Novel bisisoquinolines : synthesis, resolution and application in asymmetric Henry reaction

Yao, Qiong Ji

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SYNTHESIS, RESOLUTION AND APPLICATION IN
ASYMMETRIC HENRY REACTION**

YAO QIONG JI

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YAO QIONG JI

SCHOOL OF CHEMICAL AND BIOMEDICAL ENGINEERING

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ABSTRACT

This research project focuses on the synthesis of bisoquinolines and examines their application as catalysts in the Henry reaction.

Racemic 1,2- and 1,3-bisisoquinolines have been synthesized using the classical double Bischler-Naprialski route. Resolution of 1,2-bisisoquinoline parent compound C_1 -1',2',3',4'-tetrahydro-1,1'-bisisoquinoline was achieved using (*S*)-(-)- α -methylbenzyl isocyanate, while resolution of the *racemic* 1,3-bisisoquinoline parent compound 1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) was achieved *via* the diastereomeric salt formation using (*L*)-(+)-citramalic acid. The absolute configuration of this 1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) was established by X-ray crystallographic analysis. Mono-, di- and bridged *N*-alkyl derivatives of C_1 -1',2',3',4'-tetrahydro-1,1'-bisisoquinoline and 1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) were successfully synthesized to explore their chemistry.

Application of the enantiopure 1,2- and 1,3-bisisoquinolines in the asymmetric Henry reaction was examined in details. A well-defined and efficient catalytic system comprising chiral C_1 -tetrahydro-1,1'-bisisoquinoline and CuCl in the ratio of 2:1 has been developed for the enantioselective Henry reaction. The catalytic efficiencies of the chiral C_1 -tetrahydro-1,1'-bisisoquinolines were found to be governed to a great extent by the structural constraints and the type of substituent at the sp^3 -*N* atom. Aromatic and aliphatic aldehydes reacted with nitromethane to give β -nitroalcohols in very high yields (up to 95%) and enantioselectivities (up to 91% ee). The catalyst system developed was found to be simple in operation since no special precautions were taken to exclude moisture or air from the reaction flask and no additives were required for activation.

The chiral complex derived from *N*-methyl-*C*₁-tetrahydro-1,1'-bisisoquinolines and Cu(I)Cl promoted the diastereoselective Henry reaction of nitroethane with a series of aromatic and aliphatic aldehydes. The nitroalcohol adducts were obtained in excellent yields (up to 95%), moderate *anti*-selectivity (up to 2.6:1) and good enantioselectivity (up to 92% *ee*) without any special precautions to exclude moisture or air.

The ability of 1,2- and 1,3- bisisoquinolines to function as organocatalysts for the Henry reaction was also investigated. Both successfully catalyzed the addition of nitroalkanes to α -ketoesters and aldehydes giving the corresponding nitroalcohol adducts in excellent yields under very mild conditions. Among the different bisisoquinoline types examined, *C*₁-symmetric bisisoquinolines (amine-imine types) were found to be more efficient than *C*₂-symmetric bisisoquinolines (diamine-diimine types). 1,2-bisisoquinolines were also more efficient than 1,3-bisisoquinoline. The best yields (up to 99%) were obtained using 10 mol% *C*₁-1,2,3,4,-tetrahydro-1,1'-bisisoquinolines. Moderate *syn/anti* diastereoselectivity of up to 2:1 was obtained in the addition of nitroethane to α -ketoesters and aldehydes.

The excellent catalytic results obtained in this thesis represent a major contribution to the application of chiral bisisoquinolines as ligands in asymmetric Henry reaction.

LIST OF ABBREVIATIONS

Ar	Aryl group
BINOL	1,1'-Binaphthol
BIQ	Bisisoquinoline
br	Broad
Bu ₂ O	Dibutyl ether
c	Concentration
°C	Degrees Celsius
Calcd	Calculated
CDCl ₃	Deuterated chloroform
CH ₂ Cl ₂	Dichloromethane
CH ₃ CN	Acetonitrile
ClCH ₂ CH ₂ Cl	Dichloroethane
cm ⁻¹	Wavenumber (s)
¹³ C NMR	Carbon-13 Nuclear Magnetic Resonance
CuBr	Copper(I) bromide
CuCl	Copper(I) chloride

CuCl_2	Copper(II) chloride
CuI	Copper(I) iodide
CuOAc	Copper(I) acetate
Cu(OAc)_2	Copper(II) acetate
d	Doublet
dd	Doublet of doublet
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL-H	Diisobutyl aluminium hydride
DMAP	<i>N,N</i> -Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DPEN	1,2-Diphenylethylenediamine
EA	Ethyl acetate
ee	Enantiomeric excess
equiv	Equivalent
ESI	Electrospray impact ionisation
Et_2O	Diethyl ether
Et_2Zn	Diethylzinc

Et ₃ N, TEA	Triethylamine
EtOH	Ethanol
FTIR	Fourier transform infrared spectroscopy
g	Grams
H	Hours
HMBC	Heteronuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum coherence
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
Hz	Hertz
IPA	Isopropyl alcohol
(<i>i</i> -Pr) ₂ O	Isopropyl ether
<i>J</i>	Coupling constant
m.p.	Melting point
<i>m/z</i>	Mass/charge
MeOH	Methanol
M	Multiplet

mg	Milligrams
μL	Microliter
mmol	Micromoles
NaBH_3	Sodium borohydride
NaCNBH_3	Sodium cyanoborohydride
NaOBu	Sodium butoxide
<i>n</i> -hex	Hexane
nm	Nanometer
NMR	Nuclear Magnetic Resonance
PPA	Polyphosphoric acid
ppm	Parts per million
Py	Pyridine
r.t.	Room temperature
S	Singlet
Salen	<i>N,N'</i> -disalicylidene-ethylenediaminato
t	Triplet
<i>t</i> -BuOH	<i>tert</i> -Butanol

<i>t</i> -BuOMe	<i>tert</i> -Butyl methyl ether
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
Ts	Toluenesulfonyl, tosyl group
UV	Ultraviolet
δ	Chemical shift in parts per million downfield from tetramethylsilane

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Chapter 1. Introduction

1.1. Chirality and its importance

A molecule that does not have a plane of symmetry is said to be chiral. Chirality means an object is not superimposed on its mirror image, meaning “handedness”.¹ The pair of nonsuperimposable mirror-image isomers are called enantiomers. Enantiomers have identical chemical and physical properties in the absence of an external chiral influence. Chirality is very important in nature and in our bodies. Since enzymes and cell surface receptors are chiral, the two enantiomers of a *racemic* drug may interact differently with a receptor leading to different pharmacological effects. For example, one enantiomer may be therapeutically effective, while the other one may be less effective, ineffective or even toxic. For example, (*R*)-thalidomide is effective for morning sickness, however (*S*)-thalidomide is teratogenic. Hence, chirality is of prime significance in the pharmaceutical industry. Around 56% of the currently used drugs were chiral molecules and around 88% of these chiral drugs are marketed as racemates.^{2,3} The U.S. Food and Drug Administration (FDA) announced new rules mandating that the therapeutic and toxicity effects of both enantiomers of *racemic* drugs are required to be well investigated and evaluated so their effects are predictable.⁴

There are three main approaches to produce compounds in enantiopure forms: (1) chiral pool synthesis (from naturally occurring chiral sources), (2) resolution of *racemic* compounds, and (3) asymmetric catalysis. The first two methods suffer from potentially severe drawbacks. Compounds from the chiral pool synthesis are limited while resolution of *racemic* compounds can provide only up to 50% of the desired enantiomer. Asymmetric catalysis can afford various chiral molecules in potentially quantitative yields.

Hence, asymmetric catalysis has become one of the most extensively explored research areas and approaches to chiral compounds.

The use of chiral ligands to catalyze asymmetric reactions constitutes a major research approach. To this end, many types of chiral ligands have been investigated. Specifically, application of chiral nitrogen ligands in the form of metal complexes or organocatalysts in asymmetric transformations is well documented.⁵⁻⁷ For example, privileged catalysts based on *salen* have been extensively used in many enantioselective reactions.⁸⁻¹¹

We^{12,13} and others^{14,15} have been interested in constructing chiral bidentate bisoquinolines and employing them as catalysts for various enantioselective reactions. Bisisoquinolines¹⁶⁻¹⁹ offer structurally constrained motifs that are similar to the well-used and explored chiral 1,1'-binaphthyls.²⁰⁻²⁴

1.2. Chemistry of bisoquinolines

In the following sections, synthesis, resolution and application of BIQs in various asymmetric reactions will be presented.

1.2.1. Synthesis of bisoquinolines

Bisisoquinolines have been synthesized mainly by oxidative/reductive coupling²⁵⁻³¹ and Bischler-Napieralski reactions.³²⁻³⁸

1.2.1.1. Oxidative/reductive coupling

Synthesis of 1,1'-bisisoquinolines through coupling reactions was first reported by Case in 1952.³⁹ Coupling of 1-bromisoquinoline **1** using copper powder under Ullmann reaction conditions gave 1,1'- bisisoquinolines **2** (Scheme 1).^{40,41} This method was

versatile and could also be applied to coupling of 3-bromoisoquinoline **2** to give 3,3'-bisisoquinolines **4** in 13% yield (Scheme 1).

Conditions: i. Cu powder, 210-230 °C, 2 h; ii. Cu powder, 260-270 °C, 2 h.

Scheme 1

In 1984, Tiecco *et. al.* reported novel nickel coupling catalyst which involves *in situ* generation of nickel (0) (by treatment of NiCl_2 with Zinc and PPh_3 in THF or DMF) to couple nitrogen containing heterocyclic halides. Thus, bisisoquinolines **2**, **4** were obtained in high yields (70-83%) by the homo-coupling of haloisoquinolines **5** and **6**, respectively (Scheme 2).⁴²

Conditions: i. NiCl_2 , PPh_3 , Zn, 50 °C

Scheme 2

The same coupling approach was also adopted by Chelucci⁴³ and Hirao⁴⁴ *et. al.* for the synthesis of 8,8'-dialkyl-1,1'-bisisoquinolines. The 8-alkyl-1-haloisoquinoline obtained from *o*-alkylbenzaldehydes through Pomeranz-Fritsch reaction⁴⁵⁻⁴⁹ and halogenations underwent the Ullmann coupling to give the desired 1,1'-BIQ functionalized at 8,8'-positions (Scheme 3).

Conditions: i. $(\text{MeO})_2\text{CH}_2\text{CH}_2\text{NH}_2$, benzene, reflux, 24 h;
 ii. (a). ClCO_2Et , -10 °C, THF; (b). P(OMe)_3 ; (c). TiCl_4 , CH_2Cl_2 , reflux for 36 h;
 iii. H_2O_2 , AcOH, 60 °C, 20 h; iv. Ac_2O , NaOH; v. POCl_3 , reflux, 3 h;
 vi. NiCl_2 , PPh_3 , Zn, 50 °C, 5 h.

Scheme 3

4,4'-Functionalized 1,1'-bisisoquinolines were recently reported by Laschat through the oxidative coupling of 1-chloro-4-hydroxyisoquinoline **7** (and also from related biphenyl-

and phenylpyrimidine ethers) (Scheme 4).⁵⁰ The resulting 4,4'-functionalized 1,1'-BIQs **9** were thought to be potential precursors for metallomesogens.⁵¹⁻⁵³

Conditions: i. Biphenyl/phenylpyrimidine esters, K_2CO_3 , CH_3CN , reflux for 5 h;
ii. $NiCl_2$, PPh_3 , Zn , $60\text{ }^\circ\text{C}$, 3 h.

Scheme 4

Intramolecular oxidative coupling of tethered 1-chloroisoquinolines was also used to prepare chiral 1,1'-BIQs in which complete rotation of the isoquinoline rings around the central C1-C1' bond is blocked.^{54,55} For example, the dioxo-bridged 1,1'-bisisoquinolines **13** and **14** were synthesized by Yamamoto *et al.* using Ullmann coupling (Scheme 5).⁵⁶

Conditions: i. Dibromoethane/1,3-bis(bromomethyl)-5-methoxybenzene, DMF, CaCO₃;
 ii. Copper powder, DMF.

Scheme 5

In addition, oxidative coupling of isoquinoline *N*-oxide **15**,⁵⁷ lithium salts of tetrahydroisoquinoline⁵⁸ **17** also provided the 1,1'-bisisoquinolines as shown in Scheme 6.

The stereochemistry of compound **18** was not established.⁵⁸

Scheme 6

Several reductive coupling reagents^{14,15,59-62} to prepare BIQs have been reported in the literature. In 1970, Nielsen *et. al.* reported the first coupling approach⁶⁰ where epimeric 2,2'-diacetyl-1,1',2,2'-tetrahydro-1,1'-bisisoquinoline **20** was obtained through

bimolecular reduction of isoquinoline **19** using zinc dust in acetic anhydride. Hydrogenation of BIQ **20** gave BIQ **21** which was further transformed to 1,1',2,2',3,3',4,4'-octahydro-1,1'-biisoquinolines **23** in two steps through BIQ **22** as shown in Scheme 7.

Conditions: i. Zinc, Acetic anhydride, 25-30 °C; ii. H₂, rhodium-charcocal Rh-C, HOAc, reflux; iii. aqueous HBr, HOAc, reflux; iv. NaOH, MeOH, THF.

Scheme 7

After a gap of three decades, a modified reductive coupling method using a mixture of zinc, 1,2-dibromoethane and chlorotriethylsilane was reported by Elliott.¹⁴ Using this method, the octahydro-1,1'-biisoquinolines **23** was obtained directly by coupling of 2-phenylethylamine thus avoiding the necessity for hydrogenation (Scheme 8).¹⁴ Later in 2005, low-valent niobium produced by NbCl₅ in the presence of zinc powder was also used to promote the homocoupling of imine **24** to BIQ **23** by Arai (Scheme 8).¹⁵

Conditions: i. EtOCHO, reflux, 12 h; ii. PPA, 160°C, 12 h;
 iii. Zn, BrCH₂CH₂Br, Me₃SiCl, CH₃CN; iv. NbCl₅, Zn, DME-THF, r.t., 3 h.

Scheme 8

However, the biggest disadvantage of these coupling methods is the production of a mixture of *racemic* and *meso* diastereoisomers. The *racemic* BIQ could be separated from the *racemic/meso* mixture by direct recrystallization relying on the differences in solubilities¹⁵ and by double hydrobromide salts formation¹⁴ followed by recrystallization (Scheme 9).

Conditions : i. Recrystallization; ii. HBr; iii. NaOH, H₂O, CH₂Cl₂.

Scheme 9

1.2.1.2. Bischler-Napieralski approach

Bischler-Napieralski reaction (Scheme 10) involves cyclization of *N,N'*-bis(aryethyl) oxamides promoted by condensation reagents such as phosphoryl chloride,⁶³⁻⁶⁶ phosphorus pentoxide/phosphoryl chloride,⁶⁷ polyphosphoric acid (PPA)^{14,67,68} or triflic anhydride/DMAP.³⁴ The product of the reaction is usually a tetrahydro-BIQ (Scheme 10).

Conditions: i. Diethyl oxalate, EtOH; ii. Dehydration reagents.

Scheme 10

Using Bischler-Napieralski reaction and based on Scheme 10, various BIQs have been successfully prepared. Examples of these BIQs are shown in Figure 1.⁶⁹

Figure 1

The influence of solvents especially chlorinated solvents on the cyclization of bisoxamide, was studied by Judeh.⁶⁹ Chlorinated solvents with higher boiling points like 1,1,2,2-tetrachloroethane and chlorobenzene afforded the products in shorter reaction time;

however, the purification process was problematic. Interestingly, when 1,2-dichloroethane was used, the desired 1,1'-BIQs were formed in good yields with fewer byproducts, but long reaction times were required for completion.⁶⁹ Room temperature ionic liquids such as [bmim]PF₆ **25** were also examined as an environmentally friendly substitute for chlorinated solvents. Bisoxamide **26** was successfully cyclized under short reaction times to give 1,1'-BIQ **27** in high yields (Scheme 11).⁷⁰

Scheme 11

Recently, our research group reported that when bisoxamide **28** was dehydrated by neat PPA at 190 °C for 12 h, *rac*-C₁-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline **29** was unexpectedly obtained (Scheme 12).^{12,13} The framework of C₁-1,1'-BIQ in which heterocyclic ring **A** is fully aromatic and ring **B** is fully saturated, has peculiar electronic and structural features (will be discussed in the results and discussion section).⁶⁸

Scheme 12

The mechanism of formation of the unexpected BIQ **29** was explored at relatively lower temperature of 140 °C to capture the intermediate products (Scheme 13).⁶⁸ From ¹H NMR spectra of representative crude samples taken at various time intervals over a period of 26 days, it shows that bisoxamide **28** was undergoing a two-step cyclisation: first forming partially cyclised compound **30**, then the doubly cyclised BIQ **31**. After complete conversion of compound **30** to BIQ **31**, BIQ **31** undergoes a disproportionation reaction to give *rac*-BIQ **29**.

Scheme 13

Intrestingly, treatment of *N,N'*-Bis-(3,4-dimethoxyphenethyl)oxamide **26** with Tf₂O/DMAP in CH₂Cl₂ provided the expected Bischler-Napieralski product **27**.⁶⁹ However, POCl₃ in toluene⁶⁸ or dry CH₃CN⁷¹ afforded another three different cyclized products **32-34** (Scheme 14).

Conditions: i. $\text{TiF}_2\text{O}/\text{DMAP}$ reagent, CH_2Cl_2 ; ii. POCl_3 , toluene/dry CH_3CN , reflux.

Scheme 14

1.2.1.3. Reduction of bisisoquinolines

Reduction of 1,1'-bis-dihydroisoquinolines had been thoroughly studied. *Racemic* products can be obtained by stereoselective reduction of 1,1'-bisdihydrobisisoquinolines with NaCNBH_3 ,^{34,65,71-73} while catalytic hydrogenation over PtO_2 ⁷⁴ or platinum catalyst⁶⁰ and NaBH_4 ,^{65,71} or $\text{LiAlH}_4/\text{AlCl}_3$,⁶⁵ or diisobutylaluminium hydride (DIBAL-H)⁶⁹ reduction all afforded *meso* products. The results were explained by Cram's rule, as the adjacent steric hindrance can determine the stereochemistry of the asymmetric center.⁷¹ Using NaCNBH_3 ^{34,65,71-73} as reducing reagent, BIQ **27** was easily reduced to *rac*-BIQ **35** (Scheme 15).⁶⁸

Conditions: i. NaBH_3CN , MeOH , HCl

Scheme 15

Following the same methodology, various *racemic* 1,1'-octahydro-BIQs have been successfully prepared under NaCNBH₃ reduction conditions (Figure 2).⁶⁹

Figure 2

Similarly, C₁-1,1'-BIQ framework obtained according to Scheme 13 can easily be reduced using NaBH₄ or NaCNBH₃. For example, *rac*-BIQs **36** could be obtained by the reduction of BIQ **32** (Scheme 16).⁶⁸

Scheme 16

1.2.2. Resolution of *racemic* 1,1'-bisisoquinolines

Resolution of *racemic* compounds can be achieved mainly through diastomeric salt formation or covalent bond formation.^{75,76} The diastomers can then be separated by crystallization⁷⁷⁻⁸⁰ or column chromatography.⁶⁸ Many optically active amines, such as

pyridine-amines,^{81,82} nornicotine,⁸³ and nicotine⁸⁴ have been obtained through diastereomeric salt formation. Elliott *et al.* used the diastereomeric salt formation technique to resolve *rac*-BIQ-**23** with chiral α -bromocamphor- π -sulfonic acid (BCSA) ammonium salt. Crystals of (*S,S*)-**23**•BCSA salt could be obtained when *rac*-**23** was recrystallised with *D*-BCSA in EtOH and then separated.¹⁴ When *L*-BCSA was used, crystals of (*R,R*)-**23**•BCSA salt were obtained. Consequently, after treatment of the salts (*S,S*)-**23**•BCSA and (*R,R*)-**23**•BCSA, separately, with NaOH solution followed by extraction, enantiopure BIQs (*S,S*)-**23** and (*R,R*)-**23** were obtained, respectively. Later in 2005, BIQ *rac*-**23** was also resolved by Arai *et al.* in a similar fashion using chiral camphorsulfonic acid (CSA) as resolving agent (Scheme 17).

Reagents :i. *D*-BCSA or *L*-BCSA ammonium salt (1.0 equiv), recrystallization from EtOH;
 ii. 5 M NaOH/CH₂Cl₂;
 iii. *D*-CSA or *L*-CSA (2.0 equiv), recrystallization from *i*-Pr₂O/EtOH;
 iv. 10% NaOH.

Scheme 17

Similarly, *rac*-BIQ **35** was resolved with *D*-BCSA with *L*-BCSA to give (*S,S*)-**35** and (*R,R*)-**35**, respectively (Scheme 18).⁷¹

Scheme 18

Rac-BIQ **29** was resolved through covalent bond formation method in our laboratory through the formation of diastereomeric ureas with (*S*)-(-)- α -methylbenzyl isocyanate (Scheme 19). The diastereomeric urea derivatives **37** and **38** were separated through column chromatography and fractional crystallization to give the pure diastereomers, which upon treatment with NaOBu afforded enantiopure BIQ **29**.

Scheme 19

1.2.4. Bisisoquinolines and their derivatives as chiral ligands in asymmetric synthesis

Unlike the widespread use of privileged chiral C_2 -1,1'-binaphthyls in asymmetric catalysis,^{6,20,22,85-88} only few examples using chiral C_2 -1,1'-bisisoquinolines have emerged in the literature to date, although these chiral BIQs were thought as potential asymmetric catalysts for a long time.

The first application of BIQ ligands in asymmetric catalysis was reported by Nakajima in 1998, using (*S*)-1,1'-biisoquinoline *N,N'*-dioxide **16** which was modeled after (*S*)-1,1'-binaphthalene-2,2'-diol. It was used to catalyze the addition of allyltrichlorosilane **40** to benzaldehyde **39**. Moderate results of 82% yield and 52% *ee* were obtained (Scheme 20).⁸⁹

Scheme 20

In 2005, Arai used chiral (*R,R*)-BIQ **23** in combination with CuCl to catalyze the asymmetric oxidative coupling of ester **42** to give 3,3'-substituted BINOL **43** in moderate 60% yield and up to 48% *ee* (Scheme 21).¹⁵

Scheme 21

In a related work, Cavell and Elliott *et al.* reported the application of chiral *N*-heterocyclic carbene (NHC) **44**, which is based upon *(R,R)*-BIQ **23**, in the stereoselective conjugate addition of Et_2Zn to cyclohexanone **45**. The alkylated ketone **46** was obtained in only 10% ee (Scheme 22).⁹⁰

Scheme 22

In 2006, NHC **44** was used by Herrmann *et al.* in asymmetric hydrosilylation or transfer hydrogenation to acetophenone **47**, affording product **48** in unsatisfactory low 28% ee and 24% ee respectively (Scheme 23).⁹¹

Scheme 23

In 2007, Hoffmann used iridium complex of NHC **49** in asymmetric hydrogenation of methyl 2-acetamidoacrylate **50** to afford product **51** in 67% *ee* (Scheme 24).⁹²

Scheme 24

Other BIQ-based NHC ligands for asymmetric catalysis have been described recently.⁹³⁻

⁹⁸ For example, in 2008 Seo *et al.* reported asymmetric allylic alkylation of **53** to the γ

product **55** by NHC **52** Cu(I) complex (Scheme 25). Good conversion (70%) and enantioselectivity (77% *ee*) were obtained.⁹⁷

Conditions: i. **52** (3 mol%), CuCl (3 mol%), *n*-HexMgBr (1.5 equiv), Et₂O, 0 °C, 1 h

Scheme 25

Later in 2011, Czekelines *et al.* synthesized novel class of NHC gold complexes bearing bulky substituents. With substoichiometric quantities of AgBF₄, the gold complexes **56** can catalyze the desymmetrization of diynesulfonamide **57** to give the enamide product **58** in yields up to 77% yield and enantioselectivity up to 51% *ee* (Scheme 26).⁹⁸

Conditions: i. **56** (5 mol%), AuCl (5 mol%), AgBF₄ (3 mol%), Toluene, r.t.

Scheme 26

In 2010, structurally constrained chiral *C*₁-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline **29** reported by our research group was introduced and employed for the addition of diethyl zinc to aromatic aldehydes. Yields of up to 99% and *ees* of up to 85% were obtained. Additionally, when the same BIQs were used for the addition of Grignard reagents to cyclic enones such as **45**, product **59** was obtained in 99% yield and only 35% *ee* (Scheme 27).^{12-13,68}

Conditions: i. (*R*)-**29** (15 mol%), THF/Hexane (1:3), 0 °C, 30h

Conditions: i. (*R*)-**29** (10 mol%), CuCl₂ (10 mol%), THF, -90 °C, 15 min

Scheme 27

From the above discussion, it is clear that BIQs hold clear promise and potential in asymmetric catalysis.

1.3. Henry Reaction

Henry reaction involves the addition of nitroalkanes to carbonyl compounds such as aldehydes and ketones (Scheme 28).⁹⁹⁻¹⁰² It can be catalyzed by hydroxides,^{103,104} alkoxides,¹⁰⁵ amines,¹⁰⁶⁻¹¹⁰ ammonium salts,^{111,112} and organo-phosphorus¹¹³⁻¹¹⁵ compounds. It generates β -nitroalcohol adducts that can be transformed into useful intermediates such as alkenes,¹¹⁶ β -aminoalcohols,¹¹⁷ β -aminoacids,¹¹⁶ and α -nitro ketones¹⁰³.

Scheme 28

The asymmetric version of Henry reaction was discovered first in 1992 by Shibasaki¹¹⁸ and has been developed mainly by using metal-based catalysts and to a much lesser extent by using organocatalysts.¹¹⁹⁻¹²²

A brief survey of the most important metal-based and organic chiral catalysts is presented in the following sections with special emphasis on nitrogen-based catalysts since our BIQs are nitrogen based ligands.

1.3.1. Metal-based chiral catalysts

As mentioned earlier, the first asymmetric Henry reaction was discovered in 1992 by Shibasaki using heterobimetallic complex **60** (Scheme 29).¹¹⁸

Scheme 29

A number of conceptually different types of metal-catalytic systems for the asymmetric version of this reaction have been developed in recent years.^{9,109,123-129} By far, most catalysts developed use copper (especially Cu(II) rather than Cu(I)) due to its excellent chelating properties to bi- and poly-dentate ligands.¹¹⁹ Other metals such as Zn,^{109,123-125} Co,^{126,127} Cr,^{9,128} Pd¹²⁹ and rare earth metals^{118,130,131} have also been examined with variable success. Majority of the ligands developed, e.g. bisoxazolines,¹³²⁻¹³⁸ bisoxazolidines,^{139,140} diamines,^{15,141-147} (–)-sparteine,¹⁴⁸ sulfonyldiamines,¹⁴⁹ sulphonimidamides,¹⁵⁰ aminopyridines,^{108,151-153} tetrahydrosalens,¹⁵⁴ and *N,N'*-dioxides,¹⁵⁵ are nitrogen-based with a variety of structural features that modulate their reactivity and enantioselectivity.

Evans *et al.*,¹³² reported a very efficient Cu(II)-bis(oxazoline) (BOX) catalyst **61** for a variety of aldehydes with only 5 mol% loading without the need for external base

(Scheme 30). The design is based on the Lewis acidic property of copper bearing moderately charged ligands which would facilitate the deprotonation of nitromethane. In the transition state **62** proposed by Evans *et al.* Cu(II) coordination involves a Jahn-Teller (JT) effect and both of the nitronate and the aldehyde's carbonyl group bind with copper, producing a desired boat conformation. On the basis of steric and electronic considerations, the electrophile was positioned in one of the more Lewis acidic equatorial sites of the ligand plane, while the nucleophile was perpendicular to the ligand plane.

Scheme 30

Hong *et al.* reported a base-functionalized aza-bisoxazoline catalyst **64** which encompasses a chiral scaffold with a tethered tertiary amine base. This catalyst function by the dual activation concept (Scheme 31).¹³⁶ Rate acceleration (2.5 times) and

improved enantioselectivity (72% *ee* vs. 92% *ee*) were achieved by the bifunctional aza-Box **64** in comparison to the unfunctionalized aza-Box **63**.

Conditions: i. **63/64** (5 mol%), CuTC (5 mol%), 4A MS, EtOH, -20 °C, 24 h

Scheme 31

Jørgensen was the first to apply Cu(II)-bis(oxazoline)¹⁵⁶⁻¹⁶¹ catalysts, e.g. **67**, in the asymmetric Henry Reaction between α -ketoesters and nitromethane using Et_3N as additive (Scheme 32). This reaction afforded enantiomerically pure tertiary alcohols in up to 99% *ee*.^{133,162} In general, ketones are much less reactive than aldehydes and their condensation with nitroalkanes is more challenging.

Scheme 32

Besides Cu-BOX catalysts, other Cu-imine complexes were also applied in the catalytic asymmetric Henry Reaction. Pedro *et al.* employed Cu-iminopyridine complexes derived from camphor for the addition of nitromethane to *o*-anisaldehyde. Under similar reaction conditions developed by Evans,¹³² only modest enantioselectivities were obtained and the best result (86% *ee*) was obtained using ligand **68** (Figure 3).¹⁰⁸ In 2007, Pedro *et al.* modified these types of ligands, interestingly, the two iminopyridine **69** and **70** (Figure 3) gave the products with opposite stereochemistry even though they had the same stereochemical pattern.¹⁵³

Figure 3

In 2008, Pedro *et al.* refined the iminopyridine ligands to the new aminopyridine ligands, such as compound **71**. These ligands are more flexible and the two equatorial coordination sites' electronic differentiation is more distinct. The expected products were obtained in higher yields (up to 99%), better enantioselectivities (up to 98% *ee*) and diastereoselectivities (up to 82:18) (Scheme 33).^{107,163}

$R_1 = \text{H}$, yield up to 99%, ee 47-98%;

$R_1 = \text{CH}_3$, yield up to 99%, *anti/syn* up to 82:18;
ee up to 95%;

$R_1 = \text{CH}_2\text{CH}_2\text{COOCH}_3$, yield up to 99%, *anti/syn* up to 85:15;
ee up to 96%.

Conditions: i. **71** (5 mol%), $\text{Cu}(\text{OAc})_2$ (5 mol%), DIPEA (1 equiv), EtOH, -20/-50 °C

Scheme 33

Later, a similar ligand was designed by Zhou where the pyridinyl moiety of **71** was replaced by a pyrrolidine ring to give ligand **72**. This diamine-type ligand with two $N\text{-sp}^3$ coordinating sites exhibited outstanding catalytic efficiency for Henry reaction (Scheme 34).¹⁶⁴ On the basis of X-ray diffraction and HRMS analysis, a possible transition state **73** was proposed in which the nucleophilic nitronate was oriented inside, perpendicular to the ligand plane to form a strong intramolecular hydrogen bonding with the NH of the pyrrolidine ring. The electrophilic aldehyde would occupy the outside position in consideration of steric hindrance. The *Re* face would be attacked by the nitronate thus providing the nitroaldol adduct with *S* configuration.

Consitions: i. **72**/ $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, DIPEA (1 equiv), THF

Scheme 34

C_2 -symmetric secondary diamine ligands, derived from chiral 1,2-diphenylethylenediamine and 1,2-cyclohexanediamine, have been widely applied in various asymmetric metal-catalyzed reactions such as Henry reaction.^{110,141,143,145,147,154,155,165,166} The C_2 -symmetric secondary diamine ligand **74** designed by Arai *et al.* gave the desired products in high yields and enantioselectivities with only 1 mol% loading (Scheme 35).¹⁴¹

Conditions: i. **74** (1-5 mol%), CuCl (1-5 mol%), *n*-PrOH, r.t., 16-120 h

Scheme 35

In 2007, Arai *et al.* developed a C_1 -symmetric diamine ligand **75** with two tertiary amines to catalyze the asymmetric Henry reaction. With only 5 mol% loading, the Cu(II) complex **75** gave excellent yields (up to 99%) and enantiomeric excesses (up to 99.5% *ee*) (Scheme 36).¹⁴²

Conditions: i. **75** (5 mol%), Cu(OAc)₂ (5 mol%), n-PrOH, r.t., 24-120 h

Scheme 36

One year later, Arai *et al.* developed a modified diamine ligand, the sulfonyldiamine ligand **76**, specifically for the diastereoselective Henry Reaction.¹⁴⁹ While designing ligand **76**, one of the binaphthyl azepine rings in **74** was replaced by sulfonyl group to increase the acidity of this copper complex (Scheme 37) since according to Evans *et al.*, the Lewis acidity of copper atom is crucial for activating the electrophilic aldehyde.¹³²

R' = H, yield 72-99%, ee 59-93%;

R' = CH₃, Syn : Anti = up to 92:8, ee up to 84%.

