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Review

1,3-Dipolar cycloaddition of nitrone-type dipoles to uncomplexed and metal-bound substrates bearing the C≡N triple bond

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Contents

Abbreviations: CA, cycloaddition; DCA, 1,3-dipolar cycloaddition; DHOD, 2,3-dihydro-1,2,4-oxadiazole; MWI, microwave irradiation.

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ABSTRACT

Metal-free and metal-mediated routes for 1,3-dipolar cycloaddition of nitrone-type dipoles to substrates bearing the C≡N triple bond are compared and the reactions are categorized. In 1,3-dipolar cycloaddition of nitrones to RCN species, the outcome of the reaction is determined by a degree of activation of the dipolarophile. This activation could be greatly enhanced either by introduction of electron-withdrawing substituents into a nitrile molecule or coordination of RCN to a metal center, or by both methods. The ligation makes favorable the 1,3-dipolar cycloaddition of nitrones to a wide range of RCN substrates, even those with strong electron-donor substituents. This cycloaddition reaction forms the basis for the general method for synthesis of so far poorly studied 2,3-dihydro-1,2,4-oxadiazoles, 2,3-dihydro-1,2,4-oxadiazole-based heterocycles, and 2,3-dihydro-1,2,4-oxadiazole ligand systems. The most efficient activators explored so far are Pt^{IV} and Pt^{II} centers that fortunately combine such properties as the kinetic inertness of their complexes in substitution reactions and the softness of platinum in terms of the HSAB principle. The coordination of isocyanides to a metal center also greatly activates RNC species toward cycloaddition of nitrones. The reaction of nitrones with palladium(II)-bound isocyanides allows the generation of rather stable cyclic aminocarbenes. These species are relevant to Pd complexes with *N*-heterocyclic carbenes that are widely employed in catalysis of various organic transformations.

1. Introduction

1,3-Dipolar cycloaddition (DCA) forms the basis of one of the most important methods for generation of cyclic systems of different sizes ranging from three-membered to macrocyclic. Many of these reactions proceed smoothly without additional activation of reactants. However, when reactivity of even one of the components of the dipole–dipolarophile couple is low, cycloaddition (CA) could be promoted by either physical methods (e.g., high pressure, UV, microwave irradiation (MWI), or ultrasonic treatment) or by various chemical approaches.

A superior chemical method for enhancing the reactivity of the dipole–dipolarophile pair in DCA is the introduction of a metal species into the reaction system that often triggers a key reaction for producing heterocycles. The role of metal centers does not come solely to activation of organic substrates but they could also enhance the chemo-, regio-, and stereoselectivity of CA and stabilize the formed heterocycle by coordination. Metal-catalyzed and metal-mediated processes in many instances allow the performance of certain reactions that are not feasible without the involvement of metal species.

Before the year 2005, the growth of metal-catalyzed and metal-mediated CA (conducted mostly to carbon–carbon multiple bonds) was summarized in a number of review articles and book considerations [1–6]. In the last five years, as a result of interests to DCA from both academia and industry, the number of investigations has dramatically increased and various excellent reviews considering particular aspects of such reactions recently appeared in the literature [7–20].

In the majority of DCAs studied until now, the ligation of dipolarophile and/or dipole to a metal involves the peripheral site that is remote from the reaction center (Fig. 1) [4,5,13,15]. The reactions where a metal center activates the substrate by coordination to a functional group that is directly involved in DCA (Fig. 1) are, so far, less common. However, such studies are increasing and this progress is mostly associated with the development of the click chemistry [8–12,21].

Examples of CA to complexed multiple bonds include metal-activated nitriles and isocyanides. In DCAs, these species exhibit relatively low reactivity when compared with other dipolarophilic sites, for instance, the C=C and C≡C groups. These reactions of uncomplexed and coordinated substrates bearing the C≡N bond

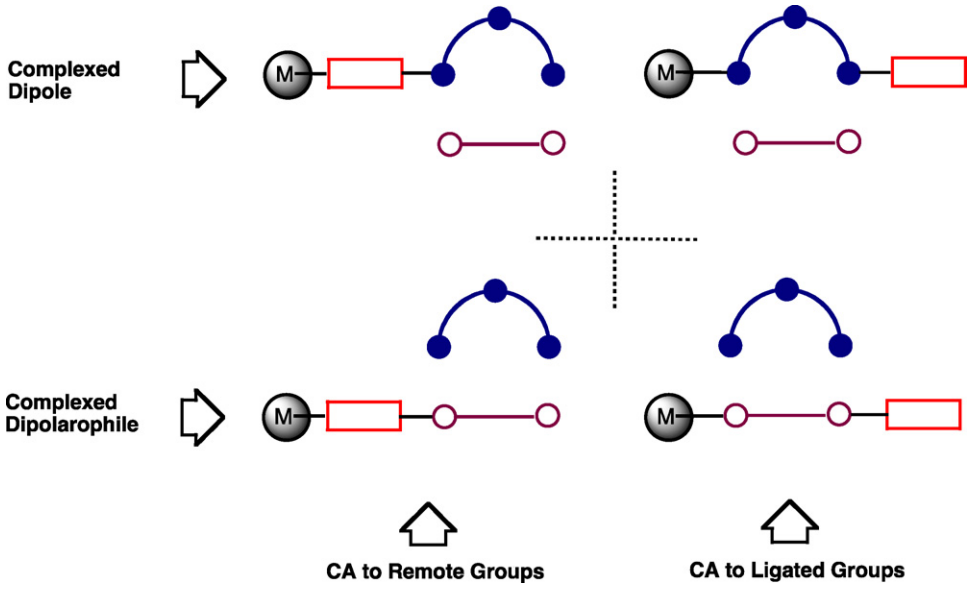


Fig. 1. Different modes of DCA between complexed and uncomplexed reactants.

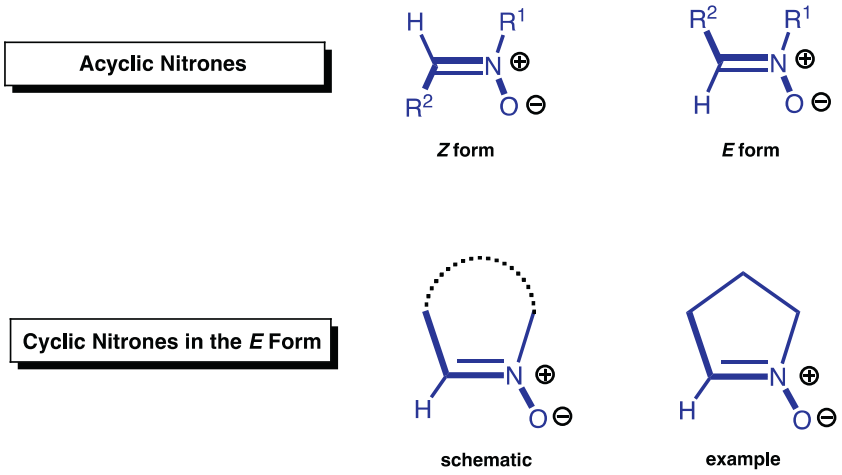


Fig. 2. Schematic representation of acyclic and cyclic nitrones.

are limited to a relatively small number of 1,3-dipoles. Among these, dipoles of the propargyl-allenyl anion type, i.e., organic and inorganic azides (for reviews see [18,19,22], for recent work see [20,23–30]) and, to a lesser extent, nitrile oxides [31,32], are the most studied. Concurrently, examples of DCA between nitriles RCN and dipoles of the allyl anion type such as, for example, nitrones (for reviews on their CA to carbon–carbon bonds see [4,5,15,22,33]) have been substantially less investigated. Furthermore, only few publications were devoted to DCA of dipoles of the propargyl-allenyl anion type to uncomplexed isocyanides [34–38], and only one study [39] deals with CA of nitrones to coordinated isocyanides.

In our previous reviews [40,41], where the coverage was more selective than comprehensive, the first attempt was undertaken to inspect and to systematize reactions of nitriles with nitrones and to compare metal-free and metal-mediated synthetic approaches. Since then many studies dealing with CA of nitrones (and relevant dipoles such as, e.g., nitronates [42]) to metal-activated nitriles and isocyanides have appeared, together with novel data on biological activity of some CA products. Moreover, the early reviews [40,41], were devoted mostly to synthetic aspects of DCA, while theoretical studies performed in this area were not thoroughly surveyed. In view of the emerging importance of DCA to metal-activated CN substrates for both coordination and organic chemistry, a *comprehensive critical survey* in this area was thought to be timely.

The essential goals of this review are at least twofold: (i) to systematize and explain diverse observations and reports and to give a general picture of reaction routes, mechanisms, and driving forces; (ii) to draw attention to the advantages that metal-mediated conversion of substrates with the C≡N triple bond gives to synthetic coordination, organometallic, and organic chemistry. The review is partitioned into two main sections beginning, after this Introduction, with a comprehensive overview of DCA to uncomplexed nitriles (Section 2) where, we systematize factors that determine CA of nitrones to RCN. In Section 3, we turned to DCAs involving metal centers and the influence of the metal on the reaction course is described and compared with that of the conventional metal-free reactions. In addition, in Section 3 we made an effort to tie together both metal-free and metal-mediated protocols and to verify generality and difference in these two approaches, in particular, by applying results from theoretical studies. Eventually, in Section 4, we consider the first studies on metal-mediated CA to isocyanide species producing cyclic aminocarbenes.

Highlighting DCA reactions of substrates bearing a C≡N triple bond is anticipated to enhance their use as synthetic intermediates for generation of heterocycles previously inaccessible (or hardly accessible) by metal-free routes. We hope that the review will stimulate interest in this area, and further experimental studies and theoretical calculations will be performed.

2. 1,3-Dipolar cycloaddition of nitrones to uncomplexed nitriles

Studies on DCA of nitrones to uncomplexed nitriles are limited in number [43–52] due to poor dipolarophilicity of RCN molecules and the progress in the area of CA to RCN species is, in many respects, associated with synthesis and application of highly reactive nitrones in the *E*-form (Fig. 2) as dipoles and, in particular with the commercial availability of a cyclic nitrone such as 5,5-dimethylpyrroline *N*-oxide. Inspection of these rather scarce publications [43–52] still allows us to understand the factors affecting DCA which include the nature of substituents in RCN, structural features of nitrones, and the additional activation of reactants. *Attention!* For convenience of the reader, all available data on CA of nitrones to nitriles are presented in the graphical form in Tables S1–S3 (see Supplementary). For ease of comprehension of the description given in the review, it is recommended to retrieve and to print out these tables. The text of this review contains entries to the tables in bold, as *E* + (number of entry), e.g., graphics for 5,5-dimethylpyrroline *N*-oxide is given in **T1**/**E24**–**E26**, that is Table S1, entries E24–E26.

In terms of orbital interactions, the nitrone–nitrile DCA is classified as an interaction with normal or borderline electron demand [53,54], when the HOMO of the dipole interacts with LUMO of the dipolarophile. Hence, such reactions can be promoted by using dipolarophiles with electron-withdrawing substituents and/or dipoles with electron-donor substituents.

2.1. Effect of substituents in nitrile

In general, RCN species bearing donor substituents R (e.g., R = alkyl) exhibit low dipolarophilicity and they do not react with acyclic nitrones even under relatively drastic conditions. However, nitriles RCN, where R is a strong electron-withdrawing group (for example, Cl_3CCN or EtO_2CCN [46,47]), are rather reactive toward acyclic nitrones even under mild conditions (**T1**/**E1**–**E4**, **T1**/**E9**).

The effect of an introduction of electron-withdrawing substituent to the nitrile molecule on the $HOMO_{nitrone}$–$LUMO_{nitrile}$ gap was quantitatively estimated using quantum chemical calculations [43–51,53–55]. Acetonitrile MeCN has a doubly degenerate LUMO (Fig. 3A). Substitution of the Me group for the Ph group results in splitting the degeneracy of this LUMO. One orbital ($\pi(CN)_{\perp}$) (Fig. 3B) significantly decreases its energy from MeCN to PhCN and

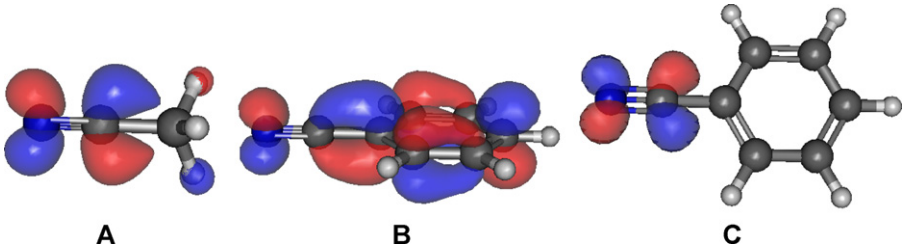


Fig. 3. Plots of the LUMOs of MeCN (A), LUMO (B) and LUMO + 1 (C) of PhCN.

is orthogonal to the plane of the Ph ring. Another orbital ($\pi(CN)_{||}$) (Fig. 3C) is unaffected by the substituent change and is an in-plane orbital. The analysis of geometry of a transition state for the reaction of *Z*-PhC(H)=N(Me)O with PhCN revealed that the second orbital (LUMO + 1) of PhCN is responsible for the interaction with the HOMO of the nitrone [55]. This explains why PhCN is only slightly more reactive than MeCN toward nitrones (**T1**/**E6**, **T1**/**E14**, and **T1**/**E16**), i.e., the calculated $\Delta G^{\neq}$ values in CH_2Cl_2 solution for the reactions of CH_2=N(Me)O with MeCN and PhCN are 29.4 and 28.5 kcal/mol, respectively [54].

The replacement of the Me group for the strong electron-acceptor CF_3 group leads to a significant decrease of the LUMO energy from +1.00 eV in MeCN to −0.76 in CF_3CN (B3LYP/6-31G*) [53]. This provides much higher reactivity of CF_3CN compared to MeCN, the calculated $\Delta G^{\neq}$ values in CH_2Cl_2 solution for the reactions of $\underline{C}H_2(CH_2)_2C(H)=\underline{N}O$ with MeCN and CF_3CN being 30.3 and 20.6 kcal/mol.

The reactivity of various nitriles in DCAs to nitrones was estimated based on synthetic experiments [46,47,50,51,56]. Thus, RCN having strong electron-withdrawing substituents (e.g., R = CO_2Me) are most reactive in the reactions with the azahomoadamantane-based nitrones (**T1**/**E14** and **T1**/**E15**) and the activity of RCN in CA decreases in the series of substituents: methoxycarbonyl > aryl ≫ alkyl [50].

The reactivity of nitriles was estimated [47] upon conducting the reactions of RCN with the β-carboline-based nitrones (**T1**/**E16**–**E23**). To reveal the factors affecting the reactivity of RCN, three types of nitriles were examined toward CA, i.e., 2-substituted 2-cyanopropanes $Me_2C(Y)CN$ (**T1**/**E6** and **T1**/**E17**), the ylidene malononitriles $X^1X^2C=C(CN)_2$ (**T1**/**E18**–**E19**), and nitriles shown in **T1**/**E6**, **T1**/**E16**, and **T1**/**E29**. The inductive effect of the substituent Y on the activation of the CN group was verified by inspection of the reactivity of substituted cyanopropanes $Me_2C(Y)CN$ (**T1**/**E17**). The ability of nitriles RCN to be involved in CAs decreases with decreasing acceptor properties of R in the series NO_2, CN > CO_2Et > Ph, Alk. The change in the reactivity of cyanocyclopropanes in CA to the nitrones (**T1**/**E20**–**E23**) follows the same trend. The dipolarophiles with the CO_2H or H substituents in the geminal position to the CN group listed in **T1**/**E22**–**E23** are not involved in DCA even upon prolonged heating of the reaction mixture under high pressure, while the nitriles bearing the second CN group in the geminal position (**T1**/**E20**–**E21**) react with the nitrones to give the corresponding 2,3-dihydro-1,2,4-oxadiazoles (DHODs) [46].

The monosubstituted ylidene malononitriles $X^1X^2C=C(CN)_2$ (X^1 = H) (**T1**/**E18**) are readily involved in CA to the nitrile group and their reactivity strongly depends on the nature of X^2. Thus, the electron acceptors increase the reactivity of the nitrile group in DCA and the data obtained illustrate the change in the reactivity of nitriles in the series of the substituents 2-furyl > *p*-(Cl)C_6R_4 > Ph.

