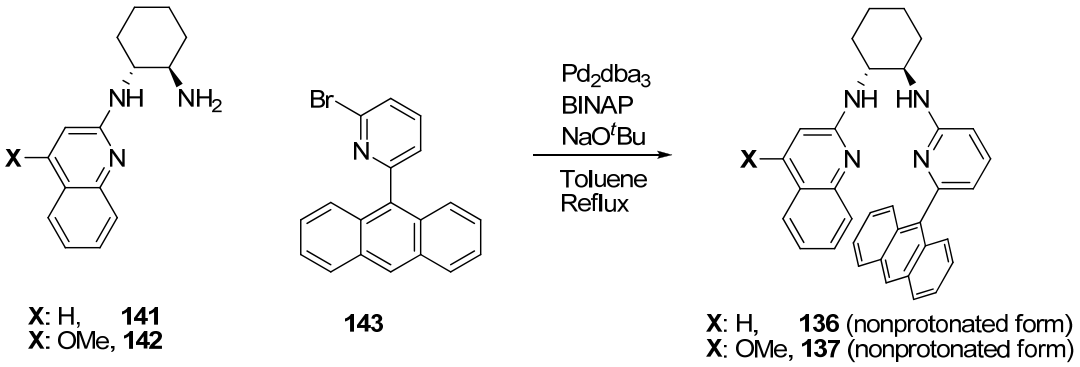
Johnston and coworkers developed following bisamidine (BAM) triflate catalysts **135-137** for enantioselective addition of nitroalkanes or nitroacetates **138** to the *t*-Boc imines **139** to furnish various structurally diverse aminoacid derivatives **140**.[85,86,87] The first example of these catalysts was a C_2-symmetric molecule **135** appeared in 2004 and shown to be a highly selective catalyst for the following transformation shown in Scheme 51.[85]



Scheme 51. Johnston's BAM catalysts

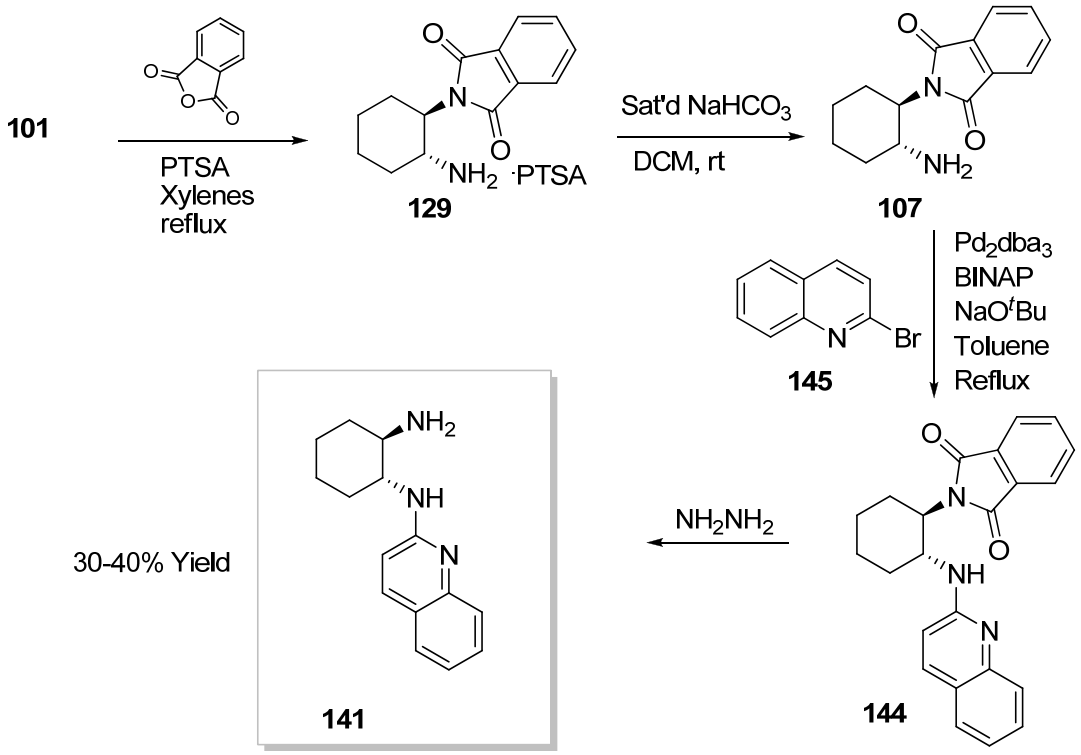
However, in the following years they published two C_1-symmetric alternatives **136** and **137** to be more selective surrogates generally producing at least 10 to 20% higher enantioselectivities than C_2-symmetric catalyst **135**.[86,87]

The synthesis of catalyst **135** was straightforward. It was directly synthesized by palladium catalysis in one step with high yield. However, for the C_1-symmetrics **136** and **137** they only presented the synthetic procedures starting from the mono-amidine precursor structures **141** and **142** respectively and 2-(anthracen-9-yl)-6-bromopyridine (**143**) given in Scheme 52. Additionally no information or references were reported for the synthesis of compounds **141** and **142**.



Scheme 52. Synthesis of nonprotonated forms of compounds **136** and **137**.

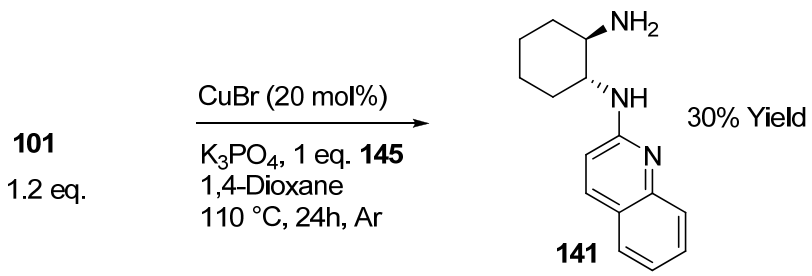
In connection with our Pd and Cu catalysis works described so far, we were interested in their synthesis. For this purpose, upon contacting the corresponding author, we got synthetic procedures for the compound **141** depicted in Scheme 53. It was interesting to observe that the synthetic protocols applied for the production of **141** by Johnston were more or less the same as that of our initial somewhat successful Pd catalyzed studies towards the formation of **100** shown in Scheme 45. In their synthesis of **141**, mono-*N*-phthaloyl protected amine compound **107** was used as the precursor structure to accomplish the synthesis of **144** *via* palladium catalyzed C-N coupling reaction with 2-bromoquinoline (**145**). Phthaloyl protected compound **144** was then deprotected with hydrazine hydrate to afford mono-amidine compound **141** in overall 30-40% yields employing 4 synthetic steps starting from the diamine **101**.



Scheme 53. Unpublished synthesis of **141** by Johnston.

Establishment of a semi-optimized copper catalyzed direct access to the Lewis basic core catalaphore **100** directed us to question a direct access to the compound **141**, which was prepared in four steps by Johnston group. In this respect, commercially available 2-bromoquinoline **145** was prepared in analogy to the synthesis of **102** and **103** by a published procedure.[88] Prepared 2-haloquinoline **145** was reacted with the diamine **101** and produced mono amidine **141** in 30% isolated yield after our first trial (Scheme 54). Although the yield of **141** produced by copper catalysis is almost identical with that of Johnston's 4 step synthesis, ours is direct and completed in only one step. Synthetic route targeting compound **141** shown in Scheme 53 comprises four synthetic steps and employs palladium catalysis as the key step for success. The expensiveness of Pd catalysis together with time and money cost of four synthetic steps involved in Johnston's synthetic pathway lowers the potential industrial applicability of their highly selective C_1-symmetric BAM catalysts **136** and **137**. These drawbacks were eliminated by employing our semi-optimized copper catalysis protocol furnishing direct access to the C_1-symmetric catalyst precursor

structure **136** thereby increasing the value of those catalysts. Another noteworthy point with this experiment is that the substrate scope for our copper catalysis work can be expanded.

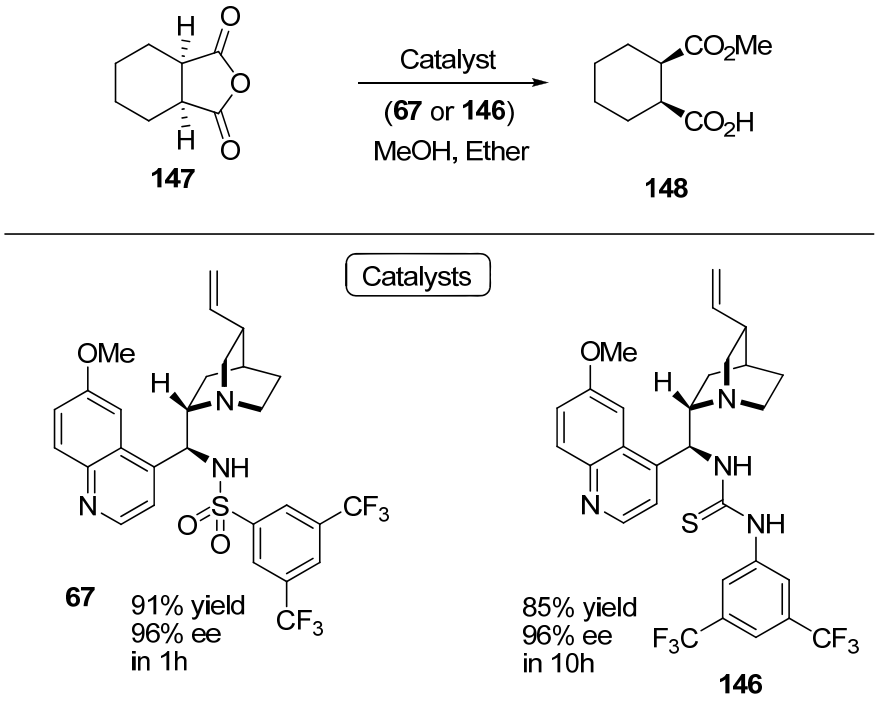


Scheme 54. Synthesis of mono-amidine **141** by our method

2.4 Synthesis and Evaluation of 2-aminoDMAP/Sulfonamide Bifunctional Organocatalysts

Successful synthesis of 2-aminoDMAP **100** directly in only one step in 60% yield encouraged us to investigate the catalytic potential of this superior basic unit further in pursuit of a more compatible acidic entity than thiourea. In this regard, we were first interested in sulfonamides since a recent literature report claimed the advantageous case of sulfonamides over thioureas. Although urea or thiourea based catalysts show excellence in catalyzing wide range of organic reactions, they suffer from self-aggregation, thereby resulting in lower reactivity and a strong dependence of enantioselectivity on concentration and temperature according to the report of Song and Chin published in 2008.[37] The first successful example of chincona alkaloid based thiourea developed by Soós was shown to encounter decomposition when working at high temperatures (100 °C).[32] In this contex, sulfonamides would serve as more robust surrogates than (thio)ureas having higher thermal stability.[37] Song and Chin compared the efficacy of the thiourea and sulfonamide catalysts **67** and **146**,

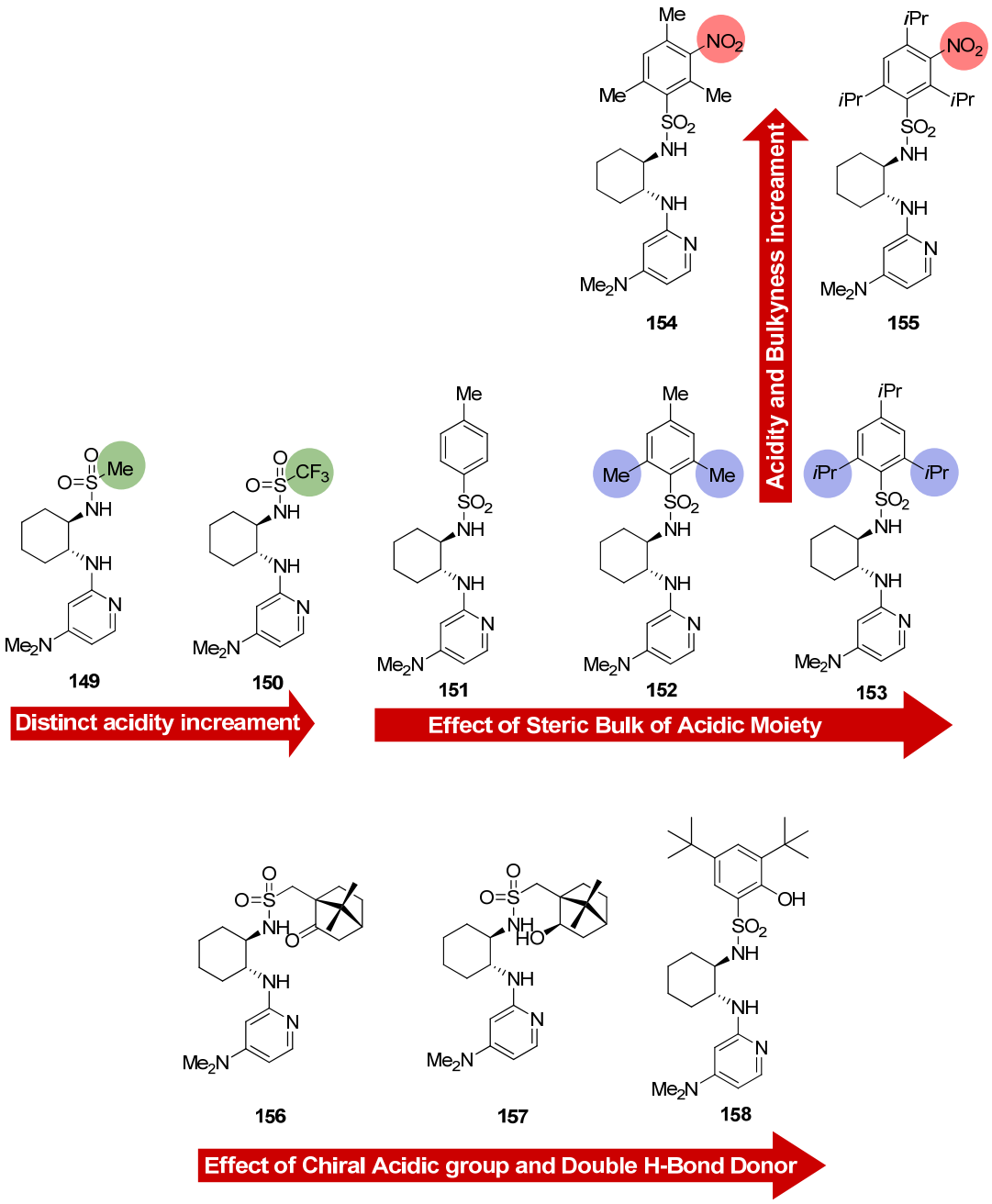
respectively in the asymmetric methanolysis of *cis*-1,2-cyclohexanedicarboxylic anhydride (**147**) depicted in Scheme 55. Sulfonamide catalyst was shown to be operating faster (91% yield in 1h vs 85% yield in 10h) and producing the hemi-ester **148** with equal stereoselectivity at ambient temperature.



Scheme 55. Catalytic activities of **67** vs. **146** in methanolytic desymmetrization

In the light of works cited above, and considering cheaper price of sulfonyl chlorides we designed 10 sulfonamide bearing catalysts incorporating diverse structural elaborations on sulfonamide moiety. Systematicity of our design approach involves the following elaborative approach outlined in Scheme 56. 2-AminoDMAP **100** moiety is constantly present in all bifunctional catalysts. Initially we aimed to investigate the distinct acidity increament effect while keeping the steric bulk constant. Methanesulfonamide **149** and trifluoromethane sulfonamide **150** were devised to establish this purpose. Although fluorine having significantly larger van der Waals radius of than that of hydrogen (1.35Å vs. 1.10Å), studies have shown that, size-wise, fluorine is actually a good hydrogen mimic, adding only limited extra steric demand at receptor sites considering fluorine containing drug development.[89] As a

result, replacing hydrogen with fluorine would cause little change in the overall steric bulk of the catalyst.



Scheme 56. Systematicity in the design of 2-aminoDMAP/Sulfonamide generation

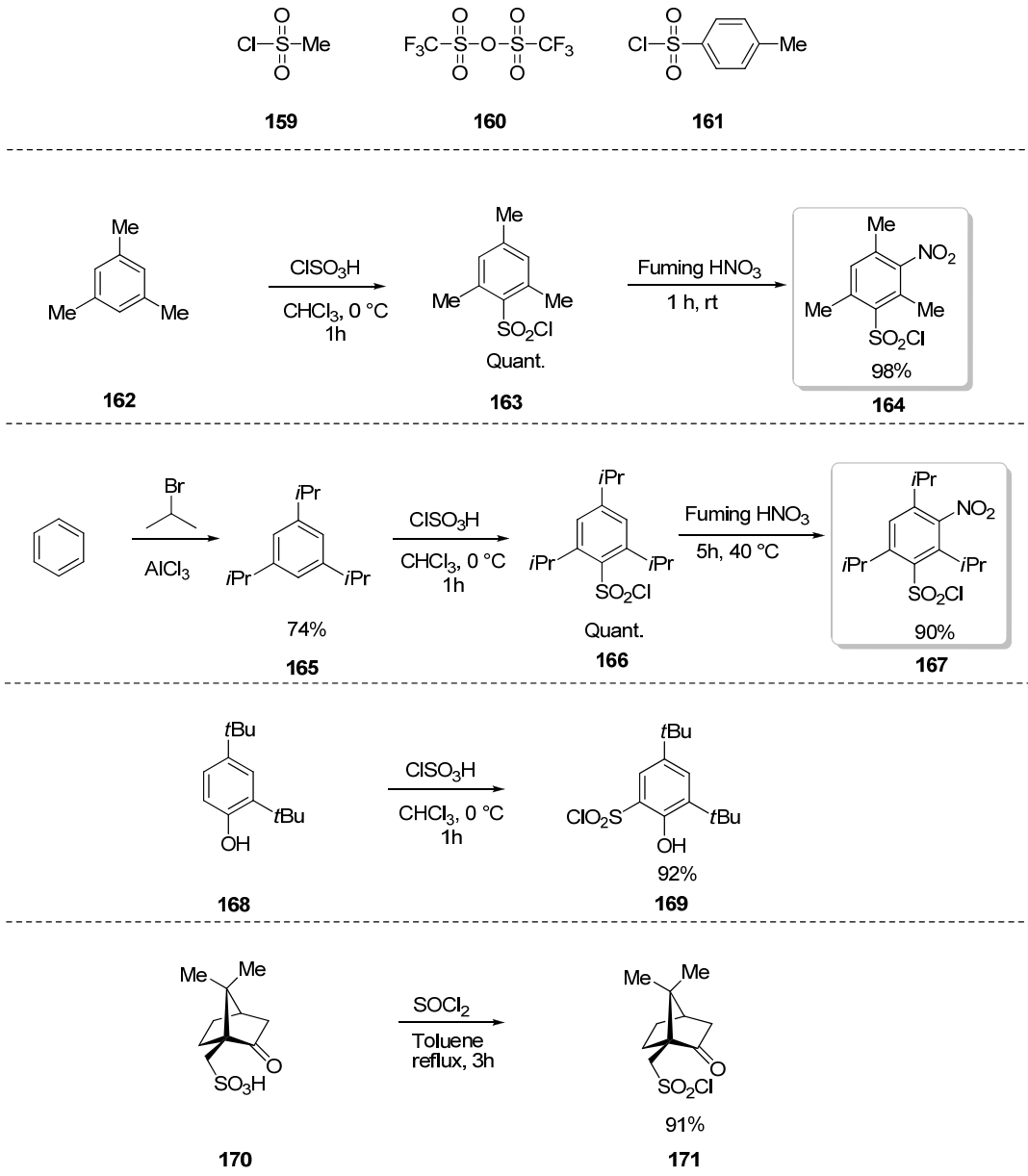
Next, sulfonamides **151-153** were designed in the order of increasing steric demand (H, Me, ^{i}Pr substitution in the *ortho*-position respectively) for tuning the steric bulk in

the vicinity of active acidic N-H group without paying cost much to the acidity. Although catalysts **154** and **155** are similar to **152** and **153** respectively, they were expected to show different catalytic activities due to the acidity and bulkyness increased in those systems in different respects. Catalysts **156** and **157** were devised to examine the effect of secondary chirality on the acidifying moiety. Camphorsulfonyl chloride derived catalysts **156** and **157** anticipated to differ however in supplying hydrogen bonds. Catalyst **157** has two potential hydrogen bond donor sites. The last example **158** was also supposed to be a double H-bond donor similar to the **157** but apparently it would acquire a different character due to bearing a phenolic proton.

2.4.1 Synthesis of 2-aminoDMAP/Sulfonamide Bifunctional Organocatalysts

In order to synthesize the bifunctional sulfonamide catalysts shown in Scheme 56, we have initiated our synthetic studies targeting the sulfonyl chlorides from appropriate precursors outlined in Scheme **57**. Methanesulfonyl chloride **159**, trifluoromethane sulfonyl chloride **160** and *p*-toluenesulfonyl chloride **161** were supplied commercially. Although all the other sulfonyl chlorides except from **164** and **167** are commercially available and cheap compounds, they were also synthesized according to literature procedures. Chlorosulfonation of mesitylene **162** with chlorosulfonic acid at zero degree afforded the desired mesitylenesulfonyl chloride **163** in quantitative yield.[90] It was then nitrated using fuming nitric acid to form 2,4,6-trimethyl-3-nitrobenzene-1-sulfonyl chloride **164** in quite high yields (98%) upon recrystalyzation in *n*-pentane. 1,3,5-triisopropyl benzene (**165**) obtained *via* triple Friedel-Craft alkylation with aluminum chloride was further chlorosulfonated by chlorosulfonic acid to yield 2,4,6-Triisopropylbenzene-1-sulfonyl chloride (**166**).[90,91] It was then nitrated to result in 90% yield of 2,4,6-triisopropyl-3-nitrobenzene-1-sulfonyl chloride (**167**) by fuming nitric acid. This time reaction required higher temperature (40 °C) and reaction time than that of **164**. Remarkably, it should be noted that there are few reports on the nitration of sulfonyl chlorides and using concentrated nitric acid and sulfuric acid as the reaction medium and also requiring high temperatures to produce nitrated derivatives in moderate yields. Here we show

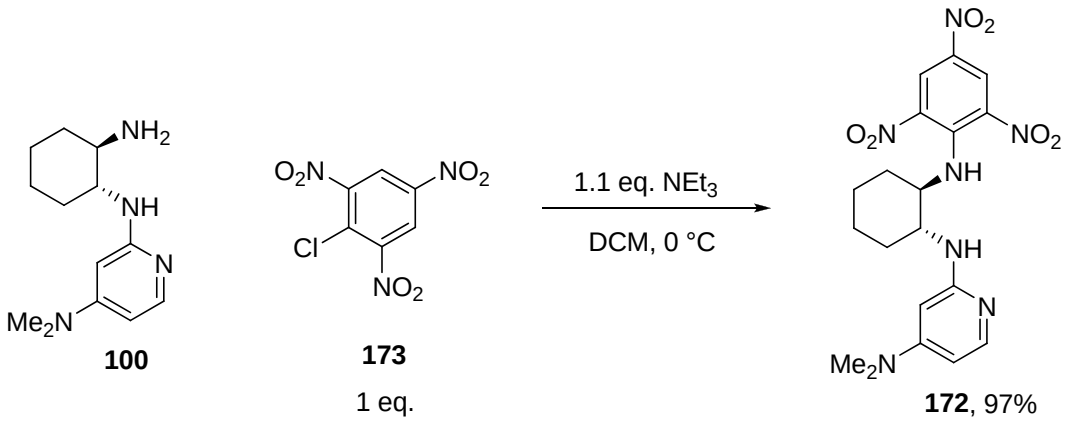
that fuming nitric acid is a quite good alternative serving almost quantitative yields under milder reaction conditions. Sulfonyl chlorides **164** and **167** are not known in the literature yet therefore they are fully characterized by ^{1}H NMR and ^{13}C NMR, IR and HRMS analytic techniques.



Scheme 57. Synthesis of sulfonyl chlorides

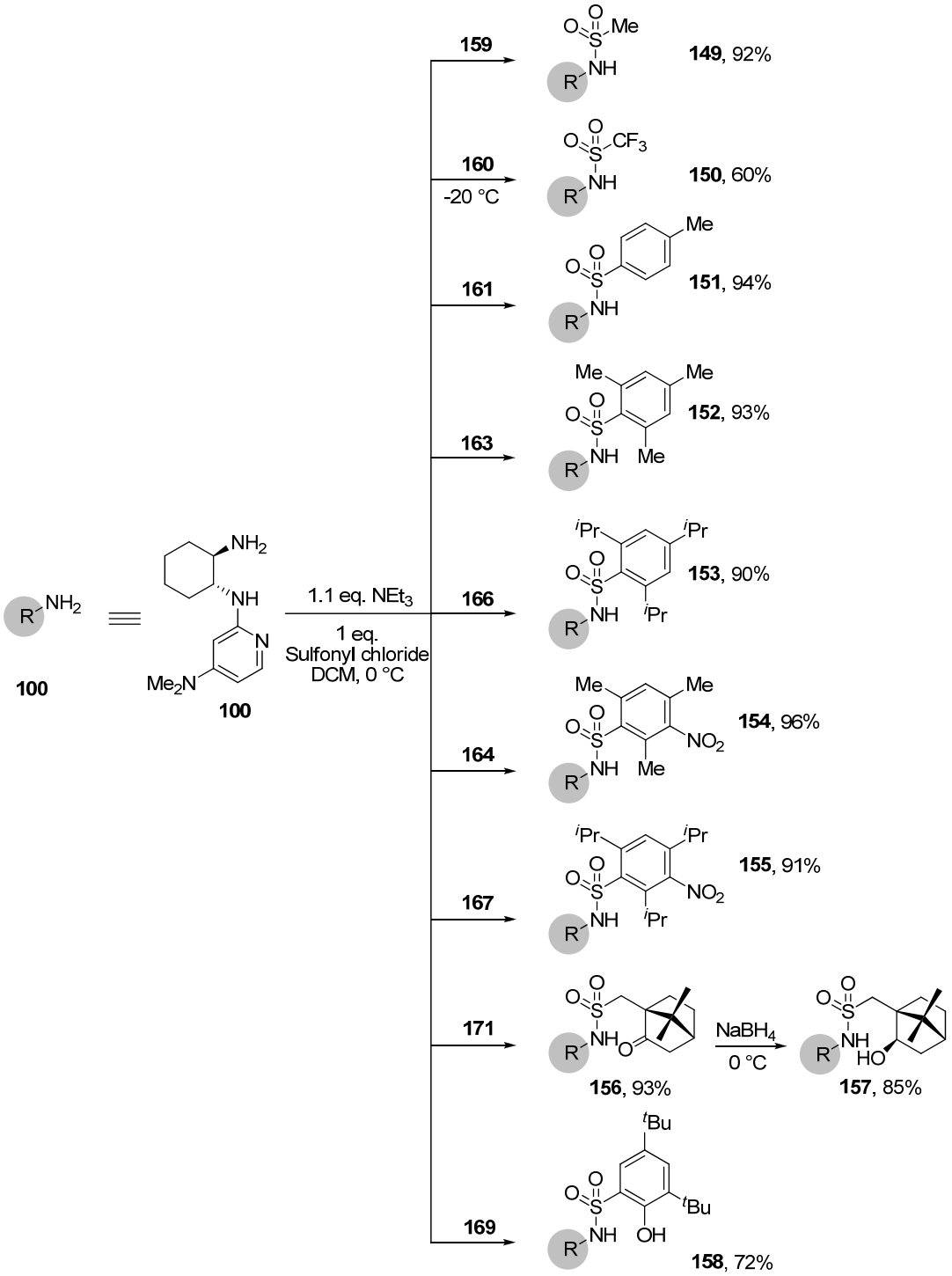
2,4-di-*tert*-Butylphenol (**168**) was treated with chlorosulfonic acid according to a German patent to yield 3,5-di-*tert*-butyl-2-hydroxybenzene-1-sulfonyl chloride (**169**) quantitatively.[92] (1*S*)-(+)-10-Camphorsulfonyl chloride (**171**) was prepared by treating (1*S*)-(+)-camphorsulfonic acid with thionyl chloride under refluxing toluene in good yield.[93]

An additional out of class catalyst **172** bearing 2,4,6-trinitro aniline group was developed also to serve a new acidifying moiety (an acidic amine resembling sulfonamides in respect of supplying mono hydrogen bond donation). Scheme 58 shows the synthesis of **172** which was developed by the reaction of picryl chloride (**173**) (commonly encountered in the synthesis of secondary explosives) and the chiral 2-aminoDMAP **100** using triethyl amine as the base. Compound **172** was prepared in 97% yield in one hour giving a blood-red solid.



Scheme 58. Synthesis of out of class catalyst **172**

Obtained sulfonyl chlorides were reacted with the Lewis basic catalaphore **100** under basic conditions to produce 9 sulfonamide catalysts in high yields (60-96%) as depicted in Scheme 59. Synthesis of **157** was achieved by reducing **156** with sodium borohydride and product is presumed to form *via* endo attack of hydride considering similar structural transformation encountered in literature.[94] 2-aminoDMAP/sulfonamides shown in Scheme 59 are purified by silica gel column chromatography and fully characterized by ^{1}H NMR and ^{13}C NMR, IR and HRMS analytic techniques. Melting point and optical rotation measurements were done for all compounds listed in Scheme 59.



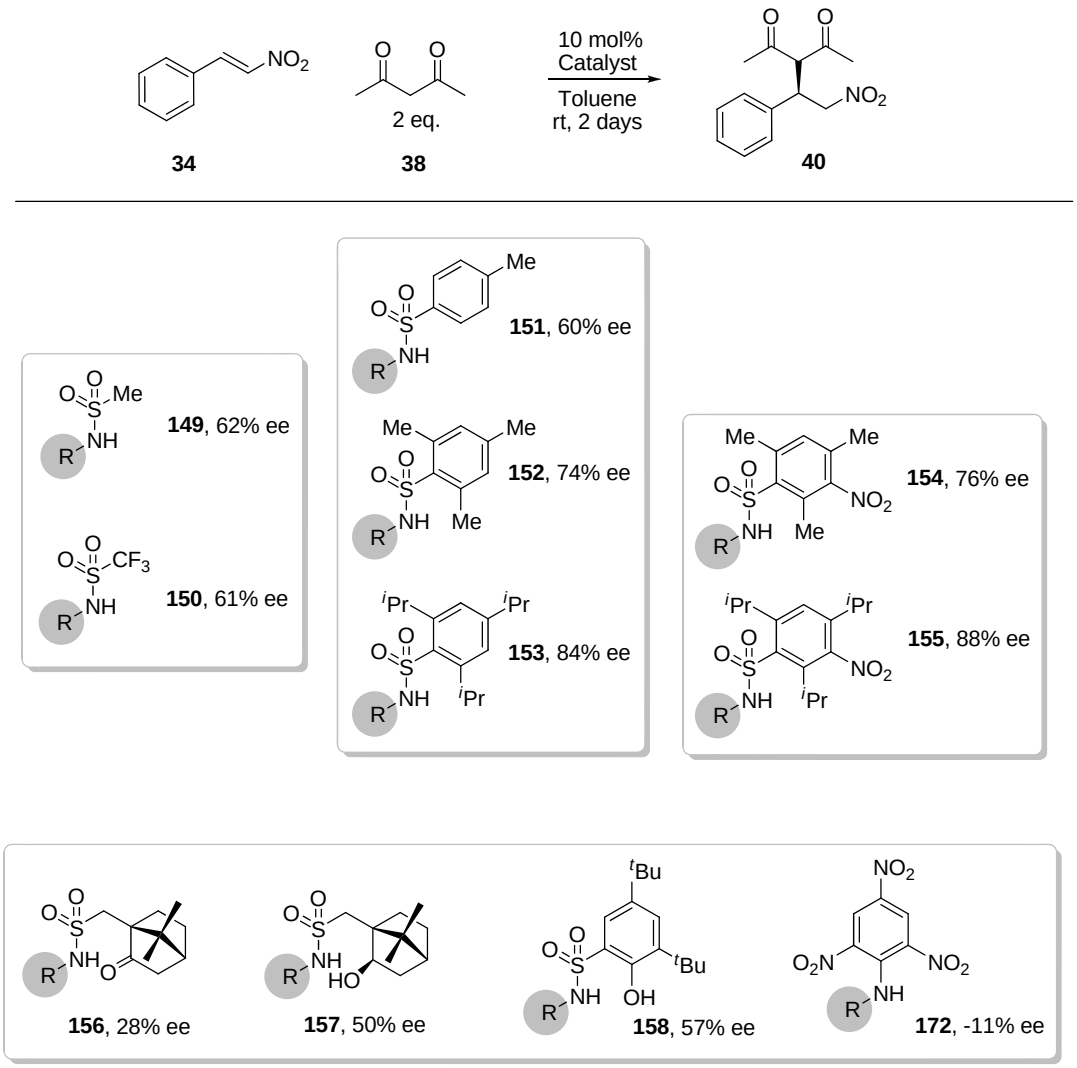
Scheme 59. Synthesis of 2-aminoDMAP/Sulfonamide bifunctional organocatalysts

2.4.2 Evaluation of 2-aminoDMAP/Sulfonamides in Asymmetric Michael Additions

All catalysts (sulfonamides and trinitroaniline bearing one) shown in Scheme 58 and 59 were initially screened. We have interested in conjugate addition of diethylmalonate to *trans*-(*β*)-nitrostyrene **34** in order to compare the catalytic performances of these novel sulfonamides with our preceding thiourea one. However it took weeks to observe reasonable formation of product with all these catalysts. We presumed the reason being the unreactivity of malonates with such catalysts donating mono hydrogen bond for activation of nitrostyrene electrophiles since it was shown that this reaction could be promoted to completion even in hours when catalyst accompanying a double bond donor thiourea **130**. Then we have turned our attention to the more acidic acetylacetone **38** (Scheme 60).

Most of the catalysts generally consumed the limiting reactant *trans*-(*β*)-nitrostyrene (**34**) in 2-3 days. Although distinct acidities of **149** and **150** had no impact on enantioselectivity producing moderate enantioselectivities (62%, 61% respectively), triflamide **150** gave very sluggish reaction (8 days). Catalyst **150** had very poor solubility in toluene too. Later the steric effects of catalysts were analyzed. Steric demand of catalysts **151-153** was clearly observed. Increasing steric bulk of the sulfonamide we observed a parallel increase in selectivity (60%, 74%, 84% *ee*s, respectively). Further increase of steric bulk and acidity by insertion of a nitro group to the *meta* positions of the best acting ones **152** and **153**, both of the catalysts **154** and **155** were observed to induce higher selectivity, however profoundly pronounced in tri-*iso*-propyl substituted catalyst **155**. Enantioselectivity achieved with this catalyst was quite impressive, 88% *ee*. Catalysts **156** and **157**, devised to examine the effect of secondary chirality on the sulfonamide unit, provided low selectivities reduced form being better (28% and 50%). Additionaly, no increase in rates was observed by introducing the second potential proton donor in **157**. Although **157** seemed superior to the catalyst **156**, asymmetry inductions of both were lower than that of the simple methane sulfonamide **149**. Catalytst **158** bearing additional phenolic proton gave significantly lower selectivity than aromatic sulfonamides **151-155**. The last example

172 was also screened however reactions were again sluggish, completed in 10 days and interestingly the other enantiomer (*S*) was obtained for which we have no explanation.



Scheme 60. 2-aminoDMAP/Sulfonamide's screening works

Choosing the catalyst **155** as the favorite, effect of solvent, temperature, molarity and catalyst loading were investigated further to catch the best working condition for this Michael addition reaction (Table 6). Of the screened seven solvents,

relatively non-polar toluene, cyclohexane, benzotrifluoride (BTF) and ether gave enantioselectivities above 70%, toluene being the best (88% *ee*). Polar solvents yielded very poor selectivity. Additionally, using ethyl acetate as the solvent, it yielded trace amount of product hardly visible on TLC, even prolonging reaction times to 60h (entry 1-7). Low selectivities encountered here is generally the case for most of the acid/ base catalysts tested in such reactions. In their seminal paper, Takemoto and coworkers reasoned similar observation resulting from the polar solvents coordinating nature to the active sites of the catalyst thereby decreasing both yield and selectivity simultaneously.[13a] Such reasoning fits well also on the account of our observations on solvent effect.

