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Understanding the Mechanism of the Divergent Reactivity of Non-Heteroatom-Stabilized Chromium Carbene Complexes with Furfural Imines: Formation of Benzofurans and Azetines

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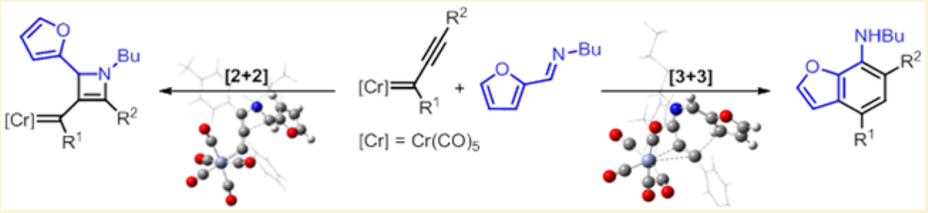
Supporting Information



ABSTRACT: The mechanisms of the reaction between non-heteroatom-stabilized alkynyl chromium carbene complexes prepared in situ and furfural imines to yield benzofurans and/or azetines have been explored by means of density functional theory method calculations. The reaction proceeds through a complex cascade of steps triggered by a nucleophilic addition of the imine nitrogen atom. The formation of two benzofuran regioisomers has been explained in terms of competitive nucleophilic attacks to different positions of the carbene complex. Each of these regioisomers can be obtained as the major product depending on the starting materials. The overall sequence could be controlled to yield benzofurans or azetines by adjusting the substituents present in the initial carbene complex. This mechanistic information allowed for the preparation of new benzofurans and azetinylcarbenes in good yields.

INTRODUCTION

Since their discovery in 1964,[1] and especially during the last few decades, group 6 Fischer carbene complexes have demonstrated high versatility as a powerful synthetic tool.[2−8] However, non-heteroatom-stabilized carbene complexes, first reported by Casey in 1973,[9] did not emerge as an alternative reagent until recently due to their low stability. Among them, non-heteroatom-stabilized alkynylcarbenes, smoothly in situ synthesized from the corresponding Fischer-type alkoxycarbenes,[10] resulted in synthetically useful and experienced significant differences in terms of reactivity with their alkoxycarbene analogues. Accordingly, these compounds are able to form open chain policonjugated compounds as endiynes[11] or linear dienynes or diendiynes[12] and also to participate in different cyclizations with the formation of three to seven-membered rings. Thus, non-heteroatom-stabilized alkynylcarbenes react with olefins to form cyclopropanes[13] or with imines to access stable azetinylcarbenes[14] or benzoazepines[15] through formal [2 + 2] and [4 + 3] heterocyclizations, respectively. Finally, a formal [3 + 3] benzofuran synthesis from furylimines has also been reported.[16] This particular reaction attracted our attention as imine nitrogen does not belong to the final structure of the molecule unlike the heterocyclizations previously reported. In addition, the coupling of furan moieties with alkynes has been demonstrated to be an effective route to complex organic molecules in organic synthesis.[17−19] Conversely, some of the benzofurans were obtained as a mixture of regioisomers, indicating two different reaction pathways. In Table 1, benzofurans **5** obtained from alkynylcarbenes **3** and 2-furaldehyde imine **4** are shown. When the R^1 and R^2 groups are interchanged (see, for instance, **5d**/**5e** in Table 1 and ref 16), the main regioisomer is different. A direct relationship between these ratios and the operating mechanisms is difficult to obtain with the methodology employed here (at both the experimental and computational levels) and only general trends will be considered (see below).

Herein, we present a deep computational study for the reported formal [3 + 3] carbocyclization between chromium non-heteroatom-stabilized alkynylcarbene complexes **3** and furfural imine **4** to give a rational explanation for the formation of the corresponding benzofurans **5** and their regioisomers. Also, the formation of azetinylcarbenes from a related mechanism is described. Finally, to provide extra experimental support for the theoretical results, several additional experiments have been performed.

