Chapter VIII: Michael addition of nitro-compounds: other catalytic methods

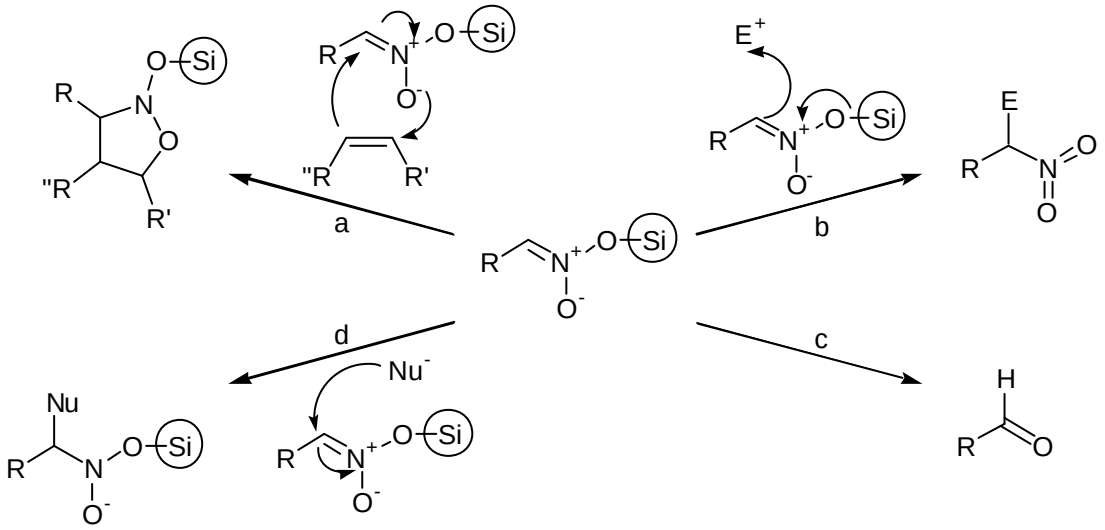
1 Introduction

Phase transfer catalysis allowed us to effect the Michael addition, but did not lead to more than 52% and 64% enantiomeric excess in the addition to cyclopentenone and cyclohexenone respectively. In this chapter we will discuss other potential methods still using nitro compounds.

2 Silylated nitronates

2.1 Introduction

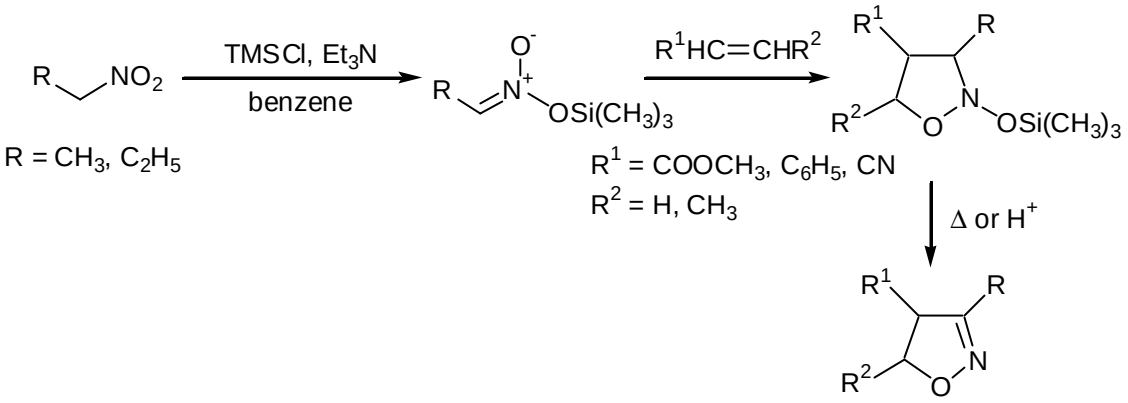
Since the late 1970's, silylated nitronates have been well documented in the literature. They are obtained by reaction of a nitroalkane with a silyl chloride in the presence of a base. Torssell has shown that they can be isolated and distilled; but they are somewhat unstable and must be stored in the presence of triethylamine.[205] Different reactivities can be thought off when one looks at these compounds (scheme 141).



Scheme 141

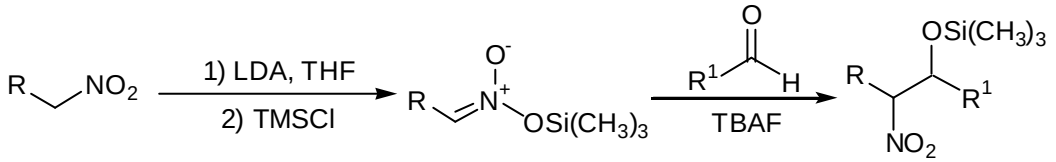
[205] Torssell, K.; Zeuthen, O. *Acta Chem. Scand., Ser. B*, **1978**, *32*, 118-124.

