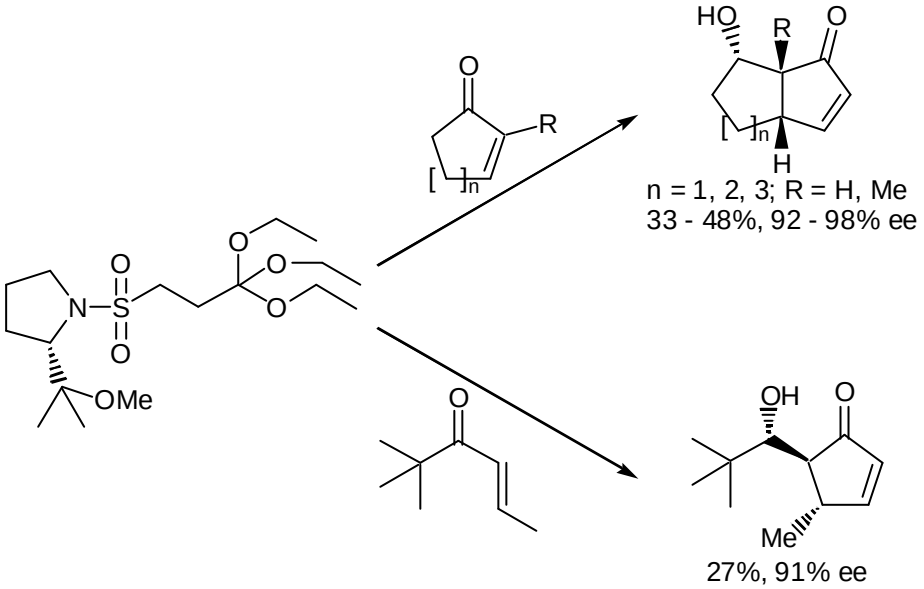
Conclusion and perspectives

1 [3+2] cyclopentannulation with sulfonamides

1.1 Conclusion

This work completes the studies on asymmetric cyclopentannulation reactions realized in our laboratory. At this stage it seems important to analyze the achievements of this research.

A highly enantioselective cyclopentannulation reaction has been developed using chiral homoenolate equivalents. Initially the sequence had been successfully applied to cyclic enones. We have shown in this work that acyclic enones could be cyclized with nearly as good enantioselectivities. This application completes the general scheme of our method (scheme 178).



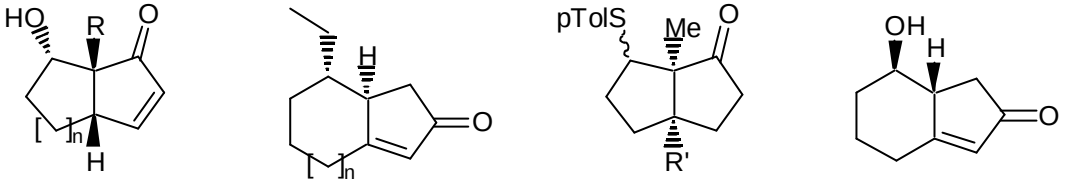
Scheme 178

It now seems interesting to position our method among those described in the literature. Our approach is relatively general as it is not sensitive to the ring size of the cyclic enones and is also exploitable with acyclic enones without loss in selectivities. Substituents at the α-position of the enone are tolerated. It appears thus

more interesting than the use of allylic sulfoxides[56] or Feringa's[60] approach that are limited to a specific enone's ring size.

The chiral inductor is easily accessible in enantiomerically pure form and does not racemize under reaction conditions or during storage. It is thus preferable to asymmetric allylsilanes[54] or allylic sulfoxides.[56] The orthoester function should not be a problem as we have shown that with a few precautions (argon atmosphere, storage at –20°C) no hydrolysis occurred even after 2 years.

A highly functionalized cyclopentenone is obtained that can easily be modified for further applications. Whereas Feringa's approach leaves only few possibilities for modification[60], other methods lead to similar substitution patterns[56] or to differently functionalized pentenones[47] (figure 30).



this work
n = 1, 2, 3

Feringa, 1999
n = 1, 2

Hua, 1987

Trost, 1989

Figure 30

Our method is thus not designed to replace other existing methods but to be a complementary tool for the synthesis of a given structure not easily accessible with another method.