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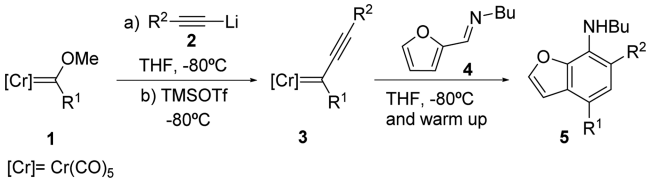
Table 1. [3 + 3] Benzofuran Synthesis from in Situ Synthesized Non-Heteroatom-Stabilized Carbene Complexes 3[16]



compound	R^1	R^2	yield (%)[a]
5a	Ph	Ph	81
5b	Ph	*p*-Tol	61[b]
5c	Ph	Bu	71
5d	Ph	*c*-C_3H_5	70[c]
5e	*c*-C_3H_5	Ph	57[d]
5f	Ph	Ph−C≡C	74

[a]Overall yield from the corresponding alkoxycarbene **1**. [b]Performed at −75 °C. Regioisomeric ratio of >10:1. [c]Regioisomeric ratio of >20:1. [d]Performed at −80 °C. Regioisomeric ratio of >8:1.

RESULTS AND DISCUSSION

A first mechanistic proposal for the formation of benzofurans **5** was outlined in the original paper.[16] It was suggested that a nucleophilic addition of furan C-3 in **4** to the carbene carbon in the non-heteroatom-stabilized carbene **3** may initiate the reaction sequence. A subsequent cascade of transformations may eventually lead to the final products **5**. An initial assessment of this first reaction step pointed out that this may not be the case as the attack of C-3 in the furan moiety to the carbene carbon led to a high energy intermediate (40.3 kcal/mol above the reactants, see Figure S1). This is in contrast with the mild reaction conditions used experimentally. An inspection of the chemical structures of the furan reagent reveals two different reaction points that may be involved in a nucleophilic attack, namely, the C-3 position and the imine nitrogen atom. Also, it is well-known[20] that alkynylcarbene complexes can suffer nucleophilic attacks in both the carbene and the alkyne C-2 carbon atoms. Thus, four different possibilities may arise as a combination of these two elements (see Figure 1).

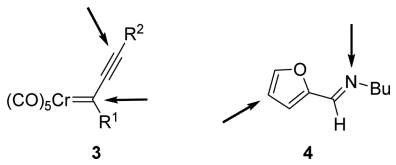


Figure 1. Electrophilic positions in **3** and nucleophilic positions in **4**.

After computing all possibilities, the attack of the imine nitrogen atom to the alkyne C-2 carbon resulted in the most favorable pathway. A TS 20.1 kcal/mol above the reagents (2-furaldehyde imine **4** and non-heteroatom-stabilized carbene complex **3b**) was found for this step at the M06/6-311+G(d,p)/LanL2TZ(f)//M06/6-31+G(d)/LanL2DZ level (see Computational Details). Intermediate **I** resulting from this attack is 8.6 kcal/mol more stable than the reagents. The stability of this intermediate (28.7 kcal/mol more stable than the TS) may be due to the extended conjugation present in the molecule. A competitive attack of the imine nitrogen to the carbene atom is slightly higher in energy (23.4 kcal/mol), but the resulting intermediate **IX** is 12.3 kcal/mol higher than the reagents (Figure 2).

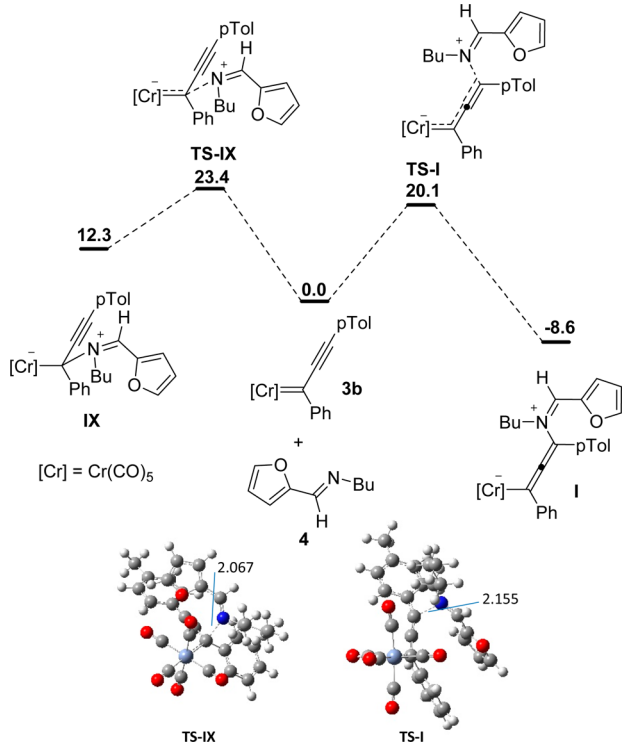


Figure 2. Competitive nucleophilic attacks of **4** to **3b**. Free energies in kcal/mol relative to **3b** + **4**.

