CHAPTER 1
INTRODUCTION

1.1 Overviews of TADDOLs

TADDOLs ($\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol) were firstly prepared by Seebach *et. al.* in 1987, which contain two adjacent diarylhydroxymethyl groups in a *trans* relationship on a 1,3-dioxolane ring as shown in Figure 1.[1]

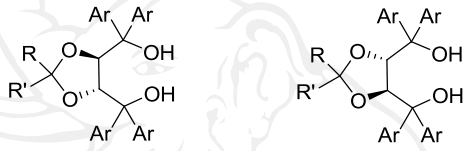
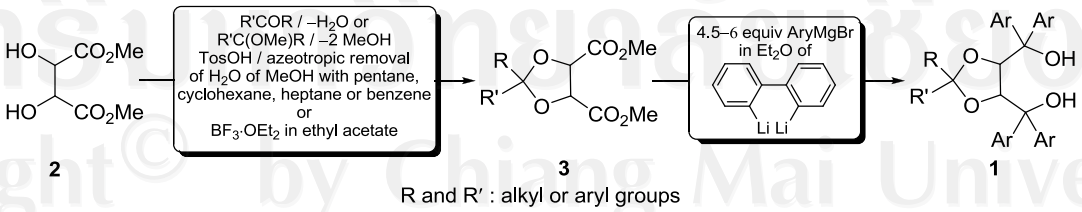


Figure 1 General structure of TADDOLs

The TADDOLs is readily obtained by the treatment of dimethyl or diethyl tartrate with the appropriate aldehyde or ketone under acid catalysis and azeotropic removal of water. The product is reacted with aromatic Grignard reagents in diethyl ether or organolithium (Scheme 1). A related and often more effective method is acid-catalyzed transacetalization, in which dimethyl tartrate is treated with the dimethyl acetal or ketal of some aldehyde or ketone with concurrent removal of the resulting methanol. Rather than resorting to distillation, one can also remove the by-product methanol or water by treatment with an equimolar amount of $BF_3{\cdot}OEt_2$.[1]



Scheme 1 Preparation of TADDOLs.

Additionally, TADDOLs analogues can be synthesized by derivatization or replacement of one or both TADDOL OH-groups. The oxygen heteroatoms of TADDOLs may be functionalized with alkyl, aryl or silyl ethers, phosphonite, sulfites or phosphoric acid esters. These heteroatoms may be replaced by other heteroatoms or functional groups, such as N, P, OOH, S, F, Cl, Br, with and without formation of five-, six-, and seven-membered rings.[2] The structures of these TADDOLs analogus are shown in Figure 2.

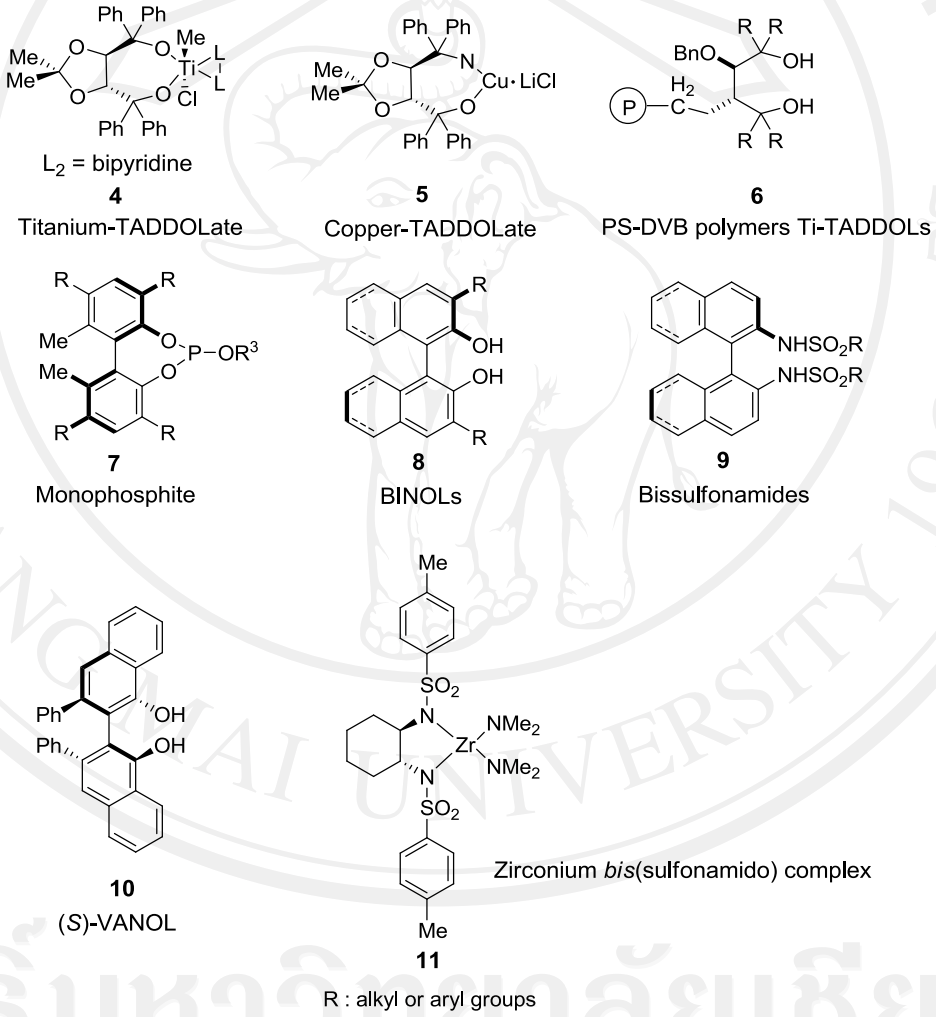


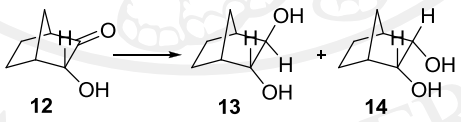
Figure 2 Examples of TADDOLs, their derivatives and TADDOLs analogues[3-7]

TADDOLs, their derivatives and TADDOLs analogues are employed as stoichiometric chiral reagents, chiral ligands for both stoichiometric chiral reagents and catalytically asymmetric reaction as well as, more recently, chiral organocatalysts. TADDOLs, their derivatives and TADDOLs analogues are widely

used in asymmetric reactions. For example, nucleophilic addition to C=O bonds, nucleophilic conjugate addition to electron-deficient C=C double bonds, nucleophilic substitutions, cycloaddition reaction, oxidation and reduction reactions. Moreover, the TADDOLs were used as chiral ligands for some metal ions such as Ti(IV), which were effective catalysts in Diels–Alder reaction[4,8], Aldol reaction[9] and Pinacol coupling reaction[10], *etc*. In addition, the TADDOLs can be used as the chiral auxiliaries for purification of the enantiomeric compound[11, 12] and other applications are illustrated in the literature reviews (Sec. 1.4).

1.2 Asymmetric reaction

Asymmetric reaction is the reaction in which a reactant is converted into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amount. The stereoisomeric product could be enantiomeric or diastereomeric, they will be chiral and nonracemic with rare exception. A few reactions give achiral product have to be called asymmetric reaction as shown in Scheme 2. The reduction of ketone **12** gives chiral glycol **13** and glycol **14**, respectively. If the reaction were 100% stereoselective giving the achiral product **14**, the reaction would still be considered an asymmetric reaction.[13]

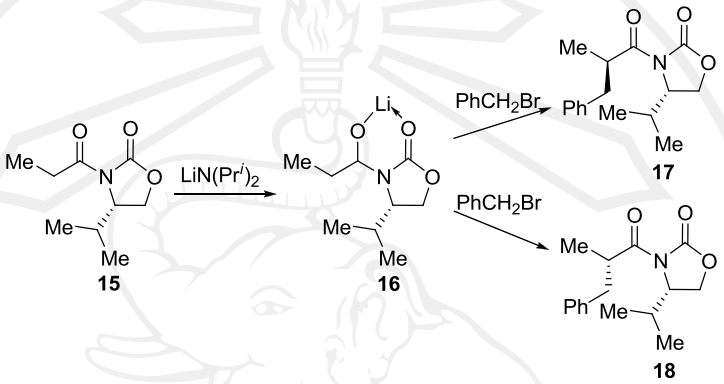


Scheme 2 The reduction reaction of the chiral hydroxyl ketone **12**.