For the nitriles shown in **T1**/**E16**, the reactivity decreases in the series of substituents CCl_3 > CO_2Et > NMe_2 > Ph, whereas acetonitrile does not react with nitrones even at a prolonged reaction time. The relatively high reactivity of the cyanamide Me_2NCN – which is an exception from the series – was attributed [47] to the inversion of the control of the reaction by FMOs. Therefore, the above-mentioned data provide evidence that in most cases the stronger the electron-withdrawing properties of R in RCN, the higher the reactivity of the corresponding nitriles in CA with nitrones.

Pombeiro and coworkers [52] reported on different reaction routes observed upon interaction between various phthalonitriles and the highly reactive cyclic nitrone (**T1**/**E25**–**E26**); occurrence of these process determined by the nature of substituents in the dinitriles. Thus, under the same reaction conditions (80 °C, sealed tube), *o*-phthalonitriles bearing electron donor substituents (e.g., Me), produced phthalimides rather than underwent CA. In contrast, phthalonitriles with electron-withdrawing substituents afforded monocycloadducts (**T1**/**E25**), whereas both nitrile groups of $F_5C_6(CN)_2$-*o* were involved in DCA to furnish *bis*-DHOD (**T1**/**E26**).

2.2. Structural features of nitrones

Nitrones in the *Z*-configuration having aromatic substituents at the C atom of the C=N group found a broad application in organic chemistry due to their high stability (**T1**/**E1**–**E13**) [5,50,57]. However, these species are insufficiently reactive toward most of the conventional alkyl- and arylnitriles RCN (e.g., R = Me, Et, or Ph). Specifically more reactive *E*-form may be stabilized, e.g., in the cyclic nitrones (see below), and these dipoles can be involved in CA to some nitriles giving corresponding DHODs.

A comparative qualitative synthetic study [50,51] of CA between various nitrones such as the azahomoadamantane derivatives (**T1**/**E14**), the cyclic (**T1**/**E24**) and the acyclic (**T1**/**E11**) nitrones, and the nitriles RCN (R = *o*-, *m*-, or *p*-(MeO)C_6H_4, *o*-, *m*-, or *p*-(NO_2)C_6H_4, Ph, CO_2Me) demonstrated that the reactivity decreases in the series of nitrones shown in entries **T1**/**E14A** > **T1**/**E14B** > **T1**/**E24** > **T1**/**E11**. Thus, the reaction of the nitrone (**T1**/**E14**) with the highly reactive electron-deficient nitrile $NCCO_2Me$ proceeds smoothly at 20–25 °C. At higher temperatures (80–125 °C), the azahomoadamantane-derived nitrones (**T1**/**E14**), react with less reactive nitriles RCN (R = *o*-, *m*-, or *p*-(MeO)C_6R_4, *o*-, *m*-, or *p*-(NO_2)C_6H_4, Ph, Me). Nitrone (**T1**/**E24**), involved in CA to rather reactive aromatic nitriles and $NCCO_2Me$ in a similar way to the dipole shown in **T1**/**E14**, whereas the acyclic nitrone (**T1**/**E11**) is less reactive in DCA.

The reactivity study of CA involving the β-carboline-based nitrones (**T1**/**E19**) indicated [47] that the reactivity of these species in DCA should correlate with the electron enrichment of the O atom of the nitrone group. The enrichment could be estimated from the first two average-weighted ionization potentials. The reactivity decreases in the following order: **T1**/**E19** (**B**) > **T1**/**E19** (**C**, **D**, **A**) > (**T1**/**E29**) > (**T1**/**E6**). This corresponds with a decrease in the ionization potentials. The β-carboline nitrone (**T1**/**E19B**) bearing the electron-donor group OMe appeared to be most reactive, whereas the Cl substituents do not exhibit a noticeable effect on the reactivity of the nitrone in CA compared to unsubstituted nitrone (**T1**/**E19A**). All dipoles (**T1**/**E19A**–**D**) are more reactive than the cyclic nitrone (**T1**/**E29**) and substantially more reactive than the acyclic compound (**T1**/**E6**).

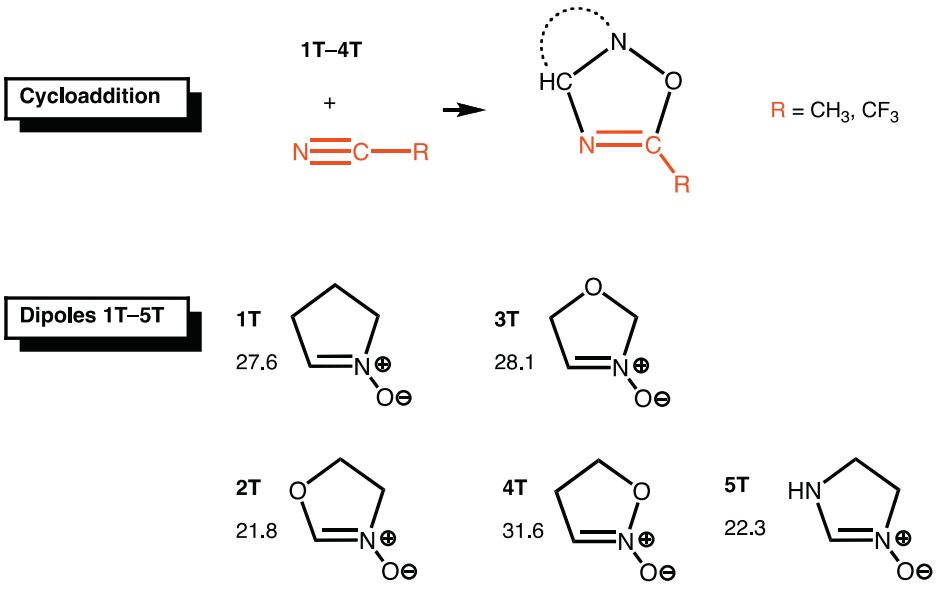


Fig. 4. Reaction of cyclic nitrones **1T**–**5T** with RCN. Gas phase $\Delta G^{\neq}$ values (kcal/mol) are indicated for the reactions with MeCN.

The study of the kinetics of DCA of the nitrones ArC(H)=N(O)Bu^t to $C(CN)_3Cl$ demonstrated that electron-donor substituents in the aryl ring of the dipole favor an increase of CA rate, whereas electron-withdrawing substituents bring about an inhibition of the reaction (**T1**/**E2**) [43].

The reactivity of five cyclic nitrones **1T**–**5T** (Fig. 4) with both MeCN and CF_3CN as well as of the acyclic nitrone MeC(H)=N(Me)O (**6T**) with MeCN have been studied theoretically (B3LYP/6-31G* method) [53,58]. Acyclic nitrone **6T** in the *Z*-form was less reactive than the cyclic one with a purely hydrocarbon chain (**1T**) by 2.7 kcal/mol, i.e. by a factor of 100. The higher reactivity of the cyclic vs. acyclic dipole is explained by the fixation of **1T** in the more strained and, hence, more reactive *E*-configuration. Comparison of dipoles **1T**–**5T** indicated that the reactivity of nitrones decreases along the series **5T** ~ **2T** > **1T** ~ **3T** > **4T**. Thus, dipoles **5T** and **2T** are the most reactive toward nitriles, while nitronate **4T** is the least reactive dipole in this series. The reactivity of **1T** and **3T** is similar because the cyclic oxygen in **3T** is far from the reacting C=N–O site and does not significantly affect the reactivity. Finally, comparison of the reactivity of acyclic *alkyl* and *aryl Z*-nitrones (MeC(H)=N(Me)O and (p-C_6H_4R)C(H)=N(Me)O, R = Me, OMe) with MeCN indicates that the former is by 2.9–3.2 kcal/mol more reactive than the latter (i.e., by a factor of 134–222) [54].

To summarize this section, the reactivity of nitrones toward DCA to uncomplexed RCN species should increase, on the one hand, in the presence of stronger electron-donor substituents at the carbon atom of the C=N moiety and, on the other hand, on going from acyclic to cyclic nitrones. Nitrones with alkyl substituents are typically more reactive than those having aromatic substituents. Among dipoles (**T1**/**E19A**–**D**), the β-carboline derivative bearing the OMe group in the β-carboline ring (**E19B**) and azahomoadamantane-based nitrones (**T1**/**E14A**) are the most reactive.

2.3. The steric factor

The effect of this factor on the reaction rate and the yield of the product was revealed for substituted aromatic nitriles in the reactions with the nitrones given in **T1**/**E14** [50]. Thus, CA to the *o*-substituted aromatic nitriles proceeds more slowly than that with *m*- and *p*-substituted derivatives and produces DHOD in lower yields. The presence of the methyl group at the C atom of the azomethine group of the nitrone (**T1**/**E14B**) also hinders the reaction and leads to a decrease in the yields of DHODs by 30–50% compared to the unsubstituted product, see **T1**/**E14A**. The reactions of the monosubstituted ylidene malononitriles (**T1**/**E18A**–**D**) with the nitrones produce one sterically unhindered stereoisomer [47]. The ylidene malononitriles X^1X^2C=C(CN)$_2$ (**T1**/**E18E**–**F**) are involved in CAs with difficulty, which is reflected, in particular, in the yield of DHODs. The yield was increased only when CA was performed under high pressure. Just one sterically less hindered CN group is involved in the reaction of the dinitrile (**T1**/**E20** and **T1**/**E27**) with the nitrones. CA of the dinitrile (**T1**/**E21**) to the nitrones affords two sterically less hindered diastereomers of four possible diastereomers [46].

2.4. The solvent effect

This effect was *experimentally* studied [47] only for CA of the cyclic nitrone to dimethylmalononitrile $Me_2C(CN)_2$ (**T1**/**E29**). CA was carried out in three different solvents (toluene, ethoxybenzene, and 2-methoxyethanol). The reaction proceeds more readily in less polar toluene, and this effect was attributed to a slight decrease in the polarity of the transition state compared to the polarity of the reactants.

These results were confirmed by extensive *theoretical* investigations of the solvent effect for the reactions of the acyclic (CH_2=N(Me)O) and cyclic (**1T**–**4T**) nitrones with MeCN, CH_2=CH–C≡N and CH≡C–C≡N [53–55,58,59]. The stabilization of the reactants level due to solvation is higher than that of the transition state and product levels. This accounts for an increase of the activation barriers and decrease of the exoergonic character of the CAs (i) from the gas phase to solution and (ii) from the lesser to the greater polar solvents (Table 1). Furthermore, solvation is one of the key factors determining the chemo-, regio-, and stereoselectivity of CAs to bifunctional nitriles (Section 3).

2.5. Other factors

CA of nitrones to various dipolarophiles [43,51], and, in particular, to nitriles [46,51], could be enhanced by high pressure. Thus, the reaction of the acyclic nitrone (**T1**/**E11**) with the nitriles RCN

Table 1
Calculated (B3LYP/6-31G*) activation ($E_{a,g}$ and $E_{a,s}$) and reaction (ΔE_g and ΔE_s) energies for the gas phase and solution (in kcal/mol).

Dipole	Dipolarophile	Solvent[a]	$E_{a,g}$	$E_{a,s}$	ΔE_g	ΔE_s	Ref.
CH_2=N(Me)O	MeCN	CH_2Cl_2	14.0	15.7	−23.8	−19.9	[54]
CH_2=N(Me)O	CH≡CC≡N	CH_2Cl_2	13.5	15.2	−21.3	−21.6	[59]
CH_2=N(Me)O	CH≡CC≡N	C_6H_6	13.5	14.4			[59]
CH_2=N(Me)O	CH≡CC≡N	heptane	13.5	14.7			[59]
CH_2=N(Me)O	CH_2=CHC≡N	CH_2Cl_2	13.3	16.3	−25.5	−24.4	[59]
PhC(H)=N(Me)O	MeCN	CH_2Cl_2[b]	21.7	31.6[b]	−11.1	−1.3[b]	[55]
1T	MeCN	CH_2Cl_2	13.8	16.5	−22.0	−19.4	[53]
2T	MeCN	H_2O	7.8	11.9	−30.7	−28.0	[53]
2T	MeCN	$MeNO_2$	7.8	10.8	−30.7	−28.3	[53]
2T	MeCN	MeCN	7.8	10.4	−30.7	−28.8	[53]
2T	MeCN	EtOH	7.8	11.9	−30.7	−27.6	[53]
2T	MeCN	CH_2Cl_2	7.8	11.1	−30.7	−28.2	[53]
2T	MeCN	$CHCl_3$	7.8	10.2	−30.7	−29.0	[53]
2T	MeCN	C_6H_6	7.8	9.9	−30.7	−29.0	[53]
2T	MeCN	heptane	7.8	9.4	−30.7	−29.7	[53]
3T	MeCN	CH_2Cl_2	13.6	17.0	−27.6	−25.6	[53]
4T	MeCN	CH_2Cl_2	18.1	20.9	−23.7	−22.3	[53]
5T	MeCN	CH_2Cl_2	8.6	15.6	−25.3	−12.6	[58]

[a] The CPCM model was used for the solvent effect calculations unless stated otherwise.
[b] The SCRF model was used for the solvent effect calculations (ε = 8.9).

(R = Me or Ph) at 10 kbar leads to a 3–12-fold decrease in the reaction time [51]. In addition, CA of the nitrone (**T1**/**E21**) to the nitrile performed at 12 kbar leads to higher yield of the corresponding heterocycle (90% vs. 74% under the normal pressure) [46]. The use of MWI in CA of the nitrone *Z*-PhC(H)=N(O)Ph to the reactive nitrile $NCCO_2Et$ leads to acceleration of the reaction and an increase in the yield (from 24 h to 5 min and from 4 to 39%, respectively, [48]) as compared to the conventional heating [48]. Focused MWI was also successfully employed for assistance of CA of nitrones to metal-ligated nitriles [60].

In the end of Section 2, it is worthwhile mentioning that DHOD systems have recently been obtained by treatment of RCN with various oxaziridines at elevated temperatures (120–140 °C) [61,62], but this successful method for generation of DHODs is so far restricted to electron-deficient aryl nitriles (see Table S2; **T2**/**E1**–**E13**).

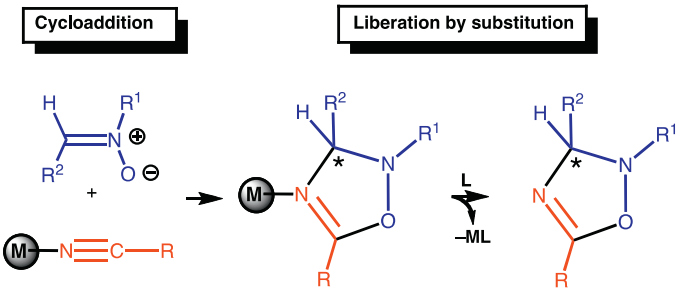
3. 1,3-Dipolar cycloaddition of nitrones to complexed nitriles

Publications devoted to CA of nitrones to complexed RCN substrates emerged approximately a decade ago and they include experimental (see Table S3; **T3**/**E1**–**E28**) and theoretical studies (carried out by quantum chemical calculations at the Hartree–Fock, DFT, MP2–MP4, CCSD(T), and CBS-Q levels of theory). Coordination of a nitrile to metal centers results in their dipolarophilic activation and also affected chemo- and stereoselectivity of CA.

Thus, e.g., the $[Pt^{IV}Cl_4(RCN)_2]$ (R = Me, Et, Ph) and $[Pt^{II}Cl_2(RCN)_2]$ (R = Ph) complexes react with nitrones even at room temperature (20–25 °C, 1.5–6 h for the Pt^{IV}- and 24–48 h for the Pt^{II}-complexes; yields are 70–90 and 56–74%, respectively) to form (DHOD)Pt(IV- and II) species (cycloaddition, Scheme 1; **T3**/**E4**, **T3**/**E5** and **T3**/**E20**–**E22**) [60,63,64]), whereas uncomplexed nitriles RCN does not react with the same nitrones even under much more drastic reaction conditions.

3.1. Factors affecting the cycloaddition to complexed nitriles

The coordination of dipolarophile to a Lewis acid modifies their reactivity. The type and degree of such a modification is traditionally interpreted in terms of the FMO theory. For the normal electron demand reactions [65,66] predominantly controlled by the $HOMO_{dipole}$–$LUMO_{dipolarophile}$ type of the interaction (the case of nitrone-to-nitrile CAs), the coordination of the dipolarophile



Scheme 1. Schematic representation of CA of nitrones to metal-bound nitriles followed by liberation of heterocycles formed.

results in a decrease of the $LUMO_{dipolarophiles}$ energy and of the HOMO–LUMO gap (Fig. 5).

