Chapter IV: Michael addition of chiral sulfonamides

1 Introduction

This chapter will primarily describe the additions of chiral sulfonamides to cyclohexenone. General procedure and analytical methods were as in the previous chapter. The sulfonamide was deprotonated and added to cyclohexenone at –78°C in the presence of 8 equivalents of HMPA. The reaction was quenched by the addition of triethylamine and trimethylsilyl chloride. The resulting enol ether was then hydrolyzed by addition of a dilute solution of HCl. HMPA was removed by washing the organic phase with brine and the resulting crude product was analyzed by GC and ^{13}C NMR.

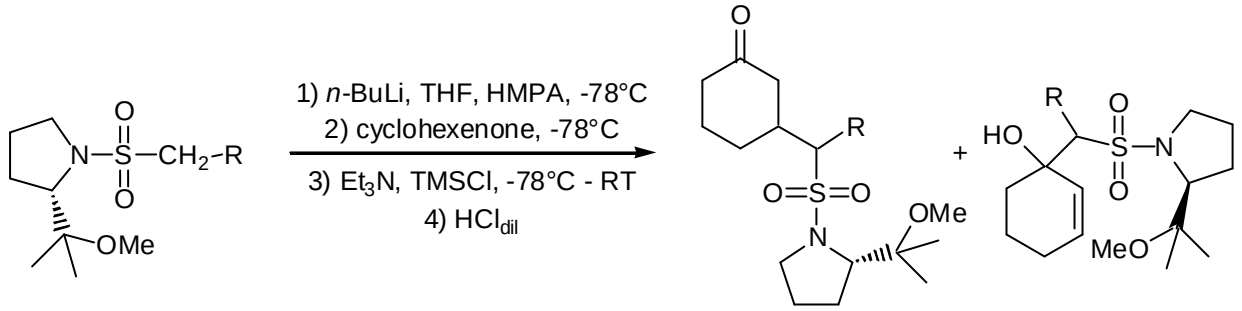
The study will focus on the regiochemical and stereochemical outcome of the addition reaction. Some attempts to extend the reaction to other Michael acceptors will be described.

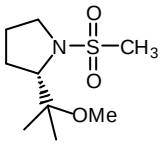
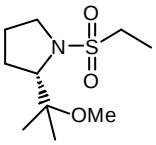
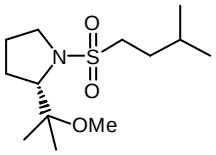
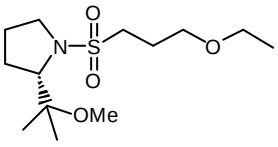
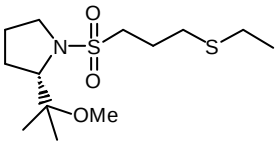
2 Addition of chiral sulfonamides to cyclohexenone

2.1 Results

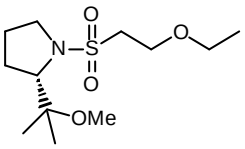
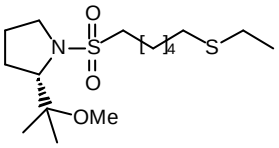
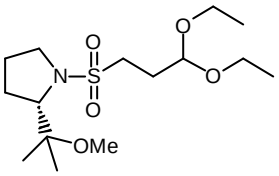
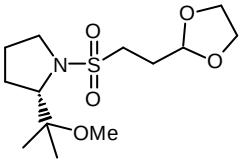
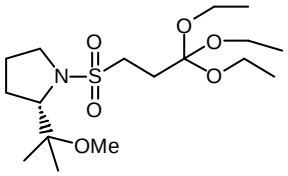
The results are summarized in table 21.

Table 21: *Addition of chiral sulfonamides to cyclohexenone.*



Entry	Sulfonamide	1,4 : 1,2	dr (1,4)[a]	dr (1,2)[b]	Remarks
1	 **14**	< 1 : 20 **115**			
2	 **43**	1 : 1 **116 117**	1.3 : 1[c,d]	1.6 : 1[d]	
3	 **44**	2.1 : 1 **118 119**	9 : 1[c,d]	2.5 : 1[d]	
4	 **65**	> 20 : 1 **120**	11.8 : 1.4 : 1[c]		
5	 **66**	> 20 : 1 **121**	9 : 1[c]		

[a] diastereomeric ratio of the 1,4 adduct
[b] diastereomeric ratio of the 1,2 adduct
[c] measured by GC
[d] measured by ^{13}C NMR

6	 **70**		degradation
7	 **67**		no reaction
8	 **57**	> 20 : 1 **122**	5.7 : 1[c]
9	 **58**	> 20 : 1 **123**	34.5 : 14.5 : 1[c]
10	 **10**	> 20 : 1 **124**	> 20 : 1

2.1.1 Regioselectivity

As we had already pointed out the addition reaction occurred under kinetic control.[67]

Sulfonamide **14** only gave 1,2-addition (entry 1). We had already observed the same behavior for sulfonamide **11** (table 17, entry 1): in the conditions where all the other sulfonamides gave at least 50% of 1,4-adduct, these two sulfonamides showed complete regioselectivity in favor of the 1,2-adduct.