From intermediate **I**, the reaction cascade progresses by a cyclization to afford a seven-membered ring by attack of the furan C-3 to the carbene carbon with simultaneous 1,2 migration of the metal pentacarbonyl moiety. An energy barrier of 20.1 kcal/mol was found for this step, and **II** is located 8.4 kcal/mol below the initial reactants (see Figure 3). This type of cyclization is related to similar processes recently reported.[15]

Next, a [1,5] hydrogen atom migration allows for recovery of the aromaticity of the furan moiety and yields **III** as a stable intermediate 14.5 kcal/mol below the reactants. Following the mechanistic proposal of Echavarren and co-workers[17] in a similar reaction of the coupling between alkynes and furfural derivatives, we also explored the possibility of a hydrogen [1,3] migration from intermediate **II**. This new species could undergo electrocyclization processes to obtain the final aromatic compound. Despite our efforts, we were unable to find this new intermediate. Instead, the transition state leading to a [1,2] hydrogen migration was found to be very high in energy (34.9 kcal/mol) (see Figure S2). Thus, this pathway seems not competitive. In addition, starting from intermediate **III**, a sequence of [1,5] hydrogen migrations could lead to the protonation of the metal−carbon bond, but this pathways is also disfavored (16.4 kcal/mol, Figure S2) with respect to the reversible reaction. In contrast, the positive charge located in the quaternized nitrogen atom allows for a charge distribution and fragmentation of the carbon−nitrogen single bond to yield **IV** via a TS that is 5.3 kcal/mol above the reactants. In this new intermediate, a reactive aldimine is formed next to the metal center. A preparative step transforms **IV** in **V** by a single bond rotation. The barrier height of 3.3 kcal/mol leads to the slightly more stable compound **V** in which the iminic hydrogen atom is

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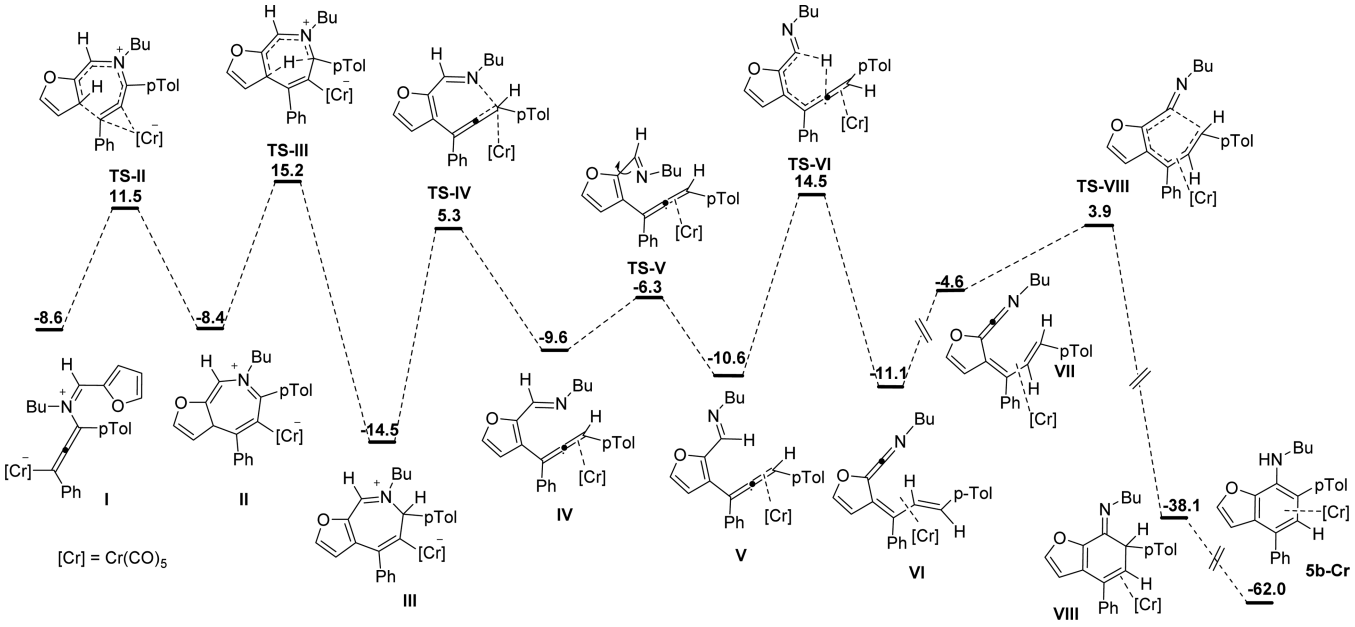