As a result, the dipolarophile becomes more reactive toward CA. At the same time, for the highly asynchronous reactions another factor starts to play a role, i.e., the charge factor [67].

When CA is asynchronous, one of two new contacts in transition state is formed well before the second one (Fig. 6). Therefore, such a reaction may be partially considered as a nucleophilic addition, which is driven by the effective charges on the interacting atoms (mostly of the nitrile C atom for CAs to nitriles).

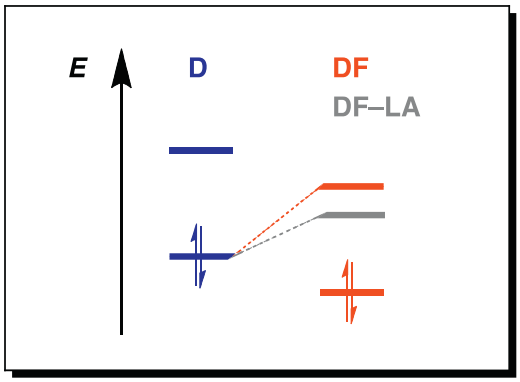


Fig. 5. Frontier molecular orbitals of dipole (**D**), uncomplexed dipolarophile (**DF**), and **DF** coordinated to Lewis acid (**LA**).

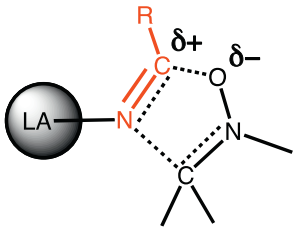


Fig. 6. Transition state of asynchronous CA of a nitrone to a coordinated nitrile.

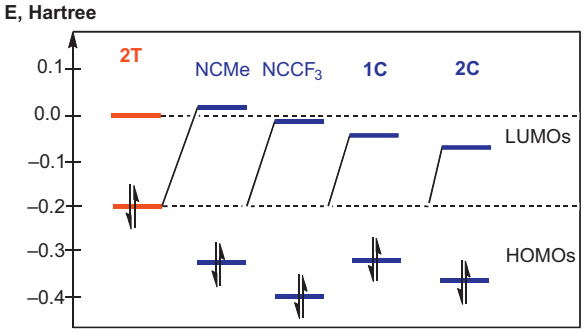


Fig. 7. Energies of frontier MOs of nitrone **2T**, nitriles NCR, and complexes $[PtCl_2(NCMe)_2]$ (**1C**) and $[PtCl_4(NCMe)_2]$ (**2C**) [53].

3.1.1. Nature of the metal center

The nature of metal centers plays the major role in metal-mediated CA. In terms of FMO, there are several criteria for choice of the metal that provides an efficient activation of the nitrile group. First, the metal should form a strong coordination bond with nitrile, or, in other words, the metal should have high "nitrilophilicity". Second, the metal should be in a relatively high oxidation state, to provide a significant shift of the electron density from the nitrile group sufficiently lowering the $LUMO_{nitrile}$ energy and increasing the atomic charge on the nitrile C atom. Furthermore, the selective coordination of nitrile (but not nitrone) is important, insofar as the joint coordination of dipole and dipolarophile lowers the FMO energies of both reactants and leads to a lower activation or even to an inhibition (see, for example, **T3**/**E24**). The selectivity of RCN ligation could be achieved by using a "soft" metal center, which is coordinated only to the relatively "soft" nitrogen atom of RCN rather than to the "hard" oxygen atom of a nitrone.

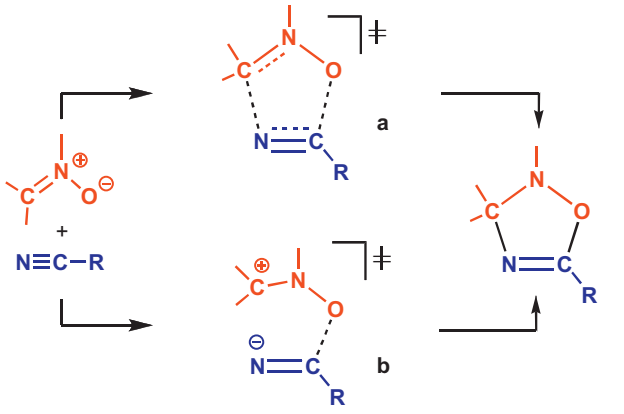
The platinum group metals (first of all, Pt and Pd) generally fulfill these criteria. Indeed, theoretical calculations demonstrated that the $LUMO_{nitrile}$ energy in *trans*-$[PtCl_2(NCMe)_2]$ (**1C**) is even lower than that in CF_3CN that bears the very strong electron-acceptor substituent CF_3 (Fig. 7) [53], and the positive charge on the nitrile C atom increases from 0.29 in MeCN to 0.48 in *trans*-$[PtCl_2(NCMe)_2]$ [68]. Coordination of MeCN to Pt^{II}, Pt^{IV}, or Pd^{II} dramatically decreases the activation barriers of CA (by 6.6–20.4 kcal/mol that corresponds to enhancement of the reaction rate by a factor of 7×10^4–9×10^{14}) (Table 2) [53,54,58,59,69–71]. It is important that coordination usually activates nitriles better than the introduction of an electron-acceptor substituent even such strong as CF_3; the activation energy decreases on going from MeCN to CF_3CN by 5.5–8.1 kcal/mol. Furthermore, the reactions of platinum-bound nitriles are also more thermodynamically favorable than CAs to free RCN. In some cases, the latter processes are endoergonic (e.g., the reaction between $\underline{C}H_2CH_2NHC(H)=\underline{N}O$ (**5T**) and MeCN in CH_2Cl_2 solution) that explains a low stability of uncomplexed DHODs, some of them split upon the liberation from the coordination sphere of the metal [58]. Thus, the activation of nitriles in Pt or Pd complexes can be interpreted in terms of both kinetic and thermodynamic arguments.

The highest enhancement of the reactivity may be achieved when the C≡N group is doubly activated, i.e., by coordination to a metal center and by the introduction of an electron-acceptor

Table 2
Theoretically calculated (at the B3LYP/6-31G* level) gas-phase Gibbs free energies of activation and reaction (in kcal/mol) for CAs of nitrones to the C≡N group of free and Pt or Pd bound nitriles.[a]

Dipole	Dipolarophile	$\Delta G^{\neq}$	ΔG	Refs.
CH_2=N(Me)O	N≡CMe	27.65	−7.60	[54,70]
	N≡CF_3	20.13	−13.96	[71]
	N≡CC≡CH	25.72	−6.20	[59]
	N≡CCH=CH_2	26.83	−8.81	[59]
	trans-$[PtCl_2(N{\equiv}CMe)_2]$ (**1C**)	19.58	−15.31	[54,70]
	trans-$[PtCl_2(N{\equiv}CC{\equiv}CH)_2]$	16.49	−15.54	[59]
	trans-$[PtCl_2(N{\equiv}CCH{=}CH_2)_2]$	17.14	−17.67	[59]
	trans-$[PtCl_2(N{\equiv}CMe)(N{\equiv}CCF_3)]$[b]	4.34	−25.31	[71]
	trans-$[PtCl_4(N{\equiv}CMe)_2]$ (**2C**)	8.04	−22.17	[54,70]
	trans-$[PtCl_4(N{\equiv}CC{\equiv}CH)_2]$	7.79	−20.24	[59]
	trans-$[PtCl_4(N{\equiv}CCH{=}CH_2)_2]$	5.82	−25.24	[59]
Z-MeCH=N(Me)O	N≡CMe	30.30	−4.73	[53]
	trans-$[PtCl_2(N{\equiv}CMe)_2]$	19.0	−12.8	[69]
	trans-$[PdCl_2(N{\equiv}CMe)_2]$	20.7	−13.9	[69]
Z-PhCH=N(Me)O	N≡CCH=CHPh	20.4[c]	−13.1[c]	[72]
	F_3B–N≡CCH=CHPh	6.6[c]	−28.5[c]	[72]
	trans-$[PtCl_2(N{\equiv}CMe)(N{\equiv}CCH{=}CHPh)]$[d]	11.3[c]	−21.6[c]	[72]
2T	N≡CMe	21.84	−13.94	[53]
	N≡CCF_3	13.75	−19.45	[53]
	trans-$[PtCl_2(N{\equiv}CMe)_2]$	9.39	−21.95	[53]
	trans-$[PtCl_4(N{\equiv}CMe)_2]$	1.44	−22.61	[53]
4T	N≡CMe	31.62	−7.55	[53]
	N≡CCF_3	26.14	−13.60	[53]
	trans-$[PtCl_2(N{\equiv}CMe)_2]$	25.01	−15.53	[53]
	trans-$[PtCl_4(N{\equiv}CMe)_2]$	16.97	−17.63	[53]
5T	N≡CMe	22.3 (29.3)	−9.0 (+3.7)	[58]
	trans-$[PtCl_2(N{\equiv}CMe)_2]$	4.6 (18.8)	−19.7 (0.0)	[58]

[a] Energies corrected on the solvent effect for CH_2Cl_2 taken as solvent are in parentheses.
[b] $NCCF_3$ participates in CA.
[c] Values based on the total energies rather than Gibbs free energies.
[d] NCCHCHPh participates in CA.



Scheme 2. Formation of cyclic (**a**) and acyclic (**b**) transition states upon the reaction of nitrones with nitriles.

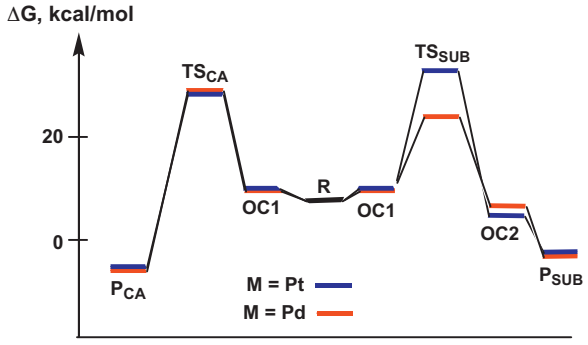


Fig. 8. Energy profile of the cycloaddition and substitution reactions between MeC(H)=N(Me)O and complexes *trans*-[$MCl_2(NCMe)_2$]; R – reactants, P – products, TS – transition states, OC – orientation complexes.

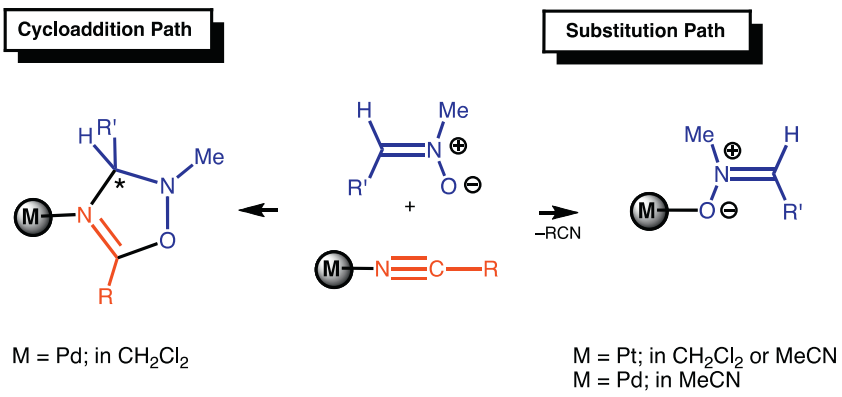
group R (**T3**/**E1**–**E2**, **T3**/**E15**, **T3**/**E28**). The calculated activation barrier of the reaction between CH_2=N(Me)O and CF_3CN ligated in the model complex *trans*-[PtCl(NCMe)($NCCF_3$)] is much lower (by 15.2 kcal/mol) than that of the reaction CH_2=N(Me)O + *trans*-[$PtCl_2(NCMe)_2$] (Table 2). At the same time, the use of the highly activated C≡N group in RCN species may decrease the reaction selectivity due to a decomposition of formed DHODs as a result of the N–O bond cleavage (see Sections 3.4.1 and 3.4.2) [73].

The coordination of nitriles also often changes the reaction mechanism. CAs of nitrones to free RCN occur via a 5-membered cyclic transition state (**a**, Scheme 2). The mechanism is concerted highly synchronous even in the case of dipolarophiles bearing strong electron-acceptor substituents (i.e. $NCCF_3$) [53–55,59,70]. The parameter S_y proposed as a quantitative measure of the synchronicity [74–77] is 0.85–0.95 for these processes (S_y = 1 for the perfectly synchronous reactions and S_y = 0 for stepwise processes). In contrast, CAs to metal-bound nitriles are significantly asynchronous with the S_y value of 0.51–0.81. Despite such high asynchronicity, the topological analysis of the electron density distribution indicated that transition states formed upon these reactions are usually cyclic (type **a**, Scheme 2). Meanwhile, examples of the formation of acyclic transition states for the concerted mechanism (type **b**, Scheme 2) are known (e.g., for the reaction of **2T** with *trans*-[$PtCl_4(N{\equiv}CMe)_2$]) [53]. In some cases, the coordination of RCN provokes the switch of the global type of the mechanism. For example, the mechanism of the reaction of PhC(H)=N(Me)O with $F_3B{\cdots}N{\equiv}CMe$ is borderline between the concerted and stepwise types [55].

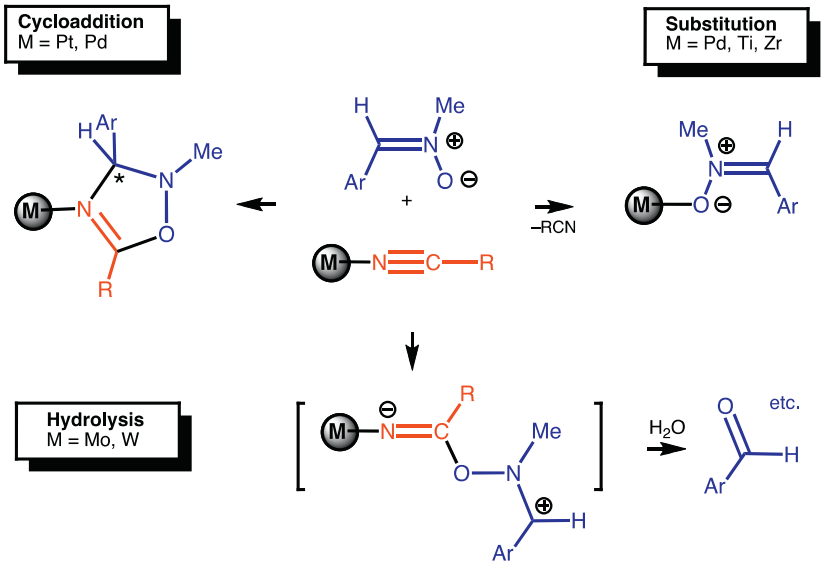
In agreement with the theoretical results described, an inspection of the published data given in Section 3 suggests that DCAs proceed successfully only with nitriles that are bound to platinum(II and IV) and, sometimes, to palladium(II) centers (see Table S3). In the attempted reactions with nitrones of other RCN species bound to other metal centers (i.e., Ti^{IV}, Zr^{IV}, Mo^{IV}, W^{IV}), no evidence for the generation of DHODs was obtained [78].

The dependence of the reaction pathway on the nature of solvent is associated with the higher lability of palladium complexes when compared with relevant platinum species and with more pronounced hardness of the Pd^{II} center (in terms of the HSAB principle [78–80]) than that of the Pt^{II} center. This factor determines the facile replacement of a softer base (RCN) by a harder base (*O*-center of the nitrone) in the absence of an excess nitrile (Scheme 3) [78,81]. In experiment, the reaction between the nitrone *p*-MeC_6H_4CH=N(Me)O and [$PdCl_2(RCN)_2$] (R = Ph, Me) in the corresponding RCN proceeds at 45 °C (R = Ph) or reflux (R = Me) for 1d and allows the isolation of [$PdCl_2(DHOD)_2$] (**T3**/**E24**). In CH_2Cl_2 or acetone, this reaction proceeds in another direction to achieve the unstable nitrone complex [$PdCl_2${ON(Me)=CH(C_6H_4Me-*p*)}$_2$] [81].