Silyl nitronates can be viewed as analogues of nitronates and they could thus react as a 1,3-dipole (pathway a). Indeed, Torssell showed that they reacted with olefins in a regioselective 1,3-dipolar addition to form isoxazolidines, which often decomposed spontaneously to 2-isoxazolines (scheme 142).[205]



Scheme 142

One could also compare the chemistry of silylated nitronates with silylated enol ethers (scheme 141, pathway b). Thus Seebach used silyl nitronates to improve the nitro-aldol (Henry) reaction.[206] Deprotonation of nitroalkanes by lithium diisopropylamide and reaction of the anion with a silyl chloride furnished the silylated nitronates (scheme 143). In the presence of tetrabutylammonium fluoride (TBAF), they reacted with aldehydes to give the corresponding silylated 2-nitroalcohol.



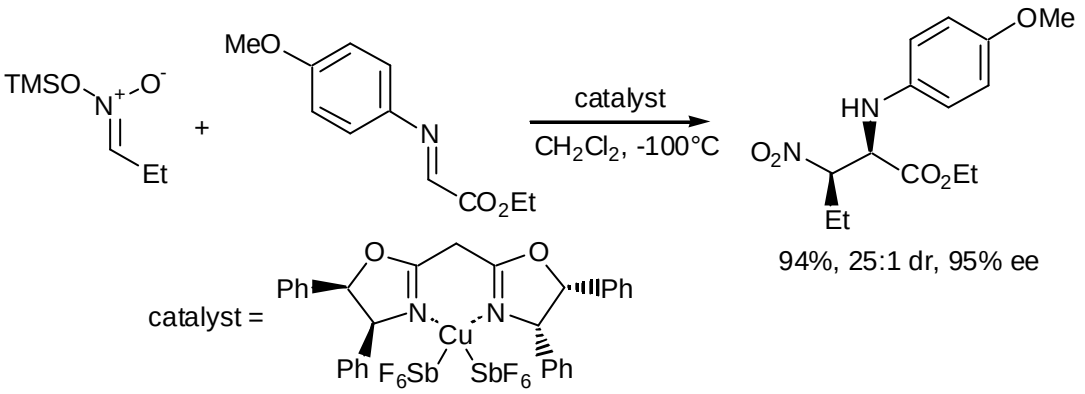
Scheme 143

Seebach's method was used later on by Martin for the synthesis of higher nitro sugars[207] and by Jäger for the synthesis of L-acosamine[208].

Another recent example of the use of silylated nitronates was given by Jørgensen in the first catalytic asymmetric *aza*-Henry reaction of nitronates to imines.[209] Silylated nitronates reacted with imines of α-ketoesters at -100°C in the

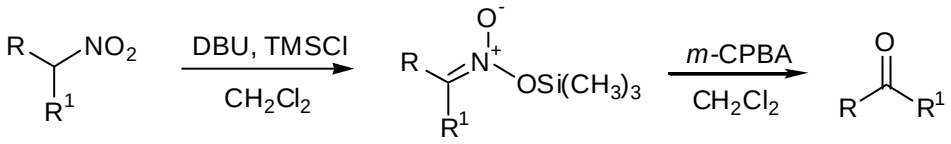
[206] Colvin, E. W.; Seebach, D. *J. Chem. Soc. Chem. Commun.*, **1978**, 689-691.
[207] Martin, O. R.; Khamis, F. E.; El-Shenawy, H. A.; Rao, S. P. *Tetrahedron Lett.*, **1989**, *30*, 6139-6142.
[208] Menzel, A.; Öhrlein, R.; Griesser, H.; Wehner, V.; Jäger, V. *Synthesis*, **1999**, 1691-1702.
[209] Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.*, **2001**, *123*, 5843-5844.

presence of a chiral copper complex (scheme 144). Thus β-nitro-α-amino acids were obtained in high diastereo- and enantioselectivity.



Scheme 144

One could also imagine that they react in the same way than imines (scheme 141, pathway c). Silyl nitronates were used for the transformation of nitro compounds into carbonyl groups (the Nef reaction[#]). Palomo transformed secondary nitroalkanes into the corresponding silylated nitronates which were oxidized by *m*-CPBA into a ketone (scheme 145).[210] This method is a rather mild version of the Nef reaction, that quite often requires harsh conditions.



Scheme 145

A last possibility could be to use silylated nitronates as an electrophilic species (scheme 141, pathway d). To the best of our knowledge, there is no example of this reactivity.

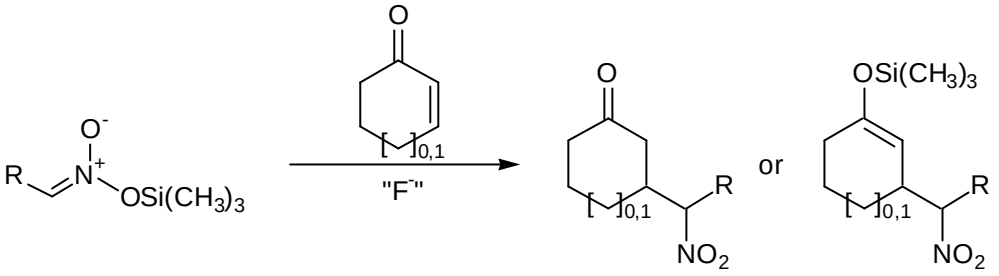
2.2 Our objective

In view of these examples, we thought that it could be interesting to use silylated nitronates to realize the Michael addition. As the related aldol reactions gave excellent results, we were quite confident about the outcome of the Michael reaction. The use of a fluoride source should liberate the nitronate which, according to our previous results, should undergo the Michael addition (scheme 146). This reaction should be faster than the reaction with a base; the formation of the anion starting from the silylated nitronate should indeed be easier than the deprotonation of a

[#] for other methods of the Nef reaction: see next chapter

[210] Aizpurua, J. M.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett.*, **1987**, *28*, 5361-5364.

