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1,3-Dipolar Cycloaddition of Diazomethane to Chiral Azlactones. Experimental and Theoretical Studies

Carlos Cativiela, María D. Díaz-de-Villegas*, José I. García*, Ana I. Jiménez

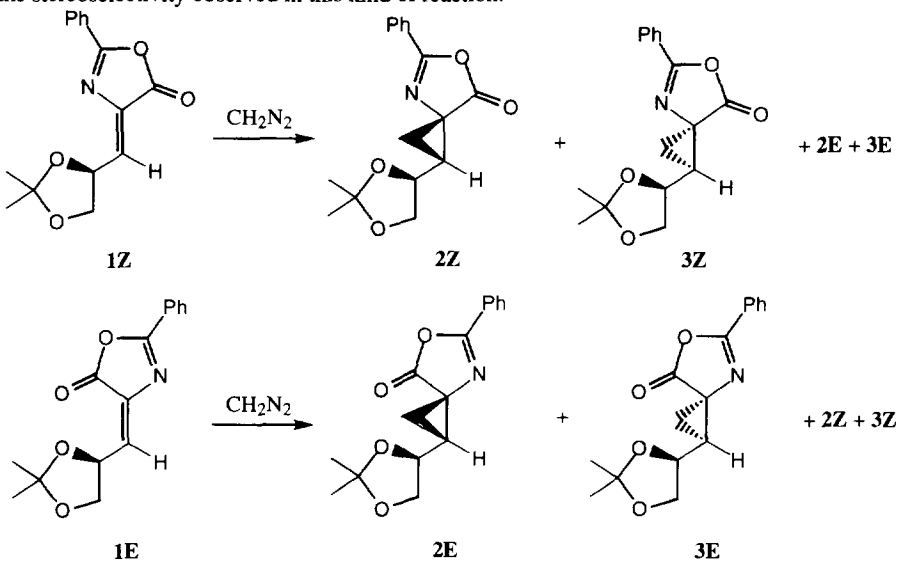
Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Facultad de Ciencias, C.S.I.C.–Universidad de Zaragoza, E-50009 Zaragoza (España).

Abstract: The reaction of (*E*)-2-phenyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4*H*)-oxazolone with diazomethane has been studied under a variety of reaction conditions, and the results compared with those obtained with the corresponding (*Z*)-isomer. The origin of the high diastereofacial selectivity in the cyclopropane products, observed with both oxazolones, is discussed in the light of theoretical calculations of the first reaction step, *i.e.*, the 1,3-dipolar cycloaddition of diazomethane, carried out at the semiempirical (AM1) and *ab initio* (RHF/3-21G) levels. Both theoretical levels correctly predict the direction of the asymmetric induction in the concerted reaction pathway leading to the Δ^1-pyrazoline. AM1 calculations predict also the existence of a stepwise reaction pathway leading to an open-chain reaction intermediate, which is not supported by the *ab initio* results. © 1997 Elsevier Science Ltd.

The development of new therapeutic agents based on non-proteinogenic amino acid has led to increased interest in the synthesis of new conformationally constrained amino acids.[1] Peptide analogues from 2,3-methanoamino acids are relatively rigid compounds due to the bond stretching imposed by the cyclopropyl moiety and the unsaturated character of this molecular fragment which, owing to *pseudoconjugation*, hinders rotation around the C_α–CO bond. These conformational restrictions give rise to important changes in peptide conformations,[2] modulating the ability of cyclopropyl analogues to interact with the active site of an enzyme or bio-receptor. Moreover, the presence of the cyclopropyl moiety also alters the reactivity of the peptidomimetic, increasing its stability towards enzymatic hydrolysis[3] in comparison with that of the parent-peptide and incorporating a reactive centre capable of capturing nucleophiles and electrophiles. Consequently, a number of cyclopropyl analogues can act as suicide inhibitors.[4] In this way, introduction of these methanologues into peptides provides a virtually unlimited means of manipulating their properties and, as a consequence, their bioactivities.

The undoubted interest in these compounds coupled with the excellent reactivity of (*Z*)-2-phenyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4*H*)-oxazolone (**1Z**), an azlactone derived from 2,3-*O*-isopropylidene-*D*-glyceraldehyde, towards diazomethane,[5] and its versatility in the synthesis of a wide variety of cyclopropylamino acids of *cis* configuration[6] encouraged us to study to the behaviour of (*E*)-2-phenyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4*H*)-oxazolone (**1E**). The use of this compound should lead to a new family of cyclopropyl derivatives which are stereoisomeric with those obtained from the (*Z*)-isomer.

