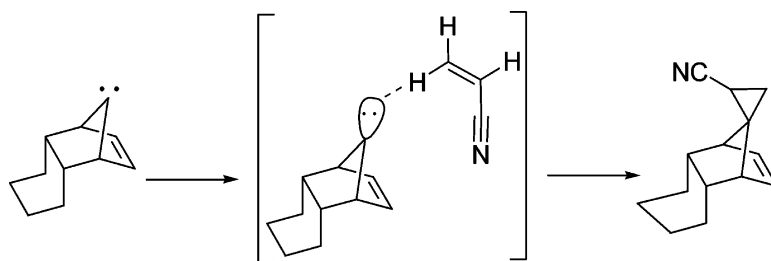


Carbene#Alkene Complexes between a Nucleophilic Carbene and Electron-Poor Alkenes

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Carbene–Alkene Complexes between a Nucleophilic Carbene and Electron-Poor Alkenes[†]

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Abstract: Spirooxadiazoline **5** is a clean thermal source of tricyclo[6.2.1.0^{2,7}]undec-9-en-11-ylidene (**7**), a typical foiled carbene. Species **7** can be trapped efficiently at 165 °C by electron-deficient alkenes like acrylonitrile and fumaronitrile whereby the anti addition products are obtained exclusively. Higher temperatures, however, favor intramolecular reactions. Density functional theory (DFT) calculations predict the formation of a strong complex between both reactants which actually is a minimum on the free energy scale. These results confirm the nucleophilic character of foiled carbenes and the presence of a significant barrier toward rearrangement.

Introduction

A few years ago, we started to reinvestigate the stabilization of carbenic centers resulting from interactions between the divalent carbon and an appropriately positioned C=C double bond by means of modern computational methods.¹ This type of carbene was coined “foiled methylenes” by Gleiter and Hoffmann who took norborn-2-en-7-ylidene (**2**) as prime example.² Although their intramolecular chemistry is quite well-known,³ foiled carbenes have proven to be reluctant toward intermolecular reactions. Indeed, as stabilized nucleophilic carbenes,⁴ their addition to standard alkenes proceeds in extremely low yields (Scheme 1). Moreover, an intermolecular insertion into C–H bonds was not observed. Meanwhile, it has been shown that these carbenes react with methanol by protonation and formation of methyl ethers, to some extent, after rearrangement of the intermediate carbenium ion,⁵ and with diethyl amine after ylide formation.⁶ Recently, we have shown that photolysis of oxadiazoline **5** with 1 equiv of alcohol leads to the exclusive formation of nonrearranged ethers all of which carry the alkoxy group at C(11) away from the double bond.⁷ However, foiled carbenes have still not been efficiently trapped

by alkenes, although this cheletropic reaction is extremely valuable from a mechanistic point of view. Since such an addition is concerted, it offers a unique occasion to obtain meaningful results on the strength of the interactions between the double bond and the carbene center and about control of the stereochemistry of the resulting product. In this study, we will show that foiled carbenes are most efficiently trapped by electron-poor alkenes.

Results and Discussion

Stereoselectivity from Cyclopropanation of *t*-Butylethylene. Moss and Dolling examined the decomposition of tosylhydrazone salt **1** to generate norborn-2-en-7-ylidene (**2**) in the presence of (*Z*)-4-methylpent-2-ene. With 0.067% (thermally) and 0.24% (photolytically)⁸ the yields for the cyclopropane adducts **3** were extremely low. This result is compatible with the concerted addition of a singlet carbene since the *cis* configuration is conserved in the cyclopropane. Later, Moss and Ho investigated the addition of **2** to *t*-butylethylene (3,3-dimethylbut-1-ene) in order to obtain evidence for a participation of the double bond to the stabilization of the carbene.⁹ Earlier in their seminal work, Gleiter and Hoffmann had suggested that bulky substituents should prefer the side anti to the alkene.² However, experimentally, thermolysis of precursor **1** in a glass ampule at 200 °C leads to a strong preference for formation of the product with the *t*-butyl group above the double bond (*syn*/*anti* ratio up to 7:1), i.e., *syn* hydrocarbon **4b**. This quite surprising result at first sight motivated us to analyze this reaction more thoroughly: are these apparently contradictory results compatible with an anchimeric stabilization of the carbene and the transition state?

