Synthesis and exploration of chiral aza-bis(oxazolines) and organocatalysts in asymmetric reactions

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Ramesh Rasappan

Aus
Pandamangalam (Indien)

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Prüfungsausschluß:	Prof. Dr. S. Elz	(Vorsitzender)
	Prof. Dr. O. Reiser	(1. Gutachter)
	Prof. Dr. F. E. Kühn	(2. Gutachter)
	Prof. Dr. B. König	(3. Prüfer)

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for my Parents
& sister

"The setting sun
asked who will
light this
world after me"
"A little lamp
said I WILL
DO MY
PART"

Abbreviations

Abs	absolute
AIBN	azo-isobutyronitrile
BOC	*tert*-butoxycarbonyl
Bn	benzyl
Bu	*n*-butyl
BuLi	*n*-butyl lithium
Bu_3P	tri-*n*-butyl phosphine
Bz	benzoyl
CAN	ceric ammonium nitrate
cat	catalytic
dr	diastereomeric ratio
DBU	1,8-Diazabicyclo[4.4.0] undec-7-ene
DCE	dichloroethane
DEAD	diethylazodicarboxylate
DMAP	*N,N*-dimethylamino pyridine
DMF	dimethyl formamide
DMS	dimethyl sulfide
ee	enantiomeric excess
eq	equivalents
EI	electronic ionization
epi	epimer
Et	ethyl
EWG	electron withdrawing group
Glc	glucose
h	hour
HAT	histone-acetyl-transferase
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectrometry
^{i}Pr	*iso*-propyl
IR	infrared
L	ligand
LAH	lithium aluminium hydride
LDA	lithiumdiisopropylamide
LiHMDS	lithium hexamethyldisilazide
M	metal
*m*CPBA	*m*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
Mes	mesyl
min	minute
MS	molecular sieves
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
NMO	*N*-methylmorpholin-*N*-oxide
NOE	nuclear overhauser effect
Nu	nucleophile
p-	para
PCC	pyridinium chlorochromate
Ph	phenyl
PPh_3	tri-phenyl phosphine
PMB	*p*-methoxy-benzyl
pyr	pyridine
quant	quantitative
RCM	ring closing metathesis
rt	room temperature
sat.	saturated
t/(*tert*)	tertiary
TBME	*tert*-butyl-methyl-ether
TBDMS	*tert*-butyldimethylsily
TBAF	tetrabutylammonium fluoride
Tf	trifluormethanesulfonate
^{t}Bu	*tert*-butyl
TES	triethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Tf	trifluormethanesulfonate
Ts	tosyl
X	halogens

1 Introduction

1.1 Catalysis

Organic synthesis is a science and art brought by chemists for the chemical construction (reaction) of carbon containing molecules; being naturally abundant or biologically active. Many chemical reactions are known to be thermodynamically favorable, yet occur at extremely slow rates at room temperature. A dramatic increase in the rate of these reactions can be achieved by the presence of catalysts, this phenomenon is called "catalysis" being defined as "A substance that increases the rate of a reaction without modifying the overall standard Gibbs energy change in the reaction".[1] Catalysts can even activate the reactions that may not have negative free energies of reaction.[2] Figure 1 depicts the free energy diagram for the catalyzed (dashed line) and uncatalyzed (solid line) reaction coordinate. In general uncatalyzed reactions require higher activation energy (ΔG) than catalyzed reactions (ΔG*). The different transition states TS_{C1-3} for the catalyzed reaction represents the coordination or absorption of substrates to the catalyst (TS_{C1}), progress of the reaction (TS_{C2}), and dissociation of the products from the catalyst (TS_{C3}) (Figure 1 and 2).

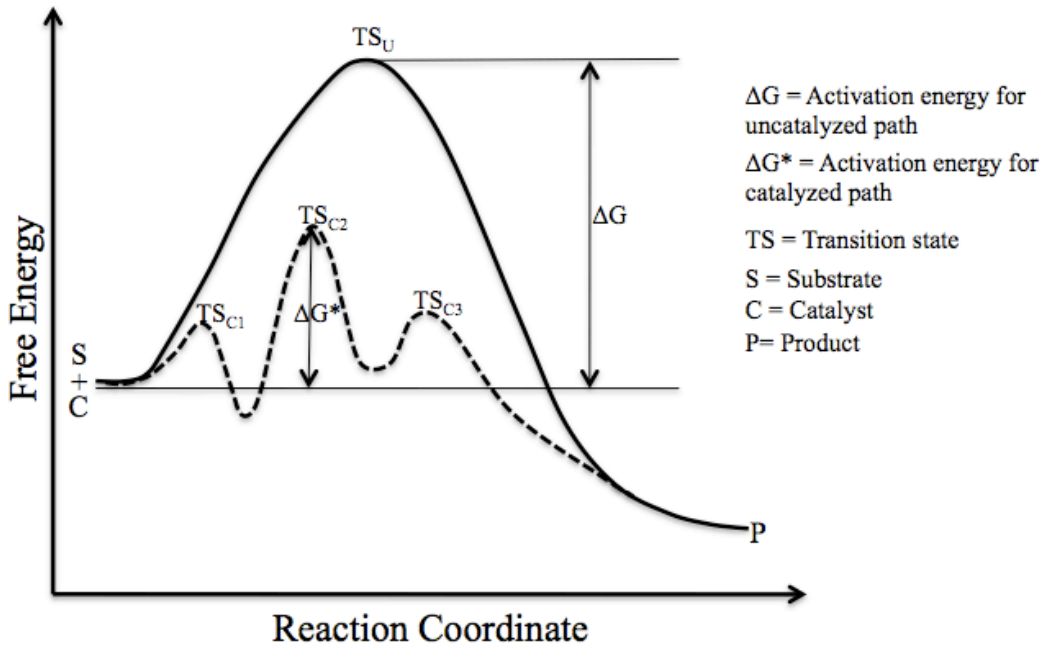


Figure 1. A schematic diagram showing the free energy profile of the course of a catalyzed and uncatalyzed reaction

1.2 Historical development

1.2.1 History of catalysis

It is well known that catalyses were first discovered in the beginning of 19-th century, and several scientists are acknowledged as pioneers in this area including Thénard (1813; NH_3 and H_2O_2 decomposition),[3] Kirchhoff (1814; hydrolysis of starch by acid),[3] Davy (1817; incandescence of platinum wire over coal gas and air in miner's safety lamp)[3] and Faraday (1834; reaction between H_2 and O_2 over platinum)[3] (Figure 1). In 1835, the Swedish scientist Berzelius coined[4] the word "catalytic power" as "*the substances are able to awake affinities that are asleep at this temperature by their mere presence"* later in 1902, Ostwald defined[4] a catalyst as *"a substance that increases the rate at which a chemical system approaches equilibrium, without being consumed in the process."*

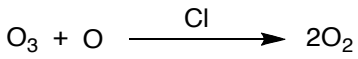
Tremendous advances have been made in the development of catalysis since the industrial revolution started early in the last century including the ammonia process (Haber-Bosch process, first industrial catalytic process, BASF 1904), hydroformylation (1938), olefin polymerization (1953), and acetaldehyde synthesis (1959).[5] Consequently, the chemical industry is largely based upon catalysis: Roughly 85–90% of all products are made in catalytic processes, and the percentage is increasing steadily.[6]

1.2.2 Catalysis and organometallic chemistry

Since then, catalysis became an interdisciplinary science and organometallic chemistry has been one of the fruitful areas to develop in this field. There were numerous organometallic compounds developed and some notable achievements were made; Discovery of Grignard reagents in 1898 (1913, Nobel laureate),[7, 8] activation of H_2 by a transition metal complex in the late 1930's (Calvin, 1961 Nobel laureate);[9, 10] sandwich compound ferrocene in 1951, homogeneous hydrogenation of olefinic substrates with $RuCl_3$ in 1961 (Halpern, Harrod, and James);[11] and hydrogenation of olefinic compounds using $RhCl[P(C_6H_5)_3]_3$ in 1965 (G. Wilkinson, 1973 Nobel laureate),[12] are few of the outstanding examples.

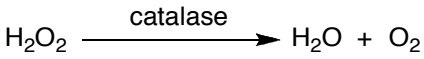
1.2.3 Subdisciplines

It is customary to have subdisciplines in such a field; In general catalysis can be classified into homogeneous, heterogeneous and biocatalysis.[6] In homogeneous catalysis, both the catalyst and the reactants are in the same phase. One of the simplest examples is the decomposition of ozone by chlorine atoms (Scheme 1).



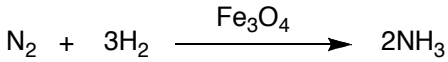
Scheme 1. Decomposition of ozone (homogeneous catalysis).

Enzymes are known as nature's biocatalysts. Having shapes that are optimally suited to guide reactant molecules in the optimum configuration for reaction, enzymes are highly specific and efficient catalysts.[6] For example, the enzyme "*catalase*" catalyzes the decomposition of hydrogen peroxide into water and oxygen at an incredibly high rate of up to 107 hydrogen peroxide molecules per second (Scheme 2).[6]



Scheme 2. Decomposition of hydrogen peroxide (biocatalysis) by *catalase.*

In heterogeneous catalysis, the catalyst and the reactants are in the different phases. Heterogeneous catalysts are the workhorses of the chemical and petrochemical industry. The most important industrial preparation of ammonia-the Haber Bosch process- is carried out by nitrogen fixation in the presence of Fe_3O_4 (Scheme 3).



Scheme 3. Nitrogen fixation in ammonia synthesis (heterogeneous catalysis).

1.2.4 Molecular chirality and drug design

Until the mid of 20-th century researchers and industries were mainly focused on the improvement of catalyst design to achieve higher selectivity and TON (Turn Over Number). However, most of them were applied in the racemic synthesis of natural or bioactive products. Even in the early 1990s, about 90% of synthetic drugs were racemic.[13, 14] In 1960, racemic thalidomide was prescribed against morning sickness for pregnant women, unfortunately, this racemic drug led to a historic tragedy.[15] The different isomers of thalidomide (*R* & *S*) were showing differing pharmacological activities, (*R*)-thalidomide has the desired sedative properties while its *S* enantiomer is teratogenic and induces fetal malformations. In 1992, the Food and Drug Administration (FDA) in the US introduced a guideline regarding "racemic switches", in order to encourage the commercialization of clinical drugs consisting of single enantiomers.[16]

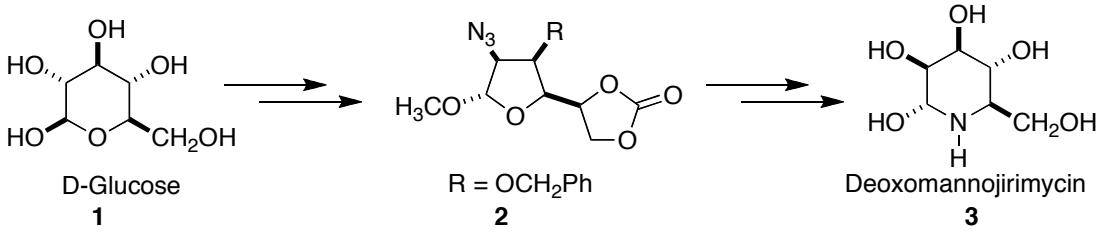
1.2.5 Classical methods

Since then, the research interest turned towards the synthesis of enantiomerically pure compounds. Historically, enantiomerically pure compounds were obtained by the classical resolution of a racemate, such as Pasteur's (1858) first enzymatic resolution of racemic ammonium tartrate. The microorganism *Penicillium glauca* destroys *D*-ammonium tartrate more rapidly than its *L*-enantiomer from a solution of a racemic ammonium tartrate.[17] Soon after Pasteur's report Marckwald and McKenzie observed enantioselective esterification of racemic mandelic acid by (-)-menthol upon heating the reactants,[18, 19] and they were able to recover a small amount of the less-reactive *L*-mandelic acid in pure form after multiple crystallizations, marking the first non-enzymatic reagent used in kinetic resolutions.

1.2.6 Modern concept in asymmetric synthesis

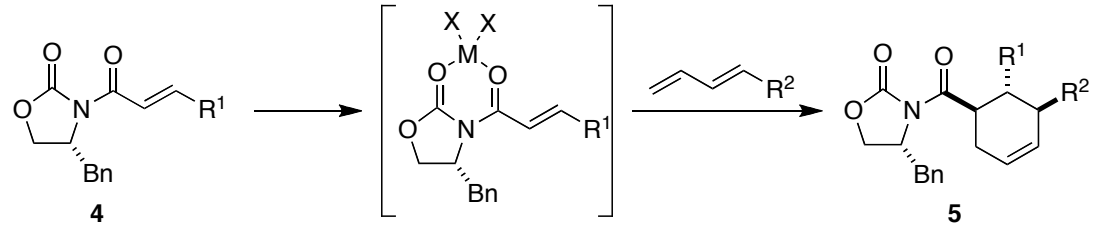
Apart from classical kinetic resolution, other techniques were introduced for asymmetric syntheses (eqs 1-3).[20] For example, transformation of readily available enantiopure molecules such as amino acids, tartaric acid, lactic acid, carbohydrates, terpenes, and alkaloids were developed (Scheme 4, eq 1). Another technique is the use of a chiral auxiliary,[21] in which a chiral group in the vicinity of the reaction site controls the stereochemistry that is easily removed afterwards (requires a three-step approach of (1) attachment of the fragment, (2) asymmetric synthesis and (3) disconnection)[20] (Scheme 4, eq 2), and stereoselective conversion of a prochiral compound into a chiral product by a chiral catalyst, which can be an enzyme or a synthetic entity (Scheme 4, eq 3).[22]

Transformation of chiral compounds:



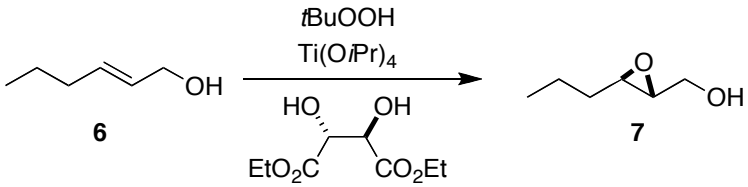
D-Glucose **1** | R = OCH_2Ph **2** | Deoxomannojirimycin **3** (1)

Chiral auxiliary approach:



4 **5** (2)

Stereoselective conversion of a prochiral compound:



(3)

Scheme 4. Chiral transformation, chiral auxiliary and asymmetric conversion of prochiral compounds.

Even though stereoselective conversion of a prochiral compound to a chiral product through an asymmetric reaction is the most attractive approach, practical access to pure enantiomers relied largely on biochemical or biological methods. However, the scope of such methods using enzymes, cell cultures or microorganisms is limited because of the inherent single-handed, lock-and-key specificity (introduced by Fischer) of biocatalysts.[23] On the other hand, a chemical approach allows the flexible synthesis of a wide array of enantiopure organic substances from achiral precursors. Figure 2 illustrates the general principle of asymmetric catalysis which provides an ideal way for multiplying molecular chirality.[23] In the first stage of catalysis, substrates A and B get coordinated to the catalyst (Figure 1 and 2, TSc1). Reaction between A and B proceeds in the chiral environment of the catalyst (Figure 1 and 2, TSc2). Finally product AB dissociates (Figure 1 and 2, TSc3) from the catalyst and the free catalyst is ready for the next cycle.

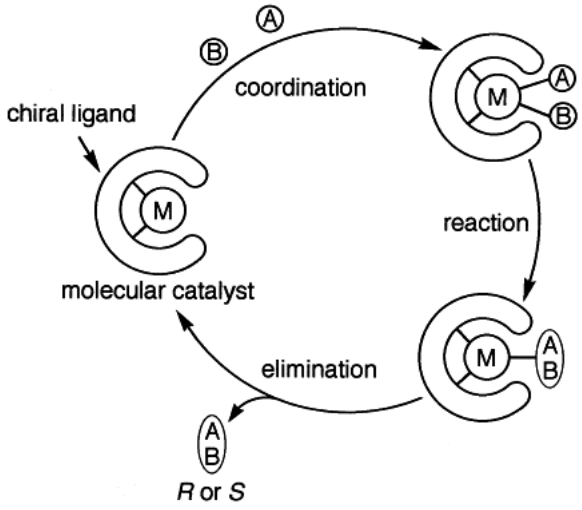


Figure 2. A general principle of asymmetric catalysis with chiral organometallic molecular catalyst. M = metal; A, B = reactant and substrate

The first use of a chiral non-enzymatic catalyst can be traced to the work of Bredig and Fajans in 1908.[24] They studied the decarboxylation of camphorcarboxylic acid by nicotine or quinidine. In 1931, Shibata et al. studied oxidation reactions by molecular oxygen with a

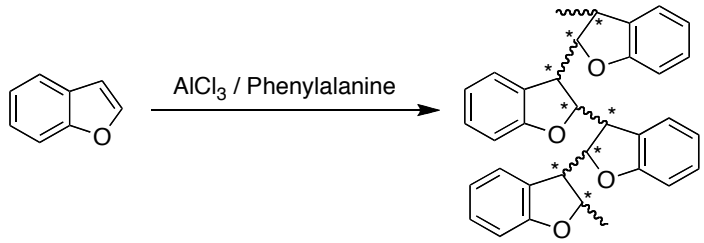
chiral cobalt catalyst for the kinetic resolution of a racemic mixture.[25] Akabori et al. achieved the first heterogeneous enantioselective synthesis in 1956 with a silk-palladium catalyst by hydrogenating derivatives of oximes and oxazolones.[26]

1.3 Landmarks in asymmetric catalysis

1.3.1 Chiral polymers

A high proportion of recent asymmetric syntheses uses organometallic or coordination chemistry. There are several reasons for this, in particular the ability of metals to complex with common functional groups in organic molecules in a reversible manner, and the ability to activate simple reactants such as hydrogen and carbon monoxide. Moreover, the reactive complexes are well defined spatially, which is vital for stereochemical control.

Based on the above concept, numerous metal complexes have been prepared to catalyze various reactions. In 1981, the synthesis of optically active polymers was achieved by Natta (Nobel laureate, 1963) by treating benzofurane **8** with $AlCl_3$ and phenylalanine (Scheme 5).[27] This reaction is known as the first example of homogeneous asymmetric catalysis by a metal complex.

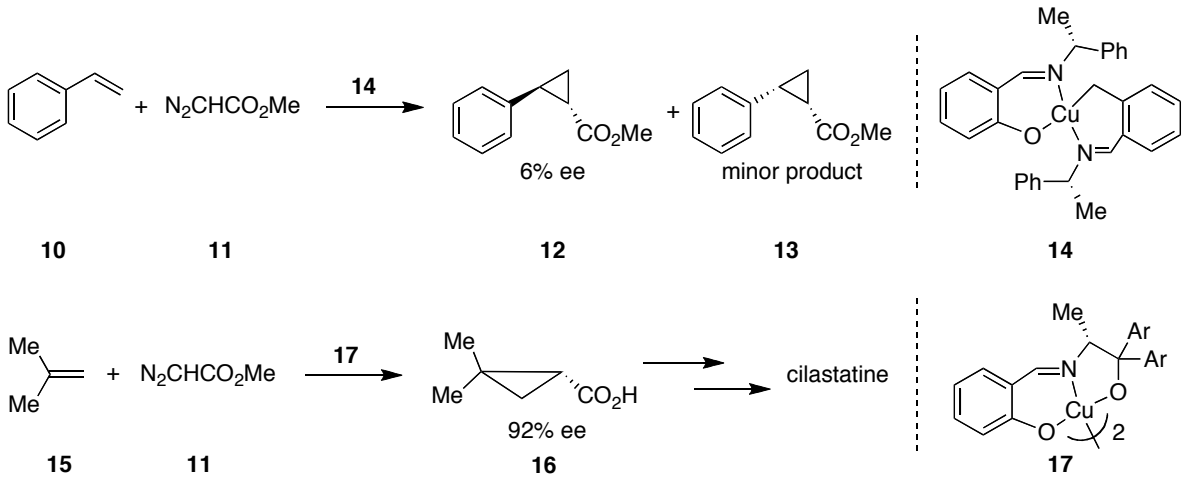


8 **9**

Scheme 5. Enantioselective polymerization of benzofurane.

1.3.2 Asymmetric cyclopropanation

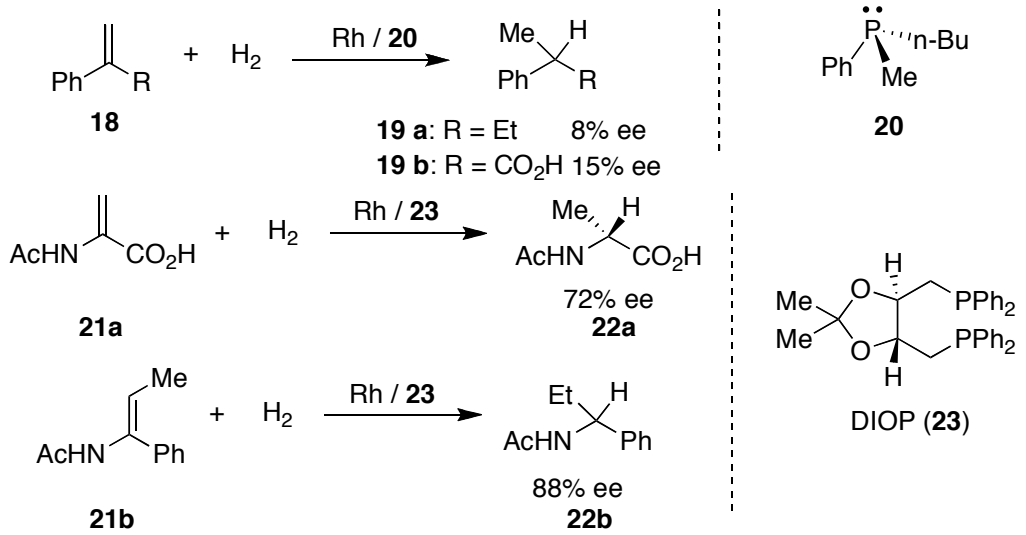
The first example of asymmetric organometallic catalysis outside the area of polymer chemistry was the cyclopropanation of alkenes as described by Nozaki in 1966.[28] They used the chiral salen-copper complex **14** (Scheme 6), which gave a maximum enantioselectivity of 10%. Later, Aratani et al. initiated the tuning of the structure of the copper catalyst at Sumitomo (corp.).[29] They were able to reach a quite high level of enantioselectivity with copper catalyst **17**. For example, 2,2-dimethyl-cyclopropane carboxylic acid **16** was obtained in 92% ee, which was subsequently used in a process to prepare cilastatine.



Scheme 6. Asymmetric cyclopropanation of alkenes.

1.3.3 Rhodium mediated hydrogenation

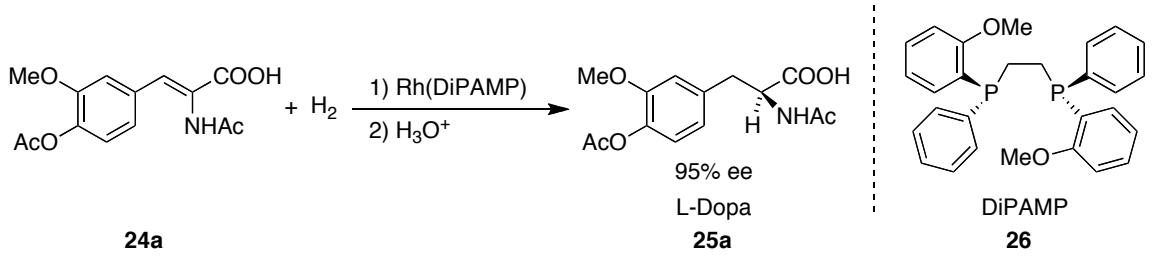
In 1968, two years after asymmetric cyclopropanation in 1966, W. S. Knowles[30] (Nobel laureate in 2001) and L. Horner[31] independently reported the first homogeneously catalyzed asymmetric hydrogenation of olefins with chiral monodentate tertiary phosphine **20**–Rh complexes, albeit in low optical yield (3-15% ee; Scheme 7). H. Kagan reported a major breakthrough in this area in 1971, when he devised DIOP **23**, a C_2 chiral diphosphine derived from tartaric acid. He used the Rhodium complex of **23** for the asymmetric hydrogenation of dehydroamino acids **21** leading to 72% ee for **22a** and 88% ee for **22b**.[32] This represented the first example for the use of a C_2-symmetric ligand, a strategy[33] that has been widely used since then, for which many chiral di- phosphines of C_2-symmetry have been subsequently prepared (*vide infra*).



Scheme 7. Rhodium catalyzed asymmetric hydrogenation.

1.3.4 DiPAMP mediated L-Dopa synthesis

One of the major achievements in asymmetric catalysis was the preparation of C_2-symmetric DiPAMP in 1975 by Knowles.[34] The Rhodium complex of DiPAMP **26** gave up to 95% ee in asymmetric hydrogenation of dehydroaminoacids **24a**, which led to the synthesis of *L*-Dopa **25a**, marking the first industrial asymmetric synthesis.[35]



Scheme 8. DiPAMP mediated asymmetric synthesis of L-Dopa.

Halpern[36] and Brown[37] have elucidated the reaction mechanism of this diphosphine-Rh complex mediated hydrogenation: Dehydroamino acid **24b** coordinates to the Rh(I) complex **27a** in a reversible manner with the displacement of solvent molecules. Oxidative addition of molecular hydrogen in **27b** leads to the Rh(III) complex **27c**, in which the hydrogen transfers to **24b** is initiated leading to **27d**. Finally, the reductive elimination releases the reduced amino acid **25b** and the free Rh(I) catalyst **27a**.

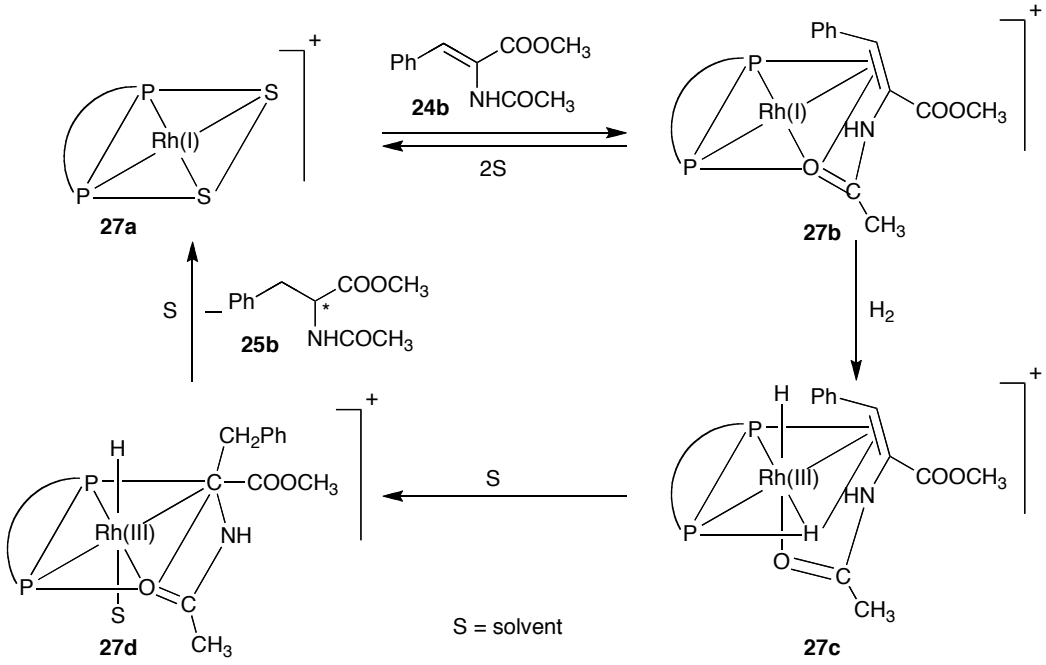


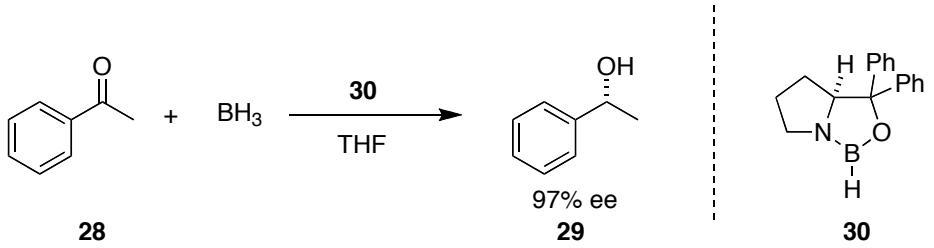
Figure 3: Mechanism for Rh-diphosphine-catalyzed hydrogenation of an enamide.

Apart from the development of Rh catalyzed hydrogenations, several asymmetric reactions have been developed involving different metals. A Diels-Alder reaction catalyzed by a chiral Lewis acid was described for the first time in 1979 by Koga et al.[38] The catalyst was prepared by action of (–)-menthol on $EtAlCl_2$ and gave 55% ee in the formation of the exo-cycloadduct between cyclopentadiene and methacroleine.

A major breakthrough was accomplished when Sharpless (Nobel laureate, 2001) introduced a very general method for the asymmetric epoxidation of allylic alcohols (Scheme 4, eq 3).[22] The generality, broad scope and high ee's of this methodology became a routine reaction in asymmetric synthesis.

1.3.5 Chemozymes

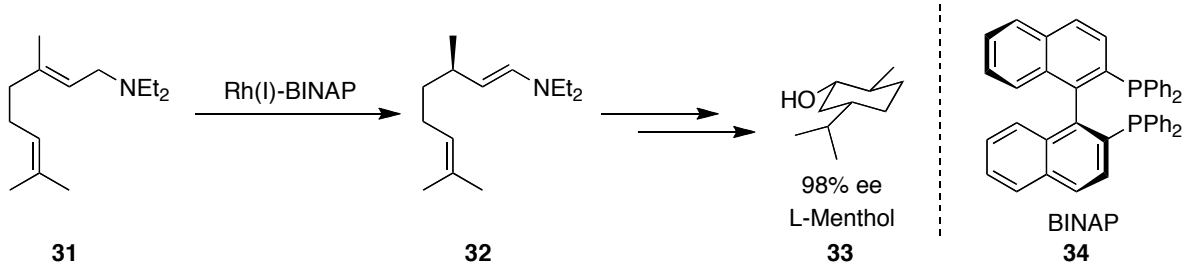
Itsuno introduced the borane mediated asymmetric reduction of ketones in 1983.[39] A remarkable extension of this methodology was achieved by Corey when he developed the chiral oxaborolidines **30**, giving rise to 97% ee in the reduction of acetophenone **28** (Scheme 9).[40]



Scheme 9. Oxaborolidines mediate reduction of acetophenone.

1.3.6 BINAP in L-menthol synthesis

Another landmark in asymmetric catalysis is the introduction of the BINAP **34** (C_2 symmetric) ligand by Noyori (Nobel laureate, 2001) in 1980.[41] The Ru/BINAP complex has found spectacular applications in asymmetric hydrogenations of many types of unsaturated substrates (C=C or C=O double bonds). Another important development was the isomerization of allylamine **31** into enamine **32** catalyzed by cationic rhodium/BINAP complexes.[42] This reaction has been applied since 1985 in Japan at the Takasago Company for the synthesis of (–)-menthol **33** (Scheme 10).

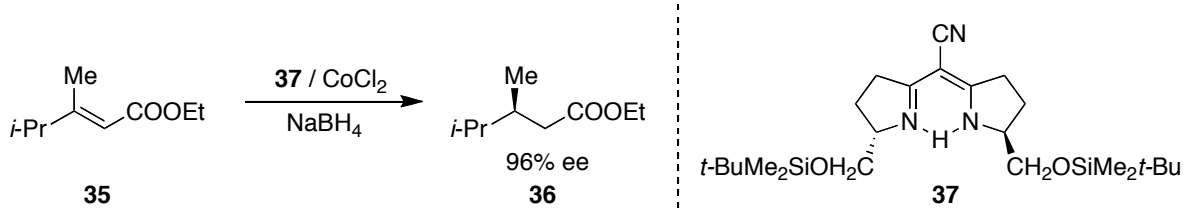


Scheme 10. BINAP mediated asymmetric synthesis of L-Menthol.

1.4 New generation of catalyst design

1.4.1 Bidentate nitrogen ligands

Until the early 1990's, bidentate phosphorous ligands played a major role in asymmetric catalysis. The discovery and development of C_2 symmetric nitrogen bidentate ligands was more attractive in catalyst design. The C_2 symmetric semicorrin **37** was introduced by Pfaltz and the corresponding cobalt complex gave 96% ee in enantioselective reduction of α,β-unsaturated esters **35** (Scheme 11).[43] Subsequently a new generation of chiral ligands "Bis(oxazoline)" **38** which are structurally related to semicorrin **37**, were reported independently by several research groups in 1990-1991.[44-51]



Scheme 11. Conjucate reduction by Co-semicorrin complex.

1.4.1 C_2-Symmetry and bis(oxazoline) ligands

Of the thousands of chiral ligands prepared so far, a relatively small number of structural classes stand out because of their broad applicability.[52] The structural analysis of these "privileged ligands" revealed that the majority of them are C_2 symmetric (Figure 4), a feature that has proven most beneficial in designing asymmetric processes. In general this is due to the reduction of possible transition states caused by the equivalency of structures upon rotation by 180°.[53, 54]

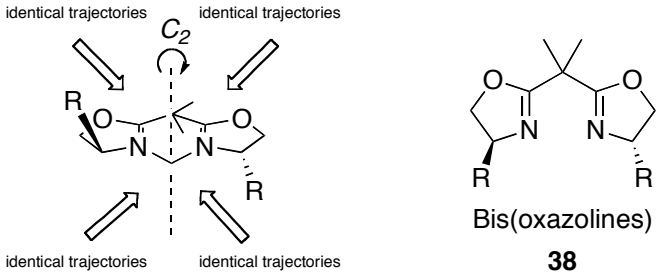
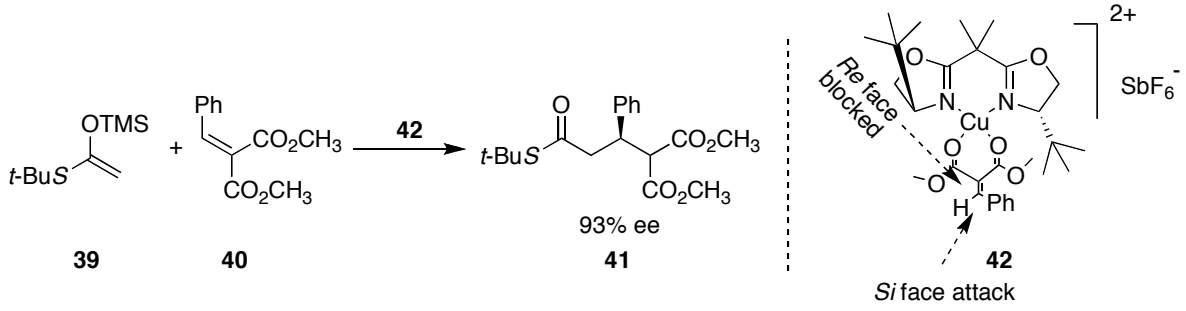


Figure 4. C_2-symmetry of metal-bis(oxazoline) complexes.

Bis(oxazoline) (box) **38** ligands have developed into one of the most useful ligand classes for asymmetric catalysis due to their ability to coordinate with a large number of metals.[53] These ligands were applied for catalytic asymmetric allylic substitution, allylic oxidation, aziridination of olefins, and imines, cyclopropanation, hetero Diels-Alder reaction, and nucleophilic addition reactions to aldehydes and imines.[55] It is important to note the seminal contributions of Evans and co-workers in the development of bis(oxazoline) complexes.[56, 57]

1.4.1 Models for stereoselective discrimination of prochiral substrates

Unlike for other chiral ligand classes the principles of the function of metal-bis(oxazoline) complexes, especially with respect to chiral discrimination of substrates, have been well recognized. For the first time Evans et al. have isolated and analyzed the bis(oxazoline)-metal complex **42** being bound to the substrate.[56, 57] The observation of enantioselectivity in Michael addition was clearly understood from the X-ray structures (Scheme 12); the proximity of bulky substitutions to the prochiral center influences the incoming reagent to attack preferentially from one face of the system (Scheme 12).



Scheme 12. Enantioselective Michael addition of alkylidene malonates.

1.4.2 Hybrid of bis(oxazoline) and aza-semicorrin

Our group, was also attracted by the advantages and aesthetics of C_2 symmetry when we introduced the aza-bis(oxazolines) **45** (Figure 5) as a new type of chiral ligands.[58, 59] They

combine the advantage of being accessible from the chiral pool like the bis(oxazolines) **44** and the structural variability of aza-semicorrins **43** due to the possibility of functionalizing the central nitrogen atom. Therefore, these features of azabox are expected to have a strong direct effect on immobilization and exploring them in a broad scope of asymmetric reactions.

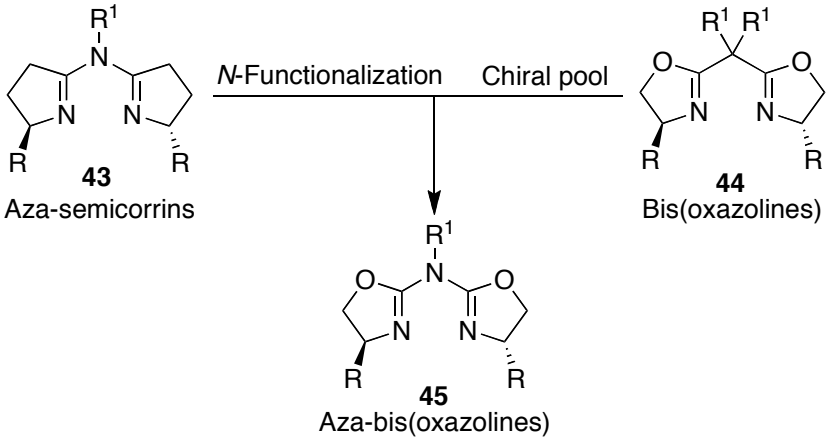


Figure 5. Aza-bis(oxazolines) as hybrids of bis(oxazolines) and aza-semicorrins.

These ligands gave excellent results in the Cu-catalyzed cyclopropanations, kinetic resolutions and cobalt catalyzed conjugate reductions. Moreover, the immobilized aza-bis(oxazolines) anchored to MeOPEG and polystyrene showed comparable enantioselectivity to the non-immobilized ligands.[60-63]

1.5 Conclusion

The ingenuity and creativity of the researchers involved has led to unprecedented success in asymmetric synthesis, but there remain many new opportunities yet to be explored. One important goal to be achieved for making such processes attractive for industrial application is the development of methods for the recycling of the precious catalysts by tuning the electron density of the ligands to achieve high reactions rates but at the same time stable complexes to allow efficient recovery. Aza-bis(oxazolines) seem to be advantageous in these respects to bis(oxazolines), which makes it attractive to further explore applications with these ligands and it is highly desirable to explore aza-bis(oxazolines) in this field.

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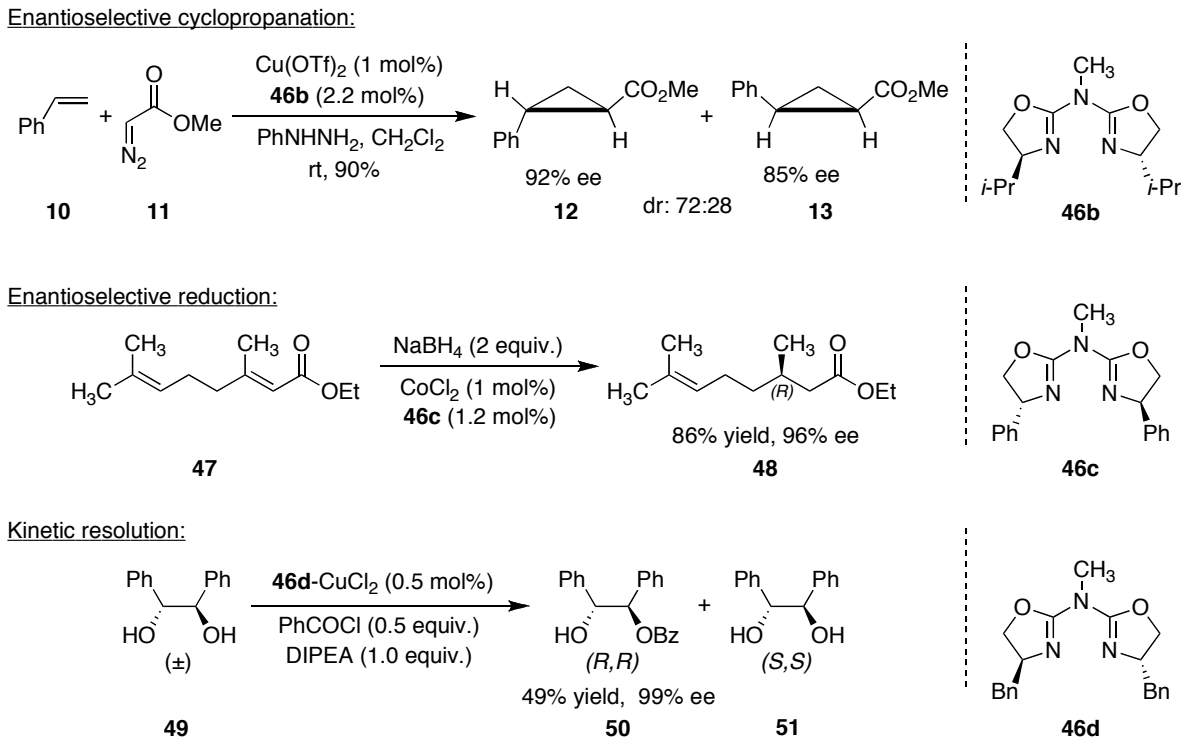
2 Aim of the work

Aza-bis(oxazolines) (Azabox) are very successful in distinct asymmetric reactions since their inception in 2000,[1] A few examples are depicted in Scheme 13. The benchmark cyclopropanation of styrene **10** was carried out with methyl diazoacetate **11** in the presence of **46b**-$Cu(OTf)_2$ complex and the *trans* product **12** was isolated in 92% ee.[1] Cobalt mediated enantioselective reduction of enone **47** gave 97% ee for the corresponding ester **48**.[2] Kinetic resolution of (±)-hydrobenzoin **49** by asymmetric monobenzoylation was carried out in the presence of **46d**-$CuCl_2$ complex and the product **50** was isolated in 99% ee.[3]

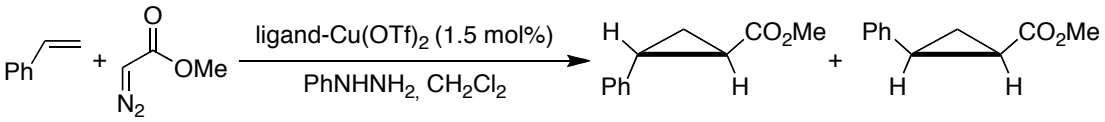


Scheme 13. Enantioselective reactions catalyzed by aza-bis(oxazolines).

2.1 Secondary activation of azabox-MX_n complex

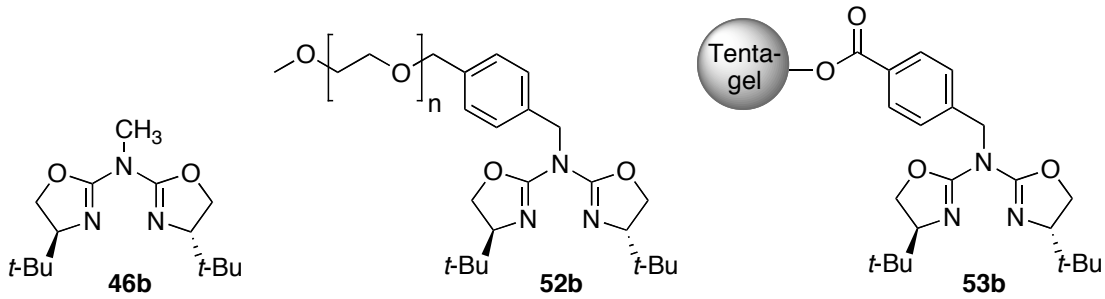
Following the success of azabox ligands in distinct asymmetric reactions, immobilization of these ligands on MeOPEG and Tentagel were carried out (Scheme 22).[1, 4] Screening of these immobilized aza-bis(oxazolines) **52b** and **53b** showed good enantioselectivities only in few asymmetric reactions. However, these immobilized ligands suffered from comparatively lower enantioselectivities and yields (Table 1).[1, 4] Especially, a dramatic drop

of enantioselectivity was observed when heterogeneous ligand (Tentagel) **53b** was employed in cyclopropanation of styrene **10** (Table 1, entry 3).[4]



10 **11** **12** **13**

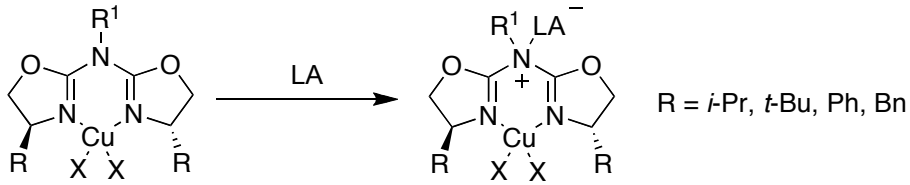
entry	ligand	time (h)	yield (%)	**12 : 13**	(**12**) ee (%)
1	**46b**	8	82	73 : 23	92
2	**52b**	8	70	70 : 30	86
3	**53b**	48	35	64 : 34	47



46b **52b** **53b**

Table 1 Cyclopropanation of styrene catalyzed by polymer bound aza-bis(oxazoline)-copper complexes.

To circumvent these limitations, secondary activation of the immobilized aza-bis(oxazoline)-metal complexes **55** by another Lewis acid (secondary LA) is envisioned as a novel methodology. Accordingly, the secondary LA could strongly coordinate with the central nitrogen atom of complex **55**, thus increasing the Lewis acidity of a metal such as copper in the complex **56**.

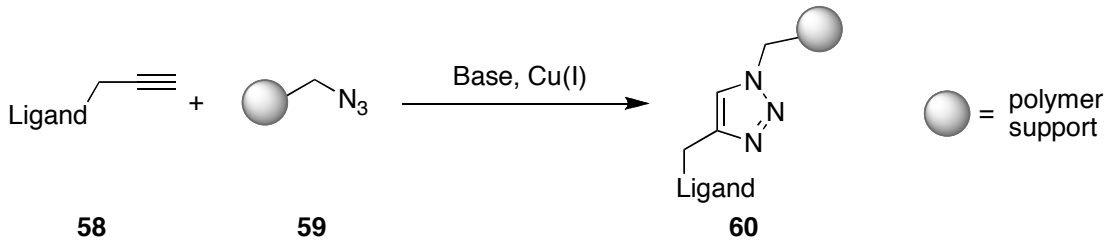


55 **56**

Scheme 14. Proposed secondary activation of aza-bis(oxazoline)-copper complex by the addition of secondary Lewis acid.

2.2 Immobilization of azabox on fluorous tag and dendrimer

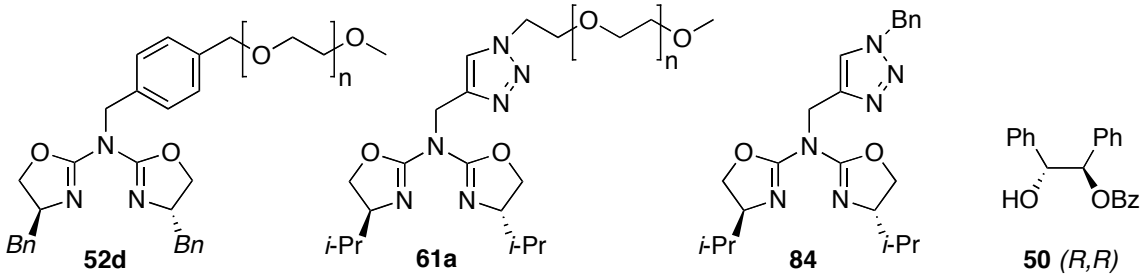
Recent studies in the field of catalyst immobilization revealed that a facile way to attach ligands and polymeric supports is to apply the copper-catalyzed[5, 6] azide-alkyne cycloaddition[7] (CuAAC), coined a "click reaction" (Scheme 15).[8] This reaction has proven to be most powerful for ligating functional molecules to supporting scaffolds or to each other.[9, 10] Also CuAAC reactions are modular, wide in scope, high yielding, stereospecific, and simple to perform. Moreover, they create only inoffensive by-products and can be carried out in benign or easily removable solvent.



Scheme 15. Cu(I) mediated 1,3-dipolar cycloaddition (click reaction).

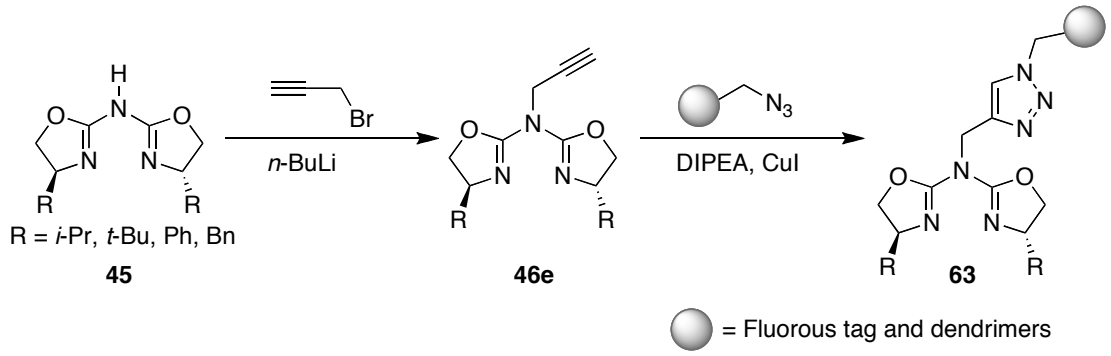
Following the seminal contributions of Gmeiner and co-workers,[11-13] there is a growing awareness that this reaction can also be used for the synthesis of functional polymers and dendrimers.[3, 14-19] In addition, the CuAAC, offering a wide tolerance for reactive or sensitive groups, should have great potential for the synthesis of heterogeneously immobilized catalysts and reagents.

Aza-bis(oxazolines) were immobilized on $MeOPEG_{5000}$ as well as benzylated by following the click reaction (Scheme 23). Unfortunately, these ligands **61a** and **84** having triazole linker showed moderate enantioselectivity in comparison to the triazole lacking MeOPEG-immobilized ligand **52d**. For example, catalyst **61a** and **84** gave only 63% and 66% ee for the monobenzoylated product **50** (Scheme 16).



Scheme 16. Azabox-$CuCl_2$ mediated kinetic resolution of (±)-hydrobenzoin

A possible explanation for the observed erosion of enantioselectivity could be the nitrogen donor of the triazole unit may compete with the nitrogen donor of the ligand for the complexation with metals and leading to the lower enantioselectivity. In order to test this hypothesis, it was aimed to introduce a polymeric backbone with electron deficient fluorous chains. Alternatively globular polymeric supports like dendrimers were thought to shield the inner located triazole moieties, thus preventing their complexation by copper metal (Scheme 17). Propargylation of **45** can be readily performed in presence of *n*-BuLi and propargylbromide to yield **46e**. Further treatment of **46e** with fluorous /dendrimer azide in presence of DIPEA and CuI could lead to the synthesis of fluorous immobilized azabox **63**.



Scheme 17. Immobilization of azabox over electron deficient or globular polymeric support.

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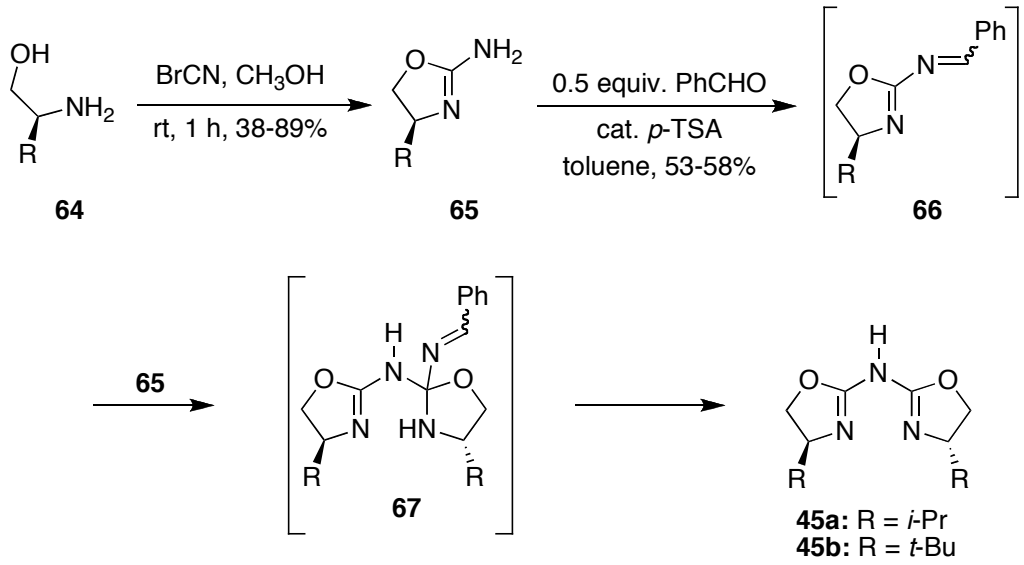
3 Synthesis and immobilization of aza-bis(oxazolines)

3.1 Synthesis of aza-bis(oxazolines)

The initial protocol for the synthesis of aza-bis(oxazolines) **45** called the formal dimerization of 2-aminooxazoline **65**.[1] Aminoalchohol **64** is reacted with BrCN in MeOH to give rise to the corresponding 2-aminooxazoline **65** in 38-89% yield and the subsequent treatment of **65** with 0.5 equiv. of benzaldehyde in the presence of catalytic amount of *p*-TSA led to the formation of the desired aza-bis(oxazoline) **45** in moderate yield (Scheme 18).

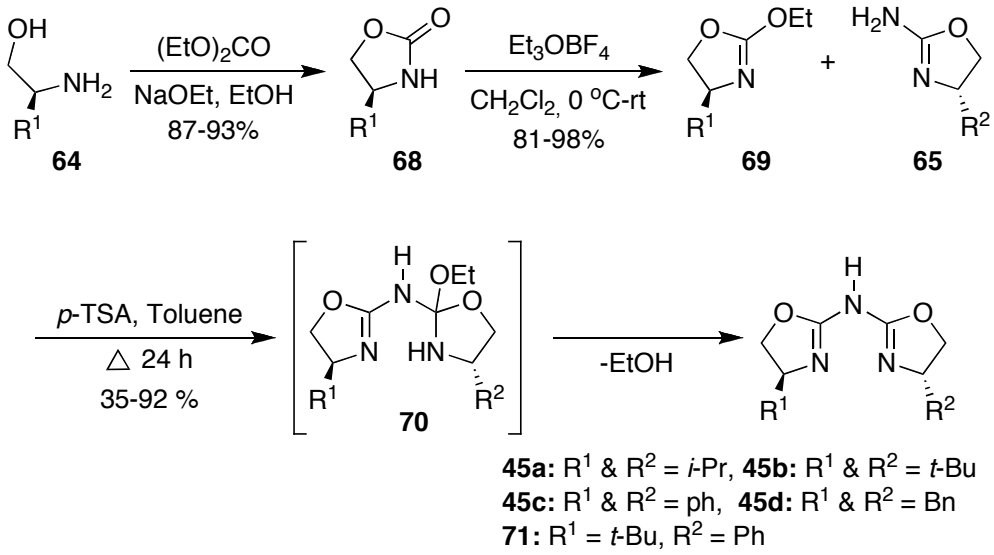


Scheme 18. Synthesis of aza-bis(oxazolines) *via* dimerization of 2-amino oxazolines.

Even though this dimerization towards azabox constituted of an elegant and short synthesis, the purification of the ligands turned out to be problematic in many cases. The isopropyl and *tert*-butyl substituted aza-bis(oxazolines) **45a-b** were obtained in pure form but only with moderate yield. The synthesis of azabox ligands with other substitutions like Ph and Bn was unsuccessful. The intermediate **66** may explain the moderate yield of this methodology, since it has two different electrophilic carbons, so that an incoming nuceophile, e.g the amine **65** might attack at both centers, which might lead to side product formation.

To circumvent these limitations, another synthetic route was introduced, which adopts the coupling of 2-amino-and 2-ethoxy oxazolines.[2] Amino alcohol **64**, was transformed either into the 2-amino oxazoline **65** as described earlier (Scheme 18), or by treatment with

diethyl carbonate and sodium ethoxide to the oxazolidinone **68**, which was subjected to alkylation with Meerwein's salt (Triethyloxonium tetrafluoroborate) to give rise to 2-ethoxy oxazoline **69** in 81-98% yield. The final coupling between these two intermediates (**69** and **65**) was carried out in the presence of catalytic amounts of *p*-TSA in toluene, which may proceed *via* the intermediate **70** (Scheme 19). This way not only **45a-b** were successfully obtained, but also the phenyl (**45c**) and benzyl (**45d**) substituted aza-bis(oxazolines) could be synthesized in pure form, albeit only with moderate yield.[2] This methodology not only offers the synthesis of symmetrical aza-bis(oxazolines), but also of non-symmetrical aza-bis(oxazolines) such as **71** (Scheme 19).

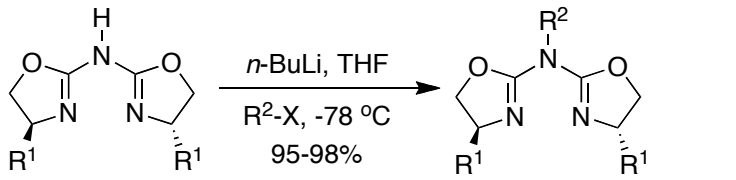


Scheme 19. Synthesis of aza-bis(oxazolines) by coupling of 2-amino and 2-ethoxy oxazolines.

3.2 Immobilization of aza-bis(oxazolines)

3.2.1 Functionalization of aza-bis(oxazolines)

Azabox ligands can be easily functionalized on the central nitrogen by simple deprotonation with *n*-BuLi followed by trapping the anion with electrophiles (Scheme 20).[7] By this way, azabox has been functionalized with methyl (**46a)**, benzyl (**46ab)**, allyl (**46ac**) and propargyl (**46ad**) groups.

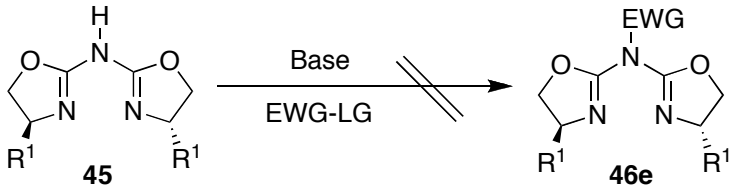


45a: R^1 = *i*-Pr
45b: R^1 = *t*-Bu
45c: R^1 = Ph
45d: R^1 = Bn

46a: R^1 = *i*-Pr, R^2 = Me
46ab: R^1 = *i*-Pr, R^2 = Bn
46ac: R^1 = *i*-Pr, R^2 = Allyl
46b: R^1 = *t*-Bu, R^2 = Me
46c: R^1 = Ph, R^2 = Me
46d: R^1 = Bn, R^2 = Me

Scheme 20. Functionalization of aza-bis(oxazolines).

However, functionalization of aza-bis(oxazolines) **45** with electron deficient groups was unsuccessful. Neither varying the base nor the electrophiles allowed to obtain the products of type **46e** (Scheme 21).[7]

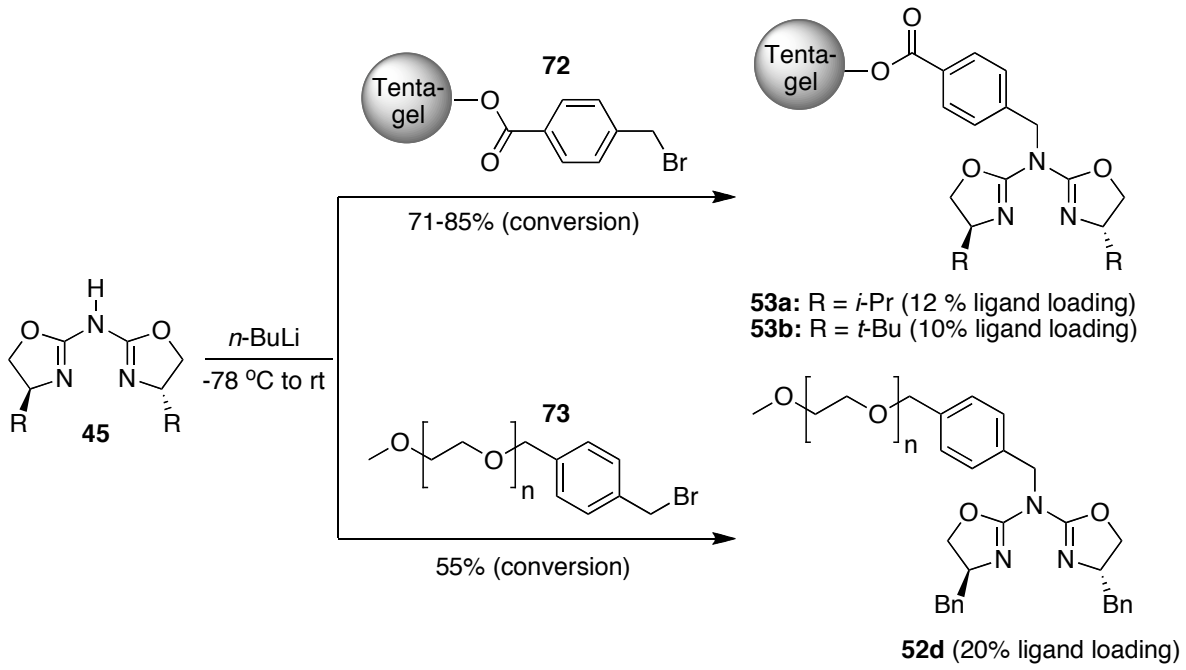


Base: *n*-BuLi, KOH, DABCO, DMAP.
EWG-LG: PhCOCl, CH_3COCl, CCl_3COCl, TosCN, CH_2ClBr, CH_2I_2, *p*-NO_2BzBr, CF_3CH_2I, $C_8F_{17}CH_2Br$, Boc_2O, $BrCH_2COOEt$.

Scheme 21. Functionalization of azabox with electron deficient groups.

3.2.2 Direct immobilization

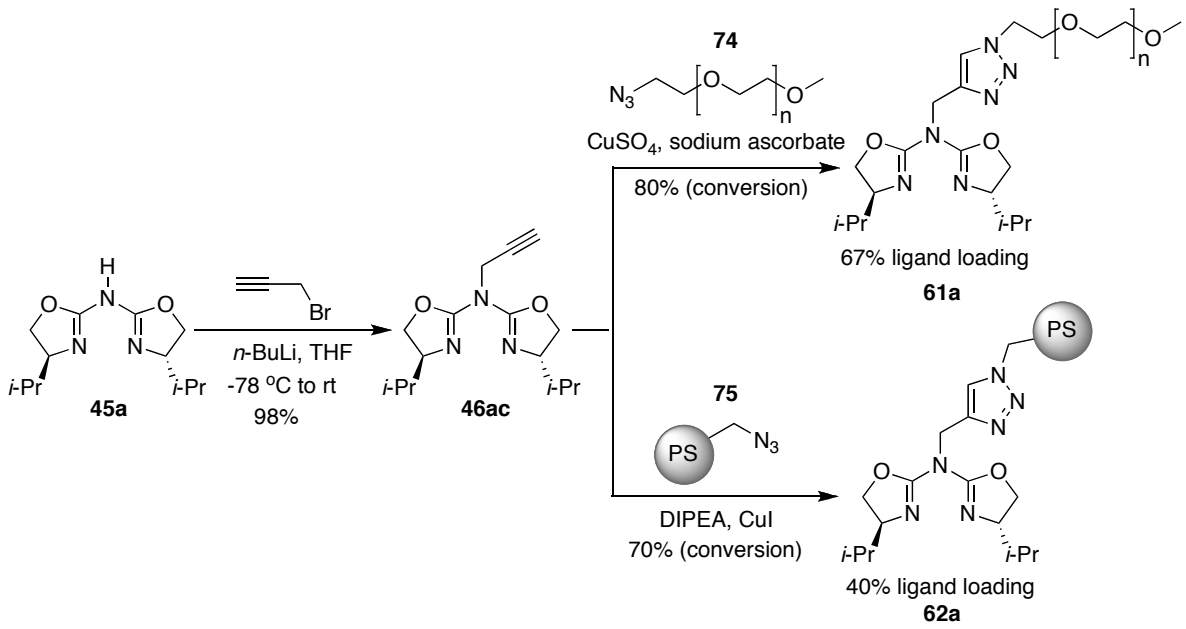
Aza-bis(oxazolines) **45** were immobilized on $MeOPEG_{5000}$ as well as on Tentagel (hybrid of polystyrene interior and MeOPEG exterior) by the direct reaction between the azabox **45** and polymers **72** and **73** (Scheme 22).[9] Tentagel carrying benzylic bromide **72** was treated with azabox **45** to obtain the immobilized azabox **53** in 71% and 85% conversion, respectively. Likewise $MeOPEG_{5000}$ immobilized aza-bis(oxazoline) **52d** was synthesized in 55% yield (Scheme 22). Even though immobilization of aza-bis(oxazolines) was successful by this way, the ligand loading was only 10-12% for **53** and 20% for **52d** with respect to the maximum loading capacity of the resin. Employing excess of ligand **45** corresponds did not improve the ligand loading.



Scheme 22. Immobilization of aza-bis(oxazolines) onto Tentagel and $MeOPEG_{5000}$.

3.2.3 Immobilization *via* click reaction

Since the direct immobilization (Scheme 22) led to the low ligand loading, a more efficient immobilization strategy by utilizing the copper mediated[3-5] azide-alkyne cycloaddition[6] (CuAAC) reaction was envisioned (Scheme 23).



Scheme 23. Immobilization of aza-bis(oxazolines) by CuAAC.

Propargylation of **45a** was readily performed to yield **46ac** in nearly quantitative yield

(Scheme 23). Further treatment of **46ac** with $MeOPEG_{5000}$ azide in the presence of $CuSO_4$ and sodium ascorbate led to the formation of $MeOPEG_{5000}$ immobilized azabox **61a** in 80% yield with 67% of ligand loading (Scheme 23).[9] Polystyrene immobilized azabox **62a** was synthesized by utilizing CuI and DIPEA rather than the use of $CuSO_4$ and sodium ascorbate. By this way **62a** was obtained in 70% yield with 40% ligand loading (Scheme 23).

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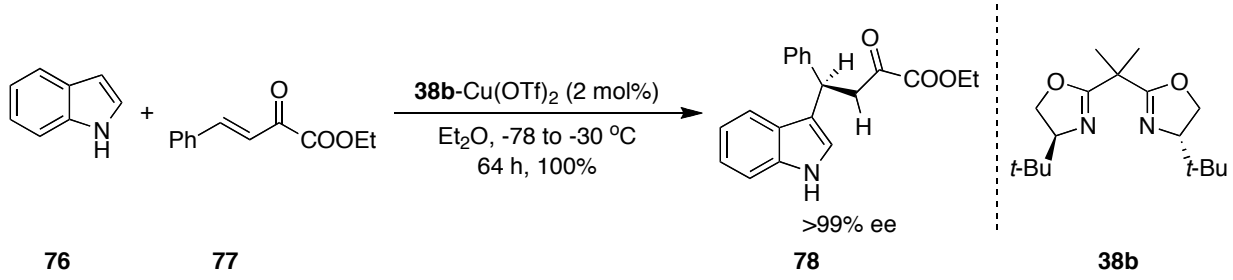
4 Michael Additions of Indole to Benzylidene Malonate

4.1 Bis(oxazolines) mediated asymmetric Friedel-Crafts alkylations

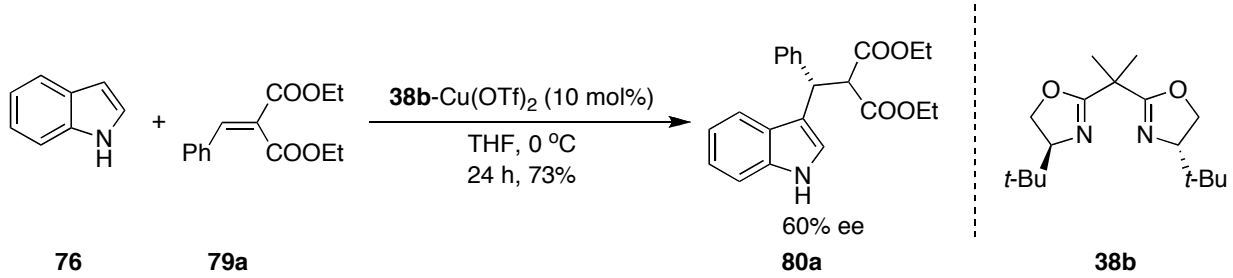
Asymmetric Friedel-Crafts alkylations of indoles have been recently of great interest[1] due to the high relevance of indole derivatives as privileged structures in pharmaceutical drugs. Many synthetic methods towards this structure are known, among them, the copper-bis(oxazoline)-catalyzed enantioselective 1,4-addition of indoles to α,β-unsaturated carbonyl compounds plays a prominent role, representing a facile, catalytic asymmetric process for this transformation.[2] In the pioneering work of Jørgensen and co-workers it was demonstrated that copper(II) complexes with bis(oxazolines) **38b** can catalyze the asymmetric addition of indole **76** to α,β-unsaturated ketoester **77** with enantioselectivities of >99% (Scheme 24).[2]



76 **77** **78** **38b**

Scheme 24. Enantioselective 1,4-addition of indoles to α,β-unsaturated carbonyl compounds.

However, the extension to benzylidene malonate **79a** as a substrate proceeded only with moderate selectivities (up to 69% ee) under the same reaction conditions (Scheme 25).[3]



76 **79a** **80a** **38b**

Scheme 25. Enantioselective 1,4-addition of indoles to benzylidene malonates.

4.2 Tris-(oxazoline) ligands

Tang and co-workers reported a significant improvement of this reaction with bis-(oxazoline) ligand **81** by employing alcoholic solvents (Figure 6).[4] When isobutanol was used as solvent they could obtain 82% ee and in EtOH 76% ee was obtained (Figure 6) for the product **80a**. But most importantly they demonstrated in a number of elegant studies that tris-(oxazoline) ligands such as **82** were superior ligands for this process, giving the adduct **80a** with improved

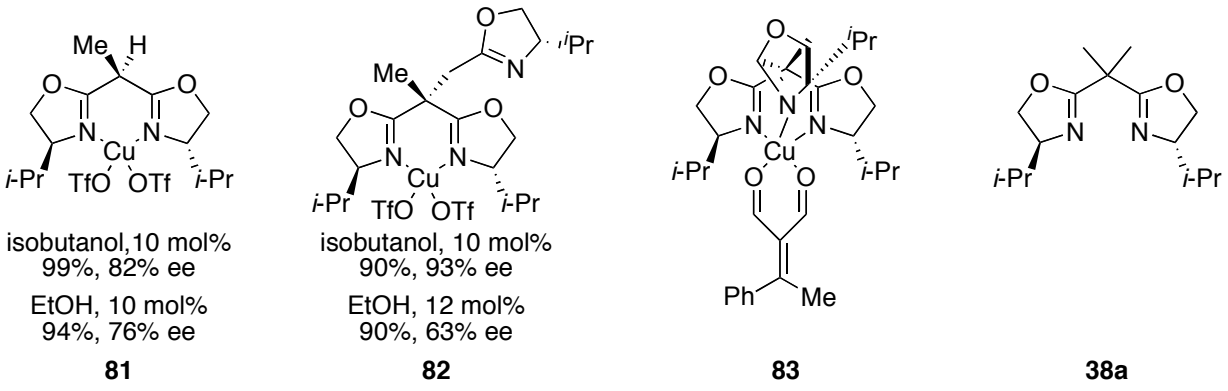


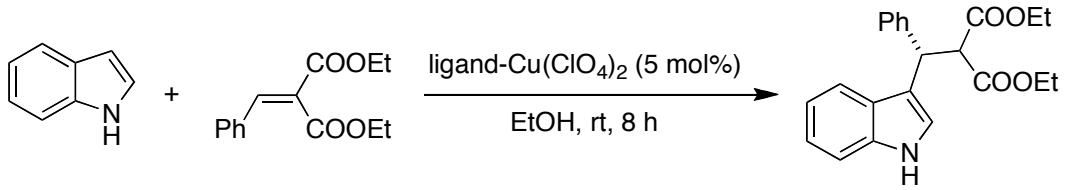
Figure 6. Bis and tris(oxazolines).

yields and selectivities up to 93% ee.[5-8] A pentacoordinated copper(II) complex **83** was postulated as the decisive intermediate to account for the high selectivity. It was concluded from these studies that bis(oxazolines) are unsuitable ligands for the title reaction.

4.3 Aza-bis(oxazolines)

4.3.1 Triazole functionalized aza-bis(oxazoline)

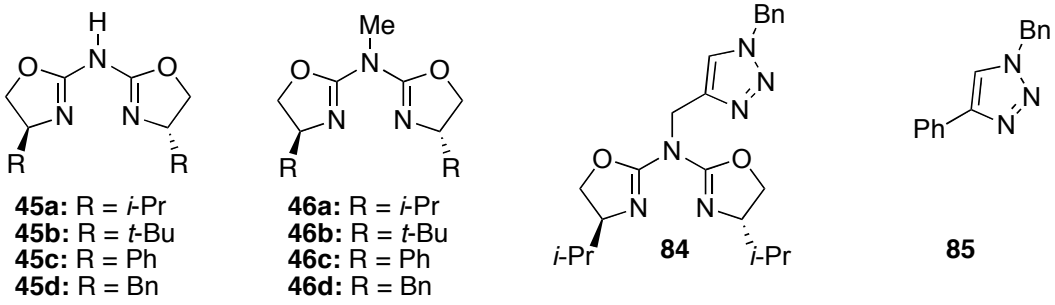
Our investigations began with the finding that under standard conditions (5 mol% of $Cu(ClO_4)_2$, 5.5 mol% of ligand in an alcoholic solvent), aza-bis(oxazoline) **84**,[20] having a triazole side arm, was able to catalyze under commonly employed conditions the transformation of indole **76a** to **80a** with significantly higher enantioselectivity than that of the parent ligand **45a**[9-11] or its corresponding *N*-methylated derivative **46a** (Table 2, entries 1-3), and it also exceeded the best values obtained with any tris(oxazoline) so far.



76 **79a** **80a**

entry	ligand	**85** (equiv.)[a]	yield (%)[b]	ee (%)[c]
1	**46a**	-	88	70
2	**45a**	-	85	66
3	**84**	-	93	95
4[d]	**45a**	1.1	92	81

[a] triazole added as an additive, [b] isolated yield, [c] determined by HPLC, [d] ref 18.



45a: R = *i*-Pr
45b: R = *t*-Bu
45c: R = Ph
45d: R = Bn

46a: R = *i*-Pr
46b: R = *t*-Bu
46c: R = Ph
46d: R = Bn

84

85

Table 2. Aza-bis(oxazolines) mediated Michael adition of indole to benzylidene malonate.

This result was unexpected since the rigid aza(bisoxazoline) framework should not allow tridentate coordination involving the triazole moiety. This hypothesis was confirmed by the X-ray structure of copper complex $Cu(ClO_4)_2$·**84**[20] (Figure 7) in acetonitrile, but it also revealed the ability of the triazole unit to coordinate copper in an intermolecular fashion *via* a second ligand molecule, resulting in a polymeric ligand structure bridged by copper atoms (Figure 7).

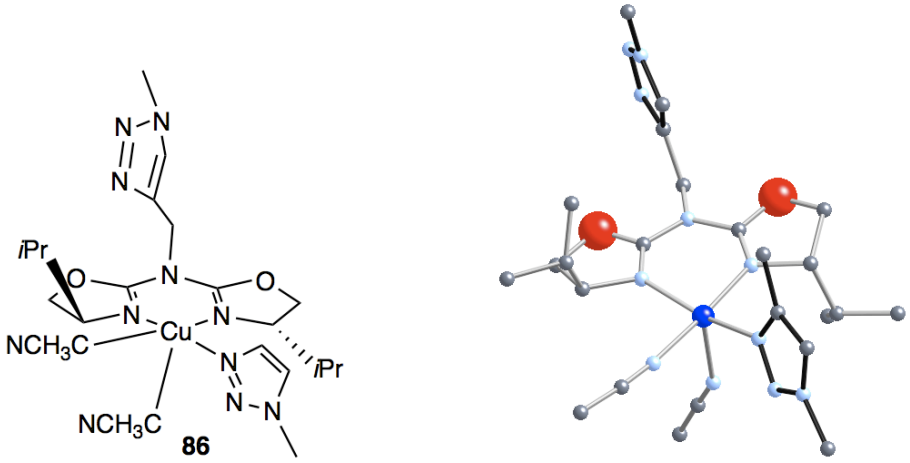


Figure 7. X-ray structure of $[Cu(ClO_4)_2(CH_3CN)_2 \cdot \mathbf{84}]_n$; Ph and ClO_4 groups are omitted for clarity. (X-ray from the ref 20.)

Consequently, we reasoned that a bidentate bis(oxazoline) in combination with an external ligand such as a triazole might be sufficient to provide an effective chiral environment for the asymmetric addition of indoles to benzylidene malonates.

However, employing 1.1 equiv (based on copper) of triazole **85** as an additive in combination with ligand **45a**, while showing some benefit compared to ligand **45a** alone (Table 2, entries 2 and 4), could not equalize the result obtained with ligand **84** (Table 2, entry 3).

This observation suggested an alternative mechanism for the title reaction: While coordination by three nitrogen ligands to copper might represent a resting state of the catalyst, to reach the active species one of the nitrogen ligands has to dissociate off first. If bis(oxazoline) ligands **38** are employed, the excess ligand used might provide a third oxazoline moiety for coordination, and if subsequent dissociation of one of the chelating oxazoline moieties occurs to create a species such as **B**, selectivity should be low (Figure 8). Having weaker coordinating triazole moieties present would favor dissociation of that moiety, resulting in a species such as **C** that gives rise to high selectivity.

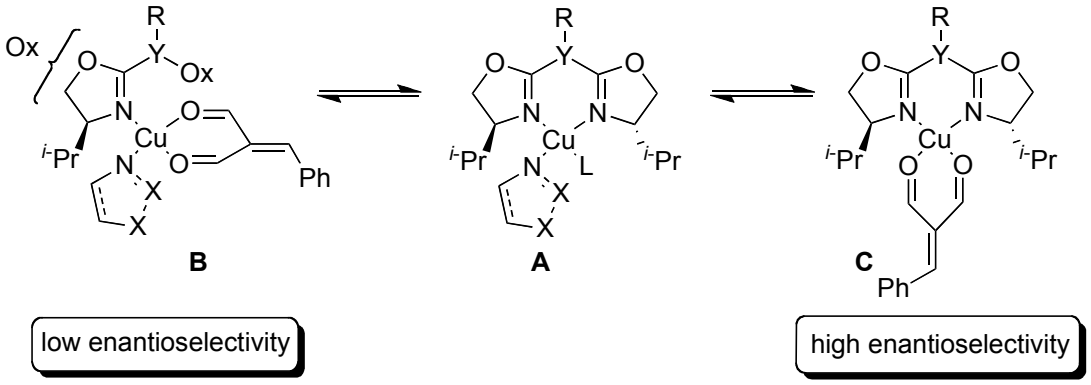


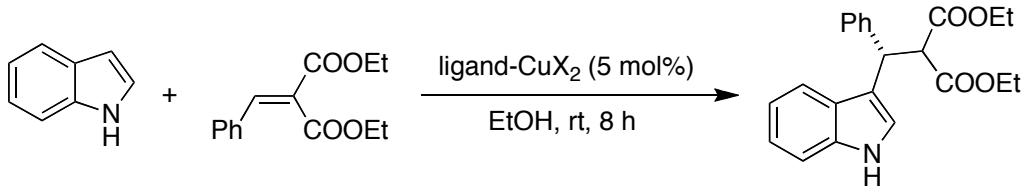
Figure 8. Mechanistic model for the asymmetric 1,4-addition to benzylidene malonates.

Following this line of argument, the superior results obtained with C_3-symmetrical tris(oxazoline) **82** in comparison with bis(oxazolines) **38** can also easily be understood since dissociation of any of the three oxazoline moieties should result in a species of type **C**.

With ligand **84**, coordination of a third oxazoline moiety by the excess of ligand might be prevented due to steric effects, which is exhibited by the benzyl substituent on the triazole unit, again resulting in a species of type **C** giving rise to the high selectivity observed in contrast to employing ligand **45a** with an external triazole additive.

4.4 Importance of ligand/metal ratio

The rationale put forward above suggests that the ligand/copper ratio might have a decisive influence on the selectivity of the title reaction and, especially, that any *excess of ligand* might be detrimental. This is quite in contrast to the usual observation in asymmetric catalysis that an excess of chiral ligand is beneficial in order to avoid background reactions by uncomplexed metal. Indeed, variation of the ratio of **45a**/copper showed a dramatic dependence on the enantioselectivity of **80a**, with the optimum being found when a ligand to copper ratio of 1.04/1 is used (Table 3, entries 1-9).



