Tetrahedron 64 (2008) 6395–6401

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Diastereo- and regioselective Diels–Alder reactions of 2-phosphaindolizines

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ARTICLE INFO

Article history:
Received 8 February 2008
Received in revised form 19 April 2008
Accepted 22 April 2008
Available online 25 April 2008

Keywords:
Diels–Alder reactions
2-Phosphaindolizines
Regioselectivity
DFT calculations

ABSTRACT

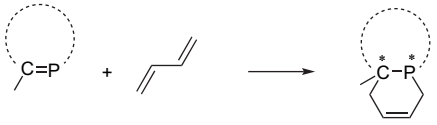
1,3-Bis(alkoxycarbonyl)-2-phosphaindolizines undergo Diels–Alder reactions at the >C=P– functionality with 2,3-dimethylbutadiene and with isoprene in the presence of sulfur with complete diastereoselectivity. The reaction with isoprene occurs with 100% regioselectivity as well. 3-Ethoxycarbonyl-1-methyl-2-phosphaindolizine, however, fails to undergo Diels–Alder reaction under these conditions. Difference in the dienophilic reactivities of mono- and bis(alkoxycarbonyl) substituted 2-phosphaindolizines and the observed regioselectivity in the Diels–Alder reaction has been rationalized on the basis of DFT calculations. The relative stabilities of the transition structures have been explained on the basis of the NBO analysis.

1. Introduction

Diastereo- and regioselectivity accompanying the Diels–Alder (DA) reaction makes it a preferred synthetic method, particularly for those six-membered rings in which one or more stereogenic centres are created in the process.[1] The recently realized carbon–phosphorus analogy[2] and the weakness of >C=P– π-bond as compared to the >C=C< π-bond[3] have contributed to the broadening of the scope of the DA reaction, extending it to various organophosphorus compounds incorporating >C=P– functionality, namely phosphaalkenes,[4] heterophospholes[5,6] and phosphinines.[7] Even the phospholes that may have a CP double bond resulting from a 1,5-sigmatropic shift have been found to undergo DA reactions.[8] Recently, interesting phosphinine-based multidentate ligands[9] as well as silacalix[*n*]phosphinines[10] have been obtained through a synthetic strategy involving successive DA reactions/retro-DA reactions of 1,3,2-diazaphosphinines.

In appropriately substituted phosphaalkene, heterophosphole or phosphinine, both the phosphorus and the carbon atoms of the >C=P– functionality are prochiral and DA reaction with it leads to the generation of two chiral centres in one step (Scheme 1).

We developed two synthetic methods for [1,3]azaphospholo-[1,5-*a*]pyridines, i.e., 2-phosphaindolizines, namely [4+1]cyclocondensation[11] and 1,5-electrocyclization.[12] [4+1]Cyclocondensation of 1-(ethoxycarbonylmethyl)pyridinium bromide with phosphorus trichloride in the presence of triethylamine afforded 3-ethoxycarbonyl-1-methyl-2-phosphaindolizine (**1**, Z=Me, R^1=Et, R^2=H),[11a] while the reaction of 2-unsubstituted 1-(alkoxycarbonylmethyl)pyridinium bromide with phosphorus trichloride and triethylamine first generated bis(pyridinium ylidyl)phosphenium chloride that subsequently changed into 1,3-bis(alkoxycarbonyl)-2-phosphaindolizines (**1**, Z=CO_2R^1, R^1=Me, Et, R^2=H, Me) through intramolecular 1,5-electrocyclization followed by 1,2-elimination.[12a]



Scheme 1.

In view of an activated >C=P– moiety being incorporated in these compounds, they were considered as suitable candidates for the DA reactions. We therefore investigated their DA reactions with 2,3-dimethylbutadiene and with isoprene. While 1,3-bis(alkoxycarbonyl)-2-phosphaindolizines reacted with 1,3-dienes in the presence of sulfur at room temperature with complete diastereo- and regioselectivity affording stable [2+4] cycloadducts, 3-ethoxycarbonyl-1-methyl-2-phosphaindolizine unexpectedly did not show any reactivity towards 2,3-dimethylbutadiene even on refluxing alone or with sulfur in toluene for several hours. The observed regioselectivity and the difference in the dienophilic reactivities of the two types of the starting compounds have been investigated at the DFT level (B3LYP/6-311++G**//B3LYP/6-31G**). The experimental and theoretical results are presented here.

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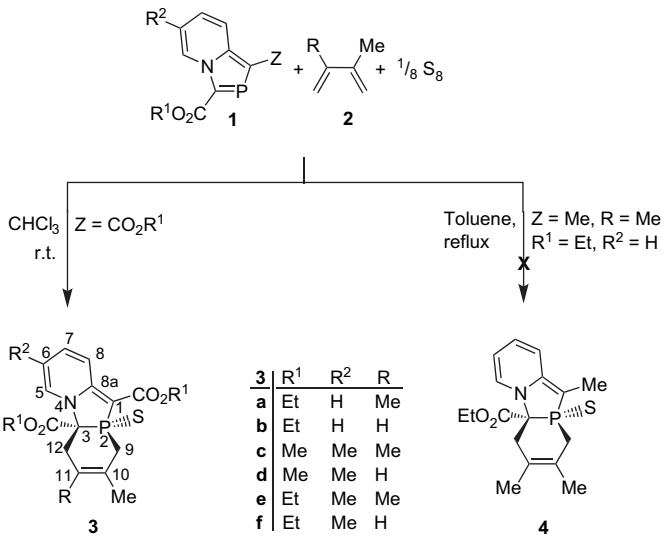
doi:10.1016/j.tet.2008.04.080

2. Results and discussion

1,3-Bis(alkoxycarbonyl)-2-phosphaindolizines **1** (Z=CO_2R^1) react with 2,3-dimethylbutadiene in the presence of sulfur in chloroform at room temperature to give [2+4] cycloadducts **3** with complete diastereoselectivity. The reaction of **1** with isoprene under these conditions occurs with total regioselectivity to afford only one regioisomer in each case (Scheme 2).