[†] Carbene Rearrangements. 75. For Part 74 see: Miesusset, J.-L.; Billing, P.; Abraham, M.; Arion, V. B.; Brecker, L.; Brinker, U. H. *Eur. J. Org. Chem.*, DOI: 10.1002/ejoc.200800709.

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Scheme 1

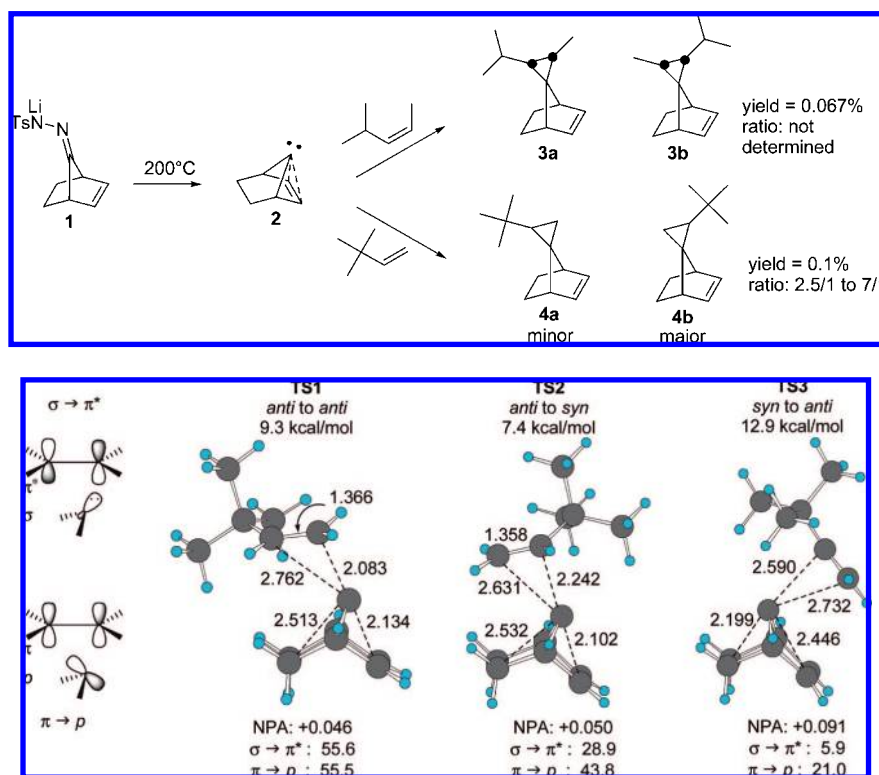


Figure 1. Transition states for the addition of norbornen-7-ylidene to *t*-butylethylene: B3LYP/6-31G(d) geometries and activation energies. Distances are in angstroms, and energies are in kcal/mol. The NPA charge on the *t*-butylethylene unit as well as the major donor interactions between the two units are also given. The quantification was performed by a second-order perturbation theory analysis of the Fock matrix (kcal/mol).

Therefore, we investigated the addition of norbornen-7-ylidene to alkenes by density functional theory (DFT) calculations at the B3LYP/6-31G(d) level of theory. Fortunately, because norbornen-7-ylidene (**2**) is a stabilized species, it belongs to the few carbenes for which a transition state (TS) can be calculated. Further examples can be found with stable phosphinosilylcarbene which adds by a concerted mechanism and presents the properties of a nucleophilic carbene¹⁰ and with difluorocarbene for which the addition may occur stepwise^{11,12} or more classically with dichlorocarbene.¹³ Stabilization can also be reached by ylide formation¹⁴ or complexation with a transition metal like copper.¹⁵ In both cases, the reactivity of the former carbene is modified, usually lowered, so that better selectivities are reached, and these reactions too have an enthalpic barrier.

