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Selective organic synthesis *via* group 6 metal carbene complexes

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Abstract : The first examples of asymmetric Michael addition of lithium reagents to chiral vinylalkoxycarbene chromium complexes **2** is reported. The [4+3] annulation of azadienes and 2-aminodienes is accomplished with complexes **2**. Vinylaminocarbenes cyclopropanate alkenes and dienes and allows to isolate two new intermediates in the Dötz reaction. Some features of the [4+2] cycloaddition of chiral 2-aminodienes with both *s-cis* and *s-trans* Fischer vinylcarbene complexes are also presented.

Fischer carbene complexes are proving to be increasingly attractive reagents in modern organic synthesis. Particularly useful are complexes of group 6 (chromium, molibdenum, tungsten) and, among them, vinyl carbenes have been reported to exhibit great and versatile reactivity (1). We have been for some time involved in developing synthetic methodologies using functionalized organolithium derivatives (2) as well as carbo- and aminoazadienes (3), which are in turn readily available from enynes and imines, respectively (Figure 1). Because of the electrophilic nature of vinyl carbenes we became interested in studying their behaviour towards electron-rich reagents, such as organolithium, hetero- and carbodiene derivatives.

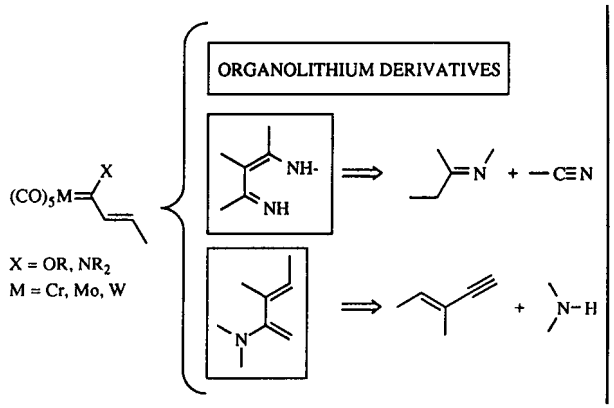


Figure 1

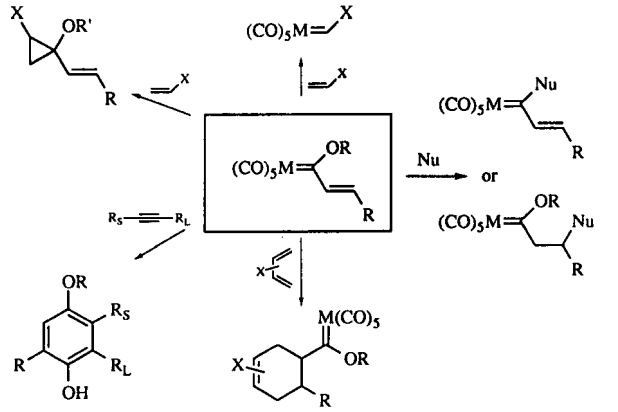


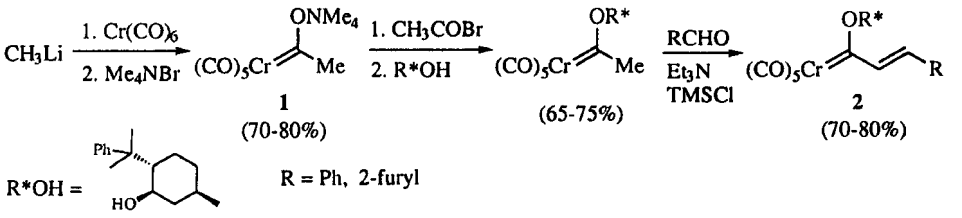
Figure 2

The major features concerning the reactivity of vinyl carbene complexes are outlined in Figure 2. As electrophilic species they undergo 1,2- and/or 1,4-addition of nuclephiles and [4+2] cycloaddition with electron-rich dienes. Vinyl carbenes may also act as carbene transfer species by reaction with alkenes giving substituted cyclopropanes (cyclopropanation reaction) and new carbenes (metathesis reaction). Finally, the namely Dötz reaction, which implies annulation of an alkyne with the three-carbon skeleton and one CO ligand of the carbene, seems to be one of the most expeditious route for the construction of the phenyl ring.

Reaction of group 6 vinyl carbenes with organolithium reagents

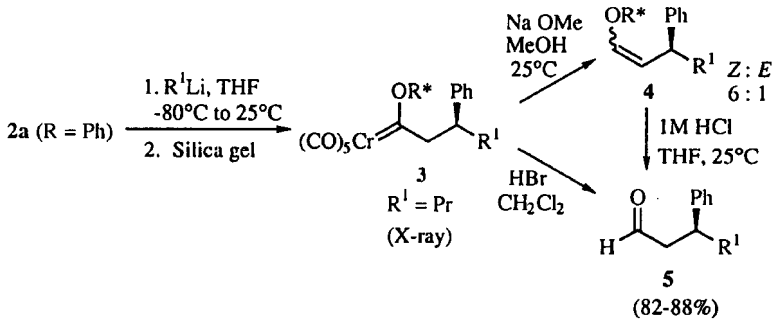
The (-)-8-phenylmenthol-derived vinylcarbenes **2** were first realized as acceptors for achieving asymmetric Michael additions. They are prepared starting from the tetramethylammonium complex **1** by alkylation and condensation reactions following general literature procedures (Scheme 1) (4).