Table 6. Solvent, temperature, molarity and catalyst loading optimizations with **155**[a]

Entry	Solvent	Temp.	Cat. Loading (%)	Time (h)[b]	*ee* (%)
1	Toluene	rt	10 mol	48	88
2	Cyclohexane	rt	10 mol	22	80
3	Ether	rt	10 mol	48	70
4	THF	rt	10 mol	60	10
5	DCM	rt	10 mol	56	58
6	BTF	rt	10 mol	40	75
7	EtOAc	rt	10 mol	60	nd
8[c]	Toluene	rt	10 mol	30	82
9[d]	Toluene	rt	10 mol	90	89
10	Toluene	0 °C	10 mol	60	**90**
11	Toluene	-10 °C	10 mol	96	**92**
12	Toluene	-10 °C	5 mol	144	**93**
13	Toluene	-10 °C	20 mol	72	**92**

[a]Reactions were carried out in 0.2 M concentration of *trans*-(*β*)-nitrostyrene. [b]Time for consumption of nitrostyrene by TLC. [c]0.4 M concentration. [d]0.1 M concentration.

These solvent screening works proved toluene to be the most promising for additionally investigating the temperature and catalyst loading effect. Before investigating these parameters, the effect of molarity was also examined. Increasing the molarity to 0.4 M in entry 1, enantioselectivity declined to 82% with higher reaction rate (entry 8). Lowering the molarity to 0.1 yielded a slow reaction and only a slight increase in chirality induction (89% *ee*, entry 9). Reactions were decided to carry out in 0.2 M concentration to examine the temperature effect. 2% *ee* increament was observed when the temperature was lowered to zero degree. Further cooling the system to -10 °C, *ee* again increased 2 % however it took 4 days for the completion of the reaction. Therefore, reaction temperature was kept at -10 °C to investigate catalyst loading effect. Although lowering catalyst amount by half caused only 1% increase in *ee*, this time it had deleterious effect on rate (6 days), doubling catalyst loading to 20% smoothly produced the enantioenriched adduct 92% *ee* with faster reactions. These observations presented in entries 11-13 shows that enantioselectivity has nearly no dependence on catalyst loadings, which is quite good result since catalyst aggregation is observed generally in such cases. However our catalytic system shows strong dependence on molarity of reaction on the sake of obtaining fast reactions (entries 1, 8 and 9). Yield calculations performed for some arbitrarily chosen experiments presented in Scheme 60 and Table 6 provided Michael adduct **40** in 89 to 94% isolated yields after column chromatographic separations. Lower reaction rates observed herein compared to the thiourea case was thought to stem from mono-hydrogen bond donation capacity of sulfonamides. Especially the catalysts bearing trifyl unit **150** and trinitroaniline unit **172** were believed to poison catalyst activity by the intermolecular hydrogen bond lowering the basicity of DMAP unit (Figure 11).

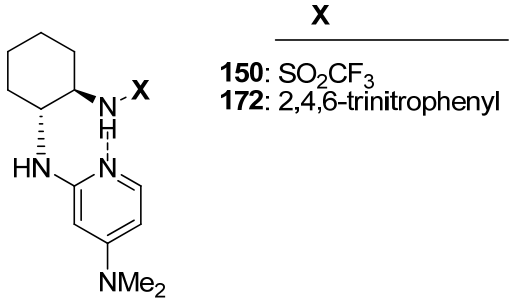
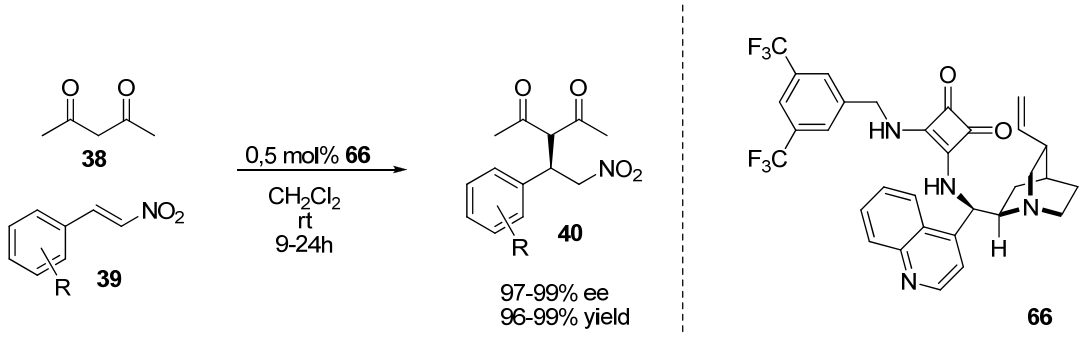


Figure 11. Intramolecular H-bond lowering activity of catalysts **150** and **172**

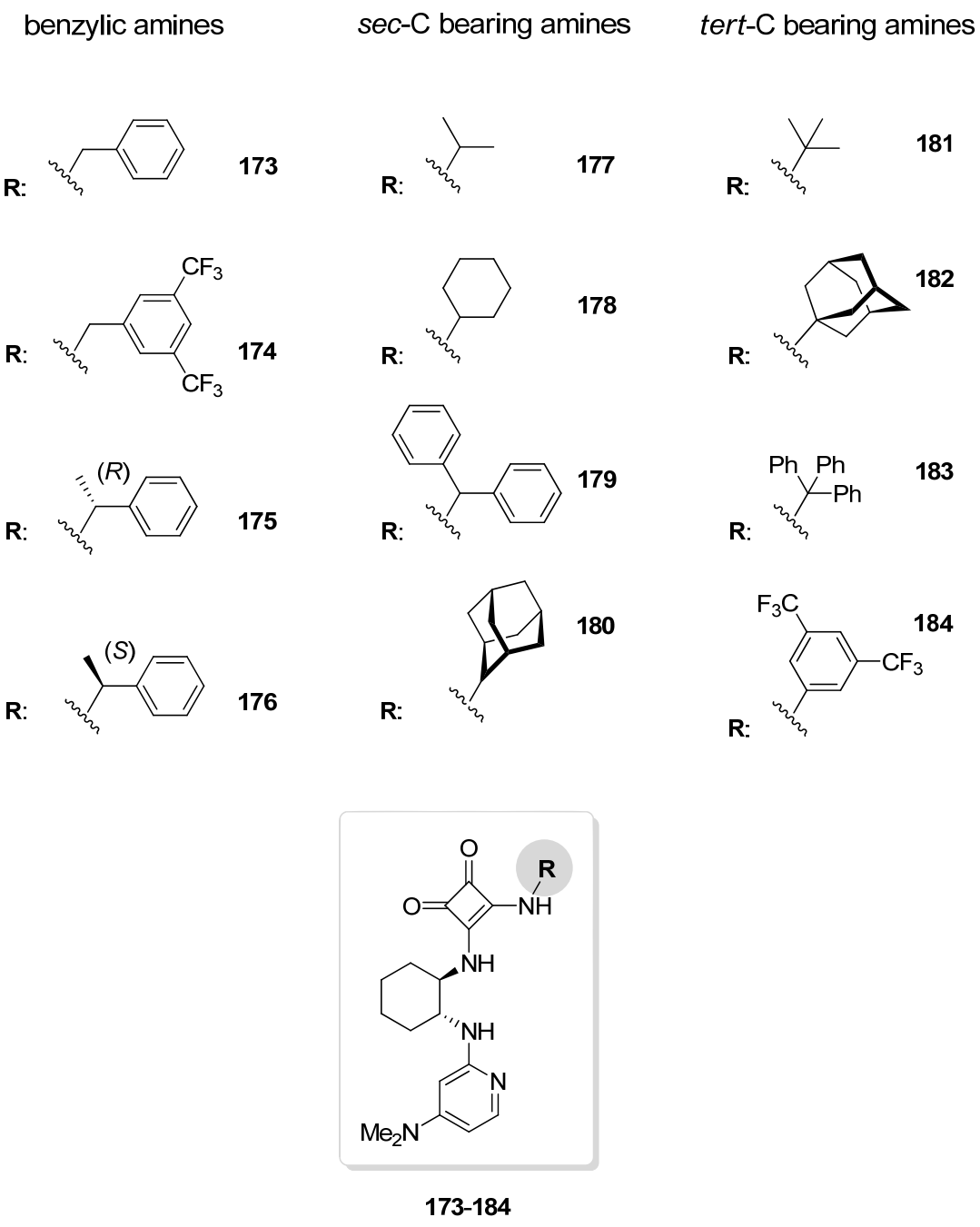
2.5 Synthesis and Evaluation of 2-aminoDMAP/Squaramide Bifunctional Organocatalysts

Up to now we have shown the practicality of using a stronger base (an aminoDMAP unit) in thiourea catalysis, however *ee* levels were only moderate (61% *ee*). In search for a better accompanying acidic moiety, sulfonamide generation was synthesized and tested to provide very good enantioselectivity (up to 93%), however this time protocols needed 3-6 days for complete conversion. With these results in hand, we have pursued a more active catalyst generation where we could easily tune the catalyst structure. In 2008, Rawal (very well known for his diene for Diels-Alder reaction) and coworkers introduced squaramides as new hydrogen bond donor catalysts.[36] In their pioneering work, a bifunctional catalyst **66** derived from a chinchona alkaloid were developed in two chemically high yielding steps. This catalyst was shown to be very effective in promoting the Michael reaction of acetyl acetone **38** and nitroolefins **39**. The results of this work were quite impressive both in terms of both stereoselectivity (97-99% *ee*) and yield (96-99%) in short reaction times (9-24h) employing as low as 0.5 mol% catalyst as depicted in Scheme 61.



Scheme 61. Rawal's squaramide catalyzed Michael addition

Motivated by their work, it was thought that easy structural modification on the squaramide moiety under mild conditions would be a convenient way of catalyst tuning. Scheme 62 shows the list of catalysts devised to tune their activities based on steric and electronic factors.



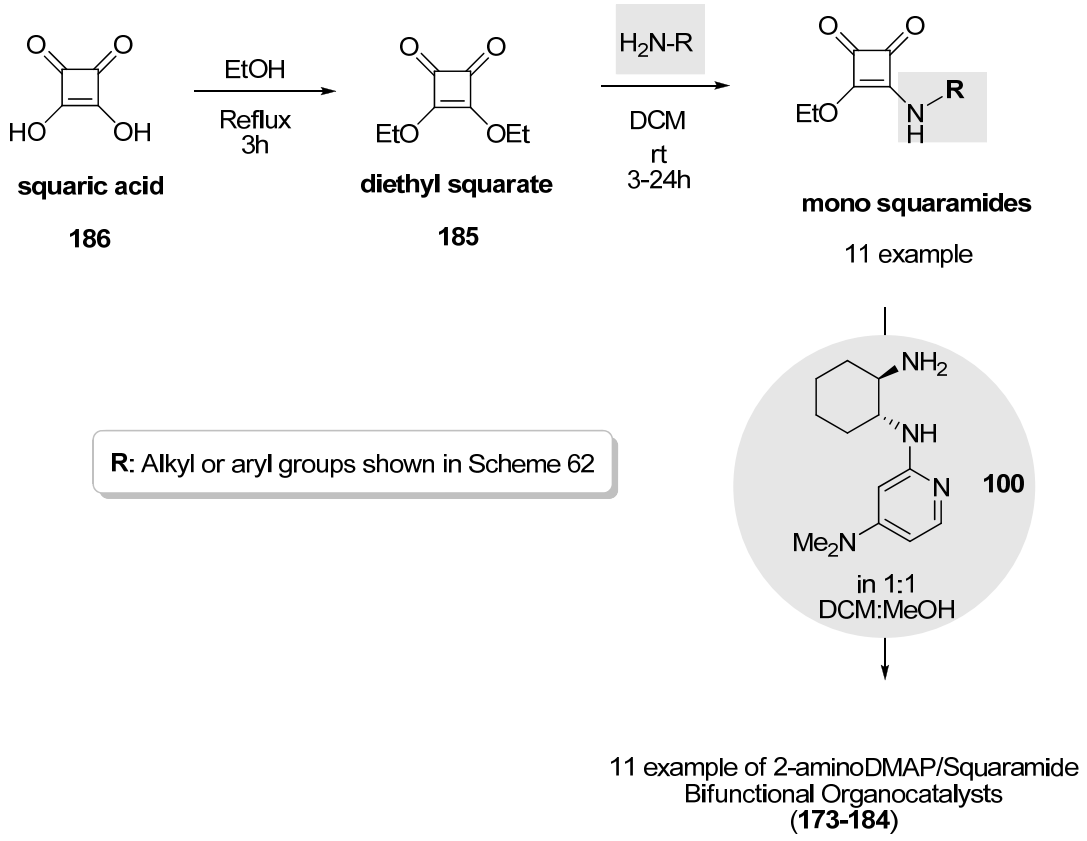
Scheme 62. Designed 2-aminoDMAP/Squaramide bifunctional organocatalysts

Catalysts depicted in Scheme 62 were grouped in to three according to the substitution degree of carbon vicinal to the amine functional group. Benzylic amine derivatives **173-176** are further grouped in to two. Catalysts **173** and **174** are designed to investigate the effect of small acidity difference resulting inductively by CF_3

groups substituted on aromatic ring of **174**. Next **175** and **176** are devised to see whether any match-mismatch effect that would affect the activity of catalysts. Secondary carbon neighboring amine derived catalysts **177**-**180** are designed to impose increasing steric bulk. Namely, *iso*-propyl **177**, cyclohexyl **178**, benzhydryl **179** and 2-adamantyl **180** units are incorporated to observe the steric demand of the catalysts. To explore the effect of increasing steric bulkiness around the active squaramide region, tertiary carbon bearing (*tert*-butyl **181**, 1-adamantyl **182** and trityl **183**) amine derived catalysts are devised. Last is the only example of aromatic amine derivative **184**, developed from 3,5-bis(trifluoromethyl)aniline. This squaramide is the generic of frequently addressed thiourea incorporating unit and believed to be the most acidic of all.

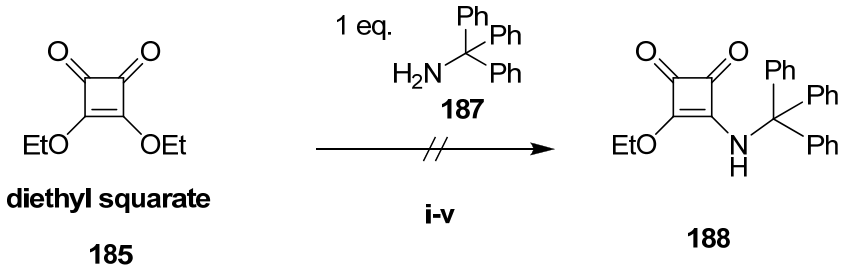
2.5.1 Synthesis of 2-aminoDMAP/Squaramide Catalysts

We have chosen to form squaramide unit starting from diethyl squarate (**185**) which was easily prepared upon refluxing squaric acid (**186**) in absolute ethanol (Scheme 63). All the amines were commercially supplied and most mixed with diethyl squarate (**185**) in one to one ratio in dichloromethane at room temperature according to a literature procedure.[36] Their synthesis was quite straightforward and yielded the corresponding mono-squaramides in good yields following literature procedures. Next was simply mixing the prepared mono-squaramides with our basic core compound **100** prepared *via* copper catalyzed C-N coupling reaction. Stirring at room temperature within two days, 11 catalysts devised in Scheme 62 were prepared in good yields (66-84 %). Despite our all efforts, we could not synthesize the mono squaramide **188** bearing the trityl moiety shown in Scheme 64. Therefore synthesis of trityl bearing designed catalyst **183** could not be accomplished. Due to the availability of the mono-squaramides in the literature, they were directly used after chromatographic separation without characterization. Structure of all catalysts prepared was elucidated using their NMR spectra, HRMS, IR. Melting point and optical rotation measurements were also done for each.



Scheme 63. Synthetic pathway for 2-aminoDMAP/Squaramide catalysts

The standard procedure was to mix diethyl squarate (**185**) and corresponding primary amine in one to one ratio in dichloromethane at room temperature however it failed when the amine was trityl amine (**187**) even after 48 hour of stirring (condition i. in Scheme 64). Triethyl amine was added as base in one equivalent next (ii) to activate the primary amine, but no product **188** was observed. Then nucleophile catalysis was tried to promote reaction using DMAP even employing in one equivalent (iii). As a next trial, 1,2-dichloroethane was used as high boiling solvent (84 °C) in the presence of DMAP but no conversion was observed (iv). Using a literature procedure achieving mono and disubstituted squaramides by lewis acid catalysis involving unreactive amine substitution, again the fate did not change (v).[95] It was reasoned that the trityl amine's unreactivity could be attributed to three phenyl rings imposing highly steric bulkiness shielding the lone pair electrons on amine strongly.



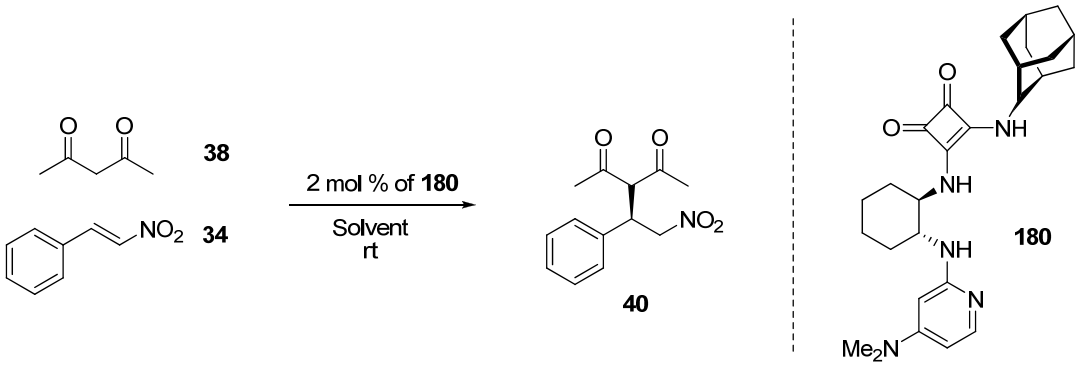
i: DCM, 48h at rt,
ii: DCM, 1 eq. TEA, 24h at rt,
iii: DCM, 1 eq. DMAP, 24h at rt,
iv: $ClCH_2CH_2Cl$, 1 eq. DMAP, 24h reflux
v: 20 mol% $Zn(OTf)_2$, Toluene/DMF (19/1), 100 °C, 24 h

Scheme 64. Unsuccessful attempts targeting the synthesis of **188**

2.5.2 Evaluation of 2-aminoDMAP/Squaramide Catalysts in Michael Reaction

Squaramide catalysts obtained are given in Scheme 62. All eleven catalysts are subjected to conjugate addition of acetyl acetone (**38**) to *trans*-(*β*)-nitrostyrene (**34**) in order to compare the catalytic activities of these novel squaramides with our preceding sulfonamides and with the catalyst **66** developed by Rawal group as an initial point of investigation. Additionally reactions shown in Scheme 65 were performed also to understand the residual water content tolerance of squaramide catalyst **180** which was arbitrarily chosen. Since higher activity compared to that of sulfonamide generation was expected due to double hydrogen bonding capacity of squaramides, 2 mol% catalyst loading was employed. As seen from Table 7, reaction smoothly proceeded in toluene whether using reagent grade or Na/benzophenone ketyl radical dried (entries 1-3). Such a tolerance made it easy to perform asymmetric synthesis experiments. Quite notable is the reaction time (2h for complete conversion) as in the thiourea case (in acceleration aspect only) yielding 70% *ee*. Using some most commonly encountered solvents, ether and dichloromethane too, it was observed that ether giving the same selectivity likewise toluene and same in respect of reaction time. Dichloromethane gave slower reaction also lower *ee* (60%) (entries 4 and 5). Due to its safer handling and considering its higher boiling point providing lower

possibility of concentration change during the reaction, toluene was chosen as the solvent for further screening studies. Sodium wire dried toluene was used.



Scheme 65. Squaramide catalyst **180** promoting conjugate addition of **38** to **34**

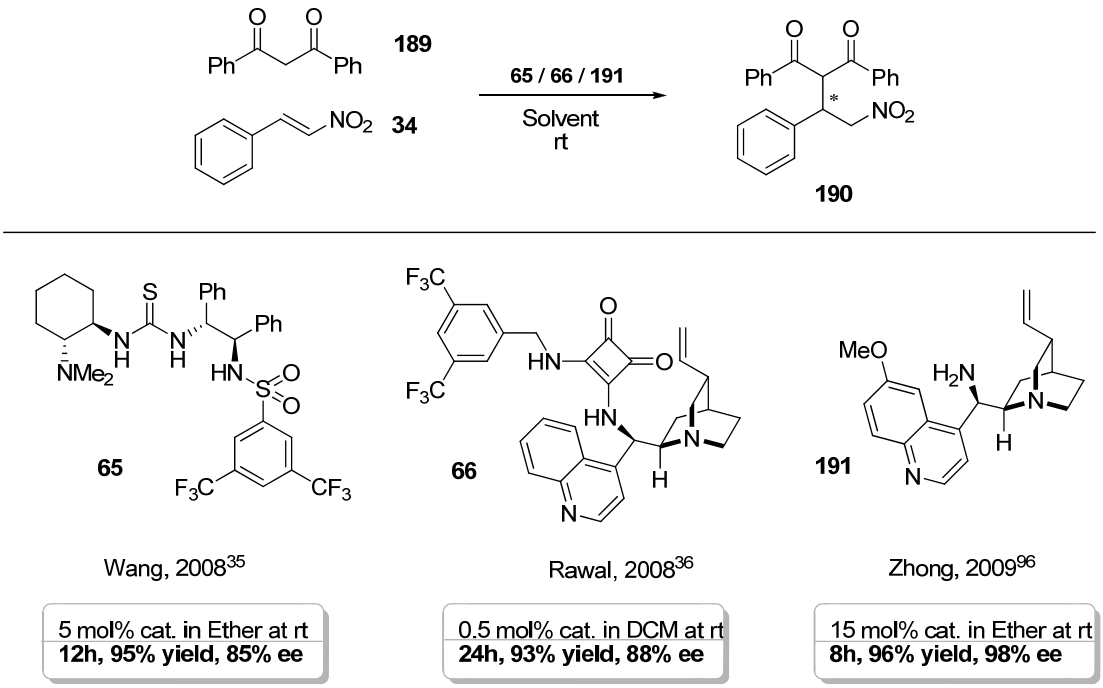
Table 7. Residual water tolerance of squaramide catalyst **180**

Entry[a]	Solvent	Time (h)[b]	*ee* (%)
1	Toluene (Reagent grade)	2	70
2	Toluene (Na-wire dried)	2	70
3	Toluene (Na-benzophenone dried)	2	69
4	Ether (Na-wire dried)	2	70
5	DCM (Reagent grade)	3	60

[a]All reactions were carried out in 0.2 M concentration. [b]Represents the duration for complete conversion.

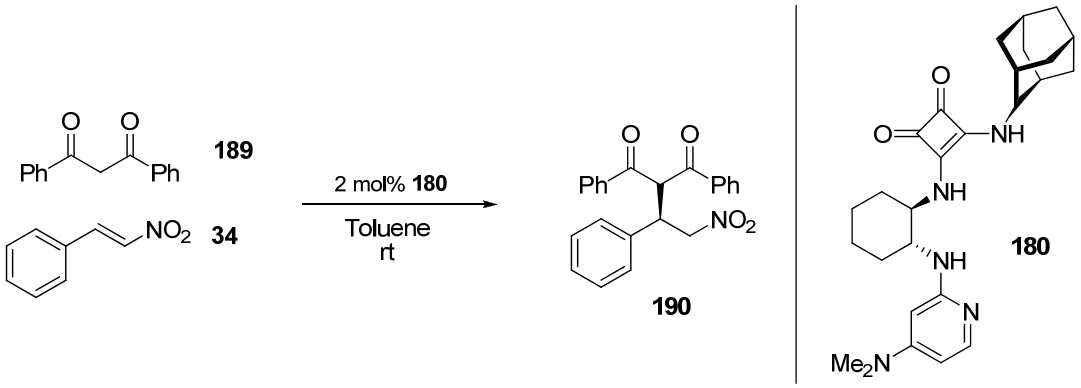
Although promising results were obtained with the arbitrarily selected catalyst **180**, we have turned our attention to a less frequently employed nucleophile for such 1,4-addition reaction, where to date there were only three reports utilizing dibenzoyl

methane (**189**). However excellent enantioselectivity was attained only in one report authored by Zhong. The results by Wang and Rawal were 85% *ee* and 88% *ee* respectively. However considering the catalyst loading employed for this transformation, Rawal's is the most impressive utilizing only 0.5 mol%. Although Zhong's chincona alkaloid derived primary amine **191** shown excellent enantioselectivity, utility of 15 mol% catalyst should be challenged considering green chemistry approach.



Scheme 66. Literature achievement of dibenzoyl methane addition

We have therefore interested in this particular reaction to challenge the literature achievements. In this respect, the first action taken was to study the effect of relative equivalency of the substrates again testing the performance of 2-adamantyl amine derived catalyst **180**.



Scheme 67. In search for the effect of equivalency of subtrates on activity of **180**

To our delight, reaction proceeded swiftly and yielded 87% *ee* (Table 8, entries 1 and 4) in our initial investigations. Interestingly the highest enantioselectivities were accessed when equivalencies were either 1:3 or 1:1. In case of 1:3 of **34**:**189** equivalency, reaction was 4-fold faster. As a result, this equivalency of substrates was used to explore effect of catalyst structure on selectivity of this reaction.

Table 8. Effect of equivalency of **34** and **189**

Entry	Eq. of **34**	Eq. of **189**	Time (h)[a]	% *ee*
1	1	3	2	87
2	1	1.5	3.5	83
3	1.5	1	5	82
4	1	1	8	87

[a]Time for completion.

All bifunctional 2-aminoDMAP/squaramide catalysts were screened in dibenzoyl methane addition and the results are outlined in Table 9. The two benzylic amine derivatives **173** and **174** gave more or less the same selectivity (62 vs 64), however these results were among the worst (entries 1 and 2). Acidity had little impact on both selectivity and reaction rate. Next we investigated the effect of matching-mismatching chirality of acidic squaramide unit with **175** (*R,R* and *R*) and **176** (*R,R* and *S*) but no appreciable matching or mismatching was observed. Remarkable was that, about 20% more asymmetry induction was observed increasing the degree of substitution around the carbon neighbouring the amine one more (entries 3 and 4). This effect was constantly observed with *iso*-propylamine and

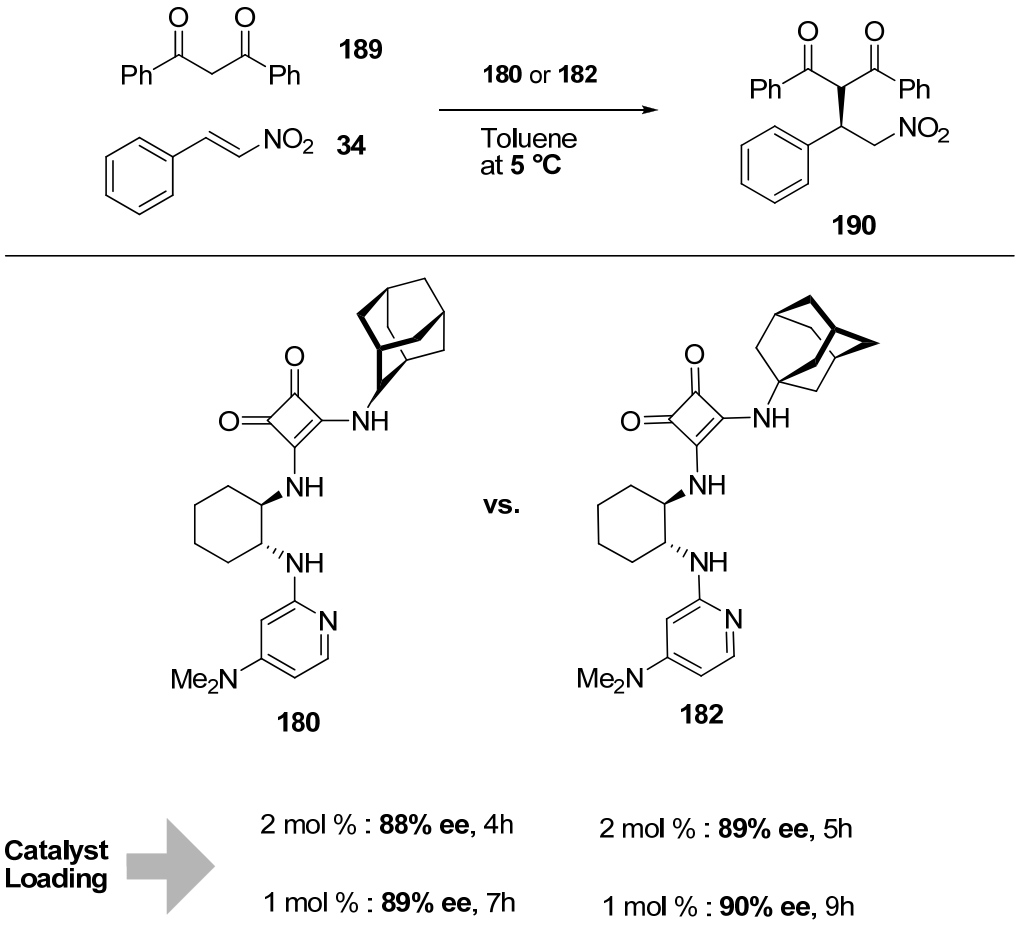
cyclohexylamine derived catalysts (**177** and **178** respectively). For these two, enantioselectivities were 83% and 82% similar to the results of catalysts **175** and **176** although having different bulkyness around squaramide unit. From these results, it was understood that more than the steric bulkyness of the squaramide unit, substitution pattern of carbon vicinal to the amine played crucial role on selecetivity. Among these *sec*-carbon incorporating squaramides, interestingly benzhydryl **179** and 2-adamantyl **180** group bearing ones gave extraordinary results such that former produced lower selectivity (70 % *ee*) and latter higher (87% *ee*) than the other class members. As expected from these initial screening works, *tert*-butyl **181** and 1-adamantyl **182** bearing catalysts having tertiary carbon in the vicinity of nitrogen afforded better results not only in terms of selectivity but also yields. Highest enantiocontrol was achieved by 1-adamantyl unit incorporating catalyst **182** (88% *ee*) and the worst by 3,5-bis(trifluoromethyl)benzene bearing one **184** (50% *ee*) although this unit proved to act well generally when incorporated to thioureas.

Table 9. Screening of 2-aminoDMAP/squaramide catalysts

Entry	Catalyst	Time (h)[a]	*ee* (%)
1	**173**	8	62
2	**174**	7	64
3	**175**	7	81
4	**176**	7	82
5	**177**	6	83
6	**178**	4	82
7	**179**	4	70
8	**180**	2	87
9	**181**	5	85
10	**182**	3	89
11	**184**	8	50

[a]Time for completion.

These findings presented in Table 9 demonstrated the superiority of both 2-adamantyl **180** and 1-adamantyl **182** unit incorporating catalysts over the other nine. Additionally observing best catalytic activities in the context of enantiocontrol and reaction rate with **180** and **182**, providing competitive results, they were further tested to decide the best catalyst of all. In order to realize this aim, reactions were fixed to 5 ºC to eliminate the effect of fluctuations encountered in room temperatures. Comparison of performances of the catalysts **180** and **182** were depicted in Scheme 68. Employing either 2 mol% or 1 mol% catalyst loadings, **182** was providing higher enantioselectivities but slightly slower reactions. 1-Adamantyl unit incorporated catalyst **182** decided to be the catalyst of the choice for further solvent, temperature and substrate screening works. As concluded in sulfonamide generation catalysts, here also it was clearly revealed that the structural tuning of catalysts had considerable effect on their performances.



Scheme 68. Comparison of catalytic performances of **180** and **182**

CHAPTER 3

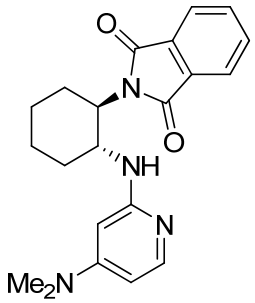
EXPERIMENTAL

In this part, synthetic procedures and characterization of novel compounds are reported only. For the compounds which are present in literature, related citations are given where appropriate in Chapter 2. Structural characterizations of the compounds were done with the instruments written below.

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Spectrospin Avance DPX 400 spectrometer using $CDCl_3$ or d_6-DMSO as the solvent. Chemical shifts values are repoted in ppm from tetramethylsilane. Spin multiplicities are reported as the following: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), dq (doublet of quartet) t (triplet), q (quartet), sept (septet), m (multiplet). Polarimetric measurements were made by Rudolph Scientific Autopol III polarimeter and reported as follows $[\alpha]_D^{31}$ (*c* in g per 100 ml, solvent). Enantiomeric excess (*ee*) values of chiral adducts were detected by a Thermo-Finnigan HPLC system using Daicell AS-H chiral column (0.46cmØ × 25cm). HRMS data were acquired on a Waters Synapt Mass Spectrometer at Central Laboratory of Middle East Technical University. IR spectra of all new compounds were obtained by Thermo-Fisher Scientfic IR spectrometer.

Flash column chromatography (FC) was performed by using glass columns with a flash grade silica gel (Merck Silica Gel 60). Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates (Merck Silica Gel PF-254), visualized by UV-light and *p*-anisaldehyde, ninhydrin and potassium permanganate stains as appropriate. All organic extracts were dehydrated over oven-dried $MgSO_4$ and concentrated by using rotary evaporator before being subjected to FC.

3.1 Synthesis and Characterization of Compound 110



110

In a Schlenk flask, mono-*N*-phthalolyl protected amine **107** (489 mg, 2 mmol), 2-bromoDMAP **103** (402mg, 2 mmol), Cs_2CO_3 (978 mg, 3 mmol), BINAP (280 mg, 0.30 mmol) and $Pd(OAc)_2$ (34 mg, 0.15 mmol) were mixed and 15 mL toluene (distilled over Na-benzophenone under Ar atmosphere) was added under Ar atm. The resulting mixture was refluxed for 60 hours. At the end of the reaction, mixture was cooled to rt and transferred to a separatory funnel. Organic phase was washed with 20 mL water and separated organic phase was dried with $MgSO_4$ and filtered. Filtrate was concentrated under vacuum. The dark residue was purified with flash chromatography using 98:2 EtOAc:TEA to give product **110** as a pale yellow solid (109 mg, 15% yield).

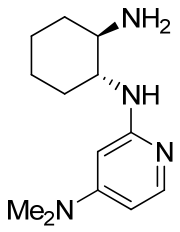
mp: 196-201 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 – 1.26 (m, 2H), 1.26 – 1.36 (m, 1H), 1.37 – 1.51 (m, 1H), 1.69 – 1.86 (m, 3H), 2.24 – 2.13 (m, 1H), 2.41 (qd, *J* = 32, 9 Hz, 1H), 2.75 (s, 6H), 3.93 (d, *J* = 9.4 Hz, 2H), 4.27 (qd, *J* = 10.9, 4.1 Hz, 1H), 5.38 (d, *J* = 2.1 Hz, 1H), 5.56 (dd, *J* = 6.1, 2.2 Hz, 1H), 7.41 (d, *J* = 6.1 Hz, 1H), 7.50 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.59 (dd, *J* = 5.5, 3.0 Hz, 2H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.1, 25.6, 29.3, 34.0, 39.1, 52.2, 56.2, 88.0, 98.9, 122.8, 131.9, 133.4, 147.9, 155.7, 159.4, 168.9.

HRMS (ESI) calcd for $C_{21}H_{25}N_4O_2$ $[M + H]^+$ 365.1978, found 365.1965.

3.2 Synthesis and Characterization of (1*R*,2*R*) 2-aminoDMAP 100



100

Compound **110** (94 mg, 0.25 mmol) was dissolved in 0.5 mL absolute ethanol and hydrazine hydrate (30 μL) was added and the mixture heated to reflux for 2 hours. After cooling to rt, Ethanol was removed under high vacuum to afford a solid residue. Resulting crude mixture was dissolved in 0.5 mL dichloromethane and subjected to flash column chromatography using dichloromethane saturated with aqueous ammonia to afford the product **100** as a tan brown solid (53 mg, 90% yield).

mp: 138-140 °C.