The conclusions of our DFT calculations are shown in Figures 1 and 2, and they are in agreement as well with Gleiter and Hoffmann expectations as with the experiments. Indeed, the bending of the bridge with the divalent carbon is still pronounced at transition states **TS1–TS3**, a sign that intramolecular electron donation to the carbenic center still occurs. Since the double bond is a much better electron donor than the σ -bonds, the

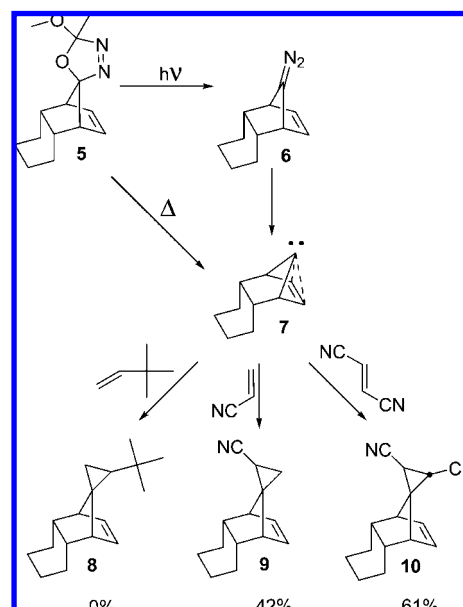


Figure 2. Decomposition of oxadiazole **5** in presence of 3,3-dimethylbut-1-ene, acrylonitrile, and fumaronitrile.

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transition states **TS1** and **TS2** corresponding to an anti approach (anti in relation to the double bond) are lower in energy (9.3 and 7.4 kcal/mol, respectively) than the TS for the syn approach (**TS3**, a syn approach leads to an anti product, 12.9 kcal/mol).¹⁶ However, the most favored TS (**TS2**, anti to syn, 7.4 kcal/mol) leads to the syn product. Indeed, due to steric hindrance, the TS (**TS1**, anti to anti, 9.3 kcal/mol) is higher in energy. Overall, in all cases, at the transition state, the carbene behaves already as an electrophile because alkyl-substituted double bonds are good electron donors but poor electron acceptors. This can be seen from the population analysis which shows that the electron density on the *t*-butylethylene unit is reduced leading to a small positive charge in the range of +0.046 to +0.091 e. These results are confirmed by a second-order perturbation theory analysis of the Fock matrix which reveals that in **TS2** and **TS3**, electron donation from the π -orbital of *t*-butylethylene to the unoccupied p-orbital of the carbene is more significant for the stabilization of the TS than interactions between the filled σ -orbital of the divalent carbon with the antibonding orbital π^* on the alkene unit (see Figure 1).¹⁷ The low absolute values obtained for the TS syn to anti are due to the earliness of this transition state. Since the two molecules are still far off, the interactions are still weak. To our knowledge, this reaction represents *the first example where the addition of the carbene is more advanced at the highest substituted end of the alkene*. Indeed, it has previously been demonstrated that dichlorocarbene attacks propene on the CH₂ group¹⁸ and that difluorocarbene attacks isobutene also on the CH₂ group.^{11a} Of course, the bulkiness of the *t*-butyl group has to be taken into account to explain the reversal of selectivity, but the fact that most alkyl carbenes are less electrophilic and more nucleophilic⁴ than dihalocarbenes is also of prime importance. The transition state is not highly charged; natural population analyses (NPA) show that only a small positive charge arises on the alkene unit, and therefore, the difference in the ability to delocalize the electron deficiency does not play a big role in the stabilization of the transition state.