At this stage we are however aware that the sulfonamide-based method still shows some inconveniences. Global yields are not very good resulting mostly from the three steps necessary to eliminate the chiral inductor. Moreover we have shown that acceptors less active than enones could not be cyclized.

Beyond the study of asymmetric cyclopentannulation reactions this work also represents an important study on the Michael addition of sulfonamides to enones. It revealed several interesting points.

Sulfonamides derived from pyrrolidine showed a reactivity similar to the one observed with sulfones. The conjugate addition needed the presence of HMPA. However regioselectivity was somewhat lower with sulfonamides than with sulfones. The most important point was the finding that a heteroatom correctly situated on the

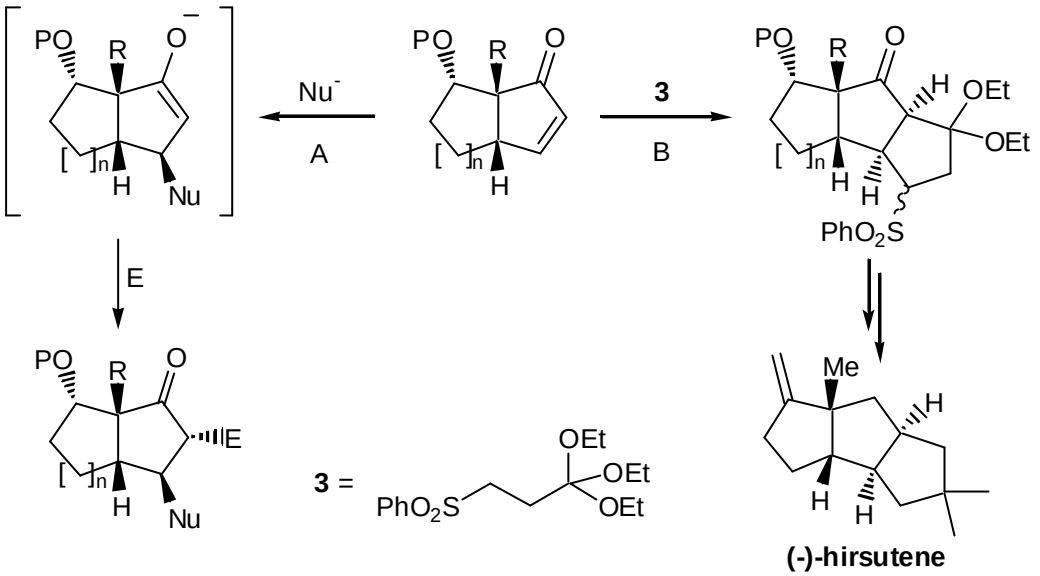
substituent of the sulfonamide could help to control the regioselectivity. Diastereoselectivity, on the other side, was not influenced by the nature of the sulfonamide. The ratio of *anti* / *syn* isomers varied from 70 / 30 to 80 / 20. These results were in complete agreement with previous results obtained with sulfones or sulfonamides. When the 1,2-adduct was formed no diastereoselectivity was observed.

Chiral sulfonamides reacted with nearly the same regioselectivity as their achiral analogues. Again the presence of a heteroatom in the sulfonamide substituent was crucial for the outcome of the reaction. In this case some influence of the substituent on diastereoselectivity was observed. We could also show that HMPA was, in some cases, responsible for changes in the stereochemistry of the reaction.

Based on the combined results of C. Huart's thesis and our work, we were able to propose a model for the transition state that could explain the selectivities observed in the Michael addition.