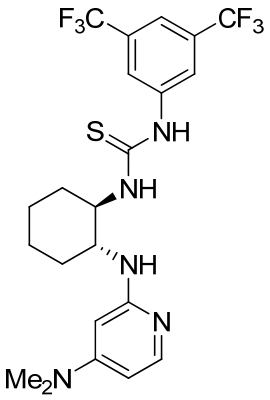
$[\alpha]_D^{31}$ -55.0 ° (*c* 0.25, CH_2Cl_2)

^{1}H 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, 1495, 1444, 1265, 1145, 979, 964, 804.
HRMS (ESI) calcd for $C_{13}H_{22}N_4$ $[M + H]^+$ 235.1923, found 235.1918.

3.3 Synthesis and Characterization of 2-aminoDMAP/Thiourea Catalyst 130



130

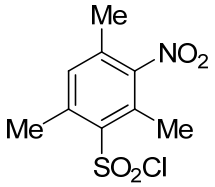
(*R*,*R*)-Configurated compound 2-aminoDMAP **100** (47 mg, 0.2 mmol) was dissolved in 1 mL THF (dried on Na wire) in a screw capped vial. To this vial, 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (54 mg, 36 μL, 0.2 mmol) was added dropwise in 1 min. at room temperature. This mixture was stirred for 1 hour at rt then directly loaded on to column. Applied flash column chromatography using 90:10 MeOH: CH_2Cl_2 yielded 2-aminoDMAP/thiourea catalyst **130** as an off-white amorphous solid (0.89 mg, 88% yield).

mp: 115-121 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 – 1.29 (m, 3H), 1.66 – 1.52 (m, 1H), 1.68 – 1.83 (m, 2H), 1.94 – 2.04 (m, 2H), 2.04 – 2.14 (m, 2H), 2.99 (s, 6H), 3.80 (bs, 1H), 4.47 (bs, 1H), 5.77 (bs, 1H), 6.03 (dd, *J* = 2.4, 7.5Hz, 1H), 6.77 (bs, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.46 (s, 1H), 8.00 (s, 2H), 8.76 (bs, 1H), 10.11 (bs, 1H).

IR (neat) 2930, 2857, 1609, 1525, 1471, 1377, 1274, 1168, 1126, 884, 700, 680.
HRMS (ESI) calcd for $C_{22}H_{26}F_6N_5S$ $[M + H]^+$ 506.1813, found 506.1800.

3.4 Synthesis and Characterization of 2,4,6-trimethyl-3-nitrobenzene-1-sulfonyl chloride (164)



164

To the solid 2,4,6-trimethylbenzene-1-sulfonyl chloride (**163**) (437 mg, 2 mmol), 1 mL fuming nitric acid was added dropwise in 1 minute. The resulting brown solution was stirred 1 hour at rt. It was then diluted with 10 mL ice cold water. Resultantly a yellow solid precipitation was observed. This mixture was extracted with ether (25 mL) twice. Obtained organic phase was dried on potassium carbonate and filtered. Organic filtrate was concentrated under vacuum. Product was recrystalized on *n*-pentane to give 2,4,6-trimethyl-3-nitrobenzene-1-sulfonyl chloride (**164**) as pale yellow solid needles (517 mg, 98% yield).

mp: 60-61 °C.

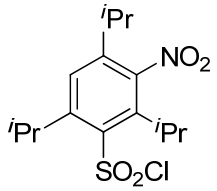
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.65 (s, 3H), 2.78 (s, 3H), 7.23 (s, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.4, 17.6, 23.2, 131.0, 134.0, 135.9, 141.3, 152.3.

IR (neat) 3648, 2987, 2884, 1594, 1525, 1442, 1372, 1363, 1177, 843, 671, 599.

HRMS (ESI) calcd for $C_9H_{12}N_2O_4S$ $[M - H]^-$ 243.0440, found 243.0054. Due to ambiguity in HRMS analysis of the compound **164**, it was converted to the corresponding sulfonamide.

3.5 Synthesis and Characterization of 2,4,6-triisopropyl-3-nitrobenzene-1-sulfonyl chloride (167)



167

To the solid 2,4,6-triisopropylbenzene-1-sulfonyl chloride (**166**) (437 mg, 2 mmol), 2 mL fuming nitric acid was added dropwise in 1 minute. The resulting brown heterogeneous mixture was stirred 5 hour in a water bath at 40 °C. It was then diluted with 20 mL ice cold water. Resultantly a yellow solid precipitation was observed. This mixture was extracted with ether (25 mL) twice. Obtained organic phase was dried on potassium carbonate and filtered. Organic filtrate was concentrated under vacuum. Product was chromatographed on a silica gel column using 20:1 *n*-hexane:EtOAc to give 2,4,6-triisopropyl-3-nitrobenzene-1-sulfonyl chloride (**167**) pale yellow solid (626 mg, 90 % yield).

mp: 149-151 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.8 Hz, 6H), 1.26 (d, J = 6.7 Hz, 6H), 1.30 (d, J = 7.1 Hz, 6H), 2.68 (sept, J = 6.8 Hz, 1H), 4.18 (sept, J = 6.8 Hz, 1H), 4.33 (bs, 1H), 7.42 (s, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.3, 23.6, 24.3, 29.6, 30.7, 125.6, 139.5, 141.5, 147.1, 150.0, 153.1.

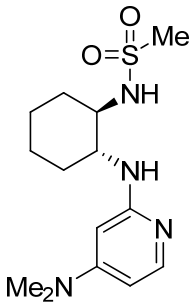
IR (neat) 2974, 2925, 2872, 2854, 1728, 1529, 1584, 1455, 1392, 1368, 1361, 1173, 1112, 563.

HRMS (ESI) calcd for $C_{15}H_{24}N_2O_4S$ $[M - H]^-$ 327.1379, found 327.1402. Due to ambiguity in HRMS analysis of the compound **164**, it was converted to the corresponding sulfonamide.

3.6 General Procedure for the Synthesis of 2-aminoDMAP/Sulfonamides

To a solution of (*R*,*R*) 2-aminoDMAP **100** (47 mg, 0.2 mmol) and triethylamine (22.2 mg, 30 µL, 0.22 mmol) in CH_2Cl_2 (1 mL) was added sulfonyl chloride (0.2 mmol as solid or liquid) at 0 °C. The mixture was brought to room temperature and stirred for 1 hour. The mixture was directly loaded on to a silica gel column and eluted with EtOAc:TEA (98 : 2) to afford 2-aminoDMAP/Sulfonamides (60-96% yield) as solid.

3.6.1 Synthesis and Characterization of 149



149

Starting from methanesulfonyl chloride (**159**) (23 mg, 16 µL, 0.2 mmol) compound **149** (57 mg, 92% yield) was obtanined as colorless amorphous solid.

mp: 183-186 °C.

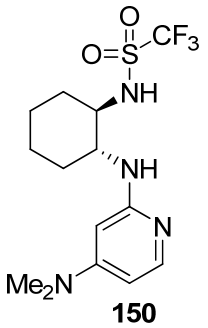
$[\alpha]_D^{31}$ +4.7 ° (*c* 0.25, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 – 1.52 (m, 4H), 1.73 (m, 2H), 1.96 – 2.07 (m, 1H), 2.14 – 2.28 (m, 1H), 2.67 (s, 3H), 2.94 (s, 6H), 2.92 – 2.98 (m, 1H), 3.74 – 3.55 (m, 1H), 4.28 (d, *J* = 5.4 Hz, 1H), 5.59 (d, *J* = 2.2 Hz, 1H), 6.02 (dd, *J* = 2.3, 6.2 Hz, 1H), 7.72 (d, *J* = 6.2 Hz, 1H), 1 exchangeable sulfonamide H not located.

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.4, 25.1, 33.4, 35.2, 39.2 (2C), 54.6, 62.2, 89.0, 100.2, 146.9, 156, 159.7.

IR (neat) 3376, 2921, 2854, 1608, 1530, 1495, 1444, 1259, 1016, 793.
HRMS (ESI) calcd for $C_{14}H_{24}N_4O_2S$ $[M + H]^+$ 313.1698, found 313.88

3.6.2 Synthesis and Characterization of 150



150

This reaction was carried out at -20 °C and triflic anhydride (**160**) was added dropwise over 2 min. Starting from triflic anhydride (**160**) (56 mg, 33 μL, 0.2 mmol) compound **150** (44 mg, 60% yield) was obtanined as amorphous off-white solid.

mp: 230-235 °C.

$[\alpha]_D^{31}$ +14.1 ° (*c* 0.25, CH_2Cl_2)

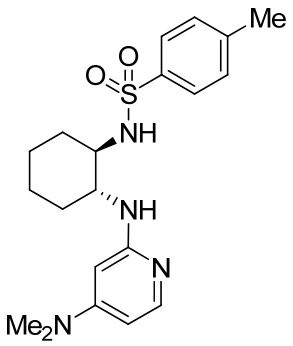
^{1}H NMR (400 MHz, d_6-DMSO) δ 1.12 – 1.43 (m, 5H), 1.55 – 1.73 (m, 2H), 1.85 – 2.02 (m, 2H), 2.97 (s, 6H), 3.08 – 2.94 (m, 1H), 5.81 (d, *J* = 2.3 Hz, 1H), 6.23 (dd, *J* = 2.4, 6.9 Hz, 1H), 6.72 (d, *J* = 5.9 Hz, 1H), 7.56 (d, *J* = 6.9 Hz, 1H).

^{13}C NMR (100.6 MHz, DMSO) δ 23.9, 24.3, 31.8, 34.4, 39.0, 57.4, 60.8, 88.0, 99.9, 116.1, 119.4, 122.6, 125.9, 139.6, 155.98, 156.17.

IR (neat) 3342, 3111, 2926, 2849, 2458, 2108, 1651, 1724, 1523, 1372, 1204, 1173, 1142, 1085, 831, 792, 594.

HRMS (ESI) calcd for $C_{14}H_{22}F_3N_4O_2S$ $[M + H]^+$ 367.1404, found 367.1416.

3.6.3 Synthesis and Characterization of 151



151

Starting from *p*-toluenesulfonyl chloride (**161**) (38 mg, 0.2 mmol) compound **151** (73 mg, 94% yield) was obtanined as colorless amorphous solid.

mp: 176-178 °C.

$[\alpha]_D^{31}$ +85.7 ° (*c* 0.25, CH_2Cl_2)

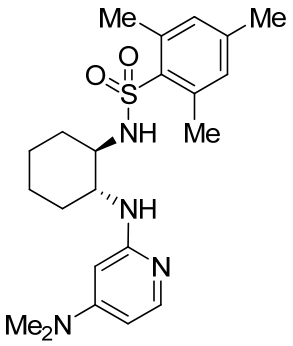
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 – 1.32 (m, 3H), 1.35 – 1.50 (m, 1H), 1.68 (m, 2H), 1.86 (m, 1H), 2.20 – 2.29 (m, 1H), 2.32 (s, 3H), 2.69 (dt, *J* = 4.2, 11.0 Hz, 1H), 2.92 (s, 6H), 3.51– 3.68 (m, 1H), 3.73 (d, *J* = 5.2 Hz, 1H), 5.19 (d, *J* = 2.1 Hz, 1H), 6.02 (dd, *J* = 2.2, 6.2 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 6.2 Hz, 1H); 1 exchangeable sulfonamide H not located.

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.9, 22.7, 23.4, 31.7, 33.2, 37.6, 52.1, 60.0, 87.8, 98.4, 125.2, 127.4, 136.4, 145.0, 154.2, 157.6.

IR (neat) 3421, 3065, 2942, 2921, 2854, 1605, 1522, 1489, 1370, 1324, 1295, 1259, 1158, 1089, 799, 660, 567.

HRMS (ESI) calcd for $C_{20}H_{29}N_4O_2S$ $[M + H]^+$ 389.2011, found 389.2008.

3.6.4 Synthesis and Characterization of 152



152

Starting from 2,4,6-trimethylbenzene-1-sulfonyl chloride (**163**) (44 mg, 0.2 mmol) compound **152** (77 mg, 93% yield) was obtanined as colorless amorphous solid. mp: 190-191 °C.

$[\alpha]_D^{31}$ +38.3 ° (*c* 0.25, CH_2Cl_2)

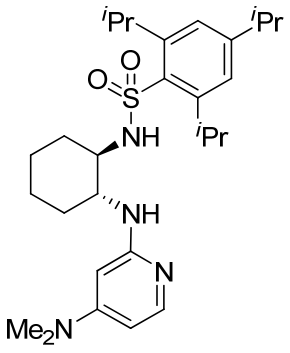
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 – 1.37 (m, 4H), 1.53 – 1.75 (m, 2H), 1.92 – 2.00 (m, 1H), 2.09 (m, 1H), 2.26 (s, 3H), 2.50 (s, 6H), 2.90 (s, 6H), 2.90 – 3.02 (m, 1H), 3.68 (m, 1H), 3.98 (d, *J* = 6.7 Hz, 1H), 5.41 (d, *J* = 2.2 Hz, 1H), 5.99 (dd, *J* = 2.2, 6.2 Hz, 1H), 6.85 (s, 2H), 7.68 (d, *J* = 6.2 Hz, 1H); 1 exchangeable sulfonamide H not located.

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.9, 22.9, 24.4, 25.0, 33.5, 33.6, 39.2, 53.9, 60.3, 89.2, 100.1, 131.6, 135.7, 138.8, 141.1, 147.0, 155.9, 159.6.

IR (neat) 3413, 3170, 2942, 2854, 1603, 1522, 1489, 1445, 1325, 1297, 1287, 1158, 1145, 1071, 800, 659.

HRMS (ESI) calcd for $C_{22}H_{32}N_4O_2S$ $[M + H]^+$ 417.2324, found 417.2325.

3.6.5 Synthesis and Characterization of 153



153

Starting from 2,4,6-triisopropylbenzene-1-sulfonyl chloride (**166**) (61 mg, 0.2 mmol) compound **153** (90 mg, 90% yield) was obtanined as colorless amorphous solid.

mp: 186-187 °C.

$[\alpha]_D^{31}$ +69.8 ° (*c* 0.25, CH_2Cl_2)

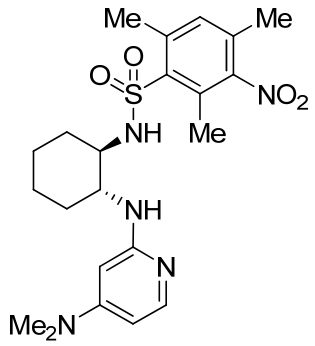
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.7 Hz, 6H), 1.24 (d, *J* = 7.0 Hz, 12H), 1.25 – 1.36 (m, 4H), 1.59 (m, 1H), 1.69 (m, 1H), 1.94 – 2.10 (m, 2H), 2.89 (s, 6H), 2.83 – 2.93 (m, 1H), 3.19 (dt, *J* = 3.9, 10.4 Hz, 1H), 3.60 – 3.74 (m, 1H), 4.12 (sept, *J* = 7.2 Hz, 1H), 4.16 (sept, *J* = 6.4 Hz, 2H), 4.27 (d, *J* = 5.8 Hz, 1H), 5.56 (d, *J* = 2.2 Hz, 1H), 5.99 (dd, *J* = 2.2, 6.2 Hz, 1H), 7.10 (s, 2H), 7.66 (d, *J* = 6.2 Hz, 1H); 1 exchangeable sulfonamide H not located.

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.6, 24.3, 24.8, 25.0, 29.6, 33.3, 33.4, 34.0, 39.2, 54.6, 59.6, 89.6, 100.1, 123.5, 135.0, 146.6, 149.9, 151.8, 155.9, 159.6.

IR (neat) 3373, 2954, 2927, 2864, 1607, 1457, 1290, 1145.

HRMS (ESI) calcd for $C_{28}H_{45}N_4O_2S$ $[M + H]^+$ 501.3263, found 501.3273.

3.6.6 Synthesis and Characterization of 154



154

Starting from 2,4,6-trimethyl-3-nitrobenzene-1-sulfonyl chloride (**164**) (53 mg, 0.2 mmol) compound **154** (88 mg, 96% yield) was obtanined as yellow amorphous solid.

mp: 181-184 °C.

$[\alpha]_D^{31}$ +43.2 ° (*c* 0.25, CH_2Cl_2)

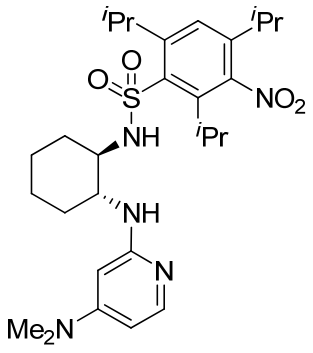
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 – 1.41 (m, 4H), 1.58 – 1.79 (m, 2H), 1.88 – 1.97 (m, 1H), 2.12 – 2.20 (m, 1H), 2.23 (s, 3H), 2.30 (s, 3H), 2.59 (s, 3H), 2.86 – 2.96 (m, 1H), 2.93 (s, 6H), 3.54 – 3.77 (m, 1H), 3.91 (bs, 1H), 5.42 (d, *J* = 2.2 Hz, 1H), 6.01 (dd, *J* = 2.2, 6.2 Hz, 1H), 6.98 (s, 1H), 7.64 (d, *J* = 6.2 Hz, 1H); 1 exchangeable sulfonamide H not located.

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.7, 17.1, 23.7, 24.4, 25.1, 33.5, 33.9, 39.2, 54.2, 61.40, 89.0, 100.4, 129.9, 131.4, 133.0, 138.1, 140.7, 146.5, 152.4, 155.9, 159.5.

IR (neat) 3403, 3100, 2942, 2866, 1620, 1527, 1491, 1447, 1371, 1326, 1298, 1161, 1095, 842, 612.

HRMS (ESI) calcd for $C_{22}H_{32}N_5O_4S$ $[M + H]^+$ 462.2175, found 462.2159.

3.6.7 Synthesis and Characterization of 155



155

Starting from 2,4,6-triisopropyl-3-nitrobenzene-1-sulfonyl chloride (**167**) (53 mg, 0.2 mmol) compound **155** (88 mg, 96% yield) was obtanined as pale yellow fluffy solid.

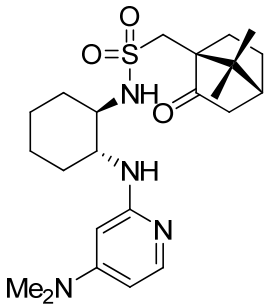
mp: 150-155 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 – 1.06 (m, 24H), 1.56 (d, *J* = 11.2 Hz, 1H), 1.66 (d, *J* = 10.0 Hz, 1H), 2.01 – 1.89 (m, 2H), 2.62 (sept, *J* = 6.8 Hz, 1H), 2.85 (s, 6H), 3.14 (dt, *J* = 3.9, 10.7 Hz, 1H), 3.48 – 3.66 (m, 1H), 3.92 – 4.18 (m, 2H), 4.21 – 4.41 (m, 1H), 5.48 (d, *J* = 2.1 Hz, 1H), 5.95 (dd, *J* = 2.3, 6.3 Hz, 1H), 7.26 (s, 1H), 7.56 (d, *J* = 6.2 Hz, 1H); 1 exchangeable sulfonamide H not located.

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.6, 21.7, 23.7, 24.1, 24.6, 24.8, 25.1, 28.9, 29.1, 30.5, 33.4, 33.6, 39.2, 55.1, 89.6, 100.5, 124.4, 138.5, 139.0, 143.2, 150.0, 152.4, 156.0.

IR (neat) 3377, 2966, 2930, 2860, 1609, 1528, 1447, 1366, 1290, 1157, 1108.
HRMS (ESI) calcd for $C_{28}H_{44}N_5O_4S$ $[M + H]^+$ 546.3114, found 546.3107.

3.6.8 Synthesis and Characterization of 156



156

Starting from (1*S*)-(+)-10-Camphorsulfonyl chloride (**171**) (50 mg, 0.2 mmol) compound **156** (83 mg, 93% yield) was obtanined as white amorphous solid.

mp: 257-258 °C.

$[\alpha]_D^{31}$ -4.6 ° (*c* 0.25, CH_2Cl_2)

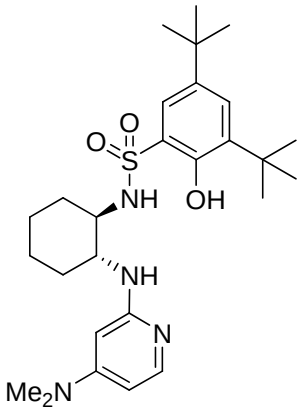
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (s, 3H), 0.93 (s, 3H), 1.53 – 1.22 (m, 5H), 1.83 – 1.59 (m, 3H), 1.88 (d, *J* = 18.4 Hz, 1H), 2.10 – 1.91 (m, 3H), 2.24 – 2.13 (m, 2H), 2.29 (dt, *J* = 3.6, 18.4 Hz, 1H), 2.56 – 2.38 (m, 1H), 2.90 (s, 6H), 3.13 (dt, *J* = 4.2, 10.5 Hz, 1H), 3.58 (d, *J* = 14.8 Hz, 1H), 3.73 – 3.85 (m, 1H), 4.21 (d, *J* = 6.3 Hz, 1H), 5.52 (d, *J* = 2.2 Hz, 1H), 6.01 (dd, *J* = 2.3, 6.2 Hz, 1H), 7.75 (d, *J* = 6.2 Hz, 1H), 7.83 (bs, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.4, 19.9, 24.4, 24.8, 24.9, 27.0, 33.2, 35.2, 39.2, 42.5, 42.7, 47.8, 53.7, 58.3, 61.8, 88.9, 100.0, 147.2, 156.0, 159.6, 215.6.

IR (neat) 3358, 2946, 2918, 2854, 1744, 1608, 1526, 1496, 1321, 1290, 1090, 807, 793.

HRMS (ESI) calcd for $C_{23}H_{37}N_4O_3S$ $[M + H]^+$ 449.2586, found 449.2575.

3.6.9 Synthesis and Characterization of 158



158

Starting from 3,5-di-tert-butyl-2-hydroxybenzene-1-sulfonyl chloride (**169**) (61 mg, 0.2 mmol) compound **158** (72 mg, 72% yield) was obtanined as off-white amorphous solid.

mp: 140-150 °C.

$[\alpha]_D^{31}$ +98.5 ° (*c* 0.25, CH_2Cl_2)

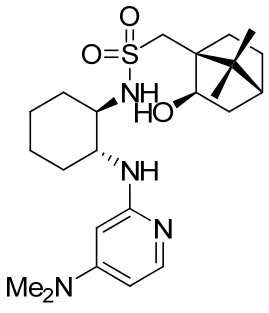
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.11 – 1.20 (m, 4H), 1.28 (s, 9H), 1.62 (t, *J* = 11.7 Hz, 2H), 1.80 1.88 (m, 1H), 2.20 (d, *J* = 13.2 Hz, 1H), 2.72 (td, *J* = 11.0, 4.1 Hz, 1H), 2.83 (s, 6H), 3.39 – 3.50 (m, 1H), 3.71 (bs, 1H), 5.29 (d, *J* = 2.1 Hz, 1H), 5.95 (dd, *J* = 2.3, 6.3 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.67 (d, *J* = 6.3 Hz, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.3, 25.0, 29.5, 31.2, 33.5, 34.0, 34.2, 35.4, 39.1, 55.1, 61.1, 89.4, 100.4, 122.2, 122.8, 128.7, 137.6, 141.1, 146.2, 152.1, 155.9, 159.1.

IR (neat) 3381, 3240, 2924, 2855, 1612, 1479, 1529, 1362, 1269, 1184, 1169, 1103, 698, 634, 598.

HRMS (ESI) calcd for $C_{27}H_{43}N_4O_3S$ $[M + H]^+$ 503.3056, found 503.3060.

3.7 Synthesis and Characterization of 157



157

Compound 2-aminoDMAP/Sulfonamide **156** (90 mg, 0.2 mmol) was dissolved in ethanol (2.5 mL) and treated with $NaBH_4$ (45 mg, 1.2 mmol) portionwise at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 24 h. After this time, ethanol was removed under reduced pressure and the resulting residue was dissolved in a saturated solution of NH_4Cl (2 mL) and extracted twice with CH_2Cl_2 (2x15 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated. The residue was purified by flash chromatography on silica gel using with EtOAc:TEA (98 : 2) as the eluant to afford 2-aminoDMAP/Sulfonamide **157** as white amorphous solid (77 mg, 85% yield).

mp: 250-256 °C.

$[\alpha]_D^{31}$ -32.9 ° (*c* 0.25, CH_2Cl_2)

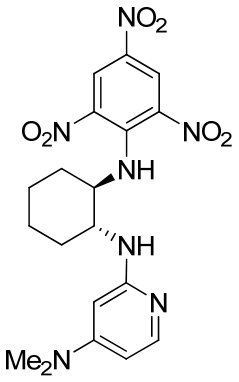
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.51 (s, 3H), 0.98 (s, 3H), 0.99 – 1.12 (m, 1H), 1.19 – 1.41 (m, 4H), 1.41 – 1.54 (m, 3H), 1.55 – 1.66 (m, 2H), 1.66 – 1.83 (m, 4H), 1.99 – 2.09 (m, 2H), 2.16 (d, *J* = 12.4 Hz, 1H), 2.93 (s, 6H), 3.01(dt, *J* = 4.0, 11.2 Hz, 1H), 3.42 (d, *J* = 13.7 Hz, 1H), 3.71 – 3.88 (m, 1H), 4.03 (dd, *J* = 4.3, 8.0 Hz, 1H), 4.10 – 4.25 (m, 1H), 5.53 (d, *J* = 2.2 Hz, 1H), 6.03 (dd, *J* = 6.2, 2.3 Hz, 1H), 7.74 (d, *J* = 6.2 Hz, 1H); 1 exchangeable sulfonamide H not located.

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.0, 20.1, 24.5, 25.0, 27.3, 30.5, 33.4, 35.6, 38.8, 39.1, 44.3, 48.3, 50.2, 51.0, 53.7, 62.7, 76.4, 88.7, 100.2, 147.0, 156.1, 159.5.

IR (neat) 3381, 3307, 2955, 2924, 2856, 1614, 1530, 1507, 1447, 1311, 1299, 1263, 1173, 1136, 1079, 989, 807.

HRMS (ESI) calcd for $C_{23}H_{39}N_4O_3S$ $[M + H]^+$ 451.2743, found 451.2732.

3.8 Synthesis and Characterization of 172



172

To a solution of (*R*,*R*) 2-aminoDMAP **100** (47 mg, 0.2 mmol) and triethylamine (22.2 mg, 30 μL, 0.22 mmol) in CH_2Cl_2 (1 mL) was added picryl chloride **173** (0.2 mmol as solid or liquid) at 0 °C. The mixture was brought to room temperature and stirred for 1 hour. The mixture was directly loaded on to a silica gel column and eluted with EtOAc:TEA (98 : 2) to afford compound **172** as blood-red solid (86 mg, 97% yield).

mp: 202-205 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 – 1.49 (m, 4H), 1.55 (ddd, *J* = 3.6, 12.7, 24.0 Hz, 1H), 1.76 – 1.99 (m, 3H), 2.23 – 2.30 (m, 1H), 2.74 (s, 6H), 2.96 (bs, 1H), 3.65 (d, *J* = 9.0 Hz, 1H), 3.98 – 4.21 (m, 1H), 4.91 (d, *J* = 2.2 Hz, 1H), 5.85 (dd, *J* = 2.2, 6.1 Hz, 1H), 7.43 (d, *J* = 6.1 Hz, 1H), 8.60 (s, 2H), 8.82 (bs, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.6, 25.0, 31.7, 32.9, 38.7, 54.8, 63.1, 87.8, 99.5, 125.6, 132.8, 144.0, 147.3, 155.2, 158.2.

IR (neat) 3412, 3283, 3103, 2929, 2848, 1590, 1515, 1312, 1280, 1170, 1086, 732.
HRMS (ESI) calcd for $C_{19}H_{24}N_7O_6$ $[M + H]^+$ 446.1788, found 446.1790.

3.9 Copper Catalyzed Optimized Synthesis of 100

An oven-dried resealable Schlenk tube was charged with CuBr (29 mg, 0.2 mmol), K_3PO_4 (424 mg, 2.0 mmol), evacuated and backfilled with argon thrice. (*R,R*)-1,2-Cyclohexanediamine (137 mg, 1.20 mmol), 2-bromoDMAP **103** (201 mg, 1.0 mmol) and dioxane which was distilled over Na-benzophenone under Ar atmosphere (1.0 mL) were added under Schlenk line. The Schlenk tube was sealed and the reaction mixture was stirred at 110 °C for 24h. The resulting green-blue suspension was allowed to reach room temperature. Then 2 mL water and 2 mL conc. ammonia were added consecutively. Resulting Prussian blue solution was extracted with dichloromethane thrice (3x25 mL). Combined dichloromethane phase was dried with brine (10 mL) and $MgSO_4$ respectively. Filtrate was concentrated and the residue was purified by flash chromatography on silica gel using dichloromethane, which was saturated with aqueous ammonia. The yield of compound **100** obtained by this procedure was 60% (140 mg).

3.10 Copper Catalyzed Synthesis of 141

An oven-dried resealable Schlenk tube was charged with CuBr (29 mg, 0.2 mmol), K_3PO_4 (424 mg, 2.0 mmol), evacuated and backfilled with argon thrice. (*R,R*)-1,2-Cyclohexanediamine (137 mg, 1.20 mmol), 2-bromoquinoline (**145**) (208 mg, 1.0 mmol) and dioxane which was distilled over Na-benzophenone under Ar atmosphere (1.0 mL) were added under Schlenk line. The Schlenk tube was sealed and the reaction mixture was stirred at 110 °C for 24h. The resulting green-blue suspension was allowed to reach room temperature. Then 2 mL water and 2 mL conc. ammonia were added consecutively. Resulting Prussian blue solution was extracted with dichloromethane thrice (3x25 mL). Combined dichloromethane phase was dried with brine (10 mL) and $MgSO_4$ respectively. Filtrate was concentrated and the residue was purified by flash chromatography on silica gel using dichloromethane, which was saturated with aqueous ammonia. The yield of compound **141** obtained by this procedure was 30% (72 mg).

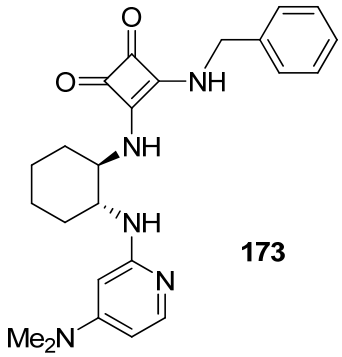
^{1}H NMR (400 MHz, 70:30 $CDCl_3$:CCl_4) δ 0.97 – 1.43 (m, 4H), 1.58 – 1.99 (m, 5H), 2.01 – 2.15 (m, 1H), 2.15 – 2.28 (m, 1H), 2.45 (bs, 1H), 3.65 (bs, 1H), 4.76 (bs, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 6.75 – 7.23 (m, 2H), 7.49 – 7.37 (m, 2H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H).

^{13}C NMR (100.6 MHz, 70:30 $CDCl_3$:CCl_4) δ 25.1, 25.3, 32.9, 35.3, 56.3, 57.5, 111.6, 121.9, 123.5, 126.2, 127.3, 129.5, 137.2, 148.0, 157.2.

3.11 General Procedure for the 2-aminoDMAP/Squaramide Catalysts 173-182 and 184

To a solution of (*R*,*R*)-configurated 2-aminoDMAP **100** (47 mg, 0.2 mmol) in one to one (volume) DCM:MeOH mixture (1 mL) was added solid mono-squaramide (0.2 mmol) at rt. The solution was stirred for 48 hour at this temperature. The mixture was directly loaded on to a silica gel column and eluted with DCM:MeOH (90 : 10) to afford 2-aminoDMAP/Squaramides (66-84% yield) as solid.

3.11.1 Synthesis and Characterization of 173



173

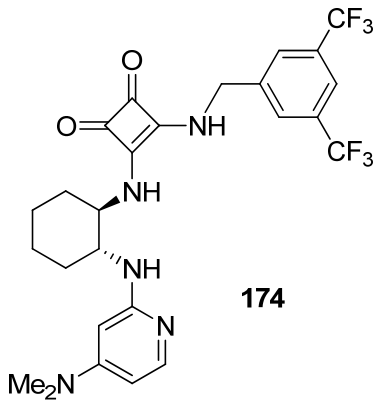
Starting from 3-(benzylamino)-4-ethoxycyclobut-3-ene-1,2-dione (46 mg, 0.2 mmol) compound **173** (60 mg, 72% yield) was obtanined as pale yellow amorphous solid.

mp: 142.5 – 159.6 °C -decomp.

$[\alpha]_D^{31}$ -145.1° (*c* 0.25, CH_2Cl_2)

^{13}C NMR (101 MHz, DMSO) δ 181.89, 181.37, 166.95, 166.68, 158.28, 154.69, 145.75, 138.12, 127.88, 126.74, 126.64, 98.26, 87.86, 54.18, 52.88, 46.04, 38.07, 32.98, 31.53, 24.77, 23.58.

3.11.2 Synthesis and Characterization of 174



174

Starting from 3-(3,5-bis(trifluoromethyl)benzylamino)-4-ethoxycyclobut-3-ene-1,2-dione (73 mg, 0.2 mmol) compound **174** (91 mg, 82% yield) was obtanined as pale yellow amorphous solid.

mp: 162.2 – 173 °C.

$[\alpha]_D^{31}$ -141.7 ° (*c* 0.25, CH_2Cl_2)

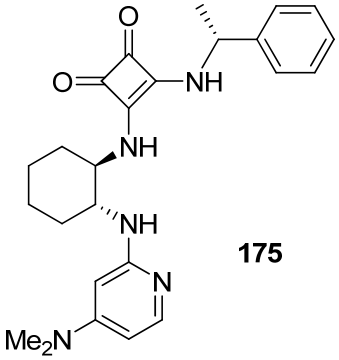
^{1}H NMR (400 MHz, DMSO) δ 1.09 – 1.55 (m, 4H), 1.71 (bs, 2H), 1.91 – 2.15 (m, 2H), 2.85 (s, 3H), 3.61 – 3.91 (m, 2H), 4.85 (bs, 2H), 5.59 (s, 1H), 5.81 – 6.06 (m, 2H), 7.60 (d, *J* = 4.4 Hz, 1H), 8.06 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 24.32, 25.39, 32.24, 33.76, 38.63, 45.70, 53.47, 57.97, 61.98, 88.69, 98.80, 119.16, 121.07, 121.88, 124.59, 127.30, 128.45, 129.90, 130.23, 130.56, 130.88, 142.44, 146.66, 155.28, 159.24, 167.19, 168.00, 182.06, 182.91.

IR (neat) 2935, 2860, 1796, 1605, 1526, 1378, 1276, 1168, 1126, 982.

HRMS (ESI) calcd for $C_{26}H_{25}N_5O_2F_6$ $[M + H]^+$ 554.1991, found 554.1837.

3.11.3 Synthesis and Characterization of 175



175

Starting from (*R*)-3-ethoxy-4-(1-phenylethylamino)cyclobut-3-ene-1,2-dione (49 mg, 0.2 mmol) compound **175** (59 mg, 68% yield) was obtanined as colorless amorphous solid.

mp: 185 – 190 °C -decomp.

$[\alpha]_D^{31}$ -33.4 ° (*c* 0.25, CH_2Cl_2)

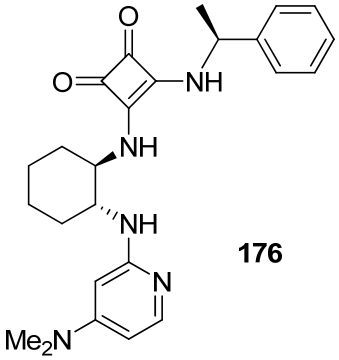
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 – 1.04 (m, 4H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.55 – 1.70 (m, 2H), 1.86 – 1.95(m, 1H), 1.99 – 2.09 (m, 1H), 2.86 (s, 6H), 3.57 – 3.75 (m, 2H), 5.08 (bs, 1H), 5.44 (d, *J* = 1.8 Hz, 1H), 5.89 (dd, *J* = 2.3, 6.4Hz, 1H), 7.13 – 7.33 (m, 5H), 7.48 (d, *J* = 6.4 Hz, 1H).

^{13}C NMR (101 MHz, DMSO) δ 23.00, 24.36, 25.44, 32.22, 33.63, 38.75, 52.54, 53.66, 57.68, 88.57, 98.92, 125.95, 127.25, 128.56, 143.41, 146.61, 155.37, 159.08, 166.68, 167.65, 181.67, 182.51.

