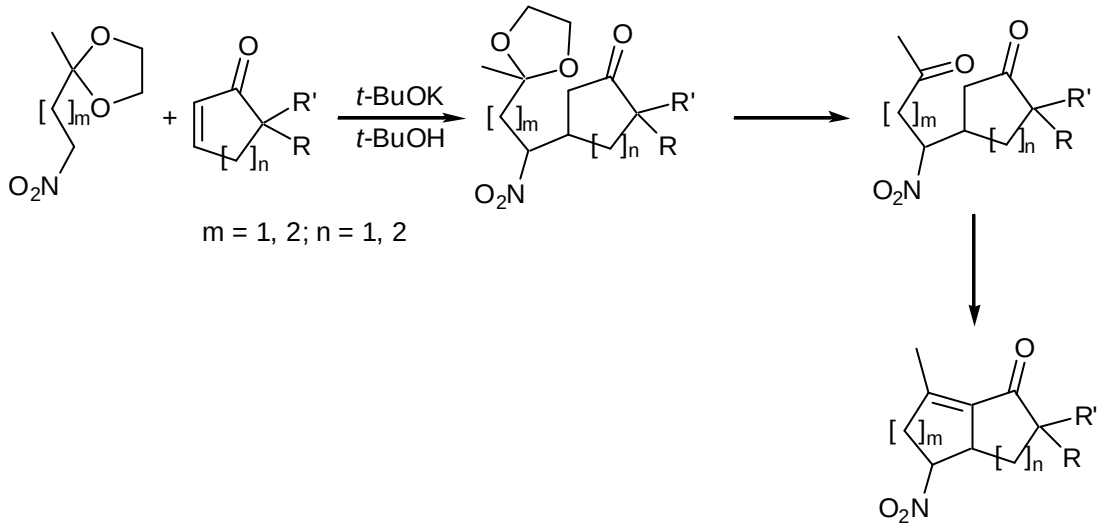
Chapter VII: Phase transfer catalysis with nitrocompounds as nucleophiles

1 Literature survey

1.1 Nitrocompounds as pentannulation reagents

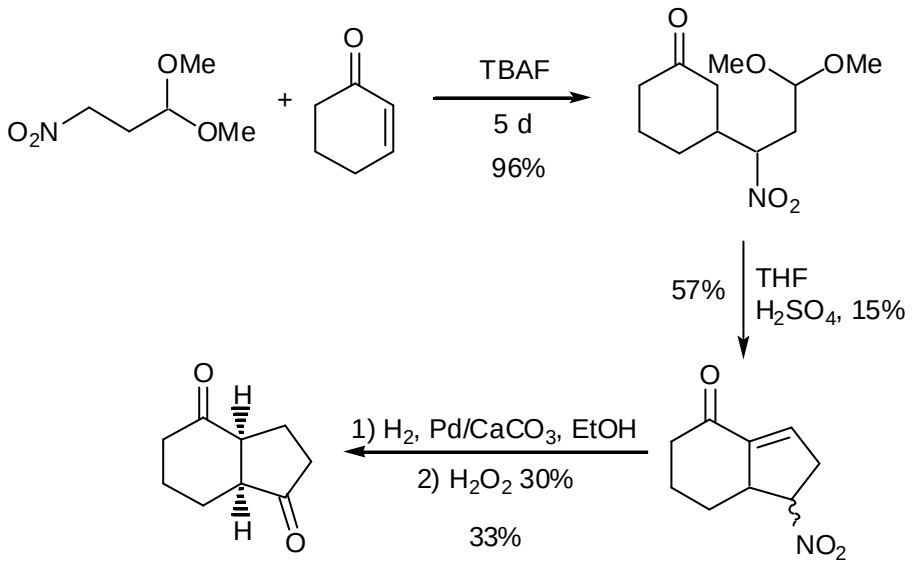
Nitroalkanes containing a ketal have been used in the synthesis of five- or six-membered rings. Toke has described the synthesis of sorgolactone and analogues by a method similar to the one we are interested in (scheme 118).[183] The Michael addition was realized by using potassium *tert*-butoxide in *tert*-butanol.[184]



Scheme 118

In the experimental part of an article published by the group of Hoffmann, the synthesis of a bicyclic diketone was shown starting from cyclohexenone and 3-nitropropanaldehyde dimethylacetal (scheme 119).[185] Tetrabutylammonium fluoride (TBAF) was used for the Michael addition of the nitroalkane.

[183] Mikló, K.; Jaszberenyi, J. C.; Kádas, I.; Árvai, G.; Töke, L. *Tetrahedron Lett.*, **1996**, *37*, 3491-3494.
[184] Kádas, I.; Árvai, G.; Töke, L. *Monatsh. Chem.*, **1996**, *127*, 887-893.
[185] Nowitzki, O.; Münnich, I.; Stucke, H.; Hoffmann, H. M. R. *Tetrahedron*, **1996**, *52*, 11799-11810.

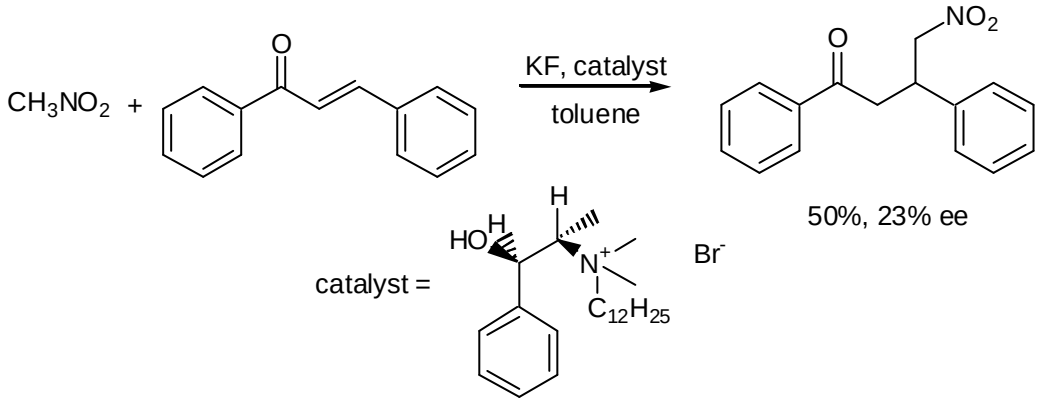


Scheme 119

These two examples confirm our idea that nitrocompounds can be used as cyclopentannulation reagent. To the best of our knowledge no asymmetric method has been described until now. This led us to examine the possibility of using asymmetric phase transfer conditions for the Michael addition of a potential nitro-containing annulation reagent to an enone.

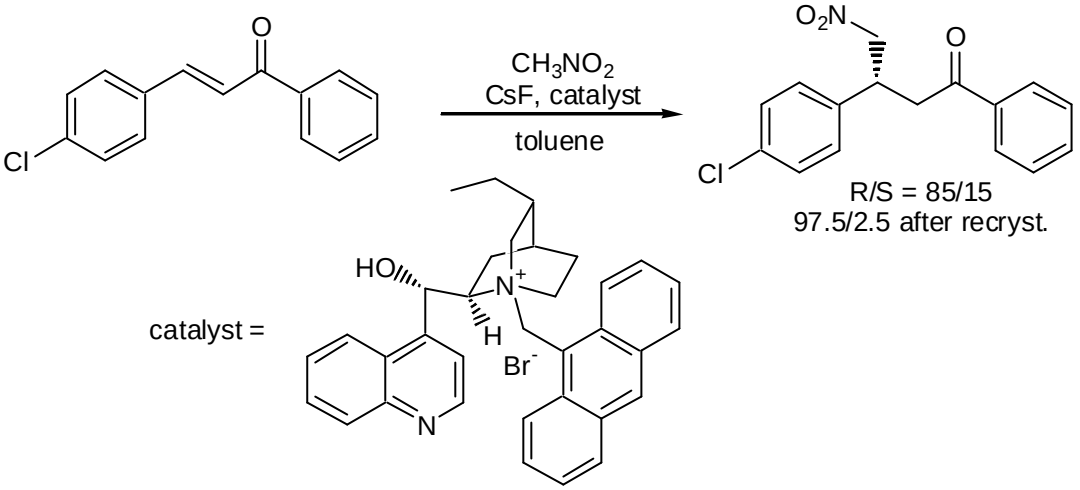
1.2 Asymmetric Michael addition of nitrocompounds under phase transfer conditions

Astonishingly only a few examples of asymmetric Michael additions with nitroalkanes have been described. We will briefly examine the different results using phase transfer catalysis. The first example was given by Wynberg in 1978.[168] Addition of nitromethane to chalcone was effected in the presence of potassium fluoride and a chiral quaternary ammonium salt. Enantioselectivity remained low (23% ee) (scheme 120).



