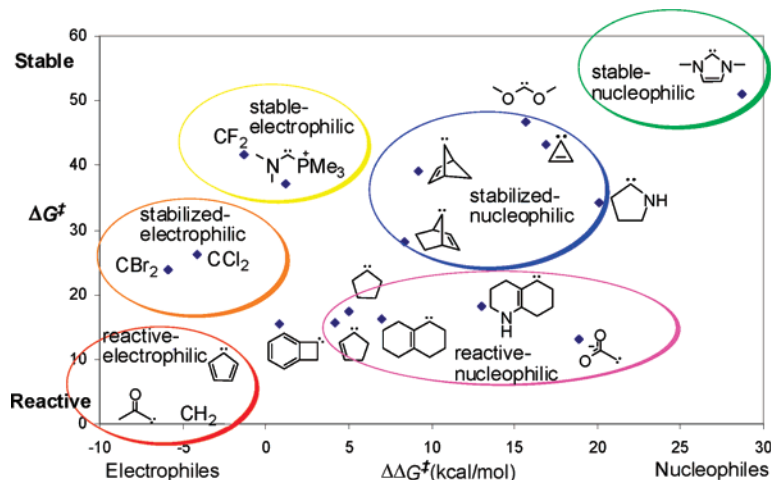# The Carbene Reactivity Surface: A Classification[†]

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A new two-dimensional classification of singlet carbenes based on the difference in reactivity of their *insertion* reactions into the C−H bonds of acetonitrile and isobutane is presented. This classification combines the stability *and* the philicity of divalent species. Until now all of the experimentally based philicity scales are based on the *addition* to alkenes. Moreover, a new terminology for describing the reactivity of carbenes is introduced. Among the alkyl carbenes, acetyl carbene (**2**) and cyclopentadienylidene are shown as highly reactive electrophilic carbenes, whereas the other alkylidenes and alkenylidenes investigated are all less active than **2** and more nucleophilic. The stabilized-nucleophilic bicyclo[2.1.1]hex-2-en-5-ylidene (**13**) possesses a stability similar to that of cyclic alkyl amino carbene (CAAC) **18** and aminophosphoniocarbene **7**. Strong hydrogen bridging is found between a C−H bond of acetonitrile and the nucleophilic carbenes **13** and **14**.

Introduction

Carbenes[1] are species bearing a divalent carbon. In their singlet state, they possess a lone pair and a low-lying unoccupied orbital at the same atom. This special electron configuration gives them a high reactivity, especially toward additions to double bonds, e.g., cyclopropanation or insertion into single bonds. Depending on their structure and on other functional groups in the vicinity of the carbenic center, their properties can change considerably. First of all, they can possess either a triplet or a singlet ground state. But also the consideration of their stability and philicity is very significant to describe their reactivity properly and to answer the question whether the electrophilic or the nucleophilic reactivity predominates. Until now, several one-dimensional scales have been proposed in order to better understand the reactions of singlet carbenes.[2] In a related field, a general equation for reactions between an electrophile and a nucleophile has been developed on the basis of kinetic investigations (eq 1).[3] This concept has been extended to a wide range of reactions, for example for superelectrophilic heteroaromatic substrates.[4]

$$\log k = s_E s_N (E + N) \qquad (1)$$

where s_E = electrophile-specific slope, s_N = nucleophile-specific slope, E = electrophilicity parameter, and N = nucleophilicity parameter.

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† Carbene Rearrangements. 70. For Part 69 see: Mieusset, J.-L.; Brinker, U. H. *J. Org. Chem.* **2007**, *72*, 10211.

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CHART 1
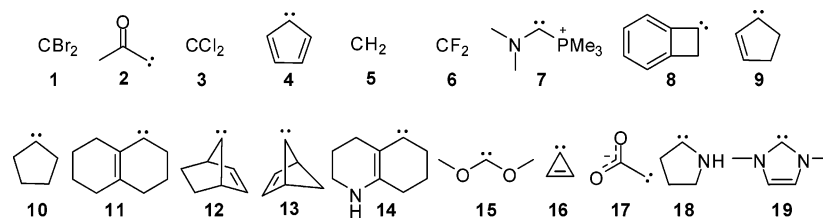
For carbenes, the most popular scale remains the experimentally determined philicity scale proposed by Moss,[5] which is based on competitive cyclopropanations of alkenes. For a special carbene CXY, the resulting *carbene selectivity index* m_{CXY} is defined as the slope of $\log(k_i/k_o)_{CXY}$ vs $\log(k_i/k_o)_{CCl2}$.[5a] Compounds with a low selectivity index are then described as electrophiles.[5a] m_{CXY} can also be calculated from Taft parameters (eq 2).[5a]

$$m_{CXY} = -1.10\sum_{X,Y} \sigma_R^+ + 0.53\sum_{X,Y} \sigma_i - 0.31 \qquad (2)$$

