

**Chemistry with Chiral Lithium Amides:
Enantiotopic Group- and Face-Selective Reactions**

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for the degree of
Master
in the
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Saskatoon
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Abstract

The accomplishment of the γ -alkylation reaction from β -keto esters of tropinone and the enantioselective aziridine formation from nortropinone is first reported. This opened two new paths to develop tropinone enolate chemistry. One is indirect α -alkylation of tropinone, another is the nucleophilic attack from α -C enolate to the nitrogen atom.

Seven interesting chiral amines have been synthesized and applied into the enolate chemistry of two interesting precursors of synthesis of natural products: 1,4-cyclohexanedione monoethylene ketal and tropinone.

The aldol reaction between the lithium enolate of 1,4-cyclohexanedione monoethylene ketal and benzaldehyde demonstrated the high diastereoselectivity (up to 98% de) and the moderate to high enantioselectivity (up to 75% ee) induced by those chiral lithium amides. On the other hand, high diastereoselectivity (up to 100% de) and the low enantioselectivity were obtained from the aldol reaction of tropinone enolate with benzaldehyde differentiated by chiral lithium amides with extra electron donor atoms.

An analysis method to determine enantioselectivity from racemic α -hydroxytropinone was developed. That will, no doubt, benefit the further enantioselective α -hydroxylation reaction of tropinone.

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List of abbreviations

aq	aqueous
Ac	acetyl
Ar	aryl
Bn	benzyl
Boc	tert-butoxycarbonyl
<i>n</i> -BuLi	<i>n</i> -butyllithium
<i>t</i> -Bu	<i>tert</i> -butyl
bp	boiling point
Bz	benzoyl
Cbz	carboxybenzyl
CI	chemical ionization
¹³ C NMR	carbon-13 nuclear magnetic resonance
CSA	(1 <i>R</i>)-10-camphorsulfonic acid
d	day
de	diastereomeric excess (100%)
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DIAD	diisopropyl azodicarboxylate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone.
DMSO	dimethyl sulfoxide
ee	enantiomeric excess (100%)
EI	electron impact ionization
eq.	equivalent(s)
EPC	enantiomerically pure compound
Et	ethyl
Eu(hfc) ₃	europium tris[3-(heptafluoropropylhydroxymethylene)- (+)-camphorate

Eu(tfc) ₃	europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate
FCC	flash column chromatography
GC	gas chromatography
h	hour(s)
HMPA	hexamethylphosphoramide
¹ H NMR	proton nuclear magnetic resonance
HPLC	high performance liquid chromatography
<i>i</i> -Pr	<i>iso</i> -propyl
IPA	<i>iso</i> -propyl alcohol
IR	infrared
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
Me	methyl
MHz	megahertz; 10 ⁶ Hertz
m-CPBA	m-chloroperbenzoic acid
min	minute(s)
mp	melting point
Ms	mesyl
MS	mass spectroscopy
NMO	N-methylmorpholine-N-oxide
Pd/C	palladium on charcoal
Ph	phenyl
PLE	pig liver esterase
<i>p</i> -TsOH	<i>para</i> -toluenesulphonic acid
Py	pyridine
Ref	reference
R _f	retention factor
rt	room temperature
satd.	saturated; as in a saturated aqueous solution
s	second (s)
TBDMS	<i>tert</i> -butyldimethylsilyl

Tf	triflyl
TFAE	(<i>S</i>)-(+)-2, 2, 2-trifluoro-1-(9-anthryl)ethanol
Tg	tigloyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	N,N,N',N' – tetramethylethylenediamine
TMSCl	trimethylchlorosilane
Troc	2,2,2-trichloroethyloxycarbonyl
Ts	tosyl
UV	ultraviolet
$[\alpha]_D^t$	specific rotation

CHAPTER 1: INTRODUCTION

Since Whitesell^[1] successfully applied a chiral lithium amide to enantioselective epoxide opening in 1980, the chemistry of chiral lithium amides has been greatly extended. During the following 27 years, more and more studies have been focusing on the deprotonation reactions of ketones and also on the enolate chemistry. Many methodology studies were completed, and a variety of interesting chiral lithium amides were synthesized, but the mechanism of the differentiating process controlled by chiral lithium amides is still not well understood.

The research described in this thesis centers on enantiotopic group and face selective reactions induced by chiral lithium amides.

1.1. Stereoselectivity control by chiral lithium amides: a brief overview

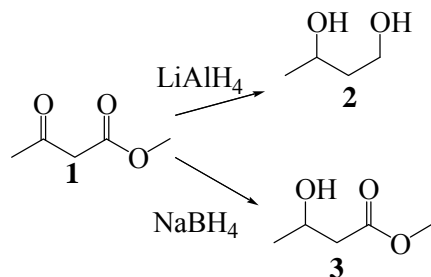
1.1.1. Selectivity in synthesis^[2-4]

Organic compounds' biological and physical properties depend to a large degree on the substituents and functional groups. The selectivity occurs when these functional groups have different reactivity or they react at different sites or orientations in the molecule under the same or different reaction conditions.

Selectivity in organic reactions can be defined as chemo-, regio-, or stereoselectivity according to the reaction outcome. If a reaction occurs preferentially at one of the two similar functional groups, this is referred to as chemoselectivity. For example,

the reaction of the keto ester (**1**) with a powerful reducing reagent in Scheme 1, e.g. lithium aluminum hydride, results in the reduction of both the ketone and the ester to give a diol (**2**) without selectivity whereas the reduction with a mild reagent such as sodium borohydride, gives the hydroxyl ester (**3**) by only reduction of the ketone group.

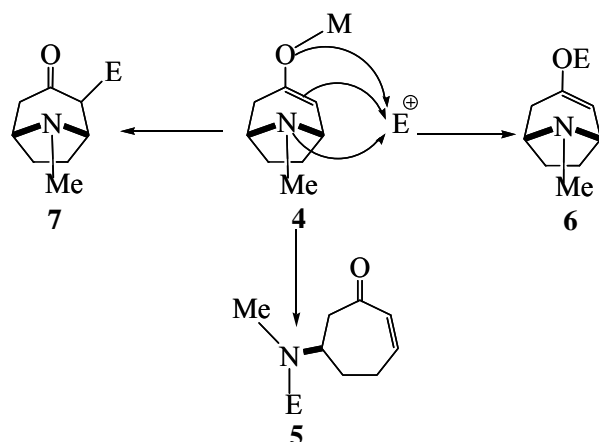
Scheme 1



The word “regio” comes from the Latin word “regionem” meaning direction. When a reaction that can potentially yield two or more constitutional isomers produces one predominant product, the reaction is said to be regioselective.

Tropinone enolate (**4**) has three reactive termini. The nucleophilic reaction of the enolate could happen on the carbon, or the oxygen or the nitrogen atom (Scheme 2) to give three different products (constitutional isomers **5**, **6** and **7**). Regioselectivity needs to be controlled for efficient use of this enolate in synthesis.

Scheme 2

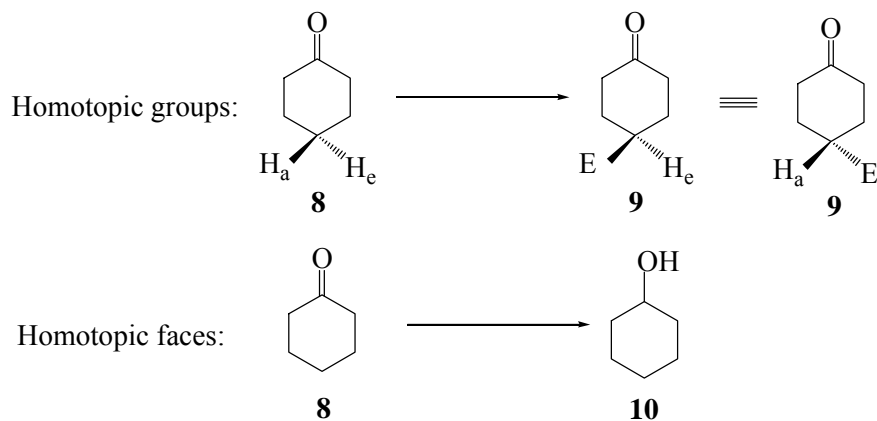


During development of enantioselective synthesis of natural products the most difficult issue is usually stereoselectivity, which refers to the control of the absolute configuration. The common stereoselective reactions involve two or more groups or faces which might have different relationships.

i). Homotopic groups or faces

Homotopic groups or faces are interchangeable by a proper C_n axis of rotation. Selectivity is not an issue because the same product is obtained from the reaction at both groups and faces. For example, protons (H_a and H_e) of cyclohexanone (**8**) are homotopic. Only one alkylated product (**9**) can be produced by alkylation reaction (Scheme 3). There also are two homotopic faces on the carbonyl group in this ketone. Only one product (**10**) can be generated by reduction with lithium aluminum hydride (Scheme 3).

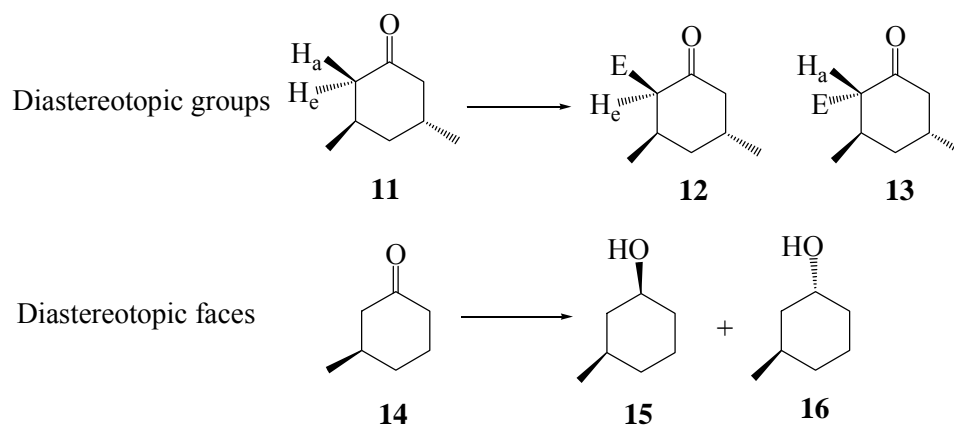
Scheme 3



ii). Diastereotopic groups or faces

Diastereotopic groups or faces are not interchangeable by any symmetry operation. The addition or replacement of a chiral or an achiral reagent will lead to the formation of diastereomers. An example is shown in the Scheme 4.

Scheme 4



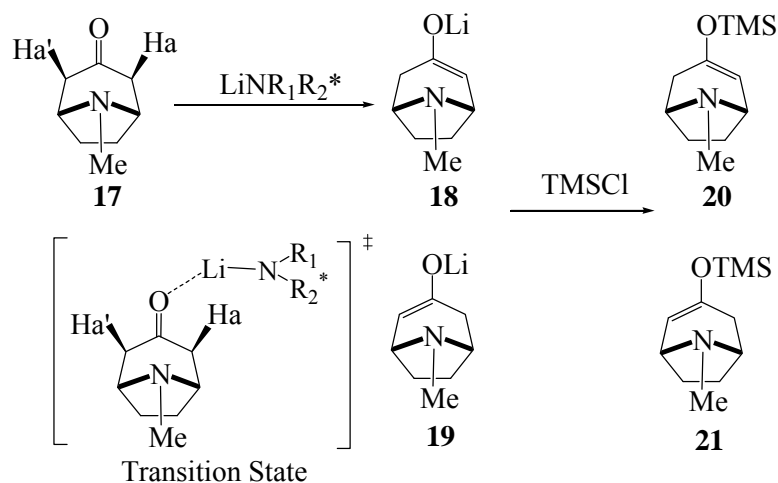
iii) Enantiotopic groups or faces

Groups or faces that are interchangeable only by an improper axis of rotation such as the mirror plane, an inversion center or a rotation reflection axis, are enantiotopic.

Enantiotopic group selectivity:

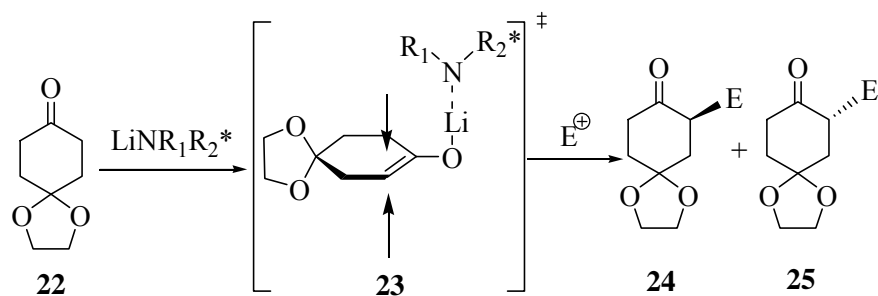
There are two pairs of enantiotopic α -protons (axial H_a and H'_a or equatorial H_e and H'_e in Scheme 5) in tropinone (**17**) with C_s symmetry point group. It is known that axial-protons are abstracted preferentially over the equatorial ones by a base due to the stereoelectronic effect.^[5-6] A pair of lithium enolate enantiomers (**18**) and (**19**) will be formed after deprotonation with a lithium amide. This process is an example of the enantiotopic group selective process. If the lithium amide is chiral, the transition states involving the amide will be diastereomeric with different free activation energy. One of the axial α -protons will be extracted preferentially over another one. The lithium enolate enantiomers will be produced at different rates. Stereoselectivity observed in this reaction is called enantiotopic group selectivity (Scheme 5).

Scheme 5

Enantiotopic face selectivity:

1,4-Cyclohexanedione monoethylene ketal (**22**) is an achiral cyclic ketone and belongs to C_{2v} symmetry point group. Only one lithium enolate (**23**) restricted to the E-configuration can be produced by a deprotonation reaction with lithium amide. The two faces in this lithium enolate are enantiotopic. If we introduce the electrophile, two faces of the enolate (**23**) will attack the electrophile selectively and two enantiomeric products will be formed. If lithium amide is chiral, one enantiomer will be produced preferentially over another one due to the difference in free energy of activation between the two diastereomeric complexes formed between the enolate and the chiral lithium amine via non-covalent bonds (Scheme 6)

Scheme 6



Selectivity measurement:

The objective of all asymmetric reactions is usually to obtain one enantiomer in high excess over the other one. Enantioselectivity is expressed by the enantiomeric excess (ee): $ee = |(R-S)/(R+S)| \times 100\%$. The larger the enantiomeric excess, the better the result of the asymmetric reaction, which is often referred to as the higher efficiency of the asymmetric induction by a chiral reagent.

To determine the enantiomeric excess, the chromatographic determination of the enantiomer method by using GC or HPLC with chiral columns is the most reliable. NMR analysis with a chiral shift reagent or chiral solvating reagent is often useful, and so are methods using optical rotation.^[3]

In my project, it was possible to use small amounts of chiral shift reagents or chiral solvating reagents to measure ee by using NMR. In such case two diastereomeric complexes are formed between the sample and the chiral shift or solvating reagents, this affords two sets of signals in NMR spectra and ee can be calculated by integration of these two signals. Some reagents are illustrated in the Figure 1.^[3]

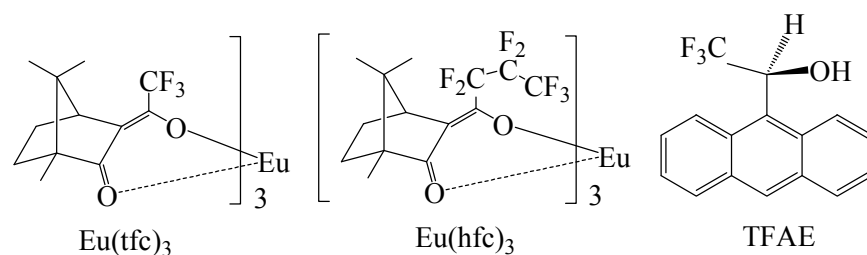


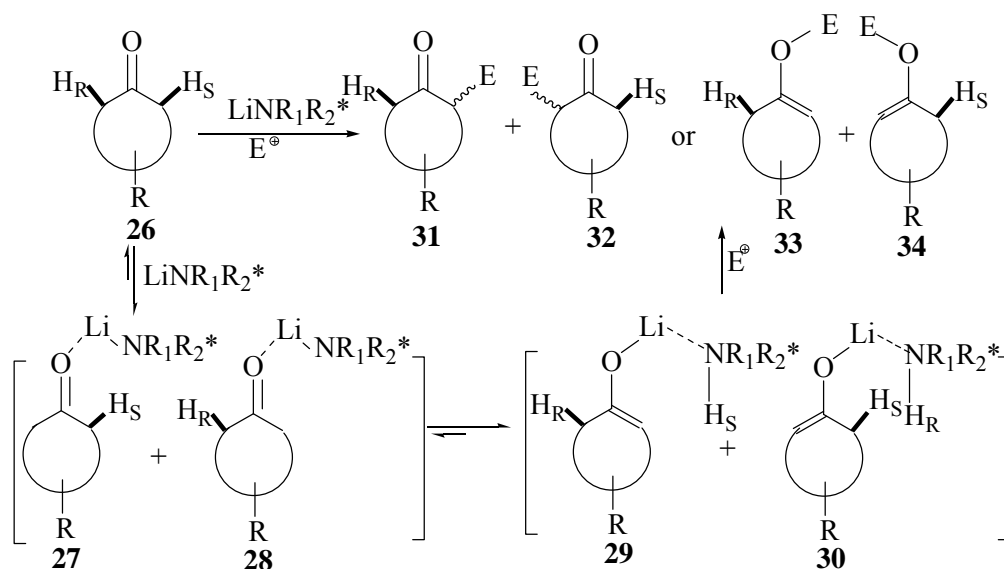
Figure 1: Two chiral shift reagents and one chiral solvating agent

1.2. Stereoselectivity control by chiral lithium amides

Since the enantioselective deprotonation of cyclic ketones induced by chiral lithium amide was first demonstrated in 1986,^[7-8] chiral lithium amides have been applied widely in asymmetric synthesis. In this thesis, I focus on their applications in the stereoselective deprotonation of cyclic ketones.

Enantioselective deprotonation of cyclic ketones induced by chiral lithium amides is depicted in the Scheme 7.

Scheme 7



Enantiotopic group or/and face selective processes are possible depending on the symmetry of the substrate ketones.

If the cyclic ketone belongs to the C_s point group, removal of one of the two enantiotopic α-protons by the lithium amide produces a mixture of chiral lithium enolates (29) and (30) through the intermediate complexes (27) and (28). If the lithium amide is chiral, the enantiomeric enolates (29) and (30) should be generated in different amounts.

Lithium enolates are not stable and their chirality has to be preserved by a following nucleophilic reaction with electrophile. The reaction could take place either at the oxygen or at the α -carbon depending on the electrophile.

If the reaction takes place at oxygen, enol ether products **(33)** and **(34)** will be produced in unequal amounts by preserving the enantiotopic group selectivity from the first deprotonation stage. If the reaction takes place at the α -carbon, the lithium enolate enantiomers **(29)** and **(30)** will react with the electrophile following the kinetic resolution process. One of the lithium enolate enantiomers **(29)** and **(30)** will likely react faster than another one. Enantiomerically enriched chiral products might be obtained.

If the achiral ketone **(26)** belongs to the C_{2v} point group only one enolate is generated in the deprotonation reaction. If it is further applied into the corresponding nucleophilic reaction in the presence of a chiral lithium amide, the enantiotopic face selectivity can result.

Most of the studies of deprotonation of cyclic ketones were done under kinetic control. A chemical reaction is said to be under kinetic control if the relative amounts of the products are determined before the thermodynamic equilibrium is achieved, otherwise, the system is under thermodynamic control.^[9]

Many selective reactions are irreversible (kinetic control) at least under some reactions conditions. The selectivity is thus determined by the ratio of products.

Deprotonation in an achiral environment:

A racemic mixture of lithium enolates will be obtained in an achiral environment, because the transition states between cyclic ketone and lithium amide (T_1 and T_2) leading to the two enantiomers are enantiomeric and thus equal in energy (Figure 2).

The racemic lithium enolates, as intermediate, then react with nucleophile still in an achiral environment. The racemic mixture of final products will be obtained, because the transition states of lithium enolate and lithium amide leading to the two enantiomers are enantiomeric and thus equal in energy.

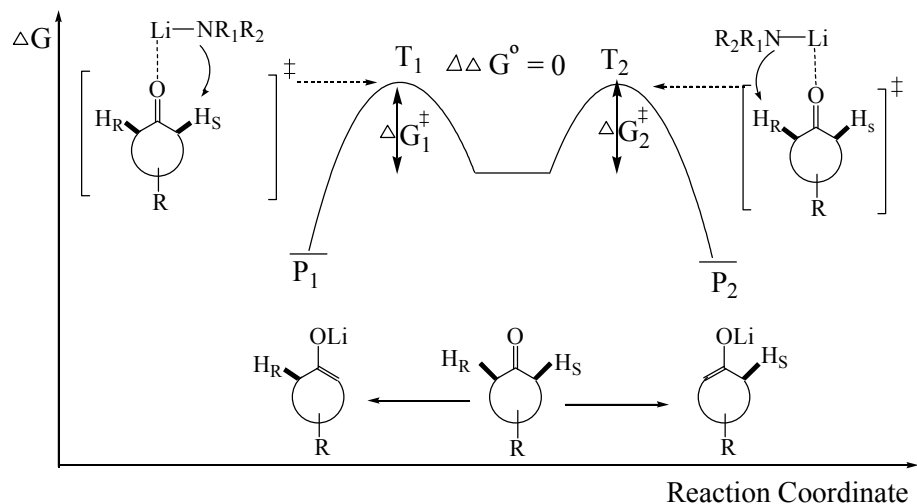


Figure 2: Deprotonation in an achiral environment

Deprotonation in a chiral environment:

If a chiral environment (chiral substrate, auxiliary, solvent or catalyst) is present during deprotonation, they might be covalently attached to the starting material. The transition states of reaction between cyclic ketone and lithium amide will become diastereomeric. That will make intermediate enolates or products enantiomers as diastereoisomers. Diastereoisomers are chemically different and the two diastereomeric transition states (T_3 and T_4) have unequal energy. The lower-energy transition state will be favoured and one of the enantiomeric products will be obtained more than the other (Figure 3).

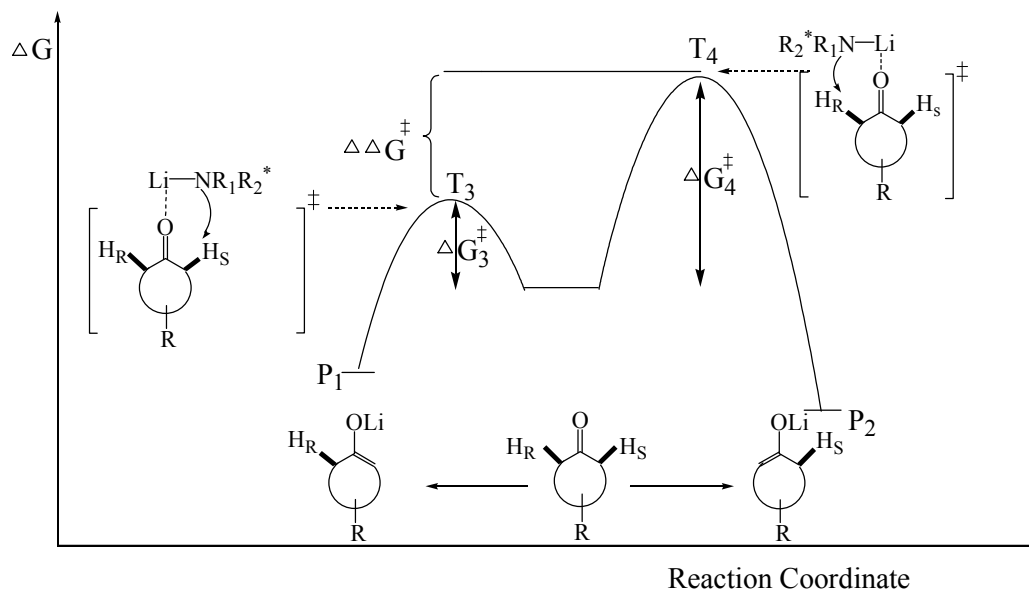


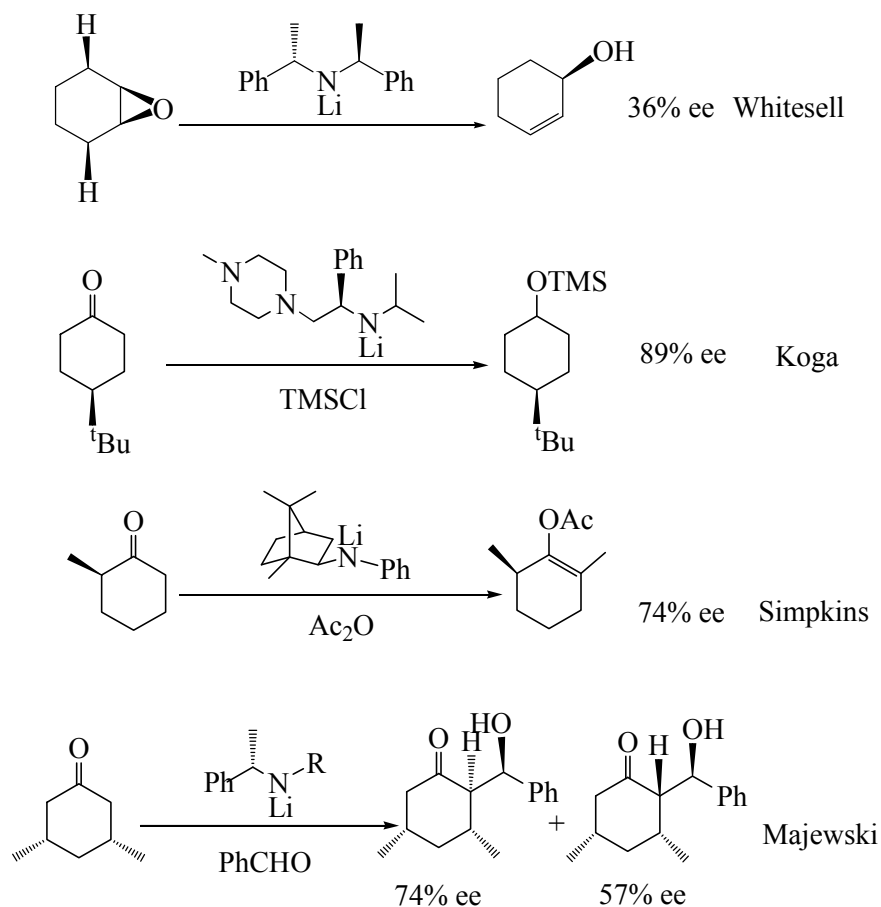
Figure 3: Deprotonation in a chiral environment

Therefore, in order to get high enantioselectivity it is necessary for the reaction to be run in the chiral environment under kinetic conditions. Chiral lithium amides are considered to be efficient reagents for yielding high enantioselectivity in the asymmetric deprotonation of ketones because they can often discriminate between the enantiotopic groups or faces to produce enantiomerically enriched products.

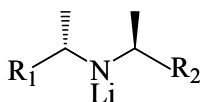
Chiral lithium amides are prepared by deprotonation of chiral amines with strong alkyllithium bases, such as *n*-butyllithium. Amides are strong bases and fairly weak nucleophiles, and can be used for deprotonation reactions of ketones without other side reactions such as the nucleophilic addition to the carbonyl group.

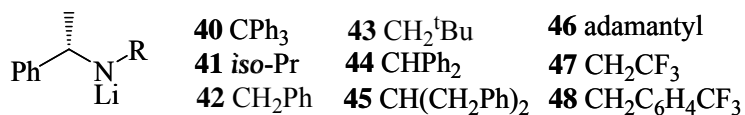
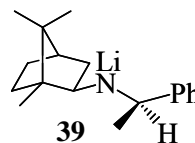
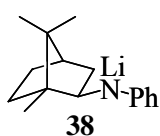
The use of lithium amides as chiral reagents for enantiotopic group-selective reactions was pioneered by Whitesell in 1980 by treating cyclohexene oxide with chiral lithium amide resulting in opening of the epoxide,^[1] and was then further developed by Simpkins,^[7] Koga^[8] and Majewski^[10] mostly in deprotonation of prochiral ketones (Scheme 8) in 1986.

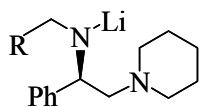
Scheme 8

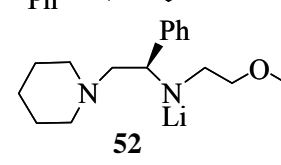
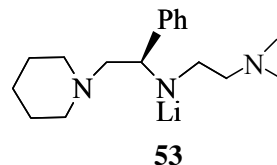


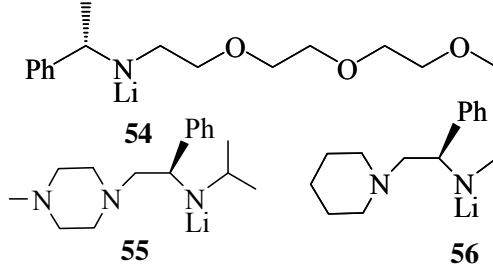
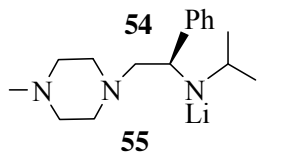
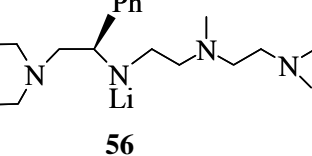
After that, striking advancements have been made. Chiral lithium amides with diverse structures were synthesized (Figure 4) and methods for maximizing the enantioselective outcome involving cyclic ketone substrates with different symmetry point groups, additives (inorganic salts and achiral amines) and other reaction conditions (such as temperature, solvents) were developed.

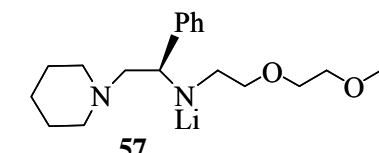
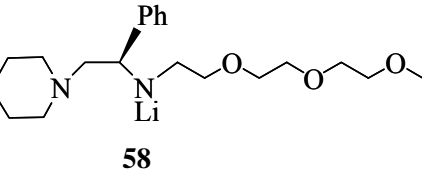
Monodentate:  **35** R₁=Ph, R₂=Ph **36** R₁=R₂=Nph
37 R₁=Ph, R₂=Me

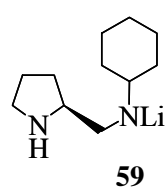
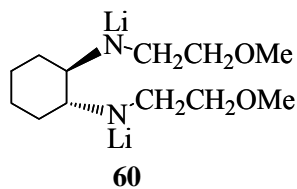


Bidentate  **49** ^tBu **50** iso-Pr **51** CH₂CF₃

Tridentate:  **52**  **53**

Tetradentate  **54**  **55**  **56**

 **57**
 Pentadentate  **58**

Diamine  **59**  **60**

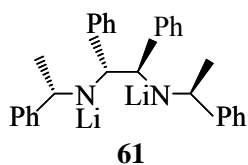
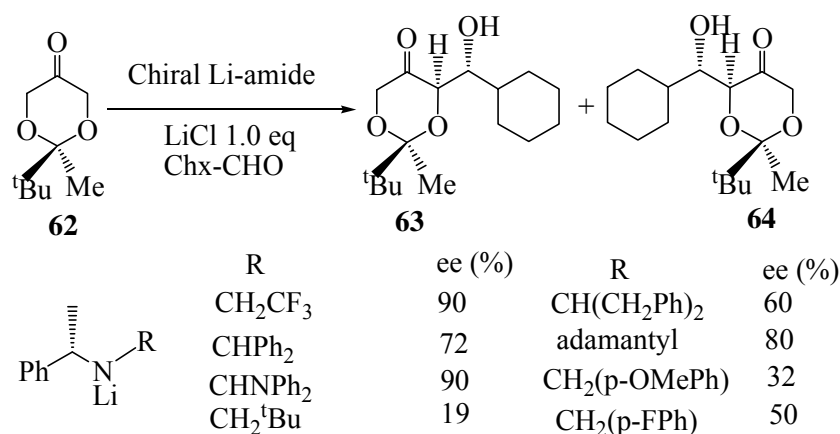


Figure 4: Structures of chiral lithium amides

Effect of the structure of lithium amide on deprotonation:

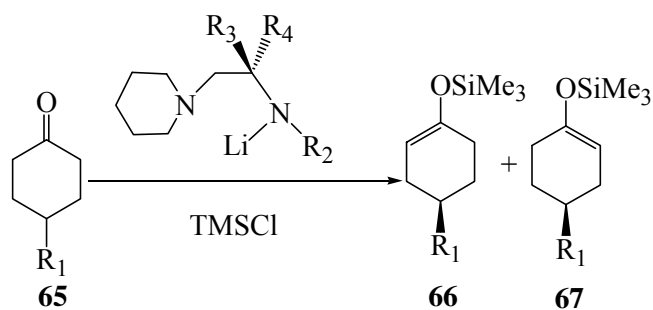
In order to study the relationship between the enantioselectivity and the structure of chiral lithium amides, our group synthesized and investigated several diverse chiral lithium amides in the deprotonation reaction of the dioxanone (**62**) followed by the aldol addition with cyclohexanecarboxaldehyde to give the aldol products (**63**) and (**64**). The results suggested that increasing the steric bulk of the R group attached on the nitrogen atom yielded greater enantioselectivity (ee), and, especially, relatively small but more electronegative CF₃ group in the amide could lead to high ee (Scheme 9).^[11-12]

Scheme 9



Studying the enantioselective deprotonation of 4-substituted cyclohexanones (**65**), Koga's group observed that the enantioselectivity of reactions was decreased when the substituent (R₃ or R₄) on the chiral carbon of the chiral lithium amides and the substituent (R₁) at the 4-position of cyclohexanones became bulky (Scheme 10).^[13]

Scheme 10

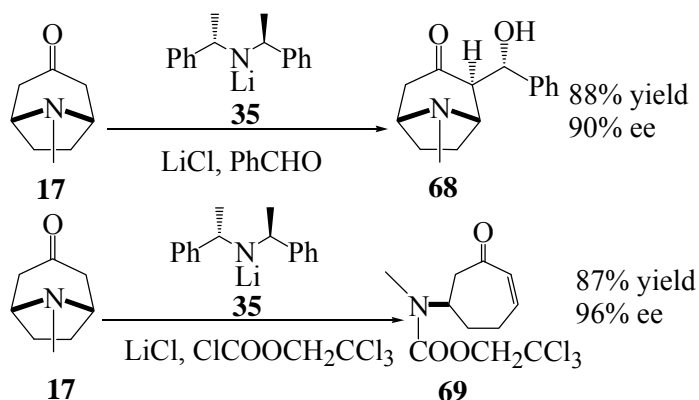


It was also found that the ee was dependent not only on the chiral lithium amides but also on the ketone substrates with different point groups.

