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A DFT Study of 1,4-Biradical Intermediates Involved in Stereoselective Paternò–Büchi Reactions

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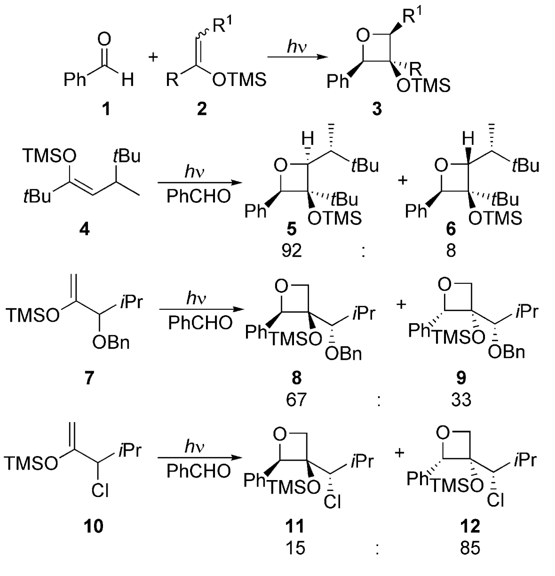
The stereoselectivity of the reaction of silyl enol ethers with benzaldehyde is explained by using DFT calculations, considering the relative stability of the possible stereoisomers of the biradical intermediates and the coupling between the single occupied molecular orbitals (SOMOs) of these intermediates. The same approach can be used to justify the observed *endo* stereoselectivity in the reaction of 2,3-dihydrofuran with 2,4,6-trimethylbenzaldehyde and the *exo* stereoselectivity in the reaction of the same substrate with 2-naphthaldehyde.

Introduction

The Paternò–Büchi reaction is one the oldest and most studied photochemical reactions in organic photochemistry.[1] The reaction is a photocycloaddition of an n,π* carbonyl compound to an alkene in the ground state from either the S_1 or the T_1 state. A frontier orbital approach can be used to explain the formation of oxetanes. Thus, interactions between the highest single occupied molecular orbital (HSOMO) and the lowest unoccupied molecular orbital (LUMO), in which the half-occupied π* carbonyl orbital interacts with the unoccupied π* molecular orbital of an electron-deficient alkene, have been observed that lead to the formation of a C,O biradical. The LSOMO–HOMO interaction, in which the half-occupied n-orbital of the carbonyl oxygen atom interacts with the π-orbital of an electron-rich alkene, leads to the formation of a C,C biradical.[2] The carbonyl compound normally serves as the light-absorbing species, which, upon excitation, adds to the alkene. The majority of Paternò–Büchi reactions occur from the carbonyl triplet state, which is accessed by an intersystem crossing (ISC). Intermediate 1,4-biradicals derived from carbonyl triplets were studied spectroscopically[3] and trapped by radical quenchers.[4] In the reaction between 1,4-dioxene and benzaldehyde, theoretical calculations showed that the only transition able to give the observed transient absorption is that from LSOMO to LUMO (549 nm), which is a π→π* transition; the same result was obtained for the reaction between furan and benzaldehyde.[5]

Recently, it was shown that the oxetane ring can play an important role in the scaffold of new drugs.[6] The possible synthetic uses of this reaction depends on the knowledge of factors controlling the stereochemical behaviour of the reaction. Several examples of stereoselective Paternò–Büchi reactions can be found in the literature. 3-(Silyloxy)oxetanes **3** were successfully prepared from silyl enol ethers containing carbon–chlorine, carbon–silicon, or carbon–sulfur bonds (Scheme 1).[7] When a β-alkyl-substituted silyl enol ether is used, *trans* oxetanes are obtained; this result does not depend on the (*E*) or (*Z*) nature of the alkene. The products were obtained with high diastereoselectivity.[8]



Scheme 1. Stereoselectivity observed in the photochemical reaction between silyl enol ethers and benzaldehyde.

