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Chiral nitrogen-stabilized Fischer carbene complexes: an efficient tool in the stereocontrolled elaboration of additional stereogenic centers*

Stefano Maiorana,† Emanuela Licandro, Laura Capella, Dario Perdicchia and Antonio Papagni

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, Via C. Golgi 19, I-20133 Milan, Italy

Abstract: The elaboration of the organic ligand of amino and hydrazino carbene complexes of the Fischer type through the reactions of their anions with electrophiles is a useful tool for achieving the stereoselective formation of new carbon-carbon bonds. Anions of chiral carbene complexes substituted with a C_2 symmetry amine give stereoselective 1,4-Michael additions to nitroolefins, thus achieving a new entry to β-aryl-γ-aminobutyric acid derivatives, which are biologically important molecules. Moreover, two new and complementary protocols for the synthesis of alkyl hydrazino carbene complexes have been developed and the first reactions of their conjugated bases with alkyl halides and aldehydes are reported.

AMINOCARBENE COMPLEX

Introduction

The reactivity of group 6 transition metal carbene complexes (known as Fischer-type carbene complexes) has been exploited in a wide variety of new thermal and photochemical synthetic methodologies, thus making it possible to reach—also stereoselectively—a very large number of valuable organic and organometallic targets [1].

Furthermore, a great contribution to organic synthesis has been provided by the chemistry of the carbenes in which the organic ligand is elaborated through the generation of a conjugate base and reaction with electrophilic reagents. In these reactions, carbene complexes behave like d^2 synthons, and their reactivity is often complementary and/or more selective than that of their corresponding organic isolobal derivatives, such as ester or amide enolates [2]. The electrophiles that have been shown to react with carbene anions include alkyl halides, epoxides, carbonyl compounds and Michael acceptors. The value of this chemistry is further increased by its application to stereoselective syntheses [3].

In aminocarbene complexes **1** (Fig. 1), due to the π-donation from the nitrogen atom to the chromiumpentacarbonyl moiety, a double carbon-nitrogen bond is present. When R_1 and R_2 are different, this generates two different and stable rotamers, **1A** and **1B**, which usually equilibrate under basic conditions.

Therefore, the use of chiral amino complexes in stereoselective syntheses often implies the formation of complex reaction mixtures, which, in addition to the isomers created by the newly formed stereogenic center, also include the two stable rotamers. For this reason, in several cases, in order to determine the degree of asymmetric induction, it has been found to be necessary to transform the complex, under even harsh oxidative or acidic conditions, into an organic molecule, thus removing the problem of rotamers [4].

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†*Corresponding author:* E-mail: maior@icil64.cilea.it

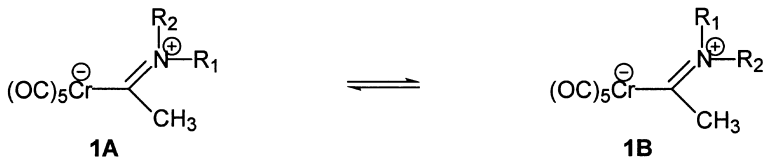
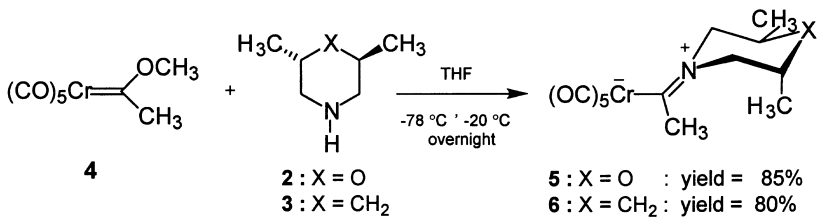


Fig. 1 Rotamers **1A** and **1B** of aminocarbenes.

We thought that C_2 symmetric amines might help to overcome this kind of problems and we decided to try using them in aminocarbene complexes because the two rotamers should be identical. When a new stereogenic centre is formed, this would lead to a simplification of the reaction mixtures and therefore a simplified spectroscopic analysis. Furthermore, C_2 symmetry amines had never been used as chiral auxiliaries in carbene chemistry.

