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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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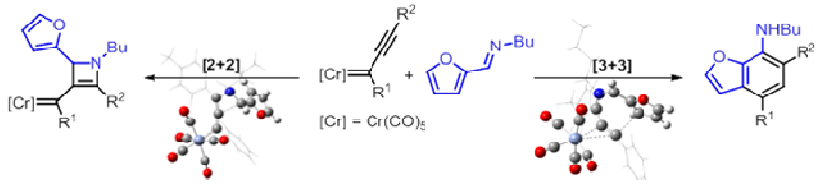


Abstract

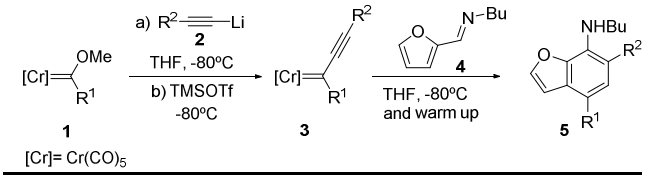
The mechanisms of the reaction between non-heteroatom-stabilized alkynyl chromium carbene complexes prepared in situ and furfural imines to yield benzofurans and/or azetines have been explored by means of density functional theory method calculations. The reaction proceeds through a complex cascade of 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 decades, group 6 Fischer carbene complexes have demonstrated a high versatility as a powerful synthetic tool.[2-8] However, non-heteroatom-stabilized carbene complexes, first reported by Casey in 1973,[9] did not emerged 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 synthetically useful and experienced significant differences in terms of reactivity with their alkoxycarbene analogs. 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, also a formal [3+3] benzofuran synthesis from furylimines has been reported.[16] This particular reaction focused 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] On the other hand, 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).

Table 1. [3+3] Benzofuran synthesis from, in situ synthesized, non-heteroatom-stabilized carbene complexes **3** (Ref: 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 -75ºC. Regioisomeric ratio (>10:1)
c Regioisomeric ratio (>20:1)
d Performed at -80ºC. Regioisomeric ratio (>8:1)

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** in order 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 give an extra experimental support for the theoretical results, several additional experiments have been performed.

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 the 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 the 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 experimentally used. 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 combination of these two elements (see Figure 1).

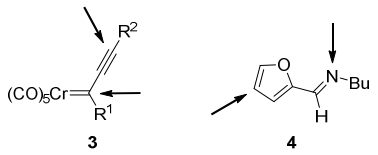


Figure 1. Electrophilic positions in **3** and nucleophilic positions in **4**.

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). The 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 above the reagents (Figure 2).

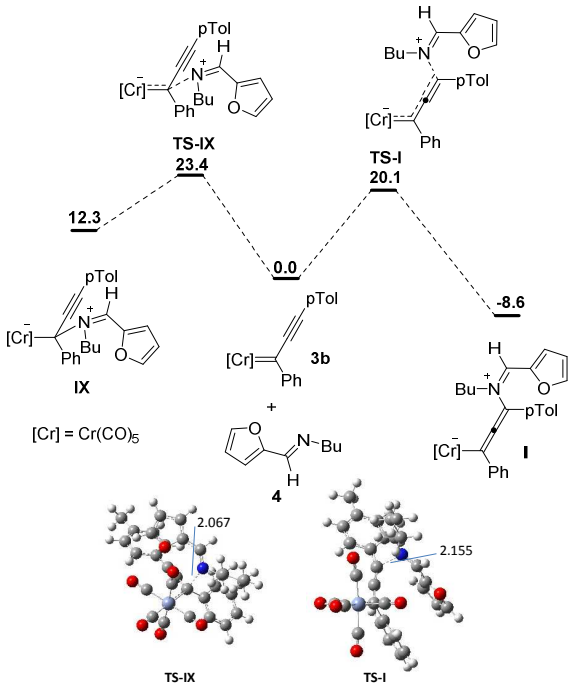


Figure 2. Competitive nucleophilic attacks of **4** to **3**. Free energies in kcal/mol relative to **3b** + **4**.

From intermediate **I**, the reaction cascade progress 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]

