Chapter VI: Phase transfer catalysis with sulfur stabilized nucleophiles

1 Introduction

As shown previously, the cyclopentannulation method developed in our laboratory gave very good results for the cyclopentannulation of cyclic enones.[67] We have shown in this work that it could be extended to acyclic enones but we were not able to apply it to less reactive acceptors.

In the second part of this work our goal was the development of a more generally applicable cyclopentannulation sequence.

The method developed by C. Huart and L. Ghosez was stoechiometric in chiral inductor. We became interested in a catalytic method keeping as much as possible the nature of the pentannulation reagent. Therefore we needed a three-carbon reagent with an electron-withdrawing group and an orthoester function at the terminal carbon atom. This compound should react in a Michael addition with an enone in the presence of a chiral catalyst and the resulting adduct should then be cyclized to the desired product.

If we wanted to conserve the orthoester function, methods using chiral Lewis acids are inappropriate, since orthoesters are not stable under these conditions.[154]

We decided to have a look at phase transfer catalysis. We will first present a literature survey that led us to opt for this method.

2 Phase transfer catalysis: literature survey

2.1 General description

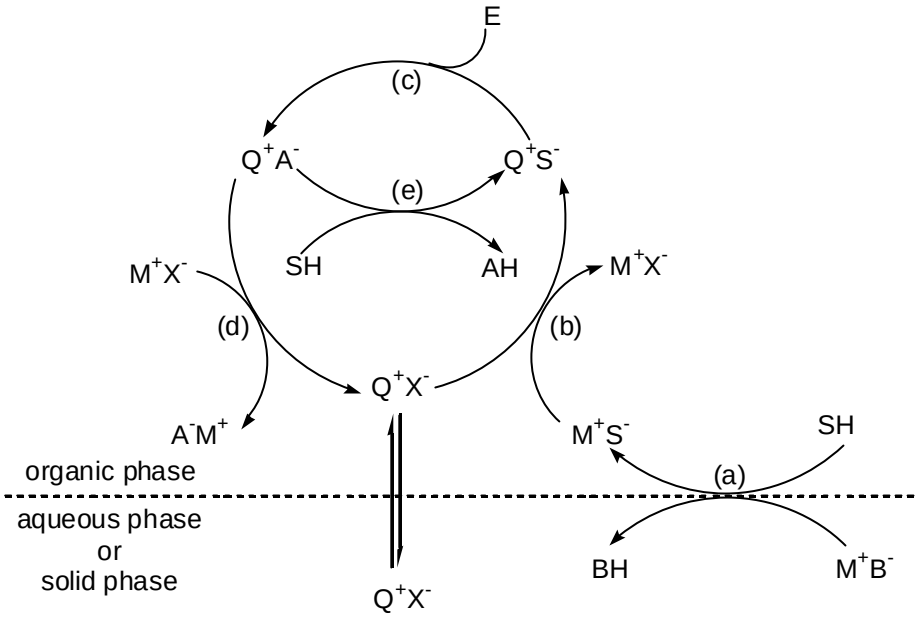
Phase transfer catalysis involves generally a simple reaction procedure, mild conditions and inexpensive reagents.[166] The principle of phase transfer catalysis is to introduce a highly active anionic species into an aprotic, most often apolar, organic phase, where it should react with the substrate. The transfer into the organic phase is realized by a catalyst which forms with the anion a tight ion pair. By using a chiral catalyst, one could in principle achieve a catalytic asymmetric reaction.

The inorganic phase can be a non-miscible solvent, in general water, or a solid. So one distinguishes between liquid-liquid phase transfer catalysis or solid-liquid phase transfer catalysis. Whatever the second phase the general scheme remains valid.

2.1.1 General scheme

In scheme 98 is shown a phase transfer catalysis reaction that needs a base to form the anion. The base (M^+B^-) is in the non-organic phase and the anionic species (S^-) is formed at the interface of the two phases (a). The negatively charged nucleophile forms an ion pair with the catalyst (Q^+S^-) and is brought into the organic phase (b) to react with the electrophile (c). The product forms a new ion pair with the catalyst (Q^+A^-). In order to continue the catalytic cycle, the catalyst has to be released (d). If the product formed (A^-) can act as a base (e), only a catalytic amount of base will be necessary.

[166] O'Donnell, M. J., *Asymmetric Phase Transfer Reactions*, in *Catalytic Asymmetric Synthesis*, Ojima, I., Editor. VCH Publishers, Inc.: New York. 1993, p. 389-411.



Scheme 98

2.1.2 The base

As the base is not solvated in the organic phase, it's strength is enhanced. Therefore even weak bases, such as potassium carbonate, can be used to deprotonate weakly acidic compounds. Thus reaction conditions are very mild and sensitive compounds can be reacted under phase transfer conditions.

2.1.3 The catalyst

The catalyst will form an ion pair which should be soluble in the organic phase. Two major families of catalysts are used: quaternary ammonium salts and crown ethers.

The ammonium salts have to exchange their counter-anion with the substrate to form a new ion pair which constitutes the active species that will undergo the reaction. The initial catalyst should form a rather loose ion-pair, for the exchange to take place. The interaction between the catalyst and the anionic nucleophile has to be sufficiently strong to form a soluble species in the organic solvent but weak enough to allow the reaction.

Crown ethers have a different mode of action. They complex a cation to form a soluble positively charged complex which forms an ion-pair with the anionic reagent. Different crown ethers are available for various sizes of cations.

Besides its role as transfer agent the catalyst is also the carrier of the chiral information in asymmetric synthesis. The chiral quaternary ammonium salts are easily formed from the readily available alkaloids of the *cinchona* and the *ephedra* family.[166] The situation is somewhat more complicated for the crown ethers where chiral compounds have to be synthesized by mostly fastidious methods starting from chiral alcohols or sugars.[166] We will see later some examples of chiral catalysts.