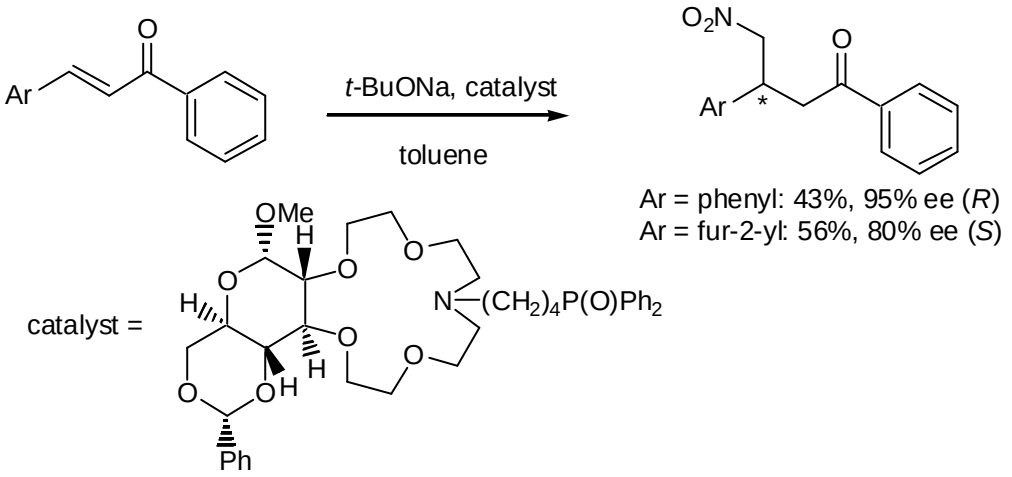
Scheme 120

Corey reported the addition nitromethane to chalcone in the presence of cesium fluoride and a chiral ammonium salt. Enantioselectivity was good (scheme 121).[186]



Scheme 121

Finally, Toke used D-glucose-based azacrown ethers as catalyst and sodium *tert*-butoxide as base for the addition of nitromethane to chalcone or to 3-fur-2-yl-1-phenylpropenone (scheme 122).[187]



Scheme 122

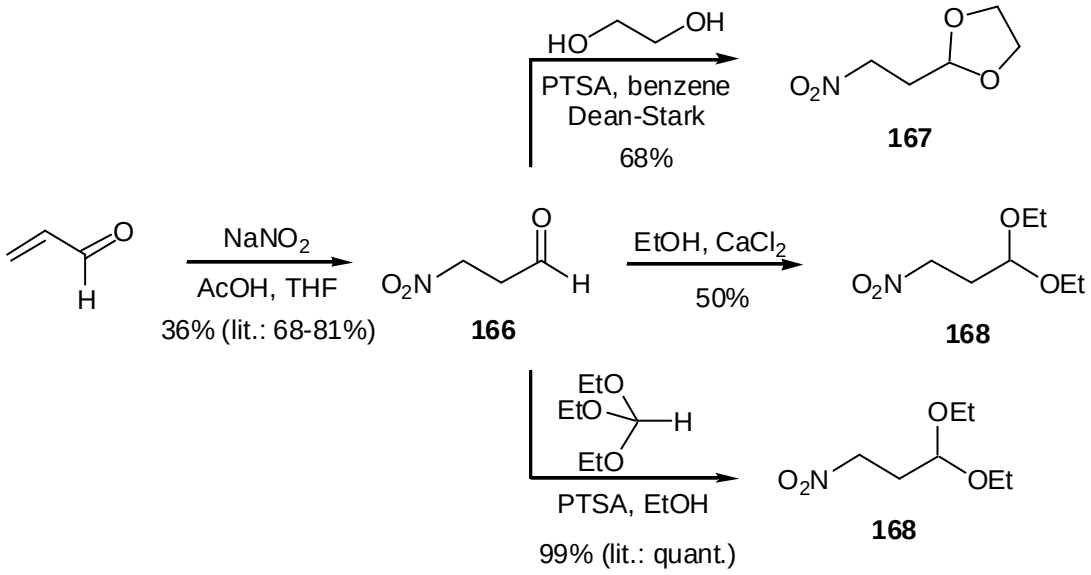
So we see that despite the high versatility of the nitro group, only a few results of asymmetric 1,4-addition have been published at this time. Moreover most work was done using chalcone as Michael acceptor so that these methods seem limited in scope.

[186] Corey, E. J.; Zhang, F.-Y. *Org. Lett.*, **2000**, *2*, 4257-4259.
[187] Novak, T.; Tatai, J.; Bako, P.; Czugler, M.; Kegelvich, G.; Töke, L. *Synlett*, **2001**, 424-426.

2 Results: Synthesis of a potential annulation reagent

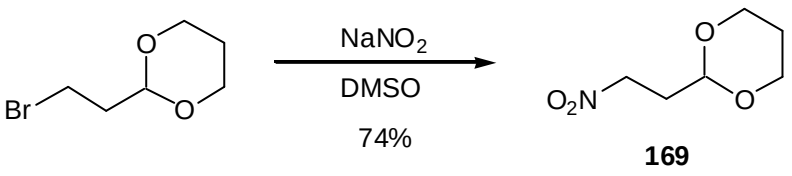
2.1 Synthesis of the ketals

As we have seen ketals derived from 3-nitropropanal **166** can be used as annulation reagent. The first step in this synthesis was the addition of sodium nitrite to acrolein.[188] Yields in our case were always lower than those described in the literature (68-81%[188]). In a second step the aldehyde **166** was transformed into a ketal. When reacted with ethylene glycol, it yielded 2-(2-nitroethyl)-1,3-dioxolane **167** (scheme 123).[188] We also reacted **166** with ethanol in the presence of calcium chloride[189] but the ketal **168** was obtained with moderate yield only. This yield could be optimized by reacting **166** with triethylorthoformate.[188]



Scheme 123

2-(2-nitroethyl)-1,3-dioxane **169** was synthesized as shown in scheme 124 by nucleophilic substitution of the commercially available 2-(2-bromoethyl)-1,3-dioxane.



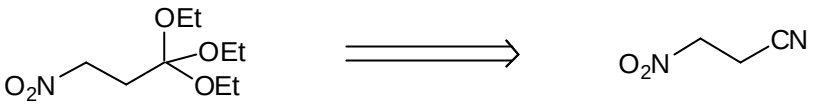
Scheme 124

[188] Öhrlein, R.; Schwab, W.; Ehrler, R.; Jäger, V. *Synthesis*, **1986**, 535-538.
[189] Rohrer, A.; Ocampo, R.; Callot, H. J. *Synthesis*, **1994**, 923-925.

2.2 Synthesis of orthoester 170

2.2.1 First approach

In our previous work on cyclopentannulation reactions the electrophilic component of the 1,3-dipole equivalent was an orthoester function which was generated from the corresponding nitrile.[118] Our first goal was thus the synthesis of nitrile **171** (scheme 125).

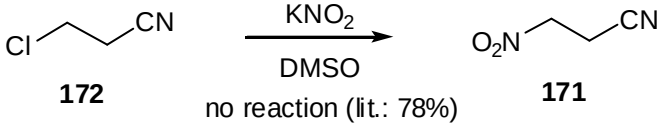


170 **171**

Scheme 125

2.2.1.a Unsuccessful attempts to the synthesis of **171**

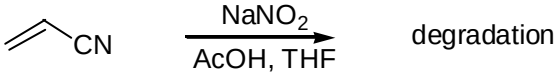
3-nitropropionitrile **171** has been prepared previously by nucleophilic substitution of the commercially available 3-chloropropionitrile **172** (scheme 126).[190] However we were not able to reproduce these results. Even when using additives known to reduce side-reactions in this kind of transformation, such as urea or catechol[191], we did not obtain the desired compound.



172 no reaction (lit.: 78%) **171**

Scheme 126

By analogy with the reaction shown in scheme 123[188] we tried to use the nitrite anion as a Michael donor on acrylonitrile (scheme 127). In this case we observed only degradation of acrylonitrile.

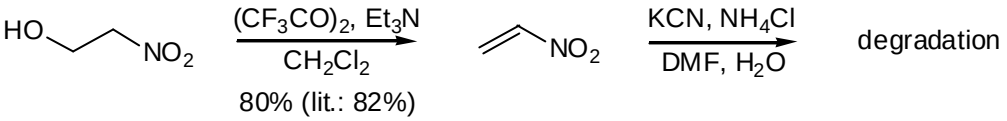


Scheme 127

[190] Movsumzade, E. M.; Kulieva, D. A.; Mamedov, M. G.; Nasirov, Y. F. *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, **1985**, *28*, 12-16.

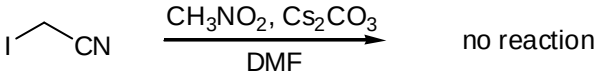
[191] Kornblum, N., *The Synthesis of Aliphatic and Alicyclic Nitro Compounds*, in *Organic Reactions*. John Wiley & Sons, Inc.: New York. 1962, p. 101-156.

The same observation was made when we tried to add the cyanide anion to nitroethene, which could be obtained by dehydration of 2-nitroethanol (scheme 128).[192]



Scheme 128

Another possibility was the reaction of nitromethane with iodoacetonitrile in the reaction conditions described by Desmaële[193], namely using cesium carbonate as base (scheme 129). This was also unsuccessful.

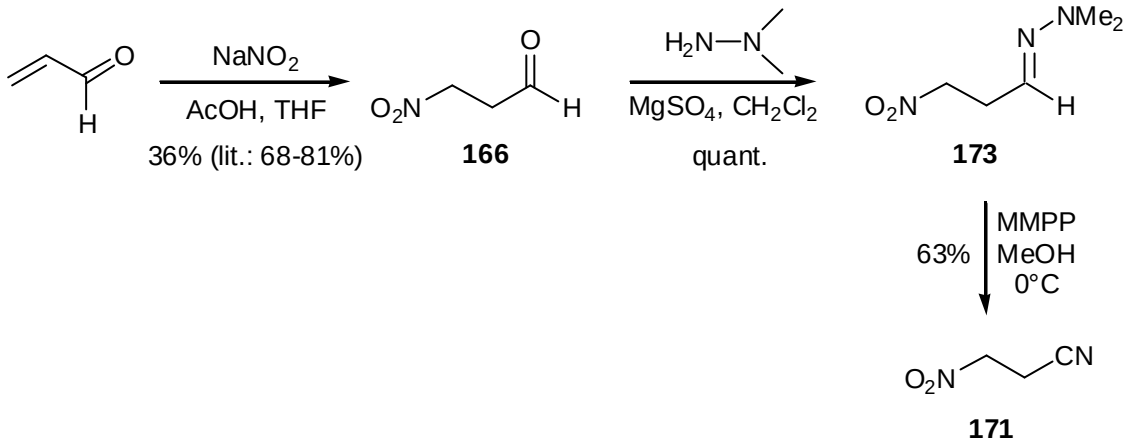


Scheme 129

2.2.1.b Synthesis of **171**

Finally we adopted a somewhat longer reaction sequence. As we showed earlier (scheme 123), sodium nitrite could be reacted with acrolein to yield 3-nitropropanal **166** (scheme 130).[188] The second step was the reaction of aldehyde **166** with dimethylhydrazine in the presence of magnesium sulfate to furnish quantitatively the corresponding hydrazone **173**.[194] Finally, hydrazone **173** was oxidized by magnesium monoperoxyphtalate hexahydrate (MMPP) to yield the desired 3-nitropropionitrile **171**.[195]

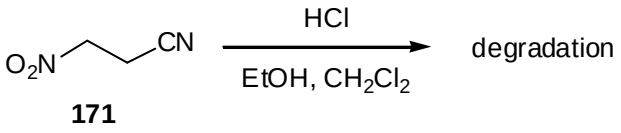
[192] Lucet, D.; Sabelle, S.; Kostelitz, O.; Le Gall, T.; Mioskowski, C. *Eur. J. Org. Chem.*, **1999**, 2583-2591.
[193] Desmaële, D.; Louvet, J. M. *Tetrahedron Lett.*, **1994**, *35*, 2549-2552.
[194] Solladié-Cavallo, A.; Bonne, F. *Tetrahedron Asymmetry*, **1996**, *7*, 171-180.
[195] Fernandez, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M.; Vazquez, J. *Tetrahedron Lett.*, **1993**, *34*, 141-144.