Recently, most modern drugs provided to patients are enantiomeric compounds for activation specifically target molecules. Thus, stereomeric reactant, chiral catalyst and chiral auxiliary of asymmetric organic reactions to provide enantiomerically or diastereomerically enriched products in the central importance to modern synthetic and pharmaceutical chemistry.[14]

If the reactant itself is chiral and nonracemic, creation of another chiral center using this reactant provides the possibility of diastereomeric products. In case of the products themselves are diastereomers, the transition states lead to diastereomeric and a diastereoselective reaction should expected. This principle is illustrated in Scheme

3 which shows two possible alternatives for alkylation of the chiral enolate **16**. The electrophile is attacked from above the plane of the enolate, the product will be compound **17**, but this one is attacked from below will lead to compound **18**, which is diastereomer with **17**. This reaction is diastereomeric excess ratio of **17**:**18** which is 99:1.[14]

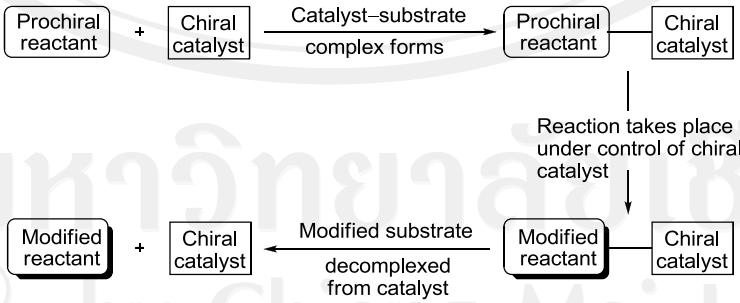


Diastereomeric excess (*d.e.*) = major diastereomer(%) – minor diastereomer(%)

= x1(%) – x2(%) = 99 – 1 = 98%

Scheme 3 The alkylation reaction of the chiral enolate **16**.

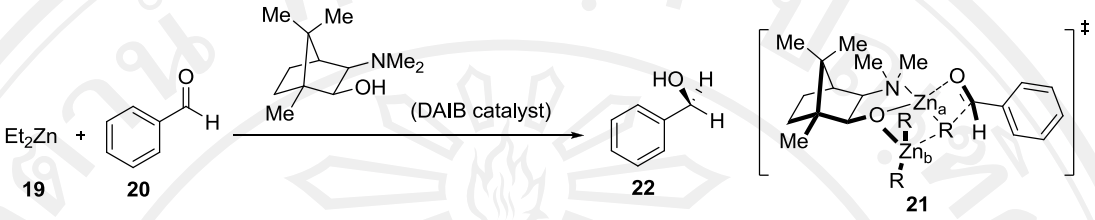
A chiral or nonracemic catalyst can be used for asymmetric reaction. The reaction in which the new chiral center is created only occurs when the catalyst brings together the reagent and reactant. The catalyst is involved in the transition states which lead to the enantiomeric or diastereomeric products. A schematic representation of symmetric catalysis is shown in Scheme 4.[14]



Scheme 4 The schematic representation of asymmetric catalysis.

For example of asymmetric catalysis is the alkylation of diethylzinc to benzaldehyde promoted by chiral amino alcohol (DAIB catalyst) as a chiral catalyst.

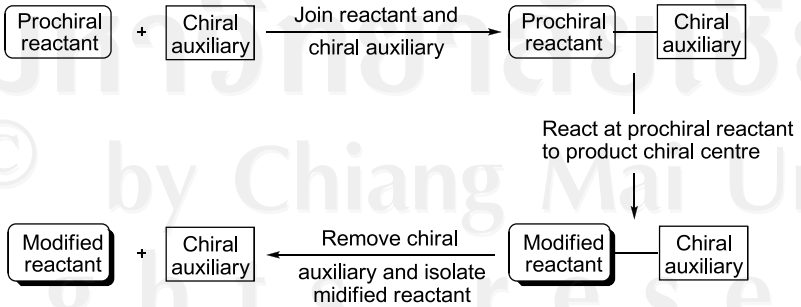
This reaction occurs *via* the transition state **21** to give the *S*-configurated product alcohol **22** in 97% yield and 98% enantiomeric excess as illustrated in Scheme 5.[15]



Scheme 5 The alkylation of diethylzinc to benzaldehyde promoted by DAIB catalyst.

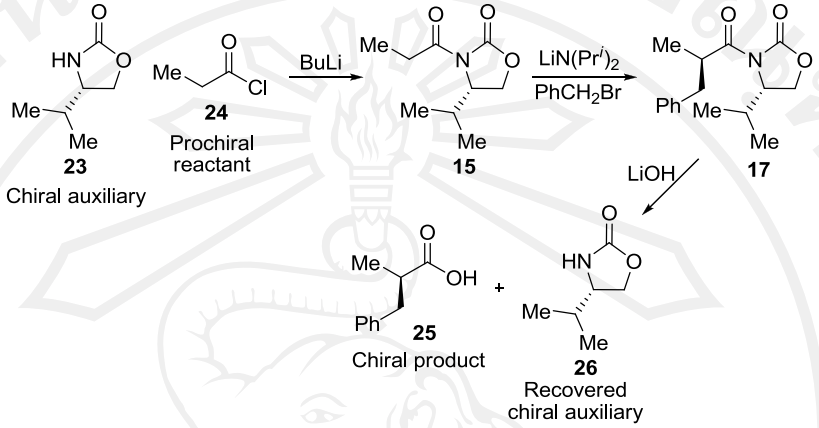
Another general approach to asymmetric reaction involves the use of chiral auxiliaries. The overall strategy is shown in Scheme 6 and has clear similarities with the asymmetric catalysis cycle as shown in Scheme 4. In this approach, the prochiral reactant is attached to a chiral, nonracemic group, known as the chiral auxiliary, prior to reaction. The two or more possible products become enantiomeric or diastereomeric and one should formed in excess. The major product can be isolated and the chiral auxiliary can be removed to provide the chiral nonracemic product. The performance of chiral auxiliary to be practically useful are listed below.[14]

1. Enantiomerically pure
2. Cheap and easy to obtain in high quantity
3. Easy to be attached to a reactant
4. High control of stereoselectivity and predicable
5. Easy to purify major product
6. Easily removal without loss of enantiomeric or diastereomeric purity
7. Easily separated from product and recovered



Scheme 6 The schematic representation of asymmetric chiral auxiliary.

The oxazolidinone chiral auxiliary provides an excellent example of what can be achieved using chiral auxiliary. A simple pathway which uses the oxazolidinone chiral auxiliary in the alkylation reaction to give the major product is shown below.[14]



Scheme 7 The simple pathway of the alkylation reaction of prochiral reactant **24** gives the major product.

1.3 Optical activity of organic compounds

1.3.1 The polarimeter

The device that is used for measuring the effect of optically active compounds on plane-polarized light is a polarimeter. The polarimeter diagram is shown in Figure 3. The principle working parts of a polarimeter are a light source (usually a sodium lamp), a polarizer, a sample tube containing organic molecules, an analyzer and a scale for measuring the number of degree that the plane of polarized light has been rotated. A solution of optically active organic molecule is placed in a sample tube, plane-polarized light is passed through the tube, and rotation of the plane occurs. The light then goes through an analyzer. By rotating the analyzer until light passes through it, the observer can detect the maximum amount of light passing through. The amount of rotation observed is denoted by α (Greek alpha) and is expressed in degree.[16,17]

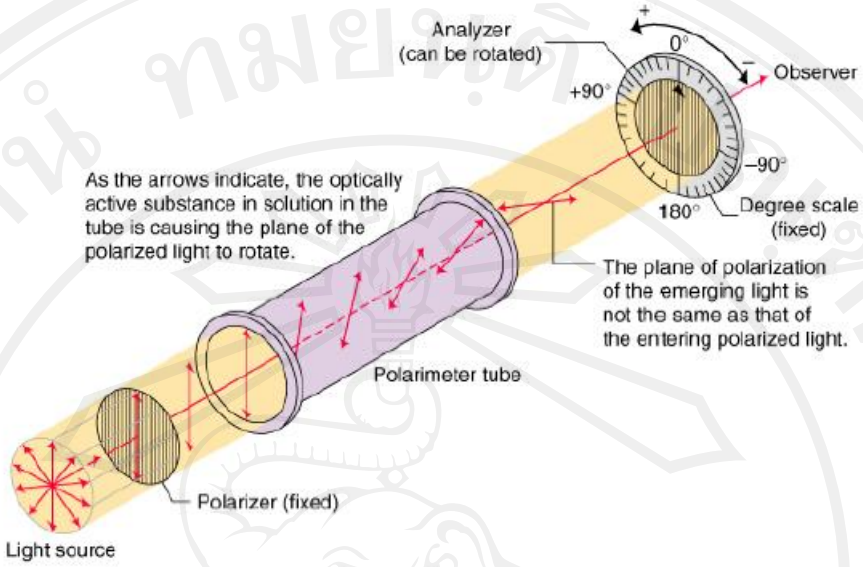


Figure 3 Polarimeter[17]

In addition to the determination of the rotation extent, the observer will have to rotate the axis of the analyzer in either a clockwise or counterclockwise direction. If the analyzer is rotated in clockwise direction, the rotation, α (measured in degree), is said to be positive (+). If the rotation is counterclockwise, the rotation is said to negative (–). A substance that rotated plane-polarized light in the clockwise direction is also said to be dextrorotatory, and one that rotated plane-polarized light in counterclockwise direction is said to be levorotatory.[16,17]