2.1.4 The solvent

The choice of the solvent is important. Neither the base nor the anionic species should be soluble in the organic phase; in liquid-liquid phase-transfer reactions, hydrocarbons, dichloromethane or chloroform are commonly used. The two latter however have to be used with care as chloroform can also be deprotonated to form a carbene and dichloromethane can suffer nucleophilic displacement.[167]

2.2 Examples of asymmetric phase transfer catalysis reactions

Phase transfer catalysis has been widely used to effect a lot of different reactions.[167] We will focus on the Michael additions.

Michael addition under phase transfer catalysis generally gave almost exclusively the 1,4-adducts. As we have already discussed in Chapter I the regiochemistry is among others influenced by the complexation of the enone by a cation. In the absence of complexation the enone essentially reacts in a 1,4-addition.[104] Under phase transfer conditions the cation, a bulky ammonium or a crown ether complex, should not complex the enone. That is probably why 1,2-addition is nearly never observed. Moreover equilibration is often possible which favors the formation of the thermodynamic 1,4-adduct.

One of the first examples of asymmetric phase transfer catalyzed 1,4-addition was given by Wynberg and Colonna.[168] They described the addition of nitromethane to chalcone (scheme 99) using potassium fluoride as a base in the presence of a chiral ammonium salt. Enantioselectivities were however low. According to the authors the active catalyst was ammonium fluoride, obtained by *in situ* transhalogenation of the initial bromide. This is one of the few examples where a catalyst from the *ephedrina* family gave better results than a catalyst of the *cinchona* family.

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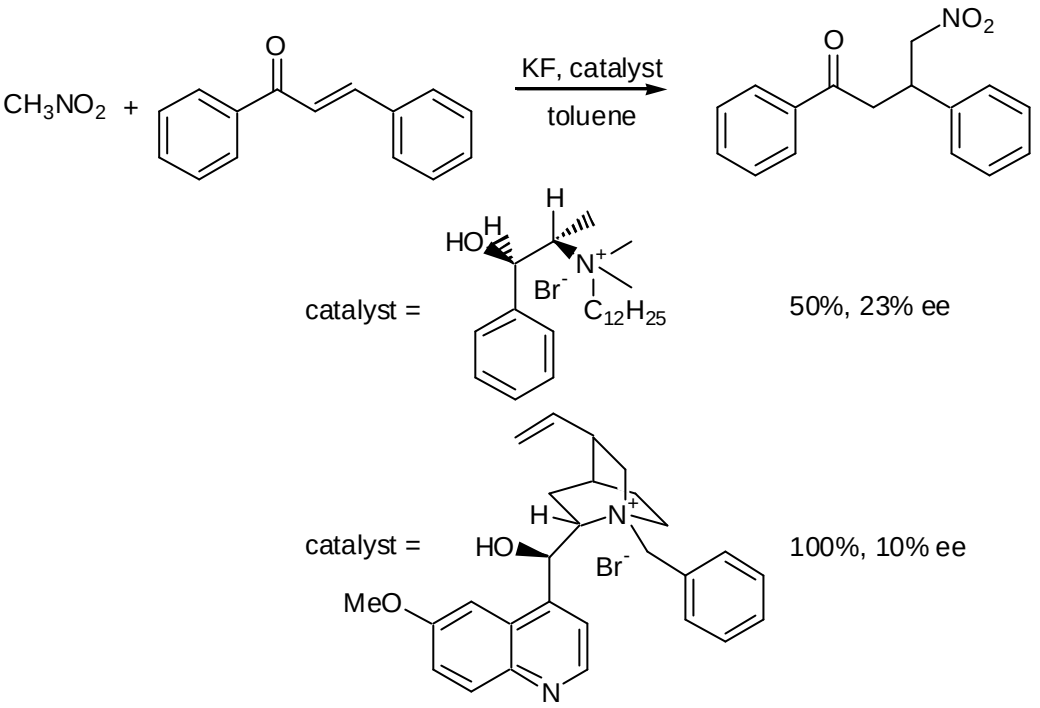
[167] Weber, W. P.; Gokel, G. W., *Phase Transfer Catalysis in Organic Synthesis*; Springer-Verlag: Berlin, 1977.

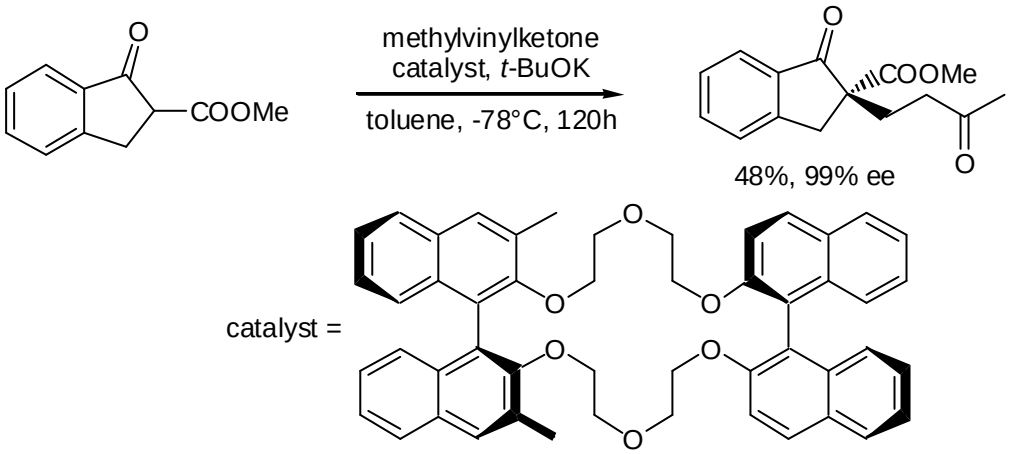
[168] Colonna, S.; Hiemstra, H.; Wynberg, H. *J. Chem. Soc. Chem. Commun.*, **1978**, 238-239.



Scheme 99

Other examples were described by these two groups.[169] Whereas the addition of thiophenol and nitromethane to chalcone was realized with 36% and 23% ee respectively, the addition of malonates resulted in complete absence of selectivity.

