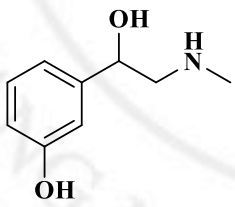
CHAPTER 1

INTRODUCTION

Phenylephrine **(1)** is an α_1-adrenergic receptor agonist and β-receptor sympathomimetric drug; its main use as a nasal decongestant, an agent to dilate the pupil, and increase blood pressure. It is also a mydriatic, a cardiotonic and a vasoconstrictor. It was first marketed in 1936 by Boehringer Ingelheim, under the name Adrianol, as the optically active *(R)*-form **(2)** and the hydrochloride salt **(3)**.[1,2]



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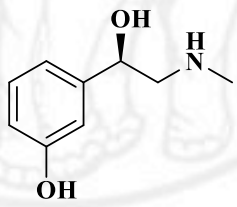

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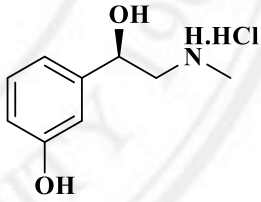

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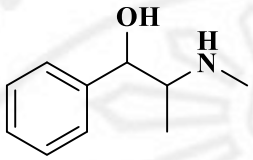
Furthermore, the systemic bioavailability of phenylephrine in nasal decongestants is only about 38% that of orally administered pseudoephedrine **(4)**.[3,4] Phenylephrine does not cause the release of endogenous noradrenaline[5] and is less likely to cause side effects like central nervous system stimulation, insomnia, anxiety, irritability and restlessness.[6] Moreover, the Combat Methamphetamine Epidemic Act of 2005 permits the banning of counter sales of medications containing

pseudoephedrine **(4)**, in order to control the clandestine manufacture of methamphetamine **(5)** from pseudoephedrine in the USA. This has resulted in the substitution of *(R)*-phenylephrine for pseudoephedrine in many decongestants.[7, 8]



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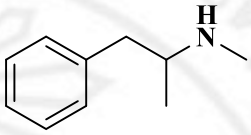

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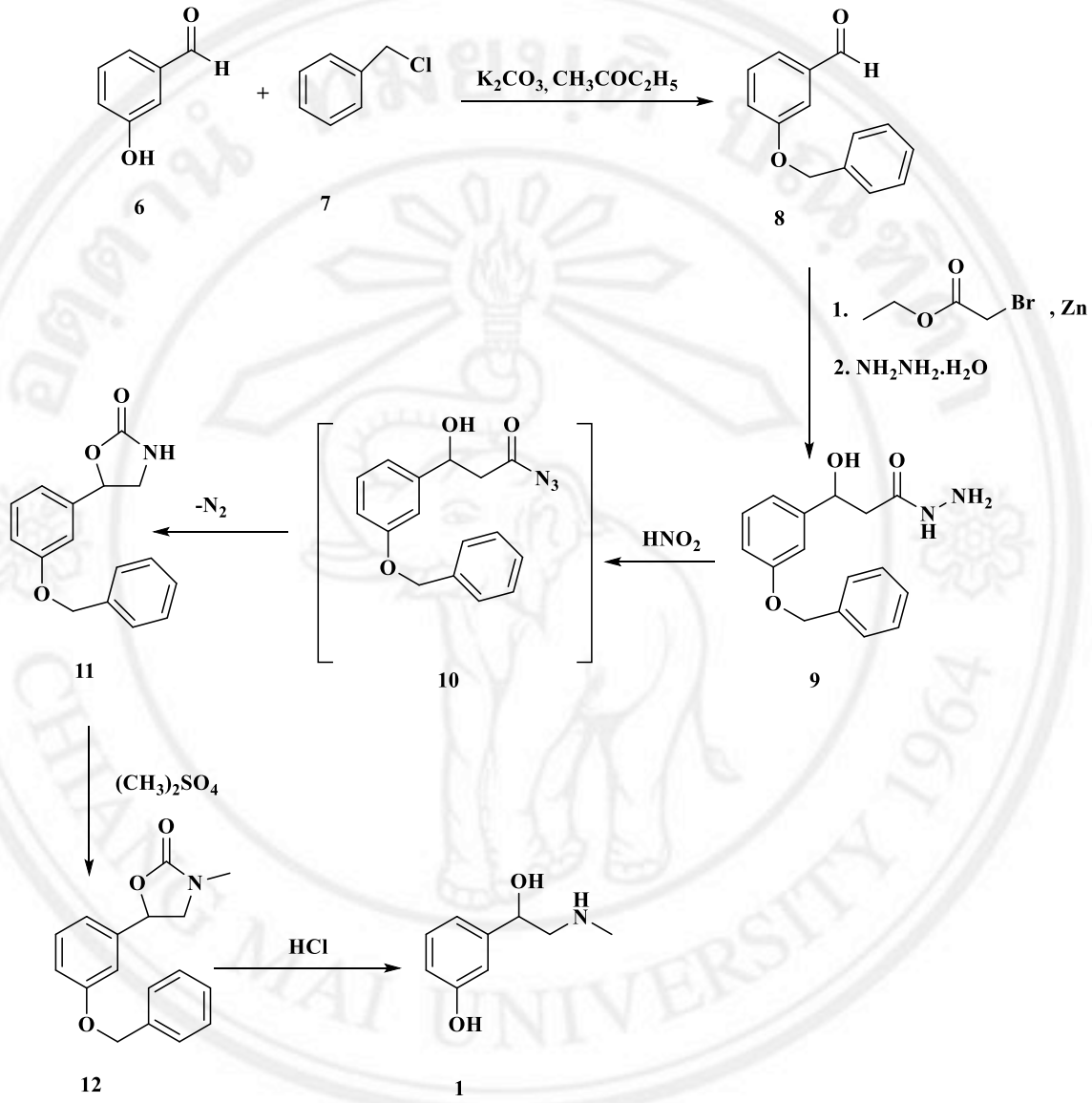
1.1 Synthesis of (±)-phenylephrine

Various methods have been reported for synthesizing racemic phenylephrine. The classical industrial synthetic route was developed in the late 1920s and early 1930s and published in a series of patents by H. Legerlotz.[9-11] These describe the synthesis of racemic phenylephrine and give details of the resolution procedure using tartaric acid and the Walden inversion by which the undesired isomer is transformed into the desired isomer. This route was subsequently investigated and refined.[12-14]