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In most of the reactions, benzaldehyde is used as a carbonyl compound, which exhibits quantitative intersystem crossing to the triplet state. The reaction occurs through this triplet state of the carbonyl compound and requires the formation of a triplet biradical intermediate. The triplet biradical for this type of reaction is a C,C biradical derived from attack of the oxygen atom of the carbonyl compound on the alkene.[3,4] In the triplet biradical, free rotation leads to the highly preferred, sterically least congested conformation. Further steps in the reaction pathway of this species includes ISC and an assumed selection step (cleavage vs. ring-closure) at the singlet 1,4-diradical level, which accounts for the high diastereoselectivity at C-2/C-3.

The presence of a stereogenic carbon atom in the β-alkyl group (as in **4**) induced a facial diastereoselectivity with high diastereoisomeric ratios in some cases (Scheme 1).[9] The diastereoselectivity is probably due to the presence of a conformational preference represented in Figure 1, which allows the *Si* attack.[10]

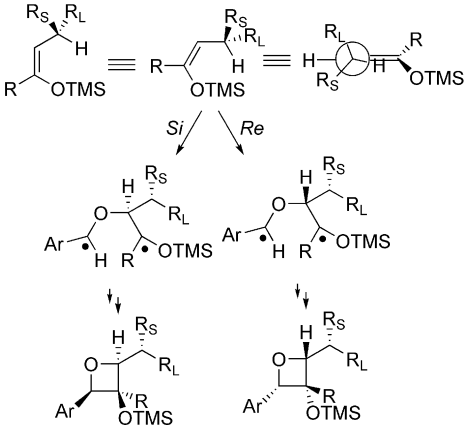
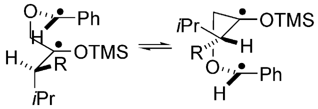


Figure 1. Diastereoselectivity in the reaction of chiral silyl enol ethers with benzaldehyde.

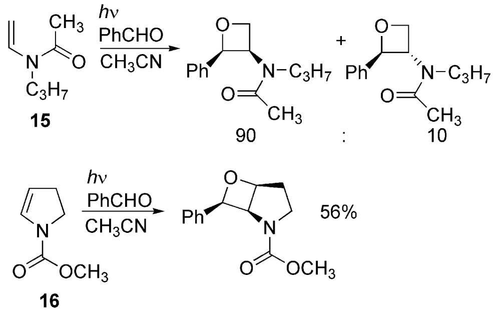
When the chiral carbon atom is in the α-position a low facial diastereoselectivity was observed.[11] The best results were obtained by using both the silyl enol ether **7**, which gave the adducts **8** and **9** with a 67:33 *dr* and by using compound **10**, giving the adducts **11** and **12** in 15:85 *dr* (Scheme 1).[11] In the case of compounds **7** and **10**, the observed stereoselectivity requires that, in the case of the former, conformation **13** for the biradical intermediate is preferred, whereas by using the latter, conformation **14** should be preferred (Figure 2).



13 **14**

Figure 2. Possible conformations of the biradical intermediates in the reaction of **7** and **10** with benzaldehyde.

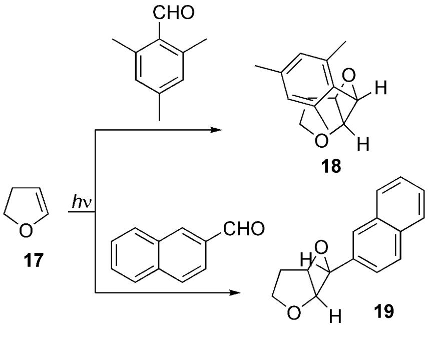
N-Acyl enamines **15** and **16** gave the corresponding adducts with high regio- and stereoselectivity (Scheme 2).[12] The thermodynamically less stable isomer seems to be obtained.[13] It is not clear why, in this case, the less stable compound is obtained, whereas, if nitrogen is replaced by oxygen (see below), the more stable compound is the main product of the reaction.



15 **16**

Scheme 2. Photochemical reaction between enamines and benzaldehyde.