Figure 3. Computed mechanism for the formation of **5b**.

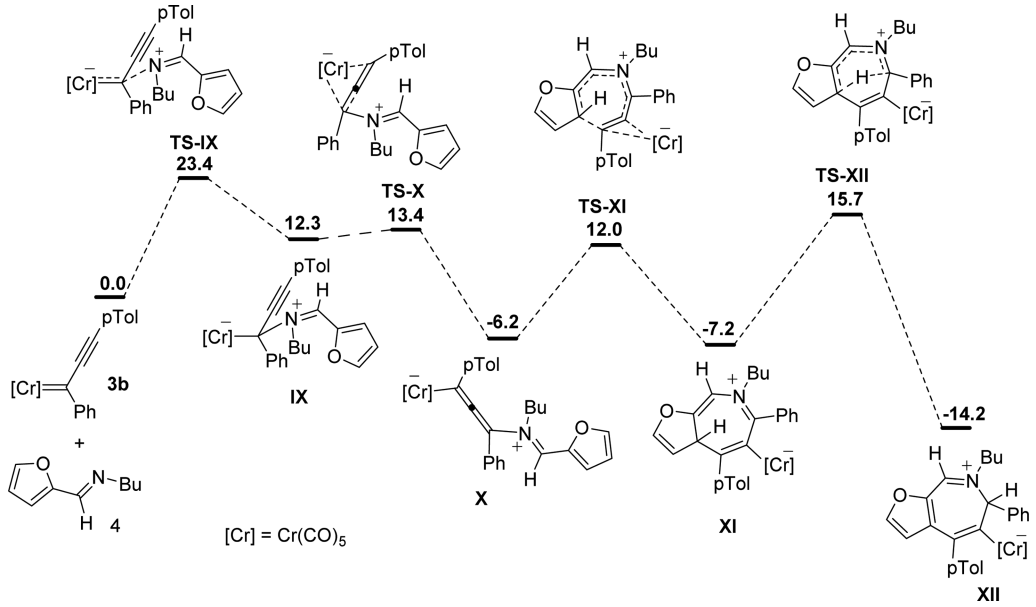

Figure 4. Computed mechanism for the formation of the regioisomeric benzofurans.

in the right position for the next steps. A hydrogen atom migration now takes place, surmounting a barrier of 25.1 kcal/mol to yield **VI**. A geometrical modification (from *s-trans* to *s-cis* in **VII**) provides the molecule with the right conformation to allow the electrocyclization to yield **VIII**. Finally, an imine-enamine tautomerization yields the final product. These last steps are driven by the high stability of the final benzofurans.

As reported previously,[16] when the non-heteroatom-stabilized carbene complex is not symmetric, two regioisomeric benzofurans can arise in different ratios. In all cases, a major isomer is obtained, but a minor isomer could also be found. This is not a drawback for the preparation of specific benzofurans as both regioisomers can be conveniently obtained as major compounds from the adequate selection of alkoxycarbene complex **1** and alkyne **2** to provide the desired product. However, the formation of the minor product is relevant from a mechanistic point of view. Thus, we explored different possibilities to explain the formation of these regioisomers. Some alternatives include cyclizations and different migrations. However, the formation of the minor regioisomers is not evident from any of these reaction paths. The right explanation may come from the different nucleophilic attacks discussed in Figure 1. Although the attack of imine to alkyne C-2 carbon is favored and explains the major isomer, the attack to the carbene carbon is also available and may be competitive in the experimental conditions. Thus, we explored the fate of intermediate **IX** (see Figure 4).