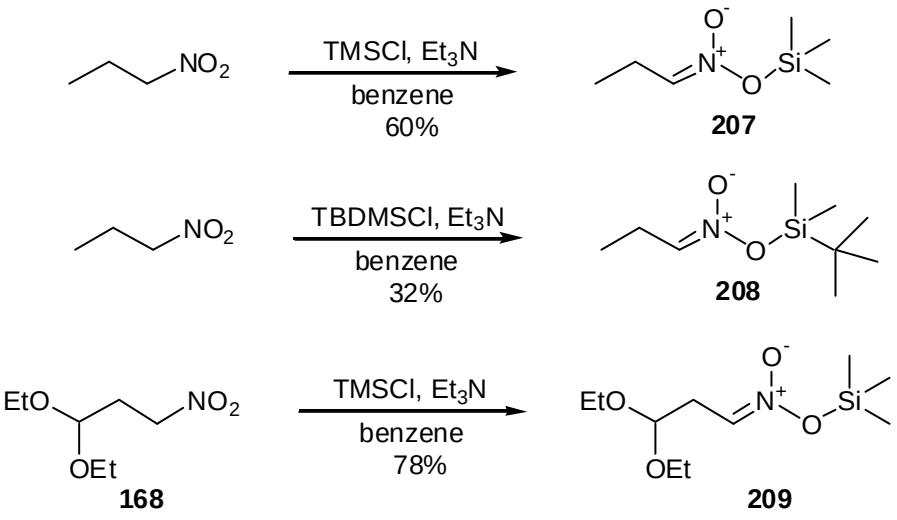
nitroalkane. We wanted to see whether we would be able to realize a stereoselective addition using a chiral source of fluoride.



Scheme 146

2.3 Synthesis of silylated nitronates

We synthesized three different silylated nitronates. Starting from nitropropane we produced the trimethylsilyl ester **207** and the *tert*-butyldimethylsilyl ester **208**; starting from 3,3-diethoxy-1-nitropropane **168** we synthesized the trimethylsilyl ester **209** (scheme 147). For these syntheses we applied the method described by Torssell[205] and Jørgensen[209]; the nitroalkane was reacted with a silyl chloride in benzene in the presence of triethylamine. After filtration of the reaction mixture and evaporation of the solvent, the product was purified by bulb-to-bulb distillation and could be stored under argon at -30°C.



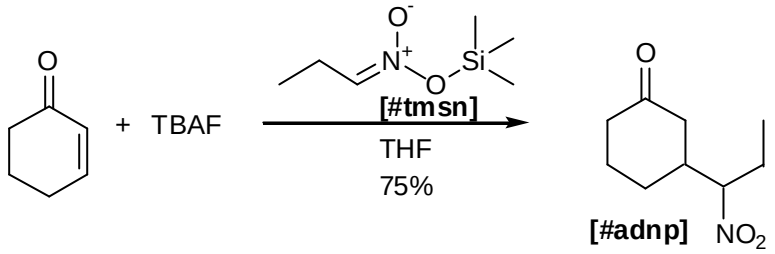
Scheme 147

2.4 Michael addition of silylated nitronates

2.4.1 TBAF

We first adopted the conditions used by Seebach for the related aldol reactions.[206] Cyclohexenone and TBAF were dissolved in THF and the silylated

nitronate was added to the mixture. After 4 hours we obtained the Michael adduct **178** in 75% purified yield (scheme 148). No example of such a reaction had been described in the literature. However some days before finishing the writing of this thesis, Maruoka submitted a study of the Michael addition of silylated nitronates.[211]



Scheme 148

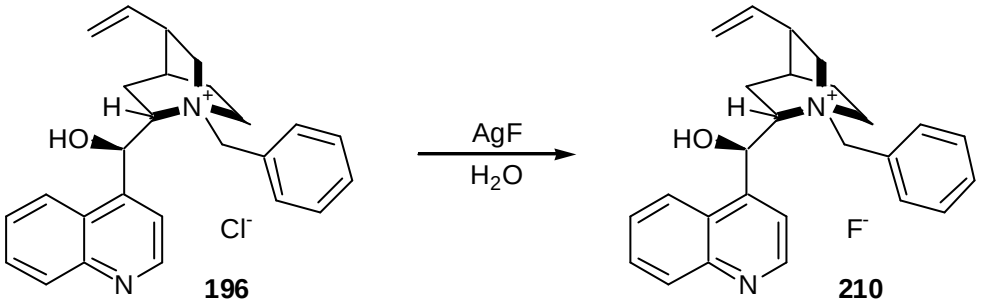
2.4.2 KF and a phase transfer agent

One possibility to introduce a chiral source of fluoride is the use of insoluble potassium fluoride and a chiral phase transfer agent. We hoped that the fluoride anion would be brought into the organic phase where it could play its role of a desilylating agent. The resulting nitronate would than form a chiral ion pair with the phase transfer catalyst. However the use of potassium fluoride in the presence of benzyltriethylammonium chloride (TEBACl) or *N*-(1-methylnaphthalenyl)cinchoninium chloride did not allow us to obtain the desired product. Either there was no reaction, or the reaction stopped at low conversion.