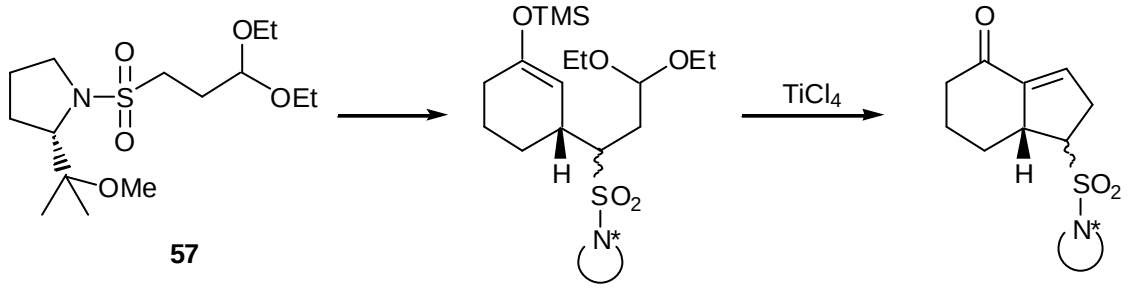
1.2 Perspectives

We completed the study of the sulfonamide-based cyclopentannulation and we showed its limitations. To demonstrate its utility it would be interesting to apply it to total synthesis. The bicyclic motive offers indeed the possibility for further transformation. Stereoselective attack by a nucleophile and reaction of the resulting enolate would generate a bicyclic compound with five stereocenters (pathway A, scheme 179). The enone could also be used to initiate another [3+2] cycloaddition reaction. In that case triethyl phenylsulfonylorthopropionate **3** could be used, as the existing chiral centers would induce the absolute configuration of the new ones (pathway B, scheme 179). Thus the framework of (-)-hirsutene is easily accessible



Scheme 179

The use of sulfonamide **57** could be an interesting alternative for the synthesis of bicyclic cyclopentenones with a different substitution pattern. Cyclization will result in the formation of an enone that could be another interesting motive for further transformation (scheme 180).



Scheme 180

A major problem in such an approach will be the elimination of the chiral inductor. However Marek has shown that zirconium complexes could be used for the elimination of sulfur containing groups on sp^2 carbons.[249] According to the author the method should also work for sp^3 carbons.[250] This could be a complementary method to the β-elimination.

We have shown that monocyclic cyclopentenones could be formed with high enantioselectivities starting from acyclic enones. Our method could therefore be applied to the synthesis of prostaglandins.

[249] Farhat, S.; Marek, I. *Angew. Chem. Int. Ed. Engl.*, **2002**, *41*, 1410-1413.
[250] Marek, I., *Conference*, Louvain-la-Neuve, 2002.

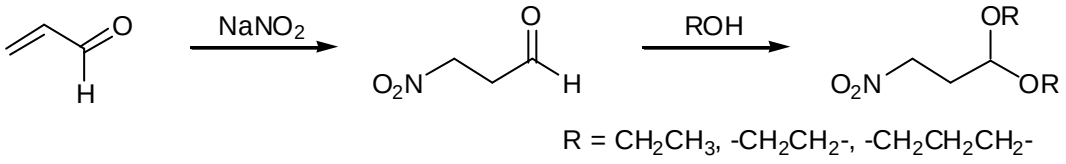
2 [3+2] cyclopentannulation with nitro-compounds

2.1 Conclusion

To circumvent the limitations of the sulfonamide-based method we initiated a study towards a catalytic asymmetric pentannulation sequence.

In a first approach we studied phase-transfer catalysis. In these conditions sulfur-stabilized electron-withdrawing groups were not appropriate: sulfonamides could not be deprotonated; sulfones could form the anion but did not react with electrophiles; finally nucleophiles containing both a sulfone and an ester as electron-withdrawing group were too hindered to realize the Michael addition.

Nitro-compounds were thus chosen as potential annulation agents. Whereas the orthoester could not be synthesized, ketals were easily accessible from acrolein (scheme 181).