Scheme 130

2.2.1.c Attempts to the synthesis of **10**

We then ran the Pinner reaction following the procedure described for orthoesters **52** and **10**. Anhydrous HCl was bubbled into a CH_2Cl_2 solution of nitrile **171** in the presence of ethanol (scheme 131). Evaporation left a complex mixture where no trace of imidate could be found.

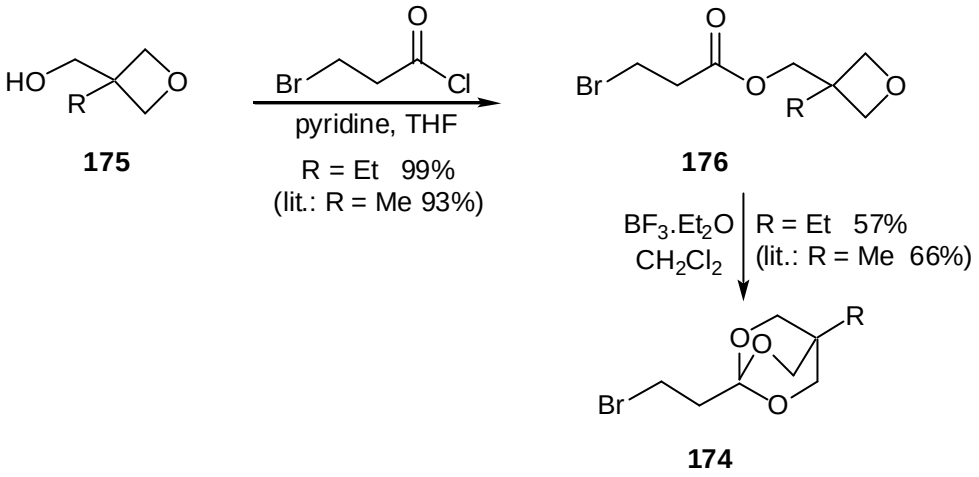


Scheme 131

2.2.2 Second approach

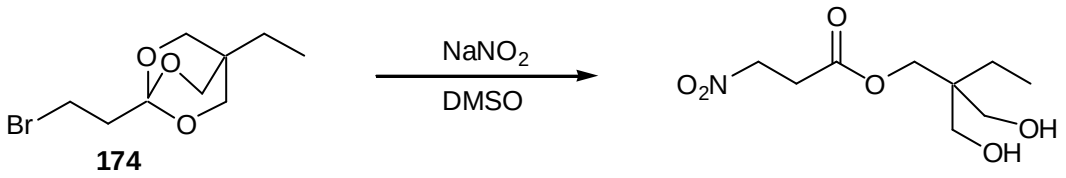
We decided to synthesize first the orthoester function and then introduce the nitro group by a nucleophilic substitution. Orthoester **174** was synthesized as described in the literature (scheme 132).[196] Alcohol **175** was reacted with 3-bromopropionyl chloride to give the ester **176**, which could be cyclized in acceptable yields to orthoester **174**.

[196] Keinan, E.; Sinha, S. C.; Singh, S. P. *Tetrahedron*, **1991**, *47*, 4631-4638.



Scheme 132

We then used the conditions generally used to transform a halogenated compound into its nitro analogue (scheme 133).[191] However besides the nitration we also observed complete hydrolysis of the orthoester. It is interesting to note that in the same reaction conditions 2-(2-bromoethyl)-1,3-dioxane was easily transformed into its nitro analogue **169** without any side reaction (see scheme 124).



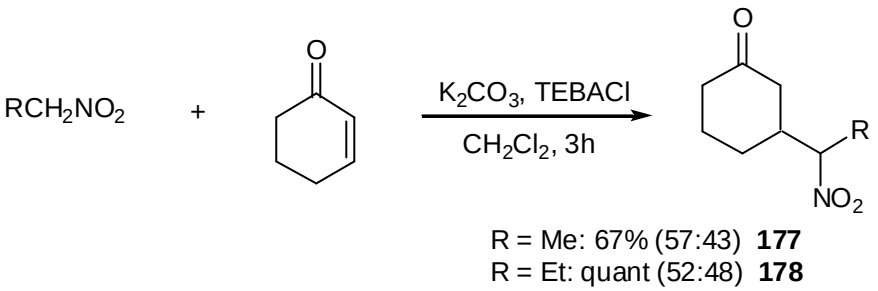
Scheme 133

It appears that a nitro and the orthoester group were incompatible.

3 Michael addition under phase transfer catalysis

3.1 Michael addition of nitroethane and nitropropane

We studied the optimization of the reaction conditions of the Michael reaction with commercially available nitroethane and nitropropane. We began our study with the best conditions established before. As we hoped the nitro-compound to be more reactive, we did not add methanol. No proton source should indeed be needed; the enolate formed could be a sufficiently strong base to deprotonate a nitroalkane, thus pushing the equilibrium towards the addition. The reaction was fast and complete after 3 hours (scheme 134). Without catalyst we did not see any reaction after that time. As expected only the 1,4-addition product was observed.



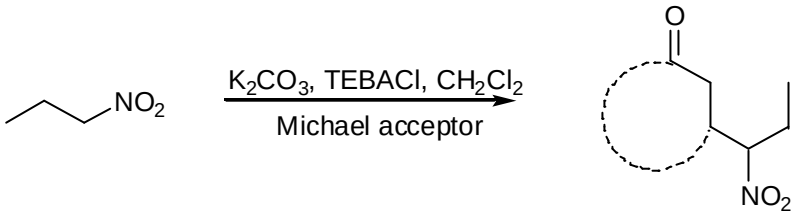
R = Me: 67% (57:43) **177**
R = Et: quant (52:48) **178**

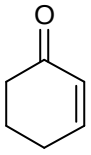
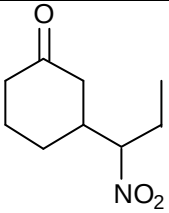
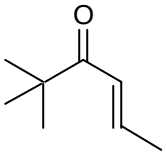
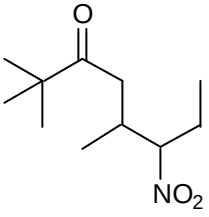
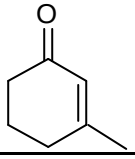
Scheme 134

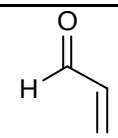
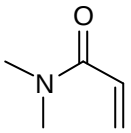
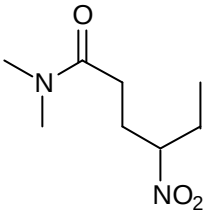
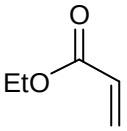
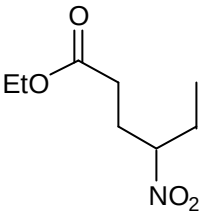
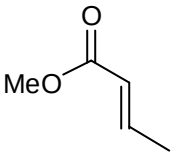
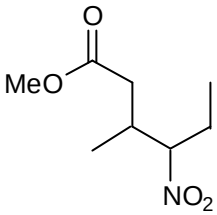
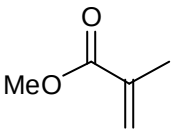
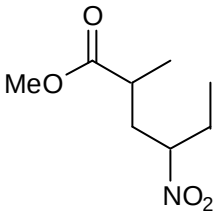
Unlike the case of sulfonamides, where one diastereomer was formed as major isomer, the addition of nitro-compounds leads to the formation of an equimolar mixture of two diastereomers. This is due to the epimerization of the stereocenter α to the nitro-group under the reaction conditions.

Other Michael acceptors were also used (table 31). Cyclic (entry 1) and acyclic enones (entry 2), unsaturated esters (entries 6-8) and amides (entry 5) were suitable acceptors. No reaction was observed with 3-methylcyclohex-2-enone (entry 3); acrolein polymerized (entry 4).

Table 31: *Michael addition of nitropropane to various acceptors*

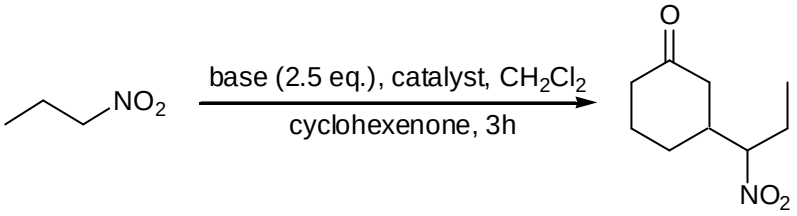


Entry	Michael acceptor	Reaction time	Product	Yield
1		4 h	 **178**	quant
2		4 h	 **179**	55%
3		96 h		0%

4		4 h		polym.
5		20 h	 **180**	83%
6		4 h	 **181**	quant.
7		24 h	 **182**	40%
8		4 h	 **183**	54%

While potassium carbonate gave good results no reaction was observed with lithium and sodium carbonate (entries 1 and 2, table 32). On the other hand, cesium carbonate worked very well (entry 4), but the reaction did not need a phase transfer catalyst (entry 5).