For this reason we selected two C_2 symmetric amines: *trans*-2,6-dimethylmorpholine, **2**, and *trans*-3,5-dimethylpiperidine, **3**, which are commercially available as a 3:1 *cis/trans* mixture. The *trans* isomers were easily separated by medium pressure column chromatography, thus making it possible to process as much as 50 g of the mixture each time.

Used as racemic mixtures, both amines **2** and **3** led to the aminolysis of the methoxymethyl carbene **4**, and high yields of the corresponding chiral complexes **5** [5] and **6** (see note 3 in [6] were obtained (Scheme 1).



Scheme 1 Synthesis of aminocarbenes **5** and **6**.

It is interesting to note that these complexes exist in solution, as well as in the solid state as a single rotamer, in which the axial methyl in the amine ring lies on the same side as the methyl substituent of the carbene carbon atom. The bottom face of the molecule in these complexes is shielded by the axial methyl group. These factors appeared to provide a unique opportunity to use them in stereoselective synthesis, athrough the reactions of their anions with electrophiles, and we decided to study the stereoselective Michael additions of the anions generated from complexes **5** and **6** to nitroolefins.

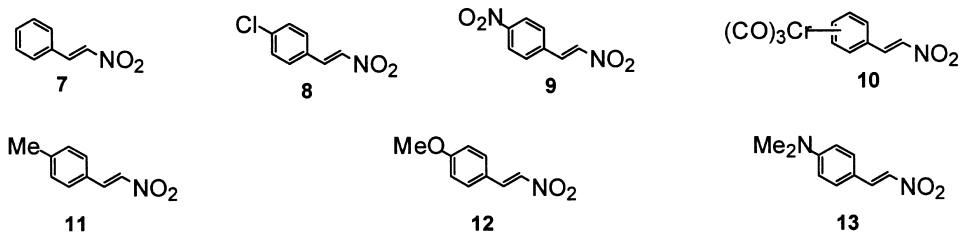
Nitroalkenes are very interesting reagents because of the versatility of the NO_2 group which can be transformed for a variety of different functions. However, despite their potential usefulness, the synthetic applications of nitroalkenes have been somewhat limited by the fact that they easily polymerize in the presence of nucleophiles.

The anions of Fischer amino carbenes could be good candidates in the addition to nitroolefins, insofar as they are soft nucleophiles and have proved to be reactive with a variety of electrophiles under very mild conditions.

Results

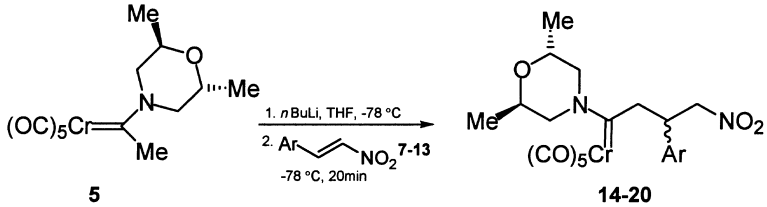
For this study we initially selected the *E*-2 arylnitroalkenes **7–13** reported in Scheme 2.

Compounds **8–10** bear an electron-withdrawing substituent on the aromatic ring, while compounds **11–13** an electron-donor one. Only nitrostyrene is commercially available: all of the others nitroolefins were synthesised following known procedures, through the Henry reaction between the appropriate aromatic aldehyde and nitromethane.



Scheme 2 Nitroolefins **7–13** utilized for the Michael addition.

