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Hetero-Diels–Alder Reaction of Phosphinyl and Phosphonyl Nitroso Alkenes with Conjugated Dienes: An Aza-Cope Rearrangement

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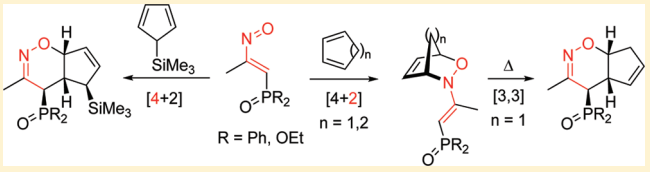
Supporting Information

ABSTRACT: Phosphorylated nitroso alkenes react with cyclic dienes such as cyclopentadiene or cyclohexadiene to afford hetero Diels–Alder-type cycloadducts where the nitroso alkene participates as dienophile component and the cyclic olefin acts as the 4π-electron (diene) system. Subsequent aza-Cope rearrangement affords highly functionalized 5,6-dihydro-4*H*-1,2-oxazines. Conversely, the reaction of TMS-substituted cyclopentadiene (dienophile) with nitroso alkenes as heterodienes leads directly to bicyclic 1,2-oxazines. Theoretical studies are in agreement with the experimental results and with the new aza-Cope rearrangement proposed.



INTRODUCTION

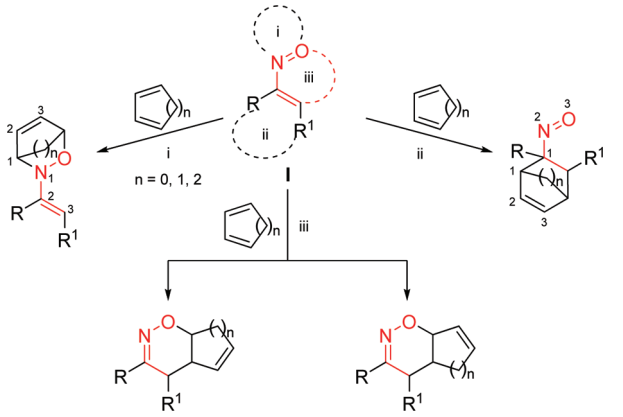
The nitroso function has been widely recognized as a useful source of nitrogen- and oxygen-containing molecules. The chemistry of nitroso compounds has been widely studied in recent decades, especially because of their applications in the fields of asymmetric synthesis and cycloaddition processes.[1] In addition, nitroso-Diels–Alder (nDA) reaction[2,3] is a remarkable synthetic transformation, providing easy access to synthetically useful compounds such as 1,2-oxazines.

Nitroso alkenes[4] are functionalized nitroso derivatives, which have attracted a great deal of attention owing to their usefulness as heterodienes for a [4 + 2]-cycloaddition reaction. These nitroso alkenes **I** may react with dienes, in a Diels–Alder reaction,[5] either as dienophile (2π-electron) systems through the nitroso group (mode i) or involving the carbon–carbon double bond (mode ii) or as 4π-electron (heterodiene) components (mode iii) (see Scheme 1).

Acyclic and cyclic conjugated dienes, as a dienophile system, add to nitroso alkenes **I** involving reaction at the terminal carbon and oxygen atoms (1,4-positions), most of which are unsubstituted at the terminal carbon atom (R^1 = H) (route iii, Scheme 1).[6] Likewise, cyclopentadiene and cyclohexadiene add to the nitroso group of substituted nitroso alkenes **I** (R^1 = Cl, Br, CO_2R) (route i) to give [4 + 2]-adducts[7,8] which may isomerize at room temperature to form epoxyaziridines.[7] Clearly, the nitroso alkene substituents play a crucial role. Early works of Gilchrist et al.[9] also suggested cycloadditions involving only the terminal carbon–carbon double bond of nitroso alkenes (route ii, Scheme 1).

We previously described the generation of phosphinyl **II** (R = Ph) and phosphonyl nitroso alkenes **II** (R = OEt) and the conjugate addition (1,4-addition) of some nucleophiles, such as amines and amino-esters, for the preparation of α-amino phosphonate derivatives[10] **III** (see Scheme 2). Likewise, formal [3 + 2] cycloaddition processes of phosphorated nitroso alkenes **II** have also been used for the regioselective preparation of highly functionalized *N*-hydroxypyrroles[11] **IV** (see Scheme 2).

Scheme 1. Hetero-Diels–Alder Reactivity Pattern of Nitroso Alkenes I with Dienes



Taking into account the interest of phosphorated substituted heterocycles[12] and following from our interest in the preparation of three-,[13] five-,[14] and six-membered[15] heterocycles and in the reactivity of phosphorated nitroso alkenes,[10,11] we report here the combined theoretical and experimental study of the [4 + 2]-cycloaddition reaction of phosphonyl and phosphinyl nitroso alkenes **II** (R = Ph, OEt) to cyclic conjugated nucleophilic dienes such as cyclopentadiene, cyclohexa-1,3-diene, and silyl-substituted cyclopentadiene. Moreover, we report the first example of a tandem process involving an initial cycloaddition reaction followed by a consecutive new [3,3]-sigmatropic rearrangement.

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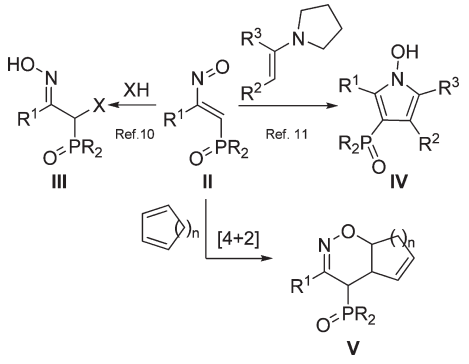
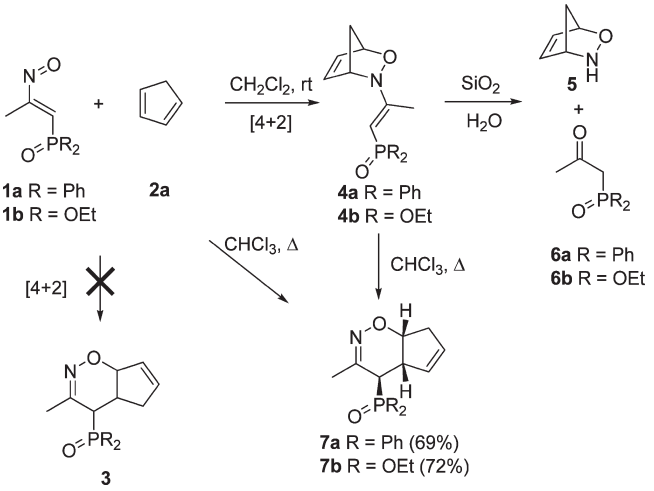
Scheme 2. Reactivity Pattern of Nitroso Alkenes II



Scheme 3. Hetero-Diels–Alder Reaction of Phosphorated Nitroso Alkenes 1 with Cyclopentadiene 2a



This process, in which the conjugated diene acts as a 4π-electron component toward the nitrogen–oxygen double bond of the nitroso alkene, provides an efficient access to a variety of phosphorus-substituted cycloadducts **V** (see Scheme 2).

