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A computational study of the thermal opening of benzocyclobutenes to (*E*)- and (*Z*)-xylylenes☆

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Abstract—The structures of eleven 1-substituted benzocyclobutenes and corresponding (*E*)-*o*-xylylenes and (*Z*)-*o*-xylylenes have been calculated at the Becke3LYP/6-311G(d,p) level. Some *o*-xylylenes are plane and even some (*Z*)-isomers. In three cases (substituent: methoxy, amino and formamido groups), *the* (*Z*)-*isomer is more stable than the* (*E*)-*isomer*. The regioselectivity of the Diels–Alder reaction between (*o*)-xylylenes and propene or ethylvinylether is discussed according to the frontier OM coefficients.

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1. Introduction

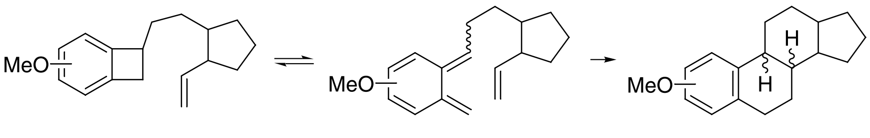
In the course of a program directed towards the development of new steroids which could exhibit improved therapeutic actions over existing drugs,[1] we reported a convergent steroid synthesis[2] based on the approach A+D→AD→ABCD. This latter involved the use of an intramolecular cycloaddition of *o*-xylylenes developed first by Oppolzer[3] and Kametani[4] for the generation of the BC ring system of steroids.[5]

On heating, conveniently substituted benzocyclobutenes undergo reversible conrotatory ring opening to the corresponding *o*-xylylenes. Then, these species can readily participate to an intramolecular Diels–Alder type cycloaddition reaction. Consequently, the stereochemistry of the B/C ring system depends on the steric control of the opening of the benzocyclobutenes and the intramolecular xylylene-cycloaddition (Scheme 1).

Generally, the cycloaddition reaction exhibits a high degree of regio- and stereoselectivities. The four possible approaches are summarized in Scheme 2. They provide either a *trans* B/C ring junction (for the two first cases) (the *endo* transition state from the *Z*-xylylene seems to be too constraint) or a *cis* B/C ring junction (for the two other cases).

2. Structure of benzocyclobutenes and (*E*)- or (*Z*)-*o*-xylylenes

To the best of our knowledge, no study has been devoted to determine the relative stability of substituted *o*-xylylenes. However, Jefford and Houk reported experimental findings on the thermolytic behavior of several benzocyclobutene derivatives.[6] They studied the torquoselectivity of the ring opening of 1-substituted benzocyclobutenes by means of ab initio molecular orbital calculations (3-21G). The ring opening of substituted benzocyclobutene can involve either an outward or an inward rotation of the substituent. As for 3-substituted cyclobutenes,[7] ab initio calculations on the transition states indicate that the tendency for outward rotation of substituents leading to (*E*)-xylylenes, increases with the donor character of the substituent.[8]



Scheme 1.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.01.049

Keywords: Benzocyclobutenes; *o*-Xylylenes; Diels–Alder reaction.

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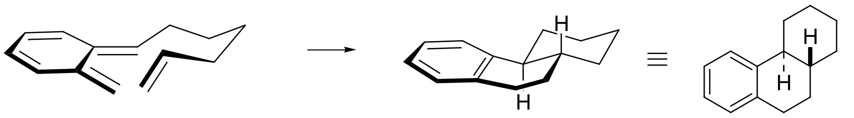
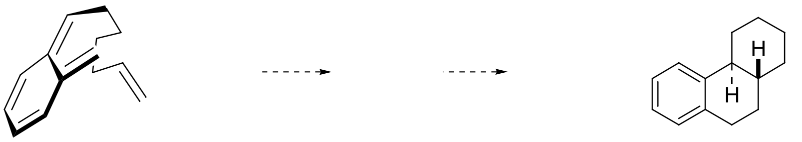
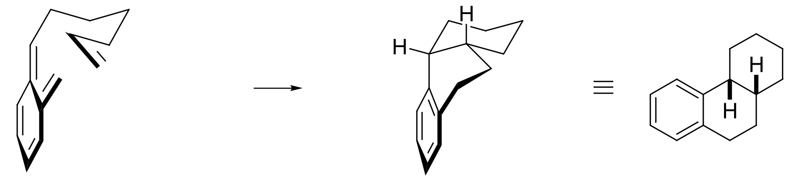


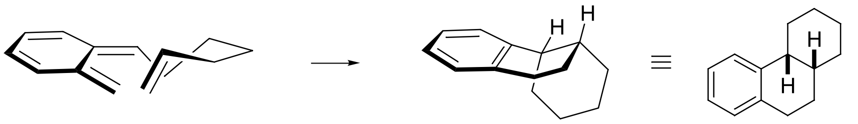
Formation of an *E*-xylylene followed by an exo-transition state



Formation of a *Z*-xylylene followed by an endo transition state



Formation of an *E*-xylylene combined with an endo-transition state



Formation of a *Z*-xylylene combined with an exo-transition state

Scheme 2.