Scheme 1



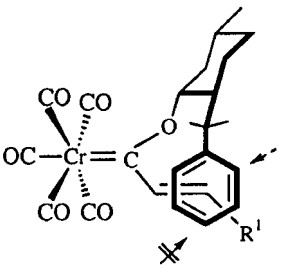
The addition of alkyllithium reagents to chiral carbene complex **2a** leads diastereoselectively to the Michael adducts **3** (5). Treatment of **3** with either sodium methoxide/methanol/1N HCl or hydrogen bromide gives rise to the optically active β-substituted aldehydes **5** with high enantiomeric excesses (80-95%) (Scheme 2). The absolute configuration was determined by a single-crystal X-ray structure analysis.

Scheme 2



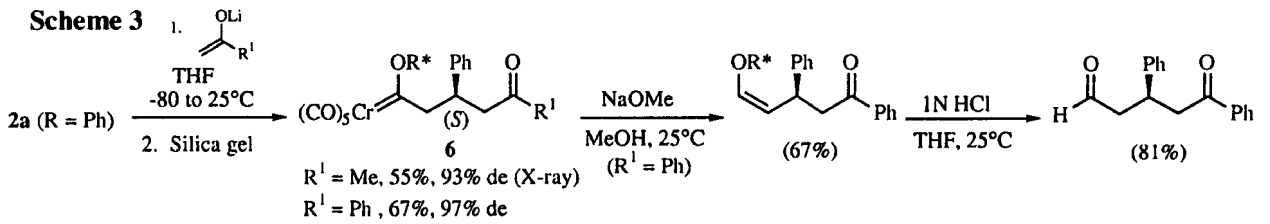
The asymmetric induction that has been observed in these reactions can be explained in terms of the model shown in Figure 3 (6). In this drawing of the most stable conformation the appropriately positioned phenyl group shields selectively the front face of the double bond by π,π-orbital overlap forcing the nucleophile to attack preferentially on the opposite side.

Figure 3



Methyl ketones lithium enolates may also be added to the optically active acceptor **2a** yielding the 1,4-adducts **6** with good diastereoselectivities (Scheme 3). Metal and chiral auxiliary-free products are easily accessible in high enantiomeric purity as described above.

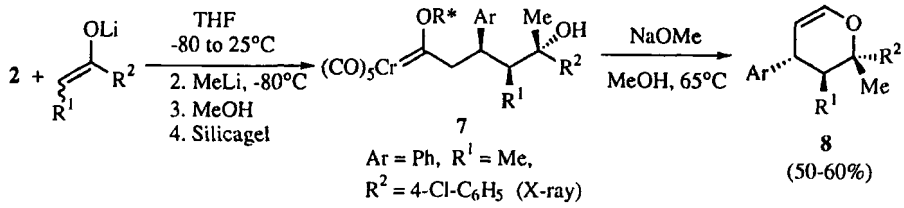
Scheme 3



It is known that Michael addition of an enolate to both alkoxy- (7) and amino-stabilized (8) vinylcarbene complexes occurs with *syn* diastereoselectivity. We have found that these chiral (-)-8-phenylmenthyloxy Fischer vinylcarbene reagents **2** show much better *syn* diastereoselectivity than the

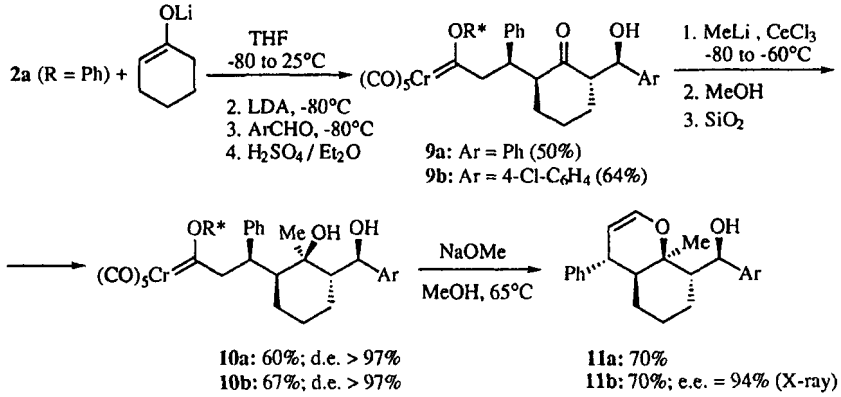
methoxy (or ethoxy) and imidazolidinone analogues in the reactions with lithium enolates; significantly, the use of carbenes **2** in these Michael reactions allows to achieve excellent enantioselectivities. As shown in Scheme 4, 1,4-addition of ketone lithium enolates to **2** followed by treatment with methyllithium results in the formation of *syn* 1,4-adducts **7** (30-89%) as single diastereoisomers in most instances. Removal of the pentacarbonylchromium fragment and recovering of the chiral auxiliary group was accomplished with sodium methoxide affording the cyclic enol ethers **8** with consistently high enantiomeric excesses (93-98%). A single crystal X-ray structure determination proved the relative and absolute configuration of **7**.

