

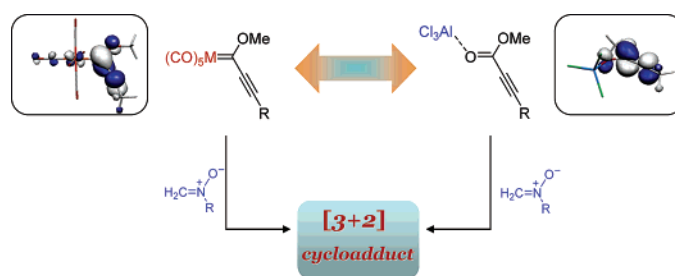
Effect of the Metal Fragment in the Thermal Cycloaddition between Alkynyl Metal(0) Fischer Carbene Complexes and Nitrones

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The thermal cycloaddition between alkynyl metal(0) Fischer carbenes and nitrones has been studied computationally within the Density Functional Theory framework. It is found that the $[3+2]$ cycloaddition takes place via transition structures that are more asynchronous and less aromatic than their nonorganometallic analogues. These reactions are also found to be completely regioselective in favor of the cycloadduct possessing the Fischer carbene moiety and the oxygen atom of the nitron in a 1,3-relative disposition. These results are consistent with the role of the Fischer carbene moiety as an electron withdrawing group that enhances the electrophilic character of the alkyne group acting as a Michael acceptor as a dipolarophile. In terms of the isolobal analogy model, it can be concluded that alkynylalkoxy metal(0) carbene complexes act in this reaction as organometallic analogues of organic alkyl-propiolates with enhanced electrophilic character.

Introduction

The isolobal analogy¹ is a landmark in understanding the relationship between organometallic and organic processes, especially for those reactions occurring outside the metal coordination sphere. According to this analogy, alkynylalkoxy metal(0) carbene complexes are the organometallic analogues of organic alkyl-propiolates. The activating effect of the pentacarbonylchromium(0) moiety makes the velocity of the reaction of [(methoxy)(vinyl)pentacarbonyl]chromium(0) carbene and isoprene comparable to the velocity of the reaction of isoprene and methyl acrylate catalyzed by $AlCl_3$.² The term super ester was coined for these complexes based on these and other analogous reactions.³

However, the role of the metal as a mere activating spectator was compromised after the participation of the metal in simple

hydride addition reactions to alkynylalkoxy metal(0) carbene complexes demonstrated by us few years ago.⁴ Deuteration experiments unambiguously showed that upon hydride addition to an α,β -unsaturated complex, the pentacarbonylchromium(0) moiety experiences a $[1,3]$ -metalotropic process (Scheme 1).

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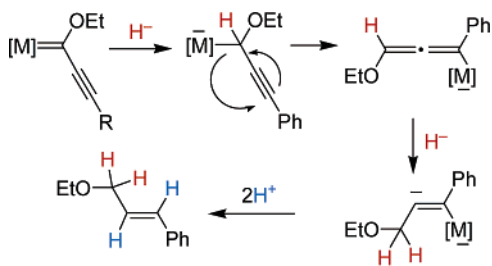
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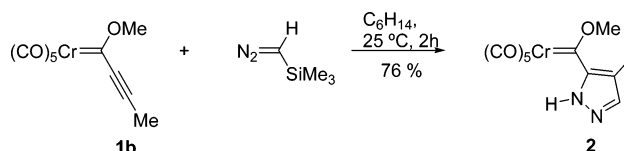
SCHEME 1



Recently, the interaction of the pentacarbonyl metal fragment with the double or triple bond in α,β -unsaturated complexes has been shown to be decisive in the bias of group 6 Fischer carbene complexes for the syn-isomer in contrast with the metal free congeners.⁵ In this context, it would be of interest to study if analogous effects are involved in processes such as 1,3-dipolar cycloadditions, a reaction previously studied by us in its metal free version.⁶

The interest in the reactions between group 6 α,β -unsaturated Fischer carbene complexes and different 1,3-dipoles is longstanding.⁷ The first example of a [3 + 2] cycloaddition involving Fischer carbene complexes was reported by Chan and Wulff^{7a} in the reaction of alkyne complex **1b** and trimethylsilyldiazomethane to yield complex **2** (Scheme 2).

SCHEME 2



On the basis of wide experimental evidence, Chan et al.^{7c} proposed that the highly regioselective [3 + 2] cycloaddition between alkyne Fischer carbene complexes and nitrones is a bimolecular process occurring through a one-step polar and concerted pathway. This process leads to 2,3-dihydroisoxazole carbene complexes in excellent yields with a rate enhancement of 10^4 over the analogous alkyne organic esters. However, the origins of the observed regioselectivity and the nature of the transition state of the process were not studied.