After the nucleophilic attack and formation of **IX**, the system evolves through a 1,3-metal migration[21] to yield **X**. A very small barrier (1.1 kcal/mol) and the increased stability of **X** imply that after the formation of **IX** this step should take place very fast. Also, as **X** and **I** are quite stable (6.2 and 8.6 kcal/mol

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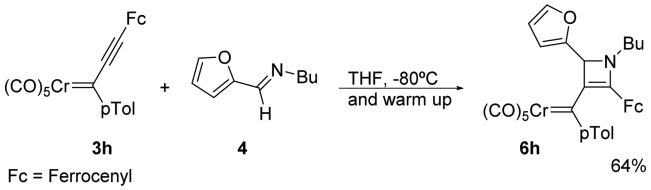
below the reactants), these two species will not equilibrate, and the ratio of the regioisomers will be governed by the initial nucleophilic attacks. The next step comprises a cyclization together with a 1,2-metal migration to form **XI** in a similar fashion as the previously described formation of **II** (see Figure 3). Once the seven-membered cycle is formed (**XI** or **II**), the regiochemistry of the final products is fixed. The final steps are then equivalent to those reported in Figure 3.

Once a reasonable explanation for the formation of the minor regioisomer from carbene **3b** has been computationally found, it can be inferred that the formation of the major isomer is controlled by the difference between the energy of the transition states **TS-I** and **TS-IX** (see Figure 2). To provide experimental support for these computational results, we decided to perform a single experiment to discard a major influence of the nature of the substituents of the carbene. Thus, in situ synthesized non-heteroatom-stabilized carbene complex **3g** (R^1= *p*-Tol; R^2= Ph), an isomer of **3b** (R^1= Ph; R^2= *p*-Tol), was reacted with imine **4**. After 4 h of reaction at −75 °C, benzofuran **5g** was obtained as the major regioisomer (**5g**:**5b**; approximately 6:1; 64% overall yield). This result indicates a prevalence of the choice between the two electrophilic positions of carbene **3** to be attacked by the imine over the nature of the substituents (Ph or *p*-Tol).

Once the mechanisms leading to both regioisomeric benzofurans have been determined, we aimed for a related reaction of non-heteroatom-stabilized carbene complexes with a furfural imine. In a previously reported work,[14] the reaction of carbene complex **3h** (the substituent R^2 is changed by a ferrocenyl group) yielded azetinyl carbene **6h** in good yield (see Scheme 1). This azetine could later be used in a subsequent

Scheme 1. Formation of Azetinylcarbene 6h[14]



reaction to form complex oxazines.[14] Intrigued by this different behavior when only a substituent is changed, we explored the mechanism of the azetine formation to try to control the formation of the different products.

The alternative mechanism leading to the formation of the azetine should be relevant in the early stages of the reaction. Once the cyclization process (to yield **II**) has taken place, it seems very improbable that a complex fragmentation and rearrangement process could lead to **6**. The results obtained are shown in Figure 5.

Once intermediate **I** is formed, a cyclization process could allow for the formation of **6b**. A similar transformation has been previously reported.[15] The transition structure leading to this transformation is 17.7 kcal/mol above the reactants, clearly above the 11.5 kcal/mol energy barrier leading to the formation of the benzofurans (see Figure 3). This energy difference of 6.2 kcal/mol should be enough to drive the reaction to the exclusive formation of benzofurans. However, the resulting azetine **6b** is very stable (15.9 kcal/mol below the reactants compared with the value of −8.4 kcal/mol of **II**). Thus, it seems plausible to alter the reaction outcome by modifying the relative energy of these two TSs through directed structural