Reactivity of Foiled Carbenes toward Alkenes. Finally, we resumed the experimental investigation of the addition of foiled carbenes to alkenes with a few modifications in comparison to the early works. First of all, the precursor was changed. Tosylhydrazone salts are insoluble in most organic solvents and are therefore not really suited for intermolecular reactions. Instead, a photolysis with oxadiazoline¹⁹ **5** in 3,3-dimethylbut-1-ene was performed. However, at room temperature **8** could not be detected. If one considers the high free energy barrier (7.4 kcal/mol, $\Delta G_{298} = 20.1$ kcal/mol) calculated for the cyclopropanation, this is not unexpected. Even more so, for an

alkyl carbene which may undergo competing intramolecular reactions, this is prohibitive. Indeed, norborn-2-en-7-ylidene is known to rearrange to bicyclo[3.2.0]hepta-1,6-diene^{3a} by overcoming a barrier of only 11.0 kcal/mol ($\Delta G_{298} = 11.3$ kcal/mol).^{1c} Therefore, in order to minimize the entropy effect, the photolysis of **5** was repeated in a cooling bath at -110 °C. However, even at this low temperature, cyclopropane **8** was not formed.

Since foiled carbenes are predicted to be nucleophilic,^{1c,d} it may be appropriate to try to trap them with an electron-deficient alkene. And indeed, this reaction was successful! We were able to trap carbene **7** efficiently at 165 °C with acrylonitrile (yield 42%) and fumaronitrile (61%). The remaining material consists of polymeric products probably derived from an intramolecular reaction product of **7**. One of the major issues to perform this reaction is the choice of the precursor. However, all precursors that first decompose to a diazo compound are unsuitable because diazo compound **6** would be trapped by the double bond of the aforementioned reagents resulting in pyrazoline formation. Therefore, oxadiazoline **5** cannot be employed for photochemical experiments. But **5** can be used for thermolyses because it is known that it decomposes exclusively to foiled carbene **7** through a very labile carbonyl ylide⁷ that cannot be intercepted. Indeed, under these conditions a [3 + 2] cycloaddition between the carbonyl ylide and the alkene did not take place; no tetrahydrofuran derivative was formed, and solely carbene **7** was trapped by the alkene. And in contrast to the earlier reaction with *t*-butylethylene (see above), with the electron-deficient alkenes employed the anti product was formed exclusively. The stereochemistry was assigned with the help of 2D NMR experiments, especially from the cross peaks in the NOESY (nuclear Overhauser enhancement spectroscopy) spectrum.

The calculations shown in Figure 3 help us to better understand this difference in reactivity. For the addition to acrylonitrile, a large difference in the energy barriers is predicted between the TS leading to the anti product (**TS6**, -0.4 kcal/mol) and the TS leading to the syn product (**TS7**, 6.4 kcal/mol). The facile formation of the anti product corresponds to a nucleophilic transition state as can be seen from the negative charge on the acrylonitrile fragment. This is confirmed by the results of the natural bond order (NBO) analysis ($\sigma \rightarrow \pi^* = 34.4$ kcal/mol²⁰ vs $\pi \rightarrow p = 20.7$ kcal/mol) and from the large distance between the carbenic carbon and C(2) of acrylonitrile (2.877 Å). These facts are best explained by the good ability of the cyano group to stabilize a negative charge in α -position. The short C(2)–C(7) distance (1.979 Å) in the norbornenylidene unit shows that the electron deficiency of the carbenic center still is mainly stabilized intramolecularly. On the contrary, the data gathered for the TS leading to the syn product (**TS7**) reveal that the attack of the carbene on the substituted carbon already possess a high electrophilic character: the NPA charge on acrylonitrile is very small (-0.06 e). **TS7** is a late TS if one considers the intramolecular stabilizing interaction between the double bond and the divalent carbon atom resulting in a short C(2)–C(7) distance (2.074 Å). Most notably, the donor–acceptor interactions are of similar strength in both directions ($\sigma \rightarrow \pi^* = 52.8$ kcal/mol vs $\pi \rightarrow p = 49.7$ kcal/mol). This means, that

(20) In stabilized carbenes, the p-orbital is already partly filled because of intramolecular electron donation. Therefore, during cyclopropanation, electron density can also flow from the p- to the antibonding π -orbital of the alkene. For norbornenylidene, about three-quarters of the interactions arise from donation of the σ -orbital into the π^* -orbital; the rest comes from the p-orbital.