This approach has been used in the synthesis of (±)-oxetin[14] and in the synthesis of (+)-preussin.[15] The reaction of 2,3-dihydrofuran with carbonyl compounds has also been extensively studied.[16] Griesbeck reported that 2,3-dihydrofuran **17** gave the corresponding *endo* adduct **18** when it reacted with 2,4,6-trimethylbenzaldehyde, and the *exo* adduct **19** when it reacted with 2-naphthaldehyde (Scheme 3).[16] The first reaction occurred through the first excited triplet state, whereas the second occurred through the first excited singlet state (experimental results, i.e., fluorescence quenching, support this statement). However, no reason for the different stereochemical behaviour was offered.



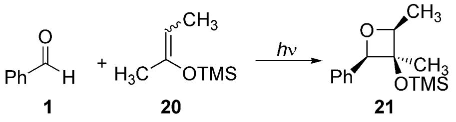
17 **18** **19**

Scheme 3. Photochemical reaction of 2,3-dihydrofuran with 2,4,6-trimethylbenzaldehyde and 2-naphthaldehyde.

In conclusion, the results reported above show the ad hoc nature of the interpretations, the lack of explanation in some cases, and the absence of a common framework able to explain all the experimental results. In this paper we want to contribute to the understanding of the behaviour described above.

Results and Discussion

Calculations [DFT/UB3LYP/6-31G+(d,p) on Gaussian03][17] were performed on the biradical intermediates involved in the reactions described above. We first focussed on the reaction of the silyl enol ether **20** with benzaldehyde to give oxetane **21** (Scheme 4).



Scheme 4. Reaction of 2-trimethylsilyloxy-2-butene (**20**) with benzaldehyde.

In this case, the formation of two possible diastereoisomeric biradical intermediates **A** and **B** is possible (Figure 3). The stereoisomer **A** was calculated to be more stable than isomer **B** by 1.64 kcal/mol.

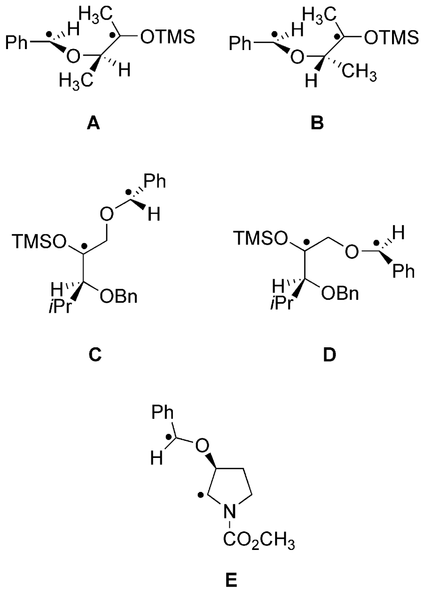
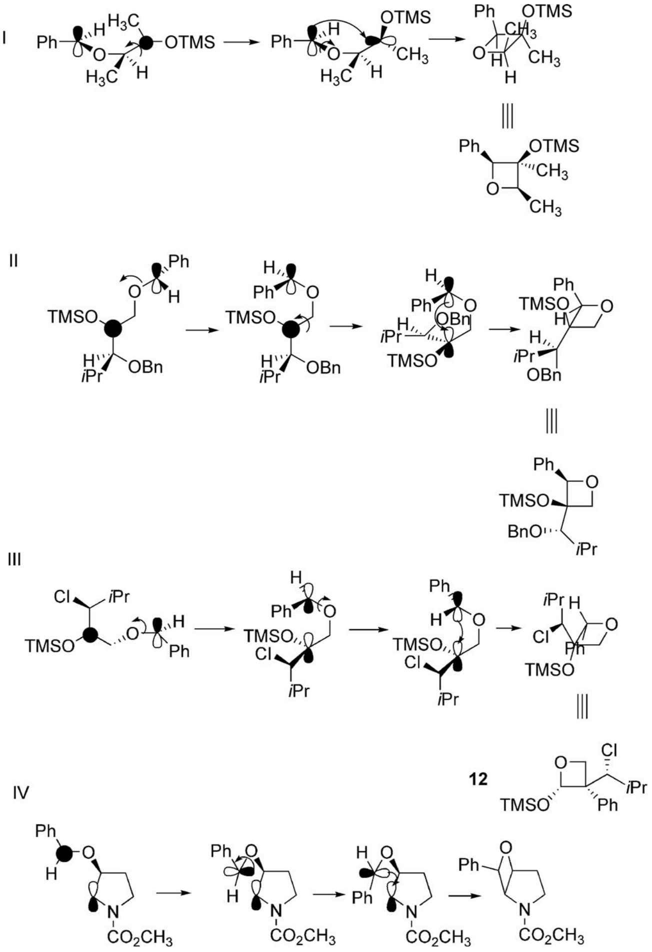


