Reviews

1,3-Dipolar cycloaddition of nitrones to free and coordinated nitriles: routes to control the synthesis of 2,3-dihydro-1,2,4-oxadiazoles*

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Data on 1,3-dipolar cycloaddition of nitrones to free and coordinated nitriles producing 2,3-dihydro-1,2,4-oxadiazoles (or Δ^4-1,2,4-oxadiazolines) are summarized. The latter compounds belong to the virtually unknown class of heterocyclic systems. The main factors responsible for the cycloaddition reactions are discussed. Particular attention is given to the role of metal centers in controlling the synthesis of 2,3-dihydro-1,2,4-oxadiazoles.

Key words: 1,3-dipolar cycloaddition, nitriles, nitrile complexes, nitrones, reactivity.

1. Introduction

1,3-Dipolar cycloaddition (1,3-DCA) forms the basis of the most preparatively useful procedures for the synthesis of five-membered heterocycles, and these reactions are particularly often employed when the stereochemical control of the reaction is required.[1] In particular, allyl-anion-type dipoles, such as nitrones (R´´R″C=N(O)R´), are widely used in the 1,3-dipolar cycloaddition reactions with dipolarophilic alkenes giving rise to isoxazolidines.[2—37] It is convenient to use nitrones in these reactions because of their stability under normal conditions, due to which there is no need to prepare these compounds *in situ* to perform cycloaddition (CA). There are several convenient procedures for the synthesis of these dipoles, such as condensation of carbonyl compounds with *N*-substituted hydroxylamines, alkylation of oximes, oxidation of *N*,*N*-dialkylhydroxylamines, imines, and amines, and reduction of nitroalkanes and nitroarenes in the presence of aldehydes.[5,7,8,38] The factors responsible for the reaction pathway, such as the reactivity of dipole—dipolarophile pairs, the influence of their structures on chemo-, stereo-, and regioselectivity of the reaction, and the influence of the metal center on cycloaddition, were examined using a large number of cycloaddition reactions of nitrones with compounds containing C=C bonds.[2,6,9] Due to a considerable number of the known cycloaddition reactions of nitrones with alkenes, their systematization, and a deep understanding of the process, these reactions can be successfully employed for asymmetric synthesis of various heterocycles, in-

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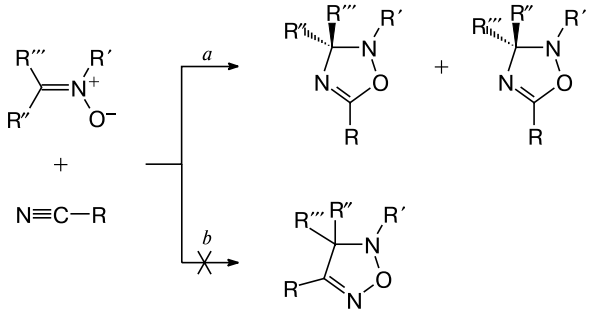
cluding those of preparative and pharmaceutical importance.[2,9]

Unlike alkenes, nitriles are poorly reactive in cycloadditions,[39,40] and, as a consequence, the reactions with RCN are much less studied than the cycloaddition of nitrones to the C=C bonds. Nevertheless, the available data are sufficient to make the first attempt to analyze and systematize cycloadditions of R‴R″C=N(O)R′ to RCN, and these issues are considered in the present review. Moreover, 1,3-DCA of nitrones to nitriles affords 2,3-dihydro-1,2,4-oxadiazoles. The properties of this class of heterocycles are virtually unknown because procedures for their synthesis are poorly developed and the available 2,3-dihydro-1,2,4-oxadiazoles are few in number. Therefore, the development of approaches[41] to the synthesis of this class of compounds is of interest on its own. It should be noted that isomeric 4,5-dihydro-1,2,4-oxadiazoles, which differ in the position of the double bond, have been studied in much more detail, the number of procedures for their synthesis is larger,[42–51] and these heterocycles have found use in various fields of medicine.[52–60]

In a few studies[61–65] concerned with cycloadditions of nitrones to nitriles, it was indicated that the reactions of these compounds are selective and produce one regioisomer, *viz.*, 2,3-dihydro-1,2,4-oxadiazole (Scheme 1, path *a*), whereas evidence for the formation of the second possible regioisomer, *viz.*, 2,3-dihydro-1,2,5-oxadiazole (see Scheme 1, path *b*), is lacking.

Scheme 1



The regioselectivity of this cycloaddition is, apparently, attributed to the fact that in the course of the reaction, the negative center (the oxygen atom) of the dipole (nitrone) points toward the more positively charged fragment of nitrile, *i.e.*, toward the carbon atom of the nitrile group. The reactions with nitrones R‴R″C=N(O)R′ (R‴ ≠ R″) having different substituents at the carbon atom are accompanied by the formation of a new chiral center, and, consequently, two stereoisomers of 2,3-dihydro-1,2,4-oxadiazole can be generated (see Scheme 1, path *a*).

The reactivity of dipole—dipolarophile pairs in 1,3-DCA is often analyzed based on the Sustmann classification, which divides the reactions into three groups according to the character of interactions between LUMO and HOMO of the reagents.[66,67] The first group includes the reactions controlled by interactions between HOMO of the dipole and LUMO of the dipolarophile (normal electron demand reactions). Reactions of an intermediate type, which are controlled by both types of HOMO—LUMO interactions, belong to the second group. The third group includes reactions controlled by interactions between LUMO of the dipole and HOMO of the dipolarophile (inverse electron demand reactions) (Fig. 1).

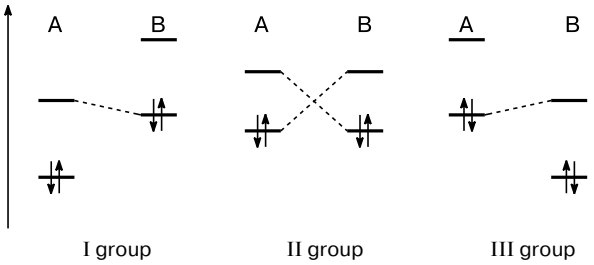


Fig. 1. Sustmann classification of cycloaddition reactions (A is a dipolarophile and B is a dipole).

Theoretical studies demonstrated that 1,3-dipolar cycloadditions of nitrones to nitriles belong to either the first type of reactions, *i.e.*, normal electron demand reactions, or to the second intermediate type approaching the first type.[68,69] For these reactions, the synthesis is controlled and the cycloaddition is promoted by introducing electron-donor substituents at the carbon atom of the azomethine group in nitrone and/or electron-withdrawing substituents in nitrile, resulting in a decrease in the energy gap between the interacting frontier molecular orbitals (FMO) of the dipole and the dipolarophile (Fig. 2, *a*). The methodology of controlling the 1,3-DCAs by introducing various substituents R into RCN molecules is considered in Section 2.1. Section 2.2 deals with the influence of the nature of substituents in nitrone.

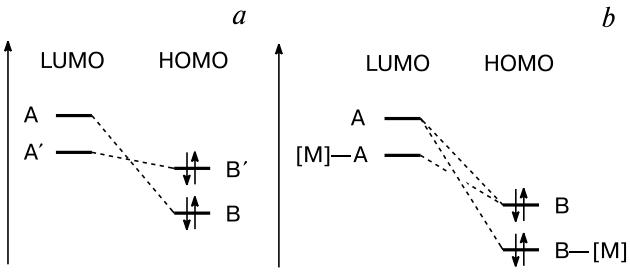


Fig. 2. Influence of the nature of substituents and coordination to metal on the pathway of normal electron demand reactions. A is a dipolarophile, B is a dipole, A′ is a dipolarophile containing an electron-withdrawing substituent, and B′ is a dipole containing an electron-releasing substituent.

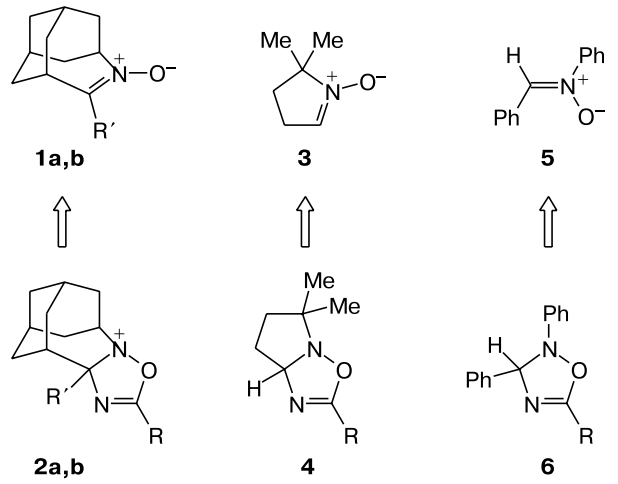
Coordination to a metal changes the FMO energy of the ligands and, correspondingly, the metal center can influence the 1,3-DCA. For example, coordination of nitrile to metal leads to a decrease in the MO energy of nitrile, which, in turn, leads to a decrease in the gap between the LUMO of nitrile and the HOMO of nitrone and, consequently, cycloaddition occurs more readily (see Fig. 2, *b*). Coordination of nitrone to a metal center lowers the MO energy of the dipole, which increases the difference between the LUMO of nitrile and the HOMO of nitrone, with the result that cycloaddition becomes less probable (see Fig. 2, *b*).

Activation of nitrile by its coordination and the control of the synthesis of ligated 2,3-dihydro-1,2,4-oxadiazoles are considered in Sections 3.1.1—3.1.2.

