

UNIVERSITE CATHOLIQUE DE LOUVAIN
FACULTE DES SCIENCES

Département de Chimie
Professeur L. Ghosez



**Asymmetric cyclopentannulation reactions:
scope and limitation**

Dissertation présentée en vue
de l'obtention du grade de
Docteur en Sciences

par **Patrick SCHANEN**

2003

Ph.D. thesis committee:

Prof. **A. Alexakis**

Université de Genève, Switzerland

Dr **W. Dumont**

Facultés universitaires Notre-Dame
de la Paix, Namur

Prof. **L. Ghosez** (Supervisor)

Université catholique de Louvain

Prof. **J. Marchand-Brynaert** (President)

Université catholique de Louvain

Prof. **I.E. Markó**

Université catholique de Louvain

Prof. **O. Riant**

Université catholique de Louvain

*to my parents,
to Isabelle and Louis*

At the end of this work, I would like to thank Professor L. Ghosez for having accepted me in his laboratory. During all these years, he guided me with his advises and he had always confidence in my work.

I would also thank the academic staff of the Chemistry Department who taught us the basics and the backgrounds necessary to realize a research project.

Then I would like to thank all the people that helped, somehow or other, in the realization of this work:

Professor de Hoffmann and Professor Habib Jiwan and all the staff in the laboratory of mass spectrometry.

Professor Flammang, at Université de Mons-Hainaut, for the high resolution mass spectroscopy.

Mrs Maxwell of University College London for elemental analyses.

The FRIA, FNRS and UCL for financial support.

Anny, Huguette and Van for all their work realized in the laboratory.

Chantal for all the administrative work and the good humor she shared whatever the quantity of work to realize.

Luc, Jean-Michel and Frederic for showing me the secrets and mysteries of computers and networks, and Raphael and Patrick for their precious help in restoring and repairing crashed computers.

All the members of the laboratories of Professor Ghosez and Professor Riant, who have left or who are still there, especially those who worked in laboratory c227 and c266: Marc, Flo, Déo, Delphine, Claire, Michel, Gaëtan, Chloé and Olivier.

Those who have helped in the final corrections of this manuscript: Yann, Patrick, Stéphane, Olivier, Jérôme and Chloé.

I would also like to thank my parents for their support during all these years.

Finally I would especially like to thank Isabelle for all the patience she showed over the past years and her support during the more difficult periods, and Louis who has been an exceptionally calm and quiet baby allowing me to finish this work in good conditions: Villmols Merci!

Abstract

The first part of this dissertation is devoted to the study of an asymmetric [3+2] cycloaddition sequence developed in our laboratory.

The cycloaddition sequence used a sulfonamide-based homoenolate equivalent which was cyclocondensed with a cyclic enone. The stereochemistry of the final product was fixed during the first step, the Michael addition to the enone. Our study focused thus on the Michael addition of sulfonamides to enones.

We have synthesized a series of chiral and achiral sulfonamides. We then studied the regiochemistry and the stereochemistry of the addition of the anions derived from these sulfonamides to cyclohexenone. The presence of a heteroatom at the γ -carbon of the sulfonamide was crucial for the regiochemical outcome of the reaction. The substituent on the sulfonamide also influenced the facial selectivity of the reaction with chiral sulfonamides, but had no influence on the diastereoselectivity with achiral sulfonamides.

The sequence had been applied to various cyclenones. We were also able to apply the method to an acyclic enone with good enantioselectivities. However the method could not be applied to other Michael acceptors.

Another part of the present work was devoted to search a new catalytic asymmetric cyclopentannulation sequence. Two different approaches were studied.

Phase-transfer catalysis seemed the most appropriate strategy for our objective. We soon realized that sulfur-stabilized nucleophiles could not be used under these conditions. Ketals derived from 3-nitropropanal were thus chosen as potential annulation agents. The racemic version was quite efficient and could be applied to less active acceptors such as unsaturated lactams and lactones. Unfortunately we were not able to realize the reaction with good enantioselectivities. However two new catalysts, obtained by the reaction of cinchonine with 1- and 2-methylnaphthyl chloride, emerged as interesting candidates for the phase-transfer reactions.

Organocatalysis was our second approach. The use of rubidium prolinate or the use of proline in the presence of a base proved to be very efficient and the Michael adducts could be obtained with good enantioselectivities. The Michael adducts were easily cyclized and the nitro group could be removed under mild conditions.

Résumé

La première partie de ce travail est consacrée à l'étude d'une séquence de cycloaddition [3+2] asymétrique développée dans notre laboratoire.

Cette séquence de cycloaddition fait appel à un équivalent de homoénolate contenant un sulfonamide, qui est condensé sur une énone cyclique. La stéréochimie du produit final est fixée à la première étape, l'addition de Michael sur l'énone. Notre étude s'est donc concentrée sur l'addition de Michael de sulfonamides aux énonés.

Nous avons synthétisé une série de sulfonamides chiraux et achiraux. Ensuite nous avons étudié la régiochimie et la stéréochimie de l'addition des anions dérivés de ces sulfonamides sur la cyclohexénone. La présence d'un hétéroatome sur le carbone en γ par rapport au sulfonamide s'est révélée cruciale pour le contrôle de la régiochimie de la réaction. Le substituant sur le sulfonamide a aussi influencé la sélectivité faciale dans la réaction avec les sulfonamides chiraux, alors qu'aucune influence sur la diastéréosélectivité n'est observée avec les sulfonamides achiraux.

La séquence avait été appliquée à diverses énonés cycliques. Nous avons pu l'appliquer à une énone acyclique avec de bonnes énantiosélectivités. Par contre, la méthode n'est pas applicable à d'autres accepteurs de Michael.

Une deuxième partie de ce travail a été consacrée à la recherche d'une nouvelle méthode de cyclopentannélation asymétrique catalytique. Nous avons étudié deux approches.

La catalyse par transfert de phase nous a semblé la stratégie la plus appropriée pour atteindre notre objectif. Il s'est rapidement avéré que des nucléophiles stabilisés par un atome de soufre étaient inutilisables. Des acétals dérivés du 3-nitropropanal ont donc été choisis comme réactifs de pentannélation potentiels. La version asymétrique a été très efficace et a pu être appliquée à des accepteurs moins réactifs tels que les lactones ou lactames unsaturés. Malheureusement, nous n'avons pas réussi à réaliser la réaction avec de bons excès énantiomériques. Cependant, deux catalyseurs, obtenus par réaction de la cinchonine avec le chlorure de 1- et 2-méthyl-naphthyl, se sont révélés comme candidats intéressants pour la catalyse par transfert de phase.

La catalyse organique a constitué notre deuxième approche. L'utilisation de prolinate de rubidium ou de proline en présence d'une base s'est montrée très efficace et les adduits de Michael ont pu être obtenus avec de bonnes énantiosélectivités. Les adduits de Michael ont pu être facilement cyclisés et la fonction nitro a pu être éliminée dans des conditions douces.

INTRODUCTION: ASYMMETRIC CYCLOPENTANNULATION REACTIONS1

1	FIVE-MEMBERED RINGS: SYNTHETIC IMPORTANCE	1
2	ASYMMETRIC CYCLOPENTANNULATION REACTIONS: LITERATURE REVIEW	3
2.1	Non-connective asymmetric cyclopentannulations	3
2.2	Connective asymmetric cyclopentannulations	6
2.2.1	[4+1] cyclopentannulation reactions	6
2.2.2	[2+2+1] cyclopentannulation reactions	6
2.2.2.a	The Pauson-Khand reaction	6
2.2.2.b	[2+2] cycloaddition followed by a ring expansion	8
2.2.3	[3+2] cyclopentannulation reactions	13
2.2.3.a	Trimethylenemethane equivalents	13
2.2.3.b	Methylenecyclopropanes	15
2.2.3.c	Cyclopropene ketals	16
2.2.3.d	Allylsilanes	16
2.2.3.e	Allylic sulfoxides	18
2.2.3.f	1,4-addition – aldol cyclization	21
3	PREVIOUS WORK OF OUR LABORATORY	22
3.1	Concept	22
3.2	Cyclopentannulation reactions	23
3.3	A new approach to an asymmetric cyclopentannulation reaction	25
3.3.1	Chiral enones	25
3.3.2	Chiral homoenolates	25
3.3.2.a	A chiral masked cation	26
3.3.2.b	A chiral electron-withdrawing group	26
3.4	Aims of this work	29

CHAPTER I: MICHAEL ADDITION OF CARBANIONS STABILIZED BY SULFUR-SUBSTITUENTS 31

1	SULFAMOYLATED CARBANIONS	31
1.1	Stabilization of the anion	31
1.2	Geometry of the anion	34
1.3	Configurational stability	38
1.4	Reactivity of α -sulfamoylated carbanions	41
2	ADDITION TO ENONES	42
2.1	Generalities	42
2.2	Regioselectivity	44
2.2.1	Nucleophile	44
2.2.2	The enone	45
2.2.3	The cation	46
2.2.4	Solvent	46
3	A PARTICULAR CASE: ADDITION OF α -SULFONYLATED OR α -SULFAMOYLATED ANIONS TO ENONES	47
4	CONCLUSION	51

CHAPTER II: SYNTHESIS OF STARTING MATERIAL 53

1	INTRODUCTION	53
2	SYNTHESIS OF (2S)-(1-METHOXY-1-METHYLETHYL)PYRROLIDINE 27	53
2.1	First method	53
2.2	Second method	54
2.3	Conclusion	56

3	SYNTHESIS OF THE SULFONAMIDES.....	56
3.1	Synthesis of sulfonyl chlorides.....	56
3.2	Synthesis of the sulfonamides	57
3.3	Functionalization of the sulfonamides.....	59
3.3.1	Introduction of the orthoester function	59
3.3.2	Introduction of a ketal function	59
3.3.2.a	Reduction of 48	60
3.3.2.b	Addition of an acyl anion analogue to 40	61
3.3.2.c	Oxidation of 55	63
3.3.2.d	Reaction of 11 and 14 with a ketal of bromoacetaldehyde	64
3.3.3	Introduction of an ether or thioether function.....	65
4	SYNTHESIS OF MICHAEL ACCEPTORS	67
4.1	Synthesis of unsaturated lactams.....	68
4.2	Synthesis of 2,2-dimethylhex-4-en-3-one 75	70
	CHAPTER III: MICHAEL ADDITION OF ACHIRAL SULFONAMIDES.....	73
1	INTRODUCTION.....	73
2	ADDITION OF ACHIRAL SULFONAMIDES TO CYCLOHEXENONE.....	73
2.1	General procedure	73
2.2	Analysis.....	73
2.3	Results	74
2.3.1	Regioselectivity.....	76
2.3.2	Diastereoselectivity	76
2.4	Discussion	77
2.4.1	Kinetic or thermodynamic control?	77
2.4.2	Organolithium compounds: literature.....	78
2.4.3	HMPA: literature	79
2.4.4	Regioselectivity.....	82
2.4.5	Diastereoselectivity	83
3	ADDITION OF ACHIRAL SULFONAMIDES TO OTHER MICHAEL ACCEPTORS	86
4	CONCLUSION	89
	CHAPTER IV: MICHAEL ADDITION OF CHIRAL SULFONAMIDES.....	91
1	INTRODUCTION.....	91
2	ADDITION OF CHIRAL SULFONAMIDES TO CYCLOHEXENONE	91
2.1	Results	91
2.1.1	Regioselectivity.....	93
2.1.2	Diastereoselectivity	94
3	STUDIES OF OTHER EXPERIMENTAL CONDITIONS.....	97
3.1	Solvent	98
3.2	Temperature.....	98
3.3	Additives	98
4	ADDITION OF CHIRAL SULFONAMIDES TO OTHER ACCEPTORS.....	99
5	PROPOSAL OF MECHANISM	102
6	CONCLUSION	106
	CHAPTER V: CYCLIZATION	109
1	CYCLIZATION STARTING FROM CYCLOHEXENONE	109
2	CYCLIZATION STARTING FROM 2,2-DIMETHYLHEX-4-EN-3-ONE 75	111
2.1	Addition to 2,2-dimethylhex-4-en-3-one 75	111
2.2	Cyclization of adducts 135 and 136	111
2.3	Reduction of 138 and 139	112

2.4	Hydrolysis of 140 and 141.....	113
2.5	Elimination of the chiral inductor	113
2.6	Stereochemistry.....	113
CHAPTER VI: PHASE TRANSFER CATALYSIS WITH SULFUR STABILIZED NUCLEOPHILES		117
1	INTRODUCTION	117
2	PHASE TRANSFER CATALYSIS: LITERATURE SURVEY.....	118
2.1	General description.....	118
2.1.1	General scheme.....	118
2.1.2	The base.....	119
2.1.3	The catalyst.....	119
2.1.4	The solvent	120
2.2	Examples of asymmetric phase transfer catalysis reactions	120
2.3	Sulfur containing electron-withdrawing groups under phase transfer conditions	125
3	RESULTS	126
3.1	The choice of the electron-withdrawing group	126
3.1.1	Sulfonamides	127
3.1.2	Sulfones	127
3.1.3	α -Sulfonylcarboxylic esters	129
4	CONCLUSION.....	132
CHAPTER VII: PHASE TRANSFER CATALYSIS WITH NITROCOMPOUNDS AS NUCLEOPHILES		135
1	LITERATURE SURVEY	135
1.1	Nitrocompounds as pentannulation reagents	135
1.2	Asymmetric Michael addition of nitrocompounds under phase transfer conditions	136
2	RESULTS: SYNTHESIS OF A POTENTIAL ANNULATION REAGENT	138
2.1	Synthesis of the ketals	138
2.2	Synthesis of orthoester 170	139
2.2.1	First approach.....	139
2.2.1.a	Unsuccessful attempts to the synthesis of 171	139
2.2.1.b	Synthesis of 171	140
2.2.1.c	Attempts to the synthesis of 10	141
2.2.2	Second approach	141
3	MICHAEL ADDITION UNDER PHASE TRANSFER CATALYSIS	142
3.1	Michael addition of nitroethane and nitropropane	142
3.2	Michael addition of the ketals 169, 167 and 168: racemic conditions.....	145
3.2.1	Quantity of the base	146
3.2.2	Nature of the catalyst.....	147
3.3	Asymmetric Michael addition of ketal 168 under phase transfer conditions 148	
3.3.1	Synthesis of chiral catalysts	148
3.3.2	A first screening.....	151
3.3.3	Choice of the solvent.....	152
3.3.4	Michael addition to cyclopentenone under phase transfer conditions	153
3.3.5	Michael addition to cyclohexenone under phase transfer conditions.....	155
3.3.6	The nature of the base	157
3.3.6.a	KF	157
3.3.6.b	<i>t</i> -BuOK.....	159
3.3.6.c	Hydroxides	159

3.3.6.d TMSOK.....	160
3.3.7 Quality of the base (KF)	161
3.3.8 Quantity of the base.....	162
4 CONCLUSION	163
CHAPTER VIII: MICHAEL ADDITION OF NITRO-COMPOUNDS: OTHER CATALYTIC METHODS	165
1 INTRODUCTION.....	165
2 SILYLATED NITRONATES	165
2.1 Introduction.....	165
2.2 Our objective	167
2.3 Synthesis of silylated nitronates.....	168
2.4 Michael addition of silylated nitronates.....	168
2.4.1 TBAF.....	168
2.4.2 KF and a phase transfer agent.....	169
2.4.3 N-benzylcinchonidinium fluoride	169
3 LEWIS ACID CATALYSTS	171
3.1 Hetero-bimetallic catalysts.....	171
3.1.1 Literature results.....	171
3.1.2 Results	172
3.2 Copper based Lewis acids	173
3.2.1 Literature results.....	173
3.2.2 Results	174
4 OTHER CHIRAL CATALYSTS	175
4.1 Rubidium prolinat	175
4.1.1 Literature results.....	175
4.1.2 Results	176
4.2 Organocatalysis.....	177
4.2.1 Literature results.....	177
4.2.2 Results	178
5 CONCLUSION	178
CHAPTER IX: TRANSFORMATION OF THE MICHAEL ADDUCTS	181
1 CYCLIZATION.....	181
1.1 Literature survey.....	181
1.2 Cyclization catalyzed by a Brønsted acid.....	183
1.3 Cyclization using a Lewis acid	184
2 NEF REACTION	184
2.1 Literature survey.....	184
2.1.1 The Nef reaction in oxidative conditions	185
2.1.2 Nef reaction in reductive conditions	187
2.2 Results	189
3 CONCLUSION	191
CONCLUSION AND PERSPECTIVES	193
1 [3+2] CYCLOPENTANNULATION WITH SULFONAMIDES	193
1.1 Conclusion.....	193
1.2 Perspectives.....	195
2 [3+2] CYCLOPENTANNULATION WITH NITRO-COMPOUNDS	197
2.1 Conclusion.....	197
2.2 Perspectives.....	200
EXPERIMENTAL PART.....	203