1.3.2 Specific rotation

The number of degree's rotation observed in a polarimetry experiment depends on the structure of the sample molecules and on the number of molecules encountered by the light beam. The number of molecules encountered depends, in turn, on the sample concentration and the sample path length. If the concentration of the sample in a tube is doubled, the observer rotation is doubled. If the concentration is kept constant but the length of sample tube is doubled, the observed rotation is doubled. In order to place measured rotation on a standard basis, chemistry calculate a quantity called the specific rotation[16,17], $[\alpha]$, by the following equation:[16,17]

$$[\alpha] = \frac{\alpha}{c \cdot l}$$

where $[\alpha]$ = the specific rotation

α = the observed rotation

c = the concentration of the solution in gram per milliliter of solution (or density in g mL^{-1} for near liquids)

l = the length of the tube in decimeter

The specific rotation also depends on the temperature and the wavelength of light that is employed. Specific rotation are reported so as to incorporate these quantities as well.[17] A specific rotation might be given as follows:

$$[\alpha]_D^{25} = +3.12°$$

This mean that the D line of sodium lamp (λ = 589.6 nm) was used for the light, that a temperature of 25 °C was maintained, and that a sample containing, and a sample containing 1.00 g mL^{-1} of the optically active substance, in a 1 dm tube, produced a rotation of 3.12° in a clockwise direction.[17]

1.3.3 Enantiomeric excess

A sample of an optically active substance that consists of a single enantiomer is said to be enantiomerically pure or to have enantiomeric excess of 100%. For example, an enantiomerically pure sample of (+)-(*S*)-2-butanol shows a specific rotation of +13.52° ($[\alpha]_D^{25}$=+13.52°). On the other hand, a sample of (+)-(*S*)-2-butanol that contains less than an equimolar amount of (–)-(*R*)-2-butanol will show a specific rotation that is less than +13.52° but greater than 0°. Such a sample is said to have an enantiomeric excess less than 100%.[17] The enantiomeric excess (*ee*) is defined below.

$$\%\text{enantiomeric excess} = \frac{\text{moles of one enantiomer} - \text{moles of one enantiomer}}{\text{total moles of both enantiomers}} \times 100$$

In addition, the enantiomeric excess can be calculated from optical rotation as shown below. This equation should be applied to a single enantiomer or to mixtures of enantiomers only. It is not applicable to mixtures in which some other compound are present.[17]

$$\%\text{enantiomeric excess} = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomer}} \times 100$$

For instance, the mixture of the 2-butanol enantiomers showed a specific rotation of +6.76°. The enantiomeric excess of (+)-(*S*)-2-butanol can be calculated below

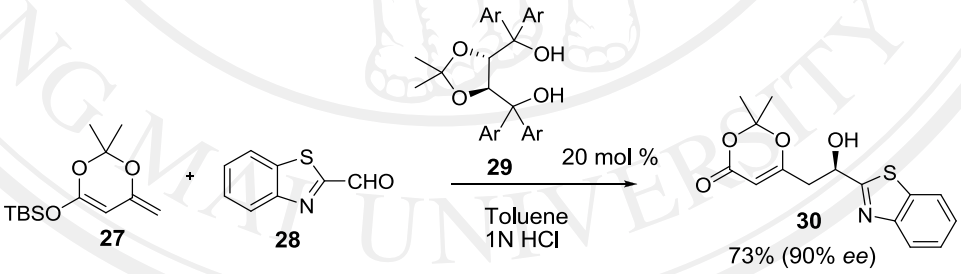
$$\%\text{enantiomeric excess} = \frac{+6.67^{\circ}}{+13.52^{\circ}} \times 100 = 50\%$$

Also, the enantiomeric excess of the (+)-(*S*)-2-butanol is 50%, it means that 50% of the mixture consist of the (+) enantiomer (the excess) and the other 50% consist of the racemic form.[17]

1.4 Literature reviews

1.4.1 TADDOLs

In 2005, Vijaya *et al.*[18] had demonstrated the successful use of hydrogen-bonding catalysis (TADDOL catalyst) in enantioselective vinylogous Mukaiyama aldol reaction (VMA), as shown in Scheme 8. The reaction is the most effective with highly reactive aldehyde **28** and gives the expected product **30** in good to excellent yields and *ee* values as high as 99%.

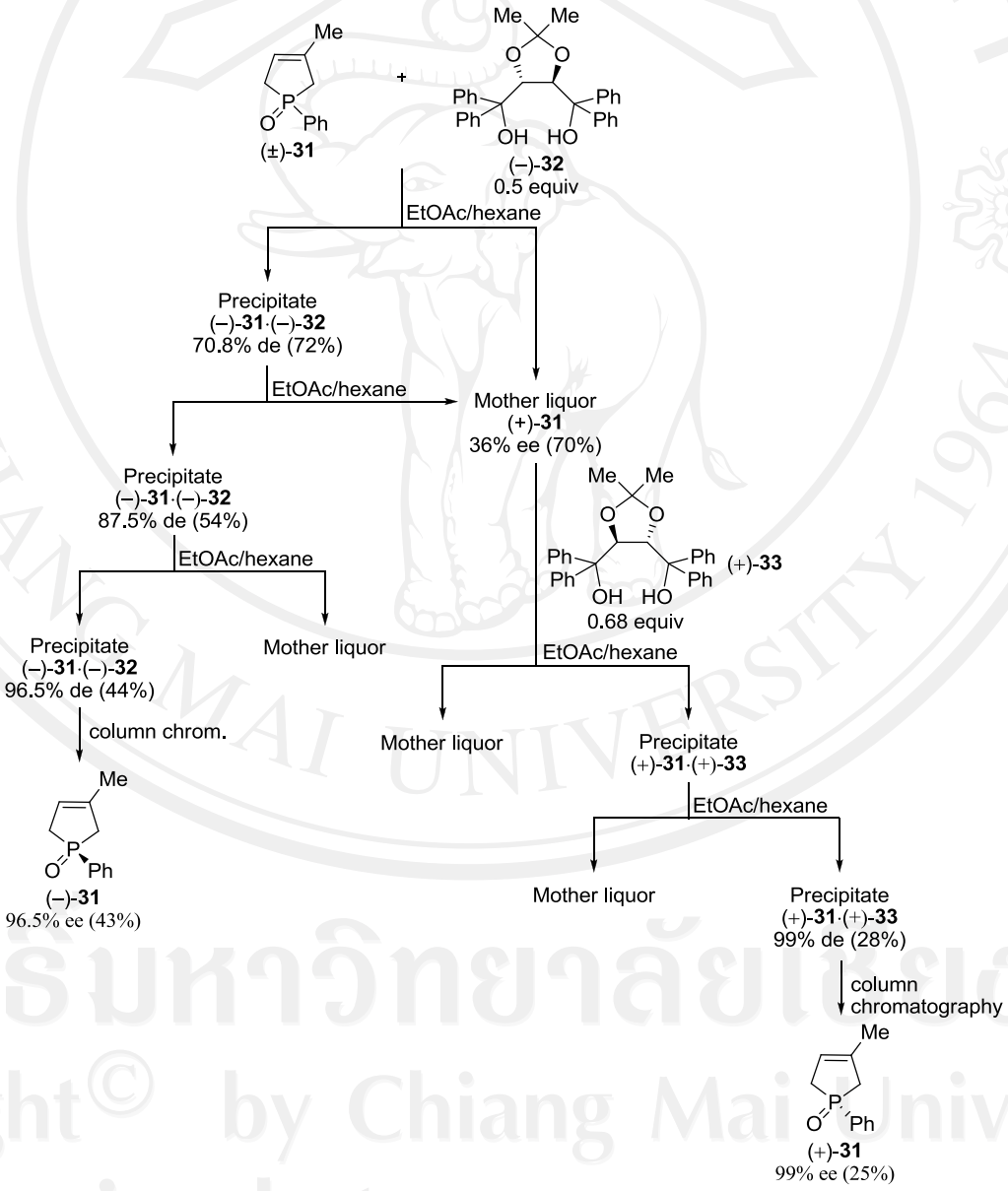


Scheme 8 Enantioselective vinylogous Mukaiyama aldol reaction.

In 2006, Novak and co-workers[12] separated the antipodes of 1-phenyl-3-methyl-3-phospholene-1-oxide ((±)-**31**) in high enantiomeric excess by resolution *via* formation of diastereomeric complex with (–)-TADDOL **32** and (+)-TADDOL **33** (Scheme 9). The racemic 1-phenyl-3-methyl-3-phospholene-1-oxide ((±)-**31**) was resolved by adding half equivalence of (–)-TADDOL **32** to its hot ethyl acetate solution and precipitating (–)-**31**·(–)-**32** by addition of hexane. This precipitate was recrystallized in 1:5 mixture of ethyl acetate-hexane to give (–)-**31**·(–)-**32** with an

excellent enantiomeric excess based on compound (±)-**31**. After flash chromatography on a silica gel, 96.5% *ee* of (–)-**31** was recovered in 43% yield.

To obtain the enantiomerically pure (+)-**31**, the mother liquors of the crystallization and the first recrystallization were combined. The combined portion was added (+)-TADDOL **33** in hot ethyl acetate, crystal of complex (+)-**31**·(+)-**33** were obtained after the addition of hexane. After flash column chromatography using silica gel, (+)-**31** of 99% *ee* was obtained in 27% yield based on compound (±)-**31**.

