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TRANSITION METAL COMPLEXATION IN 1,3-DIPOLAR CYCLOADDITIONS

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Abstract - Transition metal complexation of organic molecules is becoming common in the field of 1,3-dipolar cycloadditions as a successful methodology to increase reactivities and to control selectivities. The literature data on this subject are here reviewed in a systematic way as a function of the different dipoles and principally of the stoichiometric or catalytic role of the metal containing reactants.

1. INTRODUCTION

Some degree of familiarity with the organometallic chemistry has became an essential requisite for the synthetic organic chemists, who increasingly make recourse to the temporary formation of organometal bonds in order to improve reactivity and/or selectivity as well as to open new opportunities in organic syntheses.[1] In this context, metals of transition groups are more usual than those of main groups.

On the other hand, 1,3-dipolar cycloadditions have been recognized as one of the most important classes of organic reactions because of a number of factors: *(i)* the broad variety, not yet exhausted, of dipoles and dipolarophiles; *(ii)* the stereochemical advantage of the pericyclic cycloaddition mechanism; *(iii)* the easy and multifarious manipulation of the heterocyclic cycloaddition products.[2,3] 1,3-Dipolar cycloadditions involving transition metal complexed species are a matter of fact. Mention of them can be found in a few valuable, but massive reviews where, in our opinion, they are presented in a rather dispersive form and therefore may escape the attention of the readers lacking a specialistic knowledge.[4-6]

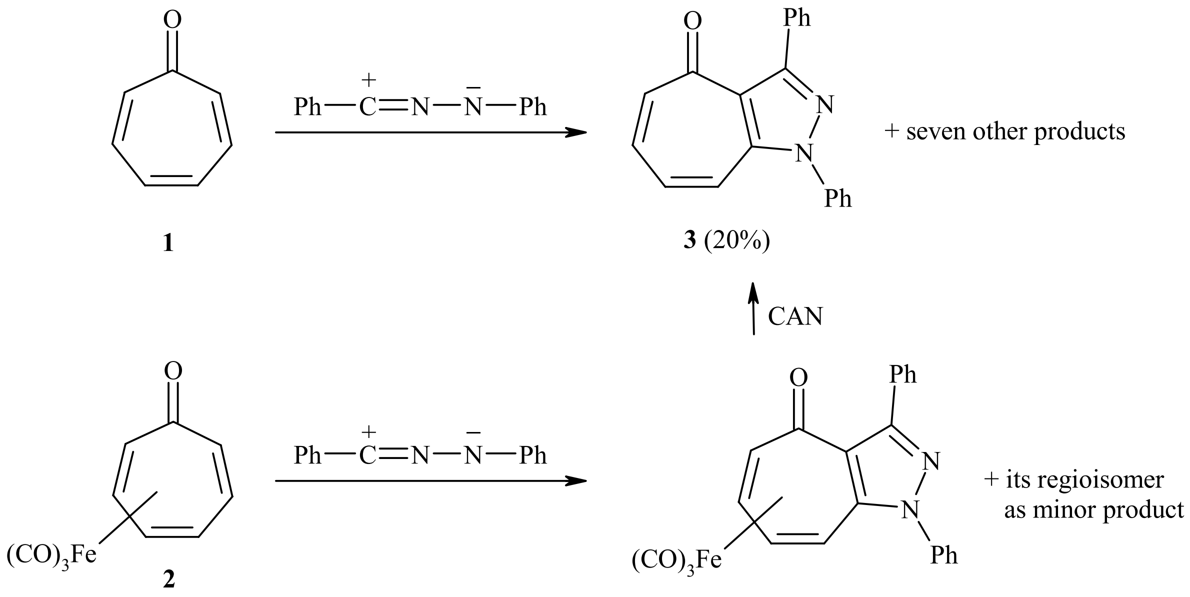
Our aim is here to offer a systematic, critical, and concise survey of the literature reports on the title subject with the hope of facilitating the rationalization of the experimental evidence as well as the definition of the scope and limitations of the methodology.

The literature data have been collected and organized on the basis of the following criteria. First of all, we have taken into account those cases where the final target of the reaction sequence is a metal-free organic molecule, i.e. where the transition metal complexation merely serves as a synthetic device to obtain the desired product. Furthermore, we have felt advisable to emphasize the difference between transient and (more or less) stable complexes, the latter being usually prepared and isolated prior to cycloaddition, while the former being necessarily generated in situ within the cycloaddition medium. This corresponds, in another sense, to distinguish between catalytic and stoichiometric role of the metal containing reactant. Such an aspect is very important from the practical point of view.

It is worthy of noting that metal complexation can induce 1,3-dipolar behavior by organic three-atom sequences which are not intrinsically 1,3-dipoles. The following are two significant examples: *(i)* the stabilization of the trimethylenemethane fragment upon proper metal coordination and its consequent reactivity as a *C-C-C* dipolar sequence to form the cyclopentane ring;[7] *(ii)* the synthesis of oxazolidines or imidazolidines by cycloaddition of tungsten and manganese complexes of ketenimines (*C-C-N* dipolar sequence) to C=O or C=N double bonds.[8] However, the chemistry of these anomalous 1,3-dipoles, having no metal-free counterpart, is outside the argument of the present review.

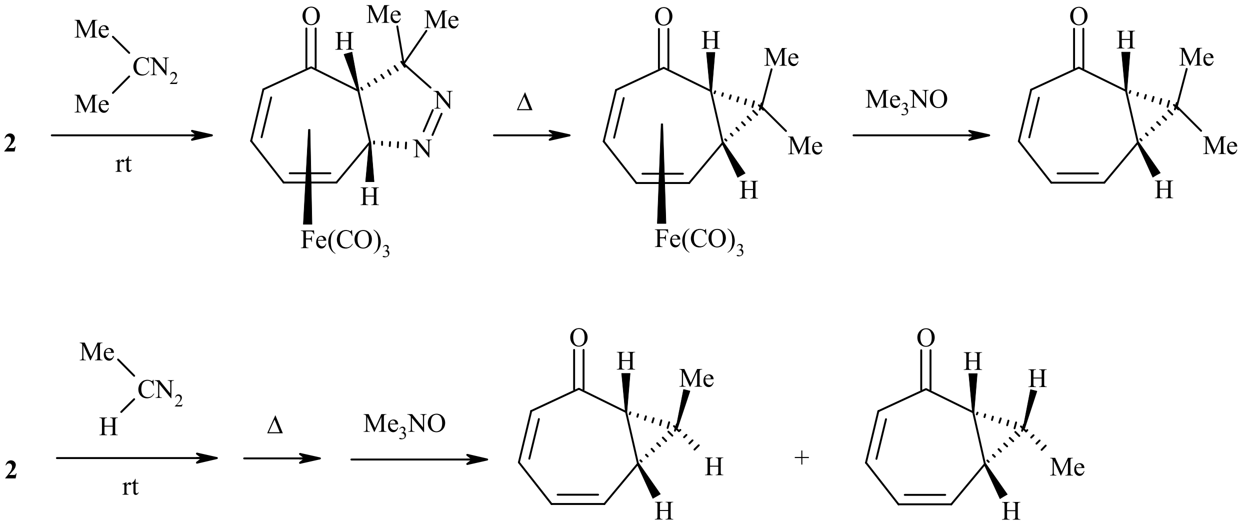
2. 1,3-DIPOLAR CYCLOADDITIONS TO TRICARBONYLIRON COMPLEXED DIPOLAROPHILES

The tricarbonyliron complexation of polyenes is a long-known methodology for modulating their reactivity.[9] Due to the peculiar characteristics of tropone and related ketimines in terms of periselectivity as well as of site-selectivity and regioselectivity, the corresponding tricarbonyliron complexes have attracted the attention of several authors, who studied their dipolarophilic behavior towards nitrilimines[10] and diazoalkanes.[11-14]

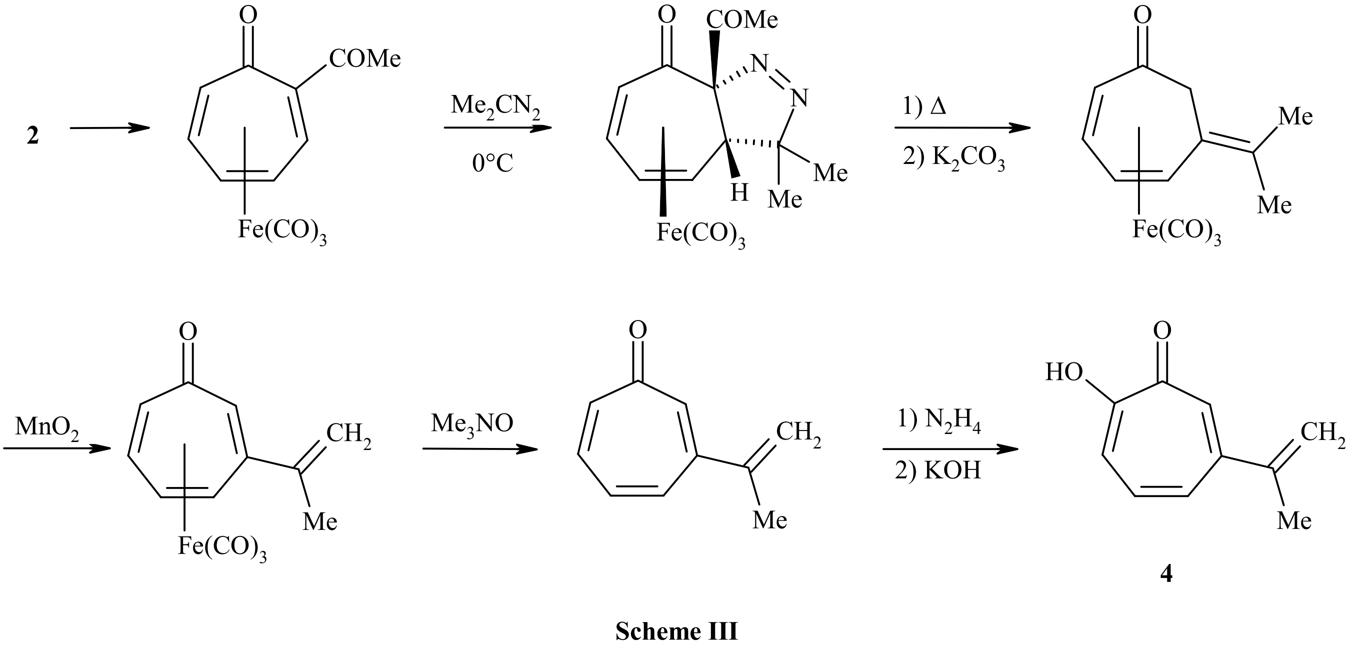


Scheme I

Tropone (**1**) reacts with diphenylnitrilimine to give a product mixture containing a few [4+2] cycloadducts and one [6+4] cycloadduct. In contrast, the reaction of tricarbonylirontropone (**2**) with the same dipole proceeds exclusively at the free double bond, so offering a better entry to compound (**3**) (Scheme I).[10a] Analogously, the treatment of **1** with diazoalkanes results in a complex product mixture with no preparative utility, while the complexed species (**2**) adds diazoalkanes in a more selective and efficient fashion (Scheme II).[11-13] However, in the case of diazoethane, the cycloaddition exhibits a very modest degree of diastereoselectivity. The tricarbonyliron complexation of tropone has also been exploited to attain the desired site- and regio-preference in an elegant synthesis of β-dolabrin (**4**) (Scheme III).[14]

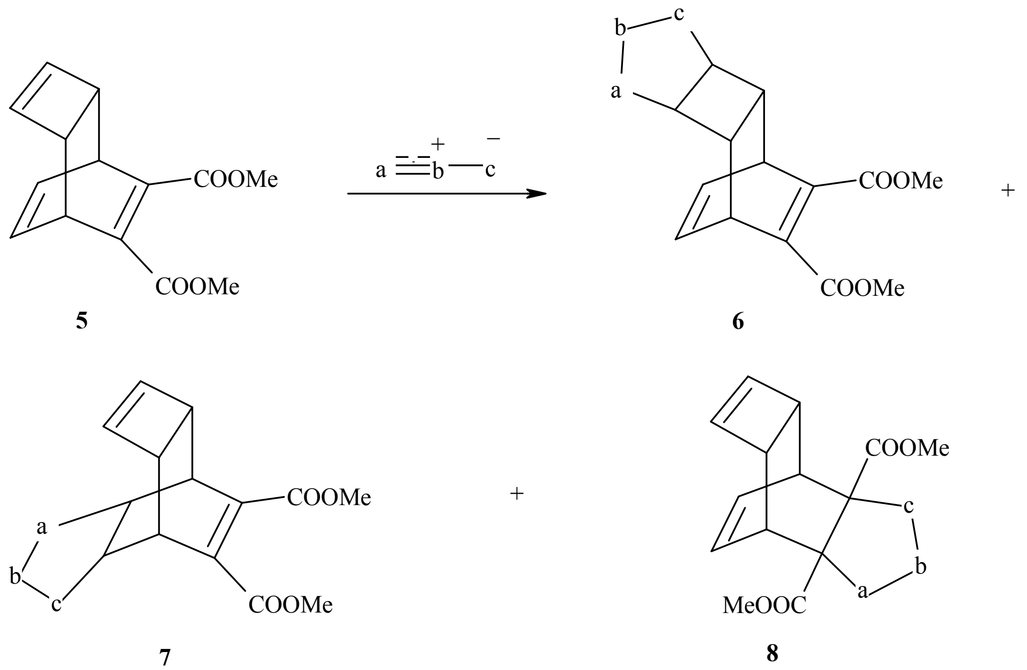


Scheme II

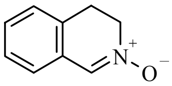
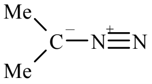


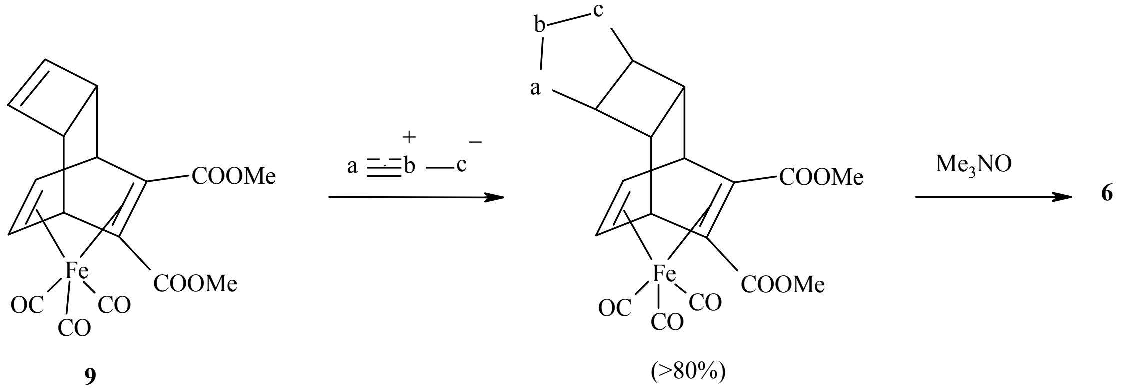
Scheme III

One of the above cited research group has also investigated the tricarbonyliron complexes of cycloheptatriene[15] and of the bridged-ring triene (**5**).[16] In the latter interesting case, the 1,3-dipolar cycloaddition can be forced to occur exclusively at the cyclobutene moiety if the other unsaturations are engaged in the organoiron linkage (Scheme IV).