76a **79a** **80a**

entry	X in CuX_2	ligand	Cu/ligand ratio	Cu/ligand mol%	yield (%)[a]	ee (%)[b]
1	ClO_4	**45d**	1/1.3	3.8/5.0	90	87
2	ClO_4	**45d**	1/1.04	4.8/5.0	96	95
3	OTf	**45a**	1/1.3	3.8/5.0	98	81
4	OTf	**45a**	1/1.1	4.5/5.0	93	85
5[c]	OTf	**45a**	1/1.04	4.8/5.0	97	>99
6	OTf	**45a**	1/1	5.0/5.0	90	98
7	OTf	**45a**	1.1/1	5.5/5.0	96	98
8	OTf	**45a**	1.3/1	6.5/5.0	95	91
9	OTf	**38a**	1/1.04	4.8/5.0	89	99
10	OTf	-	-	7.5/0	90	0

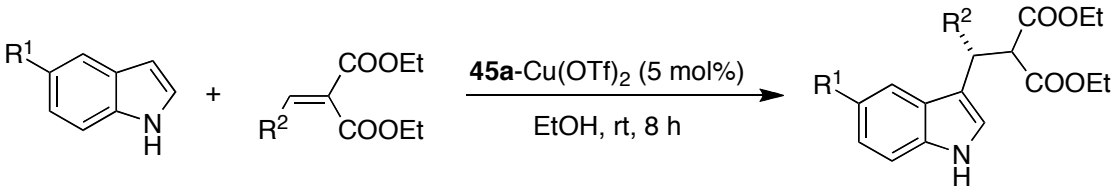
[a] isolated yield, [b] determined by HPLC, [c] obtained in three independent runs.

Table 3. Ratio dependent enantioselectivity in Michael addition.

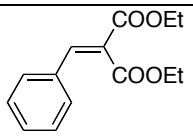
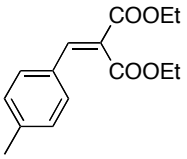
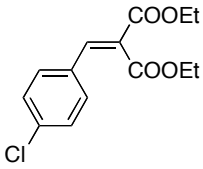
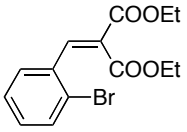
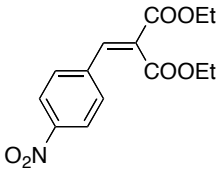
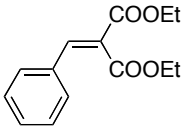
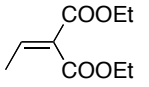
Even employing an excess of copper (entries 7 and 8) still gives respectable but somewhat inferior selectivities, giving further credit to the hypothesis of an intermediate **C** as the decisive species for the catalytic process. A control experiment (entry 10) showed that the reaction proceeds well also in the absence of ligand, clearly demonstrating that the overall process is ligand accelerated. While we noticed a similar trend employing $Cu(ClO_4)_2$ as the copper source (entries 1 and 2), using $Cu(OTf)_2$ gave better results and was therefore used for all subsequent reactions. Finally, although we generally obtained somewhat better results with the aza-(bisoxazoline) ligands, employing a copper/ligand ratio of 1/1.04 also gives very high selectivities with bis(oxazoline) **38a** (entry 9).

Applying this protocol for the reaction between other indoles and benzylidene malonates also

gave good results, and with the exception of the strongly electron-deficient *p*-nitro derivative (Table 4, entry 5), presumably an especially weak coordinating substrate for the copper-ligand complex, equaling or exceeding the selectivities obtained with tris-(oxazolines)[5].



76 **79** **80**

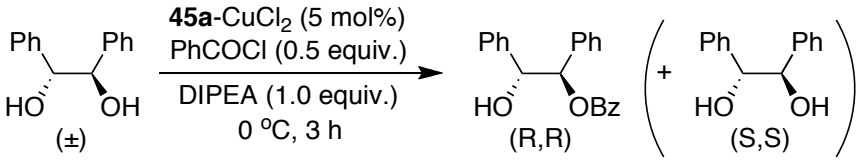
entry	**79**		R^1	product	yield (%)[a]	ee (%)[b]
1		**79a**	H	**80a**	97	99
2		**79b**	H	**80b**	80	93
3		**79c**	H	**80c**	91	98
4		**79d**	H	**80d**	89	85
5		**79e**	H	**80e**	94	80
6		**79f**	OMe	**80f**	80	90
7		**79g**	H	**80g**	95	25

[a] isolated yield, [b] determined by HPLC.

Table 4. Asymmetric conjugate addition between indoles **6** and benzylidene malonates **7**.

4.5 Conclusion

In conclusion, simple copper(II)-bis(oxazoline) complexes are excellent catalysts for the asymmetric addition of indoles to benzylidene malonates provided that *excess of ligand with respect to copper metal employed is avoided*. This observation could also be significant for related asymmetric copper-(II)- and other metal-bis(oxazoline) processes known[12, 13] that follow the paradigm that a slight excess of chiral ligands is advantageous to achieve higher



49 **50** **51**

entry	Cu/ligand ratio	Cu/ligand mol%	yield (%)[a]	ee (%)[b]
1	1.5/1.0	7.5/5.0	46	84
2	1.1/1.0	5.5/5.0	44	88
3	1.0/1.0	5.0/5.0	48	88
4	1.0/1.04	4.8/5.0	43	85
5	1.0/1.1	4.5/5.0	49	87
6	1.0/1.5	3.3/5.0	46	85

[a] isolated yield, [b] determined by HPLC.

Table 5. Dependence of enantioselectivity on copper(II)/metal ratios in the asymmetric benzoylation of diol (±)**49**

asymmetric inductions. Especially in cases of reactions with substrates that only weakly coordinate to the metal complex, making binding of an oxazoline moiety from a second ligand a competitive process suggests that metal/ligand ratios must be carefully assessed. On the other hand, excess of bis(oxazoline) ligands in metal catalyzed reactions is clearly not always detrimental to selectivity. For example, the copper(II)-azabis(oxazoline)-catalyzed[14] asymmetric benzoylation of 1,2-diols[15-17] seems to be indifferent both to excess ligand as well as to excess metal (Table 5).

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5 Immobilization of aza-bis(oxazoline) on fluorous supports

5.1 Introduction

Azabis(oxazolines)[1, 2] have proved to be especially suitable ligands for attachment onto supports owing to their strong binding to metals and therefore greatly reduced leaching when they are used in repeating cycles in catalyzes.[3-6] Our early studies on immobilization[14-16] revealed that high catalyst loading could be obtained using the CuAAC of propargylated azabox ligands and azido resins compared to the direct coupling of azabox **45** and resins with halide leaving groups. Nevertheless, lower enantioselectivities were generally observed with these ligands. It is more likely that the nitrogen donor of the triazole unit may compete with the nitrogen donor of the ligand for the complexation with metals and leading to the lower enantioselectivity. In order to overcome these limitations, we envisioned the immobilization *via* click reaction with strong electron deficient polymeric supports like fluorous tail. The use of perfluorinated alkyl chains as tags has been broadly applied to impose fluorous properties onto a given molecule. Arguably, the most important application of this strategy is to separate a perfluorinated compound from a complex reaction mixture by fluorous biphasic separations, such as by extraction, retaining the tagged molecule into a perfluorinated solvent, or by its retention onto fluorous silica or

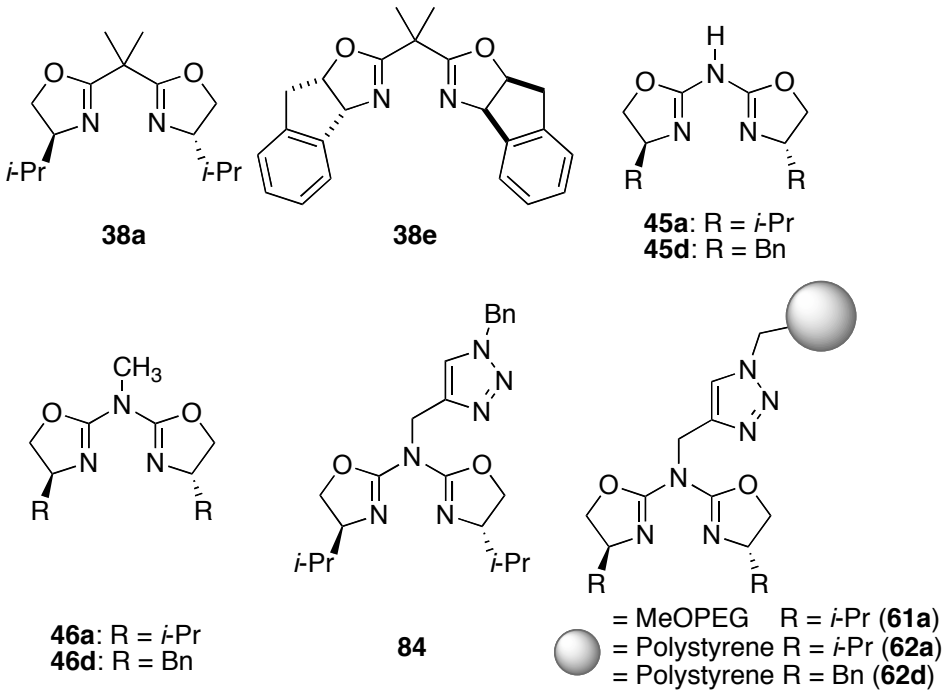
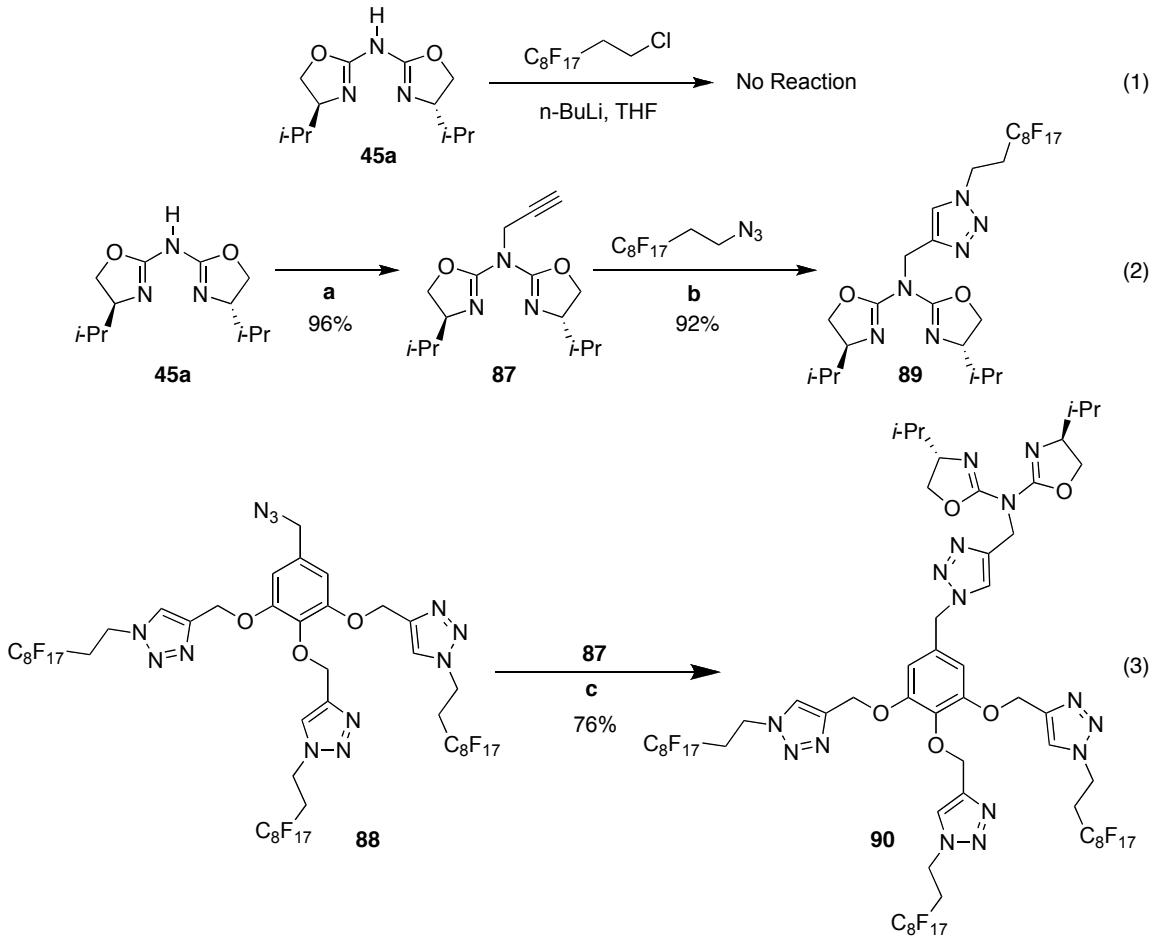


Figure 9. Structure of bis(oxazolines) and aza-bis(oxazolines).

perfluorinated polymers.[7, 8] This property has provided an attractive method for catalyst recovery and recycling, and consequently, perfluorinated tags were attached to several metal-based catalysts[21-25] including bis(oxazolines)[9-12] and organocatalysts.[13, 14]

5.2 Immobilization of azabox on perfluorinated supports

The direct reaction between aza-bis(oxazoline) **45a** and perfluorinated alkyl iodide in the presence of *n*-BuLi was unsuccessful (Scheme 26, eq 1). Consistent with our earlier observations,[3, 6, 15, 16] the copper-catalyzed azide-alkyne cycloaddition (CuAAC; a click reaction) represented a simple method for the immobilization of TEMPO[15, 16] and aza-bis(oxazolines).[3, 6] Based on these results, azabox **45a** was propargylated in the presence of *n*-BuLi and propargyl bromide in quantitative yield, which subsequently underwent CuAAC to afford **89** in 92% yield (Scheme 26), which dissolved in most of the organic solvents (eq 2).

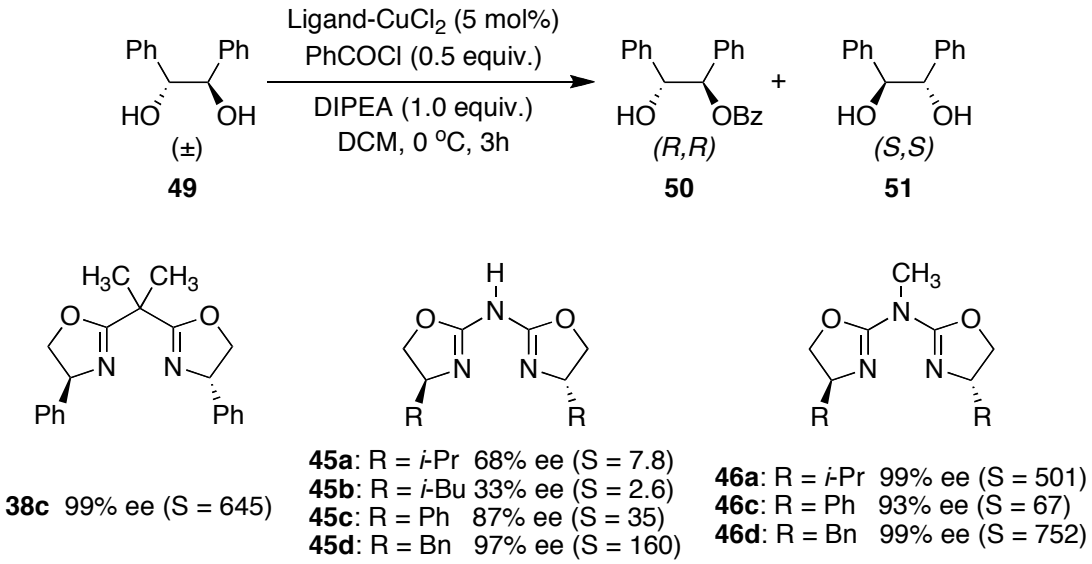


Scheme 26. Synthesis of fluorous tag bound azabis(oxazoline). a) propargyl bromide (4 equiv.), *n*-BuLi (1.2 equiv.), THF, -78 °C – rt, 24 h, 96% b) DIPEA (1.1 equiv.) CuI (6 mol%), THF, rt, 12 h, 92%. c) CuI (6 mol%), DIPEA (1.2 equiv.), THF, rt, 70 h, 76 %.

The synthesis of three ponytailed azabox **90** is described in eq 3 (Scheme 26): the required benzyl azide **88** can be readily synthesized in a multi-step procedure starting from commercially available benzoic acid ester.[17] Our laboratory has established this synthetic scheme for the immobilization of TEMPO.[17] Ligation with azide **88** using catalytic amounts of CuI[18] led to the formation of final product **90** in 76% yield, which is not soluble in any solvents.

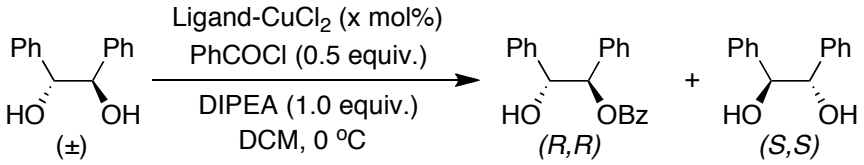
5.3 Kinetic resolution of (±)-hydrobenzoin

Enzyme-catalyzed asymmetric acylation reactions are powerful tools for the kinetic resolution or desymmetrization of alcohols.[19] Likewise, a number of efficient metal- and organocatalysts have been developed to effect this and related transformations.[20-24] We were especially intrigued by a report of Matsumura and co-workers[25, 26] who reported the asymmetric benzoylation of (±)-hydrobenzoin **49** with the Cu-(II)-bis(oxazoline) **38c** in high yields and excellent selectivities (Scheme 27). Following the protocol developed by Matsumura and coworkers,[25] ligands **45** and **46** were screened for the asymmetric benzoylation of (±)-hydrobenzoin **49**.[27] Initial studies showed that the *i*-Pr, *t*-Bu, Ph substituted ligands **45** are giving moderate selectivity while the Bn substituted ligand **45d** showed excellent enantioselectivity. Interestingly, *N*-methylated ligands **46** were more suitable for the transformation (Scheme 27).



Scheme 27. Bis(oxazoline) mediated kinetic resolution of (±)-hydrobenzoin.

To evaluate the new fluorous tagged ligands **89** and **90** for metal catalysis, we chose the copper(II)-catalyzed asymmetric mono benzoylation of diols.[28] The reaction was carried out with different mol% of ligands **89** and **90**, and the results are summarized in Table 6. The homogeneous ligand **89** showed excellent reactivity as well as high enantioselectivity: Complete conversion was observed within 2 h at 2 mol% of the ligand (Table 6, entries 6-14). The heterogeneous three pony tailed azabox **90** gave 95% ee at 5 mol% of the ligand (Table 6, entry 15), which is an inferior selectivity to the non-immobilized ligand **46a**. Interestingly, the single pony tailed **89**-$CuCl_2$ complex was recovered quantitatively[29] by the addition of diethylether to the reaction mixture and recycled up to 6 cycles without loss of its activity (Table 6, entries 6-14). Throughout all 6 cycles the enantioselectivity consistently stays at 99% ee. The heterogeneous ligand **90** was recovered by simple filtration, washed with THF, MeOH, dried and recycled into further catalytic cycles.[29] It is worth to note the superiority of fluorous tailed ligands **89** and **90** over the MeOPEG **61a** (63% ee), polystyrene **62a** (66% ee) as well as **84** (66% ee) ligands (entries 3-5).



entry	ligand	mol%	run	time (h)	yield (%)[a]	ee **50** (%)[b]	S[c]
1	**45a**	5	1	3	45	>99	501
2	**46a**	5	1	3	46	>99	536
3	**84**	5	1	3	38	66	7.2
4	**61a**	5	1	3	28	63	5.6
5[d]	**62a**	5	1	3	38	66	7.2
6[d]	**62d**	5	1	3	32	93	42
7	**89**	5	1	2	43	>99	449
8	**89**	1	1	2	46	>87	32
9	**89**	2	1	2	45	>99	501
10	**89**	2	2	2	43	>99	449
11	**89**	2	3	2	46	99	536
12	**89**	2	4	2	46	99	536
13	**89**	2	5	2	41	99	412
14	**89**	2	6	2	47	99	581
15	**90**	5	1	6	42	94	429

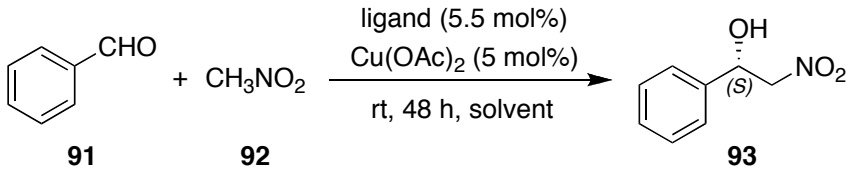
16	**90**	5	2	6	39	95	73
17	**90**	5	3	6	44	94	72
18	**90**	5	4	6	43	82	19

[a] Isolated yield based on *(R,R)* (maximum theoretical yield 50%), [b] determined by chiral GC, [c] $S = \ln[1-C(1+ee_{pr})]/\ln[1-C(1-ee_{pr})]$ ref 34, [d] rt (23 °C).

Table 6. Copper(II) catalyzed asymmetric benzoylation of hydrobenzoin with fluorous tag bound azabis(oxazoline) ligands.

5.4 Henry reaction

Prompted by the above results, we began to investigate the efficiency of these immobilized ligands in nitroaldol reactions. $Cu(OAc)_2$ mediated nitroaldol reaction was extensively studied by Evans,[30] who showed that the reaction proceeds without the requirement of additional base, since the counter anion OAc^- of $Cu(OAc)_2$ acts as a base. Inspired by their work, we began to screen the reaction in different solvents. When THF was used as solvent, it gave significant improvement in yield and enantioselectivity compared to EtOH (Table 7, entries 8 and 9 *vs* entries 6 and 7). It is interesting to note that the ligands **45a** and **45b** were inactive in this reaction (entries 4 and 5, Table 7), probably the counter ion (OAc^-) was trapped by the labile proton of azabis(oxzoline) **45**-$Cu(OAc)_2$ complex.



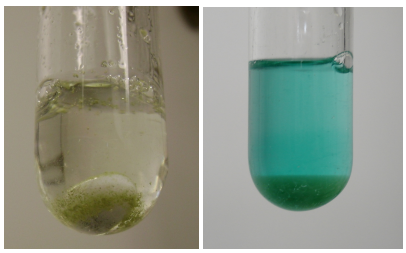
91 **92** **93**

entry	ligand	solvent	yield (%)[a]	ee (%)[b]
1[c]	**38e**	EtOH	76	-94
2	**38a**	EtOH	73	+63
3	**38a**	THF	75	+61
4	**45a**	EtOH	NR	-
5	**45b**	EtOH	NR	-
6	**46d**	EtOH	69	+73
7	**46a**	EtOH	71	+86
8	**46a**	THF	76	+92
9[d]	**46a**	THF	75	+90

[a] Isolated yield. [b] Determined by HPLC. [c] Taken from reference 37. [d] 5.0 mol% of **4a** and 5.0 mol% of $Cu(OAc)_2 \cdot H_2O$. NR = no reaction.

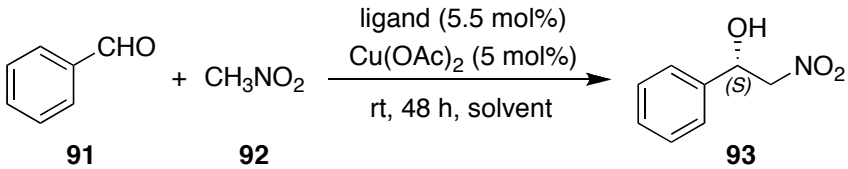
Table 7. Copper(II) catalyzed asymmetric nitroaldol reaction.

Reactions were carried out with single and three ponytailed azabox (**89** and **90**) and the results are summarized in Table 8. The reactions were sluggish with the immobilized ligands; ligand **89** gave 90% ee in THF (Table 8, entry 5), which is close to the non-immobilized ligand **46a** (92% ee). In case of 3-ponytailed azabox **90** again we observed inferior reactivity and selectivity. To examine the possibility of recycling, both the $Cu(OAc)_2$ complexes of ligands **89** and **90** were recovered by the addition of the non-polar solvent hexane to the reaction mixture[29] and the precipitated complex was reused for a few runs (Table 8). It is worth noting that the **90**-$Cu(OAc)_2$ complex was soluble in THF (forms gel material, Figure 10), whereas the corresponding $CuCl_2$ complex was insoluble.



a b

Figure 10. [a] **90**·$CuCl_2$ complex in THF, [b] **90**·$Cu(OAc)_2$·H_2O complex in THF.



91 **92** **93**

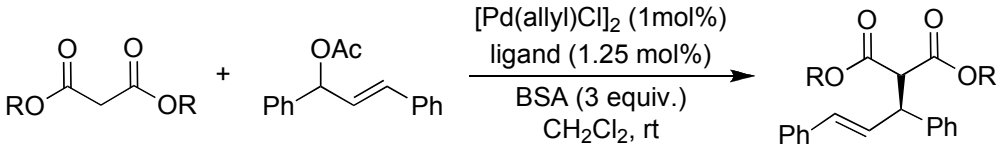
entry	ligand	solvent	run	yield (%)[a]	ee (%)[b]
1	**89**	EtOH	1	64	70
2	**89**	EtOH	2	66	62
3	**84**	THF	1	57	85
4	**89**	THF	1	64	86
5[c]	**89**	THF	1	68	90
6	**89**	THF	2	65	90
7	**89**	THF	3	63	86
8	**89**	THF	4	65	72
9	**90**	THF	1	59	86
10	**90**	THF	2	54	82
11	**90**	THF	3	57	70

[a] isolated yield. [b] determined by HPLC. [c] pre-form complex.

Table 8. Copper(II) catalyzed asymmetric nitroaldol reaction.

5.5 Palladium mediated allylation

Pd-catalyzed asymmetric allylation is one of the benchmark reaction for bis(oxazoline) ligands,[31, 32] consistent with the early results, azabox also showed excellent reactivity and selectivity. It is interesting to note that the azabox was a superior ligand in this reaction, the complete conversion was observed in 24 h with 99% ee at 1 mol% of ligand **46a**, whereas the bis(oxazoline) required 160 h for the completion with 90% of ee. Moreover, the methyl malonate **94a** reacted with allylic acetate at 1 mol% of the catalyst (Table, entries 1 and 2), but the ethyl malonate **94b** required 5 mol% of the catalyst (Table 9, entries 5-7). Also the complex formation does not require high temperature (Table 9, entries 5 and 6). Ligands **89** and **90** also gave 99% ee at 5 mol%. These fluorous immobilized ligands **89** and **90** have significant advantage over the corresponding benzyl triazole **84** or MeOPEG **61a** substituted ligands. Only traces of product formation observed with ligands **84** and **61a**. After the completion of reaction, ligand was precipitated by the addition of nonpolar solvent hexane.[29] The recovered ligand was recycled by the addition of fresh $[Pd(allyl)Cl]_2$, however, no reaction was observed.



94a: R = Me
94b: R = Et

95

96a: R = Me
96b: R = Et

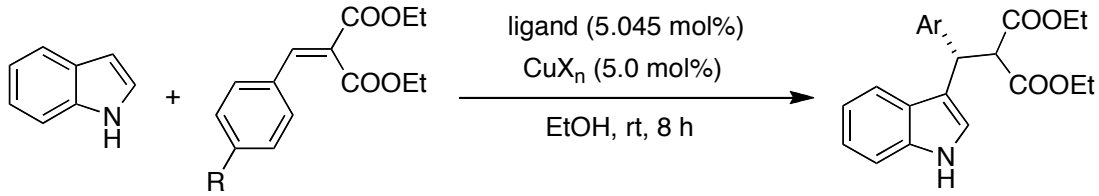
entry	R	ligand	mol (%)	time (h)	temp (^oC)	yield (%)[a]	ee (%)[b]
1	Me	**38a**	1	160	rt	94	90
2	Me	**46a**	1	24	rt	92	99
3	Et	**38a**	1	120	50	NR	-
4	Et	**46a**	1	120	50	trace	-
5[c]	Et	**46a**	5	24	rt	90	99
6	Et	**46a**	5	24	rt	94	99
7	Et	**89**	5	48	rt	90	99
8	Et	**90**	5	64	rt	86	99

[a] Isolated yield. [b] determined by HPLC. [c] complexation made at 50 ^oC and the raction continued at rt.

Table 9. Palladium(II) catalyzed allylation of malonates.

5.6 Michael addition of indoles to benzylidene malonate

Recently, we reported the highly enantioselective Friedel-Crafts alkylation of indoles,[33] for which we have shown the cruciality of metal-ligand ratio and moreover, that slight excess of ligand was detrimental for the reaction (Table 10, entries 1 and 2). Furthermore, we screened the reaction with ligand **89** and **90** (Table 10), which showed however, somewhat inferior enantioselectivity compared to the non-immobilized azabox **45a** and **46a**. The best result was obtained with $Cu(OTf)_2$ in EtOH (entry 5), giving rise to **80** in 82% of ee. Varying the ratio of ligand/MX_n, solvent and metal counter anion did not improve the selectivity of the reaction (Table 10).



76 **79** **80**

entry	ligand	R	CuX_n	yield (%)[a]	*ee* (%)[b]
1[c]	**45a**	H	$Cu(OTf)_2$	93	85
2	**45a**	H	$Cu(OTf)_2$	97	99
3	**46a**	H	$Cu(OTf)_2$	95	95
4	**84**	H	$Cu(ClO_4)_2$	93	95
5	**89**	H	$Cu(OTf)_2$	86	82
6	**89**	Cl	$Cu(OTf)_2$	82	78
7	**89**	H	$CuCl_2$	NR	-
8	**89**	H	$Cu(ClO_4)_2$	93	72
9	**90**	H	$Cu(OTf)_2$	84	68

[a] Isolated yield. [b] determined by HPLC. [c] ligand (5.5 mol%), $Cu(OTf)_2$ (5.0 mol%).

Table 10. Copper(II) catalyzed enantioselective 1,4-addition to benzylidene malonates.

5.7 Conclusion

In conclusion, fluorous tagged aza-bis(oxazolines) are efficient ligands for copper catalyzed asymmetric benzoylations and palladium-catalyzed allylic alkylation, showing equal results to the non-immobilized analogs with respect to reactivity and selectivity. In nitroaldol reactions, these ligands showed good enantioselectivity, while in Michael additions of

indoles to benzylidene malonates the fluorous ligands stayed behind their non-fluorous counterparts.

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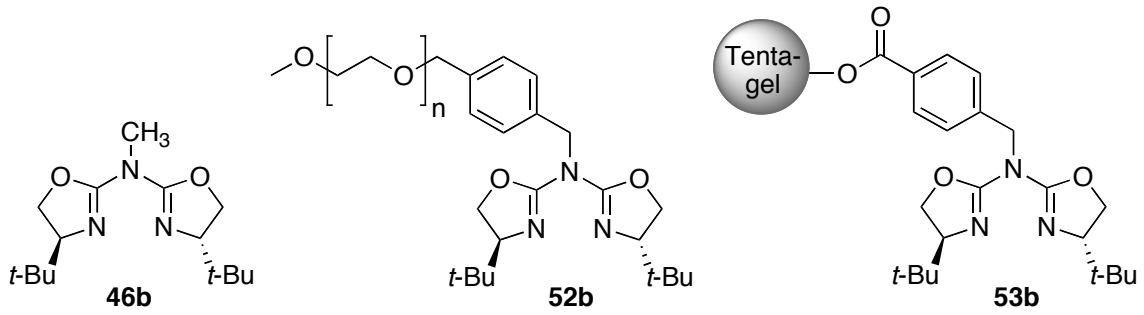
6 Secondary activation of azabox-MX_n complex

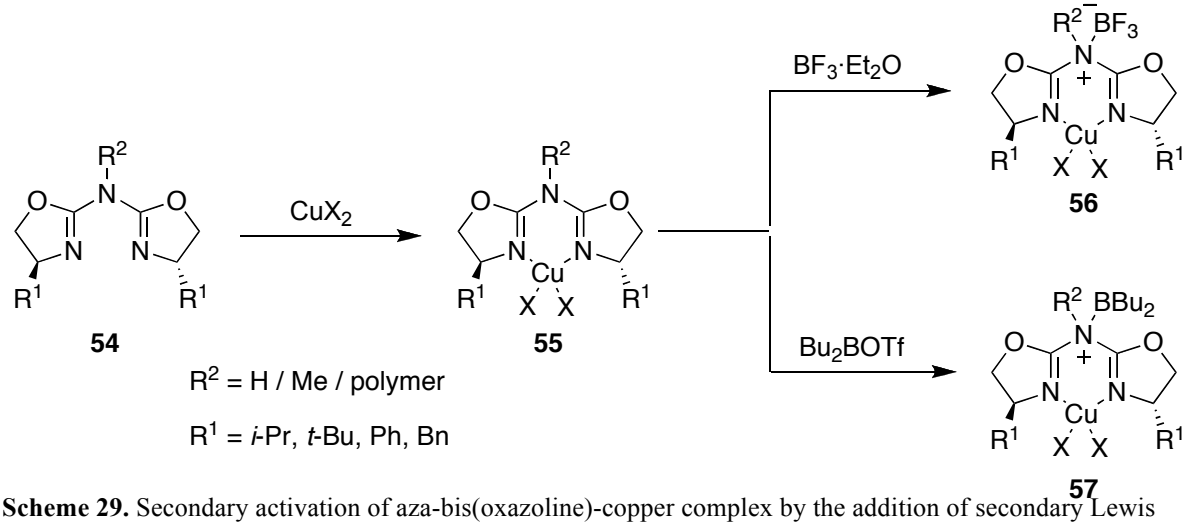
6.1 Introduction

As described earlier (Table 1) the immobilized aza-bis(oxazolines) on MeOPEG **52b** and Tentagel **53b** showed good enantioselectivities in asymmetric reactions as well, but comparatively lower yields and selectivities than their non-immobilized counterparts.[1, 2]



Scheme 28. Immobilized aza-bis(oxazolines).

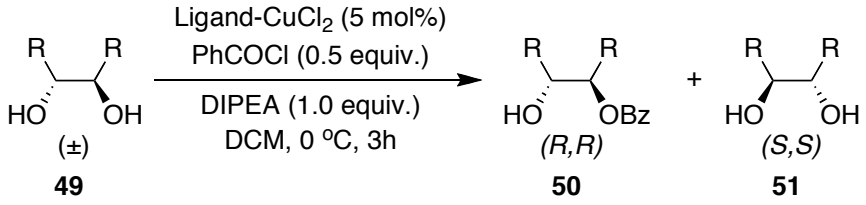
To circumvent these limitations, secondary activation of the immobilized aza-bis(oxazoline)-metal complexes by another Lewis acid (secondary LA) is envisioned as a novel methodology. Boron based Lewis acids were chosen for the preliminary investigation, since they are known to strongly coordinate with nitrogen donors. Complex **55** was investigated either in combination with $BF_3{\cdot}OEt_2$ (anionic borane intermediate **56** formation) or with Bu_2BOTf (neutral borane intermediate **57** formation). In the later method, it was envisioned that aza-bis(oxazoline) displaces the OTf from Bu_2BOTf and leads to the formation of neutral activated intermediate **57** (Scheme 29). It was aimed to carry out the preliminary investigation with non-immobilized azabox and extension to the immobilized analogs was planned (Scheme 29).

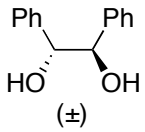


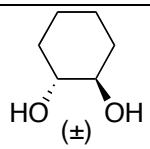
Scheme 29. Secondary activation of aza-bis(oxazoline)-copper complex by the addition of secondary Lewis acid.

6.2 Kinetic resolution of (±) 1,2-diols

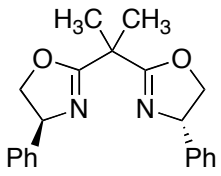
In order to work on the concept of secondary activation, we have chosen kinetic resolution of (±) 1,2-diols. We were especially intrigued by a report of Matsumura and co-workers[3, 4] who reported the asymmetric benzoylation of (±) 1,2-diols with the Cu-(II)-bis(oxazoline) **38c** in high yields and excellent selectivities (Scheme 27). Following the protocol developed by Matsumura and co-workers,[3] ligands **45** and **46** were screened for the asymmetric benzoylation of (±)1,2-diols and the results are summarized in Table 11.[5]



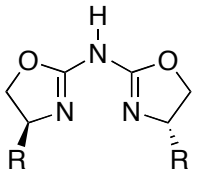
entry	1,2-diols	ligand	yield **50** (%)[a]	ee **50** (%)[b]	S[c]
1	 (±) **49a**	**38c**	48	99	645
2		**45a**	38	68	8
3		**45d**	45	97	160
4		**46a**	45	99	501
5		**46d**	49	99	752

5		**38c**	37	80	14
		45a	44	67	9
6		**45d**	41	70	9
7	**49b**	**46d**	45	73	12

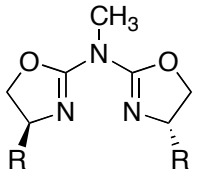
[a] isolated yield, [b] determined by chiral GC or HPLC, [c] $S = \ln[1-C(1+ee_{pr})]/\ln[1-C(1-ee_{pr})]$ ref 16.



38c



45a: R = *i*-Pr
45b: R = *t*-Bu
45c: R = Ph
45d: R = Bn



46a: R = *i*-Pr
46c: R = Ph
46d: R = Bn

Table 11. Bis(oxazolines) mediated kinetic resolution of (±)1,2-diols.

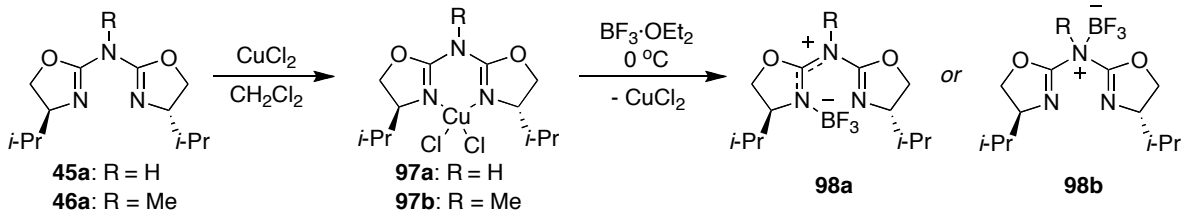
6.3 Boron trifluoride as a secondary Lewis acid

6.3.1 NMR studies

In order to work on the concept of secondary activation described in Scheme 29, we have chosen $BF_3{\cdot}OEt_2$ as a Lewis acid. Prior to the activation studies of azabox-$CuCl_2$ complex **97**, the stability of azabox ligands against $BF_3{\cdot}OEt_2$ has been studied *via* NMR spectroscopy. There were no significant changes in the ^1H and ^{13}C spectra upon the addition of $BF_3{\cdot}OEt_2$. From these studies it is apparent that the ligands **45** and **46** are stable against $BF_3{\cdot}OEt_2$. Also azabox-$Zn(ClO_4)_2$ complexes were prepared and detailed NMR studies were carried out at 0 to -78 ^oC in CD_3CN. However, ^1H and ^{13}C spectra were similar before and after the addition of $BF_3{\cdot}OEt_2$ to the **45a** and **46a**-$Zn(ClO_4)_2$ complex.

Complexes **97** were prepared by stirring ligands **45a** and **46a** with $CuCl_2$ (1 equiv) in DCM for 1 h. Recrystallization of complexes **97** was performed from DCM in order to remove uncomplexed $CuCl_2$. After cooling the complexes **97** to 0 ^oC, $BF_3{\cdot}OEt_2$ was added. The immediate precipitation of $CuCl_2$ was observed in the reaction vessel, suggesting that the $BF_3{\cdot}OEt_2$ either displaces $CuCl_2$ directly (leading to **98a)** or coordination to the central nitrogen and thereby releasing $CuCl_2$ from the complex **97** (leading to **98b)** (Scheme **30**). To circumvent the precipitation of $CuCl_2$, the reaction medium was cooled to -78 ^oC and no

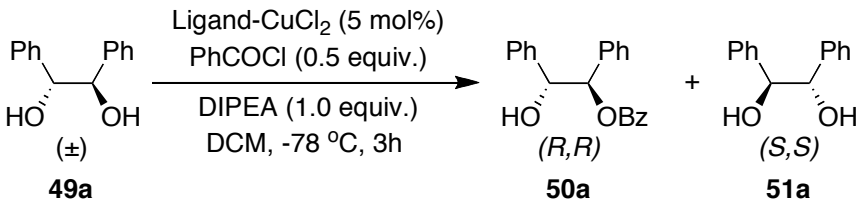
precipitation of $CuCl_2$ was observed upon addition of $BF_3{\cdot}OEt_2$. Therefore, reactions were carried out subsequently at -78 °C.



Scheme 30. Secondary activation of complex **97** with $BF_3{\cdot}OEt_2$.

6.3.2 Kinetic resolution of (±)-hydrobenzoin 49

To the metal complex **97** $BF_3{\cdot}OEt_2$ was added and the solution was stirred for an hour at -78 °C in prior to the addition of reactants. Reactions were carried out with different equivalent of $BF_3{\cdot}OEt_2$ (in correspondence to the complex **97**). Completion of reaction was observed in 3 h, however a decrease in enantioselectivity was observed with ligand **45** as well as with ligand **46** (Table 12).



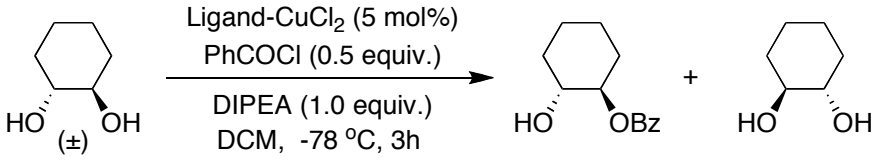
entry	ligand	$BF_3{\cdot}OEt_2$ (equiv)	yield **50** (%)[a]	ee **50** (%)[b]	S[c]
1	**45a**	0	46	92	57
2	**45a**	0.4	46	89	39
3	**45a**	0.8	45	96	118
4	**45a**	1.0	48	87	35
5	**45a**	1.2	45	95	92
6	**45a**	2.0	44	94	72
7	**46a**	0	44	>99	473
8	**46a**	0.4	47	96	134
9	**46a**	0.8	45	93	63
10	**46a**	1.0	47	95	104
11	**46a**	1.2	40	95	75
12	**46a**	2.0	45	93	63

[a] isolated yield, [b] determined by chiral GC, [c] $S = \ln[1-C(1+ee_{pr})]/\ln[1-C(1-ee_{pr})]$ ref 16.

Table 12. Secondary activation mediated kinetic resolution of (±)-hydrobenzoin.

6.3.3 Kinetic resolution of (±)-cyclohexane diol 49b

Earlier studies on kinetic resolution of (±)-cyclohexane diol **49b** revealed that the bis(oxazoline) ligands **38** and azabox ligands **45** and **46** are not very efficient for this transformation.[3, 5] Since moderate selectivities were obtained with bis(oxazoline) ligands, this could be an appropriate substrate to work on the concept of secondary activation to improve the enantioselectivity. Kinetic resolution of (±)-cyclohexane diol **49b** with complex **97** was carried out with different equivalents of $BF_3{\cdot}OEt_2$ at -78 ^oC, however a decrease in enantioselectivity was observed with ligand **45** as well as with ligand **46** (Table 13).



49b **50b** **51b**

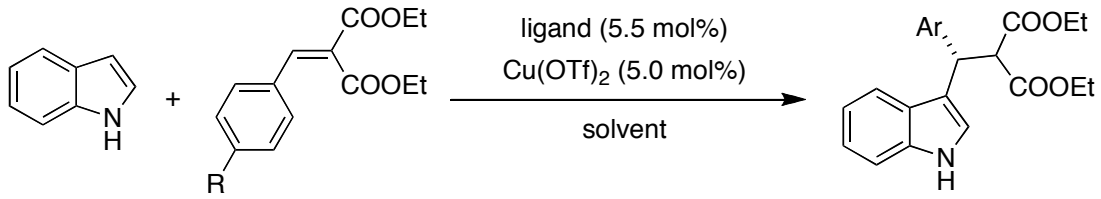
entry	ligand	$BF_3{\cdot}OEt_2$ (equiv)	yield **50b** (%)	ee **50b** (%)	S[c]
1	**45a**	0	33	87	22
2	**45a**	1.0	41	70	9
3	**45a**	2.0	33	57	5

[a] isolated yield, [b] determined by chiral GC, [c] $S = \ln[1-C(1+ee_{pr})]/\ln[1-C(1-ee_{pr})]$ ref 16.

Table 13. Secondary activation mediated kinetic resolution of (±)cyclohexane diol **49b**.

6.4 Enantioselective Friedel-Craft alkylations of Indole

Recently, we reported the highly enantioselective Friedel-Crafts alkylation of indoles to benzylidene malonates.[6] Ligand **45a** gave 99% ee when the reactions were carried out in EtOH at room temperature. In order to work on secondary activation, it was decided to screen different solvents for the title reaction. Even though the reaction proceeds smoothly in EtOH, it may deactivate the secondary Lewis acid $BF_3{\cdot}OEt_2$. Reactions were sluggish in DCM and the product **80** was isolated only in 37% yield (Table 14, entry 3). Moderate reactivity was observed in THF and the product **80** was isolated in 63% yield (Table 14, entry 4). Reactions were carried out with $BF_3{\cdot}OEt_2$ with different equivalents (corresponding to the copper-azabox complex) and in different solvents. However no significant improvements in enantioselectivity were observed. Also reactions were carried out with $SnCl_4$, unfortunately no improvement in the selectivity was observed.



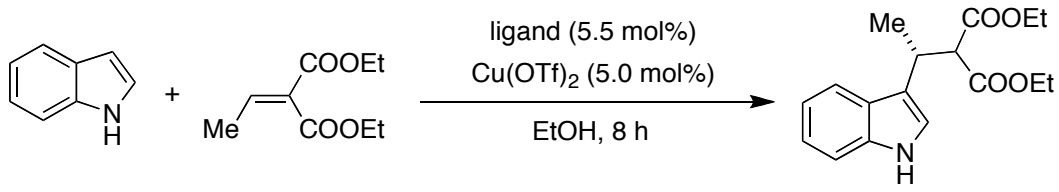
76 **79** **80**

entry	ligand	solvent	LA (equiv)	temp (^oC)	time (h)	yield (%)[a]	ee (%)[b]
1	**45a**	EtOH	-	RT	6	84	95
2	**46a**	EtOH	-	RT	6	95	95
3	**45a**	DCM	-	RT	48	37	1
4	**45a**	THF	-	RT	48	63	30
5[c]	**45a**	THF	$BF_3{\cdot}OEt_2$ (1)	-78 –RT	48	66	12
6	**45a**	THF	$BF_3{\cdot}OEt_2$ (1)	-78 –RT	48	66	5
7	**45a**	EtOH	$BF_3{\cdot}OEt_2$ (1)	-78 –RT	6	89	95
8[c]	**45a**	EtOH	$BF_3{\cdot}OEt_2$ (1)	-78 –RT	6	94	95
9	**45a**	EtOH	$BF_3{\cdot}OEt_2$ (0.6)	-78 –RT	6	90	97
10	**45a**	EtOH	$BF_3{\cdot}OEt_2$ (1.6)	-78 –RT	6	93	95
11	**46a**	EtOH	$BF_3{\cdot}OEt_2$ (1)	-78 –RT	6	94	95
12	**45a**	EtOH	$SnCl_2$ (1)	-78 –RT	6	95	86
13	**46a**	EtOH	$SnCl_2$ (1)	-78 –RT	6	95	95

[a] isolated yield, [b] determined by chiral HPLC, [c] $BF_3{\cdot}OEt_2$ was added after the addition of **79** to the ligand-$Cu(OTf)_2$ formation.

Table 14. Michael addition of benzylidene malonate **79** to indole.

Ligand **45a** gave excellent enantioselectivity in Friedel-Crafts alkylation with a broad scope of indole derivatives and benzylidene malonates.[6] However, the ethylidene malonate **79c** gave only 25% ee (Table 15, entry 1), lowering the reaction temperature did not help to improve the enantioselectivity. Secondary Lewis acid activation for this transformation was carried out with $BF_3{\cdot}OEt_2$, reaction proceeds in very good yield; unfortunately the product was racemic (Table 15).



76 **79c** **80c**

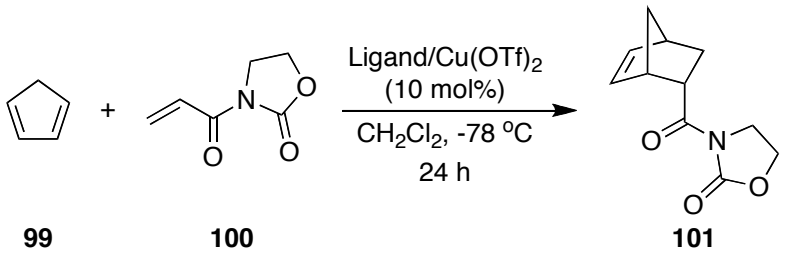
entry	ligand	$BF_3{\cdot}OEt_2$ (equiv)	yield (%)[a]	ee (%)[b]
1	**45a**	0	95	25
2	**45a**	1.0	90	0

[a] isolated yield, [b] determined by chiral HPLC.

Table 15. Michael addition of ethylidene malonate **79c** to indole.

6.5 Diels-Alder reaction

C_2-symmetric bis(oxazoline)copper complexes have proven to be excellent catalysts for enantioselective olefin cyclopropanation[7] and aziridination.[8] In addition, Corey has demonstrated that Mg(II) and Fe(III) complexes[9, 10] of the same ligands show promising results for the Diels-Alder reactions of unsubstituted acrylimides. Several research groups carried out Diels-Alder reaction between cyclopentadiene **99** and acrylimides **100** in the presence of box ligands **38**.[11-14] *t*-Bu substituted ligand **38b** gave 98% ee whereas *i*-Pr substituted ligand **38a** gave only 58% ee for the product **101** (Table 16, entries 1 and 2).[15] We also carried out Diels-Alder reactions with azabox ligand **45a** with the similar conditions reported and observed 87% ee for the product **101** (Table 16, entry 4). Moderate yield was obtained in the absence of catalyst; still the endo selectivity stays at 90% (Table 16, entry 3). Secondary activation mediated Diels-Alder reactions were carried out with $BF_3{\cdot}OEt_2$ as well as with *p*TSA. The reaction proceeded with excellent yields and endo selectivity, however a drop in enantioselectivity was observed with both Lewis acids (Table 16, entries 6 and 7).



99 **100** **101**

entry	ligand	LA (equiv)	yield (%)[a]	endo:exo[b]	ee (%)[b]
1[c]	**38b** (*t*-Bu)	-	86	98:2	98
2[c]	**38a** (*i*-Pr)	-	93	96:4	58
3	**-**	-	43	95:5	0
4	**45a** (*i*-Pr)	-	92	99:1	87
5	**45a** (*i*-Pr)	BF_3 (1.0)	80	99:1	50
6	**45a** (*i*-Pr)	$_P$TSA (1.0)	84	99:1	75
7[d]	**45a** (*i*-Pr)	-	91	98:2	82

[a] isolated yield, [b] determined by chiral HPLC, [c] from reference 17, [d] 5 mol% catalyst loading.

Table 16. Diels-Alder reaction between cyclopentadiene and unsubstituted acrylimide.

Conclusion:

In conclusion, the affinity of azabox complex **97** towards the secondary Lewis acids was observed in several reactions, however they led to a drop in enantioselectivity rather than the expected improvement. The displacement of $CuCl_2$ from complex **97** by $BF_3{\cdot}OEt_2$ clearly showed that there is a greater affinity between complex **97** and the additional secondary Lewis acid like $BF_3{\cdot}OEt_2$. However the formation of activated intermediates like **56** or **57** are not proven yet. Finally, secondary activation of azabox-metal complex by additional Lewis acid is an impressive methodology and still needs to be optimized with different Lewis acids and in various reactions.

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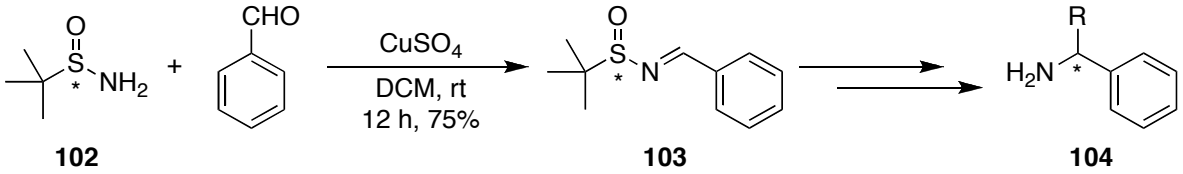
7 Kinetic resolution of sulfinamide

7.1 Introduction

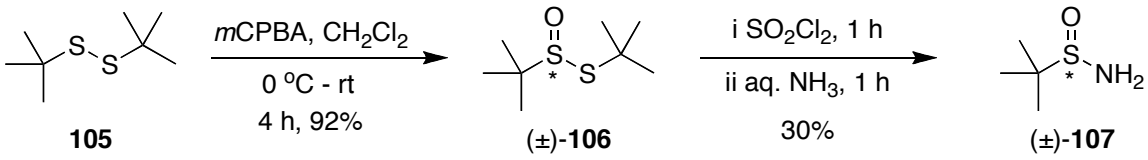
Optically pure sulfoxides are very important as synthons, as chiral auxiliaries in asymmetric synthesis and as bioactive ingredients in the pharmaceutical industry.[1,2] Sulfoxides have long been employed for a wide-range of stereoselective C-C bond forming reactions,[3] while sulfinamides and sulfinimines are increasingly being utilized as versatile chiral nitrogen intermediates for the preparation of a range of chiral amines, including α-branched amines, α- and β-amino acids, aziridines, and amino phosphonic acids. Ellman et al. reported,[4] the application of chiral *N*-*tert*-Butanesulfinimines **103** in the preparation of chiral amines **104** by highly diastereoselective 1,2-additions of organometallic reagents (Scheme 31).



Scheme 31. Synthesis of sulfinimines and 1,2 additions of organometallic reagents.

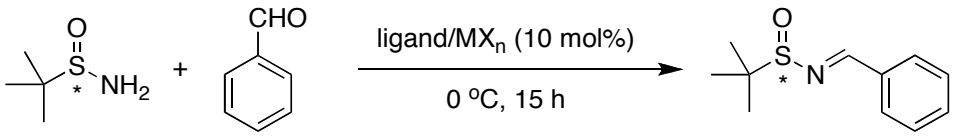
7.2 Kinetic resolution of sulfinamide

Consistent with our early studies on kinetic resolution of (±)1,2-diols,[5] we envisioned to resolute the racemic sulfinamide **107** in presence of chiral bis(oxazoline)-CuX_n complex. *tert*-Butyl sulfinamide **107** was synthesized by following the literature[6] in 2 steps (Scheme 32). *tert*-Butyl disulfide **105** was exposed to *m*CPBA in DCM to obtain (±)-**106** in 92% yield and the subsequent treatment with SO_2Cl_2 followed by aq. NH_3 afforded **107** in 30% yield (Scheme 32).



Scheme 32. Synthesis of racemic sulfinamide.

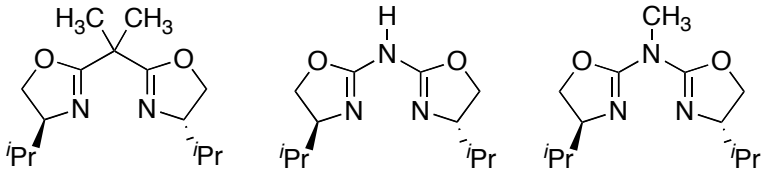
Having the racemic sulfinamide **107** in our hand, it was planned to resolve **107** by treatment with 0.5 equiv of benzaldehyde and varying solvents, ligands, dehydrating agents and metal salts. Sulfinamide (±)-**107** (1 equiv.) was treated with benzaldehyde (0.5 equiv.) in presence of bis(oxazoline)-$CuCl_2$ complex (10 mol%), the complete consumption of benzaldehyde was observed in 15 h. A dehydrating agent $CuSO_4$ (4.4 equiv) was employed in this reaction and the product **103** was isolated in 36% yield, however it was racemic (Table 17, entry 1). Also reactions were carried out in the presence of azabox-$Cu(OTf)_2$ and azabox-$CuCl_2$ complexes. Product **103** was isolated only in moderate yield (entries 2-5), when there was no dehydrating agent employed. Unfortunately, none of these conditions gave enantiomerically enriched product **103** (Table 17).



(±)-**107** **103**

entry	ligand	time (h)	solvent	MX_n	yield (%)[a]	ee (%)[b]
1[c]	**38a**	24	DCM	$CuCl_2$	36	0
2	**46a**	24	DCM	$CuCl_2$	30	0
3	**38a**	48	DCM	$CuCl_2$	12	0
4	**38a**	48	DCM	$Cu(OTf)_2$	12	0
5	**38a**	48	EtOH	$Cu(OTf)_2$	15	0

[a] isolated yield, [b] determined by chiral HPLC, [c] 4.4 equiv $CuSO_4$ added.

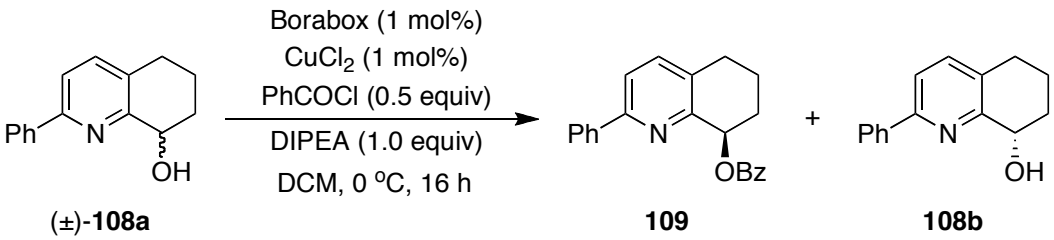


38a **45a** **46a**

Table 17. Kinetic resolution of sulfinamide by bis(oxazoline)-MX_n complex.

7.3 Kinetic resolution of sulfinimines

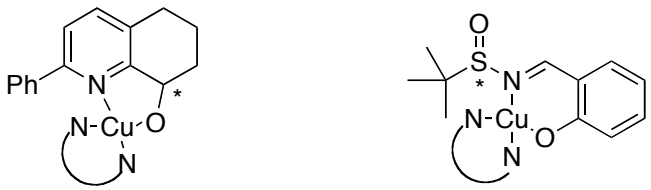
Recently Pfaltz et al. have reported[7] the kinetic resolution of racemic pyridyl alcohol (±)-**108a** by treating with 0.5 equiv of benzoylchloride at 0 °C in DCM. The Borabox-$CuCl_2$ mediated reaction completed in 16 h with 94% ee for the product **109** (Scheme 33).



(±)-**108a** **109** **108b**

Scheme 33. Kinetic resolution of racemic pyridyl alcohol.

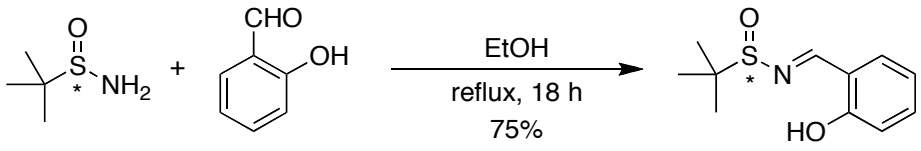
A five membered transition state **110** was proposed to account for the observed selectivity. By observing the structural features of their transition state **110**, we envisioned to prepare the racemic sulfinimine **113**. Since the sulfinimine **113** has multi-coordination sites and we expected the formation of a six membered transition state **111** with box-$CuCl_2$ complex (Figure 11) that might also give rise to the kinetic resolution of the enantiomers of **113**.



110 **111**

Figure 11. Transition states for kinetic resolution of pyridyl alchol and sulfinimine.

The synthesis of racemic sulfiniminyl alcohol **113** was accomplished in moderate yield by coupling sulfinamide (±)-**107** with salicylaldehyde **112** under reflux in EtOH for 18 h (Scheme 34).

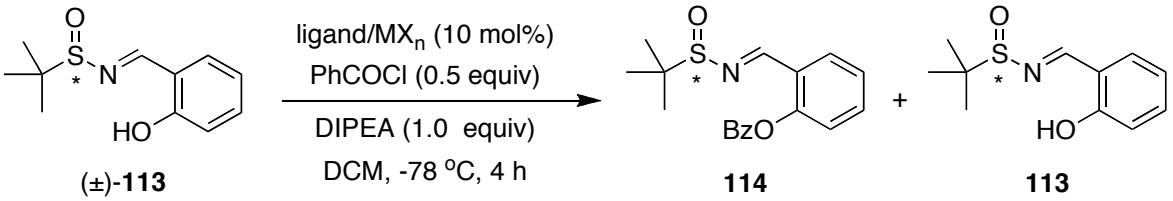


(±)-**107** **112** (±)-**113**

Scheme 34. Synthesis of racemic sulfiniminyl alcohol **113**.

Following the synthesis of (±)-**113**, it's kinetic resolution was carried out by treatment with 0.5 equiv. of benzoylchloride in the presence of bis(oxazoline) as well as with aza-bis(oxazoline)-Cu(II) complexes (Table 18, entries 1 and 2). Complete consumption of

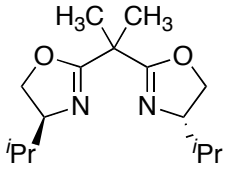
benzoylchloride was observed in 4 h with quantitative yield (maximum yield is 50%), however the isolated product **114** was racemic. The lack of selectivity could be due to the fact that in **111** the chiral center is not part of the metal chelate in contrast to **110**.



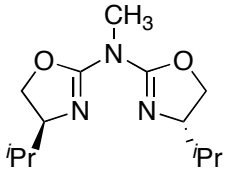
(±)-**113** **114** **113**

entry	ligand	MX_2	yield (%)	ee (%)
1	**38a**	$Cu(OTf)_2$	46	0
2	**38a**	$CuCl_2$	47	0
3	**46a**	$Cu(OTf)_2$	44	0
4	**46a**	$CuCl_2$	40	0

[a] isolated yield, [b] determined by chiral HPLC



38a



46a

Table 18. Kinetic resolution of sulfiniminyl alcohol.

7.4 Conclusion

The kinetic resolution of sulfinamide would be a valuable method since several research groups showed the versatility of these compounds as chiral auxiliaries in several syntetic applications. Still we have not succeeded to resolve the racemic sulfinamides and sulfinimines in analog to 1,2-diols with copper-azabox catalysts. The exocyclic location of the chiral center in **111** could be a reason for the unsuccessful kinetic resolution of sulfinimines and we are looking for a novel methodology to resolve it.

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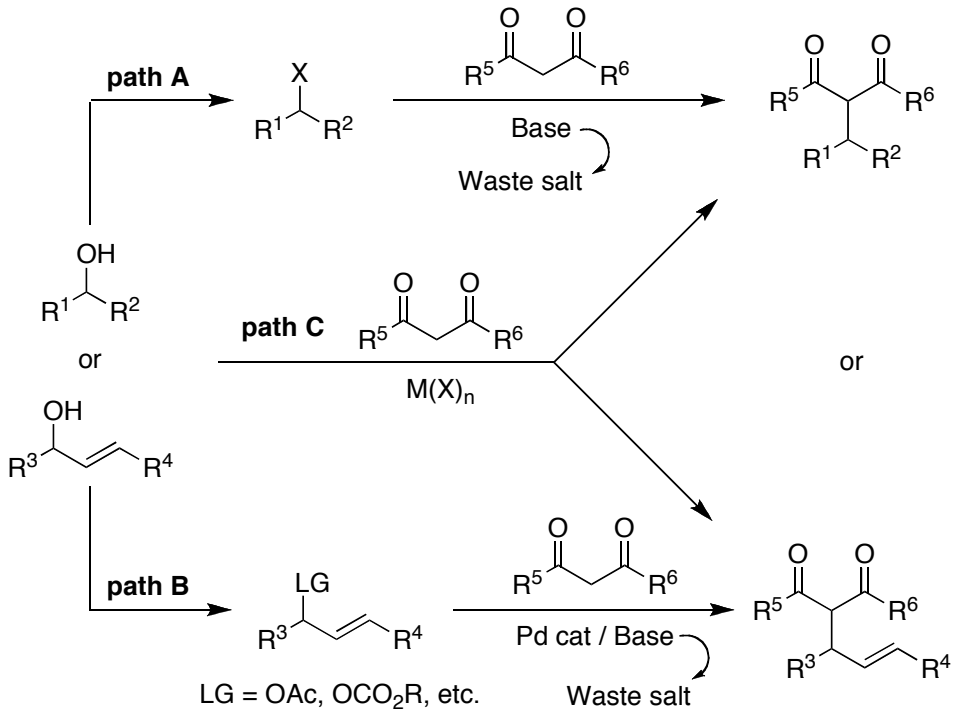
8 Copper(II) mediated direct C-C coupling reaction

8.1 Introduction

The construction of C–C bond is a fundamental reaction in organic synthesis and coupling reactions between active methylene compound, such as 1,3-dicarbonyl compounds and halides are one of the most used strategies.[1] Generally, these transformations are carried out in the presence of stoichiometric amounts of base. Although this method works well even on large scale, often it is associated with significant drawbacks including non-availability of halogenated substrates, toxicity of halogenated substrates, the use of strong bases and production of large amounts of salts as by-products. Among a variety of approaches for the alkylation of 1,3-dicarbonyl compounds, alcohols are arguably one of the most ideal substrates that are receiving increased attention.[2-8] Nevertheless, nucleophilic substitution of the hydroxy group in alcohols is generally difficult due to its poor leaving ability. As a result, hydroxy groups usually require pre-activation through transformation into good leaving groups such as halides, carboxylates, carbonates, and phosphonates before treatment with 1,3-dicarbonyl compounds can occur (Scheme 35, paths A and B).[9] However, such a process inevitably produces salt waste, which limits the scope of substrates and its use for industrial applications.[9]

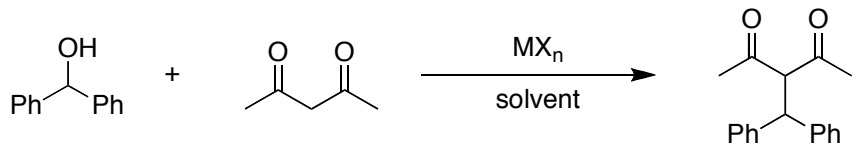


Scheme 35. General methods for the alkylation of 1,3-dicarbonyl compounds.

Therefore, the development of a practical and economical process for C–C bond formation between active methylene compounds and alcohols would be an attractive salt-free and atom-economic process with water being the only by-product (Scheme 35, path C).[10, 11]

8.2 In(III) and Yb(III) mediated direct C-C coupling

Recently, several Lewis acid and Brønsted acid catalytic systems have been proved successful for the alkylation of 1,3-dicarbonyl compounds using alcohols as electrophiles directly.[3-6, 12] Baba et al. recently reported[4] $InCl_3$ mediated C-C coupling of benzylic and allylic alcohols with 1,3-dicarbonyl compound: refluxing benzylic alcohol **115** with acetylacetone **116** in toluene at 80 ^oC afforded **117** in 99% yield (Table 19, entry 1).



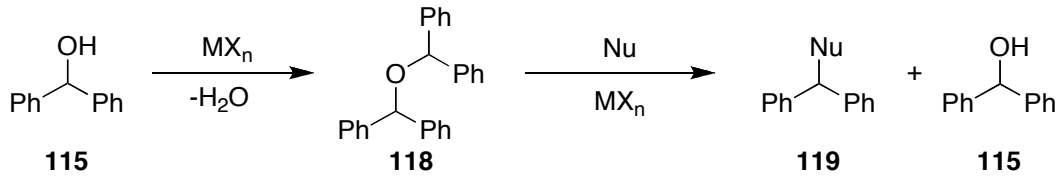
115 **116** **117**

entry	MX_n	solvent	temp (^oC)	time (h)	yield (%)
1	$InCl_3$	toluene	80	15	99
2	$Yb(OTf)_3$	CH_3NO_2	60	1	96
3	$FeCl_3$	DCM	45	3	92

Table 19. Metal mediated carbon-carbon coupling between benzylic alcohol and acetylacetone.

Zhou et al. also investigated the same reaction in the presence of $Yb(OTf)_3$ and observed 96% yield for the product **117** (Table 19, entry 2).[9] More interestingly, Jana has recently reported that the cheap iron-salts such as $FeCl_3$ can catalyze the reaction in quantitative yield (Table 19, entry 3).[1]

The mechanism for this transformation is proposed to proceed *via* the dimerization of **115** by eliminating one molecule of water followed by the nucleophilic attack on the dimer **118** (Scheme 36). The isolation of dimer **118** in the absence of a nucleophile, confirms that the reaction passes through the dimerization of benzylic alcohols **115**.[4]

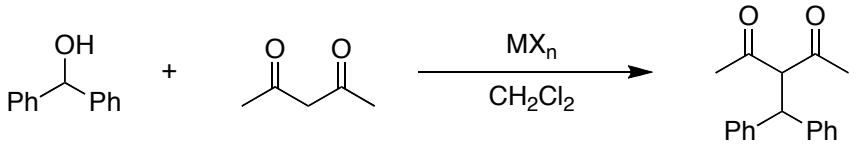


115 **118** **119** **115**

Scheme 36. Mechanism for the metal catalyzed alkylation of benzylic alcohols.

8.3 Fe(III), Cu(II) and Sc(III) mediated direct C-C coupling

Attracted by the above transformations, we wondered whether the asymmetric fashion of this reaction could be an interesting and challenging task. We began our investigation by screening various metal salts. Especially we were more interested to see the activity of $Cu(OTf)_2$ and $Sc(OTf)_3$, since it is well known that they form strong complexes with chiral bis(oxazoline) ligands. To our delight, $FeCl_3$ can catalyze the reaction in 30 min at room temperature rather than the reported requirement of 3 h and reflux condition (Table 20, entries 1 and 2). When $Sc(OTf)_3$ was employed the complete conversion of benzylic alcohol **115** into the product **117** was observed in 2 h (Table 20, entry 4)., whereas $Cu(OTf)_2$ took 24 h for the complete conversion (Table 20, entry 3).



115 **116** **117**

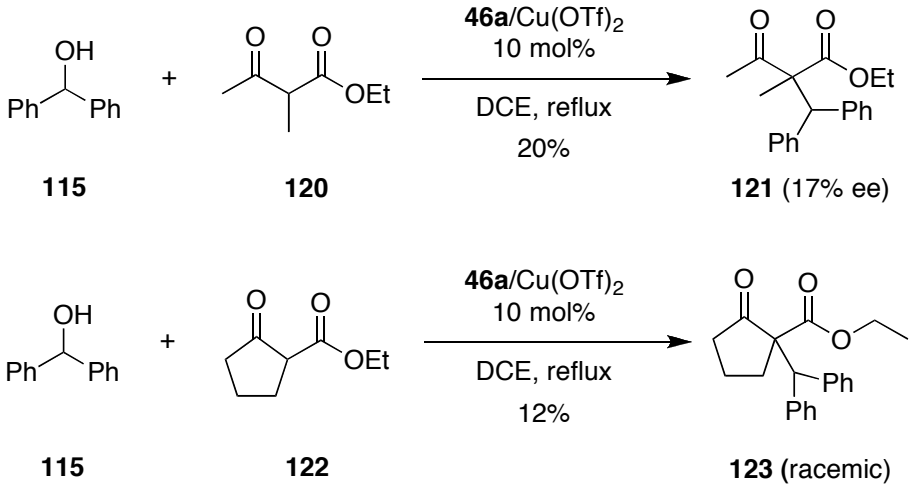
entry	MX_n	temp (^oC)	time (h)	yield (%)[a]
1[b]	$FeCl_3$	reflux	3	97
2	$FeCl_3$	RT	0.5	97
3	$Cu(OTf)_2$	RT	24	90
4	$Sc(OTf)_3$	RT	2	92

[a] isolated yield, [b] from ref 1.

Table 20. Cu(II) and Sc(III) mediated carbon-carbon coupling between benzylic alcohol and acetylacetone.

When nitroethane was employed as a nucleophile, no reaction was observed either by employing $FeCl_3$ or $Cu(OTf)_2$. In order to introduce and explore the asymmetric induction, reactions were carried out with α-substituted 1,3-dicarbonyl compounds in presence of bis(oxazoline)-$Cu(OTf)_2$ complex. Conversion of **120** into the product **121** was observed

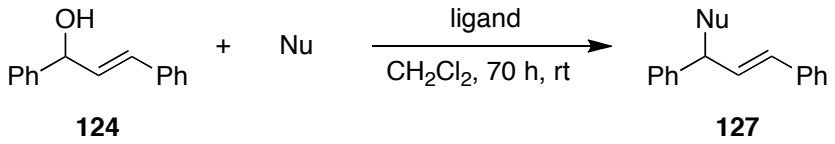
with poor yield (20%), however the enantiopurity stays only at 17% (Scheme 37). Interestingly, sterically more hindered 1,3-diketone **122** converted into the product **123** in presence of **46a**-Cu(OTf)$_2$ complex, unfortunately **123** was also racemic (Scheme 37).

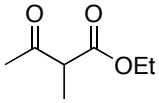
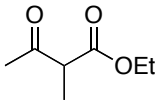
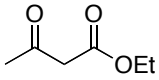
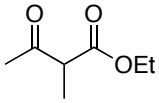
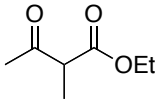
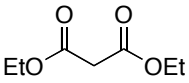
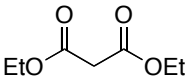
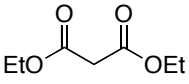
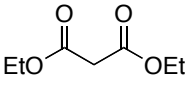
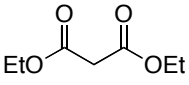
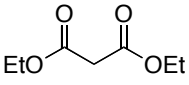
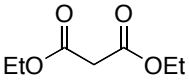


Scheme 37. Asymmetric C-C coupling of α-substituted 1,3-dicarbonyl compounds with benzylic alcohols.

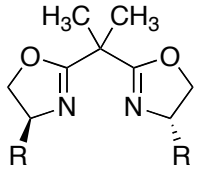
8.4 Allylic alcohols as an electrophile

Like benzylic alcohols, allylic alcohols are also known to undergo C-C coupling in the presence of various metal salts; again there is no report on copper mediated coupling reaction. Reactions were carried out between allylic alcohol **124** and various 1,3-diketones in presence of $FeCl_3$ and Cu(OTf)$_2$. Allylic alcohol **124** underwent reaction with diketone **120** in presence of $FeCl_3$ and afforded **127a** in 82% yield. Fortunately Cu(OTf)$_2$ also gave 87% yield for the product **127a** and 91% yield for the product **127b**. Chiral bis(oxazolines) are employed in order to explore the asymmetric synthesis of **127**. All reactions were proceeded with very good yield in presence of ligand-Cu(OTf)$_2$ complex. Of the numerous ligands and substrates screened, only ligand **38a** and **46a** gave 22% ee for the product **127c**. Employing additives like 4Å MS also did not help to improve the ee. Even though all substrates underwent smooth conversion into the product with very good yield, selectivities were either low or nil.

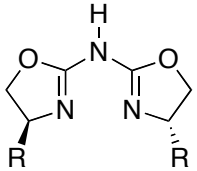


entry	substrate (Nu)	product	MX_n	ligand	yield (%)[a]	ee (%)[b]
1	**120** 	**127a**	$FeCl_3 \cdot 6H_2O$	-	82	-
2	**120** 	**127a**	$Cu(OTf)_2$	-	87	-
3	**125** 	**127b**	$Cu(OTf)_2$	-	91	-
4	**120** 	**127a**	$Cu(OTf)_2$	**38a**	83	0
5	**120** 	**127a**	$Cu(OTf)_2$	**45d**	81	0
6[c]	**126** 	**127c**	$Cu(OTf)_2$	**38a**	86	15
7	**126** 	**127c**	$Cu(OTf)_2$	**45d**	84	4
8[c]	**126** 	**127c**	$Cu(OTf)_2$	**38c**	84	13
9[c]	**126** 	**127c**	$Cu(OTf)_2$	**46a**	90	22
10	**126** 	**127c**	$Cu(OTf)_2$	**38a**	82	22
11	**126** 	**127c**	$Cu(OTf)_2$	**38c**	78	14
12	**126** 	**127c**	$Cu(OTf)_2$	**46a**	87	19

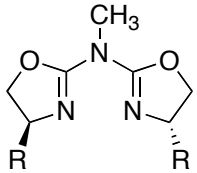
[a] isolated yield, [b] determined by chiral HPLC, [c] 4Å MS was employed as an additive.



38a: R = *i*-Pr
38c: R = Ph



45a: R = *i*-Pr
45d: R = Bn

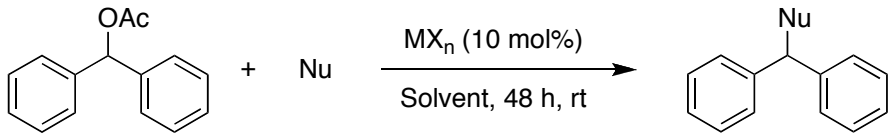


46a: R = *i*-Pr
46d: R = Bn

Table 21. Asymmetric C-C coupling of 1,3-dicarbonyl compounds with allylic alcohol.

8.5 Benzylic acetate as an effective electrophile

Since the asymmetric C-C coupling with benzylic and allylic alcohols gave low enantioselectivities, we decided to work on benzylic acetates, since the acetate carbonyl can assist the coordination of substrate to the metal complex. Also the metal mediated reaction between benzylic acetate and 1,3-diketones is unexplored. Initial reactions are carried out without chiral ligands, benzylic acetate **128** was treated with various 1,3-diketones in the presence of copper(II) and iron(III) salts. $Cu(OTf)_2$ mediated reaction between **128** and **120** gave **121a** in 92% yield in DCM, where as $FeCl_3{\cdot}6H_2O$ gave **121a** in 89% yield (Table 22, entries 1 and 2). Also reactions were carried out in DCE and observed the similar reactivity and yield (Table 22, entries 3-7). To expand the scope of this reaction, small libraries of substrates were screened under the same reaction condition and observed excellent yield (Table 22), however no reaction was observed with substrate **126**.



128 **121/123**

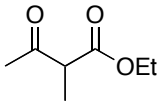
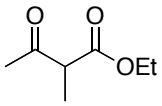
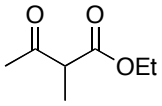
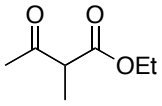
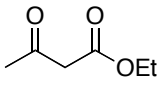
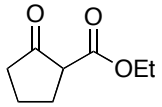
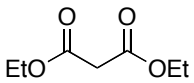
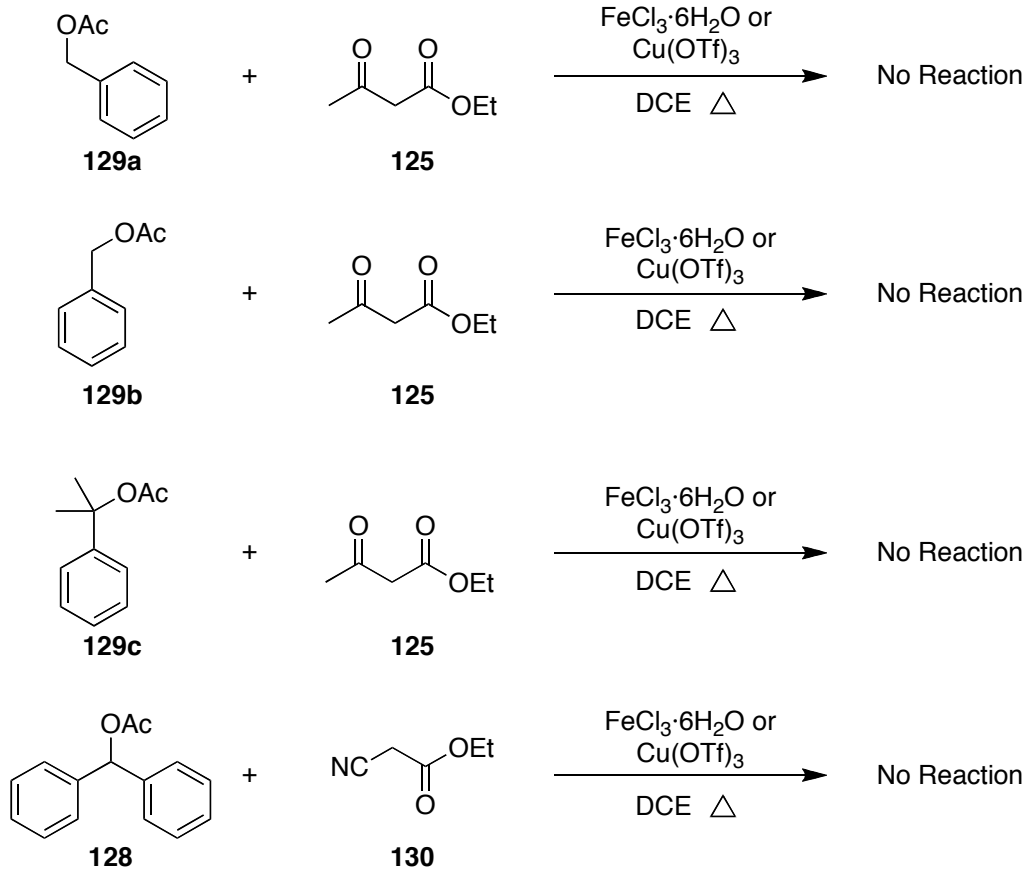
entry	substrate (Nu)	product	MX_n	solvent	yield (%)
1	**120** 	**121a**	$Cu(OTf)_2$	DCM	92
2	**120** 	**121a**	$FeCl_3{\cdot}6H_2O$	DCM	89
3	**120** 	**121a**	$Cu(OTf)_2$	DCE	92
4	**120** 	**121a**	$FeCl_3{\cdot}6H_2O$	DCE	94
5	**125** 	**121b**	$FeCl_3{\cdot}6H_2O$	DCM	96
6	**122** 	**123a**	$FeCl_3{\cdot}6H_2O$	DCM	92
7	**126** 	**121c**	$FeCl_3{\cdot}6H_2O$	DCM	No rxn

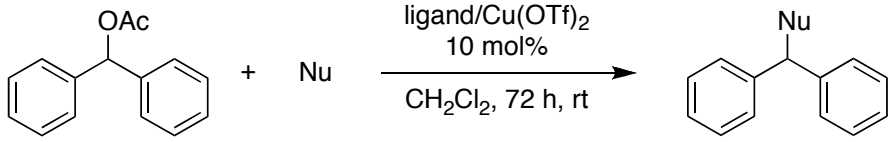
Table 22. Cu(II) and Fe(III) mediated Carbon-Carbon coupling between benzylic acetate and β-keto esters.

