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COMPUTATIONAL STUDY ON THE CYCLOPROPANATION REACTION OF YLIDES GENERATED FROM α -PYRIDINIUMACETATES

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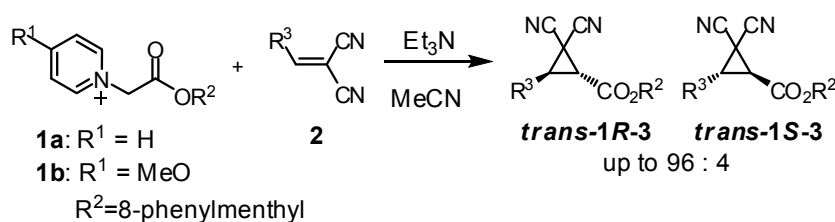
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Abstract – *Ab initio* MO calculations were performed on the cyclopropanation reaction of methylenemalononitriles with the ylide generated from α -pyridiniumacetates. The calculations indicated that the rate-determining step was the final cyclopropane forming step for the gas phase reaction, whereas solvent effect approximations implied that it was the initial Michael addition leading to the *cis* intermediate for reaction in water. It was also revealed that the plausible [3+2] cycloaddition reaction to give bicyclic products is more likely to be a stepwise and not an asynchronous concerted process in DFT calculations at the B3LYP/6-31G(d) level of theory.

INTRODUCTION

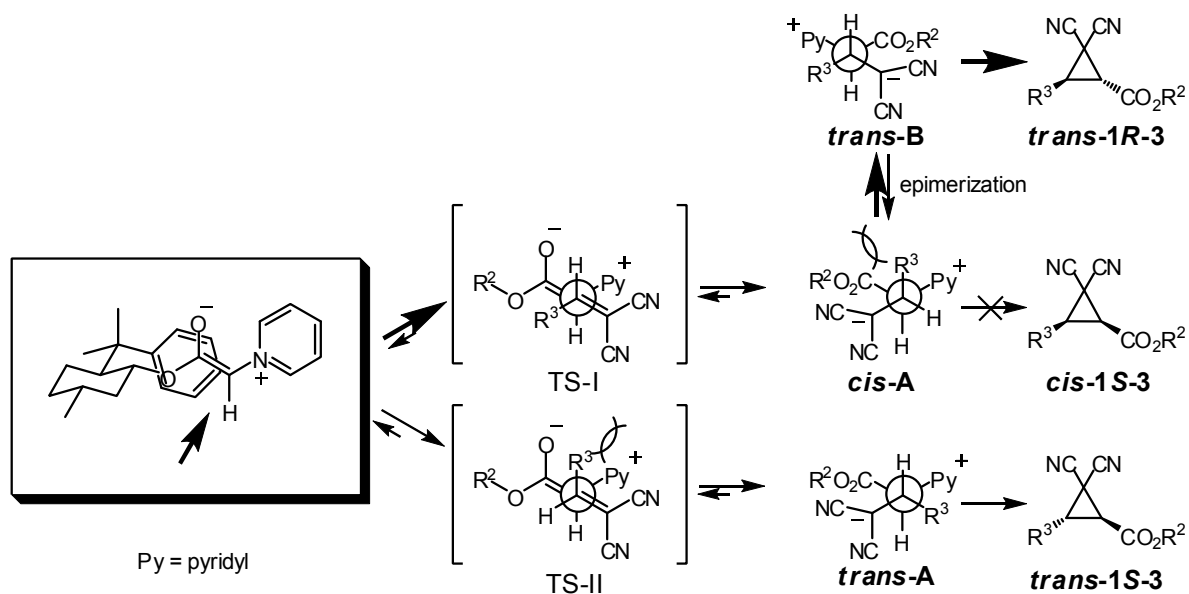
Cyclopropane derivatives have been known to show indigenous reactivity due to their intrinsic ring strain.¹ Therefore, cyclopropanes have been utilized as synthetic intermediates² and certain cyclopropanes have been found to show unique bioactivity.³ Optically active cyclopropanes bearing multiple numbers of electron withdrawing groups such as carbonyls are expected to be particularly useful since these substituents can all potentially be utilized as points of compound modification and enlargement. Previously known methods efficient for the asymmetric synthesis of such multi-functionalized cyclopropanes involve the use of Michael addition of ylide-type nucleophiles to activated olefins followed by a subsequent

intramolecular S_N2 reaction,⁴ with either a halogen,^{5,6} a sulfide (Corey-Chaykovski reaction),⁷ an arsine⁸ or an amine⁹ as the leaving group. The amine case involves the intermediacy of ammonium ylides and the reaction mechanism is similar to that of other ylide reactions. Pyridinium ylides, well known for their use as the 1,3-dipole component in [3+2] cycloaddition reactions,¹⁰ have also been shown to undergo the cyclopropanation reaction with pyridine as the leaving group.¹¹ Pyridinium ylides with electron withdrawing groups such as carbonyls are a unique class of reagents in that they can be generated from the corresponding pyridinium salts by the use of a base as weak as Et_3N . Furthermore, they are inert to carbonyls as acceptors and thus do not give rise to epoxides in contrast to ylides involving sulfide and halide (Cl and Br) leaving groups. Therefore, pyridinium ylides of this type can be regarded as completely chemoselective reagents. We¹² and then others¹³ have disclosed that asymmetric versions of the reaction could also be carried out. In our efforts, we used 8-phenylmenthol^{12a,c} as the chiral auxiliary of the pyridinium reagents to effect diastereoselective reactions with β -substituted methylenemalononitriles, and give highly functionalized cyclopropanes were obtained in exclusively the *trans* form with diastereoselectivities up to 96:4 favoring the ***trans-1R-3*** diastereomer (Scheme 1). We also later found 8-phenylmenthylamine to be effective and give the opposite *trans* diastereomer (*trans-1S*) as the major product.^{12b} In the reaction involving the ester reagent, based upon the stereochemistry of one product established by X-ray structural analysis, we postulated the mechanism of the reaction to be as outlined in Scheme 2. That is, in the initial Michael addition to conjugated alkenes, the thermodynamically more stable *E*-enolate reacts from the face opposite to that blocked by the phenyl group of the chiral auxiliary, and the relative orientation between the two reactants is *anti* so that dipole cancellation becomes the largest. This gives rise to a *cis*-cyclopropane precursor as the Michael adduct. However, since the *cis*-product was not obtained in the reaction, it was reasoned that the eclipse-type alignment of bulky substituents in the transition state conformation required for *cis* ring closure disfavors the process to occur and that epimerization at the highly acidic site α to the pyridine nitrogen in the Michael adduct intermediate precedes ring-closure to give the epimeric Michael adduct which subsequently furnishes the observed *trans*-cyclopropane with the observed 1*R* configuration. Facile deprotonation to generate the ylide by a base as weak as an alkylamine (vide supra) provides support for the assumption of epimerization. This mechanistic speculation on stereochemistry requires that the initial Michael addition step be rate determining. In order to determine whether or not our assumption on the



Scheme 1.