3	R^1	R^2	R
a	Et	H	Me
b	Et	H	H
c	Me	Me	Me
d	Me	Me	H
e	Et	Me	Me
f	Et	Me	H

Scheme 2.

The reaction of **1** (Z=CO_2Me, R^1=R^2=Me) with 2,3-dimethylbutadiene alone at room temperature was complete in 10 days (δ ^{31}P=56.2). The three-coordinate, tervalent (σ^2,λ^3) phosphorus atom of the initially formed phosphine, however, gets oxidized with traces of oxygen during work-up and cannot be separated from the unoxidized product.

3-Ethoxycarbonyl-1-methyl-2-phosphaindolizine (**1**, Z=Me, R^1=Et, R^2=H) does not react with 2,3-dimethylbutadiene alone or in the presence of sulfur even on refluxing in toluene, as revealed by ^{31}P NMR of the reaction mixture (Scheme 2).

The cycloadducts are obtained as yellow to green crystalline solids, soluble in polar solvents such as chloroform, methylene chloride and acetonitrile. These products are stable for prolonged periods under inert atmosphere, but decompose on exposure to atmosphere, particularly to moisture. The physical data and ^{31}P, ^{1}H and ^{13}C NMR data of the cycloadducts are given in Section 4. Assignment of the ^{1}H and ^{13}C NMR data was made on the basis of a ^{1}H, ^{13}C HETCOR NMR experiment done on a representative compound **3a**. The increase in the coordination number of the phosphorus atom resulting from the DA reaction with the >C=P– functionality is revealed by an upfield shift of the ^{31}P NMR chemical shifts, which lie in the range δ 64.5–66.2 for **3**, characteristic for a four-coordinated phosphorus atom.[13]

The DA reaction with the >C=P– moiety creates chiral centres at the phosphorus and C-3 atoms. The presence of these chiral centres induces diastereotopy in the methylene protons at C-9 and C-12 and also those of the ethoxycarbonyl group at C-3. Due to diastereotopic induction, methylene protons of the ethoxycarbonyl group at C-3 constitute an ABC_3 spin system and each of these gives a doublet of quartets at δ 4.10–4.33 ($^2J_{HAHB}$=10.6–11.2 Hz, $^3J_{HH}$=6.9–7.2 Hz). On the other hand, methylene protons of the ethoxycarbonyl group at C-1 give a quartet at δ 4.27–4.34 ($^3J_{HH}$=6.9–7.2 Hz). The methylene protons at C-9 and C-12 constitute each an ABX spin system, X being the phosphorus atom. H_A and H_B of 9-CH_2 appear as triplets at δ 3.13–3.32 ($^2J_{HAHB}$=$^2J_{PHA}$=14.3–17.8 Hz), and δ 2.83–2.85 ($^2J_{HBHA}$=$^2J_{PHB}$=14.3–17.8 Hz), respectively. However, in the case of **3e**, H_A of 9-CH_2 gives a doublet of doublets at δ 3.14 ($^2J_{HAHB}$=15.0, $^2J_{PHA}$=13.4 Hz). The two protons, H_A and H_B, of 12-CH_2 appear as triplet at δ 3.22–3.40 ($^2J_{HAHB}$=$^3J_{PHA}$=13.5–15.0 Hz) and doublet of doublets at δ 2.64–2.80 ($^3J_{PHB}$=22.5–24.0, $^2J_{HBHA}$=15.0 Hz), respectively. However, for the cycloadducts, **3b** and **3f**, resulting from the DA reaction with isoprene, H_B of 12-CH_2 experiences an additional three bond coupling with H-11, and appears as a doublet of double doublets (**3b**, δ 2.80, $^3J_{PH}$=30.0, $^2J_{HAHB}$=15.6, $^3J_{HH}$=7.3 Hz) or a triplet of doublets (**3f**, δ 2.75, $^2J_{HAHB}$=$^3J_{PH}$=15.8, $^3J_{HH}$=7.3 Hz). The proton at C-11 for the cycloadducts **3b**, **3d** and **3f** appears at δ 5.30–5.38 as a broad singlet probably due to unresolved coupling with phosphorus, protons at 12-CH_2 and methyl group at C-10. The methyl group at C-10 does not couple with phosphorus and shows a singlet at δ 1.58–1.72, but the methyl group at C-11 gives a doublet at δ 1.43–1.45 due to five bond coupling with phosphorus ($^5J_{PH}$=5.1–5.7 Hz) as observed in the DA cycloadducts of 1,3-bis(ethoxycarbonyl)[1,3]azaphospholo-[5,1-*a*]isoquinoline with isoprene whose structure was confirmed by X-ray crystal determination also.[14]

The ^{13}C NMR spectra of the cycloadducts are characterized by typical carbon–phosphorus couplings.[15] The C-3 and C-9 show characteristically strong one bond coupling with phosphorus ($^1J_{PC}$=50.9–53.6 Hz). The expected one bond coupling of C-1, however, could not be resolved due to partial overlapping of its signal by $CDCl_3$ peaks. But it could be determined for **3a** ($^1J_{PC}$=91.8 Hz) by scanning its ^{13}C NMR spectrum at 125.8 MHz. The C-10 also shows appreciably strong two bond coupling with phosphorus ($^2J_{PC}$=11.4–11.8 Hz), but no coupling could be detected with C-12. Likewise, no coupling of C-8a with phosphorus could be resolved. As observed earlier,[15,16] C-11 shows appreciably strong coupling with phosphorus over three bonds ($^3J_{PC}$=12.4–13.6 Hz).

