CATALYTIC ASYMMETRIC ADDITION REACTIONS LEADING TO CARBON–CARBON BOND FORMATION: PHENYL AND ALKENYL TRANSFER TO ALDEHYDES AND ALKYNYLATION OF α-AMINO ESTER

A thesis submitted in partial fulfilment of the requirements for the the Degree of Doctor of Philosophy

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January, 2004

Declaration

I hereby declare that this thesis summarizes my own research work carried out since my registration for the degree of Doctor of Philosophy in May of 2001, and that it has not previously been included in a thesis, dissertation or report presented to this or any other institutions for a degree, diploma, or other qualifications.

Jianxin Ji

January, 2004

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Submitted by Jianxin Ji
for the degree of Doctor of Philosophy
at The Hong Kong Polytechnic University in January 2004

Catalytic asymmetric addition reactions of nucleophiles to carbonyl and imine electrophiles are important processes in asymmetric synthesis. Such addition reactions are intrinsically efficient in the production of a wide range of valuable enantiomerically pure compounds since a new chiral center and a new carbon-carbon bond are established in a single operation. The quest for efficient catalytic systems and chiral ligands plays a crucial role in expanding the utility of this strategy. Furthermore, for the practical applications of useful catalytic asymmetric synthesis, it is highly desirable to develop convenient methods for the preparation of effective chiral ligands.

Over the past two decades, catalytic asymmetric addition reactions employing enolsilanes (aldol addition), allyl-stannanes (allylation), and dialkylzinc (alkylation) have proved to be remarkably effective and products with excellent enantiomeric excesses have been achieved for different types of C=X electrophiles. Compared to the above well-established reactions, however, catalytic asymmetric alkenyl, phenyl and alkynyl transfers to carbonyl and imine compounds are substantially less developed in spite of their importance in organic synthesis. In this study, we have developed a convenient, one-

step synthesis of optically active tertiary aminonaphthols, which have been found to be very effective chiral ligands in catalytic asymmetric phenyl and alkenyl transfers to aldehydes. A novel and efficient synthetic methodology of Ag (I) and Cu (I)/(II)-catalyzed alkynlation of α-amino ester has also been developed.

Chiral ligand 1-((*S*)-phenyl(((1′*S*)-1′-phenylethyl)methylamino)methyl)-2-naphthol was synthesized by direct condensation of the corresponding aldehyde, naphthol and secondary amine. A successful application of this chiral ligand in the enantioselective alkenylzinc addition to aldehydes was achieved and a variety of (*E*)-allyl alcohols were obtained in high yields and ee's (92%-99%).

Considering that a bulkier group at the newly generated chiral center could increase the rigidity of the ligand which may be beneficial for chiral induction, a novel chiral tertiary aminonaphthol ligand 1-((*S*)-1′-naphthyl(((1″*S*)-1″-phenylethyl)methylamino)methyl)-2-naphthol was designed and prepared by the one-step procedure which we have developed. This ligand was employed in the phenyl boronic acids-diethyl zinc-aryl aldehydes system and a variety of chiral diaryl methanols were achieved in high chemical yields with excellent enantioselectivities. To the best of our knowledge, this is the first example of a ligand devoid of planar- and axial-chirality which is able to generate high enantioselectivites in phenyl transfer reactions. Especially noteworthy is that (*R*)-*ortho*-methyl benzhydrol, which was obtained in 99% ee, is the direct precursor of Orphenadrine, an anticholinergic and antihistaminic agent.

β, γ-Alkynyl α-amino acid derivatives are a special class of nonproteinogenic amino acids which possess important biological activities. We have not only developed

the first catalytic synthesis of β, γ-alkynyl α-amino acid derivatives but have also extended the applications of Ag alkynilide in organic synthesis by showing the feasibility of direct addition of terminal alkynes to α-imino ester in the presence of a catalytic amount of Ag (I) salts under mild reaction conditions. Cu (I)/(II) salts were also found to be effective catalysts in the above reaction system. Furthermore, moderate ee (67%) was achieved in the experiment for asymmetric version of this novel synthetic methodology.

ABBREVIATION

Ac	acetyl group
Ar	aryl group
BINOL	(R)-2, 2'-dihydroxy-1, 1'-binaphthyl
Cy	cyclohexyl
DAIB	3-exo-(dimethylamino)isoborneol
L-DOPA	*L*-3-(3,4-Dihydroxyphenyl)analine
ee	enantiomeric excess
HPLC	high performance liquid chromatography
LDA	lithium diisopropylamide
NMR	nuclear magnetic resonance
PMP	*p*-methoxyphenyl
R.T.	room temperature
THF	tetrahydrofuran
Tf	trifluromethanesulfonyl

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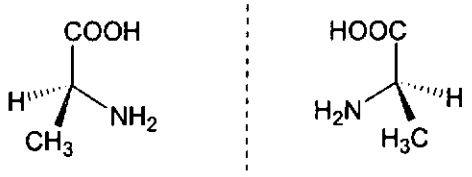
Chapter 1

Introduction

1.1 The Significance of Chiral Compounds

An object can be called chiral if it cannot be superimposed upon its mirror image. The word 'chiral' derives from the Greek word cheir, meaning hand. Our hands are chiral–the right hand is a mirror image of the left–as are most of life's molecules such as (*S*)-alanine (**1**, Figure 1-1) and (*R*)-alanine (**2**), which are mirror images of each other but are not superimposable.

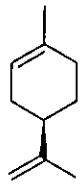


(*S*)-alanine (**1**) (*R*)-alanine (**2**)

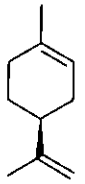
Figure 1-1 Chirality in the amino acid alanine is illustrated with models of its two forms, which are mirror images of each other.

Chirality is a fundamental property of three-dimensional objects. Molecular chirality plays a key role in science and technology. In particular, life depends on molecular chirality, in that most of the important building blocks making up the biological macromolecules of living system are in one enantiomeric form only. In addition, a wide range of biological and physical functions are generated from highly

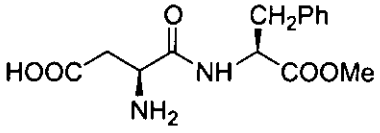
precise molecular interactions, in which chiral host molecules recognize two enantiomeric guest molecules in different ways.



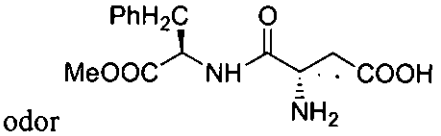
(*R*)-Limonene (**3**),
Orange odor



(*S*)-Limonene (**4**),
Lemon odor

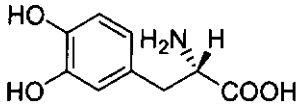


N-α-(*S*)-Aspartyl-(*S*)-phenylalanine methyl ester (Aspartame) (**5**),
Sweetener

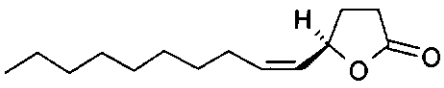


odor

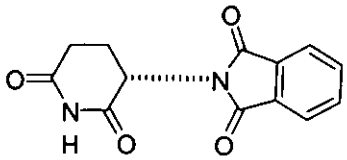
N-α-(*S*)-Aspartyl-(*R*)-phenylalanine methyl ester (Aspartame) (**6**),
Bitter



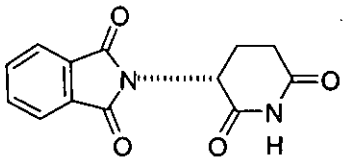
L-DOPA (**7**)



Sex pheromone (**8**) of Japanese



(*S*)-Thalidomide (**9**)
Potent teratogen



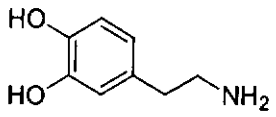
(*R*)-Thalidomide (**10**)
Sedative and hypnotic

Figure 1-2 Different behavior of enantiomers.

Human enzymes are chiral, as are other receptors that play an important part in the cell machinery. These receptors are extremely selective and prefer to bind to one of the enantiomers. The enantiomers of a chiral compound may have different tastes, different odors, and most importantly, enantiomers may exhibit very different pharmacological behaviors. There are numerous examples of pairs of enantiomer that show dramatically different effects (Figure 1-2). The enantiomers of limonene, both formed naturally, smell differently-one of the enantiomers, (*R*)-limonene (**3**) gives smell of oranges while the mirror image compound (*S*)-limonene (**4**) gives smell of lemons. We can distinguish between these enantiomers because our nasal receptors are also made up of chiral molecules that recognize the difference. The coupling of (*S*)-asparic acid with (*S*)-phenylalanine methyl ester gives a sweetener (aspartame, **5**), which is 200 times sweeter than sugar. In contrast, the dipeptide from (*S*)-asparic acid and (*R*)-phenylalanine methyl ester (**6**) has a bitter taste.[1] Insects use chiral chemical messengers (pheromones) as sex attractants and chemists have discovered that one of the enantiomers of the insect pheromone, olean, attracts male fruit flies, while its mirror image operates on the female of the species.

Medicinal chemists are now paying increasing attention towards enzymes, hormones and other compounds in patients' cells and in cells of microorganisms. Additional targets are receptors on cell surfaces. These compounds and receptors are made up of chiral amino acids, carbohydrates, and lipids. The structural difference between enantiomers can be serious with respect to the actions of synthetic drugs. Most drugs consist of chiral molecules which interact with these receptors in a chiral manner. Therefore, it is no surprise that the biological systems, in most cases, recognize a pair of

enantiomers of drug as different substances, and the two enantiomers will elicit different responses. The two enantiomers of racemic drugs may be absorbed, activated or degraded in different ways both *in vivo* and *in vitro*. The two enantiomers may have equal pharmacological activities; one may be therapeutically effective, the other may be inactive or even toxic; or the two may have unequal degrees or different kinds of activities.[2] One example is the case of *L*-DOPA (7) (Figure 1-2) which can be used for treating Parkinson's disease. The active drug is the achiral compound dopamine formed by *in vivo* decarboxylation of compound **7** (Figure 1-3). Prodrug *L*-Dopa is administered because it is very difficult for the active drug dopamine **11** to across the "Blood-Brain-Barrier" to reach its active site of action. Enzyme catalyzed *in vivo* decarboxylation of **7** releases the drug in its active form dopamine. As the enzyme dopamine decarboxylase is specific and only decarboxylates the (-)-enantiomer of **7**, it is therefore essential to administer DOPA **7** as the pure *L*-(-) form for otherwise there would be a dangerous accumulation of (+)-**7** which can not be metabolized by enzymes in the human body.



dopamine (**11**)

Figure 1-3 Dopamine: The active drug for treating Parkinson's disease

A more compelling example of the relationship between pharmacological activity and molecular chirality is the tragedy happened in Europe during the 1960s, involving the drug thalidomide, which was prescribed to treat morning sickness for pregnant women from 1957 to 1962. However, the drug had caused serious birth defects in more than 10,000 babies. The teratogenic origin of the drug was later discovered in 1961 to reside in the (*S*)-isomer (**9**) while the other enantiomer (**10**) possesses the therapeutic sedative activities and was claimed not to cause deformities in animals even in high doses.[3] People should avoid such problems arising from inappropriate molecular recognition at all costs. Nevertheless, even in the early 1990s, about 90% of synthetic chiral drugs were still racemic—that is, equimolar mixtures of both enantiomers, which reflects the difficulty in the practical synthesis of single-enantiomeric compounds.[4]

In order to encourage the commercialization of clinical drugs consisting of single enantiomers, the Food and Drug Administration in the U.S. introduced a guideline regarding "racemic switches" in 1992.[5] According to the regulation of the U.S. Food and Drug Administration, pharmaceutical companies nowadays have to make sure that both enantiomers of a racemic drug are tested for their biological activity and toxicity before they are marketed. The administration of enantiomerically pure drugs can have the following advantages: (1) decreased dosage, lowering the load on metabolism; (2) increased latitude in dosage; (3) increased confidence in dose selection; (4) fewer interactions with other drugs; (5) enhanced activity, increased specificity and less risk of possible side effects caused by the enantiomer. Such marketing regulations for synthetic drugs, coupled with recent progress in stereoselective organic synthesis, resulted in a significant increase in the proportion of single-enantiomer drugs. Over 50% of the

world's top-selling drugs are single enantiomers,[2] and it has been estimated that up to 80% of all drugs currently entering development are chiral and will be marketed as single-enantiomer entities. The manufacture of single-enantiomer drugs ineluctably requires the synthesis of high-value, enantiomerically pure materials, that is, with 100% enantiomeric excess (100% ee), for construction of the final bulk active compounds.

Thus, gaining access to enantiomerically pure compounds plays a pivotal role in the development of pharmaceuticals, agrochemicals, flavors, and fragrances as well as certain other materials. Worldwide, the market for chiral fine chemicals sold as single enantiomers was $6.63 billion in 2000 and will grow at 13.2% annually to $16.0 billion by 2007. The drug industry is the engine that drives this strong growth, accounting for 81.2% of the total $6.63 billion. The remaining $1.25 billion is divided among such uses as agricultural chemicals, electronics chemicals, flavors and fragrances. The numbers look even more impressive when considered as the sale of single-enantiomer compounds made into the pharmaceutical formulations that people actually consume. In 2000, the worldwide sales of single-enantiomer compounds reached 123 billion U.S. dollars (Table 1-1).[6]

Table 1-1 Worldwide sales of single-enantiomer drugs

	SINGLE-ENANTIOMER DRUGS			
$ BILLIONS	**1999**	**2000**	**1999**	**2000**
Cardiovascular	$42.7	$46.6	$24.8	$26.9
Antibiotics/antifungals	29.3	31.7	23.9	23.9
Hormones	20.0	22.0	13.8	14.6
Cancer	13.7	15.6	9.4	10.4
Central nervous system	47.7	53.9	8.6	9.0
Hematology	16.5	15.4	8.6	9.1
Antiviral	17.7	19.1	6.2	6.5
Respiratory	36.5	40.5	5.1	6.1
Gastrointestinal	43.9	47.2	3.0	3.5
Vaccines	6.5	7.3	2.0	3.0
Ophthalmic	7.1	7.4	1.8	2.0
Dermatological	17.9	18.4	1.3	1.2
Analgesic	21.5	23.0	1.0	1.3
Other	39.0	41.9	5.5	5.6
TOTAL	$360.0	$390.0	$115.0	$123.3

SOURCE: Technology Catalysts International

1.2 Development of Asymmetric Catalysis

Because optically active compounds are very important both industrially and academically, discovery of truly efficient methods of obtaining chiral substances is a substantial challenge for synthetic chemists.

So far, a variety of ways have been developed to obtain optically pure organic compounds: (1) resolution methods including chemical resolution, chiral chromatography, kinetic resolution and so on; (2) the conversion or derivatization of readily available natural chiral compounds such as amino acids, tartaric and lactic acids, terpenes, carbohydrates and alkaloids; (3) biological transformations using enzymes, cell cultures, or whole microorganisms; (4) asymmetric synthesis using a prochiral compound as the starting material.

Earlier, enantiomerically pure compounds were primarily obtained by stoichiometric methods utilizing resolution of racemates or starting from readily accessible, naturally occurring chiral compounds. Resolutions require the use of a resolving agent to form diastereoisomers that then must be separated. This process can be quite wasteful since the undesired diastereoisomer of the racemate has to be either racemized or discarded. Recovery of the resolving agent also has to be considered. This results in the inefficient use of raw materials and the need for disposal of increased amounts of organic chemical wastes. While transformation of the chiral pool to chiral products can be limited by the availability of the inexpensive reagents that possess the correct stereochemistry and structure similarities to the final target. The scope of biochemical or biological methods using enzymes, cell cultures, or whole

microorganisms are limited on account of the inherent single-handed, lock-and-key specificity of biocatalysts. Traditional asymmetric synthesis using stoichiometric amount of a chiral compound, though convenient for small to medium-scale reactions, is practical only if the expensive chiral auxiliary deliberately attached to a substrate or reagent is readily recyclable.

The requirements for the practical asymmetric synthesis include high stereoselectivity, high rate and productivity of reaction, atom economy, cost effectiveness, operational simplicity, environmental friendliness, and low-energy consumption. The most significant advance in the past three decades has been the application of chiral catalysts to induce the conversion of achiral substrates to chiral products, which turned chemists' dreams into reality at both academic and industrial levels.[7] The obvious benefit of catalytic asymmetric synthesis is that using only a small amount of man-made chiral catalysts containing the chiral information can generate a large amount of naturally occurring or nonnaturally occurring chiral products from precursors that may be chiral or achiral. Of various possibilities, the use of chiral organometallic molecular catalysts would be the most powerful strategy for this purpose. Asymmetric catalysis is an integrated chemical approach in which the maximum chiral efficiency can be obtained only by a combination of suitable molecular design with proper reaction conditions. The chiral ligands that modify intrinsically achiral metal atoms must possess suitable three-dimensional structures and functionality, to generate sufficient reactivity and the desired stereoselectivity. Sometimes the properties of achiral ligands are also important. The chiral catalyst can permit *kinetically* precise discrimination among enantiotopic atoms, groups, or faces in achiral molecules. Similarly, enantiomeric molecules can also be

discriminated. The diverse catalytic activities of metallic species, as well as the virtually unlimited structural variation of organic ligands, provide enormous opportunities for asymmetric catalysis.

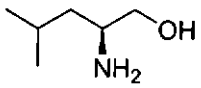
The great economic potential of asymmetric catalysis has made it one of the most extensively explored areas of research in recent years. Asymmetric catalysis has come to the fore and now provides one of the most cost-effective and environmentally responsible methods for production of a truly vast array of structurally diverse, enantiomerically pure compounds. Spectacular enantioselectivities have been obtained in numerous reactions including asymmetric hydrogenation, hydrometalation of unsaturated compounds, vicinal hydroxylation of olefins, hydroformylation, cyclopropanation, olefin isomerization, hydrosilylation, epoxidation of allylic alcohol, addition of organometallic reagents to aldehydes, allylic alkylation, Diels-Alder and ene reactions. These developments have had an enormous impact on academic and industrial organic syntheses. The manufacture of key chiral intermediates using catalytic asymmetric methods will allow provision of drugs displaying higher potencies, greater specificities, and fewer side effects, but at a lower cost to the consumers. In addition to pharmaceutical applications, catalytic asymmetric methods are being employed to a great avail in the flavor and fragrance, agrochemical, animal health, polymer, and liquid crystal industries.[8]

1.3 Development of Catalytic Asymmetric Addition Reactions of Nucleophiles to C=X Electrophiles

1.3.1 Amino Alcohols Catalyzed Asymmetric Dialkylzinc Additions to Aldehydes: A Classical Asymmetric Addition Reaction

Catalytic enatioselective addition of dialkylzinc to aldehydes is one of the most fundamental and representative catalytic asymmetric reactions. The products of this reaction, optically active secondary alcohols, are components of many naturally occurring compounds, biologically active compounds, and useful materials. They are also important as synthetic intermediates of various functionalities such halides, amine, ester and ether, etc. Owing to the tremendous efforts of a great number of researchers, the catalytic asymmetric dialkylzinc addition to aldehydes has become a mature method. Ligands with diverse structures have been obtained and high enantioselectivities for a wide range of aldehydes have been achieved.

1.3.1.1 Historical background



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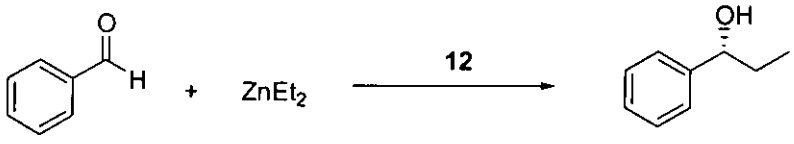
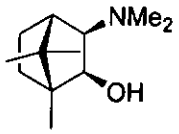


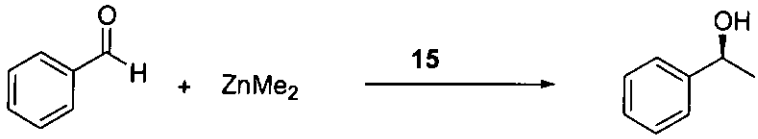
13 **14** (49% ee)

Scheme 1-1

Since the initial report of Oguni and Omi on the reaction of diethylzinc with benzaldehyde (**13**) in the presence of a catalytic amount of (*S*)-leucinal (**12**) with moderate enantioselectivity (49% ee, Scheme 1-1) in 1984,[9] research on asymmetric organozinc additions to carbonyl compounds has grown dramatically. In 1986, (−)-DAIB (**15**) was discovered by Noyori and co-workers to be the first highly enantioselective ligand for the dialkylzinc addtion to aldehyde.[10] In the presence of 2 mol% of **15**, reaction of dimethylzinc with benzaldehyde at 25–40 °C in toluene gave (*S*)-1-phenylethanol (**16**) with up to 95% ee after aqueous work up (Scheme 1-2). The catalyst system is also effective for other aromatic aldehydes, but the reaction involving aliphatic aldehydes gave only moderate enantioselectivities.



(-)-DAIB (**15**)



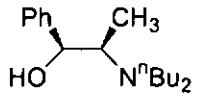
13 **16**

Scheme 1-2

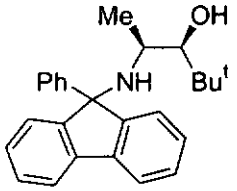
1.3.1.2 Dialkylzinc Additions to Aldehydes Promoted by Chiral Amino Alcohol Ligands

Amino alcohols constitute an important part of the chiral ligands developed for dialkyzinc additions to aldehydes. Previous studies have shown that coordination of

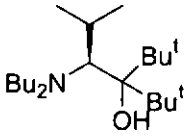
ligands to dimethylzinc converts its linear structure into an approximately tetrahedral structure, [11] which reduces the bond order of the Zn-C bond and increases the nucleophilicity of the zinc alkyl groups. Thus, chiral ligands not only control the stereochemistry of the organozinc addition, but also activate the zinc reagents. Over the past decades, a number of chiral ligands developed for the asymmetric dialkyzinc additions have been derived from amino alcohols. These compounds react with dialkylzincs to generate a zinc-based chiral Lewis acid complex which can further coordinate with both the aldehyde substrates and the dialkylzinc reagents to conduct the catalytic addition. The *in situ* generated zinc complex is therefore a multifunctional catalyst. It acts as a Lewis acid to activate the carbonyl substrates and also as a Lewis base to activate the organozinc reagents. The chiral environment of the ligand controls the stereoselectivity. Scheme 1-3 summarizes some representative amino alcohol ligands and the results obtained by these ligands in the reaction of diethylzinc addition to benzaldehyde.



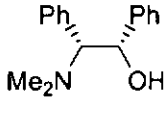
17, 92% ee[12]



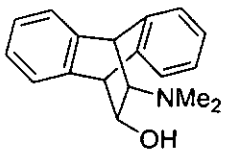
18, 97% ee[13]



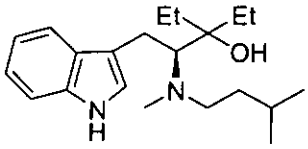
19, 97% ee[14]



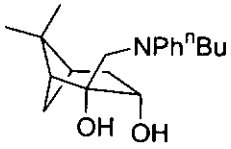
20, 97% ee[15]



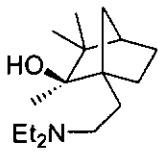
21, 96% ee[16]



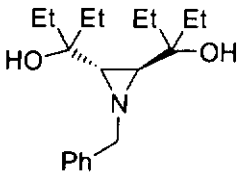
22, 94% ee[17]



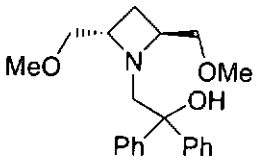
23, 88% ee[18]



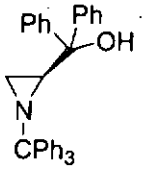
24, 88% ee[19]



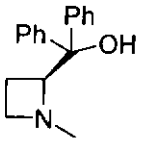
25, 91% ee[20]



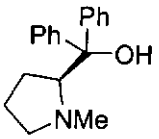
26, 99% ee[21]



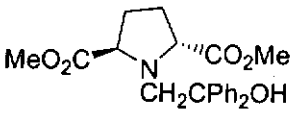
27, 98% ee[22]



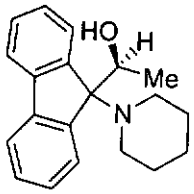
28, 92% ee[23]



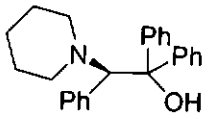
29, 93% ee[24]



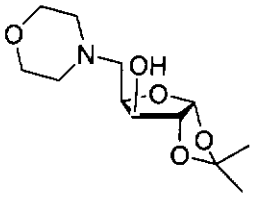
30, 91% ee[25]



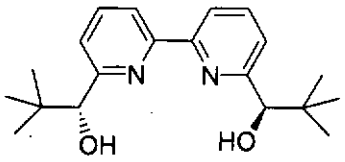
31, 98% ee[26]



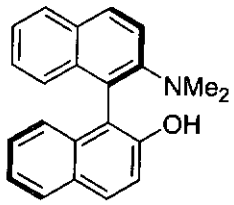
32, 96% ee[27]



33, 97% ee[28]



34, 96% ee[29]



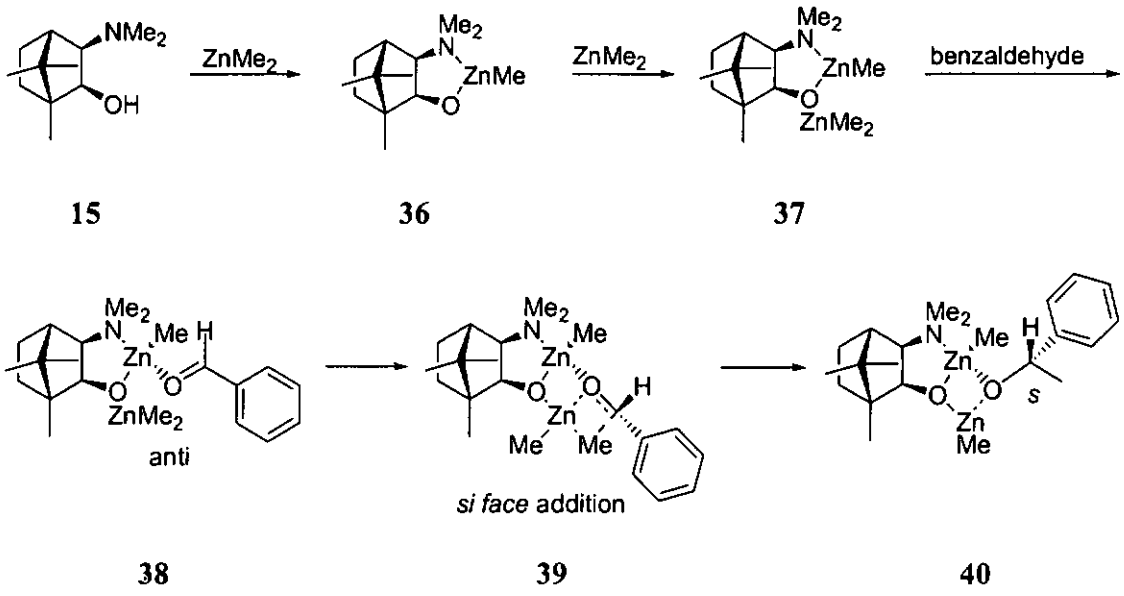
35, 98% ee[30]

Scheme 1-3 Some representative amino alcohol ligands for the reaction of diethylzinc addition to benzaldehyde.

1.3.1.3 Mechanism

Noyori and co-workers conducted extensive experimental and theoretical studies on the mechanism of the diakylzinc addition to aldehyde catalyzed by (-)-DAIB (**15**). [31], [32] Scheme 1-4 shows a proposed mechanism of dimethylzinc addition to benzaldehyde catalyzed by **15**. In the first step, **15** reacts with dimethylzinc to generate the zinc complex **36**. It was found that 1 equivalent of **36** cannot react with benzaldehyde, namely, the Zn-Me group of **36** cannot add to an aldehyde and a second equivalent of

dimethylzinc is needed. The alkoxy oxygen atom in **36** coordinates with dimethylzinc to give **37**. Coordination of benzaldehyde with **37** generates **38**. Molecular orbital and density functional calculations indicate that the anti coordination of benzaldehyde (with respect to the chiral ligand) in **38** and a 5/4/4 tricyclic transition state **39** are most favorable. In transition state **39**, methyl migrates to the *si* face of the aldehyde to form (**20**), which can react with dimethylzinc to dissociate (*S*)-(1-phenyl)ethoxy-ZnMe and regenerate **40**. Aqueous workup gives (*S*)-1-phenylethanol (**16**).