In accord with the quantum-chemical calculations [69], this switch of the reactivity from CA (in the case of Pt) to substitution (in the case of Pd) is accounted for by the significantly lower Pd–N bond energy in comparison with the Pt–N bond energy that is consistent with the higher lability of the Pd complexes. Indeed, the calculated M–N bond energies are 48.8 and 36.2 kcal/mol for the complexes *trans*-[$PtCl_2(NCMe)_2$] and *trans*-[$PdCl_2(NCMe)_2$], respectively. Correspondingly, the activation barrier of CA between the nitrone MeC(H)=N(Me)O and *trans*-[$PtCl_2(NCMe)_2$] is lower than that of the substitution reaction (ΔG in CH_2Cl_2 solution is 24.3 kcal/mol vs. 28.8 kcal/mol), while the opposite trend was found for complex *trans*-[$PdCl_2(NCMe)_2$] (ΔG_s is 26.1 kcal/mol vs. 22.6 kcal/mol) (Fig. 8).



Scheme 3. Interaction of nitrones with nitrile complexes.



Scheme 4. Various reactivity modes of nitrones toward metal-bound nitriles.

Wagner and colleagues studied reactions of the acetonitrile ligands in $[MCl_4(MeCN)_2]$ (M = Ti^{IV}, Zr^{IV}, Mo^{IV}, and W^{IV}) with the nitrones *Z*-ArC(H)=N(O)Me (Scheme 4) [78] and in neither case CA products, similar to those observed at Pt^{IV} centers, were detected.

For the titanium(IV) and zirconium(IV) complexes, which act as hard acids, rapid substitution of the nitrile ligand by the nitrone led to polymeric complexes with the overall formula $[MCl_4\{ON(Me)=CHAr\}_n]$ (n = 1.3–1.8); it is anticipated that the polymer is formed via Cl or O bridges. For the molybdenum(IV) and tungsten(IV) species, the nitrone undergoes hydrolysis to furnish, in particular, the aldehyde ArC(H)=O. The authors [78] suggested that the hydrolysis occurs as indicated in Scheme 4.

Thus, among metals studied until now, platinum centers are the most promising activators of RCN substrates in DCA with nitrones. The combination of such properties as significant kinetic inertness of Pt complexes and softness of this metal center makes the $Pt–N_{nitrile}$ bond robust toward substitution with the *O*-center of the nitrone, while the significant shift of electron density from the nitrile group upon coordination provides favorable conditions for CA between metal-bound RCN and uncomplexed nitrone.

3.1.2. Metal center oxidation state

In complexes, metal oxidation state substantially affects reactivity of RCN ligands toward CA. This is illustrated, for instance, by CAs of rather unreactive *Z*-configurated acyclic nitrones to RCN ligands in the complexes $[PtCl_n(PhCN)_2]$ (n = 2, 4) conducted under similar conditions for both platinum(II) and platinum(IV) species (CH_2Cl_2, 20–25 °C; yields are 56–74% for Pt^{II}- and 71–84% for Pt^{IV}-species) (**T3**/**E4**–**E10** and **T3E20**–**E22**). Thus, CA of the nitrones *Z*-ArC(H)=N(O)R (Ar/R = Ph/Me; *p*-tol/Me; Ph/CH_2Ph) to the PhCN ligands in the Pt^{IV} complex occurs much faster as compared to the PhCN species in the Pt^{II} compound (1.5 h vs. 24 h, respectively, **T3**/**E4** and **T3**/**E22**) [63]. The more reactive *E*-configurated cyclic nitrone 5,5-dimethylpyrroline *N*-oxide reacts (CH_2Cl_2, 20–25 °C; yields are 60–90%) with the propiononitrile complexes $[PtCl_n(EtCN)_2]$ for 1 d (n = 2) or for only 15 min in the case of the platinum(IV) complex (n = 4) (**T3**/**E13** and **T3**/**E23**) [60].

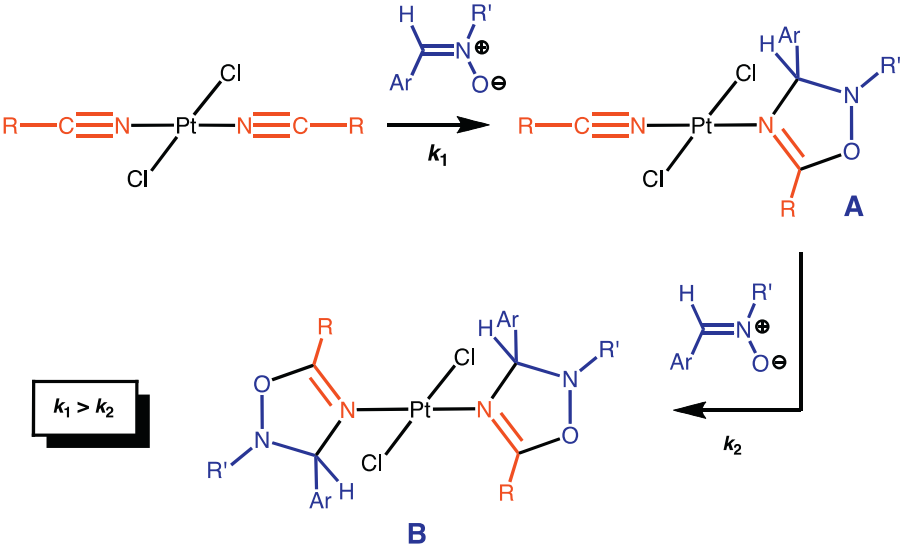
Quantum chemical calculations rationalize the higher reactivity of platinum(IV) nitrile complexes when compared to the relevant platinum(II) species [53,54,67]. The higher oxidation state of platinum in *trans*-$[PtCl_4(NCMe)_2]$ than that in *trans*-$[PtCl_2(NCMe)_2]$ provides a greater shift of electron density from the nitrile to the metal and, hence, a more significant decrease of the $LUMO_{nitrile}$ energy upon coordination (Fig. 7) and a higher enhancement of the effective charge on the nitrile carbon atom (0.53 in *trans*-$[PtCl_4(NCMe)_2]$ vs. 0.48 in *trans*-$[PtCl_2(NCMe)_2]$ [68]). Correspondingly, the calculated activation barriers of CA to the Pt^{IV}-activated nitriles are by 8.0–11.5 kcal/mol lower compared to the Pt^{II}-mediated reactions (Table 2).

The reactivity of the RCN ligand in platinum(II) complexes also substantially depends on the nature of the substituent R (see also Section 3.1.4). Thus, the complexes bearing RCN ligands with an electron-donor substituent, e.g., $[PtCl_2(MeCN)_2]$, do not react with the nitrone *Z*-PhC(H)=N(O) even upon a prolonged heating (56 °C, CH_2Cl_2, 2 d) [63]. However, ligated electron-deficient nitriles RCN (R = CH_2Cl, CH_2CO_2Me, Ph [63,82]) react with the nitrone smoothly (CH_2Cl_2, 8–24 h) at 20–60 °C furnishing coordinated DHODs (**T3**/**E1**–**E2**, **T3**/**E4**–**E9**). Ligation of a nitrile to the Pt^{IV} center leveled off the effect of the substituent in the ligand so that the reaction rates of nitriles with donor and acceptor groups R (R = Me, Ph) in $[PtCl_4(RCN)_2]$ complexes with the nitones *Z*-ArC(H)=N(O)R (Ar/R = Ph/Me, *p*-tol/Me, *o*-HOC_6H_4/Me, *p*-$MeOC_6H_4$/Me, *p*-$NO_2C_6H_4$/Me, *p*-$NMe_2C_6H_4$/Me, HCl·*p*-$Me_2NC_6H_4$/Me, Ph/CH_2Ph, Bu^t/CH_2Ph) turned out to be approximately the same (20–25 °C, CH_2Cl_2, 1.5–4 h, yields are 70–90%; **T3**/**E20**–**E22**) [63,64].

3.1.3. Effect of ligand environment in nitrile complexes

Besides other factors, ligand environment in nitrile complexes can also affect CA. Thus, rate of CA depends on the nature of *trans*-ligand with respect to the metal-bound nitrile.

The reaction depicted in Scheme 5 (R = Ph; Ar/R′ = Ph/Me, *p*-tol/Me [64]; R = NMe_2, NEt_2, NC_5H_{10}; Ar/R′ = *p*-tol/Me; Ph/CH_2Ph [83]) proceeds in two consecutive steps and the first step (a molar ratio nitrone:$[PtCl_2(RCN)_2]$ is 15:1, $CDCl_3$, 20–25 °C, 2 h, 100% conversion, **T3**/**E10** [83]; nitrone:*trans*-$[PtCl_2(PhCN)_2]$ 2:1, $CDCl_3$, 40 °C, 75 min, 50% conversion, **T3**/**E5** [84]) is substantially faster that the second one (a molar ratio nitrone:$[PtCl_2(RCN)_2]$ is 15:1, $CDCl_3$, 20–25 °C, 24 h, 100% conversion, **T3**/**E10** [83]; nitrone:*trans*-$[PtCl_2(PhCN)_2]$ 2:1, $CDCl_3$, 40 °C, 450 min, 50% conversion, **T3E4** [84]). Products of *mono*- (**A**, Scheme 5) and *bis*-CA (**B**) were isolated and characterized be various methods including X-ray crystallography (Fig. 9).



Scheme 5. Stepwise CA of nitrones to nitrile ligands in platinum(II) complexes.

This observation is attributed to different electronic effects of RCN or DHOD ligands in the *trans* position to the reacting nitrile. Indeed, the difference in the reaction rates between two steps of DCA could be accounted for by a higher electron donor ability of the newly formed heterocycle as compared to the corresponding nitrile ligand. As a result of the more intensive shift of electron density from DHOD to the metal, the Pt–NCR bond in *mono*-CA product **A** (Scheme 5) is weaker than that in the starting dinitrile complex and nitrile *mono*-CA complex **A** is less activated. At the same time, other factors (i.e., entropic factors and solvent effects) also may add to the general picture (see Section 4).

Ligands in the *cis* position with respect to the reacting nitrile also have an effect on the reaction. Thus, the *cis*-[$PtCl_2(PhCN)_2$] complex reacts only with one nitrone molecule R′C(H)=N(O)Me (R′ = Ph or *p*-MeC_6H_4) (CH_2Cl_2, 20–25 °C, 24 h, yields 43–48%, **T3E5** [84]) and, after the generation of *cis*-[$PtCl_2$(PhCN)(DHOD)], further step of CA is not observed. In contrast to the *cis*-isomer, the *trans*-configuration complex [$PtCl_2(PhCN)_2$] reacts with the nitrone in a molar ratio 1:2 to form *trans*-[$PtCl_2(DHOD)_2$] (CH_2Cl_2, 20–25 °C, 24 h, yields 56–76%, **T3E4** and **T3E9**) [84]. This difference in reactivity of the isomers is attributed to steric factors in CA, i.e., the bulky DHOD ligand generated in the first step hinders next CA to the *cis*-coordinated nitrile. For an effect of the *cis*-ligands on the stereoselectivity of CA see Section 3.2.2.

3.1.4. The nature of the nitrile

In Section 3.1.2, we indicated that the nature of the substituent in the RCN ligand in the platinum(II) complexes plays a considerable role in DCA. A similar situation was also observed for CAs of *p*-tolC(H)=N(O)Me to PhCN dipolarophiles in the palladium(II) complex [$PdCl_2(PhCN)_2$] that reacted at 50 °C for 24 h (in PhCN, 50%, **T3**/**E24**), whereas the analogous reaction of the complexes [$PdCl_2(RCN)_2$] bearing electron-donor (R = Me) substituents at the nitrile ligands under the same and more drastic conditions gives poorer yields (in MeCN, reflux, 24 h, 12%, **T3**/**E24**) and lower selectivity and MWI was used to enhance the reaction (in MeCN, sealed tube, 20 min, 10–15%, **T3**/**E24**) [81].

3.1.5. The nature of the nitrone

The nature of nitrone in CAs to RCN ligands plays the same role as in the reactions with uncomplexed nitriles. According to the results of quantum chemical calculations [53,58], the reactivity of these dipoles increases on going from acyclic to cyclic structures (for example, **T3**/**E2** and **T3**/**E16**) and, in the latter case, upon introduction of a heteroatom (O or N) to position 1 of the cycle (**T3**/**E17**–**E19**); dipoles **2T** and **5T** (Fig. 4, Table 2) appearing to be the most reactive. These results were fully confirmed in the subsequent experimental study. Thus, the cyclic nitrone 5,5-dimethylpyrroline *N*-oxide easily reacted with the nitrile ligand

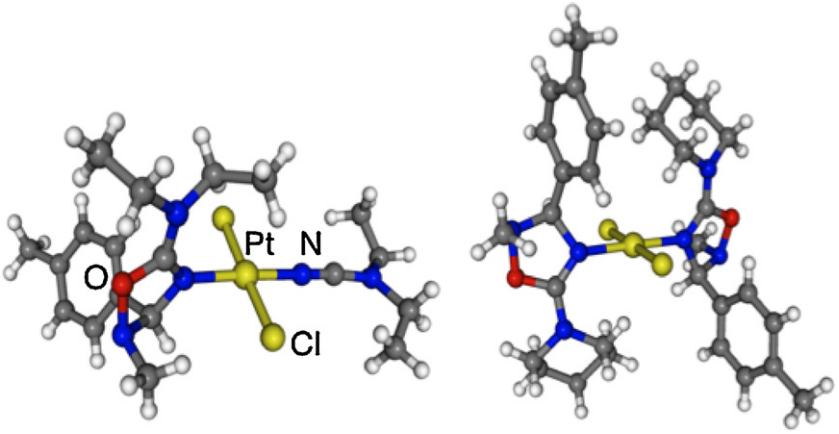
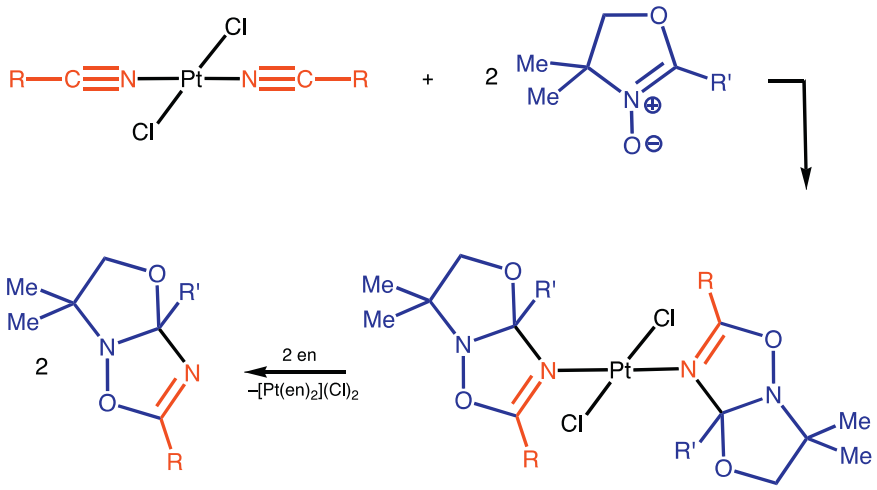


Fig. 9. X-ray structures and *mono*- and *bis*-CA products.

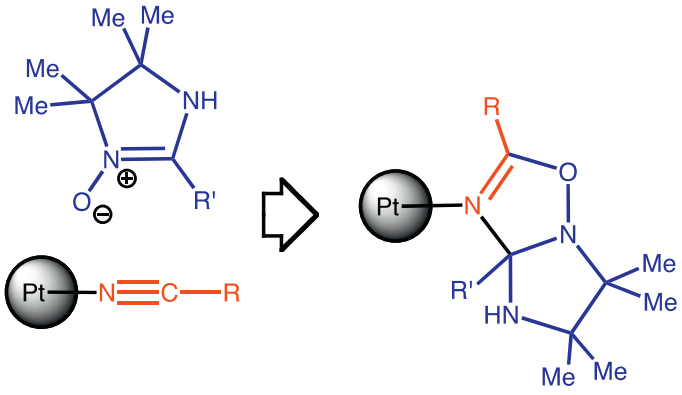


Scheme 6. Stepwise CA of oxazoline *N*-oxides to Pt^{II}-bound nitriles and liberation of heterocycles formed.

in the platinum(II) complexes, $[PtCl_2(EtCN)_2]$ (CH_2Cl_2, 20–25 °C, 24 h, yield 65%, **T3**/**E13**) and $(Ph_3PCH_2Ph)[PtCl_3(EtCN)]$ (CH_2Cl_2, 20–25 °C, 48 h, yield 60%, **T3E14**) [60], and the palladium(II) complexes $[PdCl_2(RCN)_2]$ (R = Me, Et) (RCN or acetone, 20–25 °C, 12 h, yields 75 and 77%, **T3**/**E27**) [85], while the acyclic nitrones ArC(H)=N(O)R do not react with RCN ligands with electron-donor substituents (R = Me, Et) in the $[PtCl_2(RCN)_2]$ complexes [63].

