Chapter I: Michael addition of carbanions stabilized by sulfur-substituents

In the present dissertation we shall first study the Michael addition of carbanions stabilized by sulfur-containing electron-withdrawing groups. Before presenting our results we will review previous work on these carbanions, in particular that related to their addition to enones.

Although sulfonamides have been known for many years[69-71] little information is available on sulfonamide-stabilized (or sulfamoylated) carbanions. Therefore most of the discussion has to be based on α-sulfonylated carbanions.

1 Sulfamoylated carbanions

1.1 Stabilization of the anion

The stability of an anion can be measured by the acidity of its conjugate acid. As shown by Bordwell the pK_a for acetone in DMSO is 26.5, whereas the pK_a of dimethylsulfone is 31.1.[72] The values shown in table 4 allow to compare ketones, amides, sulfones and sulfonamides.

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[69] Doub, M., in *Encyclopedia of Chemical Technology*, Grayson, M., Editor. Wiley: New York. 1983, p. 795.

[70] Hoyle, J., *Preparation of sulphonic acids, esters, amides and halides*, in *The chemistry of sulphonic acids, esters and their derivatives*, Pataï, S. and Rappoport, Z., Editors. John Wiley & Sons: Chichester, England. 1991, p. 351-399.

[71] Tanaka, K., *Sulfonic acids, esters, amides and halides as synthons*, in *The chemistry of sulphonic acids, esters and their derivatives*, Patai, S. and Rappoport, Z., Editors. John Wiley & Sons Ltd: Chichester, England. 1991, p. 401.

[72] Bordwell, F. G. *Acc. Chem. Res.*, **1988**, 456-463.

Table 4: *pK_a of selected carbon acids.*[72]

Entry	acid	pK_a
1	CH_3COCH_3	26.5
2	$CH_3SO_2CH_3$	31.1
3	CH_3COCH_2Ph	19.9
4	$PhSO_2CH_2Ph$	23.4
5	H_2NCOCH_2Ph	24.7
6	$Me_2NSO_2CH_2Ph$	25.2

It appears that hydrogen atoms α to a carbonyl group are more acidic than those α to a sulfone. The difference is 4 to 5 pK_a units when no other stabilization mode is possible (entries 1 and 2), it is somewhat lower in the case of another stabilization, such as conjugation with a phenyl group (entries 3 and 4). The difference between amides and sulfonamides however is low (entries 5 and 6). Thus whereas a ketone is significantly more acidic than an amide, there is only a small difference between a sulfone and a sulfonamide.

To explain these observations the stabilization of the resulting anions has to be considered. Two modes of stabilization are possible for an anion stabilized by a carbonyl. There is first an electrostatic interaction between the anion and the partial positive charge on the carbonyl (figure 9). More important however is the possible conjugation between the lone pair of the anion and the π-electrons of the double bond.

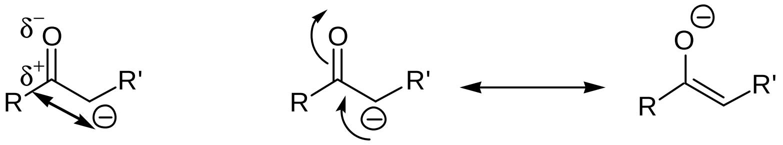

Figure 9

In the amide a possible conjugation between the nitrogen lone pair and the double bond diminishes the partial charge on the carbonyl, and also the weight of the enolate-type resonance form (figure 10).

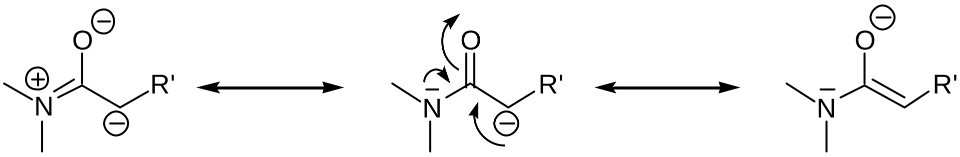

Figure 10

Things are more complicated in the case of sulfur-containing electron-withdrawing groups and the stabilization mode of these anions has been a subject of controversy during many years. The stabilization by electrostatic interactions is quite important in this case (figure 11). It has indeed been shown that the sulfur atom has essentially a +2 charge in sulfones and their anions.[73]

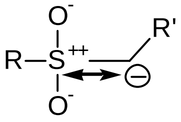

Figure 11

However resonance forms such as for an enolate can not be written due to a bad overlap between the p-orbital of the anion and the S-O double-bond. In the 1960's and 1970's stabilization by the d-orbitals of the sulfur atom was generally accepted, as shown by the work of Cram[74,75], Lipscomb[76] or Kaiser.[77] However Schleyer, Clark, Houk and coworkers have shown that such a stabilization may be neglected.[78] Today it is assumed that d-orbitals on sulfur do not contribute to an energetic stabilization of the corresponding anions.[73]

The stabilization results from an overlapping between the n orbital of the carbon atom and the σ* orbital of the C-S bond as suggested by Wolfe [79] and later by Bors and Streitwieser[80] (figure 12).

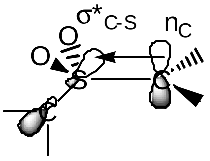

Figure 12

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[73] Boche, G.; Lohrenz, J. C. W.; Cioslowski, J.; Koch, W., *Carbon acidity resulting from sulfur substituents*, in *The chemistry of sulphur-containing functional groups*, Patai, S. and Rappoport, Z., Editors. John Wiley & Sons Ltd. 1993, p. 339-362.

[74] Cram, D. J.; Scott, D. A.; Nielsen, W. D. *J. Am. Chem. Soc.*, **1961**, *83*, 3696-3707.

[75] Cram, D. J., *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965, p. 71-84.

[76] Jordan, T.; Smith, H. W.; Lohr, L. L.; Lipscomb, W. N. *J. Am. Chem. Soc.*, **1963**, *85*, 846-851.

[77] Kaiser, E. M.; Solter, L. E.; Schwarz, R. A.; Beard, R. D.; Hauser, C. R. *J. Am. Chem. Soc.*, **1971**, *93*, 4237-4242.

[78] Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.*, **1984**, *106*, 6467-6475.

[79] Wolfe, S.; Stolow, A.; LaJohn, L. A. *Tetrahedron Lett.*, **1983**, *24*, 4071-4074.

[80] Bors, D. A.; Streitwieser, A. J. *J. Am. Chem. Soc.*, **1986**, *108*, 1397-1404.

1.2 Geometry of the anion

The geometry of anions stabilized by sulfur-substituents has also been a matter of controversy. A lot of discussion aroused whether the anion is planar[81,82] or tetrahedral.[83] *Ab initio* calculations by Wolfe came to the conclusion that the anion is tetrahedral with the lone pair gauche with respect to the S-O bonds.[84]

Experimental evidence was brought by the ^{13}C NMR studies realized by Chassaing et Marquet.[85,86] $^1J_{^{13}C\text{-}H}$ coupling constants are highly sensitive to the hybridization state and to the electron density on the carbon. They increase when passing from an sp^3 hybridized carbon atom to an sp^2 hybridization. On the other hand a charge increase induces a decrease of $^1J_{^{13}C\text{-}H}$. Experimental results of a series of α-sulfonylated carbanions are shown in table 5.