IR (neat) 3158, 2930, 1796, 1640, 1549, 1447, 1375, 1159, 1121, 981, 758, 695.

HRMS (ESI) calcd for $C_{25}H_{31}N_5O_2$ $[M + H]^+$ 434.2556, found 434.2547.

3.11.4 Synthesis and Characterization of 176



176

Starting from (S)-3-ethoxy-4-(1-phenylethylamino)cyclobut-3-ene-1,2-dione (49 mg, 0.2 mmol) compound **176** (61 mg, 70% yield) was obtanined as colorless amorphous solid.

mp: 194 – 203 °C.

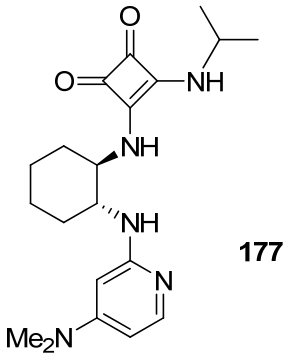
$[\alpha]_D^{31}$ -103.6 ° (*c* 0.25, CH_2Cl_2)

^{1}H NMR (400 MHz, DMSO) δ 1.10 – 1.41 (m, 4H), 1.47 (d, *J* = 6.4 Hz, 3H), 1.60 – 1.76 (s, 3H), 1.90 – 2.10 (m, 2H), 2.83 (s, 7H), 3.59 – 381 (m, 2H), 5.12 (bs, 1H), 5.54 (s, 1H), 5.85 – 6.02 (m, 2H), 7.21 – 7.39 (m, 5H), 7.52 (bs, 1H), 7.57 (d, *J* = 5.6 Hz, 1H), 7.82 (bs, 1H).

^{13}C NMR (101 MHz, DMSO) δ 23.09, 24.30, 32.13, 33.70, 38.75, 38.85, 39.06, 39.27, 39.48, 39.69, 39.90, 40.10, 48.56, 52.53, 53.61, 57.60, 88.50, 98.97, 125.86, 127.21, 128.56, 143.54, 146.07, 155.36, 158.80, 166.80, 167.52, 181.67, 182.47.

IR (neat) 3152, 2932, 2836, 1796, 1603, 1541, 1446, 1374, 1290, 1160, 757, 696.

3.11.5 Synthesis and Characterization of 177



177

Starting from 3-ethoxy-4-(*iso*-propylamino)cyclobut-3-ene-1,2-dione (37 mg, 0.2 mmol) compound **177** (59 mg, 80% yield) was obtanined as colorless amorphous solid.

mp: 206.6 – 227.4 °C -decomp.

$[\alpha]_D^{31}$ -7.1 ° (*c* 0.25, DMSO)

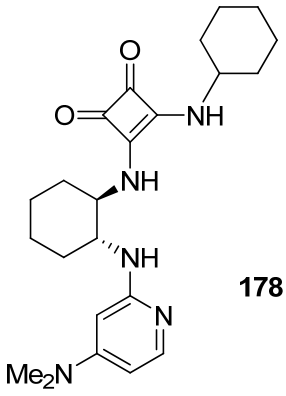
^{1}H NMR (400 MHz, DMSO) δ 1.17 (d, *J* = 6.3 Hz, 6H), 1.26 – 1.55 (m, 4H), 1.74 (bs, 2H), 1.95 – 2.18 (m, 2H), 2.90 (s, 6H), 3.0 – 3.75 (m, 1H), 3.77 – 3.92 (m, 1H), 4.04 (bs, 1H), 5.59 (bs, 1H), 5.92 (bs, 1H), 6.04 (dd, *J* = 2.0, 6.1 Hz, 1H), 7.44 (bs, 2H), 7.65 (d, *J* = 6.2 Hz, 1H).

^{13}C NMR (100.6 MHz, DMSO) δ 23.6, 23.8, 30.4, 32.2, 33.6, 34.3, 38.8, 45.4, 53.7, 88.5, 98.9, 146.2, 155.4, 158.9, 167.0, 167.5, 181.7, 182.2.

IR (neat) 3367, 3208, 2930, 2858, 1795, 1602, 1403, 1386, 1155, 800.

HRMS (ESI) calcd for $C_{20}H_{29}N_5O_2$ $[M + H]^+$ 372.2400, found 372.2399.

3.11.6 Synthesis and Characterization of 178



178

Starting from 3-(cyclohexylamino)-4-ethoxycyclobut-3-ene-1,2-dione (45 mg, 0.2 mmol) compound **178** (62 mg, 76% yield) was obtanined as colorless amorphous solid.

mp: 144 – 152.8 °C.

$[\alpha]_D^{31}$ -66.4 ° (*c* 0.25, CH_2Cl_2)

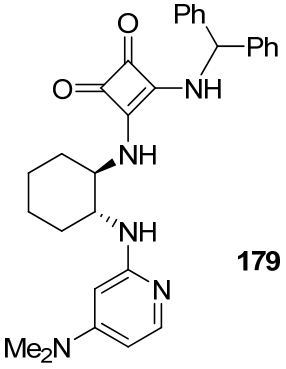
^{1}H NMR (400 MHz, DMSO) δ 0.99 – 1.37 (m, 10H), 1.39 – 1.50 (m, 1H), 1.50 – 1.66 (m, 4H), 1.66 – 1.83 (m, 2H), 1.83 – 2.06 (m, 2H), 2.78 (s, 6H), 3.61 (bs, 1H), 3.65 – 3.80 (m, 1H), 5.45 (bs, 1H), 5.75 (d, *J* = 8.0 Hz, 1H), 5.91 (dd, *J* = 2.1, 6.2 Hz, 1H), 7.33 (bs, 2H), 7.52 (d, *J* = 6.2 Hz, 1H).

^{13}C NMR (101 MHz, DMSO) δ 23.85, 24.32, 24.76, 32.15, 33.45, 33.68, 38.75, 51.79, 53.80, 54.85, 57.52, 88.41, 98.91, 146.07, 155.37, 158.75, 166.99, 167.54, 181.64, 182.24.

IR (neat) 3153, 2928, 2854, 1795, 1648, 1525, 1455, 1367, 1159, 981.

HRMS (ESI) calcd for $C_{23}H_{33}N_5O_2$ $[M + H]^+$ 412.2713, found 412.2718.

3.11.7 Synthesis and Characterization of 179



179

Starting from 3-(benzhydrylamino)-4-ethoxycyclobut-3-ene-1,2-dione (61 mg, 0.2 mmol) compound **179** (70 mg, 71% yield) was obtanined as colorless amorphous solid.

mp: 182.3 – 187.5°C-decomp.

$[\alpha]_D^{31}$ -111.4° (*c* 0.25, CH_2Cl_2)

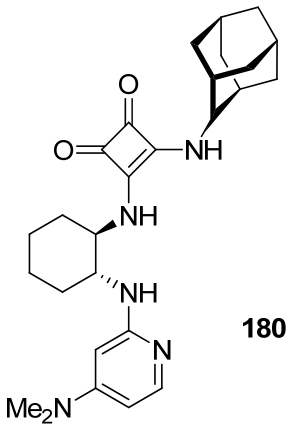
^{1}H NMR (400 MHz, DMSO) δ 1.11 – 1.56 (m, 4H), 1.62 – 1.81 (m, 2H), 1.94 – 2.16 (m, 2H), 2.85 (s, 6H), 3.65 – 3.78 (m, 1H), 3.79 – 3.93 (m, 1H), 5.58 (s, 1H), 5.88 (bs, 1H), 5.96 (d, *J* = 4.8 Hz, 1H), 6.36 (bs, 1H), 7.12 – 7.44 (m, 10H), 7.54 (bs, 1H), 7.64 (d, *J* = 5.1 Hz, 1H), 8.28 (bs, 1H).

^{13}C NMR (101 MHz, DMSO) δ 24.31, 24.40, 32.29, 33.75, 38.72, 53.62, 57.93, 60.16, 88.65, 98.90, 126.83, 126.96, 127.32, 127.38, 128.60, 128.65, 141.86, 142.00, 146.78, 155.31, 159.22, 166.52, 167.78, 181.69, 182.89.

IR (neat) 3150, 2929, 2855, 1797, 1644, 1525, 1262, 986, 695.

HRMS (ESI) calcd for $C_{30}H_{33}N_5O_2$ $[M + H]^+$ 496.2713, found 496.2676.

3.11.8 Synthesis and Characterization of 180



180

Starting from 3-(2-adamantylamino)-4-ethoxycyclobut-3-ene-1,2-dione (55 mg, 0.2 mmol) compound **180** (64 mg, 69% yield) was obtanined as pale yellow amorphous solid.

mp: 160.1 – 174 °C.

$[\alpha]_D^{31}$ -50.9 ° (*c* 0.25, DMSO)

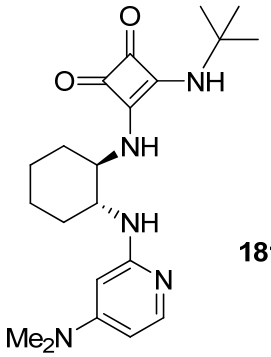
^{1}H NMR (400 MHz, DMSO) δ 1.09 – 1.69 (m, 8H), 1.69 – 2.02 (m, 14H), 2.02 –2.23 (m, 2H), 2.91 (s, 6H), 3.78 (s, 1H), 3.93 (bs, 1H), 4.12 (bs, 1H), 5.57 (bs, 1H), 5.74 (bs, 1H), 6.01 (bs, 1H), 7.42 – 7.64 (m, 2H), 7.69 (d, *J* = 2.4 Hz, 1H). Two protons extra located.

^{13}C NMR (101 MHz, DMSO) δ 23.0, 23.08, 24.01, 24.88, 25.18, 28.82, 28.90, 30.97, 31.26, 31.37, 32.28, 34.93, 34.98, 35.41, 37.24, 52.42, 55.63, 56.34, 60.57, 87.28, 97.39, 145.57, 153.80, 157.97, 165.54, 166.34, 180.24, 181.22.

IR (neat) 2904, 2852, 1663, 1581, 1517, 1365, 1292, 1101, 980.

HRMS (ESI) calcd for $C_{27}H_{35}N_5O_2$ $[M + H]^+$ 462.2869, found 462.2786.

3.11.9 Synthesis and Characterization of 181



181

Starting from 3-(*tert*-butylamino)-4-ethoxycyclobut-3-ene-1,2-dione (39 mg, 0.2 mmol) compound **181** (56 mg, 73% yield) was obtanined as pale yellow amorphous solid.

mp: 250.4 – 254.3 °C.

$[\alpha]_D^{31}$ +59.2 ° (*c* 0.25, DMSO)

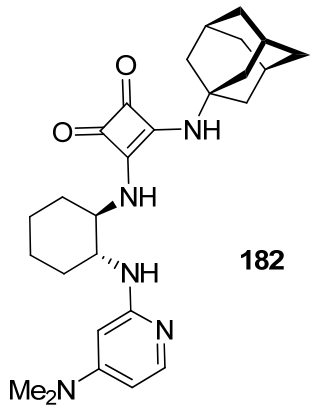
^{1}H NMR (400 MHz, DMSO) δ 1.01 – 1.50 (m, 4H), 1.22 (s, 9H), 1.54 – 1.72 (m, 2H), 1.86 – 2.04 (m, 2H), 2.78 (s, 6H), 3.55 – 3.78 (m, 2H), 5.45 (d, *J* = 1.8 Hz, 1H), 5.79 (d, *J* = 8.5 Hz, 1H), 5.92 (dd, *J* = 2.1, 6.2 Hz, 1H), 7.49 (bs, 2H), 7.52 (d, *J* = 6.2 Hz, 1H).

^{13}C NMR (100.6 MHz, DMSO) δ 24.3, 30.1, 32.1, 33.4, 38.8, 52.0, 53.9, 57.6, 88.3, 98.9, 145.6, 155.4, 158.4, 167.6, 168.3, 180.4, 182.3.

IR (neat) 2928, 2855, 1791, 1668, 1520, 1446, 1358, 1300, 1163, 979.

HRMS (ESI) calcd for $C_{21}H_{31}N_5O_2$ $[M + H]^+$ 386.2556, found 386.2509.

3.11.10 Synthesis and Characterization of 182



182

Starting from 3-(1-adamantylamino)-4-ethoxycyclobut-3-ene-1,2-dione (55 mg, 0.2 mmol) compound **182** (61 mg, 66% yield) was obtanined as colorless amorphous solid.

mp: 254.7 – 259 °C.

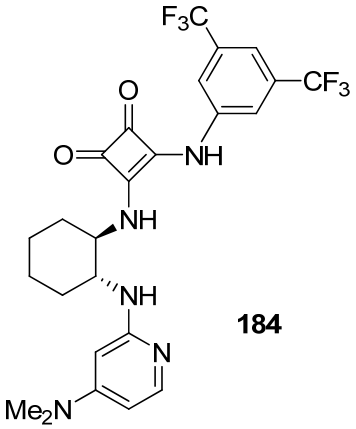
^{1}H NMR (400 MHz, DMSO) δ 1.01 – 1.45 (m, 10H), 1.46 – 1.56 (m, 1H), 1.57 – 1.87 (m, 6H), 1.90 – 2.10 (m, 2H), 2.85 (s, 6H), 3.59 – 3.87 (m, 4H), 5.52 (s, 1H), 5.85 (d, J = 7.6 Hz, 1H), 5.99 (dd, J = 2.0, 6.2 Hz, 1H), 7.41 (bs, 2H), 7.59 (d, J = 6.2 Hz, 1H). Two protons could not be located.

^{13}C NMR (101 MHz, DMSO) δ 23.84, 24.32, 24.75, 32.16, 33.45, 33.68, 38.75, 51.79, 53.80, 54.84, 57.57, 88.40, 98.93, 146.04, 155.39, 158.73, 166.99, 167.54, 181.62, 182.24.

IR (neat) 3321, 3233, 2905, 2855, 1785, 1655, 1519, 1490, 1379, 1307, 1071, 945.

HRMS (ESI) calcd for $C_{27}H_{37}N_5O_2$ $[M + H]^+$ 464.3026, found 464.2982.

3.11.11 Synthesis and Characterization of 184



184

Starting from 3-(3,5-bis(trifluoromethyl)phenylamino)-4-ethoxycyclobut-3-ene-1,2-dione (71 mg, 0.2 mmol) compound **184** (91 mg, 84% yield) was obtanined as pale yellow amorphous solid.

mp: 196.7 – 204 °C -decomp.

$[\alpha]_D^{31}$ -325.2 ° (*c* 0.25, CH_2Cl_2)

^{1}H NMR (400 MHz, DMSO) δ 1.14 – 1.57 (m, 4H), 1.66 – 1.81 (m, 2H), 1.92 – 2.03 (m, 1H), 2.04 – 2.15 (m, 1H), 2.74 (s, 3H), 3.69 – 3.81 (m, 1H), 3.82 – 3.96 (m, 1H), 5.53 (s, 1H), 5.75 (d, *J* = 4.9 Hz, 1H), 5.88 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 6.0 Hz, 1H), 7.63 (s, 1H), 7.93 (s, 2H).

^{13}C NMR (101 MHz, DMSO) δ 24.31, 24.50, 32.05, 33.44, 38.54, 53.61, 59.60, 88.76, 98.67, 114.33, 117.73, 119.06, 121.78, 124.49, 127.20, 130.76, 131.08, 131.41, 131.73, 141.19, 146.70, 155.16, 159.36, 162.28, 169.88, 180.32, 184.74.

IR (neat) 3322, 2936, 2860, 1792, 1696, 1604, 1529, 1448, 1378, 1276, 1125, 850.

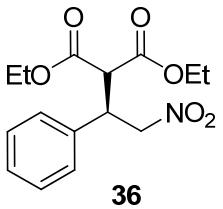
HRMS (ESI) calcd for $C_{25}H_{25}N_5O_2F_6$ $[M + H]^+$ 542.1991, found 542.2019.

3.12 General Procedure for Asymmetric Michael Additions of Diethylmalonate

To a solution of *trans*-(*β*)-nitrostyre (**34**) (29.8 mg, 0.20 mmol) in solvent (1.0 mL) was added 2-aminoDMAP/Thiourea **130** (0.002 to 0.004 mmol) and diethylmalonate **35** (64 mg, 61 μL, 0.4 mmol). Upon consumption of substrate **34** (monitored by

TLC), the reaction mixture was directly subjected to column chromatography using 1:8 EtOAc:Hexanes as the eluant to afford the conjugate addition product **36**.

3.12.1 (*R*)-diethyl 2-(2-nitro-1-phenylethyl)malonate (36)



36

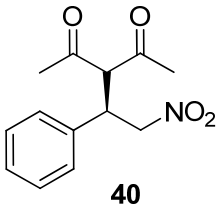
Best condition = Solvent: cyclohexane (1.0 mL); Temperature: room temperature; Catalyst (Loading): 2-aminoDMAP/Thiourea **130** (2.0 mg, 0.004 mmol).

Flash column chromatography afforded conjugate addition product **36** (45 mg, 73%) as colorless oil. Analytical data matched previously reported value.[13a] HPLC (AS-H, 90:10 *n*-Hexane:Isopropanol, 1 mL/min, 210 nm): t_{major} = 21.5 min, t_{minor} = 17.8 min, 61% *ee*.

3.13 General Procedure for Asymmetric Michael Additions of Acetylacetone

To a solution of *trans*-(*β*)-nitrostyre (**34**) (29.8 mg, 0.20 mmol) in solvent (0.5 to 2.0 mL) was added 2-aminoDMAP/sulfonamide (0.004 mmol) and acetylacetone **38** (40 mg, 41 μL, 0.4 mmol). Upon consumption of substrate **34** (monitored by TLC), the reaction mixture was directly subjected to column chromatography using 1:2 EtOAc:Hexanes as the eluant to afford the conjugate addition product **40**.

3.13.1 (*R*)-3-(2-nitro-1-phenylethyl)pentane-2,4-dione (40)



40

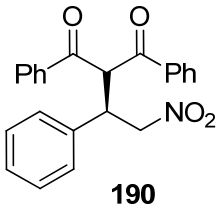
Best condition = Solvent: toluene (2.0 mL); Temperature: -10 °C; Catalyst (Loading): 2-aminoDMAP/Sulfonamide **155** (21.8 mg, 0.04 mmol).

Flash column chromatography afforded conjugate addition product **40** (44 mg, 89%) as colorless solid. Analytical data matched previously reported value.[36] HPLC (AS-H, 80:20 *n*-Hexane:Isopropanol, 1 mL/min, 210 nm): t_{major} = 37.2 min, t_{minor} = 21.6 min, 93% *ee*; $[\alpha]_D^{31}$ -75.5 ° (*c* 0.25, CH_2Cl_2), Lit: $[\alpha]_D^{26}$ -200.2 (*c* 1.0, $CHCl_3$).

3.14 General Procedure for Asymmetric Michael Additions of Dibenzoylmethane (189)

To a solution of *trans*-(*β*)-nitrostyre (**34**) (29.8 mg, 0.20 mmol) in toluene (1.0 mL) was added 2-aminoDMAP/Squaramide (0.002 to 0.004 mmol) and dibenzoylmethane **35** (134 mg, 0.6 mmol). Upon consumption of substrate **34** (monitored by TLC), the reaction mixture was directly subjected to column chromatography using 1:10 EtOAc:Hexanes as the eluant to afford the conjugate addition product **190**.

3.14.1 (*R*)-2-(2-nitro-1-phenylethyl)-1,3-diphenylpropane-1,3-dione



190

Best condition = Temperature: 5 °C; Catalyst (Loading): 2-aminoDMAP/Squaramide **182** (0.93 mg, 0.002 mmol).

Flash column chromatography afforded conjugate addition product **40** (68 mg, 92%) as colorless solid. Analytical data matched previously reported value.[96] HPLC (AS-H, 80:20 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm): t_{major} = 27.3 min, t_{minor} = 20.4 min, 90% *ee*.

CHAPTER 4

CONCLUSION

Herein, synthesis of the chiral 2-aminoDMAP **100** derived from *trans*-(*R,R*)-cyclohexane-1,2-diamine **101** was achieved by both Pd and Cu catalysis. Palladium catalyzed works indicated the incompatibility of the *trans*-(*R,R*)-cyclohexane-1,2-diamine as the substrate thereby necessitated mono-*N*-protection. Employing mono-*N*-phthaloyl protected substrate, synthesis of this chiral DMAP derivative was accomplished with at the most 11% yield over 4 synthetic steps. A 2-aminoDMAP/Thiourea catalyst was developped starting from compound **100** and showed promising results (61% *ee*) in Michael addition reaction of diethylmalonate and trans-(*β*)-nitrostyrene. Next, a highly practical direct method targetting 2-aminoDMAP **100** was developed *via* selective mono-*N*-pyridilization of *trans*-(*R,R*)-cyclohexane-1,2-diamine by Cu catalysis. Developed method is the first successful mono-*N*-heteroarylation of *trans*-(*R,R*)-cyclohexane-1,2-diamine. This protocol was employed succesfully for the formal synthesis of a Johnston's BAM catalyst, which was previously synthesized over 4 steps *via* expensive Pd catalysis.

Facile preparation of chiral 2-aminoDMAP core catalaphore led to the development of various 2-aminoDMAP/Sulfonamides (10 examples) which showed quite good results in asymmetric conjugate addition of acetylacetone to *trans*-(*β*)-nitrostyrene. Systematic structural elaborations done on sulfonamide unit in catalysts yielded enantioselectivities ranging from 28% to 88% revealing the importance of the art of catalyst design. Enantiomeric excesses (*ee*) up to 93% were attained for this asymmetric reaction. Eleven examples of 2-aminoDMAP/Squaramides were developed as the second generation bifunctional acid/base organocatalysts which showed good results in asymmetric conjugate addition of dibenzoylmethane to *trans*-(*β*)-nitrostyrene. Michael adducts were afforded in high enantioselectivities. Semi

optimized conditions yielded 90% *ee* in short reaction times with catalyst loadings low as to 1 mol%. Lower catalyst loadings and faster reactions encountered with both thiourea and squaramide catalysts implied the superior activation of electrophiles by such double hydrogen bond donor entities than the mono hydrogen bond donor sulfonamides.

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2002 Internship, TED College, Ankara

2002-2011 Research Assistant, Middle East Technical University, Chemistry Department,

Ankara

2004-2008 Instructor, International Chemistry Olympiads, Student Training Programme,

TUBİTAK, Ankara

2008-2009 Researcher, Government Project (KAMAG 107G263)

FOREIGN LANGUAGES

Fluent English

PUBLICATIONS

Tanyeli, C.; Akhmedov, I. M.; Işık, M.; Synthesis of various camphor-based chiral pyridine derivatives, *Tetrahedron Lett*. **2004**, *45*, 5799-5801.

Işık, M.; Tanyeli, C.; A concise synthesis of building blocks for novel conducting polythiophenes, S08P82, 2007 41st IUPAC International Congress Turin, Italy

Işık, M.; Tanyeli, C.; Enantioselective Morita-Baylis-Hillman reaction catalyzed by a (-)-*β*-Pinene derived chiral DMAP (PINDMAP), P501_027, 2009 42nd IUPAC International Congress, Glasgow, Scotland, UK

HOBBIES

Music, Swimming, Reading, Cooking.