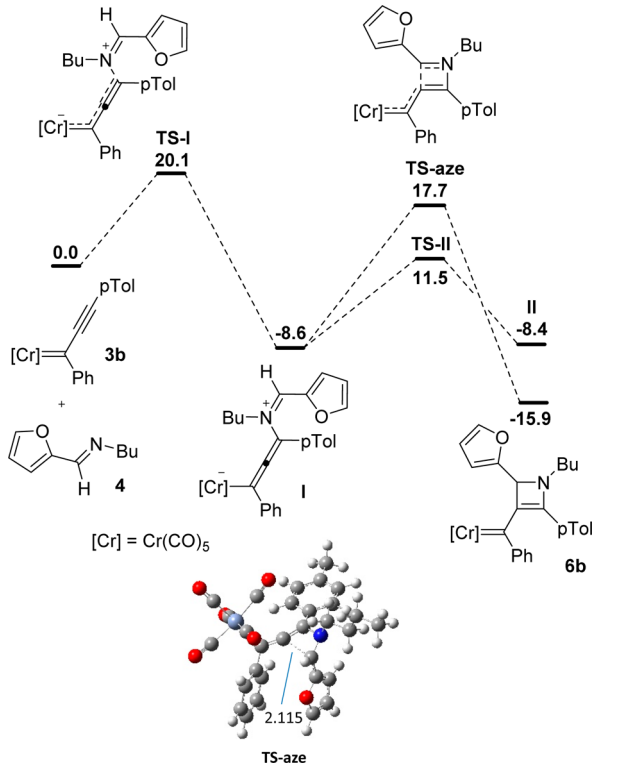
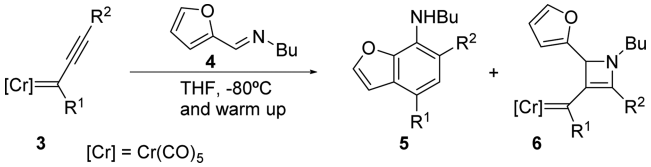


Figure 5. Computed mechanism for the formation of **6b**.

modification. In this sense, an electron-donating group as a ferrocenyl should contribute to increase the nucleophilicity at the C-2 carbon in intermediate **I**, favoring the pathway leading to azetinylcarbene **6h** formation.

To test this hypothesis, we decided to study the reactivity of imine **4** with other non-heteroatom-stabilized carbene complexes wearing electron-donating groups, and compare the results with the model compounds **3b**[16] and **3h**[14] (Table 2).

Table 2. Synthesis of Benzofurans 5 or Azetinylcarbenes 6



carbene	R^1	R^2	yield (%)[a]
3b	Ph	*p*-Tol	**5b**, 61[b]
3h	*p*-Tol	Fc	**6h**, 64
3i	Ph	*p*-$MeOC_6H_4$	**5i**, 22[c] **6i**, 49[d]
3j	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	**6j**, 74

[a]Overall yield from the corresponding alkoxycarbene **1**. [b]Performed at −75 °C. Regioisomeric ratio of >10:1. [c]Regioisomeric ratio of approximately 4:1. [d]Regioisomeric ratio of approximately 2:1.

For this purpose, we selected first alkynylcarbene **3i** wearing a *p*-methoxyphenyl group at the alkyne position. Thus, in situ synthesized non-heteroatom-stabilized carbene complex **3i** reacted with imine **4** allowing the reaction to warm until reaching −20 °C, yielding a mixture of benzofuran **5i** and azetine **6i** in 22 and 49% overall yield, respectively, from the corresponding alkoxycarbene **1**. In both cases, benzofuran **5i** and azetine **6i** are obtained as a mixture of regioisomers. The

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formation of both types of heterocycles and their isomers is in agreement with a connection between both pathways and indicates a similar energy for both transition states **TS-aze** and **TS-II**. On the other hand, placing a second *p*-methoxyphenyl group at the carbene carbon (complex **3j**) resulted, under the same reaction conditions, in the formation of azetinylcarbene **6j** in high yield and as a sole compound. In this case, both substituents contributed to increase the mentioned nucleophilicity at C-2 in intermediate **I**.

CONCLUSIONS

We have shown here a complete computational exploration of the different mechanisms operating for the reaction of non-heteroatom-stabilized chromium carbene complexes with the furfural imine using density functional method calculations. Complex reaction cascades were found to operate in the preparation of regioisomeric benzofurans and the related synthesis of azetines. The different nucleophilic attacks to the alkyne C-2 and carbene positions were found to control the formation of the regioisomers. Thus, small differences in these key transition structures influence the reaction outcome to yield the diverse regioisomers experimentally found. Also, the computed mechanisms provide an explanation for the formation of azetinylcarbene complexes also found in the reaction mixture. In addition, the directed structural modifications of these selected transition structures allowed for the control of the main product of the reaction. Therefore, the collected mechanistic information was used to tune the reaction outcome by selection of the substituents present in the starting material. Thus, the possibility of obtaining both types of valuable compounds, benzofurans and azetines, using a similar methodology confers an added value to the use of non-heteroatom-stabilized chromium carbene complexes.

