DESIGN, SYNTHESIS AND APPLICATIONS OF TETRADENTATE TRANSITION METAL COMPLEXES TOWARDS ASYMMETRIC ALKYLATIONS

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UDAYA BHASKAR TADIKONDA

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DEDICATION

This dissertation is dedicated to my parents Shri & Smt. Prasad, brothers Chandu and Pratap and sister-in-law Saroja. I learnt the meaning of the magical trinity: Commitment, Compassion and Consecration from all of you and this dissertation is a token of my love and appreciation to you.

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ABSTRACT

Controlling the absolute stereochemistry of molecules is a major challenge to contemporary chemists. Achieving high enantioselectivity with catalytic amounts of a chirality transfer (or inducing) agent, and the ease of regenerating such catalysts is yet another challenge. Due to the involvement of various transition metal complexes, the relatively young field of enantioselective catalysis has emerged as a powerful tool for organic chemistry.

In our efforts towards the synthesis of a *universal catalyst,* O'Donnell Schiff base derived tetradentate ligands were shown to catalyze dialkylzinc additions to aldehydes in high selectivity. The three pot synthesis of bifurcated dipeptides in very good yields and the mechanistic aspects of diethylzinc additions to aromatic aldehydes are described in this dissertation. The chiral Lewis acidic behavior of these ligands was supported by a mechanistic study done examining the nonlinear effect. Unlike bidentate ligands such as (-)-3-*exo*-*N,N*-dimethylaminoisoborneol (DAIB), the tetradentate ligands in this study show strictly linear behavior. Also, the linear free energy relationships studied by observing the enantioselectivity with respect to electron donating or withdrawing substituents on the benzaldehyde substrates supported a Lewis acid role for the zinc complexes. A negative slope was obtained when ee's were plotted against sigma values of the substituted benzaldehydes.

Since they bind to various bivalent transition metal cations, these ligands can be viewed as *privileged structures,* and may potentially become catalysts for various asymmetric reactions. As catalyst screening can be greatly facilitated by heterogeneous

catalysis, solid phase ligands were synthesized using Wang and Merrifield resin supports. The synthetic methodology was developed using a diarylketimine linker with the aid of on-bead characterization techniques such as ^{13}C NMR and UV-VIS spectroscopy.

The ligands were shown to asymmetrically catalyze the alkenylzinc additions to aromatic aldehydes. *In situ* generation of alkenylzinc reagents by boron to zinc transmetalation followed by the addition to benzaldehyde in the presence chiral zinc complexes resulted in enantiomerically enriched allylic alcohols. The preliminary results for this transformation resulted in 3:1 selectivity in favor of *S*-isomer.

CHAPTER ONE

INTRODUCTION

1.1. Catalysis in organic chemistry

1.1.1. Need for catalysis

Chemistry, being one of the fundamental sciences, can be viewed as a central science, one in which phenomena are defined at a molecular level. Chemical synthesis plays a very significant role in understanding the functions that occur at the molecular level, ranging from material science to biology. As in any other field, efficiency plays a significant role in achieving the best results. In chemical terminology, efficiency may be defined as the ability to convert readily available building blocks into the target molecule, in a relatively few synthetic operations that require minimal quantities of raw materials and produce minimal waste.

Success of a chemical reaction can be viewed in terms of two factors, selectivity[1] and efficiency.[22] Based on selectivity, chemical reactions can be categorized in to four types.[3] First, differentiation among bond types, termed as chemoselectivity. Such selectivity can be rather simple, such as selective additions to a carbon-carbon double bond in the presence of a carbon-oxygen double bond or *vice versa*. This differentiation could also be very subtle, as in the case of differentiating between several carbonyl groups present in the same molecule. Second, orientation of reactants with respect to each other, named as regioselectivity. An example for such reactivity is Markonikov *vs*. anti-Markonikov addition to a carbon-carbon double bond. The third and fourth categories of selective reactions are stereoselective reactions, which involve controlling

relative stereochemistry, called diastereoselectivity, and absolute stereochemistry, known as enantioselectivity. Usually, achieving the diastereoselectivity is easier than the enantioselectivity and hence the concept of chiral auxiliaries to convert enantiomers into diastereomers was introduced.[4-6] While the challenges of chemo- and regioselective bond formations are well understood, perhaps even conquered, stereoselective reactions still pose problems and constitute a formidable task if required on a plant-scale, as for example, in the manufacture of enantiopure pharmaceutical reagents. Even though the selectivity helps in the reduction of by-products or reduces the amount of waste generated in the chemical reactions, it does not clearly convey the message of efficiency. In most cases, the efficiency of a reaction is neglected to achieve better enantioselectivity. For example, for the synthesis of a methylenecycloalkane, if Wittig reagent precursor $BrCH_2PPh_3$ with a molecular weight of 357 $gmol^{-1}$ was used, the resulting gain in the mass of substrate from product is only 14 $gmol^{-1}$ (mass of CH_2). The reminder of the mass was turned in to by-product or waste product. The development of reactions and reagents that achieve both selectivity and atom efficiency should be a prime goal of synthetic chemistry. The ability of transition metal complexes to catalyze organic reactions constitutes one of the most powerful strategies to address these fundamental issues. Choice of the transition metal in addition to the design of the ligand environment provides opportunities for electronic and steric tuning of reactivity to a high degree.

1.1.2. Choice of metals for catalysis

Unlike the main group metals, transition metals exhibit variable oxidation states and coordination numbers. Because of this property, transition metals can assemble

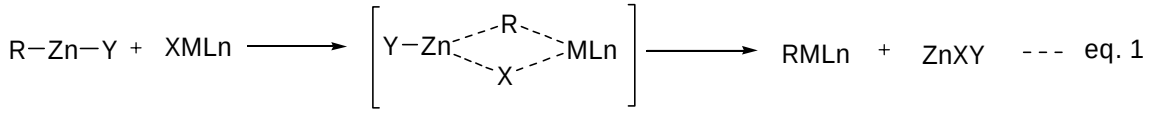
organic units as ligands and bring about their reaction. Transition metals complex with almost every organic functional group, and upon complexation, the chemistry of the functional group can be dramatically changed, reacting by mechanisms available to the transition metal. Furthermore, the chemistry of the transition metal can be changed by changing the "spectator" ligands on the metal. Thus, a reaction may be fine-tuned by making subtle adjustments in the ligands.

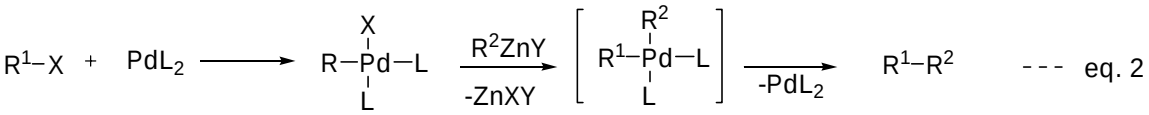
1.1.3. Choice of organometallic reagents for catalysis

Of the numerous organometallic compounds bearing a metal-carbon σ bond, organolithium and magnesium compounds represent the most popular polar organometallic reagents serving as particularly useful reagents for organic synthesis. These reagents have the properties of high basicity and nucleophilicity, deprotonating an acidic substrate or transferring an alkyl group to an electrophilic carbon center, due to the less electronegative counter-ionic metal. Also, they are frequently used as the source of alkyl groups in the preparation of organometallic reagents through transmetalation reactions. Organozinc compounds were the first group of compounds possessing a metal-carbon σ-bond. Their preparation dates back to 1849,[7] when Frankland discovered that heating a mixture of metallic zinc with methyl iodide or ethyl iodide in a sealed tube affords self-inflammable dialkylzinc. The reactivities of organozinc compounds toward acid halides were reported before the end of 1870s, leading to the discovery of the synthetically versatile Reformatsky reagent in 1887.[8] Even though by the end of nineteenth century, the use of organozinc reagents in organic synthesis was established, the discovery of Grignard reagents put a hold on the use of organozinc reagents. The

ease of preparation of Grignard reagents and their enhanced reactivity acquired a wide popularity. In spite of functionalized organozinc reagents being available in 1940s, the lack of modern transition metal catalysts resulted in poor use of such reagents.[9] The invention of lithium enolates[10] decreased the popularity of the Reformatsky reaction. The major problem of organozinc reagents, the low nucleophilic reactivity was turned in to a very good feature of these reagents in the early 1980s and organozinc chemistry found various applications thereafter.

The breakthrough in the use of organozinc compounds in organic synthesis was the reactions of functionalized organozinc reagents in the presence of Ni[11] and Pd[12] catalysts as shown by Negishi. The empty low-lying p-orbitals of zinc allow many transmetalations with metallic salts to proceed as long as they are thermodynamically favored. This ability of zinc is exploited in the preparation of various organometallic reagents. In these reactions, the alkyl group(R) of organozinc (R-Zn-Y) migrates to the transition metal (XMLn), generating the transition metal based reagents (RMLn), which have various synthetic applications (eqs 1 and 2).

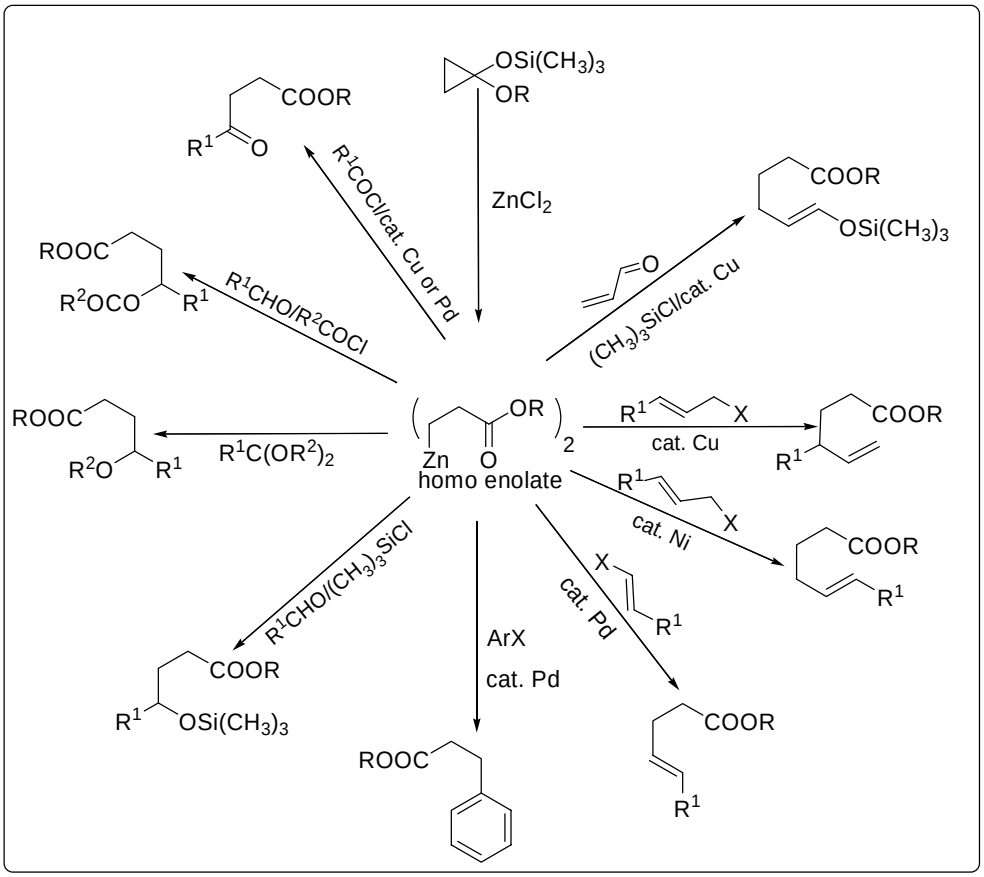




R^1 = alkyl, vinyl, aryl R^2 = vinyl, aryl, X = halogen, $-CF_3SO_3$

The use of zinc reagents in organic synthesis had tremendously increased after the pioneering study by Boersma[13] and Thiele[14] groups on functionalized organozinc

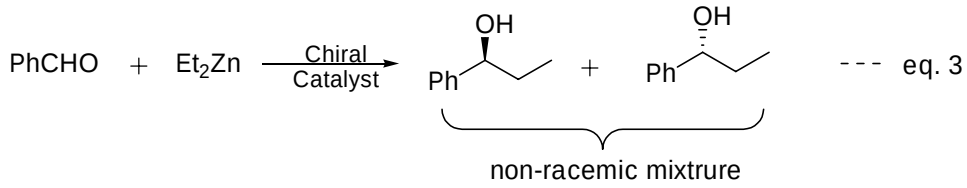
reagents. Unlike other organometallics, organozinc reagents are capable of having an electrophilic group such as an ester group within the reagent.[15] Many previous attempts to use alkali or alkaline earth metal homoenolates had failed because of the intrinsic instability of such functionalized nucleophiles which undergo rapid intramolecular reactions. A zinc homoenolate reported in 1984 is synthetically more versatile.[16, 17] The versatile nature of zinc homoenolates is summarized in **Scheme 1.1**. As a result of extensive investigations in recent years, the chemistry of functionalized organozinc reagents is firmly established.



Scheme 1.1 Synthetic versatility of zinc homoenolates

The use of organozinc reagents in organic chemistry was further established after Oguni's discovery of catalytic asymmetric carbonyl addition in 1984.[18-20] Ordinary organozinc reagents, except for allylic and propargylic zinc reagents, display a low reactivity toward carbonyl compounds.[21] Alkenylzinc reagents seem to be more reactive than their alkyl counterparts.

Asymmetric catalysis is one of the significant areas in modern organic chemistry.[3, 22, 23] Within this field, the construction of carbon-carbon bonds in an asymmetric fashion is of major relevance. A well known example is the dialkylzinc addition to aldehydes, catalyzed by β-aminoalcohols or chiral catalysts (eq 3).[18, 19, 24, 25]



--- eq. 3

Over the last two decades, there had been an explosion in this area of asymmetric catalysis, with the invention of new catalysts that deliver levels of stereocontrol that was believed to be impossible to achieve via non-enzymatic ways.[26] These new tools (catalysts) have dramatically redefined the way the stereochemical issues in organic synthesis are being addressed both in academia and in industry.

1.2. Evolution of asymmetric reactions

The quest for conducting asymmetric reactions is more than a century old. In the year 1904 Mc Kenzie[27] reported the first asymmetric addition of a Grignard reagent to the menthyl ester of benzoylformic acid. After a series of unsuccessful attempts by various scientists, Cohen and Wright obtained optically active products *via* the use of (2*R*,3*R*)-dimethoxybutane, an optically active solvent.[28] Noyori *et al.*[29] demonstrated the use of (-)-sparteine (**1.1**, **Fig. 1.1)** as a chiral bidentate ligand towards the reactions of organolithium and magnesium reagents. The addition of ethylmagnesium bromide to benzaldehyde in the presence of (-)-sparteine (**1.1**) resulted in (*R*)-1-phenyl-1-propanol in 22% ee. Almost 70 years after the first asymmetric alkylation reaction, in 1978 Soai *et al*. reported the first highly enantioselective addition of a dialkylmagnesium to aldehydes.[30] They used the lithium salt of (2*S*,2'*S*)-2-hydroxymethyl-1-[(1-methylpyrolidin-2-yl)methyl] pyrrolidine (**1.2**) as a chiral ligand ((S)-proline based lithium salt).

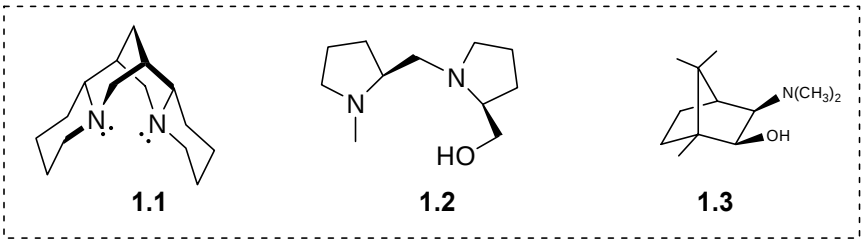


Figure 1.1 The ligands involved in development of asymmetric catalysis.

Year 1986 was a breakthrough for the asymmetric alkylation reactions. Excellent asymmetric induction with good yield was obtained when catalytic amounts of (-)-3-exo-dimethylaminoisoborneol (DAIB, **1.3**) was used for alkylation of aldehydes.[31] The

authors published mechanistic aspects of dialkylzinc additions to aldehydes with a complete description of the observed nonlinear effect in 1989.[32]

About the same time, in 1986, cinchona alkaloids (**Fig 1.2**) were shown to have a very good catalytic activity towards the asymmetric diethylzinc additions to benzaldehyde by Smardijk and Wynberg.[33] Quinine (**1.4**) as the catalyst, in toluene, authors obtained 68% of *R*-isomer. The ee increased up to 92% when benzaldehyde was replaced by *o*-ethoxybenzaldehyde due to steric bulk on the aromatic ring. When quinidine (**1.5**) was used as the catalyst they observed the opposite enantioselectivity and this is attributed to the change in stereochemistry at C8 and C9 positions of the alkaloid (eq 4).

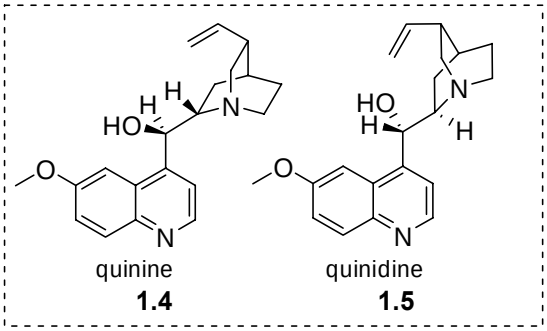
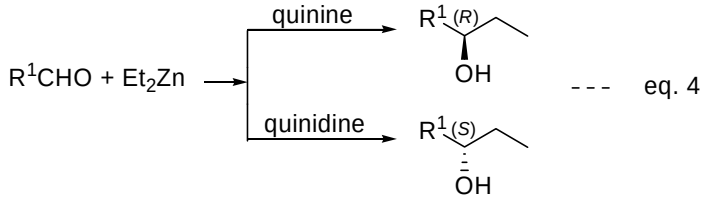


Figure 1.2 Cinchona alkaloids, used for alkylations



--- eq. 4

The enantiopure β-amino alcohols used by Pericas *et al.* for asymmetric alkylations were synthesized by the nucleophilic ring opening of 1,1,2-triphenylepoxide by a secondary amine like piperidine, an N-substituted piperazine or morpholine in presence of $LiClO_4$.[34] These β-amino alcohols catalyze the addition of diethylzinc to aldehydes at 0 °C. After studying 20 different aldehydes (aliphatic and aromatic), the

authors concluded that the use of piperidine derived ligands were most effective in obtaining the chiral induction.

1.3. Catalyst design

In general, most of the β-amino alcohols exhibit the catalytic behavior function very effectively towards the asymmetric alkylations of aromatic aldehydes and not towards the aliphatic aldehydes. In addition to the inability of these catalysts for aliphatic aldehydes and the ease of synthesis and/or isolation from naturally occurring materials, the synthetic applications of these ligands to various reaction conditions keep them from being effective catalysts. Due to such reasons, the search for an ideal catalyst had been a challenge to many research groups and various catalysts were introduced. The mechanistic aspects of alkylations and the concepts involved in the design of the catalyst were illustrated by different classes of compounds. In view of the vast selection of these catalysts, selective catalysts were discussed in the following section to demonstrate the key features in the catalyst design.

1.3.1. Acyclic amino alcohol based ligands

Uncatalyzed reaction between diethylzinc and benzaldehyde to yield 1-phenyl-1-propanol is usually sluggish, and side reactions such as reduction of aldehyde occur.[35] Mukaiyama *et al.* reported the first catalyzed alkylation of benzaldehyde with no enantioselectivity using (S)-proline.[36, 37] Even though no chiral induction is obtained by this β-amino alcohol, the formation of carbon-carbon bond from dialkylzinc and aldehyde suggested the possibility of asymmetric induction using the appropriate chiral β-amino

alcohol. Later on, in 1984, Ouguni and Omi used (S)-leucinol (a primary β-amino alcohol) as a chiral catalyst and obtained optically active 1-phenyl-1-propanol in moderate optical purity of 49% ee.[20] The first highly enantioselective catalytic addition of dialkylzincs to aromatic aldehydes (99% yield, 98% ee of (S)-1-phenyl-1-propanol) was reported by Nyori *et al.*[31] using the camphor derivative (-)-3-exo-(dimethyl amino)isoborneol.

The serine derived ligands **1.6** and **1.7** of Sibi (**Fig. 1.3**), when reacted in presence of ^{n}BuLi, catalyzed the asymmetric alkylation of benzaldehyde.[38] Interestingly, when the reactions were performed under same conditions, the ligand with phenyl substituents produced (S)-1-phenyl-1-propanol with 83% ee and the ligand with ^{n}Bu substituents yielded (R)-1-phenyl-1-propanol with 79% ee. It was proposed that this change in stereochemistry is due to the formation of different chair confirmations (**1.8** and **1.9**) in the transition states.

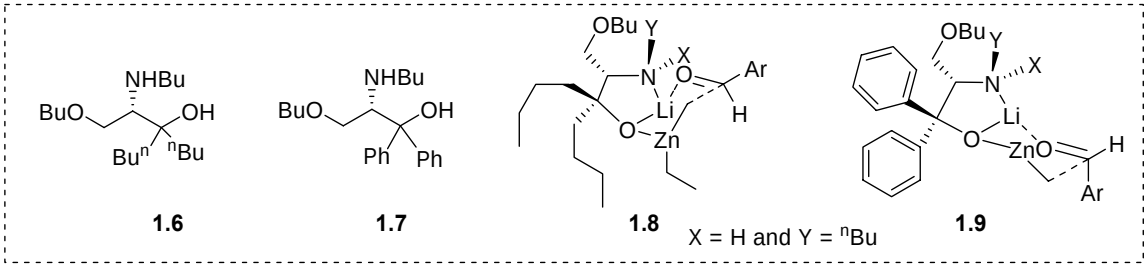


Figure 1.3 Serine derived ligands and their corresponding transition states

The ligand (**1.10**, **Fig. 1.4**) prepared by Fujita and co-workers for the diethylzinc additions showed very good enantioselectivity for the reactions of benzaldehyde and also *para*-substituted benzaldehydes.[39] This camphor derived ligand (δ-amino alcohol) when used for the alkylation of aromatic aldehydes, had a very good chiral induction (73-95%),

whereas the reactions with *E*-cinnamaldehyde or hydrocinnamaldehyde gave very low selectivity (60 and 54% ee respectively). Another ligand (**1.11**) with similar structure had poor selectivity (44-62% ee) for the diethylzinc reaction with benzaldehyde.[40, 41]

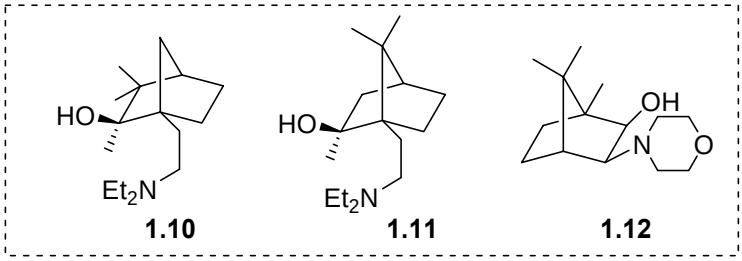


Figure 1.4 Modified camphor based ligands for asymmetric alkylations

Nugent in 1998 introduced the slightly modified DAIB, 3-*exo*-morphilinoisoborneol (**1.12**, MIB), as the catalyst for alkylation reactions.[42] Even though DAIB had excellent selectivity towards the addition of aromatic aldehydes, it was not very successful in case of α-branched aliphatic aldehydes, slowly decomposed on storage and required three steps for the synthesis. The observed ees for a number of aromatic and aliphatic aldehydes were in the range of 91-99%.

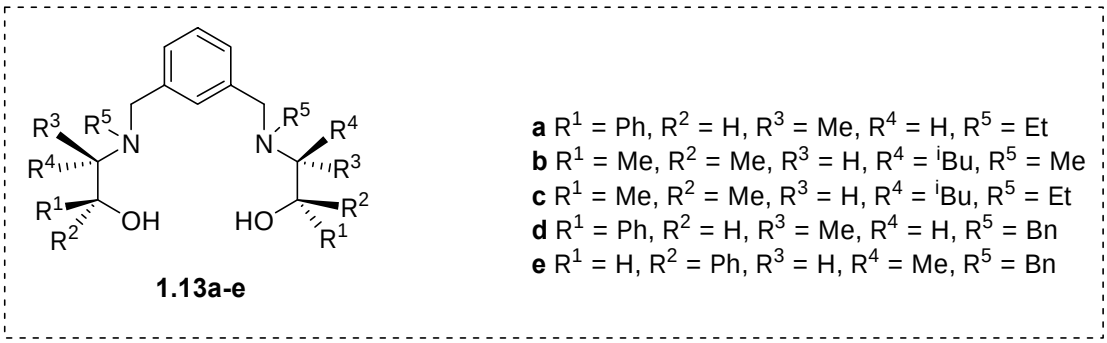


Figure 1.5 Examples of chiral ligands having bis(β-aminoalcohol)

Compounds containing two amino alcohol units (**1.13a-e**, **Fig. 1.5**) were synthesized and studied by Pedrosa and co-workers.[43] The reactions were performed with different aromatic aldehydes in toluene:hexane (2:1) solvent system. The yields and

enantiomeric excesses were in the range of 72-95% and 64-96% respectively. When the enantiomeric ligands were used, the opposite enantioselectivity was achieved. Similarly another C_2-symmetric diamino alcohol was synthesized by Kossenjans and Martens starting with (*R*)-cysteine for asymmetric reactions.[44] When used in 10 mol%, this ligand catalyzed diethylzinc additions to benzaldehyde giving 94% ee of (*S*)-1-phenyl-1-propanol.

1.3.2. Ephedrine and norephedrine based ligands

It is advantageous to use ephedrine and norephedrine as the sources of chirality, as the ligands thus generated would be enantiomeric in nature and with the proper enantiomer, the outcome of the asymmetric reaction can be manipulated. (1*R*,2*S*)-*N*-isopropylephedrine (**1.14**, **Fig. 1.6**) was shown to catalyze the addition of diethylzinc to benzaldehyde to give (R)-1-phenyl-1-propanol with 80% ee in 72% yield.[45] Even though this catalyst had effective chirality induction with aromatic and aliphatic aldehydes, cyclohexyl aldehyde gave no enantioselectivity and the yield dropped down to 40%. The same ligand gave better selectivity when excess diethylzinc was added during the reaction (about 4-5 times of the aldehyde).

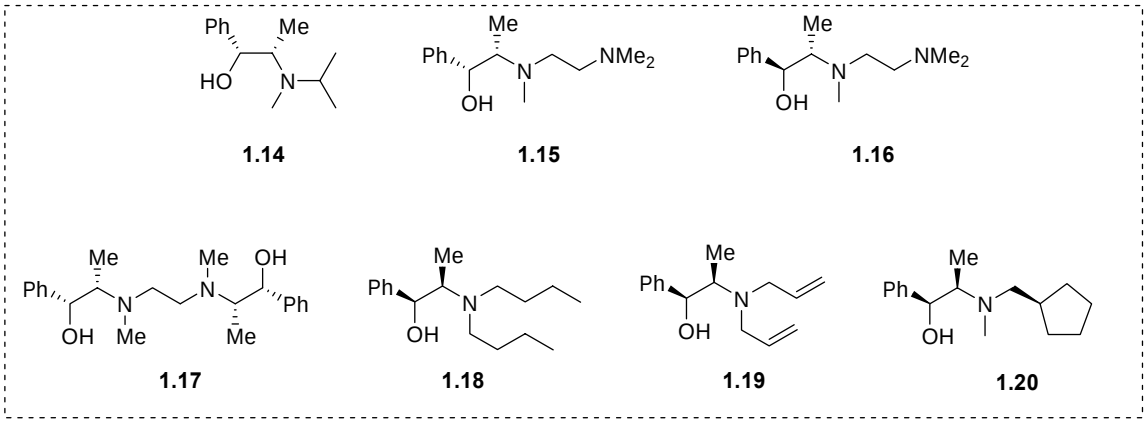


Figure 1.6 Examples of ephedrine and norephedrine based ligands

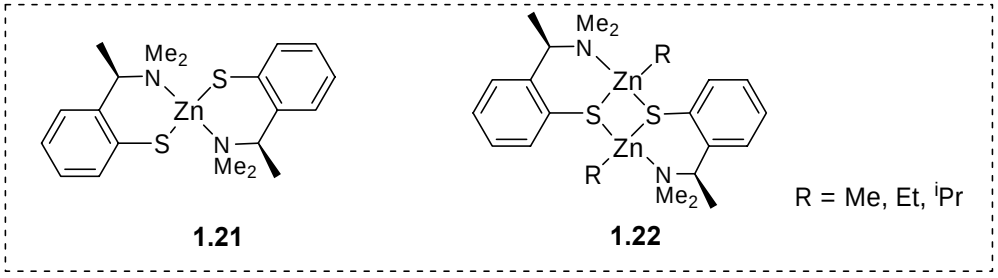
Not just ephedrine, but the lithium salt of ephedrine was also shown to have catalytic activity. One such ligand (lithium salt of (1*R*,2*S*)-N-[2-(dimethylamino)ethyl]-ephedrine, **1.15**) was proposed by Corey and Hannon *et al.* towards the addition of organocopper reagent[46] to cyclohexenone. When the diethylzinc addition to aromatic aldehydes was performed, the reaction with benzaldehyde produced 90% ee of (*R*)-1-phenyl-1-propanol.[47] When the ligand was changed to the lithium salt of (1*S*, 2*S*)-N-[2-(dimethylamino)ethyl]pseudoephedrine (**1.16**), the enantiomeric product (*S*)-1-phenyl-1-propanol was obtained in 91% yield, indicating that the stereochemistry of the product was dependent on the stereochemistry of the alcohol portion of the ephedrine moiety. The lithium salt of the chiral diol, obtained by the dimerization of (1*R*,2*S*)-ephedrine with a trimethylene chain (**1.17**), with C_2-symmetry also catalyzed the diethylzinc addition to benzaldehyde producing 85% ee of (*R*)-1-phenyl-1-propanol.[48]

The chiral *N,N*-dialkylnorephedrines catalyze the diethylzinc additions to aromatic and aliphatic aldehydes in good yields and selectivity. It was found experimentally that the optimum chain length of N-alkyl groups is four, limiting the ligand synthesis to the use of n-butyl side chains (**1.18**).[49] Various aliphatic secondary

alcohols in good to high enantioselectivity were obtained by the use of this catalyst towards alkylations. Along the same lines, (1*S*,2*R*)-*N,N*-diallylnorephedrine (**1.19**) and (1*S*, 2*R*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (**1.20**) were shown to be effective chiral catalysts.[50]

1.3.3. Amino thiols, disulfides and diselenides

Not only β-amino alcohols, but also β-amino thiols, disulfides and deselinides function as catalysts for alkylations. A number of research groups studied this aspect of asymmetric catalysis and found interesting results.[51-57]



1.21 **1.22**

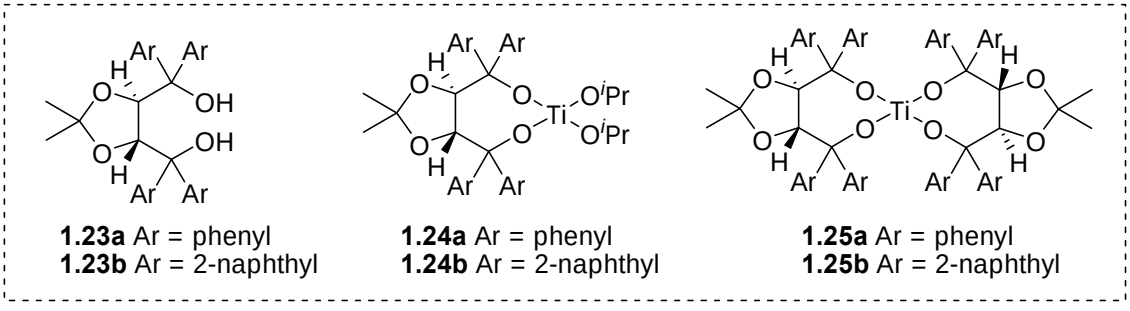
Figure 1.7 Zinc complex of bis(aminoarene thiolate) ligand

Inspired by the results obtained in the study of chiral monoanionic aminoarenethiolate (R)-2-[(1-dimethylamino)ethyl]thiophenolate, towards the asymmetric 1,4-additions of organometallics to α,β-unsaturated ketones,[58-60] and 1,6-additions to enyne-esters,[61] van Koten and co-workers introduced the use of S_2N_2 chelating chiral zinc bis(aminoarene thiolates) (**1.21**, **Fig. 1.7**)[62, 63] to 1,2-carbonyl additions. Interestingly, this tetradentate N_2S_2 ligand shows a positive nonlinear effect as observed with Noyori's catalyst (DAIB, **1.3**).[18] In view of this observation and the experimental results with air stable complex **1.22**, the authors proposed that the

bis(aminoarene thiolate) decomposes during the catalysis to a coordinatively unsaturated monomeric unit, and the catalysis proceeds via monomeric complexes.

1.3.4. TADDOLs and BINOLs

Even though β-amino alcohols are widely used for the asymmetric 1,2-additions to carbonyl functionality, the ligands with out nitrogen atoms also have been used. For example, α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs). TADDOLs are a family of chiral diols derived from optically active tartaric acid. TADDOL based ligands (**1.23a** and **b**) were extensively studied by Seebach and co-workers.[64-69] They found that 20 mol% of **1.24a** and **b** or 10 mol% of the spirotitanate complex (**1.25a** & **b**) in the presence of excess of $Ti(O^iPr)_4$, catalyzed the dialkylzinc addition to aromatic and aliphatic aldehydes. 82-99% ees were obtained, in toluene as the solvent, when the reactions were carried out between -76 to -20°C (**Table 1.1**).



1.23a Ar = phenyl
1.23b Ar = 2-naphthyl

1.24a Ar = phenyl
1.24b Ar = 2-naphthyl

1.25a Ar = phenyl
1.25b Ar = 2-naphthyl

Figure 1.8 TADDOLs, and their titanium complexes

When the optical purity of product was plotted against the enantioselectivity of titanates, linear plot was obtained, indicating the involvement of single molecule of catalyst in the catalysis.[64]

Table 1.1 Results of selective TADDOL catalyzing asymmetric alkylation reactions.

aldehyde	catalyst (mol%)	T(°C)	t(h)	Yield (%)	ee (%)	config
benzaldehyde	**1.24b** (20)	-25	30	76	98.6	S
3-phenylpropionaldehyde	**1.24b** (20)	-22	15	87	>98	S
cinnamaldehyde	**1.24b** (20)	-27	24	87	91	S
cyclohexanecarboxaldehyde	**1.24b** (20)	-27	30	77	99	S
heptanal	**1.24b** (20)	-28	50	70	97	S
phenypropargyl aldehyde	**1.24b** (20)	-27	22	83	>99	S
crotonaldehyde	**1.24b** (20)	-76 to -27	20	56	>98	S
1-cyclopentene-1-carboxaldehyde	**1.24b** (20)	-29	20	79	98	S
terephthalaldehyde	**1.24b** (20)	-76 to -23	42	79	>99% de 98% ee	S,S
isophthalaldehyde	**1.24b** (20)	-76 to -25	50	95	>93% de 99% ee	S,S
benzaldehyde	**1.25a** (10)	-75 to r.t.	15 to 24	75	99	S
3-phenylpropionaldehyde	**1.25a** (10)	-75 to r.t.	15 to 24	85	82	S
cinnamaldehyde	**1.25a** (10)	-75 to r.t.	15 to 24	89	96	S
cyclohexanecarboxaldehyde	**1.25a** (10)	-75 to r.t.	15 to 24	67	82	S
heptanal	**1.25a** (10)	-75 to r.t.	15 to 24	75	92	S

Different analogs of TADDOLs were prepared by changing the dioxolane ring to carbocycles including cyclobutane, cyclopentane, cyclohexene, cyclohexane, bicyclo-[2.2.1]heptene, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and bicyclo[2.2.2]octane moieties.[25] By analyzing the X-ray crystallography results and molecular mechanics study of their use towards asymmetric organozinc additions, it was revealed that a better selectivity was achieved with a smaller torsion angle between the chelating oxygen atom and the ortho carbon atom of the axial phenyl group and the higher "degree or perpendicularity" of the axial phenyl group.

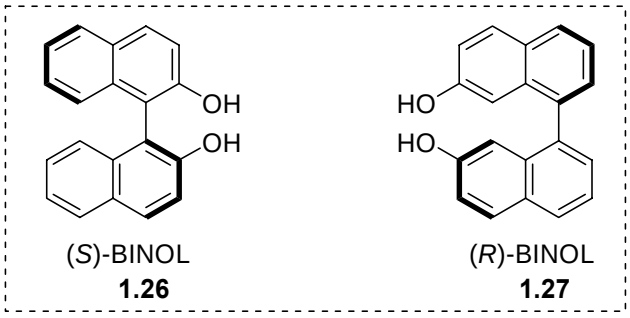


Figure 1.9 Structures of BINOLs

In spite of the success of boron,[70-72] aluminum,[73-76] titanium,[77-89] zirconium,[90-92] and lanthanum[93-99] catalysts in, for example, enantioselective aldol and ene reactions, not much research was done in the use of C_2-symmetric binaphthol (BINOL) derivatives towards asymmetric alkylzinc additions. BINOLs were introduced into asymmetric alkylations in 1997 by two independent research groups, Naki[100] and Chan.[101, 102]

The alkylations were performed in the presence of titanium complexes formed by the reaction of $Ti(O^iPr)_4$ with BINOL. In these reactions, it was observed that the ratio of $Ti(O^iPr)_4$ to BINOL affected the enantioselectivity of the product. A ratio of 1:7 [(*S*)-BINOL / $Ti(O^iPr)_4$] gave best result in methylene chloride and a ratio of 1:12 in toluene.

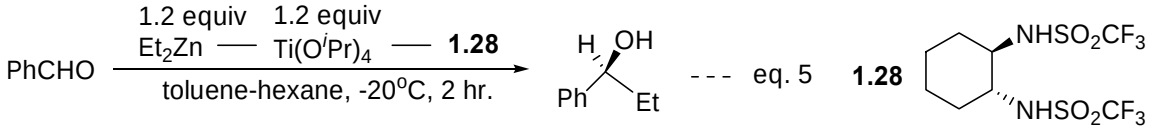
In the presence of 20 mol% of (S)-BINOL and 1.4 equivalents of $Ti(O^iPr)_4$, the addition of diethylzinc to aromatic aldehydes, aliphatic aldehydes and α,β-unsaturated aldehydes gave up to 92% ee.

Table 1.2 Results of selective BINOL catalyzing asymmetric alkylation reactions

entry	aldehyde	ligand (mol%)	Ti(O*i*Pr)4 (eq.)	*T* (°C)	t (h)	yield (%)	ee (%)
a	benzaldehyde	20	0.8	-30	20	89	85
b	benzaldehyde	20	1.2	0	1	97	85
c	benzaldehyde	10	1.2	0	1	>98	85
d	nonyl aldehyde	20	1.2	0	3	90	81
e	nonyl aldehyde	20	1.2	-30	40	94	86
f	cyclohexanecarboxaldehyde	10	1.2	0	3	51	79
g	cyclohexanecarboxaldehyde	20	1.2	-30	40	75	85
h	cinnamaldehyde	10	1.2	0	1	>98	78
i	cinnamaldehyde	20	1.2	0	1	97	82
j	trimethylsilylpropargylaldehyde	20	1.2	-30	20	>98	26
k	*tert*-butyldimethylsilylpropargylaldehyde	10	1.2	0	1	>98	62
l	*tert-butyldimethylsilylpropargylaldehyde*	20	1.2	0	1	>98	79

1.3.5. Titanium sulfonamide and phosphoramide complexes

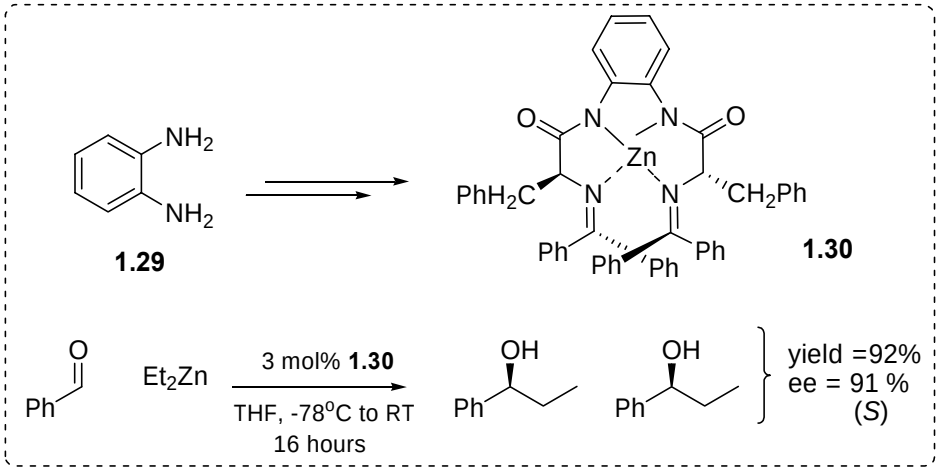
In their initial study with titanium complexes, Ohno *et al.* found that the complex generated by mixing diethylzinc and $Ti(O^iPr)_4$ transferred an ethyl group to benzaldehyde even in the absence of any other chiral ligand.[103] This reaction was rather slow and the rate of reaction was enhanced by the addition of chiral ligands such as C_2-symmetric bistriflamide (**1.28**, eq 5). The coordination of sulfamide with titanium complex thus enhanced the Lewis acidity of titanium, causing the rate enhancement. In other words, sulfamide not only transferred the chirality to product, but also acted as the activator of the titanium complex. The reaction between benzaldehyde and diethylzinc yielded up to 97% and 98% ee. In their proposed mechanism, the involvement of alkyltitanium complex was believed to play a key role.[104]



After the initial reports of Ohno *et al*[103-105] on the use of C_2-symmetric bistriflamide in catalytic asymmetric alkylations, an enormous amount of research was conducted in the use of sulfamides for catalysis. Most of the work in this area was summarized in the review articles written by Knochel *et al*.[106, 107]

1.4. Tetradentate ligands for asymmetric alkylations

As discussed in previous sections, most of the catalytic asymmetric alkylations were performed by virtue of bidentate ligands. Even the bis(amino alcohols) and bisarenethiolates (N_2O_2 and N_2S_2 systems) performed the catalysis not as tetradentate, but bidentate ligands.[63]



Scheme 1.2 Catalysis with tetradentate ligands

Inspired by Nature's transition metal binding enzymes and their ability to perform catalysis, Polt *et al.* introduced the synthetic metalloproteins.[108] These metalloporteins are 4 and 5 coordinated bifurcated dipeptides, with two amino acids bound together by amide linkages onto phenylene diamine backbones with the Schiff bases locking the molecule to generate a chiral pocket (as shown in the structure **1.30**). Upon treatment with base like triethylamine and transition metal halide (MX_2), these metalloproteins bind to transition metals and are capable of performing various catalytic reactions. In the preliminary work, these tetradentate ligands were shown to be very efficient catalysts towards asymmetric alkylations.[109] With C_2-symmetric ligand synthesized from L-Phe

(Zn^{II}-L-Phe-L-Phe complex **1.30**), addition of diethylzinc to n-nonal was quantitative with 96% ee. Dimethylzinc addition was performed on benzaldehyde with the same ligand in 92% yield with 91% ee.

Finding new applications for metalloproteins and understanding the mechanism and mode of catalysis towards asymmetric alkylations was the intention in the present study. Also the methodology development for synthesis of these ligands on polymer support using diarylketimne linker was developed.

CHAPTER TWO

SYNTHESIS OF POLYMER SUPPORT CATALYSTS

As was discussed in the previous chapter, a large number of catalysts were developed for the enantioselective addition of organozinc reagents to aldehydes. The majority of these ligands were β-amino alcohols and/or bidentate ligands. So far, only a few tridentate[47, 110-112] and tetradentate ligands[113-117] were shown to have catalytic activity towards asymmetric alkylation reactions.

Recently the tetradentate ligands derived from O'Donnell's Schiff bases were shown to have very good catalytic activity towards asymmetric alkylations.[109] As the synthesis of catalysts on polymer supports and the use of heterogeneous catalysts for catalysis can lead to the design of highly enantioselective catalysts, these bifurcated dipeptides (**Fig. 2.1**) were immobilized on polymer supports. This chapter summarizes the optimization of solid phase ligand synthesis.

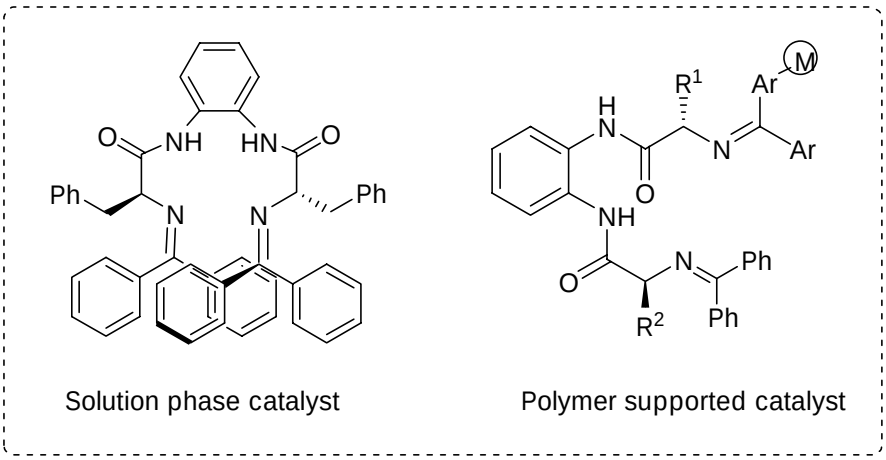


Figure 2.1 Schiff base derived tetradentate ligands

2.1. Introduction to heterogeneous catalysis

The enantioselective formation of C-H, C-C, C-O and C-N bonds represents one of the biggest challenges in synthetic chemistry. Significant progress has been made in this area due to the invention of new catalysts with a vast variety of ligands. In 2001, the significant achievements in the design and application of asymmetric homogeneous catalysts were recognized by the award of the Chemistry Nobel Prize to W. S. Knowles and R. Noyori for enantioselective hydrogenation catalysis and K. B. Sharpless for enantioselective oxidation catalysis.[118-120] In the branch of catalysis, the emphasis is on the active center stereochemistry, and how the ligands lead to the face selective (stereo-selective) addition of the reactants to prochiral substrates. Due to the cost constraints involved in the use of chiral catalysts, it is highly desirable to reuse the catalyst after each reaction. A common solution to this problem is to 'heterogenize' a homogeneous catalyst, by anchoring the catalyst on a solid support or by using a liquid-liquid two phase system.[121] Indeed, many examples of polymer-supported reagents, catalysts and reactions have been reported.[122-124] The advantages of such heterogeneous reactions include: i) The polymers are easily separable from the reactants. ii) They are efficiently reusable (in theory at least). iii) Potentially toxic or expensive reagents can be made safer or recoverable. iv) The polymer supports are potentially usable in a continuous flow type reactor.

Ever since the concept of solid phase peptide synthesis was introduced by Merrifield in 1963,[125] automated solid phase synthesis of peptides,[126-129] oligo-nucleotides,[130, 131] and oligosaccharides[132-135] has been carried out with increasing

regularity. The growth and extent of using solid phase methodologies developed into solid phase peptide synthesis (SPPS) and solid phase organic synthesis (SPOS). SPOS primarily has emphasis on methodologies used to carry out classical organic synthesis on solid supports, which bear little or no resemblance to peptide, oligonucleotide, and poly-saccharide chemistry (SPPS). In the discussions of syntheses on polymer supports one must differentiate between: a) polymer bound reagents and b) polymeric protecting groups. Reactions with polymer bound reagents are one step reactions in which the dissolved substrate is allowed to react with chemical reagents, mostly catalysts or enzymes, which are bound to solid supports. Many support bound reagents have been developed and used for example, for immobilizing triarylphosphanes,[136-138] hydrogenation catalysts, oxidizing and reducing agents, chiral auxiliaries and catalysts. Reactions with polymer support as protecting group are the reactions in which the polymer support functions as a protecting group for one functional group of the substrate while another site on the substrate is derivatized.[124]

In all types of solid phase reactions, the attachment of an active molecule to the solid phase is very critical and important step. This is achieved through a linker (or anchor) moiety. The linker has been described as a bifunctional protecting group that is attached to the molecule being synthesized through a bond labile to the cleavage conditions (e.g. silyl ethers, esters, and carbamates) and to the solid phase polymer through a more stable bond (alkyl ethers, amides, or alkanes; **Fig. 2.2**).[139] There are, however, many linkers that are not based on common protecting group methods, such as the increasing range of traceless linkers, or those that rely on β-cleavage or cyclization.

These fall in to a broader definition of a linker as a connection between the molecule being synthesized and the solid phase polymer that is cleaved to release the desired molecule.

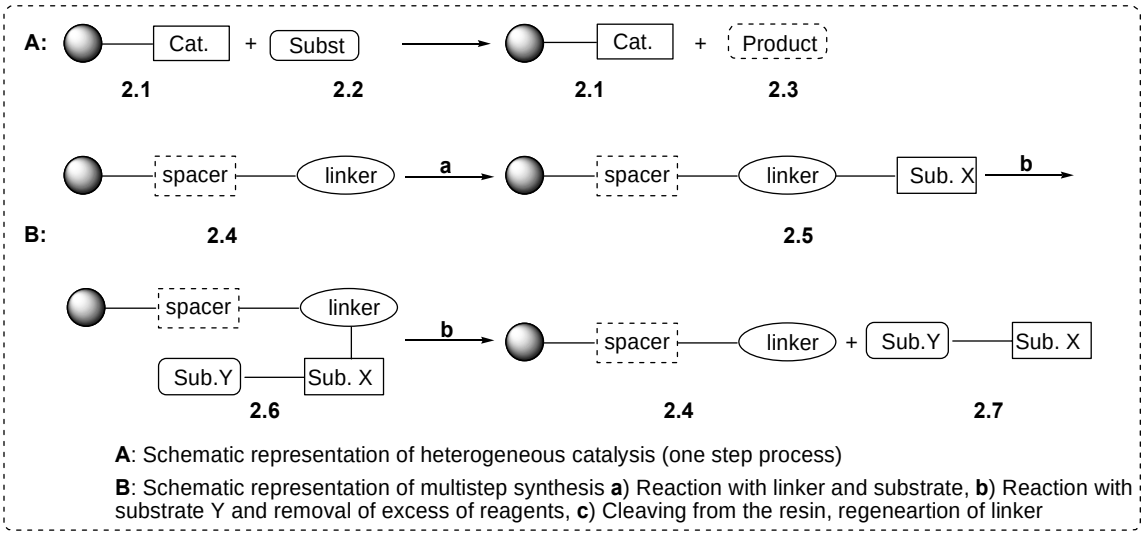


Figure 2.2 Cartoon diagram depicting the solid phase syntheses

2.2. Linker design for immobilizing tetradentate ligands

Invariably for any solid phase reaction scheme, the choice of base polymer, spacer (any atoms between the polymer and the linker) and the linker have very significant roles.[124] Similar to the reactions in solution phase, synthesis at higher temperatures, the use of reactive substrates, and reactions under inert gas have to be accounted while choosing the support and suitable linker. So far no special supports, but a few linkers have been developed for solid phase chemistry and the resins like Merrifield[125] and Wang[140] which were developed for peptide chemistry can also be used for numerous organic syntheses.