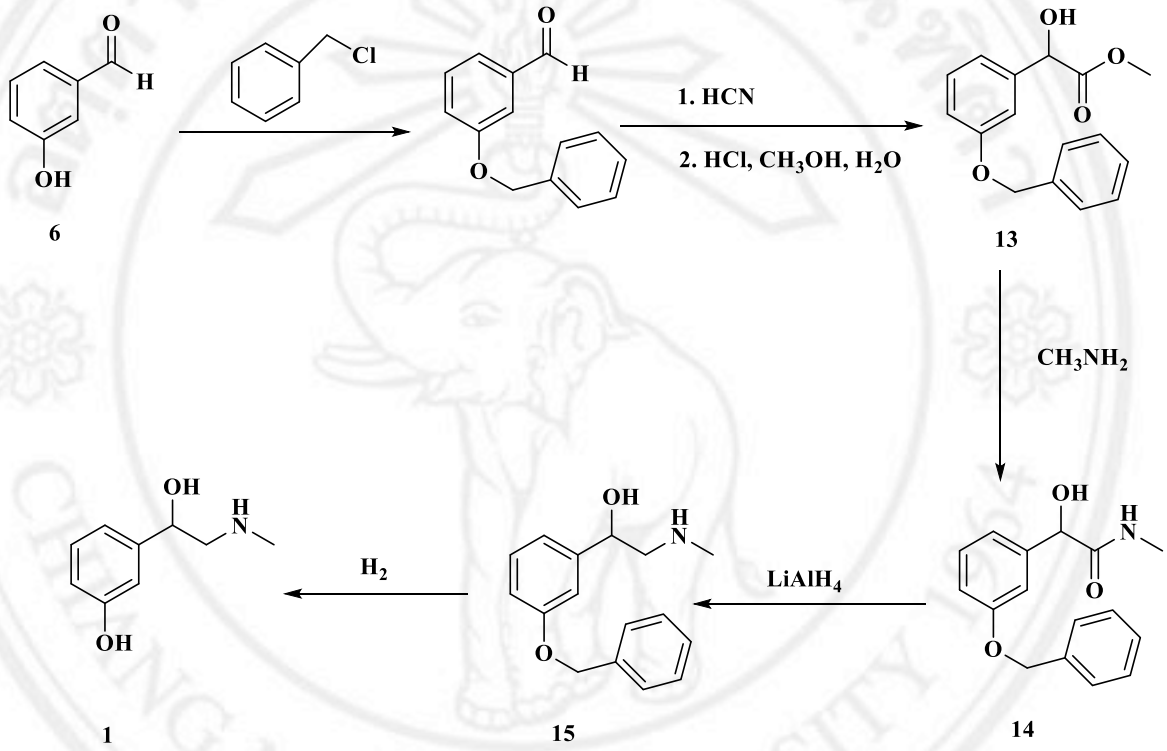
In 1951 Bergmann and Sulzbacher[15] prepared (±)-phenylephrine from *m*-hydroxybenzaldehyde **(6)** as a starting material. *m*-Hydroxybenzaldehyde **(6)** was protected with benzyl chloride **(7)** and followed by another 3 steps, the Curtius rearrangement of β-hydroxyacid azides **(10)** occurred. The pathway of synthesis was shown in Scheme 1. The overall yield was quite low (20%). Although the desired product was obtained but every step used benzene as a solvent, the reaction proceeded under heat at a long period of time and applied the multiple steps synthesis.



Scheme 1 Synthesis of (±)-phenylephrine by Bergmann and Sulzbacher pathway

In 1961 Russell and Childress[16] reported the new route to (±)-phenylephrine. This reaction was started by using *m*-hydroxybenzaldehyde **(6)** as a starting material. The ketone compound **(14)** was reduced with lithium aluminium hydride, followed by deprotection of benzyl group with hydrogen palladium-charcoal to provide the

(±)-phenylephrine (Scheme 2) in 43% overall yield. Although this reaction was improved from Bergmann's procedure, the reaction still proceeded under heat at a long period of time.

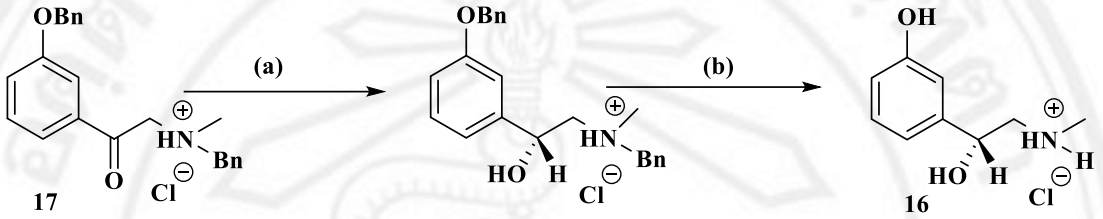


Scheme 2 Synthesis of (±)-phenylephrine by Russell and Childress pathway

1.2 Synthesis of (R)-phenylephrine

Phenylephrine contains a chiral center in the C_α of the side chain, and *(R)*-phenylephrine **(16)** exhibits more potential than the *(S)*-enantiomer in activating of α_1-adrenergic receptors[6]. In 1989 Takeda and co-workers[17] published the first asymmetric route to phenylephrine (Scheme 3). It utilized the asymmetric hydrogen-nation of an aminoacetophenone derivative **(17)** employing MCCPM rhodium

complex as a chiral catalyst. Although high yield and selectivity were obtained, the awkward step was the synthesis of the complicated chiral rhodium catalyst. In addition, the optical purity of the crude product is only 88% ee, and the final product cannot be efficiently purified by recrystallization.