Table 5: *^{13}C NMR characteristics of α-sulfonylated carbanions.*[85,86]

Entry	Anion	$^1J_{^{13}C\text{-}H}$	Δ^1J^a	δ	$\Delta\delta^a$
1	$PhCHLiSO_2CH_3$	163	+23	59.8	-1.9
2	$PhCHLiSO_2$-*t*-Bu	160	+21	51.1	-2.1
3	*t*-$BuSO_2CH_2Li$	142	+4	21.1	-13.5
4	$PhSO_2CH_2Li$	139	0	35.4	-9
5	$(CH_3)_3P=CH_2$	149	$+20^b$	-2.3	-21.2^b

Two different behaviors were found. Benzylic anions (entries 1 and 2) showed a large increase in the coupling constant and nearly no variation in the chemical shift. In alkyl anions (entries 3 and 4) the coupling constants did not change significantly upon deprotonation, however a decrease in the chemical shift was observed.

The Δ^1J value observed in benzylic anions was consistent with a planar configuration or sp^2 hybridization. It was the same as in methylenic compound of $(CH_3)_3P=CH_2$ (entry 5) where the sp^2 hybridization had been established.

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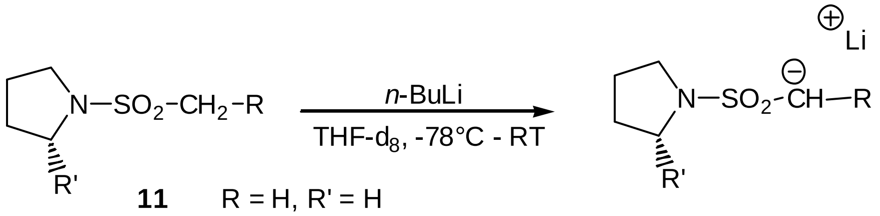
[81] Corey, E. J.; Lowry, T. H. *Tetrahedron Lett.*, **1965**, 793-801.
[82] Corey, E. J.; Lowry, T. H. *Tetrahedron Lett.*, **1965**, 803-809.
[83] von E. Doering, W.; Levy, L. K. *J. Am. Chem. Soc.*, **1955**, *77*, 509-513.
[84] Wolfe, S.; Rauk, A.; Csizmadia, I. G. *J. Am. Chem. Soc.*, **1969**, *91*, 1567-1569.
[85] Lett, R.; Chassaing, G.; Marquet, A. *J. Organomet. Chem.*, **1976**, *11*, C17-C20.
[86] Chassaing, G.; Marquet, A. *Tetrahedron*, **1978**, *34*, 1399-1404.
[a] Difference of J or δ compared to the neutral starting compound
[b] ΔJ and Δδ with respect to the CH_3 of the same molecule

The smaller Δ^1J observed in alkyl anions corresponded to a hybridization state intermediate between sp^2 and sp^3. The complex origin of ^{13}C chemical shifts does not allow to conclude on the geometry from the observations made.

These results lead to the interesting conclusion that for a sulfone group it appears to be irrelevant whether the negative charge to be stabilized is situated on a planar or on a pyramidalized α-C atom.[87]

The same approach was applied in our laboratory to the case of α-sulfamoylated anions.[67] The results of these studies are summarized in table 6.

Table 6: *^{13}C NMR characteristics of α-sulfamoylated carbanions.*[67]



11 R = H, R' = H
12 R = Et, R' = H
13 R = Ph, R' = H
14 R = H, R' = $C(CH_3)_2OCH_3$

Entry	Sulfonamide	$^1J_{^{13}C\text{-}H}$	Δ^1J	δ	$\Delta\delta$
1	**11**	140	+3	19.9	-13.7
2	**12**	142	+7	41.5	-9.4
3	**14**	140	+3	27.3	-9.8
4	**13**	166	+30	52.4	-3.5

A slight increase of the coupling constant upon deprotonation was observed for the sulfonamides **11**, **12** and **14** (entries 1-3). A tetrahedral geometry with a hybridization intermediate between sp^2 and sp^3 could therefore be proposed for these anions.

The Δ^1J value measured for **13** was higher (entry 4). In this compound the anion adopted a nearly planar geometry thus allowing a delocalization of the carbon lone pair to the aromatic cycle. The measured value was in agreement with an sp^2 hybridization of the carbon atom.

This study showed that anions stabilized by a sulfonamide followed the trend of their sulfone analogues.

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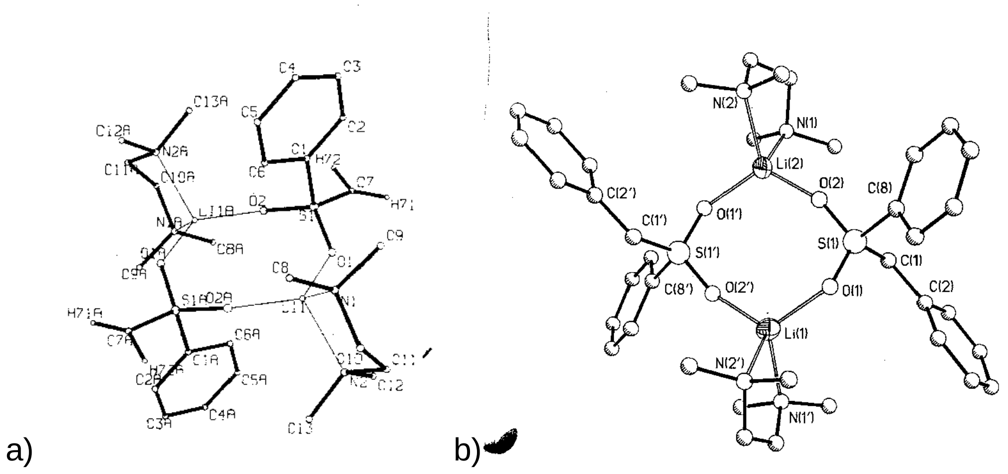
[87] Boche, G. *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 277-297.

The bond lengths have also been well studied. An important bond shortening of the C-S bond together with a slight increase of the S-O bonds was observed by infra-red spectroscopy.[88] These observations were in agreement with the calculations carried out by Wolfe.[79] To account for the bond shortening two explanations were given. A first was the electrostatic interaction between the carbanion and the positively charged sulfur-atom. The second was a n_c-σ^*_{C-S} bonding as described above. Here again no influence of the sulfur d-orbitals could be proven. Bors and Streitwieser obtained indeed the same geometry whether they used or not d-orbitals (3-21G(*)+ or 3-21G+ set respectively) for their calculations.[80]

A last important point is the position of the cation (Li$^+$). Chassaing and Marquet concluded from the coupling constant observed in the benzylated anions to the presence of a very loose C-Li bond.[85] They observed however an interaction between the lithium cation and the carbanion in the infra-red spectra.[88] The ^{6}Li,^{1}H heteronuclear NOE experiments by Gais led to the conclusion that the major interaction was between Li$^+$ and the two oxygen atoms of the sulfone.[89]

X-ray analyses of anions by Boche[90] and Gais[89,91] confirmed the results obtained by other methods (figure 13).



a) b)

Figure 13

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[88] Chassaing, G.; Marquet, A.; Corset, J.; Froment, F. *J. Organomet. Chem.*, **1982**, *232*, 293-313.