5 **6** **7** **8**

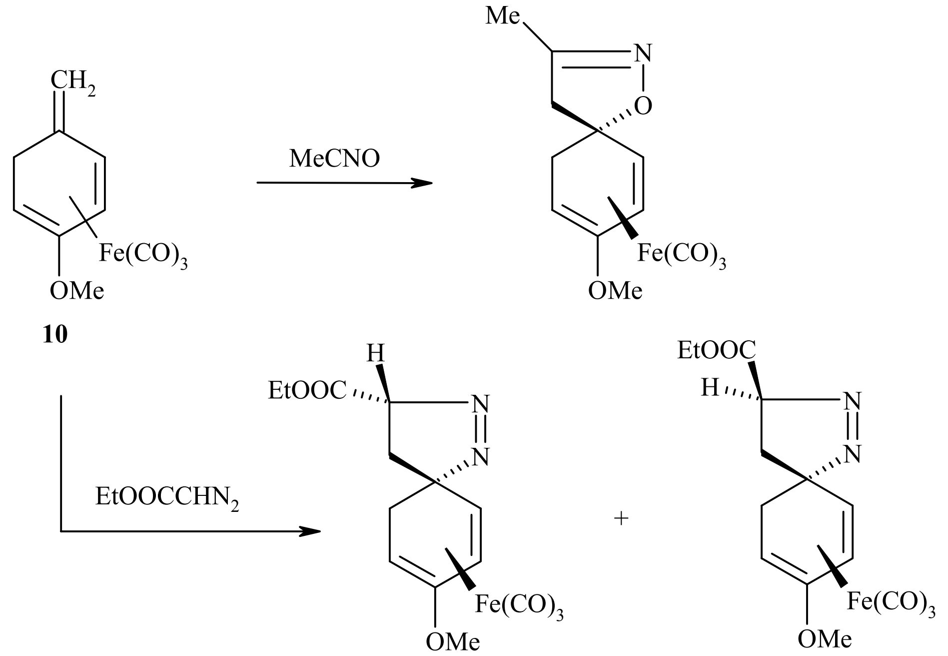
Dipole	Product distribution (%)		
	6	**7**	**8**
	53	47	-
$Ph-\equiv\overset{+}{N}-\overset{-}{O}$	23	77	-
$Ph-\equiv\overset{+}{N}-\overset{-}{N}-Ph$	21	58	21
 $Me_2\overset{-}{C}-\overset{+}{N}\equiv N$	-	-	100



9 (>80%)

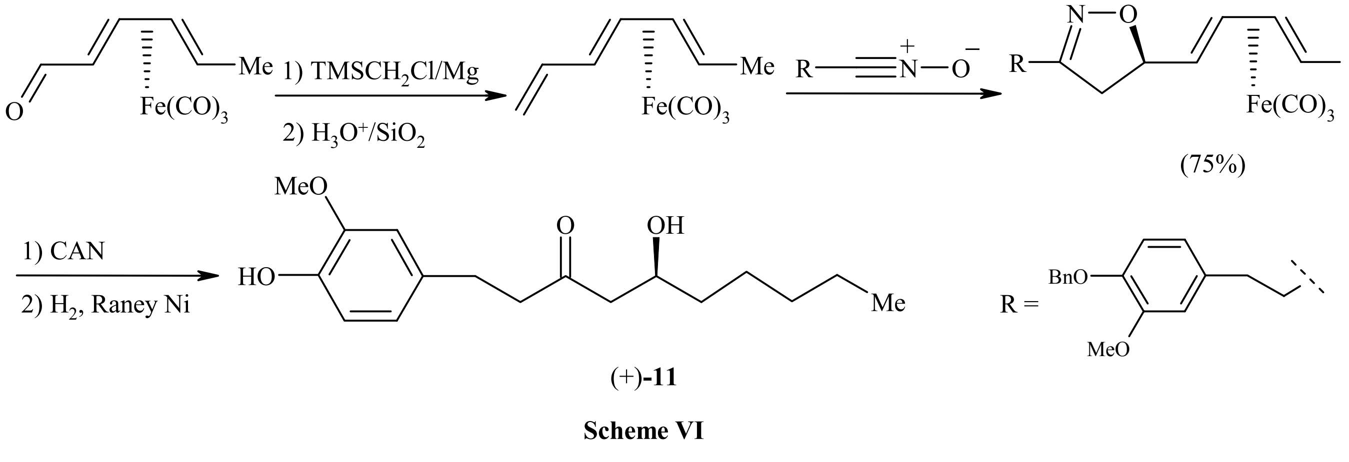
Scheme IV

Complexed triene (**10**) has been studied as dipolarophile towards nitriloxides and diazoalkanes (Scheme V).[17] The following features have been observed: *(i)* exclusive site preference in favor of the exocyclic double bond; *(ii)* complete stereoselectivity as the *si* and *re* faces of the dipolarophile are concerned, accompanied however by a modest degree of discrimination with respect to the two faces of the dipole π-system. Somehow surprisingly, decomplexation of the cycloadducts is not reported.

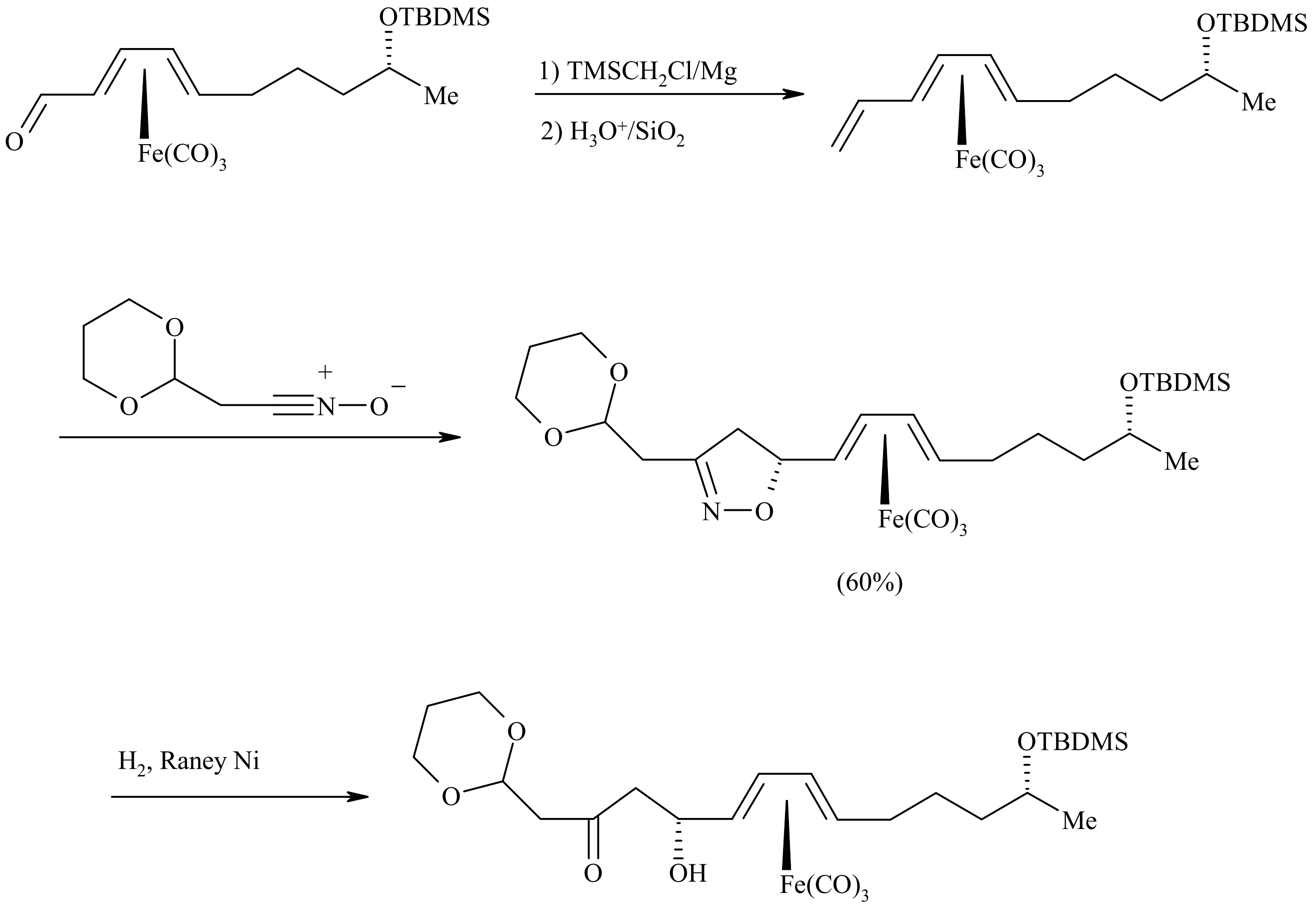


Scheme V

1,3-Dipolar cycloadditions to tricarbonyliron complexes of linear polyenes have been described.[18-21] Once again, the complexation represents an efficient site-directing tool. Furthermore, due to the stereogenic nature of the complexation centre and to the accessibility of enantiomerically pure substrates, the tricarbonyliron pendant can serve as a chiral auxiliary. This is a matter of fact in the preparations of (+)-gingerol (**11**) (Scheme VI)[19b] and of compound (**12**), a key intermediate for a synthetic entry to the antiviral 24-membered macrolide known as macrolactin A (Scheme VII).[20] In both cases, the observed diastereochemical preference may be explained on assuming that the dipole approaches to the less encumbered face of the *s-trans* rotamer of the dipolarophile. It is worthwhile to note that Schemes VI and VII involve two examples of the so-called cycloadditive route to β-hydroxy ketones.[3]



Scheme VI



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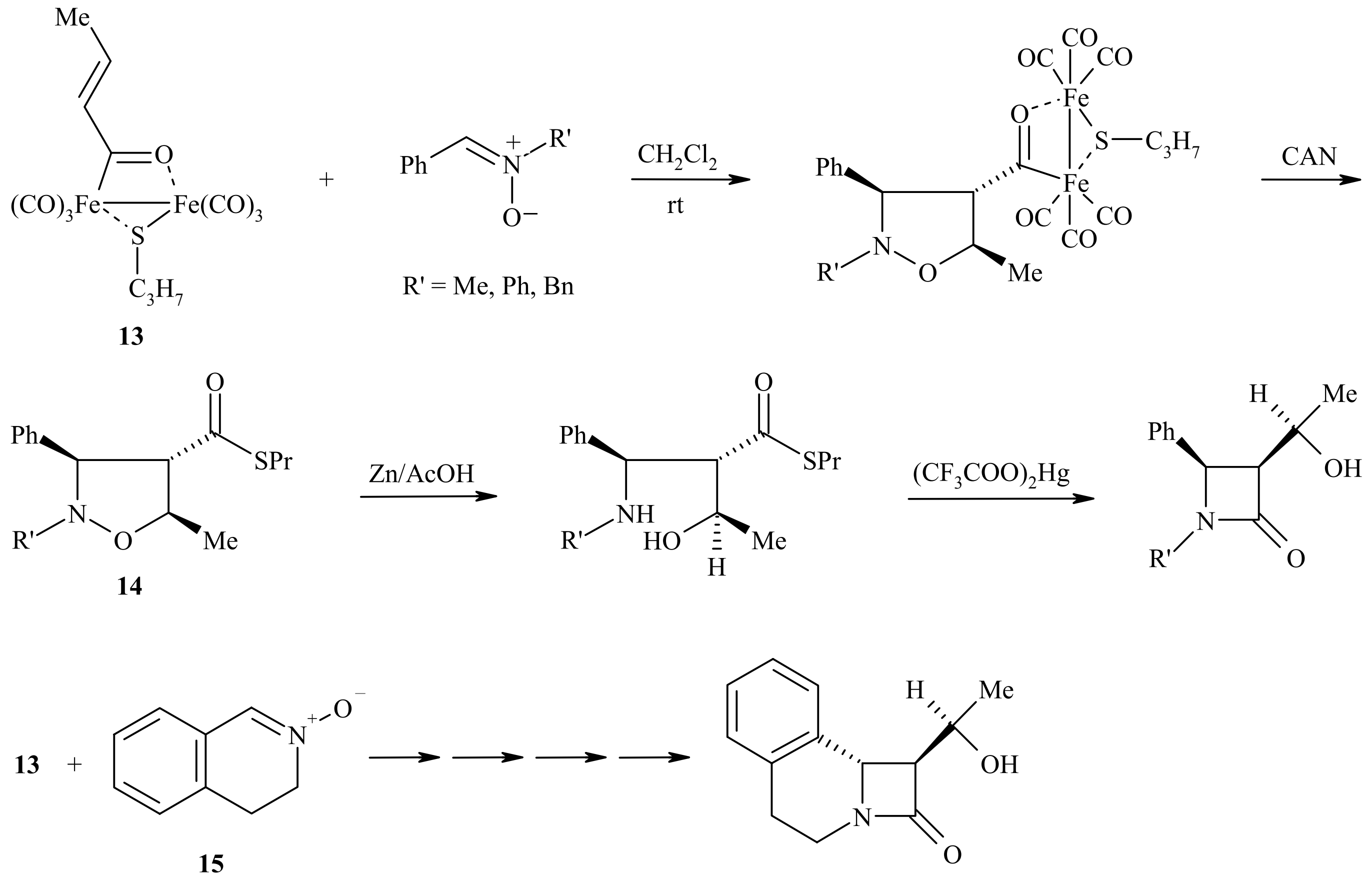
Scheme VII

A disappointing degree of diastereoselectivity has been found in the 1,3-dipolar cycloaddition of *N*-(benzyl)azomethinylide to the enantiopure tricarbonyliron complex of methyl *E*,*E*,*E*-6,9-dioxo-9-phenyl-nona-2,4,7-trienoate.[21]

The last reports[22,23] we mention in this paragraph deal with the strange dipolarophiles (**13**), which constitute an unusual kind of bis-tricarbonyliron derivatives. As illustrated in Scheme VIII, the cycloaddition between compounds (**13**) and various acyclic nitrones was fully regioselective and stereoselective, at variance with the literature data about nitrone cycloadditions to crotonic esters. The observed regiochemical and stereochemical outcomes may be ascribed, respectively, to the pronounced electron-attracting effect and to the massive encumberance of the organoiron group linked at the dipolarophilic site.[22] Usefully, oxidative removal of the metal from the primary cycloadducts led to isoxazolidines (**14**) bearing a thioester function, which in turn were exploited as intermediates to β-lactams. Control of the absolute stereochemistry was achieved by means of a homochiral *S*-substituent, namely D or L *N*-Boc-prolinyl group. A selective , but opposite stereochemical course was operative in the case of the cyclic *E*-blocked nitrone (**15**).[23]

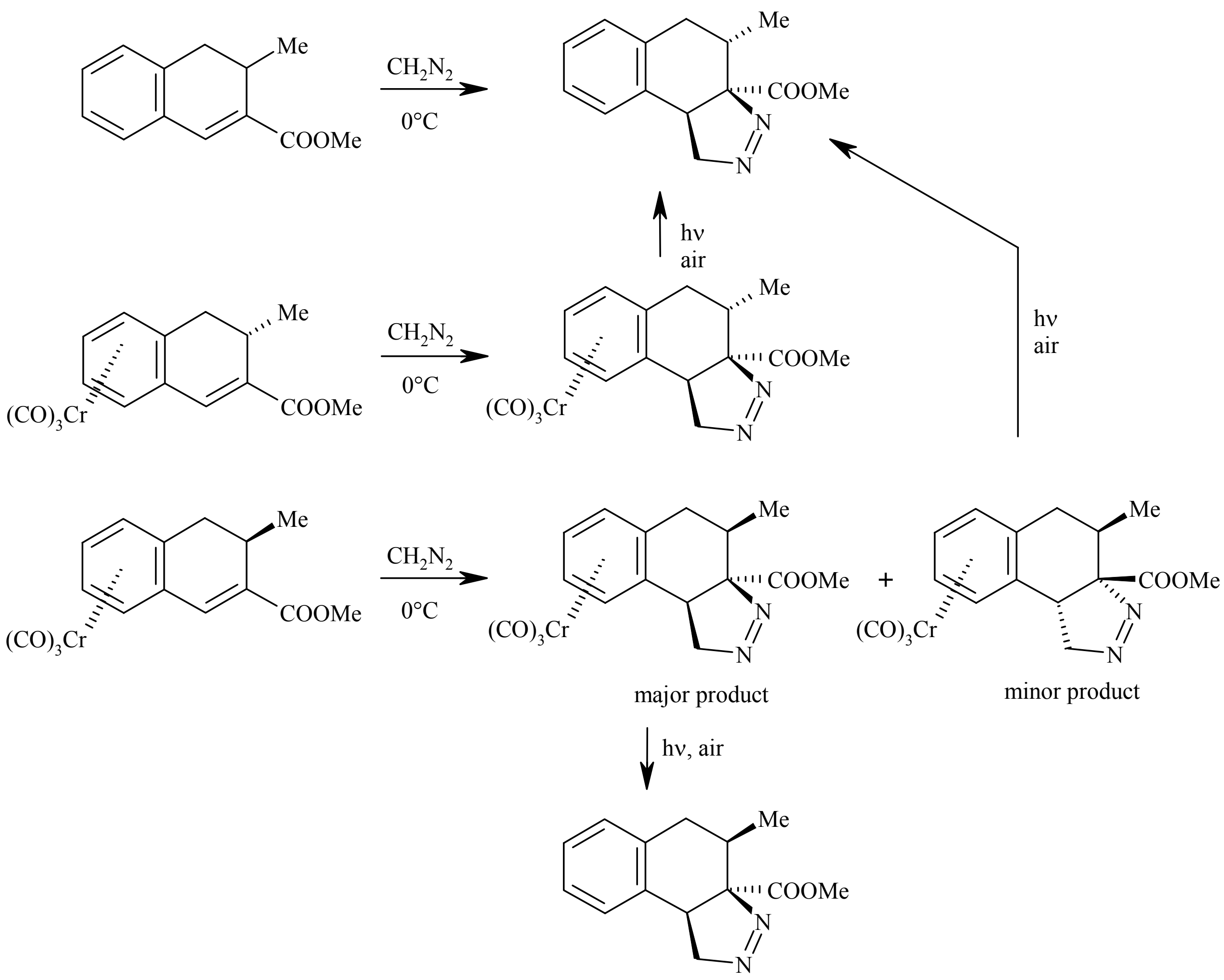


Scheme VIII

3. 1,3-DIPOLAR CYCLOADDITIONS TO TRICARBONYLCHROMIUM COMPLEXED DIPOLAROPHILES

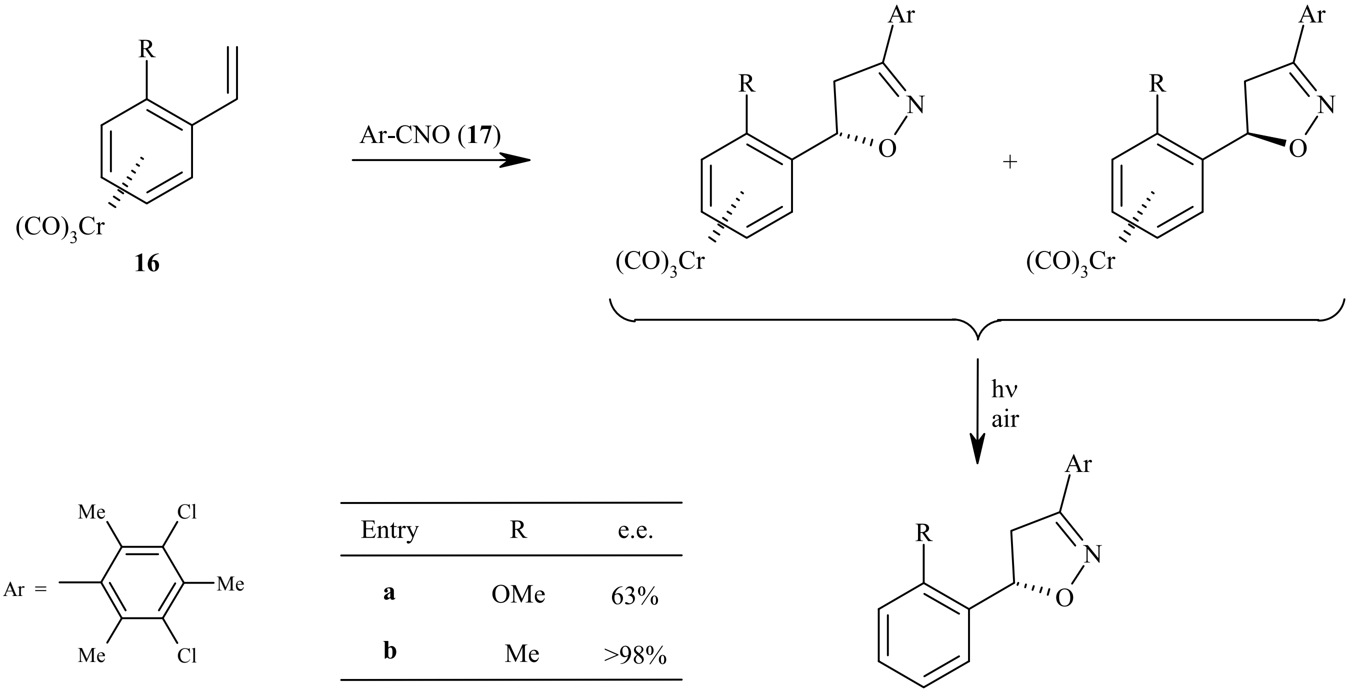
In the last decades, the tricarbonylchromium η^6-complexes of arene derivatives have acquired popularity in organic synthesis[24] in the light of the following characteristics of the tricarbonylchromium unity: *(i)* the strong effect, both electronic and steric in origin, on the reactivity of anular and adjacent functionalities; *(ii)* the stereogenic nature whenever the benzene ring is dissymmetrically substituted, i.e. when there are two different groups in *ortho* or *meta* relationship; *(iii)* the mild conditions required to remove the metal from the organic backbone. Therefore, particularly as a consequence of points *(ii)* and *(iii)*, the tricarbonylchromium pendant can behave as an efficient chiral auxiliary.