EXPERIMENTAL SECTION

General Experimental Methods. All operations were carried out under an argon atmosphere using conventional Schlenck techniques. All common reagents were obtained from commercial suppliers and used without further purification unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium benzophenone prior to use. Hexane and ethyl acetate were used from commercial suppliers. TLC was performed on aluminum-backed plates coated with silica gel 60 with F254 indicator or neutral aluminum oxide. Flash chromatographic columns were carried out on silica gel 60 (230−400 mesh). High-resolution mass spectra were determined by electronic impact using a mass spectrometer with a triple sector analyzer. NMR spectra were run on a 300 or 400 MHz spectrometer using $CDCl_3$ or C_6D_6 as solvents.

General Experimental Procedure for the Preparation of the New Benzofurans 5g and 5i and Azetinylcarbenes 6i and 6j. To a freshly prepared solution of 0.95 mmol of lithium acetilyde **2** (0.95 mmol of acetylene, 0.95 mmol of butyllithium (1.6 M in hexane)) in 20 mL of tetrahydrofuran under argon atmosphere at −80 °C was added 0.5 mmol of chromium alkoxycarbene **1**. The mixture was stirred for 15 min at that temperature, and 0.19 mL (1.1 mmol) of trimethylsilyl trifluoromethanesulfonate (TMSOTf) was added to form the non-heteroatom-stabilized metal carbenes **3** (blue solution). At this point, 1 mmol of 2-furaldehyde imine **4** was added, and the mixture was kept at −75 °C for **5g** or allowed to warm until a color change was observed. Removal of the solvents under reduced pressure followed by a chromatographic column through silica gel of the residue yielded the corresponding benzofurans **5** and azetinylcarbenes **6**.[22]

*N-Butyl-6-phenyl-4-p-tolylbenzofuran-7-amine (**5g**).* ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): colorless oil; 114 mg (64% yield) (mixture of regioisomers **5g**:**5b**; approximately 6:1); R_f = 0.49 (20:1 hexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): (major isomer) δ 7.69 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.58−7.24 (m, 7H), 7.15 (s, 1H), 6.98 (d, J = 4.0 Hz, 1H), 4.00 (m, 1H), 3.56 (t, J = 8.0 Hz, 2H), 2.46 (s, 3H), 1.54 (m, 2H), 1.35 (m, 2H), 0.92 (t, J = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): (major isomer) δ 145.3 (C), 144.8 (CH), 140.4 (C), 136.9 (C), 136.7 (C), 131.4 (C), 129.7 (2 x CH), 129.6 (2 x CH), 128.6 (2 x CH), 128.1 (2 x CH), 126.5 (C), 126.4 (CH), 125.5 (CH), 125.3 (C), 124.6 (C), 106.2 (CH), 46.4 (CH_2), 33.1 (CH_2), 21.3 (CH_3), 20.1 (CH_2), 13.9 (CH_3). HRMS (EI) for $C_{25}H_{25}NO$ $[M]^+$: 355.1936; found 355.1940.

*N-Butyl-4-phenyl-6-(4-methoxyphenyl)benzofuran-7-amine (**5i**).* Colorless oil; 41 mg (22% yield) (mixture of regioisomers, approximately 4:1); R_f = 0.25 (20:1 hexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): (major isomer) δ 7.69 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.53−7.47 (m, 5H), 7.14 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 2.2 Hz, 1H), 4.06−3.78 (bm, 1H), 3.88 (s, 3H), 3.52 (t, J = 7.1 Hz, 2H), 1.61−1.44 (m, 2H), 1.33 (m, 2H), 0.91, (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): (major isomer) δ 158.4 (C), 145.5 (C), 144.7 (CH), 139.8 (C), 132.9 (C), 130.9 (C), 129.7 (2 x CH), 129.1 (2 x CH), 128.8 (2 x CH), 127.1 (CH), 126.4 (C), 125.4 (C), 125.1 (CH), 124.5 (C), 114.0 (2 x CH), 106.2 (CH), 55.3 (CH_3), 46.5 (CH_2), 33.0 (CH_2), 20.0 (CH_2), 13.9 (CH_3). HRMS (EI) for $C_{25}H_{25}NO_2$ [M]: calcd, 371.1885; found, 371.1870.