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

Studies on 1,3-DCAs of nitrones to free (in other words, uncoordinated to a metal center) nitriles and the progress in this field of organic chemistry are largely associated with the synthesis of highly reactive nitrones, which can react with a broad range of dipolarophiles. Among such reactive nitrones are adamantane derivatives **1a,b** (Scheme 2) and indole (β-carboline) derivatives **7—10** (Scheme 3), which react with RCN to give 2,3-dihydro-1,2,4-oxadiazoles **2a,b** (see Scheme 2) and **11—14** (see Scheme 3).[61—65]

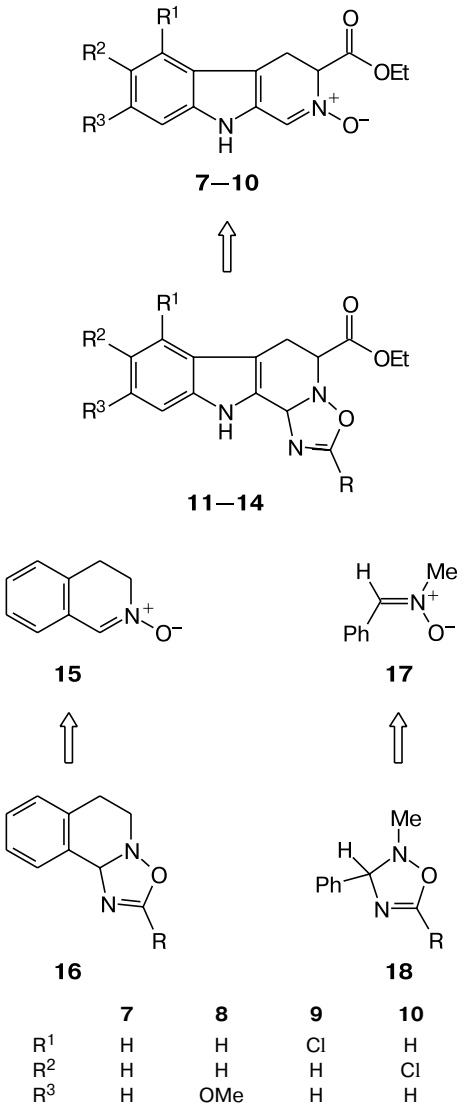
Scheme 2



R′ = H (**1a**, **2a**), Me (**1b**, **2b**)

Analysis of studies on cycloaddition of nitrones to free nitriles[61—65,70] revealed the factors responsible for the reaction pathway. Variations of these factors enable the control of the synthesis of 2,3-dihydro-1,2,4-oxadiazoles.

Scheme 3



	7	8	9	10
R^1	H	H	Cl	H
R^2	H	H	H	Cl
R^3	H	OMe	H	H

Among these factors are the nature of substituents in nitrile and nitrone molecules, the steric properties of the reactants, the solvent effect, and the use of special reaction conditions, such as high pressure or microwave irradiation (MWI).

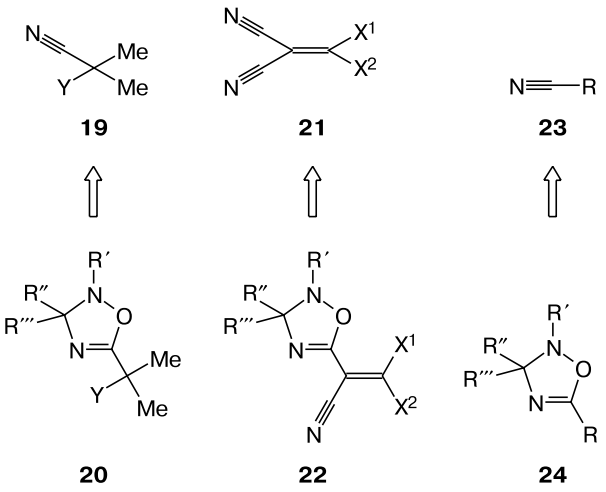
2.1. Effect of substituents in nitrile. It was noted[65,70] that only nitriles bearing strong electron-withdrawing substituents, such as CCl_3CN or $NCCH_2CN$, are involved in cycloadditions with such acyclic nitrones as PhCH=N(O)Me, whereas MeCN remains intact in this reaction when drastic conditions are applied.

The reactivity of different nitriles in 1,3-DCAs to nitrones was estimated.[62—65,70] For example, nitriles containing strong electron-withdrawing substituents (for example, *e.g.*, $NCCO_2Me$) are most reactive in the reactions with nitrones, adamantane derivatives **1a,b** (see

Scheme 2), the activity of RCN being decreased in the following series of substituents: methoxycarbonyl > aryl > > alkyl.[62]

The reactivity of nitriles was estimated[70] also in the study of the reactions of RCN with indole-based nitrones **7**—**10**. To reveal the factors influencing the reactivity of RCN, three types of compounds having the nitrile group (Scheme 4) were examined: 2-substituted 2-cyanopropanes **19**, ylidene malononitriles **21**, and nitriles **23** giving oxadiazolines **20**, **22**, and **24**, respectively.

Scheme 4



19, 20: Y = NO_2, CN, CO_2Et, Ph, Me

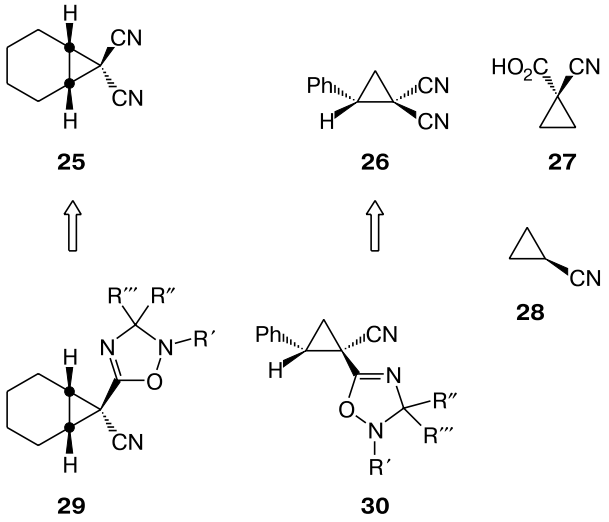
21, 22: X^1 = H, X^2 = Ph, *p*-(Cl)C_6H_4, 2-furyl; $X^1 = X^2$ = Ph; $X^1 = X^2$ = SMe

23, 24: R = CCl_3, CO_2Et, Ph, Me, NMe_2

The dependence of the degree of activation of the nitrile group on the inductive effect of the substituent Y was found by estimating the reactivity of substituted cyanopropanes **19**. The ability of nitriles to be involved in cycloaddition reactions was demonstrated to decrease with decreasing electron-withdrawing properties of the substituents in the series NO_2, CN > CO_2Et > Ph, Alk. The change in the reactivity of cyanocyclopropanes **25**—**28** (Scheme 5) in the cycloaddition to nitrones **7** and **8** is consistent with the same trend. Compounds **27** and **28** containing the CO_2H or H substituents in the geminal position with respect to the CN group are not involved in the 1,3-DCA reaction even upon prolonged heating of the reaction mixture under high pressure, and only nitriles **25** and **26** bearing the second CN group in the geminal position react with nitrones R′′′R″C=NO(R′) to give 2,3-dihydro-1,2,4-oxadiazoles **29** and **30**.[65]

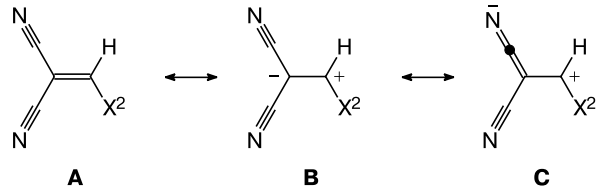
For ylidene malononitriles **21** (see Scheme 4) acting as bifunctional dipolarophiles, it was found that monosubstituted compounds (X^1 = H) are readily involved in the cycloaddition, which occurs selectively at the CN group,

Scheme 5



the reactions with nitriles containing groups X^2 with both strong electron-releasing and pronounced electron-withdrawing properties proceeding more easily. The reactivity of nitrile **21** substantially depends on the nature of the β substituent X^2. For example, the electron-withdrawing substituents X^2 lead to a decrease in the contribution of the form **C** to the mesomeric hybrid of the molecule (Scheme 6), which can somewhat increase the reactivity of the nitrile group in 1,3-DCA.

Scheme 6



This assumption is confirmed by experimental data, which are indicative of a change in the reactivity of nitriles in the series of the substituents 2-furyl ≫ ≫ *p*-(Cl)C_6H_4 ≫ Ph. Disubstituted ylidene malononitriles react more slowly, and the reactions require more drastic conditions, in particular, high pressure.

For nitriles **23** (see Scheme 4), the reactivity decreases in the series of the substituents CCl_3 > CO_2Et > NMe_2 > > Ph, whereas acetonitrile does not react with nitrones even in attempting to increase the reaction time. The relatively high reactivity of dimethylcyanamide $NCNMe_2$, which is an exception from the overall series, was attributed[70] to the inversion of the control of the reaction by frontier MOs. Therefore, the above-mentioned data provide evidence that in most cases the stronger the electron-withdrawing properties of the substituent R in RCN the

higher the reactivity in cycloaddition reactions with nitrones.

2.2. Structural characteristics of nitrones. Nitrones containing an aromatic substituent at the carbon atom, which have found wide use in organic chemistry due to their high stability (see Scheme 2, compound **5**),[2,4,62] are insufficiently reactive in reactions with the most common nitriles RCN (R = Me, Et, or Ph). Only more reactive nitrones can be involved in cycloadditions to some nitriles, including inactivated nitriles. These reactions proceed under relatively mild conditions to form 2,3-dihydro-1,2,4-oxadiazoles in good yields.