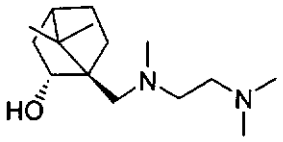
Scheme 1-4 The mechanism of the diakylzinc addition to aldehyde catalyzed by (-)-DAIB (**15**)

1.3.2 Catalytic Asymmetric Alkenylzinc Additions to Aldehydes

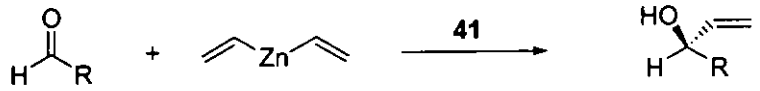
Alkenylzinc addition to aldehydes can afford the synthetically very useful allyl alcohols which are not only key intermediates for a large number of natural products and biological active compounds, but also important substrates for various reactions, such as cyclopropanation reactions, aziridination reactions, ene-reactions, epoxidations, dihydroxylations, methoxy selenations, iodo hydroxylations, brominations, and allylic substitution reactions.

Generally, three methods were used to generate alkenylzinc reagents, namely, (1) the reaction of ZnX_2 (X = Cl, Br) with alkenylmagenium reagents[33] or alkenyllithium reagents; (2) the reaction of alkyne with borane followed by boron-zinc exchange[34] and (3) hydrozirconation of alkyne followed by zirconium-zinc exchange.[35]

1.3.2.1 Addition Reactions Using Alkenyllithium or Alkenylmagnesium as Alkenyl Source



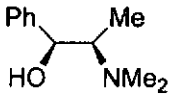
41



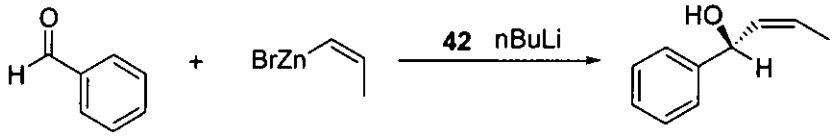
82–96% ee

Scheme 1-5

In 1988, Oppolzer and Radinov[33] used a catalytic amount of **41** to carry out the addition reaction of divinylzinc to aldehydes with 82–96% ee (Scheme 1-6). In this reaction, the divinylzinc was prepared from the reaction of the corresponding vinyl Grignard reagent with $ZnCl_2$.



42



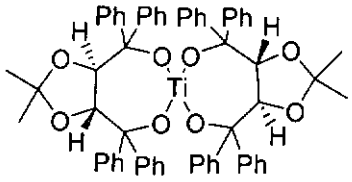
13 **43** **44**

86% ee, 68% yield

Scheme 1-6

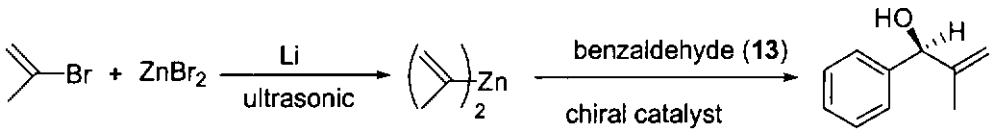
Later, the same author developed another procedure to realize the asymmetric alkenylation of aldehydes involving vinylzinc bromide (**43**) which was prepared from lithiation of pure (*Z*)-1-bromo-1-propene with lithium metal in Et_2O followed by transmetallation with $ZnBr_2$.[36] As shown in Scheme 1-6, the addition of **43** to benzaldehyde (**13**) in the presence of a stoichiometric amount of lithium salt of ligand **42** gave (*Z*, *S*)-(1-propenyl)benzenemethanol **44** with 86% ee and 68% yield.

In 1992, the titanium TADDOLate **45** was used by Seebach et al. to catalyze the reaction of divinylzinc prepared from Grignard reagent with benzaldehyde to give 84% ee.[37]



45

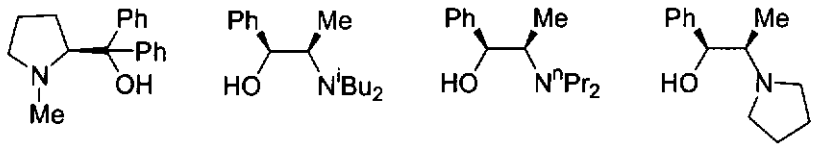
In 1999, Soai et al reported enantioselective catalytic isopropenylation of aldehydes using diisopropenylzinc as addition reagent.[38] Diisopropenylzinc **46** was prepared by the reaction between zinc bromide, isopropenyl bromide and lithium under ultrasonic condition followed by extraction and sublimation.



46 **47**

80–90% ee

Scheme 1-7



29 **48** **49** **50**

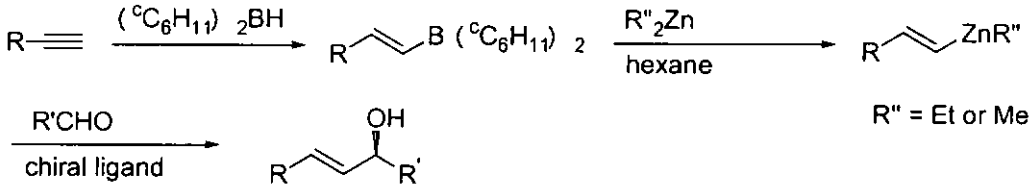
The amino alcohols **29**, **48**, **49** and **50** were used to catalyze the reaction of diisopropenylzinc (**46**) with benzaldehyde (**13**) to generate the allyl alcohol **47** with 80–90% ee (Scheme 1-7). Ligands **29** and **48** were found to be the best among these compounds and then were also used to catalyze the addition of other aldehydes with 73–92% ee (Table 1-2).

Table 1-2 Diisopropenylzinc addition to aldehydes catalyzed by ligand **29** or **48**[a]

Entry	Aldehyde	Ligand	Time (h)	Yield (%)	ee (%)
1[b]	*p*-chlorobenzaldehyde	**29**	3	67	87
2	*p*-chlorobenzaldehyde	**48**	2	84	89
3	*p*-methoxybenzaldehyde	**29**	3	50	82
4	*p*-methoxybenzaldehyde	**48**	2	68	92
5	1-naphthaldehyde	**48**	2	85	79
6	cinnamaldehyde	**48**	2	75	73
7	3-phenylpropionaldehyde	**48**	2	81	73

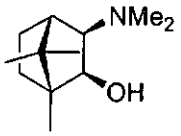
[a] The reactions were carried out in toluene at 0 °C in the presence of 5 mol % of the catalysts and 3 equiv of diisopropenylzinc unless indicated otherwise.[b] Hexane was used as the solvent.

1.3.2.2 Addition Reactions Using Alkenylborane as Alkenyl Source

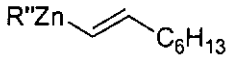


Scheme 1-8

In 1992, Oppolzer reported the asymmetric addition of alkenylzinc reagents to aldehydes, in which, alkenylzinc reagents were prepared by reaction of alkyne with borane followed by boron- zinc exchange[34] (Scheme 1-8). By using the amino alcohol **15**, good enantioselectivity (73-94% ee) was achieved in the reaction of alkenylzinc reagent **51** addition to certain aromatic and aliphatic aldehydes (Table 1-3).



15



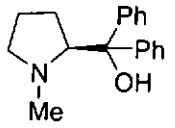
51

Table 1-3 Ligand **15** catalyzed addition of alkenylzinc **51** to aldehydes[a]

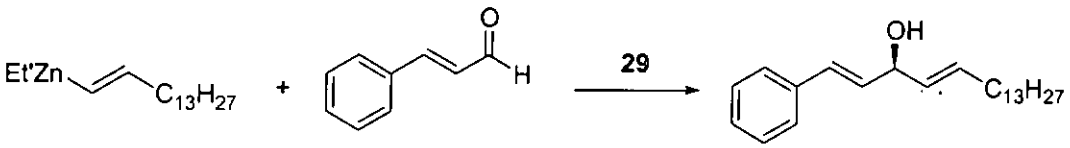
Entry	R''_2Zn	Aldehyde	Yield (%)	ee (%)
1	Et_2Zn	benzaldehyde	77	92
2	Me_2Zn	benzaldehyde	85	94
3	Et_2Zn	propionaldehyde	91	84
4[b]	Et_2Zn	propionaldehyde	86	86
5	Me_2Zn	valeraldehyde	85	80
6	Et_2Zn	isovaleraldehyde	78	85
7	Et_2Zn	cyclohexanecarboxaldehyde	70	91
8	Et_2Zn	trimethylacetaldehyde	28	73

[a] The additions to aldehydes were carried out in hexane at 0 °C in the presence of 1 mol % of **15** unless indicated otherwise. [b] 5 mol % of **15** was used.

Soai et al. used the amino alcohol **29** to catalyze the reaction of alkenylzinc **52** with cinnamaldehyde (**53**) to provide **54** with 77% ee. The zinc reagent was prepared from the boran-zinc exchange reaction (Scheme 1-9).[39]



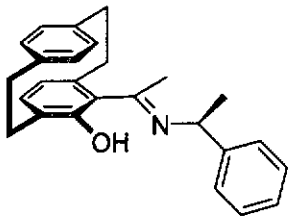
29



52 **53** **54**

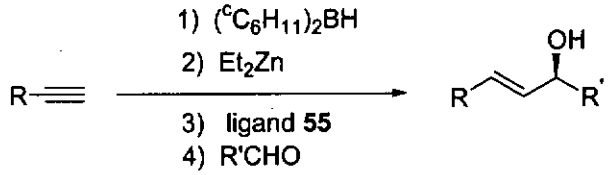
Scheme 1-9

In 2001, Bräse et al reported the application of planar and central chiral [2,2]-paracyclophane-based *N,O*-Ligands in alkenylzinc additions to aldehydes.[40] Among these paracyclophane ligands, **55** gave the best enantioselectivity. The reagents of the asymmetric addition of alkenylzinc reagents to aldehydes with 2 mol % of ligand **55** is illustrated in Table 1-4. Electron-withdrawing substituents on aromatic aldehydes are well tolerated and lead to increased enantioselecivity of 97% ee for *p*-chlorobenzaldehyde (entry 2). The electron-rich *p*-methoxybenzaldehyde, also provided a very good ee of 91% although with a diminished yield of 62% (entry 3). Especially, high levels of enantioselection were achieved when α-branched aliphatic aldehydes were applied as substrates in this reaction system.



55

Table 1-4 Ligand **55** catalyzed alkenylzinc addition to aldehydes[a]

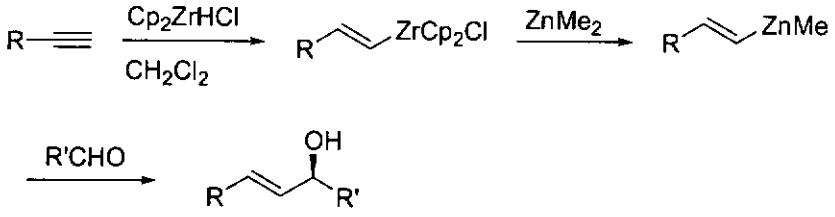


Entry	Alkyne	Aldehyde, R' =	Yield (%)	ee (%)
1	1-octyne	phenyl	71	86
2	1-octyne	4-Cl-phenyl	88	97
3	1-octyne	4-MeO-phenyl	62	91
4	1-octyne	cyclohexyl	80	>98
5	1-octyne	*tert*-butyl	89	>98
6	3-hexyne	phenyl	86	75
7	*tert*-butyl ethyne	4-Cl-phenyl	78	64
8[b]	*tert*-butyl ethyne	4-Cl-phenyl	88	89

[a] In the presence of 2 mol % of chiral ligand **55** at –30 °C. [b] Dimethylzinc was used instead of diethylzinc.

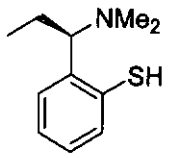
1.3.2.3 Addition Reactions Using Alkenylzirconium as Alkenyl Source

Wipe and Xu developed a method to prepare alkenylzinc reagents by treatment of terminal alkynes with Cp_2ZrClH followed by exchanging with Me_2Zn (Scheme 1-10).[35]



Scheme 1-10

Later, Wipe and Ribe discovered that the alkenylzinc reagents underwent moderate to highly enantioselectivity additions to aldehydes in the presence of the amino thiol **56** (Table 1-5) [37].



56

Table 1-5 Ligand **56** catalyzed alkenylzinc addition to aldehydes[a]

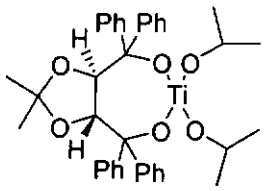
Entry	R of alkyne	Aldehyde	Yield (%)	ee (%)
1	*n*-C_4H_9	*p*-chlorobenzaldehyde	83	97
2	*n*-C_4H_9	*p*-trifluoromethylbenzaldehyde	71	93
3	*n*-C_4H_9	*p*-methoxybenzaldehyde	75	63
4	*n*-C_4H_9	*m*-methoxybenzaldehyde	79	99
5	*n*-C_4H_9	cyclohexanecarboxaldehyde	63	74
6	*n*-C_4H_9	3-phenylpropionaldehyde	71	64
7	$(CH_3)_3C$	benzaldehyde	73	83
8	3-hexyne	benzaldehyde	66	99
9[b]	TIPSOC(O)CH_2CH_2	benzaldehyde	67	92

[a] The additions to aldehydes were carried out in toluene at -30 °C in the presence of 10 mol % of **56**. [b] TIPS = triisopropylsilyl.

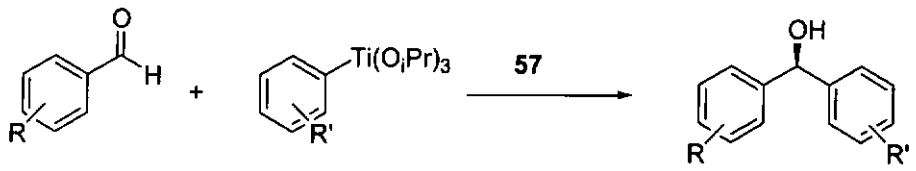
1.3.3 Catalytic Asymmetric Aryl Addition to Aldehydes

1.3.3.1 Original Study

Enantioselective aryl addition to aldehydes can afford useful chiral secondary alcohols including chiral diarylmethanols which are important intermediates for the synthesis of biologically and pharmaceutical active substances.



57

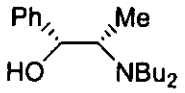


58

Scheme 1-11

Whereas a stoichiometric enantioselective aryl transfer onto aldehydes was reported by Seebach et al. as early as 1985,[41] it took until 1994 before a catalyzed version of this reaction, which employed titanium-TADDOLate complex (**57**) as the chiral catalyst, was described by the same group.[42] The aryltitanium reagents (**58**), which were used as the aryl sources, were prepared by treatment of the appropriate aryl Grignard or aryllithium reagents with chlorotriisopropoxytitanium (Scheme 1-11). Since the inorganic magnesium/lithium salts had a detrimental effect on the catalysis, they had to be removed

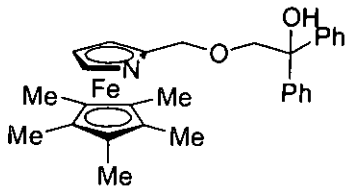
by centrifugation followed by filtration. The resulting soluble titanium reagents were then applied to the catalyzed aldehyde additions. By using phenyl derivative **58** (R=H), both electron-poor and electron-rich aromatic substrates showed remarkable levels of enantioselection (up to 96 % ee).



17

An alternative asymmetric transfer of an aryl group to an aldehyde was described by Soai et al., who reported on the use of a zinc species generated in situ from zinc dichloride and phenylmagnesium bromide.[43] Excess of stoichiometric amounts of *N,N*-dibutylnorephedrine (**17**) served as the chiral modifier giving enantiomerically enriched products with up to 82 % ee.

Unlike the dialkylzinc addition which proceeds extremely slowly in the absence of a catalyst, the diphenylzinc addition to aldehydes can take place smoothly even without a catalyst. This background reaction makes it more challenging to develop enantioselective catalysts for the arylzinc additions. The use of diphenylzinc in asymmetric aldehyde additions was first decribed by Fu and co-workers.[44]



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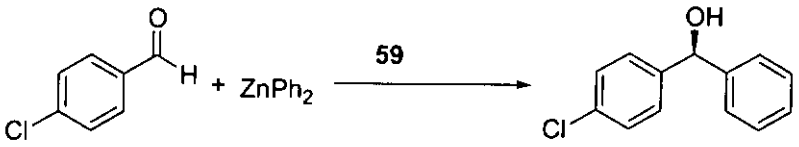


60 **61** **62**

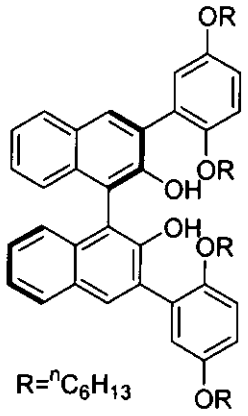
Scheme 1-12

In an asymmetric catalysis using 3 mol % of chiral azaferrocene (**59**) the reaction of 4-chlorobenzaldehyde (**60**) with diphenylzinc (**61**) afforded the corresponding diarylmethanol **62** with 57 % ee in nearly quantitative yield at room temperature (Scheme 1-12). The report by Fu and co-workers initiated intense research in this area and shortly thereafter two other catalytic asymmetric arylation of aldehydes were described which relied on structurally very different ligands.

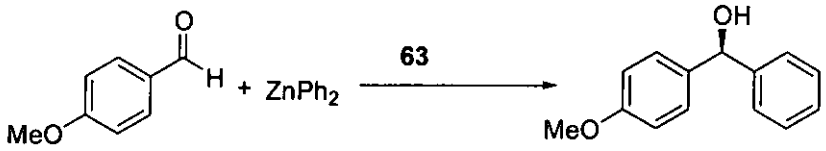
1.3.3.2 Addition Reactions Catalyzed by Ligands Containing Axial-Chirality

In 1999, Huang and Pu found that the chiral binaphthyl ligand (*R*)-**63**, a highly enantioselective catalyst for dialkylzinc additions,[45,46] was also highly enantioselective for the diphenylzinc addition to aldehydes (Scheme 1-13).[47] Because of the competitive background reaction, a low ee was observed when a 5 mol % of (*R*)-**63** was used (entry 3, Table 88). When a larger amount of (*R*)-**63** was pretreated with diethylzinc, the resulting chiral zinc complex catalyzed the reaction of diphenylzinc with *p*-methoxybenzaldehyde

64 to generate (*R*)-*p*-methoxyphenyl phenyl carbinol (**65**) with up to 93% ee and 84% yield at -30 °C in toluene.



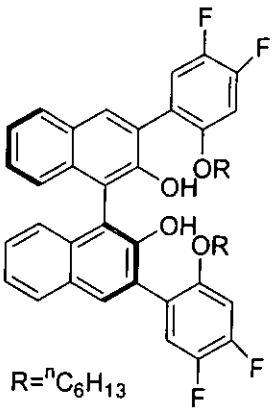
63



64 **65**

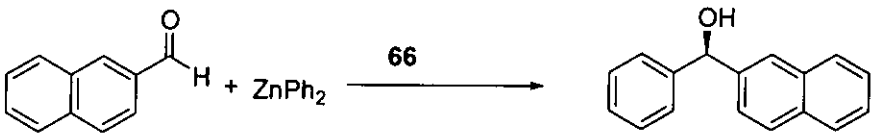
Scheme 1-13

The factors that influence the enantioselectivity of these reactions are summarized as follows. (1) Pretreatment of the chiral ligand (*R*)-**63** with diethylzinc generally increased the enantioselectivity. (2) Reducing the concentration of the substrates in the reaction led to dramatically increased enantioselectivity. (3) In the case of unsaturated aldehyde, such as cinnamaldehyde addition of methanol might have modified the structure of the catalyst formed from the reaction of (*R*)-**63** with diethylzinc, leading to a much improved enantioselectivity.



66

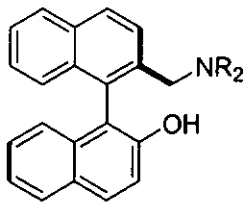
Ligand (*S*)-**66** was used to catalyze the reaction of various aryl aldehydes with diphenylzinc for the synthesis of optically active diarylcarbinols (Scheme 1-14).[48] Unlike (*R*)-**63** which required a longer reaction time and 0° C in some cases as well as very different reaction conditions for different substrates in order to achieve high enantioselectivity, (*S*)-**66** catalyzed the reaction of various aryl aldehydes with diphenylzinc at room temperature in methylene chloride in 5 h with high enantioselectivity. For example, the reaction of 2-naphthaldehyde **67** catalyzed by (*R*)-**63** took 4 days at -10 °C with incomplete conversion and gave **68** in 66% isolated yield. However, in the presence of (*S*)-**66**, this reaction was completed in 5 h at room temperature with 90% isolated yield.



67 **68**

Scheme 1-14

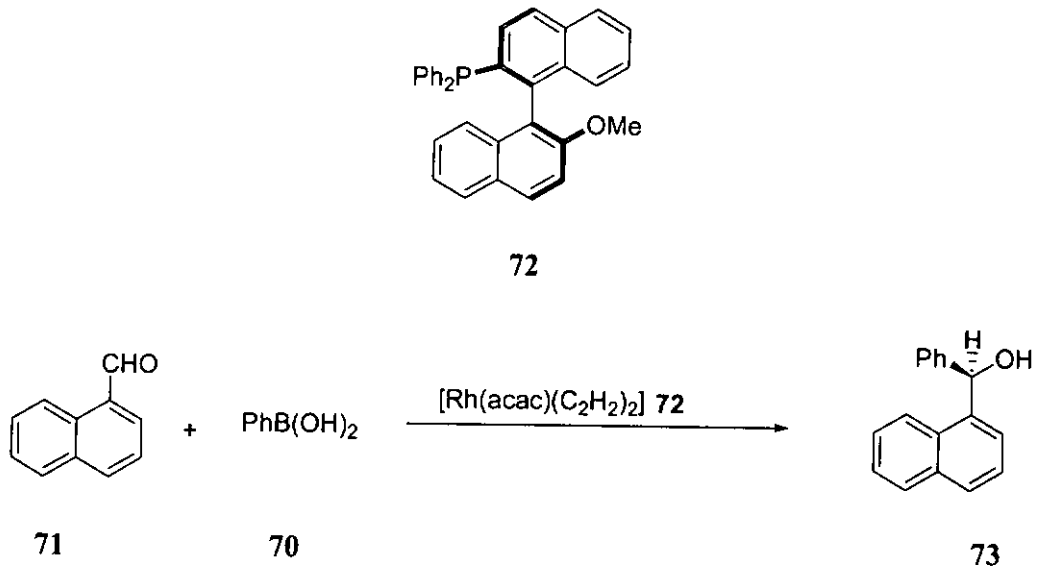
As we had mentioned, enantioselective addition of diphenylzinc to aldehydes is more challenging on account of the rapid competitive uncatalyzed phenylation and one of the methods to suppress the undesired background reaction is to use a mixture of diphenylzinc and diethylzinc. Ha et al synthesized compound **69**, a binaphthyl-based axially chiral amino alcohol and found it is a highly efficient ligand for the phenylation of aldehydes using diphenylzinc only.[49]



69

Various aromatic and aliphatic aldehydes were studied for the phenylation with 10 mol % of **69** at 0 °C. Excellent yields and enantiomeric excesses were accomplished with aromatic aldehydes, and moderate enantioselectivities were obtained for α, β-unsaturated and aliphatic aldehydes. Use of the mixture of diphenylzinc and diethylzinc gave similar enantioselectivity, but with much decreased isolated yield.

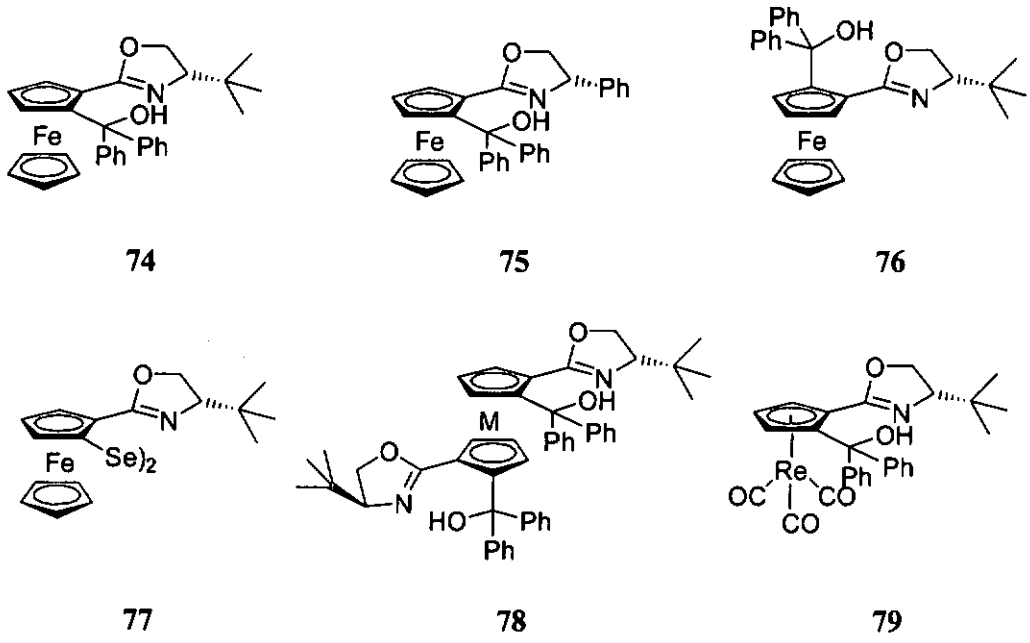
Arylboronic acid were also applied as aryl source in the asymmetric aryl transfer reactions to aldehydes. In 1998, Miyaura and co-workers described an asymmetric 1,2-addition of phenylboronic acid (**70**) to 1-naphthaldehyde (**71**) using (*S*)-MeO-MOP (**72**) as a chiral ligand and only a moderate enantioselectivity (47% ee) of **73** was achieved (Scheme 1-15).[50]



Scheme 1-15

1.3.3.2 Addition Reactions Catalyzed by Ligands Containing Planar-Chirality

At the same time, Bolm and Muñiz described a catalyst system based on the chiral ferrocene **74** and **75** (Scheme 1-16).[51] The use of 5 to 10 mol % of the catalyst in toluene at 0 °C led to a smooth addition of diphenylzinc to various aldehydes to give secondary alcohols with good enantioselectivities. Aromatic substrates afforded synthetically interesting diarylmethanol compounds with up to 88 % ee. In addition, a range of aliphatic aldehydes were converted into the corresponding enantiomerically enriched benzyl alcohols with enantioselectivities of up to 75 % ee. Asymmetric amplification studies illustrated that the actual catalytic species was monomeric. It is again important to note that the absolute stereochemistry of the product suggested an analogous reaction path as in the related diethylzinc addition with **74**, which had been investigated by the same authors earlier.[52]

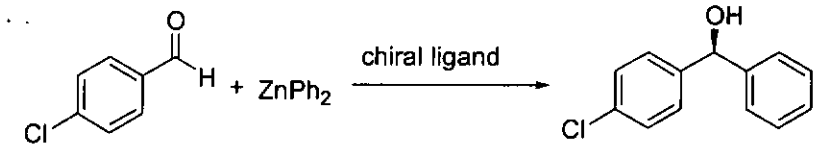


74 **75** **76**

77 **78** **79**

Scheme 1-16

Ferrocene **74** is *S* configured at the stereogenic center and has an R_p configuration at the plane of chirality.[53] Comparative studies with its S,S_p-configured diastereomer **76** revealed how well-balanced the stereogenic elements of the ligand had to be in order to achieve high enantioselectivity.[54]



60 **62**

Scheme 1-17

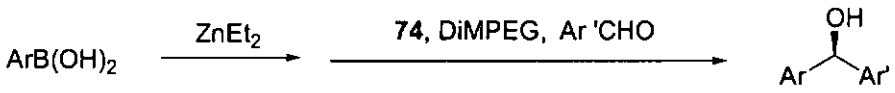
Thus, the addition of $ZnPh_2$ to aldehyde **60** in the presence of the ferrocene **76** gave diarylmethanol **62** with only 9 % ee (Scheme 1-17).[55] This result was again attributed to the significant uncatalyzed background reaction between $ZnPh_2$ and the aldehyde giving

a racemic product. As had previously been shown in alkylation reactions,[56] the relative rate enhancements by the two diastereomers **74** and **76** are distinctively different and the competitive unselective background reaction therefore becomes more important in the catalysis with the less active catalyst **76** and leads to a reduction in the enantiomeric excess of the final product.