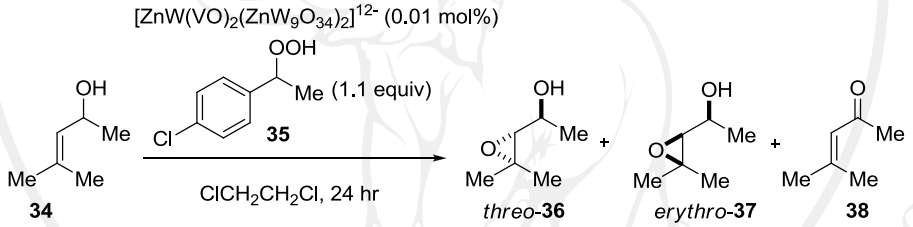


Scheme 9 The optical resolution of 1-phenyl-3-methyl-3-phospholene-1-oxide with TADDOLs.

1.4.2 TADDOLs–hydroperoxide

Waldemar and co-workers[19] used the TADDOLs–hydroperoxide (TADOOH) as a catalyst in epoxidation reaction of allylic alcohol, in 2003. They used medityol (**34**) as the model substrate for the assessment of the chemoselectivity (epoxidation versus allyic oxidation) in the metal catalyzed oxidation, and the racemic [1-(4-chlorophenyl)]ethylhydroperoxide (**35**) as oxygen donor atom. They found that the oxovanadium(IV)–substituted POM, namely $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$ or OV(IV)-POM, was the most reactive and selective catalyst for the epoxidation of allylic alcohol (Table 1).

Table 1 Catalytic oxidation of mesitylol (**34**) by the various transition-metal–substituted polyoxometalates with racemic hydroperoxide



Entry	Metal	Temp[b] (°C)	Convn[a] (%)	mb[a] (%)	Selectivity[a] **36:37**	Selectivity[a] Diastereo (*threo*:*erythro*)
1	OV(IV)	20	>95	>95	>95:5	91:9
2	OV(IV)	50[c]	>95	>95	>95:5	91:9
3	Mn(II)	50	85	85	90:10	90:10
4	Ru(III)	50	94	70	70:30	90:10
5	Fe(III)	50	18	95	90:10	94:6
6	Zn(II)	50	8	90	85:15	95:5
7	Pd(II)	50	18	92	93:7	92:8
8	Pt(II)	50	12	95	88:12	95:5

[a] Conversion (allylic alcohol), material balance and product ratios were determined by ^{1}H-NMR analysis of the crude reaction miture, ca 5% error of the stated value.

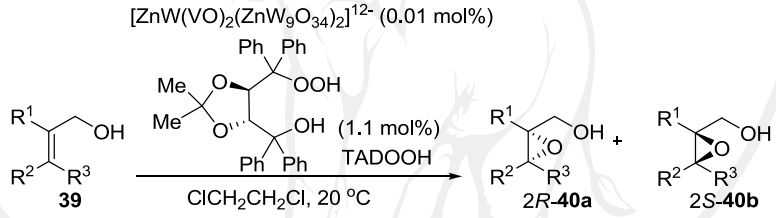
[b] For entry 3-8, 0.02 mol% of catalyst loading was employed: no conversion was observed at 20 °C.

[c] Reaction time was 6 h.

Also, the oxovanadium(IV)–substituted POM and TADDOLs–hydroperoxide (TADOOH) are used as the catalytic enantioselective epoxidation of the primary

allylic alcohols. These results are summarized in Table 2. The TADOOH was used as the chiral oxygen source for the asymmetric epoxidation of a variety of allylic alcohols. The similarly *cis*-disubstituted allylic alcohols **39b** and **39c** (entries 5 and 6) were epoxidized in with as high enantioselective and yields as alcohol **39a** (entries 1-4), but for the *p*-anisyl derivative **39b**, the enantiomeric ratio dropped slightly to 85:15 (entry 6) from 92:8 (entry 5). The epoxidation of the monosubstituted allylic alcohols **39d** and **39e** afforded the corresponding epoxides in moderate enantioselectivies (entries 7 and 8), but in high yield. Compound **39f** was regioselectively epoxidized exclusively to the 2,3-epoxide in high yield, but in poor enantioselectivity (entry 9).

Table 2 Catalytic enantioselective epoxidation of the primary allylic alcohol by $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$ with TADOOH



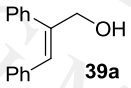
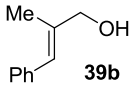
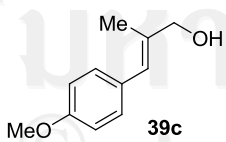
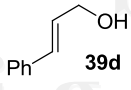
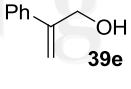
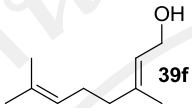
Entry	Allylic alcohol **39**	Time (h)	Convn (%)[b]	Yield **40b** (%)[c]	*er*[d]	Configuration[e]
1	 **39a**	48 (0°C)	40	90[f]	95:5	(–)-(2*R*,3*R*)
2	**39a**	30	>95	94	91:9	(–)-(2*R*,3*R*)
3[a]	**39a**	48	90	82	90:10	(–)-(2*R*,3*R*)
4	**39a**	6 (50 °C)	>95	92	85:15	(–)-(2*R*,3*R*)
5	 **39b**	30	>95	92	92:8	(+)-(2*R*,3*R*)
6	 **39c**	24	90	86	85:15	(+)- (2*R*,3*R*)
7	 **39d**	48	>95	88	75:25	(+)- (2*R*,3*R*)
8	 **39e**	36	95	93	72:28	(–)-(2*R*)

Table 2 Catalytic enantioselcective epoxidation of the primary allylic alcohol by $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$ with TADOOH (continued)

Entry	Allylic alcohol **39**	Time (h)	Convn (%)[b]	Yield **40b** (%)[c]	*er*[d]	Configuration[e]
9	 **39f**	24	>95	96	59:41	(+)- (2*R*,3*R*)

[a] Unless otherwise specified, all reactions were carried out in 1,2-dichloroethane at 20 °C with the particular allylic alcohol **39** (0.05 mmol), 1.1 equiv of TADOOH, and 0.01 mol% of $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$, except for entry 3, for which 0.002 mol% of catalyst loading was used.

[b] Determined by ^{1}H-NMR analysis of the crude reaction mixture, ca. 5% error of the stated values; material balances >95%.

[c] Isolated material after silica gel chromatography.

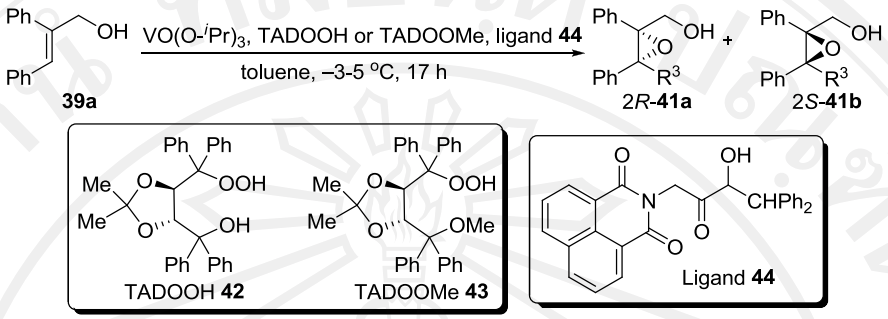
[d] Enantiomeric ratio (*er*), determined by HPLC analysis on a chiral column (Chiralcel OD), except entry 9, for which GC-MS analysis on a chiral β-TG column was employed.

[e] Assigned by direct comparison of the specific rotation, determined on a polarimeter, with the literature value.

[f] Based on 100% conversion of allylic alcohol.

In addition, Adam Waldemar and co-worker[20] studied the control of enantioselective through a hydrogen-bonding template in the catalyst. They used of the vanadium(V)–catalyzed asymmetric epoxidation of allylic alcohol by an optically active TADDOL–derived hydroperoxides (TADOOH **42** and TADOOMe **43**) as the asymmetric controller. They found that the TADOOH **42** has a hydroxyl group which can chelate *via* hydrogen–bonding to oxyvanadyl group to provide (*R*)-epoxide in 72% *ee*. On the other hand, TADOOMe **43** does not have any hydrogen-bonding to oxyvanadyl group to give the same product in just 20% *ee*. Therefore, hydrogen bonds between TADDOL–modified peroxide and oxyvanadyl group can control enantioselectivity in the reaction (Table 3).

Table 3 Vanadium-catalyzed epoxidation of allylic alcohol with optically active hydrogen peroxide



Entry	Hydroperoxide	Convn (%)[b]	*ee* (%)[c]	Confign
1	TADOOH **42**	>95	72	(2*R*,3*R*)-(–)
2	TADOOMe **43**	18	20	(2*R*,3*R*)-(–)

[a] All reaction were carried out at 5 °C with 0.15-0.70 mmol of allylic of allylic alcohol, 1.5 equiv of hydroperoxide and 5 mol% of vanadium catalyst, prepare in situ by mixing $VO(O\text{-}^{i}Pr)_3$ and ligand **44** in a molar ratio 1:1.5; reaction time 17 h.

