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Cycloaddition of nitrones to metal-activated nitriles and isocyanides

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Abstract. 1,3-Dipolar cycloaddition reactions of nitrones to nitriles and isocyanides are considered. Attention is focused on metal-mediated processes and the role played by the nature of the metal centre and its oxidation state. The published data on the selectivity of metal-mediated cycloaddition of nitrones to nitriles and the new data on the cycloaddition of nitrones to coordinated isocyanide ligands are summarized and analyzed. The bibliography includes 69 references.

I. Introduction

Cycloaddition reactions form the basis of one of the most important methods of generating cyclic systems of different sizes, from three-membered to macrocyclic. With reactive starting compounds, these reactions can proceed without any additional external impact. Otherwise, the cycloaddition reaction should be promoted by either physical [elevated pressure, intense heating, microwave irradiation (MWI), UV irradiation and sonication] or chemical methods. The latter include catalysis with activating Lewis acids and the coordination of the reagents to the metal centre.

A promising method for enhancing the reactivity of the dipole – dipolarophile pair is the introduction of a metal into the reaction system. The role of the metal is not reduced only to activation of relatively inert organic substrates but may also enhance the chemo-, regio- and stereoselectivity of the reaction and stabilize the cycloaddition product. Quite a number of recent publications were devoted to metal-mediated cycloaddition reactions (*e.g.*, see reviews [1 – 10]) of which the reactions of 1,3-dipolar cycloaddition (1,3-DCA)[1] ranks next in the total number of publications to the Diels – Alder processes that involve metal complexes (see, *e.g.*, Refs 1 – 3, 7 – 10).

In the majority of studied systems, the coordination of dipolarophile and/or dipole to a metal involves the peripheral groups remote from the reaction centre (Fig. 1 *a*).[8, 9] The reactions in which the metal centre activates the substrate through coordination to a functional group directly involved in the 1,3-DCA (Fig. 1 *b*) were so far extremely scarce. Particularly, they include the cycloaddition of dipoles to metal-activated nitriles and also to isocyanides isomeric to the latter.

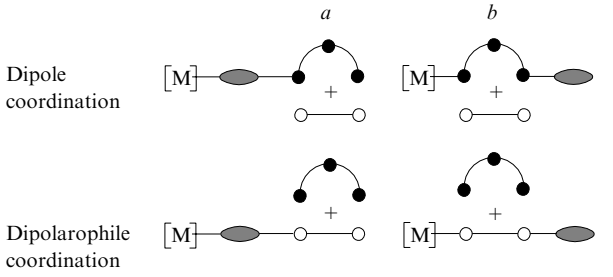


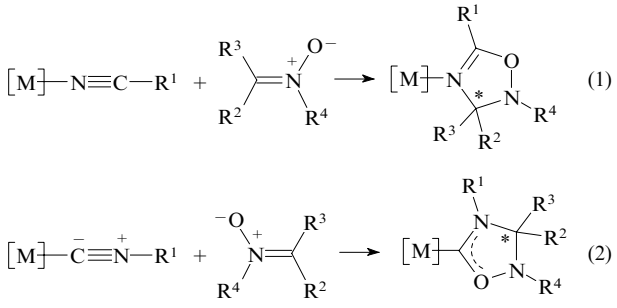
Figure 1. 1,3-Dipolar cycloaddition reactions with different modes of coordination of a dipole and a dipolarophile to the metal: (*a*) with involvement of remote groups, (*b*) with involvement of groups connected with the metal centre.

In 1,3-DCA reactions, nitriles and isocyanides exhibit relatively low reactivity as compared with other dipolarophiles. These reactions of coordinated or free nitriles are limited to a relatively small number of 1,3-dipoles. Among the latter, dipoles of the propargyl – allenyl anion type, *i.e.*, organic and inorganic azides [11 – 17] and, to a lesser extent, nitrile oxides,[18, 19] were the most abundant. At the same time, the examples of reactions of nitriles with dipoles of the allyl anion type, for example, nitrones [reaction (1)] are known far less. Only few publications were devoted to 1,3-DCA of dipoles of the propargyl – allenyl anion type to isocyanides,[20 – 24] and only one experimental study [25] deals

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with cycloaddition of nitrones to coordinated isocyanides [reaction (2)].



(1)

(2)

In the past decade, the reactivity of coordinated nitriles and isocyanides with respect to nucleophilic and electrophilic reagents and also to 1,3-dipoles is being actively studied.[25–33] The accumulated data on the reaction of nitrones with substrates containing a metal-activated C≡N group allow one to summarize and systematize the factors that determine the cycloaddition of nitrones to nitriles and to isocyanides bound to the metal centre. In our previous review,[28] the first attempt was undertaken to analyze reactions of nitriles with nitrones and compare the metal-free and metal-mediated syntheses of heterocyclic compounds. Recently, several studies dealing with the metal-activated cycloaddition to nitriles and isonitriles have appeared, together with data on biological activity and the catalytic properties of the reaction products, namely, platinum and palladium complexes with 2,3-dihydro-1,2,4-oxadiazoles.[34,35] The present publication discusses the results of these studies with attention focused on the effect of the metal centre on the mechanism of reactions of nitrones with nitriles and isocyanides and their selectivity.

II. 1,3-Dipolar cycloaddition of nitrones to uncoordinated nitriles

Only few studies on the metal-free synthesis of 2,3-dihydro-1,2,4-oxadiazoles are known. Nonetheless, the analysis of even these scarce publications made it possible to reveal several factors that determine the possibility of 1,3-DCA reaction to proceed. They include the nature of substituents in the nitrile molecules, structural features of nitrones and the additional activation of reagents. The results of theoretical studies[36–38] suggested that the cycloaddition of nitrones to nitriles pertains to the normal electron demand reactions, *i.e.*, is controlled by the interaction between the frontier molecular orbitals, namely, HOMO of the dipole and LUMO of the dipolarophile (Fig. 2). Hence, such reactions can be promoted by using dipolarophiles with electron-withdrawing substituents and/or dipoles with electron-donating substituents.

It was noted[39–41] that it is only nitriles with strong electron-withdrawing substituents (for example, Cl_3CCN or $NCCH_2CN$) that enter the cycloaddition reaction with acyclic nitrones such as PhCH=N(O)Me. Nitriles with electron-donating substituents (*e.g.*, MeCN) do not react with these dipoles even under more drastic conditions. Recently, it has been found that the structures of the reaction products of substituted phthalonitriles **1a–e** with cyclic nitrone **2** depend on the nature of substituents in the aromatic ring of the dinitrile.[42] Thus under the same reaction conditions (80 °C, sealed tube), phthalonitriles

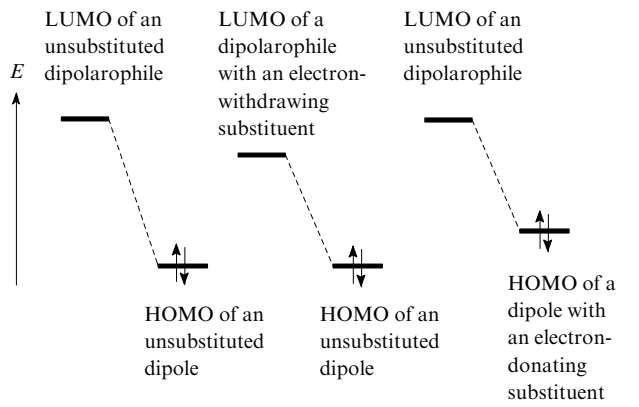
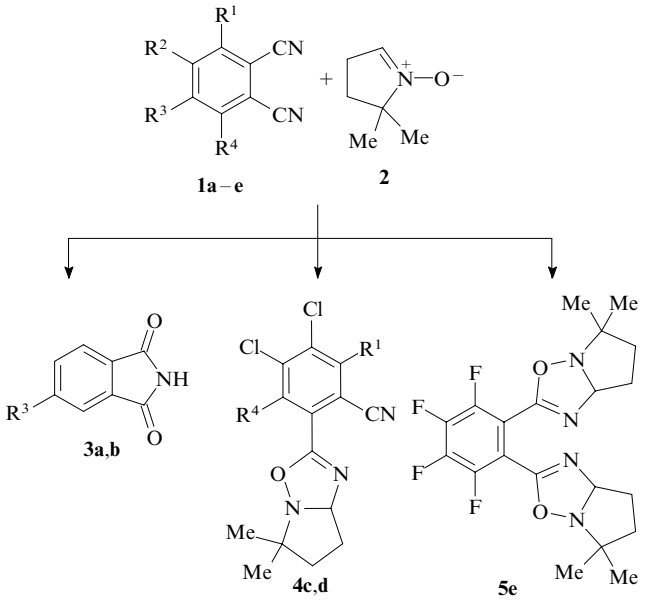


Figure 2. Changes in the energies of frontier orbitals of a dipolarophile and a dipole upon introduction of electron-withdrawing and electron-donating substituents, respectively.