There are different kinds of chiral lithium amides. The monodentate amides (Figure 4) called by Koga^[14] the chiral versions of LDA have two bulky alkyl groups attached to the nitrogen atom, like LDA. Another group of amides can be called polydentate (bidentate, tridentate, tetradentate, pentadentate etc.) and in these cases the amide ligand has extra electron donor atoms such as oxygen, sulfur or nitrogen.

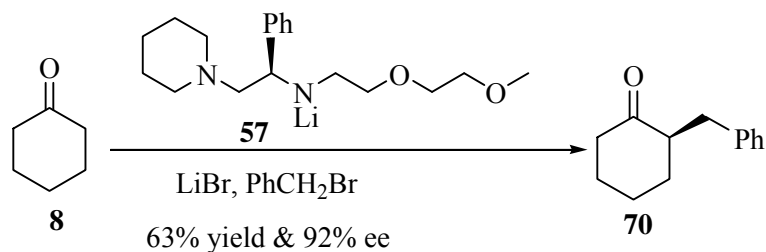
These two kinds of chiral lithium amides play different roles in enantiotopic group or face selective reaction of ketones with different symmetry point groups. For example, our group applied chiral lithium amide (35), a chiral version of LDA in the enantiotopic group selective aldol reaction of tropinone 17 with C_s symmetry point group to generate aldol products (68) with 90% ee and 88% yield.^[15-16] Furthermore, the ring opening product, cycloheptenone (69) having excellent 96% ee was also obtained in our group in 80% yield by using the same chiral amide (35) in the enantiotopic group selective ring open reaction of tropinone (Scheme 11).^[17]

Scheme 11



On another hand, Koga's group applied the chiral lithium amide (**57**) with extra electron donor atoms in the enantiotopic face selective alkylation reaction of cyclohexanone which gave alkylated product (**70**) in 92% ee (Scheme 12).^[18]

Scheme 12



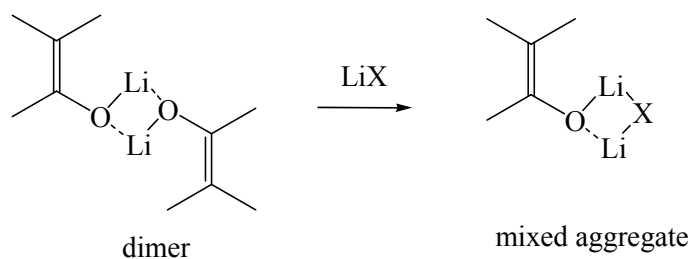
It appears that the efficiency of different kinds of chiral lithium amides in the enantiotopic face selective reaction of ketone enolate was not systematically investigated. Therefore, the objectives of my research project were to synthesize these two kinds of chiral lithium amides and apply them to reactions of 1,4-cyclohexanedione monoethylene ketal (**22**).

Additives and solvents effects:

It is known that lithium enolates are aggregated in solution and exist as oligomers^[19-21] with the lithium atom usually being tri- or tetra- coordinated.^[22-24] The crystals of some lithium enolates were collected and analyzed by X-ray crystallography, and the enolates were found to exist as dimers, tetramers or hexamers. Furthermore, Seebach identified the oligomer structures of lithium enolates by NMR studies, which indicated that the aggregates of enolates were directly involved in reactions with electrophiles and that the reactivity was decreased comparing to the monomer.^[25] Further studies had established that solvents and additives such as lithium halide salts or achiral amines could change deaggregation of lithium enolates and lithium amides.

Seebach^[25] demonstrated some effects of lithium halide salts on lithium enolate chemistry (Scheme 13). In the absence of lithium halide salt, lithium enolates usually exist as dimers and the yield and ee of the process were decreased due to the lower reactivity of the dimers. Lithium halide salt could convert the dimers into the reactive mixed aggregates and therefore, the yield and ee of the reaction were increased.

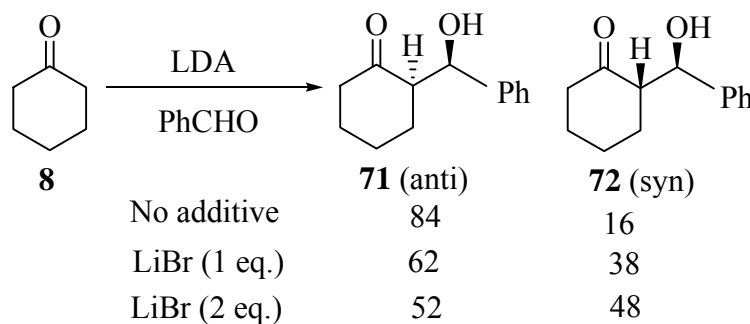
Scheme 13



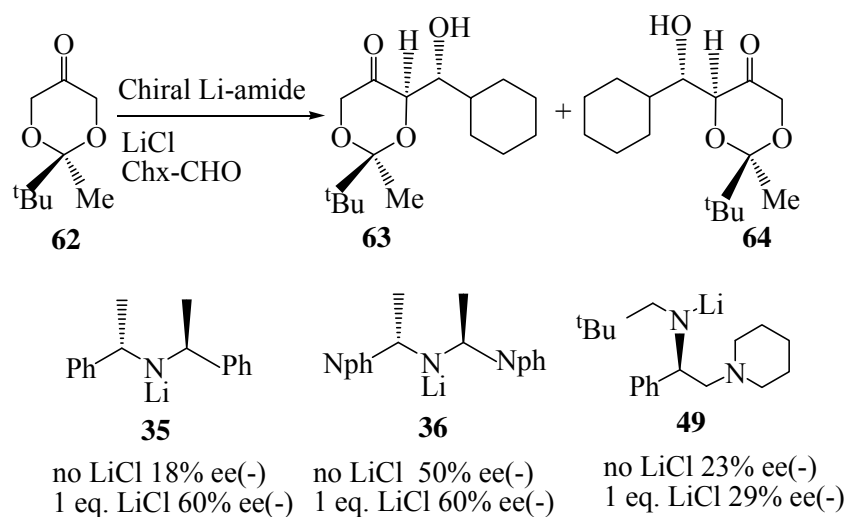
Our group investigated the effect of additives, especially inorganic salt such as LiBr and LiCl. In 1989, Majewski and Gleave^[26] reported that the addition of two or more equivalents of LiBr could greatly decrease the diastereoselectivity of aldol reaction of cyclohexanone (Scheme 14). It was also reported that addition of one equivalent of

LiCl could dramatically increase the ee of aldol reaction of dioxanone (**62**) with a few chiral lithium amides (Scheme 15).^[11-12]

Scheme 14

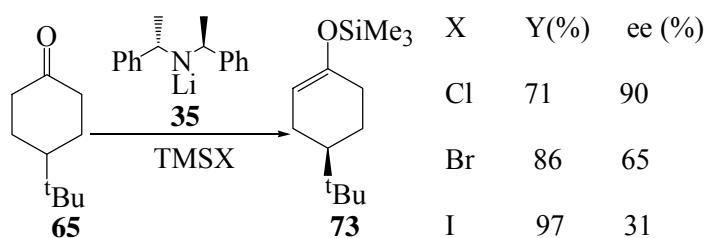


Scheme 15



Koga studied lithium halide effect on silylation (Scheme 16).^[27] It was shown that the ee of the product was highly dependent on the nature of the trimethylsilyl halide employed (lithium halide was generated in the reaction).

Scheme 16



Another study in our group also revealed the dramatic effect of several diverse additives on the enantioselectivity of deprotonation of tropinone (Figure 5).^[28]

Even small amounts of LiBr, LiCl, CeCl₃ or ZnCl₂ added to the reaction led the prominent increase of enantioselectivity. On the other hand, organic co-solvents such as HMPA, TMEDA, and DMPU did not affect the enantioselectivity greatly.

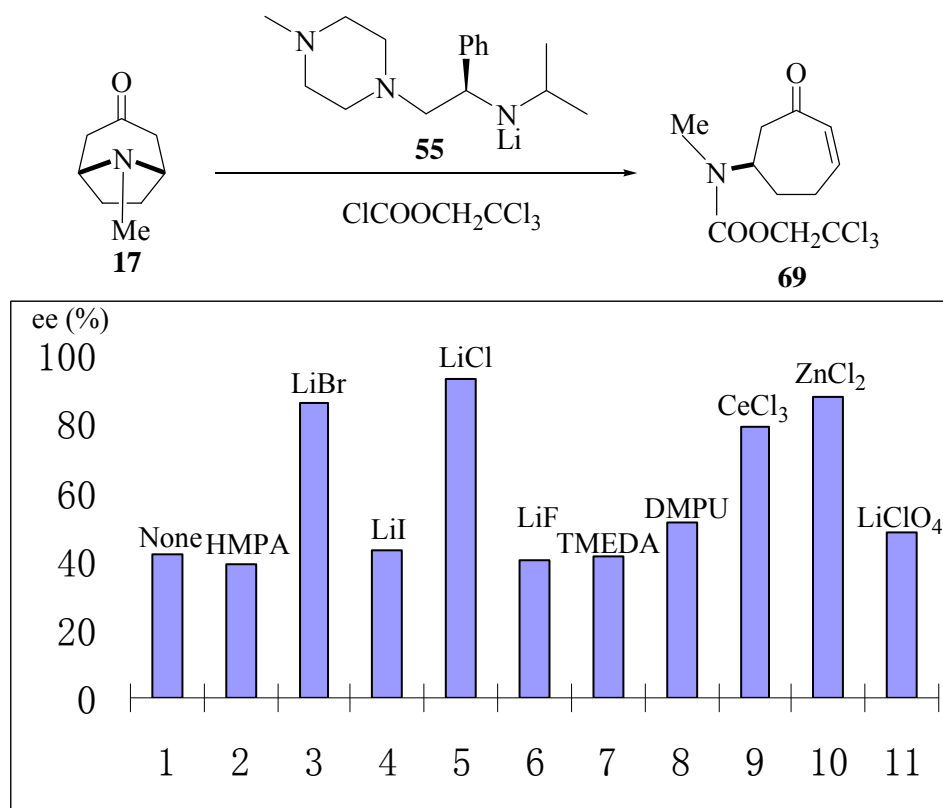
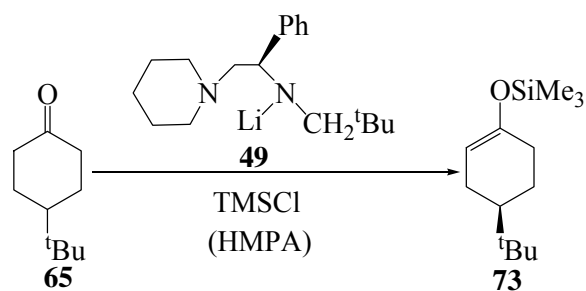


Figure 5: Effect of additives on the enantioselectivity of tropinone deprotonation

Koga's group investigated the effect of solvents^[14] on enantioselectivity of the silylation and found that it varied greatly with ketones and additives. For the 4-t-butylcyclohexanone (**65**), polar solvents resulted in higher enantioselectivity without additive HMPA, but in the presence of HMPA, the effects caused by the solvents were decreased (Scheme17).

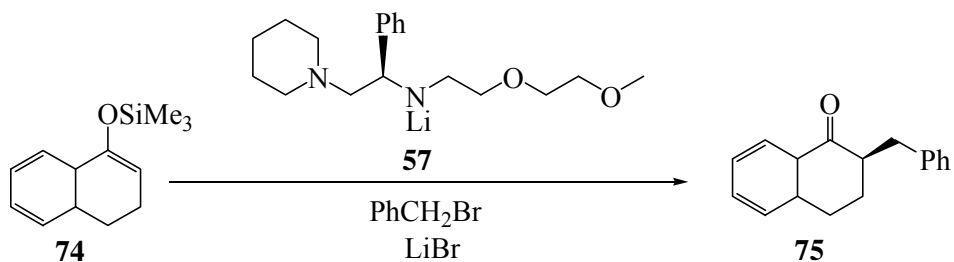
Scheme 17



Solvent	Without HMPA		With HMPA (2.0 eq)	
	yield (%)	ee (%)	yield (%)	ee (%)
THF	86	84	82	82
DME	86	70	87	81
Ether	8	64	89	82
Toluene	12	58	87	82

Koga reported that the less polar aprotic solvent toluene rather than THF led to higher enantioselectivity in the alkylation reaction of 1-tetralone (Scheme 18).^[13]

Scheme 18

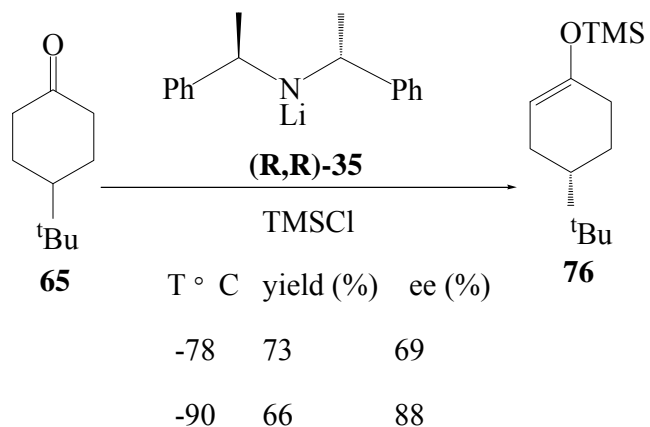


	Yield (%)	ee (%)
THF	87	0
DME	86	41
Ether	56	91
Toluene	63	92

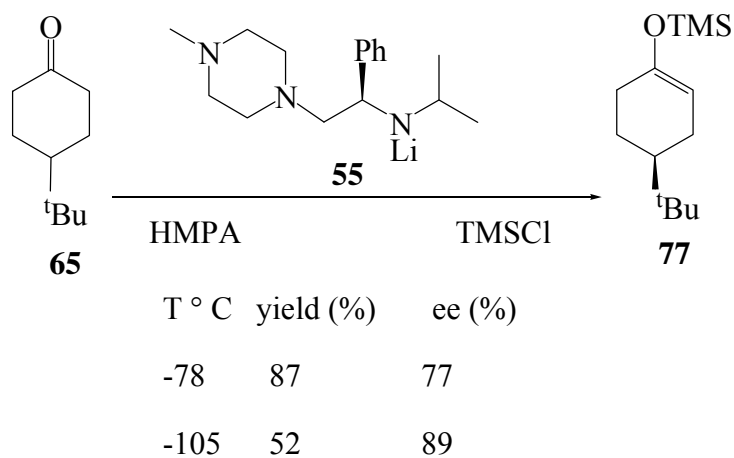
Temperature effects:

Temperature often affects the stereoselective reactions, because most of these reactions are accomplished under kinetic control and selectivity is based on the difference of free activation energy. The lower temperature usually results in higher stereoselectivity. The investigation by Simpkins^[29] (Scheme 19) and Koga^[30] (Scheme 20) of temperature effects demonstrated this point.

Scheme 19



Scheme 20



Catalytic asymmetric reaction using achiral amines as additives:

Recently, chemists focused their interests on catalytic asymmetric reactions in which substoichiometric amounts of chiral amides were applied. They found some achiral amines such as TMEDA (**78**) or N, N, N, N'-tetramethylpropylenediamine (**80**) can play a key role as additive in the catalytic asymmetric process. Koga elaborated their function with respect to both chemical and optical yields of the product in the catalytic asymmetric alkylation reaction of 1-tetralone (Scheme 21).^[31]

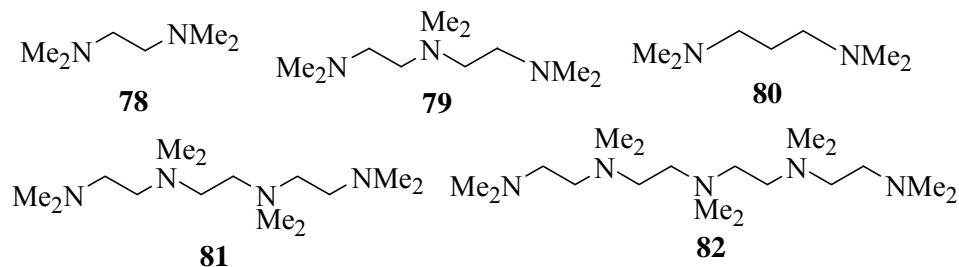
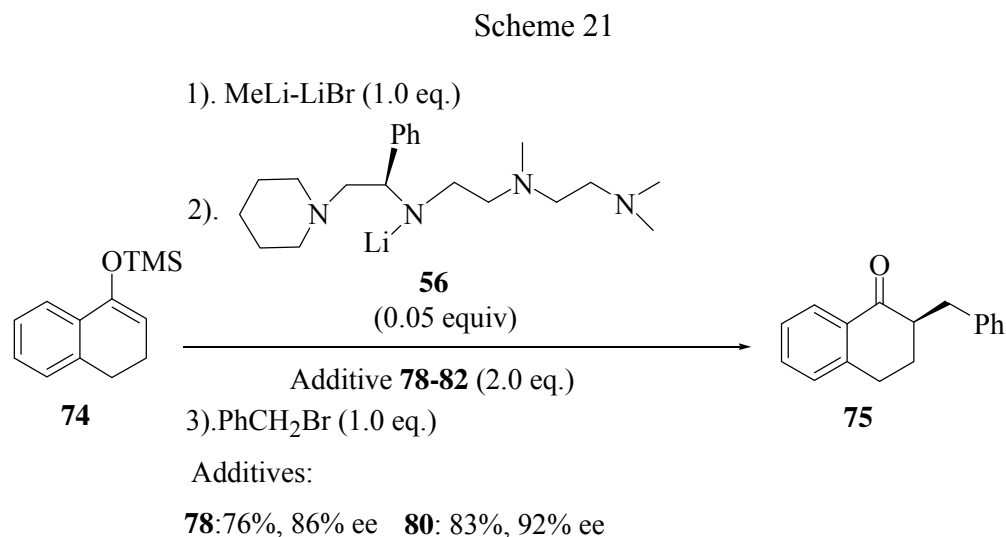


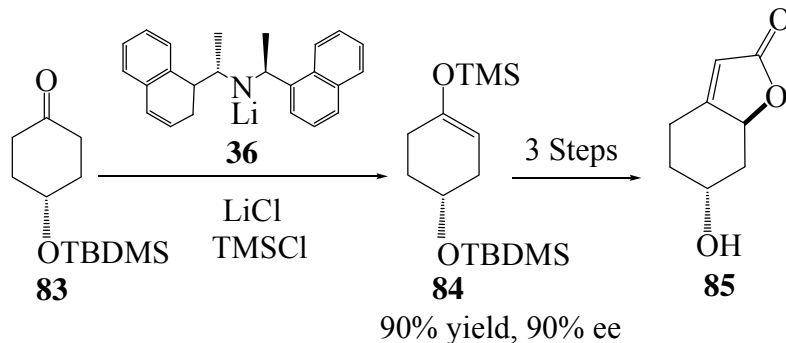
Figure 6: Achiral amines used in catalytic deprotonation.



Enantioselective deprotonation of cyclic ketones in total synthesis of natural products:

The methodology development in the enantioselective deprotonation of cyclic ketones has been applied successfully in a lot of total syntheses.^[33a] For example, Majewski et al. utilized the base (**36**) and LiCl to prepare silyl enol ether (**84**) in 90% ee which was used for synthesis of a natural product, (-)-dihydroaquilegiolide (**85**, Scheme 22).^[33b]

Scheme 22



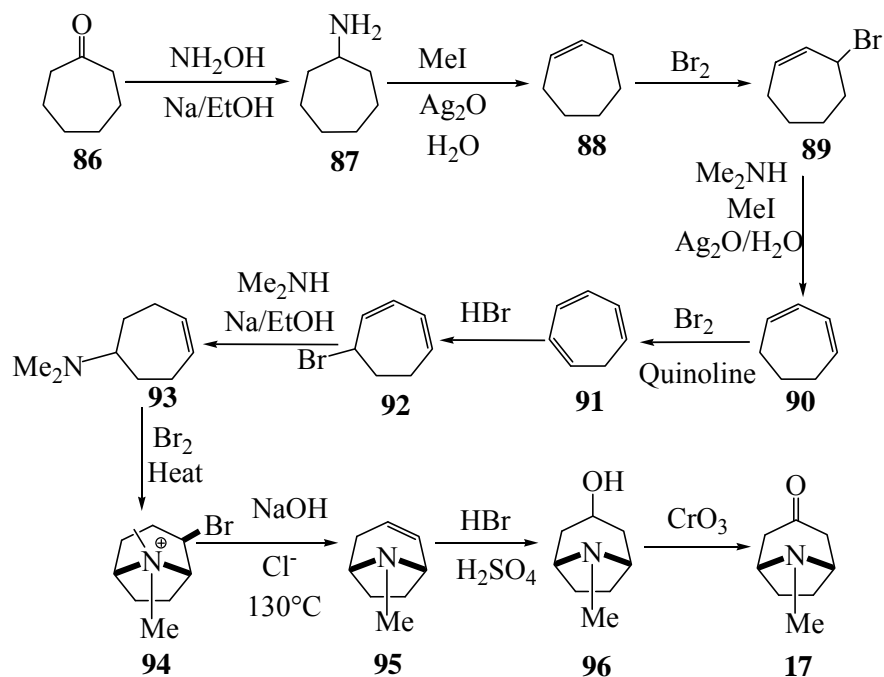
1.3. Synthesis of tropane alkaloids

Tropane alkaloids have been synthesized for more than one hundred years. A number of synthesis paths and methodology studies have been developed. But the enantioselective synthesis has been unknown until recently.

Dr. Ryszard Lazny reviewed synthesis of tropane alkaloids in his PhD thesis,^[34] where he discussed the developments from 1901 to 1996 (74 papers). The brief review of tropane alkaloids synthesis in this thesis includes a summary of Ryszard's review, his research and other review of EPC synthesis of tropinone from 1996 to present.

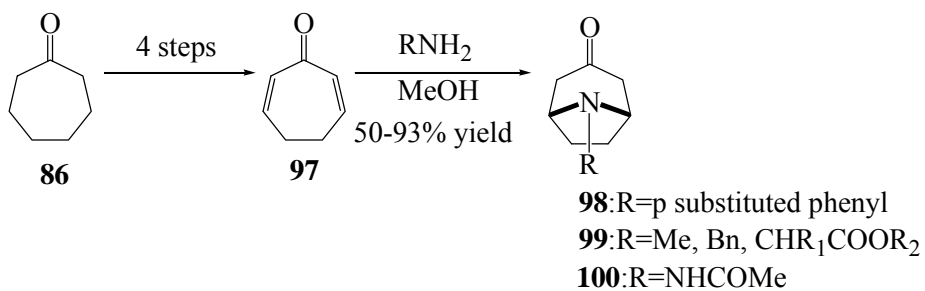
Early research started with the first Willstatter's synthesis of tropinone in 1901, is the classical synthesis of tropinone (**17**) without the formation of C-C bonds and obtained total yield of 0.75% from cycloheptanone (Scheme 23).^[35-36]

Scheme 23

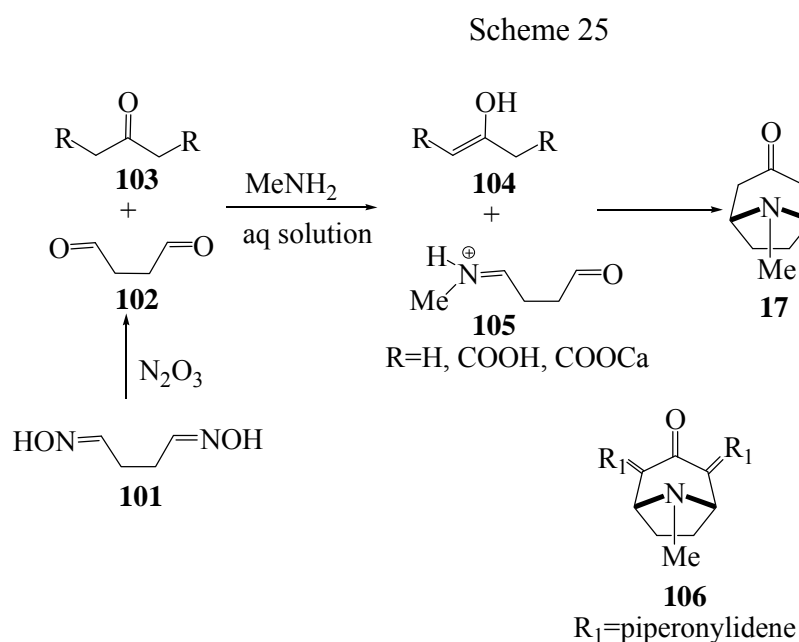


The synthesis of tropinone and N-substituted nortropinone derivatives using double Michael addition of amine to 2,6-cycloheptadiene (**97**) was also described^[37-40]. 2,6-Cycloheptadiene is easily prepared via a four steps procedure developed by Garbisch,^[41] Bottini and Gal^[37] also obtained tropinone and its analogs of benzyl and ethyl from 2,6-cycloheptadiene (Scheme 24).

Scheme 24

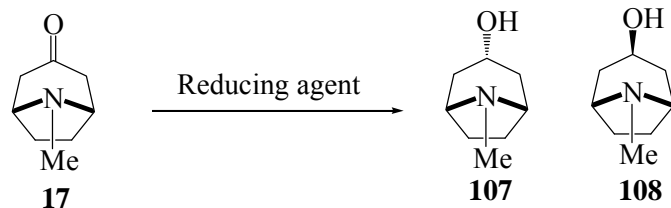


The original Robinson's synthesis involved a double Mannich reaction of acyclic substrate such as succindialdehyde with methylamine and acetone (Scheme 25).^[42] The problem of the synthesis was associated with the unstable succindialdehyde (**102**) which was prepared by applying 'nitrous fumes' (N₂O₃) on succinaldoxime (**101**) and only 42% yield was obtained in a form of diperonylidene derivative (**106**). Schopf et al.^[43-45] could increase the yield of the synthesis to over 90% by optimization of the reaction conditions. Other preparations of tropinone through the Robinson-Schopf synthesis by Keagle & Hartung,^[46] Willstatter,^[47] Raphael^[48] and Lansbury^[49] were demonstrated.



In the synthesis of 3-substituted tropinone using stereoselective reduction of tropinone, Willstatter's studies with endo/exo selectivity of 5:2^[50] and especially, Keagle and Hartung's method with endo / exo selectivity of 99.4:0.6^[46] were reviewed (Scheme 26 and Table 1.1).

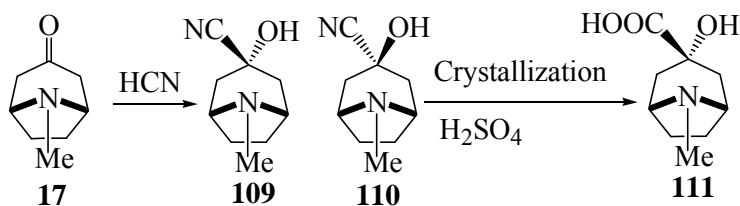
Scheme 26

Table 1.1. Stereoselective reduction of tropinone (**17**)

Reducing reagent	Zn/HI	Na/EtOH	Na/ <i>iso</i> -BuOH	H ₂ /PtO ₂ , EtOH	H ₂ /PtO ₂ , EtONa	NaBH ₄	DIBAL-H/THF
107:108	5:2	1:24	1:27	99.4:0.6	12:1	54:46	32:1
References	50	53a	53a	46	53a	53b, 53c	53d

A few 3 α and 3 β -tropane derivatives were prepared from the preparation of the intermediate of tropinone cyanohydrin.^[51-52] For example, α -ecgonine methyl ester (**111**) was first produced by Willstätter^[54] via acid hydrolysis of tropinone cyanohydrin (**109/110**, Scheme 27). Later, other synthesis of 3 α and 3 β -tropane derivatives based on the transformation of different tropinone cyanohydrin by Daum,^[55] Tufariello,^[56] Backvall,^[57-58] Malpass,^[59-62] and Kibayashi^[63-64] were also reported.

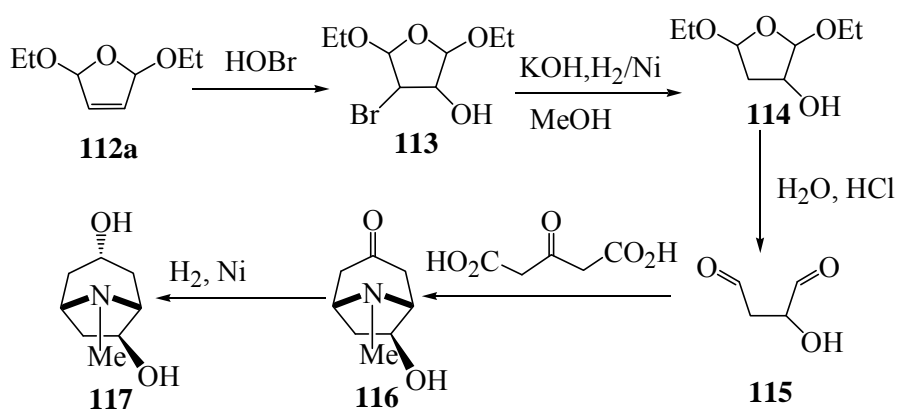
Scheme 27



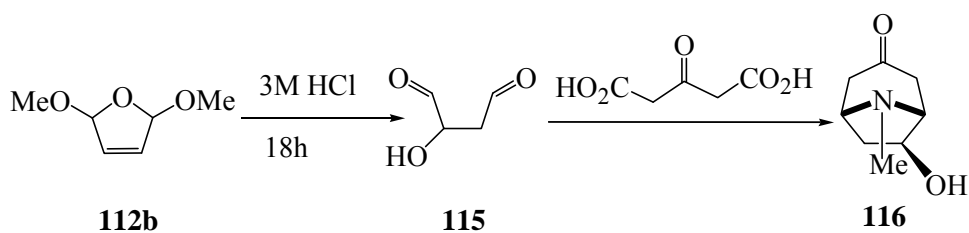
The methodology of racemic alkaloids synthesis was also illustrated. The synthesis of 6-hydroxytropinone was accomplished by a few modifications of Robinson-

Schopf which were reported by Stoll (Scheme 28)^[65-66] and Clauson-Kaas (Scheme 29)^[67] from 2,5-dialkoxy-2,5-dihydrofuran (**112a/b**). Fodor (Scheme 30)^[68] used 6-hydroxytropinone for the synthesis of racemic valeroidine. The synthesis of baogongteng A (**131**) was also reported by Xiang (Scheme 31)^[69] with 1,2-carbonyl transposition etc. reactions.

