

## On the Reaction of Diaminocarbenes with Aroylimines

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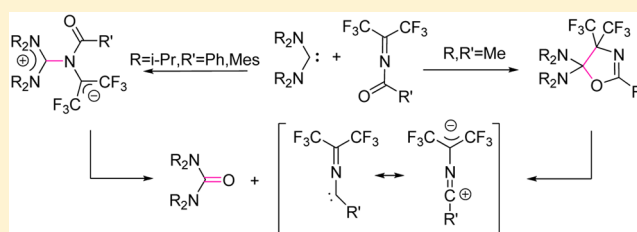
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### Supporting Information

**ABSTRACT:** Several possible reaction pathways are analyzed for the recently studied experimental reaction of diaminocarbenes with aroylimines, where the carbene acted as an oxygen-abstracting agent. A number of structures corresponding to local minima and transition states are located by geometry optimization. In contrast to the more recent interpretation of the mechanism of this process, the reaction does not proceed via the direct formation of the corresponding carbonyl ylide resulted from the electrophilic addition of diaminocarbene to the carbonyl oxygen atom. Two other, more favorable pathways were predicted instead: the nucleophilic attack of the carbene lone pair on the imino nitrogen (pathway "a") or on the carbon atom in the C=N moiety of aroylimine (pathway "b"), in agreement with predictions of the frontier molecular orbital (FMO) theory. Both intermediate adducts undergo a subsequent decomposition onto nitrile ylide and urea. Which of the two pathways becomes preferential depends on the nature of the substituents: pathway "a" is more favored for the experimentally studied species, whereas pathway "b" is thermodynamically preferable for the small-sized model structures.



## INTRODUCTION

Unique chemical properties of carbenes have provided their wide application in synthetic organic chemistry as reagents and versatile ligands for preparing efficient metal complex catalysts.<sup>1–8</sup> In recent years, nucleophilic N-heterocyclic carbenes (NHCs) have also been widely used as catalysts of different chemical reactions,<sup>9–25</sup> in particular, for syntheses using carbonyl compounds as starting materials.<sup>26–36</sup> The energy profiles of the benzoin condensation for the reactions catalyzed by imidazol-2-ylidene, triazol-5-ylidene, and thiazol-2-ylidene have been investigated theoretically by Nyulászi et al.<sup>37</sup> It is also known that the reaction of carbonyl compounds with electrophilic carbenes leads to an intermediate formation of carbonyl ylides,<sup>38,39</sup> which are very reactive species and quickly undergo further transformations, for example, participate in 1,3-dipolar addition.<sup>40</sup> The electronic structure of carbonyl ylides and their reactivity have been investigated theoretically.<sup>41</sup> Even less is known about the reactions of carbonyl compounds with nucleophilic carbenes, which demonstrate quite different reactivity.<sup>42–54</sup> For example, in the reaction with fumaric acid dimethyl ester, 1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene joined to the carbon atom in  $\alpha$ -position to the carbonyl moiety forming the carbon–carbon double bond.<sup>42,43</sup> The same carbene reacted with acetylenedicarboxylic acid dimethyl ester at the  $\alpha$ -position yielding an adduct in a 1:2 ratio.<sup>43</sup> The imidazol-2-ylidene in the reaction with halides of carboxylic acids nucleophilically substituted halogens,<sup>45</sup> whereas in

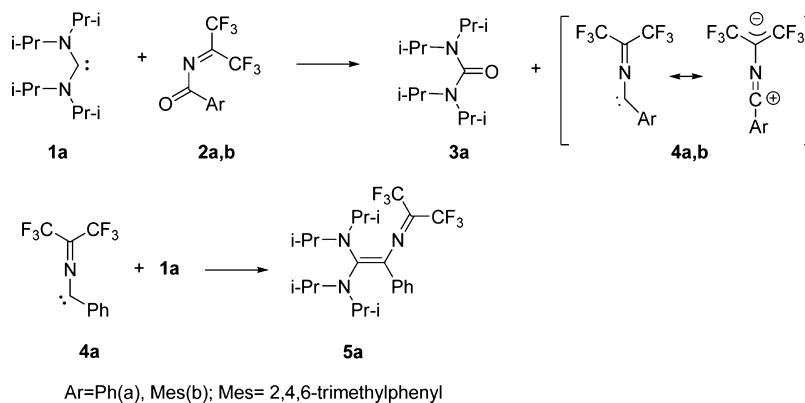
reactions with 5-bromo- or 5,5-dibromo-derivatives of 2,2-dimethyl-[1,3]dioxane-4,6-dione it behaved as a proton- or brom-abstracting agent.<sup>46</sup> In 2007 Polyakov and Shevchenko reported on the insertion of Alder's bis(diisopropylamino)-carbene into the O–(CO) bond of phthalic anhydride,<sup>49</sup> and Jeong et al. introduced 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene in a similar reaction with  $\beta$ -propionic lactone.<sup>52</sup> Finally, several examples are known regarding forming stable products from the direct nucleophilic addition of carbenes to carbons of the ketone carbonyl groups.<sup>50,54</sup>

Recently, some of us have reported on a quite unusual type of carbene reactivity.<sup>55,56</sup> In the reaction with aroylimines **2a,b**, diaminocarbene **1a** acts as the oxygen-abstracting agent (Scheme 1, top). Presumably, the nitrile ylide **4a** is formed intermediately and then it reacts with the second mole of diaminocarbene (Scheme 1, bottom) yielding product **5a**, or undergoes some side chemical transformations. The mechanism proposed for the formation of **4a** has included a formation of carbonyl ylide,<sup>55,57</sup> but electrophilic reactivity is still *hitherto* unknown for Alder's diaminocarbenes. A thorough theoretical study might provide a proper understanding of the reaction pathway and a prospective expansion of the synthetic usage of the nucleophilic carbenes.

Received: September 19, 2014

Published: December 30, 2014

Scheme 1. Reaction of Diaminocarbene 1a with Aroylimines 2a,b



The main aim of the current work is to elucidate the mechanism of the reaction of diaminocarbenes with aroylimines by studying its potential energy surface (PES). As the reaction was carried out experimentally in less polar benzene, the gas-phase approximation used for quantum chemical calculations is quite acceptable.