1	GENERALITIES.....	203
1.1	Apparatus.....	203
1.2	Techniques.....	204
1.3	Abbreviations and symbols.....	205
1.3.1	Reagents and solvents.....	205
1.3.2	Abbreviations.....	205
2	SYNTHESIS OF 27.....	207
2.1	Synthesis of 2-(1-hydroxy-1-methylethyl)pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester 31.....	207
2.2	Synthesis of 2-[(2 <i>S</i>)-pyrrolidin-2-yl]propan-2-ol 30.....	208
2.3	Synthesis of 2-(1-hydroxy-1-methylethyl)pyrrolidine-1-carbaldehyde 33..	208
2.4	Synthesis of (2 <i>S</i>)-2-(1-methoxy-1-methylethyl)pyrrolidine-1-carbaldehyde 34	209
2.5	Synthesis of (2 <i>S</i>)-(-)-2-(1-methoxy-1-methylethyl)pyrrolidine 27.....	210
3	SYNTHESIS OF SULFONYL CHLORIDES.....	211
3.1	Synthesis of 3-methyl-1-butanefonyl chloride 35.....	211
3.2	Synthesis of 6-chloro-1-hexanesulfonyl chloride 37.....	211
4	SYNTHESIS OF SULFONAMIDES.....	212
4.1	General procedure.....	212
4.2	Synthesis of sulfonamides containing no other function.....	212
4.2.1	Synthesis of 1-methylsulfonylpyrrolidine 11	212
4.2.2	Synthesis of (2 <i>S</i>)-1-methylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine 14	213
4.2.3	Synthesis of 1-ethylsulfonylpyrrolidine 38	214
4.2.4	Synthesis of (2 <i>S</i>)-1-ethylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine 43	214
4.2.5	Synthesis of 1-[(3-methylbutyl)sulfonyl]pyrrolidine 39	215
4.2.6	Synthesis of (2 <i>S</i>)-(1-methoxy-1-methylethyl)-1-[(3-methylbutyl)sulfonyl]pyrrolidine 44	216
4.3	Synthesis of orthoesters.....	217
4.3.1	Synthesis of 1-(ethenylsulfonyl)pyrrolidine 40	217
4.3.2	Synthesis of (2 <i>S</i>)-1-ethenylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine 45	218
4.3.3	Synthesis of 3-(pyrrolidinofonyl)propionitrile 48	219
4.3.4	Synthesis of 3-[(2 <i>S</i>)-(1-methoxy-1-methylethyl)pyrrolidine-1-sulfonyl]propionitrile 49	220
4.3.5	Synthesis of 1-(ethoxy)-3-(pyrrolidin-1-ylsulfonyl)propan-1-iminium chloride 50	221
4.3.6	Synthesis of 1-(ethoxy)-3-[(2 <i>S</i>)-2-[1-methyl-1-(methoxy)ethyl]pyrrolidin-1-yl]sulfonyl-propan-1-iminium chloride 51	222
4.3.7	Synthesis of 1-[(3,3,3-triethoxypropyl)sulfonyl]pyrrolidine 52	223
4.3.8	Synthesis of (2 <i>S</i>)-2-(1-methoxy-1-methylethyl)-1-[(3,3,3-triethoxypropyl)sulfonyl]pyrrolidine 10	223
4.4	Synthesis of ketals.....	225
4.4.1	Synthesis of 1-[(3,3-diethoxypropyl)sulfonyl]pyrrolidine 56	225
4.4.2	Synthesis of (2 <i>S</i>)-1-[(3,3-diethoxypropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 57	225
4.4.3	Synthesis of (2 <i>S</i>)-1-{[2-(1,3-dioxolan-2-yl)ethyl]sulfonyl}-2-(1-methoxy-1-methylethyl)-pyrrolidine 58	226
4.5	Synthesis of ethers and thioethers.....	228
4.5.1	Synthesis of 1-[(3-chloropropyl)sulfonyl]pyrrolidine 41	228
4.5.2	Synthesis of 1-[6-chlorohexyl)sulfonyl]pyrrolidine 42	228
4.5.3	Synthesis of (2 <i>S</i>)-1-[(3-chloropropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 46	229

4.5.4	Synthesis of (2S)-1-[(6-chlorohexyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 36	230
4.5.5	Synthesis of 1-[(3-iodopropyl)sulfonyl]pyrrolidine 55	231
4.5.6	Synthesis of 1-[(6-iodohexyl)sulfonyl]pyrrolidine 60	231
4.5.7	Synthesis of (2S)-1-(3-iodopropane-1-sulfonyl)-2-(1-methoxy-1-methylethyl)pyrrolidine 61	232
4.5.8	Synthesis of (2S)-1-(6-iodohexane-1-sulfonyl)-2-(1-methoxy-1-methylethyl)pyrrolidine 62	233
4.5.9	Synthesis of 1-[(3-ethoxypropyl)sulfonyl]pyrrolidine 59	234
4.5.10	Synthesis of (2S)-1-[(3-ethoxypropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 65	235
4.5.11	Synthesis of 1-[[3-(ethylsulfanyl)propyl]sulfonyl]pyrrolidine 63	236
4.5.12	Synthesis of (2S)-1-[[3-(ethylsulfanyl)propyl]sulfonyl]-2-(1-methoxy-1-methylethyl)-pyrrolidine 66	236
4.5.13	Synthesis of 1-[[6-(ethylsulfanyl)hexyl]sulfonyl]pyrrolidine 64	237
4.5.14	Synthesis of (2S)-1-[[6-(ethylsulfanyl)hexyl]sulfonyl]-2-(1-methoxy-1-methylethyl)-pyrrolidine 67	238
4.5.15	Synthesis of 1-[(2-ethoxyethyl)sulfonyl]pyrrolidine 69	239
4.5.16	Synthesis of (2S)-1-[(2-ethoxyethyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 70	240
5	SYNTHESIS OF MICHAEL ACCEPTORS.....	241
5.1	Synthesis of unsaturated lactams.....	241
5.1.1	Synthesis of 1-methyl-3-phenylsulfanylpyrrolidin-2-one 76	241
5.1.2	Synthesis of 1-methyl-3-(phenylsulfanyl)piperidin-2-one 77	242
5.1.3	Synthesis of 1-methyl-3-(phenylselanyl)pyrrolidin-2-one 80	242
5.1.4	Synthesis of 1-methyl-3-phenylselanylpiperidin-2-one 81	243
5.1.5	Synthesis of 1-methyl-3-(phenylsulfinyl)pyrrolidin-2-one 78	244
5.1.6	Synthesis of 1-methyl-3-(phenylsulfinyl)piperidin-2-one 79	245
5.1.7	Synthesis of 1-methyl-1,5-dihydro-2H-pyrrol-2-one 73	246
5.1.8	Synthesis of 5,6-dihydro-1-methyl-2(1H)-pyridinone 74	247
5.2	Synthesis of 2,2-dimethylhex-4-en-3-one 75	248
5.2.1	Synthesis of 5-hydroxy-2,2-dimethylhexan-3-one 83	248
5.2.2	Synthesis of (E)-2,2-dimethylhex-4-en-3-one 75	249
6	MICHAEL ADDITION OF SULFONAMIDES.....	249
6.1	General procedure.....	249
6.2	Michael addition of achiral sulfonamides to cyclohexenone.....	250
6.2.1	Addition of 1-methylsulfonylpyrrolidine 11	250
6.2.2	Addition of 1-ethylsulfonylpyrrolidine 38	251
6.2.3	Addition of 1-[(3-methylbutyl)sulfonyl]pyrrolidine 39	253
6.2.4	Addition of 1-[(3-ethoxypropyl)sulfonyl]pyrrolidine 59	254
6.2.5	Addition of 1-[[3-(ethylsulfanyl)propyl]sulfonyl]pyrrolidine 63	256
6.2.6	Addition of 1-[[3,3,3-tris(ethyloxy)propyl]sulfonyl]pyrrolidine 52	257
6.3	Michael addition of chiral sulfonamides to cyclohexenone.....	258
6.3.1	Addition of (2S)-(1-methoxy-1-methylethyl)-1-methylsulfonylpyrrolidine 14 ..	258
6.3.2	Addition of (2S)-1-ethylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine 43 ..	259
6.3.3	Addition of (2S)-(1-methoxy-1-methylethyl)-1-[(3-methylbutyl)sulfonyl]pyrrolidine 44	261
6.3.4	Addition of (2S)-1-[(3-ethoxypropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 65	263
6.3.5	Addition of (2S)-1-[(3-ethoxypropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 65 (0 eq. of HMPA).....	264
6.3.6	Addition of (2S)-1-[[3-(ethylsulfanyl)propyl]sulfonyl]-2-(1-methoxy-1-methylethyl)-pyrrolidine 66	265

6.3.7	Addition of (2S)-1-[(3,3-diethoxypropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 57	266
6.3.8	Addition of (2S)-1-[[2-(1,3-dioxolan-2-yl)ethyl]sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 58	267
6.3.9	Addition of (2S)-2-(1-methoxy-1-methylethyl)-1-[(3,3,3-triethoxypropyl)sulfonyl]pyrrolidine 10	268
6.4	Michael addition to other acceptors	269
6.4.1	Addition of 65 to crotonaldehyde	269
6.4.2	Addition of 65 to 2,2-dimethylhex-4-en-3-one 75	271
6.4.3	Addition of (2S)-2-(1-methoxy-1-methylethyl)-1-[(3,3,3-triethoxypropyl)sulfonyl]pyrrolidine 10 to 2,2-dimethylhex-4-en-3-one 75	272
6.4.4	Addition of 1-[(3-methylbutyl)sulfonyl]pyrrolidine 39 to N,N-dimethylacrylamide 273	273
6.4.5	Addition of pyrrolidine to 5,6-dihydro-2H-pyran-2-one 72	274
6.4.6	Addition of pyrrolidine to furan-2(5H)-one 71	275
6.4.7	Addition of pyrrolidine to 1-methyl-5,6-dihydropyridin-2(1H)-one 74	276
7	CYCLIZATION	277
7.1	Cyclization of cyclohexenone	277
7.1.1	Synthesis of (2S)-(1-methoxy-1-methylethyl)-1-[3,3,3-triethoxy-1-(3-trimethylsilyloxy)cyclohex-2-enyl]propane-1-sulfonyl]pyrrolidine 130	277
7.1.2	Synthesis of 3,3-bis(ethoxy)-1-((2S)-2-[1-methyl-1-(methoxy)ethyl]pyrrolidin-1-yl)sulfonyl]octahydro-4H-inden-4-one 131	278
7.1.3	Synthesis of 3,3-bis(ethoxy)-1-((2S)-2-[1-methyl-1-(methoxy)ethyl]pyrrolidin-1-yl)sulfonyl]octahydro-1H-inden-4-ol 132	279
7.1.4	Synthesis of 7-hydroxy-3-((2S)-2-[1-methyl-1-(methoxy)ethyl]pyrrolidin-1-yl)sulfonyl]octahydro-1H-inden-1-one 133	280
7.1.5	Synthesis of 7-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one 134	280
7.2	Cyclization of 2,2-dimethylhex-4-en-3-one 75 with 10	281
7.2.1	Synthesis of (2S)-(1-methoxy-1-methylethyl)-1-(1,1,1-triethoxy-4,7,7-trimethyl-6-trimethylsilyloxyoct-5-ene-3-sulfonyl)pyrrolidine 135	281
7.2.2	Synthesis of 1-[2,2-bis(ethoxy)-5-methyl-4-((2S)-2-[1-methyl-1-(methoxy)ethyl]pyrrolidin-1-yl)sulfonyl]cyclopentyl]-2,2-dimethylpropan-1-one 138	282
7.2.3	Synthesis of 1-(2,2-diethoxy-4-[(2S)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]sulfonyl)-5-methylcyclopentyl]-2,2-dimethylpropan-1-ol 140	283
7.2.4	Synthesis of 2-(1-hydroxy-2,2-dimethylpropyl)-4-[(2S)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]sulfonyl]-3-methylcyclopentanone 142	284
7.2.5	Synthesis of 5-(1-hydroxy-2,2-dimethylpropyl)-4-methylcyclopent-2-en-1-one 144	285
7.3	Cyclization of 2,2-dimethylhex-4-en-3-one 75 with 52	285
7.3.1	Synthesis of 1-(1,1,1-triethoxy-4,7,7-trimethyl-6-trimethylsilyloxyoct-5-ene-3-sulfonyl)pyrrolidine 136	285
7.3.2	Synthesis of 1-[2,2-bis(ethoxy)-5-methyl-4-(pyrrolidin-1-ylsulfonyl)-cyclopentyl]-2,2-dimethylpropan-1-one 139	286
7.3.3	Synthesis of 1-[2,2-bis(ethoxy)-5-methyl-4-(pyrrolidin-1-ylsulfonyl)-cyclopentyl]-2,2-dimethylpropan-1-ol 141	287
7.3.4	Synthesis of 2-(1-hydroxy-2,2-dimethylpropyl)-3-methyl-4-(pyrrolidin-1-ylsulfonyl)cyclopentanone 143	288
7.3.5	Synthesis of 5-(1-hydroxy-2,2-dimethylpropyl)-4-methylcyclopent-2-en-1-one 144	289
8	PHASE-TRANSFER CATALYSIS: SULFUR-CONTAINING NUCLEOPHILES	290
8.1	Sulfones as nucleophiles	290
8.1.1	Synthesis of ethylphenylsulfone 157	290
8.1.2	Synthesis of ethylphenylsulfone d₂ 228	290
8.2	α -Sulfonylcarboxylic esters as nucleophiles	291

8.2.1	Synthesis of methyl 2-(phenylsulfonyl)propanoate 160	291
8.2.2	Synthesis of methyl 2-(phenylsulfonyl)propanoate 158	292
8.2.3	Synthesis of methyl 2-(phenylsulfonyl)butanoate 161	293
8.2.4	Synthesis of {[1-(phenylsulfonyl)propyl]sulfonyl}benzene 162	293
8.2.5	Synthesis of methyl 2-methyl-3-phenyl-2-(phenylsulfonyl)propanoate 163 ...	294
8.2.6	Synthesis of methyl 2-(3-oxocyclohexyl)-2-(phenylsulfonyl)propanoate 164 .	295
8.2.7	Synthesis of methyl (3-oxocyclohexyl)(phenylsulfonyl)acetate 229	296
8.2.8	Synthesis of methyl 2-(3-oxocyclohexyl)-2-(phenylsulfonyl)butanoate 230 ...	297
8.2.9	Synthesis of 3-[bis(phenylsulfonyl)methyl]cyclohexanone 231	298
9	PHASE-TRANSFER CATALYSIS: NITRO-CONTAINING NUCLEOPHILES	299
9.1	Synthesis of ketals	299
9.1.1	Synthesis of 3-nitropropanal 166	299
9.1.2	Synthesis of 2-(2-nitroethyl)-1,3-dioxolane 167	300
9.1.3	Synthesis of 1,1-diethoxy-3-nitropropane 168	300
9.1.4	Synthesis of 2-(2-nitroethyl)-1,3-dioxane 169	301
9.2	Synthesis of orthoester.....	302
9.2.1	Synthesis of 3-nitropropanal dimethylhydrazone 173	302
9.2.2	Synthesis of 3-nitropropanenitrile 171	303
9.2.3	Synthesis of 3-ethyloxetan-3-yl 3-bromopropanoate 176	303
9.2.4	Synthesis of 1-(2-bromoethyl)-4-ethyl-2,6,7-trioxabicyclo[2,2,2]octane 174 ..	304
9.2.5	Attempted synthesis of 4-ethyl-1-(2-nitroethyl)-2,6,7-trioxabicyclo[2.2.2]octane 232	305
9.3	Michael addition of nitro-compounds: racemic.....	305
9.3.1	General procedure.....	305
9.3.2	Addition of nitroethane to cyclohexenone.....	306
9.3.3	Addition of nitropropane to cyclohexenone.....	306
9.3.4	Addition of nitropropane to 2,2-dimethylhex-4-en-3-one 75	307
9.3.5	Addition of nitropropane to N,N-dimethylacrylamide	308
9.3.6	Addition of nitropropane to ethyl acrylate	309
9.3.7	Addition of nitropropane to methyl crotonate.....	310
9.3.8	Addition of nitropropane to methyl methacrylate	310
9.3.9	Addition of 2-(2-nitroethyl)-1,3-dioxolane 167 to cyclohexenone.....	311
9.3.10	Addition of 2-(2-nitroethyl)-1,3-dioxane 169 to cyclohexenone.....	312
9.3.11	Addition of 1,1-diethoxy-3-nitropropane 168 to cyclohexenone.....	313
9.3.12	Addition of 1,1-diethoxy-3-nitropropane 168 to cyclopentenone.....	314
9.4	Synthesis of catalysts	315
9.4.1	General procedure.....	315
9.4.2	Monobenylation of 1,4-diazabicyclo[2.2.2]octane.....	315
9.4.3	Dibenylation of 1,4-diazabicyclo[2.2.2]octane	316
9.4.4	Reaction of cinchonidine with 9-(chloromethyl)anthracene.....	317
9.4.5	Reaction of quinine with 9-(chloromethyl)anthracene	317
9.4.6	Reaction of quinidine with 9-(chloromethyl)anthracene	318
9.4.7	Reaction of cinchonine with 1-(chloromethyl)naphthalene.....	319
9.4.8	Reaction of cinchonine with 4-(chloromethyl)biphenyl)	320
9.4.9	Reaction of cinchonine with 2-(chloromethyl)naphthalene.....	321
9.4.10	Reaction of cinchonidine with 1,3-bis(bromomethyl)benzene.....	321
9.4.11	Reaction of N-benzylcinchonidinium chloride 196 with allyl bromide.....	322
9.4.12	Reaction of N-(9-anthrylmethyl)cinchonidinium chloride 189 with allyl bromide 323	
9.5	Michael addition of nitro-compounds: asymmetric.....	324
9.5.1	Addition to cyclopentenone	324
9.5.2	Addition to cyclohexenone	325
10	MICHAEL ADDITION OF NITRO-COMPOUNDS: OTHER CATALYTIC METHODS	326
10.1	Silylated nitronates.....	326