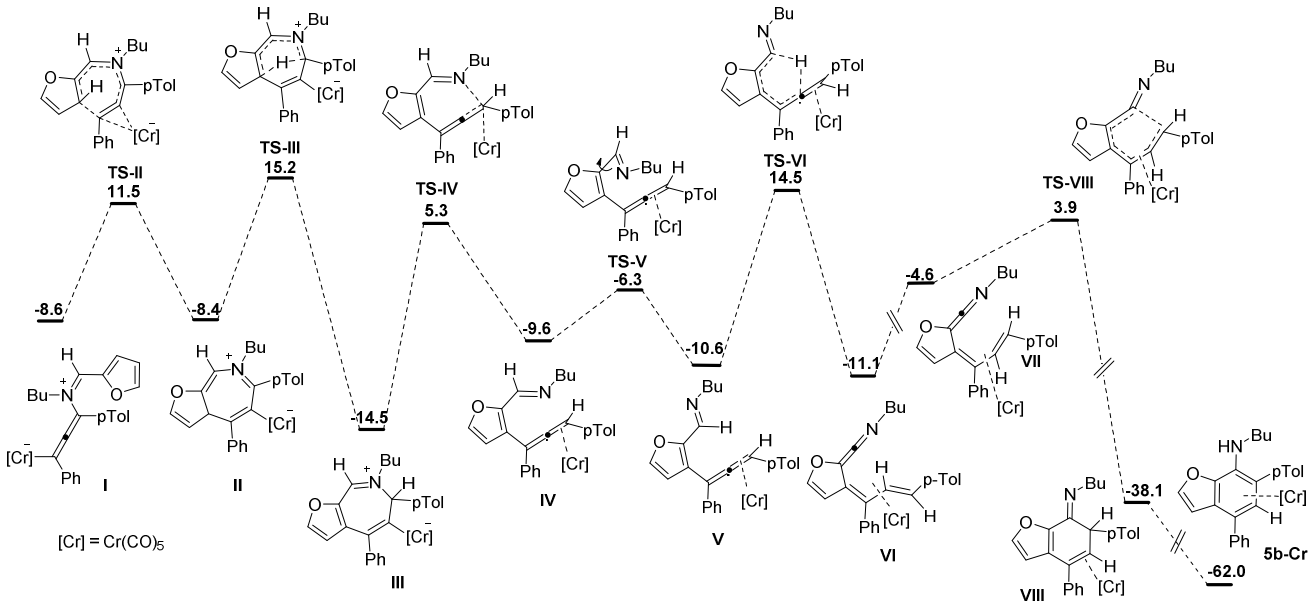


Figure 3. Computed mechanism for the formation of **5**.

Next, a [1,5] hydrogen atom migration allows recovering 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 an electrocyclization processes to obtain the final aromatic compound. In spite of our efforts, we were unable to find this new intermediate. Instead, the transition state leading to a [1,2] hydrogen migration was found very high in energy (34.9 kcal/mol) (see Figure S2 in the Supporting Information). 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 which 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 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 before,[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 when the substituents in the carbene and conjugated carbon atoms are different. 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 the mechanistic point of view. Thus, we explored different possibilities to explain the formation of these regioisomers. Some alternatives include cyclizations and different migrations. However, it is not evident the formation of the minor regioisomers from any of these reaction paths. The right explanation may come from the different nucleophilic attacks discussed in Figure 1. While 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 the intermediate **IX** (see Figure 4).

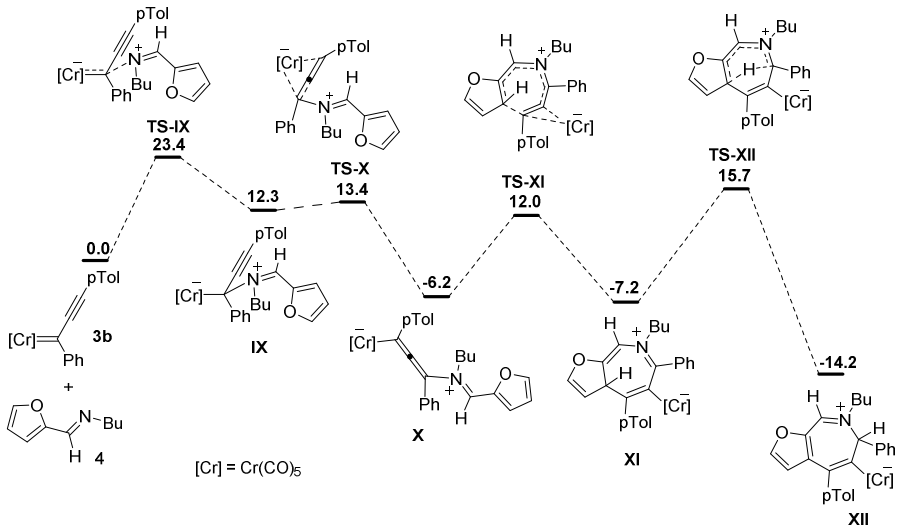


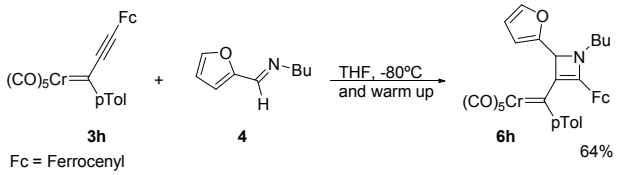
Figure 4. Computed mechanism for the formation of the regioisomeric benzofurans.

