CHAPTER 1

INTRODUCTION

1.1 Asymmetric synthesis[1]

In our modern life, the chiral compounds play an important role such as pharmaceuticals, perfumes, cosmetics, nutrient foods, vitamins and even in biological molecules which are enzymes, amino acids and carbohydrates. Most of these products are obtained in the enantiomerically pure forms. Besides, the absolute *configurations* of the enantiomeric compounds have the important effects especially in odor and taste. For instance, carvone, (*R*)-(–)-carvone tastes like spearmint while (*S*)-(+)-carvone tastes like caraway.

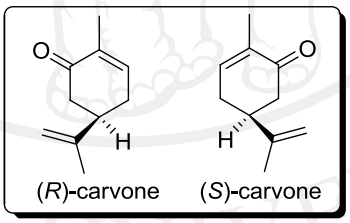


Figure 1 Structure of carvones

In order to access the enantiomerically pure compounds, asymmetric synthesis is the main strategy.

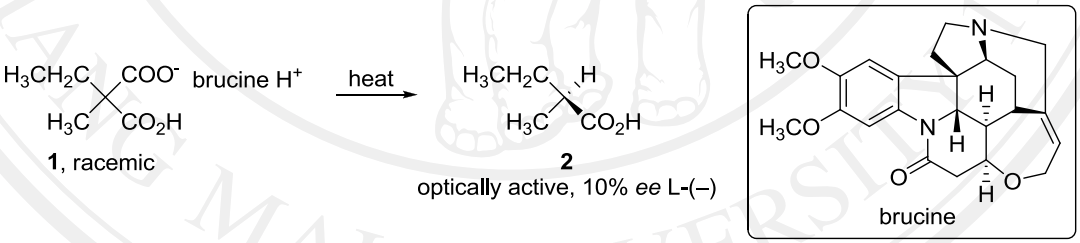
1.1.1 Principle of asymmetric synthesis

Asymmetric synthesis is a reaction or reaction sequence that *selectively* creates one configuration of one or more new *stereogenic elements* by the action of a

chiral regent or auxiliary, acting on *heterotopic* faces, atoms, or groups of substrate. In 1974, Eliel stated the requirement of a feasible asymmetric synthesis:[2]

1. It must induce to the desire enantiomer in high stereoselective.
2. The chiral product must be readily separable from the auxiliary which is needed in the synthesis.
3. The chiral auxiliary or reagent must be recoverable in good yield and without racemization.
4. The chiral auxiliary or catalyst should be readily and inexpensively available in enantiomerically pure form.

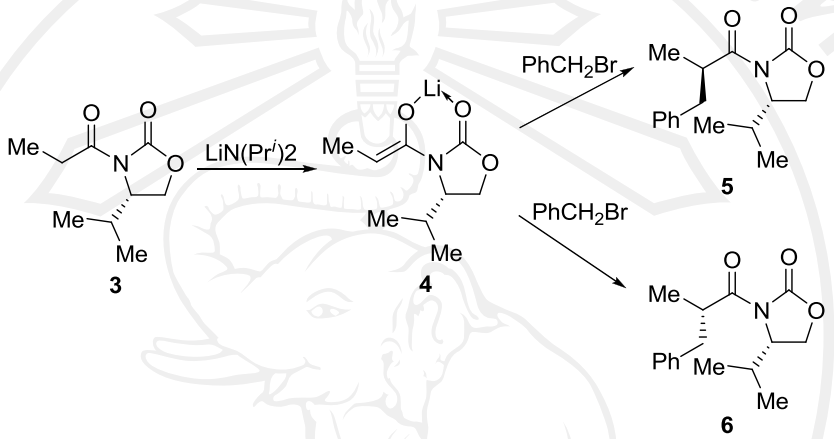
The first achievement in the asymmetric synthesis is an enantioselective decarboxylation reaction of the brucine salt of 2-ethyl-2-methylmalonic acid (**1**) to obtained 2-methylbutyric acid (**2**) with 10% *ee* by Marckwald in 1904 (Scheme 1).[3]



Scheme 1 Enantioselective decarboxylation of brucine and 2-ethyl-2-methylmalonic acid (**1**).

If the substrate itself is chiral and non-racemic, creation of another chiral center using this substrate provides the possibility of diastereomeric products. If the products themselves are diastereomers, the transition states which lead to them are diastereomeric, and a diastereoselective reaction should be expected. This principle is shown in Scheme 2 which shows the two possible trails for alkylation of the chiral enolate **4**. If the electrophile attacks from above of the plane of the enolate as drawn,

the product will be compound **5**, and attack from below will lead to compound **6**, which is diastereomeric excess (Scheme 2). This reaction is an example of an extremely powerful method for asymmetric synthesis based on the use of 'chiral auxiliary' controlled enolate alkylation.[4]



Diastereomeric excess (d.e.) = major diastereoisomer (%) - minor diastereoisomer (%)

= **5** (%) – **6** (%) = 99-1 = 98%

Scheme 2 The possibilities of alkylation to chiral enolate **4**.

1.1.2 Analytical Methods

Over the past decade, various methodologies have been improved for the resolution of the enantiomers on both analytical and preparative scales. Before the mid-1960s, the enantiomeric purity of a chiral molecule was usually evaluated using chiroptical methods. This often involved measuring the optical rotation of the sample with use of a polarimeter. Besides, other techniques to analyze the enantiomers or diastereoisomers had been developed in sensitivity and accurate chromatography techniques, GC or HPLC analysis, and NMR method.

1.1.2.1 Polarimetry[1a, 5, 6]

Polarimetry, the former technique, measures the rotation of a plane of monochromic polarized light after having passed through a sample which is optically active fluid, as shown in Figure 2.

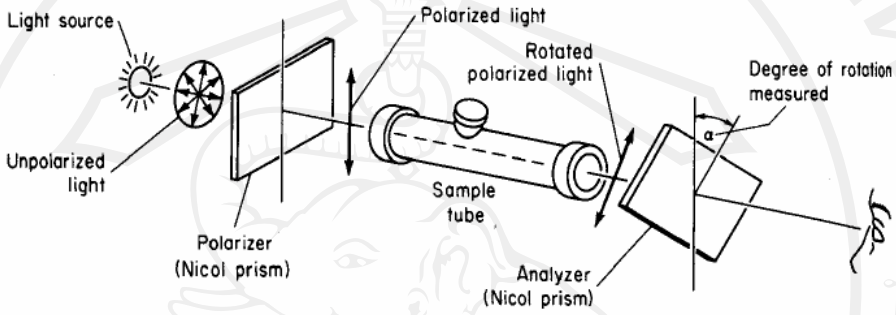


Figure 2 Components of polarimeter[5]

The degree of rotation observed in a polarimeter, α, is dependent on the number of chiral species the light encounters on its passage through the sample chamber, as well as the wavelength of the light. Hence, analytical accuracy dictates strict control of a number of experimental parameters, such as temperature, concentration, light source and path length. To mimimize the effects of these variables and to increase the reproducibility, specific rotation, [α], is defined as:

$$[\alpha]_{\lambda}^{T} = \frac{100\alpha}{l \cdot c}$$

where T is the temperature, λ is the wavelength of the light source (often the D lines of sodium at 589.0 and 589.6 nm and abbreviated simple 'D'), α is the observed rotation, l is the sample path length in decimeters and in the concentration in grams per 100 millimeters solution. This value was then compared to the known rotation for an enantiomerically pure sample of the same compound, measured under identical

conditions. This value is commonly termed 'optical purity'. Provided that the measurement is carried out under rigorously controlled conditions along with appropriate calibrations, and then this value may be equated with 'enantiomeric purity'. Sign of rotation reflects absolute configuration (and is often used to assign it), and the magnitude of the rotation is used to determine the optical purity, usually expressed as a percent:

$$\% \text{ optical purity} = \frac{100[\alpha]_{\lambda}^{T}}{[\alpha_0]_{\lambda}^{T}}$$

where $[a]_{\lambda}^{T}$ is the observed specific rotation, and $[\alpha_0]_{\lambda}^{T}$ is the specific rotation of the pure enantiomer under identical conditions. The optical purity of an enantiomerically pure compound is 100%, and 0% for a recemate. For a chiral compound, percent enantiomer excess (*ee*) is defined as:

$$\% \text{ enantiomeric excess} = 100\frac{R-S}{R+S}$$

where *R* and *S* represent the amount of the two enantiomers.

There are two major problems with this method of analysis. Firstly, optical purity and enantiomeric purity are not necessarily equivalent. A second limitation is that the literature is infected with many examples of incorrect optical rotation for compounds considered to be enantiomerically pure. Finally, the use of optical rotation for determination of enantiomeric purity is subject to the uncertainty of contamination with an optically active impurity. This is particularly serious if the impurities have a high rotation or a rotation of the opposite sign to that of the substrate being analyzed. Although the method is a convenient one it is a rather unsatisfactory method for determining accurate enantiomeric purity unless stringent

control conditions are followed. Nevertheless, if used carefully, polarimetry can provide a simple, efficient, and inexpensive method for the analysis of enantiomeric purity.

1.1.2.1 Nuclear Magnetic Resonance Spectroscopy[1a, 6]

Nuclear magnetic resonance spectroscopy, NMR, is a technique to analyze the diastereoisomeric mixture and derivatization of enantiomers with a chiral reagent can also be an excellent method of analysis. There are three types of chiral auxiliaries that are used to convert the mixture of enantiomers into a diastereoisomeric mixture. Chiral derivatizing agents require the separate formation of discrete diastereoisomers prior to NMR analysis and care has to be taken to ensure that neither kinetic resolution non racemization of the derivatizing agent occurs during derivatization. Chiral lanthanide shift reagents and chiral solvating agents form diastereoisomeric complexes *in situ* with substrate enantiomers and may be used directly.