Conditions: i. **76** (5.5 mol%), CuCl (5 mol%), py, r.t., 16-96 h

Scheme 37

In 2010, Bolm *et al.* employed another amino-functionalized sulfonimidamide **77** for the enantioselective addition of nitromethane to various aromatic aldehydes. The products were obtained in up to 95% ee and in good yields of up to 99% (Scheme 38).¹⁵⁰

Scheme 38

(-)-Sparteine **78** is well-known natural chiral diamines. Because of its conformational rigidity, its Cu(II) complexes were examined in the Henry reaction (Scheme 39). Surprisingly, while Cu(OAc)₂–(-)-sparteine complex give only *racemic* products, CuCl₂–(-)-sparteine complex gave good to excellent *ee*.

Scheme 39

In 2009, Breuning *et al.* investigated 9-oxabispidine **79**, which carries an 2-*endo*, *N*-annellated piperidine ring showing closely related structure to (-)-sparteine **79**. The CuCl₂ complex of **79** gave (*S*)-products in 91-98% *ee* (Scheme 40).¹⁶⁷

Scheme 40

Recently, Noole *et al.* reported the application of an easily available catalyst formed by bipiperidine **80** and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in asymmetric Henry reaction. This catalyst system is practical, simple in operation, and afforded the products in high yields and enantioselectivities (Scheme 41).¹⁴⁶ According to ESI HRMS and B3LYP/6-31+G* level calculations, the transition state **81** was proposed where the copper complex is tetra-coordinated and almost planar, and the *N*-*i*-Pr group is perpendicular to this structure. The activated nitronate is in the opposite axial position to *i*-Pr group, and fixed by hydrogen bonding, while the electrophile was oriented in the equatorial position.

Conditions: i. **80** (10 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (10 mol%), Et_3N (5 mol%), -25°C

Scheme 41

In 2007, Feng employed a novel copper(I)-tetrahydrosalen complex in the enantioselective Henry reaction, and extended its application in the synthesis of (*S*)-norphenylephrine.¹⁵⁴ This chiral hydrogenated salen catalyst **82** (10 mol%), together with $(\text{CuOTf})_2 \cdot \text{C}_7\text{H}_8$ (5 mol%) gave the nitroaldol adducts in excellent enantioselectivities

(Scheme 42). Asymmetric reaction of *m*-hydroxybenzaldehyde **83** with nitromethane in presence of **82** followed by reduction of the nitro group of the product **84** gave (*S*)-norphenylephrine **85**. (*S*)-norphenylephrine **85** is used in the treatment of pain, depression and hypertension.¹⁶⁸

Conditions: i. **82** (10 mol%), $(CuOTf)_2 \cdot C_7H_8$ (5 mol%), MeOH, 4A MS, 45 °C;
ii. Pb/C (5 mol%), H_2 , MeOH.

Scheme 42

In 2006, Wang has reported copper tridentate chiral Schiff-base complexes **86k** and **86l**,¹⁶⁹ and modified these ligands in 2008 (Figure 4).¹⁷⁰ X-ray analysis of single crystals showed the dimeric nature of these type of catalysts. However, both the yields and the *ee* values were moderate, especially with aliphatic aldehydes (almost 45-64% *ee*).

Figure 4

1.3.2. Organocatalytic Henry Reaction

Because of the enormous economic potential of using small organic molecules in asymmetric catalysis, organocatalysis has become one of the most extensively explored areas of research in the last few decade.¹⁷¹⁻¹⁸⁰ Considering the mechanism of Henry reaction, there are three requirements for an organic compound to be a suitable organocatalysts: (a) should be a base or function with an external co-catalyst base; (b) should possess a unit that is capable of forming hydrogen bonding with the acceptor carbonyl oxygen; (c) should possess a unit that is capable of binding the nitronate group through electrostatic interaction or hydrogen bonding.^{119,120}

In 1994, Najera *et al.* reported the first example of enantioselective Henry reaction using chiral guanidines **87** and **88** (Figure 5), the *ee* values were up to 54%.¹⁸¹ Poor *ee* values were obtained using guanidine tetrafluoroborate salt **89** (Figure 5).¹⁸²

Figure 5

In 2005, a big breakthrough was brought by Nagasawa in the area of guanidine catalysis.¹⁸³ He reported a novel ligand **90** which combined one quaternised guanidine moiety and one thiourea moiety into the same chiral framework. This arrangement greatly improved the efficiency of guanidine-type catalysts in Henry reactions (Scheme 43). In the proposed intermediate **91**, the nitronate was paired with the guanidine unit while the carbonyl group formed hydrogen bond with the thiourea unit, and the configuration of product was controlled by the R² group of nitroalkane.

Conditions: i. (S,S)-**90** (10 mol%), KOH (5-40 mol%), H₂O, KI (50 mol%), 0 °C, 5-45 h

Scheme 43

Organic molecules bearing both amine and thiourea moieties are also potential catalysts for Henry reactions. Hiemstra reported the application of compound **92** in Henry reaction which afforded the desired products in very good yields and *ee* for various aromatic aldehydes (Scheme 44).¹⁸⁴ In the proposed transition model **93**, nitromethane was deprotonated by the basic quinucidine nitrogen and in the meantime the aldehyde was activated by the thiourea residue through double hydrogen bonding.

Scheme 44

In 2006, Deng reported a novel catalyst **94** which lacks both the guanidinium/amidinium moieties. It showed excellent efficiency in the asymmetric Henry reaction between nitromethane and α -ketoesters **95** to yield nitroalcohol **96** (Scheme 45).¹⁸⁵

Scheme 45

1.4. Objectives

This project focuses on the synthesis and application of bisisoquinolines as ligands for asymmetric reaction. It aims to:

1. Design, synthesize and explore the chemistry of structurally novel enantiopure bisisoquinolines.
2. Examine the application of chiral BIQ-based ligands in asymmetric Henry reaction
3. Investigate the effect of various structural features that control the efficiency in the asymmetric Henry reaction.

Chapter 2. Synthesis of novel chiral BIQs

In this chapter we will discuss the synthesis and resolution of BIQs.

2.1. Synthesis of BIQ 98

To our knowledge, all the reported chiral BIQs^{13,15,68,90-92,97,186} have the chelating nitrogens of the heterocyclic rings in a 1,2-disposition (e.g. **23**, Figure 6), and would form five-membered chelating rings after coordinating with metal ions. In order to investigate the differences between a five-membered (as in 1,2-BIQs) and six-membered chelation rings we envisioned the synthesis of 1,3-BIQ (e.g. **98**, Figure 6).

Figure 6

As mentioned in Chapter 1, there are two strategies to construct BIQ-based compounds: metal mediated coupling and Bischler-Napieralski reaction. A wide range of BIQ-based compounds using Bischler-Napieralski reaction has been prepared.^{12,13,68,70,73,187-189} We adopted a similar synthetic sequence for the synthesis of 1,3-BIQ **98** (Scheme 46). At first, the bisoxamide **100** was synthesized by condensation of phenethylamine with diethyl malonate **99**. Compound **100** under Bischler-Napieralski reaction condition should provide 1,1'-methylene-bis(3,3',4,4'-tetrahydroisoquinoline) **101**, which in turn

should provide the desired 1,3-BIQ *rac*-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-**98** upon reduction.

Conditions: i. Condensation; ii. Dehydration; iii. Reduction.

Scheme 46

The presence of an additional methylene moiety between the two carbonyl units in diethyl malonate **99** makes it much less reactive compared to diethyl oxalate **102** which was used to synthesize bisoxamide **28**. Thus, the reaction between phenethylamine and diethyl malonate **99** proceeded at higher temperature (80 °C vs r.t.), higher concentration (neat vs Ethanol) and longer reaction time (2 days vs 4 h) in comparison with diethyl oxalate reaction (Scheme 47). The fluffy white solid obtained was confirmed to be bisoxamide **100** by various analytical tools.^{12,190}

Conditions: i. **99**, 80 °C, 2 days;
Conditions: i. **102**, EtOH, r.t., 4 h.

Scheme 47

Following the procedure developed by Chan *et al.*,¹⁹¹ cyclization of bismalonamide **100** was achieved using a combination of phosphorus oxychloride (POCl₃) and diphosphorus pentoxide (P₂O₅) (Scheme 48). The expected 1,1'-methylene-bis(3,3',4,4'-tetrahydroisoquinoline) **101** was obtained as a brown gum in 81% yield after column chromatography, and confirmed as structure **101** through analytical tools.

Scheme 48

According to the previous research on the reduction of similar bisimines **31** and **27**, reductive treatment with NaCNBH₃ afforded only *racemic* BIQs **23** and **35**, respectively, while NaBH₄ gave mixtures of *racemic* and *meso* isomers (See Chapter 1, Scheme 13, Scheme 15 and Figure 2).^{60,65,71,73,191} Therefore, we used NaCNBH₃ for the reduction of **101** in anticipation to produce **99**. The expected 1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) **99** was obtained as light-yellow crystals in 77% yield after recrystallization from EtOH, and the obtained product was assigned as structure **99**.

The stereochemistry of **99** was examined through synthesis of derivative **103** (Scheme 49). If **99** is *racemic*, the N-CH₂-N' protons of compound **103** should be in the same chemical environment, and thus these two protons would appear as one signal in the ¹H NMR spectrum. While for the *meso*-**99** isomer, these two protons would show two different, splitted signals.⁶⁰ The ¹H NMR spectrum of **103** (Figure 7) has shown only one

singlet which was found at δ 3.73 ppm corresponding to the N-CH₂-N' protons. Hence, the *racemic* nature of the synthesized compound **99** was confirmed.

Conditions: i. NaCNBH₃, MeOH, HCl, 0.5 h;
ii. HCHO(37%), EtOH, 4A MS, reflux.

Scheme 49

Figure 7

2.2. Resolution of BIQ **98**

As mentioned in Chapter 1 (section 1.4), one of the aims of this work is to find a feasible way to obtain novel BIQ-based compounds in enantiomerically pure form. Therefore, resolution of BIQ **98** was attempted by using various techniques.

Racemic bases and optically active acids as well as *racemic* acids and optically active bases, can produce pairs of diastereomeric salts. Members of these pairs show different physicochemical properties like solubility, boiling point, melting point, adsorption *etc.* Out of these different physicochemical parameters, solubility is most commonly utilized for the separation of the enantiomeric pairs using fractional crystallization. Using diastereomeric salts formation approach, enantiomerically pure BIQs were obtained by various research groups.^{14,15,192-201} In this respect, (*D*)-(+)- α -bromocamphor- π -sulfonic acid (*D*-BCSA) and (*D*)-(+)-camphor-10-sulfonic acid (*D*-CSA) were utilized to resolve *rac*-BIQ **23** and *rac*-BIQ **35** successfully. Hence, these two chiral acids were considered as potential resolving agents for *rac*-BIQ **98**.

Rac-BIQ **98** was mixed separately with equimolar *D*-BCSA and two equivalents of *D*-CSA in MeOH, affording mixtures of diastereomeric salts **104/105** and **106/107** as off-white solids in quantitative yields (Figure 8) (note: different ratios of **98** and the chiral acids were also attempted). The ¹H NMR spectra of these compounds showed the characteristic signals of the diastereomeric salts. However, recrystallization of the diastereomeric salt mixtures from different solvents like CH₂Cl₂, MeOH, EtOH, EtOH-H₂O, Et₂O, Acetone, CH₃CN, THF or EtOAc failed to produce single or enriched diastereomers.

Figure 8

Other diastereomeric salt mixtures were prepared by mixing *rac*-BIQ **98** with different enantiopure organic acids such as (*D*)-(-)-mandelic acid, (*R*)-(-)-3-chloromandelic acid and (*L*)-(+)-lactic acid in MeOH. All attempts to recrystallize one single diastereomeric salt from the mixtures or obtain enriched fraction were unsuccessful. Nevertheless, the salt of (*L*)-(+)-citramalic acid and *rac*-BIQ **98** (1:1) was found to afford one isomer in around 60% *ee* after one time recrystallization from EtOH. After optimization of the recrystallization conditions by screening different solvents and different ratios between BIQ and (*L*)-(+)-citramalic acid, it was found that using two equivalents of the acid in a mixed solvent of EtOH/H₂O (1.5:1, v:v) gave the best separation results for diastereomeric salts **108** and **109** (Figure 9).

Figure 9

The crystals of **108** and **109** were separately treated with 10% aqueous NaOH and extracted with CH₂Cl₂ to afford enantiopure products (-)-**98** and (+)-**98**, respectively. These enantiomeric purities of (-)-**98** and (+)-**98** were found to be > 99% by chiral HPLC analysis (Figure 10).

Figure 10

The mixture of (+)-**98** and (*L*)-(+)-citramalic acid were recrystallised from EtOH, affording colorless cubic crystals which were suitable for single X-ray crystallographic analysis. From analysis of the crystal structure, we found both of the two heterocyclic rings adapted as twisted chair conformations. In addition, the absolute configuration of (+)-**98** was confirmed as (*R,R*)-configuration and thus (-)-**98** was confirmed to be (*S,S*)-configuration (Figure 11). The crystal structure also proved the *racemic* nature of compound **98** produced by NaBH₃CN in the reduction step (Scheme 49).

Figure 11

2.3. Alkylation of BIQ **98**

With the enantiomerically pure BIQ **98** in hand, a range of symmetric and unsymmetric alkyl derivatives of chiral BIQ **98** (Figure 12) were designed to explore their efficiency in the asymmetric Henry reaction. The symmetric (*C*₂) and unsymmetric (*C*₁) derivatives are

expected to exhibit different selectivities and reactivities due to their distinct structural conformations. The unsymmetric C_1 -derivatives possess two electronically different sp^3 nitrogens (i.e. one is alkylated N , the other is NH). The electronic and steric properties at the coordinating nitrogens can easily be modified in this design.¹⁶⁴

Figure 12

2.3.1. Alkylation of *rac*-BIQ **98**

Initial attempts to prepare derivatives of **98** were examined using *rac*-BIQ **98**. The successful approach could then be applied to enantiopure BIQ **98**.

2.3.1.1. Synthesis of symmetric *N*-alkyl derivatives of *rac*-BIQ **98**

Typical condensation reactions were applied for the synthesis of symmetric *N*-alkyl derivatives.^{12,14} Nucleophilic *rac*-BIQ **98** reacted with the corresponding alkyl halides to give the desired *N*-alkyl derivatives. However, when simple alkyl halide such as iodomethane was used, ammonium salts are obtained due to multi alkylations. For example, Gao reported that when *rac*-BIQ **29** was reacted with iodomethane, multiple alkylation occurred to give *rac*-**110** and *rac*-**111** since the initially formed product *rac*-**110** is more nucleophilic than the starting *rac*-**29** (Scheme 50).⁶⁸

Scheme 50

To avoid multiple alkylation problem mentioned above, *rac*-BIQ **98** was reacted with neat iodomethane and the final reaction mixture was treated with aqueous NaOH solution to give *rac*-112 in 41% yield (Scheme 51).¹⁴ The other two symmetric alkyl derivatives *rac*-113 and *rac*-114 were synthesized using typical alkylation reaction conditions (Scheme 52). The final alkylated products were obtained in 73%, 91% yield, respectively.

Scheme 51

Conditions: i. 2.2 equiv ethyl bromide/benzyl bromide, K_2CO_3 , THF, 60°C , overnight

Scheme 52

2.3.1.2. Synthesis of C_1 -symmetric N -alkyl derivatives of *rac*-BIQ **98**

Initial attempts to synthesize C_1 -symmetric N -alkyl derivatives by directly treating *rac*-BIQ **98** with equimolar alkyl halides in THF failed to provide the relative mono N -alkyl products exclusively in high yields. Instead, mixtures of mono, double N -alkyl derivatives were produced along with recovered starting material (Scheme 53). This result indicated that the alkylation reaction on *rac*-BIQ **98** was stepwise, and the second alkylation step was faster than the first step. Consequently, the formed mono derivatives were competing for alkyl halides with the parent *rac*-BIQ **98**. To overcome this problem, different reaction conditions were tested. Disappointingly, all attempts failed and the direct alkylation approach was thought an inappropriate route for the synthesis of mono N -alkyl derivative.

Conditions: i. one equiv alkyl halides, K_2CO_3 , THF, r.t., overnight

Scheme 53

Next, the reductive alkylation approach used for the synthesis of tertiary amines from secondary amines was chosen.²⁰²⁻²⁰⁹ As shown in Scheme 54, the method involved the formation of intermediate imine from condensation of a ketone or aldehyde with an amine, followed by a reduction step with suitable reducing agents (e.g. $NaBH_4$, $NaCNBH_3$, $LiAlH_4$, etc.).

Scheme 54

Read *et.al* successfully applied the reductive alkylation procedure for the synthesis of various mono alkylated *rac*-**35** in very good yields (Scheme 55).¹⁹¹ Instead of imine formation, aminal was isolated and was subjected to reduction with NaCNBH₃ to provide the desired mono *N*-alkylated *rac*-**35**.

Scheme 55

Due to the structural similarities between *rac*-**98** and *rac*-**35**, synthesis of mono *N*-alkyl derivatives of *rac*-**98** utilizing the sequence of aminal formation followed by reduction was attempted (Scheme 56).

Conditions: i. Condensation ii. Reduction

Scheme 56

At the outset, *rac*-BIQ **98** was reacted with 1.3 equivalent of 37% formaldehyde in refluxing EtOH for two days, to furnish, after workup and column chromatography purification, a yellow solid in 85% yield (Scheme 49). *Rac*-**103** was used to distinguish between the *racemic* and the *meso* isomers of **98** as discussed before (Figure 7).

The resulting piperimidine *rac*-**103** was then subjected to reductive cleavage using NaCNBH_3 (Scheme 57) to give a light yellow gum in 72% yield after treating the reaction mixture with aqueous NaOH solution and purification by column chromatography. The product was assigned structure *rac*-**115** through various analytical tools.

Conditions: i. NaCNBH_3 , TFA, MeOH, r.t.

Scheme 57

Similar reaction conditions developed for the preparation of mono *N*-methyl BIQ derivative *rac*-**115** were adapted for the preparation of other derivatives *rac*-**117** and *rac*-**119**. Treatment of compound *rac*-**98** with acetaldehyde in the presence of 4 Å molecular sieves in Et₂O gave a light yellow gum in 80% yield after chromatographic purification (Scheme 58). All analytical results confirmed the product's structure as *rac*-**116** (Scheme 58).

Scheme 58

Treatment of piperimidine *rac*-**116** with NaCNBH₃ under the same reaction conditions developed for reductive cleavage of piperimidine *rac*-**103** afforded the final product *rac*-**117** as a light yellow gum in 70% yield (Scheme 59).

Scheme 59

Based on the successful synthesis of mono *N*-ethyl derivative *rac*-**117**, another derivative with bulkier substituent (benzyl group) was attempted. *Rac*-BIQ **98** was firstly treated

with benzaldehyde under the reaction conditions utilized for the preparation of piperimidine *rac*-**118**, to provide a yellow fluffy solid in 90% yield after column chromatography (Scheme 60).

Scheme 60

Subsequently, *rac*-**118** was subjected to the reductive cleavage by treatment with NaCNBH₃ in acidic MeOH (TFA) to afford the final product *rac*-**119** as a light yellow gum in 80% yield (Scheme 61).

Scheme 61

2.3.2. Alkylation of (*R,R*)-BIQ **98**

Since the reaction conditions for the synthesis of *N*-substituted derivatives of *rac*-**98** were established, we then turned our attention to the synthesis of the chiral counterparts. Therefore, the reaction conditions described for the synthesis of *rac*-BIQ **98** derivatives

were used to synthesize the derivatives (*R,R*)-**112-115**, **117** and **119** starting from (*R,R*)-**98**. The structures of the enantiomerically pure derivatives (*R,R*)-**112-115**, **117** and **119** were confirmed by HRMS, FTIR, ^1H NMR and ^{13}C NMR spectra and by comparison with the corresponding *racemic* compounds. The enantiomeric purities of these derivatives were examined by HPLC using chiral columns.

2.3.2.1. Synthesis of double *N*-alkyl derivatives of (*R,R*)-BIQ **98**

The alkylation conditions used for the preparation of the double *N*-alkyl derivatives were followed using the appropriate alkyl halide. The stereochemistry of (*R,R*)-**98** would remain the same during the alkylation process. During the preparation of the doubly *N*-methyl substituted derivative (*R,R*)-**112**, only the amine salt was formed during the reaction between (*R,R*)-**98** and neat iodomethane avoiding further multiple alkylation. Work-ups by aqueous NaOH solution gave the free enatiopure base (Scheme 62). Chiral HPLC testing using Chiralcel OD-H column proved that (*R,R*)-**112** was obtained in >99% *ee* indicating no racemization during the alkylation process. The HPLC spectra of *rac*-**112** and (*R,R*)-**112** are shown in Figure 13.

Scheme 62

Figure 13

(*R,R*)-**113** was prepared and characterized in a similar fashion to *rac*-**113** starting from (*R,R*)-**98**. The HPLC separation results of (*R,R*)-**113** along with its relative *racemic* counterpart are shown in Figure 14. There was no evidence of racemization in the alkylation process of (*R,R*)-**98** with ethyl bromide.

Figure 14

2.3.2.2. Synthesis of mono *N*-alkyl derivatives of (*R,R*)-BIQ 98

Reductive amination reaction followed by reductive cleavage was applied for the synthesis of mono alkylated derivatives (*R,R*)-**115**, (*R,R*)-**117** and (*R,R*)-**119**. Their structures were confirmed by HRMS, FTIR, ^1H NMR and ^{13}C NMR spectra and by comparison with the corresponding *racemic* compounds. The condensation followed by amination cleavage with NaCNBH_3 had no effect on the stereochemistry of the chiral carbon centre, and the configurations at the mono *N*-alkyl derivatives' were unchanged. The HPLC results of the *racemic* and chiral mono *N*-benzyl derivatives **119** proved that no racemization had taken place during the reaction (Figure 15).

Figure 15

2.4. Synthesis of 1,2-BIQs

Several 1,2-BIQs were also prepared according to the literature⁶⁸ for further investigation in the Henry reaction and to serve as comparators to the 1,3-BIQs.

2.4.1. Synthesis of 1,2-BIQs 23, 27, 29, 32, 33, 35, 36, 120, 121, 123

According to Bischler-Napieralski reaction conditions, bisoxamide **30** underwent cyclization to form tetrahydro-BIQ **31**. *Racemic* 1,1'-octahydro-BIQ **23** was easily obtained by the NaCNBH₃ reduction of BIQ **31** (Scheme 63). All compounds were characterized by ¹H and ¹³C NMR spectra and were found to be identical to those reported in the literature.⁶⁸

Conditions: i. Diethyl oxalate, EtOH; ii. POCl₃, P₂O₅, toluene reflux, 24 h; iii. NaCNBH₃.

Scheme 63

Following Elliott's method,¹⁴ *rac*-BIQ **23** was further reacted with neat iodomethane and the final mixture was treated with aqueous NaOH solution to give methylated derivative *rac*-BIQ **120** (Scheme 64).

Conditions: i. neat CH₃I, 12 h; ii. 10% NaOH, H₂O, CH₂Cl₂.

Scheme 64

BIQs **27**, **29**, **32** were readily prepared under the Bischler–Napieralski conditions (Chapter 1, Scheme 13-14), and *rac*-BIQs **35**, **36** were obtained by reduction of BIQs **27** and **32**, respectively (Chapter 1, Scheme 15-16) (Figure 16).

Figure 64

Further oxidation of BIQ **27** can lead to the fully unsaturated *rac*-BIQ **121** (Scheme 65).

Conditions: i. Pd/C, toluene, reflux, 3 d

Scheme 65

Synthesis of *rac*-BIQ **123** from *rac*-BIQ **35** was performed by the Judeh method.⁶⁹

Urethane **122** was firstly prepared by addition of ethyl chloroformate to diamines **35**, then

followed by reductive treatment using LiAlH_4 / AlCl_3 in dry THF to afford *rac*-BIQ **123** (Scheme 66).

Conditions: i. Ethyl chloroformate, triethylamine, CH_2Cl_2 ; ii. LiAlH_4 , AlCl_3 , dry THF.

Scheme 66

2.4.2. Resolution of *rac*-BIQ **23** and *rac*-BIQ **29**

Resolution of *rac*-BIQ **23**, was achieved using Elliott¹⁴ route with *L*-BCSA (Chapter 1, Scheme 17), thus affording (*R,R*)-**23**. The enantiomeric purities were found to be above 99% by chiral HPLC analysis and the configuration of the major enantiomer was confirmed to be (*R,R*) by comparing the sign of optical rotation values with the literature.¹⁴

For the resolution of *rac*-BIQ **29**, (*S*)-(+)- α -methylbenzyl isocyanate was used to form diastereomeric urea derivatives. After column chromatography separation and fractional crystallization, pure diastereomers were obtained, which upon treatment with NaOBu afford (*R*)-**29** (Chapter 1, Scheme 19). The FTIR, ^1H and ^{13}C NMR spectra of (*R*)-BIQ **29** were identical to those reported in the literature, and its enantiopurity and configuration was confirmed by chiral HPLC analysis.⁶⁸

In conclusion, a new ligand framework 1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) **98** and its symmetric **112-114**, asymmetric **115**, **117**, **119** derivatives in both *racemic* and enantiopure forms were prepared. The absolute stereochemistry of this new BIQ-based compound was established by X-Ray crystallography. The enantiomeric purities of the obtained derivatives of (*R,R*)-**98** were confirmed by chiral HPLC analysis. Meanwhile, several classical 1,2-BIQs **23**, **27**, **29**, **31**, **32**, **35**, **36**, **120**, **121** and **123** were prepared for further exploration. Among the 1,2-BIQs, (*R,R*)-**23** and (*R*)-**29** were also prepared as these two BIQs were the most widely used asymmetric catalysts. The chiral BIQs and derivatives will be used as ligands in classical C-C bond forming reaction—Henry reaction (nitroaldol reaction) and the results will be discussed in detail.

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Chapter 3. Asymmetric catalysis of Henry reaction using chiral BIQ ligands

In this chapter, asymmetric catalysis of Henry reaction will be explored using various BIQs synthesized in Chapter 2. The reaction scope will be investigated.

3.1. Enantioselective Henry reaction catalyzed by novel chiral 1,3-BIQs

As mentioned in Chapter 1, Henry (Nitroaldol) reaction is a base-catalyzed addition reaction of nitroalkanes to aldehydes or ketones. It is one of the most valuable methodologies for carbon-carbon bond formation. Its enantioselective version has been discovered in 1992.¹¹⁸ Asymmetric catalysis of Henry reaction using copper complexes of C_1/C_2 -symmetric amines is widely applied. Due to the structural similarities between the reported amine ligands^{6,146,164} and our newly synthesized enantiopure C_2 -symmetric 1,3-BIQs (*R,R*)-**98** and its alkyl derivatives (*R,R*)-**112-115**, (*R,R*)-**117** and (*R,R*)-**119** (Figure 17), we considered using these ligands for the asymmetric Henry reaction.

Figure 17

In this Chapter, we will discuss the application of chiral (*R,R*)-**98** and its alkyl derivatives (*R,R*)-**112-115**, (*R,R*)-**117** and (*R,R*)-**119** in the enantioselective Henry reaction. Additionally, we will examine the modular effects of the alkyl substituents attached to the chelating sp³ nitrogen atoms and the symmetry properties of ligands on the reactivity and selectivity of Henry reaction between nitromethane and benzaldehyde.

3.1.1. Ligand effects

We started our investigation by screening chiral ligands (*R,R*)-**98**, (*R,R*)-**112-115**, (*R,R*)-**117** and (*R,R*)-**119** in the enantioselective reaction between nitromethane and benzaldehyde **39**. All the reactions were performed using 1 equiv benzaldehyde and 20 equiv of nitromethane in the presence of 10 mol% ligand and 10 mol% Cu(OAc)₂ in EtOH at room temperature for 48 h. To ensure complexation between the ligands and copper, the mixture was stirred for 1 h before addition of the aldehyde and nitromethane. No special precautions were taken to exclude air or moisture from the reaction flask. The results are shown in Table 1.

Table 1 Asymmetric nitromethane addition to benzaldehyde in the presence of (*R,R*)-98**, (*R,R*)-**112-115**, (*R,R*)-**117**, and (*R,R*)-**119****

Conditions: i. Ligand (0.1 equiv), Cu(OAc)₂ (0.1 equiv), EtOH (1.5 ml), r.t., 48 h

Entry	Ligand (<i>R,R</i>)-	Yield ^a (%)	<i>ee</i> ^b (%)
1	98	90	18
2	112	70	0
3	113	68	0
4	114	40	0
5	115	82	9
6	117	78	9
7	119	70	10

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*S*) was determined by comparing with the literature values.²¹⁰

Reactions involved the use of double alkylated (*R,R*)-**112**- **114**, β -nitroalcohol **123** was obtained in completely *racemic* form, while the other chiral ligands (*R,R*)-**98**, (*R,R*)-**115**, (*R,R*)-**117**, (*R,R*)-**119** yielded the β -nitroalcohol (*S*)-**123** in 9-18% *ee* (Table 1, entries 2-4 vs 1 and 5-7). Presumably, the lack of induction using ligands (*R,R*)-**112**-**114** may be due to inability of the ligands to chelate with the copper to effectively induce chirality as shown in the proposed intermediate state (Figure 18). From the results in Table 1, the parent ligand (*R,R*)-**98** bearing no substituent was more efficient than the other alkylated BIQs affording product (*S*)-**124** in 90% yield and 18% *ee* (Table 1, entry 1). Interestingly, as the bulkiness of the alkyl group on BIQ increased, the yield of β -nitroalcohols (*S*)-**124** dropped (Table 1, entry 2 vs 3 vs 4). Similar trend was also found from the results of

mono *N*-alkyl BIQs (*R,R*)-**115**, (*R,R*)-**117** and (*R,R*)-**119** (Table 1, entry 5 vs 6 vs 7). These results showed that steric effect at the copper coordination site would have a profound effect on the reactivity and enantioselectivity. Subsequently, screening of other reaction conditions was accomplished using parent ligand (*R,R*)-**98**.

Figure 18

3.1.2. Copper sources effects

Next the influence of frequently used copper salts was examined in this enantioselective Henry reaction. The results obtained are summarized in Table 2. Copper (I) sources (Table 2, entries 4-7) were superior in both activity and selectivity, compared to copper (II) sources which are quite sluggish (Table 2, entries 2-3). Among the examined copper (I) salts, CuCl and CuI showed similar results to those with CuBr (Table 2, entries 5, 7 vs 6), while copper (I) acetate gave lower enantiomeric excess (Table 2, entry 4). These results indicated that the counter anion (e.g. halide ions) had no profound effect in the process of catalysis. Considering that the *ee* result obtained using copper(I) bromide was the highest, and that this metal salt was inexpensive and less toxic, it was chosen as the copper source for further optimizations of the asymmetric Henry reaction.

Table 2 Screening of copper sources for asymmetric nitromethane addition to benzaldehyde

Conditions: i. (*R,R*)-**98** (0.1 equiv), Copper sources (0.1 equiv), EtOH (1.5 ml), r.t., 48 h

Entry	Cu salt	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
1	Cu(OAc) ₂	90	18
2	Cu(OTf) ₂	43	10
3	CuCl ₂	40	13
4	CuOAc	95	14
5	CuCl	89	20
6	CuBr	90	25
7	CuI	90	23

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*S*) was determined by comparing with the literature values.²¹⁰

3.1.3. Solvent effects

Optimization of the solvents used in the enantioselective Henry reaction was carried out with solvents like alcohols, ethers and chlorinated solvents (Table 3). Generally, protic

solvents like EtOH and MeOH (Table 3, entries 1-2) were found to be more efficient than the aprotic solvents (Table 3, entries 3-9) in terms of the yield of the product (*S*)-**124**. However in terms of enantioselectivities, compared with protic solvents (Table 3, entries 1-2), ether-type solvents, toluene and chlorinated solvents, except CH₂Cl₂, (Table 3, entries 3-4, 6, 8-9) all showed better results dioxane showed optimal results in terms of *ee* value (38% *ee*) (Table 3, entry 4). Therefore, based on these results, dioxane was chosen for further optimization.