RESULTS AND DISCUSSION

Experimental Study. The reaction of 1,2-oxazabuta-1,3-dienes **1** with conjugated dienes was explored. Thus, as outlined in Scheme 3, the addition of cyclopentadiene **2a** to the highly reactive 4-phosphinyl (**1a**, R = Ph) or 4-phosphonyl nitroso alkene (**1b**, R = OEt), generated in situ from α-bromooximes,[10] in CH_2Cl_2 at room temperature was performed. The highly colored 1,2-oxazabuta-1,3-dienes **1** disappeared very quickly, and instead of the hetero-Diels–Alder 1,2-oxazine **3**, the 2-oxa-3-azabicyclic derivatives **4** were observed in the reaction mixture as sole adducts (Scheme 3). *N*-Vinyl bicyclic compounds **4** were very sensitive to hydrolysis because all attempts to isolate these adducts **4** by chromatographic methods were unsuccessful, and the cleavage of the enaminic C–N bond in these intermediates afforded the α-ketophosphine oxide **6a** or α-ketophosphonate **6b** and bicyclic amine **5** (Scheme 3, and Experimental Section). Formation of adducts **4a,b** may be explained by a [4 + 2]-cycloaddition,

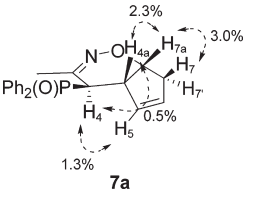
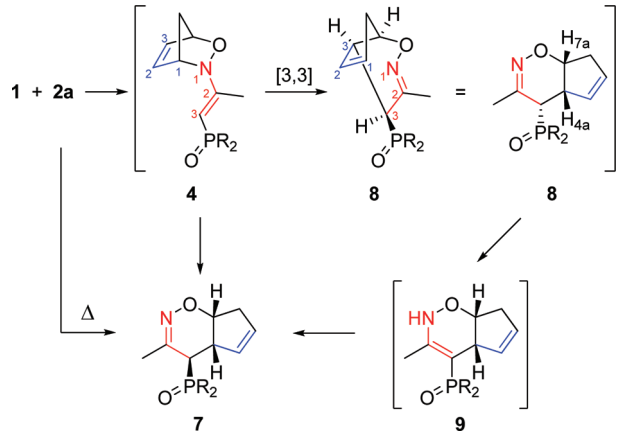


Figure 1. NOE observed for 4-phophinyl-5,6-dihydro-4*H*-1,2-oxazine **7a**.

Scheme 4. Mechanism for the Conversion of Adducts 4 into 1,2-Oxazines 7



in which the nitroso group of compound **1** may act as a dienophile and the cyclopentadiene acts as diene. However, the in situ heating of adducts **4a,b** in refluxing chloroform for 48 h gave rise to a stable phosphinyl-5,6-dihydro-4*H*-1,2-oxazine **7a** or the phosphonyl-5,6-dihydro-4*H*-1,2-oxazine **7b** in good yields. These products **7** could also be obtained from diene **2a** and nitroso derivatives **1**, when these reagents were heated in refluxing chloroform.

The regio- and stereochemistry of 1,2-oxazine **7a** was based upon the NOE, ^{1}H, ^{13}C, and ^{1}H–^{1}H COSY NMR spectral data. Namely, the stereochemistry of **7a** was assigned on the basis of NOE experiments. The 5,6-*cis* relationship of H-4a and H-7a in the ring of 1,2-oxazine **7a** was evident since a NOE was observed between H-4a and H-7a (2.3%) (*cis* relative stereochemistry) and between H-7a and H-7 (3.0%) after irradiation of proton H-7a (Figure 1). These results clearly suggest a *cis* relative stereochemistry between H-4a and H-7a. Conversely, a very small NOE was observed between H-4 and H-4a (0.5%) suggesting a *trans* relationship between both protons. Likewise, the regiochemistry of **7a** was also confirmed by a NOE effect between H-4 and H-5 (1.3%). Comparable values were observed when selective irradiations were performed with oxazine **7b**.

1,2-Oxazines **7** generated by the reaction of the nitroso alkenes **1** and the cyclopentadiene **2a** seems to be the result of an initial [4 + 2]-cycloaddition, in which the nitroso alkene acts as a dienophile, through the nitroso group, while the cyclopentadiene acts as diene to afford 2-oxa-3-azabicyclic compounds **4**. These adducts **4** may undergo an aza-Cope rearrangement[16] to give 1,2-oxazines **8** (Scheme 4). Compounds **8**, with the bulky phosphorus substituent at C-4 in *anti* position with respect to H-4a and H-7a, may suffer an imine-enamine tautomeric process (**8** to **9**) to give 1,2-oxazines **7** with the bulky phosphorus substituent in *syn* position with respect to H-4a and H-7a, as confirmed by

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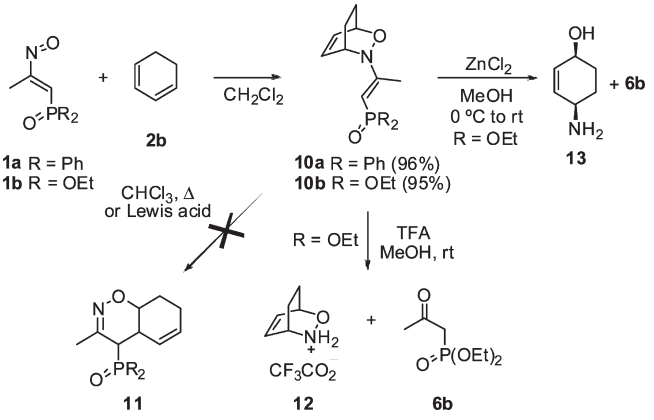
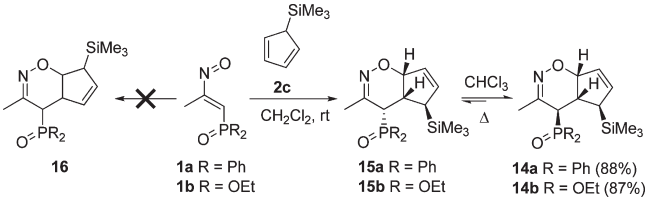
Scheme 5. Hetero-Diels–Alder Reaction of Phosphorated Nitroso Alkenes 1 with 1,3-Cyclohexadiene 2b



Scheme 6. Hetero-Diels–Alder Reaction of Phosphorated Nitroso Alkenes 1 with Substituted Cyclopentadiene 2c



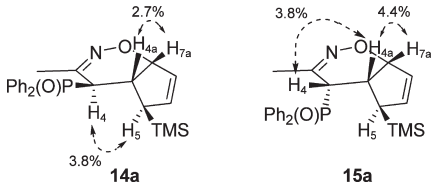


Figure 2. NOE observed for 4-phophinyl-5,6-dihydro-4*H*-1,2-oxazine **14a**/**15a**.

the NOE experiments. The isolation of thermodynamically more stable oxazine **7** toward **8** is in agreement with the calculated free energy differences (see computational studies in Supporting Information), which show that oxazines **7** are approximately 2 kcal/mol more stable than the corresponding oxazines **8**. As far as we know, this process represents the first example of a tandem reaction of an initial [4 + 2]-cycloaddition reaction of the nitroso alkene and subsequently a new [3,3]-sigmatropic (aza-Cope) rearrangement to give 1,2-oxazine derivatives **7**.

The process was extended to the reaction of 4-phosphorated-1,2-oxazabuta-1,3-dienes **1** toward cyclohexa-1,3-diene **2b** in CH_2Cl_2 at room temperature to give hetero-Diels–Alder cycloadducts **10a**,**b** in excellent yield (Scheme 5). Similar behavior as before was observed, and all attempts to isolate these cycloadducts **10a**,**b** by chromatographic methods were unsuccessful (see Experimental Section). Although cycloadducts **10a**,**b** were fully characterized from the crude reaction, in this case neither heating these adducts in refluxing chloroform nor the use of Lewis acids such as $TiCl_4$, $BF_3 \cdot Et_2O$, or $AlMe_3$ afforded phosphorated 1,2-oxazines **11** (Scheme 5).