Scheme 4



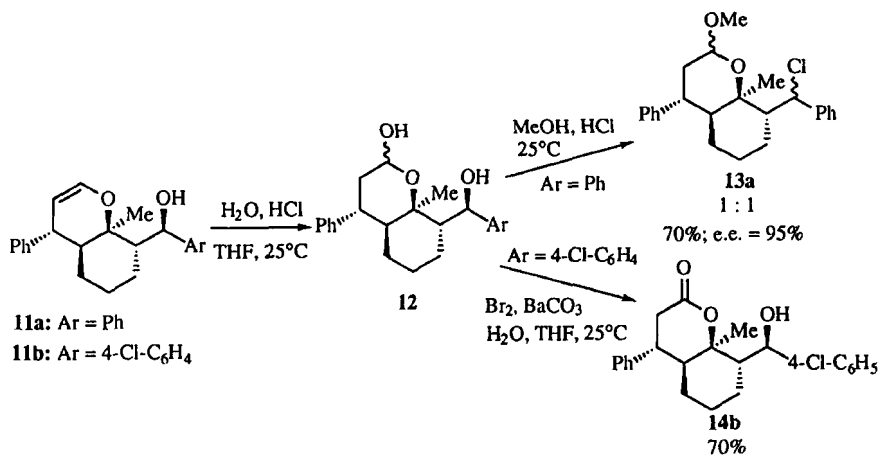
The utility of the present asymmetric carbon-carbon bond formation to further generate up to five contiguous stereogenic centers, is proved with the transformations outlined in Scheme 5. Compounds **9** were obtained as single aldol adducts having the *threo* relationship. Addition of MeLi to **9** gave compounds **10**, again as single diastereoisomers, which afforded the bicyclic enol ethers **11** with high enantiomeric excess on standard treatment; the stereochemical assignment was confirmed by an X-ray crystal structure determination performed on racemic **11b**.

Scheme 5



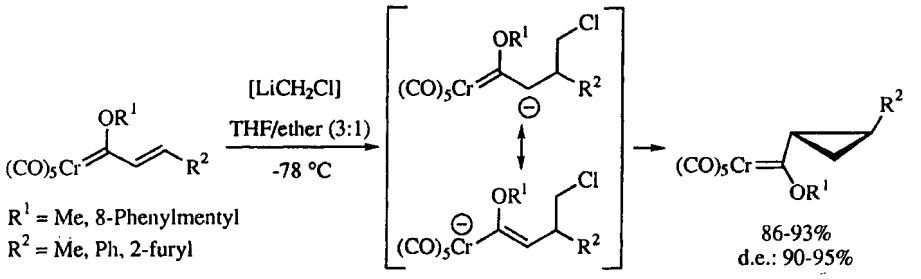
The optical purity of compound **11a** was determined at the stage of acetal **13a**, which is prepared as an equimolecular diastereoisomeric mixture from **11a** via the hemiacetal **12a** (Scheme 6). A further synthetic use of this methodology is illustrated by the bromine oxidation of lactol **12b** to lactone **14b**.

Scheme 6



On the other hand, the conjugate addition of *in situ* generated chloromethyllithium to α,β-unsaturated alkoxycarbene chromium complexes, yields diastereoselectively *trans*-disubstituted cyclopropylcarbene complexes. Presumably, α,γ-elimination of lithium chloride occurs from the initial Michael adduct (Scheme 7).

Scheme 7

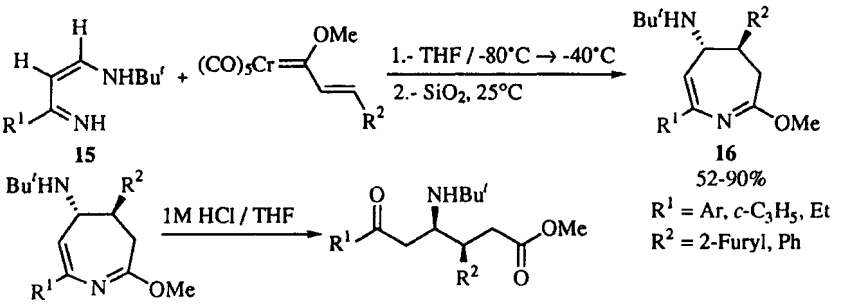


Reaction of group 6 vinyl carbenes with 1-azadienes

Vinyl Fischer carbenes have been found to efficiently cyclopropanate electron-rich dienes through the more electron-rich carbon-carbon double bond; the resulting *cis*-divinyl derivatives undergo Cope rearrangement to form ultimately seven-membered carbocycles. Thus, Wulff *et al.* reported that the Danishefsky's diene gave rise to a mixture of cycloheptadiene and *trans*-divinylcyclopropane derivatives (9); we observed that 2-aminodienes reacted with vinyl carbenes at 25°C affording, after hydrolysis, cycloheptane-1,3-diones in 62-82% yield (10).