(16) Despite many attempts, we could not find the fourth TS (syn to syn), probably because of excessive steric hindrance.

(17) For the purpose of clarity, the usual designations σ , p, π , and π^* are used for the description of the orbitals involved in carbene–alkene interactions to present the results of the NBO analysis instead of the notation commonly used by NBO. Therefore, LP corresponds to σ , LP* to p, BD(2) to π , and BD*(2) to π^* .

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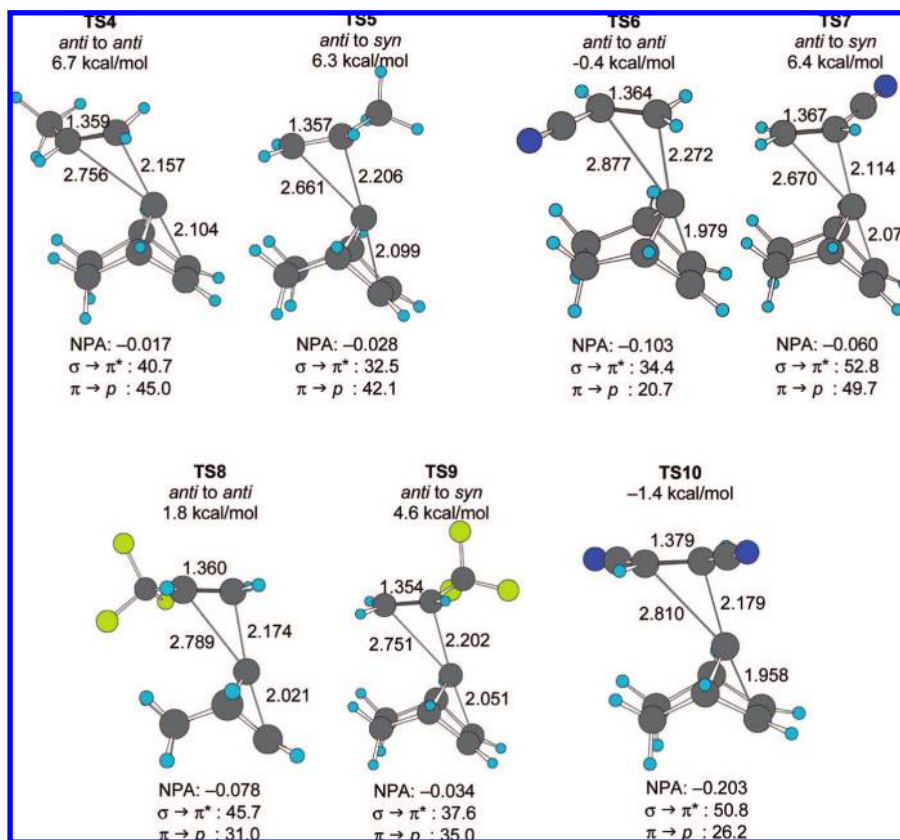


Figure 3. Transition states for the addition of norbornen-7-ylidene to propene (TS4 and TS5), acrylonitrile (TS6 and TS7), trifluoromethylethylene (TS8 and TS9), and fumaronitrile (TS10): B3LYP/6-31G(d) geometries and activation energies. Distances are in angstroms, and energies are in kcal/mol. The NPA charge on the alkene unit as well as the major donor–acceptor interactions between the two units are also given. The quantification was performed by a second-order perturbation theory analysis of the Fock matrix (kcal/mol).

by an attack on C(2), acrylonitrile is a poor electron acceptor, and therefore, this pathway is strongly disfavored in comparison to the attack on C(3). Similar results are obtained for the addition to fumaronitrile (TS10) and to trifluoromethylethylene (TS8 and TS9). The latter is also predicted to give exclusively the anti product. In contrast, with propene (TS4 and TS5), a mixture is expected in which the syn addition product dominates resulting from addition on the highest substituted carbon. This all shows that for the prediction of stereoselectivity not only electronic but also steric effects have to be considered.