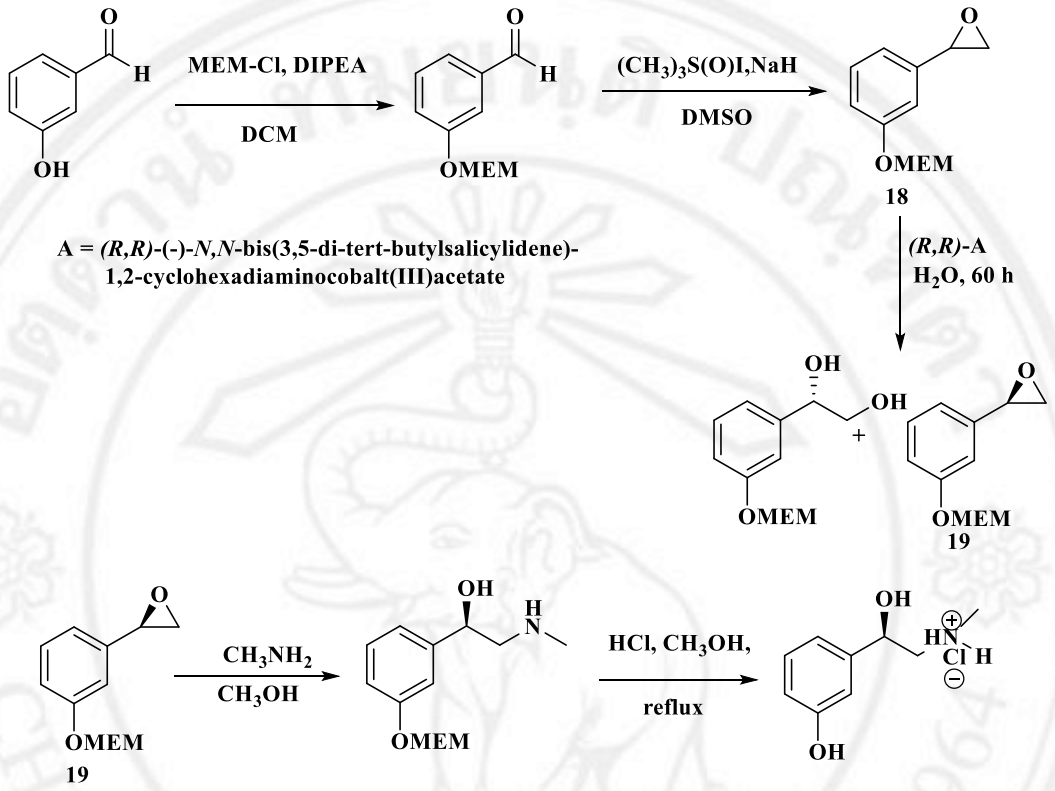


(a) chiral rhodium catalyst, triethylamine, H_2, methanol

(b) 10% (w/w) Pd/C, H_2(10 atm), 3 h

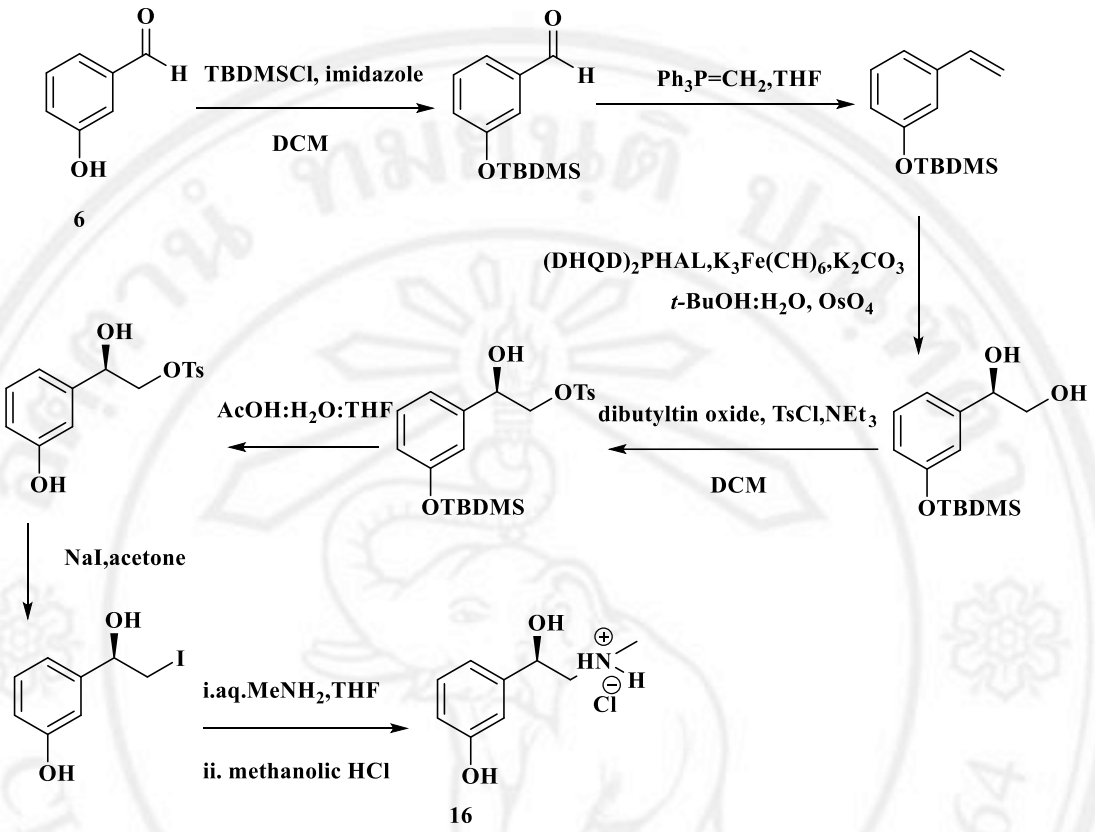
Scheme 3 Synthesis of *(R)*-phenylephrine by Takeda and co-workers pathway

Another interesting synthesis strategy was based on hydrolytic kinetic resolution of styrene oxide derivative **(18)** using a (*R*,*R*)-Salen $Co^{III}OAc$ ((*R*,*R*)-(-)-*N*,*N*-bis(3,5-di-*tert*-butylsalicydiene))-1,2-cyclo-hexanediaminocobalt (III) acetate complex by Gujar and co-workers[18,19] in 1998. *m*-Hydroxybenzaldehyde **(6)** was used as a precursor. The pathway of the synthesis is shown in Scheme 4. Once again, the disadvantage in this pathway are the employment of a complicated complex as a catalyst and low overall yield (26%). However, this pathway provied in relatively high enantiomeric excess (95%).



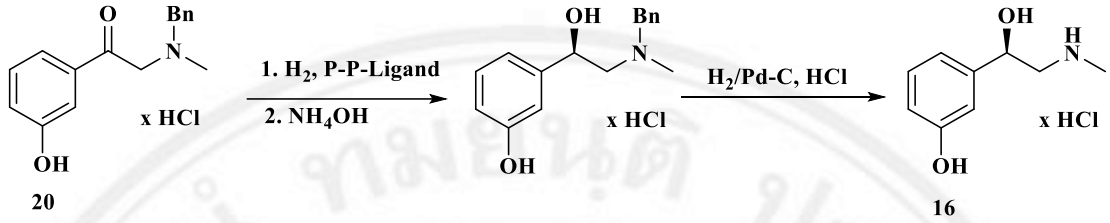
Scheme 4 Synthesis of *(R)*-phenylephrine by Gujar and co-workers pathway

In 2003, Pandey and co-workers[20] reported the synthesis of *(R)*-phenylephrine hydrochloride **(16)** employing Sharpless asymmetric dihydroxylation procedure (Scheme 5). *m*-Hydroxybenzaldehyde **(6)** was used as a precursor similar to Gujar's route. It was found that the complicated chiral catalyst, $(DHQD)_2PHAL$, was necessary in order to obtain the stereoselective reaction.



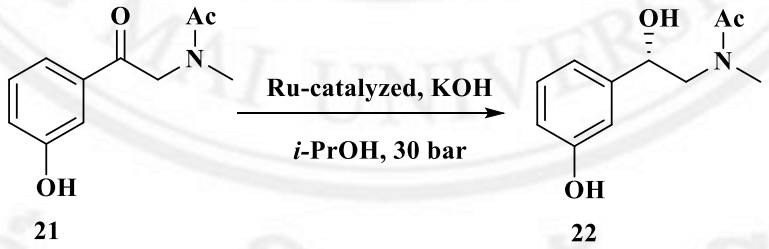
Scheme 5 Synthesis of *(R)*-phenylephrine by Pandey and co-workers pathway

In 2007 Klingler[21] studied asymmetric hydrogenation of *N*-benzylphenyl-ephrone **(20)**, which is an intermediate in the classical industrial synthesis, as the starting material and bisphosphine ligand was used as a catalyst (Scheme 6). It gave low to high enantiomeric excess (4-92%) but a very low reactivity, the conditions were under high pressure.



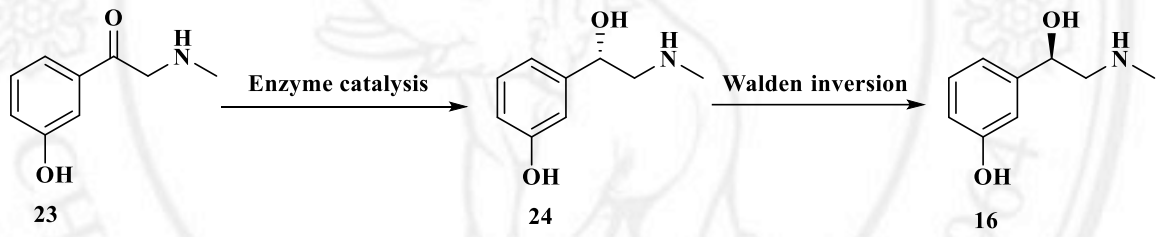
Scheme 6 Synthesis of *(R)*-phenylephrine by Klingler pathway

In 2010 McGarrity and Zanotti-Gerora[22] reported a feasibility study on a new route to *(R)*-phenylephrine, based on the ruthenium-catalyzed asymmetric hydrogen-nation of an *N*-protected aminoketone precursor **(21)** (Scheme 7). The direct and fast asymmetric reduction of *N*-protected aminoketone was achievable at low catalyst loadings (molar substrate to catalyst ratio, S/C, >25,000/1) with high enantioselectivity (>95% ee) but the *(S)*-phenylephrine **(22)** was the main product in most conditions, not the desired *(R)*-enantiomer. Moreover, these conditions employed high pressure and heated for a long period of time.



Scheme 6 Synthesis of *(R)*-phenylephrine by McGarrity and Zanotti-Gerora pathway

In 2010 Lin and co-workers[23] studied enantioselective synthesis of (*S)*-phenyl ephrine by enzyme catalysis (Scheme 8). The 1-(3-hydroxyphenyl)-2-(methylamino) ethanone **(23)** was converted to *(S)*-phenylephrine **(24)** by high performance liquid chromatography tandem mass spectrometry analysis. It gave 78% yield and >99% ee*(S).* Then the *(S)*-phenylephrine **(24)** was converted to *(R)*-phenylephrine **(16)** (>99%) by Walden inversion reaction. The set-back of this procedure was that it had a limit of the starting material concentration that was quite low in enzyme reaction and it could be done only in a small scale.