This scale has been corroborated by FMO theory[6] and by the global electrophilicity[7] ω, a value derived from density functional theory.[8]

However, this one-dimensional depiction does not allow visualizing the differences in reactivity, placing for example dichlorocarbene and methylene into the same electrophilic group, although these two carbenes show different chemistries. Therefore, we thought that a two-dimensional surface would facilitate the understanding of carbene reactions. Until now, only Sander has classified carbenes on a two-dimensional scale.[9] This scale is based on a comparison of electron affinities with ionization potentials. In contrast, *the surface presented here takes into account not only the philicity but also the reactivity of carbenes.* In order to obtain results comparable with the experimentally observed reactivity, we based our investigation on kinetic parameters. Indeed, it has been found that the reactivity of carbenes is only poorly related to the HOMO–LUMO gap or the HOMO–LUMO energies.[10] A better correlation is found with singlet–triplet gaps.[10a] We have determined our kinetic parameters in silico to gain information about

the potential properties of the carbene prior to the synthesis of its precursor and its generation. Until now, all of the experimentally based philicity scales for carbenes are based on the addition to alkenes. However, for most carbenes, no enthalpic barrier can be computed. Therefore, our scale is based upon the comparison of two different C–H insertion reactions. This allows the transition state to be computed in most of the cases. Moreover, we concentrated our efforts on alkyl carbenes, since their position in the philicity scales to a large extent is still unknown. And, we were especially interested in stabilized-nucleophilic carbenes.

Computational Methods

The Gaussian 03 program[11] was used for density functional theory calculations, employing Becke's[12] three-parameter hybrid method, and the exchange functional of Lee, Yang, and Parr (B3LYP).[13] Geometries were optimized at the B3LYP/6-31G(d) level of theory. The stationary points were characterized by vibrational analysis.

Results and Discussion

For the realization of our in silico experiments, we choose to compare the insertion reactions of a variety of alkyl carbenes into the tertiary C–H bond of the highly symmetric isobutane (C_{3v}) and into the primary C–H bonds of acetonitrile (C_{3v}). Isobutane was chosen as a nucleophilic counterpart, due to its high hydride transfer potential (HTP, 75.8 kcal/mol)[14] and its high pK_a (53).[15] Especially, the C–H bond in acetonitrile represents an electrophilic partner, since it possesses a very low HTP (4.5 kcal/mol)[14] and moderately acidic hydrogen atoms ($pK_a = 31.3$ in DMSO).[16] Therefore, isobutane is thought to reveal the electrophilic reactivity of a carbene, whereas nucleophilic carbenes should preferably react with acetonitrile. The averaged height of the calculated barrier is an indicator for the overall reactivity of the carbene. The results are summarized in Table 1. As shown in Figure 1, for every carbene investigated, the insertion into methane has proven to necessitate more energy than for the insertion into the activated bonds of acetonitrile and isobutane. For an electrophilic carbene, the energy barrier is considerably lowered for the reaction with a nucleophilic

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TABLE 1. Free Activation Energies and Activation Enthalpies for the Insertion of Carbenes 1−19 into Acetonitrile, Methane, and Isobutane