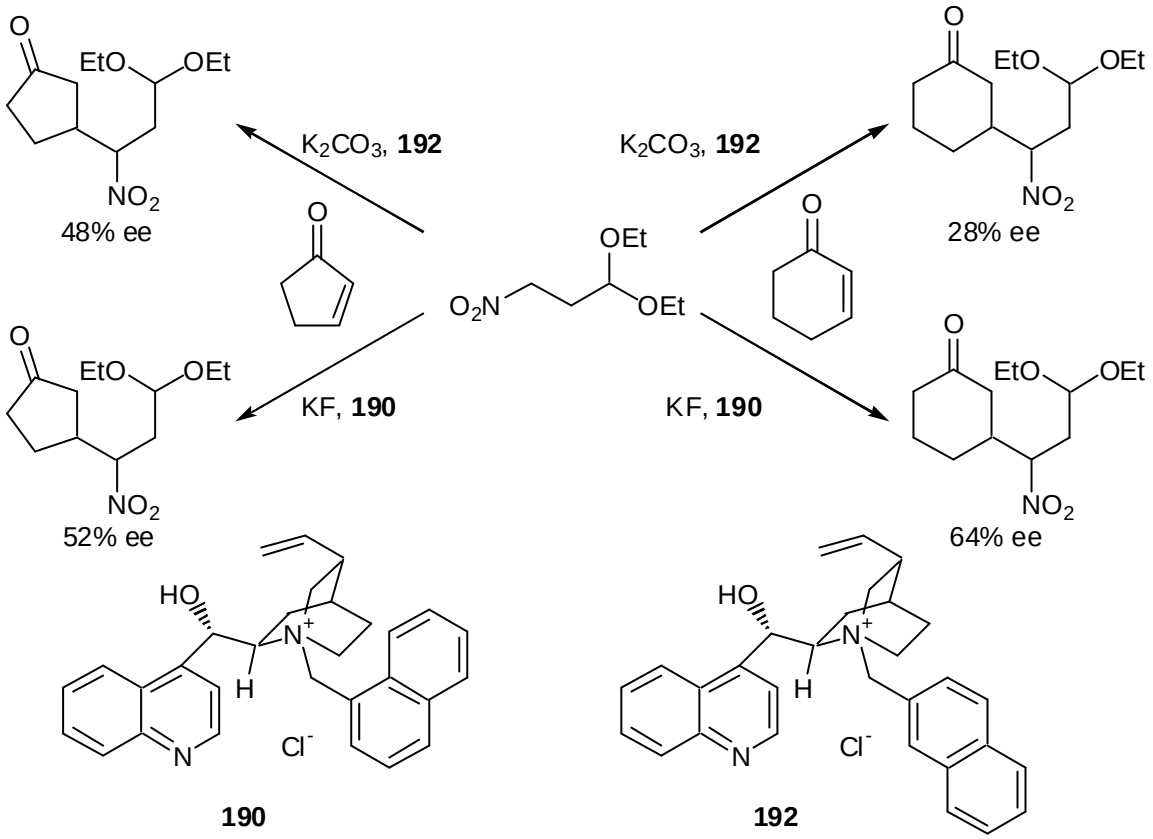


R = CH_2CH_3, -CH_2CH_2-, -$CH_2CH_2CH_2$-

Scheme 181

Nitro-compounds proved to be excellent nucleophiles under phase transfer conditions and could be reacted readily with a series of Michael acceptors. Among them were also unsaturated esters and amides that could not be reacted with sulfonamides.

The use of chiral phase transfer catalysts allowed to realize the addition reaction with modest selectivities. From this study emerged two new catalysts synthesized from cinchonine and 1- and 2-methylnaphthyl chloride (scheme 182). They allowed to obtain the adduct of cyclopentenone and cyclohexenone with better enantioselectivities than catalysts already described in the literature.