Carbene–Alkene Complexes. The negative activation energies computed suggest that noncovalent interactions may exist between carbene and trapping reagent. Figure 4 shows the results from our search for the most stable arrangement between norborn-2-en-7-ylidene (**2**) and alkenes. Indeed, an interesting complex (Cx4) was found with fumaronitrile. The two molecules are held together by a strong hydrogen bond resulting in an energy gain of 9.4 kcal/mol. Even on the free energy scale, this complex is still a minimum ($\Delta G_{298} = -0.7$ kcal/mol). Although this study has revealed that fumaronitrile belongs to the few alkenes which react with norbornenylidene derivatives, complex Cx4 is predicted to have a significant lifetime because the energy barrier toward the formation of a cyclopropane is quite high (TS10 is 8.0 kcal/mol higher in energy than Cx4). This high barrier is due to the fact that the two processes require totally different orientations. The complex results from electrostatic dipole–dipole interactions assisted by electron donation into the C–H antibond,²¹ but carbenes are reluctant toward insertion into the C–H bonds of alkenes. For the cyclopropanation, the two species have to rotate by 90° with complete breaking of

the hydrogen bond, and therefore, the complex is relatively stable. Rotation around the hydrogen bond is almost free, and consequently, other complexes with similar energy can be found. With tricyanoethylene, an even stronger complex is predicted (Cx5, -12.4 kcal/mol) with a short distance between the carbenic center and the hydrogen of tricyanoethylene (2.098 Å).

On the opposite of the alkene reactivity scale, alkenes bearing no electron-withdrawing groups do not form complexes. The gain in energy by the association of norbornenylidene with (*Z*)-butene is small (Cx2, -1.2 kcal/mol), and the C(7)–H distance is large (2.670 Å). A comparison with the complex with (*E*)-butene (Cx1, -2.8 kcal/mol for two hydrogen bonds) shows that the stabilization is even stronger with the ubiquitous aliphatic C–H bonds. The formation of carbene alkene complexes, especially π -complexes with electrophilic chlorocarbenes, has often been proposed²² to explain the results of kinetic experiments, but the actual consensus seems to be that they do not exist.^{13,23} Therefore, the hydrogen-bonded complexes between a nucleophilic carbene and an electron-deficient alkene presented in this paper represent the sole examples for this new type of noncovalent interaction. In a closely related field,

(21) As a carbene, norbornenylidene possesses a significant dipole moment (2.44 D, see the Supporting Information). Therefore, the specific geometry found for the complex is due to an additional stabilization resulting from dipole–dipole interactions which favors an antiparallel orientation of the dipole of the carbene and of the alkene (Supporting Information, p S15). The stabilization is also partly due to dipole–induced dipole interactions (Supporting Information, p S16).