The pioneering work in this field, as far as the 1,3-dipolar cycloadditions are concerned, is due to Carrié *et al.*,[25] who explored the reaction of diazomethane with tricarbonylchromium complexed 1,2-dihydronaphthalenes (Scheme IX). In terms of diastereofacial selectivity, the experimental findings demonstrate that the tricarbonylchromium moiety really works to drive the dipole towards the *anti* face. Nevertheless, the facial discrimination is not total when an opposite steric effect comes from the substituent in allylic position.



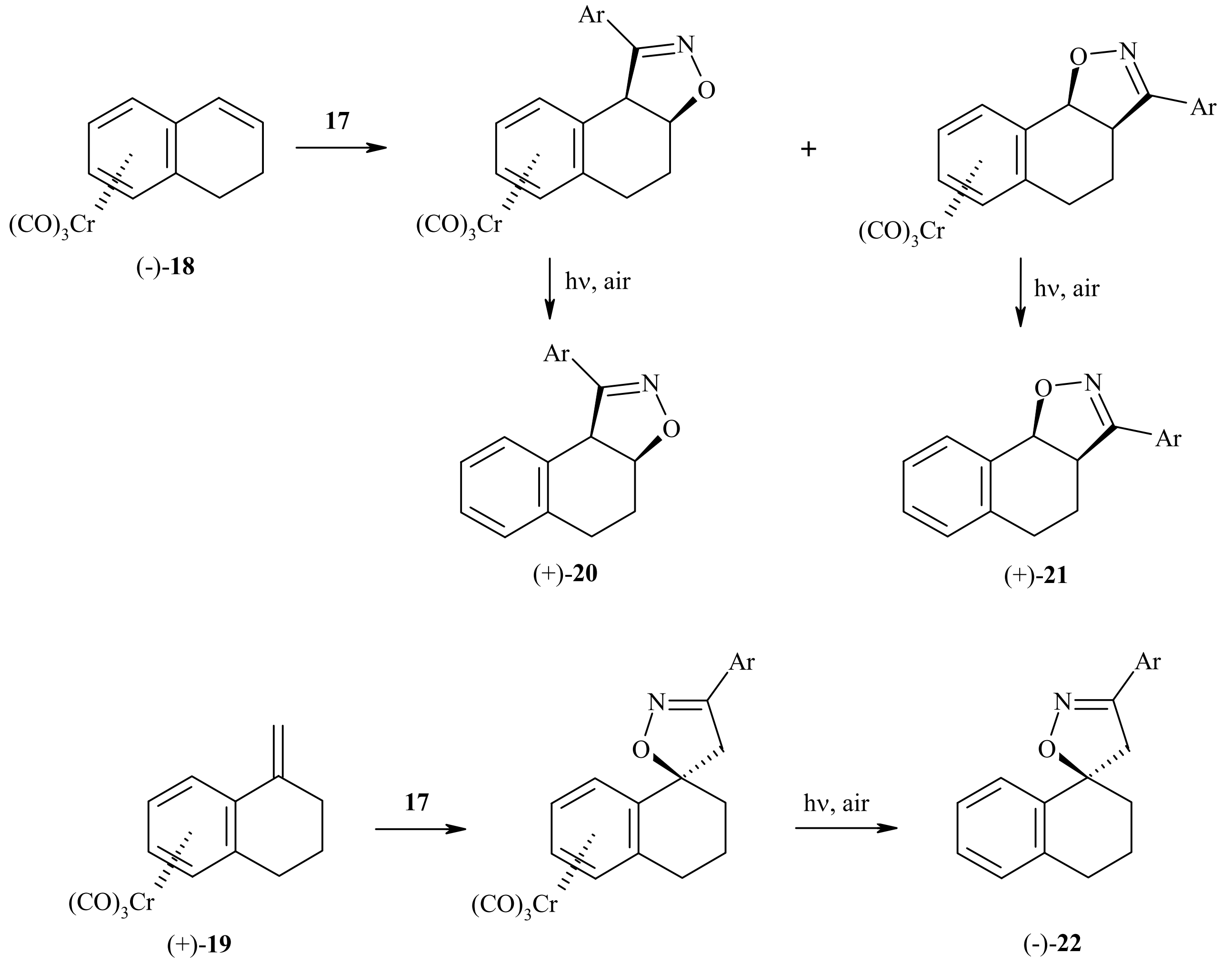
Scheme IX

An Italian research group has investigated the reaction of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide (**17**) with the chiral tricarbonylchromium complexed styrenes (**16**), both racemic and enantiopure. (Scheme X).[26] The diastereoisomeric ratio (that is the enantiomeric ratio after decomplexation of the optically active cycloadducts) was markedly dependent on the *ortho*-substituent. The experimental results were rationalized on the basis of the following assumptions: *(i)* due to steric reasons, the nitriloxide attacks the π face opposite to the tricarbonylchromium tripod; *(ii)* the diastereoselectivity arises from the reactivity gap between the *s-trans* and *s-cis* rotamers of the dipolarophile; *(iii)* such a gap is smaller in the case of **15a** since the angular geometry of the methoxy group reduces steric repulsions between the reactants. This view was proven to be correct on taking into account the cyclic styrene-like substrates (**18**) and (**19**), which suffer from rotational restriction and are actually blocked in the *s-cis* and *s-trans* conformation, respectively (Scheme XI).[27] Of course, according to the typical regiochemistry of nitrile oxide cycloadditions to 1,2-disubstituted ethylenes,[28] two regioisomeric pathways were operative in the case of **18**. However, in harmony with the above assumptions, all cycloadditions took place in a fully diastereoselective manner, thus providing a facile entry to the enantiomerically pure products (**20**, **21**, and **22**).



Entry	R	e.e.
a	OMe	63%
b	Me	>98%

Scheme X

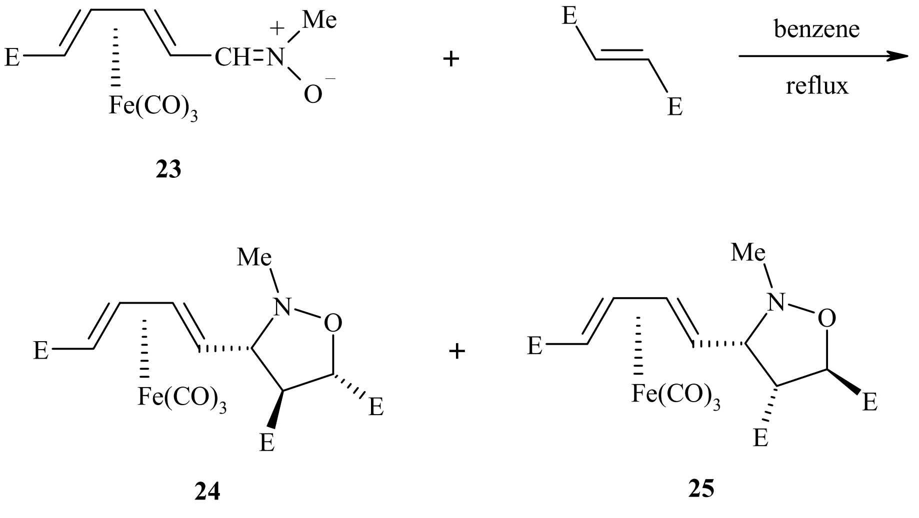


Scheme XI

Attempts to enhance the dipolarophilic reactivity of benzofuran and benzothiophene through tricarbonylchromium complexation were unsuccessful.[27] In fact, the complexes did not react at all with nitriloxide **17** and prolonged heating caused decomplexation. However, this result is not totally unexpected because the reaction times reported in the previously cited papers indicate that, as a general trend, the tricarbonyliron and tricarbonylchromium complexed dipolarophiles are usually less reactive than the corresponding uncomplexed species.

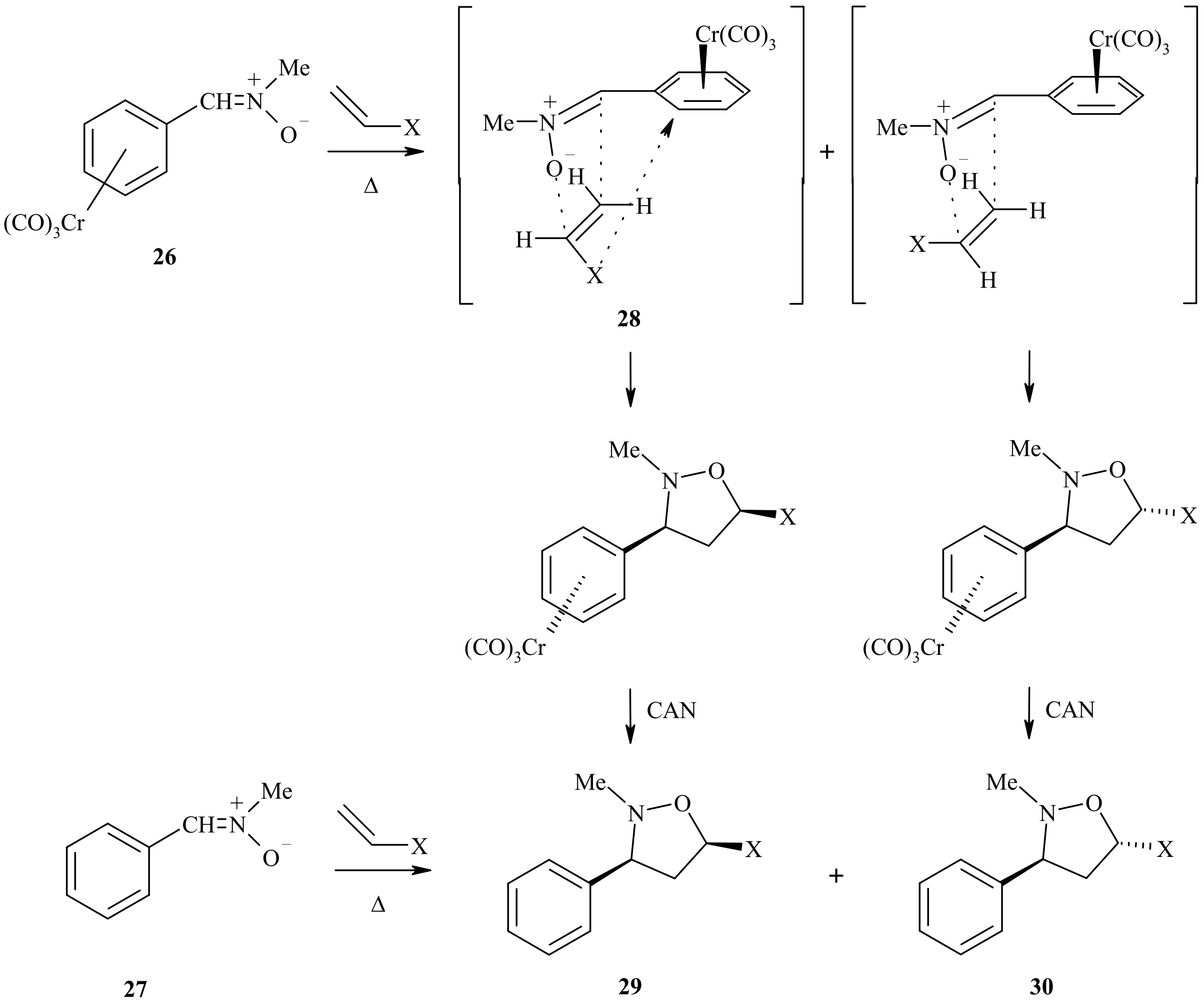
4. CYCLOADDITIONS OF TRICARBONYLIRON AND TRICARBONYLCHROMIUM COMPLEXED 1,3-DIPOLES

Several years ago, Grée *et al.* reported the synthesis of the tricarbonyliron complexed *C*-(butadienyl)-nitrone (**23**).[29] Its reaction with dimethyl fumarate gave a mixture of the two diastereoisomeric cycloadducts (**24**) and (**25**), the former being largely preferred (Scheme XII). More recently, Hanaoka's research group[30] described the behavior of the tricarbonylchromium complexed *C*-phenyl-*N*-methylnitrone (**26**) towards a series of monosubstituted ethylenes (Scheme XIII). A very striking feature is the stereochemical course of the cycloaddition resulting in *cis*-3,5-disubstituted isoxazolidines as exclusive or greatly predominant products, at variance with that observed in the reaction of the uncomplexed nitrone (**27**) with the same dipolarophiles. The authors have tentatively explained the experimental findings on invoking, as stabilizing factor of the *endo*-type transition state (**28**), an attractive interaction between the (usually electron-rich) X substituent and the electron-poor complexed benzene nucleus. Of course, it cannot be so for the uncomplexed nitrone (**27**). The use of both enantiomers of **26** allowed preparation of (+)-**29a,c** and (-)-**29a,c**.



E = COOMe

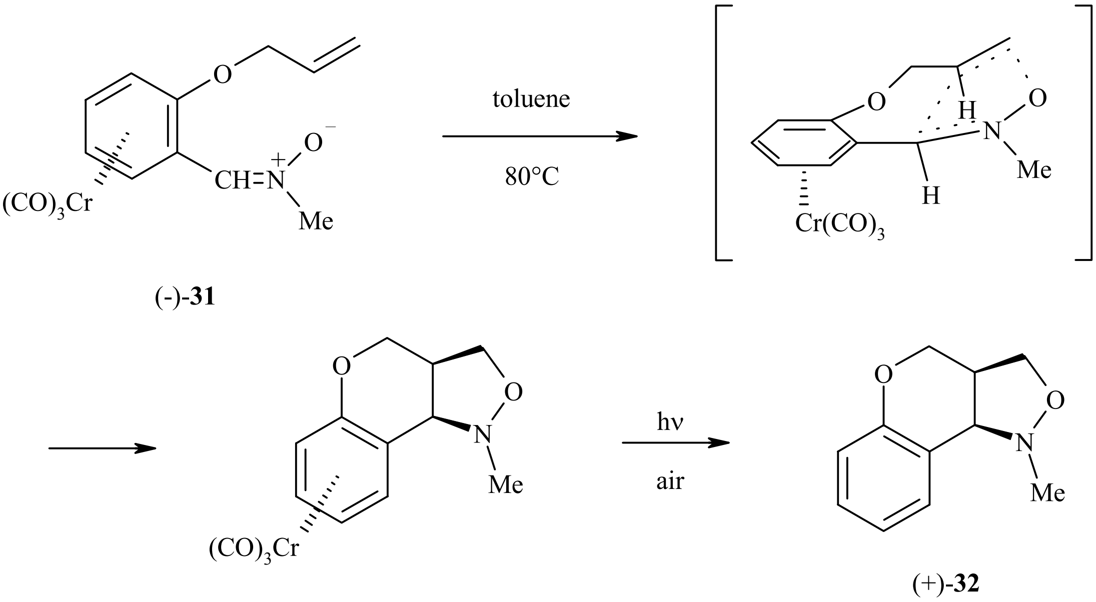
Scheme XII



Entry	Nitrone	X	**29** : **30**
a	**26**	Ph	>98:2
b	**27**	Ph	69:31
c	**26**	OEt	>98:2
d	**27**	OEt	46:54
e	**26**	OAc	>98:2
f	**27**	OAc	67:33
g	**26**	TMS	80:20
h	**27**	TMS	40:60

Scheme XIII

We have thought to insert in this paragraph a unique case of intramolecular cycloaddition by the tricarbonylchromium complex (in racemic and enantiopure form) of *C*-(2-allyloxyphenyl)-*N*-methylnitrone (**31**) (Scheme XIV).[31] As supported by others reports,[32,33] the intramolecular cycloaddition of *C*-(2-allyloxyphenyl)nitrones can only proceed, due to geometric constraints, on the *Z* dipole configuration with the allyl moiety oriented towards the inner of the molecule. Within this model, in the case of **31**, the tricarbonylchromium tripod forces the dipolarophilic л bond to attack the *anti* (i.e. *re*) face of the dipole, thus dictating the absolute stereochemistry observed experimentally. One should note that the illustrated syntheses of **29**, **30**, and **32** constitute paradigmatic examples of the use of the tricarbonylchromium group as chiral auxiliary.