Table 3 Screening of solvents for asymmetric nitromethane addition to benzaldehyde

Conditions: i. (*R,R*)-**98** (0.1 equiv), CuBr (0.1 equiv), Solvent (1.5 ml), r.t., 48 h

Entry	Solvent	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
1	EtOH	90	25
2	MeOH	89	24
3	THF	80	27
4	Dioxane	70	38
5	CH ₃ CN	45	15
6	Toluene	65	30

7	CH ₂ Cl ₂	65	16
8	CHCl ₃	75	21
9	ClCH ₂ CH ₂ Cl	50	26

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*S*) was determined by comparing with the literature values.²¹⁰

3.1.4. Effects of catalyst loading and ligand ratio

Other factors to be optimized were the ratio of ligand (*R,R*)-**98** to CuBr and the catalyst loading (Table 4). Initially, the amount of CuBr was constantly kept at 10 mol% (with respect to aldehyde **39**) while the ligand amount was gradually increased in ratios of (*R,R*)-**98**/CuBr from 1:2, 1:1, 1.5:1 to 2:1 (Table 4, entries 1-4). In terms of enantioselectivity, the optimal ratio between ligand (*R,R*)-**98** and copper(I) bromide was 1:1 (Table 4, entry 2). Using the optimal ratio of ligand (*R,R*)-**98** and copper(I) bromide of 1:1, attempts to decrease the catalyst loading to half provided the expected product in only 45% yield (Table 4, entry 5 vs entry 2) whereas attempts to increase the loading from 10 to 20 mol% afforded β -nitroalcohol (*S*)-**124** in higher 85% yield but unfortunately in lower enantioselectivity of 30% *ee* (Table 4, entry 6 vs entry 2). BIQ (*R,R*)-**98** was also applied as organocatalyst without any metal salts, expected product in racemice form is afforded in 43% yield (Table 4, entry 8). Thus for this reaction, the optimal catalyst loading of (*R,R*)-**98** /CuBr is 10 mol%.

Table 4 Screening of the ratio of (*R,R*)-98** to CuBr and catalyst loading in the asymmetric nitromethane addition to benzaldehyde**

Conditions: i. (*R,R*)-**98**, CuBr, Dioxane (1.5 ml), r.t., 48 h

Entry	(<i>R,R</i>)- 98 (mol%)	CuBr (mol%)	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
1	5	10	65	35
2	10	10	70	38
3	15	10	80	28
4	20	10	88	18
5	5	5	45	36
6	20	20	85	30
7	-	10	0	0
8	10	-	43	0

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*S*) was determined by comparing with the literature values.²¹⁰

Overall, the optimized reaction conditions were 10 mol% (*R,R*)-**98**, 10 mol% CuBr in dioxane at room temperature. Under these conditions, the adduct (*S*)-**124** was obtained in 70% yield and 38% *ee*. These results were moderate. Hence, substrate scope of the reaction using this (*R,R*)-**98** was not examined.

3.2. Enantioselective Henry reaction catalyzed by chiral 1,2-BIQs

As discussed in section 3.1, attempts to employ chiral 1,3-BIQs in the enantioselective Henry reaction furnished moderate results. This may be attributed to the flexibility of the six-membered chelating ring.

It was logical to examine 1,2-BIQs ligands (Figure 19), and investigate their catalytic ability in the asymmetric Henry reaction and compare them to 1,3-BIQs. An additional objective was also to compare the efficiencies of C_1 vs C_2 1,2-BIQs. From the X-Ray analysis of BIQs C_2 -symmetric **23** and C_1 -**29**'s^{12,14,62} major structural differences were observed. BIQ (*R,R*)-**23** showed a C_2 -symmetric structure, and the two heterocyclic rings are fully saturated. However, aromaticities of the two heterocyclic rings of BIQ (*R*)-**29** are different: one ring is fully aromatic while the heterocyclic ring is saturated, hence BIQ (*R*)-**29** has C_1 -symmetry.

Figure 19

3.2.1. Ligand effects

Initially the CuBr complexes with (*R,R*)-**23** and (*R*)-**29** were used in the enantioselective nitroaldol reaction between nitromethane and benzaldehyde **39** to examine their

reactivities and selectivities. These complexes were examined under the following reaction conditions: 10 mol% ligand and 10 mol% CuBr were stirred in THF at ambient temperature for 1.5 h followed by dropwise addition of nitromethane (20 equiv) and benzaldehyde **39** (1 equiv). The reaction mixture was allowed to proceed for another 36 h at room temperature. The obtained results are summarized in Table 5.

As shown in Table 5, (*R*)-**29** afforded higher yield (up to 94%) and higher *ee* values (up to 68%) in comparison to the results obtained by (*R,R*)-**23**, presumably owing to the structural difference (Table 5, entry 1 vs 2). Both nitrogen atoms in the *C*₂-1,1'-bisisoquinolines (*R,R*)-**23** are sp³ hybridized and thus were assuming a twist-boat conformation. However, the *C*₁-tetrahydro-1,1'-bisisoquinoline (*R*)-**29** with two dissimilar nitrogen atoms demonstrated a twist-boat conformation for the sp³-N containing ring and the sp²-N containing ring is flat due to its aromaticity. The configuration of (*R*)-**29** give better results. When the reactions are undergoing under inert conditions, similar results are obtained (Table 5, entries 3-4 vs entries 1-2). So in the following reaction process, no special precautions were taken to exclude air or moisture from the reaction tubes. And (*R*)-**29** was chosen for subsequent screening and optimization.

Table 5 Enantioselective nitromethane addition to benzaldehyde in the presence of (*R,R*)-23** and (*R*)-**29****

Conditions: i. Ligand (0.1 equiv), CuBr (0.1 equiv), THF (1.5 ml), r.t., 36 h

Entry	Ligand	Yield ^a (%)	<i>ee</i> ^b (%)
1	(<i>R,R</i>)- 23	90	59
2	(<i>R</i>)- 29	94	68
3 ^d	(<i>R,R</i>)- 23	89	59
4 ^d	(<i>R</i>)- 29	90	69

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*R*) was determined by comparing with the literature values.²¹⁰

^d Inert conditions

3.2.2. Solvent effects

The effects of different types of solvents in the asymmetric Henry reaction were explored using (*R*)-**29** and CuBr under the reaction conditions mentioned in Table 6. The results show that protic solvents like EtOH and MeOH (Table 6, entries 1-2) afforded the final product β -nitroalcohols (*R*)-**124** in reasonable yields. However, in term of enantioselectivities, these solvents were less effective than the aprotic ones (Table 6, entries 1-2 vs 3-13). Among the tested aprotic solvents, ether-type solvents (except diethyl ether) exhibited more efficient catalytic abilities—higher yields and *ees* (Table 6, entries 3-7 vs entries 8-13). The highest *ee* value (77% *ee*) was obtained when this reaction was performed in 1,2-dichloroethane (Table 6, entry 10), though moderate enantioselectivities were obtained in other two chlorinated solvents. The catalyst reactivity in 1,2-dichloroethane seems sluggish as only 45% yield was achieved.

However, in consideration of the resulting optimal enantioselectivity, this chlorinated solvent was chosen for further screening to optimize the reaction conditions.

Table 6 Screening of solvents for enantioselective nitromethane addition to benzaldehyde

Conditions: i. (*R*)-**29** (0.1 equiv), CuBr (0.1 equiv), Solvent (1.5 ml), r.t., 36 h

Entry	Solvent	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
1	MeOH	84	30
2	EtOH	89	26
3	THF	94	68
4	Dioxane	99	42
5	Bu ₂ O	99	64
6	Et ₂ O	35	58
7	<i>t</i> -BuOMe	90	62
8	CH ₂ Cl ₂	78	57
9	CHCl ₃	56	34
10	ClCH ₂ CH ₂ Cl	45	77
11	Toluene	91	29

12	CH ₃ CN	89	55
13	1,2-Dimethoxyethane	38	70

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*R*) was determined by comparing with the literature values.²¹⁰

3.2.3. Effects of copper sources

The influence of frequently used copper salts were examined in the enantioselective catalysis of Henry reaction, and the obtained results were summarized in Table 7. Generally, copper (I) sources (Table 7, entries 5-7) showed superior catalytic ability in terms of both the activity and selectivity in comparison with the results obtained by copper (II) salts which were quite sluggish (Table 7, entry 4) or ineffective (Table 7, entries 1-3). Among the tested copper (I) salts, CuCl showed similar results to those with CuBr (Table 7, entries 5 vs 6) while CuI gave better yield but lower enantiomeric excess of only 41% *ee* (Table 7, entry 7).

Considering both the yields and *ee* values, copper(I) chloride will be used as the copper source of choice in the next optimization processes.

Table 7 Screening of copper sources for asymmetric nitromethane addition to benzaldehyde

Conditions: i. (*R*)-**29** (0.1 equiv), Copper sources (0.1 equiv), ClCH₂CH₂Cl (1.5 ml), r.t., 36 h

Entry	Cu salt	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
1	Cu(NO ₃) ₂	0	-
2	Cu(OTf) ₂	0	-
3	CuCl ₂	0	-
4	Cu(OAc) ₂	21	68
5	CuCl	55	79
6	CuBr	45	77
7	CuI	70	41

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*R*) was determined by comparing with the literature values.²¹⁰

3.2.4. Catalyst loading, ligand ratio and temperature effects

Other factors like the ratio between ligand (*R*)-**29** and CuCl, the catalyst loading, and temperature were further optimized. The results are shown in Table 8. The amount of CuCl was first kept constant at 10 mol% (with respect to aldehyde **39**) while the ligand (*R*)-**29** amount was increased gradually from 5, 10, 15 to 20 mol% (Table 8, entries 1-4). The obtained results showed a tremendous increase in the reaction activity, yielding the

β -nitro alcohols (*R*)-**124** in more than double yield when the amount of (*R*)-**29** was increased from 5 to 10 mol% (Table 8, entry 1 vs entry 2). Further increase in the amount of (*R*)-**29** did not improve the yield of product (*R*)-**124**, however a slight increase in enantiomeric excess was observed (Table 8, entries 1-4). An increase the amount of CuCl from 5, 15 to 20 mol%, while keeping the amount of (*R*)-**29** constant at 10 mol%, resulted in a significant decrease in the reaction rates (Table 8, entries 5-7) and a drop in the *ee* values from 83% to 74%, to 71%, respectively, (Table 8, entry 5 vs entry 6 vs entry 7). These combined results indicated the optimal ratio between ligand (*R*)-**29** and copper(I) chloride as 2:1 (Table 8, entry 5).

The reaction became much more sluggish after attempts to decrease the catalyst loading from 5 mol% Cu(I) and 10 mol% (*R*)-**29** to 2.5 mol% Cu(I) and 5 mol% (*R*)-**29**. The adduct (*R*)-**124** was produced in only 16% yield even after extending the reaction time to 120 h (Table 8, entry 8). Therefore, the optimal loading is 10 mol% ligand (*R*)-**29** and 5 mol% CuCl.

Next, the effect of the reaction temperature was tested at 40 °C, 0 °C and -20 °C (Table 8, entries 9-11). When the reaction temperature was increased from r.t. to 40 °C, the reaction rate increased affording the product (*R*)-**124** in 78% yield in 12 h. However, the enantioselectivity was inferior to the one obtained at room temperature (Table 8, entry 9 vs entry 5). When the temperature was decreased from r.t. to 0 °C, (*R*)-**124** was obtained in higher enantioselectivity and comparable yield (Table 8, entry 10 vs entry 5). However, when the reaction temperature was lowered to -20 °C, the poor solubility of the catalytic copper complex made the reaction sluggish (Table 8, entry 11). Thus 0 °C was chosen as the optimal temperature for the asymmetric Henry reaction.

Table 8 Screening of the ratio of (*R*)-29** to CuCl, catalyst loading and temperature in the asymmetric nitromethane addition to benzaldehyde**

Conditions: i. (*R*)-**29**, CuCl, ClCH₂CH₂Cl (1.5 ml)

Entry	CuCl (mol%)	(<i>R</i>)- 29 (mol%)	Temperature (°C)	Time (h)	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
1	10	5	r.t.	84	25	73
2	10	10	r.t.	36	55	79
3	10	15	r.t.	36	56	80
4	10	20	r.t.	36	56	82
5	5	10	r.t.	36	63	83
6	15	10	r.t.	36	19	74
7	20	10	r.t.	36	13	71
8	2.5	5	r.t.	120	16	80
9	5	10	40	12	78	70
10	5	10	0	72	60	85
11	5	10	-20	120	-	-

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*R*) was determined by comparing with the literature values.²¹⁰

As the most efficient ratio of ligand (*R*)-**29** to CuCl was 2:1, the solvent and copper source effects were re-tested in the hope to obtain better results (Table 9). The results shown in Table 9 were in agreement with the conclusions made from Table 6 and Table 7. Overall, the optimized reaction conditions involved using ligand (*R*)-**29** (10 mol%) and CuCl (5 mol%) in 1,2-dichloroethane at 0 °C, furnishing final product (*R*)-**124** in 60% yield and 83% *ee*.

Table 9 Screening of solvents and copper sources using a 2:1 ratio of (*R*)-29**-copper source for asymmetric nitromethane addition to benzaldehyde**

Conditions: i. (*R*)-**29** (0.1 equiv), Copper sources (0.05 equiv), Solvent (1.5 ml), 0 °C, 36 h

Entry	Solvent	Cu salt	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
1	ClCH ₂ CH ₂ Cl	CuCl	60	85
2	MeOH	CuCl	90	36
3	CH ₂ Cl ₂	CuCl	78	70
4	Toluene	CuCl	70	65
5	CH ₃ CN	CuCl	85	70
6	THF	CuCl	90	66
7	ClCH ₂ CH ₂ Cl	CuBr	55	78
8	ClCH ₂ CH ₂ Cl	Cu(OAc) ₂	40	62

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*R*) was determined by comparing with the literature values.²¹⁰

3.2.5. Scope of (*R*)-**29** in the enantioselective Henry reaction

The substrate scope in Henry reaction using ligand (*R*)-**29** was then examined under the optimized reaction conditions mentioned in Table 9, entry 1. This reaction was found to be general since a wide range of aldehydes including aliphatic, conjugated, heteroaromatic and aromatic aldehydes with different electron-donating and electron-withdrawing substituents reacted smoothly with nitromethane to afford the corresponding β -nitroaldol products in good yields and enantioselectivities (Table 10). Interestingly, aromatic aldehydes with either electron-donating (Table 10, entries 7-13) or electron-withdrawing groups (Table 10, entries 2-6) all gave similar yields and enantioselectivities. However, the strongly electron-withdrawing nitro group was an exception as the reaction rate was accelerated and was completed in only 12 hours providing the desired product in only 64% *ee* (Table 10, entry 2). The lower *ee* value was attributed to the higher reaction rate than the other aromatic aldehydes. Meanwhile, the substitution pattern (Table 10, entries 3-5, entries 7-9 and entries 11-13) at the phenyl rings seems to have no major effect on the reactivity or enantioselectivity of the catalyst system, producing the relative adducts in moderate yields from 48-80% and with excellent enantiomeric excess ranging from 82-91% *ee*. The reaction proceeded smoothly even with straight chain aldehydes of different length (Table 10, entries 14-16), affording comparable yields and excellent *ee* values (up to 91% *ee*). Moreover, the bulky 2-naphthylaldehyde **140**, heteroaromatic 2-

furalaldehyde **141** and conjugated *trans*-cinnamaldehyde **142** gave the expected nitro products (*R*)-**158-160** in similar yields (78-85%) and enantiomeric excesses (80-85% *ee*) (Table 10, entries 17-19). In addition, no aldol side reactions or dehydration products were observed.

Table 10 Scope of (*R*)-29** in the asymmetric Henry reaction**

Conditions: i. (*R*)-**29** (0.1 equiv), Cu(I)Cl (0.05 equiv), ClCH₂CH₂Cl (1.5 ml), 0 °C

Entry	Substrate	Product	Time	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
1	39	(<i>R</i>)-124	72	60	85
2	126	(<i>R</i>)-143	12	95	64
3	127	(<i>R</i>)-144	48	70	91

4	128	(R)-145	60	59	87
5	129	(R)-146	48	72	87
6	130	(R)-147	72	59	87
7	131	(R)-148	60	65	88
8	132	(R)-149	60	57	86
9	133	(R)-150	48	70	87

10	134	(R)-151	48	80	82
11	135	(R)-152	72	60	89
12	136	(R)-153	48	75	90
13	65	(R)-154	48	79	91
14	137	(R)-155	60	76	88
15	138	(R)-156	60	73	90

16			48	72	91
	139	(R)-157			
17			48	85	80
	140	(R)-158			
18			48	80	85
	141	(R)-159			
19			48	78	81
	142	(R)-160			

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H, OJ-H or Chiralpak AD-H columns.

^c The absolute configuration (*R*) was determined by comparing with the literature values.^{110,132,210}

3.2.6. Proposed mechanism

As mentioned previously, the optimum ratio between (*R*)-**29** and CuCl was found to be 2:1 suggesting the formation of copper complex in a 2:1 ratio of (*R*)-**29** to CuCl. When (*R*)-**29** and CuCl were mixed in a 2:1 ratio in MeOH and the product analyzed by mass spectrometry, major molecular ion peak at *m/z* 584 (molecular formula C₃₆H₃₂CuN₄ = 2 × (*R*)-**29** + Cu) was observed confirming the presence of a dinuclear complex.

Accordingly, chelation of copper(I) to (*R*)-**29** is shown in Figure 22. Due to the strong coordination ability of the nitro group to soft metals, MeNO₂ is activated and deprotonated to generate the active nucleophile - nitronate in the Cu(I) transition state.^{132,154,187,211} In consideration of both of the stereoelectronic influences and the outcomes of this nitroaldol adduct, the *Si* face of the carbonyl functionality of benzaldehyde is favored for nucleophilic attack to yield the corresponding (*R*)-product (Figure 20).

Figure 20

Recently, a number of reports have demonstrated that nonlinear effects (NLEs) can shed light on the molecular interactions in the process of stereoselective catalysis, thus supplying useful mechanistic information.²¹²⁻²¹⁵

Hence, the NLEs were examined for Henry reaction of nitromethane with benzaldehyde **39** using BIQ (*R*)-**29** with different enantiomeric purities (Table 11). Interestingly, the collected experimental data gave a double-shaped curve (Figure 23), which could be produced by Kagan's ML₄ model system (or (ML)₄ model system).

Table 11 Nonlinear effects under 2:1 ratio of (*R*)-29**:Cu(I)Cl in the enantioselective Henry reaction**

Conditions: i. (*R*)-**29** (0.1 equiv), Cu(I)Cl (0.05 equiv), $\text{ClCH}_2\text{CH}_2\text{Cl}$ (1.5 ml), 0 °C

Entry	% <i>ee</i> Ligand, (<i>R</i>)- 29	% <i>ee</i> Product, (<i>R</i>)- 124 ^a
1	0	0
2	15	10
3	40	28
4	50	40
5	70	61
6	90	81
7	99	85

^a Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column. The absolute configuration (*R*) was determined by comparison with the literature values.¹³²

Kagan *et al.* simplified the ML_4 system assuming ligands are distributed in the statistical mode, and derived equation (1) to express enantiomeric excesses of product (ee_{prod}) as a function of ligands' enantiopurity (ee_{cat}).²¹⁶ In equation (1), four basic parameters were

introduced: g and f represent reactivities of hetero complexes ($M(L_R)_3L_S$) and hetero-meso one ($M(L_R)_2(L_S)_2$) over homochiral complexes ($M(L_R)_4$) ($g = k_{RRRS}/k_{RRRR}$, $f = k_{RRSS}/k_{RRRR}$) respectively, while ee_0 defines the enantiomeric excesses of product by using enantiopure homochiral $M(L_R)_4$ complexes and ee_o' stands for the enantiomeric excesses of the product by the use of enantiopure heterochiral $M(L_R)_3L_S$ complexes. $M(L_R)_2(L_S)_2$ were considered as meso complexes and assumed no additional stereoisomers involving the metal center.

$$ee_{prod} = 8ee_o \times ee_{cat}$$

$$\times \frac{1 + ee_{cat}^2 + 2g(1 - ee_{cat}^2) \frac{ee_o'}{ee_o}}{(1 + ee_{cat})^4 + (1 - ee_{cat})^4 + 8g(1 - ee_{cat}^4) + 6f(1 - ee_{cat}^2)^2} \quad (1)$$

Supposing the catalytic BIQ ligands **29** are distributed²⁰² in statistical mode between the complexes, curve fitting was calculated from equation (1) with these parameters $ee_o = 85\%$, $K = \frac{[M(L_R)_3L_S]^2}{[M(L_R)_4][M(L_R)_2(L_S)_2]} = \frac{[M(L_S)_3L_R]^2}{[M(L_S)_4][M(L_R)_2(L_S)_2]} = 1000$, $ee_o' = 64\%$, $g = 0.41$ and $K' = \frac{[M(L_R)_2(L_S)_2]^2}{[M(L_R)_3L_S][M(L_S)_3L_R]} = 1$, $f = 2.0$. The resulting curve indicated the predominance of fairly active, moderate selective heterochiral catalyst speices and more active meso complexes. This computer-drawn curve calculated by Kagan's ML_4 model system (or $(ML)_4$ model system) was fitting well with these collected experimental data (Figure 21), and the standard deviation (S) is 0.0084565. This could be evidence for the involvement of an aggregation of dimers (with four BIQs **32** ligands) in the process of enantioselective Henry reaction by the catalytic system comprising of (*R*)-**32** and CuCl in

the 2:1 ratio.^{212-215,217}

Figure 21

In conclusion, the reactivities and selectivities of chiral 1,2-BIQ ligands (*R,R*)-**23**, (*R*)-**29** in the Henry reaction were examined. Chiral *C*₁-tetrahydro-1,1'-bisisoquinoline (*R*)-**29** proved to be more effective ligand in the copper(I)-catalyzed Henry reaction. The desired nitroaldol adducts were obtained in excellent yields (up to 95%) and enantioselectivities (up to 91% *ee*) with a broad range of aromatic and aliphatic aldehydes. Nonlinear effects have been studied, the results fit well with the Kagan's ML₄ model system.

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3.3. Enantioselective Henry reaction catalyzed by derivatives of BIQ (*R*)-29

Encouraged by the great results obtained using BIQ (*R*)-29 in the enantioselective Henry reaction (Table 10), we then turned our attention to explore the modular effects of its derivatives on the reactivity and selectivity in the asymmetric catalysis of Henry reaction.²¹⁸ Based on the DFT calculation and X-ray structural analysis of (*R*)-29, two fully aromatic isoquinoline ring with sp^2 -N atom is flat, while hetrocyclic ring in the other isoquinoline moiety assumes a twist boat conformation. The dihedral angle between $N_1-C_1-C_1'-N_1'$ is affected by the size (bulkiness) and type (alkyl, sulfonyl, acyl *etc.*) of substituents attached to the sp^3 -N atom of (*R*)-29.^{12,13,187}

Treatment of (*R*)-29 with the respective halides, isocyanate and isothiocyanate afforded its alkyl, amide, urea and thiourea derivatives (*R*)-161-170, respectively, in excellent yields (Figure 22). The substituents at the sp^3 -N of ligands (*R*)-161-170 were chosen to modulate the steric bulkiness around the chelating centers and show contrasting electronic effects on the metal center.

Figure 22

3.3.1. Ligand effects

Initially, ligands **(R)-161-170** were examined in the enantioselective Henry reaction between nitromethane and benzaldehyde **39** to test the efficiencies of these compounds as chiral inductors. The reactions were performed under the same standard reaction conditions (10 mol% ligand, 10 mol% copper source CuBr and 20 equiv MeNO₂ in THF at r.t. developed earlier). The results are shown in Table 12.

As shown in Table 12, β -nitroalcohol **(R)-124** was obtained in 98% yield and up to 83% *ee* using chiral ligand **(R)-161**, the one bearing the smallest alkyl substituent—methyl group (Table 12, entry 1). Under the same reaction conditions, other alkylated ligands **(R)-162-164** afforded comparable yields (85-98%) but lower enantioselectivities (65-69% *ee*) than ligand **(R)-161** (Table 12, entry 1 vs entries 2-4). Surprisingly, BIQ **(R)-165** (with 2-hydroxy-5-nitro-benzyl group), BIQs **(R)-166** and **(R)-166** (with amide functional group), and BIQ **(R)-168** (with urea functional group) were found to be completely inactive and the starting material benzaldehyde **39** was recovered back unchanged (Table 12, entries 5-8). The lack of reactivities may be due to the obvious steric bulkiness of these ligands, resulting in the inefficient formation of the copper complexes. Based on the analysis of these ligands' X-Ray

crystallography shows that bulky attachments around sp^3 -N force these chelating nitrogens to adapt an *anti* conformation preventing efficient chelation. In contrast, copper ion could coordinate with the *syn*-oriented nitrogens in the cases of alkylated BIQs with relatively smaller substituents (Table 12, entries 5-8 vs entries 1-4). However, the desired product (*R*)-**124** was obtained in 20-30% yield and 21-24% *ee* by the use of ligands (*R*)-**169** and (*R*)-**170** with large substituents (Table 12, entries 9-10). To ensure that the catalytic induction was due to the relative formation of copper complexes, and not due to the ligands themselves, the nitroaldol reactions were repeated in the exactly same reaction conditions by the use of ligands (*R*)-**169** and (*R*)-**170** without metal salts, separately. In both cases, no expected products were formed and the starting materials were recovered back, indicating ligands (*R*)-**169** and (*R*)-**170** themselves were inefficient organocatalysts in this addition reaction.

Based on the above results, BIQ (*R*)-**161** was chosen for further optimization of reaction conditions (Table 12, entry 1).

Table 12 Enantioselective nitromethane addition to benzaldehyde in the presence of (*R*)-161**-**170****

Conditions: i. Ligand (0.1 equiv), CuBr (0.1 equiv), THF (1.5 ml), r.t.

Entry	Ligand	Time	Yield ^a (%)	<i>ee</i> ^b (%)
-------	--------	------	------------------------	----------------------------

1	(<i>R</i>)- 161	20	98	83
2	(<i>R</i>)- 162	20	98	65
3	(<i>R</i>)- 163	20	95	67
4	(<i>R</i>)- 164	20	85	69
5	(<i>R</i>)- 165	20	0	-
6	(<i>R</i>)- 166	36	0	-
7	(<i>R</i>)- 167	36	0	-
8	(<i>R</i>)- 168	36	0	-
9	(<i>R</i>)- 169	36	30	24
10	(<i>R</i>)- 170	36	20	21

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*R*) was determined by comparing with the literature values.²¹⁰

3.3.2. Effects of copper sources

A series of frequently used copper sources were examined using (*R*)-**161** in THF. In each case, the asymmetric nitroaldol reaction was performed at room temperature for over 20 h. The results summarized in Table 13 showed that the reaction was most sluggish by the use of Cu(II) chloride (40% yield) while the other tested copper sources all provided above 70% yield (Table 13, entry 2 vs entries 1 and 3-7). In general, copper (I) sources (Table 13, entries 3-7) are superior in reactivity in comparison to copper (II) sources (Table 13, entries 1-2). In comparison with the results obtained by copper (II) acetate, the nitroaldol adduct (*R*)-**124** was produced in higher yields but lower *ee* values in the

presence of copper (I) acetate (Table 13, entry 1 *vs* entry 4). However, copper (I) salts with halide ions were capable of providing highest yields (up to 99%) and the best enantiomeric excesses (up to 83% *ee*) (Table 13, entries 5-7). CuCl and CuBr showed very similar reactivities to those of CuI, but higher enantioselectivities (Table 13, entries 5-6 *vs* entry 7). These results indicated that small counter anions (e.g. halide ions) had no prominent effect on the catalytic process of Henry reaction.

Therefore, considering CuCl was inexpensive and less toxic, so it was chosen as the copper source for the next optimizations of the asymmetric Henry reaction (Table 13, entry 5).

Table 13 Screening of copper sources for asymmetric nitromethane addition to benzaldehyde by (*R*)-161

Conditions: i. (*R*)-**161** (0.1 equiv), Copper sources (0.1 equiv), THF (1.5 ml), r.t., 20 h

Entry	Cu salt	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
1	Cu(OAc) ₂	70	65
2	CuCl ₂	40	31
3	CuOTf	75	3
4	CuOAc	85	45

5	CuCl	99	83
6	CuBr	98	83
7	CuI	99	70

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*R*) was determined by comparing with the literature values.²¹⁰

3.3.3. Solvent effects

Next, different types of solvents were also examined in combination with the copper complex (*R*)-**161**/CuCl for the catalytic enantioselective nitroaldol reaction between benzaldehyde and nitromethane. As the results shown in Table 14, both protic solvents and the nonprotic ones were found to yield the final product β -nitro alcohols (*R*)-**124** in similar *ee* values; however, ether-type solvents and alcohols gave much higher yields than the chlorinated ones (Table 14, entries 1-5 and entries 11-12 vs entries 6-8). Surprisingly, the reaction was very sluggish in CH₃CN, and the final nitroaldol adduct (*R*)-**124** was achieved in only 12% yield (Table 14, entry 9). Presumably, poor solubility of the forming copper complexes by (*R*)-**161**/CuCl in CH₃CN resulted in the notable sluggishness. In consideration of both the reactivity and selectivity, (*i*-Pr)₂O was proved to be the best solvent of choice for the enantioselective Henry reaction catalyzed by (*R*)-**161**/CuCl, providing very high yield (90%) and the highest *ee* value (up to 86% *ee*) (Table 14, entry 5).

Therefore, this ether-type solvent (*i*-Pr)₂O was chosen in the following optimization process of reaction conditions.

Table 14 Screening of solvents for enantioselective nitromethane addition to benzaldehyde by (*R*)-161/CuCl

Conditions: i. (*R*)-161 (0.1 equiv), CuCl(0.1 equiv), Solvent (1.5 ml), r.t., 20 h

Entry	Solvent	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
1	THF	99	83
2	Dioxane	92	73
3	Bu ₂ O	70	84
4	Et ₂ O	78	83
5	(<i>i</i> -Pr) ₂ O	90	86
6	CH ₂ Cl ₂	52	83
7	CHCl ₃	65	83
8	ClCH ₂ CH ₂ Cl	62	83
9	CH ₃ CN	12	86
10	Neat	90	82
11	EtOH	95	84
12	<i>i</i> -PrOH	89	85

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*R*) was determined by comparing with the literature values.²¹⁰

3.3.4. Catalyst loading, ligand ratio and temperature effects

The impacts of other parameters like the ratio between ligand (*R*)-**161** and CuCl, the catalyst loading, and the temperature in the asymmetric catalytic process were further explored (Table 15).

Typically, lowering the reaction temperature from r.t. to 0 °C was believed to result in improvement in the catalyst system's enantioselectivity according to the previous reports.^{118,123-125,130,219,220} (*R*)-**124** of higher enantioselectivity and comparable yield were obtained by (*R*)-**161**/CuCl catalyst system when the temperature was decreased from r.t. to 0 °C (Table 15, entry 2 vs entry 1). Thus in the optimization of other factors, the asymmetric nitroaldol reactions were performed at 0 °C.

Keeping the amount of ligand (*R*)-**161** constant at 10 mol% (with respect to aldehyde **39**), the amount of copper salt was changed gradually from 5 to 10, 15 and 20 mol% (Table 15, entries 2-5), and a range of (*R*)-**161**/CuCl ratios (from 1:1 to 1:2, 1:1.5 and 2:1) were achieved for examination. The results showed a tremendous decrease in the reaction rate, affording the β -nitro alcohols (*R*)-**124** less than half even after extending the reaction time. The optimal ratio between ligand (*R*)-**161** and copper source is clearly 1:1 (Table 15, entry 2).

