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Asymmetric cyclopentannulation reactions: scope and limitation

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par **Patrick SCHANEN**

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to my parents,
to Isabelle and Louis

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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 énones.

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 énones 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-methylnaphthyl, se sont révélés comme candidats intéressants pour la catalyse par transfert de phase.

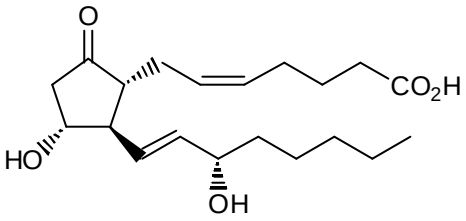
La catalyse organique a constitué notre deuxième approche. L'utilisation de prolinate de rubidium ou de proline en présence d'une base s'est montrée très efficace et les adduits de Michael ont pu être obtenus avec de bonnes énantiosélectivités. Les adduits de Michael ont pu être facilement cyclisés et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

Introduction: Asymmetric cyclopentannulation reactions

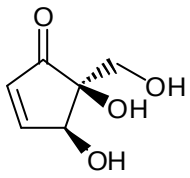
1 Five-membered rings: synthetic importance

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 PGE_2 intervenes in the aggregation of blood platelets, the relaxation of smooth muscles and also shows anti-inflammatory activity (figure 1).

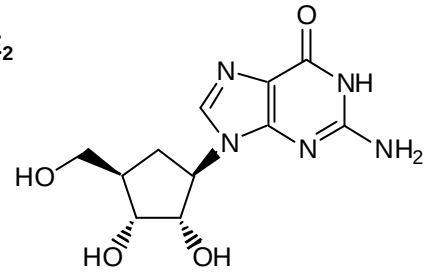
Several antibiotics, such as (-)-pentenomycin[2] and (-)-aristeromycin[3] (figure 1) are five-membered ring derived compounds.



PGE_2



(-)-pentenomycin I

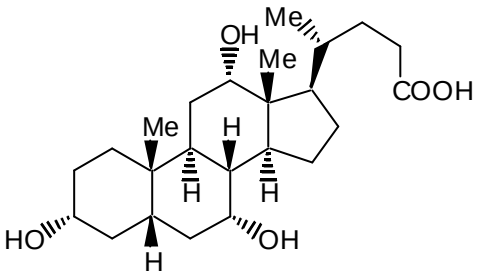


(-)-aristeromycin

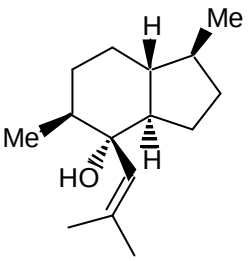
Figure 1

[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, (-)-tamariscol[5], has a pleasant odor and is exploited industrially (figure 2).



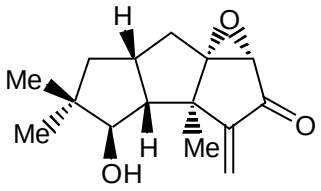
cholic acid



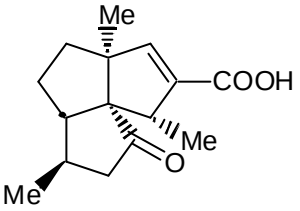
(-)-tamariscol

Figure 2

The triquinane family contains three fused five-membered rings. (-)-Hypnophilin[6], 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]



(-)-hypnophilin

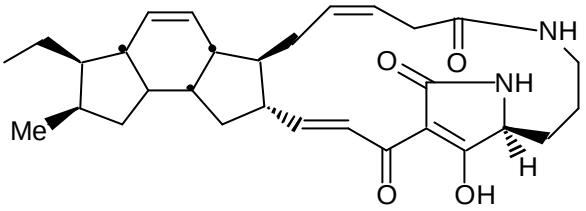


subergorgic acid

Figure 3

Other more complex polycyclic antibiotics, such as (+)-ikarugamycin[10], (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 Ramaiah[11], Trost[12], Hudlicky[13], Welker[14] and Lautens.[15]

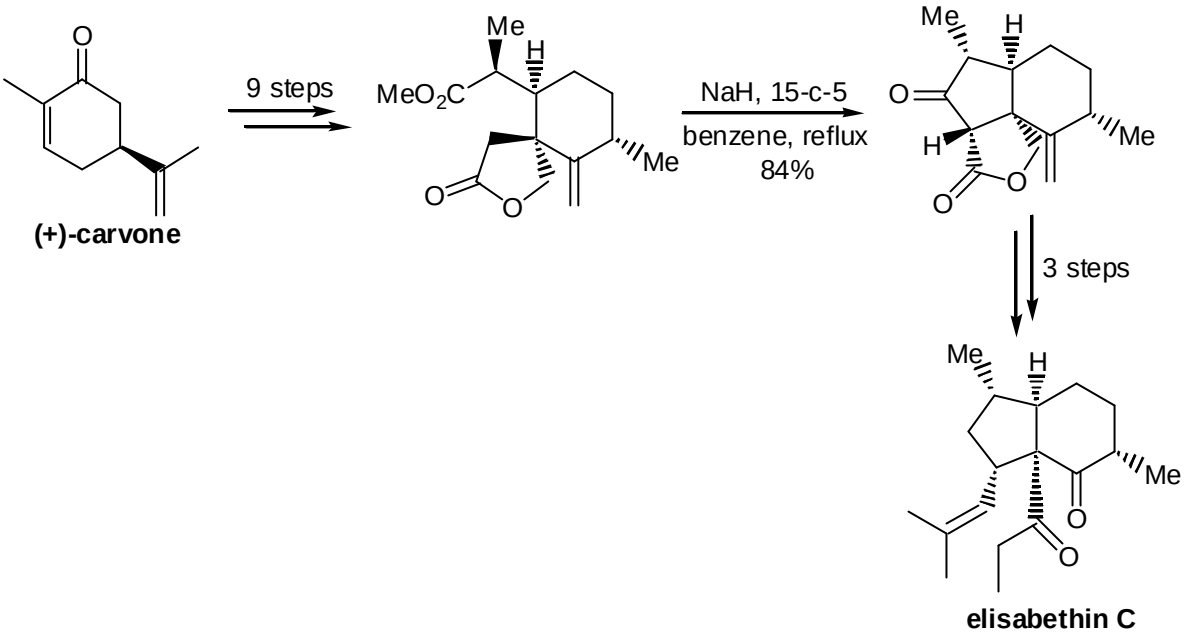
On the other hand, there are still only few methods for the asymmetric synthesis of five-membered carbon rings.

2 Asymmetric cyclopentannulation reactions: literature review

2.1 Non-connective asymmetric cyclopentannulations

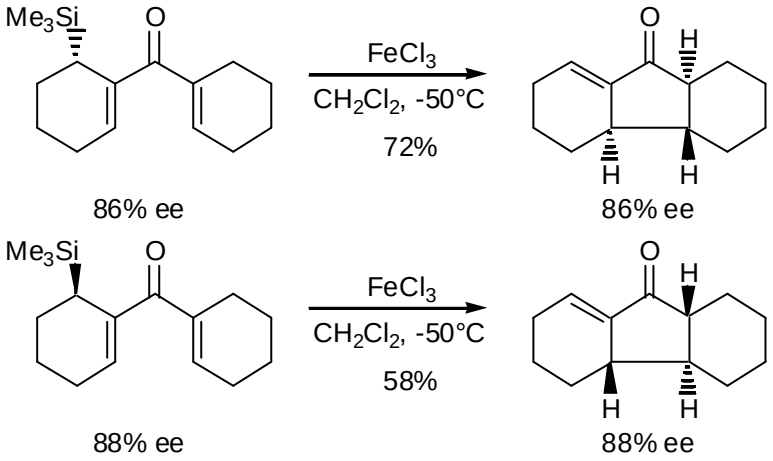
The Dieckmann condensation is the oldest method involving an anionic species for a ring-closing strategy.[16] An example of an asymmetric Dieckmann condensation was recently described by the group of Yamada in the synthesis of elisabethin C, a marine *bisnor*-diterpenoid (scheme 1).[17]

[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

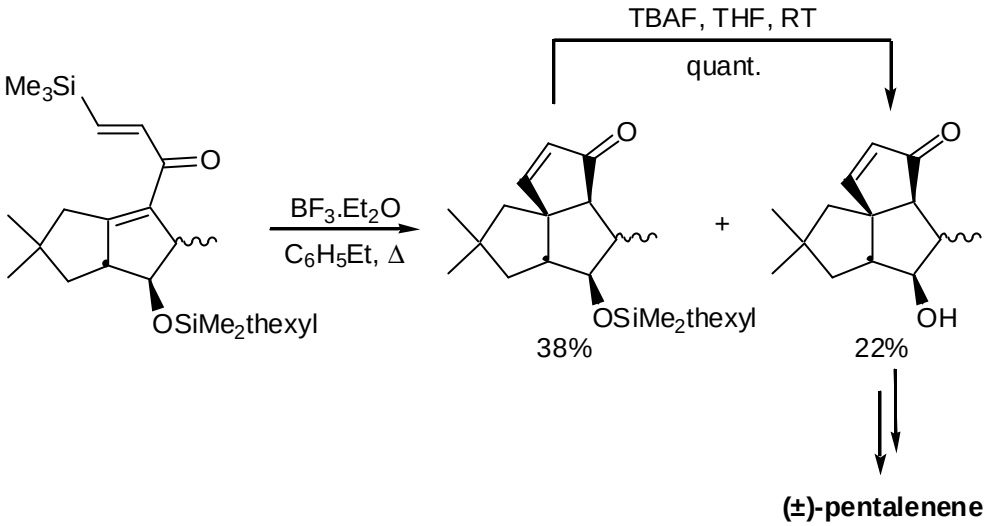
The Nazarov reaction is a cyclization reaction based upon the formation of a cationic species. It consists in the cyclization of divinylketones catalyzed by an acid.[18,19] An example of an asymmetric version of this reaction has been described by Denmark (scheme 2).[20]