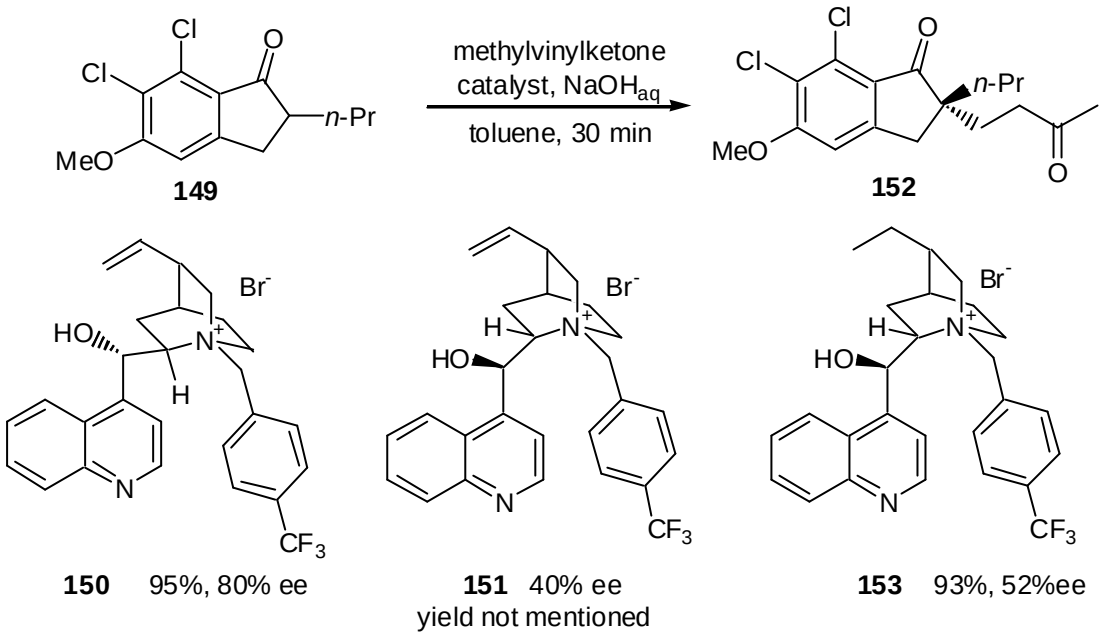
In the meantime Cram published his work using chiral crown ethers for the addition of β-ketoesters to methylvinylketone (scheme 100).[170] Yields were modest but enantioselectivities were excellent. Chiral crown ethers were however less readily available than chiral ammonium salts which limited the application of this method.



Scheme 100

[169] Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc. Perkin Trans. 1*, **1981**, 547-552.
[170] Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc. Chem. Commun.*, **1981**, 625-628.

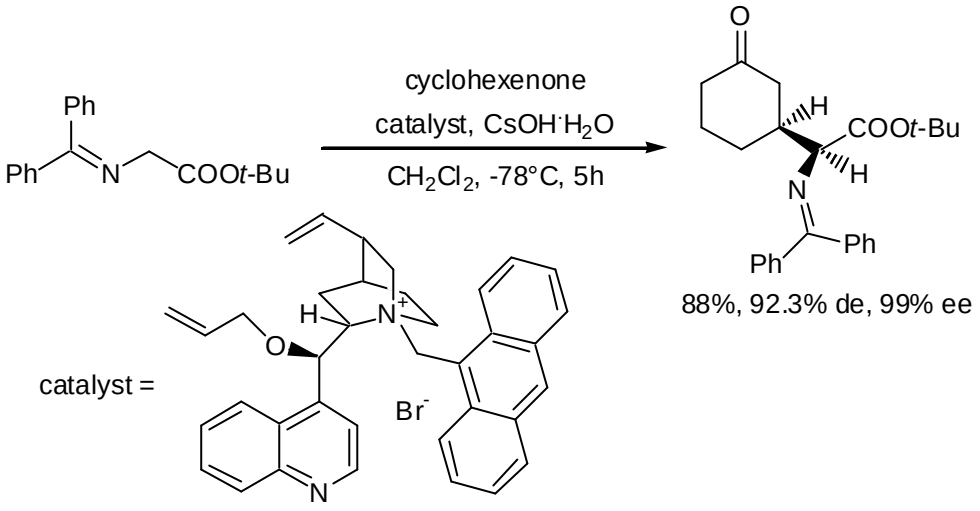
In 1986, Conn described the first examples of high enantioselective additions using a catalyst derived from an alkaloid of *cinchona*.[171] The addition of ketone **149** to methylvinylketone was achieved in 30 minutes with high yields and good enantioselectivities (80% ee) with catalyst **150** (scheme 101). The pseudo-enantiomeric effect was studied by the authors. However catalyst **151**, pseudo-enantiomer of **150**, furnished the enantiomer of **152** with only 40% ee. The hydrogenated catalyst **153** was slightly better (52% ee).



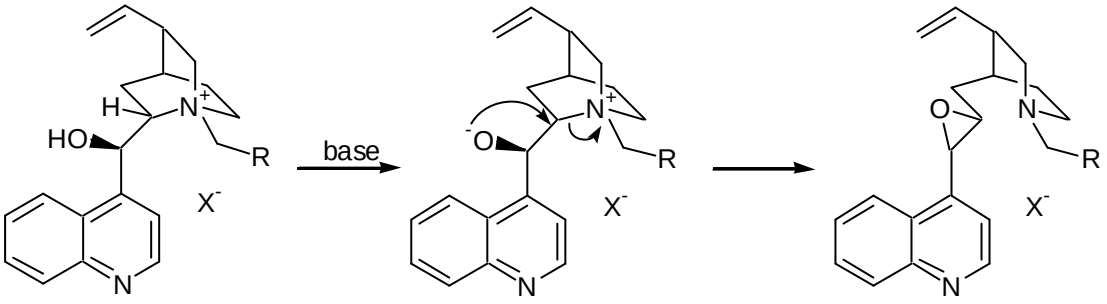
Scheme 101

More recent results confirm that these chiral ammonium salts were indeed excellent. Corey developed a new catalyst to add imines derived from α-aminoesters to Michael acceptors (scheme 102).[172] It is one of the few examples where the free alcohol function was not necessary for the catalyst to be active. Rather allylation of the free alcohol function was necessary. The formation of an alkoxide was indeed responsible for the degradation of the catalyst (scheme 103).[166]

[171] Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.*, **1986**, *51*, 4710-4711.
[172] Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.*, **1998**, *39*, 5347-5350.