Figure 3. Conformers **A** and **B** of the biradical intermediate in the photoreaction between **20** and benzaldehyde, conformers **C** and **D** of the biradical intermediate in the photoreaction between **7** and benzaldehyde, and biradical intermediate **E** in the photoreaction of **16** with benzaldehyde.

For the more stable stereoisomer **A**, the LSOMO (lowest single occupied molecular orbital) was localised on the radical carbon atom near the trimethylsilyloxy (TMSO) group (–0.174 H), and the HSOMO was mainly localised on the benzyl radical carbon atom (–0.151 H).

These orbital calculations allow us to understand the behaviour of our reactive system when it is under frontier orbital control. On the basis of the Klopman–Salem equation,[18] we can suppose that the driving force of the coupling reaction of the biradical has to be frontier orbital controlled.

Considering the reactive sites and the atomic coefficients at these sites, the coupling of the radical carbon atoms can occur only as depicted in Scheme 5 (I). It can be seen that, in this way, conformer **A** leads to the stereoisomer **21** observed in the reaction, and the computational results are thus in agreement with the experimental results.



Scheme 5. (I) Coupling of the radical carbon atoms of the main stereoisomer in the reaction **20** → **21**. (II) Coupling of the radical carbon atoms of the main conformer of the biradical intermediate in the reaction **7** → **8** + **9**. (III) Coupling of the radical carbon atoms of the main conformer of the biradical intermediate in the reaction **10** → **11** + **12**. (IV) Coupling of the radical carbon atoms of the biradical intermediate in the reaction of **16** with benzaldehyde.

In the reaction of **7** with benzaldehyde, two conformers of the biradical intermediate were obtained with almost the same calculated energy (conformer **C** is more stable than **D** by 3.11 kcal/mol); the conformers of the biradical are shown in Figure 3.

Considering the biradical conformer **C**, the LSOMO of this biradical was at –0.077 H, whereas the HSOMO was at –0.073 H [Figure 4 (A)]. In this case, the same approach described above can be applied: by considering the reactive sites and the atomic coefficients at these sites, the coupling of the radical carbon atoms can occur only as depicted in Scheme 5 (II). It can be seen that conformer **C** can lead to the major stereoisomer **8** observed in the reaction. The results are in agreement with the experimental results and show that the stereocontrol of this reaction is strictly related to the level of frontier orbital control. The other biradical conformer gave the second diastereoisomer. The observed diastereoisomeric ratio (67:33) can be explained by the small difference between the energies of the conformers of the biradical intermediates (3.11 kcal/mol).

To support this result, we studied the behaviour of **10**. In this case an inverse diastereoselectivity was observed.[11] Our calculated results are in agreement with the observed results. In this case we also obtained two conformers of the biradical intermediate (see the Supporting Information) with an energy difference between the two conformers of 4.6 kcal/mol. Using the same procedure described above, we found the HSOMO and LSOMO energies to be –0.080 H and –0.093 H, respectively. The coupling between the carbon atoms, considering the atomic coefficients, explains the formation of the observed diastereoisomers (**11** and **12**): the most stable conformer led to the formation of compound **12** [Scheme 5 (III)]. The larger diastereoisomeric ratio (85:15) observed here, in comparison with that found in **8** and **9**, is in agreement with the larger energy difference between the conformers of the biradical intermediates.

The photochemical behaviour of the *N*-acyl enamine **16** was also studied. In this case, the structure of the biradical intermediate was optimised; its structure **E** is depicted in Figure 3. The HSOMO of this biradical intermediate was at –0.215 H and the LSOMO was at –0.241 H [Figure 4 (B)]. The coupling of the radical carbon atoms, considering the atomic coefficients on the SOMOs, allowed the formation of the *exo* isomer, in agreement with the experimental results [Scheme 5 (IV)].