Efforts to overcome the problem of the parallel unselective addition of $ZnPh_2$ led to the development of an improved protocol, which relied on a modified phenyl transfer reagent. Thus, when isolated $ZnPh_2$ was replaced by a zinc reagent formed in situ by combining $ZnPh_2$ with $ZnEt_2$ in a ratio of 1:2, the enantioselectivity of the aryl transfer catalyzed by **74** was significantly improved to 90-98 % ee for a wide spectrum of substrates.[57] Three more aspects are particularly noteworthy: Firstly, the reaction temperature could be raised from 0 to 10 °C without loss of enantioselectivity. Secondly, *ortho* substituents were better tolerated in aromatic aldehydes. For example, compounds such as 2-bromobenzaldehyde gave greatly improved enantioselectivities (91 versus 73 % ee). Thirdly, the amount of the relatively expensive diarylzinc reagent $ZnPh_2$ was reduced to 0.65 equivalents (versus 1.5 equiv), which indicates that both phenyl groups could now be activated and then transferred to the aldehydes, while the product alcohols were still obtained in almost quantitative yields.

Under these improved conditions the less-active S,S_p-configured ferrocene **76** directed the addition of the modified phenylzinc reagent to 4-chlorobenzaldehyde **60** and yielded **62** with 68 % ee rather than 9 % ee as before. Using a 1:1 mixture of the diastereomeric ferrocenes **74** and **76** gave (*R*)-**62** with 91 % ee.[55]

Early attempts to improve the activity and enantioselectivity of the catalysts led to the development of other metallocenes such as ferrocenes and ruthenocenes **77** and **78**.[58,59] Although in several reactions a good asymmetric induction in the aryl transfer was achieved, the overall catalyst performance was at best equal to that of ferrocene **74**. Other metal catalysts were prepared and tested, and, finally, a major breakthrough was achieved by the introduction of cyrhetrene **79**.[60] The enantioselectivities in the phenyl transfer to aldehydes were further improved and *ee* values of up to 99 % were reached in the formation of diarylmethanols by application of 2-10 mol % of this chiral Re complex. Furthermore, the use of **79** enabled the reaction to be carried out with a decreased catalyst loading; the enantiomeric excesses remained remarkably high even with less than 5 mol % of **79**. For example, use of only 2 mol % of **79** gave **62** with 96 % ee, as compared to the previously obtained 97 % ee with 10 mol % of **74**.[57] Clearly, cyrhetrene **79** is an outstanding catalyst for the transfer of a phenyl group to an aldeyde.



Scheme 1-18

In 2002, Bolm et al. developed a new reaction system for aryl addition to aldehydes using arylboronic acid as aryl source and compound **74** as chiral ligand (Scheme 1-18).[61] In this case, the transmetalation required harsh reaction conditions, and the procedure involved stirring of a toluene solution of arylboronic acid in the presence of a 3-fold excess of $ZnEt_2$ at 60 °C for 12 h prior to the catalysis. A enhancement of product's ee's was observed when 10 mol% DiMPEG (M = 20000 g·mol^{-1}) was added to the reaction

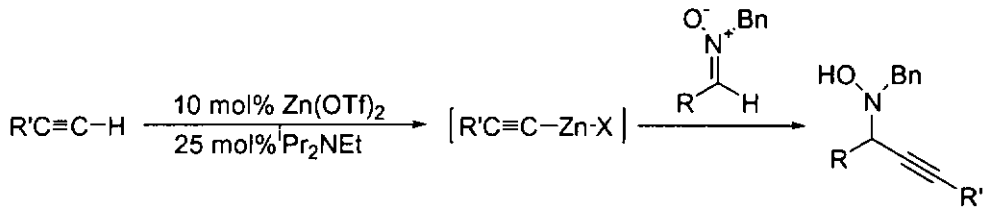
mixture. A variety of arylphenylmethanols were achieved by this new reaction system with ee values of up to 98% (Scheme 1-18).

1.3.4 Catalytic Direct Additions of Terminal Alkynes to C=O and C=N Electrophiles

The discovery and study of new stoichiometric and catalytic reactions that lead to C-C bond formation by additions to C=O or C=N are of fundamental importance in the continuing development of efficient processes for chemical synthesis. Metalated terminal alkynes are an ideal class of versatile nucleophiles that add to a wide range of electrophiles, affording adducts of great synthetic versatility. The alkynilides typically employed in such processes are commonly prepared from an acetylene and organolithium (i.e., BuLi)[62] or organomagnesium bases (i.e., EtMgBr).[63] Because the aldehydes and imines used are incompatible with such basic and nucleophilic reagents, alkyne deprotonation must necessarily be carried out as a separate step. The ability to carry out nucleophilic additions of alkynes to C=O or C=N without the use of such strong, pyrophoric, stoichiometric bases would lead to great simplification of the processes. Of greater importance, the *catalytic* generation of reactive transition-metal alkynilides from the corresponding terminal alkyne in *situ* under conditions that are compatible with electrophilic reaction partners would provide fresh avenues for the development of new, efficient asymmetric processes leading to C-C bond formation.

1.3.4.1 Direct Additions of Terminal Alkynes to C=N Electrophiles

In 1999, Carreira et al. reported a direct addition reaction of terminal alkynes to nitrones in the presence of both catalytic transition-metal and base, 10 mol % $Zn(OTf)_2$ in combination with 25 mol % $^{i}Pr_2NEt$, under mild conditions (23 ° C) (Scheme 1-19).[64]

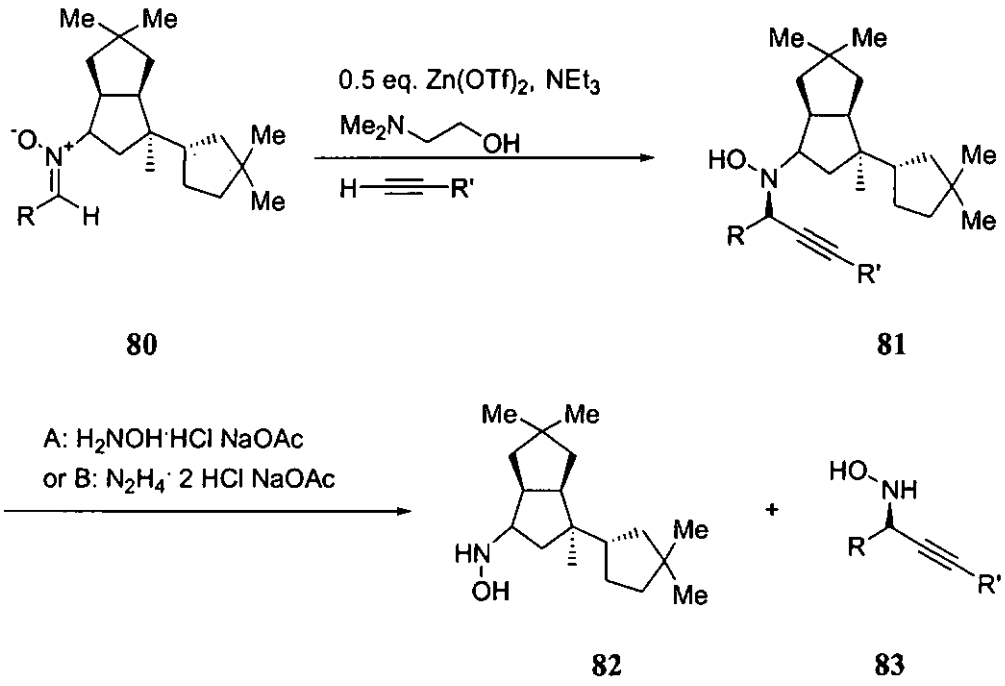


Scheme 1-19

In this attempt to induce alkynes to nitrones, lack of reactivity was observed with other metal salts such as $Mg(OTf)_2$, $Mn(OTf)_2$, $ZnCl_2$, or ZnI_2 and marginal success was accomplished utilizing $Sn(OTf)_2$. The reaction is observed to work well with *N*-benzyl nitrones and a broad range of terminal acetylenes including enynes, trimethylsilyl acetylene, propargyl trimethylsilane, as well as propargyl bromide. In general, nitrones derived from aliphatic aldehydes are more reactive than the corresponding aromatic counterparts. The process contrasts the existing more conventional methods for nucleophilic additions which require generation of the alkynilide by treatment with strong bases.

Later, Carreira et al. developed a asymmetric version of direct addition of terminal alkynes to nitrones (Scheme 1-20).[65] The method prescribes the use of nitrones **80** which are conveniently prepared through condensation of the corresponding aldehydes and a mannose-derived glycosidic N-hydroxylamine. Reaction of the **80** with terminal acetylenes in the presence of Zn (II) ions, 2-dimethylaminoethanol, and NEt_3 gives adducts **81** in high diastereoselectivity and yield. The additions can be carried out on a wide variety of branched, unbranched, aromatic, and C-substituted nitrones as well as with an equally broad range of terminal alkynes. Following its addition, the auxiliary **82**

is easily removed by treatment of the products with N-hydroxylamine hydrochloride; a process which allows for re-isolation and reuse of the auxiliary.



80 **81**

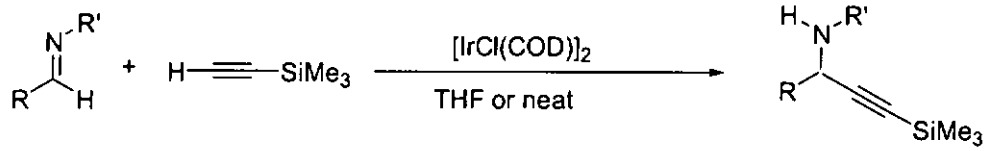
82 **83**

Scheme 1-20

The method provides access to a large range of *N*-hydroxylamines **83** in optically active form for the first time. Such compounds are of increasing importance in medicinal chemistry, where the corresponding hydroxamic acids, for example, have been shown to possess potent broad-spectrum activities against matrix metalloproteases and tumor necrosis factor α(TNF-α) converting enzymes.[66]

Propargylic amines can serve as important building blocks for organic synthesis. However, reliable methods that provide access to propargylic amines are few. On the other hand, in general, imine addition reactions typically require the use of stoichiometric quantities of alkali, alkaline earth, or transition metal carbanions, or alternatively

organoboranes, -silanes, or -stannanes. In 2001, Carreira et al report a novel process that is considerably simplified over previously documented C=N addition reactions (Scheme 1-21),[67] proceeding at room temperature and requiring only *N*-alkyl or *N*-aryl aldimines, trimethylsilylacetylene, and catalytic amounts (4-5 mol %) of $[IrCl(COD)]_2$ (Scheme 1-21).

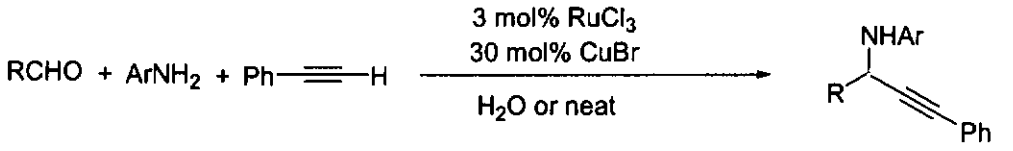


54-83 % yield

Scheme 1-21

It is worth noting that the Ir(I) catalyst is a commercially available, air-stable, and easily handled complex. Moreover, the additions can be carried out in the absence of solvent, providing for a highly atom-economical process.

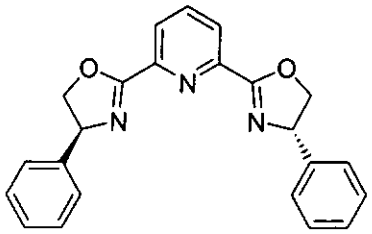
Another catalytic method for alkynylation of imine was developed by Li et al. in 2002 (Scheme 1-22).[68] They reacted imines, which were readily accessible by the *in situ* condensation of aldehydes with anilines, with phenylacetylene and found that the desired addition product was formed in high yields by using Cu/Ru catalysts in water. This catalytic system could be applied to a broad range of substituted aromatic imines and aliphatic imines to afford the corresponding propargyl amines in high yields. In a few cases, the imines were found to be prone to hydrolysis in water and the yields of the products were significantly reduced. However, in these cases, the imine additions were highly effective under solvent-free conditions.



64-96 % yield

Scheme 1-22

During their investigation, it was observed that copper salt alone also provided the desired product albeit in low conversions. By using $RuCl_3$ (3 mol%) as a co-catalyst, the yield of the desired product was dramatically increased (from 30% to 90%). However, no imine addition product was observed with $RuCl_3$ alone as the catalyst. Among the catalysts being tested, copper salts such as CuCl, $CuCl_2$, CuBr, CuI, and CuO all showed catalytic activities, with $CuSO_4$, CuCN, and $Cu(OAc)_2$ being less effective. The best yield of the addition product was obtained with CuBr as the catalyst. During these investigaton, the auther hypothesized that, although it is a disappointment at first glance, the low conversion by using only copper salt as the catalyst may in fact provide a opportunity to develop highly efficient enantioselective alkyne-imine additions.



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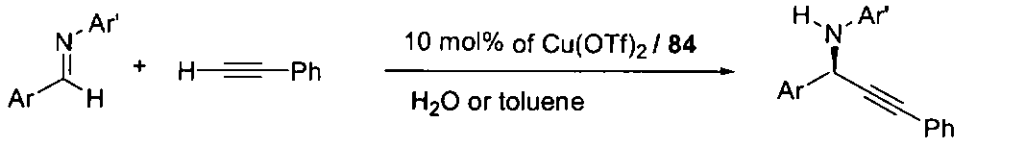
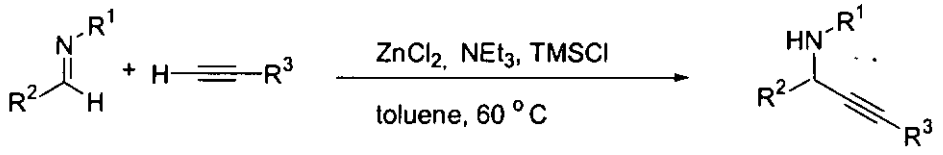


48-93 % yield, 78-96 % ee

Scheme 1-23

They examined a variety of chiral compounds as ligands in the addition reaction of phenylacetylene with *N*-benzylideneaniline with 10 mol % of CuBr and Cu(OTf) as the catalysts and found that high ee's and chemical yields could be achieved by using the combination of $Cu(OTf)_2$/ pybox **84** (Scheme 1-23).[69] The reactions in toluene provided slightly higher yields and enantioselectivities than in water. A variety of substituted aromatic imines were also used as substrates to afford the corresponding chiral propargyl amines in high ee's and yields in this reaction system.



60-93 % yield

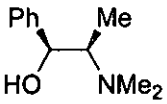
Scheme 1-24

In 2003, Jiang et al. reported the direct addition of terminal alkynes to imines in the presence of $ZnCl_2/Et_3N$ (Scheme 1-24).[70] It was found that after the addition of an activator, namely chlorotrimethylsilane, the reaction was dramatically improved. The addition of a terminal alkyne to imines either derived from alkyl or aryl aldehydes could be proceeding smoothly to give the desired propargyl amines in high yields when 1.5 eq. of chlorotrimethylsilane was added to the reaction mixture.

1.3.4.2 Direct Additions of Terminal Alkynes to C=O Electrophiles

Chiral secondary propargylic alcohols are versatile, useful building blocks for asymmetric synthesis and their utility is amply demonstrated in numerous elegant syntheses. In 2000, Carreira et al. report a facile synthesis of optically active propargylic

alcohols by direct coupling of aldehydes with a wide range of terminal alkynes in the presence of *N*-methylephedrine **42** as a chiral additive (Scheme 1-25).[71]



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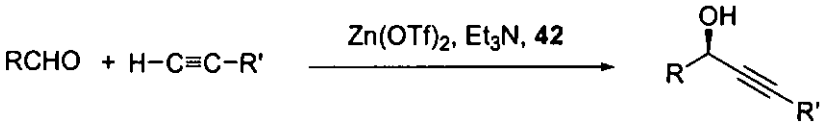


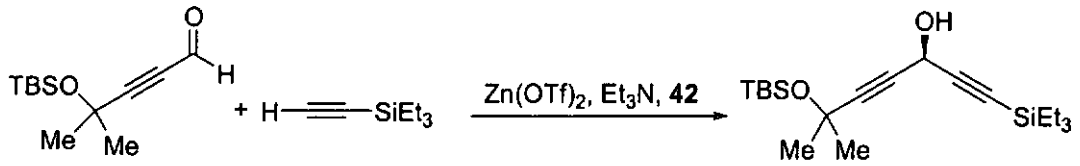
Scheme 1-25

Treatment of a solution of an aldehyde and alkyne in toluene with 1.1 equiv $Zn(OTf)_2$, 1.2 equiv each of Et_3N and (+)-*N*-methylephedrine **42** in toluene at 23 °C in 2-20 h furnishes adducts in up to 99% ee in good yields. The procedure is remarkably insensitive to the more capricious reaction variables such as solvent, concentration, and reaction atmosphere. After the reaction is complete, the (+)-*N*-methylephedrine **42** can be easily separated from the adducts by simple aqueous extraction (acid wash). It could be subsequently recovered following extraction of the alkaline aqueous layer.

Later, a catalytic version of this reaction was developed.[72] In the presence of 20 mol% of $Zn(OTf)_2$, 22 mol% of (+)-*N*-methylephedrine **42** and 50 mol% of Et_3N, a variety of optically active propargylic alcohols in up to 99% ee were achieved at 60° C by the direct addition of alkynes to aldehydes. This is the first time that Zn-carbanions have been added enantioselectively to aldehydes using *truly catalytic* amounts of metal.

To maximize the practicality and efficiency of the catalytic reaction, the auther subsequently embarked on a study aimed at examining whether alkyne addition could be

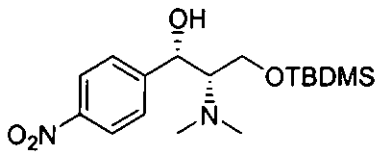
conducted in the absence of solvent. In this respect, excellent yields and enantioselectivities were achieved in a reaction mixture consisting of 1.0 equiv of aldehyde and 1.05 equiv of alkyne along with catalytic quantities of Zn(II), amine, and ligand. A number of observations which attest to the advantages of the solvent-free system are worth noting: first, unlike the reaction in toluene, the solvent-free reaction did not require the prescribed 2 h mixing period (Zn, ligand, and amine) to form the active complex, therefore reducing the overall time required for the reaction, and second, aqueous workup could be obviated, as direct transfer of the contents of the reaction vessel onto a column of silica yielded, after the chromatographic purification, analytically pure chiral propargyl alcohol adduct.



85 **86** **87**

Scheme 1-26

Moreover, it is possible to access optically active dialkynyl methanols using the catalytic addition reaction (Scheme 1-26). The addition of alkyne **86** to alkynal **85** furnished alcohol **87** in 89% ee. Such alcohols in which the ends of the alkynes are differentiated provide ideal building blocks that can be extensively synthetically elaborated, not only for use in traditional total synthesis but also for materials application.[73]



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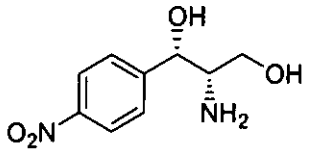
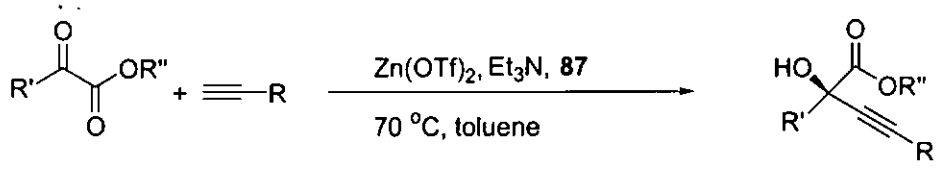


88

Scheme 1-27

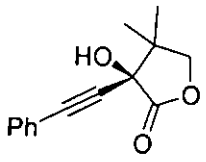
A new chiral amino alcohol-based ligand, (1*S*, 2*S*)-2-*N*,*N*-dimethylamino-1-(*p*-nitrophenyl)-3-(*t*-butyldimethylsilyloxy)propane-1-ol, **87**, was developed by Jiang et al for the direct alkynylation of aliphatic and aromatic aldehydes (Scheme 1-27). In the presence of stoichiometric or catalytic amounts of $Zn(OTf)_2$/ligand/Et_3N, the corresponding propargylic alcohols can be prepared in high yields with up to 99% ee. The precursor of ligand, inexpensive (1*S*,2*S*)-2-amino-3-(*p*-nitrophenyl)propane-1,3-diol (**88**), is obtained from chloramphenicol synthesis (its (1*R*,2*R*)-enantiomer can be obtained from the same source), and has been used in the resolution of racemic chrysanthemic acid on an industrial scale.[74] However, it has never been used in a catalytic asymmetric reaction.



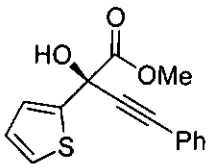
Scheme 1-28

The same auther reported that ligand **87** can also be used to catalyze the enantioselective addition of zinc alkynylide to α-ketoester to prepare chiral tertiary *α*-hydroxy-*β*-ynyl ester (Scheme 1-28).[75] A variety of *α*-hydroxyl *β*-ynyl esters (Scheme 1-29), such as **89-92** , were obtained in high ee's from this new reaction and these highly

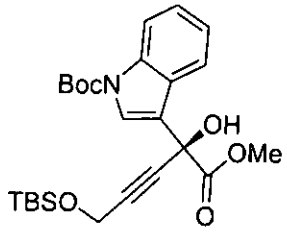
functional α-hydroxyl β-ynyl esters are valuable chiral synthons for the further preparation of complex chiral compounds.



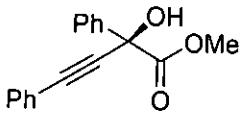
89, 93.5% ee



90, 73% ee



91, 81% ee



92, 89% ee

Scheme 1-29

1.4 The Aim and Objective of This Project

Catalytic asymmetric addition reactions of different nucleophiles to C=O and C=N electrophiles are important processes in asymmetric synthesis due to the intrinsically efficiency of such reactions in the production of a wide range of valuable enantiomerically pure compounds since a new chiral center and a new carbon-carbon bond are established in a single operation. The quest for efficient catalytic systems and chiral ligands plays a crucial role in expanding the utility of this strategy.

Up to now, catalytic asymmetric addition reactions employing enolsilanes (aldol addition), allyl-stannanes (allylation), and dialkylzinc (alkylation) have proved to be remarkably effective and products with excellent enantiomeric excesses have been achieved for different types of C=O and C=N electrophiles. However, compared to the above well-established reactions which have even reached the status of test reactions for novel ligand designs, catalytic asymmetric alkenyl, phenyl and alkynyl transfer to carbonyl and imine compounds are substantially less developed in spite of their importance in organic synthesis.

There are two main reasons for the lack of efficient versions of these synthetically very useful processes: the synthesis of suitable transfer reagents is often difficult and effective chiral catalysts are relatively rare.

Recently, a method of preparation of alkenylzinc reagents by the reaction of alkyne with borane followed by boron- zinc exchange[34] and a protocol for the generation of aryl nucleophile using aryl boronic acids as aryl sources[61] have been developed by

Oppolzer et al and Bolm et al respectively. These new methods provide reliable and inexpensive approaches to the production of alkenyl and aryl nucleophiles. In this study, above methods were used to prepare transfer reagents in the reactions of alkenyl and phenyl transfer to aldehydes. Our aim is to search effective chiral ligands which possess high catalytic activity and which can generate high enantioselectivities in these reactions. Furthermore, for the practical applications of catalytic asymmetric synthesis, it is an especially important aim to develop convenient method for the preparation of useful chiral ligands for us.

β, γ-Alkynyl α-amino acid derivatives are a special class of nonproteinogenic amino acids which possess important biological activities. However, from a synthetic standpoint, the β, γ-alkynyl α-amino acid derivatives are challenging structures to prepare. Up to now, only a few methods have been found to be successful, in which the coupling of α-haloglycinates with alkynilides were employed. These methods are not straightforward and catalytic since the alkynilides employed in the above processes were prepared from alkynes with a equivalent strong organobase as a separate step or prepared by transmetallation. In this study, another aim is to employ a new strategy of direct terminal alkynes addition to α-imino ester to realize the catalytic synthesis of β, γ-alkynyl α-amino acid derivatives. The strategy should avoid the re-preparation of alkynyl transfer reagents using strong organobase as a separate step and would lead to great simplification of the synthetic processes.

Chapter 2

Catalytic Asymmetric Alkenyl Transfer to Aldehydes Promoted by Optically Active Tertiary Aminonaphthol

2.1 Introduction

Over the past two decades, great progress has been made in the catalytic asymmetric dialkylzinc addition to aldehydes using chiral amino alcohols as ligands and products with excellent enantiomeric excesses have been achieved for all types of substrates. In contrast, the enantioselective alkenylzinc addition to aldehydes are substantially less developed in spite of its importance in organic synthesis. The asymmetric alkenylation of aldehydes affords very useful chiral allyl alcohols, which are key intermediates in various reactions and play important roles in the synthesis of a large number of natural products and biologically active compounds.

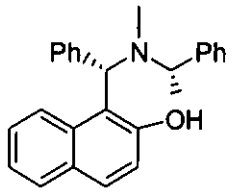
Generally, alkenylzinc reagents are not temperature-stable and are therefore prepared in situ by transmetalation protocols. Among the three routes which were used to generate alkenylzinc reagents, the method of transmetalation of ZnX_2 (X=Cl, Br) with vinyl Grignard reagents or alkenyllithium reagents has great limitation due to the difficulty in the preparation of the corresponding magnesium and lithium reagents.[33] Also, since the Schwartz reagent is expensive, the approach of hydrozirconation of alkyne followed by zirconium-zinc exchange also cannot reach a practical level.[35] In this study, alkenylzinc reagents used for the asymmetric alkenylation of aldehydes were generated

by the third method, namely hydroboration of alkyne followed by boran-zinc exchange, in which cheap $BH_3 \cdot SMe_2$ was applied as reductive reagent.[34]

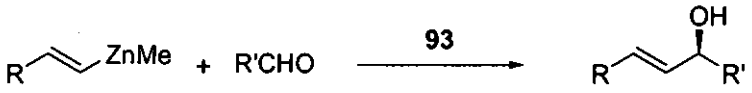
Up to now, highly effective chiral ligands for the enantioselective alkenylation of aldehydes are relatively rare. Amino alcohols ligands which were effective in the asymmetric dialkylzinc additions were studied in this reaction, but generally gave only moderate selectivities.[34,35] Oppolzer et al. found that 3-*exo*-dimethylaminoisobornenol (DAIB) ligand[34] gave good ee's in the alkenylation of certain aldehydes. Dahmen and Brase reported that a ketimine ligand[40] which contains [2, 2]-paracyalophane backbone gave moderate to high ee's for *para*-substituted benzaldehydes and α–branched aliphatic aldehydes, but this ligand shoud be synthesized through a complex route. The search for efficient chiral ligands to generate high enantioselectivities in the alkenylations of different types of aldehydes is an important challenge in this area.

On the other hand, of the approximately 600 chiral ligands in a recent review on organozinc additions by Pu and Yu,[76] only a small number can be obtained via simple synthetic methods. For the practical applications of useful catalytic asymmetric synthesis, it is highly desirable to develop convenient methods for the preparation of effective chiral ligands.

In this study, a new and one-step method for the practical synthesis of optically active tertiary aminonaphthol **93** was developed and high activities and enentioselectivities up to 99% ee were found in the enantioselective alkenylation of various aldehydes catalyzed by **93**. This provides an effective methodology for the synthesis of chiral (*E*)- allyl alcohols (Scheme 2-1).