Evidence for the formation of the 2-oxa-3-azabicycle derivative **12** and thus for the formation of cycloadducts **10** was found through treatment of crude compound **10b** with trifluoroacetic acid (TFA) in MeOH at room temperature. Under these conditions salt **12** was obtained (Scheme 5). Likewise, the treatment of adduct **10b** with $ZnCl_2$ was explored in order to test whether N–O bond cleavage could be achieved in order to obtain substituted amino alcohol **13**. Hence, compound **10b** was subjected to $ZnCl_2$ treatment in MeOH to afford the amino alcohol derivative **13** (Scheme 5). Even though phosphorated 1,2-oxazines **11** cannot be obtained by heating the cycloadducts **10** (Scheme 5), isolation of salt **12** and amine **13** support the formation of 2-oxa-3-azabicyclic cycloadducts **10** by the reaction of nitroso alkenes **1** and cyclohexa-1,3-diene **2b**.

In order to determine the scope and limitations of the cycloaddition reaction between nitroso alkenes and cyclic conjugated dienes and to investigate the regio- and stereochemistry of the additions, we extended the study to the reaction of 4-phosphorated-1,2-oxazabuta-1,3-dienes **1** with other cyclic conjugated dienes, such as 5-(trimethylsilyl)cyclopenta-1,3-diene **2c**. Thus, reaction of nitroso alkenes **1** with substituted cyclopentadiene **2c** in CH_2Cl_2 at room temperature showed a different reactivity pattern, affording a mixture of 1,2-oxazine derivatives **14a**,**b**/**15a**,**b** in good yields and in a regio- and steroselective fashion (Scheme 6). No formation of the regioisomeric oxazine **16** was detected at all. ^1H and ^{31}P NMR spectral data for crude compounds **14**/**15** reveals that a mixture of diastereoisomers in a ratio of 50:50 for compound **14a**/**15a** and 92:8 for compound **14b**/**15b** are present in the crude reaction media. However, the in situ heating of a mixture of cycloadducts **14**/**15** in refluxing chloroform afforded a stable phosphorus substituted 1,2-oxazines **14** in good yields. These oxazines **14** can also be obtained from conjugated nitroso alkenes **1** and olefine **2c**, when these reagents were heated in refluxing chloroform.

The regio- and stereochemistry of 1,2-oxazines **14**/**15** was based upon the NOE and ^1H NMR spectral data. The 4,5,6-*cis* relationship between H-4, H-4a, and H-7a in the ring of 1,2-oxazine **15a** was evident since a NOE was observed between H-4a and H-7a (4.4%) and between H-4a and H-4 (3.8%) after irradiation of proton H-4a (*cis*–*cis* relative stereochemistry) (Figure 2). Conversely, only a NOE was observed between H-4a and H-7a (2.7%) in 1,2-oxazine **14a** when proton H-4a was irradiated, suggesting a *cis* relative stereochemistry between H-4a and H-7a, and no NOE was observed between H-4a and H-4 (*trans* relative stereochemistry). Likewise, the regiochemistry of **14a** was also confirmed by a NOE between H-4 and H-5 (3.8%). Clearly different chemical shifts for H-5 were found for both diastereoisomers. When the diphenylphosphinyl group at C-4 adopts an *anti* position with respect to H-4a and H-7a (compound **15a**), H-5 resonates at 2.70 ppm, while in the ^1H NMR spectrum the absorption of H-5 for compound **14a** is shifted to higher field (δ_H 1.60 ppm). Similar values were observed for 1,2-oxazines **14b**/**15b**.

The formation of silylated oxazines **15**, without detection of the regioisomeric oxazines **16**, can be explained by a regioselective [4 + 2]-cycloaddition reaction with the nitroso alkene as the 4π-electron system[6] (route iii of Scheme 1). As before in the case of oxazine **8** and **7** (Scheme 4, vide supra), epimerization of the bulky phosphorus substituent at C-4 of compound **15** to oxazine **14** is thermodynamically favored because the latter is about 4 kcal/mol more stable than the former oxazines **15** (see Computational Studies).

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To the best of our knowledge, these novel strategies are the first examples of the preparation of 4-phosphorated 1,2-oxazines. 1,2-Oxazines are of biological importance and have been used as intermediates during the synthesis of glycosidase inhibitor analogues,[17] and functionalized pyrroles.[18] They have found numerous applications in the total synthesis of natural and biologically active nitrogen-containing compounds, such as alkaloids,[19] pheromones[20] or unnatural α-amino acids.[21] 1,2-Oxazines are important structural constituents of many fungicides and broad spectrum bactericides,[22] as well as marine-derived trichodermamides.[23]

COMPUTATIONAL STUDIES

As has been shown in Scheme 1 for conjugated nitroso derivatives **I**, nitroso alkenes **1** may potentially act in Diels−Alder reactions not only as heterodienes (route iii) but also as dienophiles (routes i and ii). Similarly, the presence of a second double bond in the cyclic conjugated dienes open a new reactivity pattern to the olefin, and these reagents may act as dienes (routes i and ii) or dienophiles (route iii). Therefore, the aim of the present study for the [4 + 2]-cycloaddition reactions of nitroso alkenes **1a** (R = Ph) and **1b** (R = OEt) with cyclic dienes such as cyclopentadiene **2a**, cyclohexa-1,3-diene **2b**, and 5-(trimethylsilyl)cyclopenta-1,3-diene **2c** was to elucidate whether nitroso alkenes **1** may play the role of dienophiles or heterodienes in the cycloaddition reaction with dienes **2** and to explore the regiocontrol and *exo*/*endo* stereocontrol of these processes in order to find a possible mechanism that may explain the different reactivity observed in each case.

The molecular DFT-based parameters, electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), and maximum number of accepted electrons (ΔN_{max}), for nitroso alkenes **1a** and **1b** and cyclic dienes **2a**−**c** are reported in Table 1. These parameters indicate that nitroso alkenes (Table 1, entries 1 and 2) are more electrophilic than cyclic dienes (Table 1, entries 3−5). Thus, cyclic dienes **2a**−**c** are harder than nitroso alkenes **1a** and **1b**, the chemical potentials for compounds **1** are lower than for compounds **2a**−**c**, the computed electrophilicities of **1** are larger than those computed for cyclic dienes **2**, and the ΔN_{max} values for **1a**,**b** are the largest.

The presence of a TMS group in the cyclic diene **2c** increases the hardness and the chemical potential and decreases the electrophilicity toward dienes **2a** and **2b**.