The conjugate base of the morpholinyl complex **5**, generated by *n*-BuLi at −78 °C, reacted with the nitroolefins **7–13** at −78 °C, to give the corresponding Michael adducts **14–20** with the yields and diastereoselectivities shown in Scheme 3 [6].



nitro adducts	Ar	yield%	d.e.%
14	Ph	86	30
15	*p*-Cl-Ph	80	50
16	*p*-NO_2-Ph	75	70
17	$Cr(CO)_3Ph$	80	70
18	*p*-MeO-Ph	70	5*
19	*p*-$N(CH_3)_2$	63	34*
20	*p*-CH_3	81	22

* In this case the opposite diastereoisomer (*R,R,R,)-(S,S,S)* was obtained

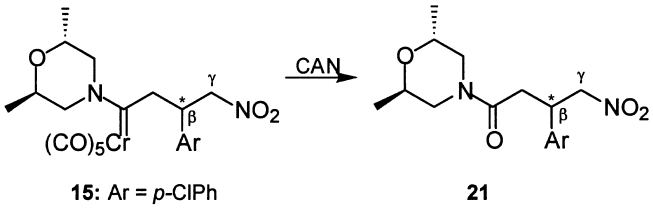
Scheme 3 Michael additions of complex **5** to nitroolefins **7–13**.

The high chemical yields reflect the expected good low-temperature reactivity of the carbene anion with nitroolefins, and we never observed the formation of any by-products arising from the polymerization of the Michael acceptors. The diastereomeric excess (d.e.) were determined from ^{1}H NMR spectra of the crude reaction mixtures and, in some cases, confirmed by ^{13}C NMR spectra and HPLC.

The two diastereoisomers of all of these products could be separated by means of column chromatography on silica gel, and the single diastereoisomers were fully characterized. However, it was impossible to get a single crystal for X-ray analysis from either of them. In order to determine the configuration of the major diastereoisomer, the mixture of the two diastereomeric nitro complexes **15**, obtained from the reaction with *p*-chloronitrostyrene, was quantitatively oxidized to the γ-nitroamide **21** with cerium ammonium nitrate at room temperature (Scheme 4).

The two isomers of the nitroamide were separated by column chromatography, and a single crystal of the major diastereoisomer was submitted to X-ray analysis, from which the resulting configuration was (*R,R,S*)-(*S,S,R*) [6].

An observation deriving from the analysis of the experimental results reported in Scheme 3 is the considerable effect that the substituents on the aromatic ring of nitroolefins have on diastereoselectivity. If there are no substituents, the d.e. is 30%, but the presence of electron-withdrawing substituents greatly increases this value, which reaches 70% in the case of the *p*-nitrostyrene and the $Cr(CO)_3$ complexed nitrostyrene. The *p*-methoxy and *p*-dimethylamino substituents have exactly the opposite effect, both leading to the other diastereoisomer (*R,R,R-S,S,S*) with d.e. values of 5% and 34%, respectively.



Scheme 4 Oxidation of complex **15** to nitroamide **21**.

To try to rationalize these results, in Fig. 2 we propose two models, **A** and **B**, which can explain the formation of the major and minor diastereoisomers, respectively.

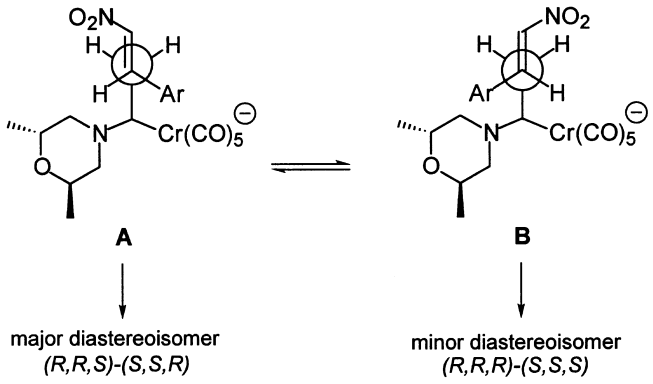
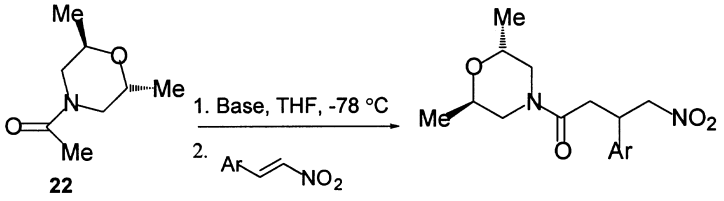


Fig. 2 Proposed transition state models **A** and **B** explaining the observed diastereoselectivities.