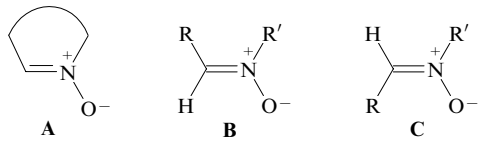
1a,**b** containing electron-donating substituents produced phthalimides **3a**,**b** rather than underwent cycloaddition, phthalonitriles with electron-withdrawing substituents **1c**,**d** afforded monocycloadducts **4c**,**d**, whereas both nitrile groups of perfluoro derivative **1e** were involved in 1,3-DCA to afford compound **5e**.



Compound **1**	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	H	Me	H
c	H	Cl	Cl	H
d	Cl	Cl	Cl	Cl
e	F	F	F	F

Nitrones with aromatic substituents at the carbon atom, which are widely used in organic chemistry due to their relativelyly high stability and accessibility,[8,43,44] are insufficiently reactive towards several most common nitriles RCN (R = Me, Et, Ph). The stronger the electron-withdrawing substituent at the carbon atom of the azomethine group the higher the reactivity of nitrones.[39,40] It was noted[35,40,44,45] that cyclic nitrones (structure **A**) are more

reactive in cycloaddition reactions to nitriles than their acyclic counterparts. This was explained by the fact that a cyclic nitrone exists in one possible *E* configuration, which, for steric reasons, is more favourable for 1,3-DCA, whereas an acyclic nitrone exists as a mixture of *E* (**B**) and *Z* isomers (**C**) with the less reactive *Z* form predominating.

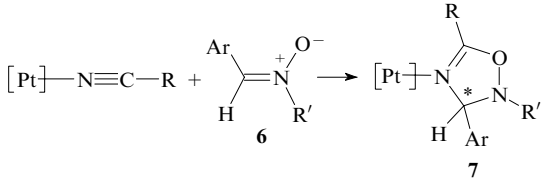


A **B** **C**

To accelerate the reaction of nitrones with different dipolarophiles,[45–47] particularly, nitriles,[20,26] the reactions can be carried out at elevated pressure. The focused MWI instead of conventional heating[29,30] accelerates the metal-free[48] and metal-mediated[49] cycloaddition reactions and increases the yields of 2,3-dihydro-1,2,4-oxadiazoles and their complexes.

III. 1,3-Dipolar cycloaddition of nitrones to coordinated nitriles

Comparatively recently, publications devoted to cycloaddition of nitrones to coordinated nitriles have appeared including experimental and theoretical studies carried out by quantum chemical calculations according to the Hartree–Fock method, density functional theory in the B3LYP basis set, the MP2 perturbation theory and the CBS-Q combined calculation methods.[34,36–38,50–65] Coordination of dipolarophiles (nitriles) to metal results in their activation and has an effect on the regio- and stereoselectivity of cycloaddition reactions. For example, nitrile complexes of platinum(IV) $[PtCl_4(RCN)_2]$ (R = Me, Bn, Ph) and platinum(II) $[PtCl_2(RCN)_2]$ (R = Bn, Ph) reacted with nitrones **6** even at room temperature to form N(4)-coordinated 2,3-dihydro-1,2,4-oxadiazoles **7**.[50,51] Uncoordinated nitriles RCN did not react with nitrones **6** even under drastic conditions.



6 **7**

[Pt]NCR = $PtCl_4(RCN)_2$ (R = Me, Bn, Ph); $PtCl_2(RCN)_2$ (R = Bn, Ph); R′ = Me, Bn.

Based on theoretical calculations of a model reaction of an acyclic nitrone with an uncoordinated or coordinated acetonitrile, the nitrile activation can be interpreted in terms of the theory of frontier MO as the result of a decrease in the LUMO energy of a dipolarophile due to coordination.[36–38]

1. Factors determining the cycloaddition reactions with coordinated nitriles

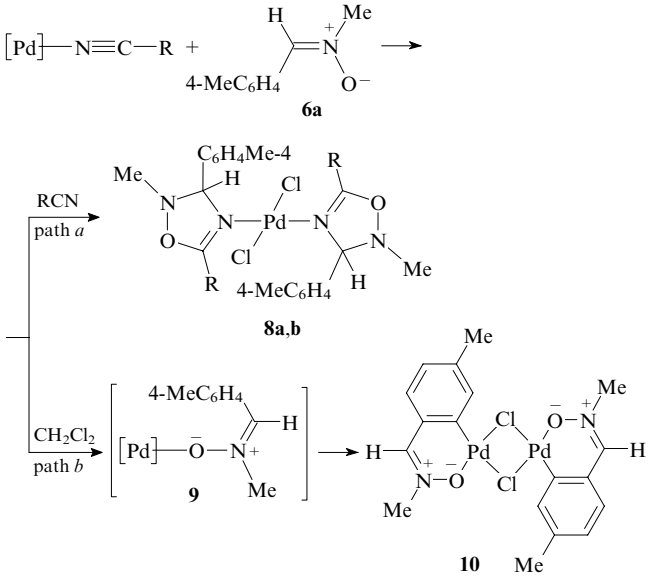
The metal-mediated cycloaddition depends (as regards its activation) on the same factors as the corresponding metal-free synthesis, namely, on the nature of substituents in the dipole and the dipolarophile. However, in 1,3-DCA reactions involving coordinated nitriles, a new factor, namely, the metal centre that largely influences the reactions, should be considered.

a. The nature of the metal centre

The nature of the metal centre is a key factor that determines the possibility of a metal-mediated cycloaddition reaction. Thus the analysis of publications[50,52,53] suggests that the 1,3-DCA reactions proceed successfully only with nitriles that form complexes with platinum(II, IV) and, sometimes, with palladium(II). For nitrile complexes with other metals [titanium(IV), zirconium(IV), molybdenum(IV), tungsten(IV)] tested in reactions with nitrones, no evidence for the formation of 2,3-dihydro-1,2,4-oxadiazoles in the reaction systems could be found.[52]

A comparison of platinum(II)- and palladium(II)-mediated cycloaddition reactions suggests that the nitriles in complexes $[MCl_2(PhCN)_2]$ [M = Pt(II), Pd(II)] have comparable degrees of activation. One can indirectly judge on the degree of activation from the reaction conditions of a coordinated nitrile with nitrone **6a**, namely, 1 day at 25 °C in CH_2Cl_2 for Pt(II) and 1 day at 40 °C in PhCN for Pd(II).[53] When selecting the metal to be used as the activator, differences in the conditions of synthesis should be taken into account. Being relatively inert in substitution reactions, platinum(II) complexes reacted with nitrones to afford 2,3-dihydro-1,2,4-oxadiazoles **7** in such solvents as dichloromethane or chloroform.[53] The cycloaddition of nitrones to nitrile ligands in kinetically more labile palladium complexes occurred only in the medium of the corresponding nitrile (path *a*)[50,53] to afford palladium complexes **8a**,**b**.