In the present work, we have calculated the structures of benzocyclobutenes **1a**–**11a** and corresponding (*E*)-*o*-xylylenes **1b***E*–**11b***E* and (*Z*)-*o*-xylylenes **1b***Z*–**8b***Z* (Scheme 3). The geometry was first optimized with the semi-empirical PM3 method followed by calculations at the HF/6-31G(d,p) level. Then, the geometries were optimized with density functional theory (DFT) using the Becke3LYP functionals[9] and 6-311G(d,p) basis set. For all optimized structures, harmonic vibrational frequencies have been calculated at the same level allowing the correction for the zero-point energies (ZPE).[10]

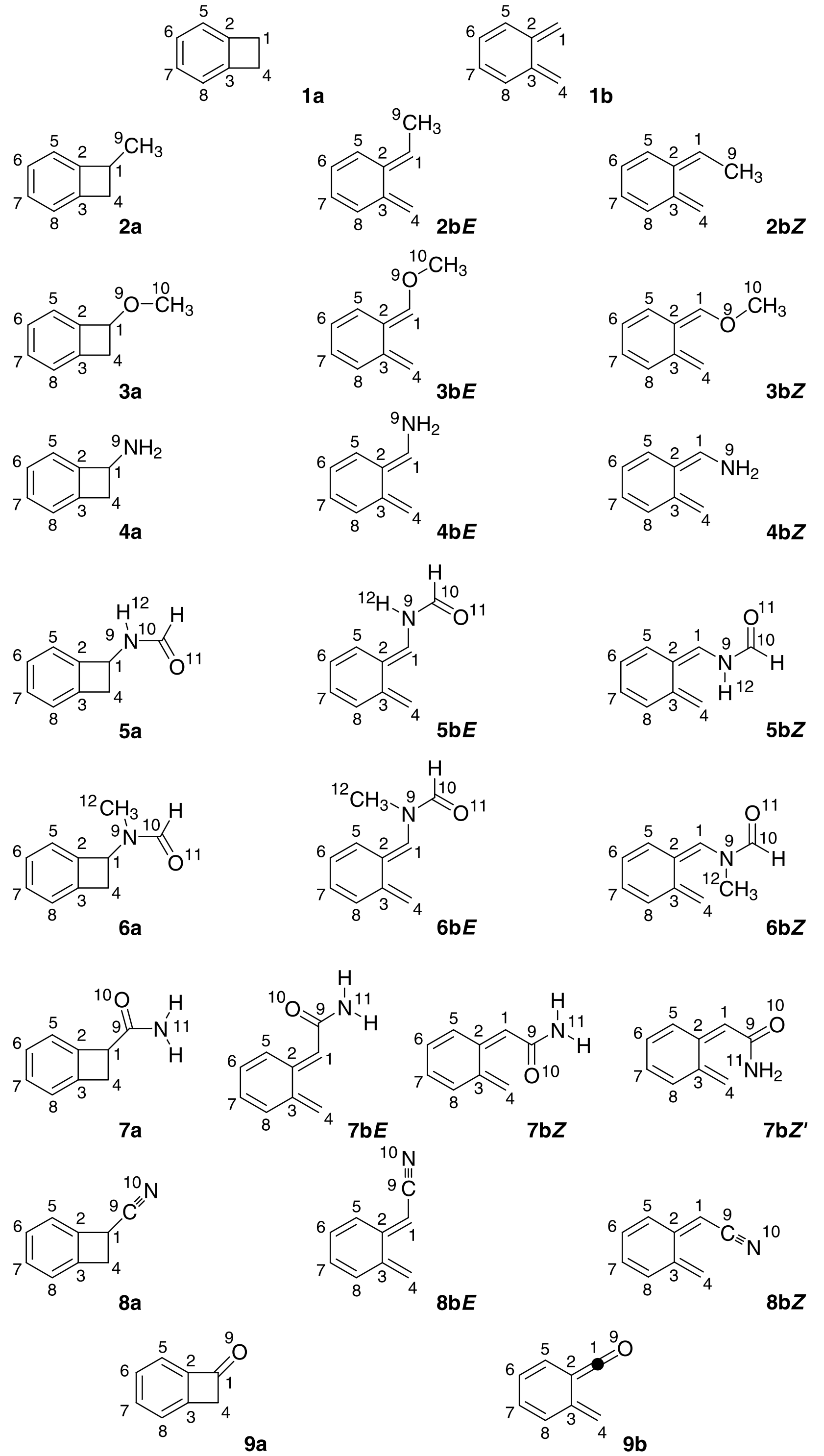
In order to compare their geometries, energies of molecular orbitals and energies, we have calculated the structure of *cis* and *trans*-*o*-xylylenes bearing either electron donating groups (methyl, methoxy, amino, formamido) or electron-withdrawing groups (carboxamido, cyano, oxo) (Scheme 3). Moreover, the structures of 1-methyl-4-methoxy-benzocyclobutene and 1-methyl-5-methoxybenzocyclobutene and those of corresponding (*E*)-xylylenes have been calculated in order to modelize the formation of the B-cycle of steroids (Scheme 4). The results concerning the geometries of benzocyclobutenes are collected in Tables 1SI and 2SI and those of *o*-xylylenes are collected in Tables 3SI–5SI (Supplementary Information, SI).