The two other sulfonamides bearing an alkyl chain, **43** and **44**, showed no or modest regioselectivity (entries 2 and 3). The size of the alkyl chain on the sulfonamide thus influenced the regioselectivity: the longer the chain, the higher the regioselectivity in favor of the 1,4 adduct.

Sulfonamides with at least one heteroatom at the third carbon atom only gave the conjugate addition under these conditions (8 equivalents of HMPA, entries 4, 5, 8-10). When the heteroatom was located at the second carbon atom the sulfonamide was degraded under the reaction conditions (entry 8). A β-elimination could be the cause of this degradation. When the heteroatom was located on the sixth carbon atom there was surprisingly no reaction (entry 9). We repeated the reaction several times, but only starting material was recovered. To assure that none of the reagents was responsible for this failure we ran the reaction in parallel with another addition reaction which worked fine. We don't have any explanation for this lack of reactivity.

The present results are in line with those obtained with achiral sulfonamides (table 17). The influence of the size of the alkyl chain and, above all, of the presence of a heteroatom on the third carbon atom was the same in both cases. Some slight differences could be observed: regioselectivity of alkyl substituted sulfonamides was somewhat higher with achiral sulfonamides, on the other hand chiral ether **65** exhibited higher selectivities than its achiral analogue **59**. As the general trend remained the same, one could assume that the presence of the chiral side chain did not alter significantly the regiochemical outcome of the reaction and the hypothesis of an internal chelate by the heteroatom should apply here as well.

2.1.2 Diastereoselectivity

Three stereocenters are found in the adducts: two are formed during the addition reaction, the third one is on the chiral inductor. Thus four diastereomers could be formed in the addition reaction (figure 21).

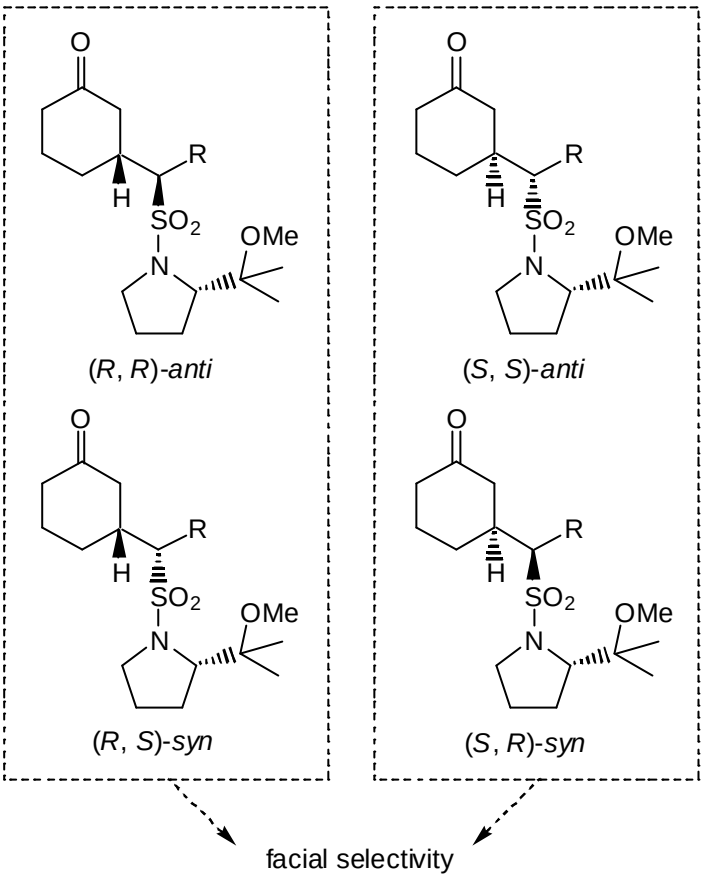


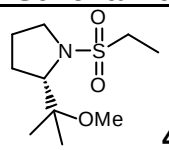
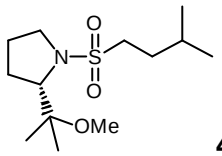
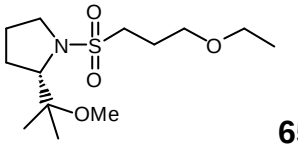
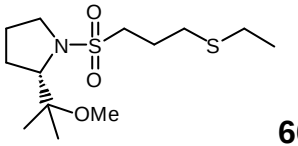
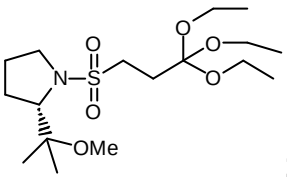
Figure 21

For synthetic purposes, the most important center is the carbon atom β to the carbonyl group. We will thus consider two couples of diastereomers. In each couple the stereogenic center on the cyclohexane ring has the same absolute configuration and the sulfonamide is *anti* or *syn*. The facial selectivity could be defined by the ratio of isomers having the same absolute configuration on the ring carbon atom.