[89] Gais, H. J.; Hellmann, G.; Günter, H.; Lopez, F.; Lindner, H. J.; Braun, S. *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 1025.

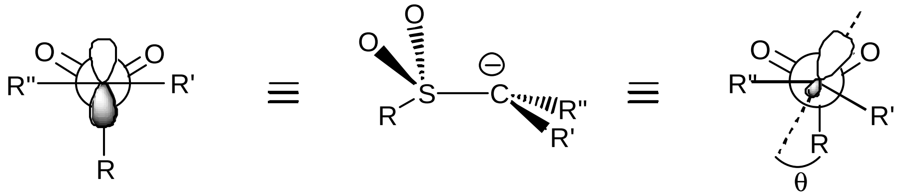
[90] Boche, G.; Marsch, M.; Harms, K.; Sheldrick, G. M. *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 573-575.

[91] Gais, H.-J.; Lindner, H. J.; Vollhardt, J. *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 859.

Figure 13a shows the X-ray structure of $[\{CH_2(SO_2C_6H_5)\}Li(tmeda)]_2$.[91] It features a nearly planar carbanion and an unusually short S-C bond. Lithium cation is coordinated by the two oxygen atoms of the sulfone and by two nitrogen atoms of TMEDA.

In figure 13b the X-ray structure of [α-(phenylsulfonyl) benzylLi(tmeda)$]_2$ shows a planar carbanion in accordance with the sp^2 hybridization of a benzylic anion.[90] Again lithium is coordinated only by the oxygen atoms of sulfone and TMEDA.

Theoretical calculations[79] as well as the above X-ray analyses have shown that the carbanion lone pair is gauche with respect to the two oxygen atoms of the sulfone group. The geometry of the anions stabilized by a sulfur substituent is represented in figure 14. When the anion can be stabilized by conjugation (e.g. R' or R" = Ph) it adopts a planar configuration (type **A**). In the other cases it will adopt a tetrahedral configuration with an hybridization intermediate between sp^3 and sp^2 (type **B**). The highest stabilization is obtained for $\theta = 0$.



type **A**
planar

type **B**
tetrahedral

Figure 14

The geometry of sulfonamides has been studied by ^{15}N NMR.[92] It was shown that the nitrogen atom adopts a tetrahedral geometry and that bulky substituents will hinder the passage to a planar geometry. The most favored conformation will be the one depicted in figure 15 with the nitrogen lone pair situated gauche between the oxygen atoms on the sulfur.[93] The barrier of rotation around the N-S bond was found to be 11.5 kcal.mol^{-1}. Thus the nitrogen atom adopts a geometry similar to that of a carbanion. It is tetrahedral with its lone pair gauche with respect to the two oxygen atoms.

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[92] Dorie, J.; Gouesnard, J.-P. *J. Chem. Phys.*, **1984**, *81*, 15-19.
[93] Jennings, W. B.; Spratt, R. *J. Chem. Soc. Chem. Commun.*, **1970**, 1418-1419.

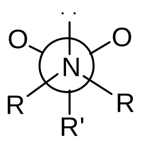
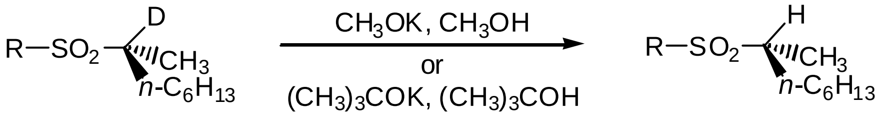


Figure 15

To the best of our knowledge no similar studies have been done on an α-sulfamoylated anion.

1.3 Configurational stability

Interest in carbanions stabilized by sulfur substituents arose from the observation that these carbanions could react with high stereoselectivity. Cram, for example, showed that the base-catalyzed hydrogen-deuterium exchange of chiral sulfones or sulfonamides resulted in retention of the absolute configuration (scheme 45).[74,94]



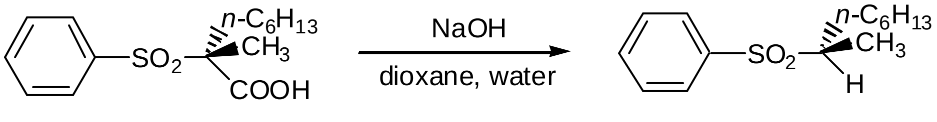
R = Ar, N(C_6H_5)CH_3, OR

Scheme 45

The measures of the rate constants for the exchange and the racemization showed that the ratio k_e/k_r varied from 10 to 1980. These values depended on the base and the solvent. Cram explained the retention either by a pyramidal geometry of the anion or an asymmetric solvation.

The results have been confirmed by Goering who observed an identical behavior for (-)-*p*-tolyl-2-octylsulfone in the hydrogen-deuterium exchange.[95]

Corey, in his studies, observed that the decarboxylation reaction of optically active sulfones occurred with retention of configuration (scheme 46).[82]



Scheme 46

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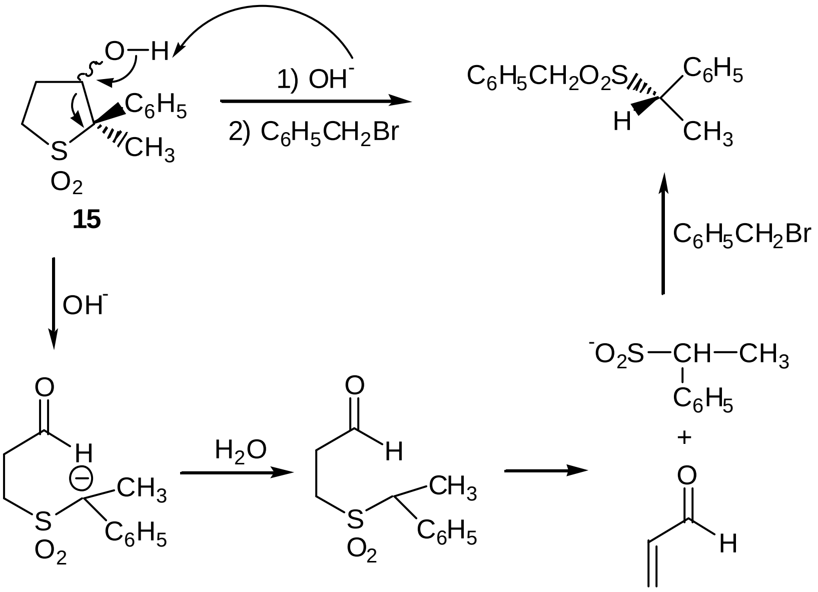
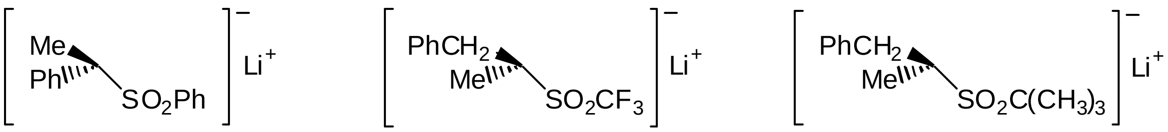
[94] Cram, D. J.; Trepka, R. D.; Janiak, P. S. *J. Am. Chem. Soc.*, **1964**, *86*, 2731-2733.
[95] Goering, H. L.; Towns, D. L.; Dittmar, B. *J. Org. Chem.*, **1962**, 736-739.