Table 32: *Michael addition of nitropropane with various bases.*



178

Entry	Base	Catalyst	Conversion
1	Li_2CO_3	TEBACl	0%
2	Na_2CO_3	TEBACl	0%
3	K_2CO_3	TEBACl	complete
4	Cs_2CO_3	TEBACl	complete
5	Cs_2CO_3	/	complete
6	*t*-BuOK	TEBACl	degradation

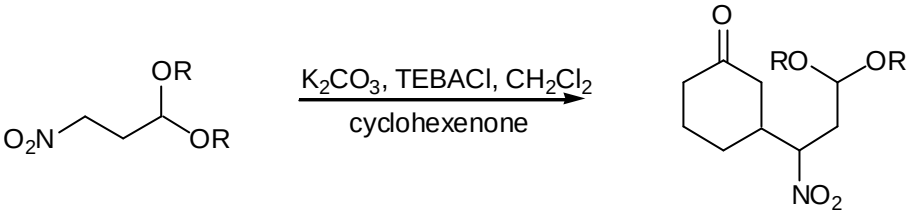
Many phase transfer reactions have been run with potassium *tert*-butoxide as a base.[197] In our case the use of this rather strong base led to complete degradation of the reaction mixture (entry 6).

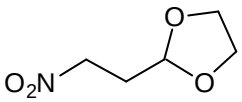
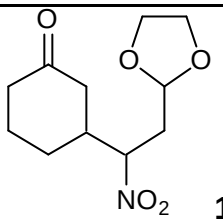
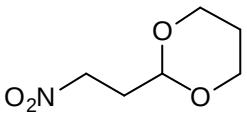
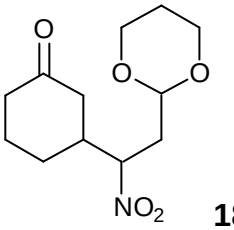
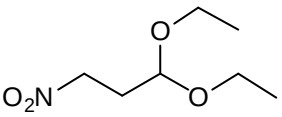
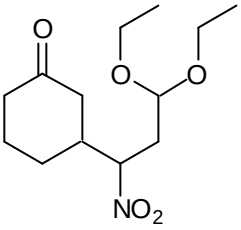
3.2 Michael addition of the ketals 169, 167 and 168: racemic conditions

The reaction had already been described[183,185], but conditions were not the same as ours. So we began our study by using exactly the same conditions as before: potassium carbonate as base, benzyl triethylammonium chloride as catalyst and dichloromethane as solvent (table 33). The three ketals worked well and gave the corresponding adduct with good to excellent yields. Here again we observed the formation of two diastereomers due to epimerization during the reaction (control by GC).

[197] Keller, W. E., *Phase-Transfer Reactions. Fluka Compendium*. Vol. 3; Thieme: Stuttgart, 1990.

Table 33: *Michael addition of ketals to cyclohexenone.*

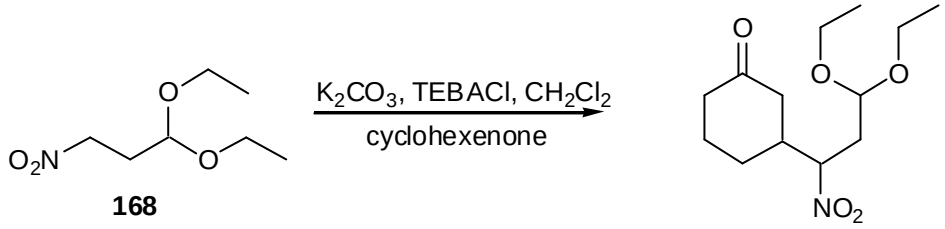


Entry	Ketal	Product	Yield
1	 **167**	 **184**	80%
2	 **169**	 **185**	96%
3	 **168**	 **186**	82%

3.2.1 Quantity of the base

We studied the influence of the quantity of base. Until now, we have used 2.5 equivalents of K_2CO_3. The reaction was run with 1 and 0.3 equivalent (table 34). We obtained the adduct, but it took 6 hours to completion when we used only a catalytic amount of base.

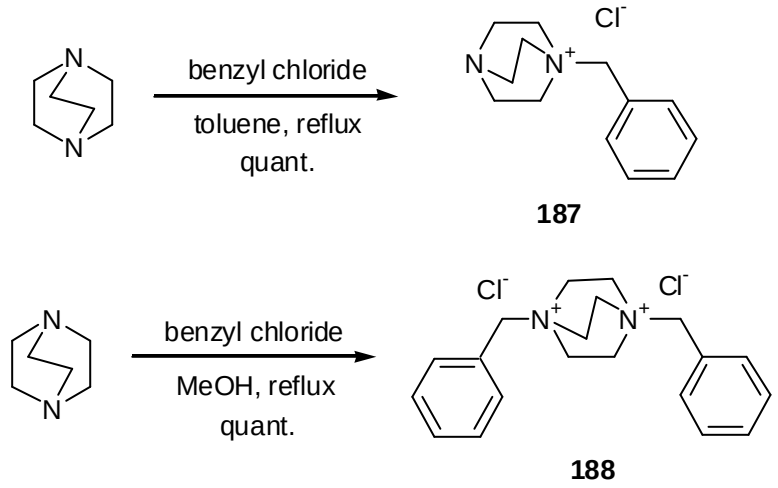
Table 34: *Addition of **168** with various quantities of K_2CO_3.*



Entry	K_2CO_3	Reaction time
1	2.5 eq.	3 h
2	1 eq.	3 h
3	0.3 eq.	6 h

3.2.2 Nature of the catalyst

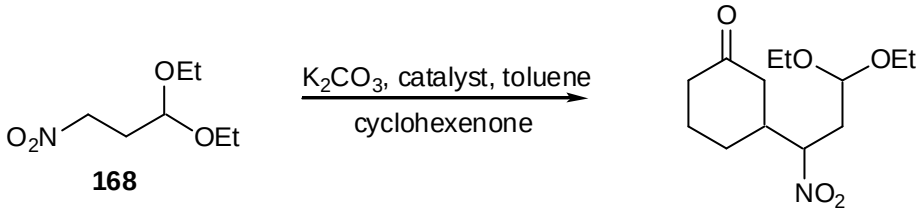
We wondered if a second cationic center in the catalyst would improve the reaction rates. Therefore we wanted to synthesize the dibenzylated derivative of diazabicyclooctane (DABCO). We refluxed DABCO in the presence of an excess of benzyl chloride in toluene (scheme 135). However only the monobenzylated compound **187** was obtained. This compound precipitated in toluene and was not reacting any further. When we conducted the reaction in refluxing methanol the dibenzylated compound **188** was formed quantitatively.



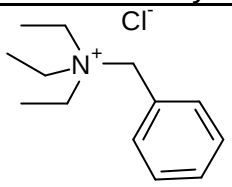
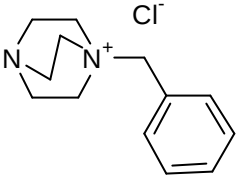
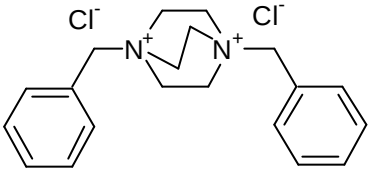
Scheme 135

We ran the addition reaction with the three catalysts (table 34). **187** and **188** indeed catalyzed the Michael addition, however no acceleration was observed due to the presence of the additional cationic center. We rather observed a significant decrease of rate with **188**.

Table 34: *Relative rates of the Michael addition.*



168 **186**

Entry	Catalyst	Relative rate
1	 TEBACl	1
2	 **187**	0.65
3	 **188**	0.04

3.3 Asymmetric Michael addition of ketal 168 under phase transfer conditions

3.3.1 Synthesis of chiral catalysts

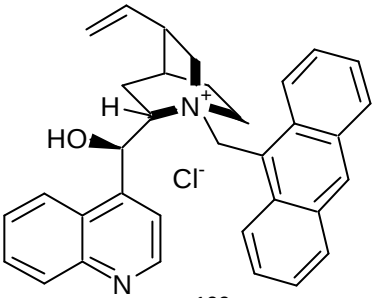
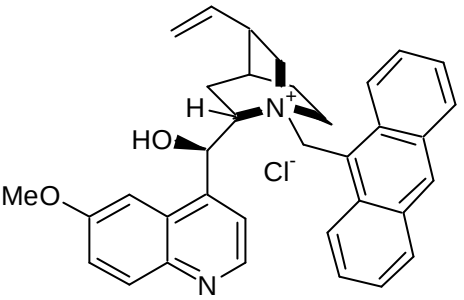
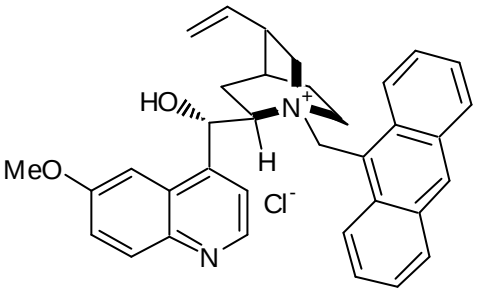
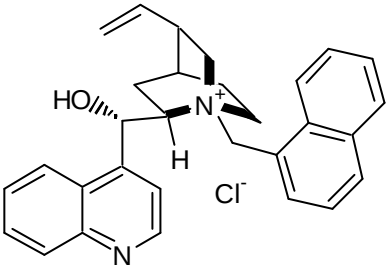
Two major possibilities for differentiation are offered by the scaffolds of the *cinchona* family. First the amine can be alkylated. Actually, most often the described catalysts are either *N*-benzylated or are carrying a 9-anthrylmethyl group. The second site of diversity is the free alcohol which can easily be alkylated or acylated.

In order to synthesize new catalysts we used the procedure described by Corey to introduce the *N*-substituent.[198] The tertiary amine was refluxed in toluene in the presence of an alkylating reagent for 3 hours. The cooled reaction mixture was poured into ether which induced the precipitation of the salt that was filtered. Six other catalysts were prepared by this method with yields ranging from 47 to 87% (table 35). Three of them had not been described before (entries 4-6).