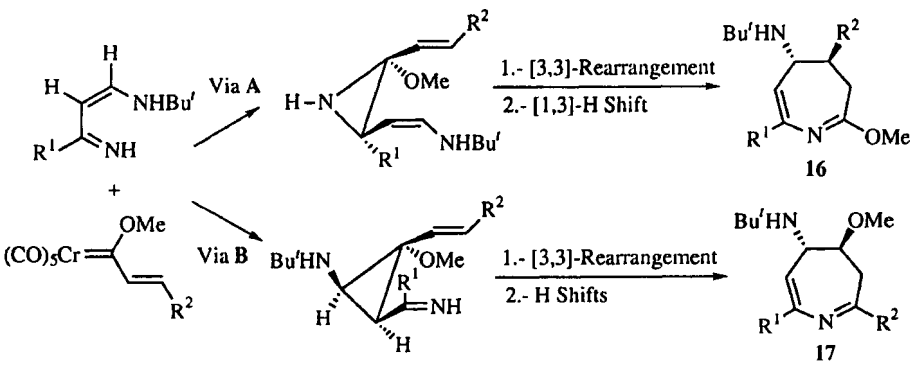
Accordingly, we turned our attention to the use of heteroatom-containing dienes, for instance 4-alkylamino-1-aza-1,3-dienes (Scheme 8); thus, azadienes **15** cleanly react at a temperature as low as -40°C to afford, after SiO_2 treatment, azepines **16** in a regio- and stereoselective fashion with yields ranging from moderate to excellent (52-91%) (11). The structure shown was confirmed by quantitative acid hydrolysis to the corresponding methyl ketoester.

Scheme 8



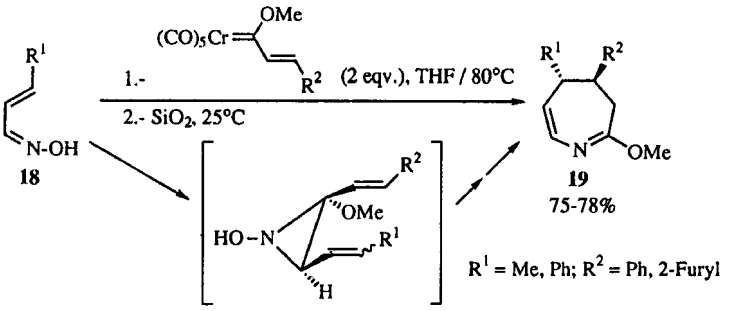
Although the reaction mechanism has not been proved as yet, a speculative cyclopropanation-based pathway can be envisioned (Scheme 9); thus, cyclopropanation of the imine group (Via **A**) (a process not described so far) (Via **A**) would result in formation of a *cis*-divinylaziridine which yields the observed azepine **16** by Cope rearrangement and hydrogen shift. It should be noted that cyclopropanation of the enamine carbon-carbon double bond (Via **B**) would lead to the wrong regioisomer **17**, which is not detected.

Scheme 9



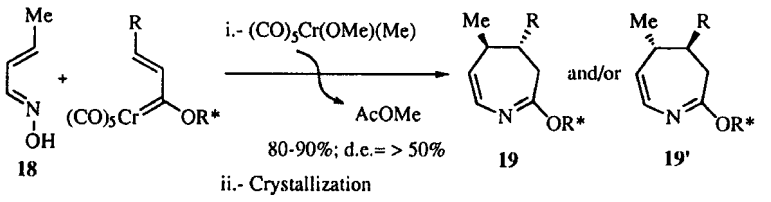
Next, the reaction of readily available α,β-unsaturated oximes with vinyl carbenes was studied and found to result in a new and more general, high yield entry into the azepine structure (Scheme 10). Thus, oxime **18** was treated at reflux in THF with two equivalents of carbene complex and then with SiO_2 to furnish azepines **19** as single isomers in yields higher than 75%. Again, cyclopropanation of the carbon-nitrogen double bond and [3,3] rearrangement accounts for the process; an additional equivalent of carbene is used because deoxygenation of the oxime function occurs during the reaction.