We next computationally examined the regio- and diastereoselectivity of the [4 + 2]-cycloaddition reactions between nitroso alkenes **1** and cyclic conjugated dienes **2**. The approach of compounds **1** to dienes **2** could lead to eight different cycloadducts (Scheme 7). The cycloadducts are defined as *endo*/*exo* in the standard way, on the basis of the orientation of the dienophile with respect to the dienic system. Thus, nitroso alkenes **1** could react with dienes **2** via transition structures **TS1**, where the nitroso alkene acts as the 2π-electron system through the nitroso moiety (nitroso Diels−Alder reaction, nDA), or via transition structures **TS2**, with the nitroso alkene as the dienophile through the C−C double bond (Diels−Alder reaction, DA), or via **TS3** or **TS4** transition structures, where the nitroso alkenes act as heterodienes with two possible approaches, a or b, to the cyclic diene **2** (so-called hetero-Diels−Alder reaction a or b, HDA_a or HDA_b, respectively) (Scheme 7). Moreover, when nitroso alkenes **1** act as dienophiles, the approach to dienic system could be in the *s-cis* conformation **1a**,**b** via transition structures **TS1** and **TS2** or in the *s-trans* conformation **1′a**,**b** via transition structures **TS1′** and **TS2′** (Scheme 7), since these approaches could afford the same cycloadducts, respectively. Note that when R′ ≠ H there are two possibilities for each pathway described above; path *syn* or *anti* refers to the TMS group orientation of the dienophile or the diene. It is also interesting to note that all of our attempts to locate **TS2**-*endo* corresponding to the DA reaction through the C−C double bond with *endo* approach met with no success, since all the starting geometries converged to **TS4**-*endo* (Scheme 7) upon the optimization at the B3LYP/6-31G* + ZPVE level.[25]

Table 1. Hardnesses[a] (η, in au), Chemical Potentials[a] (μ, in au), Global Electrophilicities[a] (ω, in eV), and Maximum Number of Accepted Electrons[a] (ΔN_{max}, in au) for Nitroso Alkenes 1a, b and Cyclic Dienes 2a−c

entry	compound	η	μ	ω	ΔN_{max}
1	**1a**	0.11528	−0.17024	0.126	1.477
2	**1b**	0.11748	−0.17219	0.126	1.466
3	**2a**	0.20159	−0.11069	0.030	0.549
4	**2b**	0.18841	−0.11175	0.033	0.593
5	**2c**	0.20447	−0.10408	0.026	0.509

[a] Computed at the B3LYP/6-31G* level of theory according to the approach and equations described previously.[24]

First, we studied the reaction of nitroso alkenes **1a** (R = Ph) or **1b** (R = OEt) with cyclopentadiene **2a**. According to our results, in all cases when nitroso alkenes **1** act as dienophile, the approach to diene in *s-cis* conformation **1a**,**b** through transition structures **TS1** and **TS2** presents lower activation barriers than the approach in the *s-trans* conformation **1′a**,**b** through transition structures **TS1′** and **TS2′**, respectively (for a full comparison of energetics see Supporting Information). Moreover, the pathways involving **TS1**-*endo*, **TS3**-*endo*, and **TS4**-*endo* transition state structures (Table 2, entries 2, 4, 8, 10, 12, and 14) exhibit activation barriers lower than those of the corresponding **TS1**-*exo*, **TS2**-*exo*, **TS3**-*exo*, and **TS4**-*exo* transition state structures (Table 2, entries 1, 3, 5−7, 9, 11, and 13). All of the processes are exothermic and occur in a concerted manner but slightly asynchronous (Table 2). The computational results indicate that the formation of cycloadducts **4a**,**b**-*endo* through transition state structures **TS1aa**,**ba**-*endo*, for the nDA, have activation barriers (Table 2, entries 2 and 4) lower than those observed when nitroso alkenes **1** act as heterodienes reacting through **TS3**-*endo* or **TS4**-*endo* for the HDA (Table 2, entries 8, 10, 12, and 14) to give cycloadducts **8** or **26**, respectively. With the inclusion of methylene chloride as the solvent, the preference for **TS1aa**,**ba**-*endo* for the nDA is more favored than **TS4aa**,**ba**-*endo* (1.8 kcal/mol for R = Ph and 0.7 kcal/mol for R = OEt, see Supporting Information). From these data, we could conclude that cycloadducts **4**-*endo* will be the sole compounds to be obtained under kinetic control, which is in agreement with the experimental results. The *endo* transition structures with the lower activation energies for each approach giving rise to the cycloaddition reaction of **1a** with **2a** are summarized in Figure 3.

Experimentally, at room temperature only the nDA adducts **4a**,**b**-*endo* are formed, but the heating of these adducts in refluxing chloroform gives cycloadducts **7a**,**b**. This may be explained by a sigmatropic rearrangement of the nDA adducts **4a**,**b**-*endo* to HDA_a adducts **8a**,**b**, which eventually gives **7a**,**b** through an imine−enamine tautomeric process. In fact, we have located transition structures (**TS5**) that are associated with a

Scheme 7. Possible Cycloadducts Corresponding to the Approach of Nitroso Alkenes 1 to Dienes 2

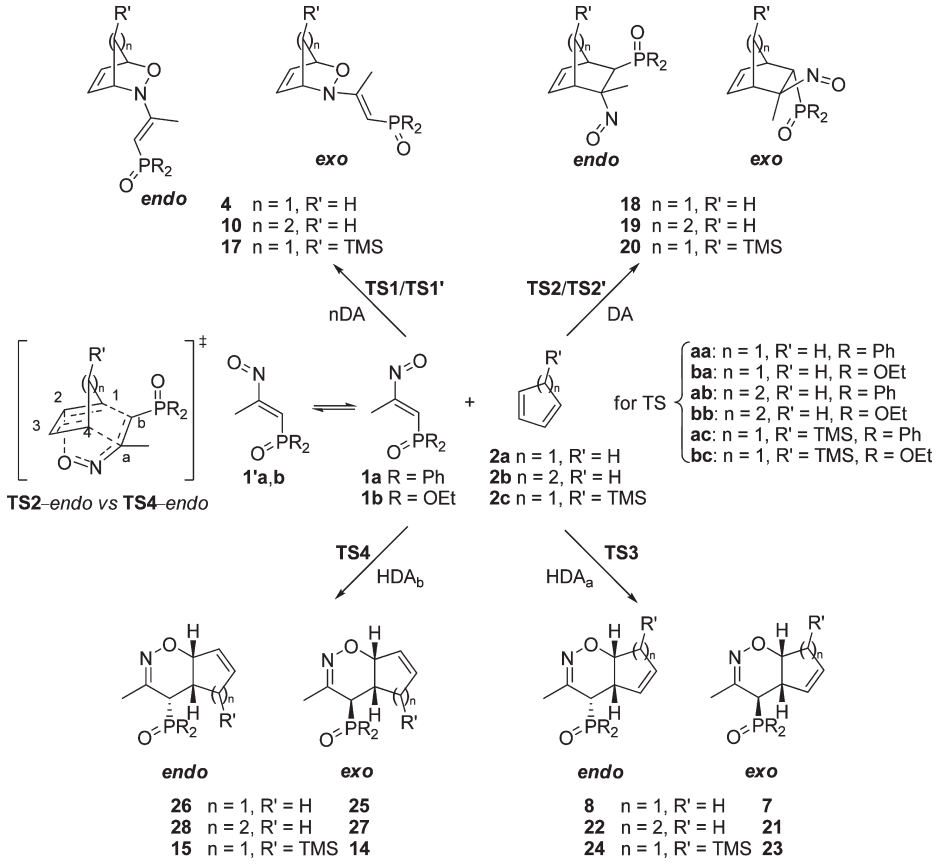

Table 2. Activation Energies[a] (ΔE_a, kcal/mol), Reaction Energies[a] (ΔE_{rxn}, kcal/mol), Synchronicities[b] (Sy) Associated with the Formation of Some Reaction [4 + 2]-Cycloadducts between Nitroso Alkenes 1a,b and Cyclopentadiene 2a (For a Full Comparison of Energetics see Supporting Information)