These results were obtained for dialkyl anions. Corey observed a similar behavior in the protonation of benzylic, and thus planar, α-sulfonyl carbanions generated by base-catalyzed decomposition of cyclic sulfone **15** (scheme 47).[81]



Scheme 47

From these results it appeared that sulfur-stabilized anions behaved as if they were chiral or asymmetrically solvated. To quantify the configurational stability Gais measured the racemization rates of α-sulfonylated carbanions depicted in figure 16.[89,96]



16 **17** **18**

Figure 16

Anion **16** racemized rapidly even at -80°C. On the other side, anions **17** and **18** had a mean half-life of 30 days at -78°C (for **17**) and 3 hours at -105°C (for **18**). These values correspond to an enantiomerization barrier of 17.2 ± 0.1 kcal.mol^{-1} for **17** and of 13.0 ± 0.3 kcal.mol^{-1} for **18**.

Anion **16** is adjacent to an aromatic ring. As we have seen these anions adopt a planar geometry, it is thus symmetric and will racemize. **17** and **18** are tetrahedral, and their stereochemistry may be fixed by the n_C-σ^*_{S-C} hyperconjugation (see figure

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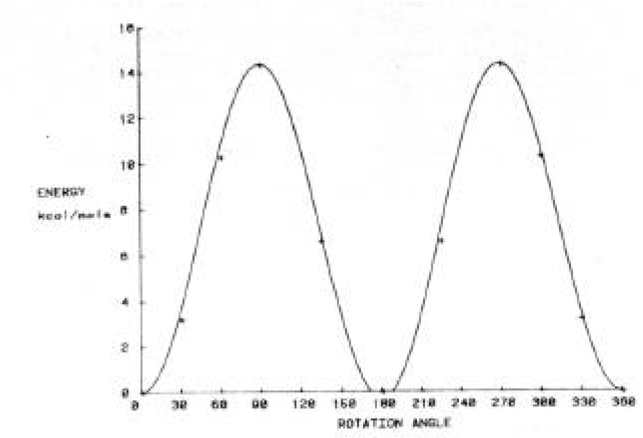
[96] Gais, H. J.; Hellmann, G. *J. Am. Chem. Soc.*, **1992**, *114*, 4439-4440.

12). The difference between these two anions can be explained by the fact that the antibonding orbital $\sigma^*_{S\text{-}C}$ is lower in energy in the case of **17**.

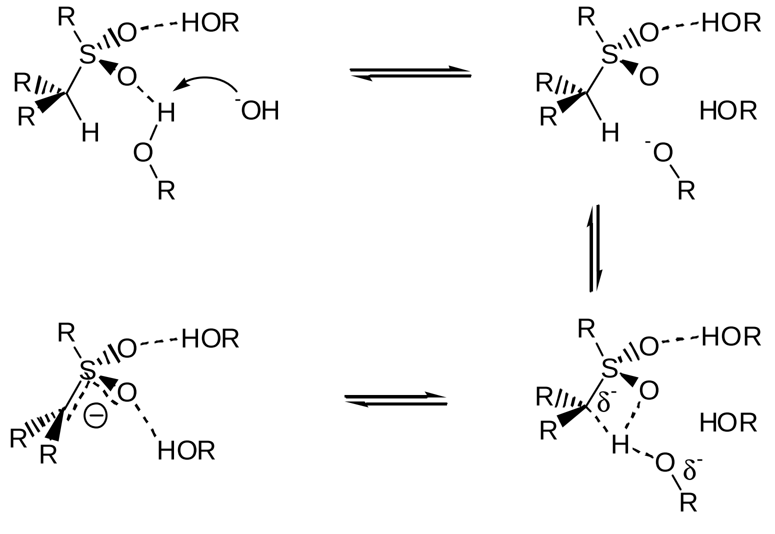
To explain the configurational stability restricted C_α-S bond rotation rather than restricted inversion of the α-carbon was evoked.[96] The calculations by Bors and Streitwieser led to the same conclusion.[80] In figure 17 we show the graphical representation obtained by a least-square fit of the values calculated for different rotation angles. A value of 14 kcal·mol^{-1}, similar to the one measured by Gais,[89,96] for the rotational barrier was obtained.[80]



Angle, deg	Energy, kcal.mol^{-1}
0	0.00
30	3.21
60	10.29
90	14.33
135	6.60
180	0.00

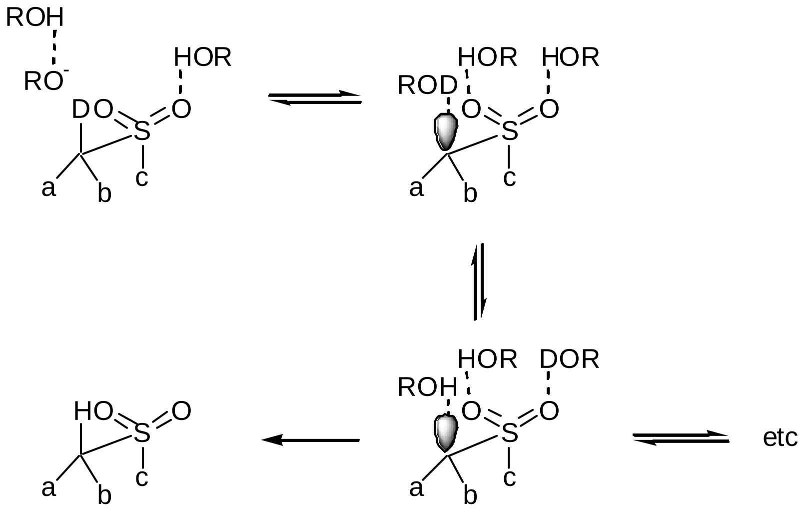
Figure 17[80]

To account for the stereoselectivity observed in planar carbanions, asymmetric solvation and/or reaction pathways were evoked. Corey assumed that planar carbanions also showed restricted rotation. Deprotonation would occur on the proton gauche to the two oxygen atoms and the electrophile would enter from the same side (scheme 48).[81]



Scheme 48

Cram evoked a similar hypothesis to explain the retention in deuterium-hydrogen exchange reactions (scheme 49). It applied to both planar and tetrahedral carbanions. According to the author "this movement of solvent molecules among the hydrogen bonding sites resembles the movement of people in the game of musical chairs".[97]



Scheme 49

To resume one can say that α-sulfonylated carbanions react stereoselectively whether planar or tetrahedral. An important barrier to rotation, asymmetric solvation and defined pathways for incoming reagents are responsible for this interesting behavior.