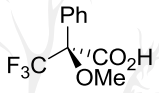
- **Chiral Derivatizing Agents, CDA**

Derivatization of enantiomers with enantiomerically pure compound remains the most widely used NMR technique for the assay of enantiomeric purity. In order to be useful, a number of requirements must be met:

1. The CDA must be enantiomerically pure or (less satisfactory) its enantiomeric purity must be known accurately.
2. The reaction of the CDA with both enantiomers must go to completion under the reaction conditions, or (again less satisfactorily) the relative rate of reaction for each enantiomer must be known.

3. The CDA must not racemize under the derivatization or analysis conditions, and its attachment should be mild enough so that the substrate does not racemize either.
4. If analysis is by HPLC, the CDA should have a chromophore to enhance detectability. If analysis is by NMR, the CDA should have a functional group that gives a singlet and that is remote from other signals for easy integration.

Although a number of CDAs have been improved over the years, by far the most popular is Mosher's acid, α-methoxy-α-(trifluoromethyl)phenylacetic acid) or MTPA **7**.



MTPA (**7**)

Figure 3 Structure of Mosher's acid (**7**)

Due to the structure of MTPA, there is no α-hydrogen to the carboxy group racemization during derivatization is impossible. It is available commercially in enantiomerically pure form, either as the acid or the acid chloride, and reacts readily with primary and secondary alcohols or amines to form diastereomeric amides or esters that may be analyzed by ^{1}H NMR, ^{19}F NMR or more accurately by chiral stationary phase gas chromatography.

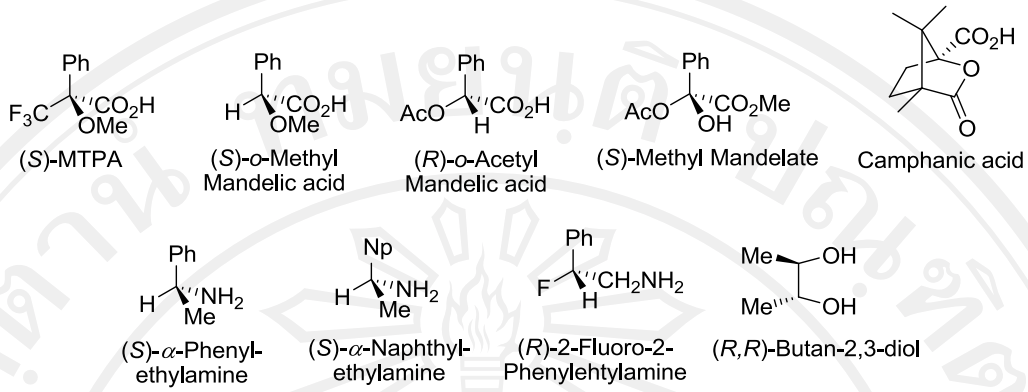


Figure 4 Common chiral derivatizing agents for ^{1}H NMR and ^{19}F NMR[6]

- **Chiral Lanthanide Shift Reagents, CSR**

Addition of lanthanide shift reagent to an organic compound may result in shifts of resonances to higher (or lower) frequency, the size of which is determined primarily by the distance of the given type of proton from the donor group. Advantages of the CSR method are:

1. The chiral shift reagent need not be enantiomerically pure.
2. There can be no accidental resolution, deresolution, or racemization during a derivatization.
3. A wide range of functional groups can be analyzed with this technique, since all that is required is a Lewis basic atom to coordinate to the lanthanide.

Table 1 illustrates the available chiral shift reagents and the abbreviation used for each.

Table 1 Common chiral lanthanide shift reagents[6]

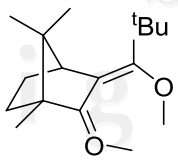
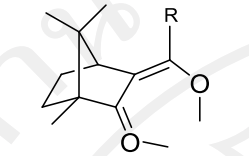
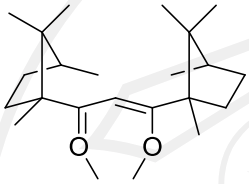
structure of L in LnL_3	lanthanon	abbreviation[a]
	Eu	$Eu[pvc]_3$

Table 1 Common chiral lanthanide shift reagents (continued)[6]

structure of L in LnL_3	lanthanon		abbreviation[a]
	$R = CF_3$	Eu	$Eu[tfc]_3$
		Pr	$Pr[tfc]_3$
		Yb	$Yb[tfc]_3$
	$R = C_3F_7$	Eu	$Eu[hcf]_3$
		Pr	$Pr[hcf]_3$
		Yb	$Yb[hcf]_3$
		Eu	$Eu[dcm]_3$

[a] pvc = pivaloyl-*d*-camphorato; tfc = trifluorohydroxymethylene-*d*-comphorato; hfc = heptafluorohydroxymethylene-*d*-campharato; dcm = dicamphoyl-*d*-menthanato.

According to the structure of lanthanide, the six-coordinate lanthanide complex forms a weak addition complex with a large variety of organic compounds that is in fast exchange with the unbound organic substrate on the NMR time scale. In addition to disadvantages of this technique, the absolute configurations cannot generally be determined without reference to a known sample, and that both enantiomers must be available to insure peak separation. An additional disadvantage has developed with the advent of high-field NMR spectrometers.

- **Chiral solving agents, CSA**

Chiral solvating agents form diastereomeric solvation complexes with solute enantiomers through rapidly reversible equilibria in competition with the bulk solvent. Besides, analysis of enantiomer ratios and the assignment of absolute configuration by this technique has become a very useful tool. The advantages of this method are that it is fast and ordinary to perform, with no problems of kinetic

resolution or sample racemization, provided that the complexes remain in solution. The most commonly used CSA is 1-(9-anthryl)-2,2,2-trifluoroethanol (**8**, Figure 4) which has been used to determine the enantiomeric purity of a very broad range of compounds, including lactones, ethers, oxaziridines and sulfinate esters.

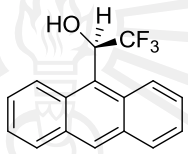


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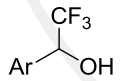
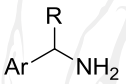
Figure 5 Structure of 1-(9-anthryl)-2,2,2-trifluoroethanol (**8**)

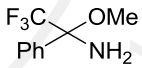
There are several of the readily available CSA along with some of the structure types with which they have been used for determination of enantiomer excess and absolute configuration as shown below.



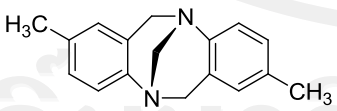
Hydroxy esters
Arylalkylamines
Amino esters
Oxiranes
Lactones
Phosphine oxides,
Amineoxides,
RS(=O)XR, X = N, O, S
Sulfoxides



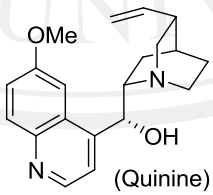
Sulfoxides
Phosphine oxides
sec-Benzylic alcohols
N-Phthalimido amino acids
2-(Aryl)carboxylic acids
Hydroxy esters



tert-Amines
Diamines

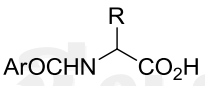


Tröger's base
sec- and *tert*-
Benzylic alcohols



(Quinine)

Binaphthyls,
sec-Benazylic amines



R = Ph, i-Bu

Diamines,
Amino esters,
Amino alcohols
Benzodiazepinones,
Naphthamides,
Lactones

Figure 6 Common chiral solvating agents and some classes of compounds which have been used.[1a]

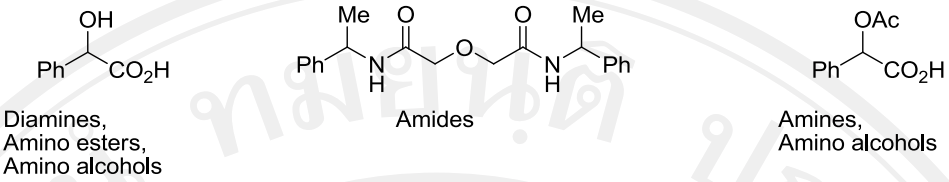


Figure 6 Common chiral solvating agents and some classes of compounds which have been used with. (continued)[1a]

1.1.2.3 Chromatography[7, 8]

Chromatographic techniques are considered as the most useful methods for chiral separation. In chromatographic methods, there are two approaches that are used: indirect which used derivatizing agents, and direct which used chiral stationary phases or chiral mobile phase additives.

- **Indirect chromatographic method**

In the indirect chromatography method, a racemic mixture is made into their enantiomers can be achieved by derivatization of the racemic with a chiral derivatizating agent (CDA) to form a pair of diastereoisomers-salt complex. Due to the different of physical and chemical properties of diastereomers, they can be separated from each other by an achiral chromatographic method. The advantages of the indirect technique are:

1. Less expensive *i.e.*, ordinary chromatographic column can be used.
2. Numerous type of derivatization chemistry are available and the cost of reagents may be less expensive than for a chiral column
3. This method is flexible because various achiral columns and mobile phase conditions can be used.

Although the indirect chromatographic method has the advantage as shown above there are some limitations to this technique as following:

1. The derivatization procedure is tedious and time-consuming owning to the different reaction rates of the individual enantiomers.
2. Suitable chiral derivatizing agents in pure form can be difficult to obtain.
3. Biased results for enantiomeric composition due to partial racemization of derivatizing agent or unequal reaction rates.