Compound **1a** is the sole benzocyclobutene whose bond lengths have been determined by X-ray crystallographic analysis at −170 °C.[11] The differences between these latter and the calculated bond lengths (after correction considering the rigid-body motion of molecules in crystals)[12] are in ±0.2% range. As expected, the bonds in the benzene ring adjacent to the annelated bond, are shortened [C(2)–C(5) or C(3)–C(8)]. Moreover, optimized angles values are identical to those determined by X-ray analysis. Calculations at the MP2/6-311G(d,p) show more discrepancies (Table 1SI).

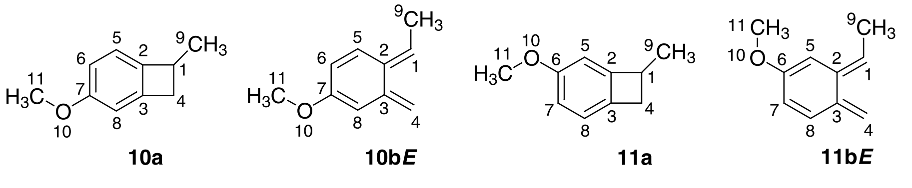
The geometries of *o*-xylylenes present some interesting features (Table 3SI). The expected bond alternation is quite marked since we note, for instance, that in the case of **10b***E*, the lengthening of the C(2)C(3) bond (1.503 Å)[C(2)C(3) bond, means for (*E*)-isomers: 1.493 Å; means for (*Z*)-isomers: 1.487 Å]. There is much more conjugation throughout the (*Z*)-amino-substituted xylylene **4b***Z* (**4b***Z* presents the shortest C(2)C(3), C(2)(C5), C(6)C(7) bonds and the longest C(1)C(2), C(3)C(4), C(7)C(8) bonds). Curiously, the C(1)X(9) bonds in (*E*)-isomers are longer than in corresponding (*Z*)-isomers, even in the case of **6b***Z* bearing a sterically hindered substituent (Δ=0.008 Å). Consequently, for (*Z*)-isomers, the (X)–C(4) distance is short (2.88 Å for the distance O–C(4) in **3b***Z*, 3.02 and 3.04 Å for the distance N–C(4) in **4b***Z* and **5b***Z*, respectively, 2.88 Å for the distance O–C(4) in **7b***Z*).

In the same way, we note that the C(2)(C1)X(9) angle is little modified by the change of geometry (**2b***E*, 128.0°, **2b***Z*, 129.5°, Δ=1.5°; **3b**, Δ=2°; **4b**, Δ=0.6°; **5b**, Δ=−0.5°; **6b**, Δ=6.9°; **7b**, Δ=4.4°) (Table 4, SI).

Amazingly, at the Becke3LYP/6-311G(d,p) level, some *o*-xylylenes are plane and even some (*Z*)-isomers (Table 5SI).[13] Even though **1b** and nine others *o*-xylylenes are nonplanar, it is astonishing that **2b***Z*, **3b***Z*, **8b***E*, **8b***Z*, **9b** and **10b***E* are plane molecules. The tendency of the planarity for the (*Z*)-isomers is underlined by the decreasing of the C(1)C(2)C(3)C(4) dihedral angle from **7b***E* (26.1°) to **7b***Z*



Scheme 3.



Scheme 4.