1.4 Reactivity of a-sulfamoylated carbanions

α-sulfamoylated carbanions easily react in nucleophilic substitution reactions with alkyl halides, in addition reactions with aldehydes, ketones and esters, opening of epoxides….[71] However to the best of our knowledge there are only two examples of Michael additions reported in the literature besides the work realized in our laboratory. Before discussing these results we would like to make a brief and general review on the Michael addition.

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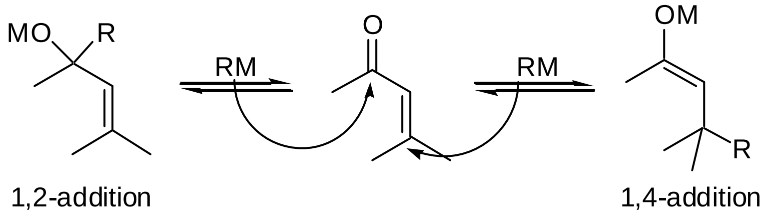
[97] Roitman, J. N.; Cram, D. J. *J. Am. Chem. Soc.*, **1971**, *93*, 2225-2231.

2 Addition to enones

2.1 Generalities

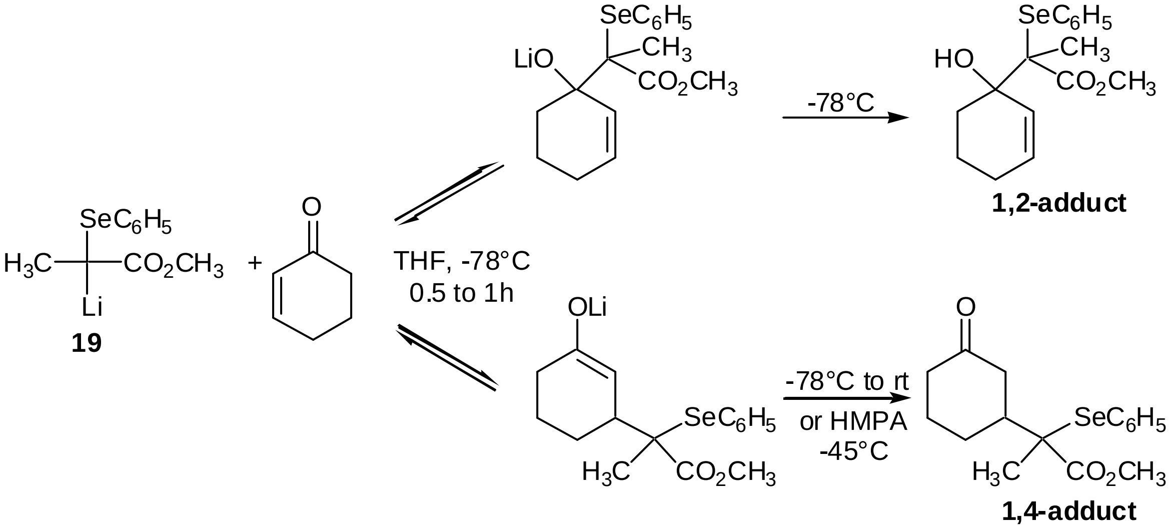
Enones are ambident reagents towards nucleophiles. Addition of a nucleophile can occur at the carbonyl, 1,2-addition, leading to an alkoxide, or at the carbon-carbon double bond, 1,4-addition, leading to an enolate (scheme 50).[98]



Scheme 50

Different parameters influence the selectivity of the reaction and all the possibilities from 100% 1,2-addition to 100% 1,4-addition have been observed. To the interpretation of the results it is necessary to know whether the reaction occurs under kinetic or thermodynamic control.

To study the influence of the temperature and the solvent on regioselectivity anion **19** was added to cyclohexenone (scheme 51).[99]



Scheme 51

When the reaction was quenched at -78°C 1,2-adduct was isolated as the major product. When the reaction was quenched after raising the temperature or

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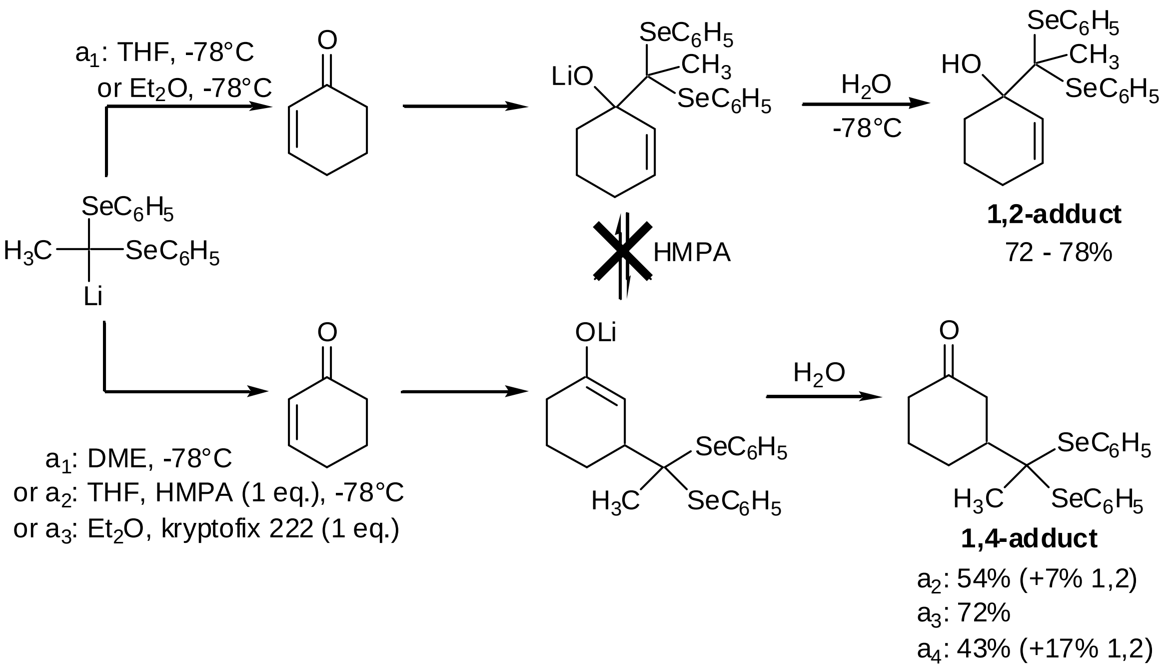
[98] Krief, A. *Tetrahedron*, **1980**, *36*, 2531-2640.
[99] Lucchetti, J.; Krief, A. *Tetrahedron Lett.*, **1978**, 2697-2700.

after adding HMPA to the reaction mixture, an equilibration towards the enolate occurred. At low temperature the reaction was under kinetic control, at higher temperature or in a more polar solvent however an equilibrium reaction between the alkoxide and the enolate occurred and favored the formation of the more stable 1,4-adduct.