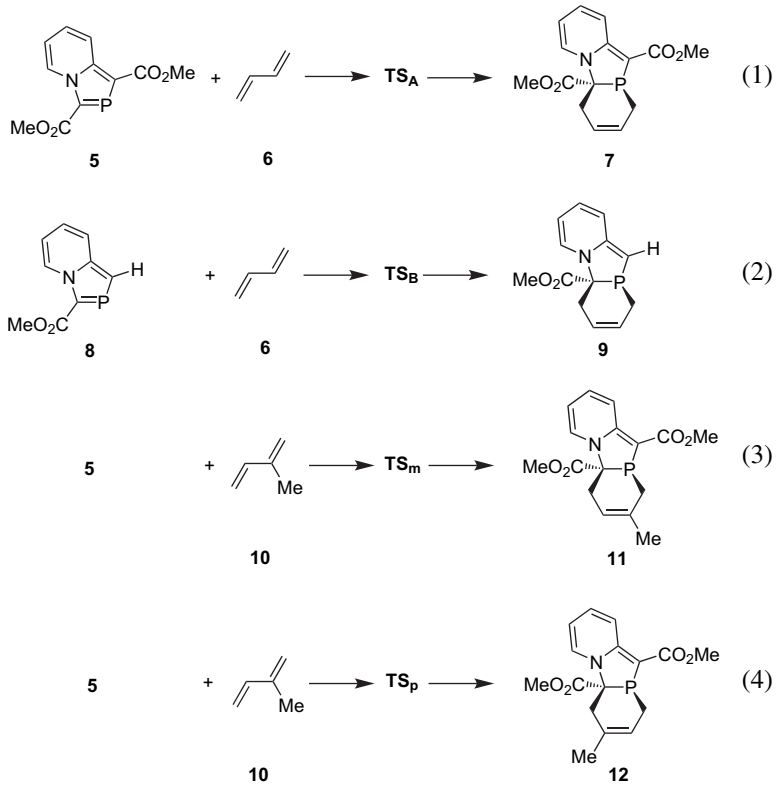
2.1. DFT calculations

In order to explain the remarkable difference in the dienophilic reactivities of 1,3-bis(ethoxycarbonyl)-2-phosphaindolizines and 3-ethoxycarbonyl-1-methyl-2-phosphaindolizine, and also the observed regioselectivity in the DA reactions with isoprene, following model DA reactions have been computed at the DFT level (B3LYP/6-311++G**//B3LYP/6-31G**) (Scheme 3). In view of the *endo*-cycloadduct characterized by X-ray crystal investigation in one case,[14] only *endo* approach for the cycloadditions has been considered.

Total energies, relative energies, ratios of the two regioisomers, calculated both in the gas phase and chloroform and also the experimental values are given in Table 1.

The gas phase optimized geometries of the transition structures, **TS_A**, **TS_B**, **TS_m** and **TS_p**, are reproduced in Figure 1.

It may be noted that the DA reaction of **5** with 1,3-butadiene involves an activation barrier of 24.8 kcal mol^{-1} in the gas phase, which is further lowered to 19.3 kcal mol^{-1} in chloroform, the actual solvent used for carrying out the reaction. Furthermore, the reaction is moderately exothermic in chloroform. The corresponding activation barrier for the DA reaction of **8** is found to be 29.5 kcal mol^{-1} in gas phase, which is raised to 30.4 kcal mol^{-1} with endothermicity in chloroform. An activation barrier of 30.4 kcal mol^{-1} with endothermicity is quite close to that calculated for the DA reaction of phosphinine with 1,3-butadiene (29.8 kcal mol^{-1}),[17] which does not occur even under drastic conditions.[18] On the other hand, the activation energy of 19.3 kcal mol^{-1} is comparable with the calculated[19] activation barrier (16–19 kcal mol^{-1}) for the DA reactions of diazaphospholes, which proceed under mild conditions at room temperature even in the absence of sulfur.[20] Thus, the observed difference in the dienophilic reactivities of 1,3-bis(alkoxycarbonyl)-2-phosphaindolizine



Scheme 3.

and 3-ethoxycarbonyl-1-methyl-2-phosphaindolizine is rationalized by the calculated difference in the activation barriers for the two reactions.

The relative stabilities of the transition structures, **TS_A** and **TS_B** as also of **TS_m** and **TS_p**, have been looked into by carrying out their NBO analysis.[21] The major second order energy lowering by perturbative donor/acceptor interactions and occupancies of the related natural localized molecular orbitals (NLMOs) in the transition structures are shown in Tables 2 and 3. It can be noted that the electronic structures of **TS_A** and **TS_B** differ remarkably in respect of the delocalization of the N-4 lone pair. In **TS_A**, presence of the CO_2Me group at C-1 induces significant delocalization of the N-4 'lone pair' into $\pi^*_{(N4-C8a)}$, $\sigma^*_{(P2-C9)}$ and $\pi^*_{(C13-O14)}$ orbitals resulting in substantial second order perturbative energy-lowering interactions (Table 2). These interactions are missing altogether in **TS_B**. The delocalization of N-4 'lone pair' in **TS_A** is corroborated by the occupancies of the NLMOs: 61.2% of this lone pair is present on C-1 and only 4.4% is left at N-4. But in **TS_B**, N-4 and C-1 have 75.3% and 3.2% of the lone pair, respectively (Table 2). The weak delocalization of N-4 in **TS_B** appears to be associated with second order energy-lowering interactions of less than 0.5 kcal mol^{-1} (threshold value), which do not show up in the printout.

The transition structures, **TS_m** and **TS_p**, are different only in the regio-orientation of the isoprene unit and hence differ very little in the second order perturbative interactions. The hyperconjugative interactions of the methyl group hydrogens with the $\pi^*_{(C10-C11)}$ orbital and other important interactions are shown in Table 3. It can be noted that these interactions, particularly $\pi_{(C10-C11)}/\sigma^*_{(C3-C12)}$,

Table 1
Total energies and relative energies for the stationary points corresponding to the DA reactions 1–4