To explore the scope of substrates, reactions were carried out with primary and tertiary benzylic acetates, however none of them led to the product formation (Scheme 38). Employing α-cyano esters as a nucleophile also did not give the product (Scheme 38).



Scheme 38. Cu(II) and Fe(III) mediated Carbon-Carbon coupling between benzylic acetate and β-keto esters.

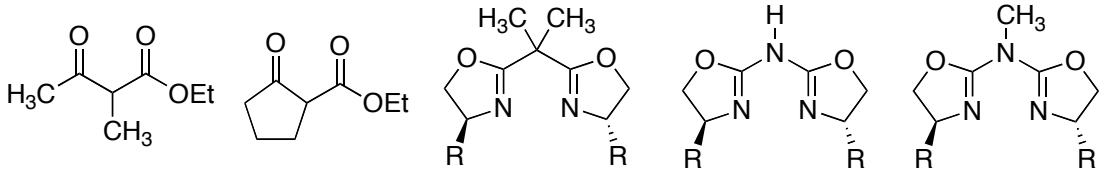
The extension of this methodology in asymmetric fashion was planned to carry out in the presence of box and azabox ligands. Benzylic acetate **128** was treated with substrate **120** in the presence of **38a**-$Cu(OTf)_2$ complex, alkylated product **121a** was isolated in 81% yield. However, the enantioselectivity for the product **121a** was only 10% (Table 23, entry 1). Further screening was carried out with various aza-bis(oxaozlines), ligand **45d** gave 23%ee for the product **121a** (Table 23, entry 3). Other ligands gave either low ee's or racemic products. It is interesting to see the seamless formation of quaternary carbon centered product **123a** from substrate **122**. Product **123a** was isolated in moderate yield (entries 9-13), however only 28% ee was observed with ligand **45d** (entry 12). Screening with other ligands did not improve the enantioselectivity (Table 23).



128 **121/123**

entry	substrate (Nu)	ligand	product	yield (%)[a]	ee (%)[b]
1	**120**	**38a**	**121a**	81	10
2	**120**	**45c**	**121a**	68	0
3	**120**	**45d**	**121a**	71	23
4	**120**	**38c**	**121a**	52	13
5	**120**	**45a**	**121a**	49	0
6	**120**	**45b**	**121a**	56	0
7	**120**	**45a**	**121a**	49	0
8	**120**	**45b**	**121a**	56	0
9	**122**	**45a**	**123a**	61	0
10	**122**	**45b**	**123a**	72	0
11	**122**	**45c**	**123a**	61	7
12	**122**	**45d**	**123a**	80	28
13	**122**	**38c**	**123a**	63	7

[a] isolated yield, [b] determined by chiral HPLC,



120 **122**

38a: R = *i*-Pr
38c: R = Ph

45a: R = *i*-Pr
45b: R = *t*-Bu
45c: R = Ph
45d: R = Bn

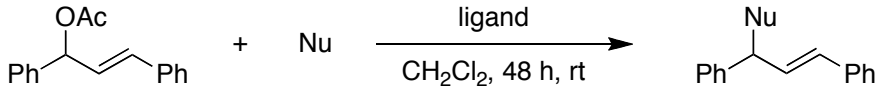
46a: R = *i*-Pr
46d: R = Bn

Table 23. Box-Cu(OTf)$_2$ complex mediated asymmetric Carbon-Carbon coupling reactions.

8.6 Coupling of allylic acetate and β-ketoesters

Allylic acetates are well known in palladium-mediated alkylations,[13] however the reaction between allylic acetate and 1,3-diketones are limited to palladium chemistry. To extend the scope of this allylation in favor of other metal salts, we planned to screen the reaction with iron and copper salts. Also this allylation is an unprecedented reaction in presence of iron or copper salts. Treatment of allylic acetate **131** with 1,3-dikentone **125** in presence of

$Cu(OTf)_2$ gave the product **132a** in 96% yield (Table 24, entry 1). Also the reaction proceeded in very good yield with $FeCl_3 \cdot 6H_2O$ and $Sc(OTf)_3$ (Table 24, entries 2 and 3). The sterically more hindered α-substituted ester **120** also gave the product **132c** in 89% yield when $FeCl_3 \cdot 6H_2O$ was employed and 84% yield when $Cu(OTf)_2$ was employed. However there was no reaction observed when diethylmalonate **126** was used as a nucleophile (Table 24, entry 4).



131 **132**

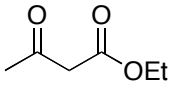
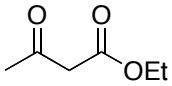
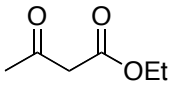
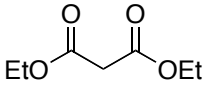
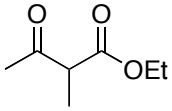
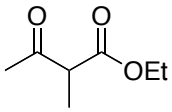
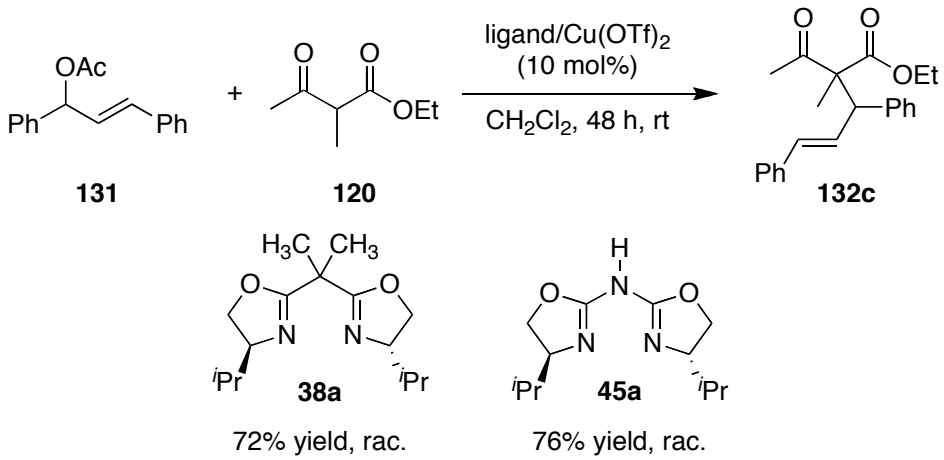
entry	Nu	product	MX_n	yield (%)
1	**125** 	**132a**	$Cu(OTf)_2$	96
2	**125** 	**132a**	$FeCl_3 \cdot 6H_2O$	92
3	**125** 	**132a**	$Sc(OTf)_3$	92
4	**126** 	**132b**	$FeCl_3 \cdot 6H_2O$	No rxn
5	**120** 	**132c**	$FeCl_3 \cdot 6H_2O$	89
6	**120** 	**132c**	$Cu(OTf)_2$	84

Table 24. Cu(II), Sc(III) and Fe(III) mediated allylations.

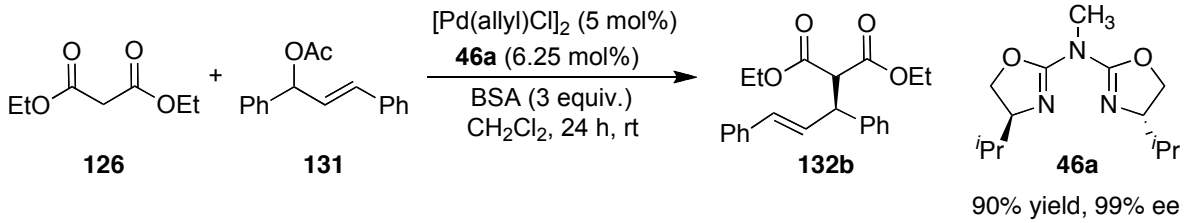
Following the success of Cu(II) mediated allylations, our interest turned to explore them in asymmetric synthesis. Reactions were carried out with box-$Cu(OTf)_2$ and azabox-$Cu(OTf)_2$ complexes. Complete conversion of starting material was observed within 48 h and the product **132c** was isolated in moderate yields. However we were again unsuccessful in obtaining enantiopure products (Scheme 39).



Scheme 39. Asymmetric allylation catalyzed by box ligands.

8.7 Palladium(II) and copper(II) combined allylations

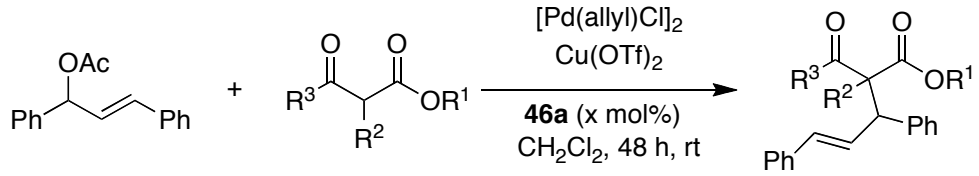
Pd-catalyzed asymmetric allylation is one of the benchmark reaction for bis(oxazoline) ligands.[13, 14] It is well known in the literature that the reaction between allylic acetate and malonate requires stoichiometric amounts of base. For example; Pd(II) mediated allylation of ethylmalonate **126** requires 3 equiv. of base (BSA) (Scheme 40). From the studies described above it might be possible that the reaction can be catalyzed in presence of catalytic amount of $Cu(OTf)_2$ without the requirement of stoichiometric Brønsted base.



Scheme 40. Palladium(II) catalyzed allylation of malonates.

Reactions were planned to perform with palladium in combination with copper salts, by this way palladium will assist the cleavage of acetate group from **131** and $Cu(OTf)_2$ could assist the deprotonation of malonates. Initial reactions were performed with a 1:1 ratio (totally 1 equiv) of Pd(II) and Cu(II) salts in complexation with bis(oxazoline) ligands (1 equiv). No reaction was observed when the ratio between $[Pd(allyl)Cl]_2$ and $Cu(OTf)_2$ was 1:1 (Table 25, entry 1), even increasing the reaction temperature also did not help the product formation. But the reaction proceeds if excess of $Cu(OTf)_2$ was employed (Table 25, entry 2), however the product was racemic. Reactions were carried out in higher catalyst loading,

but there was no reaction if the ratio between $[Pd(allyl)Cl]_2$ and $Cu(OTf)_2$ was 1:1 (entries 3 and 4). Changing the substrate from simple malonate to α-substituted esters did not allow the product formation; even increasing catalyst loading did not help to obtain the product (entries 5 and 6).



131 **132**

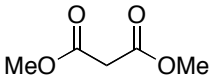
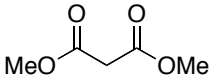
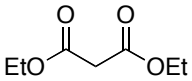
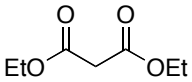
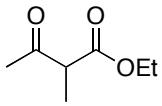
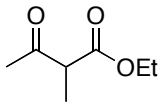
entry	substrate	**46a** mol%	**46a** (equiv)	$Cu(OTf)_2$ (equiv)	$[Pd(allyl)Cl]_2$ (equiv)	yield (%)	ee (%)
1	**133** 	1	1.25	0.50	0.25	NR	-
2	**133** 	1	1.25	0.5-10	0.50	62-95	0
3	**126** 	5	6.25	2.50	1.25	NR	-
4	**126** 	5	6.25	0.5-10	2.50	40-93	0
5	**120** 	10	1.2	0.5	0.25	NR	-
6	**120** 	1	1.2	0.5	0.25	NR	-

Table 25. Pd(II) and Cu(II) catalyzed allylation of malonates.

8.8 Conclusion

In summary, a general and highly efficient Cu(II) and Fe(III) catalyzed alkylation of diketo, keto esters, and even lower acidic diethyl malonate compounds using allylic and benzylic alcohols as electrophiles had been developed. The corresponding alkylated products were obtained in moderate to high yields, mostly at room temperature. Furthermore, the present catalyst could be recovered and reused. Highly potential asymmetric induction for this C-C coupling was not very successful; it is also known in the literature that the sterically less bulky malonates are not suitable substrates in order to obtain high enantioselectivity. The

present work focuses on the further development of this methodology is currently under way.

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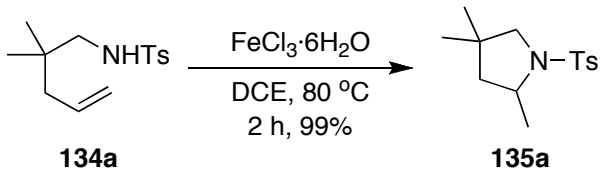
9 Hydroamination and aminohalogenation

9.1 Introduction

The direct addition of N-H bonds across alkenes and alkynes (hydroamination) is an efficient method for the formation of C-N bonds.[1] Although many catalysts for this transformation have been developed recently, the hydroamination of unactivated alkenes remains a significant challenge. Recently, Komeyama et al. reported[2] a simple efficient methodology for hydroamination, using $FeCl_3$ as well as $Cu(OTf)_2$ as catalysts (Scheme 41). *N*-Tosylated amino olefin **134a** was refluxed with $FeCl_3 \cdot 6H_2O$ in DCE for 2 h and the product pyrrolidine **135a** was isolated quantitatively (Scheme 41).

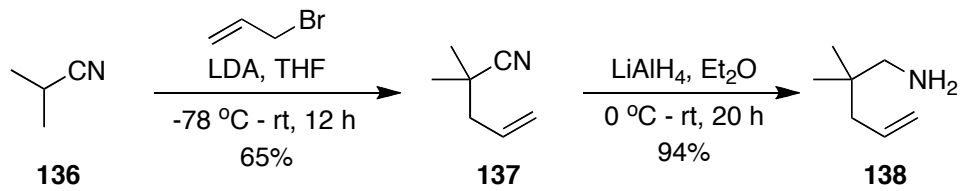


Scheme 41. Hydroamination of unactivated amino-olefin.

Enantiopure polyfunctionalized pyrrolidines are found in pharmaceuticals and in numerous natural products.[3-5] Enantiopure pyrrolidine derivatives are also valuable building blocks for the synthesis of more complex derivatives, including the pyrrolizidine and indolizidine alkaloids.[3-5] Last but not least enantiopure pyrrolidines are also useful chiral auxiliaries and ligands for asymmetric syntheses.[6, 7]

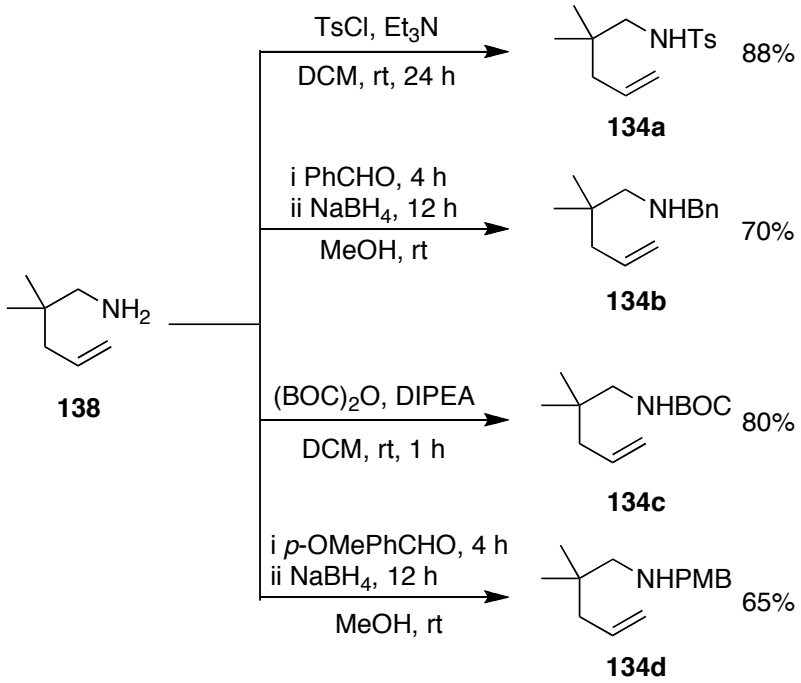
9.2 Cu(II) and Fe(III) mediated hydroamination

Impressed on the work of Komeyama et al., we aimed to utilize the same methodology in an asymmetric fashion. The unactivated amino olefin **138** was synthesized starting from isobutyronitrile **136** in 2 steps (Scheme 42). Isobutyronitrile **136** was treated with LDA followed by trapping the anion with allylbromide afforded **137** in 65% yield, subsequent reduction with LAH led to the **138** in 94% yield.[8]



Scheme 42. Synthesis of amino olefin **138**.

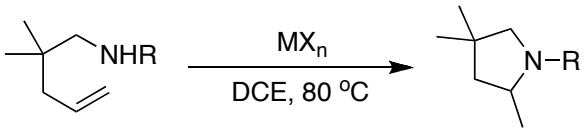
It is well known that the primary amine **138** does not undergo hydroamination under various conditions, but that a corresponding secondary amine undergoes hydroamination in the presence of various metal salts. Thus the free amine **138** was functionalized with different protecting groups by following standard methods (Scheme 43). Amine **138** was tosylated in the presence of TsCl and triethylamine; **134a** was isolated in 88% yield. Benzylation was carried out by treating **138** with benzaldehyde followed by the reduction with $NaBH_4$, likewise PMB protection succeeded this way in 65% yield. Boc protection of **138** was carried out with $(Boc)_2O$ in DCM and **134c** was isolated in 80% yield (Scheme 43).



Scheme 43. Functionalization of amino olefin **138**.

Having a variety of aminoolefins **134** in our hand, we were investigated hydroaminations by changing ligands as well as metal salts. Hydroamination proceeds smoothly in the presence of iron as well as copper salts (Table 26, entry 1 and 3) with moderate to good yields.

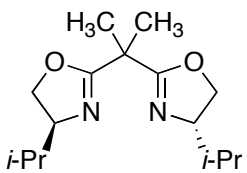
Refluxing **134a** in DCE with $FeCl_3 \cdot 6H_2O$ at 80 °C gave pyrrolidine **135a** in 90% yield (entry 1), also $Fe(ClO_4)_3 \cdot 6H_2O$ gave the product **135a** in 72% yield, $Cu(OTf)_2$ gave 83% yield (entry 3). However, no reaction was observed with either $Cu(ClO_4)_2 \cdot 6H_2O$ or $IrCl_3$. Reactions were then carried out in the presence of a variety of chiral ligands, unfortunately no reaction was observed with either **38a**-$Cu(OTf)_2$ or **38a**- $Fe(ClO_4)_3 \cdot 6H_2O$ complex (entries 8 and 9). Even though the reactions proceed in the absence of ligands, none of the complexes led to the product formation. Further increase in the reaction temperature or catalyst loading did not favor the formation of product (Table 26). Even the use of salen-$Fe(acac)_3$ complex also did not assist the reaction to proceed (entry 10).



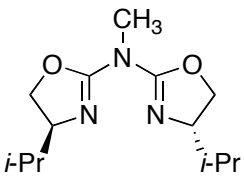
134 **135**

entry	R (**134**)	MX_n	ligand	time (h)	yield (%)[a]
1	Ts (**134a**)	$FeCl_3.6H_2O$	-	2	90
2	Ts (**134a**)	$Fe(ClO_4)_3.6H_2O$	-	2	72
3	Ts (**134a**)	$Cu(OTf)_2$	-	2	83
4	Ts (**134a**)	$Cu(ClO_4)_2.6H_2O$	-	60	NR
5	Ts (**134a**)	$IrCl_3$	-	60	NR
6	Ts (**134a**)	$Fe(ClO_4)_3.6H_2O$	**46a**	120	NR
7[b]	Ts (**134a**)	$Fe(ClO_4)_3.6H_2O$	**46a**	120	NR
8	Ts (**134a**)	$Fe(ClO_4)_3.6H_2O$	**38a**	120	NR
9	Ts (**134a**)	$Cu(OTf)_2$	**38a**	120	NR
10	Ts (**134a**)	$Fe(acac)_3$	**139**	120	NR
11	Boc (**134c**)	$FeCl_3.6H_2O$	-	60	NR
12[b]	Boc (**134c**)	$FeCl_3.6H_2O$	-	60	NR
13	H (**138**)	$FeCl_3.6H_2O$	-	60	NR
14	H (**138**)	$CuCl_2$	-	60	NR

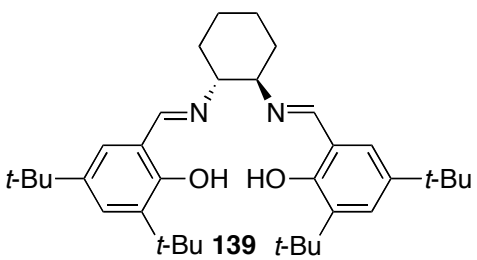
[a] isolated yield, [b] carried out in THF.



38a



46a

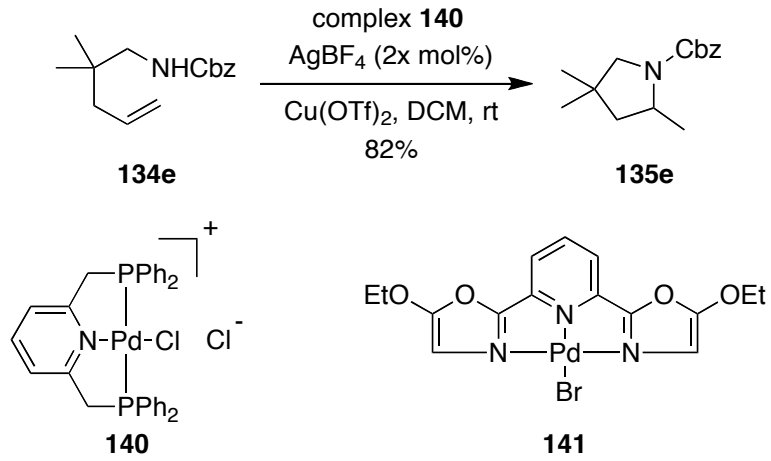


139

Table 26. Hydroamination of unactivated amino-olefin.

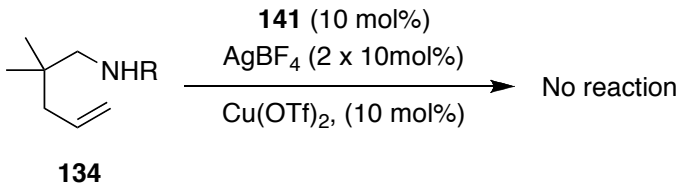
9.3 Hydroamination at room temperature

Recently, Michael et al. has reported an interesting palladium catalyzed intramolecular hydroamination of unactivated alkenes at room temperature.[1] When the substrate **134e** was treated with Pd(II)-complex **140** in presence of $AgBF_4$ and $Cu(OTf)_2$, pyrrolidine derivative **135e** was isolated in 82% yield (Scheme 44). They have hypothesized that the use of a tridentate ligand **140** would block the open coordination sites required for β-hydride elimination, and thereby prevent this process and promote alternate reactions of the alkylpalladium species (Scheme 44).



Scheme 44. Palladium-catalyzed intramolecular hydroamination of unactivated alkenes at room temperature.

Our group has recently explored the application of bis(oxazole) pincer ligand in Suzuki-Miyaura cross coupling reactions under aerobic conditions.[9] A stable Pd(II)-bis(oxazole) pincer complex **141** was used as an efficient catalyst for the coupling reactions. Hydroamination by utilizing this stable complex **141** was planned to be carried out by following procedure reported by Michael et al.[1] Substrate **134** was treated with $AgBF_4$ and $Cu(OTf)_2$ in presence of Pd(II)-bis(oxazole) pincer complex **141**, unfortunately no reaction took place after stirring for 4 days. Even increasing the reaction temperature or catalyst loading did not lead to the product formation (Table 27, entries 1-4).

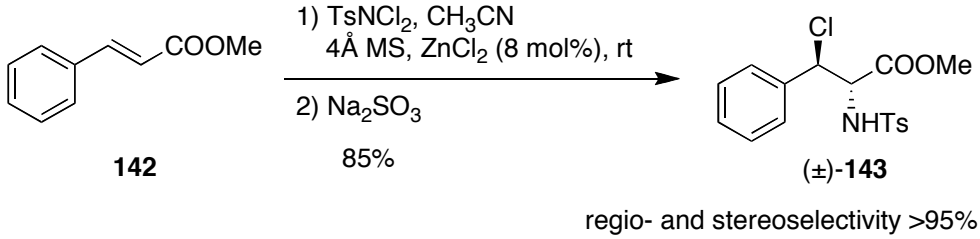


entry	R	solvent	temp (^{o}C)	time (h)	yield (%)
1	Ts	DCM	rt	120	NR
2	Ts	DCE	80	96	NR
3	Boc	DCM	rt	120	NR
4	Boc	DCE	80	96	NR

Table 27. Pd(II)-bis(oxazole) pincer complex mediated hydroamination.

9.4 Asymmetric haloamination

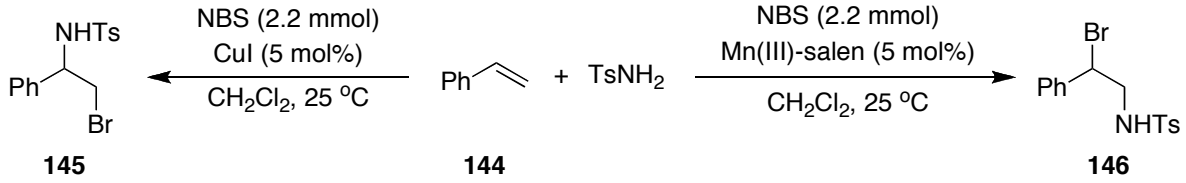
Transition metal mediated vicinal functionalization of olefins with amines and halogens (aminohalogenation) represents an important transformation in organic synthesis. These vicinal haloamine derivatives are versatile building blocks in organic and medicinal chemistry.[10] Particularly, the study of highly regioselective and stereoselective aminohalogenation of olefins still remains important and challenging to organic chemists. In the literature, the preparation of vicinal haloamines was achieved by the addition of *N*-halo,[11] *N*,*N*dihaloarylsulfonamides,[12] *N*-halocarbamates,[13] and *N*,*N*-dihalophosphoramides[14] onto olefins under noncatalytic conditions. A significant limitation with these processes is the poor yield and selectivity in terms of product distribution often obtained under such conditions. Li et al. have reported in a series of papers their significant contributions on aminohalogenation of cinnamic esters catalyzed by various transition metal salts using *N*,*N*′-dichloro-*p*-toluenesulfonamide as the nitrogen as well as chlorine sources (Scheme 45).[15, 16]



Scheme 45. Transition metal-catalyzed aminochlorination of methyl cinnamate.

Recently, Sudalai et al. reported[17] the regio and stereoselective aminobromination of various olefins with tosylamine and NBS. For example, when styrene **144** was reacted with $TsNH_2$ and NBS in the presence of catalytic amount of CuI (5 mol%) in DCM, the corresponding aminobrominated product **145** was obtained in high yield with excellent

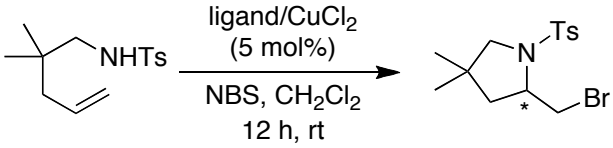
regioselectivity (>99%). Surprisingly, when Mn(III)-salen was employed as catalyst, a reversal in regiochemistry leading to product **146** was observed (Scheme 46).



145 **144** **146**

Scheme 46. Aminobromination of styrene with $TsNH_2$ and NBS.

Impressed by the above work, we decided to work on haloamination with the substrate **134**. Initial reactions were carried out with NBS in DCM. A smooth conversion was observed with the isolation of product **147a** in 89% yield (Table 28, entry 1). Following the successful synthesis of **147a**, we wondered whether the asymmetric fashion of this reaction could be an interesting and challenging task. Substrate **134a** was treated with NBS in presence of **38a**-$CuCl_2$ as well as **46a**-$CuCl_2$ complexes. Disappearance of starting material was observed in 12 h with excellent yield (Table 28, entries 2-4). However, the products were racemic, even lowering the reaction temperature did not help to obtain enantioenriched products (Table 28, entry 4).



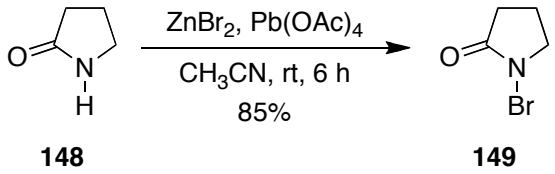
134a **147a**

entry	ligand	temp (°C)	yield (%)	ee (%)
1	-	rt	89	-
2	**38a**	rt	92	0
3	**46a**	rt	84	0
4	**46a**	0	88	0

Tale 28. Bis(oxazoline)-$CuCl_2$ mediated aminobromination.

These results turned us to modify the brominating agent as a chiral brominating source. In a search of finding chiral halogenation reagents, we observed that *N*-bromopyrrolidones **149** are one of the very good brominating reagents. *N*-bromopyrrolidone **149** can be easily synthesized starting from the corresponding pyrrolidone (Scheme 47). Pyrrolidone **148** was

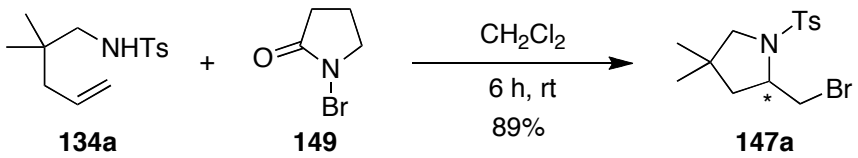
treated with $ZnBr_2$ and $Pb(OAc)_4$ in CH_3CN for 6 h and the product **149** was isolated as an light brown solid in 85% yield (Scheme 47).



148 **149**

Scheme 47. Synthesis of N-bromo pyrrolidones.

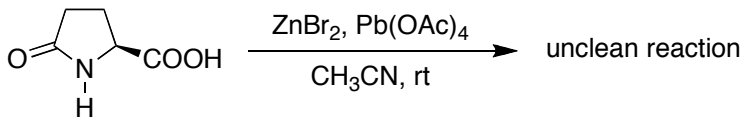
The efficiency of this achiral reagent **149** was screened with substrate **134a**. Complete conversion of the amino olefin into the product **147a** was observed in 6 h with 89% yield (Scheme 48).



134a **149** **147a**

Scheme 48. Aminobromination of unactivated aminoolefin with *N*-bromo pyrrolidones.

Since the use of achiral brominating reagent **147a** was successful in aminobromination of **134a**, the synthesis of a chiral brominating reagent was aimed for the asymmetric aminobromination. Pyrrolidine carboxylic acid **150** was chosen as the chiral substrate for the bromination. Similar to the earlier bromination (Scheme 47), pyrrolidine carboxylic acid **150** was treated with $ZnBr_2$ and $Pb(OAc)_4$ in CH_3CN, however an unclean reaction was observed (Scheme 49).

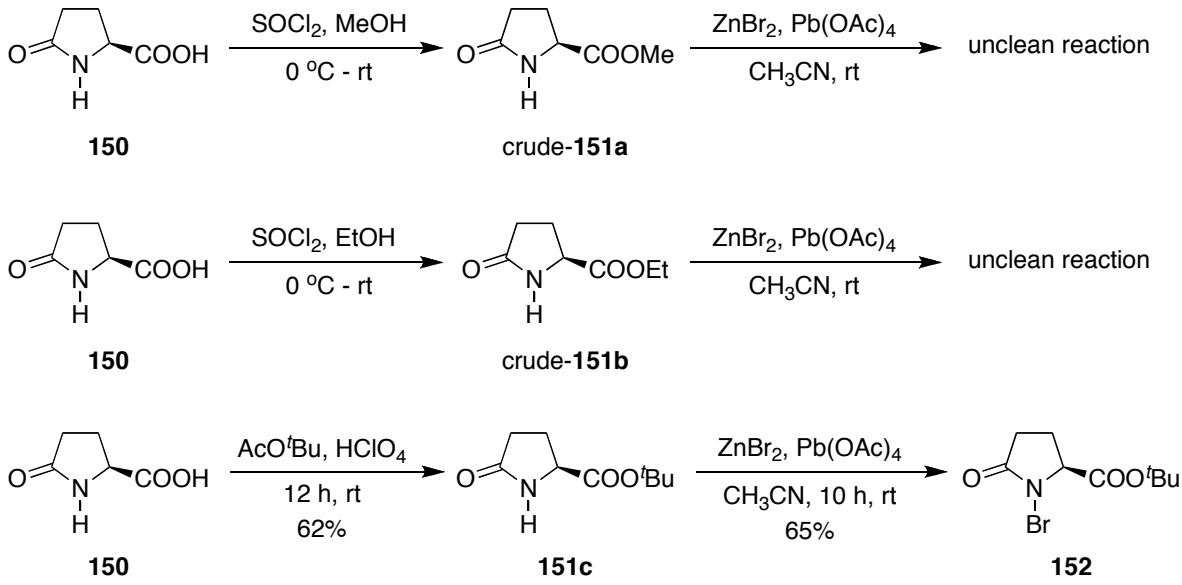


150

Scheme 49. Bromination of pyrrolidine carboxylic acid.

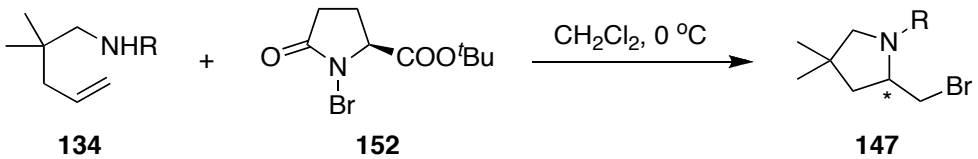
The esterification of pyrrolidine carboxylic acid **150** was carried out with $SOCl_2$ in alcoholic solvents, again we observed the unclean reaction and the crude product was subjected for the bromination, which was unsuccessful in isolating the required brominated product (Scheme 50). Successful esterification was carried out with $AcOtBu$ and $HClO_4$ for

12 h at room temperature. The esterified product **151c** was isolated in 62% yield, further bromination proceeded smoothly in presence of $ZnBr_2$ and $Pb(OAc)_4$ in CH_3CN and the product **152** was isolated in 65% yield (Scheme 50).



Scheme 50. Esterification followed by bromination of pyrrolidine carboxylic acid.

Having the chiral brominating agent **152** in hand, we proceeded further for the asymmetric aminobromination in DCM at 0 °C. The tosyl protected amino olefin **134a** was treated with **152** in DCM at 0 °C, complete conversion of **134a** was observed within 12 h in 91% yield, however the product was racemic (Table 29 entry1). Variation of the stoichiometry of the reactants was also not successful to render the process asymmetric (Table 29, entry 2). Likewise PMB protected amino olefin **134d** was treated with **152** at 0 °C with or without addition of molecular sieves (Table 29, entry 3-4), however again only racemic products were obtained (Table 29).

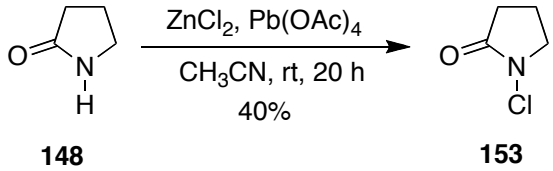


entry	R	**134:152**	time (h)	yield (%)[a]	ee (%)[b]
1	Ts (**134a**)	1.0 : 1.2	12	91	0
2	Ts (**134a**)	1.0 : 0.1	12	98[c]	0
3	PMB (**134d**)	1.0 : 1.2	17	72	0
4[d]	PMB (**134d**)	1.0 : 1.2	17	70	0

[a] isolated yield, [b] determined by chiral HPLC, [c] based on **152**, [d] 4Å MS was employed an additive.

Tale 29. Bis(oxazoline)-$CuCl_2$ mediated aminobromination.

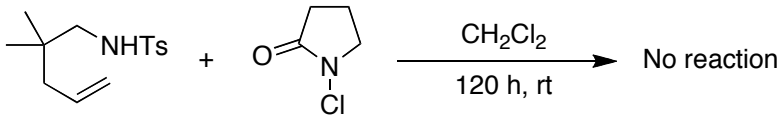
N-Bromo pyrrolidines **149** and **152** are unstable compounds which decompose even at 0 ^{o}C. Hence we were more interested to synthesize *N*-chloro pyrrolidines, which could be a stable reagent. Similar to *N*-bromination, pyrrolidone **148** was treated with $ZnCl_2$ and $Pb(OAc)_4$ in CH_3CN for 20 h and the product **153** was isolated in 40% yield (Scheme 51).



148 **153**

Scheme 51. Synthesis of *N*-Chloro pyrrolidone.

Having the chlorinating agent **153** in hand, we proceeded further for the aminochlorination. The tosyl protected amino olefin **134a** was treated with **153** in DCM at rt, however no reaction was observed after stirring the reaction mixture for 5 days (Scheme 52).



134a **153**

Scheme 52. Aminochlorination of unactivated aminoolfin with *N*-chloro pyrrolidone.

9.5 Conclusion

In conclusion, we have investigated the Cu(II) mediated potential hydroamination as well as aminohalogenation. The extension of this methodology in an asymmetric fashion is not successful yet. The pyrrolidine derivatives, which we have obtained *via* hydroamination and aminohalogen can be a valuable synthetic intermediates for the synthesis of natural products.

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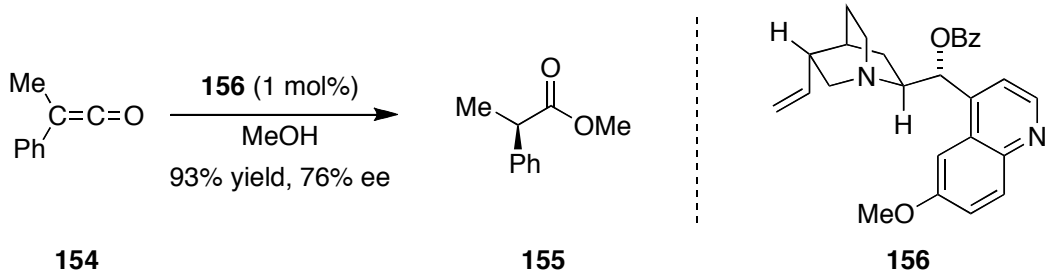
10 Organocatalysis

10.1 Introduction

Since the late 20-th century, asymmetric catalysis has become a field of central importance to chemical synthesis and has been adopted as a major research area. Moreover, widespread application of asymmetric reactions has become prevalent in pharmaceutical and biotechnology industries.[1] Chiral catalysts, which are involved in the synthesis of pharmaceutical products and agrochemicals are either transition metal complexes or enzymes.[2] Apart from those, a third approach for asymmetric catalysis has emerged – organocatalysis. Organocatalysts are purely made up of organic molecules, the catalytic activity of organocatalysts resides in the nature of the organic molecule itself, and no transition metals are required. Organocatalysts have several advantages, they are usually inert toward moisture and oxygen, robust, inexpensive, readily available, and non-toxic. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination, e.g. pharmaceutical products.[2]

10.2 Historical background

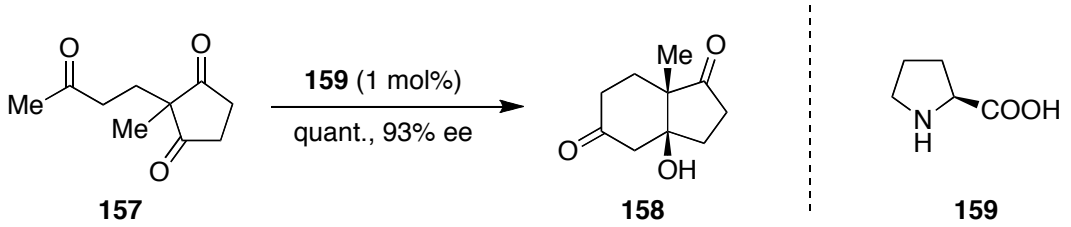
The pioneering work in organocatalysis was recognized for the work of Bredig in 1912 i.e. ca. 90 years ago.[3] He investigated the hydrocyanation of benzaldehyde accelerated by cinchona alkaloids[4, 5] affording optically active cyanohydrins in the range of ≤10% enantiomeric excess. Almost 50 years later in 1960, Pracejus et al. reported the exciting enantioselective addition of methanol to phenylmethylketene **154** in presence of 1 mol% *O*-acetylquinine **156**. This methanolysis afforded quite remarkable 76% ee for the formation of **155** (Scheme 53).[6, 7]



154 **155** **156**

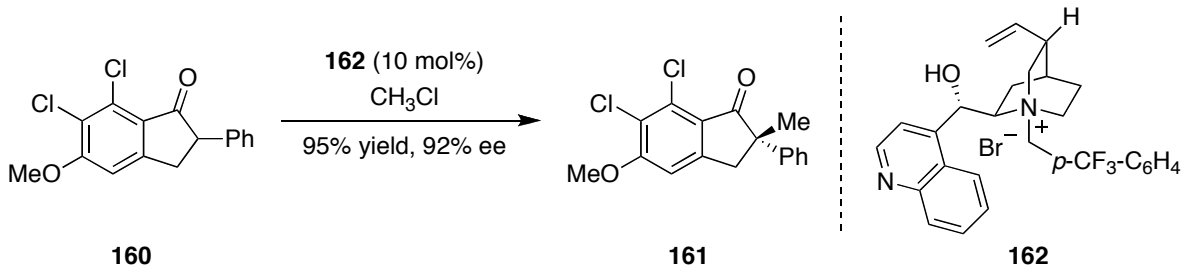
Scheme 53. Methanolysis of phenylmethylketene.

A breakthrough in enantioselectivity was achieved when Hajos and Wiechert performed the famous proline **159** catalyzed intramolecular asymmetric aldol condensation of the prochiral triketone **157**. This desymmetrization provided the enantioenriched adduct **158** in ≥93% ee, which was used for the total synthesis of steroids and other natural products (Scheme 54).[8-12]



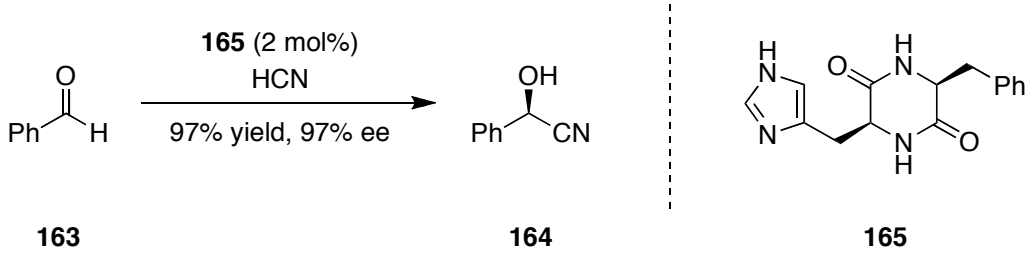
Scheme 54. Aldol condensation of prochiral triketones.

Since 1970s, several groups reported the use of cinchona alkaloids as chiral catalysts,[8, 9] in hetero-cycloadditions, phase-transfer-catalyzed epoxidations, alkylations, conjugate additions, and phosphorylation reactions of aldehydes.[2] A notable Phase Transfer Catalyst (PTC) **162** was employed as a very efficient organocatalyst in methylation of indanone **160** and the corresponding methylated product **161** was isolated in 92% ee (Scheme 55).[10, 11]



Scheme 55. PTC mediated methylation of an indanone.

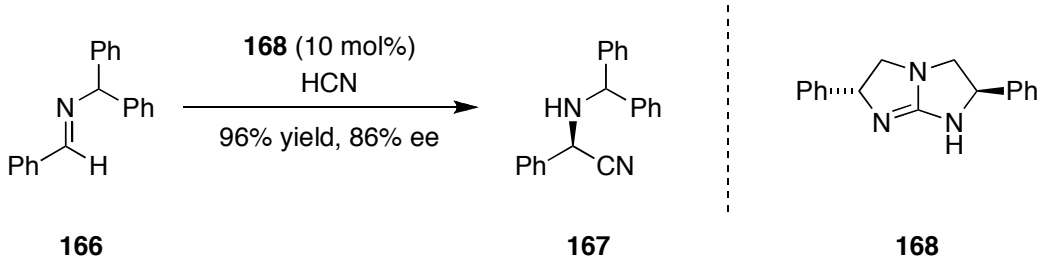
One of the most appealing approaches for enantioselective cyanohydration was outlined by Inoue and coworkers.[12, 13] In an elegant modification of work initially carried out by Bredig and Fiske in 1912.[3] In their studies, the cyclic histidine-containing dipeptide **165** was found to catalyze the HCN addition to aromatic aldehydes with high enantioselectivities (97% ee) (Scheme 56). Notably this reaction is one of the pillars for peptide-catalyzed nucleophilic addition to aldehydes and imines.[1]



163 **164** **165**

Scheme 56. Cyanohydration of benzaldehyde.

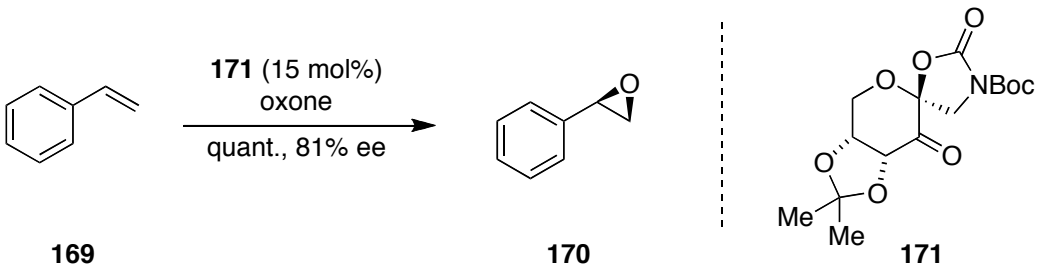
Soon after Inoue's report, the asymmetric α-amino acid synthesis *via* an enantioselective Strecker reaction (i.e., the addition of HCN to imines) appeared in the literature.[14, 15] Further developments being contributed by Corey[16] and Jacobsen[17-19] make use of guanidine or acyclic peptide-based catalysts. Corey studied the addition of HCN to the imine **166** in the presence of guanidine **168** leading to the amine **167** in 86% ee (Scheme 57).



166 **167** **168**

Scheme 57. Enantioselective Strecker reaction.

The next milestones in the realm of enantioselective organocatalysis were achieved by Yang,[20, 21] Shi,[22] and Denmark[23] who elegantly developed the nonmetal enantioselective epoxidation reactions (Scheme 58). As depicted for the Shi protocol, the chiral ketone catalyst **171** was employed to mediate the asymmetric transfer of oxygen from oxone to styrene with excellent levels of enantiocontrol (Scheme 58).

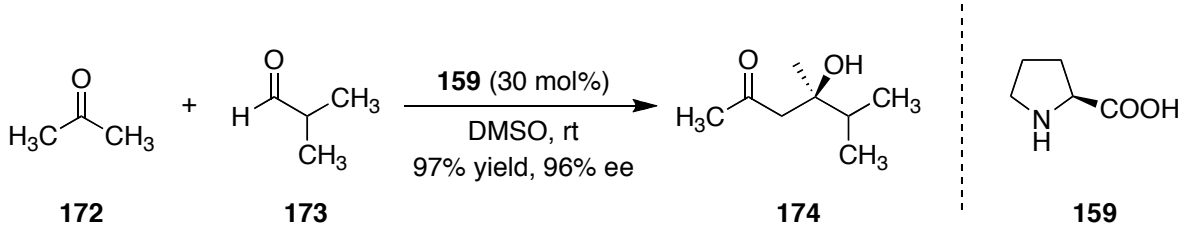


169 **170** **171**

Scheme 58. Enantioselective epoxidation of styrene.

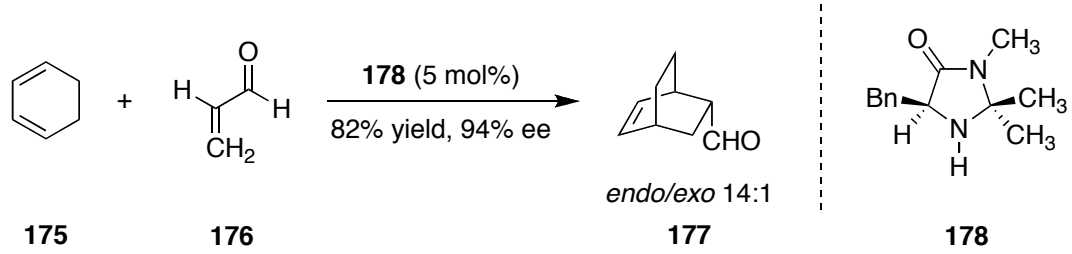
It's more surprising that the organocatalytic principle lay dormant until the pioneering

studies demonstrated by List et al. and MacMillan et al. In 2000, List et al. reported proline **159** mediated aldol reactions.[24, 25] In his article he showed that acetone underwent aldol reactions with a variety of aldehydes, affording the corresponding aldols in excellent yields and enantiomeric purity. For example, acetone was added to *iso*-butyraldehyde **173** in presence of proline **159** and the aldol product **174** was obtained in 97% yield and with 96% ee.[24, 25] The remarkable chemo- and enantioselectivity observed by List et al. triggered massive further research activity in proline-catalyzed aldol, Mannich, Michael, and related reactions.



Scheme 59. Proline mediated aldol reaction.

In the same year, MacMillan et al. reported the imidazolidinone **178** catalyzed Diels-Alder reaction of α,β-unsaturated aldehydes. In their studies cyclohexadiene **175** was treated with **176** at 5 mol% of imidazolidinone **178** and the Diels-Alder adduct **177** was obtained in 82% isolated yield and with 94% ee (Scheme 60).[26] This initial report by MacMillan et al. was followed by numerous further applications of the catalyst **178** and related secondary amines.



Scheme 60. Diels-Alder reaction of α,β -unsaturated aldehydes.

The origin of chiral induction can be easily understood from the covalent (**179** and **180**) or non-covalent (**181**) interaction of the organocatalyst to the substrate. For example, the formation of enamine **179** is accounted in proline catalyzed aldol reaction (Scheme 59). This active enamine intermediate **179** provides the chiral induction and directs the incoming electrophile to attack from the less hindered face of the system. In case of Macmillan's imidazolidinone the iminium intermediate **180** is formed with the substrate **176** in Diels-

Alder reaction. In general these covalently bound organocatalysts are employed with higher catalyst loading compared to the non-covalent catalysts.

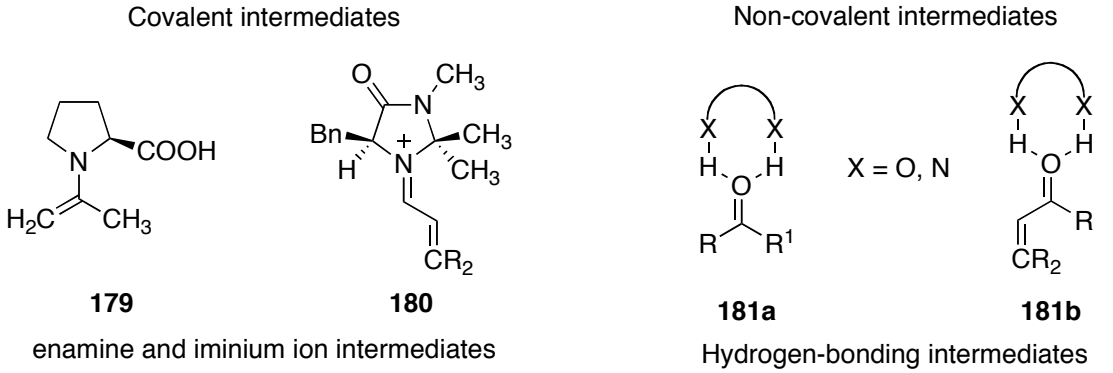
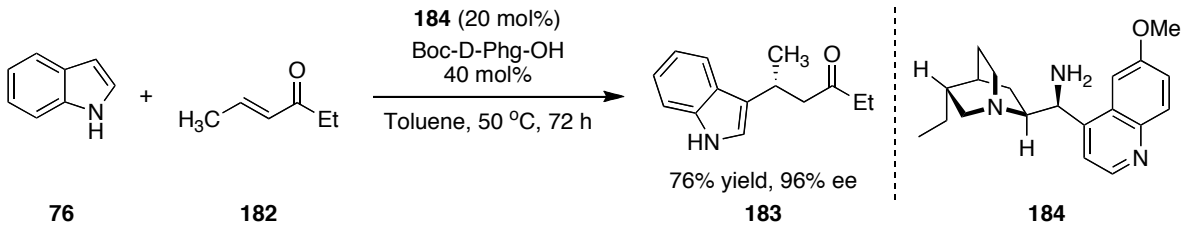


Figure 12. General reaction intermediates in enamine, iminium and hydrogen-bonding organocatalysis.

10.3 Primary amine organocatalyst

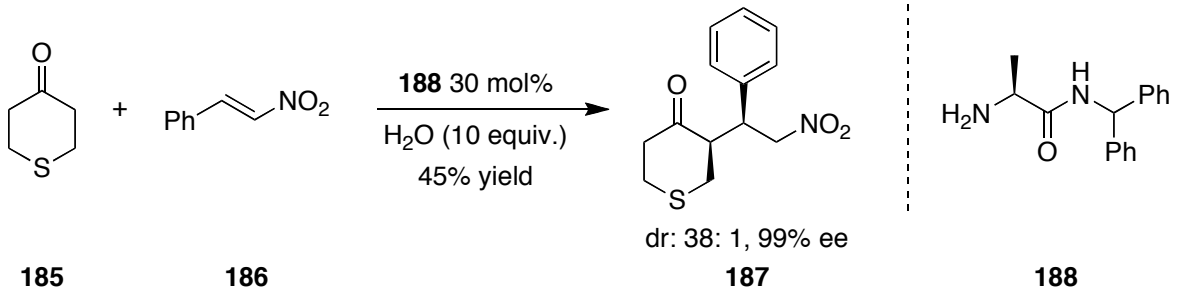
Over the past few years, thousands of chiral organocatalysts have been developed for different asymmetric transformations. Among them, chiral secondary amines are probably the most intensively used organocatalysts so far. In contrast, chiral primary amine catalysts are largely neglected, probably due to unfavorable imine-enamine equilibria. Recently, chiral primary amines have emerged as new and powerful catalysts for enantioselective organocatalytic reactions. However, latitude for further development remains, in particular with regard to the design of readily accessible and inexpensive catalyst systems capable of promoting efficient, enantio- and diastereoselective reactions.

Similar to secondary amines mediated organocatalysis, primary amines are also known to proceed *via* enamine or iminium intermediates in reactions involving carbonyl compounds. For example, Bartoli et al.[27] have developed a new method for organocatalyzed enantioselective Friedel–Crafts alkylation of indoles with simple α,β-unsaturated ketones in the presence of a primary amine salt, in which both the cation and the anion are chiral (Scheme 61). The reaction between indole and the enone **182** gave the enantioenriched β-indolyl derivatives **183** in 76% yield and with 96% ee. This transformation follows the formation of iminium ion intermediate **180** to furnish the enantioenriched adduct **183**.



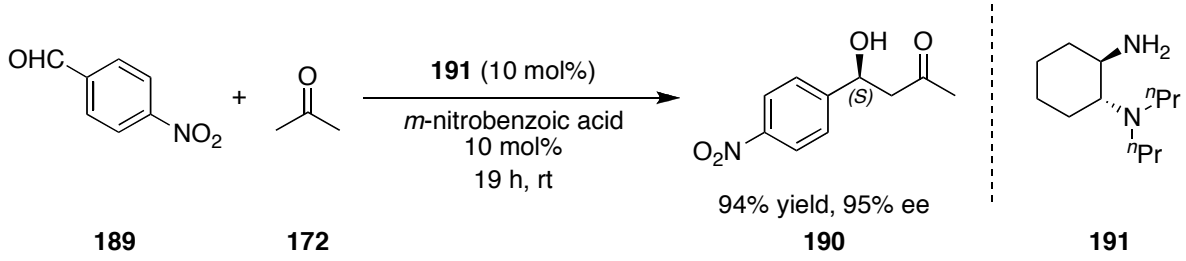
Scheme 61. Primary amine mediated asymmetric Friedel–Crafts alkylation.

Xu and Cordova[28] have demonstrated for the first time that simple primary amino acid derivatives **188** can catalyze the direct enantioselective addition of ketone **185** to the nitro olefin **186**, furnishing the corresponding ɣ-nitroketone **187** in 45% yield with 38:1 dr and 99% ee. (Scheme 62). The primary amine catalyst **188** forms the enamine intermediate **179** with substrate **185** in the course of this transformation.



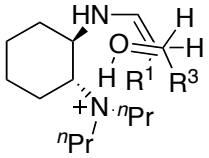
Scheme 62. Asymmetric Michael addition of ketones to nitro olefins.

More recently, Luo et al.[29] have disclosed asymmetric direct aldol reactions of linear aliphatic ketones with aromatic aldehydes in the presence of a simple chiral primary catalyst **191**. A range of aromatic aldehydes underwent the reaction with acetone in high yields and enantioselectivity at room temperature. For example the reaction of *para*-nitrobenzaldehyde **189** with acetone gave the corresponding aldol product **190** in 94% isolated yield and with 95% ee (Scheme 63).



Scheme 63. Primary amine mediated asymmetric aldol reactions of ketones to aldehydes.

To account for the observed *syn*-diastereoselectivity, the authors proposed a *Z*-enamine transition state **192**, in which the protonated tertiary amine serves as a directing hydrogen-bonding donor, as depicted in figure 13.

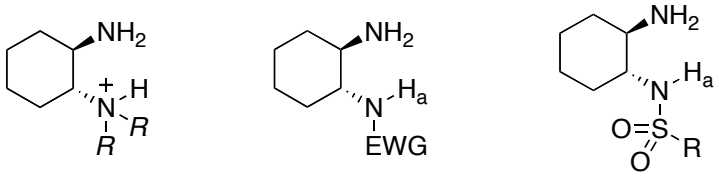


192

Figure 13. Proposed transition state for the primary amine mediated aldol reaction.

10.4 New catalyst design

Intrigued by the performance of the simple catalyst **191**, we planned to design a simple organocatalyst such as **193** with a secondary and primary amine functional group as shown in Figure 14. The introduction of an electron-withdrawing group at the amine **193** will increase the acidity of hydrogen H_a, which can therefore exhibit strong hydrogen bonding to the substrates. It's well known in the literature that the sulfonyl group works well for the purpose described above. Therefore it was planned to synthesize the sulfonyl-substituted cyclohexadiamines **194**.



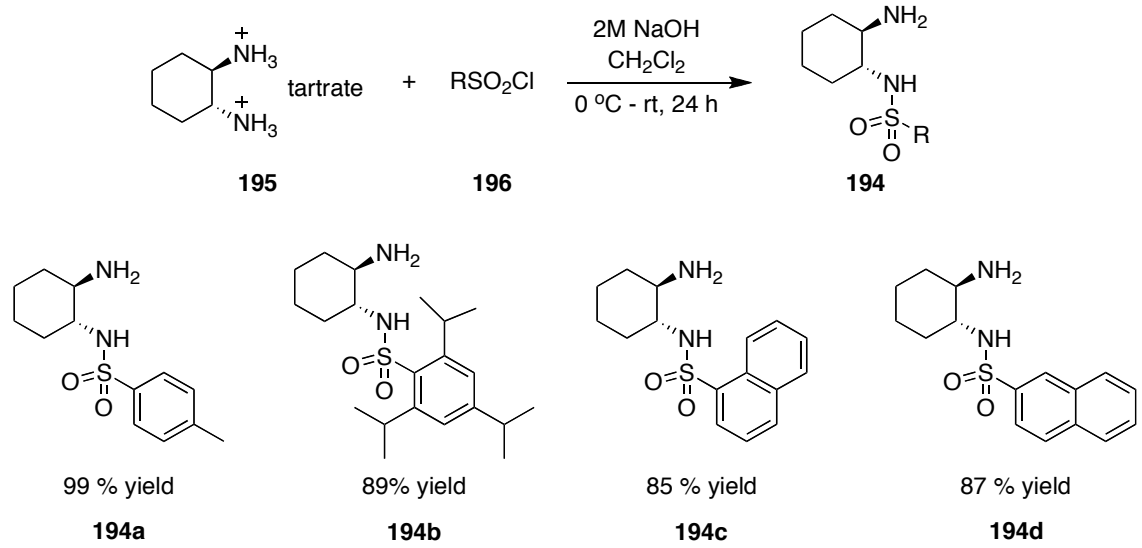
191 **193** **194**

Figure 14. Cyclohexadiamine derived organocatalysts.

10.5 Synthesis of cyclohexadiamine organocatalysts

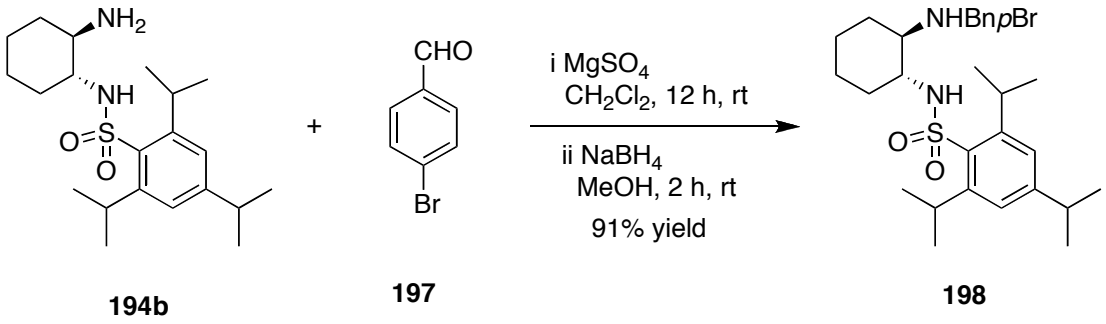
A library of catalysts was synthesized by following literature protocols:[30] the tartrate salt of (*R,R*)-cyclohexadiamine **195** (1 equiv) was treated with tosyl chloride (0.3 equiv) in presence of aqueous NaOH and dichloromethane. After stirring for 24 h, the monotosylated product **194a** was obtained in 99% isolated yield. Likewise the tri-*iso*-propyl **194b**, 1-

napthyl **194c** and 2-napthyl **194d** substituted catalysts were obtained in 89%, 87% and 85% isolated yield (Scheme 64).



Scheme 64. Synthesis of library of cyclohexadiamine derived catalysts.

The secondary amine catalyst **198** was also synthesized in order to compare the activity with the primary amine catalyst **194**. Amine **194b** was treated with *para*-bromobenzaldehyde **197** in presence of $MgSO_4$ in DCM, and after stirring for 12 h the crude imine was reduced to the corresponding amine **198** with $NaBH_4$. The overall yield for this benzylation was 91% (Scheme 65).

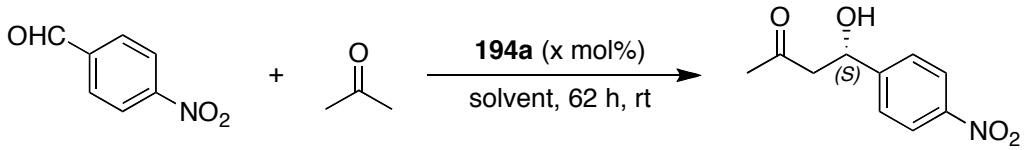


Scheme 65. Synthesis of secondary amine catalyst **198**.

10.6 Cyclohexadiamine organocatalyst mediated aldol reactions

Having a library of catalysts **194** in hand, we proceeded further to explore the catalyst in aldol reactions. *para*-Nitrobenzaldehyde **189** was treated with acetone in presence of 15

mol% of catalyst **194a** in various solvents. The reactions were sluggish, a maximum of 25% ee (22% yield) was observed in toluene (Table 30, entry 5). Employing additives like *meta*-nitrobenzoic acid (entry 1) and TFA (entry 2) did not improve the yield as well as enantioselectivity.



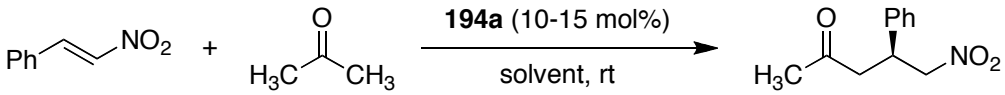
189 **172** **190**

entry	solvent	**172** (equiv)	**194a** (mol%)	additive	Yield (%)	ee (%)
1	Neat	20	10	*m*-NO_2PhCOOH	31	17
2	Neat	20	10	TFA	29	54
3	Neat	20	10	*m*-NO_2PhCOOH + TFA	25	55
4	Neat	20	15	-	34	5
5	Toluene	10	15	-	22	25
6	DCM	10	15	-	28	18
7	EtOH	10	15	-	10	2

Table 30. Enantioselective aldol reaction.

10.7 Michael additions of ketones to nitro olefins

Since the aldol reactions were sluggish with the catalyst **194**, we planned to carry out Michael additions of acetone to nitro olefins. We began our study by screening the catalyst **194a** for the addition of acetone (**172a**) to β-nitrostyrene (**186a**) in different solvents (Table 31), suggesting that toluene is most suitable with respect to yields and selectivity to give rise to **199a** in 80% yield and 73% ee (entry 8). Using additives, having proved to be successful with other catalyst for this transformation,[31-39] did not show a further improvement (Table 31, entries 9-10). Under solvent-free conditions equimolar amounts of benzoic acid seem to be beneficial for increasing enantioselectivity (Table 31, entries 5-6), nevertheless, the results that were achieved under the latter conditions were inferior with respect to yield.



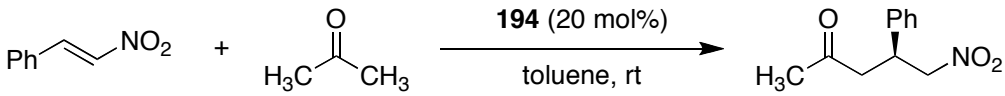
186a **172a** **199a**

entry	**194a** (mol%)	solvent	additive[a]	yield (%)	ee (%)[b]
1	10	EtOH	–	29	26
2	10	CH_2Cl_2	–	51	62
3	10	hexane	–	0	–
4	10	THF	–	43	33
5	15	neat	PhCOOH	82	32
6	15	neat	H_2O, AcOH	68	71
7	15	neat	–	84	58
8	15	toluene	PhCOOH	80	73
9	15	toluene	H_2O, AcOH	44	62
10	15	toluene		58	61

[a] equimolar amounts with respect to catalyst **194a** were employed. [b] determined by HPLC (Chiralpak AS-H), the configuration of **199a** was assigned by comparing optical rotation and HPLC retention times with literature data.[36, 40, 41]

Table 31. Conjugate Addition of acetone to β-nitrostyrene with **194a**

By varying the aromatic group of the sulfonamide in **194** the *iso*-propyl substituted derivative **194d** was found to significantly improve the enantioselectivity of **199a** to 87% ee, and by using 20 mol% of this catalyst, quantitative conversion was achieved (Table 32, entry 4). Further attempts for optimization by screening additives for this catalyst, however, were again unsuccessful: while a rate acceleration of the reaction occurs in the presence of protic additives, an undesirable erosion of enantioselectivity was observed (Table 32, entries 5-12).



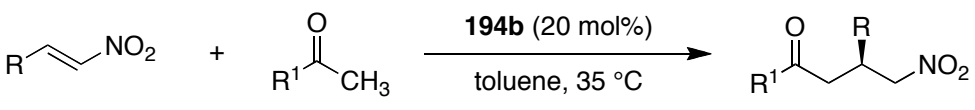
186a **172a** **199a**

entry	catalyst	time (h)	additive (mol%)	yield (%)[a]	ee (%)[b]
1	**194a**	62	–	96	73
2	**194c**	62	–	88	74
3	**194d**	44	–	86	70
4	**194b**	62	–	98	87
5	**194b**	10	PhCOOH (10)	92	64
6	**194b**	60	PhCOOH (20)	35	82
7	**194b**	70	AcOH (10)	79	85
8	**194b**	60	AcOH (20)	57	74
9	**194b**	70	MS (4Å)	84	58
10	**194b**	48	$MgSO_4$	97	82
11	**194b**	48	H_2O (1000)	99	76
12	**194b**	70	H_2O (20)	62	75

[a] isolated yield, [b] the ee values were determined by HPLC (Chiralpak AS-H).

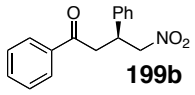
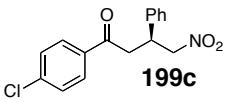
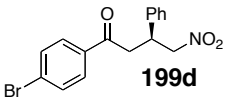
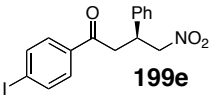
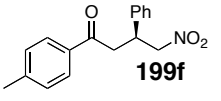
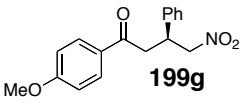
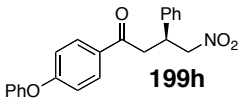
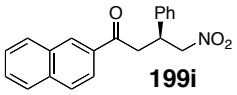
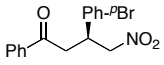
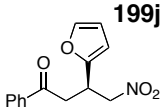
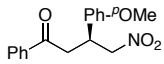
Table 32. Screening of catalysts **194.**

Turning to the more challenging aromatic ketones we were pleased to note that with catalyst **194d** enantioselectivities of up to 98% ee were achieved, however, as expected these substrates turned out to be less reactive (Table 33). Raising the reaction temperature to 35 °C was found to give improved yields while retaining the high selectivities observed at 20 °C, but still higher temperatures were not tolerated well (Table 33, entries 1-4). Under the optimized conditions, **199b-k** were obtained in 94-98% ee with acceptable yields (entries 2, 5-13). Besides β-nitrostyrene (**186a**), the p-bromophenyl and the 2-furyl analogs **186b** and **186c** could be employed as nitroalkenes, while the less electron deficient *para*-methoxy phenyl derivative **186d** proved to be not reactive enough any longer to undergo the conjugate addition reaction (Table 33, entries 13-15).



186 **172** **199**

186a: R = Ph
186b: R = *p*-Br-Ph
186c: R = 2-furyl
186d: R = 2-MeO-Ph

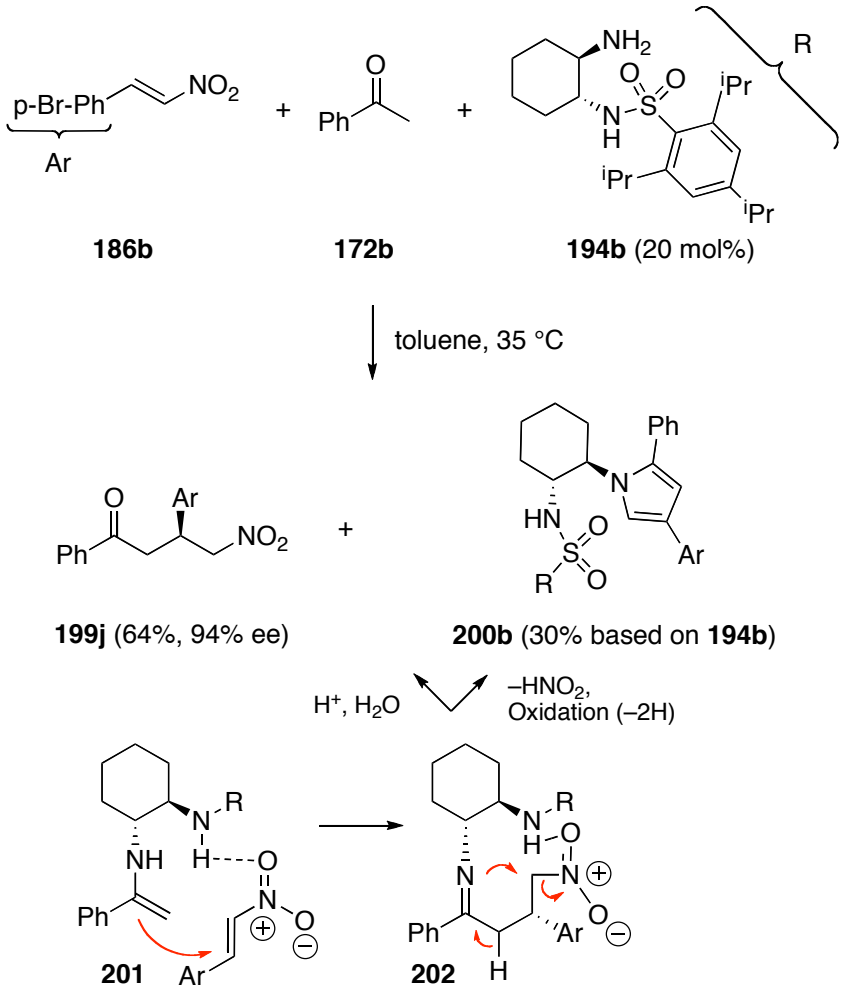
entry	**186**	R^1 (**172**)	product	yield (%)[a]	ee (%)[b]
1[c]	**186a**	Ph(**172b**)	 **199b**	45	96
2	**186a**	Ph(**172b**)		72	96
3[d]	**186a**	Ph(**172b**)		54	87
4[e]	**186a**	Ph(**172b**)		53	81
5	**186a**	*p*Cl-Ph(**172c**)	 **199c**	70	94
6	**186a**	*p*Br-Ph (**172d**)	 **199d**	65	94
7	**186a**	*p*I-Ph(**172e**)	 **199e**	59	98
8	**186a**	*p*Me-Ph(**172f**)	 **199f**	60	96
9	**186a**	*p*OMe-Ph(**172g**)	 **199g**	51	98
10	**186a**	*p*OPh-Ph(**172h**)	 **199h**	61	97
11	**186a**	2-Naphthyl(**172i**)	 **199i**	62	98
12	**186b**	Ph(**172b**)	 **199j**	64	94
13	**186c**	Ph(**172b**)	 **199k**	32	97
14	**186d**	Ph(**172b**)		0	–

[a] isolated yield [b] determined by HPLC (Chiralpak AS-H), [c] 20 °C, [d] 50 °C, [e] 70 °C.

Table 33. Conjugate addition of aromatic ketones to β-nitrostyrenes with **194b.**

The modest turn over cycles and frequencies achieved, being a quite general phenomenon with primary amine organocatalysts,[42-46] prompted us to investigate the fate of catalyst **194b** in the title reaction. Indeed, for the aromatic ketones **172b-i** employed as substrates we were able to identify an irreversible formation of pyrroles in a three-component reaction between the catalyst, the nitroalkene and the aromatic ketone as a novel pathway for the catalyst deactivation (Scheme 66).[47] For example, reacting **186b** and **172b** in the presence of **194b** (20 mol%) gave rise to **200b** in 30% yield based on the amount of catalyst employed. We

propose the formation of the intermediate **202** formed by addition of in situ formed enamine **201** to the nitroalkene, which can either undergo hydrolysis to the desired product **199**, but can alternatively undergo ring-closure with formal elimination of HNO_2 and oxidation to form pyrrole **200** (Scheme 66).

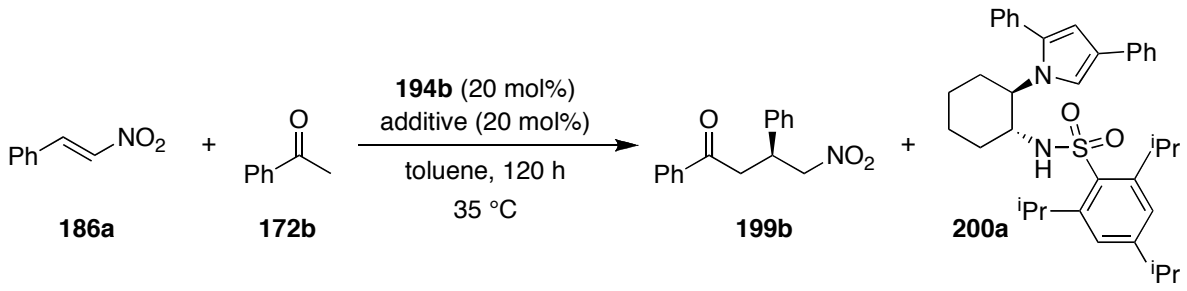


Scheme 66. Catalyst deactivation by irreversible formation of pyrrols.

10.8 Role of additives in pyrrole formation

The mechanistic proposal put forward (Scheme 66) suggests that protic additives should accelerate hydrolysis to yield **199**. On the other hand, protonation could also facilitate the extrusion of nitrous acid as a first step towards the formation of pyrroles **200**. Screening various acids, protic solvents or salts, the pyrrole side products were still observed (Table 34). A notable exception was found with 3,3',5,5'-tetrabromo-2,2'-biphenol[46] (TBBP), which was able to completely suppress the formation of **200a** when equal amounts with

respect to **194b** were employed. Nevertheless, the yield of **199** did not improve with respect to reaction conditions in which no additives were employed.



186a **172b** **199b** **200a**

entry	additive (mol%)	yield **200a** (%)[a]	yield **199b** (%)	ee (%)[b]
1	–	30	72	96
2	PhCOOH	27	58	96
3	AcOH	30	45	95
4	TFA	0	0	-
5	HCOOH	0	0	-
6	PTSA	0	10	92
7	2-ClPhCOOH	30	57	93
8	MeOH	26	64	96
9	NH_4Cl	24	58	95
10	TBBP (20 mol%)	0	56	93
11	TBBP (15 mol%)	6	53	93
12	TBBP (10 mol%)	18	62	93
13	TBBP (5 mol%)	20	61	92

[a] based on **194b**, [b] determined by HPLC (Chiralpak AS-H).

Table 34. Catalyst deactivation by formation of pyrrole **200a**

Further following the mechanistic rational depicted in scheme 66, enamine **201** should be a decisive intermediate in the catalytic cycle. However, only trace amounts of product **199** were observed when the secondary amine **198**, presumably forcing enamine formation, was employed as catalyst, even at elevated temperature or with benzoic acid as additive.

10.9 Conclusion

In conclusion, we have shown that a simple primary amine catalyst could afford excellent enantioselectivity in the conjugate addition aromatic ketones and nitroalkenes. For the first

time the formation of a pyrrole side product as a mode for catalyst deactivation was observed. Further studies focusing on the development and exploration of diamines as organocatalyst are currently underway.

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11 Summary

Chiral bis(oxazolines) have been developed into one of the most useful ligand classes for asymmetric catalysis due to their ability to coordinate with a large number of metals. In this context, we have introduced and developed chiral aza-bis(oxazolines) **45** as electron rich and immobilization friendly chiral ligands.

Michael addition: Indole derivatives are privileged structures in pharmaceutical drugs. Among the known asymmetric synthesis of indole derivatives, the copper-bis(oxazoline)-catalyzed enantioselective 1,4-addition of indoles to α,β-unsaturated carbonyl compounds plays a prominent role, representing a facile, catalytic asymmetric process for this transformation. As it is shown in Figure 15 the indole derivative **78** was obtained in excellent selectivity (99% ee) in the presence of bis(oxazoline) complex **38b**-Cu(II), however, the enantioselectivities were moderate (60% ee) for the product **80**.

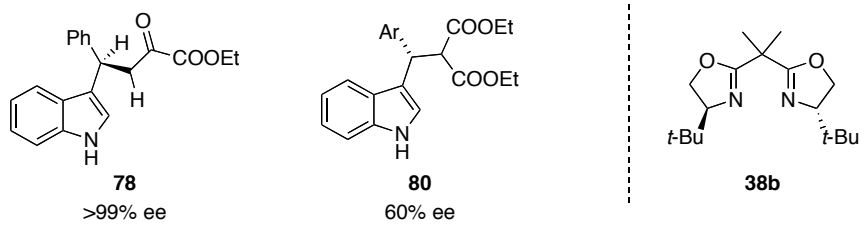
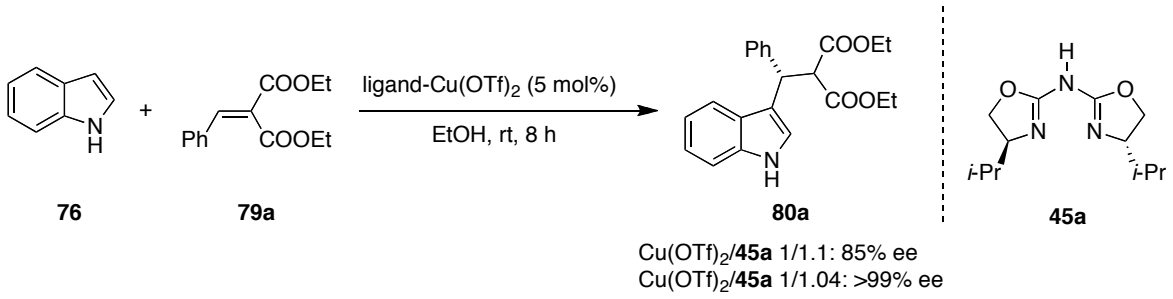


Figure 15. Chiral indole derivatives.

In the process of exploring our new azabox ligands **45**, we have shown the versatility of azabox ligand **45a** to afford the product **80a** with the maximum enantioselectivity of 99% (Scheme 67). An unprecedented, detrimental effect of excess of ligand for the enantioselectivity of the product was observed.