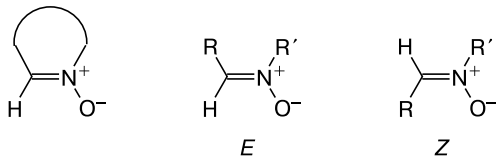
A comparative study[62,64] of such conditions, as the reaction time, the temperature, and the yields of the products, for the reactions of adamantane derivatives **1a,b**, cyclic nitrone (**3**), and acyclic nitrone (**5**) (see Scheme 2) with nitriles RCN (R = *o*-, *m*-, or *p*-(MeO)C_6H_4, *o*-, *m*-, or *p*-(NO_2)C_6H_4, Ph, or CO_2Me) demonstrated that the activity of nitrones decreases in the series **1a** > **1b** > **3** > **5**.

For example, the reactions of compounds **1a,b** with nitrile $NCCO_2Me$ proceed under normal conditions. At higher temperatures (80—125 °C), these nitrones react with less reactive nitriles RCN (R = *o*-, *m*-, or *p*-(MeO)C_6H_4, *o*-, *m*-, or *p*-(NO_2)C_6H_4, Ph, or Me). Nitrone **3** reacts with reactive aromatic nitriles and $NCCO_2Me$ in a similar way to **1a,b**, whereas acyclic nitrone **5** is less reactive. Under the same conditions (120 °C, the reaction time is 12 h), the degree of conversion is lower (the reaction with PhCN affords products in 33 (**6**) and 54% (**4**) yields[62]), or the reaction requires more drastic conditions, *e.g.*, high pressure (see Section 2.1.5).

The study of the reactivity of indole derivatives **7—10** (see Scheme 3) depending on the nature of the substituents R^1—R^3 and a comparison of the reactivity of these dipoles with the reactivity of cyclic (**15**) and acyclic (**17**) nitrones demonstrated[70] that the reactivity of these compounds in the 1,3-DCA reactions should correlate with the electron enrichment of the oxygen atom of the nitrone group, which can be estimated from the first two average-weighed ionization potentials. The reactivity of nitrones in 1,3-DCAs decreases in the following series: **8** > **9**, **10**, **7** > **15** > **17**. This corresponds to the tendency to a decrease in the ionization potentials. Indole nitrone **8** containing the electron-donor group OMe appeared to be most reactive, whereas the Cl substituents in compounds **9** and **10** have no noticeable effect on the reactivity of nitrone in cycloadditions compared to unsubstituted nitrone **7**. All dipoles **7—10** appeared to be more reactive than cyclic nitrone **15** and much more reactive than acyclic compound **17**.

The study of the kinetics of the 1,3-DCA of nitrones ArCH=N(O)Bu^t to tetracyanomethane $C(CN)_4$ demonstrated that the introduction of an electron-releasing substituent into the aryl ring of the dipole leads to an increase in the reaction rate, whereas electron-withdrawing substituents cause a retardation of the reaction rate.[61]

In the studies,[62,64,70] it was noted that cyclic nitrones are more reactive than acyclic species. This was attributed to the fact that the *E* configuration of cyclic nitrone is favorable for the formation of a heterocycle, whereas acyclic nitrones exist as an equilibrium mixture of *E* and *Z* isomers, with the *Z* isomer predominating. In the latter case, an additional step of the transformation of the *Z* isomer into the *E* isomer is required for the cycloaddition.



Therefore, the reactivity of nitrones should increase, on the one hand, in the presence of stronger electron-releasing substituents at the carbon atom of the azomethine group and, on the other hand, in going from acyclic to cyclic nitrones. Nitrones containing alkyl substituents are more reactive than those having aromatic substituents. Among dipoles **7—10**, indole derivatives bearing the OMe group in the indole ring and nitrones derived from adamantane of type **1** are most reactive.

2.3. The steric factor. The influence of this factor on the reaction rate, on the one hand, and the yield of the product, on the other hand, was revealed for substituted aromatic nitriles in the reactions with nitrones **1a,b**.[62] Thus, the cycloaddition to *o*-substituted aromatic nitriles proceeds more slowly than the corresponding reactions with *m*- and *p*-substituted derivatives and produces 2,3-dihydro-1,2,4-oxadiazole in lower yield. The presence of the methyl group at the carbon atom of the azomethine group of the nitrone (compound **1b**) also hinders the reaction and leads to a decrease in the yields of heterocycles **2b** by 30—50% compared to unsubstituted product **2a** (see Scheme 2). The reactions of monosubstituted ylidene malononitriles **21** with nitrones produce one sterically unhindered stereoisomer **22**.[70] Ylidene malononitriles **21** (see Scheme 4) are involved in cycloaddition reactions with difficulty, which is reflected, in particular, in the yield of the final product. The yield was increased only when the reaction was performed under high pressure. Only one sterically less hindered CN group is involved in the reaction of dinitrile **25** with nitrones. The cycloaddition of dinitrile **26** to nitrones affords two sterically less hindered diastereomers **30** of four possible diastereomers.[65]

2.4. The solvent effect. This effect was studied[70] only for the reaction of cyclic nitrone **15** with dimethylmalononitrile (NC)CMe_2(CN). The cycloaddition was carried out in three different solvents (toluene, ethoxybenzene, and 2-methoxyethanol). A small inverse solvent

polarity effect was observed. The reaction proceeds more readily in less polar toluene, which is attributed to a slight decrease in the polarity of the transition state compared to the polarity of the reactants.

2.5. Other factors. Cycloaddition of nitrones to different dipolarophiles[64,71] and, in particular, with nitriles,[64,65] can be accelerated under high pressure. For example, the reaction of nitrone **5** with nitriles RCN (R = Me or Ph) under a pressure of 10 kbar leads to a decrease in the reaction time from 12 h to 1—4 h.[64] In addition, the reaction of nitrone **7** with nitrile **26** performed under high pressure (12 kbar) made it possible to increase the yield of the heterocycle from 74 to 90%.[65] The use of focused MWI in the cycloaddition of PhCH=N(O)Ph to the reactive nitrile $NCCO_2Et$ leads to acceleration of the reaction and an increase in the yield of the product from 4 to 39% compared to the conventional heating mode.[72] Focused MWI was also successfully employed for accelerating cycloadditions of nitrones to metal-complexed nitriles (see Section 3.1.4).

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

Available considerable experimental data provide evidence of the influence of a metal center on 1,3-DCA reactions, to be more precise, on promotion or inhibition of the reaction and its regio- and stereoselectivity.[73] Most of studies concerned with metal-mediated 1,3-DCA were focused on the reactions of alkenes with different types of dipoles.[6,73]

Relatively recently, the cycloadditions of nitrones to coordinated nitriles have been studied by both experimental and theoretical methods.[8,69,74—83] It was demonstrated that a metal center substantially increases the reactivity of nitriles in cycloaddition reactions with nitrones and has an effect on its stereo- and chemoselectivity. For example, cycloadditions of the nitrile complexes of platinum(IV), $[PtCl_4(RCN)_2]$ (R = Me, CH_2Ph, or Ph), and platinum(II), $[PtCl_2(RCN)_2]$, (R = CH_2Ph or Ph) with nitrones ArCH=N(O)R″ (R″ = Me or CH_2Ph) proceed already at room temperature to form *N*(4)-coordinated 2,3-dihydro-1,2,4-oxadiazoles (Scheme 7, Fig. 3),[78,79] whereas uncoordinated nitriles do not react with such nitrones even under substantially more drastic conditions.

An analysis of FMOs of the reagents (see Section 1) shows that coordination of nitrile to a metal center promotes the 1,3-DCA reaction of nitrones (see Fig. 2, *b*). Moreover, theoretical studies demonstrated[68,69] that the effect of coordination of nitrile to platinum(IV) in cycloaddition reactions is even stronger than the effect of activation of nitrile due to the introduction of the strong electron-withdrawing CF_3 group. It should be noted that

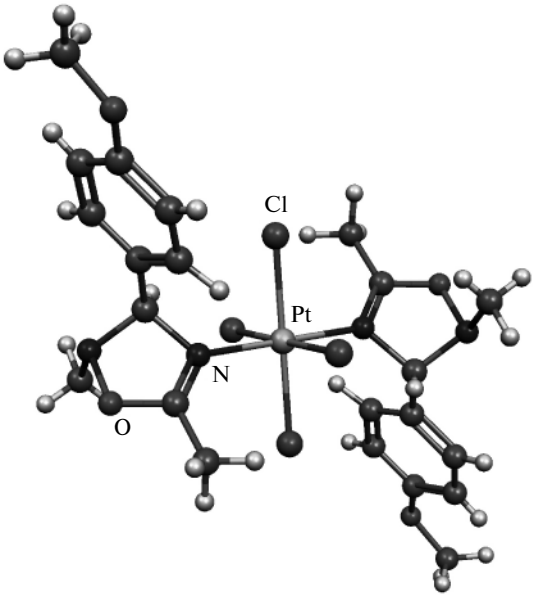
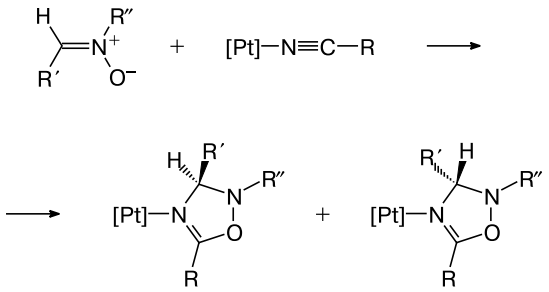


Fig. 3. Molecular structure of [bis{3-(*p*-methoxyphenyl)-2,5-dimethyl-2,3-dihydro-1,2,4-oxadiazole}$_2$]tetrachloroplatinum(IV).