Using the optimal ratio of these two substances, further attempts to decrease the catalyst loading from 10 mol% to 5 mol% afforded the final product (*R*)-**124** in prominent lower yield (20%) and lower *ee* (80% *ee*) (Table 15, entry 6 vs entry 2), whereas when doubling

the catalyst loading, the reaction rate was increased and the final product (*R*)-**124** with lower *ee* was afforded (Table 15, entry 7 vs entry 2). Therefore, the most reasonable loading of (*R*)-**161**/CuCl catalyst system was 10 mol% and 10 mol%, respectively (Table 15, entry 2).

Table 15 Screening of the ratio of (*R*)-161 to CuCl, catalyst loading and temperature in the asymmetric nitromethane addition to benzaldehyde

Conditions: i. (*R*)-**161** , CuCl, (*i*-Pr)₂O (1.5 ml)

Entry	CuCl (mol%)	(<i>R</i>)- 161 (mol%)	Temperature (°C)	Time (h)	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
1	10	10	r.t.	20	90	86
2	10	10	0	20	65	91
3	5	10	0	40	35	82
4	15	10	0	40	29	76
5	20	10	0	40	18	63
6	5	5	0	40	20	80
7	20	20	0	20	90	86
8 ^d	5	10	r.t.	20	80	70

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

^c The absolute configuration (*R*) was determined by comparing with the literature values.²¹⁰

^d The copper salt is Cu(OAc)₂.

Overall, the optimized reaction conditions were found as follows: the reaction was performed in isopropyl ether at 0 °C by the combination of ligand (*R*)-**161** (10 mol%) and CuCl (10 mol%), the final nitroaldol adduct (*R*)-**124** was achieved in the highest *ee* (91 %) and acceptable yield (65%).

3.3.5. Scope of (*R*)-**161** in the enantioselective Henry reaction

With the optimal reaction conditions (Table 15, entry 2) now in hand, the substrate scope of the asymmetric Henry reaction was then evaluated. A representative selection of aldehydes of a wide scope including aliphatic, conjugated, heteroaromatic and aromatic ones were investigated by treatment with nitromethane in the presence of 10 mol% (*R*)-**161**/CuCl (1:1) complex in (*i*-Pr)₂O at 0 °C, producing the corresponding β -nitroaldol adducts in moderate to excellent yields (45-99%) and enantioselectivities (63-94% *ee*) (Table 16).

As summarized in Table 16, whether the aromatic aldehydes are electron-poor (Table 16, entries 3-6), electron-rich (Table 16, entries 7-13) or electron-neutral (Table 16, entries 1, 22-24), the reaction proceeded smoothly, affording the desired products in similar yields and enantioselectivities (above 78% *ee*) using the above catalyst system. It indicated that the substituents' electronic nature (Table 16, entries 3-6 vs entries 7-13) and position

(Table 16, entries 4-5, entries 7-9 and entries 11-13) on the phenyl ring have no prominent effect on the reactivities and enantioselectivities. However, the most strong electron-withdrawing group (nitro substituent) was one exception, yielding the expected nitroaldol adduct (*R*)-**143** with only 64% *ee* (Table 16, entry 2). The higher reaction rate than other aromatic aldehydes' was probably the reason for that low enantiomeric excess value. Most remarkably, aliphatic straight chain aldehydes of different lengths (Table 16, entries 14-18), branched (Table 16, entries 19-20) and steric hindrance (Table 16, entry 21) could also smoothly undergo catalytic enantioselective addition of nitromethane, affording respective nitroalcohols with high yields (75-99%) and excellent *ees* (ranging from 90% to 94%). The higher yields for aliphatic aldehydes are presumably due to their inherently higher activities. In all the examined cases (Table 16), no aldol side reactions or dehydration were observed.

Table 16 Scope of (*R*)-161**/CuCl in the asymmetric Henry reaction**

Conditions: i. (*R*)-**161** (0.1 equiv), Cu(I)Cl (0.1 equiv), (*i*-Pr)₂O (1.5 ml), 0 °C

Entry	Substrate	Product	Time	Yield ^a (%)	<i>ee</i> ^{b, c} (%)
-------	-----------	---------	------	---------------------------	----------------------------------

1	39	(R)-124	20	65	91
2	126	(R)-143	20	99	63
3	130	(R)-147	40	55	90
4	127	(R)-144	20	80	86
5	128	(R)-145	20	70	87
6	171	(R)-177	20	78	80

7	131	(R)-148	40	80	92
8	132	(R)-149	40	45	90
9	133	(R)-150	40	83	91
10	134	(R)-151	20	95	94
11	135	(R)-152	40	75	90
12	136	(R)-153	40	50	86

13	65	(R)-154	40	86	90
14	172	(R)-178	20	95	93
15	138	(R)-156	20	85	91
16	137	(R)-155	20	90	94
17	173	(R)-179	20	94	90
18	139	(R)-157	20	75	90
19	174	(R)-180	20	99	92
20	175	(R)-181	20	99	91

21	176	(R)-182	20	70	93
22	140	(R)-158	20	90	78
23	141	(R)-159	20	90	86
24	142	(R)-160	20	95	84

^a Yields of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H, OJ-H or Chiralpak AD-H columns.

^c The absolute configuration (*R*) was determined by comparing with the literature values.^{107,132,149}

3.3.6. Proposed Mechanism

The mixture of ligand (*R*)-**161** and copper salt in a 1:1 ratio (the optimal ratio) was dissolved in CH₂Cl₂, and the resulting yellow solution was tested by mass spectrometry, the observed major molecular ion peaks at *m/z* 611 (molecular formula C₃₈H₃₆CuN₄ = 2 × (*R*)-**161** + Cu) and at *m/z* 613 (molecular formula C₃₈H₃₈CuN₄ = 2 × (*R*)-**161** + Cu + 2H⁺) proved the presence of copper complex in a 2:1 ratio of (*R*)-**161** to CuCl. A proposed

transition state model is shown in Figure 23, nitromethane was deprotonated to the active nitronate in this copper (I) transition state. In the process of asymmetric induction, the two reaction partners were simultaneously binding to this copper complex, the *Si* face of the carbonyl center is favored in accordance with previously discussed steric bulkiness and electronic considerations.^{12,13}

Figure 23

The Non-linear effects for this substoichiometric Henry reaction of nitromethane with benzaldehyde **39** using BIQ (*R*)-**161** with copper(I) chloride was examined in Table 18.

Table 18 The nonlinear effects under 1:1 ratio of (*R*)-161/Cu(I)Cl in the enantioselective Henry reaction

Conditions: i. (*R*)-**161** (0.1 equiv), Cu(I)Cl (0.1 equiv), (*i*-Pr)₂O (1.5 ml), 0 °C

Entry	% <i>ee</i> Ligand, (<i>R</i>)- 161	% <i>ee</i> Product, (<i>R</i>)- 124 ^a
1	0	0
2	9	19
3	18	38
4	32	57
5	41	67
6	54	78
7	61	81
8	73	85
9	80	87
10	88	89
11	99	91

^a Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column. The absolute configuration (*R*) was determined by comparison with the literature values.¹³²

Kagan *et al.* simplified the ML_2 system assuming ligands are distributed in statistical mode, and derived equation (2) to express enantiomeric excesses of product (ee_{prod}) as a function of ligands' enantiopurity (ee_{cat}).²¹³ In equation (2), two basic parameters were introduced: g represents reactivities of hetero complexes ($ML_R L_S$) over homochiral complexes ($M(L_R)_2$) ($g = k_{RS}/k_{RR}$), while ee_o defines the enantiomeric excesses of product

by using enantiopure homochiral $M(L_R)_2$ complexes (Table 18, entry 11). The meso complex ML_RL_S were assumed no additional stereoisomers involving the metal center, affording only racemic product.

$$ee_{prod} = ee_o * ee_{cat} * \frac{2}{1 + g + (1 - g)ee_{cat}^2} \quad (2)$$

The final computer-drawn curve calculated by Kagan's ML_2 model system was fitting well with collected experimental data, and the standard deviation (S) is 0.0291857 (Figure 24).

Figure 24

The observed positive non-linear effect indicated the existence of less catalytically active heterochiral species. This could be evidence for the effective catalytic system in the process of enantioselective Henry reaction is comprising of (*R*)-**161** and CuCl in 2:1 ratio.^{212-215,217}

In conclusion, the reactivities and selectivities of chiral 1,2-BIQ **29** based derivatives in the Henry reaction were examined. Chiral *N*-methyl-*C*₁-tetrahydro-1,1'-bisisoquinoline (*R*)-**161** proved to be the most effective ligand in the copper (I)-catalyzed Henry reaction. The desired nitroaldol adducts were obtained in excellent yields (up to 99%) and enantioselectivities (up to 94% *ee*) with a broad range of aromatic and aliphatic aldehydes. Nonlinear effects have been studied, the results fit well with the Kagan's ML₂ model system.

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3.4. Diastereoselective Henry reaction catalyzed by BIQ (*R*)-29** and its alkyl derivatives (*R*)-**161-164****

In the past two decades, a number of reports uncovered various metal-based catalysts, organocatalysts, and biocatalytic approaches for the asymmetric Henry reaction using nitromethane.^{105,119,120,184,221-224} However, those methods have not been examined

thoroughly or do not work with other nitroalkanes, the highly diastereo- and enantiocontrol versions of Henry reaction of other nitroalkanes still remain a challenging task.^{107,119} Since the first report of a *syn*-selective Henry reaction by Shibasaki *et al.* in 1995,^{130,131} some other *syn*-diastereoselective catalyst systems such as guanidinium-thiourea,^{225,226} bisimadozoline,²²⁷ bisoxazolidine,^{139,228} brucine,¹⁰⁹ and diamines^{142,149,166,229} have successfully achieved the transformation while fewer examples for the *anti*-diastereoselective version^{111,112,129,230} has been reported. Two distinctive transition state models have been proposed: the chelation model which offers *syn* products and the nonchelation one that prefers *anti*-selectivity.²³¹ Some clear limitations still remained in the diastereoselective Henry reaction like the narrow scope of aldehyde, low reaction temperatures, high catalyst loading, and long reaction times.¹¹⁹

The development of novel chiral catalysts for diastereoselective (especially the *anti*-selective version) Henry reaction is highly desirable. As previously discussed in this chapter, excellent results for the enantioselective Henry reaction between a wide range of aldehydes and nitromethane were obtained. Therefore, it was logical that we extend the application of these ligands such as (*R*)-**161-164** (Figure 25) to the diastereoselective Henry reaction with nitroalkanes other than nitromethane.

Figure 25

3.4.1. Ligand and copper source effects

Effective alkylated BIQs (*R*)-**161-164** and parent BIQ (*R*)-**29** (Figure 25) with different levels of steric bulkiness were screened for the asymmetric Henry reaction between nitroethane and benzaldehyde **39**, and the results are summarized in Table 19. In all cases, *anti* nitroalcohols were obtained predominantly when using the above BIQs under the optimized reaction conditions (10 mol% ligand, 10 mol% CuCl in diisopropyl ether, r.t., 48h) which was developed for the Henry reaction using nitromethane.²¹⁸ Table 19 shows that ligands (*R*)-**161-164** bearing different alkyl groups afforded the final desired product **183** in a little higher diastereoselectivity than the parent BIQ (*R*)-**29** (Table 19, entries 2-5 *vs* entry 1). BIQ (*R*)-**161** with the smallest *N*-alkyl attachment (methyl group) was confirmed to be the most effective ligand with 64% yield, an *anti/syn* diastereoselectivity of 2:1 and *ee* values of 72:28, respectively (Table 19, entry 2) while similar diastereoselectivities but lower yields and enantioselectivities were achieved in the presence of other ligands (*R*)-**161-164** with bigger substituents (Table 19, entries 3-5).

Using the most efficient ligand (*R*)-**161**, some other copper (I) and copper (II) sources were tested under the same reaction conditions (Table 19, entries 6-10). Both copper (I) and copper (II) sources yielded the expected products **183** in comparable diastereoselectivities, however, the copper (I) salts are superior to copper (II) ones in terms of enantioselectivities (Table 19, entries 2, 6-8 *vs* entries 9-10). Among these different Cu(I) sources, CuCl was clearly the best choice for this asymmetric transformation when considering reactivity, stereoselectivity and enantioselectivity (Table 19, entry 2 *vs* entries 6-8). Therefore, the optimal catalyst system formed by (*R*)-**161** and

copper (I) chloride was adopted for the further screening process of diastereoselective Henry reaction (Table 19, entry 2).

Table 19 Screening of ligands (R)-29, (R)-161-164 and copper sources for the diastereoselective Henry reaction

Conditions: i. Ligand (0.1 equiv), Copper Salts (0.1 equiv), (*i*-Pr)₂O (1.5 ml), r.t., 48h

Entry	Ligand	Copper source	Yield (%) ^a	<i>anti</i> / <i>syn</i> ^b	<i>ee</i> (%) ^c
1	(R)- 29	CuCl	49	1.7:1	64:70
2	(R)- 161	CuCl	64	2.0:1	72:78
3	(R)- 162	CuCl	50	2.1:1	68:64
4	(R)- 163	CuCl	43	1.9:1	66:67
5	(R)- 164	CuCl	36	2.0:1	65:68
6	(R)- 161	CuBr	55	2.0:1	63:73
7	(R)- 161	CuI	34	1.9:1	56:61
8	(R)- 161	CuOAc	17	1.7:1	54:40
9	(R)- 161	CuCl ₂	79	2.0:1	30:24
10	(R)- 161	Cu(OAc) ₂	70	1.7:1	44:47

^a Yields of isolated products.

^b Determined by ¹H NMR analysis and HPLC using Chiralpak AD-H column.

^c Enantiomeric excesses values were determined by HPLC using Chiralpak AD-H column.²³²

3.4.2. Solvent effects

Subsequently, the effects of different types of solvents (e.g. dioxane, THF, CH₂Cl₂, EtOH, CH₃CN and toluene) were tested in the asymmetric Henry reaction using nitroethane. All the reactions were carried out smoothly by the use of (*R*)-**161**/CuCl, the results from Table 20 indicated ether-type THF solvent was the most optimal solvent of choice (Table 20, entry 3), the nitroaldol adducts **183** of acceptable yields (65%) were produced in the highest *anti/syn* stereoselectivity (up to 2.6:1) and the highest *ee* values of both products (83% *ee* and 90% *ee*, respectively). Protic solvent EtOH was found to afford the final product β -nitro alcohols **183** in the lowest *anti/syn* ratio (1.3:1), while the highest yield (up to 89%) was achieved (Table 20, entry 5). Moreover, the reactions were significantly slowed down in the CH₃CN or toluene solution, due to the lack of proper solubility with the formed copper complex (*R*)-**161**/CuCl (Table 20, entries 6-7).

Therefore, the following optimized of reaction conditions would be performed in THF solution by the catalyst system (*R*)-**161**/CuCl (Table 20, entry 3).

Table 20 Screening of solvents for the diastereoselective Henry reaction using ligand (*R*)-161****

Conditions: i. (*R*)-**161** (0.1 equiv), CuCl (0.1 equiv), solvent (1.5 ml), r.t., 48h

Entry	Solvent	Yield (%) ^a	<i>Anti/syn</i> ^b	<i>ee</i> (%) ^c
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1	(<i>i</i> -Pr) ₂ O	64	2.0:1	72:78
2	Dioxane	55	2.1:1	74:80
3	THF	65	2.6:1	83:90
4	CH ₂ Cl ₂	38	2.3:1	72:80
5	EtOH	89	1.3:1	73:64
6	CH ₃ CN	22	2.3:1	82:80
7	Toluene	19	1.3:1	47:53

^a Yields of isolated products.

^b Determined by ¹H NMR analysis and HPLC using Chiralpak AD-H column.

^c Enantiomeric excesses values were determined by HPLC using Chiralpak AD-H column.²³²

3.4.3. Catalyst loading, ratio effects

Next, the optimization process for the diastereoselective nitroaldol reaction was focused on the impacts of catalyst loading and ratio between ligand (*R*)-**161** and CuCl (Table 21). The amount of CuCl was changed gradually while the amount of ligand (*R*)-**161** was kept constant at 10 mol%, and the resulting different ratios of (*R*)-**161**/CuCl showed a remarkable decrease in the yields of nitroalcohols **183** and comparable stereoselectivity. The catalyst system formed by ligand (*R*)-**161** and copper source (1:1) is notably the most efficient for this diastereoselective Henry reaction (Table 21, entry 2). Surprisingly, the loading of 20 mol% copper source (2 times to the ligand (*R*)-**161**'s amount) resulted in inhibition of the reaction. Applying the optimal ratio between these two substances in the catalytic system, next attempts to change the catalyst loading from 10 mol% to 5 mol% and 20 mol% yielded the expected products **183** in lower stereoselectivities and enantioselectivities (Table 21, entries 5-6 vs entry 2). Hence, the optimal amount of (*R*)-

161/CuCl catalyst system in the diastereoselective nitroaldol reaction was 10 mol% for each compound (Table 21, entry 2).

Table 21 Screening of catalyst loading and ratios of (*R*)-161** to CuCl for the diastereoselective Henry reaction**

Entry	Ratio (<i>R</i>)- 161 /CuCl	Yield (%) ^a	<i>Anti/syn</i> ^b	ee (%) ^c
1	1:0.5	70	2.3:1	81:80
2	1:1.0	65	2.6:1	83:90
3	1:1.5	36	2.2:1	76:83
4	1:2.0	-	-	-
5	2:2.0	79	2.1:1	61:75
6 ^d	0.5:0.5	17	2.3:1	84:87

^a Yields of isolated products.

^b Determined by ¹H NMR analysis and HPLC using Chiralpak AD-H column.

^c Enantiomeric excesses values were determined by HPLC using Chiralpak AD-H column.²³²

^d Reaction time is 120 h.

Overall, the optimized reaction conditions were found to be 10 mol% ligand (*R*)-**161** and 10 mol% copper (I) chloride in THF at ambient temperature, and the final product **183** was cleanly achieved in the highest stereoselectivity (2.6:1), and *ee* values (83% and 90% *ee*, respectively) with acceptable overall yield (65%).

3.4.4. Scope of (*R*)-161 in the asymmetric Henry reaction

With the optimal conditions in hand, the scope of Henry reaction using nitroethane and nitropropane was investigated, and the results were summarized in Table 22. For both aromatic and aliphatic aldehydes, the reaction proceeded cleanly to afford the desired nitroaldol products with predominately *anti* diastereoselectivity in good *ee* values and yields. The position of withdrawing or donating substituents on the phenyl ring has little effect on the diastereoselectivity (Table 22, entries 2-8). However, substrates with electron donating groups showed higher *ees* than the ones with electron withdrawing groups (Table 22, entries 2-5 vs entries 6-8). For the addition of nitroethane or nitropropane to aliphatic aldehydes, good yields and excellent *ee* values (up to 81% and 91%) were obtained even with relatively lower diastereoselectivities (Table 22, entries 10-14).

Table 22 Scope of (*R*)-161/CuCl in the diastereoselective Henry reaction with nitroethane/nitropropane

Conditions: i. (*R*)-161 (0.1 equiv), CuCl (0.1 equiv), THF (1.5 ml), r.t.

Entry	Substrate	Product	Time	Yield (%) ^a	Anti/syn ^b	ee (%) ^c
-------	-----------	---------	------	------------------------	-----------------------	---------------------

1	39	183	48	65	2.6:1	83:90
2	126	185	48	95	1.5:1	50:66
3	184	186	48	80	2.1:1	72:86
4	127	187	48	83	1.5:1	63:86
5	183	188	48	85	1.6:1	61:87
6	131	189	96	75	1.7:1	85:91

7	132	190	96	65	1.6:1	77:87
8	133	191	96	70	1.6:1	75:92
9	140	192	48	70	0.8:1	40:75
10	138	193	48	81	1.3:1	90:89
11	175	194	48	80	1.3:1	90:91
12	138	195	48	79	1.1:1	85:87
13	172	196	48	77	1.1:1	86:89

14			48	73	1.3:1	86:90
	175	197				

^a Yields of isolated products.

^b Determined by ¹H NMR analysis and HPLC using Chiralcel OD-H, OJ-H and OB-H, Chiralpak AD-H, AS-H columns.

^c Enantiomeric excesses values were determined by HPLC using Chiralcel OD-H, OJ-H, Chiralpak AD-H, AS-H columns.^{129,146,163,232}

^d Reaction time is 96 h.

Henry reaction is known to be reversible and the obtained nitroalcohols are easily epimerized on the carbon connecting to the nitro group. Herein, the further cross-over and time-course studies on the stereochemistry of reaction were conducted.

In the cross-over reaction, treatment of a THF solution of nitroaldol adducts *anti*-**183** and *syn*-**183** with (*R*)-**161**/CuCl (10 mol%, 1:1) and MeNO₂ (20 mol%) resulted in the formation of benzaldehyde **39** and 1-phenyl-2-nitroethanol **123** along with *anti*-**183** and *syn*-**183**. This result confirmed the occurrence of retro-Henry reaction. Under the optimal reaction conditions utilized, we observed that reaction time greatly affects *anti*:*syn* ratio of the nitroaldol products (Table 23, Figure 26), further confirming the retro-Henry reaction. As clearly seen from entries 1-4 (Table 23), the amount of the more thermodynamically stable *anti*-**183** gradually decreases as the reaction proceeds and then equilibrates with the *syn*-**183** (Table 23, entries 4-9).^{131,233} There is probably a competing kinetic vs. thermodynamic control in Henry reaction. Reaction was allowed for the formation of the more dominant and stable thermodynamically *anti*-**183** along with the kinetically *syn*-**183**, it was a thermodynamic control. As the reaction proceeded over

time, the kinetically *syn*-**183** equilibrates with the thermodynamically stable *anti*-**183** as a result of retro-Henry reaction and an equilibrium was established after around 30 h (Figure 26).^{131,144,233} After 62.5 h, the *anti*-**183** slowly converted to the *syn*-**183** (Table 23, entries 7-9). Furthermore, the *ee* values of the *anti*- and *syn*-nitroalcohols are similar but with a slight bias towards the *syn*-product as shown in Table 22, indicating the probability of *in-situ* epimerization of the *anti*-**183** adduct to the *syn*-**183** adduct.^{131,230,234}

Table 23 Time-course studies of diastereoselective Henry reaction of benzaldehyde with EtNO₂ catalyzed by (*R*)-**161**/CuCl.^a

Conditions: i. (*R*)-**161** (0.1 equiv), Cu(I)Cl (0.1 equiv), THF (1.5 ml), r.t.

Entry	Time (h)	<i>anti</i> - 183 / <i>syn</i> - 183 ^a
1	8	3.7:1
2	14.5	3.0:1
3	23.5	2.7:1
4	31.5	2.6:1
5	48.5	2.6:1
6	55.5	2.6:1
7	62.5	2.6:1
8	80.5	2.5:1

9	96	2.4:1
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^a Determined by ¹H NMR analysis. **Figure 26**

In conclusion, *N*-methyl BIQ (*R*)-**161** was an efficient ligand in the copper (I) catalyzed diastereoselective Henry reaction of nitroethane and nitropropane, the expected nitroaldol adducts were obtained in excellent yields (up to 95%), moderate diastereoselectivities and good enantioselectivities (up to 92% *ee*). Cross-over and time-course studies suggest competition between the kinetically and thermodynamically controlled products.

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Chapter 4. Organocatalytic Henry Reaction by BIQs

Application of organocatalysts in various reactions has witnessed an exponential increase due to the many advantages it offers over traditional metal-based catalysis.^{171-180,235-237}

Nitrogen-based chiral organocatalysts such as prolines, imidazolidinones, guanidine, cinchona alkaloids, triazolium salts, urea and thioureas have seen numerous applications in asymmetric catalysis.⁵⁻⁷ While successful applications of BIQs as ligands for metal catalyzed reactions have been reported,^{12-15,218,219,238} their use as organocatalysts has not been documented.

Given our experience in this area, it was logical to explore the applications of BIQs as organocatalysts in Henry reaction. Due to the limited number of successful organocatalysts for the asymmetric Henry reaction, there is a strong emphasis to develop robust organocatalysts with wide substrate scope that can overcome formation of the by-products due to dehydration, aldol condensation or Cannizzaro reactions.^{116,221,239} Such emphasis requires the basic understanding of the factors that control reactivity and selectivity to be considered during the design of the catalyst.

In this Chapter, the abilities of selected BIQs *rac*-**23**, **27**, *rac*-**29**, **31**, **32**, *rac*-**35**, *rac*-**36**, *rac*-**98**, **101**, *rac*-**112**, *rac*-**120**, **121-122** and *rac*-**124** (Figure 27) to function as organocatalysts were explored for the first time. Of particular interest in this work is to examine the effect of nitrogen type (sp^3 vs sp^2) and their dispositions (1,2 vs 1,3) on the efficiency in Henry reaction, and to understand what type of *N,N*-organocatalyst (e.g. diamines, diimines or amine-imine) is more effective.

BIQs *rac*-**23**, **27**, *rac*-**29**, **31**, **32**, *rac*-**35**, *rac*-**36**, *rac*-**98**, **101**, *rac*-**112**, *rac*-**120**, **121-122** and *rac*-**124** (Figure 27) were prepared according to literature procedure (Chapter 2,

Section 2.1, 2.3, 2.4). The first six BIQs (BIQs [a]) all have electron donating methoxy groups that enhance the basicity of its nitrogens through electron donation *via* its aromatic rings. The nitrogens in BIQs [a] and BIQs [b] are in 1,2-disposition while they are 1,3-disposed in BIQs [c]. The greatest disparity can be seen when comparing BIQs [a] and BIQs [c] since BIQ [a] is a representative of activated 1,2-*N,N*-ligand (with electrodonating group—methoxy group) while BIQs [c] is a representative of unactivated 1,3-*N,N*-ligand. Within each group of BIQs [a]-[c], there are distinct variations (degree of saturation, type of nitrogen, presence of substituents on the nitrogen and symmetry) to further elucidate the structural effects on the efficiency of these organic bases.

Figure 27

4.1. BIQ Screening in organocatalysis of Henry Reaction

Initially, the efficiencies of BIQs [a]-[c] were examined in the more challenging and less explored Henry reaction between α -ketoesters (ethyl pyruvate **198**) and CH_3NO_2 (Table 24). The reaction was performed using 10 mol% BIQ and 20 equiv. CH_3NO_2 in THF at r.t. for 24 h. Under these condition, all BIQs gave the expected β -nitroalcohol adduct **199** cleanly. When we compare BIQs [a] (Table 24, entries 4 and 5) and BIQs [b] (Table 24, entries 9 and 10, respectively) as examples of 1,2-*N,N*-ligands vs BIQs [c] (Table 24, entries 12 and 13, respectively) as examples of 1,3-*N,N*-ligands we can observe a decreasing trend in the yield of **199** suggesting the superiority of 1,2-*N,N*-ligands over 1,3-*N,N*-ligands for this reaction. Among BIQs [a], BIQs *rac*-**36** and *rac*-**35** gave the highest yields (88% and 78%, respectively) due to their higher basicities which allowed them to deprotonate nitromethane effectively to form the required nucleophile – the nitronate. Similar trend was also observed in cases of BIQs [b] where BIQs *rac*-**29** and *rac*-**23** gave the highest yields (95% and 82%, respectively). This trend was further supported by the results obtained using BIQs [c] where BIQ *rac*-**98** gave the highest yield of 69%. Interestingly, the BIQs with one sp^3 nitrogen (amine-imine type) gave better yields of *rac*-**199** than BIQs with two sp^3 nitrogens (diamines) (Table 24, entry 4 vs entry

5 and entry 8 vs entry 9). This indicated the superiority of C_1 - over C_2 -BIQs.

Overall, BIQ *rac*-**29** was identified as the most efficient catalyst and its scope in Henry reaction was further explored using different esters and aldehydes (Table 24).

Table 24 Screening of bisoquinoline organocatalysts

Conditions: i. BIQs (0.1 equiv), THF (1.5 ml), r.t., 24h

Entry	Bisoquinoline	Yield ^a (%)
1	121	20
2	27	18
3	32	53
4	36	88
5	35	78
6	124	66
7	31	40
8	29	95
9	23	82
10	120	68

11	101	62
12	98	69
13	112	16

^a Isolated yield.

4.2. Scope of BIQ *rac*-29 in the organocatalysis of Henry reaction

Aromatic (Table 25, entries 1 and 2), and aliphatic (Table 25, entries 3-6) α -ketoesters reacted smoothly with CH_3NO_2 to give the corresponding β -nitro- α -hydroxyesters in excellent isolated yields ranging from 85% to 99%. Likewise, aromatic and aliphatic aldehydes reacted smoothly with CH_3NO_2 to give the expected β -nitro- α -hydroxyesters. In the case of aromatic aldehydes, the type (electron donating/withdrawing) and position of the substituents on phenyl ring were found critical for high yields. Aromatic aldehydes with electron-withdrawing groups gave better yields in comparison to those with electron-donating groups (Table 25, entries 8-12 vs 13-15) especially when the substituent was on the *para*- or *ortho*-position. Moreover, aliphatic, heteroaromatic and conjugated aldehydes (Table 25, entries 16-21, 22 and 23, respectively) also reacted with CH_3NO_2 smoothly to give the corresponding β -nitro- α -hydroxyesters in excellent yields.

Table 25 Henry reaction of nitromethane catalyzed by BIQ *rac*-29

Conditions: i. BIQ *rac*-29 (0.1 equiv), THF(1.5 ml), r.t., 24h

Entry	Substrate	Product	Yield (%) ^a
1	200	206	99
2	201	207	90
3	198	199	95
4	202	208	90
5	203	209	88
6	204	210	85
7	39	124	75

8	126	143	99
9	205	211	96
10	127	144	82
11	128	145	50
12	129	146	85
13	131	148	30

14	132	149	68
15	133	150	35
16	138	156	98
17	174	180	90
18	137	155	99
19	175	181	90
20	173	179	92
21	139	157	88

22	141	159	90
23	142	160	87

^a Isolated yield.

Next, we examined the efficiency of BIQ *rac*-**29** in the diastereoselective Henry reaction (Table 26). All α -ketoesters (Table 26, entries 1 and 2), aromatic aldehydes (Table 26, entries 3-6), aliphatic aldehydes (Table 26, entries 7-9), heteroaromatic aldehyde (Table 26, entry 10) and α,β -unsaturated aldehyde (Table 26, entry 11) were found to react with EtNO₂ smoothly to give the corresponding nitroaldol adducts in excellent yields (87-99%). However, the diastereoselectivity of all the products was moderate and the best *syn/anti* selectivity of 2:1 was obtained in case of 2-furaldehyde (Table 26, entry 10).

Table 26 Henry reaction of nitroethane catalyzed by BIQ *rac*-**29**

Conditions: i. BIQ **29** (0.1 equiv), THF(1.5 ml), r.t.

Entry	Substrate	Product	Time (h)	<i>syn/anti</i> ^a	Yield (%) ^b
-------	-----------	---------	----------	------------------------------	------------------------

1	201	212	48	1.70/1	92
2	198	213	48	1.91/1	96
3	126	185	24	1.23/1	99
4	205	214	24	1.00/1	99
5	127	187	48	1.54/1	87
6	140	192	72	1.80/1	90
7	138	193	48	1.20/1	94

8			48	1.00/1	94
	137	215			
9			48	1.09/1	98
	175	194			
10			48	2.00/1	97
	141	216			
11			72	1.39/1	92
	142	217			

^a Determined by crude ¹H NMR analysis.

^b Isolated yield.

4.3. Basicity of BIQ *rac*-29

The basicity of BIQ *rac*-29 was examined since the BIQs employed here effectively acted as organic bases to generate the nitronate nucleophile. The basicity of BIQ *rac*-29 was estimated by competitive NMR studies with hexafluorophosphate salt of proton sponge **218** in deuterated acetonitrile.^{61,240} The proton exchange between the free BIQ *rac*-29 base and hexafluorophosphate salt **219** was relatively slow on the NMR timescale (Scheme 67).