2.4.3 N-benzylcinchonidinium fluoride

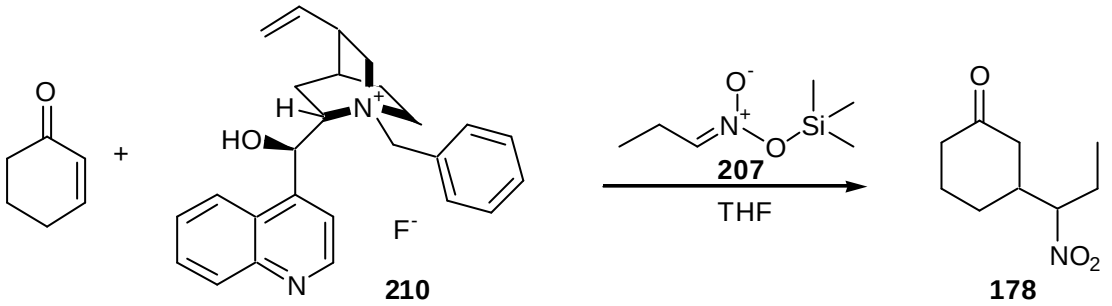
Campagne showed that fluorides of chiral ammonium salts catalyzed the vinylogous Mukaiyama-aldol reaction.[212] We thought that the use of these chiral fluorides could solve our problem. We therefore synthesized *N*-benzylcinchonidinium fluoride **210** by reaction of the corresponding chloride **196** with silver fluoride in water (scheme 149) according to the procedure described by Hayami.[213] The formation of the compound can be controlled by ^{19}F NMR where the desired compound is identified by a signal at –129 ppm. These compounds are rather unstable due to the high basicity of a naked fluoride anion. Therefore extensive drying is prohibited and the salts are used in their hydrated form.

[211] Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.*, **2003**, *125*, to be published.
[212] Bluet, G.; Campagne, J.-M. *J. Org. Chem.*, **2001**, *66*, 4293-4298.
[213] Hayami, J.; Ono, N.; Kaji, A. *Tetrahedron Lett.*, **1968**, *11*, 1385-1386.



Scheme 149

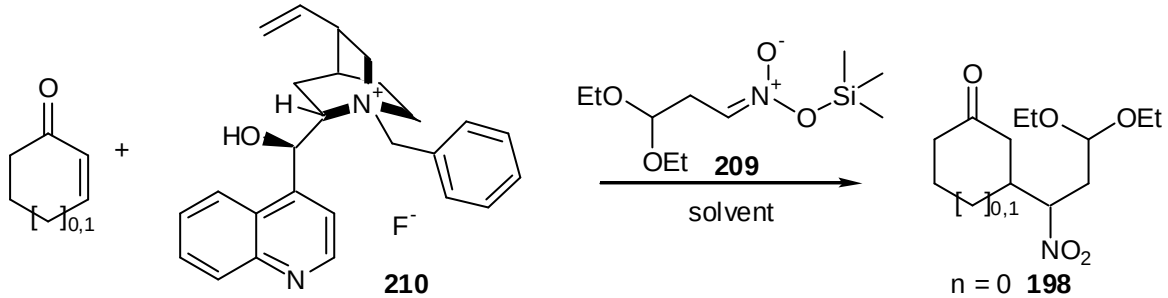
When silylated nitronate **207** was reacted with cyclohexenone in the presence of **210**, we obtained the Michael adduct **178** in a very fast reaction; the reaction was over after less than 1 hour (scheme 150) as compared to ±16 hours in the phase transfer catalyzed Michael addition of nitroalkanes.



Scheme 150

We then reacted silylated nitronate **209** with cyclohexenone and cyclopentenone in THF and toluene (table 44). Results were somewhat surprising. Reaction with cyclohexenone stopped at about 30% of conversion. No silylated nitronate remained in the reaction mixture: it had be transformed into the nitro analogue. Enantiomeric excesses were 30% in THF and 50% in toluene. Reaction with cyclopentenone was very fast and complete conversion was obtained after less than 1 hour. However the product was nearly racemic; 7% ee were measured in THF, and 2% ee in toluene.

Table 44: *Addition of **209** to cyclic enones*



Entry	Enone	Solvent	Conversion	ee
1	cyclopentenone	THF	100% (<1h)	7%
2	cyclohexenone	THF	~30%	30%
3	cyclopentenone	toluene	100% (<1h)	2%
4	cyclohexenone	toluene	~30%	50%

At this stage of our work we decided to abandon this study.