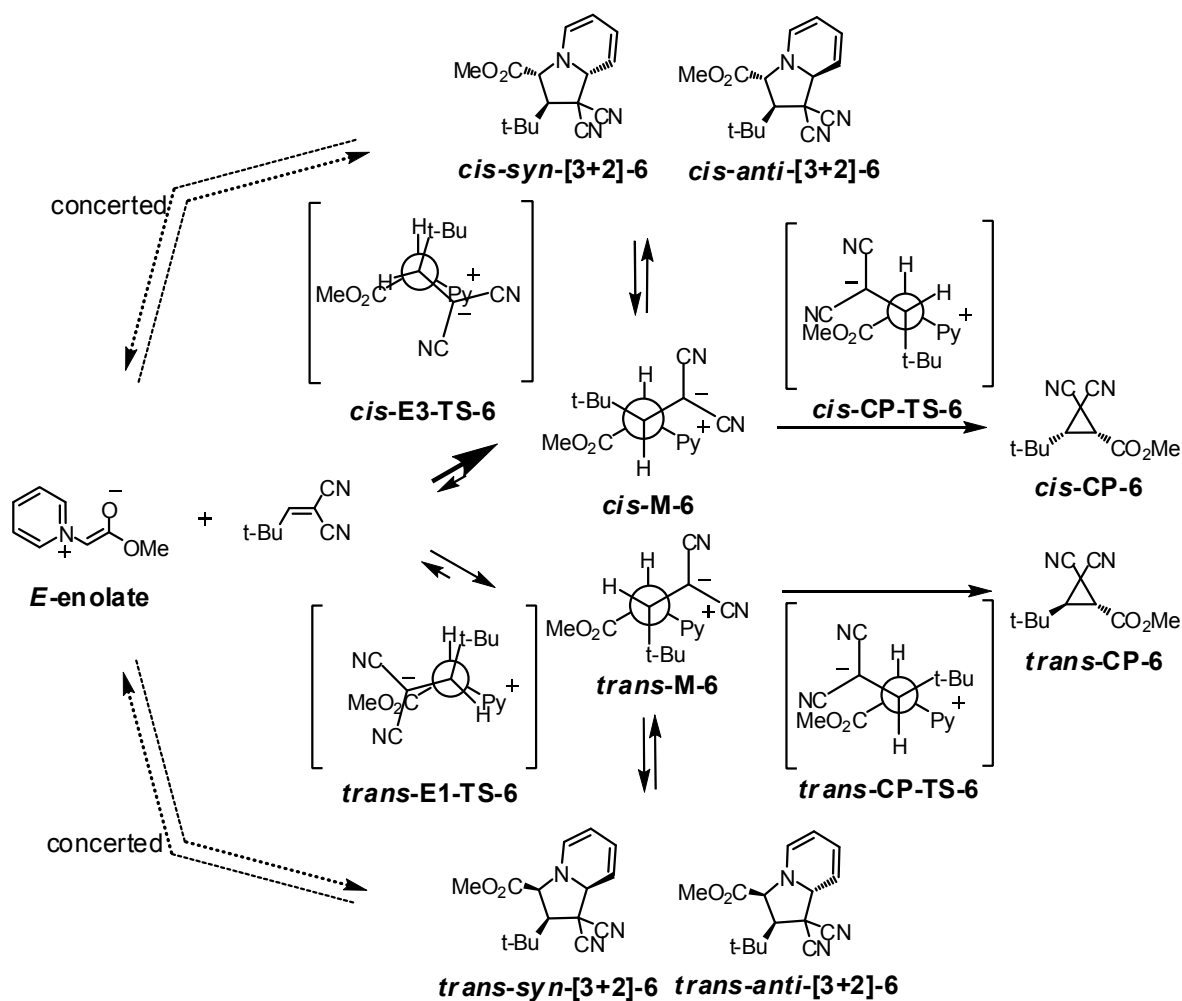
mechanism was correct and also to draw clues for designing reagents so as to increase selectivity, we thought it would be important to establish the mechanism of the whole reaction sequence. To this end, we carried out *ab initio* MO calculations at the HF/6-31G(d) level on model systems of the cyclopropanation reaction using methylenemalononitrile and ylides from α -pyridiniumacetates.^{14,15} We also carried out DFT calculations on selected processes. From the calculations, it was found that the [3+2] cycloaddition reaction involving pyridinium ylides to give bicyclic products (albeit not observed experimentally) is better described as a stepwise reaction and not a concerted one. It was also found that the global energy maximum along the reaction coordinate was dependent on the reaction phase, being the final ring closing step for the gas phase reaction, and shifting towards the initial Michael addition step upon considering water as a polar solvent. This suggested that the stereo-determining step in our experimental system is likely to be the first step as previously speculated. Furthermore, since contrary to the reactions of the pyridinium ylides, related reactions involving isoquinolinium ylides have been reported to give rise to [3+2] adducts instead of cyclopropanes, we thought theoretical calculations might allow us to rationalize the experimental discrepancies.¹⁶ Herein we present the details.



Scheme 2.

RESULTS AND DISCUSSION

In the cyclopropanation reaction of pyridinium ylides with substituted methylenemalononitriles, the first step of the reaction is deprotonation of the pyridinium salt to form the pyridinium ylide, of which two geometries are possible. As for the following step involving C-C bond formation, two routes can be envisioned for each geometrically isomeric enolate. One is Michael addition of the ylide followed by intramolecular S_N2 ring closure with extrusion of pyridine as depicted in Scheme 3. The other involves [3+2]-cycloaddition to form a bicyclic compound followed by heterolysis of the weaker C-C bond at the



Scheme 3.