Scheme 10



As described above, chiral vinyl carbenes show great face selectivity towards Michael addition of lithium reagents; therefore, we attempted the preparation of azepines in optically active form following this protocol. Vinyl carbenes derived from (+)-and (-)-menthol cycloadd to crotanaldehyde oxime in the presence of methoxymethylcarbene as the reducing agent to furnish azepines **19** as diastereoisomeric mixtures with d.e. higher than 50% and chemical yields of 80-90%. Interestingly, routine crystallization allowed to separate in nearly quantitative yield the major diastereoisomer in pure form (**19** and **19'** from carbenes derived from (-)- and (+)-menthol, respectively); it means that each enantiomer is obtained in 46-50% overall yield from the starting oxime (Scheme 11).

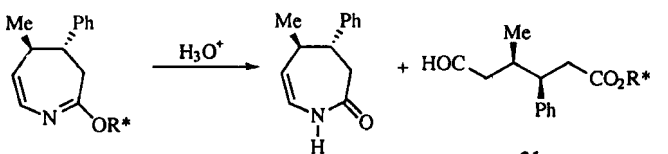
Scheme 11



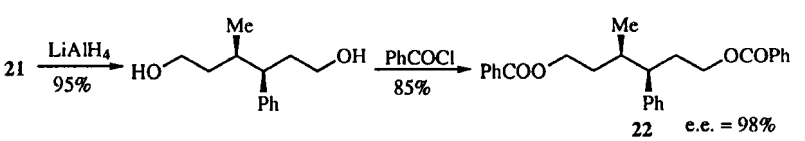
HOR*	R	Overall yield (d.e.)		
(-)-Menthol	Ph	50% (>97%)	——	(X-Ray)
(-)-Menthol	2-Furyl	48% (>97%)	——	
(+)-Menthol	Ph	——	46% (>97%)	

Optically active adducts were hydrolyzed to azepinone **20** and 1,6-dicarbonyl derivatives **21**. The ee of **20** was determined by HPLC, while **21** was transformed into the benzoylated diol **22** and its ee analyzed by HPLC (Scheme 12).

Scheme 12



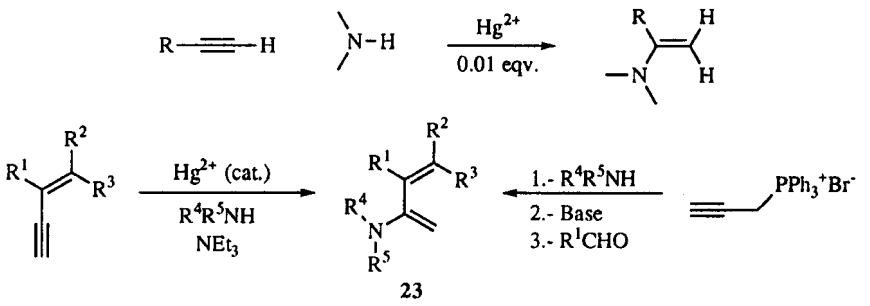
HOR* = (-)-Menthol	0.5M HCl	34%	63%
	3M HCl	< 5%	93%



Reaction of group 6 metal carbenes with 2-amino-1,3 dienes

We have been involved for long time in developing new synthetic pathways based on reactive 2-amino-1,3-dienes and recently we realized to extent their usefulness by reacting with group 6 metal carbenes. These achiral and chiral dienes **23** were shown by us to be readily available by Hg^{2+}-catalyzed addition of amine to commercial enynes (12); moreover, uncatalyzed amination of the carbon-carbon triple-bond of propargyl phosphonium bromide followed by Wittig olefination afforded *(E)*-4-aryl(alkyl)-2-aminodienes (13) (14) (Scheme 13).