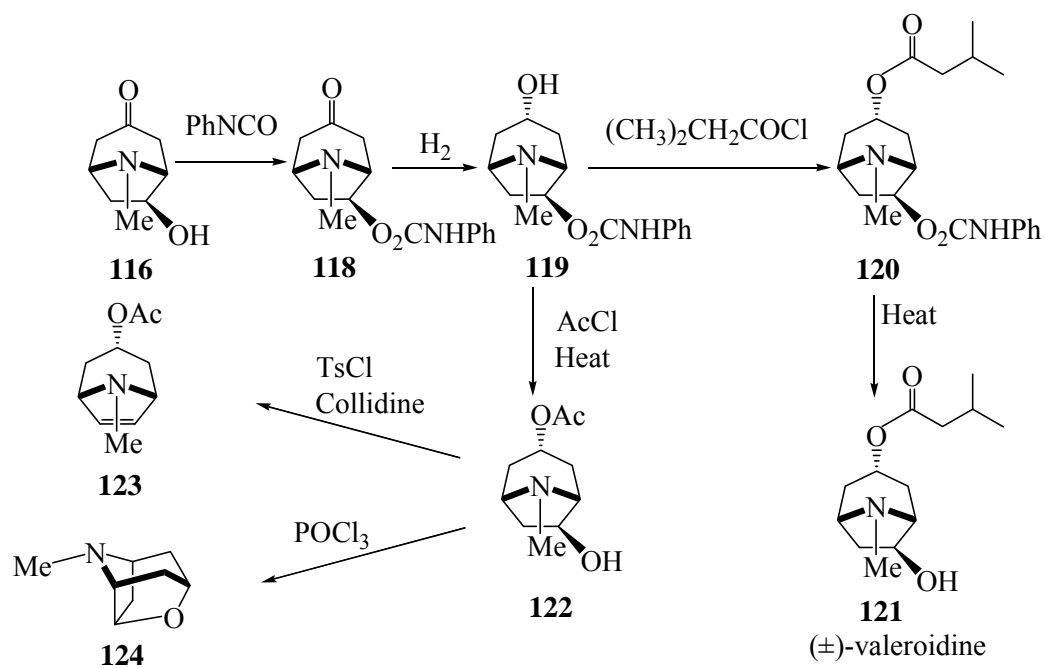
Scheme 28



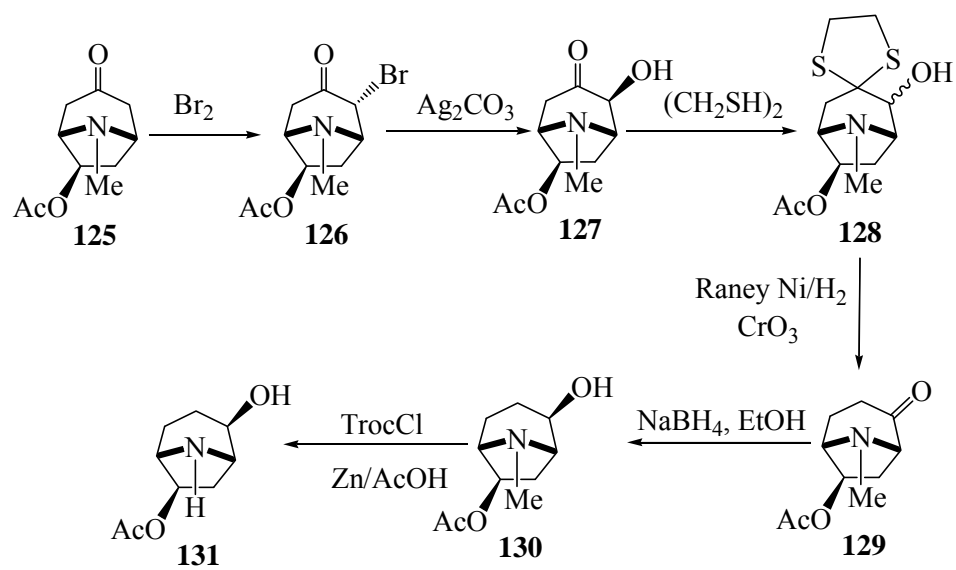
Scheme 29



Scheme 30

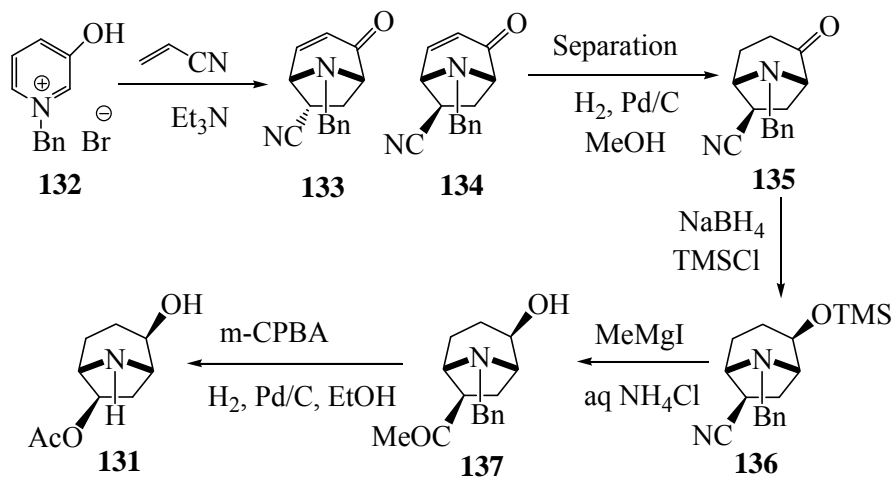


Scheme 31



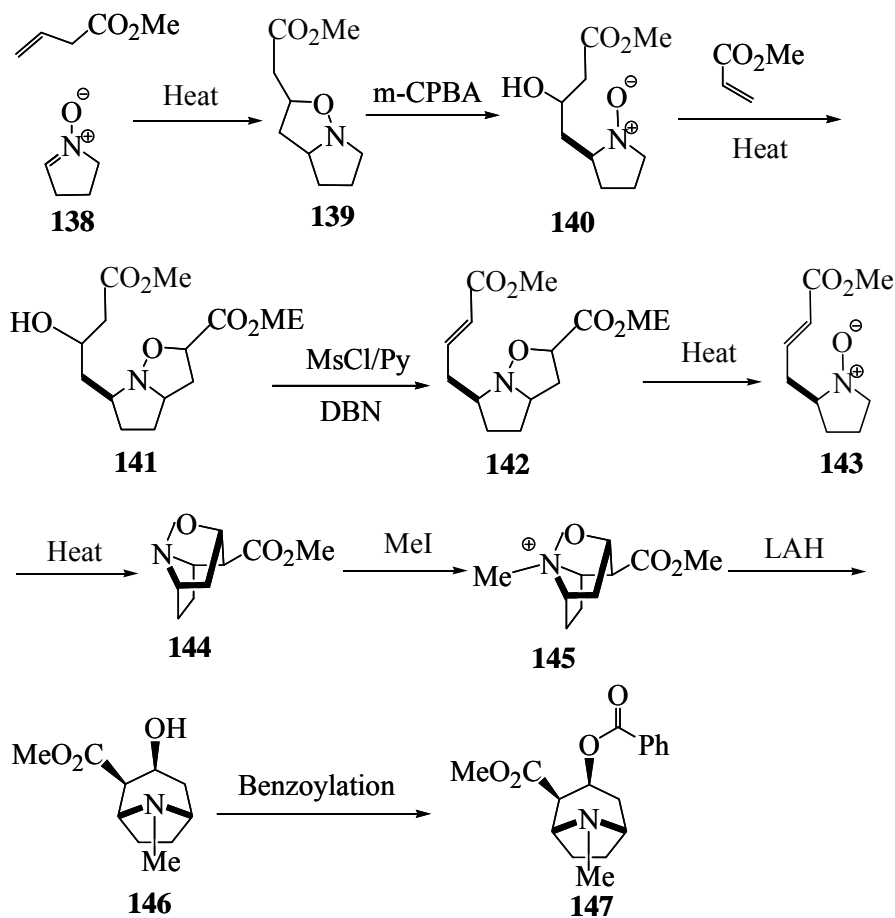
Jung^[70] also used 1,3-dipolar addition for the synthesis of baogongteng A (**131**) from 1-benzyl-3-hydroxypyridinium bromide (**132**, Scheme 32).

Scheme 32



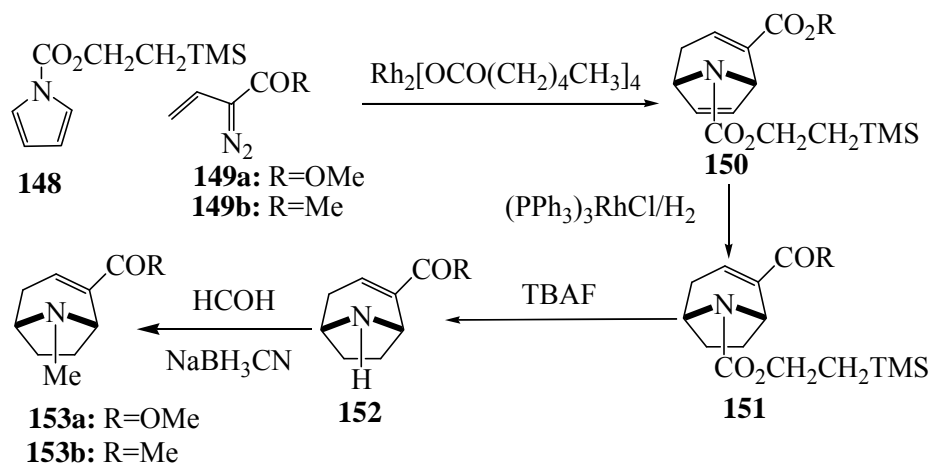
It was remarkable that Tufariello^[71-74] used a 1,3-dipolar addition of the nitron (138) in the synthesis of racemic cocaine (147) and this synthesis path could be used for the synthesis of pure natural (-)-cocaine and unnatural (+)-cocaine by the introduction of a chiral auxiliary in the 1,3-cycloaddition reaction (Scheme 33).

Scheme 33



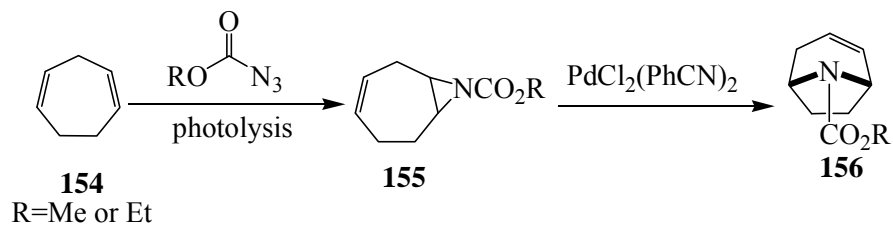
Furthermore, Davies^[75-77] used rhodium catalyzed reactions of vinylcarbenoids for the synthesis of racemic anhydroecgonine methyl ester (**153a**) and ferruginine (**153b**, scheme 34).

Scheme 34



Rettig^[78] reported the synthesis of alkoxy carbonyl derivatives of nortropidine (**156**) via a reaction with alkyl azidoformate and dichlorobis(benzonitrile) palladium (II) catalyzed rearrangement of the resulting aziridines from 1,4-cycloheptadiene (**154**, Scheme 35).

Scheme 35



The 4-functionalized tropan-7-one was synthesized from a key intermediate, aziridine^[79] which was developed by Furuya and Okamoto. They prepared the aziridine (**159**) from the deprotonation of N-chloronortropinone using sodium methoxide or basic aluminum oxide. The aziridine can react with nucleophiles such as acyl halide, acid anhydrides, Michael acceptors, dimethyl acetylenedicarboxylate (DMAD) to give the tropane derivatives (**160**) (Scheme 36, Table 1.2).

Scheme 36

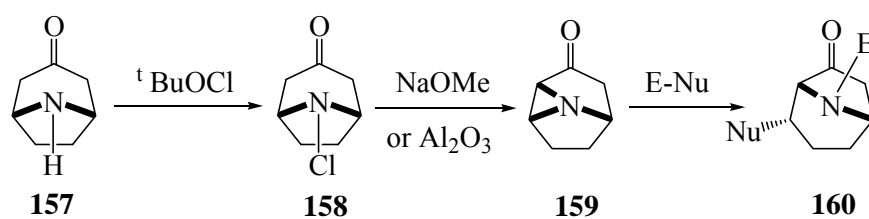
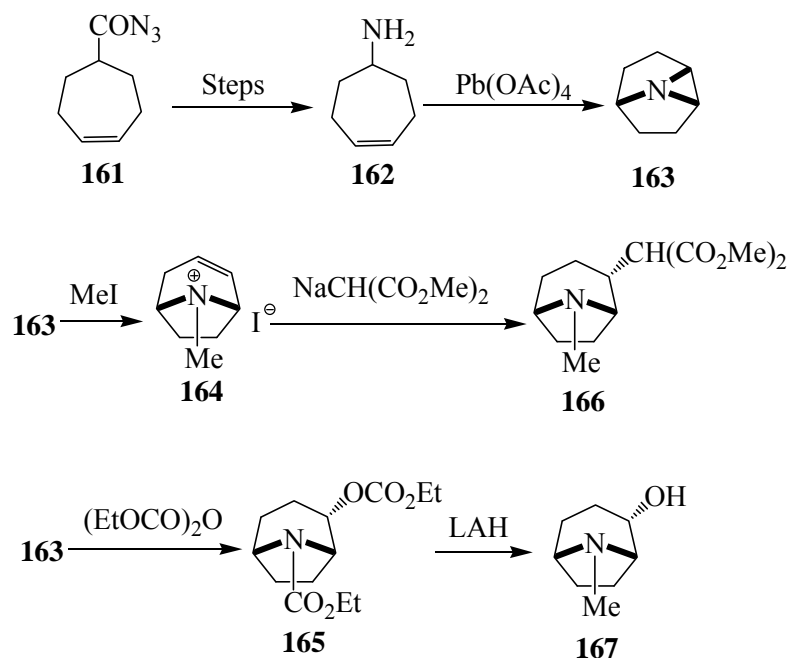


Table 1.2: Tropane derivatives (**160**)

Entry	1	2	3	4	5	6	7
E	Ts	Cl	CN	Ms	Ac	Ac	Ac
Nu	Cl	Cl	Br	Cl	Cl	OH	OAc
Yield of 160	36	80	71	58	72	32	66

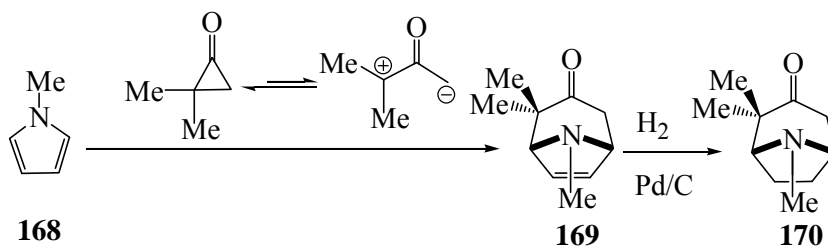
Nagata reported the synthesis of tropinone derivatives (**166**, **167**) from aziridine (**163**). The aziridine can be prepared from the acyl azide (**161**) (Scheme 37).^[80]

Scheme 37

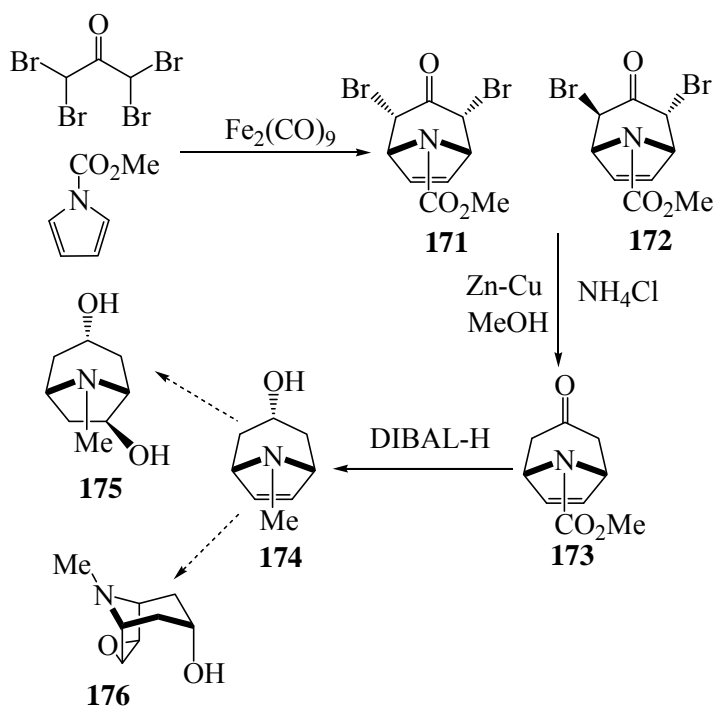


6-Tropen-3-one is a useful intermediate for the synthesis of scopine and 6-hydroxytropine. A few methods were reported based on the addition of oxyallyls to N-substituted pyrroles by Turro and Edelson (Scheme 38)^[81] Noyori (Scheme 39)^[82a, 82b] Mann and de Almeida Barbosa (Scheme 40),^[83] Hoffmann (Scheme 41).^[84]

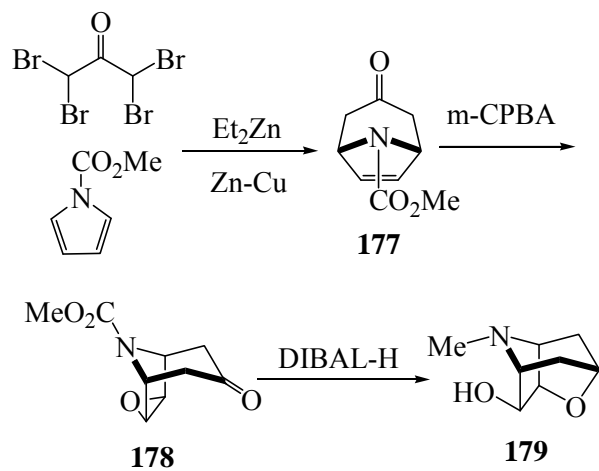
Scheme 38



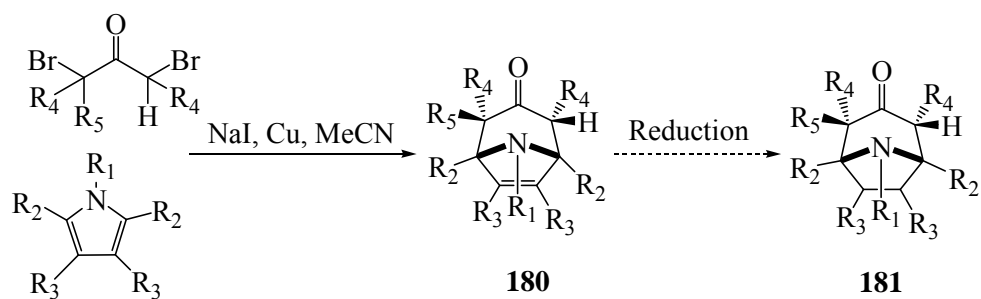
Scheme 39



Scheme 40

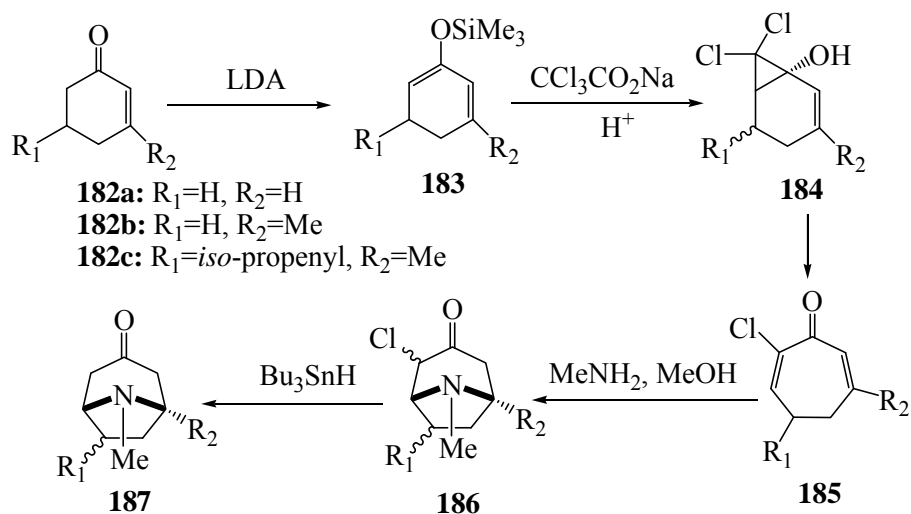


Scheme 41



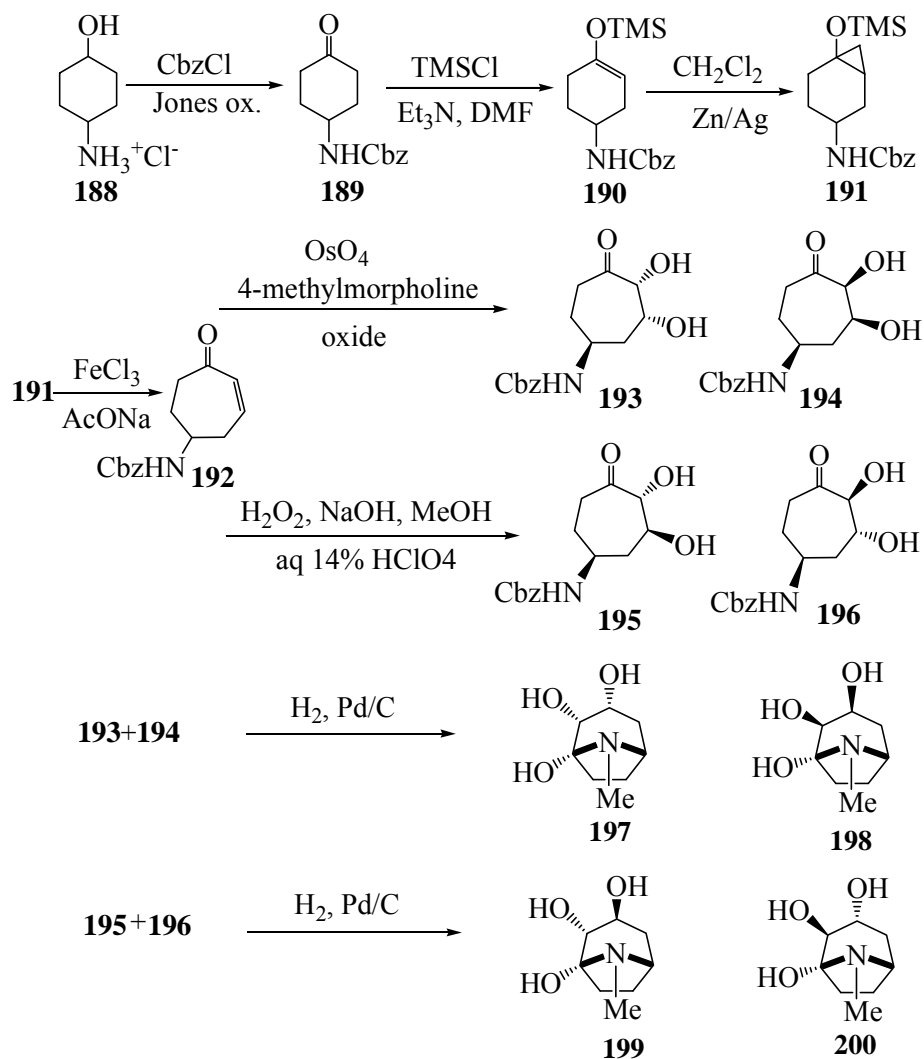
The synthesis of chiral tropanes from 2-cyclohexenones (**182**) was developed by MacDonald and Dolan (Scheme 42)^[85] via the addition of dichlorocarbene to expand the six-membered ring and double Michael type of addition.

Scheme 42



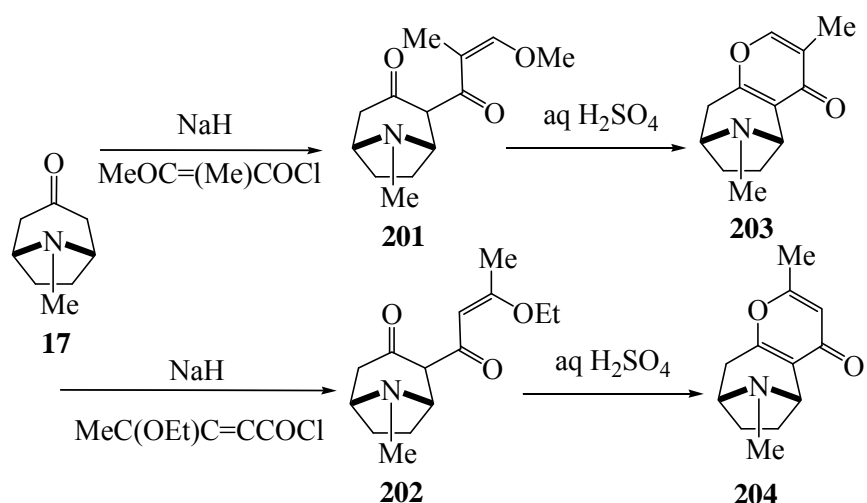
Lallemand also took use of a ring enlargement methodology,^[86] i.e. cyclopropanation, followed by the cleavage of the three membered rings with FeCl₃, to achieve the synthesis of calystegine A₃ (**191**) and its three diastereoisomers (Scheme 43).

Scheme 43



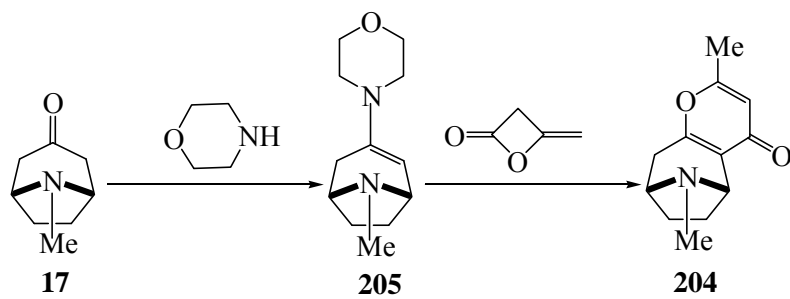
Tropinone is now commercially available compound. Further synthesis of tropane alkaloids started from the functionalization and transformation of tropinone. All synthetic approaches involve the tropinone enolate chemistry of its synthetic equivalents. In 1973, Bick^[87-88] achieved the racemic bellendine (**203**) and isobellendine (**204**) by using an acylation reaction of tropinone sodium enolate with acid chlorides followed by cyclization under acidic conditions (Scheme 44).

Scheme 44

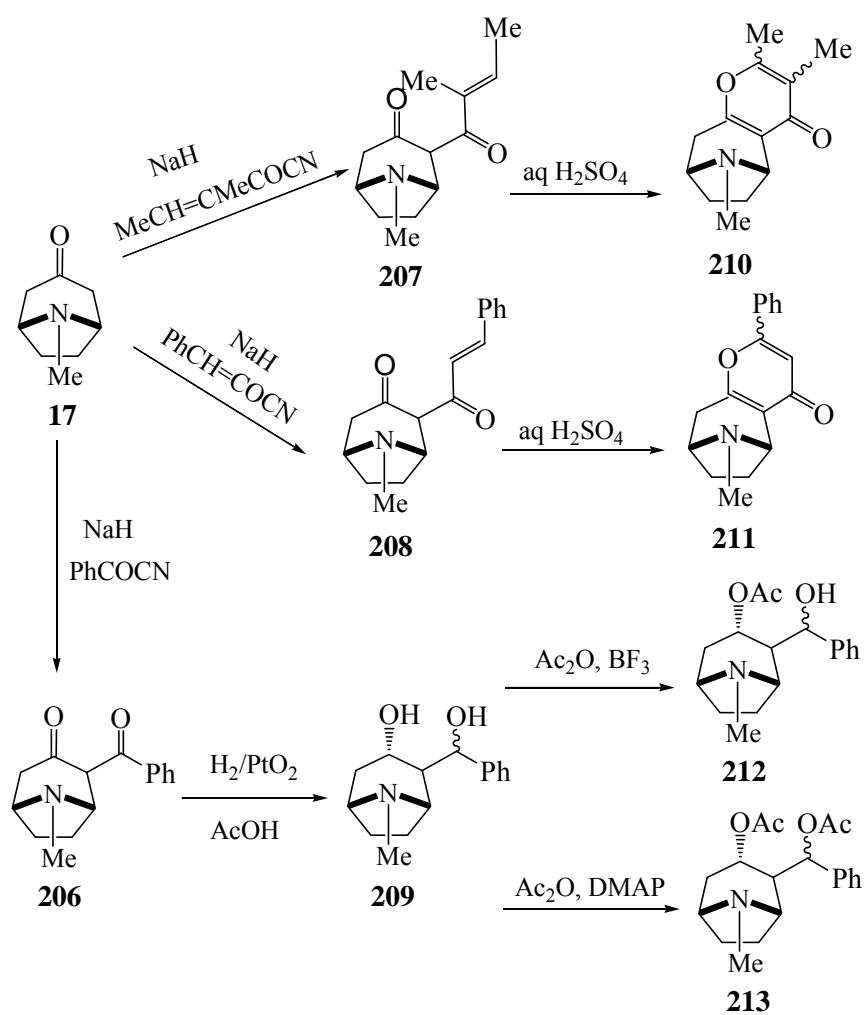


The way to synthesize the racemic isobellendine (**204**)^[89] by Lounasmaa who used an enamination reaction of tropinone with diketene was efficient (Scheme 45). Lounasmaa also reported the synthesis of (\pm)-knightinol, (\pm)-acetylknightinol, (\pm)-drodarlingine and their derivatives^[90-91] via acylation of tropinone sodium enolate with acyl cyanides (Scheme 46).

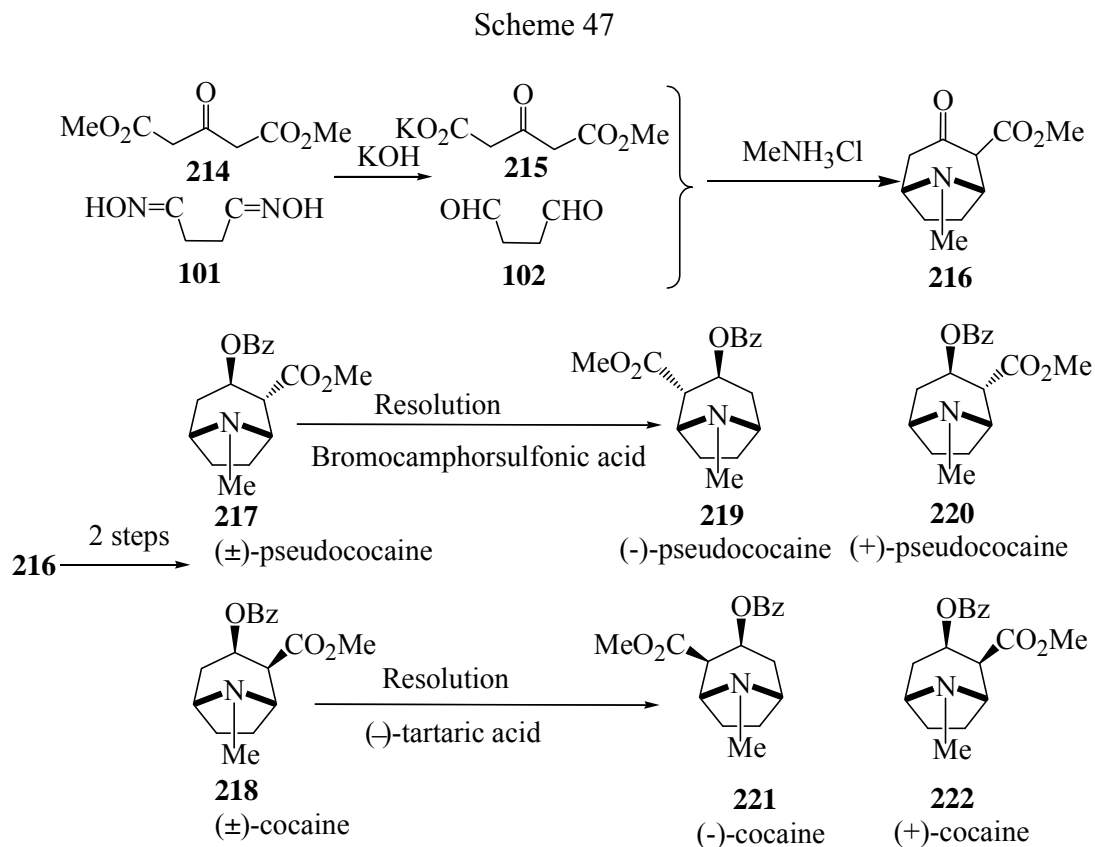
Scheme 45



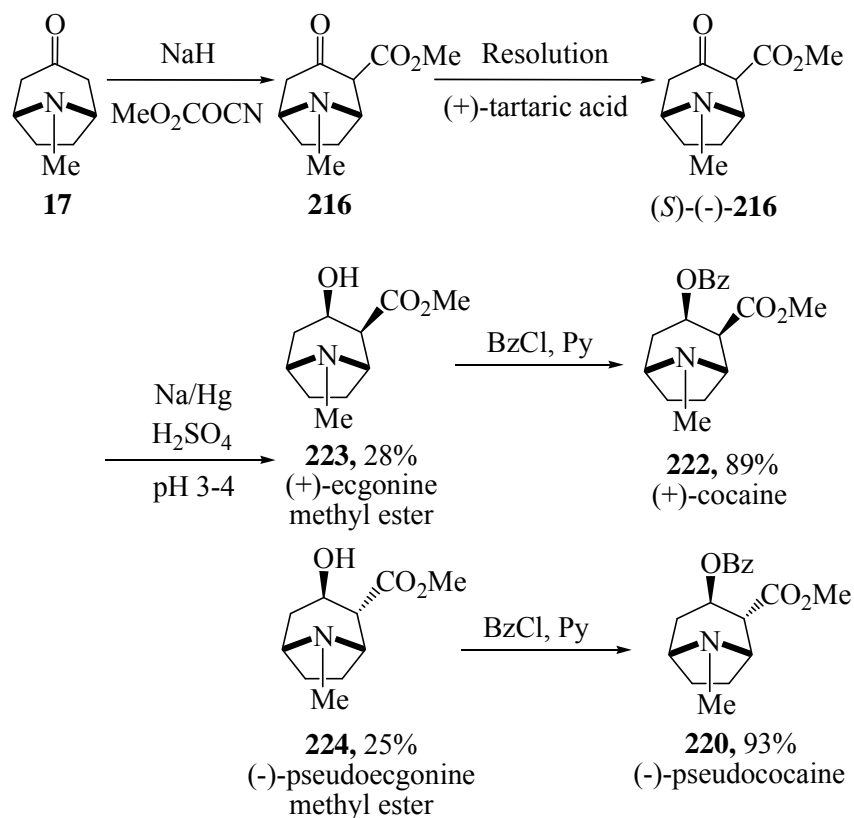
Scheme 46



Resolution of a racemic compound was the earliest approach to obtain the chiral products. For example, the optically active forms of cocaine were prepared by Willstatter (Scheme 47)^[92] in 1923, Carroll (Scheme 48)^[93] in 1987 including diastereoselective reduction of methoxycarbonyltropinone (**216**) and the resolution.