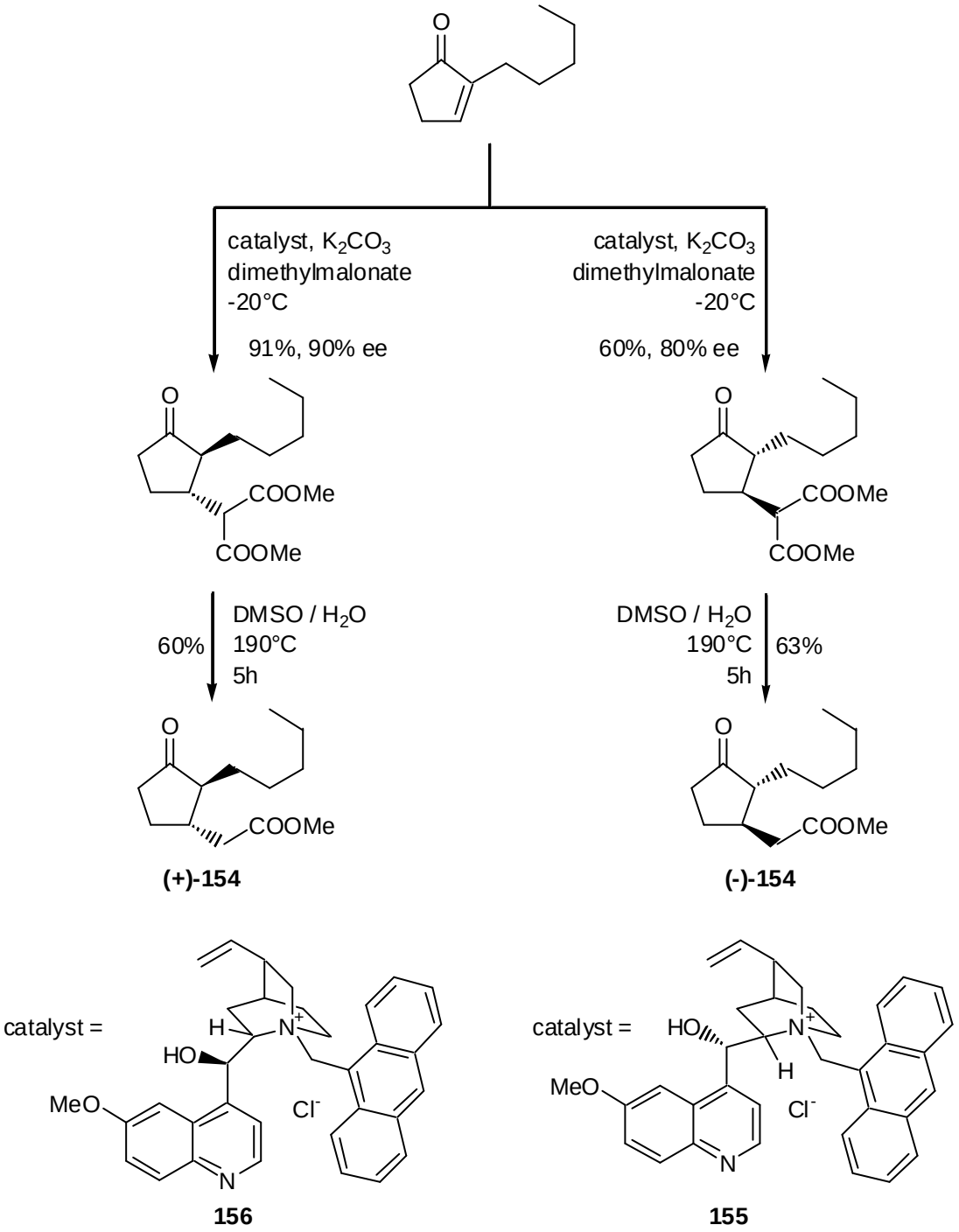
Scheme 102



Scheme 103

Asymmetric phase transfer catalysis has also been used as a key step in the total synthesis of both enantiomers of methyl dihydrojasmonate by Plaquevent.[173] Addition of dimethylmalonate to a substituted cyclopentenone was realized without solvent and with potassium carbonate as a base (scheme 104). (-)-Methyl dihydrojasmonate (**(-)-154**) was obtained by using *N*-anthrylmethylquinidinium chloride **155** as a catalyst, whereas (+)-methyl dihydrojasmonate (**(+)-154**) was synthesized by using the pseudo-enantiomer of **155**, *N*-anthrylmethylquininium chloride **156**.

[173] Perrard, T.; Plaquevent, J.-C.; Desmurs, J.-R.; Hébrault, D. *Org. Lett.*, **2000**, *2*, 2959-2962.



Scheme 104

Examination of the details of this work show the difficulties one can encounter when working under phase transfer conditions:[174]

- it has been shown that no reaction took place when a solvent was used rather then neat reaction conditions.
- the quantity and the nature of the base greatly influenced the stereoselectivity.