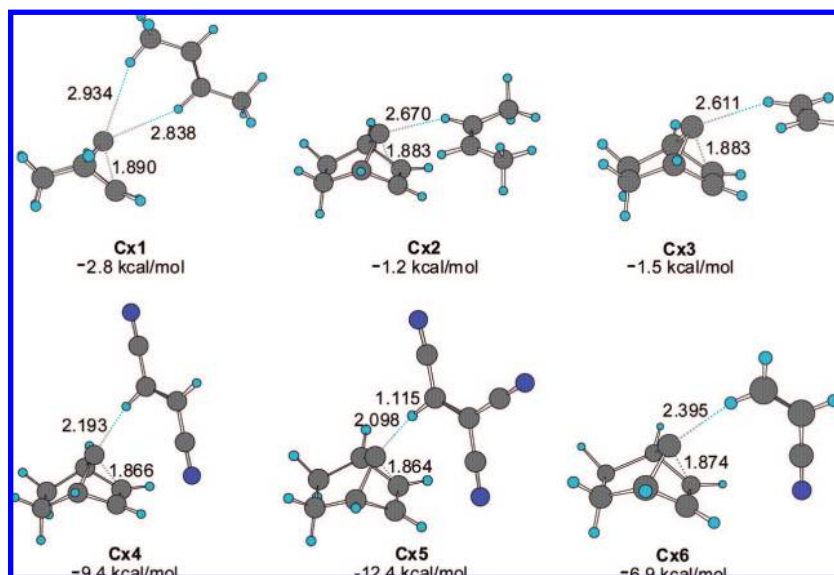


Figure 4. Complexes between norbornen-7-ylidene (**2**) and (*E*)-butene (**Cx1**), (*Z*)-butene (**Cx2**), ethene (**Cx3**), fumaronitrile (**Cx4**), tricyanoethylene (**Cx5**), and acrylonitrile (**Cx6**). Energy gains are in kcal/mol, and distances are in angstroms.

recently, spectroscopic evidence has been obtained for complexes between carbenes and aromatic compounds.²⁴

Conclusion

The results obtained from this investigation confirm the hypothesis that norborn-2-en-7-ylidene derivatives are stabilized nucleophilic⁴ carbenes with a significant lifetime. Addition to electron-rich alkenes is in fact difficult to achieve, but cyclopropanation of electron-deficient alkenes occurs readily even at 165 °C. In all cases, the alkene approaches the carbene from the side anti to the double bond. With electron-poor alkenes, the anti product is formed exclusively, whereas with electron-rich alkenes the formation of the syn compound is favored. This shows that for the prediction of the stereoselectivity of the reaction between a carbene and an alkene, steric and electronic effects have to be taken into account.

Computational Methods

The Gaussian 03 program²⁵ was used for DFT calculations, employing Becke's²⁶ three-parameter hybrid method and the

exchange functional of Lee, Yang, and Parr (B3LYP).²⁷ Geometries were optimized at the B3LYP/6-31G(d) level of theory. The stationary points were characterized by vibrational analysis. All reported energies include zero-point corrections. The zero-point vibrational energies (ZPE) were scaled by a factor of 0.9806 for B3LYP/6-31G(d).²⁸ Unless otherwise stated, all values in the text refer to B3LYP/6-31G(d) calculations. The B3LYP method is used without counterpoise correction for the basis set superposition error (BSSE).²⁹ This is quite reliable for the computation of complexes and gives results similar to the ones obtained with MP2 and the new hybrid meta-DFT method MPWB1K,³⁰ although the calculated interaction energies are slightly lower and the intermolecular distances slightly larger than the values obtained with the two latter methods.^{13,29,31} The usage of B3LYP is questionable only for weak interactions because it does not take into account contributions from the dispersion energy. Therefore, the intermolecular interaction energies presented here can be considered as lower limits.

Experimental Part

General Experimental Methods. Melting points are uncorrected. ¹H and ¹³C NMR spectra were recorded on a 400 MHz spectrometer. The chemical shifts at $\delta = 7.26$ and 77.0 ppm of CHCl₃ were used as internal standards for ¹H and ¹³C spectra. Conventional 2D COSY (correlation spectroscopy), NOESY, HMBC (heteronuclear multiple bond correlation), and HMQC (heteronuclear multiple quantum correlation) spectra were used to derive proton and carbon assignments.