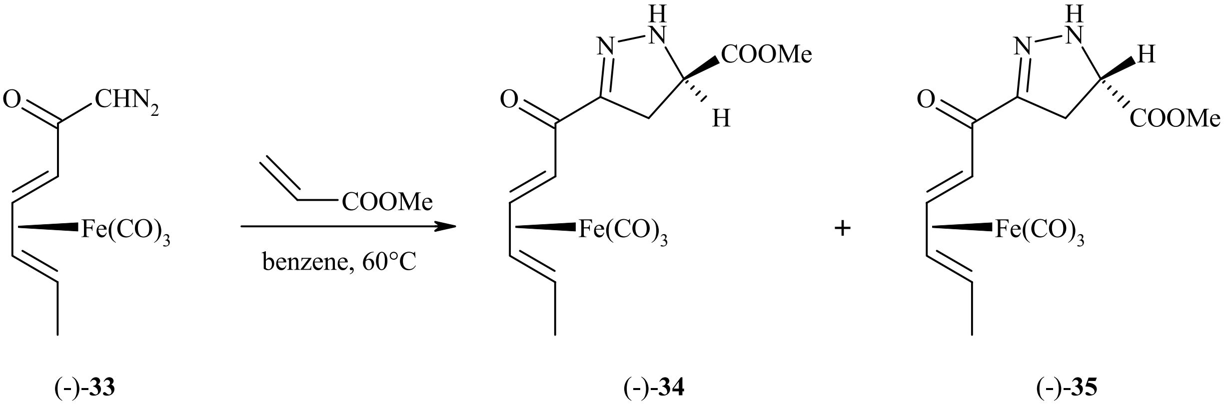


(-)-**31**

(+)-**32**

Scheme XIV

A report is available dealing with enantiopure tricarbonyliron complexes of unsaturated diazoalkanes.[34] Actually, they cycloadd to methyl acrylate with no diastereoselectivity (Scheme XV).



(-)-**33**

(-)-**34**

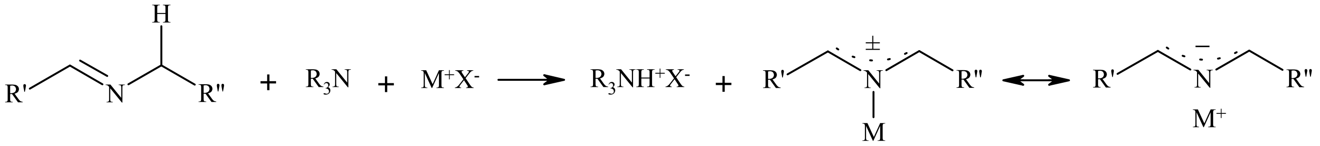
(-)-**35**

(1:1 mixture)

Scheme XV

5. CYCLOADDITIONS OF *N*-METALLO-AZOMETHINYLIDES

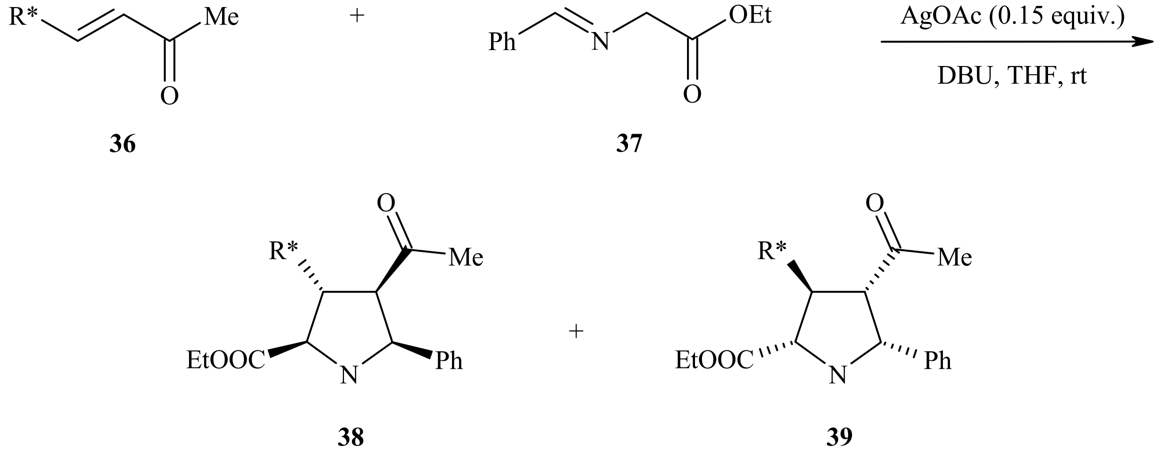
Azomethinylides are long-known 1,3-dipoles whose cycloadditions to ethylenes and acetylenes are characterized by the formation of two carbon-carbon bonds. In the last twenty years, there has been an increasing interest towards *N*-metallo-azomethinylides.[35,36] These species, which could formally be seen as salts of 2-azaallyl anions rather than true 1,3-dipoles, are exploited as synthetic equivalents of the elusive *N*-unsubstituted azomethinylides. They are formed upon α-deprotonation of aldimines (bearing an appropriate α-substituent) which can be accomplished by metal alkoxides and amides or by mixtures of a tertiary amine and a metal salt. The latter procedure, illustrated in Scheme XVI, has became the most common one and an impressive array of combinations have been explored with variable results.[35-50] Chelation of the metal by a proper functional group linked to the dipole normally reduces the rotational flexibility of the molecule and therefore can improve the facial discrimination, thus favoring high stereoselectivities. The achievement of the same target can also be facilitated if additional coordination of the metal occurs by means of the dipolarophile. In this context, the bulkness of the metal cation and its coordination number play a determinant role. Among metals of main groups, lithium is typically employed. Conversely, several transition metals have been proven effective, i.e. Ag(I), Cu(II), Zn(II), Tl(I), Ti(IV), Mn(II), Co(II), Ni(II). In reality, silver salts are mostly used. It remains to be stressed that, for the in situ generation of metallo-azomethinylides, the presence of a stoichiometric amount of the metal species does not constitute a stringent requisite. Successful efforts have been made to develop valuable catalytic procedures.

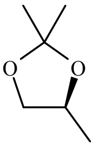
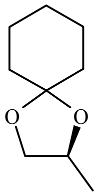
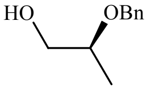
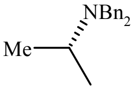
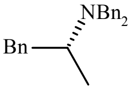


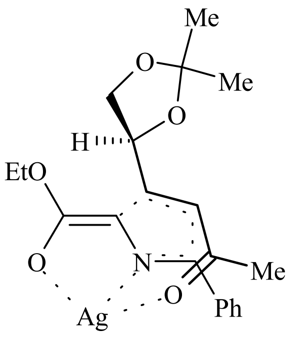
Scheme XVI

The brilliant Pätzel's contribution in this field was aimed at the synthesis of the optically active, polyfunctionalized pyrrolidines (**38**) (Scheme XVII).[38] Enantiopure α,β-unsaturated ketones (**36**), bearing an allylic stereocenter, were used as dipolarophiles towards metallo-azomethinylides derived from *N*-(benzylidene)glycine ester (**37**). Silver acetate was the catalyst of choice as determining a practically complete diastereoselectivity. Significantly, in terms of yield as well as of diastereoisomeric ratio, lithium bromide gave satisfactory results only at –78 °C, but not at room temperature. The rationalization of the observed stereochemical outcome is far from being simple. The authors have suggested the transition states (**40**) and (**41**), both of which has the bulky chiral pendant *anti* with respect to the incoming dipole. However, the conformational arrangement of the stereocentre is different in the two cases because of the known stereoelettronic preference of allylic alkoxy functionalities to occupy the inside position.

Schemes XVIII and XIX illustrate two leading reports due to Grigg's laboratory. They describe the cycloadditions of a variety of metallo-azomethinylides (derived from aryl, heteroaryl, and alkyl aldimines) onto chiral acyclic[41] and cyclic[43] dipolarophiles. Silver salts exerted in general a more efficient and selective effect than lithium bromide, but a few exceptions were observed; they were attributed to unfavourable steric distortion of the transition state when using the larger silver cation. Although acetonitrile was mostly employed as solvent, in certain cases better results were obtained in toluene. It is plausible that poorly dissociating solvents disfavor the *anti* unchelated form of the metallo-dipole (**43**), whose cycloaddition would suffer from modest facial discrimination in comparison to the *syn* chelated form (**42**). As Scheme XIX is concerned, the stereochemistry of the cycloadducts (**45**) harmonizes with *(i)* the exclusive attack of the metallo-dipole to the dipolarophilic face opposite to the isopropoxy group and *(ii)* the intermediacy of the *E,E-endo*-transition state (**44**) stabilized by way of chelation. An attractive interaction between the R group and the lactam carbonyl does not seem a stringent requisite since the stereochemical outcome was the same irrespective to the aryl or alkyl nature of R.



R*					
Yield (%)	90	96	78	88	94
38:**39**	95:5	92:8	>95:5	>95:5	>95:5



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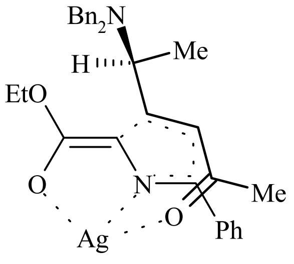

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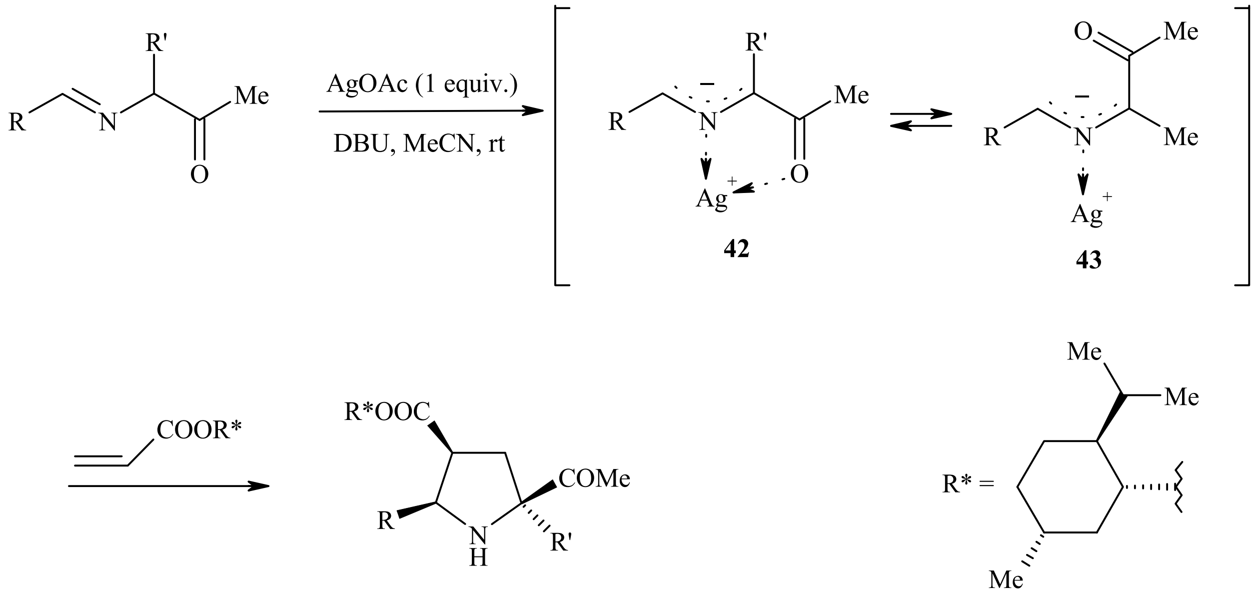
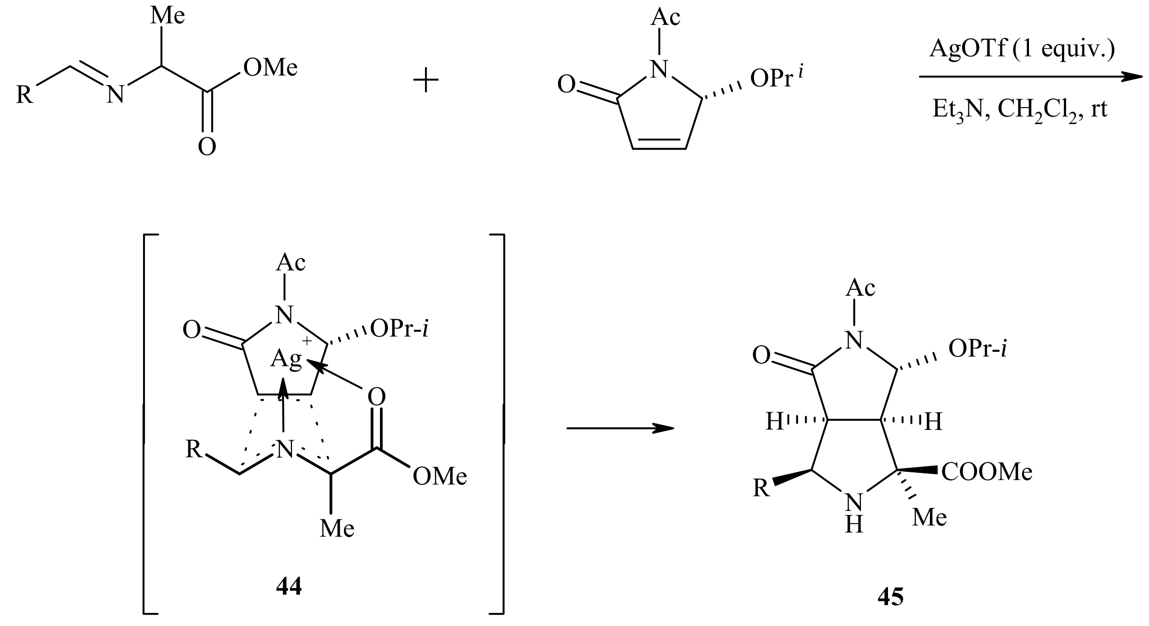
Scheme XVII



R	R'	Yield (%)
Ph	Me	63
2-Naphthyl	Me	72
3-Pyridyl	Bn	76

Scheme XVIII

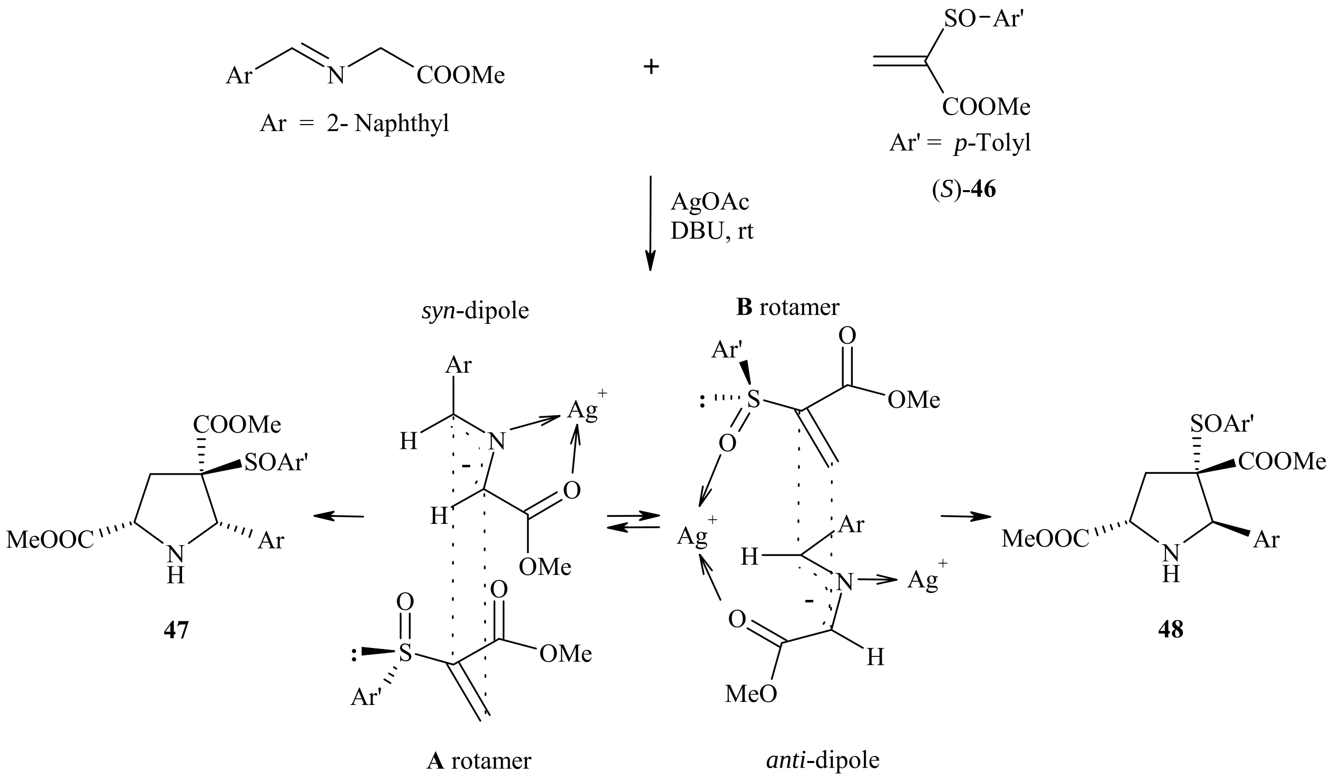


R = 2-napththyl, cyclohexyl

Scheme XIX

Other reports by Grigg and coworkers are concerned with the application of the metallo-azomethinylide methodology to the synthesis of 4-(5'-pyrrolidinyl)-β-lactams[51] and of alkaloid-like indole derivatives.[52] A recent, interesting paper of the same research group describes metallo-azomethinylide cycloadditions under solid-liquid phase-transfer conditions in the presence of substoichiometric amounts of silver acetate and potassium hydroxide.[49] Electron-poor ethylenic dipolarophiles were reacted with azomethinylides derived from *N*-benzylideneglycine and alanine esters. Other inorganic bases, i.e. LiOH, NaOH, CsOH, and K_2CO_3, gave less satisfactory results in terms of chemoselectivity (Michael adducts are concurrent products) as well as of diastereoselectivity. An analogous negative trend was observed on going from apolar to polar solvents.