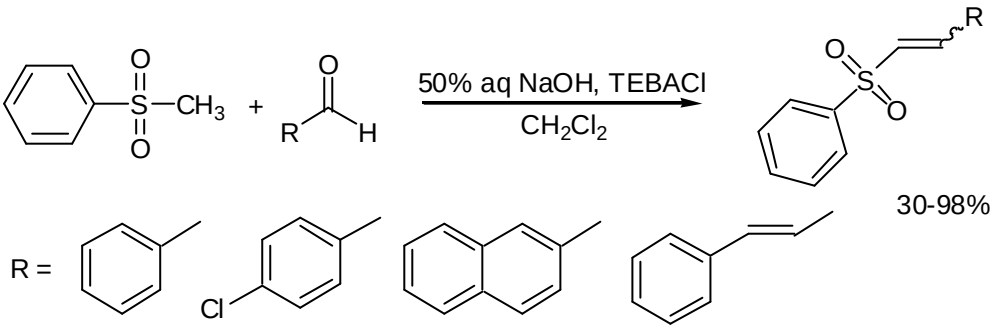
[174] Perrard, T. *PhD-Thesis Faculté des Sciences et Techniques de l'Université de Rouen*, **1999**

- traces of water seemed to be necessary as 99.995% pure K_2CO_3 in dry dimethylmalonate did not promote the reaction.
- enantioselectivities were temperature dependent.
- other nucleophiles such as methyl acetoacetate or methyl methylthioacetate did not react.

These examples show that it is possible to realize the Michael addition with excellent enantioselectivities. However quite often, slight changes in one of the reactants may greatly influence the outcome of the reaction. This implies that such systems are rarely generalizable.

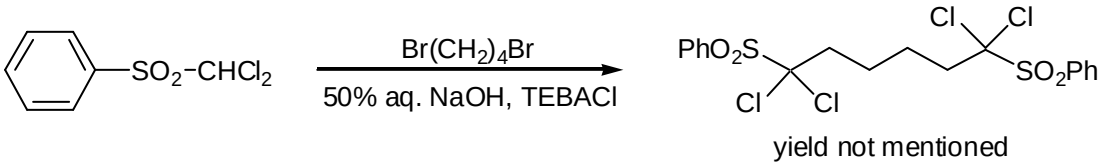
2.3 Sulfur containing electron-withdrawing groups under phase transfer conditions

In the literature we did not find any example of sulfonamides used under phase transfer conditions. However sulfones can be used under phase transfer catalysis. For example, Umani-Ronchi described the addition of methylphenylsulfone to aldehydes with moderate to excellent yields (scheme 105).[175]



Scheme 105

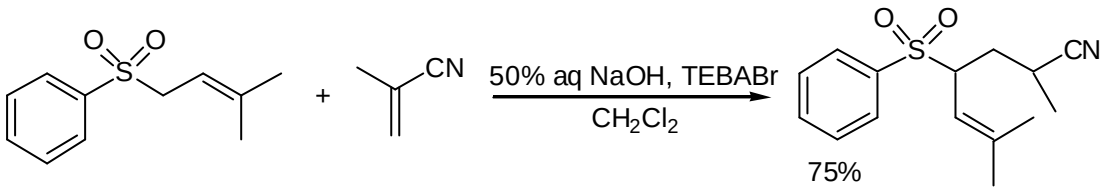
Another example was described by Makosza who showed that anions of halomethyl aryl sulfones could be formed under phase transfer conditions and that these anions could easily be alkylated (scheme 106).[176]



Scheme 106

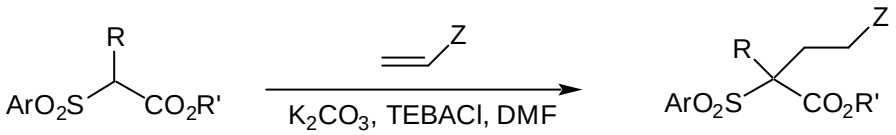
[175] Cardillo, G.; Savoia, D.; Umani-Ronchi, A. *Synthesis*, **1975**, 453-455.
[176] Jonczyk, A.; Banko, K.; Makosza, M. *J. Org. Chem.*, **1975**, *40*, 266-267.

Anions derived from allylic sulfones were added by the same group to electrophilic alkenes under similar conditions (scheme 107).[177]



Scheme 107

More stable anions were used by the group of Liu who showed that dialkylation of α-arylsulfonylacetates was possible under solid-liquid phase transfer conditions.[178] Some years later the same group described the Michael addition of these compounds to β-unsubstituted Michael acceptors (scheme 108).[179]

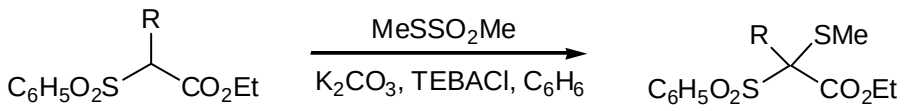


Ar = C_6H_5, MeC_6H_4; R = Me, Et, Bu, CH_2CH_2Ph
R' = Me, Et; Z = CO_2Me, CN, $COCH_3$

88 - 98%

Scheme 108

Wladislaw *et al*. showed that α-sulfonylcarboxylic esters could be sulfanylated under solid-liquid phase transfer conditions in yields that varied in function of the steric hindrance (scheme 109).[180]



R = H 75%
R = Me 96%
R = Et 70%
R = *i*-Pr 39%

Scheme 109

3 Results

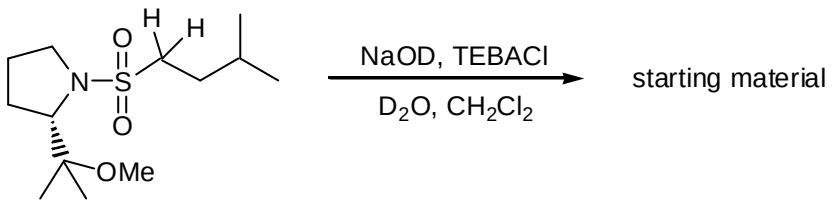
3.1 The choice of the electron-withdrawing group

We were first interested in keeping either a sulfonamide or a sulfone as electron-withdrawing group.

[177] Jonczyk, A.; Radwan-Pytlewski, T. *Polish J. Chem.*, **1995**, *69*, 1161-1167.
[178] Liu, G.-J.; Zhang, Z.; Sun, Y.-P.; Wang, Y.-L.; Cai, S.-C. *Youji Huaxue*, **1990**, *10*, 217-222.
[179] Liu, G.-J.; Zhang, Z.; Wang, Y.-L.; Sun, Y.-P.; Bai, Y.-L. *Youji Huaxue*, **1995**, *15*, 590-594.
[180] Wladislaw, B.; Marzorati, L.; Claro, N. F.; DiVitta, C. *Synthesis*, **1997**, 420-422.