Table 1. Calculated energies of the xylylene formation **1b**–**11b** from corresponding substituted benzocyclobutenes at the Becke3LYP/6-311G(d,p) level

	Total energy (hartree)	ZPE	ZPE[a]	Corrected total energy (hartree)	Formation energy (hartree)	Formation energy (kcal/mol)
1a	−309.70865	0.13382	0.13235	−309.57630		
1b	−309.68871	0.13148	0.13003	−309.55868	0.01762	11.057
2a	−349.03546	0.16164	0.15986	−348.87560		
2b_E_	−349.01565	0.15929	0.15754	−348.85811	0.01749	10.97
2b_Z_	−349.01486	0.15985	0.15809	−348.85677	0.01883	11.81
3a	−424.26066	0.16603	0.16420	−424.09646		
3b_E_	−424.24725	0.16413	0.16232	−424.08493	0.01153	7.23
3b_Z_	−424.24961	0.16448	0.16267	−424.08694	0.00952	5.97
4a	−365.07728	0.15104	0.14938	−364.92790		
4b_E_	−365.06929	0.14865	0.14701	−364.92228	0.00562	3.53
4b_Z_	−365.07346	0.14950	0.14785	−364.92561	0.00229	1.44
5a	−478.45438	0.16085	0.15908	−478.29530		
5b_E_	−478.44084	0.15894	0.15719	−478.28365	0.01165	7.31
5b_Z_	−478.44274	0.15941	0.15770	−478.28504	0.01026	6.44
6a	−517.76999	0.18886	0.18678	−517.58321		
6b_E_	−517.75150	0.18719	0.18513	−517.56637	0.01684	10.57
6b_Z_	−517.75090	0.18704	0.18498	517.56592	0.01729	10.85
7a	−478.46690	0.16071	0.15894	−478.30796		
7b_E_	−478.45014	0.15872	0.15697	−478.29316	0.01479	9.28
7b_Z_	−478.44563	0.15910	0.15734	−478.28828	0.01968	12.35
8a	−401.97213	0.13268	0.13122	−401.84091		
8b_E_	−401.96011	0.13068	0.12924	−401.83087	0.01004	6.30
8b_Z_	−401.95978	0.13103	0.12959	−401.83019	0.01072	6.73
9a	−383.74880	0.11525	0.11398	−383.63482		
9b	−383.72089	0.11299	0.11175	−383.60914	0.02568	16.11
10a	−463.59075	0.19380	0.19167	−463.39908		
10b_E_	−463.57443	0.19151	0.18940	−463.38503	0.01405	8.82
11a	−463.59072	0.19381	0.19168	−463.39904		
11b_E_	−463.57505	0.19170	0.18959	−463.38546	0.01358	8.52

[a] ZPEs (zero point energies) are scaled by a factor of 0.989, as recommended in Ref. 10.

(12.9°). In fact, the conformational change induces only a very weak difference of the total energy for the *o*-xylylenes. For example, at the B3LYP/6-311G(d,p) level, the total energy of **1b** with a planar structure is 0.23 kcal/mol less stable than **1b** with a nonplanar structure! In other part, for the (*Z*)-*o*-xylylene substituted by a formamido group, the *s-cis* conformation **7b**_Z_ is 1.52 kcal/mol more stable than the *s-trans* conformation **7b**_Z_′.

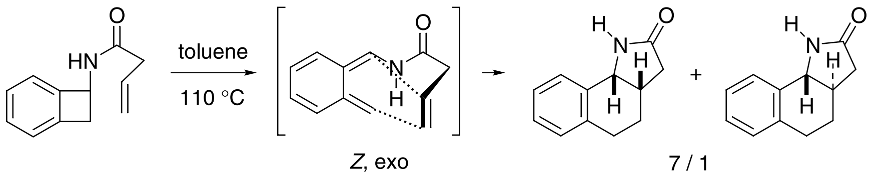
The above remarks are confirmed by results concerning the calculated formation energies (Table 1). First, it is gratifying to note that for **1b** the energy formation (11.06 kcal/mol) is in very good agreement with the experimental value (11.1 kcal/mol) determined by Roth.[14,15c] Except for **9b**, the presence of substituents induces a decreasing of the energy formation in particular in the case of donor groups, such as methoxy, amino or formamido groups. Actually, the opening of 7-aminobenzocyclobutene **4a** occurs at room temperature giving mainly (*Z*)-aminoxylylene **4b**_Z_. For a long time, it has been known that the presence of electron-rich substituents favored the opening of the benzocyclobutenes (the required temperature varies from 25 to 200 °C).[16] Moreover, in these three later cases, the (*Z*)-isomer was found to be more stable than the (*E*)-isomer.