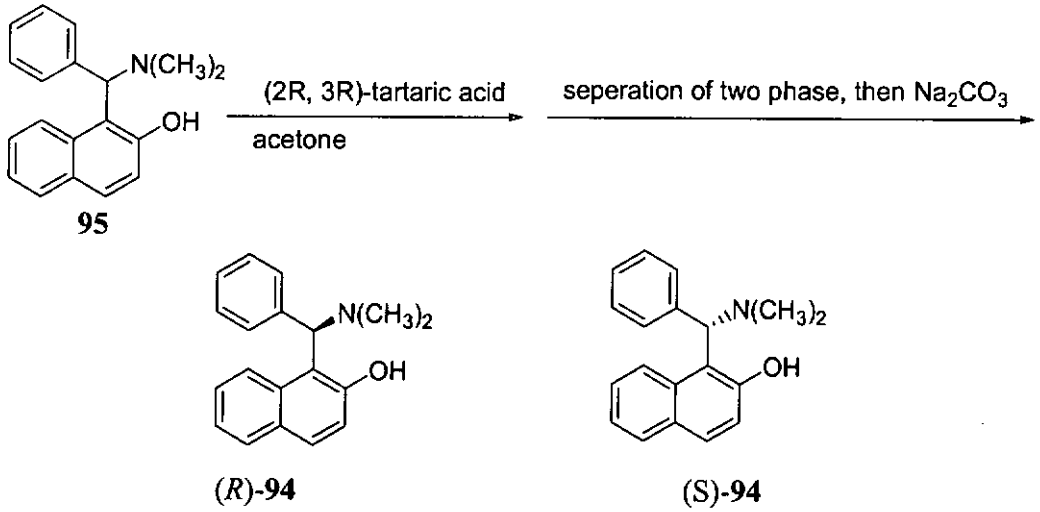
93



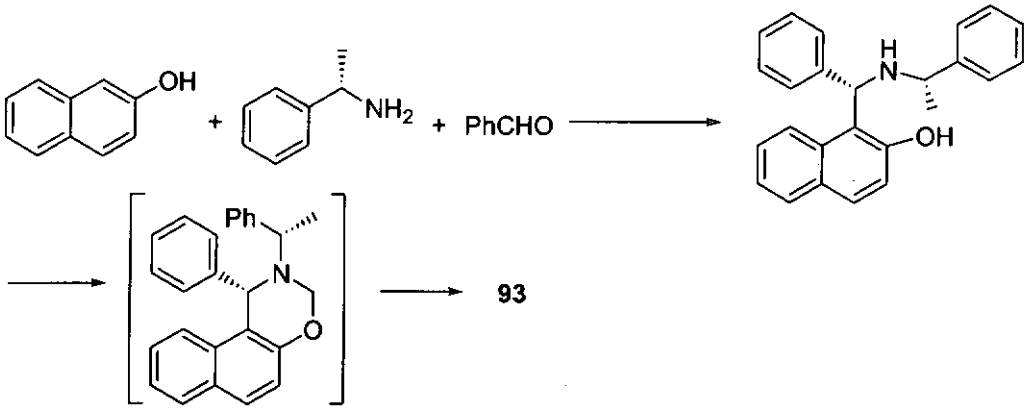
Scheme 2-1

2.2 One-Step Synthesis of Optically Active Tertiary Aminonaphthol Ligand 93

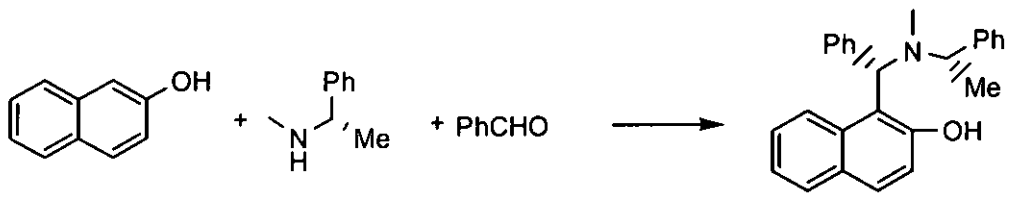
Tertiary aminonaphthol is an important class of amino alcohol ligands and different strategies have been applied to obtain their optically active form.[76] For example, optically active **94** can be achieved by resolution of its racemic mixture **95** using tartaric acid[77] (Scheme 2-2), and optically active tertiary aminonaphthol had been previously prepared through the selective alkylation of the corresponding secondary amine (Scheme 2-3).[78,79]



Scheme 2-2



Scheme 2-3



96 **97** **13** **93**

Scheme 2-4

In this study, considering that secondary amines could be used in different Mannich types reactions as the amine source,[80] we tried to use commercial (S)-(-)-N-α-dimethylbenzylamine (**97**) as one component in the Mannich type aminoalkylation of 2-naphthol (**96**). It is found that direct condensation of benzadehyde (**13**) with 2-naphthol and (S)-(-)-N-α-dimethylbenzylamine without any solvent (Scheme 2-4) proceeded smoothly to give only one diastereomer of the tertiary aminonaphthol **93** exclusively at room temperature. It means that (S)-(-)-N-α-dimethylbenzylamine, as the amine component in this Mannich type reaction, not only possesses the required activity but also can control the stereochemistry completely. This is the first example of straightforward asymmetric synthesis of optically active tertiary aminonaphthol through Mannich type reaction.

Table 2-1 Study on the effect of reaction conditions for the one-step synthesis of **93**

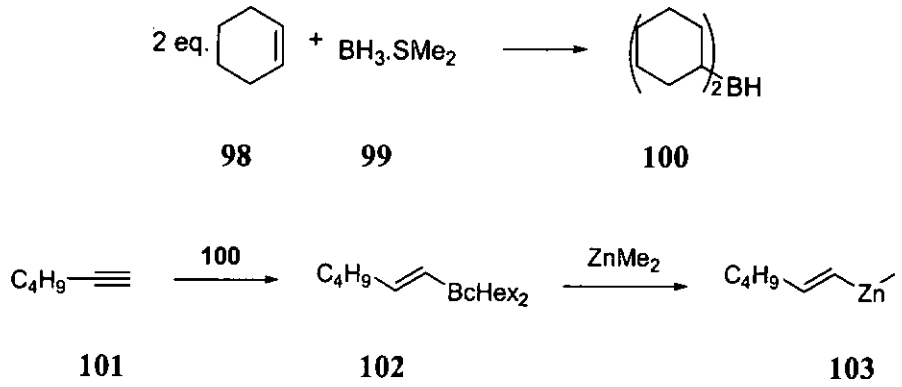
Ratio of **96**: **97**: **13**	Temperature (°C)	Time (h)	Yield (%)
1: 1.25:1.25	25	45	70
1: 1.25: 1.25	55	45	71
1: 1.25: 1.25	90	30	76
1: 1: 1	90	30	67

The effect of the ratio of the starting material and reaction temperature were studied and the results are shown in Table 2-1. Reaction at a higher temperature of 90 °C needs a shorter reaction time than the reaction at room temperature and at 55°C.

Optically pure **93** was easily obtained by simply adding methanol to the crude reaction mixture, and the precipitated product could be used directly in the asymmetric alkenylzinc addition reactions without any further purification. The operational simplicity of this synthetic methodology makes it possible to synthesize chiral ligands on a large scale.

2.3 Alkenylzinc Addition to Benzaldehyde Catalyzed by Ligand 93

Alkenylzinc reagents used in our study was prepared using a method developed by Oppolzer et al.[34]

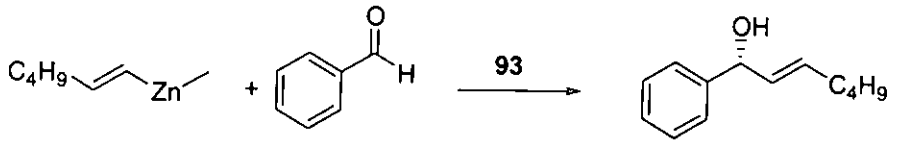


Scheme 2-5

Hydroboration of alkyne **101** with dicyclohexyborane **100**, prepared in situ from borane dimethylsulfide complex **99** and cyclohexane **98**, gives rise to the [(*E*)-1-alkenyl]boranes **102**, which were directly treated with diethyl zinc. The transmetalation to give the alkenylzinc **103** takes place at -78 °C and is complete within a few minutes.

At first, four different solvents were tested in the reaction of 1.5 eq. of alkenylzinc reagent **103** addition to benzaldehyde in the presence of 15 mol% of **93**. The solvent used in this reaction has a strong effect on the yields. (Table 2-2). It was found that the expected allyl alcohol was obtained in good yields by only using hydrocarbon solvent, such as hexane and toluene, and the reactions in THF and CH_2Cl_2 gave very low yields. Comparing hexane and toluene, the reaction gave better isolated yield and enantioselectivity in the latter.

Table 2-2 Ligand **93** catalyzed alkenylzinc reagent **103** addition to bezaldehyde[a]



103 **104**

entry	solvent	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	7	-
2	THF	9	-
3	hexane	79	90
4	toluene	85	92

[a]The reaction of 1.5 eq. of alkenylzinc reagent **103** addition to benzaldehyde was proceeded in the presence of 15 mol% of **93** at 0 °C. [b]Isolated yields. [c] Determined by HPLC (Chiracel OD column).

Further modifications were focused on the amount of addition reagent, reaction temperature and the zinc reagent for transmetalation (Table 2-3). Increasing the amount of alkenylzinc reagent improved the isolated yield to 91%. Lowering the reaction tempreture to –30 °C gave a slightly higher ee. Both diethylzinc and dimethylzinc gave similar results.

Table 2-3 Further modifications of the reaction of **103** addition to **104** catalyzed by **93**[a]

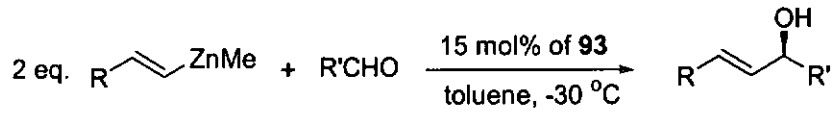
entry	**103** (eq.)	solvent	t (°C)	t (h)	yield (%)[b]	ee (%)[c]
2	1.5	hexane	-20	15	77	91
4	1.5	toluene	-20	15	80	95
5	1.5	toluene	-30	15	80	97
6	2	toluene	-20	12	91	96
7[d]	1.5	toluene	-20	15	83	95

[a]The reaction of alkenylzinc reagent **103** addition to benzaldehyde was proceeded in the presence of 15 mol% of **93**. [b]Isolated yields. [c]Determined by HPLC (Chiracel OD column). [d]$ZnEt_2$ was used in transmetallation instead of $ZnMe_2$.

2.4 Alkenylzinc Additions to Different Aromatic and Aliphatic Aldehydes Catalyzed by Ligand 93

The results of asymmetric alkenylation of aldehydes in the presence of chiral ligand **93** are summarized in Table 2-4.

Table 2-4. Results for alkenylzinc addition to a variety of aldehydes catalyzed by **93**



entry	R	R'	yield (%)[a]	ee (%)[b]
1	$Ph(CH_2)_2$	*c*-C_6H_{11}	93	95 (S)
2	$Ph(CH_2)_2$	*c*-C_6H_{11}	95	95 (S)
3	$Ph(CH_2)_2$	*i*-Pr	94	94 (S)
4	n-C_4H_9	phenyl	90	97 (R)
5	n-C_4H_9	*p*-Br-phenyl	89	94 (R)
6	n-C_4H_9	*p*-NO_2-phenyl	79	95 (R)
7	n-C_4H_9	*o*-NO_2-phenyl	77	98 (R)
8	n-C_4H_9	*o*-Cl-phenyl	90	>99 (R)
9	n-C_4H_9	*o*-Br-phenyl	87	98 (R)
10[c]	n-C_4H_9	*o*-Br-phenyl	84	96 (R)
11	n-C_4H_9	*m*-OMe-phenyl	91	94 (R)
12	n-C_4H_9	*m*-Br-phenyl	92	94 (R)

[a]Isolated yield. [b]Determined by HPLC (Chiracel OD column used for entries 1, 5-9; Chiracel AD column used for entries 2-4). The absolute configuration was assigned by comparison of the optical rotation with the reported values of known compounds (ref. 35, entries 1, 8) and with the expectation similar reaction pathways for all other substrates. [c] $ZnEt_2$ was used in transmetallation instead of $ZnMe_2$.

As shown in Table 2-4, high ee's and isolated yields were obtained for a variety of aliphatic and aromatic aldehydes. Aliphatic aldehydes, namely cyclohexylcarbaldehyde and isobutyraldehyde, gave somewhat higher yields than aromatic aldehydes (entry 1-3). Nitro-substituted benzaldehydes provided lower yields than other substrates (entry 6, 7). The electron-rich *meta*-methoxybenzaldehyde and the electron-poor *meta*-bromobenzaldehyde provided similar product ee's (entry 11, 12), while the *para*- and *meta*-subtituted benzaldehydes gave products with slightly lower ee than those from *ortho*-substituted benzaldehydes. To our knowledge, these are the best ee's in the catalytic asymmetric alkenylation of *ortho*-substituted benzaldehydes (entry 7-10).

2.5 Summary

In this section, we demonstrated a successful application of chiral tertiary aminonaphthol in the enantioselective alkenylation of aldehydes. High chemical yields and ee's were obtained for a variety of aromatic and aliphatic aldehydes. Chiral secondary amine (S)-(-)-N-α-dimethylbenzylamine was for the first time used in the Mannich type aminoalkylation of 2-naphthol to afford an efficient, one step method for the preparation of the chiral ligand **93**.

2.6 Experimental section

2.6.1 General procedure

All manipulations with air-sensitive reagents were carried out under a dry nitrogen atmosphere using standard Schlenk techniques or in a nitrogen-filled MBRAUN Lab Master 130 glovebox. Commercial reagents were used as received without further purification unless otherwise stated. All solvents were dried using standard, published methods and were distilled before use. Flash column chromatography was carried out on 230–400 (0.04–0.063 mm) silica gel (NA SILICA GEL).

^{1}H NMR, ^{13}C NMR were recorded in $CDCl_3$ on a Varian AS 500 at room temperature and using TMS as an internal standard. The chemical shifts were expressed in ppm. Mass analyses were performed on a V.G. MICROMASS, Fisons VG platform or a Finnigan Model Mat 95 ST spectrometer. Optical rotations were measured on a Perkin-Elmer Model 341 polarimeter. HPLC analysis was performed using a Hewlett-Packard Model HP 1050 LC interfaced to a HP 1050 series computer workstation.

2.6.2 Synthesis of ligand 93

1-((*S*)-Phenyl(((1′*S*)-1′-phenylethyl)methylamino)methyl)-2-naphthol (93)

A mixture of benzaldehyde (2.0 mL, 20 mmol), (*S*)-(-)-N,α-dimetylbenzylamine (2.60 g, 19 mmol) and 2-naphthol (2.43g, 16 mmol) was stirred at 95 °C for 30 h. Methanol (5 mL) was added and the precipitated product was collected and washed with methanol (5 mL). White crystals of tertiary aminonaphthol **93** (4.58 g, 78%) was obtained.

^{1}H NMR (500 MHz, $CDCl_3$) δ 14.01 (br s, 1H), 7.88-7.18 (m, 16H), 5.33 (s, 1H), 4.21 (br m, 1H), 2.10 (m, 3H), 1.51 (s, 3H): de > 98%. No other stereoisomer was observed.

2.6.4 Typical procedure for alkenylzinc addition to aldehydes.

To a stirred solution of dicyclohexylboran (1 mmol) in toluene (0.5 mL), was added 1-hexyne (114 μL, 1 mmol). The mixture was stirred for 1 h at room temperature, then was cooled to -78 °C and a solution of dimethylzinc (600 μL, 1.2 mmol, 2 M in toluene) was added slowly. After 1 h at -78 °C, a solution of ligand **93** (0.075 mmol) in toluene (2 mL) was added. Then the temperature was increased to -30 °C over a period of 0.5 h and the aldehyde (0.5 mmol) was added and the final mixture was allowed to stir for 15 h at -30 °C. The reaction was quenched with water and the mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and solvent was removed *in vacuo*. The purification of the residue by flash chromatography yielded the allyl alcohol.

(*S*)-1-Cyclohexyl-5-phenyl-pent-2-en-1-ol

According to the general procedure, the reaction of 4-phenyl-1-butyne (140 μl, 1 mmol), cyclohexanecarboxaldehyde (60 μL, 0.5 mmol) and dimethylzinc afforded 113 mg (93% yield based on the aldehyde) of (*S*)-1-Cyclohexyl-5-phenyl-pent-2-en-1-ol as a colorless oil. $[\alpha]_D^{20}$ +1.47 (c 2.0, $CHCl_3$). HPLC (Chiralcel OD, hexane:EtOAc = 99:1): 95% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.16 (m, 5H), 5.67 (dt, 1H, J = 15.0, 7.0 Hz), 5.45 (ddt, 1H, J = 15.5, 8.0, 1.5Hz), 3.72 (dd, 1H, J = 7 Hz), 2.70 (m, 2H,), 2.37 (m, 2H), 1.80-1.60 (m, 5H), 1.40-1.08 (m, 4H), 0.87 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.78, 132.44, 132.41, 128.43, 128.36, 125.94, 77.74, 43.70, 35.69, 34.18, 28.80, 26.60,

26.21, 26.14. MS (EI) m/z (rel intensity) 244 (M^+, 8), 226 (5), 161 (49), 143 (25), 105 (57), 91 (100), 55 (20), 41 (10)

(*S*)-2-Methyl-7-phenyl-hept-4-en-3-ol

According to the general procedure, the reaction of 4-phenyl-1-butyne (140 μl, 1 mmol), isobutyraldehyde (46 μL, 0.5 mmol) and dimethylzinc afforded 96 mg (94% yield based on the aldehyde) of (*S*)-2-Methyl-7-phenyl-hept-4-en-3-ol as a colorless oil. $[\alpha]_D^{20}$ +4.53 (c 0.6, $CHCl_3$). HPLC (Chiralcel OD, hexane:EtOAc = 99:1): 94% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.26 (m, 5H), 5.76 (dt, 1H, J = 15.0, 7.5 Hz), 5.58 (dd, 1H, J = 15.5, 7.0 Hz), 3.87 (dd, 1H, J = 6.0 Hz), 2.81 (t, J = 7.5, 2H), 2.48 (m, 2H), 1.77 (m, 1H), 0.99 (d, J = 6.5H, 3H), 0.93 (d, J = 6.5H, 3H)

(*R*)-1-Phenyl-hept-2-en-1-ol

According to the general procedure, the reaction of 1-hexyne (114 μl, 1 mmol), bezaldhyde (51 μL, 0.5 mmol) and dimethylzinc afforded 85.5 mg (90% yield based on the aldehyde) of (*R*)-1-Phenyl-hept-2-en-1-ol as a colorless oil. $[\alpha]_D^{20}$ -37.1 (c 1.34, $CHCl_3$). HPLC (Chiralcel OD, hexane:EtOAc = 90:10): 97% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H), 5.78 (dt, 1H, J = 15.0, 6.8 Hz), 5.60 (dd, 1H, J = 15.5, 6.5 Hz), 5.17 (d, 1H, J = 6.5 Hz), 2.08-2.04 (m, 2H), 1.44-1.26 (m, 4H), 0.89 (t, 3H, J = 6.5 Hz).

(*R*)-1-(4-Bromo-phenyl)-hept-2-en-1-ol

According to the general procedure, the reaction of 1-hexyne (114 μl, 1 mmol), 4-bromobenzaldhyde (92.8 mg, 0.5 mmol) and dimethylzinc afforded 119.3 mg (89% yield

based on the aldehyde) of (*R*)-1-(4-Bromo-phenyl)-hept-2-en-1-ol as a colorless oil. $[\alpha]_D^{20}$ –40.5 (c 1.03, $CHCl_3$). HPLC (Chiralcel AD, hexane:i-PrOH = 99:1): 94% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, 2H, J = 9.0 Hz), 7.24 (d, 2H, J = 8.0 Hz), 5.74 (dt, 1H, J = 15.5, 6.5 Hz), 5.59 (ddt, 1H, J = 15.0, 6.5, 1.5 Hz), 5.47 (d, 1H, J = 6.5 Hz), 2.07-2.02 (m, 2H), 1.38-1.28 (m, 4H), 0.89 (t, 3H, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.98, 133.60, 131.96, 131.62, 128.01, 121.37, 74.75, 31.96, 31.28, 22.36, 14.04. MS (EI) m/z (rel intensity) 270 (M^++2, 8), 268 (M^+, 8), 213 (50), 211 (52), 198 (32), 196 (33), 132 (100), 115 (10), 91 (8), 77 (56), 55 (15). HRMS (EI) Calcd for $C_{13}H_{17}OBr$: 268.0463, found 268.0449.

(*R*)-1-(4-Nitro-phenyl)-hept-2-en-1-ol

According to the general procedure, the reaction of 1-hexyne (114 μl, 1 mmol), 4-nitrobenzaldehyde (75.1 mg, 0.5 mmol) and dimethylzinc afforded 92.8 mg (79% yield based on the aldehyde) of (*R*)-1-(4-Nitro-phenyl)-hept-2-en-1-ol as a colorless oil. $[\alpha]_D^{20}$ -32.76 (c 0.62, $CHCl_3$). HPLC (Chiralcel AD, hexane:i-PrOH = 92:8): 95% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, 2H, J = 8.5 Hz), 7.55 (d, 2H, J = 9.0 Hz), 5.82 (dt, 1H, J = 15.0, 7.0 Hz), 5.59 (dd, 1H, J = 15.0, 7.5 Hz), 5.26 (d, 1H, J = 7.5 Hz), 2.09-2.04 (m, 2H), 1.40-1.24 (m, 4H), 0.89(t, 3H, J = 7.0 Hz). MS (EI) m/z (rel intensity) 235 (M^+, 4), 218 (7), 178 (31), 165 (43), 150 (21), 132 (45), 77 (11), 55 (11), 28 (69), 18 (100). HRMS (EI) Calcd for $C_{13}H_{17}NO_3$: 235.1208, found 235.1364.

(*R*)-1-(2-Chloro-phenyl)-hept-2-en-1-ol

According to the general procedure, the reaction of 1-hexyne (114 μl, 1 mmol), 2-chlorobenzaldehyde (56.0 μL, 0.5 mmol) and dimethylzinc afforded 100.8 mg (90% yield

based on the aldehyde) of (*R*)-1-(2-Chloro-phenyl)-hept-2-en-1-ol as a colorless oil. $[\alpha]_D^{20}$ -39.06 (c 1.22, $CHCl_3$). HPLC (Chiralcel OD, hexane:i-PrOH = 99:1): >99% ee. ^{1}H NMR (500 MHz, CDCl3): δ 7.56 (d, 1H, J = 8.0 Hz), 7.34-7.27 (m, 2H), 7.20 (t, 1H, J = 7.8 Hz), 5.79 (dt, 1H, J = 15.0, 7.0 Hz), 5.65 (dd, 1H, J = 15.0, 6.5 Hz), 5.56 (d, 1H, J = 7.0 Hz), 2.07-2.03 (m, 2H), 1.39-1.27 (m, 4H), 0.88 (t, 3H, J = 7.0 Hz). ^{13}C NMR (125 MHz ,CDCl3): δ 140.81, 133.60, 132.43, 130.29, 129.61, 128.65, 127.56, 127.23, 71.62, 32.04, 31.29, 22.35, 14.06. MS (EI) m/z (rel intensity) 225 (M^++1, 10), 224 (M^+, 2), 223 (M^+-1, 15), 209 (34), 207 (100), 153 (11), 151 (31), 141 (6), 139 (18), 127 (29), 125 (16), 81 (29). HRMS (EI) Calcd for $C_{13}H_{17}OCl$: 224.0968, found 224.1048.

(*R*)-1-(2-Bromo-phenyl)-hept-2-en-1-ol

According to the general procedure, the reaction of 1-hexyne (114 μl, 1 mmol), 2-bromobenzaldehyde (59 μL, 0.5 mmol) and dimethylzinc afforded 116.8 mg (87% yield based on the aldehyde) of (*R*)-1-(2-Bromo-phenyl)-hept-2-en-1-ol as a colorless oil. $[\alpha]_D^{20}$ -53.34 (c 1.52, $CHCl_3$). HPLC (Chiralcel OD, hexane:i-PrOH = 95:5): 98% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56-7.52 (m, 2H), 7.34 (m, 1H), 7.13 (m, 1H), 5.80 (dt, 1H, J = 16.0, 7.0 Hz), 5.60 (dd, 1H, J = 15.5, 6.5 Hz), 5.53 (d, 1H, J = 6.5 Hz), 2.07-2.03 (m, 2H), 1.40-1.29 (m, 4H), 0.88(t, 3H, J = 7.0 Hz). ^{13}C NMR (125 MHz ,CDCl3): δ 142.34, 133.72, 132.85, 130.27, 128.98, 127.87, 127.85, 122.57, 73.68, 32.05, 31.28, 22.35, 14.05. MS (EI) m/z (rel intensity) 270 (M^++2, 8), 268 (M^+, 8), 213 (19), 211 (20), 132 (100), 115 (9), 91 (12), 77 (32), 55 (14). HRMS (EI) Calcd for $C_{13}H_{17}OBr$: 268.0463, found 268.0533.

(*R*)-1-(2-Nitro-phenyl)-hept-2-en-1-ol

According to the general procedure, the reaction of 1-hexyne (114 μl, 1 mmol), 2-nitrobenzaldehyde (75.5 mg, 0.5 mmol) and dimethylzinc afforded 90.5 mg (77% yield based on the aldehyde) of (*R*)-1-(2-Nitro-phenyl)-hept-2-en-1-ol as a colorless oil. $[\alpha]_D^{20}$ -39.35 (c 0.89, CH_3Cl). HPLC (chiralcel AD, hexane:i-PrOH = 98:2): 98% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, 1H, J = 8.5 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.63 (t, 1H, J = 7.3 Hz), 7.42 (t, 1H, J = 7.0 Hz), 5.80 (dt, 1H, J = 15.5, 6.5 Hz), 5.75 (d, 1H, J = 6.0 Hz), 5.65 (dd, 1H, J = 16.0, 6.0 Hz), 2.06-2.02 (m, 2H), 1.36-1.25 (m, 4H), 0.88(t, 3H, J = 7.3 Hz). MS (EI) m/z (rel intensity) 235 (M^+, 1), 234 (M^+-1, 6), 219 (12), 218 (90), 207 (14), 206 (100), 202 (49), 188 (45), 118 (9), 106 (10). HRMS (EI) Calcd for $C_{13}H_{17}NO_3$: 235.1208, found 235.0912.

(*R*)-1-(3-Methoxy-phenyl)-hept-2-en-1-ol

According to the general procedure, the reaction of 1-hexyne (114 μl, 1 mmol), m-anisaldhyde (61 μL, 0.5 mmol) and dimethylzinc afforded 100.4 mg (91% yield based on the aldehyde) of (*R*)-1-(3-Methoxy phenyl)-hept-2-en-1-ol as a colorless oil. $[\alpha]_D^{20}$ -44.35 (c 1.78, $CHCl_3$). HPLC (Chiralcel OD, hexane:i-PrOH = 95:5): 94% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (m, 1H), 6.96-6.94 (m, 2H), 6.83-6.80 (m, 1H), 5.77 (dt, 1H, J = 15.5, 6.5 Hz), 5.66 (dd, 1H, J = 15.0, 7.0 Hz), 5.14 (d, 1H, J = 7.0 Hz), 3.81 (s, 3H), 2.08-2.04 (m, 2H), 1.44-1.28 (m, 4H), 0.89 (t, 3H, J = 7.0 Hz).