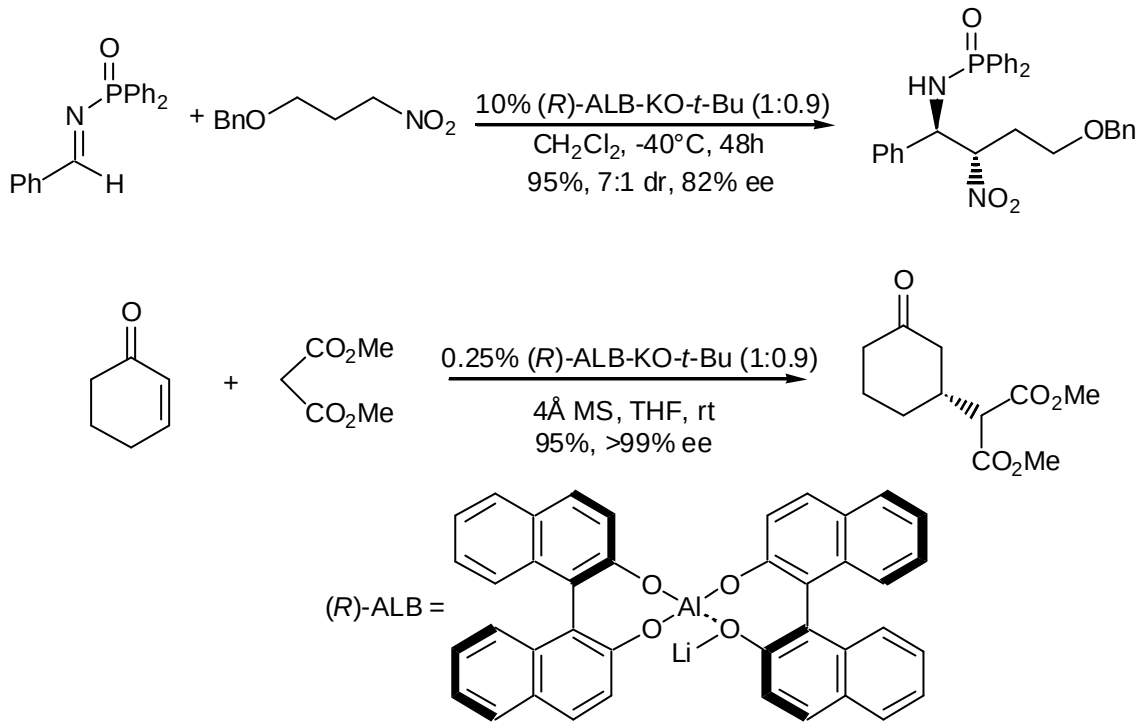
3 Lewis acid catalysts

3.1 Hetero-bimetallic catalysts

3.1.1 Literature results

Shibasaki has shown that functionalized nitroalkanes could be added to imines by the use of a catalytic amount of (*R*)-AlLi-bis(binaphthoxide) complex ((*R*)-ALB) in the presence of *tert*-BuOK (scheme 151).[214] It has also been shown by the same group that dimethylmalonate can be added to cyclohexenone by using similar reaction conditions.[215]

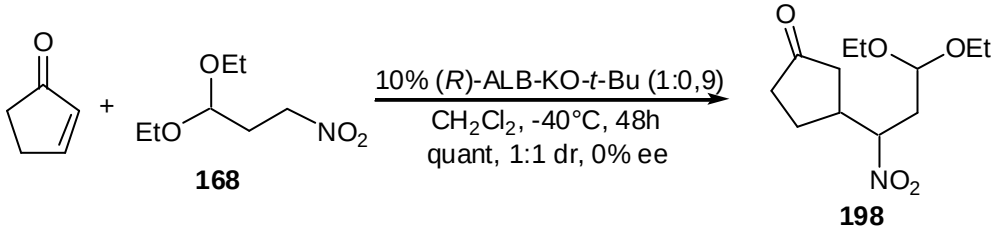
[214] Yamada, K.-i.; Moll, G.; Shibasaki, M. *Synlett*, **2001**, 980-982.
[215] Xu, Y.; Ohori, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron*, **2002**, *58*, 2585-2588.



Scheme 151

3.1.2 Results

We thought that an application of Shibasaki's method to our chemistry could be possible. Nitroalkanes were versatile substrates and the Michael addition was catalyzed with excellent enantioselectivities. So we tried the Michael addition of nitroalkanes. We reacted 3,3-diethoxy-1-nitropropane **168** with cyclopentenone in the presence of (*R*)-ALB (scheme 152). The reaction proceeded smoothly and quantitative yield of the Michael adduct **198** was obtained. However, analysis by chiral GC showed that a racemic mixture of **198** had been formed.