In acetone or dichloromethane as the solvent, the reaction of nitrone **6a** with $[PdCl_2(RCN)_2]$ produced neither free nor coordinated 2,3-dihydro-1,2,4-oxadiazoles. In this case, only the substitution products of nitrone for the nitrile ligands could be observed. The further transformation of the coordinated nitrone **9** afforded a dimeric Pd(II) nitrone complex **10** (path *b*).[53]



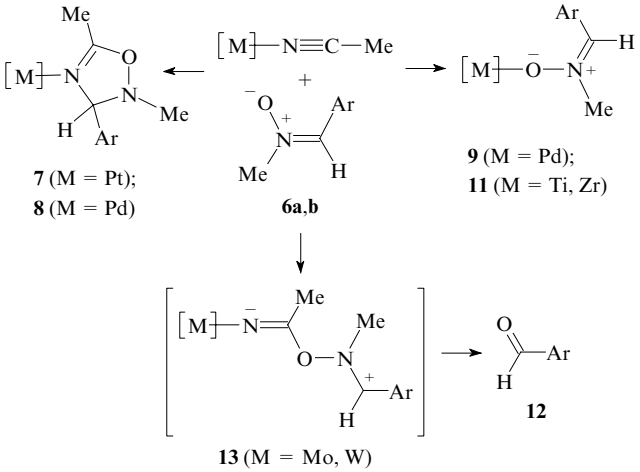
6a **8a,b** **9** **10**

R = Me (**a**, 15%), Ph (**b**, 50%); [Pd] = $PdCl_2$.

The dependence of the reaction pathway on the nature of solvent is associated with the higher lability of the palladium complexes as compared with the platinum complexes and with more pronounced ‘hardness’ of palladium (in terms of the soft and hard acids and bases theory). This factor determines the facile replacement of a ‘softer’ base

(RCN) by a 'harder' O-coordinated nitrone in the absence of an excess of the nitrile.[53, 54]

The reactions of the nitrile complexes $[MCl_4(MeCN)_2]$ [M = Ti(IV), Zr(IV), Mo(IV), W(IV)] with nitrones **6a**,**b** were studied.[52]



7 (M = Pt);
8 (M = Pd)

6a,**b**

9 (M = Pd);
11 (M = Ti, Zr)

13 (M = Mo, W)

12

Ar = 4-MeC_6H_4 (**a**), Ph (**b**).

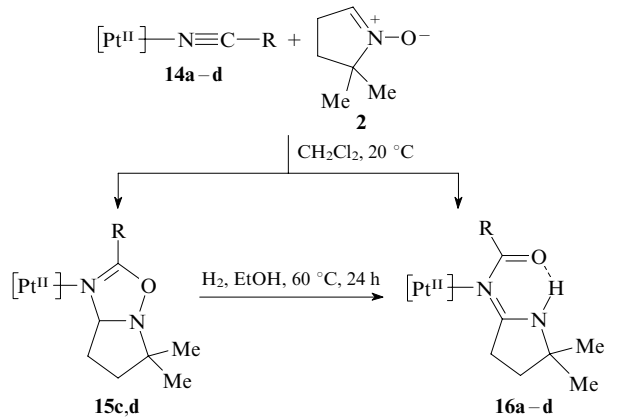
In neither case, were cycloadducts of nitrone to nitrile formed. For titanium(IV) and zirconium(IV) complexes, which are hard acids, rapid substitution of the nitrone for the inner-sphere nitrile resulted in polymeric complexes **11** such as $[MCl_4(ON(Me)=CHAr)_n]$ (n = 1.3–1.8). In the presence of molybdenum(IV) and tungsten(IV) complexes, the nitrone underwent hydrolysis to the corresponding aldehyde **12**. Presumably,[52] hydrolysis occurred *via* 1,5-dipole **13**, *i.e.*, the adduct of the nitrone oxygen atom to the carbon atom of a coordinated nitrile. Dipole **13** reacted with water to eliminate aromatic aldehyde **12**. This reaction mechanism was confirmed by quantum chemical calculations that suggested a stepwise cycloaddition mechanism in the presence of a Lewis acid.[36, 37, 55]

Thus, among the metals studied so far, platinum is the most promising activator of nitriles in their 1,3-DCA reaction with nitrones. It is only for platinum complexes, which are soft Lewis acids and exhibit relative kinetic inertness, that the conditions favourable for the cycloaddition reaction are realized, namely, the selective coordination of the dipolarophile to the metal centre and, simultaneously, the absence of analogous coordination for the dipole.

b. The oxidation state of the metal centre

The oxidation state of the metal centre in the complex substantially affects the activation of the coordinated nitrile, which is exemplified by reactions of acyclic nitrones with platinum(II) and platinum(IV) nitrile complexes. Thus, benzonitrile in the complex $[PtCl_4(PhCN)_2]$ reacted with nitrones **6a**,**b** at room temperature faster (1.5 h) than nitrile in the platinum(II) analogous complex (1 day).[51] For more reactive cyclic nitrone **2**, it took from 1 to 2 days to react with the nitrile in the platinum(II) complex $[PtCl_2(EtCN)_2]$. The reaction of the same nitrone with the analogous platinum(IV) complex took 15 min.[49] The reaction of nitriles **14a**–**d** with cyclic nitrone **2** afforded stable complexes **15c**,**d** and **16a**,**b** (Scheme 1).[65] Note that compounds **15c**,**d** were rearranged into the corresponding ketimine complexes **16c**,**d** (see below, Section IV.2).

Scheme 1



14a–**d**

2

CH_2Cl_2, 20 °C

H_2, EtOH, 60 °C, 24 h

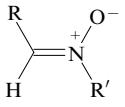
15c,**d**

16a–**d**

R = CH_2CO_2Me (**a**), CH_2Cl (**b**), Ph (**c**), Et (**d**).

Quantum chemical calculations rationalize the higher reactivity of platinum(IV) nitrile complexes as compared with platinum(II) complexes.[36–38] Thus the difference between the energies of the HOMO of a free nitrone and the LUMO of a nitrile in the complex decreased with the increase in the oxidation state of the metal, which corresponded to the higher activation of the CN group in 1,3-DCA reactions with platinum(IV) nitrile complexes as compared with platinum(II) complexes.

It should be noted that the reactivity of the RCN ligand in platinum(II) complexes also substantially depends on the nature of the substituent R. Thus the complexes of nitriles with an electron-donating substituent, for example, $[PtCl_2(MeCN)_2]$, did not react with nitrones **6** even on prolonged heating.[51] At the same time, ligated nitriles that contained an electron-withdrawing substituent CH_2CO_2Et (Ref. 66) or a phenyl group conjugated with the C≡N bond [51] reacted with nitrones at room temperature to afford coordinated 2,3-dihydro-1,2,4-oxadiazoles. Coordination of a nitrile to platinum(IV) levelled off the effect of the substituent in the ligand so that the reaction rates of nitriles in $[PtCl_4(RCN)_2]$ complexes (R = Me, Ph) with nitrones **6a**–**i** turned out to be approximately the same.[50, 51]



6a–**i**

R′ = Me: R = 4-MeC_6H_4 (**a**), Ph (**b**), 4-$MeOC_6H_4$ (**c**), 2-HOC_6H_4 (**d**), 4-$O_2NC_6H_4$ (**e**), 4-$Me_2NC_6H_4$ (**f**), 4-$(HCl\cdot Me_2N)C_6H_4$ (**g**); R′ = Bn: R = Ph (**h**), Bu^t (**i**).