Table 2.1 Selected examples of polymer supports

Solid Support	Remarks	Ref.
PS/DVB (1-5% cross linking)	Good swelling properties, swells up to five times its dry volume; at low levels of cross linking, (1%) only low thermal stability (105-130 °C, dependent on solvent)	141, 137
Hexamethylenediamine-polyacryl resins and related polymers	Polar resins, good swelling properties in H_2O and DMF. No swelling in CH_2Cl_2	142, 143
Poly[*N*-{2-(4-hydroxy-phenyl)ethyl}acrylamide] (Core Q)	SPPS with high loading	144
Poly(*N*-acrylopyrrolidine) resins, PAP- and SPARE-polyamide resins	SPPS with high loading; swell in H_2O, DMF and CH_2Cl_2	145-147
Polyethylene functionalized with acrylic acid	Synthesis on pins	148, 149
Kieselgur/polyamide (Pepsyn K)	Pressure stable; used in continuous-flow SPPS, low swelling properties due to inorganic support;; shaking results in marked wear of the organic polymers	10
polyHipe, PS/polydimethyl-acrylamide copolymer	Continuous-flow SPPS, loading capacity up to 5 $mmolg^{-1}$, high cross-linking of the PS chain	150
CPG	Pressure and heat stable; stable toward aggressive reagents, low loading	151, 152
PS macrobeads	Diameter ≤1mm; loading 50mmnmol per bead; available with three different anchors	153
Tenta Gel, PEG-PS/DVB copolymers	Polarl swell in H_2O, MeOH, MeCN, DMF and CH_2Cl_2; pressure stable; suitable for bioassays on resins	154

Table 2.2 Selected examples of acid labile linkers

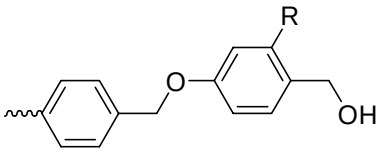
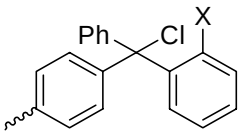
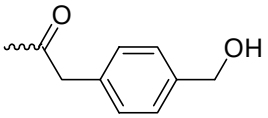
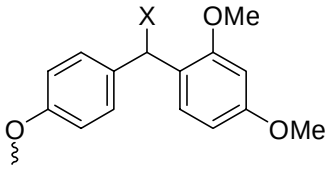
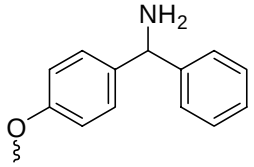
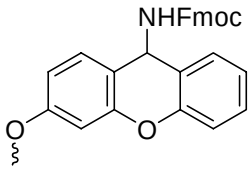
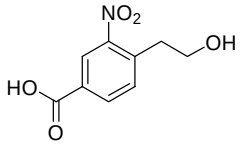
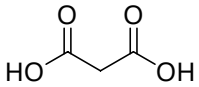
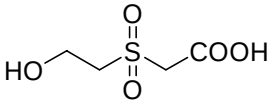
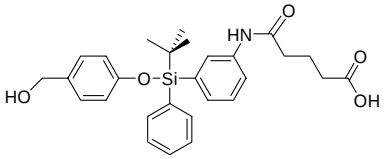
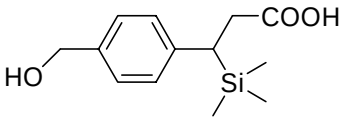
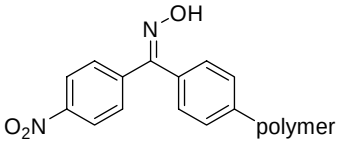
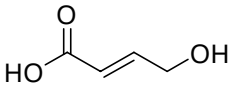
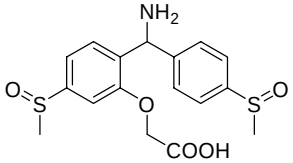
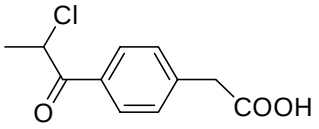
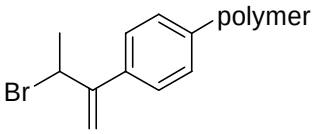
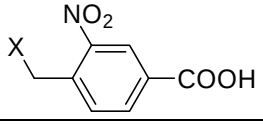
Linker	Name	Cleavage conditions	Ref.
	a)Wang resin (R = H); b)SASRIN (R = OMe)	a) 95% TFA b) 1% TFA	140, 155
	Trityl chloride (R = H); 2-Chlorotrityl chloride (R = Cl)	Very weak acids, HOAc	156-158
	PAM linker	HF, TFMSA	159
	a) Rink acid (X =OH) b) Rink amide (X = NH-Fmoc)	a) HOAc b) TFA	160
	BHA linker	TFMSA	161
	Sieber amide	TFA/ CH_2Cl_2 (1/99)	162

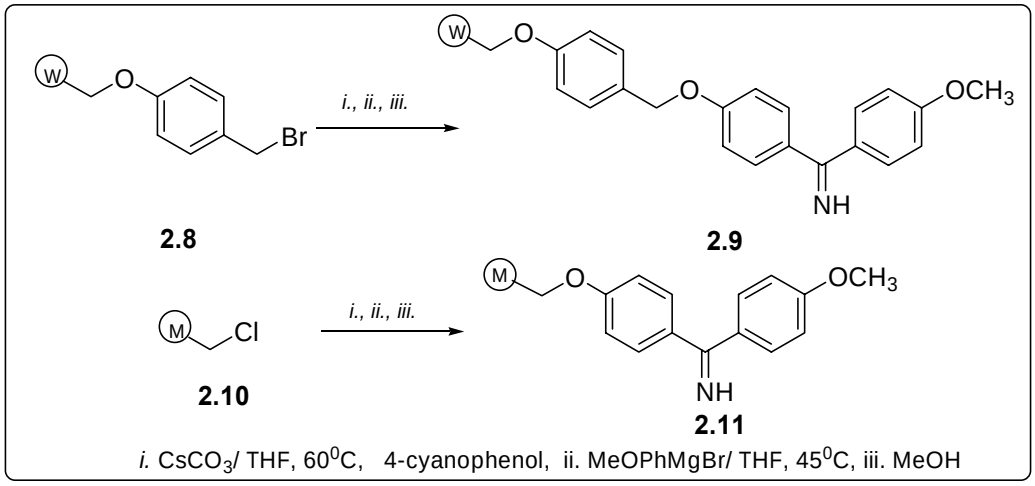
Table 2.3 Examples of base labile linkers

Linker	Cleavage conditions	Ref.
	DBU/ piperidine, β-elimination	163, 164
	NaOH, saponification	165
	NaOH, β-elimination	166
	Bu_4NF	167
	Bu_4NF	167, 168
	Hydrazine hydrate, hydrogenolysis	169
	Pd0/H2, cat. hydrogenation	170
	$(Et_2O)_2P(S)SH$/TFA, reductive acidolysis	171
	Photolysis, 350 nm.	172
	Photolysis, 350 nm. Labile in piperidine/ DMF	
	Phtotolysis, 350 nm. X = Hal, OH, NH_2	173

The choice of linker solely depends on the planned reaction scheme and its requirements. According to the cleavage conditions, most linkers can be classified into acid and base labile linkers. Photolabile linkers can be cleaved under neutral conditions. A few examples of these polymer supports and linkers were shown in **Table 2.1-2.3**.

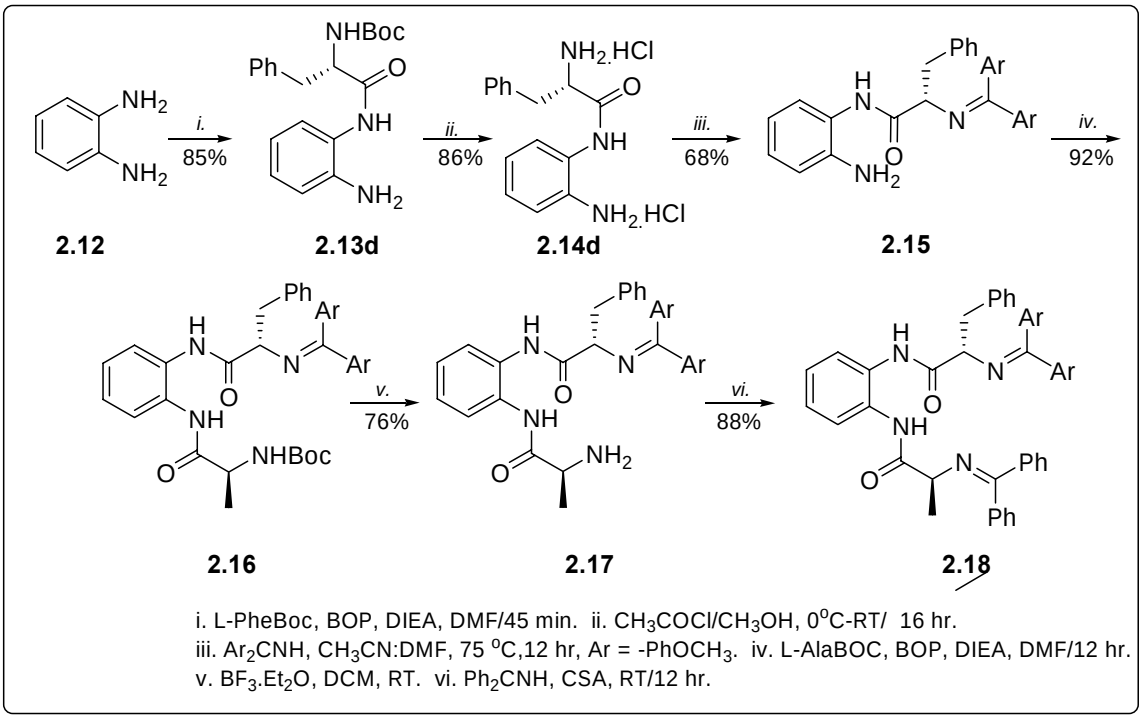
As in the solution phase chemistry, linkers which also function as protecting groups should be stable (robust) to all the reaction conditions (orthogonality principle), and also able to be cleaved under mild reaction conditions when desired. The linkers that are used for peptide chemistry are generally stable to either weak acids or bases, but for the most part they are suitable only for immobilization of carboxylic acids.[129]

A new diarylketimine linker was proposed for the synthesis of tetradentate ligands on a polymer support as shown in the **Scheme 2.1**. The tetradentate ligand was bound to the resin *via* the formation of Schiff base using primary amine hydrochloride salts. Although Schiff bases are sometimes considered to be unstable intermediates, O'Donnell *et al.*[174] demonstrated that sterically hindered benzophenone imine Schiff bases can serve as stable, extremely versatile protecting groups for primary amines.[175-177]



Scheme 2.1 Synthesis of diarylketimine linker

Merrifield and bromo-Wang resins were transformed in to the diarylketimine linker through a three step synthesis. The first step was the conversion of aryl halides **2.8** and **2.10** into aryl nitriles using the cesium salt of 4-cyanophenol. The nitrile was then reacted with the Grignard reagent of *p*-bromoanisole followed by quenching with anhydrous methanol to get the diarylketimine (4,4'-alkoxy diphenyl ketimine) resin (**2.9** and **2.11**). This linker is air stable and can be stored without any special precautions in moisture free environments. The reaction was monitored through IR spectroscopy (KBr pellet; strong peak at 2228 cm^{-1}). Similarly the disappearance of this peak was observed for the imine formation.



Scheme 2.2 Synthesis of solution phase model ligand

2.3. Solution phase model ligand synthesis

In order to maintain the integrity of the chiral pocket created by O'Donnell's Schiff base derived tetradentate ligands, and to have the scope for modifying the backbone of the ligand at diamido linkage, the ideal site for binding to the polymer support is through the aromatic rings of the Schiff bases. With this constraint, the solution phase model ligand was synthesized as shown in the **Scheme 2.2** to ensure the efficiency and reproducibility of reactions. The monoacylated Phe-HCl_2 salt (**2.14d**) was reacted with *p*-methoxydiphenylketimine (4,4'-methoxybenzophenone imine) to get the Schiff base **2.15** in 68% yield. This Schiff base **2.15** was reacted with L-Ala-Boc to get

the diacylated compound **2.16**. The key step in the synthesis was to deprotect the t-Boc group of **2.16** in the presence of Schiff base and attempts were made to achieve this with different protic and aprotic acids (**Table 2.4**). $BF_3 \cdot Et_2O$ successfully cleaved the t-Boc in the presence of the Schiff base, in 76% yield. The final step was to cap the free amine of **2.17** by benzophenone imine to get the complete ligand **2.18**.

Table 2.4 Optimization of tert-Boc cleavage conditions

Acid	Triflic acid	Camphor sulfonic acid	Methanolic acetyl chloride	*p*-Toluene-sulfonic acid	$BF_3 \cdot Et_2O$
Result	No reaction	No Reaction	SB cleavage	No Reaction	Boc Cleavage

When the same methodology was adapted to the solid phase synthesis, the use of $BF_3 \cdot Et_2O$ for the deprotection of *tert*-Boc group found to be problematic. The resin lost its texture and the solution became dark red. Thus the initial methodology was changed to the use of Fmoc amino acids. The Fmoc group being base labile, the deprotection did not interfere with the Schiff base and the complete ligand was synthesized without increasing the number of steps. Indeed the use of Fmoc group was advantageous in the characterization as discussed in the next section.

2.4. Characterizing the solid phase compounds

The solid phase multi-step syntheses consist of a series of steps having polymer supported intermediates and analyzing these intermediates can be problematic. Unlike the solution phase counterparts, the analysis of polymer support compounds is not straightforward. Some of the standard protocols of quantification in peptide chemistry

include UV analysis of the cleavage product formed from the amino acid protecting group Fmoc, ES-MS and Edman degradation (for peptides bound on single beads).

Although analysis of polymer bound substrates is vital in optimizing the reaction conditions, very few methods of characterization have been described in the literature. The common analytical methods that are used in solid phase syntheses are:

1. FT-IR and FT-Raman spectroscopy
2. Solid-state and gel-phase ^{13}C NMR spectroscopy[178-181] and ^{1}H and ^{13}C correlation NMR spectroscopy
3. High resolution ^{1}H MAS (magic angle spinning) and MAS-CH correlation in the gel phase[182-184]
4. Matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry[185]
5. Elemental analysis
6. Titration of reactive groups ($-NH_2$, -COOH, ArOH, -SH)
7. Gravimetric analysis
8. Photometry ($-NH_2$ monitored by photometric Fmoc determination)

Due to the low loading and the interference of the polymer backbone, conventional IR and Raman spectra are very difficult to interpret. But the FT-IR measurements performed under defined conditions furnish qualitative as well as quantitative data. When free and loaded supports are compared, the difference measurements give the information about the absorption bands, which are other wise considered as shoulders.

Gel-phase NMR spectroscopy is a mixture of standard solution-phase and solid-state NMR spectroscopy. Usually, a solid sample is transferred to an ordinary NMR tube and allowed to swell in a suitable solvent (CD_2Cl_2 or $CDCl_3$). After the sample is degassed, it can be measured under the conditions typically used for dissolved samples. ^{13}C NMRs are usually masked by the strong resonances of the polymer support and relatively small amounts of substrate signals are difficult to see. But the resonances away from the aromatic region are easier to interpret as the polymer signals do not interfere in this region. Due to strong line broadening, one dimensional ^{1}H-NMR spectra can not be interpreted. The line broadening in case of ^{1}H-NMR can be reduced greatly by the use of magic angle spinning and clear spectra comparable to solution phase can be obtained. However, the proton coupling patterns can be resolved only for support-linker combinations like polystyrene or polyethylene glycol (PS or PEG).

The solid phase synthesis of tetradentate ligands was optimized using spectroscopic techniques such as IR, UV and ^{13}C NMR in addition to the elemental analysis (**Fig. 2.3**). The details of such techniques were discussed in next section. (Note: The assignment of labels to various polymer support compounds was shown in **Table 2.5**).

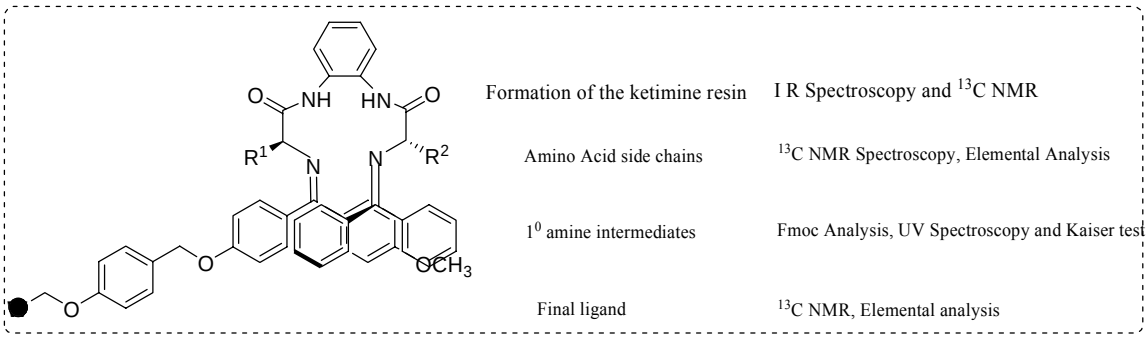


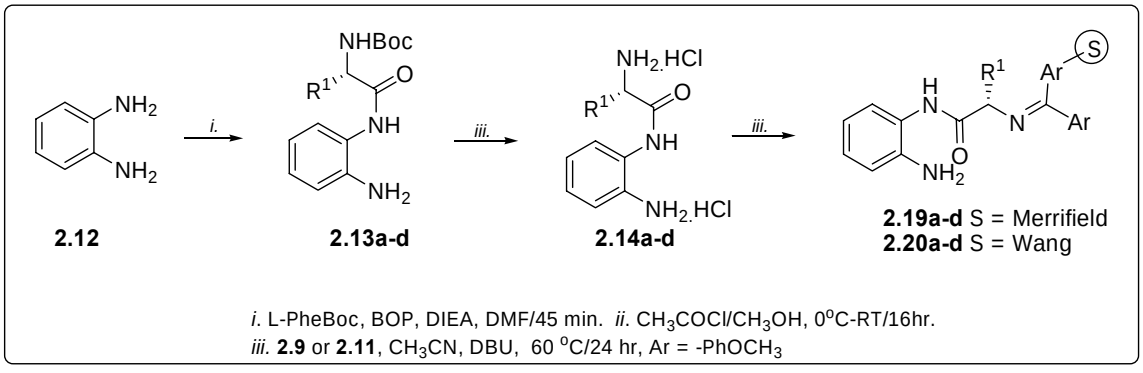
Figure 2.3 Characterization of solid phase ligands

Table 2.5 The assignment of different labels used

Label	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R'	CH_3	H	$CH(CH_3)_2$	CH_2Ph	CH_2Ph	CH_2Ph	CH_2Ph	CH_2Ph
R''	-	-	-	-	CH_2Ph	CH_3	$CH(CH_3)_2$	H
Label	**i**	**j**	**k**	**l**	**m**	**n**	**o**	**p**
R'	CH_3	CH_3	CH_3	$CH(CH_3)_2$	$CH(CH_3)_2$	H	CH_3	H
R''	CH_3	$CH(CH_3)_2$	H	$CH(CH_3)_2$	H	H	CH_2Ph	CH_3

2.5. Ligand synthesis on polymeric support

The polymer bound ligand synthesis was carried out analogous to the solution phase chemisty. Polymer support was introduced to the synthesis *via* the Schiff base formation using the dihydrochlordie salts **2.14a-d**. These salts were obtained by the *N*-Boc deprotection of **2.13a-d** as shown in **Scheme 2.3**.[186] Using Castro's reagent as coupling reagent,[187, 188] 85-96% yields were obtained for the monoacylation of *o*-phenylenediamine within 45 minutes. The monoacylated compounds were crystalline and were recrystallized from a mixture of hexane and ethyl acetate.



Scheme 2.3 Schiff base formation on polymer support

Deprotection of the t-Boc group to generate the dihydrochloride salts **2.14a-d** was done by treating **2.13a-d** with methanolic acetyl chloride under anhydrous conditions.

The product was a sticky residue after the removal of methanol using a rotary evaporator and was purified by triturating with anhydrous ether to remove traces of hydrochloric acid. Amorphous powders were obtained after purification. These dihydrochloride salts were vacuum dried over P_2O_5 and stored at room temperature. The yields of formation of monoacylated compounds (**2.13a-d**) and the dihydrochloride salts are summarized in **Table 2.6**.

Table 2.6 The yields of monoacylated compounds

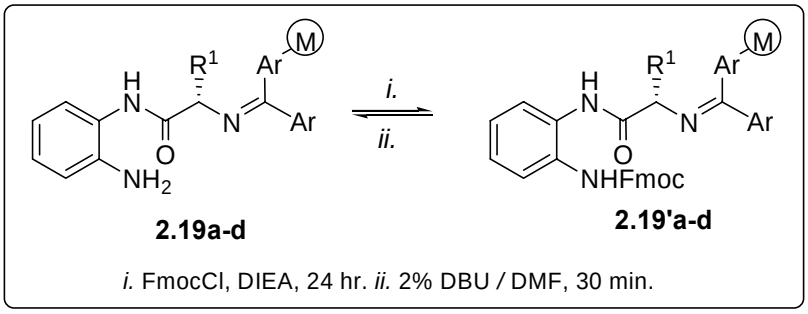
Amino Acid	Boc Protected			Dihydrochloride salt		
	Yield	[α]	M.P./ °C	Yield	[α]	M.P./ °C
Gly	96	-0.44	146-47	98	1.00	238-40
Ala	93	-71.66	144-45	78	-4.35	186-88
Val	88	-46.2	110-112	87	19.28	158-60
Phe	85	-11.91	132-133	86	42.68	165-67

2.5.1. Optimization and characterization of polymer supported Schiff bases

In the presence of mild and anhydrous acids, primary amines react with diarylketimine linkers (**2.9** and **2.11**) to form the corresponding Schiff bases. This reaction was optimized using the linker **2.9** and the dihidrochloride salt **2.14b**. When the reaction was performed in the presence of external base such as DBU to partially neutralize hydrochloride salt (HCl salt: DBU molar ratio was 0.5: 0.9), the product loading decreased to 4.8% $mmolg^{-1}$ from 12.3%. Also when the reaction was done after the complete neutralization of the HCl salt by DBU, but in the presence of anhydrous *p*-toluene sulfonic acid, the loading remained low at 4.2% $mmolg^{-1}$. Changing the reaction solvent from 100% DMF to a mixture of acetonitrile-DMF (1:1), did not improve the

loading. The Schiff bases **2.19a-d** and **2.20a-d** were synthesized under the optimized reaction conditions to obtain 12.3% of loading.

These compounds on solid support were characterized using an indirect method. The primary amine of **2.19a-d** was protected using Fmoc protecting group and the removal of Fmoc moiety was monitored using a UV-VIS spectrophotometer. For the Fmoc analysis, a small portion of the Schiff base resin (typically 50 mg of the resin) was reacted with FmocCl to obtain **2.19'a-d** and deprotection of Fmoc was done using 2% DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene) in DMF solution at room temperature for 30 minutes (**Scheme 2.4**).[189-191]



Scheme 2.4 Fmoc deprotection using DBU

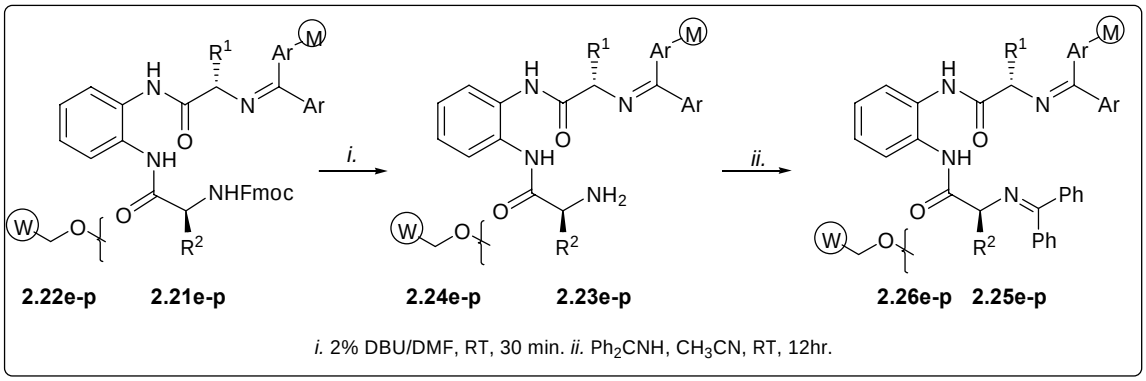
In solid phase synthesis, removal of the *N*-Fmoc group is usually achieved by treatment with 20-50% v/v piperidine in DMF. The β-proton abstraction due to the base generates cyclopentadienyl intermediate, which decomposes to generate dibenzofulvene and free amine. The dibenzofulvene generated forms an UV active chromophore that is used for analysis (ε = 7800 $Lmol^{-1}cm^{-1}$ with λ_{max} = 290.5 nm) of resin loading. When DBU is used dibenzofulvene is used in its free form for spectroscopic analysis (ε = 9254 cm^{-1} with λ_{max} = 307.2 nm). The tertiary base DBU is a very good alternative to piperidine since it causes rapid deprotection, less enantiomerization of resin-bound amino

acids and decreases the extent of broadening of UV Fmoc deprotection peaks.[192] The results of Fmoc deprotection are summarized in **Table 2.7**.

When the qualitative identification tests for amines, such as Kaiser,[193] and chloranil test[194] were performed on the Schiff bases, no distinctive color change was obtained, thus limiting the mode of analysis to UV measurements.

Table 2.7 Results of Fmoc analysis, compared to the manufacturer's loading

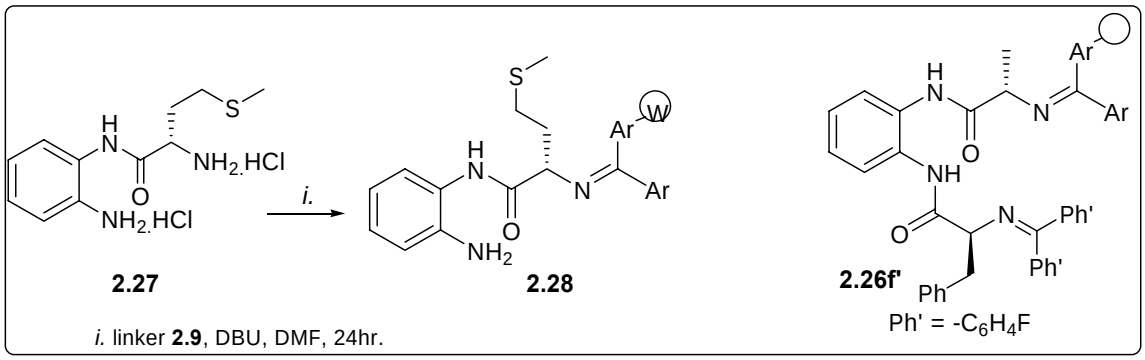
Resin	***Amino acid***	***Mfg. Loading***	***Theoretical***	***Obtained µmoles***		***% Loading***	
		mmol/g	***µmoles***	***DBU***	***Piperidine***	***DBU***	***Piperidine***
Wang	Phe	1.47	73.05	8.9	9.2	12.2	12.59
	Ala	1.47	73.05	7.47	8.6	10.2	11.77
	Val	1.47	73.05	9.05	9.6	12.4	13.14
	Gly	1.47	73.05	7.55	6.6	10.3	9.03
	Phe-Phe	1.47	294	38.8	38.08	13.2	12.95
	Phe-Val	1.47	294	29.8	36.25	10.2	12.33
	Ala-Phe	1.47	294	36.46	33.81	12.4	11.5
	Ala-Val	1.47	294	31.75	35.01	10.8	11.91
Merrifield	Phe	1.00	50		6.5		13.00
	Ala	1.00	50		7.3		14.60
	Val	1.00	50		4.8		9.60
	Gly	1.00	50		4.9		9.80
	Phe-Phe	1.00	200		26		13.00
	Phe-Val	1.00	200		35		17.50
	Ala-Phe	1.00	200		21		10.5
	Ala-Val	1.00	200		16		8.0



Scheme 2.5 Formation of the bifurcated dipeptide ligands

Synthesis of bifurcated peptides **2.21e-p** was achieved by the addition of *N*-Fmoc amino acids to the Schiff bases **2.19a-d** using BOP and HOBt as the coupling reagents. The simultaneous cleavage of the Fmoc group and generation of free amine was achieved to get **2.23e-p** using 20% piperidine in DMF or 2% DBU in DMF solutions. The loadings after the Fmoc deprotection are shown in the **Table 2.6**. The loading of the bifurcated peptides, when compared to the Schiff bases **2.19a-d**, indicated that the peptide reactions proceeded with no loss in the catalyst loading. The final step in the synthesis was to cap the bifurcated amines **2.23e-p** by formation of a second Schiff base using benzophenone imine in the presence of camphorsulfonic acid. The Schiff base was shown to be intact in the presence of camphorsulfonic acid (**Table 2.1**), while attempting to deprotect the Boc group of **2.16**, thus provides the acidic environment for the formation of second Schiff base and completing the ligand synthesis. The ligands **2.25e-p** were synthesized in an over all yield of ~10% when compared to the manufacturer's loading of polymer support. The ligands **2.26e-p** were synthesized under the same conditions and had the similar ligand loading.

2.5.2. Elemental analysis



Scheme 2.6 Resins for elemental analysis

Elements such as halides, sulfur and nitrogen, when present in an organic compound can be used to find the composition of that compound through the elemental analysis. Similarly if the polymer support contained one such element, elemental analysis can be an effective tool in obtaining information about the substituents on polymer support. Having amino acids like methionine and or cystein as the part of the ligand can give information about the ligand loading on the resin, through elemental analysis. Using Wang diarylketimne linker **2.9** and L-Met-HCl_2, **2.27b** the Schiff base **2.28** was synthesized and analyzed for elemental composition. When the result was compared to the manufacturer's loading of 1.39 $mmolg^{-1}$, only 4.4% of the loading was obtained. Under the same conditions when the free base **2.23f** was converted to **2.26f'**, using 4,4'-diflorobenzophenone imine, the elemental analysis data for fluorine gave 9.2% loading.

Elemental analysis of resins, in particular, is fraught with difficulties.[124] In general, the inaccuracy and deviation of the results obtained is associated with the low loading of the substrates on the support. Information on the real availability of reactive

or functional groups on the resin is also very difficult to obtain by such an analysis. The reproducibility of C, H, N, and halogen determinations is too poor to quantitate small variations. Several independent investigations on $BrCH_2(O)CO$-trityl PS/DVB resins gave values between 0.9-1.8 mmole of Br per gram of resin, with a possible maximum loading of 1.47 $mmolg^{-1}$. The lack of reproducibility was the result of frequently occurring side reactions (e.g. cross-linking and multiple coupling of the substrate) and the results obtained deviated severely from the actual yields of the cleaved products.[195]

2.5.3. ^{13}C NMR - a characterization tool

NMR spectroscopy had been very useful in characterizing the molecules on polymer support. The gel phase ^{13}C NMR was recorded using the solid phase ligands on Wang resin. The chemical shifts of α- and β-carbons of the amino acids generated sharp peaks in the NMR spectra as they were away from the polymer support and the aromatic regions of the spectra were masked by the line broadenings of the polystyrene support. The NMR data obtained is summarized in **Table 2.8**. The chemical shifts of the ligand intermediates were compared with the solution phase analogs.

Table 2.8 ^{13}C NMR chemical shifts of gel phase NMR

Name	C2α	C2β	C13α	C13β	OCH3	
					OCH2/3	OCH3
Phe-SB-on resin	69.642	40.000			55.154	53.298
Phe-SB	67.012	41.641			55.168	55.234
Phe-SB-Ala-Boc on resin	67.709	40+	51.883	19.234	55.221	53.311
Phe-SB-Ala-Boc	67.452	41.654	49.933	18.473	55.047	55.141
Phe-SB-Ala-Fmoc	69.736			19.114	55.181	52.350
Phe-SB-Ala-SB on resin	69.714	40.746		16.897	55.168	
Phe-SB-Ala-SB	67.906	41.908	61.323	20.997	55.154	55.234
Ala-SB-Phe-SB on resin	69.783			39.591	55.214	53.345

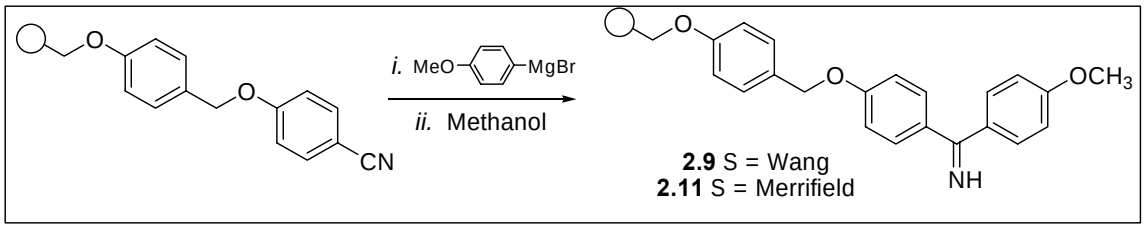
2.6. Conclusions

In conclusion, the ligands were synthesized on both Wang and Merrifield resins, with the loadings of about 10%, compared to manufacturer's loading. As it was evident from the Fmoc analysis, there had not been a big change in the loading before and after the second amino acid was added. This suggests that, the diarylketimine linkers (**2.9** and **2.11**) were robust through out the scheme, and this linker can be viewed as a stable protecting group for primary amines.

The low loading of the resin could also be a result of poor swelling behavior of Merrifield and Wang resins. By replacing the polystyrene support by resins like TantaGel, which remain swollen in protic solvents like water, might lead to better loading.

2.7. Solid phase ligand synthesis

2.7.1. Formation of ketimine linker



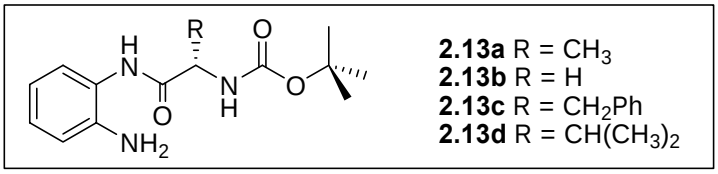
All the starting materials were purchased from Aldrich and were recrystallized, or distilled prior to use. Boc and Fmoc protected amino acids, coupling reagents and the Merrifield and Wang resins were purchased from Advanced ChemTech.

In a jacketed sintered glass funnel, with a positive flow of argon, 4-Bromo Wang resin (polystyrene supported benzyloxybenzyl bromide, 6.0 g, 1.47 $mmolg^{-1}$) was agitated in freshly distilled DMF (60 mL). After 30 minutes of swelling, Cesium carbonate (8.62 g, 26.5 mmol, 3.0 equiv.) and 4-cyanophenol (1.06 g, 26.5 mmol, 3.0 equiv.) were added and the agitation of resin with argon flow was continued at room temperature for 24 hours. The reaction was monitored using IR spectroscopy. A small aliquot of the reaction mixture, was taken, and washed with DMF and DCM to clean the resin Cesium salt of 4-cyanophenol. Using anhydrous KBr, the IR spectrum was recorded. After 24 hours, when no change in the intensity of –CN peak was observed, the reactants were washed out, using dioxane-water (1:1 mixture, 4 x 60 mL), dioxane (4 x 60 mL), and methanol (2 x 40 mL). The resin was then agitated with CH_2Cl_2 (3 x 60 mL) and dried in *vacuo*. The final resin was gray. Using elemental analysis for nitrogen, it was observed that, when the reaction was performed with ethanol as the solvent, the resin loading

decreased to 53.5% of the manufacturer's loading, compared to when acetonitrile (75.9% loading) was used as the solvent for the reaction.

In a 250 mL round bottom flask equipped with a reflux condenser with cold water circulation, magnesium (1.02 g, 44.17 mmol, 5 equiv.) was placed and freshly distilled THF (30 mL) was added. To this suspension, a few I_2 crystals were added as radical initiator and *p*-bromoanisole was added dropwise (60 mL solution in THF, 8.27g, 44.17 mmol) at 35 °C. As the color of I_2 disappeared and the reaction started to autocatalyze, the heating (oil bath) was removed and the addition of *p*-bromoanisole was completed in 30 min. This reaction was warmed to gentle reflux for 30 minutes and the resulting Grignard reagent was cannulated into the nitrile resin, pre-treated with THF for 30 min. This reaction mixture was agitated on a sintered glass funnel using argon and the final product, diarylketimine on polymer support, was obtained after 24 hours. The reaction was monitored using FT-IR spectroscopy for the disappearance of the CN stretch at 2228 cm^{-1}.

2.7.2. General procedure for preparation of monoacylated phenylene diamine



o-Phenylenediamine (1 g, 9.2 mmol) was dissolved in DMF (100 mL) in a flame dried round bottom flask (250 mL). To this brown solution, diisopropylethylamine (Hunig's base or DIEA, 2.4 mL, 13.8 mmol, 1.5 equiv., purchased from Advanced Chemtech.) was added in a single portion keeping the reaction mixture at 0 °C using an

ice bath. Boc-amino acid (1.0 equiv.) and BOP (benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate, 5.08 g, 11.5 mmol, 1.5 equiv., purchased from Advanced Chemtech) were added in one portion. The solution was allowed to warm to room temperature and the reaction progress was monitored through TLC (EtOAc:hexane 40:60, ninhydrin visualization). For the work-up, the reaction mixture was diluted with EtOAc (200 mL), washed with 1% NaCl (3 x 200 mL), saturated $NaHCO_3$ (2 x 200 mL), saturated NaCl solution (1 x 200 mL). The organic layer was dried over $MgSO_4$, filtered and reduced in *vacuo*. The product was recrystallized from ethyl acetate/hexane.

tert-Butyl (S)-1-(2-aminophenylcarbamoyl)ethylcarbamate (2.13a)

Yield = 93%, M.P. = 144-145 °C, $[\alpha]_D^{25}$ = (-)-71.66 (*c* = 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.44 (d, *J* = 7.33 Hz, -C*H*$_3$, 3H), 1.45 (s, -C(C*H*$_3$)$_3$, 9H), 3.67 (br s, -N*H*$_2$, 2H), 4.29 (t, *J* = 6.84 Hz, -C*H*-, 1H), 5.22 (d, *J* = 6.84 Hz, -N*H*-CO-O-, 1H), 6.74 (m, Ar-*H*, 2H), 7.02 (m, Ar-*H*, 1H), 7.23 (m, Ar-*H*, 1H), 8.07 (br s, -N*H*-CO, 1H).

^{13}C NMR (300 MHz, $CDCl_3$, δ): 17.76 (-*C*H$_3$), 28.30 (C*(C*H$_3$)$_3$), 50.70 (-*C*H-), 80.58 (-O-*C*), 117.34 (Ar-*C*$_3$), 119.02 (Ar-*C*$_5$), 123.40 (Ar-*C*$_6$), 125.49 (Ar-*C*$_4$), 127.15 (Ar-*C*$_1$), 140.39 (Ar-*C*$_2$), 171.38 (-NH-*C*O).

TLC: R_f = 0.39, plum color (ninhydrin, 60:40 hexane/ethyl acetate).

tert-Butyl (2-aminophenylcarbamoyl)methylcarbamate (2.13b)

Yield = 96%, M.P. = 146-147 °C, $[\alpha]_D^{25}$ = -0.44° 9 (*c*, 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (s, -(C(C*H*$_3$)$_3$, 9H), 3.47 (br s, -N*H*$_2$, 2H), 3.90 (d, *J* = 5.86 Hz, -C*H*$_2$-, 2H), 5.41 (t, *J* = 5.37 Hz, -N*H*-CO-O-, 1H), 6.74 (m, Ar-*H*, 2H), 7.02 (m, Ar-*H*, 1H), 7.18 (m, Ar-*H*, 1H), 8.01 (br s, -N*H*-CO, 1H).

^{13}C NMR (300 MHz, $CDCl_3$, δ) : 28.29 (C(*C*H$_3$)$_3$), 45.10 (-*C*H-), 80.75 (-O-*C*), 117.56 (Ar-*C*$_3$), 119.22 (Ar-*C*$_5$), 123.29 (Ar-*C*$_6$), 125.50 (Ar-*C*$_4$), 127.31 (Ar-*C*$_1$), 140.71 (Ar-*C*$_2$), 168.32 (-NH-*C*O).

TLC: R_f = 0.11, plum color (ninhydrin, 60:40 hexane/ethylacetate)

tert-Butyl (S)-1-(2-aminophenylcarbamoyl)-2-methylpropylcarbamate (2.13c)

Yield = 88%, M.P. = 110-112 °C, $[\alpha]_D^{25}$ = (-)-46.20° (*c*, 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): 0.98 (dd, J_1 = 11.23 Hz, J_2 = 6.83 Hz,-CH(C*H*$_3$)$_2$, 6H), 1.39 (s, -(C(C*H*$_3$)$_3$, 9H), 2.11 (sept, *J* = 6.83 Hz, -C*H*(CH$_3$)$_2$, 1H), 3.84 (br s, -N*H*$_2$, 2H), 4.13 (t, *J* = 7.81 Hz, -C*H*-, 1H), 5.77 (d, *J* = 8.79 Hz, -N*H*-CO-O-, 1H), 6.65 (m, Ar-*H*, 2H), 6.97 (m, Ar-*H*, 1H), 7.11 (m, Ar-*H*, 1H), 8.57 (br s, -N*H*-CO, 1H).

^{13}C NMR (300 MHz, $CDCl_3$, δ): 18.25 & 19.23 (-CH(*C*H$_3$)$_2$), 28.22 (C(*C*H$_3$)$_3$), 30.84 (-*C*H(CH$_3$)$_2$)) 60.54 (-*C*H-), 79.82 (-O-*C*), 116.96 (Ar-*C*$_3$), 118.42 (Ar-*C*$_5$), 123.13 (Ar-*C*$_6$), 125.86 (Ar-*C*$_4$), 127.02 (Ar-*C*$_1$), 141.12 (Ar-*C*$_2$), 156.34 (-NH-*C*O-O), 171.18 (-NH-*C*O).

TLC: R_f = 0.64, plum color (ninhydrin, 60:40 hexane:ethyl acetate).

tert-Butyl (S)-1-(2-aminophenylcarbamoyl)-2-phenylethylcarbamate (2.13d)

Yield = 85%, M.P. = 132-133 °C, $[\alpha]_D^{25}$ = -11.91° (*c*, 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): 1.39 (s, -(C(C*H*$_3$)$_3$, 9H), 3.09 (d, *J* = 7.33 Hz, -C*H*$_2$-Ph, 2H), 3.60 (br s, -N*H*$_2$, 2H), 4.51 (d, *J* = 6.60 Hz, -N*H*-CO-O-, 1H), 5.52 (d, *J* = 7.57 Hz, -

C*H*-, 1H), 6.70 (m, Ar-*H*, 2H), 7.05 (m, Ar-*H*, 2H), 7.29 (m, Ar-*H*, 5H), 7.89 (br s, -N*H*-CO, 1H).

^{13}C NMR (300 MHz, $CDCl_3$, δ) : 28.23 ((*C*H_3)$_3$), 38.56 (-*C*H_2-Ph) 56.48 (-*C*H-), 80.29 (-O-*C*), 117.03 (Ar-*C*), 118.74 (Ar-*C*), 122.91 (Ar-*C*), 125.80 (Ar-*C*), 126.89 (Ar-*C*), 127.21 (Ar-*C*), 128.64 (Ar-*C*), 129.36 (Ar-*C*), 136.61 (Ar-*C*), 140.90 (Ar-*C*), 155.72 (-NH-*C*O-O), 170.33 (-NH-*C*O).

TLC: R_f = 0.54, plum color (ninhydrin, 60:40 hexane/ethyl acetate)

2.7.3. General procedure for Boc deprotection

Compounds **2.13a-d** were dissolved in 50 mL anhydrous MeOH and chilled to 0 °C using an ice bath. In a separate flask 50 mL of MeOH was chilled to 0^{o}C. Acetyl chloride (4.0 equiv.) was added slowly. The resultant methanolic HCl solution was added to the chilled reaction mixture dropwise over 30 min. The reaction mixture was allowed to warm to room temperature for 18 hours. After all the starting material had been consumed, as observed by TLC (1:1:1:1, EtOAc : IPA : H_2O : AcOH), MeOH was removed by rotary evaporation. The residual HCl was removed by dissolving the residue in MeOH and subsequent rotary evaporation (5 x 200 mL). This material was placed *in vacuo* until brittle foam was obtained, then triturated in Et_2O to obtain white amorphous powder as the product. The fine suspension was filtered and dried over P_2O_5.

(S)-2-Amino-N-(2-aminophenyl)propanamide dihydrochloride (2.14a)

Yield = 78%, M.P. = 186-188 °C, $[\alpha]_D^{25}$ = (-)-4.35 (*c*, 1.00, MeOH).

^{1}H NMR (300 MHz, CD_3OD): 1.71 (d, *J* = 6.9 Hz, -C*H*$_3$, 3H), 4.33 (q, *J* = 6.9 Hz, -C*H*-, 1H), 7.42-7.56 (m, Ar-*H*, 4H), 8.51 (br s, -N*H*-CO, 0.1H).

^{13}C NMR (300 MHz, CD3OD): 17.40 (C_β), 50.86 (C_α), 125.62- 131.84 (Ar-*C*, 6), 170.93 (-*C*O-).

TLC: R_f = 0.7, red color (ninhydrin, 1:1:1:1 mixture).

2-Amino-N-(2-aminophenyl)acetamide dihydrochloride (2.14b)

Yield = 98%, M.P. = 238-240 °C, $[\alpha]_D^{25}$ = (+)-1.00 (*c*, 1.00, MeOH).

^{1}H NMR (300 MHz, D_2O): 4.06 (s, -C*H*$_2$-, 2H), 7.35 (m, Ar-*H*, 1H), 7.43 (m, Ar-*H*, 3H).

^{13}C NMR (300 MHz, CD_3OD): 42.22 (C_α), 125.50- 131.68 (Ar-*C*, 6*C*), 167.44 (-*C*O-).

TLC: R_f = 0.7, red(ninhydrin, 1:1:1:1 mixture)

(S)-2-Amino-N-(2-aminophenyl)-3-methylbutanamide dihydrochloride (2.14c)

Yield = 87%, M.P. = 158-160 °C, $[\alpha]_D^{25}$ = (-)-19.28 (*c*, 1.00, MeOH).

^{1}H NMR (300 MHz, CD_3OD): 1.10 (dd, $J_1 = J_2$ =6.70Hz, (C*H*$_3$)$_2$, 6H), 2.24 (sept, *J* = 6. 70Hz, -C*H*(CH$_3$)$_2$, 1H), 3.83 (dd, J_1 = 5.95 Hz, J_2 = 3.67 Hz, -C*H*-, 1H), 6.63 (m, Ar-*H*, 1h), 6.71 (m, Ar-*H*, 1H), 6.99 (m, Ar-H, 2H).

^{13}C NMR (300 MHz, CD_3OD): 18.00 & 19.64 (*C*H$_3$), 31.39 (C_β), 60.08 (C_α), 125.45 (Ar-*C*), 126.37 (Ar-*C*), 127.07 (Ar-C), 127.38 (Ar-*C*), 129.25 (Ar-*C*), 130.67 (Ar-*C*), 131.32 (Ar-*C*), 169.65 (-*C*O-).

TLC: R_f = 0.7, red color (ninhydrin, 1:1:1:1 mixture).

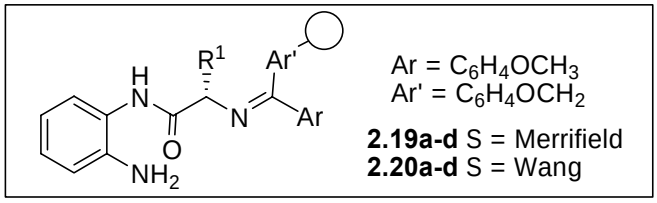
(S)-2-Amino-N-(2-aminophenyl)-3-phenylpropanamide dihydrochloride (2.14d)

Yield = 85%, M.P. = 132-133 °C, $[\alpha]_D^{20}$ +25.4° = (-)-11.91 (*c*, 1.00, MeOH)

^{1}H NMR (300 MHz, CD_3OD): 3.26 (dd, J_{AB} = 13.86 Hz, J_{AX} = 8.25 Hz, -CH_AH$_B$, 1H), 3.418 (dd, J_{AB} = 13.86 Hz, J_{BX} = 6.9 Hz, -CH$_A$$H_B$, 1H), 4.47 (dd, J_{AX} = 8.25 Hz, J_{BX} = 6.90 Hz, -CH_X-, 1H), 7.08-7.14 (m, Ar-H, 1H), 7.32-7.54 (m, Ar-H, 8H).

TLC: R_f = 0.8, ninhydrin visualization: red color

2.7.4. General procedure for polymer supported Schiff base formation



The diarylketimine resin **2.9** or **2.11** was pre-treated with CH_3CN for 30 min at room temperature in a jacketed sintered glass funnel using a stream of argon. The hydrochloride salt **2.14(a-d)** (3.0 equiv.) and DBU (5.4 equiv.) were added to this suspension and agitatated at 60°C using hot water circulation, for 24 hrs. The resulting resin was washed with methanol (3 x 20 mL) and methylene chloride (2 x 20 mL) to remove excess HCl salts. As the resin shrinks in protonated solvents, methylene chloride was used to expose all the sites for further reactions.

Procedure for the Fmoc analysis:

A small portion of the Schiff base **2.19a-d**, (50 mg) was pre-treated with DMF in a jacketed sintered glass funnel and to this suspension, Fmoc chloride (2.0 equiv.) and DIEA (2.0 equiv.) were added in one lot and the reaction mixture was agitated for 24 hrs. The resin was washed with DMF (3 x 5 mL) and finally with DCM (2 x 5 mL) and dried *in vacuo.*

The Fmoc protected amine was then deprotected using 2% DBU solution in DMF or 20% piperidine in DMF. The resin was pretreated with solvent for 30 min, so that all the pores could be exposed and the solvent was drained. The resin was treated with 2% DBU solution (or 20% Piperidine in DMF) for 30 min and solvent was collected along with DMF washings (2 x 5 mL) in a clean dry flask. These washings were then diluted to known volume using a volumetric flask and the UV-VIS absorption was noted. In the case of DBU, λ_{max} = 307.2 nm corresponding to dibenzofulvene and for piperidine cleavage, it is 290.5 nm corresponding to the dibenzofulvene-pipridine adduct The ε values of DBF and DBF-piperidine adduct are 7800L $M^{-1}cm^{-1}$ and 9254 L $M^{-1}cm^{-1}$ respectively. Using Beer's Law the concentrations of these washings were determined and the number of moles of dibenzofulvene (or DBF-piperidine adduct) was back calculated (**Table 2.7**).

The structure of the Schiff base was confirmed using the ^{13}C NMR of solid beads. The resin was taken in to the standard NMR tube and $CDCl_3$ was added dropwise without forming any air bubbles. All the parameters of solution phase ^{13}C NMR were kept constant except the line broadening, which was changed to 5 Hz. Fully resolved ^{13}C NMR of the solid supported Schiff bases can be obtained after scanning for about 12 hours on a 300 MHz Varian NMR spectrometer. The carbon nuclei situated far from the solid support gave a sharp signal, where as the nuclei close to the polymer support either generated a broad peak or were unseen in the spectrum. The NMR spectra have a very good correlation with the predicted NMR obtained by the Chemdraw software and with

the solution phase analogues. As the NMR of each compound took 12 hours, not all compounds were characterized using NMR.

The following notation was used for interpretation of ^{13}C NMR spectra of all the solid phase compounds. Numbering of carbons was started from the amino terminal of first amino acid loaded on the solid support, through ketimine linker and the amino acid side chains were identified by the corresponding Greek letters (α, β etc.). The second amino acid was numbered through the phenylenediamine backbone. The $–OCH_2$ and –CH- of the Fmoc group on the second amino acid were represented as $–OCH_{2Fmoc}$ and $–OCH_2\text{-}CH_{Fmoc}$ to distinguish them from the diarylimine backbone OCH_2 and the $\text{-}CH_\alpha$.