Scheme 48

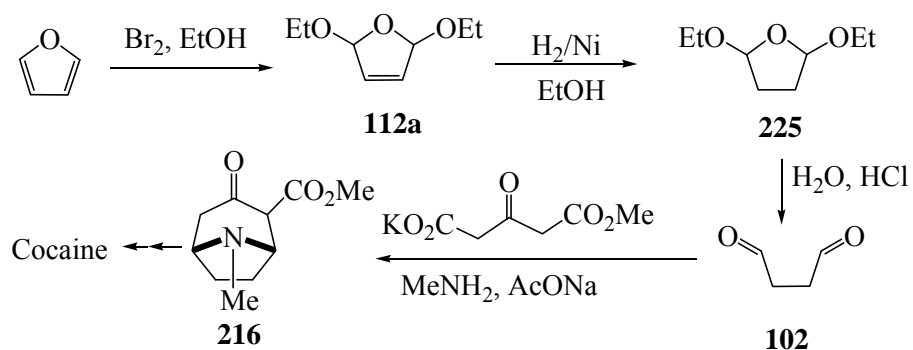


The best method of the diastereoselective reduction of methoxycarbonyltropinone was developed by Carroll^[93-94] with 3:2 selectivity in the favor of (+)-ecgonine methyl ester (**223**). The method of resolution with 3-boromocamphor-7-sulfonic acid was also applied in the Stoll's synthesis of optically active valeroidine derivative^[95] and Fodor further synthesized the natural valeroidine based on the Stoll's synthesis. With the method of the resolution, Pinder achieved the natural (+)-physoperuvine.^[96-97]

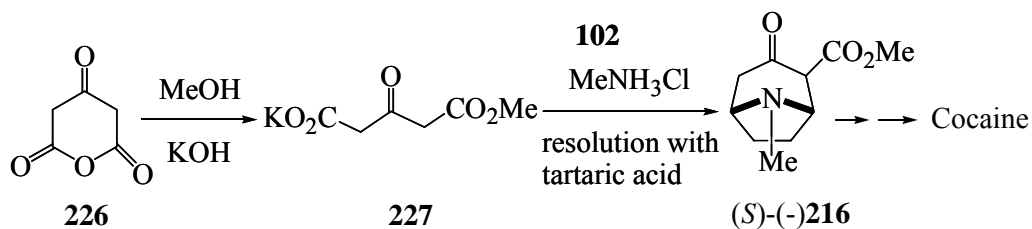
Other reports of synthesis of the optically active forms of cocaine were similar, including diastereoselective reduction of methoxycarbonyltropinone (**216**) and the resolution. The difference is the preparation method of methoxycarbonyltropinone (**216**). Findlay^[98] utilized 2,5-diethoxytetrahydrofuran prepared from furan by Clauson-Kass^[99] (Scheme 49). Findlay also reported the synthesis of (**216**) from ketoglutaric

anhydrides (**226**, Scheme 50).

Scheme 49

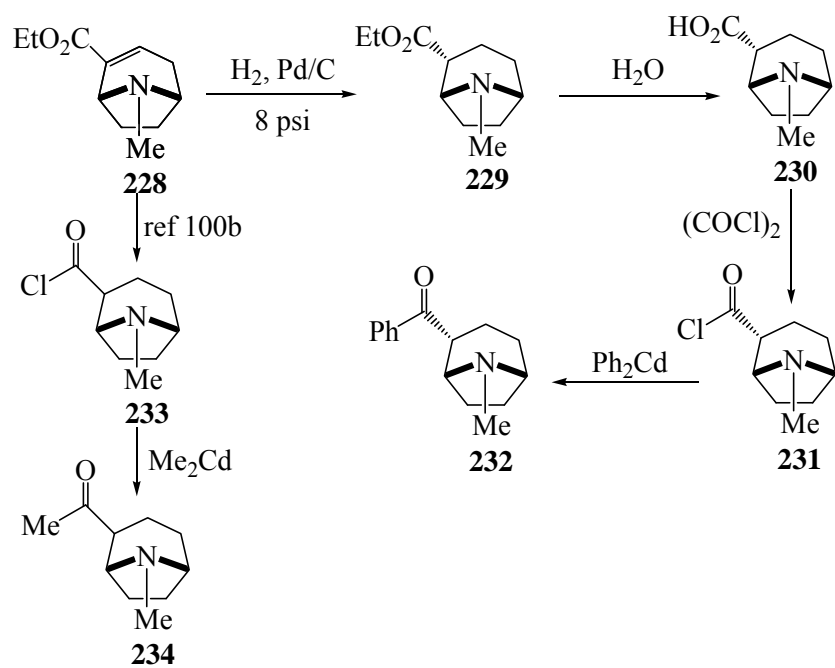


Scheme 50



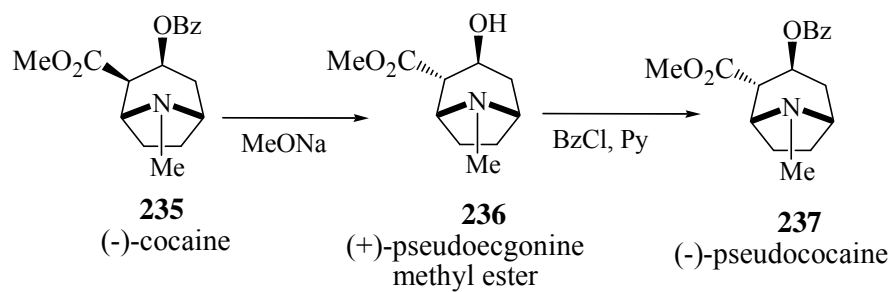
On the other hand, some of chiral natural compounds, such as (-)-cocaine, has been applied to synthesize the optically active tropane alkaloids via “chiral pool approach” EPC method. For example, Bick^[100a] accomplished the unnatural (-)-ent-ferruginine (**232**) and (-)-ent-ferrugine (**234**) from optically active anhydroecgonine ether ester (Scheme 51).

Scheme 51



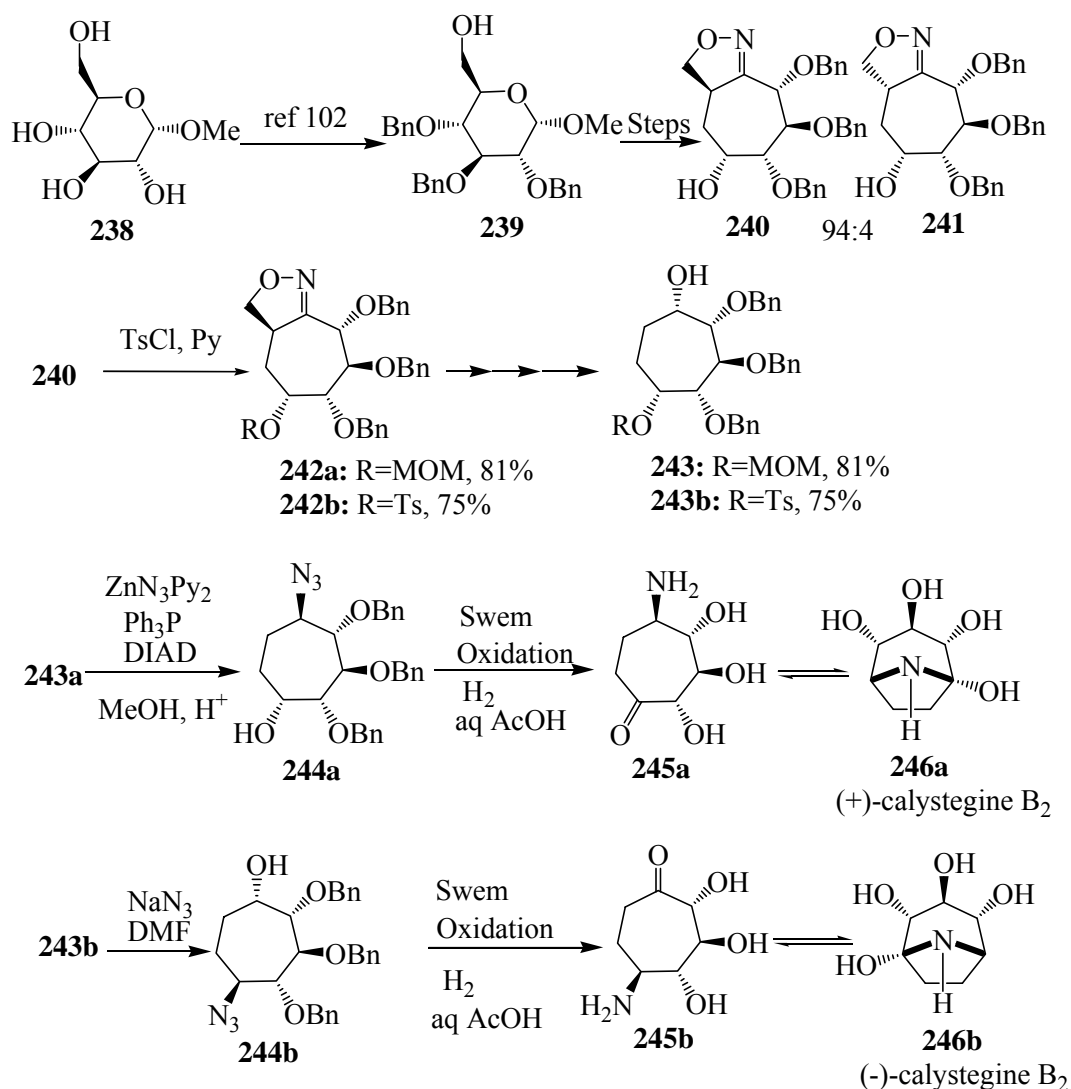
The natural (-)-cocaine (**235**) was used as the substrate by Carroll to synthesize pseudococaine (**237**), a known cocaine epimer (Scheme 52).^[101]

Scheme 52



Cycloheptano-isoxazoline intermediate (**240**) was prepared by Duclos^[103-104] from the methyl α -glucopyranoside (**238**) and then the synthesis of both enantiomers of calystegine B₂ (**246a**) and (**246b**) were accomplished via a series of reactions from the intermediate (**240**, Scheme 53).

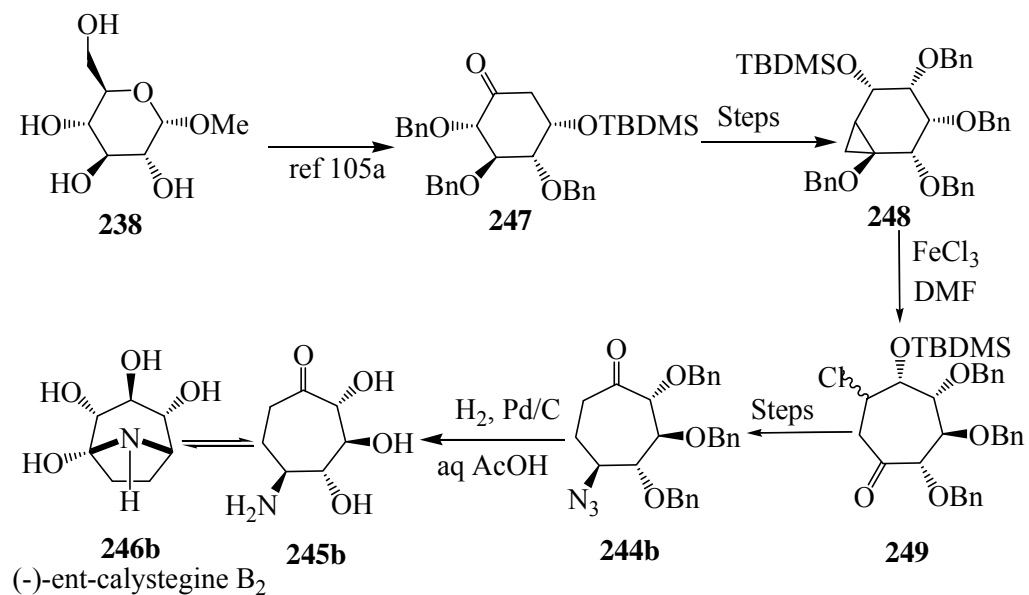
Scheme 53



Boyer and Lallemand synthesized (-)-ent-calystegine B₂ (**246b**, Scheme 54)^[105b]

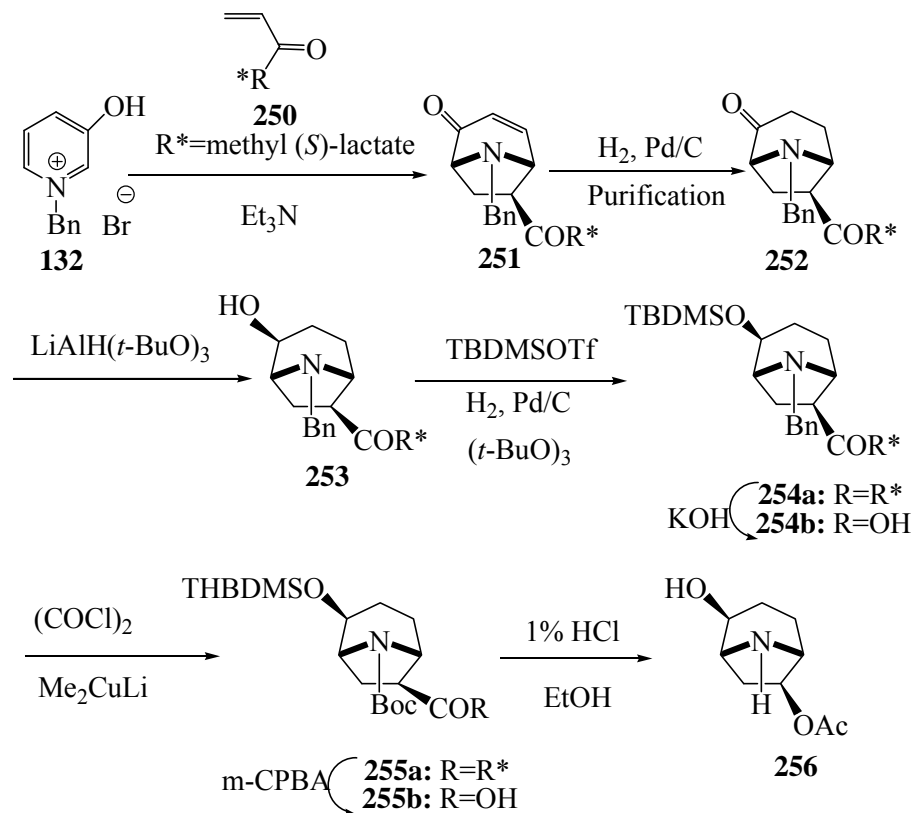
via a ring enlargement of polysubstituted cyclohexanone (**247**).

Scheme 54



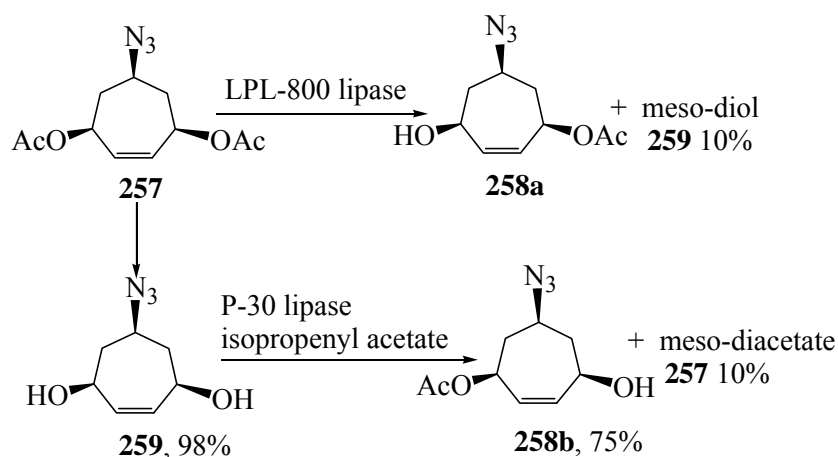
A natural enantiomer of baogongteng A (**256**) was synthesized by Pham and Charlton^[106] via an asymmetric 1,3-dipolar cycloaddition (a key intermediate reaction) from the chiral acrylate of methyl (*S*)-lactate (**250**, Scheme 55).

Scheme 55



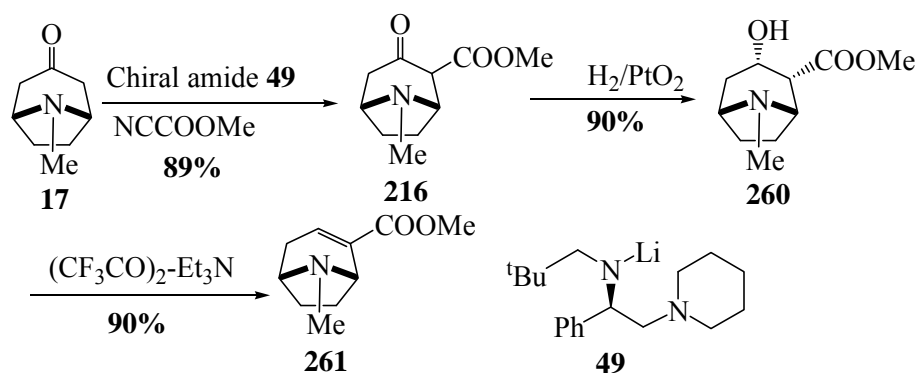
No synthesis of optically pure tropane alkaloids based on enantioselective reactions was reported until 1995. The one report on the synthesis of optically pure enantiomers of calystegine A₃ based on the enzymatic desymmetrization of meso-diols (**259**) and meso-diacetates (**257**) was described by Johnson and Bis (Scheme 56).^[107]

Scheme 56



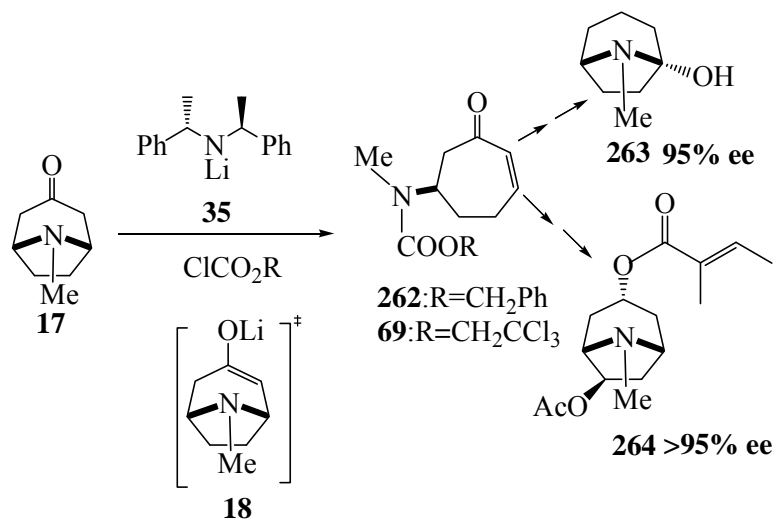
It is necessary to point out that Majewski and Zheng developed enantioselective synthesis of natural tropane alkaloids, anhydroecgonine methyl ester (**261**)^[15-16] of higher optical purity (94% ee; 72% yield from tropinone) based on the β -keto ester of tropinone (**216**) obtained by deprotonation with chiral amide (**49**), followed by methoxycarbonylation using Mander's reagent under conditions developed in our group (Scheme 57).^[16]

Scheme 57



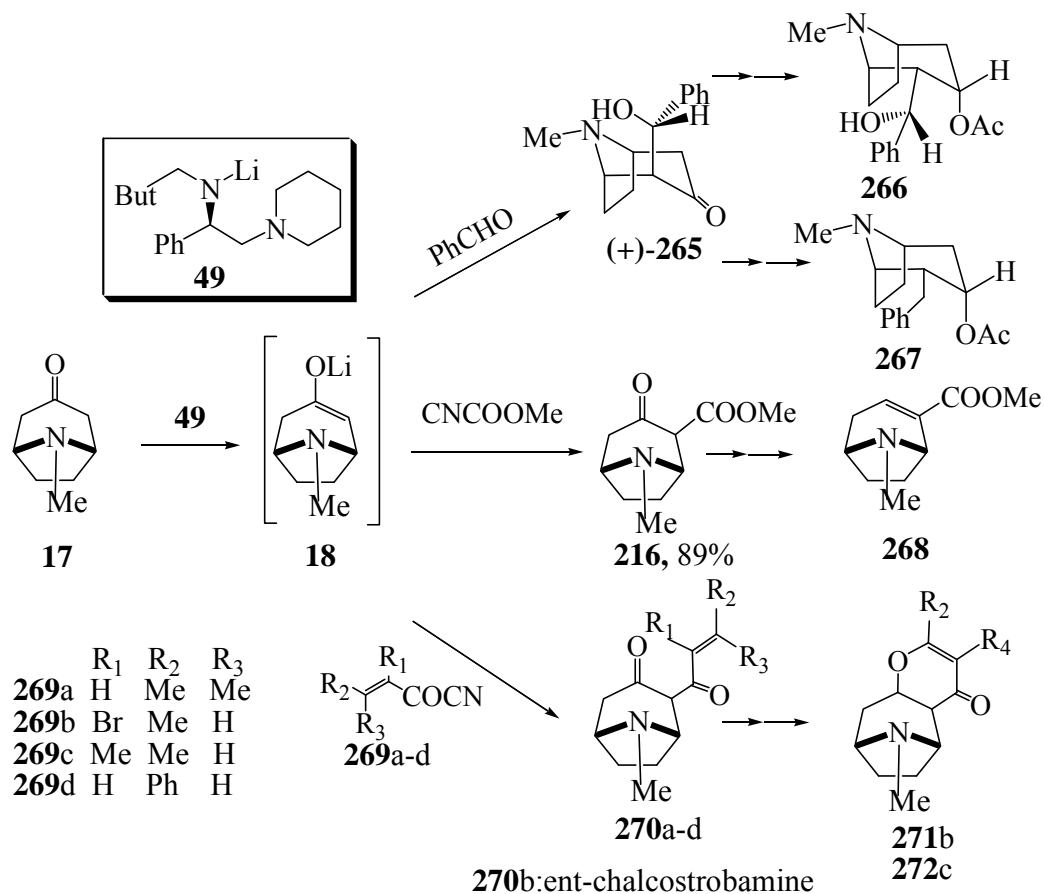
Enantioselective synthesis of other tropane alkaloids was also reported by Majewski and Lazny. They utilized tropinone lithium enolate (**18**) obtained by chiral lithium amide (**35**) to synthesize physoperuvine (**263**, 95% ee) and 7β-acetox-3α-tigloyloxytropane (**264**) in 95% ee using ring opening reaction with ethyl chloroformates as a key intermediate step and following with a series of simple reactions (Scheme 58).^[34, 108]

Scheme 58



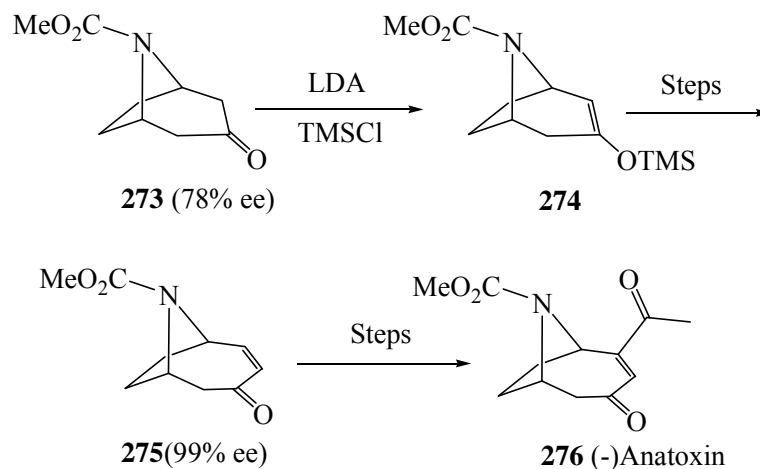
Chiral lithium amide (**49**) was applied by our group in the enantioselective deprotonation reaction of tropinone in the presence of 0.5 equivalents of lithium chloride. The optically active aldol (+)-(**265**) in up to 95% ee^[108] was obtained in the subsequent aldol reaction. Deprotonation was used as the key step in further synthesis of tropane alkaloids. Ent-knightinol (**266**, 42% yield from (**17**) and 97% optical purity) and KD-B (**267**, 62% from **17**, 94% ee) were synthesized from the aldol product (+)-(**265**). The synthesis of ent-anhydroecgonine (**268**) was accomplished (72% from **17** and 94% ee) via a series of reactions including deprotonation of tropinone with (**49**), following by methoxycarbonylation reaction using Mander's reagent under conditions developed in our lab^[34] and reduction using hydrogen gas over Adams catalyst, followed by dehydration. 2-Bromocrotonyl cyanide (**269b**) was prepared from crotonyl cyanide and proved to be a good acylating agent, yielding ent-chalcostrobamine (**270b**) which was subjected to cyclization. The ring closure reaction using elimination of HBr was finally achieved to give ent-isobellendine (**271b**) in 45% yield from tropinone. Tigloyl cyanide (**269c**) was applied in the acylation reaction of tropinone lithium enolate and other three steps sequence reactions to synthesize ent-darlingine (**272c**) in 53% overall yield from tropinone (Scheme 59).

Scheme 59



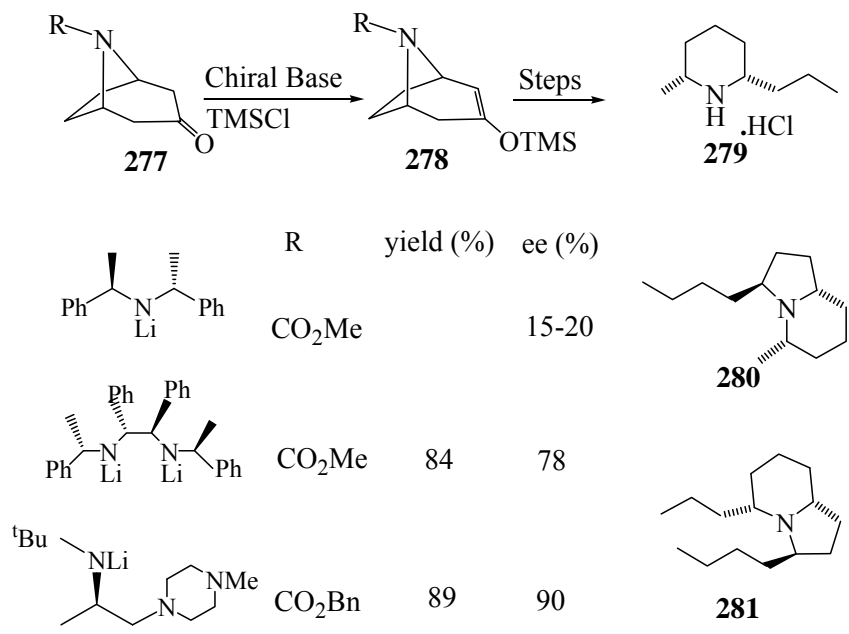
Simpkins utilized the silylation of N-protected nortropinone (**273**) to fulfill a ring expansion of a silyloxycyclopropane (**274**) as the key step to synthesize the natural alkaloid anatoxin-a (**276**), an agonist of the acetylcholine receptor (Scheme 60).^[109]

Scheme 60



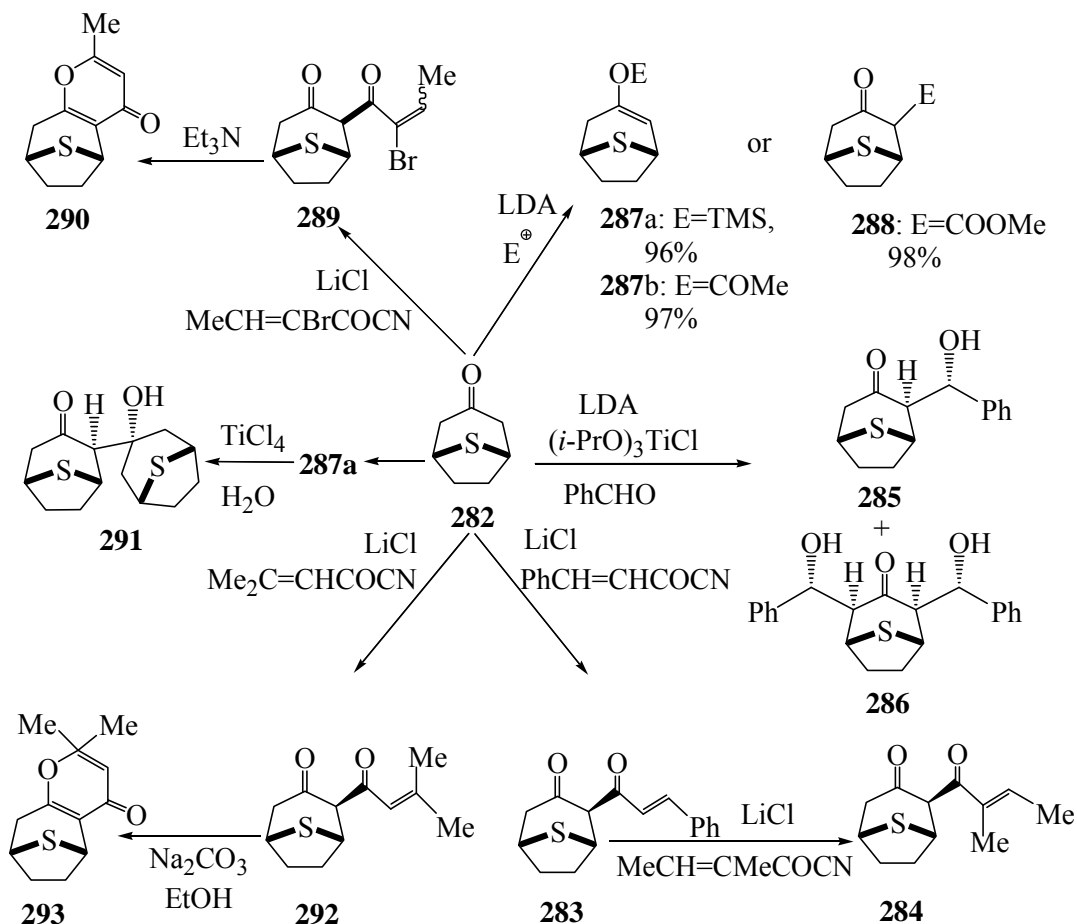
The Momose group reported the highly enantioselective (up to 90% ee) deprotonation of N-protected tropinones by using chiral amides. These silyl enol ethers were then applied as key intermediates in the synthesis of many natural alkaloids such as (+)-Pinidine hydrochloride (**279**), (+)-Monomorine (**280**), and (-)-indolizidine 223 AB (**281**, Scheme 61).^[110-111]

Scheme 61



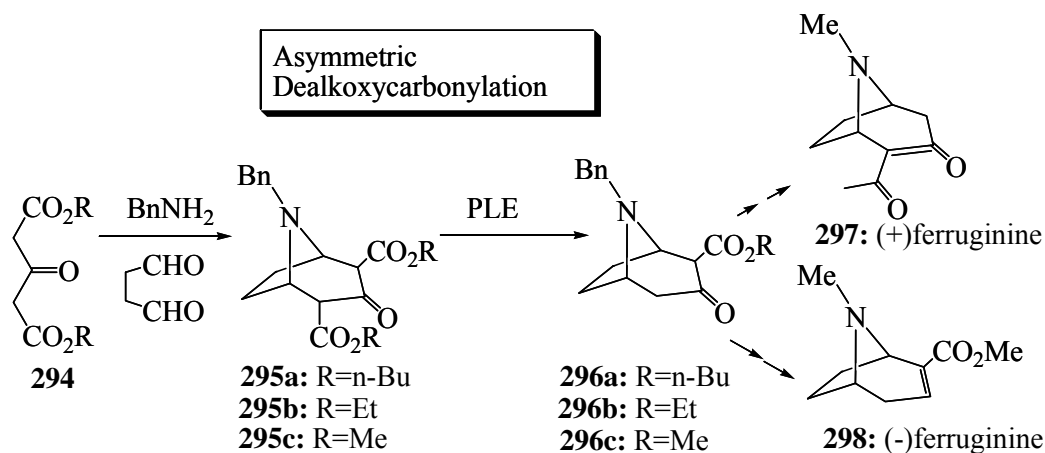
The sulfur analogs of tropane alkaloids have potential application in medicinal chemistry.^[112-114] Our group synthesized a series of sulfur analogs of tropane alkaloids by using the enantioselective deprotonation of 8-thiabicyclo [3.2.1] octane-3-one (**282**, Scheme 62).^[115]

Scheme 62



The tropane alkaloid (+)-ferruginine (**297**) was isolated from the arboreal species *Darlingia ferruginea*^[116a] and *D. darlingiana*.^[116b] A new divergent synthesis of (+)- and (-)-ferruginine (**297** and **298**), via the optically active 8-benzyl-3-oxo-8-azabicyclo[3.2.1]octane-2-carboxylates (**296**) is described by Katoh and Kakiya.^[117] The β -keto ester (**296**) was prepared by a novel PLE-catalyzed asymmetric dealkoxycarbonylation of the symmetric tropinone-type diesters (**295**). The key problem in the synthesis was controlling the regioselectivity of the reaction at the 2- and 4-positions in the tropane framework of the keto ester (**296**) for introduction of the acetyl group (Scheme 63).