Platinum(IV) activated the RCN ligand so strongly that nitrones ArCH=N(O)R underwent cycloaddition even to nitriles with electron-donating substituents.

c. The nature of nitrile

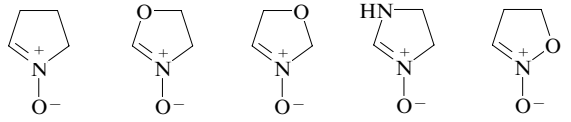
In Section II.1.b, it was noted that the nature of the substituent in the RCN ligand in the platinum(II) complexes plays a considerable role in the 1,3-DCA reactions. A similar situation was also observed for reactions of palladium(II) nitrile complexes. Thus the $[PdCl_2(PhCN)_2]$ complex reacted with nitrone **6a** under mild heating (50 °C), whereas the analogous reaction of the complexes containing electron-donating substituents $[PdCl_2(RCN)_2]$ (R = Me, Et)

required more drastic conditions, namely, prolonged heating and/or MWI.[53]

d. The nature of nitrone

The nature of nitrone in cycloaddition reactions with the ligands RCN in the metal complexes plays the same role as in the reactions with free nitriles. According to the results of quantum chemical calculations,[37] the activity of these dipoles increased on going from acyclic to cyclic structures and upon introduction of an electron-donating substituent at the carbon atom of the azomethine group. Cyclic nitrone **2** (see Scheme 1) easily reacted with the nitrile ligand in the platinum(II) complexes, $[PtCl_2(EtCN)_2]$ and $[Ph_3PBn][PtCl_3(EtCN)]$,[30] and palladium(II) complexes, $[PdCl_2(RCN)_2]$ (R = Me, Et).[35] Acyclic nitrones **6** either did not react with RCN ligands containing electron-donating substituents (R = Me, Et) in the $[PtCl_2(RCN)_2]$ complexes[51] or the reaction proceeded non-selectively.[53] On the one hand, such a difference in the reactivity of cyclic and acyclic nitrones was explained by the presence of a donor substituent at the carbon atom C=N(O) of cyclic nitrone **2** and, on the other hand, by the existence of the cyclic dipole exclusively in the more reactive *E* form (see Section 1).

Quantum chemical studies of the 1,3-DCA of cyclic nitrones **17**–**20** and nitronate **21** to free and coordinated nitriles[30, 36] showed that nitrones in which a heteroatom (O or N) is bound to the carbon atom of the C=N(O) group (structures **18** and **20**) are more reactive in the cycloaddition reactions.

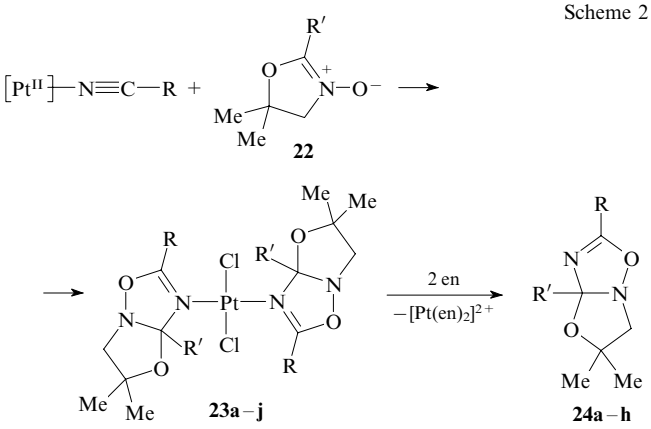


17 **18** **19** **20** **21**

According to calculations,[36] nitronate **21** in which both oxygen atoms are bound to the nitrogen atom is the least reactive. Compounds in which the ring oxygen atom was not directly bound to the nitrone group (**19**) and compounds containing no oxygen atoms in the ring (**17**) exhibited intermediate reactivity in 1,3-DCA to nitriles.

The results of theoretical studies were confirmed experimentally. Thus cyclic nitrones **22** (R′ = Me, Et) reacted with nitriles and dialkylcyanamides in the platinum(II)

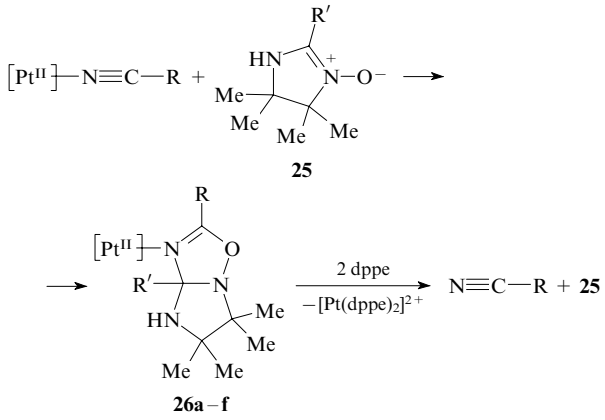
Scheme 2



R = Me: R′ = Me (**a**), Et (**b**); R = Et: R′ = Me (**c**), Et (**d**);
R = Bn: R′ = Me (**e**), Et (**f**); R = Ph: R′ = Me (**g**), Et (**h**);
R = $N(CH_2)_5$: R′ = Me (**i**), Et (**j**).

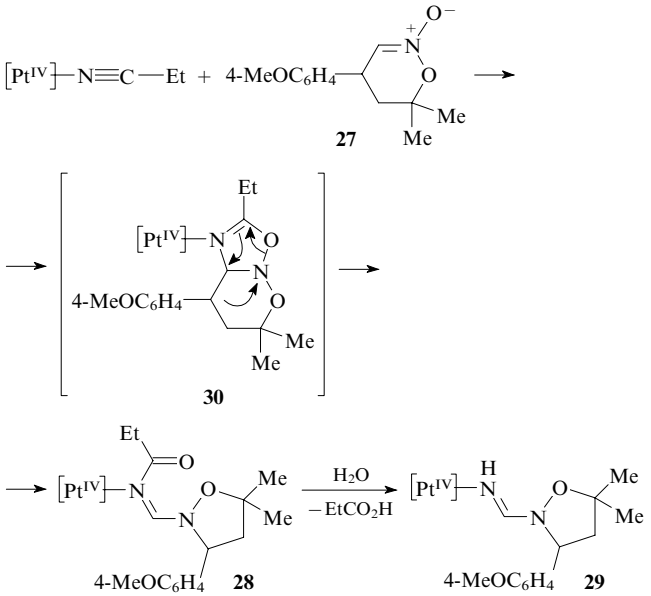
complexes even at room temperature to form the earlier unknown annulated heterocyclic systems **23a**–**j** as the ligands (Scheme 2).[63] Heterocycles **24a**–**h** were isolated in the free state upon demetallation with ethylenediamine (en).

The reaction of platinum(II) nitrile complexes with imidazoline-based nitrones **25** (R′ = H, Me) proceeded rapidly to afford coordinated annulated heterocycles **26a**–**f** in good yields. Annulated rings **26** turned out to be unstable and were characterized only in their coordinated state, whereas attempts to demetallate them led to the free dipole and the dipolarophile.



R = Et: R′ = H (**a**), Me (**b**); R = NMe_2: R′ = H (**c**), Me (**d**);
R = $N(CH_2)_5$: R′ = H (**e**), Me (**f**); dppe is 1,2-bis(diphenylphosphino)ethane.

Thus, coordinated heterocycles that do not exist in the free state can be synthesized under mild conditions due to the involvement of the metal centre in the 1,3-DCA of nitrones to nitriles. The metal served as the dipolarophile activator and stabilized the cycloadduct.



So far, no examples have been documented of the addition of nitronates to the nitrile group. It was assumed[58] that the activation of a nitrile due to its coordination to platinum(IV) would be sufficient for this process to occur. In fact, the reaction of the platinum nitrile complex *trans*-$[PtCl_4(EtCN)_2]$ with cyclic nitronate **27** afforded complex **28** containing coordinated *N*-acylamidine as the main product.

This product underwent hydrolysis in wet solvents to afford imine complex **29** and propionic acid. Although no evidence of the formation of a cycloadduct was obtained, the cascade reaction mechanism was put forward. In the first step, the 1,3-DCA of nitronate **27** to the nitrile group occurred to afford bicyclic compound **30**. This was followed by ring opening of 2,3-dihydro-1,2,4-oxadiazole with cleavage of the N−O bond and concomitant six-membered ring contraction as a result of 1,2-migration. The recently observed rearrangement of 2,3-dihydro-1,2,4-oxadiazoles to afford *N*-acylformamidine derivatives (see Section III.1) may serve as additional evidence for such a mechanism of formation of amidine complex **28**.

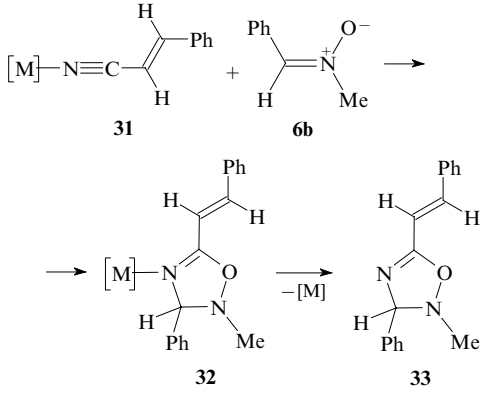
Hence, the possibility of the metal-mediated cycloaddition strongly depends on the nature of nitrone. The presence of donor substituents in the nitrone and the *E* configuration, best realized in cyclic structures, favour this process.