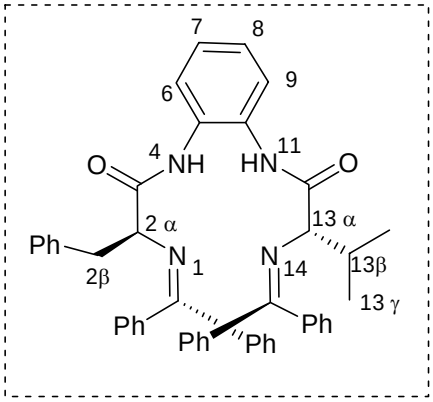


Figure 2.4 Labelling used for ^{13}C NMR

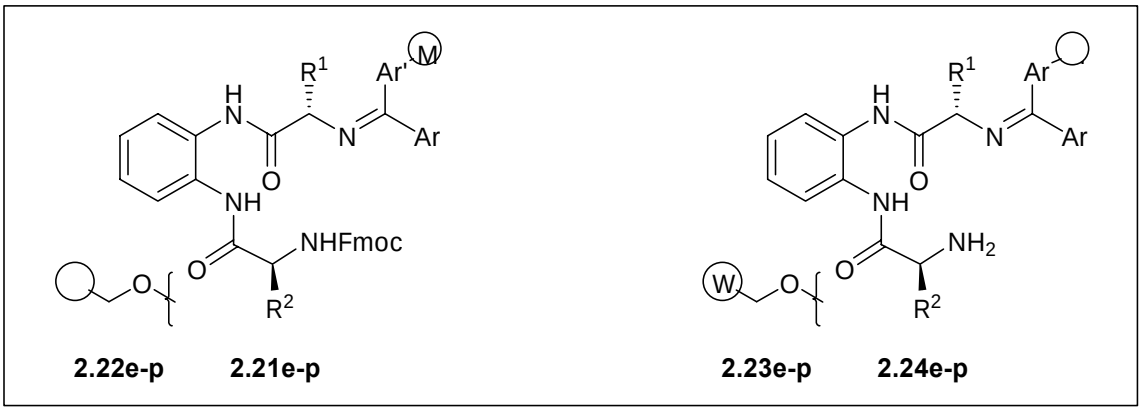
Polystyrene bound N-(2(S)-Amino-phenyl)-2-{[(benzyloxy benzyl) (4-methoxy-phenyl)-methylene]-amino}-3-phenyl-propionamide

^{13}C NMR (300 MHz, $CDCl_3$, δ) : 69.64 ($C_{2\alpha}$), 40.0 ($C_{2\beta}$), 55.15 ($\text{-}OCH_2$), 53.29 ($\text{-}OCH_3$).

Polystyrene bound N-(2(S)-Amino-phenyl)-2-{[(benzyloxy benzyl)-(4-methoxly-phenyl)-methylene]amino} propionamide

^{13}C NMR (300 MHz, $CDCl_3$, δ) : 69.67 ($C_{2\alpha}$), 55.18 ($\text{-}OCH_2$), 53.29 ($\text{-}OCH_3$).

2.7.5. General procedure for formation of Fmoc acylated Schiff Base and deprotection of Fmoc group



2.22e-p **2.21e-p** **2.23e-p** **2.24e-p**

The diarylketimine derived Schiff bases (200 mg) were acylated using the standard peptide coupling conditions using Fmoc amino acid, BOP and HOBt as the reagents. Before the addition of reagents, the Schiff base was pretreated with DMF for 30 min. DMF was drained and fresh DMF was added to the reaction to maintain a gentle agitation of the beads. BOP (2.0 equiv.), hydroxy benzotriazole (HOBt, 2.0 equiv.), DIEA (2.0 equiv.) and Fmoc amino acid (2.0 equiv.) were added in one lot and the agitation was continued for 24 hrs. After 24 hrs, the resin was washed with DMF (3 x 10 mL) and DCM (2 x 10 mL) and dried in vacuum. The overall reaction yield (after two steps) was calculated once the Fmoc group was deprotected using 2% DBU or 20% piperidine in DMF. Based on first amino acid loading, the second amino acid addition resulted in good yields (close to 100% conversion; **Table 2.7**).

Polystyrene bound {1(S)-[2-(2(S)-{[[4-(4-methoxybenzyloxy)-phenyl]-(4-methoxy-phenyl)-methylene]-amino}-3-phenyl-propionylamino)-phenylcarbamoyl]-ethyl}-carbamic acid 9H-fluoren-9-ylmethyl ester

^{13}C NMR (300 MHz, $CDCl_3$, δ): 19.11 ($C_{13\beta}$), 46.89 (-O*C*H$_2$-*C*H$_{Fmoc}$), 52.35 (-O*C*H$_3$), 55.18 (-O*C*H$_2$), 66.57 (-O-*C*H$_{2Fmoc}$), 69.73 ($C_{2\alpha}$).

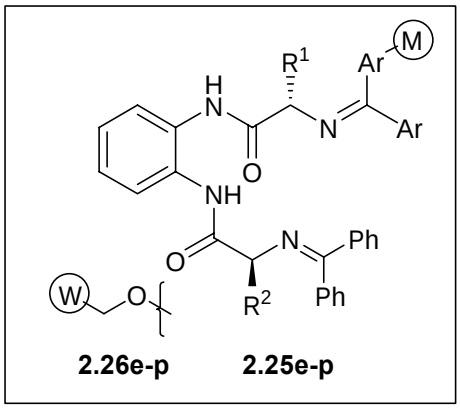
Polystyrene bound {1(S)-[2-(2(S)-{[[4-(4-methoxybenzyloxy)-phenyl]-(4-methoxy-phenyl)-methylene]-amino}-3-phenyl-propionylamino)-phenylcarbamoyl]-2-methyl-propyl}-carbamic acid 9H-fluoren-9-ylmethyl ester

^{13}C NMR (300 MHz, $CDCl_3$, δ) : 17.25 & 19.46 ($C_{13\gamma}$), 31.89 ($C_{13\beta}$), 40.0 ($C_{2\beta}$), 46.97 (-O*C*H$_2$-CH$_{Fmoc}$), 53.37 (-O*C*H$_3$), 55.21 (-O*C*H$_2$), 62.23 ($C_{13\alpha}$), 66.84 (-O*C*H$_{2Fmoc}$),.

Polystyrene bound {1-[2-(2(S)-{[[4-(4-methoxybenzyloxy)-phenyl]-(4-methoxyphenyl)-methylene]-amino}-acetylamino)-phenylcarbamoyl]-ethyl}-carbamic acid 9H-fluoren-9-ylmethyl ester

^{13}C NMR (300 MHz, $CDCl_3$, δ) : 46.89 (-O*C*H$_2$-CH$_{Fmoc}$), 52.39 ($C_{13\alpha}$), 53.31 (-O*C*H$_3$), 55.19 (-O*C*H$_2$), 66.60 (-O*C*H$_{2Fmoc}$), 69.71 ($C_{2\alpha}$).

2.7.6. Formation of the complete ligand, bifurcated dipeptide:



2.26e-p **2.25e-p**

The primary amine obtained by the deprotection of the Fmoc moiety was pretreated with acetonitrile. To this suspension, diphenyl ketimine (benzophenone imine, 3.0 equiv.) and camphorsulphonic acid (0.3 equiv.) were added and the resin was agitated in the solid phase reactor for 24 hrs. The resin was then washed with CH_2Cl_2 (4 x 5 mL) and the complete ligand was dried *in vacuo*.

Polystyrene bound 2(S)-(benzhydrylidene-amino)-N-[2-(2-{[[4-(4-methoxybenzyloxy)-phenyl]-(4-methoxyphenyl)-methylene]-amino}-acetylamino)-phenyl]-propionamide

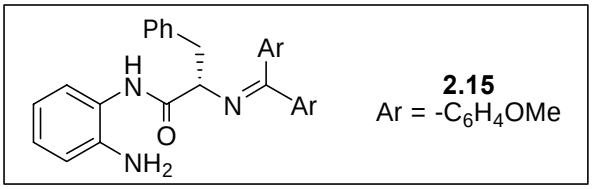
^{13}C NMR (300 MHz, $CDCl_3$, δ) : 20.89 ($C_{13\beta}$), 53.30 (-OCH_3), 55.11 (-OCH_2), 60.23 ($C_{13\alpha}$), 69.99 ($C_{2\alpha}$).

Polystyrene bound N-{2-[2(S)-(benzhydrylidene-amino)-propionylamino]-phenyl}-2(S)-{[[4-(4-methoxybenzyloxy)-phenyl]-(4-methoxyphenyl)-methylene]-amino}-3-phenyl propionamide

^{13}C NMR (300 MHz, $CDCl_3$, δ): 16.90 ($C_{13\beta}$), 40.75 ($C_{2\beta}$), 55.17 (-OCH_2), 69.71 ($C_{2\alpha}$).

2.8. Synthesis of solution phase analog

N-(2-Amino-phenyl)-2-{bis-(4-methoxyphenyl)-methylene]-amino}-e-phenyl-2(S)-propionamide



In a 50 mL flame dried round bottom flask equipped with a refluxed condenser, the dihydrochloride salt **2.14d** (2.25 g, 6.85 mmol) was dissolved in 20 mL of acetonitrile:DMF (1:1). To this solution, 4,4'-dimethoxydiphenylketimine (1.81 g, 7.53 mmol, 1.1 equiv.) was added and the reaction mixture was refluxed at -75 °C. The reaction progress was monitored using TLC (92.5:7.5 CH_2Cl_2: ethyl acetate). The reaction mixture was diluted with ethyl acetate (100 mL) and aqueous work up was performed. The organic layer was washed with 10% $NaHCO_3$ solution (2 x 50 mL) and 1% $NaHCO_3$ (2 x 50 mL). The organic layer was dried over a 1:1 mixture (w/w) of anhydrous K_2CO_3 and $MgSO_4$. The crude product containing the traces of unreacted diarylketimine and 4,4'-dimethoxybenzophenone was purified by silica gel column chromatography (92.5:7.5 CH_2Cl_2: ethyl acetate).

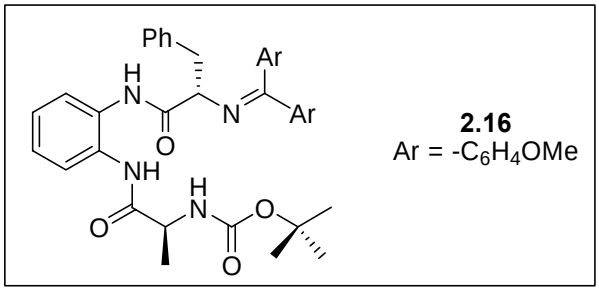
Yield = 68%, $[\alpha]_D^{25}$ = (-)-21.43° (*c* = 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.14 (m, -C*H*$_2$-Ph, 2H), 3.60 (br s, -N*H*$_2$, 2H), 3.85 (2 s, -OC*H*$_3$, 6H), 4.38 (m, -C*H*-, 1H), Aromatic CH (12H), 6.59-6.66(m), 6.69-6.87(m), 6.88-7.28 (m), 7.46-7.63 (m), 8.63 (s, -NH-CO-Ar)

^{13}C NMR (300 MHz, $CDCl_3$, δ): 41.64 (-*C*H_2), 55.17 & 55.23 (-O*C*H_3), Ar- *C* : 113.36, 113.68, 117.53, 119.17, 123.91, 124. 67, 126.27, 126.59, 127.60, 127.98, 128.73, 130.12, 130.20, 159.43 & 161.55 (Ar-O-*C*H_3), 169.15 (*C*=N), 171.38 (NH-*C*O).

TLC: R_f = 0.73, dark brown (ninhydrin, 60:40 hex: ethyl acetate)

{1(S)-[2-(2(S)-{[Bis-(4-methoxyphenyl)-methylene]-amino}-3-phenylpropionylamino)-phenylcarbamoyl]-ethyl}carbamic acid tert-butyl ester



In a 25 mL flame dried round bottom flask, compound **2.15** (220 mg, 0.45 mmol) was dissolved in freshly distilled DMF (5 mL). The solution was cooled to 0 °C and BOP (253 mg, 0.57 mmol, 1.25 equiv.), DIEA (0.12 mL, 0.69 mmol, 1.5 equiv.) were added in single portion. In a separate vial, L-Ala-Boc amino acid (95 mg, 0.50 mmol, 1.1 equiv) was dissolved in DMF (1 mL) and this solution was added to the reaction mixture at 0 °C. The reaction mixture was allowed to warm to room temperature, stirring was continued for 16 hours and the reaction was followed by TLC.

Yield = 92%, $[\alpha]^{25}_D$ = (-)-36.493° (*c* 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.29 (d, *J* = 6.58Hz, -CH_3, 3H), 1.43 (s, -C(CH_3)$_3$, 9H), 3.12(d, *J* = 8.9Hz, -CH_AH_B-Ph, 1H), 3.22(d, *J* = 13.98Hz, -CH_ACH_BPh, 1H), 3.83(s, -OCH_3, 6H), 4.18(m, -CH-, 1H), 4.36(m, -CH-,1H), 5.0(bs, -NH-CO-O-, 1H), Aromatic H's 6.48(m, 2H), 6.78(d, *J* = 8.02Hz, 2H), 6.86(d, *J* = 8.76Hz, 2H), 7.05(m, 2H), 7.19(m,

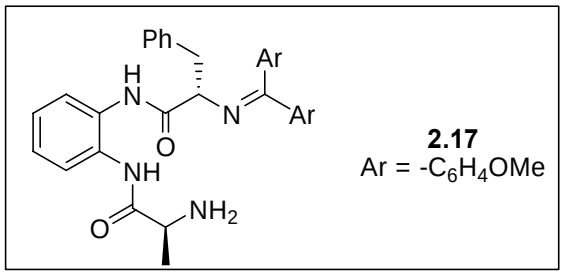
5H), 7.32(m, 2H), 7.57(d, *J* = 8.61Hz, 2H), 8.73(bs, -NH-CO-, 1H), 8.98(bs, -NH-CO-, 1H).

^{13}C NMR (300 MHz, $CDCl_3$, δ): 18.49($-CH_3$), 28.18($-C(CH_3)_3$), 41.67($-CH_2Ph$), 49.93(-CH-), 55.07 &55.18 ($-OCH_3$), 67.45(-CH-), 79.77(-OC-), Aromatic C's: 113.23, 113.51, 124.91, 125.38, 126.01, 126.21, 127.49, 127.97, 128.74, 129.81, 129.99, 130.49, 131.94, 137.36, 159.31(Ar-C-O), 161.55 (Ar-C-O), 169.58 (C=N), 171.47 &172.28 (C=O).

APT (300 MHz, $CDCl_3$, δ): 18.49(CH_3), 28.18(CH_3), 41.67($-CH_2-$), 49.93(-CH-), 55.07 & 55.18($-CH_3$), 67.45(-CH-), 79.77(-OC-). Ar-CH: 113.23, 113.51, 124.91, 125.38, 126.21, 127.97, 128.74, 129.81, 129.99, 130.49. Ar-C: 127.49, 131.94, 137.36, 159.31, 161.55. 169.58(C=N), 171.47(C=O), 172.28(C=O).

TLC: R_f = 0.73, yellow color (ninhydrin, 92.5/7.5 CH_2Cl_2: ethyl acetate).

N-[2-(2(S)-Amin-propionylamino)-phenyl]-2(S)-{bis-(4-methoxyphenyl)-methylene]-amino}-3-phenylpropionamide



2.17
Ar = $-C_6H_4OMe$

Compound **2.16** (200 mg, 0.31 mmol) was taken into a 25 mL flame dried round bottom flask. This was dissolved in anhydrous CH_2Cl_2 at room temperature and to this solution, under anhydrous conditions, boron trifloride etherate (87 µL, 0.69 mmol, 2.2 equiv.) was added in one portion using an airtight microsyringe. The solution was stirred

at room temperature for 12 hours. The reaction progress was monitored using TLC, with CH_2Cl_2 and ethyl acetate (92.5/7.5) as mobile phase. After the complete deprotection of the *t*-Boc group, the reaction mixture was evaporated using a rotovap and the residue was passed through a small plug of silica gel (as filter column, starting with 100% ethyl acetate and increasing the polarity to 3% methanol in ethyl acetate) to obtain a 92% yield (157 mg, 0.29 mmol). Due to the presence of free amine, the product had a very low R_f (using ethyl acetate as mobile phase).

Yield = 76%, $[\alpha]^{20}_D$ +25.4° = (-)-40.322° (*c* 1.00, $CHCl_3$).

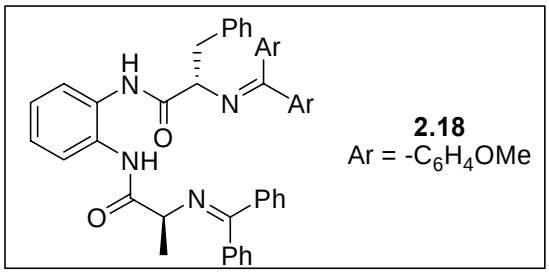
^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.33(d, J = 6.99Hz, -CH_3, 3H), 1.45(bs, -NH_2, 2H), 3.11 (dd, J_{AB} = 12.9Hz, J_{AX} = 9.3Hz, -CH_AH$_B$Ph, 1H), 3.24(dd, J_{AB} = 12.9Hz, J_{BX} = 3.2Hz, -CH$_A$$H_B$Ph, 1H), 3.81 & 3.83(s, -OCH$_3$, 3H), 4.35(dd, J_{AX} = 9.3Hz, J_{BX} = 3.2Hz, -CH_X-, 1H), Aromatic (17H): 6.41(d, J = 8.03Hz, 2H), 6.76(d, J = 8.81Hz, 2H), 6.86(d, J = 8.9Hz, 2H), 7.06(m, 2H), 7.18(m, 5H), 7.59(d, J = 8.85Hz, 2H), 7.71(d, J = 9.5Hz, 2H), 8.90 (bs, -N*H*-CO-), 9.43(bs, -N*H*-CO-). When the spectrum was recorded in the presence of D_2O, the amide peaks at 8.90 and 9.43 ppm disappeared due to H/D exchange.

^{13}C NMR (300 MHz, $CDCl_3$, δ): 21.36 (-*C*H$_3$), 41.73(-*C*H$_2$Ph), 50.87 (-CH-), 55.13 & 55.25 (-O*C*H$_3$), 67.71 (-*C*H-), Aromatic *C*'s: 113.27, 113.49, 124.11, 124.70, 125.49, 126.19, 127.49, 127.98, 128.73, 129.33, 129.97, 130.32, 132.10, 137.48, 159.37, 161.53, 169.47 (*C*=N), 171.94 (-*C*O-), 174.30 (-*C*O-).

Mass Spectroscopy: MS-FAB (*m/z*): [M + H] calcd for $C_{33}H_{34}N_4O_4$, 551.3; found, 551.5.

TLC: R_f = 0.10, bright red (ninhydrin, 100% ethyl acetate).

N-{2-[2(S)-(Benzhydrylideneamino)-propionylamino]-phenyl}-2(S)-{[bis-(4-methoxy-phenyl)-methylene]-amino}-3-phenylpropionamide



2.18
Ar = -C_6H_4OMe

The amine **2.17** (125 mg, 0.23 mmol) was dissolved in anhydrous acetonitrile at room temperature in a 25 mL flame dried round bottom flask. To this solution, benzophenone imine (42 μL, 0.25 mmol, 1.1 equiv.) and D-(+)-10 camphorsulfonic acid (5.27 mg, 0.02 mmol, 0.1 equiv.) were added and the reaction was stirred at room temperature for 12 hours. After the completion of the reaction, the reaction mixture was filtered to remove the insoluble salts and the solvent was removed using rotary evaporation. This residue was passed through a small silica gel column with ethyl acetate and CH_2Cl_2 (92.5/7.5) as mobile phase.

Yield = 88%, $[\alpha]_D^{25}$ = (-)-21.92° (*c* 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.34(d, *J* = 6.86Hz, -C*H*$_3$, 3H), 3.11(dd, J_{AB} = 12.82Hz, J_{AX} = 9.76Hz, -C*H*$_A$H$_B$-Ph, 1H), 3.30(dd, J_{AB} = 12.82Hz, J_{BX} = 2.44Hz, -CH$_A$*H*$_B$-Ph, 1H), 3.77(s, -OC*H*$_3$, 6H), 4.07(q, *J* = 6.86Hz, -C*H*-), 4.30(dd, J_{AX} = 9.76Hz, J_{BX} = 2.44Hz, -C*H*-),Aromatic H's 6.29(d, *J* = 7.93Hz, 2H), 6.67(d, *J* = 8.54Hz, 2H), 6.76(d, *J* = 8.79Hz, 2H), 7.00(m, 2H), 7.14(m, 5H), 7.34(m, 3H), 7.43(m, 3H), 7.55(d, *J* = 8.55Hz, 4H), 7.77(d, *J* = 8.02Hz, 2H), 9.10(bs, -N*H*-CO-, 1H), 9.40(bs, -N*H*-CO-, 1H).

^{13}C NMR (300 MHz, $CDCl_3$, δ): 20.99(-*C*H_3), 41.99(-*C*H_2Ph), 55.15 & 55.23(-O*C*H_3), 61.32(-*C*H-), 67.91(-*C*H-), Aromatic *C*'s: 113.24, 113.48, 125.26, 125.66, 125.98, 126.11, 126.20, 127.30, 127.74, 128.06, 128.14, 128.65, 128.67, 128.80, 130.08, 130.15, 130.53,130.67, 132.12, 135.63, 137.83, 138.77, 159.23 & 161.43(Ar-C-O), 169.10 & 169.67(*C*=N), 172.17 & 173.29 (Ar-*C*=O).

CHAPTER THREE

STUDY OF NONLINEAR RELATIONSHIP

3.1. Origin of nonlinearity

Enantioselective catalysis has witnessed explosive growth in the last two decades as it has become the most versatile and efficient method for the preparation of molecules with high enantiomeric excess.[22] Over the past decade an increasing number of reports have appeared describing asymmetric catalytic reactions where the product enantioselectivity is not proportional to the enantiomeric excess of the chiral ligand employed. Such nonlinear effects can be traced to earlier observations of unusual physical and chemical properties sometimes exhibited by mixtures of enantiomers in solution, attributed to the formation of diastereomeric species or higher order aggregates.[196-198]

In 1848 Pasteur demonstrated that tartaric acid rotated the plane of polarized light, but in a different way depending on its origin.[199] Since this discovery, polarimetry is used as a technique for gathering information on the enantiomeric purity of compounds. Horeau's work on 1-ethyl-1-methylsuccinic acid showed that its specific rotation in chloroform was not strictly related to enantiomeric composition.[197] He showed that the enantiomeric excess was not always linearly correlated with the optical rotation value, and this phenomenon was explained on the basis of diastereomeric associations by hydrogen bonding that gave rise to a nonlinear relationship between the enantiomeric excess (ee) of the acid and its optical purity (op). When methanol was used as the solvent, the aggregation was prevented by the solvent and a linear relationship was observed (ee=op). According

to Horeau "*Certain effects observed by polarimeter, NMR and calorimetry can only be explained when the existence of diastereomeric interactions of enantiomers in solution are taken into account and the energy differences involved between the interactions of molecules of like configurations and molecules of opposite configurations are too small to be used to change the optical composition of a mixture upon distillation.*" Uskokovic *et al.* in 1969 had reported that the ^{1}H NMR of optically active dihydroquinine and of racemic dihydroquinine are significantly different when taken at same concentration in deuteriochlorofom.[198] The spectral differences are greatly reduced when deuteriomethanol was used to record the NMR. These facts can be rationalized by consideration of solute-solute interactions of the enantiomers. In solutions of the pure enantiomers, the racemate, and mixtures thereof, the molecules of each individual enantiomer reside in environments which are by intrasolution comparision identical, enantiomeric, and diastereomeric respectively. Such kind of behavior was shown in non-optical properties such as dielectric constants,[200] boiling points,[201] IR spectroscopy[202, 203] and chromatographic behavior.[128, 204-210] Chemical consequences of nonideal behavior of a mixture of enantiomers was reported by Wynberg and Feringa in 1976.[211] Both on the basis of symmetry considerations, as well as a free energy argument, it was evident that the molecular environment of the *R*-isomer in solution was different from the molecular environment of that R-isomer in an *R*,*S*-mixture. The presence of nonbonding interactions was proposed in the case of racemic mixture undergoing a reaction, and due to a lack of such interactions in the case of enantiopure starting materials. Small differences in $\Delta\Delta G^{\#}$ influences the product ratios appreciably. The authors proposed

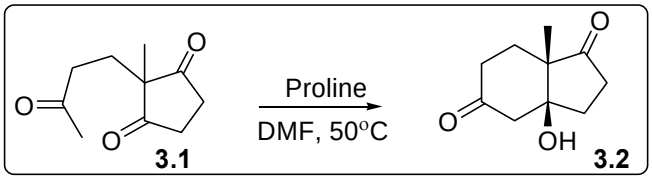
the following principle: "*When a chiral substance undergoes a reaction, the reaction rate and the product ratio will depend –inter alia- upon the enantiomeric excess present in the starting material*". To demonstrate this principle, the authors (Wynberg and Feringa) considered three cases: a) Oxidative dimerization of optically pure *S*-(+)-7-hydroxy-1,5,6-trimethyl-1,2,3,4-tetrahydronaphthalene and its racemic mixture. b) The reductive dimerization of *R*- and *R*,*S*- camphor according to McMurry's method[212, 213] c) Reduction of R- and R,S-camphor to borneol and iso-borneol. Comparing these three systems, it was observed that although there was a striking difference between the reaction of optically pure and racemic substrate in the phenol coupling reaction, only small differences were observed in the camphor dimerizations and the camphor reductions.

It was only in 1986 that the quantitative aspects of the influence of the ee value of the chiral auxiliary on the corresponding ee value of the product were discussed and studied experimentally.[214] The well accepted assumption that the enantiomeric excess of the product (ee_{prod}) is proportional to the enantiomeric excess of the chiral auxiliary or the asymmetric catalyst used (ee_{aux}) and the validity of Equation 3.1 were questioned.

$$ee_{prod} = ee_o \,.\, ee_{aux} \qquad \text{--- eq. 3.1}$$

(ee_o is the proportionality constant, equals unity when enantiopure catalyst is used.) The first reaction studied for the study of such nonlinear behavior was the asymmetric Robinson annulation (Hajos-Parrish Wiechert reaction[215, 216]) of the triketone **3.1** using (S)-proline as a catalyst (**Scheme 3.1**.). In this case a negative NLE was observed, which was explained by the fact that the reaction involving

heterochiral complexes proceeds twice as fast as one of the homochiral complexes (**Fig. 3.1**).



Scheme 3.1 Robinson annulation using proline as catalyst

A positive nonlinear effect was observed in case of geraniol oxidation by Sharpless oxidation using (R,R)-(+)-diethyl tartrate of various ees.[217] The greater than expected NLE observed in this case was attributed to more stable and less reactive heterochiral species compared to the homochiral counterparts. This proposal was in agreement with the Sharpless mechanism of asymmetric epoxidation, indicating the

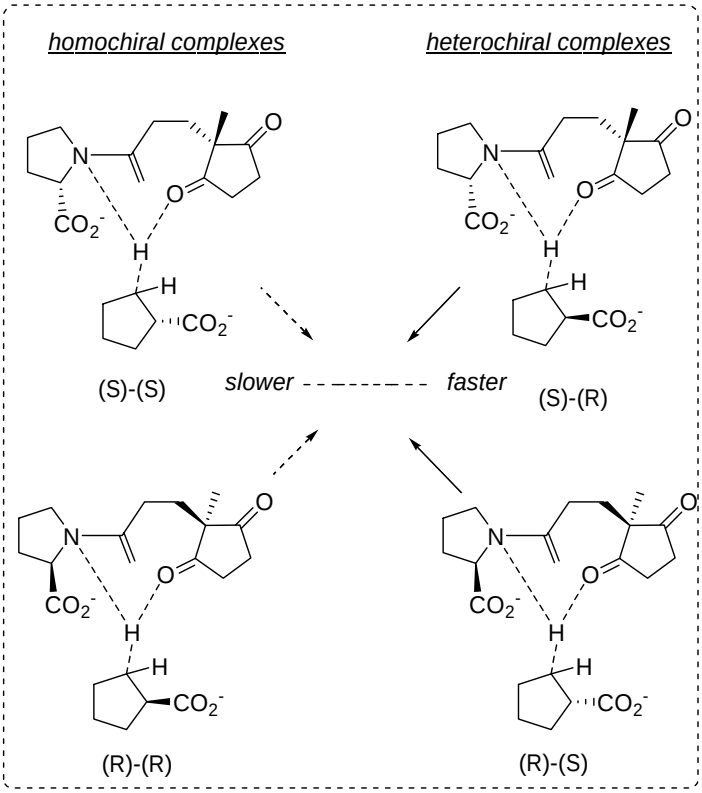


Figure 3.1. Intermediates: as homochiral and heterochiral complexes

intervention of a dimeric complex that introduces two tartrate units in the active species.[218] The positive NLE discovered in this case for the first time has been found subsequently in many reactions and has been named "asymmetric amplification" by Oguni *et al.*[219] These first experiments were a revelation in the behavior of mixtures of enantiomeric reagents or catalysts. They were an indication that some complex and subtle interactions were taking place in solution with participation from a diastereomeric species. It became clear that the presence or absence of nonlinear effects for a given system also becomes a valuable mechanistic probe for analyzing the mechanism of an enantioselective catalytic reaction.[220]

3.2. Asymmetric amplification in alkylation reactions (ethylation of benzaldehyde with diethylzinc)

An enormous amount of work was done in the field of asymmetric alkylation of aromatic aldehydes during the 1980's.[20, 31, 33, 47, 221, 222] The first highly asymmetric amplifying phenomenon in the ethylation of benzaldehyde with diethylzinc was reported by Oguni *et al.*[223] The reaction was catalyzed by sterically constrained, tertiary β-aminoalcohols with a bulky *tert*-butyl substituent on the carbon bonded to the hydroxyl group, for instance, 1-piperidino-3,3-dimethyl-2-butanol (PDB), 1-pyrrolidino-3,3-dimethyl-2-butanol (PyDB) and *N,N*-dimethyl-2-hydroxy-3,3-dimethylbutylamine (DDB, **Fig. 3.2**.). Under the influence of 2 mol% of (-)-PDB (10-20 % ee), diethylzinc reacted with benzaldehyde (1.1:1 molar ratio) in hexane at -10 ºC, (*R*)-1-phenylpropanol was obtained in 80-90% ee and in high

chemical yield. All these catalysts exhibited the positive nonlinear effect which was explained as due to the formation of dimeric species in solution.

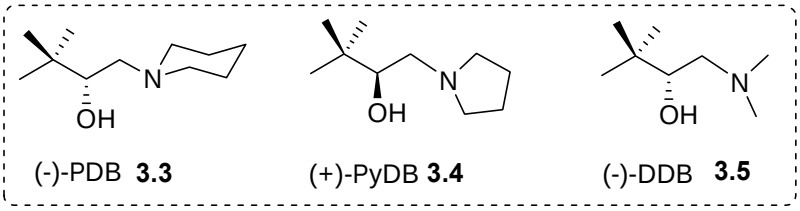
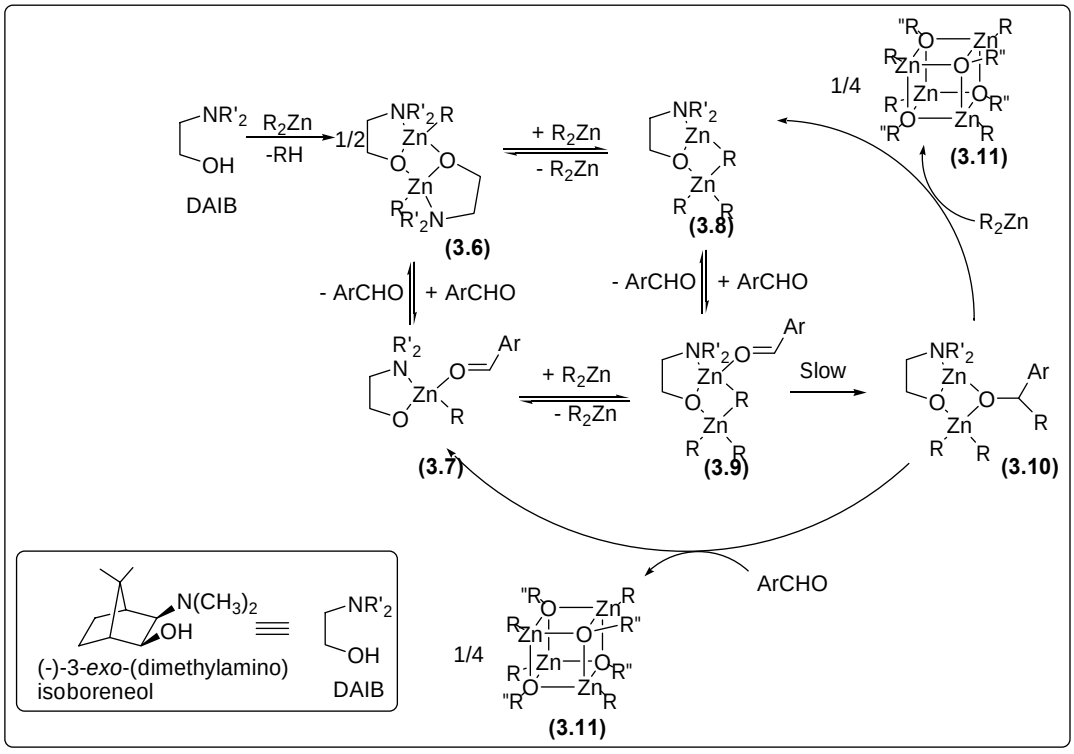


Figure 3.2. β-Aminoalcohols that lead to asymmetric amplification

The bidentate ligand (-)-3-exo-(dimethylamino)isoborneol ((-)-DAIB) was used as the catalyst by Noyori in their mechanistic study of diethylzinc addition to benzaldehyde.[32, 224] They observed a strong (+)-NLE by using changing ee's of (-)-DAIB as catalyst. In the abasence of (-)-DAIB, dialkylzincs and benzaldehyde merely have donor-acceptor type interactions in toluene.



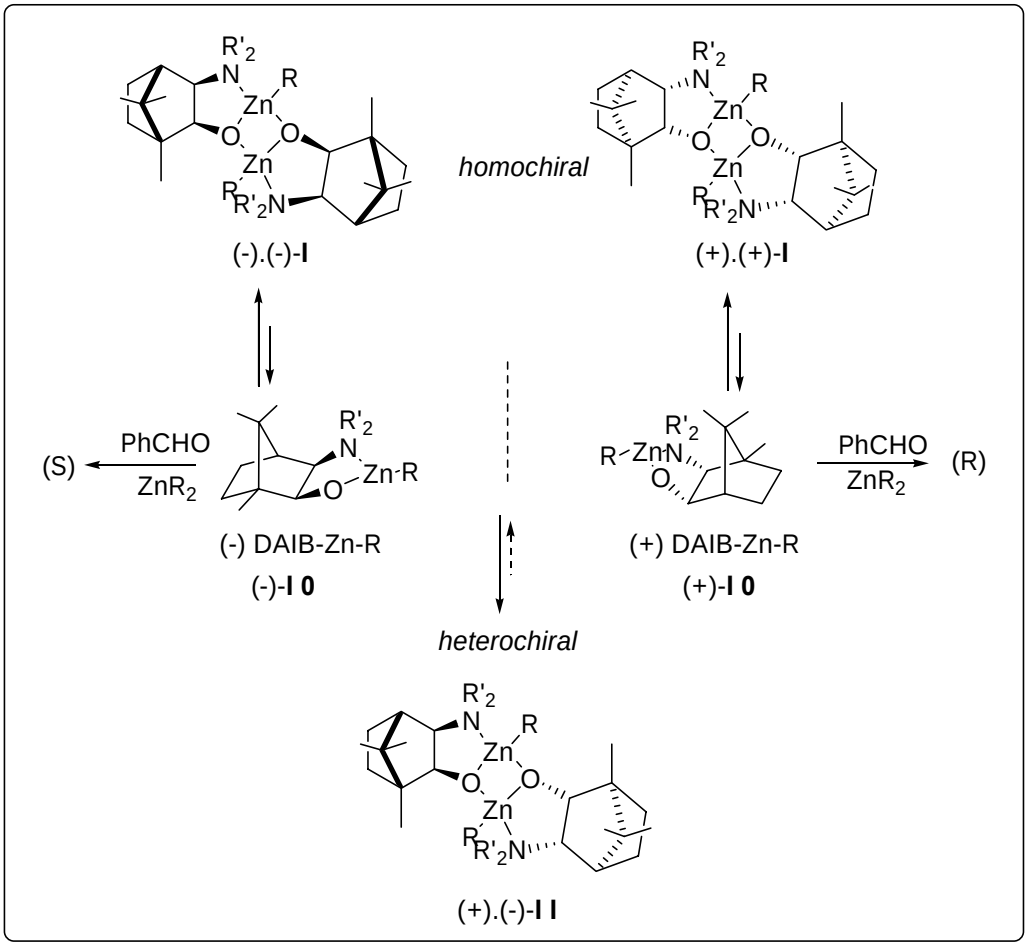
Scheme 3.2 The mechanism of dialkylzinc addition to benzaldehyde, using DAIB as catalyst

When (-)-DAIB and dimethylzinc were mixed in a 1:1 mole ratio in toluene, methane was evolved[13, 225] and a single dimeric compound **3.6** (R = CH_3), among three possible isomers was formed (**Scheme 3.2**). This complex was unable to alkylate aldehyde, but acts as a catalyst precursor. The dinuclear framework of **3.6** is ruptured spontaneously by addition of benzaldehyde to form the mononuclear complex **3.7**.[226] This process was reversible and proceeded *via* a dissociative mechanism with respect to **3.6**. Dimethylzinc also cleaved the dimeric structure of **3.6**, equilibrating with the monomeric form, leading to a new, unsymmetrical dinuclear complex **3.8**. This methyl complex, unsaturated at Zn, was highly fluxional and the three different Zn-CH_3 groups undergo rapid exchange. When an equiv of dimethylzinc was introduced to a toluene solution of **7** (R = CH_3) at 0 ºC, a new dynamic system containing **3.9** was formed. The same equilibrating mixture was obtained by mixing **3.8** and benzaldehyde in a 1:1 mole ratio. Upon standing at 20ºC, a methyl transfer reaction occurred to slowly give an alkoxide which may be assigned structure **3.10** (R = CH_3). Complex **3.10** was rather stable under such conditions, and very slowly converted to the cubic Zn alkoxide tetramer **3.6** (R = CH_3). Notably, upon exposure to benzaldehyde or dimethyzinc, **3.10** underwent instantaneous decomposition leading to stable tetramer **3.11**, and thus the catalytic process is greatly facilitated.

Typically, when benzaldehyde and diethylzinc (1:1 mole ratio) were reacted in the presence of 8 mol% of (-)-DAIB in 15% ee in toluene (0 ºC, 7 h), (*S*)-1-phenyl-1-propanol was produced in 95% ee (92% yield). This ee value achieved with partially resolved DAIB auxiliary was close to the value of 98% obtained

using enantiomerically pure DAIB. A similar chirality amplification ((+)-NLE) was observed in the case of dimethylzinc.

The enormous convexity of the curve with respect to a linear correlation was not due to participation of two chiral auxiliary molecules per aldehyde in the transition state but resulted from unique enantiomer recognition in the dinuclear catalyst precursors, **I** and **II**, as illustrated in the **Scheme.3.3**.



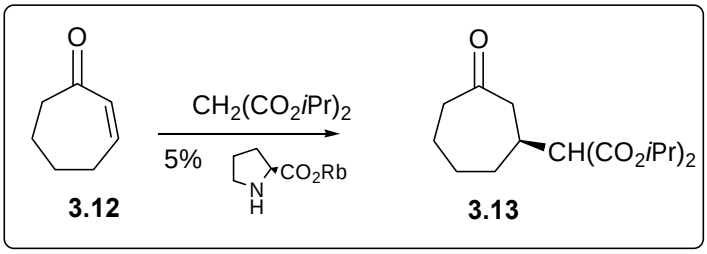
Scheme 3.3 Formation of homochiral and heterochiral dinuclearcomplexes

Bolm *et al.*[227] observed similar (+)-NLE in their study of alkylations of benzaldehyde using substituted pyridine alcohol as chiral catalyst. The alkylation of benzaldehyde was very efficient with 5 mol% of the catalyst and generated (*R*)-

1-phenyl-1-propanol. The (*R*)-cat-ZnEt and the (*S*)-cat-ZnEt can interact in solution to give the homochiral dimers and the heterochiral species. The heterochiral complex was favored over the homochiral ones, eliminating the minor enantiomer from the reaction mixture and hence increasing the ee value of the active catalyst, thus generating a strong (+)-NLE.

3.3. Nonlinear effect as a mechanistic probe

To confirm the mechanism of the asymmetric Michael additions with proline salts, Yamaguchi *et al.*[228] used nonlinear effect as a probe. The 1,4-addition of diisopropyl malonate to cycloheptenone by using a proline-rubidium salt gave them the opportunity to prepare the alkylated ketone (R)-**3.13** (**Scheme 3.4**).



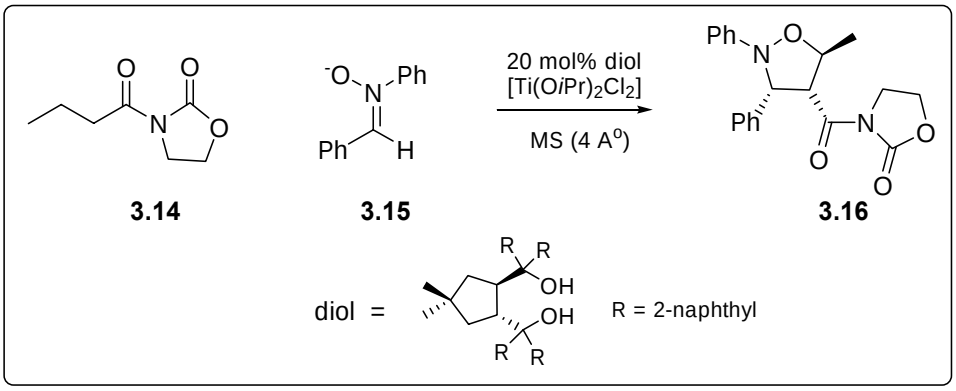
Scheme 3.4 1,4-addition of diisoporpyl malonate to cyclohepenone

In contrast to the Hajos-Parrish-Wiechert reaction, the variation of product ee with the ee of the proline salt resulted in a linear relationship. The authors concluded that the transition state of their reaction contained only one molecule of prolinate. Seebach *et al.* used NLE to get the information about the catalytic species in diethylzinc additions to aldehydes.[64] By variation of the enantiomeric purity of TADDOL-type diol used to prepare the spirotitanate catalyst, and correlating the resulting ee of the product, they obtained no NLE. This suggested that only one chiral unit was involved in the stereochemical rate determining step of

the stereoselective reaction. In their study of β-hydroxysulfoximines catalyzed enantioselective addition of diethyzinc to aldehydes, Bolm *et al.*[229, 230] used the NLE to get a better understanding of catalytic process. The positive NLE observed in this case was used to prove the dimeric or multimeric nature of the catalyst. The NMR experiments conducted[230] suggested the involvement of dimeric zinc species in the catalysis. Also, the homochiral aggregates were estimated to react five times faster than the meso species, which explained the (+)-NLE observed.

NLE can clearly suggest if the catalytic pathway involved mononuclear or multimeric active species. The studies done by Schwenkreis and Berkessel using chiral SALEN-type catalysts showed perfect linearity.[231] In their study of asymmetric oxidation of sulfides to sulfoxides, using vanadium salt and hydrogen peroxide *via* imino alcohol chiral ligand, Bolm and Bienewald reported linearity.[232]

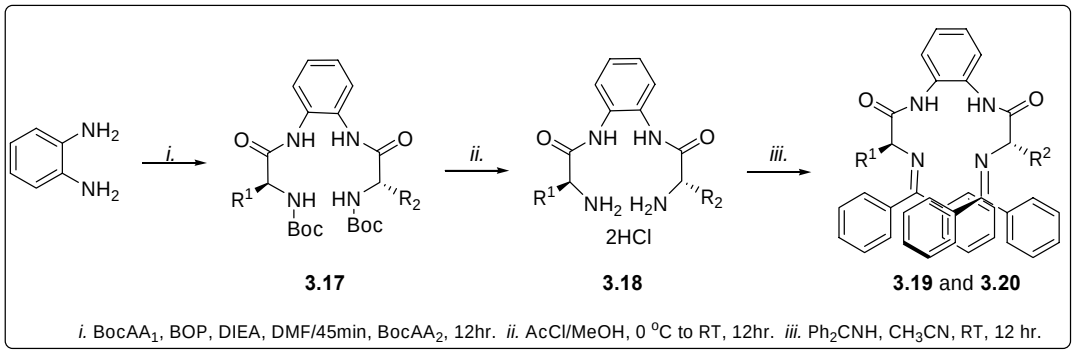
Seebach *et al*.[233] obtained a strictly linear plot between the ee value of the product and that of the chiral diol used to prepare the catalyst. In their study of TADDOL-type ligands with titanium salts towards the [3+2] cycloaddition between **3.14** and **3.15**, linear behavior was observed which was in contradiction with the (+)-NLE observed with same catalyst during Diels-Alder reaction (**Scheme 3.5**).[234]



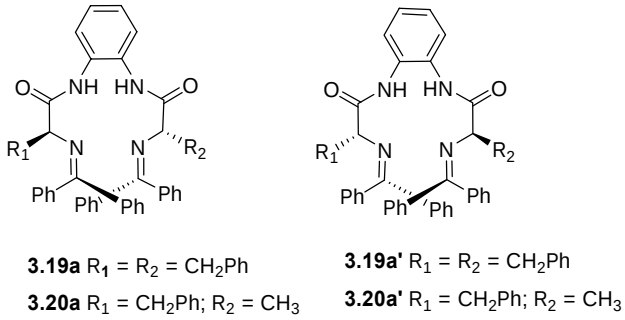
Scheme 3.5 [3+2] cycloaddition with a TADDOL-titanium catalyst

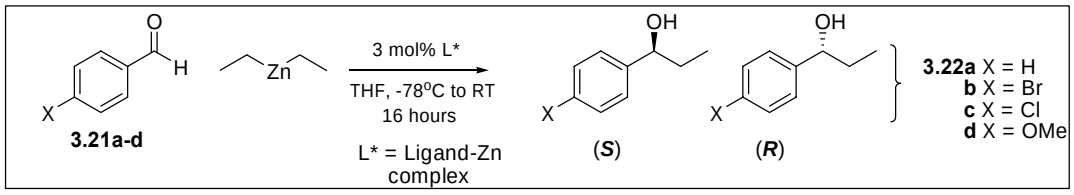
3.4. Present study with the tetradentate ligand system

The tetradentate Schiff base derived ligands L-Phe-L-Phe **3.17**, D-Phe-D-Phe **3.18**, L-Ala-L-Phe **3.19** and D-Ala-D-Phe **3.20** were used in the study of the nonlinear effect towards the addition of diethylzinc to benzaldehyde and to study the electronic effects of aldehyde on the enantioselectivity (**Scheme 3.6** and **3.7**).



Scheme 3.6 Tetradentate ligand synthesis.





Scheme 3.7 Diethylzinc addition to aromatic aldehydes

When the reactions were performed under same conditions, but with varying enantiomeric ratios of the ligand, the enantiomeric ratio of the product changed proportionate to the ratio of the ligand. The linearity of this plot in the case of both

C_2-symmetric (**3.19a** and **a'**) and C_2-asymmetric ligand systems (**3.20a** and **a'**) and also in case of diethylzinc addition to *p*-bromobenzaldehyde signifies that only one molecule of catalyst is involved during the enantioselective addition of alkyl group to aryl aldehyde, unlike the case of DAIB catalyzed reaction as proposed by Noyori and Kitamura.[32]

Table 3.1 Results of nonlinear study with ligands **3.19a** and **3.19a'**.

Ligand %		ee %	(S)	(R)	
3.	**3.19a**	**Ligand**			**roduct 3.22a**
10	0.00	100.00	86.16	13.84	72.32
95	5.00	90.00	81.68	18.32	63.37
90	10.00	80.00	78.47	21.53	56.93
85	15.00	70.00	76.16	23.84	52.32
80	20.00	60.00	70.83	29.17	41.65
75	25.00	50.00	69.50	30.50	38.99
70.00	30.00	40.00	61.48	38.52	22.96
65.00	35.00	30.00	62.45	37.55	24.90
60.00	40.00	20.00	56.84	43.16	13.68
50.00	50.00	0.00	41.79	58.21	-16.42
40.00	60.00	-20.00	43.71	56.29	-12.57
35.00	65.00	-30.00	37.48	62.52	-25.05
30.00	70.00	-40.00	36.13	63.87	-27.73
25.00	75.00	-50.00	32.96	67.04	-34.08
20.00	80.00	-60.00	26.04	73.96	-47.91
15.00	85.00	-70.00	23.05	76.95	-53.90

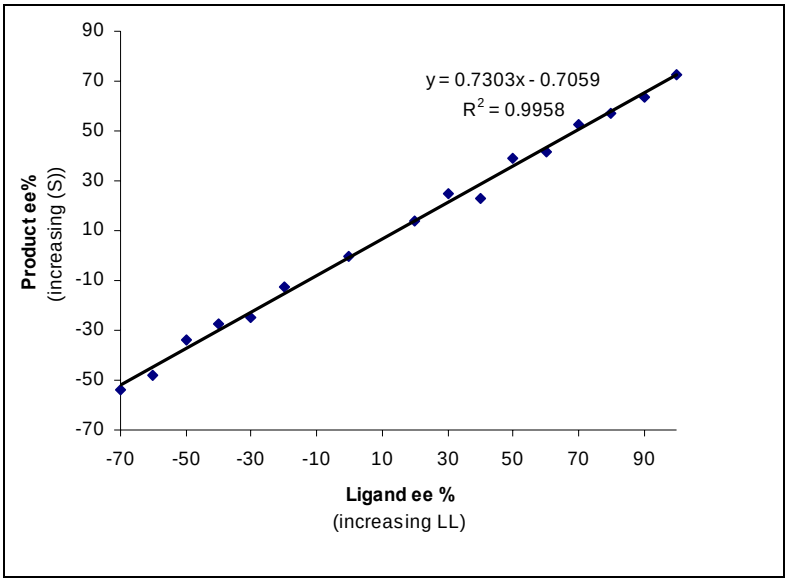


Figure 3.3 Study of Nonlinear effect using C_2-symmetric ligands and benzaldehyde

Table 3.2 Results of nonlinear study with ligands 3.19 and 3.20

Ligand (Ala-Phe) %			(S)	(R)	ee %
	3.20a'	Ligand ee %			Product 3.22a
	0.00	100.00	81.90	17.97	64.01
75.00	25.00	50.00	62.96	37.03	25.93
50.00	50.00	0.00	49.31	50.69	-1.37
37.50	62.50	-25.00	39.45	60.55	-21.11
25.00	75.00	-50.00	33.10	66.90	-33.80
0.00	100.00	-100.00		80.66	-61.32

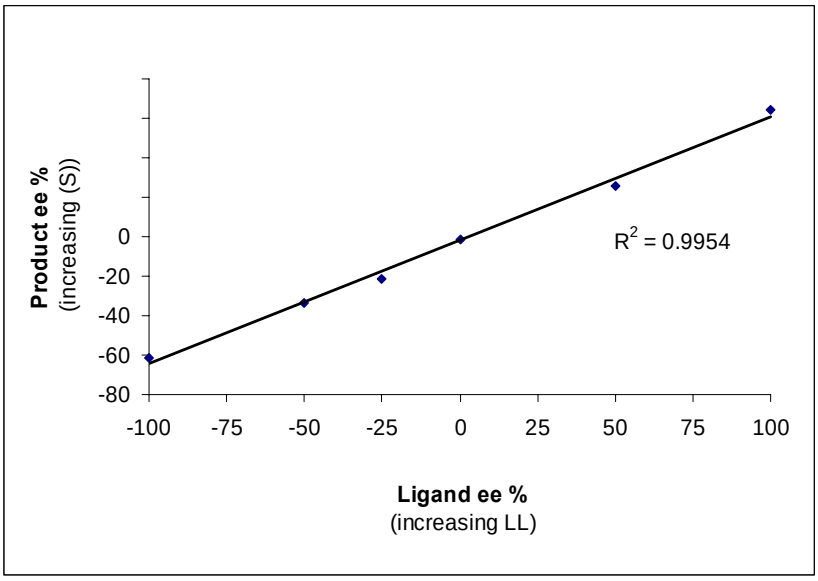


Figure 3.4 Study of Nonlinear effect using C_2-asymmetric ligands and benzaldehyde

Also, the reactions were performed to demonstrate that the observed linearity is not the property of the substrate itself (substrate dependent), by changing the aromatic aldehyde from benzaldehyde to *p*-bromobenzaldehyde. The substrate dependence of nonlinear effects has important implications for two primary reasons: 1) In the optimization of asymmetric processes it is beneficial to determine the ee of the ligand necessary to obtain a product of the desired ee, 2) Substrate dependency of nonlinear effects can be used to probe the mechanism of asymmetric reactions. In this context, Walsh *et al.* presented a study of the substrate

dependency of nonlinear effects using the MIB ligand of Nugent.[42] They found that by simply modifying the electronic properties of benzaldehyde, a change in the product ee of over 30% in the asymmetric addition was observed with 10% ee of MIB.