Some years ago, we reported⁶ that 1,3-dipolar cycloadditions between nitrones and ethyne occur through a concerted pathway close to the perfect synchronicity (S_y values in the range of 0.8–0.9). The corresponding transition states of the process exhibit in-plane aromaticity. The analogous reactions on alkyne group 6 metal carbene complexes offer a paramount opportunity to compare these processes with both the organic and the Lewis acid-catalyzed cycloadditions. Herein is reported an extensive computational–DFT study of the reaction mechanism of the [3 + 2] cycloaddition between nitrones and Fischer carbene complexes and the analogies and differences with the metal free reactions and Lewis acid-catalyzed reactions in the context of the isolobal analogy.

Computational Details

All the calculations reported in this paper were obtained with the GAUSSIAN 03 suite of programs.⁸ Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP⁹ and the standard 6-31+G* basis set¹⁰ for hydrogen, carbon, oxygen, nitrogen, chlorine, and silicon and the Hay–Wadt small-core effective core potential (ECP) including a double- ξ valence basis set¹¹ for chromium and tungsten (LanL2DZ keyword). Zero-point vibrational energy (ZPVE) corrections were computed at the B3LYP/LANL2DZ/6-31+G* level and were not scaled. Reactants and cycloadducts were characterized by frequency calculations¹² and have positive definite Hessian matrices. Transition structures (TSs) show only one negative

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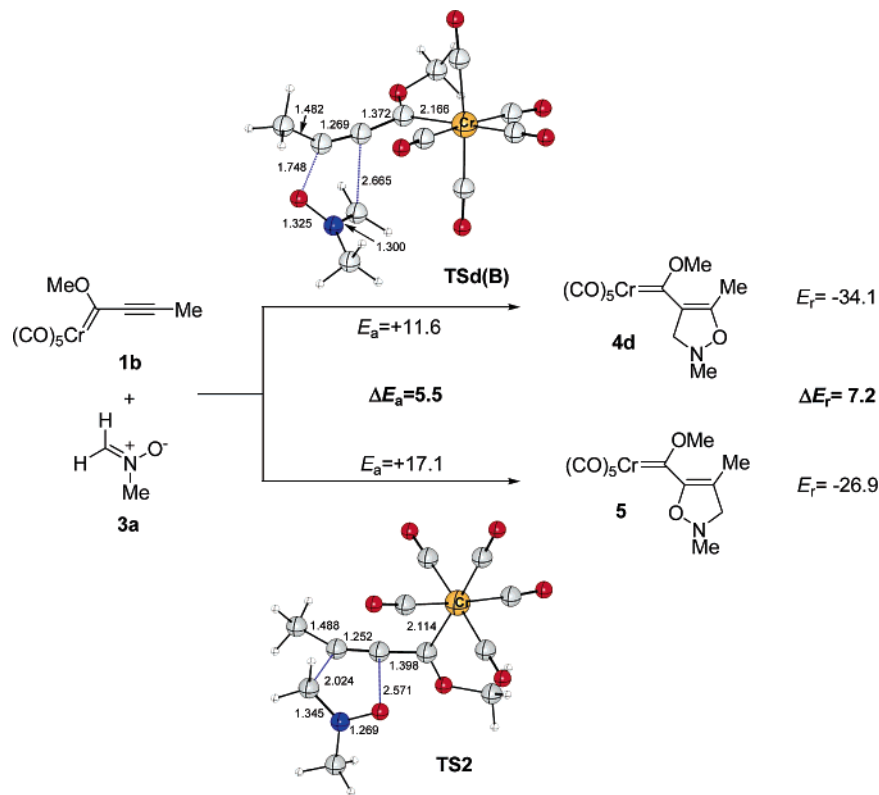


FIGURE 1. Chief geometric features of transition structures associated with the formation of the two possible regioisomers in the [3 + 2] cycloaddition reaction between Fischer carbene **1b** and nitrone **3a**. Bond distances are given in angstroms and energies in kcal/mol. Unless otherwise stated, white, gray, red, and blue denote hydrogen, carbon, oxygen, and nitrogen atoms, respectively.

eigenvalue in their diagonalized force constant matrixes, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.¹³ Nonspecific solvent effects were described by using the self-consistent reaction field (SCRF) approach in its Onsager–Kirkwood formalism.¹⁴ Nucleus-independent chemical shifts (NICS) were evaluated by using the gauge invariant atomic orbital¹⁵ (GIAO) approach, at the GIAO-B3LYP/LANL2DZ&6-31+G*.