Scheme 2

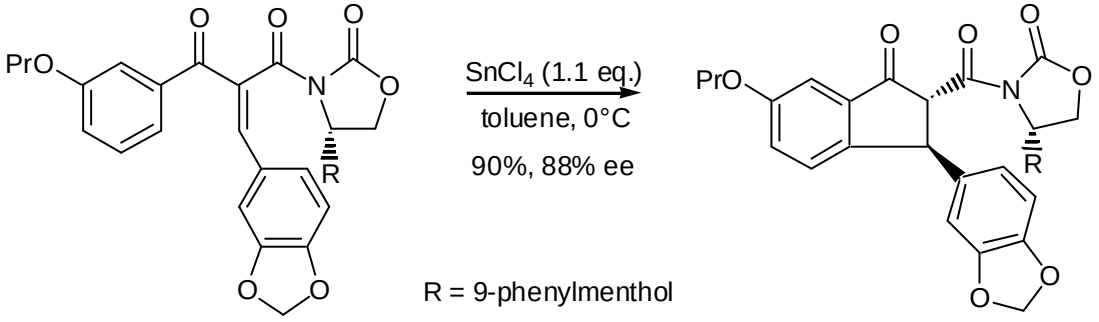
Franck-Neumann *et al.* used an asymmetric Nazarov reaction for the introduction of the third ring of (±)-pentalenene (scheme 3).[21]

[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-pentenals[23], α-diazo-β-ketoesters[24] and α-diazoketones.[25]

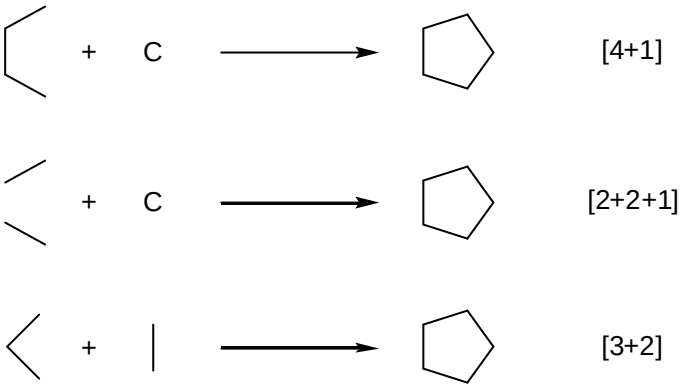
This non-exhaustive list shows the diversity of intramolecular cyclization strategies. However these methods are less attractive than the connective methods due to the often needed complex starting material and the lack of flexibility.

[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

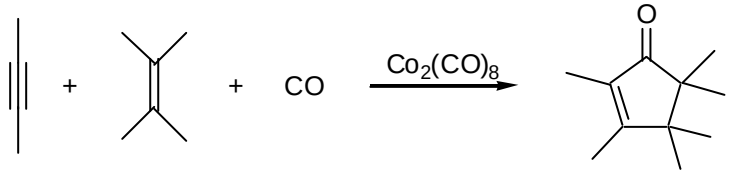
2.2.1 [4+1] cyclopentannulation reactions

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.a The 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 monoxyde are coupled, intra- or intermolecularly, in the presence of a cobalt complex (scheme 6).

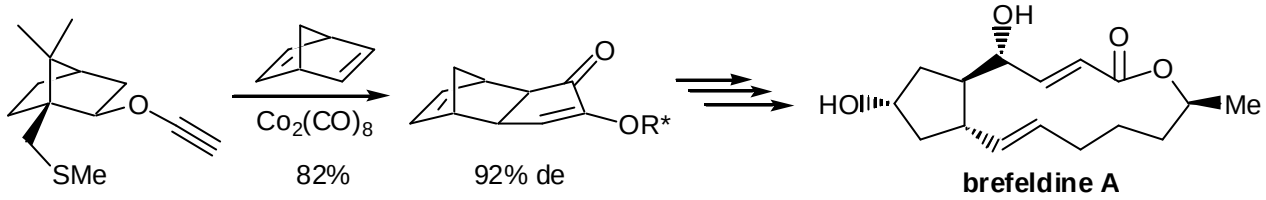


Scheme 6

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

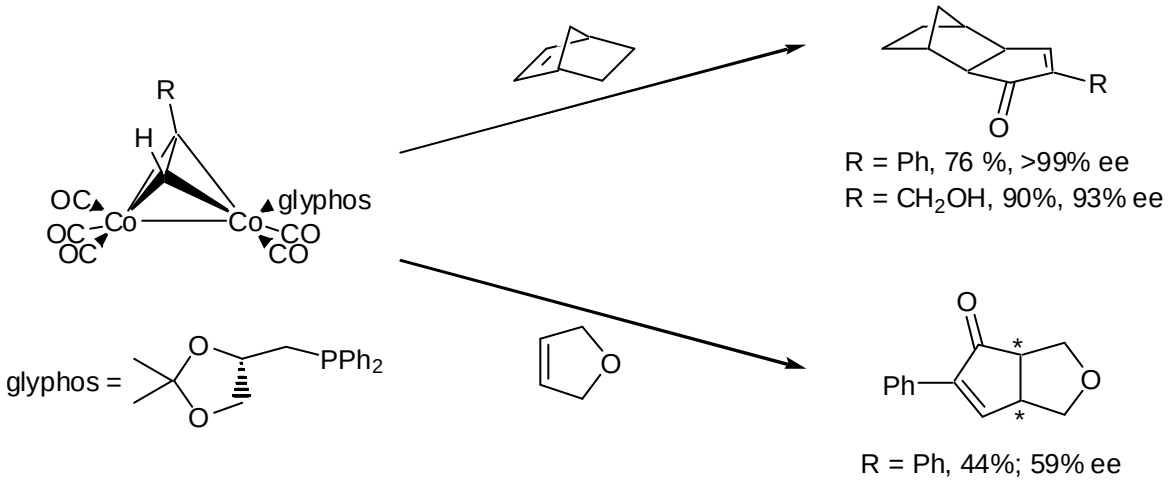
To develop an asymmetric version of the Pauson-Khand reaction one can either use a chiral inductor linked to the olefin or the acetylene, or use a chiral cobalt complex.

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



Scheme 7

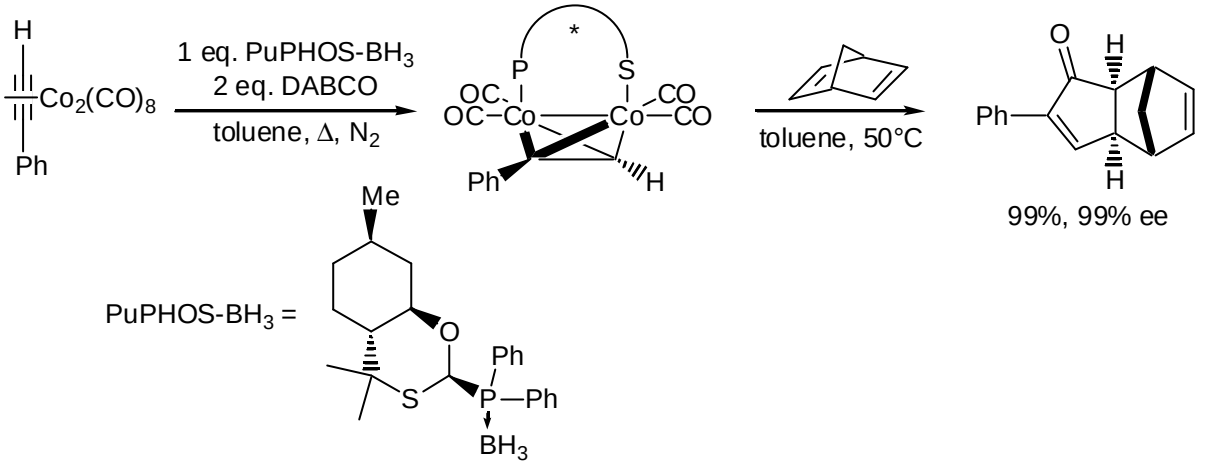
Pauson and Brunner studied chiral cobalt complexes. Modest to excellent enantioselectivities were obtained with a chiral phosphine, such as glyphos (scheme 8).[28,29]



Scheme 8

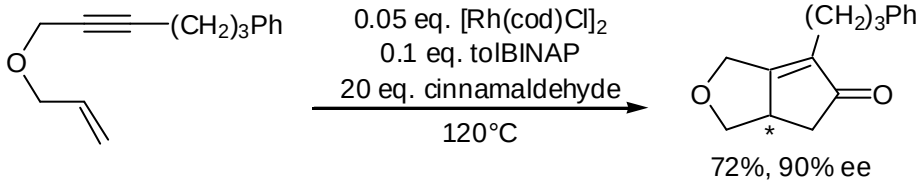
Another example of an asymmetric intermolecular Pauson-Khand reaction has been published by Pericàs and Riera.[30] A chiral bidentate (P,S) ligand on cobalt led to excellent enantioselectivities (scheme 9).

[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.