Table 3.3 Results of nonlinear study with ligands 3.20a and 3.20a' using p-BrC_6H_4CHO

Ligand %			(S)	(R)	ee %
3.20a	**3.20a'**	**Ligand % ee**			**product 3.22b**
0.00	100.00	-100.00	78.81	20.96	-57.99
50.00	50.00	0.00	50.24	49.49	-0.76
62.50	37.50	25.00	42.95	56.47	13.60
75.00	25.00	50.00	35.74	64.11	28.41
100.00	0.00	100.00	20.74	78.66	58.27

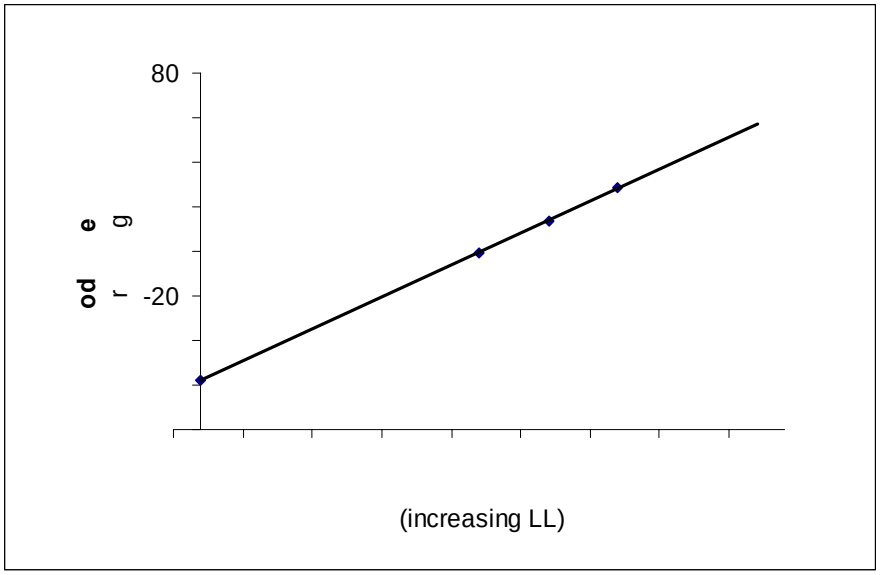


Figure 3.5 Study of Nonlinear effect using C_2-asymmetric ligands and *p*-bromobenzaldehyde

The typical reaction conditions are as follows:

3 mol% of ligand (0.03 mmol)[235] was taken in to a 25 mL flame dried round bottom flask fitted with reflux condenser and maintained at inert atmosphere by the positive flow of argon. The ligand was dissolved in 3 mL of freshly distilled THF and using an air tight microsyringe; 60 μL of diethylzinc solution (0.5M in THF, 0.03 mmol) was added in one lot. The mixture was refluxed for 1 hour to form the zinc-ligand complex which acts as chiral Lewis acid to catalyze the addition of Et_2Zn to ArCHO. Following the complexation, the reaction temperature was lowered to -78 ºC using a CO_2/acetone bath and aromatic aldehyde (1.0 mmol) was added. To this mixture being stirred at -78 ºC, Et_2Zn (0.5M solution in THF, 2.1 mL) was added through a syringe over 30 min. The reaction was then slowly warmed to room temperature and stirred overnight (16 hours). The work-up was done by diluting the reaction mixture with EtOAc (50 mL) and wash with 10% (w/v) aqueous $NaHCO_3$ (2 x 50 mL) followed by 1% (w/v) aqueous $NaHCO_3$ solution (2 x 50 mL). This was finally washed by the addition f 1% (w/v) aq. NaCl solution (2 x 50 mL) and the organic layer, was dried over anhydrous potassium carbonate. The reaction was analyzed by injecting 10 μL of the organic phase in to chiral HPLC and calculating the product %ee. (A Chiralcel OD column with 1 mL/min flow rate and 1% ipa/hex as mobile phase were used).

Even though a vast amount of work had been done in the field of enantioselective reactions through catalytic processes, the factors governing enantioselectivity remain the subject of speculation even in reactions that have been extensively studied.[18, 236] Enantioselectivity in catalytic asymmetric reactions is

usually interpreted in steric terms.[237] Even though the electronic properties of both the catalyst and substrate can have profound effects in fundamental organometallic processes, electronic effects are seldom reported.[238, 239] Watanabe *et al*. had reported a good correlation of the ^{13}C NMR chemical shifts with the σ^+ values of aryl substituted imines.[240] They conducted a study on the reactivity of (trifluoroacetimidoyl)lithium towards electrophiles, and the chemical shift of imine carbon (sp^2 carbon) was plotted against the σ^+ value of the aromatic substituent and gave a linear relationship. They concluded that the electronic effects of the *para*-substituents was transmitted through resonance to the imino carbon and also that the π-orbitals of the C=N bond of the imino group of the substrate is coplanar with those of the aryl group. Due to the interest in asymmetric catalysis, the electronic effects of the tetradentate Schiff base derived ligands was studied. Chan and co-workers observed that the enantioselectivity depends on the electronic nature of the aryl aldehydes in a linear free energy relationship and increases with more reactive substrates.[241] During the evaluation of chiral pyridylphenol as catalyst towards asymmetric diethylzinc additions to benzaldehyde, the authors observed a remote electronic effect on enantioselectivity (-CN as *para*-substituent had 89% ee, where as with NMe_2 as substituent, the enantioselectivity dropped to 40%).

In our study we found that not only the enantioselectivity depends on the electronic nature of the aryl aldehydes, but increases with a stronger electron donating group in *para*- position of aldehyde (such as a methoxy group).

Table 3.4 Free energy relationships using ligands 3.19a and 3.20a

Ligand	Ar-CHO	sigma	% ee	log (S/R)	Product
3.19a	*p*-Cl-PhCHO	0.23	62.2	0.63	**3.23c**
	p-Br-PhCHO	0.23	59.9	0.60	**3.23b**
	p-OMe-PhCHO	-0.27	82.85	1.03	**3.23d**
	PhCHO	0	72.32	0.79	**3.23a**
3.20a	*p*-Cl-PhCHO	0.23	61.19	0.62	**3.23c**
	p-Br-PhCHO	0.23	58.27	0.58	**3.23b**
	p-OMe-PhCHO	-0.27	74.62	0.84	**3.23d**
	PhCHO	0	64.01	0.66	**3.23a**

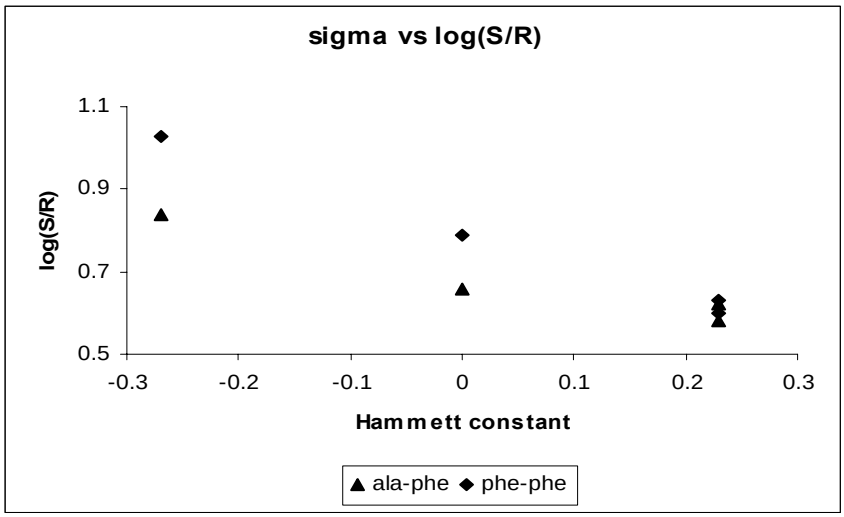


Figure 3.6 Linear free energy relationship study with substituted benzaldehyde

. Either the plot of the enantioselectivity *vs.* Hammett constants or log(S/R) *vs*. Hammett constants[242] generated a straight line with negative slope, showing that the enantioselectivity depends on the electron donating nature of the substituent on aryl aldehyde in diethylzinc additions. This result indeed supports the proposed chiral Lewis acid mechanism, in which the ethyl group migration occurs from the outside zinc and the transition metal complex binds to the aromatic aldehyde as a Lewis acid.[109]

3.5. Conclusions

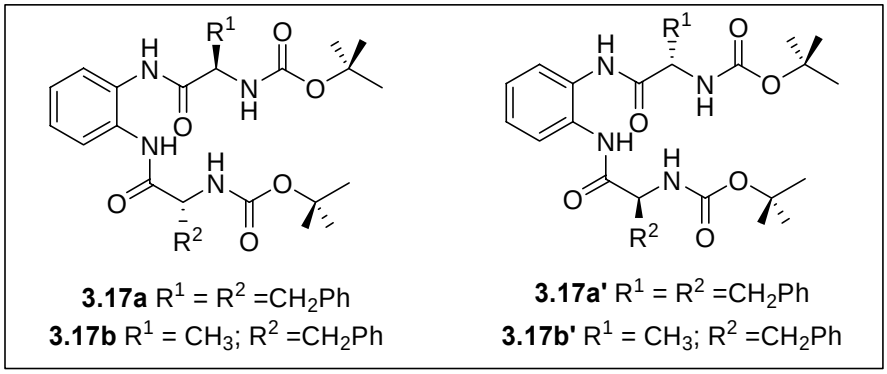
Study of nonlinear effect as a mechanistic probe suggested that the zinc complex of tetradentate Schiff base derived ligand functions as a chiral Lewis acid and that the enantioselectivity increases with the electron donating nature of the substituent on aryl aldehyde. The negative slope of the linear free energy relationship plot (Hammett constant *vs*. log(S/R) was also a proof for such behavior. Most of the bidentate ligands used for asymmetric dialkylzinc additions exhibit positive nonlinear effect and have the positive slope of linear free energy plot.

3.6. Synthesis of bifurcated dipeptides (tetradentate ligands, **3.19**, **3.20**)[243]

The *t*-Boc protected amino acids were purchased from Advanced ChemTech, and other starting materials were obtained from Aldrich. The solvents used in the synthesis were freshly distilled and the reactions were performed under anhydrous conditions unless specified.

3.6.1. Formation of *t*-Boc protected bifurcated peptides

3.6.1a. C_2-symmetric bifurcated dipeptides



3.17a $R^1 = R^2 = CH_2Ph$
3.17b $R^1 = CH_3$; $R^2 = CH_2Ph$

3.17a' $R^1 = R^2 = CH_2Ph$
3.17b' $R^1 = CH_3$; $R^2 = CH_2Ph$

ortho-Phenylenediamine (1.0 g, 9.24 mmol) was dissolved in DMF (50 mL). DIEA (4.83 mL, 27.7 mmol, 3.0 equiv.) was added in a single portion and the reaction mixture cooled to 0 ^oC. Boc-L-Phe amino acid (5.39 g, 20.3 mmol 2.2 equiv.) and BOP (10.2 g, 23.1 mmol, 2.5 equiv.) were added in one portion. The solution was allowed to warm to room temperature and stirred for 24 hours, after which complete conversion of starting material was observed by TLC. The reaction mixture was diluted with EtOAc, washed with 1% NaCl (3 x 200 ml), 1% NaCl (1 x 200 ml), saturated $NaHCO_3$ (2 x 200 ml), saturated NaCl (1 x 200 ml). The organic layer was dried over $MgSO_4$, filtered and reduced to a foam *in vacuo*.

{1(S)-[2-(2(S)-tert-Butoxycarbonylamino-3-phenylpropionylamino)-phenylcarbamoyl]-2-phenyl-ethyl}-carbamic acid tert-butyl ester (3.17a)

Yield: 98.1% (as a white solid). $[\alpha]_D^{25}$ = (+) 13.24°, (*c* 1.00, $CHCl_3$), M.P. = 120-122 °C. ^{1}H NMR (300 MHz, CD_3OD, δ) 1.38 (s, $C(CH_3)_3$, 18H), 2.98-3.07 (dd, J_{AB} = 13.3Hz, J_{BX} = 7.3Hz, $-CH_AH_B-$ 2H), 3.21-3.28 (dd, J_{AB} = 13.7J_{AX} = 5.82 Hz, Hz, $-CH_AH_B-$, 2H), 4.43-4.51 (dt, J_{AX} = 6.71Hz, J_{BX} = 6.96Hz, 2H), 5.33 (bs, N*H*-, 2H), 7.09-7.33 (m, 14H, aromatic CH), 8.49 (bs, -N*H*-CO, 2H).

^{13}C-APT NMR (300 MHz, $CDCl_3$, δ): 28.1(-*C*H_3), 38.1(-*C*H_2), 80.0(-*C*$(CH_3)_3$). Aromatic carbons: 125.1, 126.1, 126.7, 128.4, 129.2, 130.0, 136.5. 155.4(-NH-*C*O-), 170.7(-*C*O).

TLC: R_f = 0.70, red color on ninhydrin visualization (40/60 : ethyl acetate/hexane).

*Compound **3.17a'**:*

Yield 92. 16%, M.P = 120-122 °C. $[\alpha]_D^{25}$ = -13.51° (*c* 1.00, $CHCl_3$).

^{1}H and ^{13}C NMR have same values as the corresponding L-L enantiomer.

TLC: R_f = 0.70, red color on ninhydrin visualization (40/60 : ethyl acetate/hexane).

3.5.1b. C_2-asymmetric bifurcated dipeptides

ortho-Phenylenediamine (1.0 g, 9.24 mmol) was dissolved in DMF (50 mL). DIEA (2.41 mL, 13.8 mmol, 1.5 equiv.) was added in a single portion and the reaction mixture was cooled to 0 °C. L-Phe-Boc-amino acid (2.65 g, 9.24 mmol 1.0 equiv.) and BOP (5.1 g, 11.5 mmol, 1.25 equiv.) were added in one portion. The reaction was held at 0 °C for 45 min, by which time TLC showed complete mono-acylation. The second boc-amino acid, L-Ala-Boc (1.74 g, 9.24 mmol, 1.0 equiv.), was added in one portion followed by addition of BOP (1.25 equiv.) and DIEA (1.5 equiv.). The solution was allowed to warm to room temperature for 24 hours, after which complete conversion of starting material

was observed by TLC. The reaction was diluted with EtOAc, washed with 1% NaCl (3 x 200 ml), 1% NaCl (1 x 200 ml), saturated $NaHCO_3$ (2 x 200 ml), and saturated NaCl (1 x 200 ml). The organic layer was dried over $MgSO_4$, filtered and reduced to a foam *in vacuo*.

{1(S)-[2-(2(S)-tert-Butoxycarbonylaminopropionylamino)-phenyl carbamoyl]-2-phenyl-ethyl}-carbamic acid tert-butyl ester (3.17b)

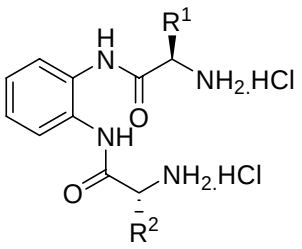
Yield = 85.23%, , $[\alpha]_D^{25}$ = -3.45°, (*c* 1.00, $CHCl_3$), M.P. = 156-158 °C.

^{1}H NMR (300 MHz, CD_3OD): 1.39(s, $C(CH_3)_3$, 9H), 1.43 (d, J = 7.2Hz, -CH_3, 3H), 1.46(s, $C(CH_3)_3$, 9H), 3.07(dd, J_{AB}= 13.8Hz, J_{AX} = 7.08Hz, -CH_AH_B-, 1H), 3.27(dd, J_{AB} = 13.8Hz, J_{BX} = 6.35Hz, -CH_AH_B-, 1H), 4.28(dd, J_{AX} = 7.08Hz, J_{BX} = 6.35Hz, -CH_X-), 4.48(q, J = 7.08Hz, -C*H*-, 1H), 5.18(bs, -N*H*-, 2H), 7.116-7.34(m, Ar-H, 8H), 7.38-7.53 (m, Ar-H, 1H), 8.34(bs. –N*H*-CO-, 1H), , 8.56(bs, –N*H*(-*C*$(CH_3)_3$)-CO-, 1H).

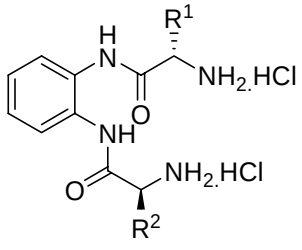
^{13}C NMR (300 MHz, CD_3OD): 18.27 (*C*H_3), 28.20 (-C(*C*H_3)$_3$), 28.30(-C(*C*H_3)$_3$), 38.20(-*C*H_2), 50.43(-*C*$(CH_3)_3$), 56.22(-*C*$(CH_3)_3$), 75.01(-*C*H-), 80.16(-*C*H-). Aromatic C: 125.03, 125.40, 126.11, 126.42, 126.79, 128.49, 129.32, 136.50, 155.47. 170.77(C=O), 172.01((C=O).

TLC: R_f = 0.55, plum color on ninhydrin visualization (40:60, ethyl acetate/hexane).

3.6.2. General procedure for Boc deprotection (3.18)



3.18a $R^1 = R^2 = CH_2Ph$
3.18b $R^1 = CH_3$; $R^2 = CH_2Ph$



3.18a' $R^1 = R^2 = CH_2Ph$
3.18b' $R^1 = CH_3$; $R^2 = CH_2Ph$

Compound **3.17** was dissolved in 50 ml of anhydrous MeOH and chilled to 0 ^oC. In a separate flask 50 ml of MeOH was chilled to 0 ^oC. AcCl (4 equiv.) was added slowly. The resultant methanolic HCl solution was added to the chilled reaction mixture dropwise over 30 min. The reaction mixture was allowed to warm to room temperature for 24 hours. After all the starting material had been consumed, as judged by TLC, MeOH was removed by rotary evaporation. The residual HCl was removed by dissolving the residue in MeOH and subsequent rotary evaporation (5 x 200 ml). This material was placed *in vacuo* until a brittle foam was obtained, then triturated in Et_2O until a fine suspension was achieved. The HCl salt was collected by filtration and dried overnight under vacuum and over P_2O_5.

2(S)-Amino-N-[2-(2(S)-amino-3-phenylpropionylamino)-phenyl]-3-phenyl-propionamide-bis-hydrochloride (3.18a):

Yield = 98.56%, $[\alpha]_D^{25}$ = (+)-92.28°, M.P. = 200 °C (dec.)

^{1}H NMR (300 MHz, D_2O,δ): 3.07-3.11(d, -CH_2- *J* = 7.27 Hz, 4H), 4.22-4.27(t, -CH_X-, *J* = 7.23 Hz, 2H), 6.99-7.26 (m, Ar-*H*,14H).

^{13}C NMR (300 MHz, D_2O): 38.47(-*C*H_2-), 55.16(-*C*H-). Ar-C: 126.25, 127.32, 128.76, 130.02, 130.83, 135.56. 168.89 (-NH-*C*O).

*Compound **3.18a'**:*

Yield = 98.56%, $[\alpha]_D^{25}$ = (-)-90.05°, M.P. = 200 °C (dec.)

2(S)-Amino-N-[2-(2(S)-aminopropionylamino)-phenyl]-3-phenylpropionamide-bis-hydrochloride (3.18b)

Yield = 98.23%, , $[\alpha]_D^{25}$ = 72.13°, M.P. = 178 °C (dec.).

^{1}H NMR (300 MHz, D_2O, δ): 1.60(d, *J* = 7.14 Hz, -C*H*$_3$, 3H), 3.23-3.36(m, -C*H*$_2$-, 2H), 4.25(q, *J* = 7.48Hz, -C*H*-, 1H), 4.45(t, *J* = 7.27Hz, -C*H*-, 1H), 7.17-7.27 (m, Ar-H, 1H), 7.32-7.48(m, Ar-H, 8H).

^{13}C NMR (300 MHz, D_2O): 32.5(-*C*H_2-), 50.42(-*C*H-). Ar-C: 119.69, 121.79, 122.47, 123.81, 124.79, 124.95, 125.10, 125.40, 129.16. 164.74(C=O).

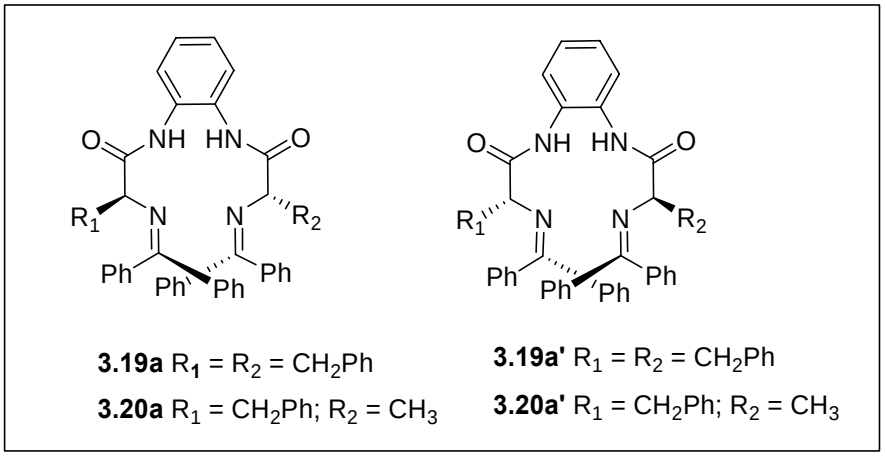
*Compound **3.18b'**:*

Yield = 85.73%, $[\alpha]_D^{25}$ = (-)-62.73°, M.P. = 178 °C (dec.)

^{1}H NMR and ^{13}C NMR have the same values as the corresponding L-L enantiomer.

3.6.3. General procedure for Schiff base formation (3.19 and 3.20):

Compound **3.18** was suspended in 60 mL of CH_2Cl_2. Benzophenone imine (2.05 equiv.) was added in a single portion. The resultant slurry was stirred at room temperature for 12 hours. Upon completion, the reaction was diluted with 100 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$ (3 x 100 mL). The organic layer was taken, dried over K_2CO_3, filtered and concentrated *in vacuo*.



2(S)-(Benzhydrylidene-amino)-N-{2-[2(S)-(benzhydrylidene-amino)-3-phenyl-propionylamino]-phenyl}-3-phenyl-propionamide (3.19a):

Yield = 72.45%, $[\alpha]_D^{25}$ = (-)-62.73°, M.P. = 80-82 °C (dec.)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.09-3.14 (dd, 2H, -CH_AH_B-CH_X-, J_{BX} = 9.39 Hz, J_{AB} = 13.0 Hz), 3.26-3.29 (dd, 2H, -C$H_A$$H_B$-$CH_X$-, J_{AX} = 3.18 Hz, J_{AB} = 13.1 Hz), 4.21-4.24 (dt, 2H, -CH_AH_B-CH_X-, J_{AX} = 3.26 Hz, J_{BX} = 9.39 Hz), (aromatics, 34 H): 6.39-6.41 (d, J = 7.23 Hz), 7.00-7.02 (dd, J = 1.88 Hz, J = 7.15 Hz), 7.15-7.29 (m), 7.32-7.35 (t, J = 7.47 Hz), 7.46-7.48 (m), 7.61-7.63 (dd, J = 1.29 Hz, J = 7.44 Hz), 9.06 (s, 2H, amide NH).

^{13}C-APT NMR (300 MHz, $CDCl_3$, δ): CH_2 41.7, CH 67.9, Aromatics: CH 125.4, 126.0, 126.3, 127.2, 128.0, 128.1, 128.2, 128.7, 130.0, 130.5; C 130.2, 135.3, 137.5, 138.7, -NH-CO-R 170.4, -N=CPh_2 171.7.

2(S)-(Benzhydrylideneamino)-N-{2-[2(S)-(benzhydrylideneamino)propionylamino] – phenyl}-3-phenylpropionamide(3.20a)

Yield = 72.62%, $[\alpha]_D^{25}$ = (+)-60.54°, M.P. = 76-78 °C

1.33(d, J = 6.83Hz, CH_3, 3H), 3.12(dd, J_{AB} = 13.19Hz, J_{AX} = 9.76Hz, -CH_AH$_B$-, 1H), 3.35(dd, J_{AB} = 13.19Hz, J_{BX} = 2.93Hz, -CH$_A$$H_B$-, 1H), 4.05(q, J = 6.83Hz, -CH-, 1H), 4.28(dd, J_{AX} = 9.76Hz, J_{BX} = 2.93Hz, -CH_X-, 1H). Aromatic H: 6.30-6.38(d, J = 7.16Hz, 2H), 6.96-7.02(m, 2H), 7.09-7.19(m, 8H), 7.19-7.26(m, 5H), 7.27-7.31(m, 2H), 7.31-7.39(m, 4H), 7.40-7.47(m, 3H), 7.50-7.57(m, 2H), 7.58-7.63(d, J = 7.16Hz, 2H), 7.72-7.80(d, J = 6.83Hz, 2H). 9.08(-NH-CO), 9.38(-NH-CO).

^{13}C NMR ($CDCl_3$, 300MHz, δ): 20.96(CH$_3$), 41.83(CH$_2$), 61.28(-CH-), 68.16(-CH-). Aromatic C's: 125.37, 125.55, 126.02, 126.10, 126.29, 127.26, 127.96, 128.12, 128.22, 128.44, 128.61, 128.69, 128.78, 130.05, 130.17, 130.45, 130.68, 135.29, 135.59, 137.59, 138.75. 169.15(C=N), 170.38(C=N), 171.77(CO), 173.24(CO).

TLC: R_f = 0.83, light brown color on ninhydrin visualization (10/90 : ethyl acetate/ hexane).

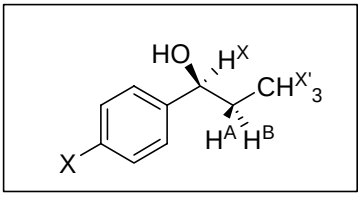
3.7. Preparation of HPLC standards and the methodology development

The products of diethylzinc additions to benzaldehyde, and substituted benzaldehydes, lead to the formation of 1-phenyl-1-propanol and its analogs. After the reaction, the products were analyzed by HPLC. Analytical chiral column *Chiralcel OD* was used for analysis. The HPLC methods were generated using hexane and *iso*-propanol as the mobile phase. The flow rate of the HPLC was maintained below 1 $mLmin^{-1}$ and the use of solvents was restricted to hexane and *iso*-propanol.

Substituted (±)-1-phenyl-1-propanols were synthesized *via* Grignard (Ethylmagnesium Chloride) addition to aromatic aldehyde, and used as the standards for HPLC analysis.

Synthesis of substituted (±)-1-phenyl-1propanols:

Ethyl magnesium chloride solution (25 % wt., 10.66 mL, 0.03 mol, purchased from Fluka) was transferred in to a flame dried round bottom flask, and was diluted with freshly distilled THF (5 mL). To this brown solution, aromatic aldehyde (dissolved in 5 mL THF, 0.02 mol) was added drop wise, maintaining the reaction mixture at 0 °C. The complete conversion of aldehyde to the product was observed using TLC (3-6 hours). The reaction mixture was diluted with ethyl acetate (60 mL) and the magnesium salts were washed with 10% ammonium chloride solution (wt/v). The organic layer was dried over K_2CO_3 and solvent was evaporated using rotary evaporator to get final product.



X	J_{AB}	$J_{AX} = J_{BX}$	$J_{AX'} = J_{BX'}$
-H	28.11	7.25	7.25
-Cl	25.4	6.84	7.32
-Br	21.0	6.34	7.32
$-OCH_3$	22.87	7.33	8.02

1-Phenyl-1-propanol (3.22a):

Commercially available (±)-1-phenyl-1-propanol was used as the standard for HPLC. To confirm the purity of the standard, the ^{1}H NMR data was collected.

^{1}H NMR, (300MHz, $CDCl_3$, δ): 0.87(t, $J_{AX'}$ = 7.25Hz, -C*H*$_3$, 3H), 1.74(dqq, J_{AB} = 28.1Hz, $J_{AX'}$ = 7.25Hz, J_{AX} = 7.25Hz, -C*H*$_2$-, 2H), 2.83(bs, -O*H*, 1H), 4.40(t, J_{AX} = 7.25Hz, -C*H*-, 1H), 7.20-1.31(m, Ar-*H*, 5H). $R_{t(R)}$ = 21.58 min.; $R_{t(S)}$ = 26.45 min. (*Chiralcel OD*, 1% IPA/Hexane, 1.0 mL/min. flow rate, λ_{max} = 210.0 nm).

1-(4-Bromophenyl)-1-propanol (3.22b):

Yield = 93%, b.p. =232-234 °C

^{1}H NMR, (300MHz, $CDCl_3$, δ): 0.80(t, $J_{AX'}$ = 7.32Hz, -C*H*$_3$, 3H), 1.63(dqq, J_{AB} = 21.4Hz, $J_{AX'}$ = 7.32Hz, J_{AX} = 6.34Hz, -C*H*$_2$-, 2H), 2.83(bs, -O*H*, 1H), 4.40(t, J_{AX} = 6.84Hz, -C*H*-, 1H), 7.10(d, *J* = 8.4Hz, Ar-*H*, 2H), 7.37(d, *J* = 8.4Hz, Ar-*H*, 2H). $R_{t(S)}$ = 29.39 min.; $R_{t(R)}$ = 31.22 min. (*Chiralcel OD*, 1% IPA/Hexane, 1.0 mL/min. flow rate, λ_{max} = 210.0 nm).

l-(4-Chlorophenyl)-1-propanol (3.22c):

Yield = 89%, b.p. = 202-4 °C,

^{1}H NMR, (300MHz, $CDCl_3$, δ): 0.87(t, $J_{AX'}$ = 7.32Hz, -C*H*$_3$, 3H), 1.72(dqq, J_{AB} = 25.4Hz, $J_{AX'}$ = 7.32Hz, J_{AX} = 6.34Hz, -C*H*$_2$-, 2H), 2.25(bs, -O*H*, 1H), 4.53(t, J_{AX} = 6.84Hz, -C*H*-, 1H), 7.23(d, *J* = 8.52Hz, Ar-*H*, 2H), 7.29(d, *J* = 8.58Hz, Ar-*H*, 2H).

^{13}C NMR (300MHZ, $CDCl_3$, δ): 9.91(-*C*H$_3$), 31.84(-*C*H$_2$-), 75.18(-*C*H-), 127.31(Ar-*C*), 128.42(Ar-*C*), 132.98(Ar-*C*), 142.94(Ar-*C*). $R_{t(S)}$ = 28.36 min.; $R_{t(R)}$ = 29.96 min. (*Chiralcel OD*, 1% IPA/Hexane, 1.0 mL/min. flow rate, λ_{max} = 210.0 nm).

1-(4-Methoxyphenyl)-1-propanol (3.22d):

Yield = 69%, b.p. 251-252 °C

^{1}H NMR, (300MHz, $CDCl_3$, δ): 0.89(t, $J_{AX'}$ = 8.02Hz, -C*H*$_3$, 3H), 1.72(dqq, J_{AB} = 22.9Hz, $J_{AX'}$ = 8.02Hz, J_{AX} = 7.33Hz, -C*H*$_2$-, 2H), 2.25(bs, -O*H*, 1H), 4.53(t, J_{AX} = 7.33Hz, -C*H*-, 1H), 7.23(d, *J* = 8.52Hz, Ar-*H*, 2H), 7.29(d, *J* = 8.58Hz, Ar-*H*, 2H).

^{13}C NMR (300MHZ, $CDCl_3$, δ): 10.10(-*C*H$_3$), 31.86(-*C*H$_2$-), 75.44(-*C*H-), 113.60(Ar-*C*), 127.11(Ar-*C*), 136.74(Ar-*C*), 158.80(Ar-*C*). $R_{t(R)}$ = 32.08 min.; $R_{t(S)}$ = 37.58 min. (*Chiralcel OD*, 1% IPA/Hexane, 1.0 mL/min. flow rate, λ_{max} = 210.0 nm).

CHAPTER FOUR

ALKENYLZINC ADDITIONS

4.1. Introduction

The use of asymmetric catalysis in the synthesis of complex chiral molecules has been increasing, as these reactions involve the transfer and multiplication (or amplification) of chirality. Asymmetric organozinc additions to aldehydes had been studied thoroughly over the past two decades. In their review about organozinc additions to aldehydes, Pu and Yu summarized the results of diethylzinc additions carried out with approximately 600 individual catalysts used in the past decade.[25] Recent advances in the area of asymmetric organozinc additions to aldehydes include asymmetric arylation reactions (the addition of arylzinc reagents) to carbonyl compounds, generating diphenylmethanols.[244]

However, there have not been many examples of alkenylzinc additions to carbonyl compounds, and the methodology is far from being general.[245] The addition of alkenylzinc moieties to carbonyl compounds yield optically active allylic alcohols, which are key intermediates in various reactions[246] and also biologically active.[247-252]

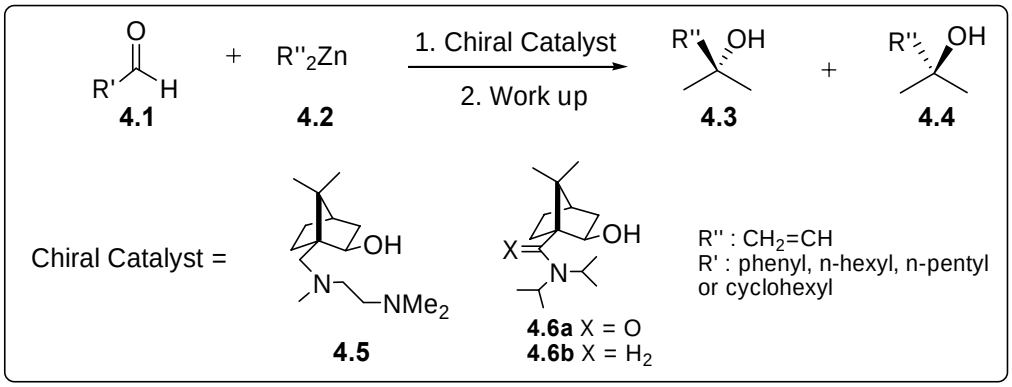
4.2. Boron to zinc transmetalation reaction

Generally, alkenylzinc reagents are temperature sensitive and are therefore prepared *in situ* using transmetalation protocols. In 1988 Radinov and Oppolzer reacted divinylzinc reagent (**Scheme 4.1**) with aromatic aldehydes in the presence of tridentate ligand **4.5** and bidentate **4.6a,b** to generate allyl alcohols.[219] The divinylzinc used was

prepared by reacting $ZnCl_2$ with vinylmagnesium bromide.[253] High enantioselectivity up to 92% was obtained when 2 mol% of tridentate ligand was used and did increase close to 100% when the loading was increased to 20 mol%. Also they demonstrated that the use of such tridentate ligand was effective in catalysis even in the case of aliphatic aldehydes.

Table 4.1 Divinylzinc additions to aldehydes with tridentate ligand 6a

Aldehyde	*dialkylzinc*	*ligand (mol%)*	*yield (%)*	*ee (%)*
benzaldehyde	idethylzinc	5	85	87
benzaldehyde	diethylzinc	20	85	92
benzaldehyde	di(n-propyl)zinc	20	85	92
benzaldehyde	divinylzinc	2	96	87
n-octanal	divinylzinc	2	88	88
n-octanal	divinylzinc	10	82	92
n-octanal	divinylzinc	20	90	>96
n-nonal	divinylzinc	2	86	87
cyclohexyl	divinylzinc	2	83	82

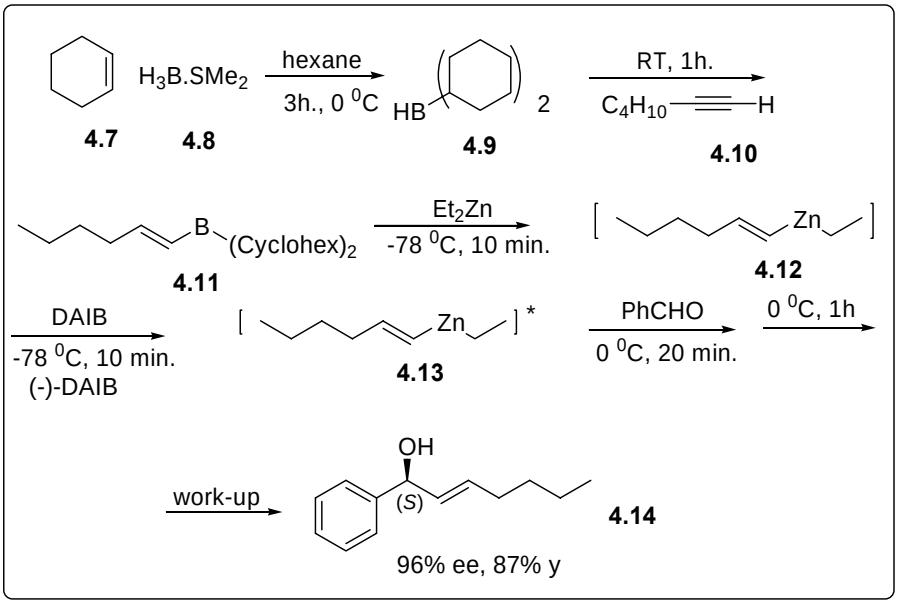


Scheme 4.1 Divinylzinc addition to aldehydes

The same authors had reported the use of lithium (*1S*, *2R*)-*N*-methylephedrate in stoichiometric amounts for the enantioselective additions of 1-alkenylzinc bromides to aldehydes in good yields and selectivity.[252] In this case, the alkenylzinc reagents were obtained by lithium to zinc transmetalation (treatment of pure 1-bromoalkene with

lithium metal in ether, followed by transmetalation with $ZnBr_2$ generated the alkenylzinc reagent). Even though high selectivity of product was obtained in alkenylation of aldehydes, there were several cases that needed enhancement in face selectivity.

The use of β-amino alcohols as catalyst towards alkenylation was introduced by Oppolzer and Radinov in 1992 (**Scheme 4.2**).[247] Asymmetric alkenylzinc compounds were generated by hydroboration of terminal alkynes using freshly prepared dicyclohexylborane followed by treatment with diethylzinc. The addition of this reagent to aldehydes in the presence of (-)-3-exo-(dimethylamino)isoborneol (10 mol%) yielded (*E*)-allyl alcohols in 70-95% with 79-98% ee. El-Sayed *et al*. used the same methodology in the synthesis of macrocyclic (*E*)-allylic alcohols from *ω*-alkynals *via* intramolecular 1-alkenylzinc/aldehyde additions.[248] The observed stereoselectivity (practically constant) with respect to the ligand loading (mol %) revealed that these reactions were independent of ligand loading.



Scheme 4.2 DAIB catalyzed alkenylzinc addition to benzaldehyde

Walsh *et al*. have used β-amino alcohol (-)-MIB (Nugent's morpholeno isoborneol) for the alkenylzinc addition to aldehydes. In an efficient and highly enantioselective synthesis of protected D- and L-α amino acids from terminal alkynes, catalytic asymmetric vinylation of aldehydes was one of the key steps.[254] The yields of the allylic alcohols generated range from 65 to 94% with enantiomeric excess ranging from 88 to 97%. This was the first report to generate the C_2-symmetric bis(allylic) alcohols starting from the symmetric diterminal alkyne. Not only did (-)-MIB catalyze the reaction, it showed a strong (+)-NLE (nonlinear effect) towards vinylation of aldehydes. This NLE was similar to the one observed in case of diethylzinc addition to aldehydes in the presence of MIB as chiral ligand, signifying the involvement of two ligand molecules in the catalysis.

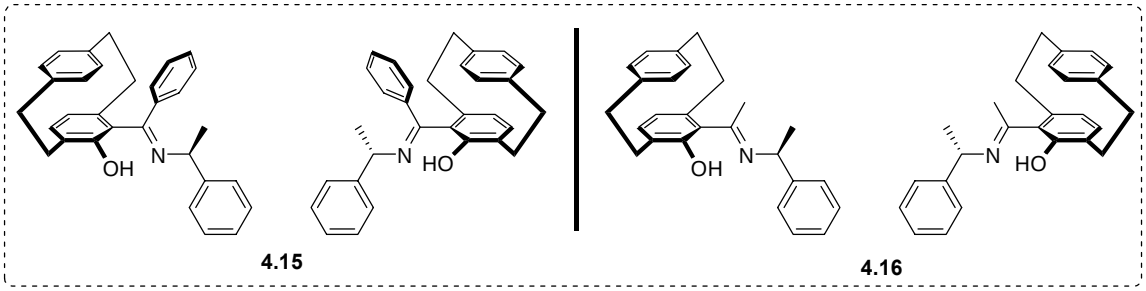


Figure 4.1 [2,2]paracyclophane ligands for asymmetric alkenylzinc additions

During the ligand screening involving various hydroxyl imine, hydroxyl ketimine, and amino alcohol ligands based on the [2,2]paracyclophane backbone, Brase and Dahmen discovered that ketimines such as **4.15** and **4.16** showed a superior selectivity and reactivity in the diethyzinc addition to benzaldehyde.[245] Unlike the initial Oppolzer's protocol for *in situ* preparation of alkenylzinc compound at 0 ^{o}C, the transmetalation was performed at -78 ^{o}C. The change of equimolar ratios of reagents in the original protocol

to 1.5:2.0:1.0 of cyclohexylborane adduct:diethylzinc:aldehyde produced better yields (from 50 to 80%). The catalyst loading was only 2 mol % in these reactions. In addition to β-amino alcohols, β-amino thiols were found to catalyze the addition of alkenylzinc to aldehydes with high enantioselectivity and good yields.[255]

4.3. Zirconium to zinc transmetalation

4.3.1. Use of zirconium in organic chemistry

Although zirconium was discovered by Klaproth in 1790[256] and was isolated by Berzelius in 1824,[257] it was only in 1953 that the first zirconocene Cp_2ZrBr_2 was prepared by Wilkinson[258] and the further development of the zirconocene chemistry took place in 1970's. Landmark events for the applications of organochlorobis(cyclopentadienyl)-zirconium(IV) complexes in organic chemistry were the preparation of zirconocene hydrides by Wailes and Weigold in 1970[259] and the use of hydrozirconation for the functionalization of organic compounds by Schwartz and Hart in 1974.[260] Due to the ease of preparation of alkenyl- and alkylzirconocenes by hydrozirconation of alkynes and alkenes with $Cp_2Zr(H)Cl$ (Schwartz's reagent),[261] the application of these organometallics for carbon-carbon and carbon-heteroatom bond formations has become an important aspect of synthetic strategy and tactics.

The polarity of the carbon-zirconium bond is comparable to that in Grignard reagents. However, due to the steric crowding around the zirconium atom, the organo-metallic bond is quite shielded and only small electrophiles attack the complex directly. Much of the development of the chemistry of organozirconocenes has therefore focused

on indirect reaction pathways where other metals participate in carbon-carbon bond formations, or where access to the metal center is facilitated by the preparation of formally cationic complexes.

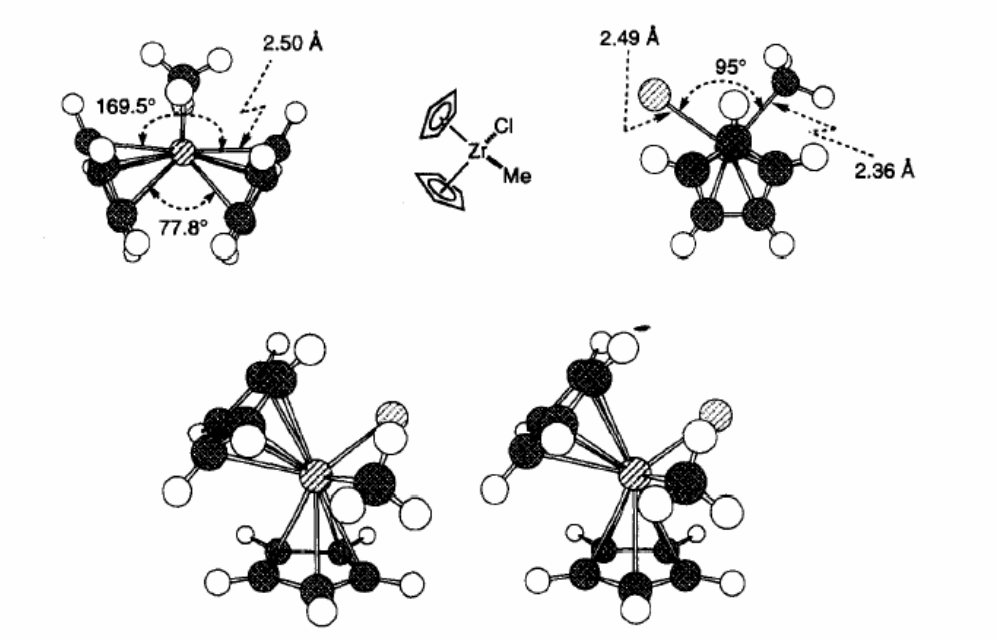


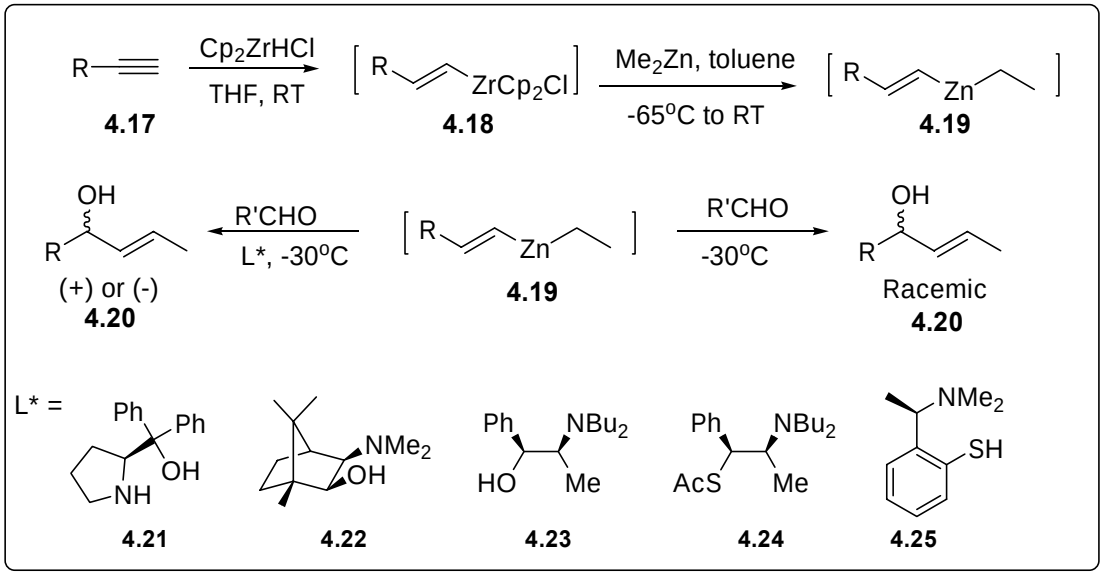
Figure 4.2 Bond lengths, bond angles, and stereo-representations of the X-ray structure of $Cp_2Zr(Cl)Me$[262]

In organochlorobis(cyclopentadienyl)zirconium(IV) complexes, two cyclopentadienyl groups occupy three coordination sites each, and provide steric shielding as well as electron donating power to the metal. Carbon-zirconium bond lengths vary between 2.3 and 2.5 Å and both the methyl-zirconium and the hydrogen-zirconium bond energies range around 75-85 kcal/mol. The chlorine-zirconium bond distance is relatively constant at 2.4 to 2.5 Å, and its bond dissociation enthalpy lies close to 110 kcal/mol.

4.3.2. Hydrozirconation and its utility in generating alkenylzinc reagents

The insertion of C,C-double and triple bonds into the Zr-H bond represents the default stepping stone for the preparation of synthetically useful organochlorobis

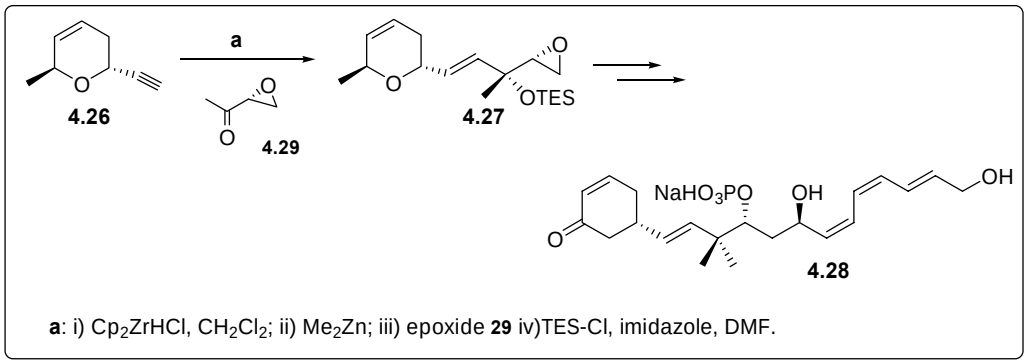
(cyclopentadienyl)zirconium(IV) complexes.[263] Hydrozirconation is analogous to hydroboration, except that the four-atom concerted transition state formed in hydrozirconation is formally symmetry allowed due to the vacant d-orbitals on Zr[264] and in case of hydroboration, the transition state is symmetry forbidden.[265] Even though the mechanism of hydrozirconation process is not completely understood, the solvent effects on rate of reaction were studied by the Wipf group.[263] They observed that the hydrozirconation is orders of magnitude faster in THF than in hydrocarbon solvents such as benzene, and the most effective solvent identified was oxetane.