2-position of the pyridine ring to give a Michael adduct-like species, which then undergoes ring closure. That is, there is a possibility between a two-step (the former) and a three-step (the latter) mechanism. The possibility of the latter mechanism evolves from the enormous precedence of [3+2]-type cycloaddition reactions involving 1,3-dipoles like the pyridinium ylides treated with here. In fact, reactions involving isoquinolinium ylides, which are structurally very similar to pyridinium ylides have been shown by Tsuge, Kanemasa and co-workers to experimentally give rise to [3+2] adducts and the authors have suggested that the reactions are concerted, judging from the stereochemistry of the adducts.¹⁶

Previous theoretical calculations on [3+2] cycloaddition involving aromatic imminium ylides, such as the pyridinium ylide in our case, have mostly centered on discussion involving the frontier orbitals of optimized reactant 1,3-dipole structures.¹⁷ As for computations involving the transition state for reactions involving pyridinium ylides and related 1,3-dipoles, there have been only a few previous examples. Namely, they are on the reactions between pyridinium ylides,¹⁸ phthalazinium ylides¹⁹ or pyridine oxides²⁰ and several alkenes, and the conclusion drawn from these examinations has been that the [3+2]

process corresponds to an asynchronous concerted mechanism. In the case of phthalazinium ylides, it was also suggested that in reactions involving either 1,3-dipoles bearing anion stabilizing groups on the carbanions or dipolarophiles with electron-withdrawing groups, the degree of asynchronicity increases but the reaction still remains concerted. Most calculations on the parent system of azomethine ylides, have also suggested a concerted but slightly asynchronous mechanism for the [3+2] reaction.^{21,22} Although examples are few, there are some instances where stepwise reactions are computed to be favored. Calculations on reactions involving *N*-metalated azomethine ylides have implied stepwise mechanisms.^{23,24} Furthermore, in the reaction with highly polar nitroethylene as the dipolarophile, computations have disclosed that the introduction of anion stabilizing phenyl groups to the azomethine ylide switches the mechanism from asynchronous concerted to stepwise.²⁴ Also, it has been implied for reactions involving allenes as the dipolarophile that cumulenetic strain imposes a stepwise cycloaddition reaction.²⁵ As a special case, for the reaction between non-polar unsubstituted ethylene and a charged partner such as allyl anion, where there is a large difference in the polar character between the two reactants, calculations suggested that the reaction is stepwise.^{25c}

In regards with our pyridinium system, we did not experimentally observe the formation of [3+2] adducts, either because the formation of such species is unfavorable compared with cyclopropanation or because they form only as transient species. Nonetheless, despite all the previous reports on closely related systems which suggest concerted mechanisms,¹⁸⁻²⁰ we thought it might be likely for the [3+2] cycloaddition reaction to shift completely towards a stepwise reaction since the 1,3-dipoles in our experimental system have one anion stabilizing group and the dipolarophile has two electron-withdrawing groups.

Calculations on the unsubstituted methylenemalononitrile system

As model compounds for the calculations, we decided to look into the parent unsubstituted methylenemalononitrile system with the DFT method with focus on the [3+2]-cycloaddition process (Scheme 4). Tabulated in Table 1 and illustrated in Figure 1, 2 are the results for the pyridinium ylides. In the transition state of the first step, there was a large difference in the distance between the two bonds to be formed (ca. 2.3 and ca. 3.1 Å) for the [3+2]-type reaction mode, thus suggesting that the cycloaddition

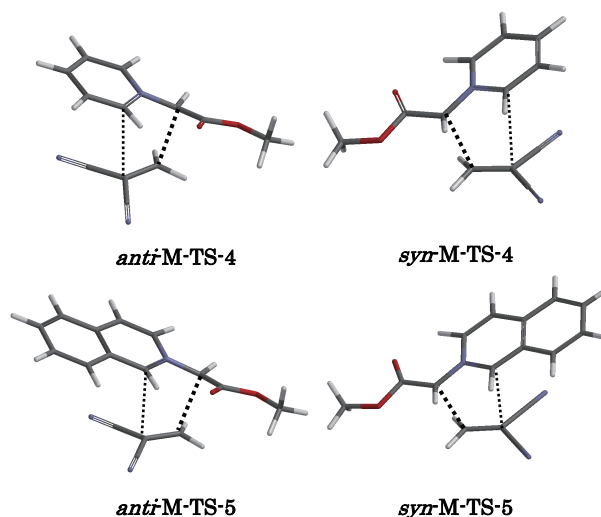
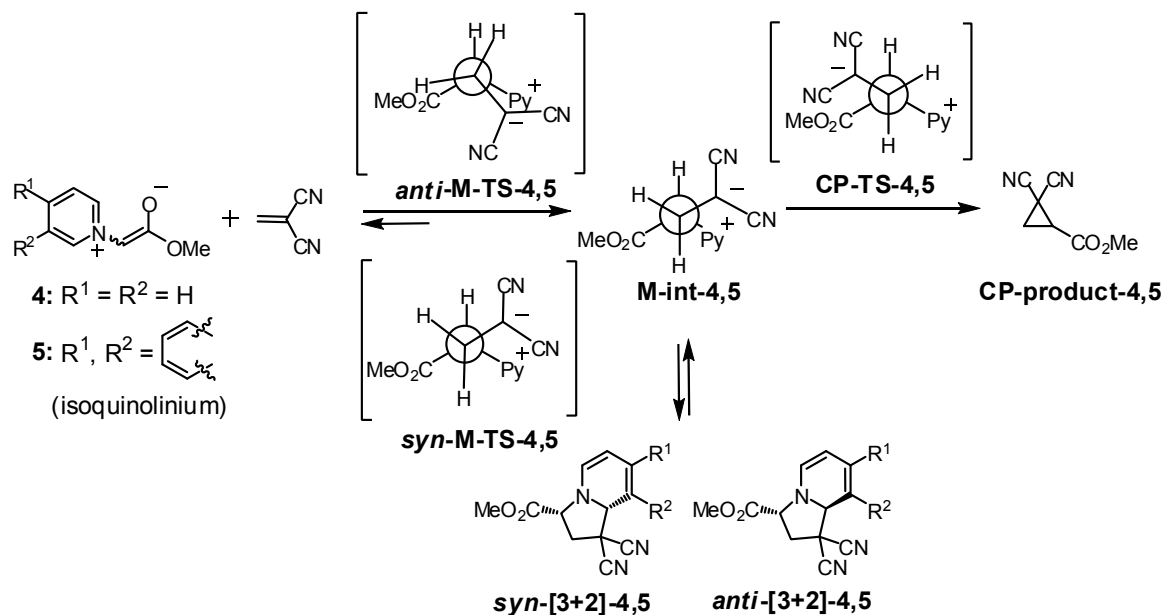


Figure 1. Main geometric features of the TS to Michael adduct found in the reactions between methyl α -pyridiniumacetate and methylenemalononitrile and between methyl α -isoquinoliniumacetate and methylenemalononitrile.