In most cases only two of the four possible isomers could be observed. Only ether **65** and ketal **58** led to a small quantity of a third diastereomer (entry 4 and 9).

For all adducts, we observed identical features for the chemical shifts of the carbon atom α to the sulfonamide. The signal for the minor isomer was slightly downfield compared to that of the major isomer (table 22). For the adducts of **57** and **58** we were not able to determine the chemical shift of the minor isomer.

Table 22: *Chemical shifts of the carbon atom α to the sulfonamide.*

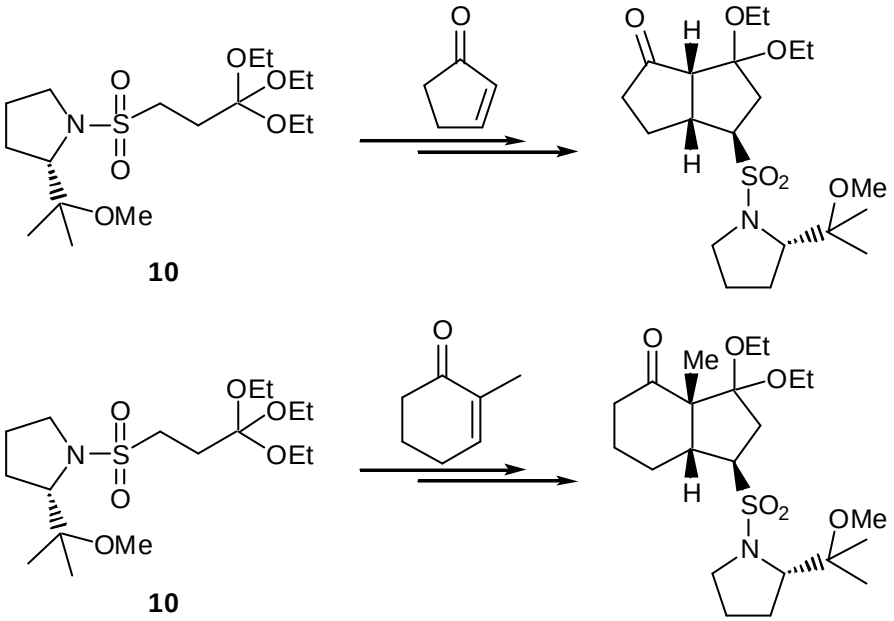
Entry	Sulfonamide	δ_{major} (ppm)	δ_{minor} (ppm)
1	 **43**	61.0	61.3
2	 **44**	63.9	64.7
3	 **65**	62.9	63.5
4	 **66**	64.8	66.1
5	 **10**	61.9	not detected

Based on these results we could assume that in all the cases the same couple of diastereomers was formed.

Several other data could help us in the configurational assignments. We have seen in the previous chapter that all the adducts were formed in a diastereomeric ratio that varied from 3.2 : 1 to 10 : 1 in favor of the *anti* adduct (table 17). The diastereomeric ratios obtained here were about the same.

We thus believe that the major isomer formed in the addition reaction of chiral sulfonamides had also the *anti* relative stereochemistry. For the second isomer we propose the diastereomer with the same absolute configuration on the carbon atom β to the carbonyl group but with the sulfonamide group being *syn*.

The absolute configuration has been determined by X-ray analyses of the major isomer resulting from the cyclization of cyclopentenone and 2-methylcyclohexenone.[67] It showed that the initially formed chiral center had the absolute configuration *R* and the ring junction was *cis*. Moreover the sulfonamide was *exo* in both cases (scheme 87).



Scheme 87

This confirmed the observations of the previous chapter that the major adduct formed had an *anti* relative configuration.

Based on these results we propose therefore for the major adduct the absolute configuration shown in figure 22.