(*R*)-1-(3-Bromo-phenyl)-hept-2-en-1-ol

According to the general procedure, the reaction of 1-hexyne (114 μl, 1 mmol), 3-bromobenzaldehyde (58 μL, 0.5 mmol) and dimethylzinc afforded 123.4 mg (92% yield

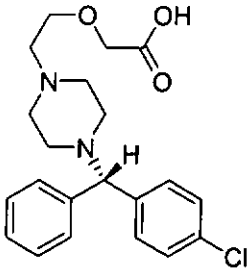
based on the aldehyde) of (*R*)-1-(3-Bromo-phenyl)-hept-2-en-1-ol as a colorless oil. $[\alpha]_D^{20}$ -39.51 (c 0.92, $CHCl_3$). HPLC (Chiralcel AD, hexane:i-PrOH = 99:1): 94% ee. ^1H NMR (500 MHz, CDCl3): δ 7.50 (s, 1H), 7.39 (m, 1H), 7.28 (t, 1H, J = 7.5 Hz), 7.21 (t, 1H, J = 7.7 Hz), 5.77 (dt, 1H, J = 15.5, 7.0 Hz), 5.60 (dd, 1H, J = 15.0, 7.0 Hz), 5.12 (d, 1H, J = 7.0 Hz), 2.08-2.01 (m, 2H), 1.41-1.26 (m, 4H), 0.89 (t, 3H, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.77, 133.93, 131.79, 130.57, 130.13, 129.37, 124.89, 122.69, 74.72, 31.97, 31.26, 22.38, 14.04. MS (EI) m/z (rel intensity) 270 (M^++2, 3), 268 (M^+, 3), 241 (96), 239 (100), 213 (32), 211 (34), 132 (68), 77 (20), 55 (16). HRMS (EI) Calcd for $C_{13}H_{17}OBr$: 268.0463, found 268.0585.

Chapter 3

Catalytic Asymmetric Phenyl Transfer to Aldehydes Promoted by Optically Active Tertiary Aminonaphthol

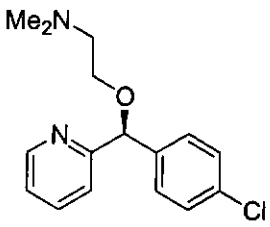
3.1 Introduction

Chiral diarylmethanols are valuable intermediates for the manufacture of pharmacologically and biologically active compounds (Scheme 3-1).[81] The development of highly effective catalyst system for the synthesis of these compounds is of substantial interest not only to the academic world but also to industrial scientists.



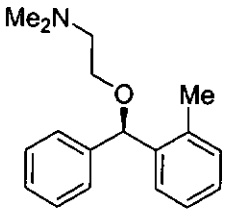
104

(*S*)-cetirizine



105

(*S*)-carbinoxamine



106

(*R*)-orphenadrine

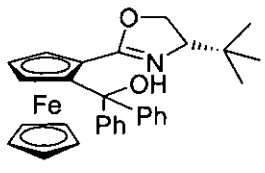
Scheme 3-1 some biologically active diarylmethol derivatives

Three general approaches have been engaged in this context, namely (i) enantioselective hydrogenation, (ii) CBS reduction of the corresponding unsymmetrical diaryl ketones, and (iii) enantioselective aryl transfer to aromatic aldehydes. Whilst the catalytic use of transition-metal activiated molecular hydrogen as a reductant represents

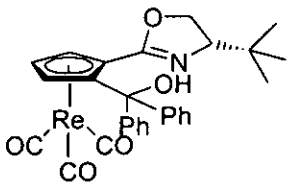
the most attractive strategy, it only works best for substrates containing aryl groups with considerable steric bias.[82] Although this substrate constraint is less stringent with the use of the CBS catalyst, the cost associated with the (*R*)-proline-derived CBS catalyst should the product of the opposite configuration be desired, and the need to perform the reaction at very low temperatures render this method less practical for large scale preparations.[83]

The last strategy outlined above, though still somewhat underdeveloped, appears to be more suitable for chiral induction because of the large steric and electronic differences between an aryl group and a hydrogen atom on an aldehyde substrate.[55] Compared to the well established enantioselective alkylations of aldehydes,[76] which have reached the status of test reactions for new ligand designs, the corresponding aryl transfer reactions have not yet reached a high level of maturity.[55]

Up to now, ligands which have been successfully applied to catalyze the aryl transfer reactions with high ee's are relatively rare and the known catalysts intensively rely on planar-chiral ligands[55] such as ferrocene **74**, [51, 57], [61]cyrhetrene **79**[60] (Figure3-1) and other axial-chiral ligands.[47-49] These ligands, however, are synthesized in multi-steps (Scheme 3-2).[49,52]

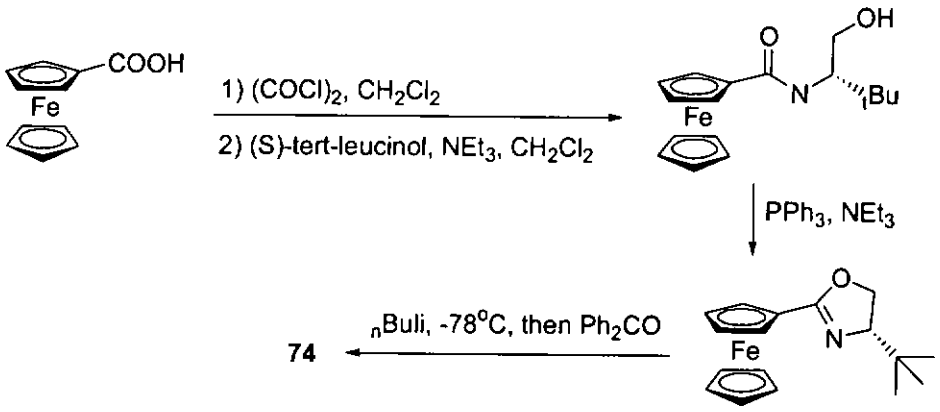


74



79

Figure 3-1

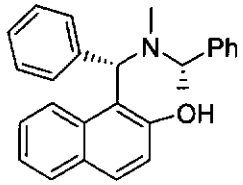


Scheme 3-2 Synthesis of **74**

The development of other types of effective chiral ligands is thus an important challenge in the area of catalytic aryl transfer reactions. For the practical applications of useful catalytic asymmetric synthesis, ligands which can be easily prepared are especially desirable. In this study, we demonstrated, based on a method recently developed by Bolm et al,[61] a successful application of chiral tertiary aminonaphthol in the phenylations of aromatic aldehydes with phenyl boronic acid employed as aryl source. This is the first example of a ligand devoid of planar- and axial-chirality which is able to generate high enantioselectivites in the phenyl transfer reactions. A new chiral tertiary aminonaphthol ligand was designed and prepared by a very convenient procedure from inexpensive materials and the present catalytic reaction system of "tertiary aminonaphthol/phenyl boronic acid/dialkylzinc" provides a highly effective access to a variety of chiral diarylmethanols.

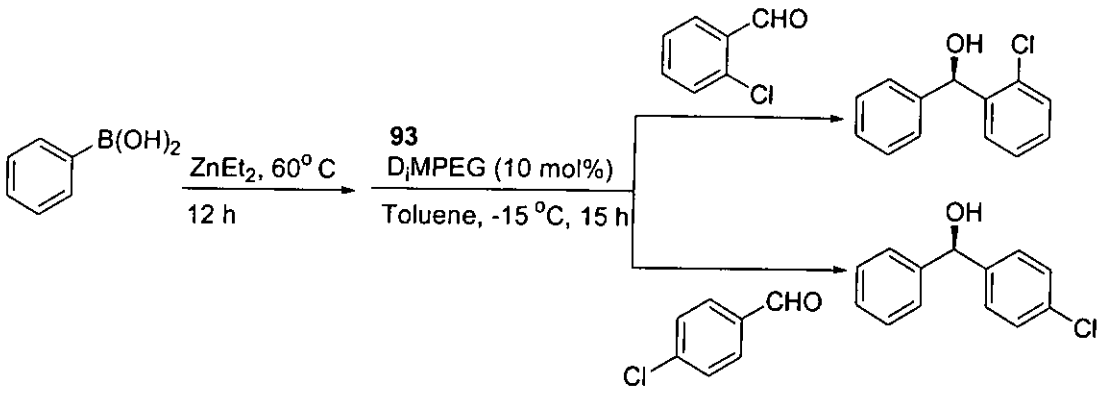
3.2 Phenyl Transfer to *ortho*-chlorobenzaldehyde and *para*-chlorobenzaldehyde Catalyzed by Ligand 93

In Chapter 2, we had developed a highly stereoselective one-step, three-component, Mannich-type reaction to prepare chiral tertiary aminonaphthol **93**. Here, a preliminary study was performed to test the catalytic properties of **93** in the phenyl transfer reaction to *ortho*-chlorobenzaldehyde and *para*-chlorobenzaldehyde.



93

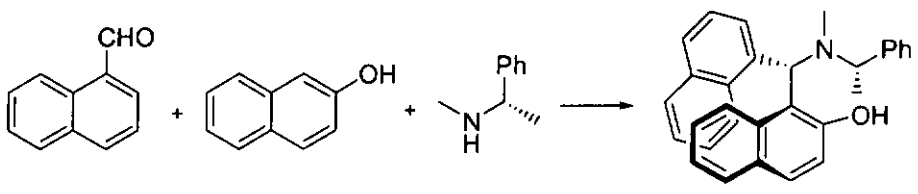
To our delight, the reaction of **93** (16 mol% with respect to aldehyde) with the requisite nucleophile, pre-formed from phenyl boronic acid **105** and diethylzinc in toluene according to Bolm's protocol (Scheme 3-3),[61] gave a homogeneous phase at 0 °C, whose treatment with the aldehydes in the presence of a polyether (DiMPEG) afforded (*R*)-*ortho*-chlorobenzhydrol and (*R*)-*para*-chlorobenzhydrol in 95.3% and 89.6% ee, respectively, with over 90% yield after 10 h at -15 °C.


B(OH)2
ZnEt2, 60° C
12 h
93
DiMPEG (10 mol%)
Toluene, -15 °C, 15 h
CHO
Cl
OH
Cl
OH
CHO
Cl
Cl

Scheme 3-3

3.3 Phenyl Transfer to Different Aromatic Aldehydes Catalyzed by Ligands 93 and 107

Encouraged by the results of tertiary aminonaphthol **93** catalyzed phenyl transfer to *ortho*-chlorobenzaldehyde and *para*-chlorobenzaldehyde, a new optically active tertiary aminonaphthol ligand was designed for this addition reaction. Considering that a bulkier group at the newly generated chiral center could increase the rigidity of the ligand which might be beneficial for chiral induction, we used the one-step methodology that we developed in the preparation of **93** to synthesize **107**. The direct condensation of 1-naphthaldehyde with 2-naphthol and (S)-(-)-N-α-dimethylbenzylamine **97** without any solvent proceeded smoothly at 85 °C and adding of methanol to the reaction mixture after 3 days precipitated **107** (51% yield) as a white solid with absolute stereoselectivity (Scheme **3-4**). This crude product could be used directly in the following phenyl transfer reaction without any further purification. Up to 50 g of **107** can be easily prepared at one shot, indicating the practicality of this method. The reaction is also "atom-economic" in that no reaction solvent is required and only water was produced as the by-product. The operational simplicity, as well as the use of inexpensive reagents make this synthetic methodology suitable for a large-scale preparation.

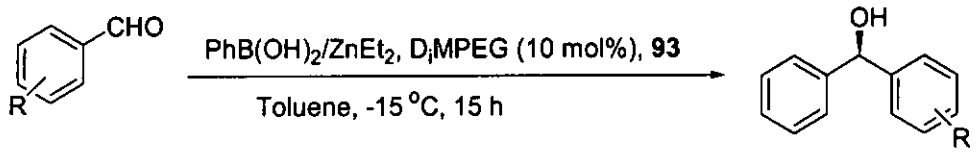


106 **96** **97** **107**

Scheme 3-4

Table 3-1 and Table 3-2 show the results of asymmetric phenyl transfer to substituted benzaldehydes catalyzed by **93** and **107** respectively. A number of chiral diarylmethanol were produced in high ee values and yields. In most cases, ligand **107** demonstrated higher enantioselectivities than **93**, which was in line with our anticipation. $ZnMe_2$ in toluene was also used to generate the phenyl transfer reagent with $PhB(OH)_2$, giving similar ee's but with lower chemical yields under identical reaction conditions (entries 8 and 11). For *ortho*-substituted benzaldehydes, a catalyst loading of 8 mol% of **107** was sufficient to achieve the same level of ee in comparison with that obtained using 16 mol% of **107** (entry 2 vs 1). Interestingly, contrary to the trends that have been previously observed with the known planar[51, 57] and axial[47] chiral catalyst, *ortho*-substituted benzaldehydes gave higher ee's than other substrates under the catalysis of **107** and **93**.

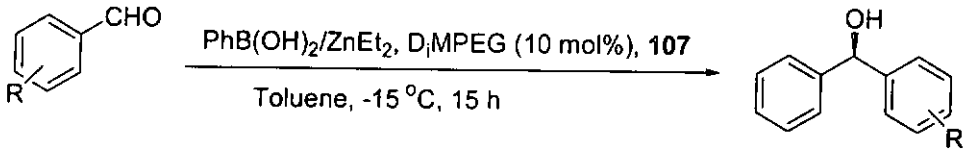
Table 3-1. Asymmetric phenyl transfer to various aldehydes catalyzed by **93**[a]



entry	R	cat. (mol%)	yield (%)[b]	ee (%)[c]
1	*o*-Cl	**3** (8)	91.3	94.3
2	*o*-Br	**3** (8)	90.2	95.3
3	*o*-OMe	**3** (8)	92.7	94.3
3	*o*-Me	**3** (8)	93.1	97.1
4	*m*-Me	**3** (16)	83.4	92.1
5	*p*-Cl	**3** (8)	85.2	88.4
6	*p*-Br	**3** (16)	91.6	91.1
21	*p*-Me	**3** (16)	91.5	90.5

[a] 2.0 eq. of $Ph(OH)_2$ and 6.5 eq. $ZnEt_2$ were employed to produce the phenyl transfer reagent as described in the typical procedure. [b] Isolated yieids. [c] Determined by chiral HPLC analysis; all products were in *R* configuration based on the comparison of the HPLC peak elution order with known data.

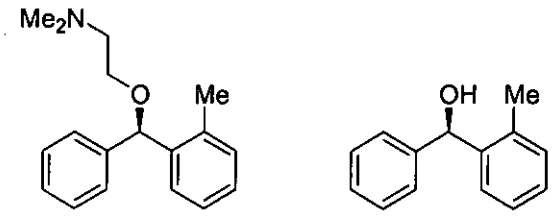
Table 3-2. Asymmetric phenyl transfer to various aldehydes catalyzed by **107**[a]



entry	R	cat. (mol%)	yield (%)	ee (%)[b]
1	*o*-Cl	**4** (16)	92.5	97.3
2	*o*-Cl	**4** (8)	91.1	96.9
3	*o*-F	**4** (8)	92.6	97.2
4	*o*-Br	**4** (8)	89.8	96.7
5	*o*-OMe	**4** (8)	93.4	96.1
6[c]	*o*-OMe	**4** (8)	86.6	97.0
7	*o*-Me	4 (8)	93.6	98.9
8[c]	*o*-Me	**4** (8)	89.5	99.0
9	*m*-Me	**4** (16)	86.5	94.6
10	*p*-Cl	**4** (16)	90.2	94.1
11	*p*-Cl	**4** (8)	88.7	91.9
12	*p*-Br	4 (16)	90.1	93.7
13	*p*-Me	**4** (16)	93.2	94.3

[a] 2.0 eq. of $Ph(OH)_2$ and 6.5 eq. $ZnEt_2$ were employed to produce the phenyl transfer reagent as described in the typical procedure. [b] Determined by chiral HPLC analysis; all products were in *R* configuration based on the comparison of the HPLC peak elution order with known data. [c]$ZnMe_2$ was used instead of $ZnEt_2$.

Especially noteworthy is that (*R*)-*ortho*-methyl benzhydrol **108**, which was obtained in 99% ee, is the direct precursor of Orphenadrine **106**, an anticholinergic and antihistaminic agent (Scheme 3-5).[81a, 81b] To the best of our knowledge, this is the best ee value attained in the catalytic asymmetric synthesis of this useful intermediate.



106 **108**

(*R*)-orphenadrine

Scheme 3-5

3.4 Summary

In conclusion, central chiral tertiary aminonaphthol ligand **93** and **107** have been proved to be highly efficient in phenyl transfer reactions. An array of chiral diarylmethanols were prepared in high ee values and yields from the catalytic system of tertiary aminonaphthol **93**/$PhB(OH)_2$/$ZnEt_2$ or **107**/$PhB(OH)_2$/$ZnMe_2$. The simple synthetic methodology used for the preparation of ligand **107** provides an excellent opportunity for large-scale applications.

3.5 Experimental Section

3.5.1 Preparation of Ligand 107

1-((*S*)-1′-naphthyl(((1″*S*)-1″-phenylethyl)methylamino)methyl)-2-naphthol (107)

1-Naphthaldehyde (2.7 mL, 20 mmol), (*S*)-(-)-N,α-dimetylbenzylamine (2.60 g, 19 mmol) and 2-naphthol (2.43g, 16 mmol) were charged into a 25 mL flask with a magnetic stirring bar. The mixture was heated to 85 °C and stirred for 72 h. After the system was cooled to rt., methanol (5 mL) was added and the precipitated product was collected and washed with methanol (5 mL). White crystals of tertiary aminonaphthol **107** (3.41 g, 51%) was obtained. ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.01 (br s, 1H), 7.77-7.02 (m, 18H), 6.45 (s, 1H), 4.40 (br s, 1H), 1.95 (s, 3H), 1.65 (br s, 3H); MS (EI) m/z (rel intensity) 418 (M^++1), 283, 141, 136; HRMS (EI) Calcd for $C_{30}H_{28}NO$ (M^++1): 418.2171, found 418.2135.

3.5.2 Typical Procedure of Asymmetric Phenyl Transfer to Aldehydes Catalyzed by Tertiary Aminonaphthol 107

Phenylboronic acid (122 mg, 1.0 mmol) and diethylzinc (334 μL, 3.25 mmol) in toluene (1 mL) was charged to a 10 mL flask under a nitrogin atmosphere. This mixture was heated to 60 °C and stirred for 10 h with a magnetic stirrer. Then the mixture was cooled to 0 °C and tertiary aminonaphthol tertiary aminonaphthol **107** (16.7 mg, 0.04 mmol) in toluene (0.5 mL) and DiMPEG (100 mg, 0.05 mmol) in toluene (0.5 mL) was added. After stirring for additional 15 min, the solution was cooled to -15 °C and 2-chlorobenzaldehyde (70.0 mg, 0.5 mmol) in toluene (1 mL) was added. After stirring 15

h at -15 °C, the reaction was quenched with 1 N HCl (2 mL) and the mixture was extracted with EtOAc (5 mL), dried over Na_2SO_4 and the solvent was removed in vacuo. The purification of the residue by flash chromatography (EtOAc/hexane, 1:10) gave (*R*)-(2-chlorophenyl)phenylmethanol (92.7 mg), 97.0% e.e., 86.6% yield. (The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column).

(*R*)-(2-bromophenyl)phenylmethanol:

The reaction was carried out through the same procedure as in example 2 using 2-bromobenzaldehyde (92.5 mg, 0.5 mmol) instead of 2-chlorobenzaldehyde to give (*R*)-(2-bromophenyl)phenylmethanol (118.1 mg), 96.7% e.e., 89.8% yield. (The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column).

(*R*)-(2-fluorophenyl)phenylmethanol:

The reaction was carried out through the same procedure as in example 2 using 2-fluorobenzaldehyde (62.1 mg, 0.5 mmol) instead of 2-chlorobenzaldehyde to give (*R*)-(2-fluorophenyl)phenylmethanol (93.5 mg), 97.2% e.e., 92.6% yield. (The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column).

(*R*)-(2-tolyl)phenylmethanol:

The reaction was carried out through the typical procedure using 2-methylbenzaldehyde (60.1 mg, 0.5 mmol) instead of 2-chlorobenzaldehyde to give (*R*)-(2-tolyl)phenylmethanol (92.7 mg), 98.9% e.e., 93.6% yield. (The enantiomeric excess was determined by HPLC using a Chiralcel OB-H column).

(*R*)-(2-methoxyphenyl)phenylmethanol:

The reaction was carried out through the typical procedure using 2-methoxybenzaldehyde (68.0 mg, 0.5 mmol) instead of 2-chlorobenzaldehyde to give (*R*)-(2-methoxyphenyl)phenylmethanol (99.9 mg), 96.1% e.e., 93.4% yield. (The enantiomeric excess was determined by HPLC using a Chiralcel OB-H column).

(*R*)-(3-tolyl)phenylmethanol:

The reaction was carried out through the typical procedure using 3-methylbenzaldehyde (60.2 mg, 0.5 mmol) instead of 2-chlorobenzaldehyde and tertiary aminonaphthol **107** (33.4 mg, 0.08 mmol) as catalyst to give (*R*)-(3-tolyl)phenylmethanol (85.6 mg), 94.6% e.e., 86.5% yield. (The enantiomeric excess was determined by HPLC using a Chiralcel OB-H column).

(*R*)-(4-chlorophenyl)phenylmethanol:

The reaction was carried out through the typical procedure using 4-chlorobenzaldehyde (70.1 mg, 0.5 mmol) instead of 2-chlorobenzaldehyde and tertiary aminonaphthol **107** (33.4 mg, 0.08 mmol) as catalyst to give (*R*)-(4-chlorophenyl)phenylmethanol (98.5 mg), 94.1% e.e., 90.2% yield. (The enantiomeric excess was determined by HPLC using a Chiralcel OB-H column).

(*R*)-(4-tolylphenyl)phenylmethanol:

The reaction was carried out through the typical procedure using 4-methylbenzaldehyde (60.1 mg, 0.5 mmol) instead of 2-chlorobenzaldehyde and tertiary

aminonaphthol **107** (33.4 mg, 0.08 mmol) as catalyst to give (*R*)-(4-tolylphenyl)phenylmethanol (92.3 mg), 94.3% e.e., 93.2% yield. (The enantiomeric excess was determined by HPLC using a Chiralcel OB-H column).

(*R*)-(4-bromophenyl)phenylmethanol:

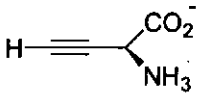
The reaction was carried out through the typical procedure using 4-bromobenzaldehyde (92.5 mg, 0.5 mmol) instead of 2-chlorobenzaldehyde and tertiary aminonaphthol **107** (33.4 mg, 0.08 mmol) as catalyst to give (*R*)-(4-bromophenyl)phenylmethanol (118.5 mg), 93.7% e.e., 90.1% yield. (The enantiomeric excess was determined by HPLC using a Chiralcel OB-H column).

Chapter 4

Catalytic Direct Alkynylation of α-Imino Esters: Efficient Synthesis of β, γ-Alkynyl α-Amino Acid Derivatives

4.1 Introduction

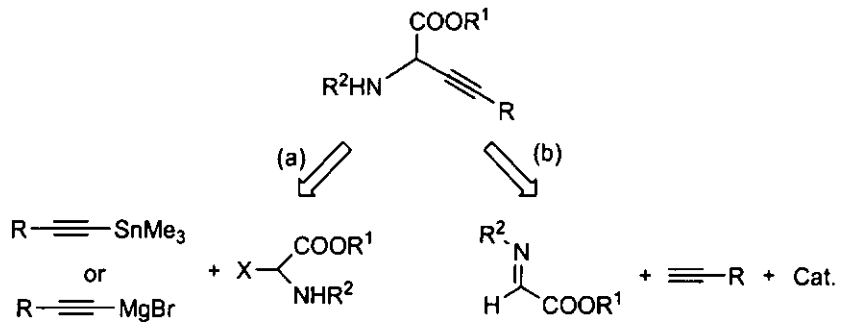
α-Amino acid derivatives are fundamental constituents of numerous natural products and other highly valuable bioactive compounds. The importance of these molecules in pharmaceutical research and natural products synthesis has lead to intense study on their synthetic methods and many different approaches have been established.[84] However, for the efficient construction of different types of naturally occurring amino acids and rational design of bioactive nonproteinogenic amino acids, the development of new catalytic methodology for the synthesis of α-amino acid derivatives from simple and readily available starting compounds is an ongoing challenge for chemists.



109

β, γ-Alkynyl α-amino acid derivatives are a special class of nonproteinogenic amino acids. It is now recognized that α-ethynyl substituents can remarkably change the biological properties of certain natural amino acids, converting them from enzyme substrates to irreversible inhibitors, thereby profoundly altering a number of metabolisms, especially those of microorganisms with potential therapeutic utility.[85] For example,

ethynylglycine (FR-900130) **109**, a secondary metabolite, displays antimicrobial activity against gram-positive bacteria and acts synergistically with D-cycloserine, which could be explained by its inhibitory activity on alanine racemase.[86]



Scheme 4-1 Approaches to β,γ-alkynyl α-amino acid derivatives based on carbon-carbon bond-forming reaction

From a synthetic standpoint, the β, γ-alkynyl α-amino acid derivatives are challenging structures to prepare. Up to now, only a few methods have been found to be successfully used: coupling of α-haloglycinates with either (i) an excess of (environmentally unfriendly) alkynyltin reagents [87] under reflux conditions or (ii) alkynylmagnesium reagents[88] at -78 °C (Scheme 4-1, path a). These methods are neither straightforward, nor are they catalytic. The alkynilides used were generated from alkynes with an equivalent amount of strong base such as BuLi or EtMgBr as a separate step or generated by transmetallation. Both for scientific interest and for practical applications, it is highly desirable to develop efficient and convenient methods for the preparation of β, γ-alkynyl α-amino acid derivatives.

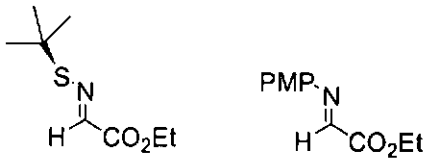
An alternative synthon for α-amino acids is α-imino ester, which has attracted increasing attention. Various nucleophilic reagents such as enol silane, TMS-nitronates, α-protio glyoxyl ketones have been employed in the catalytic addition reaction to α-imino esters.[89] In connection with our recent studies on the alkynylation of carbonyl compounds,[90] we envisaged that the addition of terminal alkynes to α-imino esters using an appropriate metal catalyst should readily provide alkynyl amino acids (Scheme 4-1, path b). In this study, the above synthetic strategy has been proved to be successful and the first catalytic synthesis of β, γ-alkynyl α-amino acid derivatives has been achieved by direct addition of terminal alkynes to α-imino esters in the presence of a Ag (I) or Cu (I)/(II) salt under mild reaction conditions.

4. 2 Direct Additions of Terminal Alkynes to α-Imino Esters

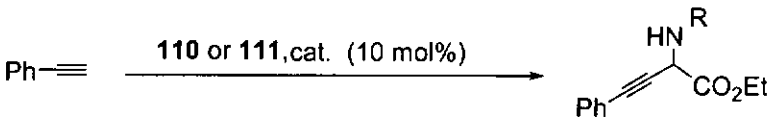
To date, Zn(II)[64] and Cu(I)[68] have been reported as catalysts in the direct addition of alkynes to other different types of C=N electrophiles including nitrones and imines prepared from aromatic aldehydes and anilines. On the other hand, it has long been known for a long time that the complexation of alkynes to Ag (I) yields π-complexes, and a large number of Ag-alkyne complexes have been synthesized and characterized.[91] Despite this knowledge, the application of Ag-alkynilide in organic synthesis is very limited. In order to not only develop a efficient synthetic method for β, γ-alkynyl α-amino acid derivatives but also extend the applications of metal-alkynilide in organic synthesis, different Zn (II), Ag (I) and Cu (I)/(II) salts were examined as catalyst in our initial experiment of direct alkynylation of α-imino esters.

Firstly, *N*-tert-butanesulfinyl α-imino ethyl glyoxylate **110** and *N*-PMP α-imino ethyl glyoxylate **111**[89] were synthesized and used as substrates in the phenylacetylene addition reactions (Table 4-1).

Table 4-1 Phenylacetylene addition to substrate **110** or **111**[a]



110 **111**



112 **113** (R = PMP)

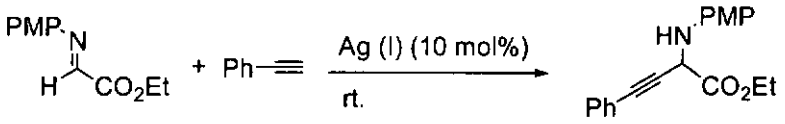
enrty	substrate	catalyst	Time (h)	T (°C)	Yield (%)
1	**110**	$ZnCl_2$	5	25	-
2	**111**	$ZnCl_2$	5	25	-
3	**110**	$Zn(OTf)_2$	5	25	-
4	**111**	$Zn(OTf)_2$	5	25	-
7	**110**	$AgNO_3$	1	25	-
8	**111**	$AgNO_3$	1	25	89
9	**110**	CuCl	3	25	-
10	**111**	CuCl	3	25	23
12	**111**	CuCl	3	60	67

[a]The reactions were carried out using 1 mmol phenylacetylene and 0.5 mmol **110** or **111** in 2.5 mL toluene.