The major diastereoisomer is formed from model **A** through the attack of the carbene anion on the *Si-face* of the nitroolefin. This transition state could be stabilized by the existence of an electronic interaction between the negatively charged $Cr(CO)_5$ group of the complex anion and the aromatic ring of the nitroolefin. In this transition state, the electronic interactions can be expected to be greater if electron-withdrawing substituents are present on the aromatic ring, something which is in line with the experimental results. In the case of electron-donor substituents, such as *p*-methoxy and *p*-dimethylamino groups, in which the minor becomes the major diastereoisomer, the attack on the *Re-face* of the nitroolefins becomes competitive. This is probably due to a less favorable interaction between the electron-rich arene ring and the negatively charged $Cr(CO)_5$ moiety. Some theoretical calculations currently in progress seem to support this rationalization, showing that the model **A** is more stable than **B** and the calculated energy difference is 1.324 kcal/mol in the case of nitrostyrene **7** [7].

The possible role of the lithium counterion in the stereoselection of the reactions is under investigation: we complexed it with the 12-crown-4 ether. The preliminary results of these experiments are: (i) the general reduction in reaction rates associated with the lithium coordination, and (ii) the noticeable increase in d.e.-values for nitrostyrene, *p*-Cl-nitrostyrene and *p*-CH_3-nitrostyrene.

Finally, the organic isolobal analogue of the complex **5**, *N*-acetyl dimethylmorpholine **22**, affords the Michael adduct with nitrostyrene and *p*-chloronitrostyrene at lower chemical yields and a very low d.e., when BuLi or LDA are used as bases (Scheme 5 [6]).



Ar	*base*	*Y %*	*d.e.%*
p-ClPh	BuLi	50	10
	LDA	77	5
Ph	BuLi	40	10
	LDA	45	0

Scheme 5 Michael addition of the acetamide **22** to nitroolefins **14** and **15**.

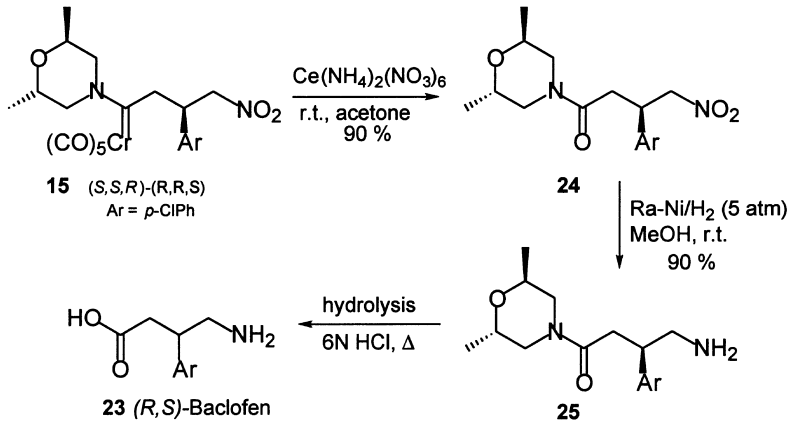
These results indicate that the $Cr(CO)_5$ moiety, coupled with the presence of the stereogenic *trans*-2,6-dimethylmorpholine unit, has a marked effect on both the reactivity of the anion of the carbene complex and on the stereochemical outcome of the reactions. Thus, the conjugate base of the dimethyl morpholine substituted carbene complex serves as a convenient chiral acetamide enolate equivalent.

Synthesis of β-aryl-γ-aminobutyric acid derivatives

As a result of the oxidation of the chromium-carbon bond, the synthesised β-aryl-γ-nitrocarbene complexes **14–20** can be transformed into β-aryl-γ-nitrobutyric acid amides, and therefore the nitro-complexes **14–20** are precursors of β-aryl-γ-aminobutyric acid derivatives, a class of important organic molecules that have a potent effect on the central nervous system.