Scheme 67

Different molar ratios between BIQ *rac*-**29** and hexafluorophosphate salt **219** were adopted to test the competitive NMR studies. According to equations (3)-(4), the pK_{BH^+} of BIQ **29** was determined to be 16.8 ± 0.7 by equation (3)-(4).²⁴⁰

$$K = \frac{[BIQ-PF_6][Proton\ sponge]}{[Proton\ sponge-PF_6][BIQ]} \quad (3)$$

$$pK_{[BIQ]} = pK_{[proton\ sponge]} + \log K \quad (4)$$

In conclusion, both C_1 - and C_2 -symmetric BIQ acted as organocatalysts and successfully catalyzed Henry reaction where addition of nitroalkanes to α -ketoesters and aldehydes proceeded cleanly under mild conditions. C_1 -symmetric BIQs (amine-imine) proved to be more efficient than C_2 -symmetric ones (diamines, diimines), C_1 -1,2,3,4,-tetrahydro-1,1'-bisisoquinolines *rac*-**29** proved to be the most efficient (up to 99%). In the diastereoselective Henry reactions, excellent yields and moderate *syn/anti* selectivities (up to 2.0:1) were obtained in the addition of EtNO₂ to α -ketoesters and aldehydes. This study paves the way for application of chiral BIQs as organocatalysts.

4.4. Application of BIQ (*R*)-**29** as organocatalyst in the asymmetric Henry reaction

Application of organocatalysts such as nitrogen based compounds in various reactions has witnessed an exponential increase due to the many advantages it offers over traditional metal-based catalysis.^{171-180,235-237}

Based results obtained using BIQ *rac*-**29** in the organocatalysis of Henry reaction, application of BIQ (*R*)-**29** as organocatalyst to the asymmetric version of the Henry reaction was tested (Table 27).

Table 27 Asymmetric Henry reaction of nitromethane catalyzed by (*R*)-**29**

Conditions: i. BIQ (*R*)-**29** (0.1 equiv), THF(1.5 ml), r.t., 24h

Entry	Substrate	Product	Yield (%) ^a	ee ^b
1	200	206	99	0
2	198	199	95	0

3	39	124	75	0
4	138	156	98	0

^a Yield of isolated products.

^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H or Chiralpak AD-H columns.

Based on the results obtained by the use of (*R*)-**29** in the asymmetric Henry reaction of different substrate, only *racemic* products were afforded. Considering the mechanism of Henry reaction, the reason for this situation is probably because those bisisoquinoline-based catalysts are unable to forming bonding (e.g. hydrogen bonding, electrostatic interaction) with the acceptor carbonyl oxygen and nitronate group at the same time.

Chapter 5. Experimental

General

All commercial chemicals used in the whole project were obtained from Sigma-Aldrich, Merck, Alfa Aesar, Acros and Fisher Scientific, and were used as received unless otherwise indicated. The anhydrous solvents (including toluene, THF and diethyl ether) used in reaction were freshly taken from PURE SOLV PS-400-5-MD system.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F₂₅₄ precoated silica gel plate (0.2 mm thickness). The products on the TLC plate were visualized under UV light (254 nm) or by using chromogenic agent—solution of anisaldehyde in sulfuric acid EtOH (v/v/v = 2.68/0.5/50). Flash chromatography and column chromatography for purification of compounds were carried out on Merck silica gel 60 (230-400 mesh).

FTIR spectra were recorded in KBr thin film on Perkin-Elmer FTIR system Spectrum BX spectrometer. Melting points were tested by Barnstead Electrothermal 9100 melting point analytical instrument. ¹H NMR spectra were measured at 300 MHz on a Bruker Advanced DPX 300 spectrometer. Unless otherwise specified, data refer to solutions in CDCl₃ with the TMS as internal reference. ¹H NMR multiplicities were assigned as singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), triplet (t), triplet of doublet (td), quartet (q), multiplet (m) and broad (br). ¹³C NMR spectra were measured at 75.47 MHz on a Bruker Advanced DPX 300 spectrometer. C-H (HMBC, HMQC) spectra were also measured on the same apparatus using Bruker automation programs. LC-Mass spectra were recorded on Agilent LC system with

Agilent Mass selective detector. High resolution mass spectra were recorded on Finigan MAT 95*P spectrometer. X-ray single crystal diffraction data were measured on Bruker-AXS Smart Apex CCD single-crystal diffractometer. HPLC separations were performed on Agilent 1100 using Diacel chiralcel OB-H, OD-H, OJ-H and chiraopak AD-H, AS-H chiral columns. The optical rotation values were measured on JASCO P-1020 polarimeter.

5.1. Synthesis of 1,3-BIQs 98

5.1.1. *N,N'*-bisphenethylmalonamide 100

Diethyl malonate (3.2 mL, 0.021 mol) was added dropwise over a period of 10 minutes to phenethylamine (5.2 mL, 0.042 mol). After the addition, the resulting yellow solution was stirred at 80 °C for two days. In the reaction process, thick yellow solids were generated. After complete reaction (tested by TLC analysis), the

yellow solid was separated by a Buckner funnel, washed with hexane (3×10 mL) and dried under reduced pressure. The final *N,N'*-bisphenethylmalonamide **100** was obtained as a fluffy white solid (5.8 g, 89%), m.p. 102-104 °C. FTIR (Nujol) $\nu_{\max}$: 3298, 1659, 1633, 1548, 1229, 747, 698, 575 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 2.82 (4H, t, $J = 7.2$ Hz, H2 and H2'), 3.04 (2H, s, H7), 4.16 (4H, t, $J = 7.2$ Hz, H1 and H1'), 6.93 (2H, br s, 2×NH), 7.17-7.56 (10H, m, H2'', H3'', H4'', H5'', H6'' and H2''', H3''', H4''', H5''', H6'''). ^{13}C NMR (75.6 MHz, CDCl_3) δ : 35.5 (C2 and C2'), 40.9 (C1 and C1'), 43.2 (C7), 126.6 (C4'' and C4'''), 128.6 (C2'', C6'' and C2''', C6'''), 128.7 (C3'', C5'' and C3''', C5'''), 138.6 (C1'' and C1'''), 167.2 (2×CO). Mass (ESI) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$: 310.15, found 311.12 (M+1).

5.1.2. 1,1'-methylene-bis(3,3',4,4'-tetrahydroisoquinoline) **101**

POCl₃ (3.66 mL, 0.04 mol) was added dropwise over 10 min into a suspension of bisoxamide **100** (1.24 g, 0.004 mol) and P₂O₅ (5.7 g, 0.04 mol) in toluene (15 mL). After addition was complete, the mixture was heated to reflux overnight with vigorous stirring. The reaction mixture was then cooled to room temperature, the solvent was decanted and

saturated NaHCO₃ solution (20 mL) was added into the remaining brown solid until bubbling was no longer observed. The yellow mixture was then treated by addition of saturated NaOH solution (25 mL) to adjust pH of the mixture to 10. The resulting alkaline solution was extracted with CH₂Cl₂ (4 × 30 mL) and the combined organic extracts were washed with brine, dried over MgSO₄ and filtered. The solvent was removed under reduced pressure, and the obtained dark brown gum was subjected to column chromatography to afford 1,1'-methylene-3,3',4,4'-tetrahydrobisisoquinoline **101** as brown gum (0.89 g, 81%). FTIR (Nujol) ν_{max} : 1618, 1311, 1272, 1232, 1029, 746 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 2.80 (4H, t, *J* = 6.6 Hz, H4 and H4'), 3.60 (4H, t, *J* = 6.9 Hz, H3 and H3'), 5.93 (2H, s, H9), 7.17-7.19 (2H, m, H5 and H5'), 7.25-7.35 (4H, m, H6, H7 and H6', H7'), 7.72-7.77 (2H, m, H8 and H8'). ¹³C NMR (75.6 MHz, CDCl₃) δ : 28.5 (C4 and C4'), 42.4 (C3 and C3'), 84.9 (C9), 124.6 (C8 and C8'), 126.7 (C5 and C5'), 127.8 (C7 and C7'), 129.2 (C8a and C8'a), 131.5 (C6 and C6'), 137.2 (C4a and C4'a), 157.8 (C1 and C1'). HRMS (ESI) calcd for C₁₉H₁₈N₂: 274.1548, found 275.1553 (M+1).

5.1.3. *rac*-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) **98**

1,1'-methylene-3,3',4,4'-tetrahydrobisisoquinoline **101** (0.89 g, 3.25 mmol) was dissolved in 0.5 M HCl/MeOH solution (10 mL), and the generating brown solution was

evaporated under reduced pressure to give a dark brown gum. The resulting residue was redissolved in MeOH (6 mL) to afford a dark brown solution which was added dropwise into a stirred suspension of NaCNBH₃ (0.35 g, 5.52 mmol) in 3% HCl/MeOH (2 mL) and MeOH (8mL) solution at room temperature. After addition completion, the generated dark brown solution was stirred vigorously at room temperature for another 0.5 h. Then the solvent was removed under reduced pressure, 10% NaOH solution (20 mL) was added to adjust pH of the above mixture to 11. The alkaline solution was extracted with CH₂Cl₂ (3 × 15 mL), and the combined organic extracts were washed with brine, dried over MgSO₄ and filtered. After solvent removal, the obtained dark brown solid was subjected to be recrystallized from EtOH to afford *rac*-1,1'-methylenebis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-**98** as light-yellow crystals (0.70 g, 77%). m.p. 98-102 °C. FTIR (Nujol) $\nu_{\max}$: 3325, 3249, 2923, 2853, 1497, 1453, 1127, 866, 767, 702 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 2.19 (2H, t, *J* = 6.6 Hz, 2×H₉), 2.46 (2H, br s, 2×NH), 2.63-2.72 (2H, m, H _{α} 4 and H _{β} 4'), 2.76-2.85 (2H, m, H _{α} 4' and H _{β} 4), 2.19-2.99 (2H, m, H _{α} 3', H _{β} 3'), 3.18-3.26 (2H, m, H _{α} 3 and H _{β} 3'), 4.17 (2H, t, *J* = 6.6 Hz, H1 and H1'), 6.99-7.10 (8H, m, H5, H6, H7, H8 and H5', H6', H7', H8'). ¹³C NMR (75.6 MHz, CDCl₃) δ : 30.0 (C4 and C4'), 40.9 (C3 and C3'), 42.0 (C9), 52.9 (C1 and C1'), 125.8 (C8 and C8'), 125.9 (C7 and C7'), 126.0 (C6 and C6'), 129.4 (C5 and C5'), 135.5 (C4a and C4'a), 139.7 (C8a and C8'a). HRMS (ESI) calcd for C₁₉H₂₂N₂: 278.1861, found 279.1855 (M+1). ¹H NMR and ¹³C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

rac-**98**

5.1.4. Resolution of BIQ *rac*-**98** through diastereomeric salt formation with (*L*)-(+)-citramalic acid

A mixture of *rac*-BIQ **98** (1.0 g, 3.5 mmol) and (*L*)-(+)-citramalic acid (1.04 g, 7.0 mmol) dissolved in EtOH/H₂O (1.5/1, v/v, 15 mL) was stirred at 40 °C for 15 min. The resulting yellow solution was allowed to cool down, kept undisturbed at room temperature for several days. In total six batches of crystals were obtained, the first two batches of crystals were combined, washed by cold EtOH and dissolved in a mixture of CH₂Cl₂ (6 mL) and 10% NaOH aqueous solution (10 mL). The two layers were separated and the aqueous one was further extracted with CH₂Cl₂ (3×6 mL). The combined organic extracts were dried over MgSO₄ and filtered. The solvent was then evaporated under reduced pressure to afford (*S,S*)-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydrobisisoquinoline) (*S,S*)-**98** as a light yellow solid (150 mg, 15%, >99% *ee*). The next three batches of crystals followed similar work-up procedure, affording (*S,S*)-**98** as yellow solids (240 mg, 24%, 70-80% *ee*). The sixth batch of crystals was treated in a similar manner, producing (*R,R*)-**98** as a white solid (30 mg, 3%, >99% *ee*). The remaining mother liquid was dried and treated similarly as mentioned for the above batches to afford (*R,R*)-**98** as a white solid (540 mg, 54%, 40% *ee*). Melting points, FTIR, ¹H NMR, ¹³C NMR and HRMS spectra of those obtained BIQs **98** were same as those of *rac*-**98**. The *ees* of 99% was determined by HPLC (Chiralcel OD-H column): hexane/IPA/Et₃N = 90/9.9/0.1, 1.0 mL/min, 25 °C, 256 nm, *t*₁ = 12.12 min for (*R,R*) and *t*₂ = 17.72 min for (*S,S*). = +20.53 (*c* = 1.00, CHCl₃) for (*R,R*)-**98**; = -22.94 (*c* = 1.01, CHCl₃) for (*S,S*)-**98**.

5.2. Synthesis of *racemic* derivatives based on BIQ *rac*-**98** and chiral derivatives based on BIQ (*S,S*)-**98**

5.2.1. Preparation of *racemic* derivatives based on BIQ *rac*-**98**

Double *N*-Alkyl derivatives

General Procedure: Alkyl bromides or alkyl iodides were added into a mixture of BIQ *rac*-**98** and K₂CO₃ in dry THF under nitrogen atmosphere. The mixture was heated up to reflux and stirred for overnight. The reaction mixture was then cooled down to room temperature, filtered, and the solid was washed with CH₂Cl₂. The combined organic phases were evaporated under reduced pressure to almost dryness. The residue was allowed to be recrystallized from EtOH or subjected to column chromatography to afford pure double *N*-alkyl derivatives of BIQ *rac*-**98**.

5.2.1.1. *N,N'*-dimethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-**112**

BIQ *rac*-**98** (560 mg, 2 mmol) was treated with iodomethane (5 mL) in neat condition, and the reaction mixture was vigorously stirred at 50 °C for 5 h. The volatiles were evaporated under reduced pressure to afford a yellow gum. The resulting gum was then stirred in a mixture of 5 M NaOH (15 mL) aqueous solution and CH₂Cl₂ (15 mL) for 2 h at room temperature. The organic layer was separated, dried over NaOH (pellets) and filtered.

rac-**112**

After solvent removal, yellow solids were obtained to be recrystallized from EtOH solution, producing pure *rac*-*N,N'*-dimethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-**112** as light-yellow crystals (245 mg, 41%). m.p. 106-109 °C. FTIR (Nujol) $\nu_{\max}$: 2924, 1448, 1378, 1284, 1116, 1031, 775, 743, 609 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 1.84 (2H, apparent t, J = 7.2 Hz, 2×H₉), 2.40-2.47 (2H, m, H₄ and H_{4'}), 2.51 (6H, s, 2×CH₃), 2.88-2.98 (2H, m, H_{4'} and H₄), 2.99-3.05 (2H, m, H_{3'},

H_β3), 3.27-3.36 (2H, m, H_α3 and H_β3'), 3.91 (2H, t, $J = 6.6$ Hz, H1 and H1'), 7.00-7.06 (8H, m, H5, H6, H7, H8 and H5', H6', H7', H8'). ¹³C NMR (75.6 MHz, CDCl₃) δ: 22.5 (C4 and C4'), 42.2 (2×CH₃), 44.5 (C3 and C3'), 45.9 (C9), 59.9 (C1 and C1'), 125.5 (C8 and C8'), 125.8 (C7 and C7'), 128.3 (C6 and C6'), 128.7 (C5 and C5'), 134.0 (C4a and C4'a), 139.1 (C8a and C8'a). HRMS (ESI) calcd for C₂₁H₂₆N₂: 306.2174, found 307.2166 (M+1). ¹H NMR and ¹³C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

5.2.1.2. *N,N'*-diethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-**113**

BIQ *rac*-**98** (560 mg, 2 mmol) was treated with bromoethane (360 μL, 4.4 mmol), following the general procedure mentioned above. The resulting yellow solid was subjected to silica gel column chromatography (EtOAc/Hexane = 1/5), affording pure *rac*-*N,N'*-diethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-**113** as light yellow solids (490 mg, 73%). m.p. 118-121 °C. FTIR (Nujol)

rac-**113**

ν_{max} : 2957, 1447, 1379, 1117, 1095, 1035, 768, 743, 616 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 1.24 (6H, t, $J = 7.2$ Hz, 2×CH₂CH₃), 1.97 (2H, apparent t, $J = 6.6$ Hz, 2×H9), 2.41-2.50 (2H, m, H_α4 and H_β4'), 2.66-2.85 (4H, m, 2×CH₂CH₃), 3.02-3.20 (4H, m, H_α4', H_β4 and H_α3', H_β3), 3.36-3.42 (2H, m, H_α3 and H_β3'), 4.13 (2H, t, $J = 6.6$ Hz, H1 and H1'), 7.08-7.16 (8H, m, H5, H6, H7, H8 and H5', H6', H7', H8'). ¹³C NMR (75.6 MHz, CDCl₃) δ: 13.8 (2×CH₂CH₃), 22.3 (C4 and C4'), 41.5 (C3 and C3'), 46.0 (C9), 46.9 (2×CH₂CH₃), 57.8 (C1 and C1'), 125.4 (C8 and C8'), 125.7 (C7 and C7'), 128.4 (C6 and C6'), 128.8 (C5 and C5'), 134.4 (C4a and C4'a), 139.8 (C8a and C8'a). HRMS (ESI) calcd

for $C_{23}H_{30}N_2$: 334.2487, found 335.2477 ($M+1$). 1H NMR and ^{13}C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

5.2.1.3. *N,N'*-dibenzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-114

BIQ *rac*-**98** (560 mg, 2 mmol) was reacted with benzyl bromide (523 μ L, 4.4 mmol), following the general procedure mentioned above. The resulting yellow solid was subjected to silica gel column chromatography (EtOAc/Hexane = 1/10), affording pure *rac*-*N,N'*-dibenzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-**114**

as light yellow solids (852 mg, 93%). m.p. 159-161 $^{\circ}C$. FTIR

rac-**114**

(Nujol) ν_{max} : 2951, 2818, 1493, 1450, 1346, 1097, 1023, 744, 698 cm^{-1} . 1H NMR (300 MHz, $CDCl_3$) δ : 1.87 (2H, apparent t, J = 6.6 Hz, $2 \times H_9$), 2.27-2.34 (2H, m, $H_{\alpha}4$ and $H_{\beta}4'$), 2.80-2.98 (4H, m, $H_{\alpha}4'$, $H_{\beta}4$ and $H_{\alpha}3'$, $H_{\beta}3$), 3.13-3.19 (2H, m, $H_{\alpha}3$ and $H_{\beta}3'$), 3.40 (2H, d, J = 13.2 Hz, $C_6H_5CH_2$), 3.66 (2H, d, J = 12.9 Hz, $C_6H_5CH_2$), 4.02 (2H, t, J = 6.9 Hz, H_1 and $H_{1'}$), 6.96-7.23 (18H, m, H_5 , H_6 , H_7 , H_8 , H_5' , H_6' , H_7' , H_8' and $2 \times C_6H_5CH_2$). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ : 22.2 (C_4 and C_4'), 40.7 (C_3 and C_3'), 46.9 (C_9), 57.5 ($2 \times C_6H_5CH_2$), 57.5 (C_1 and $C_{1'}$), 125.6 (C_8 and C_8'), 126.0 (C_7 and C_7'), 126.9 ($C_6H_5CH_2$), 128.2 ($C_6H_5CH_2$), 128.3 (C_6 and C_6'), 129.0 (C_5 and C_5'), 129.1 ($C_6H_5CH_2$), 134.3 (C_{4a} and $C_{4'a}$), 139.7 (C_{8a} and $C_{8'a}$), 140.1 ($C_6H_5CH_2$). HRMS (ESI) calcd for $C_{33}H_{34}N_2$: 458.2800, found 459.2808 ($M+1$). 1H NMR and ^{13}C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

Mono *N*-Alkyl derivatives

General Procedure:

Synthesis of piperimidines through condensation of *rac*-**98** with aldehydes: *rac*-**98** (560 mg, 2 mmol) was dissolved in EtOH or Et₂O (10 mL) at r.t., and then the relative aldehyde (2.7 mmol) was added dropwise into the above solution. The resulting mixture was stirred vigorously at room temperature or heated to reflux for a specific time (TLC). After reaction has completed, the mixture was filtered through Celite, then the solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel, affording pure piperimidine products *rac*-**103**, **116** and **118**.

Reductive cleavage of piperimidines: Piperimidine compound (0.49 mmol) was dissolved in MeOH, the generated solution was added dropwise into a mixture of NaCNBH₃ (47 mg, 0.75 mmol) and TFA (154 μ L, 2 mmol) in MeOH at 0 °C. The reaction mixture was kept stirring for another 1 h at r.t., then quenched with 30% NaOH aqueous solution (10 mL) and extracted by EtOAc (3 $\times$ 8 mL). The obtained organic extracts were dried over MgSO₄, filtered, and the volatile material was evaporated to dryness. The residue was purified by silica gel column chromatography to afford pure mono *N*-substituted derivatives *rac*-**115**, **117** and **119**.

5.2.1.4. Preparation of *N*-methyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-**115**

Reaction with formaldehyde: *rac*-**98** (560 mg, 2 mmol) reacted with 37% formaldehyde (205 μ L, 2.7 mmol, methanol solution) in EtOH solution, and the reaction mixture was heated to reflux for 2 days. Following by the general procedure, yellow solids were

obtained and purified by column chromatography on silica gel (EtOAc/Hexane, 1/1), affording pure piperimidine **rac-103** as a light

yellow solid (490 mg, 85%). m.p. 116-119 °C. FTIR (Nujol) ν_{max} :

1492, 1454, 1361, 1287, 1156, 1093, 1026, 750 cm^{-1} . ^1H NMR (300

MHz, CDCl_3) δ : 2.57 (2H, t, $J = 5.7$ Hz, $2 \times \text{H}_9$), 2.68-2.75 (2H, m,

$\text{H}_{\alpha 4}$ and $\text{H}_{\beta 4'}$), 2.91-3.15 (4H, m, $\text{H}_{\alpha 4'}$, $\text{H}_{\beta 4}$ and $\text{H}_{\alpha 3'}$, $\text{H}_{\beta 3}$), 3.24-3.31 (2H, m, $\text{H}_{\alpha 3}$ and

$\text{H}_{\beta 3'}$), 3.73 (2H, s, $2 \times \text{H}_{10}$), 3.90-4.05 (2H, m, H_1 and $\text{H}_{1'}$), 6.99-7.15 (8H, m, H_5 , H_6 ,

H_7 , H_8 and $\text{H}_{5'}$, $\text{H}_{6'}$, $\text{H}_{7'}$, $\text{H}_{8'}$). ^{13}C NMR (75.6 MHz, CDCl_3) δ : 26.6 (C_4 and $\text{C}_{4'}$), 32.0

(C_9), 47.7 (C_3 and $\text{C}_{3'}$), 55.6 (C_1 and $\text{C}_{1'}$), 69.7 (C_{10}), 125.6 (C_8 and $\text{C}_{8'}$), 126.2 (C_7

and $\text{C}_{7'}$), 126.3 (C_6 and $\text{C}_{6'}$), 129.3 (C_5 and $\text{C}_{5'}$), 134.9 (C_{4a} and $\text{C}_{4'a}$), 136.8 (C_{8a} and

$\text{C}_{8'a}$). HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2$: 290.1861, found 291.1860 ($\text{M}+1$). ^1H NMR and

^{13}C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

Reductive cleavage of piperimidines **rac-103:** Following the general

procedure above, piperimidine **rac-103** (142 mg, 0.49 mmol) was

reduced by NaCNBH_3 in acidic MeOH solution, affording pure *N*-

methyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) **rac-**

115 as light yellow gum (103 mg, 72%). FTIR (Nujol) ν_{max} : 3300, 2930,

1675, 1452, 1373, 1200, 1125, 1068, 1026, 745 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ :

2.31-2.33 (2H, m, $2 \times \text{H}_9$), 2.46-2.47 (3H, m, CH_3), 2.78-2.89 (6H, m, $\text{H}_{\alpha 4}$, $\text{H}_{\beta 4}$, $\text{H}_{\beta 3}$ and

$\text{H}_{\alpha 4'}$, $\text{H}_{\beta 4'}$, $\text{H}_{\alpha 3'}$), 3.01-3.32 (2H, m, $\text{H}_{\alpha 3}$ and $\text{H}_{\beta 3'}$), 3.73-3.80 (1H, m, $\text{H}_{1'}$), 4.08 (1H, s,

NH), 4.14-4.18 (1H, m, H_1), 7.13-7.20 (8H, m, H_5 , H_6 , H_7 , H_8 and $\text{H}_{5'}$, $\text{H}_{6'}$, $\text{H}_{7'}$, $\text{H}_{8'}$).

^{13}C NMR (75.6 MHz, CDCl_3) δ : 24.7 ($\text{C}_{4'}$), 29.9 (C_4), 40.5 (C_9), 40.8 (C_3), 42.2 (CH_3),

rac-103

rac-115

47.0 (C3'), 53.8 (C1), 61.3 (C1'), 125.8 (C8), 125.96 (C7'), 125.99 (C7), 126.1 (C6'), 126.2 (C6), 127.4 (C8'), 128.9 (C5'), 129.3 (C5) 134.7 (C4'a), 135.5 (C4a), 137.7 (C8'a), 139.1 (C8a). HRMS (ESI) calcd for $C_{20}H_{24}N_2$: 292.2018, found 293.2021 (M+1). 1H NMR and ^{13}C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

5.2.1.5. Preparation of *N*-ethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-117

Reaction with acetaldehyde: *rac*-**98** (560 mg, 2 mmol) reacted with acetaldehyde (151 μ L, 2.7 mmol) in Et₂O solution, and the reaction mixture was then stirred vigorously at room temperature for overnight. Following the general procedure, a yellow gum was obtained and purified by column chromatography on silica gel

rac-**116**

(EtOAc/Hexane, 1/1), affording pure piperimidine *rac*-**116** (483 mg, 80%). FTIR (Nujol) $\nu_{\max}$: 1490, 1452, 1376, 1161, 1074, 1032, 746 cm^{-1} . 1H NMR (300 MHz, CDCl_3) δ : 1.31 (3H, d, $J = 6.0$ Hz, CH_3), 2.24-2.29 (1H, m, H9), 2.41-2.46 (2H, m, H9 and $\text{H}_{\beta}4'$), 2.74-2.97 (5H, m, $\text{H}_{\alpha}4$, $\text{H}_{\beta}4$, $\text{H}_{\beta}3$ and $\text{H}_{\alpha}4'$, $\text{H}_{\alpha}3'$), 3.12-3.20 (1H, m, $\text{H}_{\alpha}3$), 3.27-3.29 (1H, m, $\text{H}_{\beta}3'$), 3.78-3.82 (1H, m, H1), 3.90 (1H, q, $J = 7.2$ Hz, H10), 4.25-4.35 (1H, m, H1'), 6.90-7.17 (7H, m, H5, H6, H7 and H5', H6', H7', H8'), 7.28 (1H, d, $J = 7.2$ Hz, H8). ^{13}C NMR (75.6 MHz, CDCl_3) δ : 18.3 (CH_3), 23.8 (C4'), 29.9 (C4), 31.8 (C9), 37.2 (C3), 47.2 (C3'), 55.4 (C1), 57.1 (C1'), 68.9 (C10), 125.6 (C8), 126.10 (C7'), 126.14 (C7), 126.3 (C6'), 126.5 (C6), 126.7 (C8'), 128.9 (C5'), 129.4 (C5), 134.6 (C4a), 135.9 (C4'a), 136.7 (C8'a), 139.2 (C8a). HRMS (ESI) calcd for $C_{21}H_{24}N_2$: 304.2018, found 305.2019 (M+1).

^1H NMR and ^{13}C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

Reductive cleavage of piperimidines *rac*-116: Following the above general procedure, piperimidine *rac*-116 (150 mg, 0.49 mmol) was reduced by NaCNBH_3 in acidic MeOH solution, affording pure *N*-ethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline)

rac-117 as light yellow gum (105 mg, 70%). FTIR (Nujol) ν_{max} : 3251, 2930, 1676, 1490, 1452, 1378, 1270, 1200, 1118, 1034, 768, 744 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 0.92 (3H, t, $J = 7.2$ Hz, CH_2CH_3), 2.05-2.09 (1H, m, H₉), 2.16-2.21 (1H, m, H₉), 2.40-2.48 (3H, m, CH_2CH_3 and H $_{\beta 4'}$), 2.65-2.85 (5H, m, H $_{\alpha 4}$, H $_{\beta 4}$, H $_{\beta 3}$ and H $_{\alpha 4'}$, H $_{\alpha 3'}$), 3.14-3.29 (2H, m, H $_{\alpha 3}$ and H $_{\beta 3'}$), 3.70-3.73 (2H, m, H $_{1'}$ and NH), 4.11 (1H, d, $J = 7.8$ Hz, H $_1$), 6.91-7.04 (8H, m, H $_5$, H $_6$, H $_7$, H $_8$ and H $_{5'}$, H $_{6'}$, H $_{7'}$, H $_{8'}$). ^{13}C NMR (75.6 MHz, CDCl_3) δ : 13.4 (CH_2CH_3), 23.4 (C $_{4'}$), 30.1 (C $_4$), 41.2 (C $_9$), 41.4 (C $_3$), 42.9 (C $_3'$), 47.0 (CH_2CH_3), 54.0 (C $_1$), 58.0 (C $_{1'}$), 125.8 (C $_8$), 125.89 (C $_{7'}$), 126.04 (C $_7$), 126.0 (C $_6'$), 126.1 (C $_6$), 127.8 (C $_{8'}$), 129.0 (C $_{5'}$), 129.3 (C $_5$), 134.7 (C $_{4'a}$), 135.7 (C $_{4a}$), 138.4 (C $_{8'a}$), 139.4 (C $_{8a}$). HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{26}\text{N}_2$: 306.2174, found 307.2168 (M+1). ^1H NMR and ^{13}C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

5.2.1.6. Preparation of *N*-benzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-119

Reaction with benzaldehyde: *rac*-98 (560 mg, 2 mmol) reacted with benzaldehyde (270 μL , 2.7 mmol) in Et_2O solution, and the reaction mixture was stirred vigorously at room

temperature for overnight. Following the general procedure, yellow solids were obtained and purified by column chromatography on silica gel (EtOAc/Hexane, 1/1), affording pure piperimidine *rac*-**118** as yellow fluffy solids (659 mg,

rac-**118**

90%). m.p. 73-76 °C. FTIR (Nujol) ν_{max} : 1603, 1494, 1453, 1308, 1149, 1124, 1032, 842, 743 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 2.14 (1H, td, J = 11.4, 3.6 Hz, H₉), 2.46-2.53 (3H, m, H₄, H₃ and H_{4'}), 2.62-2.74 (1H, m, H₉), 2.86-2.94 (3H, m, H₄, and H_{4'}, H_{3'}), 3.08-3.17 (2H, m, H₃ and H_{3'}), 3.64 (1H, d, J = 11.1 Hz, H_{1'}), 4.30 (1H, s, H₁₀), 4.64-4.72 (1H, m, H₁), 7.06-7.49 (11H, m, H₅, H₆, H₇, H_{5'}, H_{6'}, H_{7'}, H₈ and C₆H₅), 7.62-7.65 (2H, m, H₈ and C₆H₅). ^{13}C NMR (75.6 MHz, CDCl_3) δ : 24.2 (C_{4'}), 29.8 (C₄), 34.5 (C₃), 46.5 (C₉), 47.1 (C_{3'}), 56.1 (C₁), 57.1 (C_{1'}), 80.8 (C₁₀), 124.9 (C₈), 125.6 (C₇), 125.8 (C_{7'}), 126.0 (C_{6'}), 126.3 (C₆), 126.7 (C_{8'}), 128.3 (C₅), 128.4 (C_{5'}), 128.8 (C₆H₅), 129.1 (C₆H₅), 129.2 (C₆H₅), 129.6 (C₆H₅), 129.8 (C₆H₅), 135.3 (C_{4a}), 135.7 (C_{4'a}), 136.8 (C_{8'a}), 138.5 (C_{8a}), 140.9 (C₆H₅). HRMS (ESI) calcd for C₂₆H₂₆N₂: 366.2174, found 367.2158 (M+1). ^1H NMR and ^{13}C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

Reductive cleavage of piperimidines rac-118: Following the above general procedure, piperimidine *rac*-**118** (180 mg, 0.49 mmol) was reduced by NaCNBH₃ in acidic MeOH solution, affording pure *N*-benzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac*-**119** as light yellow gum (144 mg,

rac-**119**

80%). FTIR (Nujol) ν_{max} : 3340, 2930, 1651, 1490, 1453, 1360, 1201, 1118, 1023, 972, 743, 699 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 1.97-2.05 (1H, m, H₉), 2.39 (1H, apparent

t, $J = 12$ Hz, H9), 2.62-2.70 (1H, m, H $_{\beta}$ 4'), 2.73-2.89 (4H, m, H $_{\alpha}$ 4, H $_{\beta}$ 4, H $_{\beta}$ 3 and NH), 3.05-3.12 (3H, m, H $_{\alpha}$ 3 and H $_{\alpha}$ 3', H $_{\alpha}$ 4'), 3.43-3.60 (1H, m, H $_{\beta}$ 3'), 3.69-3.81 (3H, m, H1' and C $_6$ H $_5$ CH $_2$), 3.87 (1H, dd, $J = 11.1, 3.0$ Hz, H1), 4.30 (1H, d, $J = 8.7$ Hz, H1'), 7.08-7.21 (8H, m, H5, H6, H7, H8 and H5', H6', H7', H8'), 7.31-7.38 (5H, m, C $_6$ H $_5$ CH $_2$). ^{13}C NMR (75.6 MHz, CDCl $_3$) δ : 23.0 (C4'), 30.1 (C4), 41.4 (C3), 42.9 (C9), 43.3 (C3'), 53.1 (C1), 56.8 (C1'), 57.6 (C $_6$ H $_5$ CH $_2$), 125.8 (C8), 125.9 (C7), 126.0 (C7'), 126.2 (C6'), 126.3 (C6), 127.4 (C8'), 128.2 (C5), 128.6 (C5'), 129.28 (C $_6$ H $_5$ CH $_2$), 129.33 (C $_6$ H $_5$ CH $_2$), 129.4 (C $_6$ H $_5$ CH $_2$), 134.3 (C4a), 135.5 (C4'a), 138.3 (C8'a), 139.5 (C8a), 139.6 (C $_6$ H $_5$ CH $_2$). HRMS (ESI) calcd for C $_{26}$ H $_{28}$ N $_2$: 368.2331, found 369.2328 (M+1). ^1H NMR and ^{13}C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

5.2.2. Preparation of chiral derivatives based on BIQ (*R,R*)-98

The same reaction procedure for preparation of *racemic* derivatives *rac*-112 ~ *rac*-115, *rac*-117 and *rac*-119 were followed accordingly to prepare chiral derivatives (*R,R*)-112 ~ (*R,R*)-115, (*R,R*)-117 and (*R,R*)-119.