3.1.1 Sulfonamides

We first studied the hydrogen-deuterium exchange of sulfonamide **44** under phase transfer conditions, using a solution of deuterated potassium hydroxide in deuterated water. If the anion is formed, we should observe a complete isotope exchange (scheme 110). However, even when the reaction was run for several hours, no exchange was observed. We thus concluded that the sulfonamide was not acidic enough to be deprotonated under such conditions.

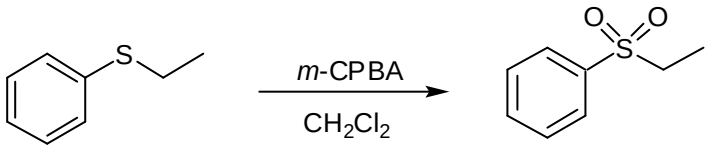


44

Scheme 110

3.1.2 Sulfones

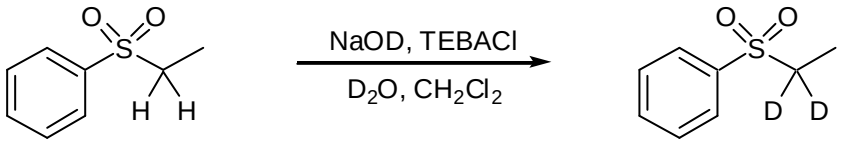
We synthesized ethylphenylsulfone **157** by oxidation of ethylphenylsulfide with *meta*-chloroperbenzoic acid (scheme 111).



157

Scheme 111

When sulfone **157** was reacted with NaOD and a phase transfer catalyst, we observed after 3 hours of reaction the complete disappearance of the proton signals α to the sulfone. This showed that a complete isotope exchange had taken place (scheme 112) and thus, that the anion had been formed.



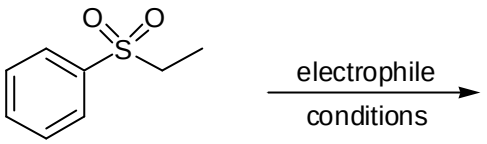
157

Scheme 112

We then tried the addition of ethylphenylsulfone **157** to cyclohexenone under various phase transfer conditions (table 27). But unfortunately, whatever the conditions used, we never observed the addition product. In the presence of D_2O, the isotope exchange took place (entry 2). So the anion was formed but the addition

reaction did not take place. We also tried to use benzyl bromide as electrophile but again only starting material was recovered. However addition of the anion to benzaldehyde took place but yields were lower than those described by Umani-Ronchi.[175]

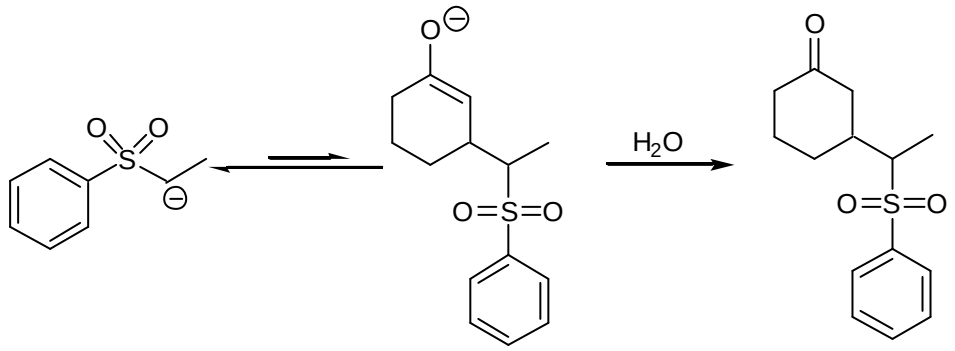
Table 27: *Attempts for the Michael addition of **157** to cyclohexenone under phase transfer conditions.*



157

Entry	Electrophile	Conditions	Yield	Remark
1	cyclohexenone	NaOH, TEBACl, H_2O, CH_2Cl_2	0%	degradation
2	cyclohexenone	NaOD, TEBACl, D_2O, CH_2Cl_2	0%	deuteration
3	cyclohexenone	KOH, TEBACl, CH_2Cl_2	0%	degradation
4	cyclohexenone	$CsOH{\cdot}H_2O$, TEBACl, CH_2Cl_2	0%	degradation
5	cyclohexenone	K_2CO_3, 18-crown-6, acetone	0%	SM
6	benzyl bromide	NaOH, TEBACl, H_2O, CH_2Cl_2	0%	SM
7	benzyl bromide	KOH, TEBACl, CH_2Cl_2	0%	SM
8	benzaldehyde	NaOD, TEBACl, D_2O, CH_2Cl_2	58%	

Two explanations were possible for the lack of reactivity in our case. Either the anion formed is too unstable to "survive" and is thus reprotonated by the water; or the equilibrium of the Michael addition lies towards the reagents. This second point however is less probable as there are possible proton-donors due to the presence of water that could trap the enolate formed and thus displace the equilibrium towards the Michael adduct (scheme 113). We had also tried to realize the reaction in the presence of trimethylsilyl chloride. However no reaction occurred under these conditions.



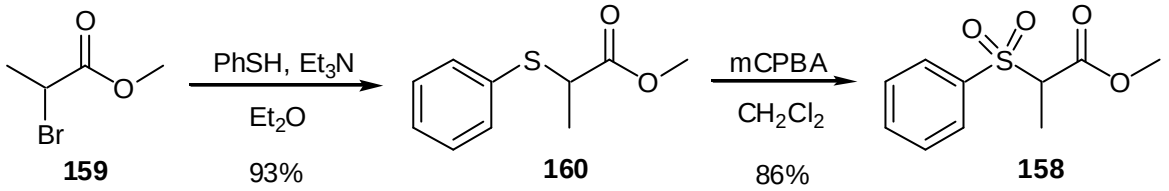
Scheme 113

For that reason we think that the first hypothesis is the right one. And we propose therefore to synthesize a precursor of the anion that would better stabilize the anion and thus favor the reaction.