Baclofen **23** (β-*p*-chlorophenyl-γ-aminobutyric acid) is widely used as an anti-spastic agent. There is current interest in synthesising both of the enantiomers, and a number of rather complicated syntheses of this drug have appeared in the literature over the last two years [8,9].

We have performed the synthesis of racemic Baclofen through the chemistry of chiral aminocarbenes described (Scheme 6).



Scheme 6 Synthesis of *(R,S)*-Baclofen **23**.

In particular, the two diastereoisomers of the Michael adduct **15** were separated by column chromatography and the *(S,S,R)-(R,R,S)* isomer was quantitatively oxidized to the γ-nitroamide **24** with cerium ammonium nitrate.

The nitro group was then reduced to the amine **25** using Ni-Raney under five atmospheres of H_2, and the amide was quantitatively hydrolized by refluxing in 6 N HCl to give (±)-Baclofen.

HYDRAZINO CARBENE COMPLEXES

Introduction

Apart from the use of C_2 symmetry amines, another widely used strategy for stereocontrol is the coordination of an organic ligand to metal centres. In the chemistry of carbene complexes, it is well known that an oxygen or a nitrogen atom can chelate to the metal with the displacement of a CO ligand. This chelation leads to the formation of cyclic and conformationally rigid complexes. Wulff has successfully employed the chiral complex shown in Fig. 3 in stereoselective Michael additions to enones and aldol reactions [3].

In this regard we were attracted by the structure of hydrazino carbene complexes of general formula **26**, on the basis of the fact that the nitrogen atom that is not directly bound to the carbenic carbon has a lone pair available which should be able to coordinate to the metal by displacing a CO ligand. This would generate a four-membered ring chelate such as **27**, and it seemed of interest to study the stereodynamic properties and reactivity of such a complex. In addition to this, the presence of a rigid structure could be useful in the case of chiral derivatives for achieving stereoselective synthesis.

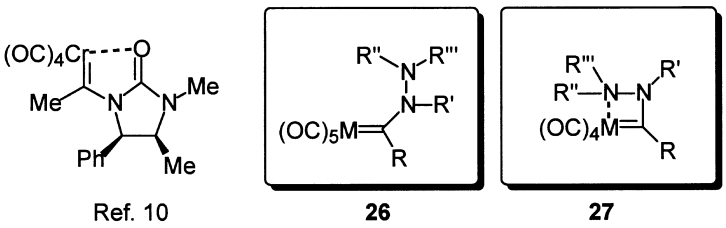


Fig. 3 Wulff chelate complex of imidazolidinone and general formulas of hydrazinocarbens **26** and chelate hydrazinocarbenes **27**.

Only a few hydrazino carbene complexes have so far been reported [10a–c]. This is certainly due to the very limited applicability of the hydrazinolysis reaction of alkoxy carbenes. In fact, Professor E. O. Fischer reported [11] that the reaction between the methoxy methyl carbene of chromium and

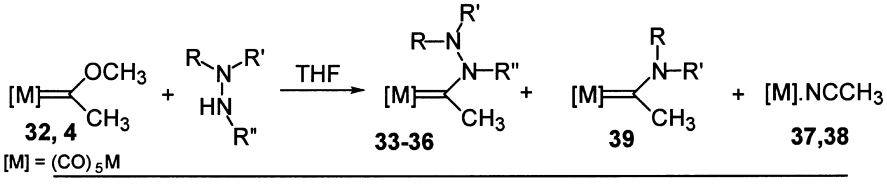
1,1-dimethylhydrazine was unsuccessful, due to the instability of the intermediate hydrazino complex, which decomposes giving the chromiumpentacarbonyl complexed acetonitrile.

However, hydrazinolysis has recently been shown by Professor Aumann to be partially successful in the case of alkynyl carbene complexes [10b].