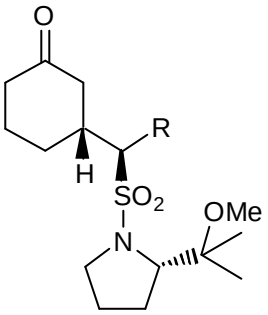
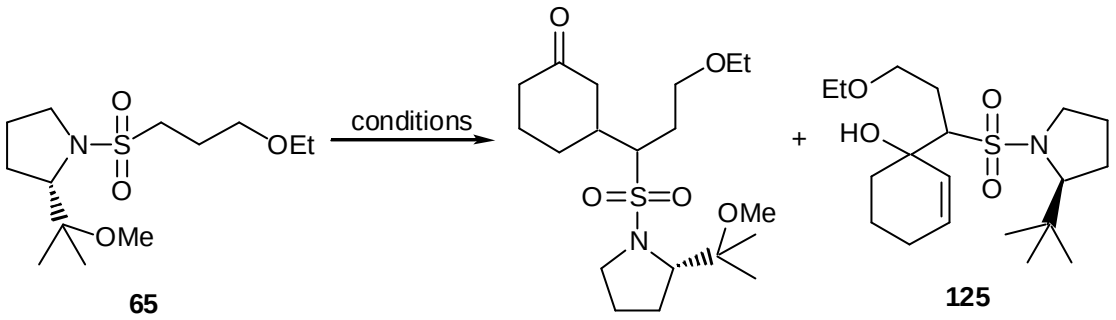


Figure 22

3 Studies of other experimental conditions

We have also studied the addition of ether **65** to cyclohexenone in other experimental conditions (table 23).

Table 23: *Addition of **65**.*



Entry	Conditions	1,4 : 1,2	dr (1,4)	Remarks
1	THF, 8 eq. HMPA, -78°C	> 20 : 1	11.8 : 1.4 : 1	quant.
2	**Et_2O**, 8 eq. HMPA, -78°C	~1 : 1	not measured	important degradation
3	THF, 8 eq. HMPA, **0°C**	> 20 : 1	8.1 : 2 : 1	50% yield
4	THF, **64 eq. DMPU**, -78°C	> 20 : 1		80% yield
5	THF, **2 eq. TMEDA**, -78°C	< 1 : 20		
6	THF, **4 eq 12-c-4**, -78°C	< 1 : 20		
7	THF, **4 eq. HMPA**, -78°C	14.4 : 1	21.2 : 2.7 : 1	
8	THF, **0 eq. HMPA**, -78°C	< 1 : 20		

3.1 Solvent

The reaction in diethyl ether was messy (entry 2). A lot of degradation products appeared and we were not able to determine exactly what the product distribution was. In this solvent, a significant quantity of 1,2-adduct **125** was observed.

3.2 Temperature

It is generally accepted that temperature can strongly influence stereoselectivity; thus working at lower temperature could improve the stereochemical outcome of a reaction. When we realized the reaction at 0°C, yield was however considerably lower (entry 3). An explanation could be that enolization became a major side-reaction thus limiting the formation of the adduct. Variations in diastereoselectivity were low.

3.3 Additives

In the absence of HMPA complete regioselectivity in favor of the 1,2-addition was observed (entry 8). With only 4 equivalents of HMPA, the 1,4 regioselectivity was still high (entry 7).

It has been shown by Reich that HMPA influenced the stereochemical outcome of the addition reaction of 3-methylbenzyl phenyl sulfide to 5-trimethylsilyl-2-cyclohexen-1-one.[155] He also showed that the change in stereochemistry was observed upon the addition of HMPA; further increase in the quantity of HMPA had no influence.

In our case no change in diastereoselectivity was observed when only half of the quantity of HMPA was used (entry 7). We were not able to control the effect when passing from 0 to 1 equivalent of HMPA as 1,2-adduct was the product obtained in that case.

Other additives than HMPA could be used to control the regiochemistry of the addition reaction.

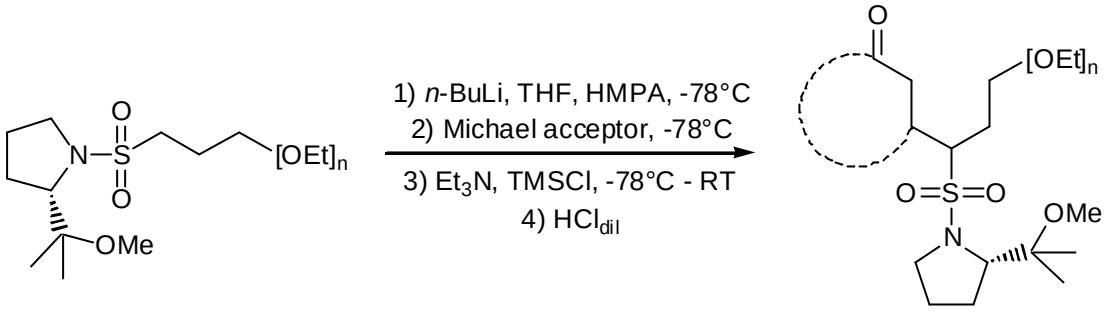
64 equivalents of DMPU were necessary to obtain the same regioselectivity than with 8 equivalents of HMPA as had been already shown by C. Huart (entry 4). Conversion was however never complete under these conditions. The use of TMEDA resulted in only 1,2-addition (entry 5). It has been suggested that TMEDA is to hindered to be a good ligand for the lithium cation.[147] This result was however disappointing as the use of chiral diamines, *e.g*. sparteine[156], with achiral orthoester **3** could have been an interesting alternative for the asymmetric addition. With 4 equivalents of 12-crown-4, a crown ether with the specific size for the lithium cation, only 1,2-addition was observed (entry 6).