In this paper we describe the experimental results obtained in the cyclopropanation reactions of **1E** with diazomethane under a variety of conditions (Scheme 1), and we also present a theoretical study dealing with the origin of the stereoselectivity observed in this kind of reaction.



Scheme 1

RESULTS AND DISCUSSION

The reaction of **1E** with diazomethane takes place smoothly at low temperature in only a few minutes. As in the case of **1Z**, no traces of Δ^1-pyrazolines could be detected in any case, and the reaction leads directly to the corresponding cyclopropane **2E** as the major product. Examination of the crude reaction mixture by hplc indicated a high *trans/cis* selectivity ([**2E**+**3E**]:[**2Z**+**3Z**], ≥85:≤15) as well as excellent diastereoselectivity for both *trans* (**2E**:**3E**, ≈95:5) and *cis* (**2Z**:**3Z**, ≈90:10) compounds. The results obtained in the reaction of **1E** with diazomethane in several solvents at different temperatures are given in Table 1. The results obtained in a previous study[5] of the reactions of **1Z** are also included for the sake of comparison.

It is worth noting that *cis/trans* isomerization takes place to a greater extent in the case of **1Z**. This isomer is the thermodynamically most stable and so isomerization of the azlactone prior to the reaction with diazomethane can be ruled out as the cause of the appearance of mixtures of isomers in the products.

Performing a complete theoretical study of the possible reaction paths of these systems is undoubtedly a difficult task and we have therefore concentrated our efforts on the first step of the reaction; the 1,3-dipolar cycloaddition of diazomethane to the corresponding azlactones **1Z** and **1E**. Given the size of the system in question, we started with quantum chemical calculations at a semiempirical level. In previous studies we have shown that the AM1 Hamiltonian[7] is able to provide results which are in good agreement with the experimental observations made in the Diels–Alder reactions of **1Z**[8] and **1E**[9] with cyclopentadiene and other dienes. As a consequence, we chose this method to study the reactants, transition structures (TS), and Δ^1-pyrazoline intermediates of the reactions considered in this investigation.

Table 1. Results obtained in the reactions of **1E** and **1Z** with diazomethane under various experimental conditions.

		1E			**1Z**[a]		
solvent	T (°C)	*cis* **2Z:3Z**	*trans* **2E:3E**	*cis/trans*	*cis* **2Z:3Z**	*trans* **2E:3E**	*cis/trans*
hexane	0	89:11	95:5	14:86	84:16	87:13	77:23
	–20	89:11	94:6	13:87	84:16	87:13	78:22
	–40	90:10	94:6	13:87	88:12	90:10	83:17[b]
CCl_4	0	91:9	94:6	9:91	88:12	91:9	84:16
	–20	90:10	94:6	8:92	85:15	91:9	83:17
benzene	0	89:11	95:5	15:85	90:10	93:7	81:19

[a] Ref. 5. [b] –50°C.

Firstly, we considered the reactants (**1Z**, **1E**, and diazomethane), the transition structures corresponding to a concerted mechanism (**TSZ_Re**, **TSZ_Si**, **TSE_Re**, and **TSE_Si**), and the corresponding Δ^1-pyrazolines as the intermediate products (**PZ_Re**, **PZ_Si**, **PE_Re**, and **PE_Si**). A number of relevant geometric parameters are shown in Figures 1 and 2 and the calculated heats of formation are given in Table 2.

Table 2. Calculated (AM1) energies of the reactants, transition structures, reaction intermediates, and Δ^1-pyrazolines for the reactions of **1Z** and **1E** with diazomethane.