entry	reaction	TS	ΔE_a[a]	ΔE_{rxn}[a]	Sy[c]
1	**1a** + **2a** → **4a**-*exo*	**TS1aa**-*exo*	14.4	−10.8	0.93
2	**1a** + **2a** → **4a**-*endo*	**TS1aa**-*endo*	7.4	−13.0	0.80
3	**1b** + **2a** → **4b**-*exo*	**TS1ba**-*exo*	13.4	−8.7	0.92
4	**1b** + **2a** → **4b**-*endo*	**TS1ba**-*endo*	9.4	−13.8	0.79
5	**1a** + **2a** → **18a**-*exo*	**TS2aa**-*exo*	11.7	−12.3	0.78
6	**1b** + **2a** → **18b**-*exo*	**TS2ba**-*exo*	14.2	−11.6	0.74
7	**1a** + **2a** → **7a**	**TS3aa**-*exo*	13.0	−34.8	0.92
8	**1a** + **2a** → **8a**	**TS3aa**-*endo*	10.0	−32.7	0.87
9	**1b** + **2a** → **7b**	**TS3ba**-*exo*	14.3	−38.4	0.91
10	**1b** + **2a** → **8b**	**TS3ba**-*endo*	9.8	−36.3	0.91
11	**1a** + **2a** → **25a**	**TS4aa**-*exo*	16.1	−31.3	0.91
12	**1a** + **2a** → **26a**	**TS4aa**-*endo*	9.2	−29.6	0.89
13	**1b** + **2a** → **25b**	**TS4ba**-*exo*	10.8	−35.5	0.92
14	**1b** + **2a** → **26b**	**TS4ba**-*endo*	9.6	−35.2	0.91
15	**4a**-*endo* → **8a**	**TS5aa**	21.7	−19.3	0.82
16	**4b**-*endo* → **8b**	**TS5ba**	23.0	−21.9	0.82

[a] Computed at the B3LYP/6-31G* + ZPVE level of theory. [b] Computed at the B3LYP/6-31G* level of theory according to approach and equations described previously.[26] [c] For a perfectly synchronous reaction Sy = 1.

[3,3]−shift and provide a pathway for the conversion of cycloadducts **4a,b**-*endo* into cycloadducts **8a,b** through a hetero −Claisen rearrangement, allowing us to explain the experimental results (Figure 4). This process is exothermic and occurs in a concerted manner with an asynchronous bond formation (see Table 2, entries 15 and 16). These **TS5-aa,ba** show activation energies of 21.7 kcal/mol (21.9 kcal/mol in chloroform) for the conversion of compound **4a**-*endo* into **8a** and of 23.0 kcal/mol (22.9 kcal/mol in chloroform) for the conversion of compound **4b**-*endo* into **8b**. M06−2X calculated energetics which are expected to be more accurate, also predicted analogous activation barriers (for a full comparison of energetics see Table 3 in Supporting Information). Hence, computational predictions are consistent with our experimental results.

Analogously, we next investigated the regioselectivity in the reaction of 1,3-cyclohexadiene **2b** (Scheme 7, R′ = H, *n* = 2) and nitroso alkenes **1a,b**. Similarly to cycloadditions with **2a**, when nitroso alkenes **1** act as dienophile, the approach to nitroso alkene in *s-cis* conformation **1a,b** through transition structures **TS1** and **TS2** presents activation barriers lower than those of the approach to nitroso alkene in the *s-trans* conformation **1′a,b** through transition structures **TS1′** and **TS2′** (for a full comparison of energetics see Supporting Information). The pathways involving *endo* transition state structures (Table 3, entries 2, 4, 8, 10, 12 and 14) exhibit activation barriers lower than those involving *exo* transition state structures (Table 3, entries 1, 3, 5−7, 9, 11, and 13). All of the processes are exothermic and occur in a concerted but asynchronous manner (see Table 3). Similarly to the cyclopentadiene study, computational results indicate that

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the nDA reaction between nitroso alkenes **1a** (R = Ph) or **1b** (R = OEt) with cyclohexa-1,3-diene **2b** through the **TS1**-*endo*, to give cycloadduct **10a**,**b**-*endo*, have the lowest activation barriers. This may explain the kinetically favored formation of cycloadducts **10a**,**b**-*endo* as compared to the formation of other cycloadducts, in agreement with the experimental results.

Our experimental results show that heating of compounds **10a**,**b**-*endo* in refluxing chloroform did not afford compounds **21** or **22**. In this case, we also located the transition structures (**TS5ab**,**bb**) corresponding to the hetero Claisen rearrangement that could provide a pathway for the conversion of cycloadducts **10a**,**b**-*endo* into cycloadducts **22a**,**b** through a [3,3]-sigmatropic rearrangement (Figure 5), but these transition structures lie in higher activation energies (Table 3, entries 15 and 16) than for cyclopentadiene derivatives (Table 2, entries 15 and 16) and the processes are less exothermic than in the latter case. M06−2X calculated energetics, which are expected to be more accurate, predicted that activation barriers for **TS5ab**,**bb** for cyclohexa-1,3-diene derivatives are bigger than for the corresponding cyclopentadiene derivatives (see Figure 5 and Supporting Information for a full comparison of energetics computed with different methods). These results indicate that the conversion of compounds **10a**,**b**-*endo* into compounds **22a**,**b** are not favored.

Moreover, the N−O and C−N bond distances in compounds **4**-*endo* derived from cyclopentadiene are higher than in compounds **10**-*endo* derived from cyclohexa-1,3-diene. Conversely, the C−N−O and N−O−C bond angles in compounds **4**-*endo* are lower than those observed for compounds **10**-*endo* (Figure 6). These structural differences could explain both the greater stability observed for compounds **10**-*endo* as compared with compounds **4**-*endo* and why heating these compounds in refluxing chloroform did not afford compounds **22**.

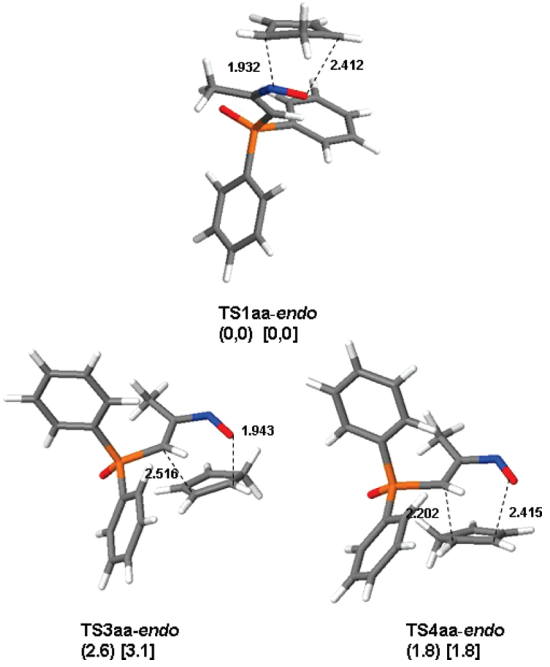

Figure 3. Fully optimized *endo* transition structures with the lower activation energies for the reaction of nitroso alkene **1a** and cyclopentadiene **2a**. Selected bond lengths are given in Å. The numbers given in parentheses correspond to the relative energy differences (in kcal/mol) of **TS3aa**-*endo* and **TS4aa**-*endo* with respect to **TS1aa**-*endo* calculated at B3LYP/6-31G* + ΔZPVE level of theory. Numbers in square brackets are the relative energies differences calculated a B3LYP(PCM)/6-31G* using methylene chloride as the solvent.