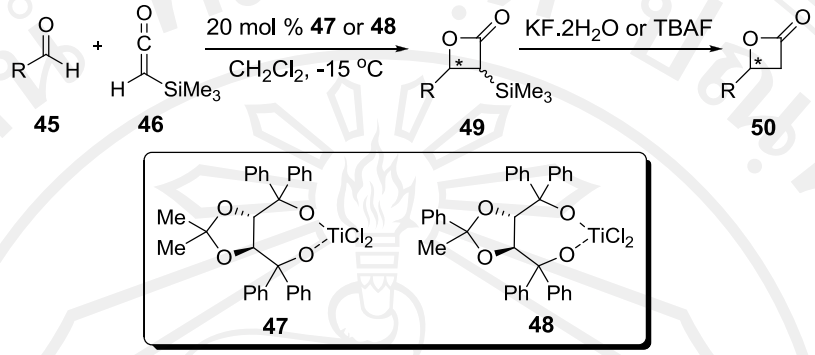
[b] Conversion of the allylic alcohol was determined by ^{1}H-NMR analysis of the crude reaction mixture with dimethyl isophtalate as internal standard (error ±5% of the stated values), material balances >95%.

[c] Determined by HPLC analysis of the isolated, purified epoxides on a chiral column (Chiralcel OD); averaged values of several runs.

1.4.3 Titanium–TADDOLs complex

In 1998, Yang and Romo[21] used TADDOLs Lewis acids as catalysts for asymmetric [2+2] cycloaddition reaction of various aldehydes and TMS–ketene. The results showed that, the tartrate derived dichlorotitanium–TADDOL catalysts **47** and **48** provided the best results. The various aldehydes and trimethylsilylketene were studied for this reaction (Table 4). Unfortunately, the intermediate **49** were not successfully isolated. After the determination of the diastereoselectivity based on ^{1}H MNR of the crude reaction, the mixture of *cis* and *trans* isomers was directly treated with $KF.2H_2O$ or TBAF and enantiomeric purities of *β*-lactones **50** were determined by GC or HPLC.

Table 4 Catalytic, asymmetric [2+2] cycloaddition reaction of various aldehydes and TMS–ketene



Entry	R	Lewis acid	*cis*/*trans* (**49**)[a]	Yield (%)[b]	rxn time (h)[c]	% *ee* (**50**)[d]
1	*n*-Bu	**47**	34:1	49	24	41
2	$PhCH_2$	**47**	9:1	58	24	9
3	*c*-C_6H_{11}	**47**	>19:1[e]	66	24	80
4	4-NO_2Ph	**47**	>19:1[e]	71	48	21
5	$PhCH_2CH_2$	**47**	>19:1[e]	78	73	41[f] 34[g]
6	$PhCH_2CH_2$	**48**	>19:1[e]	78	72	27
7	$BnOCH_2CH_2CH_2CH_2$	**47**	19:149	76	76	45[f] 2[h]
8	$BnOCH_2CH_2CH_2CH_2$	**48**	>19:1[e]	66	64	43

[a] Ratios determined on the crude reaction mixtures by ^{1}H-NMR (200 or 300 MHz).

[b] Yield is for 2 steps.

[c] Reaction time is for the [2+2] cycloaddition.

[d] % *ee* determined by chial HPLC (chiralcel OD) or chiral GC (TBS-cyclodextrin).

[e] The minor *trans* diastereomer could not be detected by ^{1}H NMR (200 or 300 MHz).

[f] From pure *cis*-silylated-*β*-lactones **49**.

[g] From a mixture of *β*-lactones **49** (*cis*/*trans* = 1:1.2).

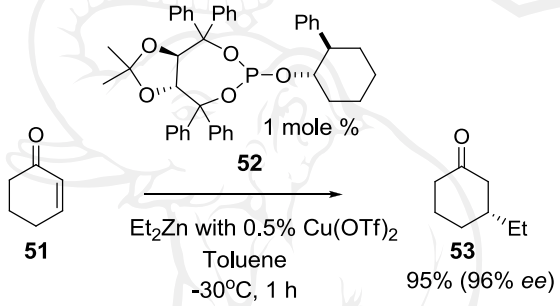
[h] From a mixture of *β*-lactones **49** (*cis*/*trans* = 1.6:1).

Cis isomers of the *α*-silylated-*β*-lactones (**49**) were formed almost exclusively with the exception of phenyllacetaldehydes (entry 2, Table 4). The reactions which have the moderate to good yield for the two steps were obtained dependent on the reaction time for the cycloaddition. In general, reaction times of 48-76 h led to consistent yields of 66-78%. Although they were unable to obtain the pure

trans-β-lactones in most cases, it appears that the enantioselectivity is highest for the *cis*-β-lactones (entries 5 and 7, Table 4).

1.4.4 Phosphorus–TADDOLs complex

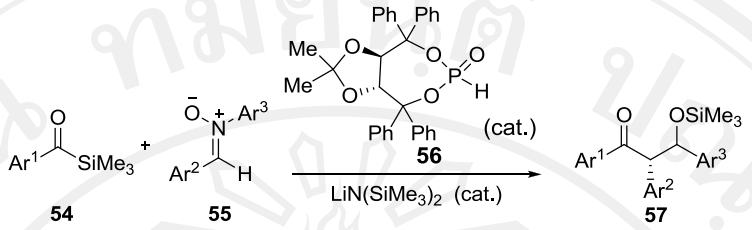
In 1998, Alexakis *et al.*[22] studied the asymmetric conjugation addition of diethylzinc to enone with chiral phosphorus ligand derived from TADDOL which was used the chiral phosphorus ligand based on TADDOL as compound **52** for the conjugate addition of diethylzinc to cyclohexenone to give compound **53** in high yield (95%) and with excellent enantioselectivity (96% *ee*) as shown in Scheme 10.

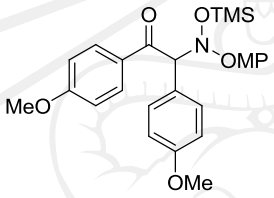
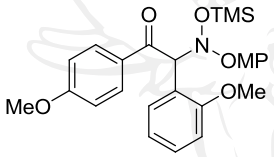
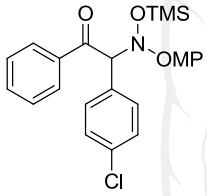
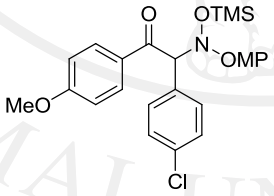


Scheme 10 Asymmetric conjugation addition with chiral phosphorus ligand based on TADDOL.

After that, Mary and co-workers[23] studied the enantioselective metallophosphite–catalyzed *c*-acylation of nitrones in 2007. This communication reported the details of the asymmetric metallophosphite–catalyzed 1,3-silylacylation of nitrones as shown in Table 5. In these cases, the reaction was preceded with good isolated yield (94%) and with high enantioselectivity (up to 97% *ee*). All products were purified by flash column chromatography.

Table 5 Asymmetric nitrone acylation[a]



Entry	Products		Yield (%)[b]	er[c]
1		**57a**	94	98.5:1.5
2		**57b**	86	97:3
3[d]		**57c**	82	98.2
4[d]		**57d**	93	98.5:1.5

[a] Ar^1 $C(O)SiMe_3$ (1.5 equiv), $Ar^2CHN(O)Ar^3$ (1.0 equiv), (*R*,*R*)-TADDOL–phosphite (0.25 equiv), $LiN(SiMe_3)_2$ (0.23 equiv) in 6 mL of 2-MeTHF at room temperature unless otherwise stated. OMP = *o*-MeOPh.

[b] Yield of isolated, analytically pure **57** as judged by ^{1}H-NMR spectroscopy and combustion analysis.

[c] Enantiomeric ratio determined by CSP-SPC.

[d] Phosphite (0.20 equiv), LHMDS (0.17 equiv).

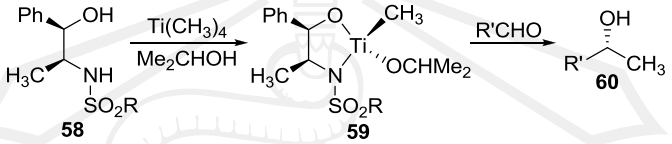
1.4.5 Synthesis and application of aminoalcohols

1.4.5.1 1,2-aminoalcohols

In 1986, Reetz and co-workers[24] examined *N*-sulfonylation of norephedrine by using RSO_2Cl, triethylamine and diethyl ether afforded good yields of the novel sulfonamides **58**. These compounds were treated with $Ti(CH_3)_4$ followed

by the addition of isopropanol to give compound **59** which is the intermediate dimethyltitanium compound. The stereoisomer of compound **59** is only a formal representation. After that the authors tested compound **59** in the addition reaction with aldehydes to give products **60** as shown in Table 6. In all cases these products **60** have the *R*-configuration as the major product.