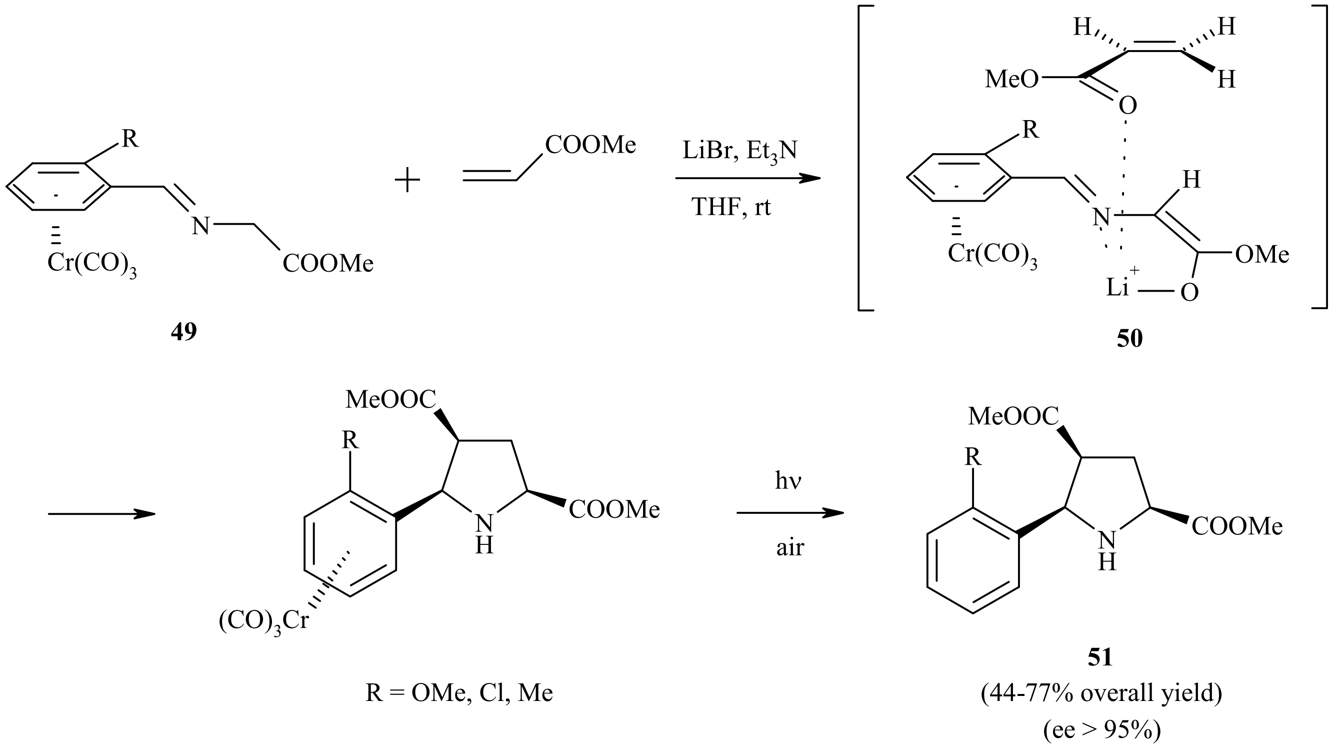
The first cycloaddition of metallo-azomethinylides to an enantiopure vinyl sulfoxide (**46**) has been recently reported.[50] While silver acetate was once again the metal salt of choice, a dramatic difference was observed between tetrahydrofuran and acetonitrile as solvent. The latter, less associating medium required a larger amount of salt and determined a reversed stereopreference in comparison to THF. Scheme XX illustrates the experimental findings and the rationale proposed by the authors.



Solvent	AgOAc (equiv.)	DBU (equiv.)	Yield (%)	
			47	**48**
THF	0.15	1.2	21	56
MeCN	1.5	1.0	51	12

Scheme XX

Finally, we mention a paper of Kündig and *et al.*[53] who studied the peculiar lithium azomethinylides (**49**) bearing a tricarbonylchromium complexed phenyl group (Scheme XXI). According to the presumed arrangement (**50**), concomitant chelation by lithium and facial discrimination by chromium promoted a highly diastereoselective cycloaddition, by which the nonracemic pyrrolidines (**51**) were ultimately obtained.



Scheme XXI

6. TRANSITION METAL ASSISTED CYCLOADDITIONS OF NITRONES

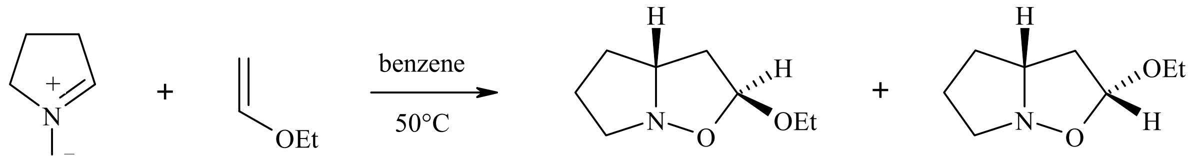
Nitrone cycloadditions to alkenes are endowed with an astonishingly versatile potential in organic syntheses, principally because the resulting isoxazolidine ring can undergo an easy cleavage of the C-N bond to form 1,3-bifunctional open-chain molecules. An impressive array of natural and unnatural complex structures have been attained in such way.[3,28,54,55] Metal assisted cycloadditions of nitrones are the object of extensive investigation since several years and conspicous progresses have been made in going from stoichiometric to catalytic methodologies. Two consecutive, lucid surveys of the literature data on this matter are available.[56] Hence, our argument in this paragraph will be very concise.

6.1 Intermolecular cycloadditions

6.1.1 Enol ethers as dipolarophiles

Altough enol ethers are generally good dipolarophiles, they are reluctant to react with 1,3-dipoles characterized by a high-lying HOMO. This is often true in the case of nitrones due to the electrondonating effect of the *N*-substituent. Consequently, coordination of the nitrone oxygen by a Lewis acid can facilitate the cycloaddition to enol ethers. A theoretical study on this point has recently appeared.[57] As transition metals are concerned, a few experimental data are available.[58-62]

A Spanish research group[58] has reported that several Ti(IV) derivatives exerted an accelerating effect on the cycloaddition of cyclic and acyclic nitrones to enol ethers. Furthermore, the stereochemistry of the reaction was influenced by the ligands at the metal centre (Scheme XXII). Since NMR studies indicated a more effective nitrone complexation by $TiCl_4$ and $TiCl_2(i\text{-}PrO)_2$ with respect to $Ti(i\text{-}PrO)_4$, one may deduce that the *endo* transition state leading to **53** benefits from chelation at the metal center by the oxygen atoms of both dipole and dipolarophile.

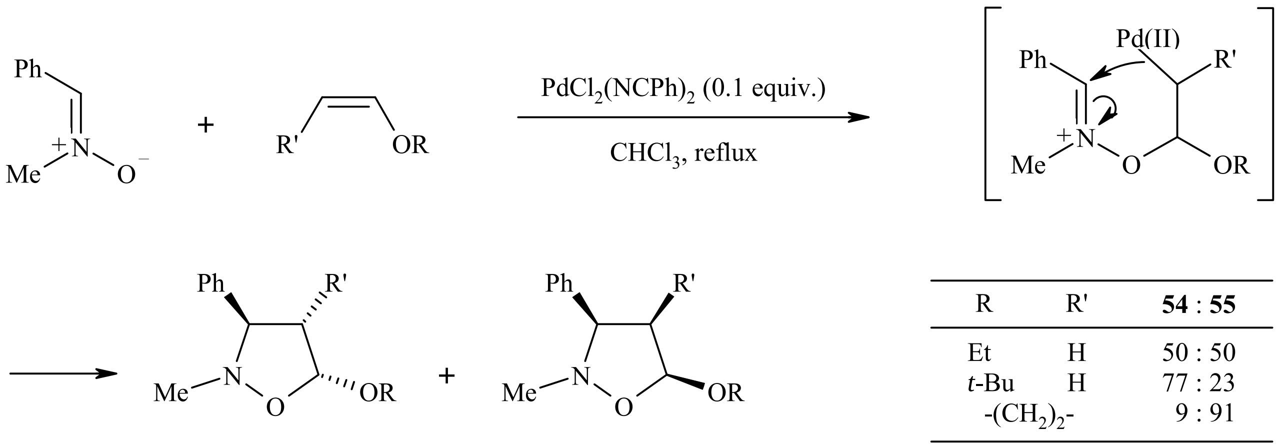


52 **53**

Catalyst	Time	**52** : **53**
none	7 days	10 : 1
$Ti(i\text{-}PrO)_4$	4 days	10 : 1
$Ti(i\text{-}PrO)_2Cl_2$	21 h	2 : 1
$TiCl_4$	7.5 h	2 : 1

Scheme XXII

On reasoning that soft Lewis acids such as metal cations of the late transition groups could have been more suitable to facilitate nitrone cycloadditions to electron-rich alkenes, Furukawa *et al.* tested the effectiveness of palladium(II) catalysts, among which bis(benzonitrile)palladium dichloride showed the best activity (Scheme XXIII).[59] However, a good diastereoselectivity was found only in the case of cyclic dipolarophiles. A multistep mechanism has been proposed.

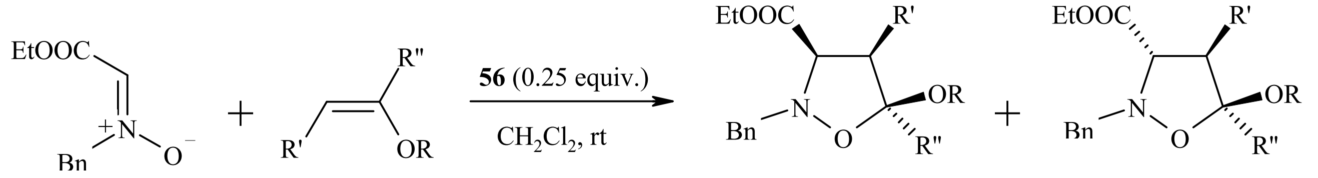


54 **55**

R	R'	**54** : **55**
Et	H	50 : 50
t-Bu	H	77 : 23
$-(CH_2)_2-$		9 : 91

Scheme XXIII

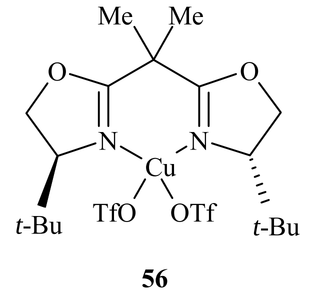
An interesting contribution by Jørgensen's laboratory deals with nitrone cycloadditions to enol ethers in the presence of various copper(II) and zinc(II) salts coordinated with chiral bisoxazoline ligands.[61] In terms of both reactivity and selectivity, the former ones gave the most valuable results; analogously to what already known for Cu(II)-bisoxazoline catalyzed Diels-Alder reactions,[63] a marked influence of the solvent was operative on rate, yield, and stereoselectivity. A few significant results are illustrated in Scheme XXIV. In the case of ethyl vinyl ether, the authors have tentatively conceived the intervention of the pentacoordinated transition state (**59**), where the chelated nitrone lies in the equatorial plane, whilst the ethereal oxygen occupies an axial position. Consequently, the dipolarophile should approach the *re*-face of the dipole in an *endo*-selective fashion. However, the mechanistic question is still open, particularly for the other substrates.



57

58

R	R'	R''	**57 : 58** (ee in parentheses)
Et	H	H	77(89%) : 23(35%)
Me	H	Me	31(90%) : 69(94%)
- $(CH_2)_2$ -		H	50(12%) : 50(0%)



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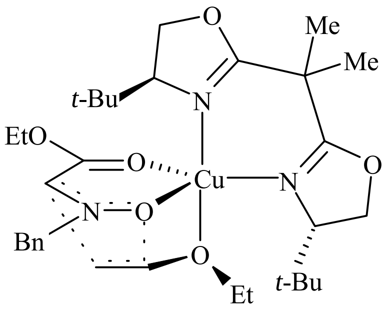
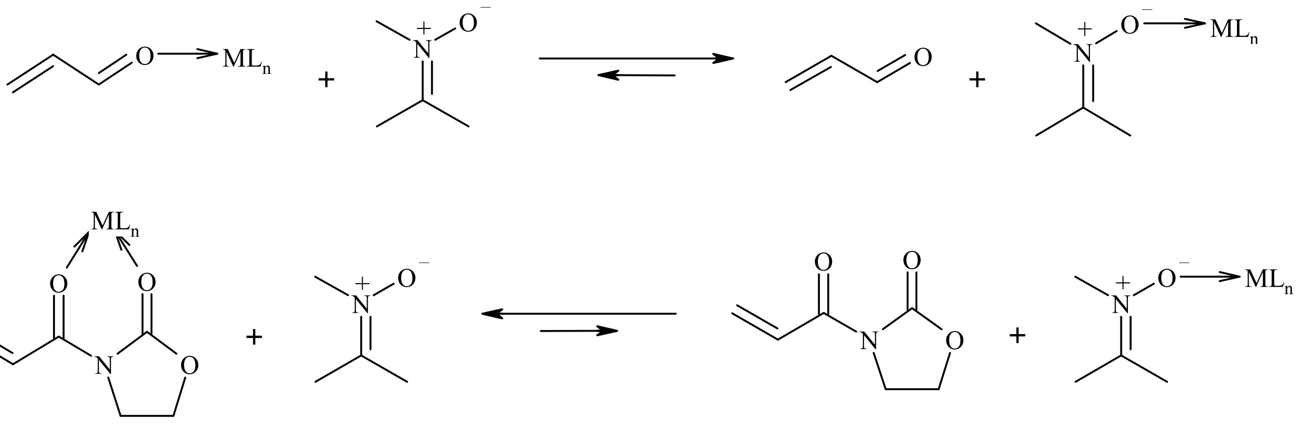


59

Scheme XXIV

6.1.2. α,β-Unsaturated carbonyl compounds as dipolarophiles

Metal assisted cycloadditions of nitrones to α,β-unsaturated carbonyl compounds offer a subtle scenario. In fact, the metal coordination occurs competitively at the carbonyl and at the nitrone oxygen. The former one is favorable because α,β-unsaturated carbonyl compounds, unlike enol ethers, are electron-deficient alkenes and the HOMO(dipole)-LUMO(dipolarophile) interaction is dominant in their cycloadditions. On the other hand, the coordinated nitrone suffers from reduced reactivity. Fortunately, the carbonyl coordination is largely preferred whenever an adjacent functionality allows the formation of a chelated species. Actually, *N*-alkenoyl-1,3-oxazolidin-2-ones have became popular dipolarophiles as synthetic equivalents of α,β-unsaturated esters and amides in view of their propensity towards chelation by metal cations (Scheme XXV). The most extensive, systematic, and valuable work in this area is due to Jørgensen's laboratory. However, we think that the readers can easily find elsewhere[56] an exhaustive illustration of it and therefore we mention here a few selected contributions by other research groups.