Scheme 9

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]



Scheme 10

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

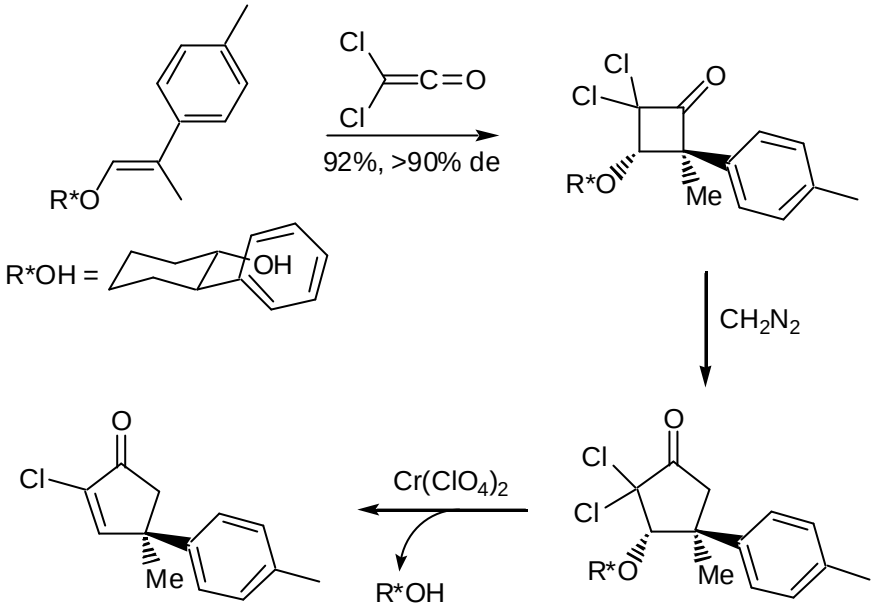
An interesting strategy for the construction of five-membered rings is the [2+2] cycloaddition followed by a ring expansion of the strained four-membered ring. The stereochemistry of the final product is fixed during the cycloaddition whereas the ring expansion has to be regioselective to obtain the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

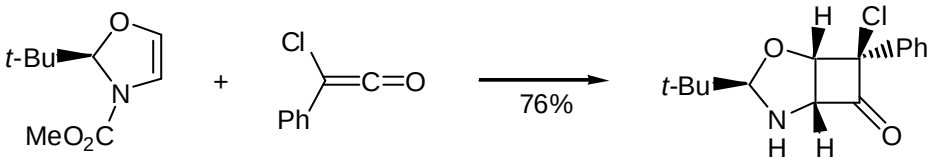
[31] Shibata, T.; Toshida, N.; Takagi, K. *J. Org. Chem.*, **2002**, *67*, 7446-7450.
[32] Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.*, **1987**, *109*, 4752-4753.

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

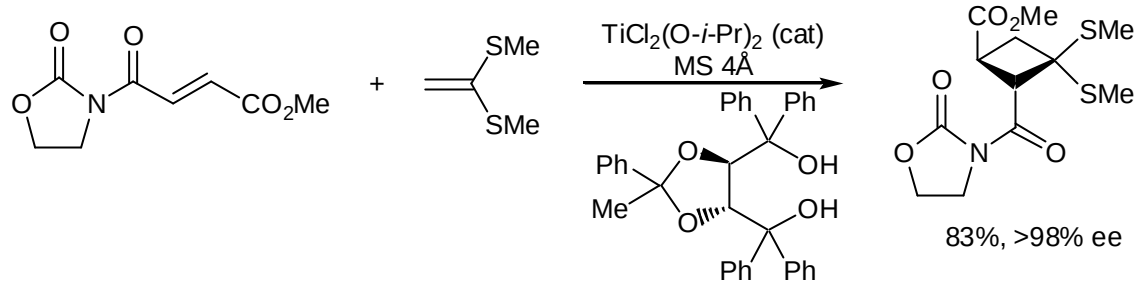
A second strategy implying the chirality on the ketene substituents was not successful (figure 5).[34] These disappointing results could be assigned to the fact that the chiral substituents were too far away from the carbon atom C1.

Figure 5

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

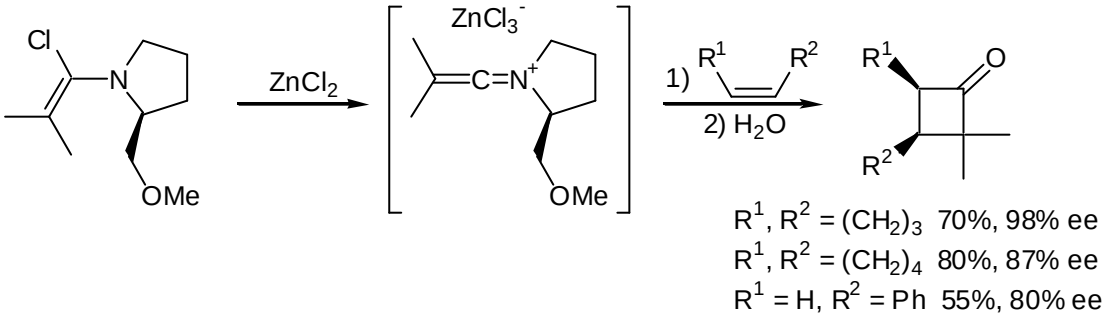
[34] Ghosez, L.; Chen, L.-Y.; Gobeaux, B.; Houge, C.; Markó, I. E.; Perry, M.; Saimoto, H., *Strain and its Implication in Organic Chemistry*; Kluwer Academic Publishers, 1989.

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.



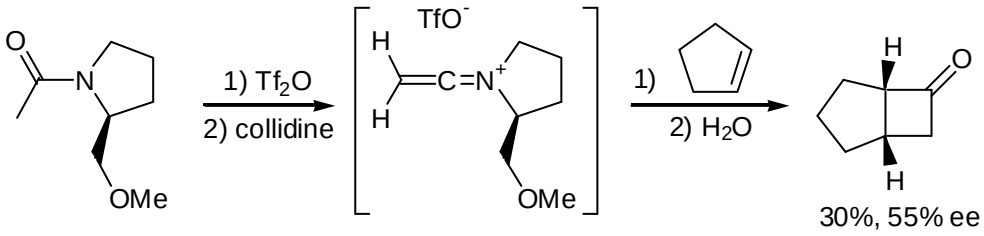
Scheme 13

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 to diastereomeric keteniminium salts (figure 6).

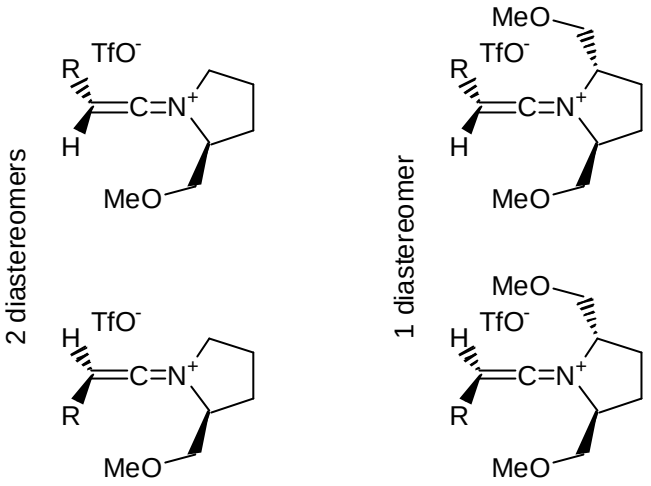
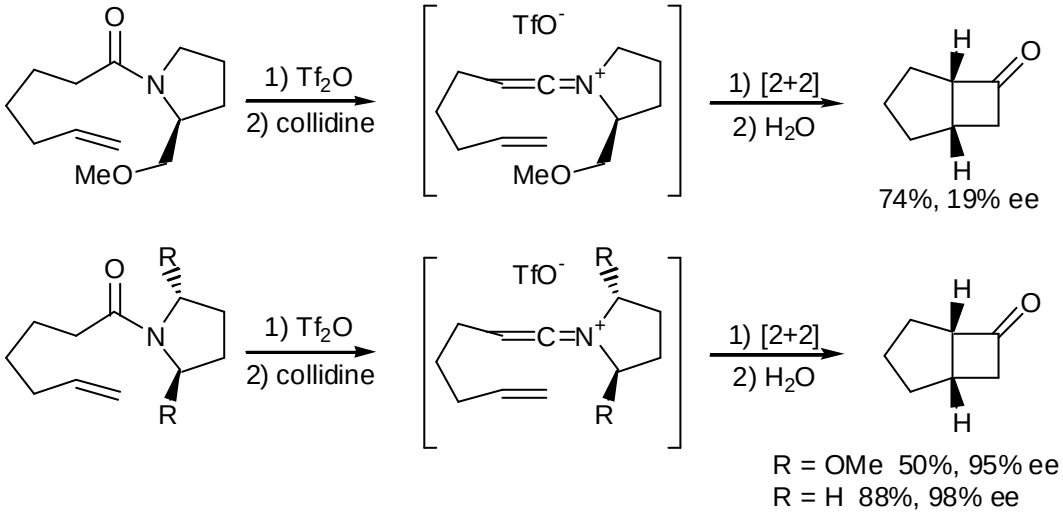


Figure 6

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]



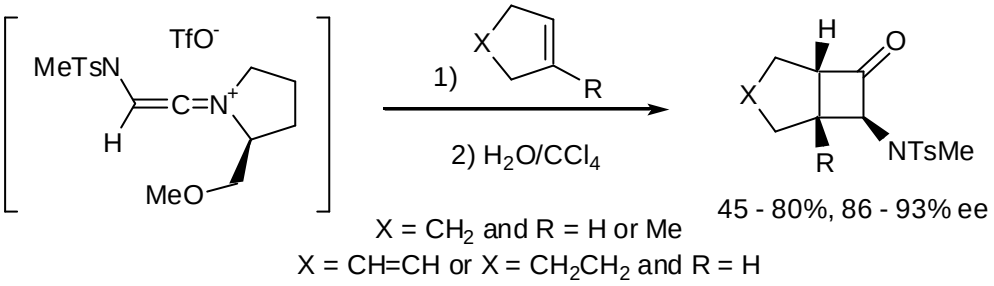
Scheme 16

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).



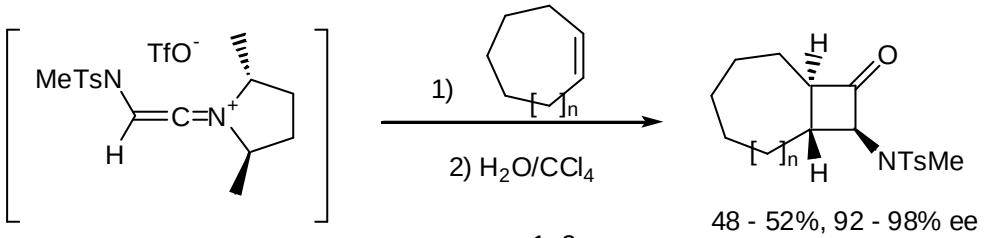
45 - 80%, 86 - 93% ee

X = CH_2 and R = H or Me

X = CH=CH or X = CH_2CH_2 and R = H

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.