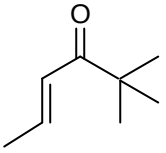
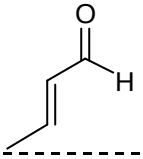
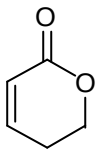
4 Addition of chiral sulfonamides to other acceptors

Other Michael acceptors than cyclic enones had not been tested before. We had already shown in the previous chapter that unsaturated lactams were not suitable Michael acceptors. Table 24 show our results with other Michael acceptors.

[155] Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.*, **2001**, *123*, 6527-6535.
[156] for a review on the use of sparteine see Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2283-2316.

Table 24: *Addition of chiral sulfonamides to other Michael acceptors.*



Entry	Sulfonamide	Michael acceptor	Product	1,4 : 1,2	dr (1,4)	Remarks
1	n=1, **65**	 **75**	**126**	> 20 : 1	8.3 : 5 : 1	74% yield
2	n=3, **10**		**127**	> 20 : 1	10.1 : 1	22% yield
3	n=3, **65**		**128**	> 20 : 1	1.3 : 1	40% yield
4	n=1, **65**	 **72**	complex mixture			
5	n=1, **65**		complex mixture			no HMPA
6	n=3, **10**		**129**	< 20 : 1		23% yield
7	n=3, **10**		complex mixture			no HMPA

The addition to 2,2-dimethylhex-4-en-3-one **75** selectively gave the 1,4-adduct (entries 1 and 2). The low yield for the orthester adduct was due to purification problems as the reaction worked well, as we will see in the next chapter. Stereoselectivity was lower than with cyclohexenone especially with ether **65**. Hexenone **75** is indeed less rigid than cyclohexenone which could then decrease the facial selection. The stereoselectivity remained however quite high when orthoester **10** was used. This result was very promising for the perspective of a cyclization of this enone.

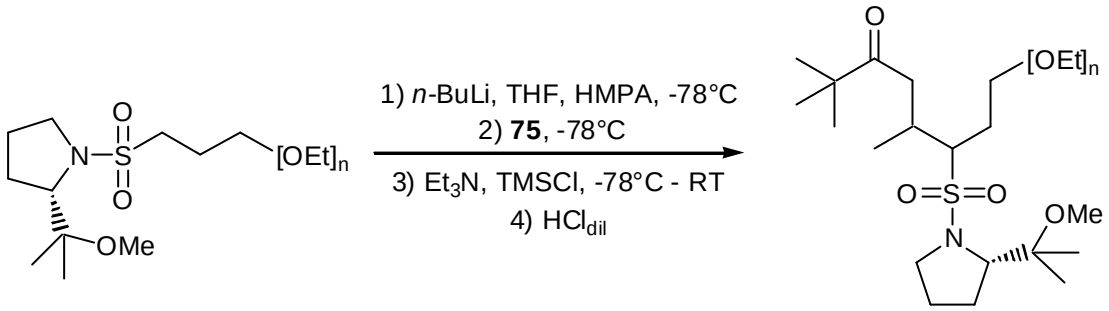
As one could have expected, the addition to crotonaldehyde only led to the formation of the 1,2-adduct (entry 3).

Addition to lactone **72** was disappointing. Only orthoester **10** gave, albeit in low yield, the addition product (entry 6). Moreover the reaction mixture was very messy. In the absence of HMPA or with ether **65** complex mixtures where no addition

product could be isolated were formed (entries 4, 5 and 7). The pentannulation sequence could thus not be extended to unsaturated lactones either.

To complete the study on the influence of HMPA on the diastereoselectivity we needed a Michael acceptor that would react in a 1,4-addition even in the absence of HMPA. (*E*)-2,2-dimethylhex-4-en-3-one **75** seemed a good candidate as we believed that the bulky *tert*-butyl group should prevent an attack onto the carbonyl (table 25).

Table 25: *Influence of HMPA on the stereoselectivity.*



Entry	n	HMPA	1,4 : 1,2	dr (1,4)
1	1 (**65**)	8 eq.	> 20 : 1	5 : 1 : 8.3
2	1 (**65**)	4 eq.	> 20 : 1	4.1 : 1 : 2.5
3	1 (**65**)	0 eq.	> 20 : 1	4.6 : 1.5 : 1
4	3 (**10**)	8 eq.	> 20 : 1	10.1 : 1
5	3 (**10**)	0 eq.	> 20 : 1	13.7 : 2 : 1

Our hypothesis was correct: only the 1,4-adduct was formed even in the absence of HMPA.