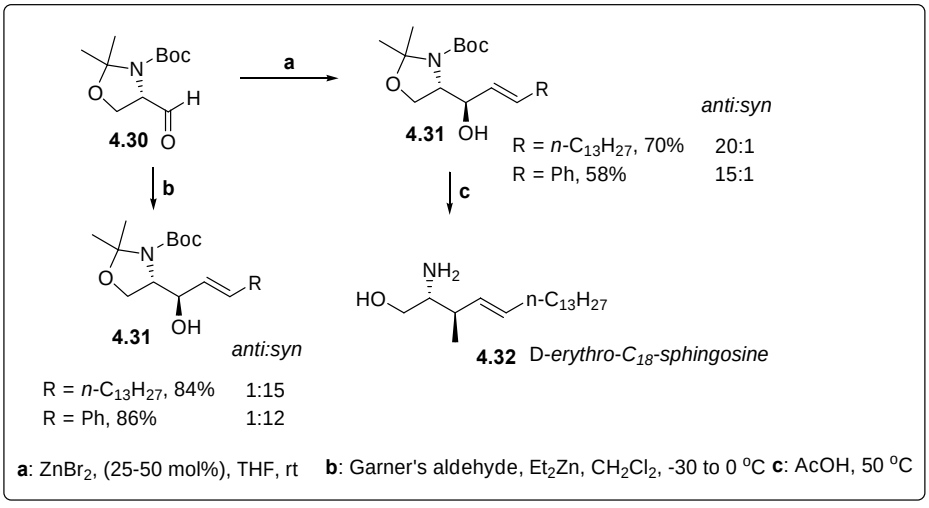
Scheme 4.3 Zirconium to zinc transmetalation reaction

Hydrozirconation with Cp_2ZrHCl (Schwartz reagent) provides organozirconocene reagents that can readily be added to enones,[260, 266-269] aldehydes,[270-272] epoxides,[273] and isocyanates.[274] Wipf and Ribe in 1988 performed the first asymmetric alkenylation reaction using Schwartz reagent.[275] The terminal alkyne was converted to the alkenylzirconocene complex at room temperature, followed by the addition of dialkylzinc

at -65 °C in toluene. This transmetallated alkenylzinc was added to the aldehyde in the presence of a chiral ligand to get enantioselective *syn* addition of an alkene moiety onto aldehyde, generating allyl alcohol. Even though this procedure did generate the product in good yield (63-83%) and high enantioselectivity (64-99%), it required the use of 8 mol% of chiral ligand. Even a ligand like (-)-DAIB (Noyori's catalyst), which catalyzes the asymmetric addition of dialkylzinc and alkenylzinc additions to aldehydes produced only 3% ee (77% yield) when used in 10 mol%. Interestingly, the ligand used by the authors (Wipf and Ribe), the β-amino thiol, induced up to 95% ee (80% yield).



Scheme 4.4 Zirconium to zinc transmetalation in the synthesis of fostriecin



Scheme 4.5 Zirconium to zinc transmetalation reaction in the synthesis of sphingosine

Several natural product total syntheses have used this methodology as a key step in the construction of allylic alcohol moieties, and it has been applied to the preparation of polyene segments in (+)-curacin A and in the manumycin family.[261, 276-278] An interesting diastereoselective version of the Zr→Zn transmetalation was reported by Jacobsen and Chavez in the synthesis of fostriecin, **4.28**.[279] After hydrozirconation of alkyne **4.26**, the alkenylzinc intermediate added diastereoselectively in a 1,2-fashion to the chiral epoxyketone. Protection of the tertiary alcohol provided **4.27** in 45% yield and >30:1 diastereoselectivity. An efficient stereodivergent synthesis of D-*erythro*-C_{18}-sphingosine **4.32** has been reported by Murakami and Furusawa, who explored the enantioselective addition of alkenylzirconocenes to the L-serine-derived chiral aldehyde **4.30**.[280] The addition of zinc or silver salts to the reaction did change the *syn/anti* selectivity of the product. The use of $ZnBr_2$ as additive induced the product formation in 20:1 *syn/anti* selectivity, while with methylene chloride as solvent and equilibrating the transmetalation mixture from -30 to 0 °C changed the selectivity to 1:15 *syn/anti* ratio.

Despite its versatility, the enantioselective protocol for the Zr→Zn transmetalation –aldehyde addition is still being refined.[281] In their first report on this subject, Wipf and Xu did not obtain a satisfactory enantiomeric excess of allylic alcohols when 8 mol% of ligand was used.[272] The main reason for the low ee of 38% was attributed to the presence of stoichiometric zirconocene complex catalyzing the formation of racemic product. The competitive aldehyde addition kinetics are a result of the presence of two Lewis acidic metals in the Zr→Zn transmetalation mixture. In subsequent work, Wipf and co-workers

achieved significant ee improvements by the use of larger amounts of lingad and lower reaction temperatures.[275, 282]

4.4. Catalytic activity of tetradentate ligands towards alkenylations

When compared to the development of alkylzinc additions to aldehydes, the field of alkenylzinc additions to aldehydes has not been thoroughly researched. There have only two classic ways of forming the alkenylzinc reagents, other than treating the vinyl Grignard reagents with zinc halides. Introduced in the year 1992 by Oppolzer, the boron to zinc alkenyl transfer reaction is still used by several research groups for the *in situ* preparation of asymmetric alkenyl-alkyl zinc reagents. The other methodology is Wipf's Zr to Zn trnsmetalation using Schwartz's reagent.

In the ongoing research with O'Donnel Schiff base derived, tetradentate ligands, the asymmetric alkenylation of aromatic aldehydes is being explored. Both B→Zn and Zr→Zn transmetalation reactions were explored with terminal alkynes and aromatic aldehydes.

4.4.1. Optimization of Zr→ Zn transmetalation

The methodology developed by Wipf in 1998 demonstrated the use of multiple solvents.[275] Initially, the alkenylzirconocene complex was prepared in methylene chloride followed by the removal of methylene chloride using rotary evaporation and Zr to Zn transmetalation was performed in dry toluene. Even though this procedure leads to product formation with benzaldehyde and heptyne, with Phe-Phe as the chiral ligand, it was seldom reproducible. The methylene chloride had to be removed completely prior to

the transmetalations and the alkenylzirconocene complex had a short life time and before its decomposition, transmetalation had to be completed. In general, with most of the bidentate ligands, alkylation and alkenylation reactions were done using hydrocarbon solvents like toluene or hexane, but the use of such solvents with the tetradentate ligands decreases the enantioselectivity.[109] In view of these limitations, the solvents methylene chloride and toluene in original methodology were replaced by THF. As the hydrozirconation is orders of magnitude faster in THF than in other solvents, changing solvent should improve the reactivity and aid in product formation.

The effect of temperature in Zr to Zn transmetalations

The hydrozirconation was performed at room temperature and the loss of heterogeneity of the reaction mixture indicates the reaction completion. The formation of alkenylzirconocene complex from Schwartz's reagent occurs within 5 minutes, but the reaction was maintained at room temperature for 30 minutes to ascertain the complete conversion.

The reaction mixture was then cooled to -65 ^{o}C and diethylzinc (0.5M in THF) was added over 15 minutes and the reaction mixture was equilibrated to -35 ^{o}C. The equilibration of reaction mixture was crucial in order to complete the transmetalation. The reactions when performed at -78 °C, 0 °C and room temperature yielded either no product or unwanted ethyl addition to aldehyde. These observations disclose the significance of equilibration for transmetalation to take place.

The final step of the synthesis was the addition of alkenylzinc reagent to benzaldehyde in the presence of catalyst. The active catalyst was the zinc complex of the

tetradentate ligand (in 3 mol%), prepared *in situ* by refluxing the mixture of diethylzinc and ligand in a 1:1 mole ratio in THF for an hour and monitoring the reaction *via* TLC. After the zinc-ligand complex was formed, a mole of benzaldehyde was added at -78 ^{o}C. To this chiral aldehyde mixture, the alkenylzinc reagent maintained at -40 ^{o}C was added dropwise by cannulation. The reaction mixture was allowed to warm to room temperature over an hour and the reaction was stirred for 24 hours. After 24 hours the reaction was quenched by diluting the reaction mixture with ethyl acetate and transferring to 10% w/v solution of aqueous ammonium chloride. The organic layer was then washed twice by 10% NH_4Cl solution (50 mL) followed by washing by 1% w/v $NaHCO_3$ solution (2 x 50 mL). The organic layer was dried over anhydrous K_2CO_3. The organic layer was reduced using a rotary evaporator and organic solvents were displaced by $CHCl_3$ to obtain a clear ^{1}H NMR in $CDCl_3$. The enantiomeric excess of the product was obtained through HPLC analysis using a Chiralcel OD column. 1% isopropanol in hexanes was used as the mobile phase with a flow rate of 1 mL/min. The racemic mixture of 1-phenyl-1-propanol was used as an external standard to differentiate the peaks of alkenyl addition from alkyl addition to benzaldehyde and also the product peaks were later compared to the product obtained through B to Zn transmetalation procedure described in the next section.

4.4.2. Boron to zinc transmetalation

In situ preparation of alkenylzinc compound was achieved by Oppolzer's procedure. At 0 °C, to a stirred solution of cyclohexene (2.0 mmol), borane dimethyl sulfide complex was added and stirred for 3 hours. To this turbid solution, terminal

alkyne (1.0 mmol) was added at room temperature and continued to stir under an inert atmosphere for one hour. Diethylzinc solution in hexane (1.0M, 1.0 mmol) was added to this alkenylborane solution at -78 °C and the solution was maintained at that temperature for 30 minutes to achieve complete B to zinc transmetalation. Thus formed alkenylzinc solution was cannulated to the round bottom flask containing the ligand-zinc complex (0.03 mmol) and aromatic aldehyde (1.0 mmol) at -78 °C and the reaction mixture was slowly warmed to room temperature over an hour and stirred at room temperature for 24 hours. The reaction was finally quenched by the addition of aq. ammonium chloride and then washed with 1% $NaHCO_3$ solution.

Unlike the diethylzinc, alkenylzinc reagent, being unsymmetrically substituted, can be readily migrated to benzaldehyde, even in the absence of catalyst. This feature was taken into advantage, and the reacemic product was synthesized and isolated in very good yield to obtain the HPLC standards.

4.5. Conclusions

Even though the generation of alkenylzinc reagent was easier *via* Zr to Zn transmetalation, the chirality induction was achivied only when boron to zinc transmetalation was performed. When zirconium to zinc transmetalation was performed, the absence of selectivity could be attributed to the presence of zirconium species in solution. The use of 10 mol% of ligand, as used by Wipf *et al.*[275] may lead to a better selectivity and decrease the formation of 1-phenyl-1-propanol. As it was observed in case of Zr to Zn transmetalations, the reaction temperatures were very crucial in achiving the enantiorich allylic alcohols and the reaction conditions are still need to be optimized.

4.6. Experimental details

4.6.1. Zr to Zn transmetalation

The starting materials were purchaseds from Aldrich and the solvents used in the synthesis were freshly distilled. The aromatic aldehydes and alkynes used for synthesis were freshly distilled and kept under inter atmosphere.

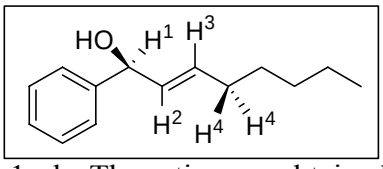
To a solution of Cp_2ZrHCl (Schwartz's regent, 0.21 g, 0.81 mmol), in THF (5 mL), terminal alkyne 1-heptyne (94 μL, 0.81 mmol, 1.0 equiv.) was added in one portion. The complexation of alkyne with zirconium reagent was indicated by the color change from clear to yellow (sometimes, transition through an intermediate green zirconium species), and transition to a homogeneous phase. An additional amount of alkyne (0.5 equiv.) was added to ensure the complete hydrozirconation. After 30 min, the reaction mixture was cooled to -65 °C and diethylzinc solution in THF (0.5M, 162 μL, 0.81 mmol, 1.0 equiv.) was added. For effective transmetalation, the reaction mixture was equilibrated at low temperature, from -65 to -30 °C for one hour.

Addition of alkenylzinc to aldehyde:

In a 25 mL round bottom flask, equipped with a reflux condenser and cold water circulation, Schiff base derived tetradentate ligand (compound **2.19a**, 21 mg, 28 μmol, 0.03 equiv.) was dissolved in THF (2.0 mL). Diethylzinc (0.5 M, 56 μL, 0.03 mmol) was added to the ligand and refluxed at 65 °C for one hr. The chiral ligand-zinc complex was then cooled to -78 °C (acetone/CO_2) and benzaldehyde (85 mg, 0.81 mmol 1.0 equiv.) was added. Alkenylzinc reagent was cannulated into this solution maintaining the temperature at -78 °C, and after the addition was complete, the reaction mixture was

allowed to get to room temperature over an hour and stirred at room temperature for 16 hrs. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with 10% NH_4Cl solution (3 x 50 mL), 1% $NaHCO_3$ (2 x 50 mL) and finally with 1% NaCl solution (2 x 50 mL). Zirconium salts that were formed during the work-up created emulsions, which were broken with difficulty. The use of NH_4Cl during work-up facilitated the extraction process. The organic layer was dried over K_2CO_3. Ethyl acetate was evaporated using a rotovap, and the crude residue product was analyzed using ^{1}H NMR and HPLC. The reaction yielded a mixture of 1-phenyl-1-propanol and 1-phenyl-oct-2-enol and on repeating the reaction, the ratio of ethyl *vs*. alkenyl addition had been inconsistent. The HPLC chromatographs were difficult to analyze due to impurities overlapping with the product peaks. Also it was observed that the $R_{t(S)}$ of 1-phenyl-1-propanol was same as $R_{t(S)}$ of product, 1-phenyloct-2-enol.

(E)-1-phenyloct-2-en-1-ol (crude):



The crude product (*E*)-1-phenyloct-2-en-1-ol could not be purified, and the spectral data was extracted from the 1:2 mixture of 1-phenyl-1-propanol and 1-phenyloct-2-ene-1-ol. The ratio was obtained by comparing integration of benzylic protons in ^{1}H NMR data. These compounds were unable to be separated using silica gel column chromatography.

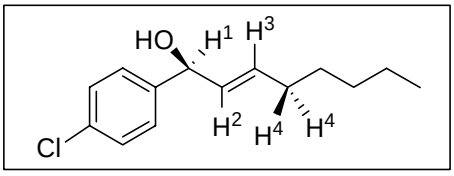
^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.91(t, *J* = 7.34Hz, -C*H*$_3$, 6H), 1.23-1.44(m, -C*H*$_2$-, 4H), 1.67-1.89(m, -C*H*$_2$- 2H), 2.01-2.10(m, -C*H*$_2$-, 2H), 7.20-7.37(m, Ar-*H*, 10H).

4.6.2. Boron to zinc transmetalations

In a 25 mL round bottom flask, cyclohexene (205 µL, 2.0 mmol), was dissolved in freshly distilled hexane (3.0 mL). Borane-dimethylsulfide complex ($BH_3 \cdot SMe_2$, 10.0 M solution in hexanes, 100 µL, 1.0 mmol), was added to cyclohexene solution at 0 °C. The white turbid solution was stirred at 0 °C for 3 hrs, after which 1-heptyne (96.13 mg, 1.0 mmol, 1 equiv.) was added using a microsyringe. The reaction mixture was stirred at room temperature for an hr, for alkenylborane formation. The reaction temperature was lowered to -78 °C and then diethylzinc solution in hexane (1.0M, 1 mL, 1.0 equiv.) was added dropwise over 15 min. The alkenylzinc reagent was stirred at -78 °C for 30 min.

In another round bottom flask, the tetradentate ligand-zinc complex was formed and *p*-chlorobenzaldehyde (140 mg, 1.0 mmol, 1.0 equiv.) was added as described earlier. The alkenylzinc complex was then cannulated into this solution at -78 °C. The reaction mixture was slowly warmed to room temperature over an hour, and the reaction was stirred for 12 hours at room temperature. The reaction mixture was then diluted with ethyl acetate (50 mL), and washed with 10% NH_4CO_3 solution (2 x 50 mL), 1% $NaHCO_3$ solution (2 x 50 mL) and 1% NaCl solution (2 x 50 mL). The organic layer was dried over K_2CO_3 and ethyl acetate was evaporated using a rotovap. The product (yellow oil) was analyzed using HPLC and ^{1}H NMR.

(E)-1-(4-Chlorophenyl)-oct-2-enol:



^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.80-0.94(m, -C*H*$_3$, 3H), 1.20-1.43(m, -C*H*$_2$-C*H*$_2$-C*H*$_2$-, 6H), 1.93(bs., -O*H*, 1H) 1.98-2.077(m, =CH-C*H*$_2$-,

2H), 5.13(d, J_{12} = 6.81Hz, -C*H*-, 1H), 5.60(dd, J_{23} = 15.36Hz, J_{12} 6.81Hz, -CH-C*H*=CH-, 1H), 5.75(dt, J_{23} = 15.36Hz, J_{34} = 6.54Hz, -CH-CH=C*H*-, 1H), 7.28-7.45(m, Ar-*H*, 4H). HPLC data: $R_{t(R)}$ = 11.62 min., $R_{t(S)}$ = 8.84 min. (*Chiralcel OD*, 1.0 mL/min flow rate; 5/95 *ipa*/hexane as mobile phase).

OUTLOOK AND FUTURE DIRECTIONS

The key feature of transition metal complexes of tetradentate ligands (Schiff base derived bifurcated dipeptides) as chiral Lewis acids was supported by the diethylzinc additions to aldehydes. The study of nonlinear effect using ligands **3.19** and **3.20** showed a linear relationship between the enantiomeric excess of ligands and the enantiomeric excess of product (1-phenyl-1-propanol). The observed linearity in these plots (**Fig. 3.3-3.5**) suggested that only one molecule of the ligand was responsible for the chirality transfer in the transition state. Also, the plot of Hammett constant *vs* log(*S/R*) was resulted in a straight line with negative slope, suggesting that electron donating groups on benzaldehyde increase the enantiomeric excess of the product (**Fig 3.6**). Thus it can be inferred that tetradentate ligands having similar structural features as **3.19**(C_2-symmetric) and **3.20**(C_2-asymmetric), when bound to transition metal cations, can function as Chiral Lewis acids.

As they bind to various bivalent transition metal cations, these ligands can be viewed as *privileged structures*, and may potentially become catalysts for various asymmetric reactions.

Even though the ligand synthesis on polymer support resulted in low yields, the polymer supported ligands can be utilized in the catalyst screening and optimizing the reaction conditions, which in solution phase can be very time consuming. The synthesis, of polymer supported ligands, when compared to first Schiff base formation (using diarylketimine resins **2.9** or **2.10**), resulted in high yields. Thus it can be concluded that

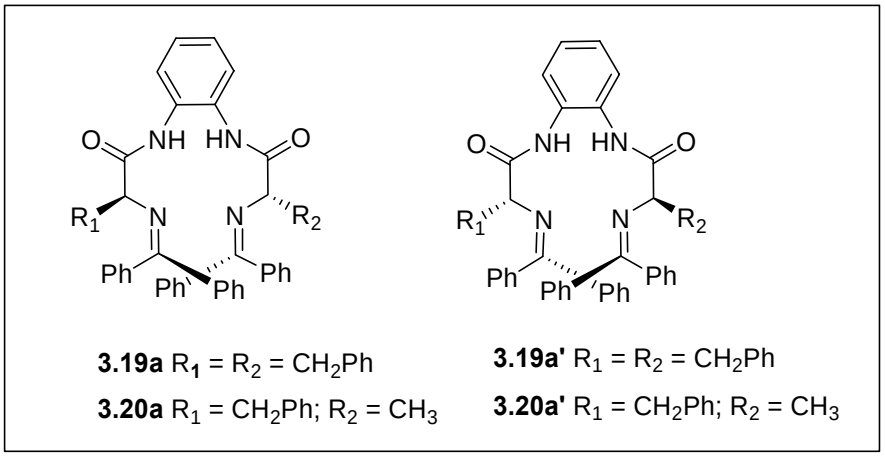
by optimizing the reaction conditions to improve the loading of Schiff base formation, the final resin loading can be increased.

The formation of allylic alcohols *via* alkenylzinc additions to aromatic aldehydes, expanded the applicability of tetradentate ligands. Boron to zinc alkenyl transfer reactions, were shown to produce better selectivity, compared to the zirconium to zinc alkenyl transfer reactions. The use of higher quantities of ligand may result in better selectivity in case of zirconium to zinc transmetalations. As suggested by Wipf *et al*.[275] the involvement of zirconium species that compete with the ligand-metal complex to catalyze the reaction, resulted in low yields, or the formation of by-products. Increasing the catalyst to 10 mol% may overcome the involvement of zirconium species in reaction and produce the allylic alcohols in enantioselective manner.

APPENDIX A

All the ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian 300MHz spectrophotometer (unless other wise mentioned), in appropriate solvent. The HPLCs were run using Varian Prostar 330 with the Star workshop 5.0 interface. The integrations on HPLC runs were performed using the Star report writer (Integral part of Star workshop 5.0). HPLC solvents were purchased from Aldrich and the samples were injected at 1 mg/mL concentrations.

The ligands that were used for the study of nonlinear effect are shown in the following figure.

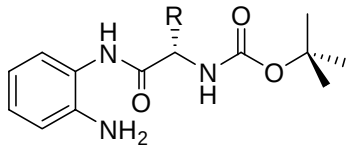


3.19a $R_1 = R_2 = CH_2Ph$

3.20a $R_1 = CH_2Ph$; $R_2 = CH_3$

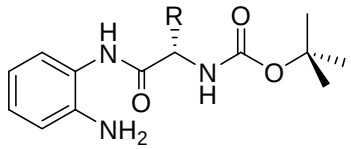
3.19a' $R_1 = R_2 = CH_2Ph$

3.20a' $R_1 = CH_2Ph$; $R_2 = CH_3$


H
N
R
O
N
H
O
O
NH2

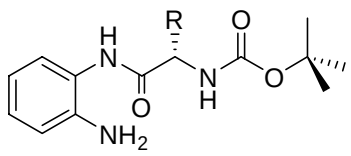
2.13a R = CH_3

1.04
1.24
1.01
1.88
1.00
1.12
2.08
13.28
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)



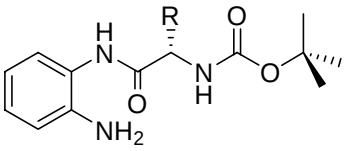
2.13a R = CH_3

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)


R
O
H
N
N
H
O
O
NH2

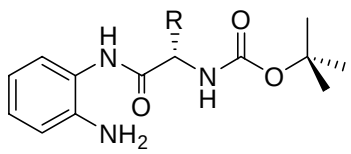
2.13b R = H

1.02
1.18
1.19
2.20
1.00
2.43
2.29
10.67
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

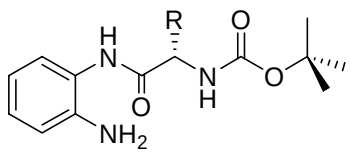

H
N
R
O
N
H
O
O
O
NH2

2.13b R = H

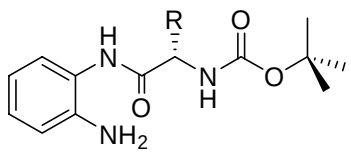
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (t1)



2.13c R = $CH(CH_3)_2$

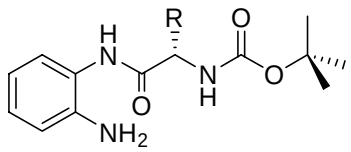


2.13c R = $CH(CH_3)_2$


H
N
R
O
N
H
O
O
NH2

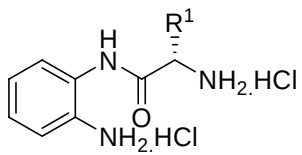
2.13d R = CH_2Ph

0.87
5.10
1.98
2.03
1.00
0.98
1.97
2.02
9.45
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


R
O
H
N
N
H
O
O
NH2

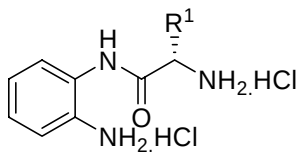
2.13d R = CH_2Ph

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)


R1
H
N
NH2.HCl
O
NH2.HCl

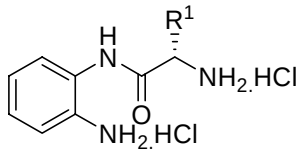
2.14a $R^1 = CH_3$

3.73
0.96
3.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

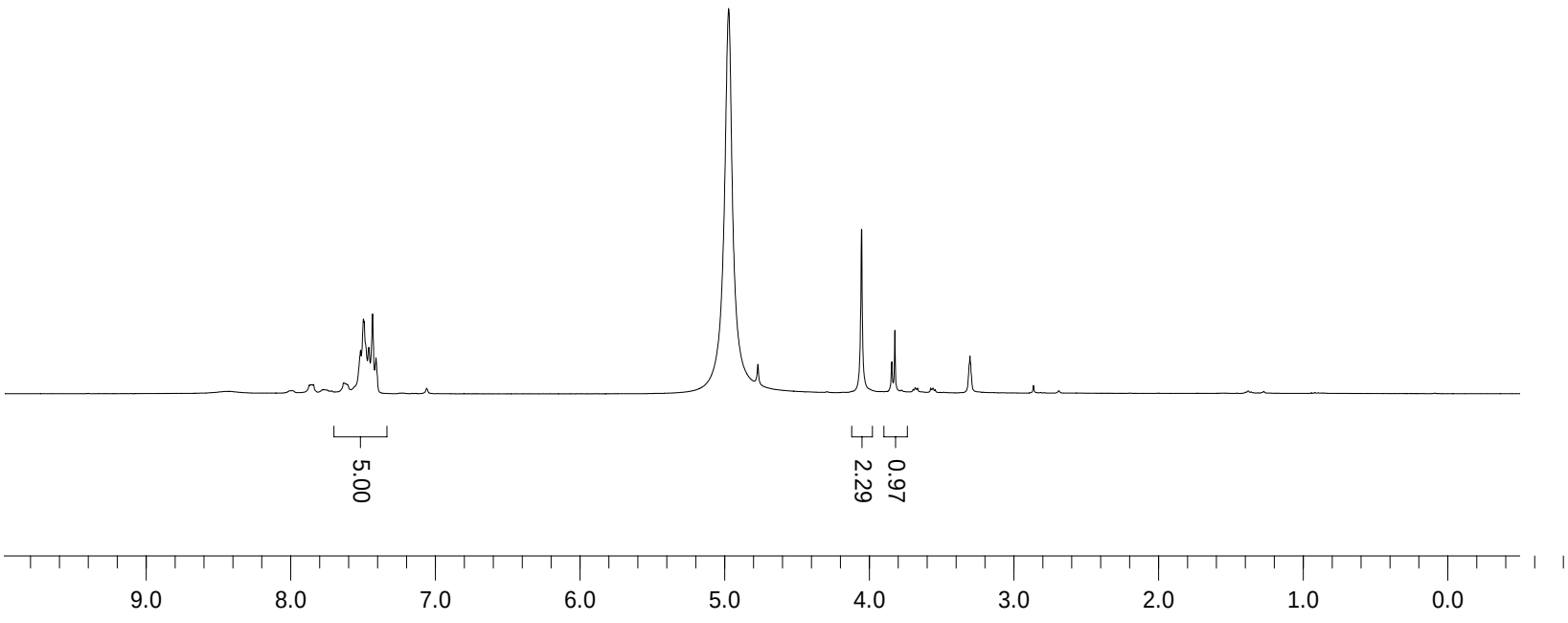

R1
H
N
NH2.HCl
O
NH2.HCl

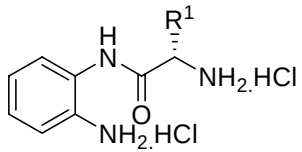
2.14a $R^1 = CH_3$

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)


R1
H
N
NH2.HCl
O
NH2.HCl

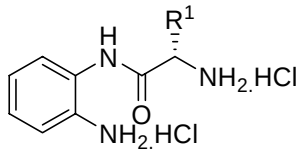
2.14b R^1 = H


5.00
2.29
0.97
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

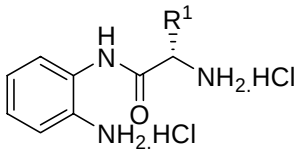

R1
H
N
NH2.HCl
O
NH2.HCl

2.14b R^1 = H

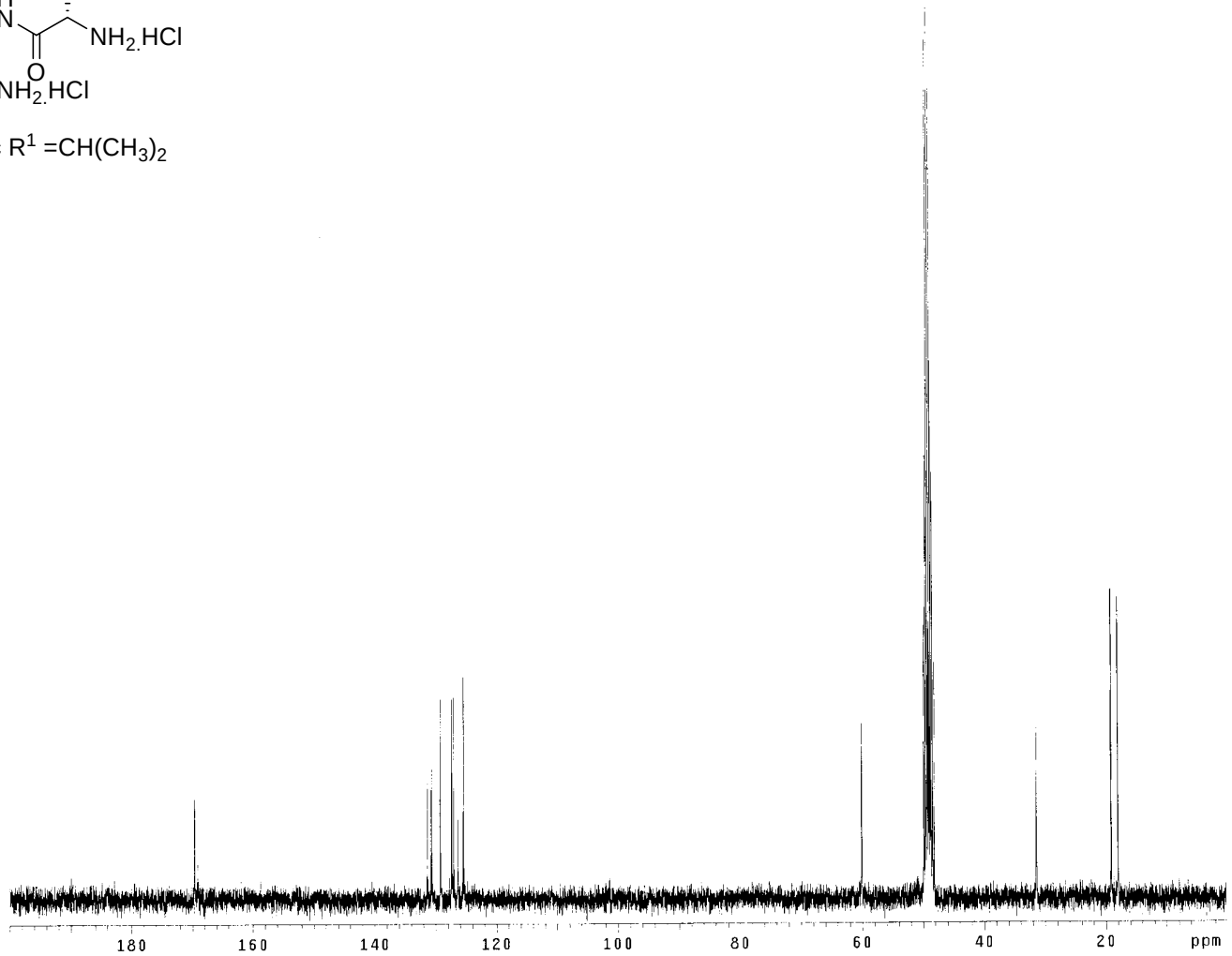
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)

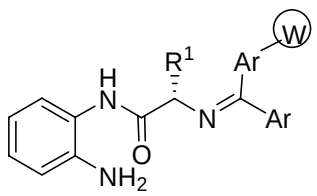


2.14c R^1 =$CH(CH_3)_2$



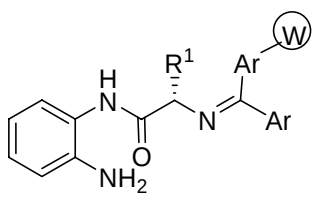
2.14c R^1 =$CH(CH_3)_2$



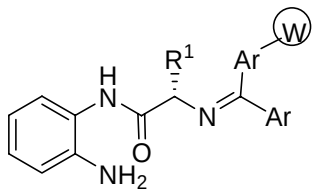

W
R1
Ar
H
N
N
Ar
O
NH2

2.20b R^1 = H

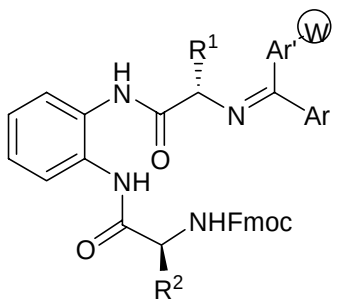
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)



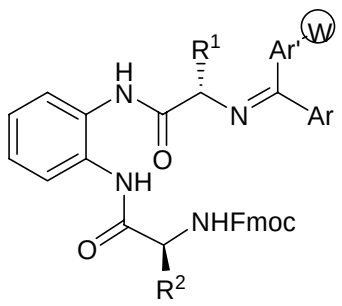
2.20d $R^1 = CH_2Ph$



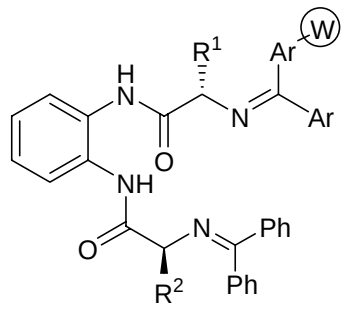
2.28 $R^1 = (CH_2)_2SCH_3$



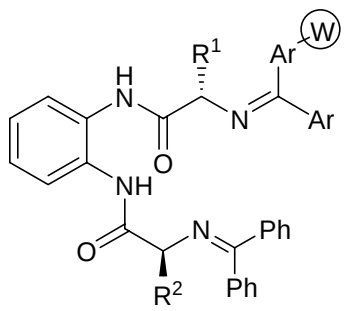
2.22f $R^1 = CH_2Ph$, $R^2 = CH_3$



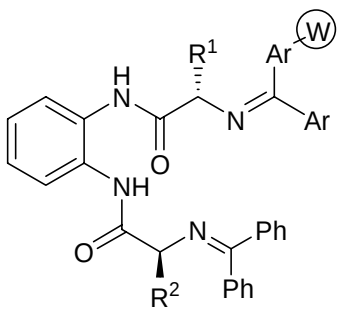
2.22g $R^1 = CH_2Ph$, $R^2 = CH(CH_3)_2$



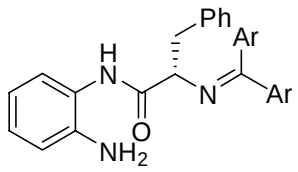
2.26f $R^1 = CH_2Ph$, $R^2 = CH_3$



2.26g $R^1 = CH_2Ph$, $R^2 = CH(CH_3)_2$

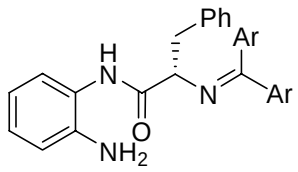


2.26o $R^1 = CH_3$, $R^2 = CH_2Ph$


Ph
Ar
H
N
N
Ar
O
NH2

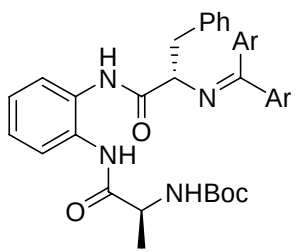
2.15

0.83
1.81
7.60
5.99
1.93
0.99
6.00
1.64
1.87
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


Ph
Ar
H
N
N
Ar
O
NH2

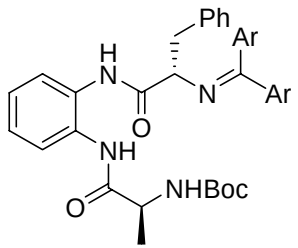
2.15

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)


Ph
Ar
H
N
N
Ar
O
NH
O
NHBoc

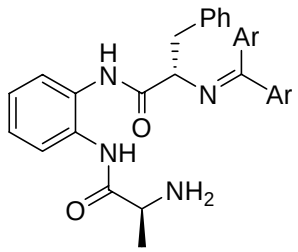
2.16

0.93
0.73
2.84
0.50
6.71
2.03
3.87
1.72
1.06
1.04
1.03
6.00
2.61
9.55
5.28
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


Ph
Ar
H
N
N
Ar
O
NH
O
NHBoc

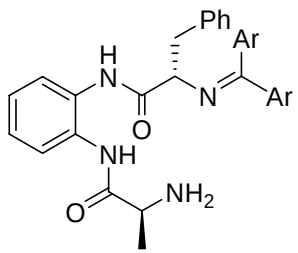
2.16

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)


Ph
Ar
H
N
N
Ar
O
NH
O
NH2

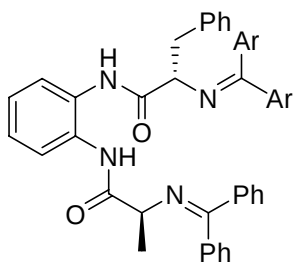
2.17

0.73
0.77
3.89
8.09
4.03
1.73
0.91
6.20
1.15
1.00
1.00
2.16
3.96
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


Ph
Ar
H
N
N
Ar
O
NH
O
NH2

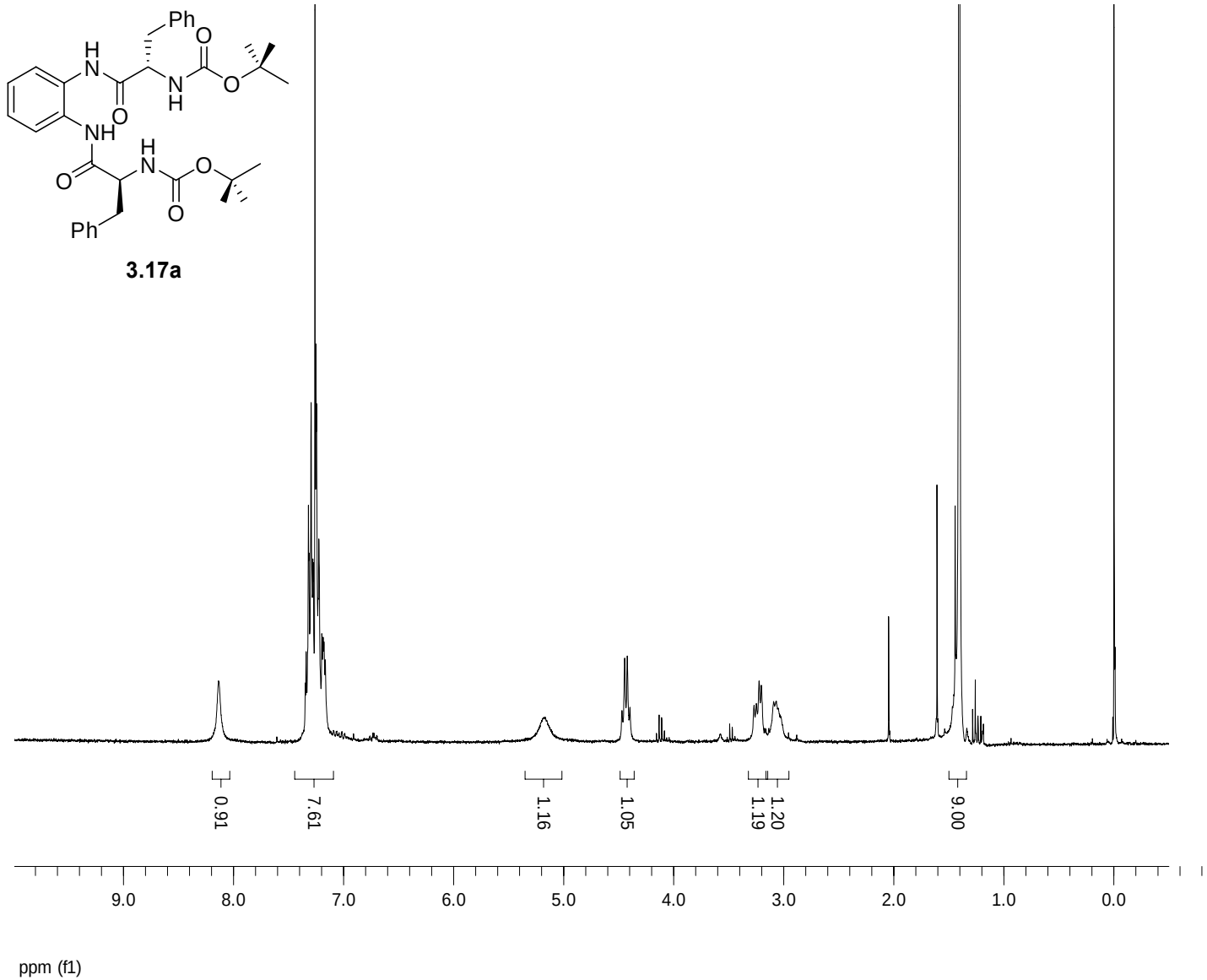
2.17

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)

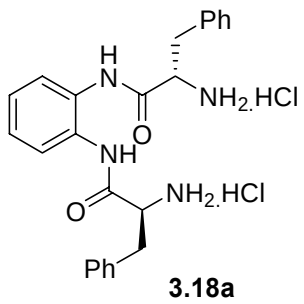

Ph
Ar
H
N
N
Ar
O
NH
O
N
Ph
Ph

2.18

0.81
0.82
2.05
4.04
3.20
7.42
2.28
3.66
1.82
0.95
1.02
5.78
1.00
1.07
4.83
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

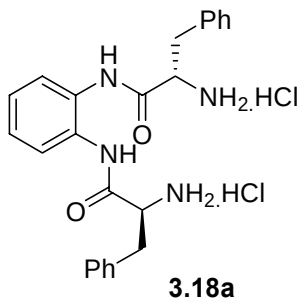

Ph
O
H
N
N
H
O
O
NH
H
N
O
O
O
Ph
0.91
7.61
1.16
1.05
1.19
1.20
9.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

3.17a


Ph
H
N
NH2.HCl
O
NH
O
NH2.HCl
Ph

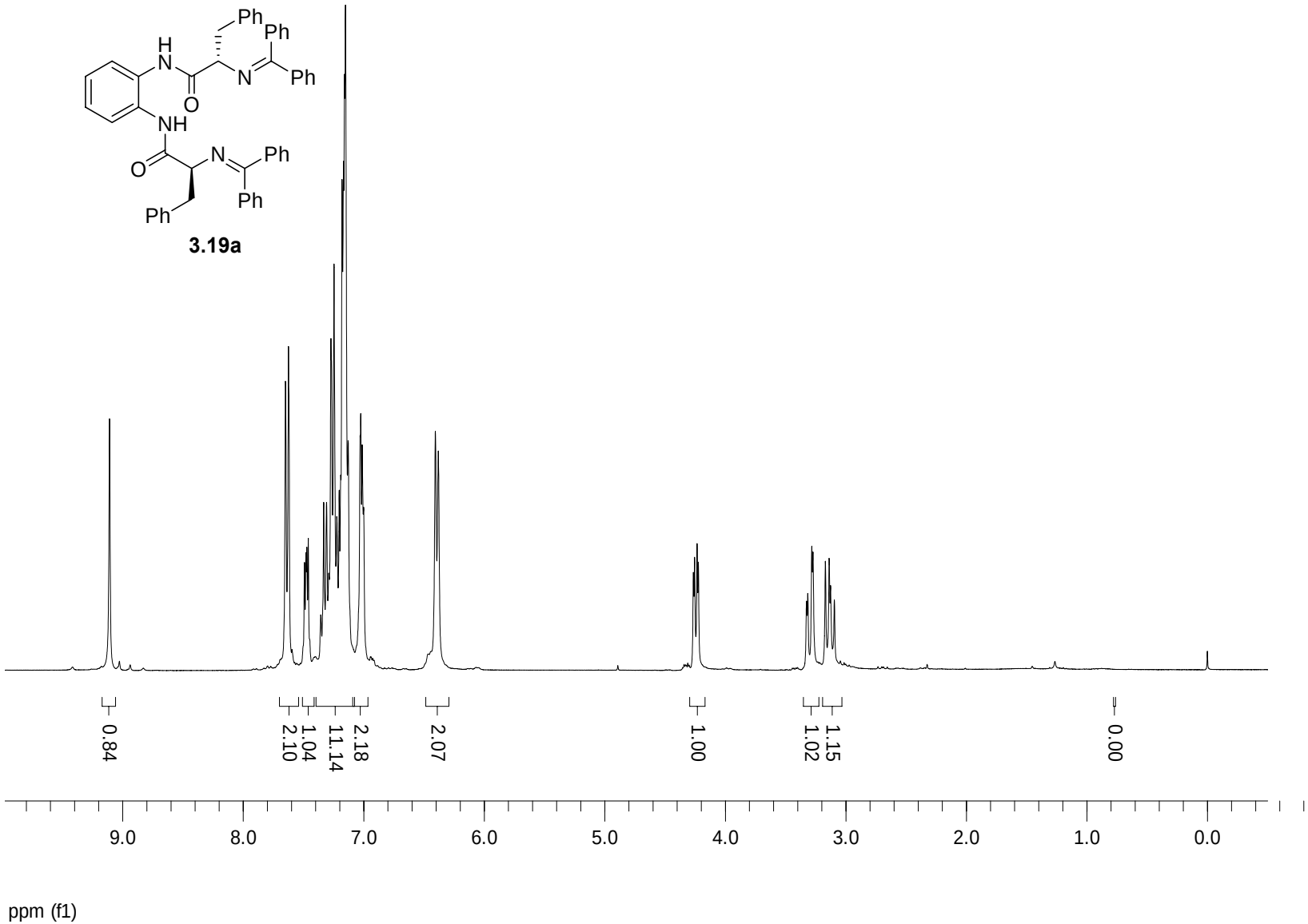
3.18a

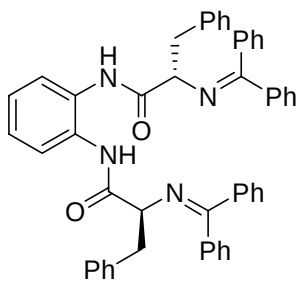
4.61
0.65
1.76
1.00
0.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


Ph
H
N
NH2.HCl
O
NH
O
NH2.HCl
Ph

3.18a

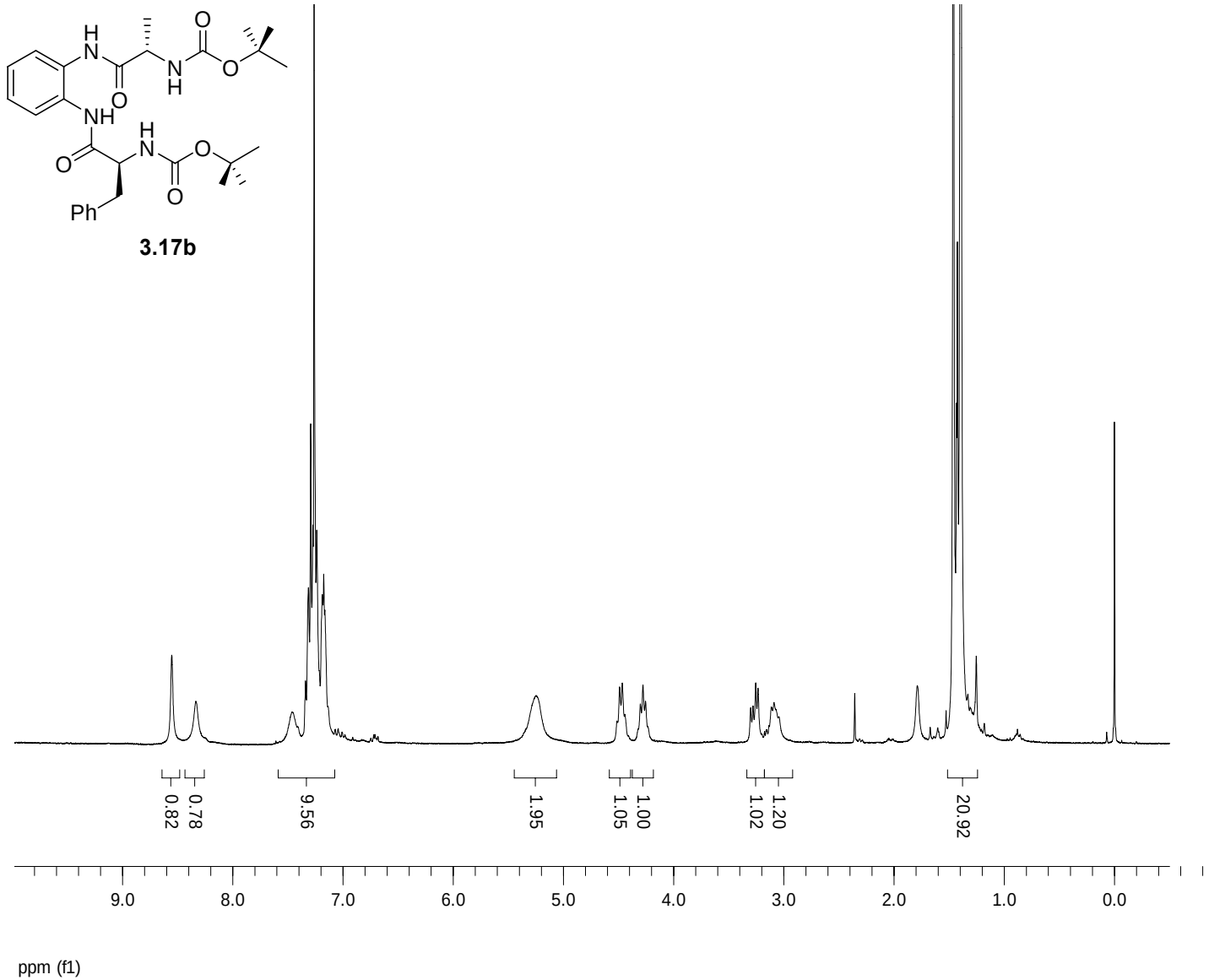
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (f1)

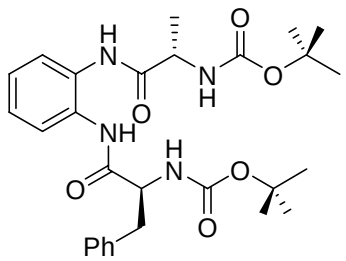

Ph
Ph
H
N
N
Ph
O
NH
O
N
Ph
Ph
Ph
3.19a
0.84
2.10
1.04
11.14
2.18
2.07
1.00
1.02
1.15
0.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


Ph
Ph
H
N
N
Ph
O
NH
O
N
Ph
Ph
Ph

3.19a

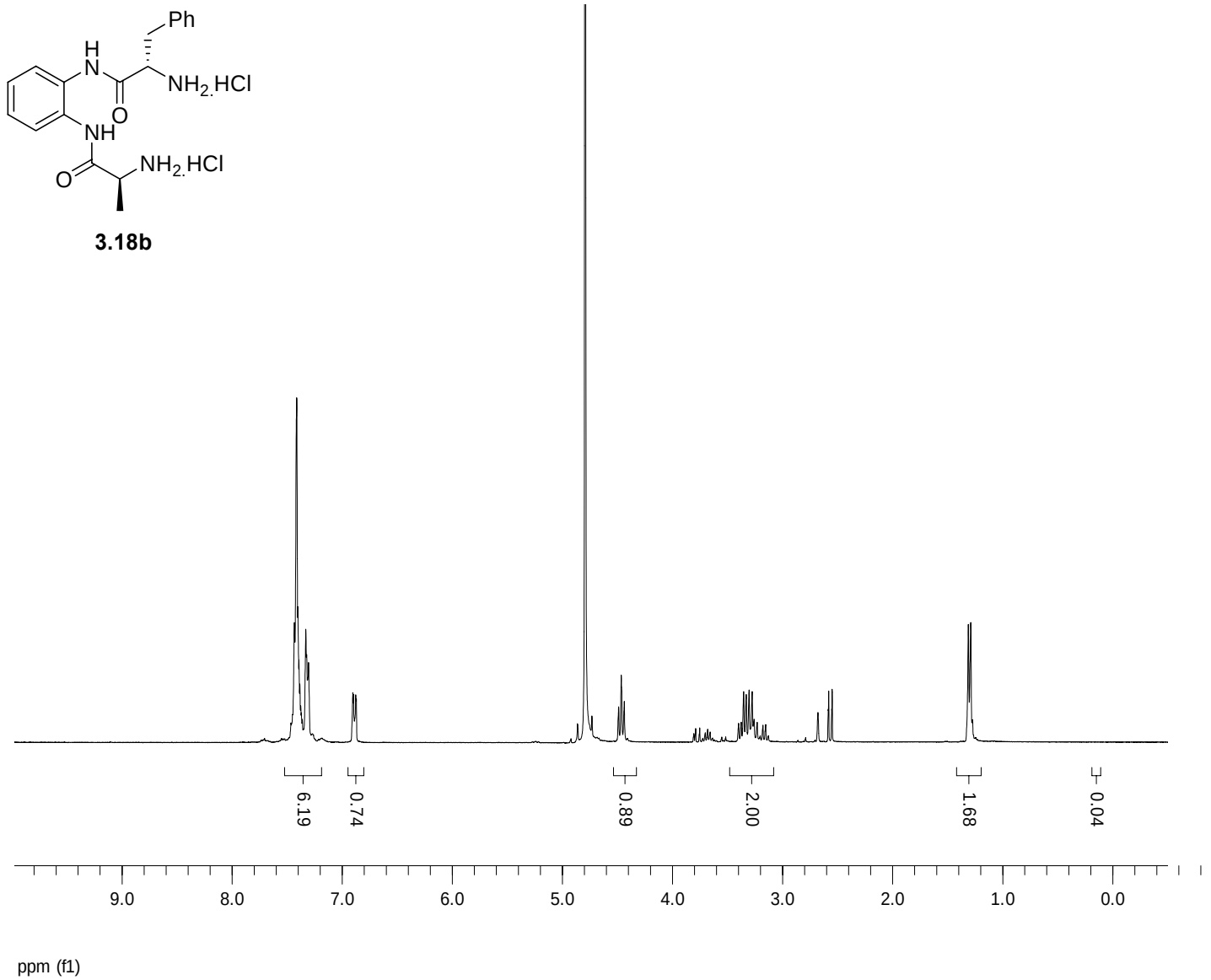
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (f1)