- **Direct chromatographic method**

The direct chromatographic approach involves the use of chiral selector either in the mobile phase, chiral mobile phase additives (CMPAs), or in the stationary phase, chiral stationary phases (CSPs). For the chiral mobile phase additives or CMPAs method, enantiomeric separation is accomplished by the formation of a pair of transient diastereomeric complexes between racemic analyte and the chiral mobile phase additive. Chiral discrimination is due to differences in the stabilities of the diastereomeric complexes, solvation in the mobile phase, and/or binding of the complexes to the solid support. Many racemic mixtures can be separated on conventional achiral column by using an appropriate chiral mobile phase additive such as α, β, and γ-cyclodextrins. In contrast, chiral stationary phases or CSPs is based on the formation of transient diastereomeric analyte-CSP complexes between the enantiomers and the chiral molecule that is an integral part of the stationary phase. Nowadays, CSPs have achieved great repute in the chiral separation of enantiomers by chromatography and today are the tools of the choice of almost all analytical, biochemical, pharmaceutical and pharmacological institutions and industries.

1.2 TADDOLs and their derivatives[9]

The chiral diol which were acquired from the optically active tartaric acid and Grignard reagents, TADDOLs (*α*,*α*,*α′*,*α′*-tetraaryl-1,3-dioxolane-4,5-dimethanols, Figure 7) containing 1,3-dioxolane ring in *trans*- relationship with diarylhydroxymethyl groups, are the most effective chiral catalysts for many asymmetric synthesis, for instance, hetero Diels–Alder reactions, vinylogous Mukaiyama–aldol reactions, oxidation reactions, nucleophilic addition to C=O double bonds.

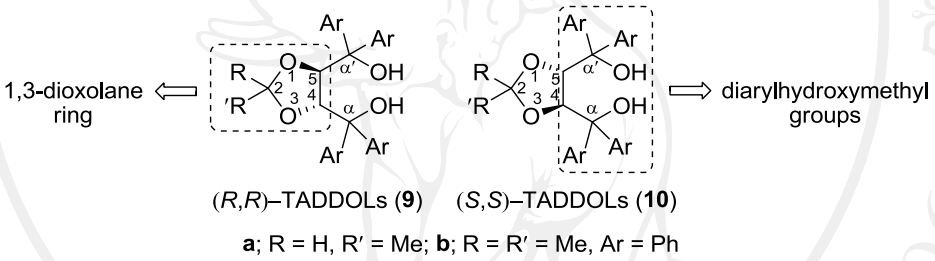
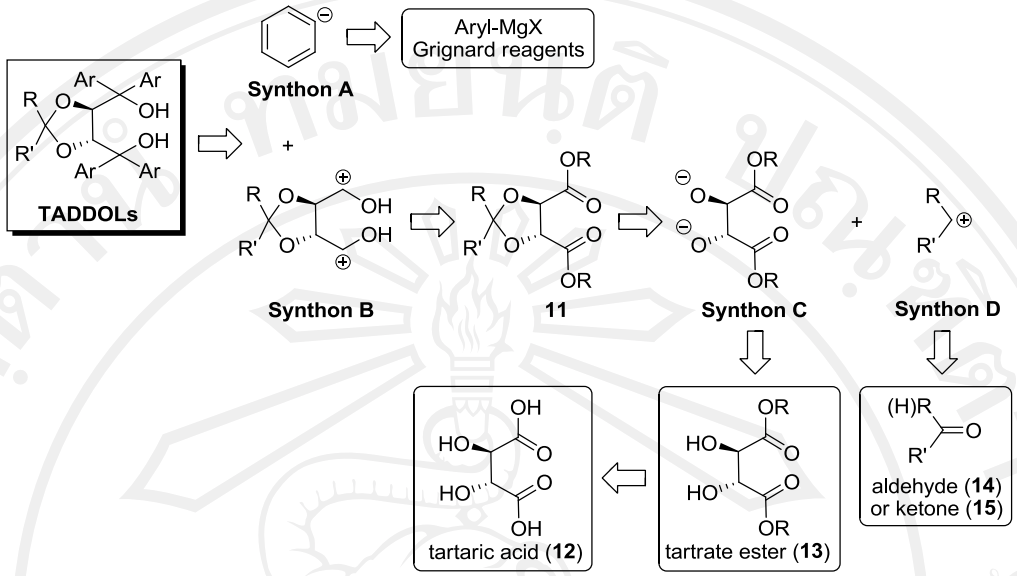


Figure 7 Structures of TADDOLs

Considered the TADDOLs structure, the one hydrogen atom of the hydroxyl group showed the interaction in an intramolecular hydrogen bond and the other is free for intermolecular interaction. Thus, at these two hydroxyl groups on the diarylhydroxymethyl groups could be chelated with other metals. The retrosynthesis of TADDOLs was shown in Scheme 3. The TADDOLs provided synthon **A** and synthon **B** which were prepared from Grignard reagent and ester **11**. Then, diester compound **11** afforded synthon **C** and synthon **D** which could be prepared from the tartrate ester **13** and aldehydes or ketones, respectively.



Scheme 3 Retrosynthesis of TADDOLs.

1.3 Literature reviews

Due to the achievement of using the TADDOLs as catalysts in asymmetric syntheses, applying of TADDOLs as catalysts has been discovered and modified to other analogues. In this chapter, modified TADDOLs *i.e* amino TADDOLs, titanium TADDOLates, TADDOL-derived hydroperoxide, TADDOL-derived chiral phosphorus and TADDOL-derived lithium aluminium hydride and utilized of TADDOLs for asymmetric synthesis *i.e.* addition to carbonyl compounds, reduction reactions, oxidation reactions and rearrangement reactions would be reviewed.

1.3.1 Modified TADDOLs

1.3.1.1 Amino TADDOLs

In 2000, the first application of five amino-TADDOL derivatives (**16**-**20**, Figure 8) as catalysts for the enantioselective addition of diethylzinc to aromatic aldehydes had been reported by Qian *et al.*[10]

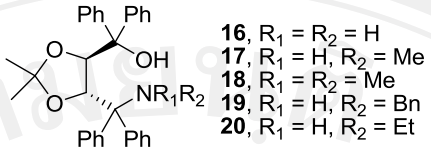


Figure 8 Amino-TADDOL derivatives

The results showed that the moderate to good enantioselectivities were obtained (up to 88% *ee*). Furthermore, the substituents on the nitrogen atom strongly affected both the chemical yield and the enantioselectivity, and in some cases showed a reverse stereochemistry.

Table 2 Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by amino-TADDOL[a]

Entry	Substrate	Catalyst	%yield[b]	%ee	Configuration[f]
1	C_6H_5CHO	**16**	91	9[c]	*R*
2		**17**	83	16[c]	*R*
3		**18**	98	2.4[c]	*S*
4		**19**	100	10[d]	*R*
5	4-MeO-C_6H_4CHO	**17**	60	71[d]	*R*
6		**18**	94	88[d]	*S*
7		**19**	100	87[d]	*S*
8	2-Meo-C_6H_4CHO	**17**	100	57[d]	*R*
9		**18**	95	69[d]	*S*
10		**19**	100	83[d]	*S*
11	4-Me-C_6H_4CHO	**17**	82	70[c]	*R*
12		**18**	47	79[c]	*S*
13		19	93	78c	*S*
14	4-F-C_6H_4CHO	17	87	70e	*R*
15		18	33	72e	*S*
16		19	85	82e	*S*
17	4-Cl-C_6H_4CHO	17	100	70c	*R*
18		18	89	68c	*S*

Table 2 Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by amino-TADDOL (continued)[a]

Entry	Substrate	Catalyst	%yield[b]	%ee	Configuration[f]
19		19	99	80c	*S*
20	4-Br-C_6H_4CHO	17	100	67c	*R*
21		18	100	72c	*S*
22		19	100	81c	*S*
23	4-CF_3-C_6H_4CHO	17	95	70c	*R*
24		18	70	43c	*S*
25		19	87	79c	*S*
26	1-C_10H_7CHO	17	100	67d	*R*
27		18	86	86d	*S*
28		19	100	88d	*S*

a. Aldehyde: Cat: Et_2Zn = 1.0:0.5:2.1. (molar ratio): at 0 °C and 24 hours;

b. Isolated yield;

c. *e.e* determined by HPLC with a chiraicel OJ column;

d. *e.e* determined by HPLC with a chiraicel OD column;

e. determined by comparison of specific rotation with literature data or known compounds

Table 3 illustrates the enantioselectivities addition of diethylzinc to aldehydes using compound **20** as catalyst, this compound afforded low *ee* (Table 3).