Reaction of **1Z**		Reaction of **1E**	
Compound	Heat of form. (kcal·mol^{-1})	Compound	Heat of form. (kcal·mol^{-1})
diazomethane	62.63		
1Z	–85.47	**1E**	–84.57
TSZ_Re	–8.96	**TSE_Re**	–3.51
TSZ_Si	0.95	**TSE_Si**	–8.41
PZ_Re	–49.98	**PE_Re**	–48.65
PZ_Si	–49.35	**PE_Si**	–48.70
TSZ2_Re	–8.36	**TSE2_Re**	0.83
TSZ2_Si	–0.16	**TSE2_Si**	–7.41
IZ_Re	–14.32	**IE_Re**	–10.32
IZ_Si	–11.90	**IE_Si**	–13.66

Compounds **1Z** and **1E** both exhibit similar conformational preferences. In each case, there is only one deep minimum in the potential energy surface, indicating that there is only a single preferred conformation for each compound. For **1E**, the dihedral angle between the double bond and the chiral group (H–C_1—C_2–H, see Figure 1) in the minimum has a value of –149.3°, whereas the same angle has a value of –131.2° in the case of **1Z**. As a consequence the opposite face of the double bond is preferentially shielded by the chiral group in each case (Figure 1), *i.e.*, the C_α-Si face is shielded in the case of **1Z** and the C_α-Re face in the case of **1E**. From a thermochemical viewpoint, **1Z** is calculated to be more stable than **1E** by 0.90 kcal·mol^{-1} and this is in excellent agreement with the isomer distribution observed in the synthesis of these azlactones.

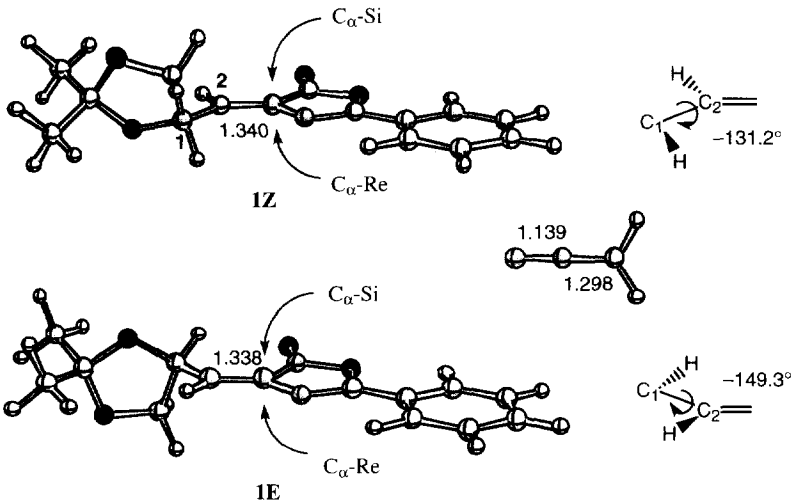


Figure 1. Calculated (AM1) structures of **1Z**, **1E**, and diazomethane.

As regards the transition structures (Figure 2), it is worth noting that they are all very asynchronous, with the new C–C bond formed to a greater extent than the corresponding new N–C bond. However, intrinsic reaction coordinate (IRC) calculations show that these TS lead to the reactants and Δ^1-pyrazolines in a continous path without the formation of intermediates, *i.e.*, the mechanism is concerted. The calculated heats of formation of these TS show that **TSZ_Re** is more stable than **TSZ_Si** by 9.91 kcal·mol^{-1}, which is in qualitative agreement with the high diastereofacial selectivity in the cyclopropane products observed in the reactions of **1Z**. Likewise, **TSE_Si** is more stable than **TSE_Re** by 4.90 kcal·mol^{-1}, which is also in agreement with the experimental results.