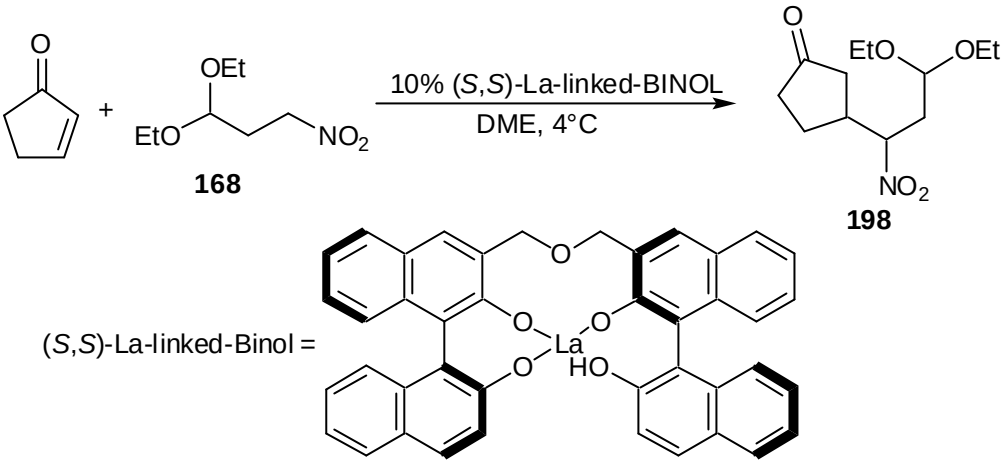


168 **198**

Scheme 152

We also tried the catalyst (*S*,*S*)-La-linked-BINOL used by Shibasaki for the Michael addition of more hindered malonates[216], but in both the absence and the presence of 1,1,1,3,3,3-hexafluoroisopropanol, we observed nearly no reaction (scheme 153). Moreover the small amount of isolated product was racemic.

[216] Takita, R.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.*, **2002**, *43*, 4661-4665.



Scheme 153

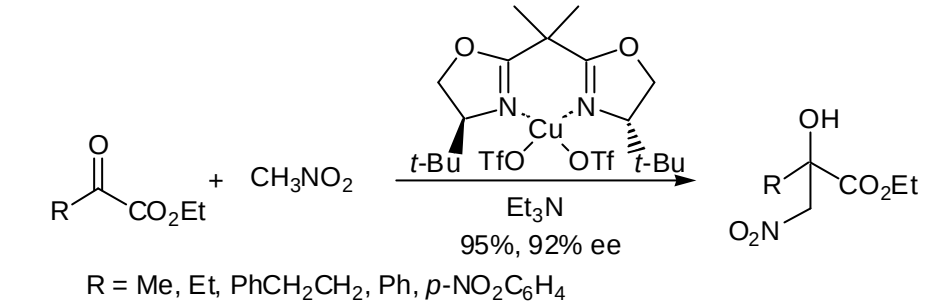
3.2 Copper based Lewis acids

3.2.1 Literature results

Chiral Lewis acids formed by complexation of a copper salt by a chiral bisoxazoline[217] or a semicorrin[218] were widely applied for a series of reactions.

Jørgensen has applied this methodology to the asymmetric addition of nitromethane to α-ketoesters (scheme 154).[219] The same group also described the addition of nitroalkanes to imines under similar conditions.[220]

[217] Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.*, **2000**, *33*, 325-335.
[218] Pfaltz, A. *Acc. Chem. Res.*, **1993**, *26*, 339-345.
[219] Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Comm.*, **2001**, 2222-2223.
[220] Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem. Int. Ed. Engl.*, **2001**, *40*, 2992-2995.

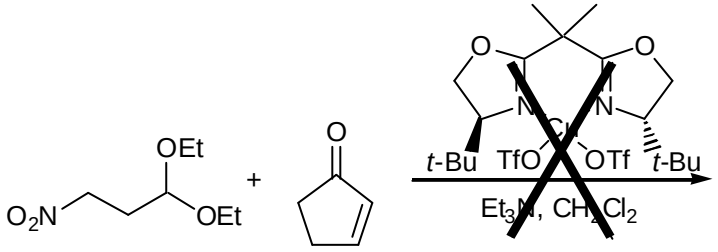


Scheme 154

It has also been shown that the addition of silylated nitronates to imines was possible in the presence of a Lewis acid (scheme 144).[209]

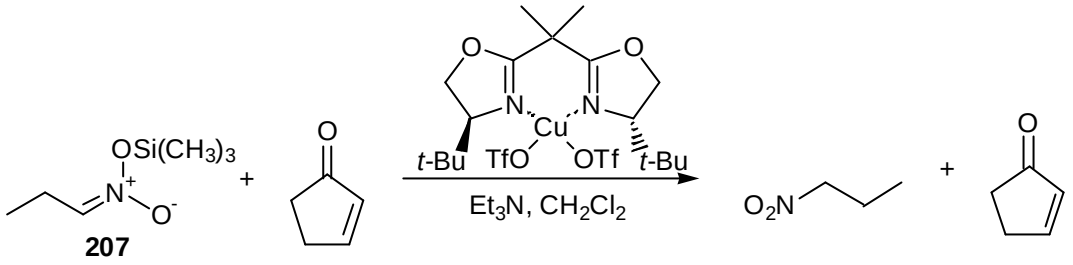
3.2.2 Results

We wondered if it could be possible to apply one of the above mentioned methods to realize the Michael addition of nitroalkanes. We prepared the catalyst by mixing copper(II) triflate with 2,2'-isopropylidenebis((4*S*)-4-*tert*-butyl-2-oxazoline). 3,3-diethoxy-1-nitropropane **168** was reacted in the presence of this catalyst and triethylamine with cyclopentenone (scheme 155). Unfortunately no reaction occurred under these conditions.