### CALCULATION DETAILS

All the structures corresponding to the energy local minima were fully optimized without symmetry constraints using the GAUSSIAN-09 program set<sup>58</sup> at the M06-2X/6-311++G\*\* approximation level.<sup>59–61</sup> Vibration frequencies were calculated analytically. No imaginary vibrations for the local minima were found, yet one imaginary vibration for the transition state structures was. The relaxed potential energy surface scans along the reaction coordinates were carried out using the BP86 DFT functional<sup>62,63</sup> in combination with the smaller 6-31G\* basis sets.<sup>64–66</sup> The loose geometry convergence criterion and middle integration grid were used for higher performance. All the transition state (TS) structures were then located at the BP86/6-311++G\*\* approximation level using the structures, corresponding to energy maxima at the reaction coordinate, as starting geometries. First, the force constants were calculated for these structures at the BP86/6-31G\* level of theory, and then the optimization routine was continued using the larger 6-311++G\*\* standard basis set and the option *Opt=(ReadFC,TS)*. The tight optimization convergence criteria and fine grid (*Int=UltraFine*) were used for the final stage of calculations. The transition state structures were then reoptimized at the M06-2X/6-311++G\*\* level of theory.

The NBO<sup>67–70</sup> program implemented into the GAUSSIAN-09 set of program was used for calculations of atomic charges. The Jmol<sup>71</sup> program was used for the graphical presentation of the optimized structures. Molecular orbitals were derived using the gOpenMol<sup>72</sup> program from the density matrix generated at the HF/6-31G\* level of theory using the equilibrium structures optimized at the M06-2X/6-311++G\*\* approximation level.

### RESULTS AND DISCUSSION

The reaction pathways can often be predicted using the frontier molecular orbital (FMO) theory.<sup>73</sup> The highest occupied molecular orbital (HOMO) of the model bis(dimethylamino)-carbene 1c (Figure 1) is mainly the carbenic lone pair ( $E^{\text{HOMO}} = -8.11$  eV), and the lowest unoccupied molecular orbital (LUMO) is the p-orbital at C<sup>carb</sup>, the methylenic carbon atom ( $E^{\text{LUMO}} = 5.95$  eV), which agrees well with the previous theoretical study.<sup>74</sup> In turn, the antibonding LUMO of the model aroylimine 2c, localized mainly at the N=C moiety, is significantly lower in energy (2.08 eV) than the LUMO in 1c and, hence, can efficiently interact with the HOMO of carbene. The HOMO of aroylimine 2c mainly includes the oxygen and

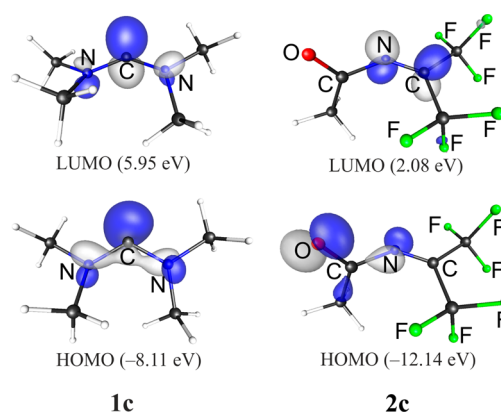
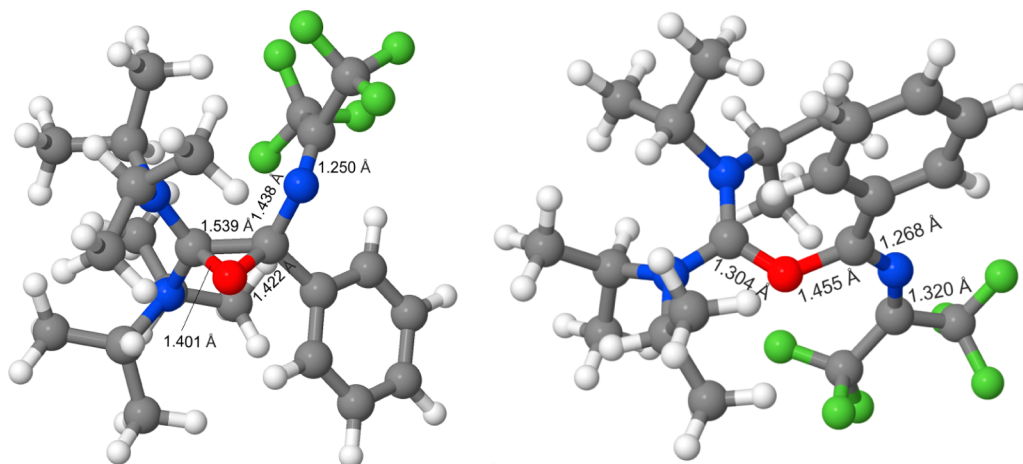
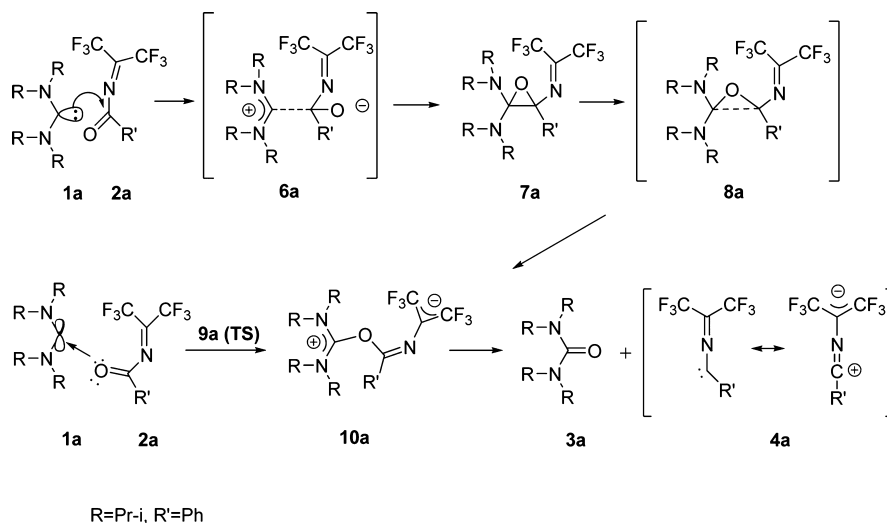


Figure 1. gOpenMol plot of the frontier molecular orbitals (RHF/6-31G\*/M06-2X/6-311++G\*\*) for 1c and 2c with corresponding orbital energies.