48 - 52%, 92 - 98% ee

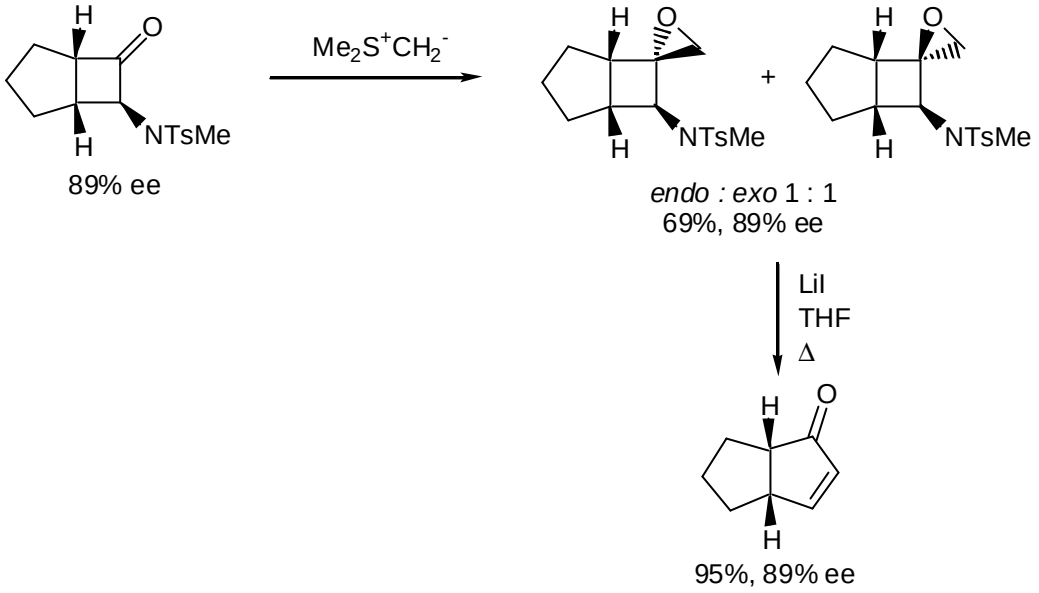
n = 1, 2

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.

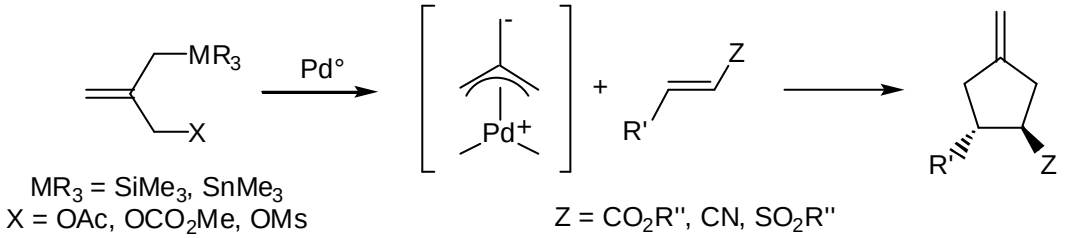


Scheme 19

2.2.3 [3+2] cyclopentannulation reactions

2.2.3.a Trimethylenemethane equivalents

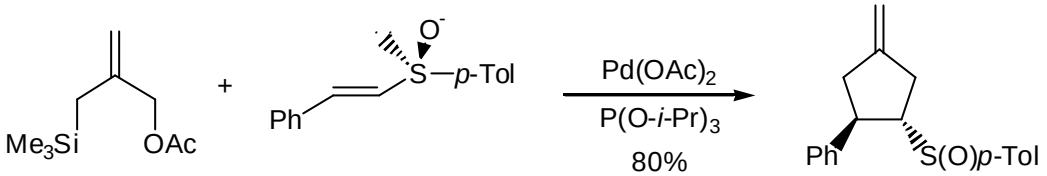
The chemistry of trimethylenemethane (TMM) has been studied in detail by Trost.[12,44,45] Equivalents of TMM are zwitterionic 3 carbon synthons. They react with electron-poor olefins in the presence of a palladium catalyst (scheme 20).



Scheme 20

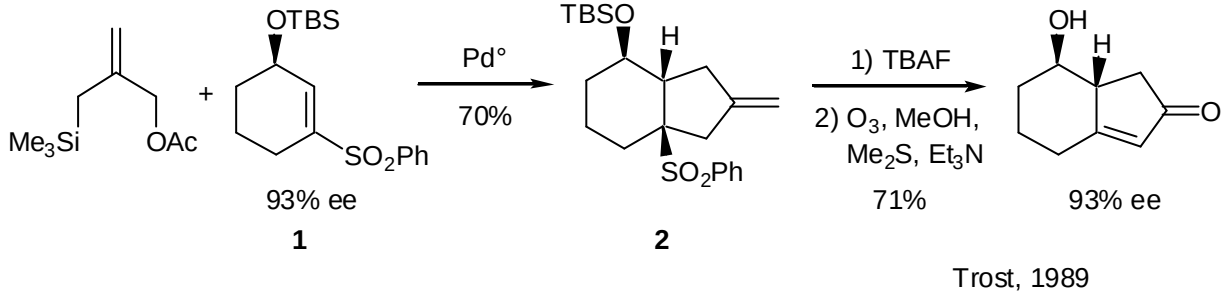
Asymmetric versions of this reaction have been carried out using chiral olefins. Good diastereoisomeric excesses were obtained in the cycloaddition of TMM to chiral vinylsulfoxydes (scheme 21).[46]

[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.

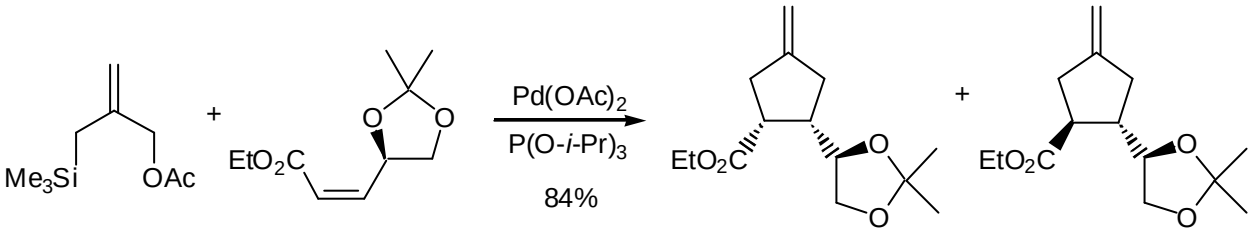


Scheme 21

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



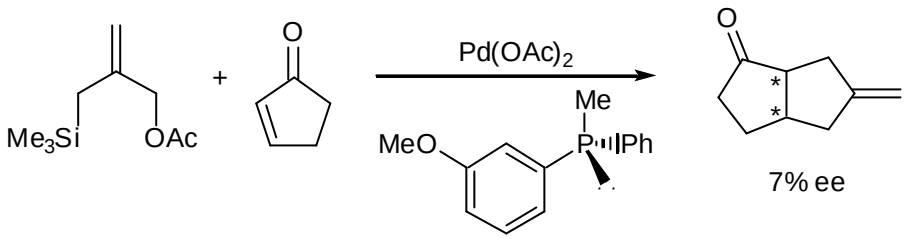
Samuelson, 1993

Scheme 22

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

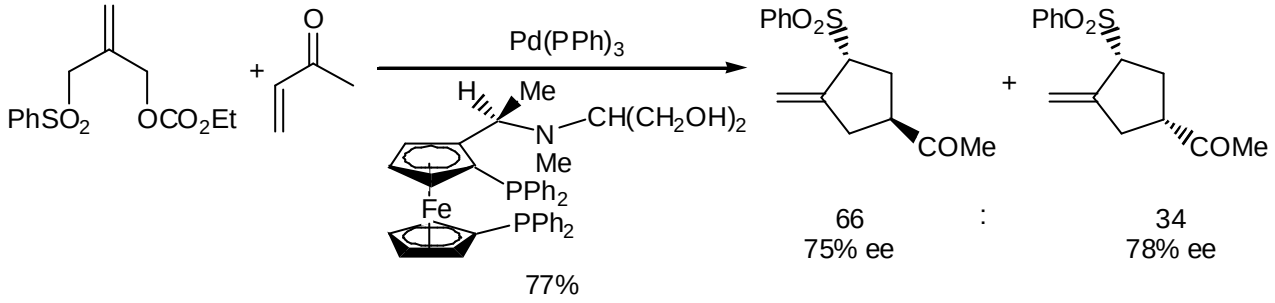
An attractive possibility for an asymmetric version of this reaction is the use of a chiral ligand on the palladium catalyst. The first examples of this strategy have been reported by Trost.[49] A chiral phosphine was used but enantiomeric excesses remained steadily low (scheme 23).