The same approach can be used to explain the behaviour of dihydrofuran **17** (Scheme 3). When this compound reacts with 2,4,6-trimethylbenzaldehyde, the *endo* isomer **18** is obtained.[16] In this case, the biradical intermediate contained the HSOMO at –0.148 H and the LSOMO at –0.181 H. The shapes of these orbitals are depicted in Figure 5 (A). It can be seen that the HSOMO is mainly localised on the dihydrofuran section of the molecule and is mainly concentrated on the radical carbon atom, whereas the LSOMO is mainly localised on the aromatic section of the molecule.

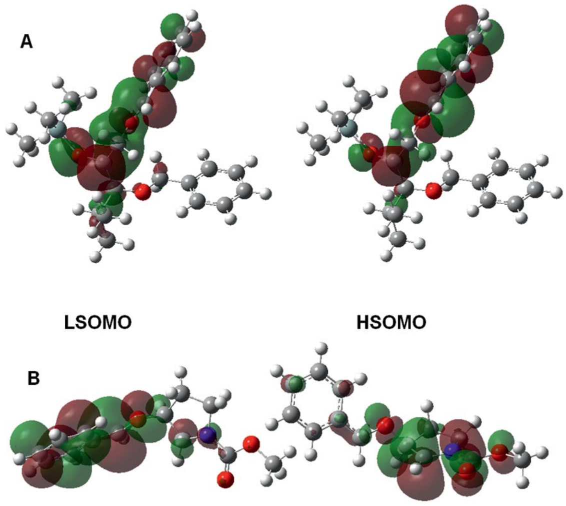


Figure 4. (A) HSOMO and LSOMO of the biradical **C** obtained in the reaction of **7** with benzaldehyde; (B) HSOMO and LSOMO of the biradical intermediate obtained in the reaction of **16** with benzaldehyde.

The interaction between the radical carbon atoms in these two orbitals can only lead to the formation of the *endo* isomer [Scheme 6 (I)].

On the other hand, the energy of the singlet biradical of the intermediate formed in the reaction **17** → **19**, which was obtained at the HF/6-31G+(d,p) level, gave the HSOMO at –0.215 H and the LSOMO at –0.246 H [Figure 5 (B)]. In this case, it can be seen that the HSOMO is mainly localised on the aromatic part of the molecule, whereas the LSOMO is mainly localised on the dihydrofuran ring and, in particular, on the radical carbon atom.

The interaction between the radical carbon atoms in these two orbitals leads to the *exo* isomer, in agreement with the experimental results [Scheme 6 (II)].

In the case of the reaction **17** → **19**, a second hypothesis has to be considered: a concerted [2+2] cycloaddition reaction in the singlet state. In this case, the reaction should be

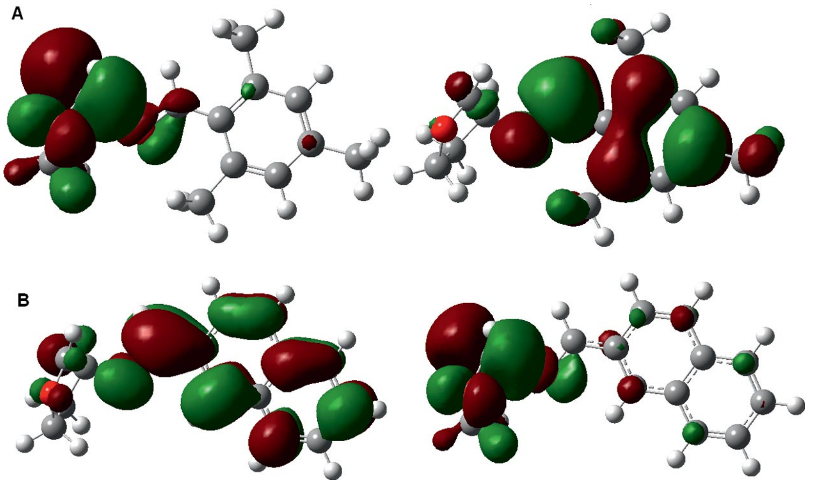


Figure 5. (A) HSOMO (left) and LSOMO (right) of the biradical intermediate in the reaction **17** → **18**; (B) HSOMO (left) and LSOMO (right) of the biradical intermediate obtained in the reaction **17** → **19**.