5.2.2.1. *N,N'*-dimethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (*R,R*)-112

BIQ (*R,R*)-98 (112 mg, 0.4 mmol) was treated with iodomethane (1 mL) in neat condition, and the reaction mixture was vigorously stirred at 50 °C for 5 h. The volatiles were evaporated under reduced pressure to afford a yellow gum. The resulting gum was then stirred in a mixture of 5 M NaOH (3 mL) aqueous solution and CH $_2$ Cl $_2$ (3 mL) for 2 h at r.t.

(*R,R*)-112

The organic layer was separated, dried over NaOH (pellets) and filtered. After solvent removal, yellow solids were obtained to be recrystallized from EtOH solution, affording pure (*R,R*)-*N,N'*-dimethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (*R,R*)-**112** as light-yellow crystals (48 mg, 40%). The melting point, FTIR, ¹H NMR, ¹³C NMR spectra and HRMS of (*R,R*)-**112** were identical to those of *rac*-**112**. The ee of > 99% was tested by HPLC (Chiralcel OD-H column): *n*-hex/IPA/Et₃N = 95/5/0.05, 0.4 mL/min, 25 °C, 254 nm, t₁ = 9.7 min for (*R,R*) and t₂ = 10.4 min for (*S,S*). [α]_D²⁵ = +16.4 (c = 1.10, CHCl₃).

5.2.2.2. *N,N'*-diethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (*R,R*)-113

BIQ (*R,R*)-**98** (112 mg, 0.4 mmol) was treated with bromoethane (72 μ L, 0.88 mmol), following the general procedure mentioned above.

The resulting yellow solid was subjected to silica gel column chromatography (EtOAc/Hexane = 1/5), affording pure (*R,R*)-*N,N'*-

diethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline)

(*R,R*)-**113**

(*R,R*)-**113** as light yellow solids (98 mg, 73%). The melting point, FTIR, ¹H NMR, ¹³C NMR spectra and HRMS of (*R,R*)-**113** were identical to those of *rac*-**113**. The ee of > 99% was tested by HPLC (Chiralcel OD-H column): *n*-hex/IPA/Et₃N = 95/5/0.05, 0.5 mL/min, 25 °C, 254 nm, t₁ = 7.4 min for (*R,R*) and t₂ = 7.8 min for (*S,S*). [α]_D²⁵ = +15.7 (c = 1.00, CHCl₃).

5.2.2.3. *N,N'*-dibenzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (*R,R*)-114

BIQ (*R,R*)-**98** (112 mg, 0.4 mmol) was reacted with benzyl bromide (105 μ L, 0.88 mmol), following the general procedure mentioned above. The resulting yellow solid was subjected to silica gel column chromatography (EtOAc/Hexane = 1/10), affording pure (*R,R*)-*N,N'*-dibenzyl-1,1'-methylene-

(*R,R*)-**114**

bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (*R,R*)-**114** as light yellow solids (167 mg, 91%). The melting point, FTIR, ^1H NMR, ^{13}C NMR and HRMS of (*R,R*)-**114** were identical to those of *rac*-**114**. The ee of > 99% was tested by HPLC (Chiralcel OD-H column): *n*-hex/IPA/Et₃N = 98/2/0.02, 0.5 mL/min, 25 °C, 254 nm, t_1 = 9.7 min for (*R,R*) and t_2 = 11.3 min for (*S,S*). $[\alpha]_D^{25}$ = +145.6 (c = 1.11, CHCl₃).

5.2.2.4. *N*-methyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (*R,R*)-**115**

(*R,R*)-**98** (112 mg, 0.4 mmol) reacted with 37% formaldehyde (41 μ L, 0.54 mmol, methanol solution) in EtOH solution, and the reaction mixture was then heated to reflux for 2 days. Following the general procedure, pure piperimidine (*R,R*)-**103** was obtained and reduced by NaCNBH₃ in acidic MeOH solution, affording pure *N*-methyl-1,1'-

(*R,R*)-**115**

methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (*R,R*)-**115** as light yellow gum (80 mg, 69%). The FTIR, ^1H NMR, ^{13}C NMR spectra and HRMS of (*R,R*)-**115** were identical to those of *rac*-**115**. $[\alpha]_D^{25}$ = +18.1 (c = 1.11, CHCl₃).

5.2.2.5. *N*-ethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (*R,R*)-**117**

(*R,R*)-**98** (112 mg, 0.4 mmol) reacted with acetaldehyde (31 μ L, 0.54 mmol) in Et₂O solution, and the reaction mixture was then stirred vigorously at r.t. for overnight. Following the general procedure, pure piperimidine (*R,R*)-**116** was obtained and reduced by NaCNBH₃ in acidic MeOH solution, affording pure *N*-ethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (*R,R*)-**117** as light yellow gum (87 mg, 70%). The FTIR, ¹H NMR, ¹³C NMR spectra and HRMS of (*R,R*)-**117** were identical to those of *rac*-**117**. $[\alpha]_D^{25} = +16.3$ (c = 1.03, CHCl₃).

5.2.2.6. *N*-benzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (*R,R*)-**119**

(*R,R*)-**98** (112 mg, 0.4 mmol) reacted with benzaldehyde (54 μ L, 0.54 mmol) in Et₂O solution, and the reaction mixture was then stirred vigorously at room temperature for overnight. Following the general procedure, pure piperimidine (*R,R*)-**118** was obtained and reduced by NaCNBH₃ in acidic MeOH solution, affording pure *N*-benzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (*R,R*)-**119** as light yellow gum (122 mg, 83%). The FTIR, ¹H NMR, ¹³C NMR spectra and HRMS of (*R,R*)-**119** were identical to those of *rac*-**119**. The ee of > 99% was tested by HPLC (Chiralcel OD-H column): *n*-hex/IPA/Et₃N = 90/10/0.1, 0.3 mL/min, 25 °C, 254 nm, t₁ = 18.1 min for (*R,R*) and t₂ = 19.0 min for (*S,S*). $[\alpha]_D^{25} = +150.2$ (c = 1.03, CHCl₃).

5.3. Synthesis of 1,2-diposd BIQs

1,2-BIQs **23**, **27**, **29**, **31**, **32**, **35**, **36**, **120-122** and **124** were prepared according to the reported procedure, and the obtained compounds' melting points, FTIR, ^1H NMR, ^{13}C NMR spectra and HRMS were same as those reported.^{12,68,69} Chiral 1,2-diposd BIQs (*R,R*)-**23**, (*R*)-**29** were obtained by the reported resolution methods.^{12,68} Enantiopurity was confirmed by chiral HPLC analysis.

5.4. Synthesis of chiral derivatives based on BIQ (*R*)-**29**

Chiral derivatives based on 1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (*R*)-**32** and its derivatives ((*R*)-**161**, (*R*)-**162**, (*R*)-**164** ~ (*R*)-**170**) were prepared according to the reported methods.⁶⁸ The obtained compounds' melting points, FTIR, ^1H NMR, ^{13}C NMR spectra and HRMS were same as those reported.

5.4.1. Preparation of (*R*)-*N'*-isopropyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (*R*)-**163**

In CH_3CN solution (4 mL) of (*R*)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (*R*)-**29** (130 mg, 0.5 mmol), 2-bromopropane (67.6 mg, 51.6 μL , 0.55 mmol) was added in the presence of K_2CO_3 (138 mg, 1.0 mmol). The reaction mixture was then heated at reflux for

(*R*)-**163**

two days (TLC). The mixture was filtered and K_2CO_3 was washed with CH_2Cl_2 (2×3 mL). The combined organic filtrates were evaporated to dryness, and the obtained yellow gum was subjected to column chromatography to afford (*R*)-**163** as white solid (84.6 mg, 56%). Enantiomeric purity (98% *ee*) was determined by HPLC (Daicel Chiralcel OD-H column), *n*-hex/*i*-PrOH = 98/2, 1.0 mL/min, 254 nm, t_1 = 5.0 min for (*S*)-**163**, t_2 = 5.4 min for (*R*)-**163**. $[\alpha]_D^{25} = +157.5$ (c = 0.86, CH_2Cl_2). FTIR (KBr)

$\nu_{\max}$: 3402, 3052, 2965, 1623, 1585, 1560, 1496, 1452, 1342, 1171, 1057, 826, 734, 648 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 0.82 (3H, d, $J = 7.2$ Hz, CH_3), 0.89 (3H, d, $J = 7.2$ Hz, CH_3), 2.52-2.61 (2H, m, $\text{CH}(\text{CH}_3)_2$ and $\text{H}_{\alpha}3'$), 3.21-3.40 (1H, d, $J = 15.9$ Hz, $\text{H}_{\beta}4'$), 3.16-3.27 (2H, m, $\text{H}_{\beta}3'$ and $\text{H}_{\alpha}4'$), 5.47 (1H, s, $\text{H}1'$), 6.48 (1H, d, $J = 7.8$ Hz, $\text{H}5'$), 6.71 (1H, t, $J = 7.5$ Hz, $\text{H}7'$), 6.92 (1H, t, $J = 7.2$ Hz, $\text{H}6'$), 7.05 (1H, d, $J = 7.5$ Hz, $\text{H}8'$), 7.18 (1H, t, $J = 7.5$ Hz, $\text{H}6$), 7.39 (1H, t, $J = 7.5$ Hz, $\text{H}7$), 7.46 (1H, d, $J = 5.7$ Hz, $\text{H}4$), 7.61 (1H, d, $J = 8.7$ Hz, $\text{H}5$), 8.40 (1H, d, $J = 5.7$ Hz, $\text{H}3$), 8.64 (1H, d, $J = 8.7$ Hz, $\text{H}8$). ^{13}C NMR (75.6 MHz, CDCl_3) δ : 12.5 (CH_3), 21.3 (CH_3), 30.5 ($\text{C}4'$), 41.5 ($\text{C}3'$), 49.5 ($\text{NCH}(\text{CH}_3)_2$), 70.7 ($\text{C}1'$), 120.8 ($\text{C}4$), 125.7 ($\text{C}8$), 125.9 ($\text{C}7'$), 126.0 ($\text{C}7$), 126.7 ($\text{C}6'$), 126.8 ($\text{C}5$), 127.2 ($\text{C}8\text{a}$), 127.8 ($\text{C}5''$), 128.6 ($\text{C}8'$), 129.7 ($\text{C}6$), 134.5 ($\text{C}4'\text{a}$), 137.3 ($\text{C}4\text{a}$), 138.5 ($\text{C}8'\text{a}$), 141.0 ($\text{C}3$), 162.8 ($\text{C}1$). HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2$: 302.1861, found 303.1857 ($\text{M}+1$).

5.5. Catalytic enantioselective addition of nitromethane to aldehydes using ligand (*R*)-23 or (*R*)-161

Ligand (0.02 mmol, 10 mol%) and CuCl (0.01 mmol, 5 mol%) were dissolved in $\text{ClCH}_2\text{CH}_2\text{Cl}/(i\text{-Pr})_2\text{O}$ (1.5 mL), and the mixture was allowed to stir vigorously at r.t for 1 h, whereby a green/yellow solution was obtained. To the above solution, aldehyde (0.2 mmol) was added and the mixture was stirred for another 5 min before dropwise addition of CH_3NO_2 (4 mmol, 20 equiv). The reaction mixture was further stirred at the given temperature for a specific time (TLC). The β -nitroalcohol product was purified on silica gel by flash column chromatography. Enantiomeric excesses were determined by HPLC using Chiralcel OD-H, OJ-H and Chiraopak AD-H columns. The absolute configuration of the major enantiomer of product was assigned by comparing with literature precedents.^{110,132,140}

5.5.1. (R)-1-Phenyl-2-nitroethanol (R)-124

Benzaldehyde **39** (20 μ L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to

give (*R*)-1-phenyl-2-nitroethanol (**(R)-124**) (60%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.76 (1H, br s, OH), 4.39-4.56 (2H, m, CH_2NO_2), 5.37 (1H, dd, $J = 9.3, 9.6$ Hz, CHOH), 7.34-7.40 (5H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 71.0, 81.3, 126.0, 129.0, 129.1 and 138.2. The ee of 85% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 90:10, flow rate = 0.8 ml/min, wavelength = 215 nm, $t_1 = 18.1$ min for (*R*), $t_2 = 22.2$ min for (*S*).

5.5.2. (R)-1-(4-Nitrophenyl)-2-nitroethanol (R)-143

4-nitrobenzaldehyde **126** (30 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-(4-nitrophenyl)-2-nitroethanol

(**(R)-143**) (95%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=3:7). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 3.28 (1H, br, s, OH), 4.47-4.66 (2H, m, CH_2NO_2), 5.48-5.56 (1H, m, CHOH), 7.63 (2H, d, $J = 8.7$ Hz, ArH), 8.27 (2H, d, $J = 8.7$ Hz, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 70.0, 80.6, 124.1, 127.0, 145.4 and 148.0. The ee of 64% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 85:15, flow rate = 1.0 ml/min, wavelength = 215 nm, $t_1 = 21.1$ min for (*R*), $t_2 = 25.5$ min for (*S*).

5.5.3. (R)-1-(4-Chlorophenyl)-2-nitroethanol (R)-144

4-chlorobenzaldehyde **127** (23 μ L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-(4-chlorophenyl)-2-nitroethanol (*R*)-**144**

(70%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.89 (1H, br, s, OH), 4.47-4.62 (2H, m, CH_2NO_2), 5.44-5.47 (1H, m, CHOH), 7.34-7.40 (4H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 70.3, 80.1, 127.3, 129.3, 134.9 and 136.5. The ee of 91% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 215 nm, t_1 = 13.9 min for (*R*), t_2 = 17.7 min for (*S*).

5.5.4. (*R*)-1-(3-Chlorophenyl)-2-nitroethanol (*R*)-**145**

3-chlorobenzaldehyde **128** (23 μ L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-(3-chlorophenyl)-2-nitroethanol (*R*)-**145**

(59%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.96 (1H, br, s, OH), 4.49-4.63 (2H, m, CH_2NO_2), 5.37-5.44 (1H, m, CHOH), 7.26-7.73 (4H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 70.3, 81.0, 124.0, 126.2, 129.1, 130.3, 135.0 and 140.0. The ee of 87% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 215 nm, t_1 = 13.6 min for (*R*), t_2 = 16.8 min for (*S*).

5.5.5. (R)-1-(2-Chlorophenyl)-2-nitroethanol (R)-146

2-chlorobenzaldehyde **129** (23 μ L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of (R)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(2-chlorophenyl)-2-nitroethanol (R)-**146** (72%, isolated

(R)-146

yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 3.00 (1H, br, s, OH), 4.59-4.64 (1H, m, CH_2NO_2), 4.62 (1H, dd, J = 13.5, 2.4 Hz, CH_2NO_2), 5.79 (1H, d, J = 9.3 Hz, CHOH), 7.26-7.34 (3H, m, ArH), 7.60 (1H, dd, J = 9.3, 2.1 Hz, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 67.8, 79.3, 127.5, 127.6, 129.7, 129.9, 131.5 and 135.5. The ee of 87% was determined by HPLC. HPLC (Chiralcel OJ-H column): *n*-hex: IPA = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, t_1 = 82.0 min for (R), t_2 = 94.3 min for (S).

5.5.6. (R)-1-(4-Fluorophenyl)-2-nitroethanol (R)-147

4-fluorobenzaldehyde **130** (22 μ L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of (R)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(4-fluorophenyl)-2-nitroethanol (R)-**147**

(R)-147

(59%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=3:7). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.89 (1H, s, OH), 4.46-4.63 (2H, m, CH_2NO_2), 5.47 (1H, d, J = 7.5 Hz, CHOH), 7.07-7.13 (2H, m, ArH), 7.37-7.42 (2H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 70.3, 81.2, 115.9, 116.1, 127.7 and 127.8. The ee of 87% was determined by HPLC. HPLC

(Chiralcel OD-H column): *n*-hex: IPA = 90:10, flow rate = 0.8 ml/min, wavelength = 215 nm, t_1 = 15.4 min for (*R*), t_2 = 18.4 min for (*S*).

5.5.7. (*R*)-1-(4-Methylphenyl)-2-nitroethanol (*R*)-148

4-methylbenzaldehyde **131** (24 μ L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-(4-methylphenyl)-2-nitroethanol

(*R*)-148

(*R*)-**148** (65%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:8). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.36 (3H, s, CH_3), 2.48 (1H, s, OH), 4.46-4.64 (2H, m, CH_2NO_2), 5.40-5.46 (1H, m, CHOH), 7.26-7.30 (4H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 21.2, 70.9, 81.3, 125.9, 129.7, 135.2 and 139.0. The ee of 88% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, t_1 = 27.8 min for (*R*), t_2 = 35.6 min for (*S*).

5.5.8. (*R*)-1-(3-Methylphenyl)-2-nitroethanol (*R*)-149

3-methylbenzaldehyde **132** (23.5 μ L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-(3-methylphenyl)-2-nitroethanol (*R*)-**149**

(*R*)-149

(57%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.38 (3H, s, CH_3), 2.81 (1H, s, OH), 4.50-4.65 (2H, m, CH_2NO_2), 5.37-5.45 (1H, m, CHOH), 7.23-7.32 (4H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 21.4, 71.1, 81.8, 123.0,

126.6, 128.9, 129.7, 138.0 and 138.9. The ee of 86% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, t_1 = 23.9 min for (*R*), t_2 = 27.9 min for (*S*).

5.5.9. (*R*)-1-(2-Methylphenyl)-2-nitroethanol (*R*)-150

2-methylbenzaldehyde **133** (23 μ L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-(2-methylphenyl)-2-nitroethanol (*R*)-**150**

(*R*)-**150**

(70%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.40 (3H, s, CH_3), 2.72 (1H, d, J = 3.6 Hz, OH), 4.42-4.60 (2H, m, CH_2NO_2), 5.67-5.72 (1H, m, CHOH), 7.25-7.31 (3H, m, ArH), 7.51-7.56 (1H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 18.9, 68.0, 80.2, 125.6, 126.8, 128.8, 130.9, 134.4 and 136.2. The ee of 87% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, t_1 = 23.3 min for (*R*), t_2 = 36.6 min for (*S*).

5.5.10. (*R*)-1-(4-Phenylphenyl)-2-nitroethanol (*R*)-151

4-phenylbenzaldehyde **134** (37 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-(4-phenylphenyl)-2-nitroethanol

(*R*)-**151**

(*R*)-**151** (80%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.88 (1H, d, J = 3.3 Hz, OH), 4.36-4.69 (2H, m, CH_2NO_2), 5.52 (1H, d, J = 9.3 Hz,

CHOH), 7.34-7.64 (9H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 70.8, 81.2, 126.4, 127.1, 127.7, 127.8, 128.9, 137.0, 140.3 and 142.0. The ee of 82% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, t_1 = 19.5 min for (*R*), t_2 = 23.8 min for (*S*).

5.5.11. (*R*)-1-(4-Methoxyphenyl)-2-nitroethanol (*R*)-152

4-methoxybenzaldehyde **135** (24 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-(4-methoxyphenyl)-2-

nitroethanol (*R*)-**152** (60%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.73 (1H, br, s, OH), 3.81 (3H, s, CH_3O), 4.45-4.66 (2H, m, CH_2NO_2), 5.62-5.68 (1H, m, CHOH), 6.93 (2H, d, J = 8.7 Hz, ArH), 7.26-7.34 (2H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 55.4, 70.7, 81.3, 114.4, 127.3, 130.2 and 160.1. The ee of 89% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, t_1 = 17.0 min for (*R*), t_2 = 21.8 min for (*S*).

5.5.12. (*R*)-1-(3-Methoxyphenyl)-2-nitroethanol (*R*)-153

3-methoxybenzaldehyde **136** (24 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-(3-methoxyphenyl)-2-nitroethanol (*R*)-**153**

(75%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:4). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.97

(1H, br, s, OH), 3.19 (3H, s, CH₃O), 4.72-4.84 (2H, m, CH₂NO₂), 5.42-5.48 (1H, m, CHOH), 6.88-6.97 (3H, m, ArH), 7.28-7.57 (1H, m, ArH); ¹³C NMR (75.6 MHz, CDCl₃, δ ppm): 55.3, 70.9, 81.2, 111.5, 114.4, 118.1, 130.1, 139.8 and 160.1. The ee of 90% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, t₁ = 48.2 min for (*R*), t₂ = 63.6 min for (*S*).

5.5.13. (*R*)-1-(2-Methoxyphenyl)-2-nitroethanol (*R*)-154

2-methoxybenzaldehyde **65** (24 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-(2-methoxyphenyl)-2-nitroethanol (*R*)-**154**

(*R*)-**154**

(79%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:9). ¹H NMR (300 MHz, CDCl₃, δ ppm): 3.24 (1H, s, OH), 3.90 (3H, s, CH₃O), 4.55-4.69 (2H, m, CH₂NO₂), 5.62-5.68 (1H, m, CHOH), 6.93 (1H, d, *J* = 8 Hz, ArH), 7.03 (1H, t, *J* = 7.5 Hz, ArH), 7.35 (1H, t, *J* = 8 Hz, ArH), 7.46 (1H, d, *J* = 7.5 Hz, ArH); ¹³C NMR (75.6 MHz, CDCl₃, δ ppm): 55.4, 67.8, 79.9, 110.6, 121.2, 126.0, 127.2, 129.8 and 156.0. The ee of 91% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 215 nm, t₁ = 11.1 min for (*R*), t₂ = 12.9 min for (*S*).

5.5.14. (*R*)-1-Nitrohexan-2-ol (*R*)-155

Valeraldehyde **137** (22 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure

(*R*)-**155**

to give (*R*)-1-nitrohexan-2-ol (*R*)-**155** (76%, isolated yield). The β-nitroalcohol product

was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 0.94 (3H, t, $J = 6.9$ Hz, CH_3), 1.34-1.61 (6H, m, alkyl- H), 2.54 (1H, s, OH), 4.31-4.49 (3H, m, CHOH , CH_2NO_2); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 13.9, 22.4, 27.3, 33.4, 68.7 and 80.6. The ee of 88% was determined by HPLC. HPLC (Chiralpak AD-H column): n -hex: IPA = 98:2, flow rate = 0.8 ml/min, wavelength = 215nm, t_1 = 37.8 min for (R), t_2 = 50.5 min for (S).

5.5.15. (R)-1-Nitropentan-2-ol (R)-156

Butyraldehyde **138** (18 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (R)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-nitropentan-2-ol (R)-**156** (73%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 0.98 (3H, t, $J = 6.9$ Hz, CH_3), 1.50-1.59 (4H, m, alkyl- H), 2.53 (1H, br, s, OH), 4.35-4.46 (3H, m, CHOH , CH_2NO_2); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 13.7, 18.4, 35.8, 68.4 and 80.7. The ee of 90% was determined by HPLC. HPLC (Chiralpak AD-H column): n -hex: IPA = 98:2, flow rate = 1.0 ml/min, wavelength = 215 nm, t_1 = 33.7 min for (R), t_2 = 57.2 min for (S).

5.5.16. (R)-1-Nitrodecan-2-ol (R)-157

Nonanal **139** (34.4 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (R)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-nitrodecan-2-ol (R)-**157** (72%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column

chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 0.88 (3H, t, J = 6.3 Hz, CH_3), 1.47-1.50 (14H, m, alkyl- H), 2.49 (1H, d, J = 4.5 Hz, OH), 4.34-4.47 (3H, m, CHOH , CH_2NO_2); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 14.1, 22.6, 25.2, 29.2, 29.3, 29.4, 31.8, 33.7, 68.7, and 80.6. The ee of 91% was determined by HPLC. HPLC (Chiralpak AD-H column): n -hex: IPA = 98:2, flow rate = 1.0 ml/min, wavelength = 215 nm, t_1 = 23.1 min for (R), t_2 = 36.7 min for (S).

5.5.17. (R)-1-(2-Naphthyl)-2-nitroethanol (R)-158

2-naphthaldehyde **140** (31.2 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (R)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(2-naphthyl)-2-nitroethanol (R)-**158**

(85%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:4). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 3.04 (1H, br, s, OH), 4.54-4.82 (2H, m, CH_2NO_2), 5.61 (1H, d, J = 6.9 Hz, CHOH), 7.26-7.54 (3H, m, Ar H), 7.84-7.88 (4H, m, Ar H); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 71.2, 81.2, 123.2, 125.3, 126.7, 126.7, 127.8, 128.1, 129.0, 133.2, 133.4 and 135.4. The ee of 80% was determined by HPLC. HPLC (Chiralcel OD-H column): n -hex: IPA = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, t_1 = 36.1 min for (R), t_2 = 51.6 min for (S).

5.5.18. (R)-1-(2-Fural)-2-nitroethanol (R)-159

2-furaldehyde **141** (18 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (R)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(2-fural)-2-nitroethanol (R)-**159** (80%, isolated yield). The

β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.90 (1H, br, s, OH), 4.63-4.84 (2H, m, CH_2NO_2), 5.40-5.50 (1H, m, CHOH), 6.38-6.40 (2H, m, ArH), 7.40-7.42 (1H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 64.9, 78.4, 108.2, 100.7, 143.2 and 150.7. The ee of 85% was determined by HPLC. HPLC (Chiralcel OJ-H column): *n*-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 215 nm, t_1 = 23.1 min for (*R*), t_2 = 28.5 min for (*S*).

5.5.19. (*R, E*)-1-Nitro-4-phenyl-3-buten-2-ol (*R*)-160

Trans-cinnamaldehyde **142** (26 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the

general procedure to give (*R*)-1-nitro-4-phenyl-3-buten-2-ol (*R*)-**160** (78%, isolated yield).

The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.68 (1H, br s, OH), 4.51-4.61 (2H, m, CH_2NO_2), 5.02-5.08 (1H, m, CHOH), 6.15 (1H, dd, J = 6.3, 15.9 Hz, $\text{CH}=\text{CH}$), 6.79 (1H, d, J = 15 Hz, $\text{CH}=\text{CH}$), 7.30-7.46 (5H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 69.6, 79.9, 124.9, 126.7, 128.6, 128.8, 133.7, 135.5. The ee of 81% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 90:10, flow rate = 0.8 ml/min, wavelength = 215 nm, t_1 = 38.6 min for (*S*), t_2 = 42.8 min for (*R*).

5.5.20. (*R*)-1-(4-bromophenyl)-2-nitroethanol (*R*)-177

4-bromobenzaldehyde **171** (37 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general

procedure to give (*R*)-1-(4-bromophenyl)-2-nitroethanol (*R*)-**177** (78%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 2.96 (1H, s, OH), 4.40-4.54 (2H, m, CH_2NO_2), 5.36-5.39 (1H, m, CHOH), 7.19-7.23 (2H, m, ArH), 7.45-7.48 (2H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 70.3, 80.9, 123.0, 127.6, 132.2 and 137.1. The ee of 80% was determined by HPLC. HPLC (Chiralcel OD-H column): *n*-hex: IPA = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, t_1 = 13.5 min for (*R*), t_2 = 17.4 min for (*S*).

5.5.21. (*R*)-1-Nitrobutan-2-ol (*R*)-178

Propionaldehyde **172** (14.3 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-nitrobutan-2-ol (*R*)-**178** (95%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 0.94-0.98 (3H, m, CH_3), 1.46-1.61 (2H, m, alkyl-H), 2.57 (1H, br s, OH), 4.18-4.59 (3H, m, CHOH , CH_2NO_2); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 9.6, 26.9, 69.9 and 80.4. The ee of 93% was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 98:2, flow rate = 1.0 ml/min, wavelength = 215 nm, t_1 = 49.7 min for (*R*), t_2 = 84.6 min for (*S*).

5.5.22. (*R*)-1-Nitroheptan-2-ol (*R*)-179

Hexanal **173** (24.6 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general

procedure to give (*R*)-1-nitroheptan-2-ol (*R*)-**179** (94%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 0.84 (3H, t, J = 6.9 Hz, CH_3), 1.15-1.53 (8H, m, alkyl- H), 2.75 (1H, br s, OH), 4.24-4.40 (3H, m, CHOH , CH_2NO_2); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 13.9, 22.5, 24.8, 31.5, 33.7, 68.7 and 80.7. The ee of 90% was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 98:2, flow rate = 1.0 ml/min, wavelength = 215 nm, t_1 = 23.8 min for (*R*), t_2 = 35.6 min for (*S*).

5.5.23. (*R*)-3-Methyl-1-nitrobutan-2-ol (*R*)-**180**

Isobutyraldehyde **174** (18.3 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-**180** (*R*)-3-methyl-1-nitrobutan-2-ol (*R*)-**180** (99%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 0.70-0.78 (6H, m, $2\times\text{CH}_3$), 1.66-1.81 (1H, m, $\text{CH}(\text{CH}_3)_2$), 2.58 (1H, br s, OH), 4.00-4.11 (1H, m, CHOH), 4.30-4.44 (2H, m, CH_2NO_2); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 17.4, 18.4, 31.8, 73.4 and 79.3. The ee of 92% was determined by HPLC. HPLC (Chiralpak OD-H column): *n*-hex: IPA = 98:2, flow rate = 0.5 ml/min, wavelength = 215 nm, t_1 = 40.2 min for (*R*), t_2 = 44.6 min for (*S*).

5.5.24. (*R*)-4-Methyl-1-nitropentan-2-ol (*R*)-**181**

Isovaleraldehyde **175** (21.6 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-4-methyl-1-nitropentan-2-ol (*R*)-**181** (99%, isolated yield). The β -nitroalcohol

product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 0.85-0.91 (6H, m, $2\times\text{CH}_3$), 1.12-1.20 (1H, m, alkyl-*H*), 1.39-1.49 (1H, m, alkyl-*H*), 1.72-1.81 (1H, m, alkyl-*H*), 2.53 (1H, br s, OH), 4.27-4.37 (3H, m, CHOH and CH_2NO_2); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 21.8, 23.2, 24.3, 42.4, 67.0 and 81.0. The ee of 91% was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 95:5, flow rate = 0.5 ml/min, wavelength = 215 nm, t_1 = 20.6 min for (*R*), t_2 = 29.1 min for (*S*).