Scheme 8 Synthesis of *(R)*-phenylephrine by Lin and co-workers pathway

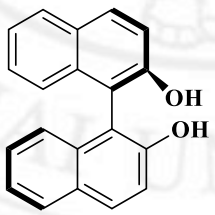
1.3 Asymmetric reduction of carbonyl compound

Synthesis of *(R)*-phenylephrine in previous studies was composed of two pathways which were the resolution from racemate synthesis and the asymmetric synthesis. In 2000 the worldwide market for single-enantiomer chiral fine chemicals was $6.63 billion and projected to grow to $16.0 billion by 2007.[24] Asymmetric synthesis describes that area of organic chemistry in which the preparation of a specific stereoisomer is targeted and which does not rely on the elimination of one of a pair of stereoisomers or on the isolation of one stereoisomer from a mixture of several.

Generally, asymmetric synthesis can be accomplished through the use of chiral auxiliaries, chiral reagents and chiral ligands and catalysts. Apart from synthesis of phenylephrine as a racemate, one of the objectives of this project involved the asymmetric reduction of ketone in order to get the *(R)*-form, discussion in this respect will be prefaced with a broad summary of reagents that are commonly used for the reduction of carbonyl compounds.

1.3.1 Modified lithium aluminium hydride

Chiral modifications of lithium aluminium hydride ($LiAlH_4$) were prepared by reacting $LiAlH_4$ with chiral natural products of known absolute stereochemistry such as (-)-camphor, prior to the introduction of prochiral ketone.[25, 26] Other examples of modified $LiAlH_4$ are those obtained from its reaction with *(R)*-1,1'-bi-2-naphthol **(25)** or *(S)*- 1,1'-bi-2-naphthol **(26)** to give BINAL-H **(27, 28)**.



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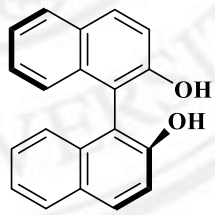

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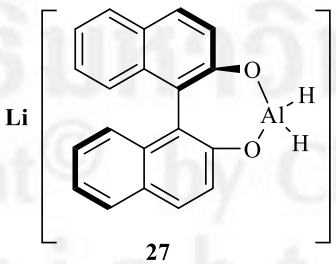

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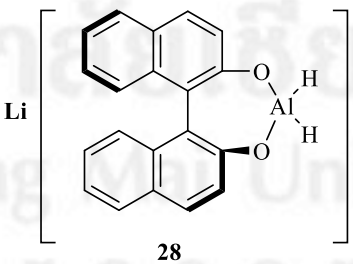

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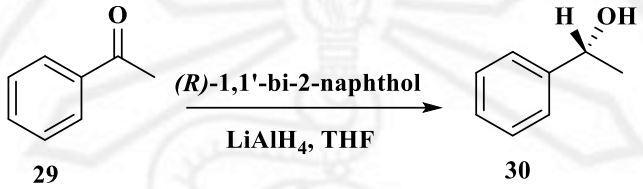
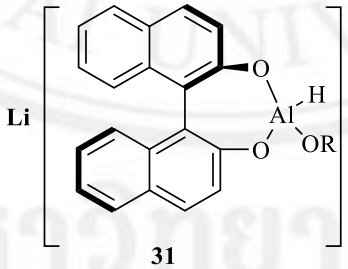
In 1984 Noyori and co-workers[27] studied asymmetric reduction of prochiral acetopenone **(29)** by BINAL-H **(27)** (Scheme 9). BINAL-H **(27)** was prepared by

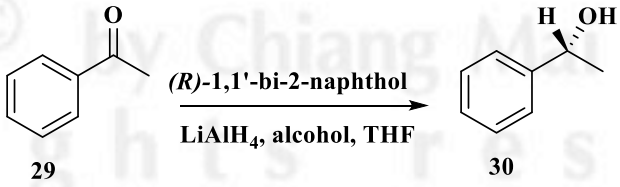
mixing $LiAlH_4$ and an equimolar amount of optically pure *(R)*-1,1'-bi-2-naphthol **(25)** in tetrahydrofuran (THF). However, the initial attempt failed to reduce prochiral acetophenone **(29)** in high optical yield. Thus exposure of acetophenone **(29)** to this solution at 30°C resulted in the formation of *(R)*-(+)-1-phenylethylalcohol **(30)** in only 85% yield (2% ee).



Scheme 9 Asymmetric reduction of prochiral acetophenone by BINAL-H (27)

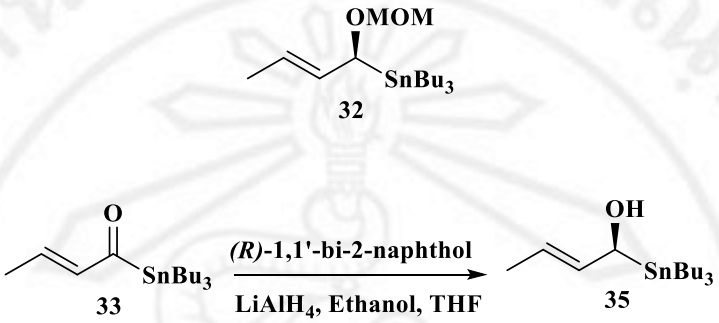
The modification of BINAL-H **(31)** was prepared by $LiAlH_4$, alcohol and *(R)*-1,1'-bi-2-naphthol **(25)** in THF. Sueprisingly, use of this binaphthol-modified aluminium hydride reagent (BINAL-H, **31**) resulted in a remarkable increase in optical yield in the reduction of acetophenone **(29)** to give *(R)*-(+)-1-phenylethyl alcohol **(30)** in 95% yield (73% ee) (Scheme 10).





Scheme 10 Asymmetric reduction of prochiral acetophenone by BINAL-H (31)

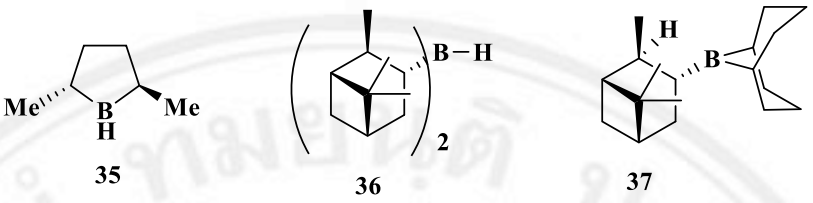
In 2004 Marshall and co-workers[28] synthesized *(S,E)*-1-(methoxy- methoxy)-1-tributylstannyl-2-butene **(32)** in 49% yield and >90% ee. Asymmetric reduction of unsaturated ketone **(33)** by BINAL-H **(31)** was a key step (Scheme 11).



Scheme 11 Asymmetric reduction of unsaturated ketone by BINAL-H (31)

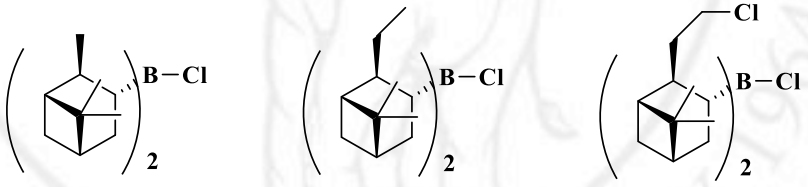
1.3.2 Modified Borane

Numerous chiral boranes have been developed for the asymmetric reduction of carbonyl compounds. A simple example is *(R,R)*-2,5-dimethylborolane (**35**, Masamune's reagent).[29] However, even earlier, the reaction of α-pinene and diborane had been shown to give (-)-(1*R*,2*S*,3*R*,5*R*)-diisopinocamphenylborane **(36)** which was found to reduce carbonyl compounds to alcohols with high asymmetric induction.[30,31] Trialkylboranes have also been found to reduce carbonyl compounds; such as Midland's complex between α-pinene and 9-borabicyclo[4.4.1]nonane (**37**, B-Ipc or Alpine Borane®) was developed and have been used for the asymmetric reduction of aldehydes and ketones, frequently with high enantioselectivity.[32-36]