10.1.1	Synthesis of propylidene[(trimethylsilyl)oxy]azane oxide (1-aci-nitropropane trimethylsilylester) 207	326
10.1.2	Synthesis of {[tert-butyl(dimethyl)silyl]oxy}(propylidene)azane oxide (1-aci-nitropropane tert-butyldimethylsilylester) 208	326
10.1.3	Synthesis of 7-ethoxy-2,2-dimethyl-3,8-dioxa-4-aza-2-siladec-4-ene 4-oxide (1-aci-nitro-3,3-diethoxypropane trimethylsilylester) 209	327
10.1.4	Synthesis of N-benzylcinchonidinium fluoride 210	328
10.1.5	Michael addition of 207 : TBAF	329
10.1.6	Michael additon of 207 : KF and benzyltriethylammonium chloride or N-(1-naphthylmethyl)cinchoninium chloride 190	329
10.1.7	General procedure for the Michael addition of silylated nitronates catalyzed by N-benzylcinchonidinium fluoride 210	330
10.1.8	Michael additon of 207 to cyclohexenone: N-benzylcinchonidinium fluoride 210	330
10.1.9	Michael addition of 209 to cyclopentenone: N-benzylcinchonidinium fluoride 210	330
10.1.10	Michael addition of 209 to cyclohexenone: N-benzylcinchonidinium fluoride 210	331
10.1.11	Michael addition of 209 to cyclopentenone: N-benzylcinchonidinium fluoride 210	331
10.1.12	Michael addition of 209 to cyclohexenone: N-benzylcinchonidinium fluoride 210	331
10.2	AlLi[(R)-binaphthoxide] ₂ complex as catalyst.....	332
10.2.1	Preparation of a 0.1M solution of AlLi[(R)-binaphthoxide] ₂ ((R)-ALB).....	332
10.2.2	Michael addition of 168 to cyclopentenone.....	332
10.3	Rubidium prolinatate as catalyst	333
10.3.1	Synthesis of rubidium prolinatate 211	333
10.3.2	Michael addition of 209 to cyclopentenone.....	333
10.3.3	Michael addition of 209 to cyclohexenone	334
10.4	L-proline as catalyst.....	334
10.4.1	Michael addition of 209 to cyclopentenone.....	334
10.4.2	Michael addition of 209 to cyclohexenone	335
11	CHEMICAL MODIFICATION OF ADDUCTS.....	335
11.1	Cyclization.....	335
11.1.1	Cyclization of adduct 186	335
11.1.2	Cyclization of 198	336
11.2	The Nef reaction	337
11.2.1	Nef reaction of adduct 178	337
11.2.2	Nef reaction of 186	337

BIBLIOGRAPHY.....203

Introduction:

Asymmetric cyclopentannulation reactions

1 Five-membered rings: synthetic importance

Five-membered rings are ubiquitous in natural and biologically interesting products. An important class consists of the prostaglandins,¹ which act on various systems of the organism (cardio-vascular, gastro-intestinal...). One group of this family deriving from PGE₂ intervenes in the aggregation of blood platelets, the relaxation of smooth muscles and also shows anti-inflammatory activity (figure 1).

Several antibiotics, such as (-)-pentenomycin² and (-)-aristeromycin³ (figure 1) are five-membered ring derived compounds.

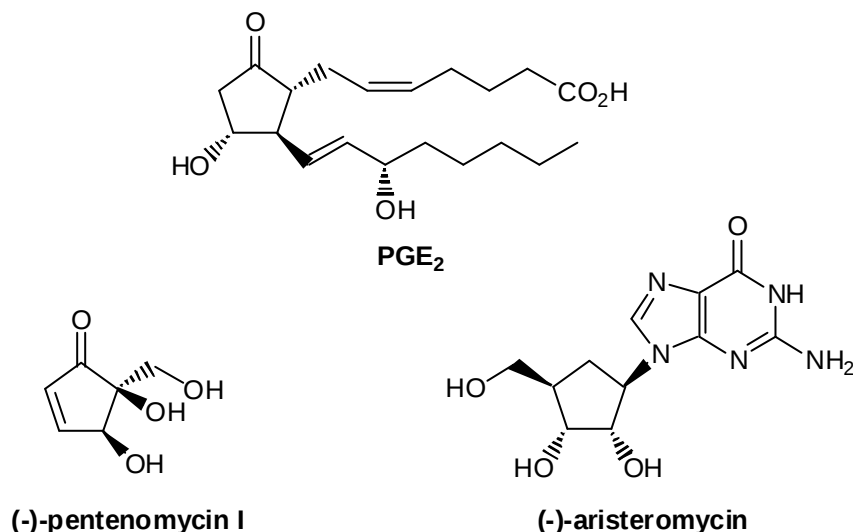


Figure 1

¹ Von Euler, U. S.; Eliasson, R., *Prostaglandins*; Academic Press: New York, 1967.

² Achab, S.; Das, B. C. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2863.

³ Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.*, **1968**, *21*, 255-263.

The hydrindane scaffold is present in the skeleton of steroids, such as cholic acid.⁴ Another example of a natural hydrindane, (-)-tamariscol⁵, has a pleasant odor and is exploited industrially (figure 2).

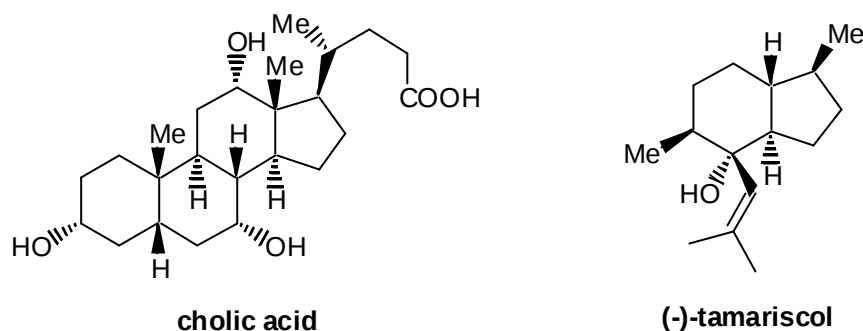


Figure 2

The triquinane family contains three fused five-membered rings. (-)-Hypnophilin⁶, a linear triquinane, is an antibiotic isolated from the mushroom *Pleurotellus hypnophilus*⁷ which presents an important cytotoxic activity (figure 3).⁸ Subergorgic acid is an angular triquinane which shows strong cardiotoxic activity by inhibiting neuromuscular transmission (figure 3).⁹

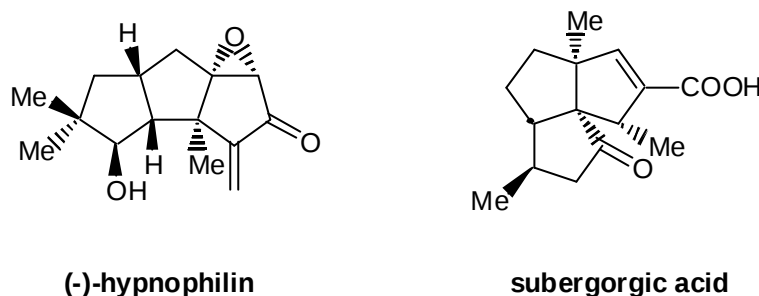


Figure 3

Other more complex polycyclic antibiotics, such as (+)-ikarugamycin¹⁰, (figure 4), also incorporate five-membered rings.

⁴ Fieser, L. F.; Fieser, M., *Steroids*; Reinhold Publishing: New York, 1959.

⁵ Tori, M.; Sono, M.; Nishigaki, Y.; Nakashima, K.; Asakawa, Y. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 435-445.

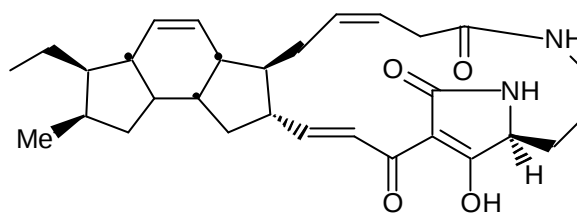
⁶ Weinges, K.; Dietz, U.; Oeser, T.; Irngartinger, H. *Angew. Chem. Int. Ed. Engl.*, **1990**, 29, 680-682.

⁷ Giannetti, B.-M.; Steffan, B.; Steglich, W.; Kupka, J.; Anke, T. *Tetrahedron*, **1986**, 42, 3587-3593.

⁸ Steglich, W. *Pure Appl. Chem.*, **1981**, 53, 1233-1240.

⁹ Paquette, L. A.; Meister, P. G.; Friedrich, D.; Sauer, D. R. *J. Am. Chem. Soc.*, **1993**, 115, 49-56.

¹⁰ Paquette, L. A.; Romine, J. L.; Lin, H.-S.; Wright, J. *J. Am. Chem. Soc.*, **1990**, 112, 9284-9292.



(+)-ikarugamycin

Figure 4

It is therefore not surprising that many research groups have devoted considerable efforts to the development of powerful methods for the synthesis of five-membered carbon rings. Many strategies leading to racemic compounds have been developed, as shown in the reviews by Ramaiah¹¹, Trost¹², Hudlicky¹³, Welker¹⁴ and Lautens.¹⁵

On the other hand, there are still only few methods for the asymmetric synthesis of five-membered carbon rings.

2 Asymmetric cyclopentannulation reactions: literature review

2.1 Non-connective asymmetric cyclopentannulations

The Dieckmann condensation is the oldest method involving an anionic species for a ring-closing strategy.¹⁶ An example of an asymmetric Dieckmann condensation was recently described by the group of Yamada in the synthesis of elisabethin C, a marine *bisnor*-diterpenoid (scheme 1).¹⁷

¹¹ Ramaiah, M. *Synthesis*, **1984**, 529-570.

¹² Trost, B. M. *Angew. Chem. Int. Ed. Engl.*, **1986**, 25, 1-20.

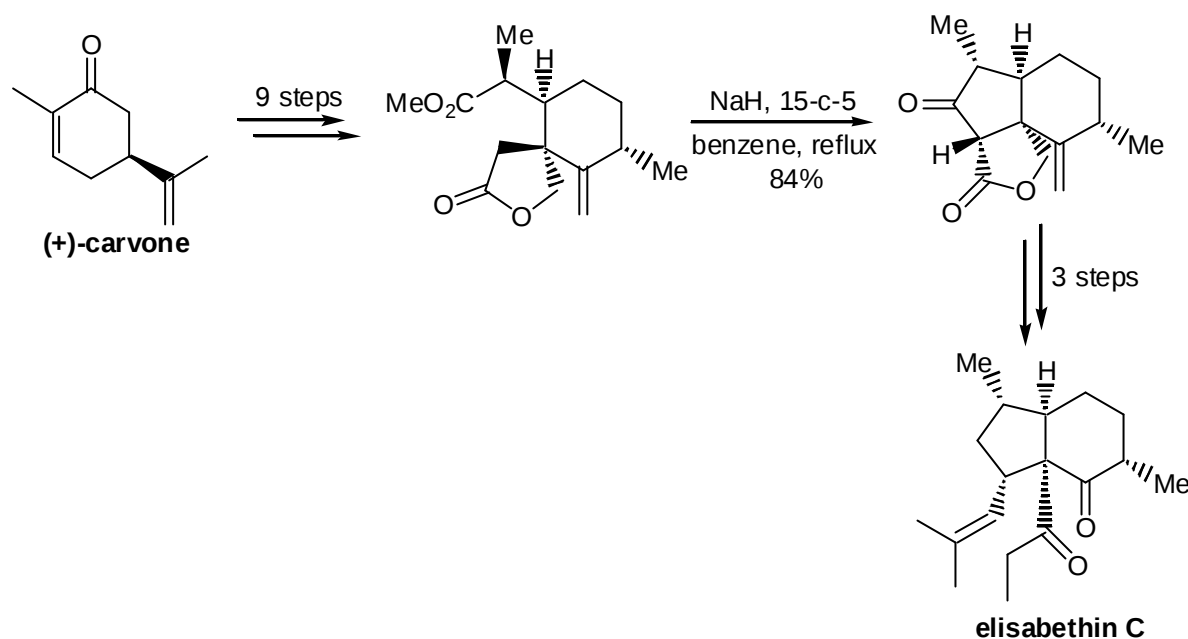
¹³ Hudlicky, T.; Price, S. D. *Chem. Rev.*, **1989**, 89, 1467-1486.

¹⁴ Welker, M. E. *Chem. Rev.*, **1992**, 92, 97-112.

¹⁵ Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.*, **1996**, 96, 49-92.

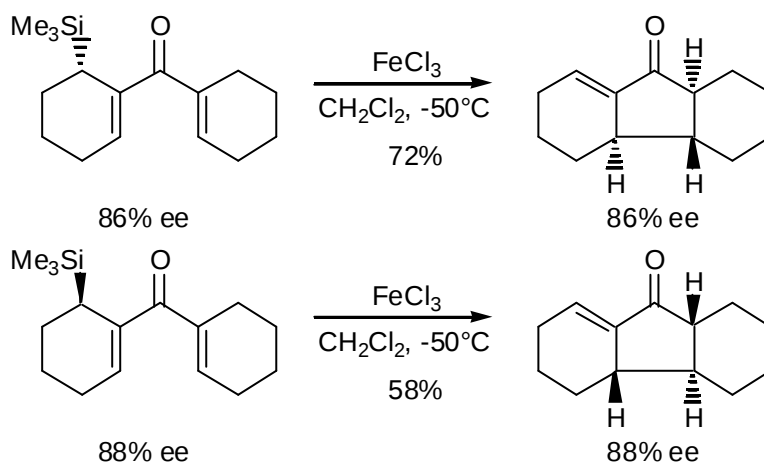
¹⁶ Dieckmann, W. *Ber.*, **1894**, 27, 103.

¹⁷ Miyaoka, H.; Honda, D.; Mitome, H.; Yamada, Y. *Tetrahedron Lett.*, **2002**, 43, 7773-7775.



Scheme 1

The Nazarov reaction is a cyclization reaction based upon the formation of a cationic species. It consists in the cyclization of divinylketones catalyzed by an acid.^{18,19} An example of an asymmetric version of this reaction has been described by Denmark (scheme 2).²⁰



Scheme 2

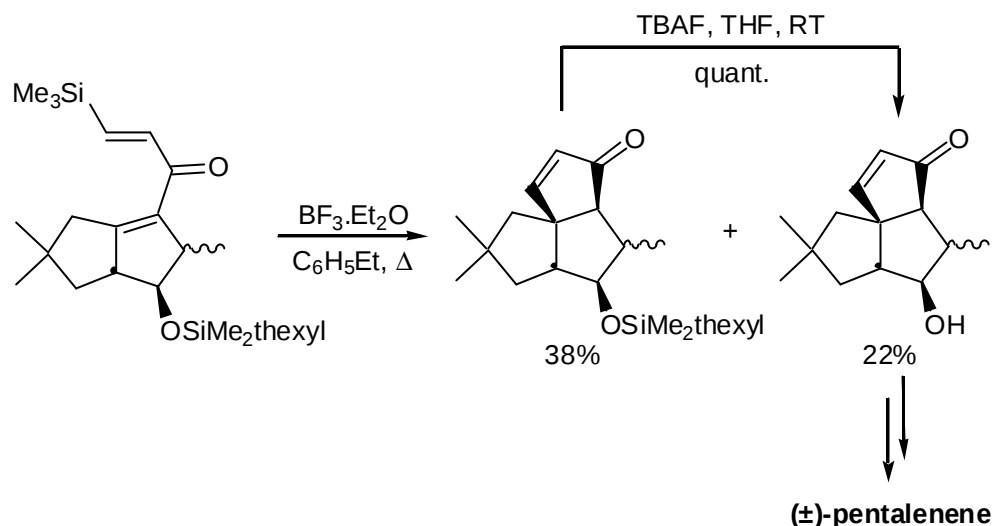
Franck-Neumann *et al.* used an asymmetric Nazarov reaction for the introduction of the third ring of (±)-pentalenene (scheme 3).²¹

¹⁸ Nazarov, N. I. *Usp. Khim.*, **1949**, 18, 377.

¹⁹ Nazarov, N. I.; Zaretskaya, I. I. *Zh. Obshch. Khim.*, **1957**, 27, 693.

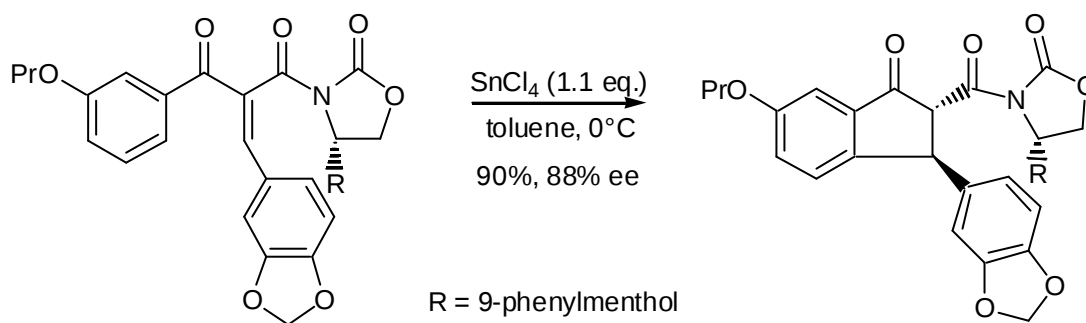
²⁰ Denmark, S. E.; Wallace, M. A.; Walker, C. B. J. *J. Org. Chem.*, **1990**, 55, 5543-5545.