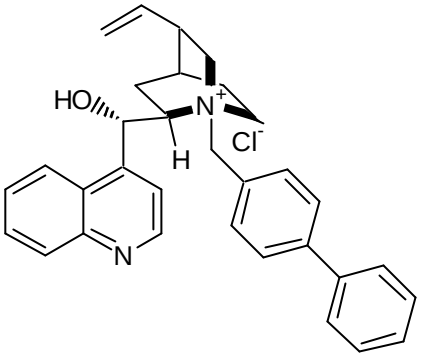
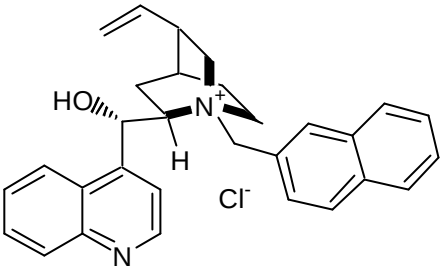
[198] Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.*, **1997**, *119*, 12414-12415.

Table 35: *Synthesis of chiral catalysts*.

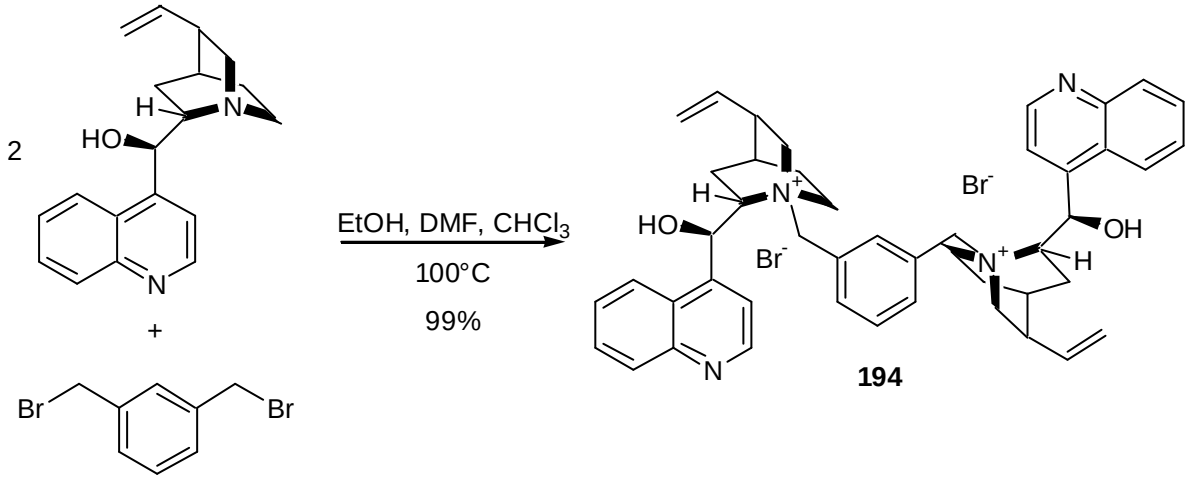
Chiral amine + $ArCH_2X$ → (toluene, reflux) → (1) precipitation in ether, (2) filtration → chiral catalyst

Entry	Chiral amine	$ArCH_2X$	Catalyst	Yield
1	cinchonidine	9-chloromethyl-anthracene	 **189**[199]	87%
2	quinine	9-chloromethyl-anthracene	 **156**[199]	65%
3	quinidine	9-chloromethyl-anthracene	 **155**[199]	47%
4	cinchonine	1-chloromethyl-naphthalene	 **190**	82%

[199] Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.*, **1997**, *38*, 8595-8598.

5	cinchonine	4-chloromethyl-biphenyl	 **191**	72%
6	cinchonine	2-chloromethyl-naphthalene	 **192**	69%

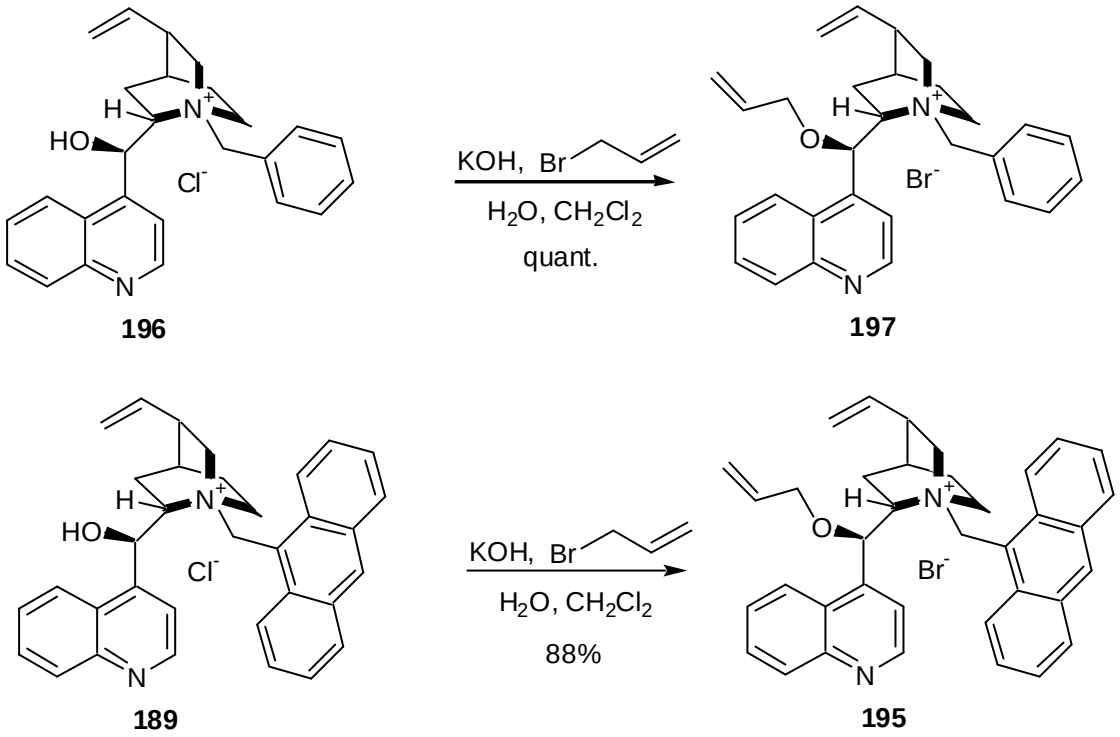
We also synthesized catalyst **193** by reaction of 2 equivalents of cinchonidine with α,α'-dibromo-*m*-xylene (scheme 136).[200] The presence of 2 chiral amines should increase the enantioselectivity and the scope of the substrate.



Scheme 136

For the introduction of an *O*-substituent, we also refer to Corey's article.[198] As substituent we decided to use an allyl function.[201] The reaction of the alcohol with allyl bromide was realized in a biphasic mixture with potassium hydroxide as base (scheme 137).

[200] Jew, S.-S.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-G. *Chem. Comm.*, **2001**, 1244-1245.
[201] O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron*, **1994**, *50*, 4507-4518.

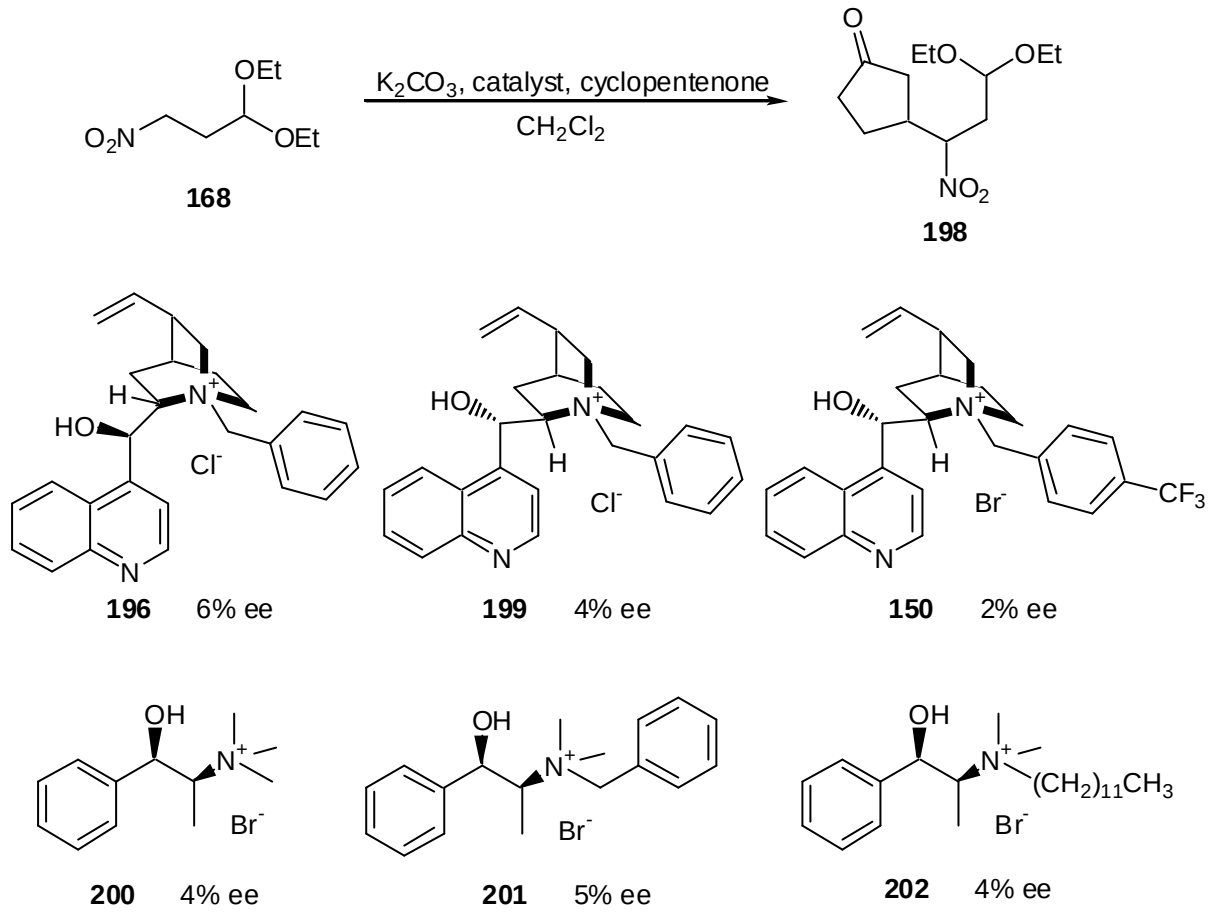


Scheme 137

3.3.2 A first screening

We began our study with six commercially available catalysts. All these catalysts were quaternary ammonium salts derived from cinchonine, cinchonidine or ephedrine. We chose also cyclopentenone as Michael acceptor because separation on chiral GC was better than with cyclohexenone. In opposition to the achiral catalyst, the reaction times were rather long and varied between 16 hours for the *cinchona* derived catalysts and three days for the ephedrine derived catalysts. Conversion was complete in all the cases. Diastereoselectivity was low, as observed before with achiral catalysts. Enantioselectivities could only be measured for one of the diastereomers as we were not able to separate completely the second one.