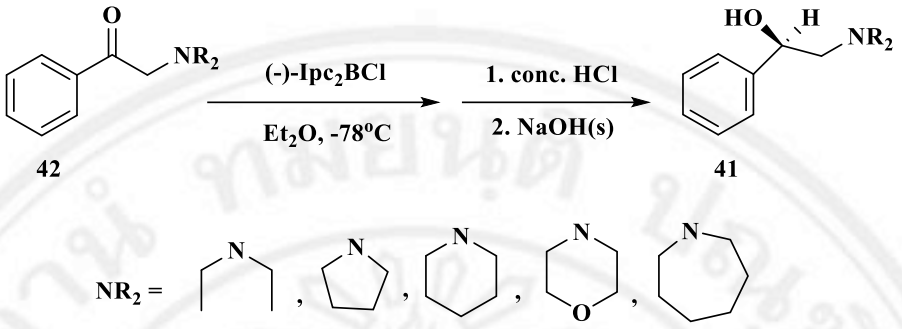
35 36 37

B-Ipc **(37)** has been found to be less effective in the case of reactive ketones, but this has been remedied by increasing the Lewis acidity of the boron atom so that stronger coordination between the carbonyl oxygen and the boron atom results. Examples of derivatives where this has been achieved include diisopinylcampheyl chloroborane (Ipc_2BCl, **38**)[37-45], 2-ethyl-diisopinylcampheyl chloroborane (Eap_2BCl, **39**)[46] and 2-β-chloroethyl-diisopinylcamphenyl chloroborane ($Cleap_2BCl$, **40**)



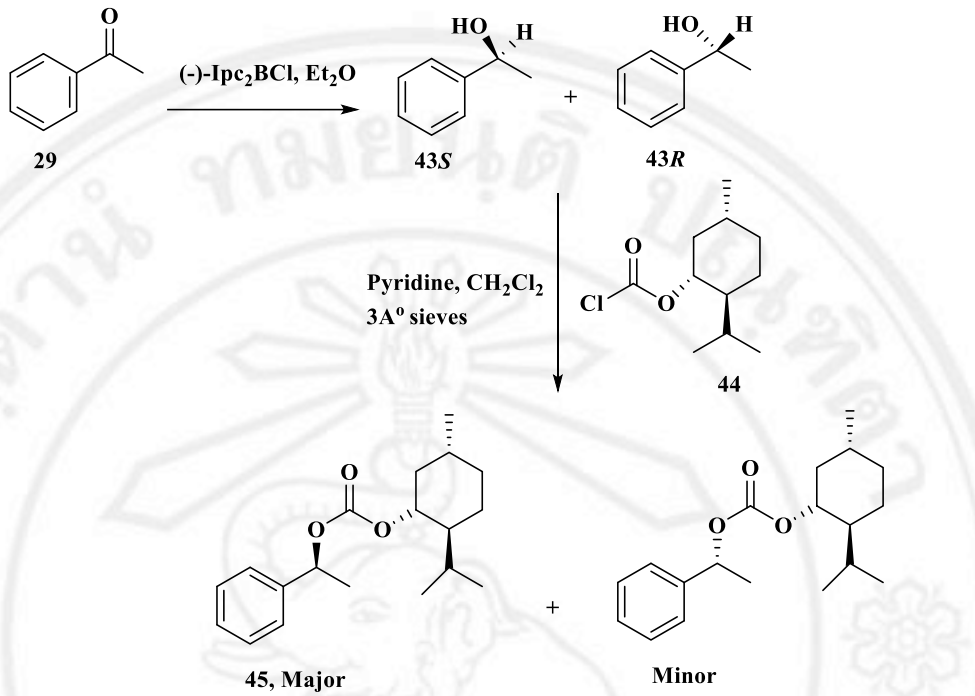
38 39 40

In 1994 Beardsley and co-workers[47] studied the asymmetric synthesis of β-amino alcohols **(41)** with (-)-*B*-chlorodiisopinocampheylborane (Ipc_2BCl, **38**) (Scheme 12). They investigated the asymmetric reduction of 2-amino acetophenone **(42)** using Ipc_2BCl **(38)** as the asymmetric reducing agent. When 2-amino acetophenone **(42)** was reduced in diethyl ether at -78°C with Ipc_2BCl **(38)** followed by a simple acid work-up, optically β-amino alcohols was obtained in 81-88% yield and the enantiomeric excesses found ranged from 75-99% and the β-amino alcohols were enriched in the *R*-enantiomer.



Scheme 12 The asymmetric synthesis of β-amino alcohols by Beardsley and co-workers

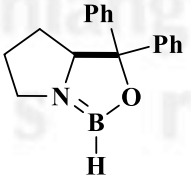
In 1998 Eisenberg[48] reported the asymmetric reduction of acetophenone **(29)** with (-)-*B*-chlorodiisopinocampheylborane (Ipc_2BCl, **38**) and derivatization with (-)-menthyl chloroformate (Scheme 13). Acetophenone **(29)** was reduced by Ipc_2BCl **(38)** in diethyl ether under nitrogen gas. The reaction was stirred at 0°C for 3 hours and allowed to stand at room temperature, work-up and without further purification yield a clear colorless liquid **(43*R*, 43*S*)**. After that, the compound **(43)** was treated with (-)-menthyl chloroformate **(44)** and pyridine in dichloromethane. The reaction was stirred at room temperature, under nitrogen gas for 2-3 hours, work-up and then separated and indentified by gas chromatography to give *(R)*-sec-phenethyl alcohol **(45)** in 81% yield and 97.3% ee as a major product.



Scheme 13 The asymmetric reduction of acetophenone by Eisenberg

1.3.3 Corey-Bakshi-Shibata (CBS) reduction

Examples given earlier have illustrated the use of chiral borolanes such as Masamune's reagent in asymmetrically reducing ketones. However, it has been shown that a similar effect can be achieved with B_2H_6 or catecholborane mediated by a chiral catalyst such as an oxazaborolidine **(46)**.[49-51] This approach (known as the Corey-*Bakshi-Shibata* reduction[52]) has developed into one of the most versatile and successful asymmetric reducing system known.



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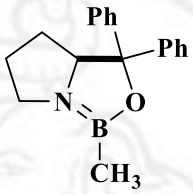
The use of oxazaborolidines **(46)** in asymmetric reductions was the first reported by Itsuno and co-workers[53] and from that a wide range of new catalysts and improved methods have grown.[54, 55] Moreover, oxazaborolidines **(46)** was air and moisture sensitive. In 1987 Singh and co-workers[56] prepared *B*-methylated oxazaborolidine **(47)** for the enantioselective reduction of ketones. *B*-methylated oxazaborolidine **(47)** can be stored in containers at room temperature and weighed or transferred easyly.



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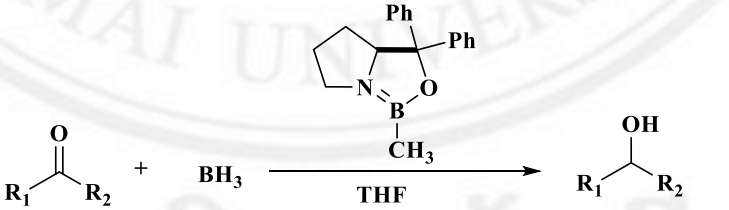
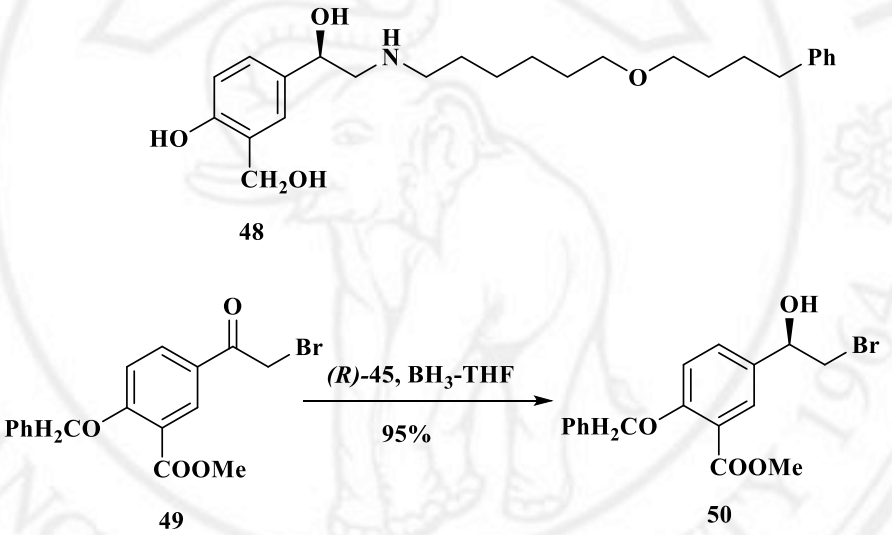
In general the reduction of ketones with *B*-methylated oxazaborolidine **(47)** as a catalyst proceeds with either appreciable higher or the same enantioselectivity as observed for corresponding reaction catalyzed by oxazaborolidine **(46)** (Scheme 14).