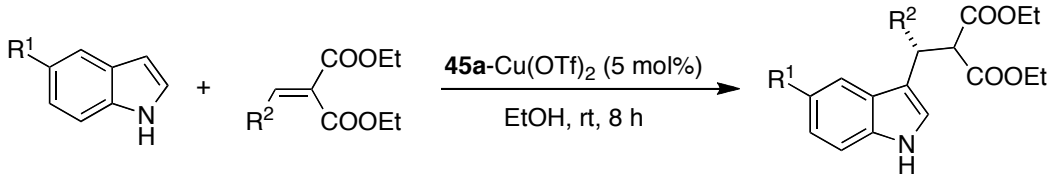


Scheme 67. Ratio dependent enantioselectivity in asymmetric Michael addition.

This is quite in contrast to the usual observation in asymmetric catalysis that an excess of chiral ligand is beneficial in order to avoid background reactions by uncomplexed metal.

Variation of the ratio of **45a**/Cu(OTf)$_2$ showed a dramatic dependence on the enantioselectivity of **80a**. The optimum ratio 1.04/1 (ligand/Cu(OTf)$_2$) afforded **80a** with 99% ee, whereas the slight excess of ligand (1.1/1: ligand/Cu(OTf)$_2$) drastically reduced the enantioselectivity to 85% (Scheme 67).

Applying this protocol for the reaction between other indoles **76** and benzylidene malonates **79** also gave good results (Table 35), and with the exception of the strongly electron-deficient *p*-nitro derivative (Table 35, entry 5), presumably an especially weak coordinating substrate for the copper-ligand complex.



76 **79** **80**

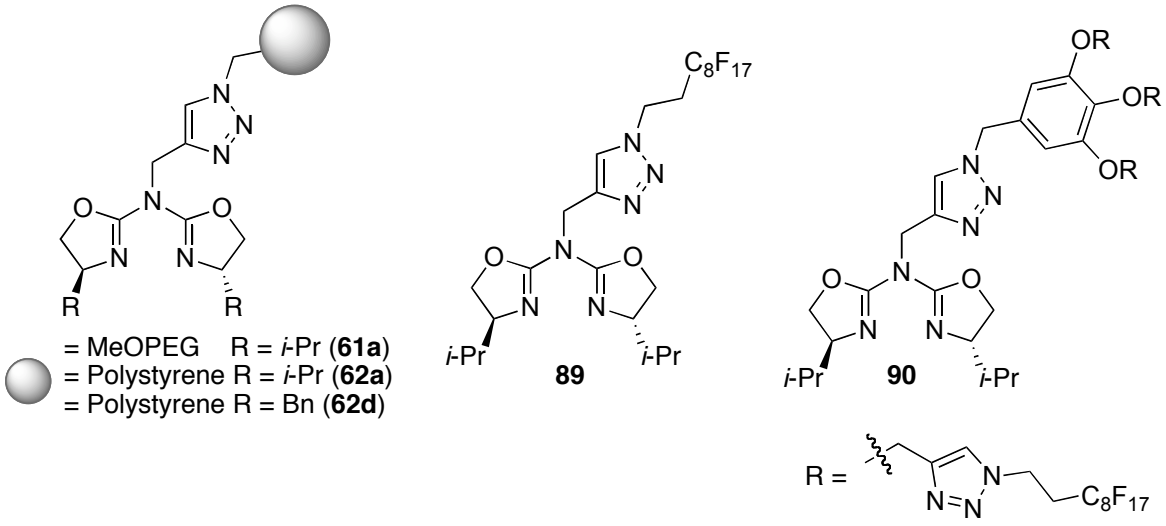
entry	**79**	R^1	product	yield (%)[a]	ee (%)[b]
1	Ph (**79a**)	H	**80a**	97	99
2	p-Me-Ph (**79b**)	H	**80b**	80	93
3	p-Cl-Ph (**79c**)	H	**80c**	91	98
4	o-Br-Ph (**79d**)	H	**80d**	89	85
5	p-NO_2-Ph (**79e**)	H	**80e**	94	80
6	Ph (**79a**)	OMe	**80f**	80	90

[a] isolated yield, [b] determined by HPLC.

Table 35. Asymmetric conjugate addition between indoles **76** and benzylidene malonates **79**.

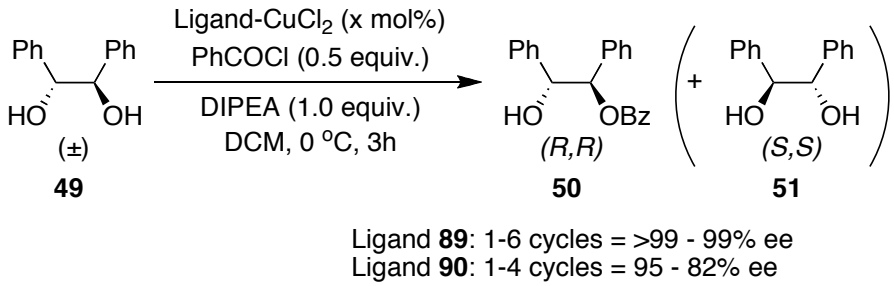
Immobilization: Aza-bis(oxazolines) are attractive in the field of immobilization since the functionalization of the ligand on the central nitrogen works well with a good variety of substrates. In this context, our group and several other groups have observed that the seamless way to ligate ligand with a polymeric support is to follow click reaction, i.e. the copper-catalyzed azide-alkyne cycloaddition (CuAAC). However, some of these immobilized ligands **61a** and **62a** having triazole linker showed moderate enantioselectivity in comparison to the triazole lacking MeOPEG-immobilized ligand **52d**.

To overcome this limitation, a polymeric backbone with electron deficient fluorous tag was introduced. The successful immobilization of ligand **45a** led to the single fluorous tag ponytailed ligand **89** and three fluorous tag ponytailed ligand **90** (Scheme 68).



Scheme 68. Immobilized aza-bis(oxazolines) over MeOPEG, Polystyrene and fluorous tag.

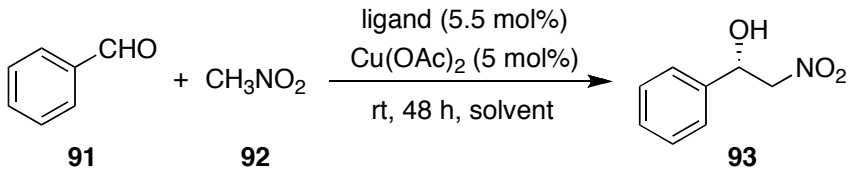
Kinetic resolution of (±)-hydrobenzoin: These immobilized ligands **89** and **90** were evaluated in copper(II)-catalyzed asymmetric mono benzoylation of (±)-diols. The homogeneous ligand **89** showed excellent reactivity as well as high enantioselectivity: Complete conversion was observed within 2 h at 2 mol% of the ligand. The heterogeneous three ponytailed azabox **90** gave 95% ee at 5 mol% of the ligand. Interestingly, the single ponytailed **89**-$CuCl_2$ complex was recovered quantitatively by the addition of diethylether to the reaction mixture and recycled up to 6 cycles without loss of its activity (Scheme 69). Throughout all 6 cycles the enantioselectivity consistently stays at 99% ee. It is worth to note the superiority of fluorous tailed ligands **89** and **90** over the MeOPEG **61a** (63% ee), polystyrene **62a** (66% ee) as well as **84** (66% ee) ligands.



Scheme 69. Kinetic resolution of (±)-hydrobenzoin **49**.

Henry reaction: Prompted by the above results, we screened these ligands **89** and **90** in nitroaldol reactions. When THF was used as solvent; it gave significant improvement in

yield and enantioselectivity compared to result obtained in EtOH (Table 36, entries 3 and 4). It is interesting to note that ligands **45a** and **45b** were inactive in this reaction (entries 1 and 2), probably the counterion (OAc^-) was trapped by the labile proton of azabis(oxzoline) **45**-$Cu(OAc)_2$ complex. The reactions were sluggish with the immobilized ligands; ligand **89** gave 90% ee (Table 36, entry 5) and ligand **90** gave 86% ee. To examine the possibility of recycling, both the $Cu(OAc)_2$ complexes of ligands **89** and **90** were recovered by the addition of the non-polar solvent hexane to the reaction mixture and the precipitated complex was reused for a few runs (Table 36, entries 5-6).

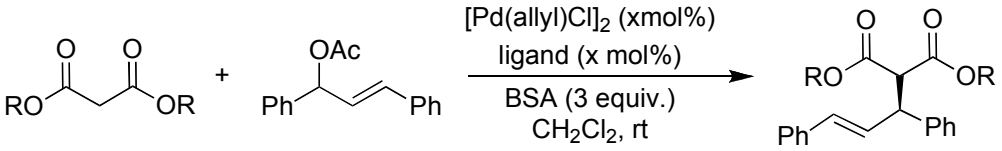


entry	ligand	solvent	run	yield (%)[a]	ee (%)[b]
1	**45a**	EtOH	1	NR	-
2	**45b**	EtOH	1	NR	-
3	**46a**	EtOH	1	71	86
4	**46a**	THF	1	76	92
5	**89**	THF	1-4	63-68	72-90
6	**90**	THF	1-3	54-59	70-86

[a] isolated yield. [b] determined by HPLC. NR = no reaction.

Table 36. Copper(II) catalyzed asymmetric nitroaldol reaction.

Palladium mediated allylation: Pd-catalyzed asymmetric allylation is one of the benchmark reaction for bis(oxazoline) ligands, consistent with the early results, azabox also showed excellent reactivity and selectivity for the allylation of **94**. It is interesting to note that the azabox ligand **46a** was a superior in this allylation, the complete consumption of **95** was observed in 24 h with 99% ee at 1 mol% of the ligand **46a**, whereas the bis(oxazoline) **38a** required 160 h for the completion with 90% ee (Table 37, entries 1 and 2). Moreover, the methyl malonate **94a** reacted with allylic acetate **95** at 1 mol% of the catalyst (Table 37, entries 1 and 2), but the ethyl malonate **94b** required 5 mol% of the catalyst for the completion of reaction (Table 27, entries 5-7). Immobilized ligands **89** and **90** also gave 99% ee at 5 mol%.



94a: R = Me
94b: R = Et

95

96a: R = Me
96b: R = Et

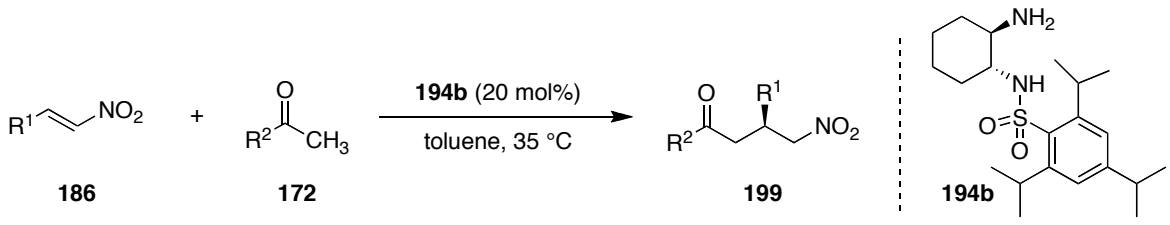
entry	R	ligand	mol (%)	time (h)	yield (%)[a]	ee (%)[b]
1	Me	**38a**	1	160	94	90
2	Me	**46a**	1	24	92	99
4	Et	**46a**	5	24	94	99
5	Et	**89**	5	48	90	99
6	Et	**90**	5	64	86	99

[a] isolated yield. [b] determined by HPLC.

Table 37. Palladium(II) catalyzed allylation of malonates.

Organocatalysis: In the development of new catalyst design, we have utilized chiral cyclohexadiamine derivative **194** as an organocatalyst and observed for the first time the catalyst deactivation in asymmetric organocatalysis.

Catalyst **194b** showed excellent reactivity for the addition of acetone (**172a**) to β-nitrostyrene (**186a**) to give rise to **199a** in 98% yield and 87% ee (Table 38, entry 1). Turning to the more challenging aromatic ketones we were pleased to note that with catalyst **194b** enantioselectivities of up to 98% ee were achieved, Under the optimized conditions, **199b-k** were obtained in 94-98% ee with acceptable yields (Table 38, entries 2-4). Besides β-nitrostyrene (**186a**), the *p*-bromophenyl and the 2-furyl analogs **186b** and **186c** could be employed as nitroalkenes (Table 38, entries 10 and 11).



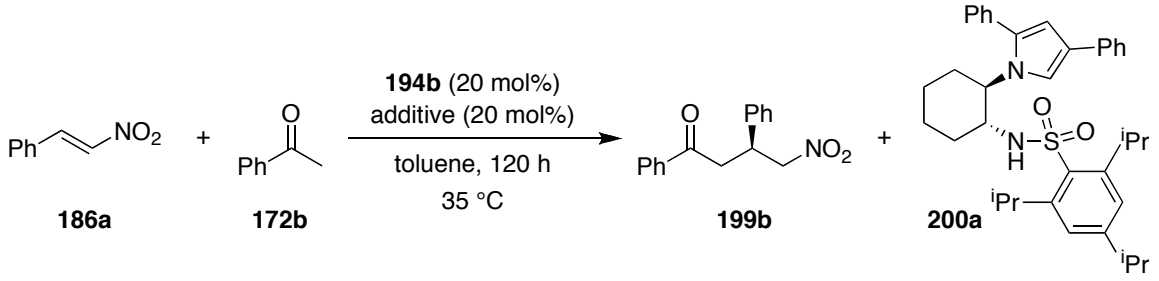
186 **172** **199** **194b**

entry	R^1 (**186**)	R^2 (**172**)	product	yield (%)[a]	ee (%)[b]
1[c]	Ph (**186a**)	CH_3 (**172a**)	**199a**	98	87
2	Ph (**186a**)	Ph (**172b**)	**199b**	72	96
3	Ph (**186a**)	*p*Cl-Ph(**172c**)	**199c**	70	94
4	Ph (**186a**)	*p*Br-Ph (**172d**)	**199d**	65	94
5	Ph (**186a**)	*p*I-Ph (**172e**)	**199e**	59	98
6	Ph (**186a**)	*p*Me-Ph (**172f**)	**199f**	60	96
7	Ph (**186a**)	*p*OMe-Ph(**172g**)	**199g**	51	98
8	Ph (**186a**)	*p*OPh-Ph (**172h**)	**199h**	61	97
9	Ph (**186a**)	2-Naphthyl (**172i**)	**199i**	62	98
10	*p*-Br-Ph (**186b**)	Ph (**172b**)	**199j**	64	94
11	2-furyl (**186c**)	Ph (**172b**)	**199k**	32	97

[a] isolated yield [b] determined by HPLC (Chiralpak AS-H), [c] rt.

Table 38. Conjugate addition of ketones to β-nitrostyrenes with **194b.**

When aromatic ketone **172b** was employed as substrate we were able to identify an irreversible formation of pyrroles **200a** (30% with respect to catalyst **194b**) in a three-component reaction between the catalyst **194b**, the nitroalkene **186a** and the ketone **172b** as a novel pathway for the catalyst deactivation (Scheme 70). In order to suppress the formation of pyrrole side product various acids, protic solvents and salts were screened. However, pyrrole formation was still observed.



Scheme 70. Catalyst deactivation by formation of pyrrole **200a**

12 Experimental Part

12.1 General information

Catalytic reactions were carried out in Schlenk tube under nitrogen atmosphere, unless otherwise stated. Column chromatography was performed on silica gel Geduran SI 60 (70-230 mesh) purchased from Merck and flash chromatography on flash-silica gel 60 (230-400 mesh ASTM) purchased from Merck. Thin layer chromatography (TLC) was performed on TLC-aluminium sheets (Merck, silica gel 60 F254, 0.2 mm).

Materials

Dry solvents were prepared by following the standard methods. THF and toluene were distilled over sodium/benzophenone and stored over sodium wire. Dichloromethane and DMF were distilled over calcium hydride. Ethanol and Methanol were distilled over magnesium and stored under nitrogen over 4 Å MS. Commercial grade reagents were used without further purification

Stereochemical assignment

The absolute configurations of the products were assigned by the comparison of their optical rotations with literature values. All other absolute configurations were assigned by analogy based on a uniform HPLC data.

^{1}H and ^{13}C NMR spectrums

^{1}H NMR spectrums were recorded on a Bruker Avance 600 (600 MHz), Bruker ARX 400 (400 MHz) and Bruker Avance 300 (300 MHz). The chemical shifts are reported in δ (ppm) relative to chloroform ($CDCl_3$, 7.26 ppm), dimethylsulfoxide (DMSO-d6, 2.50 ppm), methanol (CD_3OD, 3.31 ppm) and tetramethylsilane (TMS, 0 ppm). The spectra were analyzed by first order; the coupling constants are reported in Hertz (Hz). Characterization of signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd = double of a doublet, dt = double of a triplet, dq = double of a quartet, ddd = double of a

doublet of a doublet, Integration is determined as the relative number of atoms.

^{13}C NMR spectrums were recorded on a Bruker ARX 400 (100.6 MHz), Bruker Avance 300 (75.5 MHz). The chemical shifts are reported in δ (ppm) relative to chloroform ($CDCl_3$, 77.16 ppm), dimethylsulfoxide (DMSO-d6, 36.52 ppm), methanol (CD_3OD, 49.0 ppm) and tetramethylsilane (TMS, 0 ppm).

Mass spectrometry (Varian MAT 311A) was done in the Central Analytical Laboratory (Universität Regensburg). Elemental analysis (Vario EL III or Mikro-Rapid CHN) was done in microanalytical department of the University of Regensburg.

IR spectra, optical rotation and melting points

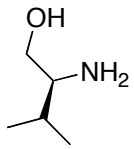
IR Spectrums were recorded on a Bio-Rad Excalibur Series FT-IR. Solid compounds were measured in KBr, liquid compounds as a neat film between NaCl-plates. The wave numbers are given in [cm^{-1}]. Melting points were measured on a Büchi SMP 20 in a silicon oil bath. Optical rotations were measured on a 241 MC Perkin-Elmer polarimeter with sodium lamp (589 nm) in the specified temperature and solvent. Either 1 dm or 0.1 dm cell was used and the concentrations are given in g/100 ml.

HPCL and GC

Chiral HPLC (335 UV detector) was performed on a Kontron Instruments 325 System. Chiracel OD/OD-H, AS and OJ columns were used (50x4.6 mm, 10 µm,) at the mentioned flowed rate and wavelength. Gas chromatography (GC) was measured on Fisons Instruments GC 8000 series (Data Jet Integrator, CP-chiralsil-DEX-CP column).

12.2 Synthesis of aza-bis(oxazolines)

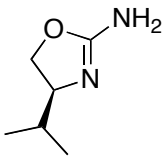
L-Valinol (64a)



A dry 2-L three-necked round-bottom flask equipped with a mechanical stirrer and a 250-mL addition funnel was charged with sodium borohydride (24.2 g, 0.64 mol) and 600 mL of anhydrous THF. The solution was stirred while *L*-Valine (30 g, 0.26 mmol) was added in one portion. The flask was cooled to 0 °C and fitted with a reflux condenser. The addition funnel was charged with a solution of I_2 (65.0 g, 0.26 mmol) in 140 mL of THF, which was added dropwise to the flask over the period of 1.5 h with considerable gas evolution. The solution was allowed to warm to room temperature. When the brown color had dissipated to give a cloudy white solution, the reaction was brought to reflux for 19 h. The cloudy white suspension was cooled to room temperature with the aid of a water bath. The addition funnel was charged with 120 mL of MeOH, which was added dropwise with rapid stirring. Vigorous gas evolution was observed. Small aliquots of MeOH were then added until all of the solid white material had dissolved. The solution was concentrated by rotary evaporation to give a white pasty oil that was dissolved in 1.0 L of 20% (w/w) aqueous KOH and mechanically stirred for 6 h at room temperature. The light green solution was extracted with CH_2Cl_2 (3 x 1.0 L). To minimize the emulsion, 150 mL of brine was added to the aqueous layer after the first extraction. The combined organic extracts were dried over Na_2SO_4, filtered through glass wool, and concentrated in *vacuo* to give *L*-valinol **64a** (23.7 g 90%) as colorless gummy oil, which solidified upon cooling to room temperature.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 3.63 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.27 (dd, *J* = 10.5, 8.8 Hz, 1H), 2.54 (ddd, *J* = 8.8, 6.4, 4.0 Hz, 1H), 1.55 (dq, *J* = 13.5, 6.7 Hz, 1H), 0.91 (dd, *J* = 6.8, 4.2 Hz, 6H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 64.79, 58.52, 31.68, 19.36, 18.46.

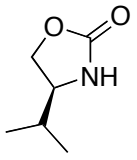
(*S*)-4-isopropyl-4,5-dihydrooxazol-2-amine (65a)



To an ice cooled solution of bromine (22.3 g, 0.14 mol) in methanol (120 mL) sodium cyanide (6.8 g, 0.14 mol) was added in portions over 30 min. After all was dissolved a solution of (*S*)-valinol (12.5 g, 30 mmol) in methanol (40 mL) was added and stirring continued for 1 h. To the reaction mixture 25% ammonia solution (100 mL) at 0 ^{o}C was added and the solvent was removed under reduced pressure. The resulting residue was dissolved in NaOH (120 mL of 20 % solution) and extracted three times with CH_2Cl_2 (3 x 70 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The resulting colorless solid **65a** (8.9 g, 57%) was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): d = 4.4 (bs, 2 H), 4.29 (dd, 1 H, *J* = 8.1, 8.1 Hz), 3.95 (dd, 1 H, *J* = 7.5, 7.5 Hz), 3.74 (ddd, 1 H, *J* = 8.8, 7.1, 7.1 Hz), 1.72-1.57 (m, 1 H), 0.93 (d, 3 H, *J* = 6.7 Hz, 0.87 (d, 3 H, *J* = 6.7 Hz); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): d = 165.8, 69.5, 65.4, 33.1, 18.7, 18.1.

(*S*)-4-isopropyloxazolidin-2-one (68a)

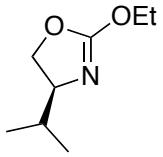


To the stirred solution of NaOEt (generated is situ by the addition of tiny Na (1.0 g, 45 mmol) in 60 mL of EtOH) L-valinol **64a** (4.7 g, 45 mmol) in 15 mL of EtOH was added and the solution was stirred for 2 min. in prior to the addition of diethylcarbonate (5.9 g, 50 mmol). The reaction mixture was brought to reflux for 24 h and cooled to rt. EtOH was removed under vacuum and the residue was dissolved in CH_2Cl_2. To this CH_2Cl_2 sat. NH_4Cl was added and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried

over $MgSO_4$ and the solvent was removed in *vacuo*. The resulting colorless solid (4.7 g, 80 %) was used without further purification.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.84 (s, 1H), 4.43 (t, *J* = 8.7 Hz, 1H), 4.08 (dd, *J* = 8.7, 6.3 Hz, 1H), 3.63-3.56 (m, 1H), 1.71 (dq, *J* = 13.5, 6.8 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 160.58, 68.69, 58.46, 32.76, 18.06, 17.70.

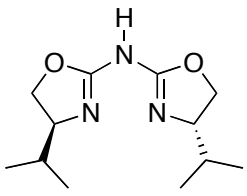
(*S*)-2-ethoxy-4-isopropyl-4,5-dihydrooxazole (69a)



A solution of oxazolidinone **68a** (3.6 g, 28 mmol) in CH_2Cl_2 abs. (70 mL) was cooled to 0 °C and Et_3OBF_4 (5.8 g, 31 mmol in 10 mL CH_2Cl_2) was added dropwise. The solution was stirred overnight at room temperature and was then poured onto cold saturated sodium carbonate solution (80 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated to give the crude product as colorless oil **69a** in 94% yield (4 g). The substance was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.39-4.25 (m, 3 H), 4.06-3.9 (m, 1 H), 3.78 (dd, 1 H, *J* = 9.0, 6.6 Hz), 1.72–1.60 (m, 1 H), 1.28 (t, 3 H, *J* = 7.1 Hz) 0.89 (d, 3 H, *J* = 6.7 Hz), 0.81 (d, 3 H, *J* = 6.7 Hz); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): d = 162.4, 70.9, 58.4, 53.5, 33.0, 18.5, 17.6, 14.4.

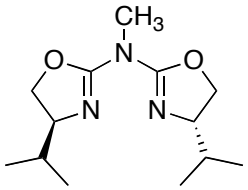
(*S,S*)-Bis-(4-isopropyl-4,5-dihydro-oxazol-2-yl)-amine (45a)



A mixture of the aminooxazoline **65a** (1.57 g, 11 mmol), benzaldehyde (1.17 g, 11 mmol, 1.11 mL) and *p*-toluenesulfonic acid monohydrate (104 mg, 0.55 mmol) in toluene was refluxed for 22 h using a Dean Stark trap. The solvent was evaporated and the residue chromatographed on silica gel (1:1 hex/EA to pure EA as eluant). The product **45a** was isolated as colorless solid: 852 mg (58%).

^{1}H-NMR (300 MHz; $CDCl_3$): δ 4.37 (t, *J* = 8.8 Hz, 2H), 4.04 (dd, *J* = 8.5, 7.1 Hz, 2H), 3.81 (dt, *J* = 8.9, 7.1 Hz, 2H), 1.71 (dq, *J* = 13.5, 6.8 Hz, 2H), 0.98 (d, *J* = 6.7 Hz, 6H), 0.89 (d, *J* = 6.7 Hz, 6H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 165.87, 69.44, 65.55, 33.09, 18.72, 18.16.

(*S*,*S*)-Bis-(4-isopropyl-4,5-dihydro-oxazol-2-yl)-methyl-amine (46a)



To a solution of **45a** (225 mg, 1 mmol) in THF (10 mL), was slowly added at –78 °C *n*-butyllithium (1.13 mmol, 708 µL of a 15% solution in hexane). After stirring for 10 min, MeI (667 mg, 4.7 mmol) was added dropwise, the solution was slowly warmed to room temperature overnight and stirred for another 10 h. Na_2CO_3 aq. was added and the mixture was concentrated. The residue was separated between dichloromethane and Na_2CO_3 aq., the aqueous phase was extracted twice with dichloromethane, and the combined organic phases were dried over $MgSO_4$ and concentrated to give **46a** in 98% yield (233 mg).

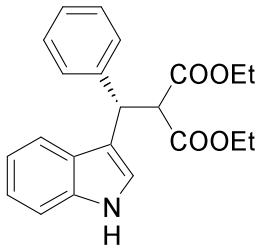
^{1}H-NMR (600 MHz; $CDCl_3$): δ 4.41 (t, *J* = 8.8 Hz, 2H), 4.14 (t, *J* = 7.7 Hz, 2H), 3.88 (dt, *J* = 9.1, 6.8 Hz, 2H), 3.40 (s, 3H), 1.76 (dq, *J* = 13.4, 6.7 Hz, 2H), 0.97 (d, *J* = 6.8 Hz, 6H), 0.88 (d, *J* = 6.8 Hz, 6H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 156.65, 70.65, 68.73, 36.24, 31.92, 17.80, 16.76.

12.3 Michael addition of indoles to benzylidene malonates

Catalytic asymmetric Michael additions

To a Schlenk tube Ligand **46a** (12.0mg, 0.05 mmol) and $Cu(OTf)_2$ (18.1mg, 0.05 mmol) were added under air atmosphere. Ethanol (2 mL) was added and the mixture was stirred for 1h at room temperature (20-25°C). To the resulting blue-green solution malonate (1 mmol, 1.0 eq.) in EtOH (2 mL) was added and the stirring was continued for 20 min before the indole (1.2 mmol, 1.2 eq.) was added. After the stirring for 8 h at room temperature, the red colored solution was concentrated under reduced pressure. The crude product was purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM).

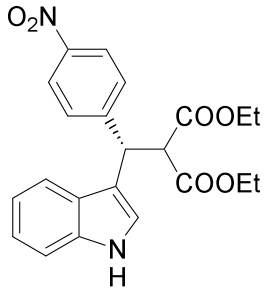
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–phenyl propanoate (80a)



Prepared according to the general procedure described above and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93-1.06 (m, 6 H), 3.93-4.06 (m, 4 H), 4.30 (d, *J* = 11.8 Hz, 1 H), 5.09 (d, *J* = 11.8 Hz, 1 H), 7.00-7.07 (m, 1 H), 7.09-7.31 (m, 6 H), 7.37 (d, *J* = 7.4 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 8.07 (brs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.1, 167.9, 141.4, 136.2, 128.4, 128.2, 126.8, 126.7, 122.3, 120.9, 119.5, 119.4, 117.0, 111.0, 61.5, 61.4, 58.4, 42.9, 13.8, 13.8; MS (CI): m/z (%) = 383 (MNH_4^+, 89), 366 (MH^+, 3), 206 (100), 178 (5); mp 174-176 °C; HPLC analysis (Chiralcel OD/OD-H, 10% *i*PrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (minor) = 26.67 min, t_r (major) = 31.40 min); >99 % *ee*; $[\alpha]_D^{25}$ = + 65.4 (20mg/2 mL CH_2Cl_2).

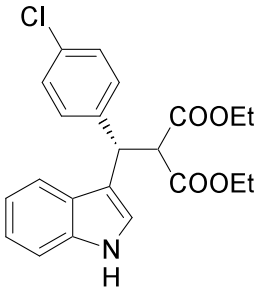
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(*p*-nitrophenyl) propanoate (80e)



Prepared according to the general procedure described above and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.1 Hz, 3 H), 1.07 (t, *J* = 7.10 Hz, 3 H), 3.97-4.08 (m, 4 H), 4.32 (d, *J* = 11.8 Hz, 1 H), 5.20 (d, *J* = 11.5 Hz, 1 H), 7.00-7.10 (m, 1 H), 7.12-7.20 (m, 1 H), 7.21 (d, *J* = 2.5 Hz, 1 H), 7.32 (d, *J* = 8.2 Hz, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.50-7.63 (m, 2 H), 8.05-8.27 (m, 2 H), 8.15 (brs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.5, 167.4, 149.3, 146.7, 136.2, 129.2, 126.3, 123.7, 122.7, 121.3, 119.9, 118.9, 115.4, 111.3, 61.8, 57.7, 42.5, 13.9, 13.8; MS (CI): m/z (%) = 428 (MNH_4^+, 100), 410 (2), 398 (7), 251 (25), 221 (22), 178 (11); mp 105-107 °C; HPLC analysis (Chiralcel AS, 15% *i*PrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (major) = 29.13 min, t_r (minor) = 39.83 min); >80 % *ee*; $[\alpha]_D^{25}$ = + 6.9 (20mg/2 mL CH_2Cl_2).

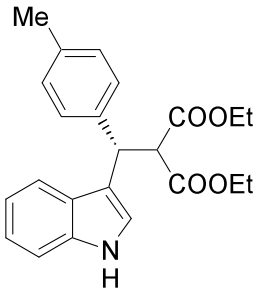
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(*p*-chlorophenyl) propanoate (80c)



Prepared according to the general procedure described above and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (t, *J* = 7.1 Hz, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H), 3.96-4.06 (m, 4 H), 4.24 (d, *J* = 11.8 Hz, 1 H), 5.06 (d, *J* = 11.8 Hz, 1 H), 7.00-7.07 (m, 1 H), 7.10-7.23 (m, 4 H), 7.27-7.34 (m, 3 H), 7.49 (d, *J* = 8.2 Hz, 1 H), 8.05 (brs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.9, 167.8, 140.1, 136.3, 132.5, 129.6, 128.5, 126.5, 122.4, 121.0, 119.7, 119.2, 116.4, 111.1, 61.6, 58.2, 42.3, 13.9, 13.8; MS (CI): m/z (%) = 417 (MNH_4^+, 100), 399 (3), 242 (30), 240 (67), 206 (2), 178 (8); mp 157-158 °C; HPLC analysis (Chiralcel OD/OD-H, 15% *i*PrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (minor) = 9.75 min, t_r (major) = 17.66 min); >98 % *ee*; $[\alpha]_D^{25}$ = + 48.2 (20mg/2 mL CH_2Cl_2).

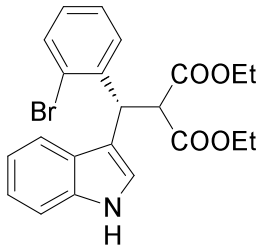
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(*p*-methylphenyl) propanoate (80b)



Prepared according to the general procedure described above and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.1 Hz, 3 H), 1.04 (t, *J* = 7.1 Hz, 3 H), 2.24 (s, 3 H), 3.94-4.05 (m, 4 H), 4.27 (d, *J* = 11.8 Hz, 1 H), 5.04 (d, *J* = 11.8 Hz, 1 H), 6.99-7.06 (m, 3 H), 7.08-7.18 (m, 2 H), 7.22-7.31 (m, 3 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.99 (brs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.1, 167.9, 138.4, 136.2, 136.2, 129.0, 128.0, 126.7, 122.2, 120.8, 119.5, 119.5, 117.3, 110.9, 61.4, 61.4, 58.4, 42.4, 21.0, 13.8, 13.8; MS (CI): m/z (%) = 397 (MNH_4^+, 73), 379 (2), 220 (100), 178 (7); mp 140-142 °C; HPLC analysis (Chiralcel OD/OD-H, 10% *i*PrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (major) = 22.12 min, t_r (minor) = 25.47 min); >94 % *ee*; $[\alpha]_D^{25}$ = + 26.7 (10mg/2 mL CH_2Cl_2).

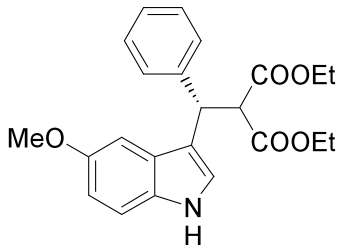
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(*o*-bromophenyl) propanoate (80d)



Prepared according to the general procedure described above and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a brown gummy solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.1 Hz, 3 H), 1.03 (t, *J* = 7.1 Hz, 3 H), 3.92-4.07 (m, 4 H), 4.37 (d, *J* = 11.5 Hz, 1 H), 5.64 (d, *J* = 11.5 Hz, 1 H), 6.97-7.31 (m, 5 H), 7.41 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.53 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.72 (d, *J* = 7.7 Hz, 1 H), 8.08 (brs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.0, 167.7, 140.8, 136.1, 133.2, 129.1, 128.2, 127.6, 126.7, 124.9, 122.3, 122.2, 119.7, 115.6, 111.2, 61.6, 58.0, 41.8, 41.4, 14.1, 13.8, 13.7; MS (CI): m/z (%) = 461 (MNH_4^+, 100), 444 (MH^+, 4), 284 (58), 206 (3), 178 (12); HPLC analysis (Chiralcel OD/OD-H, 10% *i*PrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (minor) = 24.30 min, t_r (major) = 37.42 min); >85 % *ee*; $[\alpha]_D^{25}$ = + 48.5 (20mg/2 mL CH_2Cl_2).

(S)–Ethyl 2–ethoxycarbonyl–3–[3–(5-methoxyindolyl)]–3–phenyl propanoate (80f)



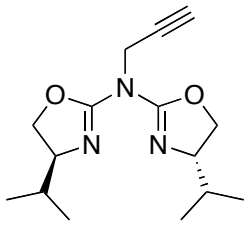
Prepared according to the general procedure described above and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97-1.04 (m, 6 H), 3.78 (s, 3 H), 3.93-4.07 (m, 4 H), 4.26

(d, *J* = 11.8 Hz, 1 H), 5.02 (d, *J* = 11.8 Hz, 1 H), 6.78 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.96 (d, *J* = 2.2 Hz, 1 H), 7.10-7.25 (m, 5 H), 7.33-7.40 (m, 1 H), 7.92 (brs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.1, 167.9, 154.0, 141.4, 131.3, 128.4, 128.2, 127.2, 126.8, 121.6, 116.8, 112.5, 111.6, 101.3, 61.5, 61.4, 58.4, 55.8, 42.9, 13.8; MS (CI): m/z (%) = 413 (MNH_4^+, 71), 396 (MH^+, 3), 236 (100), 178 (13); mp 146-148 °C; HPLC analysis (Chiralcel OD/OD-H, 10% *i*PrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (minor) = 31.91 min, t_r (major) = 39.78 min); >89 % *ee*; $[\alpha]_D^{25}$ = + 11.3 (20mg/2 mL CH_2Cl_2).

12.4 Immobilization of aza-bis(oxazoline) on fluorous tag

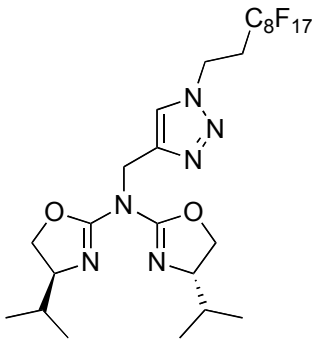
(*S*,*S*)-Bis-(4-isopropyl-4,5-dihydro-oxazol-2-yl)-prop-2-ynyl-amine (87)



To a stirred solution of **45a** (152 mg, 1 mmol) in THF (10 mL) *n*-butyllithium (1.2 mmol, 482 µL of 15% solution in hexane) was added slowly at -78 °C. After stirring for 10 min, propargylbromide (4.0 mmol, 274 µL of a 80% solution in xylene) was added dropwise, and the solution was slowly warmed to room temperature overnight and stirred for another 10 h. Na_2CO_3aq. was added and the mixture was concentrated. The residue was separated between CH_2Cl_2 and Na_2CO_3 aq. The aqueous phase was extracted twice with dichloromethane, and the combined organic phases were dried over $MgSO_4$ concentrated to give **87** (170 mg, 97%) as a light brown liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.58 (d, 2H, *J* = 2.3 Hz), 4.34 (dd, 2H, *J* = 9.2, 8.3 Hz), 4.12 (dd, 2H, *J* = 8.3, 6.7 Hz), 3.86 (ddd, 2H, *J* = 9.2, 6.6, 6.1 Hz), 2.18 (t, 1H, *J* = 2.4 Hz), 1.80-1.66 (m, 2H), 0.88 (d, 6H, *J* = 6.8 Hz), 0.81 (d, 6H, *J* = 6.8 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 156.4, 79.1, 71.7, 71.5, 69.7, 39.7, 32.7, 18.6, 17.6; IR: 3290, 3220, 2965, 2915, 2885, 1703, 1640, 1485, 1428, 1273, 1100, 985 cm^{-1}; $[\alpha]_D^{20}$ -58.7 (*c* 1.0, CH_3OH); MS (ES-MS, m/z): 278.2 (MH^+); HRMS (m/z): MH^+calcd. for $C_{15}H_{23}N_3O_2$: 278.1869, found: 278.1875.

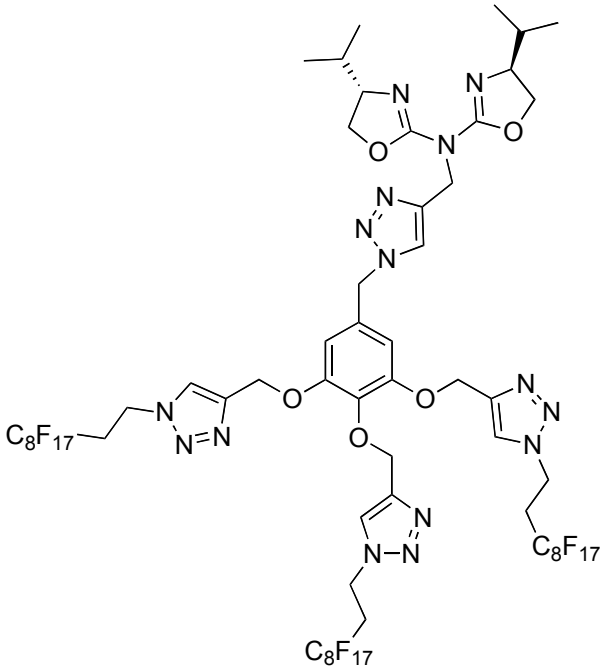
1-Ponytail perfluorinated azabox (89)



To a stirred solution of **87** (830 mg, 2.99 mmol) in degassed dry THF (15 mL), 1-azido-perfluorodecane (1.46 g, 2.99 mmol), CuI (34 mg, 0.18 mmol) and DIPEA (606 μL, 3.29 mmol) were added and the reaction mixture was stirred at rt for 12 h. Then the reaction mixture was quenched with 0.1 M EDTA solution; the product was extracted with CH_2Cl_2 (3 x 10 mL). Then the combined organic layer washed with brine and dried over Na_2SO_4. After removal of the solvent, the crude product was recrystallized from hexane and ethylacetate to give **89** (2.1 g, 92%) as a colorless solid; m. p. 124-125 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.69 (s, 1H), 5.13 (s, 2H), 4.63 (t, 2H, *J* = 7.5 Hz), 4.39 (dd, 2H, *J* = 9.1, 8.5 Hz), 4.13 (dd, 2H, *J* = 8.3, 7.1 Hz) 3.87 (dt, 2H, *J* = 9.1, 6.6 Hz), 2.69-2.86 (m, 2H), 1.77-1.66 (m, 2H), 0.91 (d, 6H, *J* = 6.8 Hz), 0.82 (d, 6H, *J* = 6.8 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 155.8, 143.9, 122.5, 70.6, 68.9, 44.1, 31.8, 17.6, 16.7; IR: 2963, 1750, 1635, 1553, 1485, 1416, 1373, 1333, 1196, 1146, 1095, 1048, 967, 935, 808, 704, 658, 609, 559, 529, 413 cm^{-1}; MS (ES): m/z = 767 (MH^+); HRMS (m/z): MH+ calcd. for $C_{25}H_{27}F_{17}N_6O_2$: 766.1917, found: 766.1924.

3-Ponytails perfluorinated azabox (90)



To a stirred solution of **87** (100 mg, 0.36 mmol) in degassed dry THF (10 mL), **88** (397 mg, 0.23 mmol), CuI (2.6 mg, 14 μL) and DIPEA (45 μL, 0.27 mmol) were added and the reaction mixture was stirred at rt for 70 h. Then the reaction mixture was quenched with 0.1 M EDTA solution, the product was filtered and washed with water followed by diethylether and dried under reduced pressure to give **90** (559 mg, 76%) as a light brown solid. m. p. 153-155 °C;

IR: 3200, 2963, 2104, 1642, 1437, 1327, 1200, 1146, 1112, 972, 705, 657, 530 cm^{-1}; MS (ES) m/z (%) = 2042 (72), 2041 (MH^+, 100), 1931 (38), 1930 (74), 1781 (31), 1764 (47).

Kinetic resolution

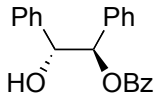
Preparation of the copper(II)-aza(bisoxazoline) complexes

Ligand (1.1 mmol) and $CuCl_2$ (1.0 mmol) were stirred in CH_2Cl_2 for 2 h, filtered off and the filtrate was concentrated under reduced pressure. Recrystallization from CH_2Cl_2 gave the complex as green crystals.

General procedure for the catalytic asymmetric benzoylation

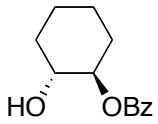
1,2-Diol (1.0 mmol), diisopropylethylamine (DIPEA, 1.0 mmol) and 0.02 mmol of the polymer-supported catalyst were dissolved in 4 mL of CH_2Cl_2 and cooled to 0 °C. Benzoyl chloride was added and the mixture was stirred at 0 °C until the benzoyl chloride disappeared (TLC). Then the reaction mixture was poured into water and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexane).

(*R*)-Benzoic acid 2-hydroxy-1,2-diphenyl-ethyl ester (50)



White solid, m. p. 146-148 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.14-8.10 (m, 2H), 7.62-7.56 (m, 1H), 7.50-7.44 (m, 2H), 7.25-7.17 (m, 10H), 6.11 (d, 1H, *J* = 7.3 Hz), 5.10 (d, 1H, *J* = 7.3 Hz), 2.73-2.56 (bs, 1H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 165.8, 139.0, 136.8, 133.3, 130.0, 129.8, 128.5, 128.3, 128.3, 128.2, 127.3, 127.2, 80.6, 77.3; IR: 3472, 3034, 1721, 1453, 1273, 1113, 704 cm^{-1}; GC: CP-Chirasil-Dex CB, 25m x 0.25mm Di, 0.25 μm Film, Inj. 250 °C, Det. 350 °C, retention time: 101.9 min (+), 104.0 min (-), >99 % *ee*, $[\alpha]_D^{20}$ +75.4 (*c* 1.0, $CHCl_3$); R*f*: 0.54 (25% EtOAc/Hexanes as eluent).

(*R,R*)-Benzoic acid 2-hydroxy-cyclohexyl ester (50b):



White solid, m. p.: 91-94 °C; ^{1}H-NMR (300 MHz, CDCl3): δ = 8.04-7.98 (d, 2 H, J = 9.0 Hz), 7.57-7.49 (m, 1 H), 7.45-7.36 (m, 2 H), 4.86-4.75 (m, 2 H), 3.78-3.64 (m, 1 H), 2.21-2.02 (m, 2 H), 1.77-1.67 (m, 2 H), 1.50-1.20 (m, 4 H); IR: 2939, 2862, 1718, 1603, 1453, 1281 cm-1; CP-Chirasil-Dex CB, 25m x 0.25mm Di, 0.25μm Film, Inj. 250 °C , Det. 300 °C , retention time: 266 min (-), 282 min (+), 82 % *ee*, $[\alpha]_{20}^D$ –66.8 (c = 1.37, CH_3OH); R*f*:

0.55 (hexanes/ethyl acetate: 2:3).

Recovery and recycling

Single-ponytailed azabox (89)-$CuCl_2$ complex recovery (homogeneous)

After the completion of reaction, the reaction mixture was filtered; cold diethyl ether was added to the filtrate to precipitate the complex. The precipitated complex was filtered, dried and directly used for the further cycles.

Three-ponytailed azabox (90)-$CuCl_2$ complex recovery (heterogeneous)

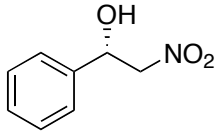
After the completion of reaction, the reaction mixture was filtered in order to recover the complex and washed with THF, dried and reused directly.

Henry reaction

General procedure: Copper acetate catalyzed direct nitroaldol reaction of nitromethane with aldehydes.

To a Schlenk tube ligand **89** (42 mg, 0.055 mmol) and $Cu(OAc)_2 \cdot H_2O$ (9.98 mg, 0.05 mmol) were added under air atmosphere. THF (2.5 mL) was added and the mixture was stirred for 1 h at room temperature (20-25 °C). To the resulting blue-green solution nitromethane (537 µL, 10 mmol) and benzaldehyde (102 µL, 1 mmol) were added. After stirring for the amount of time indicated, the volatile components were removed under reduced pressure and the crude product was purified by column chromatography (performed with hexanes/EtOAc 85:15).

(*S*)-1-Phenyl-2-nitroethanol (93)



Prepared according to the general procedure described above and purified by column chromatography (performed with hexanes/EtOAc 85:15) to obtain the pure product as colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$)): δ = 7.43-7.33 (m, 5H), 5.49- 5.44 (m, 1H), 4.61 (dd, 1H, *J* = 13.4, 9.4 Hz), 4.51 (dd, 1H, *J* = 13.4, 3.2 Hz), 2.87 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$)): δ = 138.1, 129.1, 129.0, 126.0, 81.2, 71.0; IR: 3540, 2921, 2349, 1547, 1494, 1454, 1418, 1377, 1288, 1193, 1065, 894, 847, 763 cm^{-1}; Ms (CI): m/z (%) = 202 (14), 185 (MNH_4^+, 100), 167 (7), 137 (7); 90% *ee* ; $[\alpha]_D^{20}$ +38.0 (*c* 1.3, $CHCl_3$).

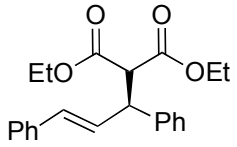
Recovery and recycling

After the completion of reaction, EtOH was removed; hexane was added to the reaction mixture in order to precipitate the complex. The precipitated complex was filtered, dried and directly used for the further cycles.

Allylation

To a schlenk tube allylpalladium chloride dimer (4.4 mg, 12 μmol) and ligand **89** (23 mg, 30 μmol) were added under air atmosphere. CH_2Cl_2 (2 mL) was added and the mixture was stirred for 1h at room temperature (20-25 °C). To the resulting light yellow solution 1,3-diphenylacetate **95** (120 mg, 0.48 mmol), diethylmalonate **94b** (218 μl, 1.43 mmol), N,O-bis- (trimethylsilyl)acetamide (BSA) (351 μl, 1.43 mmol) and a few crystals of potassium acetate were added. After three more freeze/thaw cycles the mixture was stirred for the amount of time indicated. To the reaction mixture sat. NH_4Cl was added and extracted with diethylether (2 x 10 mL). The organic phase was dried over $MgSO_4$. The solvent was evaporated and the residue chromatographed on silica (hexanes/ethylacetate (10/1)) to give the product **96b** as colorless oil (158 mg, 94 %).

(*S*,*Z*)-diethyl 2-(1,3-diphenylallyl)malonate (96b)



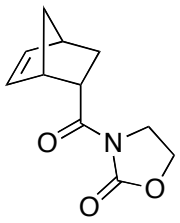
^{1}H NMR (300 MHz, $CDCl_3$)): δ = 7.34-7.18 (m, 10H), 6.49 (d, 1H, *J* = 15.79 Hz), 6.36 (dd, 1H, *J* = 15.74 Hz, 8.36 Hz), 4.29 (dd, 1H, *J* = 10.96 Hz, 8.33 Hz), 4.19 (q, 2H, *J* = 7.13 Hz), 4.02-3.92 (m, 3H), 1.22 (t, 3H, *J* = 7.13 Hz), 1.02 (t, 3H, *J* = 7.13 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$)): δ = 166.8, 166.4, 139.3, 135.8, 130.6, 128.3, 127.6, 127.4, 127.0, 126.5, 126.1, 125.3, 60.5, 60.3, 56.7, 48.2, 13.1, 12.8; IR: 3060, 3028, 2981, 2937, 2905, 2336, 1880, 1753, 1728, 1600, 1495, 1453, 1390, 1368, 1307, 1253, 1223, 1172, 1152, 1094, 1030, 965, 858, 745 cm^{-1}; MS (CI): m/z (%) = 370.2 (MNH_4^+, 100), 363.2 (9), 353.1 (11); HPLC analysis (Chiralcel OJ column (heptane/isopropanol = 99/1, 0.5 mL/min, 254 nm; t_r(minor) = 62.33 min, t_r(major) = 69.62 min); 99% ee; $[\alpha]_D^{20}$ -11.3 (*c* 1.15, $CHCl_3$).

Recovery and recycling

After the completion of reaction, CH_2Cl_2 was removed; hexane was added to the reaction mixture in order to precipitate the ligand. The precipitate was filtered and could be reused.

12.5 Secondary activation of azabox-MX_n complex Diels-Alder reaction

3-((1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-enecarbonyl)oxazolidin-2-one (101)



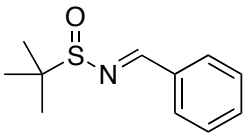
To a stirred suspension of $Cu(OTf)_2$ (36 mg, 0.1 mmol) in CH_2Cl_2 (2 ml) at rt, ligand **45a** (24 mg, 0.1 mmol) was added. The resulting mixture was stirred for 1 h to provide green solution. The resulting complex was cooled to -78 °C, and oxazolidinone **100** (141 mg, 1.0 mmol) in CH_2Cl_2 (0.5 ml) was added. Freshly cracked cyclopentadiene (0.25 mL, 3.03 mmol) was added dropwise at -78 °C and the resulting mixture was stirred for 24 h. After this period, the reaction was quenched with aqueous $NaHCO_3$ solution. The mixture was extracted with chloroform (2 ×10 ml) and the combined organic layer was washed successively with water and brine, and dried over anhydrous Na_2SO_4. Evaporation of the

solvents under reduced pressure afforded a crude residue which was purified by column chromatography over silica gel (25% EtOAc:Hexane as eluent) to provide the cycloadduct **101** (191 mg, 92% yield) and its *endo* isomer as a mixture (99:1) by HPLC. Chiralcel OD/OD-H, 10% *i*PrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (minor) = 47.70 min, t_r (minor) = 50.11 min, tr (major) = 52.42 min, tr (major) = 57.80 min; endo:exo 99:1, >87% *ee*; $[\alpha]_D^{25}$ = - 119.9 (16.6 mg/2 mL CH_2Cl_2).

^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.19 (dd, *J* = 5.7, 3.1 Hz, 1H), 5.82 (dd, *J* = 5.7, 2.9 Hz, 1H), 4.38-4.32 (m, 2H), 3.96-3.86 (m, 3H), 3.26-3.25 (m, 1H), 2.90-2.88 (m, *J* = 0.8 Hz, 1H), 1.90 (ddd, *J* = 11.6, 9.1, 3.7 Hz, 1H), 1.46-1.33 (m, 3H).

12.6 Kinetic resolution of sulfinamide and sulfinyl imines

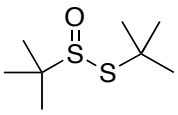
(*E*)-*N*-Benzylidene-2-methylpropane-2-sulfinamide (103)



To the solution of sulfinamide **107** (35 mg, 0.29 mmol) in 5 mL of CH_2Cl_2, $CuSO_4$ (317 mg, 1.27 mmol) and benzaldehyde (34 mg, 0.32 mmol) was added at 0 ^oC. The reaction mixture was stirred for 15 h at 0 ^oC and the solvent was removed under reduced pressure. The crude product was loaded directly in the silica column and eluted with 12% EtOAc/Hexane to obtain the sulfinamide **103** in 67% yield (40 mg) as white solid.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 8.58 (s, 1H), 7.85 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.52-7.46 (m, 3H), 1.26 (s, 9H).

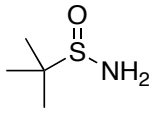
***S-tert*-Butyl 2-methylpropane-2-sulfinothioate (106)**



m-CPBA (7.5 g, 31 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a stirred solution of *tert*-butyldisulfide **105** (5 g, 28 mmol) in CH_2Cl_2 (15 mL) at 0 °C over 15 min. The solution was stirred for 30 min at 0 °C and rt until the reaction was complete by TLC (4 h). The reaction mixture was poured into a separatory funnel containing CH_2Cl_2 (70 mL) and sat. $NaHCO_3$ (80 mL) and further extracted with CH_2Cl_2 (2 x 60 mL). The organic layer was removed and washed with sat. $NaHCO_3$ (3 x 60 mL), sat. NaCl (60 mL), dried over Na_2SO_4 and concentrated in *vacuo* to give *tert*-butylthiosulfinate **106 (**5.04 g 92%). This crude product was used in the next reaction without any further purification.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.55 (s, 9H), 1.37 (s, 9H).

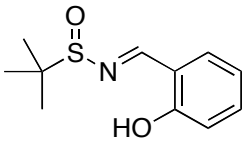
2-Methylpropane-2-sulfinamide (107)



The intermediate sulfinate **106** (5.04 g) was dissolved in CH_2Cl_2 (20 mL) and a solution of SO_2Cl_2 (4 g, 2.4 mL) in CH_2Cl_2 (6 mL) was added dropwise at 0 °C. The resulting yellow solution was stirred for 1 h allowing it to gradually reach rt. Excess of SO_2Cl_2 was removed under vacuum and the resulting product, *tert*-butylsufinyl chloride, was diluted in CH_2Cl_2 (60 mL) and added dropwise to NH_4OH (120 mL) at 0 °C over 30 min. After stirring for 30 min at rt, the reaction mixture was saturated with NaCl and extracted with CH_2Cl_2 (3 x 70 mL). The combined organic layers were washed with sat. NaCl (100 mL), dried over Na_2SO_4 and concentrated in *vacuo* to give the crude sulfinamide. Purification using flash chromatography (12:1 $CHCl_3$/MeOH as eluent) gave the sulfinamide **107** (0.94 g, 30%) as a white solid.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 3.79 (s, 2H), 1.16 (s, 9H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 55.36, 22.19.

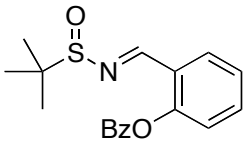
(*E*)-*N*-(2-hydroxybenzylidene)-2-methylpropane-2-sulfinamide (113)



To the solution of sulfinamide **107** (150 mg, 1.24 mmol) in 15 mL of CH_2Cl_2, $CuSO_4$ (1.4 g, 5.46 mmol) and salicylaldehyde **112** (167 mg, 1.37 mmol) was added at rt. After stirring for 18 h at reflux, solvent was removed under reduced pressure. The crude product was loaded directly in the silica column and eluted with 80% CH_2Cl_2/Hexane to obtain the hydroxy sulfinamide **113** (210 mg, 75%).

^{1}H-NMR (300 MHz; $CDCl_3$): δ 11.04 (s, 1H), 8.70 (s, 1H), 7.49-7.41 (m, 2H), 7.03-6.96 (m, 2H), 1.26 (s, 9H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 165.41, 160.25, 134.76, 133.38, 119.91, 118.30, 117.35, 57.85, 22.32.

(*E*)-2-((*tert*-butylsulfinylimino)methyl)phenyl benzoate (114)



To the ligand **38a** (2.8 mg, 0.01 mmol) in CH_2Cl_2 (1 mL), $Cu(OTf)_2$ (3.8 mg, 0.01 mmol) was added under N_2 atmosphere and the solution was stirred for 1 h. To the resulting green complex, sulfinamide **113** (24 mg, 0.10 mmol) and diisopropylethylamine (DIPEA, 17 µL, 0.10 mmol) were added and cooled to 0 °C. Benzoyl chloride (7.3 mg, 0.05 mmol) was added and the mixture was stirred at 0 °C until the benzoyl chloride disappeared (TLC). Then the reaction mixture was poured into water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc/Hexane) to afford **114** (15.8 mg, 46%) as white solid.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 8.71 (s, 1H), 8.19-8.17 (m, 1H), 8.16-8.15 (m, 1H), 7.99 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.63-7.51 (m, 2H), 7.50-7.44 (m, 2H), 7.38-7.32 (m, 1H), 7.26

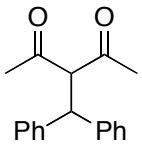
(dd, *J* = 8.2, 1.0 Hz, 1H), 1.11 (s, 9H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 163.97, 157.29, 149.75, 132.92, 132.30, 129.41, 129.19, 127.90, 127.70, 125.64, 125.44, 122.55, 56.78, 21.51.

12.7 Copper(II) mediated C−C coupling reaction

General procedure A

To the ligand (0.1 mmol) in CH_2Cl_2 (1 mL), MX_n (0.1 mmol) was added under N_2 atmosphere and the solution was stirred for 1 h. To the resulting complex, benzylic/allylic alcohol (1 mmol) and diketone was added. The reaction mixture was stirred under the reaction conditions noted in the text. Then H_2O (5 mL) was added to the reaction mixture. The resulting mixture was extracted with Et_2O, and organic layer was dried over $MgSO_4$. The volatile solvent was evaporated under reduced pressure to obtain the corresponding product.

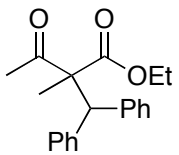
3-Benzhydrylpentane-2,4-dione (117)



Prepared according to the general procedure **A**.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.27-7.14 (m, 10H), 4.78 (q, *J* = 11.8 Hz, 2H), 2.00 (s, 6H).

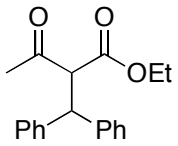
Ethyl 2-benzhydryl-2-methyl-3-oxobutanoate (121)



Prepared according to the general procedure **A**.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.32-7.15 (m, 10H), 5.27 (s, 1H), 4.09-3.93 (m, 2H), 2.07 (s, 3H), 1.53 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 204.60, 171.75, 141.20, 140.59, 130.04, 129.81, 128.27, 128.11, 126.71, 126.60, 65.08, 61.68, 53.76, 27.01, 18.31, 13.69.

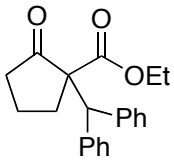
Ethyl 2-benzhydryl-3-oxobutanoate (121b)



Prepared according to the general procedure **A**.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.32-7.14 (m, 10H), 4.77 (d, *J* = 12.2 Hz, 1H), 4.53 (d, *J* = 12.2 Hz, 1H), 3.98 (qd, *J* = 7.1, 0.7 Hz, 2H), 2.10 (s, 3H), 1.00 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 200.74, 166.64, 140.54, 140.24, 127.83, 127.60, 126.79, 126.70, 125.94, 125.82, 64.19, 60.49, 49.88, 29.03, 12.76.

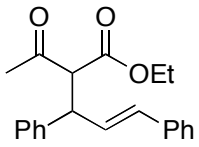
Ethyl 1-benzhydryl-2-oxocyclopentanecarboxylate (123)



Prepared according to the general procedure **A**.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.27 (s, 2H), 7.26 (s, 2H), 7.22-7.07 (m, 6H), 5.26 (s, 1H), 3.98 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.87 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.08-3.02 (m, 1H), 2.30-2.22 (m, 2H), 1.93-1.81 (m, 1H), 1.76-1.66 (m, 1H), 1.51-1.42 (m, 1H), 0.84 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (101 MHz; $CDCl_3$): δ 213.87, 168.67, 141.23, 140.32, 130.11, 128.85, 128.31, 128.23, 126.74, 126.42, 66.07, 61.61, 54.94, 38.47, 29.41, 19.69, 13.41.

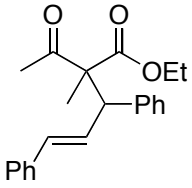
(*E*)-Ethyl 2-acetyl-3,5-diphenylpent-4-enoate (132a)



Prepared according to the general procedure **A**.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.35-7.20 (m, 20H, diast. A & B), 6.45 (dd, *J* = 15.9, 11.0 Hz, 2H, diast. A & B), 6.27 (td, *J* = 15.5, 8.2 Hz, 2H, diast. A & B), 4.33-4.26 (m, 2H, diast. A & B), 4.14 (dq, *J* = 20.2, 6.4 Hz, 4H), 3.94 (q, *J* = 7.1 Hz, 2H, diast. A), 2.31 (s, 3H, diast. A), 2.04 (s, 3H, diast. B), 1.22 (t, *J* = 7.1 Hz, 3H, diast. A), 0.98 (t, *J* = 7.1 Hz, 3H, diast. B). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 200.70, 200.46, 166.90, 166.54, 139.33, 139.16, 135.80, 135.64, 130.81, 130.48, 128.47, 128.27, 127.90, 127.66, 127.47, 126.99, 126.94, 126.61, 126.52, 126.17, 126.08, 125.36, 125.32, 64.57, 64.25, 60.63, 60.38, 47.97, 47.75, 29.03, 28.87, 13.17, 12.76.

(*E*)-Ethyl 2-acetyl-2-methyl-3,5-diphenylpent-4-enoate (132c)

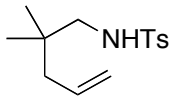


Prepared according to the general procedure **A**.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.37-7.21 (m, 23H), 6.71 (dd, *J* = 15.7, 8.8 Hz, 1H), 6.55-6.41 (m, 3H), 4.48 (d, *J* = 7.7 Hz, 1H), 4.34 (dd, *J* = 8.8, 0.8 Hz, 1H), 4.24-4.17 (m, 3H), 4.12-4.00 (m, 2H), 2.20 (s, 3H), 2.11 (s, 4H), 1.49 (s, 3H), 1.42 (s, 4H), 1.25 (t, *J* = 7.1 Hz, 4H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 205.12, 204.54, 171.81, 171.48, 139.89, 139.53, 137.32, 137.13, 133.10, 132.56, 129.65, 129.01, 128.55, 128.52, 128.40, 128.27, 128.21, 127.56, 127.42, 127.18, 127.13, 126.43, 126.39, 64.66, 61.57, 61.50, 53.42, 52.45, 27.59, 18.70, 17.15, 14.13, 13.94.

12.8 Hydroamination and aminohalogenation

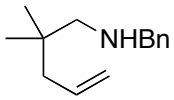
N-(2,2-dimethylpent-4-enyl)-4-methylbenzenesulfonamide (134a)



A solution of toluenesulfonyl chloride (180 mg, 0.94 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of amine **138** (89 mg, 0.79 mmol) and triethyl amine (0.13 mL, 0.94 mmol) in CH_2Cl_2 (3 mL). After the reaction was allowed to stir for 24 h, the mixture washed several times with water, dried over $MgSO_4$, and concentrated. Silica gel chromatography (10% EtOAc/Hexanes) yielded tosyl amine **134a** (185 mg, 88% yield) as a colorless oil.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.75-7.71 (m, 2H), 7.32-7.29 (m, 2H), 5.80-5.66 (m, 1H), 5.05-4.96 (m, 2H), 4.41-4.36 (m, 1H), 2.68 (d, *J* = 7.0 Hz, 2H), 2.43 (s, 3H), 1.96 (dt, *J* = 7.5, 1.1 Hz, 2H), 0.86 (s, 6H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 134.31, 129.73, 127.09, 117.95, 52.87, 44.10, 34.17, 24.91, 21.58.

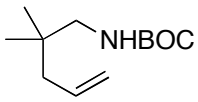
N-Benzyl-2,2-dimethylpent-4-en-1-amine (134b)



A solution of **138** (110 mg, 0.97 mmol) and benzaldehyde (103 mg, 1.07 mmol) in MeOH (5 mL) was stirred at room temperature for 3.5 h, treated with $NaBH_4$ (55 mg, 1.46 mmol) and stirred overnight. The resulting mixture was treated with water (5 mL) and 1 M NaOH (5 mL) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting oily residue was chromatographed (15% EtOAc/Hex) to give **134b** (138 mg, 70%) as viscous oil that formed a white solid upon standing.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.39-7.26 (m, 6H), 5.88-5.74 (m, 1H), 5.05-5.03 (m, 1H), 5.01-4.98 (m, 1H), 3.80 (s, 2H), 2.38 (s, 2H), 2.04 (dt, *J* = 7.5, 1.1 Hz, 2H), 0.91 (s, 6H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 140.96, 135.63, 128.59, 128.34, 128.02, 127.03, 126.81, 116.83, 65.31, 59.71, 54.73, 44.71, 34.40, 25.59.

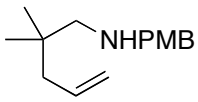
***tert*-Butyl 2,2-dimethylpent-4-enylcarbamate (134c)**



To a solution of diisopropylethyl amine (0.26 mL, 1.58 mmol) and di-*t*-butyldicarboxylate (287 mg, 1.316 mmol) in CH_2Cl_2 (4 mL) was added amine **138** (149 mg, 1.32 mmol) dropwise. The reaction was stirred for 1 h and was then quenched by addition of a saturated aqueous solution of NH_4Cl. The mixture was stirred and the layers were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford the crude oil. The crude product was purified by chromatography (10% EtOAc/Hex) to obtain colorless oil **134c** (159 mg, 80%).

^{1}H-NMR (300 MHz; $CDCl_3$): δ 5.83-5.69 (m, 1H), 5.02-4.94 (m, 2H), 4.52 (bs, 1H), 2.89 (d, *J* = 6.6 Hz, 2H), 1.90 (d, *J* = 7.5 Hz, 2H), 1.39 (s, 9H), 0.81 (s, 6H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 156.23, 134.89, 117.44, 79.05, 50.32, 44.37, 34.79, 28.45, 24.76.

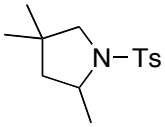
***N*-(4-methoxybenzyl)-2,2-dimethylpent-4-en-1-amine (134d)**



A solution of **138** (106 mg, 0.94 mmol) and *p*OMe-benzaldehyde (140 mg, 1.03 mmol) in MeOH (5 mL) was stirred at room temperature for 3.5 h, treated with $NaBH_4$ (53 mg, 1.41 mmol) and stirred overnight. The resulting mixture was treated with water (5 mL) and 1 M NaOH (5 mL) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting oily residue was chromatographed (hexanes/EtOAc 8:1) to give **134d** (142 mg, 65%) as a white solid.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.27-7.23 (m, 2H), 6.89-6.84 (m, 2H), 5.87-5.73 (m, 1H), 5.04-5.02 (m, 1H), 4.99-4.96 (m, *J* = 1.1 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 2H), 2.35 (s, 2H), 2.02 (dt, *J* = 7.5, 1.1 Hz, 2H), 0.89 (s, 6H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 158.50, 135.68, 133.18, 129.14, 116.77, 113.69, 59.64, 55.30, 54.14, 44.70, 34.37, 25.59.

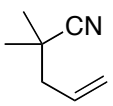
2,4,4-Trimethyl-1-tosylpyrrolidine (135a)



A mixture of **134a** (70 mg, 1 mmol) and $Fe(ClO_4)_3$·6H2O (12 mg, 0.1 mmol) in DCE (5 mL) was heated at 80 ^{o}C for 2 h while being monitored by silica-gel TLC. The reaction was allowed to cool and quenched with water (5 mL). The aqueous phase was extracted with diethyl ether (10 mL). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on silica gel (20% EtOAc/Hexanes) to provide **135a** (50 mg, 72%) as a white solid.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.74-7.73 (m, 1H), 7.71-7.70 (m, *J* = 1.8 Hz, 1H), 7.31-7.31 (m, *J* = 0.6 Hz, 1H), 7.29-7.28 (m, *J* = 0.6 Hz, 1H), 3.70-3.58 (m, 1H), 3.16 (d, *J* = 10.4 Hz, 1H), 3.06 (dd, *J* = 10.4, 1.2 Hz, 1H), 2.42 (s, 3H), 1.72 (ddd, *J* = 12.5, 7.2, 1.2 Hz, 1H), 1.43-1.36 (m, 4H), 1.03 (s, 3H), 0.54 (s, 3H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 143.13, 135.29, 129.51, 127.51, 61.52, 56.01, 48.95, 37.22, 26.63, 25.95, 22.79, 21.57.

2,2-Dimethylpent-4-enenitrile (137)

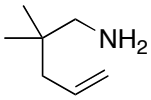


Isobutyronitrile **136** (1 g, 14.5 mmol) was added to a solution of LDA [generated *in situ* from *n*-BuLi (13.6 mL in hexanes, 15%) and diisopropylamine (4.1 mL, 29 mmol) in THF (60 mL)] at –78 °C and stirred for 45 min. To the resulting solution was added allyl

bromide (2.5 mL, 29 mmol). The solution was warmed to room temperature overnight with stirring. CH_2Cl_2 (60 mL) was added and the resulting biphasic mixture washed with water (3 × 20 mL), dried ($MgSO_4$), and concentrated. The residue was distilled under reduced pressure to give 2,2-dimethyl-4-pentenenitrile **137** (1.03 g, 65%) as colorless liquid.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 5.93-5.80 (m, 1H), 5.24-5.15 (m, 2H), 2.27 (dt, *J* = 7.4, 1.1 Hz, 2H), 1.33 (s, 6H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 132.23, 119.95, 45.12, 32.22, 26.27.

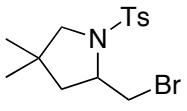
2,2-Dimethylpent-4-en-1-amine (138)



A suspension of $LiAlH_4$ (267 mg, 7 mmol) in ether (10 mL) was treated with **137** (197 mg, 1.8 mmol) at 0 °C and then warmed slowly to room temperature and stirred overnight. The resulting suspension was cooled to 0 °C and quenched by slow addition of 6 M NaOH (5 mL). The resulting mixture was extracted with ether (4 × 10 mL) and the combined ether extracts were dried ($MgSO_4$) and concentrated to give 2,2-diphenyl-4-pentenylamine **138** (192 mg, 94%) as pale yellow, viscous oil.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 5.87-5.73 (m, 1H), 5.04-4.98 (m, 2H), 2.43 (s, 2H), 1.96 (d, *J* = 7.5 Hz, 2H), 1.21 (bs, 2H) 0.84 (s, 6H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 134.34, 115.91, 51.69, 43.02, 33.92, 23.61, 0.03.

2-(Bromomethyl)-4,4-dimethyl-1-tosylpyrrolidine (147a)

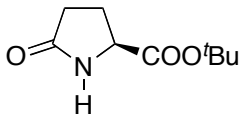


To the amino olefin **134a** (18 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) NBS (17 mg) was added at rt. The mixture was stirred for overnight and the crude product was purified by column chromatography (90:10 hexane/EtOAc) to afford **147** (27 mg, 89 %) as a light brown solid.

1-Bromopyrrolidin-2-one (149)

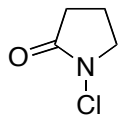
$Pb(OAc)_4$ (1.77 g, 4.0 mmol) was dissolved in MeCN (20 mL). $ZnBr_2$ (2.0 g, 4.0 mmol) was added to the MeCN solution, and the mixture was stirred for 5 min at rt. in prior to the addition of pyrrolidinone **148** (170 mg, 2 mmol). The resulting mixture was stirred at rt. until the pyrrolidinone disappeared. After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column. The column was eluted with CH_2Cl_2-hexane (1:1). Fractions containing the product were combined and evaporated under reduced pressure to give **149** (278 mg, 85%) as light brown solid.

(*S*)-*tert*-Butyl 5-oxopyrrolidine-2-carboxylate (151c)



To 587 mg (4.6 mmol) of *S*-pyrrolidinone carboxylicacid **150** in 25 mL of *tert*-butyl acetate was added 0.84 mL (5.0 mmol) of 60% $HClO_4$, and the reaction mixture was stirred overnight at room temperature in a tightly closed flask. Then, the reaction mixture was slowly poured into a saturated solution of $NaHCO_4$, and the product was extracted with ethyl ether. Drying ($MgSO_4$), filtration, and evaporation of the provided **151c** (522 mg, 62%) as colorless solid.

1-Chloropyrrolidin-2-one (153)



$Pb(OAc)_4$ (887 mg, 2.0 mmol) was dissolved in MeCN (20 mL). $AlCl_3$ (267 mg, 2.0 mmol) was added to the MeCN solution, and the mixture was stirred for 5 min at r.t. in prior to the

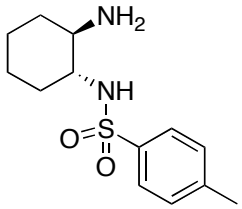
addition of pyrrolidinone **148** (170 mg, 2 mmol). The resulting mixture was stirred at r.t. until the pyrrolidinone disappeared. After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column. The column was eluted with CH_2Cl_2-hexanes (1:1). Fractions containing the product were combined and evaporated under reduced pressure to give **153** (96 mg, 40%) as colorless solid.

12.9 Organocatalysis

General procedure B: Catalyst synthesis

To a 100 mL round bottom flask L-tartrate salt of (*R*,*R*)-1,2 diaminocyclohexane **195** (800 mg, 3.03 mmol), 5 mL of aqueous 2 N NaOH and 10 mL of dichloromethane were added. The mixture was cooled to 0 °C and a solution of 2,4,6-triisopropylbenzene sulfonyl chloride **196** (302 mg, 0.99 mmol) in 10 mL of dichloromethane was added drop wise over 15 min. After the addition was complete, the mixture was allowed to warm to room temperature and stirred overnight.

N-((1*R*,2*R*)-2-aminocyclohexyl)-4-methylbenzenesulfonamide (194a)



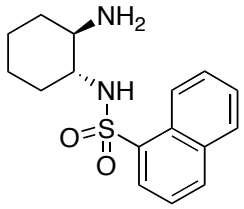
General procedure **B** is followed to obtain the compound.

The reaction mixture was extracted with a 2 N HCl solution (3 x 20 mL). The organic layer was discarded and the aqueous phase was basified with 2 N NaOH, and extracted with CH_2Cl_2 (3 x 20 mL). Removal of the solvent at reduced pressure yielded **194a** as a white solid, (in case of minor impurities, the product was purified by washing with either n-pentane or diethylether) 99% yield. mp 108-110 °C.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.78-7.74 (m, 2H), 7.30-7.27 (m, 2H), 2.62-2.57 (m, 1H),

2.39-2.38 (m, 3H), 2.37-2.29 (m, 1H), 1.93-1.87 (m, 1H), 1.83-1.77 (m, 1H), 1.65-1.57 (m, 2H), 1.18-1.05 (m, 4H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 143.28, 137.90, 129.70, 127.11, 60.51, 54.91, 35.68, 32.72, 24.99, 24.88, 21.58; IR: 3349, 3286, 3042, 2920, 2857, 2691, 1592, 1493, 1446, 1324, 1156, 1089, 949; MS (EI-MS, m/z): 113.1 (Cyclohexadiamine-H+), 268.2 (M+), 269.2 (MH+); HRMS (m/z): M+ calcd. for $C_{13}H_{20}N_2O_2S$: 268,1246, found: 268.1244; $[\alpha]_D^{25}$ = - 23.7 (10.1 mg/1 mL $CHCl_3$).

_N_-((1_R_,2_R_)-2-aminocyclohexyl)naphthalene-1-sulfonamide (194c)

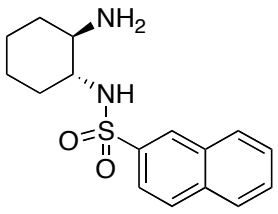


General procedure **B** is followed to obtain the compound.

The reaction mixture was washed with water (3 x 20 mL) and the solvent removed at reduced pressure to obtain **194c** as a light brown solid, (in case of minor impurities, the product was purified by washing with either n-pentane or diethylether) 85% yield. mp 67-69 °C.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 8.67 (d, *J* = 8.6 Hz, 1H), 8.31 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.70-7.52 (m, 3H), 2.66-2.60 (m, 1H), 2.39-2.31 (m, 1H), 1.87-1.81 (m, 1H), 1.65-1.48 (m, 3H), 1.15-0.93 (m, 4H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 135.34, 134.30, 134.22, 129.77, 129.17, 128.38, 128.12, 126.90, 124.53, 124.26, 60.62, 54.75, 35.39, 32.59, 24.87, 24.74; IR: 3289, 3059, 2931, 2858, 1594, 1508, 1448, 1315, 1160, 1132, 983, 770, 677; $[\alpha]_D^{25}$ = - 12.2 (9.8 mg/1 mL $CHCl_3$).

***N*-((1*R*,2*R*)-2-aminocyclohexyl)naphthalene-2-sulfonamide (194d)**

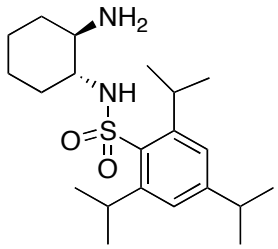


General procedure **B** is followed to obtain the compound.

The reaction mixture was washed with water (3 x 20 mL) and the solvent removed at reduced pressure to obtain **194d** as a light brown solid, (in case of minor impurities, the product was purified by washing with either n-pentane or diethylether) 87% yield. mp 102-104 °C.

^{1}H-NMR (600 MHz; CDCl3): δ 8.47 (d, *J* = 1.4 Hz, 1H), 7.97 (dd, *J* = 8.1, 6.1 Hz, 2H), 7.91-7.87 (m, 2H), 7.66-7.60 (m, 2H), 2.69 (td, *J* = 10.3, 3.8 Hz, 1H), 2.39 (td, *J* = 10.4, 3.8 Hz, 1H), 1.91-1.85 (m, 2H), 1.62-1.55 (m, 2H), 1.20-1.01 (m, 4H); ^{13}C-NMR (151 MHz; $CDCl_3$): δ 137.57, 134.74, 132.14, 129.43, 129.28, 128.72, 128.35, 127.91, 127.51, 122.44, 60.38, 54.87, 35.69, 32.72, 24.86, 24.80; IR: 3340, 3277, 3054, 2943, 2855, 1594, 1446, 1319, 1155, 1074, 962, 821, 748, 660; MS (EI-MS, m/z): 113.1 (Cyclohexadiamine-H+), 304.1 (M+); HRMS (m/z): M+ calcd. for $C_{16}H_{20}N_2O_2S$: 304.1246, found: 304.1244; $[\alpha]_D^{25}$ = - 19.2 (10.4 mg/1 mL $CHCl_3$).

***N*-((1*R*,2*R*)-2-aminocyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (194b)**

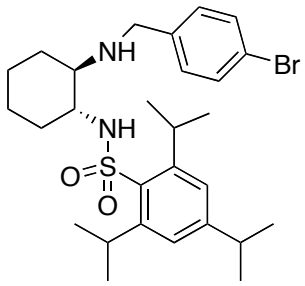


General procedure **B** is followed to obtain the compound.

The reaction mixture was washed with water (3 x 20 mL) and the solvent removed at reduced pressure to obtain **194b** as a white solid, (in case of minor impurities, the product was purified by washing with either n-pentane or diethylether) 94% yield. mp 200-204 °C.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.15 (s, 2H), 4.19-4.12 (m, 2H), 2.90-2.84 (m, 2H), 2.35-2.34 (m, 1H), 1.96-1.92 (m, 2H), 1.67-1.61 (m, 2H), 1.27 (dd, *J* = 6.8, 1.6 Hz, 12H), 1.25 (d, *J* = 6.9 Hz, 6H), 1.22-1.07 (m, 4H); ^{13}C NMR (151 MHz; $CDCl_3$): δ 152.54, 149.89, 133.84, 123.80, 60.07, 54.89, 36.04, 34.08, 32.95, 29.82, 24.99, 24.95, 24.82, 23.58, 23.57, 23.57; IR: 3348, 3287, 2936, 2862, 1593, 1447, 1424, 1384, 1362, 1313, 1256, 1149, 1116, 1099, 1040, 947; MS (EI-MS, m/z): 113.1 (Cyclohexadiamine-H+), 380.2 (M+); HRMS (m/z): M+ calcd. for $C_{21}H_{36}N_2O_2S$: 380.2498, found: 380.2496; $[\alpha]_D^{25}$ = - 19.3 (9.9 mg/2 mL $CHCl_3$).