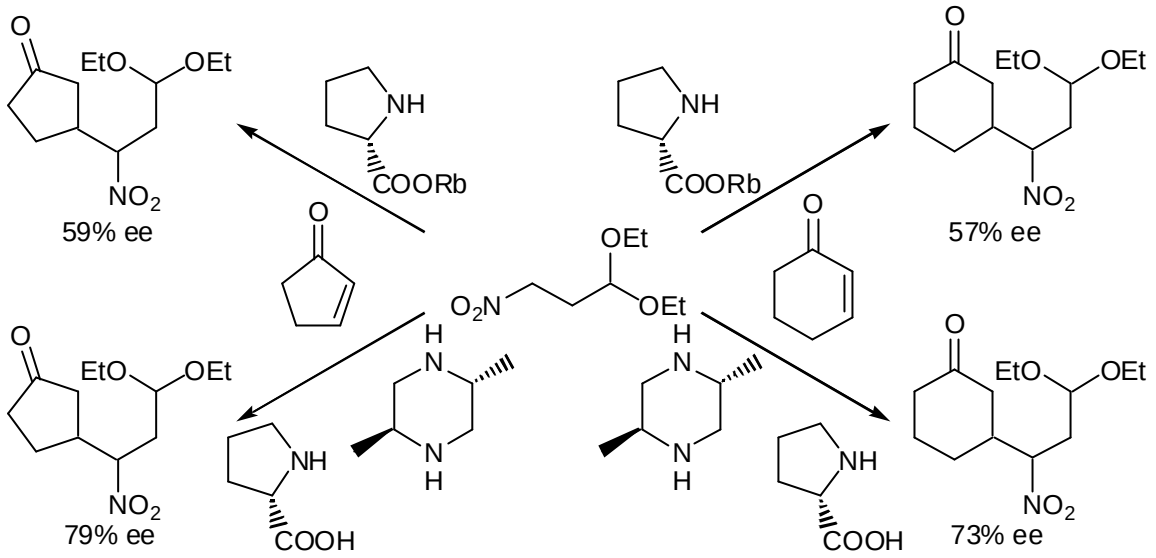


Scheme 182

A mixture of diastereomers was obtained but as the carbon atom bearing the nitro group was supposed to be removed this was not a real obstacle.

Despite the only modest selectivities these are the best results obtained with such substrates under phase transfer conditions when compared to the literature.

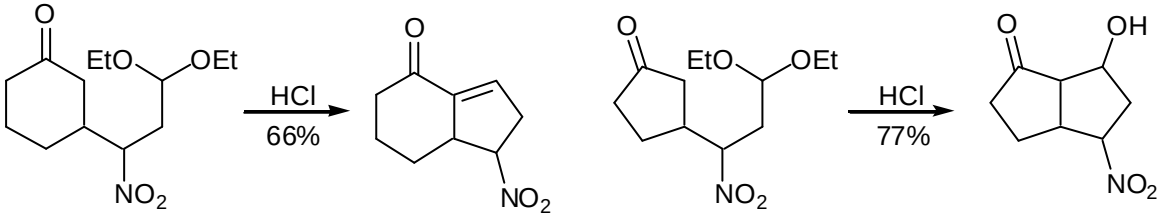
Better enantioselectivities than with phase transfer catalysts could be obtained when organocatalytic methods were used. Catalysis by rubidium prolinate and especially by proline yielded the desired adducts with good enantioselectivies (scheme 183).



Scheme 183

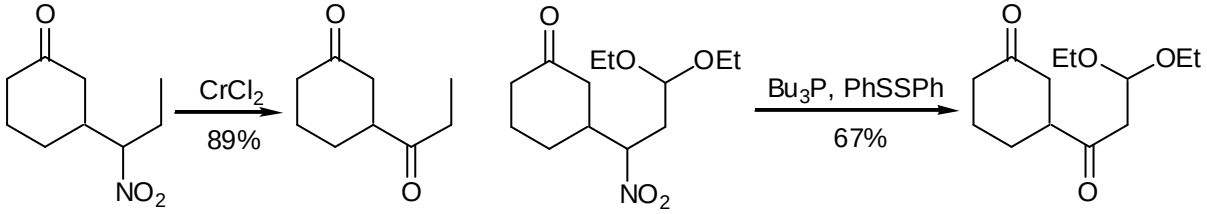
The Michael addition could also be realized starting from silylated nitronates, a reaction that had never been described when we began our studies. Fast reaction rates were observed with an achiral catalyst, but the extension to an asymmetric version failed.

The different Michael adducts could easily be transformed. Cyclization occurred under acidic conditions and yielded an hydroxyketone starting from cyclopentenone and an enone starting from cyclohexenone (scheme 184).



Scheme 184

As supposed, the nitro function could easily be removed and transformed into a carbonyl group (scheme 185).