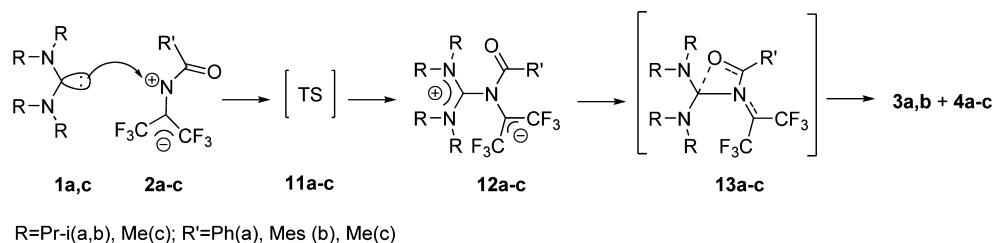
nitrogen lone pairs. It lies deeply in energy ( $E^{\text{HOMO}} = -12.14$  eV) and will interact less effectively with the high-lying LUMO of 1c. Thus, the qualitative FMO analysis predicts the nucleophilic behavior for diaminocarbene 1c in the reaction of interest, whereas the alternative electrophilic attack seems to be less probable. Nevertheless, a comprehensive analysis of the potential energy surface (PES) for these different reaction pathways is necessary to properly understand the reaction mechanism.

For reasons of clarity, let us begin with the analysis from the reaction pathways, which refer to the behavior of the carbonyl compounds in related reactions and do not match the conclusions based on the FMO approach. The first reaction pathway is the nucleophilic attack of bis(diisopropylamino)-carbene 1a on the electron-poor carbonyl carbon in 2a (Scheme 2, top), resulting in adduct 6a. This interaction would be similar to the first stage of the carbene-catalyzed benzoin condensation.<sup>37</sup> However, geometry optimization starting from adduct 6a results in oxirane structure 7a (Figure 2). Similar reactivity was predicted recently for the aroylimines in the reaction with phosphorus(III) nucleophiles.<sup>75</sup> However, 7a is even less stable than the separate starting molecules, 1a and 2a ( $\Delta G = +18.4$  kcal/mol). In turn, 6a can only be located as the transition state (TS) structure with high activation energy ( $\Delta G = +49.0$  kcal/mol). The next TS structure 8a is related to the C–C bond dissociation in the oxirane ring in 7a. It proceeds via an intermediate formation of the corresponding carbonyl ylide 10a (Figure 2), which is the local minimum in

Scheme 2. Two Less Probable Mechanisms of the Reaction of 1 with 2



**Figure 2.** Jmol plots of the optimized structures **7a** (left) and **10a** (right). Color code here and in the following Figures: C in gray, H in white, N in blue, O in red, and F in green.

Scheme 3. Nucleophilic Addition of Carbenes **1** to Aroylimines **2** at Imino-nitrogen

energy ( $\Delta G = -7.8$  kcal/mol). The calculated activation energy values for **8a** relative to starting compounds **1a** and **2a** ( $\Delta G = +24.7$  kcal/mol) are approximately 6 kcal/mol higher than the energy values predicted for **7a**. As our calculations indicate, during the next stage carbonyl ylide **10a** (Figure 2) easily decomposes into **3a** and nitrile ylide **4a** via TS **16a** (*vide infra*, Figure S1 in the Supporting Information) with a low activation energy ( $\Delta G = +4.5$  kcal/mol relative to **10a**).

It is worthy to note that other conformations of **7a** and **10a** have also been located by geometry optimization (see the Supporting Information, structures **7a'**, **10a'** and **7a''**, **10a''**). However, **7a** arises directly from the reaction between the most

favorable conformations of **1a** and **2a**, whereas **7a'** ( $\Delta G = -1.0$  kcal/mol relative to **7a**) and **7a''** ( $\Delta G = -7.2$  kcal/mol) are the conformational isomers of **7a**. They can be formed via rotation of *i*-Pr group(s) in adduct **7a** or in the source carbene **1a**, before the reaction. Similarly, **10a'** is significantly more stable than **10a** (by 6.1 kcal/mol) and can be formed as the last intermediate preceding the final stage of decomposition into **3a** and **4a**, whereas **10a''** is slightly less favored than **10a'** (by 1.6 kcal/mol). However, such isomerization represents a side process and it should be considered independently from the formations of the adducts studied here.

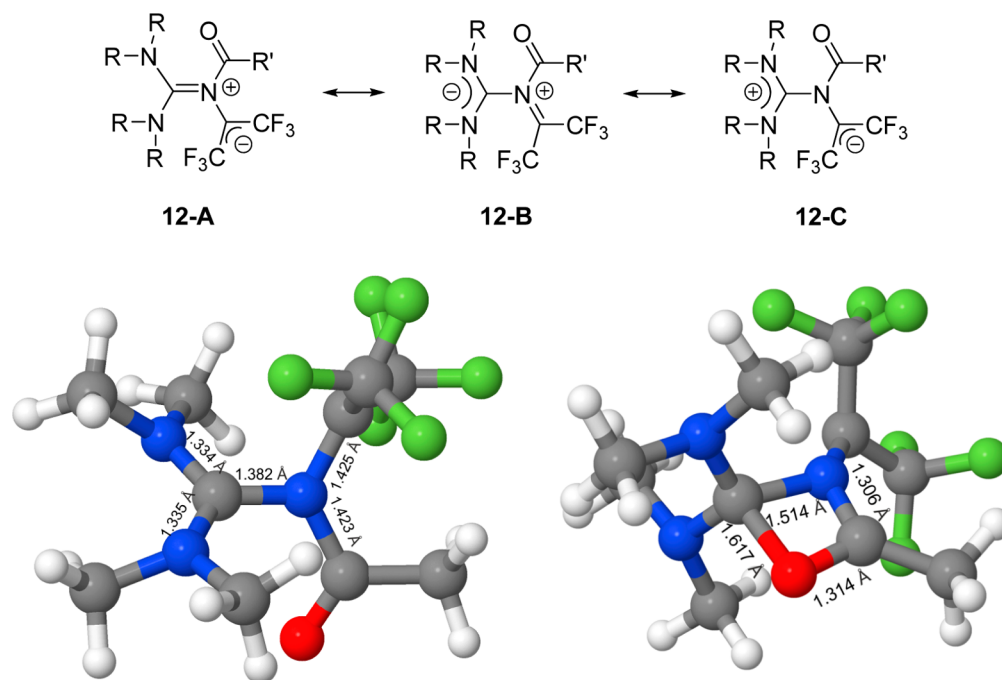
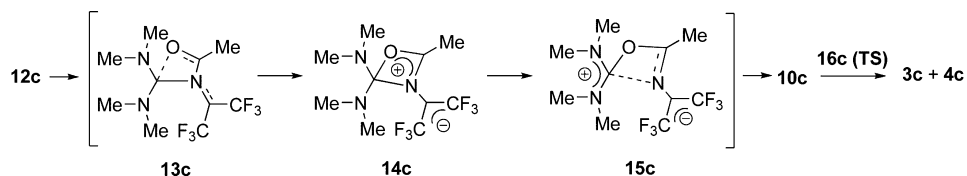