5.5.25. (*R*)-1-Cyclohexyl-2-nitroethanol (*R*)-182

Cyclohexane carbaldehyde **176** (24.2 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give (*R*)-1-cyclohexyl-2-nitroethanol (*R*)-**182** (70%, isolated yield).

The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 1.00-1.23 (5H, m, alkyl-*H*), 1.42-1.54 (1H, m, alkyl-*H*), 1.60-1.70 (2H, m, alkyl-*H*), 1.72-1.78 (3H, m, alkyl-*H*), 2.38 (1H, d, J = 5.1 Hz, OH), 4.02-4.04 (1H, m, CHOH), 4.36-4.44 (2H, m, CH_2NO_2); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 25.9, 28.0, 28.8, 41.4, 72.8 and 79.3. The ee of 93% was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 98:2, flow rate = 0.6 ml/min, wavelength = 215 nm, t_1 = 48.6 min for (*R*), t_2 = 51.9 min for (*S*).

5.6. Catalytic diastereoselective addition of nitroethane/nitropropane to aldehydes using ligand (*R*)-161

Ligand (0.02 mmol, 10 mol%) and CuCl (0.01 mmol, 5 mol%) were dissolved in THF (1.5 mL) and the mixture was allowed to stir vigorously at r.t. for 1 h, whereby a yellow

solution was obtained. To the above solution, aldehyde (0.2 mmol) was added and the mixture was stirred for another 5 min before dropwise addition of $\text{CH}_3\text{CH}_2\text{NO}_2/\text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2$ (4 mmol, 20 equiv). The reaction mixture was further stirred at room temperature for a specific time (TLC). The β -nitroalcohol product was purified on silica gel by flash column chromatography. Diastereomeric ratios were determined by ^1H NMR and HPLC. Enantiomeric excesses were determined by HPLC using Chiralcel OD-H and OB-H columns, Chiralpak AD-H and AS-H columns. The absolute configuration of the major enantiomer of product was assigned by comparing with literature precedents.^{107,129,146,232}

5.6.1. 1-Phenyl-2-nitropropan-1-ol **183**

Benzaldehyde **39** (20 μL , 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-phenyl-2-nitropropan-1-ol **183** (65%, isolated yield). The β -nitroalcohol

product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*— 1.48 (3H, d, $J = 6.9$ Hz, CH_3), 3.05 (1H, s, OH), 4.65-4.82 (1H, m, CHNO_2), 5.33-5.39 (1H, m, CHOH), 7.31-7.42 (5H, m, ArH); *syn isomer*—1.30 (3H, d, $J = 6.9$ Hz, CH_3), 3.05 (1H, s, OH), 4.65-4.82 (1H, m, CHNO_2), 5.01 (1H, d, $J = 9.0$ Hz, CHOH), 7.31-7.42 (5H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*—12.1, 73.9, 87.4, 125.9, 128.6, 128.8, 138.4; *syn isomer*—16.5, 76.3, 88.4, 126.9, 129.0, 129.2, 138.3. Diastereomeric ratios (*anti/syn*, 2.6:1) were determined by ^1H NMR and HPLC. *anti/syn* = 83%/90% *ee* was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength =

210 nm, t_1 = 8.4 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 9.2 min for *anti*_{major} (1*R*, 2*S*), t_3 = 10.7 min for *syn*_{minor} (1*S*, 2*S*), t_4 = 11.8 min for *syn*_{major} (1*R*, 2*R*).

5.6.2. 1-(4-Nitrophenyl)-2-nitropropan-1-ol **185**

4-nitrobenzaldehyde **126** (30 mg, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(4-nitrophenyl)-2-nitropropan-1-ol **185** (95%,

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isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:4). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti* isomer- 1.49 (3H, d, J = 6.9 Hz, CH_3), 3.10 (1H, s, OH), 4.68-4.82 (1H, m, CHNO_2), 5.55-5.59 (1H, m, CHOH), 7.58-7.62 (2H, m, ArH), 8.24-8.28 (2H, m, ArH); *syn* isomer-1.39 (3H, d, J =6.9 Hz, CH_3), 3.10 (1H, s, OH), 4.68-4.82 (1H, m, CHNO_2), 5.20 (1H, d, J = 9.0 Hz, CHOH), 7.58-7.62 (2H, m, ArH), 8.24-8.28 (2H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti* isomer-11.9, 72.9, 86.8, 124.0, 127.0, 145.6, 148.5; *syn* isomer-16.1, 75.0, 87.8, 124.1, 127.9, 145.6, 148.0. Diastomeric ratios (*anti*/*syn*, 1.5:1) were determined by ^1H NMR and HPLC. *anti*/*syn* = 50%/66% *ee* was determined by HPLC. HPLC (Chiralcel OD-H + Chiralpak AD-H column): *n*-hex: IPA = 80:20, flow rate = 1.0 ml/min, wavelength = 210 nm, t_1 = 17.0 min for *anti*_{major} (1*R*, 2*S*), t_2 = 18.7 min for *anti*_{minor} (1*S*, 2*R*), t_3 = 21.6 min for *syn*_{major} (1*R*, 2*R*), t_4 = 24.8 min for *syn*_{minor} (1*S*, 2*S*).

5.6.3. 1-(2-Fluorophenyl)-2-nitropropan-1-ol **186**

2-Fluorobenzaldehyde **184** (24 μ L, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(2-

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fluorophenyl)-2-nitropropan-1-ol **186** (80%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 1.49 (3H, d, $J = 6.9$ Hz, CH_3), 2.91 (1H, d, $J = 6.9$ Hz, OH), 4.79-4.88 (1H, m, CHNO_2), 5.70-5.76 (1H, m, CHOH), 7.03-7.13 (1H, m, ArH), 7.19-7.59 (3H, m, ArH); *syn isomer*- 1.41 (3H, d, $J = 6.9$ Hz, CH_3), 2.77 (1H, s, OH), 4.79-4.88 (1H, m, CHNO_2), 5.38-5.39 (1H, m, CHOH), 7.03-7.13 (1H, m, ArH), 7.19-7.59 (3H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 11.9, 68.3, 85.2, 115.4, 124.6, 125.4, 127.8, 130.1, 157.5; *syn isomer*- 16.2, 70.0, 87.9, 115.8, 125.0, 125.6, 128.3, 130.6, 160.8. Diastomeric ratios (*anti/syn*, 2.1:1) were determined by ^1H NMR and HPLC. *anti/syn* = 72%/86% *ee* was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 95:5, flow rate = 1.0 ml/min, wavelength = 210 nm, t_1 = 11.5 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 14.1 min for *anti*_{major} (1*R*, 2*S*), t_3 = 18.9 min for *syn*_{minor} (1*S*, 2*S*), t_4 = 22.6 min for *syn*_{major} (1*R*, 2*R*).

5.6.4. 1-(4-Chlorophenyl)-2-nitropropan-1-ol **187**

4-Chlorobenzaldehyde **127** (23 μL , 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(4-chlorophenyl)-2-nitropropan-1-ol **187** (83%,

isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 1.49 (3H, d, $J = 6.0$ Hz, CH_3), 2.82 (1H, s, OH), 4.62-4.75 (1H, m, CHNO_2), 5.62-5.68 (1H, m, CHOH), 7.30-7.40 (4H, m, ArH); *syn isomer*- 1.33 (3H, d, $J = 6.0$ Hz, CH_3), 2.71 (1H, s, OH), 4.62-4.75 (1H, m, CHNO_2), 5.39 (1H, d, $J = 8.1$ Hz, CHOH), 7.30-7.40 (4H,

m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 12.0, 73.2, 87.2, 127.4, 129.0, 134.4, 136.9; *syn isomer*- 16.4, 75.5, 88.2, 128.3, 129.2, 135.1, 136.8. Diastomeric ratios (*anti/syn*, 1.5:1) were determined by ^1H NMR and HPLC. *anti/syn* = 63%/86% *ee* was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 95:5, flow rate = 1.0 ml/min, wavelength = 210 nm, t_1 = 16.1 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 17.3 min for *anti*_{major} (1*R*, 2*S*), t_3 = 22.8 min for *syn*_{major} (1*R*, 2*R*), t_4 = 25.4 min for *syn*_{minor} (1*S*, 2*S*).

5.6.5. 1-(4-Bromophenyl)-2-nitropropan-1-ol **188**

4-Bromobenzaldehyde **171** (37 μL , 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(4-bromophenyl)-2-nitropropan-1-ol **188** (85%,

isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 1.40 (3H, d, J = 6.9 Hz, CH_3), 2.89 (1H, d, J = 3.9 Hz, OH), 4.53-4.69 (1H, m, CHNO_2), 5.25-5.31 (1H, m, CHOH), 7.16-7.20 (2H, m, ArH), 7.42-7.47 (2H, m, ArH); *syn isomer*- 1.24 (3H, d, J = 6.9 Hz, CH_3), 2.83 (1H, d, J = 3.9 Hz, OH), 4.53-4.69 (1H, m, CHNO_2), 4.90-4.94 (1H, m, CHOH), 7.16-7.20 (2H, m, ArH), 7.42-7.47 (2H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 12.0, 73.3, 87.2, 122.5, 127.7, 131.9, 137.6; *syn isomer*- 16.3, 75.5, 88.2, 123.2, 128.6, 132.1, 137.4. Diastomeric ratios (*anti/syn*, 1.6:1) were determined by ^1H NMR and HPLC. *anti/syn* = 61%/87% *ee* was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 90:10, flow rate = 1.0 ml/min,

wavelength = 210 nm, t_1 = 9.8 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 10.5 min for *anti*_{major} (1*R*, 2*S*), t_3 = 13.3 min for *syn*_{major} (1*R*, 2*R*), t_4 = 15.3 min for *syn*_{minor} (1*S*, 2*S*).

5.6.6. 2-Nitro-1-*p*-tolylpropan-1-ol **189**

4-methylbenzaldehyde **131** (24 μ L, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general

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procedure to give 2-nitro-1-*p*-tolylpropan-1-ol **189** (75%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti* isomer- 1.51 (3H, d, J = 6.9 Hz, CH_3), 2.36 (3H, s, Ar- CH_3), 2.62 (1H, br s, OH), 4.67-4.79 (1H, m, CHNO_2), 5.32-3.39 (1H, m, CHOH), 7.21-7.28 (4H, m, ArH); *syn* isomer- 1.31 (3H, d, J = 6.9 Hz, CH_3), 2.36 (3H, s, Ar- CH_3), 2.49 (1H, br s, OH), 4.67-4.79 (1H, m, CHNO_2), 5.06 (1H, d, J = 8.1 Hz, CHOH), 7.21-7.28 (4H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti* isomer- 12.3, 21.1, 73.9, 87.5, 125.9, 129.4, 135.4, 138.4; *syn* isomer- 16.5, 29.7, 76.2, 88.5, 126.8, 129.7, 133.4, 139.2. Diastomeric ratios (*anti*/*syn*, 1.7:1) were determined by ^1H NMR and HPLC. *anti*/*syn* = 85%/91% *ee* was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 95:5, flow rate = 1.0 ml/min, wavelength = 210 nm, t_1 = 14.6 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 16.4 min for *anti*_{major} (1*R*, 2*S*), t_3 = 22.5 min for *syn*_{minor} (1*S*, 2*S*), t_4 = 26.7 min *syn*_{major} (1*R*, 2*R*).

5.6.7. 2-Nitro-1-*m*-tolylpropan-1-ol **190**

3-methylbenzaldehyde **132** (23.5 μ L, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give

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2-nitro-1-*m*-tolylpropan-1-ol **190** (65%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 1.44 (3H, d, J = 6.9 Hz, CH_3), 2.29 (3H, s, Ar- CH_3), 2.63 (1H, d, J = 3.6 Hz, OH), 4.57-4.74 (1H, m, CHNO_2), 5.28 (1H, dd, J = 3.6, 3.4 Hz, CHOH), 7.05-7.11 (3H, m, ArH), 7.17-7.24 (1H, m, ArH); *syn isomer*- 1.23 (3H, d, J = 6.9 Hz, CH_3), 2.30 (3H, s, Ar- CH_3), 2.51 (1H, d, J = 3.6 Hz, OH), 4.57-4.74 (1H, m, CHNO_2), 4.90 (1H, dd, J = 3.6, 3.6 Hz, CHOH), 7.05-7.11 (3H, m, ArH), 7.17-7.24 (1H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 12.1, 21.4, 74.0, 87.5, 123.0, 126.6, 128.6, 129.3, 138.5, 138.6; *syn isomer*- 16.5, 21.5, 76.3, 88.5, 124.1, 127.5, 128.9, 130.0, 138.3, 138.9. Diastomeric ratios (*anti*/*syn*, 1.6:1) were determined by ^1H NMR and HPLC. *anti*/*syn* = 77%/87% *ee* was determined by HPLC. HPLC (Chiralpak AS-H column): *n*-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 210 nm, t_1 = 8.7 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 9.7 min for *anti*_{major} (1*R*, 2*S*), t_3 = 10.4 min for *syn*_{minor} (1*S*, 2*S*), t_4 = 12.9 min *syn*_{major} (1*R*, 2*R*).

5.6.8. 2-Nitro-1-*o*-tolylpropan-1-ol **191**

2-methylbenzaldehyde **133** (23 μL , 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 2-nitro-1-*o*-tolylpropan-1-ol **191** (70%, isolated yield). The β -

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nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 1.43 (3H, d, J = 6.9 Hz, CH_3), 2.29 (3H, s, Ar- CH_3), 2.58 (1H, s, OH), 4.54-4.57 (1H, m, CHNO_2), 5.50-5.56 (1H, m, CHOH), 7.08-7.19 (3H, m, ArH), 7.46 (1H, d, J = 7.2 Hz, ArH); *syn isomer*-

1.22 (3H, d, $J = 6.9$ Hz, CH_3), 2.36 (3H, s, Ar- CH_3), 2.48 (1H, s, OH), 4.77-4.80 (1H, m, CHNO_2), 5.27-5.30 (1H, m, CHOH), 7.08-7.19 (3H, m, ArH), 7.29-7.32 (1H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 11.5, 18.9, 70.9, 85.4, 126.0, 126.4, 128.4, 130.8, 134.3, 136.7; *syn isomer*- 16.1, 19.6, 72.2, 88.8, 126.5, 126.8, 128.8, 131.0, 135.9, 136.6. Diastomeric ratios (*anti/syn*, 1.6:1) were determined by ^1H NMR and HPLC. *anti/syn* = 75%/92% *ee* was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 95:5, flow rate = 1.0 ml/min, wavelength = 210 nm, t_1 = 11.4 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 12.8 min for *anti*_{major} (1*R*, 2*S*), t_3 = 15.6 min for *syn*_{minor} (1*S*, 2*S*), t_4 = 19.4 min *syn*_{major} (1*R*, 2*R*).

5.6.9. 1-(Naphthalen-2-yl)-2-nitropropan-1-ol **192**

2-naphthaldehyde **140** (31.2 mg, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(naphthalen-2-yl)-2-nitropropan-1-ol **192**

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(70%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*-1.52 (3H, d, $J = 6.9$ Hz, CH_3), 2.84 (1H, s, OH), 4.79-4.93 (1H, m, CHNO_2), 5.54-5.62 (1H, m, CHOH), 7.43-7.55 (3H, m, ArH), 7.84-7.94 (4H, m, ArH); *syn isomer*- 1.33 (3H, d, $J = 6.9$ Hz, CH_3), 2.69 (1H, s, OH), 4.79-4.93 (1H, m, CHNO_2), 5.20 (1H, d, $J = 9.3$ Hz, CHOH), 7.43-7.55 (3H, m, ArH), 7.84-7.94 (4H, m, ArH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*-12.0, 74.0, 87.3, 123.3, 125.3, 126.5, 126.6, 127.7, 128.09, 128.7, 133.11, 133.2, 135.7; *syn isomer*- 16.6, 76.5, 88.4, 123.8, 126.7, 126.74, 126.8, 127.8, 128.07, 129.1, 133.09, 133.6, 135.6. Diastomeric ratios (*anti/syn*, 0.8:1)

were determined by ^1H NMR and HPLC. *anti/syn* = 40%/75% *ee* was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 210 nm, t_1 = 11.6 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 13.9 min for *anti*_{major} (1*R*, 2*S*), t_3 = 18.0 min for *syn*_{minor} (1*S*, 2*S*), t_4 = 20.6 min *syn*_{major} (1*R*, 2*R*).

5.6.10. 2-Nitrohexan-3-ol **193**

Butyraldehyde **138** (18 μL , 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give

2-nitrohexan-3-ol **193** (81%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 0.87-0.92 (5H, m, alkyl-*H*), 1.34-1.40 (2H, m, alkyl-*H*), 1.46 (3H, d, J = 6.9 Hz, CH_3), 2.13 (1H, br s, OH), 4.12-4.15 (1H, m, CHNO_2), 4.45-4.50 (1H, m, CHOH); *syn isomer*- 0.87-0.92 (5H, m, alkyl-*H*), 1.34-1.40 (2H, m, alkyl-*H*), 1.49 (3H, d, J = 6.9 Hz, CH_3), 2.22 (1H, br s, OH), 3.75-3.85 (1H, m, CHNO_2), 4.45-4.50 (1H, m, CHOH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 13.8, 16.3, 18.4, 35.1, 72.7, 86.4; *syn isomer*- 12.4, 13.9, 19.0, 29.7, 71.8, 87.7. Diastomeric ratios (*anti/syn*, 1.3:1) were determined by ^1H NMR and HPLC. *anti/syn* = 90%/89% *ee* was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 98:2, flow rate = 0.8 ml/min, wavelength = 220 nm, t_1 = 25.4 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 27.9 min for *anti*_{major} (1*R*, 2*S*), t_3 = 31.6 min for *syn*_{major} (1*R*, 2*R*), t_4 = 35.1 min *syn*_{minor} (1*S*, 2*S*).

5.6.11. 5-Methyl-2-nitrohexan-3-ol **194**

Isovaleraldehyde **175** (21.6 μL , 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6

mg, 0.02 mmol, 10 mol%) following the general procedure to give 5-methyl-2-nitrohexan-3-ol **194** (80%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 0.86-0.91 (6H, m, $2\times\text{CH}_3$), 1.15-1.23 (1H, m, alkyl-*H*), 1.48 (3H, d, $J = 6.6$ Hz, CH_3), 1.76-1.80 (2H, m, alkyl-*H*), 2.28 (1H, br s, OH), 4.20 (1H, d, $J = 6.6$ Hz, CHNO_2), 4.40-4.46 (1H, m, CHOH); *syn isomer*- 0.86-0.91 (6H, m, $2\times\text{CH}_3$), 1.06-1.14 (1H, m, alkyl-*H*), 1.30-1.39 (2H, m, alkyl-*H*), 1.49 (3H, d, $J = 6.9$ Hz, CH_3), 2.28 (1H, br s, OH), 3.86-3.90 (1H, m, CHNO_2), 4.40-4.46 (1H, m, CHOH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 16.3, 21.7, 23.6, 24.3, 42.0, 71.2, 86.7; *syn isomer*- 12.4, 21.4, 23.3, 24.5, 41.8, 70.2, 88.2. Diastomeric ratios (*anti/syn*, 1.3:1) were determined by ^1H NMR and HPLC. *anti/syn* = 90%/89% *ee* was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 98:2, flow rate = 0.8 ml/min, wavelength = 220 nm, t_1 = 20.2 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 21.7 min for *anti*_{major} (1*R*, 2*S*), t_3 = 26.1 min for *syn*_{major} (1*R*, 2*R*), t_4 = 28.0 min *syn*_{minor} (1*S*, 2*S*).

5.6.12. 3-Nitroheptan-4-ol **195**

Butyraldehyde **138** (18 μL , 0.2 mmol, 1 equiv) was treated with nitropropane (360 μL , 4.0 mmol, 20 equiv) in the presence of (*R*)-**161**

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(5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 3-nitroheptan-4-ol **195** (79%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 0.85-0.95 (6H, m, alkyl-*H*), 1.32-1.49 (4H, m, alkyl-*H*), 1.80-1.85 (1H, m, alkyl-*H*), 2.00-2.06 (2H, m, alkyl-*H* + OH), 3.90-4.00 (1H, m, CHNO_2), 4.30-4.39 (1H, m, CHOH); *syn isomer*- 0.85-0.95 (6H, m, alkyl-*H*), 1.32-1.49

(4H, m, alkyl-*H*), 1.80-1.85 (1H, m, alkyl-*H*), 2.00-2.06 (2H, m, alkyl-*H* + *OH*), 3.81-3.88 (1H, m, *CHNO*₂), 4.30-4.39 (1H, m, *CHOH*); ¹³C NMR (75.6 MHz, CDCl₃, δ ppm): *anti* isomer-10.5, 13.7, 18.8, 21.5, 35.2, 72.0, 93.9; *syn* isomer-10.2, 13.8, 18.5, 23.9, 35.5, 71.6, 94.4. Diastomeric ratios (*anti/syn*, 1.1:1) were determined by ¹H NMR and HPLC. *anti/syn* = 85%/87% *ee* was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 99.5:0.5, flow rate = 1.0 ml/min, wavelength = 215 nm, *t*₁ = 27.4 min for *anti*_{minor} (1*S*, 2*R*), *t*₂ = 29.2 min for *anti*_{major} (1*R*, 2*S*), *t*₃ = 38.7 min for *syn*_{minor} (1*S*, 2*S*), *t*₄ = 40.7 min *syn*_{major} (1*R*, 2*R*).

5.6.13. 3-Nitrohexan-4-ol **196**

Propionaldehyde **172** (14.3 μL, 0.2 mmol, 1 equiv) was treated with nitropropane (360 μL, 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give

3-nitrohexan-4-ol **196** (77%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ¹H NMR (300 MHz, CDCl₃, δ ppm): *anti* isomer- 0.96-0.99 (6H, m, alkyl-*H*), 1.26-1.41 (2H, m, alkyl-*H*), 1.65-1.91 (2H, m, alkyl-*H*), 2.33-2.60 (1H, m, *OH*), 3.77-3.83 (1H, m, *CHNO*₂), 4.16-4.21 (1H, m, *CHOH*); *syn* isomer- 0.96-0.99 (6H, m, alkyl-*H*), 1.26-1.41 (2H, m, alkyl-*H*), 1.65-1.91 (2H, m, alkyl-*H*), 2.33-2.60 (1H, m, *OH*), 3.60-3.75 (1H, m, *CHNO*₂), 4.16-4.21 (1H, m, *CHOH*); ¹³C NMR (75.6 MHz, CDCl₃, δ ppm): *anti* isomer-10.0, 10.5, 21.5, 26.3, 73.6, 93.7; *syn* isomer- 9.6, 10.2, 24.0, 26.5, 73.1, 94.1. Diastomeric ratios (*anti/syn*, 1.1:1) were determined by ¹H NMR and HPLC. *anti/syn* = 86%/89% *ee* was determined by HPLC. HPLC (Chiralpak OB-H column): *n*-hex: IPA = 98:2, flow rate =

0.6 ml/min, wavelength = 215 nm, t_1 = 18.7 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 22.1 min for *anti*_{major} (1*R*, 2*S*), t_3 = 28.0 min for *syn*_{major} (1*R*, 2*R*), t_4 = 32.2 min *syn*_{minor} (1*S*, 2*S*).

5.6.14. 2-Methyl-5-Nitroheptan-4-ol **197**

Isovaleraldehyde **175** (21.6 μ L, 0.2 mmol, 1 equiv) was treated with nitropropane (360 μ L, 4.0 mmol, 20 equiv) in the presence of (*R*)-**161** (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give

2-methyl-5-nitroheptan-4-ol **197** (73%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 0.84-0.96 (9H, m, $3\times\text{CH}_3$), 1.11-1.23 (2H, m, alkyl-*H*), 1.34-1.41 (1H, m, alkyl-*H*), 1.76-1.84 (2H, m, alkyl-*H*), 2.02-2.19 (1H, m, OH), 4.08-4.13 (1H, m, CHNO_2), 4.25-4.30 (1H, m, CHOH); *syn isomer*- 0.84-0.96 (9H, m, $3\times\text{CH}_3$), 1.11-1.23 (2H, m, alkyl-*H*), 1.34-1.41 (1H, m, alkyl-*H*), 1.76-1.84 (2H, m, alkyl-*H*), 2.02-2.19 (1H, m, OH), 3.89-3.92 (1H, m, CHNO_2), 4.25-4.30 (1H, m, CHOH); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*-10.5, 21.3, 21.5, 23.5, 24.5, 42.0, 70.4, 94.2; *syn isomer*-10.2, 21.5, 23.4, 23.9, 24.3, 42.5, 70.0, 94.8. Diastomeric ratios (*anti/syn*, 1.3:1) were determined by ^1H NMR and HPLC. *anti/syn* = 86%/90% *ee* was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 99:1, flow rate = 0.6 ml/min, wavelength = 210 nm, t_1 = 22.1 min for *anti*_{minor} (1*S*, 2*R*), t_2 = 25.0 min for *anti*_{major} (1*R*, 2*S*), t_3 = 30.8 min for *syn*_{minor} (1*S*, 2*S*), t_4 = 32.1 min *syn*_{major} (1*R*, 2*R*).

5.7. Catalytic addition of nitromethane/nitroethane to α -esters and aldehydes using BIQ *rac*-**29**

BIQ (0.02 mmol, 10 mol%) was dissolved in THF (1.5 mL) and nitromethane (205 μ L, 4 mmol, 20 equiv)/nitroethane (285 μ L, 4 mmol, 20 equiv) was added and the mixture was

stirred for another 5 mins before dropwise addition of α -ketoester/aldehyde (0.2 mmol). The reaction mixture was further stirred at r.t. for a certain time (TLC). The solvent was then removed under vacuum and the residue was purified on silica gel by flash column chromatography. Diastereomeric ratios were determined by ^1H NMR.

5.7.1. 2-Hydroxy-3-nitro-2-(4-nitro-phenyl)-propanoic Acid Ethyl Ester **206**

Ethyl 4-nitrophenyl glyoxylate **200** (44.6 mg, 0.2 mmol, 1 equiv)

was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%)

following the general procedure to give 2-Hydroxy-3-nitro-2-(4-

nitro-phenyl)-propanoic Acid Ethyl Ester **206** (99%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 1.35 (3H, t, $J = 7.2$ Hz), 4.34-4.46 (2H, m), 4.54 (1H, s), 4.70 (1H, d, $J = 13.5$ Hz), 5.32 (1H, d, $J = 13.5$ Hz), 7.83-7.87 (2H, m), 8.23 (2H, d, $J = 8.7$ Hz); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 13.8, 64.3, 76.0, 80.4, 123.9, 126.8, 143.3, 148.3, 170.6.

5.7.2. 2-Hydroxy-2-Nitromethyl-4-Phenyl-butanoic Acid Ethyl Ester **207**

Ethyl 2-oxo-4-phenylbutyrate **201** (38 μL , 0.2 mmol, 1 equiv)

was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%)

following the general procedure to give 2-hydroxy-2-nitromethyl-4-phenyl-butanoic acid ethyl ester **207** (90%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 1.36 (3H, t, $J = 7.2$ Hz), 1.98-2.06 (2H, m), 2.52-2.56 (1H, m), 2.83-2.87 (1H, m),

3.96 (1H, s), 4.32-4.39 (2H, m), 4.61 (1H, d, $J = 13.6$ Hz), 4.86 (1H, d, $J = 13.5$ Hz), 7.18-7.35 (5H, m); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 14.1, 29.0, 38.2, 63.2, 75.0, 80.8, 126.4, 128.3, 128.6, 140.2, 172.6.

5.7.3 2-Hydroxy-2-methyl-3-nitro-propanoic Acid Ethyl Ester **199**

Ethyl pyruvate **198** (23 μL , 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure

to give 2-hydroxy-2-methyl-3-nitro-propanoic acid ethyl ester **199** (95%, isolated yield).

The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 1.26 (3H, t, $J = 7.2$ Hz), 1.39 (3H, s), 3.77 (1H, s), 4.19-4.35 (2H, m), 4.50 (1H, d, $J = 13.5$ Hz), 4.78 (1H, d, $J = 13.8$ Hz); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 14.0, 23.9, 63.1, 72.4, 81.0, 173.4.

5.7.4 2-Hydroxy-2-nitromethyl-butanoic Acid Ethyl Ester **208**

Ethyl 2-oxobutanoate **202** (26 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL , 4.0 mmol, 20 equiv) in the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general

procedure to give 2-hydroxy-2-nitromethyl-butanoic acid ethyl ester **208** (90%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 0.84 (3H, t, $J = 7.5$ Hz), 1.26 (3H, t, $J = 6.9$ Hz), 1.47-1.75 (2H, m), 3.79 (1H, s), 4.20-4.35 (2H, m), 4.51 (1H, d, $J = 13.5$ Hz), 4.78 (1H, d, $J = 13.5$ Hz); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 6.9, 13.9, 30.0, 62.9, 75.6, 80.6, 172.8.

5.7.5. 2-Hydroxy-4-methyl-2-nitromethyl-pentanoic Acid Ethyl Ester **209**

Ethyl 4-methyl-2-oxopentanoate **203** (31 mg, 0.2 mmol, 1 equiv)

was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the

presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%) following

the general procedure to give 2-hydroxy-4-methyl-2-nitromethyl-pentanoic acid ethyl ester **209** (88%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 0.83 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.6 Hz), 1.29 (3H, t, J = 7.2 Hz), 1.49-1.61 (2H, m), 1.69-1.80 (1H, m), 3.80 (1H, s), 4.20-4.24 (2H, m), 4.50 (1H, d, J = 13.5 Hz), 4.71 (1H, d, J = 13.6 Hz); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 13.9, 23.3, 23.7, 24.0, 44.5, 62.9, 75.4, 81.5, 173.3.

5.7.6. 2-Hydroxy-2-nitromethyl-octanoic Acid Ethyl Ester **210**

Ethyl 2-oxooctanoate **204** (37 mg, 0.2 mmol, 1 equiv) was

treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in

the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%)

following the general procedure to give 2-hydroxy-2-nitromethyl-octanoic acid ethyl ester **210** (85%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300MHz, CDCl_3 , δ ppm): 0.80 (3H, t, J = 6.9 Hz), 1.06-1.19 (1H, m), 1.20-1.29 (9H, m), 1.38-1.52 (1H, m), 1.55-1.63 (2H, m), 3.81 (1H, s), 4.22-4.40 (2H, m), 4.50 (1H, d, J = 13.5 Hz), 4.77 (1H, d, J = 13.5 Hz); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 13.8, 13.9, 22.3, 22.4, 28.9, 31.4, 36.4, 62.8, 75.3, 80.8, 172.9.

5.7.7. 1-(2-Nitrophenyl)-2-nitroethanol **211**

2-Nitrobenzaldehyde **205** (30 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(2-nitrophenyl)-2-nitroethanol **211** (96%,

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isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=3:7). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 3.64 (1H, s), 4.42-4.49 (1H, m), 4.71-4.77 (1H, m), 5.89-5.93 (1H, m), 7.43-7.48 (1H, m), 7.63-7.68 (1H, m), 7.84 (1H, d, $J = 7.2$ Hz), 7.95 (1H, d, $J = 7.6$ Hz); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): 66.8, 80.2, 125.0, 128.7, 129.7, 134.3, 134.5, 147.1.

5.7.8. 2-Hydroxy-2-nitromethyl-4-phenyl-pentanoic Acid Ethyl Ester **212**

Ethyl 2-oxo-4-phenylbutyrate **201** (38 μ L, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μ L, 4.0 mmol, 20 equiv) in the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%) following

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the general procedure to give 2-hydroxy-2-nitromethyl-4-phenyl-pentanoic acid ethyl ester **212** (92%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*-1.24-1.30 (3H, m), 1.55 (3H, d, $J = 6.9$ Hz), 1.88-1.90 (1H, m), 2.05-2.17 (1H, m), 2.25-2.37 (1H, m), 2.69-2.79 (1H, m), 3.79 (1H, s), 4.21-4.29 (2H, m), 4.74-4.85 (1H, m), 7.06-7.20 (5H, m); *syn isomer*-1.24-1.30 (3H, m), 1.55 (3H, d, $J = 6.9$ Hz), 1.84-1.93 (2H, m), 2.25-2.37 (1H, m), 2.69-2.79 (1H, m), 3.60 (1H, s), 4.21-4.29 (2H, m), 4.74-4.85 (1H, m), 7.06-7.20 (5H, m); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*-12.8, 15.0, 29.5, 37.7, 63.3, 77.1, 89.0, 126.3, 128.4, 128.6, 140.4, 140.5, 172.4; *syn isomer*-14.1, 14.2, 29.6, 37.9, 63.0, 76.7, 87.2, 126.4, 128.3, 128.5, 140.44, 140.6, 173.2.