3.1.3 α-Sulfonylcarboxylic esters

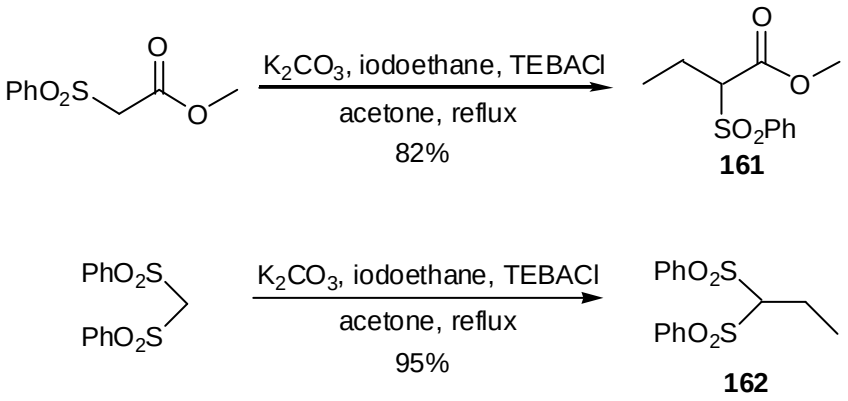
The addition of a second electron-withdrawing group should significantly increase the acidity of the α-proton. Some uses of such compounds under phase transfer conditions have been described (see schemes 108[179] and 109[180]).

Methyl-2-phenylsulfonylpropanoate **158** was prepared from the commercially available methyl-2-bromopropanoate **159** (scheme 114). Reaction of **159** with thiophenol in the presence of triethylamine gave excellent yields of the methyl-2-phenylsulfanylpropanoate **160** which was oxidized in good yields by *meta*-chloroperbenzoic acid to give the desired product **158**.



Scheme 114

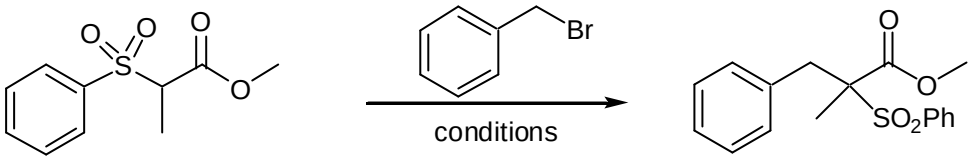
Other precursors for an anion were also synthesized. α-Sulfonylcarboxylic ester **161** and 1,1-bis(phenylsulfonyl)propane **162** were synthesized as shown in scheme 115. With the latter compound we should overcome possible problems with diastereoselectivity, as in this case only one chiral center is formed in the addition product.



Scheme 115

We first studied the phase transfer catalysis by benzylation of **158**. The reaction proceeded well in both solid-liquid and liquid-liquid phase transfer conditions. However when run without catalyst the reactions were nearly as fast (table 28). Therefore these conditions cannot be applied to asymmetric phase transfer conditions.

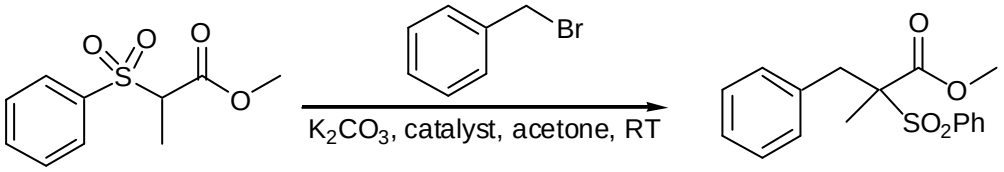
Table 28: *Benzylation reaction under phase transfer conditions.*



158 **163**

Entry	Conditions	Yield
1	KOH, TEBACl, CH_2Cl_2, RT, 3h	86%
2	NaOD, TEBACl, CH_2Cl_2, D_2O, RT, 3h	64%
3	$CsOH \cdot H_2O$, TEBACl, CH_2Cl_2, RT, 3h	quant.*
4	KOH, CH_2Cl_2, RT, 3h	quant.*
5	$CsOH \cdot H_2O$, CH_2Cl_2, RT, 3h	quant.*
6	$CsOH \cdot H_2O$, CH_2Cl_2, -78°C, 6h	quant.*
7	KOH, toluene, RT, 16h	quant.*

Thus it appeared that hydroxide bases were too strong. We then ran the benzylation reaction in the presence of potassium carbonate in acetone.[181] The reaction proceeded well in the presence of a catalyst but not at all without a phase transfer agent (scheme 116).



no catalyst 0%
catalyst = 18-crown-6 100%

158 **163**

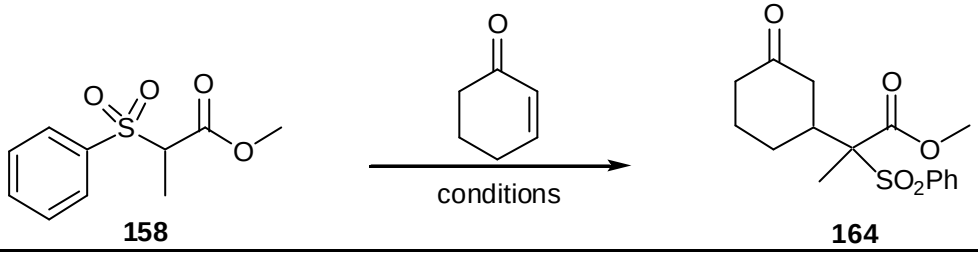
Scheme 116

Then we studied the Michael addition of **158** to cyclohexenone. We began our study with acetone as solvent and by varying the nature of the catalyst (table 29).

* measured by GC

[181] Miesch, M.; Mislin, G.; Franck-Neumann, M. *Tetrahedron Lett.*, **1998**, *39*, 6873-6876.