The synchronicity^{16,17} of the reactions was quantified by using a previously described approach.¹⁸ For a given concerted reaction, synchronicity is defined as¹⁹

$$S_y = 1 - \frac{\sum_{i=1}^n \frac{|\delta B_i - \delta B_{AV}|}{\delta B_{AV}}}{2n - 2}$$

where n is the number of bonds directly involved in the reaction

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(in this case, $n = 5$) and δB_i stands for the relative variation of a given bond index B_i at the transition state (TS), according to the following formula:

$$\delta B_i = \frac{B_i^{\text{TS}} - B_i^{\text{R}}}{B_i^{\text{P}} - B_i^{\text{R}}}$$

where the superscripts R and P refer to the reactants and product, respectively. The average value of δB_i , denoted as δB_{AV} , is therefore

$$\delta B_{AV} = n^{-1} \sum_{i=1}^n \delta B_i$$

The Wiberg bond indices²⁰ B_i were computed using the natural bond orbital (NBO)²¹ method.

Results and Discussion

DFT calculations (B3LYP/LANL2DZ&6-31+G*) were carried out beginning with the syn-form of alkynyl metal-carbenes, the most stable conformation in the gas phase and in the solid state.⁵ The regiochemistry of the reaction was studied first using the reaction between Fischer carbene **1b** and nitrone **3a** as a model example. The results are reported in Figure 1. From these

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TABLE 1. Relative Energies (ΔE^a , kcal/mol) for the Cycloaddition Reaction between Fischer Carbene Complexes **1** and Nitrones **3**

Entry			$E_a(\mathbf{A})^b$	$E_a(\mathbf{B})^c$	$\Delta E_a(\mathbf{A-B})^d$
1	1a , M=Cr(CO) ₅ , R ₁ =H	3a , R ₂ =Me	+10.8	+9.9	+0.8
2	1b , M=Cr(CO) ₅ , R ₁ =Me	3b , R ₂ =H	+15.6	+13.6	+2.0
3	1c , M=W(CO) ₅ , R ₁ =Me	3b , R ₂ =H	+15.1	+12.8	+2.3
4	1b , M=Cr(CO) ₅ , R ₁ =Me	3a , R ₂ =Me	+14.8	+11.6	+3.2
5	1c , M=W(CO) ₅ , R ₁ =Me	3a , R ₂ =Me	+14.0	+13.1	+0.9
6	1d , M=Cr(CO) ₅ , R ₁ =SiH ₃	3a , R ₂ =Me	+16.0	+15.1	+0.9
7	1e , M=Cr(CO) ₅ , R ₁ =Ph	3a , R ₂ =Me	+17.5	+16.6	+0.9
8	1f , M=O, R ₁ =Me	3a , R ₂ =Me		+13.8	
9	1g , M=H ₃ AlO, R ₁ =Me	3a , R ₂ =Me		+4.7	

^a All values have been calculated at the B3LYP/LANL2DZ&6-31+G*+ΔZPVE level. ^b $E_a(\mathbf{A})$ values computed as $E_a(\mathbf{A}) = E(\text{TS} - \text{pathway A}) - E(\mathbf{1}) - E(\mathbf{3})$. ^c $E_a(\mathbf{B})$ values computed as $E_a(\mathbf{B}) = E(\text{TS} - \text{pathway B}) - E(\mathbf{1}) - E(\mathbf{3})$. ^d ΔE_a values computed as $\Delta E_a = E(\text{TS} - \mathbf{A}) - E(\text{TS} - \mathbf{B})$.

results, we can conclude that the reaction is completely regioselective leading to the exclusive formation of cycloadducts **4**. This regioselectivity takes place under both kinetic and thermodynamic control, in view of the considerably higher activation energy required for the formation of cycloadduct **5**, as well as the lower reaction energy calculated for this latter cycloadduct.