Species	Total energy[a] (a.u.)		Relative energy (kcal mol^{-1})		Percentages of regioisomers		
					Calcd.		Exp.
	Gas phase	$CHCl_3$	Gas phase	$CHCl_3$	Gas phase	$CHCl_3$	$CHCl_3$
5	−1122.250863	−1122.259748	—	—	—	—	—
6	−155.955501	−155.958194	—	—	—	—	—
TS_A	−1278.166914	−1278.178251	24.8[b]	19.3[b]	—	—	—
7	−1278.204131	−1278.217922	1.4[b]	−5.6[b]	—	—	—
8	−894.344930	−894.509556	—	—	—	—	—
TS_B	−1050.253382	−1050.262223	29.5[c]	30.4[c]	—	—	—
9	−1050.287369	−1050.287927	8.2[c]	8.0[c]	—	—	—
10	−195.255067	−195.257169	—	—	—	—	—
TS_m	−1317.469540	−1317.480446	22.8[d]	22.9[d]	—	—	—
TS_p	−1317.465851	−1317.476624	25.2[d]	25.3[d]	—	—	—
11	−1317.506648	−1317.519639	−0.4[d]	−1.7[d]	98	98	100
12	−1317.505464	−1317.518606	0.3[d]	−1.1[d]	02	02	00

[a] Energy at B3LYP/6-311++G**//B3LYP/6-31G** level.
[b] Relative to the sum of the energies of **5** and **6** (*s*-trans).
[c] Relative to the sum of the energies of **8** and **6** (*s*-trans).
[d] Relative to the sum of the energies of **5** and **10** (*s*-trans).

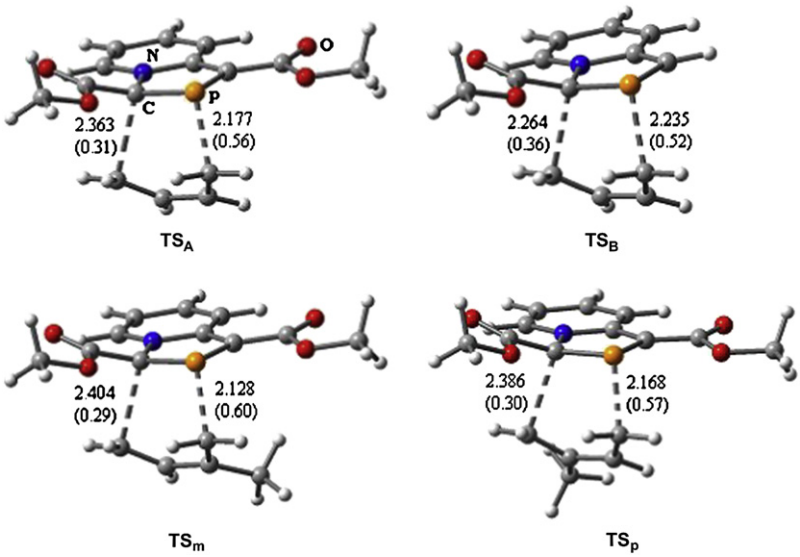


Figure 1. Gas phase optimized geometries (B3LYP/6-31G**) of the transition structures along with the bond lengths (in angstrom) and Wiberg bond indices (in parentheses) of the two forming bonds.

$\sigma_{(C3-C12)}/\pi^*_{(C17-O18)}$ and $\sigma_{(C21-H22)}/\pi^*_{(C10-C11)}$, are slightly more energy lowering in **TS$_m$** than in **TS$_p$**, which explains the greater stability of the former (Table 3).

The stereo- and regioselectivity observed in various DA reactions has been rationalized theoretically by carrying out the computational calculations at the DFT level.[22–29] It has been possible to calculate the ratios of different products formed in the DA reactions of vinylboranes with 1,3-dienes using Boltzmann distribution equation, $k_1/k_2=e^{-\Delta E/RT}$ where ΔE is the difference between the calculated activation energies for the two processes leading to two regioisomers/stereoisomers, T=298.15 K and R=1.9872 cal K^{-1} mol^{-1}.[22,30] The calculated values were found to be in very good agreement with the experimental results.[22,30]

It can be noted from Table 1 that the solvent does not influence the ratios of the two regioisomers and the calculated value of the regioisomer having P/Me in 1:3 position is 98%, which is in very good agreement with the actual value (100%) obtained experimentally.

3. Conclusion

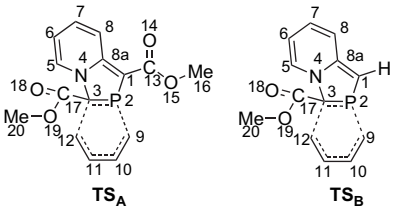
1,3-Bis(alkoxycarbonyl)-2-phosphaindolizines undergo Diels–Alder reactions at the >C=P– functionality with *endo* stereoselectivity and total regioselectivity, the regioisomer having phosphorus and methyl group in the 1:3 positions being the only product. The DFT calculations rationalize the difference in the dienophilic reactivities of 1,3-bis(alkoxycarbonyl)- and 3-ethoxycarbonyl-2-phosphaindolizine and also reproduce the experimentally observed regioselectivity results.

4. Experimental

4.1. General

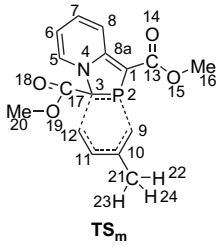
All reactions were carried out under an atmosphere of dry argon or nitrogen in flame dried glass apparatus using Schlenk technique. Solvents were freshly dried and distilled. Commercially available

Table 2
Selected second order energy-lowering E_{ij} (kcal mol^{-1}) by perturbative donor/acceptor interactions and the corresponding NLMO occupancy and percentage composition in the transition structures, **TS$_A$** and **TS$_B$**