Scheme 155

We also tried the addition of the silylated nitronate **207** in the presence of a copper complex. However the only products which could be isolated were cyclopentenone and nitropropane (scheme 156).



Scheme 156

It seems thus that enones were not reactive enough for these conditions.

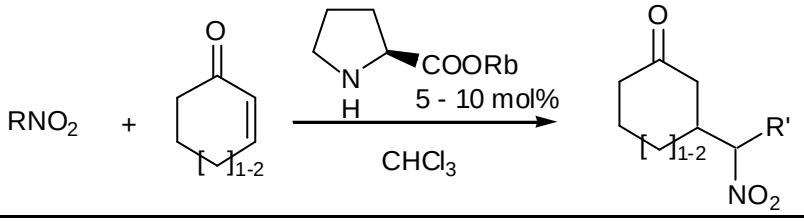
4 Other chiral catalysts

4.1 Rubidium prolinate

4.1.1 Literature results

In 1997 Yamaguchi described the catalytic asymmetric addition of nitroalkanes to cyclic and acyclic enones.[221] The catalyst used was rubidium prolinate. Primary, secundary and even functionalized nitroalkanes gave enantioselectivities which varied from moderate to good. Examples using cyclic enones are shown in table 45.

Table 45: *Michael addition of nitroalkanes to cyclic enones.*[221]

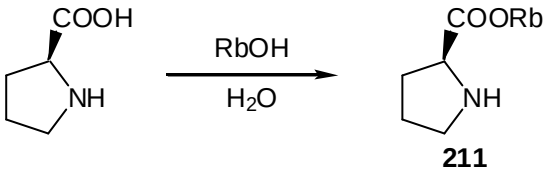


Entry	enone	RNO_2	yield (%)	ee (%)	config
1	2-cycloheptenone	CH_3NO_2	47	41	(+)
2		*i*-$C_3H_7NO_2$	79	73	*R*
3		*cyclo*-$C_5H_9NO_2$	74	67	(+)
4		*cyclo*-$C_6H_{11}NO_2$	84	84	(+)
5	2-cyclohexenone	CH_3NO_2	55	45	(+)
6		*n*-$C_4H_9NO_2$	84 [1:1,4]	53, 47	*R, R*
7		*i*-$C_3H_7NO_2$	81	59	*R*

[221] Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron*, **1997**, *53*, 11223-11236.

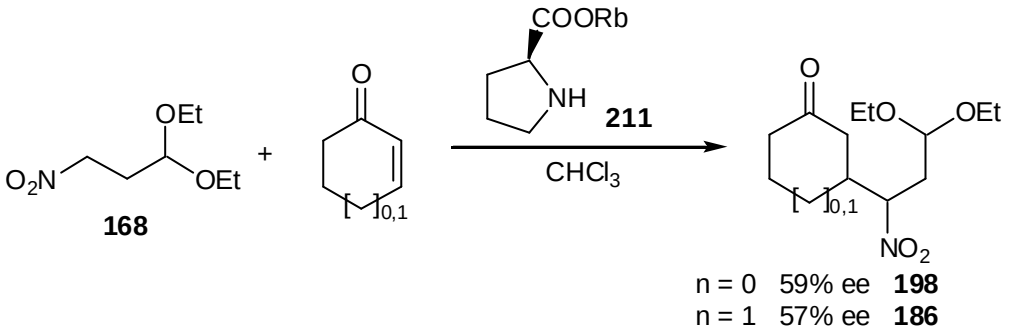
4.1.2 Results

We synthesized the catalyst **211** as described by the reaction of proline with rubidium hydroxide (scheme 157).



Scheme 157

The Michael addition of 3,3-diethoxy-1-nitropropane to enones was carried out in chloroform, passed through basic alumina prior to use, in the presence of a catalytic amount of catalyst **211** (scheme 158). The reaction was slow (4 days to complete conversion) but allowed to obtain the adduct with selectivities in the same range than the best results obtained with a phase transfer catalyst. We measured 59% ee for the addition to cyclopentenone and 57% ee in the case of cyclohexenone. The products were obtained as a mixture of diastereomers.



Scheme 158

The authors claimed that the addition of CsF was increasing the reaction rate.[222] In our case we did not observe any acceleration of the reaction, and the selectivity went down to 47% ee for the addition to cyclohexenone.

It has been shown be the authors that the addition to a cyclic enone always resulted in the formation of a stereocenter with the absolute configuration *R* on the β-carbon of the carbonyl group. Addition to (*E*)-enones led to the (*S*)-adduct. These results were independent of the nucleophile, as both nitro-compounds[221] and malonates[222] had the same behavior. We could thus reasonably assume that the major enantiomer of each couple of diastereomers had the absolute configuration *R* on the β-carbon of the carbonyl.