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 below the reactants) these two species won't 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 it has been computationally found a reasonable explanation for the formation of the minor regioisomer from carbene **3b**, 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). In order to give 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), isomer of **3b** (R^1= Ph; R^2= *p*-Tol), was reacted with imine **4**. After 4h of reaction at -75ºC, benzofuran **5g** was obtained as the major regioisomer (**5g:5b**; ca. 6:1; 64% overall yield). This result indicates a prevalence of the choice between

the two electrophilic positions of the carbene **3** to be attacked by the imine, over the nature of the substituents (Ph or *p*-Tol).

Once determined the mechanisms leading to both regioisomeric benzofurans, 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 the 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 be later used in a subsequent 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 in order to try to control the formation of the different products.



Scheme 1. Formation of azetinylcarbene **6h** (see ref.14).

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.

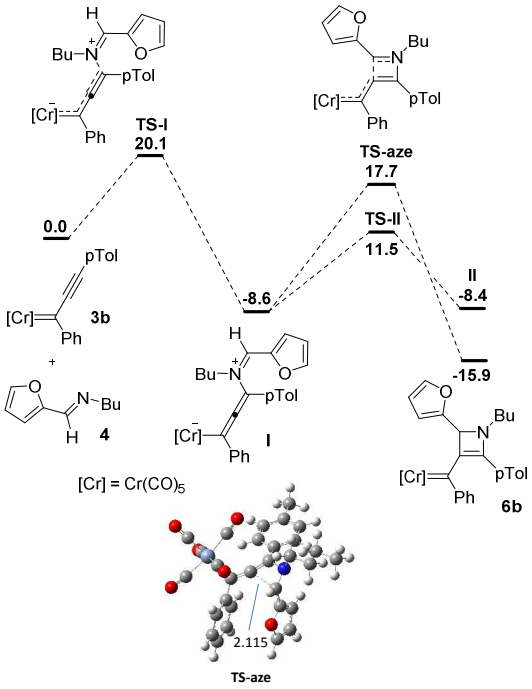


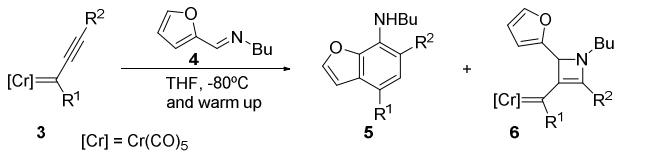
Figure 5. Computed mechanism for the formation of **6b**.

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

To test this hypothesis, we decided to study the reactivity of the 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). For that 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 up until -20ºC, yielding a mixture of benzofuran **5i** and azetine **6i** in 22% and 49%, respectively overall yield, from the corresponding alkoxycarbene **1**. In both cases, benzofuran **5i** and azetine **6i** are obtained as a mixture of regioisomers. The 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 the 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**.

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 -75ºC. Regioisomeric ratio (>10:1)
c Regioisomeric ratio (ca.4:1)
d Regioisomeric ratio (ca.2:1)

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 C2 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 transitions structures allowed to control 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 to obtain both types of valuable compounds, benzofurans or 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 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 aluminium-backed plates coated with silica gel 60, with F254 indicator or neutral aluminium oxide. Flash chromatographic columns were carried out on silica gel 60, (230-400 mesh). High-resolution mass spectra were determined by electronic impact using 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,5i and azetinylcarbenes 6i-j: To a freshly prepared solution, under argon atmosphere at -80ºC, 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, 0.5 mmol of chromium alkoxycarbene **1** were added. The mixture was stirred for 15 min at that temperature and 0.19 mL (1.1 mmol) of trimethylsilyl trifluoromethanesulfonate (TMSOTf) were 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 kept at -75ºC for **5g** or allowed to warm up, until colour 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 ºC, TMS): Colourless oil; 114 mg (64% yield) (mixture of regioisomers **5g:5b**; ca. 6:1); Rf = 0.49 (Hexane/Ethyl acetate 20:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC, 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 ºC): (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):** Colourless oil; 41 mg (22% yield) (mixture of regioisomers ca. 4:1); Rf = 0.25 (Hexane/Ethyl acetate 20:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC, 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, $CDCl_3$, 25ºC): (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]: Calc: 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 ca. 2:1); Rf = 0.41 (Hexane/Ethyl acetate 3:1); ^{1}H NMR (400 MHz, C_6D_6, 25ºC, TMS): (Mayor 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, 25ºC): (Mayor 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); Rf = 0.22 (Hexane/Ethyl acetate 3:1); ^{1}H NMR (300 MHz, C_6D_6, 25ºC, 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, 25ºC): 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 metal 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 were used for the optimizations and frequencies calculations, while 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 in order 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 the structures were optimized using the SMD as implicit solvation model[31] with tetrahydrofuran as solvent (ε = 7.4257). All the energies in the presented profiles are Gibbs Free energies in solution and in kcal/mol 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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Supporting Information Available. Figure S1, Figure S2, Computed energies, Cartesian coordinates for computed compounds, NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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