The [3 + 2] cycloaddition reaction between nitrones and Fischer carbenes may lead to two regioisomeric 2,3-dihydroisoxazole carbene complexes of which only the regioisomer **4** is experimentally observed. These reactions may also lead to the cycloadducts **4** in their *s-cis* (**4-s-cis**) or *s-trans* (**4-s-trans**) conformations (Scheme 3). Complex **4-s-trans** is experimentally observed, and according to our calculations, it is formed through the lower activation energy pathway B (Table 1). As expected, one remarkable geometric feature of the latter compound is that the methyl group is directed toward the metal fragment (an orientation we also denoted as anti in a recent paper on the structure and conformations of group 6 alkoxy Fischer carbene complexes).⁵

SCHEME 3

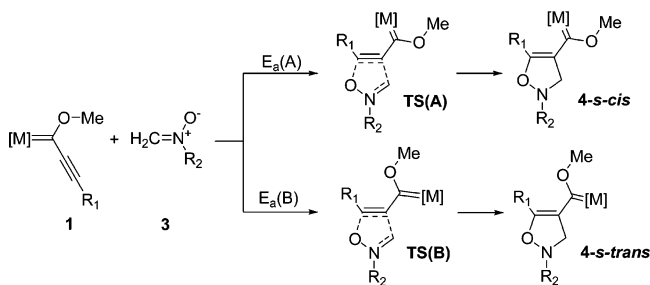


Table 1 compiles the values of the calculated activation energies for conformations A and B (Scheme 3) for several representative reagents. In all cases, conformer B has a lower activation barrier, and therefore, its formation is kinetically favored, leading to the products experimentally observed. From the data in Table 1, it is clear that bulky substituents in the alkynyl carbene complex lead to higher activation energies, while less steric demanding substituents facilitate the process.

In fact, the highest value was found for pentacarbonyl-[methoxyphenylethynyl]chromium(0) carbene complex **1e** (Table 1, entry 7). The in vacuo calculated activation energy (16.6 kcal/mol) for this complex is comparable to the experimental value of $\Delta G_{288} = 18.9$ kcal/mol^{7c} obtained for the reaction between **1e** and *N-t*-butyl phenyl nitron in a THF solution. Moreover, no systematic difference was observed between iso-structural chromium (Table 1, entries 2 and 4) and tungsten complexes (Table 1, entries 3 and 5).

The computed activation energy for the analogous organic reaction between methyl but-2-ynoate **1f** and nitron **3a**, which leads to the cycloadduct **4h**, was 13.8 kcal/mol. This value is higher than the corresponding activation energy for the reaction between complex **1b** and nitron **3a** ($E_a = 11.6$ kcal/mol, Table 1, entry 4), which is in agreement with the experimentally observed acceleration of this reaction for Fischer carbene complexes.²²

Transition states depicted in Figure 2 show the cycloadditions of alkynylcarbene complexes **1** and nitrones **3** occurring by a concerted pathway.^{7e} Highly asynchronous transition structures were obtained in contrast to the transition states obtained for the analogous organic reaction.⁶ This result pointed to a strong participation of the metal in the reaction. The ability of the metal to accept charge permits a strong delocalization in the metal fragment and leads to the observed asynchronicity in the different transition states computed. In fact, in all cases, the C(alkynyl complex)–O(nitron) NBO bond orders are higher (ranging from 0.48 in **TSa(B)** to 0.55 in **TSf(B)**) than the respective C(alkynyl complex)–CH₂(nitron) bond orders (ranging from 0.10 in **TSa(B)** to 0.18 in **TSf(B)**; see Figure 2 for the corresponding bond distances). The computed synchronicities are therefore quite low as can be found in Table 3. Actually, these values are close to the limit between concerted and stepwise mechanisms. This result contrasts with the higher synchronicities computed for the nonmetal assisted cycloadditions whose values lie in the 0.8–0.9 range.⁶ As a comparison,

(22) The reaction between carbene complex **1e** and *t*-BuCH=N(Ph)O occurs at room temperature in only 15 min in quantitative yield, while the analogous reaction with methyl 2-phenylethynyl carboxylate requires 75 days in boiling THF to yield the cycloadduct in only 32% yield. See ref 7c.