Scheme 7



the reactions of nitriles with nitrones giving rise to heterocycles can occur only upon coordination of nitrile to a metal center. No reactions of coordinated nitrones with nitriles were documented.

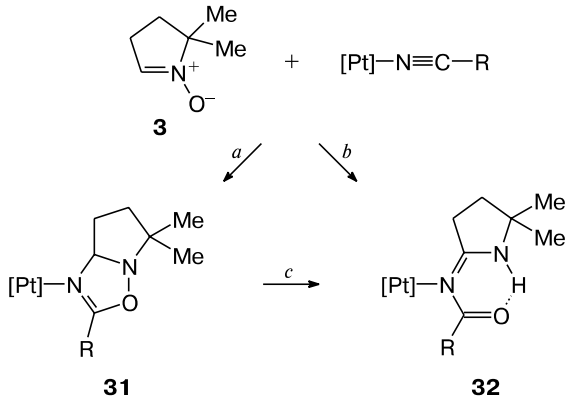
3.1. Factors influencing metal-mediated 1,3-DCA

The 1,3-DCAs of nitrones to nitriles depend on a number of factors, which can be revealed from the analysis of the experimental data:[74—79,82—84] the oxidation state and the nature of a metal center, the ligand environment in nitrile complexes, the nature of nitrile and nitrone, and the use of additional methods of activation.

3.1.1. The oxidation state of the metal center has a substantial effect on activation of coordinated nitrile, which was exemplified by the reactions of acyclic nitrones with platinum(II and IV) nitrile complexes. For example, ligated benzonitrile in the platinum(IV) complex $[PtCl_4(PhCN)_2]$ reacts with nitrones R′CH=N(O)Me (R′ = Ph and

p-MeC_6H_4) more rapidly (1.5 h at room temperature) than the nitrile in the analogous platinum(II) complex $[PtCl_2(PhCN)_2]$ (1 day at room temperature).[79] More reactive cyclic nitrone **3** reacts with nitriles in the platinum(II) complexes $[PtCl_2(EtCN)_2]$, the reaction time varying from 1 to 2 days, whereas the reaction of this nitrone with the platinum(IV) complex $[PtCl_4(EtCN)_2]$ is completed in 15 min (Scheme 8, path *a*).[74]

Scheme 8



R = Et, Ph (**31**); CH_2CO_2Me, CH_2Cl (**32**)

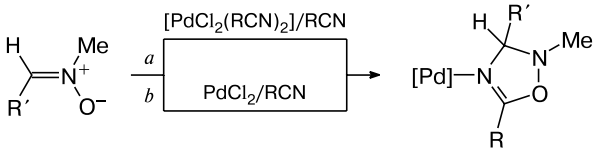
Theoretical calculations[68,69] confirmed higher reactivity of platinum(IV) nitrile complexes toward nitrones compared to (nitrile)Pt(II) complexes and free nitriles.

It should be noted that the reactivity of the RCN ligand in platinum(II) complexes substantially depends on the nature of the substituent in the RCN molecule. Thus, complexes with nitriles containing an electron-releasing substituent, for example, $[PtCl_2(MeCN)_2]$, do not react with nitrones ArCH=N(O)Me even upon prolonged heating[79] and only the complex with aromatic nitrile (R = Ph) reacts with nitrones at room temperature to form complexed 2,3-dihydro-1,2,4-oxadiazoles. Coordination of RCN to platinum(IV) diminishes the effect of the substituent in the ligand, and the rates of the reactions of nitriles in the $[PtCl_4(RCN)_2]$ complexes with nitrones R″CH=N(O)R′ (R = Me, R′ = Me, R″ = Ph, *o*-C_6H_4OH, *p*-C_6H_4Me, *p*-C_6H_4OMe, *p*-$C_6H_4NO_2$, *p*-$C_6H_4NMe_2$, or *p*-$C_6H_4NMe_2 \cdot HCl$; R = Me, R′ = CH_2Ph, R″ = Ph or Bu^t; R = Ph, R′ = Me, R″ = Ph or *p*-C_6H_4Me; R = Ph, R′ = CH_2Ph, R″ = Ph) are approximately equal.[78,79] Platinum(IV) activates the RCN ligand to an extent that the cycloadditions of nitrones ArCH=N(O)R′ become possible even with nitriles containing electron-releasing substituents and the influence of the nature of the substituent R on the reactivity of coordinated nitrile is virtually absent.

3.1.2. The nature of the metal center is one of the key factors determining the possibility of metal-mediated cycloaddition. The analysis of the studies[63,64,76,80] showed that the cycloaddition reactions proceed successfully only with platinum(II and IV) and palladium(II) nitrile complexes. For other nitrile complexes (titanium(IV), zirconium(IV), molybdenum(IV), and tungsten(IV)) attempted in the reactions with nitrones, no evidence for the formation of 2,3-dihydro-1,2,4-oxadiazoles was obtained.[80]

A comparison of the cycloadditions involving platinum(II) and palladium(II) revealed a comparative degree of activation of nitrile in the $[MCl_2(PhCN)_2]$ complexes (M = Pt^{II} or Pd^{II}), which is indirectly supported by the reaction with *p*-MeC_6H_4CH=N(O)Me (1 day at 25 °C in CH_2Cl_2 for Pt^{II} and 1 day at 40 °C in PhCN for Pd^{II}).[75] There are certain differences in the synthesis conditions depending on the nature of metal used as the activator. Platinum(II) complexes, which are relatively inert in substitution reactions, react with nitrones to give 2,3-dihydro-1,2,4-oxadiazoles in such solvents as dichloromethane or chloroform.[78] Cycloaddition to nitriles in kinetically more labile palladium complexes can occur only in the corresponding nitrile (Scheme 9, path *a*).[75,78]

Scheme 9



a. R = Ph, PhCH=CH; R′ = Ph, MeC_6H_4

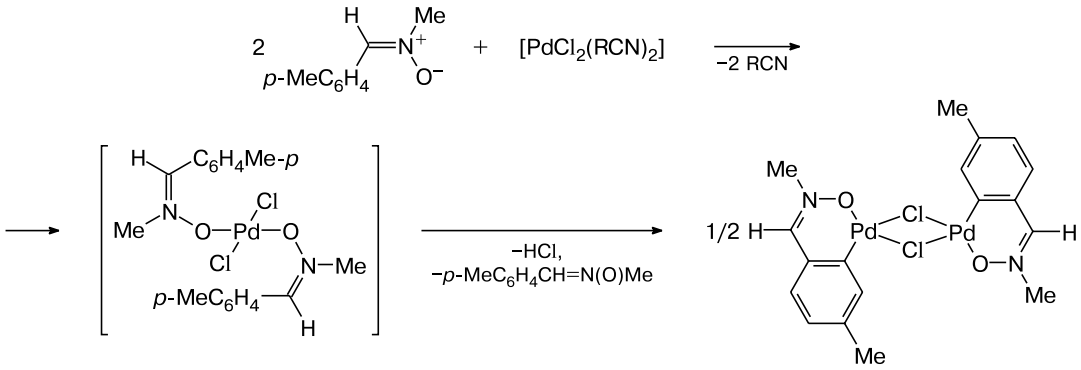
b. R = Me, Ph; R′ = MeC_6H_4

The reactions of ArCH=N(O)Me with $[PdCl_2(RCN)_2]$ in such solvents as acetone or dichloromethane produce neither free nor coordinated 2,3-dihydro-1,2,4-oxadiazoles. In this case, only complexes generated through the replacement of the nitrile ligands with nitrone were detected, and the product of the further transformation of coordinated nitrone, *viz.*, the dimeric Pd^{II} complex with cyclometallated nitrone (**33**), was isolated (Scheme 10, Fig. 4).[75]

This dependence of the reaction pathway on the nature of the solvent is associated with higher lability of palladium complexes compared to platinum complexes and higher "hardness" of palladium (in terms of hard and soft acids and bases theory), which is responsible for the facile replacement of the "softer" base RCN by the "harder" *O*-coordinated nitrone in the absence of excess nitrile.[75] It was assumed[80] that the nitrile is insufficiently activated because of the formation of the dimeric palladium complex $[Pd(\mu\text{-}Cl)Cl(RCN)]_2$ in dichloromethane and, consequently, cycloaddition does not occur.