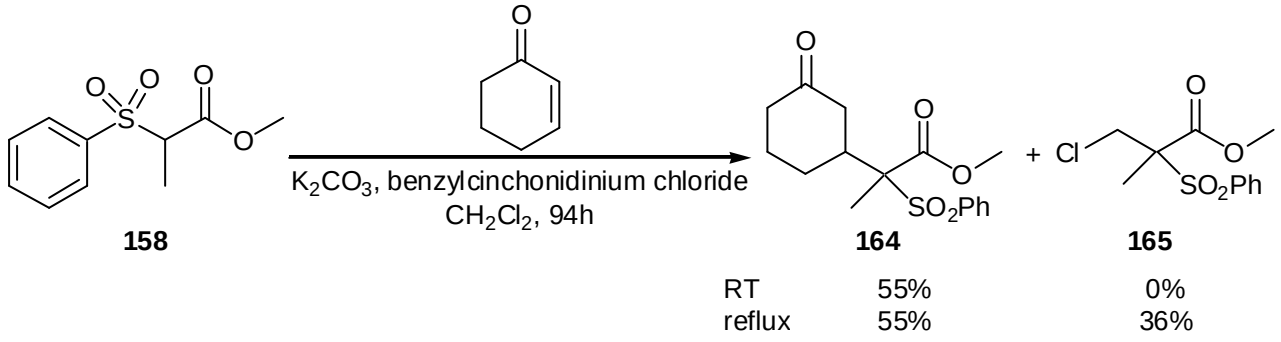
Table 29: *Addition of **158** under phase transfer conditions with different catalysts.*



158 **164**

Entry	Conditions	Yield
1	K_2CO_3, acetone, RT, 24h	0%
2	K_2CO_3, 18-crown-6, acetone, RT, 24h	79%
3	K_2CO_3, TEBACl, acetone, RT, 24h	10%
4	K_2CO_3, benzylcinchonidinium chloride, acetone, RT, 92h	7%
5	K_2CO_3, benzylcinchonidinium chloride, CH_2Cl_2, RT, 94h	55%
6	K_2CO_3, benzylcinchonidinium chloride, CH_2Cl_2, reflux, 94h	55%
7	K_2CO_3, TEBACl, 1 eq. MeOH, CH_2Cl_2, RT, 3h	84%
8	K_2CO_3, 1 eq. MeOH, CH_2Cl_2, RT, 3h	0%

Here again there was no reaction in the absence of a phase transfer catalyst (entry 1). We found that 18-crown-6 was the best catalyst by far (entry 2). The combination potassium carbonate / quaternary ammonium salt in acetone did not seem to be a good system for our reaction (entries 3 and 4). Another solvent could therefore be necessary to realize the reaction. We decided first to work in dichloromethane (scheme 117). But the improvement was not great. It took 94 hours to obtain 55% of the desired adduct **164** (entry 5). Working at reflux of dichloromethane did not enhance the reaction rate; we still observed 55% conversion after 94 hours, but besides we had 36% of a product **165** resulting from the addition to the solvent (entry 6 and scheme 117).



158 **164** **165**

RT	55%	0%
reflux	55%	36%

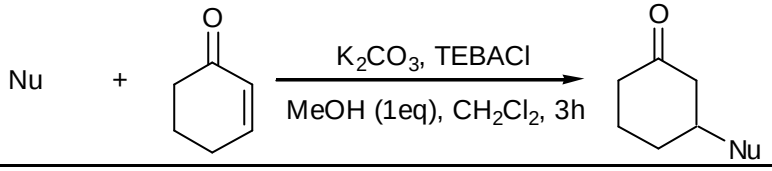
Scheme 117

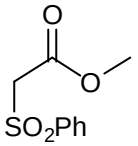
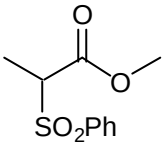
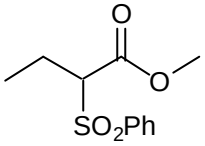
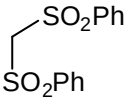
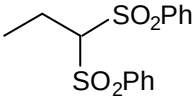
Yields obtained when using an ammonium salt as catalyst (table 29, entries 3 and 4) were similar to the quantity of catalyst used. Could it be that the catalyst was not dissociating from the enolate obtained? In order to check this hypothesis we

added 1 equivalent of MeOH to trap the enolate (table 29, entry 7). This led indeed to 84% of the desired adduct in 3 hours. No reaction was observed without catalyst (table 29, entry 8).

We then ran the addition reaction under these conditions with various nucleophiles (table 30).

Table 30: *Addition of various nucleophiles to cyclohexenone.*



Entry	Nu	Yield
1		65%
2	 **158**	84%
3	 **161**	13%
4		21% after 24h reflux
5	 **162**	0%

We saw that once the α-phenylsulfonylcarboxylic ester was more hindered the reaction dramatically slowed down (entry 3). The bis(phenylsulfonyl) containing nucleophiles were far less reactive and we did not observe any reaction with the more hindered one (entry 4 and 5).

4 Conclusion

In this chapter we showed that neither the sulfonamide nor the sulfone allowed to realize the Michael addition under phase transfer conditions. However we were able to realize this reaction when we used compounds containing simultaneously an ester and a sulfone as electron-withdrawing groups. But once these compounds

became more hindered the reaction slowed down, and were no longer of synthetic interest. The bis-phenylsulfonyl as electron-withdrawing group suffered from a lack of reactivity, which made it also uninteresting for us.

Not every electron-withdrawing group can be used for the phase transfer catalyzed Michael addition. It has to be rather strong in order to allow the formation of a relatively stable anion. On the other hand it cannot be too hindered, which prevents us from using two electron-withdrawing groups to stabilize the anion. So the solution to our problem would be an electron-withdrawing group which is stronger than the sulfone. The nitro group could play this role. The other interesting point is that the nitro group can easily be eliminated or transformed into another function.[182]

[182] Rosini, G.; Ballini, R. *Synthesis*, **1988**, 833-847.