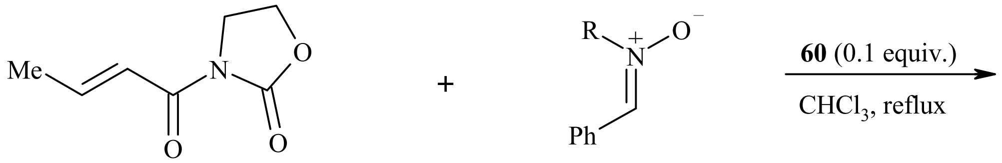


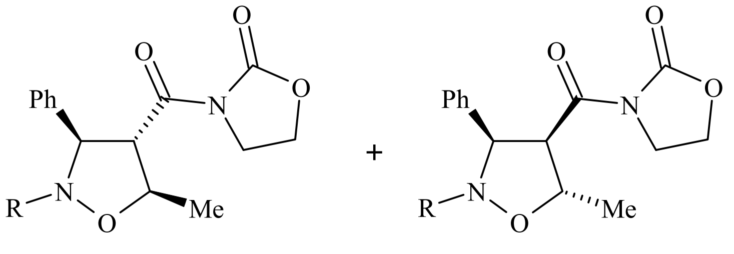
Scheme XXV

Furukawa *et al.*[64] described the use of chiral phosphinepalladium(II) catalysts in the reaction of 3-crotonoyl-1,3-oxazolidin-2-one with various nitrones. For instance, compound (**60**) furnished very good yields, but *endo/exo*- and enantio-selectivities ranged widely in dependence of the nitrone substituents (Scheme XXVI). On the basis of molecular modeling, the geometry depicted in formula **63** was inferred for the complexed dipolarophile, where the *si* face is less sterically hindered than the *re* face. Attack of the nitrone would occur preferably in the *endo* fashion when R = Me, Bn. On the contrary, when R = Ph, some repulsive interaction with a *p*-tolyl group would destabilize this mode of attack and consequently the *exo* transition state happens to be preferred.

Nichel(II) catalysts were investigated by two independent research groups.[65,66] As illustrated in Schemes XXVII and XXVIII, respectively, the results were astonishingly excellent from all points of view. It must be said that the catalytic species (**64**) and (**65**) are formed in situ upon treatment of the proper organic ligand with $Ni(ClO_4)_2 \cdot 6H_2O$.

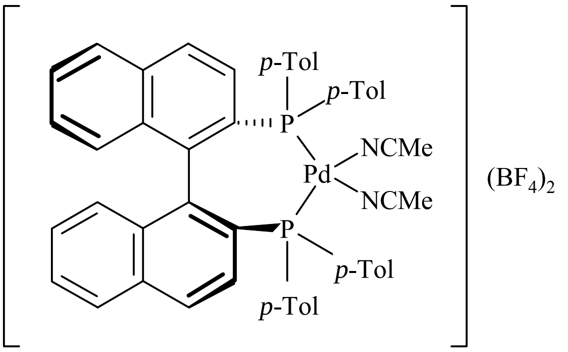
Several reports are concerned with nitrone cycloadditions to electron-poor alkenes in the presence of catalysts containing scandium, lantanium, and lantanides.[67-70] Zinc(II) salts were proven effective catalysts by an Italian research group.[71] The couple ZnI_2/BF_3 has been recently reported as the best choice to catalyze both the Michael addition of aldoximes and the subsequent cycloaddition of the so-formed nitrones.[72]





61 **62**

R	Overall yield (%)	**61 : 62** (ee in parentheses)
Me	89	60(91%) : 40(34%)
Bn	94	93(89%) : 7(93%)
Ph	94	28(54%) : 72(48%)



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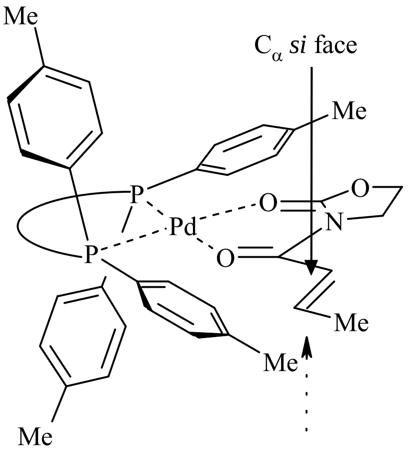

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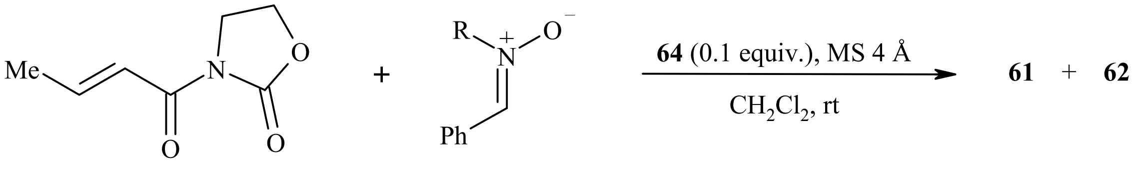
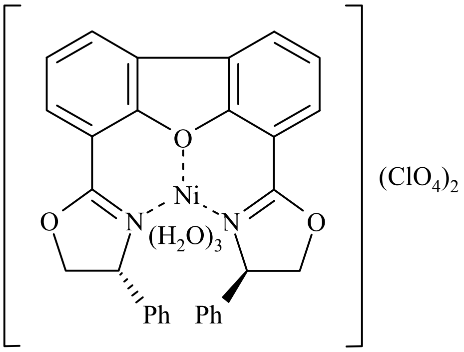
Scheme XXVI

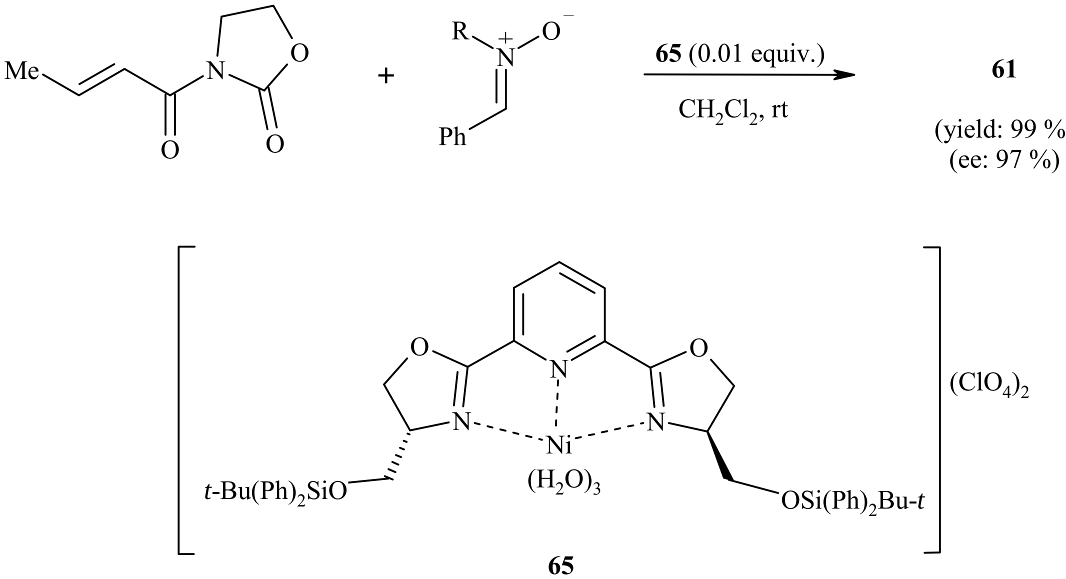




64

R	Overall yield (%)	**61 : 62**	ee of **61** (%)
Me	72	99 : 1	>99
Bn	76	98 : 2	>99
Ph	96	>99 : 1	95

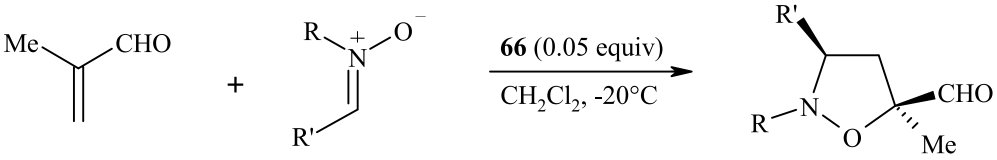
Scheme XXVII

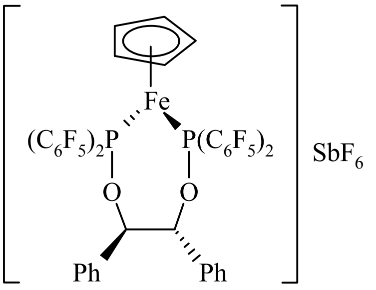


65

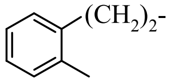
Scheme XXVIII

TiX_2-TADDOLates, amply and successfully employed in Jørgensen's laboratory[56] as homogeneous catalysts for nitrone cycloadditions to electron-poor alkenes, have been also applied in heterogeneous state, namely immobilized on silica gel[73] or bound to polymeric and dendrimeric backbones.[74] Although the catalytic performance was not better than that shown by the free molecule in solution, the easy recovery of such sophisticated and expensive catalyst offers a valid advantage from the practical point of view. A polymer-anchored, chiral crotonoyl derivative has been experienced as dipolarophile towards nitrones in the presence of $Sc(OTf)_3$.[75]





66

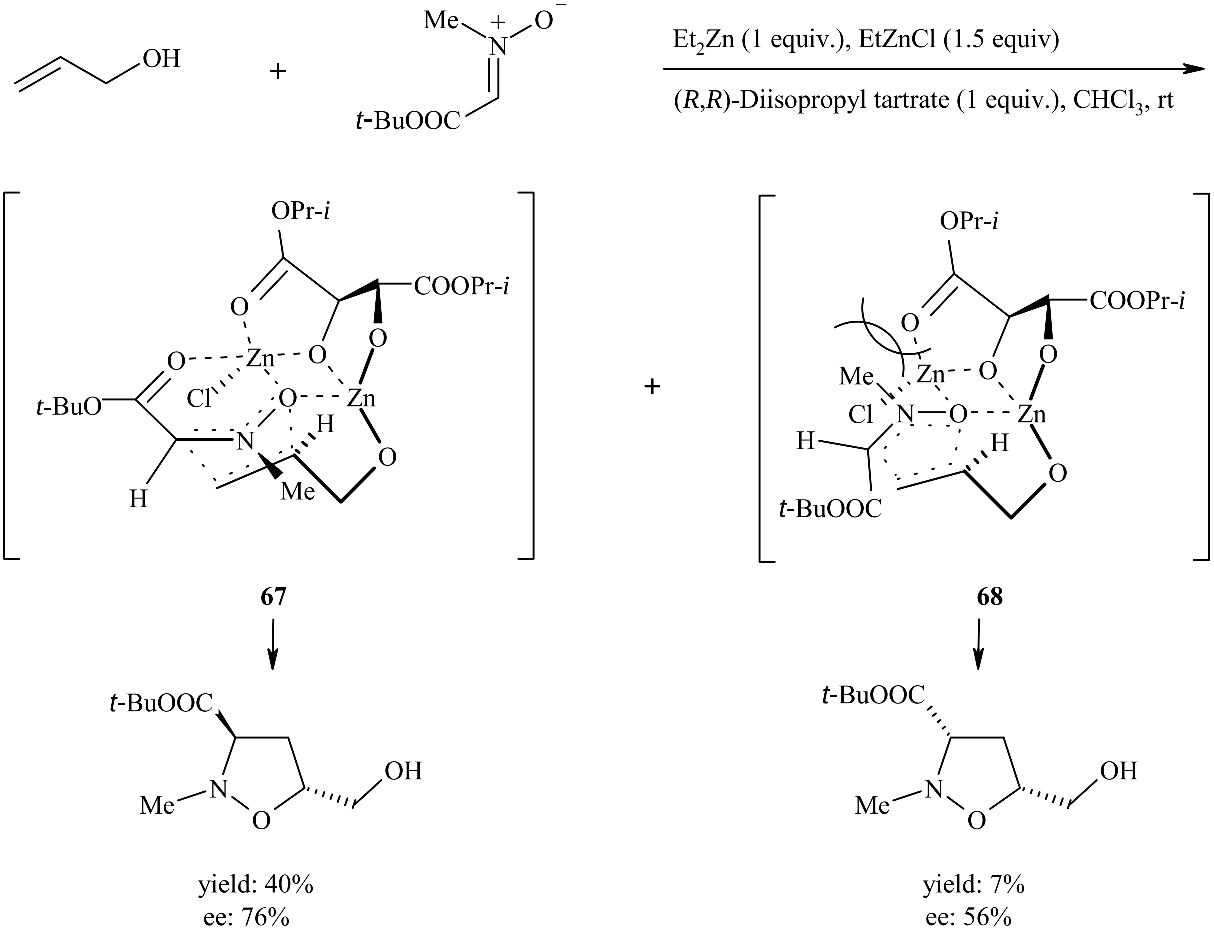
R, R'	Yield (%)	ee (%)
$-(CH_2)_3-$	92	96
$-(CH_2)_4-$	71	96
	71	94

Scheme XXIX

A recent report by Kündig *et al.* is noteworthy as describing highly stereoselective cycloadditions of cyclic nitrones to very simple 2-alkenals in the presence of enantiopure organoiron and organoruthenium catalysts (Scheme XXIX).[76] The first-formed complex between **66** and methacrolein was isolated and submitted to X-Ray analysis. The latter showed that *(i)* a single coordination site is present, *(ii)* the enal moiety has adopted the *s-trans* conformation, and *(iii)* the C_α-*si*-face of the dipolarophile is more prone towards an *endo*-like dipole approach. The inferior performance of ruthenium in comparison to iron catalysts was accounted for by a less stringent coordination due to both the weaker Lewis acidity and the larger catalytic site. The same kind of catalysts, though racemic, have been described almost simultaneously by another research group.[77]

6.1.3 Allylic alcohols as dipolarophiles

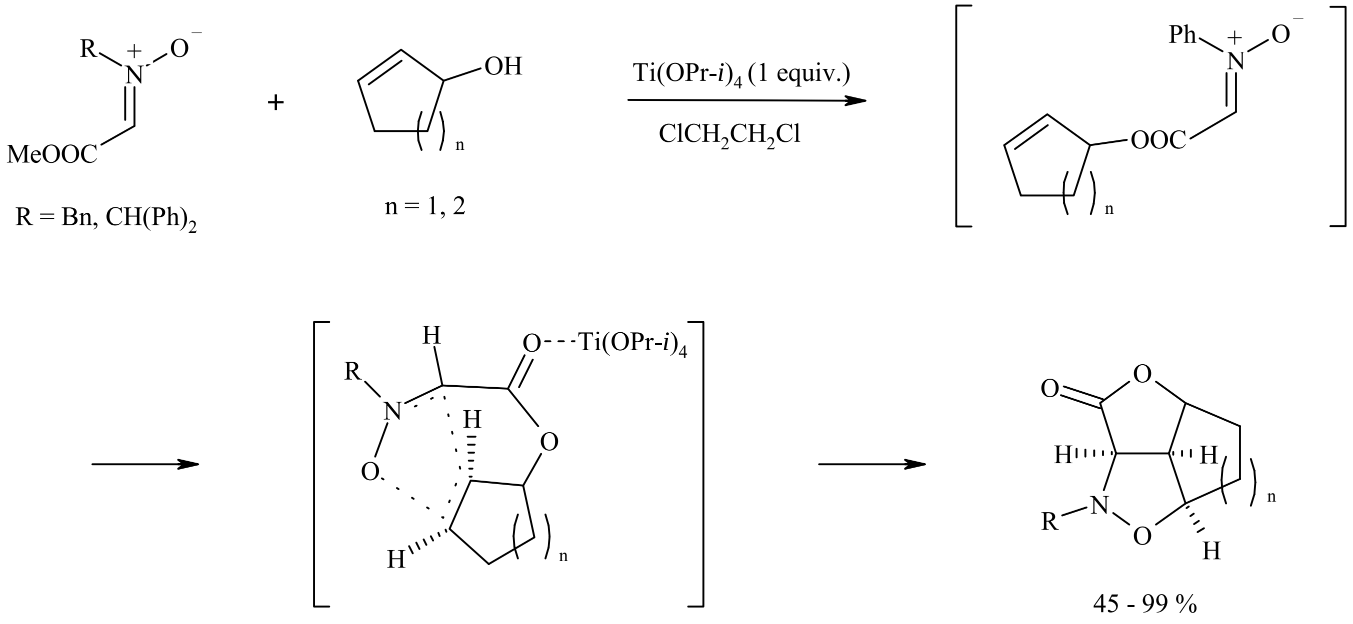
The dipolarophilic behavior of allylic alcohols is matter of investigation since long time. In order to increase the reactivity, to modify the regiochemistry, and to improve the steroselectivity, a few authors have done nitrone cycloadditions to allylic alcohols in the presence of metal cations suitable for complexation at the oxygen of either dipole or dipolarophile. Among transition metals, zinc(II) was the catalyst of choice.[78-80] The additional presence of a chiral chelating agent such as diisopropyl (*R,R*)-tartrate induced diastereo- and enantioselective nitrone cycloadditions to 2-propenol (Scheme XXX).[79] The authors have suggested competition between the bimetallic transition states *Z-endo* **67** and *Z-exo* **68**, the latter suffering from more intense steric repulsions.