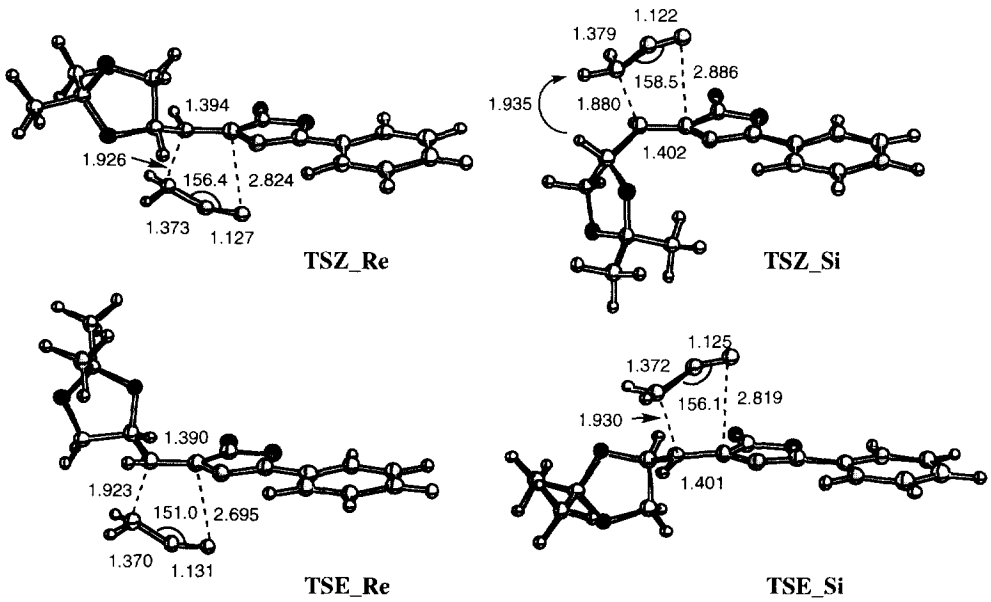


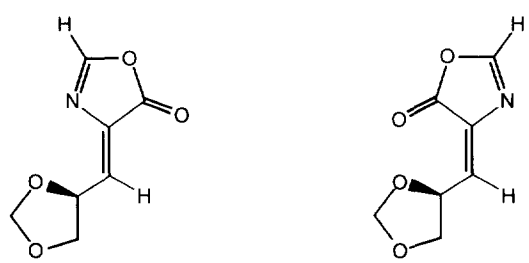
Figure 2. Calculated (AM1) structures of **TSZ_Re**, **TSZ_Si**, **TSE_Re**, and **TSE_Si**.

As far as the chiral auxiliary is concerned, the relative position of the diololane ring with respect to the double bond and the oxazolone plane is changed to a lesser extent for those attacks leading to the most stable TS, *i.e.*, the C_α-Re attack in the case of **1Z** and the C_α-Si attack in the case of **1E**. Thus, in the first case the H–C_1—C_2–H dihedral angle changes from −131.2° (**1Z**) to −164.3° (**TSZ_Re**) and 104.7° (**TSZ_Si**) respectively, whereas in the second case, this dihedral angle changes from −149.3° (**1E**) to −166.2° (**TSE_Si**) and 172.6° (**TSE_Re**) respectively. The change in the dihedral angle caused by the approach of the diazomethane molecule, which is far from its equilibrium value in the case of **TSZ_Si** and **TSE_Re**, can explain to some extent the energy differences calculated for the four TS. Furthermore, in the case of **TSZ_Si**, a close contact between two hydrogen atoms, one from the chiral auxiliary and one from the diazomethane, can help to explain the greater energy difference between C_α-Re and C_α-Si attack for **1Z** when compared with **1E** (Figure 2).

The pronounced asynchronicity of the calculated TS, in which only the C–C bond is partially formed, led us to consider stepwise reaction paths with diradical open-chain intermediates. The corresponding TS (**TSZ2_Re**, **TSZ2_Si**, **TSE2_Re**, and **TSE2_Si**) and intermediates (**IZ_Re**, **IZ_Si**, **IE_Re**, **and IE_Si**) were indeed found, and their calculated heats of formation are shown in Table 2.

As can be seen, the same preference for the attack of diazomethane is observed in both the open-chain TS and the cyclic TS. In the case of the favoured attacks, the cyclic TS is always more stable than the corresponding open-chain TS, which indicates that the concerted mechanism is favoured over the stepwise process. The calculated energy differences are 0.60 and 1.00 kcal·mol^{-1} for the reactions of **1Z** and **1E** respectively. On the other hand, the same does not hold for the attack at the disfavoured face. Thus, whereas the cyclic **TSE_Re** is more stable than the open-chain **TSE2_Re** by 4.34 kcal·mol^{-1}, the opposite is true for the corresponding **TSZ_Si** and **TSZ2_Si**, with the latter being more stable by 1.11 kcal·mol^{-1}.

In any case, it is well-known that semiempirical calculations tend to favour stepwise mechanisms over concerted mechanisms,[10] so we decided to investigate the modelling of the addition of diazomethane by means of *ab initio* calculations. Given the complexity of the system, we performed the theoretical study on simpler model structures of **1Z** and **1E** (Scheme 2).