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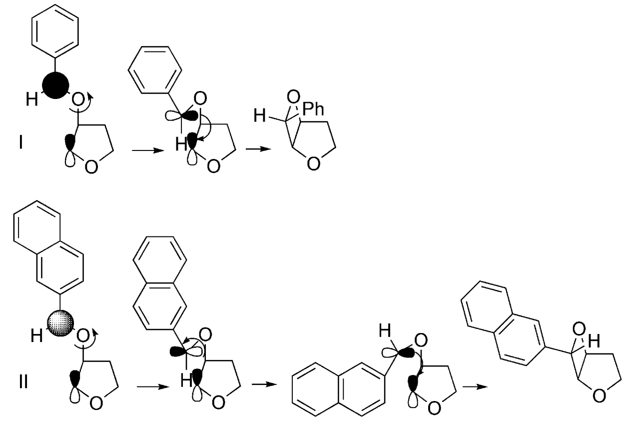

Scheme 6. (I) Coupling of the radical carbon atoms of the biradical intermediate in the reaction **17** → **18**. (II) Coupling of the radical carbon atoms of the biradical intermediate in the reaction **17** → **19**.

controlled by the frontier orbital interactions. We calculated the optimised structure of dihydrofuran and 2-naphthaldehyde and characterised the first excited singlet state at the TD-DFT/B3LYP/6-31G+(d,p) level. The energy of the involved frontier orbitals is depicted in Figure 6. It can be seen that the main frontier orbital interaction occurs between the LSOMO of the singlet excited 2-naphthaldehyde and the HOMO of dihydrofuran. These orbitals are represented in the Figure 7.

It can be seen that a concerted [2+2] cycloaddition reaction cannot occur in this case. In fact, the LSOMO of 2-naphthaldehyde does not show an appreciable atomic coefficient at the carbonyl carbon atom, thus preventing such a concerted cycloaddition reaction. Nevertheless, these results are in agreement with the formation of a singlet biradical intermediate derived from the attack of the carbonyl oxygen atom on the C-3 atom of dihydrofuran.

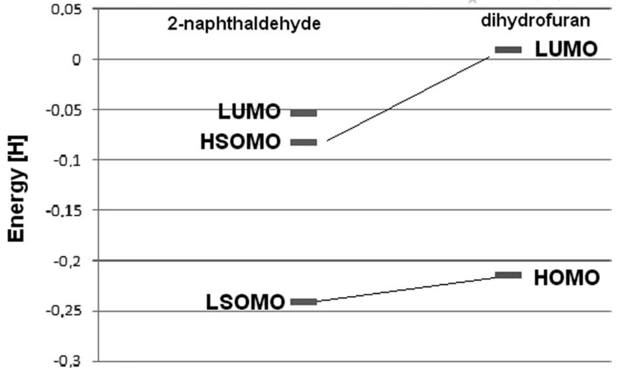

Figure 6. Frontier orbitals involved in the photochemical reaction between the first excited singlet state of 2-naphthaldehyde and dihydrofuran.

Conclusions

We have shown that the approach described above, whereby the possible stereoisomers and conformers of the biradical intermediates in the Paternò–Büchi reaction were considered for the coupling reaction to give the corresponding oxetanes, occurs through the interaction of the SOMOs of these biradical intermediates and is able to explain the observed stereoselectivity.

Experimental Section

Gaussian 03 was used to generate the computed geometries. All the computations were based on DFT[19] by using the B3LYP hybrid functional.[20] Geometry optimisations from the Gaussian 03 program were obtained at the B3LYP/6-31G(d,p) level of approximation, and were performed with default settings on geometry convergence (gradients and displacements), integration grid and electronic density (SCF) convergence. Redundant coordinates were used for geometry optimisation as produced by the Gaussian 03 program.