Scheme 14 The asymmetric reduction of ketones by Singh and co-workers

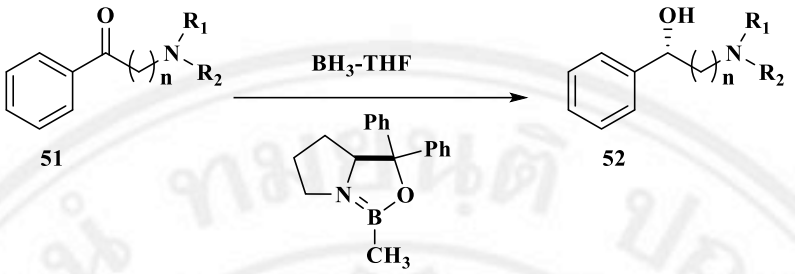
In 1994 Hett and co-workers[57] studied the enantoselective synthesis of salmeterol **(48)** *via* asymmetric borane reduction. The synthesis started with

bromoketone **(49)**, enantioselective reduction of **49** with borane and a catalytic amount of oxazaborolidine *(R)*-**47** or *(S)*-**47** gave bromohydrin **(50)** in almost quantitative yield. The bromohydrin was purified by chromatography. The *(S)*-catalyst gave *(S)*-bromohydrin **(50)** and the *(R)*-catalyst gave *(R)*-bromohydrin **(50)**. The enantiomeric excess of bromohydrin **(50)** can be concluded to be at least 94% by HPLC analysis (Scheme 15).



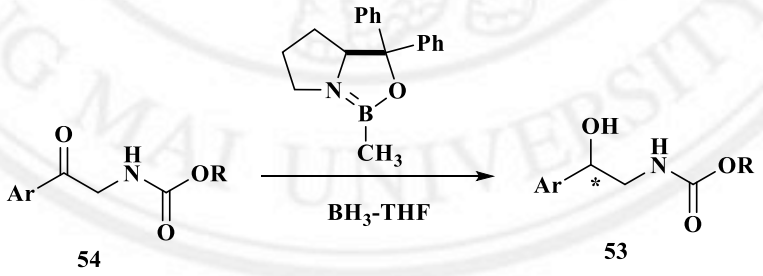
Scheme 15 The asymmetric reduction of bromoketone by Hett and co-workers

In 2001 Ya-Wen and co-workers[58] studied the asymmetric reduction of aminoketones **(51)** with borane and chiral oxazaborolidine catalyst **(47)** (Scheme 16). The aminoketone **(51)** was treated with BH_3-THF and oxazaborolidine **(47)** under nitrogen atmosphere, followed by work-up to give the aminoalcohol **(52)** in 68-91% yield and 57-99% ee.



Scheme 16 The asymmetric reduction of aminoketones by Ya-Wen and co-workers

In 2004 Shin and Cho[59] studied efficient synthesis of optically active 2-*N*-BOC (or Cbz)-amino-1-arylethanols **(53)** as key intermediates for synthesis of chiral drugs *via* asymmetric reduction. 2-*N*-BOC (or Cbz)-amino-1-arylethanones **(54)** was treated with *(R)*-oxazaborolidine **(47)** or *(S)*-oxazaborolidine **(47)** and BH_3-THF complexed in THF at 25°C. It gave 2-*N*-BOC (or Cbz)-amino-1-arylethanols **(53)** in high isolated yield (>93%) and high enantiomeric excess (>80%) (Scheme 17).



Boc: R = *t*-Bu
Cbz: R = Bn

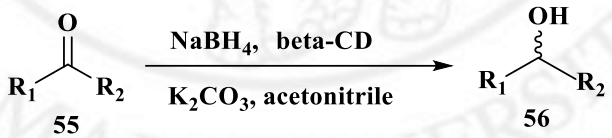
Scheme 17 The asymmetric reduction of aminoketones by Shin and Cho

1.3.4 Cyclodextrins

Cyclodextrins are useful in asymmetric synthesis since they provide a chiral cavity into which the substrate or reagent can be complexed. Although

enantioselective reactions can occur in such an asymmetric environment, the enantioselectives observed are frequently low. This can be attributed to the prochiral center either assuming an incorrect orientation in the cavity, or experiencing greater mobility than might have been anticipated.[60] Mobility can be reduced through the use of crystalline inclusion complexes,[61] or through the inclusion of a second inert molecule into the cavity.[60]

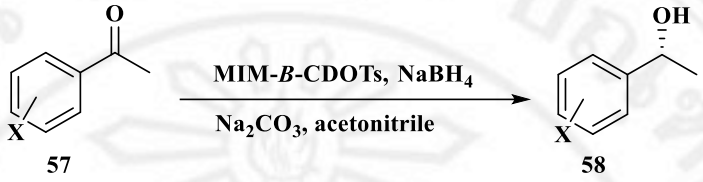
In 1997 Park and Sim[62] reported the asymmetric reduction of ketones **(55)** with sodium borohydride as a reducing agent and *β*-cyclodextrins as a chiral catalyst (*β*-CD) (Scheme 18). *β*-CD was suspended in aqueous potassium carbonate solution. Then, the ketone in acetonitrile was added and the mixture was stirred for a day at 35ºC. Sodium borohydride was added and allowed to react at 35ºC for a further 16 h. The reaction was work-up and purification to give *sec*-alcohols **(56)** in high yield (71-95%) but low enantiomeric excess (2-24%).



Scheme 18 The asymmetric reduction of ketones by Park and Sim

In 2006 Tang and co-workers[63] studied the asymmetric reduction of acetophenones and their derivatives **(57)** with sodium borohydride in the presence of mono-6-(1-methyl-3-imidazolium)-6-deoxy-*β*-cyclodextrin tosylate (MIM-*β*-CDOTs) (Scheme 19). The reactions were performed in a one-pot procedure. MIM-*β*-CDOTs was suspended in aqueous sodium carbonate solution. An equimolar amount of ketone in acetonitrile was added and the mixture stirred for a day at a fixed temperature

(either 0ºC, 20ºC or 35ºC). An excess of sodium borohydride was then added and the slurry stirred for 12 h followed by work-up and purification to give the alcohols **(58)** in 55-89% with 3-32%ee.



57 58

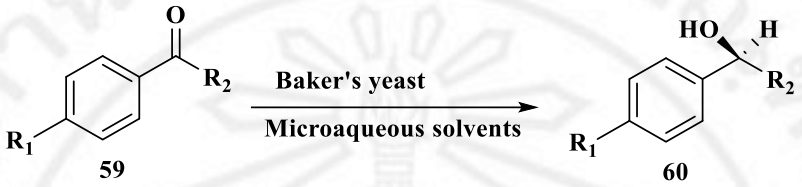
Scheme 19 The asymmetric reduction of acetophenones and their derivatives by Tang and co-workers

1.3.5 Enzyme Reducing Agents

In nature asymmetric reductions are widespread and 100% ee's are common. Nature uses enzymes as chiral reducing agents. Humans have tried to explore this possibility, but problems are often experienced with the use of enzymes because they have usually evolved to be highly substrate-specific and their general use may therefore be limited. However, this problem can be overcome through the muti-enzyme systems.