Scheme XXX

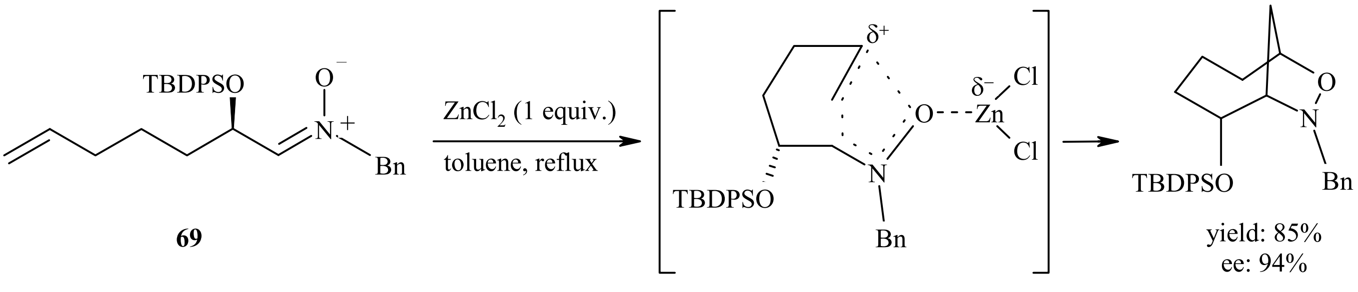
6.2 Intramolecular cycloadditions

Intramolecular nitrone cycloadditions intrinsically benefit from geometric constraints working in favor of high regio- and stereoselectivities. Perhaps for this reason, examples involving metal assistance are rare.[81-84] A pioneering contribution in this field is due to Tamura *et al.*, who submitted *C*-(methoxycarbonyl)nitrones to transesterification with 2-alkenols in the presence of titanium isopropoxide.[81] The so-formed unsaturated nitrones underwent spontaneously an intramolecular cycloaddition, which was fully diasteroselective thanks to the combined effects of intramolecularity and metal complexation (Scheme XXXI). Such methodology was subsequently employed for an asymmetric synthesis of the *N*-terminal aminoacid component of nikkomycin Bz.[82]



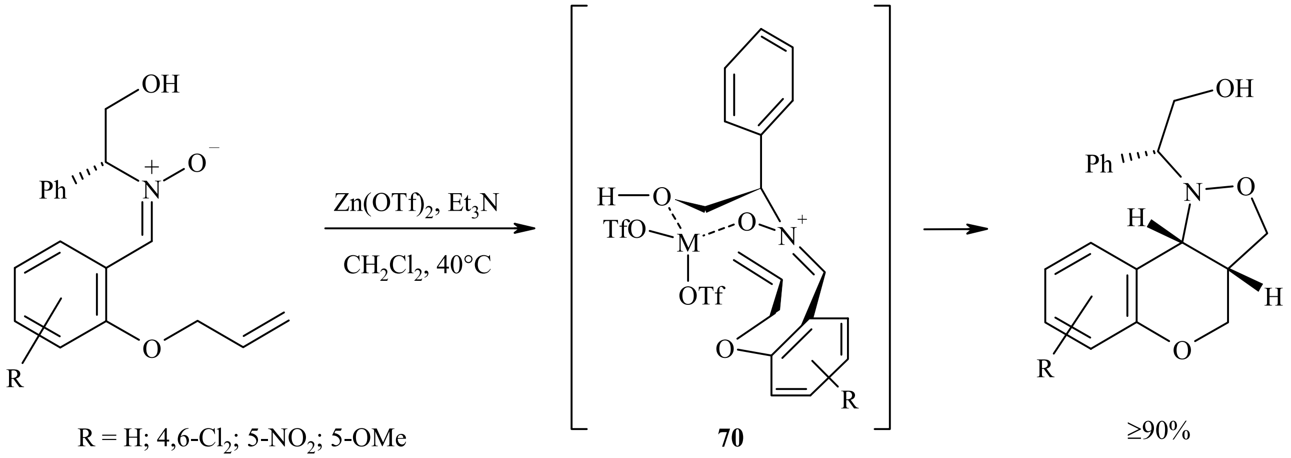
Scheme XXXI

Zinc dichloride was found effective (to a surprising extent) as activating, regiodirecting, and stereocontrolling tool in the intramolecular cycloaddition of the otherwise unreactive nitrone (**69**) (Scheme XXXII).[83] The observed regiopreference seems plausible if one thinks that metal complexation of the dipole may determine a rather asynchronous, although concerted, mechanism where the dipolarophilic site happens to assume some carbocationic character.



Scheme XXXII

The already known intramolecular cycloaddition of *C*-(2-allyloxyaryl)nitrones has been recently carried out in a diastereoselective fashion by a new procedure which profits from *(i)* a benzyl-like chiral auxiliary bearing an hydroxyl group and *(ii)* the presence of a zinc(II) salt (Scheme XXXIII).[84] Hence, the chelated species (**70**), lacking repulsive interactions, was probably involved to afford the observed diastereoisomer. Once again, a faster reaction took place in more polar solvents, but endowed with a poorer stereoselectivity. Interestingly, when R = 4-OMe, the presence of a Lewis acid shut down the reaction completely, reasonably because the HOMO(dipole)-LUMO(dipolarophile) interaction is the dominant one in this instance and therefore the coordination of the nitrone oxygen is deactivating.

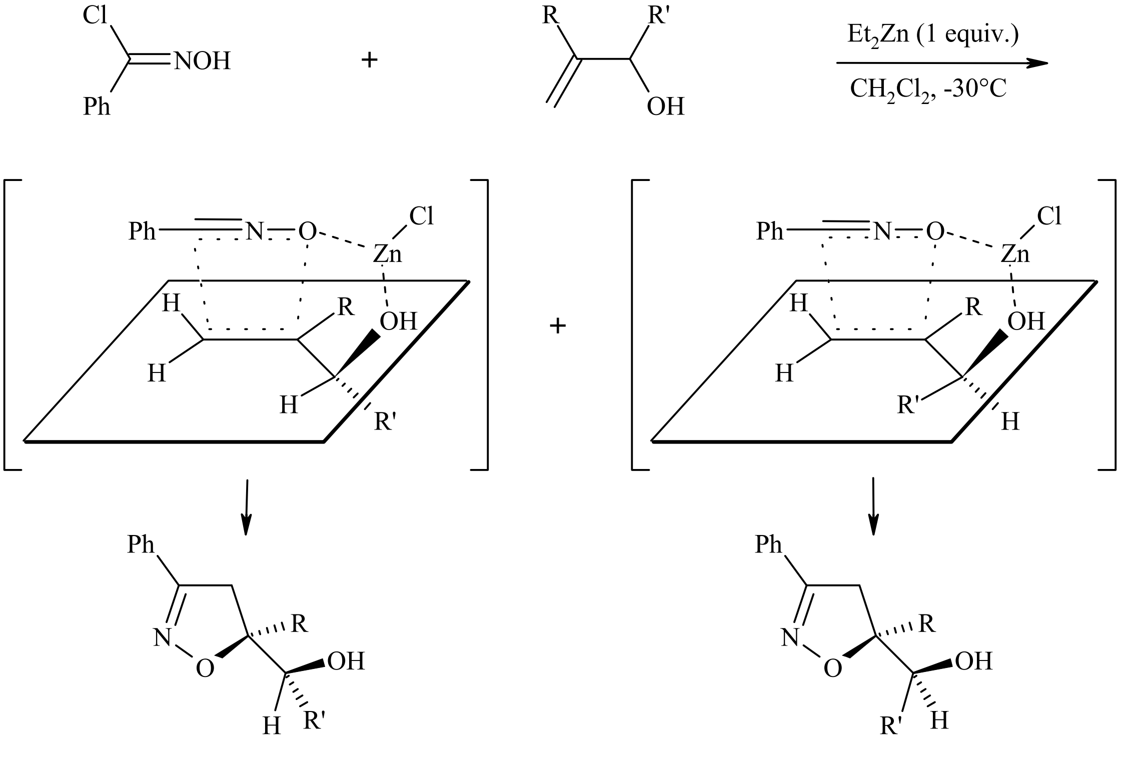


Scheme XXXIII

7. TRANSITION METAL ASSISTED CYCLOADDITIONS OF NITRILE OXIDES

Nitrile oxide cycloadditions to ethylenes produce 4,5-dihydroisoxazoles, which share with isoxazolidines the easy rupture of the C-N bond. Therefore, the so-called cycloadditive route to 1,3-bifunctional frameworks comprises both nitrone and nitriloxide cycloadditions.[3,55] However, metal assisted cycloadditions of nitrile oxides are less common than those of nitrones, possibly because the complexation process tends to have contradditory effects on the reactivity. The most of the available evidence is concerned with allyl alcohols as dipolarophiles.[85-88]

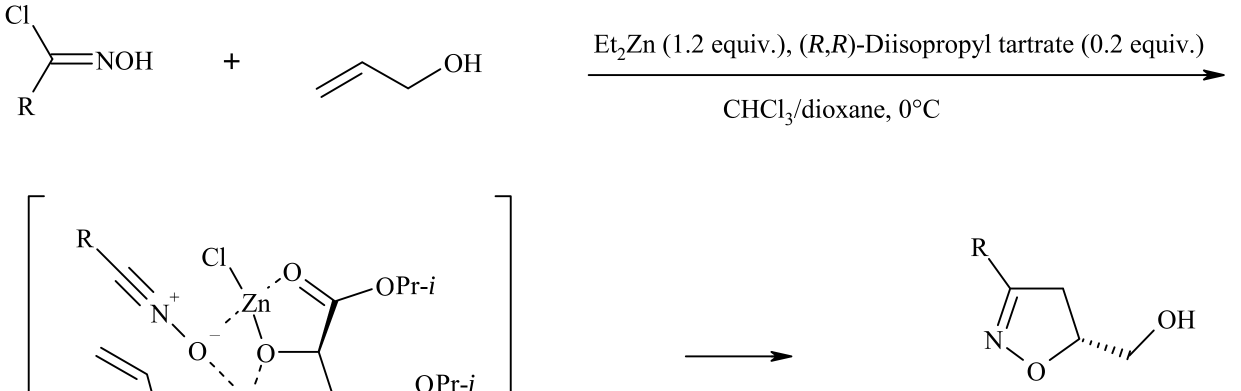
Among the variety of procedures for generating nitrile oxides, base treatment of *C*-chloro- or *C*-bromo-aldoximes is the most typical one. Kanemasa *et al.* first brought to light, when using organometallic bases in nitrile oxide cycloadditions to allyl alcohols, that the reaction outcome was influenced by the metal counterion. Enhanced diastereoselectivities were observed as a consequence of the simultaneous coordination of the oxygen atoms of dipole and dipolarophile (Scheme XXXIV).[85] The same strategy was developed and improved by Ukaji *et al.*, who used diethylzinc in the presence of the chiral organic ligand diisopropyl (*R,R*)-tartrate to promote asymmetric induction (Scheme XXXV).[86,87] Analogously to what depicted in Scheme XXX, a bimetallic aggregate was suggested as primary intermediate. An enantioselective synthesis of alkaloid lasubine II constitutes a brilliant application of Ukaji's methodology.[88]



71 **72**

R	R'	Overall yield (%)	**71 : 72**
H	Et	79	77 : 23
COOMe	Me	92	74 : 26

Scheme XXXIV

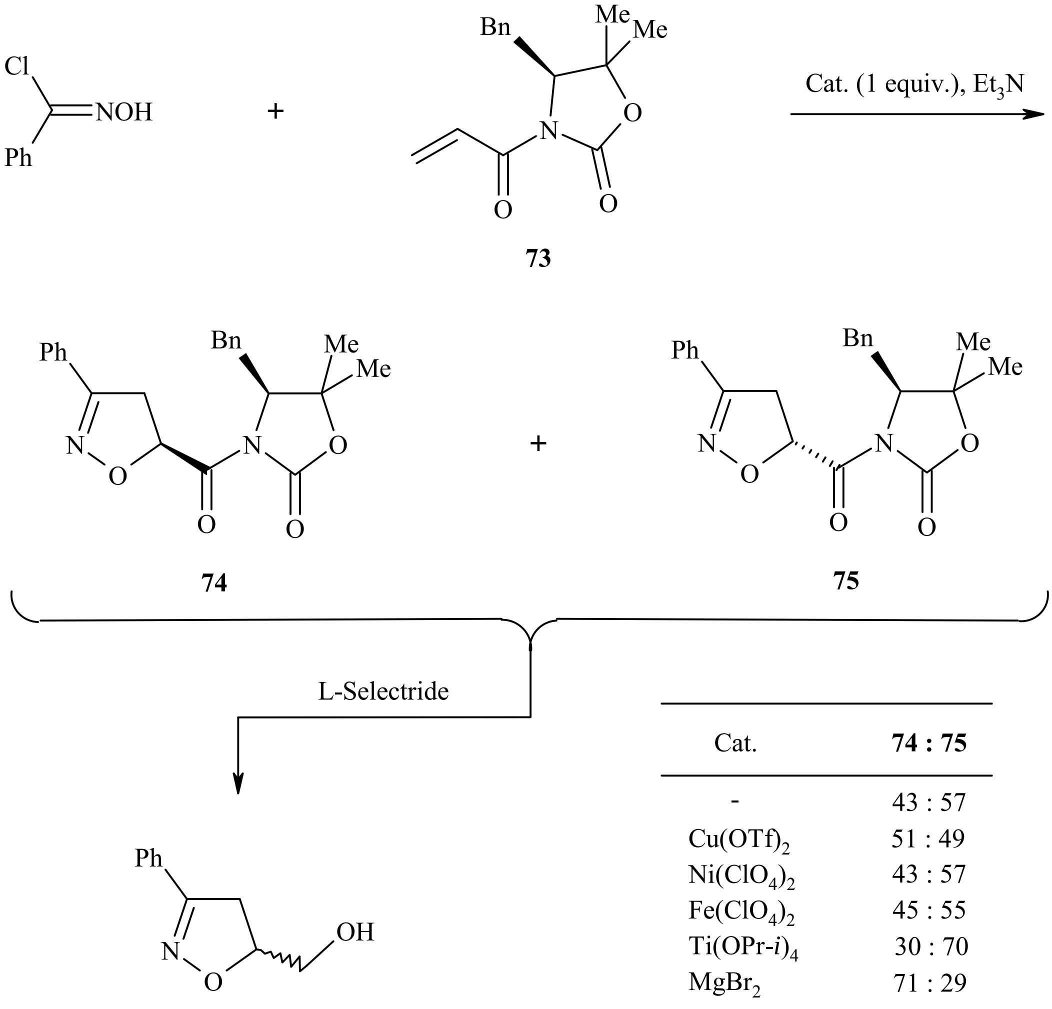


Yield: 62 - 91 %
ee: 84 - 93 %

R = Ph, 4-ClC_6H_4, *t*-Bu, $Me(CH_2)_6$

Scheme XXXV

Transition metal assisted cycloadditions of nitrile oxides to α,β-unsaturated carbonyl compounds have hitherto received little attention.[76,89] A noticeable study, recently published,[89] is focused to the influence of a large array of metal species on nitrile oxide cycloadditions to the chiral 3-acryloyl-1,3-oxazolidin-2-one (**73**) (Scheme XXXVI). The rather disappointing results do not find a sound rationale.



73

74

75

Cat.	**74 : 75**
-	43 : 57
$Cu(OTf)_2$	51 : 49
$Ni(ClO_4)_2$	43 : 57
$Fe(ClO_4)_2$	45 : 55
$Ti(OPr\text{-}i)_4$	30 : 70
$MgBr_2$	71 : 29

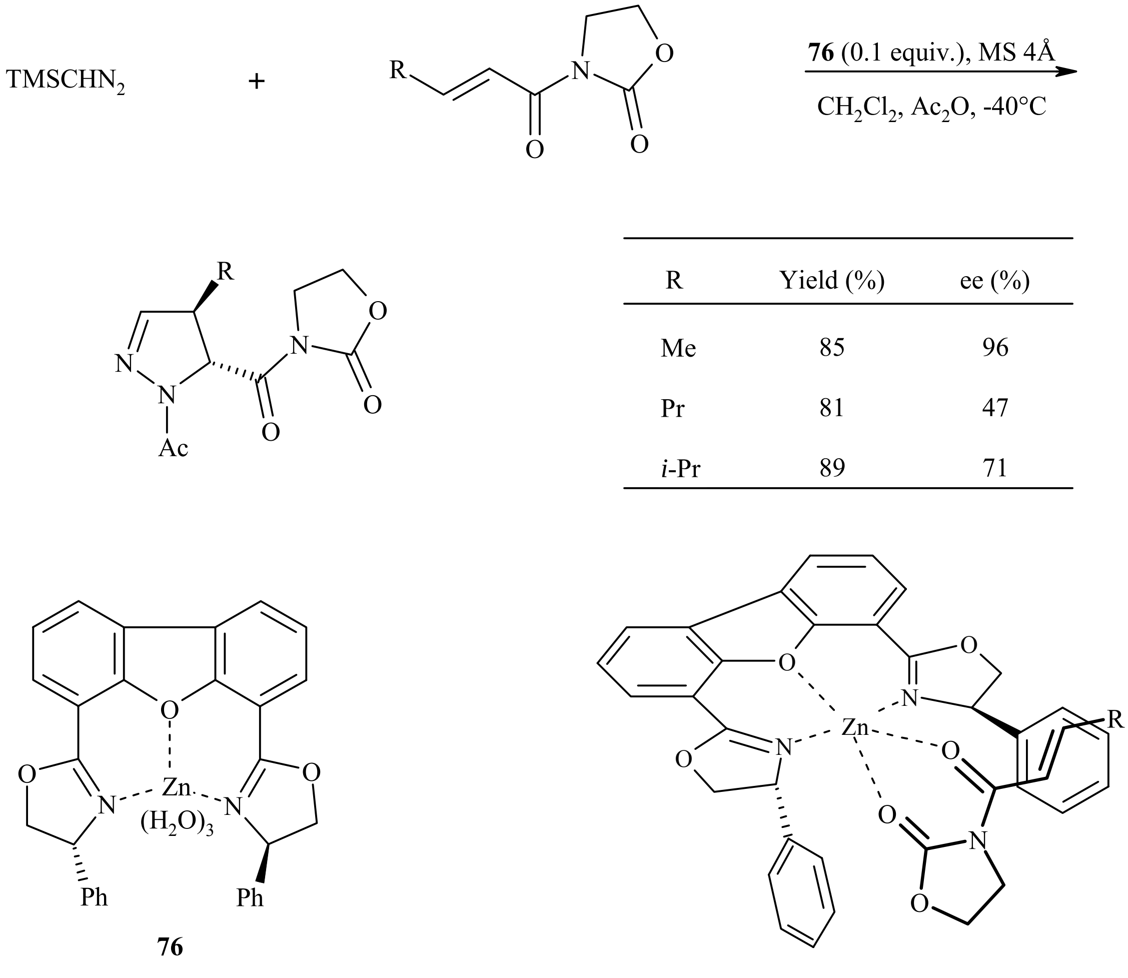
Scheme XXXVI

7. MISCELLANEA AND CONCLUSION

7.1 Transition metal assisted cycloadditions of diazoalkanes

The dipolarophilic behavior of transition metal complexed *N*-alkenoyl-1,3-oxazolidin-2-ones has been also explored towards trimethylsilyldiazomethane. The latter compound is attracting an increasing attention as synthetic equivalent of the less handlable diazomethane.[90] Scheme XXXVII illustrates the interesting results obtained by Kanemasa and Kanai by using a zinc(II) salt in the presence of the chiral organic ligand (**76**).[91] The authors have proposed the intervention of the complexed species (**77**), where the C_α-*si*-enantioface of the dipolarophile suffers from a shielding effect by one phenyl of the ligand.