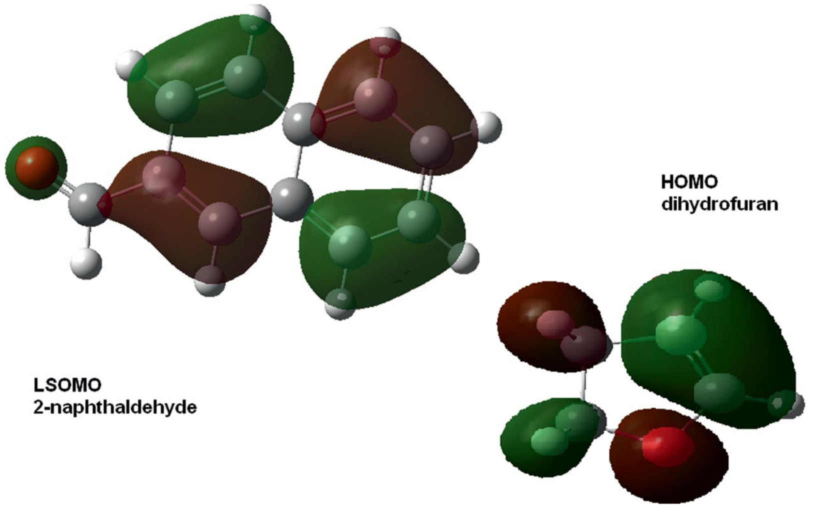

Figure 7. LSOMO of the first excited state of 2-naphthaldehyde and the HOMO of dihydrofuran.

Supporting Information (see footnote on the first page of this article): Molecular modelling coordinates and total energies of all the biradical intermediates.

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[1] a) E. Paternò, *Synthesis in Organic Chemistry by Means of Light* (Ed.: M. D'Auria), Società Chimica Italiana, Rome, **2009**, pp. 85–105; b) G. Büchi, C. G. Inman, E. S. Lipinsky, *J. Am. Chem. Soc.* **1954**, *76*, 4327–4331; c) D. R. Arnold, *Adv. Photochem.* **1968**, *6*, 301–423; d) G. Jones, *Org. Photochem.* **1981**, *5*, 1–122; e) H. A. J. Carless in *Synthetic Organic Photochemistry* (Ed.: W. M. Horspool), Plenum, New York, **1984**, pp. 425–487; f) J. A. Porco, S. L. Schreiber in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Plenum, New York, **1991**, vol. 5, pp. 151–192; g) A. G. Griesbeck in *Handbook of Photochemistry and Photobiology* (Eds.: W. A. Horspool, P.-S. Song), CRC Press, Boca Raton, **1994**, pp. 522–535, 550–559.

[2] a) J. Kopecký, *Organic Photochemistry*, VCH, New York, **1992**, p. 126; b) N. J. Turro, J. C. Dalton, K. Dawes, G. Farrington, R. Hautala, D. Morton, M. Niemczyk, N. Schore, *Acc. Chem. Res.* **1972**, *5*, 92–101.

[3] a) S. C. Freilich, K. S. Peters, *J. Am. Chem. Soc.* **1981**, *103*, 6255–6257; b) R. A. Caldwell, T. Majima, C. Pac, *J. Am. Chem. Soc.* **1982**, *104*, 629–630; c) S. C. Freilich, K. S. Peters, *J. Am. Chem. Soc.* **1985**, *107*, 3819–3822; d) M. Abe, T. Kawakami, S. Ohata, K. Nozaki, M. Nojima, *J. Am. Chem. Soc.* **2004**, *126*, 2838–2846.

[4] a) R. M. Wilson, S. W. Wunderly, T. F. Walsh, A. K. Musser, R. Outcalt, F. Geiser, S. K. Gee, W. Brabender, L. Yerino Jr., T. T. Conrad, G. A. Tharp, *J. Am. Chem. Soc.* **1982**, *104*, 4429–4446; b) W. Adam, U. Kliem, V. Lucchini, *Liebigs Ann. Chem.* **1988**, 869–875.

[5] M. D'Auria, L. Emanuele, R. Racioppi in *Photochemistry Research Progress* (Eds: A. Sanchez, S. J. Gutierrez), Nova Science Publishers Inc., Hauppage, NY, **2008**, pp. 373–438.