Figure 3. Jmol plots of the optimized model structures 12c (left) and 13c (right).

#### Scheme 4. Detailed Description of Transformation of 12c to 3c and 4c



An alternative reaction pathway (Scheme 2, bottom) is based on the previously suggested electrophilic behavior of diaminocarbene:<sup>55,57</sup> the lone pair on the carbonyl oxygen in 2a nucleophilically attacks the vacant p-orbital of carbene 1a forming 10a. However, the high activation energy predicted for the corresponding TS 9a ( $\Delta G = +37.9$  kcal/mol) is in contradiction with the previously studied reactions, spontaneously proceeding in the experiment at room temperature.<sup>55–57</sup>

Therefore, two other, FMO-controlled reaction pathways should be considered instead. As already noticed above, in the model aroylimine 2c, the atomic orbitals of the carbon and nitrogen atoms in the C=N moiety contribute most strongly into the LUMO. Hence, both of these atoms can serve as electrophilic attractors in the reaction with diaminocarbenes. The nucleophilic attack on the imino-nitrogen in 2a provides substituted guanidine 12a as the first intermediate, which was located as the true local minimum in energy. The following transformations of 12a result in the direct formation of urea 3a and nitrile ylide 4a (Scheme 3). In the experiment, intermediately formed 4a reacts with the second mole of 1a yielding 5a (Scheme 1). Our calculations predict that the latter stage is strongly exergonic ( $\Delta G = -43.0$  kcal/mol) and probably can serve as the energy source for the previous, less favored processes. To make the reaction pathway more transparent and to avoid the conformational ambiguity mentioned above, we have studied it for the simpler model species. The relaxed potential energy surface scans along the reaction coordinate by using the parent diaminocarbene

$\text{H}_2\text{N}-\text{C}(\cdot)-\text{NH}_2$  resulted in a spontaneous NH proton migration; therefore, bis(dimethylamino)carbene 1c and methyl substituted amide 2c were used instead. The corresponding adduct of the reaction of 1c with 2c (12c, Figure 3) has been located by geometry optimization as the deeply lying true local minimum at the reaction pathway ( $\Delta G = -31.7$  kcal/mol). The reaction proceeds via TS 11c with a rather low activation Gibbs free energy (Figure S2,  $\Delta G = +10.5$  kcal/mol).

In compound 12c, C<sup>carb</sup>-NMe<sub>2</sub> bonds in the carbenic moiety (1.334 and 1.335 Å) are significantly shorter than the C<sup>carb</sup>-N(CO) bond (1.382 Å), which excludes a substantial contribution from Lewis structure 12-A. The dominating Lewis structure 12-B would mean donation of the imino-nitrogen  $\sigma$ -lone pair into the formally vacant p-orbital of the carbene carbon atom and provide the pyramidal configuration for the latter, which is not observed in our case: in the corresponding equilibrium structure the carbon atom is almost ideally planar ( $\Sigma \angle \text{NC}^{\text{carb}}\text{N} = 359.9^\circ$ ). Noteworthy, the C(CF<sub>3</sub>)<sub>2</sub> moiety bonded to the electronegative nitrogen atom is still negatively charged ( $-0.57e$ , calculated using the NBO method), supporting the Lewis structure 12-C. Additionally, the (F<sub>3</sub>C)<sub>2</sub>C=N bond is significantly elongated (1.423 Å), and the planes involving the N-C(=O) and C(CF<sub>3</sub>)<sub>2</sub> moieties are mutually almost orthogonal. Therefore, 12-C is probably the most correct representation of the charge distribution in 12.

The final stage of the reaction, the C-N/C=O-rearrangement of the model adduct 12c consists of three computationally separable steps (Scheme 4, Figure S3 in the Supporting



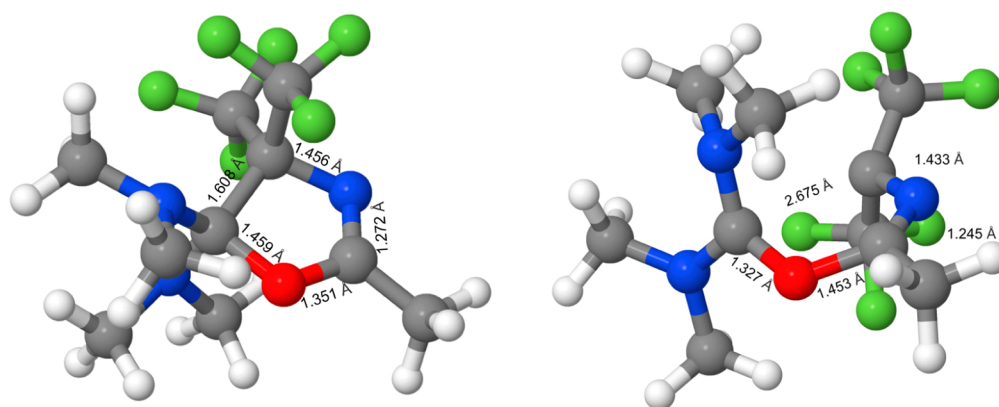


Figure 4. Jmol plots of the optimized structures **18c** (left) and **20c** (right).