Scheme 13

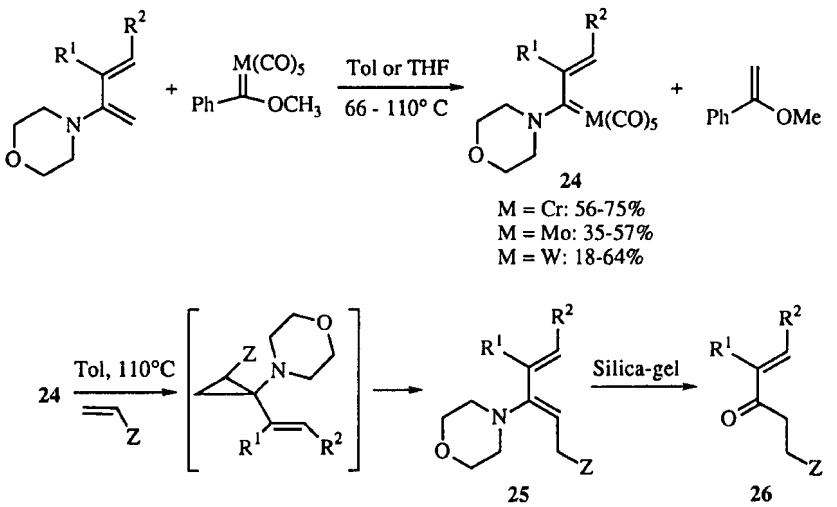


23

R^4R^5NH = Pyrrolidine, Piperidine, (*S*)-2-(Methoxymethyl)pyrrolidine

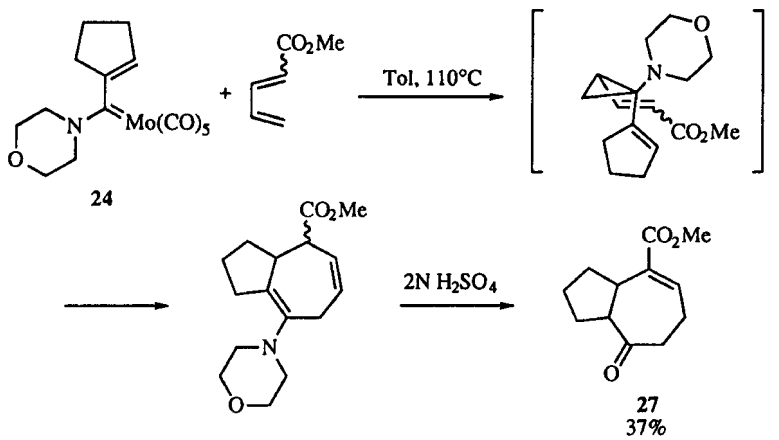
Heating 2-morpholino-1,3-dienes **23** with group 6 methoxyphenyl carbenes results in the formation of vinylaminocarbenes **24** (M= Cr, Mo, W) in moderate yields; this metathesis reaction appears to be the first approach reported to vinylaminocarbene molibdenum complexes (Scheme 14). Studies concerning the reactivity of aminocarbenes are less common than for the alkoxy counterparts (15); in particular the intermolecular cyclopropanation reaction has only been postulated (16). Aminocarbene complexes thus obtained were found to react with methyl acrylate and acrylonitrile on heating in toluene at 110°C to yield, after silica gel purification, ketones **26** derived from C-H insertion/hydrolysis; this result is explained in terms of cyclopropanation of the olefine followed by ring opening to form new 2-aminodienes **25** which are not isolated but hydrolyzed to carbonyl derivatives. The reaction involving molibdenum carbenes seems to be superior, the yields being higher than 70% in most instances (Scheme 14).

Scheme 14



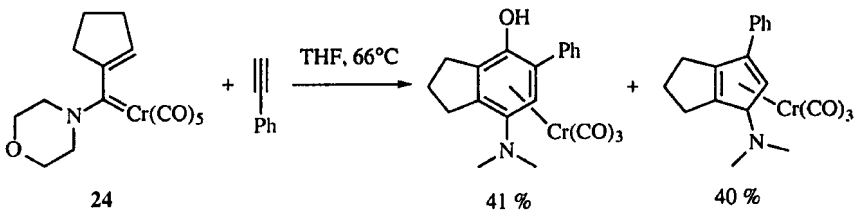
On the basis of this cyclopropanation and taken advantage of the ease with which *cis*-divinylcyclopropanes suffer [3,3] rearrangement, the reactivity of these aminocarbenes towards dienes was tested. Thus, the molibdenum complex **24** (M=Mo) was treated with methyl 2,4-pentadienoate in refluxing toluene and the mixture hydrolyzed to give the expected 5-bicyclo[5,3,0]decen-2-one **27** in 37% yield (Scheme 15).

Scheme 15



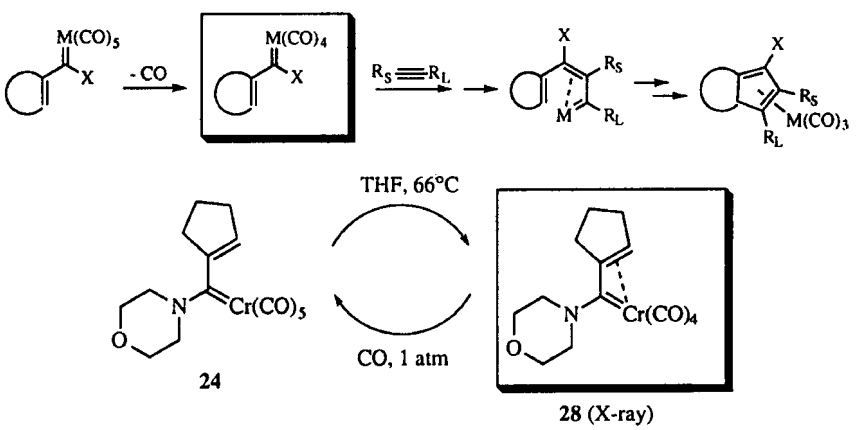
The annulation of vinyl carbenes with alkynes to six- and/or five-membered carbocycles, the so-called Dötz reaction, has been recognized as one of the most emblematic reaction of transition metal carbenes. Actually, a 1:1 mixture of six- and five-membered cycloadducts is formed in high yield when the chromium cyclopentenylamino carbene **24** is heated in THF (Scheme 16).