*Pentacarbonyl[(1-butyl-2-furyl-4-(4-methoxyphenyl)-1,2-dihydroazet-3-yl)benzylidene]chromium(0) (**6i**).* Red oil; 136 mg (49% yield) (mixture of regioisomers, approximately 2:1); R_f = 0.41 (3:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, C_6D_6, 25 °C, TMS): (major isomer) δ 7.31 (s, 1H), 7.35−6.70 (m, 8H), 6.30 (m, 2H), 6.46 (d, J = 8.8 Hz, 2H), 3.35 (s, 3H), 3.05−2.75 (m, 2H), 1.15−0.75 (m, 4H), 0.60 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6, 25 °C): (major isomer) δ 253.2 (C), 227.5 (C), 220.6 (4 x C), 166.9 (C), 158.4 (C), 151.3 (C), 146.5 (C), 144.5 (CH), 131.4 (2 x CH), 128.7 (2 x CH), 128.6 (2 x CH), 128.5 (CH), 115.1 (CH), 114.4 (2 x CH), 113.4 (CH), 111.9 (CH), 72.8 (CH), 55.1 (CH_3), 45.4 (CH2), 30.2 (CH_2), 20.3 (CH_2), 13.7 (CH_3).

*Pentacarbonyl[(1-butyl-2-furyl-4-(4-methoxyphenyl)-1,2-dihydroazet-3-yl)4-methoxybenzylidene]chromium(0) (**6j**).* Red oil; 220 mg (74% yield); R_f = 0.22 (3:1 hexane/ethyl acetate). ^{1}H NMR (300 MHz, C_6D_6, 25 °C, TMS): δ 7.30 (s, 1H), 7.05−6.95 (m, 1H), 6.85 (d, J = 3.1 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.7−6.51 (m, 3H), 6.48 (d, J = 8.8 Hz, 2H), 6.33−6.26 (m, 2H), 3.34 (s, 3H), 3.20 (s, 3H), 3.10−2.78 (m, 2H), 1.17−0.93 (m, 2H), 0.85 (m, 2H), 0.63 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ 250.9 (C), 227.4 (C), 220.7 (4 x C), 166.5 (C), 162.7 (C), 158.2 (C), 151.7 (C), 146.9 (C), 144.5 (CH), 139.1 (C), 131.2 (2 x CH), 128.7 (2 x CH), 118.9 (C), 115.1 (CH), 114.3 (2 x CH), 113.7 (2 x CH), 111.9 (CH), 72.6 (CH), 55.3 (CH_3), 55.2 (CH_3), 45.5 (CH_2), 30.3 (CH_2), 20.4 (CH_2), 13.7 (CH_3).

Computational Details. All calculations were carried out using the Gaussian09 program package[23] and the density functional theory (DFT) method. We used the hybrid meta-GGA M06 functional[24] with two different basis sets. This functional has been recently reported to give good results with other group VI metals as Mo and W.[25] The standard basis set[26] 6-31+G(d) was used for C, N, O, and H, and LANL2DZ[27] with the associated pseudopotential for Cr was used for the optimizations and frequencies calculations, whereas the 6-311+G(d,p) basis set[28] for C, N, O, H, and LANL2TZ(f) for Cr[−29,30] (with the LANL2DZ pseudopotential) were used to refine the potential energies to reduce the basis set superposition error. All points were characterized as minima (no imaginary frequency) or TS (one imaginary frequency, IRC was done when it was necessary). In addition, all of the structures were optimized using the SMD as the implicit solvation model[31] with tetrahydrofuran as the solvent (ε = 7.4257). All of the energies in the presented profiles are Gibbs Free energies in solution in kcal/mol and referred to the separated reactants. These energies have been calculated by adding the free energy correction calculated with the smaller basis set plus the SCF energy calculated with the larger basis set.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02729.

Computed energies, Cartesian coordinates for computed compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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