Table 3 Enantioselective addition of diethylzinc to aldehydes catalyzed by **20**[a]

Entry	Substrate	Catalyst	%yield[b]	%ee	Configuration[f]
1	C_6H_5CHO	**20**	91	9[c]	R
2	4-MeO-C_6H_4CHO	**20**	83	16[d]	R
3	4-CF_3-C_6H_4CHO	**20**	98	2.4[c]	S
4	1-$C_{10}H_7CHO$	**20**	100	10[d]	R

a. Aldehyde: Cat: Et_2Zn = 1.0:0.5:2.1. (molar ratio): at 0 °C and 24 hours;

b. Isolated yield;

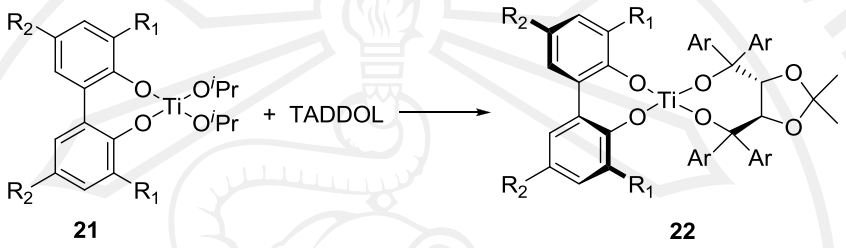
c. *e.e* determined by HPLC with a chiraicel OJ column;

d. *e.e* determined by HPLC with a chiraicel OD column;

e. determined by comparison of specific rotation with literature data or known compounds

1.3.1.2 Titanium TADDOLates

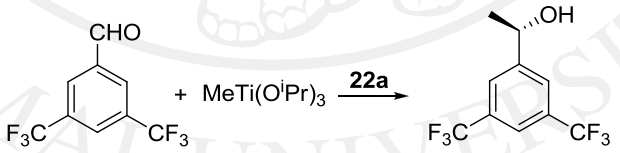
The development of chiral BIPOLate/TADDOLate-Ti catalyst **22** (Scheme 4) for methylation reaction of aldehydes with an achiral methyl-titanium reagent had been reported by Ueki and coworkers affording to the highest enantioselectivities.[11]



Scheme 4 Synthesis of chiral BIPOLate/TADDOLate-Ti catalyst **22**

The methylation of the achiral methyl reagent catalyzed by titanium catalyst **22a** obtained the methylcarbinol in good isolated yields but in moderate enantioselectivities (Table 1).

Table 4 Catalysis by BINOLate/TADDOLate-Ti complexe **22a**[a]



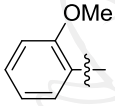
Entry	Temp (°C)	Yield (%)[a]	Enantioselectivity (% *ee*)
1	0	79	45
2	-70 to -35	60	73
3	-70 to -35	18	66

[a] Catalyzed by 3 mol% of **22a** (R_1=R_2=H)

Hence, modified BIPOLate/TADDDOLate-Ti complexes by the introduction of sterically demanding substituents at the 3,3′-positions was applied to this reaction. They found that the sterically bulky 3,3′-substituents led to the increasing of

enantioselectivity other than the phenylated ones (**22b** and **22c**, Table 5). Compound **22e**, in contrast, 3,3′-dimethoxy derivatives gave completely enantioselectivity (100% *ee*) while compound **22c** with *o*-methoxyphenyl derivatives obtained in moderate enantioselectivity (Table 5).

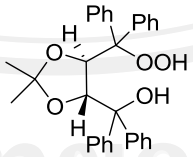
Table 5 3,3′-Modified BIPOLate/TADDOLate-Ti complexe **22**[a]

22	R_1	R_2	Yield (%)[a]	Enantioselectivity (% *ee*)
22b	Ph	H	36	69
22c		H	40	65
22d	Me	H	56	88
22e	MeO	Me	60	100

[a] Condition: toluene, 12 hours, -78 to -35 °C.

1.3.1.3 TADDOLs derived hydroperoxide

In 2003, Adam and coworkers reported the first oxovanadium(IV)-substituted POM, $[ZnW(VO)_2(ZNW_9O_{34})_2]^{-12}$, catalyzed asymmetric epoxidation of allylic alcohol by TADDOL (Figure 9) derived hydroperoxide as chiral oxygen source.[12]



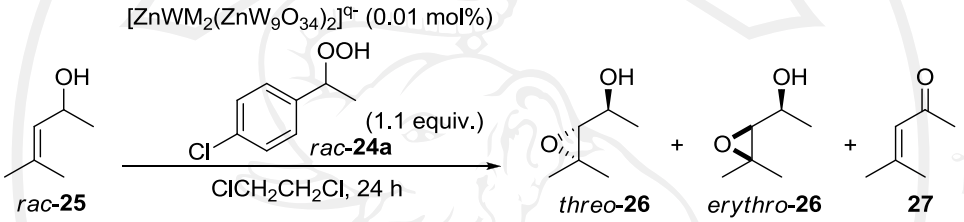
TADOOH (**23**)

Figure 9 Structure of TADOOH (**23**)

Mesitylol **25** as the model compound for the chemoselectivity (epoxidation or allylic oxidation) and diastereoselectivity (*threo* or *erythro* epoxidation) in the metal

catalyzed oxidations, and the racemic [1-(4-chlorophenyl)]ethyl hydroperoxide (**24**) as oxygen donor (Table 6). The screening revealed that the oxovanadium(IV)-substituted POM, $[ZnW(VO)_2(ZNW_9O_{34})_2]^{-12}$,was the most reactive and selective catalyst for the epoxidation of allylic alcohols.

Table 6 Catalytic oxidation of mesitylol **25** by the various transition-metal-substituted polyoxometalates with the racemic hydroperoxide **24**



Entry	M	temp[b] (°C)	convn[a] (%)	mb[a] (%)	selectivity[a] **26**:**27**	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 balances, and product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture, ca. 5% error of the stated value.

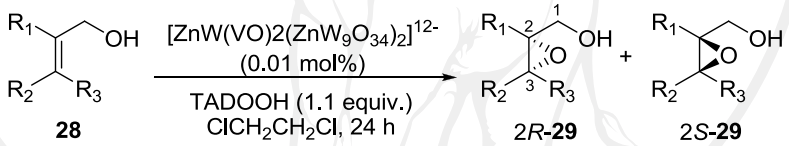
[b] For entries 3-8, 0.02 mol% of catalyst loading was employed; no conversion was observed at 20 °C.

[c] Reaction time was 6 h.

A screening of diverse chiral hydroperoxides under a variety of experimental conditions disclosed that the sterically demanding TADDOL-derived hydroperoxide TADOOH **23** was especially effective for the intended purpose, as representative results show in Table 7. In view of advantages, 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 **28e** and **28f** (entries 5 and 6, Table 7) were epoxidized in about as high enantioselectivities and yields as **28d**, but for the *p*-anisyl derivative **28e**, the enantiomeric ratio dropped slightly to 85:15 (entry 6) from 92:8 (entry 5). The epoxidation of the monosubstituted allylic alcohols **28g** and **28h** afforded the corresponding epoxides in moderate enantioselectivities (entries 7 and 8), but in high yield. Geraniol **28i** was regioselectively, even though in poor enantioselectivity (entry 9).

Table 7 Catalytic enantioselective epoxidationa of the primary allylic alcohols **28** by $[ZnW(VO)_2(ZNW_9O_{34})_2]^{-12}$ with TADOOH **23**



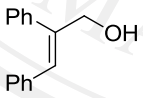
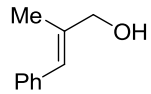
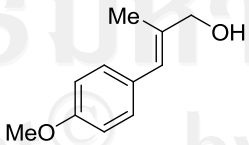
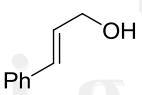
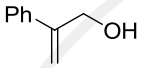
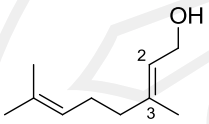
Entry	allylic alcohol **28**	time (h)	comvn[b] (%)	yield[c] **29** (%)	er[d]	Confign[e]
1	 **28d**	48 (0 °C)	40	90[f]	95:5	(2*R*, 3*R*)-(–)
2		30	>95	94	91:9	
3[a]		48	90	82	90:10	
4		6 (50 °C)	>95	92	85:15	
5	 **28e**	30	>95	92	92:8	(2*R*, 3*R*)-(+)
6	 **28f**	24	90	86	85:15	(2*R*, 3*R*)-(+)
7	 **28g**	48	>95	88	75:25	(2*R*, 3*R*)-(+)

Table 7 Catalytic enantioselective epoxidationa of the primary allylic alcohols **28** by $[ZnW(VO)_2(ZNW_9O_{34})_2]^{-12}$ with TADOOH (**23**) (continued)

Entry	allylic alcohol **28**		time (h)	comvn[b] (%)	yield[c] **29** (%)	er[d]	Configr[e]
8		**28h**	36	95	93	72:28	(2*R*)-(+)
9		**28i**	24	>95	96	59:41[d]	(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 **28** (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 (ChiralcelOD), except entry 9, for which GC-MS analysis on a chiral β-TG column was employed.

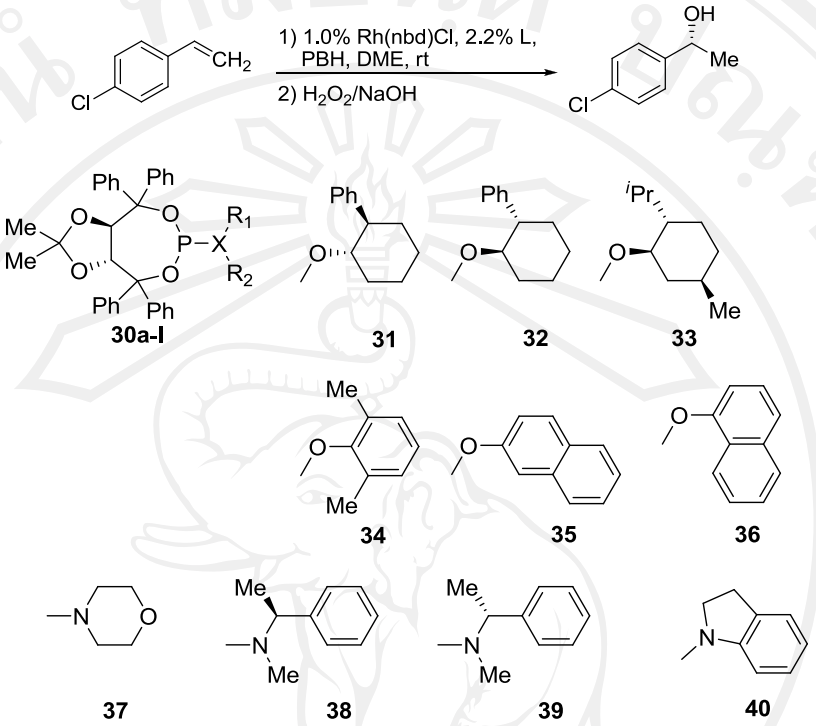
[e] Assigned by direct comparison of the specific rotation, determined on a Polarimeter, with the literature value.