[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

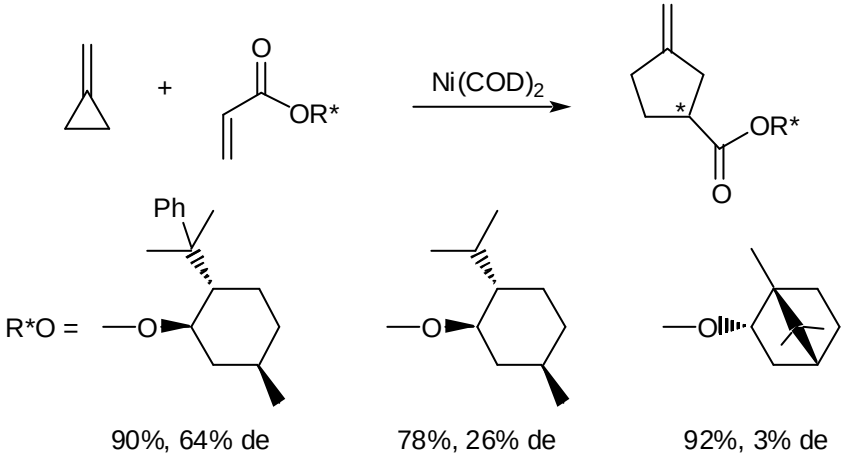
Chiral ferrocenyl diphosphines gave enantiomeric excesses up to 78% ee (scheme24).[50]



Scheme 25

2.2.3.b Methylenecyclopropanes

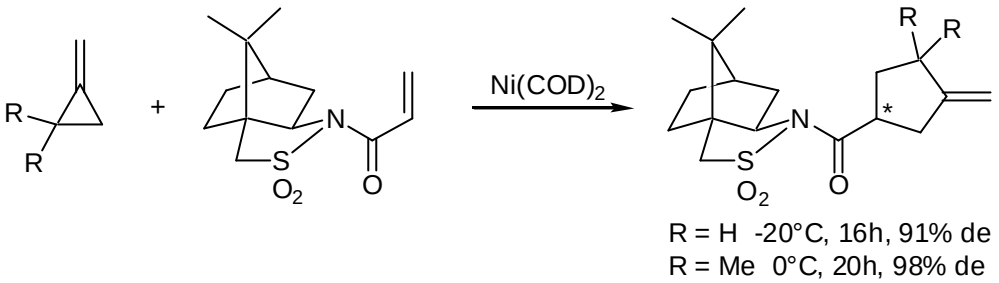
Methylenecyclopropane can be used as a 3-carbon synthon for [3+2] annulation reactions catalyzed by bis(cycloocta-1,5-diene)nickel. As shown by Binger, the use of a chiral electron-poor olefin gave bad to modest diastereoselectivities (scheme 26).[51]



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.

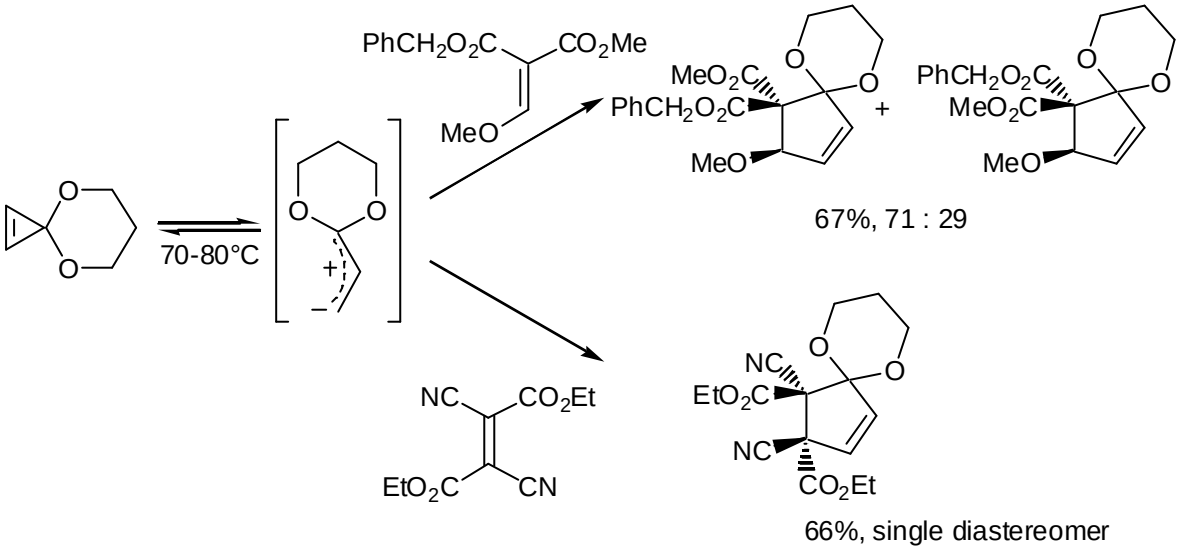
However, the stereoselectivity was significantly higher when the olefin compound was (-)-camphorsultamacrylate (scheme 27).[52]



Scheme 27

2.2.3.c Cyclopropene ketals

Cylopropene 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

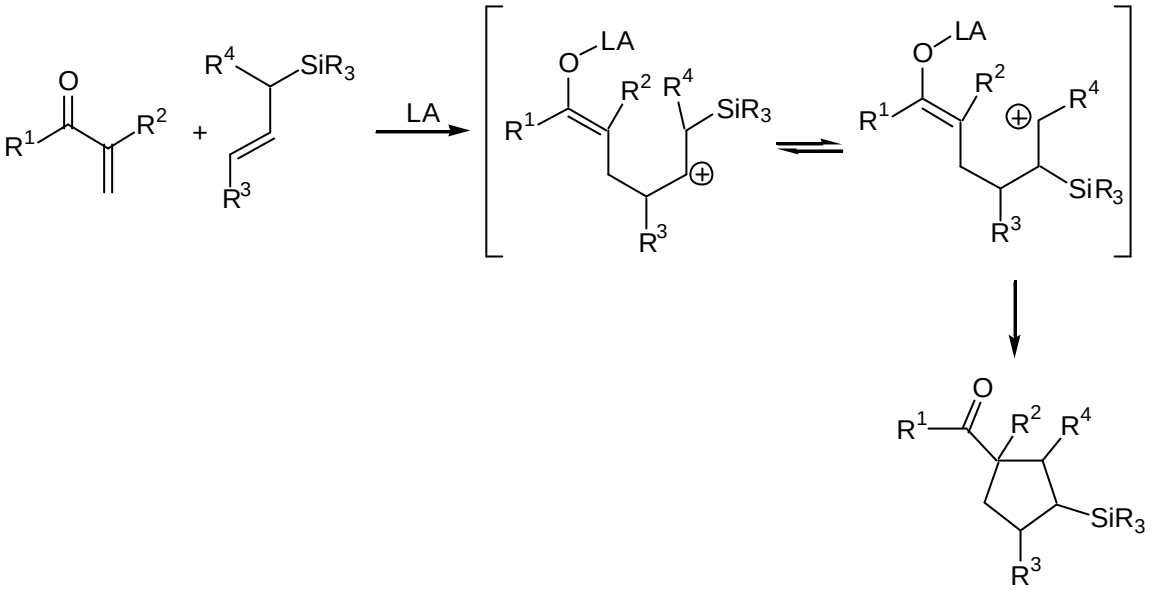
However to the best of our knowledge, no enantioselective version of this method has been described.

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. *J. Org. Chem.*, **1988**, *53*, 3408-3421.

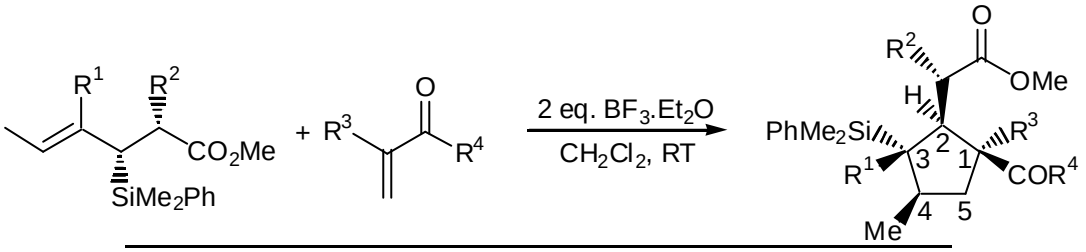
The conjugate addition is followed by a 1,2-migration of the silyl group. The newly formed carbocation reacts with the enolate to form the five-membered ring.



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]



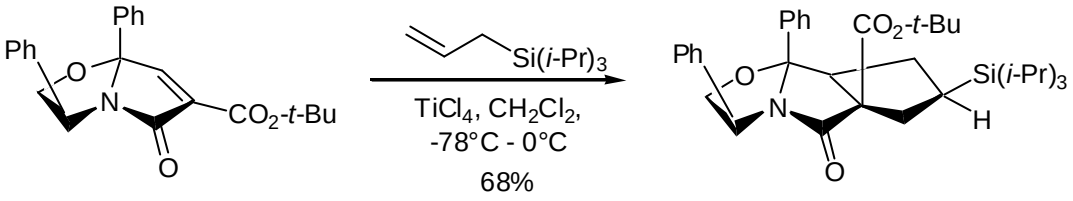
R^1	R^2	R^3	R^4	Yield	dr
H	H	Me	H	93%	> 30 : 1
H	OMe	Me	H	73%	> 30 : 1
Me	H	Me	H	65%	> 30 : 1
H	OMe	H	H	62%	> 30 : 1
H	H	H	Me	56%	6 : 1

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 synthsize 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]