The oxazoline *N*-oxides shown in Scheme 6 (R = Me, Et) react with the nitrile ligands in $[PtCl_2(R'CN)_2]$ (R′ = Me, Et, CH_2Ph, Ph, $N(C_5H_{10})$) even at room temperature to form the previously unknown novel type heterocycles, viz., 2,3a-disubstituted 5,6-dihydro-3a*H*-[1,3]oxazolo[3,2-*b*][1,2,4]oxadiazoles as the ligands (CH_2Cl_2, 20–25 °C, 24 h, yields 65–70%, **T3**/**E17**) [86]. These heterocycles were liberated by the substitution with ethylenediamine in CH_2Cl_2 at 20–25 °C for 1 d.

Likewise, the reaction of the platinum(II) nitrile complexes *cis*- and *trans*-$[PtCl_2(RCN)_2]$ (R = NMe_2, NC_5H_{10}, Et) with imidazoline *N*-oxides proceeds rapidly to afford the coordinated fused heterocycles, *viz.* tetrahydroimidazo[1,2-*b*][1,2,4]oxadiazoles, in good yields (CH_2Cl_2, 20–25 °C, 0.5–3 h, yields 50–81%, **T3**/**E19**). The heterocycles so formed exist only in the coordinated state and attempts to liberate the heterocyclic ligands from their complexes by treatment with two equivs dppe led to formation of the parent uncomplexed imidazoline *N*-oxides and the nitriles (Scheme 7). Thus, coordinated heterocycles that do not exist in the uncomplexed state can be synthesized under mild conditions due to the involvement of the metal center in DCA of nitrones to nitriles.



Scheme 7. Schematic representation of CA of imidazoline *N*-oxides to Pt^{II}-bound nitriles.

The metal served as the dipolarophile activator and stabilized the cycloadduct.

In both cases (**T3E17**, **T3E19**) [58,86], a dipolarophilic activation of the C≡N group in organonitriles upon their coordination to a platinum(II) center was sufficient for CA and was performed under mild conditions starting even from complexed RCN species bearing electron-donor groups R. It was reported that the activation of RCN by a Pt^{IV} center toward DCA is so significant that the reaction loses its selectivity and formation of a broad of mixture of products was observed.

The reactions described above are the first examples of CA between oxazoline *N*-oxides or imidazoline *N*-oxides and nitriles and they can be applied to the direct synthesis (performed under mild conditions and using easily prepared Pt^{II} compounds) of the previously inaccessible families of fused heterocycles (Fig. 10) and their metal complexes.

The DFT calculations predicted that nitronate **4T** (Fig. 4) should be less reactive in CA than the acyclic *N*,*C*-dimethylnitrone MeCH=N(Me)O (Table 2) [53]. Moreover, the reaction with nitronate **4T** is much less affected by coordination of RCN than the reactions with reactive nitrones **2T** and **5T**: in the latter case the activation reaches 20.4 kcal/mol upon coordination of RCN to Pt^{IV}, whereas in the case of nitronate the maximum activation is 14.7 kcal/mol (Table 2). Nevertheless, the activation barrier of the reaction **4T** + *trans*-$[PtCl_4(NCR)_2]$ is still sufficiently low (17.0 kcal/mol) to allow this process to occur under relatively mild conditions.

These theoretical predictions were later completely confirmed by experiment. Reaction between *trans*-$[PtCl_4(EtCN)_2]$ and the cyclic nitronate (R = *p*-$MeOC_6H_4$) shown in Scheme 8 proceeds at room temperature for 12 h and gives *N*-acylimine complex as the major product, when the synthesis was carried out in freshly distilled CH_2Cl_2. The *N*-acylimine compound is unstable in nondried solvents and is hydrolyzed to form the imine complex also indicated in Scheme 8. The latter complex can be alternatively synthesized from *trans*-$[PtCl_4(EtCN)_2]$ and the nitronate in moderate yield if the reaction was performed in nondried solvents. Although no evidence

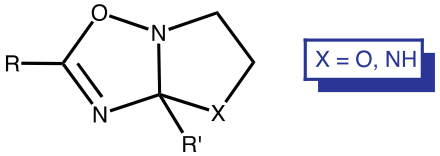
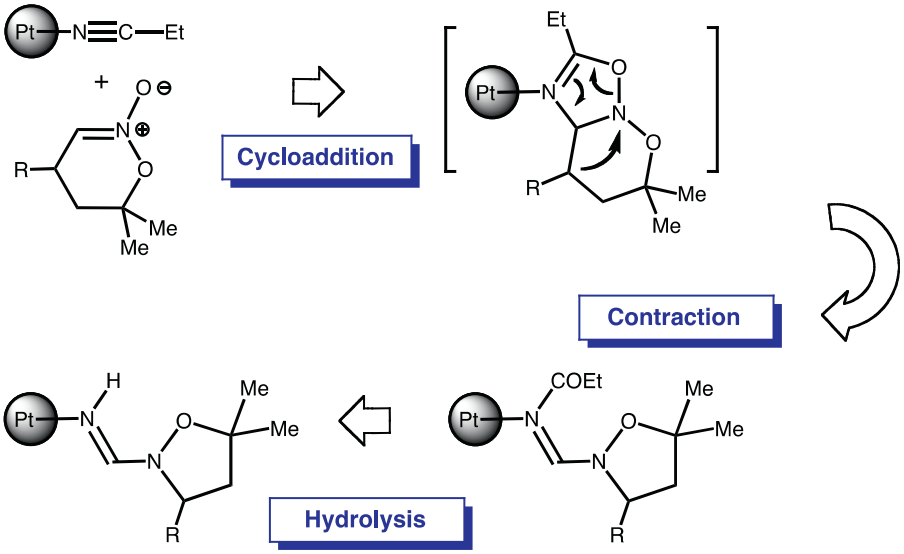


Fig. 10. Novel families of fused heterocycles.



Scheme 8. Plausible mechanism of the reaction between a cyclic nitronate and a ligated nitrile.

for generation of a cycloadduct was obtained, the authors [42] suggested a mechanism of this cascade reaction with the involvement of CA. In the first step, DCA of the nitronate to the nitrile functionality occurred to afford the bicyclic intermediate followed by the ring opening of DHOD with the cleavage of the N–O bond and concomitant contraction of the six-membered ring, as a result of 1,2-migration, to furnish the isoxazolidine. The recently observed rearrangement of DHODs affording *N*-acylformamidine derivatives (see Section 3.4.1) provides additional evidence favoring this mechanism. Eventually, the *N*-acylimine complex slowly hydrolyzed to give the imino species functionalized with the isoxazolidine ring (Scheme 8, Fig. 11). One should mention that before appearance of the study [42], no examples of CA of nitronates to the nitrile group had been documented.

To summarize data presented in this section, we conclude that the possibility of the metal-mediated CA strongly depends on the nature of the nitrone. The presence of O and N centers in the nitrone and the *E* configuration – realized in the best way in cyclic nitronates – favor CA.

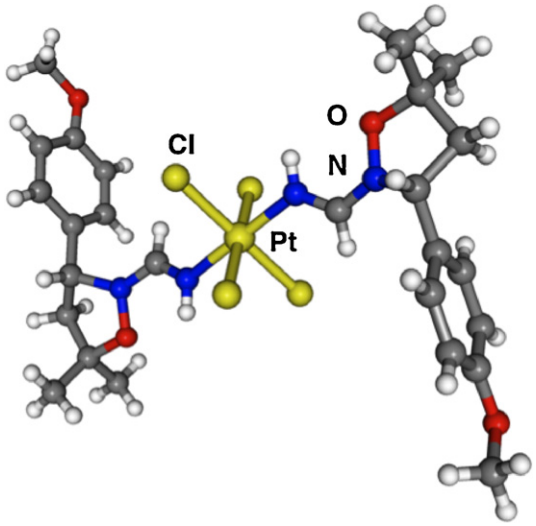


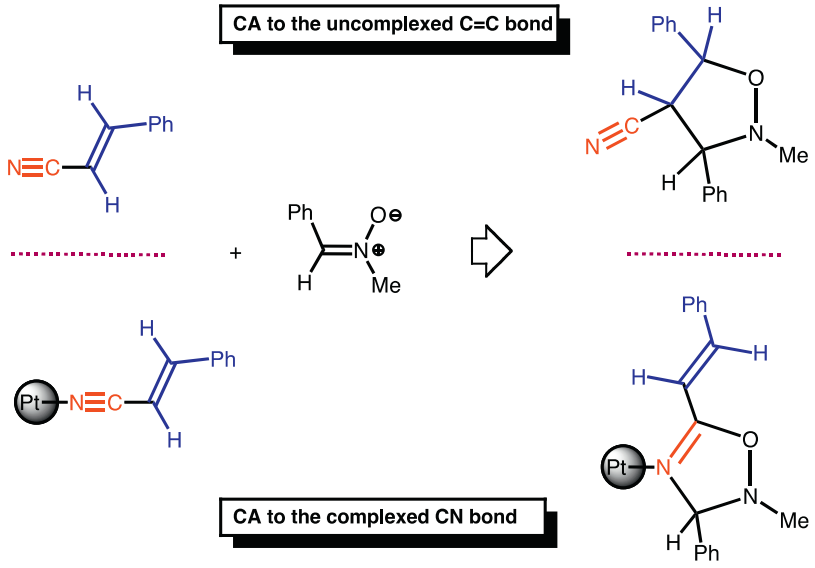
Fig. 11. X-ray structure of platinum(IV) complex bearing imino ligands functionalized with the isoxazolidine ring.

3.1.6. *Effect of focused microwave irradiation*

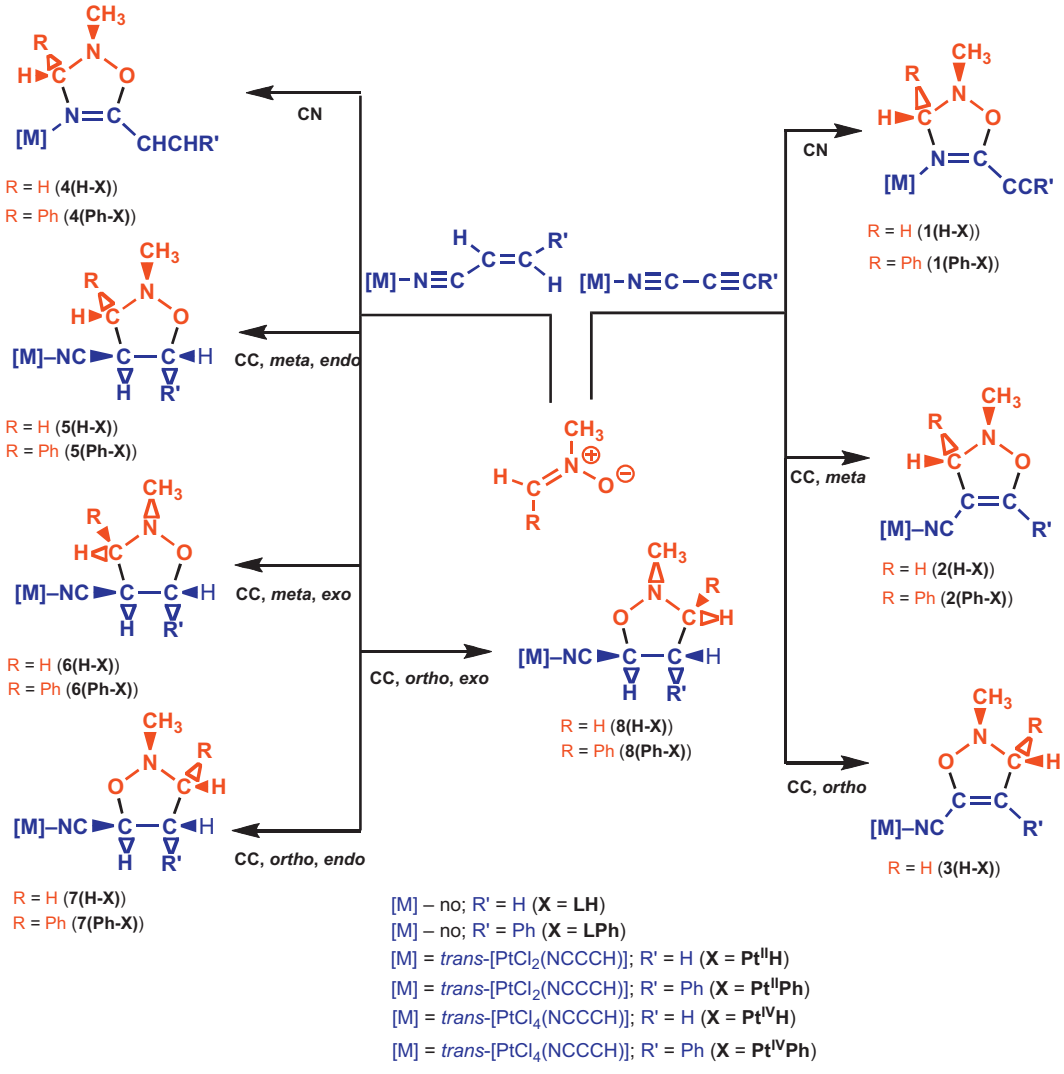
The attractiveness of MWI for synthetic applications has recently considerably increased and the effectiveness of microwave methodology in generating 1,3-dipoles in situ and in promoting the subsequent CAs has been considered in some reviews on the topic [8,33,87–90]. In particular, MWI can be applied to generate 1,3-dipoles, for instance, nitrones, and to promote subsequent CA [8,33]. This non-conventional energy source is able to reduce chemical reaction times and to increase yields and in some cases can lead to different outcomes from those obtained with the conventional heating. Focused MWI was also successfully employed for acceleration of metal-mediated CAs (**T3**/**E1**, **T3**/**E3**, **T3**/**E5**, **T3**/**E9**, **T3**/**E13**–**E14**, **T3**/**E21**, and **T3**/**E23**–**E24**). Thus, the reactions of $[PtCl_2(EtCN)_2]$ and $(Ph_3PCH_2Ph)[PtCl_3(EtCN)]$ with 5,5-dimethylpyrroline *N*-oxide at room temperature are completed in 1–2 days, whereas under MWI they are completed in 30 min at 30 °C or in 15 min at 50 °C (**T3**/**E13**–**E14**) [60]. CA of the nitrones R′C(H)=N(O)Me (R′ = Ph or *p*-MeC_6H_4) to the nitrile ligands in $[PtCl_2(RCN)_2]$ (R = Ph or PhCH=CH) are accelerated by factor of 25 (for *mono*-CA) or 7 (for *bis*-CA) under MWI (**T3**/**E3**, **T3E5**, and **T3**/**E9**) [84,91]. In addition, MWI has different effects on the first and second steps of CA to the nitrile ligands in $[PtCl_2(RCN)_2]$, the formation of the *mono*-CA product $[PtCl_2(DHOD)(RCN)]$ being more accelerated than the generation of the *bis*-CA product $[PtCl_2(DHOD)_2]$ [84]. Due to the difference in MWI effect on the rates of the first and second steps of CA of nitrones to $[PtCl_2(NCR)_2]$, the complex $[PtCl_2\{N^{(a)}{=}C(R)ON(Me)C^{(b)}HR'\}(RCN)]^{(a-b)}$ was synthesized chemoselectively (**T3**/**E9**) [84]. The use of MWI also leads to an increase in the rate of CA of *p*-$MeC_6H_4C(H)$=N(O)Me to the nitrile ligand in $[PdCl_2(MeCN)_2]$ to form the complexed DHODs (**T3**/**E24**) [81].

3.2. *Selectivity of metal-mediated cycloaddition of nitrones*

The reactions of nitriles bearing another dipolarophilic functional group, besides the C≡N moiety, may exhibit chemoselectivity (selective CA to one of the multiple bonds of dipolarophile), while the presence of an asymmetric center in CA product determines a possible stereoselectivity of these processes. At the same time, CAs to the C≡N group are 100% regioselective. Indeed, rare examples of 4,5-dihydro-1,2,5-oxadiazole were reported in Refs. [92–96] and this heterocyclic system was generated by other methods than CA of nitrones to the nitrile functionality that always lead to DHODs.