Compound **110** or **111** were added to a mixture of phenylacetylene (2.0 equiv.) and metal salts catalyst (10 mol %) in toluene at room temperature to give a solid-liquid two-phase mixture – the metal salt did not appear to be soluble, or at best only sparingly soluble. Much to our delight, despite the absence of a phase-transfer catalyst, TLC analysis showed that *N*-PMP α-imino ethyl glyoxylate (**111**) was completely consumed after 40 min at room temperature in entry 8, and the corresponding product **113** was obtained in 89% yield. To the best of our knowledge, this is the first example of catalytic synthesis of β, γ-alkynyl α-amino acid derivatives. In entry 10, 23% yield was obtained and increasing the reaction temperature led to a higher yield of 67% (entry 12). The reactions did not occur when Zn (II) salts was used as catalyst or **110** was used as substrate.

4.3 Ag (I) Catalyzed Addition of Terminal Alkynes to α-Imino Esters

Table 4-2. Ag (I)-catalyzed phenylacetylene addition to α-imino ester **111**[a]



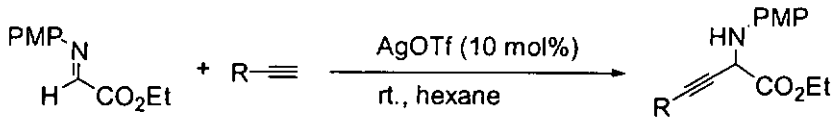
111 **112** **113**

entry	catalyst	solvent	time (h)	yield(%)[b]
1	$AgNO_3$	toluene	1	89
2	$AgNO_3$	hexane	1	92
3	$AgNO_3$	CH_2Cl_2	1	87
4	$AgNO_3$	THF	3	11
5	$AgNO_3$	EtOAc	3	34
6	AgOAc	hexane	5	9
7	AgOTf	hexane	0.5	93
8	$AgPF_6$	hexane	0.5	90
9	$AgClO_4$	hexane	0.5	88

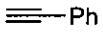
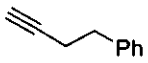
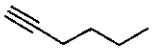
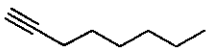
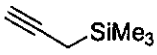
[a] Reaction condition: **111** (0.5 mmol) and phenylacetylene (1.0 mmol) in solvent (5 mL). [b] Isolated yields.

In this section, Ag (I) catalyzed additions of terminal alkynes to α-amino ester **111** were studied in detail (Table 4-2). We firstly screened a range of solvents in the addition of phenylacetylene (**112**) to **111** catalyzed by $AgNO_3$. The reactions performed in toluene, hexane and CH_2Cl_2 were much faster (Table 4-2, entries 1-3) than those in THF or EtOAc (Table 4-2, entries 4 and 5), affording good to high yields within 1 h. In the subsequent study, we investigated the catalytic activity of different Ag (I) salts. As shown in Table 4-2, AgOAc (entry 6) promoted the reaction slowly and most of the starting material did not react even after 5 h. Other Ag(I) salts (entries 7-9) in this test were demonstrated to possess higher activity than $AgNO_3$, and the reaction catalyzed by AgOTf in hexane gave the highest yield (entry 7).

Table 4-3 AgOTf-catalyzed addition of terminal alkynes to α-amino ester **111**[a]



111

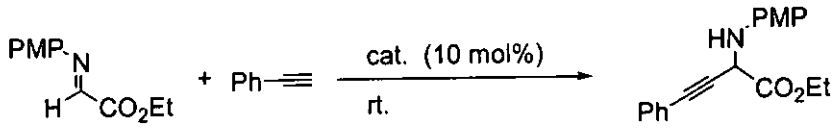
entry	alkyne	time (h)	yield (%)[b]
1		0.5	93
2		0.5	87
3		0.5	84
4		0.5	91
5		1	79

[a] Reaction conditions: **111** (0.5 mmol), alkyne (1.0 mmol), AgOTf (10 mol%), hexane (5 mL).[b] Isolated yields.

In order to establish the general utility of this methodology, the AgOTf-catalyzed alkynylations of α-imino ester **111** with an array of terminal alkynes in hexane at rt. were performed and the results are summarized in Table 4-3. The addition reactions of 4-phenyl-1-butyne (entry 2), 1-hexyne (entry 3), 1-octyne (entry 4) and propargyltrimethylsilane (entry 5) were similar to that of phenylacetylene (entry 1) — all proceeded with a fast reaction rate and gave the corresponding α-amino acid derivatives in good to high yields.

4.3 Cu (I)/(II) Catalyzed Addition of Terminal Alkynes to α-Imino Esters

Table 4-4 Cu(I)/(II)-catalyzed phenyl acetylene addition to α-imino ester **111**[a]



111 **112** **113**

entry	catalyst	solvent	time (h)	yield(%)[b]
1	CuCl	toluene	3	23
2	CuCl	toluene	3	67
3	CuBr	toluene	3	29
4	CuOTf	toluene	1	88
5	$Cu(OTf)_2$	toluene	1	81
6	CuOTf	CH_2Cl_2	1	91
7	CuOTf	THF	3	76
8	CuOTf	EtOAc	3	65
9	CuOTf	hexane	1	86

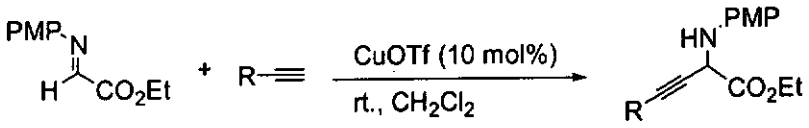
[a] Reaction condition: **111** (0.5 mmol) and phenyl acetylene (1.0 mmol) in solvent (5 mL). [b] Isolated yields.

In this section, we studied Cu (I)/(II) catalyzed additions of terminal alkynes to α-amino ester **111** in detail. Firstly, different Cu(I)/(II) were screened as catalysts in the

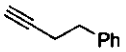
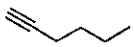
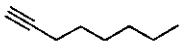
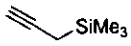
reaction of phenylacetylene **112** addition to α-imino ester **111** at room temperature in toluene. Cu(OTf) showed higher catalytic activity than CuBr and CuCl. The reaction catalyzed by $Cu(OTf)_2$ gave a somewhat lower yield compared to the reaction catalyzed by CuOTf. We also investigated the reaction catalyzed by CuOTf in different solvents at room temperature and found that the reactions performed in toluene, hexane and CH_2Cl_2 were faster (Table 4-4, entries 4, 6, 9) than those in THF or EtOAc (entries 7 and 8), affording **113** in good to high yields within 1 h. This trend is similar to that obtained in the reaction catalyzed by Ag(I).

In the subsequent study, the CuOTf-catalyzed alkynylations of α-imino ester **111** with an array of terminal alkynes in CH_2Cl_2 at room temperature were investigated.

Table 4-5. CuOTf-catalyzed addition of terminal alkynes to α-amino ester **111**[a]



111

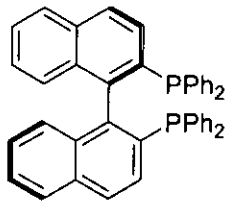
entry	alkyne	time (h)	yield (%)[b]
1		0.5	91
2		0.5	84
3		0.5	89
4		1	82
5		2	77

[a] Reaction conditions: **111** (0.5 mmol), alkyne (1.0 mmol), CuOTf (10 mol%), CH_2Cl_2 (5 mL). [b]Isolated yields.

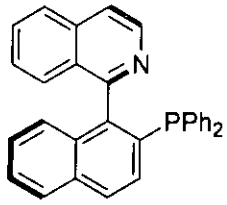
As shown in Table 4-5, 4-phenyl-1-butyne (entry 2), 1-hexyne (entry 3), 1-octyne (entry 4) and propargyltrimethylsilane (entry 5) were used as addition reagents. All the reactions proceeded smoothly and the corresponding α-amino acid derivatives were achieved in good to high yields.

4.4 Initial Study on Catalytic Asymmetric Alkynylations of α-Imino Ester

In this section, an initial study on the catalytic asymmetric alkynylation of α-imino ester was carried out.



114



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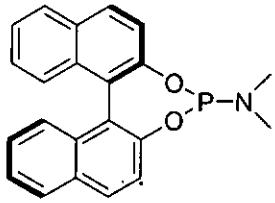
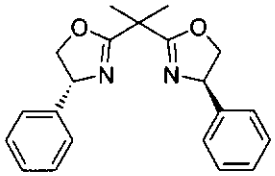


116



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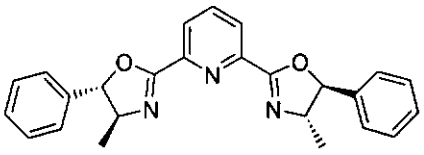

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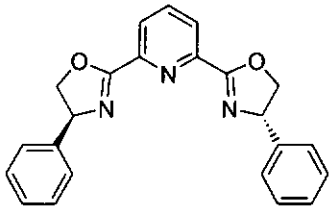

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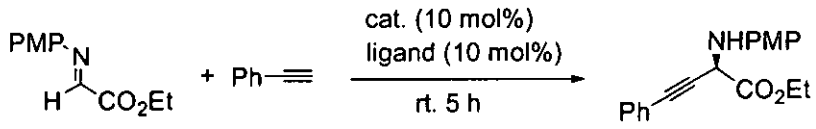


111 **112** **113**

Scheme 4-2

Firstly, various chiral ligands including diphosphane **114**, aminophosphane **115**, **116** and diamine **117–118** were screened in the reaction of phenylacetylene (**112**)

addition to α-imino ester **111** in the presence of AgOTf or CuOTf in toluene at room temperature (Scheme 4-2). The reactions catalyzed by AgOTf/ligand gave very low yields and the reactions catalyzed by CuOTf/ligand **114–118** gave > 75% yields but <5% ee's. In the reaction under the catalysis of CuOTf/ligand **119**, 82% yield and 21% ee were obtained.

The effect of reaction temperature was then studied. It was found that lowering the reaction temprature leads to a higher ee. When the reaction was proceeded at -30 °C, 74% yield, 67 % ee were achieved in the reaction of phenylacetylene (**112**) addition to α-imino ester **111** in the presence of CuOTf and ligand **119**.

Further modification of reaction conditions and the structure of chiral ligand **119** are in progress.

4.4 Summary

In conclusion, we have not only developed a highly efficient method for the synthesis of β, γ-alkynyl α-amino acid derivatives but also extended the applications of Ag alkynilide and Cu alkynilide in organic synthesis by showing the feasibility of direct addition of terminal alkynes to α-imino ester **111** in the presence of a catalytic amount of Ag (I) salts or Cu (I)/(II) under mild reaction conditions. The β, γ-alkynyl α-amino acid derivatives thus produced should be useful as building blocks for the burgeoning field of peptide-based drugs.

4.5 Experimental Section

Typical Procedure for Alkynlynation of α-Imino Ester 111

To a stirred mixture of phenyl acetylene (110μL, 1.0 mmol) and AgOTf (12 mg, 0.05 mmol) in hexane (5 mL), was added *N*-PMP-protected α-imino ethyl glyoxylate **111** (104 mg, 0.5 mmol). The reaction mixture was stirred for 0.5 h at room temperature and then was diluted with EtOAc (10 mL) to give a brown solution. The solution was concentrated *in vacuo* and the purification of the residue by flash chromatography (9:1 hexane-ethyl acetate as eluents) yielded the desired addition products as light yellow oils.

Ethyl-2-(*p*-methoyphenylamino)-4-phenyl-3-butynoate:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.40 (m, 2H), 7.30-7.26 (m, 3H), 6.82-6.80 (m, 2H), 6.76-6.74 (m, 2H), 4.96 (s, 1H), 4.34-4.30 (q, 2H, J = 7.2 Hz), 3.76 (s, 3H), 1.35-1.32 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1, 153.4, 139.5, 132.0, 128.8, 128.3, 122.2, 116.1, 114.9, 84.4, 84.2, 62.5, 55.7, 50.7, 14.2; MS (ESI): *m/z* 310 (M^++1), 264, 236, 123; HRMS (ESI): Calcd for $C_{19}H_{20}NO_3$ (M^++1): 310.1443, found (M^++1): 310.1465.

Ethyl-2-(*p*-methoyphenylamino)-6-phenyl-3-hexynoate:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28-7.25 (m, 2H), 7.20-7.16 (m, 3H), 6.80-6.78 (m, 2H), 6.67-6.65 (m, 2H), 4.69 (t, 1H, J = 2.3 Hz), 4.27-4.24 (q, 2H, J = 7.5 Hz), 3.76 (s, 3H), 2.80-2.77 (t, 2H, J = 7.3 Hz), 2.49-2.46 (dt, 2H, J = 7.3, 2.0 Hz), 1.31-1.28 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 153.7, 140.6, 137.6, 128.7, 128.6,

126.6, 116.5, 114.9, 84.8, 75.4, 62.5, 55.9, 50.5, 34.9, 21.1, 14.3; MS (ESI): *m/z* 338 (M^++1), 292, 264, 123; HRMS (ESI): Calcd for $C_{21}H_{24}NO_3$ (M^++1): 338.1756, found (M^++1): 338.1782.

Ethyl-2-(*p*-methoyphenylamino)- 3-octynoate:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.73-6.70 (m, 2H), 6.63-6.60 (m, 2H), 4.63 (t, 1H, J = 2.3 Hz), 4.22-4.17 (q, 2H, J = 7.0), 3.68 (s, 3H), 2.13-2.10 (dt, 2H, J = 7.0, 2.3 Hz), 1.40-1.18 (m, 7H), 0.83-0.78 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ =168.4, 152.4, 138.2, 115.3, 113.7, 84.6, 73.8, 61.2, 54.6, 49.3, 29.3, 20.8, 17.4, 13.0, 12.5; MS (ESI): *m/z* 290 (M^++1), 244, 216, 123; HRMS (ESI): Calcd for $C_{17}H_{24}NO_3$ (M^++1): 290.1756, found (M^++1): 290.1779.

Ethyl-2-(*p*-methoyphenylamino)-3-decynoate:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.79-6.77 (m, 2H), 6.70-6.68 (m, 2H), 4.70 (t, 1H, J = 2.3 Hz 1H), 4.29-4.24 (q, 2H, 7.3 Hz), 3.75 (s, 3H), 2.19-2.15 (dt, 2H, J = 7.0, 2.3 Hz), 1.47-1.44 (m, 2H), 1.34-1.20 (m, 9H), 0.89-0.86 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 153.7, 139.3, 116.6, 114.9, 86.0, 75.0, 62.4, 55.8, 50.6, 31.5, 28.6, 28.5, 22.8, 18.9, 14.3, 14.2; MS (ESI): *m/z* 318 (M^++1), 272, 244, 164, 123; HRMS (ESI): Calcd for $C_{19}H_{28}NO_3$ (M^++1): 318.2069, found (M^++1): 318.2091.

Ethyl-2-(*p*-methoyphenylamino)-5-(trimethy-silyl)-3-pentynoate:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.79-6.72 (m, 2H), 6.68-6.66 (m, 2H), 4.71 (t, 1H, 2.5Hz), 4.28-4.24 (q, 2H, J = 7.2 Hz), 3.74 (s, 3H), 1.46-1.45 (d, 2H, J = 3.0 Hz),

1.32-1.29 (t, 3H, J = 7.3 Hz), 0.04 (s, 9H); MS (ESI): *m/z* 320 (M^++1), 274, 202, 174, 169, 123; HRMS (ESI): Calcd for $C_{17}H_{26}NO_3Si$ (M^++1): 320.1682, found (M^++1): 320.1711.

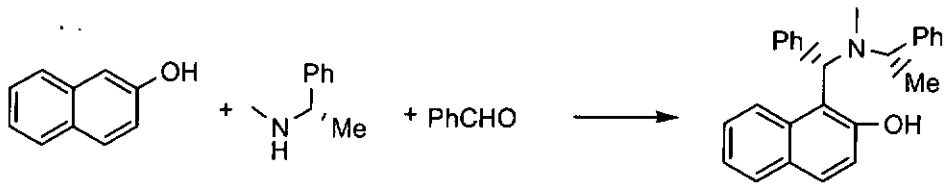
Chapter 5

Conclusions

This work focused on catalytic asymmetric phenyl and alkenyl transfer to aldehydes and alkynylation of α-amino ester.

In this work, we have developed a convenient, one-step synthesis of optically active tertiary aminonaphthols, which have been found to be very effective chiral ligands in catalytic asymmetric phenyl and alkenyl transfer to aldehydes. A novel and efficient synthetic methodology of Ag (I) and Cu (I)/(II)-catalyzed alkynylation of α-amino ester has also been developed.

1-((*S*)-Phenyl(((1′*S*)-1′-phenylethyl)methylamino)methyl)-2-naphthol, chiral ligand **93** was synthesized by direct condensation of the corresponding aldehyde, naphthol and secondary amine (Scheme 5-1).

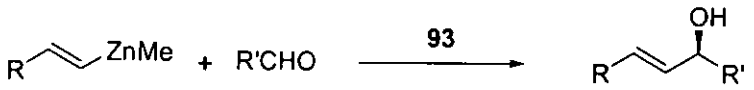


93

Scheme 5-1

This is the first example of straightforward asymmetric synthesis of optically active tertiary aminonaphthol through Mannich type reaction. It means that (S)-(-)-N-α-

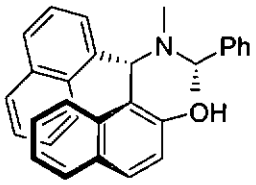
dimethylbenzylamine, as the amine component in this Mannich type reaction, not only possesses the required activity but also can control the stereochemistry completely.



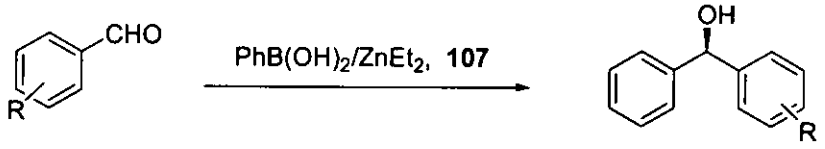
Scheme 5-2

A successful application of chiral ligand **93** in the enantioselective alkenylzinc addition to aldehydes was achieved and a variety of (*E*)-allyl alcohols were obtained in high yields and ee's (92%-99%) (Scheme 5-2).

A novel chiral tertiary aminonaphthol ligand **107**, 1-((*S*)-1'-naphthyl(((1''*S*)-1''-phenylethyl)methylamino)methyl)-2-naphthol was designed and prepared by the one-step procedure which we have developed. This ligand was employed in the phenyl boronic acids-diethyl zinc-aryl aldehydes system and a variety of chiral diaryl methanols were achieved in high chemical yields with excellent enantioselectivities (up to 99%) (Scheme 5-3).



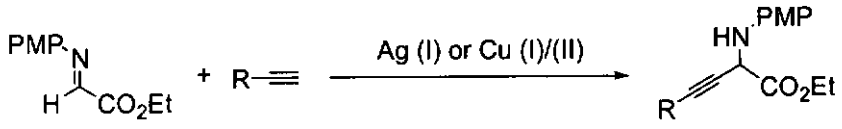
107



Scheme 5-3

To the best of our knowledge, this is the first example of a ligand devoid of planar- and axial-chirality which is able to generate high enantioselectivites in phenyl transfer reactions. Especially noteworthy is that (*R*)-*ortho*-methyl benzhydrol, which was obtained in 99% ee, is the direct precursor of Orphenadrine, an anticholinergic and antihistaminic agent.

Besides the above success in the study of catalytic asymmetric phenyl and alkenyl additions to aldehydes, we have not only developed the first catalytic synthesis of β, γ-alkynyl α-amino acid derivatives but have also extended the applications of Ag alkynilide in organic synthesis by showing the feasibility of direct addition of terminal alkynes to α-imino ester in the presence of a catalytic amount of Ag (I) salts under mild reaction conditions (Scheme 5-4).



Scheme 5-4

Cu (I)/(II) salts were also found to be effective catalysts in the above reaction system. Furthermore, encouraging results (67% ee) were achieved in the initial experiment for asymmetric version of this novel synthetic methodology.

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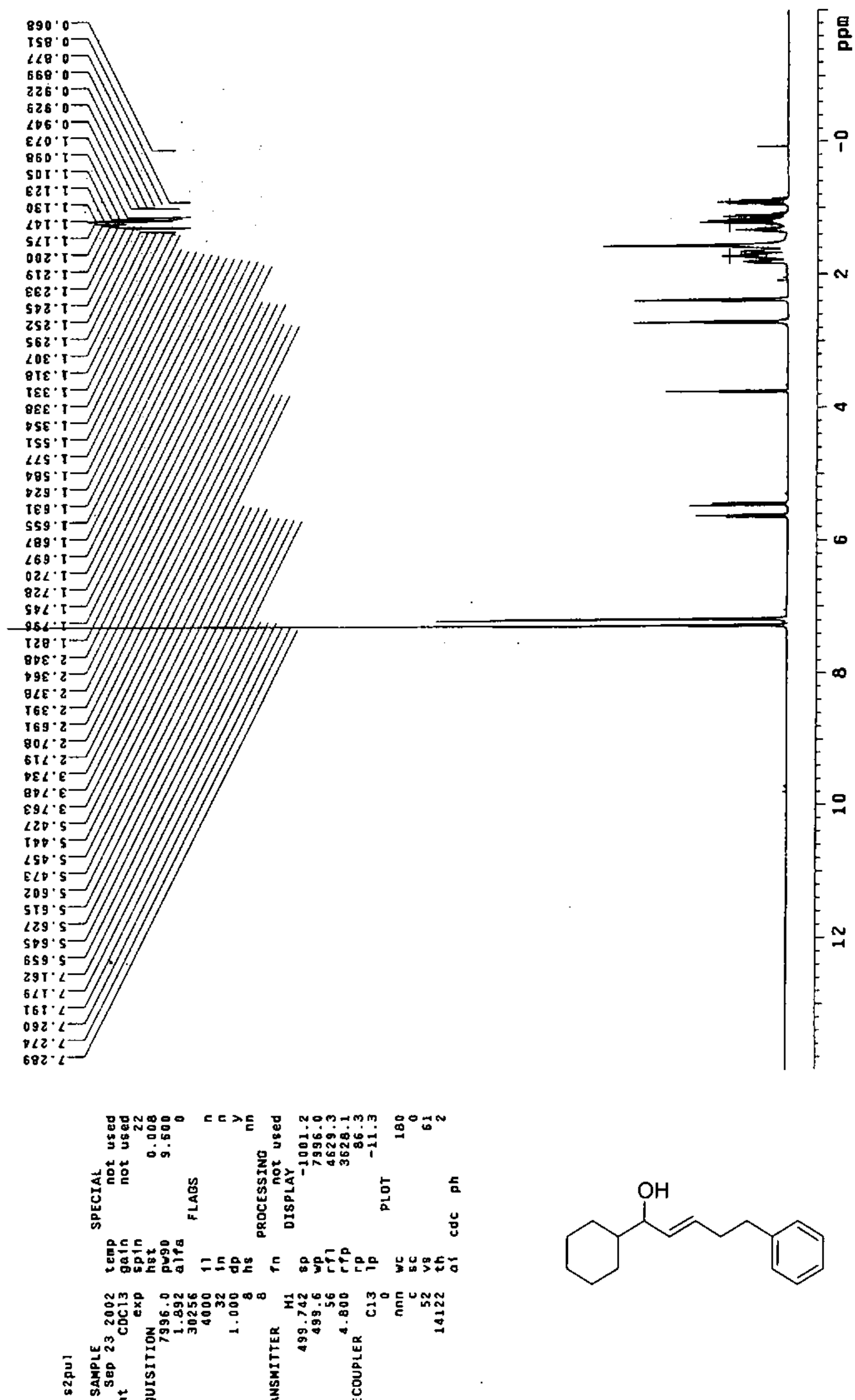
Appendix I

^{1}H NMR Spectra


ppm
OH

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expl  s2pul

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sw           7996.0  pw90          9.600
at           1.892   alfa              0
np             30256          FLAGS
fb              4000  il                n
bs                32  in                n
d1            1.000   dp                y
nt                8   hs               nn
ct                8       PROCESSING
   TRANSMITTER        fn          not used
tn                H1         DISPLAY
sfrq         499.742  sp            -950.6
tof            498.6  wp            7996.0
tpwr              56  rf1           1758.2
pw            4.800   rfp            799.6
    DECOUPLER         rp             83.3
dn               C13  lp             -5.3
dof                0         PLOT
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dmf            14122  th                3
                      at  cdc  ph
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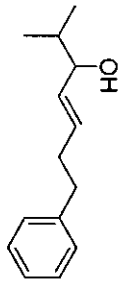