anti-Spiro[cyclopropane-1,11'-endo-tricyclo[6.2.1.0^{2,7}]undec-9-ene]-2-carbonitrile (9). Oxadiazoline **5**⁶ (300 mg, 1.206 mmol) was dissolved in 8 mL of acrylonitrile and stirred overnight at 165 °C in a pressure tube. After removal of the solvent, the crude product was submitted to column chromatography with hexane/ethyl acetate (195/5) as eluent. Yield: 101 mg (0.508 mmol, 42%). Mp = 69–70 °C. ¹H NMR (400 MHz, CDCl₃): δ 6.22 (dd, *J* = 6.0, 3.0 Hz, 1H), 6.18 (dd, *J* = 6.0, 2.7 Hz, 1H), 2.49 (t, *J* = 3.1 Hz, 1H), 2.29 (dddd, *J* = 17.0, 13.4, 9.0, 3.9 Hz, 1H), 2.14 (br s,

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1H), 2.12 (dddd, $J = 17.0, 13.4, 9.0, 3.9$ Hz, 1H), 1.64–1.58 (m, 2H), 1.51–1.34 (m, 4H), 1.32 (dd, $J = 8.1, 5.4$ Hz, 1H), 1.16 (d, $J = 8.5$ Hz, 1H), 1.16 (d, $J = 5.4$ Hz, 1H), 0.98–0.84 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 135.0, 134.8, 120.5, 50.9, 49.9, 39.2, 38.5, 22.7, 22.6, 20.0, 19.9, 14.6, 5.3 ppm (quaternary spiro C atom is missing). IR: 3060, 2935, 2864, 2233, 1568, 1460, 1334 cm^{-1} . MS (70 eV) m/z (%): 199 (M^+ , 4), 172 (2), 171 (2), 159 (3), 146 (7), 117 (100), 91 (13), 81 (22). HRMS (70 eV) calculated for $\text{C}_{14}\text{H}_{17}\text{N}$, 199.1361; found, 199.1354.

***rac*-(2*R*,3*R*,1'*R*,2'*R*,7'*S*,8'*S*)-Spiro[cyclopropane-1,11'-tricyclo[6.2.1.0^{2,7}]undec-9-ene]-2,3-dicarbonitrile (10).** Oxadiazoline **5⁶** (252 mg, 1.016 mmol) and fumaronitrile (3.12 equiv, 259 mg, 3.170 mmol) were dissolved in 3 mL of toluene and stirred overnight at 165 °C in a pressure tube. After removal of the solvent, the crude product was submitted to column chromatography with hexane/TBME (85/15) as eluent. Yield: 138 mg (0.616 mmol, 61%). $\text{Mp} = 148\text{--}149$ °C. ^1H NMR (400 MHz, CDCl_3): δ 6.30 (dd, $J = 5.9, 3.0$ Hz, 1H), 6.25 (dd, $J = 5.9, 3.0$ Hz, 1H), 2.60 (br s, 1H), 2.57 (br s, 1H), 2.31–2.21 (m, 1H), 2.21–2.11 (m, 1H), 2.09 (d,

$J = 4.5$ Hz, 1H), 2.01 (d, $J = 4.5$ Hz, 1H), 1.68–1.61 (m, 2H), 1.53–1.45 (m, 2H), 1.44–1.35 (m, 2H), 1.01–0.88 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 135.1, 134.1, 116.7, 115.9, 54.3, 49.5, 49.1, 38.34, 38.32, 22.3, 22.2, 19.7, 19.6, 13.7, 12.2 ppm. IR: 3034, 2938, 2904, 2866, 2239 cm^{-1} . MS (70 eV) m/z (%): 224 (M^+ , 18), 197 (5), 182 (6), 168 (7), 142 (16), 115 (16), 91 (15), 82 (100), 67 (69). HRMS (70 eV) calculated for $\text{C}_{15}\text{H}_{16}\text{N}_2$, 224.1313; found, 224.1307.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for all new compounds, Cartesian coordinates and energies for all relevant stationary points, and complete ref 25. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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