By this way, the concept of steric control governing the course of the conrotatory opening of 1-benzocyclobutene derivatives appears to be no relevant. Rather, the ratio of (*E*)- and (*Z*)-xylylenes is dictated by electronic factors which finally determines the stereochemical outcome.

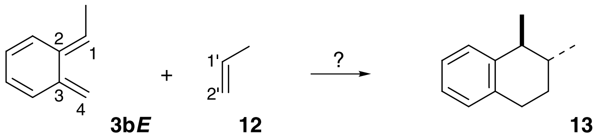
Some experimental results are in accordance with an inward rotation and the easy formation of *Z*-xylylenes. Thus, in the course of the synthesis of alkaloid skeletons, Oppolzer has observed the formation of the following tricyclic lactames by heating a benzocyclobutene amide at 110 °C. The structure of the major isomer could result of the formation of the *Z*-xylylene which cyclized according to an *exo* transition state, rather than the postulated very strained *endo* transition state with the corresponding *E*-xylylene (Scheme 5).[17]

3. Diels–Alder reactions of *o*-xylylenes with propene

In order to explain the selectivity observed during the formation of B-ring of steroids, we next decided to examine the cycloaddition step. The cycloaddition of the methylxylylene **2b**_E_ with propene **12** providing the *trans*-dimethyltetraline **13** (Scheme 6) can be an interesting model for the



Scheme 5.



Scheme 6.

Table 2. Calculated HOMO and LUMO energies, coefficients of the HOMO and the LUMO, relative weights of coefficients of *o*-xylylenes **1b**–**11b***E* and **12** at the Becke 3LYP/6-311G(d,p) level[a]

	HOMO energy (eV) (n°)	HOMO coeff.	C(4)/C(1) coeff. ratio[b]	LUMO energy (eV) (n°)	LUMO coeff.	C(4)/C(1) coeff. ratio[c]
1b	−5.547 (28)	C(1): 0.164 C(4): −0.164	1	−2.250 (29)	C(1): −0.168 C(4): −0.168	1
2b*E*	−5.358 (32)	C(1): 0.178 C(4): −0.191	1.073	−2.048 (33)	C(1): 0.195 C(4): 0.185	0.949
2b*Z*	−5.349 (32)	C(1): 0.129 C(4): −0.131	1.015	−2.041 (33)	C(1): −0.143 C(4): −0.134	0.937
3b*E*	−5.066 (36)	C(1): 0.158 C(4): −0.203	1.285	−1.905 (37)	C(1): 0.193 C(4): 0.178	0.922
3b*Z*	−4.952 (36)	C(1): 0.121 C(4): −0.136	1.124	−1.737 (37)	C(1): −0.143 C(4): −0.127	0.888
4b*E*	−4.787 (32)	C(1): 0.149 C(4): −0.205	1.376	−1.721 (33)	C(1): 0.199 C(4): 0.160	0.804
4b*Z*	−4.852 (32)	C(1): 0.133 C(4): −0.187	1.406	−1.615 (33)	C(1): −0.182 C(4): −0.150	0.824
5b*E*	−5.397 (39)	C(1): 0.157 C(4): −0.201	1.280	−2.373 (40)	C(1): 0.178 C(4): 0.180	1.011
5b*Z*	−5.462 (39)	C(1): 0.146 C(4): −0.197	1.349	−2.391 (40)	C(1): −0.180 C(4): −0.176	0.978
6b*E*	−5.294 (43)	C(1): 0.148 C(4): −0.218	1.473	−2.200 (44)	C(1): 0.175 C(4): 0.198	1.131
6b*Z*	−5.407 (43)	C(1): 0.150 C(4): −0.219	1.460	−2.205 (44)	C(1): −0.176 C(4): −0.213	1.210
7b*E*	−5.826 (39)	C(1): 0.171 C(4): −0.175	1.023	−2.764 (40)	C(1): 0.158 C(4): 0.205	1.297
7b*Z*	−5.727 (39)	C(1): 0.160 C(4): −0.142	0.891	−2.653 (40)	C(1): −0.131 C(4): −0.179	1.364
8b*E*	−6.122 (34)	C(1): 0.134 C(4): −0.122	0.910	−3.231 (35)	C(1): 0.121 C(4): 0.139	1.149
8b*Z*	−6.097 (34)	C(1): 0.134 C(4): −0.118	0.880	−3.138 (35)	C(1): 0.119 C(4): 0.141	1.185
9b	−5.276 (31)	C(1): 0.094 C(4): −0.151	1.596	−1.938 (32)	C(1): 0.129 C(4): 0.107	0.829
10b*E*	−5.094 (40)	C(1): 0.115 C(4): −0.146	1.269	−1.929 (41)	C(1): −0.144 C(4): −0.113	0.785
11b*E*	−5.168 (40)	C(1): 0.179 C(4): −0.161	0.899	−1.849 (41)	C(1): 0.161 C(4): 0.195	1.211
12	−7.154 (12)	C(1′): 0.169 C(2′): 0.185	1.095	0.021 (14)	C(1′): 0.188 C(2′): −0.155	0.824

[a] Atom numbering is as in Schemes 3 and 4.