2. Selectivity of metal-mediated 1,3-dipolar cycloaddition

The metal not only activates the dipolarophile in the 1,3-DCA reaction but also affects the selectivity of this process.

a. Regioselectivity of metal-mediated 1,3-dipolar cycloaddition

Coordination of nitrile substrates to a metal centre can switch the reaction direction. Studies of the reaction of complexes $[MCl_2(N{\equiv}C-CH{=}CHPh)_2]$ (**31**) containing a bifunctional dipolarophile with nitrone **6b** [56] showed that in the presence of a considerable excess of nitrone **6b**, no cycloaddition to the C=C bond occurred. The reaction carried out at 60 °C for 2 days afforded complexes **32**, *i.e.*, the regiospecific cycloaddition products of the nitrone to the nitrile.

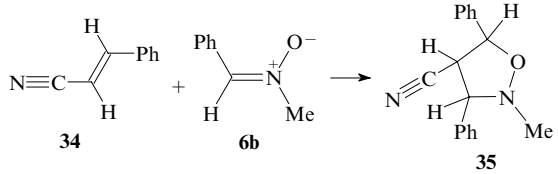


31 **6b** **32** **33**

M = Pt(II), Pd(II).

Treatment of 2,3-dihydro-1,2,4-oxadiazole complexes **32** with an aqueous solution of methylamine afforded heterocycle **33** isolated in the free state.[56]

At the same time, the reaction of uncoordinated nitrile N≡C−CH=CHPh (**34**) with nitrone **6b** proceeded exclusively at the C=C bond to afford isoxazolidine **35** without affecting the C≡N bond.

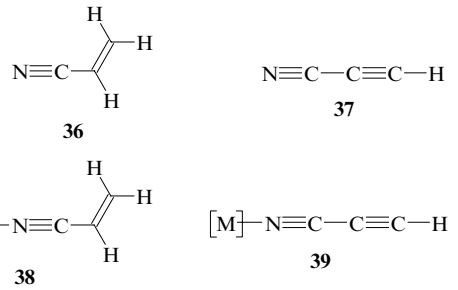


34 **6b** **35**

Hence, coordination of a nitrile to the metal shifts the reaction site in the N≡C−CH=CHPh fragment from the C=C bond to the C≡N group, so that the cycloaddition proceeded regiospecifically to the C≡N group.

Thus, the 1,3-DCA reaction of a nitrile coordinated to a metal followed by demetallation of the heterocycle results in highly regioselective formation of 2,3-dihydro-1,2,4-oxadiazoles **33** with the intact C=C bond in the side chain. These heterocyclic systems cannot be formed by the 1,3-DCA of nitrones to free bifunctional nitriles.

Recent theoretical studies of regioselectivity of model cycloaddition reactions of nitrones to bifunctional dipolarophiles **31**, **34**, **36**–**39**, which contained C≡N and C=C (or C≡C) bonds and existed in both coordinated (compounds **31**, **38**, **39**) and free (compounds **34**, **36**, **37**) states, demonstrated the enormously higher dipolarophilic activity of multiple carbon-carbon bonds as compared with the nitrile group in non-coordinated compounds.[59]



36 **37** **38** **39**

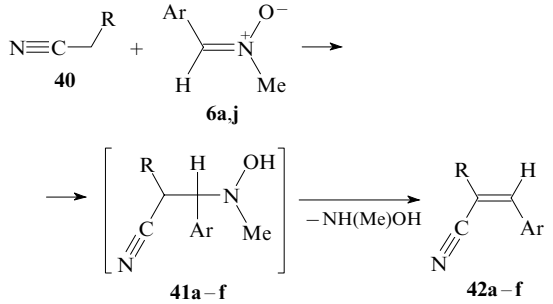
M = Pt(II), Pt (IV).

Coordination of the nitrile group to platinum(II, IV) substantially activated the C≡N bond with respect to 1,3-DCA reactions, but nonetheless the reactivity of the nitrile group remained inferior as compared with those of the C=C and C≡C bonds even for platinum(IV) complexes. However, varying the substituents in the dipolarophile made it possible to substantially affect the reactivity of C≡N and C≡C groups. The switch of the reaction site from the C≡C to C≡N group observed experimentally [56] for the coordination of cinnamonitrile to platinum(II) was associated with both the increase in the nitrile group activity as a result of its coordination and the higher activation energy of the transition state in the nitrone addition to the C=C bond. The latter factor was accounted for by steric repulsions of the Ph groups and the loss of conjugation in phenylnitrone and phenylcyanoalkene upon the transition state formation.[59, 60]

The reactions of free and coordinated nitriles RCH_2CN (R = SO_2Ph, CO_2Me, COPh, Cl) with acyclic nitrones was studied.[61]

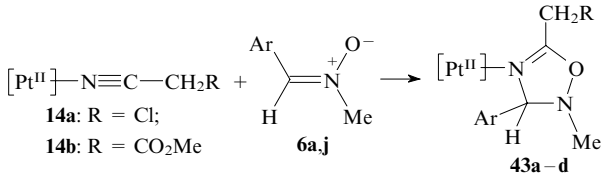
In addition to the electrophilically activated C≡N group, these nitriles contained a reactive α-CH_2 group. The reaction of free nitriles **40** with acyclic nitrones **6a**,**j** proceeded under fairly drastic conditions (heating for 12 h at 80 °C in a sealed tube or focused MWI for 2 h). The Michael-type addition of the nitrone followed by abstraction of *N*-methylhydroxylamine from intermediates **41a**–**f** afforded *E*-configured substituted alkenes **42a**–**f** (Scheme 3).

Scheme 3



Ar = 4-MeC_6H_4 (**6a**): R = CO_2Me (**41a**, **42a**); SO_2Ph (**41b**, **42b**); COPh (**41c**, **42c**); Ar = 2,4,6-$Me_3C_6H_2$ (**6j**): R = CO_2Me (**41d**, **42d**); SO_2Ph (**41e**, **42e**); COPh (**41f**, **42f**).

The reaction of coordinated nitriles **14a**,**b** with nitrones **6a**,**j** proceeded under milder conditions, namely, refluxing in CH_2Cl_2 at 40 °C for 8 h or MWI for 1 h (sealed tube), and afforded cycloadducts **43a**–**d**. Under more drastic conditions, *e.g.*, upon increase in the reaction time, a mixture of 2,3-dihydro-1,2,4-oxadiazole complexes **43a**–**d** and the corresponding *E* alkenes was obtained.



Ar = 4-MeC_6H_4 (**6a**): R = Cl (**43a**); CO_2Me (**43b**);
Ar = 2,4,6-$Me_3C_6H_2$ (**6j**): R = Cl (**43c**); CO_2Me (**43d**).