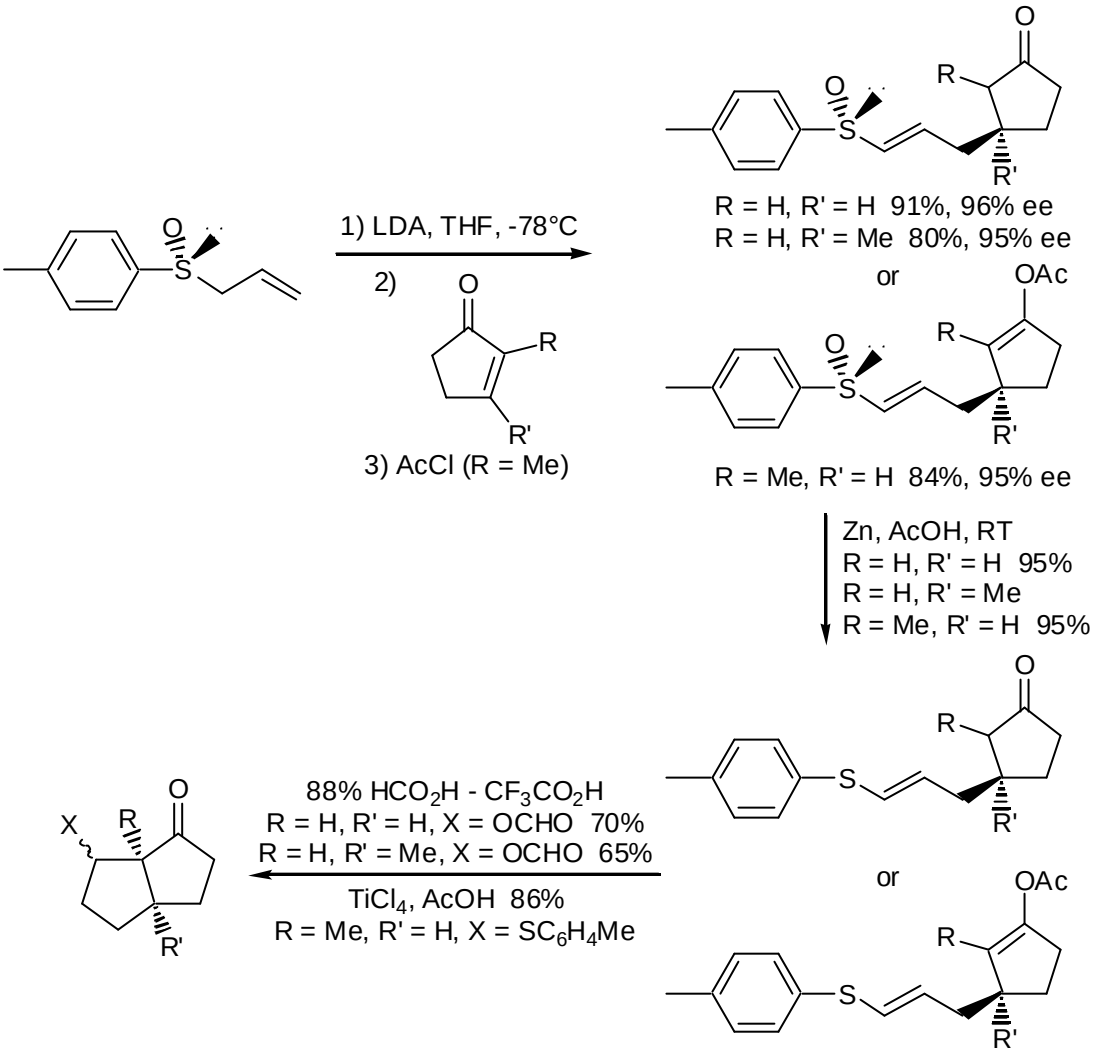
Scheme 30

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]

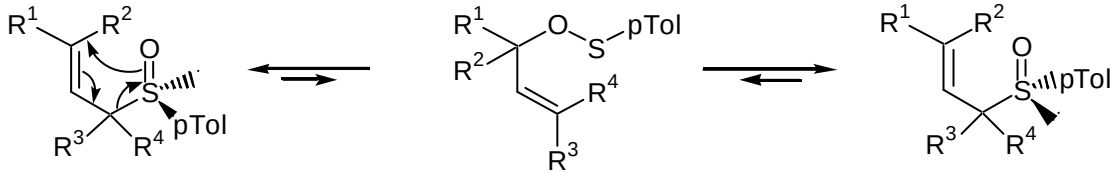
The pentannulation sequence was realized in 3 steps (scheme 31): the first one was the conjugate addition of the allylic sulfoxide where the intermediate enolate was trapped with acetyl chloride, the sulfoxide was then reduced and finally the cyclization occurred by the use of a Lewis acid.[56]

[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

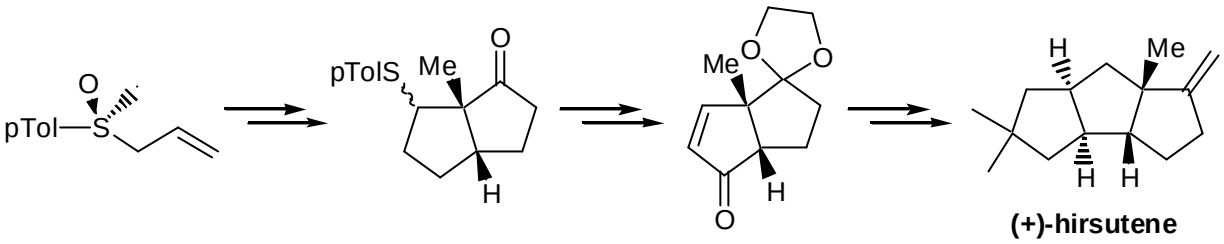
There remains however a drawback. Allylic sulfoxides easily undergo racemization by a reversible [2,3] sigmatropic rearrangement (scheme 32).[57] Only the unsubstituted sulfoxide ($R^1 = R^2 = R^3 = R^4 = H$) showed configurational stability when handled at low temperature.



Scheme 32

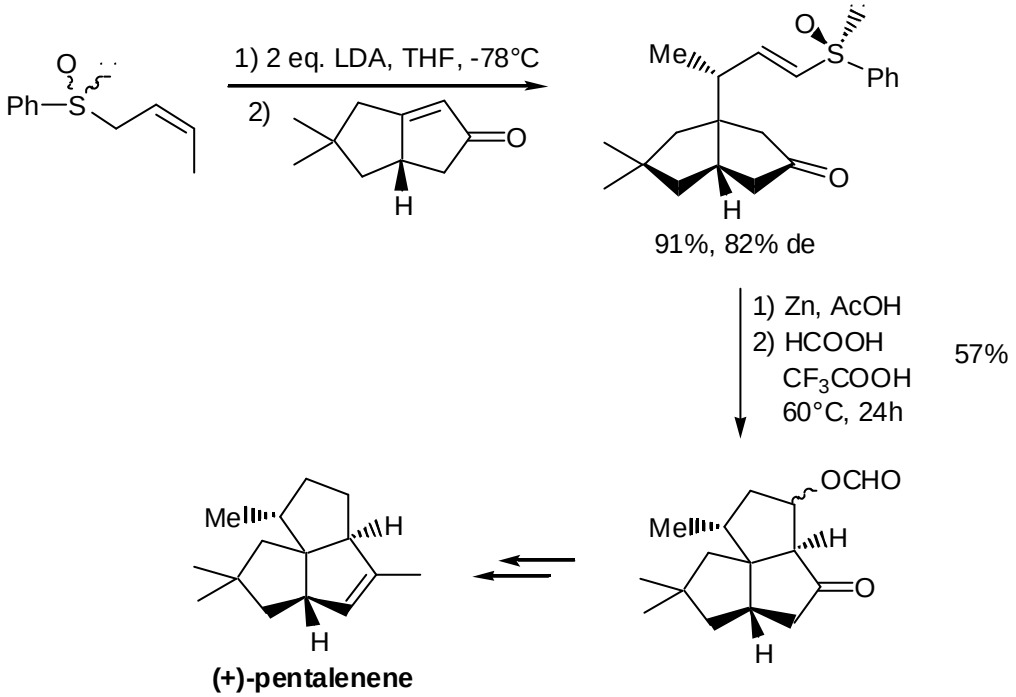
[57] Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.*, **1974**, *7*, 147-155.

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



Scheme 33

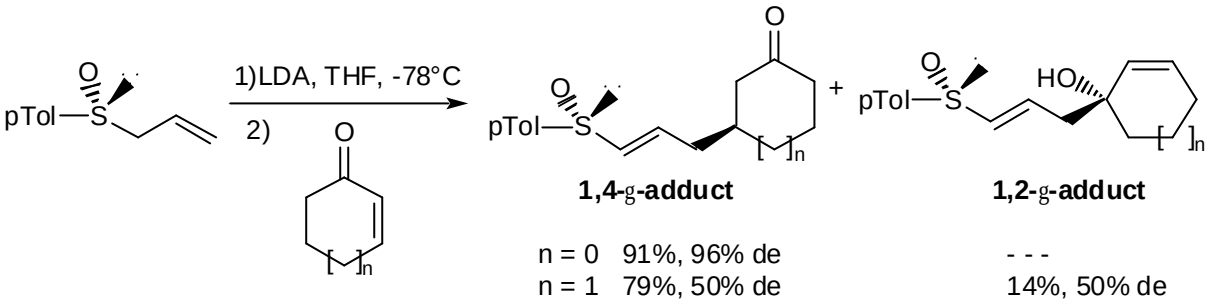
In order to circumvent the problem of racemization of the sulfoxide, the same group had adopted the alternative strategy of using a chiral enone with a racemic sulfoxide.[59] (+)-pentalenene could be synthesized in 82% de by this method (scheme 34).



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.