M1Z **M1E**

Scheme 2

The structures of the reactants and the transition structures were located at the RHF/3-21G level, and single point energy calculations were carried out at the RHF/6-31G* level using the 3-21G geometries. The same structures were also located at the semiempirical AM1 level for the purpose of comparison. The calculated geometries of some selected structures are shown in Figure 3, and the corresponding energies of all structures are given in Table 3.

Table 3. Calculated energies of the reactants, transition structures and reaction intermediates for the reaction of **M1Z** and **M1E** with diazomethane at semiempirical (AM1, kcal·mol^{-1}) and *ab initio* (RHF/3-21G and RHF/6-31G*, atomic units) theory levels.

Reaction of **M1Z**				Reaction of **M1E**			
structure	AM1	3-21G	6-31G*// 3-21G	structure	AM1	3-21G	6-31G*// 3-21G
CH_2N_2	62.63	−146.995820	−147.843202				
M1Z	−106.64	−619.524672	−623.007468	**M1E**	−105.55	−619.523643	−623.005824
TSMZ_Re	−30.02	−766.501413	−770.815105	**TSME_Re**	−24.49	−766.485229	−770.801695
TSMZ_Si	−25.08	−766.485846	−770.803651	**TSME_Si**	−29.42	−766.501040	−770.813628
TSMZ2_Re	−29.39	—[a]	—	**TSME2_Re**	−20.02	—[a]	—
TSMZ2_Si	−21.04	—[a]	—	**TSME2_Si**	−28.45	—[a]	—
IMZ_Re	−34.90	—[a]	—	**IME_Re**	−23.18	—[a]	—
IMZ_Si	−24.06	—[a]	—	**IME_Si**	−34.25	—[a]	—

[a] These structures could not be located at this theoretical level.

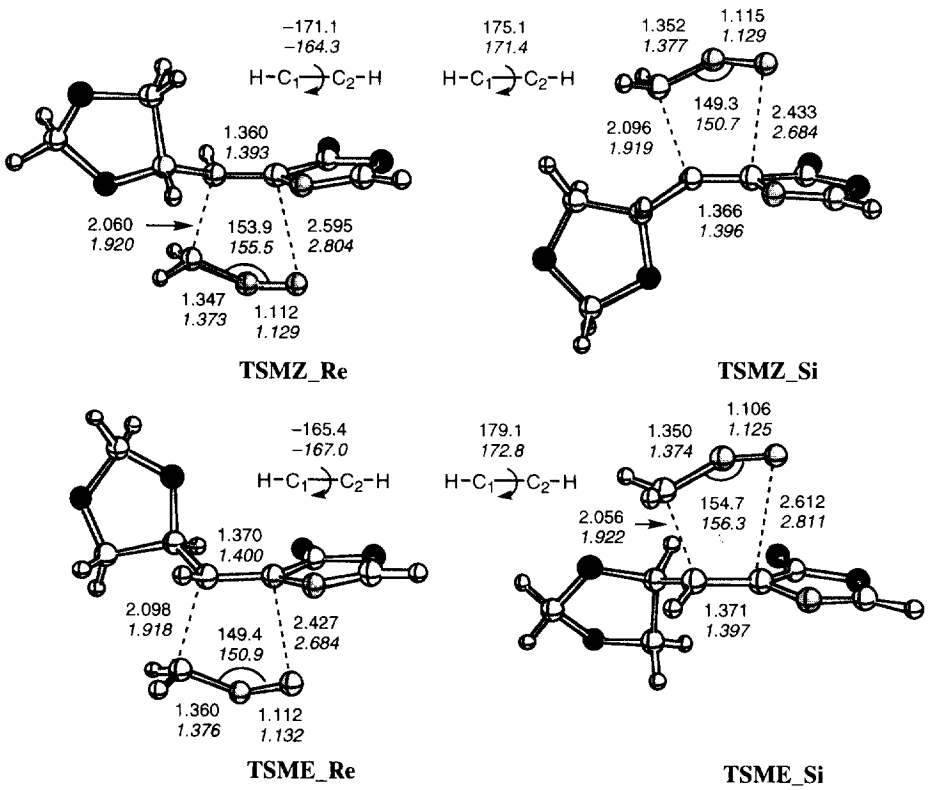


Figure 3. Calculated *ab initio* RHF/3-21G (normal typeface) and AM1 (italic typeface) structures of **TSMZ_Re**, **TSMZ_Si**, **TSME_Re**, and **TSME_Si**.