When the anion was less stabilized, the addition reaction was not reversible and it was thus under kinetic control. In this case the reaction conditions play an important role (scheme 52).[100]



Scheme 52

Thus in THF or ether only the 1,2-addition was observed. To prove that the reaction was irreversible HMPA has been added once the alkoxide formed, no formation of the 1,4-adduct was observed. However when a ligand for the lithium cation was added before the addition took place, the 1,4-adduct was the major product.

Once one has established whether the reaction is under kinetic or thermodynamic control, different factors influence the regioselectivity. Under thermodynamic conditions 1,4-addition generally predominates. Under kinetic control different factors, that we will discuss, are important.

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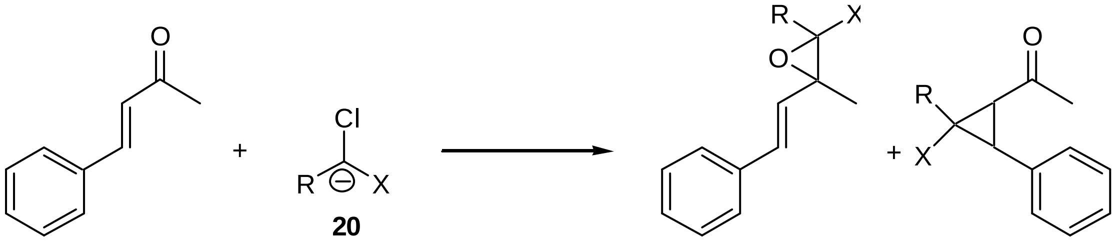
[100] Lucchetti, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.*, **1979**, 2695-2696.

2.2 Regioselectivity

The regioselectivity can be explained by the generalized perturbation theory: under charge control 1,2-addition occurs, under frontier (orbital) control 1,4-addition is the major reaction. Thus the two factors of importance are a) net charges on the nucleophile and the carbonyl carbon and b) the energy difference between the HOMO* of the nucleophile and the LUMO* of the enone.[101] In the presence of high charges charge control will be dominant, on the other hand, the lower the difference between HOMO and LUMO the higher the orbital interaction.

2.2.1 Nucleophile

When applied to the nucleophile the generalized perturbation theory predicts that an anion with a localized charge would lead to 1,2-addition and a delocalized anion to 1,4-addition. To verify the hypothesis Seyden-Penne *et al.* have studied the addition of a series of anions to 4-phenylbut-3-en-2-one (scheme 53).[102]



20

a: X = CN, R = H **21**
b: X = CN, R = Ph **23**
c: X = $COOCH_3$, R = H **22**
d: X = $COOCH_3$, R = Ph **24**

Scheme 53

Anions **20a** and **20c** which were pyramidal with a localized charge only gave a 1,2-addition to yield the products of a Darzen reaction **21** and **22**. When the anion was delocalized on a phenyl substituent, **20b** and **20d**, only 1,4-addition was observed and cyclopropanes **23** and **24** were isolated. These results confirmed the hypothesis that the better the charge delocalization the higher would be the ratio of 1,4-addition.

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* HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital

[101] Anh, N. T. *Actual. Chim.*, **1974**, 9-19.

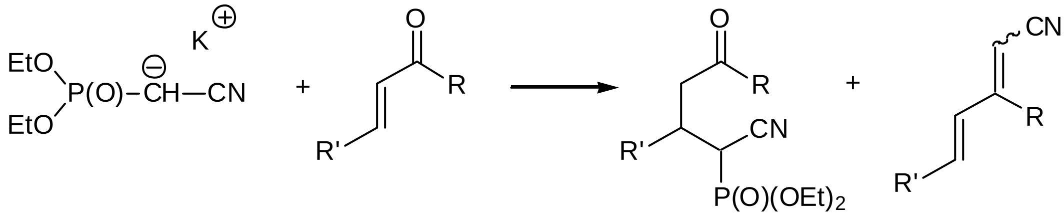
[102] Kyriakakou, G.; Roux-Schmitt, M. C.; Seyden-Penne, J. *Tetrahedron*, **1975**, *31*, 1883-1888.

2.2.2 The enone

Electronic effects in the enone can greatly influence the regiochemistry of the addition reaction. Indeed increase of frontier control is expected if the positive charge at the carbonyl is decreased and/or the LUMO level is decreased and/or the C4 coefficient in LUMO is increased. Decrease of the LUMO level by conjugation can explain the reactivity of chalcone which is known to react mostly in a conjugate addition. Scheme 54 shows the results obtained with 3 different enones (table 7).[103]

Table 7: *Electronic properties[*] of α-enones.[103]*

α-enone	E_{LUMO}	q_2	C_4
PhCH=CHCOPh	-0.132	+0.30	0.513
CH_3O-C_6H_4-CH=CHCOPh	-0.183	+0.25	0.503
$PhCH=CHCOCH_3$	-0.226	+0.38	0.563



R = Ph; R' = Ph	70	5
R = Ph; R' = CH_3O-C_6H_4	60	10
R = CH_3; R' = Ph	30	55

Scheme 54

Regioselectivity was the highest for chalcone which has the lowest LUMO. The Wittig-Horner-Emmons reaction resulting from an 1,2-addition became the major product with 4-phenylbut-3-en-2-one which has a higher LUMO.

Steric hindrance plays also an important role in the regioselectivity. Thus enals mostly produce the 1,2-adduct as well as α-enones substituted at the β-carbon. On the other hand bulky groups around the carbonyl group induced the formation of the 1,4-adduct.[98]

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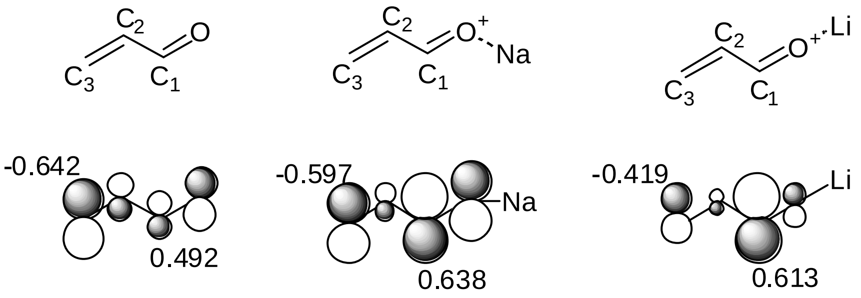
[103] Cossentini, M.; Deschamps, B.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron*, **1977**, *33*, 409-412.
[*] calculated by Hückel method

2.2.3 The cation

Lefour and Loupy had demonstrated the importance of the cation on the regioselectivity in the addition reactions to α-enones. [104] They have calculated the effect of a cation on the LUMO of an enone (table 8).

Table 8: *Properties[#] of the LUMO in naked and complexed enones.[104]*



Compound	Total energy (a.u.)	LUMO energy level (a.u.)	A.O. coefficients in LUMO	
			C_1	C_3
CH_2=CH-CH=O	-188.297	0.221	0.492	0.642
CH_2=CH-CH=O-Na^+	-348.146	0.046	0.638	0.597
CH_2=CH-CH=O-Li^+	-195.571	-0.047	0.613	0.419

The results showed that a naked enone had the highest atomic orbital coefficient at carbon C_3. Once the enone was complexed by a cation the highest coefficient shifted to carbon C_1. An evolution was observed with the hardness of the cation: the harder the cation the higher the coefficient on carbon C_1.