In the presence of palladium(II), the synthesis can be performed according to yet another procedure. The

Scheme 10



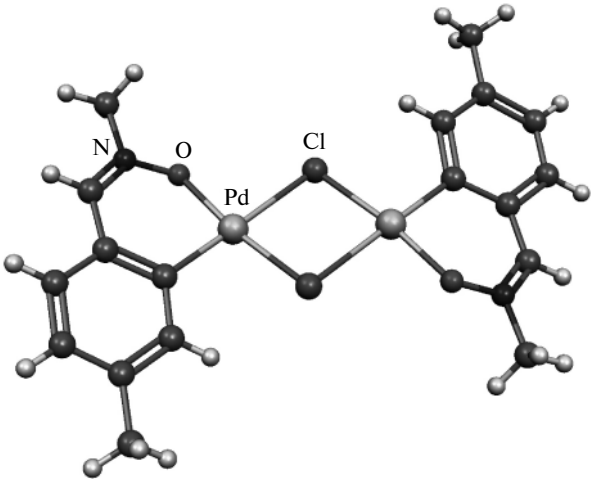
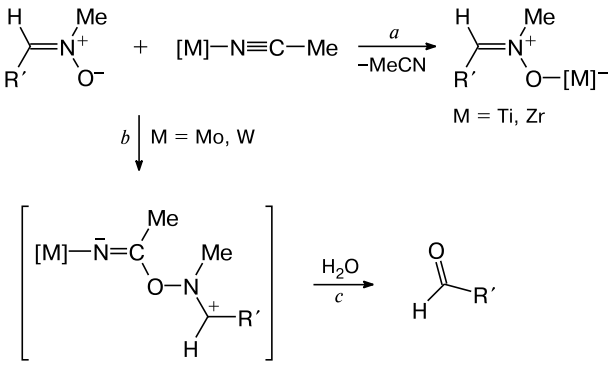


Fig. 4. Molecular structure of the $[PdCl\{ON(Me)CHC_6H_3(Me\text{-}p)\}]_2$ complex (**33**).

palladium(II) complex with 2,3-dihydro-1,2,4-oxadiazole can be prepared by the reaction of $PdCl_2$ with the nitrone *p*-MeC_6H_4CH=N(O)Me in the nitrile PhCN (see Scheme 9, path *b*). In this case, the reaction rate and the yield of the cycloaddition product are comparable with those in the reaction of $[PdCl_2(PhCN)_2]$ with the corresponding nitrone. Presumably, dissolution of $PdCl_2$ in the nitrile affords the palladium nitrile complex $[PdCl_2(PhCN)_2]$, which reacts with the nitrone.[75]

In neither case did the reactions of the nitrile complexes $[MCl_4(MeCN)_2]$ (M = Ti^{IV}, Zr^{IV}, Mo^{IV}, or W^{IV}) with the nitrones R´CH=N(O)Me (R´ = Ph or *p*-MeC_6H_4) produce the cycloaddition products with nitrile, and other transformation products of the nitrone were isolated.[80] The reactions with the titanium(IV) and zirconium(IV) complexes, which are hard acids, are accompanied by the fast replacement of the ligated nitrile to yield the polymeric complexes with coordinated nitrone $[MCl_4(R´R''C=N(O)R''')_n]$ (n = 1.3—1.8) (Scheme 11, path *a*).

Scheme 11

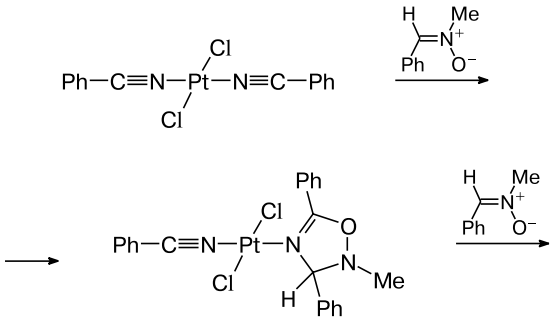


In the presence of molybdenum(IV) and tungsten(IV) complexes, nitrone is hydrolyzed to the corresponding aldehyde (see Scheme 11, path *c*). The authors[59] believe that hydrolysis can proceed through the formation of the 1,5-dipole (see Scheme 11, path *b*), which is formed as a result of the addition of the nitrone to the coordinated nitrile through the oxygen atom. This dipole reacts with water with elimination of the aromatic aldehyde. This reaction mechanism is confirmed by theoretical calculations, which are indicative of the stepwise mechanism of cycloaddition in the presence of Lewis acids.[68,69,81]

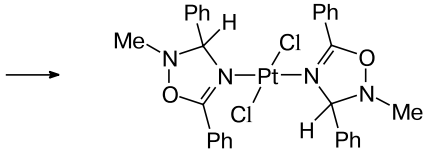
3.1.3. Ligand environment in nitrile complexes can influence the cycloaddition reaction. It was found that the reaction rate depends on the nature of the ligand in the *trans* position with respect to the coordinated nitrile. In particular, a qualitative study of the kinetics of cycloaddition of the nitrone PhCH=N(O)Me to the nitrile in the *trans*-$[PtCl_2(PhCN)_2]$ complex demonstrated[77] that the reaction proceeds in two steps. The first step involves the addition of the nitrone to one of the nitrile ligands (compound **34**, Scheme 12), which is followed by the cycloaddition to the second coordinated PhCN ligand (compound **35**, see Scheme 12), the rate of the second step being lower by a factor of approximately 6. This fact

is attributed to the electronic effects. In the starting complex, the second nitrile molecule is in the *trans* position with respect to the reacting nitrile, whereas the *trans* position in compound **34** is occupied by the coordinated 2,3-dihydro-1,2,4-oxadiazole, which is generated in the first reaction step and is a better σ-donor than the nitrile, resulting in a decrease in the electron-withdrawing properties of the metal center and inhibition of the second step of the cycloaddition.

Scheme 12



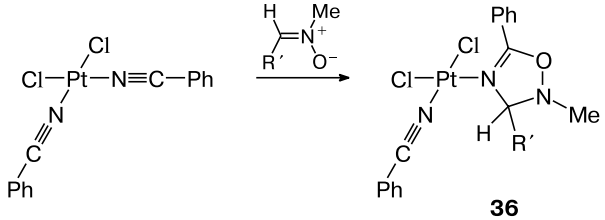
34



35

Ligands in the *cis* position with respect to the reacting nitrile also have an effect on the reaction, *i.e.*, they determine the possibility that the reaction does occur and/or the stereoselectivity of the process (see Section 3.2). For example, the *cis*-$[PtCl_2(PhCN)_2]$ complex reacts only with one nitrone molecule R´CH=N(O)Me (R´ = Ph or *p*-MeC_6H_4) (Scheme 13). After the formation of monocycloaddition product **36**, the further reaction with the nitrone is not observed. In contrast, *trans*-$[PtCl_2(PhCN)_2]$ reacts with nitrone in a molar ratio of 1 : 2 to form the bis(2,3-dihydro-1,2,4-oxadiazole)dichloroplatinum(II) complex.[77] This difference in the behavior of the isomers

Scheme 13



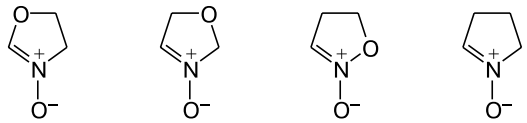
36

is attributed to the influence of the steric factor on the cycloaddition. Thus, the sterically hindered 2,3-dihydro-1,2,4-oxadiazole ligand generated in the first step hinders the cycloaddition to the coordinated nitrile located in the *cis* position.

3.1.4. The nature of nitrile and nitrone. In addition to the oxidation state, the nature of a metal center, and the ligand environment, which are factors specific for coordination compounds, the 1,3-DCAs in complexes are determined by the factors common to both these reactions and the reactions of uncoordinated dipoles and dipolarophiles. The latter factors were analyzed in Sections 2.1—2.5.

The nature of nitrile. In Section 3.1.2, it was noted that the nature of the substituent in the ligand RCN in platinum(II) complexes plays a considerable role in 1,3-DCA reactions. An analogous situation is observed for the reactions of Pd^{II} nitrile complexes. For example, the $[PdCl_2(PhCN)_2]$ complex reacts with the nitrone *p*-MeC_6H_4CH=N(O)Me under mild heating (50 °C), whereas the reactions of the complexes with electron-donor substituents $[PdCl_2(RCN)_2]$ (R = Me or Et) proceed under more drastic conditions (more prolonged heating and/or the use of MWI).[77]

The nature of nitrone plays a similar role in cycloadditions with the ligands RCN in complexes and in reactions with free nitriles. The reactivity of these dipoles increases in going from acyclic to cyclic nitrones and upon the introduction of an electron-releasing substituent at the carbon atom of the azomethine group.[69] Cyclic nitrone **3** (see Scheme 8) reacts with the coordinated EtCN in the platinum(II) complexes $[PtCl_2(EtCN)_2]$ and $[Ph_3PCH_2Ph][PtCl_3(EtCN)]$,[74] whereas the ArC(H)=N(O)Me compounds do not react with nitrile ligands bearing electron-releasing substituents in the $[PtCl_2(RCN)_2]$ complexes (R = Me or Et).[79] This difference in the reactivity is attributed, on the one hand, to the presence of an electron-releasing substituent at the carbon atom of the C=N(O) group of the cyclic nitrone and, on the other hand, to the existence of the cyclic dipole exclusively in the more reactive *E* configuration (see Section 2.1.2).



37 **38** **39** **40**

A theoretical study of the 1,3-DCA reactions of cyclic nitrones **37—40** with free and coordinated nitriles[68] demonstrated that nitrones in which the oxygen atom is bound to the carbon atom of the C=N(O) group (**37**) are more reactive in the cycloaddition reactions. Nitronate **39**, in which both oxygen atoms are bound to the nitrogen

atom, should be the least reactive compound. According to the calculations,[68] compounds containing the oxygen atom in the ring, which is not directly bound to the nitrone group (**38**), or compounds, in which the ring has no oxygen (**40**), are characterized by an intermediate reactivity in 1,3-DCAs to RCN.