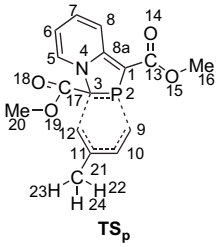


NBO			NLMO			
Donor/acceptor	E_{ij} (kcal mol^{-1})		**TS$_A$**		**TS$_B$**	
	TS$_A$	**TS$_B$**	Occupancy (%)	Composition (%)	Occupancy (%)	Composition (%)
$\sigma_{(C3-C12)}/\pi^*_{(C17-O18)}$	34.2	29.2	81.2	3.5 P2, 51.9 C3, 2.4 C10, 2.7 C11, 29.3 C12, 4.2 C17, 1.7 O18	83.1	3.1 P2, 49.9 C3, 1.8 C10, 3.4 C11, 33.2 C12, 3.6 C17, 1.4 O18
$LP_{C1}/\pi^*_{(N4-C8a)}$	237.2	—	61.2	61.2 C1, 3.9 P2, 4.4 N4, 18.7 C8a, 5.2 C13	—	—
$LP_{C1}/\sigma^*_{(P2-C9)}$	22.6	—	—	—	—	—
$LP_{C1}/\pi^*_{(C13-O14)}$	80.6	—	—	—	—	—
$LP_{O18}/\sigma^*_{(C3-C17)}$	15.6	15.7	—	—	—	—
$LP_{O18}/\sigma^*_{(C17-O19)}$	31.9	31.9	—	—	—	—
$LP_{O19}/\sigma^*_{(C17-O18)}$	7.2	7.2	—	—	—	—
LP_{N4}	—	—	—	—	75.3	3.2 C1, 1.7 P2, 2.3 C3, 75.3 N4, 4.9 C5, 2.5 C6, 6.5 C8a

Table 3
Selected second order energy-lowering E_{ij} (kcal mol^{-1}) by perturbative donor/acceptor interactions and the corresponding NLMO occupancy and percentage composition in the transition structures, **TS_m** and **TS_p**



TS_m



TS_p

NBO			NLMO			
Donor/acceptor	E_{ij} (kcal mol^{-1})		**TS_m**		**TS_p**	
	TS_m	**TS_p**	Occupancy (%)	Composition (%)	Occupancy (%)	Composition (%)
$\sigma_{(P2-C9)}/\pi^*_{(C10-C11)}$	14.4	14.1	84.6	31.2 P2, 1.8 C3, 53.6 C9, 7.3 C10, 1.4 C11, 3.5 C12	83.4	31.2 P2, 2.1 C3, 52.4 C9, 7.5 C10, 1.5 C11, 4.0 C12
$\pi_{(C10-C11)}/\sigma^*_{(P2-C9)}$	6.4	8.0	78.6	1.3 P2, 3.3 C3, 1.5 C9, 31.8 C10, 47.1 C11, 12.1 C12	79.1	2.0 P2, 4.0 C3, 2.0 C9, 35.5 C10, 43.7 C11, 9.7 C12
$\pi_{(C10-C11)}/\sigma^*_{(C3-C12)}$	29.2	25.6	—	—	—	—
$\sigma_{(C3-C12)}/\pi^*_{(C10-C11)}$	15.8	17.5	80.4	3.4 P2, 52.0 C3, 2.5 C10, 2.6 C11, 28.3 C12, 4.6 C17, 1.8 O18	80.3	3.4 P2, 50.2 C3, 2.0 C10, 3.8 C11, 30.7 C12, 4.2 C17, 1.7 O18
$\sigma_{(C3-C12)}/\pi^*_{(C17-O18)}$	37.5	35.7	—	—	—	—
$\sigma_{C21-H22}/\pi^*_{(C10-C11)}$	5.2	3.8	98.2	0.9 C10, 0.3 C11, 60.1 C21, 38.1 H22	98.9	0.2 C10, 0.6 C11, 0.2 C12, 59.8 C21, 39.1 H22
$\sigma_{(C21-H23)}/\pi^*_{(C10-C11)}$	1.7	1.9	99.1	0.4 C10, 0.2 C11, 60.0 C21, 39.2 H23	99.1	0.2 C10, 0.4 C11, 0.1 C12, 59.9 C21, 39.2 H23

2,3-dimethylbutadiene, isoprene and sulfur were used without further purification. 1,3-Bis(alkoxycarbonyl)-2-phosphaindolizines were prepared according to the method reported earlier.[12]

Melting points were determined in closed capillaries and are uncorrected. NMR spectra were recorded on a JEOL AL-300 spectrometer at 300.4 MHz (^{1}H), at 75.45 MHz (^{13}C) and at 121.5 MHz (^{31}P). ^{1}H and ^{13}C NMR chemical shifts refer to TMS as internal standard and ^{31}P NMR chemical shifts to 85% H_3PO_4 as external standard. Assignments of the ^{1}H and ^{13}C NMR signals are based on ^{1}H, ^{13}C HETCOR experiment, and ^{13}C NMR spectrum for representative compound **3a** recorded on a 500 MHz JEOL spectrometer. Elemental analysis was done on Perkin Elmer instrument.

4.2. Computational methods

All calculations were carried out using Gaussian 03 suite of programmes.[31] Reactants and the products and transition structures resulting from the DA reactions were fully optimized without any geometric constraint at B3LYP/6-31G** level. The frequency calculations were also carried out at the same level of theory to predict the nature of the stationary points and to obtain zero-point energy corrections (ZPEs). All minima and transition structures were confirmed to have none or one imaginary frequency, respectively. Unscaled ZPEs from B3LYP/6-31G** level were added to the single point energies calculated at B3LYP/6-311++G** level.

Intrinsic reaction coordinate (IRC) calculations[32] starting at all the transition structures were performed to establish their connection with the respective reactants and products. Natural bond orbital (NBO) analysis[21] was used for computing the bond orders (Wiberg bond indices)[33] of the transition structures.

The solvent effect has been studied by calculating single point energy of the B3LYP/6-31G** gas phase optimized stationary points at B3LYP/6-311++G** level using self consistent reaction field (SCRF) method[34,35] based on Tomasi's integral equation formalism polarizable continuum model (IEFPCM).[36] To the energies so-obtained was added the unscaled ZPE calculated at B3LYP/6-31G** level for the gas phase.

4.3. General procedure for the reaction of 1 with 2,3-dimethylbutadiene or isoprene and sulfur (3a–f)

To a well stirred solution of **1** (2.5 mmol) in chloroform (20 mL) were added 1 equiv of 2,3-dimethylbutadiene (205 mg, 0.28 mL, 2.5 mmol) or isoprene (170 mg, 0.25 mL, 2.5 mmol) and equimolar amount of sulfur (80 mg, 2.5 mmol) followed by stirring at room temperature (25 °C). Progress of the reaction was monitored by ^{31}P NMR. When the reaction was complete in about 10 days, the solvent was removed under reduced pressure and the residue was macerated with hexane. The product so-obtained was recrystallized from chloroform to afford spectroscopically pure yellow to green solids.