Scheme 4.

process is indeed stepwise. The profile of the imaginary frequency favors a stepwise mechanism. Furthermore, for the second bond formation a definable barrier existed. However, this barrier for the second bond formation was only ca. 0.7 kcal/mol, indicating that although the reaction is stepwise, it would be difficult to experimentally distinguish whether one or two steps are involved. The *anti* product was found to be the more stable of the two [3+2]-products. In regards with the cyclopropanation pathway of this system, the cyclopropane product is calculated to be more stable than the [3+2] adducts, as shown by the lower energy of **CP-product-4** compared with *anti*-[3+2]-4 (3.9 kcal/mol). Thus, the ultimate product would be expected to be cyclopropane. As for considerations of solvent, there was only a minimal effect on the relative energies of the intermediates and products. Thus, it is suggested that in the

Table 1. B3LYP/6-31G(d) calculations on the reaction between methyl α -pyridiniumacetate and methylidienemalononitrile^a

		Gas phase			Solution	
		ΔE (kcal/mol) ^b	Bond length 1 (Å) ^c	Bond length 2 (Å) ^d	Dipole moment (D)	ΔE (kcal/mol) ^e
TS to Michael adduct	<i>anti</i> -M-TS-4	15.7	2.310	3.060	7.30	
	<i>syn</i> -M-TS-4	14.0	2.317	3.067	5.57	
Michael adduct	M-int-4	7.2	1.607	2.646	9.06	
TS to [3+2]-adduct	<i>anti</i> -[3+2]-TS-4	7.9	1.451	2.212	7.68	
	<i>syn</i> -[3+2]-TS-4	8.2	1.579	2.098	6.89	
3+2-adduct	<i>anti</i> -[3+2]-4	3.9	1.550	1.613	6.20	3.9
	<i>syn</i> -[3+2]-4	6.6	1.555	1.686	6.32	6.4
TS to cyclopropane	CP-TS-4	24.6	—	—	14.39	
Cyclopropane ^f	CP-product-4	0.0	—	—	5.20	0.0

^aCalculated with the Spartan program. Representative gas phase energies calculated with the Gaussian 98 program gave the same relative values.

^bEnergy differences are given relative to **CP-product-4**. Values include zero point energy corrections. ^cCorresponds to the distance between the methylenecarbon atom of the acceptor and the carbon atom bearing the ester group of the ylide. ^dCorresponds to the distance between the carbon atom bearing the two cyano groups and the 2-carbon of the pyridine ring. ^eSolution values were calculated with water as the solvent using the Onsager model program implemented in the Gaussian 98 program. Values including zero point energy correction are in parentheses. ^fThe relative energies for the "Cyclopropane" section correspond to the sums of energies from structurally optimized cyclopropane and pyridine. The dipole value is that for only cyclopropane.

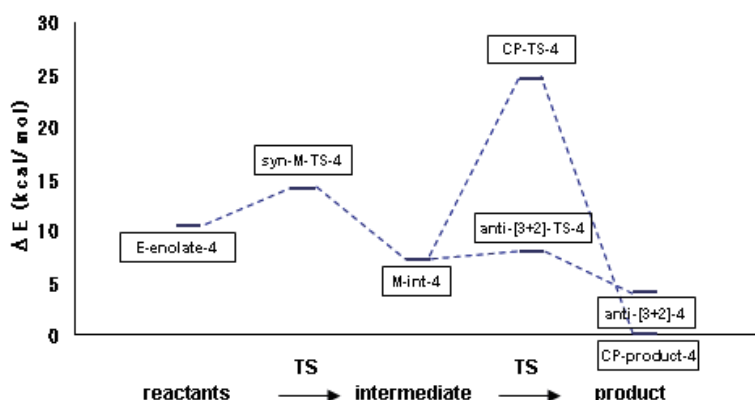


Figure 2. Energy diagram of the reaction between methyl α -pyridiniumacetate and methylidienemalononitrile. The relative energy for “*E*-enolate” corresponds to the sum of energies of the structurally optimized *E*-enolate and methylidienemalononitrile.

energy difference between the Michael adduct, **M-int-5**, and the transition state of the second bond formation, **anti-[3+2]-TS-5**. However, for **anti-[3+2]-M-5**, there is a large difference in the two distances corresponding to the bonds to be formed, and an electron density distribution analysis (isovalue = 0.03 electron/Å³) of the transition state visually shows that only one bond is formed (Figure 4). Furthermore, here again the imaginary frequency for the transition states to the Michael adduct only had intensity along the Michael addition bond forming axis. Therefore, it is more likely that the process is stepwise and not concerted. Although extensive calculations were carried for the corresponding *syn* route, the transition

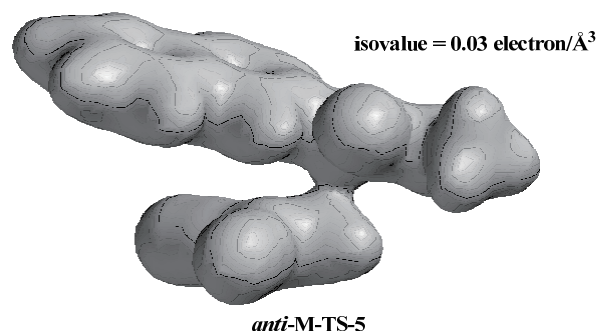


Figure 4. Bond density of the TS to the Michael adducts.

Table 2. B3LYP/6-31G(d) calculations on the reaction between methyl α -isoquinoliniumacetate and methylidienemalononitrile^a

		Gas phase			Solution	
		ΔE (kcal/mol) ^b	Bond length 1 (Å) ^c	Bond length 2 (Å) ^d	Dipole moment (D)	ΔE (kcal/mol) ^e
TS to Michael adduct	anti-M-TS-5	13.4	2.427	3.009	6.10	
	syn-M-TS-5	12.6	2.461	3.049	4.41	
Michael adduct	M-int-5	3.1	1.581	2.487	7.45	
TS to [3+2]-adduct	anti-[3+2]-TS-5	3.1	1.589	2.133	7.99	
	syn-[3+2]-TS-5^g	–	–	–	–	
3+2-adduct	anti-[3+2]-5	-5.2	1.552	1.611	5.75	-3.7
	syn-[3+2]-5	-2.3	1.552	1.659	5.90	-0.8
TS to cyclopropane	CP-TS-5	23.4	–	–	15.82	
Cyclopropane ^f	CP-product-5	0.0	–	–	5.20	0.0

^aCalculated with the Spartan program. Representative gas phase energies calculated with the Gaussian 98 program gave the same relative values.