***N*-((1*R*,2*R*)-2-(4-bromobenzylamino)cyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (198)**

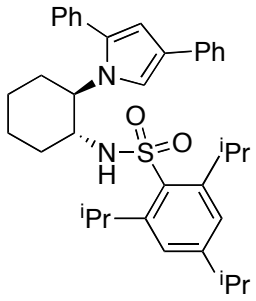


A mixture of *p*-Br-benzaldehyde (46 mg, 0.25 mmol), amine **194b** (78 mg, 0.21 mmol) and $MgSO_4$ (49 mg) in CH_2Cl_2 (5 mL), was stirred for overnight. The precipitates were removed by filtration, and the solvent was evaporated. The residue (imine) was dissolved in MeOH (5 mL), and treated with $NaBH_4$ (4 mg, 0.10 mmol) at rt for 2 h. The mixture was concentrated, and the residue was dissolved in CH_2Cl_2 (15 mL), washed with water (3 x 10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (performed with hexanes/EtOAc 3:1) to obtain the pure product **198** as a white solid, 91% Yield. mp 161-163 °C.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.43-7.39 (m, 2H), 7.17-7.13 (m, 4H), 5.30 (d, *J* = 2.7 Hz, 1H), 4.20-4.10 (m, *J* = 6.7 Hz, 2H), 3.83 (d, *J* = 13.4 Hz, 1H), 3.59 (d, *J* = 13.3 Hz, 1H), 3.06-2.97 (m, 1H), 2.89 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.22-2.14 (m, 2H), 2.03-1.97 (m, 1H),

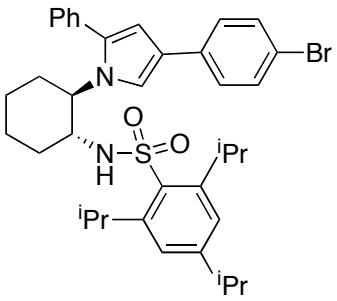
1.71-1.66 (m, 1H), 1.63-1.56 (m, 1H), 1.26-1.21 (m, 18H), 1.14-0.99 (m, 4H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 152.60, 150.06, 139.24, 133.69, 131.67, 131.55, 129.95, 128.63, 123.82, 120.86, 64.63, 59.42, 57.22, 49.46, 34.11, 32.59, 31.38, 31.20, 29.79, 25.01, 24.76, 24.43, 23.63; IR: 3296, 3197, 2953, 2861, 2163, 1601, 1460, 1398, 1360, 1316, 1276, 1165, 1068, 1010, 944, 873, 782, 701; MS (EI-MS, m/z): 281.2 (mono benzylated cyclohexadiamine-H+), 548.3 (M+); HRMS (m/z): MH+ calcd. for $C_{28}H_{42}BrN_2O_2S$: 549.2150, found: 549.2154; $[\alpha]_D^{25}$ = - 41 (10 mg/1 mL $CHCl_3$).

_N_-((1_R_,2_R_)-2-(2,4-diphenyl-1_H_-pyrrol-1-yl)cyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (200a)



White solid. mp 173-175 °C; ^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.46-7.45 (m, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.37-7.35 (m, 1H), 7.33-7.30 (m, 4H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.06 (s, 3H), 6.45 (d, *J* = 1.8 Hz, 1H), 3.96-4.02 (m, 2H), 3.91-3.87 (m, 1H), 3.76-3.81 (m, 1H), 2.85-2.80 (m, 1H), 2.28-2.25 (m, 1H), 2.10-2.08 (m, 1H), 1.81-1.74 (m, 2H), 1.68-1.65 (m, 1H), 1.37-1.12 (m, 4H), 1.19 (dd, *J* = 15.6, 6.9 Hz, 6H), 1.13 (t, *J* = 7.2 Hz, 12H); ^{13}C-NMR (151 MHz; $CDCl_3$): δ 152.80, 149.96, 135.87, 135.35, 133.64, 132.81, 129.34, 128.69, 128.48, 127.47, 125.98, 125.58, 125.14, 123.70, 114.48, 107.74, 58.70, 57.24, 34.51, 33.98, 33.34, 29.72, 25.16, 24.89, 24.51, 24.21, 23.51, 23.44; IR: 2958, 2869, 2326, 1704, 1602, 1451, 1362, 1153, 1072, 1037, 882, 755, 661; MS (EI-MS, m/z): 220.3, 315.4, 582.6 (M+); HRMS (m/z): M+ calcd. for $C_{37}H_{46}N_2O_2S$: 582.3280, found: 582.3264; $[\alpha]_D^{25}$ = - 47 (10.4 mg/1 mL $CHCl_3$).

***N*-((1*R*,2*R*)-2-(4-(4-bromophenyl)-2-phenyl-1*H*-pyrrol-1-yl)cyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (200b)**



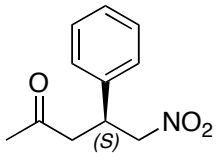
White solid. mp >200 °C ; ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.44-7.36 (m, 5H), 7.34-7.28 (m, 4H), 7.05 (d, *J* = 1.9 Hz, 3H), 6.39 (d, *J* = 1.9 Hz, 1H), 4.01-3.96 (m, 2H), 3.92-3.86 (m, 1H), 3.84-3.74 (m, 1H), 2.86-2.76 (m, 1H), 2.27-2.20 (m, 1H), 2.13-2.05 (m, 1H), 1.81-1.72 (m, 2H), 1.70-1.63 (m, 1H), 1.37-1.22 (m, 4H), 1.18 (t, *J* = 7.1 Hz, 6H), 1.12 (dd, *J* = 6.7, 3.7 Hz, 12H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 151.86, 148.89, 135.04, 133.37, 132.56, 131.57, 130.50, 128.33, 127.73, 126.62, 125.65, 123.65, 122.70, 118.01, 106.46, 56.16, 57.73 33.58, 32.98, 32.46, 28.72, 24.11, 23.89, 23.53, 23.23, 22.53, 22.40; IR: 3331, 3110, 2957, 1604, 1483, 1457, 1363, 1307, 1222, 1156, 1071, 1008, 808, 762; MS (EI-MS, m/z): 298.3, 393.4, 395.3, 582.6, 660.5(M+); HRMS (m/z): M+ calcd. for $C_{37}H_{45}BrN_2O_2S$: 660.2385, found: 660.2379; $[\alpha]_D^{25}$ = - 68 (10 mg/1 mL $CHCl_3$).

General Procedure: Catalytic asymmetric Michael additions

All the reactions were carried out without any precautions to exclude moisture. To a schlenk tube catalyst **194** (0.05 mmol), ketone **172** (0.375 mmol) and 1 mL of toluene were added under air atmosphere. The resulting solution was stirred for a minute in prior to the addition of nitroolefin (0.25 mmol) was added. After stirring for the indicated reaction time at indicated temperature, the crude product was purified by column chromatography (performed with hexanes/EtOAc 90:1).

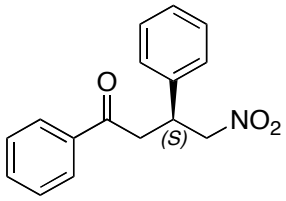
Characterization of the Michael adducts

(*S*)-5-nitro-4-phenylpentan-2-one (199a)



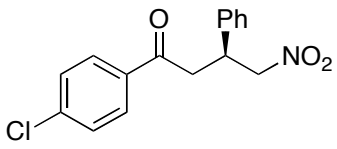
^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.36-7.20 (m, 5H), 4.73-4.56 (m, 2H), 4.10-3.96 (m, *J* = 7.2 Hz, 1H), 2.92 (d, *J* = 7.0 Hz, 2H), 2.12 (s, 3H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 205.41, 138.84, 129.11, 127.95, 127.42, 79.49, 46.17, 39.08, 30.45; MS (EI-MS, m/z): 145.1, 160.1, 207.2 (M+); HPLC analysis (Chiralcel AS, 35/65 *i*PrOH/n-heptane, 0.5 mL/min, 210 nm; t_r (major) = 35.57 min, t_r (minor) = 48.84 min); >87 % *ee*; $[\alpha]_D^{25}$ = +5 (10 mg/1 mL $CHCl_3$).

(*S*)-4-nitro-1,3-diphenylbutan-1-one (199b)



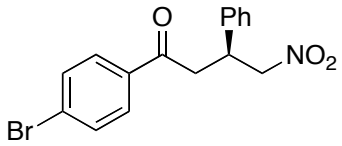
^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.98-7.95 (m, 2H), 7.65-7.59 (m, 1H), 7.52-7.47 (m, 2H), 7.41-7.29 (m, 5H), 4.88 (dd, *J* = 12.5, 6.6 Hz, 1H), 4.73 (dd, *J* = 12.4, 8.0 Hz, 1H), 4.32-4.23 (m, *J* = 7.2 Hz, 1H), 3.58-3.42 (m, 2H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 196.86, 139.13, 136.35, 133.60, 129.09, 128.77, 128.03, 127.90, 127.48, 79.58, 41.54, 39.29; MS (EI-MS, m/z): 222.8, 251.8, 269.8 (M+), 286.9 (MNH_4+); HPLC analysis (Chiralcel AS, 20/80 *i*PrOH/n-heptane, 0.5 mL/min, 210 nm; t_r (major) = 35.30 min, t_r (minor) = 47.46 min); 96 % *ee*; $[\alpha]_D^{25}$ = - 20.9 (10 mg/1 mL $CHCl_3$).

(*S*)-1-(4-chlorophenyl)-4-nitro-3-phenylbutan-1-one (199c)



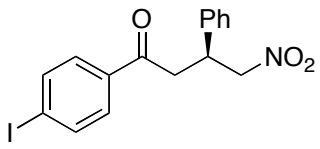
^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.87-7.83 (m, 2H), 7.45-7.40 (m, 2H), 7.37-7.24 (m, 5H), 4.82 (dd, *J* = 12.5, 6.8 Hz, 1H), 4.69 (dd, *J* = 12.5, 7.7 Hz, 1H), 4.26-4.16 (m, 1H), 3.50-3.35 (m, 2H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 195.70, 140.12, 138.94, 134.69, 129.48, 129.17, 129.12, 128.01, 127.47, 79.54, 41.52, 39.29; MS (EI-MS, m/z): 242.1, 255.1, 303.1 (M-); HPLC analysis (Chiralcel AS, 20/80 *i*PrOH/n-heptane, 0.5 mL/min, 210 nm; t_r (major) = 41.18 min, t_r (minor) = 55.11 min); >94 % *ee*; $[\alpha]_D^{25}$ = - 27.5 (20 mg/2 mL $CHCl_3$).

(*S*)-1-(4-bromophenyl)-4-nitro-3-phenylbutan-1-one (199d)



^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.79-7.75 (m, 2H), 7.61-7.57 (m, 2H), 7.37-7.25 (m, 5H), 4.81 (dd, *J* = 12.5, 6.8 Hz, 1H), 4.68 (dd, *J* = 12.5, 7.7 Hz, 1H), 4.26-4.16 (m, 1H), 3.49-3.34 (m, 2H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 195.90, 138.92, 135.08, 132.11, 129.57, 129.17, 128.88, 128.02, 127.47, 79.53, 41.50, 39.27; MS (EI-MS, m/z): 300.1, 365.1 (MNH_4+); HPLC analysis (Chiralcel AS, 20/80 *i*PrOH/n-heptane, 0.5 mL/min, 210 nm; t_r (major) = 46.10 min, t_r (minor) = 61.20 min); >94 % *ee*; $[\alpha]_D^{25}$ = - 29.5 (20 mg/2 mL $CHCl_3$).

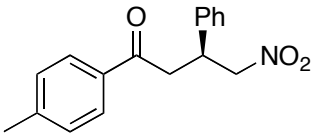
(*S*)-1-(4-iodophenyl)-4-nitro-3-phenylbutan-1-one (199e)



^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.83-7.80 (m, 2H), 7.63-7.59 (m, 2H), 7.36-7.24 (m, 5H),

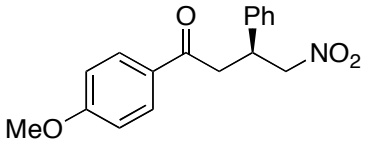
4.81 (dd, *J* = 12.5, 6.8 Hz, 1H), 4.71-4.64 (m, 1H), 4.25-4.16 (m, 1H), 3.41 (dd, *J* = 38.0, 6.9 Hz, 2H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 196.23, 138.93, 138.10, 135.61, 129.41, 129.17, 128.01, 127.47, 101.75, 79.53, 41.44, 39.26; MS (EI-MS, m/z): 348.1, 379.0, 396.0 (MH+), 413.0 (MNH_4+); HPLC analysis (Chiralcel AS, 20/80 *i*PrOH/n-heptane, 0.5 mL/min, 210 nm; t_r (major) = 56.39 min, t_r (minor) = 80.46 min); >98 % *ee*; $[\alpha]_D^{25}$ = - 25.2 (20.2 mg/2 mL $CHCl_3$).

(*S*)-4-nitro-3-phenyl-1-*p*-tolylbutan-1-one (199f)



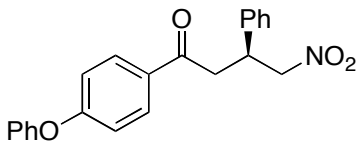
^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.79-7.76 (m, 2H), 7.29-7.19 (m, 7H), 4.79 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.64 (dd, *J* = 12.5, 8.1 Hz, 1H), 4.22-4.12 (m, 1H), 3.45-3.30 (m, 2H), 2.36 (s, 3H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 195.45, 143.49, 138.21, 132.91, 128.41, 128.04, 127.14, 126.83, 126.45, 78.59, 40.40, 38.34, 20.68, 0.03; MS (EI-MS, m/z): 234.1, 236.2, 267.2, 284.1 (MH+), 301.2 (MNH_4+); HPLC analysis (Chiralcel AS, 20/80 *i*PrOH/n-heptane, 0.5 mL/min, 210 nm; t_r (major) = 33.85 min, t_r (minor) = 43.09 min); >96 % *ee*; $[\alpha]_D^{25}$ = - 23.8 (20 mg/2 mL $CHCl_3$).

(*S*)-1-(4-methoxyphenyl)-4-nitro-3-phenylbutan-1-one (199g)



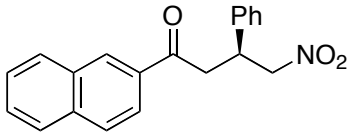
^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.93-7.88 (m, 2H), 7.36-7.24 (m, 5H), 6.95-6.90 (m, 2H), 4.84 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.68 (dd, *J* = 12.5, 8.1 Hz, 1H), 4.26-4.16 (m, 1H), 3.86 (s, 3H), 3.47-3.31 (m, 2H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 195.36, 163.87, 139.32, 130.40, 129.48, 129.08, 127.86, 127.50, 113.92, 79.67, 55.58, 41.21, 39.46; MS (EI-MS, m/z): 250.1, 283.2, 300.2(MH+), 317.2 (MNH_4+); HPLC analysis (Chiralcel AS, 20/80 *i*PrOH/n-heptane, 0.5 mL/min, 210 nm; t_r (major) = 77.64 min, t_r (minor) = 99.28 min); >98 % *ee*; $[\alpha]_D^{25}$ = - 29.6 (20 mg/2 mL $CHCl_3$).

(*S*)-4-nitro-1-(4-phenoxyphenyl)-3-phenylbutan-1-one (199h)



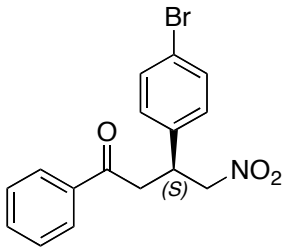
^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.88-7.83 (m, 2H), 7.38-7.14 (m, 8H), 7.04-6.99 (m, 2H), 6.96-6.91 (m, 2H), 4.79 (dd, *J* = 12.5, 6.6 Hz, 1H), 4.64 (dd, *J* = 12.4, 8.0 Hz, 1H), 4.22-4.12 (m, 1H), 3.44-3.28 (m, 2H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 195.38, 162.45, 155.27, 139.19, 130.98, 130.39, 130.15, 129.12, 127.91, 127.49, 124.84, 120.31, 117.35, 79.62, 41.32, 39.41; MS (EI-MS, m/z): 312.2, 345.2, 362.2 (MH+), 379.3 (MNH_4+); HPLC analysis (Chiralcel AS, 20/80 *i*PrOH/n-heptane, 0.5 mL/min, 210 nm; t_r (major) = 52.68 min, t_r (minor) = 73.67 min); >97 % *ee*; $[\alpha]_D^{25}$ = - 23.3 (22 mg/2 mL $CHCl_3$).

(*S*)-1-(naphthalen-2-yl)-4-nitro-3-phenylbutan-1-one (199i)



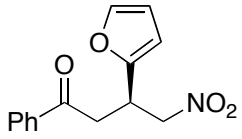
^{1}H-NMR (300 MHz; $CDCl_3$): δ 8.43 (bs, 1H), 8.00-7.86 (m, 4H), 7.64-7.53 (m, 2H), 7.38-7.25 (m, 5H), 4.89 (dd, *J* = 12.5, 6.6 Hz, 1H), 4.73 (dd, *J* = 12.5, 8.0 Hz, 1H), 4.35-4.25 (m, 1H), 3.67-3.51 (m, 2H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 196.83, 139.24, 135.78, 133.73, 132.45, 129.92, 129.64, 129.15, 128.83, 128.71, 127.95, 127.87, 127.56, 127.04, 123.61, 79.67, 41.64, 39.47; MS (EI-MS, m/z): 270.2, 303.2, 320.1 (MH+), 337.2 (MNH_4+); HPLC analysis (Chiralcel AS, 20/80 *i*PrOH/n-heptane, 0.5 mL/min, 210 nm; t_r (major) = 45.33 min, t_r (minor) = 54.95 min); >98 % *ee*; $[\alpha]_D^{25}$ = - 55.9 (20.4 mg/2 mL $CHCl_3$).

(*S*)-3-(4-bromophenyl)-4-nitro-1-phenylbutan-1-one (199j)



^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.93-7.89 (m, 2H), 7.61-7.56 (m, 1H), 7.49-7.43 (m, 4H), 7.19-7.15 (m, 2H), 4.81 (dd, *J* = 12.6, 6.5 Hz, 1H), 4.66 (dd, *J* = 12.6, 8.2 Hz, 1H), 4.25-4.15 (m, 1H), 3.50-3.35 (m, 2H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 196.51, 138.17, 136.22, 133.78, 132.23, 129.28, 128.85, 128.04, 121.86, 79.31, 41.33, 38.78; MS (EI-MS, m/z): 300.1, 331.1, 365.1 (MNH_4+); HPLC analysis (Chiralcel AS, 20/80 *i*PrOH/n-heptane, 0.5 mL/min, 210 nm; t_r (major) = 41.24 min, t_r (minor) = 56.41 min); >94 % *ee*; $[\alpha]_D^{25}$ = - 23.4 (17.8 mg/2 mL $CHCl_3$).

(*R*)-3-(furan-2-yl)-4-nitro-1-phenylbutan-1-one (199k)

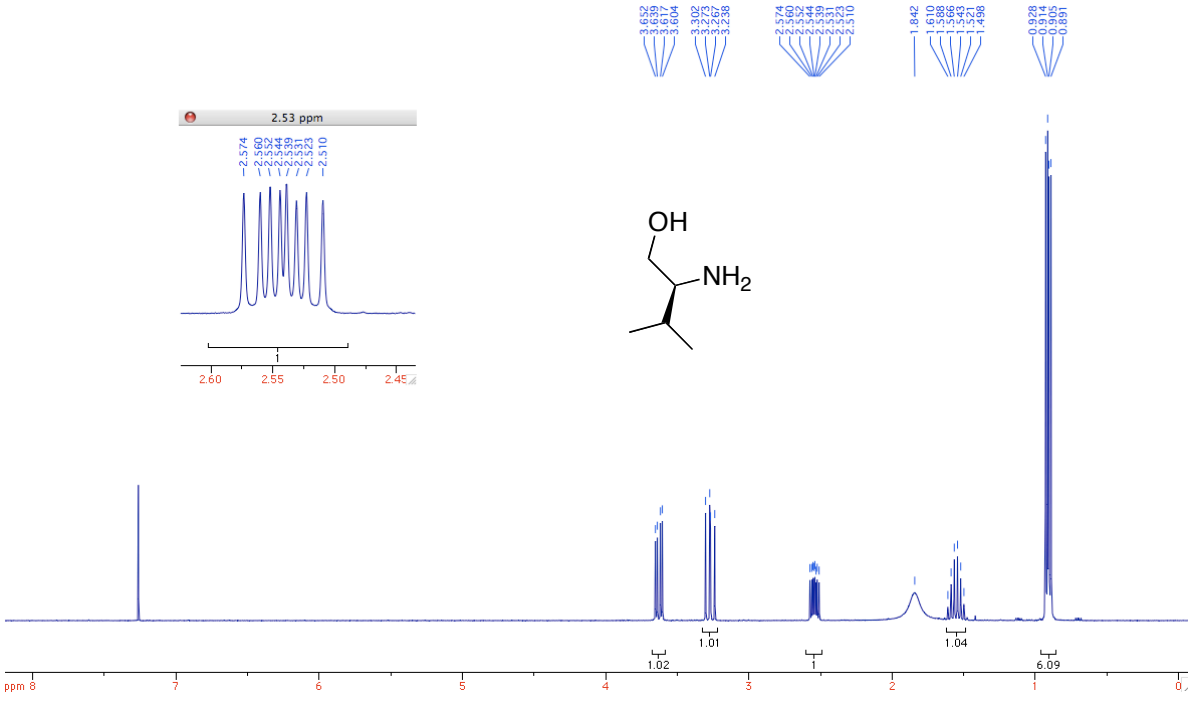


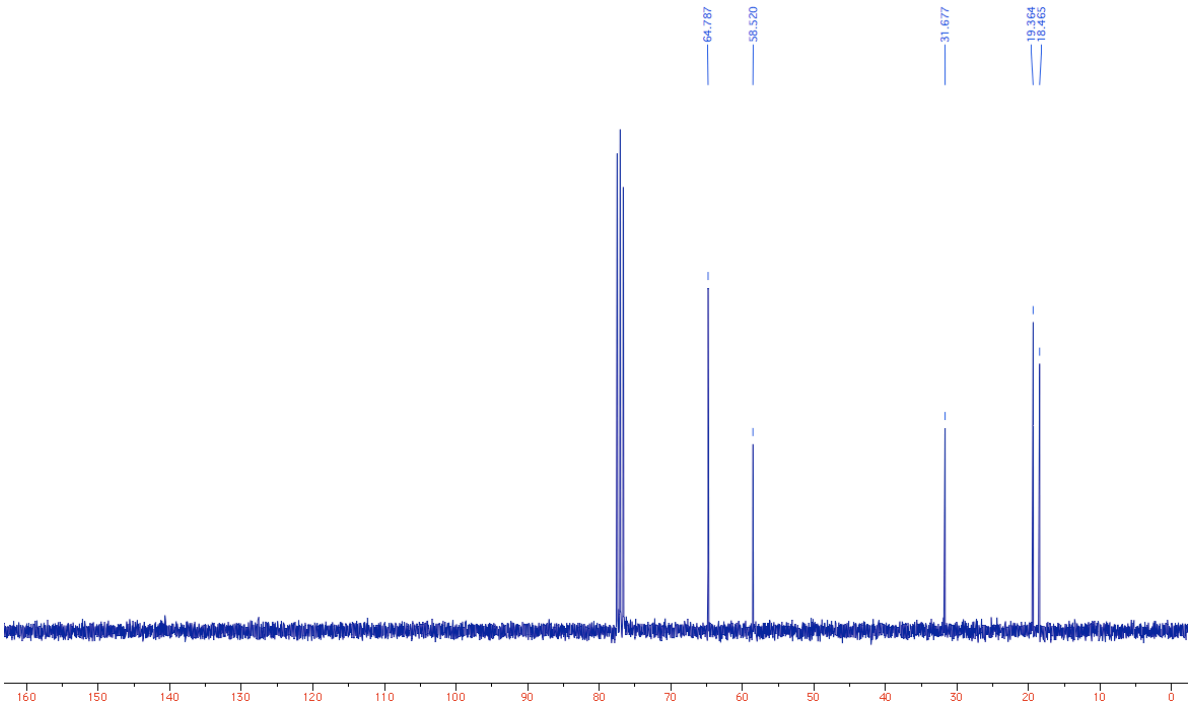
^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.93-7.89 (m, 2H), 7.58-7.52 (m, 1H), 7.46-7.40 (m, 2H), 7.30 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.25 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.15 (dt, *J* = 3.3, 0.7 Hz, 1H), 4.80-4.67 (m, 2H), 4.34-4.25 (m, 1H), 3.53-3.34 (m, 2H); ^{13}C-NMR (75.5 MHz; $CDCl_3$): δ 195.52, 150.90, 141.29, 135.21, 132.67, 127.77, 127.05, 109.51, 106.18, 37.97, 32.17, 0.03; MS (EI-MS, m/z): 212.2, 228.2, 277.2 (MNH_4+); HPLC analysis (Chiralcel AS, 20/80 *i*PrOH/n-heptane, 0.5 mL/min, 210 nm; t_r (major) = 39.37 min, t_r (minor) = 47.67 min); >97 % *ee*; $[\alpha]_D^{25}$ = - 8.6 (20 mg/2 mL $CHCl_3$).

13 Appendix

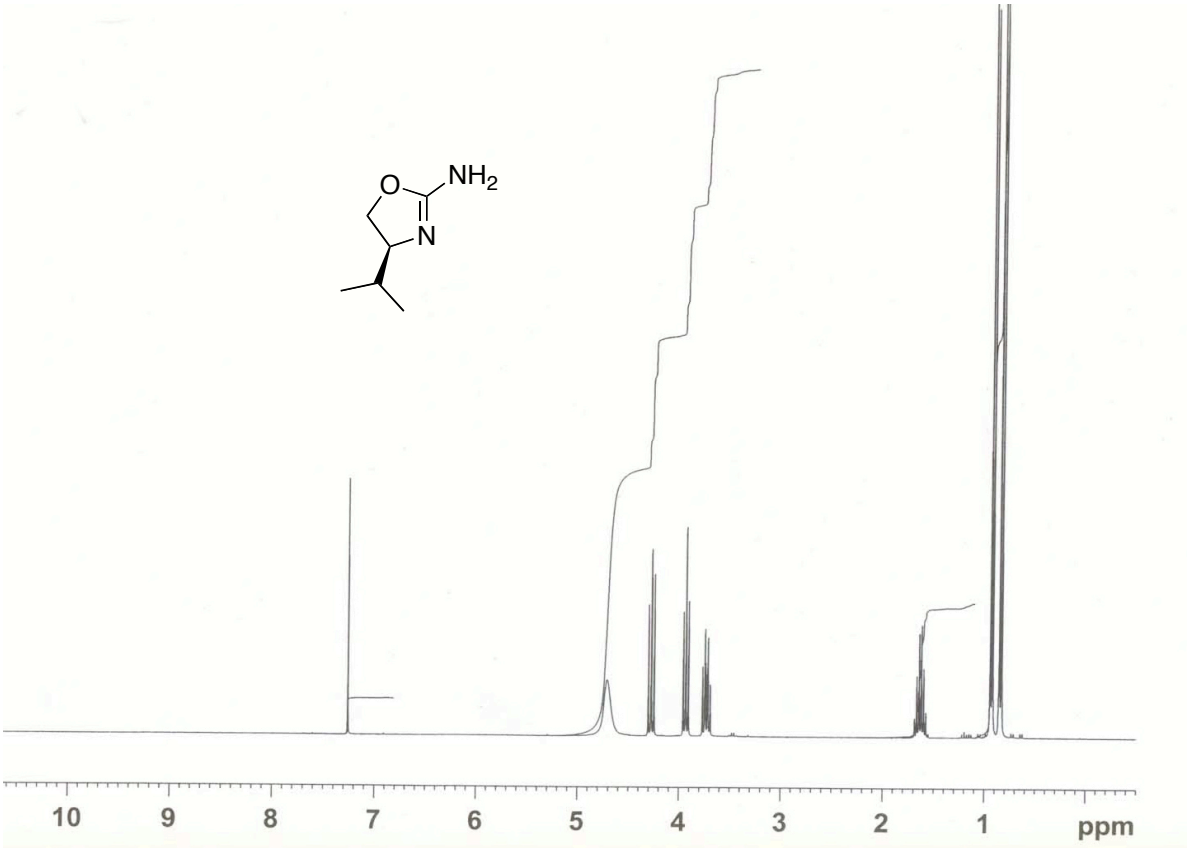
13.1 ^{1}H and ^{13}C NMR spectra

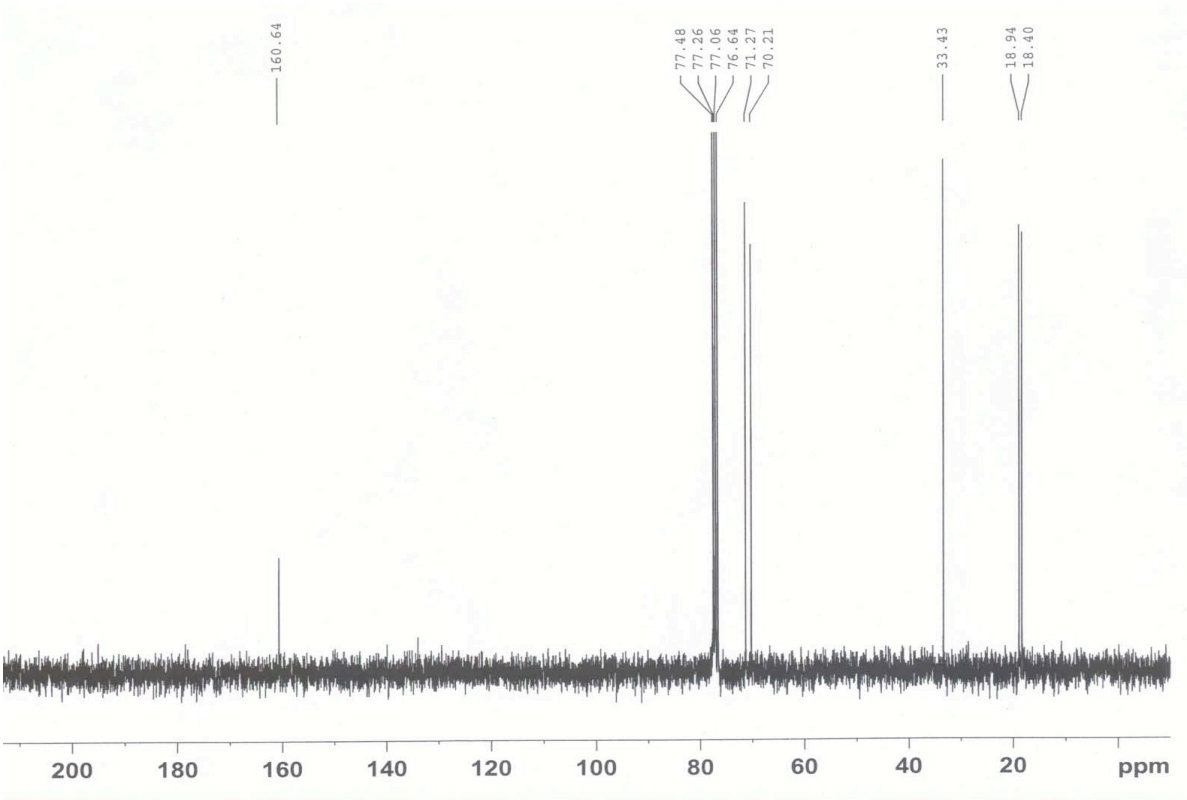
(*S*)-2-amino-3-methylbutan-1-ol (64a)



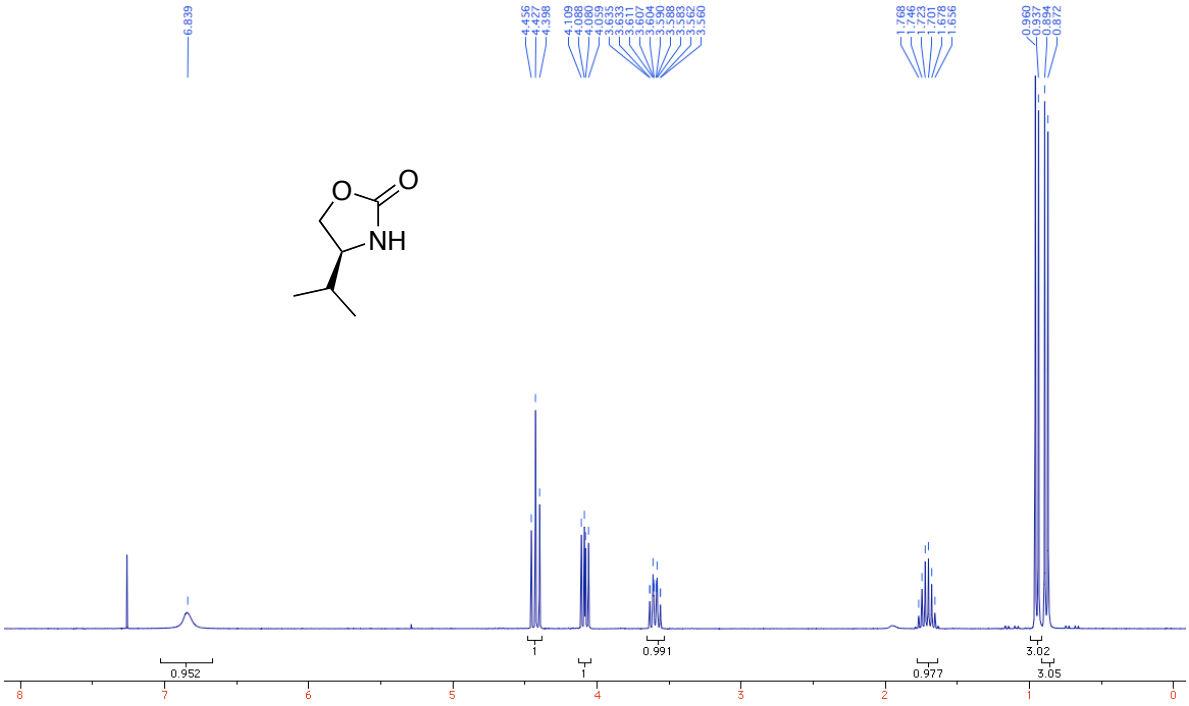


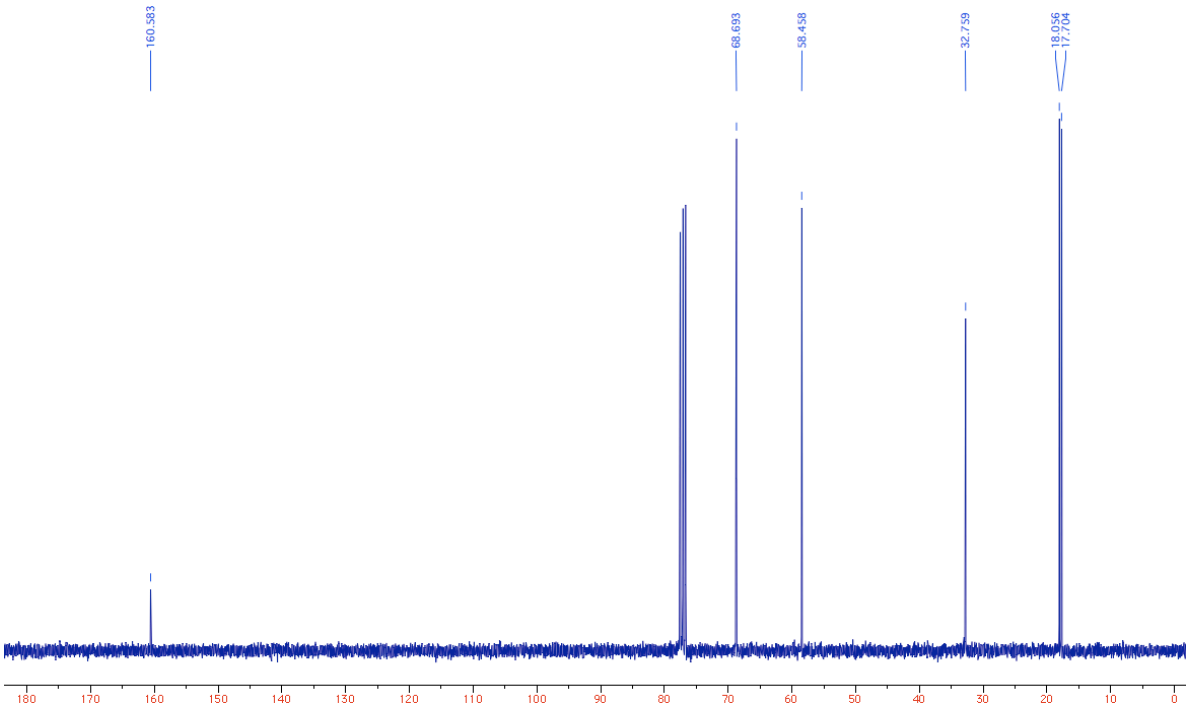
(*S*)-4-isopropyl-4,5-dihydrooxazol-2-amine (65a)



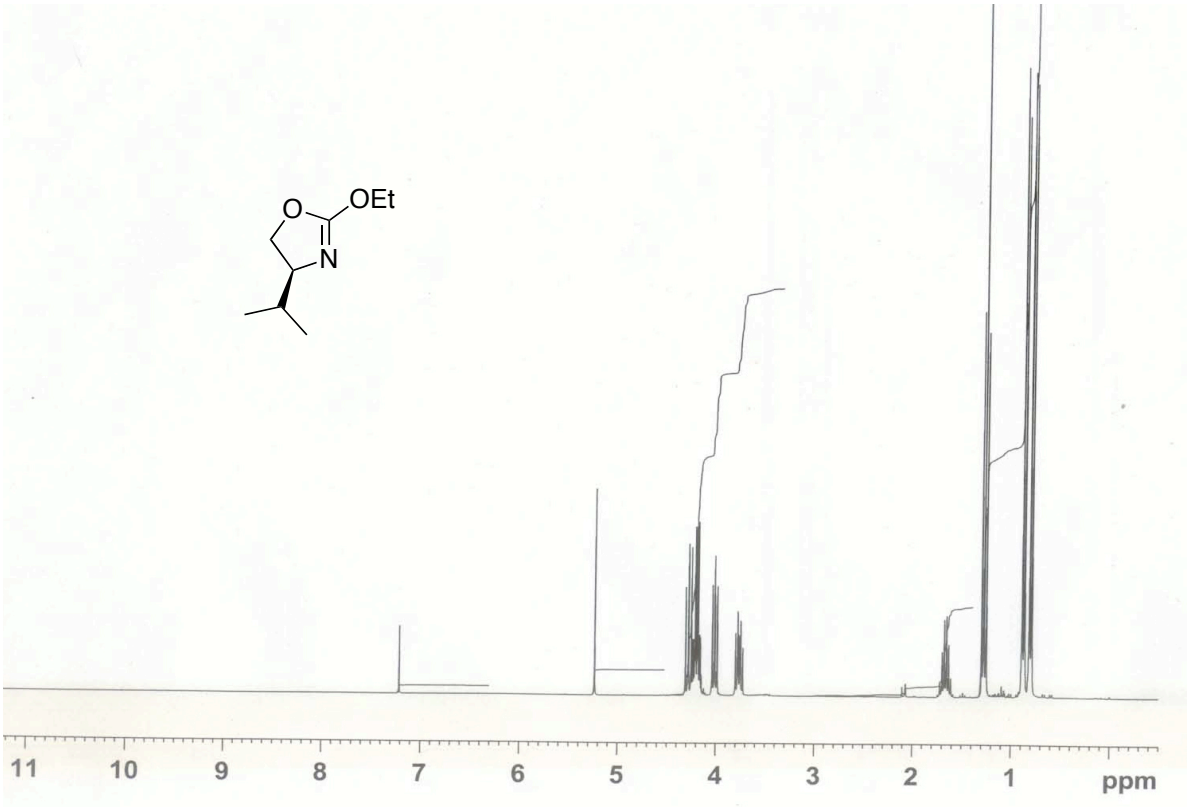


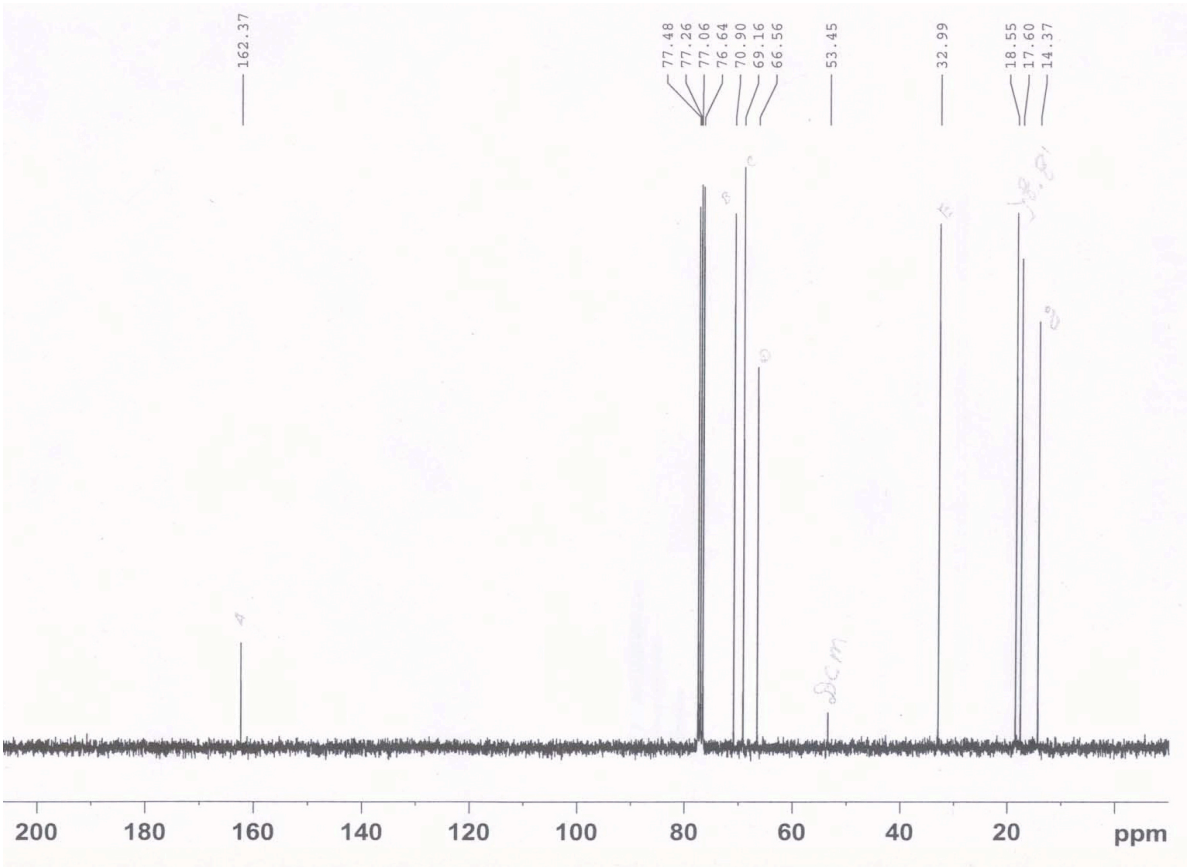
(*S*)-4-isopropyloxazolidin-2-one (68a)



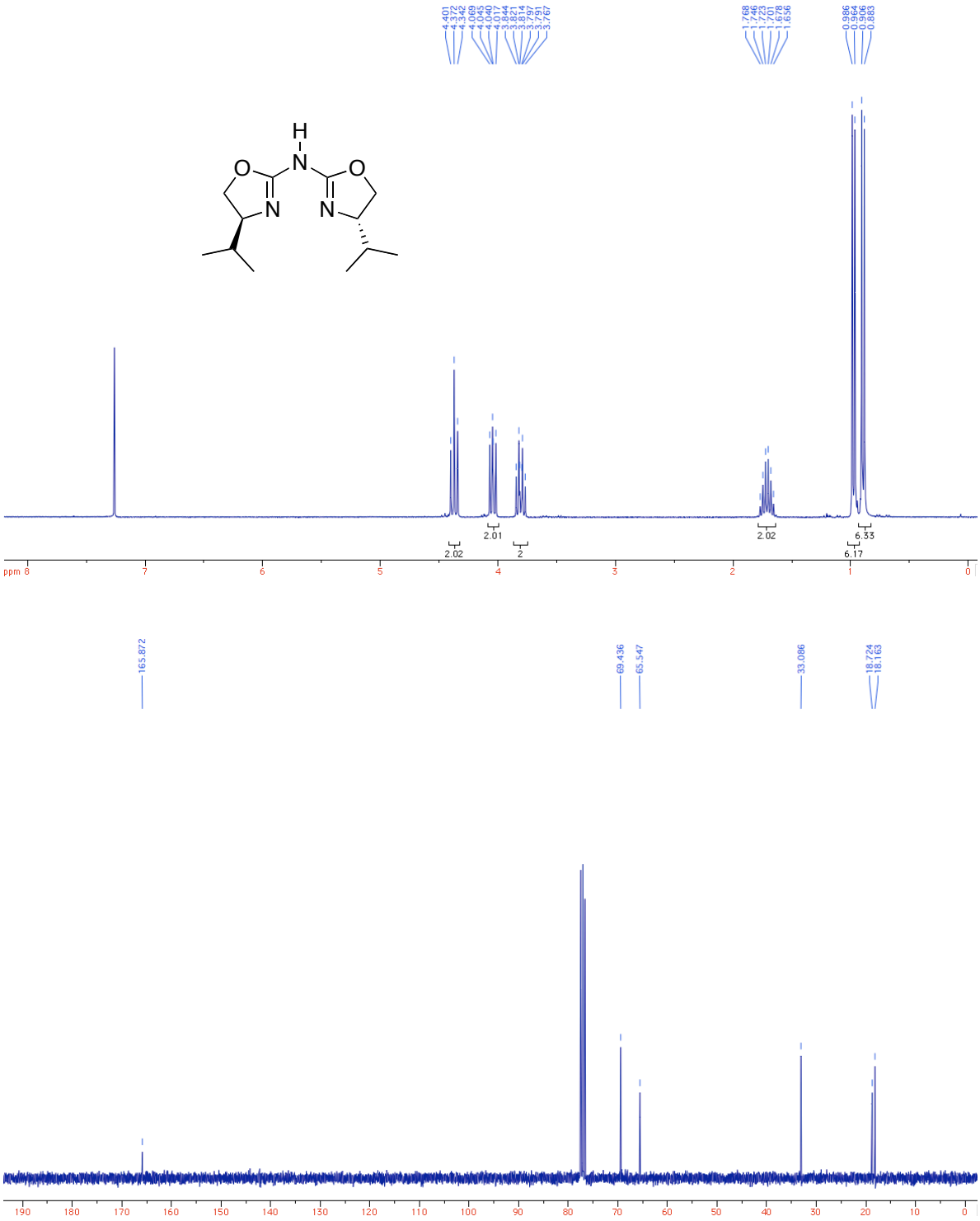


(*S*)-2-ethoxy-4-isopropyl-4,5-dihydrooxazole (69a)

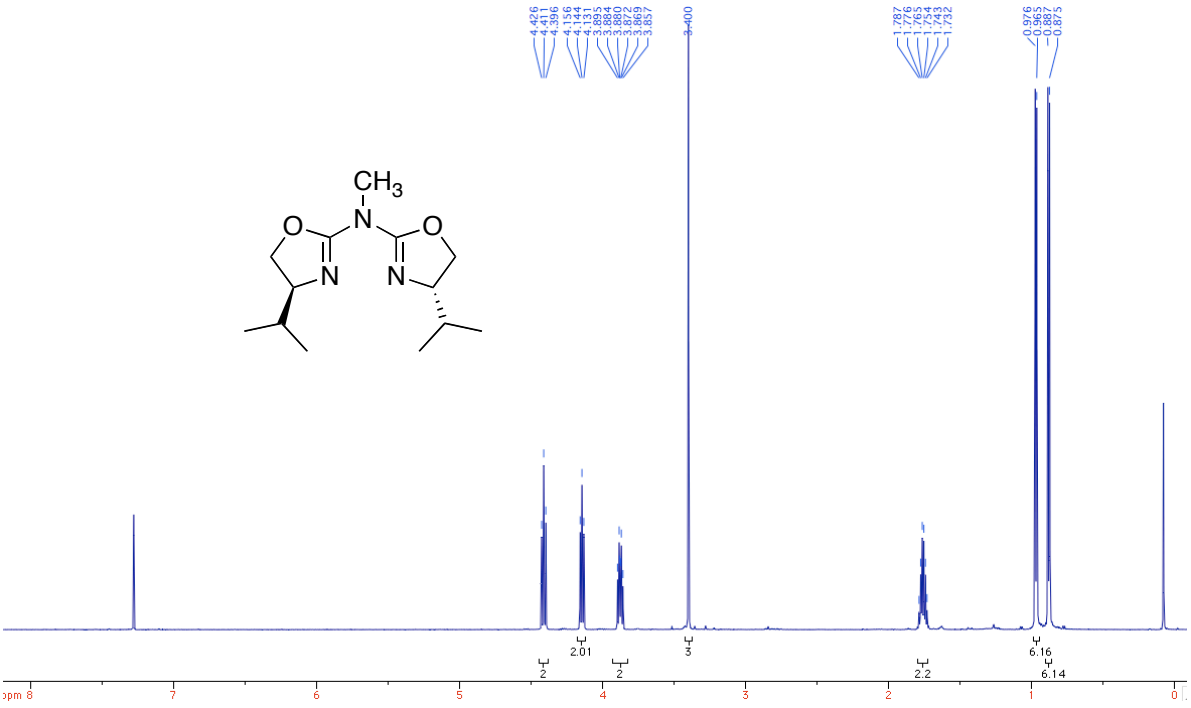


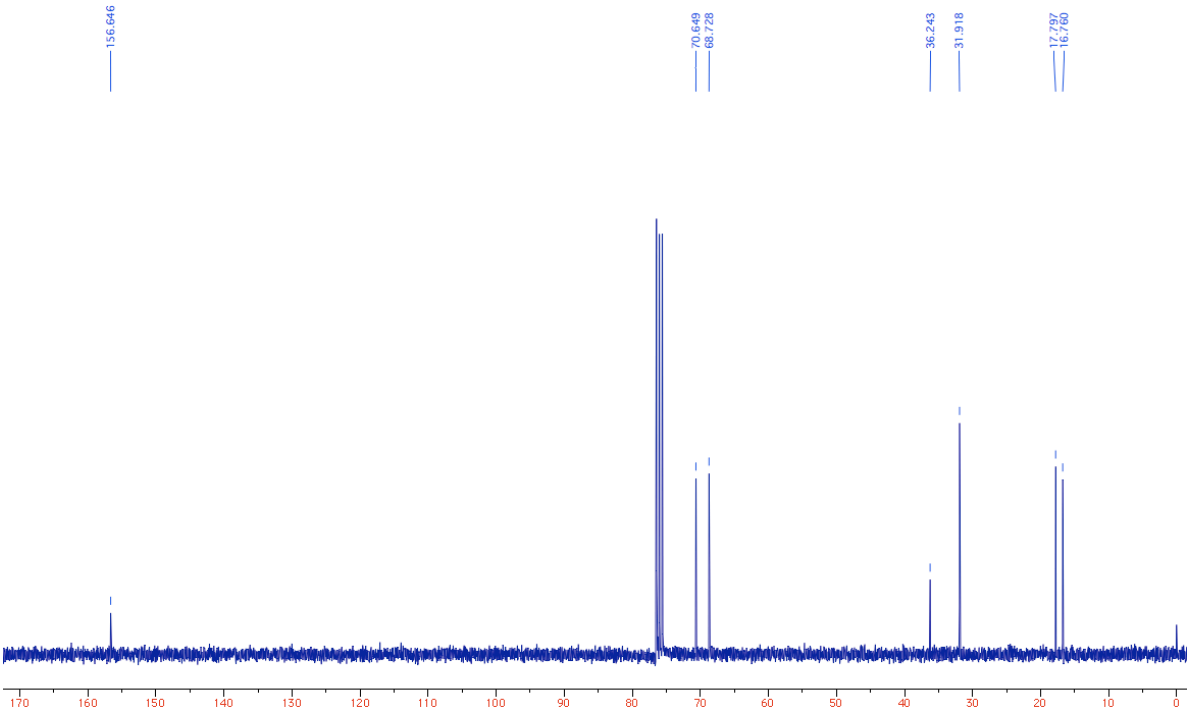


(*S*,*S*)-Bis-(4-isopropyl-4,5-dihydro-oxazol-2-yl)-amine (45a)

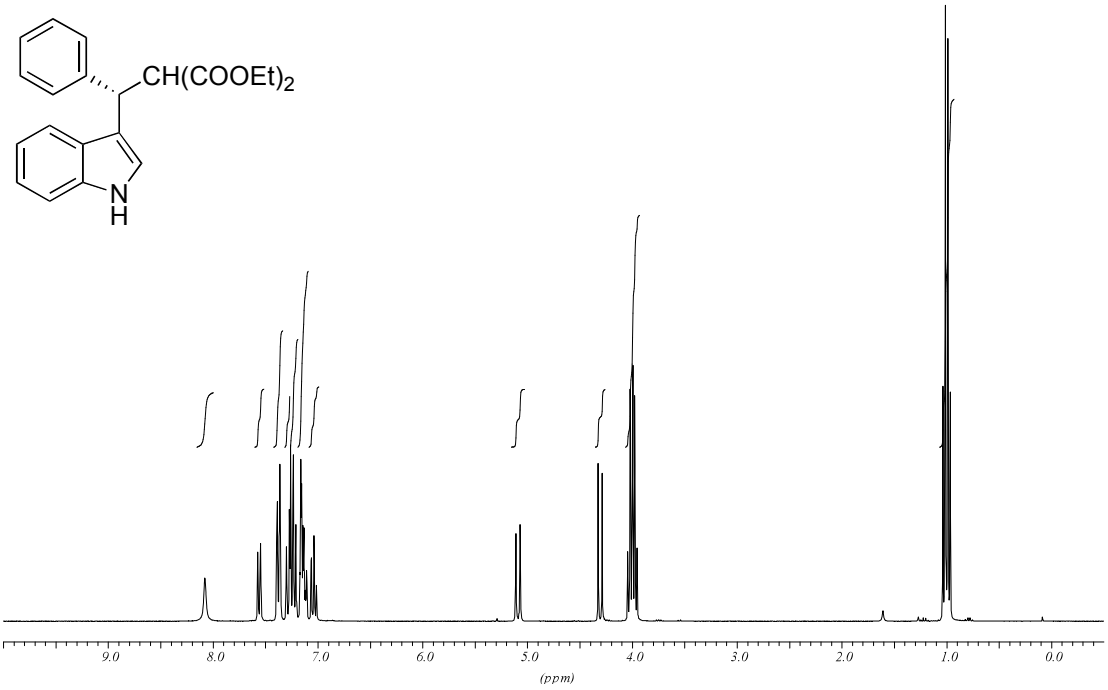


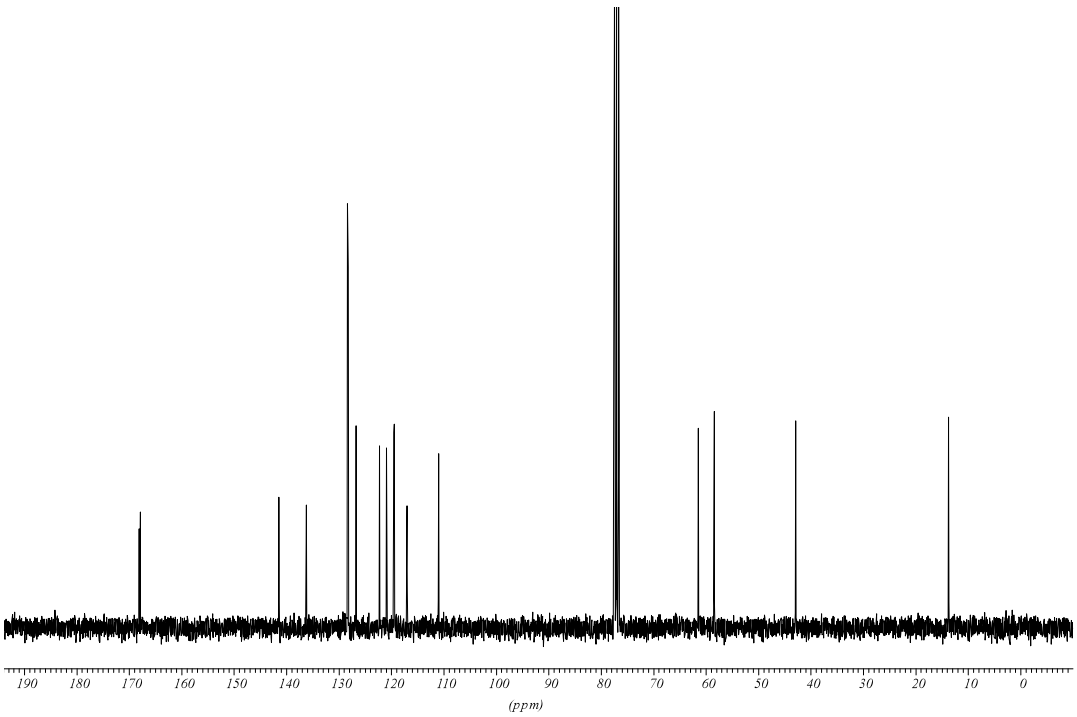
(*S*,*S*)-Bis-(4-isopropyl-4,5-dihydro-oxazol-2-yl)-methyl-amine (46a)



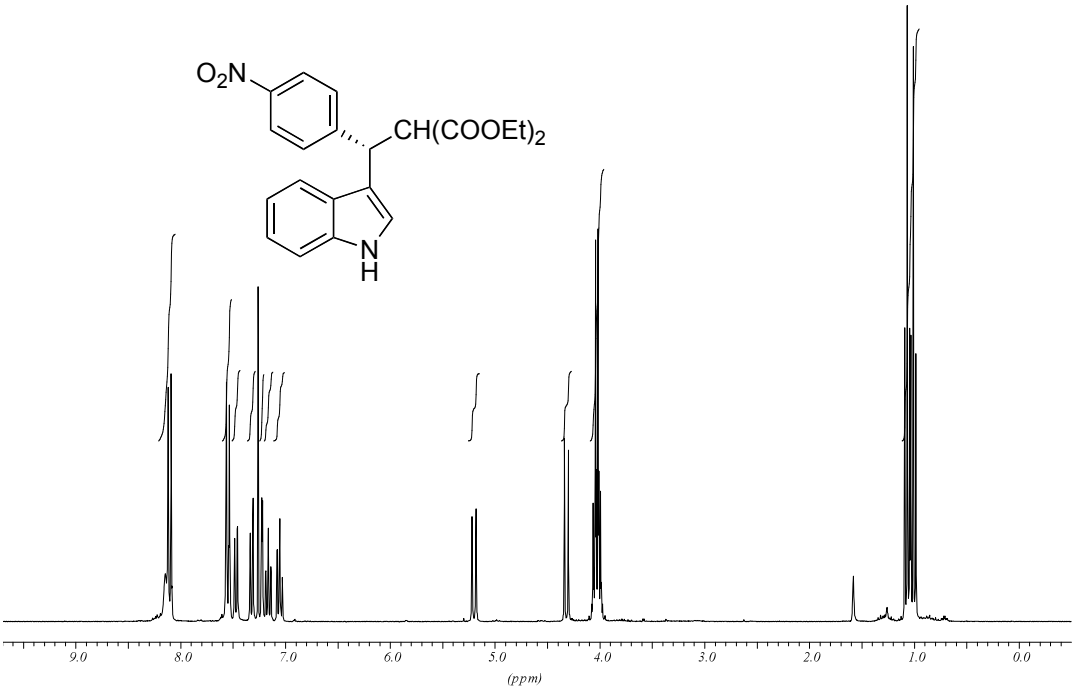


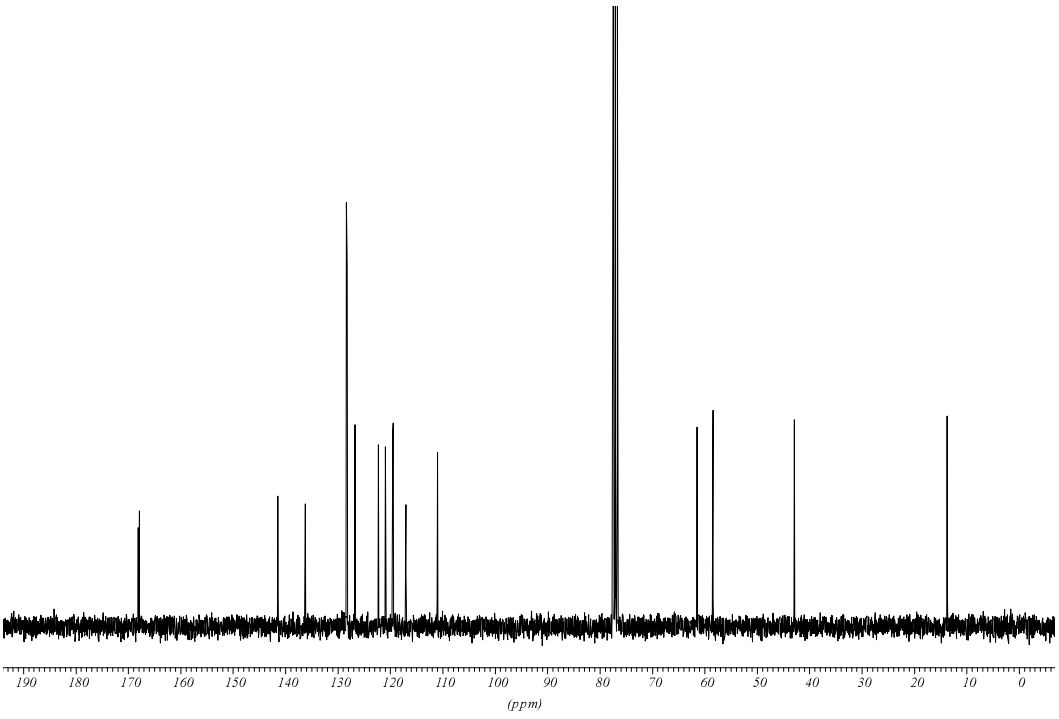
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–phenyl propanoate (80a)



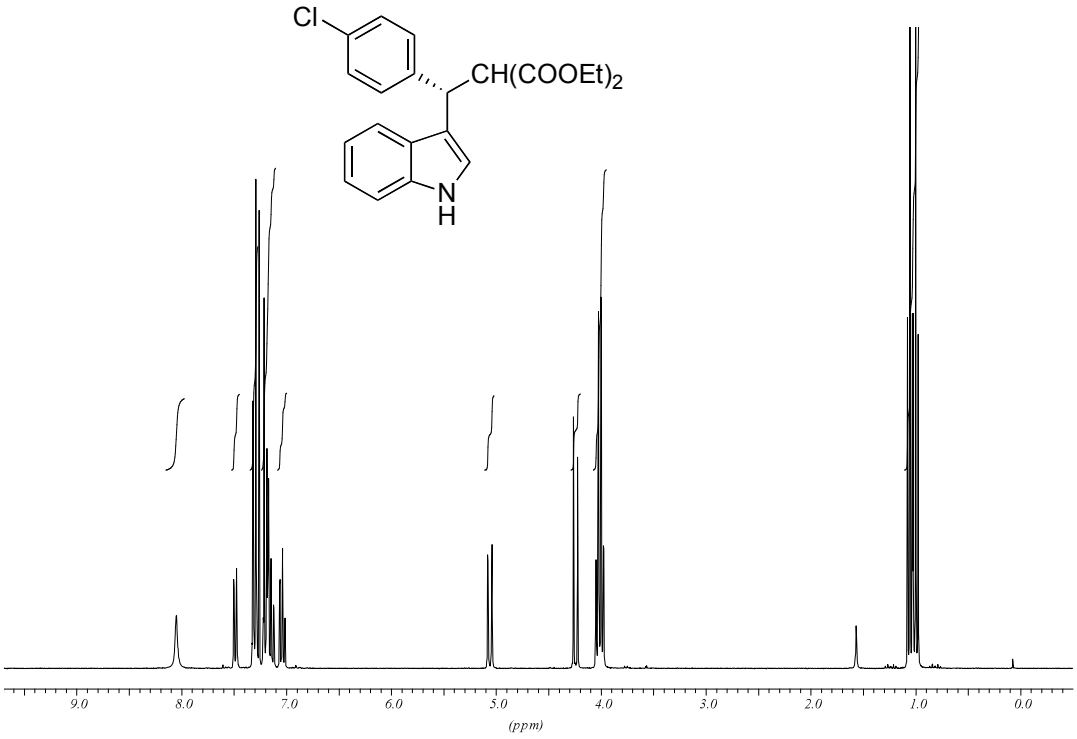


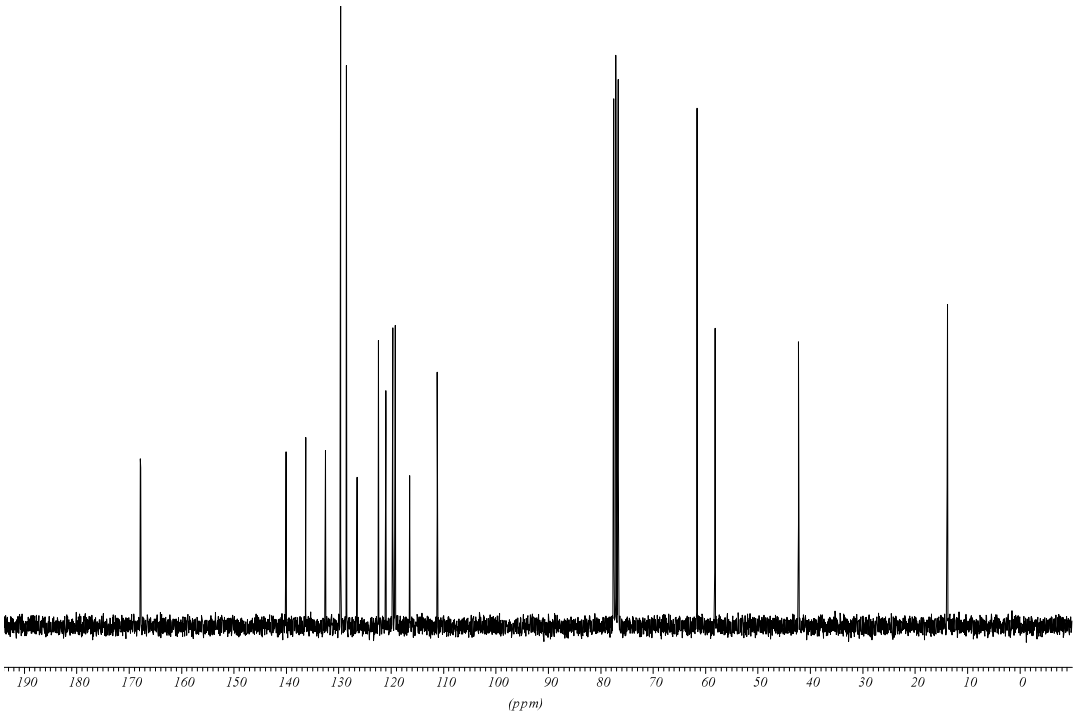
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(*p*-nitrophenyl) propanoate (80e)



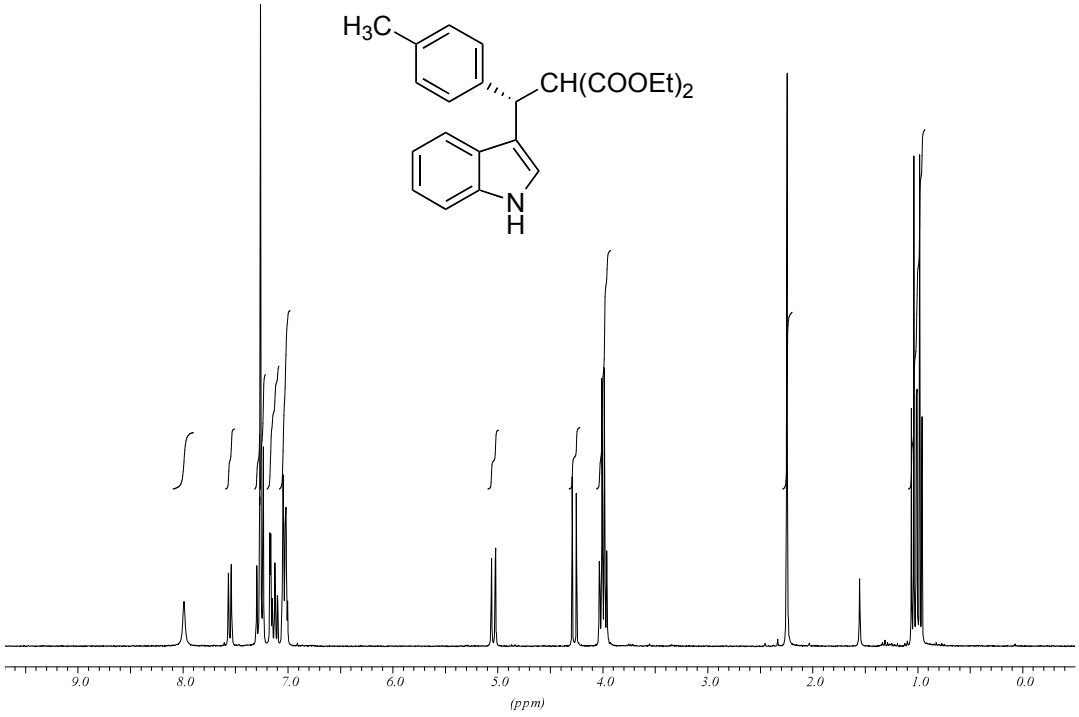


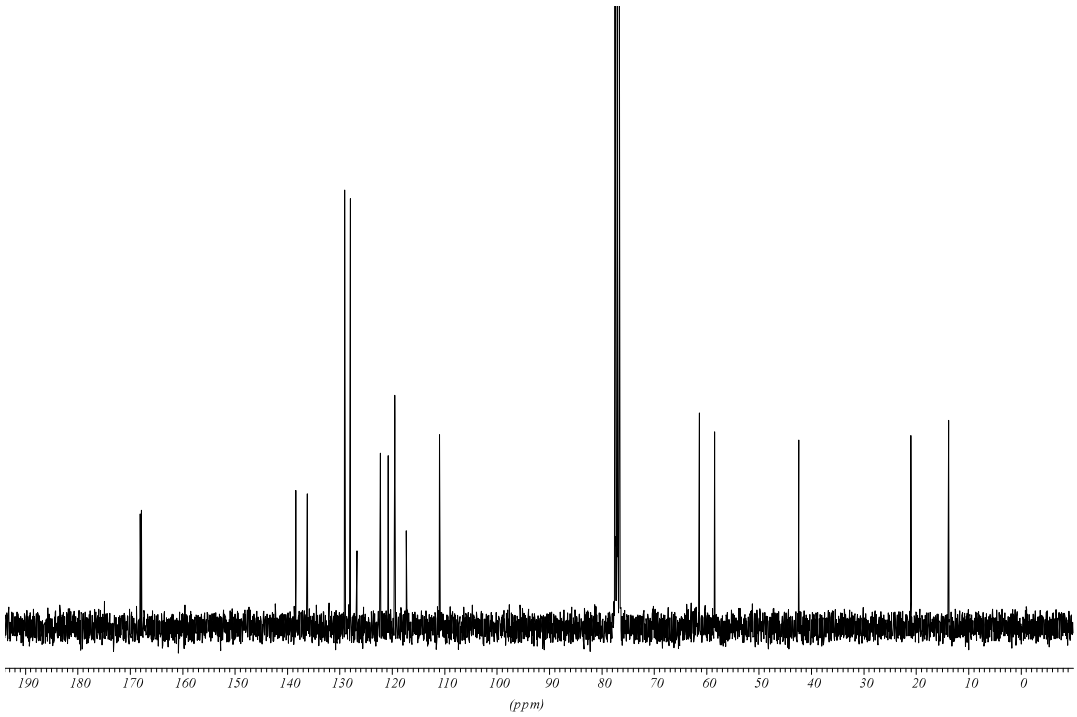
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(*p*-chlorophenyl) propanoate (80c)



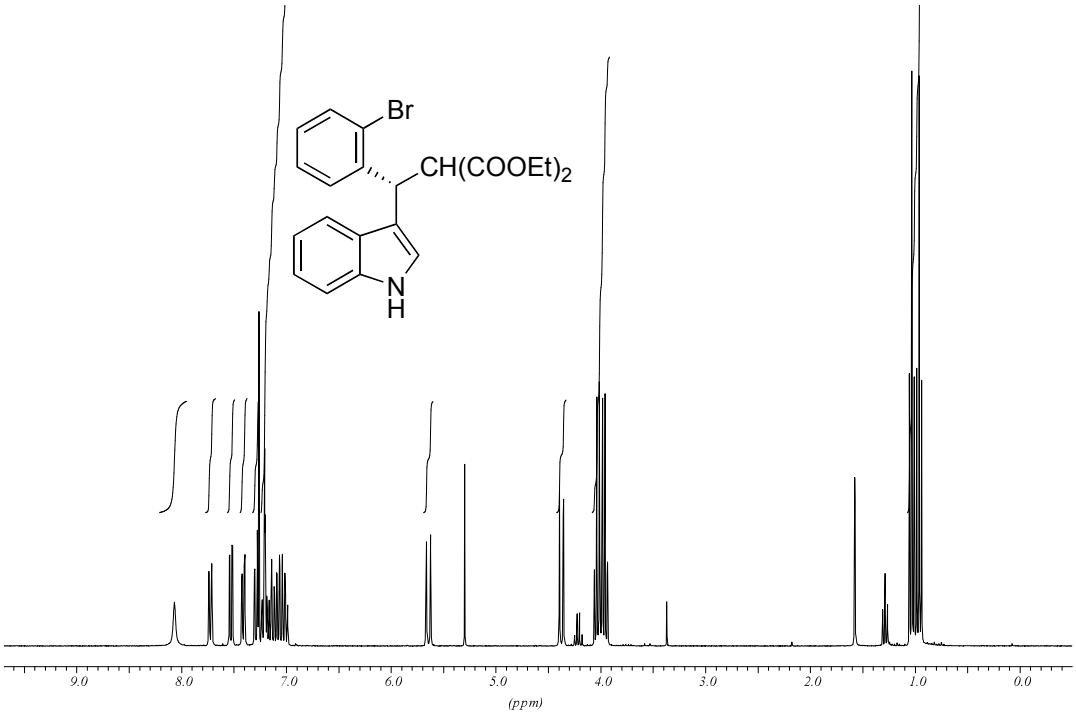


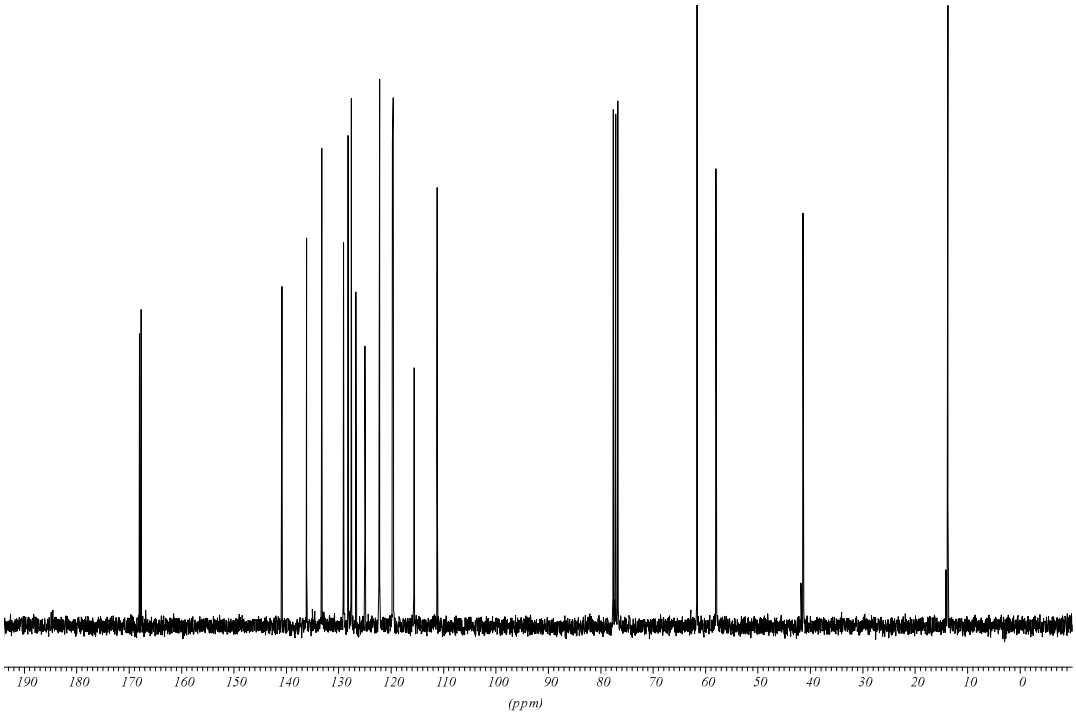
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(*p*-methylphenyl) propanoate (80b)



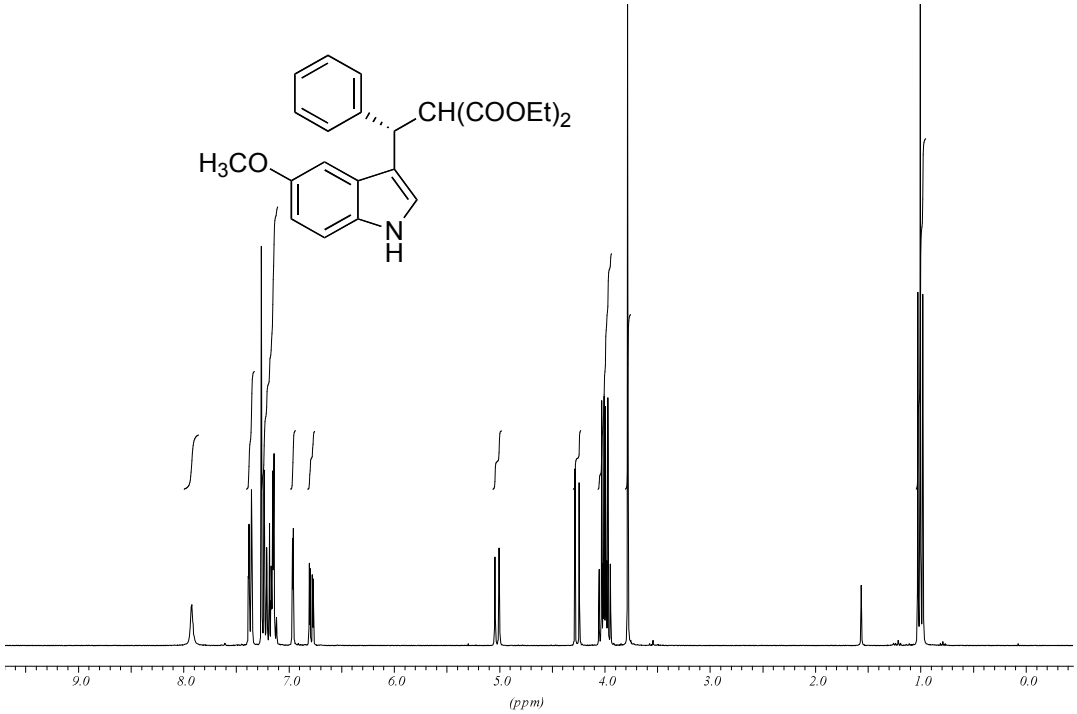


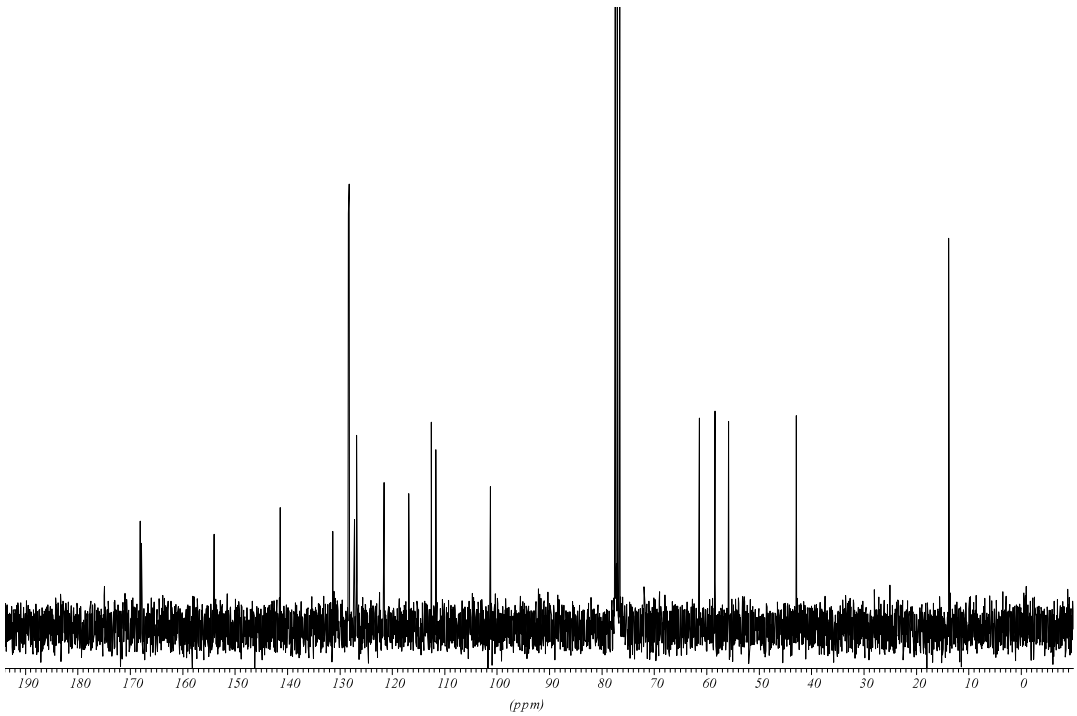
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(*o*-bromophenyl) propanoate (80d)