3.17b
0.82
0.78
9.56
1.95
1.05
1.00
1.02
1.20
20.92
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

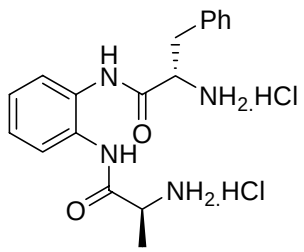


3.17b

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)


Ph
H
N
NH2.HCl
O
NH
O
NH2.HCl
6.19
0.74
0.89
2.00
1.68
0.04
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

3.18b


Ph
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N
NH2.HCl
O
NH
O
NH2.HCl

3.18b

190
180
170
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130
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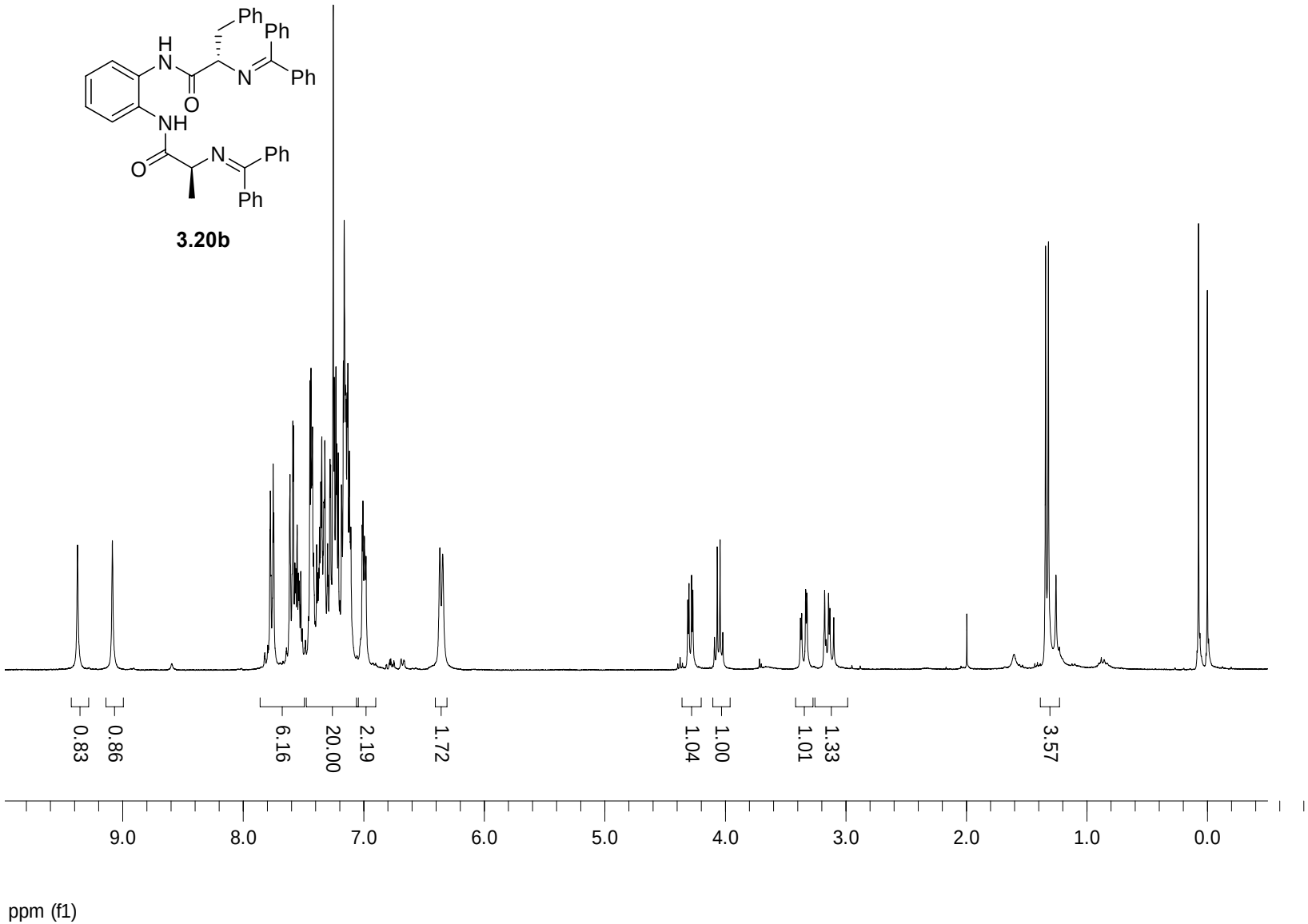
100
90
80
70
60
50
40
30
20
10
ppm (f1)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N
Ph
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0.86
6.16
20.00
2.19
1.72
1.04
1.00
1.01
1.33
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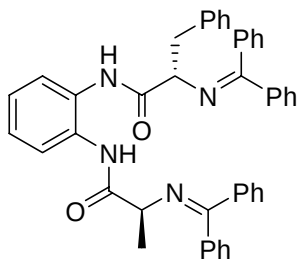
Ph
Ph
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Ph
O
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N
Ph
Ph

3.20b

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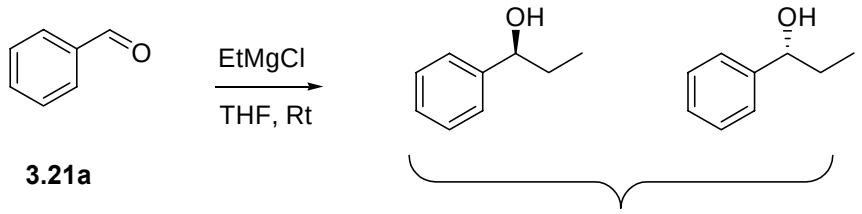
20
10
ppm (f1)



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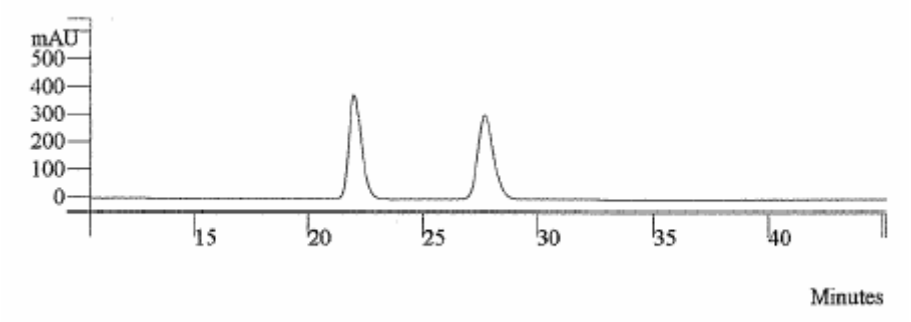
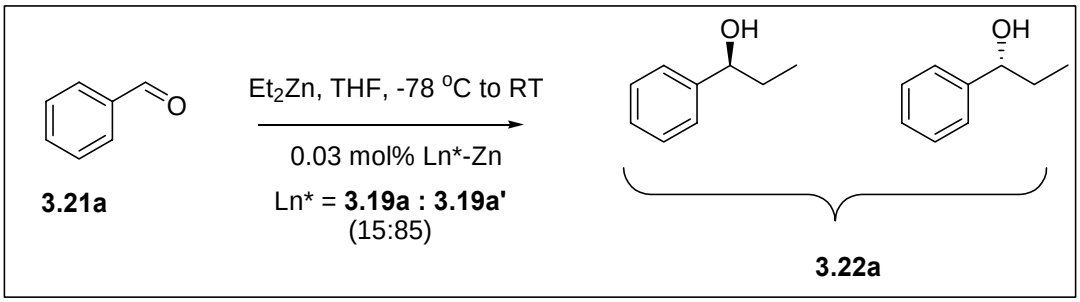
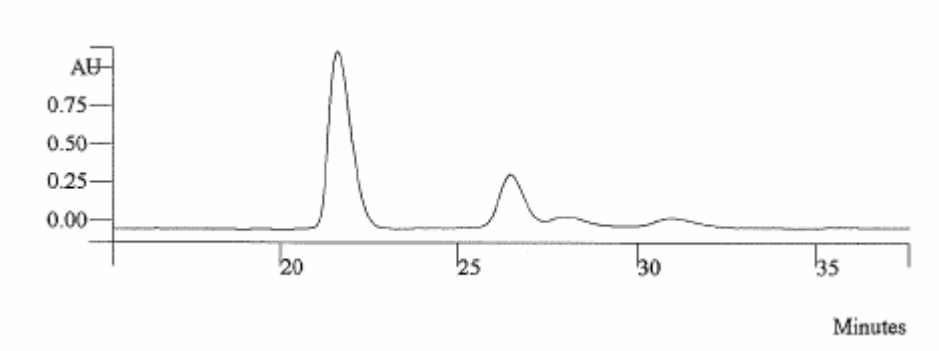


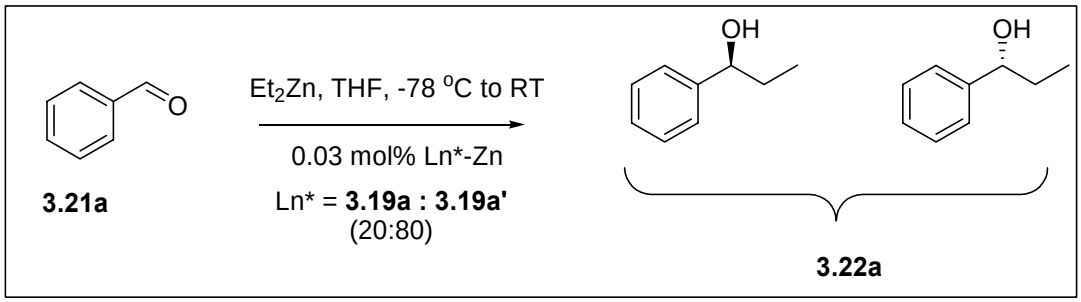
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	0.4740	3.180	715044
2	49.7164	21.978	74998760
3	49.8096	27.689	75139296
	100.0000		**150853104**

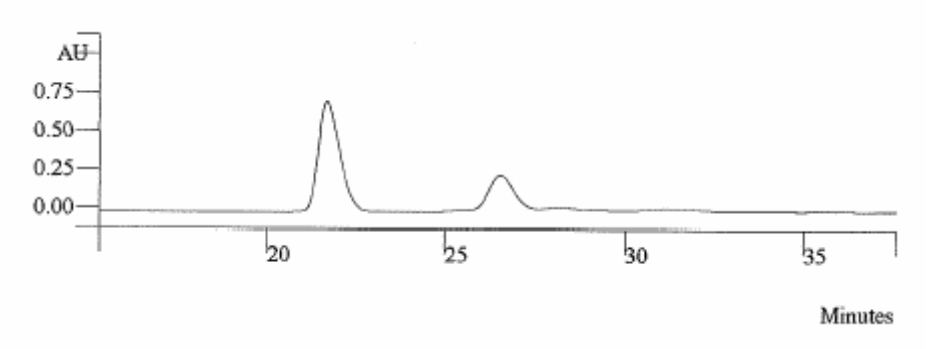
HPLC column used: *Chiralcel OD*, flow rate = 1.0 mL/min. λ_{max} = 210 nm. All the HPLCs were run under the same conditions, unless specified.



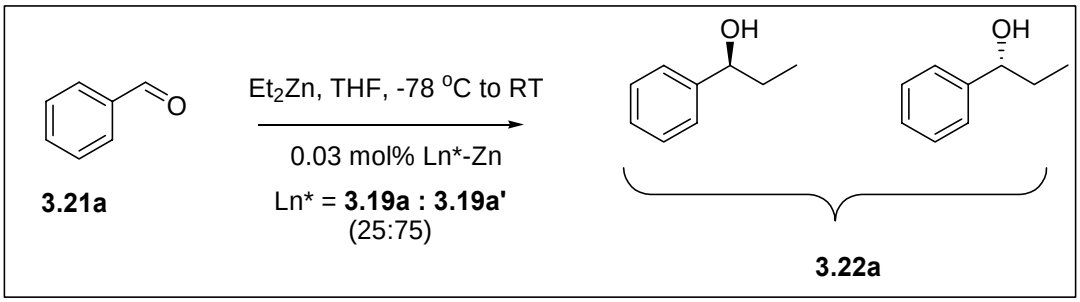


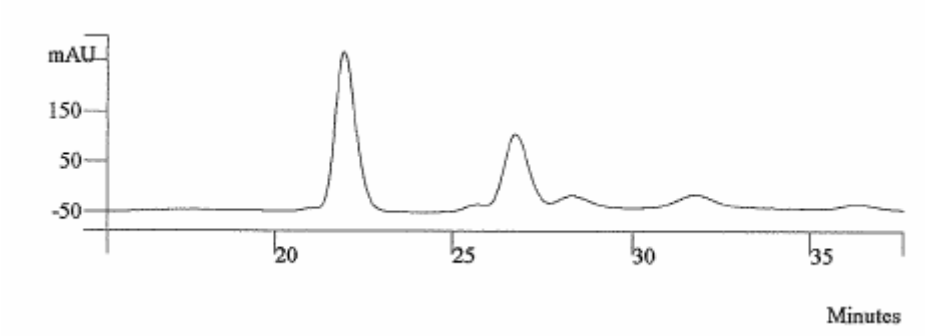
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	78.1255	21.585	262669008
2	21.8745	26.454	73545152
	100.0000		**336214144**



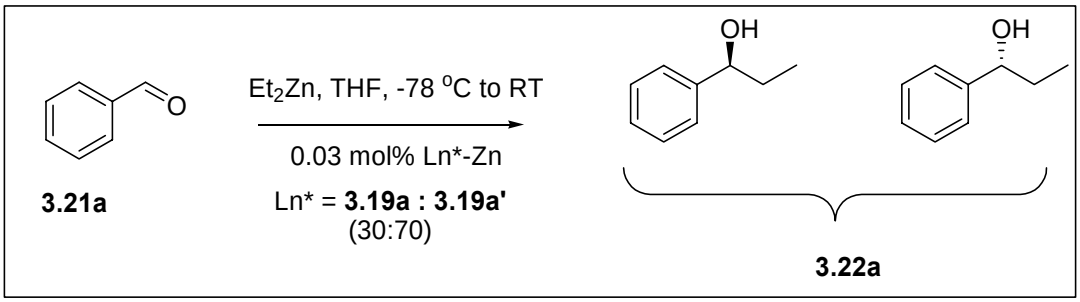


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	73.9561	21.668	153945712
2	26.0439	26.535	54212648
	100.0000		**208158368**





Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	99.5438	21.935	63367224
2	0.4562	25.680	290393
	100.0000		**63657616**



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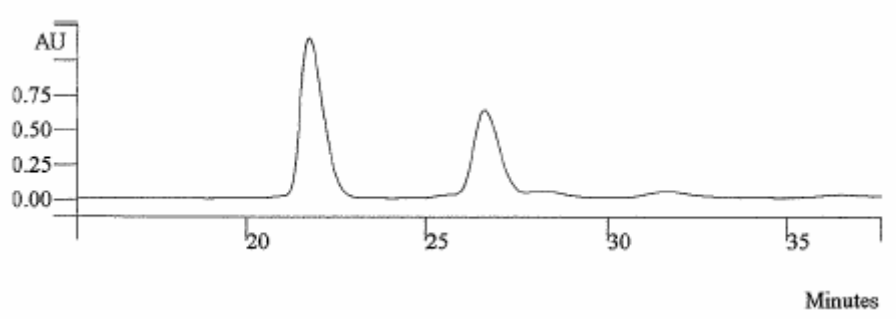
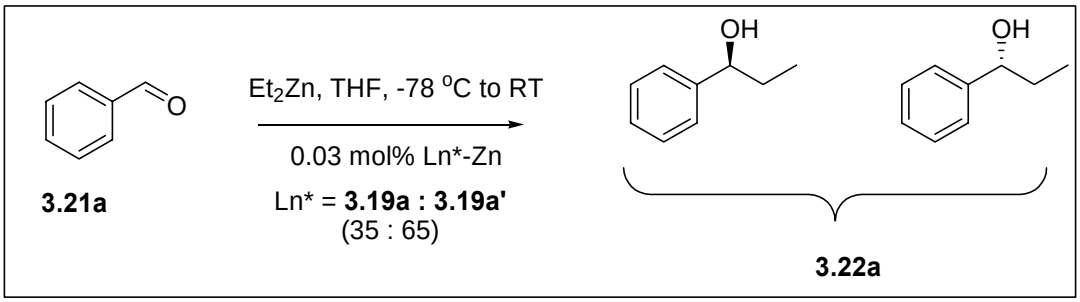
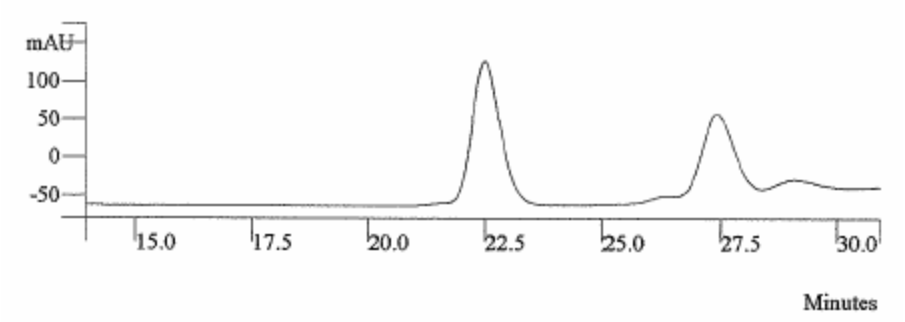
3.22a

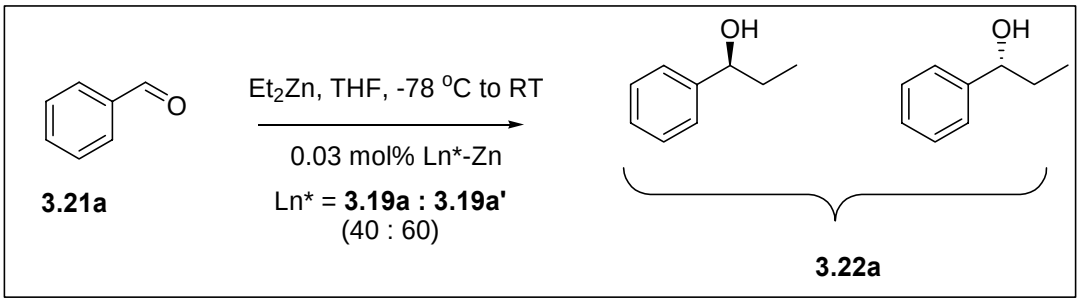


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	63.8661	21.741	264614576
2	36.1339	26.625	149712288
	100.0000		**414326848**





Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	62.5248	22.473	39916000
2	37.4752	27.408	23924270
	100.0000		**63840272**



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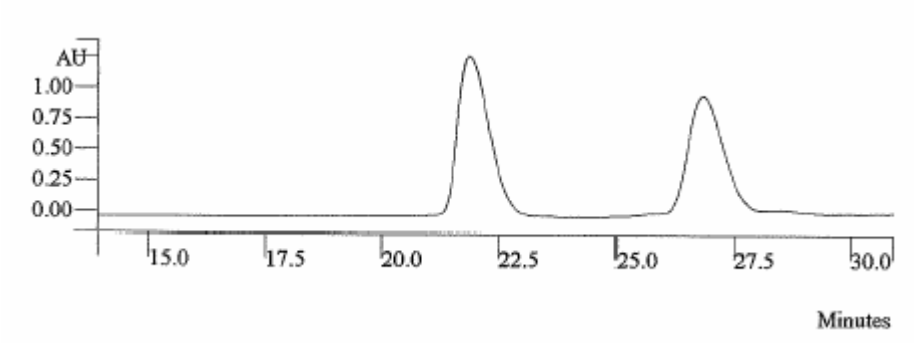
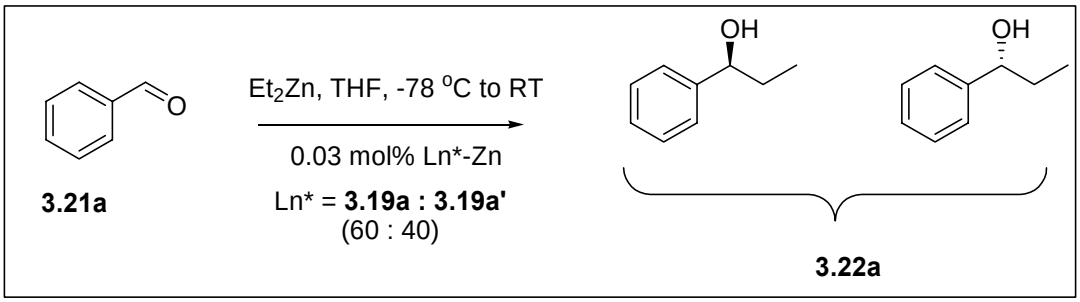


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	56.2866	21.862	310836896
2	43.7134	26.815	241403056
	100.0000		**552239936**



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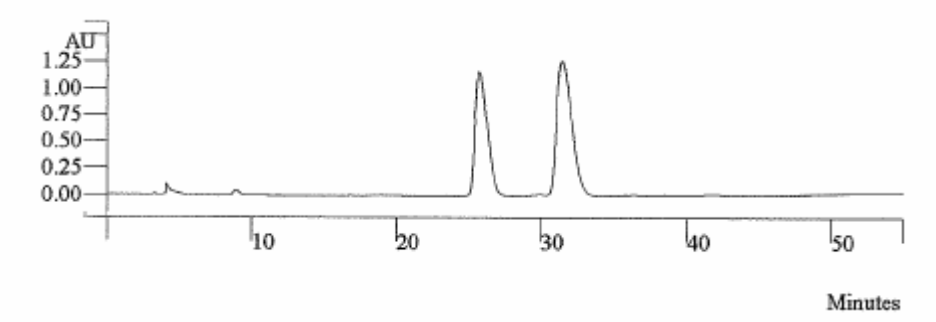
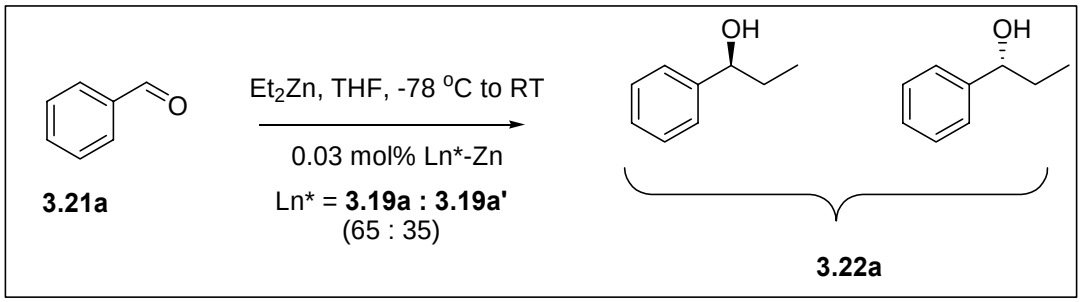


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	43.1623	25.717	356385728
2	56.8377	31.442	469301184
	100.0000		**825686912**



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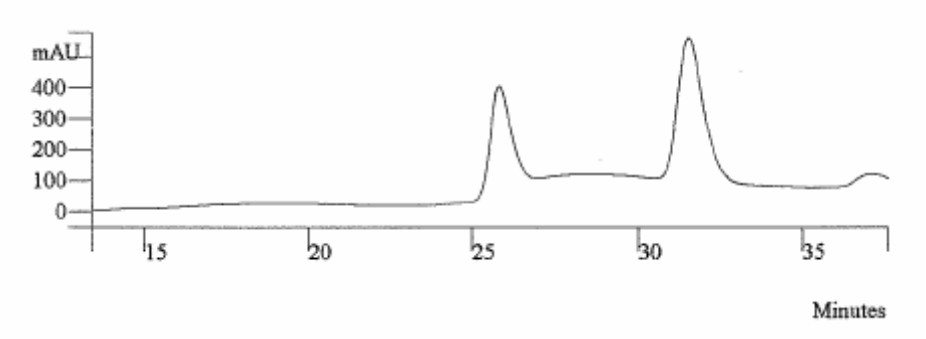
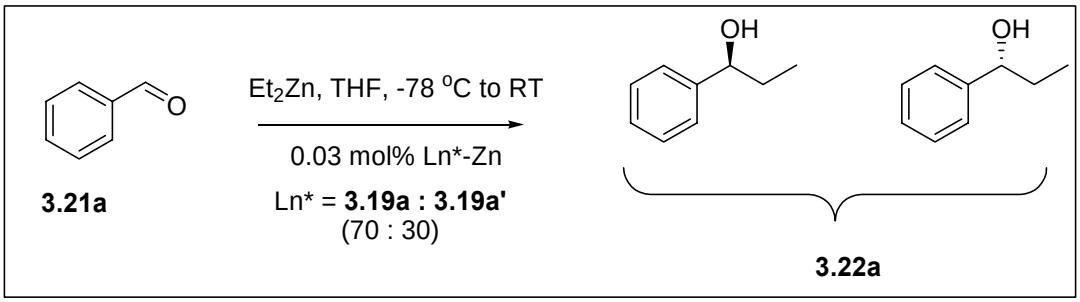


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	37.5486	25.815	75445440
2	62.4514	31.515	125481760
	100.0000		**200927200**



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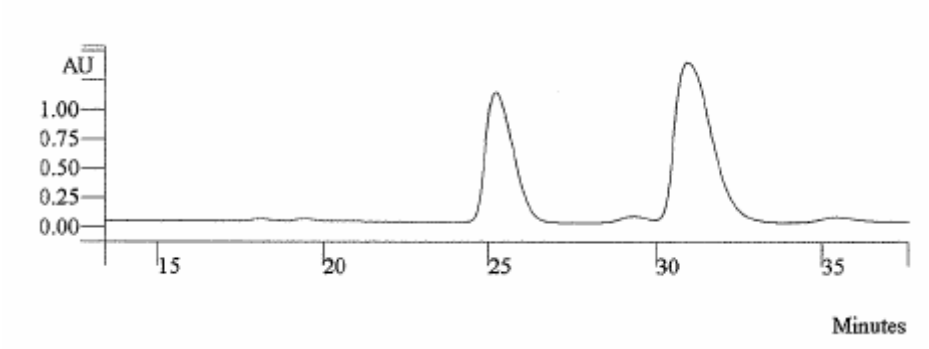
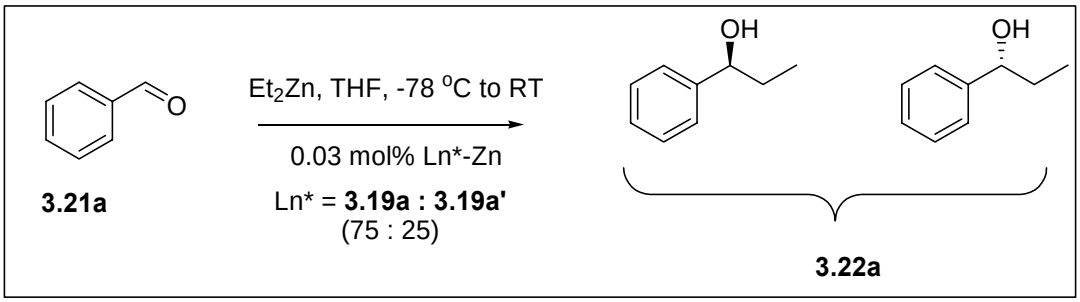


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	38.5194	25.206	328161120
2	61.4806	30.942	523776992
	100.0000		**851938112**



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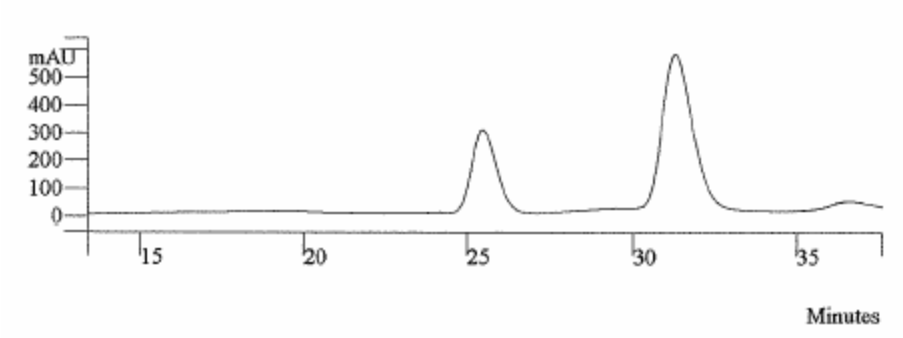
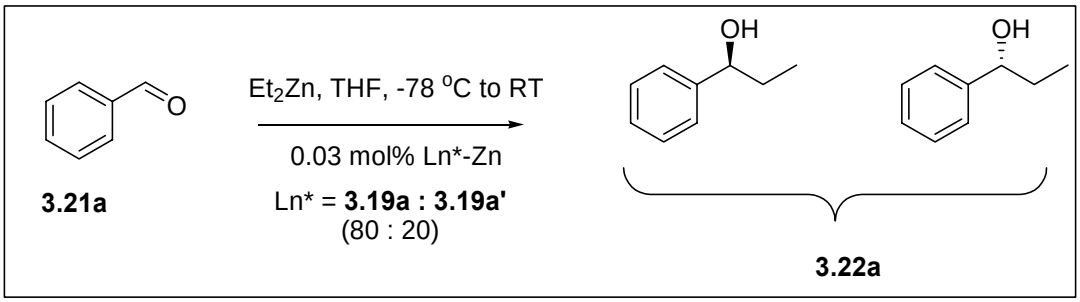


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	30.5045	25.455	80490696
2	69.4955	31.272	183374192
	100.0000		**263864896**



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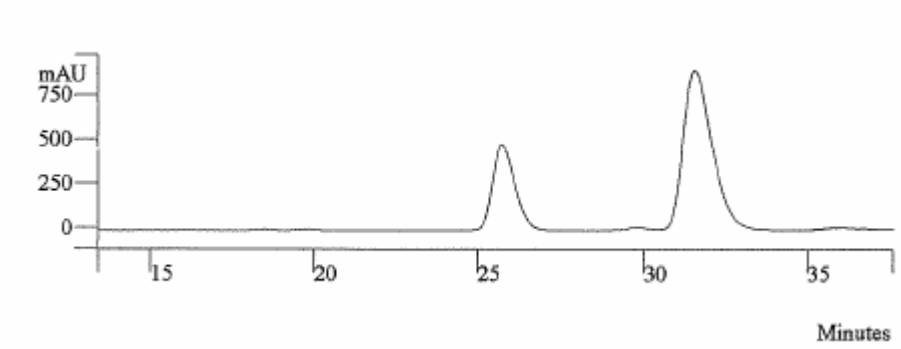
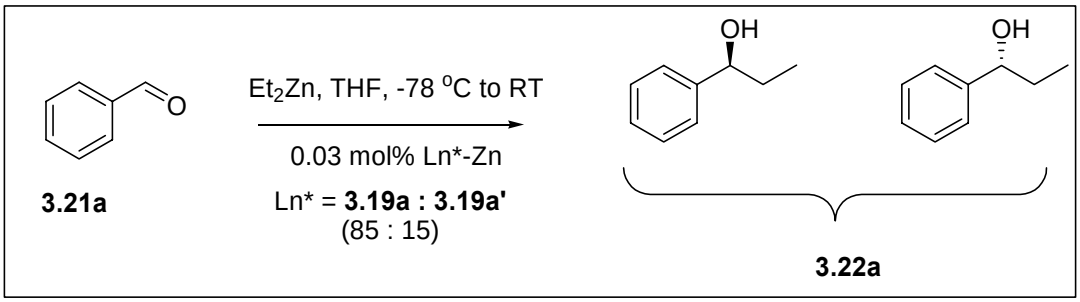


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	29.1727	25.716	115386160
2	70.8273	31.535	280141408
	100.0000		**395527552**



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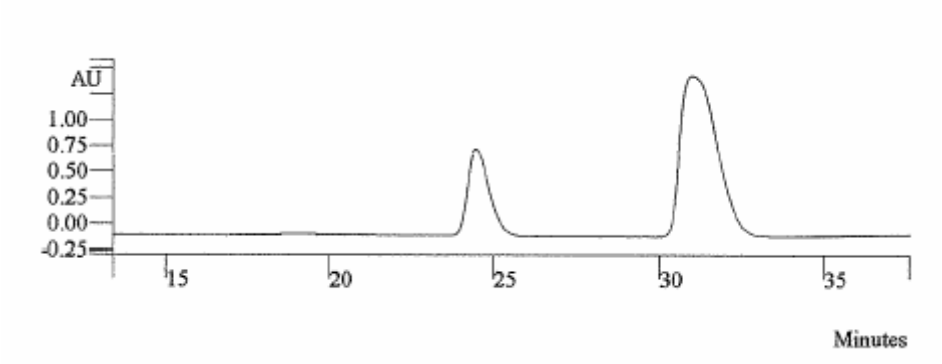
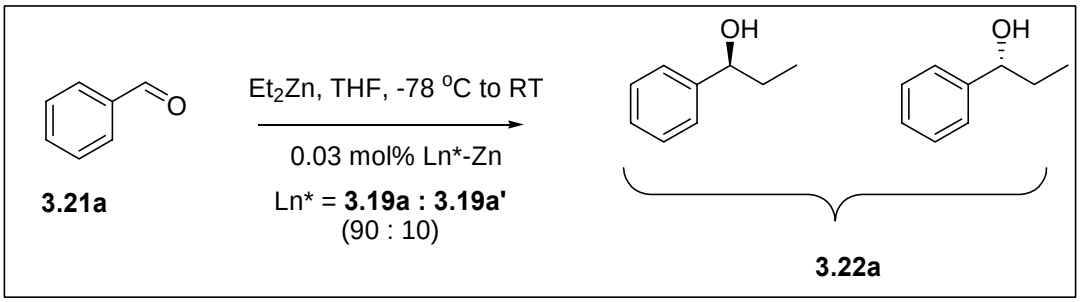


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	23.8417	24.448	191176192
2	76.1583	30.938	610678848
	100.0000		**801855040**



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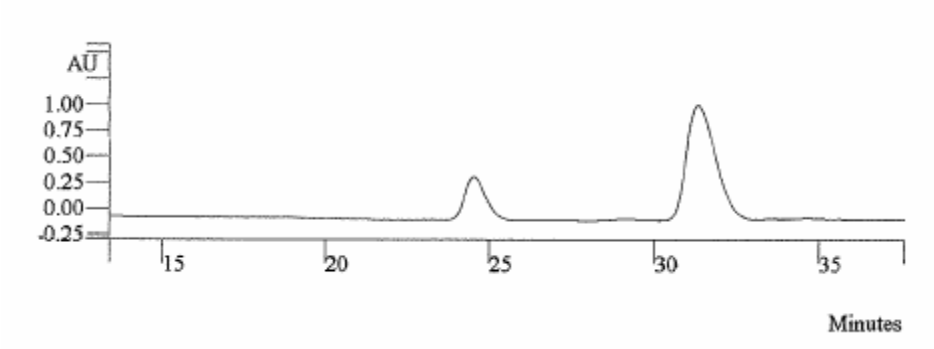
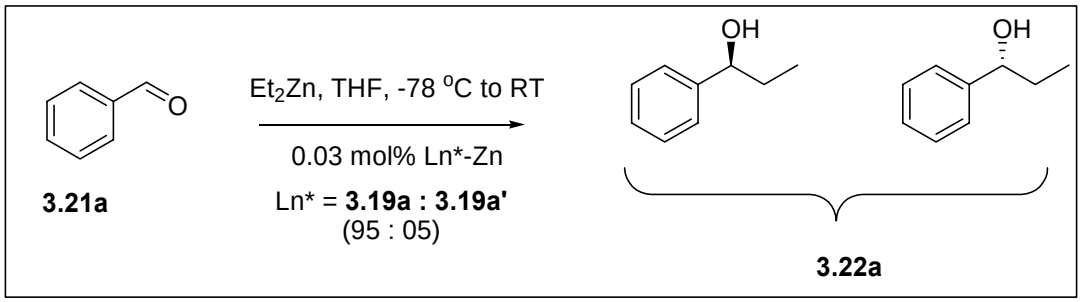


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	21.5336	24.512	95951248
2	78.4664	31.302	349637248
	100.0000		**445588480**



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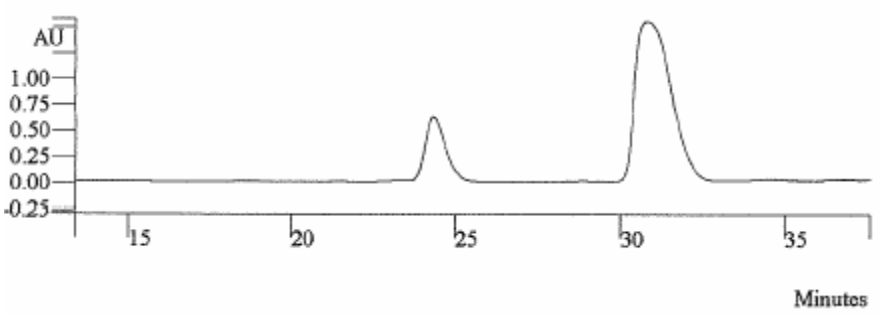
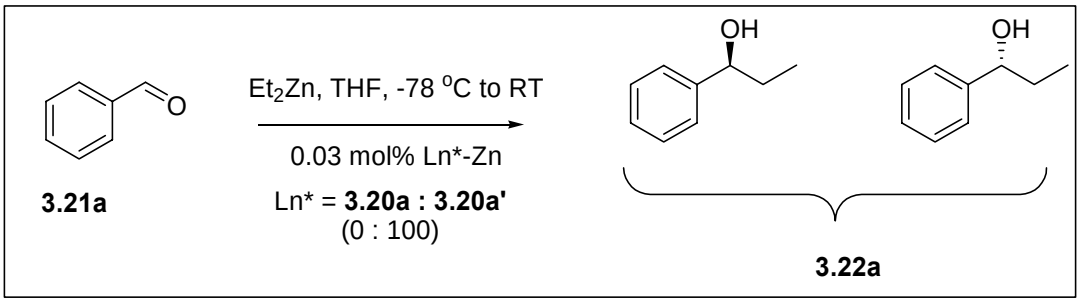


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	18.2961	24.322	133780912
2	81.7039	30.798	597419200
	100.0000		**731200128**



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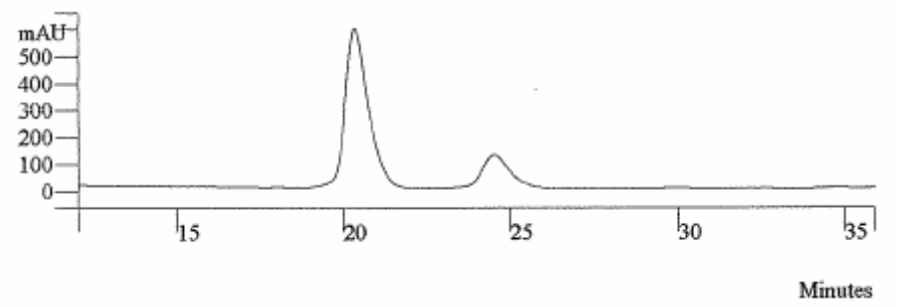
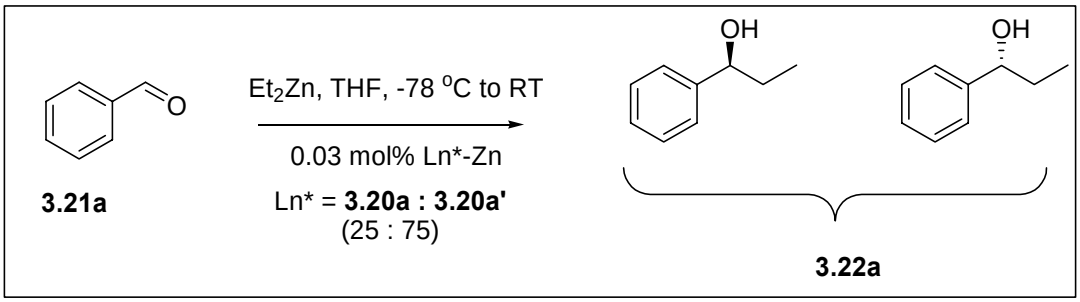


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	80.6610	20.327	147326176
2	19.3390	24.510	35322324
	100.0000		**182648496**



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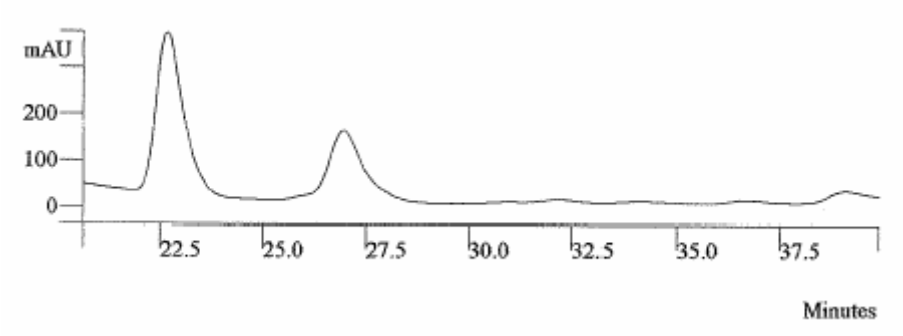
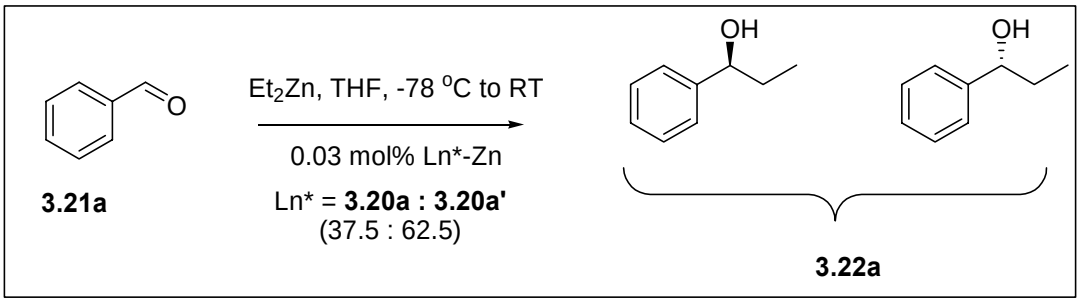


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	66.8987	22.651	80685792
2	33.1013	26.931	39923152
	100.0000		***120608944***



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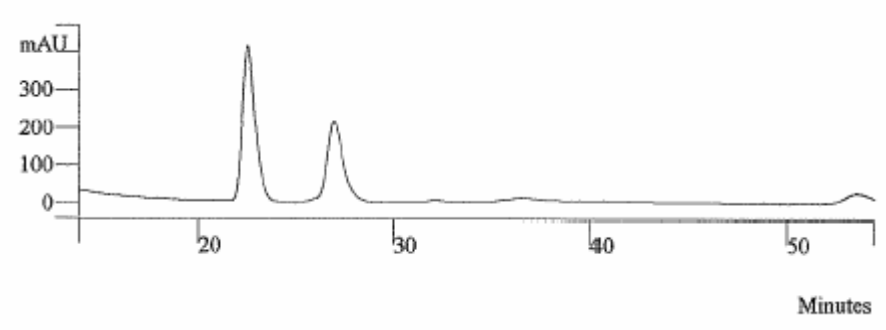
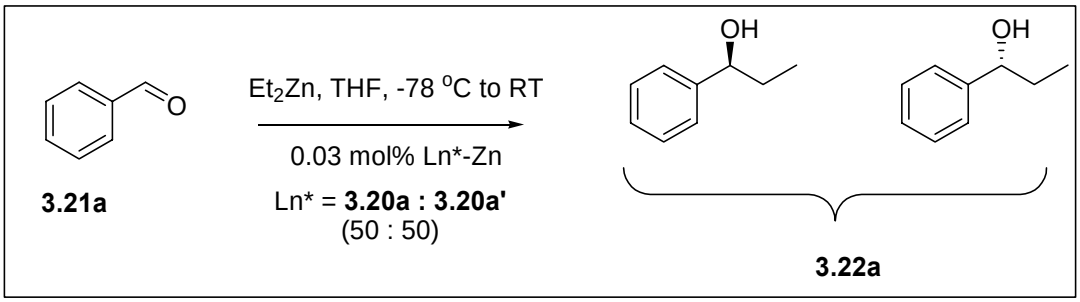


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	60.5540	22.492	96766392
2	39.4460	26.916	63035544
	100.0000		***159801936***



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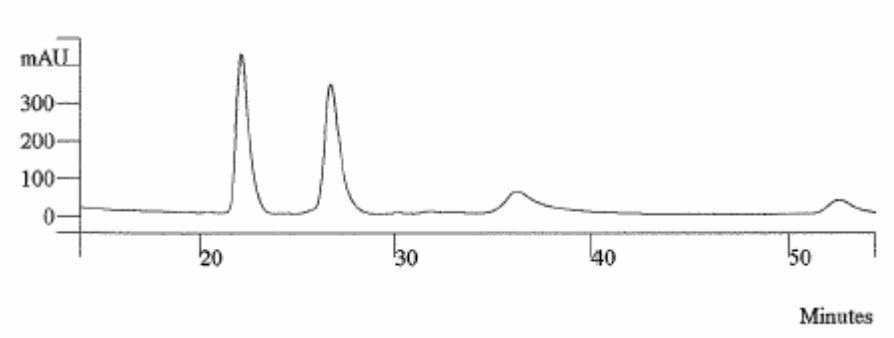
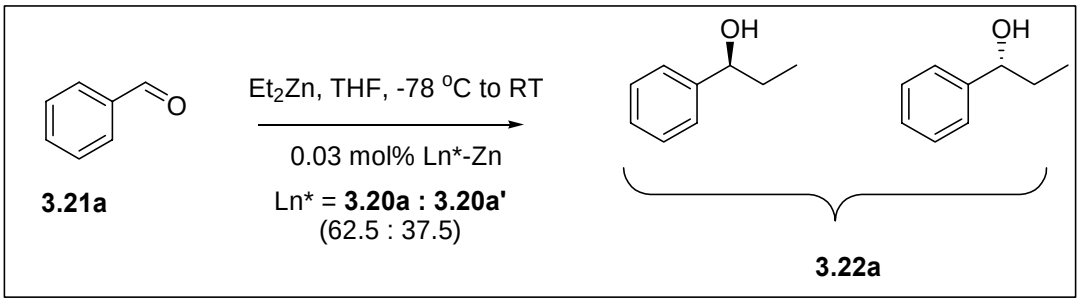
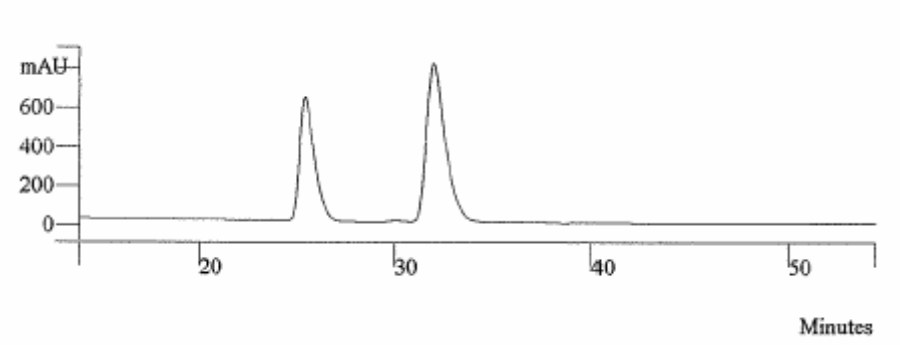
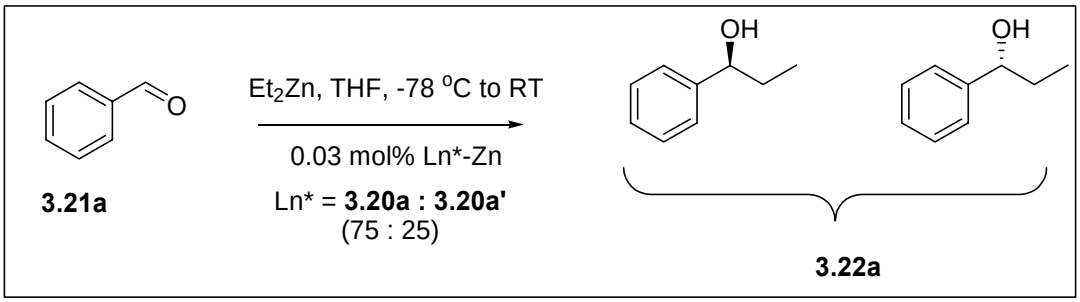


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	50.6864	22.125	97589608
2	49.3136	26.710	94946304
	100.0000		**192535904**





Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	37.8923	25.411	170391344
2	0.3084	30.031	1386740
3	61.7993	31.984	277894688
	100.0000		**449672768**