However, the facial discrimination becomes as poorer as a bulkier R substituent forces the phenyl group away from the dipolarophilic site.



R	Yield (%)	ee (%)
Me	85	96
Pr	81	47
i-Pr	89	71

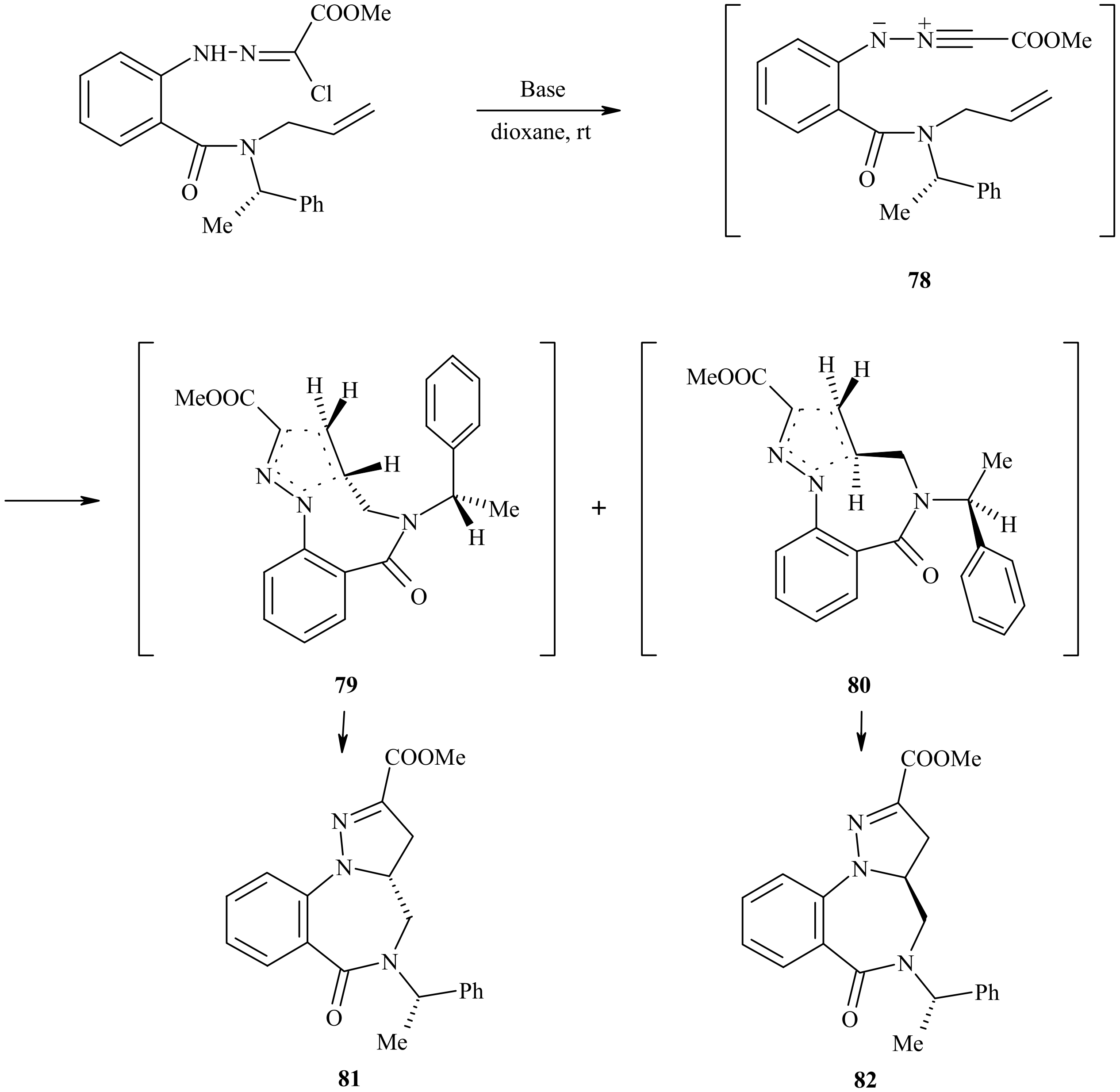
76

77

Scheme XXXVII

7.2 Silver(I) assisted cycloadditions of nitrilimines

Among the several procedures for the in situ generation of nitrile imines,[92] dehydrohalogenation of hydrazonyl halides is the most general one. It can be accomplished by way of either tertiary amines or anionic bases such as carbonates and acetates. The use of silver(I) carbonate to this end was firstly reported by Padwa and Nahm.[93] Late on, the same species was amply employed by an Italian research group.[94-96] As a general trend, in comparison to more conventional bases, milder conditions were required and better yields were obtained. Other interesting differences were observed. In some cases, particularly in the presence of poor dipolarophiles, silver carbonate favored a carbocationic rather than a dipolar behavior of the nitrile imine intermediates.[95] However, in the present context, it must be emphasized the reversal of diastereopreference in the intramolecular cycloaddition of the enantiopure nitrile imine (**78**) on going from Et_3N to Ag_2CO_3 (Scheme XXXVIII).[96] A theoretical study of the diastereoisomeric transition states (**79**) and (**80**) showed that the latter, having the phenyl pendant disposed externally and reflecting the absolute configuration of **82**, is more stable. This is just in harmony with the outcome experimentally found when using triethylamine. In view of the ability of silver cation to be coordinated by either lone electron pairs or π electronic clouds, one may assume that **79**, having the phenyl pendant oriented inside and reflecting the absolute configuration of **81**, might benefit from metal chelation. However, as a conclusion of this paragraph, we wish to underline that the role of silver(I) in nitrilimine cycloadditions is far from being elucidated and a deeper investigation should be hopefully performed.

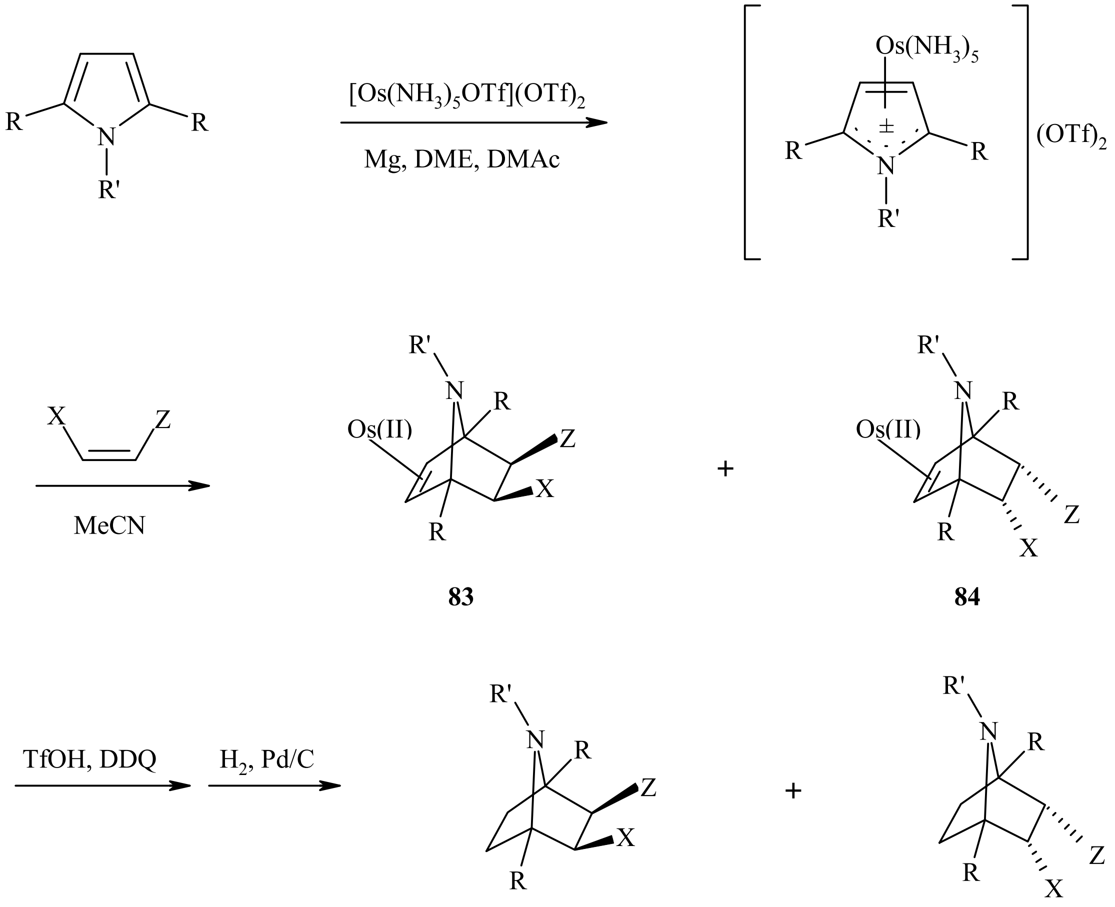


Base (equiv.)	**81** (% yield)	**82** (% yield)
Ag_2CO_3 (2)	60	26
Et_3N (5)	32	59

Scheme XXXVIII

7.3 Osmium(II) complexed pyrroles as masked azomethinylides

The pyrrole nucleus is susceptible to complexation by osmium(II) derivatives at the C3-C4 position. The uncoordinated portion of the resulting η^2-complex can behave as an azomethinylide towards electron-poor alkenes. By way of this methodology, Harman *et al.* developed a useful entry to a variety of 7-azanorbornanes analogs of the alkaloid epibatidine (Scheme XXXIX).[97]

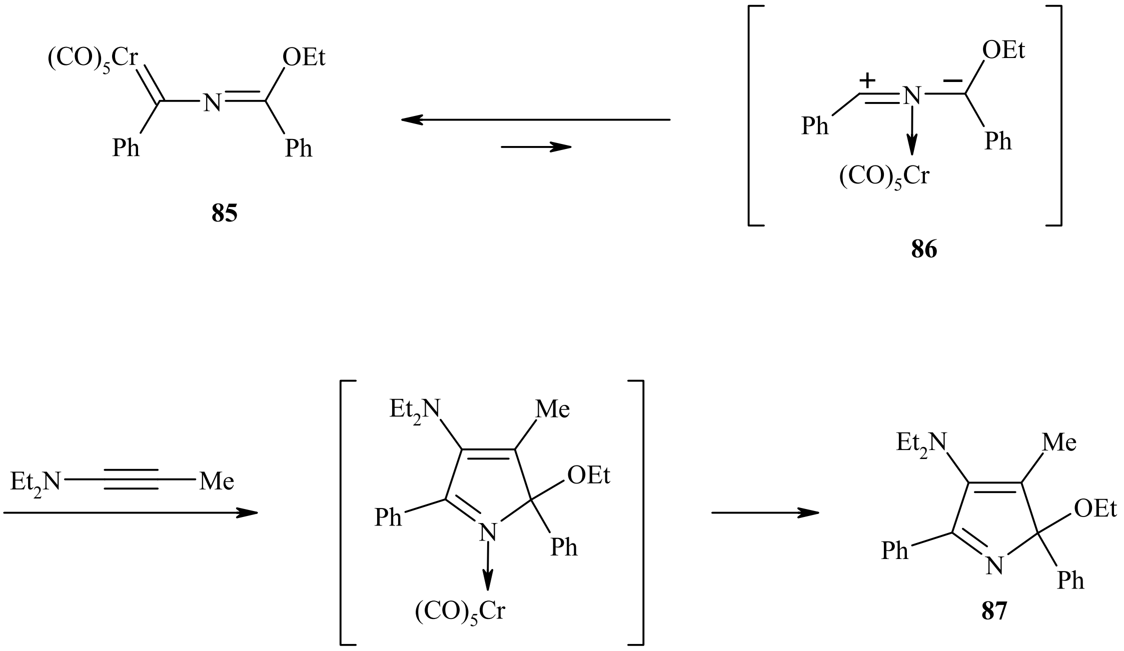


R	R'	X	Z	Overall yield (%)	**83** : **84**
H	H	-CO-N(Ph)-CO-		88	6 : 1
Me	H	-CO-N(Ph)-CO-		89	5 : 1
Me	H	H	CN	83	5 : 1
Me	H	COOMe	COOMe	82	2 : 1
Me	H	COOMe	3-Pyridyl	83	9 : 1
H	Me	-CO-N(Ph)-CO-		85	1 : 6
H	Me	H	CN	98	1 : 1
H	TMS	-CO-N(Ph)-CO-		89	1 : 20

Scheme XXXIX

7.4 Dipolar cycloadditions of *N*-metallo-nitrilylides

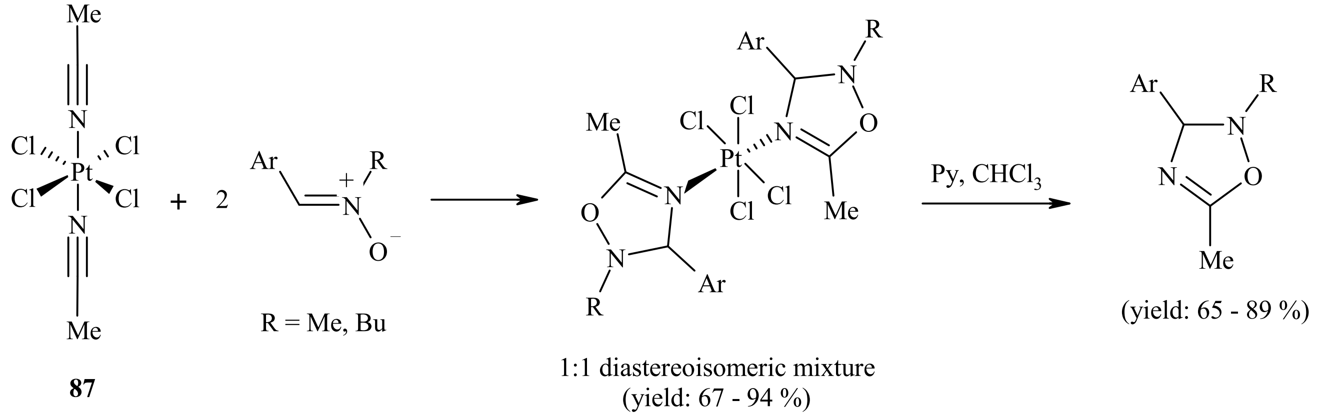
Nitrilylides are propargyl-type 1,3-dipoles having just azomethinylides as allyl-type counterparts. However, while *N*-metallo-azomethinylides are today popular species, only one example of *N*-metallo-nitrilylide has been exceptionally reported. A few years ago, Aumann *et al.* found that the reaction between 1-(pentacarbonyl)chromium-2-azaallenes (**85**) and electron-rich dipolarophiles such as ynamines produced, after spontaneous loss of the metal fragment, the 2*H*-pyrrole derivatives (**87**) (Scheme XL).[98] Such an outcome can be accounted for on assuming the initial rearrangement of **85** to the *N*-complexed nitrilylides (**86**). Since the observed regiochemistry is opposite to that typically reported for nitrilylide cycloadditions to ynamines, one may define the novel complexed species (**86**) as unpolung equivalents of classical nitrilylides.



Scheme XL

7.5 Transition metal complexed nitriles as dipolarophiles

1,3-Dipolar cycloadditions to the triple carbon-nitrogen bond are long known. However, nitriles are not intrinsically good dipolarophiles, unless a strongly electron-withdrawing group is present at the α-position.[99] Classical Lewis acids such as $AlCl_3$ have been used as activating agents, though a multistep pathway probably intervenes in such instance.[100] A novel paper has recently appeared describing nitrone cycloadditions to stoichiometric amounts of platinum(IV) complexed acetonitrile (**88**) (Scheme XLI).[101] The metal fragment can be easily removed from the cycloadducts so that the reported reaction opens a practical route to 2,3-dihydro-1,2,4-oxadiazoles.



Scheme XLI

7.6 Conclusion

In the light of the results here reviewed, one may conclude that transition metal complexation has offered new and valid opportunities also in the field of 1,3-dipolar cycloadditions. However, only a part of this field has been hitherto investigated as far as the effects of metal complexation are concerned. Since most of the experimental evidence has received a sound rationalization, synthetic chemists should be facilitated in planning further successful developments.

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