Scheme 9. Chemoselectivity of CA to uncomplexed and metal-bound cinnamonitrile species.



Scheme 10. Calculated CA reactions of nitrones to bifunctional nitriles.

Theoretical calculations indicated that the activation barriers of the formation of DHODs upon CA are by 6.9–14.9 kcal/mol lower than the barriers of the formation of 4,5-dihydro-1,2,5-oxadiazole, and the latter processes are highly endoergonic (by 25–26 kcal/mol) [70].

3.2.1. Chemoselectivity of metal-mediated 1,3-dipolar cycloaddition

Coordination of nitrile substrates to a metal center could alter the direction of the reaction. Studies on the reaction of the cinnamonitrile complexes $[MCl_2(N{\equiv}CCH{=}CHPh)_2]$ (M = Pt, Pd) – bearing the potentially bifunctional dipolarophile as the ligand – with the nitrone *Z*-PhC(H)=N(O)Me (Scheme 9) [91] indicated that in the presence of a substantial excess of the nitrone, no CA to the C=C bond occurred (**T3**/**E3**). The reaction that was carried out at 60 °C for 2 days afforded complexes derived from chemoselective CA of the nitrone to the CN triple bond (in CH_2Cl_2, 35% isolated yield) of cinnamonitrile, while the C=C functionality remains intact.

Treatment of the DHOD complexes with an aqueous solution of $MeNH_2$ afforded the free heterocycle [91]. Remarkably, the reaction of the uncomplexed nitrile N≡CCH=CHPh with *Z*-PhC(H)=N(O)Me proceeds differently. It is directed exclusively to the C=C bond giving the isoxazolidine (Scheme 9) without affecting the C≡N bond. Hence, coordination of the nitrile to the metal center switches the reaction site from the C=C to the C≡N group and CA proceeds chemoselectively to the nitrile functionality.

The quantum-chemical studies have rationalized these observations [59,72]. The calculations showed that CA of the nitrone $CH_2N(Me)O$ to the uncomplexed nitriles $N{\equiv}CCH{=}CH_2$ and N≡CC≡CH should occur exclusively at the C=C or C≡C bond. However, the coordination of these dipolarophiles via the CN group to Pt^{II} or, in particular, to Pt^{IV} centers (Scheme 10) results in a dramatic facilitation of the CN-addition mode vs. the CC-addition modes (Table 3). Moreover, the chemoselectivity strongly depends on the nature of substituents. The reactions of the nitrones $CH_2N(Me)O$ and PhCH=N(Me)O with both the free and the coordinated $N{\equiv}CCH{=}CH_2$ should occur at the C=C bond of the dipolarophile. However, CAs to the phenyl-substituted nitriles N≡CCH=CHPh in the complexes *trans*-$[PtCl_2(N{\equiv}CCH{=}CH_2)(N{\equiv}CCH{=}CHPh)]$ are already clearly CN-chemoselective (Table 3) (**T3**/**E3**). Such a switch of the chemoselectivity is in agreement with the experimental results [91] and is explained by two reasons: (i) by steric repulsions imposed by bulky Ph groups in the phenyl-substituted species and (ii) by the loss of conjugation in phenylnitrone and phenylcyanoalkene molecules upon the formation of a transition state. Both these factors are more pronounced for the CC-addition rather than for the CN-addition.

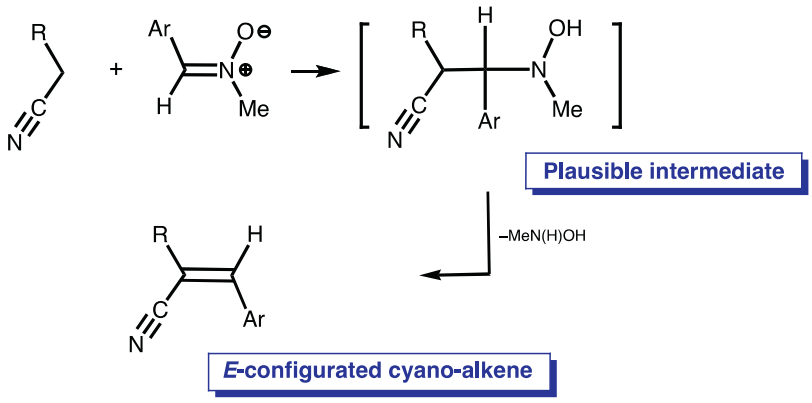
The reaction of the uncomplexed and the coordinated nitriles RCH_2CN with the acyclic nitrones *Z*-ArC(H)=N(O)Me (uncomplexed: Ar/R = SO_2Ph/*p*-tol, CO_2Me/*p*-tol, COPh/*p*-tol, SO_2Ph/2,4,6-$Me_3C_6H_2$, CO_2Me/2,4,6-$Me_3C_6H_2$, COPh/2,4,6-$Me_3C_6H_2$; coordinated: Ar/R = Cl/*p*-tol, CO_2Me/*p*-tol, Cl/2,4,6-$Me_3C_6H_2$, CO_2Me/2,4,6-$Me_3C_6H_2$) was studied by Pombeiro and coworkers [82]. In addition to the electrophilically activated nitrile group, these nitriles bear a reactive α-CH_2 group. Accordingly to the previous studies describing the interplay between nitrones and the nitriles with the reactive methylene group [97–102], the reaction of the uncomplexed nitriles with the acyclic nitrones proceeds (12 h at 80 °C in a sealed tube or focused MWI for 2 h) as the Michael-type addition of the nitrone followed by abstraction of *N*-methylhydroxylamine from the intermediates shown in Scheme 11 and afforded the *E*-configured substituted cyano-alkenes.

The reaction of Pt^{II}-bound nitriles RCH_2CN (R = Cl, CO_2Me) with the nitrones ArC(H)=N(O)Me (R = *p*-tol, 2,4,6-$Me_3C_6H_2$) proceeds under milder conditions, viz., refluxing in CH_2Cl_2 at 40 °C for 8 h (or MWI for 1 h in a sealed tube), and gives (DHOD)Pt^{II} complexes (**T3**/**E1**–**E2**). Under more drastic conditions, e.g., upon increase in the reaction time, a mixture of DHOD and the corresponding *E* cyano-alkenes (shown in Scheme 12) were formed (**T3**/**E1**). Thus, in the absence of a coordinating metal site, the CH_2 group is more reactive than the C≡N moiety toward the acyclic nitrones, undergoing deprotonation by the latter reagent to provide a route to the cyano-alkenes. However, upon binding a Pt^{II} center, the C≡N group of each of RCH_2CN becomes more reactive than the α-CH_2 group, being thus sufficiently activated by coordination to undergo DCA with the acyclic nitrone to afford DHOD complexes.

Table 3
Theoretically calculated (at the B3LYP/6-31G* level) Gibbs free energies of activation and reaction in CH_2Cl_2 solution (in kcal/mol) for CAs of nitrones RCH=N(Me)O to bifunctional nitriles (data are taken from Ref. [59] if not stated otherwise).

CA product[a]	Type of addition	$\Delta G^{\neq}$	ΔG
Dipolarophile: N≡CC≡CR′			
1(H-LH)	to CN	27.4	−6.6
2(H-LH)	to CC, *meta*	19.2	−34.5
3(H-LH)	to CC, *ortho*	19.2	−31.4
1(H-Pt^{II}H)	to CN	19.1	−12.1
2(H-Pt^{II}H)	to CC, *meta*	12.3	−41.0
3(H-Pt^{II}H)	to CC, *ortho*	14.9	−29.8
1(H-Pt^{IV}H)	to CN	11.9	−16.1
2(H-Pt^{IV}H)	to CC, *meta*	10.6	−41.2
3(H-Pt^{IV}H)	to CC, *ortho*	15.2	−31.7
1(H-Pt^{IV}Ph)	to CN	16.7	
2(H-Pt^{IV}Ph)	to CC, *meta*	16.2	
1(Ph-Pt^{II}Ph)	to CN	30.4	
2(Ph-Pt^{II}Ph)	to CC, *meta*	28.2	
Dipolarophile: N≡CCH=CHR′			
4(H-LH)	to CN	29.8	−7.7
5(H-LH)	to CC, *meta*, *endo*	23.3	−9.6
6(H-LH)	to CC, *meta*, *exo*	23.2	−9.8
7(H-LH)	to CC, *ortho*, *endo*	21.6	−9.5
8(H-LH)	to CC, *ortho*, *exo*	21.6	−9.3
4(H-LPh)	to CN	20.4[b,c]	−13.1[b,c]
5(H-LPh)	to CC, *meta*, *endo*	19.7[b,c]	−8.5[b,c]
6(H-LPh)	to CC, *meta*, *exo*	23.3[b,c]	−2.6[b,c]
7(H-LPh)	to CC, *ortho*, *endo*	24.7[b,c]	+4.5[b,c]
8(H-LPh)	to CC, *ortho*, *exo*	24.4[b,c]	−6.3[b,c]
4(H-Pt^{II}H)	to CN	21.7	−13.1
5(H-Pt^{II}H)	to CC, *meta*, *endo*	20.1	−8.8
6(H-Pt^{II}H)	to CC, *meta*, *exo*	20.5	−9.9
7(H-Pt^{II}H)	to CC, *ortho*, *endo*	18.5	−8.2
8(H-Pt^{II}H)	to CC, *ortho*, *exo*	17.7	−8.6
4(H-Pt^{IV}H)	to CN	11.2	−19.9
5(H-Pt^{IV}H)	to CC, *meta*, *endo*	12.1	−9.9
6(H-Pt^{IV}H)	to CC, *meta*, *exo*	8.5	−11.1
7(H-Pt^{IV}H)	to CC, *ortho*, *endo*	14.8	−9.2
8(H-Pt^{IV}H)	to CC, *ortho*, *exo*	15.5	−11.8
4(H-Pt^{II}Ph)	to CN	24.2	
5(H-Pt^{II}Ph)	to CC, *meta*, *endo*	28.3	
6(H-Pt^{II}Ph)	to CC, *meta*, *exo*	29.6	
7(H-Pt^{II}Ph)	to CC, *ortho*, *endo*	28.2	
8(H-Pt^{II}Ph)	to CC, *ortho*, *exo*	28.1	
4(Ph-Pt^{II}H)	to CN	28.2	
5(Ph-Pt^{II}H)	to CC, *meta*, *endo*	26.2	
6(Ph-Pt^{II}H)	to CC, *meta*, *exo*	28.2	
7(Ph-Pt^{II}H)	to CC, *ortho*, *endo*	27.0	
8(Ph-Pt^{II}H)	to CC, *ortho*, *exo*	29.4	
4(Ph-Pt^{II}Ph)	to CN	31.3	
		11.3[b,c]	−21.6[b,c]
5(Ph-Pt^{II}Ph)	to CC, *meta*, *endo*	37.1	
		18.9[b,c]	−6.2[b,c]
6(Ph-Pt^{II}Ph)	to CC, *meta*, *exo*	40.5	
		23.9[b,c]	−1.4[b,c]
7(Ph-Pt^{II}Ph)	to CC, *ortho*, *endo*	42.7	
		27.4[b,c]	+3.4[b,c]
8(Ph-Pt^{II}Ph)	to CC, *ortho*, *exo*	43.0	
		27.6[b,c]	−3.0[b,c]

[a] See Scheme 10.
[b] Ref. [72].
[c] In terms of gas-phase total energies.



Scheme 11. Generation of *E*-configured substituted cyano-alkenes.

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

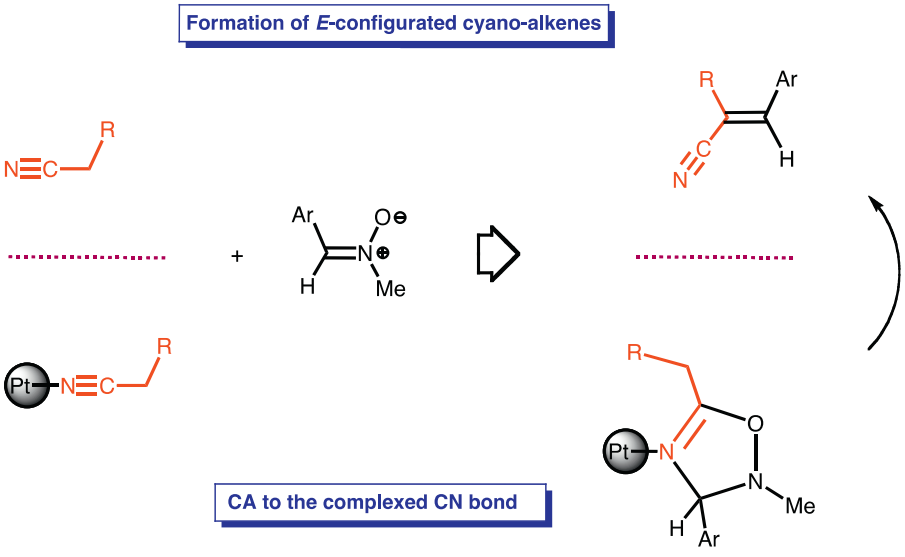
In CA of nitrones to nitriles, a new asymmetric carbon center is formed (Scheme 13), and at least two strategies can be applied to achieve stereoselectivity of these reactions: (i) stereocontrol could be provided by a chiral nitrone dipole (Scheme 13, *a*) [51], (ii) stereocontrol provided by a dipolarophile, when either a metal complex bears both achiral nitrile and chiral supporting ligands (*b*), or when a nitrile having chiral substituent is employed (*c*) [46,86,103].

Currently, only two reports related to the stereoselectivity of the metal-mediated nitrone–nitrile DCA are known from the literature (**T3**/**E12** and **T3**/**E17**) [86,103]. The first article [103] describes the Pt^{II}-mediated enantioselective formation of DHOD (CH_2Cl_2, 20–25 °C, 48 h or 56 °C, 12 h, yields 68–71%, **T3**/**E12**), when the metal center, having the chiral sulfoxide (*S*)-PhMeS*O (*ee* 79%) ligand in the *cis*-position to the reacting RCN, is used as a chiral auxiliary group. This asymmetric induction approach (Scheme 13, *b*) provided 30–70% *d.e.*, while decoordination of DHODs formed in DCA allows the generation of the *S*-enantiomers with *ee* up to 70% [103]. The second study [86] reports on a stereocontrol in a Pt^{II}-mediated DCA imposed by a bulky chiral ligand in *trans*-position to a coordinated nitrile substrate (**T3**/**E17**). This reaction also belongs to type *b* (Scheme 13), it occurred diastereoselectively but afforded mixtures of enantiomers after decoordination of heterocycles.

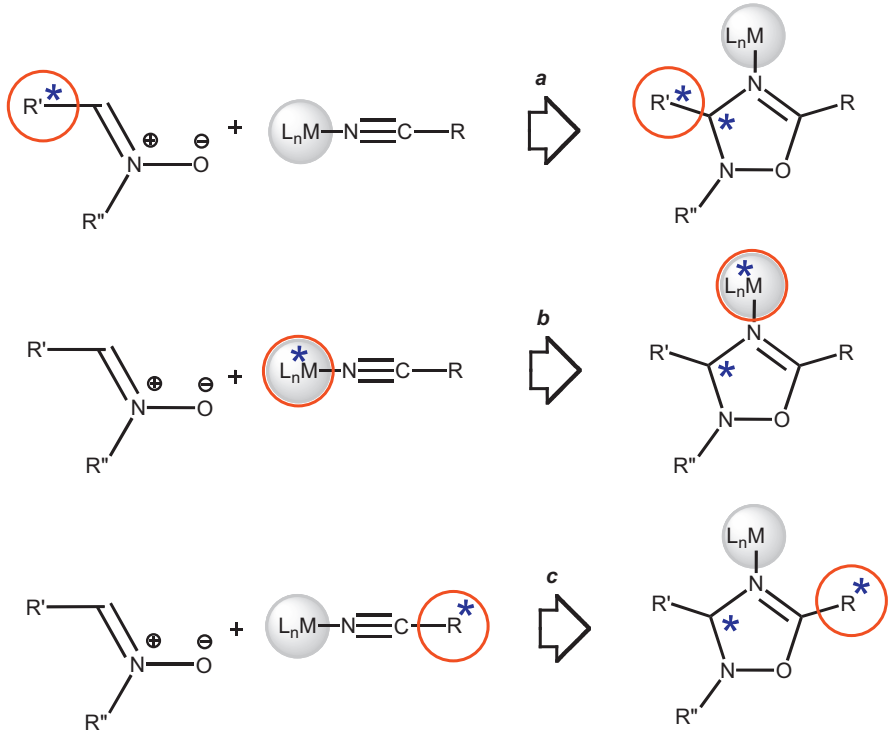
Rather recently route *a* (Scheme 13) was explored, by application of the enantiomerically pure asymmetric camphor-based nitrones (Scheme 14; R = Me, Et), to provide the stereocontrol of CA (CH_2Cl_2, 20–25 °C, 24 h, yields 66–90%, **T3**/**E18**) [104]. The reaction proceeds as depicted in Scheme 14, it has general character and was successfully employed to activated (with acceptor group, R′ = Ph), non-activated (with donor group, R′ = Et) nitriles, and even to the so-called push-pull R′CN species (R′ = NMe_2). Four complexes were characterized by X-ray crystallography and, in all structures, both asymmetric atoms C^{3a} in the heterocyclic ligands have the same absolute configuration (*S*).