Table 6 Enantiomeric addition to aldehydes of dimethyltitanium compound

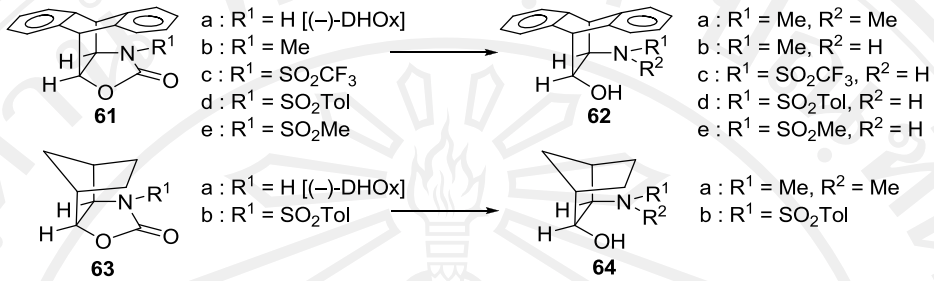


Entry	R	R′	Yield of **60** (%)[a]	*ee* (%)
1	*p*-tolyl	phenyl	78	85
2	*p*-tolyl	*o*-nitrophenyl	91	79
3	*p*-tolyl	1-naphthyl	96	81
4	methyl	Phenyl	89	62
5	mesityl	Phenyl	93	88
6	mesityl	*o*-nitrophenyl	86	90
7	mesityl	*o*-methylphenyl	75	88
8	mesityl	1-naphthyl	92	90
9	mesityl	*n*-heptyl	81	60
10	*p*-tolyl	isobutyl	53	43
11	*p*-tolyl	1-(ethyl)propyl	64	76
12	mesityl	*n*-heptyl	82	58
13	mesityl	1-(ethyl)propyl	70	31

[a] Isolated yield.

In 1992, Kimura *et al.*[25] demonstrated the successful preparation for 2-aminoalcohol or *β*-aminoalcohol (compound **62** and **64**). The compound **62** and **64** are readily obtainable from lactam **61** and **63** by ring-opening reaction, respectively (Scheme 11). The ring-opening reaction of the *N*-methyl, *N*-tosyl, *N*-mesyl and *N*-triflyl(trifluoromethanesulfonyl)-2-oxazolidinones (**61b**–**61e** and **63b**) smoothly proceeded under hydrolytic condition with barium hydroxide and cesium carbonate as bases to give quantitative yield of the *N*-methyl (**62b**) and the corresponding *N*-sulfonyl-2-aninoalcohols (**62c**–**62e** and **64b**). The *N*,*N*-dimethyl derivatives (**62a** and

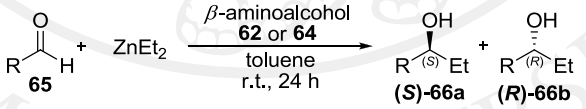
64a) were readily obtained by reductive cleavage of the *N*-methyl-2-oxazolidinones with $LiAlH_4$ of dimethylation of the parent aminoalcohol.



Scheme 11 The ring-opening reaction of compounds **61** and **63** give *β*-aminoalcohols **62** and **64**.

Additionally, these *β*-aminoalcohol compounds were used as the chiral ligands in the alkylation of aldehydes with diethylzinc. These results are summarized in Table 7. The authors presented a new class of aminoalcohols (**62a** and **62c**) which serve as excellent catalysts for the selective preparation of each of the enantiomeric alcohols with 96-98% *ee* in the addition of diethylzinc to aldehydes.

Table 7 Enantioselective alkylation of aldehydes with diethylzinc catalyzed by chiral *β*-aminoalcohols **62** and **64**



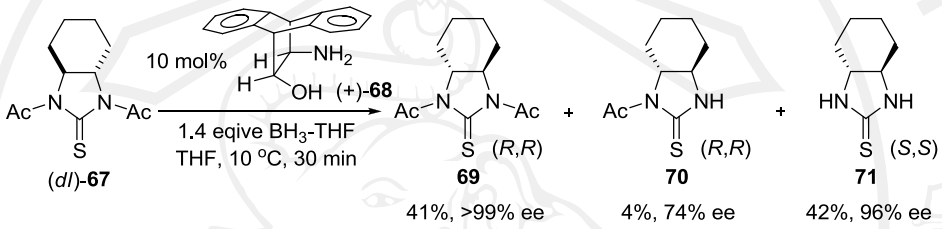
Entry	R	*β*-aminoalcohol	Yield (%)[a]	**66a** (*S*)	**66b** (*R*)[b]
1	Ph-	**62a**	91	98	2
2	$CH_3(CH_2)_5$-	**62a**	81	94	6[c]
3	Ph-	**62a**	22	60	40
4	Ph-	**62c**	80	1	99
5	$CH_3(CH_2)_5$-	**62c**	70	17	83
6	Ph-	**62d**	63	6	94
7	Ph-	**62e**	60	11	89
8	Ph-	**64a**	96	97	3
9	Ph-	**64b**	69	79	21

[a] Isolated yield

[b] Determined by direct HPLC analysis using a chiral column (DAICEL CHIRACEL OD)

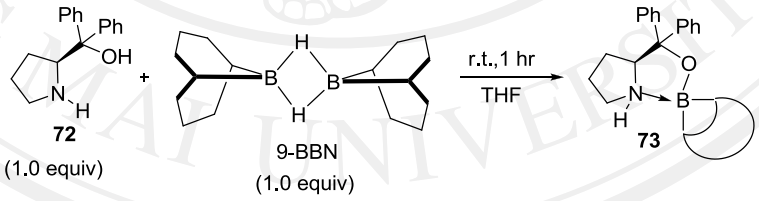
[c] Determined by HPLC analysis of the corresponding (*R*)-1-(1-napthyl)ethylcarbamate

In 1999, Yokoyama *et al.*[26] reported herein a catalytic process for the kinetic resolution of (*dl*)-C_2-symmetrical 1,3-diacetyl-4,5-tetramethylene-2-imidazolidinethiones (**67**) by a borane-mediated reductive deacetylation catalyzed by the chiral, conformationally rigid, sterically congested aminoalcohol **68**. This reductive deacetylation gave (*4R*,*5R*)-1,3-diacetyl-2-imidazolidinethiones (**69**) and (*4S*,*5S*)-2-imidazolidinethiones (**71**) with excellent enantioselectivity and yield, along with the monoacetyl product **70** with moderate selectivity as shown in Scheme 12.



Scheme 12 The reductive deacetylation of 1,3-diacetyl-4,5-tetramethylene-2-imidazolidinethiones.

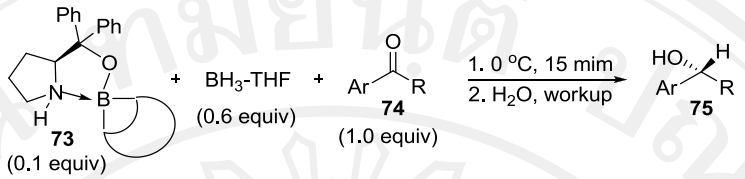
In 2002, Kant *et al.*[27] investigated a new catalytic enantioselective reducing reagent. This catalyst was prepared form (–)-α,α-diphenylpyrrolidine methanol **72** (1,2-aminoalcohol) and 9-borabicyclo[3.3.1]nonane (9-BBN) as shown below.

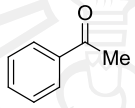
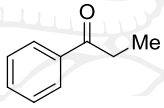
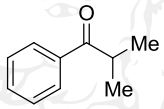
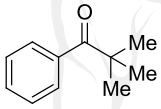
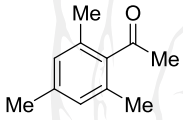
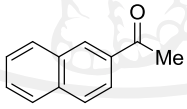
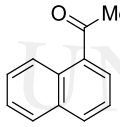


Scheme 13 Preparation for catalytic enantioselective reducing reagent from 1,2-aminoalcohol and 9-BBN.

The enantioselective complex **73** can be used as the catalyst in the reduction of prochiral aralkyl ketones to the corresponding alcohols with BH_3-THF. In all these cases, this reduction reaction gave the products with high enantioselectivity. These results are summarized in Table 8.

Table 8 Reduction reaction of aralkyl ketone using catalyst **73**



Entry	Aralkyl ketone **74**	% *ee* of product **75**[a]
1		83.2 (*R*)
2		82.1 (*R*)
3		89.3 (*R*)
4		91.5 (*R*)
5		87.5 (*R*)
6		94.5 (*R*)
7		99.2 (*R*)

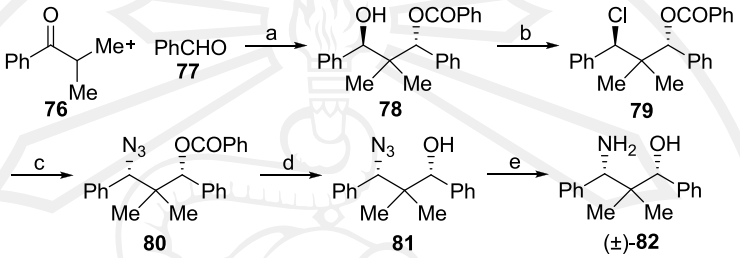
[a] Enantiomeric excess was established using chiral HPLC analysis of alcohol product on Chiralcel-OD column

1.4.5.2 1,3-aminoalcohols

In 2010, Patil and co-workers[28] successfully synthesized diastereomeric compounds of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol (1,3-aminoalcohol). Synthesis of the *syn*-1,3-aminoalcohol **82** is depicted in Scheme 14.