^bEnergy differences are given relative to **CP-product-5**. Values include zero point energy corrections. ^cCorresponds to the distance between the methylidene carbon atom of the acceptor and the carbon atom bearing the ester group of the ylide. ^dCorresponds to the distance between the carbon atom bearing the two cyano groups and the 1-carbon of the isoquinoline ring. ^eSolution values were calculated with water as the solvent using the Onsanger model program implemented in the Gaussian 98 program. Values including zero point energy correction are in parentheses. ^fThe relative energies for the “Cyclopropane” section correspond to the sums of energies from structurally optimized cyclopropane and isoquinoline. The dipole value is that for only cyclopropane. ^gCould not be located.

pyridinium ylide system, the expected product is cyclopropane and the [3+2]-adducts are formed only as transient species, and that in a stepwise manner, regardless of whether the reaction is carried out in the gas phase or in solution.

Tabulated in Table 2 and illustrated in Figure 3 are the results for the isoquinolinium ylides. Implications from calculations on the isoquinolinium system are less apparent. In this case, there is no

state could not be located. The energy relationship between **M-int-5** and **anti-[3+2]-TS-5** suggests that the potential energy surface in the vicinity of the transition state is rather flat and this flatness probably accounts for the difficulty in elucidating the transition state in the *syn* route. Thus, for the isoquinolinium ylide reaction, it could be that substituent effects could shift the mechanism to either way.

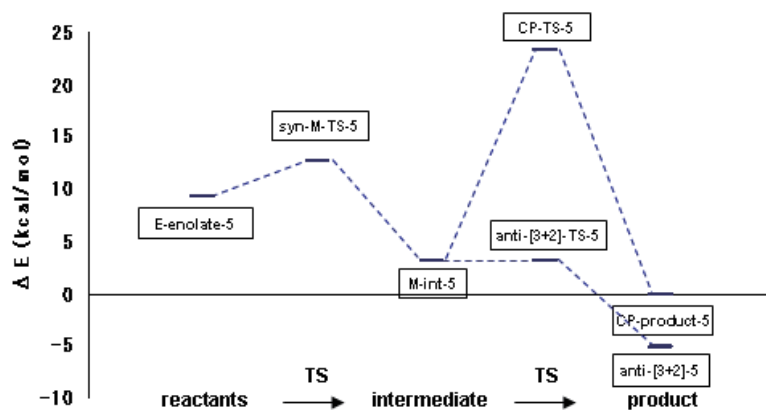


Figure 3. Energy diagram of the reaction between methyl α -isoquinoliniumacetate and methylidenemalononitrile. The relative energy for “*E*-enolate” corresponds to the sum of energies of the structurally optimized *E*-enolate and methylidenemalononitrile.

A point worthy of note on the overall results is that, **anti-[3+2]-5**, the more stable of the two adducts, was calculated to be lower in energy than the product mixture consisting of cyclopropane and isoquinoline by 5.2 kcal/mol. This conclusion also holds even when solution is considered, although the difference in energy becomes smaller. This accounts nicely for the diverse experimental results observed between the pyridine^{11,12} and the isoquinoline¹⁶ systems, with cyclopropanes as the principle products in

the former reaction and cycloadducts as the exclusive products in the latter reaction. A comparison of the two sequences, i. e., the pyridinium and the isoquinolinium ylide reactions, reveals that relative to the energy of the product cyclopropane, the barriers for the transition states leading to Michael adducts (15.7 and 14.0 kcal/mol compared with 13.4 and 12.6 kcal/mol, respectively) and to cyclopropanes (24.6 and 23.4 kcal/mol) are practically the same between the two systems, with the largest difference being only 2.3 kcal/mol between the two *anti*-M-TSs. These energetically similar processes correspond to ones where properties of the aromatics relevant to the reaction are only their inductive effects (which should be similar) and their sizes. On the other hand, a large difference was revealed upon comparing relative energies of the transition states leading to [3+2]- cycloaddition products and of the [3+2] products themselves, where the heteroaromatic rings are directly involved in the transformation. These insights imply that the preference for cyclopropane products for the pyridinium system reflects the higher aromatic nature of pyridine compared with the pyridine moiety of isoquinoline.

Calculations on the β -substituted methylidenemalononitrile system

Having established the stepwise nature of the pyridinium ylide reactions, we turned our attention to systems involving β -substituted methylidenemalononitriles, which could potentially give rise to diastereomeric *cis* and *trans* cyclopropanes. Since stereochemistry is an issue in this system, elucidating

the rate determining step would be of utmost importance.

As model compounds for the calculations, β -*t*-butylmethylidenemalononitrile was selected as the Michael acceptor, since it was the substrate that gave rise to the highest experimentally observed stereoselectivity.¹² Pyridinium 2-methoxy-2-oxoethylide which is generated upon deprotonation of methyl α -pyridiniumacetate was first examined as the pyridinium ylide. For Michael addition, it would be reasonable to assume that the ylide enolate and the Michael acceptor align gauche-like in the transition state. Thus, for both the *E*- and *Z*-enolates, all 6 gauche combinations (three for each *lk* and *ul* combination) were examined as initial structures in the search for transition states at the HF/6-31G(d) level.

Table 3 lists gas phase MO energetics for this system relative to *cis*-E3-TS-6 and the “TS to Michael adduct” section corresponds to the transition state energy for the first addition. As a result, 6 transition states were located for the *E*-enolate and 4 for the *Z*-enolate. The denotations “*trans*” and “*cis*” correspond to the adducts that are expected to give the *trans*- and *cis*-cyclopropanes, respectively, upon a subsequent intramolecular S_N2 reaction without any intervening epimerization or reverse process.