²¹ Miesch, M.; Miesch-Gross, L.; Franck-Neumann, M. *Tetrahedron*, **1997**, 53, 2111-2118.



Scheme 3

An unprecedented asymmetric Nazarov-type ring-closure of alkylidene 1,3-dicarbonyl compounds was used by the group of Pridgen at SmithKline Beecham for the synthesis of novel nonracemic endothelin receptor antagonists SB 209670 and SB 217242 (scheme 4).²²



Scheme 4

Chiral rhodium complexes have been used for the cyclization of 4-pentenals²³, α -diazo- β -ketoesters²⁴ and α -diazoketones.²⁵

This non-exhaustive list shows the diversity of intramolecular cyclization strategies. However these methods are less attractive than the connective methods due to the often needed complex starting material and the lack of flexibility.

²² Pridgen, L. N.; Huang, K.; Shilcrat, S.; Tickner-Eldridge, A.; DeBrosse, C.; Haltiwanger, R. C. *Synlett*, **1999**, 1612-1614.

²³ Taura, Y.; Tanaka, M.; Wu, X.-M.; Funakoshi, K.; Sakai, K. *Tetrahedron*, **1991**, 47, 4879-4888.

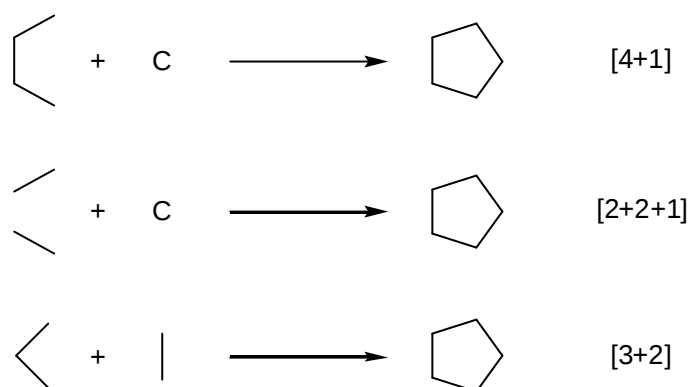
²⁴ Müller, P.; Fernandez, D. *Helv. Chim. Acta*, **1995**, 78, 947-958.

²⁵ Watanabe, N.; Ohtake, Y.; Hashimoto, S.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.*, **1995**, 36, 1491-1494.

2.2 Connective asymmetric cyclopentannulations

The major advantage of these strategies is their convergent character. The ring is constructed in one or more steps by the combination of two or three synthons. Asymmetry is introduced by the mean of a covalently bond chiral inductor or by the use of an external chiral ligand on a catalyst.

Cyclopentannulation reactions can be classified as [4+1], [2+2+1] or [3+2] annulations (scheme 5).



Scheme 5

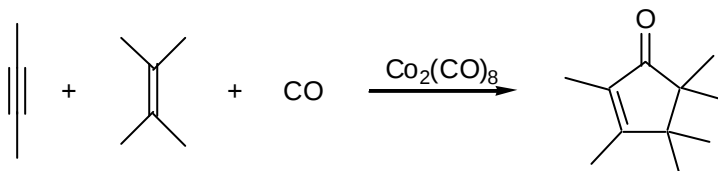
2.2.1 [4+1] cyclopentannulation reactions

To the best of our knowledge, there are no asymmetric versions of [4+1] cycloaddition reactions reported in the literature.

2.2.2 [2+2+1] cyclopentannulation reactions

2.2.2.aThe Pauson-Khand reaction

Pauson and Khand published in 1973 a new method for the generation of five-membered rings based on a [2+2+1] strategy.²⁶ In this reaction an olefin, an acetylene and a molecule of carbon monoxide are coupled, intra- or intermolecularly, in the presence of a cobalt complex (scheme 6).

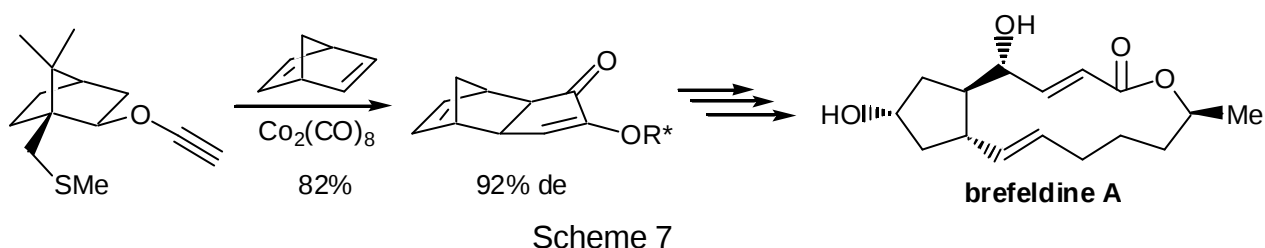


Scheme 6

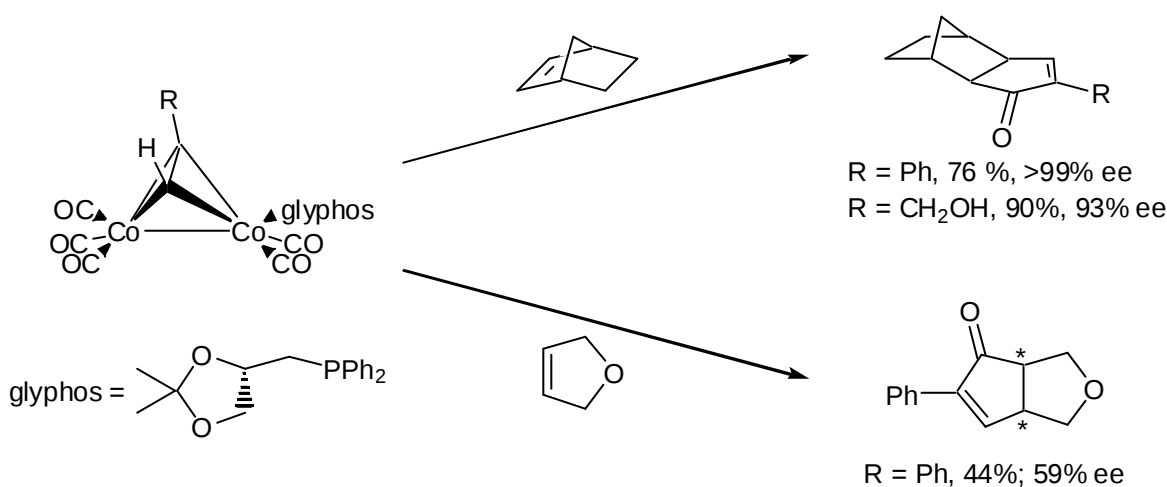
²⁶ Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc. Perkin Trans. 1* **1973**, 977-981.

To develop an asymmetric version of the Pauson-Khand reaction one can either use a chiral inductor linked to the olefin or the acetylene, or use a chiral cobalt complex.

A recent example for an intermolecular asymmetric Pauson-Khand reaction using a chiral inductor was described by Greene. A chiral ynoether was used for the introduction of the asymmetric centers in the five-membered ring of brefeldine A (scheme 7).²⁷



Pauson and Brunner studied chiral cobalt complexes. Modest to excellent enantioselectivities were obtained with a chiral phosphine, such as glyphos (scheme 8).^{28,29}



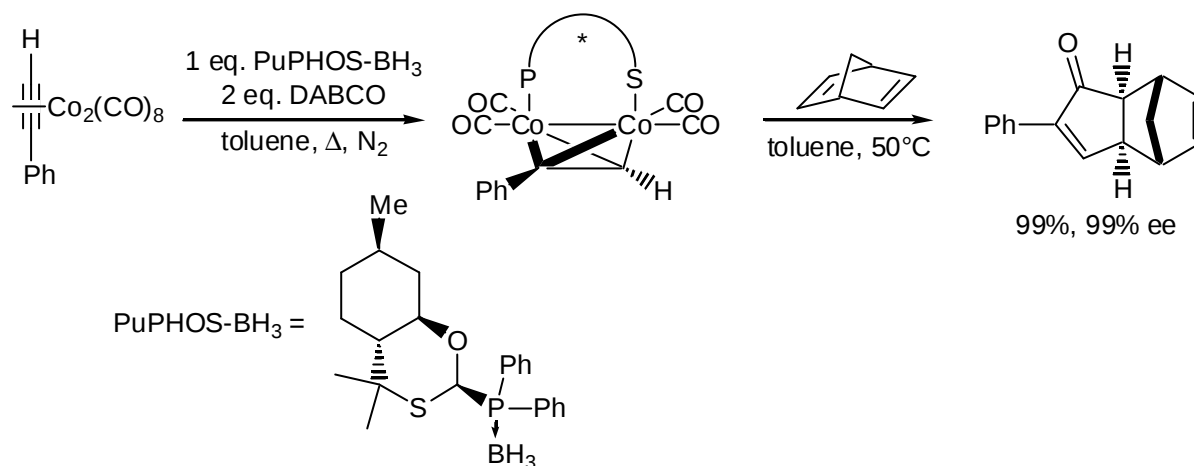
Another example of an asymmetric intermolecular Pauson-Khand reaction has been published by Pericàs and Riera.³⁰ A chiral bidentate (P,S) ligand on cobalt led to excellent enantioselectivities (scheme 9).

²⁷ Bernardes, V.; Kann, N. R., A.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Org. Chem.*, **1995**, 60, 6670-6671.

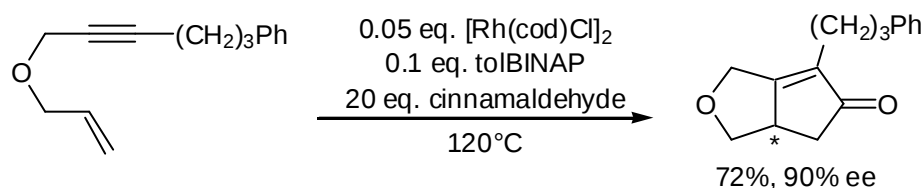
²⁸ Bladon, P.; Pauson, P. L.; Brunner, H.; Eder, R. *J. Organomet. Chem.*, **1988**, 355, 449-454.

²⁹ Brunner, H.; Niedernhuber, A. *Tetrahedron Asymmetry*, **1990**, 1, 711-714.

³⁰ Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Maestro, M. A.; Mahía, J. *J. Am. Chem. Soc.*, **2000**, 122, 10242-10243.



These examples show that asymmetric intermolecular Pauson-Khand reactions could be very powerful tools. However, unlike the examples described above, most of the other publications deal with intramolecular reactions which necessitate first the synthesis of the enyne. A recent example has been published by Shibata who used a rhodium catalyst and an aldehyde as CO source (scheme 10).³¹



2.2.2.b [2+2] cycloaddition followed by a ring expansion

An interesting strategy for the construction of five-membered rings is the [2+2] cycloaddition followed by a ring expansion of the strained four-membered ring. The stereochemistry of the final product is fixed during the cycloaddition whereas the ring expansion has to be regioselective to obtain the desired product.

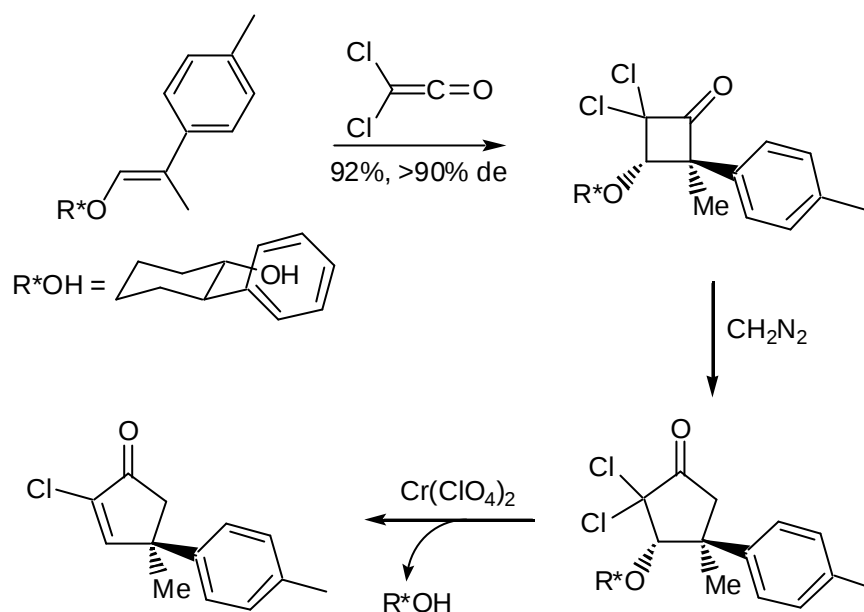
The most practical method used for the formation of cyclobutanones is the cycloaddition of olefins to ketenes or keteniminium salts. The chirality can be carried by the olefin or the cumulene.

An example of the first possibility was given by Greene, who described the cycloaddition of chiral enol ethers with dichloroketene (scheme 11).³² The facial

³¹ Shibata, T.; Toshida, N.; Takagi, K. *J. Org. Chem.*, **2002**, 67, 7446-7450.

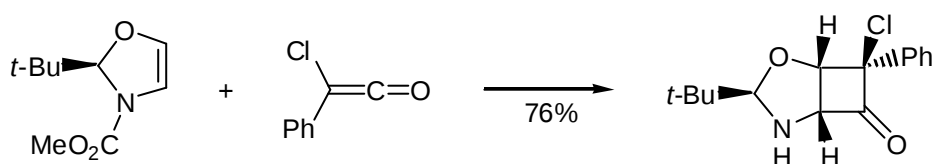
³² Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.*, **1987**, 109, 4752-4753.

selectivities were excellent. The ring expansion was realized with diazomethane. The presence of the chlorine substituents efficiently directed the regiochemistry of the ring expansion reaction.



Scheme 11

As shown recently in our laboratory, cycloaddition reactions of ketenes with chiral olefins proceeded with complete regio- and stereoselectivity (scheme 12).³³



Scheme 12

A second strategy implying the chirality on the ketene substituents was not successful (figure 5).³⁴ These disappointing results could be assigned to the fact that the chiral substituents were too far away from the carbon atom C1.

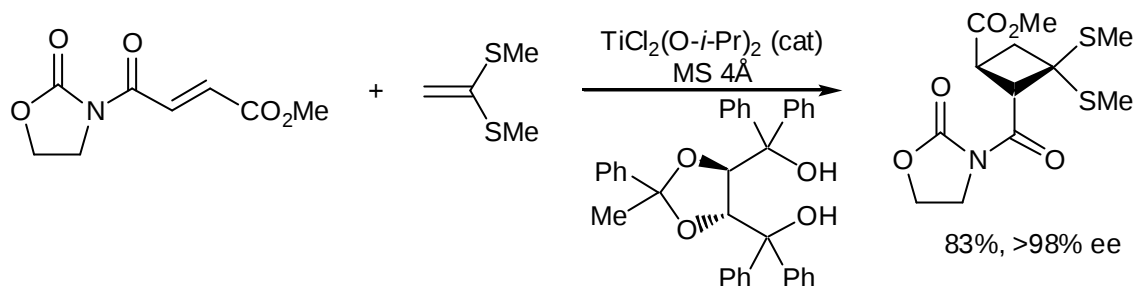


Figure 5

³³ Cagnon, R. *PhD-Thesis UCL-ORSY*, 1996

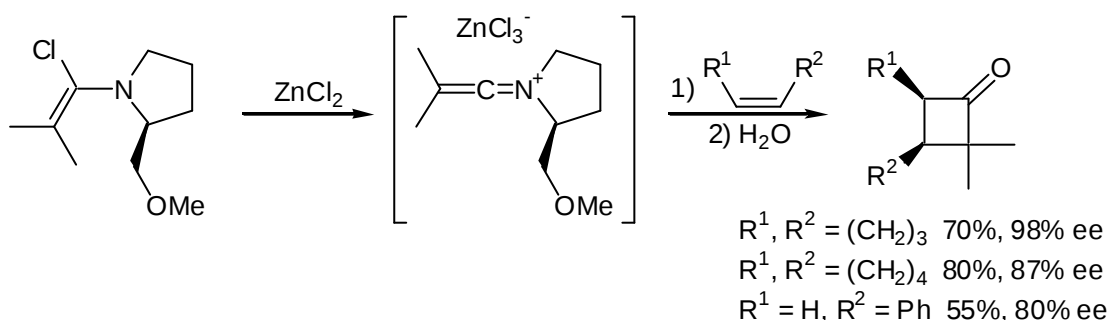
³⁴ Ghosez, L.; Chen, L.-Y.; Gobeaux, B.; Houge, C.; Markó, I. E.; Perry, M.; Saimoto, H., *Strain and its Implication in Organic Chemistry*; Kluwer Academic Publishers, 1989.

Asymmetric [2+2] cycloadditions have also been effected in the presence of chiral Lewis acids. The cycloaddition between a ketene thioacetal and an electrophilic olefin catalyzed by a chiral titanium complex proceeded with excellent enantioselectivities (scheme 13)³⁵. However the scope of the reaction appears quite limited.