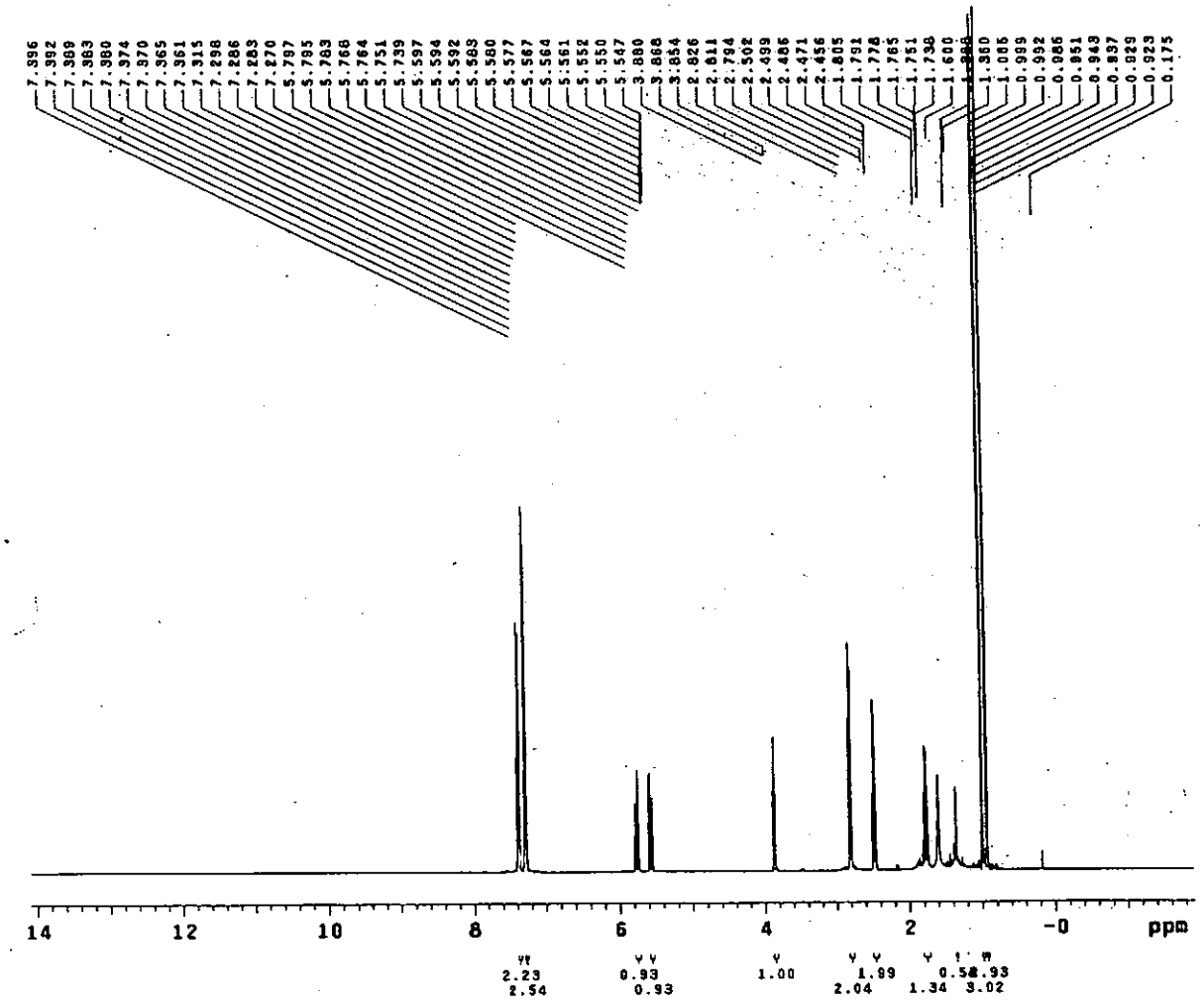

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solvent       CDCl3  gain          not used
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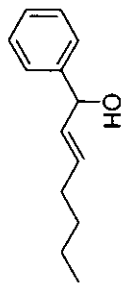
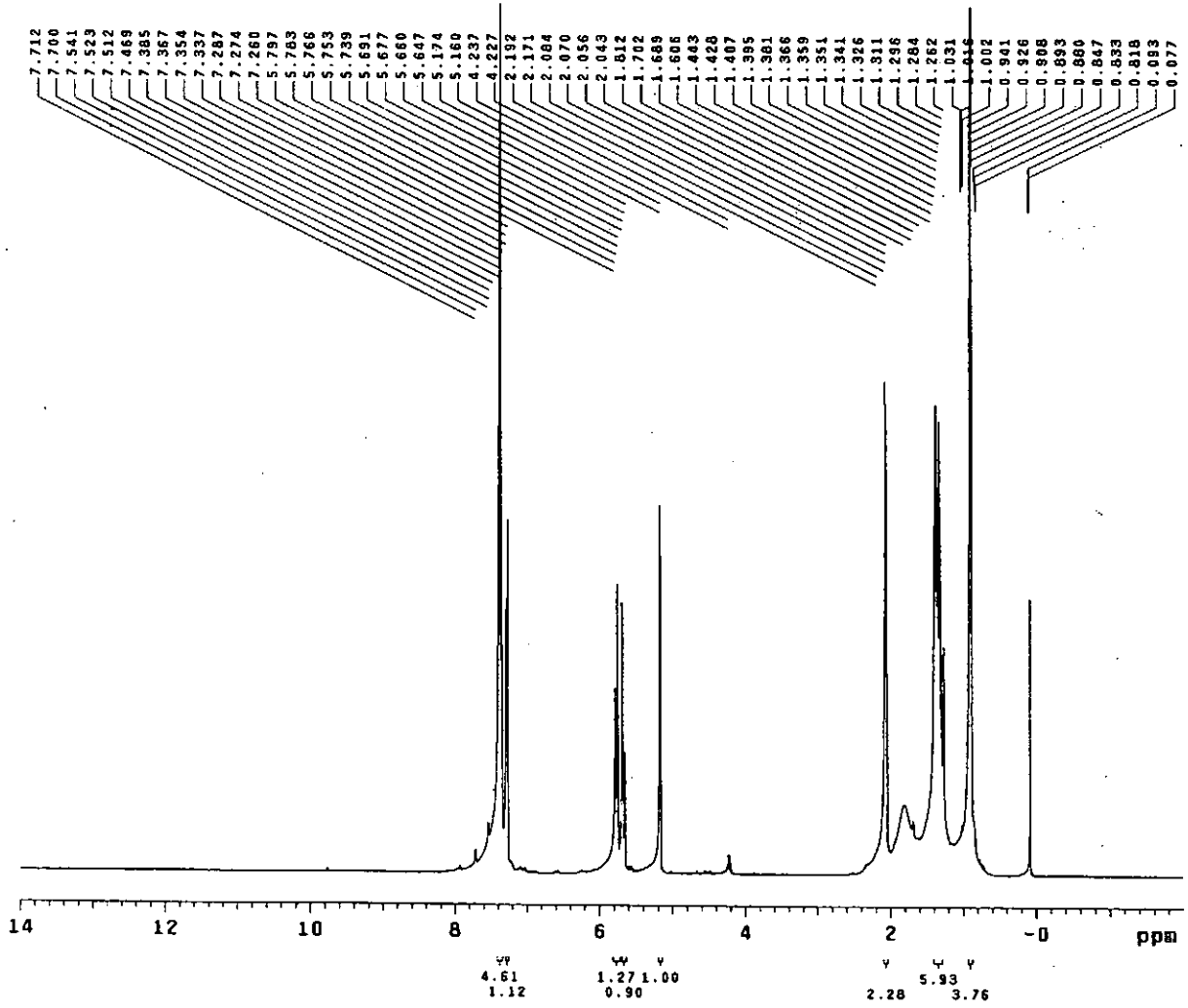
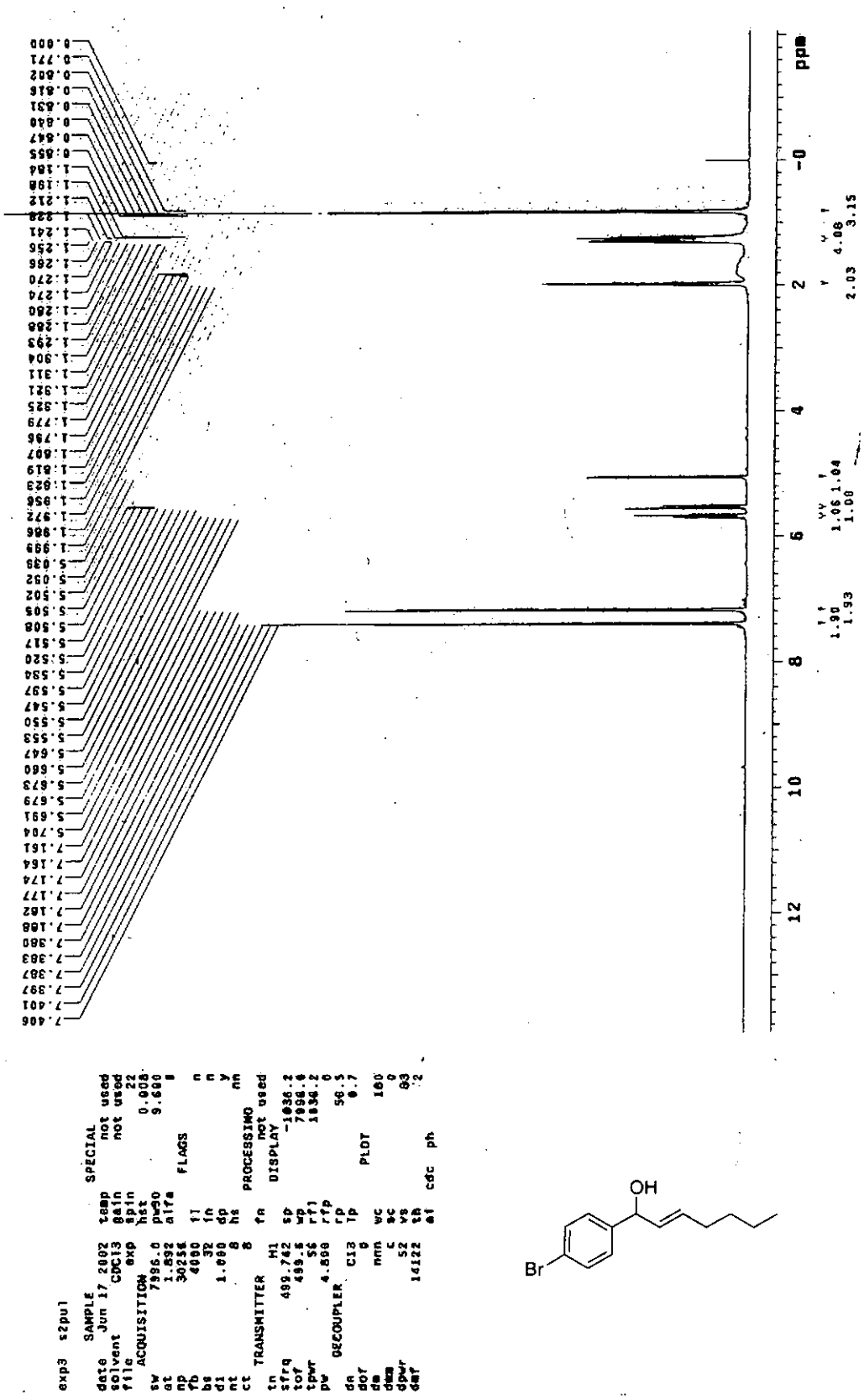
sw           7996.0  pw90           9.600
at           2.049   alfa               0
np          32768          FLAGS
fb           4000    il                 n
bs             32    in                 n
d1          1.000    dp                 y
nt             8     hs                nn
ct             8        PROCESSING
   TRANSMITTER        fn          not used
tn              H1          DISPLAY
sfrq       499.742   sp           -999.3
tof          499.8   wp           7996.0
tpwr            55   rf1          4627.4
pw           4.800   rfp          3628.1
    DECOUPLER        rp            -13.8
dn              C13  lp              3.3
dof               0          PLOT
dm               nnn  wc              180
dmm                c  sc                0
dpwr              52  vs              319
dmf            14122  th                3
                      ai  cdc  ph
```

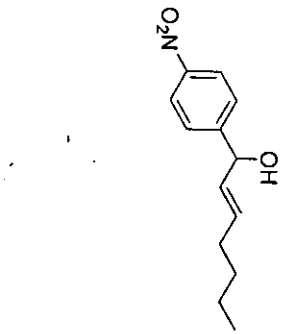


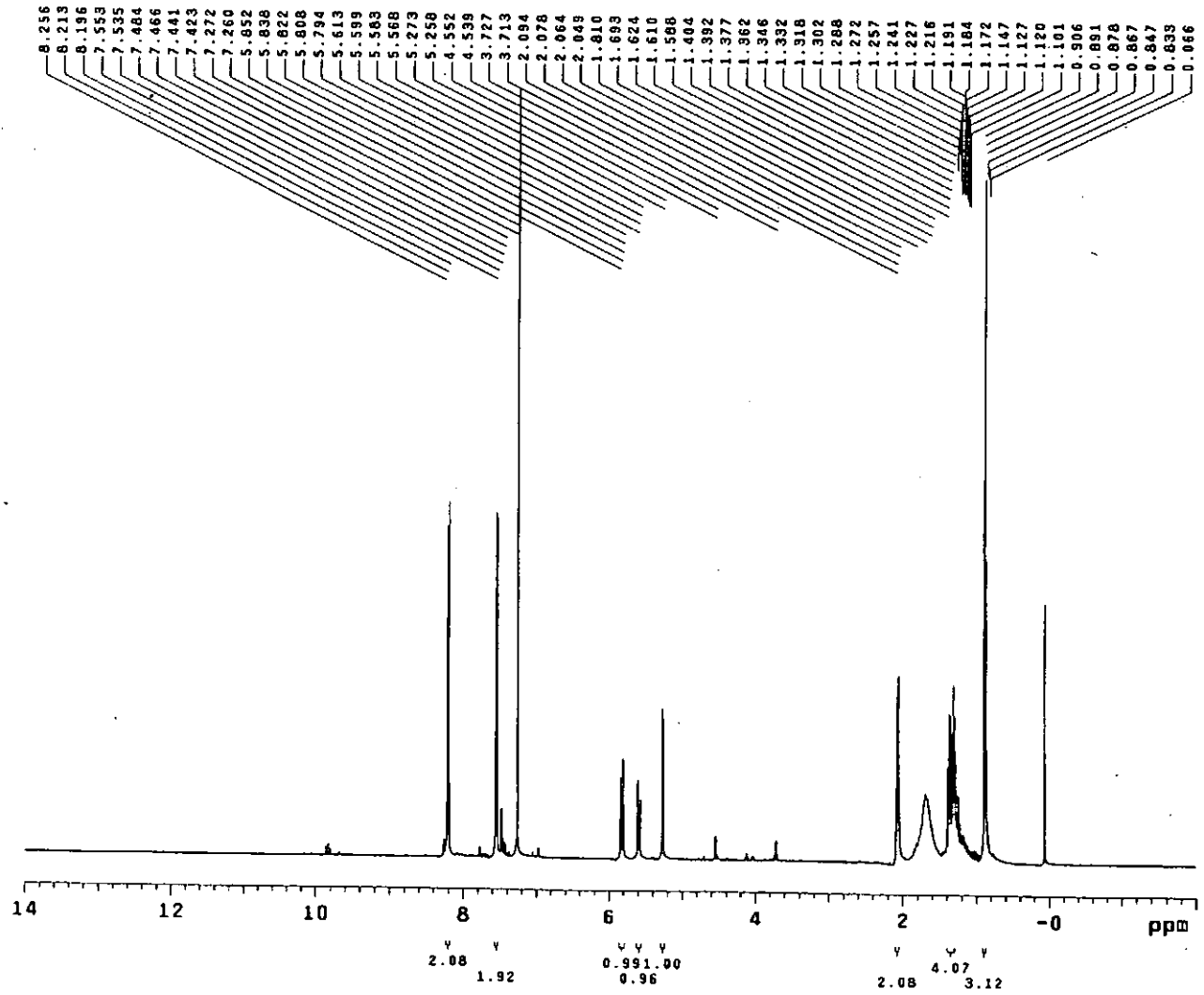


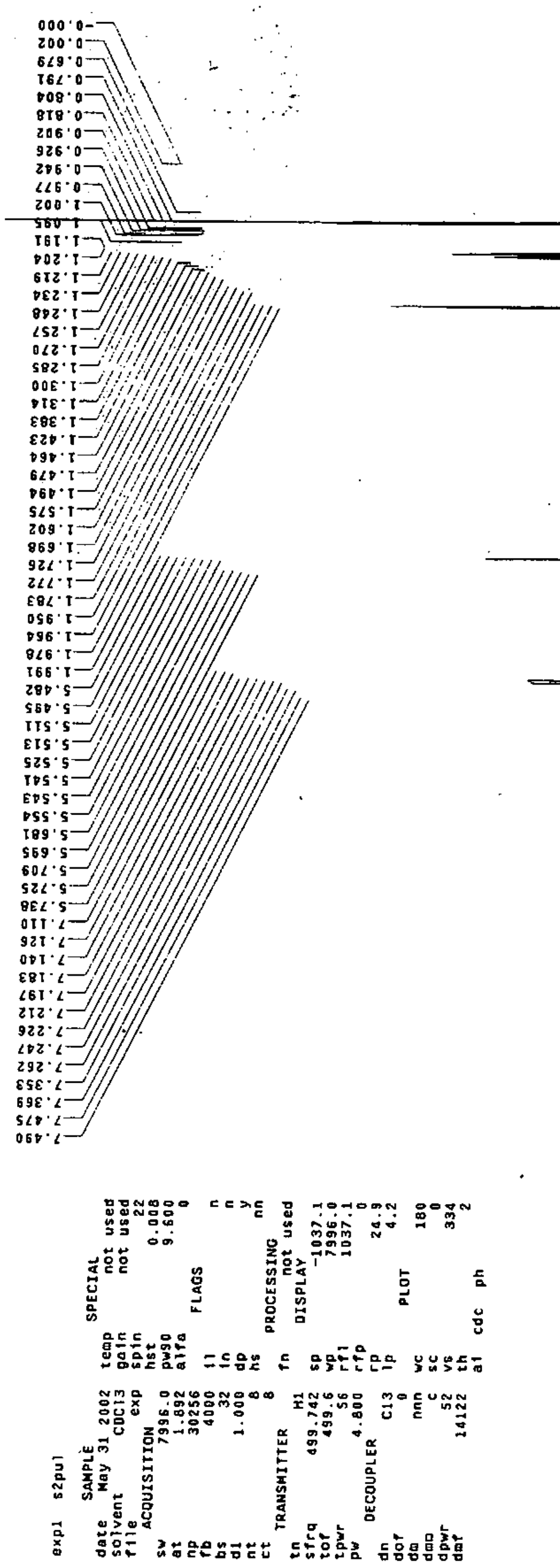

ppm
1.90
1.93
1.06
1.04
1.00
2.03
4.08
3.15
OH
Br

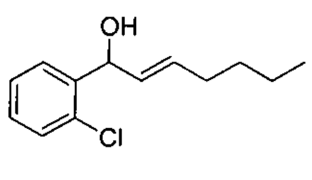
```
expl  s2pul

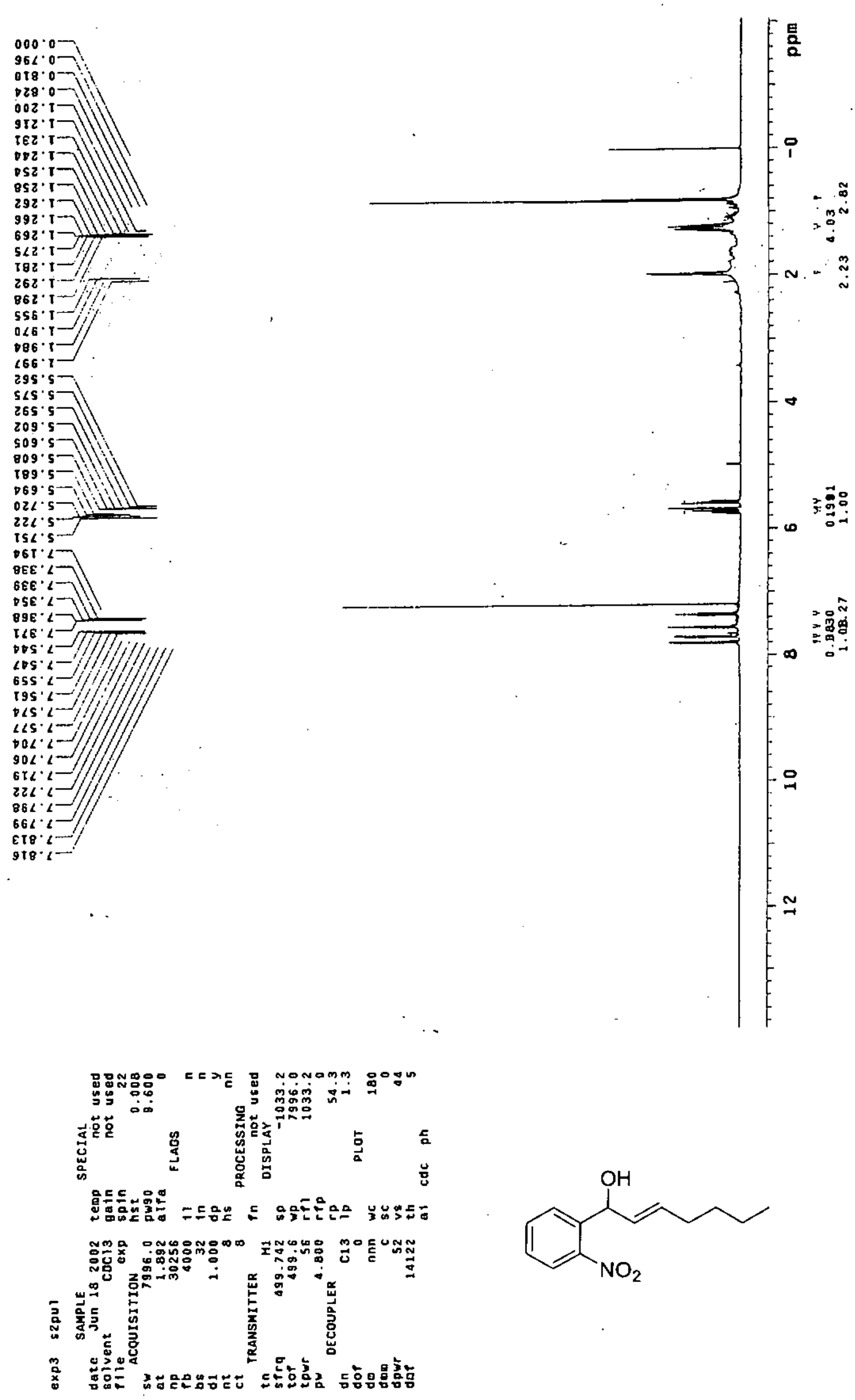
      SAMPLE                    SPECIAL
date    Mar 25 2002     temp        not used
solvent       CDCl3     gain        not used
file            exp     spin              22
   ACQUISITION          hst            0.008
sw           7996.0     pw90           9.600
at           1.892      alfa               0
np           30256           FLAGS
fb           4000       il                 n
bs             32       in                 n
d1           1.000      dp                 y
nt             8        hs                nn
ct             8    PROCESSING
   TRANSMITTER          fn          not used
tn              H1        DISPLAY
sfrq       499.742      sp              -999.7
tof          499.6      wp              7996.0
tpwr            55      rfl             4627.9
pw           4.800      rfp             3628.1
    DECOUPLER           rp               144.3
dn              C13      lp                12.5
dof               0         PLOT
dm              nnn      wc                 180
dmm               c      sc                   0
dpwr             52      vs                  71
dmf           14122      th                   2
                         ai  cdc  ph
```





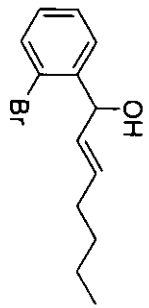


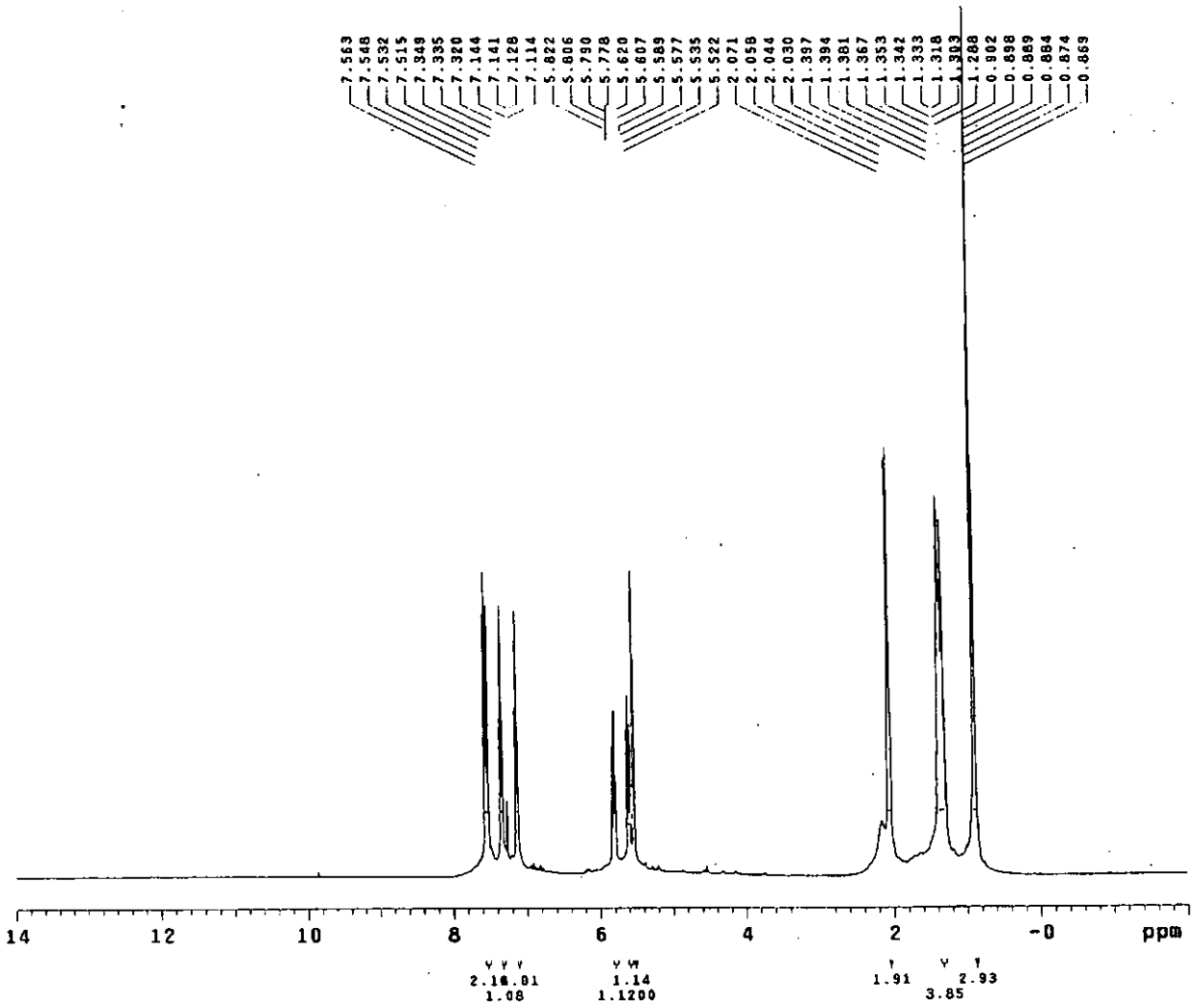

OH
Cl

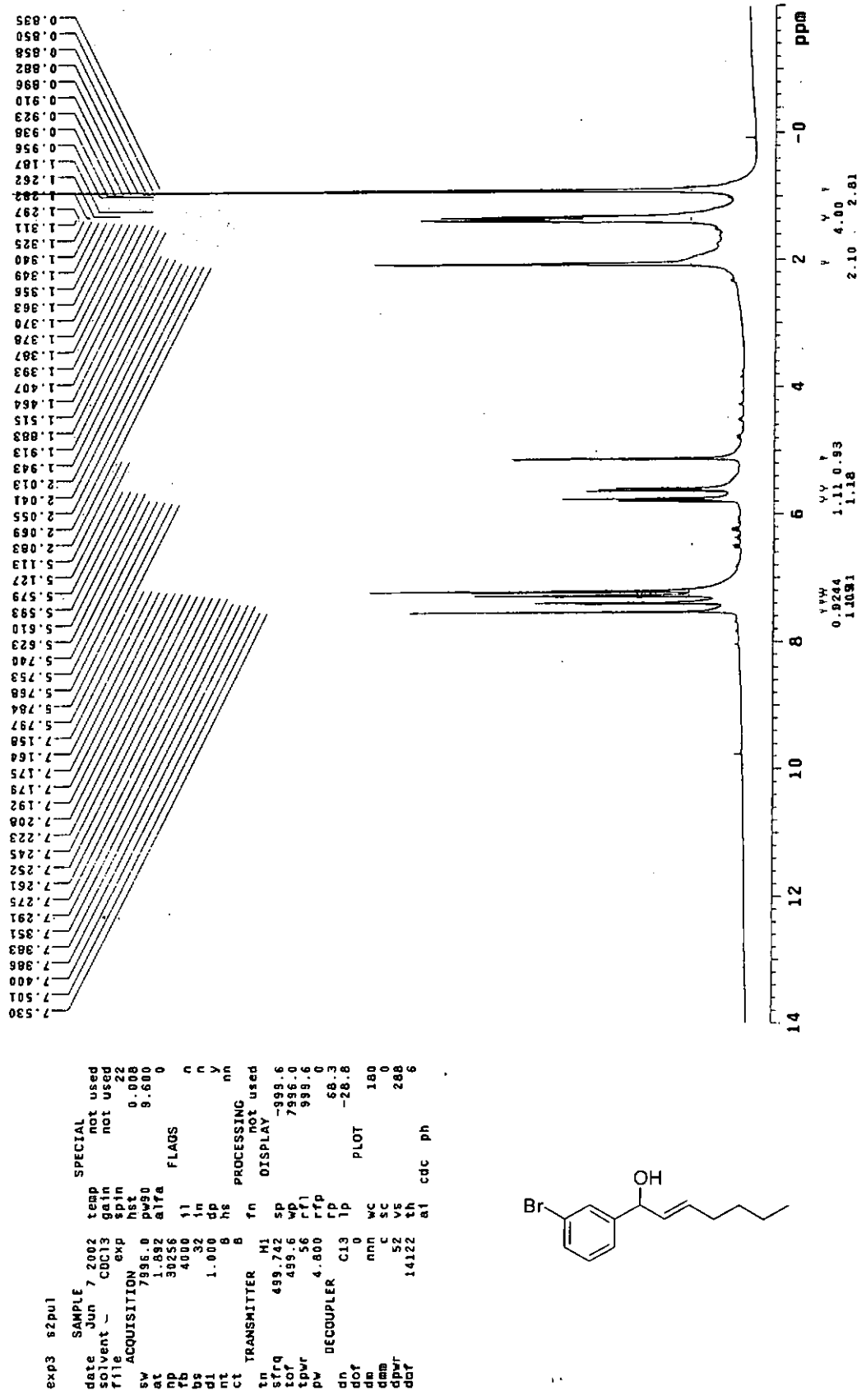

OH
NO2
ppm

exp3 s2pul

SAMPLE		SPECIAL	
date	Jun 11 2002	temp	not used
solvent	CDCl3	gain	not used
file	exp	spin	22
ACQUISITION		hst	0.008
sw	7996.0	pw90	9.600
at	1.892	alfa	0
np	30256	**FLAGS**	
fb	4000	il	n
bs	32	in	n
d1	1.000	dp	y
nt	8	hs	nn
ct	8	**PROCESSING**	
TRANSMITTER		fn	not used
tn	H1	**DISPLAY**	
sfrq	499.742	sp	-999.6
tof	499.6	wp	7996.0
tpwr	56	rf1	999.6
pw	4.800	rfp	0
DECOUPLER		rp	41.5
dn	C13	lp	-15.0
dof	0	**PLOT**	
dm	nnn	wc	180
dmm	c	sc	0
dpwr	52	vs	253
dmf	14122	th	13
		ai	cdc ph

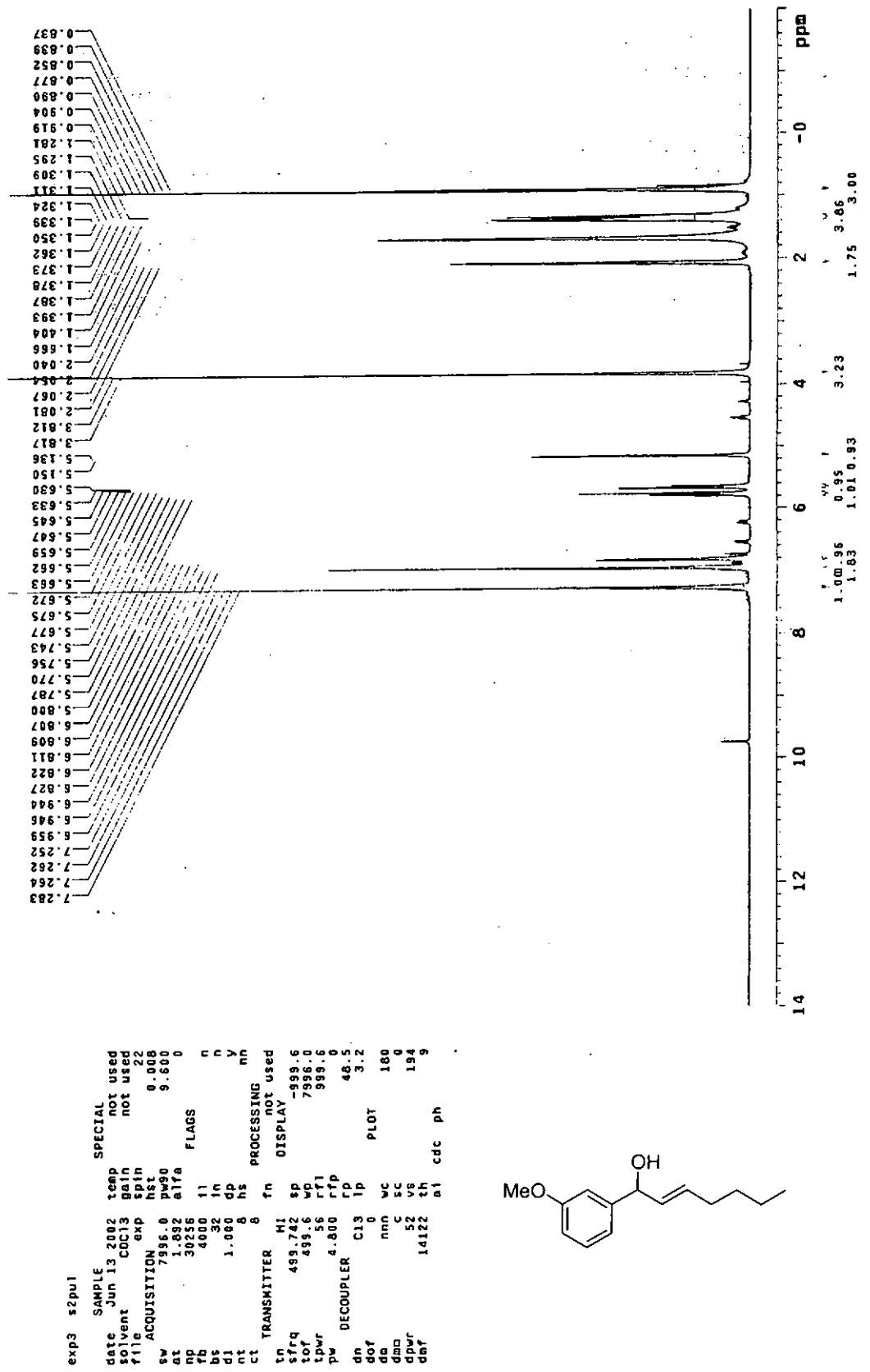




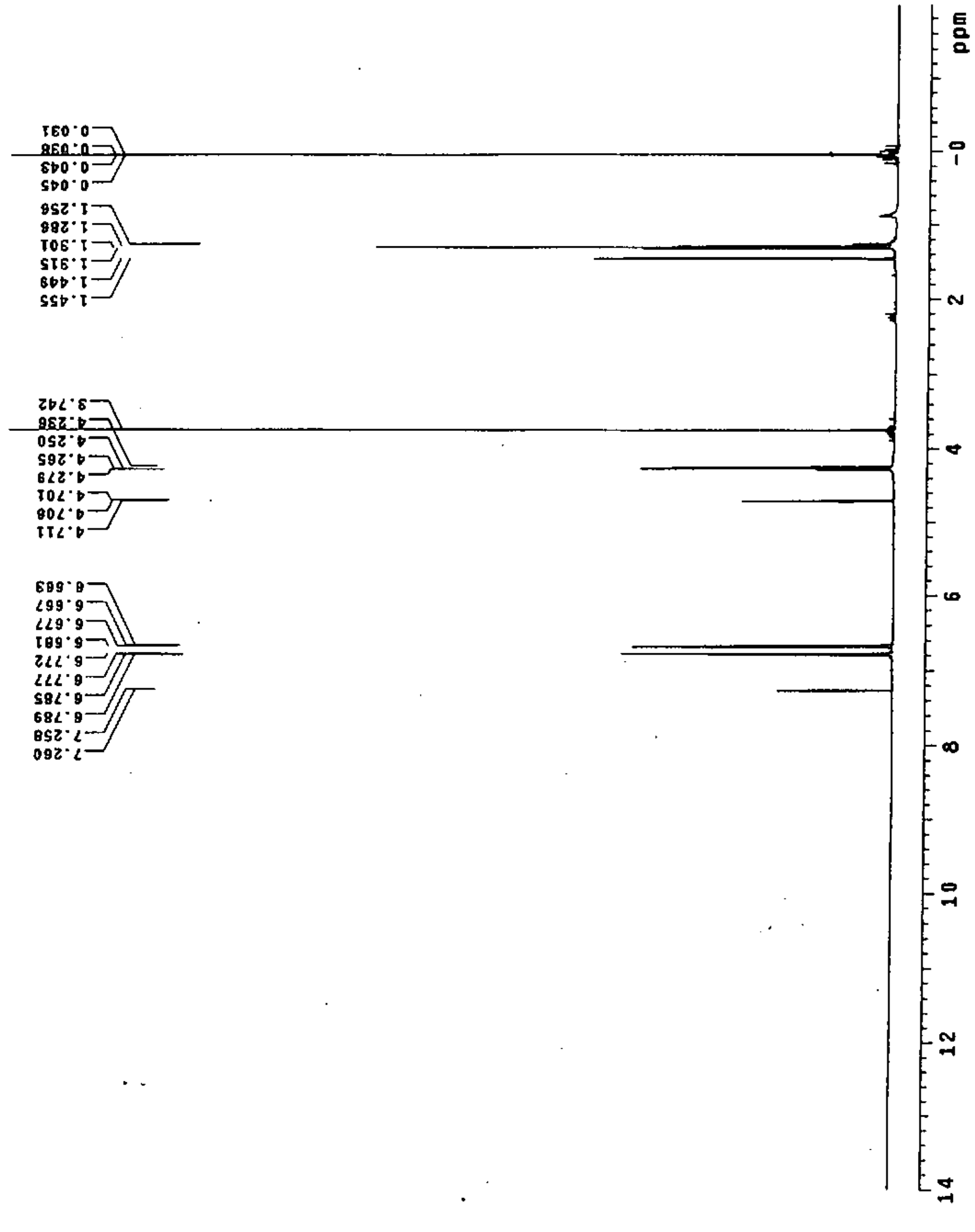


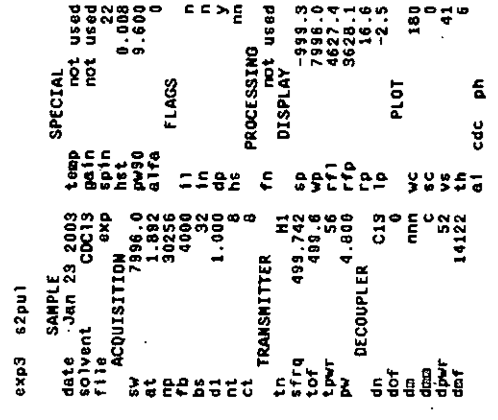