Although the heterocycles are strongly bound to the platinum(II) center, in four cases (R/R′ = Me/Et, Et/Et, Me/Ph, Et/Ph) the authors succeeded in liberating the heterocycles upon treatment of the complexes with NaCN (8 equivs, methanol-d_4/CD_2Cl_2, 35 °C, 24 h, NMR yields ca. 95%) to give the metal-free enatiomerically pure DHODs.

The presence of the soft and kinetically inert platinum(II) metal center, when the nitrone reacts selectively with the dipolarophile and does not affect the dipole, does appear key to the success of these CAs. Given that one can envisage the preparation of a spectrum of chiral nitrones (or, on the contrary, chiral nitriles), it follows that the Pt^{II}-mediated CAs could provide efficient routes to diastereomerically pure ligand systems.



Scheme 12. Reactions of an acyclic nitrone with uncomplexed and platinum-bound RCH_2CN species.



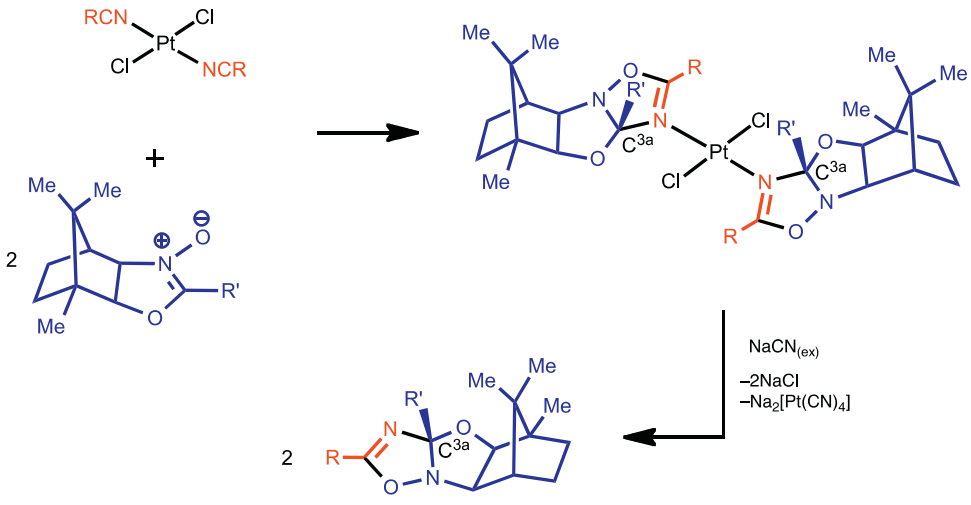
Scheme 13. Strategies for stereoselective metal-mediated CA of nitrones to nitriles.

3.3. *Liberation of 2,3-dihydro-1,2,4-oxadiazoles from their complexes*

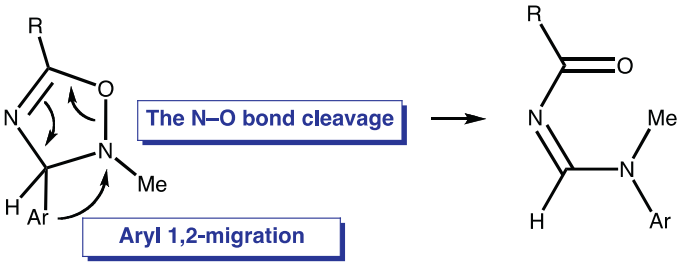
As was already mentioned above in Section 3, DCA of nitrones to complexed nitriles afforded corresponding DHOD ligands. An additional step (Scheme 1) is required for their liberation and isolation of DHOD.

Thus, DHODs were liberated from the platinum(IV and II) complexes $[PtCl_n(DHOD)_2]$ (n = 4, 2). In the former case (n = 4), the reaction occurred in the presence of an excess pyridine, while in the latter case (n = 2), the substitution of DHODs was carried out by a reaction with dppe, en, or $MeNH_2$ [63,64,103,105], or via displacement with NaCN [83,104]. Free DHODs were isolated from the corresponding palladium(II) complexes $[PdCl_2(DHOD)_2]$ under the treatment of these complexes with sodium sulfide, en, or $MeNH_2$ [78,81,91].

Despite the fact that the liberation was successfully carried out in many cases, *no general system* was so far developed for the isolation of these heterocycles from their Pt and Pd complexes. In certain cases, heterocycles in the free state were not obtained probably due to the low stability of the corresponding DHODs under conditions of the ligand substitution reaction (see Section 3.4.2) [58]. Nevertheless, the reaction sequence, consisting of the synthesis of starting nitrile species, their reaction with nitrones, and liberation of DHOD, was proposed as the general method for the synthesis of DHOD derivatives from nitriles bearing electron-donor substituents R, which were earlier inaccessible by the conventional metal-free organic approach [63,64,83,103–105] (Section 2).



Scheme 14. Application of enantiomerically pure asymmetric camphor-based nitrones to provide stereocontrol of CA.



Scheme 15. Ring opening in DHODs.

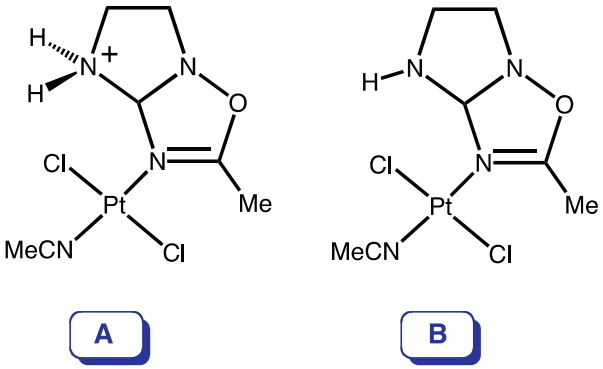


Fig. 12. Model protonated (**A**) and unprotonated (**B**) species.

3.4. Properties of 2,3-dihydro-1,2,4-oxadiazole species

At present, DHODs are still a relatively small and poorly studied class of heterocycles. This is, first of all, associated with the lack of expedient and general synthetic methods for their generation. Only a couple of dozen compounds are known in this class and few examples of their reactions and properties are documented. These data are summarized below in Sections 3.4.1–3.4.3.

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

DHODs with electron-withdrawing substituents in the ring could undergo further transformations in solutions to give the *Z*-configured *N*-acylated amidines via the N–O bond cleavage and the aryl migration (Scheme 15) [49]. The heterocycles derived from nitriles RCN with strong electron-withdrawing groups R and nitrones bearing donor substituents in Ar are easily subject to the ring opening and the 1,2-migration.

In addition to the ring opening depicted in Scheme 15, similar processes with other DHODs could be accompanied with decarboxylations or proton 3,4-shifts [46,106].

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

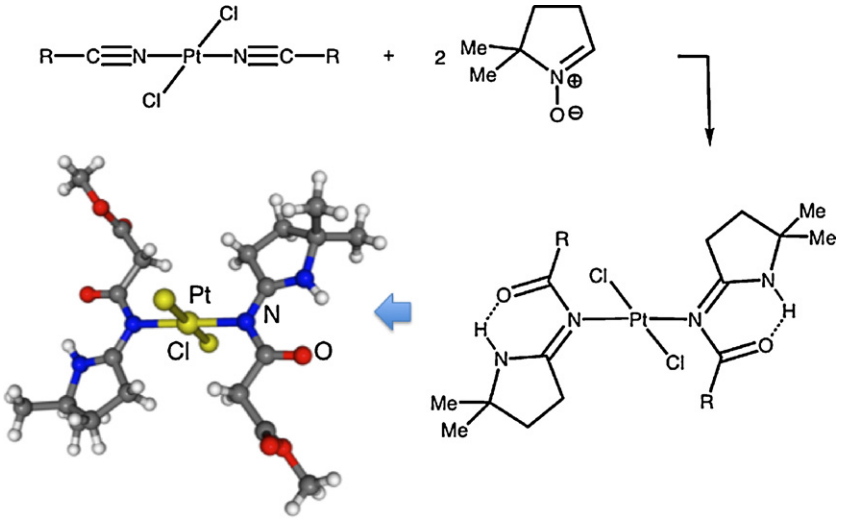
Coordination to the metal center has a pronounced effect on the chemical stability of DHODs. As mentioned above, the reaction of the platinum nitrile complexes $[PtCl_2(RCN)_2]$ ($R = CH_2CO_2Me$, CH_2C1) with 5,5-dimethylpyrroline *N*-oxide afforded the ketimine complexes with two (pyrrolidin-2-ylidene)amino ligands (Scheme 16) (**T3**/**E15**) [73].

A relevant transformation of the ring was observed in the reaction of *o*-phthalonitrile and its derivatives (R_1–R_4 = H, $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$; $R^1 = R^4 = H$, $R^2 = R^3 = Cl$; $R^1 = R^2 = R^3 = R^4 = Cl$; $R^1 = R^2 = R^3 = R^4 = F$) with 5,5-dimethylpyrroline *N*-oxide in the presence of $PdCl_2$ (Scheme 17) (**T3**/**E28**).

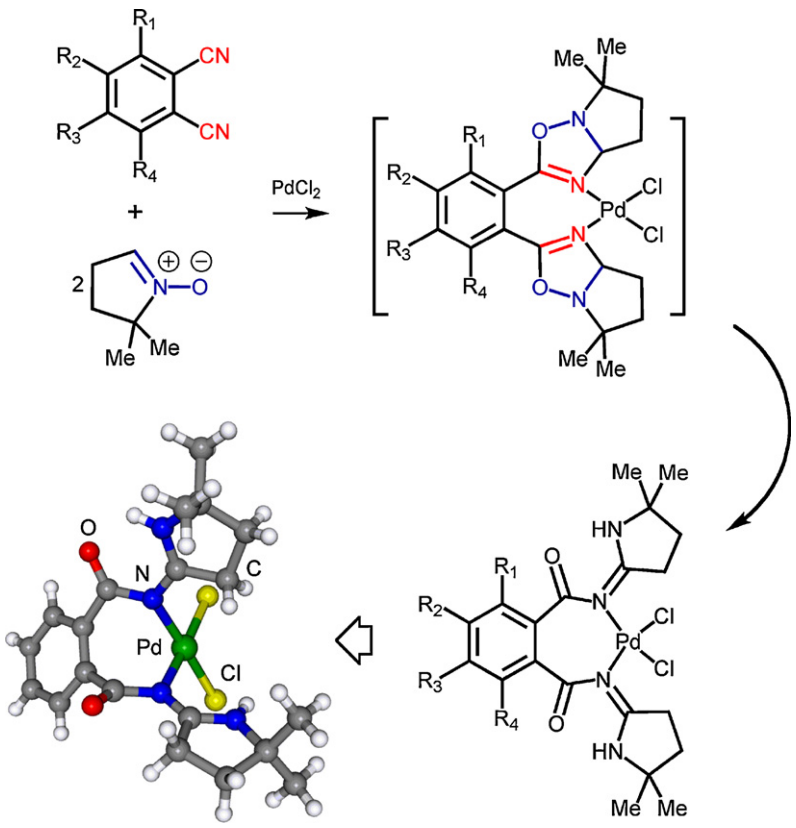
Presumably [73], the reaction proceeds via the DHOD intermediates, where the cleavage of the N–O bond proceeds easier upon the weakening of electron-withdrawing properties of the substituents in the benzene ring and due to the coordination of DHOD formed to the Pd^{II} center. As a result, the rearrangement accompanied by the proton 1,2-shift afforded the corresponding ketimine.

In Section 3.1.5, we described the generation of DHOD occurring via CA of imidazoline *N*-oxides to complexed RCN species (**T3**/**E19**). It was also reported [58] that in $CHCl_3$ and in the presence of HCl (or picric acid) these DHODs are involved in H^+-induced *retro*-CA and they split to the starting platinum(II) complexes and the protonated dipole (Scheme 18). The accompanying theoretical calculations indicated that ΔG of *retro*-CA of the model protonated complex $[PtCl_2(MeCN)(Heterocycle{-}H)]^+$ (**A**) is −11.8 kcal/mol, while ΔG for decomposition of the unprotonated species $[PtCl_2(MeCN)(Heterocycle)]$ (**B**) is 0.0 kcal/mol (Fig. 12).

Yet another procedure for DHOD ring opening was described in a publication [82] devoted to studies of the reaction of the acyclic nitrone ArC(H)=N(O)Me with nitriles having the activated α-CH_2 group (**T3**/**E1**). Presumably, the formation of the substituted *E*-alkene upon heating of platinum complex (Scheme 12) occurred as a result of *retro*-CA followed by the reaction of nitrone ArCH=N(O)Me with the uncomplexed nitrile $RCH_2C{\equiv}N$ by the mechanism shown in Scheme 11.



Scheme 16. Generation of ketimine complexes via ring opening in Pt^{II}-bound DHODs.

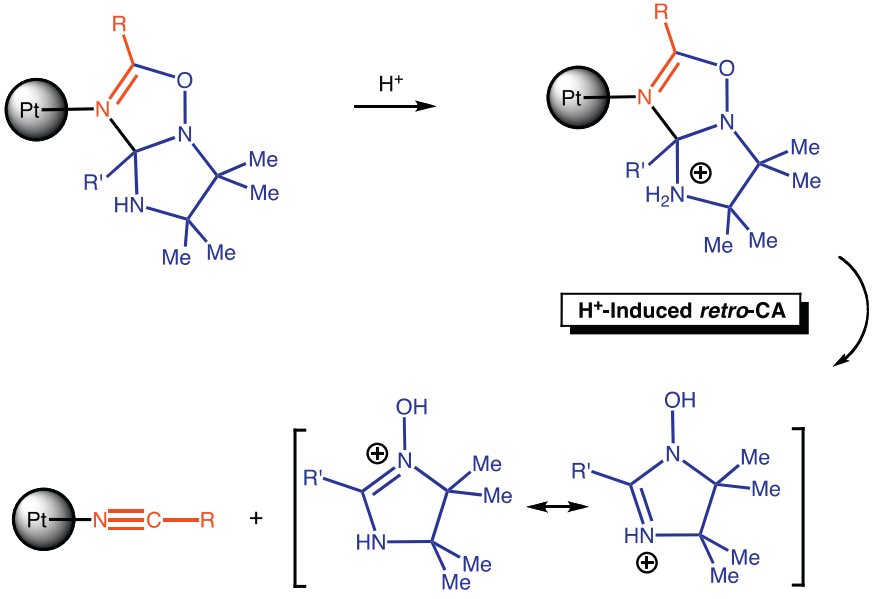


Scheme 17. Reaction of *o*-phthalonitriles with 5,5-dimethylpyrroline *N*-oxide in the presence of $PdCl_2$.

3.4.3. Antitumor properties of (2,3-dihydro-1,2,4-oxadiazole)$_2$Pt^{II} complexes

In the past twenty years anticancer properties of *trans*-platinum complexes, as an example of non cisplatin based structure–activity relations, attracted significant attention in the area of the metal based drug discovery. The most important observations in this field are summarized in several reviews [107–112].