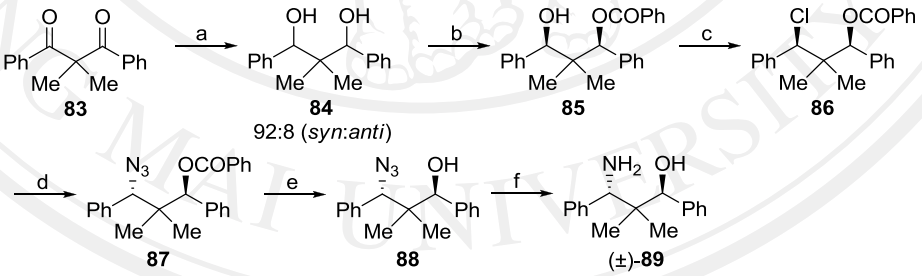
The step is an aldol–Tishchenko reaction between isobutyrophenone (**76)** and benzaldehyde to give *γ*-hydroxybenzoate (**78**) as a major product. The resulting product **78** was treated with thionyl chloride to obtain the *anti*-

chlorobenzoate (**79**) with retention of configuration. The compound **79** was converted to azidobenzoate (**80**) by reacting with sodium azide in DMF with an inversion of the configuration. After that, the azidobenzoate **80** was firstly hydrolyzed to azidoalcohol (**81**), followed by hydrogenation to obtain the *syn*-1,3-aminoalcohol **82** in overall 40% yield.



Scheme 14 Synthesis of *syn*-1,3-aminoalcohol **82**. Reagents and conditions: (a) LiO^{t}Bu, THF, 0 °C to r.t., 74%; (b) $SOCl_2$, CH_2Cl_2, r.t., 83%; (c) NaN_3, DMF, reflux, 83%; (d) KOH, MeOH; (e) H_2-Pd/C, MeOH, 90% (over two steps).

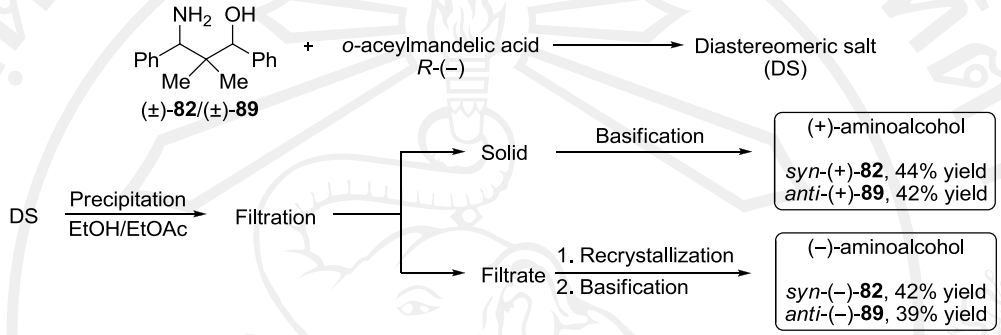
A same strategy was applied for the preparation of *anti*-1,3-aminoalcohol **89** as shown in Scheme 15.



Scheme 15 Synthesis of *anti*-1,3-aminoalcohol **89**. Reagents and conditions: (a) $LiBH_4$, $TiCl_4$, 82%; (b) BzCl, pyridine, CH_2Cl_2 r.t., 71%; (c) $SOCl_2$, CH_2Cl_2 r.t., 80%; (d) NaN_3, DMF, reflux, 70%; (e) KOH, MeOH; (f) H_2-Pd/C, MeOH, 90% (over two steps).

The required *syn*-hydroxylbenzoate (**85**), which is the key intermediate for further transformation, was prepared from the *meso*-1,3-diol (**84**). 1,3-diketone was reduced using $LiBH_4$/TiCl4 to obtain 1,3-diol in 92:8 *syn*/*anti* ratio. The mixture was treated with PhCOCl, followed by crystallization to provide the *syn*-

hydroxylbenzoate (**85**). Compound **85** was treated with $SOCl_2$ to give chlorobenzoate (**86**) (in 80% yield) with retention of configuration. The *anti*-azidobenzoate (**87**) was obtained by the reaction of compound **86** with sodium azide. Subsequently, compound **87** was hydrolyzed to give the compound **88**, followed by hydrogenation to provide the corresponding *anti*-1,3-aminoalcohol **89** in overall 33% yield.

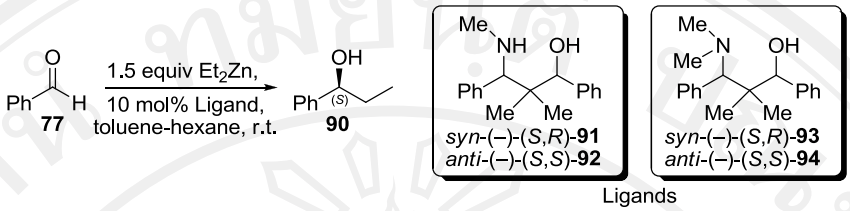


Scheme 16 Separation of 1,3-aminoalcohol **82** and **89**.

The compound **82** and **89** could be not separated into the diastereomeric forms by common chromatographic techniques. The resolution could be accomplished through the precipitation of one of the salts obtained from *R*-(–)-*O*-acetyl mandelic acid. The mixture of diastereomeric salts was prepared by dissolving the acid and the aminoalcohol in methanol and evaporating to dryness. The crude of diastereomeric mixture of salt was stirred with a mixture of EtOH/EtOAc (15:85). The precipitated solid after basification with aqueous ammonia gave the enantiomeric pure (+)-**82** while (–)-**82** was recovered from the filtrate. This protocol was also applied for the resolution of **89** (Scheme 16)

Furthermore, compound **82** and **89** were derivatized by methylation reaction to compound **91-94** which were used as the ligands for the alkylation of benzaldehyde with diethylzinc as shown in Table 9.

Table 9 Enantioselective addition of Et_2Zn to benzaldehyde



Entry	Ligand	Time (hr)	Yield (%)[a]	*er*[b]
1	(–)-**91**	4	69	92:8
2	(–)-**92**	4	70	70:30
3	(–)-**93**	1	90	97:3
4	(–)-**94**	2	80	80:20
5	(–)-**93**	2	86	97:3

[a] Isolated yield.

[b] Determined by chiral HPLC analysis.

[c] Reaction carried out at 0 °C.

1.4.5.3 1,4-aminoalcohols

Five amino–TADDOLs derivatives (**95a**–**95e**) were used as the catalysts for the enantioselective addition of diethylzinc to aromatic aldehydes, which were reported by Qian and co-worker in 2000.[29]

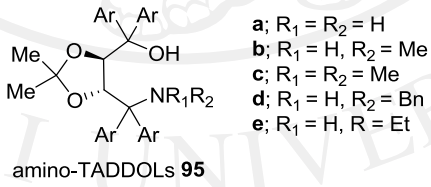


Figure 4 Amino–TADDOLs derivatives **95a**–**95e**

The compounds **95a**–**95d** which was the catalysts in the asymmetric reaction of diethylzinc to aromatic aldehydes afforded moderate to good enantioselectivity (up to 88% *ee*) as illustrated in Table 10. The authors discussed that the substituents on the nitrogen atom have effects to the overall yield and the enantioselectivity of alcohol products.

Table 10 Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by amino–TADDOLs **95a-95d**

Entry	Substrate	Catalyst	Yield (%)[a]	% *ee*	Configuration[b]
1	C_6H_5CHO	**95a**	38	40[c]	*R*
2	C_6H_5CHO	**95b**	99	80[c]	*R*
3	C_6H_5CHO	**95c**	61	80[c]	*S*
4	C_6H_5CHO	**95d**	88	81[d]	*S*
5	4-$MeOC_6H_4CHO$	**95b**	60	81[d]	*R*
6	4-$MeOC_6H_4CHO$	**95c**	94	88[d]	*S*
7	4-$MeOC_6H_4CHO$	**95d**	100	87[d]	*S*
8	2-$MeOC_6H_4CHO$	**95b**	100	57[d]	*R*
9	2-$MeOC_6H_4CHO$	**95c**	95	69[d]	*S*
10	2-$MeOC_6H_4CHO$	**95d**	100	83[d]	*S*
11	4-MeC_6H_4CHO	**95b**	82	70[c]	*R*
12	4-MeC_6H_4CHO	**95c**	47	79[c]	*S*
13	4-MeC_6H_4CHO	**95d**	93	78[c]	*S*
14	4-FC_6H_4CHO	**95b**	87	70[e]	*R*
15	4-FC_6H_4CHO	**95c**	33	72[e]	*S*
16	4-FC_6H_4CHO	**95d**	85	82[e]	*S*
17	4-ClC_6H_4CHO	**95b**	100	70[c]	*R*
18	4-ClC_6H_4CHO	**95c**	89	68[c]	*S*
19	4-ClC_6H_4CHO	**95d**	99	80[c]	*S*
20	4-BrC_6H_4CHO	**95b**	100	67[c]	*R*
21	4-BrC_6H_4CHO	**95c**	100	72[c]	*S*
22	4-BrC_6H_4CHO	**95d**	100	81[c]	*S*
23	4-$CF_3C_6H_4CHO$	**95b**	95	70[c]	*R*
24	4-$CF_3C_6H_4CHO$	**95c**	70	43[c]	*S*
25	4-$CF_3C_6H_4CHO$	**94d**	87	79[c]	*S*
26	1-$C_{10}H_7CHO$	**94b**	100	67[d]	*R*
27	1-$C_{10}H_7CHO$	**94c**	86	86[d]	*S*
28	1-$C_{10}H_7CHO$	**94d**	100	88[d]	*S*

[a] Isolated yield.