3.1.5. Focused microwave irradiation can be used as an additional factor, which enables acceleration of the cycloadditions. For example, the reactions of the platinum(II) nitrile complexes $[PtCl_2(EtCN)_2]$ and $[Ph_3PCH_2Ph][PtCl_3(EtCN)]$ with cyclic nitrone **3** (see Scheme 8) at room temperature are completed in 1—2 days, whereas these reactions under MWI are completed in 30 min at 30 °C or in 15 min at 50 °C.[74] The cycloaddition of the nitrones R´CH=N(O)Me (R´= Ph or *p*-MeC_6H_4) to the nitriles in $[PtCl_2(RCN)_2]$ (R = Ph or PhCH=CH) are accelerated by dozens of times under MWI.[77] In addition, MWI has different effects on the first and second steps of the cycloaddition, the formation of the monocycloaddition product $[PtCl_2\{N{=}C(R)ON(Me)CHR´\}(RCN)]$ being more accelerated than the formation of the bis-cycloaddition product, *viz.*, dichlorobis(2,3-dihydro-1,2,4-oxadiazole)platinum(II).[77] Due to the difference in the influence of MWI on the rates of the first and second steps of the cycloaddition to the bis-nitrile complex $[PtCl_2(NCCH{=}CHPh)_2]$, $[PtCl_2\{N{=}C(R)ON(Me)CHR´\}(RCN)]$ was synthesized chemoselectively.[76] The use of MWI also leads to an increase in the rate of the cycloaddition of *p*-$MeC_6H_4CH{=}N(O)Me$ to the nitrile in the palladium(II) complex $[PdCl_2(MeCN)_2]$ to form the coordinated 2,3-dihydro-1,2,4-oxadiazoles.[75]

3.2. Stereoselectivity of metal-mediated 1,3-dipolar cycloaddition. The steric properties of ligands in *cis*/*trans* positions can influence the stereoselectivity of the cycloaddition to coordinated nitrile.[82] For example, the cycloaddition reaction of nitrones to nitriles leads to the formation of a new chiral center at the carbon atom in the N—C*HR—N group (see Scheme 7). In the case of the *trans*-arranged nitrile ligands in the platinum complexes $[PtCl_n(RCN)_2]$ (n = 2 or 4), the coordinated 2,3-dihydro-1,2,4-oxadiazole molecule generated in the first step of the cycloaddition has no effect on the stereoconfiguration of the heterocycle formed in the second step due to a large distance between the ligands, and the diastereomers are formed in a ratio of 1 : 1.[78,82] To elucidate the role of the ligand environment in the formation of a particular stereoisomer of 2,3-dihydro-1,2,4-oxadiazole, the cycloaddition of nitrone to the coordinated benzonitrile in the *cis*-$[PtCl_2(MePhS*O)(PhCN)]$ complex containing optically active sulfoxide in the *cis* position with respect to PhCN was studied.[82] The reaction of nitrones R´CH=N(O)Me (R´ = Ph, *p*-MeC_6H_4, or *p*-$(MeO)C_6H_4$) with a complex containing a R_S/S_S racemic mixture of the sulfoxide ligand generated the cycloaddition products with the $(S_S,R_C)/(R_S,S_C)$ to $(S_S,S_C)/(R_S,R_C)$ isomer ratio of 80 : 20 (the diastereomeric excess was 60%) (R´ = Ph), 70 : 30 (*de* 40%) (R´ = *p*-MeC_6H_4), and 65 : 35 (*de* 30%) (R´ = *p*-$(MeO)C_6H_4$) (Scheme 14, compound **41**). The major product, a racemate of stereoisomers antipodes $(S_S,R_C)/(R_S,S_C)$, was isolated by fractional recrystallization of the resulting mixture with *de* 90% and characterized by X-ray diffraction (Fig. 5). The reaction with *cis*-$[PtCl_2(MePhS*O)(PhCN)]$ enriched in the R_S isomer (*ee* 79%) gave the $(S_S,R_C)/(R_S,S_C)$ to $(S_S,S_C)/(R_S,R_C)$ stereoisomer ratio identical to that obtained with the use of a racemic mixture of the starting complex. Fractional recrystallization from a $CHCl_3$—Et_2O mixture afforded the main pair of stereoisomers $(S_S,R_C)/(R_S,S_C)$ (*de* 90%).

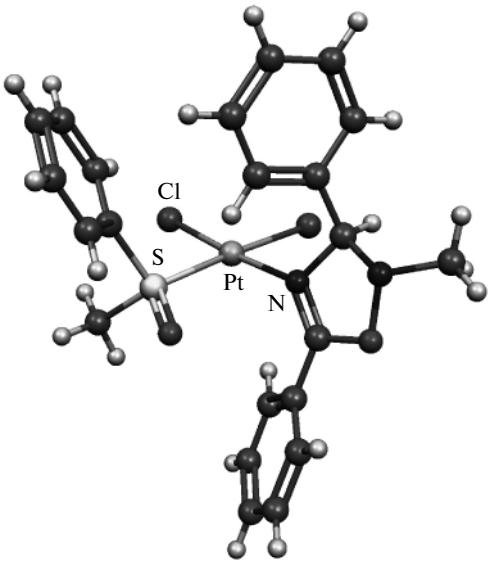
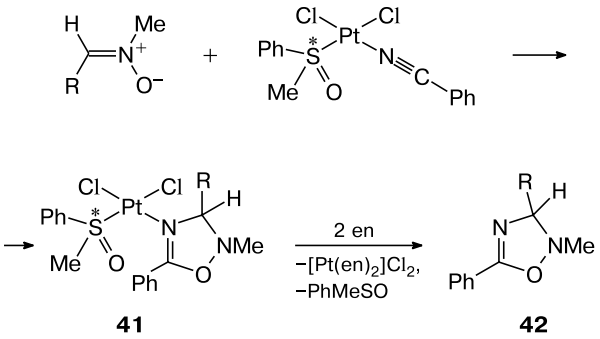


Fig. 5. Molecular structure of the *cis*-(R_S,S_C)-$[PtCl_2\{N{=}C(Ph)ON(Me)CHPh\}\{MePhSO\}]$ complex (**41**).

Scheme 14



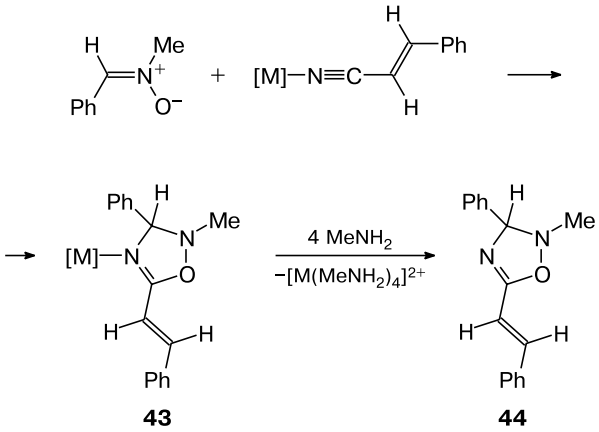
41 **42**

The substitution reaction of a racemic mixture of the complexes of the isomers $(S_S,R_C)/(R_S,S_C)$ and $(S_S,R_C)/(R_S,S_C)$ enriched in the R_S stereomer with an

excess of ethylenediamine produced free 2,3-dihydro-1,2,4-oxadiazole. In the former case, the product was obtained as the racemate R_C/S_C; in the latter case, as a mixture enriched in the S_C stereomer (*ee* 70%) (see Scheme 14, compound **42**).[82] The sequence of these reactions demonstrates the possibility of the stereoselective synthesis of chiral 2,3-dihydro-1,2,4-oxadiazoles through asymmetric induction of the starting platinum complex.

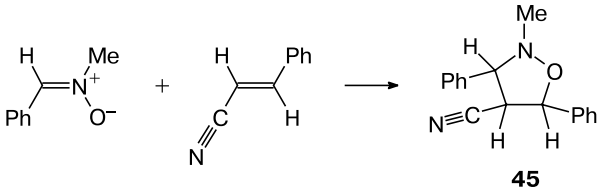
3.3. Chemoselectivity of metal-mediated cycloaddition. Coordination to a metal center can not only influence the reaction rate of cycloaddition to the nitrile group but also change the chemoselectivity of the reaction. The reaction of the $[MCl_2(N{\equiv}C{-}CH{=}CHPh)_2]$ complex (M = Pt^{II} or Pd^{II}) containing the bifunctional dipolarophile with the nitrone PhCH=N(O)Me was studied.[76] The reaction performed at 60 °C for 2 days produced complexes **43** through the chemoselective cycloaddition of the nitrone to the C≡N bond (Scheme 15).

Scheme 15



The reaction with even a substantial excess of the nitrone does not afford a cycloaddition product to the C=C bond. In contrast, the reaction of the uncoordinated nitrile N≡C—CH=CHPh with the nitrone PhCH=N(O)Me proceeds exclusively at the C=C bond to form isoxazole **45**, the C≡N bond remaining intact (Scheme 16).

Scheme 16



In other words, coordination of RCN to the metal center leads to strong activation of the nitrile group, resulting in a change in the reactivity center in N≡C—CH=CHPh with respect to nitrones, and the reaction occurs selectively at the C≡N bond, while the C=C bond remaining intact.

After treatment of the resulting 2,3-dihydro-1,2,4-oxadiazole complexes with an aqueous methylamine solution, heterocycle **44** was isolated in the free state (see Scheme 15).[76] Therefore, coordination of nitrile to a metal center and the 1,3-DCA reaction followed by the replacement of the cycloaddition product make it possible to prepare 2,3-dihydro-1,2,4-oxadiazoles containing the intact C=C bond in the side chain with high selectivity, which cannot be synthesized by the 1,3-DCA of nitrones to free bifunctional nitrile.