1,4-g-adduct **1,2-g-adduct**

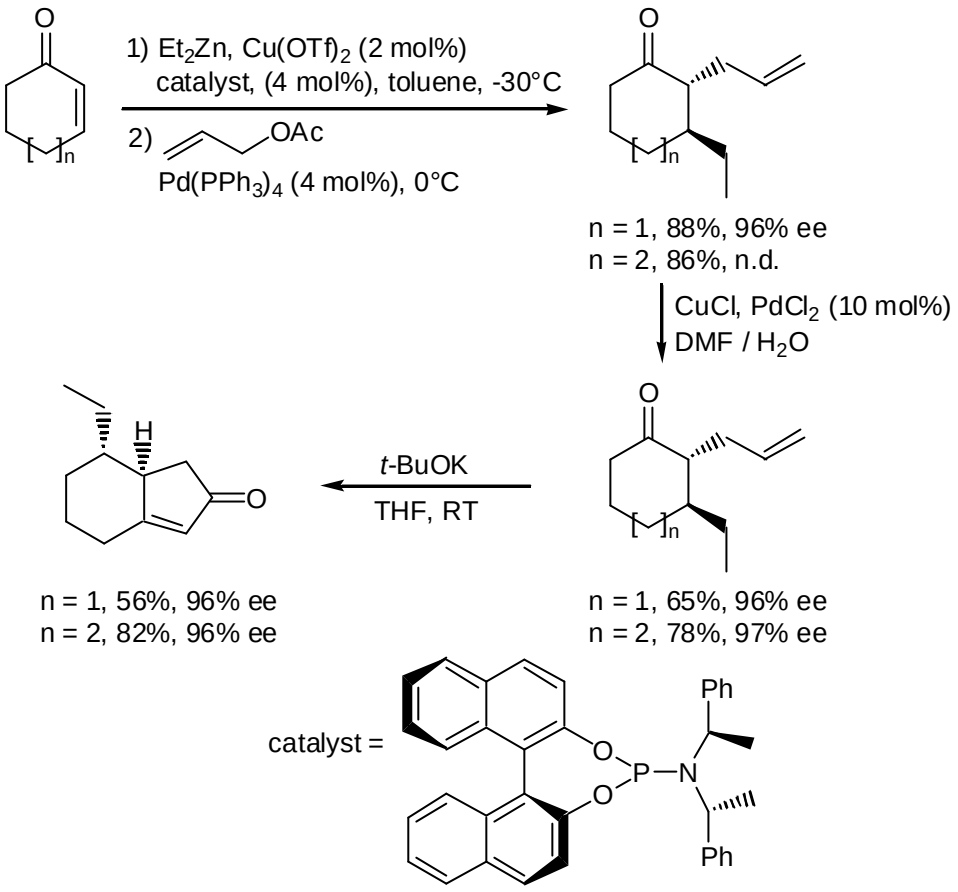
n = 0	91%, 96% de	- - -
n = 1	79%, 50% de	14%, 50% de
n = 2	25%, 50% de	58%, 50% de

Scheme 35

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 cooper 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.



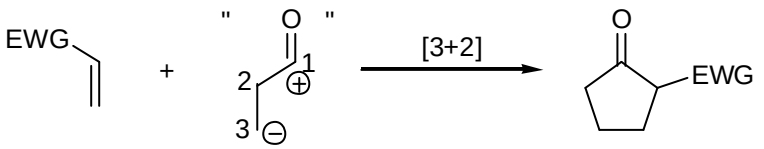
Scheme 36

3 Previous work of our laboratory

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

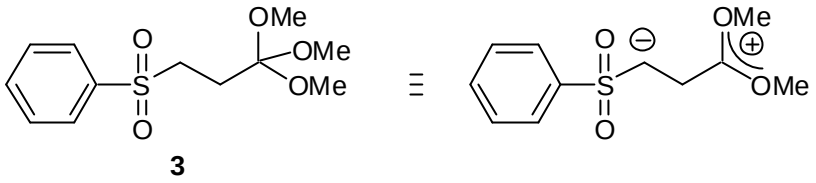
3.1 Concept

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.

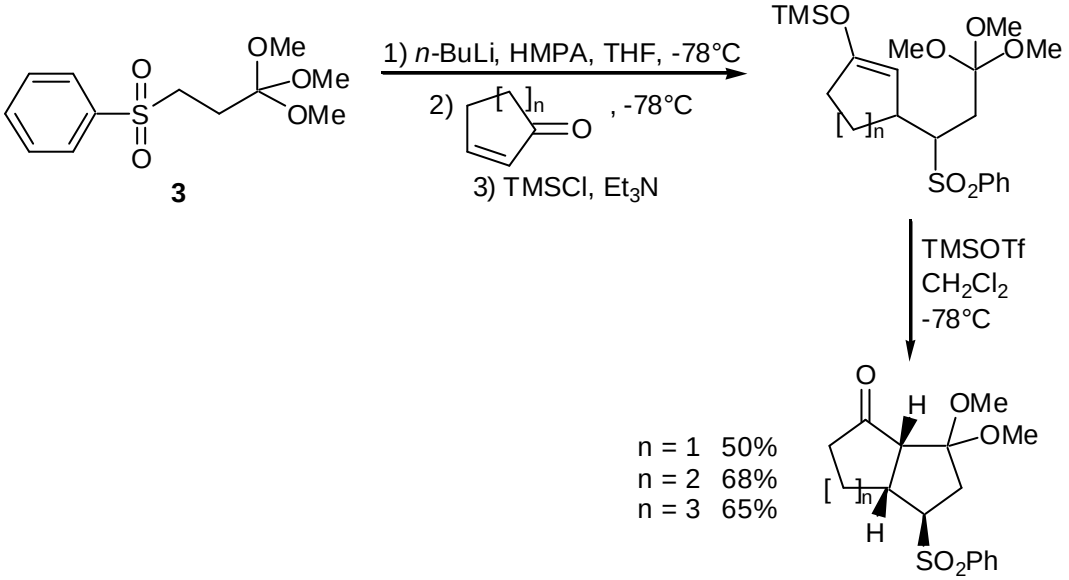


3

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 Mukayiama aldol reaction was effected in the presence of a catalytic amount of Lewis acid (scheme 38).



3

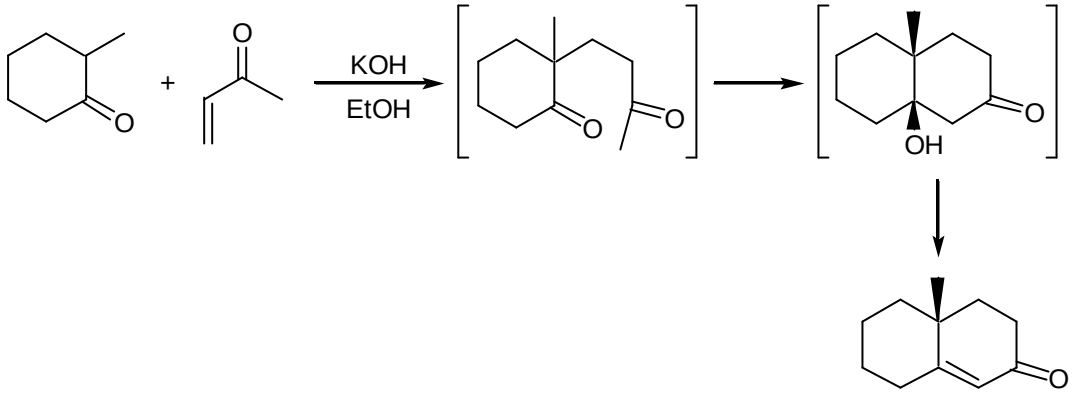
Scheme 38

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 annulation[62] 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 (-$C(OMe)_3$, -$C(OEt)_3$, -$C(O\text{-}n\text{-}Pr)_3$ and -$C(OEt)(OCH_2)_2$).

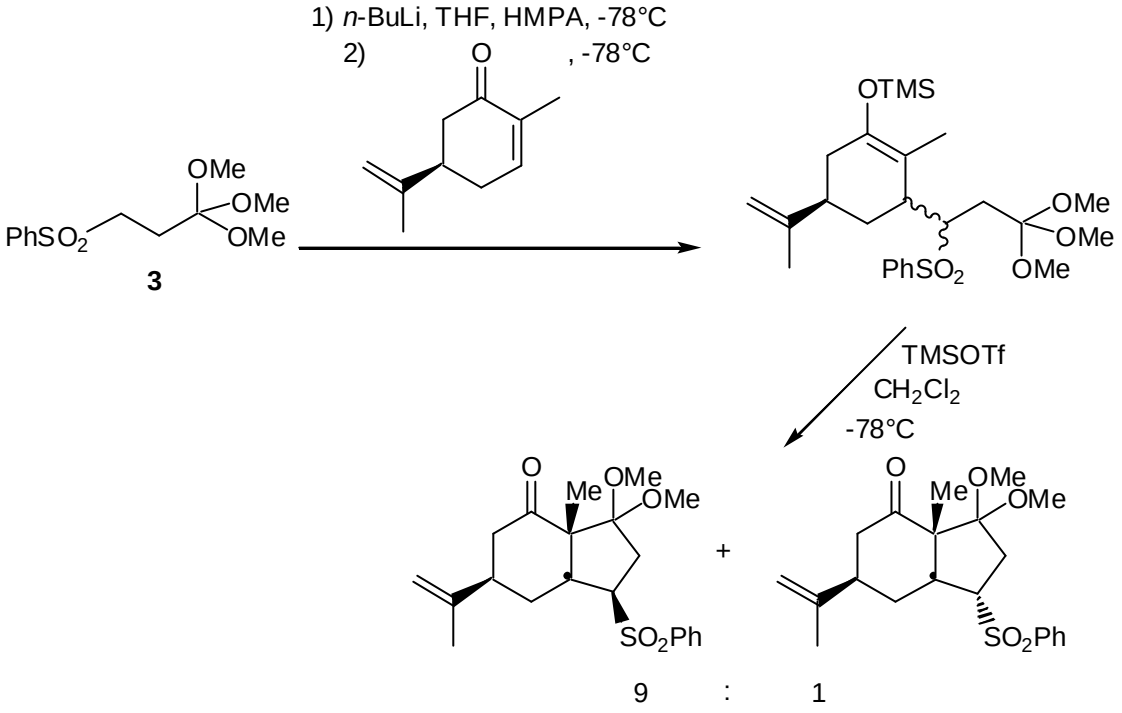
These successful results prompted our group to study the possibility of developing an asymmetric version of the annulation reagent.

[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

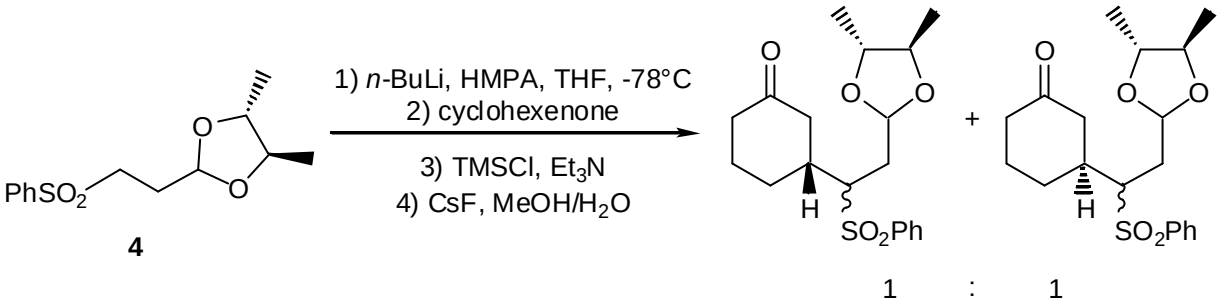
This approach should be very interesting when the enantiomerically pure enone is readily available.