Scheme 16



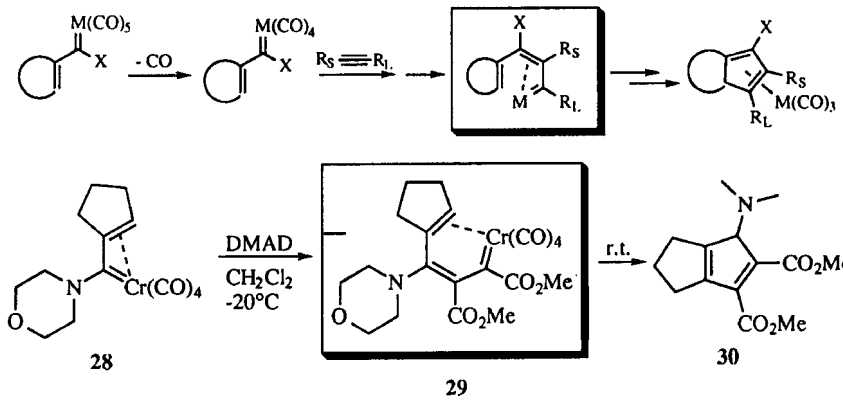
Interestingly, when a solution of pentacarbonyl aminocarbene **24** was refluxed in THF one CO ligand dissociated and the corresponding tetracarbonyl derivative **28** could be isolated in 90% yield (Scheme 17). Since the Dötz reaction iniciates by CO displacement, this 16 e^- species isolated seems to be the first intermediate of the annulation process. Conversely, bubbling CO into a THF solution of the tetracarbonyl complex gives back quantitatively the pentacarbonyl complex **24**.

Scheme 17



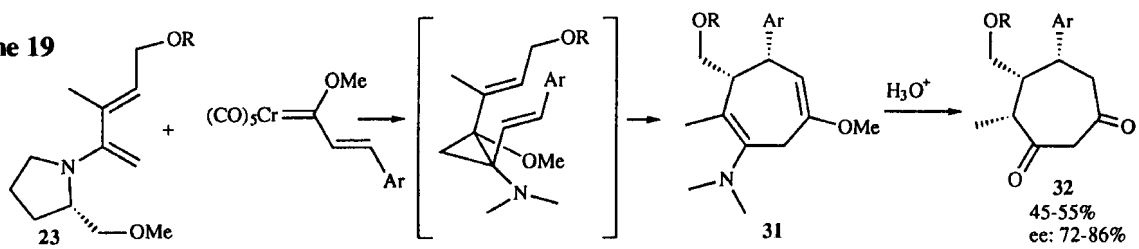
Having at hands the tetracarbonyl vinylcarbene complex, it could be feasible then to isolate the following intermediate of the Dötz reaction. Indeed, the tetracarbonyl chromium complex **28** was able to insert into the carbon-carbon triple bond of dimethyl acetylenedicarboxylate (DMAD) at -20°C affording the corresponding metalahexatriene **29**, as depicted in Scheme 18. Finally, warming the metalatriene **29** in dichloromethane at room temperature resulted in the formation of the cyclopentadiene ring **30**, as expected for aminocarbenes.

Scheme 18



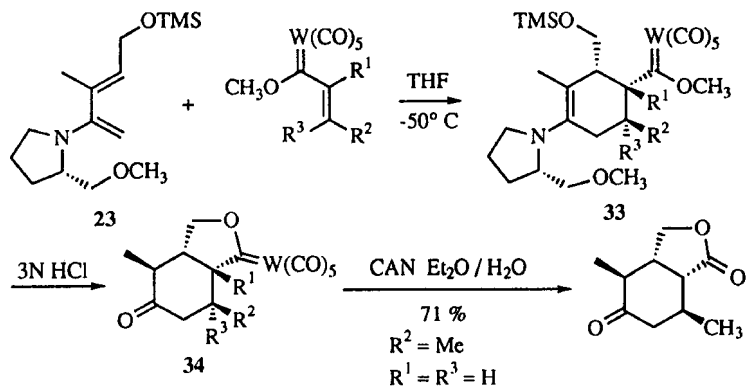
Chiral aminodienes have been also reacted with group 6 carbene complexes; so, this part covers some representative examples of asymmetric [4+3] and [4+2] cycloaddition of vinylcarbenes with 2-aminodienes derived from (*S*)-2-(methoxymethyl)pyrrolidine. Fischer chromium vinylcarbene complexes smoothly react with dienes **23** in acetonitrile at room temperature giving rise to aminocycloheptadiene derivatives **31**, which were not isolated but hydrolyzed to the corresponding 1,3-cycloheptadienones **32** in fair yields and high enantiomeric excesses (Scheme 19) (10).