Table 3. Activation Energies[a] (ΔE_a, kcal/mol), Reaction Energies[a] (ΔE_{rxn}, kcal/mol), Synchronicities[b] (Sy) Associated with the Formation of [4 + 2]-Cycloadducts of the Reaction between Nitroso Alkenes 1a,b and Cyclohexa-1,3-Diene 2b

entry	reaction	TS	ΔE_a[a]	ΔE_{rxn}[a]	Sy[c]
1	**1a** + **2b** → **10a**-*exo*	**TS1ab**-*exo*	19.3	−16.8	0.92
2	**1a** + **2b** → **10a**-*endo*	**TS1ab**-*endo*	7.5	−18.9	0.79
3	**1b** + **2b** → **10b**-*exo*	**TS1bb**-*exo*	18.1	−16.0	0.91
4	**1b** + **2b** → **10b**-*endo*	**TS1bb**-*endo*	7.3	−19.3	0.80
5	**1a** + **2b** → **19a**-*exo*	**TS2ab**-*exo*	14.1	−13.0	0.74
6	**1b** + **2b** → **19b**-*exo*	**TS2bb**-*exo*	15.4	−18.6	0.75
7	**1a** + **2b** → **21a**	**TS3ab**-*exo*	12.9	−33.1	0.91
8	**1a** + **2b** → **22a**	**TS3ab**-*endo*	10.7	−30.8	0.91
9	**1b** + **2b** → **21b**	**TS3bb**-*exo*	11.8	−38.6	0.91
10	**1b** + **2b** → **22b**	**TS3bb**-*endo*	11.3	−34.8	0.91
11	**1b** + **2b** → **27a**	**TS4bb**-*exo*	18.3	−34.9	0.91
12	**1a** + **2b** → **28a**	**TS4ab**-*endo*	12.1	−30.7	0.91
13	**1b** + **2b** → **27b**	**TS4bb**-*exo*	13.7	−37.7	0.91
14	**1a** + **2b** → **28b**	**TS4ab**-*endo*	12.2	−34.5	0.90
15	**10a**-*endo* → **22a**	**TS5ab**	28.3	−11.9	0.85
16	**10b**-*endo* → **22b**	**TS5bb**	30.6	−15.5	0.85

[a] Computed at the B3LYP/6-31G* + ZPVE level of theory. [b] Computed at the B3LYP/6-31G* level of theory according to approach and equations. described previously.[26] [c] For a perfectly synchronous reaction Sy = 1.

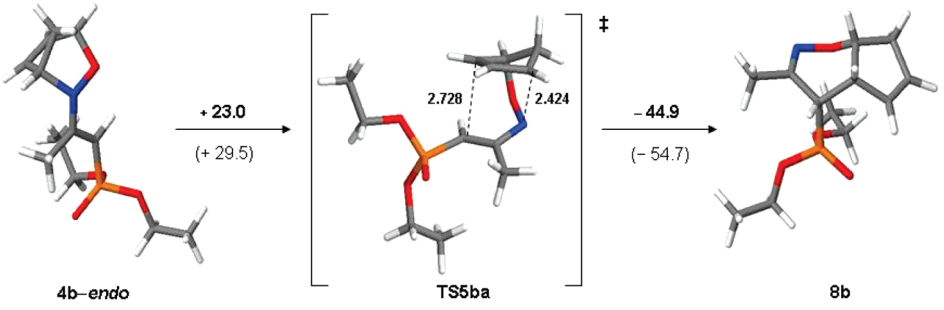

Figure 4. Stationary points (B3LYP/6-31G* level) found in the conversion of cycloadduct **4b**-*endo* to cycloadduct **8b**. Bond lengths and energies are given in Å and kcal/mol, respectively. Bold numbers over the arrows correspond to the relative energies calculated at B3LYP/6-31G* + ZPVE level. Numbers within parentheses correspond to relative energies calculated to M06-2X/6-31G*//B3LYP/6-31G* + ZPVE level.

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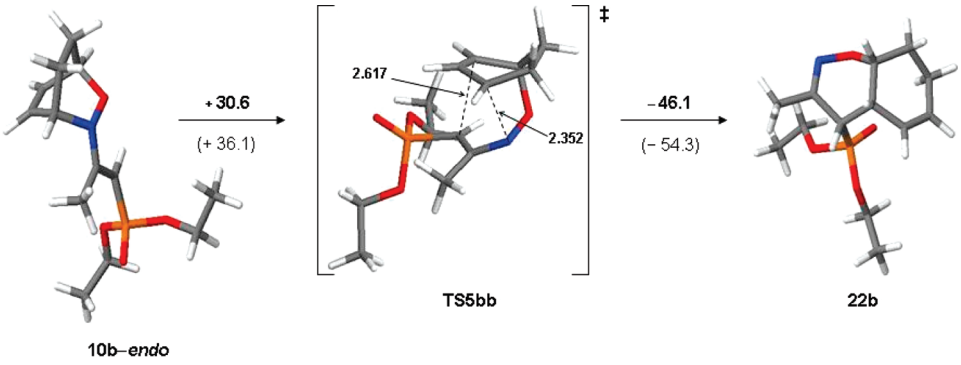

Figure 5. Stationary points (B3LYP/6-31G* level) found in the conversion of cycloadduct **10b**-*endo* to cycloadduct **22b**. Bond lengths and energies are given in Å and kcal/mol, respectively. Bold numbers over the arrows correspond to the relative energies calculated at the B3LYP/6-31G* + ZPVE level. Numbers within parentheses correspond to relative energies calculated to M06-2X/6-31G*//B3LYP/6-31G* + ZPVE level.

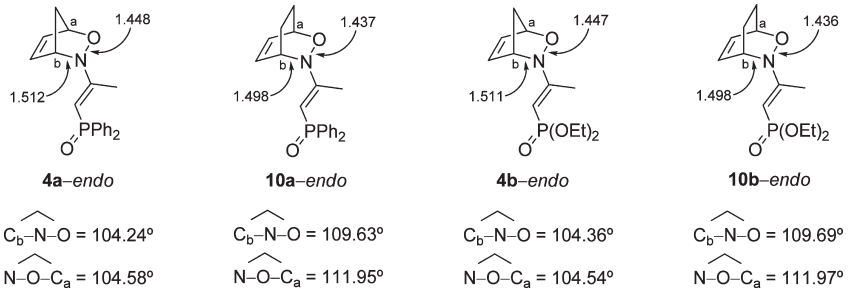

Figure 6. Structural data for optimized compounds **4**- and **10**-*endo*. Bond lengths are given in Å.

Table 4. Activation Energies[a,b] (ΔE_a, kcal/mol), Reaction Energies[a,b] (ΔE_{rxn}, kcal/mol), and Synchronicities[c] (Sy) Associated with the Formation of [4 + 2]-Cycloadducts-A of the Reaction between Nitroso Alkenes 1a,b and TMS-Cyclopentadiene 2c

entry	R	reaction	TS	ΔE_a[a]	ΔE_{rxn}[a]	ΔE_a[b]	ΔE_{rxn}[b]	Sy[d]
1	Ph	**1a** + **2c** → **17a**-*exo*-A	**TS1ac**-*exo*-A	14.6	−5.0	9.3	−17.7	0.86
2	Ph	**1a** + **2c** → **17a**-*endo*-A	**TS1ac**-*endo*-A	8.7	−6.9	5.4	−20.0	0.78
3	OEt	**1b** + **2c** → **17b**-*exo*-A	**TS1bc**-*exo*-A	15.9	−3.2	10.7	−16.2	0.94
4	OEt	**1b** + **2c** → **17b**-*endo*-A	**TS1bc**-*endo*-A	10.1	−8.1	7.1	−20.3	0.78
5	Ph	**1a** + **2c** → **20a**-*exo*-A	**TS2ac**-*exo*-A	10.8	−5.2	2.7	−25.5	0.78
6	OEt	**1b** + **2c** → **20b**-*exo*-A	**TS2bc**-*exo*-A	11.6	−4.5	5.2	−22.9	0.78
7	Ph	**1a** + **2c** → **23a**-A	**TS3ac**-*exo*-A	14.2	−25.9	9.7	−42.7	0.92
8	Ph	**1a** + **2c** → **24a**-A	**TS3ac**-*endo*-A	11.2	−28.0	5.8	−45.3	0.88
9	OEt	**1b** + **2c** → **23b**-A	**TS3bc**-*exo*-A	14.5	−32.1	11.5	−46.3	0.92
10	OEt	**1b** + **2c** → **24b**-A	**TS3bc**-*endo*-A	11.9	−29.8	7.7	−44.2	0.90
11	Ph	**1a**+ **2c** → **14a**-A	**TS4ac**-*exo*-A	16.1	−30.0	9.9	−44.3	0.91
12	Ph	**1a** + **2c** → **15a**-A	**TS4ac**-*endo*-A	9.1	−26.6	0.1	−44.3	0.86
13	OEt	**1b** + **2c** → **14b**-A	**TS4bc**-*exo*-A	13.3	−33.3	8.1	−48.1	0.89
14	OEt	**1b** + **2c** → **15b**-A	**TS4bc**-*endo*-A	9.0	−30.3	2.3	−46.2	0.87