	acetonitrile[a]		methane[a]		isobutane[a]		difference[a]	average[a]	
	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$
1	13.1	23.6	19.5	30.4	6.3	17.6	−5.9	13.0	23.9
	0.7	12.1	2.2	13.9	(−5.5)[c]	(6.6)[b]	(−5.5)	(−0.9)	(10.9)
2	*−7.2*	*5.9*	*−7.2*	*4.5*	*−12.8*	*−1.6*	*−7.5*	*−9.1*	*2.9*
	6.7	18.0	5.6	17.2	0.2	12.5	−6.5	4.2	15.9
3	15.3	25.5	21.1	31.9	10.6	21.4	−4.1	15.7	26.3
	(−0.8)[b]	(9.2)[b]	−0.8	8.6	(−3.8)[b]	(6.9)[b]	(−2.3)	(−1.8)	(8.2)
4	*−9.6*	*5.4*	*−9.0*	*2.8*	*−15.1*	*−2.2*	*−7.6*	*−11.2*	*2.0*
	8.2	19.6	7.0	18.4	2.7	14.1	−5.5	6.0	17.4
	(−6.0)[b]	(3.6)[b]	(−13.9)[b]	(−5.0)[b]	(−8.5)[b]	(1.5)[b]	(−2.1)	(−9.5)	(0.0)
5	*−12.5*	*−0.9*	*−12.8*	*−1.6*	*−16.0*	*−4.6*	*−3.7*	*−13.8*	*−2.4*
	11.1	21.3	10.8	21.0	9.0	18.7	−2.6	10.3	20.3
6	29.7	39.4	36.8	47.4	27.7	38.1	−1.3	31.4	41.6
7	24.0	34.5	30.1	41.1	24.5	35.7	1.2	26.2	37.1
8	2.6	12.8	8.9	20.0	3.0	13.6	0.8	4.8	15.5
9	−0.3	10.9	10.0	20.9	4.2	15.1	4.2	4.6	15.6
10	2.6	12.9	10.9	21.1	7.2	17.9	5.0	6.9	17.3
11	0.5	10.8	9.2	20.0	6.3	17.8	7.0	5.3	16.2
12	11.5	22.1	20.1	31.6	18.9	30.5	8.4	16.8	28.1
13	22.0	32.2	32.0	43.4	31.0	41.4	9.2	28.3	39.0
14	−2.2	8.4	14.3	24.5	10.9	21.4	12.9	7.7	18.1
15	25.6	35.1	43.7	53.7	40.8	50.8	15.7	36.7	46.7
16	19.1	29.9	42.8	53.0	36.7	46.8	16.9	32.9	43.2
	(−11.9)[c]	(−1.8)[c]	12.8	23.8	5.3	17.1	(18.9)	(2.1)	(13.0)
17	*−3.4*	*9.7*	*13.9*	*25.6*	*9.5*	*20.3*	*10.6*	*6.7*	*18.5*
	7.8	18.9	22.0	33.7	16.9	29.5	10.6	15.6	27.4
18	8.9	19.5	33.1	43.6	29.2	39.5	20.1	23.7	34.2
19	21.4	31.9	52.2	60.7	51.5	60.6	28.7	41.7	51.1

[a] All energies in kcal/mol at the B3LYP/6-31G(d) level of theory, values in italic represent B3LYP/6-31G(d)//HF/3-21G* calculations; values underlined were obtained at the HF/3-21G* level. [b] The carbenic carbon and the atoms of the breaking bond have been frozen in the geometry of the transition state for the insertion of **2** into acetonitrile. [c] The carbenic carbon and the atoms of the breaking bond have been frozen in the geometry of the transition state for the insertion of **9** into acetonitrile.
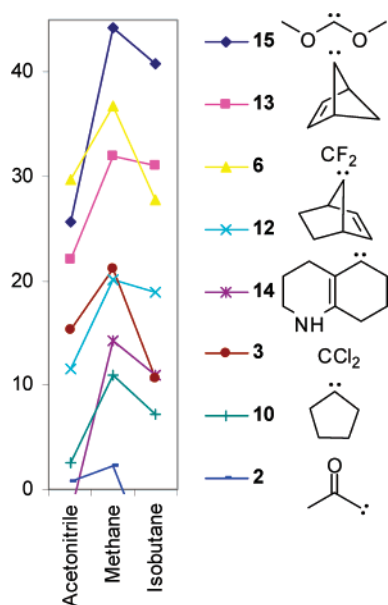

FIGURE 1. Enthalpies of activation of representative carbenes with acetonitrile, methane, and isobutane calculated at the B3LYP/6-31G-(d) level of theory.

partner but is only slightly reduced for the reaction with an electrophilic partner and vice versa.