5.7.9. 2-Hydroxy-2-methyl-3-nitro-butanoic Acid Ethyl Ester **213**

Ethyl pyruvate **198** (23 μ L, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μ L, 4.0 mmol, 20 equiv) in the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to

give 2-hydroxy-2-methyl-3-nitro-butanoic acid ethyl ester **213** (96%, isolated yield). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*-1.22-1.31 (3H, m), 1.43 (3H, s), 1.55-1.65 (3H, m), 3.70 (1H, s), 4.18-4.33 (2H, m), 4.75 (1H, q, $J = 7.0$ Hz); *syn isomer*-1.22-1.31 (3H, m), 1.35 (3H, s), 1.55-1.65 (3H, m), 3.54 (1H, s), 4.18-4.33 (2H, m), 4.84 (1H, q, $J = 7.0$ Hz); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 14.0, 14.9, 23.3, 63.1, 74.9, 88.8, 173.2; *syn isomer*- 12.6, 13.9, 23.4, 62.9, 74.8, 86.7, 174.2.

5.7.10. 1-(2-Nitrophenyl)-2-nitropropan-1-ol **214**

2-Nitrobenzaldehyde **205** (30 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(2-nitrophenyl)-2-nitropropan-1-ol **214** (99%, isolated yield).

The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane = 1:1). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*-1.53-1.57 (3H, m), 3.30-3.36 (1H, br s), 4.97-5.10 (1H, m), 6.05-6.13 (1H, m), 7.55-7.58 (1H, m), 7.93-8.12 (3H, m); *syn isomer*-1.53-1.57 (3H, m), 3.30-3.36 (1H, br s), 4.97-5.10 (1H, m), 5.69-5.80 (1H, m), 7.55-7.58 (1H, m), 7.93-8.12 (3H, m); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 11.9, 69.3, 84.8, 125.0, 128.9, 129.4, 134.0, 134.2, 147.1; *syn isomer*- 16.4, 70.5, 87.6, 125.2, 129.3, 129.7, 134.1, 134.3, 148.3.

5.7.11. 2-Nitroheptan-3-ol **215**

Valeraldehyde **137** (22 μ L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general

procedure to give 2-nitroheptan-3-ol **215** (94%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane = 1:5) to give a colorless oil (94% yield); ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 0.83-0.87 (3H, m), 1.28-1.40 (6H, m), 1.46-1.49 (3H, m), 2.43 (1H, br s), 4.11-4.19 (1H, m, *anti*-CHOH), 4.42-4.52 (1H, m); *syn isomer*- 0.83-0.87 (3H, m), 1.28-1.40 (6H, m), 1.46-1.49 (3H, m), 2.43 (1H, br s), 3.75-3.90 (1H, m, *syn*-CHOH), 4.42-4.52 (1H, m); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 13.9, 16.2, 22.4, 27.2, 32.7, 72.9, 86.4; *syn isomer*- 12.3, 16.1, 22.5, 27.9, 32.6, 72.1, 87.8.

5.7.12. 1-(2-Furyl)-2-nitropropan-1-ol **216**

2-Furaldehyde **141** (18 μ L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μ L, 4.0 mmol, 20 equiv) in the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to

give 1-(2-furyl)-2-nitropropan-1-ol **216** (94%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane = 1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 1.56-1.60 (3H, m), 3.21 (1H, br s), 4.85-5.02 (1H, m), 5.29-5.33 (1H, m), 6.38-6.42 (2H, m), 7.40-7.44 (1H, m); *syn isomer*- 1.34-1.39 (3H, m), 3.21 (1H, br s), 4.85-5.02 (1H, m), 5.06-5.09 (1H, m), 6.38-6.42 (2H, m), 7.40-7.44 (1H, m); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 13.1, 68.9, 85.0, 108.2, 110.6, 142.8, 150.8; *syn isomer*- 16.2, 69.5, 86.3, 109.3, 110.5, 143.2, 151.3.

5.7.13. (E)-2-Nitro-5-phenyl-4-buten-3-ol **217**

Trans-cinnamaldehyde **142** (26 μ L, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μ L, 4.0 mmol, 20 equiv) in the presence of BIQ *rac*-**29** (5.1 mg, 0.02 mmol, 10 mol%) following the general

procedure to give (*E*)-2-nitro-5-phenyl-4-buten-3-ol **217** (92%, isolated yield). The β -nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ^1H NMR (300 MHz, CDCl_3 , δ ppm): *anti isomer*- 1.44-1.52 (3H, m), 2.66 (1H, d, $J = 3.9$ Hz), 4.47-4.50 (1H, m), 4.69-4.77 (1H, m), 5.96-6.05 (1H, m), 6.60-6.69 (1H, d, $J = 15$ Hz), 7.24-7.29 (5H, m); *syn isomer*- 1.44-1.52 (3H, m), 2.66 (1H, d, $J = 3.9$ Hz), 4.47-4.50 (1H, m), 4.50-4.56 (1H, m), 5.96-6.05 (1H, m), 6.60-6.69 (1H, d, $J = 15$ Hz), 7.24-7.29 (5H, m); ^{13}C NMR (75.6 MHz, CDCl_3 , δ ppm): *anti isomer*- 13.0, 73.3, 86.1, 125.1, 126.7, 128.4, 128.7, 133.8, 135.6; *syn isomer*-16.2, 74.7, 87.2, 125.2, 126.8, 128.6, 128.8, 134.9, 135.8.

Chapter 6. Future Work

6.1. Application of chiral BIQs in asymmetric aza-Henry reaction

Bearing close resemblance to three of the most fundamental carbon-carbon bond forming reactions (aldol, Mannich and Henry), nitro-Mannich coupling allows access to synthetically useful β -nitroamine products. Also known as aza-Henry reaction, it involves the addition of nitro compounds to azomethine functions.¹¹⁶ This reaction is a highly valuable C-C bond forming process, as the β -nitroamine products **219** can be transformed into 1,2-diamines **220/221** via reduction or α -amino acids by a Nef oxidation (Scheme 68). Diamines are of particular interest as they can be employed as biologically active natural products, drug candidates and chiral ligands for asymmetric reactions. Hence, the stereocenters in the products must be controlled to give the required configuration.

Scheme 68

Nonetheless, development for the enantioselective version for this reaction is challenging.²³⁸⁻²³⁹ The catalyst must be able to activate the imine to a nucleophilic attack, but not be hindered by strong Lewis basic amine products. Based on the great results afforded from BIQ (*R*)-**29** and its alkyl derivatives in the Henry reaction (Chapter 3), future work can be focused to explore these BIQs for the asymmetric catalysis of aza-Henry reaction.

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APPENDIX

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¹H NMR spectrum of compound 10 in CDCl₃. The spectrum shows peaks from 0.000 to 7.553 ppm. Integration values are shown below the peaks: 5.0, 1.0, 2.07, 1.04, 2.08, and 0.39. The x-axis is labeled 'ppm'.

167.226
138.424
128.716
128.629
126.577
77.497
77.483
76.620
42.132
42.099
35.519

NAME: 10091110421 #2.6 RT: 0.03-0.17 AG: 7 SR: 70.038-1.30 NL: 2.12E9
 T: 4 e (EI) Full ms [50.00-2000.00]

m/z	Relative Intensity (%)
160.27	~1
275.27	~1
311.12	~32
333.13	~5
431.90	~10
485.26	~5
545.52	~5
552.04	~15
429.06	100
591.26	~1
794.81	~10
814.61	~5
950.19	~5
1077.13	~5
1159.82	~5
1393.26	~5
1477.15	~5
1647.04	~5
1772.75	~5
1945.45	~5

101 **¹H NMR** **¹³C NMR** **FTIR** **HRMS**

rac-98 **¹H NMR** **¹³C NMR** **FTIR** **HRMS**

rac-98

HMQC

HMBC

HPLC results:*rac-98* *(R,R)-98* **Separation conditions: Flow rate = 1.0 mL/min****Hexane/IPA/Et₃N = 90/10/0.1****Column: Chiralcel OD-H column**

rac-112 **¹H NMR** **¹³C NMR** **FTIR** **HRMS**

rac-112

HMQC

HMBC

HPLC results:*rac*-112 *(R,R)*-112 **Separation conditions: Flow rate = 0.4 mL/min****Hexane/IPA/Et₃N = 95/5/0.05****Column: Chiralcel OD-H column**

rac-113 ¹H NMR ¹³C NMR

FTIR

HRMS

rac-113

HMQC

HMBC

HPLC results:*rac*-113 *(R,R)*-113 **Separation conditions: Flow rate = 0.5 mL/min****Hexane/IPA/Et₃N = 95/5/0.05****Column: Chiralcel OD-H column**

Mass spectrum of the sample showing relative intensity versus m/z. The x-axis ranges from 190 to 0 m/z. The y-axis represents relative intensity from 0 to 100. The base peak is at m/z 130. Other significant peaks are labeled with their m/z values.

m/z	Relative Intensity (approx.)
150	5
146	5
142	5
138	15
134	10
130	100
126	10
122	10
118	10
114	10
110	10
106	10
102	10
98	10
94	10
90	10
86	10
82	10
78	10
74	10
70	10
66	10
62	10
58	10
54	10
50	10
46	10
42	10
38	10
34	10
30	10
26	10
22	10
18	10
14	10
10	10
6	10
2	10

Mass spectrum of the sample showing relative intensity (%) versus mass-to-charge ratio (m/z). The base peak is at m/z 459.2808.

m/z	Relative Intensity (%)
452.2210	~1
452.9308	~1
453.1094	~1
454.4128	~1
454.7735	~1
456.1652	~1
457.2786	~1
459.2225	~1
459.2808	100
459.4861	~10
461.2887	~15
462.2886	~1
462.9887	~1
464.2535	~1
464.6542	~1

Minimum: -1.3
Maximum: 5.0 5.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	I-FTT	I-FTT (Norm)	Formula
459.2808	459.2800	0.8	1.7	17.5	33.3	0.0	C33 H35 N2

207

rac-114

HMQC

HMBC

HPLC results:

rac-114 *(R,R)*-114

Separation conditions: Flow rate = 0.5 mL/min

Hexane/IPA/Et₃N = 98/2/0.02

Column: Chiralcel OD-H column

Mass spectrum of compound 10. The x-axis represents the mass-to-charge ratio (m/z) from 0 to 100, and the y-axis represents the relative intensity from 0 to 100%. The base peak is at m/z 311. Other significant peaks are labeled with their m/z values: 150, 165, 180, and 205. The spectrum shows a series of peaks characteristic of the compound's fragmentation pattern.

Mass spectrum of compound 10. The x-axis represents the mass-to-charge ratio (m/z) from 190 to 0, and the y-axis represents relative intensity. The spectrum shows several characteristic peaks, with the base peak at m/z 125. Other significant peaks are labeled at m/z 136, 134, 142, 138, 140, 126, 248, 125, 259, 77, 564, 77, 539, 77, 515, 77, 508, 35, 623, 47, 545, 32, 629, and 26, 605.

291.060

100

0

290.500 290.950 291.000 291.050 291.100 291.150 291.200 291.250 291.300 291.350 291.400 291.450

m/z

Minimum: -1.5
Maximum: 5.0 5.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	I-FIT	I-FIT (Norm)	Formula
291.1840	291.1861	-0.1	-0.3	10.5	12.9	0.0	C10 H23 N2

209

rac-115 **¹H NMR** **¹³C NMR** **FTIR** **HRMS** **HMQC** **HMBC**

rac-116 **¹H NMR** **¹³C NMR** **FTIR** **HRMS** **HMQC** **HMBC**

rac-117 ^1H NMR ^{13}C NMR

FTIR

HRMS

HMQC

HMBC

[illegible]

Mass spectrum of compound 10. The x-axis represents the mass-to-charge ratio (m/z) from 0 to 190, and the y-axis represents relative intensity from 0 to 100. The base peak is at m/z 132. Other labeled peaks include:

m/z	Relative Intensity (approx.)
140	8
138	10
136	12
134	15
132	100
130	18
128	25
126	20
124	15
122	10
120	8
118	5
116	3
114	2
112	1
110	1
108	1
106	1
104	1
102	1
100	1
98	1
96	1
94	1
92	1
90	1
88	1
86	1
84	1
82	1
80	1
78	1
76	1
74	1
72	1
70	1
68	1
66	1
64	1
62	1
60	1
58	1
56	1
54	1
52	1
50	1
48	1
46	1
44	1
42	1
40	1
38	1
36	1
34	1
32	1
30	1
28	1
26	1
24	1
22	1
20	1
18	1
16	1
14	1
12	1
10	1
8	1
6	1
4	1
2	1

FTIR spectrum of the polymer film. The x-axis represents wavenumber in cm^{-1} (ranging from 4000.0 to 450.0), and the y-axis represents transmittance in % (ranging from 16.2 to 30.2). The spectrum shows characteristic absorption bands for the polymer, with several peaks labeled with their corresponding wavenumbers:

- 3420.91, 32.67
- 3023.89, 24.16
- 2926.64, 23.47
- 2907.87, 24.89
- 1685.14, 23.50
- 1495.54, 20.92
- 1453.46, 20.65
- 1398.70, 19.78
- 1168.70, 21.40
- 1124.07, 21.23
- 842.30, 24.77
- 752.19, 19.90
- 742.48, 16.65

Mass spectrum plot showing relative intensity (%) versus m/z. The x-axis ranges from 366,000 to 367,500. The y-axis ranges from 0 to 100. A single sharp peak is labeled at m/z 367,2158.

Minimum	Maximum
5.0	-1.5
5.0	50.0

Mass	Calc.	Mass	mDa	PPM	DBE	I-TIT	I-TIT (Norm)	Formula
367.2158	367.2174	-1.6	-4.4	14.5	13.4	0.0	C26 H27 N2

rac-119 **¹H NMR** **¹³C NMR** **FTIR** **HRMS**

rac-119

HMQC

HMBC

HPLC results:

rac-119 *(R,R)*-119

Separation conditions: Flow rate = 0.3 mL/min

Hexane/IPA/Et₃N = 90/10/0.1

Column: Chiralcel OD-H column

(R)-163

¹H NMR ¹³C NMR

FTIR

HRMS

(R)-163 **HMQC** **HMBC****HPLC results:*****rac*-163** **(R)-163** **Separation conditions: Flow rate = 1.0 mL/min****Hexane/IPA/Et₃N = 98/2****Column: Chiralcel OD-H column**

(R)-124 **¹H NMR** **¹³C NMR****HPLC results:****(R)-124** ***rac*-124****Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 90/10****Column: Chiralcel OD-H column**

(R)-143 **¹H NMR** **¹³C NMR****HPLC results:*****rac*-143** **(R)-143** **Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 85/15****Column: Chiralcel OD-H column**

(R)-144 **¹H NMR** **¹³C NMR****HPLC results:** **Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10****Column: Chiralcel OD-H column**

¹H NMR ¹³C NMR

HPLC results:

(R)-145

rac-145

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10

Column: Chiralcel OD-H column

(R)-146 **¹H NMR** **¹³C NMR****HPLC results:****(R)-146*****rac*-146** **Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 90/10****Column: Chiralcel OJ-H column**

(R)-147 **¹H NMR** **¹³C NMR**

HPLC results:

(R)-147**rac-147**

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 90/10

Column: Chiralcel OD-H column

(R)-148 **¹H NMR** **¹³C NMR****HPLC results:****(R)-148** **rac-148****Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 90/10****Column: Chiralcel OD-H column**

¹H NMR ¹³C NMR

HPLC results:

Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 90/10

Column: Chiralcel OD-H column

(R)-150 **¹H NMR** **¹³C NMR**

HPLC results:

(R)-150 **rac-150**

Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 90/10

Column: Chiralcel OD-H column

(R)-151

¹H NMR

¹³C NMR

HPLC results:

(R)-151

rac-**151**

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 85/15

Column: Chiralcel OD-H column

(R)-152

HPLC results:

rac-152

(R)-152

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 85/15

Column: Chiralcel OD-H column

(R)-153 **¹H NMR** **¹³C NMR****HPLC results:****(R)-153****rac-153** **Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 90/10****Column: Chiralcel OD-H column**

(R)-154 **¹H NMR** **¹³C NMR****HPLC results:*****rac*-154** **(R)-154** **Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10****Column: Chiralcel OD-H column**

(R)-155 **¹H NMR** **¹³C NMR****HPLC results:****(R)-155** ***rac*-155****Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 98/2****Column: Chiralpak AD-H column**

(R)-156 **¹H NMR** **¹³C NMR****HPLC results:****(R)-156** **rac-156** **Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 98/2****Column: Chiralpak AD-H column**

(R)-157 **¹H NMR** **¹³C NMR****HPLC results:****(R)-157*****rac*-157** **Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 98/2****Column: Chiralpak AD-H column**

(R)-158 **¹H NMR** **¹³C NMR****HPLC results:****(R)-158****rac-158** **Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 85/15****Column: Chiralpak OD-H column**

(R)-159 **¹H NMR** **¹³C NMR****HPLC results:****(R)-159** **rac-159****Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10****Column: Chiralpak OJ-H column**

(R)-160 **¹H NMR** **¹³C NMR****HPLC results:****(R)-160****rac-160** **Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 90/10****Column: Chiralpak OD-H column**

(R)-177 **¹H NMR****¹³C NMR****HPLC results:****(R)-177****rac-177** **Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 85/15****Column: Chiralpak OD-H column**

(R)-178 ^1H NMR ^{13}C NMR**HPLC results:****(R)-178****rac-178**

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 98/2

Column: Chiralpak AD-H column

(R)-179 **¹H NMR** **¹³C NMR****HPLC results:****(R)-179** **rac-179****Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 98/2****Column: Chiralpak AD-H column**

¹H NMR ¹³C NMR

HPLC results:

(R)-180**rac-180**

Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 98/2

Column: Chiralpak AD-H column

(R)-181 **¹H NMR** **¹³C NMR****HPLC results:****(R)-181*****rac*-181** **Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 98/2****Column: Chiralpak AD-H column**

HPLC results:

Separation conditions: Flow rate = 0.6 mL/min, Hexane/IPA = 98/2

Column: Chiralpak AD-H column

183 **¹H NMR** **¹³C NMR****HPLC results:***nonracemic-183**rac-183* **Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10****Column: Chiralpak AD-H column**

¹H NMR spectrum of compound 1 in CDCl₃. The x-axis represents the chemical shift in ppm, ranging from 0 to 9. The spectrum shows several peaks, with integration values indicated below the baseline and chemical shift values (δ) listed above the spectrum.

Chemical Shift (δ)	Integration
8.283	1.00
8.254	1.00
8.246	1.00
7.620	1.00
7.598	1.00
7.556	1.00
7.537	1.00
7.529	1.00
5.570	1.00
5.210	1.00
4.822	1.00
4.799	1.00
4.771	1.00
4.747	1.00
4.724	1.00
4.702	1.00
4.689	1.00
4.678	1.00
3.104	1.00
1.699	1.00
1.506	1.00
1.405	1.00
1.382	1.00
1.362	1.00
0.884	1.00
0.196	1.00
0.073	1.00
0.000	1.00
-0.134	1.00

[illegible]

Figure 1 displays two X-ray diffraction (XRD) patterns for poly(2,2,5-trimethyl-6-oxo-1,3-dioxane-5-carboxylic acid). The top plot shows the experimental data, and the bottom plot shows the simulated data. Both plots have intensity in arbitrary units (a.u.) on the y-axis and the diffraction angle 2θ in degrees on the x-axis.

The experimental XRD pattern (top) shows four distinct peaks at the following 2θ values (degrees): 18.947, 19.654, 21.654, and 24.000. The simulated XRD pattern (bottom) shows four distinct peaks at the following 2θ values (degrees): 18.992, 19.595, 21.531, and 24.703.

244

186 **¹H NMR** **¹³C NMR****HPLC results:****nonracemic-186** **rac-186****Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 95/5****Column: Chiralpak AD-H column**

187 **¹H NMR** **¹³C NMR****HPLC results:***nonracemic-187**rac-187* **Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 95/5****Column: Chiralpak AD-H column**

188 **¹H NMR** **¹³C NMR****HPLC results:***nonracemic-188**rac-188* **Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10****Column: Chiralpak AD-H column**

189

¹H NMR¹³C NMR

nonracemic-189

***rac*-189**

Column: Chiralpak AD-H column

^1H NMR ^{13}C NMR

HPLC results:

*nonracemic-190**rac-190*

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10

Column: Chiralpak AS-H column

191 **¹H NMR** **¹³C NMR****HPLC results:*****nonracemic-191******rac-191*** **Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 95/5****Column: Chiralpak AD-H column**

192 **¹H NMR** **¹³C NMR****HPLC results:***nonracemic-192**rac-192* **Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10****Column: Chiralpak AD-H column**

¹³C NMR

nonracemic-193

***rac*-193**

Column: Chiralpak AD-H column

Mass spectrum of the sample showing relative intensity versus m/z. The base peak is at m/z 77. Other significant peaks are labeled with their m/z values.

m/z	Relative Intensity (approx.)
88.217	10
86.715	5
77.1388	100
76.234	10
41.9165	15
41.830	10
29.1917	5
25.341	5
23.582	5
21.642	5
19.660	5
16.290	5
12.504	5

¹³C NMR

nonracemic-194

***rac*-194**

253

1H NMR spectrum of compound 1 in CDCl₃. The x-axis represents the chemical shift in ppm, ranging from 0 to 11. The y-axis represents the intensity. The spectrum shows several peaks: a broad peak at ~10.5 ppm (integration 1.00), a multiplet between 7.5-8.5 ppm (integration 0.55), a multiplet between 6.5-7.5 ppm (integration 0.52), and a complex set of peaks between 1.0-2.5 ppm (integrations 2.42, 1.62, 4.66, 6.93).

Mass spectrum of the sample showing relative intensity versus m/z. The base peak is at m/z 77.540. Other significant peaks are labeled with their m/z values.

m/z	Relative Intensity (approx.)
94.438	10
93.042	10
77.540	100
77.034	10
76.038	10
71.906	10
71.393	10
35.544	10
33.028	10
31.032	10
21.682	10
18.002	10
13.791	10
10.015	10
6.000	10

Top XRD pattern: Indexed to PDF card 01-060-0110 (Gd₂O₃). Peaks are labeled at 27.377, 29.405, 38.605, and 40.698.

Bottom XRD pattern: Indexed to PDF card 01-060-0110 (Gd₂O₃). Peaks are labeled at 28.642, 30.888, 37.714, and 39.638.

254

HPLC results:

nonracemic-196

rac-196

Separation conditions: Flow rate = 0.6 mL/min, Hexane/IPA = 98/2

Column: Chiralpak OB-H column

¹H NMR ¹³C NMR

HPLC results:

*nonracemic-197**rac-197*

Separation conditions: Flow rate = 0.6 mL/min, Hexane/IPA = 99/1

Column: Chiralpak AD-H column

206

¹H NMR

¹³C NMR

207

¹H NMR

¹³C NMR

199

¹H NMR ¹³C NMR

208

¹H NMR ¹³C NMR

¹H NMR spectrum of compound **1** in CDCl₃. The spectrum shows peaks in the aromatic region (6.8-7.4 ppm) and aliphatic region (1.0-1.7 ppm). Integration values are provided below the peaks.

Chemical Shift (ppm)	Integration
7.38	1.00
7.32	1.00
7.27	1.00
7.21	1.00
7.15	1.00
7.09	1.00
7.03	1.00
6.97	1.00
6.91	1.00
6.85	1.00
6.79	1.00
6.73	1.00
6.67	1.00
6.61	1.00
6.55	1.00
6.49	1.00
6.43	1.00
6.37	1.00
6.31	1.00
6.25	1.00
6.19	1.00
6.13	1.00
6.07	1.00
6.01	1.00
5.95	1.00
5.89	1.00
5.83	1.00
5.77	1.00
5.71	1.00
5.65	1.00
5.59	1.00
5.53	1.00
5.47	1.00
5.41	1.00
5.35	1.00
5.29	1.00
5.23	1.00
5.17	1.00
5.11	1.00
5.05	1.00
4.99	1.00
4.93	1.00
4.87	1.00
4.81	1.00
4.75	1.00
4.69	1.00
4.63	1.00
4.57	1.00
4.51	1.00
4.45	1.00
4.39	1.00
4.33	1.00
4.27	1.00
4.21	1.00
4.15	1.00
4.09	1.00
4.03	1.00
3.97	1.00
3.91	1.00
3.85	1.00
3.79	1.00
3.73	1.00
3.67	1.00
3.61	1.00
3.55	1.00
3.49	1.00
3.43	1.00
3.37	1.00
3.31	1.00
3.25	1.00
3.19	1.00
3.13	1.00
3.07	1.00
3.01	1.00
2.95	1.00
2.89	1.00
2.83	1.00
2.77	1.00
2.71	1.00
2.65	1.00
2.59	1.00
2.53	1.00
2.47	1.00
2.41	1.00
2.35	1.00
2.29	1.00
2.23	1.00
2.17	1.00
2.11	1.00
2.05	1.00
1.99	1.00
1.93	1.00
1.87	1.00
1.81	1.00
1.75	1.00
1.69	1.00
1.63	1.00
1.57	1.00
1.51	1.00
1.45	1.00
1.39	1.00
1.33	1.00
1.27	1.00
1.21	1.00
1.15	1.00
1.09	1.00
1.03	1.00
0.97	1.00
0.91	1.00
0.85	1.00
0.79	1.00
0.73	1.00
0.67	1.00
0.61	1.00
0.55	1.00
0.49	1.00
0.43	1.00
0.37	1.00
0.31	1.00
0.25	1.00
0.19	1.00
0.13	1.00
0.07	1.00
0.01	1.00

Mass spectrum of the sample showing relative intensity versus m/z . The base peak is at m/z 24. Other significant peaks are labeled at m/z 173.2284, 81.5280, 77.181, 75.215, 62.884, 44.465, 23.850, 22.795, and 11.894.

CCCCC(C(=O)OCC)(O)CN

Mass spectrum of the sample showing relative intensity versus m/z . The base peak is at m/z 77. Other significant peaks are labeled with their m/z values.

m/z	Relative Intensity (approx.)
173.06	10
89.02	10
77.03	100
75.04	10
73.05	10
71.06	10
69.07	10
67.08	10
55.09	40
41.10	10
39.11	10
37.12	10
35.13	10
33.14	10
31.15	10
29.16	10
27.17	10
25.18	10
23.19	10
21.20	10
19.21	10
17.22	10
15.23	10
13.24	10
11.25	10
9.26	10
7.27	10
5.28	10
3.29	10
1.30	10

259

[illegible]CCOC(=O)C(O)C(c1ccccc1)C(N(=O)=O)C

¹H NMR spectrum of compound 10a in CDCl₃. The spectrum shows several peaks in the aromatic region (6.5-7.5 ppm) and a complex set of peaks in the aliphatic region (1.2-2.0 ppm). Integration values are provided below the peaks.

Chemical Shift (ppm)	Integration
7.48	1.00
7.47	1.00
7.46	1.00
7.45	1.00
7.44	1.00
7.43	1.00
7.42	1.00
7.41	1.00
7.40	1.00
7.39	1.00
7.38	1.00
7.37	1.00
7.36	1.00
7.35	1.00
7.34	1.00
7.33	1.00
7.32	1.00
7.31	1.00
7.30	1.00
7.29	1.00
7.28	1.00
7.27	1.00
7.26	1.00
7.25	1.00
7.24	1.00
7.23	1.00
7.22	1.00
7.21	1.00
7.20	1.00
7.19	1.00
7.18	1.00
7.17	1.00
7.16	1.00
7.15	1.00
7.14	1.00
7.13	1.00
7.12	1.00
7.11	1.00
7.10	1.00
7.09	1.00
7.08	1.00
7.07	1.00
7.06	1.00
7.05	1.00
7.04	1.00
7.03	1.00
7.02	1.00
7.01	1.00
7.00	1.00
6.99	1.00
6.98	1.00
6.97	1.00
6.96	1.00
6.95	1.00
6.94	1.00
6.93	1.00
6.92	1.00
6.91	1.00
6.90	1.00
6.89	1.00
6.88	1.00
6.87	1.00
6.86	1.00
6.85	1.00
6.84	1.00
6.83	1.00
6.82	1.00
6.81	1.00
6.80	1.00
6.79	1.00
6.78	1.00
6.77	1.00
6.76	1.00
6.75	1.00
6.74	1.00
6.73	1.00
6.72	1.00
6.71	1.00
6.70	1.00
6.69	1.00
6.68	1.00
6.67	1.00
6.66	1.00
6.65	1.00
6.64	1.00
6.63	1.00
6.62	1.00
6.61	1.00
6.60	1.00
6.59	1.00
6.58	1.00
6.57	1.00
6.56	1.00
6.55	1.00
6.54	1.00
6.53	1.00
6.52	1.00
6.51	1.00
6.50	1.00
6.49	1.00
6.48	1.00
6.47	1.00
6.46	1.00
6.45	1.00
6.44	1.00
6.43	1.00
6.42	1.00
6.41	1.00
6.40	1.00
6.39	1.00
6.38	1.00
6.37	1.00
6.36	1.00
6.35	1.00
6.34	1.00
6.33	1.00
6.32	1.00
6.31	1.00
6.30	1.00
6.29	1.00
6.28	1.00
6.27	1.00
6.26	1.00
6.25	1.00
6.24	1.00
6.23	1.00
6.22	1.00
6.21	1.00
6.20	1.00
6.19	1.00
6.18	1.00
6.17	1.00
6.16	1.00
6.15	1.00
6.14	1.00
6.13	1.00
6.12	1.00
6.11	1.00
6.10	1.00
6.09	1.00
6.08	1.00
6.07	1.00
6.06	1.00
6.05	1.00
6.04	1.00
6.03	1.00
6.02	1.00
6.01	1.00
6.00	1.00
5.99	1.00
5.98	1.00
5.97	1.00
5.96	1.00
5.95	1.00
5.94	1.00
5.93	1.00
5.92	1.00
5.91	1.00
5.90	1.00
5.89	1.00
5.88	1.00
5.87	1.00
5.86	1.00
5.85	1.00
5.84	1.00
5.83	1.00
5.82	1.00
5.81	1.00
5.80	1.00
5.79	1.00</

174.003
173.190

88.851
87.141
77.083
77.063
74.851
74.831
63.144
62.972

23.387
23.367
14.604
14.584
13.090
12.624

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

CC(C)(O)C1=CC=C([N+](=O)[O-])C=C1[illegible]

148.269
147.724
144.295
144.104
143.714
129.704
129.615
128.905
128.899
87.895
84.782
70.538
69.281
16.542
11.891

261

[illegible]

Mass spectrum of compound 10. The x-axis represents the mass-to-charge ratio (m/z) from 10 to 190, and the y-axis represents relative intensity from 0 to 100. The base peak is at m/z 77. Other labeled peaks include m/z 87, 79, 69, 55, 76, 62, 72, 80, 31, 46, 27, 63, 27, 37, 27, 43, 22, 44, 13, 41, 13, 30, and 12.

CC(C1=CC=CC=C1O)C(O)C2=CC=CC=C2

¹H NMR spectrum of compound 10 in CDCl₃. The spectrum shows peaks from 0 to 8 ppm. Key features include a triplet at ~1.1 ppm (3H, integration 2.77), a multiplet at ~1.5 ppm (3H, integration 3.00), a multiplet at ~3.1 ppm (2H, integration 2.00), a multiplet at ~4.8 ppm (2H, integration 1.00), a multiplet at ~5.2 ppm (2H, integration 1.00), a multiplet at ~6.8 ppm (2H, integration 1.97), and a multiplet at ~7.4 ppm (2H, integration 1.96). Solvent peaks for CDCl₃ are visible at 7.26, 7.26, and 7.26 ppm.

151.304
150.787
143.513
142.522

118.625
116.525
110.567
109.715
108.165

86.331
85.306
77.996
77.683
69.453
68.314

18.149
17.192
13.122

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

262

217

¹H NMR ¹³C NMR