APPENDIX A. SUPPORTING INFORMATION

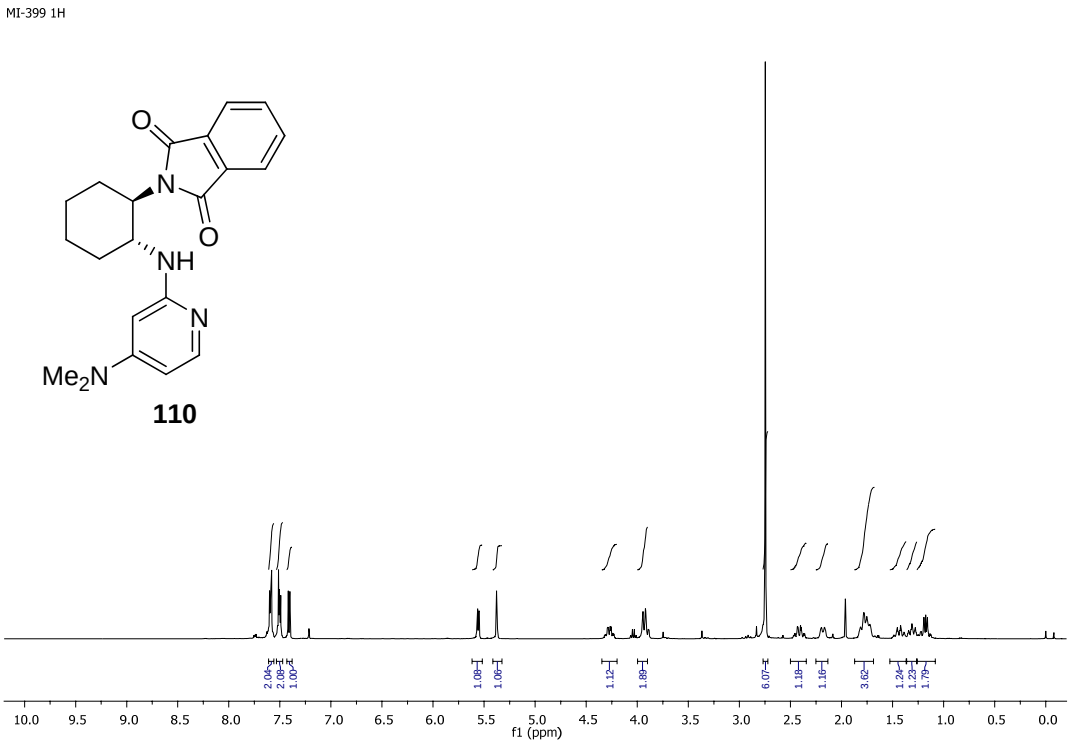

Figure A1. ^{1}H NMR spectrum of **110**

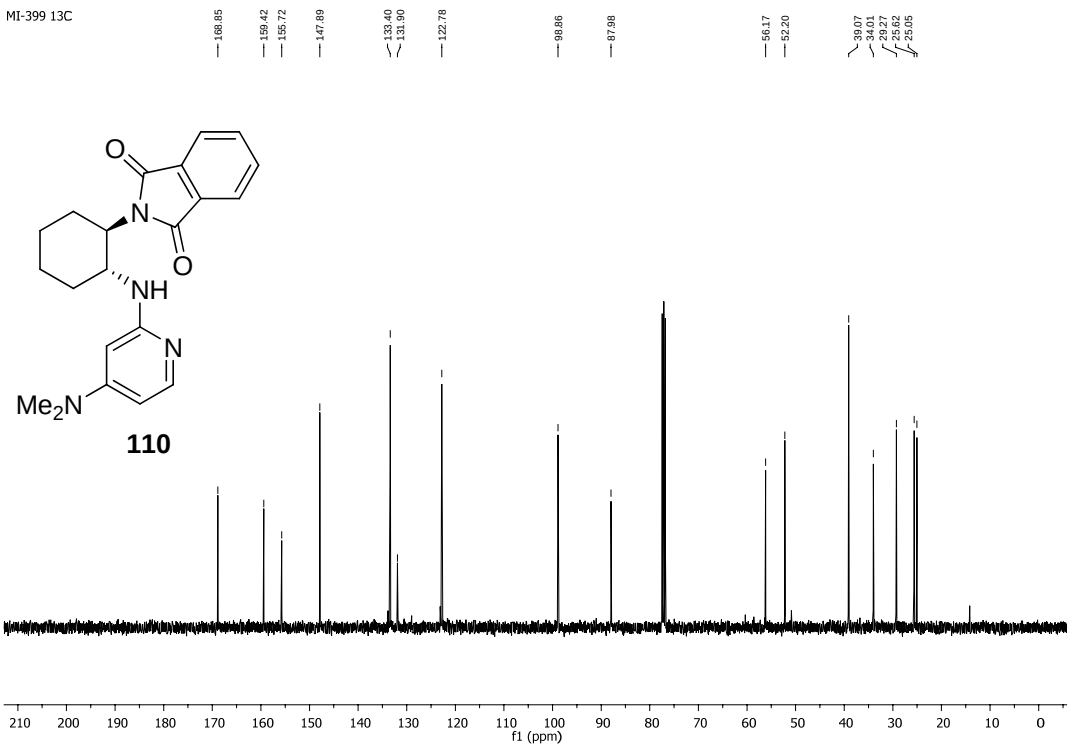

Figure A2. ^{13}C NMR spectrum of **110**

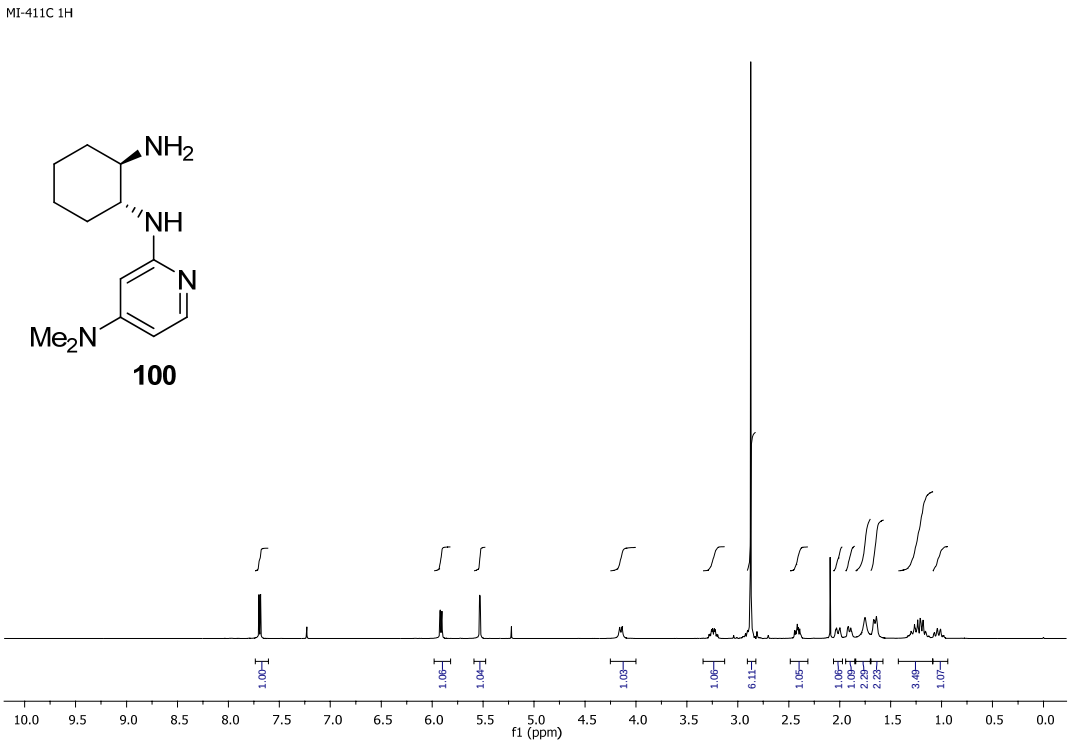

Figure A3. ^{1}H NMR spectrum of **100**

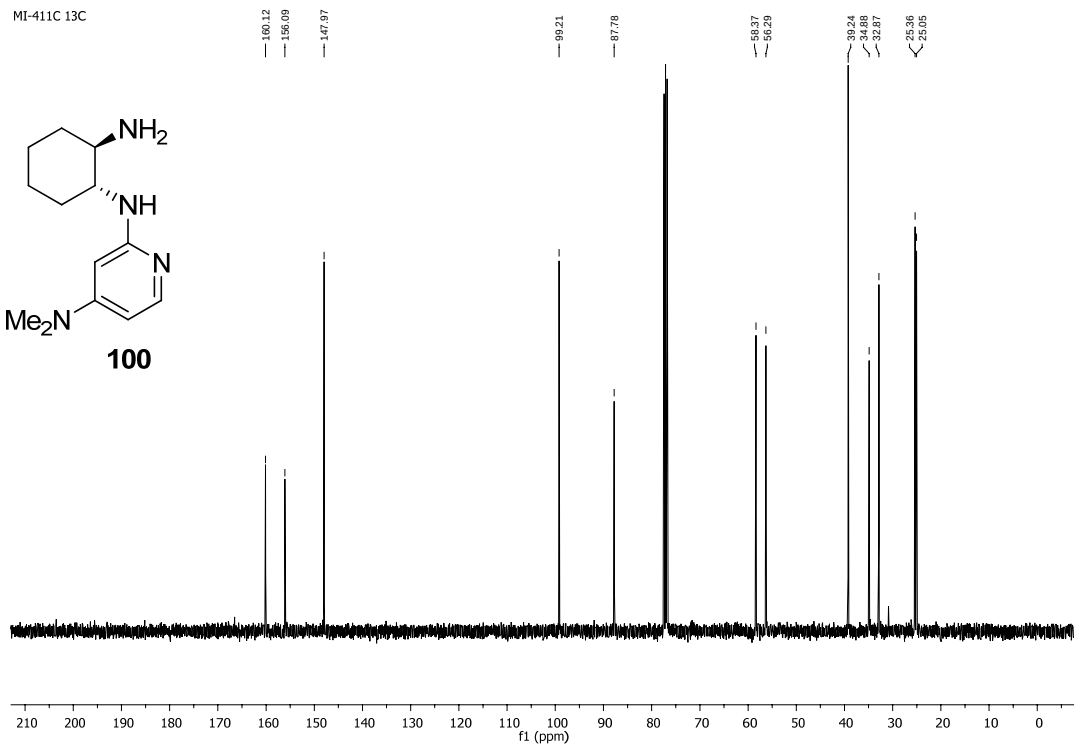

Figure A4. ^{13}C NMR spectrum of **100**

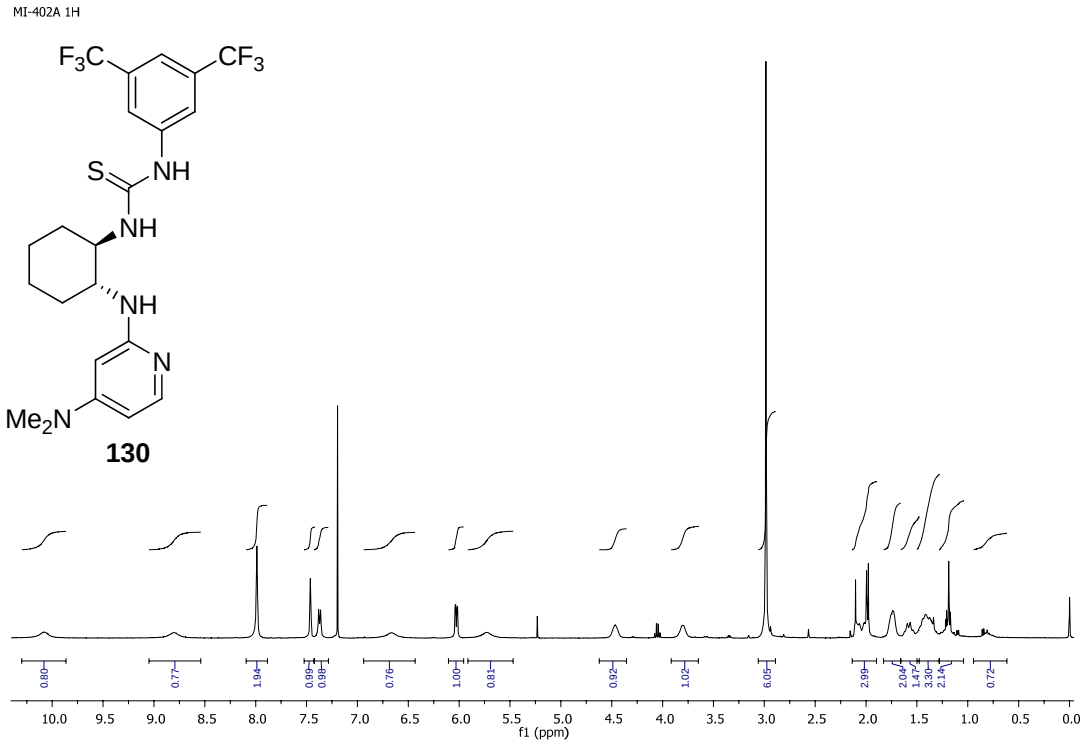

Figure A5. ^{1}H NMR spectrum of **130**

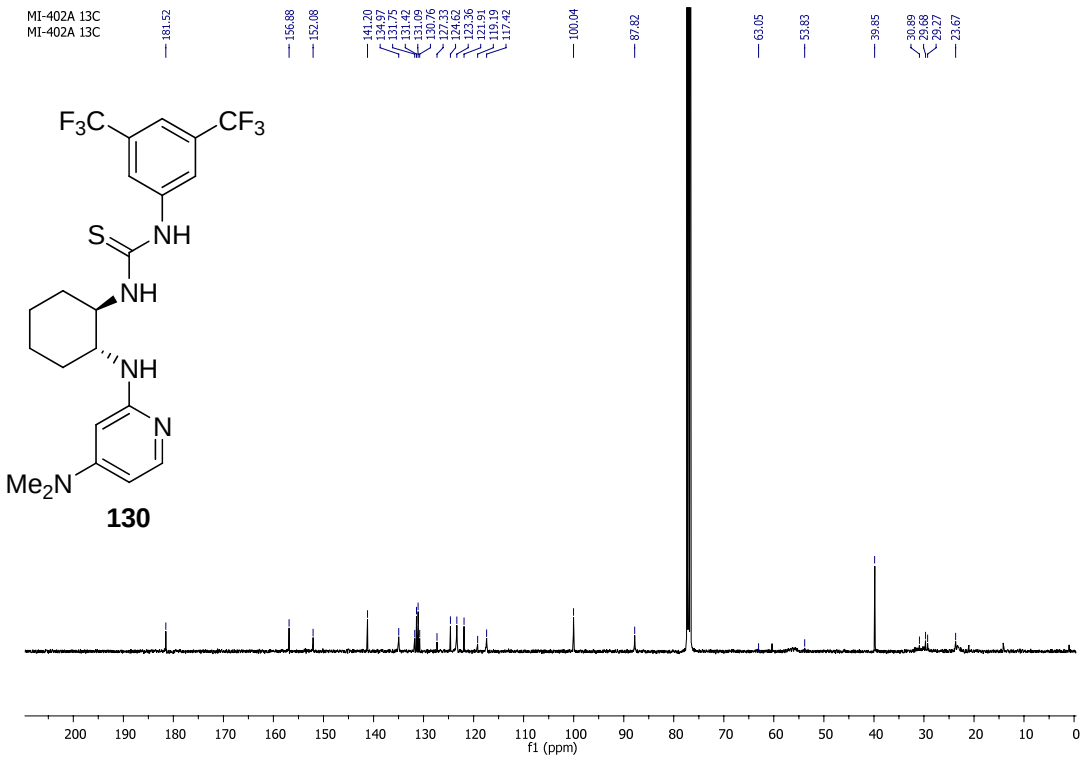

Figure A6. ^{13}C NMR spectrum of **130**

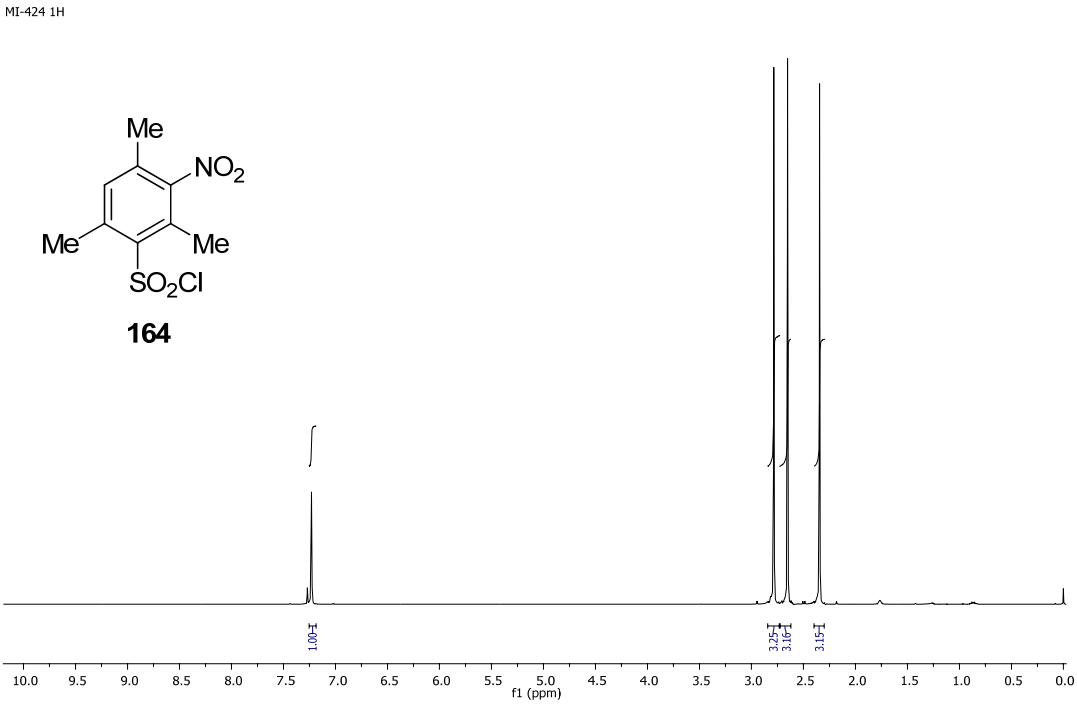

Figure A7. ^{1}H NMR spectrum of **164**

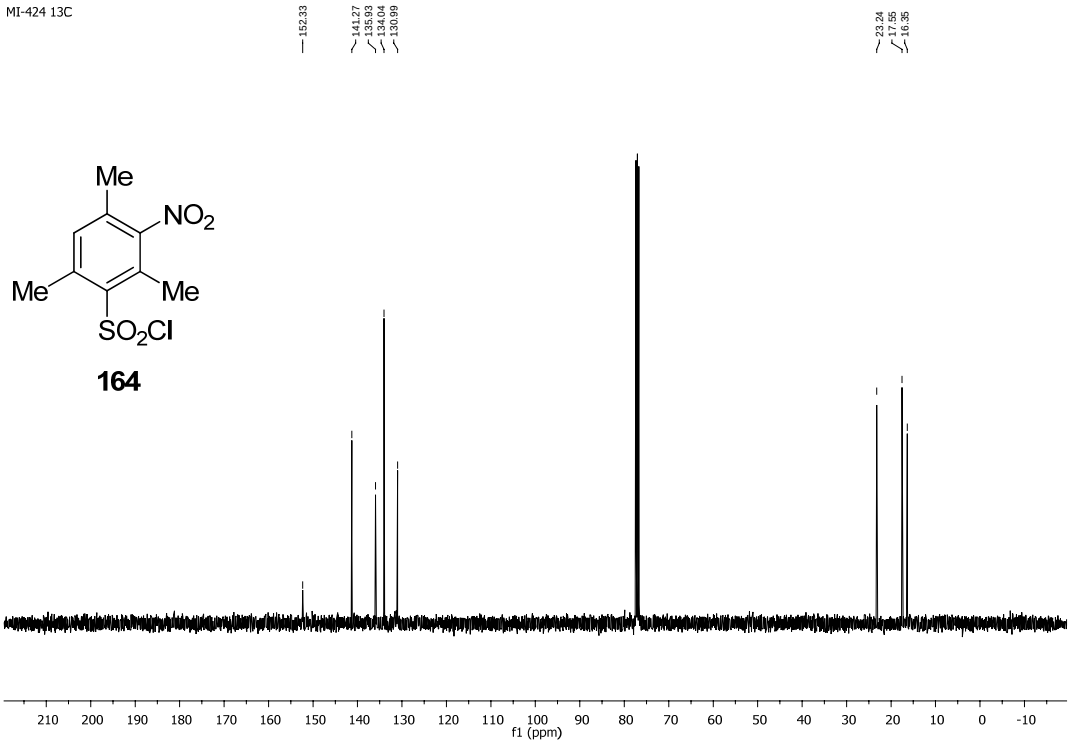

Figure A8. ^{13}C NMR spectrum of **164**

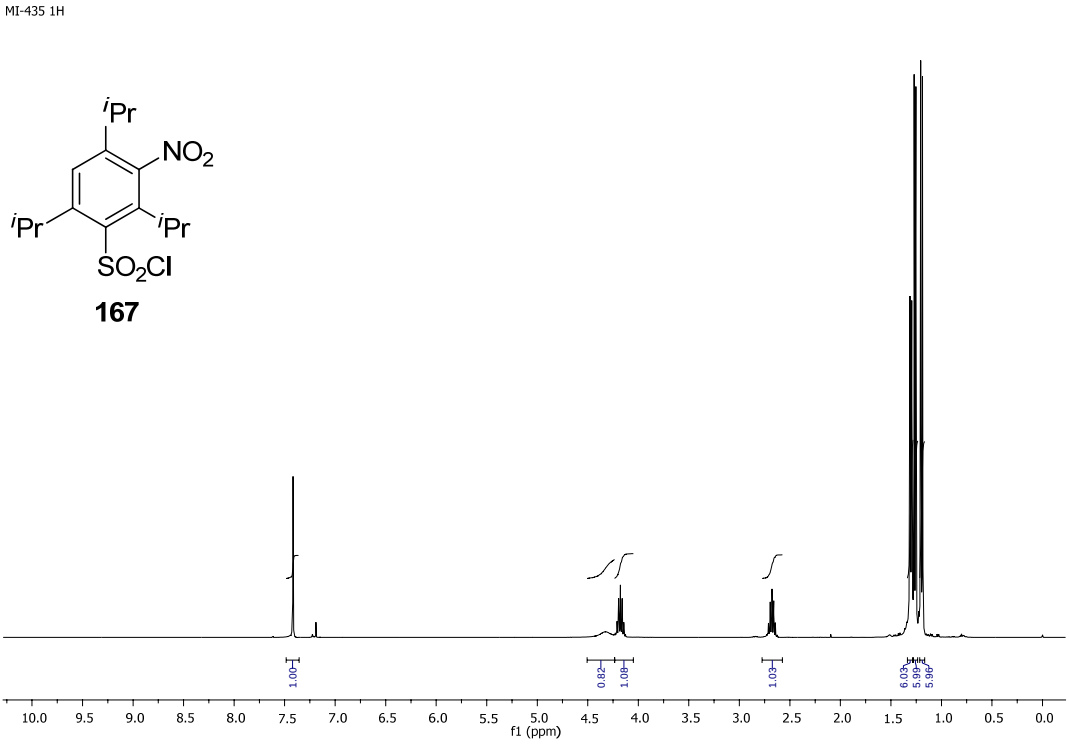

Figure A9. ^{1}H NMR spectrum of **167**

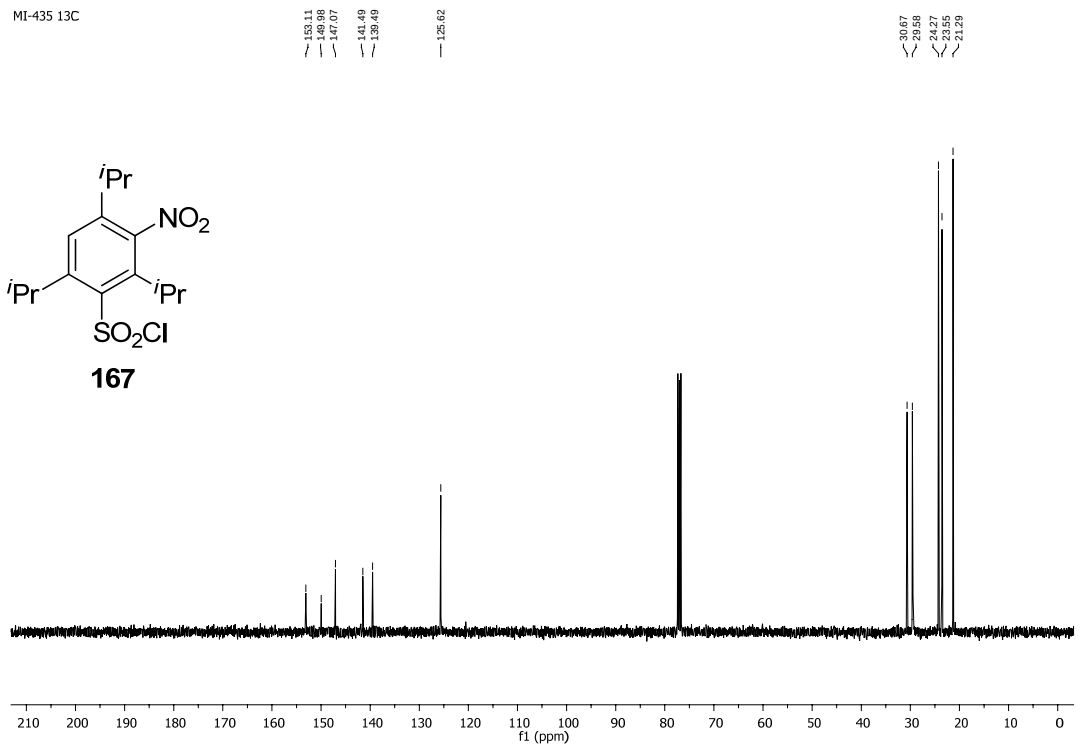

Figure A10. ^{13}C NMR spectrum of **167**

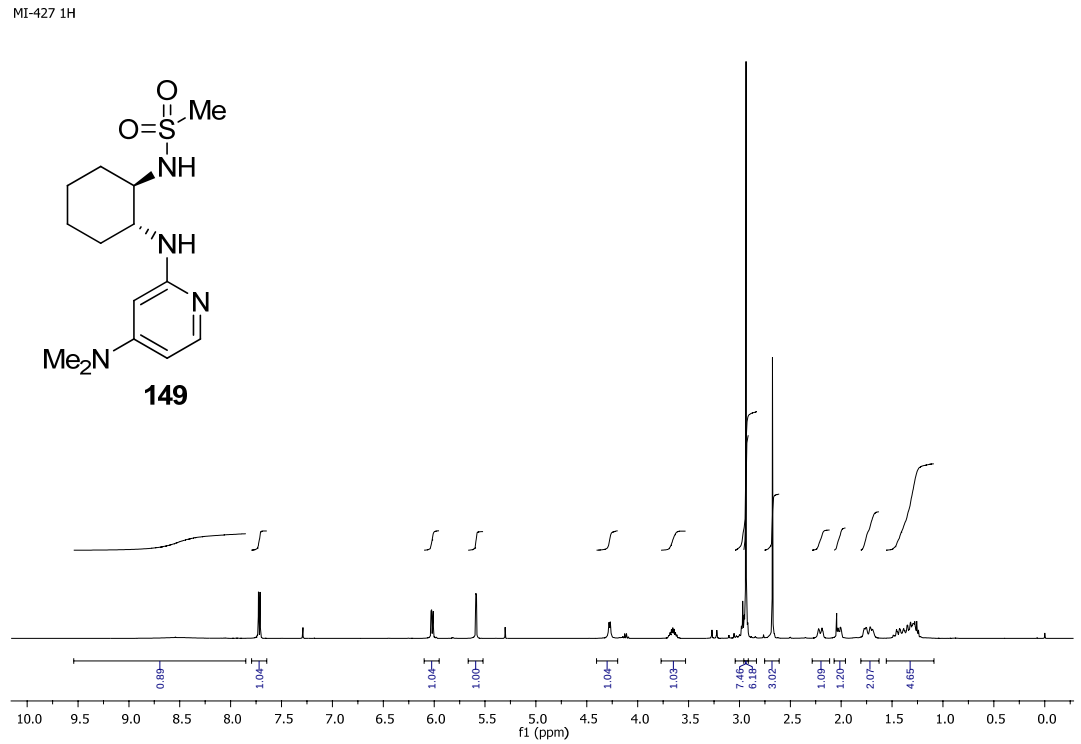

Figure A11. ^{1}H NMR spectrum of **149**

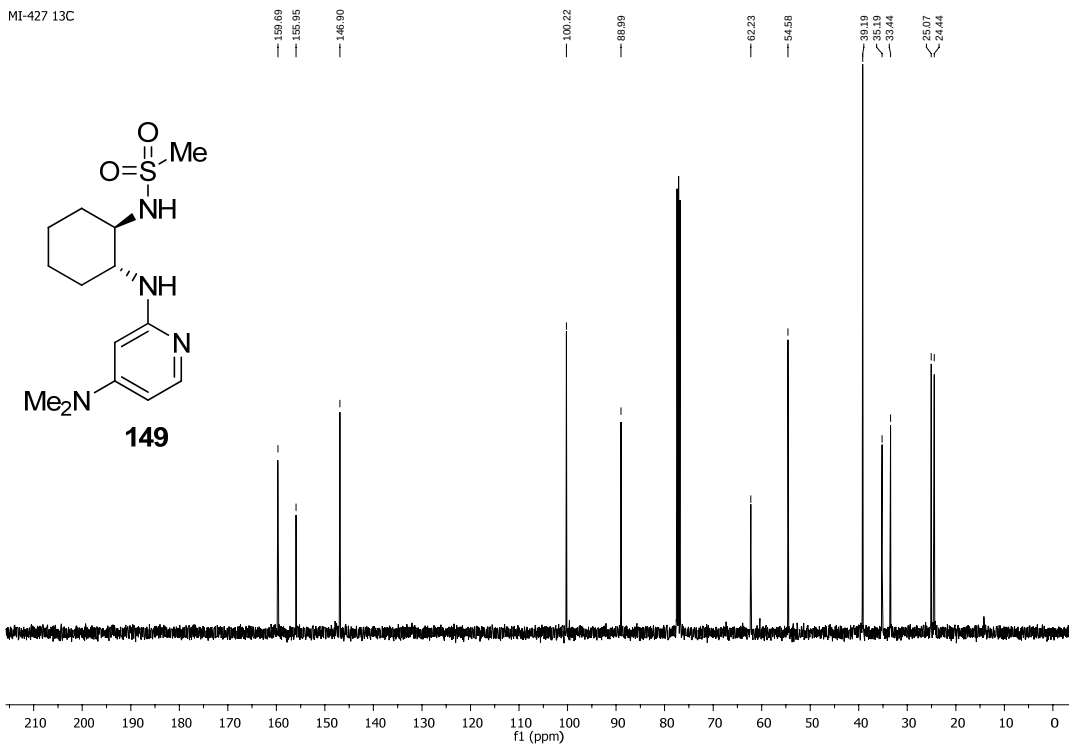

Figure A12. ^{13}C NMR spectrum of **149**

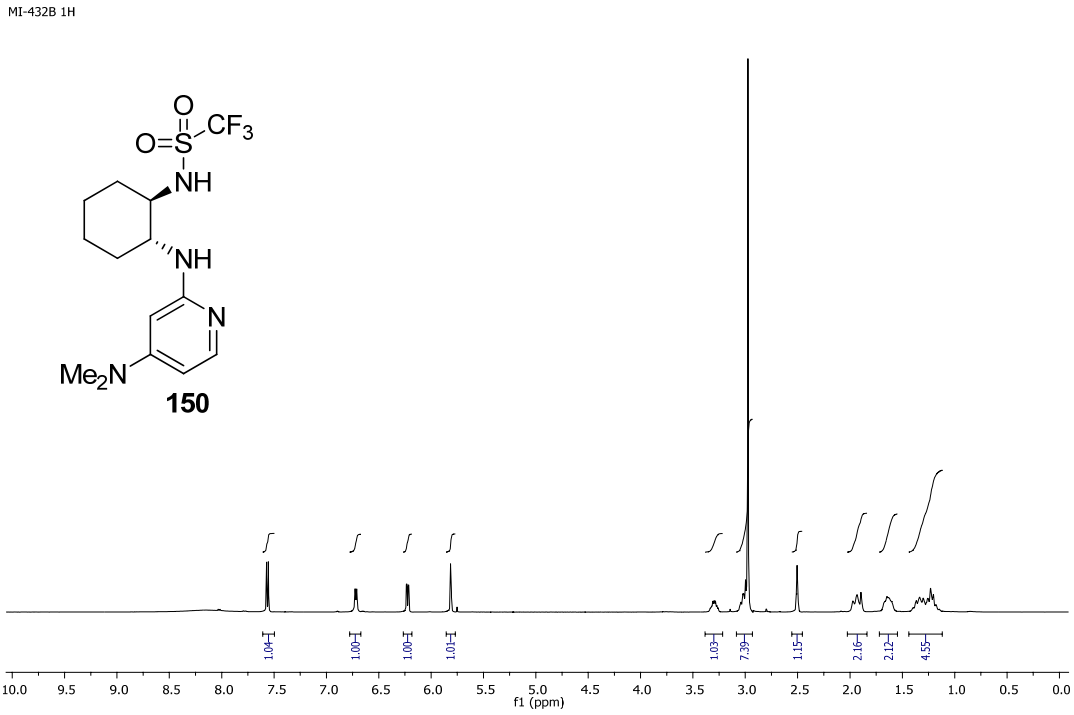

Figure A13. ^{1}H NMR spectrum of **150**

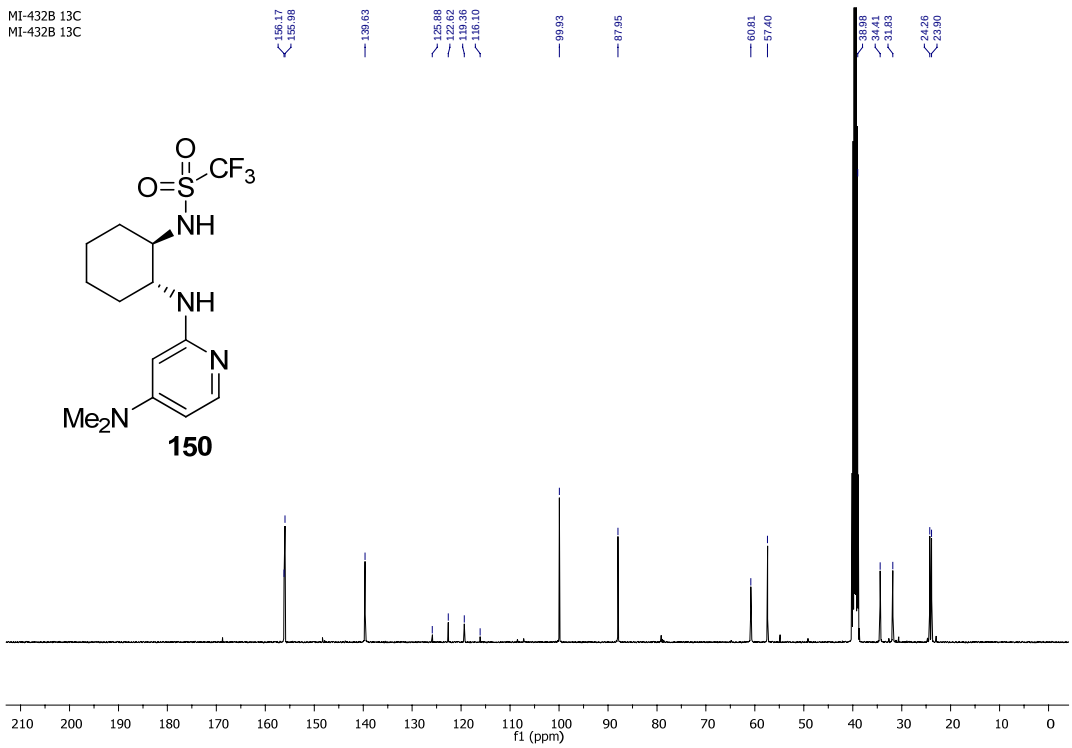

Figure A14. ^{13}C NMR spectrum of **150**

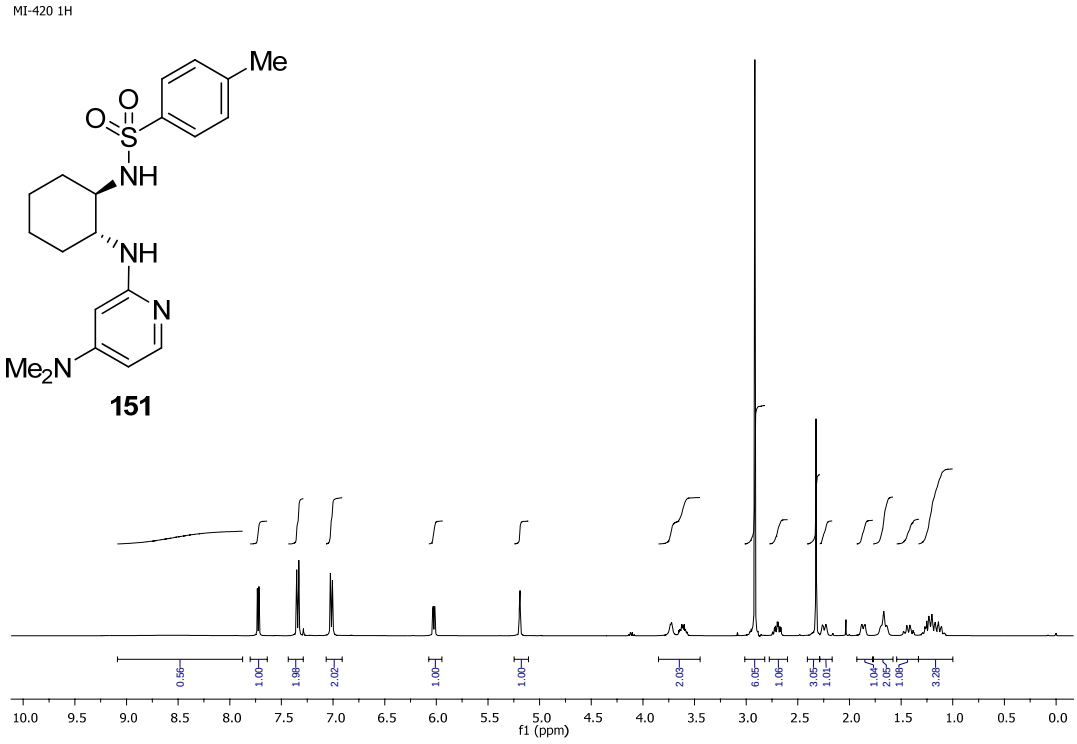

Figure A15. ^{1}H NMR spectrum of **151**

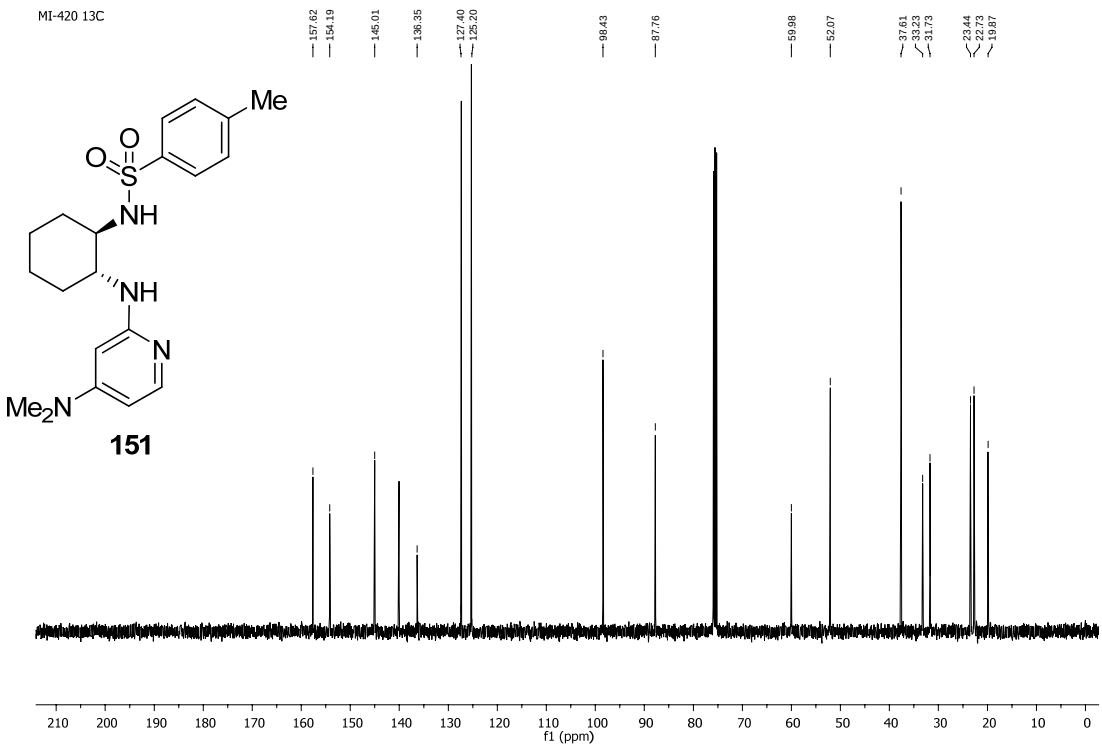