```
exp3  s2pul

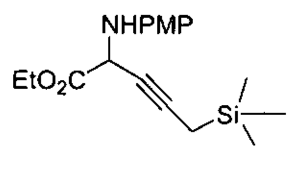
          SAMPLE
date   Jun  7 2002      temp          not used      SPECIAL
solvent =    CDCl3      gain          not used
file       exp          spin                22
  ACQUISITION           hst               0.008
sw          7996.0      pw90              9.600
at          1.892       alfa                  0
np          30256                FLAGS
fb           4000       ll                    n
bs             32       in                    n
d1          1.000       dp                    y
nt             8       hs                   nn
ct             8   PROCESSING
                       not used
tn   TRANSMITTER       fn    DISPLAY
sfrq      499.742      sp                -999.6
tof       499.6        wp                7996.0
tpwr         56        rfl               999.6
pw         4.800       rfp                   0
   DECOUPLER           rp                 68.3
dn         C13         lp                -28.8
dof           0                PLOT
dm          nnn        wc                  180
dmm             c      sc                    0
dpwr           52      vs                  288
dof         14122      th                    6
                       at    cdc  ph
```




```
exp3  s2pul
      SAMPLE                    SPECIAL
   date  Jun 13 2002  temp          not used
   solvent     CDCl3  gain          not used
   file         exp    spin                22
     ACQUISITION       hst              0.008
   sw          7996.0  pw90             9.600
   at             1.892  alfa                0
   np            30256  FLAGS
   fb             4000  il                   n
   bs               32  in                   n
   d1            1.000  dp                   y
   nt                8  hs                  nn
   ct                8  PROCESSING
     TRANSMITTER       fn      not used
   tn               H1  DISPLAY
   sfrq        499.742  sp          -999.6
   tof           499.6  wp          7996.0
   tpwr             56  rfl          999.6
   pw            4.800  rfp              0
     DECOUPLER         rp            48.5
   dn              C13  lp             3.2
   dof               0  PLOT
   dm              nnn  wc              180
   dmm               c  sc                0
   dpwr             52  vs              194
   dmf           14122  th                9
                        al   cdc  ph
```

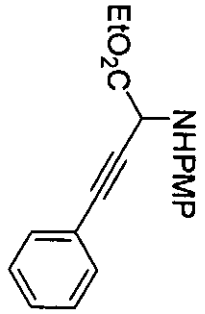

ppm

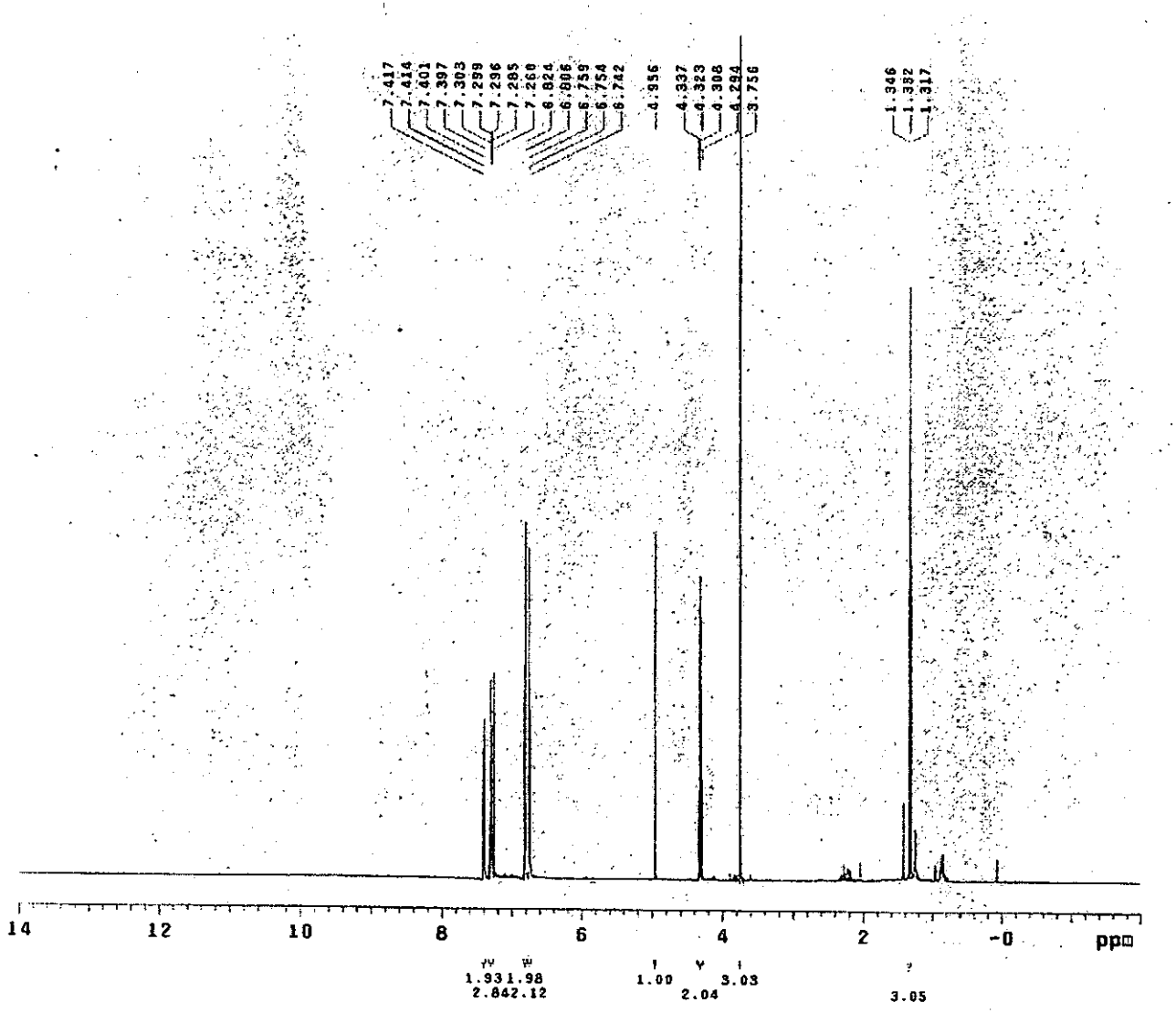



NHPMP
EtO2C
Si

```
exp1  s2pul

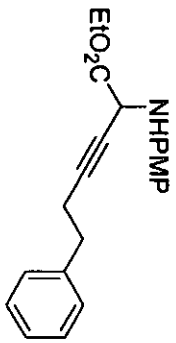
      SAMPLE                    SPECIAL
date   Nov 29 2002      temp          not used
solvent       CDCl3     gain          not used
file           exp      spin            22
   ACQUISITION          hst           0.008
sw            7996.0     pw90          9.600
at            1.892      alfa             0
np            30256                FLAGS
fb             4000      il                n
bs               32      in                n
d1            1.000      dp                y
nt                8      hs               nn
ct                8           PROCESSING
   TRANSMITTER           fn          not used
tn                H1           DISPLAY
sfrq         499.742      sp            -999.6
tof            499.6      wp            7996.0
tpwr              55      rfl.          999.6
pw            4.800      rfp              0
   DECOUPLER             rp            108.2
dn               C13      lp            -28.8
dof                0           PLOT
dm               nnn      wc              180
dmm                c      sc                0
dpwr              52      vs               30
dof            14122      th               13
                          al   cdc   ph
```

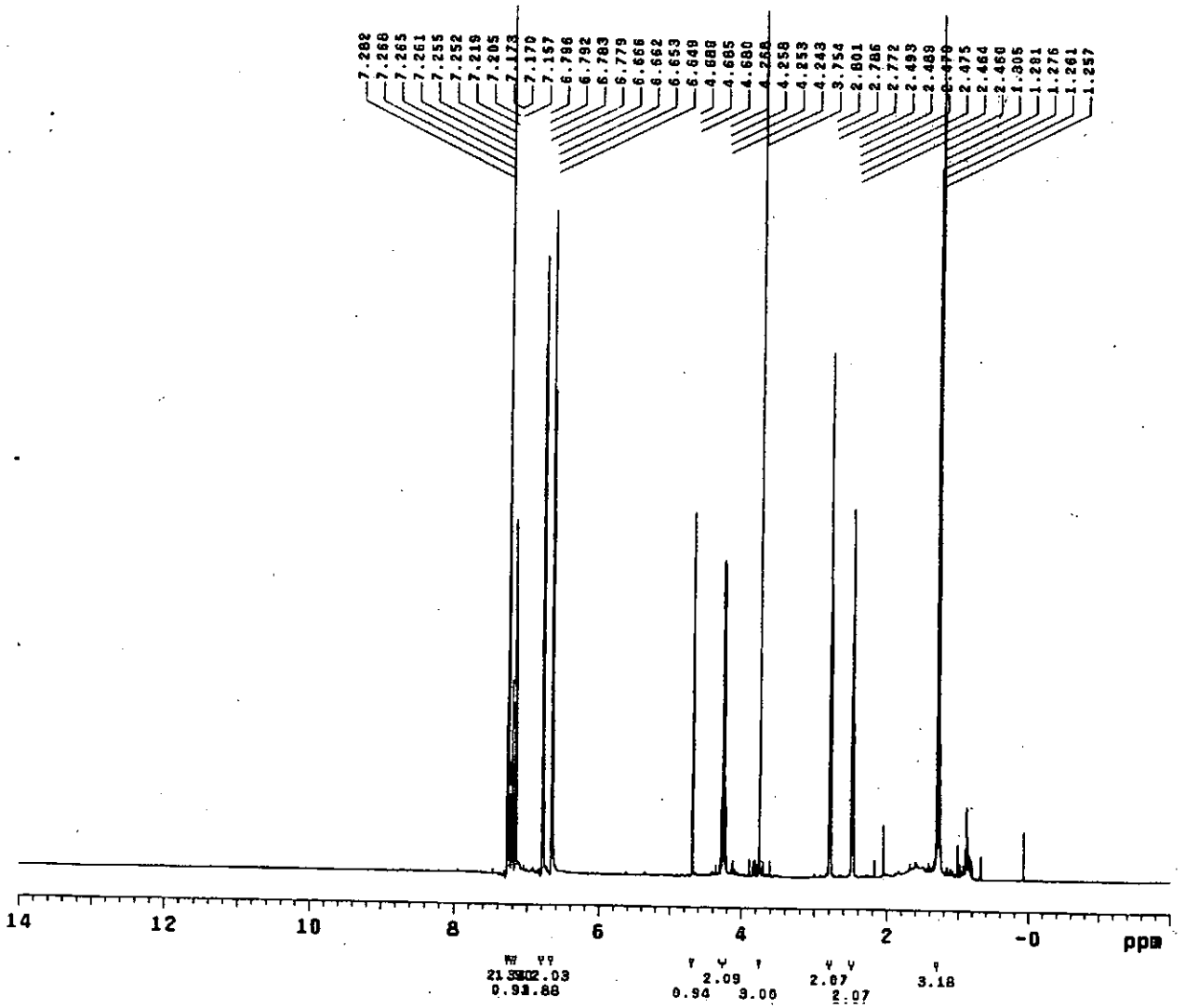


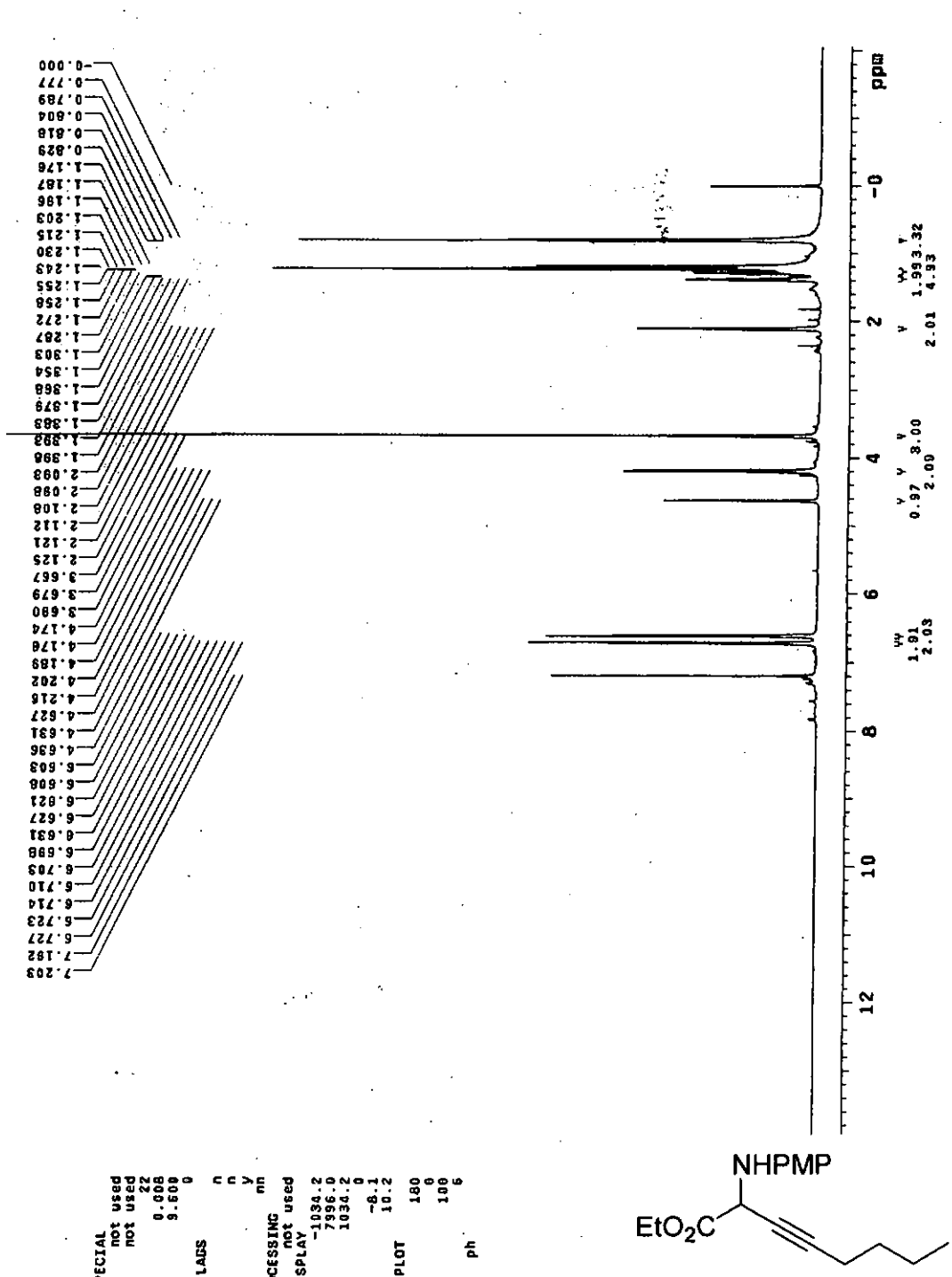


```
exp1  s2pul

        SAMPLE                  SPECIAL
date    Jan 16 2003     temp        not used
solvent       CDCl3     gain        not used
file           exp      spin              22
   ACQUISITION          hst            0.008
sw          7996.0      pw90           9.600
at            1.892     alfa               0
np           30256              FLAGS
fb            4000      il                 n
bs              32      in                 n
d1           1.000      dp                 y
nt               8      hs                nn
ct               8          PROCESSING
   TRANSMITTER          fn          not used
tn              H1          DISPLAY
sfrq        499.742     sp            -999.6
tof           499.6     wp            7996.0
tpwr             56     rfl            999.6
pw            4.800     rfp                0
    DECOUPLER           rp              14.2
dn              C13     lp             -28.8
dof               0           PLOT
dm              nnn     wc               180
dmm               c     sc                 0
dpwr             52     vs                65
dmf           14122     th                16
                        ai   cdc   ph
```






NHPMP
EtO2C

Appendix II

Publications

1. Ji, Jian-Xin; Au-Yeung, Terry T.-L.; Wu, Jing; Yip, C. W.; Chan, Albert S. C., "Efficient Synthesis of β, γ-Alkynyl α-Amino Acid Derivatives by Ag (I)-Catalyzed Alkynylation of α-Imino Ester", *Adv. Synth. Catal.*, **2004**, 346, 42-46.

2. Qiu, Li-Qin; Wu, Jing; Chan, S. S.; Au-Yeung, Terry T.-L.; Ji, Jian-Xin; Guo, Rongwei; Pai, Chengchao; Zhou, Zhongyuan; Li, Xing-Shu; Fan, Qing-hua; Chan, Albert S. C., "Remarkblely diastereoselective synthesis of a novel chiral biphenyl diphosphine ligand and its applications in asymmetric hydrogenation", *Proceedings of the National Academy of Sciences, USA*, **2004**, 101(16), 5815-5820.

3. Ji, Jian-Xin; Qiu, Li-Qin; Yip, Chiu Wing; Chan, Albert S. C., "A Convenient, One-step Synthesis of Optically Active Tertiary Aminonaphthol and Its Applications in the Highly Enantioselective Alkenylations of Aldehydes", *J. Org. Chem.* **2003**, 68(4), 1589-1590.

4. Ji, Jian-Xin; Yip, C. W.; Chan, Albert S. C., "Highly Enantioselective Alkenylation of Aldehydes Promoted by Chiral Tertiary Aminonaphthol", *Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States,* **March 23-27, 2003**, ORGN 460.

5. Wu, jing; Ji Jian-Xin; Guo, Rongwei; Yeung, Chi-Hung; Chan Albert S. C., "Chiral [RuCl(dipyridy(phosphane)(1,2-diamine)]Catalysts: Applications in Asymmetric Hydrogenation of a Wide Range of simple ketones", *Chem. Eur. J.* **2003**, 9 (13), 2963-2968.

6. Qiu, Li Qin; Qi, Jian Ying; Ji, Jian Xin; Zhou, Zhong Yuan; Yeung, Chi Hung; Choi, Michael C. K.; Chan, Albert S. C., "(R)-(6,6'-Dihydroxybiphenyl-2,2'-diyl)bis(diphenylphosphine oxide) methanol solvate", *Acta Crystallographica*, Section C: Crystal Structure Communications, **2003**, C59(1), o33-o35.

7. Ji, Jian-Xin; Wu, Jing; Au-Yeung, Terry T.-L.; Yip, C. W.; Chan, Albert S. C., "Highly Enantioselective Synthesis of Diarylmethanols: Central Chiral Tertiary Aminonaphthol Catalyzed Phenyl Transfer to Aryl Aldehydes", in preparation for submission to *Angew. Chem. Int. Ed.*

8. Qi, Jian Ying; Ji, Jian Xin; Chan, Albert S.C., "A Convenient, Highly Efficient Method for the Protections of Aldehydes Using Hydrous Ruthenium(III) Trichloride as Catalyst", in preparation for submission to *Tetrahedron Lett.*

9. Ji, Jian-Xin; Yip, C. W.; Chan, Albert S. C., "Synthesis and Applications of Novel Amino Thiol Ligands", *Nineth Symposium on Chemistry Postgraduate Research in Hong Kong,* **2002**, O-15.

10. Ji, Jian-Xin; Yip, C. W.; Chan, Albert S. C., " Catalytic Asymmetric Alkenylation of Aldehydes Promoted by Chiral Teriary Aminonaphthol", *Tenth Symposium on Chemistry Postgraduate Research in Hong Kong,* **2003**, O-25.