Overall, the investigated carbenes can be classified into six different groups (Figure 2): reactive-electrophilic (red ellipse), stabilized-electrophilic (orange), stable-electrophilic (yellow), stable-nucleophilic (green), stabilized-nucleophilic (blue), and reactive-nucleophilic (purple) carbenes.

The group of the reactive-electrophilic carbenes is composed of the singlets acetyl carbene (**2**), cyclopentadienylidene[17] (**4**), and methylene (**5**). They are characterized by a preference for reaction with the tertiary C−H bond of isobutane and, unfortunately, in many cases by the absence of an enthalpic barrier toward insertion into the test compounds. For the insertion of methylene into C−H bonds, it has been shown that for the most efficient approach, the one with a σ orientation, a transition state can only be found with low-level methods such as Hartree−Fock, which overestimate these barriers.[10] A second case where a transition state may be obtained is the investigation of inverted approaches.[10,18] Therefore, our methodology gives only qualitative results for the highly reactive species **2**, **4**, and **5**. Consequently, the calculations were repeated at the HF/3-21G* level of theory. Indeed, the preference for insertion into isobutane is confirmed. However, the calculated activation energies are unrealistically high with HF/3-21G* and much too low with B3LYP/6-31G(d)//HF/3-21G*. Further common known characteristics of **2**, **4**, and **5** are their ability to form ylides with ethers[19] and their triplet ground states.[20] For acetyl carbene

(17) Substituted cyclopentadienylidenes have already been ranked according to their selectivity: (a) Dürr, H. *Top. Curr. Chem.* **1973**, *40*, 103. (b) Dürr, H. *Top. Curr. Chem.* **1975**, *55*, 87.

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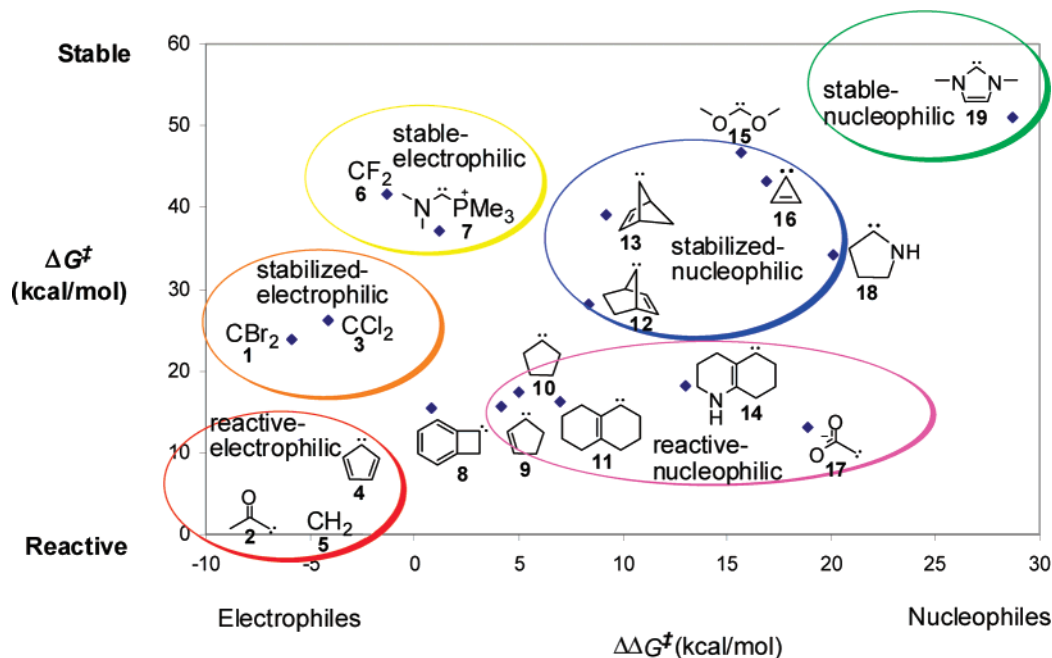
FIGURE 2. Carbene reactivity surface based on the insertion into the C—H bonds of isobutane and acetonitrile. Averaged free energies of activation against differences in free energy of activation calculated at the B3LYP/6-31G(d) level of theory. All energies given are in kcal/mol.