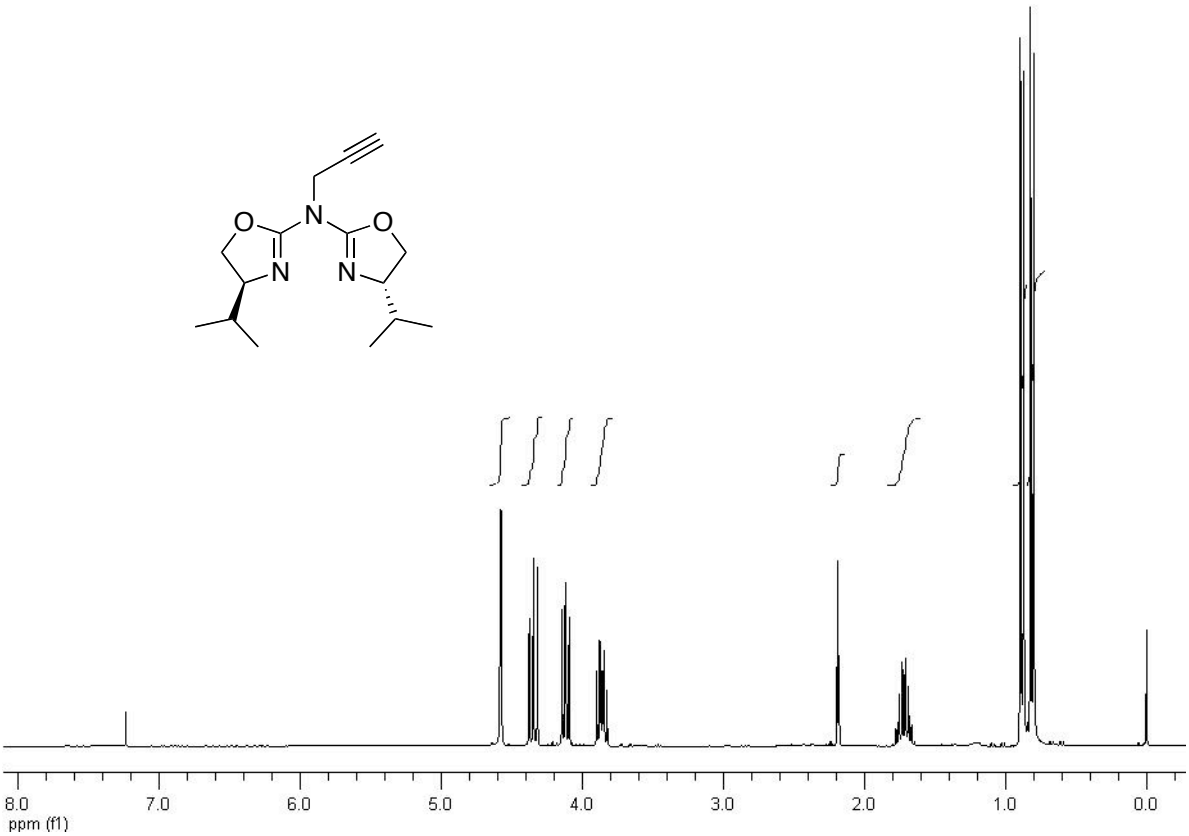


(S)–Ethyl 2–ethoxycarbonyl–3–[3–(propanoate 5-methoxyindolyl)]–3–phenyl (80f)

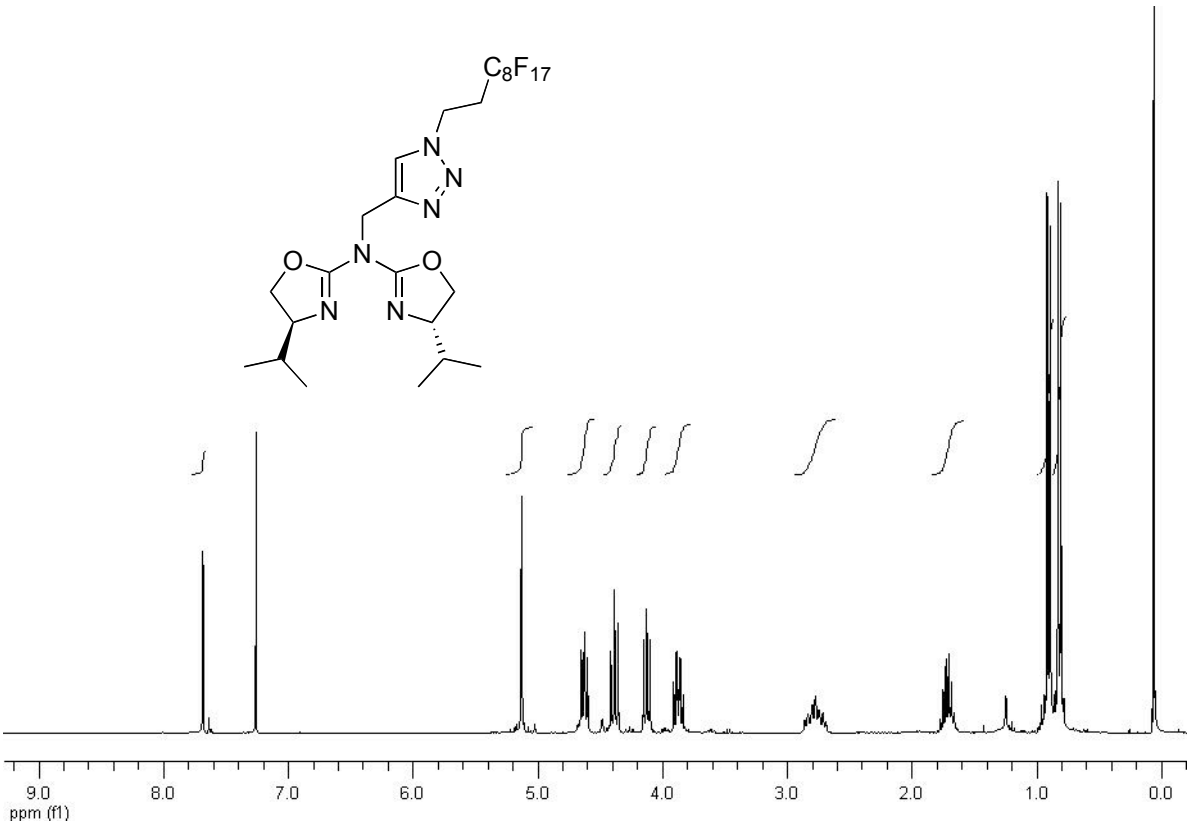


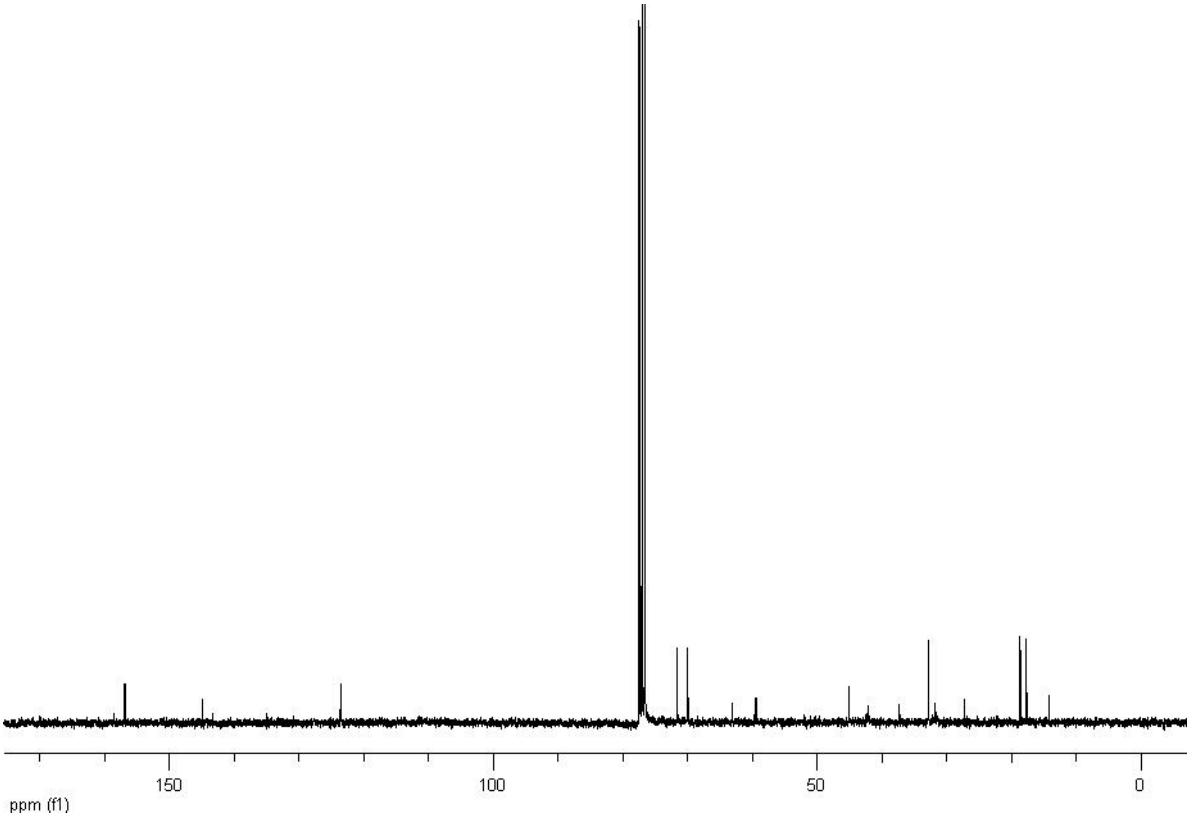


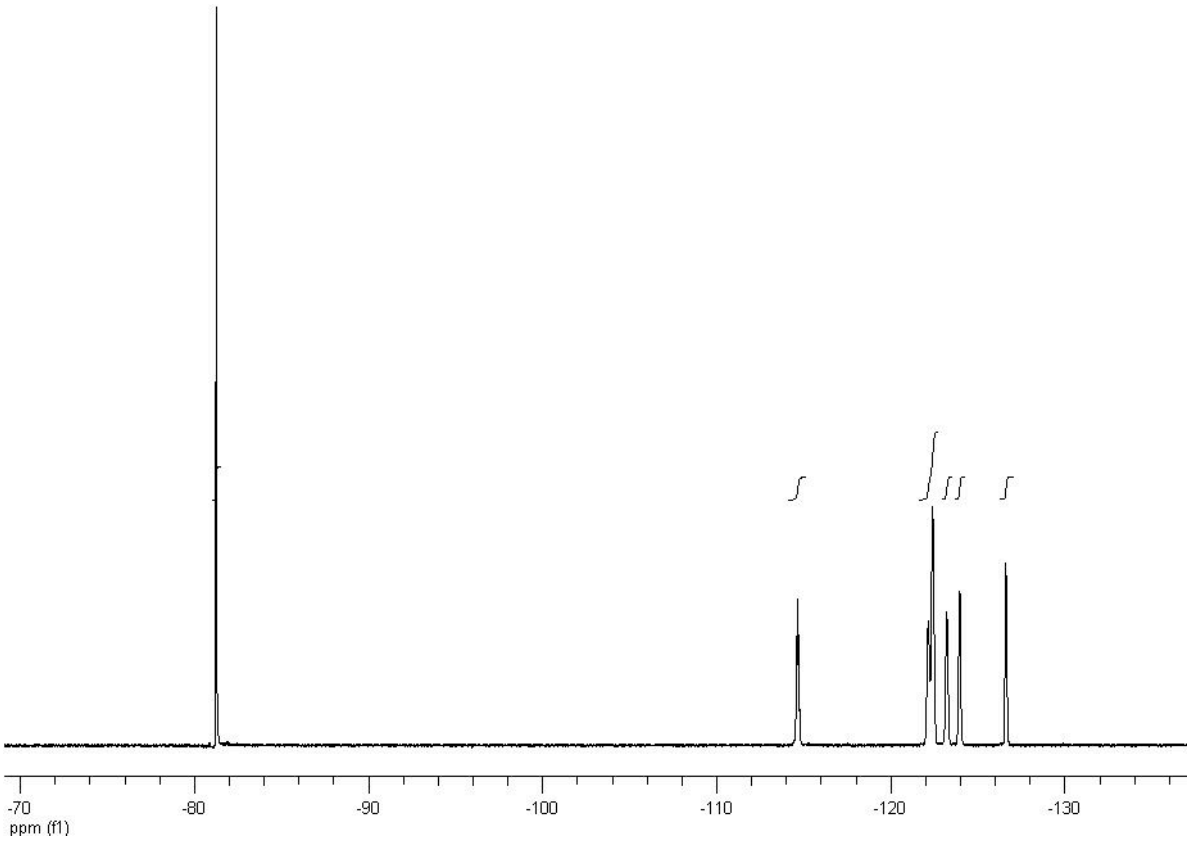
(*S*,*S*)-Bis-(4-isopropyl-4,5-dihydro-oxazol-2-yl)-prop-2-ynyl-amine (87)



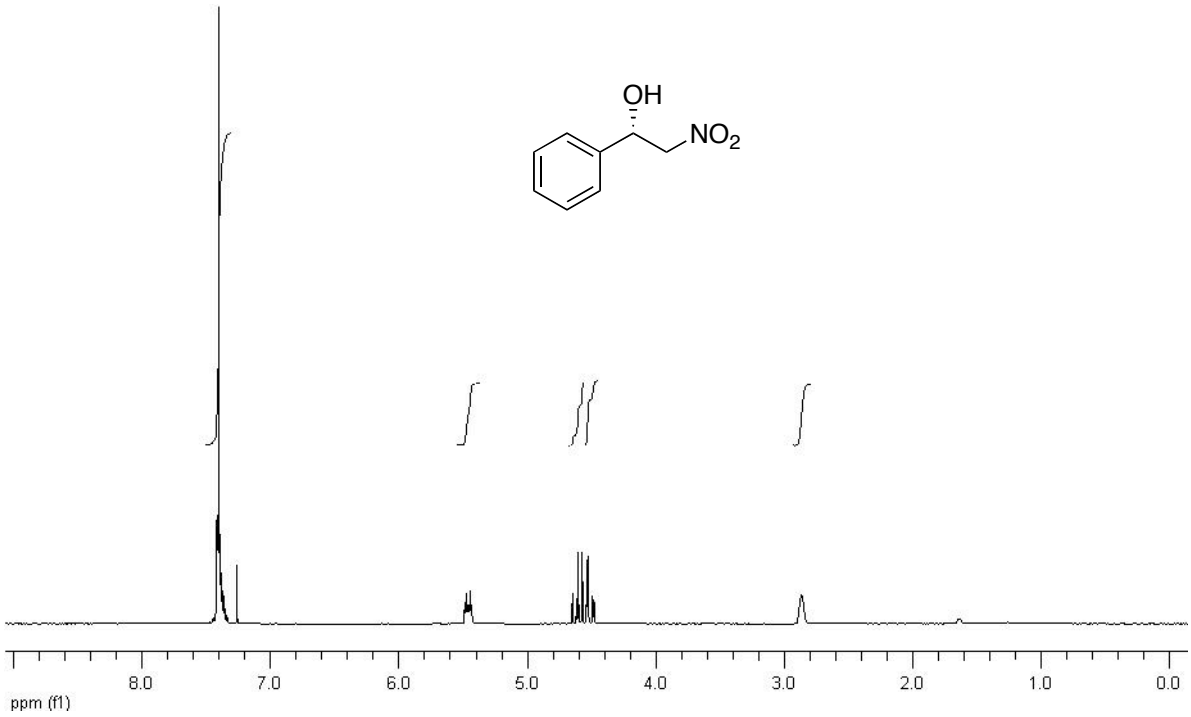
1-ponytail perfluorinated azabox (89)

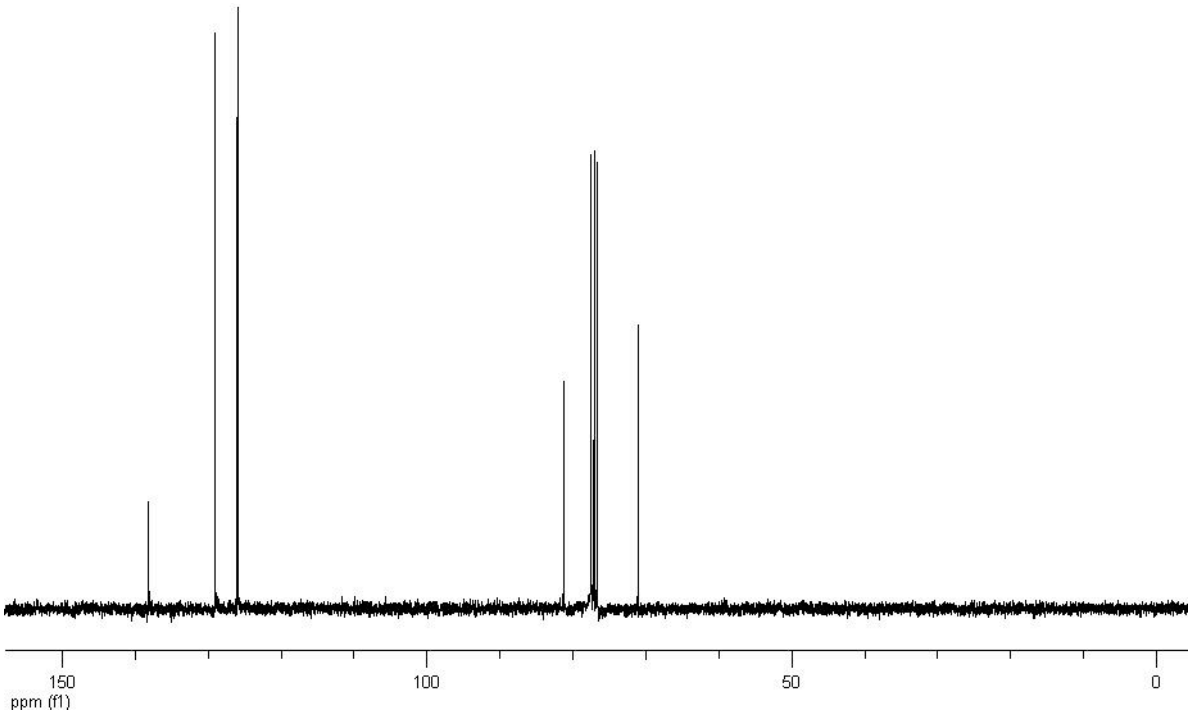



150
100
50
0
ppm (f1)

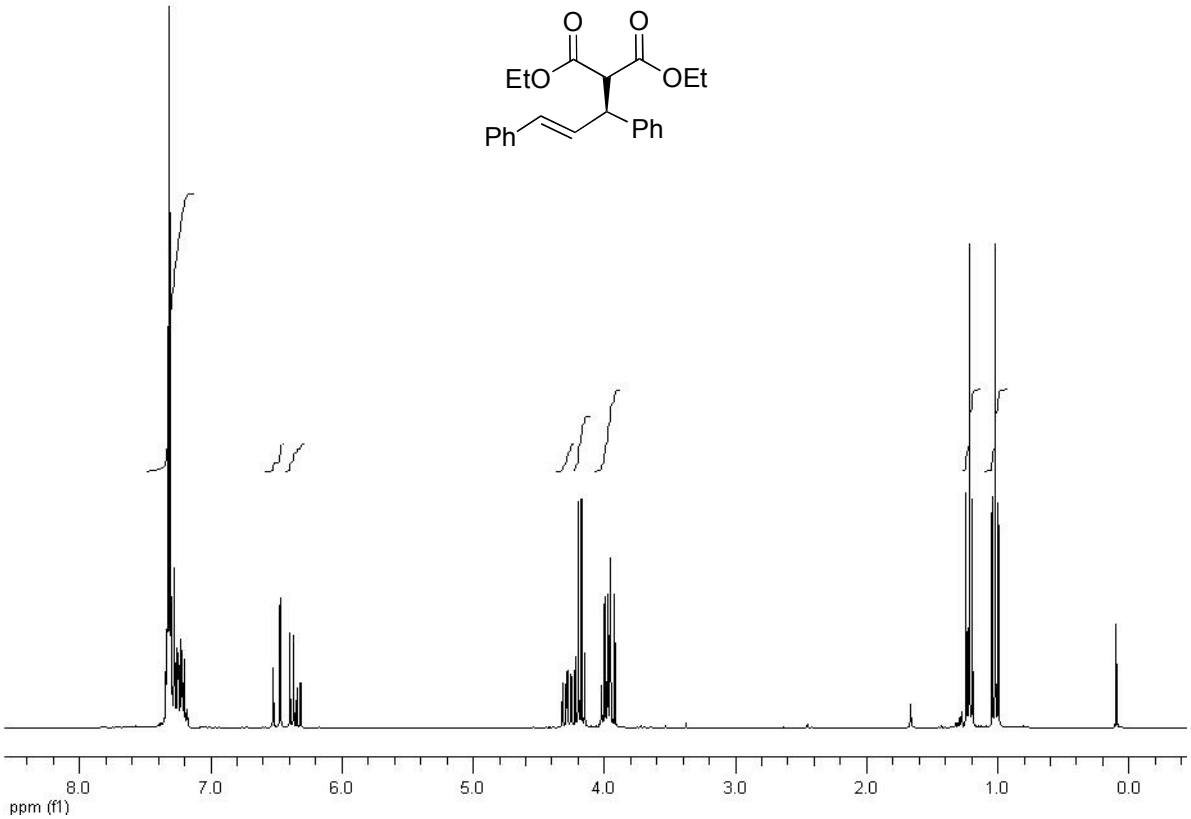

-70
-80
-90
-100
-110
-120
-130
ppm (f1)

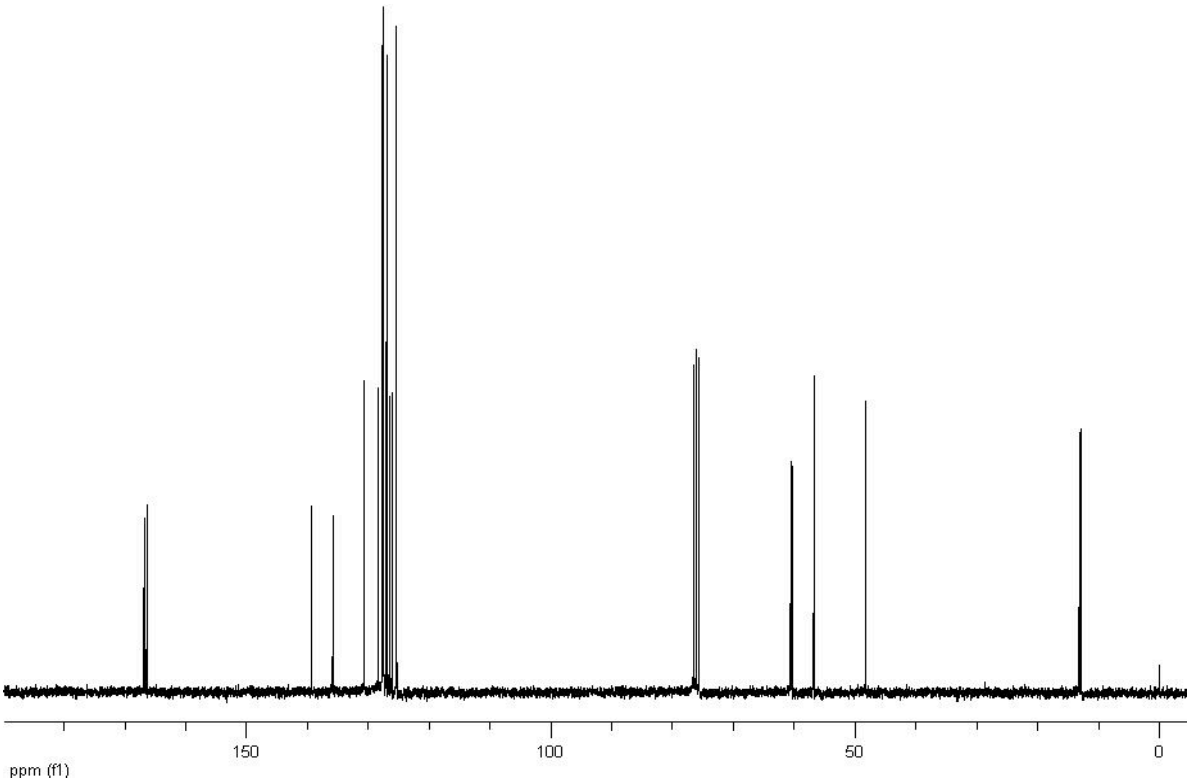
(*S*)-1-Phenyl-2-nitroethanol (93)



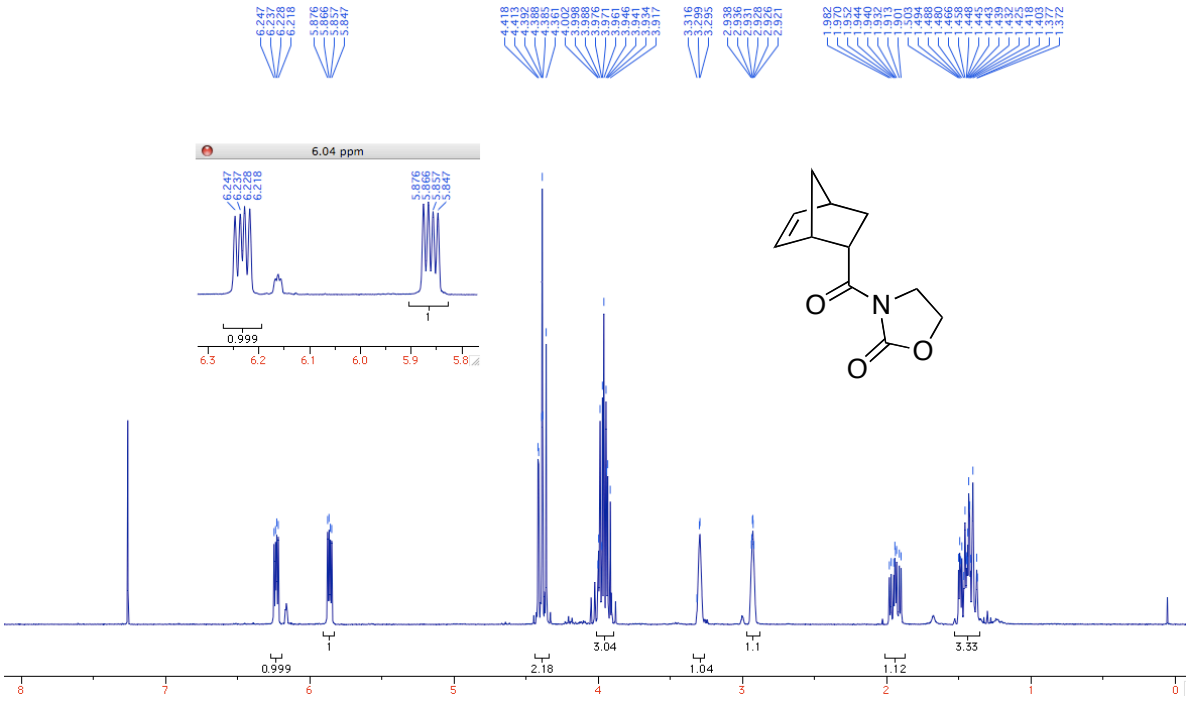


(*S*,*Z*)-diethyl 2-(1,3-diphenylallyl)malonate (96b)

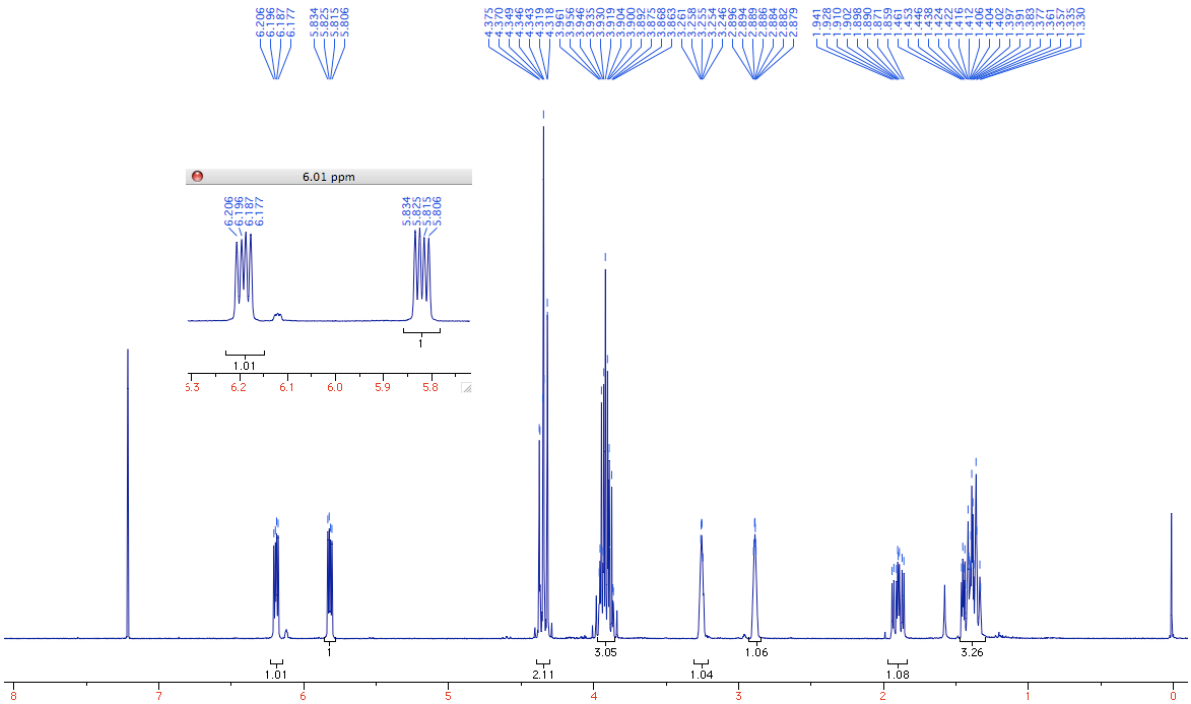




3-((1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-enecarbonyl)oxazolidin-2-one (101)

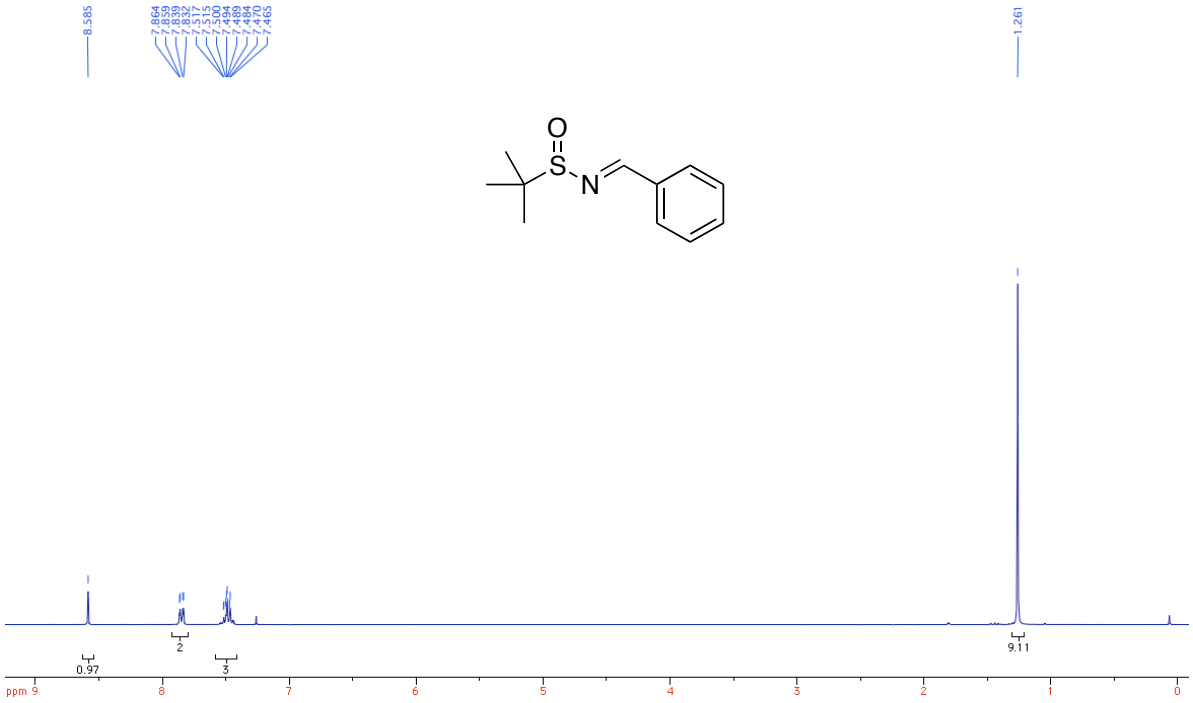


Racemic synthesis (Table 16, entry 3, *endo/exo*: 95:5 (by HPLC))

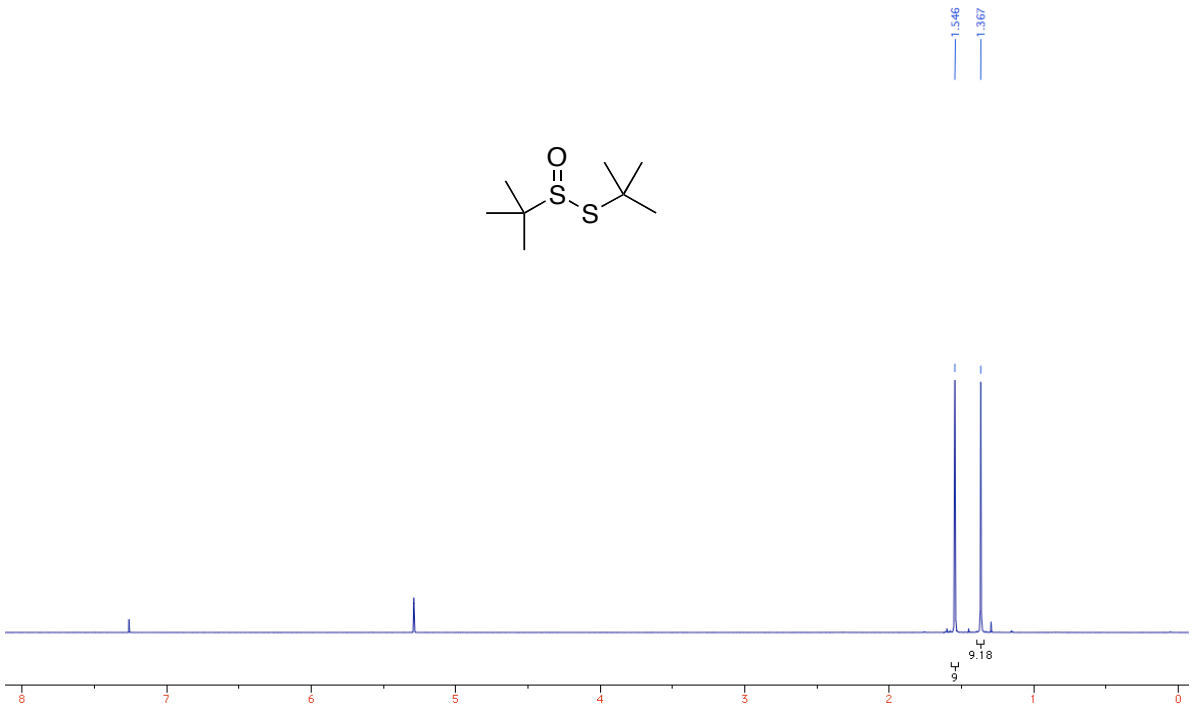


Enantioselective synthesis (Table 16, entry 4, *endo/exo*: 99:1 (by HPLC))

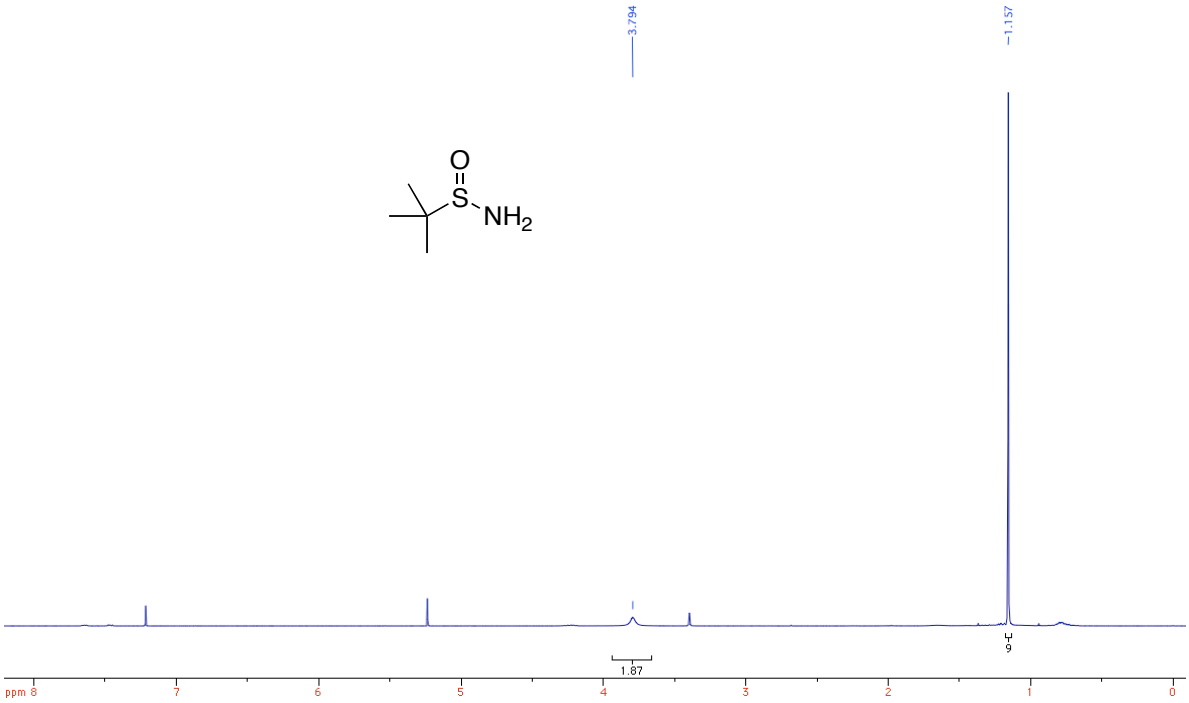
(*E*)-*N*-benzylidene-2-methylpropane-2-sulfinamide (103)

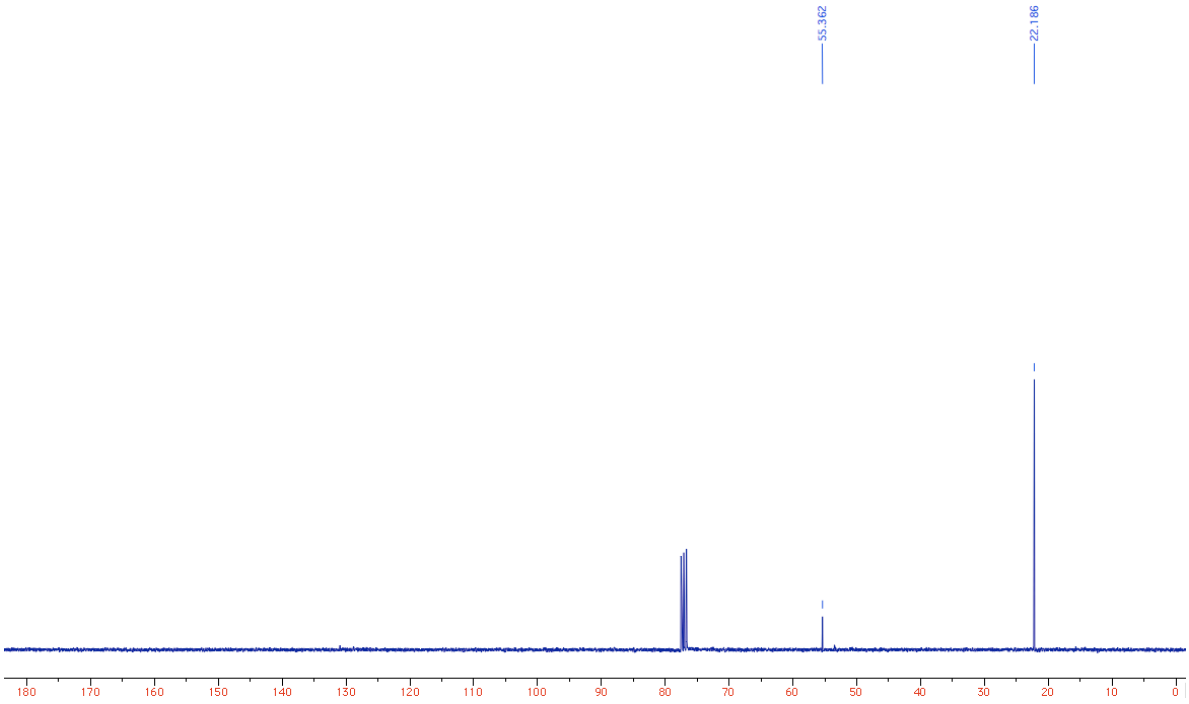


***S-tert*-butyl 2-methylpropane-2-sulfinothioate (106)**

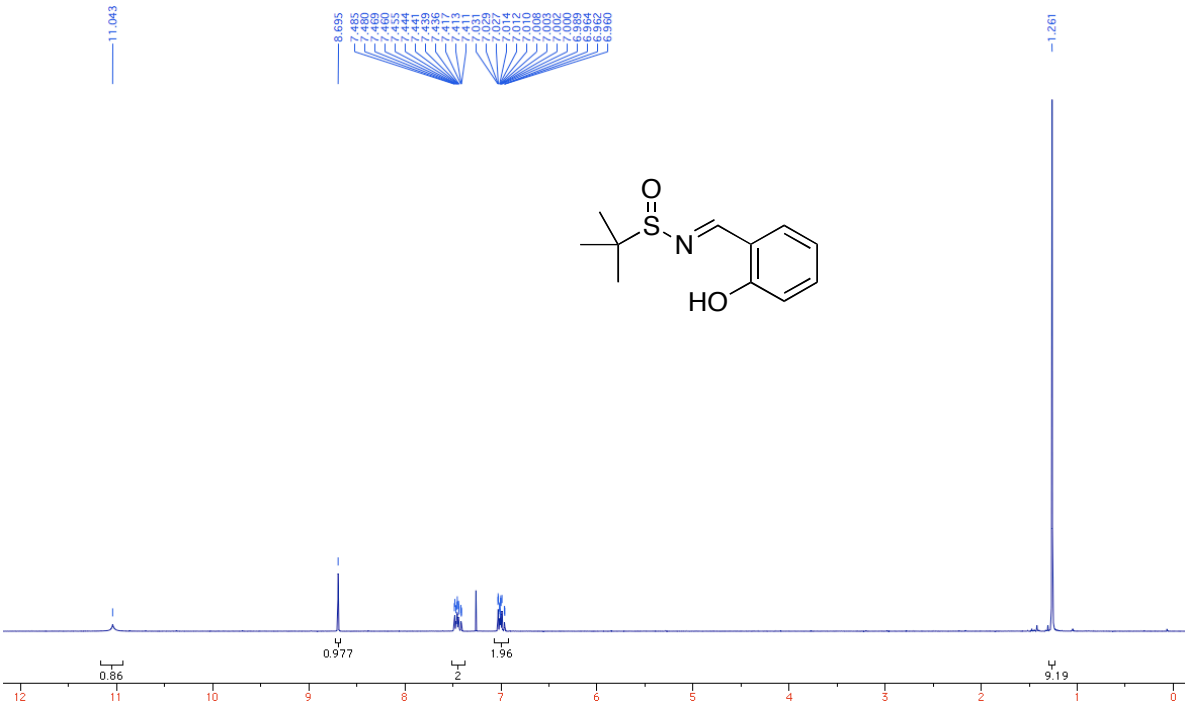


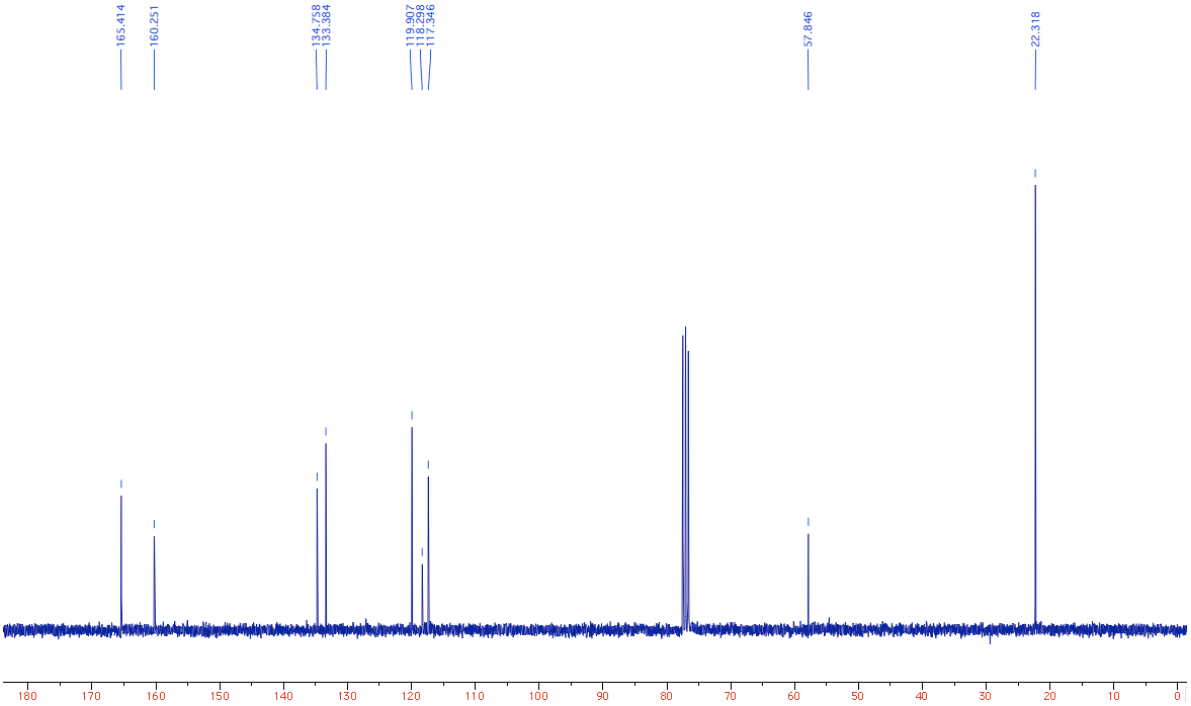
2-methylpropane-2-sulfinamide (107)



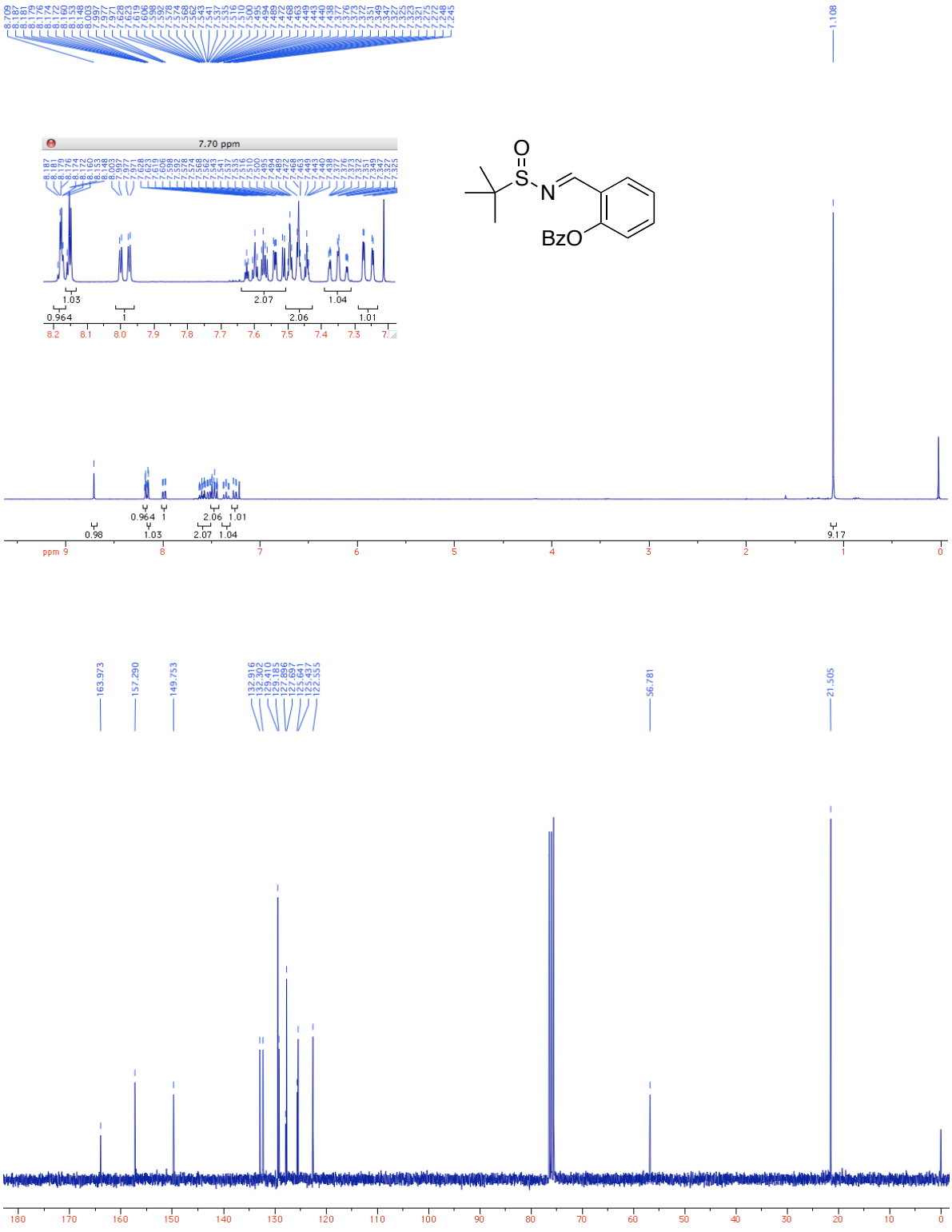


(*E*)-*N*-(2-hydroxybenzylidene)-2-methylpropane-2-sulfinamide (113)

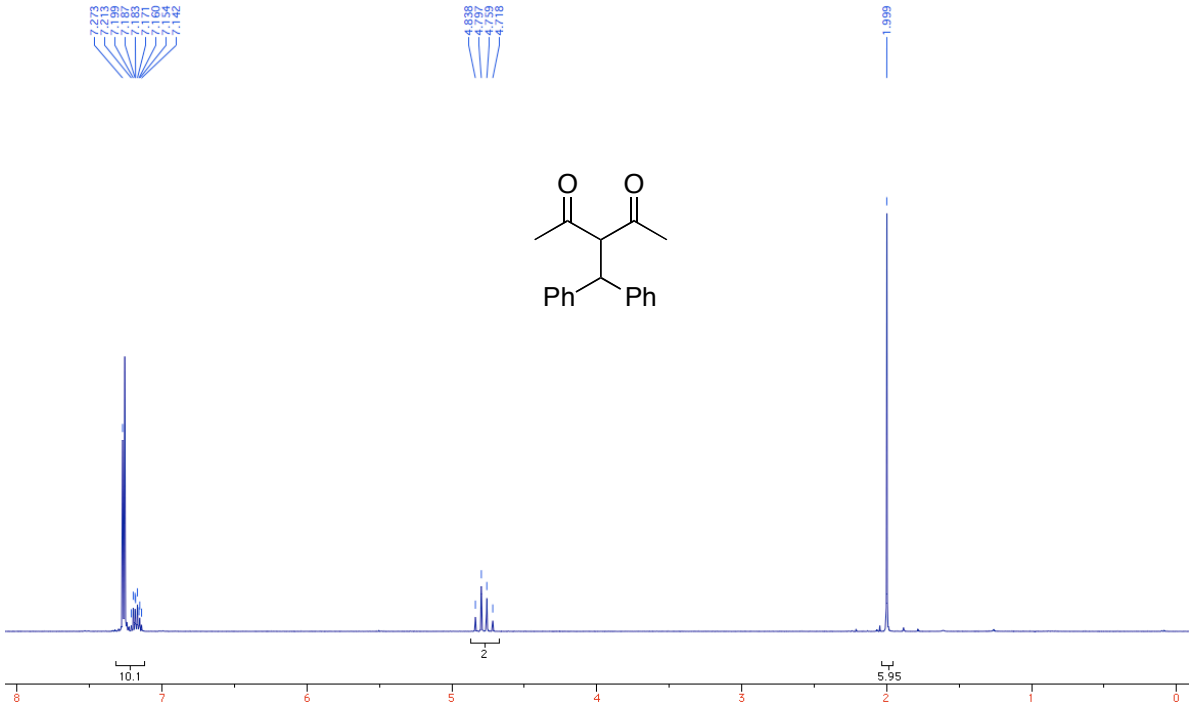




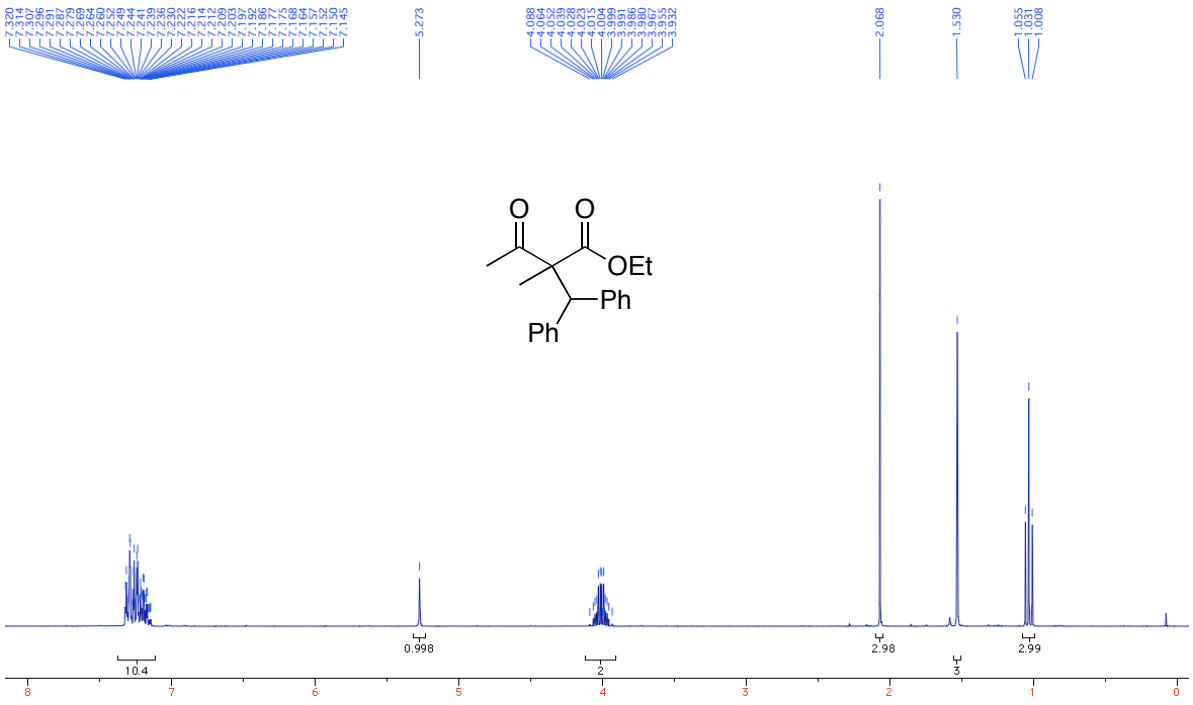
(*E*)-2-((*tert*-butylsulfinylimino)methyl)phenyl benzoate (114)

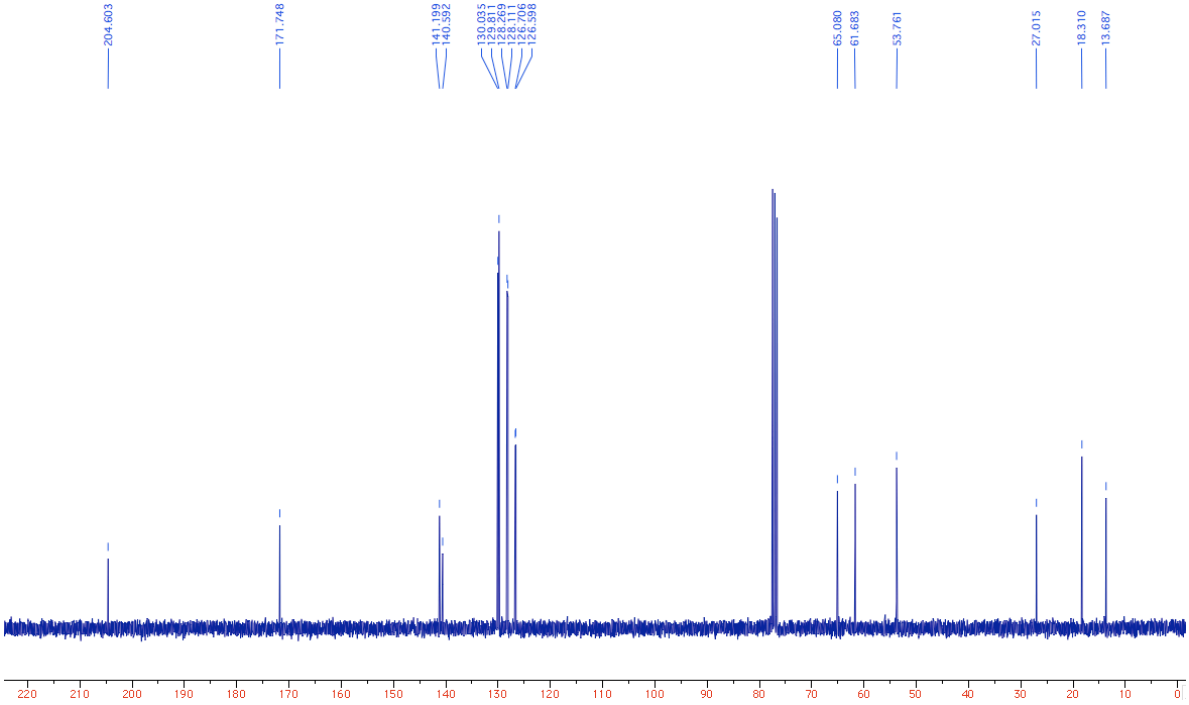


3-benzhydrylpentane-2,4-dione (117)

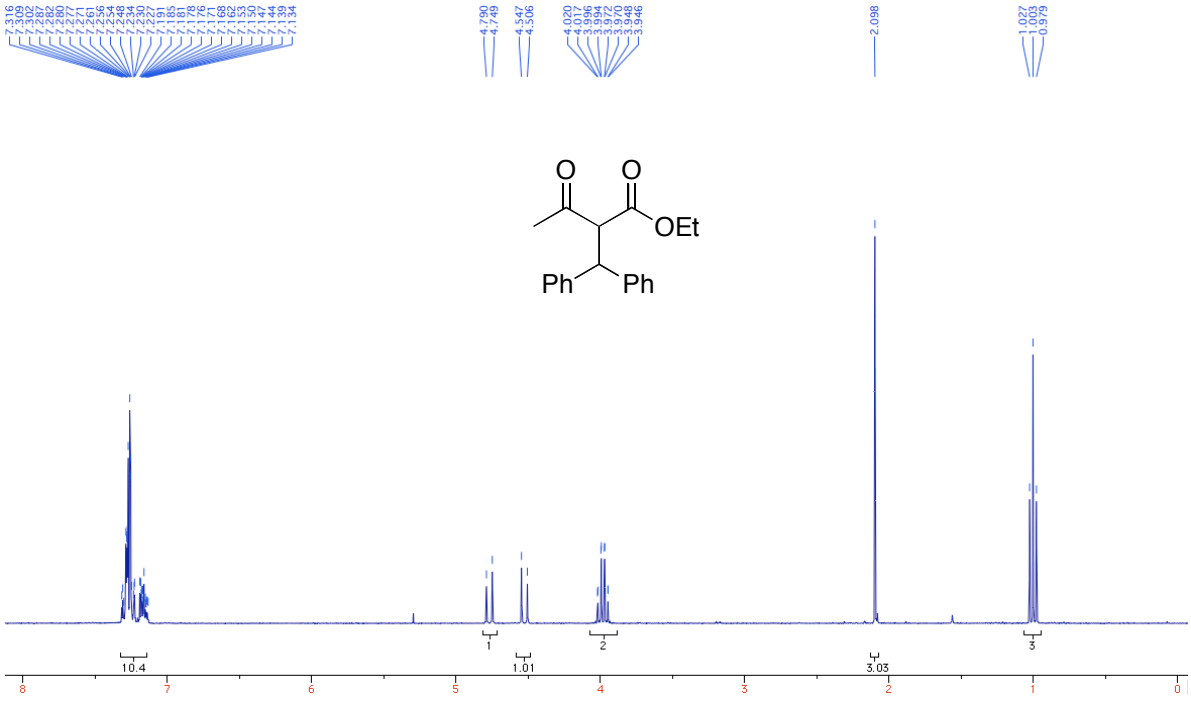


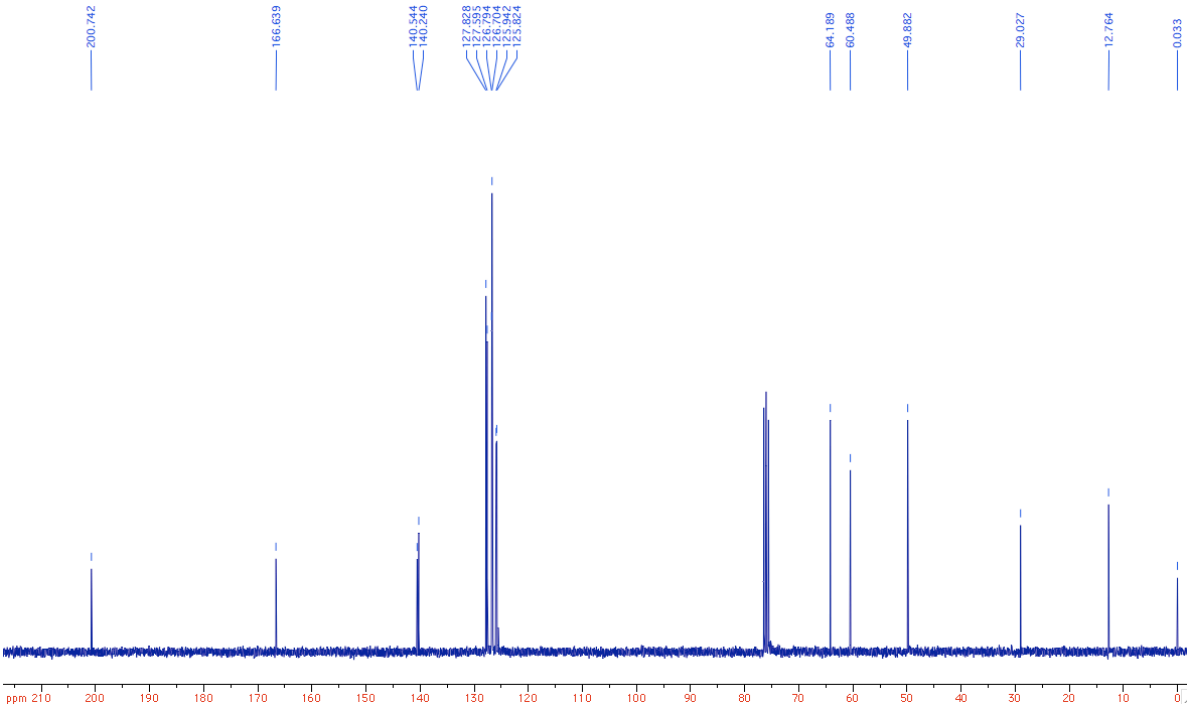
Ethyl 2-benzhydryl-2-methyl-3-oxobutanoate (121)



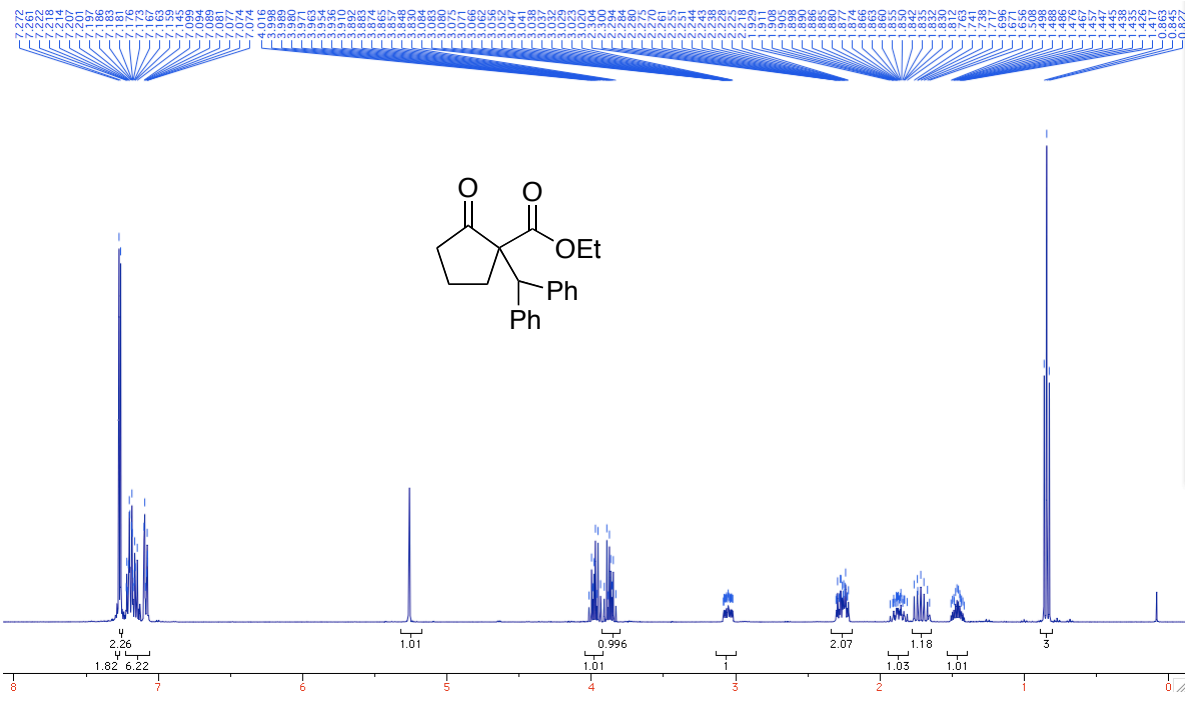


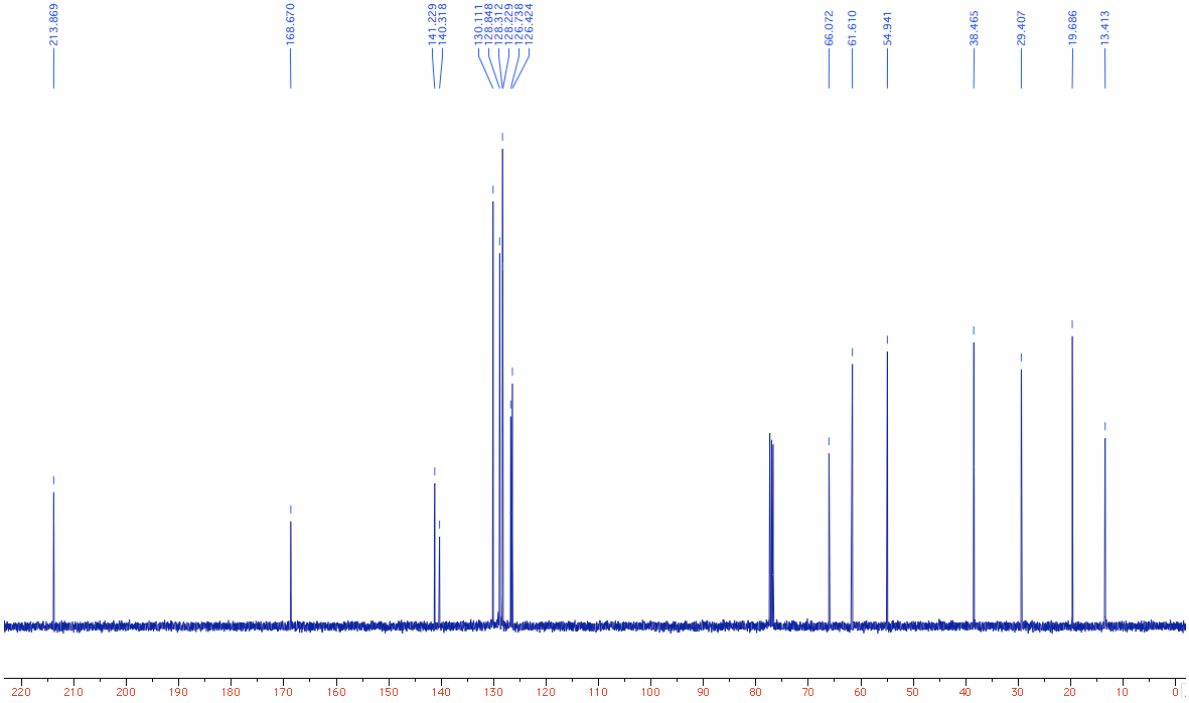
Ethyl 2-benzhydryl-3-oxobutanoate (121b)



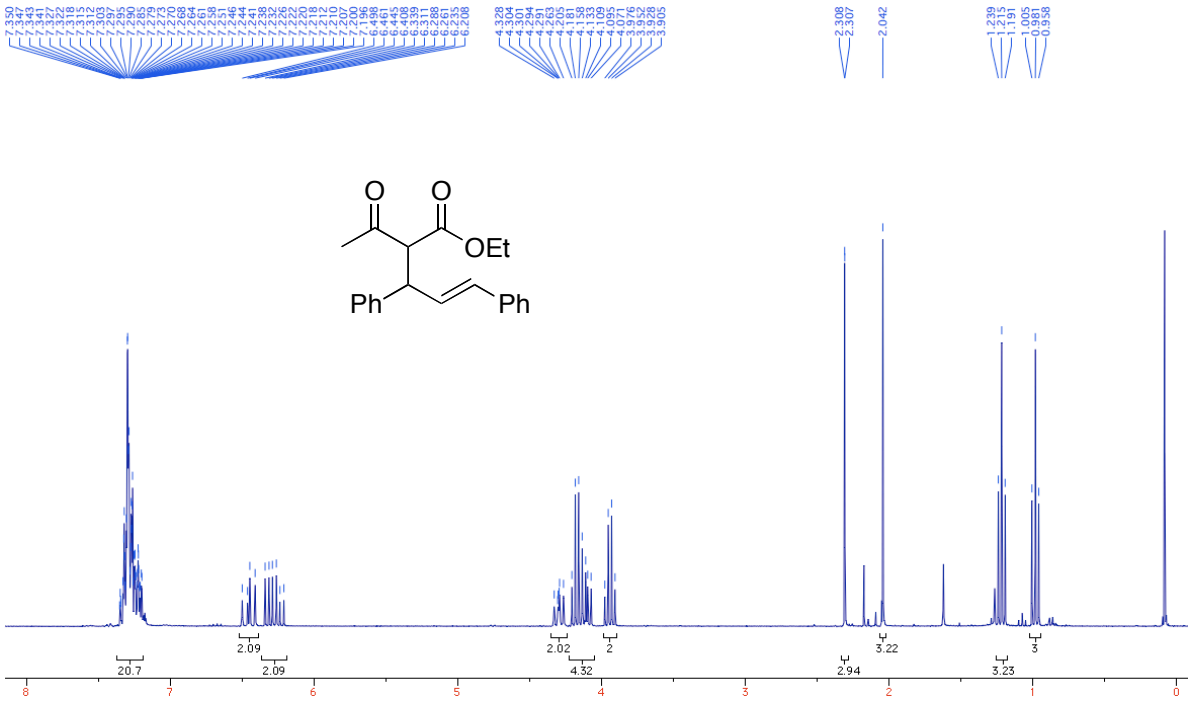


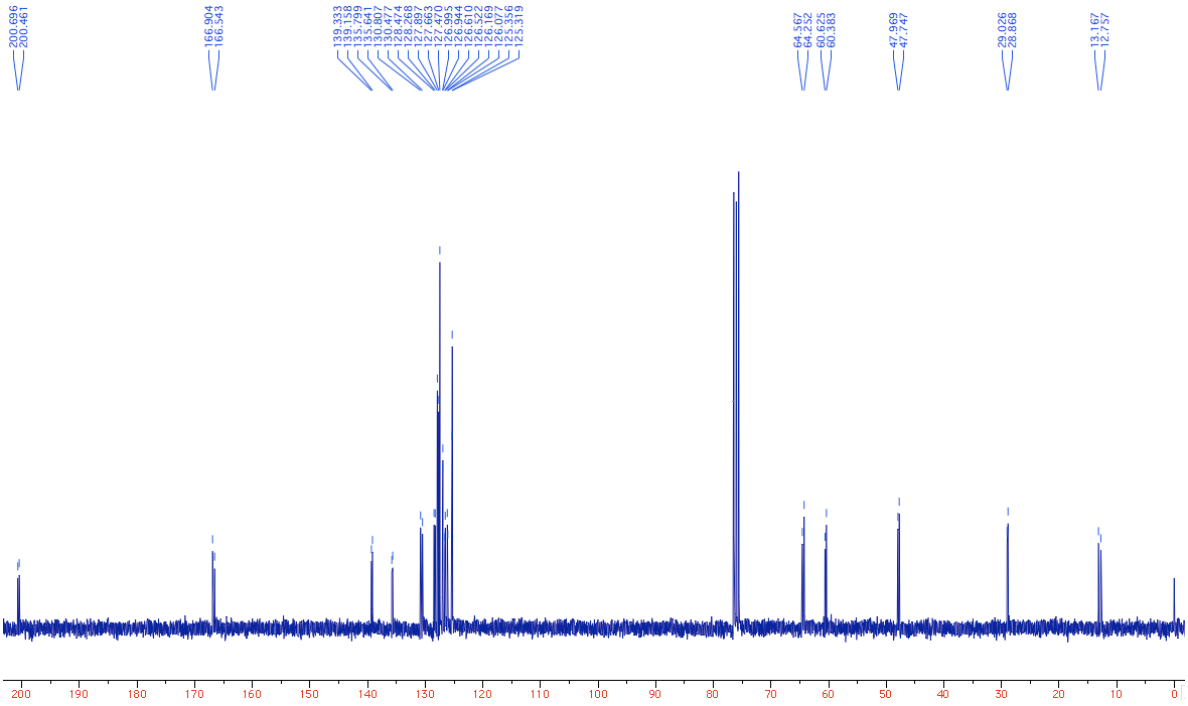
ethyl 1-benzhydryl-2-oxocyclopentanecarboxylate (123)



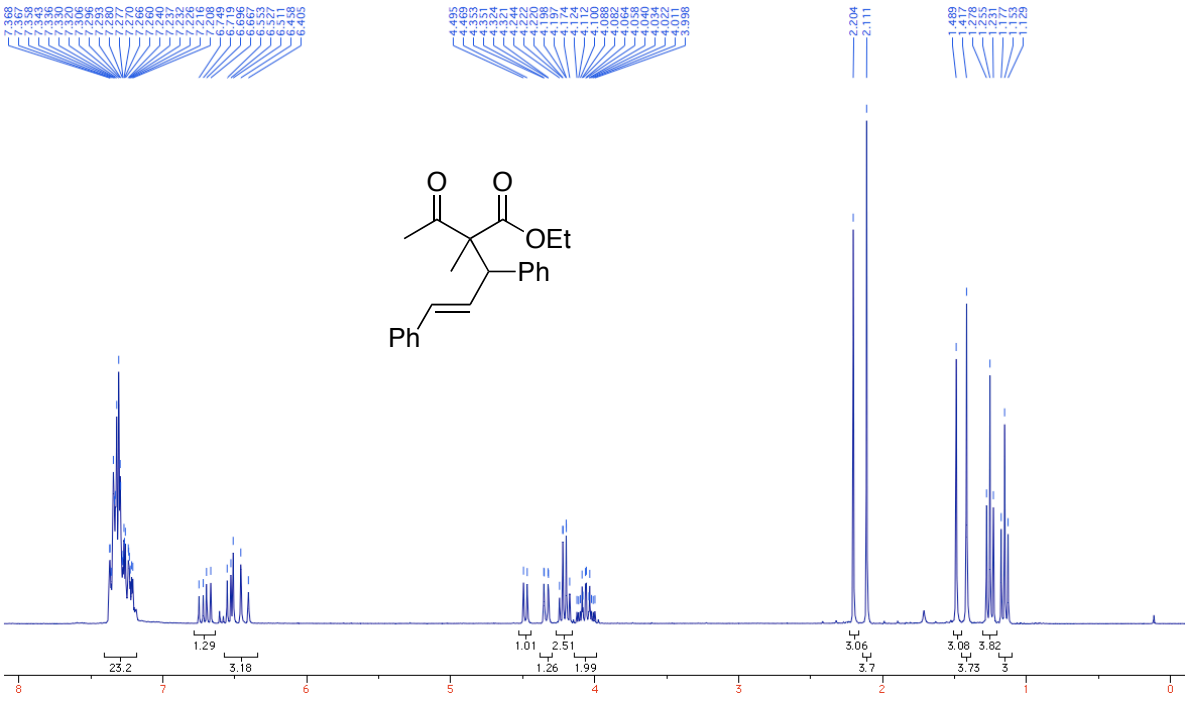


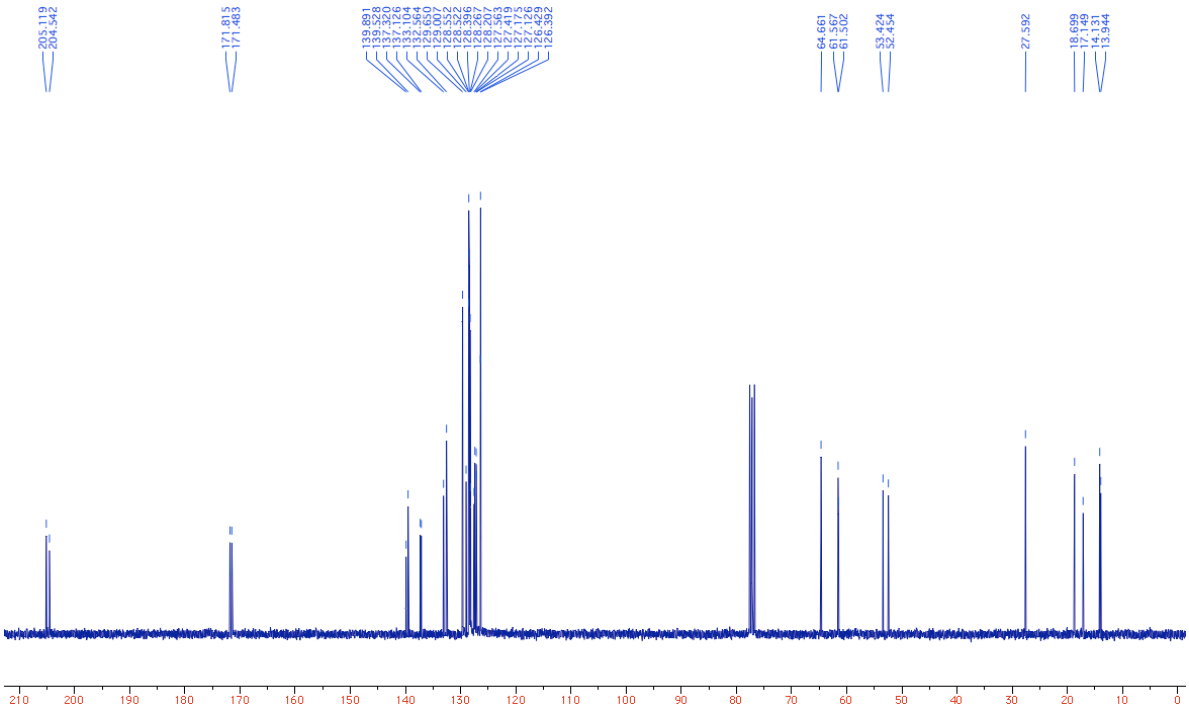
(*E*)-ethyl 2-acetyl-3,5-diphenylpent-4-enoate (132a)