As we see in scheme 138, enantioselectivities were very low. Both families of catalysts gave nearly racemic mixtures of the desired product. Only one general trend could be observed in this series of reactions: the catalysts derived from ephedrine gave slower rates than those from the *cinchona* family. It should be noted that, without catalyst, no reaction was observed after 16 hours.



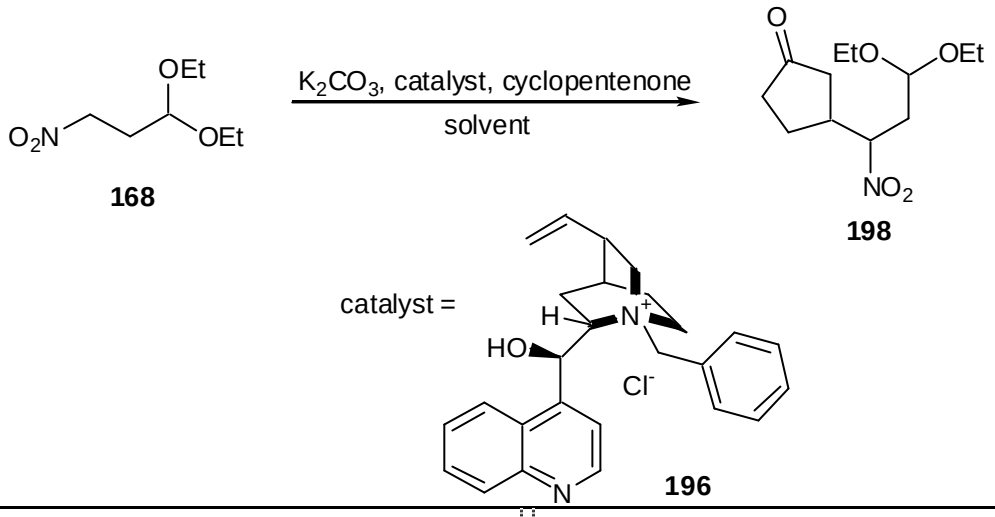
Scheme 138

None of the catalysts gave a good result, so we estimated that changing the nature of the *N*-substituent or introducing an *O*-substituent would not greatly affect the outcome of the reaction. We took a closer look at the reaction conditions, especially at the solvent.

3.3.3 Choice of the solvent

An important factor in phase transfer reactions is of course the solvent. It determines the tightness of the ion pair, so it might influence the transition state. It also plays a role in the ratio of catalyzed reaction *versus* uncatalyzed reaction. Our first concern was therefore the choice of the best solvent. We studied the reaction in a series of solvents (polar / apolar, protic / aprotic, coordinating / not coordinating) while reaction conditions remained the same with K_2CO_3 as base and **196** as catalyst (table 36).

Table 36: *Michael addition in various solvents.*



168 **198** **196**

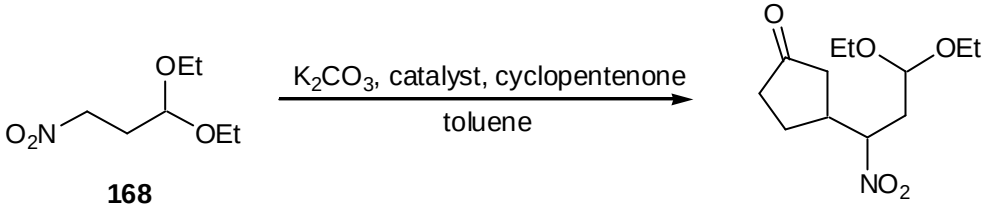
Entry	Solvent	Result	Entry	Solvent	Result
1	CH_2Cl_2	6% ee	6	ether	3% ee
2	toluene	24% ee	7	THF	0% ee
3	acetone	4% ee	8	hexane	3% ee
4	1,4-dioxane	11% ee	9	EtOH	1% ee
5	*N*-methylpyrrolidinone	2.5 % ee	10	AcOEt	1.5% ee

Toluene was by far the best solvent for our reaction (entry 2). Polar solvents gave low enantioselectivities. The use of ether and THF resulted in a nearly racemic product (entries 6 and 7), whereas 1,4-dioxane allowed to obtain some selectivity (entry 4). An interesting point is the difference between toluene and hexane, both aprotic apolar solvents (entries 2 and 8). One may conclude from this result that the aromatic ring is playing a crucial role in the outcome of the reaction. An interaction with the aromatic rings of the catalyst and the solvent could be imagined.

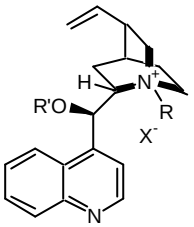
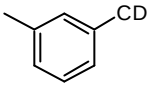
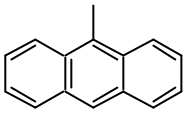
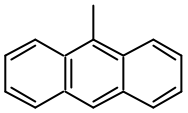
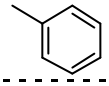
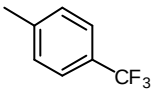
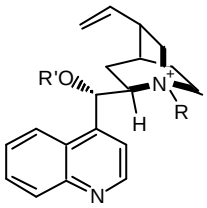
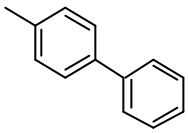
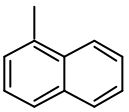
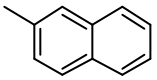
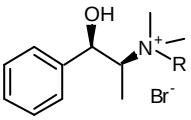
3.3.4 Michael addition to cyclopentenone under phase transfer conditions

We ran the addition reaction in the same conditions as before. The comparison between the various results should allow us to define what part of the catalyst was important, and perhaps find already the catalyst of choice for our reaction. The results for the addition to cyclopentenone with all the catalysts are summarized in table 37.

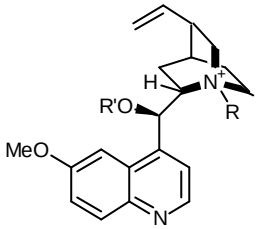
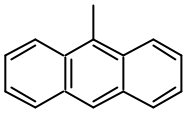
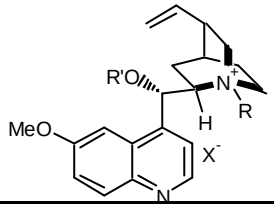
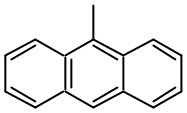
Table 37: *Addition to cyclopentenone.*



168 **198**

Entry	Catalyst	Core	R	R'	X⁻	Result	Config.[a]
1	**196**			H	Cl^-	21% ee	*S*
2	**194**			H	Br^-	2.5% ee	*(S)*
3	**189**			H	Cl^-	11% ee	*S*
4	**195**			allyl	Br^-	21% ee	*S*
5	**197**			allyl	Br^-	12% ee	*S*
6	**199**			H	Cl^-	23% ee	*R*
7	**150**			H	Br^-	21% ee	*R*
8	**191**			H	Cl^-	19% ee	*R*
9	**203**			H	Cl^-	20% ee	*R*
10	**192**			H	Cl^-	48% ee	*R*
11	**200**		Me	H	Br^-	3% ee	*(R)*
12	**201**			H	Br^-	6% ee	*R*
13	**202**		$(CH_2)_{11}CH_3$	H	Br^-	8% ee	*R*

[a] Absolute configuration of the carbon atom β to the carbonyl group in the major isomer, determined by the relative retention times on chiral GC. See chapter VII, section 4.1.2 for the configurational assignment.

14	**204**			H	Cl^-	10% ee	*R*
15	**156**			H	Cl^-	15% ee	*R*
16	**155**			H	Cl^-	11% ee	*S*
17	**205**			H	Cl^-	1% ee	*(S)*

Catalysts of the cinchona family were far better than the ephedrine derivatives (entries 11, 12 and 13). Catalyst **194**, which beared 2 chiral amines, showed nearly no selectivity, whereas the reaction was considerably slower in that case (entry 2).

Corey[198] as well as Plaquevent's[174] group showed that catalysts with bulkier *N*-substituent gave the best result. These observations could be confirmed (compare entries 4, 15, 16 to entries 5, 14, 17). Catalyst **189** (entry 3) however showed lower selectivity than its benzylated analogue (entry 1). Catalyst **192** with a *N*-(2-naphthyl)methyl substituent showed significantly improved selectivity (entry 10). This could show that a bulky group is indeed needed, but that some degrees of liberty are necessary for the substrates to adopt the good orientation.