[b] Relative weights of coefficients (2s, $2p_x$, $2p_y$, $2p_z$) at C(1) and C(4) (or C(1′) and C(2′) for **12**) of the HOMO.

[c] Relative weights of coefficients (2s, $2p_x$, $2p_y$, $2p_z$) at C(1) and C(4) (or C(1′) and C(2′) for **12**) of the LUMO.

intramolecular addition (Scheme 1).[18] At the B3LYP/6-311G(d,p) level, the *trans*-dimethyltetraline **13** is 56.7 kcal/mol more stable than the reactants.[19]

According to the frontier-orbital theory applied to the Diels–Alder reactions, the main contributor to the rate determining step is the transfer of electrons from the diene to the dienophile. Thus, the stereodirecting orbitals are the HOMO of the diene (donor) and the LUMO of the dienophile (acceptor).[20] The regioselectivity of the reactions can be predicted from the HOMO and LUMO polarization (match up the larger coefficient on one component with the larger on the other).

Propene is a dienophile without activating electron withdrawing substituent. Consequently, two interactions between either the LUMO of the xylylene **2b***E* and the HOMO of the propene (Δ*E* xylylene/propene: $E_{\text{LUMO}}-E_{\text{HOMO}}=5.106$ eV) (Type II according to the classification of Sustmann)[21] or the HOMO of **2b***E* and the LUMO of the propene (Δ*E* xylylene/propene: $E_{\text{HOMO}}-E_{\text{LUMO}}=5.379$ eV) can occur (Table 2). However, this last case presents a more favorable configuration concerning the orbital overlap (Type I). The frontier MO energies imply that the methylxylylene **2b***E* should be slightly more electrophilic than propene. The reverse situation should be noted for methoxyxylylenes **10b***E* and **11b***E* (Δ*E* (eV) xylylene/propene: **10b***E*, $E_{\text{HOMO}}-E_{\text{LUMO}}=5.12$; $E_{\text{LUMO}}-E_{\text{HOMO}}=5.23$. **11b***E*, $E_{\text{HOMO}}-E_{\text{LUMO}}=5.19$; $E_{\text{LUMO}}-E_{\text{HOMO}}=5.31$). The donor character of the methoxy group induces a decreasing of the electrophilic properties of xylylene.

The C(4)/C(1) coefficient ratios for HOMO and LUMO are given in Table 2. From the examination of these results, we would predict the formation of the '*ortho*' products for the reaction of propene with **7b***Z*, **8b***E*, **8b***Z* and **11b***E* and the '*meta*' products in the other cases. It is interesting to note that the addition reaction of **11b***E* with propene is the sole case where the regioselectivity is in accordance with the intramolecular reaction used in the synthesis of steroids (Fig. 1).

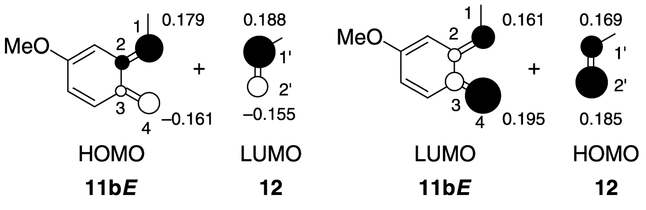
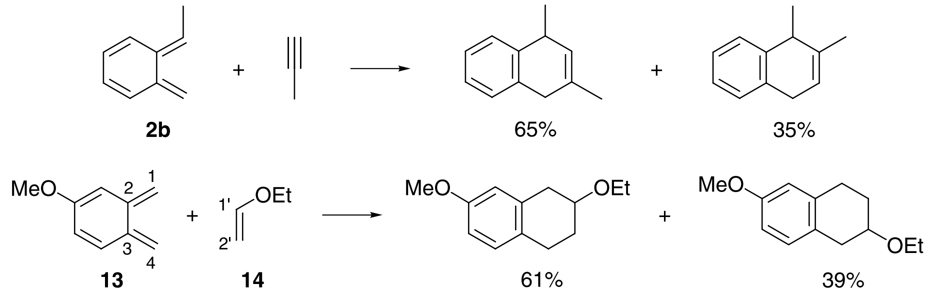


Figure 1.