As the calculations show, the most probable transition state leading to the initial adduct is expected to be *cis*-E3-TS-6 (Figure 5), with *trans*-E2-TS-6 (+1.4 kcal/mol) and *cis*-E2-TS-6 (+1.3 kcal/mol with ZPE corrections) also not too far off in energy. Incidentally, *cis*-E2-TS-6 bears the alignment of the two moieties which most closely resembles the transition state we had supposed earlier to correspond to the rate determining step that eventually gives rise to the observed major product.^{12a,c} Transition state *cis*-E3-TS-6, is also geometrically close except that the substituents are rotated about the C-C bond to be formed so as to have the pyridyl nitrogen atom and the dicyanomethylide group (in the product) nearly eclipsed (rotated by an average of about 45° from *cis*-E2-TS-6). A rationale for the preference for *cis*-E3-TS-6 would be that it is preferred due to the minimized spatial separation of the positively and negatively charged moieties in the transition state and in the ensuing immediate product. The preference of *cis*-E3-TS-6 over *cis*-E2-TS-6 could be because, as the drawings show, the rather large gauche interaction between the flat ester and the three dimensional *t*-Bu groups in *cis*-E2-TS-6 is greatly alleviated in *cis*-E3-TS-6 although the *t*-Bu and a hydrogen atom come to assume an eclipse relationship instead. Since all three of these transition states have no resemblance to [3+2]-type transition states, the preference of any of

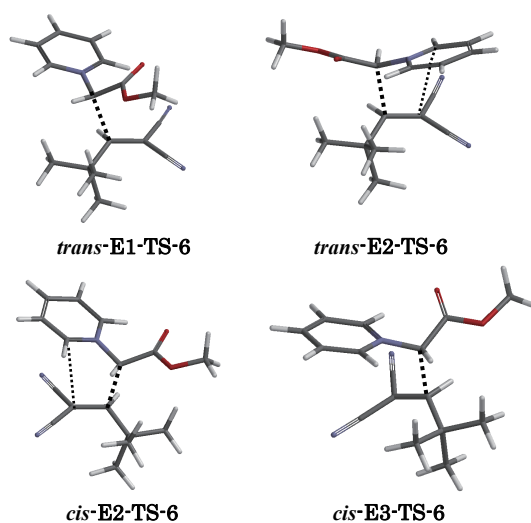


Figure 5. Main geometric features of the TS to Michael adduct found in the methyl ester system.

Table 3. HF/6-31G(d) calculations on the methyl ester system^a

		Gas phase				Solution
		ΔE (kcal/mol) ^b	Bond length 1 (Å) ^c	Bond length 2 (Å) ^d	Dipole moment (D)	ΔE (kcal/mol) ^b
Reactant ^e	<i>E</i> -enolate	0	—	—	—	0
	<i>Z</i> -enolate	6.4	—	—	—	6.0
TS to Michael adduct	<i>trans</i> -E1-TS-6	14.8	2.214	—	13.03	10.4
	<i>trans</i> -E2-TS-6	12.5	2.178	3.054	6.81	12.8
	<i>trans</i> -E3-TS-6	13.0	2.188	2.950	8.43	11.4
	<i>trans</i> -Z1-TS-6	15.1	2.198	2.922	7.66	14.3
	<i>trans</i> -Z2-TS-6	17.0	2.170	—	8.75	16.3
	<i>cis</i> -E1-TS-6	17.2	2.121	—	12.40	14.5
	<i>cis</i> -E2-TS-6	12.4	2.213	3.124	6.81	12.7
	<i>cis</i> -E3-TS-6	11.1	2.263	—	8.10	10.1
	<i>cis</i> -Z1-TS-6	16.2	2.208	3.237	9.01	15.2
	<i>cis</i> -Z2-TS-6	13.5	2.280	—	7.76	13.2
Michael adduct	<i>trans</i> -M-6	2.3	1.604	2.977	11.06	-6.4
	<i>cis</i> -M-6	-3.4	1.570	3.178	12.25	-14.1
TS to [3+2]-adduct	<i>trans-anti</i> -[3+2]-TS-6	3.6	1.598	2.335	10.51	-1.3
	<i>trans-syn</i> -[3+2]-TS-6	14.1	1.591	2.309	8.59	10.2
	<i>cis-anti</i> -[3+2]-TS-6	1.6	1.597	2.331	10.81	-2.5
	<i>cis-syn</i> -[3+2]-TS-6	2.7	1.587	2.292	9.05	1.0
3+2-adduct	<i>trans-anti</i> -[3+2]-6	-14.4	1.556	1.610	3.47	-10.7
	<i>trans-syn</i> -[3+2]-6	-13.5	1.563	1.562	3.54	-9.5
	<i>cis-anti</i> -[3+2]-6	-20.3	1.554	1.578	6.04	-16.4
	<i>cis-syn</i> -[3+2]-6	-15.6	1.559	1.550	4.01	-11.6
TS to cyclopropane	<i>trans</i> -CP-TS-6	15.1	—	—	15.88	8.0
	<i>cis</i> -CP-TS-6	21.7	—	—	14.99	16.1
Cyclopropane ^f	<i>trans</i> -CP-6	-31.7	—	—	—	-33.2
	<i>cis</i> -CP-6	-26.0	—	—	—	-27.1

^aCalculated with the Spartan program. Representative gas phase energies calculated with the Gaussian 98 program gave the same relative values. Solution values were calculated with water as the solvent using the SM5.4 model program implemented in the Spartan program.

^bEnergy differences are given relative to Reactant *E*-enolate. Values include zero point energy corrections. ^cCorresponds to the distance between the carbon atom of the acceptor bearing the *t*-Bu group and the carbon atom of the ylide bearing the ester group. ^dCorresponds to the distance between the carbon atom bearing the two cyano groups and the 2-carbon of the pyridine ring. For the "TS to Michael adduct" section, values are provided only for instances where the relative orientation of the two fragments are suitable for [3+2]-cycloaddition type bond formation. ^eThe relative energies for the "Reactant" section correspond to the sums of energies from structurally optimized enolate and β -*t*-butylmethylidenemalononitrile. ^fThe relative energies for the "Cyclopropane" section correspond to the sums of energies from structurally optimized cyclopropane and pyridine.

these transition states alone would rule out the three-step mechanism involving initial [3+2]-cycloaddition. In addition, in all of the calculated [3+2]-type transition states presented in Table 3, there is a large difference in bond distance between "bond length 1" and "bond length 2" with "bond length 2" being at least 2.9 Å, even though the relative orientation of the two moieties is appropriate for a concerted reaction. Furthermore, the imaginary frequency of the transition states does not have a vibrational component in the direction of the second bond to be formed. Thus, indications are that the assumed [3+2]-cycloaddition is stepwise and not concerted.