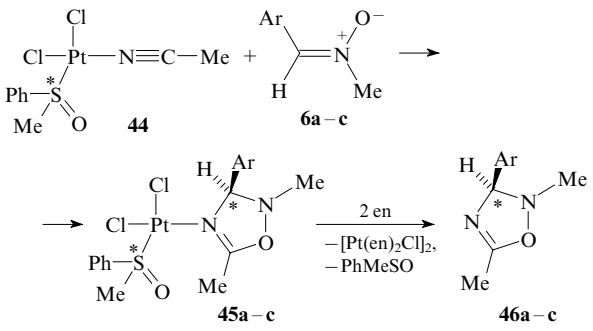
Thus, the coordination of nitriles containing a reactive methylene group to the metal centre can switch the reaction direction, namely, from the Michael addition (with the α-CH_2 group as the reaction centre) to cycloaddition (with the C≡N group as the reaction centre).

b. Stereoselectivity of metal-mediated 1,3-dipolar cycloaddition

In the metal-mediated 1,3-DCA of a nitrone to a nitrile, a new chiral centre is formed at the carbon atom of the N–C*R^1R^2–N group [see reactions (1), (2)]. For this reason, the stereochemistry of the products (the preferential formation of *R* or *S* isomers) can be influenced by introducing chiral substituents into the dipole and/or dipolarophile molecules, for example, by using a metal centre with chiral auxiliary ligands.[62]

In the reaction, the nitrile is coordinated to the metal and the product stereoconfiguration is determined by the ligand environment of the complex. The formation of 2,3-dihydro-1,2,4-oxadiazole by cycloaddition of nitrones **6a**–**c** to benzonitrile involved in the complex *cis*-[$PtCl_2$.(MePhS*O)(PhCN)] (**44**) containing a chiral sulfoxide (R_S or S_S isomer) was studied aimed at elucidating the role of the ligand environment in the asymmetric induction.[62]

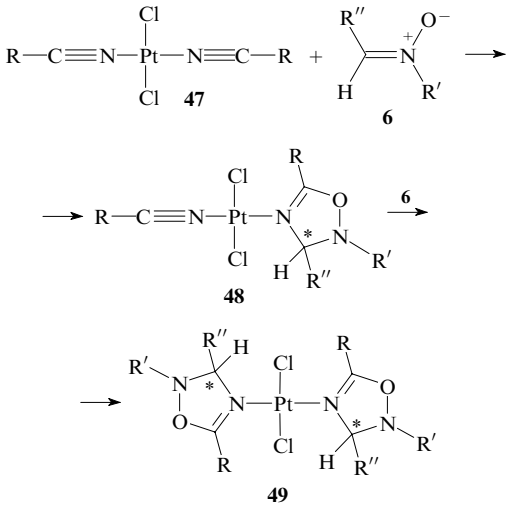
The reaction of a racemic complex [(R_S/S_S)-**44**] with nitrones **6a**–**c** led to four diastereomers with the S_S,R_C, R_S,S_C, S_S,S_C, R_S,R_C configurations. Compounds (S_S,R_C)/(R_S,S_C)-**45a**–**c** prevailed (the diastereomeric excess varied from 30% to 70% depending on the substituent in the benzene ring).



Ar = 4-MeC_6H_4 (**a**), Ph (**b**), 4-$MeOC_6H_4$ (**c**).

The reaction with a sulfoxide enantiomerically enriched in the *R* isomer (*R*-**44**) resulted preferentially in R_S,S_C-diastereomers **45a**–**c**. The latter were purified by fractional crystallization and then subjected to demetallation with ethylenediamine to afford free 2,3-dihydro-1,2,4-oxadiazoles **46a**–**c**.[62] The enantiomeric excess of the *S* isomer was 70%. This reaction sequence demonstrated the possibility of stereoselective synthesis of 2,3-dihydro-1,2,4-oxadiazoles as a result of asymmetrical induction exerted by a dipolarophile.

With *trans*-bisnitrile complexes of platinum **47** used as dipolarophiles, the cycloaddition proceeded in several steps. This was confirmed by experimental data [57] on the reactions of *cis*- and *trans*-[$PtCl_2(PhCN)_2$] complexes with acyclic nitrones ArCH=N(O)Me (Ar = Ph, 4-MeC_6H_4). The rates of the first and second cycloaddition steps differed for *trans*-platinum(bisnitrile) complexes, the first step being faster. As a result, both mono- (**48**) and bisadducts (**49**) of platinum nitrone complexes were prepared (the latter were obtained as the 1:1 diastereoisomeric mixtures). In *cis*-platinum(bisnitrile) complexes as dipolarophiles, only one of the nitrile ligands reacted, probably, for steric reasons.[57]

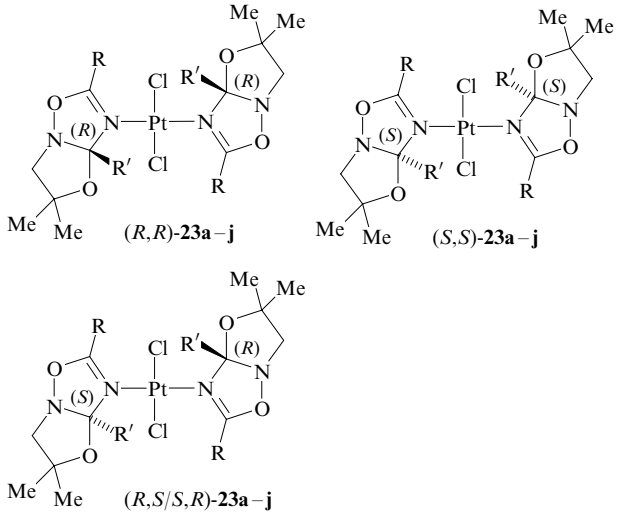


The ligand in complex **48** formed in the first step determines the configuration of the heterocycle in complex **49** formed in the second step. The following four combinations of stereoconfigurations of two asymmetric centres in the complex are possible: *R*,*R*, *S*,*S*, *R*,*S* and *S*,*R*. Insofar as *trans*-bis(2,3-dihydro-1,2,4-oxadiazole) complexes of platinum(II) **49** have a symmetry plane, the *R*,*S* and *S*,*R* isomers

represent the *meso* form. Hence, in the course of the reaction between *trans*-[$PtCl_n(RCN)_2$] (n = 2, 4) complexes and nitrones, three stereoisomers can be formed, namely, two optically active antipodes, in which both ligands have the same configuration of the chiral carbon atom (*R*,*R* and *S*,*S*), and the optically inactive *meso* isomer.

In the reaction of *trans*-[$PtCl_n(RCN)_2$] (n = 2, 4; R = Me, Bn, Ph) with nitrones **6,** the coordinated 2,3-dihydro-1,2,4-oxadiazole molecule formed in the first cycloaddition step did not affect the stereoconfigiration of the second heterocycle so that the pairs of diastereomers were formed in equal ratios.[50, 57] This can be explained by the longer distance between ligands and weak steric overloading of the acyclic nitrones used.

The reaction of compounds **47** with the more sterically hindered cyclic dipoles demonstrated stereoinduction in the formation of the second coordinated heterocycle.[63] Thus, the complexes *trans*-[$PtCl_2(RCN)_2$] [R = Me, Et, Bn, Ph, $N(CH_2)_5$] reacted with cyclic nitrone **22** to afford stereoisomers (antipodes) with *R*,*R* and *S*,*S* configurations and *meso* forms (*R*,*S*/*S*,*R*) of product **23** (see Scheme 2). Their ratio depended on the nature of substituent in the nitrile ligand.



(*R*,*R*)-**23a**–**j** (*S*,*S*)-**23a**–**j**

(*R*,*S*/*S*,*R*)-**23a**–**j**

R = Me: R′ = Me (**a**), Et (**b**); R = Et: R′ = Me (**c**), Et (**d**);
R = Bn: R′ = Me (**e**), Et (**f**); R = Ph: R′ = Me (**g**), Et (**h**);
R = $N(CH_2)_5$: R′ = Me (**i**), Et (**j**).

Thus, in the reactions with nitrones, complexes containing nitriles with alkyl substituents (R = Me, Et, Bn) formed racemic mixtures of (*R*,*R*)-**23a**–**f** and (*S*,*S*)-**23a**–**f**. The stereochemistry of this reaction with nitrile $N{\equiv}C-N(CH_2)_5$ in the *trans*-[$PtCl_2(NCN(CH_2)_5)_2$] complex as the dipolarophile changed. In this case, the *meso* form of 2,3-dihydro-1,2,4-oxadiazole complex (*R*,*S*/*S*,*R*)-**23i**,**j** was obtained. The reaction of the complex *trans*-[$PtCl_2(PhCN)_2$] and cyclic nitrones did not occur diastereoselectively resulting in a mixture of (*R*,*S*/*S*,*R*)-**23g**,**h**, (*R*,*R*)-**23g**,**h** and (*S*,*S*)-**23g**,**h**.