Firstly, it is important to note that the AM1 results are in qualitative and quantitative agreement with those previously obtained in terms of both structural and energy considerations. Only in the case of **TSMZ_Si** are there significant differences with the analogous **TSZ_Si**. The C–C and C–N bond distances for the newly forming bonds are different for both structures, as is the H–C_1—C_2–H dihedral angle. This could explain the energy difference with regard to **TSMZ_Re** (4.94 kcal·mol^{-1}), which is less than that calculated in the case of **TSZ_Re** and **TSZ_Si** (9.91 kcal·mol^{-1}). As a consequence, the comparison between semiempirical and *ab initio* results on the model compounds can be extrapolated to the reactions studied. With regard to the cyclic TS, it can be observed in Figure 3 that the *ab initio* structures correspond to a more synchronous reaction path. Thus, in all cases the distance of the newly forming C–N bond is shorter by *ca.* 0.2 Å when compared with the corresponding AM1 distance. Also, the distance of the newly forming C–C bond is longer than that deduced by *ab initio* calculations by *ca.* 0.1 Å. On the other hand, there is an almost perfect agreement between both theoretical methods as as far as the H–C_1—C_2–H dihedral angle is concerned.

The agreement between AM1 and *ab initio* calculations is also good in terms of the energy considerations. In each case the most stable TS is predicted to be the same, irrespective of the theory level used. *Ab initio* results indicate that Cα–Re attack is favoured over Cα-Si attack in the case of the (*Z*)-azlactone by 9.77 (RHF/3-21G) or 7.19 (RHF/6-31G*) kcal·mol^{-1}. The converse is true in the case of the (*E*)-azlactone, with values of 9.92 (RHF/3-21G) and 7.49 (RHF/6-31G*) kcal·mol^{-1} respectively. These results are in agreement with those previously obtained at the semiempirical level, and hence with those experimentally observed.

The question of the possible existence of a stepwise reaction pathway is also partially answered by the *ab initio* calculations. Indeed, after extensive searches, neither open-chain transition structures nor reaction intermediates could be located at the RHF/3-21G level in any case. In most cases, starting from the open-chain TS calculated at the AM1 level led to the reactants or the corresponding cyclopropane structures. Of course, the existence of stepwise reaction paths cannot be completely discarded on the basis of these results alone, but they at least corroborate the tendency of AM1 calculations to give this kind of structure, a tendency which is probably unrealistic.

In summary, we have shown that both AM1 and *ab initio* calculations can be helpful in explaining the stereochemical course of the asymmetric reaction of cyclopropanation of the chiral azlactones **1Z** and **1E**. Both methods correctly predict the sense of the diastereofacial selectivity in the cyclopropane products experimentally observed, based on the preferred attack of the diazomethane molecule in the 1,3-dipolar cycloaddition step. However, AM1 results lead to more asynchronous reaction paths, and also indicates the possible existence of diradical intermediates for these reactions. This possibility is not supported by the *ab initio* results, and the *cis/trans* isomerization observed experimentally probably takes place during the formation of the cyclopropane ring, in a step subsequent to the addition of the diazomethane.

EXPERIMENTAL

Reactions of 1E with diazomethane. The reactions were carried out following the experimental procedure described previously.[6b] The spectroscopic characterization of the corresponding cyclopropanes has also been reported elsewhere.[11]

Theoretical calculations. Semiempirical calculations were carried out using the AM1 Hamiltonian[7] as implemented in the MOPAC 6.0 program.[12] Transition structures for all the semiempirical calculations were located

by means of the eigenvector-following algorithm,[13] through the use of the "TS" keyword. Gradient norms were always below 0.1 kcal·mol^{-1}, and the existence of only one imaginary frequency, corresponding to the formation of the new C–C bond, was checked in all cases by means of "FORCE" calculations.

Ab initio calculations were carried out using the GAUSSIAN 92 program.[14] Full geometric optimizations were carried out at the RHF/3-21G level for all the minima and transition structures using the Schlegel algorithm.[15] Single point RHF/6-31G* calculations were carried out using the geometries obtained at the RHF/3-21G level.

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