Transition state energies for the second bond formation in the [3+2]-cycloaddition reaction are given in the "TS to [3+2]-adduct" section. All four combinations of diastereomers were examined. Under the same

denotation, the *trans* and *cis* species correspond to the [3+2]-adducts having the *t*-Bu and ester groups in a *syn* and *anti* relationship, respectively, in the product five-membered ring. The denotations *anti* and *syn* correspond to the relative relationship between the ester group and the pyridine ring carbon in the five membered ring. The existence of a small but unnegligible barrier for the formation of the second bond adds additional support for a stepwise cycloaddition mechanism, as apparent from the energy difference between *trans*-**M-6** and *trans-anti*-[3+2]-**TS-6** of 1.3 kcal/mol. However, since the barrier for the second bond formation is rather low, these Michael adduct intermediates should be very short-living and it is possible that stereochemical features of the reactants are retained for the next bond formation in the case of [3+2]-reactions. The order of stability of the transition states leading to the [3+2]-adducts were in good parallel correlation with the stability of corresponding products from each transition state, with the lowest transition state being *cis-anti*-[3+2]-**6-TS** and the most stable [3+2] adduct being *cis-anti*-[3+2]-**6**.

Of the four [3+2] adducts, even the most stable adduct was found to be 11.4 kcal/mol less stable than the isodesmic product mixture of pyridine and *trans*-cyclopropane. Therefore, the [3+2]-cycloaddition reaction with its low activation barrier can be regarded as only a non-productive equilibrium process, thus accounting for why the [3+2] adduct could not be experimentally observed during the reaction even though the process is kinetically viable.

Calculations on the ring-closing S_N2 reaction to give the cyclopropane product show that the barrier for transition state *cis*-**CP-TS-6**, which leads to the *cis* product, is much higher than that for the *trans* transition state *trans*-**CP-TS-6**, by 6.6 kcal/mol, suggesting that this *cis* reaction pathway is unfavorable, in accordance with experiment. This difference in transition state energy is carried on into the difference in relative product stability. Coupled with the fact that the carbon α to the quaternary pyridinium nitrogen is highly acidic (vide supra), it is not unreasonable to assume that epimerization occurs at this carbon subsequently after Michael addition. The calculated barrier of 4.0 kcal/mol for *trans*-**CP-TS-6** relative to *cis*-**E3-TS-6** indicates that ring-closure involves the global energy maximum as opposed to our original assumptions.

In the experimental reaction system, in addition to the two reacting substrates, an ammonium (formed from the applied base) and a halide remain in the media throughout the reaction. These ions are expected to stabilize ionic species arising during the multi-step reaction by weak electrostatic interaction as would a polar solvent such as methanol, which has incidentally been found to be fully sufficient as the reaction medium. Thus, the consideration of the ionic ammoniums and halides or a highly polar solvent in the calculations would be expected to assist in providing a better picture of the reaction. To make approximations as simple as possible, we decided to assume the presence of water as the solvent and use its bulk properties in our calculations. Modified energies computed by the SM5.4 program implicated in the Spartan program for the Michael addition step are shown in the right most column in Table 3. The

most probable transition state for the first bond formation remains to be *cis-E3-TS-6*, however, a significant reduction in energy is observed for *trans-E1-TS-6* (+0.3 kcal/mol relative to *cis-E3-TS-6*), which also corresponds to a non-concerted [3+2] process, whereas *cis-E2-TS-6* and *trans-E2-TS-6* have become less favorable. The largest change in relative energy upon consideration of solvent was observed for the highly polarized Michael adduct intermediates, where the relative decrease in energy was as high as 10.7 kcal/mol for *cis-M-6*. Significant drops in energy of ca. 5 kcal/mol were also estimated for the transition states of the second bond formation for both [3+2]-adducts and cyclopropanes. On the other hand, the [3+2] adducts themselves were computed to be less stable by the same magnitude of ca. 5 kcal/mol. This combined change was so large that the Michael adduct *cis-M-6* has become more stable than three of the four [3+2]-products, and the difference between *cis-M-6* and the most stable *cis-anti-[3+2]-6* was reduced to only 2.3 kcal/mol. Thus, there is the possibility that [3+2]-intermediates are not produced at all.

A comparison of the Michael addition step and ring-closure revealed that there was a reversal in relative energies with *cis-E3-TS-6* becoming less stable than *trans-CP-TS-6* by 2.1 kcal/mol relative, indicating that in solution reactions, the first step involves the global energy maximum, in contrast to the gas phase reaction (Figure 6). This is also in good agreement with the fact that no accumulation of the Michael adduct is spectroscopically observed upon monitoring the whole reaction with NMR, although computational results indicate that the Michael adduct is much more stable than the reactant pair.

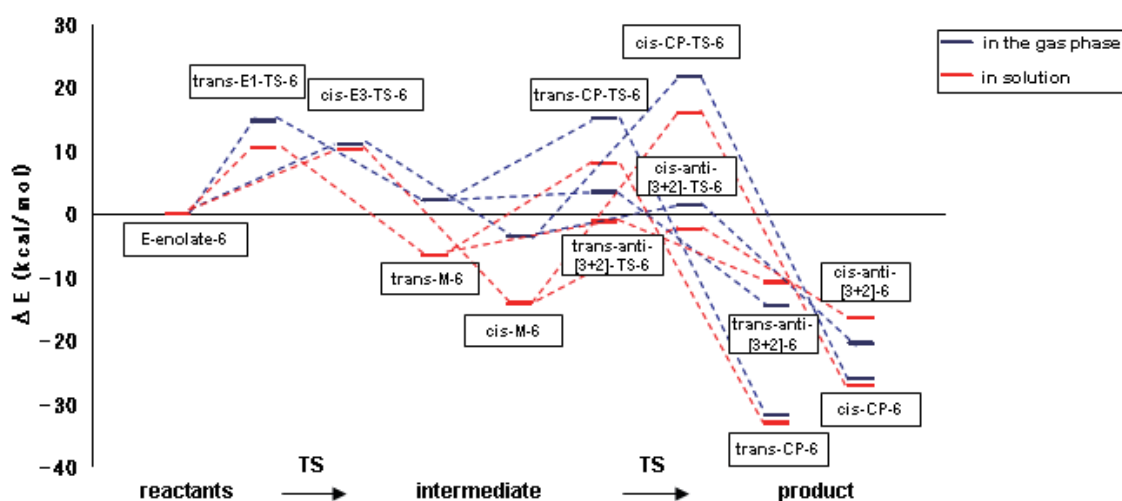


Figure 6. Energy diagram of the reaction between methyl α -pyridiniumacetate and β -*t*-butylmethylidenemalononitrile. The relative energy for “*E*-enolate” corresponds to the sum of energies of the structurally optimized *E*-enolate and β -*t*-butylmethylidenemalononitrile.