[6] G. Wuitschik, M. Rogers-Evans, K. Müller, H. Fischer, B. Wagner, F. Schuler, L. Polonchuk, E. M. Carreira, *Angew. Chem. Int. Ed.* **2006**, *45*, 7736–7739.

[7] a) T. Bach, K. Kather, *Tetrahedron* **1994**, *50*, 12319–12328; b) T. Bach, *Tetrahedron Lett.* **1991**, *32*, 7037–7038.

[8] T. Bach, *Liebigs Ann.* **1995**, 855–865.

[9] T. Bach, K. Jödicke, K. Kather, J. Hecht, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2271–2273.

[10] T. Bach, K. Jödicke, K. Kather, R. Fröhlich, *J. Am. Chem. Soc.* **1997**, *119*, 2437–2445.

[11] T. Bach, K. Jödicke, B. Wibbeling, *Tetrahedron* **1996**, *52*, 10861–10878.

[12] a) T. Bach, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 884–886; b) T. Bach, J. Schröder, *J. Org. Chem.* **1999**, *64*, 1265–1273; c) T. Bach, H. Bergmann, H. Brummerhop, W. Lewis, K. Harms, *Chem. Eur. J.* **2001**, *7*, 4512–4521; d) T. Bach, *Liebigs Ann./Recueil* **1997**, 1627–1634.

[13] T. Bach, J. Schröder, *Synthesis* **2001**, 1117–1124.

[14] T. Bach, J. Schröder, *Liebigs Ann./Recueil* **1997**, 2265–2267.

[15] a) T. Bach, H. Brummerhop, *Angew. Chem. Int. Ed.* **1998**, *37*, 3400–3402; b) T. Bach, H. Brummerhop, K. Harms, *Chem. Eur. J.* **2000**, *6*, 3838–3848.

[16] a) M. Ogata, H. Watanabe, H. Kano, *Tetrahedron Lett.* **1967**, *8*, 533–537; b) H. A. Carless, D. J. Haywood, *J. Chem. Soc., Chem. Commun.* **1980**, 1067–1068; c) S. Bondock, A. G. Griesbeck, *Int. J. Photoenergy* **2005**, *7*, 23–25; d) A. G. Griesbeck, M. Fiege, S. Bondock, M. S. Gudipati, *Org. Lett.* **2000**, *2*, 3623–3625; e) A. G. Griesbeck, *J. Photosci.* **2003**, *10*, 49–60; f) A. G. Griesbeck, *Synlett* **2003**, 451–472; g) A. G. Griesbeck, M. Abe, S. Bondock, *Acc. Chem. Res.* **2004**, *37*, 919–928; h) A. G. Griesbeck, S. Stadtmüller, *J. Am. Chem. Soc.* **1990**, *112*, 1281–1283; i) A. G. Griesbeck, S. Stadtmüller, *J. Am. Chem. Soc.* **1991**, *113*, 6923–6928; j) A. G. Griesbeck, S. Stadtmüller, *Chem. Ber.* **1990**, *123*, 357–362; k) V. Lhiaubet-Vallet, S. Encinas, M. A. Miranda, *J. Am. Chem. Soc.* **2005**, *127*, 12774–12775; l) M. Abe, *J. Chin. Chem. Soc.* **2008**, *55*, 479–486; m) A. G. Griesbeck, H. Mauder, K. Peters, E.-M. Peters, H. G. von Schnering, *Chem. Ber.* **1991**, *124*, 407–410; n) A. G. Griesbeck, S. Bondock, M. S. Gudipati, *Angew. Chem. Int. Ed.* **2001**, *40*, 4684–4687.

[17] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Revision A.1, Gaussian, Inc., Pittsburgh PA, **2003**.

[18] a) G. Klopman, *J. Am. Chem. Soc.* **1968**, *90*, 223–224; b) L. Salem, *J. Am. Chem. Soc.* **1968**, *90*, 543–552; c) L. Salem, *J. Am. Chem. Soc.* **1968**, *90*, 553–566.

[19] R. G. Parr, W. Wang, *Density Functional Theory of Atoms and Molecules*, Oxford University Press, New York, **1989**.

[20] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.

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