(**2**), we calculated a singlet–triplet gap of +4.5 kcal/mol at the B3LYP/6-31G(d) level of theory, a method that is known to overestimate the stability of the triplet by ca. 3 kcal/mol.[20d] With the more accurate G3MP2B3 procedure, the gap is reduced to −0.1 kcal/mol. However, this methodology tends to favor the singlet by ca. 0.7 kcal/mol.[20d] In this work, a positive value for the singlet–triplet gap means that the triplet is predicted to be more stable. The case of benzocyclobutenylidene (**8**) is note-worthy: it has been described as one of the strongest electro-philes with a m_{CXY} value of 0.43.[21] However, our calculations describe it as a reactive ambiphilic carbene because it is predicted to react slightly better with acetonitrile than with isobutane. This discrepancy is due to the reduced selectivity of benzocyclobutenylidene (**8**). Indeed, the cycloaddition of **8** to tetramethylethylene (TME) is about 10 times faster than the addition to cyclohexene.[21] This value can be compared to the 100-fold increase in the rate of addition of dichlorocarbene (**3**) with cyclohexene vs TME.[22] The relatively poor selectivity of **8** is the cause for the low m_{CXY} value determined experimentally and is typical for reactive-electrophilic carbenes. However, this

behavior is also characteristic for nucleophilic carbenes which react with good selectivity only with electrophiles.

The group of the stabilized-electrophilic carbenes is repre-sented here by dihalocarbenes **1** and **3**. They combine a pronounced dominance of the electrophilic reactivity ($\Delta\Delta G^{\ddagger}$ = −4.1 kcal/mol for CCl$_2$) and a high averaged enthalpic barrier (13 to 16 kcal/mol). Dichlorocarbene is known to insert into the C—H bonds of several polycyclic alkanes with a syntheti-cally useful selectivity, when the calculated barrier for insertion is lower than 12 kcal/mol at the B3LYP/6-31G(d) level of theory.[14,23] It has also been shown to insert efficiently into activated C—H bonds,[24] e.g., into secondary ethers[14,25] (calcu-lated barrier: 4.9 kcal/mol[14]) or into malonic acid derivatives (calculated barrier: 7.4 kcal/mol[14]). The highest barrier found is toward insertion into methane with 21.1 kcal/mol.[10,14,26] These large activation barriers correlate well with the significant stabilization energy previously computed.[27] In dihalocarbenes, the stabilization and the dominance of electrophilic reactivity derive from a combination of resonance and inductive effects.

To our knowledge, the group of the stable-electrophilic carbenes still has no archetypal representative. The species we

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investigated with the most similar properties is cation **7**, a model for the aminophosphoniocarbenes previously synthesized and isolated by Bertrand.[28] It is characterized by a high averaged activation barrier of more than 24 kcal/mol and a nearly comparable reactivity toward isobutane and acetonitrile.

Examples of stable-nucleophilic carbenes are the well-known isolable *N*-heterocyclic carbenes. Indeed, extremely high activation energies are calculated for insertion into methane and isobutane, if dimethylimidazolylidene **19** is used as a reactant, confirming the impossibility of these reactions. Nevertheless, insertion into acetonitrile is predicted to be strongly favored over insertion into isobutane. Indeed, it has been shown that 1-(1-adamantyl)-3,4-diphenyl-1,2,4-triazol-5-ylidene[29] and *N,N*′-dimesityl-1,3-diazacyclopentan-2-ylidene[30] do undergo insertion into acetonitrile.[31] It is also worth noticing that a closely associated complex of cyanomethanide with the imidazolyl cation can be computed as a minimum in the gas phase with an energy level lower than the barrier for the concerted insertion of **19** into acetonitrile. This suggests that a two-step mechanism initiated by protonation of the carbene may already be more efficient as previously proposed by the experimenters.[29,30,32] Other carbenes that may be used as ligands in organometallic chemistry like cyclopropenylidene[33] (**16**) or the cyclic alkyl amino carbene (CAAC)[34] **18** are already more reactive and show properties similar to those of dimethoxycarbene (**15**). This classification is in accordance with the expectations, since it has already been demonstrated by theory[17,35] and experiment[36] that **16** behaves as a nucleophile.