In order to check the feasibility of the MO results, DFT calculations at the B3LYP/6-31G(d) level of theory were also carried out on the three selected transition states (*cis-E3-TS-6*, *trans-E1-TS-6*, and

trans-CP-TS-6) found to be of relevance in the MO calculations with the inclusion of bulk water as the media. As a result, *trans*-E1-TS-6 was preferred over *cis*-E3-TS-6, in contrary with our speculations and with MO calculations. This lead us to wonder if the reason for this disagreement might be due to the size of the alkoxy moiety of the ester.

The transition state drawings of the methyl ester system (Figure 3) suggest that increasing the bulk of the ester alkoxy group in question would destabilize *trans*-E1-TS-6 relative to *cis*-E3-TS-6, since the close to eclipse interaction is only between the ester moiety and the small hydrogen atom for the latter whereas it is between the ester moiety and the much larger dicyanomethylene group for the former. In the actual experimental system, high diastereoselectivities were attained using the extremely bulky 8-phenylmenthyl group as the chiral auxiliary as opposed to the small methyl group used in the calculations (vide supra). Thus, we next substituted the methyl group with a bulky *t*-butyl group to see if calculations might indicate that the size of this moiety has some effect on the course of the reaction. Once again, to simplify the calculation procedure, full optimizations were carried out only on the three relevant transition states (vide supra).

As Table 4 shows, MO gas phase optimizations show that the energy difference between *cis*-E3-TS-7 and *trans*-CP-TS-7 is reduced to 2.7 kcal/mol from 4.0 kcal/mol for the methyl ester, as expected, reflecting the size of the alkoxides. Inclusion of solvent in the MO calculations suggested the preference of *cis*-E3-TS-7 as before with a larger difference in energy between *cis*-E3-TS-7 and *trans*-CP-TS-7 compared with that in the case of the methyl ester (increased from 2.1 to 3.6 kcal/mol). Thus, from these MO results we can conclude that the steric bulk of the alkoxy group of the ester moiety serves to

Table 4. HF/6-31G(d) and B3LYP/6-31G(d) calculations on selected transition states of the *t*-butyl ester system

		HF/6-31G(d) ^a				
		Gas phase				Solution
		ΔE (kcal/mol) ^c	Bond 1 (Å) ^d	Bond 2 (Å) ^e	Dipole moment (D)	ΔE (kcal/mol) ^c
TS to Michael adduct	<i>cis</i> -E3-TS-7	0.0	2.273	2.996	8.05	0.0
	<i>trans</i> -E1-TS-7	4.1	2.240	3.027	12.92	1.2
TS to cyclopropane	<i>trans</i> -CP-TS-7	2.7	—	—	15.59	-3.6
		B3LYP/6-31G(d) ^b				
		Gas phase				Solution
		ΔE (kcal/mol) ^c	Bond 1 (Å) ^d	Bond 2 (Å) ^e	Dipole moment (D)	ΔE (kcal/mol) ^c
TS to Michael adduct	<i>cis</i> -E3-TS-7	0.0	2.238	2.973	7.76	0.0
	<i>trans</i> -E1-TS-7	4.1	2.136	2.963	11.22	0.6
TS to cyclopropane	<i>trans</i> -CP-TS-7	7.6	—	—	15.11	-1.5

^aCalculated with the Spartan program. Representative gas phase energies calculated with the Gaussian 98 program gave the same relative values. Solution values were calculated with water as the solvent using the SM5.4 model program implemented in the Spartan program.

^bCalculated with the Gaussian 98 program. Solution values were calculated with water as the solvent using the Onsanger model program implemented in the Gaussian 98 program. ^cEnergy differences are given relative to *cis*-E3-TS-7. Values include zero point energy corrections ^dCorresponds to the distance between the carbon atom bearing the *t*-Bu group of the acceptor and the carbon atom of the ylide bearing the ester group. ^eCorresponds to the distance between the carbon atom bearing the two cyano groups and the 2-carbon of the pyridine ring.

deteriorate the intermolecular Michael addition, as anticipated. Here again, the relative lower stability of *trans*-E1-TS-7 compared with *cis*-E3-TS-7 was the same as in the methyl ester case with a ca. 4.1 kcal/mol difference, although bond distances had a similar tendency with the methyl ester case. Thus, it can be said that there is consistency in the calculations between the systems involving the different esters. As for the DFT solution calculations, although the difference in energy between *cis*-E3-TS-7 and *trans*-E1-TS-7 is only 0.6 kcal/mol, the reference lower energy state has changed from *trans*-E1-TS to *cis*-E3-TS and has thus coincided with predictions by the MO method.

In summary, we have carried out theoretical calculations of the cyclopropanation reaction of pyridinium ylides. Calculations suggested that in the gas phase reaction, the stereo-determining step is the final ring-closing process whereas it is the initial Michael addition step that should be considered limiting in the presence of a polar solvent such as water. It was also suggested that the [3+2] cycloaddition reaction involving pyridinium ylides is better described as a stepwise reaction in DFT calculations at the B3LYP/6-31G(d) level of theory. Furthermore, computations on both the gas phase and solution reactions predicted that while cyclopropanes would be the end product in the reaction of pyridinium ylides, the [3+2]-cycloaddition product would prevail in the reaction of isoquinolinium ylides, despite the structural similarities between the two. Based upon the insights gained in this study, the designing of cyclopropanation reactions that might give improved selectivity are currently in progress.

EXPERIMENTAL

Ab initio MO calculations were carried out using the HF/6-31G(d) method, and DFT calculations were carried at the B3LYP/6-31G(d) level of theory. Either Spartan 04 and 06¹⁴ or Gaussian 98¹⁵ was used for the calculations. The transition states were confirmed by the presence of only one imaginary frequency. Solution energy values were calculated with water as the solvent using the SM5.4 model program implemented in the Spartan programs or the Onsanger model program implemented in the Gaussian 98 program. The solution values correspond to single point calculations applied to the structures geometrically optimized by the HF/6-31G(d) and B3LYP/6-31G(d) methods. Spartan was used for calculating all the geometry optimizations and Gaussian 98 was used in selected cases.

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