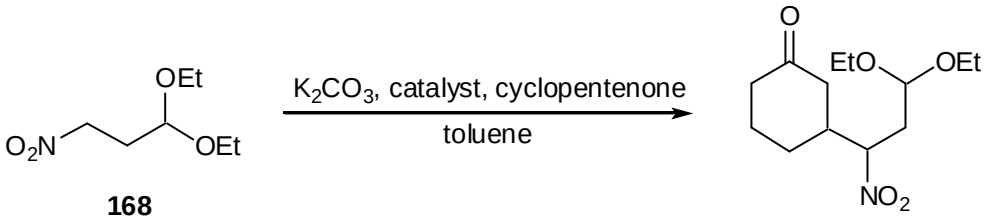
Another important feature in the catalyst is the presence or absence of the free hydroxyl group. The group of Plaquevent, for example, showed that with an *O*-allylated catalyst there was no reaction.[174] On the other side Corey got the best results with *O*-allylated or *O*-benzylated catalysts.[202] In our case however, the results were ambiguous. There were no great differences in reaction rates. However no clear influence of the allylic group on the stereochemistry could be observed. Whereas the allylated catalyst **195** carrying a *N*-anthrylmethyl substituent (entry 4) showed improved selectivity, *N*-benzylated catalyst **197** (entry 5) was less selective as compared to the catalyst with a free OH (entries 3 and 1). The influence of the allyl group seemed thus to depend on the nature of the other groups in the molecule.

3.3.5 Michael addition to cyclohexenone under phase transfer conditions

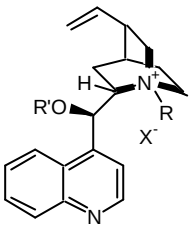
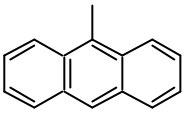
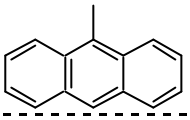
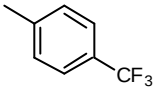
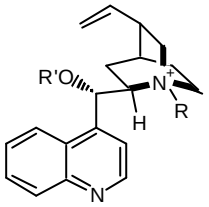
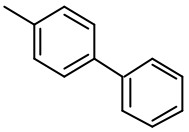
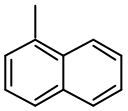
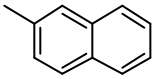
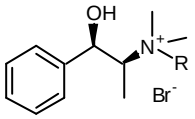
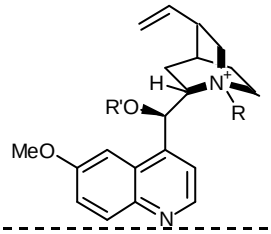
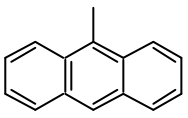
The results from the addition to cyclohexenone are summarized in table 38.

[202] Corey, E. J.; Zhang, F.-Y. *Angew. Chem. Int. Ed. Engl.*, **1999**, *38*, 1931-1934.

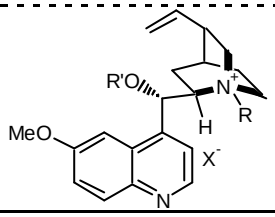
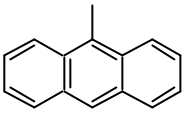
Table 38: *Addition to cyclohexenone.*



168 **186**

Entry	Catalyst	Core	R	R'	X^-	Result	Config.[a]
1	**196**			H	Cl^-	21% ee	*S*
2	**189**			H	Cl^-	3% ee	*(S)*
3	**195**			allyl	Br^-	13% ee	*S*
4	**199**			H	Cl^-	16% ee	*R*
5	**150**			H	Br^-	14.5% ee	*R*
6	**191**			H	Cl^-	17% ee	*R*
7	**203**			H	Cl^-	16% ee	*R*
8	**192**			H	Cl^-	28% ee	*R*
9	**200**		Me	H	Br^-	4% ee	*(S)*
10	**201**			H	Br^-	12% ee	*S*
11	**202**		$(CH_2)_{11}CH_3$	H	Br^-	2% ee	*(S)*
12	**156**			H	Cl^-	13% ee	*S*

[a] Absolute configuration of the carbon atom β to the carbonyl group in the major isomer, determined by the relative retention times on chiral GC. See chapter VII, section 4.1.2 for the configurational assignment.

13	**155**			H	Cl^-	8% ee *R*

Again we see that, in general, catalysts of the cinchona family were better than the ephedrine derivatives. However in this case *N*-benzyl ephedrine **201** exhibited better selectivity than before. As before, catalyst **192** with a 2-naphthylmethyl substituent was the best catalyst.

In general the selectivity in the addition reaction to cyclohexenone was somewhat lower than to cyclopentenone.

3.3.6 The nature of the base

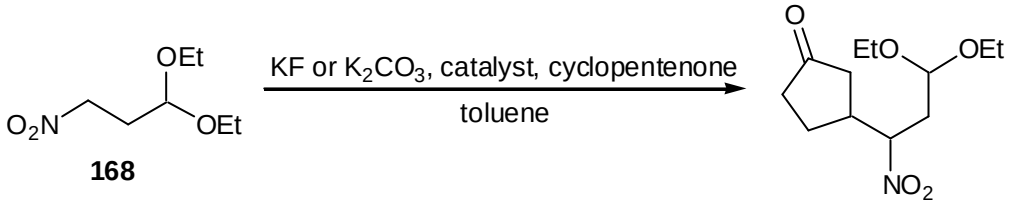
3.3.6.a KF

Quite often in the presence of strong electron-withdrawing groups under phase transfer conditions potassium fluoride was used as a base.[202,203] We wanted to see if the nature of the base could influence the stereochemical outcome of the reaction. Therefore we tried some of our catalysts in the same conditions as before but with potassium fluoride as base.

In table 39 and table 40 we compare potassium fluoride to potassium carbonate in the addition reaction to cyclopentenone and cyclohexenone respectively.

[203] Clark, J. H. *Chem. Rev.*, **1980**, *80*, 429-452.

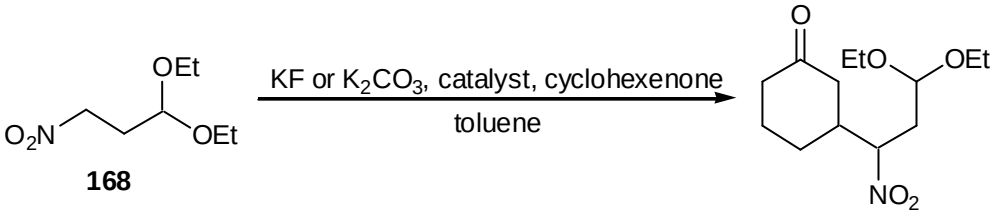
Table 39: *Michael addition to cyclopentenone.*



168 **198**

Entry	Catalyst	KF	K_2CO_3
1	**196**	39% ee	21% ee
2	**189**	2% ee	11% ee
3	**195**	5% ee	21% ee
4	**155**	36% ee	15% ee
5	**206**	35% ee	19% ee
6	**190**	52% ee	20% ee
7	**192**	37% ee	48% ee

Table 40: *Michael addition to cyclohexenone.*



168 **186**

Entry	Catalyst	KF	K_2CO_3
1	**190**	64% ee	16% ee
2	**191**	14% ee	17% ee
3	**192**	29% ee	28% ee

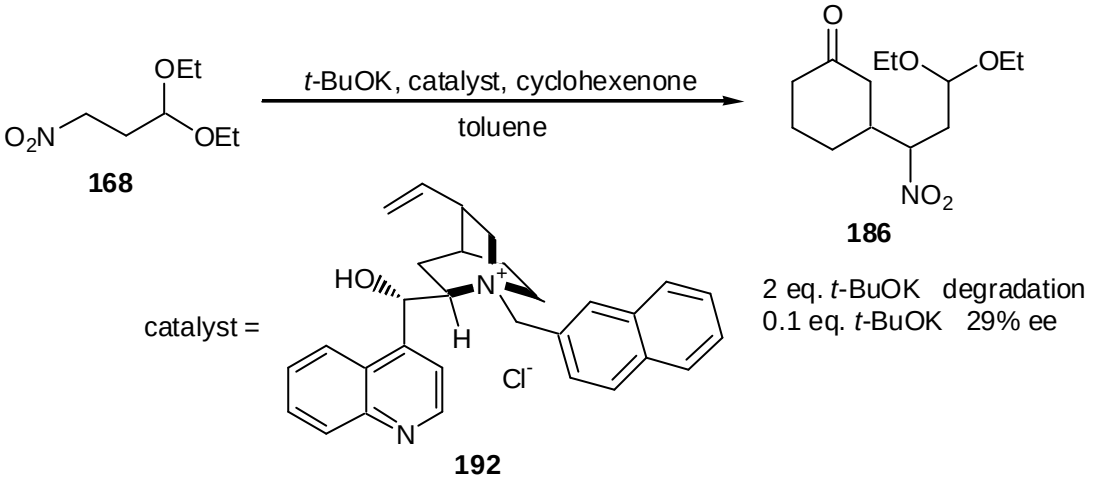
As we see conclusions are difficult to draw, some catalysts showed dramatic improvement when potassium fluoride was used as a base, others lost nearly all selectivity. In the case of cyclopentenone no significant difference between the catalysts was observed with two exceptions: 9-anthrylmethyl substituted catalysts (entries 2 and 3, table 39) showed nearly no selectivity, whereas 1-naphthylmethyl substituted catalyst **190** was the best catalyst for this base (entry 6).

With cyclohexenone, **190** again gave the best result (52% ee) (entry 1, table 40). No significant difference between the two bases was observed with the other catalysts (entries 2 and 3).

These results were somewhat surprising as they do not fit into the general scheme 98. According to this scheme the base does not participate in the addition reaction but only forms the anion which is then taken into the organic phase by the catalyst. It could therefore be that the active species is more complex than a simple ion pair involving the ammonium salt and the nucleophile.

3.3.6.b *t*-BuOK

Another possible base was potassium *tert*-butoxide. Most examples given in literature used this base in the presence of a crown or an aza-crown ether as catalyst. When we used as before 2 equivalents of base, we observed a lot of degradation (scheme 139). However when we used only a catalytic amount of potassium *tert*-butoxide (0.1 equivalent), the adduct was obtained with 29% enantiomeric excess (under the form of 2 diastereoisomers) which was no improvement compared to potassium carbonate (entry 8 of table 37).