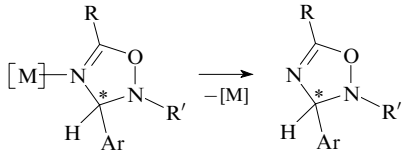
A possible explanation for this observation could be the fact that the phenyl substituent is the least sterically hindered as compared with the alkyl or piperidyl substituents and/or stronger asynchronicity of the cycloaddition process.[63] For R = Ph, when the ring formation occurs in a non-concerted process, the product can be formed in another configuration due to the rotation around the C–N bond that occurs between the first and second steps of the process.[37]

Thus sterically hindered ligands in the *trans*-position with respect to the dipolarophile can affect the configuration of the heterocycle formed in the course of reaction.

The stereoconfiguration of 2,3-dihydro-1,2,4-oxadiazole can be determined by not only asymmetric ligands in the composition of a metal complex but also the presence of chiral substituents in the dipole and/or nitrile molecules. So far, there is no information on how the substituents in nitrone and/or nitrile molecules affect the stereoselectivity of 1,3-DCA. Recently, the author of the present review in cooperation with I A Balova obtained the results suggesting that the use of enantiomerically pure dipoles gives rise to stereospecific cycloaddition reactions of nitrones to coordinated nitriles.

3. Demetallation

As was already mentioned above, the 1,3-DCA of nitrones to coordinated nitriles afforded ligated 2,3-dihydro-1,2,4-oxadiazoles. An additional step was required for demetallation and isolation of 2,3-dihydro-1,2,4-oxadiazoles in the free state.[50, 51, 56, 62]



50

M = Pt(IV): R = Me; R′ = Me, Bn; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-HOC_6H_4, Bu^t;
M = Pt(II): R = Ph, Bn; R′ = Me; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; M = Pd(II): R′ = Me; R = CH_2Cl, CH_2CO_2Me; Ar = 4-MeC_6H_4, 2,4,6-$Me_3C_6H_2$, *etc*.

Thus 2,3-dihydro-1,2,4-oxadiazoles **50** were isolated in the free state from the corresponding platinum(IV, II) complexes. In the former case, the reaction occurred in the presence of an excess of pyridine, in the latter case, the substitution of heterocyclic ligands was carried out by a reaction with bis(diphenylphosphino)ethane, ethylenediamine or methylamine.[50, 51, 62, 64] The reaction sequence, which included the synthesis of the nitrile complex of platinum(IV), its reaction with nitrone and the demetallation of 2,3-dihydro-1,2,4-oxadiazole, was proposed as the general method for the synthesis of 2,3-dihydro-1,2,4-oxadiazole derivatives from nitriles with electron-donating substituents R, which were earlier inaccessible by the conventional metal-free organic synthesis.[50, 64]

Free 2,3-dihydro-1,2,4-oxadiazoles **50** were isolated from the corresponding palladium(II) complexes under the action of sodium sulfide, methylamine or ethylenediamine.[52, 53, 56] In those cases where the activation of nitrile with palladium(II) proved to be sufficient for the cycloaddition reaction to occur, the method of synthesis of 2,3-dihydro-1,2,4-oxadiazoles can be considered as a more efficient and rapid as compared with the method utilizing platinum(II, IV) complexes.

Despite the fact that demetallation of ligated 2,3-dihydro-1,2,4-oxadiazoles was successfully carried out in many cases,[50–53, 56, 62, 64] no general system was developed so far for the isolation of these heterocycles from the platinum and palladium complexes. In certain cases, heterocycles in the free state failed to be obtained probably due to the low stability of the corresponding 2,3-dihydro-1,2,4-oxadiazoles

under conditions of the ligand substitution reaction (see Section III).[30]

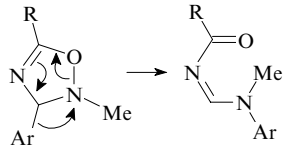
IV. Chemical properties of 2,3-dihydro-1,2,4-oxadiazoles

At present, 2,3-dihydro-1,2,4-oxadiazoles are still a relatively small and inadequately studied class of heterocyclic compounds, which is first of all associated with the lack of sufficiently simple and reliable synthetic methods. The known compounds of this class number in tens, only few examples of reactions characterizing their chemical properties are documented.[67] With the advent and the development of new methods for the synthesis of these heterocycles, accumulation of the data on their transformations has begun. It should be mentioned that the free and ligated 2,3-dihydro-1,2,4-oxadiazoles are unstable due to ring opening.

1. Ring opening in free 2,3-dihydro-1,2,4-oxadiazoles

The products of reactions between aromatic acyclic nitrones and nitriles with electron-withdrawing substituents, namely, compounds **50a**,**b**, undergo further transformations upon prolonged storage in the reaction mixture. As a result, *Z*-configured *N*-acylated amidines were formed (Scheme 4).[41] The ease of this rearrangement is determined by the nature of substituents in the heterocycle. The derivatives formed from nitriles RC≡N with strong electron-withdrawing groups R and arylnitrones containing donor substituents in the benzene ring underwent the heterocycle opening and the 1,2-migration of the aryl group under mild conditions.

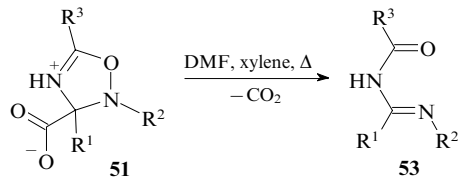
Scheme 4



50a,**b**

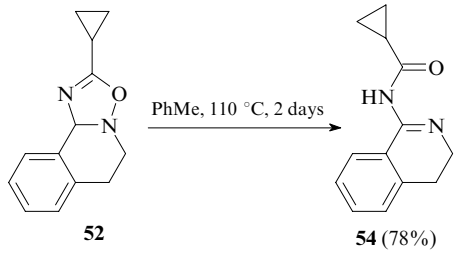
R = CCl_3 (**a**), $C(CN)_2Me$ (**b**).

In addition to the reaction shown in Scheme 4, the ring opening in 1,2,4-oxadiazoles **51** and **52** can be accompanied by decarboxylation or a proton 3,4-shift to afford *N*-acylated products **54** and **55**, respectively.[39, 68]



51 **53**

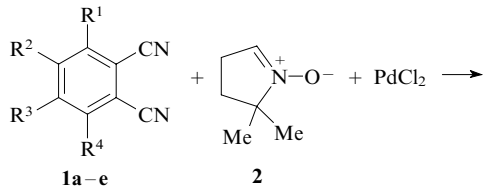
R^1–R^3 = Ar.



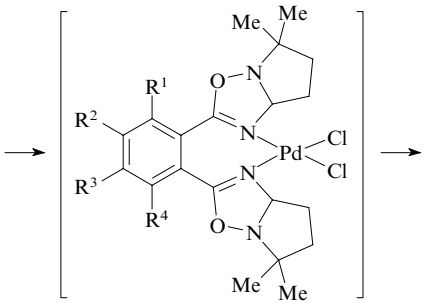
52 **54** (78%)

2. Ring opening in ligated 2,3-dihydro-1,2,4-oxadiazoles

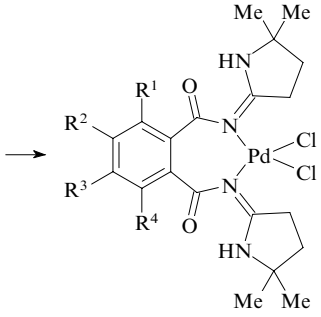
Coordination to the metal centre had a pronounced effect on the chemical stability of 2,3-dihydro-1,2,4-oxadiazoles. As mentioned above, the reaction of platinum nitrile complexes $[PtCl_2(RCN)_2]$ (R = CH_2CO_2Me, CH_2Cl) (**14a**,**b**) with cyclic nitrone **2** afforded ketimine complexes **16a**,**b** (see Scheme 1).[65] Analogous products were obtained in the reaction of phthalonitrile and its derivatives (**1a**–**e**) with nitrone **2** in the presence of palladium chloride. This reaction afforded chelate bisimine complexes **55a**–**e**.