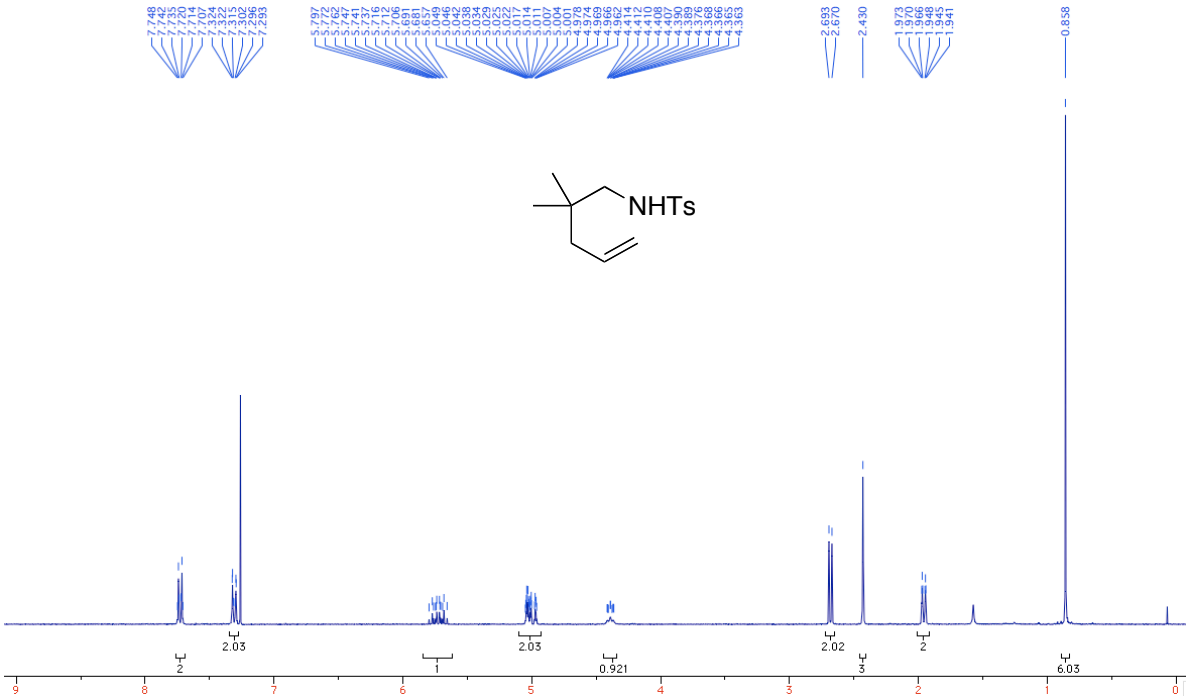


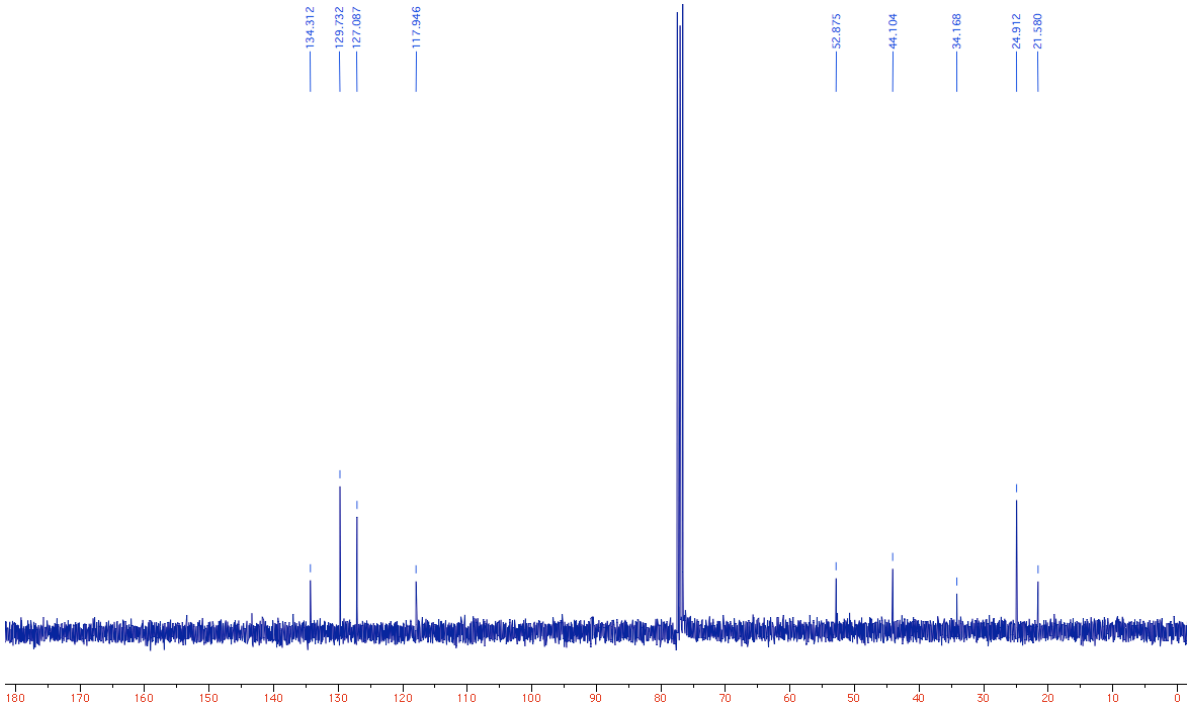
(*E*)-ethyl 2-acetyl-2-methyl-3,5-diphenylpent-4-enoate (132c)



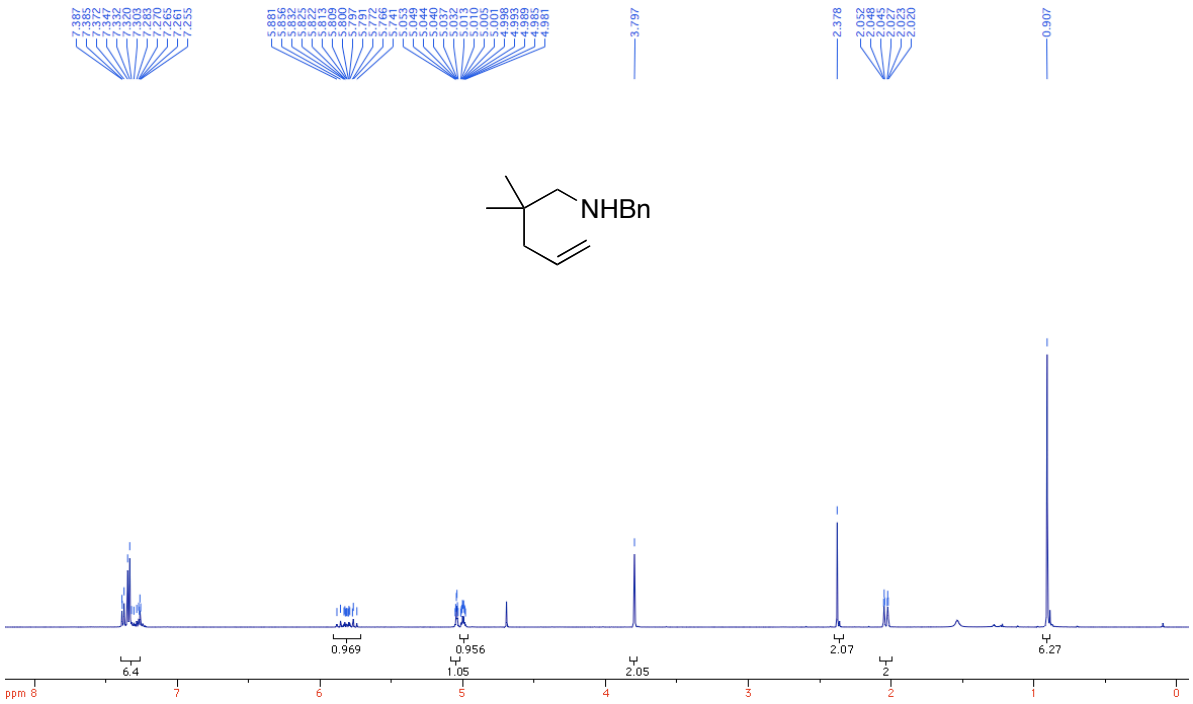


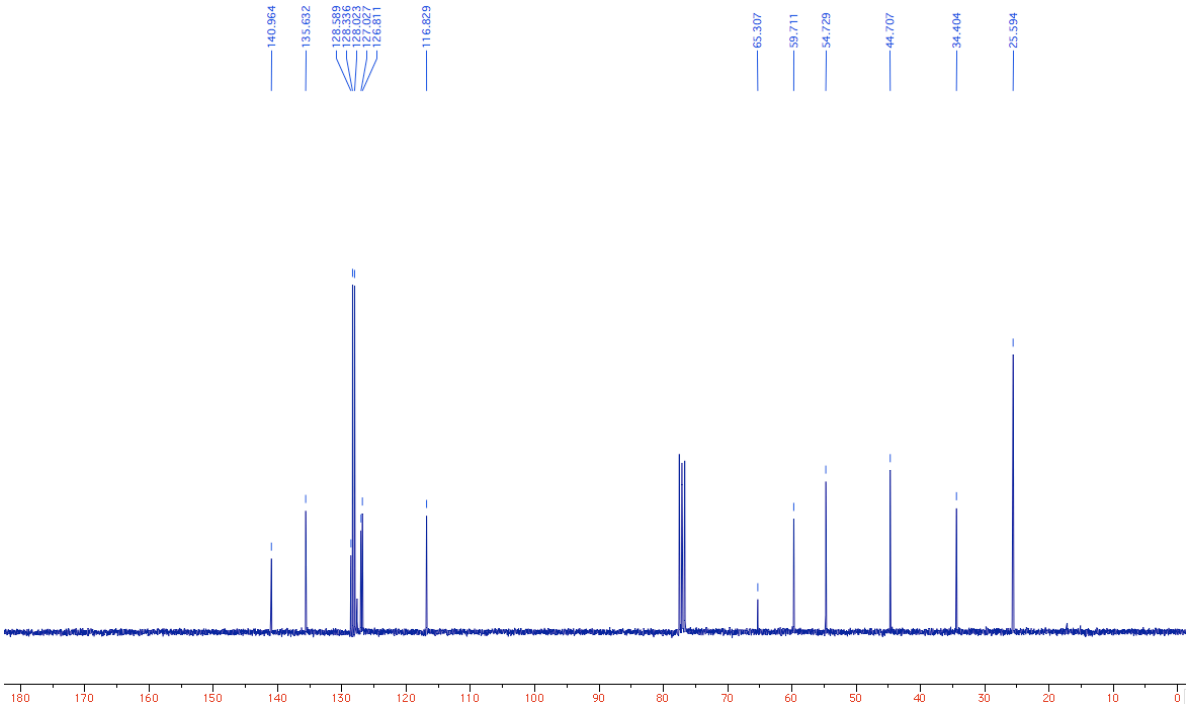
***N*-(2,2-dimethylpent-4-enyl)-4-methylbenzenesulfonamide (134a)**



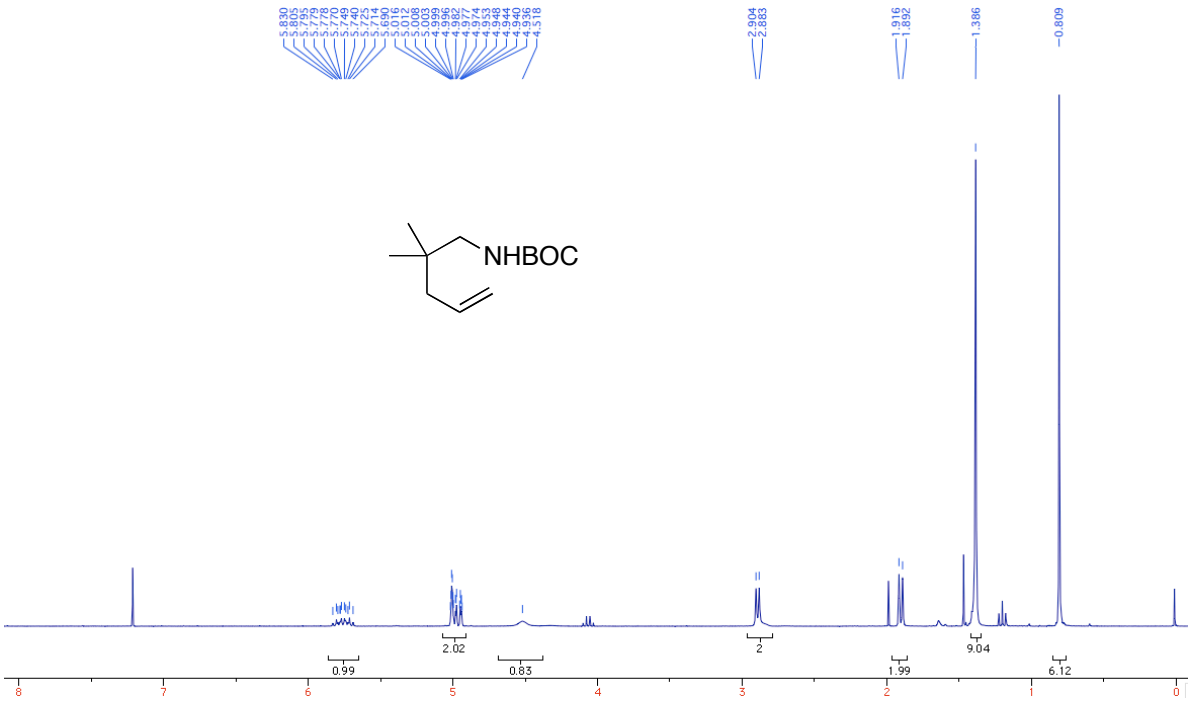


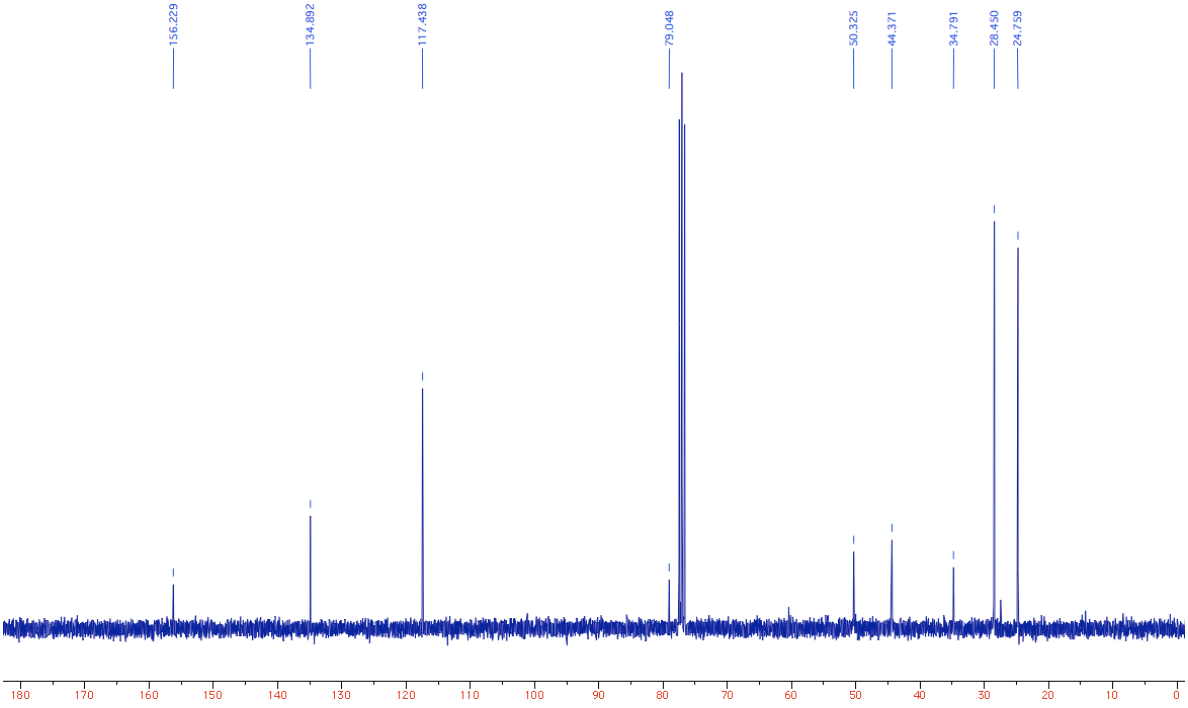
_N_-benzyl-2,2-dimethylpent-4-en-1-amine (134b)



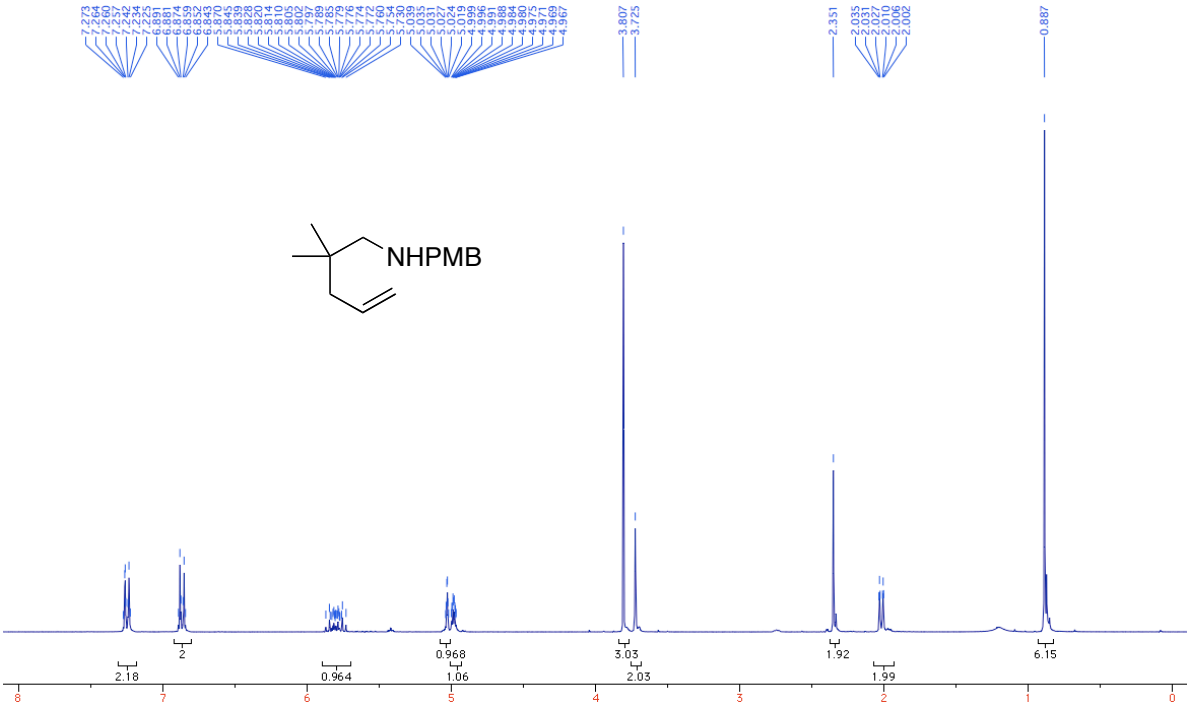


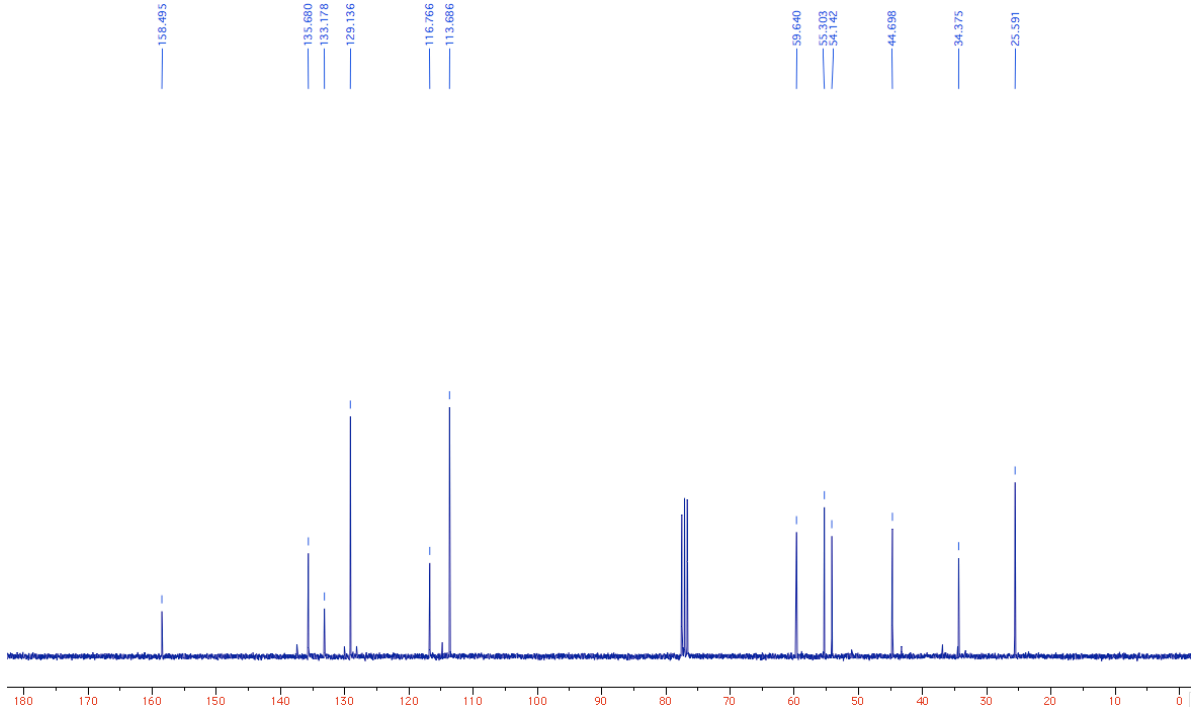
tert-butyl 2,2-dimethylpent-4-enylcarbamate (134c)



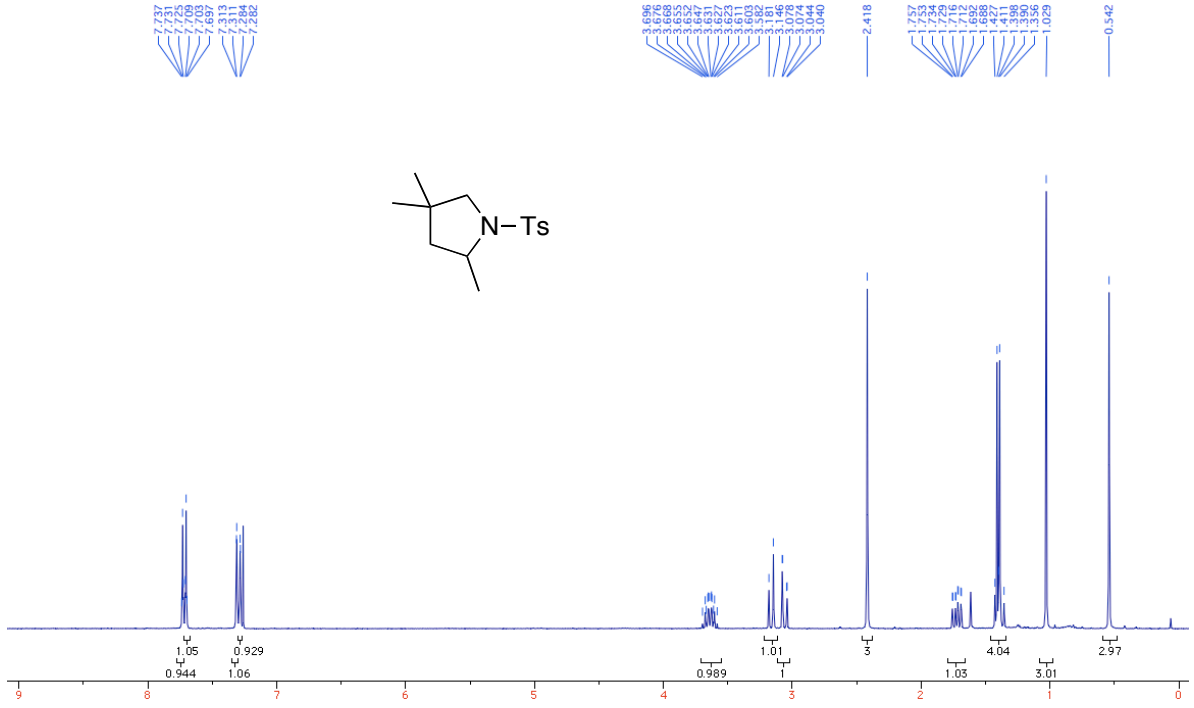


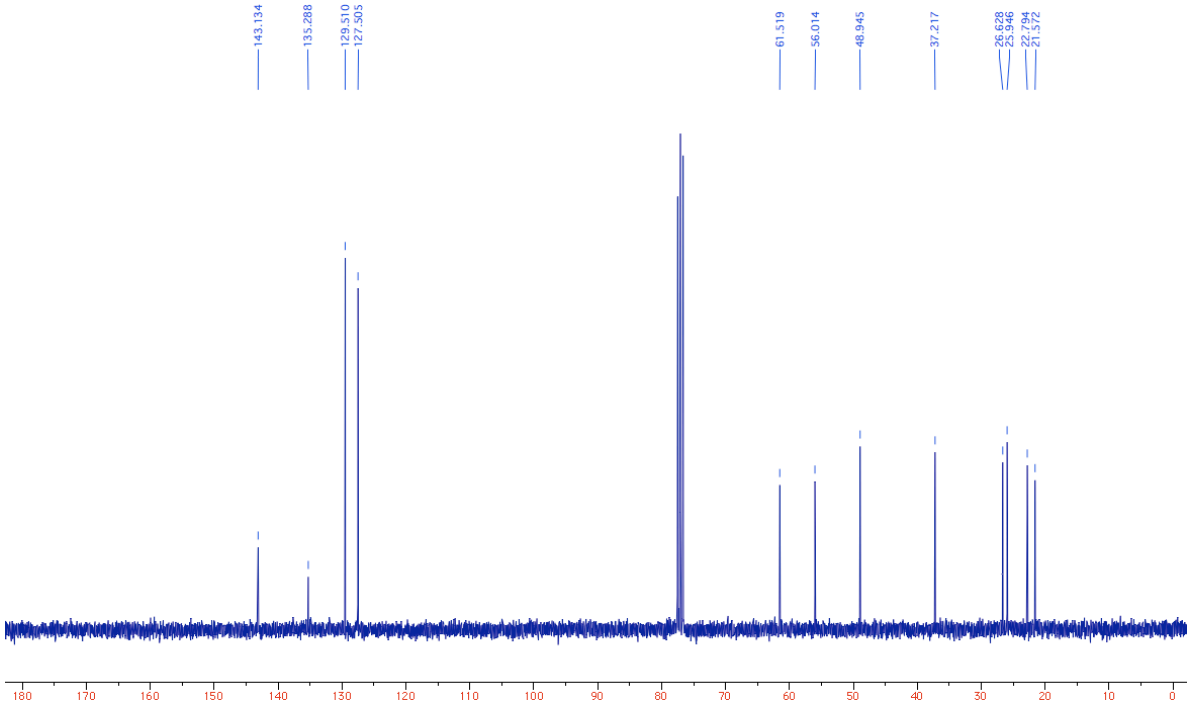
_N_-(4-methoxybenzyl)-2,2-dimethylpent-4-en-1-amine (134d)



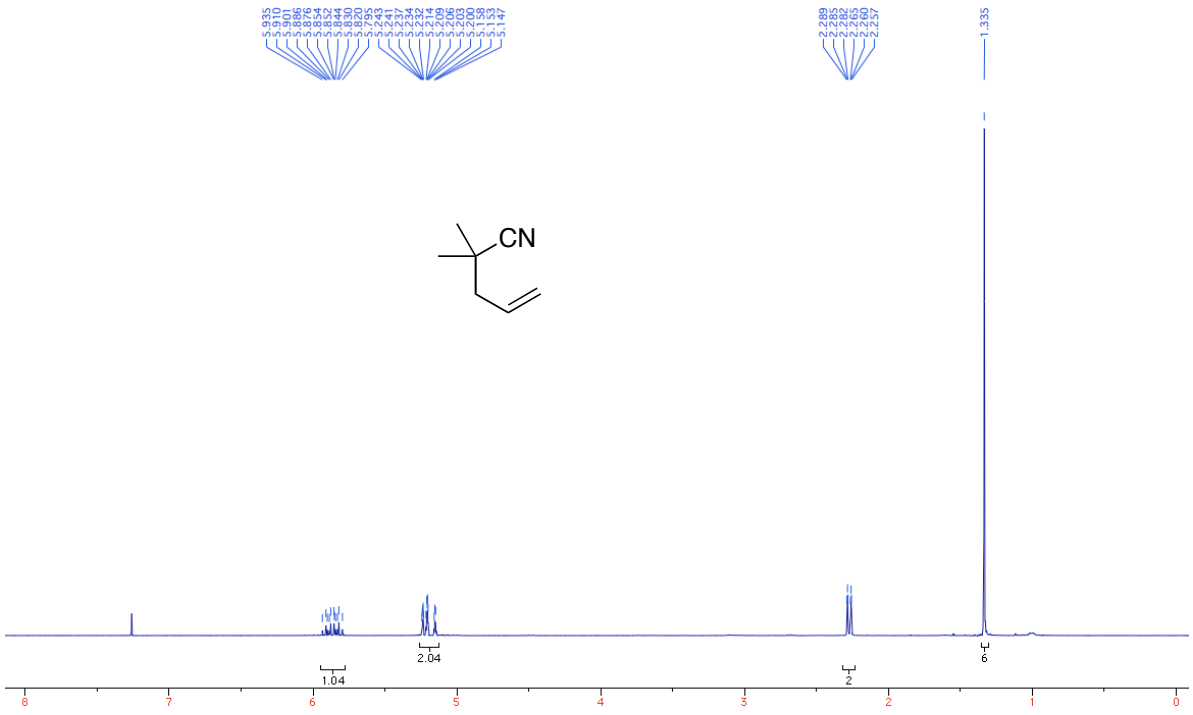


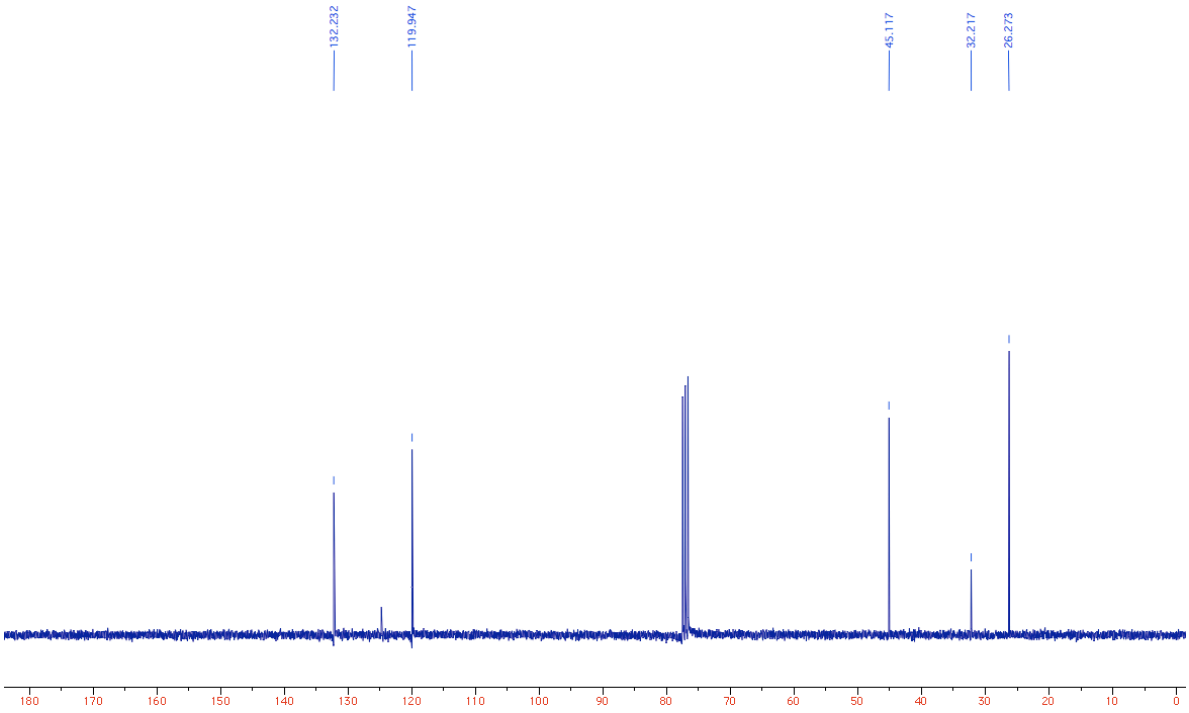
2,4,4-trimethyl-1-tosylpyrrolidine (135a)



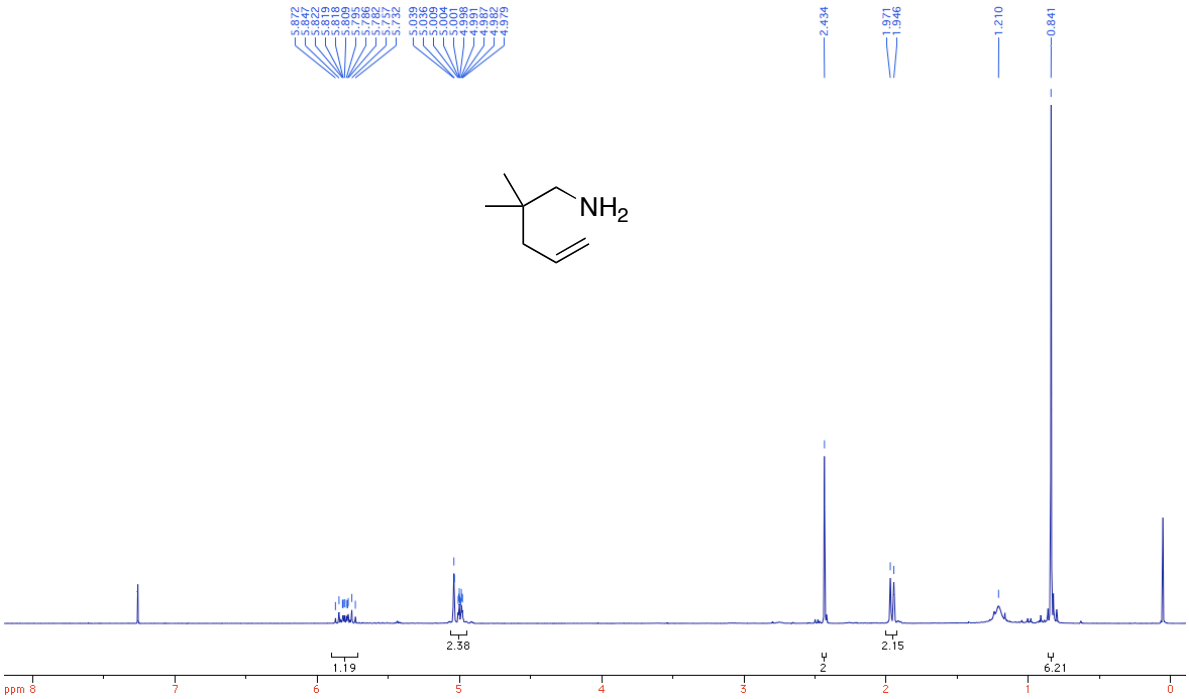


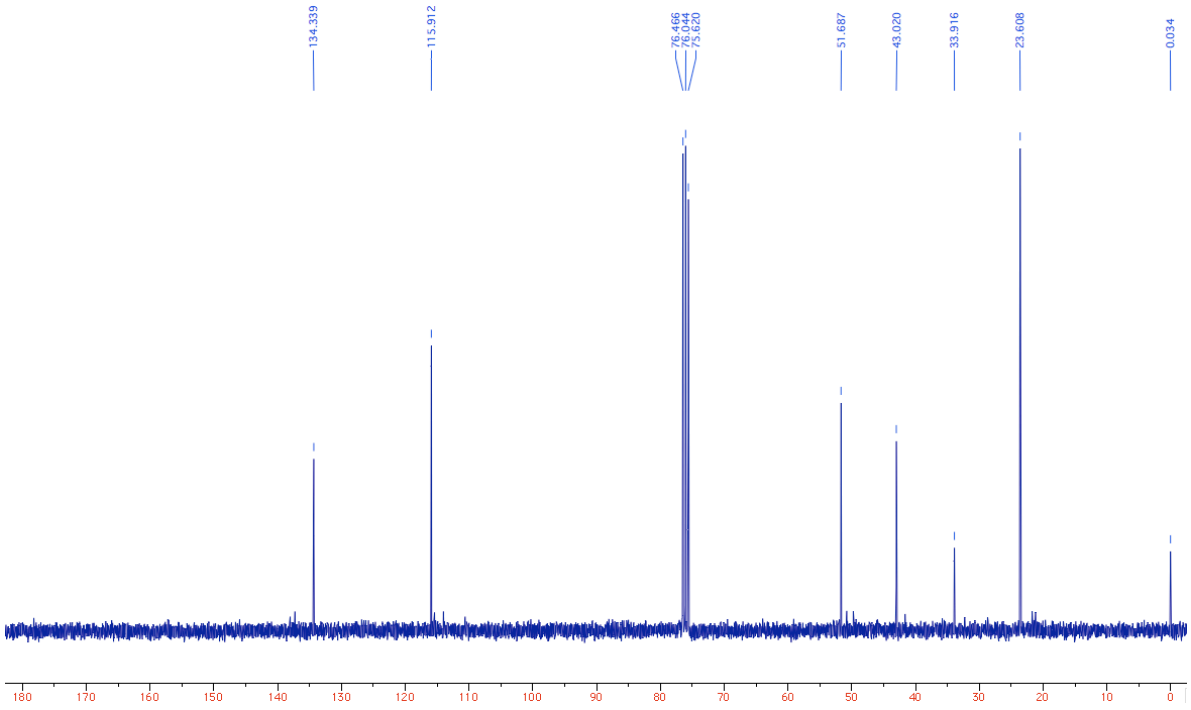
2,2-dimethylpent-4-enenitrile (137)



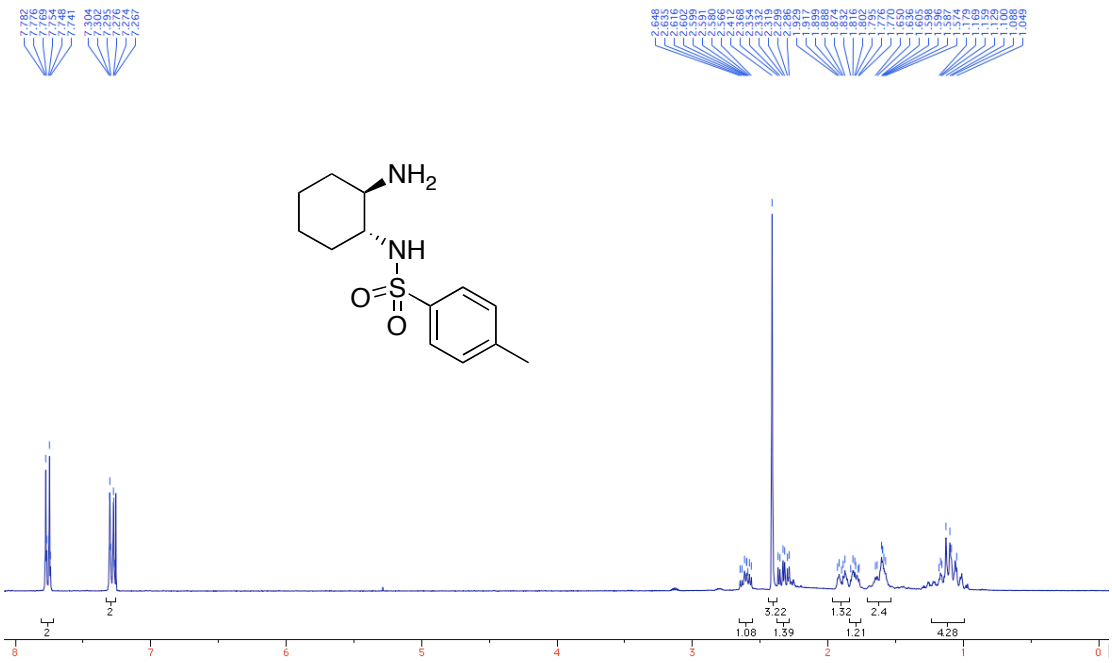


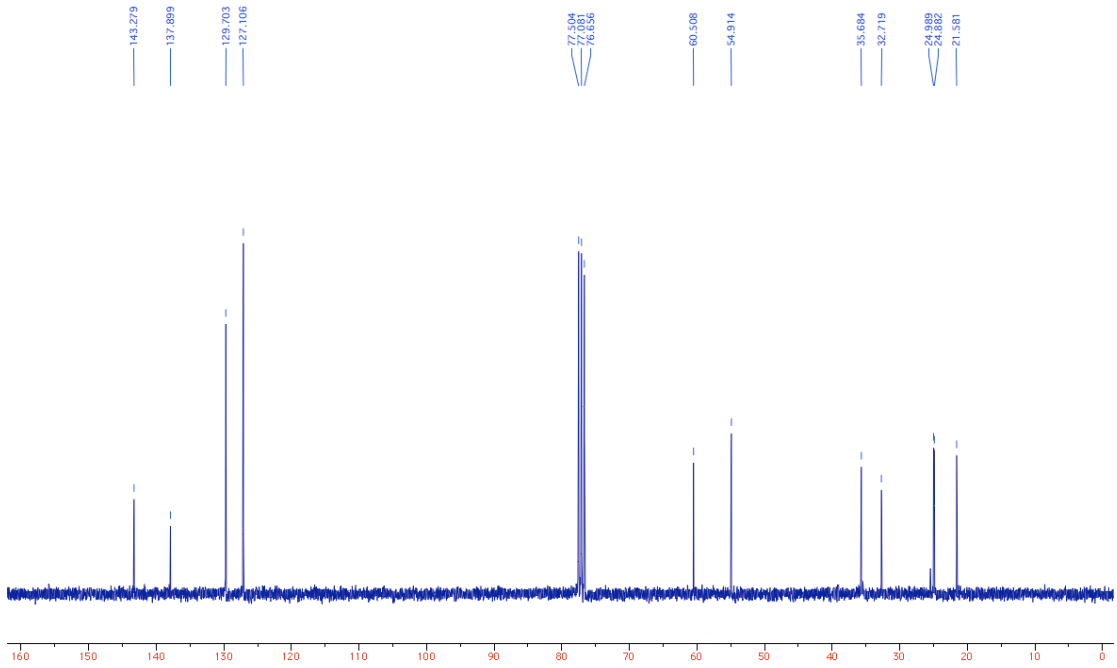
2,2-dimethylpent-4-en-1-amine (138)



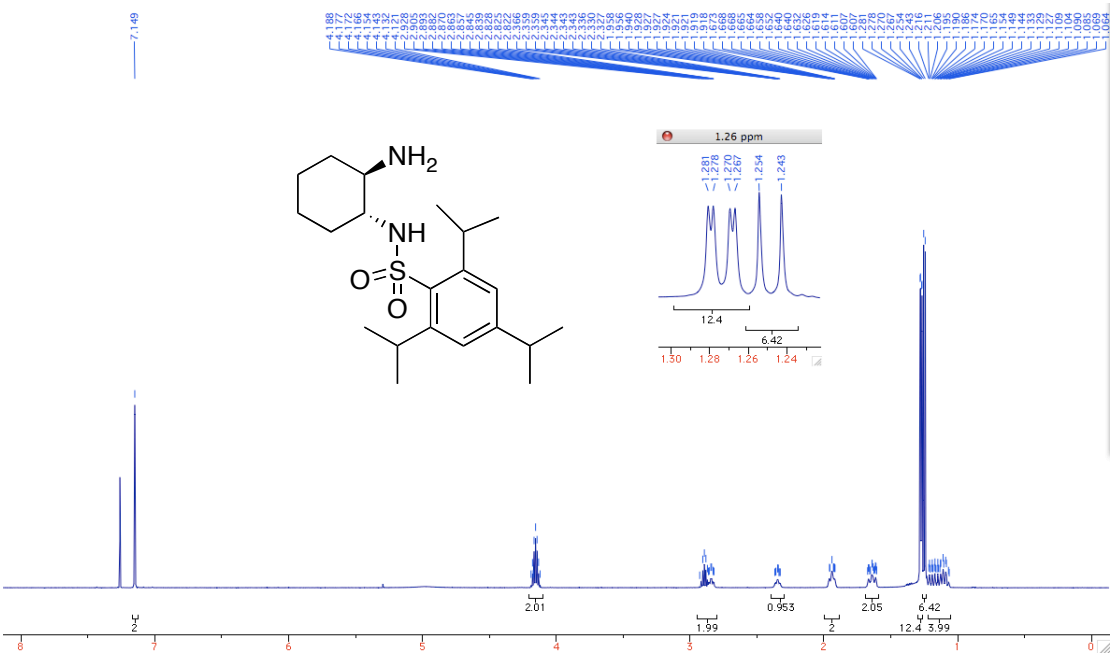

134.339
115.912
76.466
76.044
75.620
51.687
43.020
33.916
23.608
0.034
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

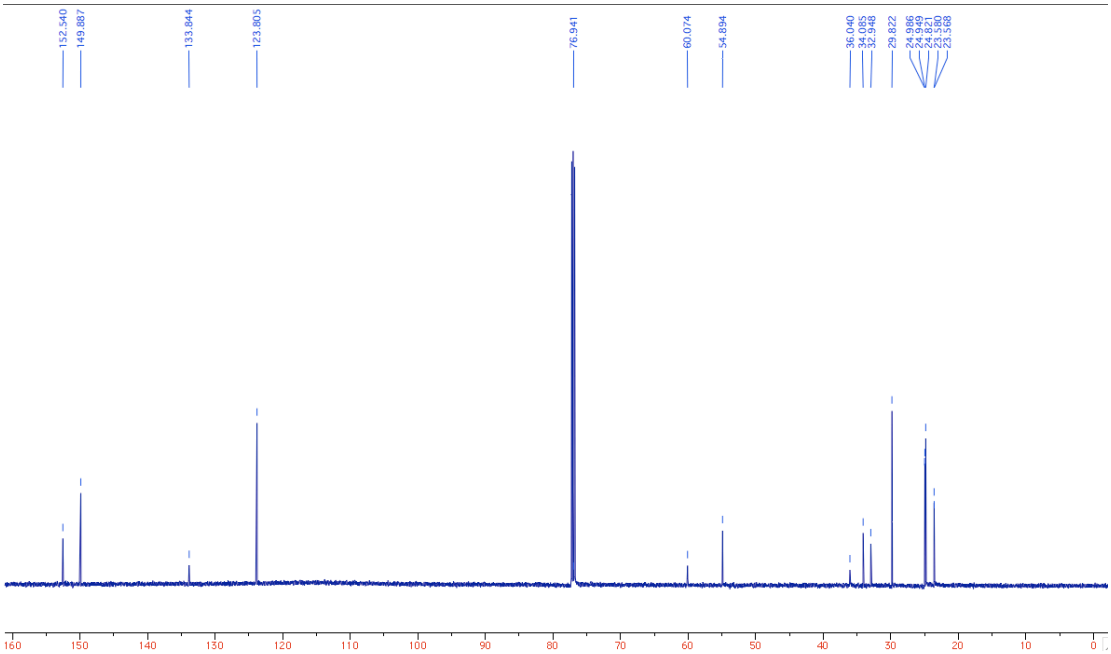
***N*-((1*R*,2*R*)-2-aminocyclohexyl)-4-methylbenzenesulfonamide (194a)**



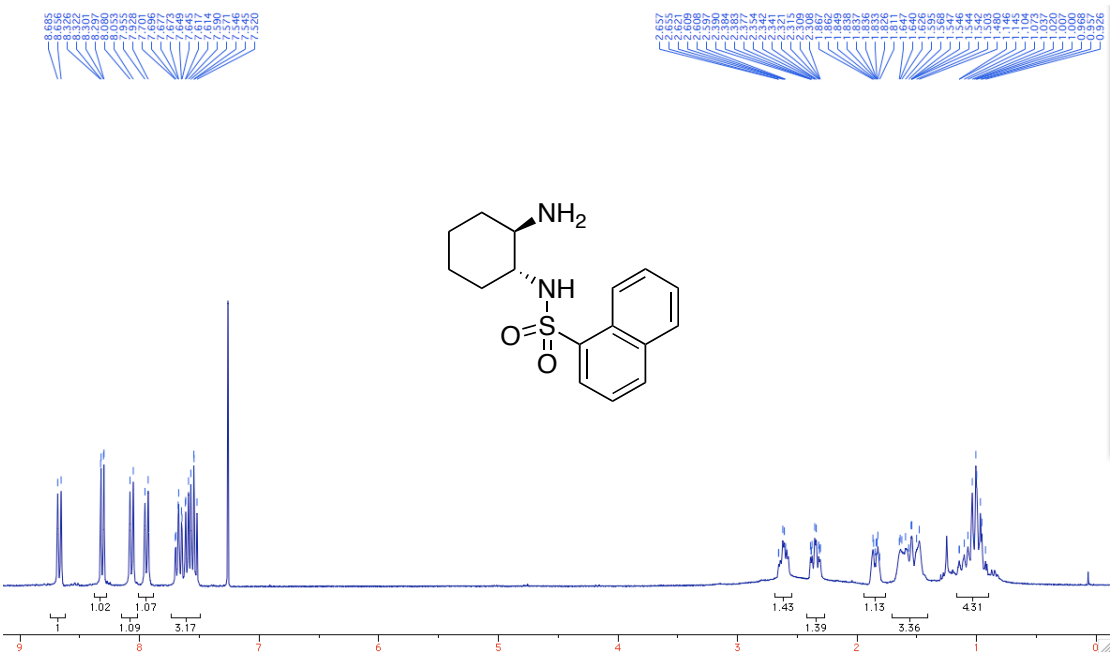


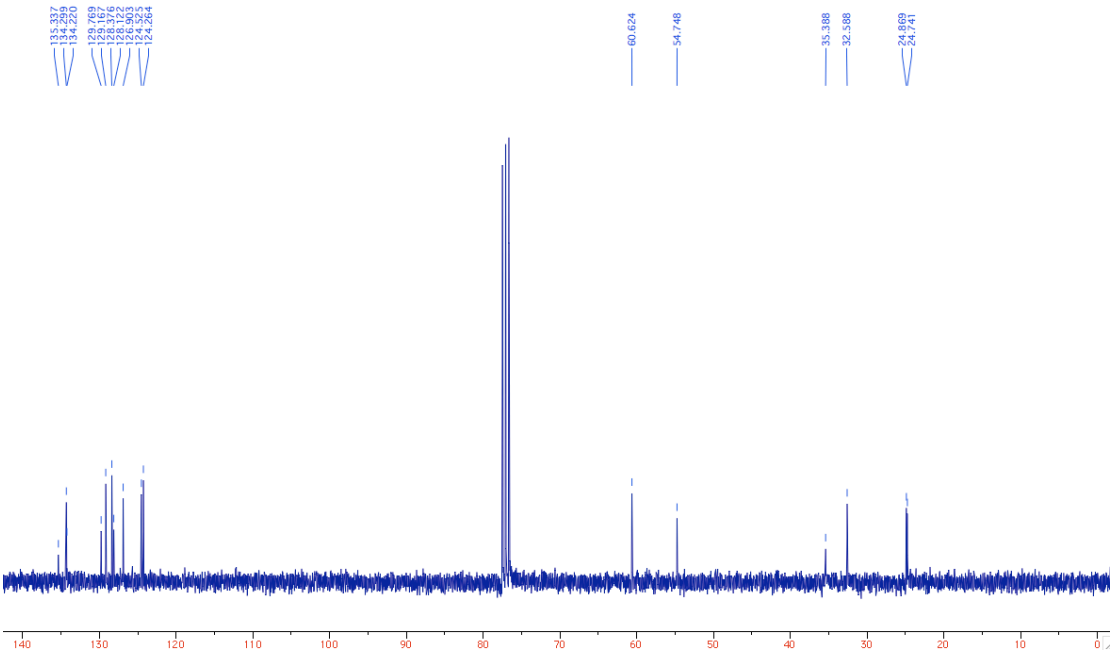
_N_-((1_R_,2_R_)-2-aminocyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (194b)



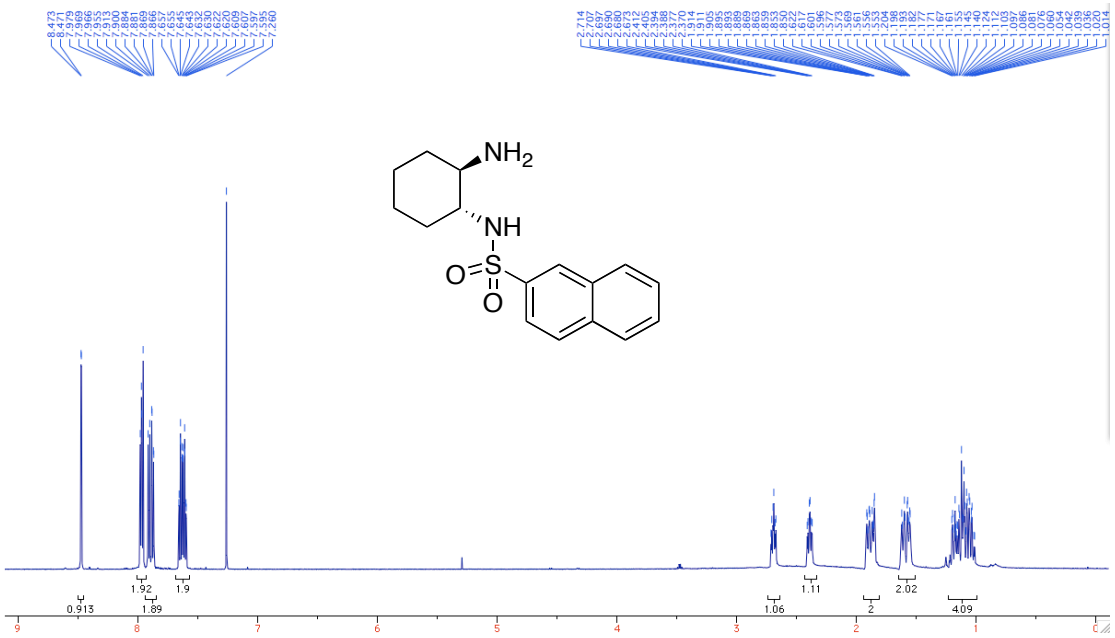


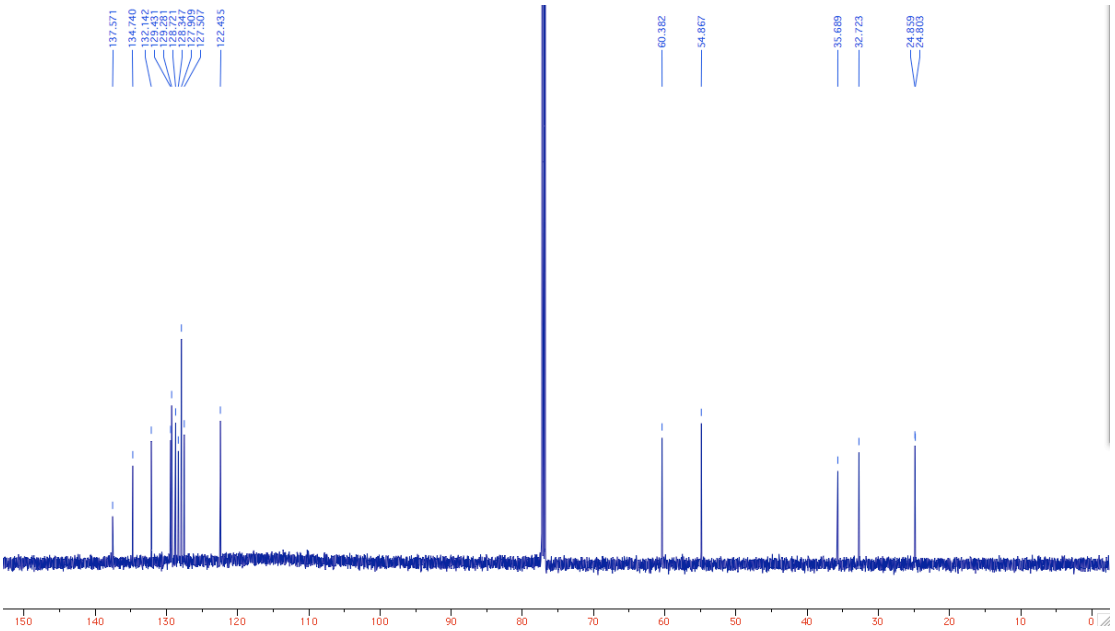
***N*-((1*R*,2*R*)-2-aminocyclohexyl)naphthalene-1-sulfonamide (194c)**



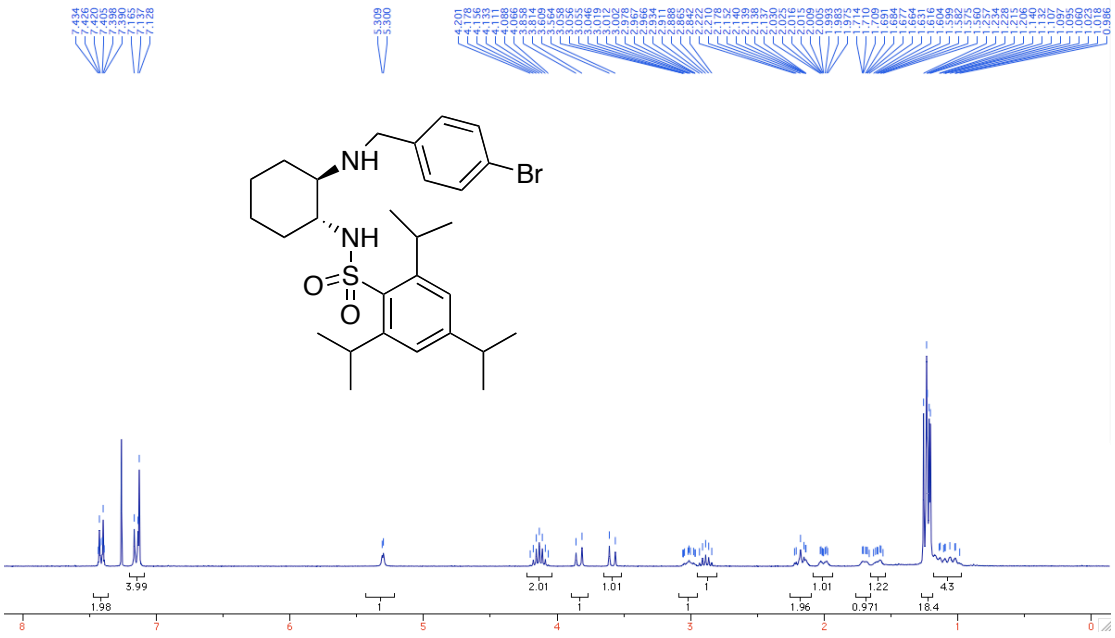


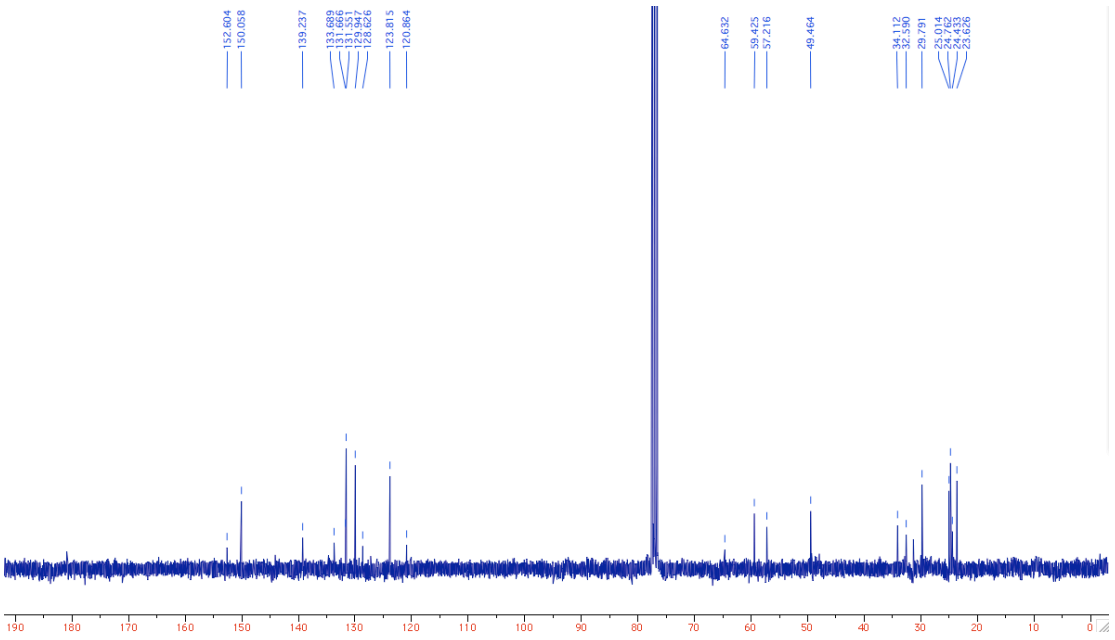
_N_-((1_R_,2_R_)-2-aminocyclohexyl)naphthalene-2-sulfonamide (194d)



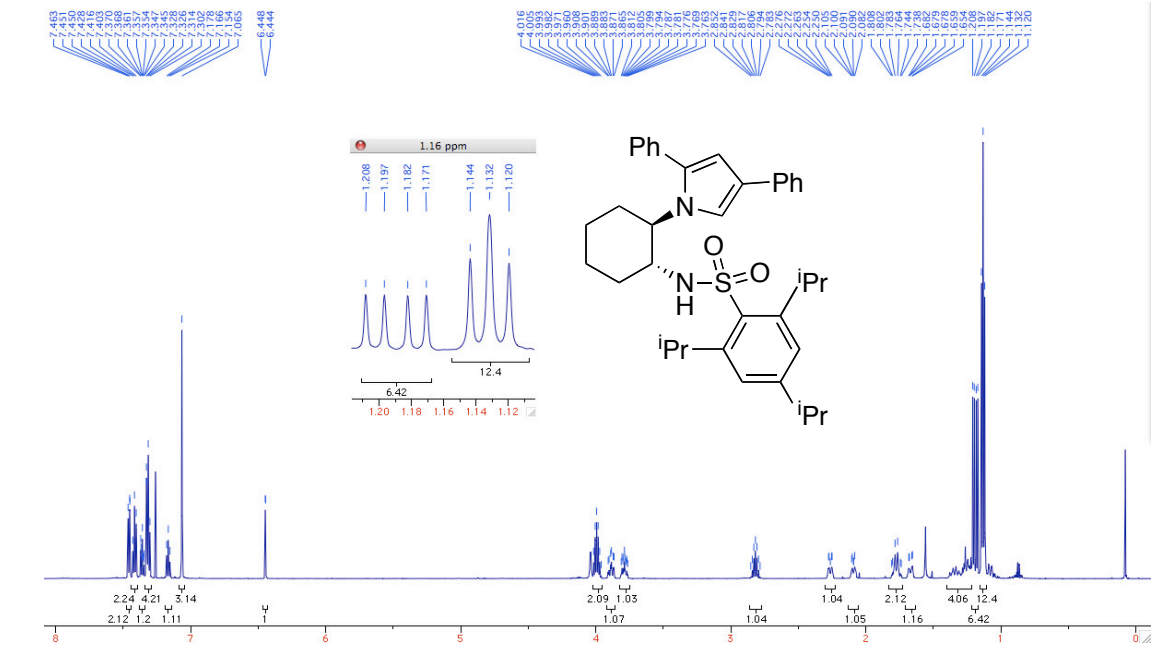


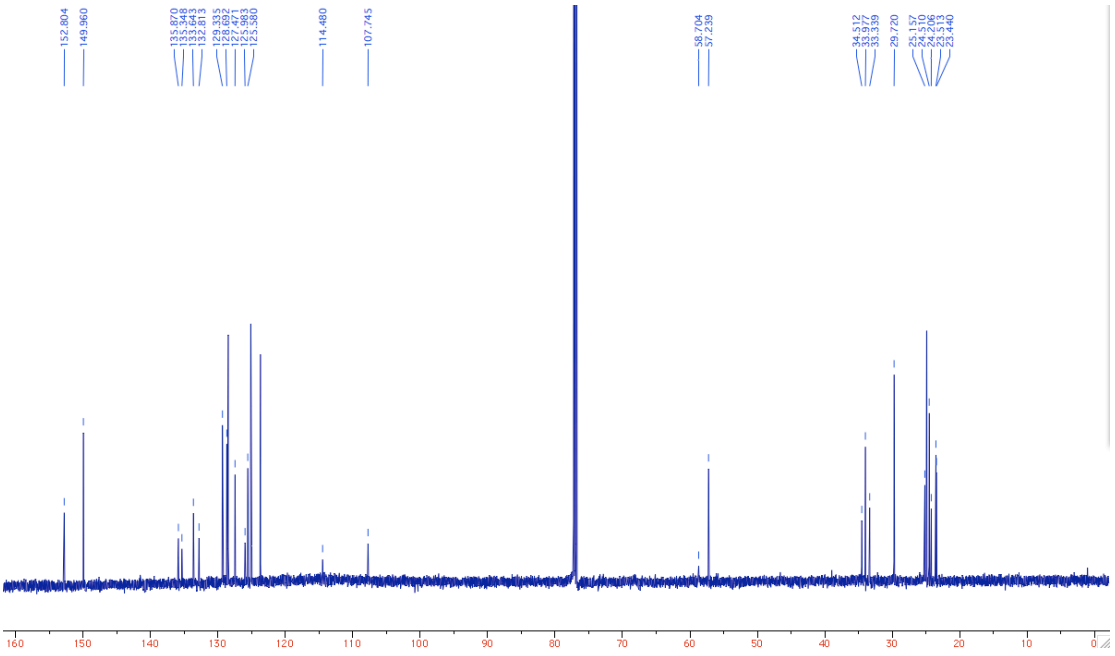
_N_-((1_R_,2_R_)-2-(4-bromobenzylamino)cyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (198)



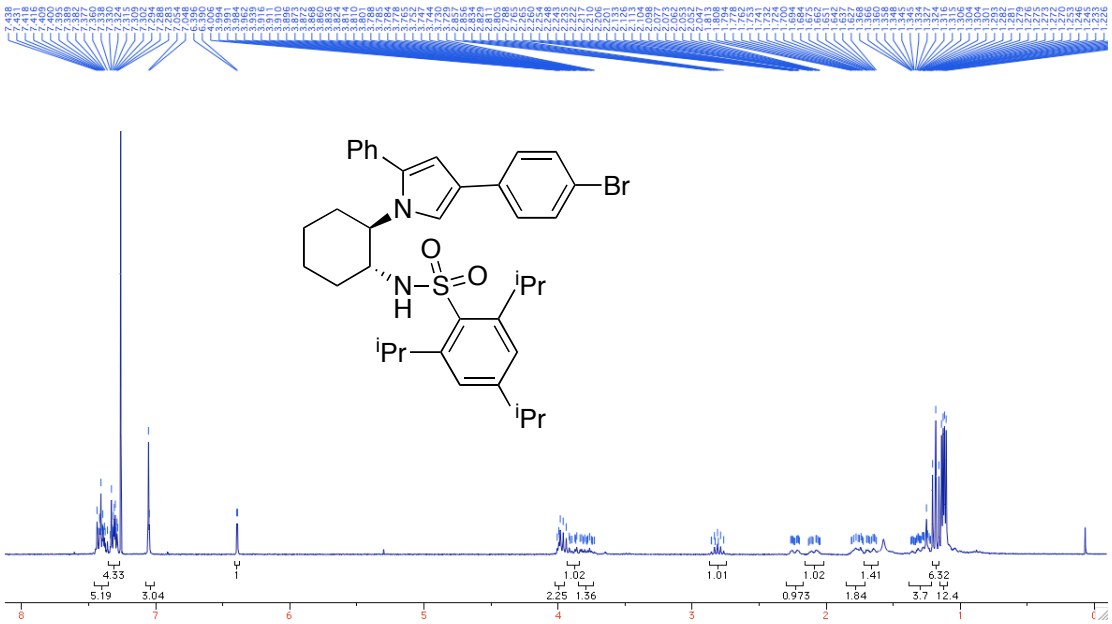


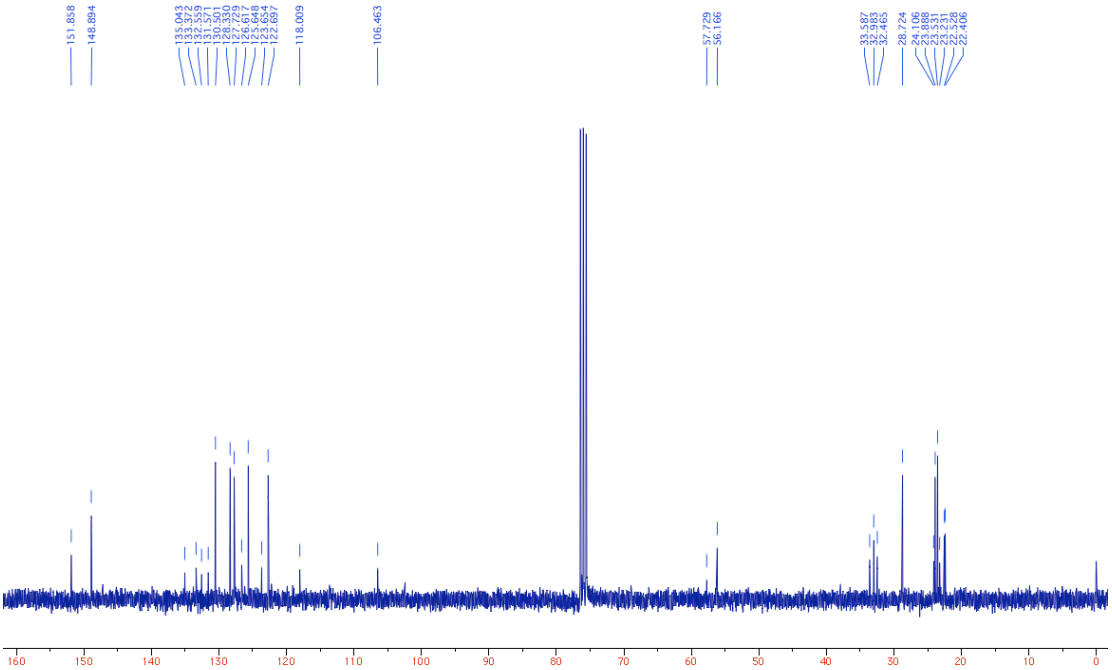
_N_-((1_R_,2_R_)-2-(2,4-diphenyl-1_H_-pyrrol-1-yl)cyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (200a)



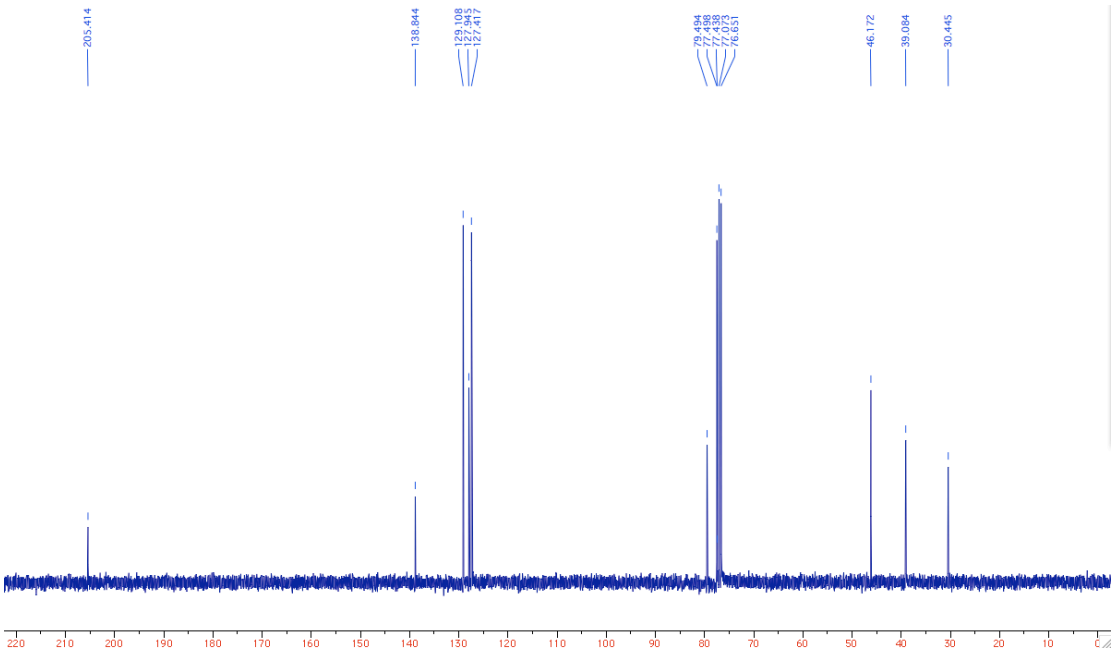


_N_-((1_R_,2_R_)-2-(4-(4-bromophenyl)-2-phenyl-1_H_-pyrrol-1-yl)cyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (200b)

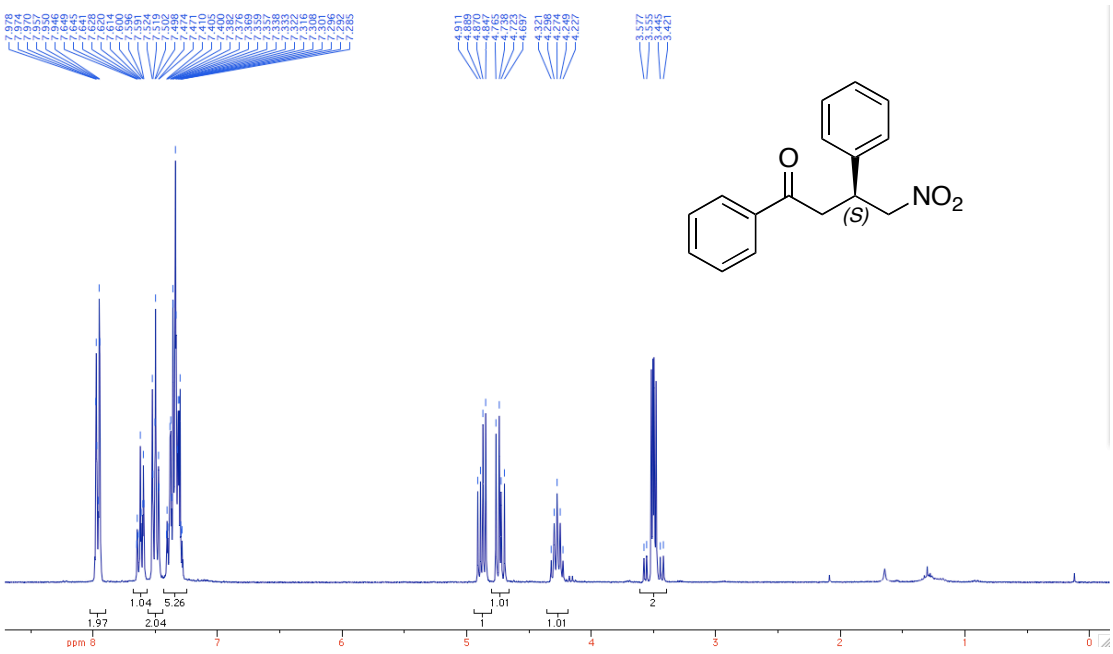


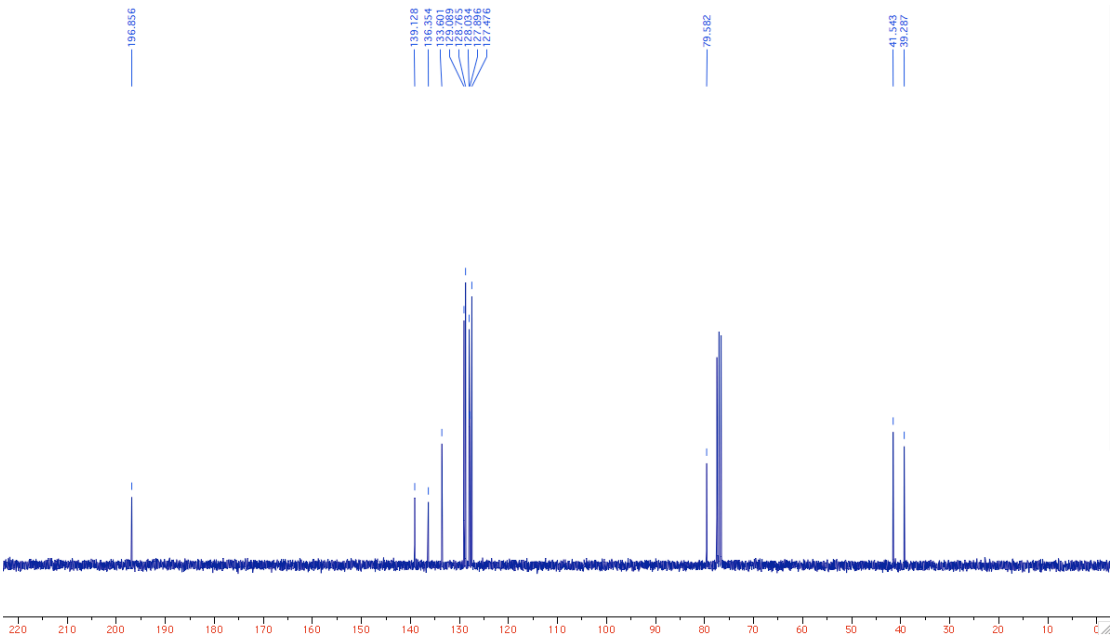


(*S*)-5-nitro-4-phenylpentan-2-one (199a)

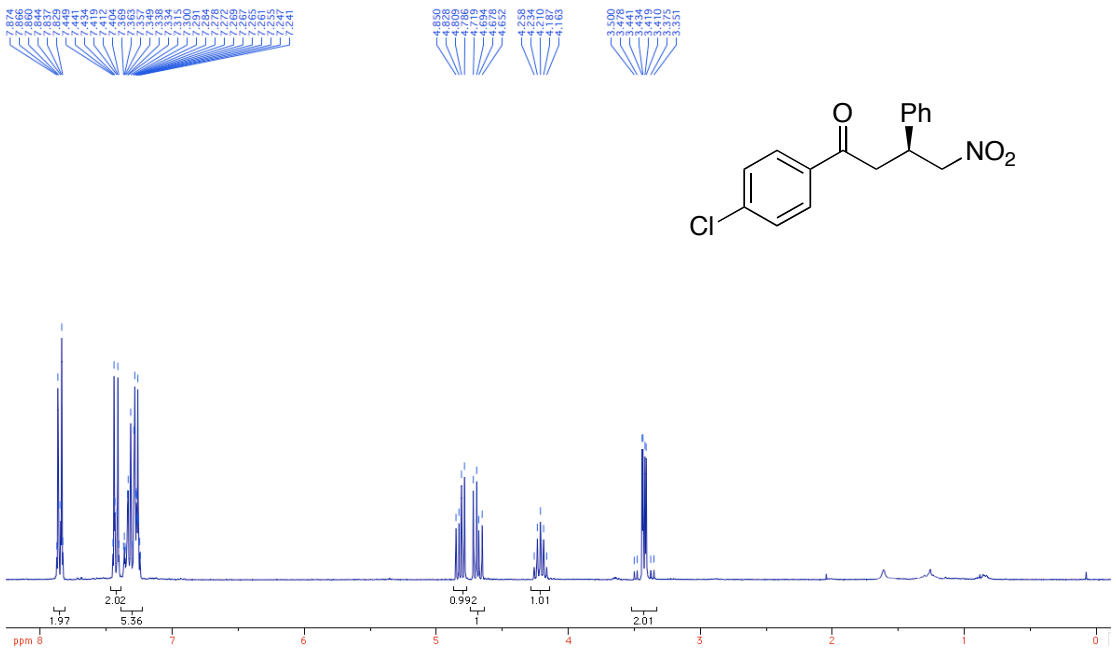


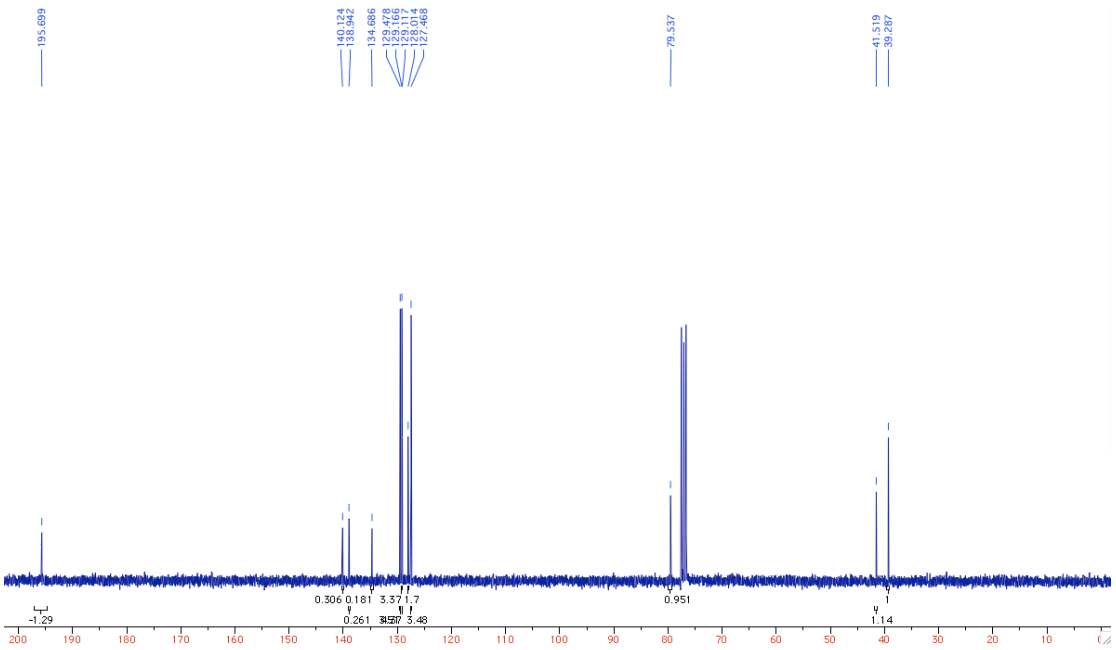
(*S*)-4-nitro-1,3-diphenylbutan-1-one (199b)