Asymmetric reduction with baker's yeast (*Saccharomyces cerevisiae*) has been utilized in organic synthesis from about the year of 1980, and about one hundred kinds of substrates have been found.[64] Among all, asymmetric reduction of ketones with baker's yeast has been employed generally as a simple production process for chiral building blocks. Baker's yeast is particular good at reducing ketones, with the best enantioselectivities being obtained when the ketone carries a β-ester group.[65-68]

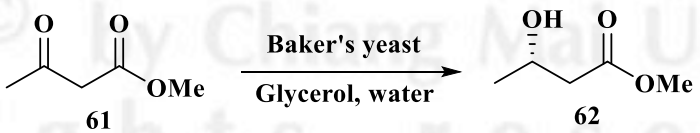
In 2001 Liu and co-workers[69] studied the asymmetric reduction of aromatic ketones **(59)** to optically active alcohols **(60)** by the baker's yeast in organic solvent systems (Scheme 20).



Scheme 20 The asymmetric reduction of aromatic ketones by Liu and co-workers

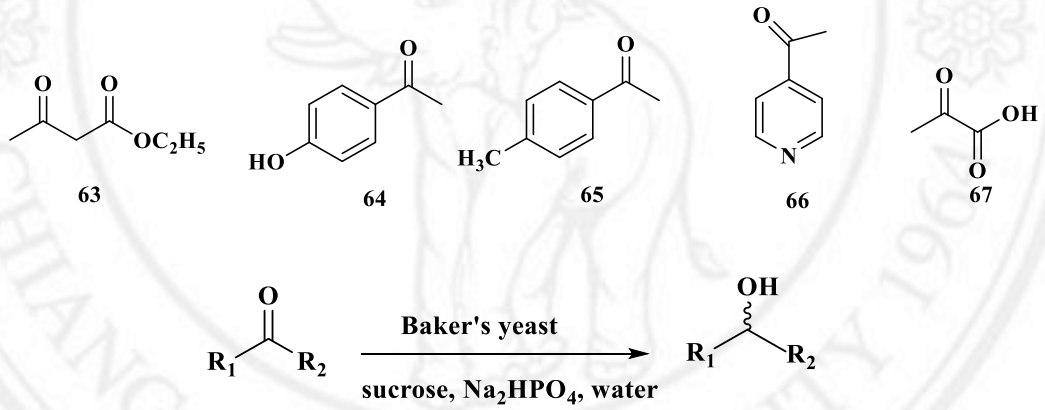
The reduction of aromatic ketones proceeded in moderate conversion with good enantioselectivity (82-91% ee) in a number of organic solvents, including petroleum ether, toluene, chloroform and tetrahydrofuran. A small amount of water was required for the reaction to proceed.

In 2008 Wolfson and co-workers[70] studied the asymmetric reduction of methyl acetoacetate **(61)** using baker's yeast as a catalyst in glycerol containing systems (Scheme 21). It was found that the reaction in a mixture of glycerol and water combined the advantages of each individual solvent and resulted in high catalytic performance and efficient product extraction yield.



Scheme 21 The asymmetric reduction of methyl acetoacetate by Wolfson and co-workers

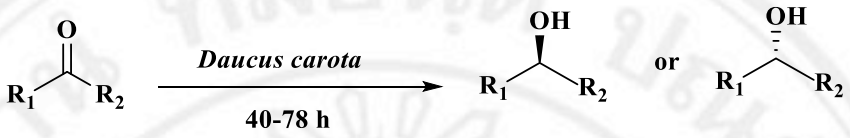
In 2008 Bawa and co-workers[71] studied the enzymatic reduction of ketones **(63-67)** to optically active secondary alcohols (Scheme 22). Sucrose and disodium hydrogen phosphate were dissolved in warm tap water. Dry active baker's yeast was added to the reaction mixture and stirred for 1 h at 40°C. Then, the reaction mixture was allowed to stand at room temperature and the ketones was added and stirred for 24-48 h at room temperature. The reaction was filtered and purified to give optically active secondary alcohols **(62)** in high percent conversion (70-90%) and high enantiomeric excess (67-98%).



Scheme 22 The asymmetric reduction of ketones by Bawa and co-workers

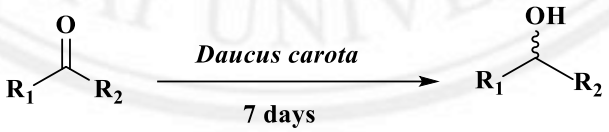
Daucus carota (from carrot) is interesting for the asymmetric reduction of ketones. In 2002 Yadav and co-workers[72] studied the efficient enantioselective reduction of ketones with *Daucus carota* root (Scheme 23). Ketones were added to a suspension of freshly cut carrot root in water and the reaction mixtures were incubated in an orbital shaker at room temperature for the time necessary to obtain the appropriate conversion. It was found that the reduction of acetophenone and

substituted acetophenones was observed in excellent chemical (70-80%) and optical purity (>90%).



Scheme 23 The asymmetric reduction of ketones by Yadav and co-workers

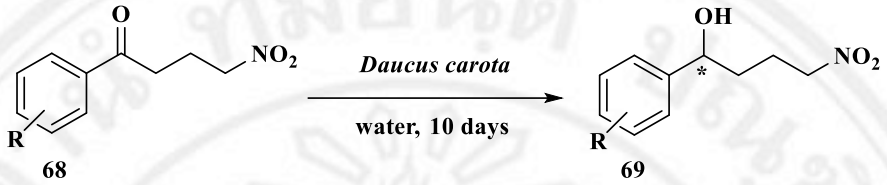
In 2005 Caron and co-workers[73] studied the selective reduction of ketones by *Daucus carota* hairy root cultures (Scheme 24). Generally, ketones in ethanol were added to a suspension of hairy roots in the culture medium. The reaction mixture was shaken at 27ºC for 7 days. After work-up and purification, it could be seen that the reduction of acetophenone afforded *(S)*-phenylethanol in high yield (96%) and excellent enantionmeric excess (ee ≥98%). Aromatic ketones, keto esters and a simple aliphatic ketone were reduced with good stereoselectivity (ee = 62-98%) and moderate to high chemical yields.



Scheme 24 The asymmetric reduction of ketones by Caron and co-workers

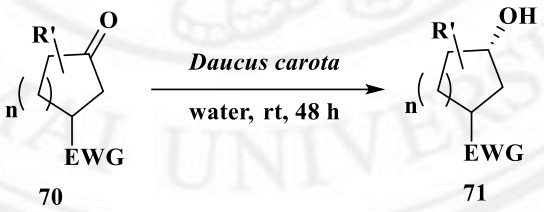
In 2005 Scapi and co-workers[74] studied the eantioselective reduction of γ-nitroketones **(68)** with *Daucus carota* (Scheme 25). The γ-nitroketones **(68)** were reduced with *Daucus carota* root in water at room temperature for 10 days. The

reaction afforded the corresponding *(S)*-alcohols **(69)** with enantiomeric excess ranging from 73-100%.



Scheme 25 The asymmetric reduction of γ-nitroketones by Scapi and co-workers

In 2009 Lacheretz and co-workers[75] studied the reduction of cyclic 3-oxo-amines **(70)** with *Daucus carota* (Scheme 26). It was realised that carrots (*Daucus carota*) were used to reduce cyclic amino-ketones in high yield (66-91%) and enantiomeric excess (75-96%). This cheap, eco-compatible and efficient reducing reagent allows the easy access to precursors of biologically active products.