Figure A16. ^{13}C NMR spectrum of **151**

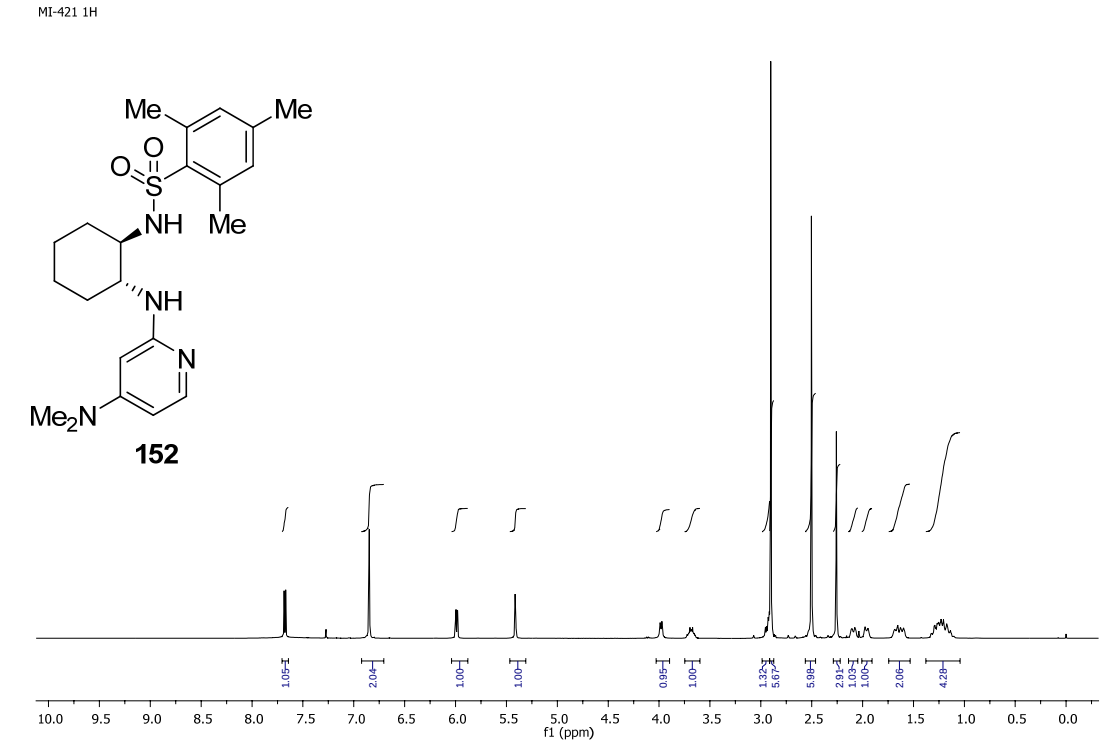

Figure A17. ^{1}H NMR spectrum of **152**

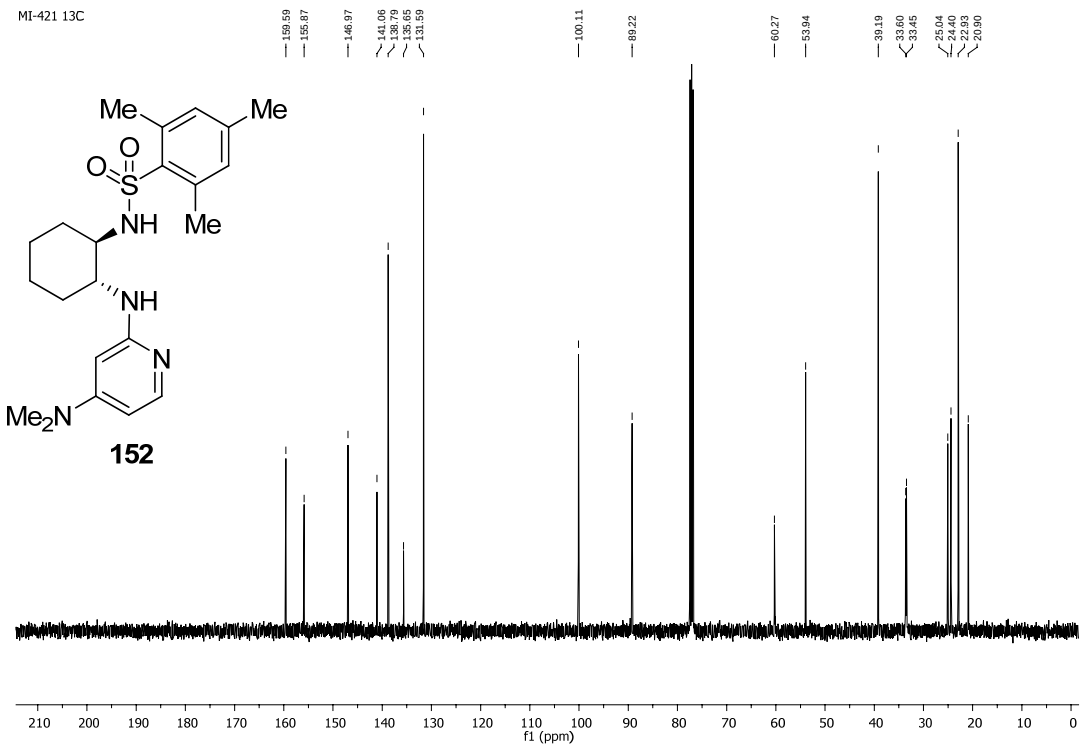

Figure A18. ^{13}C NMR spectrum of **152**

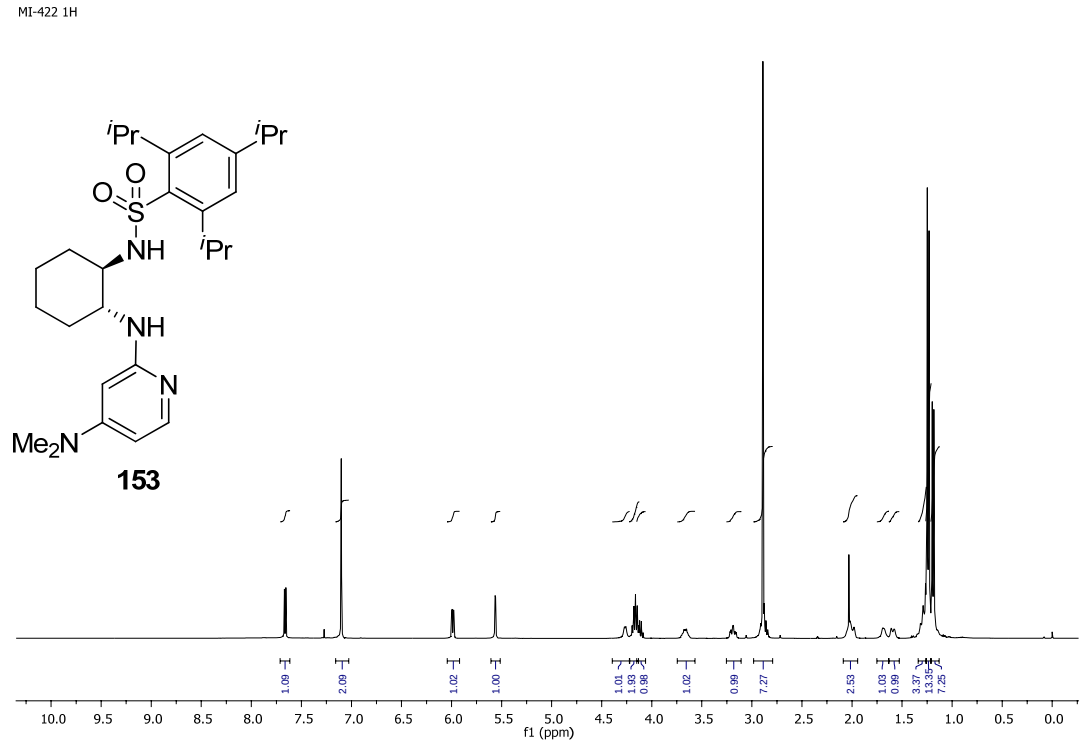

Figure A19. ^{1}H NMR spectrum of **153**

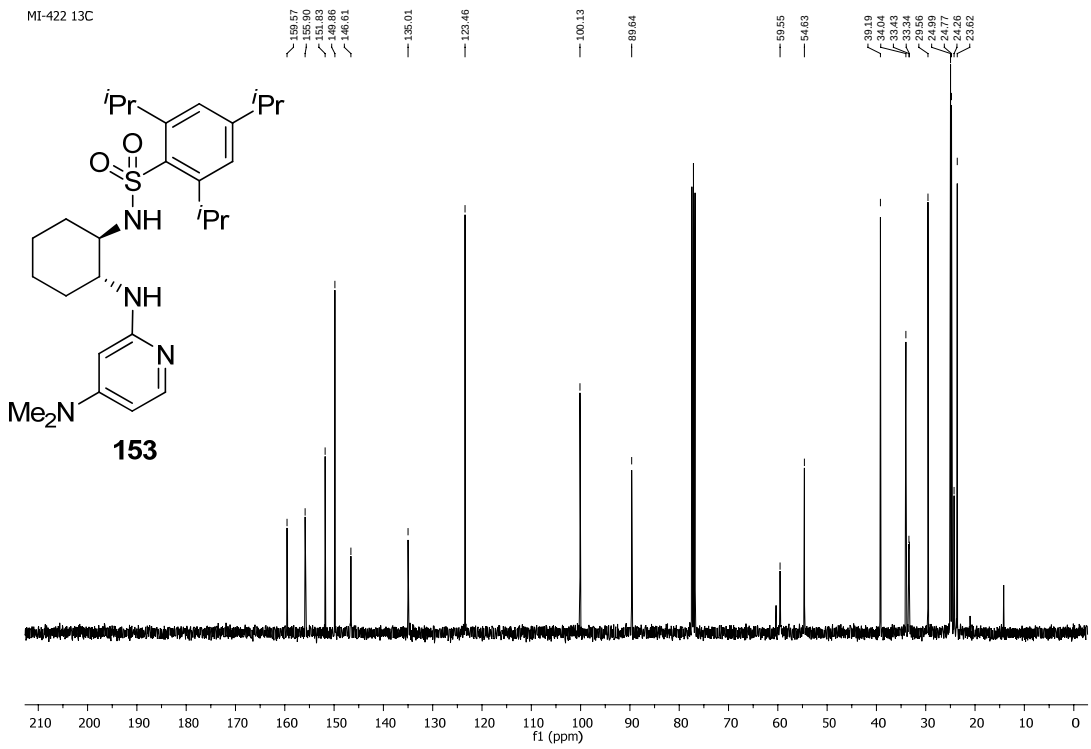

Figure A20. ^{13}C NMR spectrum of **153**

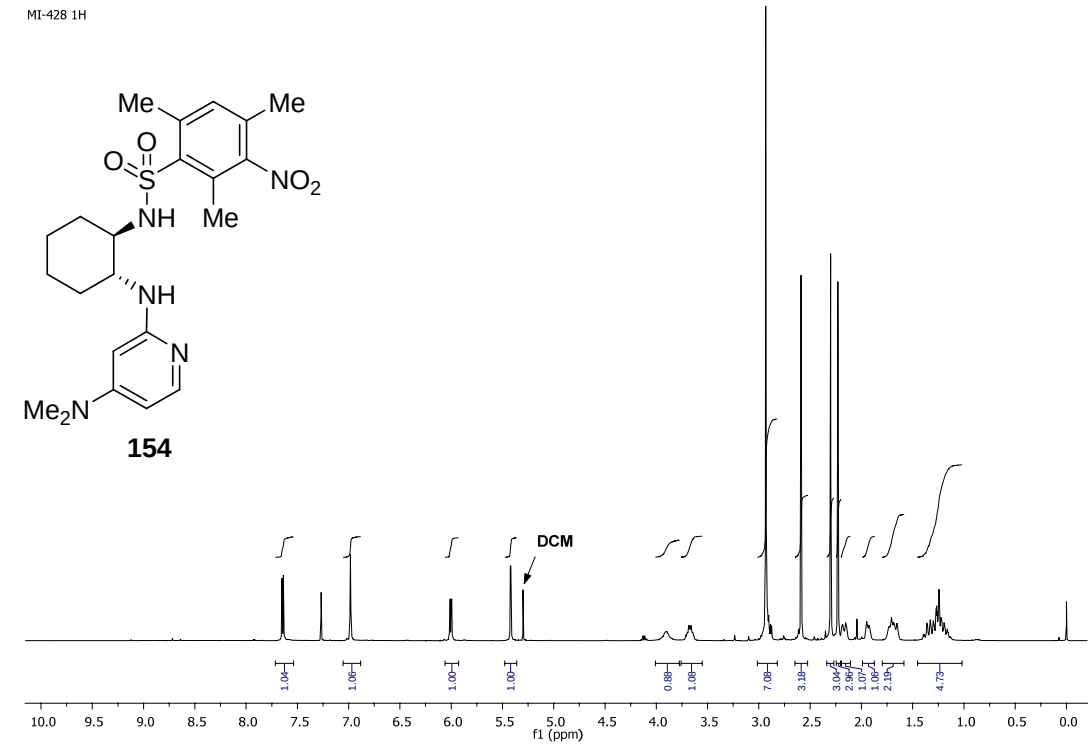

Figure A21. ^{1}H NMR spectrum of **154**

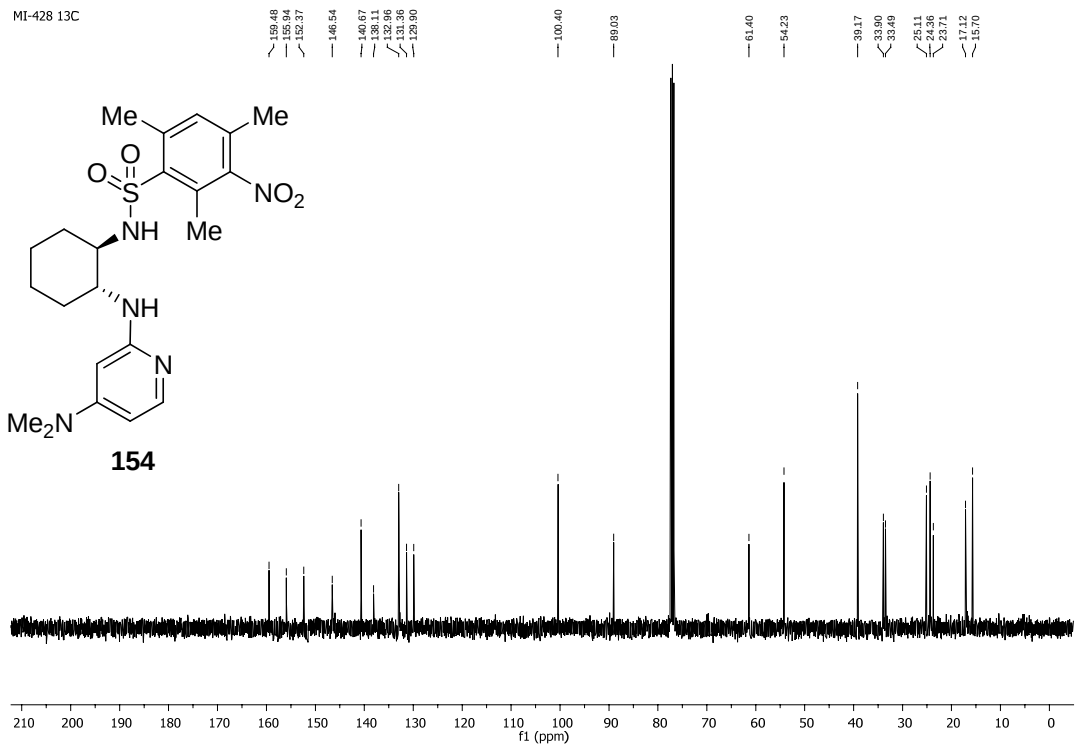

Figure A22. ^{13}C NMR spectrum of **154**

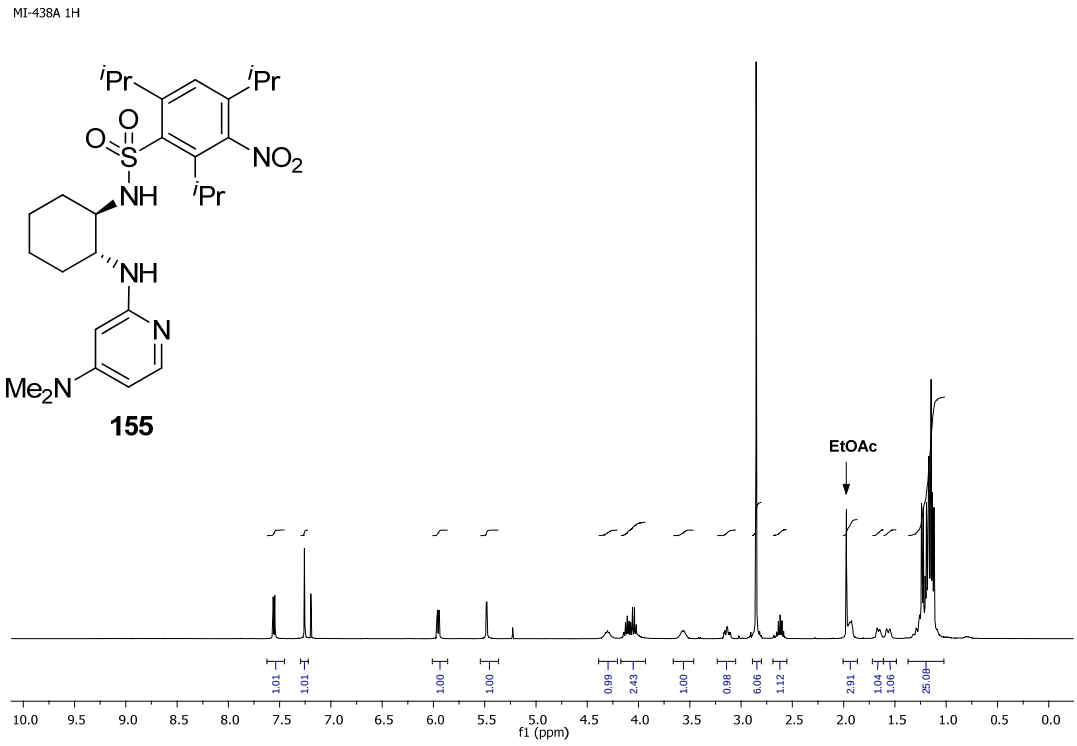

Figure A23. ^{1}H NMR spectrum of **155**

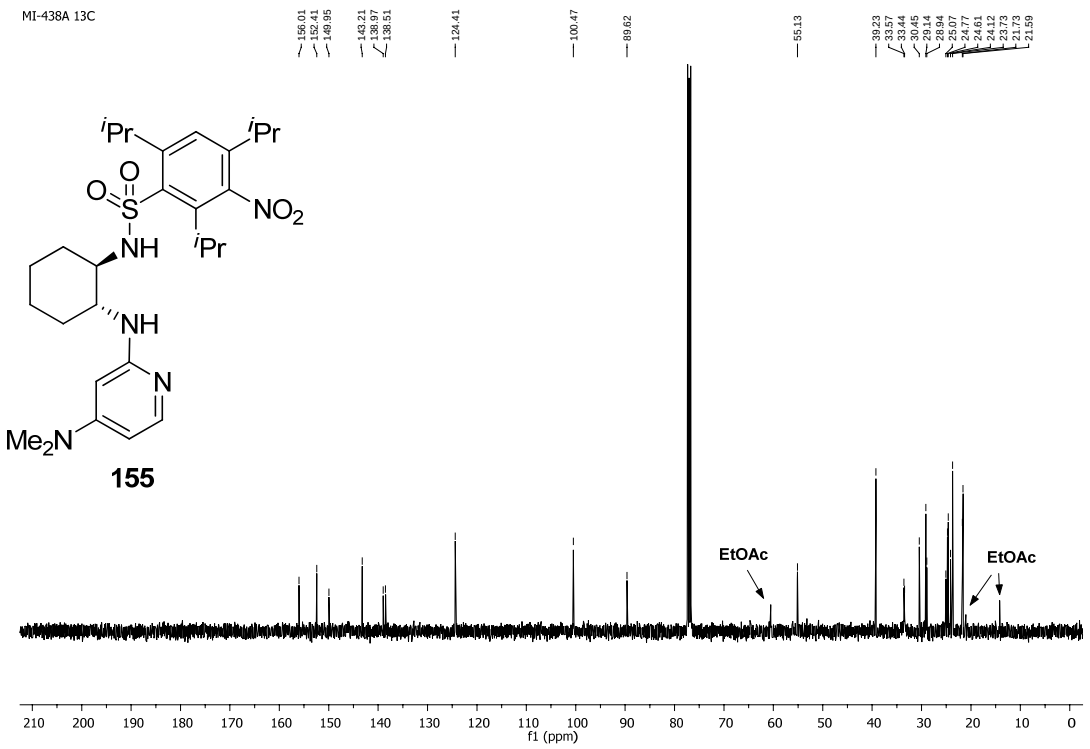

Figure A24. ^{13}C NMR spectrum of **155**

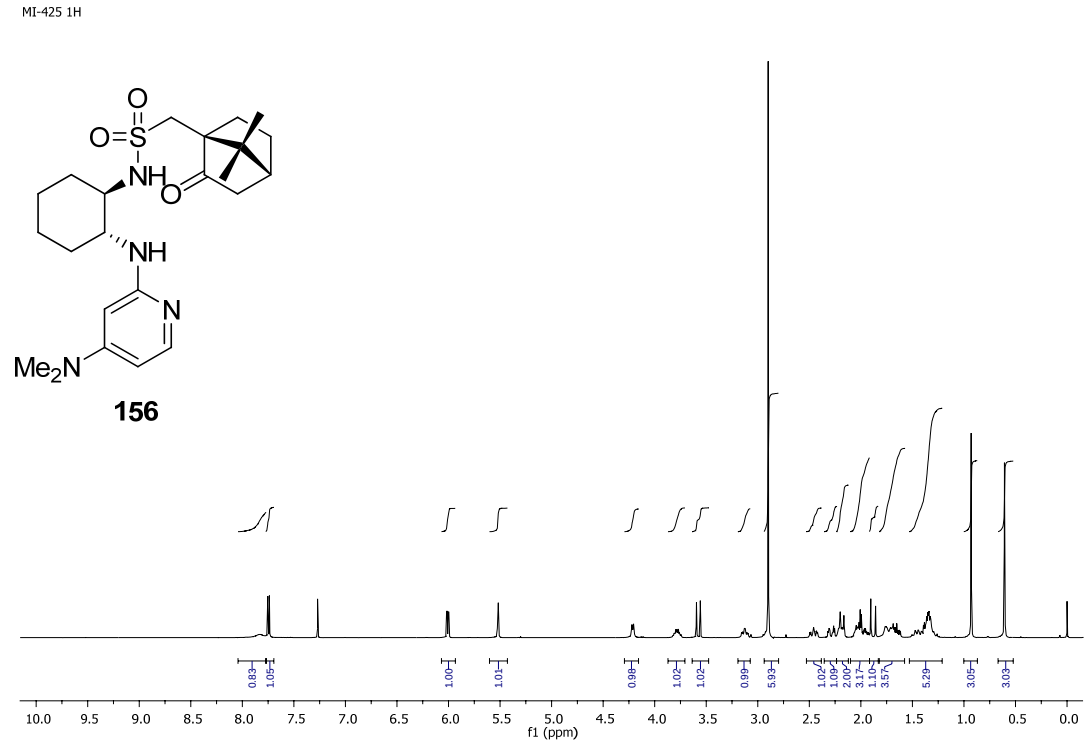

Figure A25. ^{1}H NMR spectrum of **156**

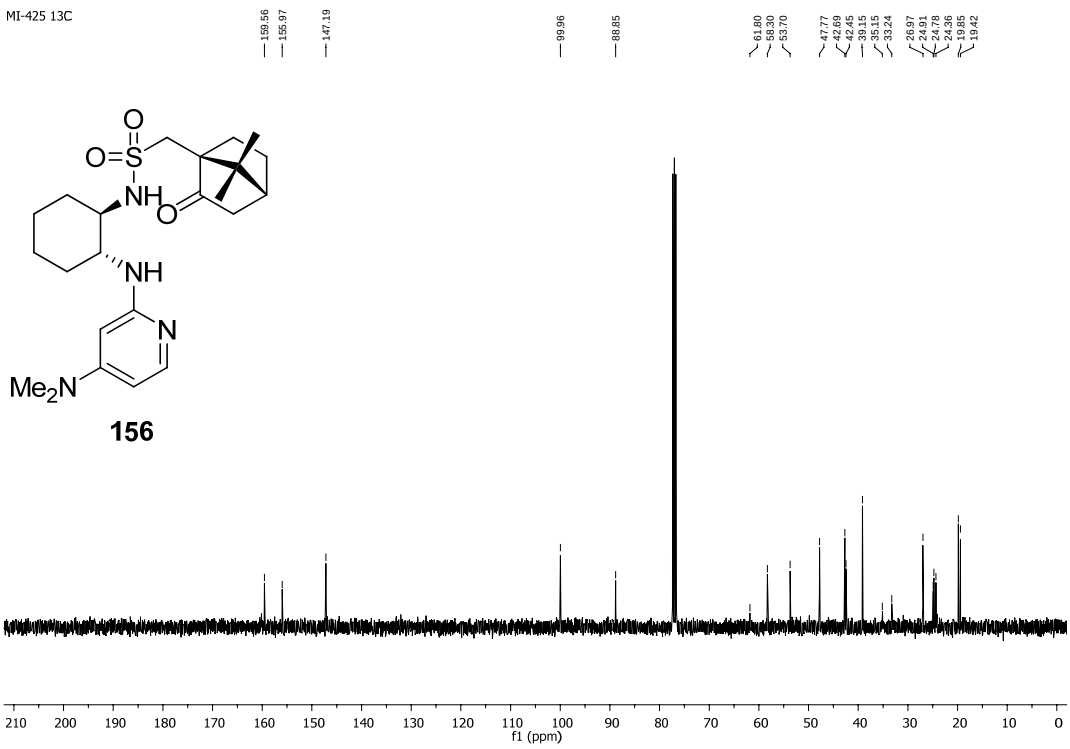

Figure A26. ^{13}C NMR spectrum of **156**

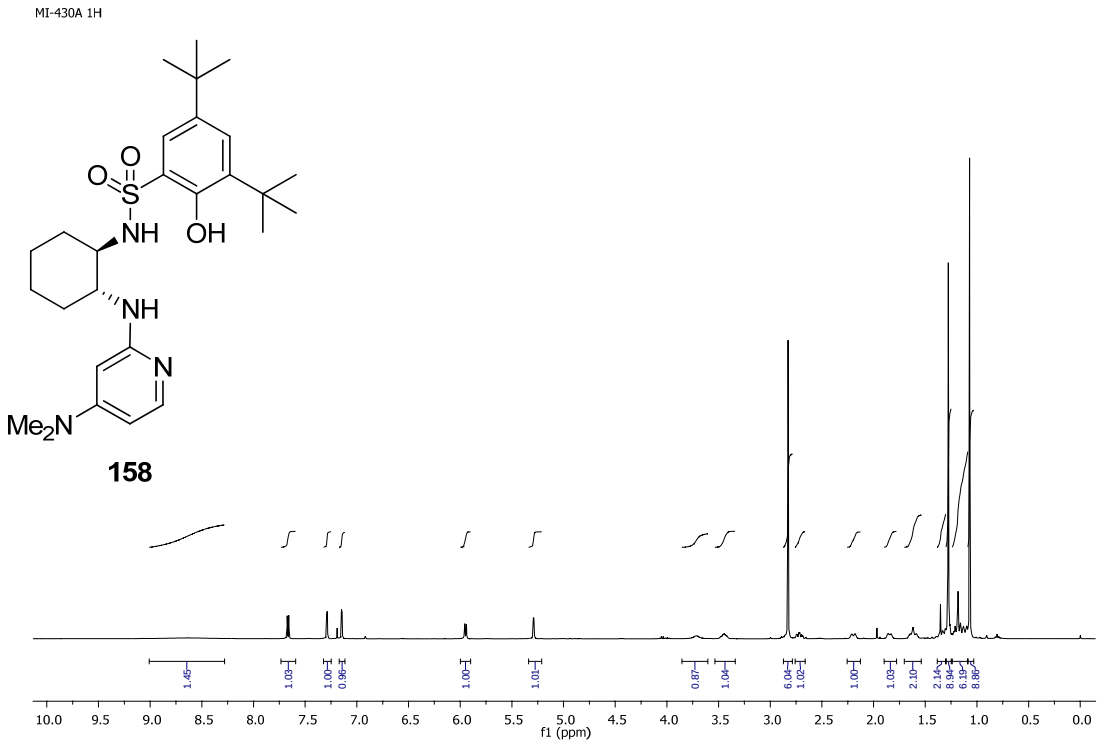

Figure A27. ^{1}H NMR spectrum of **158**

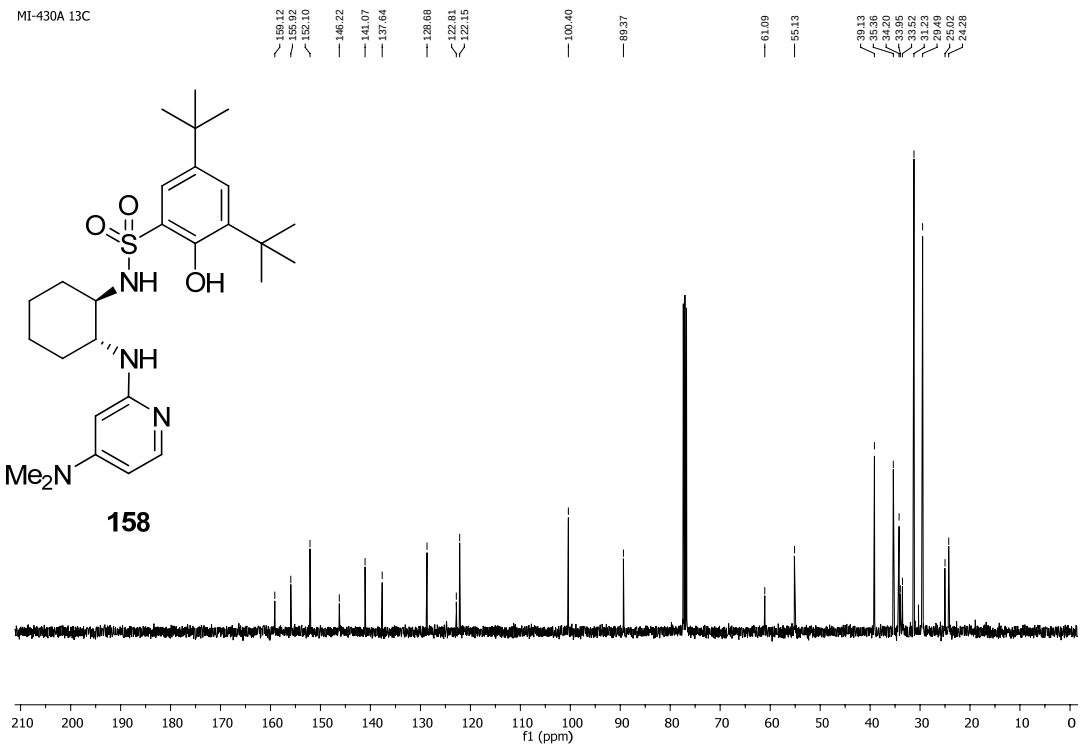

Figure A28. ^{13}C NMR spectrum of **158**

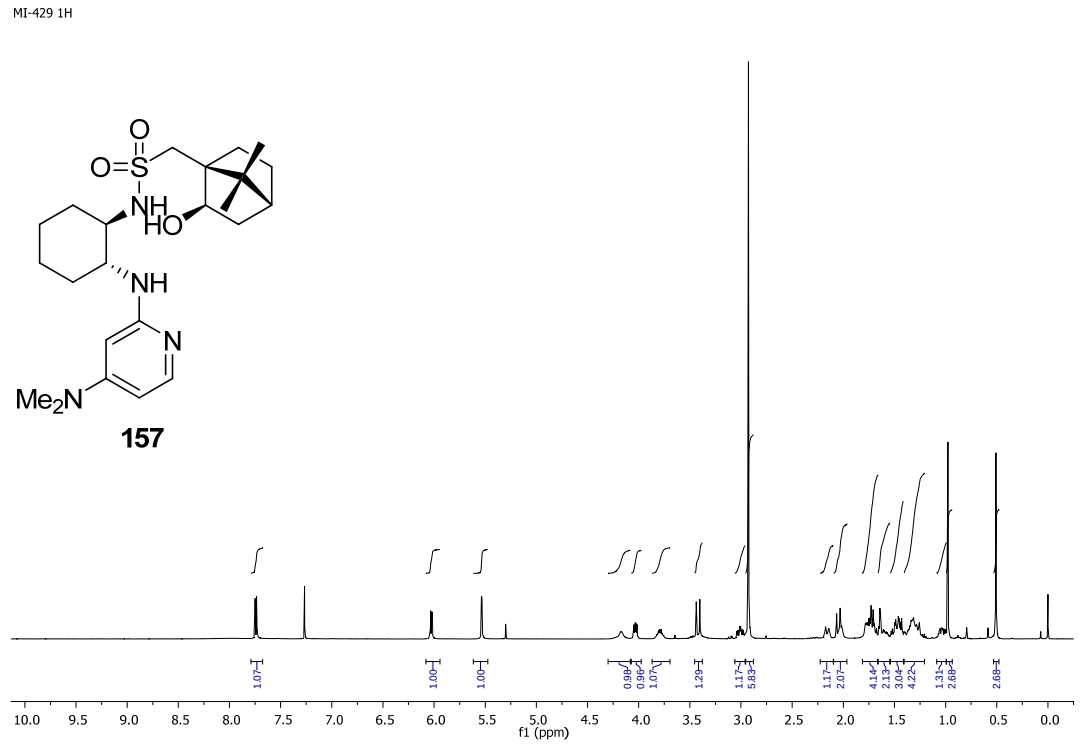

Figure A29. ^{1}H NMR spectrum of **157**

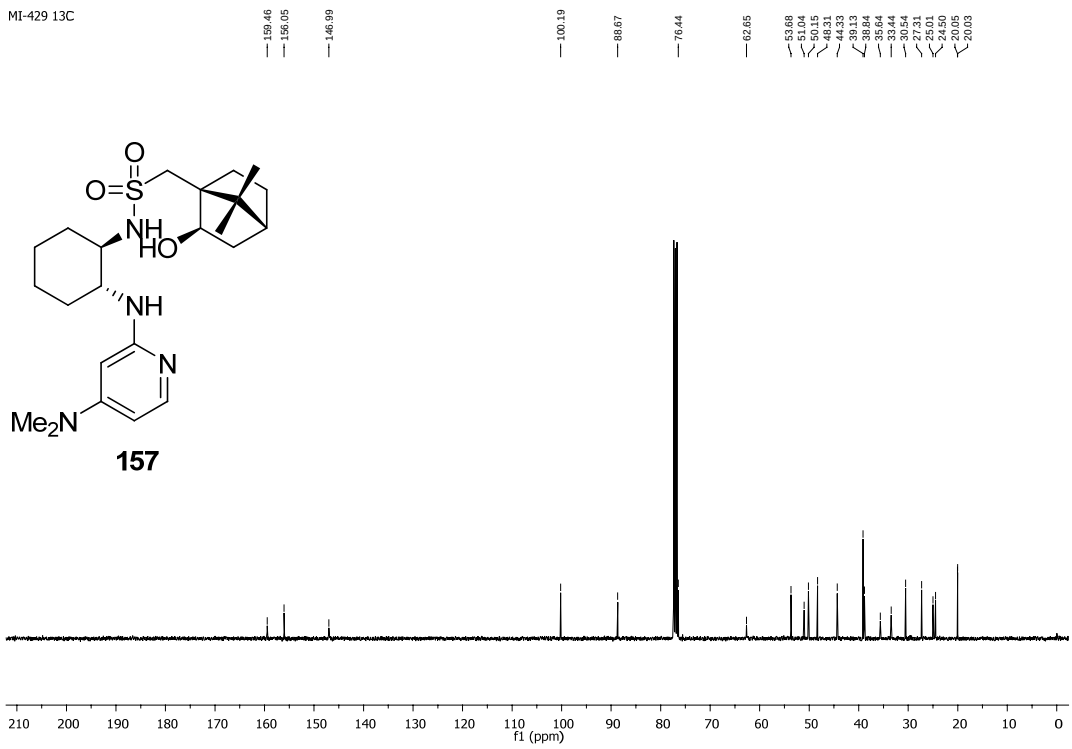

Figure A30. ^{13}C NMR spectrum of **157**

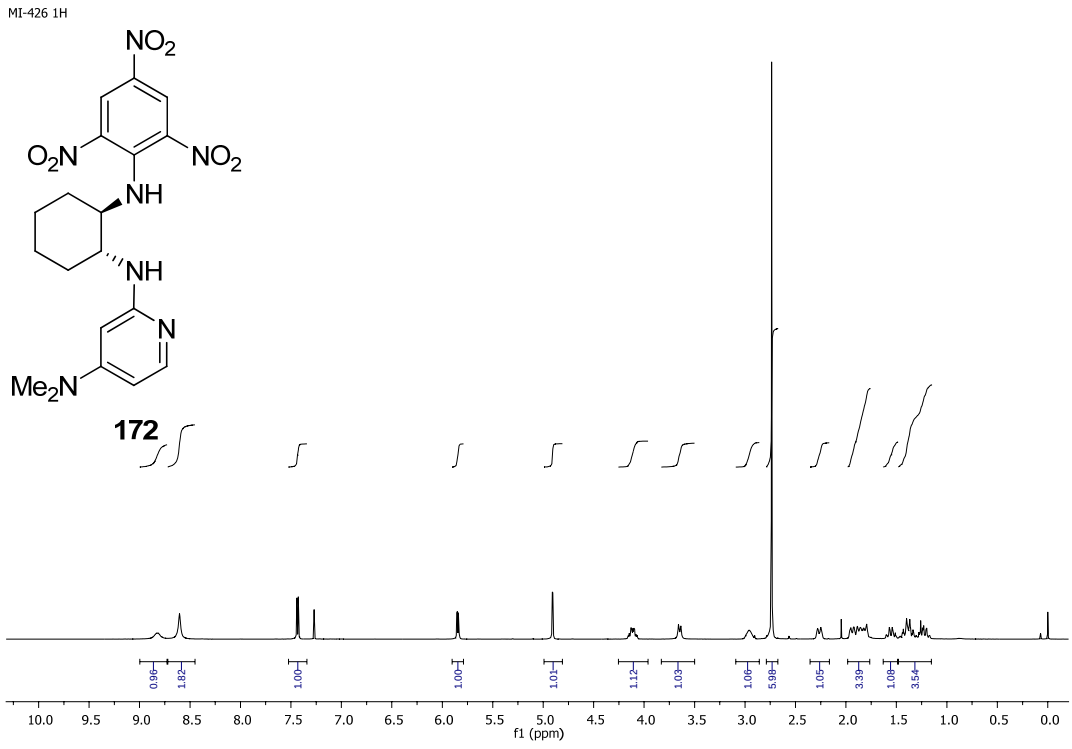

Figure A31. ^{1}H NMR spectrum of **172**

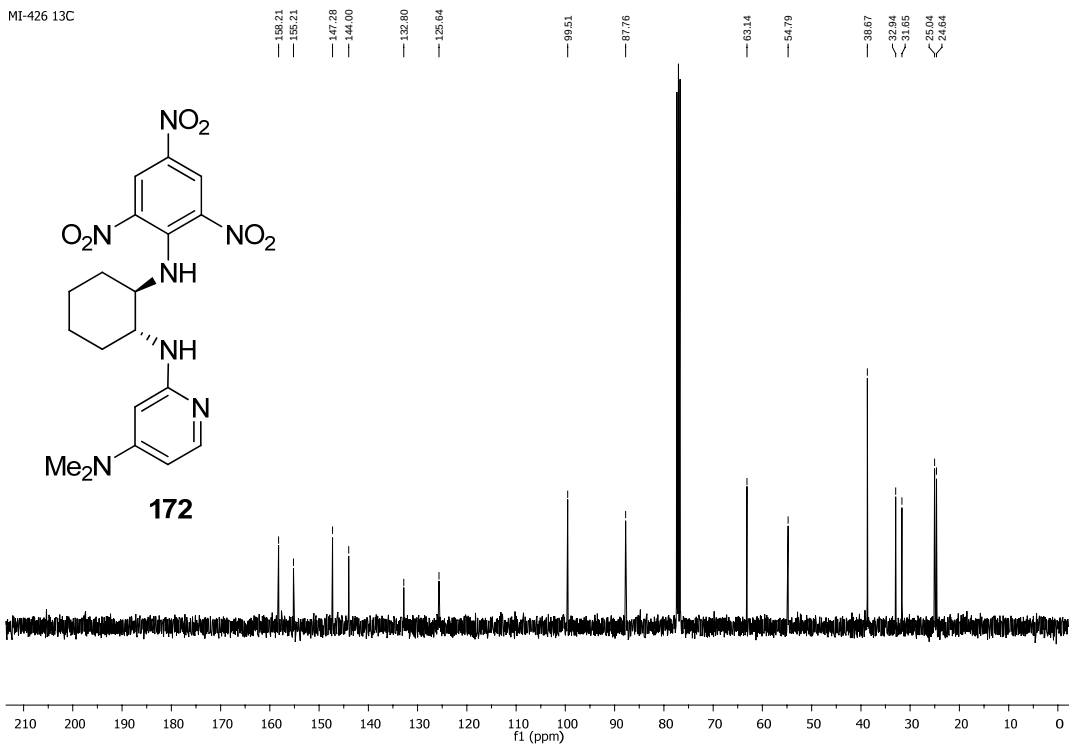