[222] Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.*, **1996**, *61*, 3520-3530.

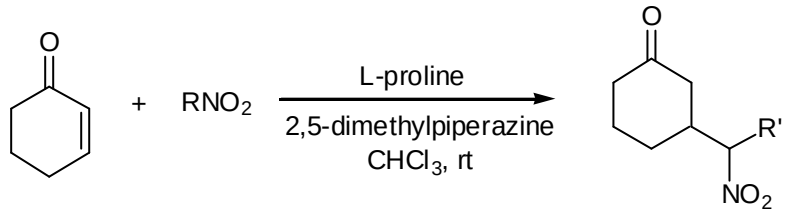
4.2 Organocatalysis

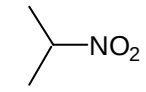
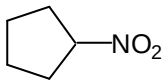
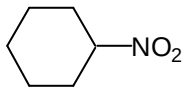
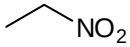
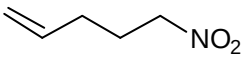
4.2.1 Literature results

Barbas has shown that amines could catalyze the addition to enones by formation of an iminium that activates the Michael acceptor. Proline derived amines were thus used to realize an asymmetric Robinson annulation.[223,224] Recent examples of amine catalyzed Michael additions by Barbas[225], Jørgensen[226] or MacMillan[227] show the interest in this approach.

Hanessian described the addition of nitroalkanes and nitroalkenes to cyclic enones using L-proline as catalyst and *trans*-2,5-dimethylpiperazine as stoechiometric additive. Yields were good and enantioselectivities good to excellent.[228] Table 46 shows as example the results obtained with cyclohexenone as Michael acceptor.

Table 46: *Michael addition of nitroalkanes to cyclohexenone.*[228]

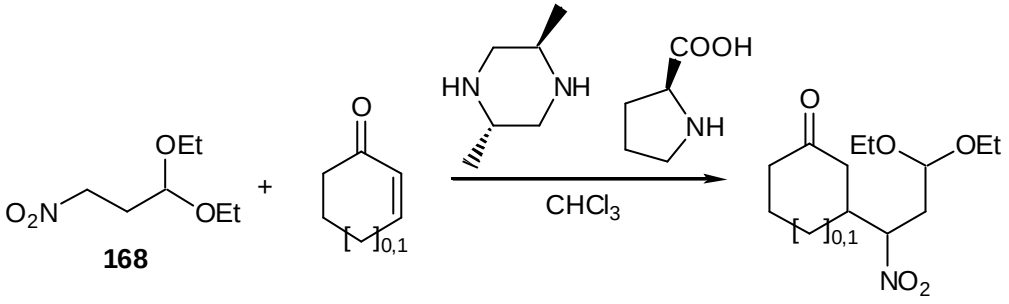


Entry	RNO_2	yield (%)	ee (%)
1		88	93
2		68	93
3		73	93
4		86 [1:2]	72, 74
5		71 [1:2]	87, 77
6	CH_3NO_2	61	71

[223] Bui, T.; Barbas III, C. F. *Tetrahedron Lett.*, **2000**, *41*, 6951-6954.
[224] for a review on proline catalyzed reactions see List, B. *Tetrahedron*, **2002**, *58*, 5573.
[225] Betancourt, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas III, C. F. *Tetrahedron Lett.*, **2001**, *42*, 4441-4444.
[226] Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.*, **2003**, *68*, 4151-4157.
[227] Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, **2003**, *125*, 1192-1194.
[228] Hanessian, S.; Pham, V. *Org. Lett.*, **2000**, *2*, 2975-2978.

4.2.2 Results

We therefore decided to run our reaction in the conditions developed by Hanessian. 3,3-diethoxy-1-nitropropane **168** was reacted with cyclopentenone and cyclohexenone in chloroform, passed on basic alumina prior to use, in the presence of a slight excess of *trans*-2,5-dimethylpiperazine (1.01 equivalents) and a catalytic amount of proline (scheme 159). The reaction was not too slow (45 hours to completion) and the enantioselectivities were quite high. We measured 73% ee for the addition to cyclohexenone (diastereomeric ratio was 1 : 1.3) and 79% ee for the addition to cyclopentenone (diastereomeric ratio was 1 : 1.2).



Scheme 159

Based on the relative retention times on chiral GC the absolute configuration of the β-carbon could be assigned to be *R*.

In toluene the conversion was low and the selectivities were lower.

It should be noted that (*S*)-(-)-α,α-diphenyl-2- pyrrolidinemethanol or proline without an added base did not catalyze the reaction in opposition to the results obtained by Barbas.[223]

5 Conclusion

In this chapter we have used other catalytic methods for the Michael addition of **168**. The use of Lewis acids proved to be unsuccessful.

The use of proline appeared to be the most promising method. Whether as rubidium salt or under its neutral form, it allowed us to obtain the Michael adducts with good enantioselectivities. These reactions are an example of the emerging field of organic catalysis where proline seems to be a very promising candidate.[224]

Another interesting result from this chapter is the use of silylated nitronates to effect the Michael addition. We were unfortunately not able to pursue this study but we think that it could be a very interesting subject.