3.4. Stability of coordinated 2,3-dihydro-1,2,4-oxadiazoles. Coordination of nitriles to a metal center influences *stability* of 2,3-dihydro-1,2,4-oxadiazole generated in the reaction. The reactions of the nitriles RCN (R = $MeCO_2CH_2$ or $ClCH_2$) in the $[PtCl_2(RCN)_2]$ complexes with cyclic nitrone **3** produce the keto imine complexes $[PtCl_2\{N(C_4H_4(Me)_2NH)C(=O)CH_2CO_2Me\}_2]$ (**32**) (see Scheme 8, Fig. 6).[83]

It was assumed[83] that the reaction proceeds through the formation of the unstable 2,3-dihydro-1,2,4-oxadiazole complex, in which the N—O bond cleavage is promoted with increasing electron-withdrawing properties of the group R and also by coordination to the metal center. As a result, the rearrangement accompanied by the 1,2-proton shift gives the corresponding keto imine. In the presence of hydrogen, stable complex **31** is rearranged under atmospheric pressure into analogous keto imine complex **32** (see Scheme 8, path *c*).

3.5. Liberation of the heterocycles from complexes. The 1,3-DCAs of nitrones to ligated nitriles produce coordinated 2,3-dihydro-1,2,4-oxadiazoles rather than free

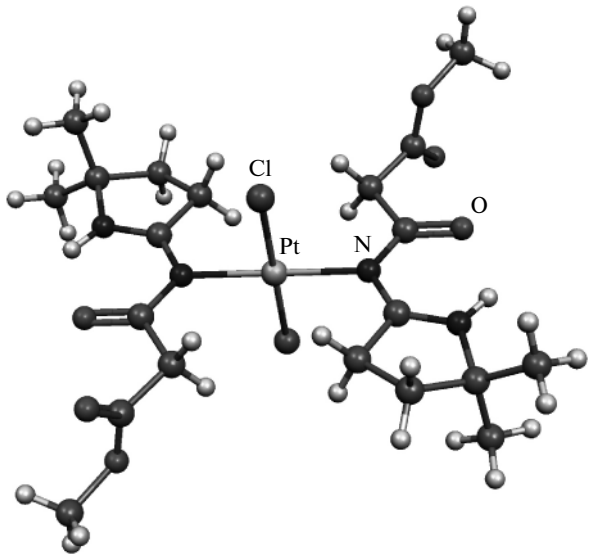
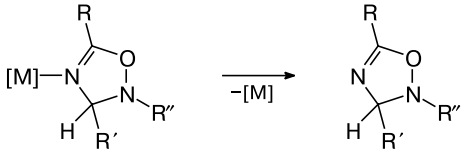


Fig. 6. Molecular structure of complex **32**.

heterocycles. An additional liberation step is required to isolate 2,3-dihydro-1,2,4-oxadiazoles in the free state (see Schemes 14, 15, and 17).[76,78,79,82] For example, 2,3-dihydro-1,2,4-oxadiazoles were prepared from platinum(IV) complexes by the substitution reaction with an excess of pyridine and from platinum(II) complexes by the replacement of heterocyclic ligands with diphenylphosphinoethane or methylamine (see Scheme 17). The reaction sequence involving the synthesis of a platinum(IV) nitrile complex, the reaction with nitrone, and liberation of 2,3-dihydro-1,2,4-oxadiazole, was proposed as a general procedure for the synthesis of 2,3-dihydro-1,2,4-oxadiazole derivatives of nitriles containing electron-releasing substituents R, which cannot be prepared by the conventional organic synthesis.[78,84]

Scheme 17



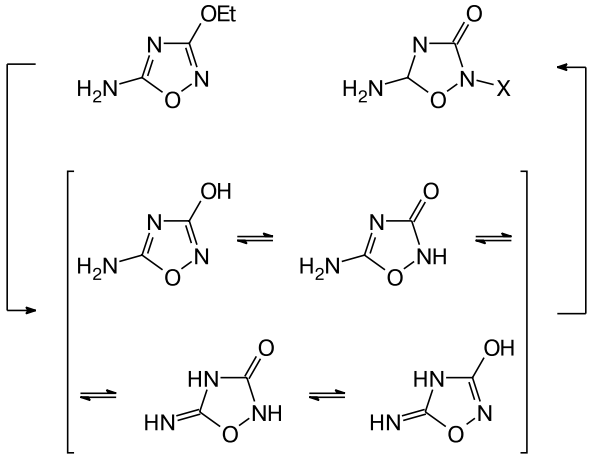
Free 2,3-dihydro-1,2,4-oxadiazoles were isolated from their palladium(II) complexes with the use of sodium sulfide, methyl amine, or ethylenediamine.[75,76,80] When activation of nitrile with palladium(II) is sufficient for the cycloadditions, this approach to the synthesis of 2,3-dihydro-1,2,4-oxadiazoles can be used as a less expensive and rapid procedure than the method with the use of platinum(II) or (IV).

4. Conclusions

The 1,3-DCA of nitrones to nitriles provides a convenient and the only (with the sole exception[41]) procedure for the synthesis of 2,3-dihydro-1,2,4-oxadiazoles. Just one synthesis of 2,3-dihydro-1,2,4-oxadiazol-3-one derivatives, which are generated from 3-ethoxy-1,2,4-oxadiazole through elimination of the Et group followed by mesitylation or acetylation (Scheme 18), rather than by the cycloaddition was documented.[41]

Due to a low reactivity of nitriles and nitrones, which are traditionally used in organic synthesis in 1,3-DCA, the synthesis of these heterocycles presents difficulty. The use of nitriles RCN containing electron-withdrawing substituents R and reactive nitrones (cyclic and/or containing electron-releasing substituents) promotes the reaction and leads to an increase in the yields of 2,3-dihydro-1,2,4-oxadiazoles. Owing the activation of nitrile through coordination to a metal center (platinum or palladium), the reactions of nitriles, which are unreactive in the free state (for example, MeCN), with virtually all nitrones can

Scheme 18



be carried out under mild conditions. Hence, a procedure for the synthesis of 2,3-dihydro-1,2,4-oxadiazoles is more versatile and is applicable to a broad range of nitriles and nitrones. In some cases, coordination to a metal center can not only change the reactivity of nitriles but also influence the chemoselectivity and stereoselectivity of 1,3-dipolar cycloaddition. In some cases, MWI and high pressure can be employed as additional routes to activation, which can shorten the reaction time for the cycloaddition of nitrones to nitriles. Therefore, the reactivity of the nitrile/nitrone pair can be controlled by varying the nature of the substituent R (electron-withdrawing substituents) in nitrile RCN, coordination of nitrile to a metal center, varying the structure of nitrone (introducing electron-releasing substituents at the carbon atom in the azomethine group or stabilization of the *E* configuration of nitrone), and the use of additional methods of activation (MWI or high pressure).

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References

1. T. L. Gilchrist, *Heterocyclic Chemistry*, Wiley, New York, 1992.
2. K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863.
3. R. Huisgen, *Angew. Chem.*, 1963, **75**, 604.