[a] Computed at the B3LYP/6-31G* + ZPVE level of theory. [b] Computed at the M06−2X/6-31G*//B3LYP/6-31G* + ZPVE level. [c] Computed at the B3LYP/6-31G* level of theory according to approach and equations described previously.[26] [d] For a perfectly synchronous reaction Sy = 1.

Finally, we investigated the regioselectivity in the reaction of TMS-cyclopentadiene **2c** (Scheme 7, R′ = TMS, *n* = 1) and nitroso alkenes **1**. It is important to note that for each cycloadduct shown in Scheme 7, there are two possible approaches of compound **2c**, named "A" (if the group TMS is placed in *anti*) and "B" (when placed at *syn*) referring to the orientation of the TMS group and the dienophile or the diene. Transition structures *endo* and *exo*, *syn* and *anti* were located for nDA, DA, and HDA cycloadditions, but all *exo* structures lie higher in energy than the corresponding *endo* structures (see Supporting Information). Also, all *syn* structures lie higher in energy than the corresponding *anti* structures (see Supporting Information). It is also interesting to note that, as in the previous studies with dienes **2a** and **2b**, all of our attempts to locate **TS2**-*endo* corresponding to the DA reaction through the C−C double bond with *endo* approach met with no success, since all of the starting geometries

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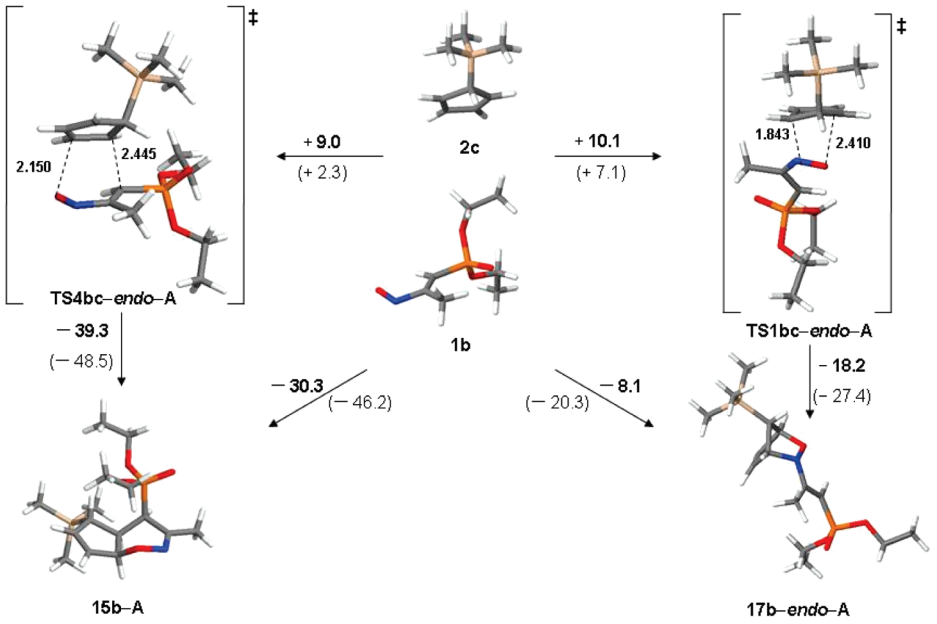
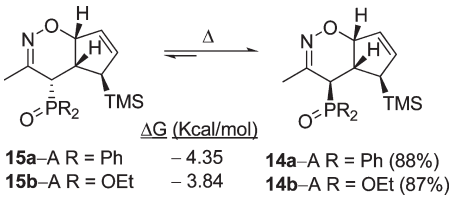


Figure 7. *endo*-A transition structures with the lower activation energies and adducts for the cycloaddition of nitroso alkene **1b** and **2c**. Bond lengths and energies are given in Å and kcal/mol, respectively. Bold numbers over the arrows correspond to the relative energies calculated at the B3LYP/6-31G* + ZPVE level. Numbers within parentheses correspond to relative energies calculated to M06-2X/6-31G*//B3LYP/6-31G* + ZPVE level.

Scheme 8. Transformation of Compounds 15a,b-A in 14a,b-A



converged to **TS4**-*endo* upon the optimization at the B3LYP/6-31G* + ZPVE level. Similarly, when nitroso alkenes **1** act as dienophiles the approach in *s-cis* conformation **1** through transition structures **TS1** and **TS2** present activation barriers lower than that observed for the approach in the *s-trans* conformation **1′** through transition structures **TS1′** and **TS2′** (for a full comparison of energetics see Supporting Information).

The activation barriers for the reaction of nitroso alkene **1a** (R = Ph) to give compounds **17a**-*endo*-A and **15a**-A, through **TS1ac**-*endo*-A and **TS4ac**-*endo*-A, respectively, are very similar (Table 4, entries 2, and 12), and thus both mechanisms are predicted to be competitive. However, for nitroso alkene **1b** (R = OEt) **TS4bc**-*endo*-A has the lower activation barrier, and compound **15b**-A could be the result expected under kinetic control conditions (Table 4, entry 14). M06-2X calculated energetics predicted that the transition structures **TS4ac,bc**-*endo*-A for the HDA_b are favored kinetically, in both cases (see Table 4 entries 12 and 14, Figure 7 and Supporting Information for a full comparison of energetics). Moreover, at all of levels of theory examined, thermodynamics favor cycloadducts **15a,b**-A over **17a,b**-*endo*-A (Table 4, Figure 7). Therefore, in these cases cycloadducts **15a,b**-A could be the only compounds obtained under both kinetic and thermodynamic control. These results are in agreement with the regioselectivity observed experimentally for the reaction of nitroso alkenes **1** and cyclic diene **2c**.

Experimentally, the reaction of **2c** with **1a,b** gives epimeric mixtures of compounds **14a,b**-A and **15a,b**-A, which after heating leads to **14a,b**-A as the only compounds through an imine–enamine tautomeric process. Calculated free energy differences computed at B3LYP(PCM)/6-31G* using chloroform as solvent indicate that these compounds **14a,b**-A are about 4 kcal/mol more stable than compounds **15a,b**-A (Scheme 8 and Supporting Information), and this result is in accord with the easy epimerization of these compounds.