On the other hand, to study the chemistry of α-anions in the case of hydrazinocarbenes, we wished to extend to saturated complexes the range of derivatives that were available. For these purposes the hydrazinolysis of oxacarbenes appeared to be a highly appealing methodology because of its simplicity. We therefore decided to study this route regardless the unsuccessful results that had been reported in the literature.

Results

The first results we obtained were encouraging: in fact, the hydrazines **28–31** we initially selected, reacted with the methoxy methyl carbene of chromium **4** and tungsten **32** giving the corresponding hydrazino complexes **33–36**, besides the complexed acetonitrile of tungsten **37** and of chromium **38** which were the main reaction products. In the case of reaction of **4** with **31** the aminocarbene complex **39** was the main reaction product recovered in 40% yield (Scheme 7).

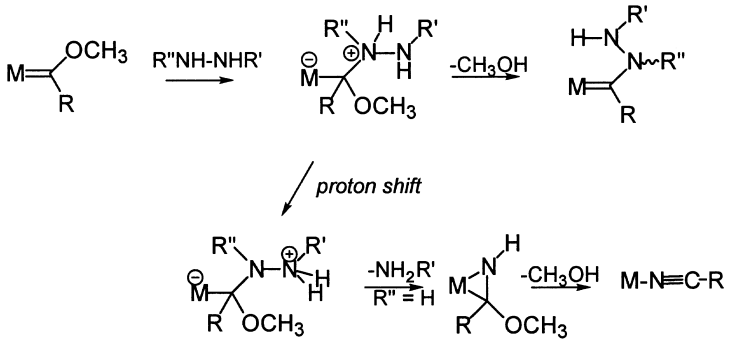


hydrazine	*M*	*hydrazinocarbene yield (E : Z)*	[M].NCCH3 **37,38**	*aminocarbene* **39**
28	W	**33**	**37**	–
		34 (0 : 100)	50	
29	Cr	**34**	**38**	–
		–	21	
30	W	**35**	**37**	–
		6 (0 : 100)	75	
31	Cr	**36**	**38**	**39**
		18 (70 : 30)	–	40

Scheme 7 Hydrazinolysis of complexes **32** and **4**.

The yields in carbene complexes were rather low, but these results were interesting since they demonstrated that the hydrazinolysis of alkyl oxacarbenes was possible.

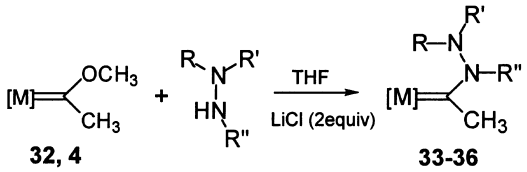
According to the accepted mechanism for aminolysis (Scheme 8), hydrazino carbenes are likely to be formed by the elimination of methanol from the tetrahedral intermediate of the reaction, whereas the acetonitrile complex arises from the breaking of the N–N bond, followed by the elimination of a molecule of amine. This latter process is a consequence of the proton shift from the α to the β nitrogen.



Scheme 8 Mechanism of the hydrazinolysis.

We made a number of unsuccessful attempts to prevent this shift, and eventually considered a Lewis acid as a possible coordinating species capable of engaging the β-nitrogen lone pair without transforming it into a good leaving group: lithium chloride appeared to be a suitable candidate for this purpose.

The results of the hydrazinolysis in the presence of lithium chloride were surprisingly good and are reported in Scheme 9 [12].



32, 4 **33-36**

[M] = $(CO)_5M$

hydrazine	*M*	*time*	*hydrazinocarbene yield (E : Z)*
28	W	*2.5h*	**33** 72 (0 : 100)
29	Cr	*2.5h*	**34** 88 (0 : 100)
30	W	*1h*	**35** 49 (0 : 100)
31	Cr	*15h*	**36** 73 (40 : 60)

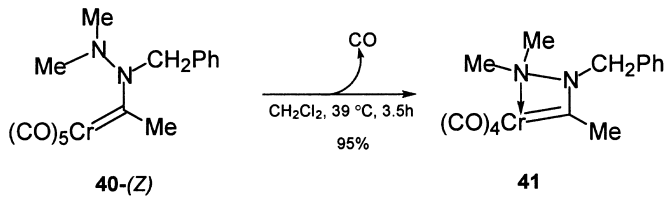
Scheme 9 Hydrazinolysis of complexes **32** and **4** with 2 equiv. of LiCl.