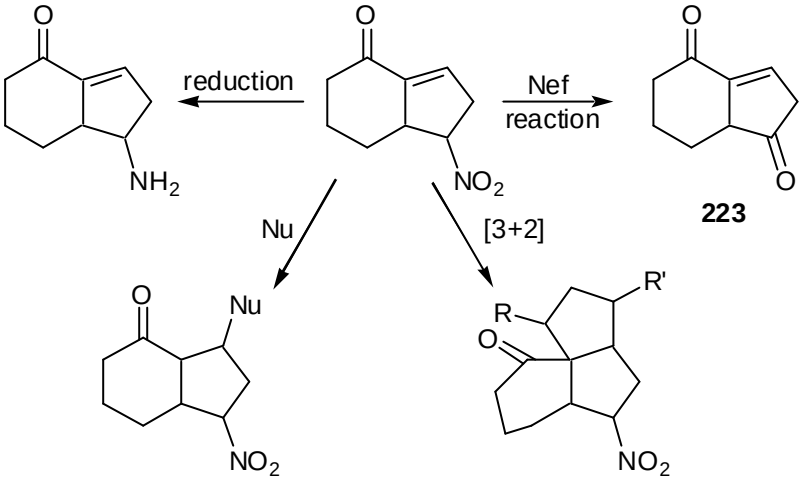


Scheme 185

2.2 Perspectives

At the end of this work we have realized some important developments, but some work has still to be done to complete this study.

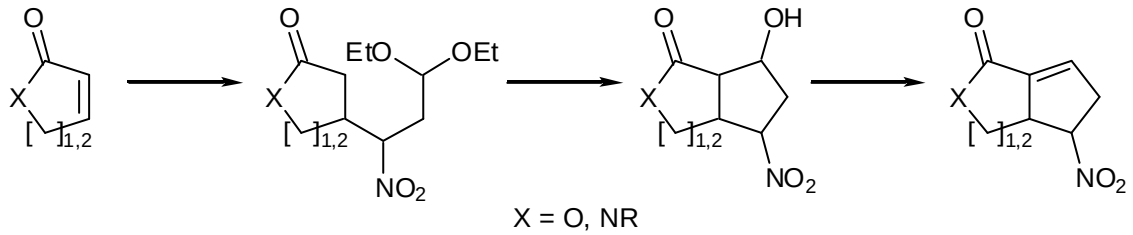
The bicyclic motive obtained with the nitro-containing annulation reagent allows a variety of chemical modifications (scheme 186). Besides the Nef reaction, the reduction of the nitro group into an amine constitutes another possibility. The enone could be reacted with a nucleophile or it could be used as starting point for another [3+2] cycloaddition sequence. Angular polycyclic structures are thus potentially accessible.



Scheme 186

Compound **223** is complementary to the motives obtained with the sulfonamide-based method and Trost's[47] or Feringa's[60] approach with the carbonyl group located in a different position in every method.

We have shown that the Michael addition to unsaturated esters or amides was possible but we did not study the cyclization. This would be a worthwhile study as it would lead to still differently substituted five-membered rings (scheme 187).



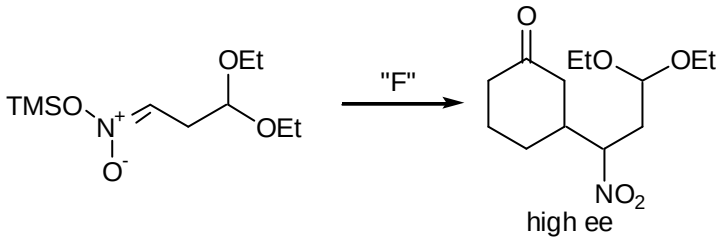
Scheme 187

It appears most interesting that the annulation reagent could easily be obtained with four carbon atoms. thus the same approach would be possible for the synthesis of six-membered rings.

Some other interesting points deserve further investigation.

We have synthesized two novel phase transfer catalysts that showed improved selectivities compared to the described catalysts that bear a benzyl or an anthrylmethyl substituent. It would be interesting to test these catalysts in known reactions, such as the alkylation of *tert*-butylglycinate benzophenone imine, the addition of malonates to enones or the addition of nitromethane to chalcone. We believe that they could improve the reaction rates and could tolerate a higher number of substrates, as they are less hindered than *N*-anthrylmethyl substituted catalysts.

We have shown that silylated nitronates can be used to realize the Michael addition. The reaction was very efficient with TBAF as catalyst. We think that it could therefore be interesting to further develop this method. We were not able to pursue this study but we believe that it is possible to realize the Michael addition with high enantioselectivities and thus have access to the enantiomerically pure bicyclic compounds (scheme 188). The recent results by Maruoka confirm our hypothesis.[211]



Scheme 188

In our opinion the most promising method to realize the asymmetric addition of our annulation reagent will be organocatalysis. The short study that we have realized gave good enantioselectivities. Thus optimization of the catalytic system should lead to a system that produces the adduct with even higher enantioselectivities.