Scheme 63



Parkinson's disease (PD) is characterized by a significant reduction in density of the presynaptic dopamine transporter (DAT) in the striatum of PD patients.^[118a, 118b, 118c]

A few radiolabelled tropane derivatives (^{99m}Tc-TRODAT-1, ^{99m}Tc-Technepine and ^{99m}Tc-Integrated-tropane-BAT; Figure 7) that bind to the DAT, were synthesized by Kieffer and Cleynhens^[119] via combining a tridentate ligand, *N*-(2-picolylamine)-*N*-acetic acid (**2-PAA**, **302**), and a phenyltropane derivative. It was labelled with a [^{99m}Tc(CO)₃]⁺ moiety, resulting in the formation of two stable and neutral lipophilic isomers (Scheme 64).

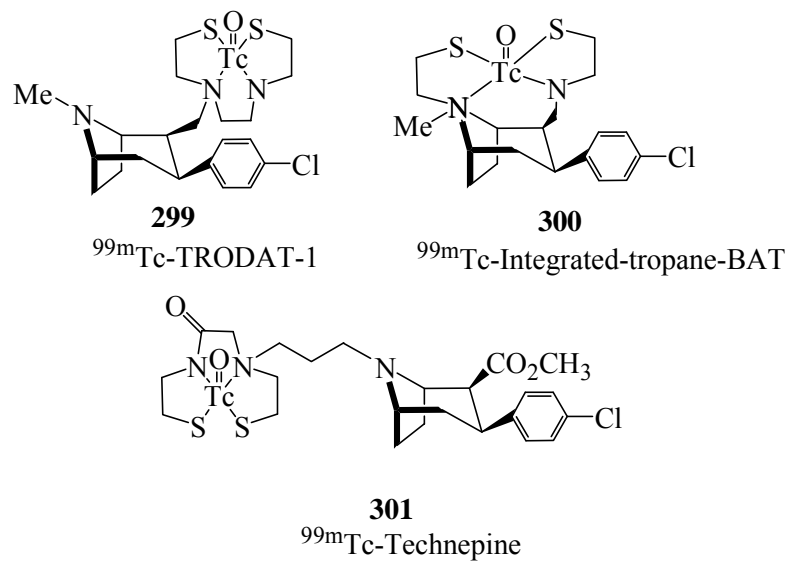
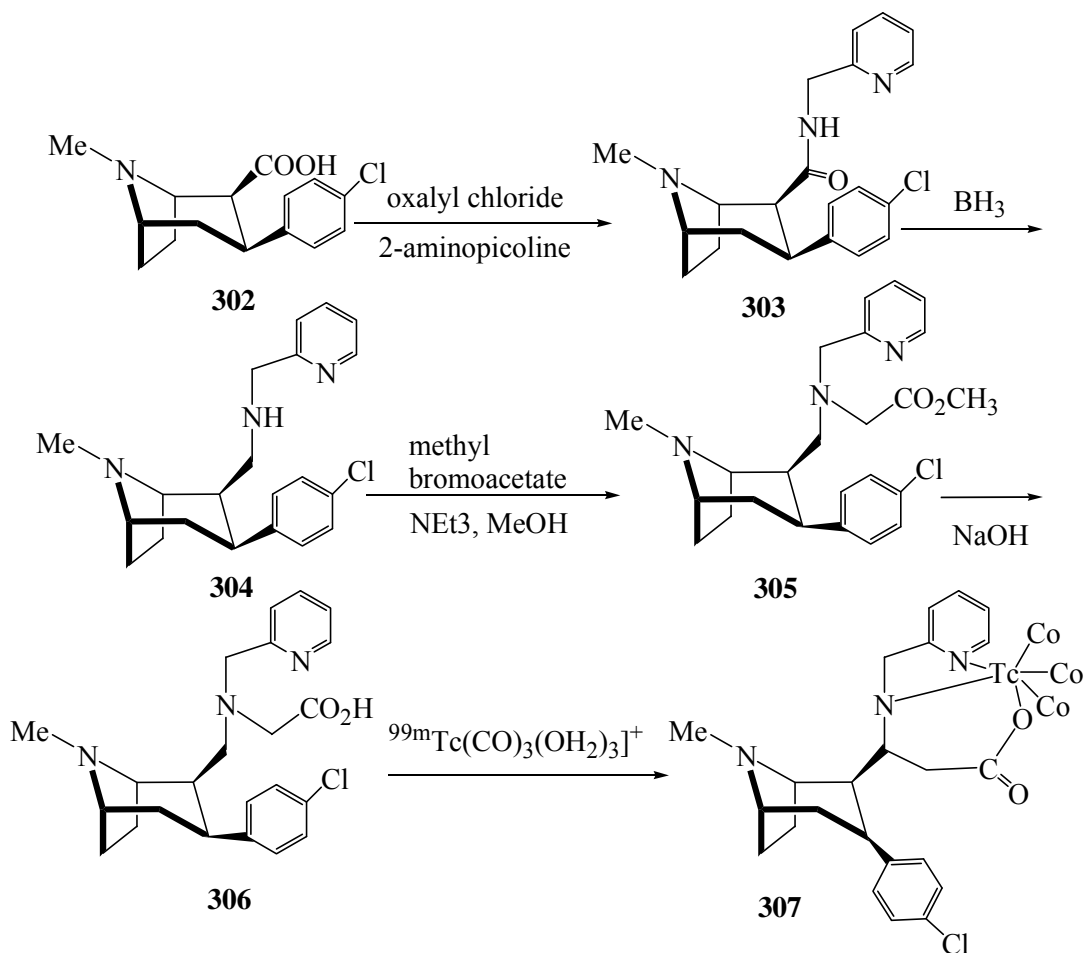


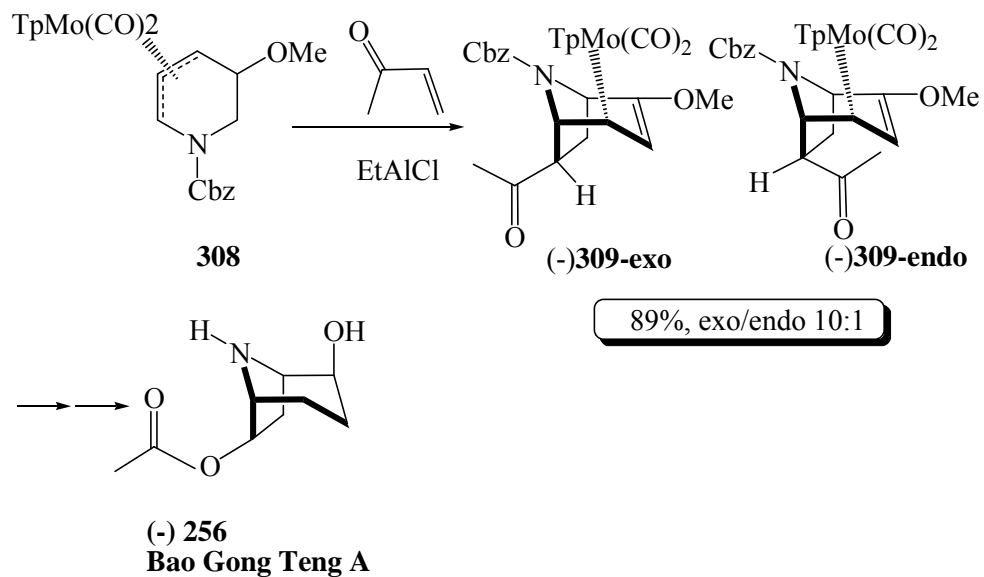
Figure 7: Structures of dome radiolabelled tropane derivatives

Scheme 64

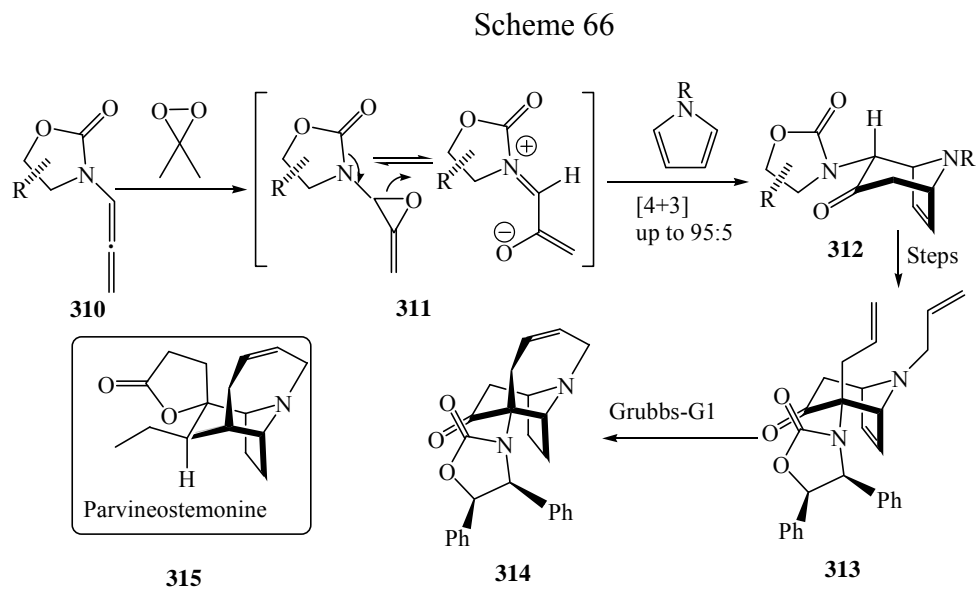


Recently, Bao Gong Teng A (**256**) was also synthesized by Zhang and Liebeskind^[120] via an "organometallic chiron" strategy in which single enantiomers of $\text{TpMo}(\text{CO})_2(\eta^3\text{-pyridinyl})$ complexes are produced in quantity and the tropane core (**309**) was generated via a [5+2] Cycloaddition (Scheme 65).

Scheme 65



A highly stereoselective [4+3] cycloaddition of N-substituted pyrroles with allenamide (**310**)-derived nitrogen-stabilized chiral oxyallyl cations (**311**) was reported by Antoline and Hsung.^[121] The method provides an approach for obtaining parvineostemonine (**315**, Scheme 66).



Conclusions:

Most of the syntheses of tropane alkaloids involved building the tropane skeleton (e.g. Robinson-Schopf synthesis) and achiral tropane alkaloids were often the products. Diastereoselective reduction of tropinone was available to synthesize tropine. A few synthetic methods for construction of racemic tropane alkaloids (e.g. Stoll's 6-hydroxytropinone **117**, Tufariello's cocaine **147**, Lounasmaa's isobellendine **204**) were also reported. Some chiral tropane alkaloids (e.g. optically active forms of cocaine **221/222** from Willstatter, Carroll, Carroll's (+)-ecgonine methyl ester (**223**), Fodor's natural valeroidine and Pinder's (+)-physoperuvine) were prepared by diastereoselective reduction of methoxycarbonyltropinone (**216**) and resolution. The "chiral pool approach" (EPC methods) were also developed to prepare the optically active tropane alkaloids by Bick [(-)-ent-ferruginine (**232**) and (-)-ent-ferrugine (**234**)] and others.

EPC synthesis based on an enantioselective reaction to obtain calystegine **A3** was first published by Johnson and Bis in 1995. Then, our group reported the anhydroecgonine methyl ester (**261**), physoperuvine (**263**), 7 β -acetoxy-3 α -tigloyloxytropane (**264**), other tropane alkaloids (**266-268**, **270b**, **271b**, **272c**) and their sulfur analogs (**284-286**, **288**, **290-291**, **293**) in high ee by the enantioselective deprotonation approach. Tropinone enolate chemistry was successfully applied in their asymmetric synthesis through reactions such as enantioselective acylation, alkoxylation and aldol.

The literature review shows that there is still need for development of a general approach to enantioselective synthesis of tropane alkaloids.

CHAPTER 2: RESULTS AND DISCUSSION

2.1. Stereoselectivity of aldol reactions of the lithium enolate of 1,4-cyclohexanedione monoethylene ketal mediated by chiral lithium amides.

2.1.1. Objectives

As an equivalent to the protected 4-hydroxycyclohexanone in synthesis, the ketone (**22**), 1,4-cyclohexanedione monoethylene ketal, has two oxygen functional groups which proved useful in synthesis of natural products such as dihydroaquilegionolide (**316**),^[33b, 122] parthenin (**317**),^[123] a key intermediate for paniculide B (**318**)^[124] and the enyne A-ring synthon of the 1- α -hydroxy vitamin A (**319**)^[125] (Figure 8).

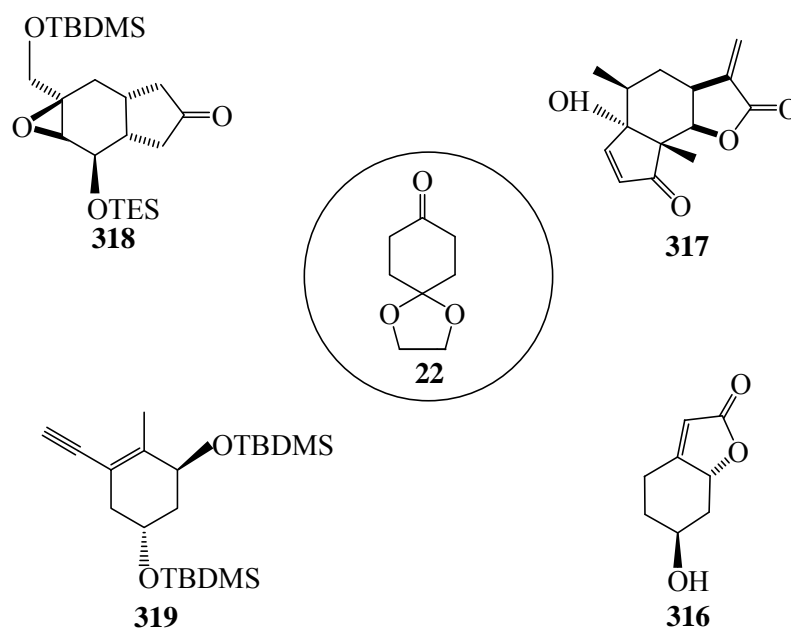
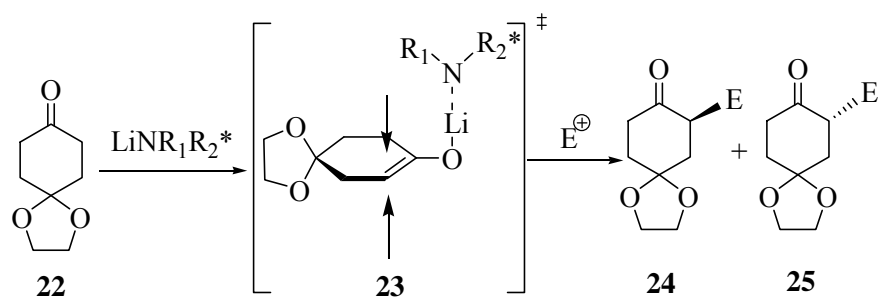


Figure 8: Natural products synthesized from ketone (**22**)

Ketone (**22**) has the C_{2v} symmetric structure. Only one lithium enolate (**23**) can

be produced by deprotonation with lithium amide, so there is no selectivity in the first deprotonation stage. The lithium enolate is not stable enough to be isolated, and thus one usually adds an electrophile to trap it. Two enantiotopic faces of the enolate will attack the electrophile selectively at different rates. If the lithium amide is chiral, the enantiomeric products can be generated in different amounts, and thus enantiotopic face selectivity in the second stage can be achieved (Scheme 6).

Scheme 6



The aldol reaction is one of the most important reactions in organic synthesis, because it can form new C-C bond, which gives a convenient method for the preparation of the larger organic compounds from the smaller ones. The reaction also can produce two new stereogenic centers at the same time. An aldol unit, i.e. β -hydroxy carbonyl group, can be found in a lot of natural products having valuable biological activities. Moreover, the aldol unit contains two functional groups that will be useful for the sequential chemical transformation.

In my project, the aldol reaction of the enolate (23) with benzaldehyde was used to study the enantiotopic face selectivity. One advantage was that the ee of aldol products could be conveniently measured by ¹H NMR with chiral shift reagents.

The ketone (22) with C_{2v} symmetry structure is an excellent model to focus on

only the enantiotopic face selectivity involved the deprotonation process. A study of this ketone was started by Ulaczyk^[126] in our group in 2002. I decided to continue the study and attempt to apply two kinds of chiral lithium amides (Figure 9) to the deprotonation and follow the aldol reaction of the ketone (**22**).

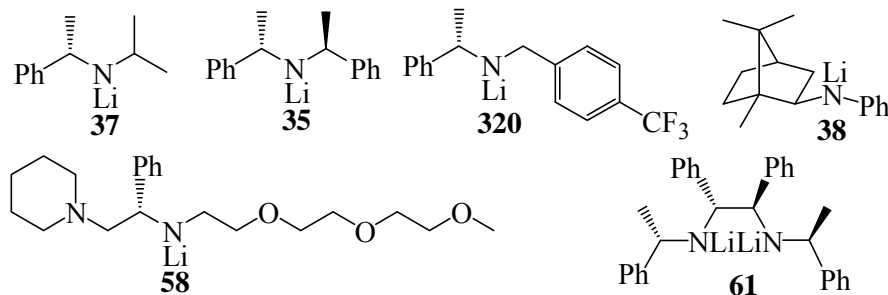


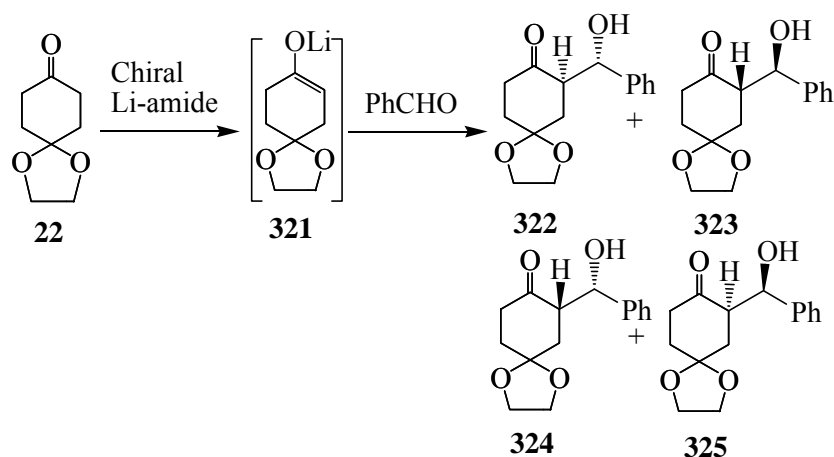
Figure 9: Chiral lithium amides

2.1.2. Diastereoselectivity in aldol reaction

In 1984, Heathcock^[127] reported his studies on the stereoselectivity of lithium enolate in aldol reaction. It was found that the syn or anti aldol was produced preferentially affected by the use of a Z-enolate or E-enolate with one bulky substituent. From his work, high stereoselectivity can be obtained by choosing E or Z- bulky enolates of ketones.

In my project, the lithium enolate of the ketone (**321**) was first generated by a chiral lithium amide before aldol reaction with benzaldehyde was started (Scheme 67). The reaction could produce two pairs of diastereomers (products **322** and **323** are called anti isomers, **324** and **325** are called syn isomers) in different amounts.

Scheme 67



The lithium enolate of the ketone (**321**) was E-enolate due to the six member ring. The anti aldol was expected to be produced more than the syn aldol. Stereoselectivity of aldol reaction can be expressed by diastereomeric excess (% de). The de is the ratio of one of the diastereomer's mixture over another one: $de = |(\text{syn} - \text{anti}) / (\text{syn} + \text{anti})| \times 100\%$.

The de value could be measured from the ^1H NMR assignment with the crude aldol products by calculating the integration of signals from syn and anti isomers (the PhCH(OH) protons of syn and anti isomers have chemical shifts at 4.82 - 4.78 ppm with the different vicinal coupling constant $J_{\text{vic}}=1.8$ Hz and 8.6 Hz). A vicinal coupling constant is depended on the bond distance between the protons, the angle between the two C-H bonds and the electronegative substituents. Therefore, the different vicinal coupling constant of a compound might represent the different conformation of three bonds (H-C-C-H) in the compound. For example, the vicinal coupling constant of syn and anti isomers in the crude aldol product is different due to the different angles between the two C-H bonds. This difference can be used to figure out the syn and anti isomers by ^1H NMR assignment

The de results of aldol reaction are summarized in Table 2.1. As could be predicted, the reaction was highly diastereoselective (up to 96% de).

Table 2.1: Yield and de of aldol reactions by using general procedure I

Entry	Base	Yield (%)	de * (%)
1	35	76	89
2	37	80	92
3	58	81	96
4	61	77	93
5	320	73	90

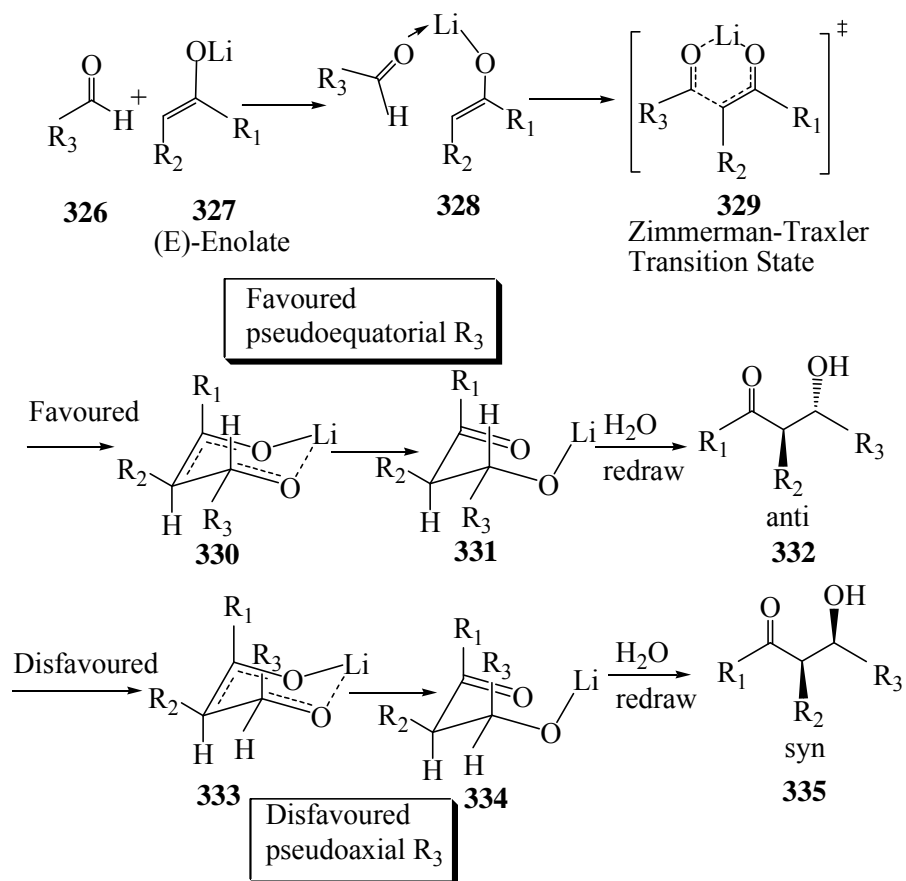
*de was measured by ^1H NMR with the crude aldols

2.1.3. Mechanistic interpretations:

The high diastereoselectivity up to 96% of aldol reaction can be interpreted by the possible transition states based on the Zimmerman-Traxler model.^[128]

In the Zimmerman-Traxler transition state model, the counter ion of the enolate, usually a metal ion (e.g. lithium cation), is bonded to the oxygen of the enolate and coordinated to the oxygen of aldehyde (Scheme 68). If the carbonyl group lies within a ring (the most common ring size is four to seven), the enolate geometry will be fixed E. For example, the enolate of the ketone (**22**) containing the six-membered ring has an E geometry.

Scheme 68



The most stable arrangement is that all the substituents are in the equatorial positions. It will be possible and more stable for the larger R₃ group of aldehyde (**326**) to be equatorial in the aldol (**332**). Obviously, anti aldol (**332**) is favored and syn aldol (**335**) is not. The major product is anti aldol (**332**).

2.1.4. Enantioselectivity of the aldol reaction

The ^1H NMR chiral shift reagent technique^[3] was used in the present work. The measurement of the aldol products was found to be effective by using a shift reagent, $\text{Eu}(\text{tfc})_3$ (Figure 1 in chapter 1.1). In the ^1H NMR of aldol products with $\text{Eu}(\text{tfc})_3$, the proton signal of $\text{PhCH}\underline{\text{H}}\text{OH}$ splits from single signal (d, 4.88 ppm) to two vicinal signals (d, d, 6.05-5.80 ppm).

The accuracy of this method^[109, 129] is a concern, because this method could be boundened with large random errors due to the arbitrary integration in the NMR spectrum. In order to estimate the accuracy, the ^1H NMR spectrum of a pure anti aldol product was recorded in the presence of the shift reagent $\text{Eu}(\text{tfc})_3$. Ten independent results which are shown in Table 2.2 were produced by the integration of the two signals corresponding to both enantiomers.

Table 2.2: Accuracy analysis of ee results produced by the integration in ^1H NMR

Entry	1	2	3	4	5	6	7	8	9	10
ee (%)	76.3	75.2	77.8	75.8	75.3	73.1	75.0	74.6	76.1	74.4

The most common estimates of errors are the standard deviation (s) and the confidence interval (μ).^[130] The confidence interval is an expression stating that the true mean, is likely to lie within a certain distance from the measured mean. The confidence interval μ is given by: $\mu = \text{measured mean} \pm t s \div n^{1/2}$ (t is Student's t^[130] and n is the number of the replicates).

After calculation of the data from Table 2, the measured mean and the standard deviation (s) of ee are 75.4% and 1.26%. You can choose a confidence interval (such as 95%) for the estimates of errors. The 95% confidence interval for ten replicates is

expressed by $\pm ts\div n^{1/2}=0.9\%$ (when n is 10, t is 2.26^[130], t is obtained from Table 4-2 in page 72 of reference 130). If the same method is used to analyze samples of similar enantiopurity, the standard deviation of the method should be unchanged. Thus the estimated standard deviation can be used to predict the reliability of results obtained by the two replicate measurements, and this method should give results with a 95% confidence interval of $\pm ts\div n^{1/2}=2\%$ (when n is 2, t is hypothesized to be constant 2.26). The estimated experimental error is $\pm 2\%$. The accuracy of measurements of enantiopurities reported here was estimated in the way analogous to that described above.

Enantiomeric excess (ee) in the aldol reaction:

As discussed in the review in the “Introduction” part (page 17), there are two kinds of chiral lithium amides: chiral versions of LDA and amides with one or more extra donor atoms which show different influence on the ee in the enantiotopic group or face selective reaction of ketones with different symmetry structures. The chiral versions of LDA usually gave higher ee's and yields in the enantiotopic group selective reaction of ketones with C_s symmetry (such as tropinone), and chiral lithium amides with extra donor atoms worked very well in the enantiotopic face selective reaction of ketones with C_{2v} symmetry (such as cyclohexanone). It seems that no one has tried these two kinds of chiral lithium amides in the the enantiotopic face selective reaction of ketone (**22**) with C_{2v} symmetry. In order to investigate the controlling factors of enantiotopic face selective aldol reactions of the lithium enolate of the ketone (**22**), two kinds of chiral lithium amides (Figure 9) were applied in the aldol reaction of (**22**) with benzaldehyde. Four different sets of reaction conditions (Scheme 69-72, General procedures I-IV)^[34,126] were designed for obtaining the generation of lithium enolates and keeping their

performance in the aldol reaction.

Procedure I is basic, the ketone (**22**) was deprotonated by the chiral lithium amide and the lithium enolate was generated. Benzaldehyde was then added into the reaction mixture (Scheme 69). The ee and yield of the reaction are recorded in Table 2.3.

Scheme 69

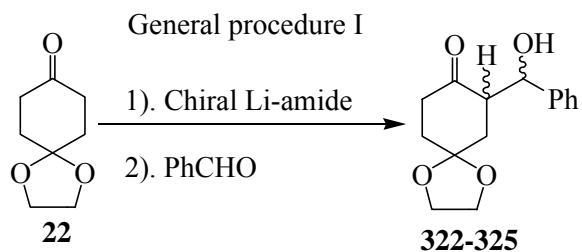


Table 2.3: The yield and ee of the aldol reactions using general procedure I

Entry	Base	Yield (%)	ee (%)*
1	37	80	7
2	35	76	14
3	320	73	14
4	58	81	48

*ee was measured by ^1H NMR with anti aldols **322/323** and $\text{Eu}(\text{tfc})_3$.

Estimated experimental errors are $\pm 2\%$.

Procedure II is based on the procedure I, according to the general procedure II (Scheme 70). The ketone (**22**) was deprotonated by chiral amides and after addition of one more equivalent of n-BuLi, the resulting chiral enolates reacted with benzaldehyde. Corresponding results are recorded in Table 2.4.

Scheme 70

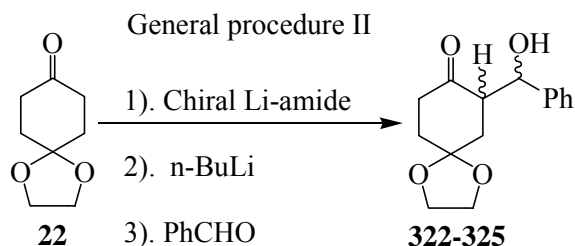


Table 2.4: The yield and ee of the aldol reaction using general procedure II

Entry	Base	Yield (%)	ee *(%)
5	35	74	14
6	320	90	14
7	61	71	55
8	58	88	50

*ee was measured by ^1H NMR with anti aldols **322/323** and $\text{Eu}(\text{tfc})_3$.

Estimated experimental errors are $\pm 2\%$.

In procedure III (Scheme 71), the silyl enol ether of the ketone (**341**) was also prepared (82% yield) under Corey's^[131] internal quench method. The lithium enolate was generated from (**336**) by reacting with n-BuLi. Lithium amides were then added into the reaction mixture before the aldol reaction with benzaldehyde was started. The relative results are recorded in the Tables 2.5.

Scheme 71

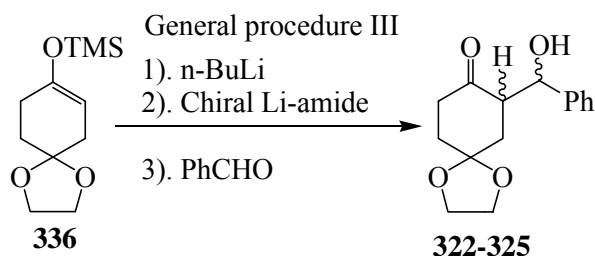


Table 2.5: The yield and ee of the aldol reaction using general procedure III

Entry	Base	Yield (%)	ee * (%)
9	35	71	15
10	37	55	19
11	58	75	55
12	320	70	23

*ee was measured by ¹H NMR with anti aldols **322/323** and Eu(tfc)₃.

Estimated experimental errors are ± 2%.

In the general procedure IV (Scheme 72), the lithium enolate was also prepared from the silyl enol ether (**336**) by reacting with MeLi-LiBr mixture. The chiral lithium amides were then added into the reaction mixture before the aldol reaction with benzaldehyde was started. Maximum ee (75% ee) was achieved with 70% yield through the reaction (Entry 16 in Table 2.6).

Scheme 72

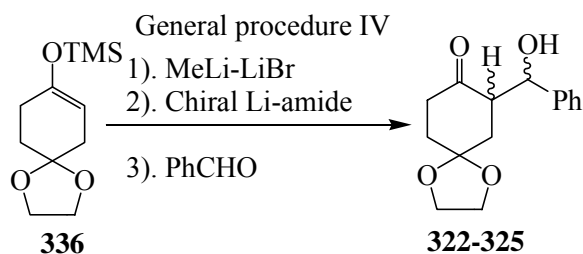


Table 2.6: The yield and ee of the aldol reactions using the general procedure IV

Entry	Base	Yield (%)	ee * (%)
13	35	83	42
14	320	68	34
15	38	73	42
16	58	70	75

*ee was measured by ¹H NMR with anti aldols **322/323** and Eu(tfc)₃.

Estimated experimental errors are ± 2%.