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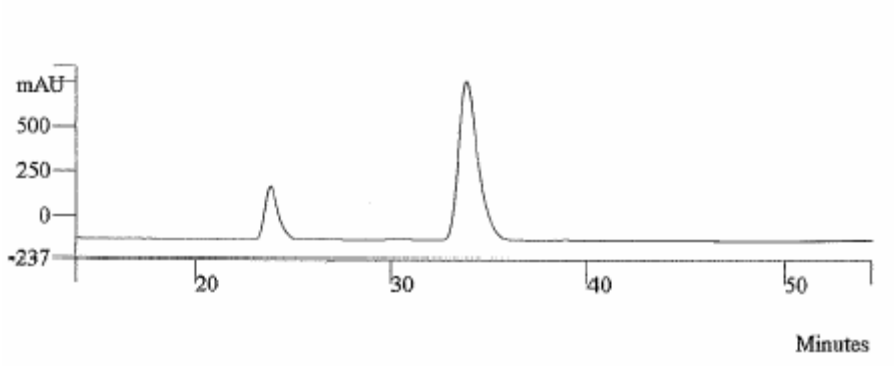
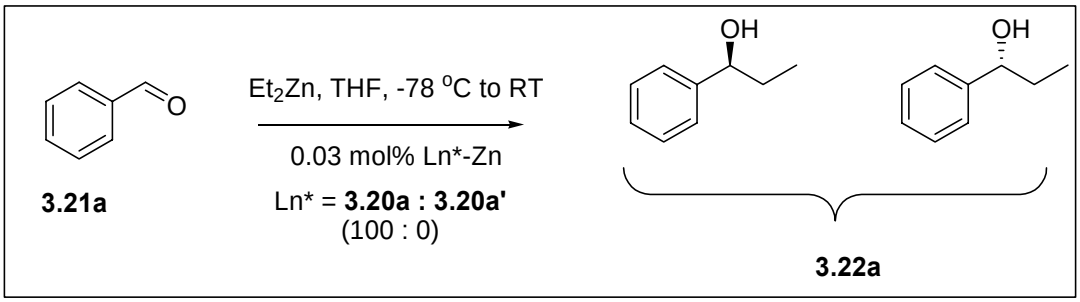
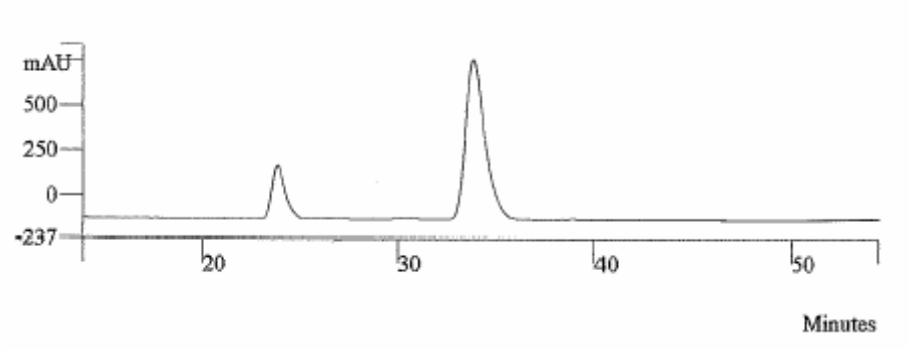
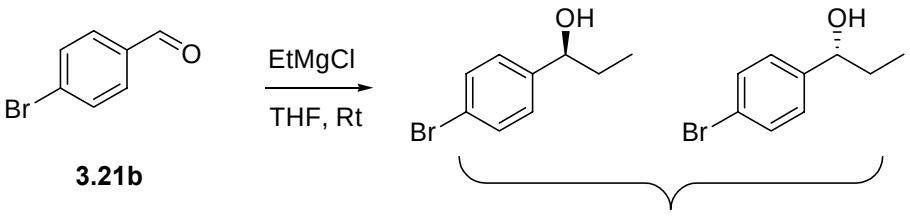


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	18.4641	23.806	71684696
2	81.5359	33.832	316553344
	100.0000		**388238048**



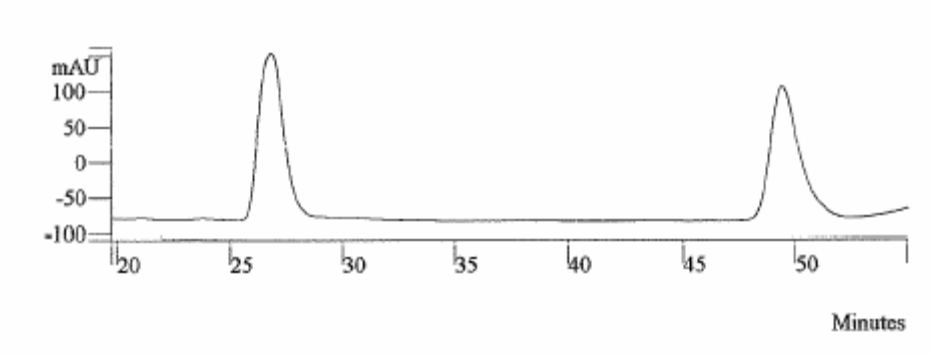


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	18.4641	23.806	71684696
2	81.5359	33.832	316553344
	100.0000		**388238048**

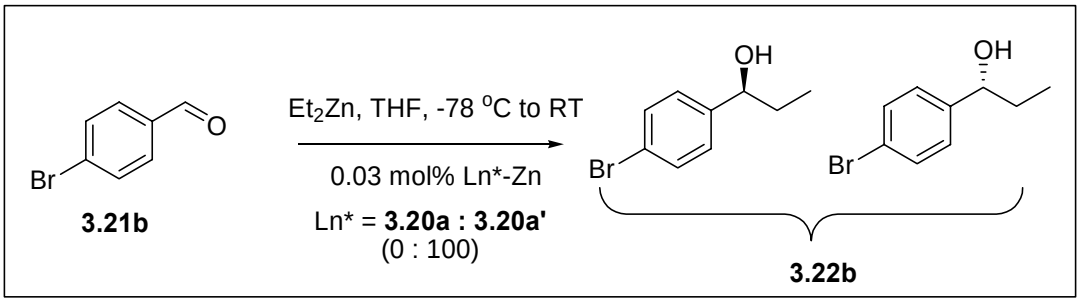


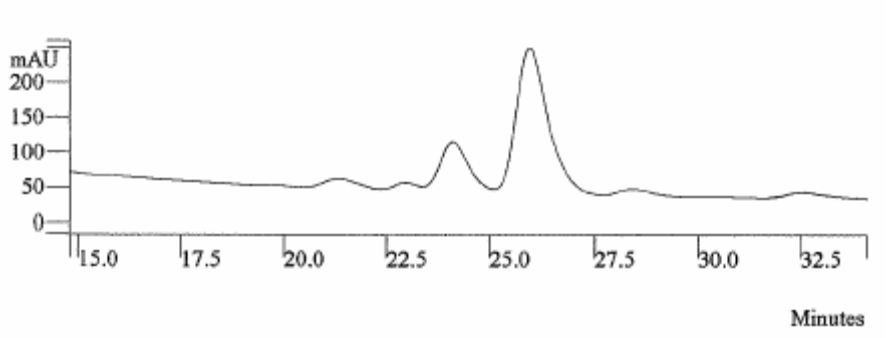
3.21b

3.22b

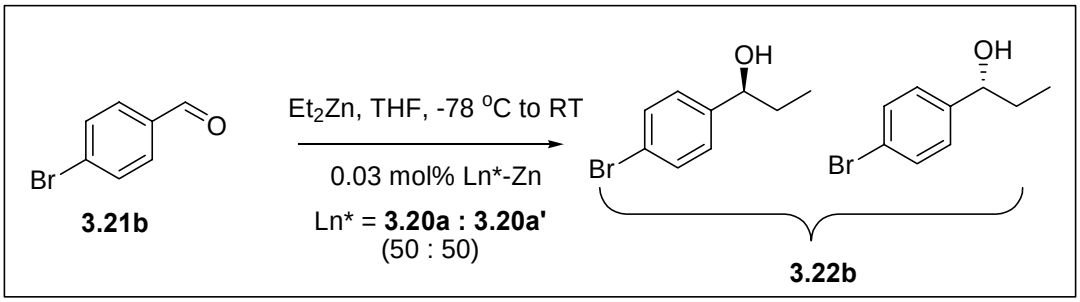


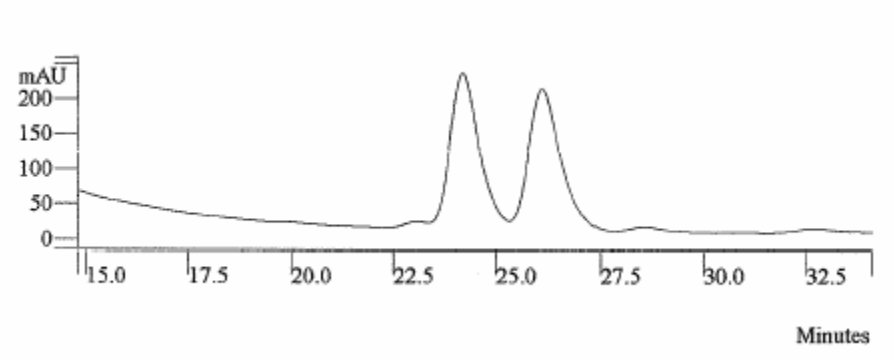
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	0.0829	21.022	134807
2	0.3347	23.764	544480
3	48.2194	26.822	78442600
4	51.3631	49.385	83556776
	100.0001		**162678656**



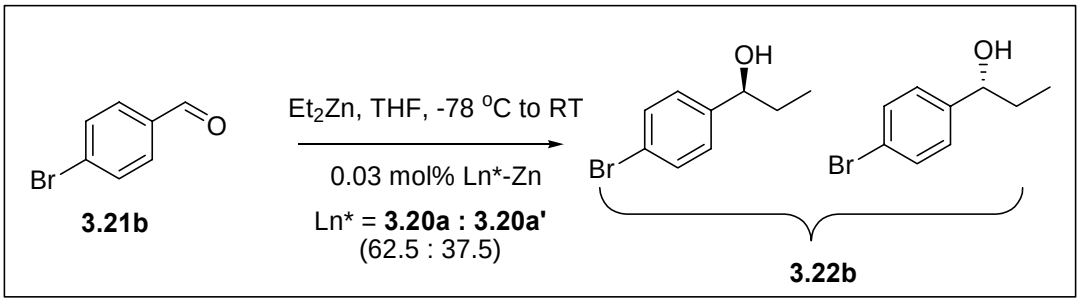


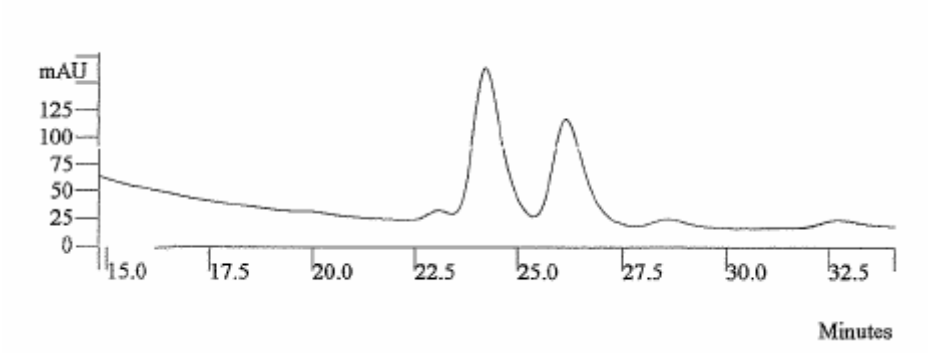
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	0.2307	22.939	163458
2	20.9578	24.086	14849166
3	78.8115	25.955	55840044
	100.0000		**70852672**



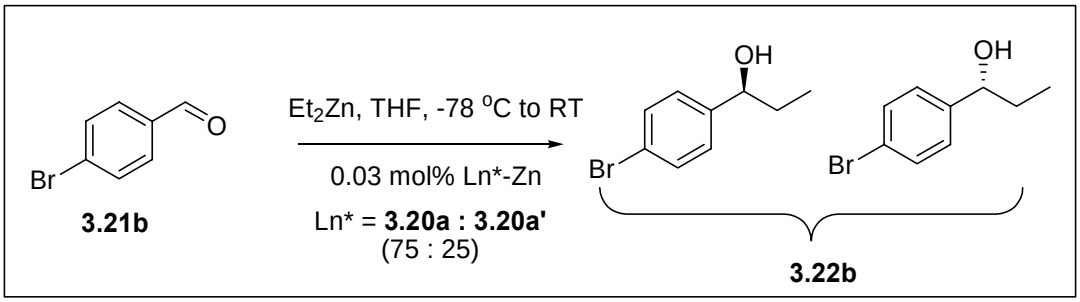


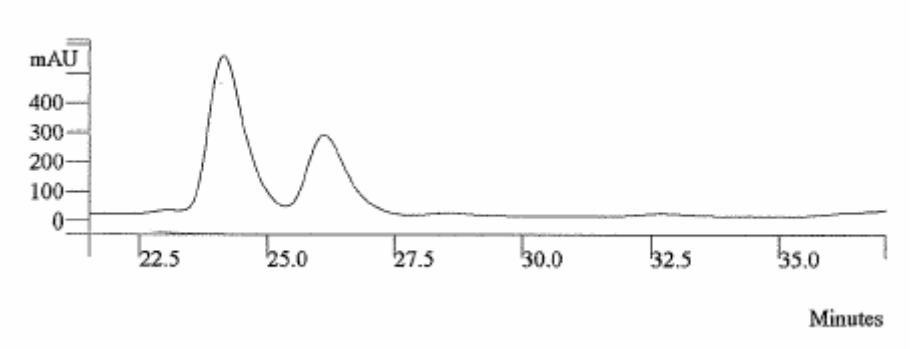
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	0.2676	23.049	291600
2	49.4885	24.170	53919700
3	50.2438	26.103	54742620
	99.9999		**108953920**



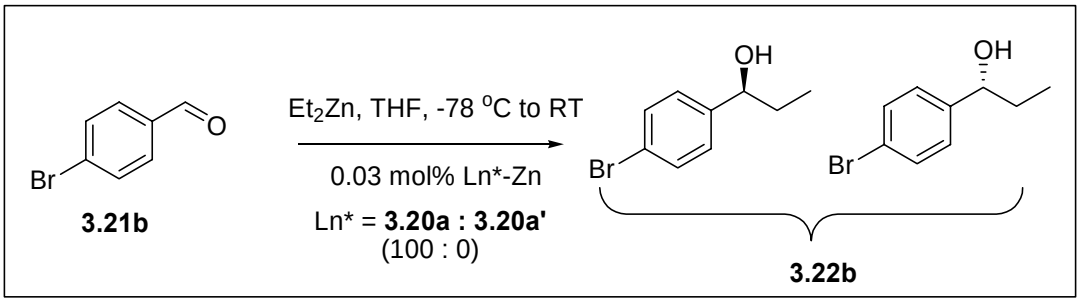


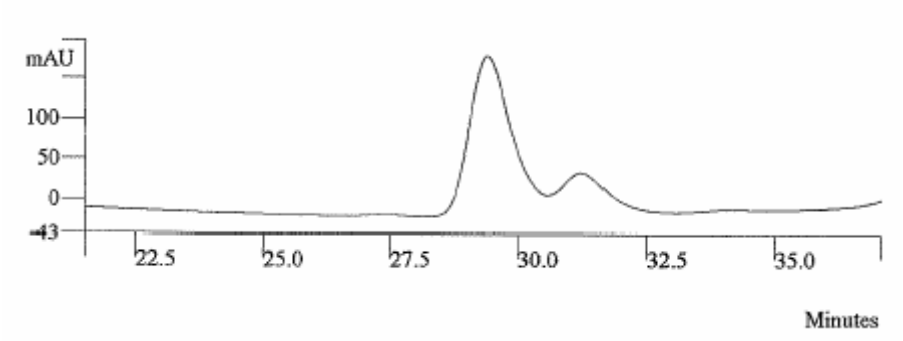
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	0.5737	23.064	344704
2	56.4745	24.206	33930968
3	42.9518	26.162	25806230
	100.0000		**60081904**



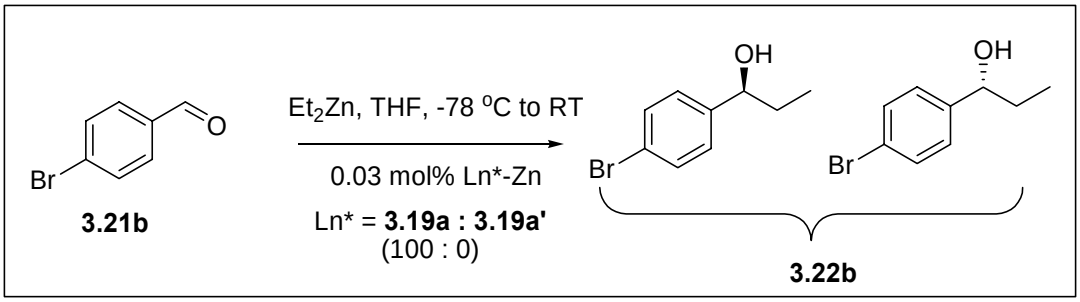


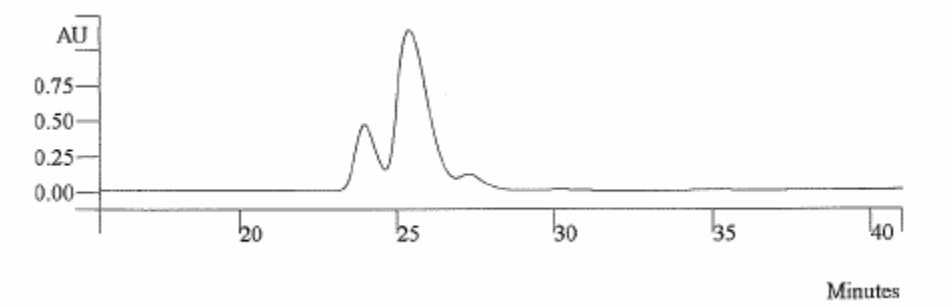
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	0.8916	23.040	1959216
2	63.8031	24.132	140209616
3	35.3053	26.097	77584744
	100.0000		**219753568**



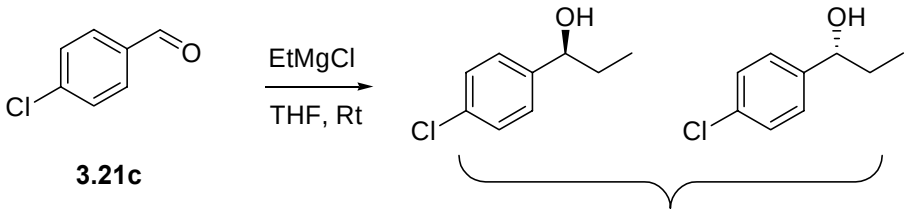


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	0.6006	0.341	449076
2	78.6607	29.393	58815800
3	20.7387	31.218	15506639
	100.0000		**74771512**



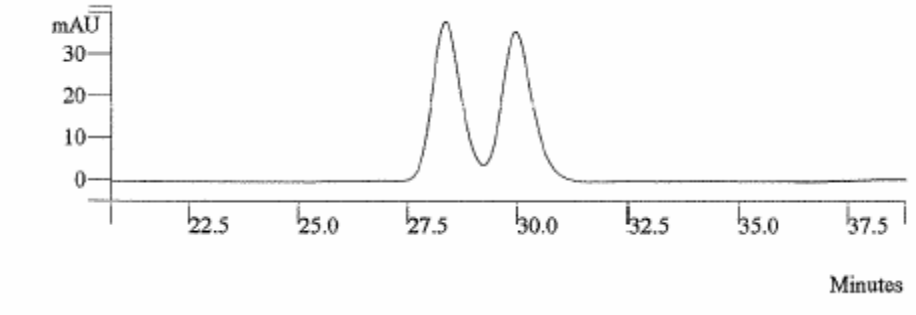


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	0.0228	21.536	122644
2	20.3742	23.946	109765440
3	73.2180	25.383	394460576
4	6.0402	27.278	32541680
5	0.3448	30.141	1857451
	100.0000		**538747840**

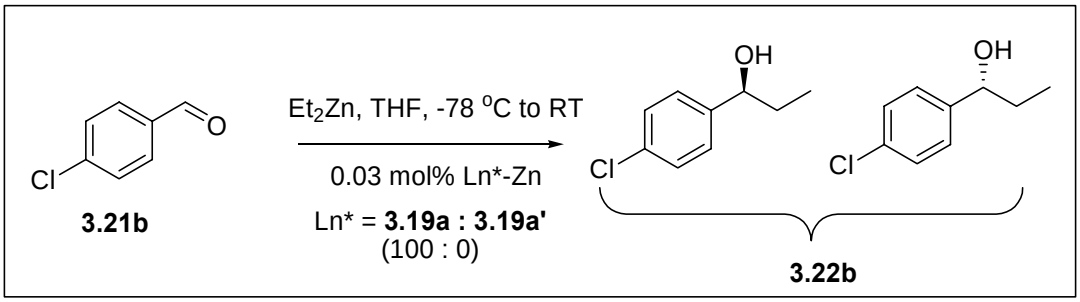


3.21c

3.22c

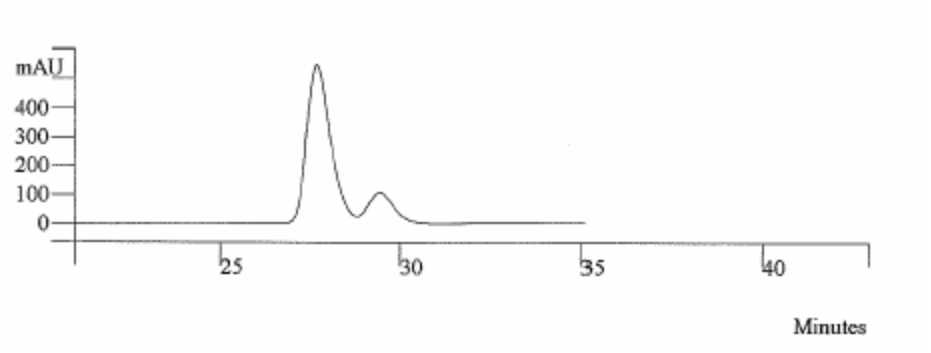


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	51.5420	28.355	7876948
2	48.4580	29.975	7405632
	100.0000		**15282580**

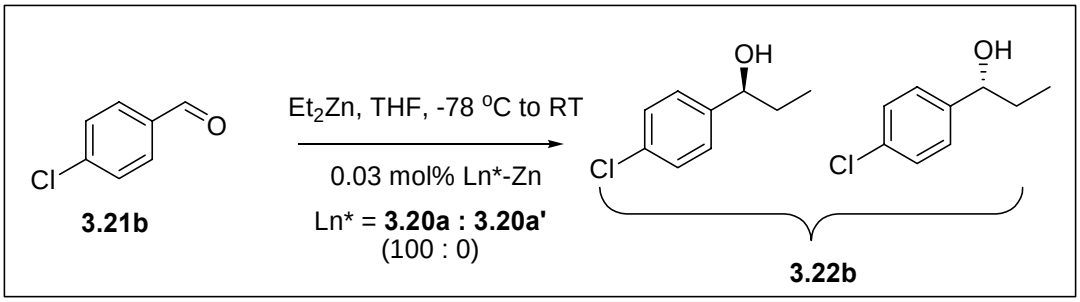


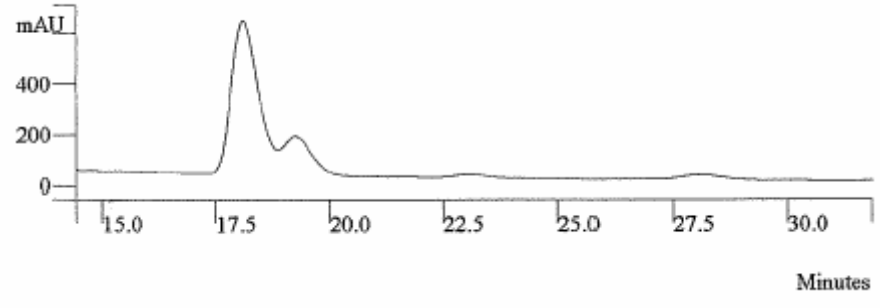
3.21b

3.22b

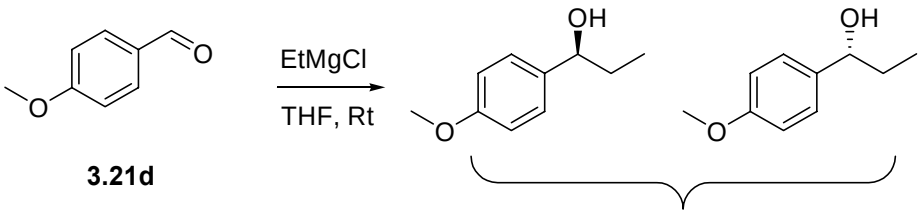


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	82.1472	27.665	131396040
2	17.7607	29.414	28408536
3	0.0922	32.942	147438
	100.0001		**159952016**



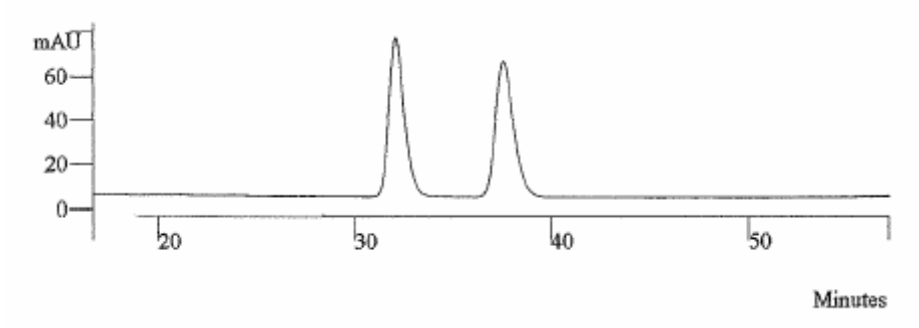


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	79.0124	18.079	129450584
2	20.9876	19.222	34385136
	100.0000		**163835712**

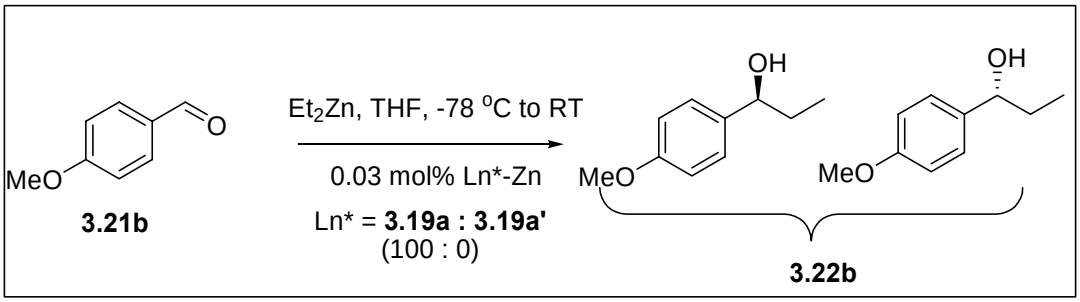


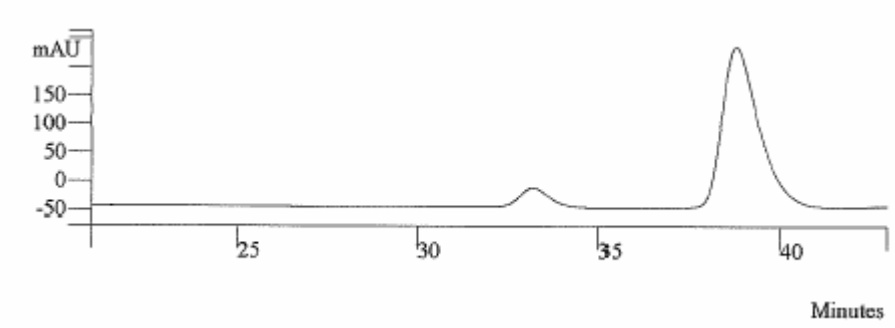
3.21d

3.22d

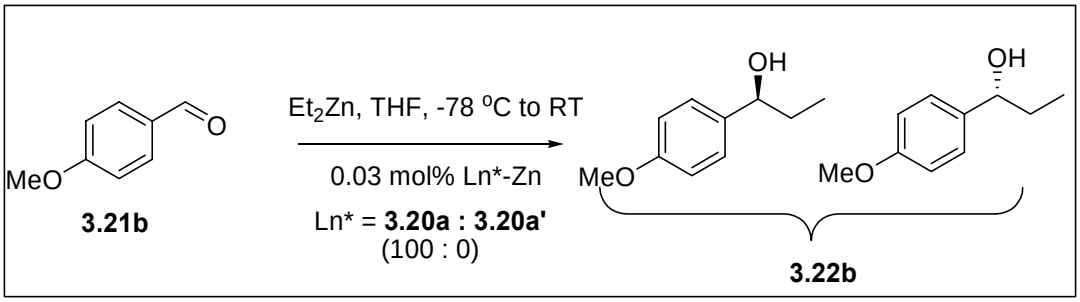


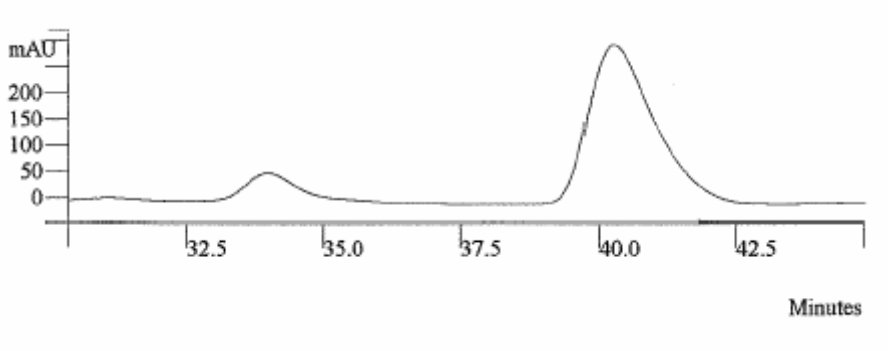
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	27.9138	0.948	15835277
2	36.1057	32.081	20482530
3	35.9638	37.582	20402030
4	0.0167	48.065	9450
	100.0000		**56729288**



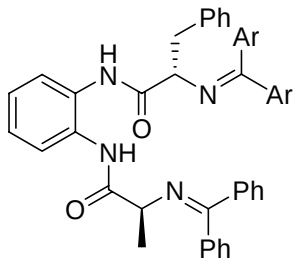


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	8.5775	33.188	9609749
2	91.4225	38.778	102424080
	100.0000		**112033832**



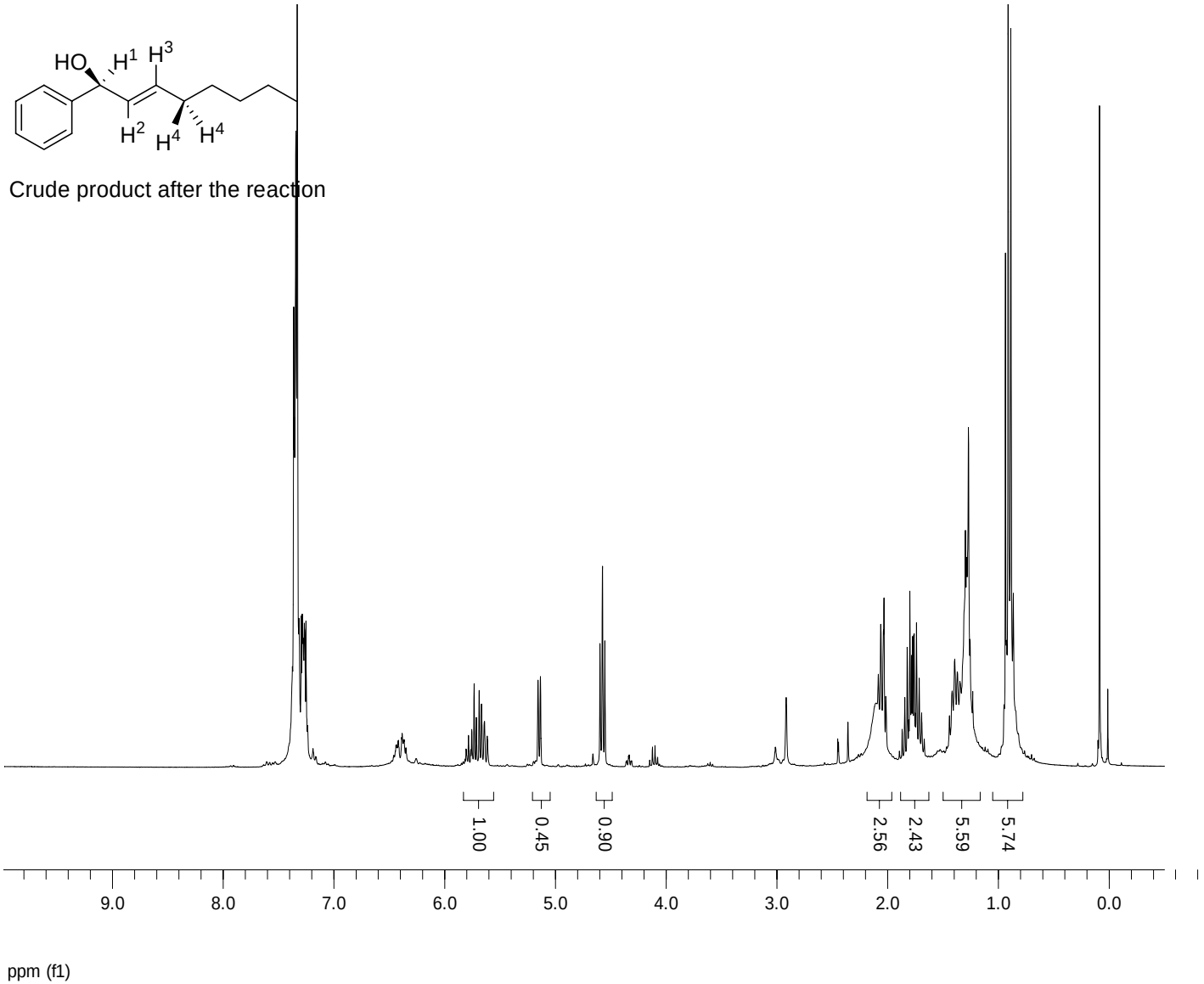


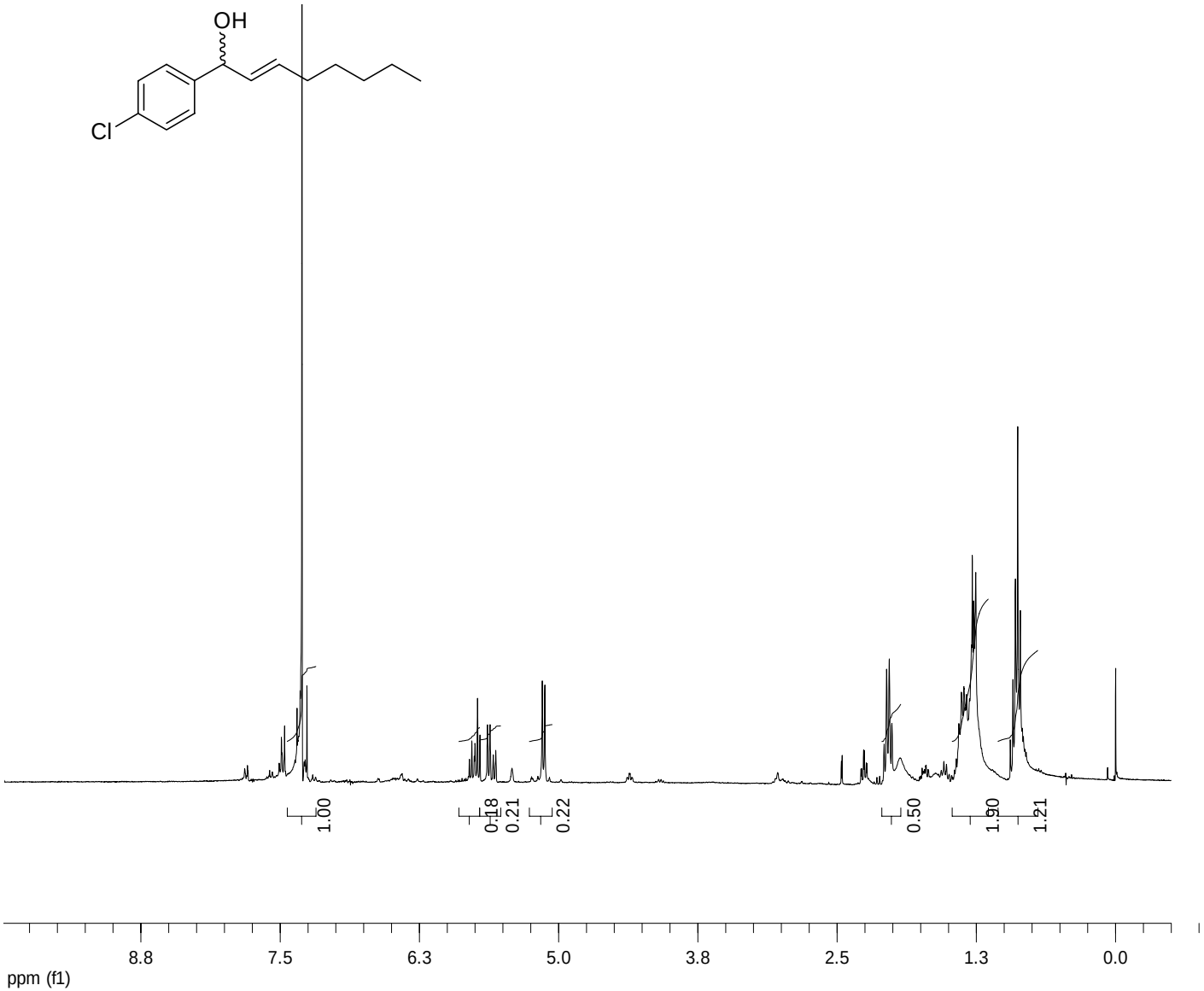
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	13.1899	33.964	19830420
2	86.8101	40.260	130514832
	100.0000		**150345248**


Ph
Ar
H
N
N
Ar
O
NH
O
N
Ph
Ph

2.18

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)


HO
H1
H3
H2
H4
H4
Crude product after the reaction
1.00
0.45
0.90
2.56
2.43
5.59
5.74
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


OH
Cl
1.00
0.18
0.21
0.22
0.50
1.90
1.21
8.8
7.5
6.3
5.0
3.8
2.5
1.3
0.0
ppm (f1)

REFERENCES

1.) Trost, B. M., Selectivity: a key to synthetic efficiency. *Science (Washington, DC, U. S.)* **1983,** 219, (4582), 245-250.

2.) Trost, B. M., The atom economy--a search for synthetic efficiency. *Science* **1991,** 254, (5037), 1471-1477.

3.) Beller, M.; Bolm, C., *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*. ed.; 1998; 'Vol.' p 595 pp.

4.) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E., Asymmetric synthesis of R and S a-alkylalkanoic acids from metalation and alkylation of chiral 2-oxazolines. *J. Am. Chem. Soc.* **1976,** 98, (2), 567-576.

5.) Evans, D. A.; Ennis, M. D.; Mathre, D. J., Asymmetric alkylation reactions of chiral imide enolates. A practical approach to the enantioselective synthesis of a-substituted carboxylic acid derivatives. *J. Am. Chem. Soc.* **1982,** 104, (6), 1737-1739.

6.) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W., Highly Practical Methodology for the Synthesis of D- and L-a-Amino Acids, N-Protected a-Amino Acids, and N-Methyl-a-amino Acids. *J. Am. Chem. Soc.* **1997,** 119, (4), 656-673.

7.) Frankland, E., Isolation of organic radicals. *Justus Liebigs Annalen der Chemie* **1849**, 171-213.

8.) Reformatsky, S. N., *Ber. Dtsch. Chem. Ges.* **1887,** 20, 1210-1211.

9.) Hunsdiecker, H.; Erlbach, H.; Vogt, E. Zn organic compounds. 722467, 1942.

10.) Rathke, M. W., Reformatskii reaction. *Org. React. (N.Y.)* **1975,** 22, 423-460.

11.) Negishi, E.; King, A. O.; Okukado, N., Selective carbon-carbon bond formation via transition metal catalysis. 3. A highly selective synthesis of unsymmetrical biaryls and diarylmethanes by the nickel- or palladium-catalyzed reaction of aryl- and benzylzinc derivatives with aryl halides. *J. Org. Chem.* **1977,** 42, (10), 1821-1823.

12.) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F. T.; Miller, J. A.; Stoll, A. T., Selective carbon-carbon bond formation via transition metal catalysis. 36. Palladium-catalyzed acylation of organozincs and other organometallics as a convenient route to ketones. *Tetrahedron Lett.* **1983,** 24, (47), 5181-5184.

13.) Boersma, J.; Noltes, J. G., Organozinc compounds. X. Coordination chemistry of organozinc compounds: organozinc-oxygen derivatives of potential bidentate ligands. *J. Organomet. Chem.* **1968,** 13, (2), 291-299.

14.) Thiele, K. H.; Heinrich, M.; Brueser, W.; Schroeder, S., Investigations on the coordination chemistry of zinc dialkyls. XIII. On the existence of organozinc chelates. *Z. Anorg. Allg. Chem.* **1977,** 432, 221-230.

15.) Kuwajima, I.; Nakamura, E., Metal homoenolates from siloxycyclopropanes. *Top. Curr. Chem.* **1990,** 155, (Small Ring Compd. Org. Synth. 4), 1-39.

16.) Nakamura, E.; Kuwajima, I., Copper-catalyzed acylation and conjugate addition of zinc homoenolate. Synthesis of 4- and 5-oxo esters. *J. Am. Chem. Soc.* **1984,** 106, (11), 3368-3370.

17.) Nakamura, E.; Kuwajima, I., Stereocontrolled construction of oxygenated steroidal side chains. Synthesis and stereochemistry of depresosterol. *J. Am. Chem. Soc.* **1985,** 107, (7), 2138-2141.

18.) Noyori, R.; Kitamura, M., Enantioselective addition of organometallic reagents to carbonyl compounds: Chirality transfer, multiplication and amplification. *Angew. Chem. Int. Ed. Engl.* **1991,** 30, (1), 49-69.

19.) Soai, K.; Niwa, S., Enantioselective addition of organozinc reagents to aldehydes. *Chemical Reviews* **1992,** 92, (5), 833-856.

20.) Oguni, N.; Omi, T., Enantioselective addition of diethylzinc to benzaldehyde catalyzed by a small amount of chiral 2-amino-1-alcohols. *Tetrahedron Lett.* **1984,** 25, (26), 2823-2824.

21.) Erdik, E.; Editor, *Organozinc Reagents in Organic Synthesis*. ed.; 1996; 'Vol.' p 464 pp.

22.) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., *Comprehensive Asymmetric Catalysis*. ed.; Springer: Berlin, 1999; 'Vol.' 1-3, p.

23.) Bolm, C.; Gladysz, J. A., Introduction: Enantioselective Catalysis. *Chem. Rev. (Washington, DC, U. S.)* **2003,** 103, (8), 2761-2762.

24.) Evans, D. A., Stereoselective organic reactions: catalysts for carbonyl addition processes. *Science* **1988,** 240, (4851), 420-426.

25.) Pu, L.; Yu, H., Catalytic asymmetric organozinc additions to carbonyl compounds. *Chem. Rev.* **2001,** 101, (3), 757-824.

26.) Coppola, G. M.; Schuster, H. F., *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*. ed.; 1987; 'Vol.' p 393 pp.

27.) McKenzie, A., Studies in asymmetric synthesis. I. Reduction of menthyl benzoylformate. II. Action of magnesium alkyl haloids on menthyl benzoylformate. *Journal of the Chemical Society* **1904,** 85, 1249-1262.

28.) Cohen, H. L.; Wright, G. F., Reactions of Grignard reagents in optically active solvents. *J. Org. Chem.* **1953,** 18, 432-446.

29.) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R., Asymmetric syntheses by means of (-)-sparteine-modified organometallic reagents. *Tetrahedron* **1971,** 27, (5), 905-913.

30.) Soai, K.; Mukaiyama, T., Effects of solvents on the enantioface-differentiating (asymmetric) addition of butyllithium to benzaldehyde using (2S, 2'S)-2-(hydroxymethyl)-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine as a chiral ligand. *Chem. Lett.* **1978**, (5), 491-492.

31.) Noyori, R.; Kitamura, M.; Suga, S.; Kawai, K., Catalytic asymmetric induction. Highly enantioselective addtion of dialkylzincs to aldehydes. *J. Am. Chem. Soc.* **1986,** 108, (19), 6071-6072.

32.) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R., Enantioselective addition of dialkylzincs to aldehydes promoted by chiral amino alcohols. Mechanism and nonlinear effect. *J. Am. Chem. Soc.* **1989,** 111, (11), 4028-4036.

33.) Smaardijk, A. A.; Wynberg, H., Stereoselective addition reaction of diethylzinc to aldehydes, catalyzed by cinchona alkaloids. *J. Org. Chem.* **1987,** 52, (1), 135-137.

34.) Sola, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J. F., A superior, readily available enantiopure ligand for the catalytic enantioselective addition of diethylzinc to alpha-substituted aldehydes. *J. Org. Chem.* **1998,** 63, (20), 7078-7082.

35.) Marx, B.; Henry-Basch, E.; Freon, P., Reactivity of organozincs. *Comptes Rendus des Seances de l'Academie des Sciences, Serie C: Sciences Chimiques* **1967,** 264, (6), 527-530.

36.) Sato, T.; Soai, K.; Suzuki, K.; Mukaiyama, T., Enantioface-differentiating (asymmetric) addition of dialkylmagnesium to aldehydes by using the lithium salt of (2S, 2'S)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine as a chiral ligand. *Chem. Lett.* **1978**, (6), 601-604.

37.) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K., Enantioface-differentiating (asymmetric) addition of alkyllithium and dialkylmangesium to aldehydes

by using (2S, 2'S)-2-Hydroxymethyl-1-[(1-alkylpyrrolidin-2-yl)-methyl]pyrrolidines as chiral ligands. *J. Am. Chem. Soc.* **1979,** 101, (6), 1455-1460.

38.) Sibi, M. P.; Chen, J.-X.; Cook, G. R., Reversal of stereochemistry in diethylzinc addition to aldehydes by a simple change of the backbone substituent in L-serine derived ligands. *Tetrahedron Lett.* **1999,** 40, (17), 3301-3304.

39.) Hanyu, N.; Mino, T.; Sakamoto, M.; Fujita, T., Facile synthesis of amino bicyclo[2.2.1]heptyl alcohol and its application for enantioselective additions of diethylzinc to aldehydes. *Tetrahedron Lett.* **2000,** 41, (23), 4587-4590.

40.) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T., New chiral 1,4-aminoalcohols derived from (+)-camphor and (-)-fenchone for the enantioselective addition of diethylzinc to aldehyde. *Tetrahedron: Asymmetry* **2000,** 11, (20), 4127-4136.

41.) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T., Enantioselective addition of diethylzinc to aldehydes catalyzed by optically active 1,4-amino alcohols. *Tetrahedron: Asymmetry* **2000,** 11, (14), 2971-2979.

42.) Nugent, W. A., MIB: an advantageous alternative to DAIB for the addition of organozinc reagents to aldehydes. *Chemical Communications (Cambridge)* **1999**, (15), 1369-1370.

43.) Andres, J. M.; Hartinez, M. A.; Pedrosa, R.; Perez, E., Enantioselective ethylation of aldehydes catalyzed by chiral C2-symmetrical b-hydroxy-m-xylylene diamines. *Tetrahedron: Asymmetry* **1994,** 5, (1), 67-72.

44.) Kossenjans, M.; Martens, J., Synthesis of C2-symmetrical bis-b-amino alcohols from (R)-cysteine and their application in enantioselective catalysis. *Tetrahedron: Asymmetry* **1998,** 9, (8), 1409-1417.

45.) Chaloner, P. A.; Perera, S. A. R., Enantioselective addition of diethylzinc to benzaldehyde in the presence of ephedrine derivatives. *Tetrahedron Lett.* **1987,** 28, (26), 3013-3014.

46.) Corey, E. J.; Naef, R.; Hannon, F. J., Enantioselective conjugate addition of rationally designed chiral cuprate reagents to 2-cycloalkenones. *J. Am. Chem. Soc.* **1986,** 108, (22), 7114-7116.

47.) Corey, E. J.; Hannon, F. J., Chiral catalysts for the enantioselective addition of organometallic reagents to aldehydes. *Tetrahedron Lett.* **1987,** 28, (44), 5233-5236.

48.) Soai, K.; Nishi, M.; Ito, Y., Enantioselective addition of diethylzinc to aldehydes catalyzed by chiral diamino diols derived from ephedrine. *Chem. Lett.* **1987**, (12), 2405-2406.

49.) Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T., A new chiral catalyst for the highly enantioselective addition of dialkylzinc reagents to aliphatic aldehydes. *J. Chem. Soc., Chem. Commun.* **1987**, (22), 1690-1691.

50.) Soai, K.; Yokoyama, S.; Hayasaka, T., Chiral N,N-dialkylnorephedrines as catalysts of the highly enantioselective addition of dialkylzincs to aliphatic and aromatic aldehydes. The asymmetric synthesis of secondary aliphatic and aromatic alcohols of high optical purity. *Journal of Organic Chemistry* **1991,** 56, (13), 4264-4268.

51.) Poelert, M. A.; Hof, R. P.; Peper, N. C. M. W.; Kellogg, R. M., Enantiomerically pure b-amino sulfides and b-amino thiols from ephedrine. *Heterocycles* **1994,** 37, (1), 461-475.

52.) Hof, R. P.; Poelert, M. A.; Peper, N. C. M. W.; Kellogg, R. M., Sulfur derivatives of Ephedra alkaloids; new and highly efficient chiral catalysts. *Tetrahedron: Asymmetry* **1994,** 5, (1), 31-34.

53.) Fitzpatrick, K.; Hulst, R.; Kellogg, R. M., Thiol and disulfide derivatives of Ephedra alkaloids. 2. A mechanistic study of their effect on the addition of diethylzinc to benzaldehyde. *Tetrahedron: Asymmetry* **1995,** 6, (8), 1861-1864.

54.) Kang, J.; Kim, J. B.; Kim, J.; Lee, D., The interaction of chiral amino thiols with organozinc reagents and aldehydes: a mechanism of amino thiol-catalyzed addition of organozinc reagents to aldehydes. *Bull. Korean Chem. Soc.* **1998,** 19, (4), 475-481.

55.) Kang, J.; Lee, J. W.; Kim, J. I., Enantioselective Addition of Diethylzinc to Alpha-Branched Aldehydes. *Journal of the Chemical Society-Chemical Communications* **1994**, (17), 2009-2010.

56.) Gibson, C. L., An L-proline-based beta-amino tertiary thiol: synthesis and use as a catalyst in the enantioselective addition of diethylzinc to aldehydes. *Tetrahedron-Asymmetry* **1999,** 10, (8), 1551-1561.

57.) Braga, A. L.; Vargas, F.; Silveira, C. C.; de Andrade, L. H., Synthesis of new chiral imidazolidine disulfides derived from L-cystine and their application in the enantioselective addition of diethylzinc to aldehydes. *Tetrahedron Lett.* **2002,** 43, (13), 2335-2337.

58.) Lambert, F.; Knotter, D. M.; Janssen, M. D.; Van Klaveren, M.; Boersma, J.; Van Koten, G., On the way to chiral copper(I) arenethiolate catalysts for the enantioselective conjugate addition of methyllithium and methylmagnesium iodide to benzylideneacetone. *Tetrahedron: Asymmetry* **1991,** 2, (11), 1097-1100.

59.) Knotter, D. M.; Grove, D. M.; Smeets, W. J. J.; Spek, A. L.; Van Koten, G., A new class of organocopper and organocuprate compounds derived from copper(I) arenethiolates. *J. Am. Chem. Soc.* **1992,** 114, (9), 3400-3410.

60.) van Klaveren, M.; Lambert, F.; Eijkelkamp, D. J. F. M.; Grove, D. M.; van Koten, G., Arenethiolatocopper(I) complexes as homogeneous catalysts for Michael addition reactions. *Tetrahedron Lett.* **1994,** 35, (33), 6135-6138.

61.) Haubrich, A.; van Klaveren, M.; van Koten, G.; Handke, G.; Krause, N., 1,6-Addition of organolithium compounds to acceptor-substituted enynes catalyzed by a copper(I) arenethiolate. *J. Org. Chem.* **1993,** 58, (21), 5849-5852.

62.) Rijnberg, E.; Jastrzebski, J. T. B. H.; Janssen, M. D.; Boersma, J.; van Koten, G., Application of N,S-chelating chiral zinc bis(arenethiolate) complexes as new precursor catalysts in the enantioselective addition of diethylzinc to aldehydes. *Tetrahedron Lett.* **1994,** 35, (35), 6521-6524.

63.) Rijnberg, E.; Hovestad, N. J.; Kleij, A. W.; Jastrzebski, J. T. B. H.; Boersma, J.; Janssen, M. D.; Spek, A. L.; van Koten, G., Application of S,N-Chelating Chiral Zinc Bis(aminoarenethiolates) as New Precursor Catalysts in the Enantioselective Addition of Dialkylzincs to Aldehydes. *Organometallics* **1997,** 16, (13), 2847-2857.