*4.3.1. Compound **3a***

Yellow solid (308 mg, 68%), mp 137–138 °C ($CHCl_3$). (Found: C, 57.90; H, 5.98; N, 3.30. $C_{19}H_{24}NO_4PS$ (393.4) requires: C, 58.00; H, 6.15; N, 3.56%.) ^{31}P NMR ($CDCl_3$): δ 65.4; ^{1}H NMR ($CDCl_3$): δ 7.92 (d, 1H, $^3J_{HH}$=9.3 Hz, H-5), 7.21 (dd, 1H, $^3J_{HH}$=9.3, 6.0 Hz, H-6), 7.12 (d, 1H, $^3J_{HH}$=6.0 Hz, H-8), 6.27 (t, 1H, $^3J_{HH}$=6.0 Hz, H-7), 4.28 (q, 2H, $^3J_{HH}$=7.2 Hz, 1-CO_2CH_2), 4.25 (dq, 1H, $^2J_{HAHB}$=10.8 Hz, $^3J_{HH}$=7.0 Hz, H_A of 3-CO_2CH_2), 4.10 (dq, 1H, $^2J_{HAHB}$=10.8 Hz, $^3J_{HH}$=7.0 Hz, H_B of 3-CO_2CH_2), 3.40 (t, 1H, $^2J_{HAHB}$=$^3J_{PH}$=15.0 Hz, H_A of 12-CH_2), 3.15 (t, 1H, $^2J_{HAHB}$=$^2J_{PH}$=15.0 Hz, H_A of 9-CH_2), 2.85 (t, 1H, $^2J_{HAHB}$=$^2J_{PH}$=15.0 Hz, H_B of 9-CH_2), 2.64 (dd, 1H, $^3J_{PH}$=24.0 Hz, $^2J_{HAHB}$=15.0 Hz, H_B of 12-CH_2), 1.60 (s, 3H, 10-CH_3), 1.45 (d, 3H, $^5J_{PH}$=5.5 Hz, 11-CH_3), 1.26 (t, 3H, $^3J_{HH}$=7.0 Hz, 3-$CO_2CH_2CH_3$), 1.25 (t, 3H, $^3J_{HH}$=7.2 Hz, 1-$CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 166.8 (s, 1-CO), 165.5 (d, $^2J_{PC}$=10.5 Hz, 3-CO), 160.7 (s, C-8a), 137.7 (s, C-6), 134.4 (s, C-8), 127.3 (d, $^2J_{PC}$=11.8 Hz, C-10), 125.1 (d, $^3J_{PC}$=13.6 Hz, C-11), 119.3 (d, $^3J_{PC}$=9.3 Hz, C-5), 110.1 (s, C-7), 76.6 (overlapped by the signal of $CDCl_3$, C-1), 74.8 (d, $^1J_{PC}$=53.3 Hz, C-3), 63.2 (s, 1-CO_2CH_2), 59.1 (s, 3-CO_2CH_2), 40.0 (d, $^1J_{PC}$=51.5 Hz, C-9), 40.0 (s, C-12), 20.3 (d, $^3J_{PC}$=5.0 Hz, 10-CH_3), 20.2 (d, $^4J_{PC}$=3.7 Hz, 11-CH_3), 14.7 (s, 1-$CO_2CH_2CH_3$), 14.3 (s, 3-$CO_2CH_2CH_3$).

*4.3.2. Compound **3b***

Green solid (392 mg, 74%), mp 108–110 °C ($CHCl_3$). (Found: C, 56.88; H, 5.79; N, 3.60. $C_{18}H_{22}NO_4PS$ (379.4) requires: C, 56.98; H,

5.84; N, 3.69%.) ^{31}P NMR ($CDCl_3$): δ 64.5; ^{1}H NMR ($CDCl_3$): δ 7.99 (d, 1H, $^3J_{HH}$=9.3 Hz, H-5), 7.26 (dd, 1H, $^3J_{HH}$=9.3, 6.6 Hz, H-6), 7.13 (d, 1H, $^3J_{HH}$=6.6 Hz, H-8), 6.33 (t, 1H, $^3J_{HH}$=6.6 Hz, H-7), 5.38 (br s, 1H, H-11), 4.34 (q, 2H, $^3J_{HH}$=6.9 Hz, 1-CO_2CH_2), 4.33 (dq, 1H, $^2J_{HAHB}$=10.6 Hz, $^3J_{HH}$=6.9 Hz, H_A of 3-CO_2CH_2), 4.18 (dq, 1H, $^2J_{HAHB}$=10.6 Hz, $^3J_{HH}$=6.9 Hz, H_B of 3-CO_2CH_2), 3.38–3.27 (1H, not resolved, H_A of 12CH_2), 3.32 (t, 1H, $^2J_{HAHB}$=$^2J_{PH}$=17.8 Hz, H_A of 9-CH_2), 2.91 (t, 1H, $^2J_{HAHB}$=$^2J_{PH}$=17.8 Hz, H_B of 9-CH_2), 2.80 (ddd, $^3J_{PH}$=30.0 Hz, $^2J_{HAHB}$=15.6 Hz, $^3J_{HH}$=7.3 Hz, H_B of 12-CH_2), 1.72 (s, 3H, 10-CH_3), 1.33 (t, 3H, $^3J_{HH}$=6.9 Hz, 3-$CO_2CH_2CH_3$), 1.31 (t, 3H, $^3J_{HH}$=6.9 Hz, 1-$CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 166.9 (s, 1-CO), 165.9 (d, $^2J_{PC}$=10.3 Hz, 3-CO), 160.1 (s, C-8a), 138.0 (s, C-6), 137.4 (d, $^2J_{PC}$=11.5 Hz, C-10), 134.2 (s, C-8), 119.4 (d, $^2J_{PC}$=9.3 Hz, C-5), 118.0 (d, $^3J_{PC}$=13.3 Hz, C-11), 110.5 (s, C-7), 76.5 (overlapped by the signal of $CDCl_3$, C-1), 74.7 (d, $^1J_{PC}$=53.6 Hz, C-3), 63.3 (s, 1-CO_2CH_2), 59.2 (s, 3-CO_2CH_2), 38.9 (d, $^1J_{PC}$=50.9 Hz, C-9), 33.1 (s, C-12), 24.4 (s, 10-CH_3), 14.7 (s, 1-$CO_2CH_2CH_3$), 14.3 (s, 3-$CO_2CH_2CH_3$).