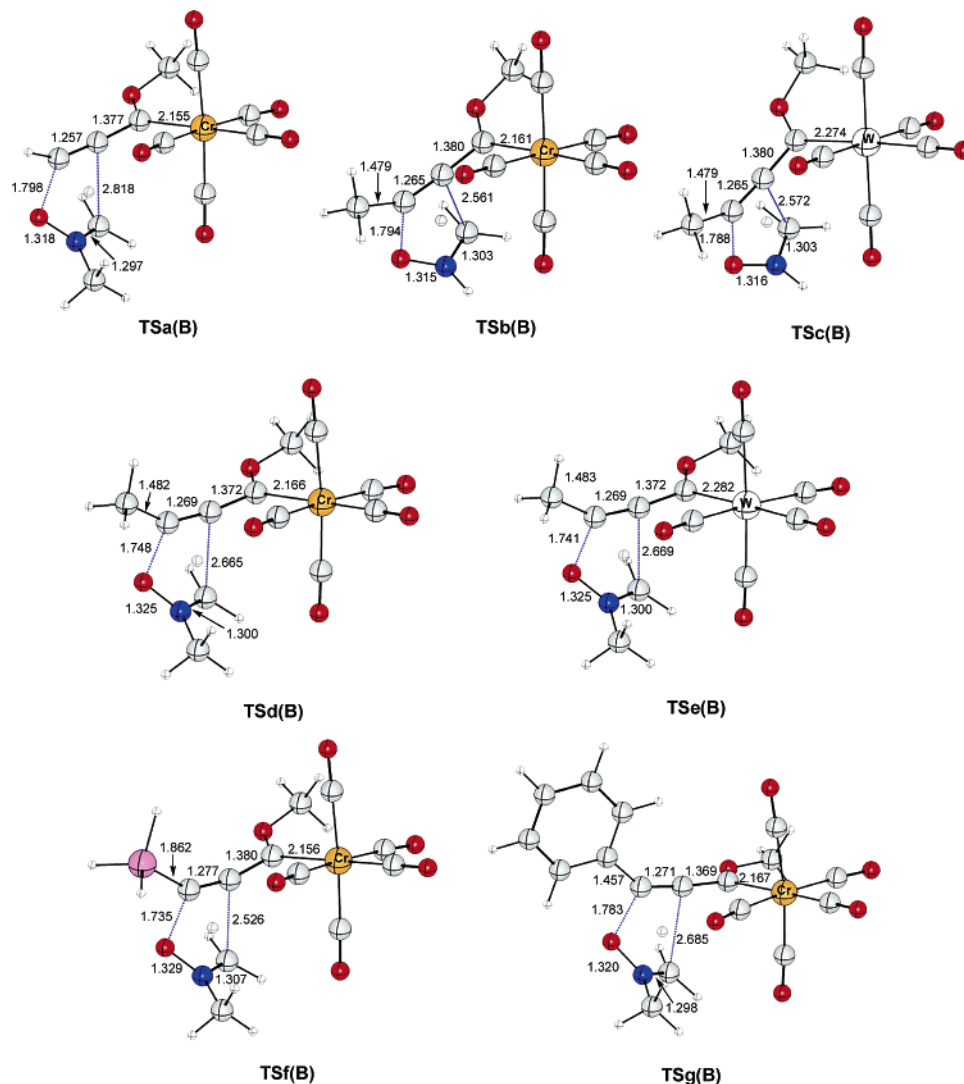


FIGURE 2. Ball-and-stick representations of the TSs corresponding to the reaction of complexes **1** and the nitrones **3a,b** to yield 2,3-dihydroisoxazole carbene complexes **4-s-trans** through pathway B (see Scheme 3). All structures correspond to fully optimized B3LYP/LANL2DZ&6-31+G(d) geometries. Bond distances are given in angstroms. The dummy atoms denote the ring point of electron density. Pink denotes silicon atoms. See Figure 1 caption for additional details.

TABLE 2. Calculated E_a (Pathway B, kcal/mol) for the Cycloaddition of Complexes **1b,e** and Nitrene **3a** in Different Solvents^a

ϵ (solvent)	E_a (1b)	E_a (1e)
1 (gas phase)	+11.6	+16.6
7.58 (THF)	+14.2	+23.1
20.7 (acetone)	+19.2	+25.9

^a All values have been calculated at the B3LYP/LANL2DZ&6-31+G*+ Δ ZPVE level.

the TS of the reaction between methyl but-2-ynoate **1f** and nitrene **3a** exhibits quite similar bond orders for the C–O and C–C bonds (0.33 for the C–O bond and 0.30 for the C–C bond; see the corresponding bond distances in Figure 3), thus yielding a S_y value of 0.95.²³ Therefore, Fischer carbene complexes lead to transition states where the C–O bond is almost fully developed while the C–C bond is emerging, in contrast to their organic counterparts.

(23) These results are in agreement with those found in the reaction between $\text{CH}_2=\text{N}(\text{H})\text{O}$ and acetylene. See ref 6.