In contrast with what we had observed with cyclohexenone, varying the quantity of HMPA led to a significant change in stereoselectivity. With ether **65** diastereoselectivity was low in every case. We observed however that the major isomer formed was not the same whether HMPA was used or not (entries 1-3). The observations were in contradiction with Reich's results. The variation in the stereoselectivities was most pronounced with more than 4 equivalents of HMPA.

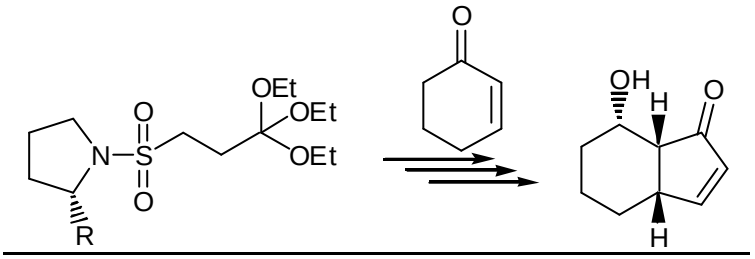
The effect was less important when orthoester **10** was used (entries 7-8). Diastereoselectivity dropped when no HMPA was used and a third diastereomer was formed in this case. However the same isomer was formed as major compound in both cases.

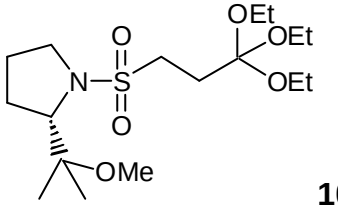
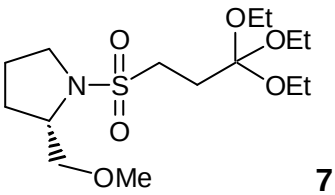
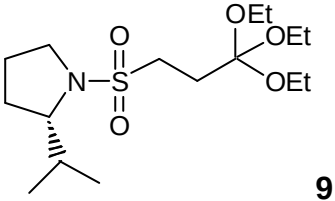
These results could be explained by a chiral solvation sphere where HMPA remained close to the reaction center. The difference between ether **65** and **10** could be explained as follows. The orthoester could form a stronger complex with the cation than the ether. Less HMPA would then be present in the solvation sphere or HMPA would complex less tightly to the cation. In that case its influence on diastereoselectivity should be diminished.

5 Proposal of mechanism

We would now like to propose a rational explanation for the stereochemical outcome of the Michael addition. We believe that a chelation by the heteroatom on the γ carbon atom is likely to occur as shown by the effect of the heteroatom on the regioselectivity. Moreover a chelation by the oxygen atom on the chiral inductor should also be envisaged. Support for this hypothesis is brought about by considering the enantioselectivities measured with the three annulation reagents shown in table 26.[67]

Table 26: *Enantioselectivities measured with different annulation reagents.*[*]



Reagent	ee
 **10**	96%
 **7**	62%
 **9**	53%

[*] Measured on cyclized product

On the basis of steric hindrance, reagent **9** should display higher selectivities than orthoester **7**. This was not the case: one should therefore invoke a complexation of the lithium cation by the oxygen atom. Two reasons could explain the still higher selectivities observed with **10**. The presence of the additional two methyl groups creates more steric hindrance. Moreover these methyl substituents would favor the formation of the chelate by a Thorpe-Ingold effect.[157]

HMPA should be present close to the reaction center as we have seen that it has some influence on the diastereoselectivity.

We thus propose a model for the sulfamoylated anion that is closely related to the one proposed by C. Huart[67] (figure 23), but we made some corrections.

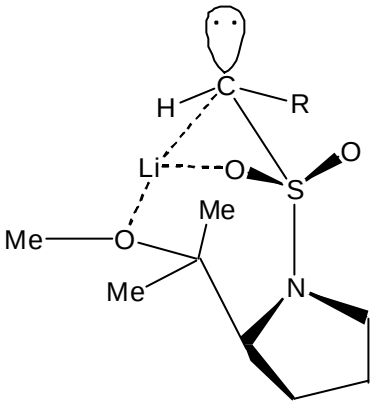


Figure 23

First we believe that, for steric reasons the sulfonamide will be *anti* with respect to the chiral side chain, which could still complex the cation in this configuration. The lone pair of the carbanion is gauche with respect to the oxygen atoms on the sulfur. Based on the discussion of chapter I we do not include the carbanion in the solvation sphere of the lithium cation. Instead we consider a molecule of HMPA complexing the cation. We thus propose the geometry shown in figure 24.

[157] Hammond, G. S., *Steric Effects on Equilibrated Systems*, in *Steric Effects in Organic Chemistry*, Newman, M. S., Editor. John Wiley & Sons, Inc.: New York. 1956, p. 462-465.