In vitro antitumor activity of *trans*-(DHOD)$_2$Pt^{II} and *trans*-(DHOD)(RCN)Pt^{II} complexes (Fig. 13; **A**: R/R′ = *p*-MeOCH$_2$CH$_2$O–C$_6$H$_4$/Ph; **B**: R/R′ = *p*-MeOCH$_2$CH$_2$O–C$_6$H$_4$/Ph, *p*-HO–C$_6$H$_4$/Ph, Ar/R = Ph/*p*-HO–C$_6$H$_4$; **T3**/**E8**) has been studied on the cisplatin-sensitive (PEO1) and cisplatin (PEO1CisR) and carboplatin (PEO1carboR)-resistant human ovarian cancer cell lines, as well as on the colon (SW948), and testicular (N-TERA) cancer cell lines. All the platinum complexes investigated were active on the cisplatin sensitive and on cisplatin- and carboplatin-resistant cancer cell lines [113]. The higher cytotoxicity of *trans*-(DHOD)Pt^{II} compounds may relate to various features of interactions of the



Scheme 18. H$^+$-induced *retro*-CA.

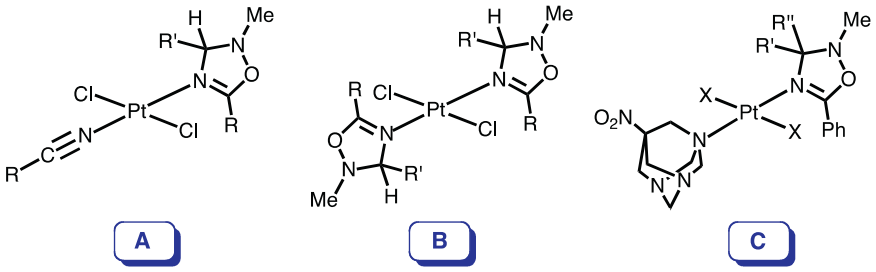


Fig. 13. Complexes studied for their *in vitro* antitumor activity.

former on a cellular level. The authors [113] suggest that the DHOD containing *trans*-platinum compounds may affect the cell cycle differently to cisplatin and carboplatin

trans-Configured mixed ligand platinum(II) DHOD complexes with a labile and reactive 1-nitro-1,3,5-triazaadamantane ligand (Fig. 13, **C**: X = Cl, Br; R′/R″ = 2-MeOC$_6$H$_4$/H, 2,4-(MeO)$_2$C$_6$H$_3$/H, 2,6-(MeO)$_2$C$_6$H$_3$/H, 2,4,6-(MeO)$_3$C$_6$H$_2$/H, 2-(furyl)C$_6$H$_4$/H, EtCO$_2$/EtCO$_2$; **T3**/**E6**–**E7**) were synthesized as promising cytotoxic agents [114]. The azaadamantane ligand can be selectively replaced by heterocycles such as pyridine, and DFT/AIM calculations suggest that this reaction should be enhanced in an aqueous medium when the azaadamantane is protonated. The authors assume that a similar azaadamantane ligand substitution should be feasible with purine nucleobases of DNA and they believe that DNA binding is very likely to happen in the cell [114].

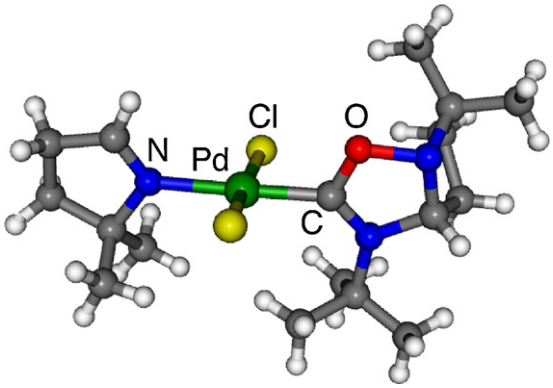


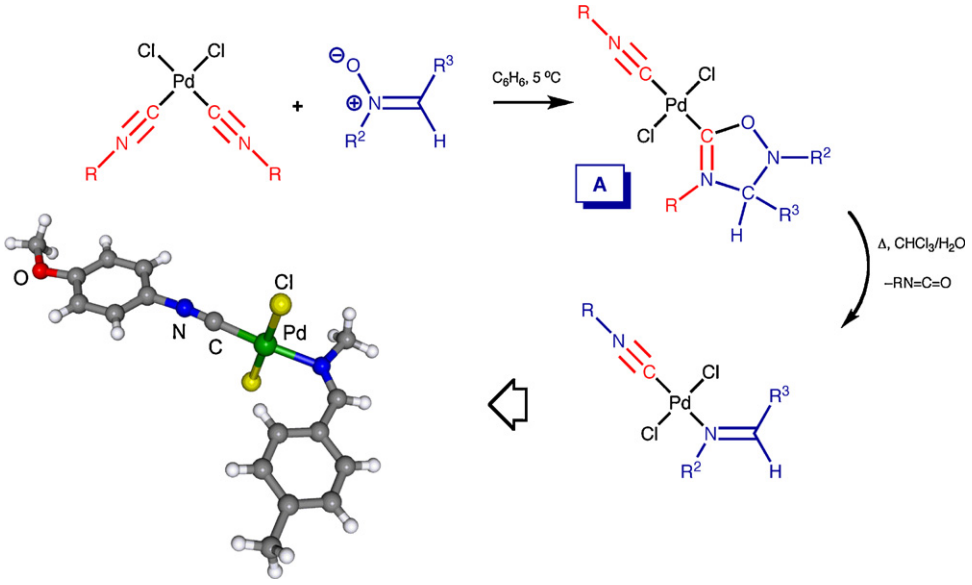
Fig. 14. X-ray structure of a CA product.

4. 1,3-Dipolar metal-mediated cycloaddition of nitrones to isocyanides

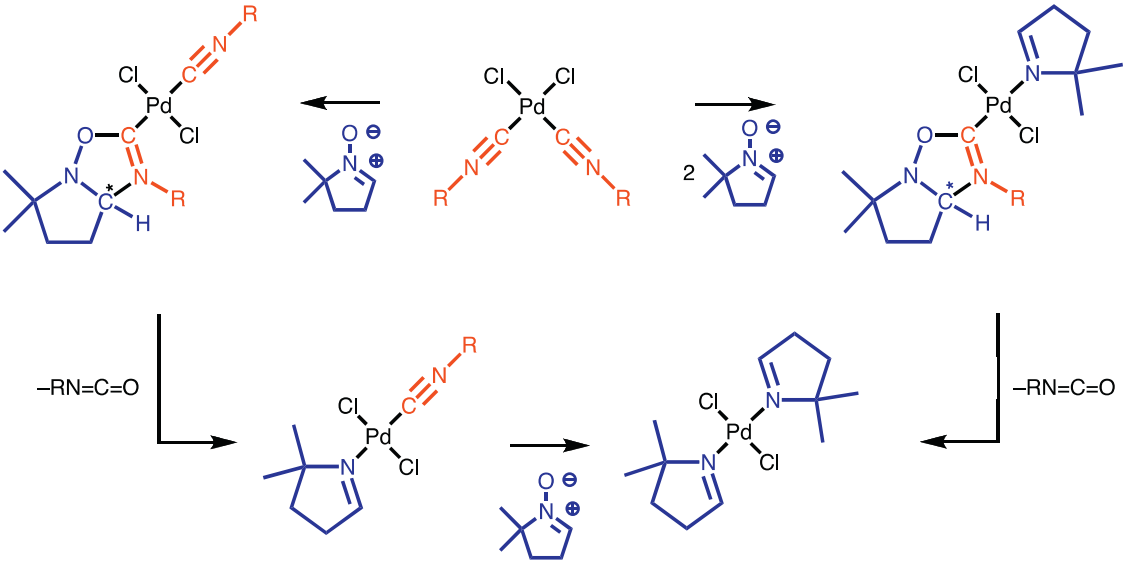
Reactions between uncomplexed isocyanides, RNC, and nitrones are as yet unknown and only one example of metal-mediated DCA to complexed RNC species has been reported [115]. The reaction between equimolar amounts of *cis*-[PdCl$_2$(CNR)$_2$] (R = Cy, Bu^t, C$_6$H$_3$(2,6-Me$_2$)) and the acyclic nitrones R^{3}C(H)=(R^2)NO (R^2 = Me, R^2 = CH$_2$Ph; R^3 = C$_6$H$_4$Me-4) proceeds in C$_6$H$_6$ at 5 °C for ca. 4 h followed by maintaining the system at 20–25 °C for 20 h and provides the carbene complexes **A** shown in Scheme 19 in good to moderate (54–70%) yields. For the reaction of *cis*-[PdCl$_2$(CNR)$_2$]and R^3(H)C=N(R^2)O (R^2 = Me, R^2 = CH$_2$Ph) performed in C$_6$H$_6$ at 20–25 °C, DCA loses selectivity, and the reaction leads to a mixture of the carbenes with the complexes with the imino species that are derived from intramolecular deoxygenation of the nitrones.

The reaction with 5,5-dimethylpyrroline *N*-oxide, as a highly reactive *E*-configuration dipole, proceeds analogously providing the carbene and the imine species, the latter formed upon deoxygenation (Scheme 20). The complex derived from CA was characterized by X-ray diffraction (Fig. 14).

The theoretical study of the model reaction between the nitrone CH$_2$=N(Me)O and isocyanide C≡NMe – both free and coordinated in the complexes *trans*-[MCl$_n$(CNMe)$_2$] (M = Pd, *n* = 2; M = Pt, *n* = 2,



Scheme 19. CA of acyclic nitrones to Pd^{II}-bound isonitriles.



Scheme 20. CA followed by deoxygenation.

Table 4
Theoretically calculated (at the B3LYP/6-31G* level) gas-phase Gibbs free energies of activation and reaction (in kcal/mol) for CAs of the nitrone CH_2=N(Me)O to isocyanides [116].

Dipolarophile	$\Delta G^{\neq}$	ΔG
C≡NMe	34.9	−0.7
trans-[$PdCl_2(CNMe)_2$]	21.3	−10.1
trans-[$PtCl_2(CNMe)_2$]	23.7	−9.0
trans-[$PtCl_4(CNMe)_2$]	18.9	−12.0

4) – was carried out at the DFT (B3LYP) level of theory [116]. The mechanism of all reactions is concerted and is highly synchronous in the case of free CNMe and asynchronous for CAs to metal-bound isocyanides. As in the case of nitriles, the coordination of CNMe to a metal results in a dramatic decrease of the activation barrier (by 11.2–16.0 kcal/mol, Table 4). The reactivity of complexes [$MCl_n(CNMe)_2$] toward nitrones was lower than that of the similar nitrile species [$MCl_n(NCMe)_2$]. Nevertheless, the activation of isocyanide due to its coordination is sufficiently high to allow the reaction proceeding under mild conditions, in accord with the experimental observations [115].

The experimentally observed easy decomposition of CA product **A** to the imine complex and isocyanate (Scheme 19) was interpreted to result from the low stability of the N–O bond in **A** due to electrostatic repulsion between two strongly electronegative atoms N and O. The N–O is particularly unstable in uncomplexed *N*-heterocyclic carbenes C=N(R)CH(R′)N(R″)O and it was predicted that the heterocycles of this type may exist only when ligated to a metal center but not in a free state. The lower reactivity of the CNR ligand in **A** toward CA compared to the starting diisocyanide complexes [$PdCl_2(CNR)_2$] is accounted for by the electronic influence on CNR from the *trans*-carbene ligand in **A**, entropic factor and solvent effects.

5. Concluding remarks

Substrates bearing the CN triple bond exhibit much lower reactivity toward DCA with nitrones compared with other dipolarophiles with, e.g., carbon–carbon multiple bonds. In the reaction of RCN with nitrone-type dipoles, the outcome of CA is strongly determined by the degree of activation of the dipolarophile that could be strongly enhanced by both the introduction of electron-withdrawing substituents into a nitrile molecule (Section 2) and the coordination of RCN to a metal center (Section 3). Complexation makes DCA of nitrones favorable to a wide range of nitrile substrates, even including those with electron-donor substituents. This reaction forms the basis for the general method for syntheses of DHODs and DHOD-based heterocycles. In particular, as a result of the Pt^{II}-mediated reaction of cyclic nitrones with nitriles, novel types of annulated heterocyclic systems such as 3a,4,5,6-tetrahydroimido[l,2-*b*][l,2,4]oxadiazoles and 5,6-dihydro-3aH-[l,3]oxazolo[3,2-*i*][l,2,4]oxadiazoles (Section 3.1.5) were synthesized or enantiomerically pure tetrahydro-5,8-methanocyclohexa[3′,2′:4,5][1,3]oxazolo[3,2-*b*][1,2,4]oxadiazoles were formed (Section 3.2.2). It is important that the coordination could change the reaction site of potentially bifunctional dipolarophiles providing species that are inaccessible in metal-free synthetic approaches (Section 3.2.1).

In the DCA reactions discussed, the choice of metal center is important. Thus, the most efficient activators explored so far are Pt sites that fortunately combine such properties as the kinetic inertness of its complexes in substitution and the softness of platinum as the Lewis acid (Section 3.1.1). In accord with the theoretical calculations, the role of Pt centers in the normal electron-demand CA is for *selective* coordination of the dipolarophile RCN to a Pt site and this complexation significantly lowers the $HOMO_{dipole}$–$LUMO_{dipolarophile}$ gap between the reactants thus facilitating the interplay. Hence, involvement of platinum metal centers, which react selectively with the dipolarophile RCN but do not affect the nitrone dipole, is crucial for these CAs. The skeptical reader, however, may feel some dissatisfaction with the use of the Pt starting material, which makes the suggested synthesis of DHODs rather expensive. We still believe that the Pt-mediated CA is so far the only route to certain types of these heterocycles and for a while we should be satisfied just with achieving these compounds by any means. In addition, the conventional recycling of platinum might strongly reduce all expenses associated with this two-step synthetic transformation. Moreover, we do hope that by selecting a proper metal and by tuning electronic/steric properties of its ligand environment, one can modulate both inertness and softness of this metal site and eventually direct CA in the catalytic course.

So far only two studies devoted to DCA of nitrones to isocyanides, RNC, are known (Section 4). Despite small amount of synthetic data, one can assert that the coordination of RNC species to a metal center greatly activates isocyanide substrates toward CA of nitrones. It is not less important that the DCA of nitrones to Pd-bound isocyanides allows the generation of rather stable cyclic

aminocarbenes. These species are relevant to palladium complexes with *N*-heterocyclic carbenes. The latter are widely employed in catalysis of various organic transformations as a powerful alternative to the commonly used phosphine complexes [117,118] and – becoming popular among the organic catalytic community – acyclic aminocarbene metal species [115,119–126]. It is anticipated that further progress in DCA to complexed isocyanides could well be associated with application of novel cyclic aminocarbenes for catalysis of organic reactions.

Studies focused on the metal-mediated CA of nitrones to substrates with the CN group substantially amplify our knowledge of the chemistry of DHODs (Section 3.4), *N*-heterocyclic carbenes and their complexes (Section 4), and also give the first results pointing to the possible practical application of cycloadducts. Further development may be focused on the stereoselectivity of CA in the presence of chiral centers in the dipole–dipolarophile pair, synthesis of enantiomerically pure products for biological tests, and also studies of the catalytic activity of metal aminocarbenes in various cross-coupling reactions. Yet another direction in this field might be an extension of DCA involving metal-activated RCN and RNC substrates to other dipoles of the allyl anion type or attempting this reaction with propargyl-allenyl anion type dipoles other than already well-explored azides.

Acknowledgements

One of Russian great physicists Lev A. Artsimovich said, that "science is a way to satisfy one's own curiosity at the government's expense". Following this definition, the authors express their deepest gratitude to the governmental foundations that along the years generously supported their curiosity in studying reactions of metal-activated substrates. In particular, we acknowledge the current grants and funded programs, viz., Federal Grant-in-Aid Program "Human Capital for Science and Education in Innovative Russia" (Governmental Contract No. P676 from 20/05/2010 and P1294 from 09/06/2010), Russian Fund of Basic Research (grants 11-03-00262, 11-03-12044-ofim, 11-03-90417-ukr_f, and 09-03-00065), Saint-Petersburg State University (research grant 2011–2013), RAS Presidium Subprogram coordinated by acad. N.T. Kuznetsov (grant No. 18P), Fundação para a Ciência e a Tecnologia (FCT), Portugal (Project PTDC/QUI-QUI/098760/2008), and to both FCT and Instituto Superior Técnico (IST) for the research contract provided for MLK (Ciência 2007 Programme). Dr. Alexey Nazarov is thanked for stimulation discussions.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ccr.2011.07.001.

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