In view of these results one easily understands why nucleophiles that gave only 1,2-addition in THF gave 1,4-addition when HMPA[**] or a kryptand, which complex the cation, was added to the reaction mixture (see for example scheme 52).[100]

2.2.4 Solvent

The role of the solvent can easily be understood when the complexation by the cation is taken into account. A polar solvent will dissociate the cation from the enone thus favoring the 1,4-addition.[**]

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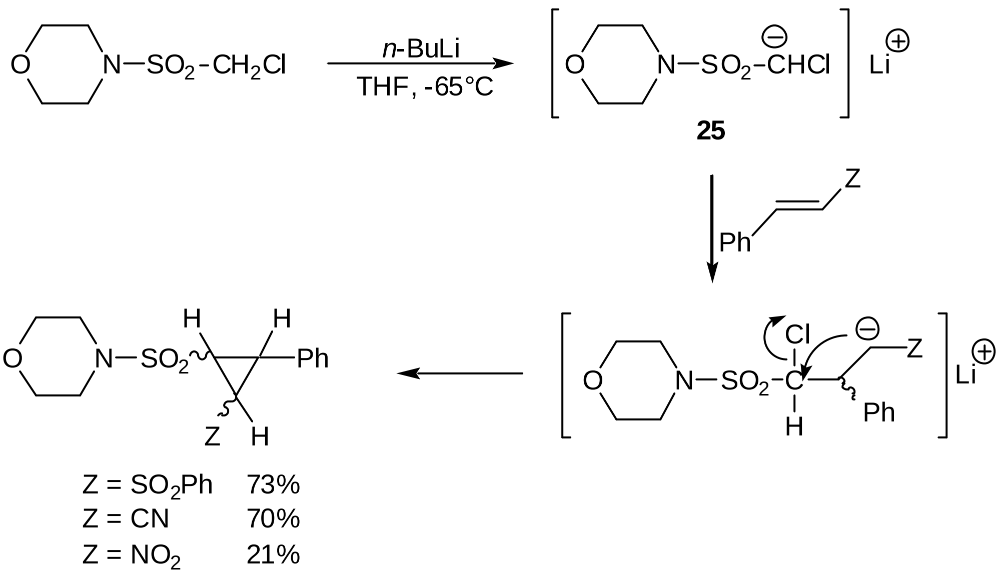
[104] Lefour, J.-M.; Loupy, A. *Tetrahedron*, **1978**, *34*, 2597-2605.

[#] calculated with STO-3G set

[**] A detailed discussion on the role of Li^+ and HMPA will be shown in Chapter III

3 A particular case: addition of α-sulfonylated or α-sulfamoylated anions to enones

To the best of our knowledge there are only 2 publications dealing with the Michael addition of α-sulfamoylated anions. A very first example was described by Christensen and Truce.[105] They studied the reaction of α-halocarbanion **25** with a series of Michael acceptors. Conjugate addition followed by an intramolecular substitution reaction was observed in all the cases (scheme 55). However the acceptors that were used could not undergo 1,2-additon, thus the problem of the regioselectivity was avoided.



$Z = SO_2Ph$ 73%
$Z = CN$ 70%
$Z = NO_2$ 21%

Scheme 55

The second publication dealing with the Michael addition of sulfonamides has been published by the group of Mladenova.[106] They were interested in the regioselectivity of the addition of α-metallated *N,N*-dimethylsulfonamides to α,β-unsaturated carbonyl compounds. The results obtained under different conditions when using chalcone as acceptor are represented in table 9.

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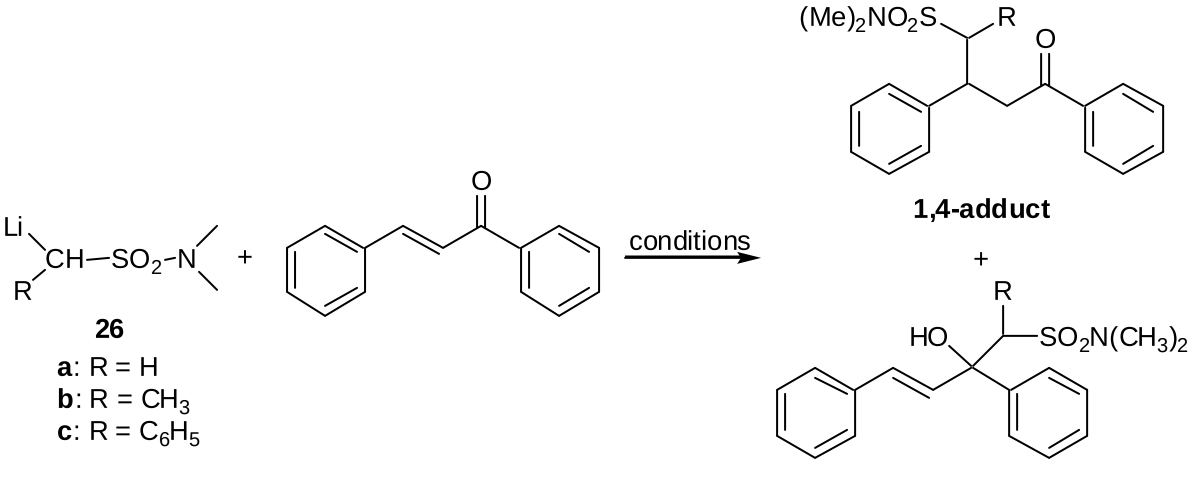
[105] Christensen, L. W.; Seaman, J. M.; Truce, W. E. *J. Org. Chem.*, **1973**, *38*, 2243-2245.
[106] Mladenova, M.; Biserkova, M.; Kaneti, J. *Phosphorus, Sulfur and Silicon*, **1995**, *104*, 151-159.