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).

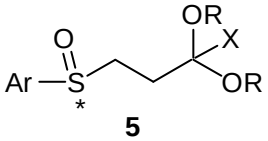


Scheme 41

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 accessible[66], 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.



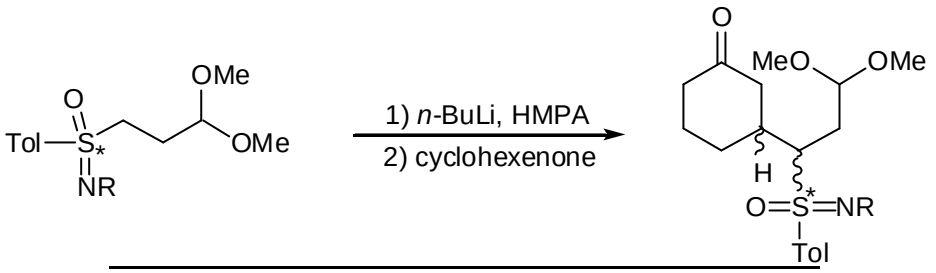
5

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).

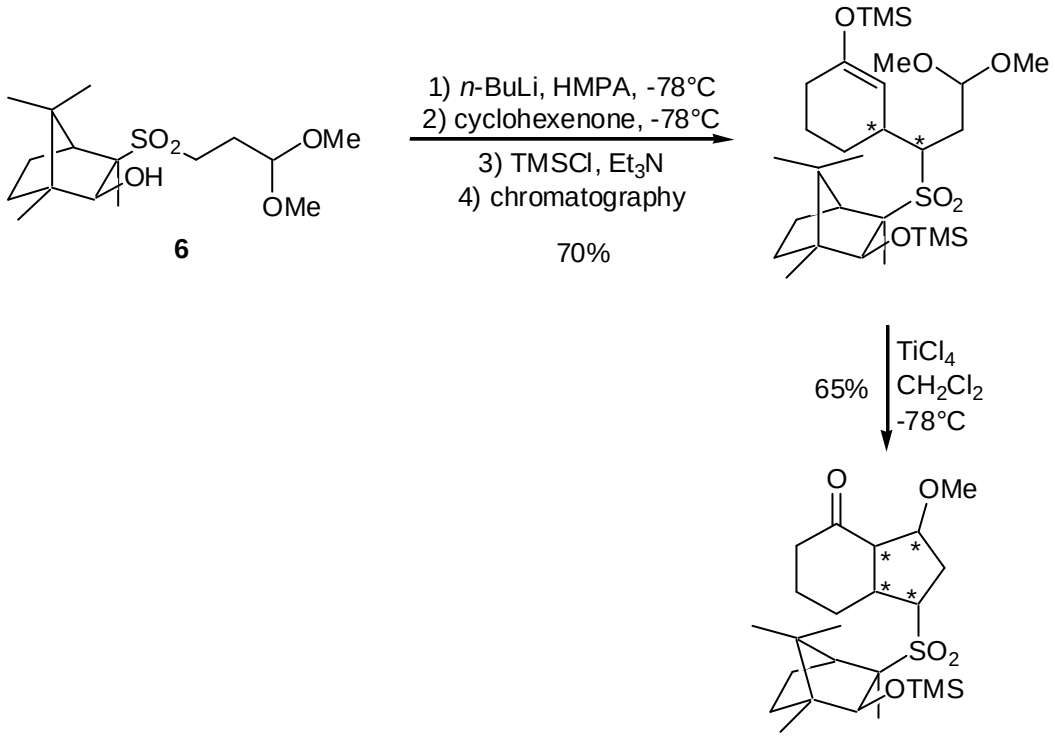
[66] Kagan, H. B., *Oxidation of hetero atoms: asymmetric oxidation of sulfides and selenides*, in *Asymmetric Oxidation Reactions (2001)*, Katsuki, T., Editor. Oxford University Press: Oxford, UK. 2001, p. 153-170.

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
$Si(i\text{-}Pr)_3$	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 Mukayiama 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.

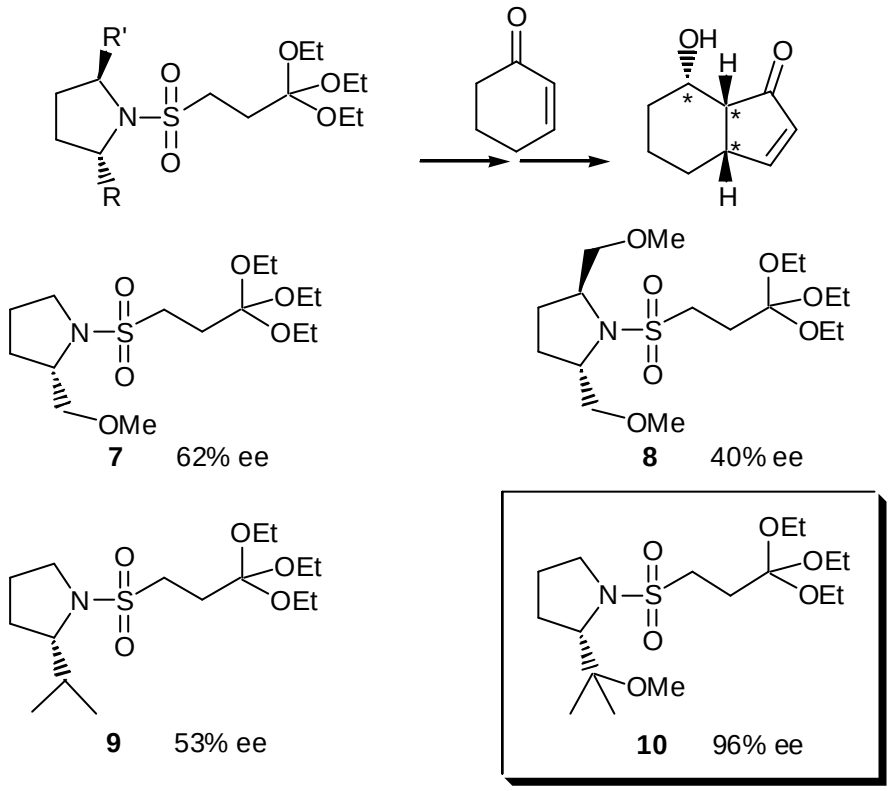


Scheme 42

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

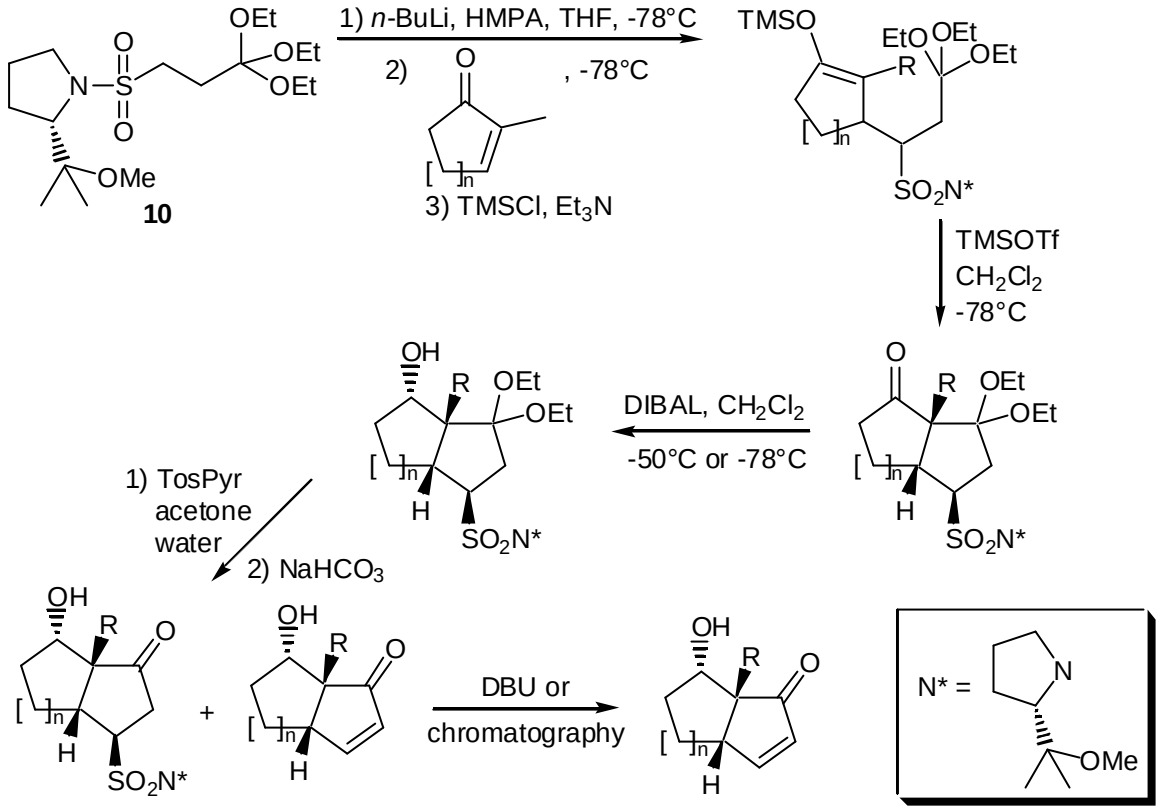
The major drawback was the cleavage of the chiral inductor. It was extremely difficult to remove. Also the synthesis of the chiral auxiliary was tedious.

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.