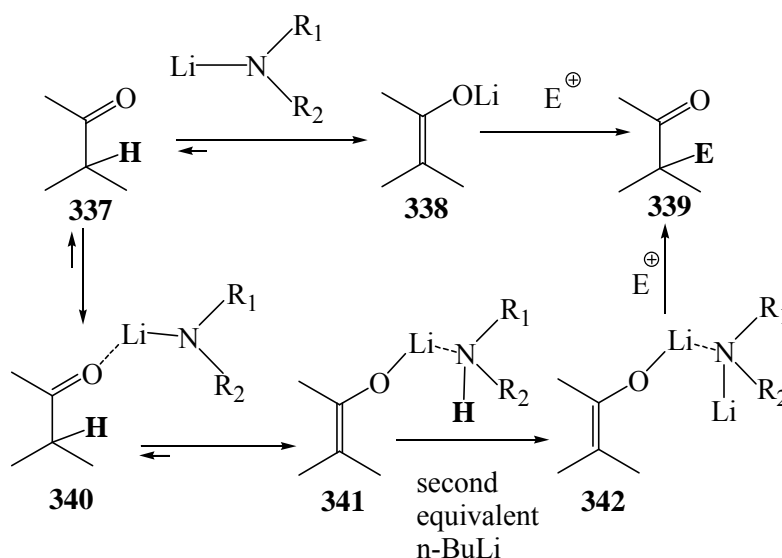
Factors that affect the enantiotopic face selectivity:

Because the mechanism of this enantiotopic face selective aldol reaction is still not known, a variety of factors in the reaction might affect the enantioselectivity.

i). The addition of the second equivalent of n-BuLi

By comparing the results from Table 2.3 and Table 2.4 one will find that the addition of the second equivalent of n-BuLi slightly increases the ee and yield. This can be explained by the known phenomenon of “internal proton return” (Scheme 73).^[132]

Scheme 73



After deprotonation, the lithium enolate was generated as the complex (341) (Scheme 73) with amine. The equilibrium between (340) and (341) might exist because enolate complex (341) is a potential source of proton donor. If this proton transfer is rapid, more and more enolate complexes (341) will be converted back to the ketone complexes (340) so that the ee and yield of the reaction will be decreased. After the addition of the second equivalent of n-BuLi, the lithium atom of n-BuLi quickly replaced the proton in the enolate complex (341) and new enolate complex (342) is formed. The proton transfer between (340) and (341) will be avoided, and thus the yield

and ee will be increased.

ii). The structure of lithium amides:

From Tables 2.3-6, the aldol reaction with chiral lithium amides with extra Lewis base sites (**58** and **61**) yielded higher ee's than the chiral lithium amide with chiral version of LDA (**35**, **37**, **38** and **320**). That means the (**58** and **61**) can form a strong and effective chiral environment for the transition state (lithium enolate complexes and largely differentiate the one face over another one of the enolates).

iii). Formation of mixed aggregates

It is known that both lithium enolates and lithium amides are aggregated in solution in order to satisfy the valency requirement (tetravalency or trivalency) of the lithium atom ^[22-24], and the reactivity of the lithium enolates and lithium amides is thus decreased. Lithium amides with extra donor atoms (such as **58** and **61**) usually exist as the monomer forms because the extra donor atoms usually satisfy the valency requirement of the lithium atom. The lithium amides as chiral version of LDA and lithium enolates usually exist as the dimer forms in order to satisfy the valency requirement of the lithium atom (Figure 10).

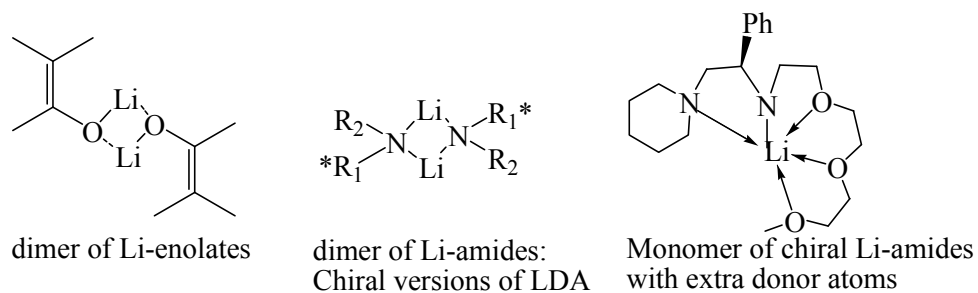


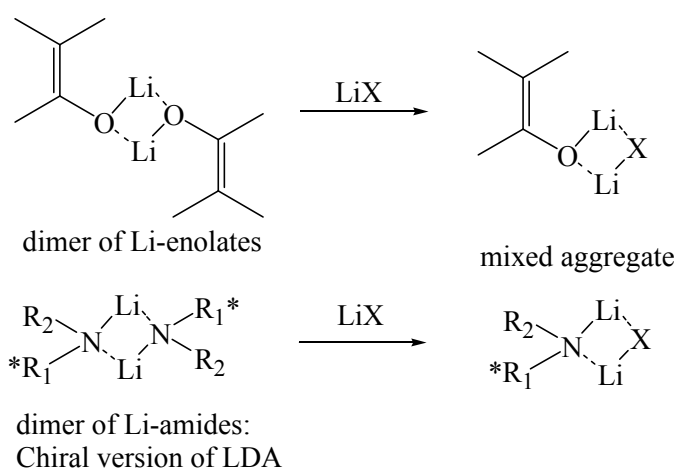
Figure 10: Aggregation of lithium enolates or lithium amides

Two ways are proved to be efficient to deaggregate the lithium enolates or lithium amides in the solution and form stable mixed aggregates.

1). Lithium halid salts:

Addition of lithium halide salt LiX can dramatically increase the enantiotopic selectivity by converting dimers to the useful mixed aggregates. Many studies have proved this point (Scheme 74).^[15-20]

Scheme 74



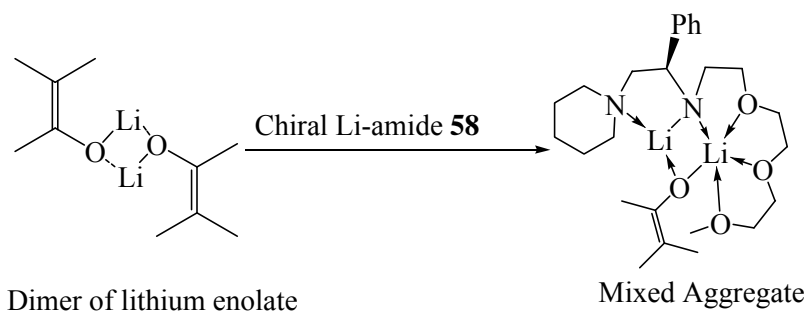
In the procedure IV (Scheme 72, Table 2.6), due to the presence of the lithium bromide which was generated in the reaction, the aggregation of lithium enolates or lithium amides were effectively converted into the reactive mix-aggregates. Therefore, the ee was increased significantly from 15% to 42% (by comparing entry 9 and 13) with the chiral lithium amide (**35**) and from 55% to 75% (entry 11 and 16) with the chiral lithium amide (**58**).

2). Chiral lithium amides with extra donor atoms

In order to investigate the mechanism of stable mixed aggregate of lithium enolates, Koga^[21] first proposed the four-membered dimer core (two lithium atoms were bridged by a nitrogen atom and an oxygen atom) which was considered to be helpful in

the formation of a stable mixed aggregate of the enolate. In the following structure of mixed aggregate of the enolate with the chiral lithium amide (Scheme 75), a four-membered dimer core was formed and supported by other extra donor atoms of the chiral lithium amides via the covalent bonds. The more extra donor atoms the chiral lithium amides contain, the stronger support will be offered to the dimer core. Such an aspect should result in a strong and effective chiral environment for the transition state complexes and largely differentiate the one face over the other one of the enolate.

Scheme 75



From Tables 2.3-6, the chiral lithium amides (**58** and **61**) with extra donor atoms gave higher ee's than the one without extra extra donor atoms. In the final, 75% ee with 71% yield was achieved by applying (**58**) into the enantiotopic face selective aldol reaction according to the procedure IV.

2.1.5. Conclusions:

The enantiotopic face selectivity in the aldol reaction of ketone (**22**) varied from low 7% to moderate 75% ee. It was affected significantly by different structures of chiral lithium amides, lithium salts as additives and other reaction conditions. For example, additional n-BuLi was added to avoid the “internal proton return”.

Four different procedures were designed to produce the lithium enolate, the intermediate, and keep its best performance in the following nucleophilic reaction.

The maximum of 75% ee was obtained in the aldol reaction using the chiral lithium amide (**58**) having four extra electron donor atoms attached to the central nitrogen atom with the help of lithium bromide. That suggests that the chiral lithium amides with extra donor atoms could be better than the lithium amides without extra donor atoms (chiral versions of LDA) in the enantiotopic face selective reactions. The extra donor atoms in the chiral amide were proven to be efficient to differentiate a pair of protons or two faces of a trigonal atom (carbonyl group or C=C double bond) in a substrate having a plane of symmetry to produce enantiomerically enriched products in the enantiotopic face selective deprotonation.

2.2. Extending enolate chemistry of tropinone

2.2.1. Objectives:

As mentioned in chapter 1.3 of this thesis, tropinone is an important precursor in the synthesis of many natural tropane alkaloids. The asymmetric synthesis of tropinone derivatives via the deprotonation reaction induced by chiral lithium amides is causing more and more interests. Further methodology studies of applications of tropinone enolate are important to fulfill the synthesis of alkaloids.^[133]

Tropinone enolate chemistry has been successfully applied in asymmetric synthesis of many tropane alkaloids through reactions such as enantioselective acylation, alkoxylation and aldol.

I have investigated tropinone enolate-related chemistry including the application of chiral lithium amides with extra donor atoms in the enantioselective aldol reaction, γ -alkylation from β -keto ester of tropinone, enantioselective hydroxylation of tropinone and the aziridine formation from nortropinone as well as the tropinone N-oxide synthesis.

2.2.2. Aldol reaction with benzaldehyde

In previous project (see part 2.1), the chiral lithium amides with extra donor atoms (Figure 11) achieved the moderate enantioselectivity of up to 75% ee in the aldol reaction of 1,4-cyclohexanedione monoethylene ketal (**22**). As a part of the extended enolate chemistry, we attempted to apply these chiral lithium amides in the enantiotopic group selective aldol reaction of tropinone.

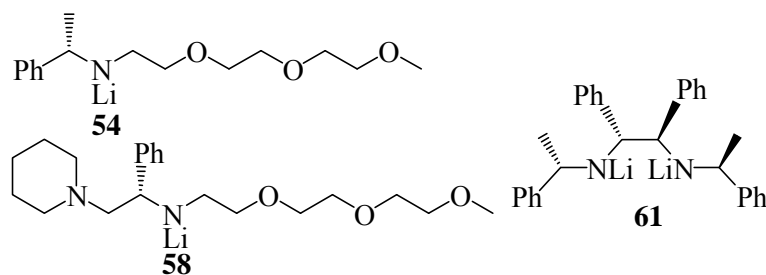
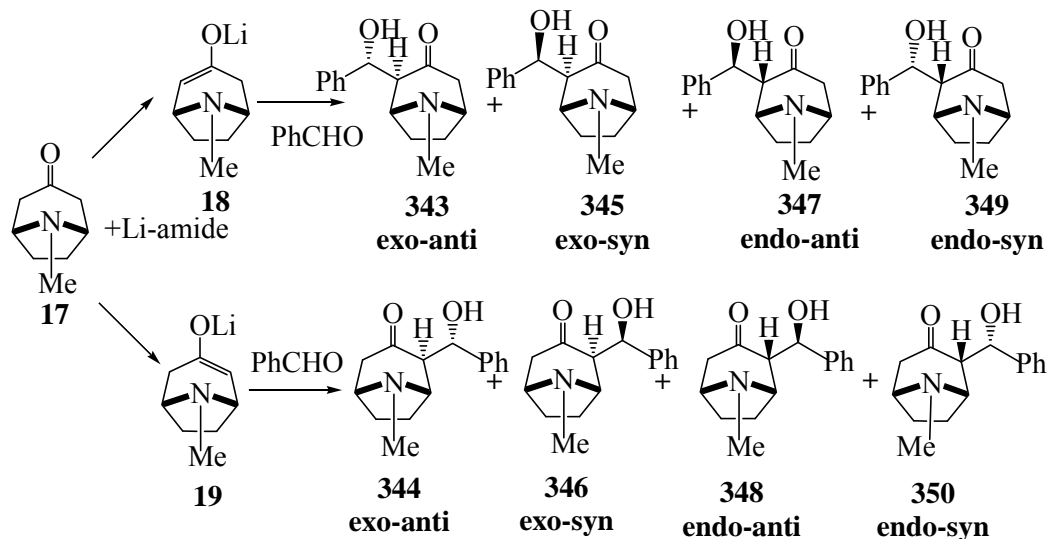


Figure 11: Chiral lithium amides with extra electron donor atoms

Tropinone belongs to C_s symmetry. Two axial (or equatorial) protons on its α -carbons are enantiotopic. After deprotonation with a chiral lithium amide, a pair of lithium enolate enantiomers could be generated. The lithium enolate enantiomers will further attack the electrophile benzaldehyde following the kinetic resolution process which one of lithium enolate enantiomers will react faster than another one. Four pairs of enantiomers can be produced (Scheme 76).

Scheme 76



To analyze this reaction, the ^1H NMR chiral solvating reagent technique^[3] was used. The measurement of the aldol products was found to be effective by using a chiral solvating agent, (*S*)-(+)-2, 2, 2-trifluoro-1-(9-anthryl)ethanol (TFAE of Figure 1 in Chapter 1.1). The proton signal of the PhCH(OH) in the ^1H NMR of the aldol products

splits with TFAE from a single signal (d, 5.21 ppm) to two vicinal doublets (d, 5.10 ppm and 5.15 ppm). It should be noted that TFAE could be recycled by chromatography.

Tropinone was deprotonated by the chiral lithium amides and the lithium enolate was generated. Benzaldehyde was then added into the reaction mixture (Scheme 77).

The aldol reaction was highly diastereoselective. One diastereoisomer only was detected by NMR but had low ee. One pair of enantiomeric *exo-anti* aldols (**343**) and (**344**) were isolated (Scheme 78). The yield, de and ee of the reaction are recorded in Table 2.7.

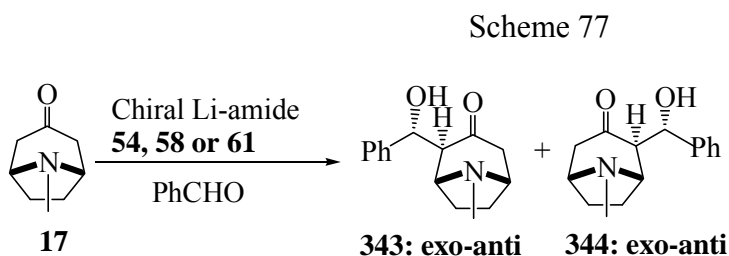


Table 2.7: The yield, de and ee of the aldol reaction

Base	Yield (%)	de ^a (%)	ee ^b (%)
61	78	≥ 99	13
54	76	≥ 99	3
58	80	≥ 99	2

a. de was measured by ¹H NMR of crude products

b. ee was measured by ¹H NMR of pure products **343/344** with TFAE.

Estimated experimental errors are ± 2%.

The diastereoselectivity of aldol reaction of tropinone enolate is mainly controlled by stereoelectronic^[5-6] and steric effects.^[15-16, 134]

Stereoelectronic effects:

In an acid-base reaction the axial protons in cyclic ketones are removed preferentially to the equatorial ones, which had been rationalized by a stereoelectronic effect.^[5-6] So, the exo-isomers will be main products.

Steric effects:

Steric effect is an effect on relative rates caused by the space-filling properties of those parts of molecule that are attached at or near to the reacting site.

Steric effects proposed by Zimmerman and Traxler can be used to explain that anti isomers are major products due to the E-lithium enolate of tropinone. Approach leading to the syn isomers (**345**) is disfavoured due to the interaction between the phenyl group and the bridge (Figure 12).^[15-16, 134]

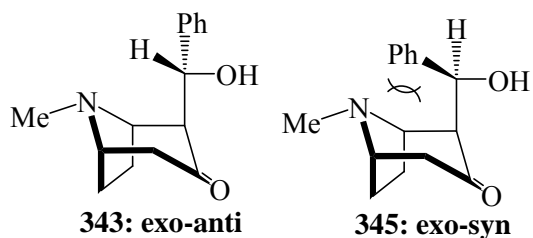


Figure 12: Steric effects

The diastereomeric complex was formed between lithium tropinone enolate and chiral lithium amide with extra electron donor atoms. The low ee implies that the complex did not differentiate largely the corresponding enantiotopic groups or faces in the enantiotopic deprotonation of tropinone. The mechanism of the complexation involving the substrate tropinone, solvents, chiral lithium amide and additives (was not

added into this reaction) is completely unknown. My current work can be data for future studies.

Conclusions:

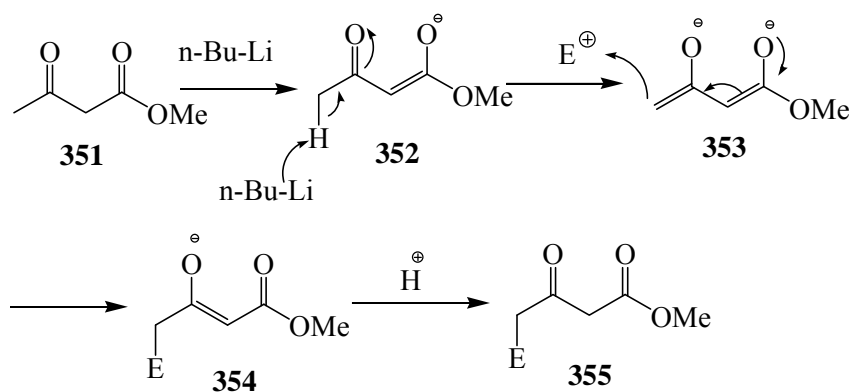
The aldol reaction of tropinone enolate induced by those amides with donor atoms was highly diastereoselective up to more than 99% de, but with low ee. Both stereoelectronic effect and steric effect favor the formation of *exo-anti* aldols (**343**) and (**344**).

Optimization of the aldol reaction (e.g. addition of additives-lithium halid salts) might be needed in future work.

2.2.3. γ - Alkylation of dianions of β -keto ester of tropinone

Direct alkylation on the α -position of tropinone was tried a number of times without success. A new transformation to get γ -alkylation from β -keto ester was reported by Weiler^[135-138] with a known mechanism (Scheme 78).^[139]

Scheme 78

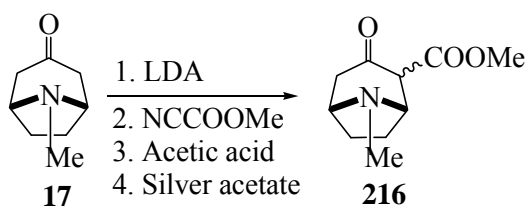


Methyl acetoacetate (**351**) can be deprotonated at the central carbon, because that site forms the most stable enolate anion (**352**). The dianion (**353**), formed by removing a

second proton from the first enolate with strong base (*n*-BuLi) reacted first at the γ position, a less stable enolate anion (**354**). Protonation of the more stable enolate then leads to the γ -alkylated product (**355**, Scheme 79).^[139]

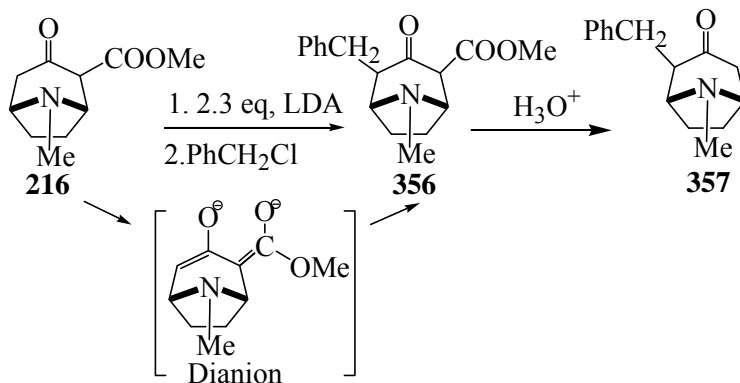
No one tried this known method on the tropinone substrate. It was reported that the β -keto ester of tropinone (**216**), α -methoxycarbonyltropinone has been synthesized using the methoxycarbonylation reaction with methyl cyanofomate (Mander's reagent) ^[109, 140-141] under conditions developed by Majewski and Zheng (Scheme 79).^[15-16]

Scheme 79



In my study, the β -keto ester of tropinone was deprotonated to form the corresponding dianion when excess LDA was employed. It was thought that the dianion may be able to be alkylated on the γ -carbon. The ester group could then be removed by using the hydrolysis reaction to form this α -alkylated tropinone derivative (Scheme 80).
[135-138]

Scheme 80



Racemic α -methoxycarbonyltropinone (the β -keto ester of tropinone) was obtained

in 82% yield using a known procedure.^[15-16] In the preliminary trials, the dianion from the β -keto ester of tropinone was able to be generated using 2.3 equivalents of lithium diisopropylamide. Although the yield was very low (5%), the dianions could be alkylated with benzyl chloride to produce the γ -alkylated product (**356**, Scheme 80). No α -alkyl products or di-alkyl products were observed. The optimization of the reaction is needed in the future, but to my knowledge, this is the first report to form the γ -alkyl- β -keto ester of tropinone using alkylation reaction from tropinone.

2.2.4. Asymmetric hydroxylation of enolate of tropinone

α -Hydroxy carbonyl compounds, acyloins, are important structural subunits of natural products and valuable synthetic intermediates. The most practical and simplest route to α -hydroxy carbonyl compounds is the direct oxidation of enolate by reagents such as molecular oxygen^[142-144] (O_2), Vedejs' reagent, molybdenum peroxide pyridinehexamethylphosphoramide (MoOPH),^[145] sulfonyloxaziridines.^[146a, 146b] Other indirect enolate oxidation routes include the reactions of silyl enol ether of ketones with *m*-chloroperbenzoic acid (*m*-CPBA)^[147] or iodosobenzene.^[148]

The oxidations of the enolates using some reagents, however, are not compatible to carbonyl structure, and byproducts are frequently formed. For example, oxidative α -carbon cleavage may occur with O_2 .^[142-144] Although the enolate oxidation using MoOPH is quite common, oxidation of 1, 3-dicarbonyl enolates fails and overoxidation to α -dicarbonyl compounds ($RC(O)C(O)R$) does occur.^[145, 149] Furthermore, stereoselectivity exhibited by these reagents is often poor, affording mixtures of stereoisomers.^[147-152]

Davis reported a procedure to form hydroxy-2-methyltetralone with a good yield

by oxidation of its lithium or sodium enolate using chiral (+)-(1*S*)-(camphorylsulfonyl)oxaziridines (16% ee, 90% yield; 12.3% ee and 75% yield).^[146a, 146b] In our initial trials, lithium enolate of tropinone was obtained using LDA. Davis's procedure of hydroxylation was then applied to tropinone enolate. As shown in Table 2.8, different reaction conditions were tried. Unfortunately, hydroxylation of tropinone with (+)-(1*S*)-(camphorylsulfonyl) oxaziridines, didn't work and almost 100% of tropinone was recovered (Scheme 81).

Scheme 81

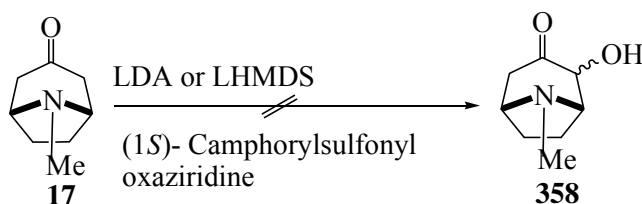
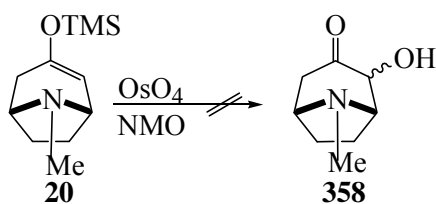


Table 2.8: Hydroxylation of tropinone enolate under different reaction conditions

Entry	Hydroxylation condition
1	-78 ° C, 30 min, quenched at -78 ° C
2	-78 ° C, 30 min, 0 ° C 10 min, quenched at -78 ° C
3	-78 ° C, 3 h, quenched at -78 ° C
4	-78 ° C, 30 min, quenched at 0 ° C
5	-78 ° C, 30 min, 0 ° C 10 min, quenched at 0 ° C
6	-78 ° C, 3 h, quenched at 0 ° C

Also, I tried the oxidation of the silyl enol ether of tropinone using osmium tetroxide and N-methylmorpholine but the reaction didn't work and the silyl enol ether of tropinone was converted back to tropinone^[153] (Scheme 82).

Scheme 82

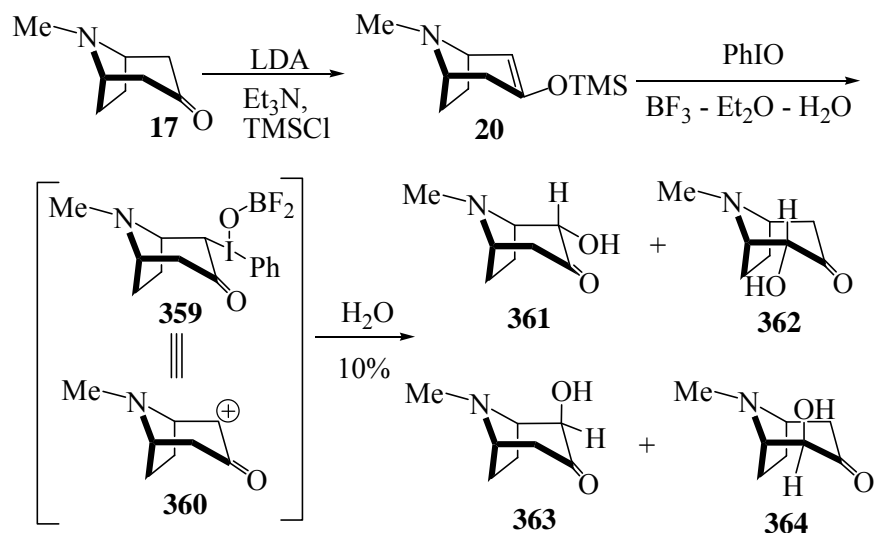


Another oxidation of tropanone silyl enol ether using iodosobenzene in the presence of boron trifluoride etherate^[148] had been reported, but the yield of the reaction was low. The advantage of this method in the successful α -hydroxylation of ketones containing an amino functionality is that the nitrogen of the amino group (primary, secondary, or tertiary) was not oxidized^[154-155] under the reaction conditions. I tried this method after experiments above (Scheme 81 and 82) failed.

Racemic tropan-3-one enol silyl ether (**20**) was prepared using LDA via silylation according to the known procedure^[156-157]. Iodosobenzene was prepared by the oxidation of benzene with 40% peracetic acid followed by hydrolysis with aqueous sodium hydroxide^[158-159] and iodometric titration showed the iodosobenzene to be more than 99% pure by the method of Lucas, Kennedy and Formo.^[160]

The hydroxylation of racemic tropan-3-one silyl enol ether (**20**) with iodosobenzene involves the addition of the electrophile $\text{Ph-I}^+-\text{O-BF}_3$ which was generated from iodosobenzene and boron trifluoride etherate to the silyl enol ether to give the intermediate (**359**) which is the synthetic equivalent of carbenium ion (**360**, Scheme 83).

Scheme 83



Two pairs of enantiomers of α -(**361** and **362**) and β -(**363** and **364**)-hydroxylated products were probably yielded by the hydroxylation with the racemic silyl enol ether (**20**). But only one pair of diastereomers was isolated from the reaction mixture. ¹H NMR assignment of the crude mixture demonstrated the signal of only one pairs of diastereomers was found in the δ 3.78 ppm). Moriarty^[148] reported that the hydroxyl group was substituted at α position (equatorial) based on the X-ray structure of oxime methiodide. This equatorial conformation of the α -hydroxyl group results in a more stable product. So the main products obtained from the reaction are α -hydroxylated products (**361** and **362**).

Since chiral α -hydroxytroponone is needed by enantioselective deprotonation of troponone using chiral lithium amides in future, a practical analysis of the ee of α -hydroxytroponone will be required. I tried several chiral shift reagents on the racemic α -hydroxytroponone using ¹H NMR technique. Fortunately, I found that europium tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorate, Eu(hfc)₃ (Figure 1 in the Chapter 1.1) was suitable for NMR analysis. After addition of Eu(hfc)₃, the proton signal of CHOH in the ¹H NMR of α -hydroxylated products splits with Eu(hfc)₃ from a single

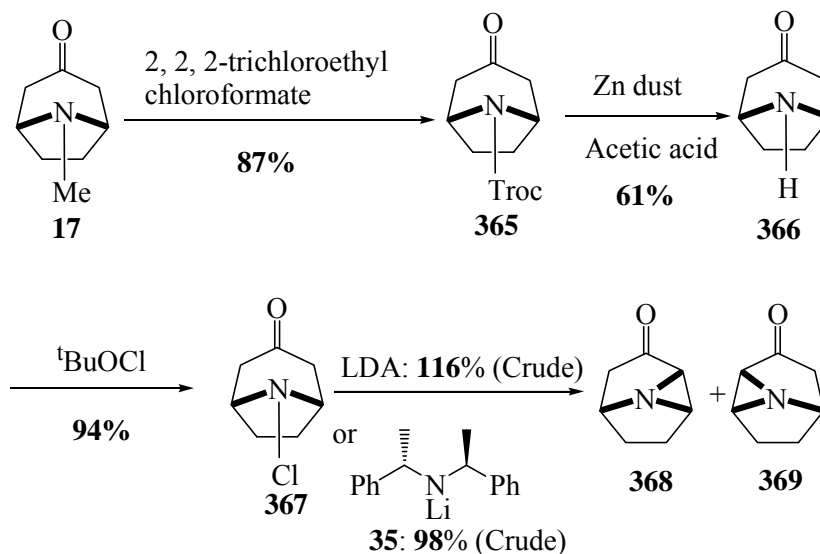
signal (d, 4.93 ppm) to two vicinal signals (d, d, 5.90-5.50 ppm). After measuring of the integration of these two signals, ee value was obtained as 3%.

Although further work is needed to improve the enantioselectivity and yield induced by using chiral lithium amides, our initial research opened a new possible route to synthesize chiral α -hydroxytropolone by enantioselective deprotonation of tropinone using chiral lithium amides.

2.2.5. Synthesis of the aziridine of tropinone^[79, 161-162]

Nortropinone (**366**) was first synthesized in 61% yield by a known procedure^[161] via N-(2, 2, 2-trichloroethylloxycarbonyl)nortropinone^[162] (**365**) from tropinone (Scheme 84).

Scheme 84



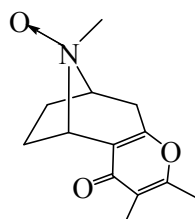
Then, N-chloro-nortropinone (**367**) was produced by a N-chlorination radical reaction with t-butyl hypochlorite and followed enolization reaction with LDA or chiral lithium amide (**35**) to generate the corresponding nortropinone enolate from which was

obtained aziridine (**368**, **369**). From ^1H NMR spectra of the crude products, the proton signal on C1 at δ 4.3 ppm is very clear, that mean the enolization process caused by LDA or chiral lithium amide (**35**), and then the internal nucleophilic attack of the enolate into the N-Cl of N-chloronortropinone (**367**), was successful.

Although further work is needed to improve the purification and find analysis method of enantioselectivity identification of aziridine, our current research is very helpful to obtain chiral, nonracemic aziridine induced by chiral lithium amides in future.

2.2.6. Synthesis of tropinone N-oxide

Recently, new natural product, darlingine N-oxide was separated from the barks and leaves of *D. darlingiana* (Figure 14).^[163] This caused our interest in the tropinone N-oxide. We thought that if the presence of the oxygen at nitrogen could change the selectivity in the enantioselective deprotonation reaction.



darlingine N-oxide

Figure 13: Darlingine N-oxide

Oxidation method of tropinone with hydrogen peroxide^[164-166] or peracid m-CPBA^[167-169] was developed and the tropinone N-oxide was synthesized successfully according to the reaction condition in Table 2.9 (Scheme 85).

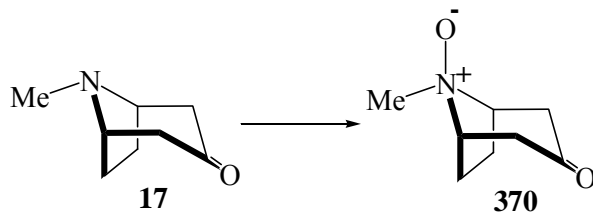


Table 2.9: Oxidation condition of tropinone

Condition	Yield	De
i). H ₂ O ₂ , toluene, 0 °C , 3h and then 25 °C , 3d. ii). Purification by Al ₂ O ₃ , MeOH.	50%	100%
i). MCPBA, CH ₂ Cl ₂ , 0 °C , 30 min; then 25 °C , 90min. ii). Purification by Al ₂ O ₃ , MeOH.	78%	100%

From the ¹H NMR spectra, it seemed that only one diastereomer product (**370**) was obtained. The axial N-oxide tropinone (**370**) was considered more stable than the equatorial one, because it could avoid 1,3-diaxial interactions between methyl and the axial hydrogen.

After purification using FCC with aluminum oxide (Al₂O₃, ten times the weight of the crude product),^[170-171] pure axial N-oxide tropinone (**370**) was obtained in 78% yield with m-CPBA and 50% yield with hydrogen peroxide. The reason might be due to the trigonal nitrogen's reduced nucleophilicity.

The mechanism of above reaction involves nucleophilic attack of the amine lone pair of electrons onto the peroxide, breaking the relatively weak oxygen-oxygen bond. Loss of a proton then furnishes the amine-N-oxide plus water.