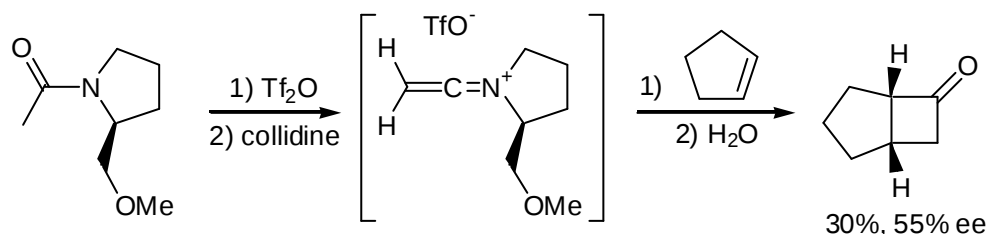
Scheme 13

The most efficient method for the preparation of non-racemic cyclobutanones uses chiral keteniminium salts. Houge *et al.* have shown that proline derived keto-keteniminium salts could be reacted with olefins to yield cyclobutanones in good yield and in good enantioselectivities (scheme 14).³⁶



Scheme 14

Enantioselectivities were lower with aldo-keteniminium salts or with terminal olefins (scheme 15).



Scheme 15

³⁵ Ichikawa, Y.-i.; Narita, A.; Shiozawa, A.; Hayashi, Y.; Narasaka, K. *J. Chem. Soc., Chem. Commun.*, **1989**, 1919-1921.

³⁶ Houge, C.; Frisque-Hesbain, A.-M.; Mockel, A.; Ghosez, L. *J. Am. Chem. Soc.*, **1982**, 104, 2920.

The C_1 symmetry of the chiral inductor could explain the lack of selectivity. It could indeed lead to the formation of two diastereomeric keteniminium salts (figure 6).

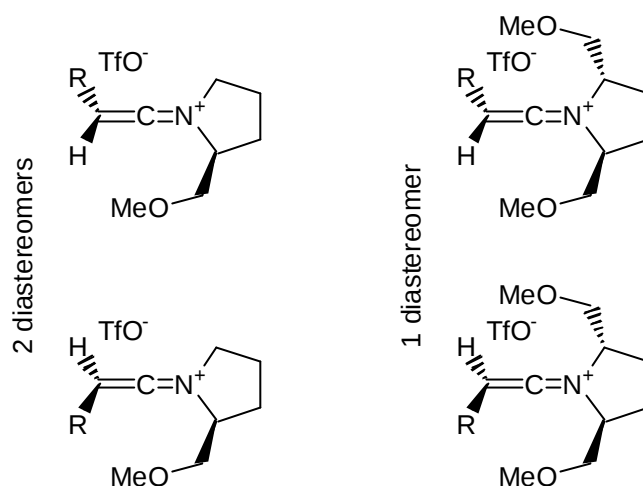
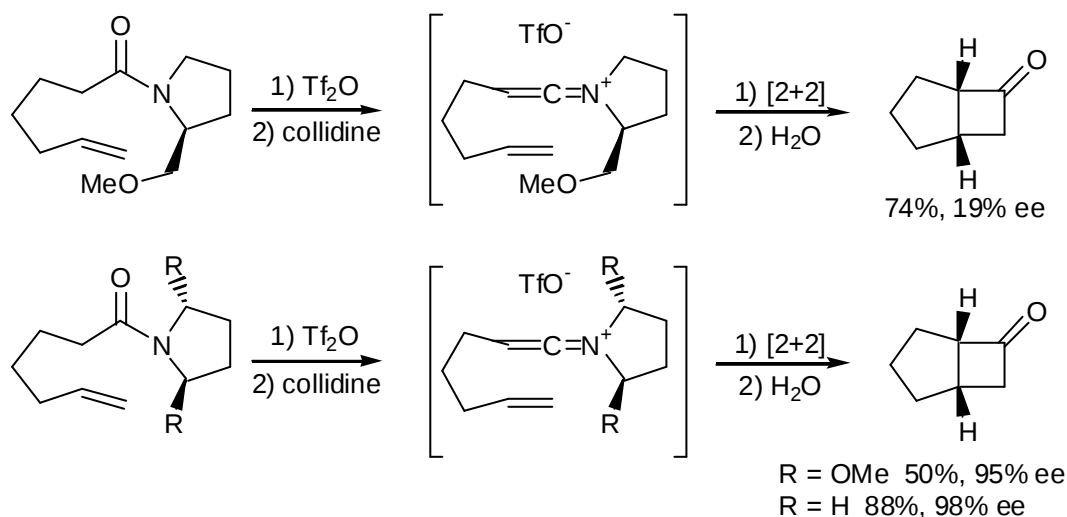


Figure 6

This hypothesis had been confirmed by Chen who showed that an intramolecular cycloaddition proceeded with low enantioselectivities when a C_1 symmetric inductor was used. Good enantioselectivities were obtained with a C_2 symmetric inductor (scheme 16).³⁷



Scheme 16

It has however been recently shown that in some cases even inductors with C_1 symmetry also led to high enantioselectivities.^{38,39} Indeed, J.-M. Adam, L. Ghosez

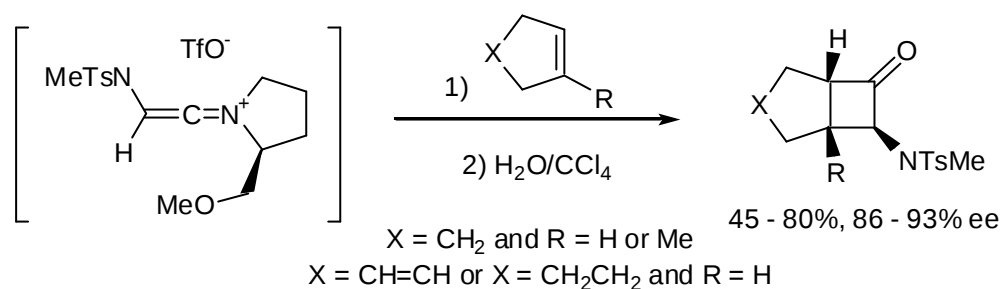
³⁷ Chen, L.-y.; Ghosez, L. *Tetrahedron Lett.*, **1990**, 31, 4467-4470.

³⁸ Cordier, J.-F. *Master Degree UCL-ORSY*, **1991**

³⁹ Genicot, C. *PhD-Thesis UCL-ORSY*, **1993**

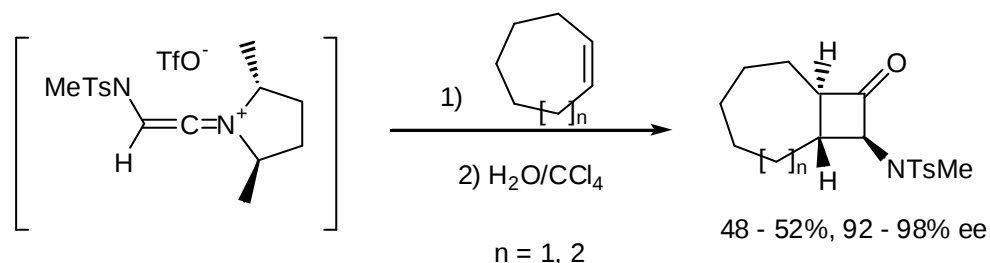
and K. Houk have shown by ab initio calculations that both diastereomers could lead preferentially to the same cycloadduct.⁴⁰

This [2+2] cycloaddition method followed by a ring expansion has been applied by F. Mahuteau for the synthesis of five-membered carbon rings. She has shown that α -*N*-methyl-*N*-tosylketeniminium salts derived from chiral pyrrolidines allowed to obtain good enantioselectivities in the cycloaddition with cyclic olefins.^{41,42} When the olefin was a 5 or 6 membered ring a chiral inductor of C_1 symmetry gave the best results (scheme 17).



Scheme 17

However with larger ring olefins a chiral inductor of C_2 symmetry gave the best results (scheme 18). In this case, the geometry of the ring junction was *trans*, as a result of an epimerization under the reaction conditions.



Scheme 18

The ring expansion was performed in two steps.⁴³ Firstly the cyclobutanone was treated with dimethylsulfonium methylide to yield diastereomeric mixture of the oxirane. Refluxing the oxirane in the presence of lithium iodide initiated the rearrangement to the cyclopentenone which was obtained as a single enantiomer with the same enantiomeric purity than the corresponding cyclobutanone (scheme

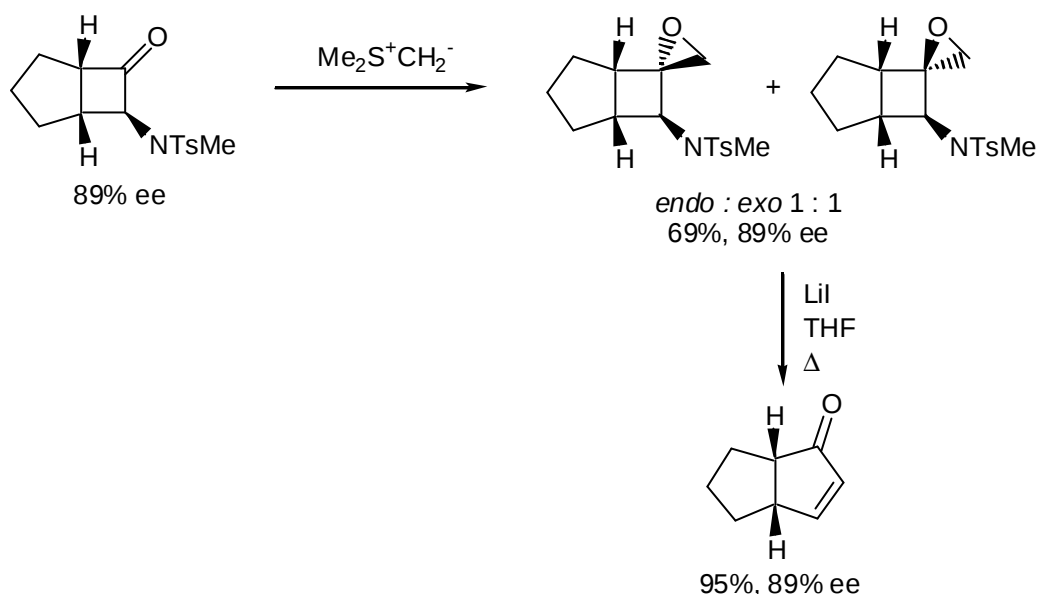
⁴⁰ Adam, J.-M. *PhD-Thesis UCL-ORSY*, **2000**

⁴¹ Ghosez, L.; Mahuteau-Betzer, F.; Genicot, C.; Vallribera, A.; Cordier, J.-F. *Chem. Eur. J.*, **2002**, 8, 3411-3422.

⁴² Mahuteau-Betzer, F. *PhD-Thesis UCL-ORSY*, **2001**

⁴³ Mahuteau-Betzer, F.; Ghosez, L. *Tetrahedron*, **2002**, 58, 6991-7000.

19). The presence of the NTsMe was crucial for the regioselectivity of the ring expansion as a result of its electron-releasing properties.

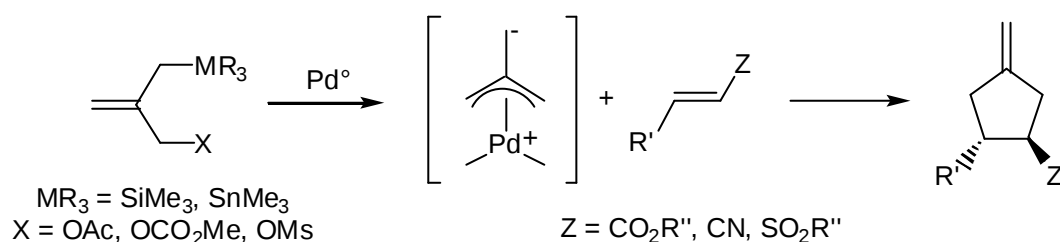


Scheme 19

2.2.3 [3+2] cyclopentannulation reactions

2.2.3.a Trimethylenemethane equivalents

The chemistry of trimethylenemethane (TMM) has been studied in detail by Trost.^{12,44,45} Equivalents of TMM are zwitterionic 3 carbon synthons. They react with electron-poor olefins in the presence of a palladium catalyst (scheme 20).



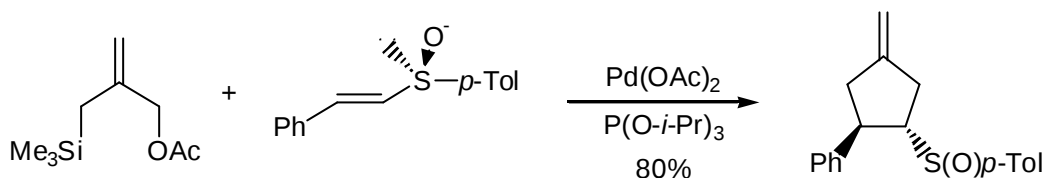
Scheme 20

Asymmetric versions of this reaction have been carried out using chiral olefins. Good diastereoisomeric excesses were obtained in the cycloaddition of TMM to chiral vinylsulfoxides (scheme 21).⁴⁶

⁴⁴ Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.*, **1979**, *101*, 6429-6432.

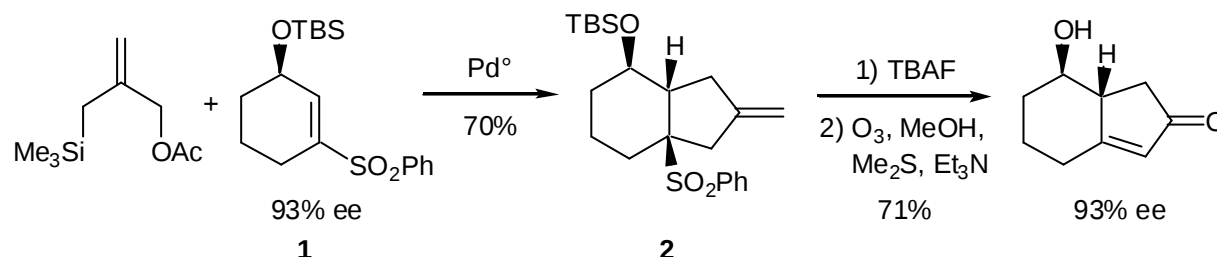
⁴⁵ Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.*, **1979**, *101*, 6432-6433.

⁴⁶ Chaigne, F.; Gotteland, J.-P.; Malacria, M. *Tetrahedron Lett.*, **1989**, *30*, 1803-1806.

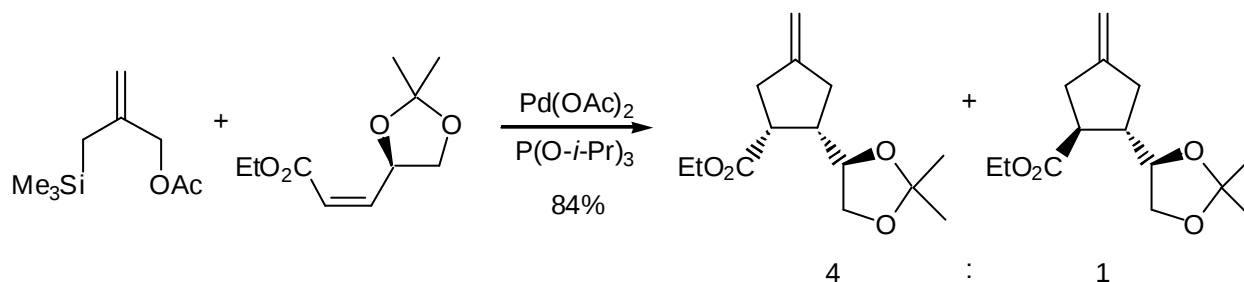


Scheme 21

The use of a chiral cyclohexenyl sulfone **1** led to a single enantiomer of compound **2** (scheme 22).⁴⁷ However with a less rigid chiral olefin the selectivity dropped to 4:1 (scheme 22).⁴⁸



Trost, 1989



Samuelson, 1993

Scheme 22

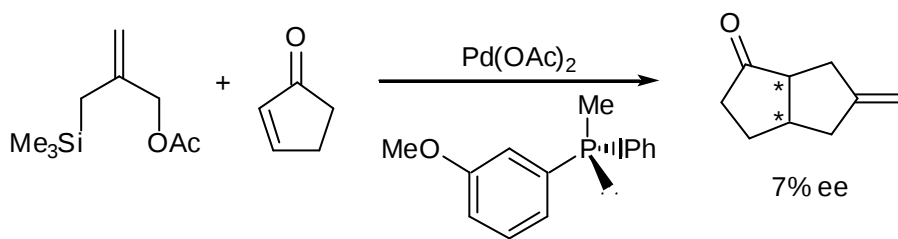
The method is not of general applicability since the chiral information was on the olefin and not on the reagent.

An attractive possibility for an asymmetric version of this reaction is the use of a chiral ligand on the palladium catalyst. The first examples of this strategy have been reported by Trost.⁴⁹ A chiral phosphine was used but enantiomeric excesses remained steadily low (scheme 23).

⁴⁷ Trost, B. M.; Seoane, P.; Mignani, S.; Acemoglu, M. *J. Am. Chem. Soc.*, **1989**, *111*, 7487-7500.