Scheme 19



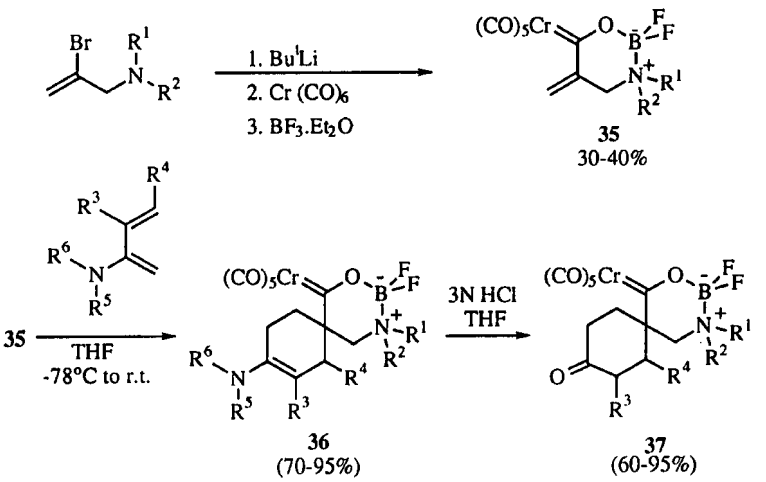
We have also accomplished the first asymmetric [4+2] cycloaddition using achiral vinyl carbene complexes (17). Thus, α,β-unsaturated Fischer type tungsten carbenes react with chiral 2-aminodienes **23** to give an *exo/endo* mixture of Diels-Alder cycloadducts **33**; hydrolysis of the reaction mixture furnished fused cyclohexanones **34** in 43-53% yield, the *endo/exo* ratio being between 4.3:1 and 15.0:1. The enantiomeric excesses of the *endo* isomers were in the range of 72-90%. Oxidative removal of the metal was effected with CAN (ceric ammonium nitrate) in good yield (Scheme 20).

Scheme 20



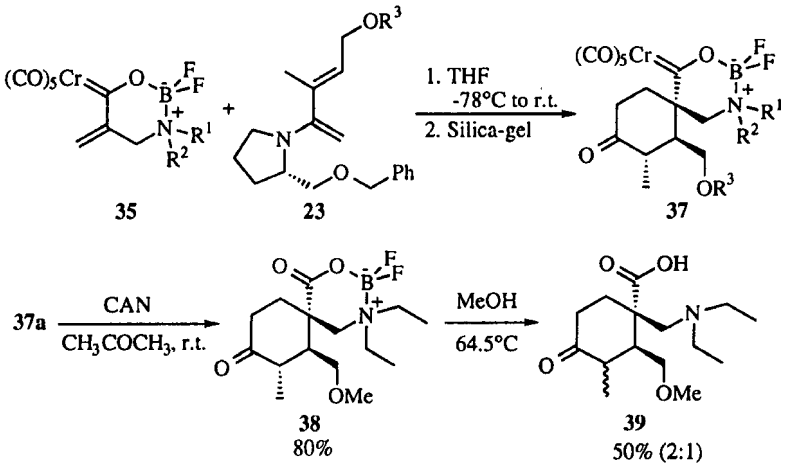
When working with functionalized organolithium compounds we have observed the formation of α,β-unsaturated Fischer-type carbenes with fixed *s-cis* conformation, which appear as attractive dienophiles towards electron-rich dienes, since the former use to produce in preference the *exo*-cycloadducts (18). These carbene complexes **35** were prepared from the corresponding β-amino-functionalized vinylic organolithium reagent (19) by successive reaction with chromium hexacarbonyl and an excess of boron trifluoride etherate at room temperature (Scheme 21). The structure of compounds **35** was unambiguously established by single-crystal X-ray analysis . The reaction of these boron difluoride complexes **35** with various 2-amino-1,3-dienes **23** derived from achiral amines afforded the corresponding Diels-Alder products **36** in high yields; further acid hydrolysis allows to isolate cycloadducts **37** as a single diastereo- and regioisomers. The stereochemistry of compounds **37** was ascertained by X-ray of the chiral analogues (see below) (20).

Scheme 21



When a chiral 2-aminodiene **23** derived from (*S*)-prolinol benzyl ether was used, the *exo* [4+2] cycloaddition with the chromium carbenes **35** takes place as well with moderate chemical yield and high level of face selectivity; thus, formation of carbene cycloadducts **37** with ee's of 90-93% is achieved by room temperature cycloaddition and silica gel purification (Scheme 22). The structure of **37** was established by X-ray determination (20). Finally, the conversion of cycloadducts **37** into metal-free organic molecules is also illustrated in Scheme 22. Oxidative cleavage of the chromium pentacarbonyl fragment of **37** (R^1=R^2=Et; R^3=Me) with CAN gave BF_2-protected aminoacid **38**; further methanolysis of the later afforded aminoacid **39** as a 2:1 mixture of diastereoisomers as a consequence of partial epimerization of the ketone C_α-carbon atom.

Scheme 22



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