64.) Schmidt, B.; Seebach, D., 2,2-Dimethyl-a,a,a',a'-tetrakis(b-naphthyl)-1,3-dioxolane-4,5-dimethanol (DINOL) for the titanate-mediated enantioselective addition of diethylzinc to aldehydes. *Angew. Chem.* **1991,** 103, (10), 1383-1385 (See also Angew Chem , Int Ed Engl , 1991, (1330)1310, 1321-1383).

65.) Schmidt, B.; Seebach, D., Catalytic and stoichiometric enantioselective addition of methyllithium and magnesium and zinc compounds to aldehydes with the aid of a novel chiral spirotitanate. *Angew. Chem.* **1991,** 103, (1), 100-101 (See also Angew Chem , Int Ed Engl , 1991, 1930(1991), 1999-1101).

66.) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D., The mechanisms of enantioselective reactions using a,a,a',a'-tetraaryl-1,3-dioxolane-4,5-dimethanol(TADDOL)-derived titanates: differences between C2- and C1-symmetrical TADDOLs - facts, implications and generalizations. *Helv. Chim. Acta* **1992,** 75, (7), 2171-2209.

67.) Weber, B.; Seebach, D., Ti-TADDOLate-catalyzed, highly enantioselective addition of alkyl- and aryl-titanium derivatives to aldehydes. *Tetrahedron* **1994,** 50, (25), 7473-7484.

68.) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M., Enantio- and diastereoselective titanium-TADDOLate catalyzed addition of diethyl- and bis(3-buten-1-yl)zinc to

aldehydes. A full account with preparative details. *Tetrahedron* **1994,** 50, (15), 4363-4384.

69.) Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohac, A.; Ganter, C.; Gawley, R. E.; Kuehnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D., Preparation and structural analysis of several new a,a,a',a'-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOL's) and TADDOL analogs, their evaluation as titanium ligands in the enantioselective addition of methyltitanium and diethylzinc reagents to benzaldehyde, and refinement of the mechanistic hypothesis. *Helv. Chim. Acta* **1994,** 77, (8), 2071-2110.

70.) Kaufmann, D.; Boese, R., A Borate Propeller Compound as Chiral Catalyst for an Asymmetrically Induced Diels-Alder Reaction. *Angewandte Chemie-International Edition in English* **1990,** 29, (5), 545-546.

71.) Hattori, K.; Yamamoto, H., Asymmetric Aza-Diels-Alder Reaction Mediated by Chiral Boron Reagent. *J. Org. Chem.* **1992,** 57, (12), 3264-3265.

72.) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H., Design of Bronsted acid-assisted chiral Lewis acid (BLA) catalysts for highly enantioselective Diels-Alder reactions. *J. Am. Chem. Soc.* **1998,** 120, (28), 6920-6930.

73.) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H., Asymmetric Hetero-Diels-Alder Reaction Catalyzed by Chiral Organo-Aluminum Reagent. *J. Am. Chem. Soc.* **1988,** 110, (1), 310-312.

74.) Bao, J.; Wulff, W. D.; Rheingold, A. L., Vaulted biaryls as chiral ligands for asymmetric catalytic Diels-Alder reactions. *J. Am. Chem. Soc.* **1993,** 115, (9), 3814-3815.

75.) Heller, D. P.; Goldberg, D. R.; Wulff, W. D., Positive cooperativity of product mimics in the asymmetric autoinduction of Diels-Alder reactions catalyzed by a VAPOL-aluminum catalyst. *J. Am. Chem. Soc.* **1997,** 119, (43), 10551-10552.

76.) Graven, A.; Johannsen, M.; Joergensen, K. A., A highly chemo- and enantio-selective hetero-Diels-Alder reaction catalyzed by chiral aluminum complexes. *Chemical Communications (Cambridge)* **1996**, (20), 2373-2374.

77.) Reetz, M. T.; Kyung, S. H.; Bolm, C.; Zierke, T., Enantioselective carbon-carbon bond formation with chiral Lewis acids. *Chemistry & Industry* **1986**, (23), 824.

78.) Seebach, D.; Beck, A. K.; Imwinkeiried, R.; Roggo, S.; Wonnacott, A., Chiral alkoxytitanium(IV) complexes for enantioselective nucleophilic additions to aldehydes and as Lewis acids in Diels-Alder reactions. *Helv. Chim. Acta* **1987,** 70, (4), 954-974.

79.) Mikami, K.; Terada, M.; Nakai, T., Asymmetric glyoxylate-ene reaction catalyzed by chiral titanium complexes: a practical access to a-hydroxy esters in high enantiomeric purities. *J. Am. Chem. Soc.* **1989,** 111, (5), 1940-1941.

80.) Mikami, K.; Terada, M.; Nakai, T., Catalytic asymmetric glyoxylate-ene reaction: a practical access to a-hydroxy esters in high enantiomeric purities. *J. Am. Chem. Soc.* **1990,** 112, (10), 3949-3954.

81.) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T., Asymmetric catalysis for carbonyl-ene reaction. *Synlett* **1992**, (4), 255-265.

82.) Ketter, A.; Glahsl, G.; Herrmann, R., Asymmetric Diels-Alder reaction of cyclopentadiene and methyl acrylate catalyzed by chiral Lewis acids. *J. Chem. Res., Synop.* **1990**, (9), 278-279.

83.) Mukaiyama, T.; Inubushi, A.; Suda, S.; Hara, R.; Kobayashi, S., [1,1'-Bi-2-naphthalenediolato(2-)-O,O']oxotitanium. An efficient chiral catalyst for the asymmetric aldol reaction silyl enol ethers with aldehydes. *Chem. Lett.* **1990**, (6), 1015-1018.

84.) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A., Catalytic asymmetric synthesis of homoallylic alcohols. *J. Am. Chem. Soc.* **1993,** 115, (15), 7001-7002.

85.) Keck, G. E.; Tarbet, K. H.; Geraci, L. S., Catalytic asymmetric allylation of aldehydes. *J. Am. Chem. Soc.* **1993,** 115, (18), 8467-8468.

86.) Maruoka, K.; Murase, N.; Yamamoto, H., Chiral helical Lewis acids for asymmetric Diels-Alder catalysts. *J. Org. Chem.* **1993,** 58, (11), 2938-2939.

87.) Gauthier, D. R., Jr.; Carreira, E. M., Catalytic, enantioselective addition of allylsilanes to aldehydes: generation of a novel, reactive TiIV complex from TiF4. *Angew. Chem., Int. Ed. Engl.* **1996,** 35, (20), 2363-2365.

88.) Weigand, S.; Bruckner, R., TiIV-BINOLate-catalyzed highly enantioselective additions of b-substituted allylstannanes to aldehydes. *Chem.--Eur. J.* **1996,** 2, (9), 1077-1084.

89.) Pu, L., 1,1'-Binaphthyl Dimers, Oligomers, and Polymers: Molecular Recognition, Asymmetric Catalysis, and New Materials. *Chemical Reviews* **1998,** 98, (7), 2405-2494.

90.) Kobayashi, S.; Ishitani, H.; Ueno, M., Catalytic Asymmetric Synthesis of Both Syn- and Anti-b-Amino Alcohols. *J. Am. Chem. Soc.* **1998,** 120, (2), 431-432.

91.) Kobayashi, S.; Komiyama, S.; Ishitani, H., The first enantioselective aza-Diels-Alder reactions of imino dienophiles on use of a chiral zirconium catalyst. *Angew. Chem., Int. Ed.* **1998,** 37, (7), 979-981.

92.) Volk, T.; Korenaga, T.; Matsukawa, S.; Terada, M.; Mikami, K., Asymmetric activation of chiral BINOL-zirconium catalysts: effect of a product-like activator. *Chirality* **1998,** 10, (7), 717-721.

93.) Kobayashi, S.; Ishitani, H., Lanthanide(III)-Catalyzed Enantioselective Diels-Alder Reactions. Stereoselective Synthesis of Both Enantiomers by Using a Single Chiral Source and a Choice of Achiral Ligands. *J. Am. Chem. Soc.* **1994,** 116, (9), 4083-4084.

94.) Kobayashi, S., Rare earth metal trifluoromethanesulfonates as water-tolerant Lewis acid catalysts in organic synthesis. *Synlett* **1994**, (9), 689-701.

95.) Kitajima, H.; Katsuki, T., Chiral Lewis acid-promoted asymmetric Michael addition reaction of 2-(trimethylsilyloxy)furans. *Synlett* **1997**, (5), 568-570.

96.) Shibasaki, M.; Sasai, H.; Arai, T., Asymmetric catalysis with heterobimetallic compounds. *Angew. Chem., Int. Ed. Engl.* **1997,** 36, (12), 1237-1256.

97.) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P., Synthesis and applications of binaphthylic C2-symmetry derivatives as chiral auxiliaries in enantioselective reactions. *Synthesis* **1992**, (6), 503-517.

98.) Whitesell, J. K., Cyclohexyl-based chiral auxiliaries. *Chemical Reviews* **1992,** 92, (5), 953-964.

99.) Bringmann, G.; Walter, R.; Weirich, R., Modern strategies for constructing biaryl compounds. *Angew. Chem.* **1990,** 102, (9), 1006-1019.

100.) Mori, M.; Nakai, T., Asymmetric catalytic alkylation of aldehydes with diethylzinc using a chiral binaphthol-titanium complex. *Tetrahedron Lett.* **1997,** 38, (35), 6233-6236.

101.) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C., Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by Ti(BINOL) complex. *Tetrahedron: Asymmetry* **1997,** 8, (4), 585-589.

102.) Zhang, F.-Y.; Chan, A. S. C., Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by titanium-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol complex. *Tetrahedron: Asymmetry* **1997,** 8, (21), 3651-3655.

103.) Yoshioka, M.; Kawakita, T.; Ohno, M., Asymmetric induction catalyzed by conjugate bases of chiral proton acids as ligands. Enantioselective addition of

dialkylzinc-orthotitanate complex to benzaldehyde with catalytic ability of a remarkable high order. *Tetrahedron Lett.* **1989,** 30, (13), 1657-1660.

104.) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M., Enantioselective alkylation of aldehyde catalyzed by a disulfonamide-titanium tetraisopropoxide-dialkylzinc system. *Tetrahedron Lett.* **1989,** 30, (50), 7095-7098.

105.) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S., A catalytic enantioselective reaction using a C2-symmetric disulfonamide as a chiral ligand: alkylation of aldehydes catalyzed by disulfonamide-Ti(O-iso-Pr)4-dialkyl zinc system. *Tetrahedron* **1992,** 48, (27), 5691-5700.

106.) Knochel, P.; Perea, J. J. A.; Jones, P., Organozinc mediated reactions. *Tetrahedron* **1998,** 54, (29), 8275-8319.

107.) Knochel, P., Stereoselective reactions mediated by functionalized diorganozincs. *Synlett* **1995**, (5), 393-403.

108.) Dangel, B.; Clarke, M.; Haley, J.; Sames, D.; Polt, R., Amino Acid-Derived Ligands for Transition Metals: Catalysis via a Minimalist Interpretation of a Metalloprotein. *J. Am. Chem. Soc.* **1997,** 119, (44), 10865-10866.

109.) Dangel, B. D.; Polt, R., Catalysis by Amino Acid-Derived Tetracoordinate Complexes: Enantioselective Addition of Dialkylzincs to Aliphatic and Aromatic Aldehydes. *Org. Lett.* **2000,** 2, (19), 3003-3006.

110.) Lake, F.; Moberg, C., Titanium-mediated addition of diethylzinc to benzaldehyde. The effect of chiral additives. *Tetrahedron: Asymmetry* **2001,** 12, (5), 755-760.

111.) Le Goanvic, D.; Holler, M.; Pale, P., Chiral tridentate versus bidentate pyridines as catalysts in the enantioselective alkylation of benzaldehyde with diethylzinc. *Tetrahedron: Asymmetry* **2002,** 13, (2), 119-121.

112.) Brase, S.; Dailova, T. I.; Rozenberg, V. I.; Sergeeva, E. V.; Starikova, Z. A., Novel chiral tridentate Schiff base ligands of the [2,2]paracyclophane series: synthesis and application. *Tetrahedron: Asymmetry* **2003,** 14, (14), 2013-2019.

113.) Zhang, X.; Guo, C., Enantioselective addition of diethylzinc to aldehydes catalyzed by chiral titanate complexes with a tetradentate ligand. *Tetrahedron Lett.* **1995,** 36, (28), 4947-4950.

114.) Guo, C.; Qiu, J.; Zhang, X.; Verdugo, D.; Larter, M. L.; Christie, R.; Kenney, P.; Walsh, P. J., Enantioselective addition of diethylzinc to benzaldehyde catalyzed by chiral titanate complexes with helical ligands. *Tetrahedron* **1997,** 53, (12), 4145-4158.

115.) Qiu, J.; Guo, C.; Zhang, X., Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by a Titanate Complex with a Chiral Tetradentate Ligand. *J. Org. Chem.* **1997,** 62, (8), 2665-2668.

116.) Pastor, I. M.; Adolfsson, H., Novel highly modular C2-symmetric oxazoline ligands-application in titanium-catalyzed diethylzinc additions to aldehydes. *Tetrahedron Lett.* **2002,** 43, (9), 1743-1746.

117.) Shang, Z.-L.; Shang, Z.-C.; Yu, Q.-S., Synthesis of (S,S)-bis(4-alkyloxazolin-2-yl-methyl)-1,5-diazacyclooctane. *Synth. Commun.* **2002,** 32, (22), 3461-3464.

118.) Sharpless, K. B., Searching for new reactivity (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002,** 41, (12), 2024-2032.

119.) Knowles, W. S., Asymmetric hydrogenations (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002,** 41, (12), 1998-2007.

120.) Noyori, R., Asymmetric catalysis: science and opportunities (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002,** 41, (12), 2008-2022.

121.) De Vos, D. E.; Vankelecom, I. F. J.; Jacobs, P. A.; Editors, *Chiral Catalyst Immobilization and Recycling*. ed.; 2000; 'Vol.' p 320 pp.

122.) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D., Solid-phase organic reactions: a review of the recent literature. *Tetrahedron* **1996,** 52, (13), 4527-4554.

123.) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C., Solid-phase organic reactions. II: a review of the literature Nov 95-Nov 96. *Tetrahedron* **1997,** 53, (16), 5643-5678.

124.) Fruechtel, J. S.; Jung, G., Organic chemistry on solid supports. *Angew. Chem., Int. Ed. Engl.* **1996,** 35, (1), 17-42.

125.) Merrifield, R. B., Solid phase peptide synthesis. I. The synthesis of a tetrapeptide. *J. Am. Chem. Soc.* **1963,** 85, (14), 2149-2154.

126.) Merrifield, R. B., Solid-Phase Synthesis (Nobel Lecture). *Angewandte Chemie-International Edition in English* **1985,** 24, (10), 799-810.

127.) Pavia, M. R.; Sawyer, T. K.; Moos, W. H., The Generation of Molecular Diversity. *Bioorg. Med. Chem. Lett.* **1993,** 3, (3), 387-396.

128.) Jung, M.; Schurig, V., Computer simulation of three scenarios for the separation of non-racemic mixtures by chromatography on achiral stationary phases. *J. Chromatogr.* **1992,** 605, (2), 161-166.

129.) Fields, G. B.; Noble, R. L., Solid-Phase Peptide-Synthesis Utilizing 9-Fluorenylmethoxycarbonyl Amino-Acids. *Int. J. Pept. Protein Res.* **1990,** 35, (3), 161-214.

130.) Beaucage, S. L.; Iyer, R. P., Advances in the Synthesis of Oligonucleotides by the Phosphoramidite Approach. *Tetrahedron* **1992,** 48, (12), 2223-2311.

131.) Montserrat, F. X.; Grandas, A.; Eritja, R.; Pedroso, E., Criteria for the Economic Large-Scale Solid-Phase Synthesis of Oligonucleotides. *Tetrahedron* **1994,** 50, (8), 2617-2622.

132.) Verduyn, R.; Vanderklein, P. A. M.; Douwes, M.; Vandermarel, G. A.; Vanboom, J. H., Polymer-Supported Solution Synthesis of a Heptaglucoside Having Phytoalexin Elicitor Activity. *Recueil Des Travaux Chimiques Des Pays-Bas-Journal of the Royal Netherlands Chemical Society* **1993,** 112, (7-8), 464-466.

133.) Danishefsky, S. J.; McClure, K. F.; Randolph, J. T.; Ruggeri, R. B., A Strategy for the Solid-Phase Synthesis of Oligosaccharides. *Science* **1993,** 260, (5112), 1307-1309.

134.) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J., Polymer-Supported Solution Synthesis of Oligosaccharides. *J. Am. Chem. Soc.* **1991,** 113, (13), 5095-5097.

135.) Schuster, M.; Wang, P.; Paulson, J. C.; Wong, C. H., Solid-Phase Chemical-Enzymatic Synthesis of Glycopeptides and Oligosaccharides. *J. Am. Chem. Soc.* **1994,** 116, (3), 1135-1136.

136.) Akelah, A., Heterogeneous Organic-Synthesis Using Functionalized Polymers. *Synthesis-Stuttgart* **1981**, (6), 413-438.

137.) Sherrington, D. C.; Hodge, P., *Syntheses and Separations Using Functional Polymers*. ed.; 1988; 'Vol.' p 454 pp.

138.) Overberg.Cg; Sannes, K. N., Polymers as Reagents in Organic Synthesis. *Angewandte Chemie-International Edition in English* **1974,** 13, (2), 99-104.

139.) James, I. W., Linkers for solid phase organic synthesis. *Tetrahedron* **1999,** 55, (16), 4855-4946.

140.) Wang, S.-S., p-Alkoxybenzyl alcohol resin and p-alkoxybenzyloxycarbonylhydrazide resin for solid phase synthesis of protected peptide fragments. *J. Am. Chem. Soc.* **1973,** 95, (4), 1328-1333.

141.) Gutte, B.; Merrifield, R. B., Synthesis of ribonuclease A. *J. Biol. Chem.* **1971,** 246, (6), 1922-1941.

142.) Atherton, E.; Clive, D. L. J.; Sheppard, R. C., Polyamide supports for polypeptide synthesis. *J. Am. Chem. Soc.* **1975,** 97, (22), 6584-6585.

143.) Atherton, E.; Caviezel, M.; Over, H.; Sheppard, R. C., Application of Polyamide Resins to Polypeptide-Synthesis - Human Beta-Endorphin. *Journal of the Chemical Society-Chemical Communications* **1977**, (22), 819-821.

144.) Arshady, R.; Atherton, E.; Gait, M. J.; Lee, K.; Sheppard, R. C., Easily prepared polar support for solid phase peptide and oligonucleotide synthesis. Preparation of substance P and a nonadeoxyribonucleotide. *J. Chem. Soc., Chem. Commun.* **1979**, (9), 423-425.

145.) Alfred, J. C.; Aubagnac, J. L.; Calmes, M.; Daunis, J.; Elamrani, B.; Jacquier, R.; Nkusi, G., New Anchors Useful in Solid-Phase Peptide-Synthesis, Evidence of an Unexpected Polyacrylic Supported Reaction by Non Destructive C-13 Nmr-Spectroscopy and Tandem Mass-Spectrometry. *Tetrahedron* **1988,** 44, (14), 4407-4413.

146.) Stahl, G. L.; Walter, R.; Smith, C. W., Preparation and Characterization of Beaded Poly(N-Acrylylpyrrolidine) - Bidirectional Synthesis of Cys-Containing, His-Containing, Gln-Containing, or Glu-Containing Polypeptides. *J. Am. Chem. Soc.* **1979,** 101, (18), 5383-5394.

147.) Calas, B.; Parello, J., New trends in solid-phase peptide synthesis. *American Biotechnology Laboratory* **1985,** 3, (2), 18, 20-18, 30-11.

148.) Geysen, H. M.; Meloen, R. H.; Barteling, S. J., Use of Peptide-Synthesis to Probe Viral-Antigens for Epitopes to a Resolution of a Single Amino-Acid. *Proceedings of the National Academy of Sciences of the United States of America-Biological Sciences* **1984,** 81, (13), 3998-4002.

149.) Dryland, A.; Sheppard, R. C., Peptide-Synthesis .8. A System for Solid-Phase Synthesis under Low-Pressure Continuous-Flow Conditions. *Journal of the Chemical Society-Perkin Transactions 1* **1986**, (1), 125-137.

150.) Small, P. W.; Sherrington, D. C., Design and Application of a New Rigid Support for High-Efficiency Continuous-Flow Peptide-Synthesis. *Journal of the Chemical Society-Chemical Communications* **1989**, (21), 1589-1591.

151.) Albericio, F.; Pons, M.; Pedroso, E.; Giralt, E., Comparative-Study of Supports for Solid-Phase Coupling of Protected-Peptide Segments. *J. Org. Chem.* **1989,** 54, (2), 360-366.

152.) Buettner, K.; Zahn, H.; Fischer, W. H., Rapid solid phase peptide synthesis on a controlled pore glass support. *Pept.: Chem. Biol., Proc. Am. Pept. Symp. 10th* **1988**, 210-211.

153.) Rapp, W.; Wiesmueller, K. H.; Fleckenstein, B.; Gnau, V.; Jung, G., New tools for libraries: Macrobeads of 750 mmol diameter and selective orthogonal functionalization of inner sites and outer surface of beads. *Peptides 1994, Proceedings of the European Peptide Symposium, 23rd, Braga, Port., Sept. 4-10, 1994* **1995**, 87-89.

154.) Bayer, E., Towards the Chemical Synthesis of Proteins. *Angewandte Chemie-International Edition in English* **1991,** 30, (2), 113-129.

155.) Mergler, M.; Tanner, R.; Gosteli, J.; Grogg, P., Peptide-Synthesis by a Combination of Solid-Phase and Solution Methods .1. A New Very Acid-Labile Anchor Group for the Solid-Phase Synthesis of Fully Protected Fragments. *Tetrahedron Lett.* **1988,** 29, (32), 4005-4008.

156.) Barlos, K.; Gatos, D.; Kapolos, S.; Papaphotiu, G.; Schafer, W.; Yao, W. Q., Esterification of Partially Protected Peptide-Fragments with Resins - Utilization of 2-Chlorotritylchloride for Synthesis of Leu-15-Gastrin-I. *Tetrahedron Lett.* **1989,** 30, (30), 3947-3950.

157.) Frechet, J. M. J.; Haque, K. E., Use of Polymers as Protecting Groups in Organic Synthesis .2. Protection of Primary Alcohol Functional Groups. *Tetrahedron Lett.* **1975**, (35), 3055-3056.

158.) Cramer, F.; Koester, H., Synthesis of oligonucleotides on a polymeric carrier. II. *Angew. Chem., Int. Ed. Engl.* **1968,** 7, (6), 473-474.

159.) Mitchell, A. R.; Erickson, B. W.; Ryabtsev, M. N.; Hodges, R. S.; Merrifield, R. B., Tert-Butoxycarbonylaminoacyl-4-(Oxymethyl)-Phenylacetamidomethyl-Resin, a More Acid-Resistant Support for Solid-Phase Peptide-Synthesis. *J. Am. Chem. Soc.* **1976,** 98, (23), 7357-7362.

160.) Rink, H., Solid-Phase Synthesis of Protected Peptide-Fragments Using a Trialkoxy-Diphenyl-Methylester Resin. *Tetrahedron Lett.* **1987,** 28, (33), 3787-3790.

161.) Tam, J. P.; DiMarchi, R. D.; Merrifield, R. B., Design and synthesis of a multidetachable benzhydrylamine resin for solid phase peptide synthesis. *Tetrahedron Lett.* **1981,** 22, (30), 2851-2854.

162.) Sieber, P., A New Acid-Labile Anchor Group for the Solid-Phase Synthesis of C-Terminal Peptide Amides by the Fmoc Method. *Tetrahedron Lett.* **1987,** 28, (19), 2107-2110.

163.) Albericio, F.; Robles, J.; Fernandez-Forner, D.; Palom, Y.; Celma, C.; Pedroso, E.; Giralt, E.; Eritja, R., NPE-resin, a new approach to the solid-phase synthesis of protected peptides and oligonucleotides. *Pept. 1990, Proc. Eur. Pept. Symp., 21st* **1991**, 134-136.

164.) Albericio, F.; Giralt, E.; Eritja, R., NPE-resin, a new approach to the solid-phase synthesis of protected peptides and oligonucleotides. II. Synthesis of protected peptides. *Tetrahedron Lett.* **1991,** 32, (11), 1515-1518.

165.) Apsimon, J. W.; Dixit, D. M., A Modified Polymer Support for Organic-Synthesis. *Synth. Commun.* **1982,** 12, (2), 113-116.

166.) Katti, S. B.; Misra, P. K.; Haq, W.; Mathur, K. B., A New Base-Labile Linker for Solid-Phase Peptide-Synthesis. *Journal of the Chemical Society-Chemical Communications* **1992**, (11), 843-844.

167.) Mullen, D. G.; Barany, G., A New Fluoridolyzable Anchoring Linkage for Orthogonal Solid-Phase Peptide-Synthesis - Design, Preparation, and Application of the N-(3 or 4)- 4-(Hydroxymethyl)Phenoxy -Tert-Butylphenylsilyl Phenyl Pentanedioic Acid Monoamide (Pbs) Handle. *J. Org. Chem.* **1988,** 53, (22), 5240-5248.

168.) Ramage, R.; Barron, C. A.; Bielecki, S.; Thomas, D. W., Solid-Phase Peptide-Synthesis - Fluoride-Ion Release of Peptide from the Resin. *Tetrahedron Lett.* **1987,** 28, (35), 4105-4108.

169.) Degrado, W. F.; Kaiser, E. T., Polymer-Bound Oxime Esters as Supports for Solid-Phase Peptide-Synthesis - Preparation of Protected Peptide-Fragments. *J. Org. Chem.* **1980,** 45, (7), 1295-1300.

170.) Kunz, H.; Dombo, B.; Kosch, W., Solid-phase synthesis of peptides and glycopeptides on resins with allylic anchoring groups. *Pept., Proc. Eur. Pept. Symp., 20th* **1989**, 154-156.

171.) Patek, M.; Lebl, M., Safety-catch anchoring linkage for synthesis of peptide amides by Boc/Fmoc strategy. *Tetrahedron Lett.* **1991,** 32, (31), 3891-3894.

172.) Tjoeng, F. S.; Heavner, G. A., Synthesis of a New Photolabile Support - 4-(2-Chloropropionyl)Phenylacetamidomethyl-Resin and Its Application in Solid-Phase Peptide-Synthesis. *J. Org. Chem.* **1983,** 48, (3), 355-359.

173.) Barany, G.; Sole, N. A.; Van Abel, R. J.; Albericio, F.; Selsted, M. E., Recent advances in solid phase peptide synthesis. *Innovation Perspect. Solid Phase Synth. Collect. Pap., Int. Symp., 2nd* **1992**, 29-38.

174.) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E., The synthesis of amino acids by phase-transfer reactions. *Tetrahedron Lett.* **1978**, (30), 2641-2644.

175.) Pirrung, M. C.; Krishnamurthy, N., Preparation of (R)-phenylalanine analogs by enantioselective destruction using L-amino acid oxidase. *J. Org. Chem.* **1993,** 58, (4), 957-958.

176.) Corey, E. J.; Noe, M. C.; Xu, F., Highly enantioselective synthesis of cyclic and functionalized a-amino acids by means of a chiral phase transfer catalyst. *Tetrahedron Lett.* **1998,** 39, (30), 5347-5350.

177.) Polt, R.; Sames, D.; Chruma, J., Glycosidase inhibitors: synthesis of enantiomerically pure aza-sugars from Schiff base amino esters via tandem reduction-alkenylation and osmylation. *J. Org. Chem.* **1999,** 64, (17), 6147-6158.

178.) Schoknecht, W.; Albert, K.; Jung, G.; Bayer, E., Synthesis of the Insulin Segment B 13-20 with the Liquid-Phase Method and Control of the Synthesis by C-13 Nmr-Spectroscopy of the Support-Bound Peptides. *Liebigs Ann. Chem.* **1982**, (8), 1514-1531.

179.) Giralt, E.; Rizo, J.; Pedroso, E., Application of gel-phase carbon-13 NMR to monitor solid phase peptide synthesis. *Tetrahedron* **1984,** 40, (20), 4141-4152.

180.) Giralt, E.; Albericio, F.; Bardella, F.; Eritja, R.; Feliz, M.; Pedroso, E.; Pons, M.; Rizo, J., Gel-phase NMR spectroscopy as a useful tool in solid phase synthesis. *Innovation Perspect. Solid Phase Synth. Collect. Pap., Int. Symp., 1st* **1990**, 111-120.

181.) Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A., Methods for Combinatorial Organic-Synthesis - the Use of Fast C-13 Nmr Analysis for Gel Phase Reaction Monitoring. *J. Org. Chem.* **1994,** 59, (25), 7588-7590.

182.) Fitch, W. L.; Detre, G.; Holmes, C. P.; Shoolery, J. N.; Keifer, P. A., High-Resolution H-1-Nmr in Solid-Phase Organic-Synthesis. *J. Org. Chem.* **1994,** 59, (26), 7955-7956.

183.) Anderson, R. C.; Jarema, M. A.; Shapiro, M. J.; Stokes, J. P.; Ziliox, M., Analytical Techniques in Combinatorial Chemistry - Mas Ch Correlation in Solvent-Swollen Resin. *J. Org. Chem.* **1995,** 60, (9), 2650-2651.

184.) Anderson, R. C.; Stokes, J. P.; Shapiro, M. J., Structure Determination in Combinatorial Chemistry - Utilization of Magic-Angle-Spinning Hmqc and Tocsy Nmr-Spectra in the Structure Determination of Wang-Bound Lysine. *Tetrahedron Lett.* **1995,** 36, (30), 5311-5314.

185.) Egner, B. J.; Langley, G. J.; Bradley, M., Solid-Phase Chemistry - Direct Monitoring by Matrix-Assisted Laser-Desorption Ionization Time-of-Flight Mass-Spectrometry - a Tool for Combinatorial Chemistry. *J. Org. Chem.* **1995,** 60, (9), 2652-2653.

186.) As the starting materials were branched after the Schiff base formation to get similar but, analogous products, a different lablel was used after Schiff base formation. The numbering of these lignands was summerized in table

187.) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C., Peptide coupling reagents. IV. N-[Oxytris(dimethylamino)phosphonium]benzotriazole hexafluorophosphate. *Tetrahedron Lett.* **1975**, (14), 1219-1222.

188.) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C., B.O.P.: a new peptide coupling reagent exemplified in the synthesis of somatostatin. *Pept., Proc. Eur. Pept. Symp., 14th* **1976**, 79-84.

189.) Kates, S. A.; Sole, N. A.; Beyermann, M.; Barany, G.; Albericio, F., Optimized preparation of Deca(L-alanyl)-L-valinamide by 9-fluorenylmethyloxyarbonyl (Fmoc) solid-phase synthesis on polyethylene glycol-polystyrene (PEG-PS) graft supports, with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) deprotection. *Peptide Research* **1996,** 9, (3), 106-113.

190.) Wade, J. D.; Bedford, J.; Sheppard, R. C.; Tregear, G. W., DBU as an Na-deprotecting reagent for the fluorenylmethoxycarbonyl group in continuous flow solid-phase peptide synthesis. *Peptide Research* **1991,** 4, (3), 194-199.

191.) Newcomb, W. S.; Deegan, T. L.; Miller, W.; Porco, J. A., Jr., Analysis of 9-fluorenylmethoxycarbonyl (FMOC) loading of solid-phase synthesis resins by gas chromatography. *Biotechnol. Bioeng.* **1998,** 61, (1), 55-60.

192.) Chan, W. C.; White, P. D.; Editors, *Fmoc Solid Phase Peptide Synthesis: A Practical Approach*. ed.; 2000; 'Vol.' p 346 pp.

193.) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I., Color test for detection of free terminal amino groups in the solid-phase synthesis of peptides. *Anal. Biochem.* **1970,** 34, (2), 595-598.

194.) Vojkovsky, T., Detection of Secondary-Amines on Solid-Phase. *Peptide Research* **1995,** 8, (4), 236-237.

195.) Frechet, J. M. J., Synthesis and Applications of Organic Polymers as Supports and Protecting Groups. *Tetrahedron* **1981,** 37, (4), 663-683.

196.) Horeau, A.; Guette, J. P., Diastereoisomeric interactions of antipodes in the liquid phase. *Tetrahedron* **1974,** 30, (13), 1923-1931.

197.) Horeau, A., Interactions between enantiomers in solution; effect on the rotatory power. Optical purity and enantiomeric purity. *Tetrahedron Lett.* **1969**, (36), 3121-3124.

198.) Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskokovic, M., Diastereomeric solute-solute interactions of enantiomers in achiral solvents. Nonequivalence of the nuclear magnetic resonance spectra of racemic and optically active dihydroquinine. *J. Am. Chem. Soc.* **1969,** 91, (7), 1871-1872.

199.) Pasteur, L., *C. R. Acad. Sci. Paris* **1848,** 26, 535-539.

200.) Le Fevre, R. J. W.; Maramba, F., *J. Chem. Soc.* **1952**, 235.

201.) McGinn, C. J., Diastereoazeotropes as a means of resolution. *J. Phys. Chem.* **1961,** 65, 1896-1897.

202.) Walden, W.; Zimmermann, C.; Kolbe, A.; Pracejus, H., Enantioselective effects in the association behavior of optically active alcohols. *Tetrahedron* **1977,** 33, (4), 419-421.

203.) Herndon, W. C.; Vincenti, S. P., Hydrogen bonding in optically active and racemic 2-butanol. *J. Am. Chem. Soc.* **1983,** 105, (19), 6174-6175.

204.) Cundy, K. C.; Crooks, P. A., Unexpected phenomenon in the high-performance liquid chromatographic analysis of racemic carbon-14-labeled nicotine: separation of enantiomers in a totally achiral system. *J. Chromatogr.* **1983,** 281, 17-33.

205.) Charles, R.; Gil-Av, E., Self-amplification of optical activity by chromatography on an achiral adsorbent. *J. Chromatogr.* **1984,** 298, (3), 516-520.

206.) Tsai, W. L.; Hermann, K.; Hug, E.; Rohde, B.; Dreiding, A. S., Enantiomer-differentiation induced by an enantiomeric excess during chromatography with achiral phases. *Helv. Chim. Acta* **1985,** 68, (8), 2238-2243.

207.) Matusch, R.; Coors, C., Chromatographic separation of excess enantiomers under achiral conditions. *Angew. Chem.* **1989,** 101, (5), 624-626.

208.) Dobashi, A.; Motoyama, Y.; Kinoshita, K.; Hara, S.; Fukasaku, N., Self-induced chiral recognition in the association of enantiomeric mixtures on silica gel chromatography. *Anal. Chem.* **1987,** 59, (17), 2209-2211.

209.) Carman, R. M.; Klika, K. D., The optical fractionation of a partially racemic natural product by chromatography over an achiral substrate. *Aust. J. Chem.* **1991,** 44, (6), 895-896.

210.) Diter, P.; Taudien, S.; Samuel, O.; Kagan, H. B., Enantiomeric enrichment of sulfoxides by preparative flash chromatography on an achiral phase. *J. Org. Chem.* **1994,** 59, (2), 370-373.

211.) Wynberg, H.; Feringa, B., Enantiomeric recognition and interactions. *Tetrahedron* **1976,** 32, (22), 2831-2834.

212.) Wynberg, H.; Lammertsma, K.; Hulshof, L. A., Synthesis and chiroptical properties of the two diastereomeric 2-bornanylidenebornanes. *Tetrahedron Letters* **1975**, (43), 3749-3752.

213.) McMurry, J. E.; Fleming, M. P., New method for the reductive coupling of carbonyls to olefins. Synthesis of b-carotene. *Journal of the American Chemical Society* **1974,** 96, (14), 4708-4709.

214.) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B., Nonlinear effects in asymmetric synthesis. Examples in asymmetric oxidations and aldolization reactions. *J. Am. Chem. Soc.* **1986,** 108, (9), 2353-2357.

215.) Hajos, Z. G.; Parrish, D. R., Asymmetric synthesis of bicyclic intermediates of natural product chemistry. *J. Org. Chem.* **1974,** 39, (12), 1615-1621.

216.) Eder, U.; Sauer, G.; Wiechert, R., Total synthesis of optically active steroids. 6. New type of asymmetric cyclization to optically active steroid CD partial structures. *Angew. Chem., Int. Ed. Engl.* **1971,** 10, (7), 496-497.

217.) Katsuki, T.; Sharpless, K. B., The first practical method for asymmetric epoxidation. *J. Am. Chem. Soc.* **1980,** 102, (18), 5974-5976.

218.) Finn, M. G.; Sharpless, K. B., Mechanism of asymmetric epoxidation. 2. Catalyst structure. *J. Am. Chem. Soc.* **1991,** 113, (1), 113-126.

219.) Oppolzer, W.; Radinov, R. N., Enantioselective synthesis of sec-allylalcohols by catalytic asymmetric additon of divinylzinc to aldehydes. *Tetrahedron Lett.* **1988,** 29, (44), 5645-5648.

220.) Kagan, H. B.; Girard, C., Nonlinear effects in asymmetric synthesis and stereoselective reactions: Ten years of investigation. *Angew. Chem. Int. Ed.* **1998,** 37, (21), 2922-2959.

221.) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K., Catalytic asymmetric induction. Highly enantioselective addition of dialkylzincs to aldehydes using chiral pyrrolidinylmethanols and their metal salts. *J. Am. Chem. Soc.* **1987,** 109, (23), 7111-7115.

222.) Soai, K.; Ookawa, A.; Ogawa, K.; Kaba, T., Complementary catalytic asymmetric induction in the enantioselective addition of diethylzinc to aldehydes. *J. Chem. Soc., Chem. Commun.* **1987**, (6), 467-468.

223.) Oguni, N.; Matsuda, Y.; Kaneko, T., Asymmetric amplifying phenomena in enantioselective addition of diethylzinc to benzaldehyde. *J. Am. Chem. Soc.* **1988,** 110, (23), 7877-7878.

224.) Yamakawa, M.; Noyori, R., An Ab Initio Molecular Orbital Study on the Amino Alcohol-Promoted Reaction of Dialkylzincs and Aldehydes. *J. Am. Chem. Soc.* **1995,** 117, (23), 6327-6335.

225.) Coates, G. E.; Ridley, D., Reactions between some organozinc compounds and 2-dimethylaminoethanol, acetoxime, phenyl isocyanate, and benzophenone. Some observations on the methoxymethylzinc tetramer. *Journal of the Chemical Society [Section] A: Inorganic, Physical, Theoretical* **1966**, (8), 1064-1069.

226.) Reetz, M. T.; Huellmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P., Structure and electronic nature of the benzaldehyde/boron trifluoride adduct. *J. Am. Chem. Soc.* **1986,** 108, (9), 2405-2408.

227.) Bolm, C.; Schlingloff, G.; Harms, K., Catalyzed enantioselective alkylation of aldehydes. *Chemische Berichte* **1992,** 125, (5), 1191-1203.

228.) Yamaguchi, M.; Shiraishi, T.; Hirama, M., Asymmetric Michael Addition of Malonate Anions to Prochiral Acceptors Catalyzed by L-Proline Rubidium Salt. *J. Org. Chem.* **1996,** 61, (10), 3520-3530.

229.) Bolm, C.; Mueller, J.; Schlingloff, G.; Zehnder, M.; Neuburger, M., b-Hydroxy sulfoximines as catalysts for the enantioselective alkylation of aldehydes. *J. Chem. Soc., Chem. Commun.* **1993**, (2), 182-183.

230.) Bolm, C.; Mueller, J., Spectroscopic studies on the b-hydroxysulfoximine-catalyzed enantioselective alkylation of aldehydes. *Tetrahedron* **1994,** 50, (15), 4355-4362.

231.) Schwenkreis, T.; Berkessel, A., A biomimetic catalyst for the asymmetric epoxidation of unfunctionalized olefins with hydrogen peroxide. *Tetrahedron Lett.* **1993,** 34, (30), 4785-4788.

232.) Bolm, C.; Bienewald, F., Asymmetric sulfide oxidation with vanadium catalysts and H2O2. *Angew. Chem., Int. Ed. Engl.* **1996,** 34, (23/24), 2640-2642.

233.) Seebach, D.; Marti, R. E.; Hintermann, T., Polymer- and dendrimer-bound Ti-TADDOLates in catalytic (and stoichiometric) enantioselective reactions. Are pentacoordinate cationic Ti complexes the catalytically active species? *Helvetica Chimica Acta* **1996,** 79, (6), 1710-1740.

234.) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kuehnle, F. N. M., On the Ti-TADDOLate-Catalyzed Diels-Alder Addition of 3-Butenoyl-1,3-oxazolidin-2-one to Cyclopentadiene. General Features of Ti-BINOLate- and Ti-TADDOLate-Mediated Reactions. *Journal of Organic Chemistry* **1995,** 60, (6), 1788-1799.

235.) 0.03 mol% in total (both eantiomers of ligand together) was utilized in the reaction.

236.) Giovannetti, J. S.; Kelly, C. M.; Landis, C. R., Molecular mechanics and NOE investigations of the solution structures of intermediates in the [rhodium(chiral

bisphosphine)]+-catalyzed hydrogenation of prochiral enamides. *J. Am. Chem. Soc.* **1993,** 115, (10), 4040-4057.

237.) Corey, E. J.; Noe, M. C., Rigid and highly enantioselective catalyst for the dihydroxylation of olefins using osmium tetraoxide clarifies the origin of enantiospecificity. *J. Am. Chem. Soc.* **1993,** 115, (26), 12579-12580.

238.) Farina, V.; Krishnan, B., Large rate accelerations in the stille reaction with tri-2-furylphosphine and triphenylarsine as palladium ligands: mechanistic and synthetic implications. *J. Am. Chem. Soc.* **1991,** 113, (25), 9585-9595.

239.) Quiros Mendez, N.; Seyler, J. W.; Arif, A. M.; Gladysz, J. A., Synthesis, structure, and spectroscopic properties of chiral rhenium aromatic aldehyde complexes [(h5-C5H5)Re(NO)(PPh3)(O:CHAr)]+X-: equilibria between p and s aldehyde binding modes. *J. Am. Chem. Soc.* **1993,** 115, (6), 2323-2334.

240.) Watanabe, H.; Yan, F.; Sakai, T.; Uneyama, K., (Trifluoroacetimidoyl)lithiums and Their Reaction with Electrophiles. *J. Org. Chem.* **1994,** 59, (4), 758-761.

241.) Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S., Enantioselectivity Increases with Reactivity: Electronically Controlled Asymmetric Addition of Diethylzinc to Aromatic Aldehydes Catalyzed by a Chiral Pyridylphenol. *J. Org. Chem.* **1996,** 61, (23), 8002-8003.

242.) The term ln (S/R) is proportional to -??G? according to the following equation: log (S/R) = - ??G?/RT where - ??G? is the free energy difference between two diastereomeric transition states leading toe enantiomeric products

243.) The synthesis of ligands was done according to the methodology developed by Brian D. Dangel during his research at University of Arizona. Ph.D. dissertation, University of Arizona, 2000.

244.) Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N., Catalyzed asymmetric arylation reactions. An*gew. Chem., Int. Ed. 20*0**1, 4**0, (18), 3284-3308.

245.) Brase, S.; Dahmen, S., [2,2]Paracyclophane-based N,*O-ligands in alkenylzinc additions to aldehydes.* Org. *Lett. 20*0**1, 3**, (25), 4119-4122.

246.) Allyl alcohols are substrates for, e.g., cyclopropanation reactions, aziridination reactions, ene-reactions, epoxidations, dihydroxylations, methoxy selenations, iodo hydroxylations, brominations, and allylic substitution reactions.

247.) Oppolzer, W.; Radinov, R. N., 13. Catalytic asymmetric synthesis of se*condary (E)*-allyl alcohols from acetylenes and aldehydes vi*a (*1-alkenyl)zinc intermediates. He*lv. Chim. Acta 19***92, 7**5, (1), 170-173.

248.) Oppolzer, W.; Radinov, R. N.; El-Sayed, E., Catalytic asymmetric synthesis of macrocyclic (E)-allylic alcohols from w-αlkynals via intramolecular 1-alkenyzinc/aldehyde additions. J. *Org. Chem. 20***01, 6**6, (14), 4766-4770.

249.) Von dem Bussche-Huennefeld, J. L.; Seebach, D., Enantioselective preparation of secondary alcohols from aldehydes and dialkyl zinc compounds, generated in situ from Grignard reagents, using substoichiometric amounts of TADDOL-titanates. Te*trahedron 19***92, 4**8, (27), 5719-5730.

250.) Soai, K.; Takahashi, K., Asymmetric alkenylation of chiral and prochiral aldehydes catalyzed by chiral or achiral amino alcohols: catalytic diastereoselective synthesis of protected erythro-sphingosine and enantioselective synthesis of chiral diallyl alcohols. Jo*urnal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) 19***94,** (10), 1257-1258.

251.) Shibata, T.; Nakatsui, K.; Soai, K., Highly enantioselective catalytic isopropenylation of aldehydes using diisopropenylzinc. In*org. Chim. Acta 19***99, 2**96, (1), 33-36.

252.) Oppolzer, W.; Radinov, R. N., Enantioselective addtion of (Z)- and (E)-alkenylzinc bromides to aldehydes: asymmetric synthesis of sec-allylalcohols. Te*trahedron Lett. 19***91, 3**2, (41), 5777-5780.

253.) Bartocha, B.; Kaesz, H. D.; Stone, F. G. A., Divinylzinc. Ze*itschrift fuer Naturforschung 19***59, 1**4b, 352-353.

254.) Chen, Y. K.; Lurain, A. E.; Walsh, P. J., A General, Highly Enantioselective Method for the Synthesis of D and L a-Amino Acids and Allylic Amines. J. *Am. Chem. Soc. 20***02, 1**24, (41), 12225-12231.

255.) Yang, X. W.; Shen, J. H.; Da, C. S.; Wang, R.; Choi, M. C. K.; Yang, L. W.; Wong, K. Y., Chiral pyrrolidine derivatives as catalysts in the enantioselective addition of diethylzinc to aldehydes. Te*trahedron-Asymmetry 19***99, 1**0, (1), 133-138.

256.) Klaproth, M., An*n. Chim. Phys. 17***90, 6**, (1), 1.

257.) Berzelius, J. J., An*n. Chim. Phys 18***24, 2**6, 43.

258.) Wilkinson, G.; Pauson, P. L.; Brirmingham, J. M.; Cotton, F. A., Bis-cyclopentadienyl derivatives of some transition metals. J. *Am. Chem. Soc. 19***53, 7**5, (4), 1011-1012.

259.) Wailes, P. C.; Weigold, H., Hydrido complexes of zirconium I. Preparation. J. *Organometal. Chem. 19***70, 2**4, 405-411.

260.) Hart, D. W.; Schwartz, J., Hydrozirconation. Organic Synthesis via Organozirconium Intermediates. Synthesis and Rearrangement of Alkylzirconium(1V) Complexes and Their Reaction with Electrophiles. J. *Am. Chem. Soc. 19***7, 9**6, (26), 8115-8116.

261.) Wipf, P.; Xu, W.; Takahashi, H.; Jahn, H.; Coish, P. D. G., Synthetic applications of organozirconocenes. Pu*re & Appl. Chem. 19***97, 6**9, (3), 639-644.

262.) Hunter, W. E.; Hrncir, D. C.; Bynum, R. V.; Penttila, R. A.; Atwood, J. L., The search for dimethylzirconocene. Crystal structures of dimethylzirconocene, dimethylhafnocene, chloromethylzirconocene, and (m-oxo)bis(methylzirconocene). Or*ganometallics 19***83, 2**, (6), 750-755.

263.) Wipf, P.; Jahn, H., Synthetic applications of organochlorozirconocene complexes. Te*trahedron 19***96, 5**2, (40), 12853-12910.

264.) Koga, N.; Morokuma, K., Ab initio molecular orbital studies of catalytic elementary reactions and catalytic cycles of transition-metal complexes. Ch*em. Rev. (Washington, DC, U. S.) 19***91, 9**1, (5), 823-842.

265.) Nagase, S.; Ray, N. K.; Morokuma, K., Reaction mechanism of hydroboration. Ab initio MO study on the C2H4 + BH3 reaction. J. *Am. Chem. Soc. 19***80, 1**02, (13), 4536-4537.

266.) Loots, M. J.; Schwartz, J., Nickel-catalyzed conjugate addition of zirconium alkenyls to a,b-unsaturated ketones. J. *Am. Chem. Soc. 19***77, 9**9, (24), 8045-8046.

267.) Lipshutz, B. H.; Ellsworth, E. L., Hydrozirconation-transmetalation. A mild, direct route to higher order vinylic cuprates from monosubstituted acetylenes. J. *Am. Chem. Soc. 19***90, 1**12, (20), 7440-7441.

268.) Wipf, P.; Smitrovich, J. H., Transmetalation reactions of alkylzirconocenes: copper-catalyzed conjugate addition to enones. J. *Org. Chem. 19***91, 5**6, (23), 6494-6496.

269.) Wipf, P.; Xu, W.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M., Copper-catalyzed conjugate additions of organozirconocenes. Synthetic and mechanistic studies. Te*trahedron 19***94, 5**0, (7), 1935-1954.

270.) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K., Grignard-type addition of alkenyl- and alkylzirconocene chloride to aldehyde: remarkable catalytic acceleration effect of silver perchlorate. Te*trahedron Lett. 19***92, 3**3, (40), 5965-5968.

271.) Zheng, B.; Srebnik, M., 1,2-Addition of Alkyl- and Alkenylzirconocene Chlorides to Aldehydes Accelerated by Catalytic Amounts of ZnBr2 as a Method of Synthesizing

Secondary Alcohols, Secondary Allylic Alcohols, and in-Situ Oppenauer-Type Oxidation of the Alcohols to Ketones. J. *Org. Chem. 19***95, 6**0, (11), 3278-3279.

272.) Wipf, P.; Xu, W., Preparation lof allylic alcohols by alkene transfer from zirconium to zinc. Te*trahedron Lett. 19***94, 3**5, (29), 5197-5200.

273.) Wipf, P.; Xu, W., Organozirconocenes in organic synthesis: tandem epoxide rearrangement-carbonyl addition. J. *Org. Chem. 19***93, 5**8, (4), 825-826.

274.) Negishi, E.; Swanson, D. R.; Miller, S. R., Migratory insertion reactions of organometallics. One-pot conversion of alkynes and alkenes into one-carbon homologated aldehydes via hydrozirconation-isocyanide insertion-hydrolysis. Te*trahedron Lett. 19***88, 2**9, (14), 1631-1634.

275.) Wipf, P.; Ribe, S., Zirconocene-zinc transmetalation and in situ catalytic asymmetric addition to aldehydes. J. *Org. Chem. 19***98, 6**3, (19), 6454-6455.

276.) Wipf, P.; Coish, P. D. G., Total synthesis of (+/-)-nisamycin. J. *Org. Chem. 19***99, 6**4, (14), 5053-5061.

277.) Wipf, P.; Coish, P. D. G., Organozirconocene-mediated polyene synthesis: Preparation of asukamycin and manumycin A side chains. Te*trahedron Lett. 19***97, 3**8, (29), 5073-5076.

278.) Wipf, P.; Xu, W. J., Total synthesis of the antimitotic marine natural product (+)-curacin A. J. *Org. Chem. 19***96, 6**1, (19), 6556-6562.

279.) Chavez, D. E.; Jacobsen, E. N., Total synthesis of fostriecin (CI-920). An*gewandte Chemie-International Edition 20***01, 4**0, (19), 3667-+.

280.) Murakami, T.; Furusawa, K., Efficient stereodivergent synthesis of erythro- and threo-sphingosines: unprecedented reversal of the stereochemistry in the addition. Te*trahedron 20***02, 5**8, (45), 9257-9263.

281.) Wipf, P.; Nunes, R. L., Selective carbon-carbon bond formations with alkenylzirconocenes. Te*trahedron 20***04, 6**0, (6), 1269-1279.

282.) Wipf, P.; Jayasuriya, N.; Ribe, S., On the role of chiral catalysts in the alkenyl zirconocene/ zinc addition to aldehydes: A studey of ligand loading and asymmetric amplification. Ch*irality 20***03, 1**5*,* (3), 208-212.