Figure A32. ^{13}C NMR spectrum of **172**

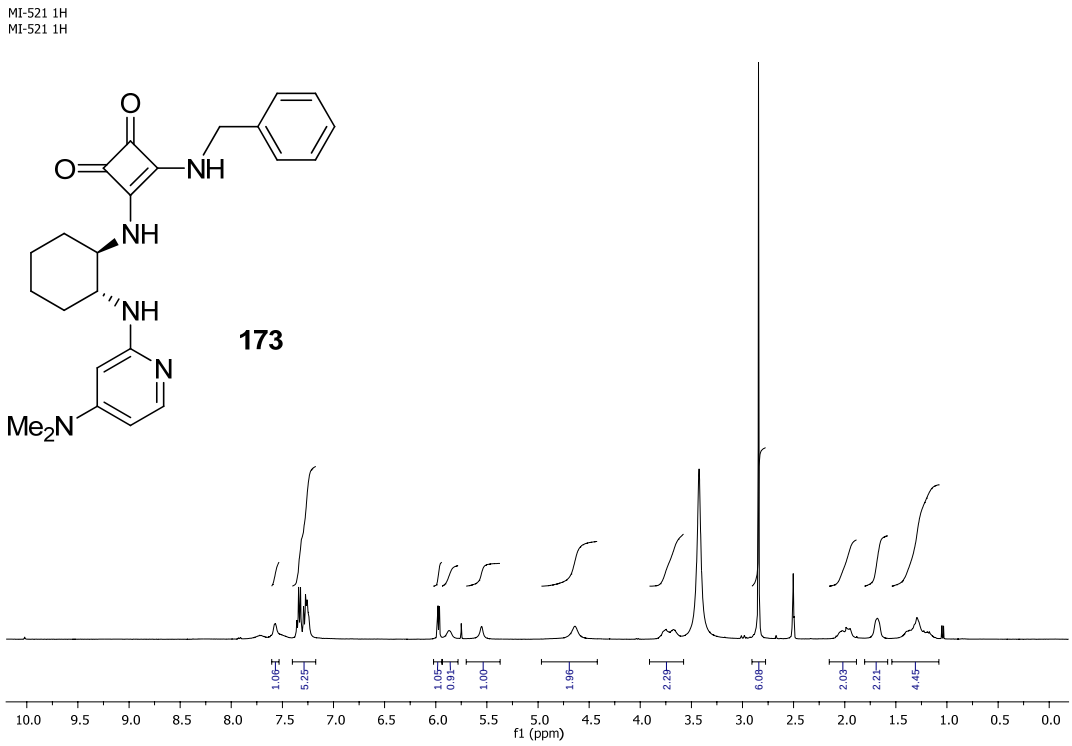

Figure A33. ^{1}H NMR spectrum of **173**

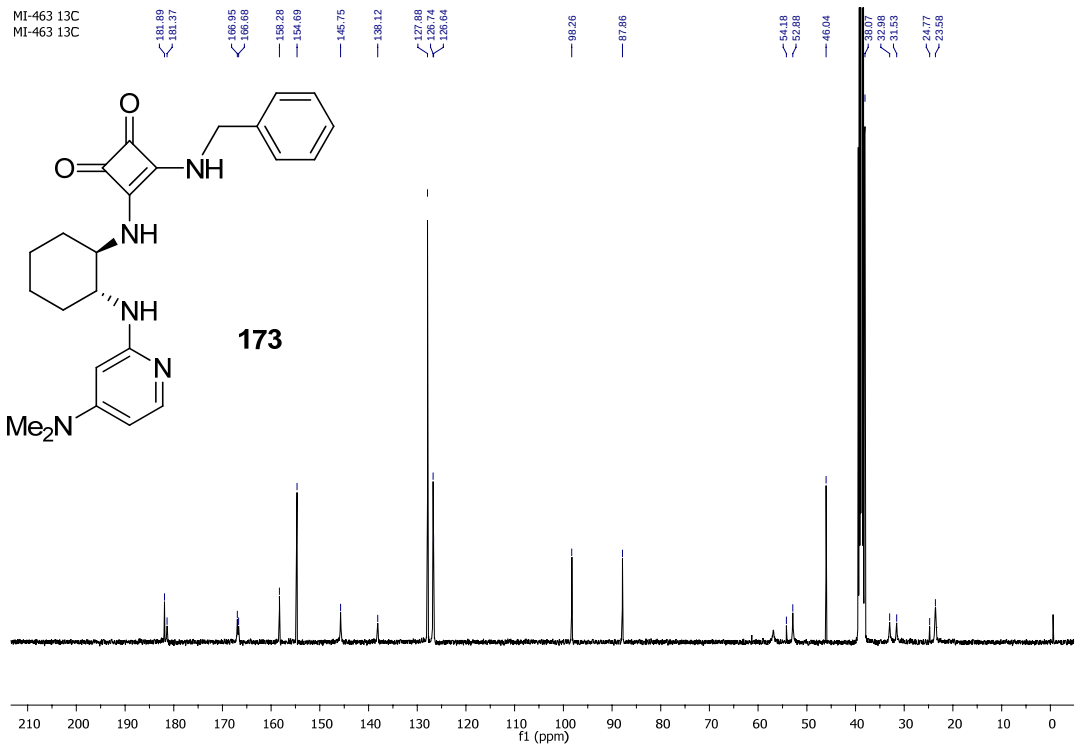

Figure A34. ^{13}C NMR spectrum of **173**

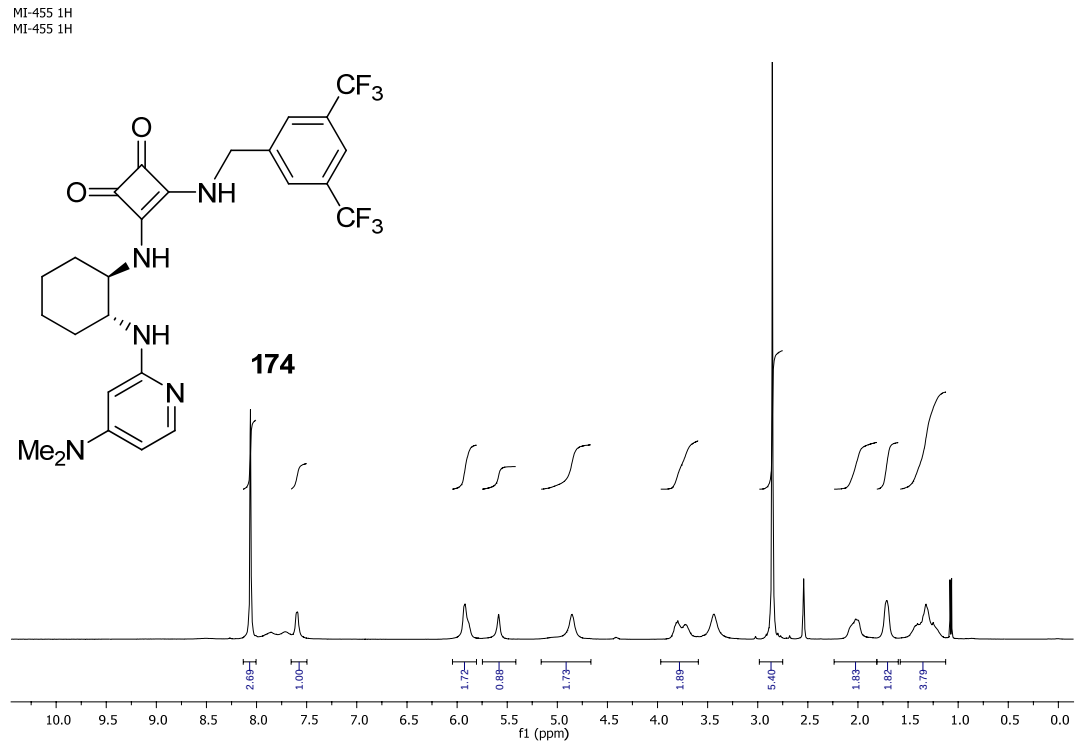

Figure A35. ^{1}H NMR spectrum of **174**

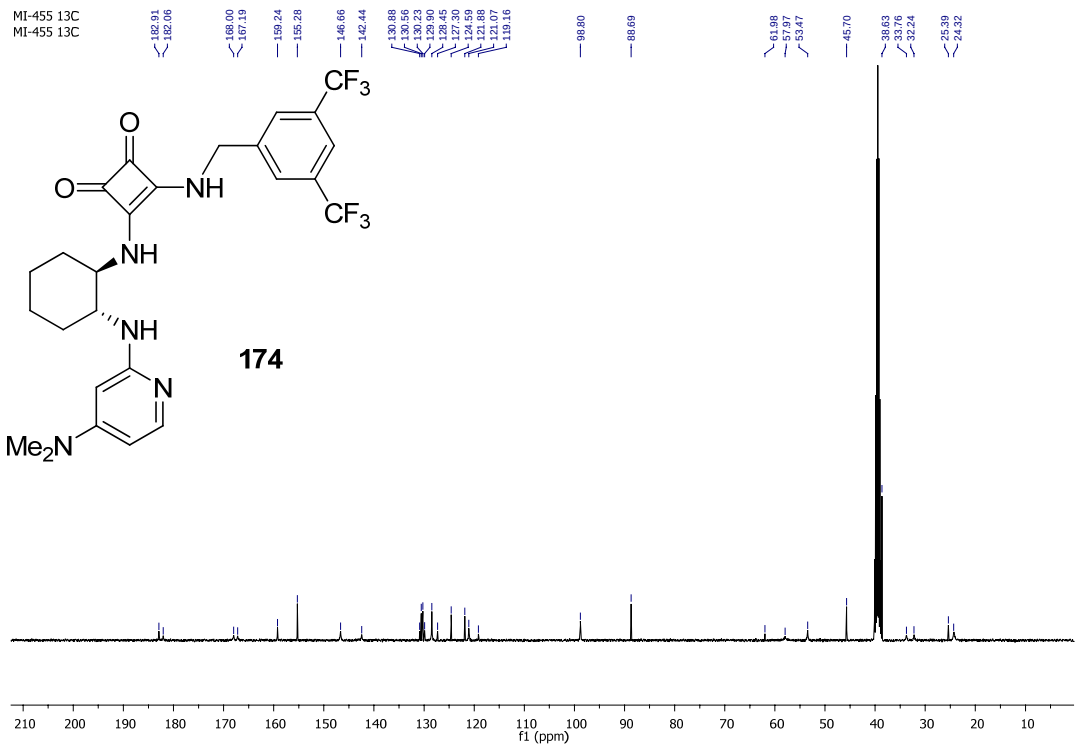

Figure A36. ^{13}C NMR spectrum of **174**

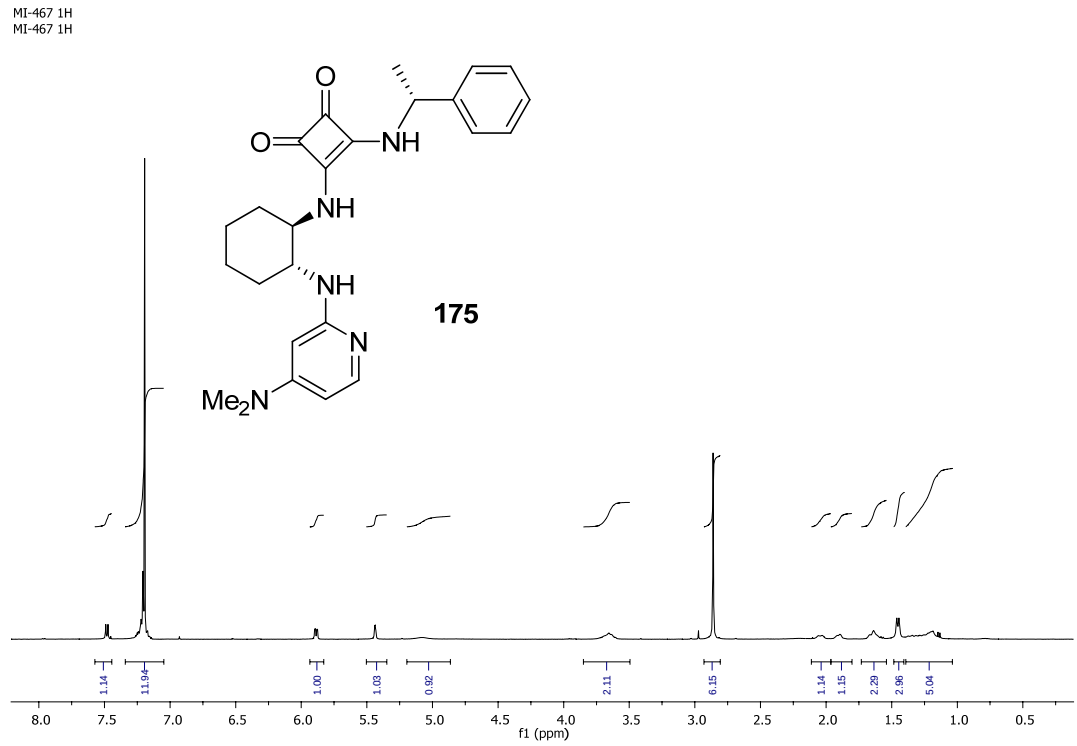

Figure A 37. ^{1}H NMR spectrum of **175**

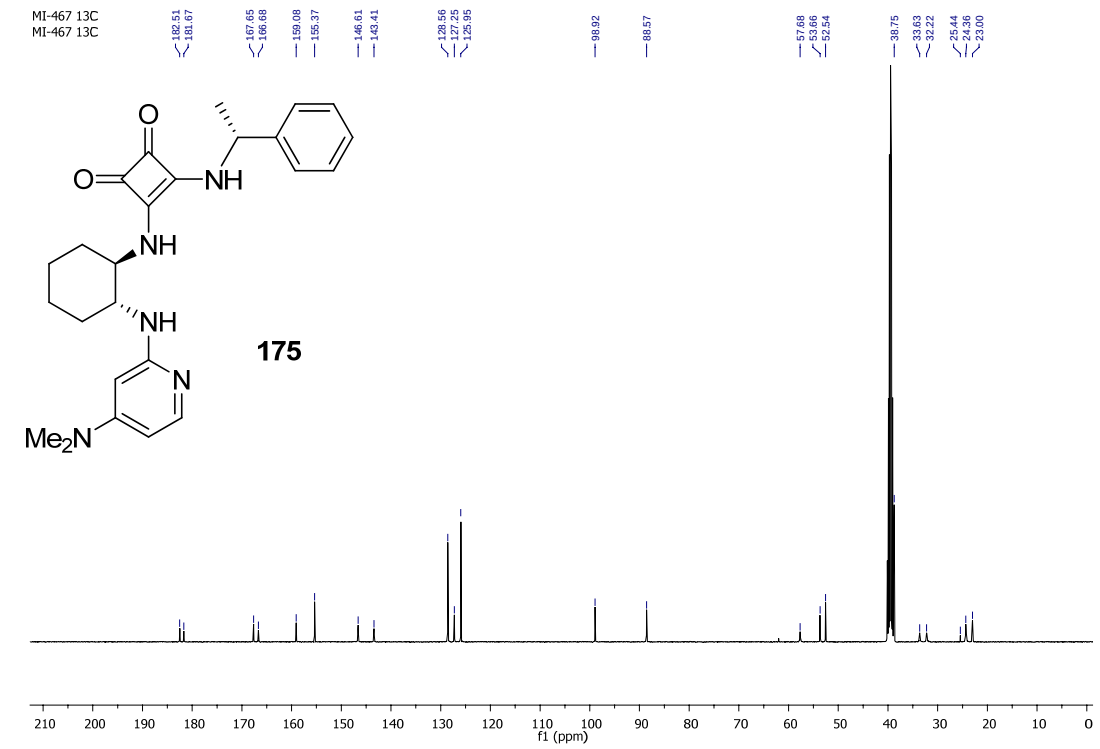

Figure A38. ^{13}C NMR spectrum of **175**

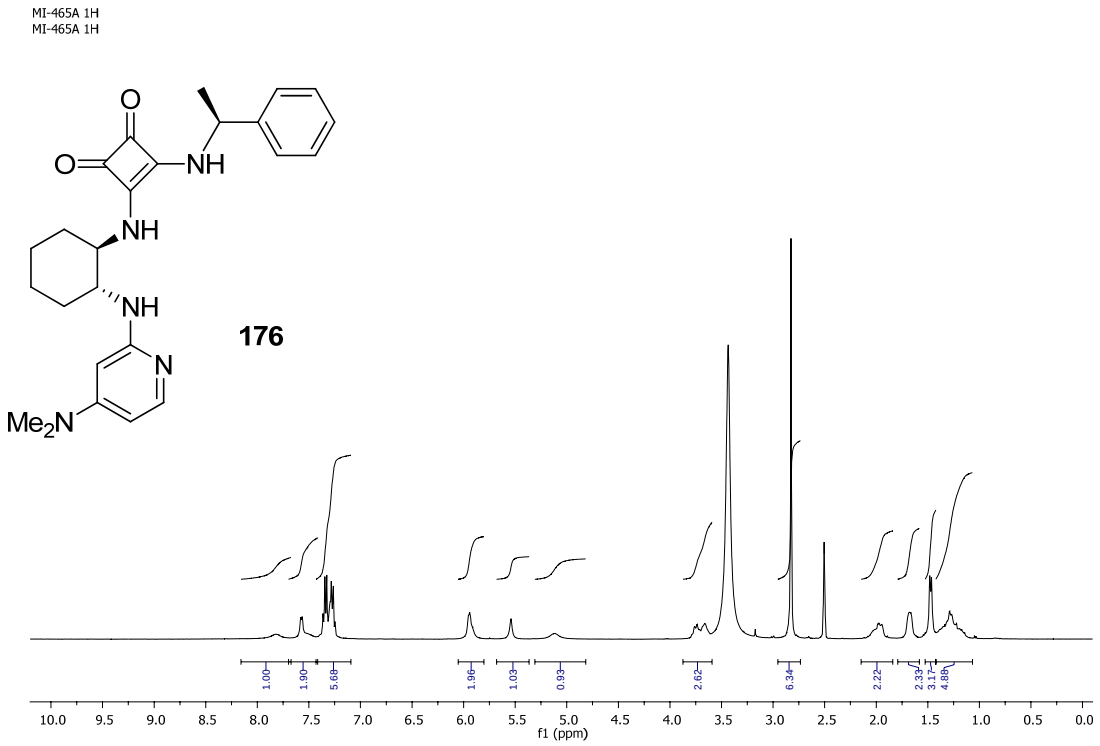

Figure A39. ^{1}H NMR spectrum of **176**

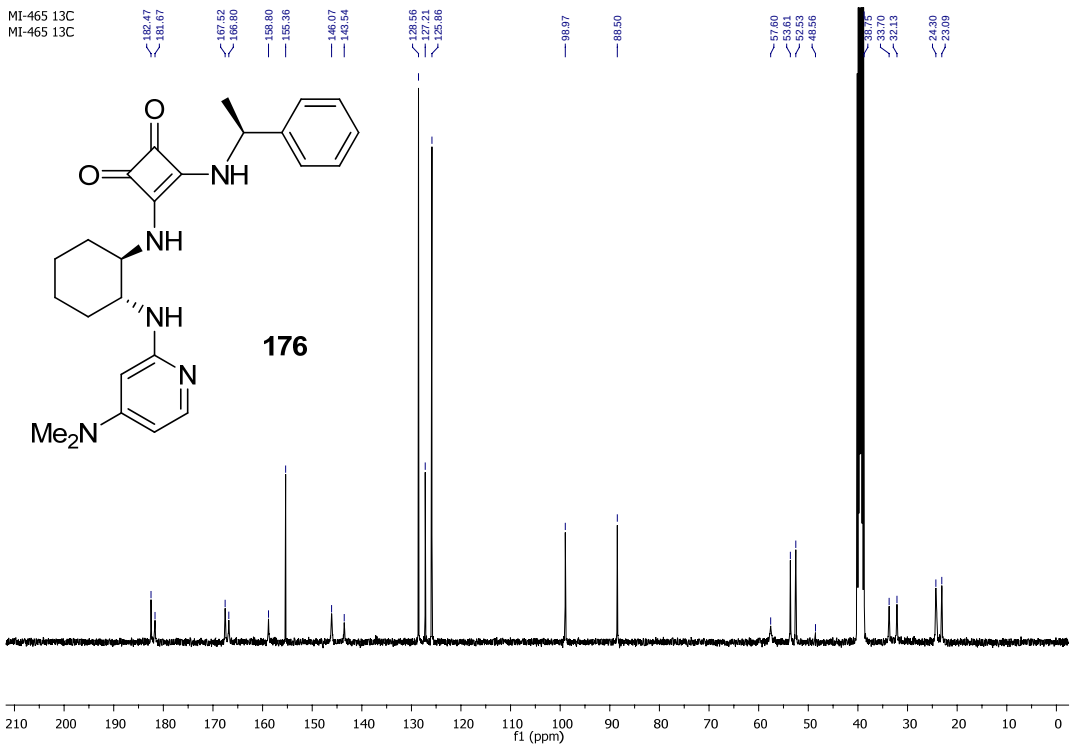

Figure A40. ^{13}C NMR spectrum of **176**

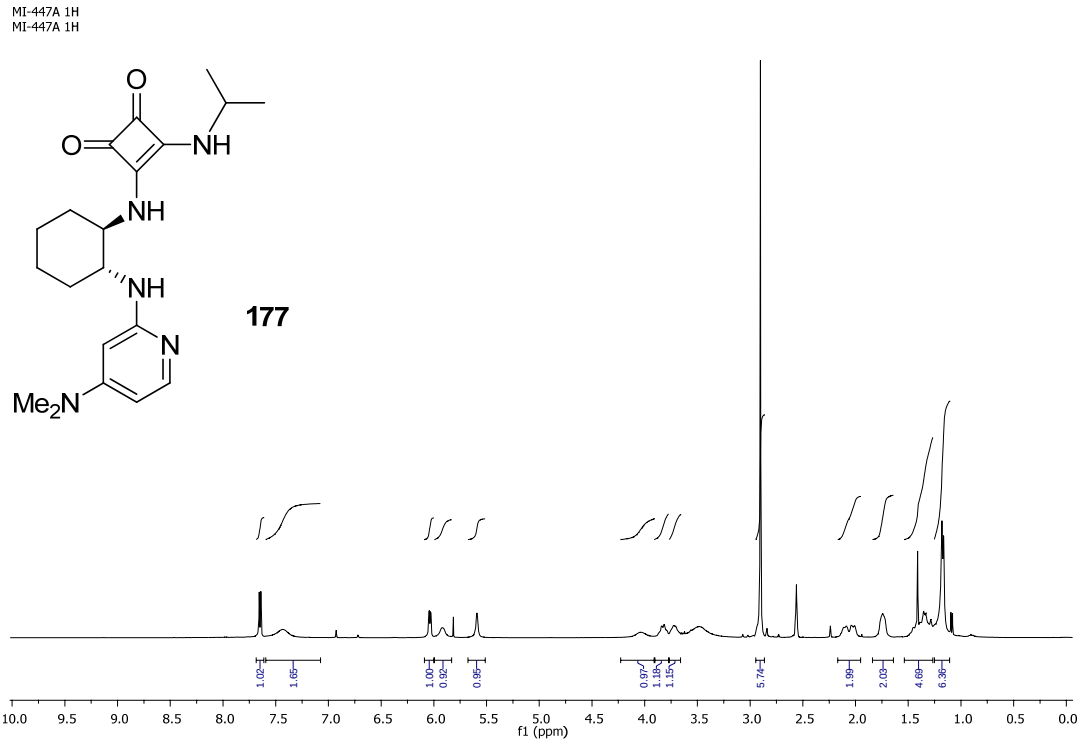

Figure A 41. ^{1}H NMR spectrum of **177**

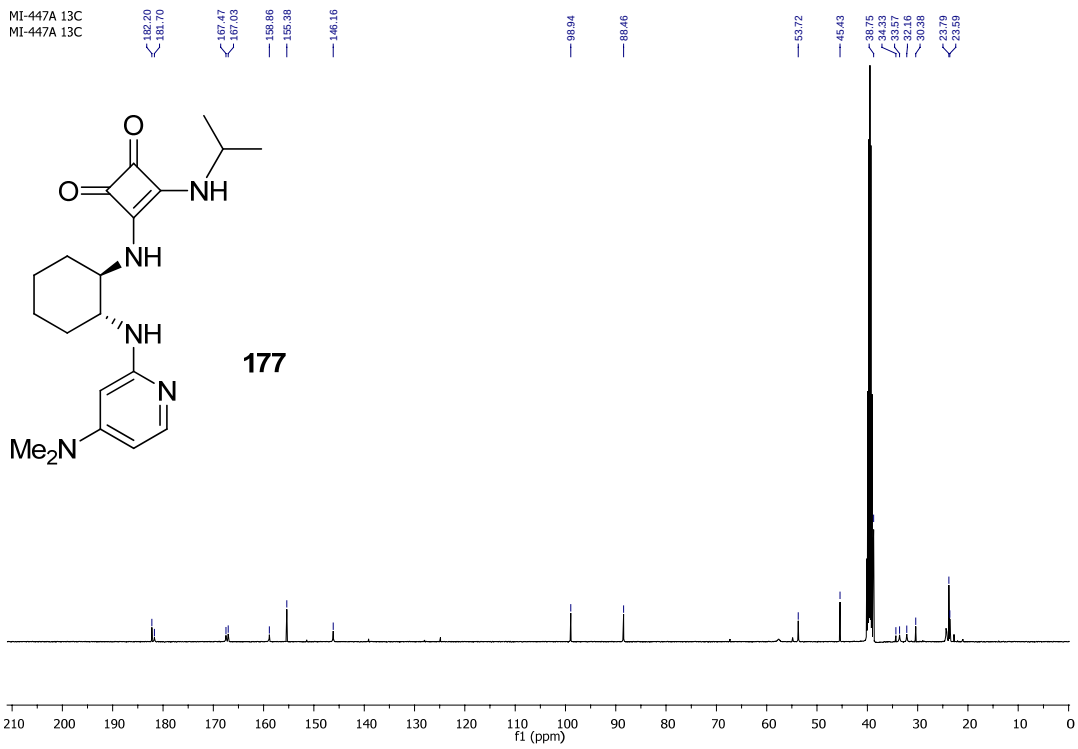

Figure A 42. ^{13}C NMR spectrum of **177**

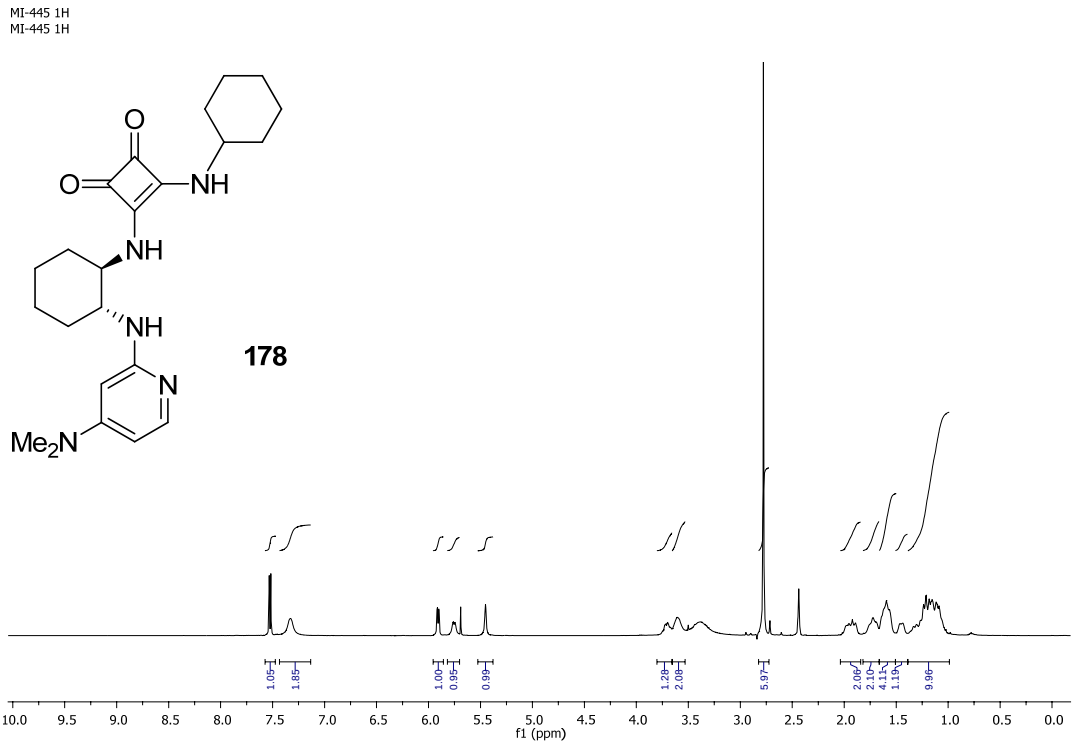

Figure A 43. ^{1}H NMR spectrum of **178**

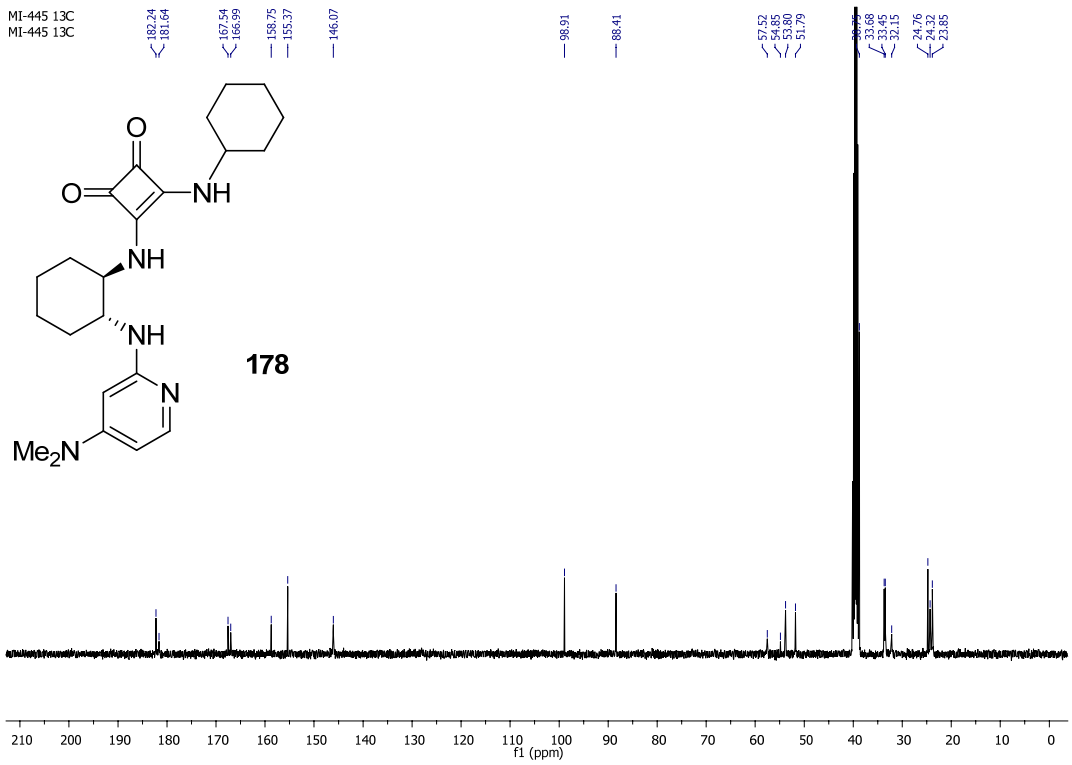

Figure A 44. ^{13}C NMR spectrum of **178**

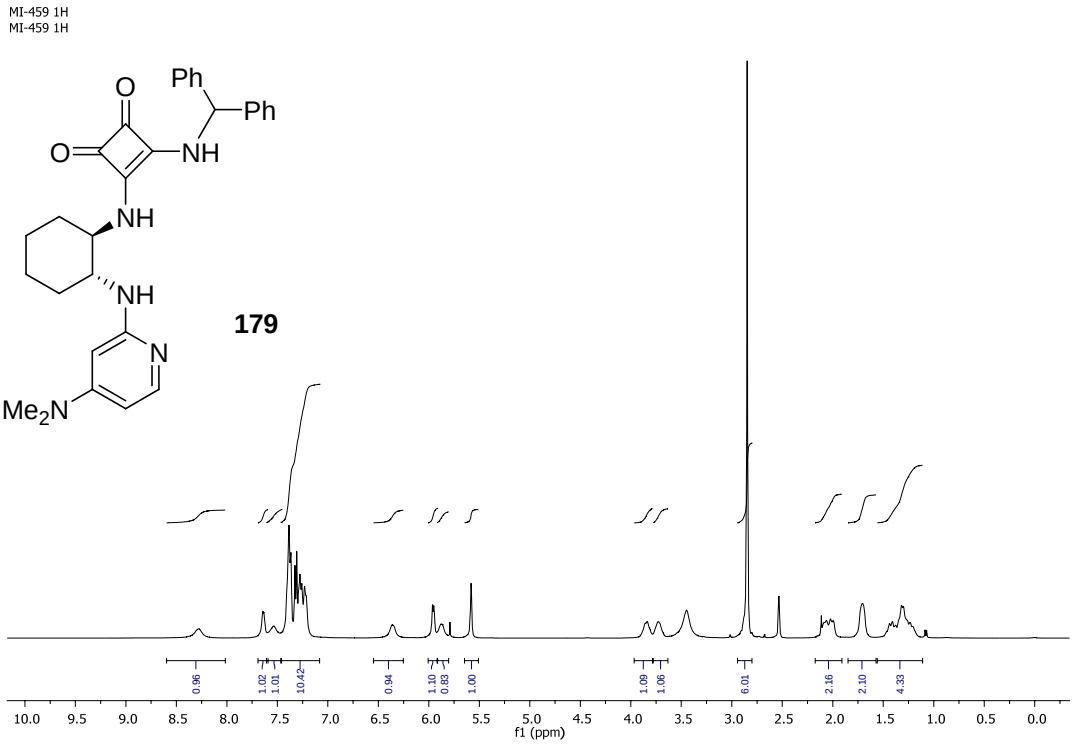

Figure A 45. ^{1}H NMR spectrum of **179**

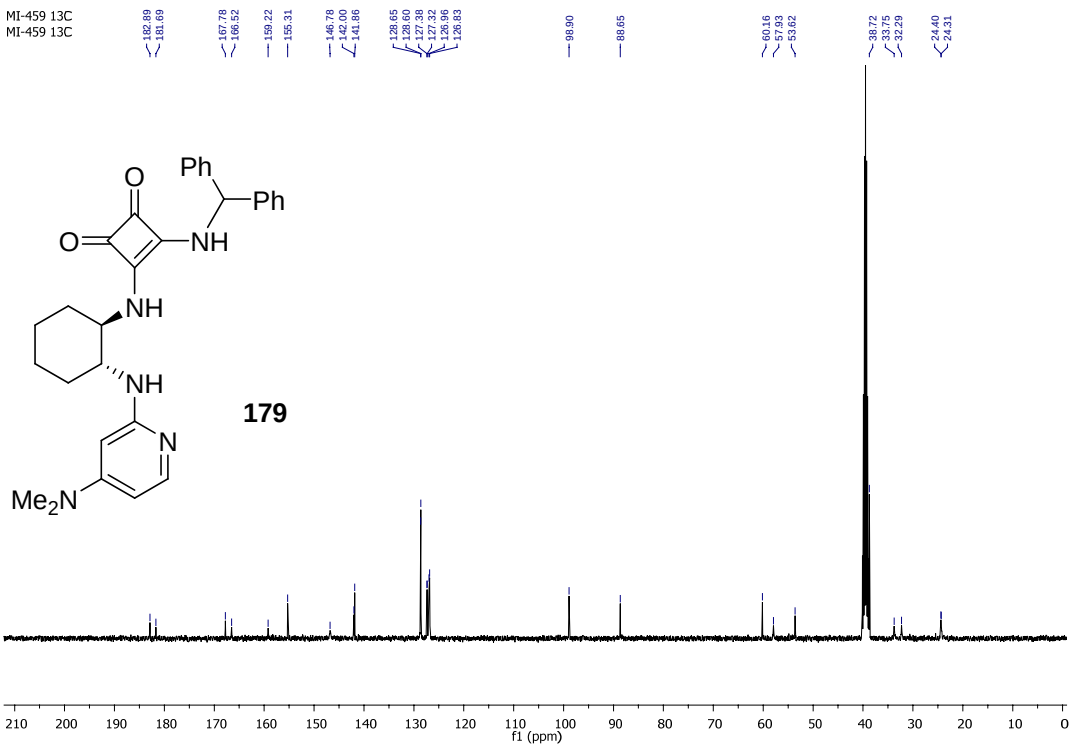

Figure A 46. ^{13}C NMR spectrum of **179**

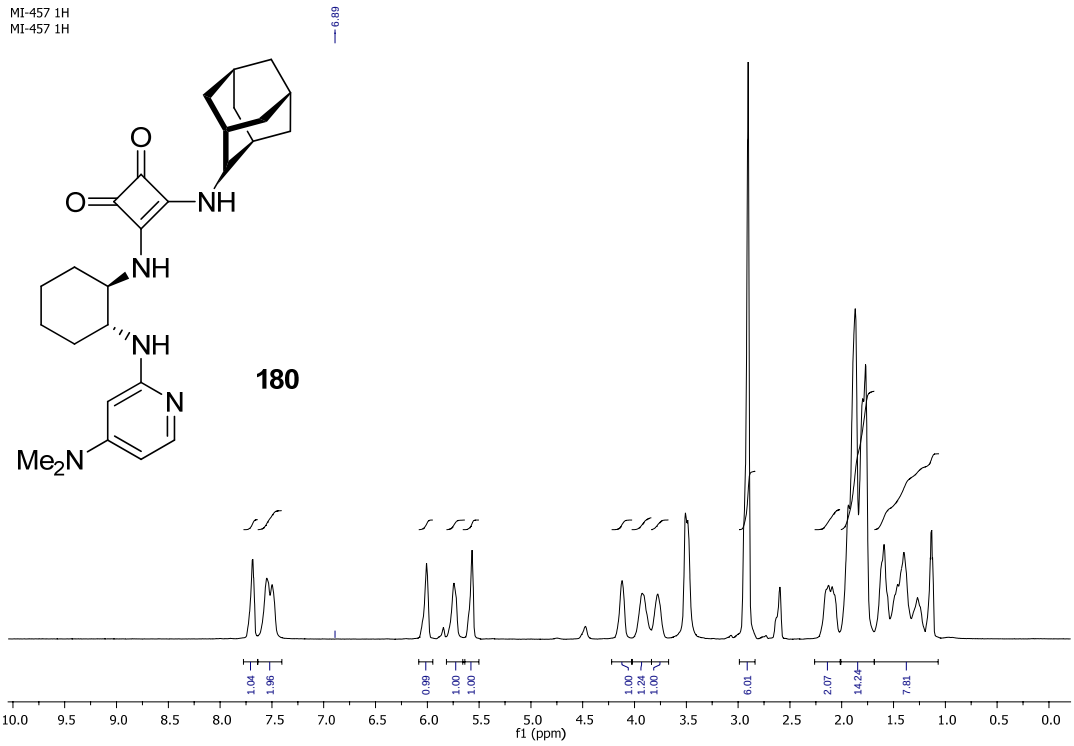

Figure A 47. ^{1}H NMR spectrum of **180**