1a–**e** **2**



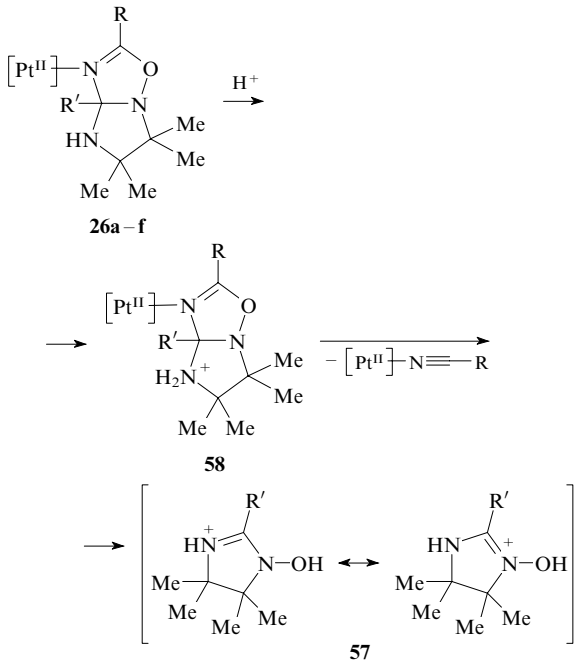
56a–**e**



55a–**e**

Presumably,[42, 65] the reaction proceeded *via* unstable 2,3-dihydro-1,2,4-oxadiazole complexes **56a**–**e**, where the cleavage of the N–O bond proceeded easier with the weakening of electron-withdrawing properties of substituents and the coordination of 2,3-dihydro-1,2,4-oxadiazole to the metal centre. As a result, the rearrangement accompanied by the proton 1,2-shift afforded the corresponding ketimine (see also Scheme 1).

It was mentioned[30] that heterocycles **26**, *i.e.*, the reaction products of coordinated nitriles with imidazoline *N*-oxides **25,** are unstable in the presence of acids. In a chloroform solution in the presence of HCl (or picric acid), they were converted into the original platinum(II) nitrile- or dialkylcyanamide complexes and a protonated dipole, *i.e.*, compound **57**. The reaction mechanism was assumed to include the initial N-protonation of the imidazolidine in the annulated heterocycle **58** was followed by retro-cycloaddition.



R = Et: R′ = H (**a**), Me (**b**); R = NMe_2: R′ = H (**c**), Me (**d**); R = $N(CH_2)_5$: R′ = H (**e**), Me (**f**).

Heterocycles **26** were not isolated in the free state. Probably, under conditions of the demetallation reaction, the retro-cycloaddition proceeded faster than the ligand exchange.

Yet another way of the 2,3-dihydro-1,2,4-oxadiazole ring opening was described in a publication [51] devoted to studies of the reaction of acyclic nitrone **6a** with nitriles containing the activated α-CH_2 group. Presumably, the formation of the substituted *E*-alkene upon heating of platinum complex **43** occurred as a result of retro-cycloaddition followed by the reaction of nitrone **6a** with free nitrile **40** by the mechanism shown in Scheme 3.

V. 1,3-Dipolar cycloaddition of nitrones to isocyanides

No studies describing the reactions of free isocyanides with nitrones have been published so far. Only two publications [25, 69] devoted to reactions of coordinated isocyanides with nitrones are known. An experimental study [25] dealt with the reaction of palladium isocyanide complexes *cis*-$[PdCl_2(CNR)_2]$ with acyclic (**6**) and cyclic (**2**) nitrones. It was shown that under mild conditions (at 5 °C in benzene for acyclic nitrones **6** and in chloroform for cyclic nitrone **2**), a previously unreported 1,3-DCA reaction of nitrone to coordinated isocyanide occurs to afford N-heterocyclic carbene complex **59** (Scheme 5, path *a*). Under more drastic conditions (20–25 °C or MWI at 60 °C) or in chloroform for nitrones **6**, this reaction afforded imine complexes **60** as the main products (path *b*).

Compounds **60** were also formed from cycloaddition products **59** when kept in chloroform at room temperature (path *c*). Thus palladium imine complexes **60** were formed in the reaction of *cis*-$[PdCl_2(CNR)_2]$ with nitrones **2** and **6,** which proceeded through a cycloaddition step as a result of intramolecular cleavage of the heterocyclic carbene ligand. The isocyanate formed upon ring opening was identified in the reaction mixture by electrospray ionization mass spectrometry.

VI. Conclusion

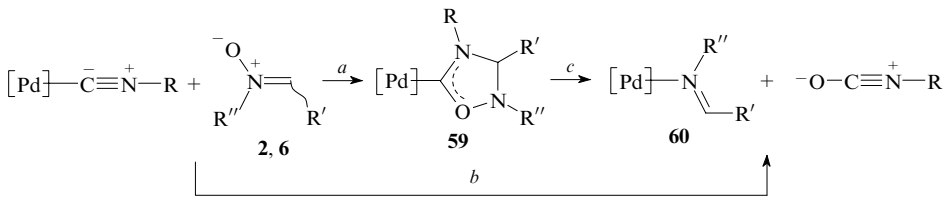
Nitriles and isocyanides proved to be relatively weakly reactive in the 1,3-DCA toward nitrones as compared with other dipolarophiles. In the reaction of nitriles with these dipoles, the possibility of cycloaddition was largely determined by the degree of dipolarophile activation that could be attained by both the introduction of electron-withdrawing substituents into nitrile molecules and the coordination of RCN to a metal. The latter method makes it possible to carry out 1,3-DCA of nitrones to a wide range of nitrile substrates and represents a general method for the synthesis of 2,3-dihydro-1,2,4-oxadiazoles.

In these reactions, the choice of the metal centre is important. Thus the most efficient activators proved to be platinum complexes containing the coordinated dipolarophile RCN. It is only due to the combination of platinum properties such as the kinetic inertness of its complexes in substitution and the 'softness' of the acid that the conditions important for cycloaddition, namely, the dipolarophile activation as a result of its coordination and, simultaneously, the presence of a non-coordinated dipole, are fulfilled. Another advantage of metal-mediated reactions is the possibility of the stereoselective cycloaddition of nitrones to a coordinated nitrile under the effect of chiral agents incorporated in the metal complex.

There are only two publications devoted to 1,3-DCA of nitrones to isocyanides. However, based on the accessible data it can be asserted that the isocyanide coordination to metal activates RCN substrates in the reaction with nitrones.

Cycloaddition of nitrones to nitrile and isocyanide ligands in platinum complexes occurs at the stoichiometric ratio of the reactants, therefore, it is not a catalytic reaction. At present, this type of reactions is the only route to the synthesis of quite a number of heterocycles. The development of the 1,3-DCA method as applied to metal-activated substrates allowed extension of the range of known heterocycles containing 2,3-dihydro-1,2,4-oxadiazole fragments. Thus, as a result of the platinum-mediated reaction of cyclic nitrones with nitriles, new types of annulated heterocyclic

Scheme 5



R = cyclo-C_6H_{11}, Bu^t, 2,6-$Me_2C_6H_3$, 4-$MeOC_6H_4$; R′–R″ = $CMe_2(CH_2)_2$; R′ = Ar, R″ = Me.

systems such as 3*a*,4,5,6-tetrahydroimido[1,2-*b*][1,2,4]oxadiazoles and 5,6-dihydro-3*aH*-[1,3]oxazolo[3,2-*b*][1,2,4]oxadiazoles were synthesized for the first time.[30, 63]

It should be noted that complexes with coordinated heterocycles formed as a result of platinum-mediated cycloaddition exhibited high antitumour activity,[34] while the reaction of coordinated isonitriles with nitrones proved to be a convenient method for the synthesis of palladium *N*-heterocyclic carbene complexes, which are employed as the catalysts of cross-coupling reactions.[32]

Studying the metal-mediated coupling of nitrones with substrates containing the C≡N group made it possible to substantially extend the knowledge of chemistry of 2,3-dihydro-1,2,4-oxadiazoles, N-heterocyclic carbenes and their complexes and gave the first results pertaining to the possible practical application of cycloadducts. The further development may be focused on studies of the dependence of the reaction stereoselectivity on the presence of chiral centres in the dipole – dipolarophile pair, synthesis of enantiomerically pure products for biological tests and also studies of their catalytic activity in cross-coupling reactions. Yet another direction in this field might be the extension of the 1,3-DCA reactions involving metal-activated RCN and RNC substrates to the dipoles of the allyl-anion type (only few examples of this type of reactions are known so far).

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