Scheme 5. Nucleophilic Addition of Carbenes **1** to Acylimines **2** at the C=N Carbon

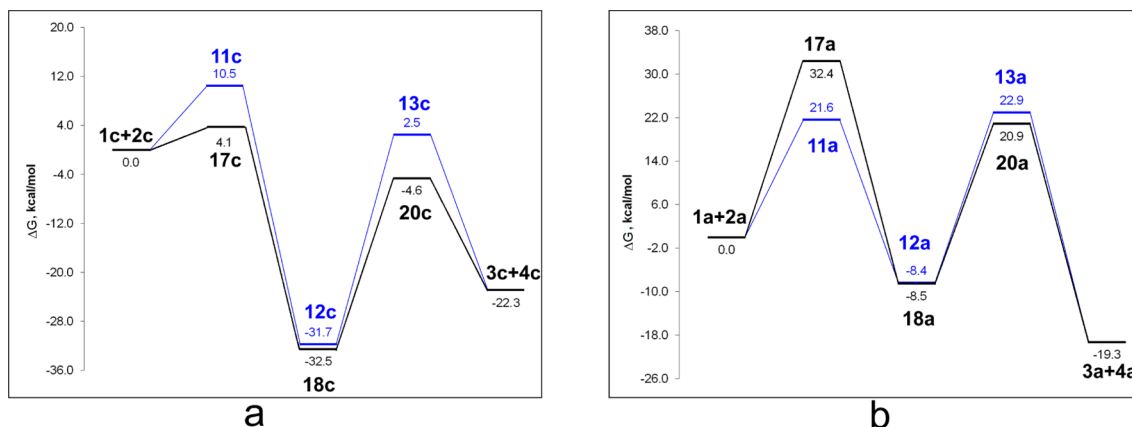
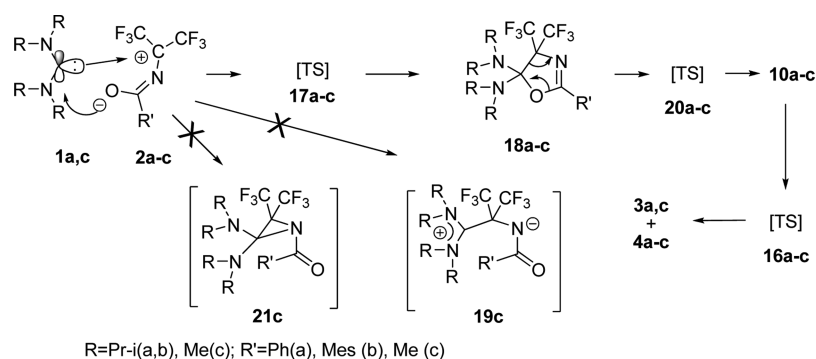


Figure 5. Two possible reaction pathways presented in Scheme 3 (in blue) and Scheme 5 (in black) for interactions **1c+2c** (a) and **1a+2a** (b).  $\Delta G$  values are given in kcal/mol. Structures **10a,c**, **13c–15c**, and **16a,c** are omitted for clarity.

Information). The first one leads to the formation of four-membered cyclic structure **14c**, corresponding to the shallow minimum in energy ( $\Delta G = +31.2$  kcal/mol relative to **12c**) via TS structure **13c** (Figure 3). The latter possesses the highest energy at the reaction pathway ( $\Delta G = +34.2$  kcal/mol), but the corresponding  $\Delta G$  value is only slightly above the sum of the Gibbs free energies of starting **1c** and **2c** species ( $\Delta G = +2.5$  kcal/mol, which is within the calculation errors). The next TS **15c** corresponds to the four-membered heterocycle splitting resulting in the formation of carbonyl ylide **10c**. Though **10c** is still more favored relative to the starting reactants, **1c** and **2c** ( $\Delta G = -11.3$  kcal/mol), the rearrangement **12c**  $\rightarrow$  **10c** is overall unfavorable ( $\Delta G = +20.5$  kcal/mol). For the dissociation of **10c** into **3c** and **4c** low activation energy is

necessary ( $+3.1$  kcal/mol, TS **16c**), and though the formation of the reaction products is exergonic, compared to **1c** and **2c** ( $\Delta G = -22.3$  kcal/mol), but it is still unfavorable in relation to **12c** ( $\Delta G = +9.4$  kcal/mol). Thus, the formation of **4c** as the product can be driven by its subsequent favorable transformations (for instance by the addition of the second molecule of diaminocarbene), or **12c** will remain the final product of the reaction.

The computational study of the nucleophilic attack on the carbon atom of the C=N moiety yields cyclic derivative **18c** (Figure 4) as the local minimum in energy (Scheme 5). Our calculations predict for **18c** the lowest energy at the reaction pathway ( $\Delta G = -32.5$  kcal/mol). The process passes through the TS **17c** with a very low activation energy ( $\Delta G = +4.1$  kcal/

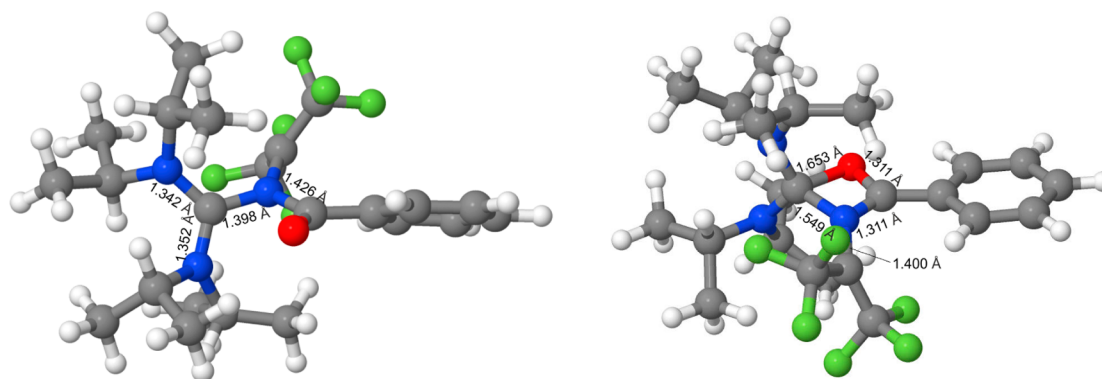


Figure 6. Jmol plots of the optimized structures 12a (left) and 13a (right).