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

1.3.1.4 TADDOLs-derived chiral phosphorus

The two simple TADDOL-derived monodentate ligands, phosphites **32** and phosphoamidites **30g** which afford comparable high levels of enantioselectivity (90-96 %*ee*) in the rhodium-catalyzed asymmetric hydroborations of substituted styrene with pinacol borane (PBH) were reported by Shin A. Moteki and coworkers.[13] The data obtained for 4-chlorostyrene are summarized in Table 8.

Table 8 [Rh(nbd)Cl]$_2$-catalyzed hydroboration of 4-chlorostyrene using TADDOL-phosphite and phosphoamidite ligands, L



Entry	L	X	R_1	R_2	yield	% α	% *ee*
1	**30d**	O	Me	–	66	25	35
2	**30b**	O	Bn	–	80	67	–17
3	**31**	O	(1*S*,2*R*) Ph-cyclohexyl	–	68	51	42
4	**32**	O	(1*R*,2*S*) Ph-cyclohexyl	–	99	74	91
5	**33**	O	L-menthyl	–	59	82	31
6	**30a**	O	Ph	–	97	86	75
7	**34**	O	2,6-$Me_2C_6H_3$	–	80	16	0
8	**35**	O	2-naphthyl	–	84	77	40
9	**36**	O	1-naphthyl	–	67	8	65
10	**37**	N	$–CH_2CH_2OCH_2CH_2–$	–	44	61	–19
11	**30e**	N	Me	Me	67	74	51
12	**30f**	N	Bn	Me	54	69	17
13	**38**	N	(*S*) phenethyl	Me	84	68	-33
14	**39**	N	(*R*) phenethyl	Me	72	61	-11
15	**30c**	N	Bn	Bn	77	71	-3

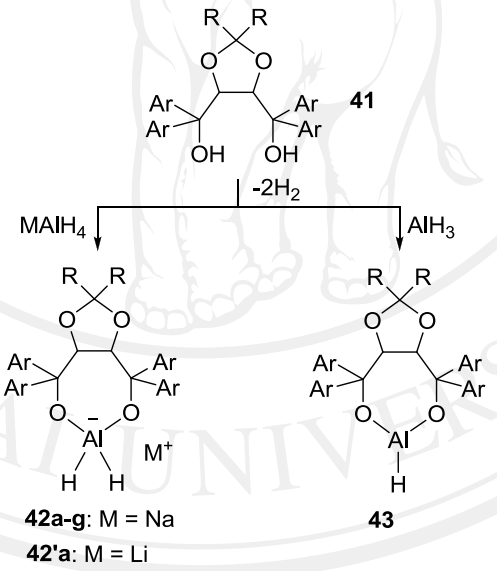
Table 8 [Rh(nbd)Cl]$_2$-catalyzed hydroboration of 4-chlorostyrene using TADDOL-phosphite and phosphoamidite ligands, L (continued)

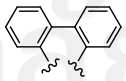
Entry	L	X	R_1	R_2	yield	% α	% *ee*
16	**30g**	N	Bn	Ph	86	75	94
17	**30h**	N	Me	Ph	98	52	85
18	**30i**	N	Ph	Ph	92	12	45
19	**40**	N	indolinyl		58	85	41

+ values for the % *ee* correspond to the *S* enantiomer predominating

1.3.1.5 TADDOL-derived lithium aluminium hydride

In 2003, Vinogradov *et al*. synthesized the TADDOL-containing hydride reagents **42** based on $NaAlH_4$ and triconaate chiral aluminium hydrides **43** and applied for the asymmetric reduction of prochiral substrates, C=O and C=N groups.[14]

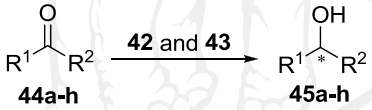


	R	R + R	Ar		R	R + R	Ar
a	Me	-	Ph	e	-		Ph
b	Et	-	Ph				
c	-	$(CH_2)_4$	Ph	f	Me	-	4-$MeOC_6H_4$
d	-	$(CH_2)_5$	Ph	g	Me	-	4-$Bu^tC_6H_4$

Scheme 5 TADDOL-containing hydride reagents.

As can be seen from Table 9 (entries 1-19), the reactions of alkyl aryl ketones **44a-f** with reagents **42** ($M^+ = Na^+$) at room temperatures from –20 °C to –70 °C proceeded with a high conversion of ketones (generally, 95-100%) and the enantioselectivity of up to 90% *ee*. Compared to complexes **42** ($M^+ = Na^+$), tricoordinate aluminium hydrides **43** illustrate much lower reactivity and stereoselectivity in asymmetric reduction of alkyl aryl ketones. The reactions of reagents **43a-d** with ketones **44a-f** are characterized by moderate conversions of the ketones and moderate optical yields (entries 20-36, Table 9), whereas aluminium hydrides **43e** and **43f** reacted non-stereoselectively with low conversions of ketone **44** (entries 37 and 38).

Table 9 Asymmetric reduction of alkyl aryl ketones **44a-f** with aluminium hydride reagents **42** ($M^+ = Na^+$) and **43** in THF giving rise to alcohols **45a-f**



44a-h **45a-h**

	R^1	R^2		R^1	R^2
a	Ph	Me	e	2-naphthyl	Me
b	Ph	Et	f	2-fluorennyl	Me
c	Ph	Pr^i	g	cyclopropyl	Me
d	1-naphthyl	Me	h	CO_2Et	$(CH_2)_2Ph$

Entry	Reagent	Configuration of **41**	SC	T_{red}/°C	Conversion (%)	*ee* (%)
1	**42a**	(*S*,*S*)	**44b**	–70	100	88 (*R*)
2	**42a**	(*S*,*S*)	**44b**	–70	98	90 (*R*)
3	**42a**	(*S*,*S*)	**44c**	–70	94	83 (*R*)
4	**42a**	(*S*,*S*)	**44c**	–20	100	76 (*R*)
5	**42a**	(*S*,*S*)	**44f**	–20	87	70 (*R*)
6	**42c**	(*R*,*R*)	**44b**	–20	99	78 (*S*)
7*	**42d**	(*R*,*R*)	**44b**	–20	100	83 (*S*)
8	**42e**	(*R*,*R*)	**44a**	–70	100	85 (*S*)

Table 9 Asymmetric reduction of alkyl aryl ketones **44a-f** with aluminium hydride reagents **42** ($M^+ = Na^+$) and **43** in THF giving rise to alcohols **45a-f** (continued)

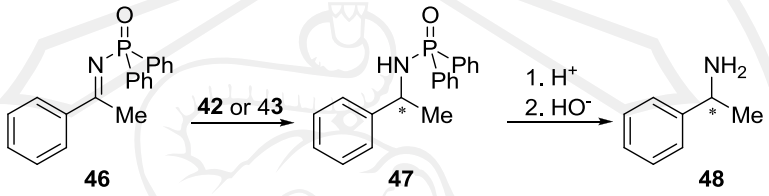
Entry	Reagent	Configuration of **41**	SC	T_{red}/°C	Conversion (%)	*ee* (%)
9	**42e**	(*R*,*R*)	**44b**	–70	100	80 (*S*)
10	**42e**	(*R*,*R*)	**44b**	–20	100	75 (*S*)
11	**42e**	(*R*,*R*)	**44c**	–70	100	78 (*S*)
12	**42f**	(*R*,*R*)	**44a**	–20	100	73 (*S*)
13	**42f**	(*R*,*R*)	**44b**	–20	99	83 (*S*)
14	**42g**	(*R*,*R*)	**44a**	–70	100	83 (*S*)
15	**42g**	(*R*,*R*)	**44b**	–70	100	78 (*S*)
16	**42g**	(*R*,*R*)	**44c**	–70	100	85 (*S*)
17	**42h**	(*S*,*S*)	**44a**	–70	100	78 (*R*)
18	**42h**	(*S*,*S*)	**44b**	–70	100	84 (*R*)
19	**42h**	(*S*,*S*)	**44c**	–70	100	83 (*R*)
20	**42a**	(*R*,*R*)	**44a**	–20	83	42 (*R*)
21	**43a**	(*S*,*S*)	**44a**	–20	79	37 (*R*)
22	**43a**	(*R*,*R*)	**44b**	–20	76	54 (*S*)
23	**43a**	(*S*,*S*)	**44c**	–20	42	36 (*R*)
24	**43a**	(*R*,*R*)	**44d**	–20	62	47 (*S*)
25	**43a**	(*S*,*S*)	**44e**	–20	70	40 (*R*)
26	**43a**	(*S*,*S*)	**44f**	–20	70	34 (*R*)
27	**43b**	(*S*,*S*)	**44a**	–20	80	50 (*R*)
28	**43b**	(*R*,*R*)	**44b**	–20	100	44 (*R*)
29	**43c**	(*S*,*S*)	**44a**	–20	57	38 (*R*)
30	**43c**	(*R*,*R*)	**44b**	–20	91	30 (*S*)
31	**43d**	(*S*,*S*)	**44a**	–20	53	47 (*R*)
32	**43d**	(*R*,*R*)	**44b**	–20	100	52 (*S*)
33	**43d**	(*R*,*R*)	**44c**	–20	50	43 (*S*)
34	**43d**	(*R*,*R*)	**44d**	–20	77	31 (*S*)
35	**43d**	(*R*,*R*)	**44e**	–20	87	30 (*S*)
36	**43d**	(*R*,*R*)	**44f**	–20	70	40 (*S*)
37	**43e**	(*R*,*R*)	**44a**	–20	3	0
38	**43f**	(*R*,*R*)	**44a**	–20	16	7 (*S*)

Note. SC is the starting compound.