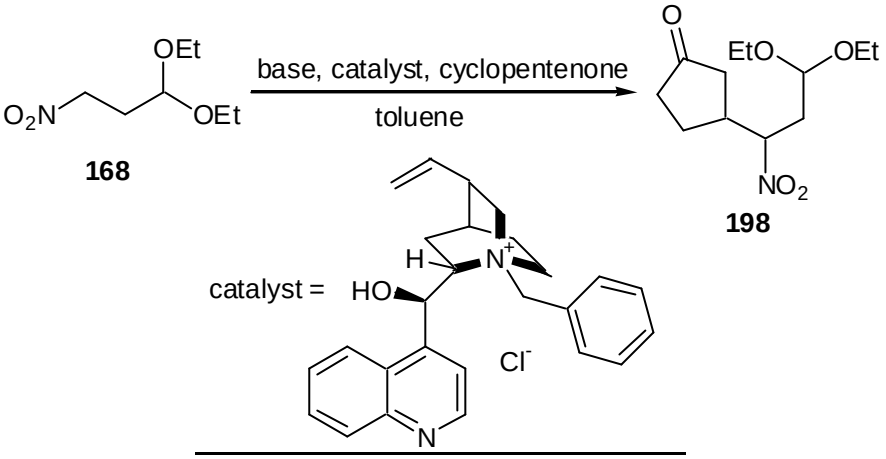


Scheme 139

3.3.6.c Hydroxides

Corey used for some of his examples cesium hydroxide as base.[198,172] As with potassium *tert*-butoxide, degradation occurred when a stoechiometric amount of potassium or cesium hydroxide was used. However with 0.1 equivalent of base the reaction proceeded smoothly and adduct **198** could be obtained with modest enantioselectivities (table 41). No reaction took place with lithium hydroxide, no difference was observed between the other bases.

Table 41: *Michael addition with hydroxides as base.*



168 **198**

catalyst =

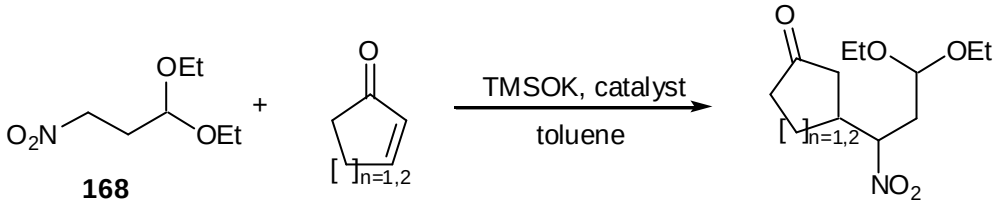
Base	ee%
LiOH	No reaction
NaOH	23% ee
KOH	21% ee
CsOH	22% ee

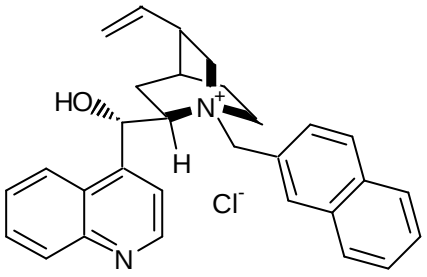
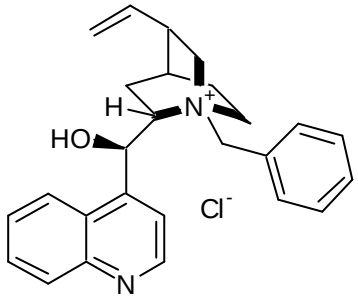
However in absence of a catalyst the reactions were nearly as fast as the catalyzed ones. We were unfortunately not able to suppress this uncatalyzed reaction and hence improve the selectivities.

3.3.6.d TMSOK

Another interesting compound is potassium trimethylsilanoate (TMSOK). We became interested in using it as a base under phase transfer conditions. With 1 equivalent of TMSOK, we observed the formation of the adduct but there was a lot of degradation. When we lowered the quantity of base to 0.1 equivalent the reaction proceeded smoothly and fast (table 42). The adduct was obtained with enantiomeric excesses similar to that obtained with potassium carbonate.

Table 42: *Michael addition with TMSOK.*



Entry	Catalyst	Enone	TMSOK	K_2CO_3
1	 **192**	cyclo-pentenone	47% ee	48% ee
2		cyclo-hexenone	26% ee	28% ee
3	 **196**	cyclo-pentenone	20% ee	21% ee
4		cyclo-hexenone	36% ee	21% ee

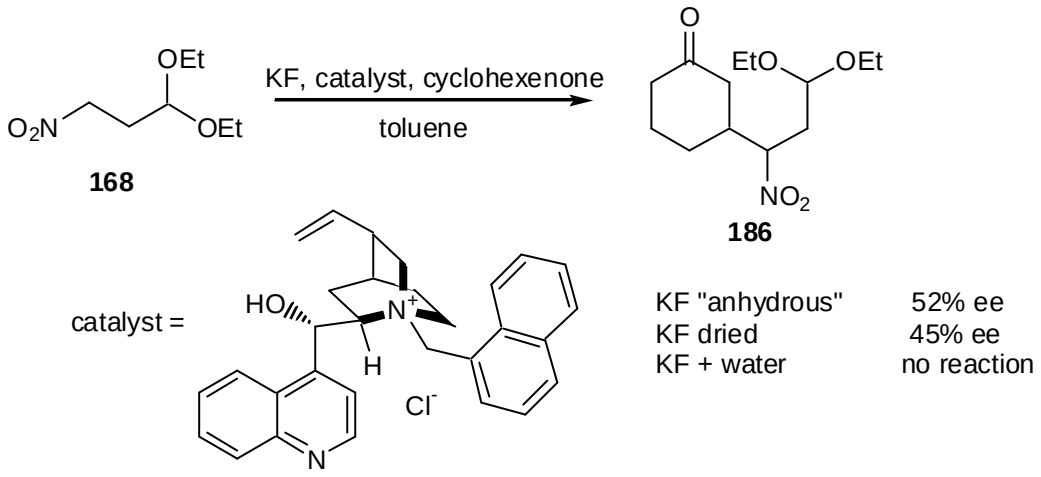
These results were very encouraging but again the uncatalyzed side reaction was very fast too. If we could suppress this uncatalyzed reaction selectivities would still be higher. We thought about reducing the quantity of base but with 0.05 equivalents of TMSOK we observed no reaction at all. Another possibility to reduce the background reaction could be to lower the reaction temperature. However when we worked at 0° or –20°C, the reaction was very slow and enantiomeric excesses were 26 and 35% respectively in the addition to cyclopentenone with catalyst **192**. So there was no improvement in that case.

3.3.7 Quality of the base (KF)

Results obtained with potassium fluoride depend a lot on the quality of the base used. Landini has shown that the nucleophilicity and above all the basicity of the fluoride anion strongly depended on the hydration factor.[204] An elimination

[204] Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.*, **1989**, *54*, 328-332.

reaction was, extrapolated, some 107 times faster with a naked fluoride than with the compound containing 4.6 molecules of water. That is why we ran three examples using for one KF taken just out of an open flask (anhydrous quality), another one using dried KF and the last with added water (scheme 140). No reaction occurred when water was added to the reaction mixture. We did not see a real difference between the “anhydrous” KF and the dried one.

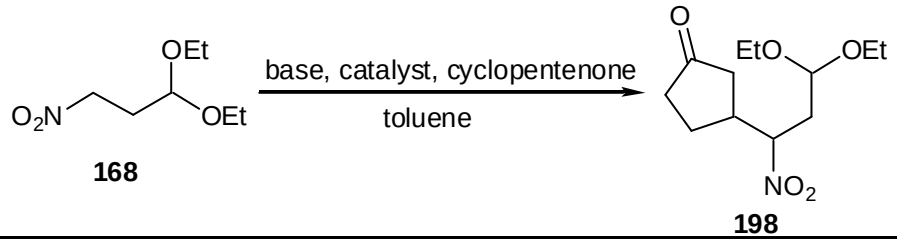


Scheme 140

3.3.8 Quantity of the base

We also wondered if the quantity of the base could play a role in the stereoselectivity. However when we ran the reaction with various amounts of base, no substantial difference was measured (table 43). With only 0.25 equivalents of KF, the reaction stopped after some time and did not go to completion.

Table 43: *Michael addition with different quantities of base.*



Entry	Base	Catalyst	ee%	Remark
1	2.5 eg. K_2CO_3	**192**	48%	
2	0.25 eq. K_2CO_3	**192**	34%	
3	2.5 eq. KF	**196**	39%	
4	1 eq. KF	**196**	42%	
5	0.25 eq. KF	**196**	34%	Very low conversion

According to these results we could exclude the non-catalyzed reaction as responsible for the low enantioselectivities observed. With less base present, an uncatalyzed reaction should be less important and enantioselectivities should increase. We did however not observe any improvement.

4 Conclusion

In this chapter we have synthesized ketals derived from 3-nitropropanal as potential annulation reagents. We were indeed not able to synthesize the corresponding orthoester. Whatever the approach for its synthesis, the orthoester was degraded in the presence of the nitro group.

We have shown that the Michael addition of nitro-compounds could easily be achieved under phase-transfer conditions. Weak bases, such as potassium carbonate and potassium fluoride, in the presence of an ammonium salt allowed us to obtain quickly the desired Michael adduct. Stronger bases, such as potassium *tert*-butoxide or hydroxides, could be used, but substoechiometric amounts were necessary to prevent degradation. We also showed that potassium trimethylsilanoate could be an interesting base for phase transfer catalysis. However we could not suppress an uncatalyzed reaction due to the solubility of this base in toluene.

When chiral phase transfer agents were used reactions were slower, but complete conversion could be reached overnight. Enantioselectivities obtained were only modest. But they are the best results obtained for such substrates under these conditions. Indeed results described in literature were most often obtained with chalcone which usually gives far better results than other substrates.

We are of course aware that reactions resulting in a mixture of diastereomers with only modest enantioslectivities can not compete with other more powerful methods.