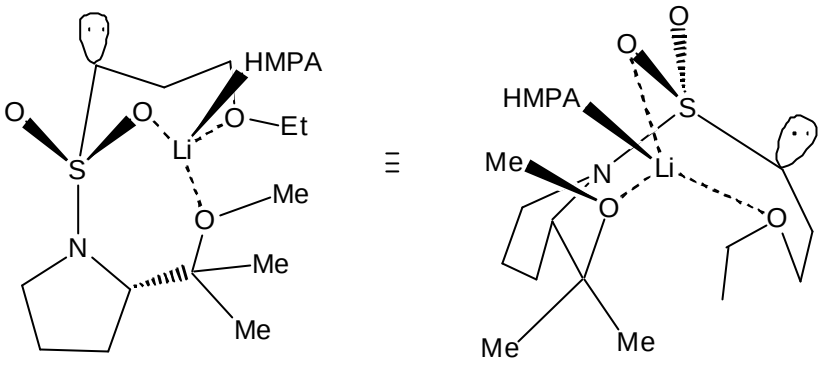
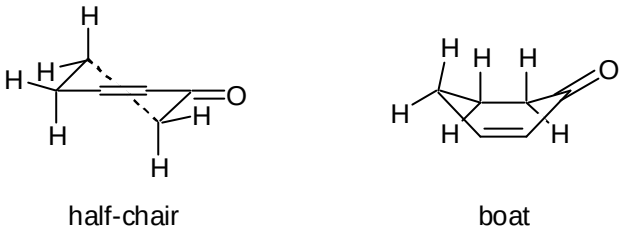


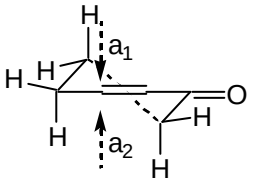
Figure 24

We must also consider the Michael acceptor. The most stable conformation of cyclohexenone is a half-chair.[158] In the boat-like conformation there are indeed unfavorable Pitzer interactions.[159] A half-chair conformation will thus be considered (scheme 88).[160]



Scheme 88

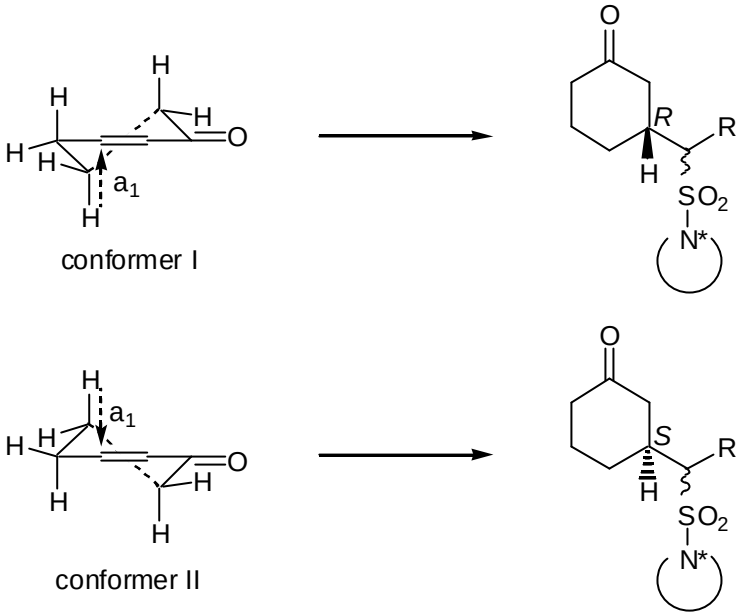
Toromanoff had shown that the direction of attack of a nucleophile was close to perpendicular to the double bond to obtain the best overlap of orbitals (stereoelectronic control).[161] The side of attack will be controlled by steric interactions. It has been shown that an attack following pathway a_1 generates 1,3-diaxial interactions (scheme 89).[160] However attack following pathway a_2 has an even more serious problem: the bond that is forming and the axial hydrogen on carbon C-4 are eclipsed and thus the steric hindrance generated by approach a_2 should be 1.5 times more important than for approach a_1.[160]



Scheme 89

[158] Anet, F. A.; Haq, M. Z. *J. Am. Chem. Soc.*, **1965**, *87*, 3147-3150.
[159] Pitzer, K. S. *J. Chem. Phys.*, **1944**, *12*, 310-314.
[160] Riviere, H.; Tostain, J. *Bull. Soc. Chim. Fr.*, **1969**, 568-576.
[161] Toromanoff, E. *Bull. Soc. Chim. Fr.*, **1962**, 708-712.

There are two enantiomeric conformations of cyclohexenone. One can easily see that an attack on conformer I leads to the *R* configuration whereas configuration *S* would be the result of an attack on conformer II (scheme 90).



Scheme 90

When we now put these two conformers in the presence of the proposed geometry for the sulfonamide it appears that conformer II shows two major steric interactions with the anion (figure 91). The equatorial proton on carbon C-4 is too close to the oxygen atom of the sulfonamide and the hydrogen on carbon atom C-5 is too close to one of the protons in the substituent of the sulfonamide. These two interactions are not found in the approach of conformer I, which leads to the observed enantiomer.