4. K. B. G. Torssel, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis, Novel Strategies in Synthesis, Organic Nitro Chemistry*, VCH Publishers, Inc, 1988.
5. H. M. I. Osborn, N. Gemmell, and L. M. Harwood, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2419, and references therein.
6. K. V. Gothelf and K. A. Jørgensen, *Chem. Commun.*, 2000, 1449.
7. J. P. Adams and J. R. Paterson, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3695.
8. J. P. Adams and J. R. Paterson, *J. Chem. Soc., Perkin Trans. 1*, 1999, 749.
9. M. Frederickson, *Tetrahedron*, 1997, **53**, 403.
10. Sk. Sahabuddin, A. Roy, M. G. B. Drew, B. G. Roy, B. Achari, and S. B. Mandal, *J. Org. Chem.*, 2006, **71**, 5980.
11. A. Chatterjee and P. K. Bhattacharya, *J. Org. Chem.*, 2006, **71**, 345.
12. A. Basak and S. C. Ghosh, *Tetrahedron Lett.*, 2005, **46**, 7385.
13. S. Moutel, M. Shipman, O. R. Martin, K. Ikeda, and N. Asano, *Tetrahedron: Asymmetry*, 2005, **16**, 487.
14. J. Yu, J. DePue, and D. Kronenthal, *Tetrahedron Lett.*, 2004, **45**, 7247.
15. K. Singha, A. Roy, P. K. Dutta, S. Tripathi, S. Sahabuddin, B. Achari, and S. B. Mandal, *J. Org. Chem.*, 2004, **69**, 6507.
16. I. A. O´Neil, V. E. Ramos, G. L. Ellis, Ed Cleator, A. P. Chorlton, D. J. Tapolczay, and S. B. Kalindjian, *Tetrahedron Lett.*, 2004, **45**, 3659.
17. O. Tamura, T. Shiro, A. Toyao, and H. Ishibashi, *Chem. Commun.*, 2003, 2678.
18. H. Ali Dondas, R. Grigg, S. Thibault, W. Anthony Thomas, and M. Thornton-Pett, *Tetrahedron*, 2002, **58**, 5827.
19. T. Aftab, R. Grigg, M. Ladlow, V. Sridharan, and M. Thornton-Pett, *Chem. Commun.*, 2002, 1754.
20. V. K. Aggarwal, S. J. Roseblade, J. K. Barrell, and R. Alexander, *Org. Lett.*, 2002, **4**, 1227.
21. Q. Zhao, F. Han, and D. L. Romero, *J. Org. Chem.*, 2002, **67**, 3317.
22. S. Kanemasa, N. Ueno, and M. Shirahase, *Tetrahedron Lett.*, 2002, **43**, 657.
23. J. D. White, P. R. Blakemore, E. A. Korf, and A. F. T. Yokochi, *Org. Lett.*, 2001, **3**, 413.
24. V. Ondrus, M. Orsag, L. Fisera, and N. Pronayova, *Tetrahedron*, 1999, **55**, 10425.
25. M. Noguchi, H. Okada, S. Nishimura, Y. Yamagata, S. Takamura, M. Tanaka, A. Kakehi, and H. Yamamoto, *J. Chem. Soc., Perkin Trans. 1*, 1999, 185.
26. A. Arnone, G. Broggini, L. Bruche, G. Molteni, and G. Zecchi, *J. Chem. Res. (S)*, 1998, 188.
27. K. Jensen, K. V. Gothelf, R. G. Hazell, and K. A. Jørgensen, *J. Org. Chem.*, 1997, **62**, 2471.
28. P. de March, M. Figueredo, J. Font, S. Milan, A. Alvarez-Larena, J. F. Piniella, and E. Molins, *Tetrahedron*, 1997, **53**, 2979.
29. U. Chicacchio, A. Rescifina, F. Casuscelli, A. Piperno, V. Pisani, and R. Romeo, *Tetrahedron*, 1996, **52**, 14311.
30. A. Goti, F. Cardona, A. Brandi, S. Picasso, and P. Vogel, *Tetrahedron: Asymmetry*, 1996, **7**, 1659.
31. G. Broggini, F. Folcio, N. Sardone, M. Sonzogni, and G. Zecchi, *Tetrahedron: Asymmetry*, 1996, **7**, 797.
32. A. Arnone, L. Bruche, L. Baranti, and G. Zecchi, *J. Chem. Res. (S)*, 1995, 282.
33. U. Chiacchio, G. Buemi, F. Casuscelli, A. Procopio, A. Rescifina, and R. Romeo, *Tetrahedron*, 1994, **50**, 5503.
34. P. J. Smith, D. J. Soose, and C. S. Wilcox, *J. Am. Chem. Soc.*, 1991, **113**, 7412.
35. D. M. Tschaen, R. R. Whittle, and S. M. Weinreb, *J. Org. Chem.*, 1986, **51**, 2604.
36. P. DeShong and J. M. Leginus, *J. Am. Chem. Soc.*, 1983, **105**, 1686.
37. A. Padwa, K. Koehler, and A. Rodriguez, *J. Am. Chem. Soc.*, 1981, **103**, 4974.
38. P. Merino, *Science of Synthesis*, 2004, **27**, 511 and references therein.
39. E. N. Zil´berman, *Reaktsii nitrilov* [*Reactions of Nitriles*], Khimiya, Moscow, 1972 (in Russian).
40. V. Yu. Kukushkin and A. J. L. Pombeiro, *Chem. Rev.*, 2002, **102**, 1771.
41. Y. R. Do, S. Ch. Nam, K. K. Sung, S. Ch. Eun, and H. S. Il, *J. Chem. Soc., Perkin Trans. 2*, 1999, 81.
42. W. Szczepankiewicz, J. Suwinski, and Z. Karczmarzyk, *Khim. Geterotsikl. Soedin.*, 2004, 932 [*Chem. Heterocycl. Compd.*, 2004, **40**, 801 (Engl. Transl.)].
43. C. Balsamini, G. Spadoni, A. Bedini, G. Tarzia, M. Lanfranchi, and M. A. Pellinghelli, *J. Heterocycl. Chem.*, 1992, **29**, 1593.
44. M. Fred, *J. Heterocycl. Chem.*, 1972, **9**, 739.
45. R. Huisgen, W. Mack, and K. Bast, Pat. DE 19610728; *Chem. Abstrs*, 1964, **61**, 47917.
46. V. G. Andrianov, E. N. Rozhkov, and A. V. Eremeev, *Khim. Geterotsikl. Soedin.*, 1991, 262 [*Chem. Heterocycl. Compd.*, 1991 (Engl. Transl.)].
47. J. Azizian, M. Madani, and S. Souzangarzadeh, *Synth. Commun.*, 2005, **35**, 765.
48. R. M. Srivastava, *Quimica Nova*, 1995, **18**, 303.
49. M. R. Manrao, K. K. Gill, J. R. Sharma, and P. S. Kalsi, *Indian J. Heterocycl. Chem.*, 1995, **5**, 151.
50. D. B. Repke, H. P. Albrecht, and J. G. Moffatt, *J. Org. Chem.*, 1975, **40**, 2481.
51. R. M. Srivastava, M. F. Rosa, C. Eduardo, M. Carvalho, S. da G. M. Portugal, I. M. Brinn, M. Da Conceicao Pereira, and O. A. C. Antunes, *Heterocycles*, 2000, **53**, 191.
52. F. M. Pallos, J. R. DeBaun, and A. D. Gutman, Pat. US 75-632603; *Chem. Abstrs*, 1976, **85**, 104204.
53. J. A. Claisse, G. I. Gregory, and W. K. Warburton, Pat. GB 1228142 (A); *Chem. Abstrs*, 1970, **72**, 21696.
54. C. P. Singh and H. Hasan, *J. Indian Council of Chemists*, 2002, **19**, 46.
55. M. R. G. Manrao, K. Karamjit, J. R. Sharma, and P. S. Kalsi, *Indian J. Heterocycl. Chem.*, 1995, **5**, 151.
56. A. Chimirri, S. Grasso, A.-M. Montforte, A. Rao, and M. Zappala, *Farmaco*, 1996, **51**, 125.
57. J. Sterne, S. Le Guilcher, and M. Rousselet, *Therapie*, 1972, **27**, 517.
58. F. Lauria, V. Vecchietti, and G. Tosolini, *Gazz. Chim. Ital.*, 1964, **94**, 478.
59. J. Sterne and C. Hirsch, *Therapie*, 1965, **20**, 89.
60. J. M. D. Aron-Samuel, 1965, Pat. FR 19640424; *Chem. Abstrs*, 1965, **63**, 63149.
61. L. Eberson, J. J. McCullough, Ch. M. Hartshorn, and M. P. Hartshorn, *J. Chem. Soc., Perkin Trans. 2*, 1998, 41.
62. Y. Yu, N. Watanabe, M. Ohno, and S. Eguchi, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1417.

63. Y. Yu, M. Ohno, and S. Eguchi, *J. Chem. Soc., Chem. Commun*., 1994, 331.
64. Y. Yu, H. Fujita, M. Ohno, and S. Eguchi, *Synthesis*, 1995, 498.
65. R. Plate, P. H. H. Hermkens, J. M. M. Smits, R. J. F. Nivard, and H. C. J. Ottenheijm, *J. Org. Chem*., 1987, **52**, 1047.
66. R. Sustmann, *Tetrahedron Lett.*, 1971, 2717.
67. R. Sustmann, *Tetrahedron Lett.*, 1971, 2721.
68. M. L. Kuznetsov and V. Yu. Kukushkin, *J. Org. Chem*., 2006, **71**, 582.
69. M. L. Kuznetsov, V. Yu. Kukushkin, A. I. Dement´ev, and A. J. L. Pombeiro, *J. Phys. Chem. A*, 2003, **107**, 6108.
70. P. H. H. Hermkens, J. H. v. Maarseveen, C. G. Kruse, and H. W. Scheeren, *Tetrahedron*, 1988, **44**, 6491.
71. V. D. Kiselev, G. G. Iskhakova, E. A. Kashaeva, M. S. Shikhab, M. D. Medvedeva, and A. I. Konovalov, *Zh. Obshch. Khim*., 2003, **73**, 1884 [*Russ. J. Gen. Chem*., 2003, **73** (Engl. Transl.)].
72. A. Díaz-Ortiz, E. Díez-Barra, A. de la Hoz, A. Moreno, M. J. Gómez-Escalonilla, and A. Loupy, *Heterocycles*, 1996, **43**, 1021.
73. G. Broggini, G. Molteni, A. Terraneo, and G. Zecchi, *Heterocycles*, 2003, **59**, 823 and references cited therein.
74. M. A. J. Charmier, V. Yu. Kukushkin, and A. J. L. Pombeiro, *J. Chem. Soc., Dalton Trans*., 2003, 2540.
75. N. A. Bokach, A. A. Krokhin, A. A. Nazarov, V. Yu. Kukushkin, M. Haukka, J. J. R. Fraústo da Silva, and A. J. L. Pombeiro, *Eur. J. Inorg. Chem*, 2005, 3042.
76. B. Desai, T. N. Danks, and G. Wagner, *J. Chem. Soc., Dalton Trans*., 2003, 2544.
77. B. Desai, T. N. Danks, and G. Wagner, *Dalton Trans*, 2004, 166.
78. G. Wagner, A. J. L. Pombeiro, and V. Yu. Kukushkin, *J. Am. Chem. Soc*., 2000, **122**, 3106.
79. G. Wagner, M. Haukka, J. J. R. Fraústo da Silva, A. J. L. Pombeiro, and V. Yu. Kukushkin, *Inorg. Chem*., 2001, **40**, 264.
80. G. Wagner, *Inorg. Chim. Acta*, 2004, **357**, 1320.
81. G. Wagner, *Chem. Eur. J*., 2003, **9**, 1503.
82. G. Wagner and M. Haukka, *J. Chem. Soc., Dalton Trans*., 2001, 2690.
83. M. A. J. Charmier, M. Haukka, and A. J. L. Pombeiro, *Dalton Trans*, 2004, 2741.
84. V. Yu. Kukushkin, A. J. L. Pombeiro, J. J. R. Fraústo da Silva, and G. Wagner, Pat. WO 2001098283; *Chem. Abstrs*, 2001, **136**, 53750.

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