Table 9: *Addition of sulfonamides to chalcone.*[106]



26

a: R = H
b: R = CH_3
c: R = C_6H_5

1,4-adduct

1,2-adduct

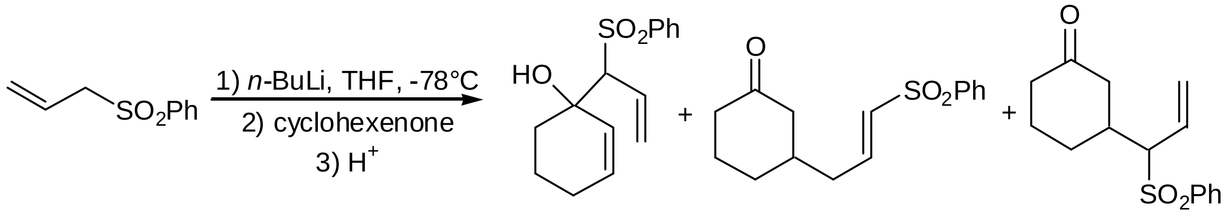
Entry	R	Conditions	Yield	1,4-adduct	1,2-adduct
1	H	THF, -50°C, 10 min	78%	0	100
2	H	THF, -50°C ? -20°C, 60 min	80%	5	95
3	H	THF + 20% HMPA, -50°C ? RT, 3 h	60%	100	0
4	CH_3	THF, -50°C, 10 min	80%	74	26
5	CH_3	THF, -50°C ? -20°C, 3 h	70%	100	0
6	C_6H_5	THF, -50°C, 2 min	80%	100	0

According to the results of Seyden-Penne[102], α-sulfamoylated anions, which bear a localized charge, should undergo 1,2-addition, the reaction being under charge control. This was indeed observed with sulfonamide **26a**. Even with chalcone as an acceptor 1,2-adduct was the major product (entries 1, 2). When HMPA was added to the mixture and the reaction allowed to come to room temperature 1,4-addition became the major reaction (entry 3). According to the authors, an equilibrium occurred, however no prove was given for this statement. With sulfonamide **26b** 1,4-adduct was the major product and an equilibrium occurred at higher temperatures (entries 4, 5). Sulfonamide **26c**, where the anion was conjugated with a phenyl ring, gave only 1,4-addition (entry 6). In this case, the delocalized anion should indeed react under frontier control to give the conjugate addition.[102]

In view of these short list of results we take a brief look at the addition of α-sulfonylated anions.

A first study has been realized by Hirama, who was interested in the addition of allylphenylsulfones to enones (table 10).[107]

Table 10: *Addition of allylphenylsulfone to cyclohexenone.*[107]



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

Entry	HMPA	Reaction conditions	1,2-α	1,4-γ	1,4-α	Yield
1	yes	-78°C, 2 min	0	0	100	89%
2	no	-78°C, 2.5 min	69	22	8	95%
3	no	-78°C, 10 min	65	27	8	100%
4	no	-78°C, 50 min	43	46	11	89%
5	no	-78°C, 10 min ? 0°C, 40 min	0	83	17	81%
6	no	-78°C, 10 min then 2 eq HMPA, -78°C, 40 min	14	44	42	75%

Regioselectivity in this case is more complicated as the anion can attack with the carbon α or γ to the sulfone. It has been shown in this work that HMPA was necessary to obtain the 1,4-α-adduct (entry 1). Without HMPA 1,2-α-adduct was the major compound (entry 2). The reaction was reversible and an equilibration occurred with formation of the 1,4-γ-adduct when the reaction time was prolonged (entry 3-5). The reversibility has been proven by treatment of the 1,2-adduct with *n*-BuLi; under these conditions the 1,4-γ-adduct was formed. Addition of HMPA at a later reaction stage resulted in the formation of a mixture of products (entry 6), showing that the 1,4-α-adduct is formed under kinetic control in the presence of HMPA.

Similar results were obtained by Haynes who also studied the addition of allylic sulfones to enones (table 11).[108]

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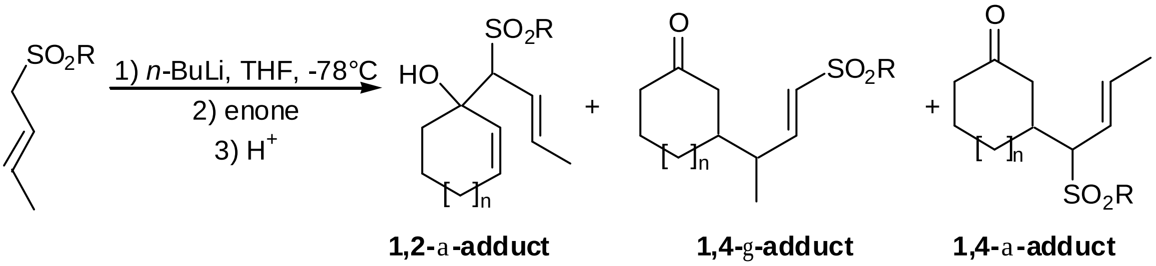
[107] Hirama, M. *Tetrahedron*, **1981**, *22*, 1905-1908.

[108] Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Org. Chem.*, **1989**, *54*, 1960-1968.

Table 11: *Addition of allylic sulfones to enones.*[108]



Entry	R	n	Conditions[*]	1,2-α	1,4-γ	1,4-α	Yield
1	*p*-Tol	0	-85°C, -85°C, -85°C	6	94	0	81%
2	*p*-Tol	0	-70°C, -3°C, 2°C	0	100	0	83%
3	*p*-Tol	0	HMPA ,-70°C, -70°C, -70°C	0	6	94	88%
4	*p*-Tol	1	-85°C, -85°C, -85°C	100	0	0	81%
5	*p*-Tol	1	-70°C, -3°C, 1°C	7	93	0	74%
6	Ph	0	-70°C, -70°C, -70°C	0	100	0	79%
7	Ph	0	HMPA, -70°C, -70°C, -70°C	0	23	77	89%
8	Ph	0	-70°C, -3°C, 4°C	0	100	0	76%
9	Ph	1	-70°C, -70°C, -70°C	62	38	0	77%
10	Ph	1	-70°C, -70°C, 0°C	0	100	0	82%
11	Ph	1	-70°C, -4°C, 2°C	0	100	0	79%

Addition to cyclopentenone proceeded with good regioselectivity to yield a 1,4-adduct (entries 1-3 and 6-8). Without HMPA the adduct was formed by attack of the γ-carbon (entries 1, 2, 6, 8), with HMPA the α-carbon of the sulfone attacked the enone (entries 3 and 7).

Interestingly addition to cyclohexenone gave the 1,2-α-adduct at low temperatures (entries 4 and 9). At higher temperatures the 1,4-γ-adduct became the major product (entries 5, 10 and 11).

The authors wanted to know whether the 1,4-γ-adduct was formed under kinetic or thermodynamic control. They therefore studied the intramolecular oxy-Cope rearrangement, proposed by Hirama[107], of the 1,2-α-adduct and found that it was slower by a factor >150 than the addition reaction. Moreover the diastereomeric ratio was different in the 1,4-γ-adduct than in the initial 1,2-adduct. An intramolecular rearrangement was thus excluded and a dissociation-recombination pathway was proposed. From these results the authors concluded that the conjugate addition also occurred under kinetic control.

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[*] temperature of lithiation, addition of enone, quench

No other studies of α-sulfamoylated or α-sulfonylated anions in the addition reaction to enones are found.

4 Conclusion

Only few information is available on α-sulfamoylated anions. It appears however that their behavior should be quite similar to the sulfonyl analogues. Indeed difference in properties that exists between a ketone and an amide is not observed for the sulfone-sulfonamide couple. Therefore conclusions made for sulfones, could still be valid for sulfonamides.

The addition of α-sulfamoylated anions seems to be under charge control with the 1,2-adduct as favored product. In our case reaction conditions to favor the conjugate addition have thus to be chosen carefully as the 1,4-adduct is the only product of interest for our cyclization sequence.

The configurational stability of the carbanion should be interesting in asymmetric synthesis.