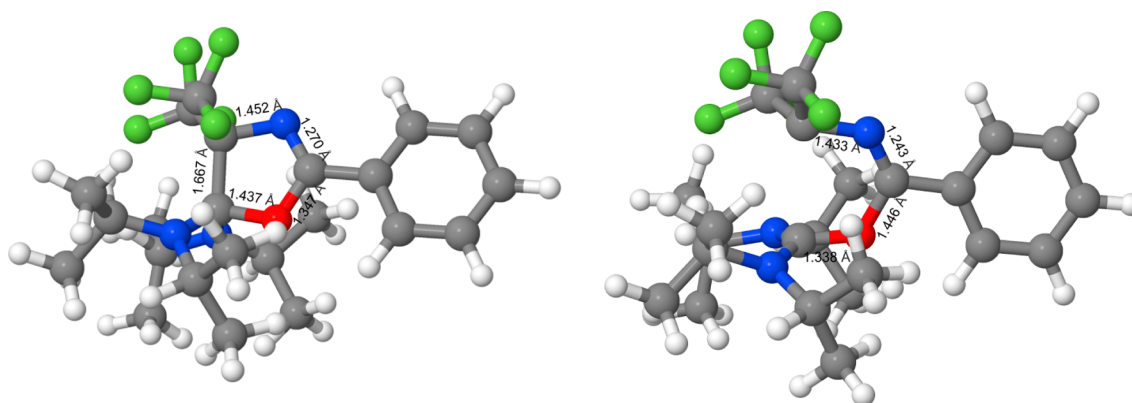


Figure 7. Jmol plots of the optimized structures 17a (left) and 20a (right).

mol relatively to the separate **1c** and **2c** molecules). Noteworthy, the  $C^{\text{carb}}\text{-C}$  (1.608 Å) and  $C^{\text{carb}}\text{-O}$  (1.459 Å) bonds in the optimized structure **18c** are elongated; in contrast, the  $(\text{O})\text{C}=\text{N}$  bond is very short (1.272 Å). Therefore, the  $C^{\text{carb}}$  atom is weakly bonded, and the structure can be classified as the donor–acceptor adduct of **1c** with **2c**, where the carbene lone pair interacts, as expected, with the carbon atom of the  $\text{C}=\text{N}$  group and the oxygen lone pair provides back-donation into the formally vacant p-orbital of  $C^{\text{carb}}$ . The calculated valence angle  $\angle\text{OC}^{\text{carb}}\text{C}$  ( $95.6^\circ$ ) is close to  $90^\circ$ , the initial angle between the carbene lone pair and p-orbital at the carbene carbon.

The isomeric three-membered adduct **21c** is significantly less stable than both **18c** and the corresponding adduct **12c** (the same is true also for the sterically bulky structure **21a**; see the Supporting Information). Additionally, the formation of **21c** cannot directly result from the  $\text{HOMO}(\mathbf{1c}) \rightarrow \text{LUMO}(\mathbf{2c})$  interaction discussed above, but only from the rearrangement of **12c** or **19c**. While structure **19c** has been located as the local minimum in energy, it is not the direct product of the C-attack of aroylimine by diaminocarbene. In addition, it is less stable thermodynamically than the separated molecules **1c** and **2c** ( $\Delta G = +2.5$  kcal/mol).

The total energies of the local minima **12c** and **18c** resulting from the two mentioned reaction pathways (C- and N-attacks) differ only slightly (Figure 5a). However, the activation energy corresponding to the TS structure **17c** at the reaction pathway toward **18c** ( $\Delta G = +4.1$  kcal/mol) is noticeably lower than the energy for TS **11c** preceding the adduct **12c** ( $\Delta G = +10.5$  kcal/mol). This allows us to assert that the formation of the five-membered cycle **18c** should be kinetically preferred compared

to the isomeric structure **12c**. Finally, **18c** decomposes into **3c** and **4c** via TS structure **20c** (Figure 4) and intermediate **10c**. The activation energy values predicted for **20c** is also lower than that in the case of **13c** (Figure 5a).

For the experimentally investigated reaction between **1a** and **2a**, the increasing activation energies and lower thermodynamic stability of the adducts are expected due to the larger negative entropy contribution into the  $\Delta G$  magnitudes. As was already mentioned above, **12a** (Figure 6) corresponds to the shallow local minimum in energy at the PES ( $-8.4$  kcal/mol, Figure 5b), which can be significantly stabilized by the rotation of the isopropyl groups (*vide supra*; see also the Supporting Information, structures **12a'** and **12a''**). The formation of **12a** proceeds via TS **11a** (Figure S2) with an activation barrier of  $+21.6$  kcal/mol.

In spite of the fact that the carbonyl ylide **10a** can be located as the local minimum in energy, the transformation of the N-adduct **12a**, related to the experiment, omits this stage. In the four-membered cyclic TS **13a** (Figure 6,  $\Delta G = +31.3$  kcal/mol relative to **12a**), corresponding to the concerted rearrangement–elimination of urea **3a**, the  $C^{\text{carb}}\text{-O}$  distance is still elongated; hence, it is more similar to **13c** than to **15c**.

In contrast, the formation of the five-membered cyclic structure **18a** (Figure 7,  $\Delta G = -8.5$  kcal/mol compared to the starting materials) proceeds through TS structure **17a** with significantly higher activation energy ( $\Delta G = +32.4$  kcal/mol) than that for **17c**. It is also more than the activation energy necessary for the alternative pathway (formation of the N-adduct **12a**). **18a** rearranges via TS **20a** ( $\Delta G = +29.4$  kcal/mol relative to **18a**, Figure 7) to carbonyl ylide **10a**, which dissociates into **3a** and **4a** via TS structure **16a** ( $\Delta G = +4.5$

kcal/mol relative to **10a**). Thus, the reaction pathway via the cyclic adduct **18a** seems to be less probable than the pathway **11a** → **12a** → **13a** → **3a+4a**, discussed above.