TABLE 3. Synchronicities^a (S_y), Nucleus-Independent Chemical Shifts^b (NICS, ppm/mol), and Reaction Energies^c (E_r , kcal/mol) of Reactions between Carbene Complexes **1a–e**, Organic Esters **1f,g**, and Nitrones **3a,b** to Produce the Cycloadducts **4**

reaction	NICS (TS)	NICS (4)	S_y	E_r
1a + 3a \rightarrow 4a-s-trans	−10.06	−5.84	0.63	−37.9
1b + 3b \rightarrow 4b-s-trans	−13.49	−5.18	0.68	−34.8
1c + 3b \rightarrow 4c-s-trans	−13.33	−5.42	0.68	−36.5
1b + 3a \rightarrow 4d-s-trans	−11.51	−5.37	0.61	−34.1
1c + 3a \rightarrow 4e-s-trans	−11.54	−5.51	0.62	−35.6
1d + 3a \rightarrow 4f-s-trans	−13.44	−5.28	0.69	−27.8
1e + 3a \rightarrow 4g-s-trans	−11.24	−4.86	0.61	−27.8
1f + 3a \rightarrow 4h	−16.89	−6.13	0.95	−45.6
1g + 3a \rightarrow 4i	−10.46	−5.94	0.62	−48.5

^a Computed at the B3LYP/LANL2DZ&6-31+G* level. ^b Computed at the GIAO-B3LYP/LANL2DZ&6-31+G* level. ^c E_r values computed as $E_r = E(4) - E(1) - E(3)$.

To compare the effect of the pentacarbonyl metal moiety with that of a Lewis acid catalyst, the reaction between the methyl but-2-ynoate- AlCl_3 complex **1g** and nitrene **3a**, which leads to **4i**, was also calculated. The activation energy of this process was only 4.7 kcal/mol, and the corresponding synchronicity

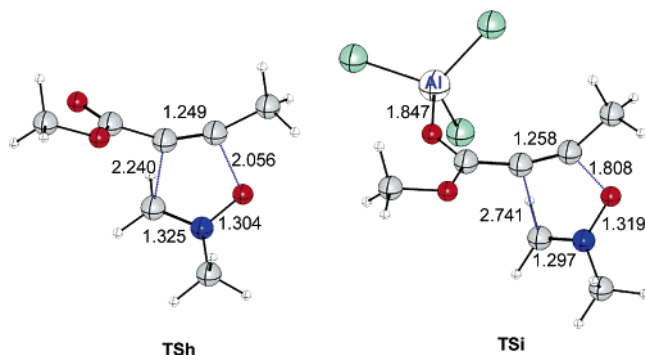


FIGURE 3. Ball-and-stick representations of corresponding TSs of the [3 + 1] cycloadditions of methyl but-2-ynoate **1f**, and its AlCl₃ complex **1g**, with nitrone **3a**, respectively. Both structures correspond to fully optimized B3LYP/LANL2DZ&6-31+G(d) geometries. See Figure 1 caption for additional details.

value is $S_y = 0.62$. As is readily seen in Figure 3, the corresponding transition state of this reaction shows geometrical features that are close to transition states of [3 + 2] cycloadditions of Fischer carbene complexes (Figure 2) and nitrones. Again, in the Lewis acid-catalyzed reaction, the C–O bond is nearly developed (1.808 Å, $B_{CO} = 0.46$) in the TS, while the C–C bond is only emerging (2.741 Å, $B_{CC} = 0.11$).

We also computed the energies of the frontier orbitals of the carbene complex **1b**, its organic ester analogue methyl but-2-ynoate **1f**, the methyl but-2-ynoate-AlCl₃ complex **1g**, and nitrone **3a** (Figure 4). As expected, the most favorable HOMO (nitrone)–LUMO (dipolarophile) interaction occurs for the Lewis acid-catalyzed reaction of methyl but-2-ynoate. The energy difference of the frontier orbitals for carbene **1b** and nitrone **3a** is only 10.6 kcal/mol (0.46 eV) higher than the energy gap of methyl but-2-ynoate-AlCl₃ complex and the same nitrone. It can be concluded that the metal fragment acts as a Lewis acid for the organic moiety in the [3 + 2] cycloadditions of Fischer carbenes and nitrones. This behavior explains the observed rate enhancement of the process as compared to organic esters and the geometrical similarities that were found in the transition states of metal carbene complexes and the Lewis acid-catalyzed cycloadditions.

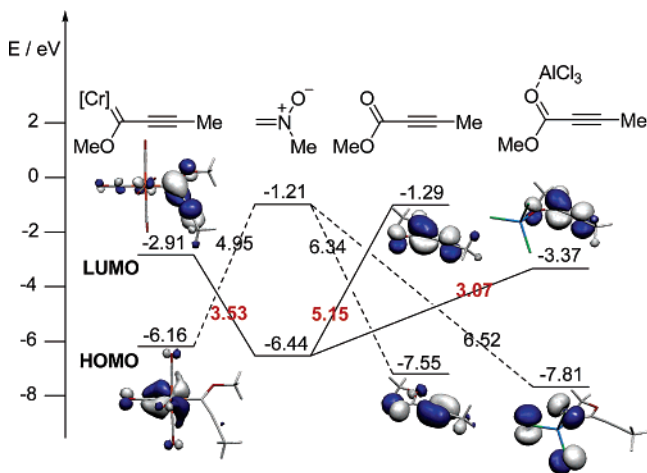


FIGURE 4. Frontier orbitals energies of nitrone **3a** and dipolarophiles **1b,f,g**. All values (in eV) were computed at the B3LYP/LANL2DZ&6-31+G(d) level of theory.