* Reduction was carried out with the use of the solid NaAl(IPTOLate)H_2•THF complexe.

The asymmetric reduction of activated imine **46** with reagents **42** ($M^+ = Na^+$) (Table 10) is characterized by both high conversion and the *ee* values comparable with the results of reduction of alkyl aryl ketones.

Table 10 Asymmetric reduction of *N*-(triphenylphosphinyl)acetophenoneimine (**46**) with aluminium hydride reagents **42** ($M^+ = Na^+$) and **43** in THF



Entry	Reagent	Configuration of **41**	T_{red}/°C	Conversion (%)	**PA**	*ee* (%)
1	**42a**	(*S*,*S*)	–70	98	**47**	77 (*R*)
2	**42a**	(*S*,*S*)	–20	97	**47 (48)**	79 (78) (*R*)
3*	**42a**	(*R*,*R*)	–20	94	**47**	36 (*S*)
4*	**42a**	(*S*,*S*)	–20	90	**47**	36 (*S*)
5	**42a**	(*R*,*R*)	+20	98	**47**	58 (*S*)
6	**42'a****	(*R*,*R*)	–20	99	**47**	30 (*S*)
7*	**42'a****	(*S*,*S*)	–20	97	**47**	30 (*R*)
8	**42b**	(*R*,*R*)	–70	95	**48**	78 (*S*)
9	**42b**	(*R*,*R*)	–20	97	**48**	76 (*S*)
10	**42b**	(*R*,*R*)	+20	96	**48**	71 (*S*)
11	**42c**	(*R*,*R*)	–20	100	**47**	75 (*S*)
12	**42e**	(*R*,*R*)	–70	100	**47**	67 (*S*)
13	**42e**	(*R*,*R*)	–20	100	**47**	69 (*S*)
14	**42f**	(*R*,*R*)	–20	100	**47**	76 (*S*)
15	**43a**	(*S*,*S*)	–20	62	**47**	42 (*R*)
16	**43b**	(*R*,*R*)	–20	72	**47**	55 (*S*)
17	**43c**	(*S*,*S*)	–20	65	**47**	61 (*R*)
18	**43d**	(*R*,*R*)	–20	64	**47**	37 (*S*)
19	**43e**	(*R*,*R*)	–20	62	**47**	64 (*S*)
20	**43f**	(*R*,*R*)	–20	60	**47**	27 (*S*)

Note. **PA** is the product analyzed.

* Reduction was carried out with the use of complex **42a** ($M^+ = Na^+$) in which one of the hydride atoms is replaced by the ethoxy groups.

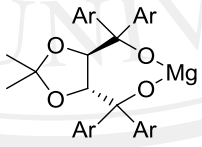
** $M^+ = Li^+$

1.3.2 TADDOLs as chiral catalysts in asymmetric syntheses

The chiral diol have long occupied a position of importance in the field of asymmetric catalysis, TADDOLs and their analogues are widely useful ligands for many asymmetric syntheses. Applied of TADDOLs and derivatives to addition to carbonyl compounds, reductions, oxidations and rearrangements have been described.

1.3.2.1 Addition to carbonyl compounds

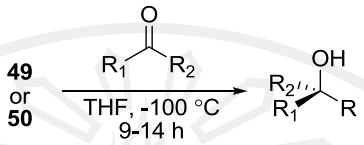
One of the most powerful methods for the catalytic asymmetric generation of C–C bonds is the enantioselective addition of organometallic reagents to aldehydes or ketones. In 1994, Weber and Seebach firstly reported the successful asymmetric addition of Grignard reagents to ketones and obtained chiral tertiary alcohols in greater than 95% *ee*.[15] The reactions of the chiral TADDOLate reagents **49** or **50** (Figure 10) with the various of methyl ketones were evaluated and very high enantioselectivities were observed (Table 11)



49, Ar = Ph; **50**, Ar = 2-naphthyl

Figure 10 TADDOLate reagents

Table 11 Reactions of methyl ketones with reagents derived from TADDOLs **49** or **50**



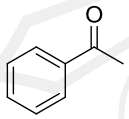
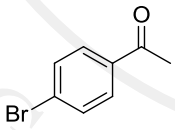
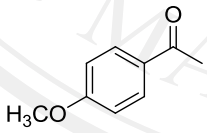
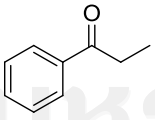
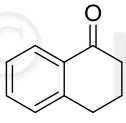
Entry	Ketones	TADDOL	R in RMgBr	Yield (%)	*ee* (rotation)[a] (%)
1		**49**	Et	62	98 (*R*)-(+)
2		**49**	*n*-Pr	84	>98 (*R*)-(+)
3		**49**	*n*-Bu	75	>98 (*R*)-(+)
4		**49**	*n*-Hex	58	>98 (+)
5		**49**	*n*-Oct	58	>98 (+)
6		**49**	CH_2Ph	14	70 (*R*)-(+)
7		**49**	$(CH_2)CH=CH_2$	60	>98 (–)
8		**49**	Et	60	98 (+)
9		**49**	Et	76	92 (+)
10		**49**	*n*-Bu	7	90 (–)
11		**49**	Et	28	89 (+)
12		**50**	Et	12	94 (+)

Table 11 Reactions of methyl ketones with reagents derived from TADDOLs **49** or **50** (continued)

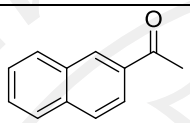
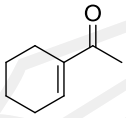
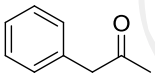
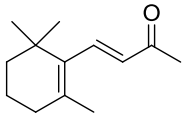
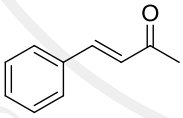
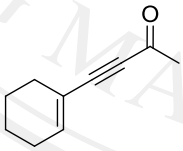
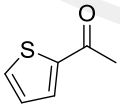
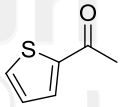
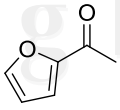
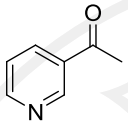
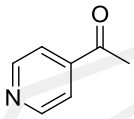
Entry	Ketones	TADDOL	R_1 in RMgBr	Yield (%)	*ee* (rotation)[a] (%)
13		**49**	Et	75	98 (+)
14		**49**	Et	55	71 (–)
15		**49**	Et	22	50
16		**49**	Et	64	83 (–)
17		**50**	Et	25	77 (–)
18		**49**	Et	40	70
19		**49**	Et	88	75
20		**49**	Et	43	96 (+)
21		**49**	$(CH_2)CH=CH_2$	30	97
22		**49**	Et	24	90
23		**49**	Et	53	66

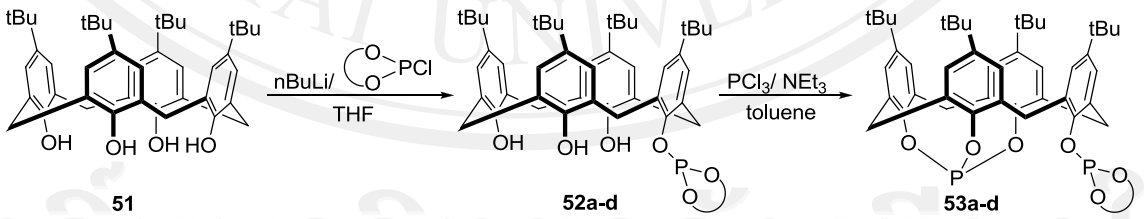
Table 11 Reactions of methyl ketones with reagents derived from TADDOLs **49** or **50** (continued)

Entry	Ketones	TADDOL	R_1 in RMgBr	Yield (%)	*ee* (rotation)[a] (%)
24		**49**	Et	51	96 (+)
25		**49**	Et	96	>98 (+)
26		**49**	$(CH_2)CH=CH_2$	51	98 (+)

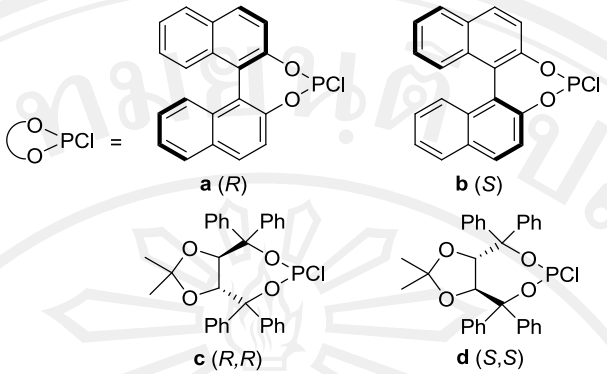
[a] A % ee > 98 means the minor enantiomer was undetectable; in those entries where the rotation sign is missing, the alcohols had very small optical rotations, or not enough sample was available for measurement.