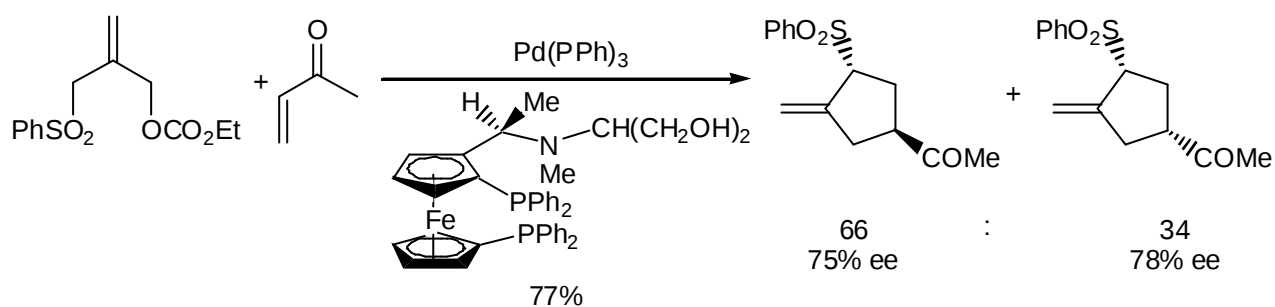
⁴⁸ Janson, M.; Kvarnström, I.; Svensson, S. C. T.; Classon, B.; Samuelsson, B. *Synthesis*, **1993**, 129-133.

⁴⁹ Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.*, **1983**, *105*, 2326-2335.



Scheme 23

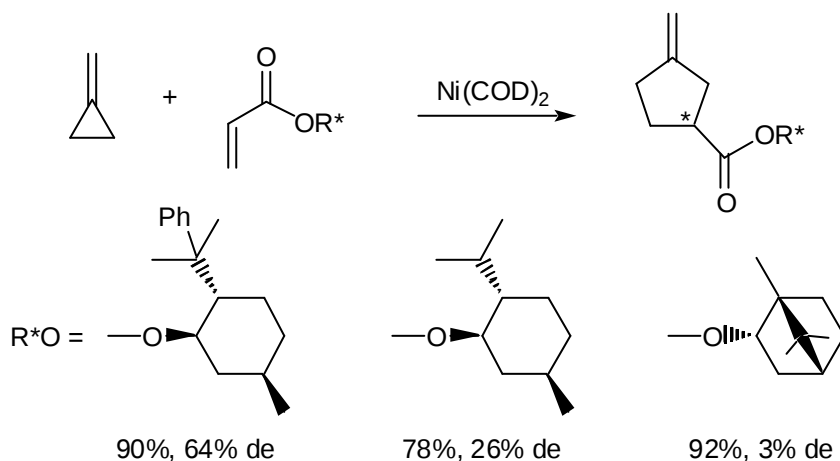
Chiral ferrocenyl diphosphines gave enantiomeric excesses up to 78% ee (scheme 24).⁵⁰



Scheme 25

2.2.3.b Methylenecyclopropanes

Methylenecyclopropane can be used as a 3-carbon synthon for [3+2] annulation reactions catalyzed by bis(cycloocta-1,5-diene)nickel. As shown by Binger, the use of a chiral electron-poor olefin gave bad to modest diastereoselectivities (scheme 26).⁵¹

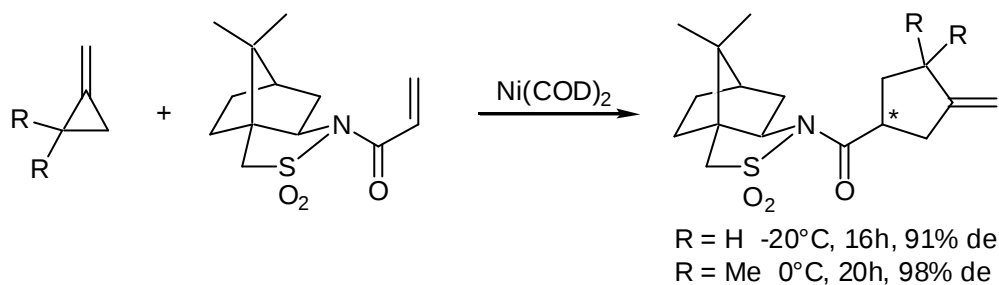


Scheme 26

⁵⁰ Yamamoto, A.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.*, **1989**, 30, 375-378.

⁵¹ Binger, P.; Brinkmann, A.; Richter, W. J. *Tetrahedron Lett.*, **1983**, 24, 3599-3602.

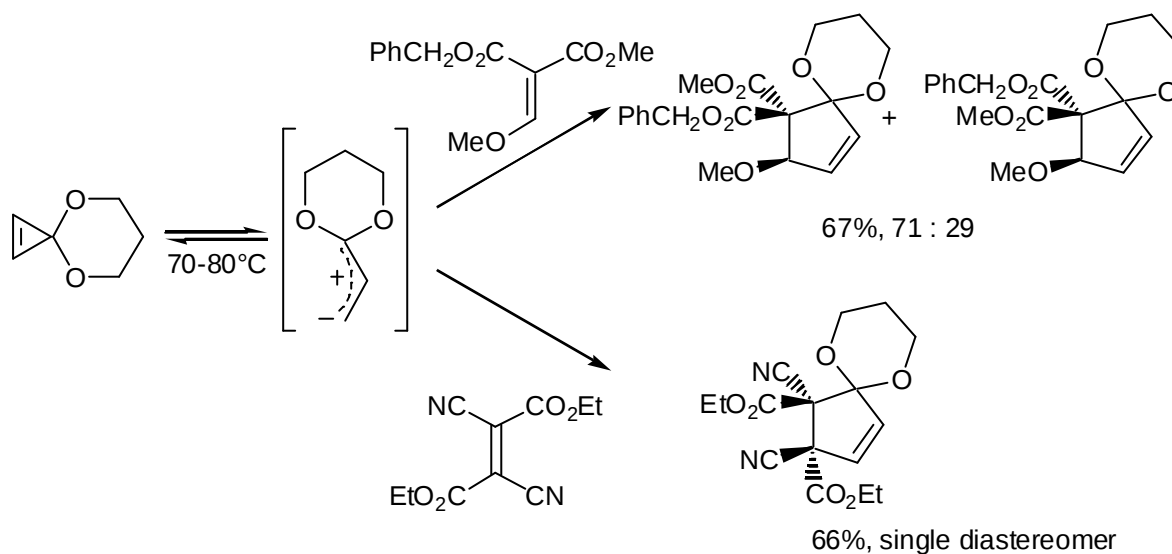
However, the stereoselectivity was significantly higher when the olefin compound was (-)-camphorsultamacrylate (scheme 27).⁵²



Scheme 27

2.2.3.c Cyclopropene ketals

Cyclopropene ketals are another family of interesting 3 carbon synthons. Whereas the reaction with olefins bearing two geminal electron-withdrawing groups showed modest diastereoselectivity, addition to 2,3-dicyanofumarate esters was stereospecific (scheme 28).⁵³



Scheme 28

However to the best of our knowledge, no enantioselective version of this method has been described.

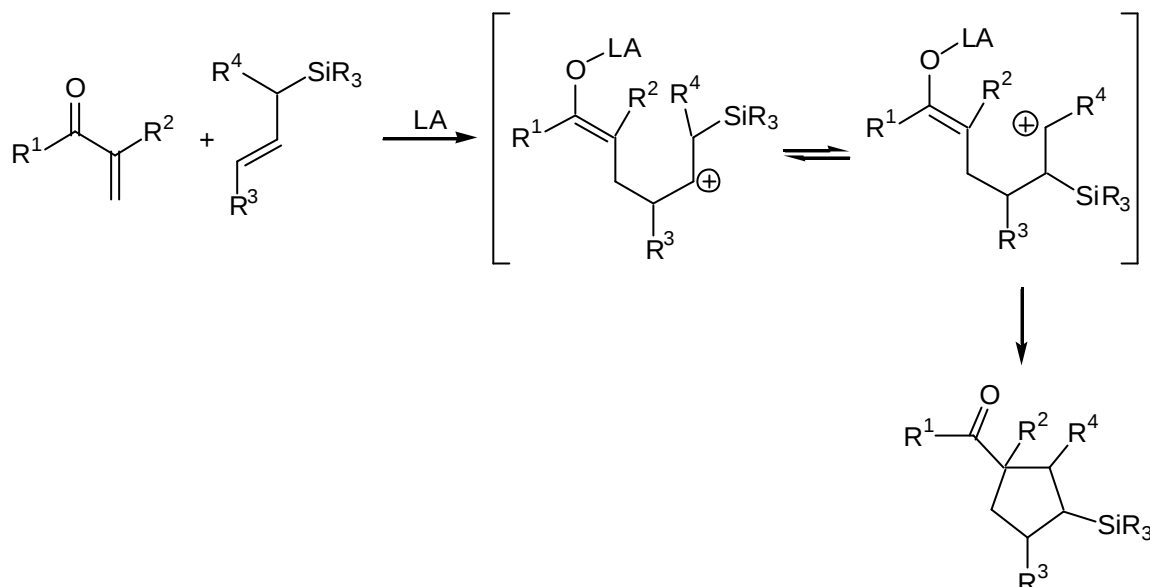
2.2.3.d Allylsilanes

Allylsilanes are another class of interesting synthons for the [3+2] annulation reaction. In the presence of a Lewis acid, they add to enones or enals (scheme 29).

⁵² Binger, P.; Schaefer, B. *Tetrahedron Lett.*, **1988**, 29, 529-530.

⁵³ Boger, D. L.; Wysocki, R. J. *J. Org. Chem.*, **1988**, 53, 3408-3421.

The conjugate addition is followed by a 1,2-migration of the silyl group. The newly formed carbocation reacts with the enolate to form the five-membered ring.



Scheme 29

The group of Panek has described an asymmetric version of this method which used chiral allylsilanes (table 1).⁵⁴ In most cases the ratio of diastereoisomers was better than 30 : 1.

Table 1: [3+2] cycloaddition with allylsilanes.⁵⁴

The reaction scheme shows the [3+2] cycloaddition of a chiral allylsilane (with substituents R¹, R², and a CO₂Me group) with a ketone (R³-C(=O)-CH=CH₂). The reaction conditions are 2 eq. BF₃·Et₂O in CH₂Cl₂ at room temperature (RT). The product is a cyclopentane derivative with a silyl group (PhMe₂Si) and a carbonyl group (COR⁴).

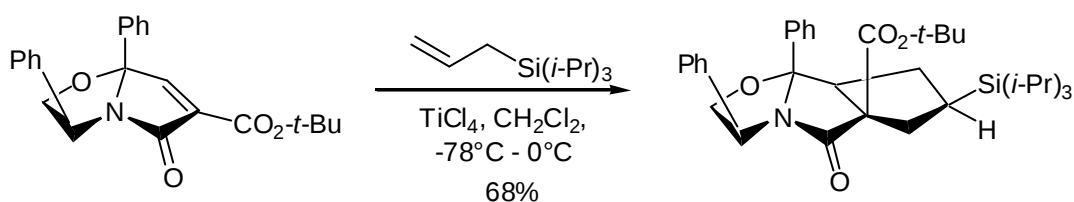
R ¹	R ²	R ³	R ⁴	Yield	dr
H	H	Me	H	93%	> 30 : 1
H	OMe	Me	H	73%	> 30 : 1
Me	H	Me	H	65%	> 30 : 1
H	OMe	H	H	62%	> 30 : 1
H	H	H	Me	56%	6 : 1

One should note an inversion of the absolute configuration at carbon C-2. Thus, in the cyclopentane product, the silyl group and the carbonyl were *trans*, whereas the methylene bearing the methylic ester was *cis* to the carbonyl group.

⁵⁴ Panek, J. S.; Jain, N. F. *J. Org. Chem.*, **1993**, 58, 2345-2348.

The major drawback of this method is the difficulty to synthesize enantiomerically pure allylsilanes. These compounds could be obtained in high optical purity only in a few cases: 93% ee when $R_1 = R_2 = H$ and 96% ee when $R_1 = Me$ and $R_2 = H$.⁵⁴

This methodology could also be applied to a chiral olefin. Meyers *et al.* used a chiral α,β -unsaturated lactam as an acceptor and obtained the cyclopentane with good yield and complete diastereoselectivity (scheme 30).⁵⁵



Scheme 30

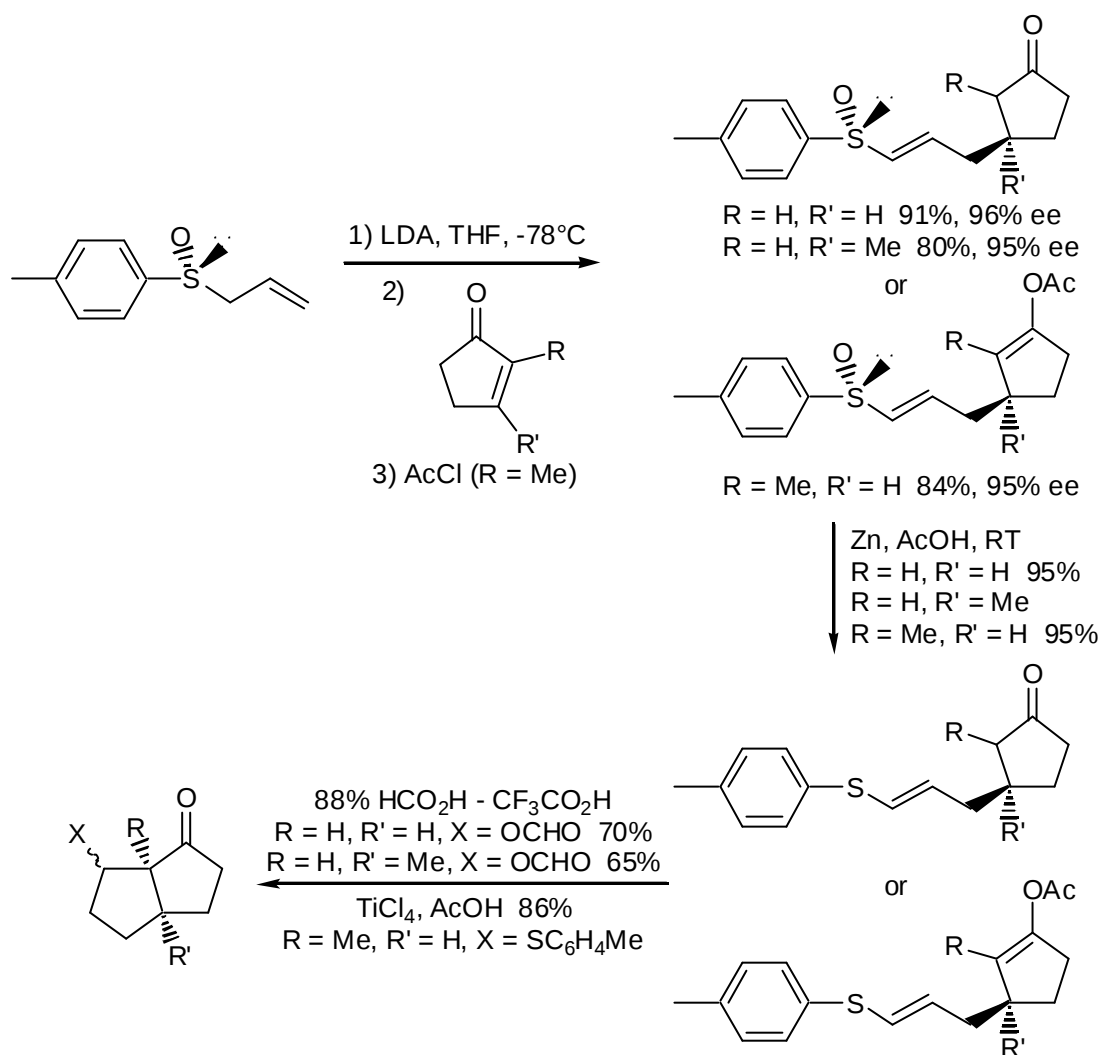
2.2.3.e Allylic sulfoxides

Some 20 years ago Hua, studied the regio- and the stereochemistry of the addition of carbanions derived from chiral allylic sulfoxides to various cyclic enones. A highly diastereoselective cyclopentannulation sequence was developed based on this study.⁵⁶

The pentannulation sequence was realized in 3 steps (scheme 31): the first one was the conjugate addition of the allylic sulfoxide where the intermediate enolate was trapped with acetyl chloride, the sulfoxide was then reduced and finally the cyclization occurred by the use of a Lewis acid.⁵⁶

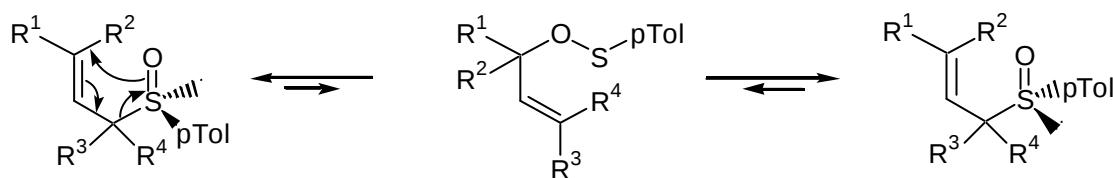
⁵⁵ Brengel, G. P.; Rithner, C.; Meyers, A. I. *J. Org. Chem.*, **1994**, 59, 5144-5146.

⁵⁶ Hua, D. H.; Venkataraman, S.; Coulter, M. J.; Sinai-Zingde, G. *J. Org. Chem.*, **1987**, 52, 719-728.