Stabilized-nucleophilic carbenes are best represented by the category of foiled carbenes.[27,37] They are represented here by

norbornenylidene (**12**) and bicyclo[2.1.1]hex-2-en-5-ylidene (homopyramidane) (**13**) which possess an unequivocal preference for acetonitrile ($\Delta\Delta G^{\ddagger}$ = 8.4 and 9.2 kcal/mol, respectively) and a high activation enthalpy ($\Delta H^{\ddagger}$ = 11 to 31 kcal/mol, $\Delta\Delta G^{\ddagger}$ = 22 to 42 kcal/mol), which is prohibitive in most of the cases, since these alkyl carbenes can still react intramolecularly and form strained alkenes.[27] Therefore, stabilized-nucleophilic carbenes can only be intercepted by extremely effective carbenophiles, e.g., ROH.[38]

The last group is represented by the reactive-nucleophilic carbenes, mainly alkyl carbenes, and by the extremely nucleophilic anionic carboxylate carbene[39] **17**. In contrast to the reactive-electrophilic carbenes, they are usually already less reactive and more selective. Furthermore, quite a few possess a singlet ground state. Among the uncharged carbenes we investigated, the alkenylidenes **11** and **14** have been shown to possess a pronounced nucleophilicity that is due to interactions with the double bond. It is well-known that vinylcarbenes readily rearrange to cyclopropenes.[40] We designed a bicyclic system in order to prevent cyclopropene formation, following the concept of foiled carbenes.[27] Nevertheless, in this case, the carbenes remain reactive with an averaged enthalpy of activation of 3.9 and 4.3 kcal/mol, respectively. The stabilization energy and the singlet−triplet gap also are low (+2.7 and −7.2 kcal/mol, respectively). The intramolecular stability of carbenes **11** and **14** is predicted to be fairly high (12.8 and 19.2 kcal/mol, respectively, for the barrier toward 1,2-H migration). These computed properties suggest that **11** and **14** may be trapped efficiently. Even in these carbenes, the 1,2-H migration occurs through the LUMO.[41] Significant supramolecular interactions are found between **14** and acetonitrile. The complex shown in Figure 3 is more stable by 7.4 kcal/mol than its components. The NBO analysis confirms that the association results from electron donation from the lone pair at the carbenic center into a C−H antibond of acetonitrile. This interaction corresponds to a hydrogen bridge. A similar complex, albeit slightly weaker (ΔH_{298} = −5.6 kcal/mol), is found for the stabilized-nucleophilic carbene **13**. Therefore, in both cases, before the reaction starts, the C−H bond is oriented toward the top of the carbene, i.e., the lone pair. However, the insertions are described as a concerted process by our calculations in the gas phase. Consequently, during the reaction, the CH$_2$CN moiety has to move toward the empty p-orbital (LP*) of the electrophilic species to complete the reaction. As a result, the computed transition states have similar geometries as the ones found for

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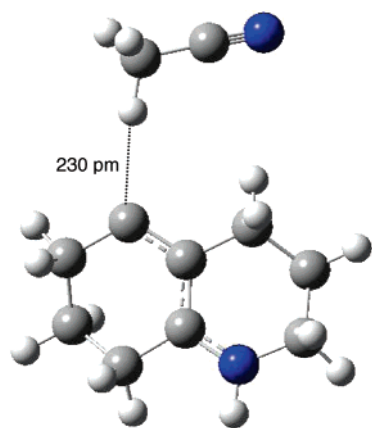
FIGURE 3. Hydrogen bridge between carbene **14** and acetonitrile.

the insertion reactions of dihalocarbenes, although the approaches are different:[14,26] with CCl_2, the beginning of the reaction resembles the abstraction of a hydride by the LP* of the carbene.

In conclusion, a convenient two-dimensional classification of carbenes in their singlet state based on experimental results obtained in silico is suggested. This classification combines the stability and the philicity of the divalent species. In this work, an electrophilic carbene is defined as a species that inserts better into the C—H bonds of isobutane than into acetonitrile. It is worth remembering that carbenes usually are extremely reactive species. Therefore, a carbene that is described here as predominantly nucleophilic is still able to react efficiently as an electrophile, if the reaction partner is a good electron donor (and vice versa). This categorization is confirmed by further investigations concerning the properties of the aforementioned carbenes, namely reactivity toward alkenes and ethers, frontier molecular orbitals, proton affinities, ionization potentials, and stabilization energies. These results will be published soon.

Supporting Information Available: Complete ref 11 and Cartesian coordinates and energies for all relevant stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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