The effect of the solvent in the process was computed next by using the SCRF approach under the Onsager–Kirkwood

formalism with sequential single point calculations at the gas-phase optimized geometries of complex **1b** and **1e** for the preferred pathway B in their reaction with nitrone **3a**. The data compiled in Table 2 indicate that the activation energies of the cycloaddition reaction are larger in solution than in the gas phase. This was expected because the large zwitterionic character of the 1,3-dipoles diminishes along the reaction coordinate, thereby resulting in lower solvation energies for the transition structures with respect to the starting reactants (nitrones).²⁴

The effect of the metal moiety on the in-plane aromaticity proposed for the analogous nonmetallic cycloaddition⁶ was finally addressed. The magnetic properties of transition structures and products were computed using the nucleus-independent chemical shifts (NICSs).²⁵ Given the strongly unsymmetrical character of our cyclic systems, we needed to define the inner points of these systems unambiguously. The (3, +1) ring critical point of the electron density, as defined by Bader,²⁶ is an unambiguous choice for the calculation of the NICSs since only at this point is the electron density a minimum with respect to motion on the ring's plane and maximum with respect to motion perpendicular to the plane defined by the ring. The position of the ring critical points of TSa–g and *s-trans*-2,3-dihydroisoxazole **4a–g** are indicated in Figures 2 and 5, respectively, and the NICSs at these points are reported in Table 3. All transition structures exhibit high negative NICSs values (ranging from –10.1 ppm/mol in TSa(B) to –13.4 ppm/mol in TSf(B)), which should be attributed to strong diamagnetic shielding due to a strong aromatic character of these TSs.²⁷ The reaction products **4a–g-s-trans** are nonaromatic, and therefore, the NICSs are considerably lower (see Table 3). In these compounds, negative NICSs values are the consequence of the diamagnetic shielding induced by the lone electron pairs. On the other hand, the calculated NICSs for both transition states and dihydroisoxazole complexes are less negative than the computed values for the corresponding organic analogue **1f** (ca. –17 ppm/mol for transition state TSh and ca. –6 ppm/mol for cycloadduct **4h**). This can be rationalized by the strong delocalization of the electrons involved in the cycloaddition on the metal fragment. Therefore, if we assume that bonding equalization and—in transition structures—the synchronicity characterize aromatic structures,²⁸ it is not surprising that the NICS values obtained for the Fischer carbene complexes are lower than those found for standard [3 + 2] cycloadditions between alkynes and nitrones. Finally, we also want to point out that the computed NICS and synchronicity values of the reaction between AlCl₃-complex **1g** and nitrone **3a** (Table 3) are quite similar to those involving Fischer carbene complexes. These latter results provide further support to the aforementioned statement that

(24) A similar effect has been observed experimentally in [3 + 2] cycloaddition between nitrones and allenes. (a) Huisgen, R.; Schug, R. *J. Am. Chem. Soc.* **1976**, *98*, 7819. (b) Huisgen, R. *Pure Appl. Chem.* **1980**, *52*, 2283. (c) Huisgen, R.; Seidl, H.; Brüning, I. *Chem. Ber.* **1969**, *102*, 1102. (d) Kadaba, P. K. *Synthesis* **1973**, 71.

(25) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317.

(26) Bader, R. F. W. *Atoms in Molecules—A Quantum Theory*; Clarendon Press: Oxford, 1990; pp 12–52.

(27) A possible explanation for the high NICS values observed for the transition structures is that the six electrons involved in the cycloaddition lie approximately in the molecular plane and give rise to an appreciable ring current. In turn, this ring current promotes a strong diamagnetic shielding at the ring critical point.

(28) (a) Schleyer, P. v. R.; Jiao, H.; Glukhoushev, M. N.; Chandrasekhar, J.; Kraka, E. *J. Am. Chem. Soc.* **1994**, *116*, 10129. (b) Schleyer, P. v. R.; Jiao, H. *Pure Appl. Chem.* **1996**, *68*, 209 and references therein.