Scheme 31

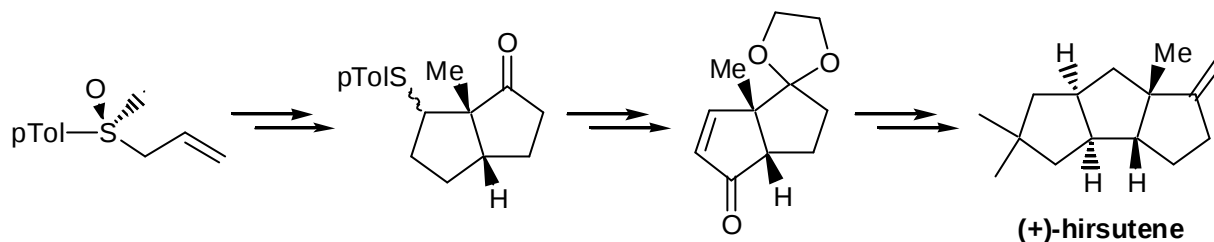
There remains however a drawback. Allylic sulfoxides easily undergo racemization by a reversible [2,3] sigmatropic rearrangement (scheme 32).⁵⁷ Only the unsubstituted sulfoxide ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$) showed configurational stability when handled at low temperature.



Scheme 32

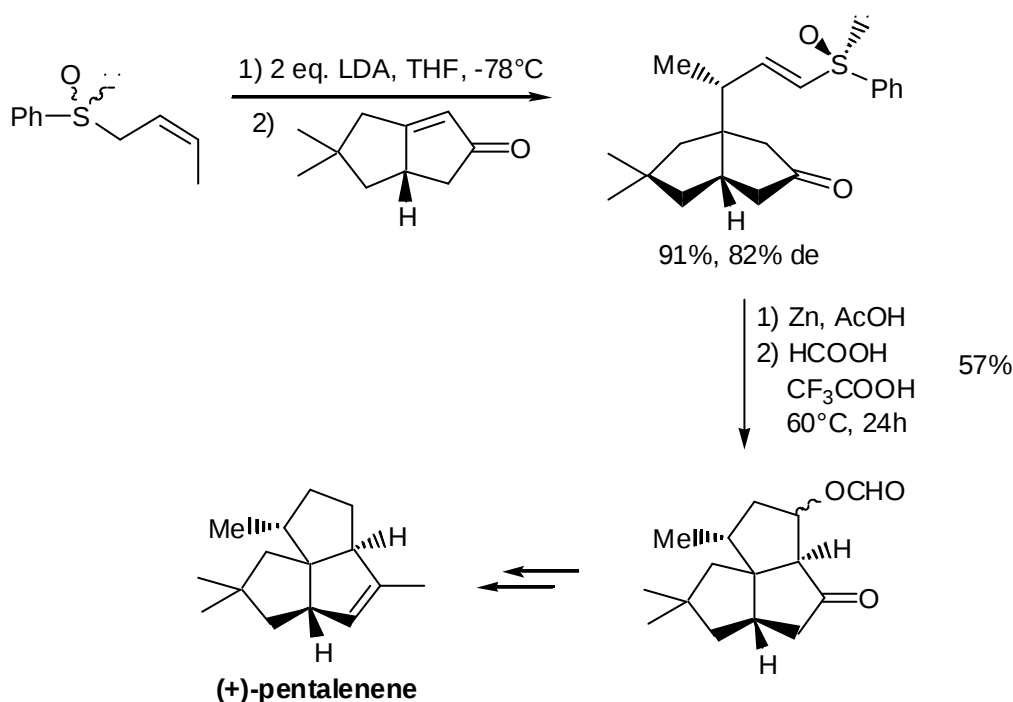
⁵⁷ Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.*, **1974**, 7, 147-155.

Nevertheless this strategy could be successfully applied to the synthesis of (+)-hirsutene, a precursor of biologically active linear polyquinanes (scheme 33).⁵⁸



Scheme 33

In order to circumvent the problem of racemization of the sulfoxide, the same group had adopted the alternative strategy of using a chiral enone with a racemic sulfoxide.⁵⁹ (+)-pentalenene could be synthesized in 82% de by this method (scheme 34).

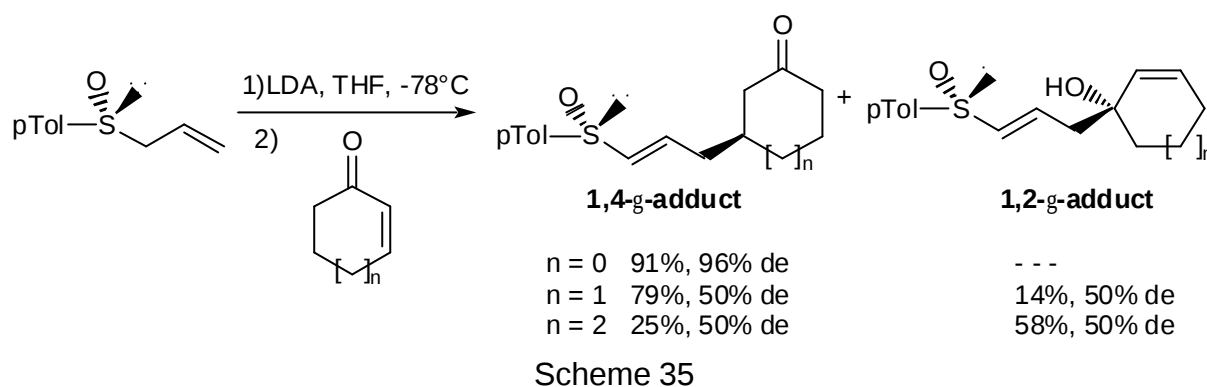


Scheme 34

Whereas the reaction with cyclopentenones was completely regioselective, Hua has shown that the addition to cyclohexenone and cycloheptenone resulted in the formation of a mixture of 1,4- γ -adduct and 1,2- γ -adduct.⁵⁶ Moreover, diastereoselectivity was considerably lower than with cyclopentenones (scheme 35). These results limit the scope of the method.

⁵⁸ Hua, D. H.; Venkataraman, S.; Ostrander, R. A.; Sinai-Zingde, G.; McCann, P. J.; Coulter, M. J.; Xu, M. R. *J. Org. Chem.*, **1988**, 53, 507-515.

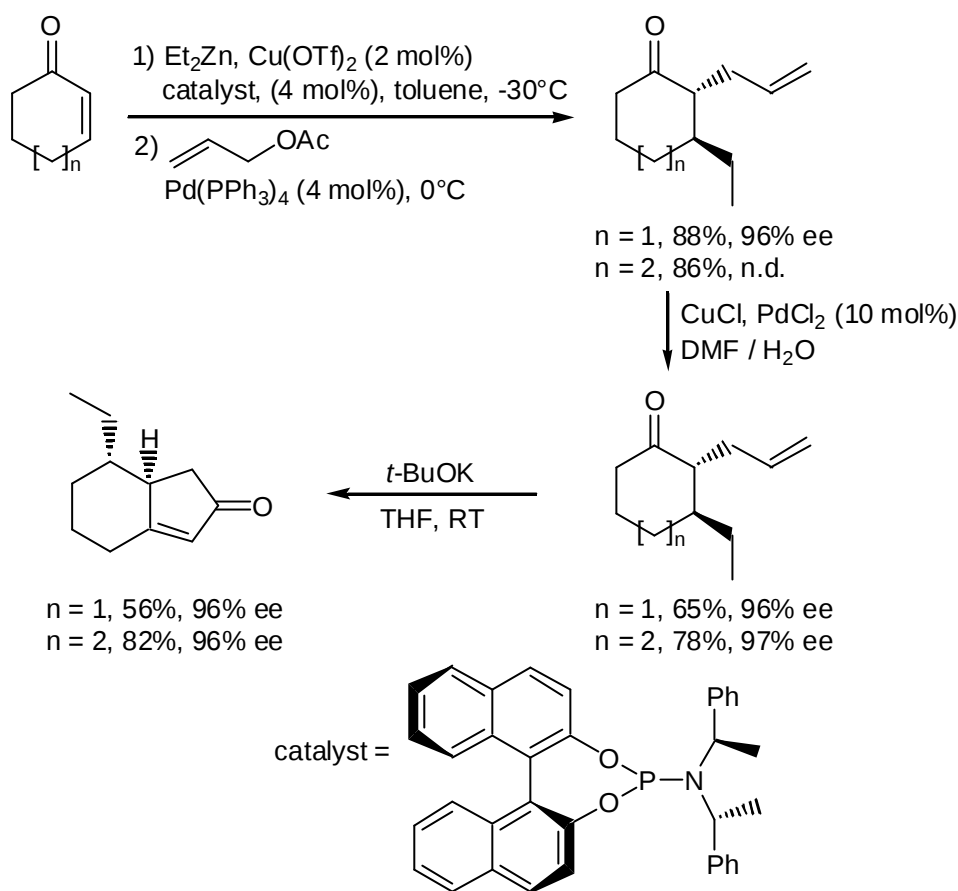
⁵⁹ Hua, D. H. *J. Am. Chem. Soc.*, **1986**, 108, 3835-3837.



2.2.3.f 1,4-addition – aldol cyclization

More recently Feringa developed an asymmetric synthesis of five-membered rings based on an asymmetric Michael addition followed by an aldol cyclization.⁶⁰ Diethylzinc was added to a cyclic enone in the presence of a catalytic amount of a copper salt and a chiral phosphorus amidite ligand (scheme 36). The resulting zinc enolate was reacted with allyl acetate in the presence of a palladium catalyst. After Wacker oxidation of the alkene, aldol cyclization led to the cyclopentenone with excellent enantioselectivities.

⁶⁰ Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.*, **1999**, *121*, 1104-1105.



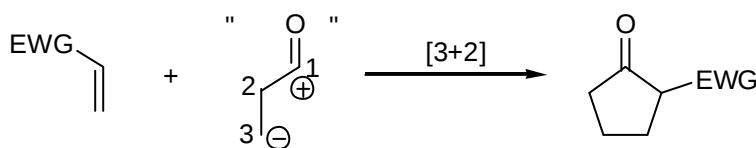
Scheme 36

3 Previous work of our laboratory

A [3+2] strategy for cyclopentannulation has also been thoroughly investigated in our laboratory.

3.1 Concept

For the [3+2] cycloaddition approach an olefin bearing an electron-withdrawing group was chosen as the 2-carbon synthon. The 3-carbon synthon was a homoenolate equivalent, which we will call the annulation reagent. This reagent bears a nucleophilic center at carbon C-3 and an electrophilic center at carbon C-1 (scheme 37).



Scheme 37

Enones were chosen as good candidates for the 2-carbon synthons. Methyl phenylsulfonyl-3-orthopropionate **3** (figure 7) could play the role of the 3-carbon synthon. It has a potential carbanionic center stabilized by the sulfone and a masked cationic center due to the presence of the orthoester function. The use of a carbonyl group as cationic center was excluded due to a competitive enolization reaction upon the formation of the anion.

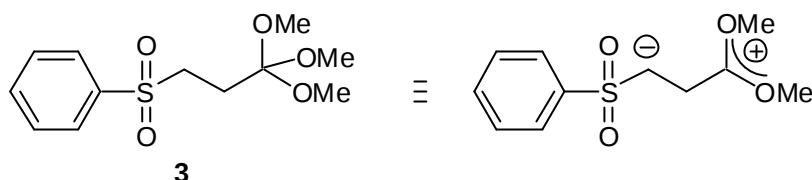
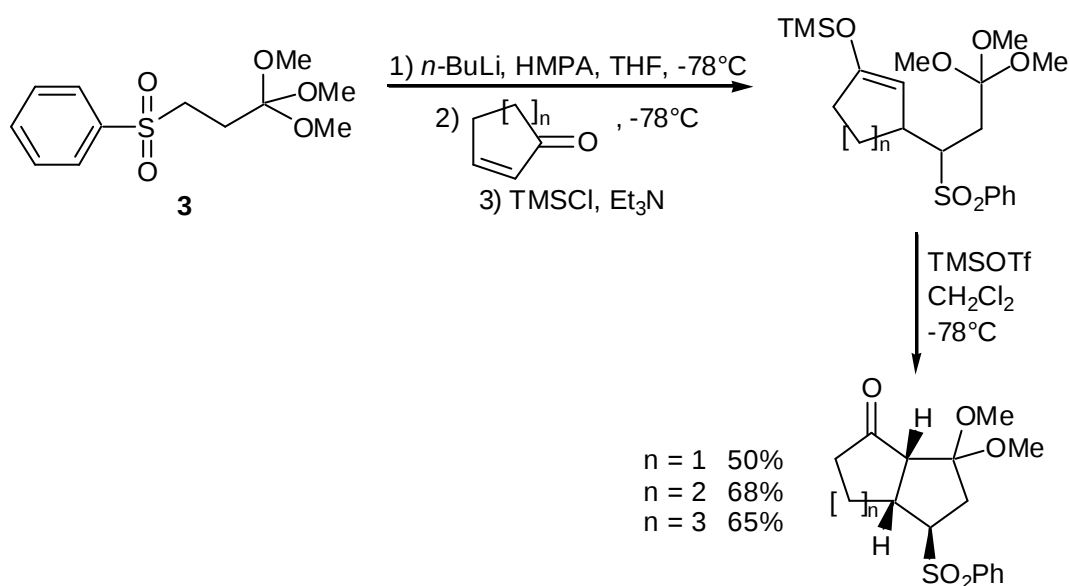


Figure 7

3.2 Cyclopentannulation reactions

Cyclopentannulation reactions have been made with reagent **3**.⁶¹ In a first step, the carbanion formed by the reaction with *n*-butyllithium was added to a cyclic enone in the presence of HMPA. The resulting enolate was trapped as a silylated enol ether. Intramolecular Mukayama aldol reaction was effected in the presence of a catalytic amount of Lewis acid (scheme 38).



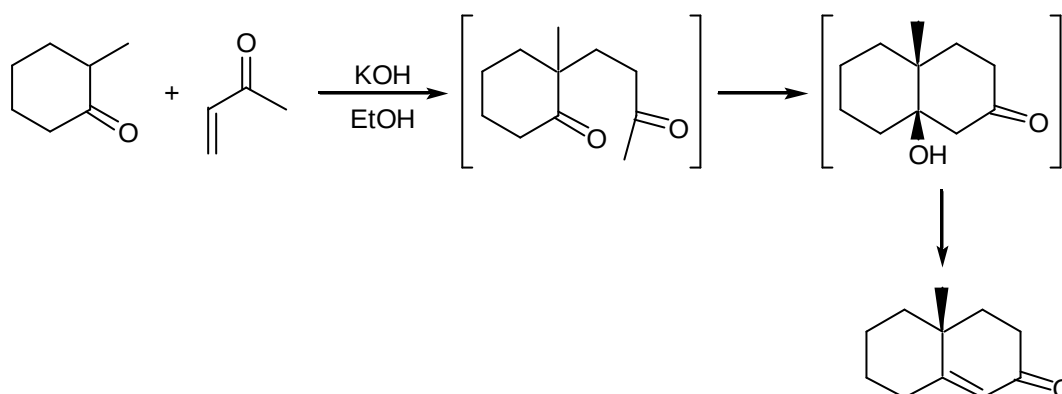
Scheme 38

Some important points should be noted. The synthesis of **3** is straightforward and can be realized on a kilogram scale. Hexamethylphosphoramide (HMPA) or *N,N'*-dimethylpropyleneurea (DMPU) was needed for a complete regioselectivity of

⁶¹ Roekens, B. *Master Degree UCL-ORSY*, **1985**

the Michael additon. The geometry of the ring junction was *cis* in practically all cases. Moreover the phenylsulfonyl group was mainly in the *exo* position. Finally the bicyclic compound bears two carbonyl functions that are differentiated. This is a useful point for further modifications of the compound.

Conceptually, this cyclopentannulation sequence can be compared to the Robinson annulation⁶² used for the construction of six-membered rings (scheme 39). A Michael addition followed by an intramolecular aldol reaction leads to the six-membered ring.



Scheme 39

The scope and limitation of the method have been studied.⁶³⁻⁶⁵ It has been shown that cyclic enones from 5 to 8 carbons can be used. Substitution at carbon atom C-2, C-4, and C-5 did not influence the reaction. However a substituent at carbon atom C-3 resulted in a complete inhibition of the 1,4-addition. The nature of the orthoester function could be varied (-C(OMe)₃, -C(OEt)₃, -C(O-*n*-Pr)₃ and -C(OEt)(OCH₂)₂).

These successful results prompted our group to study the possibility of developing an asymmetric version of the annulation reagent.

⁶² for a review see Jung, M. E. *Tetrahedron*, **1976**, 32, 3-31.