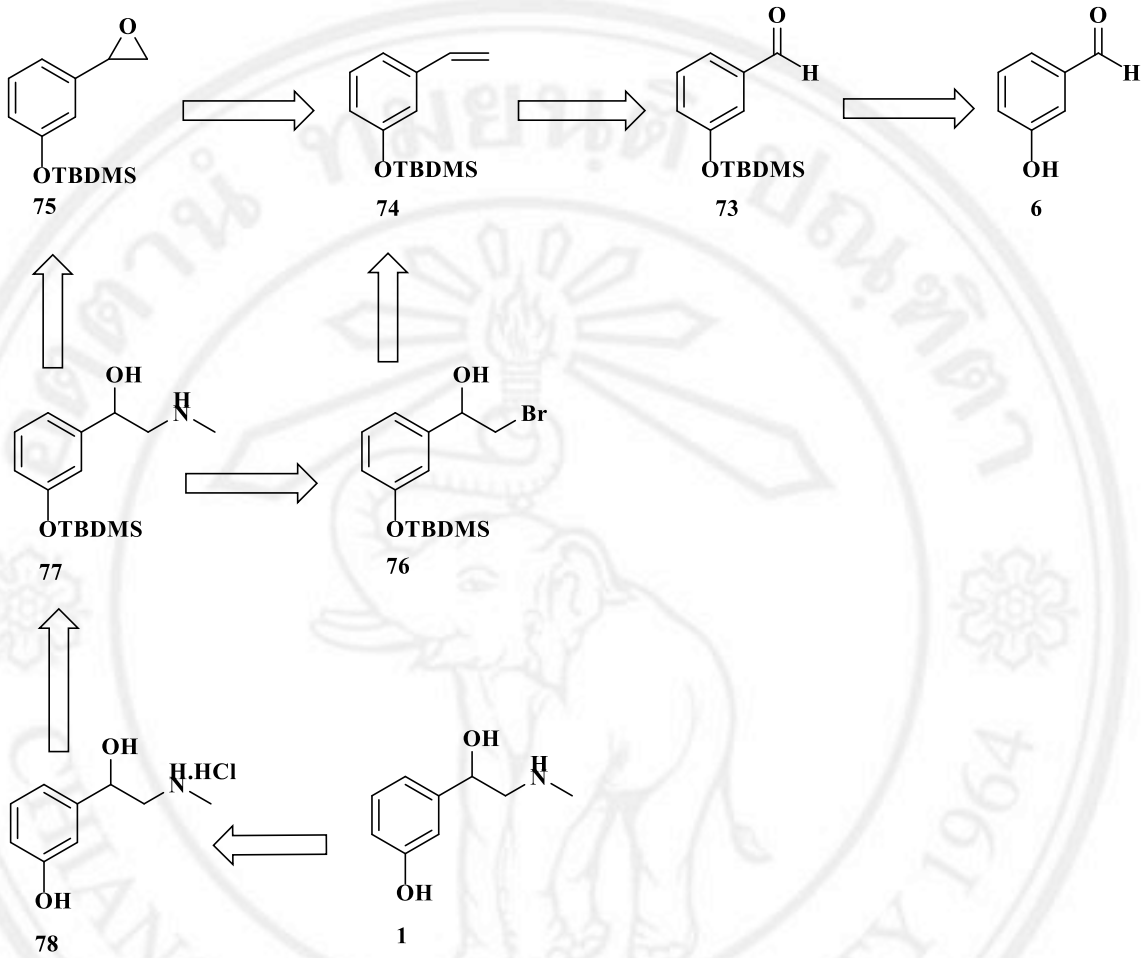
Scheme 26 The asymmetric reduction of cyclic 3-oxo-amines by Lacheretz and co-workers

1.4 Retrosynthetic pathways

Previously published literature for synthesis of *(R)*-phenylephrine still had disadvantages including usage of complicated chiral catalyst, expensive substances

and long reaction time. In our study, we have planned to synthesize the *(R)*-phenylephrine in the new pathway to avoid the problems found in previously reported routes.

In the first route (Scheme 27), the synthesis of racemic phenylephrine could be obtained from *m*-hydroxybenzaldehyde **(6)** *via* the Wittig reaction, the epoxide ring opening and the bromohydrin substitution. This type of reaction, as discussed previously, is well accepted from previously published literature and does not present any problems. The protection of hydroxyl group occurred before the Wittig reaction of compound **(73)**. Conversion of the compound **(73)** into alkene compound **(74)** was done by the Wittig reaction. Then, the alkene compound **(74)** was conversed to epoxide **(75)** with the suitable epoxidizing agent and bromohydrin **(76)** with the safe source of bromine. Formation of compound **(77)** was expected to proceed *via* the epoxide ring opening of compound **(75)** and the substitution of bromohydrine **(76)** with methylamine gas. Finally, the deprotection of protecting group was done under acid condition and the racemate phenylephrine was obtained as it's hydrochloride salt **(78)**. Basifing of the salt **(78)** would yield the phenylephrine **(1)**.

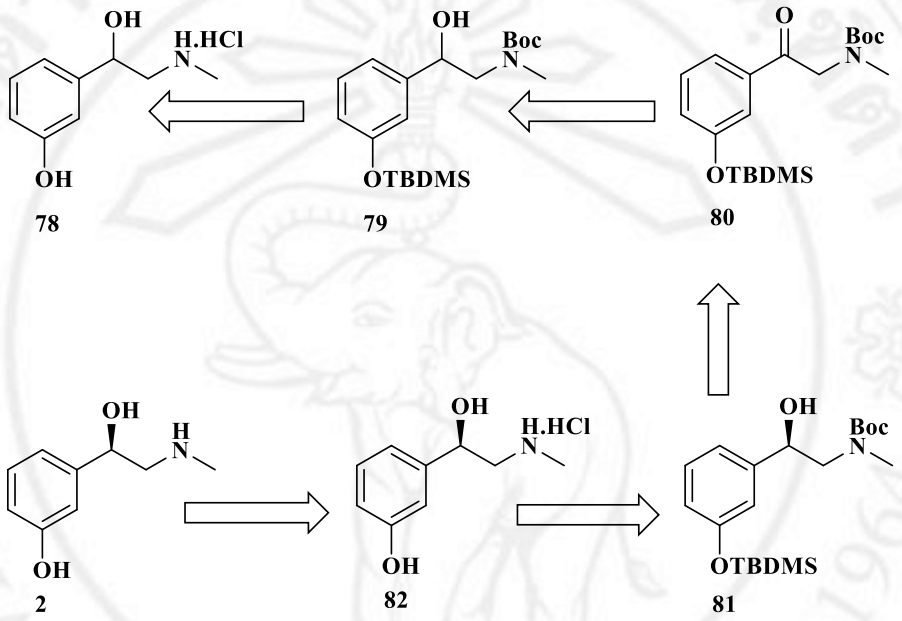


Scheme 27 The retrosynthesis pathway for (±)-phenylephrine

The second route involves the asymmetric reduction of racemic phenylephrine. Nowadays this medicine is available in the market in optically active *(R)*-form from resolution process. Consequently, this research exposed the asymmetric reduction to produce *(R)*-isomers under a simple condition, an inexpensive and environmentally benign procedure.

In order to synthesize *(R)*-phenylephrine (Scheme 28), first, the protection of racemic phenylephrine hydrochloride **(78)** was required, and then the oxidation of amino alcohol **(79)** was performed. Followed by asymmetric reduction of ketone **(80)**

to produce *(R)*-isomer amino alcohol **(81)** under the simple condition. After the completion of the reduction, the deprotection of protecting group under acidic condition should then afford *(R)*-phenylephrine as it's hydrochloride salt **(82)**. The (R)-phenylephrine could be obtained from basified of salt **(82)**.



Scheme 28 The retrosynthesis pathway for *(R)*-phenylephrine

The aim of this research involved the synthesis of (±)-phenylephrine, and ultimately the synthesis of *(R)*-phenylephrine *via* (±)-phenylephrine. The total synthesis of phenylephrine, both racemic and pure enantiomeric, should be able to go through a simple pathway which required mild conditions and inexpensive chemicals, compared to the previous routes.