To the best of our knowledge, only one experimental result concerns the Diels–Alder reaction of methylxylylene **2b**. Indeed, Fleming et al. have studied the regiochemistry of the reaction of **2b** with propyne and as expected the major product was the '*meta*' isomer (Scheme 7).[22]

The same authors have studied the cycloaddition of methoxyxylylene **13** to the ethylvinylether **14**. The adducts are obtained in poor regioselectivity which is plainly not steric in origin. We have calculated at the Becke3LYP/6-311G(d,p) level the structure of **13** and **14** (Table 3). The Diels–Alder reaction is of Type II according to the classification of Sustmann, since the separation between the LUMO of the xylylene **13** and the HOMO of **14** (Δ*E* **13**/



Scheme 7.

Table 3. Calculated HOMO and LUMO energies, coefficients of the HOMO and the LUMO, relative weights of coefficients of *o*-xylylene **13** and ethylvinylether **14** at the Becke 3LYP/6-311G(d,p) level[a]

	HOMO energy (eV) (n°)	HOMO coeff.	C(4)/C(1) coeff. ratio[b]	LUMO energy (eV) (n°)	LUMO coeff.	C(4)/C(1) coeff. ratio[c]
13	−5.15 (36)	C(1): 0.141 C(4): −0.109	0.77	−2.21 (37)	C(1): 0.119 C(4): 0.137	1.150
14	−6.29 (20)	C(1′): 0.123 C(2′): 0.180	0.68	0.17 (22)	C(1′): 0.163 C(2′): −0.140	1.16

[a] Atom numbering is as in Scheme 7.

[b] Relative weights of coefficients (2s, $2p_x$, $2p_y$, $2p_z$) at C(1) and C(4) (or C(1′) and C(2′) for **14**) of the HOMO.

[c] Relative weights of coefficients (2s, $2p_x$, $2p_y$, $2p_z$) at C(1) and C(4) (or C(1′) and C(2′) for **14**) of the LUMO.

14: $E_{\mathrm{LUMO}}-E_{\mathrm{HOMO}}=4.08$ eV) is smaller than the separation between the HOMO of **13** and the LUMO of **14** (ΔE **13/14**: $E_{\mathrm{HOMO}}-E_{\mathrm{LUMO}}=5.32$ eV). Interestingly, the observed regioselectivity is in accordance with the orbital coefficients.

4. Conclusion

In conclusion, this study show that the formation of (*Z*)-xylylenes is unexpectedly possible. Indeed, in the case of xylylenes **3b**, **4b** and **5b**, calculations have proven that the (*Z*)-isomers were the most stable in each case. Amazingly, even the presence of a sterically hindered substituent such as a *N*-methylformamido group is in agreement with the formation of a (*Z*)-xylylene.

Thus, the favored formation of (*Z*)-xylylene seems to be dictated by electronic factors rather than steric control. Moreover, most of the time, the regioselectivity of the Diels–Alder reaction is imposed by the intramolecular reaction character whereas the frontier MO coefficients are rather in favor of the opposite regioselectivity.

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References and notes

1. (a) Pellissier, H.; Santelli, M. *Tetrahedron* **1996**, *52*, 9093–9100. (b) Burtin, G.; Pellissier, H.; Santelli, M. *Tetrahedron* **1998**, *54*, 4913–4922. (c) Burtin, G.; Pellissier, H.; Santelli, M. *Tetrahedron* **1998**, *54*, 8065–8074. (d) Wilmouth, S.; Pellissier, H.; Santelli, M. *Tetrahedron* **1998**, *54*, 10079–10088. (e) Wilmouth, S.; Pellissier, H.; Santelli, M. *Tetrahedron* **1998**, *54*, 13805–13812. (f) Cachoux, F.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* **2000**, *41*, 1767–1769. (g) Cachoux, F.; Ibrahim-Ouali, M.; Santelli, M. *Synlett* **2000**, *3*, 418–420. (h) Michellys, P. Y.; Maurin, Ph.; Toupet, L.; Pellissier, H.; Santelli, M. *J. Org. Chem.* **2001**, *66*, 115–122. (i) Maurin, Ph.; Ibrahim-Ouali, M.; Santelli, M. *Eur. J. Org. Chem.* **2002**, 151–156.
2. (a) Akhrem, A. A.; Titov, Y. A. *Total steroid synthesis*; Plenum: New York, 1970. (b) Blickenstaff, R. T.; Ghoosh, A. C.; Wolf, G. C. *Total steroid synthesis*; Academic: New York, 1974.
3. (a) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3833–3834. (b) Oppolzer, W.; Keller, K. *J. Am. Chem. Soc.* **1971**, *93*, 3836–3837. (c) Oppolzer, W. *Tetrahedron Lett.* **1974**, 1001–1004. (d) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10–22. (e) Oppolzer, W.; Petrzilka, M.; Bättig, K. *Helv. Chim. Acta* **1977**, *60*, 2964–2967. (f) Oppolzer, W.; Bättig, K.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 1945–1947.
4. (a) Kametani, T.; Fukumoto, K. *Heterocycles* **1975**, *3*, 29–56. (b) Kametani, T.; Kato, Y.; Honda, T.; Fukumoto, K. *Heterocycles* **1976**, *4*, 241–246. (c) Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 3378–3379. (d) Kametani, T.; Matsumoto, H.; Nemoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1978**, *100*, 6218–6220.
5. Michellys, P. Y.; Pellissier, H.; Santelli, M. *Tetrahedron Lett.* **1993**, *34*, 1931–1934.
6. Jefford, C. W.; Bernardinelli, G.; Wang, Y.; Spellmeyer, D. C.; Buda, A.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1157–1165.
7. (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989–7991. (b) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099–2111. (c) Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3412–3416. (d) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault,