⁶³ Demillequand, M. *PhD-Thesis UCL-ORSY*, **1993**

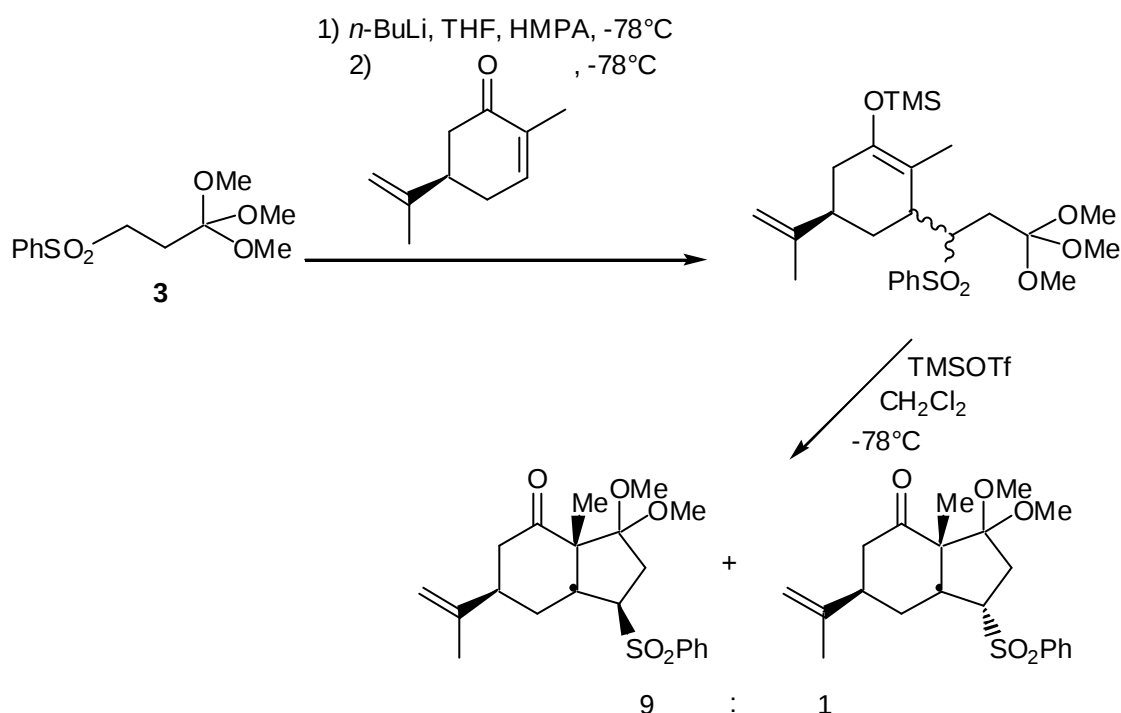
⁶⁴ Nemery, I. *PhD-Thesis UCL-ORSY*, **1991**

⁶⁵ Kallah, B. *On-going PhD-Thesis UCL-ORSY*,

3.3 A new approach to an asymmetric cyclopentannulation reaction

3.3.1 Chiral enones

M. Demillequand has briefly studied the use of chiral enones.⁶³ The addition of **3** to the commercially available optically pure *R*-(-)-carvone resulted in the formation of a 9 : 1 mixture of diastereomers. Both compounds resulted from an attack of the reagent *anti* to the isopropenyl group of the carvone (scheme 40). Both isomers had a *cis* ring-fusion. They differed by the stereochemistry of the phenylsulfonyl group which was *exo* in the major isomer.



Scheme 40

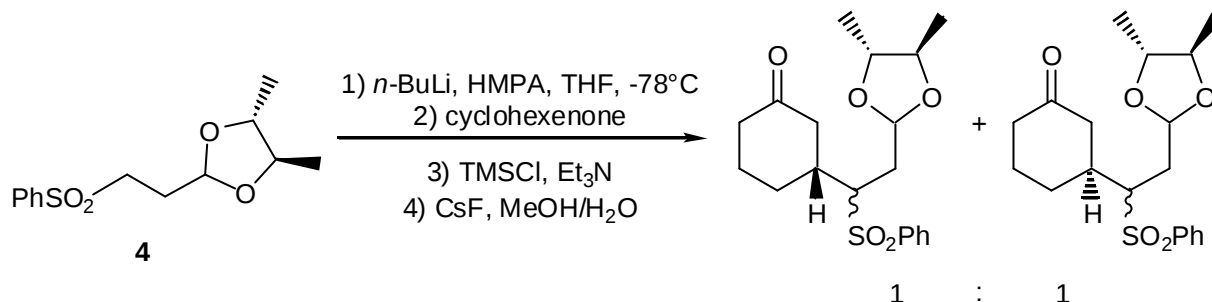
This approach should be very interesting when the enantiomerically pure enone is readily available.

3.3.2 Chiral homoenolates

A strategy with a potential broader scope uses a chiral homoenolate equivalent. Two sites are possible for introducing the chiral information: the electron-withdrawing group or the orthoester function.

3.3.2.a A chiral masked cation

I. Nemery studied the Michael addition of a chiral analogue of **3** where the orthoester function had been replaced by a chiral ketal.⁶⁴ Complexation of the lithium counter-ion by the ketal could be imagined to induce asymmetry in the addition product. Results however were disappointing: the addition of the chiral ketal **4** resulted in the formation of a mixture of 2 diastereomers in a 1 : 1 ratio (scheme 41).



Scheme 41

3.3.2.b A chiral electron-withdrawing group

Different possibilities were offered for the introduction of a chiral electron-withdrawing group. One could introduce a chiral sulfur atom or one could replace the phenyl substituent by a chiral group and thus keep the sulfone.

The use of chiral sulfoxides or chiral sulfoximines was studied by I. Nemery.⁶⁴ Chiral sulfoxides are easily accessible⁶⁶, and a potential annulation reagent **5** was synthesized in our laboratory (figure 8). However the addition of this compound to a Michael acceptor was not regioselective. The major compound was the 1,2-adduct.

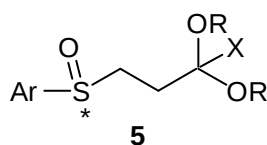
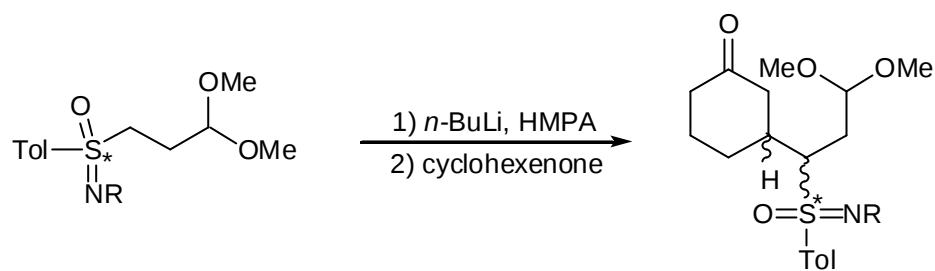


Figure 8

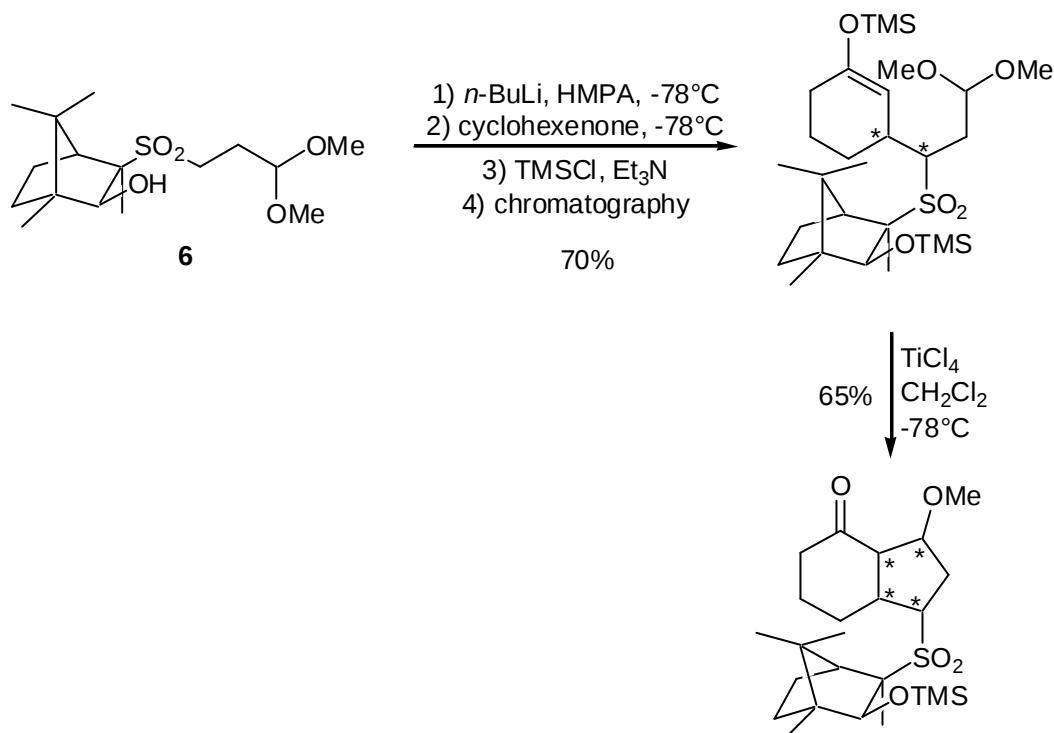
On the other hand, sulfoximines added with complete regioselectivity to enones. But the adduct was obtained as a mixture of 4 diastereoisomers, whatever the sulfoximine used (table 2).

⁶⁶ Kagan, H. B., *Oxidation of hetero atoms: asymmetric oxidation of sulfides and selenides*, in *Asymmetric Oxidation Reactions* (2001), Katsuki, T., Editor. Oxford University Press: Oxford, UK. 2001, p. 153-170.

Table 2: Michael addition of chiral sulfoximines.⁶⁴


R	Yield	d.r.
Me	95%	28 : 26 : 22 : 24
SiMePh ₂	80%	17 : 7 : 59 : 17
Si(<i>i</i> -Pr) ₃	92%	24 : 3 : 60 : 13

The last point that had been studied in our laboratory was the replacement of the phenyl by a chiral group. Sulfone **6** bearing a camphor derivative as chiral inductor was synthesized.⁶⁷ This compound could be added to cyclohexenone with good diastereoselectivity (>85% de). The Mukayama aldol reaction was realized with titanium tetrachloride (scheme 42). The ring fusion was *cis*, however the position of the methoxy group could not be controlled.

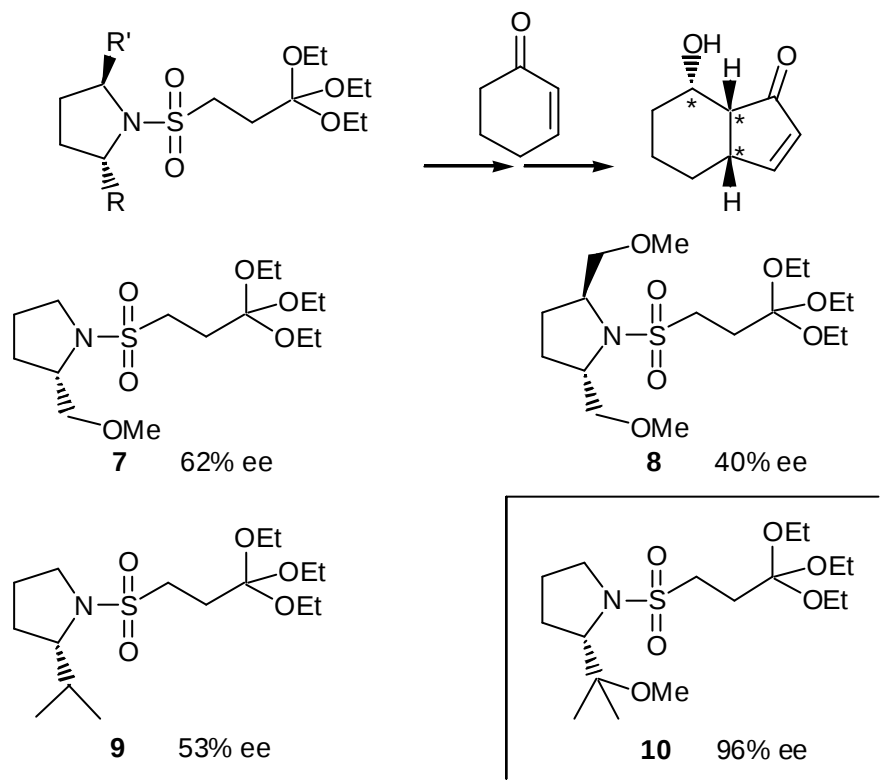


Scheme 42

⁶⁷ Huart, C. *PhD-Thesis UCL-ORSY*, 1995

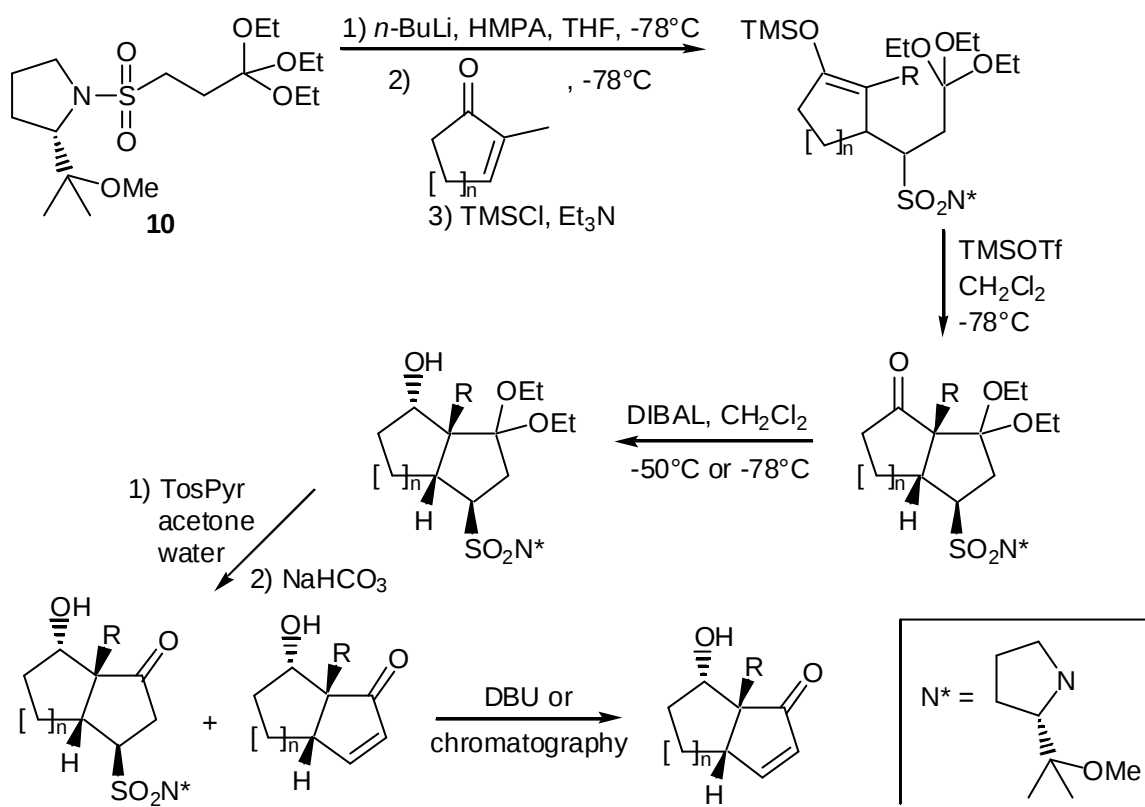
The major drawback was the cleavage of the chiral inductor. It was extremely difficult to remove. Also the synthesis of the chiral auxiliary was tedious.

The phenyl could also be replaced by a chiral amine. A series of chiral pyrrolidines and their corresponding annulation reagents have been synthesized by C. Huart. All of these compounds have been successfully used as annulation reagents. The stereoselectivity varied from modest to excellent, depending on the chiral inductor (scheme 43).⁶⁷



Scheme 43

Slight changes in the structure of the annulation reagent resulted in important variations of the stereoselectivity. The best annulation reagent **10** was applied for the pentannulation sequence of various cyclic enones. In all the cases, the selectivities were excellent (scheme 44 and table 3).



Scheme 44

Table 3: Cyclopentannulation with **10**.⁶⁸

n	R	Yield	ee
1	H	33%	92%
2	H	48%	96%
3	H	33%	98%
2	Me	48%	95%

3.4 Aims of this work

A powerful tool for the asymmetric synthesis of five-membered rings had been developed by C. Huart and L. Ghosez.⁶⁸ Total yields were good and enantioselectivities were excellent. Some points however remained unclear at the end of the work of C. Huart.

- The high enantioselectivities observed were unexplained. A transition state had been proposed to account for the observed stereochemistry but it did not take into account the presence of HMPA. As HMPA is a strong ligand for lithium, one could expect that at least one molecule would be present at the transition state.

⁶⁸ Huart, C.; Ghosez, L. *Angew. Chem. Int. Ed. Engl.*, **1997**, 36, 634-635.

- All the annulation reactions were realized on cyclic enones. No data was available about the use of other Michael acceptors in this sequence.

A first part of this work will be devoted to find answers to these questions. To explain the enantioselectivities we will realize a detailed study of the Michael addition. The stereochemistry of the final product is indeed fixed at this stage. For this reason we propose to synthesize a series of sulfonamides and to study their addition to enones in order to get a deeper insight on the parameters governing this reaction.

We would also like to investigate the scope and limitations of the reaction by using other Michael acceptors than cyclic enones. Acyclic enones, unsaturated lactones and lactams would constitute an interesting target.

In a second part we will try to develop alternative pathways for the cyclopentannulation sequence. The sulfonamide-based sequence necessitates indeed the highly toxic HMPA, which we would like to remove from the procedure. For that reason we are interested in developing another chiral inductor or a catalytic method to realize the annulation. The main objective would be to end up with a powerful and easily generalizable method, that could compete with the sulfonamide-based method.