4.3.3. Compound **3c**

Pale yellow solid (228 mg, 88%), mp 126–128 °C ($CHCl_3$). (Found: C, 56.90; H, 5.70; N, 3.58. $C_{18}H_{22}NO_4PS$ (379.4) requires: C, 56.98; H, 5.84; N, 3.69%.) ^{31}P NMR ($CDCl_3$): δ 66.2; ^{1}H NMR ($CDCl_3$): δ 7.91 (d, 1H, $^3J_{HH}$=9.3 Hz, H-7), 7.11 (d, 1H, $^3J_{HH}$=9.3 Hz, H-8), 6.92 (s, 1H, H-5), 3.80 (s, 3H, 1-CO_2CH_3), 3.69 (s, 3H, 3-CO_2CH_3), 3.38 (t, 1H, $^2J_{HAHB}$=$^3J_{PH}$=15.0 Hz, H_A of 12-CH_2), 3.13 (t, 1H, $^2J_{HAHB}$=$^2J_{PH}$=15.0 Hz, H_A of 9-CH_2), 2.84 (t, 1H, $^2J_{HAHB}$=$^2J_{PH}$=15.0 Hz, H_B of 9-CH_2), 2.65 (dd, 1H, $^3J_{PH}$=22.5 Hz, $^2J_{HAHB}$=15.0 Hz, H_B of 12-CH_2), 2.06 (s, 3H, 6-CH_3), 1.58 (s, 3H, 10-CH_3), 1.44 (d, 3H, $^5J_{PH}$=5.1 Hz, 11-CH_3); ^{13}C NMR ($CDCl_3$): δ 167.4 (s, 1-CO), 166.0 (d, $^2J_{PC}$=11.2 Hz, 3-CO), 159.5 (s, C-8a), 140.8 (s, C-8), 131.6 (s, C-7), 127.3 (d, $^2J_{PC}$=11.4 Hz, C-10), 125.1 (d, $^3J_{PC}$=12.4 Hz, C-11), 120.3 (s, C-6), 119.1 (d, $^3J_{PC}$=8.7 Hz, C-5), 76.6 (overlapped by the signal of $CDCl_3$, C-1), 75.5 (d, $^1J_{PC}$=53.3 Hz, C-3), 53.7 (s, 1-CO_2CH_3), 50.6 (s, 3-CO_2CH_3), 40.0 (d, $^1J_{PC}$=51.5 Hz, C-9), 39.7 (s, C-12), 20.3 (s, 10-CH_3, 11-CH_3), 17.5 (s, 6-CH_3).

4.3.4. Compound **3d**

Green solid (282 mg, 90%), mp 122–123 °C ($CHCl_3$). (Found: C, 55.80; H, 5.45; N, 3.70. $C_{17}H_{20}NO_4PS$ (365.4) requires: C, 55.88; H, 5.52; N, 3.83%.) ^{31}P NMR ($CDCl_3$): δ 65.4; ^{1}H NMR ($CDCl_3$): δ 7.94 (d, 1H, $^3J_{HH}$=9.9 Hz, H-7), 7.28 (d, 1H, $^3J_{HH}$=9.9 Hz, H-8), 6.86 (s, 1H, H-5), 5.32 (br s, 1H, H-11), 3.80 (s, 3H, 1-CO_2CH_3), 3.69 (s, 3H, 3-CO_2CH_3), 3.27–3.18 (H_A of 9-CH_2, partially overlapped by H_A of 12-CH_2), 3.22 (t, 1H, $^2J_{HAHB}$=$^3J_{PH}$=13.5 Hz, H_A of 12-CH_2), 2.89–2.69 (H_B of 12-CH_2, not resolved), 2.84 (t, 1H, $^2J_{HAHB}$=$^2J_{PH}$=17.2 Hz, H_B of 9-CH_2), 2.06 (s, 3H, 6-CH_3), 1.64 (s, 3H, 10-CH_3); ^{13}C NMR ($CDCl_3$): δ 167.4 (s, 1-CO), 165.1 (d, $^2J_{PC}$=11.0 Hz, 3-CO), 159.1 (s, C-8a), 141.0 (s, C-8), 137.2 (d, $^2J_{PC}$=11.8 Hz, C-10), 131.5 (s, C-7), 120.6 (s, C-6), 119.2 (d, $^3J_{PC}$=9.3 Hz, C-5), 117.9 (d, $^3J_{PC}$=13.0 Hz, C-11), 76.6 (overlapped by the signal of $CDCl_3$, C-1), 76.3 (d, $^1J_{PC}$=53.3 Hz, C-3), 53.7 (s, 1-CO_2CH_3), 50.6 (s, 3-CO_2CH_3), 38.9 (d, $^1J_{PC}$=50.9 Hz, C-9), 32.6 (s, C-12), 24.3 (s, 10-CH_3), 17.6 (s, 6-CH_3).