[b] Determined by comparison of specific rotation with literature data or known compounds.

[c] *ee* determined by HPLC with a chiraicel OJ column.

[d] *ee* determined by HPLC with achiraicel OD column.

[e] *ee* determined by HPLC with a chiraicel AS column.

On the other hand, in all cases used catalyst **95e** in the asymmetric reaction of diethylzinc to aromatic aldehydes gave low enantioselectivities values as shown in Table 11.

Table 11 Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by amino–TADDOL **95e**

Entry	Substrate	Catalyst	Yield (%)[a]	% *ee*	Configuration[b]
1	C_6H_5CHO	**95e**	91	9[c]	*R*
2	4-MeO-C_6H_4CHO	**95e**	83	16[d]	*R*
3	4-CF_3-C_6H_4CHO	**95e**	98	2.4[c]	*S*
4	1-$C_{10}H_7CHO$	**95e**	100	10[d]	*R*

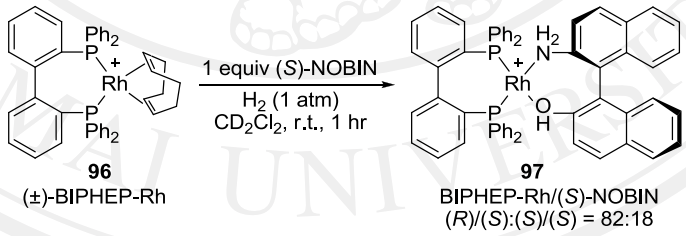
[a] Isolated yield.

[b] Determined by comparison of specific rotation with literature data or known compounds.

[c] *ee* determined by HPLC with a chiraicel OJ column.

[d] *ee* determined by HPLC with a chiraicel OD column.

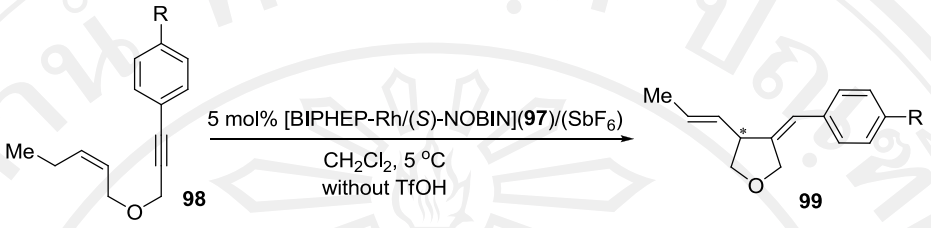
In 2006, Mikani *et al.*[30] studied the chiral aminoalcohol NOBIN which complex with the BIPHEP-Rh as the catalyst in ene-type cyclization of 1,6-enynes substrates without use of acid. The BIPHEP-Rh/(*S*)-NOBIN complex **97** can be synthesized as illustrated in Scheme 17.



Scheme 17 Synthesis of the BIPHEP–Rh/(*S*)-NOBIN (**97**).

This BIPHEP-Rh/(*S*)-NOBIN complex (**97**) can be used as an asymmetric catalyst to give high enantioselective (up to 98% *ee*) and yield in ene-type cyclization of 1,6-enynes. The results are shown in Table 12.

Table 12 Asymmetric ene-cyclization by BIPHEP–Ph/NOBIN catalyst (**97**) without TfOH



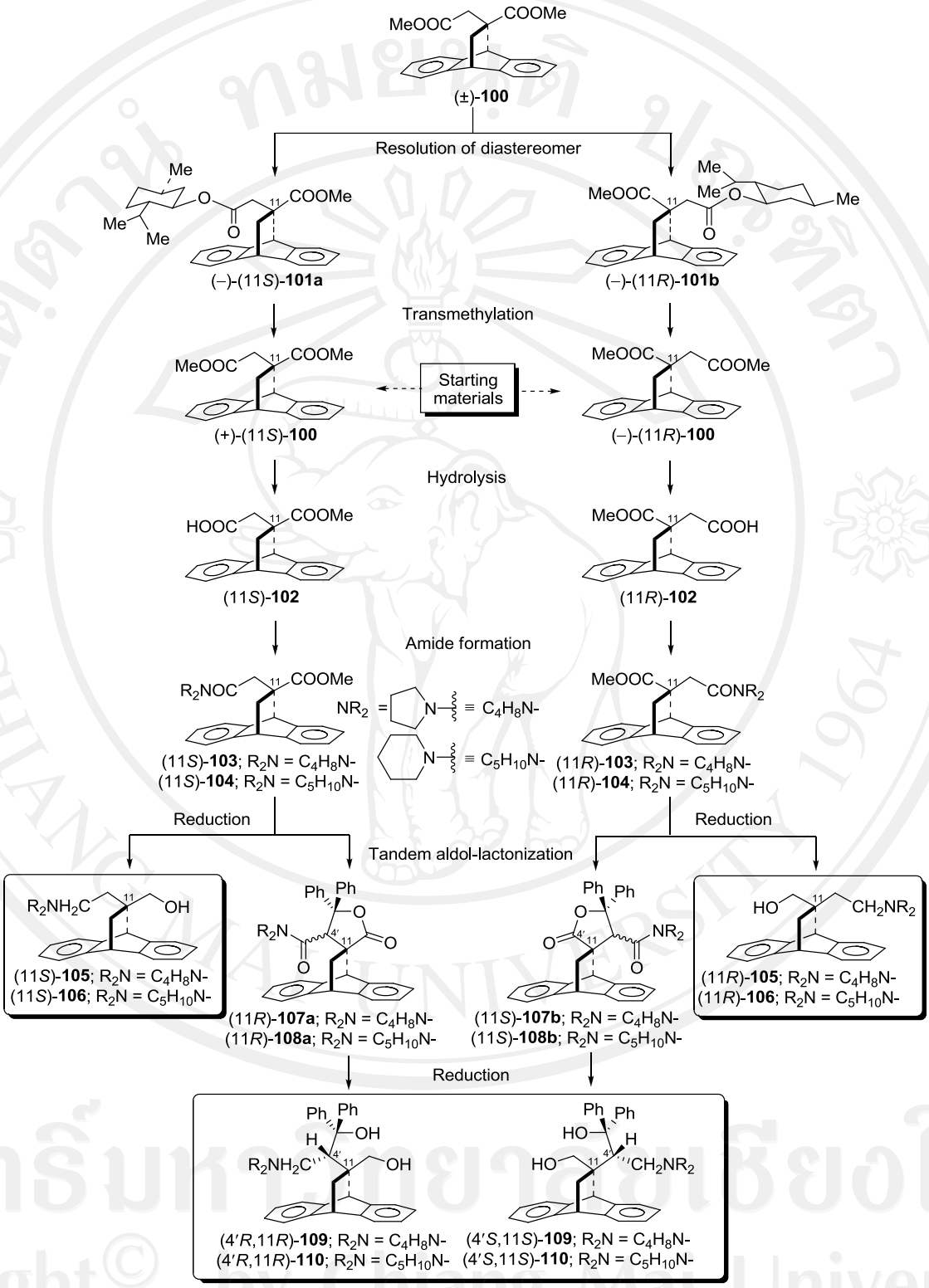
Entry	R	Time (hr)	Yield (%)	*ee*[a] (%)
1	H	3	89	91 (–)
2	OMe	8	70	98 (–)
3	Cl	3	99	92 (–)

[a] Enantiopurity was determined by chiral HPLC (Daicel CHIRALCEL OJ-H) analysis.

Application of the TADDOLs, their derivatives and TADDOLs analogues, which can be used as stoichiometric chiral reagents, chiral ligands for both stoichiometric chiral reagents and catalytically asymmetric reaction as well as. TADDOLs, their derivatives and TADDOLs analogues are widely used in asymmetric reactions. Therefore, this research is focused on synthesizing depicted *N*,*O* heteroatoms TADDOLs–anthracene adducts which are the new compounds that could be synthesized using the readily available monoacid–anthracene adducts, which are optically active catalysts, as starting materials. The *N*,*O* heteroatoms TADDOLs–anthracene adducts will be used as the asymmetric catalysis for organic asymmetric reactions.

1.5 Aims and research objectives

The aim of this research focused on the syntheses and characterization of both enantiomeric *N*,*O* heteroatoms TADDOLs–anthracene adducts (11*S*)-**105**, (11*R*)-**105**, (11*S*)-**106**, (11*R*)-**106**), (4′*R*,11*R*)-**109**, (4′*S*,11*S*)-**109**, (4′*R*,11*R*)-**110** and (4′*S*,11*S*)-**110** from both enantiomeric dimethyl-itaconate anthracene adducts (11*S*)-**100** and (11*R*)-**100** as the starting materials (Scheme 18). In the future, both enantiomeric *N*,*O* heteroatoms TADDOLs–anthracene adducts may be used in asymmetric catalysis for organic asymmetric reaction.



Scheme 18 Syntheses of *N*,*O* heteroatoms TADDOLs–anthracene adducts ((11*S*)-**105**, (11*R*)-**105**, (11*S*)-**106**, (11*R*)-**106**), (4′*R*,11*R*)-**109**, (4′*S*,11*S*)-**109**, (4′*R*,11*R*)-**110** and (4′*S*,11*S*)-**110**.