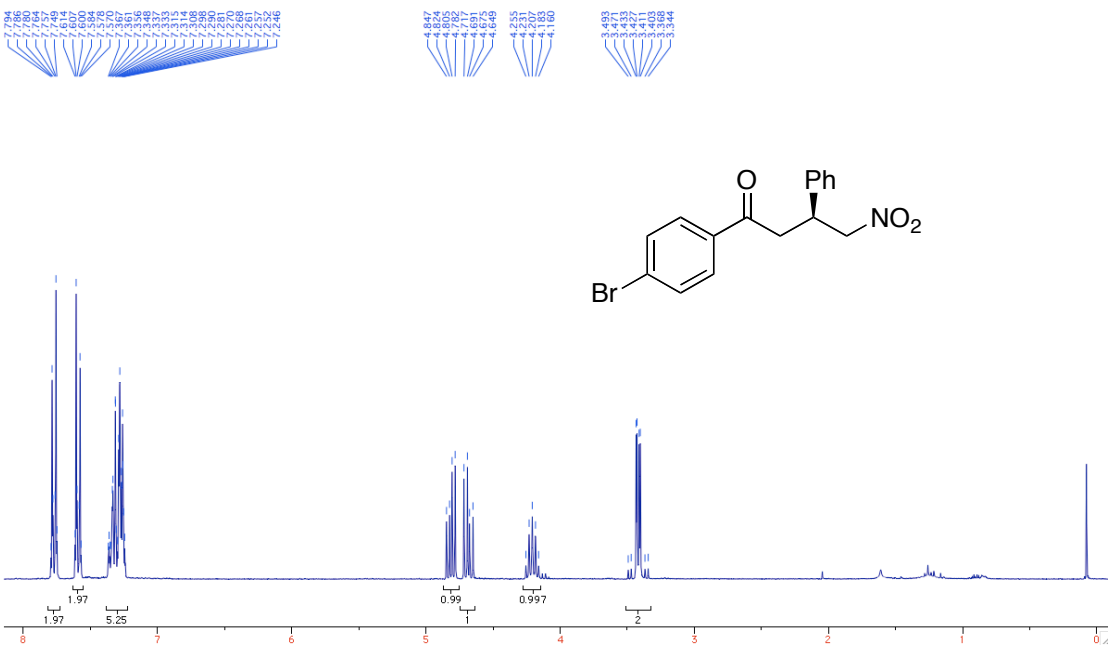


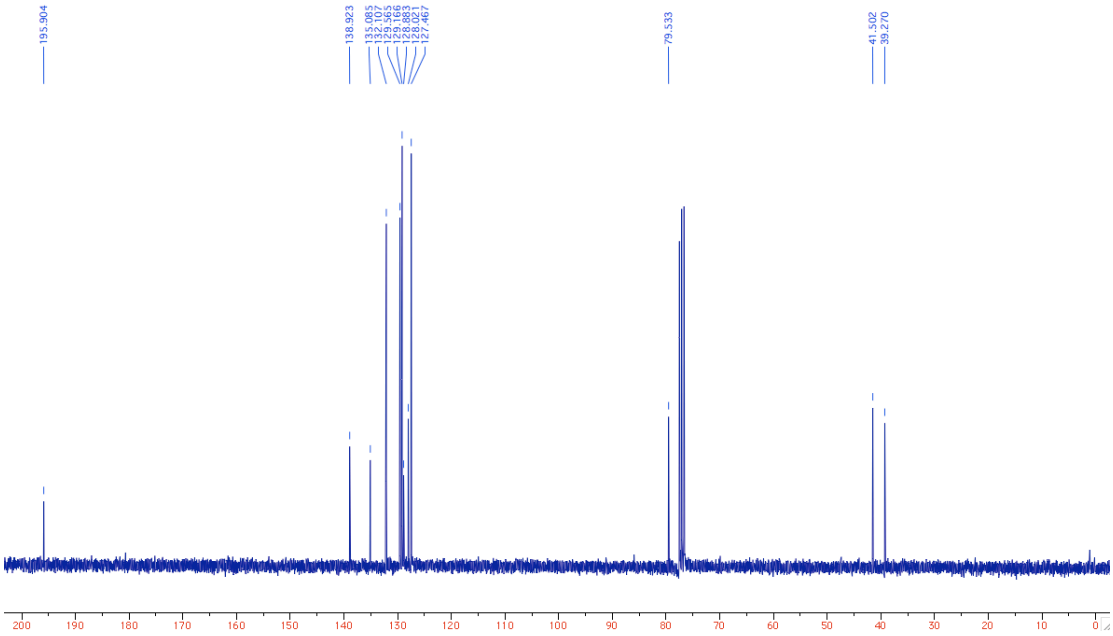
(*S*)-1-(4-chlorophenyl)-4-nitro-3-phenylbutan-1-one (199c)



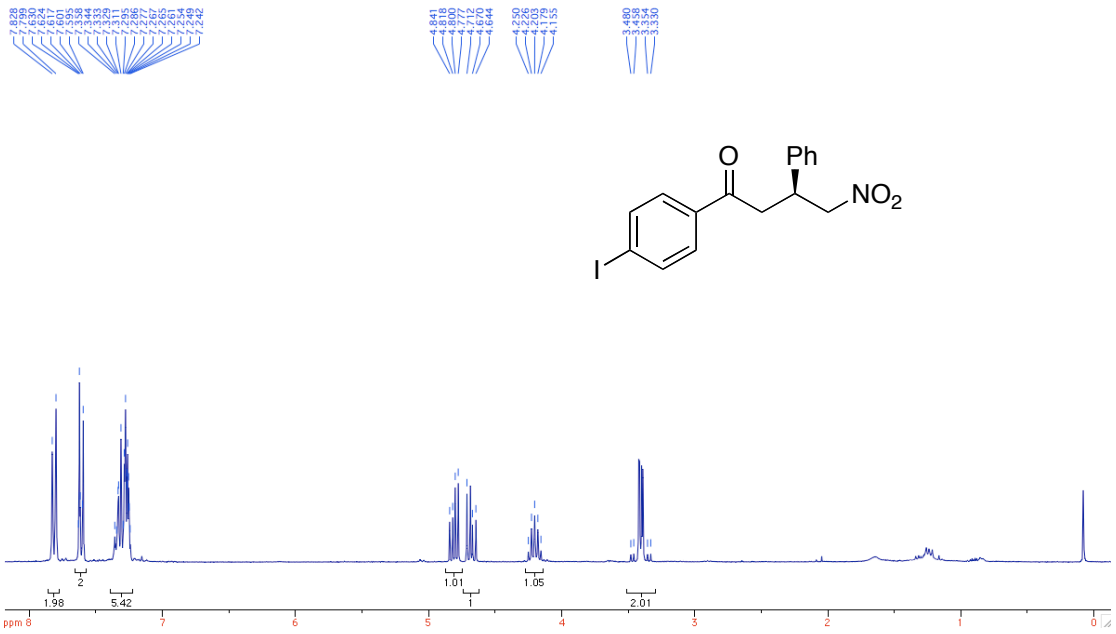


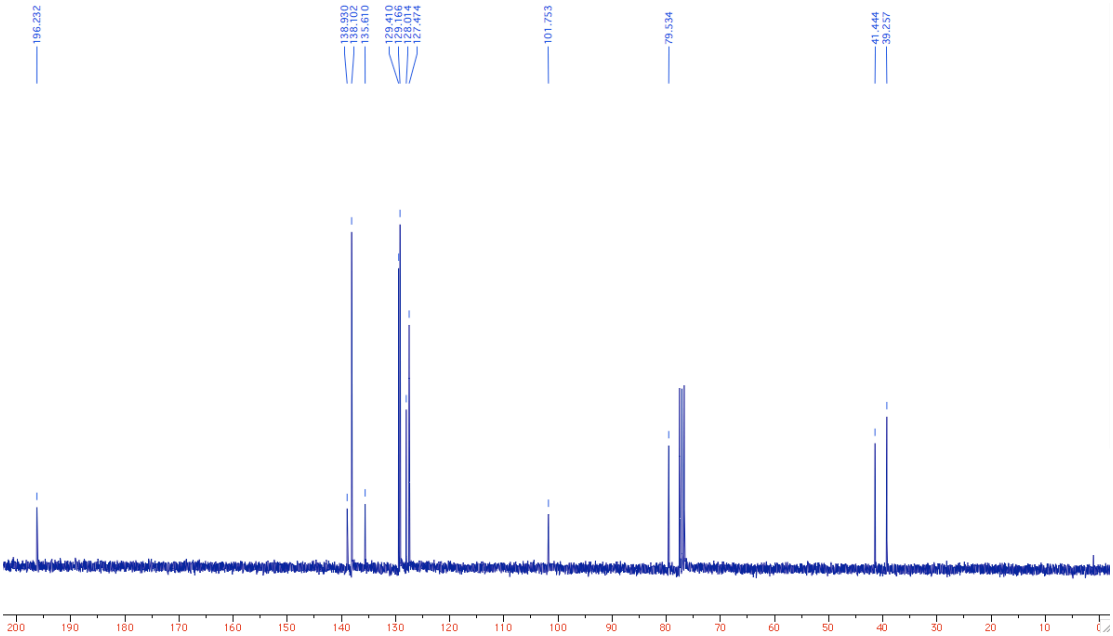
(*S*)-1-(4-bromophenyl)-4-nitro-3-phenylbutan-1-one (199d)



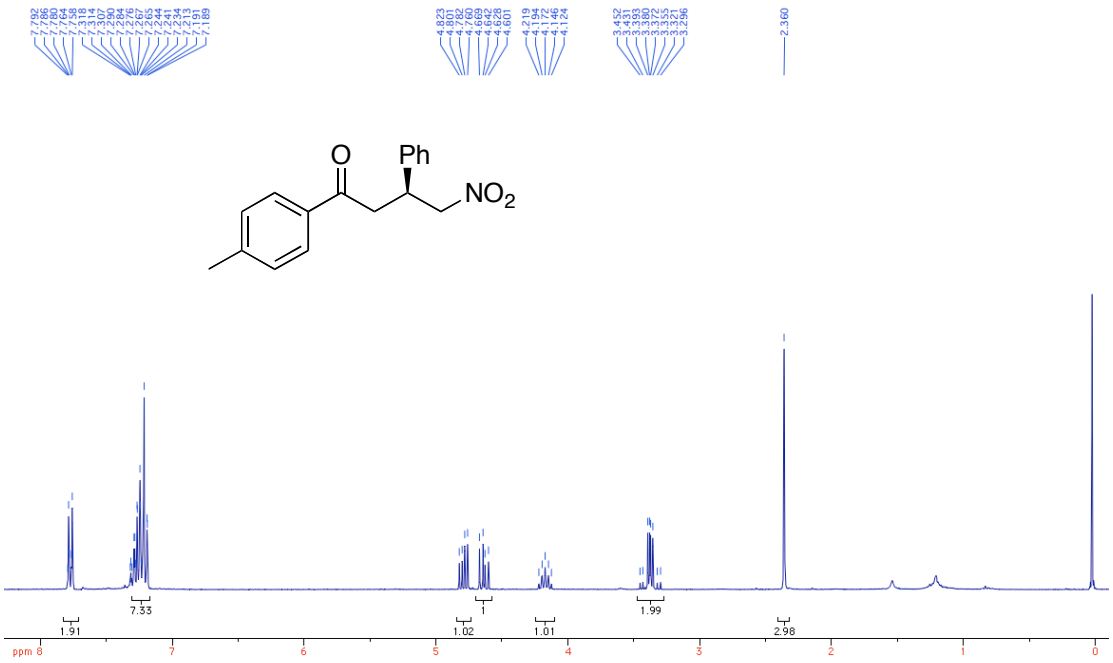


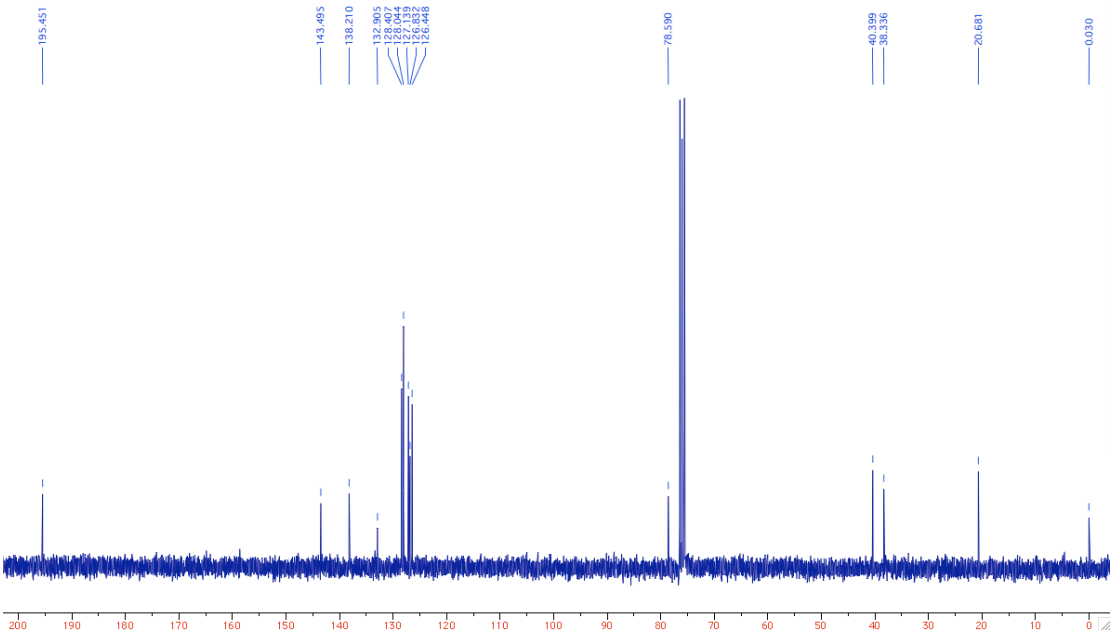
(*S*)-1-(4-iodophenyl)-4-nitro-3-phenylbutan-1-one (199e)



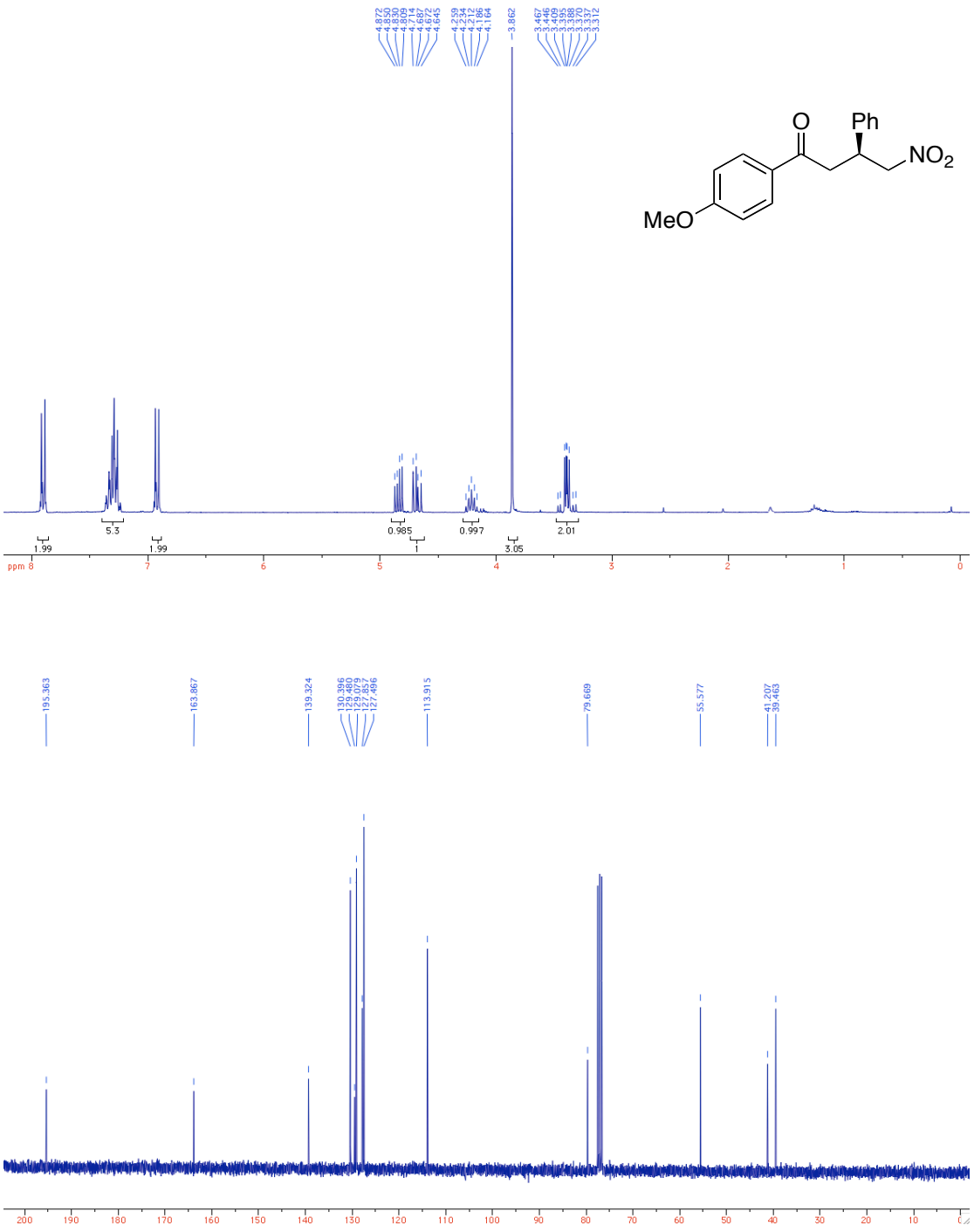


(*S*)-4-nitro-3-phenyl-1-*p*-tolylbutan-1-one (199f)

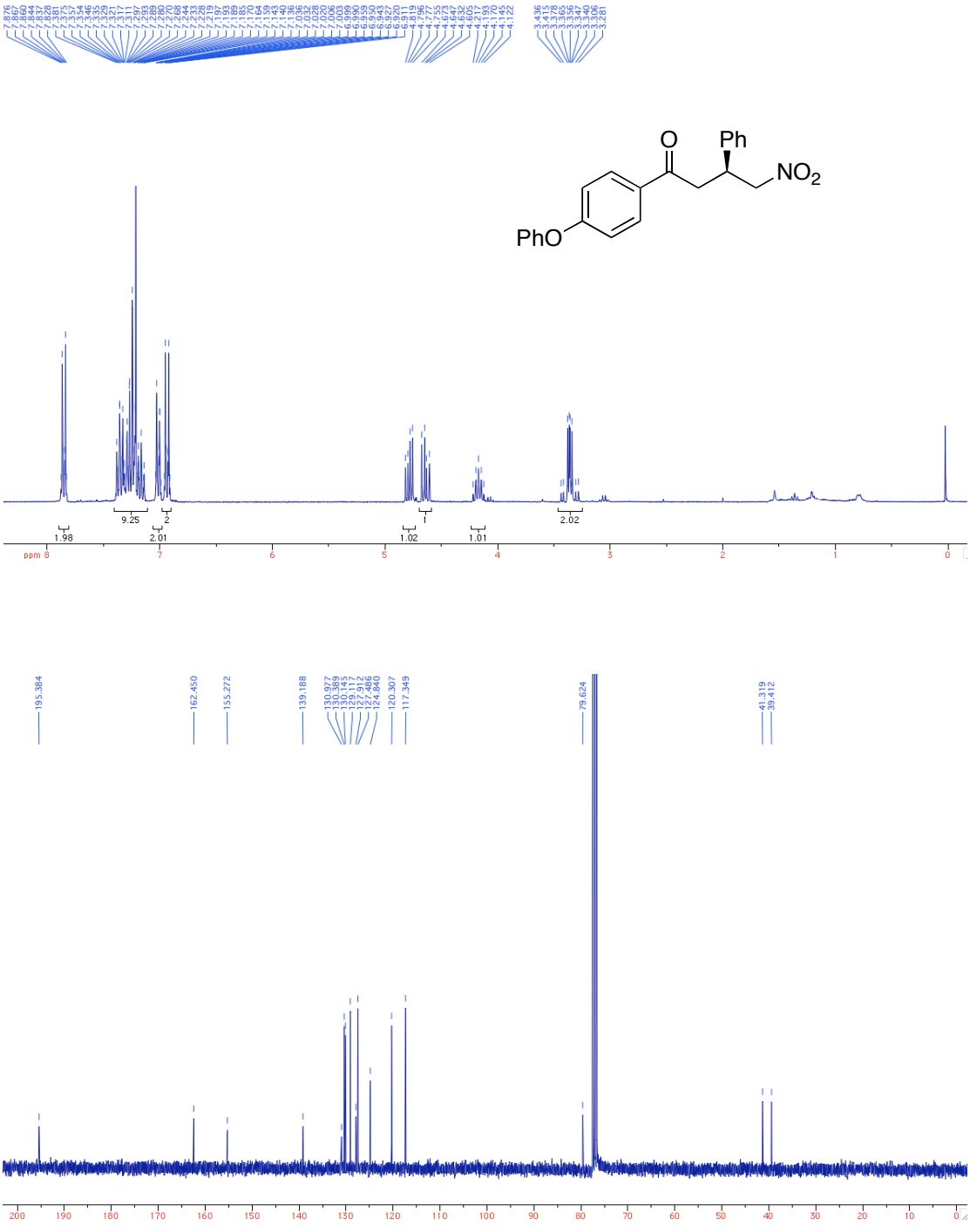




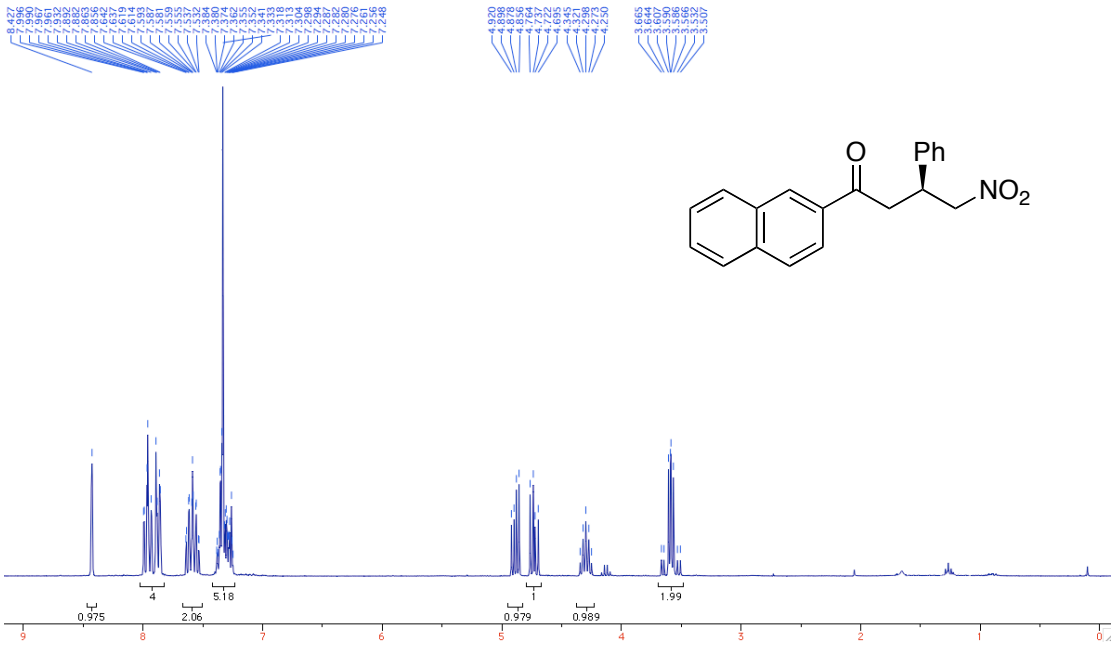
(*S*)-1-(4-methoxyphenyl)-4-nitro-3-phenylbutan-1-one (199g)

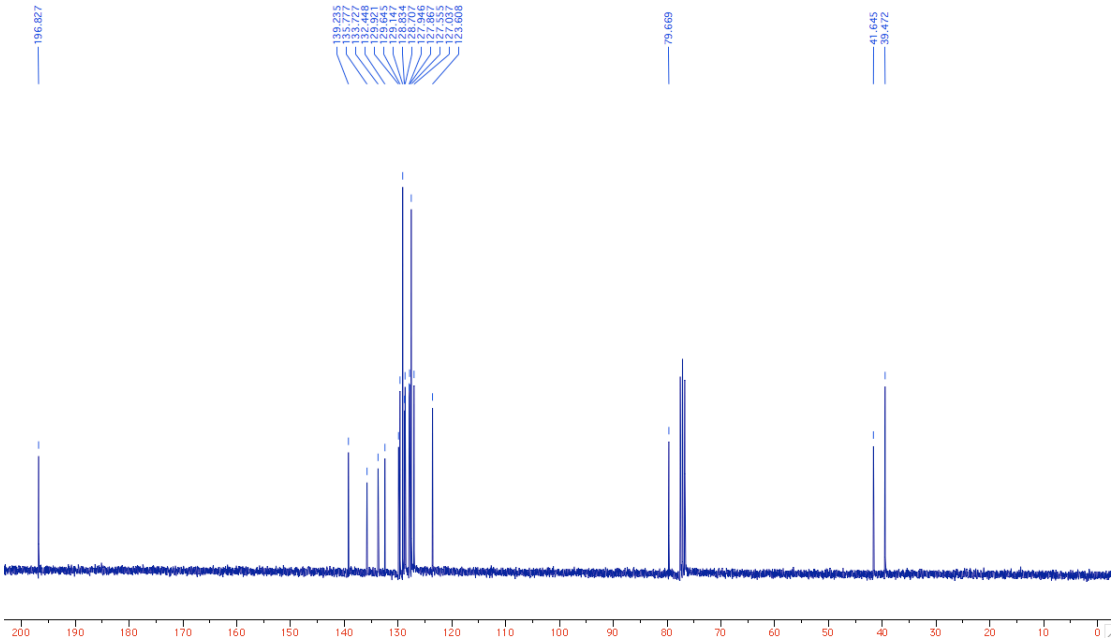


(*S*)-4-nitro-1-(4-phenoxyphenyl)-3-phenylbutan-1-one (199h)

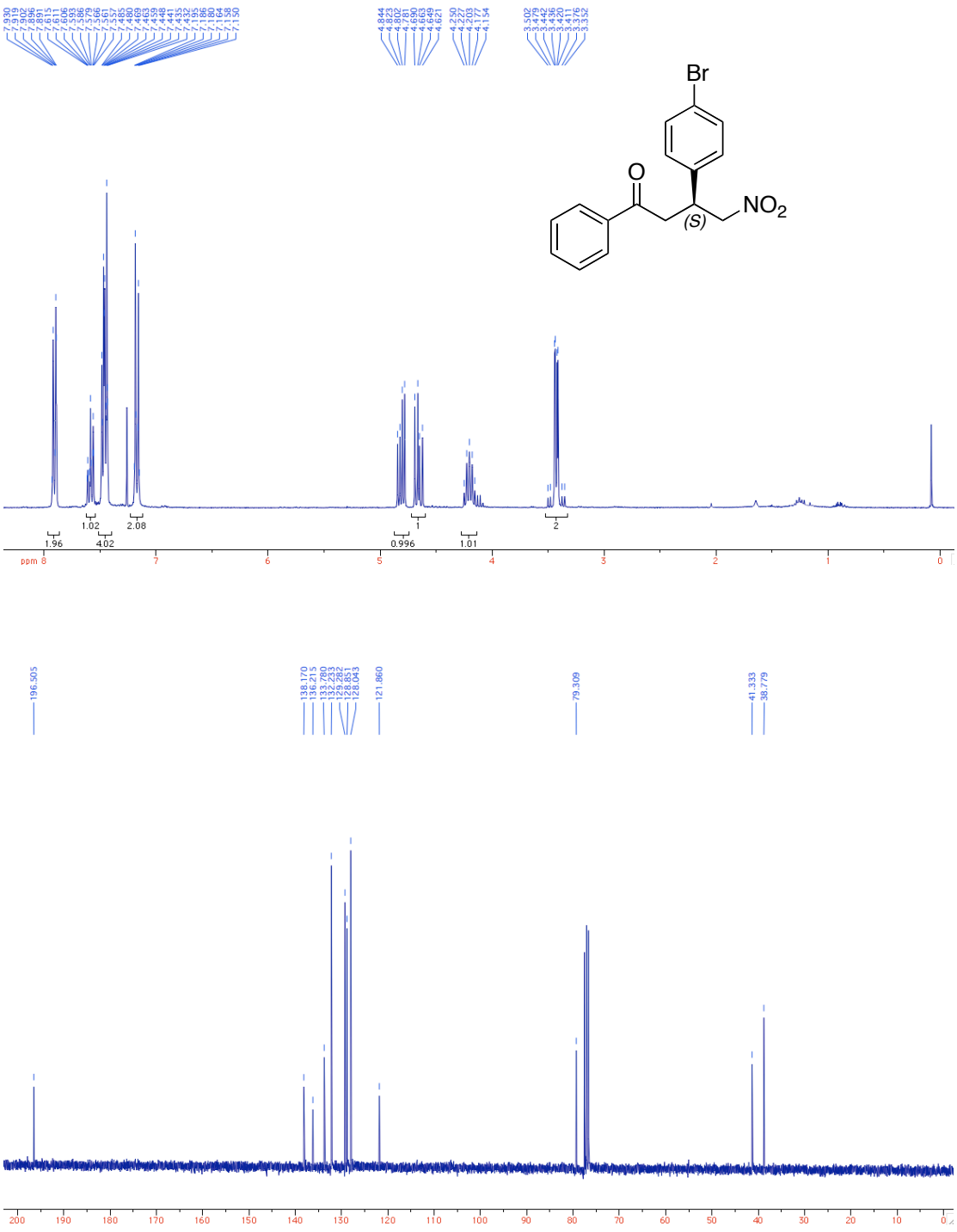


(*S*)-1-(naphthalen-2-yl)-4-nitro-3-phenylbutan-1-one (199i)

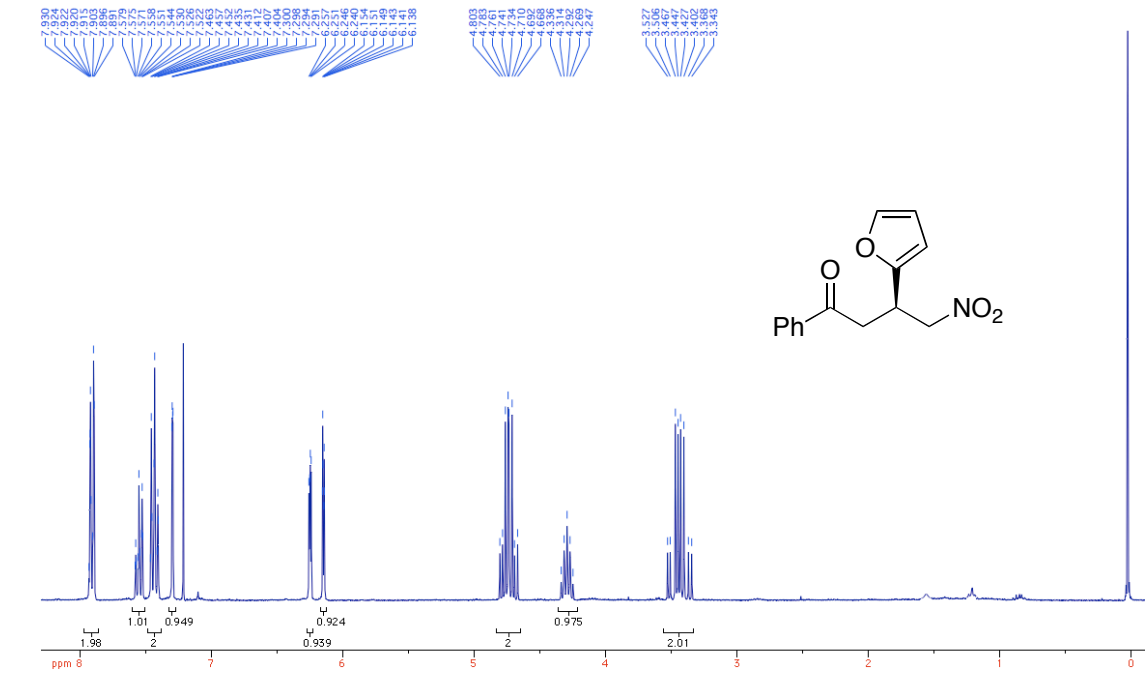


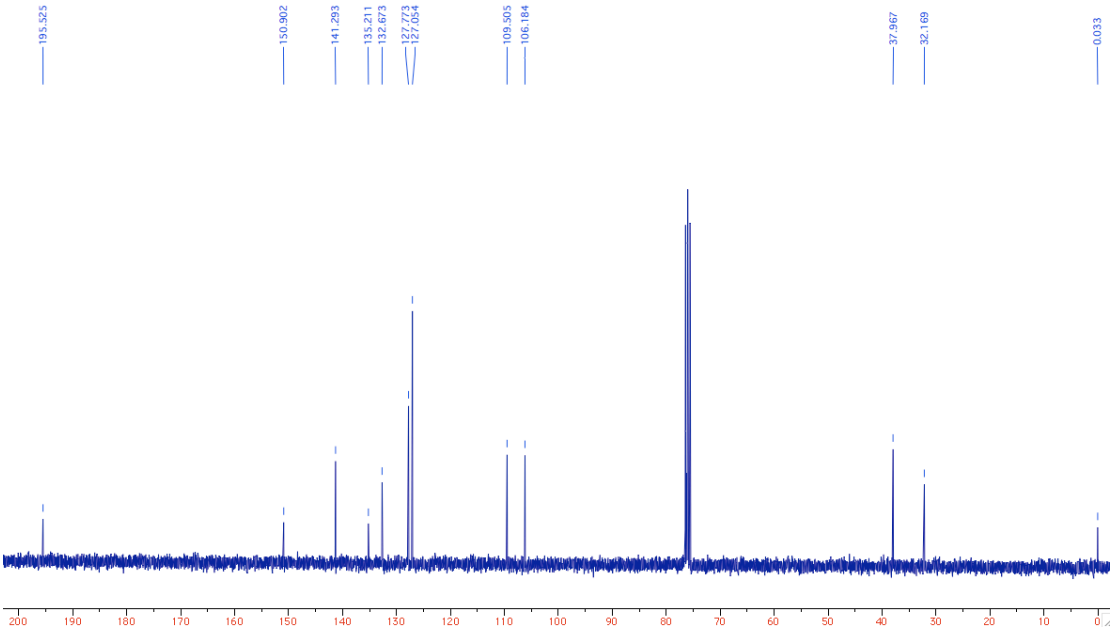


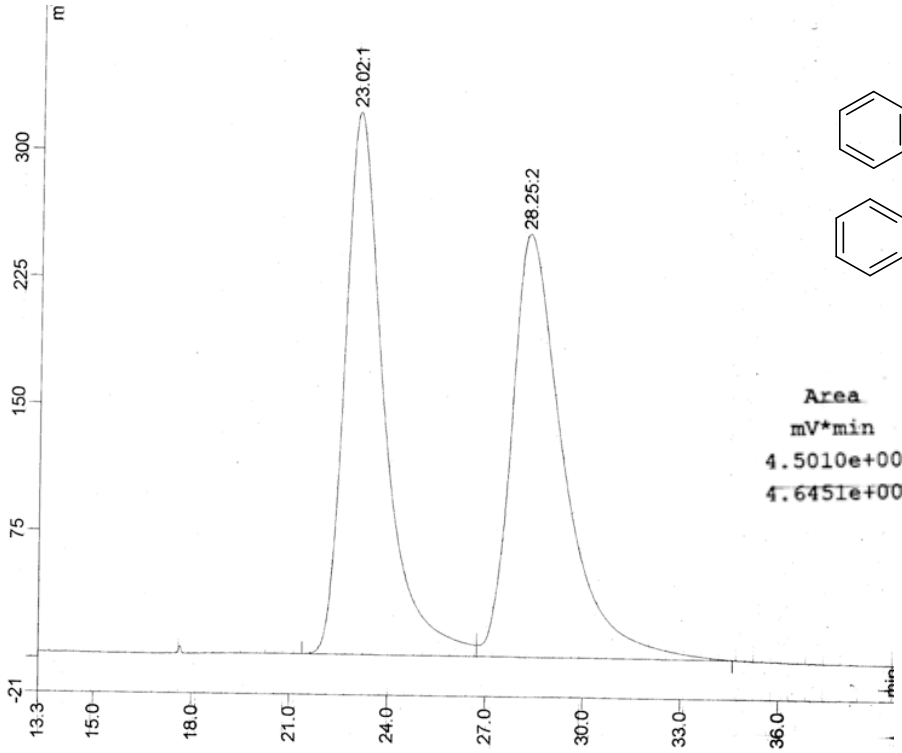
(*S*)-3-(4-bromophenyl)-4-nitro-1-phenylbutan-1-one (199j)

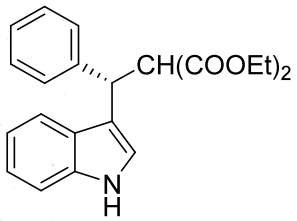


(*R*)-3-(furan-2-yl)-4-nitro-1-phenylbutan-1-one (199k)









Area	Amount	Rel.Ar
mV*min		%
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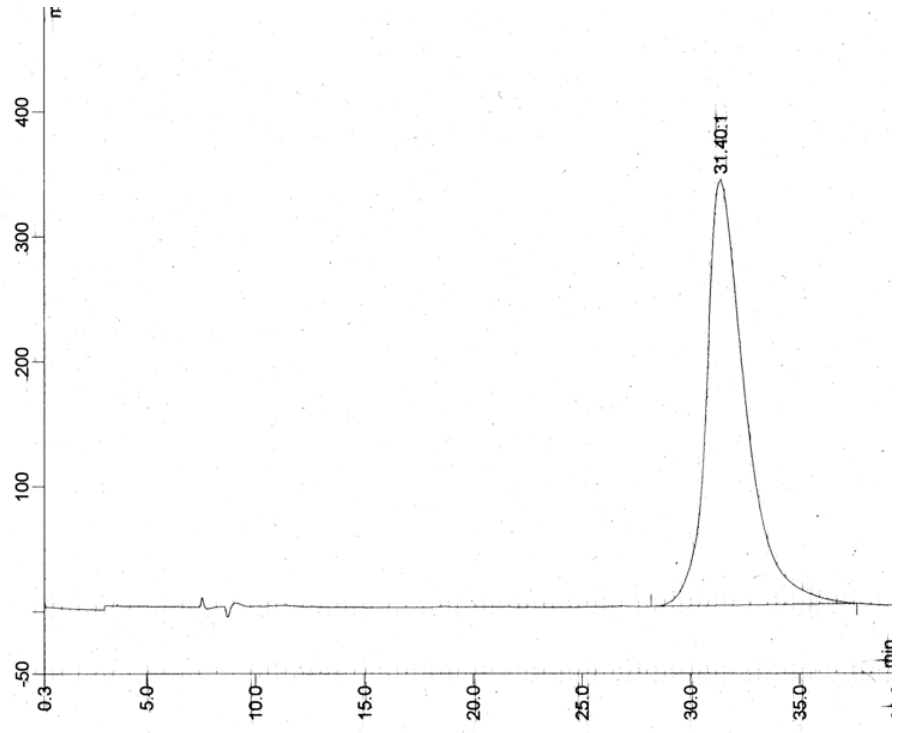
4.6451e+002	?	50.79



DATA SAVED TO BIN # 1

11-12-00 18:27 IN

FILE 1. METHOD 0. RUN 1

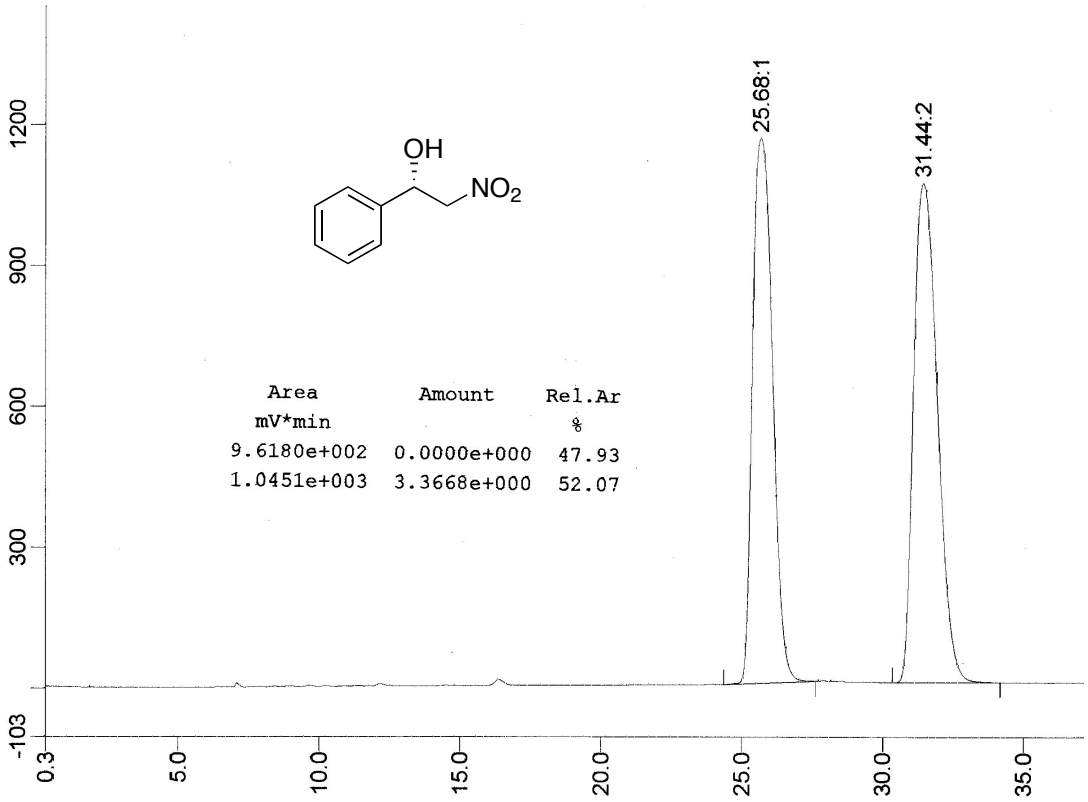
PEAK#	AREA%	RT	AREA	BC
1	0.002	0.81	57	02
2	98.73	0.87	2877057	02
3	0.055	1.06	1607	02
4	0.017	1.23	504	02
5	0.009	1.41	254	03
6	0.009	3.69	264	01
7	0.001	4.36	40	01
8	0.002	4.95	67	01
9	0.05	5.86	1470	02
10	0.009	7.04	271	02
11	0.002	7.08	50	03
12	0.007	7.45	203	01
13	0.001	7.77	33	01
14	0.003	8.13	91	01
15	0.007	9.25	218	01
16	0.002	9.57	50	01
17	0.035	10.09	1019	01
18	0.002	10.87	58	01
19	0.004	11.14	124	01
20	0.004	11.33	104	01
21	0.006	34.85	171	01
22	0.477	126.1	13903	01
23	0.564	128.34	16441	01
TOTAL	100.		2914056	

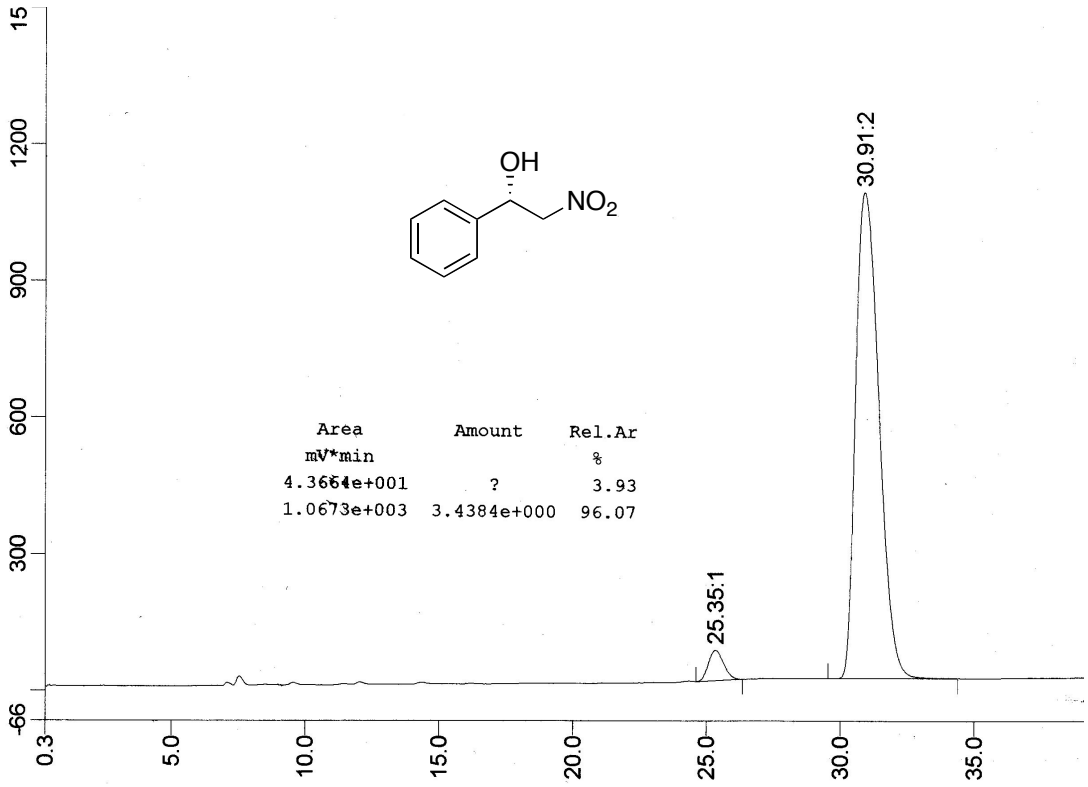
INPUT OVERRANGE AT RT= 0.92

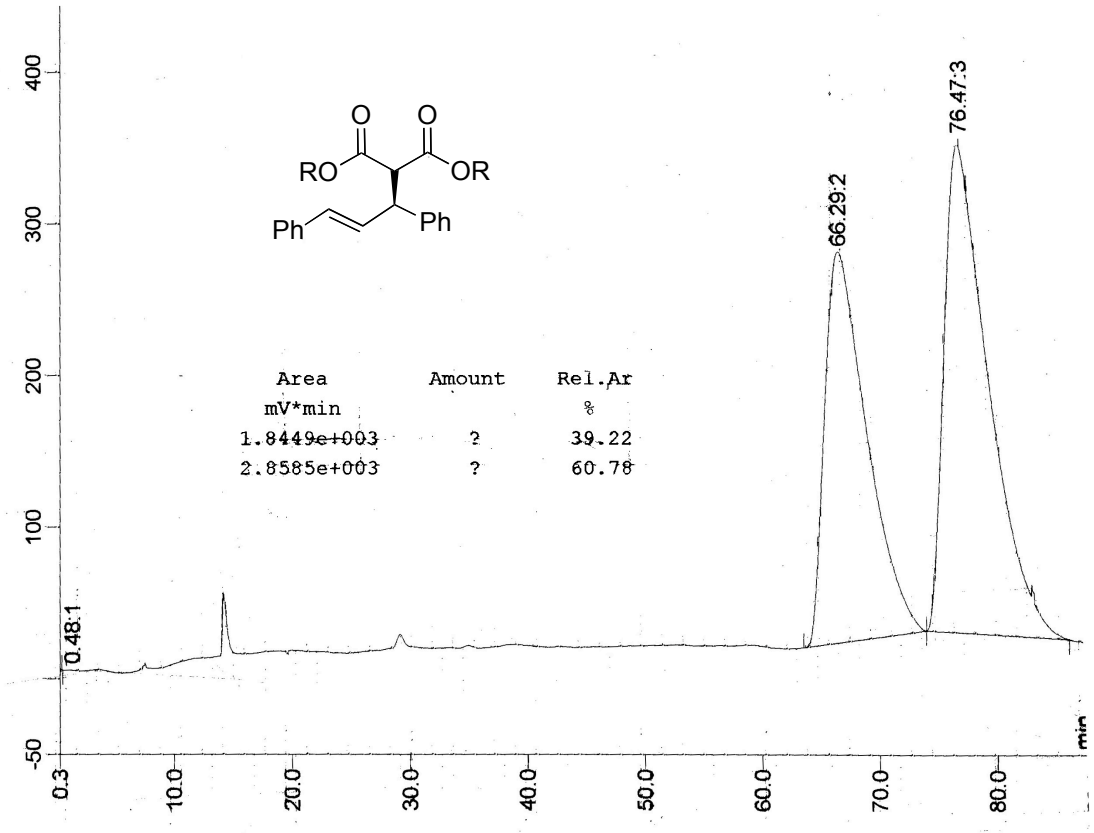
13-07-06 11:35:02

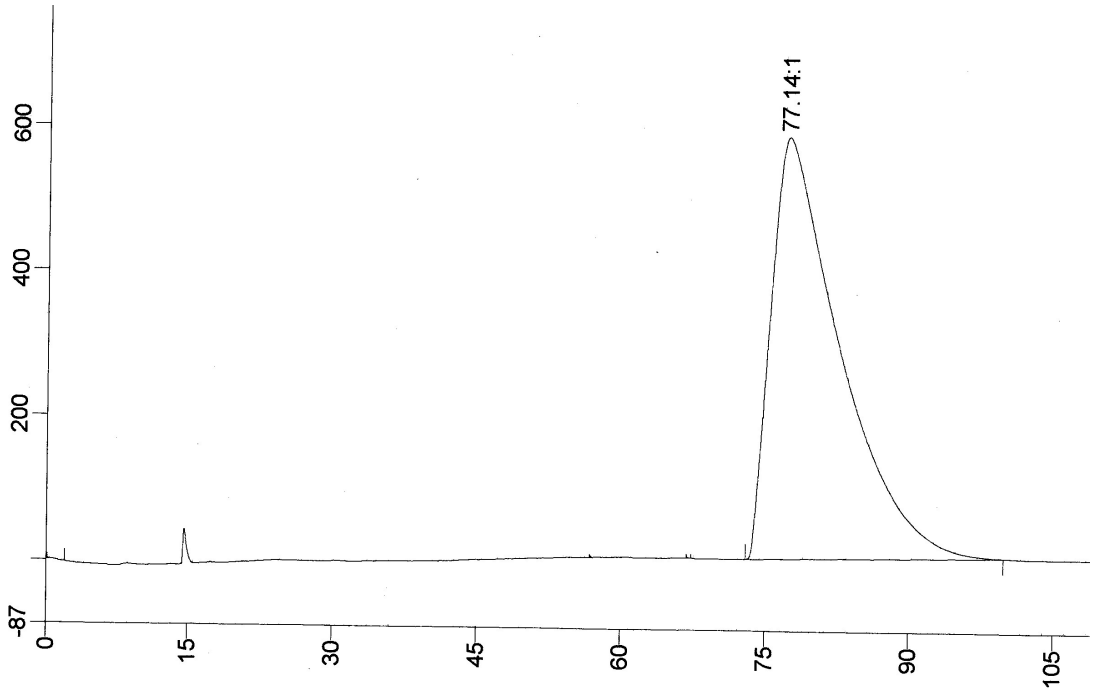
FILE 1. METHOD 0. RUN 1 INDEX

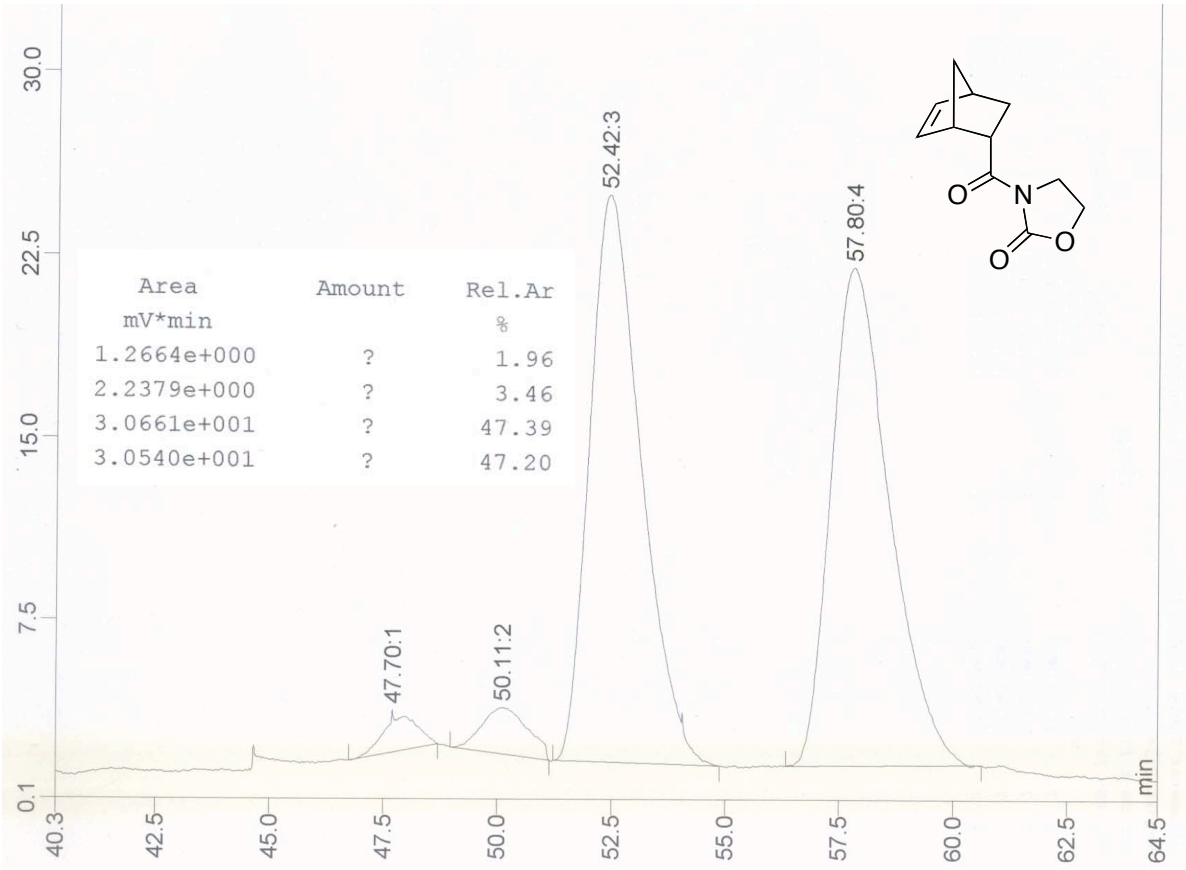
PEAK#	AREA%	RT	AREA	BC
1	99.472	0.91	5399281	02
2	0.09	1.28	4878	03
3	0.002	4.4	90	01
4	0.002	4.98	87	01
5	0.004	7.48	213	01
6	0.006	9.28	340	01
7	0.013	10.11	690	01
8	0.001	11.21	77	01
9	0.002	11.36	108	01
10	0.408	126.09	22169	01


OH
NO2
25.68:1
31.44:2
Area
mV*min
9.6180e+002
1.0451e+003
Amount
0.0000e+000
3.3668e+000
Rel.Ar
%
47.93
52.07
1200
900
600
300
-103
0.3
5.0
10.0
15.0
20.0
25.0
30.0
35.0


OH
NO2
30.91:2
25.35:1
Area
mV*min
4.3654e+001
1.0673e+003
Amount
?
3.4384e+000
Rel.Ar
%
3.93
96.07
15
1200
900
600
300
-66
0.3
5.0
10.0
15.0
20.0
25.0
30.0
35.0


O
O
RO
OR
Ph
Ph
66.29:2
76.47:3
0.48:1
Area
mV*min
1.8449e+003
2.8585e+003
Amount
?
?
Rel.Ar
%
39.22
60.78
400
300
200
100
-50
0.3
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
min


77.14:1
600
400
200
-87
0
15
30
45
60
75
90
105


Area
mV*min
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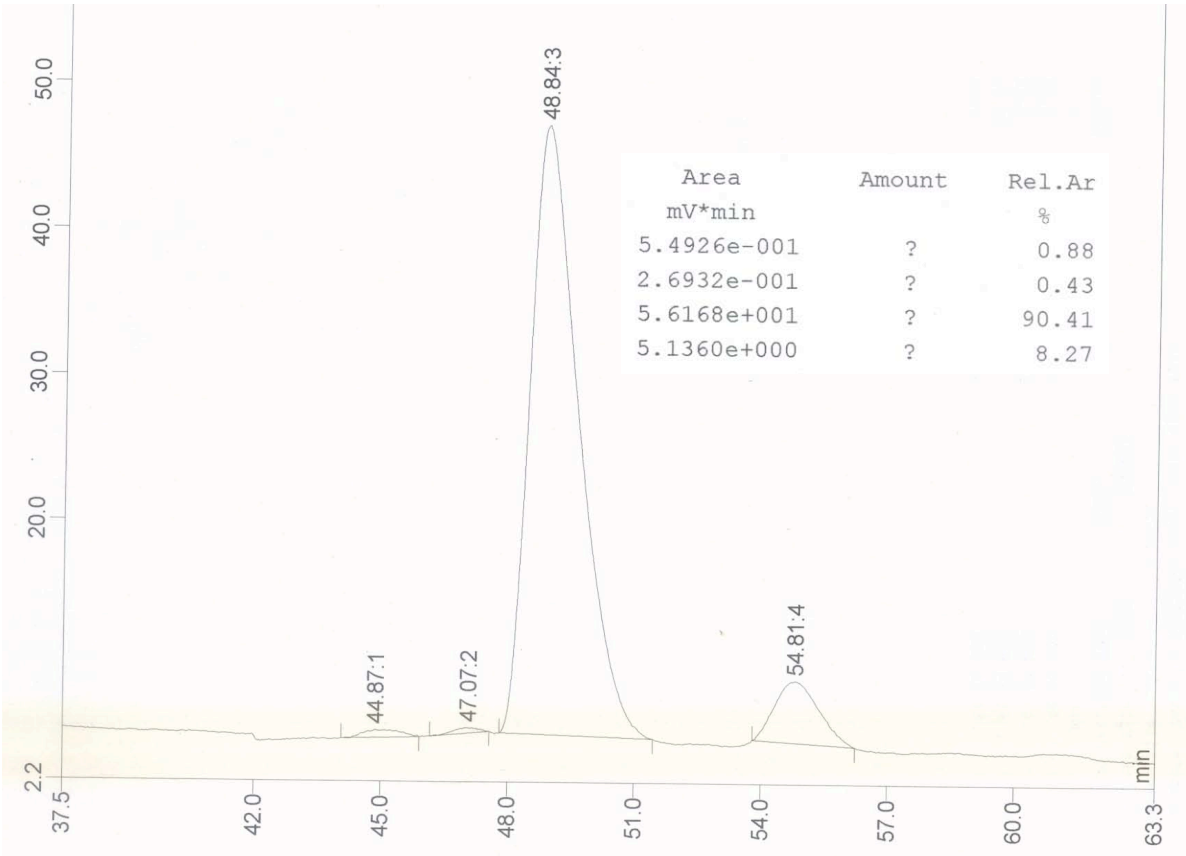
2.2379e+000
3.0661e+001
3.0540e+001
Amount
?
?
?
?
Rel.Ar
%
1.96
3.46
47.39
47.20
47.70:1
50.11:2
52.42:3
57.80:4
O
N
O
O
30.0
22.5
15.0
7.5
0.1
40.3
42.5
45.0
47.5
50.0
52.5
55.0
57.5
60.0
62.5
64.5
min


Area
mV*min
5.4926e-001
2.6932e-001
5.6168e+001
5.1360e+000
Amount
?
?
?
?
Rel.Ar
%
0.88
0.43
90.41
8.27
44.87:1
47.07:2
48.84:3
54.81:4
50.0
40.0
30.0
20.0
2.2
37.5
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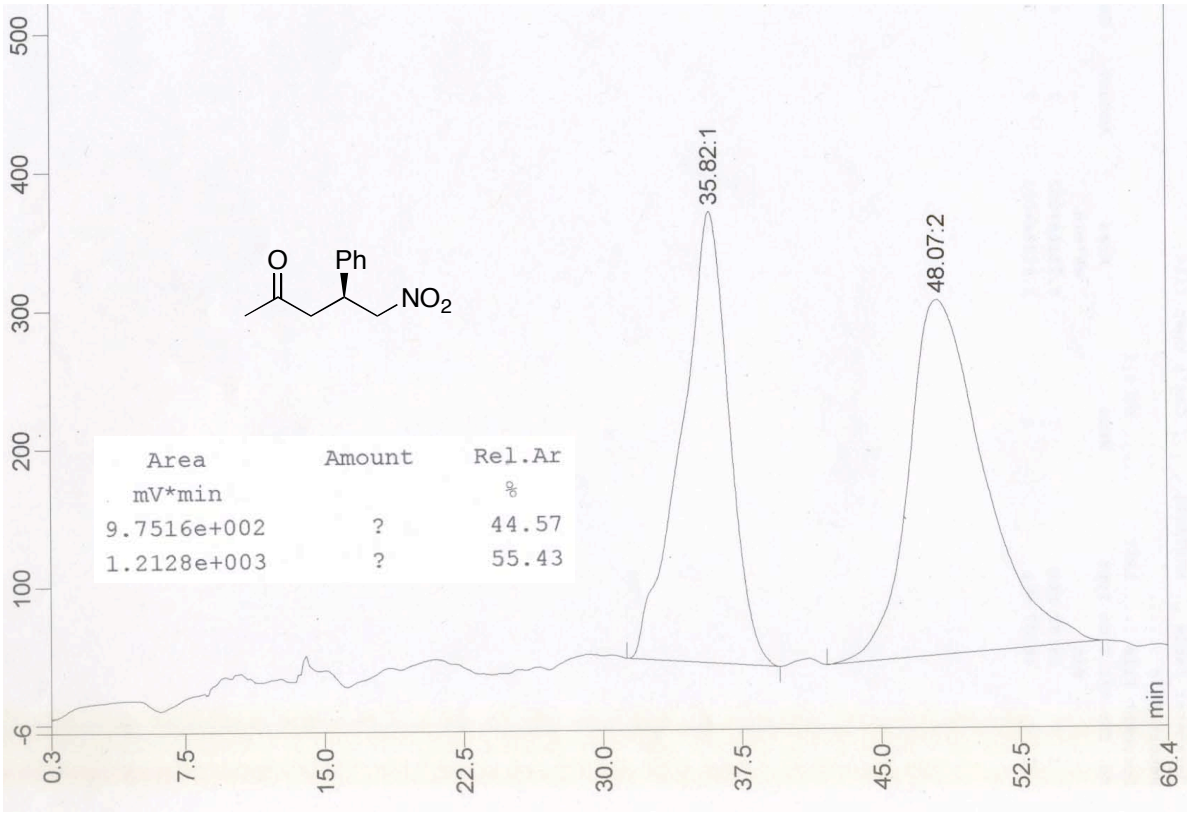
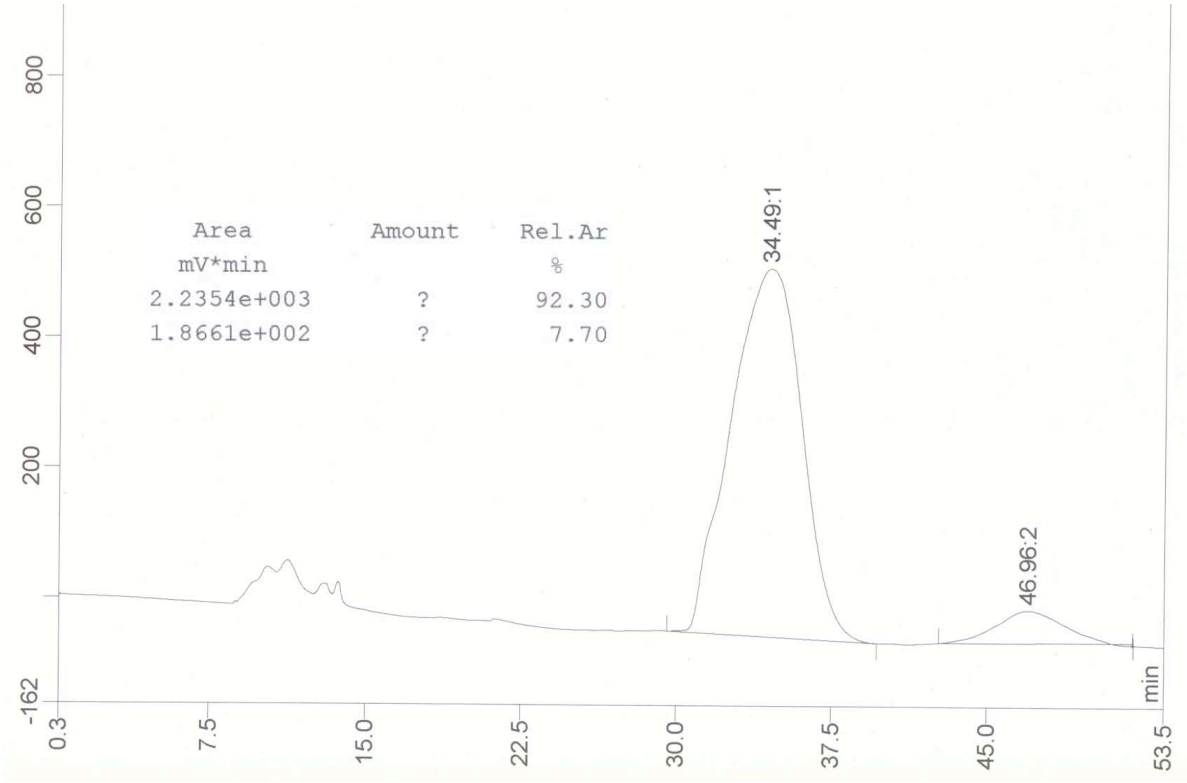
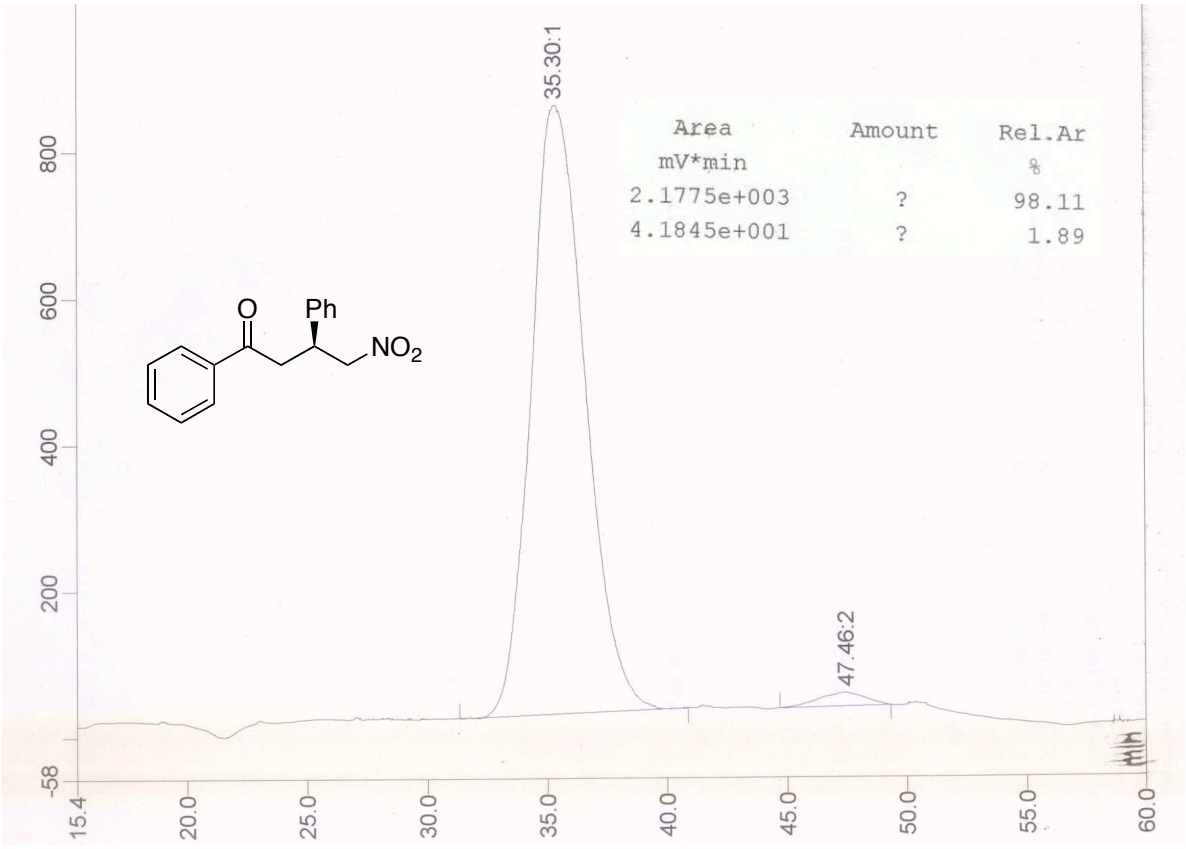
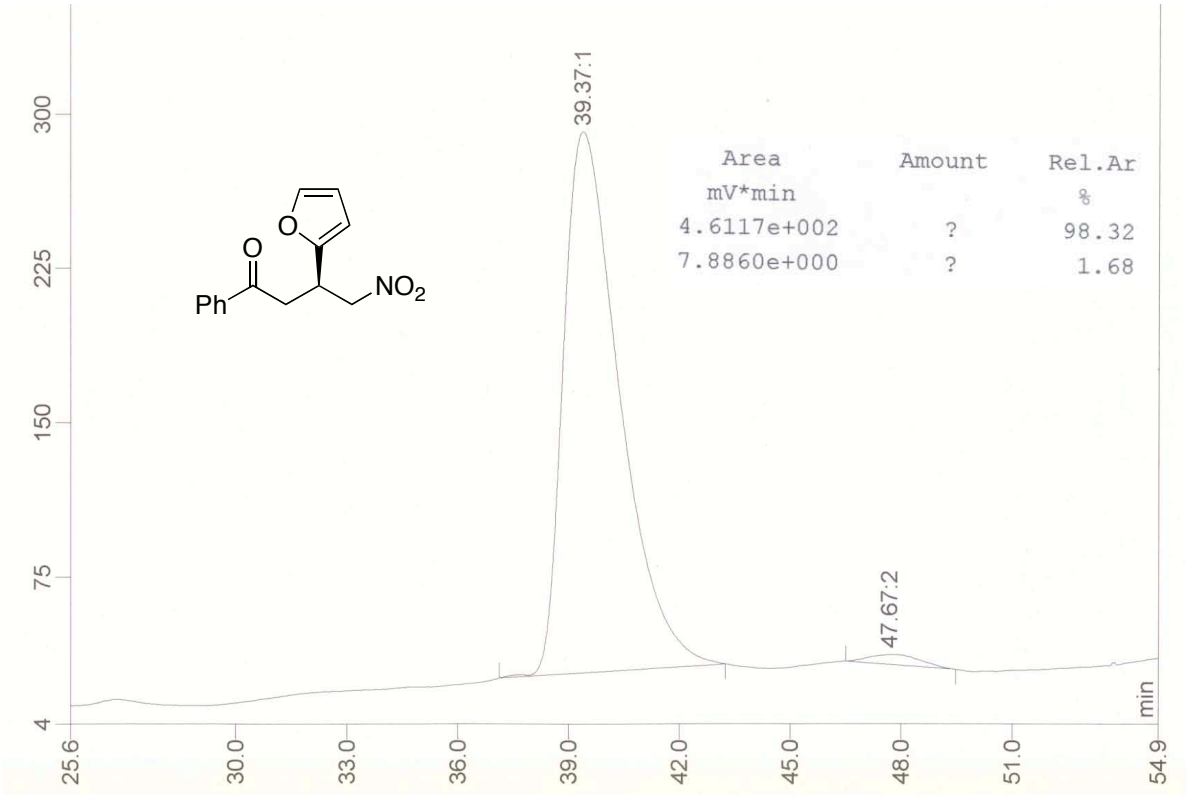
51.0
54.0
57.0
60.0
63.3
min


O
Ph
NO2
35.82:1
48.07:2
Area
mV*min
Amount
Rel.Ar
%
9.7516e+002
?
44.57
1.2128e+003
?
55.43
500
400
300
200
100
-6
0.3
7.5
15.0
22.5
30.0
37.5
45.0
52.5
60.4
min


34.49:1
46.96:2
Area
mV*min
Amount
Rel.Ar
%
2.2354e+003
?
92.30
1.8661e+002
?
7.70
800
600
400
200
-162
0.3
7.5
15.0
22.5
30.0
37.5
45.0
53.5
min


35.30:1
47.46:2
Area
mV*min
2.1775e+003
4.1845e+001
Amount
?
?
Rel.Ar
%
98.11
1.89
O
Ph
NO2
800
600
400
200
-58
15.4
20.0
25.0
30.0
35.0
40.0
45.0
50.0
55.0
60.0
min


39.37:1
47.67:2
Area
mV*min
4.6117e+002
7.8860e+000
Amount
?
?
Rel.Ar
%
98.32
1.68
O
O
Ph
NO2
300
225
150
75
4
25.6
30.0
33.0
36.0
39.0
42.0
45.0
48.0
51.0
54.9
min

Acknowledgement

It's a great pleasure and immense satisfaction in expressing my deep gratitude towards my research supervisor Prof. Dr. Oliver Reiser for introducing me to an exciting area of contemporary organic synthesis. His constructive guidance, suggestions, support and freedom made me to inspire and move further in research.

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CURRICULUM VITAE

RAMESH RASAPPAN

C/o Prof. Dr. Oliver Reiser
Institute of Organic Chemistry
University of Regensburg
D-93053, Regensburg, Germany
Tel.: +49-9419434647
Fax: +49-9419434121
ramesh.rasappan@chemie.uni-regensburg.de

S/o P. Rasappan
B-15 Kallangadu st.
Pandamangalam
Namakkal, Tamilnadu
India, Pin: 637208
Tel.: +91-4268230709
prramesh@gmail.com

Academic Record

March 2009	Ph.D (Asymmetric Catalysis)	Institute of Organic Chemistry University of Regensburg D-93053, Regensburg, Germany
April 2005	Project	Department of Organic Chemistry Indian Institute of Science Bangalore, India.
April 2003	M.Sc (Organic chemistry)	Department of Organic Chemistry University of Madras Chennai-26, India.
April 2001	B.Sc (Chemistry)	Department of Chemistry Periyar University Namakkal, India

Awards/Fellowships and Recognitions

- **DAAD** Ph.D fellowship awarded by DAAD, Bonn, Germany
- **GATE** (2003) **- 96.73** Percentiles awarded by IIT's and IISc
- **CSIR** (2003) - **Lectureship** awarded by Council of Scientific and Industrial Research

Professional Affiliation

- Member of Nanocat; International Nanocat committee, Munich, Germany

Research Interest

- Designing and synthesis of new chiral ligands
- Novel asymmetric reactions and methodologies
- Organocatalysis
- Immobilization and recycling of chiral ligands

Research Experience

10/2005 – 03/2009	Ph.D thesis	Prof. Dr. Oliver Reiser Institute of Organic Chemistry **University of Regensburg, Germany**

Asymmetric Catalysis: Synthesis and exploration of chiral aza-bis(oxazolines) and organocatalysts in asymmetric reactions.

09/2003 - 04/2005	Project	Prof. Dr. N. Jayaraman Department of Organic chemistry **Indian Institute of Science, Bangalore**

Supramolecules: Synthesis of water-soluble dendrimers and its application in photochemical reactions.

07/2002- 07/2003	Master thesis	Prof. Dr. R. Raghunathan Department of Organic Chemistry **University of Madras, India.**

1,3-Dipolar cycloaddition: Synthesis of novel dispiro heterocycles in a one-pot method using azomethine ylide as an effective dipole

Research Publications

9. **Rasappan, R**.; Chinnusamy, T.; Hilgers, P.; Reiser, O., Highly efficient recyclable fluorous tag Immobilized azabox in distinct asymmetric reactions.
Adv.Synth.Catal. Manuscript in preparation.

8. **Rasappan, R**.; Reiser, O., Cyclohexane-1,2-diamines: Efficient Catalysts for the Enantioselective Conjugate Addition of Ketones to Nitro Olefins.
European Journal of Organic Chemistry **2009**, ASAP.

7. Schätz, A.; **Rasappan**, R.; Hager, M.; Gissibl, A.; Reiser, O., Dependence of Enantioselectivity on Ligand/Metal-Ratio in the Asymmetric Michael Addition of Indole to Benzylidene Malonates: Electronic Influence of Substrate
Chemistry - A European Journal **2008**, *14*, 7259-7265.

6. **Rasappan, R**.; Laventine, D.; Reiser, O., Metal-bis(oxazoline) complexes: From coordination chemistry to asymmetric catalysis.
Coordination Chemistry Reviews **2008**, *252*, 702-714.

5. Gissibl, A.; Padie, C.; Hager, M.; Jaroschik, F.; **Rasappan, R**.; Cuevas-Yanez, E.; Turrin, C. O.; Caminade, A. M.; Majoral, J. P.; Reiser, O., Synthesis and Application of Phosphorus Dendrimer Immobilized Azabis(oxazolines).
Organic Letters **2007,** *9*, 2895-2898.

4. **Rasappan, R**.; Hager, M.; Gissibl, A.; Reiser, O., Highly Enantioselective Michael Additions of Indole to Benzylidene Malonate Using Simple Bis(oxazoline) Ligands: Importance of Metal/Ligand Ratio.
Organic Letters **2006,** *8*, 6099-6102.

3. **Rasappan, R**.; Reiser, O. "methyl diazoacetate (First update)"
Encyclopedia of Reagents for Organic Synthesis, Wiley-VCH 2006:*EROS*, **2006.**

2. Manian, R. D. R. S.; Jayashankaran, J.; **Rasappan, R**.; Raghunathan, R., Rapid synthesis of tetrahydroquinolines by indium trichloride catalyzed mono- and bis-intramolecular imino Diels-Alder reactions.
Tetrahedron Letters **2006,** *47*, 7571-7574.

1. Kaanumalle, L. S.; **Rasappan, R**.; MurthyMaddipatla, V. S. N.; Nithyanandhan, J.; Jayaraman, N.; Ramamurthy, V., Dendrimers as Photochemical Reaction Media. Photochemical Behavior of Unimolecular and Bimolecular Reactions in Water-Soluble Dendrimers.
The Journal of Organic Chemistry **2005,** *70*, 5062-5069.

Conference Posters/Lectures

Posters

3. **R. Rasappan**, O. Reiser. "Immobilized aza-bis(oxazolines): Versatile recyclable ligands for asymmetric reactions" Nanocat. Munich, Germany June 4, 2008.

2. **R. Rasappan**, O. Reiser. International 10-th Frühjahrssymposium in 2008 of the GDCh Younger Chemists Forum. Rostock, Germany on March 26 2008.

1. **R. Rasappan**,[a] M. Hager,[a] A. Gissibl,[a] C. Padié,[b] J.-P. Majoral,[b] O. Reiser[a] "Asymmetric Reactions Catalyzed by Native and Immobilized Aza-bis(oxazoline) Ligands" in Heidelberg Forum of Molecular Catalysis at University of Heidelberg, Germany on 22, June, 2007.

Lectures

1. "Immobilization of aza-bis(oxazoline) ligands on various polymeric supports for asymmetric catalysis" in Nanocat international doctorate program at Technische Universitat, Munchen on 24-th January 2006.

References

Prof. Dr. Oliver Reiser
Institute of Organic Chemistry
University of Regensburg
D-93053, Regensburg, Germany
Tel.: +49-9419434631 (4630)
Fax: +49-9419434121
oliver.reiser@chemie.uni-regensburg.de

Prof. Dr. N. Jayaraman
Department of Organic Chemistry
Indian Institute of Science
Bangalore 560 012, India
Telephone: 91-80-2293-2406
Fax: 91-80-360-0529
jayaraman@iisc.ernet.in

Prof. Dr. Burkhard König
Institute of Organic Chemistry
University of Regensburg
D-93053, Regensburg, Germany
Tel.: +49-9419434575
Fax: +49-9419431717
burkhard.koenig@chemie.uni-regensburg.de

Prof. Dr. G. Mugesh
Dep't of Inorganic and physical Chemistry
Indian Institute of Science
Bangalore 560 012, India.
Phone : +91(80)2293 2825
Fax : 2360 1552/2360 0683
mugesh@ipc.iisc.ernet.in