4.3.5. Compound **3e**

Pale yellow solid (398 mg, 74%), mp 119–120 °C ($CHCl_3$). (Found: C, 58.92; H, 6.40; N, 3.39. $C_{20}H_{26}NO_4PS$ (407.5) requires: C, 58.95; H, 6.43; N, 3.44%.) ^{31}P NMR ($CDCl_3$): δ 65.9; ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, $^3J_{HH}$=9.3 Hz, H-7), 7.09 (d, 1H, $^3J_{HH}$=9.3 Hz, H-8), 6.91 (s, 1H, H-5), 4.28 (q, 2H, $^3J_{HH}$=7.0 Hz, 1-CO_2CH_2), 4.25 (dq, 1H, $^2J_{HAHB}$=10.8 Hz, $^3J_{HH}$=7.2 Hz, H_A of 3-CO_2CH_2), 4.10 (dq, 1H, $^2J_{HAHB}$=10.8 Hz, $^3J_{HH}$=7.2 Hz, H_B of 3-CO_2CH_2), 3.37 (t, 1H, $^2J_{HAHB}$=$^3J_{PH}$=15.0 Hz, H_A of 12-CH_2), 3.14 (dd, 1H, $^2J_{HAHB}$=15.0 Hz, $^2J_{PH}$=13.4 Hz, H_A of 9-CH_2), 2.83 (t, 1H, $^2J_{HAHB}$=$^2J_{PH}$=15.0 Hz, H_B of 9-CH_2), 2.64 (dd, 1H, $^3J_{PH}$=22.5 Hz, $^2J_{HAHB}$=15.0 Hz, H_B of 12-CH_2), 2.05 (s, 3H, 6-CH_3), 1.59 (s, 3H, 10-CH_3), 1.43 (d, 3H, $^5J_{PH}$=5.7 Hz, 11-CH_3), 1.25 (t, 3H, $^3J_{HH}$=7.0 Hz, 1-$CO_2CH_2CH_3$), 1.25 (t, 3H, $^3J_{HH}$=7.2 Hz, 3-$CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 167.0 (s, 1-CO), 165.7 (d, $^2J_{PC}$=10.5 Hz, 3-CO), 141.3 (s, C-8a), 140.6 (s, C-8), 131.8 (s, C-7), 127.3 (d, $^2J_{PC}$=11.8 Hz, C-10), 125.1 (d, $^3J_{PC}$=13.0 Hz, C-11), 120.0 (s, C-6), 119.0 (d, $^3J_{PC}$=8.7 Hz, C-5), 76.7 (d, overlapped by the signal of $CDCl_3$, C-1), 75.0 (d, $^1J_{PC}$=53.3 Hz, C-3), 63.2 (s, 1-CO_2CH_2), 59.0 (s, 3-CO_2CH_2), 40.2 (d, $^1J_{PC}$=51.5 Hz, C-9), 40.0 (s, C-12), 20.3 (d, $^3J_{PC}$=7.4 Hz, 10-CH_3), 20.2 (d, $^4J_{PC}$=3.6 Hz, 11-CH_3), 17.5 (s, 6-CH_3), 14.8 (s, 1-$CO_2CH_2CH_3$), 14.3 (s, 3-$CO_2CH_2CH_3$).

4.3.6. Compound **3f**

Pale green solid (312 mg, 41%), mp 100–102 °C ($CHCl_3$). (Found: C, 57.92; H, 6.12; N, 3.42. $C_{19}H_{24}NO_4PS$ (393.4) requires: C, 58.00; H, 6.15; N, 3.56%.) ^{31}P NMR ($CDCl_3$): δ 64.9; ^{1}H NMR ($CDCl_3$): δ 7.89 (d, 1H, $^3J_{HH}$=9.3 Hz, H-7), 7.10 (d, 1H, $^3J_{HH}$=9.3 Hz, H-8), 6.85 (s, 1H, H-5), 5.30 (br s, 1H, H-11), 4.27 (q, 2H, $^3J_{HH}$=7.0 Hz, 1-CO_2CH_2), 4.25 (dq, 1H, $^2J_{HAHB}$=11.2 Hz, $^3J_{HH}$=7.2 Hz, H_A of 3-CO_2CH_2), 4.10 (dq, 1H, $^2J_{HAHB}$=11.2 Hz, $^3J_{HH}$=7.2 Hz, H_B of 3-CO_2CH_2), 3.28–3.18 (H_A of 12-CH_2, partially overlapped by H_A of 9-CH_2), 3.23 (t, 1H, $^2J_{HAHB}$=$^2J_{PH}$=14.3 Hz, H_A of 9-CH_2), 2.83 (t, 1H, $^2J_{HAHB}$=$^2J_{PH}$=14.3 Hz, H_B of 9-CH_2), 2.75 (td, 1H, $^2J_{HAHB}$=$^3J_{PH}$=15.8 Hz, $^3J_{HH}$=7.3 Hz, H_B of 12-CH_2), 2.04 (s, 3H, 6-CH_3), 1.64 (s, 3H, 10-CH_3), 1.26 (t, 3H, $^3J_{HH}$=7.0 Hz, 1-$CO_2CH_2CH_3$), 1.25 (t, 3H, $^3J_{HH}$=7.2 Hz, 3-$CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 167.0 (s, 1-CO), 165.6 (d, $^2J_{PC}$=11.2 Hz, 3-CO), 159.4 (s, C-8a), 140.8 (s, C-8), 137.2 (d, $^2J_{PC}$=11.5 Hz, C-10), 131.6 (s, C-7), 120.2 (s, C-6), 119.0 (d, $^3J_{PC}$=9.3 Hz, C-5), 117.8 (d, $^3J_{PC}$=12.8 Hz, C-11), 76.6 (d, overlapped by the signal of $CDCl_3$, C-1), 75.0 (d, $^1J_{PC}$=52.7 Hz, C-3), 63.2 (s, 1-CO_2CH_2), 60.2 (s, 3-CO_2CH_2), 39.0 (d, $^1J_{PC}$=50.9 Hz, C-9), 36.3 (s, C-12), 24.2 (s, 10-CH_3), 17.5 (s, 6-CH_3), 14.7 (s, 1-$CO_2CH_2CH_3$), 14.3 (s, 3-$CO_2CH_2CH_3$).

Acknowledgements

Financial support from University Grants Commission, New Delhi (as Emeritus Fellowship to R.K.B.) and Council of Scientific and Industrial Research, New Delhi (as SRF to S.K.K.) is gratefully acknowledged.

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