This trend does not change for the interaction of **1a** with mesityl derivative **2b** that can proceed via transition state structures **11b** and **17b** ( $\Delta G = +28.0$  kcal/mol and  $+36.9$  kcal/mol, respectively). This significant difference in the activation energies allows us to suggest that the kinetically controlled reaction via N-adduct **12b** must be preferred. However, the formation of such an adduct is already less thermodynamically favored, as compared with the starting materials ( $\Delta G = +0.9$  kcal/mol). Probably, this is the reason why in this case products of side reactions were the only isolated species in the experiment.<sup>55,56</sup>

## CONCLUSIONS

Several probable pathways for the recently investigated reaction of aroylimines with diaminocarbenes have been studied using the DFT (M06-2X/6-311++G\*\*) approach. The previously suggested opinion that the diaminocarbene can react electrophilically through the direct formation of the corresponding carbonyl ylide has not been confirmed: while the O-adducts are local minima in energy at the PESs, the direct oxygen transfer from aroylimine to diaminocarbene requires high activation energy. Two alternative and more preferable pathways have been proposed, which conform well to the FMO theory: (a) the primary attack of the methylenecarbon at the imino nitrogen atom with the subsequent rearrangement into urea **3** and nitrile ylide **4** and (b) the formation of the five-membered cyclic intermediate, which then decomposes via carbonyl ylide **10** to **3** and **4**. The formed nitrile ylide **4a** reacts exergonically with the second mole of diaminocarbene yielding corresponding alkene **5a** as the main reaction product. The pathway “a” seems to be preferred for the reaction of bis(di-isopropylamino)carbene (**1a**) with Ph(CO)-N=C(CF<sub>3</sub>)<sub>2</sub> (**2a**) and Mes(CO)-N=C(CF<sub>3</sub>)<sub>2</sub> (**2b**). Less sterically crowded bis(dimethylamino)carbene (**1c**) and model aroylimine Me(CO)-N=C(CF<sub>3</sub>)<sub>2</sub> (**2c**) will preferably react via pathway “b”. In these reactions dialkylaminocarbenes behave as nucleophilic (pathway “a”) or ambiphilic reagents (pathway “b”).

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information includes Jmol plots of structures **11a**, **16a**, and **16c** (Figures S1,S3), a diagram of the transformation of **12c**, a complete set of calculated energy values (Table S1), additional information about the isomerism in some calculated structures (Figure S4), and Cartesian coordinates for all optimized structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

The generous financial support from the Alexander von Humboldt Foundation (Germany) for buying computers and the license for the TURBOMOLE set of programs for A.B.R. is

gratefully acknowledged. The authors thank the NSF CREST Interdisciplinary Nanotoxicity Center NSF-CREST (Grant No. HRD-0833178) for support and the SKIT supercomputer team at the Institute of Cybernetic, NAS of Ukraine for providing an access to the SKIT computer cluster for A.B.R.

## DEDICATION

In memory of Professor Oleg Shishkin.

## REFERENCES

- (1) *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis: Catalysis by Metal Complexes*, Vol. 32; Cazin, C. S. J., Ed.; Springer: Netherlands, 2011.
- (2) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91.
- (3) *Carbene Chemistry. From Fleeting Intermediates to Powerful Reagents*; Bertrand, G., Ed.; FontisMedia and Marcel Dekker, 2002.
- (4) Vignolle, J.; Cattoën, X.; Bourissou, D. *Chem. Rev.* **2009**, *109*, 3333–3384.
- (5) Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 8810–8849.
- (6) Fèvre, M.; Pinaud, J.; Gnanou, Y.; Vignolle, J.; Taton, D. *Chem. Soc. Rev.* **2013**, *42*, 2142–2172.
- (7) Sommer, W. J.; Weck, M. *Coord. Chem. Rev.* **2007**, *251*, 860–873.
- (8) Velazquez, H. D.; Verpoort, F. *Chem. Soc. Rev.* **2012**, *41*, 7032–7060.
- (9) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583–3586.
- (10) Song, J. J.; Gallou, F.; Reeves, J. T.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2006**, *71*, 1273–1276.
- (11) Chiang, P.-C.; Bode, J. W. In *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*; Díez-González, S., Ed.; RSC Publishing: Cambridge, 2010; pp 399–435.
- (12) Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11782–11785.
- (13) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402–10405.
- (14) Jian, T.-Y.; He, L.; Tang, C.; Ye, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9104–9107.
- (15) Zhao, X.; Ruhl, K. E.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 12330–12333.
- (16) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53–57.
- (17) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094–8097.
- (18) Wang, X.-B.; Zou, X.-L.; Du, G.-F.; Liu, Z.-Y.; Dai, B. *Tetrahedron* **2012**, *68*, 6498–6503.
- (19) Chen, X.; Fang, X.; Chi, Y. R. *Chem. Sci.* **2013**, *4*, 2613–2618.
- (20) Han, R.; Qi, J.; Gu, J.; Ma, D.; Xie, X.; She, X. *ACS Catal.* **2013**, *3*, 2705–2709.
- (21) Fèvre, M.; Pinaud, J.; Gnanou, Y.; Vignolle, J.; Taton, D. *Chem. Soc. Rev.* **2013**, *42*, 2142–2172.
- (22) Ma, D.; Qiu, Y.; Dai, J.; Fu, C.; Ma, S. *Org. Lett.* **2014**, *16*, 4742–4745.
- (23) Kato, T.; Matsuoka, S.; Suzuki, M. *J. Org. Chem.* **2014**, *79*, 4484–4491.
- (24) Du, G.-F.; Guo, H.; Wang, Y.; Li, W.-J.; Shi, W.-J.; Dai, B. *J. Saudi Chem. Soc.* **2014**, DOI: 10.1016/j.jscs.2014.03.003.
- (25) Glorius, F.; Hirano, K. In *Ernst Schering Foundation Symposium Proceedings*, Vol. 2007/2; Reetz, M. T., List, B., Jaroch, S., Weinmann, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 2008; pp 203–225.
- (26) Song, J. J.; Tan, Z.; Reeves, J. T.; Gallou, F.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 2193–2196.
- (27) Enders, D.; Henseler, A. *Adv. Synth. Catal.* **2009**, *351*, 1749–1752.
- (28) Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. *Chem. Commun. (Camb)* **2010**, *46*, 6282–6284.
- (29) Du, G.-F.; He, L.; Gu, C.-Z.; Dai, B. *Synlett* **2010**, *2010*, 2513–2517.