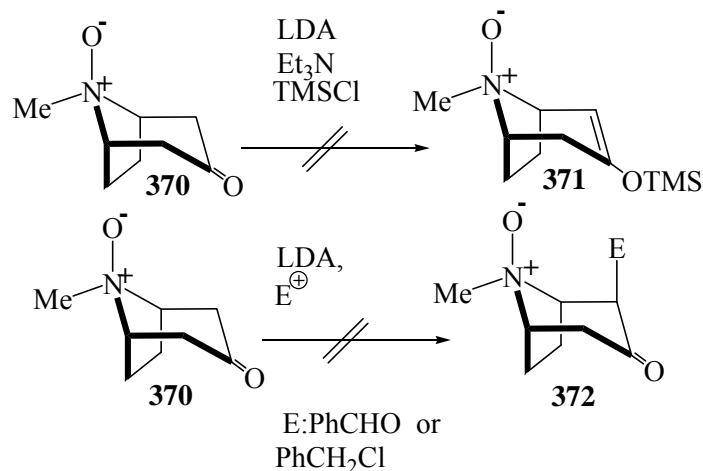
Enolate chemistry of tropinone N-oxide:

Studies on the enolate chemistry of tropinone N-oxide indicated that it might be difficult to generate the enolate of tropinone N-oxide.

Tropinone N-oxide could not be dissolved in the THF, DME, Et₂O, dioxane, Et₃N, IPA, TMEDA or other aprotic solvents, except CH₂Cl₂, but readily dissolved in water, EtOH, MeOH, CHCl₃ etc. protic solvents. Because these solvents are not compatible with strong bases, it is difficult for the tropinone N-oxide to react in the enolization reactions.

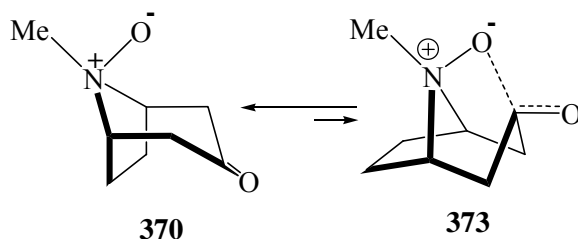
Despite the insolubility in the aprotic solvents system, the tropinone N-oxide was still tried in the aldol and C and O-alkylation reactions (Scheme 86). In the final, all reactions failed.

Scheme 86



Apart from the solubility problem, the oxygen atom in the N-oxide, a potential nucleophilic source, might attack the carbonyl group and lead to the equilibrium between (370 and 373, Scheme 87). That would reduce the acidity of hydrogen at α -carbon and might lead to failure of enolization process.

Scheme 87



2.2.7. Conclusions:

1. The aldol reaction of tropinone induced by three chiral lithium amides with extra donor atoms was accomplished, and high diastereoselectivity ($\geq 99\%$ de) but low enantioselectivity was obtained.

2. I observed γ -alkylation of the racemic β -keto esters of tropinone and obtained racemic γ -alkyl- β -keto ester of tropinone.

3. The hydroxylation reaction of racemic tropinone silyl enol ether was successful and racemic hydroxylated tropinone was obtained. I found the analysis method to determine the enantioselectivity of the reaction.

I observed the silylation with chiral lithium amide and obtained chiral tropan-3-one silyl enol ether.

4. The enantioselective azirdine formation reaction has been accomplished.

5. The oxidation methods of tropinone with hydrogen peroxide or peracid were successful and pure crystals of tropinone N-oxide were obtained in a good yield.

2.3. Synthesis of chiral amines

Chiral lithium amide bases have been used successfully in the asymmetric deprotonation reactions. The chiral base can differentiate a pair of protons or two faces of trigonal atom (carbonyl group or C=C double bond) in a substrate having a plane of symmetry to produce an enantiomerically enriched products.

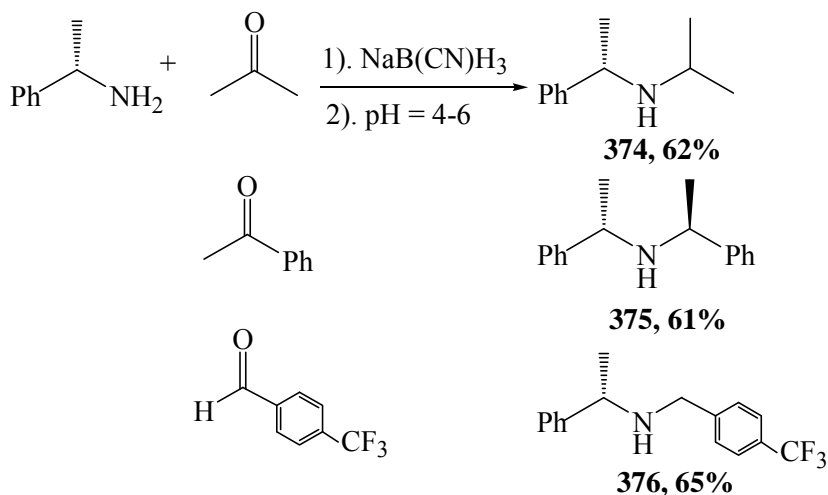
Chiral lithium amide bases are commonly prepared from secondary chiral amines by deprotonation reaction with strong base, usually, the n-butyllithium.

Most secondary chiral amines are not available commercially. They have to be synthesized for the purpose of the research. One common method is used to prepare secondary chiral amines from the primary amines involving reductive amination with ketones or aldehydes. In my program, a few interesting secondary chiral amines were synthesized by this method based on the sources of the starting primary amines such as (*R*) or (*S*)- α -methylbenzylamine, (*R*) or (*S*)-phenylglycine and terpenes

2.3.1. Chiral amines synthesized from (*R*) or (*S*)- α -methylbenzylamine:

Secondary chiral amines (**374**, **375**, **376**) were synthesized from (*S*)- α -methylbenzylamine with corresponding ketones or aldehydes by one pot reductive amination following known procedure (Scheme 88).^[172-174]

Scheme 88



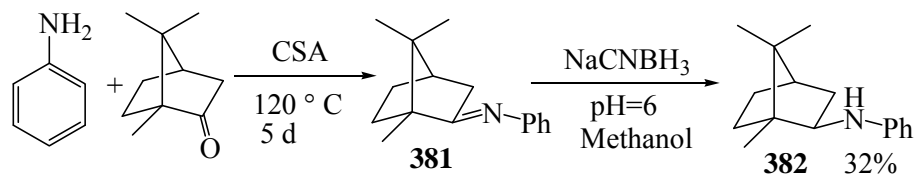
In these reactions, (*S*)- α -methylbenzylamine could be converted to the corresponding secondary amines by reacting with ketones or aldehydes and subjecting sodium cyanoborohydride in methanol at room temperature under weak acidic condition which pH value should be kept about 4-6 to ensure the maximum formation of the imine, the intermediate of the reaction. After workup, the secondary chiral amines were purified by distillation or crystallization.

Secondary chiral amine can also be synthesized by a two step procedure involving the formation of the amide from (*S*)- α -methylbenzylamine and acetyl chloride or ketone followed by a reduction with stronger reductant.

Chiral amine (**378**) was prepared by a two step known procedure^[12] in our lab involving the formation of the amide (**377**) from (*S*)- α -methylbenzylamine and acetyl chloride followed by a reduction with stronger reductant, lithium aluminum hydride (Scheme 89).

desired imine (**381**) was produced and then reduced smoothly by sodium cyanoborohydride in methanol and give the corresponding chiral amine (**382**) with total yield 32 %.

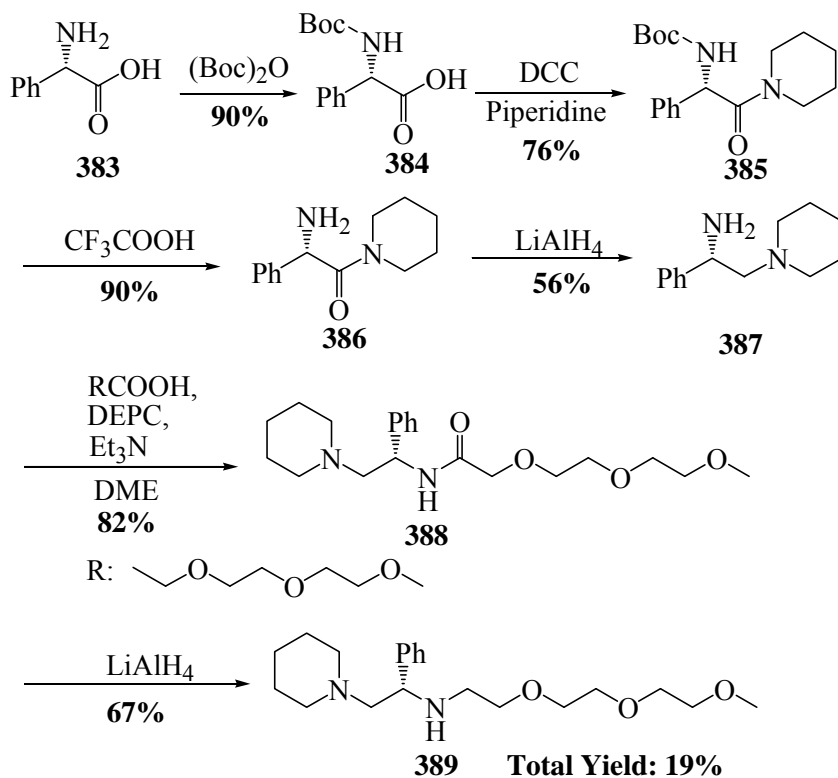
Scheme 91



2.3.3. Chiral amines synthesized from phenylglycine:

The chiral pentadentate amine (**389**) can be synthesized according to the procedures based on the research works from koga^[178], Shioiri^[179] and O'Brien^[180] (Scheme 92).

Scheme 92



(*S*)-Phenylglycine (**383**) could be easily protected with tert-butoxycarbonyl (Boc) group by reacting with di-tert-butyl dicarbonate. ^[181] Protected product (**384**) was coupled with fresh piperidine under the help of diethyl cyanosphonate, a coupling reagent, to give compound (**385**) and then was deprotected with strong trifluoroacetic acid. The deprotected product (**386**) was reduced by lithium aluminum hydride to give the decarbonyl product (**389**) and was continually coupled with corresponding [2-(2-(2-methoxyethoxy) ethoxy] acetic acid in the presence of coupling reagent diethyl cyanosphonate to give acetamide (**388**). Finally, the chiral amine (**389**) was yielded by reduction of acetamide (**388**) with lithium aluminum hydride.

CHAPTER 3: EXPERIMENTAL

3.1. General methods

All moisture and air sensitive reactions were performed under an inert atmosphere (nitrogen or argon).^[182] The syringes, needles, magnetic stirring bars and glassware (flasks etc.) were dried at 120 °C overnight and cooled in desiccators. All chemicals were purchased from Aldrich, unless stated otherwise.

The tetrahydrofuran (THF) was distilled from sodium and benzophenone under nitrogen.^[183] Dichloromethane, triethylamine,^[184-185] pyridine^[186] and diisopropylamine^[187-189] were distilled by calcium hydride and stored over 4Å molecular sieves. *n*-Butyllithium was titrated by using 2,5-dimethoxybenzyl alcohol.^[190] TMSCl^[191] was twice distilled from calcium hydride under nitrogen and stored with acid free Reillex TM 402^[192] (polyvinyl pyridine). Benzaldehyde was washed by 10% calcium carbonate (aq.) and dried over calcium chloride before fractional distillation.^[187] Benzyl chloride was fractionally distilled under reduced pressure after drying with magnesium sulfate.

Thin layer chromatography (TLC) was performed on precoated glass plates (Merck, silica gel 60, F 254) or aluminum plates. The spots were detected using UV light (254 nm), by staining with iodine, or by immersing in a developing solution and charring on a hot plate. The developing solution was prepared by dissolving concentrated sulfuric acid (25 g), phosphomolybdic acid hydrate (20 g) and cerium (IV) sulfate (5 g) in water (500ml). Flash column chromatographic separation was performed

using Merck silica Gel 230-400 mesh, or basic aluminum oxide (activated, standard grade, 150 mesh) under air pressure.^[189] Dry flash chromatography (DFC) was carried out using Sigma silica gel Type H (10-40 μm) under aspirator pressure.

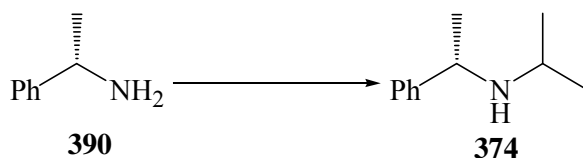
Optical rotation was measured on a Rudolph Instruments automatic polarimeter (Digipol 781, 1 dm cell, concentration is expressed in g /100ml). Melting points were measured on a Gallencamp melting point apparatus. Infrared spectra data was recorded on a Biorad FTS-40 Fourier Transform interferometer by a diffuse reflectance cell method. Only diagnostic peak frequencies are reported. Gas chromatography (GC) was performed using Helwett Packard 5890A instrument fitted with methyl silicone gum column (HP-1.5 m x 0.53 mm).

Proton magnetic resonance (^1H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded on the Bruker AM-300 and 500 (300 or 500 MHz) spectrometers in chloroform-d solvent unless otherwise noted. Chemical shifts were reported in ppm of δ scale with TMS (tetramethylsilane) ($\delta = 0.0$ ppm for ^1H NMR) or chloroform-d ($\delta = 77.0$ ppm for ^{13}C NMR) as the internal standard. Multiplicity is indicated by: s (single), d (double), t (triple), q (quartet), m (multiplet) and br (broad).

Mass spectra was recorded on a VG Analytical retrofit of a single sector, magnetic scanning MS-12 (low resolution) or a double speed VG 70-250-VSE (high resolution) and was reported as m/z ratio (relative intensity). Electron impact (EI) ionization was accomplished at 70 eV and chemical ionization (CI) at 50 eV.

3.2. Experimental

3.2.1. (-)-(S)-N-(Isopropyl)-1-phenylethylamine (374)^[172, 177, 192]



(S)-1-Phenylethylamine (3.030 g, 25.00 mmol) and acetone (1.813 g, 31.25 mmol) were dissolved in methanol, the mixture was cooled to 0 ° C and glacial acetic acid (4 mL) was added until the pH was equal to 6, and then followed the addition of sodium cyanoborohydride (1.571 g, 25.00 mmol). After 72 h, most of the methanol solvent was removed using a rotary evaporator and sodium bicarbonate (satd.) was added until the pH was equal to 10. The mixture was extracted with dichloromethane (3 x 50 mL), washed with brine (3 x 15 mL) and dried over anhydrous magnesium sulfate. The crude product was obtained after evaporation of the solvent. The crude product was then distilled to give the pure product (2.527 g, 62%).

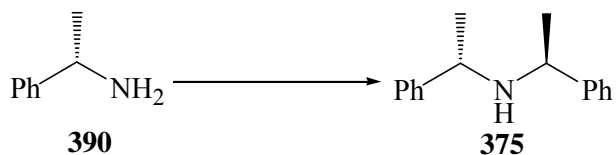
bp 122 ° C, 0.6 mm Hg (lit: 123-125 ° C, 0.6 mm Hg)^[177]

$[\alpha]_D^{24} = -60.9$ (c 1.2, chloroform) lit.^[192]: $[\alpha]_D^{25} = -61.4$ (c 1.2, chloroform)

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 7.25 – 7.10 (m, 5H), 3.90 (q, 1H), 2.65 (s, 1H), 1.32 (d, 3H), 1.23 (br, s, 1H), 1.00 (d, 3H), 0.95 (d, 3H).

¹³C NMR: 145.8, 128.0, 126.6, 55.0, 45.5, 24.8, 24.0, 22.

3.2.2. (-)-(*S,S*)-*N,N*-bis (1-Phenylethyl) amine (**375**)^[172, 177, 193]



S-1-Phenylethylamine (3.030 g, 25.00 mmol) and acetophenone (3.755 g, 31.25 mmol) were dissolved in methanol, the solution was cooled to 0 ° C and glacial acetic acid (4 mL) was added until pH was equal to 6, and then followed by addition of sodium cyanoborohydride (1.571 g, 25.00 mmol). After 72 h, most of methanol was removed on an evaporator and then a solution of sodium bicarbonate (satd.) was added until pH was equal to 10. The mixture was extracted with dichloromethane (3 x 50 mL), washed with brine (3 x 50 mL) and dried over anhydrous magnesium sulfate. The crude product was obtained after removing the solvent. The HCl salt of crude amine was then crystallized by ethanol-water, the pure product was then generated (3.422 g, 61%) by adding potassium hydroxide (satd.) into the crystals, and then distilling the amine solution at 101 ° C, 6 mm Hg.

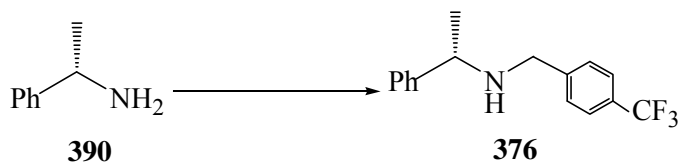
bp 101° C, 6 mm Hg (lit: 100 ° C, 5 mm Hg).^[177]

$[\alpha]_D^{25} = -153.8$ (c 2.0, methanol). lit.^[193]: $[\alpha]_D^{25} = -157$ (c 3.3, ethanol).

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 7.43 - 7.06 (m, 10H), 3.43 (q, 2H), 1.61 (br, s, 1H), 1.30 (d, 6H).

¹³C NMR: δ_C (ppm, 500 MHz, CDCl₃): 145.7, 128.3, 126.7, 126.6, 55.0, 24.9.

3.2.3. (-)-(S)-N-[4-Trifluorobenzyl]-1-phenylethylamine (376)^[173-174]



S-1-Phenylethylamine (3.030 g, 25.00 mmol) and α,α,α -trifluoro-*p*-tolualdehyde (3.760 g, 31.25 mmol) were dissolved in methanol, the solution was cooled to 0 ° C and glacial acetic acid (4 mL) was added until pH was equal to 6, and following by addition of sodium cyanoborohydride (1.570 g, 25.00 mmol). After stirring for 72 h, most of methanol was removed on an evaporator and solution of sodium bicarbonate (satd.) was added until pH was equal to 10. The mixture was extracted with dichloromethane (3 x 50 mL), washed with brine (3 x 50 mL) and dried over anhydrous magnesium sulfate. The crude product was obtained after removing solvents and then distilled to give the pure product at 120 ° C, 6 mm Hg (4.530 g, 65%).

bp 120 ° C, 6 mm Hg.

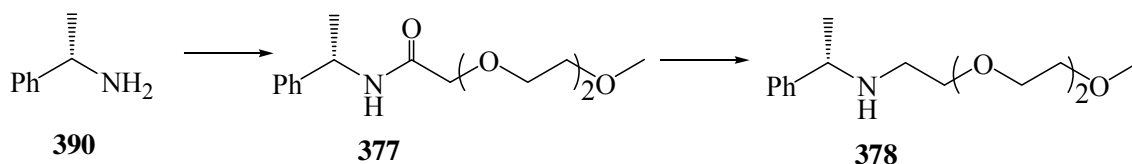
$[\alpha]_D^{24} = -46.8$ (c 1.0, chloroform).

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 7.75 – 7.25 (m, 9H), 3.90 – 3.80 (m, 1H), 3.75 – 3.60 (dd, 2H), 1.90 – 1.75 (br, 1H), 1.50 – 1.40 (d, 3H).

MS: (CI, NH₃) m/z: 281 (18.3), 280 (100.0, MH⁺), 265 (4.6), 264 (27.7), 176 (3.5), 159 (5.9), 109 (1.1), 105 (3.2).

3.2.4. (-)-(S)-N-[2-(2-(2-Methoxyethoxy)ethoxy)ethoxy]ethyl]-1

phenylethylamine (**378**)^[12]



(S)-1- Phenylethylamine (0.970 g, 8.00 mmol) and triethylamine (8.4 mL, 24.00 mmol) were dissolved in THF (8 mL) and then the mixture was slowly added to the solution of 2-[2-(2-methoxyethoxy)ethoxy]acetyl chloride (1.573 g, 8.00 mmol) in THF (40 mL). The reaction mixture was stirred for 2 h, filtered and then evaporated. The residue was dissolved in chloroform (20 mL), filtered and evaporated again to provide the crude amide, a colorless oil (2.036 g, 90% yield). The crude amide (2.000 g, 7.11 mmol) was dissolved in THF (40 mL), lithium aluminum hydride (0.540 g, 14.22 mmol) was added, and the reaction was refluxed for 24 h. After cooling to room temperature, the excess of lithium aluminum hydride was quenched with methanol (20 mL) and water (20 mL). Celite (10 g) was added and filtered. The solid was washed with methanol (3 x 50 mL) and the organic solution was combined together. The solvents and residual water were removed by evaporation. The residue was twice distilled to give the pure product (**378**) as colorless oil (1.420 g, 80% yield).

$R_f = 0.10$ (hexane : ethyl acetate = 1 : 1).

bp 150 ° C, 0.1 mm Hg (lit^[12]: 150 ° C, 0.1 mm Hg).

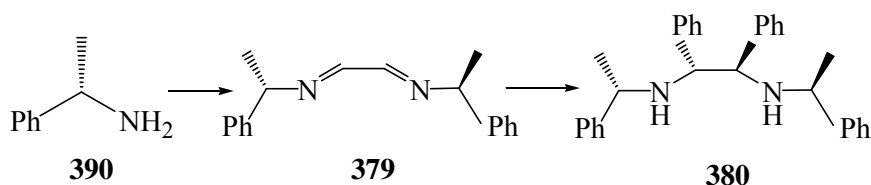
$[\alpha]_D^{26} = -20.9$ (c 1.8, ethanol) lit^[12]: $[\alpha]_D^{26} = -19.9$ (c 1.8, ethanol).

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 7.35 – 7.18 (m, 5H), 3.80 – 3.75 (q, 1H), 3.65 – 3.46 (m, 10H), 3.38 (s, 3H), 2.72 – 2.57 (m, 2H), 2.20 – 1.76 (br, s, 1H), 1.38 (d, 3H).

¹³C NMR: δ_C (ppm, 500 MHz, CDCl₃): 146.0, 128.7, 127.2, 127.0, 72.3, 71.0, 70.9 (2x), 70.6, 59.4, 58.6, 47.5, 24.8.

3.2.5. (-)-N, N'-bis [(S, S)-1-Phenylethyl]-1,2-bis [(S, S)-phenyl] ethyl diamine

(380)^[175-176]



Glyoxal (40% aq, 0.92 mL, 7.80 mmol) in dichloromethane (15 mL) was stirred with anhydrous sodium sulfate (4.000 g) and then the formic acid (98%, 0.50 mL, 1.30 mmol) and *S*-1-phenylethylamine (2.20 mL, 17.00 mmol) were added, after the mixture was stirred for 5 min, anhydrous sodium sulfate (5.000 g) was added and stirred for 2.5 h. The solution was turned slightly yellow. The mixture was then filtered and the residue was washed with dichloromethane (15 mL) and diluted with light petroleum ether (bp 30-50 ° C, 20.00 mL), and then washed with water (5 x 50 mL). The solvent from the combined filtrate was dried over molecular sieve (3Å) for 2 d. The pure diimine was obtained (1.504 g, 76%)

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 7.88 (s, 2 H), 7.50 – 7.22 (m, 10H), 4.33 (q, 2H), 1.47 (d, 6H).

Phenylmagnesium bromide (4.00 mL, 3.0 M in diethyl ether, 12.00 mmol) was added dropwise to the ether solution of the diimine (0.800 g, 3.00 mmol) under nitrogen over a period of 1 h at -78 ° C. A white precipitate was formed immediately and the mixture was then warmed to the room temperature over a period of 5 h and then stirred

for another 2 h. The mixture was then cooled to 0 ° C, and quenched by addition of ammonium chloride (satd., 10 mL). The organic product was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate and then the solvent was removed by evaporation. The crude product was purified by FCC (5% diethyl ether in light petroleum) and gave a pale yellow solid which was then recrystallized from light petroleum to give the pure product as colorless crystals (0.513 g, 40%).

mp 118 – 120 ° C (lit: 119 – 122 ° C).^[176]

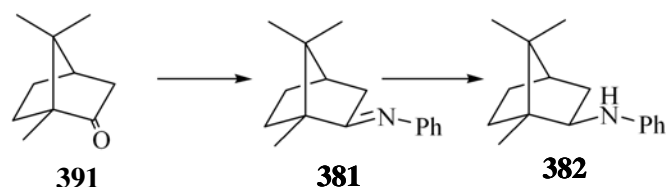
$[\alpha]_{D}^{22} = -201$ (c 0.7, CHCl₃), lit^[176]: $[\alpha]_{D}^{28} = 205$ for all-*R* isomers, c 0.7, CHCl₃).

¹H NMR: δ_{H} (ppm, 500 MHz, CDCl₃): 7.40 – 6.80 (m, 20H), 3.55 – 3.50 (q, 2H), 3.48 – 3.42 (s, 2H), 2.40 – 2.20 (br, 2H), 1.40 – 1.26 (d, 6H).

¹³C NMR: δ_{C} (ppm, 500 MHz, CDCl₃) 25.3, 55.2, 65.7, 125.5, 127.8, 127.9, 128.5, 140.5, 141.5, 142.5, 147.5.

MS: m/z (TOF) 421 (M+H), (EI): 105 (48.7), 106 (47.3), 210 (100.0), 211 (16.9).

3.2.6. (-)-exo-(1R)-N-(1-Phenyl) boranamine (382)^[177]



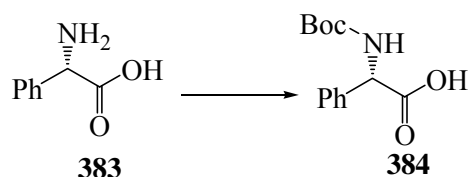
A mixture of aniline (6.020 g, 65.30 mmol), camphor (9.940 g, 65.30 mmol) and (1R)-10-camphorsulfonic acid (0.150 g) was heated with 3A molecular sieves at 120 ° C for 5 days. Then methanol (15 mL) was then added and the pH value of solution was adjusted to 6-7 by addition of 6M methanolic hydrochloric acid. Sodium cyanoborohydride (4.103 g, 65.30 mmol) was then added and the mixture was stirred at room temperature for 2 days. Methanol was removed under reduced pressure and water (25 mL) was added, followed addition of potassium hydroxide (solid) until the pH was over 10. The mixture was then saturated with sodium chloride (solid), extracted with ethyl acetate (3 x 25 mL), washed with sodium chloride (satd.), dried over magnesium sulfate and evaporated. The crude product were then distilled and the pure product was obtained as a pale oil (4.690 g, 32%) after further purification using FCC (hexane, $R_f = 0.18$).

bp 126 ° C, 0.1 mm Hg (lit: 126 ° C, 0.1 mm Hg).^[177]

$[\alpha]_D^{23} = -101.3$ (c 1.56, CHCl_3), lit^[177]: $[\alpha]_D^{22} = -103.5$ (c 1.56, CHCl_3).

$^1\text{H NMR}$: δ_{H} (ppm, 500 MHz, CDCl_3): 7.25 – 7.15 (t, 2 H), 6.72 – 6.52 (t, 3 H), 3.83 – 3.65 (br, s, 1 H), 3.34 – 3.26 (dd, 1 H), 1.94 – 1.88 (dd, 1 H), 1.80 – 1.52 (m, 4 H), 1.40 – 1.10 (m, 3 H), 1.00 (s, 3 H), 0.98 – 0.93 (s, 3H), 0.90 – 0.85 (s, 3H).

3.2.7. (-)-(*S*)-*tert*-Butoxycarbonylphenylglycine (**384**)^[178-179]



(*S*)-Phenylglycine (3.020 g, 20.00 mmol) was added to a solution of sodium hydroxide (0.880 g, 22.00 mmol) in water (22 mL) and *tert*-butanol (12 mL). Di-*tert*-butyl dicarbonate (4.460 g, 21.00 mmol) was then added over 1 h by a syringe pump. The cloudy suspension was stirred at room temperature overnight. The cloudy mixture was eluted with water (20 mL) and then extracted with hexane (2 x 100 mL). The organic extract was washed with saturated aqueous sodium carbonate (3 x 15 mL). The combined water layers were cooled to 0 °C in an ice bath and slowly acidified with a dilute sulfuric acid solution until pH was equal to 4. The white precipitated product was formed and extracted with dichloromethane (3 x 50 mL). Combined extracts were washed with brine (2 x 30 mL) twice, dried with anhydrous magnesium sulfate, and concentrated under an aspirator below 30 °C. Dichloromethane (100 mL) was added to the crude product and then removed and repeated twice. The crude product was dried under high vacuum to give the pure product as a white solid (4.530 g, 90%).

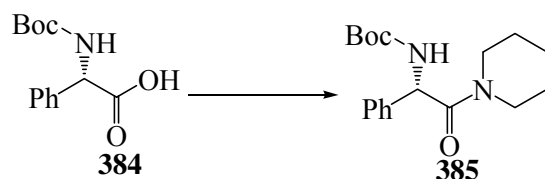
mp 79 – 81 °C (lit: 88 – 91 °C).^[179]

$[\alpha]_D^{25} = -147.6$ (c 1.2 in ethanol), literature value of *R*-isomer: $[\alpha]_D^{25} = +142 \pm 2$ (c 1.0, ethanol).^[179]

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 8.15, 5.55 (d, d, 1 H), 7.50 – 7.30 (m, 5 H), 5.35, 5.13 (d, d, 1 H), 1.46, 1.19 (s, s, 9H).

3.2.8. (-)-(S)-1-[2-*tert*-Butoxycarbonylamino]-2-phenylacetyl]

piperidine (385)^[178-179]



Solution of N, N'-dicyclohexylcarbodiimide (7.570 g, 36.7 mmol) in dry dichloromethane (20 mL) was cooled down to 0 ° C and *tert*-boc-phenylglycine (9.000 g, 36.0 mmol) in dichloromethane (40 mL) was added with a pipette. After 15 min of stirring at 0 ° C, piperidine (4.0 mL, 40.0 mmol) was added over 30 min. The resulting cloudy mixture was stirred at room temperature overnight. The solvent was removed under water pump. Ethyl acetate (150 mL) was added and the suspension was stirred for 30 min. The white precipitate was filtered off and the filtrate was washed with ethyl acetate (150 mL), water (2 x 20 mL), aqueous hydrochloric acid (2.5%, 25 mL), saturated sodium bicarbonate (3 x 20 mL) and brine. The organic layer was dried over anhydrous magnesium sulfate. Removal of solvents gave the crude product (10.800 g, 95%). Crystallization from a mixture of hexane and ether gave the pure product as white crystals (8.100 g, 76%).

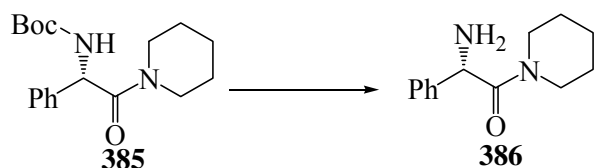
$R_f = 0.22$ (TLC, 15% ethyl acetate in hexane).

mp 95 – 96 ° C (lit: 95.5 – 98 ° C).^[179]

$[\alpha]_D^{22} = -131.7$ (lit: c 1.0, methanol).^[179]

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 7.41 – 7.20 (m, 5 H), 6.15 (d, 1 H), 5.55 (d, 1 H), 3.80 – 3.60 (m, 1 H), 3.40 – 3.30 (m, 1 H), 3.25 – 3.20 (m, 2 H), 1.55 – 1.40 (m, 5 H), 1.35 (s, 9 H), 0.85 (m, 1 H).

3.2.9. (-)-(S)-1-[2-Amino-2-phenylacetyl]piperidine (**386**)^[178-179]

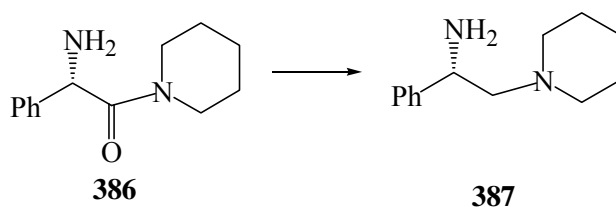


Trifluoroacetic acid (30.0 mL) was added to the **385** (8.000 g, 25.00 mmol) at 0 °C and the solution was stirred for 1 h. Benzene (100 mL) was added to the resulting mixture, and then removed it. This was repeated twice. The residue was treated with aqueous sodium hydroxide (10%) until pH was equal to 10, and was then extracted with diethyl ether (3 x 100 mL), dried over anhydrous magnesium sulfate to give the crude product, a yellow liquid. The pure product as yellow liquid was obtained (4.900 g, 90%) after purification by flash column chromatography through 15% ethyl acetate in hexane.

$$[\alpha]_{\text{D}}^{27} = -79.8 \text{ (c 0.4, CHCl}_3\text{)}.$$

¹H NMR: δ_{H} (ppm, 500 MHz, CDCl₃): 7.42 – 7.30 (m, 5 H), 4.85 (s, 1 H), 3.80 – 3.60 (m, 1 H), 3.40 – 3.30 (m, 1 H), 3.30 – 3.20 (m, 2 H), 2.95 (br. s, 2 H), 1.55 – 1.25 (m, 5 H), 0.90 – 0.80 (m, 1 H).