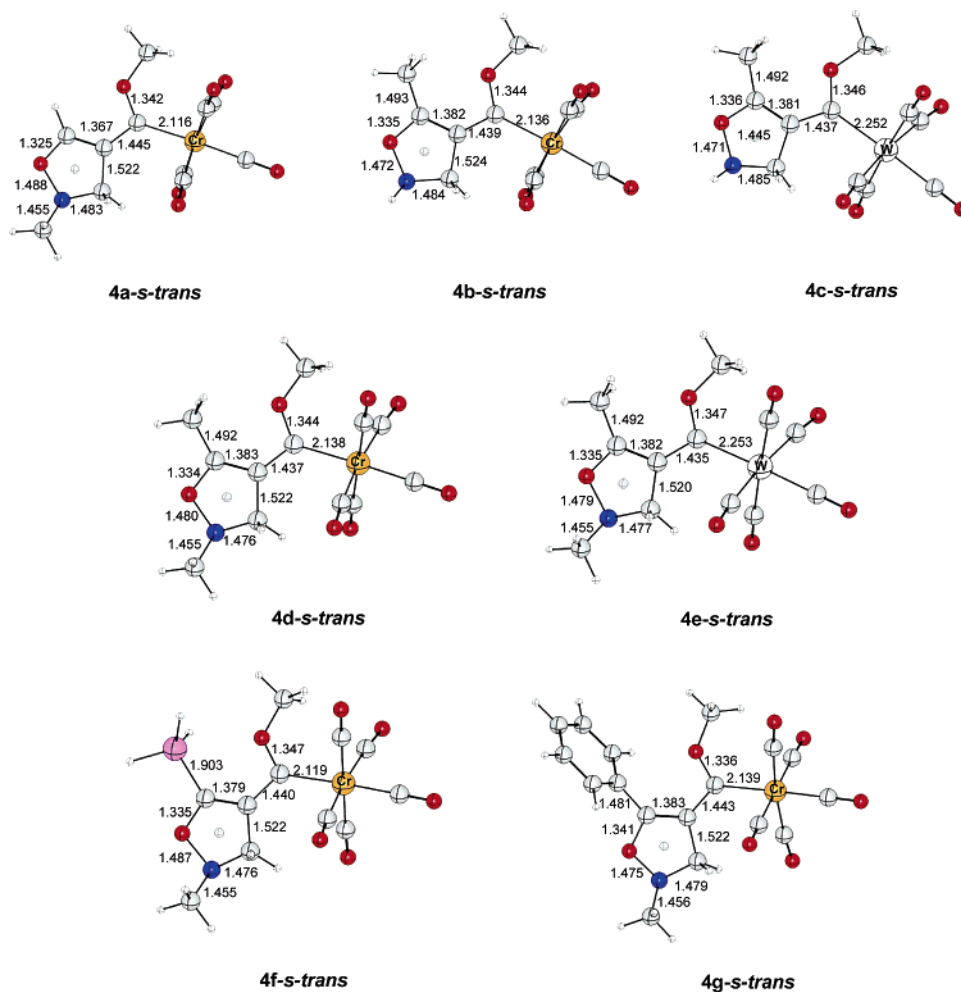


FIGURE 5. Ball-and-stick representations of complexes *s-trans*-2,3-dihydroisoxazole carbene complexes **4**. All structures correspond to fully optimized B3LYP/LANL2DZ&6-31+G(d) geometries. Bond distances are given in angstroms. The dummy atoms denote the ring point of electron density. See Figure 1 caption for additional details.

the pentacarbonyl metal fragment acts as a Lewis acid for the organic moiety in this kind of cycloaddition.

Conclusion

From the computational study reported in this paper, the following conclusions can be drawn: (i) the thermal cycloaddition between alkynyl metal(0) Fischer carbenes and nitrones takes place via transition structures that are more asynchronous and less aromatic than their nonorganometallic analogues. (ii) These reactions are also found to be completely regioselective in favor of the cycloadduct possessing the Fischer carbene moiety and the oxygen atom of the nitron in a 1,3-relative disposition. (iii) These results are consistent with the role of the Fischer carbene moiety as an electron withdrawing group that enhances the electrophilic character of the alkyne group acting as a Michael acceptor as a dipolarophile. (iv) In terms

of the isolobal analogy model, it can be concluded that alkynylalkoxy metal(0) carbene complexes act in this reaction as organometallic analogues of organic alkyl-propiolates with enhanced electrophilic character.

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Supporting Information Available: Cartesian coordinates (in angstroms) and total energies (in au, noncorrected zero-point vibrational energies included) of all the stationary points discussed in the text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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