1.3.2.2 Reduction reactions

In 2007, Marson and coworkers synthesized the novel chiral diphosphites ligands **53a-d** which had the calix[4]arene as backbones. These catalysts had been employed in the rhodium catalyzed hydrogenation of prochiral olefins providing excellent activities and enantioselectivities in the hydrogenation of dimethyl itaconate and methyl α-acetamidoacrylate (Scheme 6).[16]



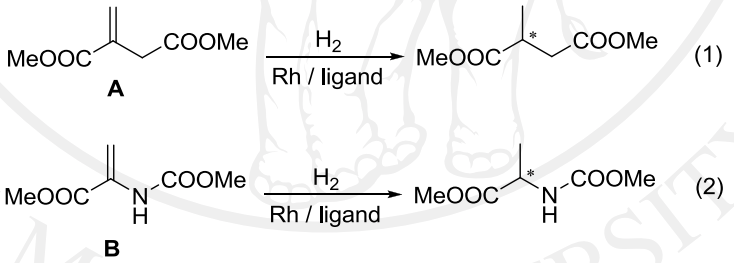
Scheme 6 Synthesis of chiral calix[4]arene-based diphosphites **53a-d**.



Scheme 6 Synthesis of chiral calix[4]arene-based diphosphites **53a-d** (continued).

Chiral diphosphites **53a-d** were applied as ligands in the asymmetric rhodium-catalysed hydrogenation of prochiral olefins using $[Rh(nbd)_2BF_4]$ as metal precursor (Table 12).

Table 12 Asymmetric hydrogenation of prochiral olefins with $[Rh(nbd)_2BF_4]$ and ligands **53a-d**[a]



Entry	Ligand	Substrate	% conv. (*t* [h])[b]	% *ee* (config.)[c]
1	**53a**	**A**	100 (20)	74 (*R*)
2	**53a**	**A**	100 (4)	74 (*R*)
3[d]	**53a**	**A**	100 (4)	76 (*R*)
4[e]	**53a**	**A**	60 (20)	20 (*S*)
5	**53a**	**B**	100 (20)	32 (*R*)
6	**53c**	**A**	100 (20)	92 (*R*)
7	**53c**	**A**	100 (4)	92 (*R*)
8[d]	**53c**	**A**	100 (4)	94 (*R*)
9[f]	**53c**	**A**	100 (20)	92 (*R*)
10	**53c**	**A**	100 (20)	94 (*R*)

Table 12 Asymmetric hydrogenation of prochiral olefins with $[Rh(nbd)_2BF_4]$ and ligands **53a-d**[a] (continued)

Entry	Ligand	Substrate	% conv. (*t* [h])[b]	% *ee* (config.)[c]
11	**53b**	**B**	100 (20)	75 (*S*)
12	**53d**	**A**	100 (20)	92 (*S*)

[a] Standard conditions: [Rh] = 1mM; [ligand/[Rh] = 1.5; [substrate]/[Rh] = 100; solvent solvent = CH_2Cl_2 92.0 mL); *p* = 5 bar; *T* = 25 °C; catalyst precursors prepared *in situ*.

[b] Percent conversion measured by GC.

[c] Percent enantiomeric excess measured by chiral GC.

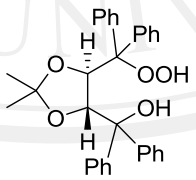
[d] [substrate]/[Rh] = 100.

[e] Solvent: CH2Cl2/toluene, 1:3.

[f] [ligand/[Rh] = 5

1.3.2.3 Oxidation reactions

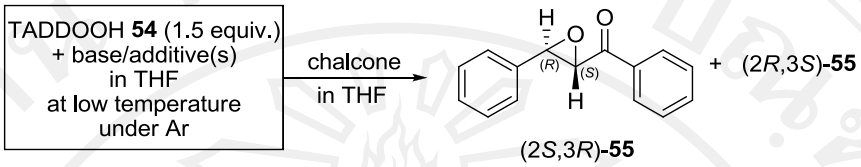
In 2001, Aoki and Seebach synthesized the new type of chiral hydroperoxide that is readily prepared from H_2O_2 and a TADDOL. The new chiral hydroperoxide catalyst was tested as chiral oxidant in the epoxidation of enones with base catalysis and the sulfonation of methyl phenyl sulfide.[17] The epoxidation of enones were tested by using the new hydroperoxide, TADOOH **54**, with the standard substrate chalcone to optimize condition (Table 13).



TADDOOH

Figure 11 TADOOH reagent **54**

Table 13 Epoxidation of 1,3-diphenylprop-2-en-1-one and of other enones with hydroperoxy alcohol **54**

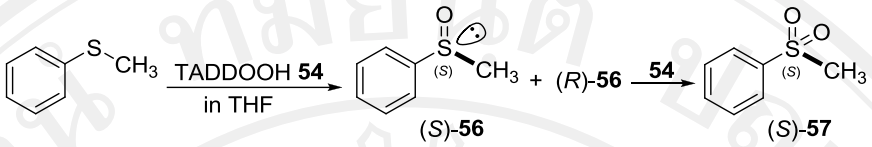


Entry	Base [equiv]	Additive(s) [equiv]	Temp [°]	Reaction time [h]	55	
					Yield [%]	(2*S*,3*R*)/(2*R*,3*S*)
1	–	–	–78 → r.t.	7	–	–
2	1.1 Et_3N	–	–78 → r.t.	7	–	–
3	1.1 DMAP	–	–78 → r.t.	7	–	–
4	1.1 KOH	–	–78 → r.t.	7	96	33:67
5	1.1 NaOH	–	–78 → r.t.	7	86	46:54
6	1.1 LiOH	–	–78 → r.t.	7	95	80:20
7	1.1 BuLi	–	–78 → r.t.	7	85	95:5
8	1.1 BuLi	–	0	4	94	90:10
9	1.1 BuLi	–	–30	24	92	95:5
10	1.1 BuLi	–	–78	120	80	98.5:1.5
11	1.1 Et_3N	1.1 LiCl	–78 → r.t.	7	–	–
12	1.1 DMAP	1.1 LiCl	–78 → r.t.	7	65	77:23
13	1.1 DBN	1.1 LiCl	–78 → r.t.	7	96	88:12
14	1.1 DBU	1.1 LiCl	–78 → r.t.	7	89	86:14
15	1.1 DBU	0.11 LiCl	–78 → r.t.	7	98	84:16

The equivalents of **54** and of the base refer to 1 equiv of chalcone. The optimization experiments were carried out with 0.5-mM amounts of chalcone. Enantiomer ratios (er) were determined on chiral GC column. Yields after FC are given.

Table 14 indicated the enantioselective oxidation of MeSPh using TADOOH **54** as catalyst (Table 14).

Table 14 Oxidation of MeSPh by the hydrogenperoxy alcohol **54**

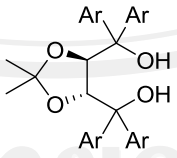


Entry	Temp [°]	Reaction time [h]	**56**		Yield [%] of **57**
			Yield [%]	(*S*)/(*R*)	
1	r.t.	4	91	82:18	6
2	r.t.	24	72	88:12	27
3	–30	72	61	90:10	<1
4	–30 ⟶ r.t.	72 + 24	73[a]	93:7	23

Reactions were carried out with a 1:1.5 molar ratio of MeSPh and **54**. Yields were detected by GC, enantiomer ratios were determined on a chiral GC column.

1.3.2.4 Rearrangements

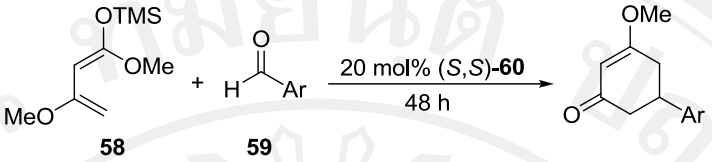
In 2004, Ding *et al*. observed the catalytic enantioselective hetero-Diels-Alder reaction of Brassard's diene **58** with aldehydes **59** which had been achieves by catalysis with TADDOL derivatives **60** through hydrogen-bonding activation to afford the corresponding δ-lactone derivatives in moderate-to-good yields and with high enantioselectivities (Table 15).[18]



60
Ar = 1-Naphthyl

Figure 12 TADDOL catalyst **60** for asymmetric hetero-Diels-Alder reaction

Table 15 The reaction of Brassard's diene with aldehydes catalyzed by **60**[a]



58 **59**

Entry	Ar	Toluene (mL)	Temp (°C)	% Yield[c]	% *ee*[d]
1[b]	Ph **59a**	0.2	–60	67	83 (*S*)
2[b]	furyl **59b**	0.2	–60	80	87 (*S*)
3	*o*-MeC_6H_4 **59c**	0.2	–30	54	68 (*R*)
4	*p*-ClC_6H_4 **59d**	0.4	–30	85	76 (*R*)
5	*p*-BrC_6H_4 **59e**	0.4	–30	72	78 (*R*)[e]
6	*m*-BrC_6H_4 **59f**	0.4	–60	67	89 (*R*)
7	*o*-BrC_6H_4 **59g**	0.4	–60	75	82 (*R*)
8	*m*-$MeOC_6H_4$ **59h**	0.2	–60	45	91[f]

[a] All the reactions were carried with 2.5 mmol of benzalddehyde and 0.5 mmol of brassard'd diene.

[b] The catalyst employed in this case was (*R*,*R*)-**60b**.