3.2.10. (-)-(*S*)-Phenyl-piperidinoethylamine (**387**)^[178-179]



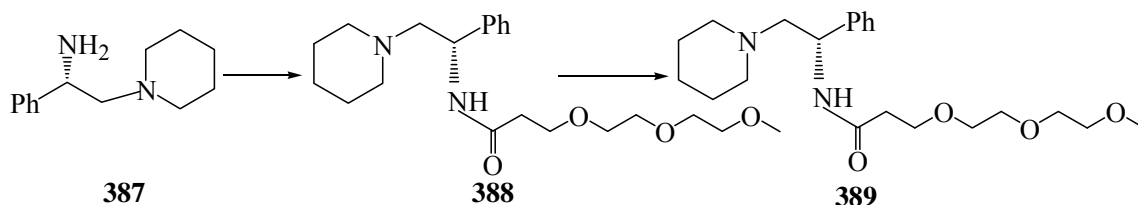
A solution of (*S*)-1-[2-amino-2-phenylacetyl]piperidine (4.500 g, 21.00 mmol) in tetrahydrofuran (100 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (2.350 g, 51.00 mmol) in THF (50 mL). The mixture was left at room temperature overnight. Then it was cooled in ice-water bath, and ethyl acetate (10 mL) was added slowly. After 10 min, aqueous sodium hydroxide (10 mL, 10%) was added followed with Celite (7 g). The mixture was filtered. The filtrate was dried with anhydrous magnesium sulfate, and evaporated to give yellow oil, which was dissolved in ice-cooled tetrahydrofuran to remove non-soluble solid. The crude product was obtained as yellow liquid after evaporation of the filtrate (1.000 g, 70%). The pure product was obtained as a yellow oil (0.810 g, 56%) after purification using FCC (15% ethyl acetate in hexane) and distillation under reduced pressure at 210 ° C (1.5 mm Hg).

bp 210 ° C, 1.5 mm Hg (lit: 210 ° C, 1.5 mm Hg).^[178]

$[\alpha]_D^{25} = -72.4$ (c 1.0, CHCl₃) (lit: $[\alpha]_D^{25} = -64.2$ (c 1.03, CHCl₃)).^[178]

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 7.55 – 7.28 (m, 5 H), 4.07 (dd, 1 H), 2.82 – 1.96 (m, 2 H), 1.91 (br. s, 2 H), 1.91 – 1.20 (m, 4 H), 1.25 – 1.87 (m, 6H).

3.2.11. (-)-(S)-N-[2-(2-Methoxyethoxy)ethoxy]-1-phenyl-
2-piperidinoethylamine (**389**)^[178-179]



Triethylamine (2.500 g, 11.00 mmol) was added drop-wisely to a solution of (*S*)-phenyl-piperidinoethylamine (4.600 g, 25.20 mmol), methoxyethoxyethoxy acetic acid (4.410 g, 24.80 mmol) and diethylphosphorocyanidate (2.660 g, 23.65 mmol) in 1, 2-dimethoxyethane (250 mL) under ice cooling, and the mixture was stirred at room temperature overnight. The solution was eluted with ethyl acetate (350 mL) and benzene (180 mL), washed successively with water (2 x 350 mL), saturated sodium bicarbonate (100 mL) and brine (150 mL), followed by being dried over anhydrous magnesium sulfate. Evaporation of solvents gave yellow oil. This crude product (**388**) (4.996 g, 82%) was used for next step without purification.

A solution of acetamide (5.00 mmol) in THF (50 mL) was added dropwise into a stirred suspension of lithium aluminum hydride (0.570 g, 15 mmol) in THF (25 mL). The mixture was left at room temperature overnight. Then it was cooled in ice-water bath, and ethyl acetate (5 mL) was added slowly. After 10 min, sodium carbonate solution (10 mL, 10%) was added followed with Celite (5 g). The mixture was filtered and the filtrate was dried with anhydrous magnesium sulfate, and evaporated to give the crude product as yellow oil. This oil was purified by FCC (dichloromethane: methanol : isopropylamine = 95 : 2.5 : 2.5), and then distilled to give the pure product as slight

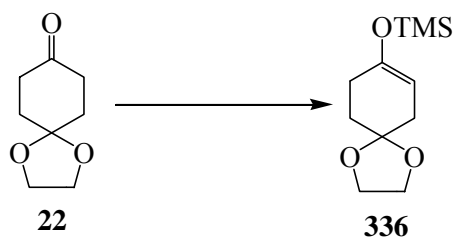
yellow oil (0.810 g, 67%).

bp 232 ° C, 1.2 mm Hg.

$[\alpha]_D^{25} = -69.6$ (c 2.07, acetone).

$^1\text{H NMR}$: δ_{H} (ppm, 500 MHz, CDCl_3): 7.62 – 7.22 (m, 5H), 5.00 (br, s, 1 H), 3.77 (dd, 1H), 3.70 – 3.50 (m, 6H), 3.40 (s, 3H), 2.63 – 2.30 (m, 9H), 1.62 – 1.40 (m, 6H).

3.2.12. **1,4-Dioxaspiro [4.5] dec-8-trimethylsilyloxy-7-ene (336)**^[125-126]



n-Butyllithium (0.98 mL, 2.27 M, 2.20 mmol) was added dropwisely to the solution of diisopropylamine (0.31 mL, 0.220 g, 2.20 mmol) in THF (10 mL) at 0 ° C under nitrogen gas, and the mixture was stirred for 0.5 h. The temperature was cooled to -78 ° C, fresh triethylamine (0.70 mL, 5.03 mmol) was added, followed by the addition of trimethylchlorosilane (0.53 mL, 0.450 g, 4.20 mmol). After stirring the mixture 5 min, the ketone solution (0.310 g, 2.00 mmol) in THF (2 mL) was added over 3 min and the mixture was then stirred for 1 h. After quenching with ammonium chloride (satd.; 20 mL), the reaction mixture was washed quickly with diethyl ether (3 x 75 mL). The combined organic layers were washed with brine, dried with magnesium sulfate. The solvent was removed by evaporation to give the crude product (0.495 g). The crude product was purified by DFC ($R_f = 0.35$, hexane, hexane: ethyl acetate 9:1) to give the pure product was yielded as slight yellow oil (0.376 g, 82 %).

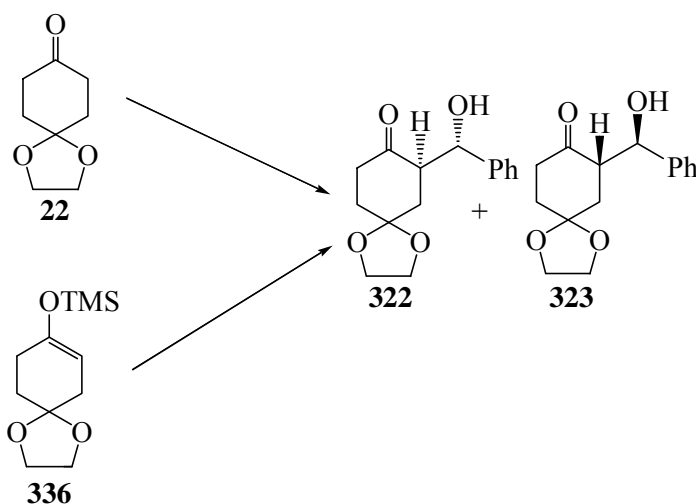
$^1\text{H NMR}$: δ_{H} (ppm, 500 MHz, CDCl_3): 4.70 – 4.68 (m, 1H), 3.92 (s, 4H), 2.24 – 2.23 (br, s, 2H), 2.23 – 2.16 (m, 2H), 1.76 – 1.72 (t, 2H), 0.15 (s, 9H).

$^{13}\text{C NMR}$: δ_{C} (ppm, 500 MHz, CDCl_3): 149.7, 107.6, 100.6, 64.3, 33.9, 31.1, 28.5, 0.2.

IR: (KBr): 3055 (CH), 2955 (CH), 1670 (C=C) cm^{-1}

3.2.13. 1,4-Dioxaspiro[4.5]decan-7-(hydroxyphenylmethyl)-8-one

(anti: **322/323**)^[125-126]



Procedure I: *n*-BuLi (0.20 mL, 2.5 M in hexane, 0.49 mmol) was added dropwise into the solution of chiral amine (0.49 mmol) in fresh THF (3 mL) under nitrogen and the solution was stirred at 0 ° C for 0.5 h, then at -78 ° C and the solution of ketone (0.094 g 0.44 mmol) in THF (1 mL) was added dropwise, stirring for 2.5 h. Benzaldehyde (0.05 mL, 0.49 mmol) was added and the mixture was stirred for 45 min. The reaction was then quickly quenched by adding of the saturated solution of ammonium chloride (satd.; 0.40 mL) and diethyl ether (25 mL), dried over least amounts magnesium sulfate and the crude products were obtained by evaporation of solvents. The crude products were purified by dry flash chromatography (dichloromethane: hexane = 1: 9, and then ethyl acetate: hexane = 1:5) in Silica Gel (10 - 40 μ, type H) from SIGMA and pure anti aldols (**322**) and (**323**) were obtained.

Procedure II: Based on the procedure I, one more equivalent *n*-BuLi (0.20 mL, 2.5 M in hexane, 0.49 mmol) was added dropwise into the solution of lithium enolates

Procedure III: *n*-BuLi (0.20 mL, 2.5 M in Hexane, 0.49 mmol) was added dropwise into the solution of (**336**) (0.10 g, 0.44 mmol) in fresh THF (3 mL) and stirred at -78 ° C for 2.5 h. A chiral lithium amide (0.49 mmol) in fresh THF (3 mL) was then added into the solution was stirred at -78 ° C for 2.5 h. Benzaldehyde (0.05 mL, 0.49 mmol) was added and the mixture was stirred for 45 min. The reaction was then quenched by adding of the saturated solution of ammonium chloride (satd.; 0.40 mL) and diethyl ether (25 mL), dried over least amounts magnesium sulfate and the crude products were attained by evaporation of solvents. The crude products were purified by dry flash chromatography (dichloromethane: hexane = 1: 9, and then ethyl acetate: hexane = 1:5) in Silica Gel (10 - 40 μ, type H) from SIGMA and pure anti aldols (**322**) and (**323**) were obtained.

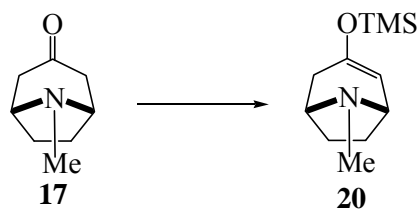
Procedure IV: Based on the procedure III, instead of *n*-BuLi, MeLi-LiBr (0.29 mL, 1.5 M solution in ether, 0.44 mmol) was added drop-wise into a solution of (**336**) (0.10 g, 0.44 mmol) in fresh THF (3 mL) at room temperature.

mp 140-141 ° C (lit. 141-142).^[125]

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 7.40 - 7.25 (m, 5H), 4.78 (d, J=8.6 Hz, 1H), 3.96 – 3.78 (m, 5H), 2.98 (m, 1H), 2.67 (m, 1H), 2.43 (m, 1H), 2.00 - 1.95 (m, 2H), 1.65-1.45 (m, 2H).

3.2.14. (±)-(1*R*, 5*S*, 8*S*)-8-Methyl-3-trimethylsiloxy-8-azabicyclo-[3.2.1]

oct-2-ene (20)^[15-16, 156, 195-196]

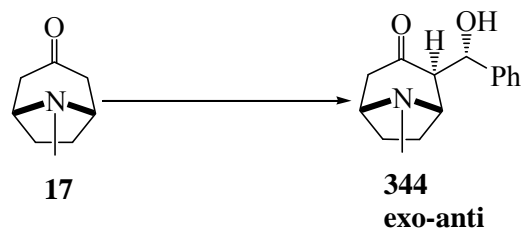


n-Butyllithium (1.09 mL, 2.02 M, 2.20 mmol) was added dropwise to the solution of diisopropylamine (0.31 mL, 0.220 g, 2.20 mmol) in THF (10.00 mL) at 0 ° C under nitrogen, and the mixture was stirred for 0.5 h. The temperature was cooled to -78 ° C, fresh triethylamine (0.70 mL, 5.03 mmol) was added, followed by the addition of trimethylchlorosilane (0.53 mL, 0.450 g, 4.20 mmol). After stirring 5 min, the solution of tropinone (0.278 g, 2.00 mmol) in THF (2 mL) was added over 3 min and the mixture was then stirred for 1 h. After quenching with ammonium chloride (satd.; 20 mL), the reaction mixture was washed quickly with diethyl ether (3 x 75 mL). The combined organic layers were washed by brine, and dried with magnesium sulfate. The solvent was removed in evaporation to give the crude product (0.428 g). The crude product was purified by distillation to yield the pure product as colorless oil (0.337 g, 85 %).

bp 97-99 ° C, 25 mm Hg (lit: 97-99 ° C, 25 mm Hg).^[16]

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 4.90 (d, 1H), 3.29 – 3.27 (d, 2H), 2.55 (dd, 1H), 2.38 (s, 3H), 2.12 (m, 1H), 2.00 (m, 1H), 1.84 – 1.80 (m, 1H), 1.63 – 1.57 (m, 2H), 0.20 (s, 9H)

3.2.15. **(1*R*, 1'*S*, 2*R*, 5*S*, 8*S*)-2-(1'-Hydroxybenzy)-8-methyl-3-oxo-8-azabicyclo [3.2.1]octane (344)**^[34, 15-16]

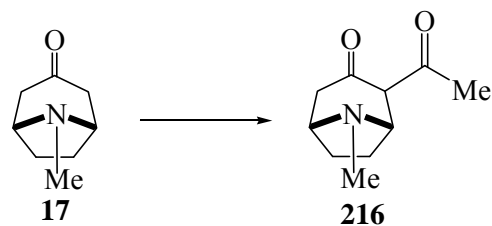


n-Butyllithium (0.20 mL, 2.5 M in hexane, 0.49 mmol) was added dropwise into the solution of the chiral lithium amide (0.49 mmol) in fresh THF (3 mL) under the nitrogen and the solution was stirred at 0 ° C for 0.5 h, then at -78 ° C, tropinone solution (0.062 g, 0.44 mmol) in THF (1 mL) was added dropwise into the whole mixture and the solution was stirred for 1 h. Then, benzaldehyde (0.05 mL, 0.49 mmol) was added and the reaction mixture was stirred for 25 min. The reaction was then quenched quickly with ammonium chloride (satd.; 0.4 mL) and diethyl ether (25 mL), dried over magnesium sulfate and the crude product was obtained by evaporation of solvents. Pure *exo-anti* aldol product (**344**) was obtained by recrystallization (chloroform-hexane) as yellow crystals.

mp 131.0 – 132.0 ° C (lit: 132.0 – 133.0 ° C).^[16]

¹H NMR: δ_{H} (ppm, 500 MHz, CDCl₃): 7.18 – 7.38 (m, 5H), 5.22 (d, 1H), 3.55 (d, 1H), 3.50 – 3.42 (m, 1H), 2.80 (ddd, 1H), 2.43 (s, 3H), 2.45 – 2.40 (m, 1H), 2.30 (ddd, 1H), 2.26 – 2.00 (m, 2H), 1.67 – 1.45 (m, 2H).

3.2.16. (\pm)-(1*R*, 2*R*, 5*S*, 8*S*)-2-Methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo-[3.2.1] octane (216)^[16, 34, 140]

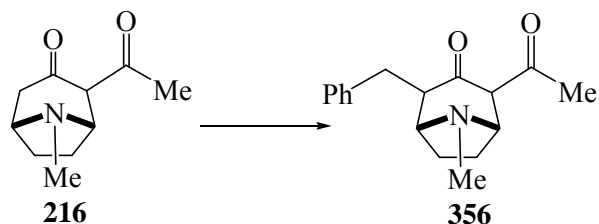


n-Butyllithium (0.49 mL, 2.27 M, 1.10 mmol) was added dropwise to the solution of diisopropylamine (0.16 mL, 0.110 g, 1.10 mmol) in THF (10 mL) at 0 ° C under nitrogen, and the mixture was stirred for 0.5 h. The temperature was cooled to -78 ° C, the solution of tropinone (0.139 g, 1.00 mmol) in THF (2 mL) was added over 3 min and the mixture was then stirred for 1 h. The methyl cyanofornate (0.12 mL, 0.129 g, 1.50 mmol) was then added to the mixture and the mixture was stirred 30 min at -78 ° C. A solution of silver nitrate (0.170 g, 1.00 mmol) in THF (1 mL), water (0.25 mL), glacial acetic acid was quickly added to quench the reaction. At room temperature ammonium chloride (aq) was added until pH was equal to 8, then the reaction was diluted with water, then extracted with chloroform (4 x 10 mL). The combined organic liquid was dried by magnesium sulfate and the crude product was obtained by evaporation of solvents. The crude product was then purified by FCC on silica gel deactivated with triethylamine (50% ethyl acetate in hexane followed by 10% methanol in dichloromethane) and pure product as white crystals was yielded (0.161 g, 82%).

mp 101 -103 ° C (lit: 104 -105 ° C).^[16]

¹H NMR: δ_{H} (ppm, 500 MHz, CDCl₃): 3.85 - 3.75 (m, 1H), 3.80 (s, 1H), 3.40 - 3.35 (m, 1H), 2.82 - 2.71 (m, 1H), 2.40 (s, 3H), 2.29 - 2.00 (m, 4H), 2.00 - 1.75 (m, 1H), 1.68 - 1.52 (m, 1H).

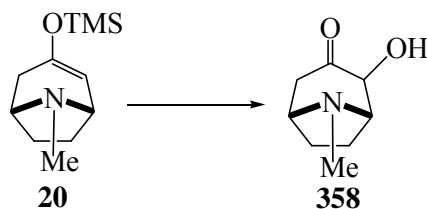
3.2.17. (±)-(1*R*, 2*R*, 4*R*, 5*S*, 8*S*)-2-Methoxycarbonyl-4-benzyl-8-methyl-3-oxo
8-azabicyclo-[3.2.1] octane (**356**)^[135-138]



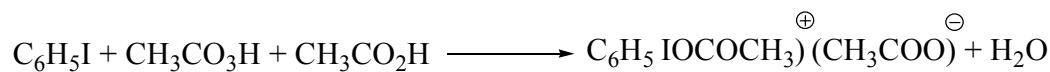
n-Butyllithium (0.89 mL, 2.1 M in hexane, 1.87 mmol) was added dropwise in the solution of diisopropylamine (0.27 mL, 1.87 mmol) in fresh THF (5 mL) under the nitrogen and the mixture was stirred at 0 ° C for 0.5 h, then at -78 ° C the solution of (**216**) (0.160 g, 0.81 mmol) in THF (2 mL) was added by dropwise and the mixture was continually stirred for 3 h at room temperature. The fresh benzyl chloride (0.10 mL, 0.89 mmol) was then added into the reaction mixture and the mixture was stirred for next 16 h at room temperature. The whole mixture was poured into ammonium chloride (aq.), extracted by ether (4 x 80 mL), dried by magnesium sulfate. The crude product was obtained by evaporation of solvents. The crude product was then purified by FCC on silica gel deactivated with triethylamine (5 % ethyl acetate in petrol-ether followed by 5% methanol in dichloromethane) and pure product as yellow oil was yielded (0.011 g, 5%).

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 7.45 – 7.10 (m, 5H), 3.92 – 3.80 (dd, 1H), 3.80 – 3.73 (s, 3H), 3.58 – 3.48 (m, 1H), 3.38 – 3.21 (m, 1H), 3.17 – 2.94 (m, 1H), 2.94 – 2.82 (m, 2H), 2.38 (s, 3H), 2.35 – 2.25 (m, 2H), 1.80 – 1.40 (m, 2H).

3.2.18. (\pm)-**(1*R*, 2*R*, 5*S*, 8*S*)-2-Hydroxyl-8-methyl-3-oxo-8-azabicyclo-**
[3.2.1] octane (358)^[148, 158-160]



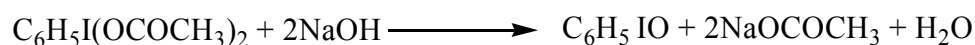
1. **Iodosobenzene diacetate**^[158]:



40% peracetic acid (15.5 mL, 0.12 mol) was added dropwise into the well-stirred solution of the iodosobenzene (10.200 g, 0.05 mol) at 30 ° C by a water bath over 30 – 40 min, then continually stirring for 20 min at 30 ° C was needed. The mixture was chilled in an ice bath for 1 hour. The crystalline product was collected on a Buchner funnel and was then washed with cold water (3 x 20 mL). After drying for 30 min on the funnel with suction, the diacetate was dried overnight in a vacuum desiccator containing calcium chloride. The dried product was yielded (14.050 g, 87%). The purity of the product determined by the titration method of Lucas, Kennedy and Formo is 98 -99 %

mp 158 -159 ° C (lit: 158 -159 ° C).^[158]

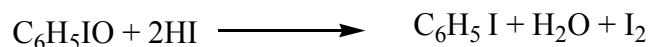
2. **Iodosobenzene**^[159]:



3M sodium hydroxide was added into the iodosobenzene diacetate (14.00 g, 0.043

mol) over a 5 min with vigorous stirring. The lumps of solid that formed were triturated with a stirring rod for 15 min and the reaction mixture was stirred for another 45 min to complete the reaction. The water (100 mL) was added and the mixture was stirred vigorously. The crude was collected on the Buchner funnel. The wet solid was triturated in water(200 mL). The solid was again collected on the Buchner funnel, washed then with water (200 mL) and dried by maintaining suction. The pure product was obtained (8.04 g 85%) by filtration and air drying. Iodometric titration showed the product to be more than 99% pure by the method of Lucas, Kennedy and Formo.^[160]

3. Titration method of Lucas, Kennedy and Formo^[160]



Water (100 mL), sulfuric acid (10 mL, 6M), iodate-free potassium iodide (2 g), chloroform (10 mL) and iodosobenzene (0.25 g) are placed in a iodine flask (200 ml). The flask was shaken for 15 min or longer if the reaction was not complete. The mixture was titrated with 0.1 M sodium thiosulfate. If the sample is pure the change of color in the coloroform layer may be taken as the end point, but if impurities were present starch must be used, for the impurities impart a brownish color to the coloroform.

4. Hydroxylation reaction of racemic silyl enol ether of tropinone^[148]

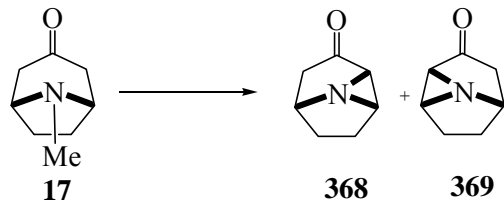
Silyl enol ether (0.052 g, 0.25 mmol) was added to a suspension of iodobenzene (0.062 g, 0.28 mmol) and boron trifluoride etherate (0.061 g, 0.50 mmol) in water (2 mL) at 0 ° C. The mixture was stirred at 0-10 ° C for 4 h. Iodobenzene was removed by extraction with dichloromethane and the aqueous layer was then basified, followed by extraction with dichloromethane (8 x 25 mL), The crude product was given as yellow oil (0.016 g, 41%). Pure product was achieved as white solid (0.040 g, 10% yield) after FCC (5% methanol in dichloromethane).

mp 65.0 – 67.0 ° C (lit: 65.0 – 66.0 ° C).^[148]

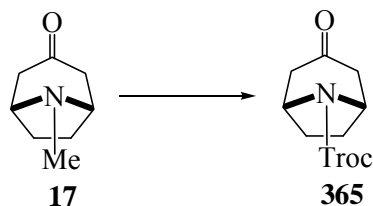
IR (KBr): 3506, 2961, 1706.

¹H NMR: δ_{H} (ppm, 500 MHz, CDCl₃): 4.35 (d, 1H), 3.62 (br, 1H), 3.55 – 3.43 (m, 2H), 2.90 – 2.75 (m, 1H), 2.54 (s, 3H), 2.47 – 2.30 (m, 2H), 2.16 – 2.10 (m, 1H), 1.97 – 1.85 (m, 1H) 1.76 – 1.65 (m, 1H).

3.2.19. (1*R*, 4*S*/2*R*, 5*S*, 8*S*)-3-oxo-8-Azabicyclo-[3.2.1]octane (368/369)^[79,161-162]



1. N-(2, 2, 2-Trichloroethyloxycarbonyl) nortropinone (365)^[79, 161].



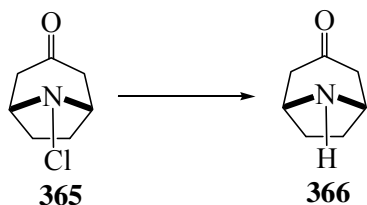
A solution of tropinone (1.390 g, 10 mmol), benzene (5 mL), potassium carbonate (0.070 g) and 2, 2, 2-trichloroethyl chloroformate (2.338 g, 11 mmol) was refluxed for 18 h. At room temperature, the mixture was added with potassium hydroxide (satd.), followed an extraction with diethyl ether. The crude was obtained by drying with magnesium sulfate and removing solvents. Purification by DFC (10% AcOEt in hexane) gave pure product as white solid (2.624 g, 87%).

mp 79.0 - 80.0 ° C (lit: 79.0 - 80.0 ° C).^[161]

¹H NMR: δ_{H} (ppm, 500 MHz, CDCl₃): 4.96 – 4.85 (s, 1H), 4.77 – 4.68 (s, 1H), 4.68 – 4.57 (m, 2H), 2.80 – 2.65 (m, 2H), 2.45 – 2.34 (m, 2H), 2.25 – 2.05 (m, 2H), 1.80 – 1.65 (m, 2H).

¹³C NMR: δ_{C} (ppm, 500 MHz, CDCl₃): 208, 152, 96, 74, 54, 49, 29.

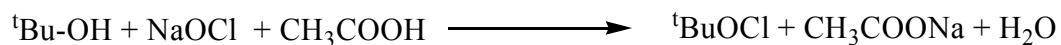
2. Nortropinone (**366**)^[79]



A solution of N-(2, 2, 2-trichloroethoxycarbonyl) nortropinone (**365**, 2.000 g, 6.67 mmol), methanol (30 mL), and zinc powder (3.4 g) was heated under reflux condenser until an exothermic reaction started. After refluxing for 30 min, the mixture was cooled to room temperature and filtered through celite. The filtrate was dried by removing solvents, then basified and extracted with chloroform. Pale gummy product was obtained (0.510 g, 61%).

¹H NMR: δ_{H} (ppm, 500 MHz, CDCl₃): 3.95 – 3.80 (m, 2H), 2.60 – 2.50 (dd, 2H), 2.40 – 2.30 (m, 2H), 2.22 – 2.11 (br, 1H), 1.92 – 1.82 (m, 2H), 1.75 – 1.60 (m, 1H).

3. tert-Butyl hypochlorite



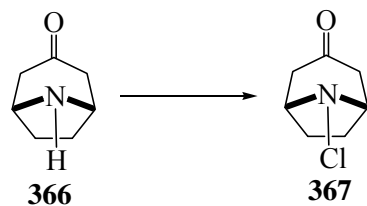
125 mL of commercial household bleach solution was placed on the 250 mL round-bottom flask under the ice bath and the temperature was controlled to be below 10 ° C. At this time the light was turned off nearby apparatus. A solution of t-butyl alcohol (9.25 mL, 97.5 mmol) and glacial acetic acid (6.13 mL, 107.5 mmol) was added, and stirred for about 3 min.

The whole mixture was poured into a separatory funnel (500 mL), the organic layer was washed by 20 mL of 10% sodium carbonate, and then 20 mL of water.

Products were dried over by calcium chloride, and filtered (9.732 g, 92%).

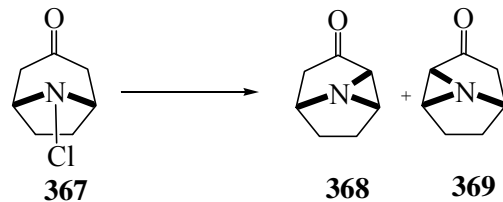
$^1\text{H NMR}$: δ_{H} (ppm, 500 MHz, CDCl_3): 3.50 (s, 3H).

4. N-Chloride-nortropinone (**367**)^[79]



t-Butyl hypochlorite (0.107 g, 1.00 mmol) was added dropwise to an diethyl ether solution of nortropinone (0.125 g, 1.00 mmol) in the presence of sodium bicarbonate (0.094 g) at 10 ° C over 20 min in the dark. The mixture was then stirred at 10 ° C for a further 4 h. The remaining precipitate was filtered off and carefully concentrated in *vacuo* to give a colorless diethyl ether solution of N-chloride-nortropinone (0.151g, 94%), which was used in the following reaction to prepare aziridine without further purification.

5. (1*R*, 4*S*/2*R*, 5*S*, 8*S*)-3-oxo-8-Azabicyclo-[3.2.1]octane (368/369)^[79]



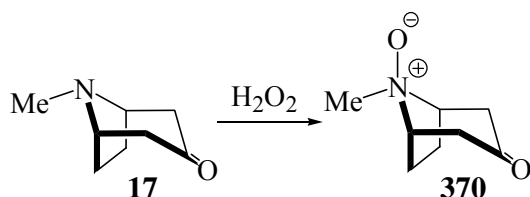
n-Butyllithium solution (0.25 mL, 0.500 mmol, 2M in cyclohexane) was added dropwise into the diisopropylamine (0.07 mL, 0.500 mmol) at 0 ° C and the mixture was stirred for 30 min. Then temperature was cooled down to -78 ° C and the ether solution of N-chloride-nortropinone (0.047 g, 0.296 mmol) was added dropwise. The mixture was then stirred for 1h. Reaction was quenched by adding methanol (2 mL). The crude product as yellow gummy oil (0.051 g, 116%) was obtained by removing the solvent. Purification by chromatography with basic aluminum oxide or silica gel (methanol – dichloromethane, or hexane – ethyl acetate) was not successful.

Chiral amide (**35**) (0.113g, 0.500 mmol) was introduced following procedure above. The crude product as yellow gummy oil (0.043 g, 98%) was obtained

¹H NMR: δ_H (ppm, 500 MHz, CDCl₃): 4.27 – 4.10 (q, 1H), 3.93 – 3.86 (m, 1H), 2.95 – 2.85 (m, 1H), 2.78 – 2.68 (m, 2H), 2.63 – 2.50 (m, 1H), 2.45 – 2.30 (m, 2H), 2.29 – 2.18 (m, 1H).

3.2.20. (1*R*, 5*S*)-8-Methyl-8-oxygen-3-oxo-8-azabicyclo-[3.2.1] octane (**370**)

1. Oxidation of tropinone with hydrogen peroxide^[164-166, 170-171]



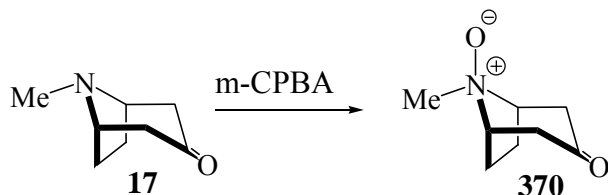
At 0 ° C, the solution of hydrogen peroxide (0.110 g, 30% solution, 1.00 mmol) in toluene (1 mL) was added dropwise into the solution of tropinone in toluene (0.14 g, 1.00 mmol, in 3mL toluene) and the mixture was stirred at 0 ° C for 3h, the solution of hydrogen peroxide (0.110 g, 30% solution, 1.00 mmol) in toluene (1 mL) was then added dropwise again. At room temperature, the mixture was stirred for further 3 days. The crude product was obtained by removing the solvent. The crude product was dissolved in dichloromethane, eluting through a short column filled with basic aluminum oxide (Al₂O₃, ten times the weight of the crude product). All the impurities were first removed with dichloromethane and then only one major product (**370**) (0.080 g, 50 %) as slight yellow solid (R_f=0.18) was obtained with 5% methanol in dichloromethane, another weak spot (minor product) in TLC (R_f= 0.10 in 10 % methanol in dichloromethane) could not be obtained due to too small amounts. Tropinone (0.05 g, 38%) was recovery.

mp 65.0 – 67.0 ° C

¹H NMR of the major product: δ_H (ppm, 500 MHz, CDCl₃): 3.90 – 3.84 (dd, 2H), 3.80 – 3.73 (m, 2H), 3.47 – 3.40 (s, 3H), 2.38 – 2.30 (m, 2H), 2.28 – 2.20 (m, 2H), 2.14 – 2.09 (m, 2H).

MS (EI): 156 (24.5, M⁺), 155 (65.8), 139 (18.2), 138 (100).

2. Oxidation of tropinone with m-CPBA^[167-171]



At 0 ° C, the solution of m-chloroperbenzoic acid (0.07g, 0.38 mmol) in dichloromethane (4 mL) was added into the solution of tropinone in dichloromethane (0.14 g, 1.00 mmol, in 1mL dichloromethane) and the mixture was then stirred at 0 ° C for 30 min. At room temperature the mixture was stirred for further 90 min. The crude product was obtained by removing the solvent (0.16 g). The crude product was dissolved in dichloromethane, eluting through a short column filled with basic aluminum oxide (Al₂O₃, ten times the weight of the crude product). All the impurities were first removed with dichloromethane and then only one major product (**370**) (0.121 g, 78%) as slight yellow solid (TLC, R_f = 0.18) was obtained with 5% methanol in dichloromethane, another weak spot (minor product) in TLC (R_f = 0.10 in 10 % methanol in dichloromethane) could not be obtained due to too small amounts. Tropinone (0.03 g, 22%) was recovered.

mp 65 – 67 ° C

¹H NMR of the major product: δ_H (ppm, 500 MHz, CDCl₃): 3.90 – 3.84 (dd, 2H), 3.80 – 3.73 (m, 2H), 3.47 – 3.40 (s, 3H), 2.38 – 2.30 (m, 2H), 2.28 – 2.20 (m, 2H), 2.14 – 2.09 (m, 2H).

MS (EI): 156 (24.5, M⁺), 155 (65.8), 139 (18.2), 138 (100).

Reference

1. Whitesell, J. K.; Felman, S. W. *J. Org. Chem.*, 1980, 45, 755.
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