C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2127–2129.

8. Michellys, P. Y.; Pellissier, H.; Santelli, M. *Org. Prep. Proc. Int.* **1996**, *28*, 545–608.
9. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B,* **1988**, *37*, 785–789.
10. ZPE-s scaled by a factor of 0.989, as recommended for the Becke3LYP/6-311G* level, see: Bauschlicher, C. W., Jr.; Partridge, H. *J. Chem. Phys.* **1995**, *103*, 1788–1791.
11. Boese, R.; Bläser, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 304–305.
12. Schomaker, V.; Trueblood, K. N. *Acta Crystallogr.* **1968**, *B24*, 63–76.
13. At the B3LYP/6-31G* level, **1b** has a planar structure, see: Di Valentin, C.; Freccero, M.; Sarzi-Amadè, M.; Zanaletti, R. *Tetrahedron* **2000**, *56*, 2547–2559.
14. The activation parameters have been measured for the equilibrated opening of benzocyclobutene into *o*-xylylene (ΔH=37.4 kcal/mol, ΔS=1.06 cal K^{-1} mol^{-1}) and for its later cyclisation (ΔH=26.3 kcal/mol, ΔS=−6.1 cal K^{-1} mol^{-1}) by shock tube technic. Consequently, benzocyclobutene exhibits a greater stability (11.1 kcal/mol) than the corresponding *o*-xylylene (see, Ref. 15c).
15. (a) Roth, W. R.; Biermann, M.; Dekker, H.; Jochems, R.; Mosselman, C.; Hermann, H. *Chem. Ber.* **1978**, *111*, 3892–3903. (b) Roth, W. R.; Scholz, B. P. *Chem. Ber.* **1981**, *114*, 3741–3750. (c) Roth, W. R.; Ebbrecht, T.; Beitat, A. *Chem. Ber.* **1988**, *121*, 1357–1358.
16. Jensen, F. R.; Coleman, W. E.; Berlin, A. J. *Tetrahedron Lett.* **1962**, 15–18.
17. (a) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3834–3835. See also, (b) Cachoux, F.; Ibrahim-Ouali, M.; Santelli, M. *Synth. Commun.* **2002**, *23*, 3549–3560. (c) Cachoux, F.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 843–845.
18. For studies concerning the reactivity and the *endo–exo* selectivity in Diels–Alder reaction of o-xylylene, see: Di Valentin, C.; Freccero, M.; Sarzi-Amadè, M.; Zanaletti, R. *Tetrahedron* **2000**, *56*, 2547–2559.
19. Total energy (hartree): propene, −117.94563; *trans*-dimethyltetraline, −467.05166. Corminboeuf et al. have performed at the B3LYP/6-31G* level of theory the reaction path of the Diels–Alder reaction of **1b** and ethene, the activation barrier is found to be 8.2 kcal/mol, and the tetraline is 68.9 kcal/mol more stable than the reactants, see: Corminboeuf, C.; Heine, T.; Weber, J. *Org. Lett.* **2003**, *5*, 1127–1130.
20. (a) Klopman, G. In *Chemical reactivity and reaction paths*; Klopman, G., Ed.; Wiley-Interscience: New York, 1974; p 145. (b) Fleming, I. *Frontier orbitals and organic chemical reactions*; Wiley-Interscience: New York, 1976.
21. Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779–807.
22. Fleming, I.; Gianni, F. L.; Mah, T. *Tetrahedron Lett.* **1976**, 881–884.