The yields in hydrazino carbenes **33–36** were between two- and eightfold those obtained in the absence of lithium chloride. Only the *Z* isomer was obtained in the case of morpholino derivatives **33–35**, whereas the 1,2-dimethylhydrazine gave the hydrazino carbene **36** as a mixture of *E*:*Z* isomers in a 4:6 ratio. The presence of lithium chloride had also a dramatic effect on the reaction times, which increased

from 30 min to 2–5 h for the morpholine derivatives and from 5 to 10 min to 15 h in the case of 1,2-dimethylhydrazine.

We believe that this effect can be rationalized in terms of the formation of an aggregate in THF between lithium chloride and the hydrazine. This makes the hydrazine less nucleophilic and therefore less reactive than a free hydrazine. We were able to isolate this aggregate in the case of 1,1-dimethyl-hydrazine, and found that its independent reaction with the alkoxy carbene gave the same results as the former 'in situ' reactions. Unfortunately, we have not yet been able to determine the structure of this adduct, but we think that this observation—concerning the formation of lithium-hydrazine aggregate—-will find more general applications.

The hydrazinolysis reaction finds a limit in the case of 1,1,2-trisubstituted and some 1,2-disubstituted hydrazines which do not react because of steric hindrance. In these cases we have found that it is possible to extend to hydrazides the known method of Hegedus for preparing aminocarbene complexes from amides [13]. In this way we have prepared the hydrazino carbene **40** as a 1:1.3 *E/Z* ratio. The treatment of (Z)-**40** in refluxing methylenechloride gives the chelate complex **41**, as reported in Scheme 10.



40-(*Z*) **41**

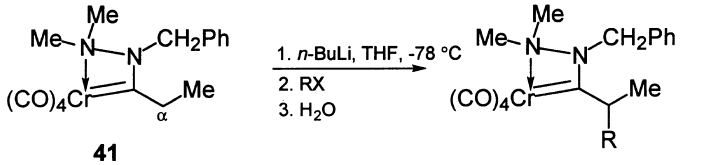
Scheme 10 Synthesis of the chelate complex **41**.

The two synthetic procedures for the synthesis of hydrazino carbenes are complementary to each other and offer a good possibility of access to a variety of alkylhydrazino complexes, including chiral derivatives.

Reactivity of hydrazinocarbenes

The complex **40** (*E/Z* mixture) can be very easily deprotonated using *n*-BuLi at −70 °C in THF and, after quenching with H_2O, it was recovered quantitatively and as a pure (*Z*)-isomer. The conjugate base of **40** is highly reactive towards alkylating reagents, giving the expected alkylated (Z)-hydrazino carbenes, together with the alkylated tetracarbonyl-*N*-chelate derivatives in excellent overall yields [13].

The reactivity of the chelate complex **41** was surprising. In fact its conjugated base (easily made with *n*-BuLi at −78 °C) can be further alkylated giving the corresponding dialkylated complexes **42** and **43** in high yields (Scheme 11 [13]. Therefore, a stereogenic center can be created on the α-carbon atom of chelate hydrazino complexes.



41

42 : RX = MeI y = 98%

43 : RX = $PhCH_2Br$ y = 92%

Scheme 11. Alkylation of chelate complex **41**.

Finally, in preliminary experiments, **41** was also found to be reactive with benzaldehyde, affording a stable aldol adduct in high yields (85%) and possessing a high diastereoselectivity (95%).

This behaviour, which is both remarkable and peculiar with respect to aminoarbene anions [14], offers some promising perspectives for the use of hydrazino complexes in stereoselective synthesis.

ACKNOWLEDGEMENTS

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