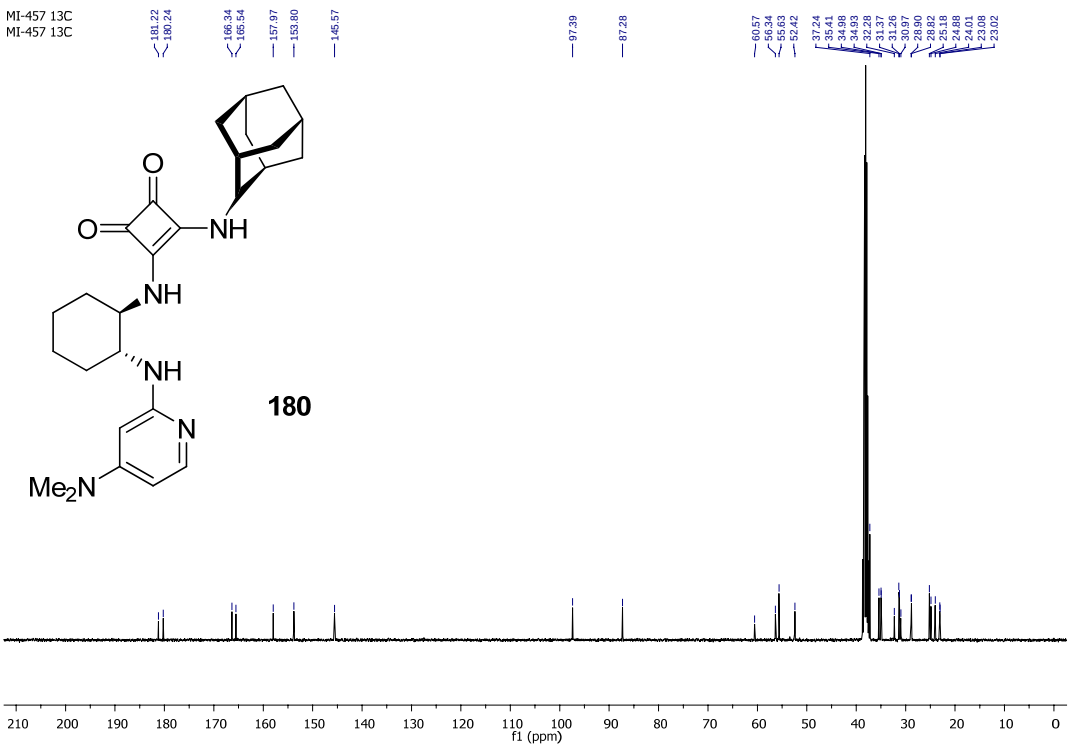

Figure A 48. ^{13}C NMR spectrum of **180**

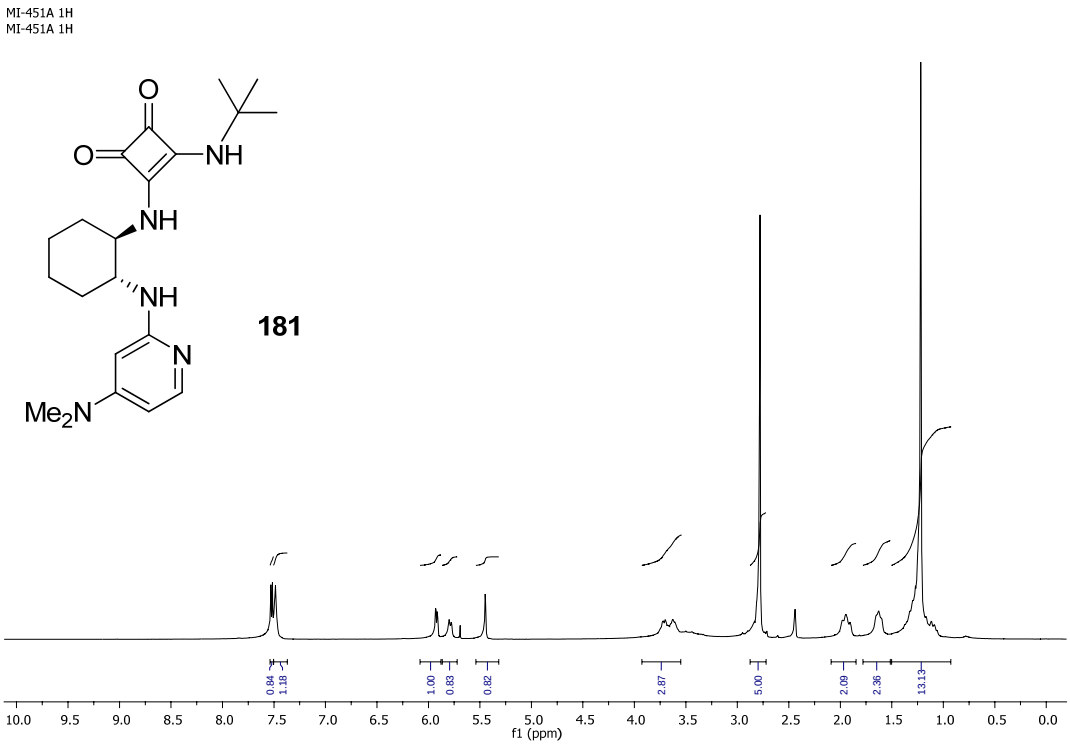

Figure A 49. ^{1}H NMR spectrum of **181**

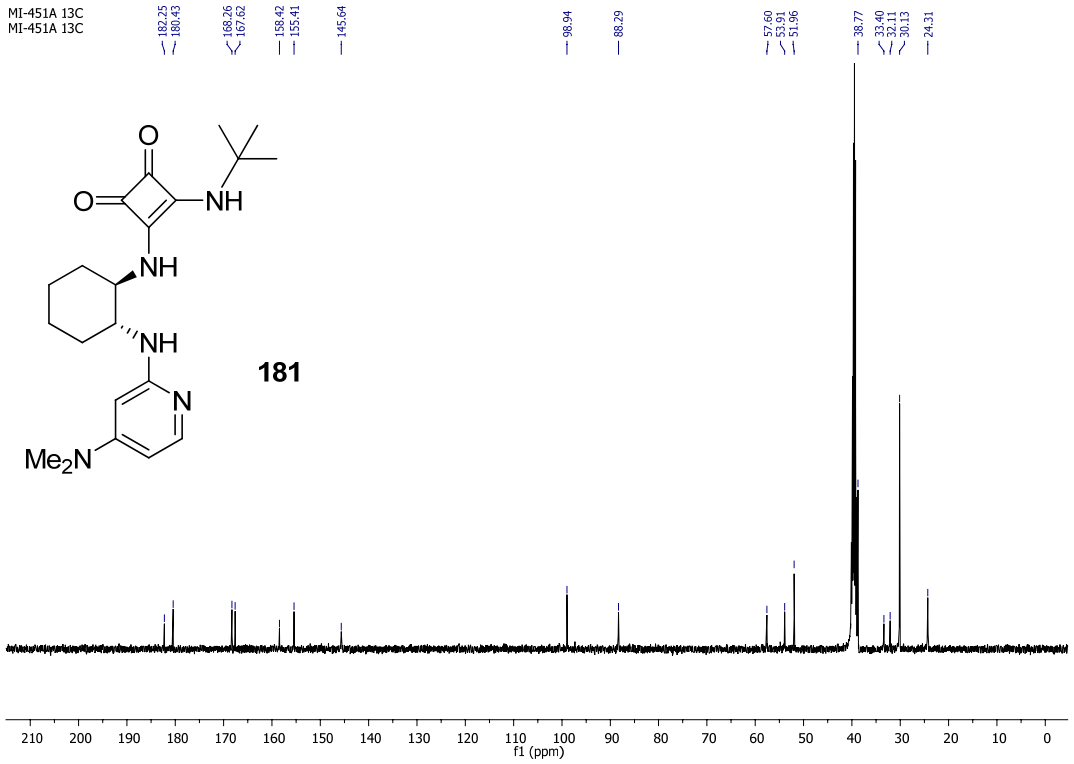

Figure A 50. ^{13}C NMR spectrum of **181**

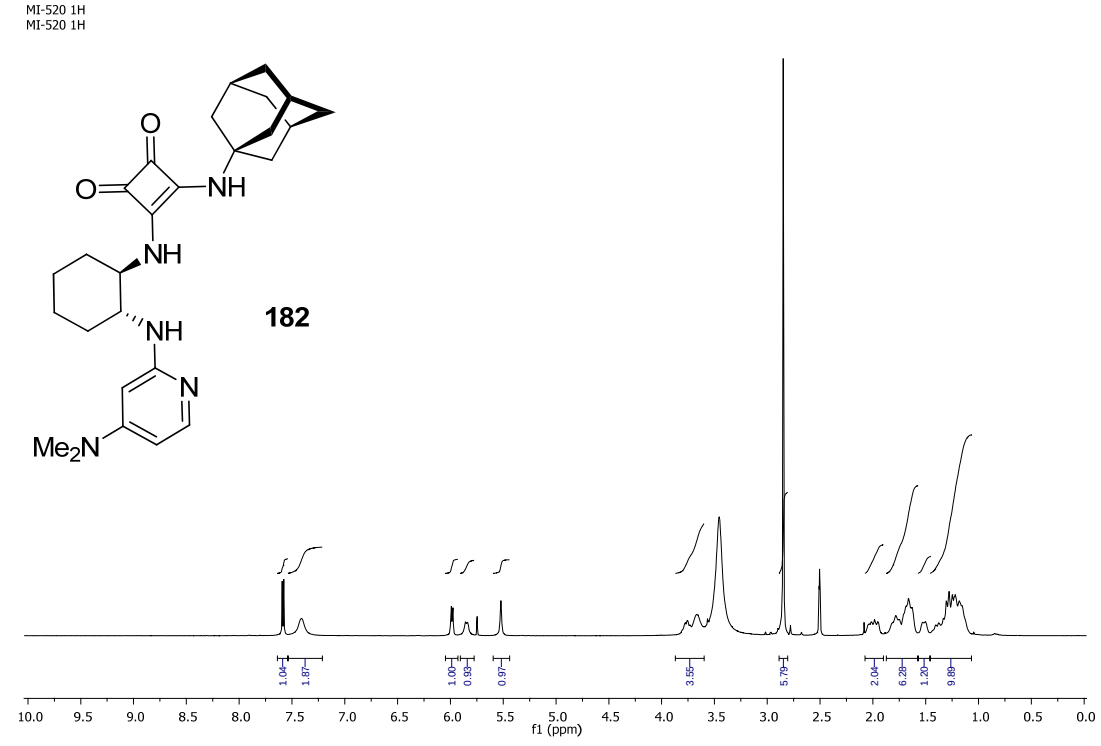

Figure A 51. ^{1}H NMR spectrum of **182**

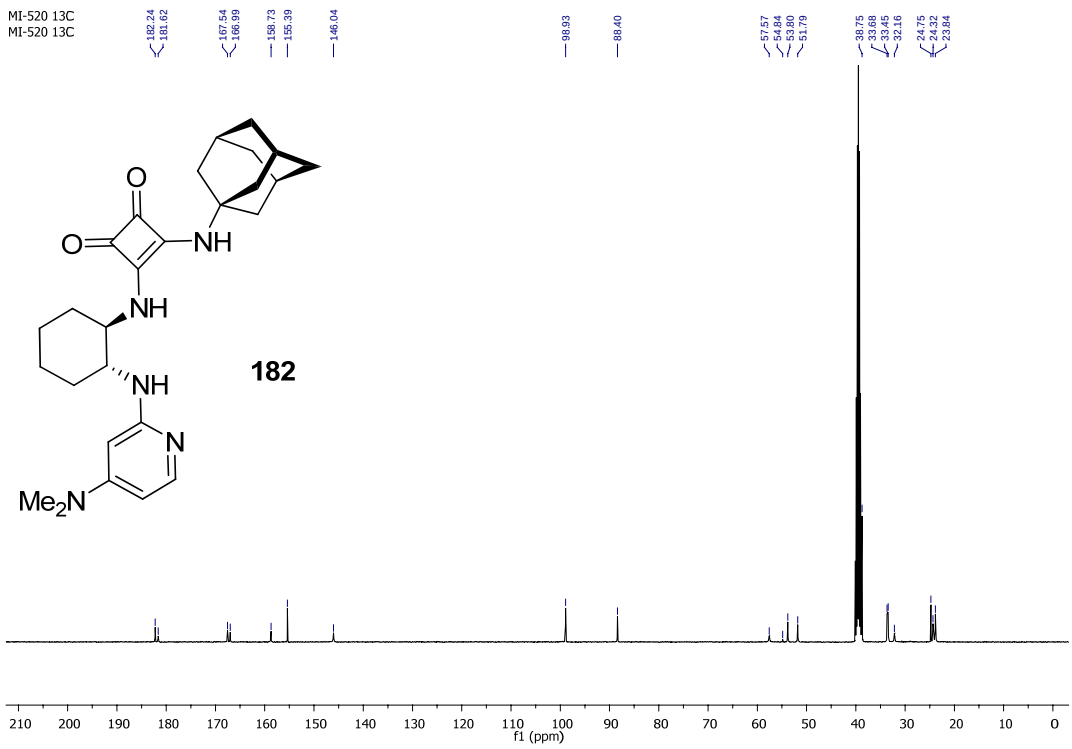

Figure A 52. ^{13}C NMR spectrum of **182**

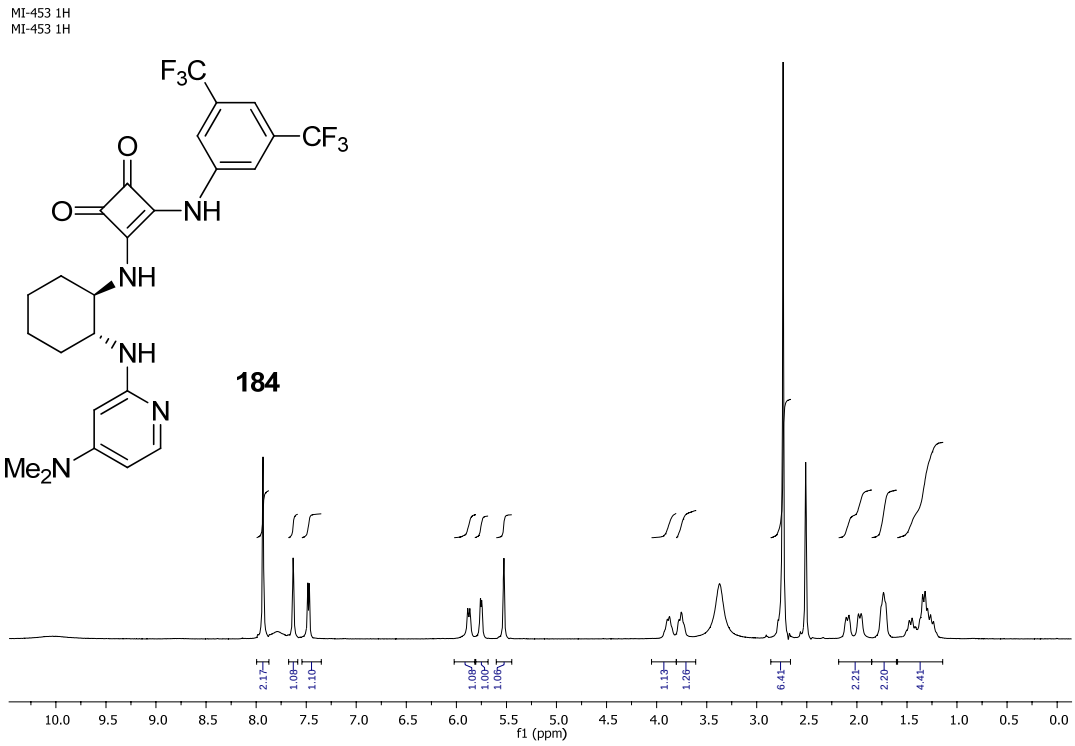

Figure A 53. ^{1}H NMR spectrum of **184**

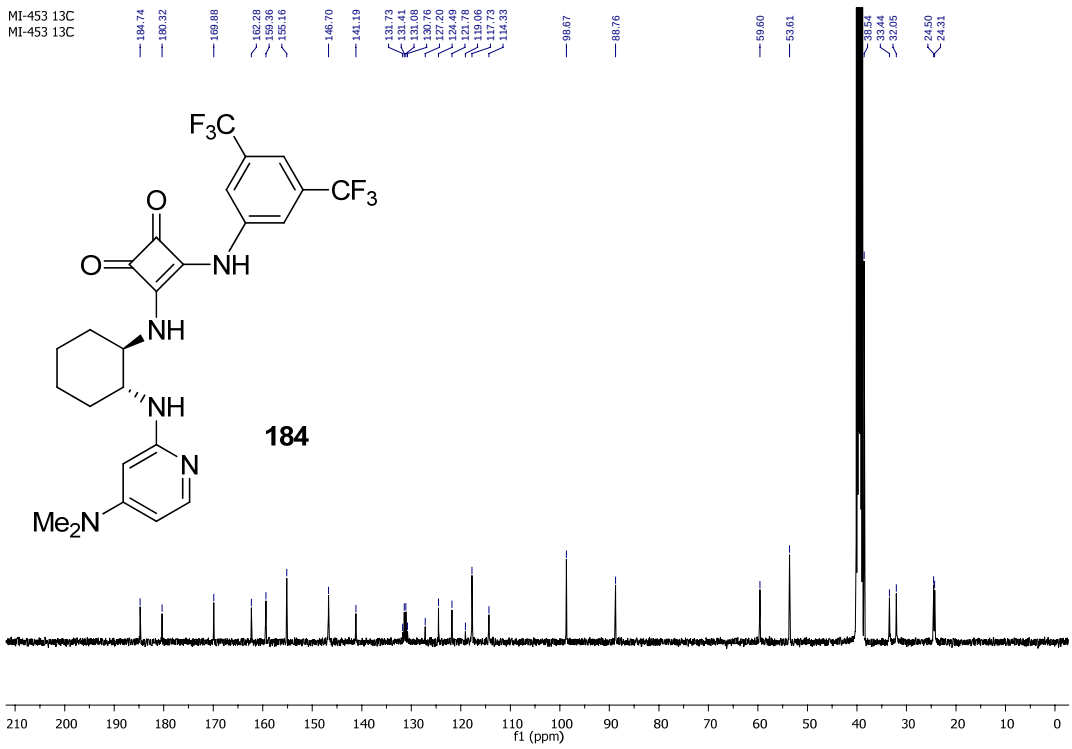

Figure A 54. ^{13}C NMR spectrum of **184**

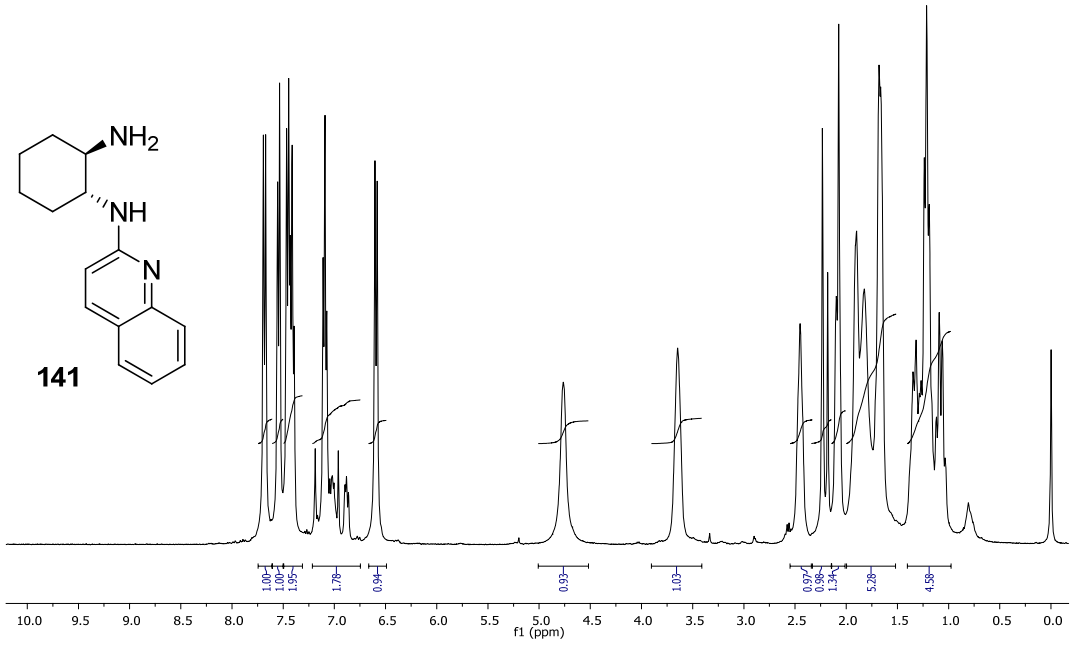

Figure A 55. ^{1}H NMR spectrum of **141**

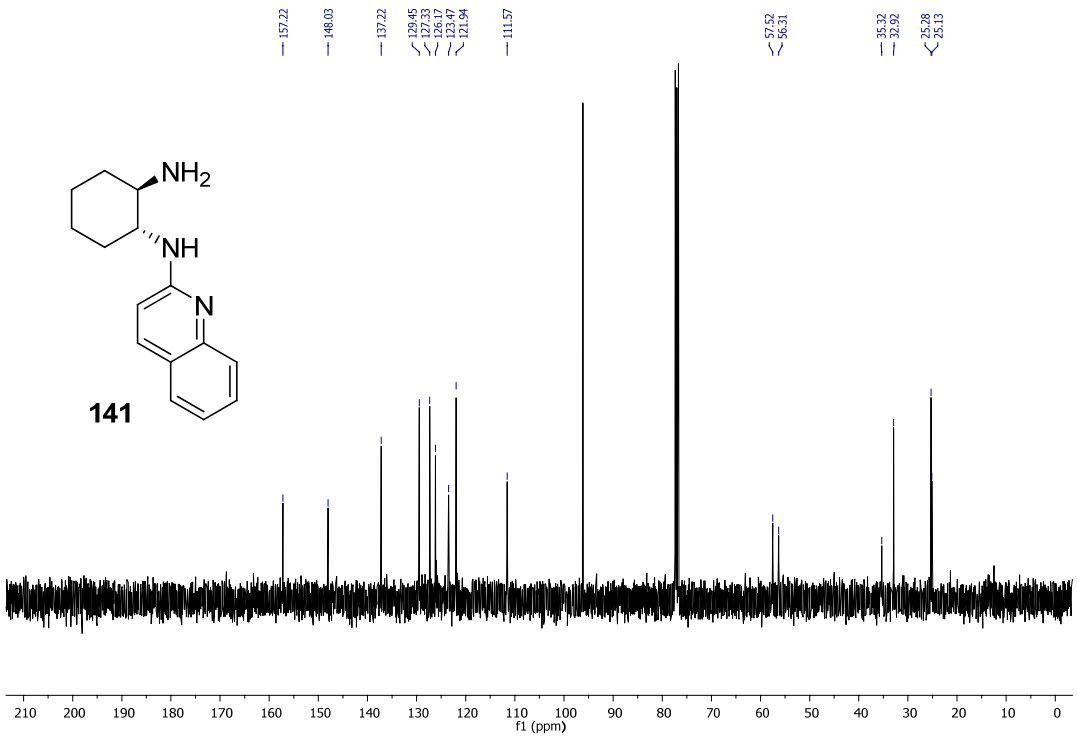

Figure A 56. ^{13}C NMR spectrum of **141**

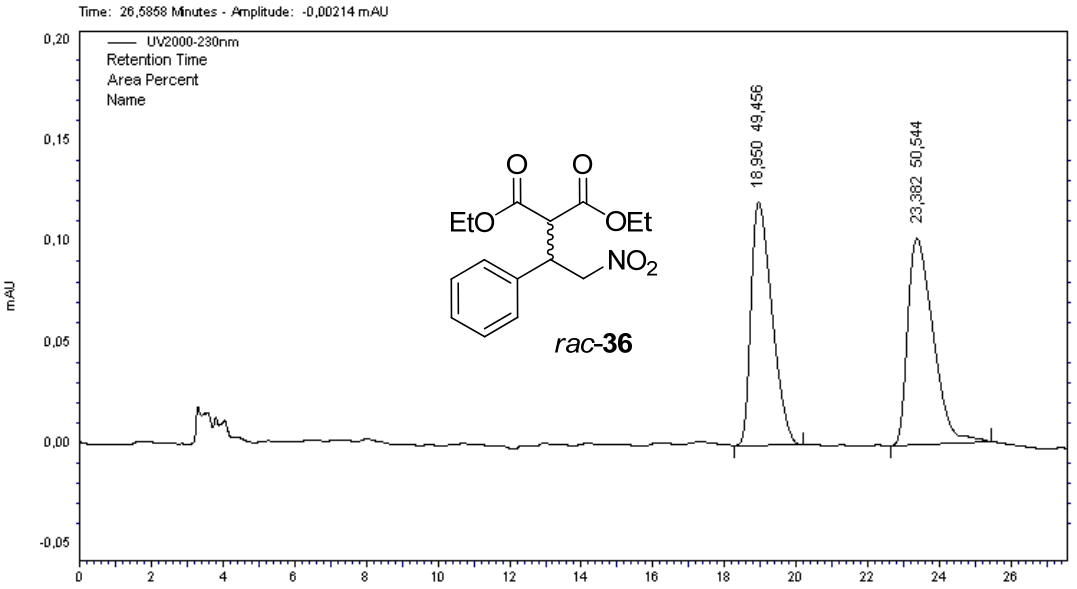

Figure A 57. HPLC chromatogram of *rac*-**36**

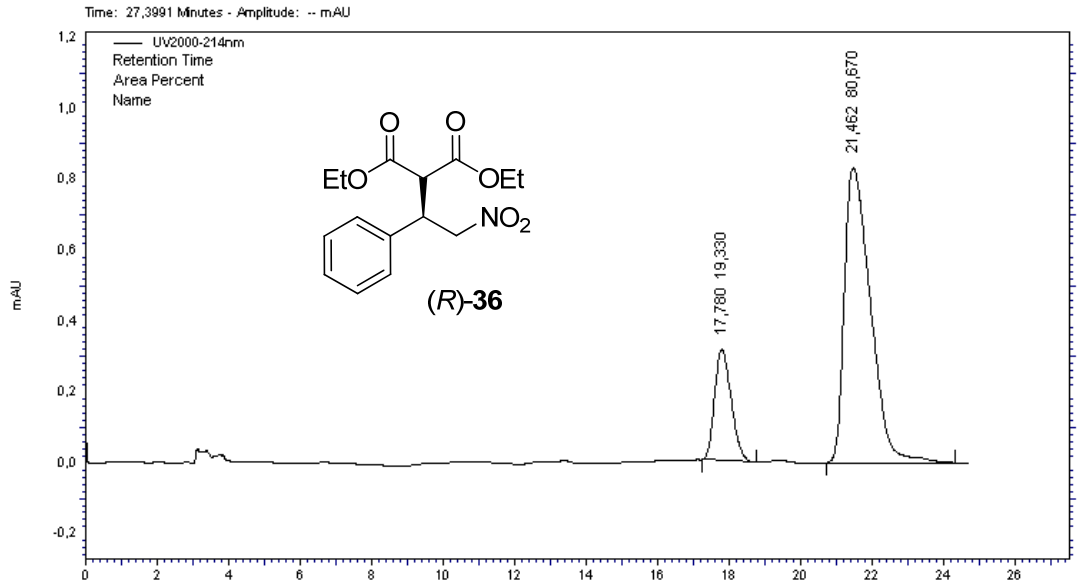

Figure A 58. HPLC chromatogram of enantioenriched **36**

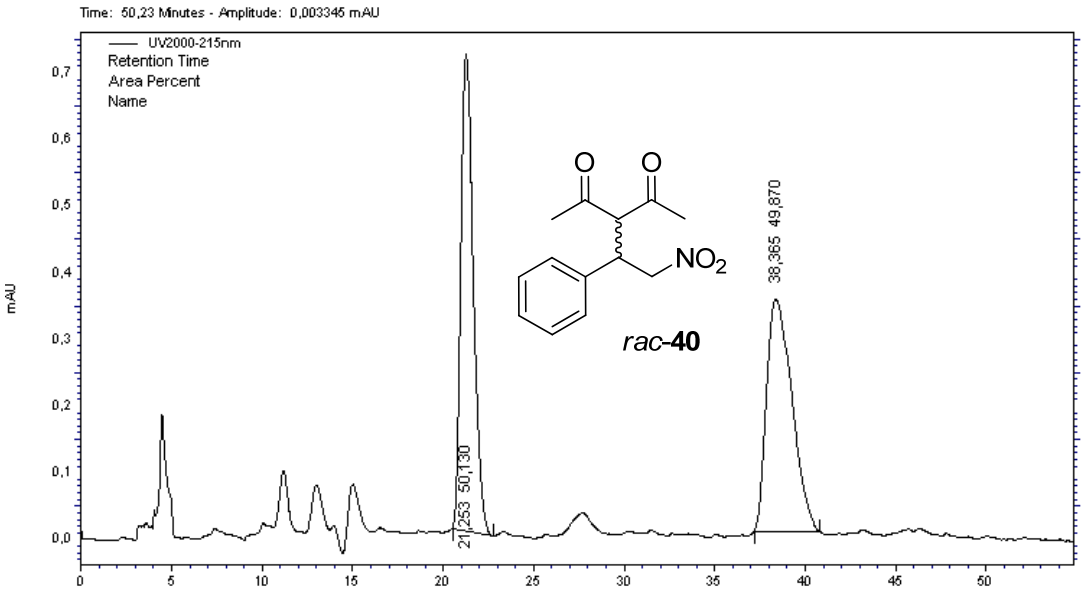

Figure A 59. HPLC chromatogram of *rac*-**40**.

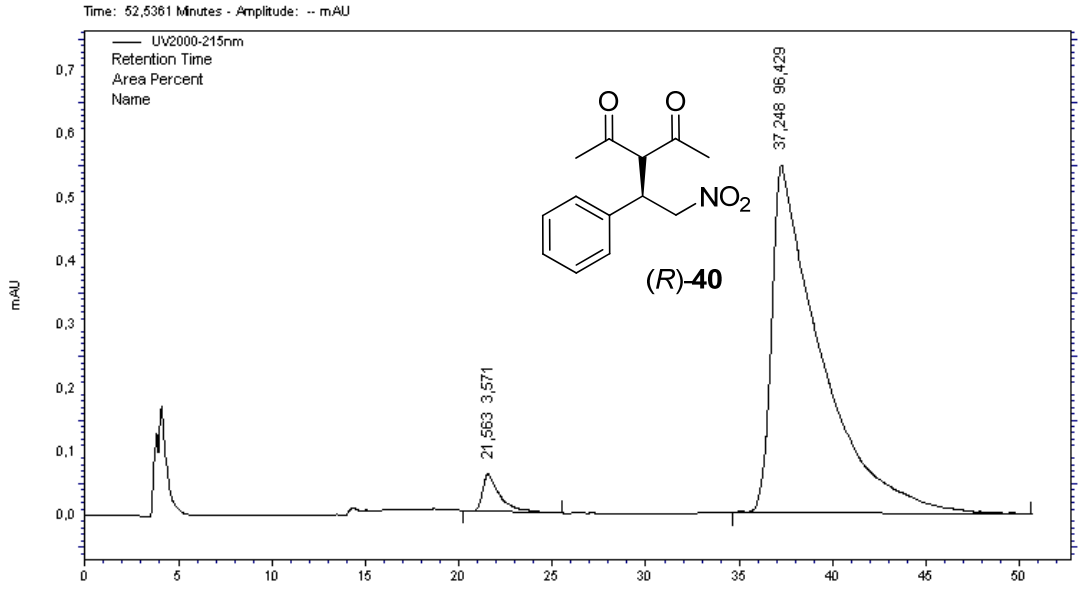

Figure A 60. HPLC chromatogram of enantioenriched **40**

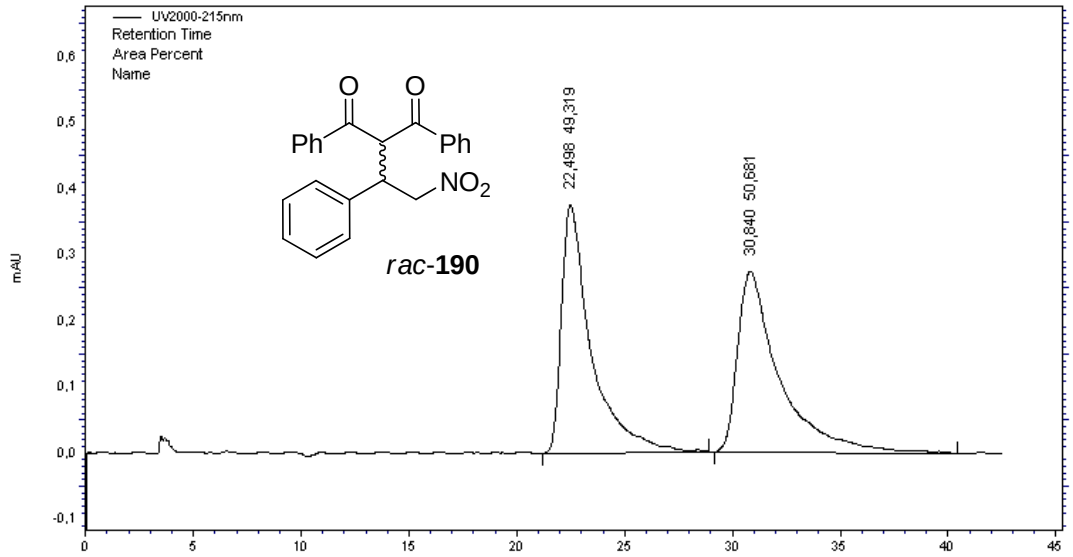

Figure A 61. HPLC chromatogram of *rac*-**190**

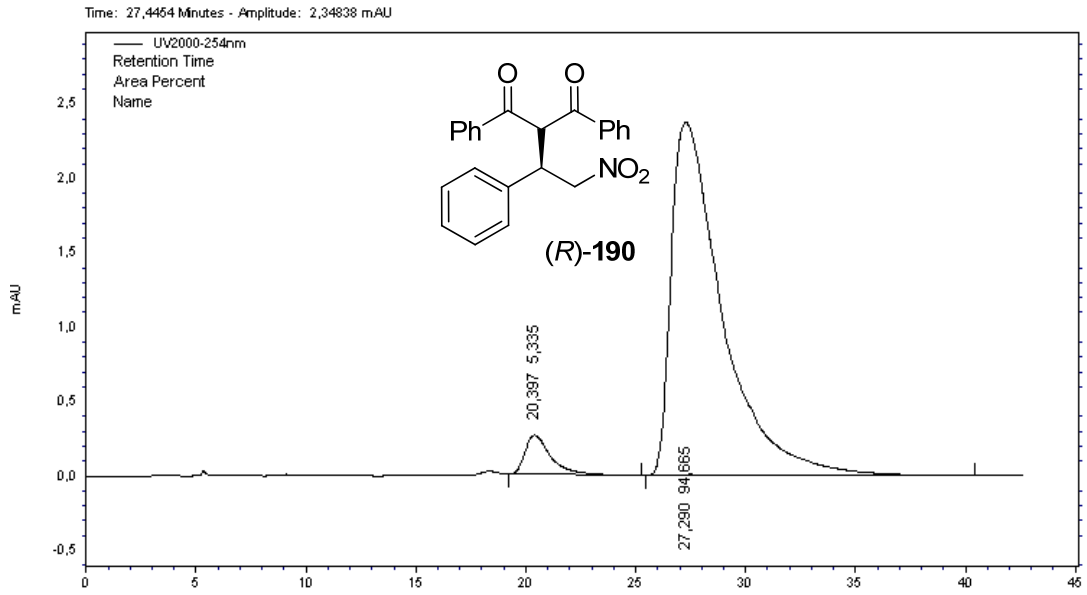

Figure A 62. HPLC chromatogram of enantioenriched **190**