- (30) Jousseume, T.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1410–1414.
- (31) Zhang, J.; Du, G.; Xu, Y.; He, L.; Dai, B. *Tetrahedron Lett.* **2011**, *52*, 7153–7156.
- (32) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810–8813.
- (33) Uno, T.; Kobayashi, Y.; Takemoto, Y. *Beilstein J. Org. Chem.* **2012**, *8*, 1499–1504.
- (34) Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2013**, *135*, 58–61.
- (35) Matsuoka, S.; Namera, S.; Washio, A.; Takagi, K.; Suzuki, M. *Org. Lett.* **2013**, *15*, 5916–5919.
- (36) Xiao, Z.; Yu, C.; Li, T.; Wang, X.-S.; Yao, C. *Org. Lett.* **2014**, *16*, 3632–3635.
- (37) Hollóczki, O.; Kelemen, Z.; Nyulászi, L. *J. Org. Chem.* **2012**, *77*, 6014–6022.
- (38) Muthusamy, S.; Krishnamurthi, J. *Heterocycles by Cycloadditions of Carbonyl Ylides Generated from Diazo Ketones*. In *Topics in Heterocyclic Chemistry*, Vol. 12; Hassner, A., Ed.; Springer: Berlin, Heidelberg, 2008; pp 147–192.
- (39) Clark, J. S. *Nitrogen, Oxygen and Sulfur Ylide Chemistry: A Practical Approach in Chemistry*; Oxford University Press: 2002; p 352.
- (40) McMills, M. C.; Wright, D. In *Synthetic Application of 1,3-Dipolar Cycloaddition Towards Heterocycles and Natural Products (The Chemistry of Heterocyclic Compounds, Vol. 59)*; Padwa, A., Pearson, H., Eds.; Wiley-Interscience: New York, 2002; pp 254–314.
- (41) Pliego, J. R., Jr.; De Almeida, W. B. *J. Braz. Chem. Soc.* **1998**, *9*, 181–186.
- (42) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1021–1023.
- (43) Enders, D.; Breuer, K.; Runsink, J.; Henrique Teles, J. *Liebigs Ann.* **1996**, 1996, 2019–2028.
- (44) Kuhn, N.; Steimann, M.; Walker, M. *Z. Naturforsch. B* **2001**, *56*, 129.
- (45) Kuhn, N.; Al-Sheikh, A.; Schwarz, S.; Steimann, M. *Z. Naturforsch. B* **2004**, *59*, 129–133.
- (46) Kuhn, N.; Maichle-Mößmer, C.; Niquet, E.; Steimann, M.; Sweidan, K. *Z. Naturforsch. B* **2005**, *60*, 715–719.
- (47) Kuhn, N.; Kuhn, A.; Niquet, E.; Steimann, M.; Sweidan, K. *Z. Naturforsch. B* **2005**, *60*, 924–928.
- (48) Kuhn, N.; Maichle-Mößmer, C.; Steimann, M.; Sweidan, K. *Z. Naturforsch. B* **2006**, *61*, 521–527.
- (49) Poliakov, D.; Shevchenko, I. *Eur. J. Org. Chem.* **2007**, 2055–2057.
- (50) Reynolds, T. E.; Stern, C. A.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 2581–2584.
- (51) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331–4334.
- (52) Jeong, W.; Hedrick, J. L.; Waymouth, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 8414–8415.
- (53) Culkin, D. A.; Jeong, W.; Csihony, S.; Gomez, E. D.; Balsara, N. P.; Hedrick, J. L.; Waymouth, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2627–2630.
- (54) Korotkikh, N. I.; Cowley, A. H.; Moore, J. A.; Glinyanaya, N. V.; Panov, I. S.; Rayenko, G. F.; Pekhtereva, T. M.; Shvaika, O. P. *Org. Biomol. Chem.* **2008**, *6*, 195–199.
- (55) Shevchenko, I.; Rogalyov, A.; Rozhenko, A. B.; Röschenhaler, G.-V. *Eur. J. Inorg. Chem.* **2007**, 254–258.
- (56) Poliakov, D.; Rogalyov, A.; Shevchenko, I. *Eur. J. Org. Chem.* **2008**, 2008, 5805–5809.
- (57) Poliakov, D.; Shevchenko, I. *Eur. J. Org. Chem.* **2010**, 2010, 2449–2451.
- (58) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision B.01; Gaussian, Inc.: Wallingford, CT, 2010.
- (59) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215–241.
- (60) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157–167.
- (61) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265–3269.
- (62) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100.
- (63) Perdew, J. *Phys. Rev. B* **1986**, *33*, 8822–8824.
- (64) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724–728.
- (65) Hariharan, P. C.; Pople, J. A. *Mol. Phys.* **1974**, *27*, 209–214.
- (66) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213–222.
- (67) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1983**, *78*, 4066–4073.
- (68) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735–746.
- (69) Glendening, E. D.; Landis, C. R.; Weinhold, F. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2012**, *2*, 1–42.
- (70) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO Version 3.1*; Theoretical Chemistry Institute, University of Wisconsin: Madison, WI, 1996.
- (71) *Jmol: an open-source Java viewer for chemical structures in 3D*. See <http://jmol.sourceforge.net/> for more detail.
- (72) Boyd, K.; Häkkinen, E.; Laaksonen, L. *gOpenMol program for the display and analysis of molecular structures*, version 3.00, 23.09.2005; 2005.
- (73) Anh, N. T. *Frontier orbitals: a practical manual*; John Wiley & Sons: Chichester, 2007; p 287.
- (74) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. N.; Paolini, F.; Schütz, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5896–5911.
- (75) Rozhenko, A. B.; Mykhaylychenko, S. S.; Pikun, N. V.; Shermolovich, Y. G.; Leszczynski, J. *Int. J. Quantum Chem.* **2014**, *114*, 241–248.