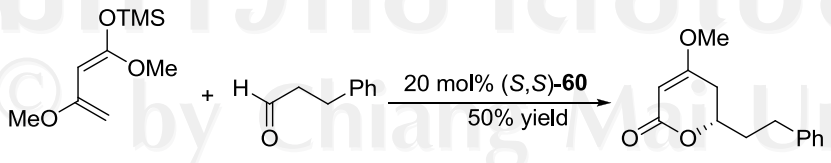
[c] Yield of isolated product.

[d] The enantiomeric excesses of the products were determined by HPLC on a Chiralpak AD column. The absolute configurations were assigned by comparing the Cotton effect of the CD spectra with that of **59e**.

[e] The absolute configuration was determined by X-ray crystal atructural analysis of **59e** on the basis of the anomalous dispersion of the heavy bromide atom.

[f] The absolute configuration was not assigned.

To demonstrate the usefulness of the methodology, a natural product, (*S*)-(+)-dihydrokawain **61** has also been synthesized in 50% yield and 69% *ee* in one step using 3-phenylpropionaldehyde (**59i**) as starting material (Scheme 7).

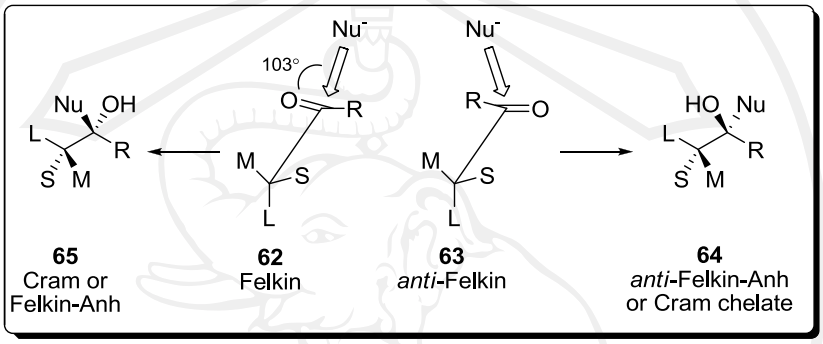


58 **59i** **61**, 69% *ee*
(*S*)-(+)-dihydrokawain

Scheme 7 One-step synthesis of (*S*)-(+)-dihydrokawain **61**.

1.4 Stereochemistry[19]

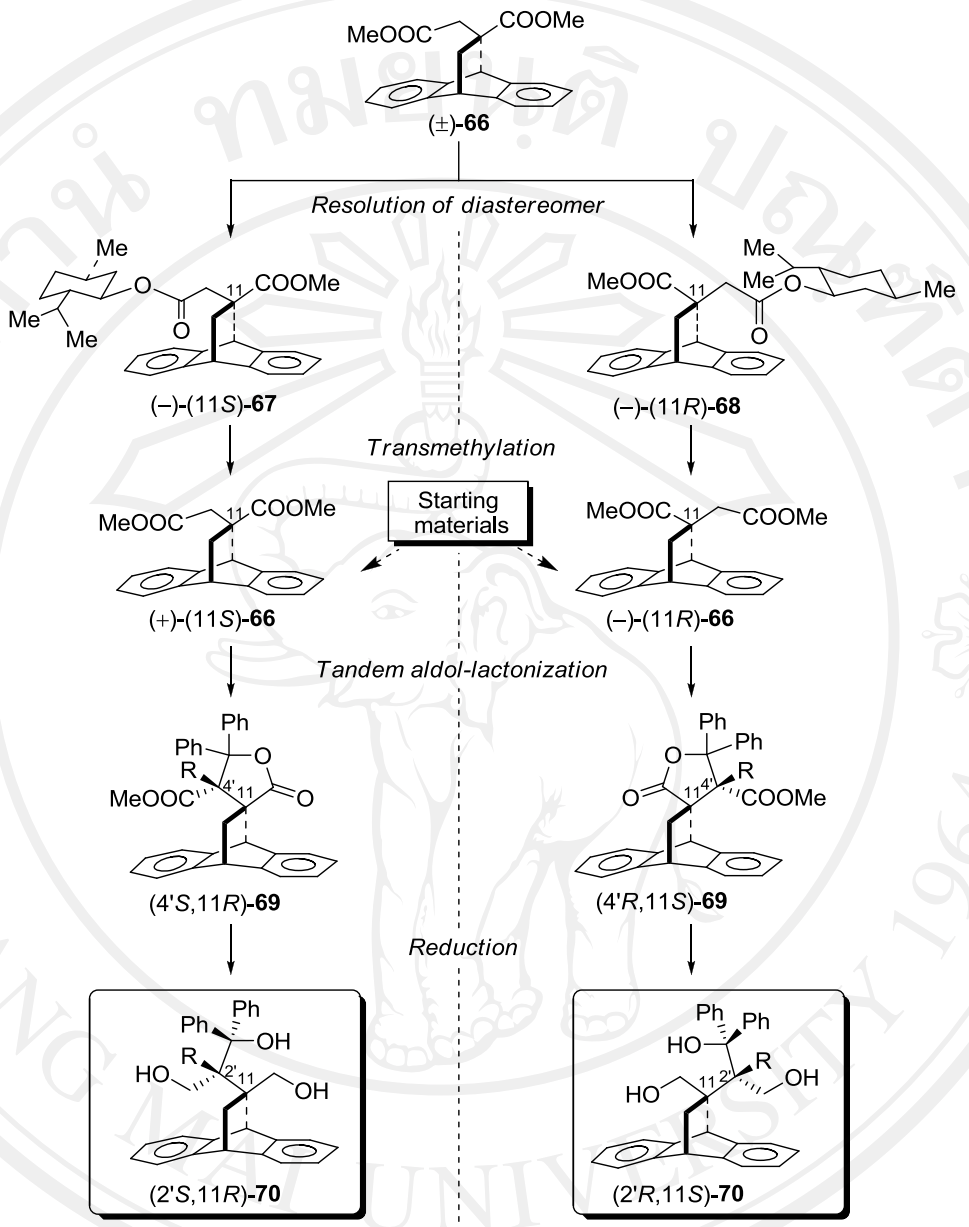
Felkin-Anh model is one of the models to examine the stereochemistry for nucleophilic addition reaction to carbonyl. The key idea was that the substituent L is placed orthogonal to the carbonyl group, allowing the nucleophile to attack *anti* to L, so most effectively avoiding steric repulsion (Scheme 8).



Scheme 8 Schematic represents the Felkin-Anh model.

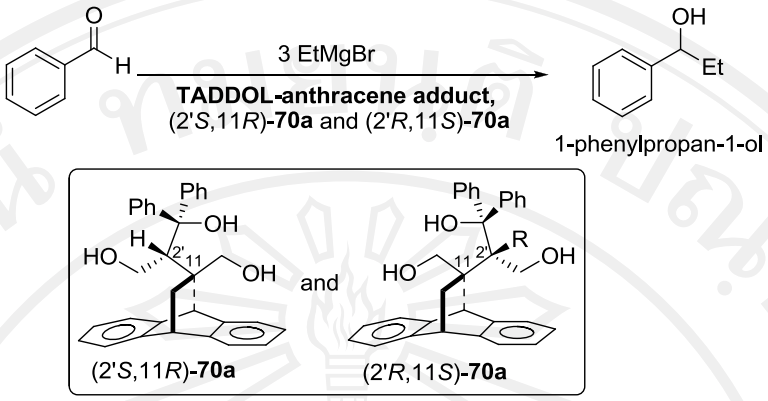
1.5 Aims and research objectives

Aim of this research focused on design both the novel TADDOL–anthracene adducts (2′*S*,11*R*)-**70** and (2′*R*,11*S*)-**70** in enantiomerically pure forms by using optically active dimethyl itconate–anthracene adducts (+)-(11*S*)-**66** and (−)-(11*R*)-**66** as starting materials (Scheme 9).



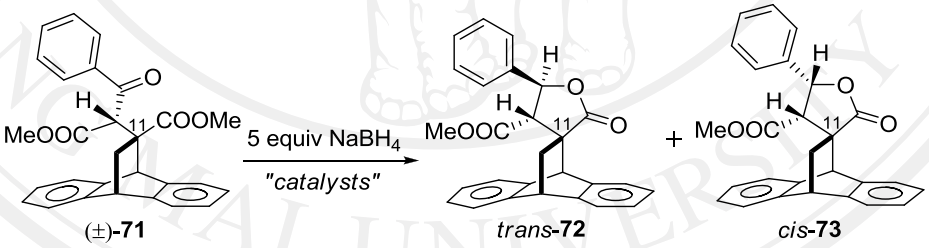
Scheme 9 Syntheses of TADDOL–anthracene analogues (2′*S*,11*R*)-**70** and (2′*R*,11*S*)-**70**.

Additionally, the novel TADDOL–anthracene catalysts (2′*S*,11*R*)-**70a** and (2′*R*,11*S*)-**70a** had been studied in the 1,2-addition of ethyl magnesium bromide to benzaldehyde (Scheme 10).



Scheme 10 Studied the 1,2-addition reaction of ethyl magnesium bromide to benzaldehyde with TADDOL–anthracene adduct (2′*S*,11*R*)-**70a** and (2′*R*,11*S*)-**70a**.

Furthermore, applied TADDOL–anthracene adduct (2′*S*,11*R*)-**70a** and (2′*R*,11*S*)-**70a** in reduction of *β*-keto ester (±)-**71** using $NaBH_4$ as reducing agent by variation the concentration of catalysts (Scheme 11) was studied.



Scheme 11 Applied of the novel TADDOL–anthracene catalysts (2′*S*,11*R*)-**70a** and (2′*R*,11*S*)-**70a** in the reduction of *β*-keto ester (±)-**71** using $NaBH_4$ as reducing agent.