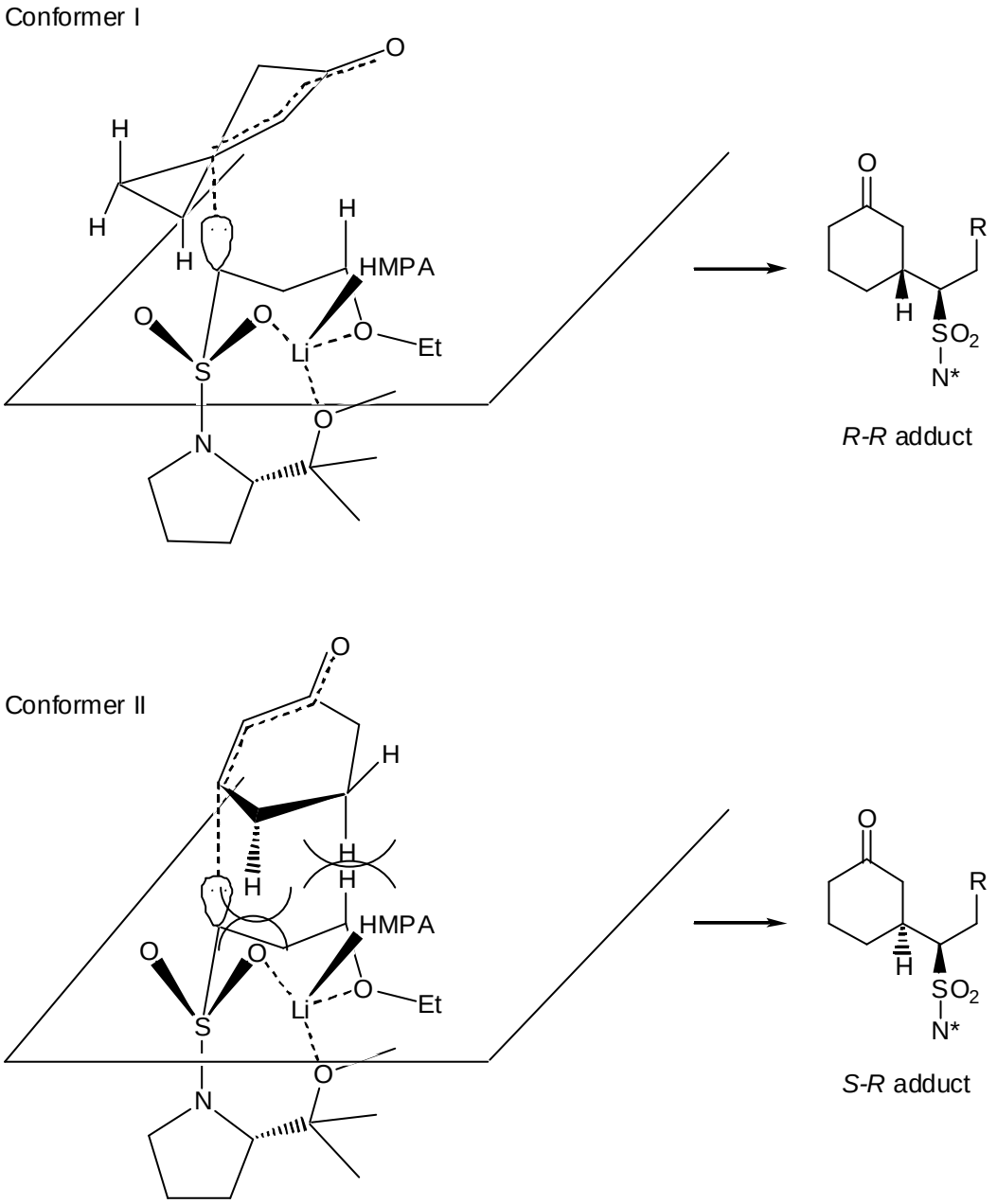


Figure 91

6 Conclusion

In this chapter we completed the study on the Michael addition of sulfonamides to enones. The observations were consistent with that of the previous chapter. The size of the substituent on the sulfonamide and, most important, the presence of a heteroatom, were crucial for the regiochemical outcome of the reaction. Diastereoselectivities remained similar to the one observed previously with the exception of the sulfonamide substituted by an ethyl group.

The Michael addition to acyclic enones could be realized however the extension to enals or unsaturated lactones was not possible.

We have studied the use of other additives than HMPA or DMPU but they resulted in complete 1,2-addition.

The use of enone **75** allowed us to show that HMPA also influenced the stereochemical outcome of the reaction.

Based on all these results we proposed a hypothesis for the transition state that could explain the stereochemistry observed in the addition reaction.