CONCLUSIONS

In conclusion, the first synthesis of functionalized 1,2-oxazines containing a phosphine oxide or phosphonate group at the C-4 position of the heterocyclic system by means of a hetero-Diels–Alder cycloaddition reaction of 4-phosphinyl or 4-phosphonyl nitroso alkenes, respectively, is described. Computational and experimental studies indicate that conjugated nitroso alkenes **1** participate as 2π-electron components (heterodienophile), through the nitroso group, toward cyclic nucleophilic dienes, such as cyclopentadiene or cyclohexa-1,3-diene to afford the corresponding cycloadducts **4** or **10**, respectively, in a nitroso Diels–Alder reaction (nDA) that takes place via an asynchronous concerted mechanism through *endo* transition states. Cycloadducts **4**, derived from cyclopentadiene, undergo a new aza-Cope type [3,3]-sigmatropic rearrangement to give 1,2-oxazines **7**. However both computational and experimental results indicate that cycloadducts **10** derived from cyclohexa-1,3-diene may be stable and its subsequent [3,3]-sigmatropic rearrangement is not favored by kinetic or thermodynamic control. Conversely, nitroso alkenes **1** could act as 4π-electron system (heterodiene) in a HDA process when they react with TMS-cyclopentadiene, which participate as the 2π-electron component, to give 1,2-oxazine derivatives **15**, and as in the preceding cases, the reaction takes place via an asynchronous concerted mechanism through *endo* transition states. It should be also emphasized that the use of

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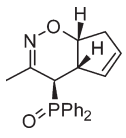
these very reactive phosphorylated heterodienes also opens a novel route to other functionalized cyclic and acyclic phosphorus compounds due to the marked ability of nitroso alkenes to add nucleophiles. These 1,2-oxazine derivatives may be important synthons in organic synthesis for the preparation of biologically active compounds of interest to medicinal chemistry.[17−23]

EXPERIMENTAL SECTION

General Methods. Et_3N was distilled and then dried over molecular sieves 70 Å. CH_2Cl_2 and cyclopentadiene were freshly distilled. All other solvents and reagents were obtained from commercial sources and used without further purification. All reactions were performed under an atmosphere of dry nitrogen. Melting points are uncorrected. IR-FT spectra were obtained as solids in KBr or as neat oils in NaCl. Mass spectra (MS) were made by electron impact (EI) at an ionizing voltage of 70 eV or by chemical ionization (CI) and high resolution mass spectra (HRMS) was measured by EI method. ^{1}H (300, 400 MHz), ^{13}C (75, 100 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a 300 or 400 MHz spectrometers, respectively, in $CDCl_3$, d_6-DMSO or CD_3OD, as specified below. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. All coupling constants (J) values are given in Hz. Chemical shifts (δ_C) are reported in parts per million (ppm) relative to $CDCl_3$, d_6-DMSO, or CD_3OD as internal standard in a broad band decoupled mode. The abbreviations used are as follows: s, singlet; bs, broad singlet, d, doublet; dd, double doublet; t, triplet; q, quartet, m, multiplet. Flash column chromatography was performed using commercial grades of silica gel finer than 230 mesh. Analytical thin layer chromatography was performed on precoated Merck silica gel 60 F_{254} plates, and spot visualization was accomplished by UV light (254 nm) or $KMnO_4$ solution. The starting materials such as phosphorylated α-bromooximes[10] were prepared according to the literature procedures.

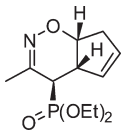
General Procedure for the Reaction of Phosphorated Nitroso Alkenes 1 with Cyclopentadiene 2a. To a stirred solution of α-bromooxime[10] (1.0 mmol) in CH_2Cl_2 (5 mL) were added cyclopentadiene **2a** (1.2 mmol) and triethylamine (1.2 mmol) at room temperature and under a nitrogen atmosphere. The reaction was allowed to stir at room temperature for 30 min. The solvent was removed by rotary evaporation, and the residue was stirred with diethyl ether. The triethyl amine hydrobromic salt was filtered through a sintered glass vacuum filtration funnel with Celite. The filtrate was concentrated to dryness in vacuum. The isolation of adducts **4** by chromatographic methods afforded bicyclic oxazine **5**,[27] together with the corresponding α-ketophosphine oxide **6a**[13b,28] or ketophosphonate **6b**.[29] These compounds were shown to exhibit spectral data consistent with those reported in the literature. Crude adducts **4** were dissolved in $CHCl_3$ and stirred under reflux for 48 h. The solvent was removed by rotary evaporation, and the crude compounds were purified by flash chromatography to give 1,2-oxazines **7**.

(4*R,4a*S**,7a*R**)-4-(Diphenylphosphoryl)-3-methyl-4,4a,7,7a-tetrahydrocyclopenta [*e*][1,2]oxazine (7a)**



Obtained as colorless oil (233 mg, 69%) from 1-bromo-1-(diphenylphosphoryl) propan-2-one oxime[10] (351 mg, 1.0 mmol), Et_3N (168 μL, 1.2 mmol), and cyclopentadiene **2a** (79 mg, 1.2 mmol) as described in the general procedure. The crude product was purified by flash chromatography (SiO_2, AcOEt/pentane 40:60). IR (NaCl) ν_{max} 2955, 1636, 1436, 1256, 1105, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.81 (m, 4H), 7.59−7.47 (m, 6H), 5.72−5.69 (m, 1H), 5.11−5.09 (m, 1H), 4.55−4.49 (m, 1H), 3.83−3.77 (m, 1H), 3.21 (dd, $^2J_{PH}$ = 13.8 Hz, $^3J_{HH}$ = 3.3 Hz, 1H), 2.59−2.56 (m, 2H), 1.81 (d, $^4J_{PH}$ = 1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (d, $^2J_{PC}$ = 4.0 Hz), 132.3, 132.3, 132.2, 132.1, 131.5, 131.4, 131.3, 130.5, 130.4, 128.9, 128.7, 128.6, 76.6, 45.9 (d, $^2J_{PC}$ = 2.0 Hz), 41.8 (d, $^1J_{PC}$ = 65.1 Hz), 39.6, 22.9 (d, $^3J_{PC}$ = 1.8 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 27.6; HRMS (EI) m/z calcd for $C_{20}H_{20}NO_2P$ [M$^+$] 337.1232, found [M$^+$] 337.1234.

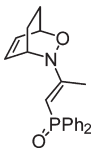
Diethyl (4*R,4a*S**,7a*R**)-3-Methyl-4,4a,7,7a-tetrahydrocyclopenta[*e*][1,2]oxazin-4-ylphosphonate (7b)**



Obtained as colorless oil (196 mg, 72%) from 1-bromo-2-hydroxyiminopropyl phosphonic acid diethyl ester[10] (287 mg, 1.0 mmol), Et_3N (168 μL, 1.2 mmol), and cyclopentadiene **2a** (79 mg, 1.2 mmol) as described in the general procedure. The crude product was purified by flash chromatography (SiO_2, AcOEt/pentane 20:80). IR (NaCl) ν_{max} 2984, 1636, 1237, 1020 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88−5.80 (m, 1H), 5.56−5.54 (m, 1H), 4.74 (td, J = 7.6 Hz, J = 2.5 Hz, 1H), 4.22−4.11 (m, 4H), 3.79−3.63 (m, 1H), 2.75−2.61 (m, 3H), 2.14 (d, $^4J_{PH}$ = 1.8 Hz, 3H), 1.37−1.34 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, $^2J_{PC}$ = 5.2 Hz), 131.8, 130.7 (d, $^3J_{PC}$ = 11.1 Hz), 76.4 (d, $^3J_{PC}$ = 4.9 Hz), 62.6 (d, $^2J_{PC}$ = 6.7 Hz), 46.4 (d, $^2J_{PC}$ = 4.2 Hz), 39.7, 37.9 (d, $^1J_{PC}$ = 141.7 Hz), 22.1 (d, $^3J_{PC}$ = 1.5 Hz), 16.4 (d, $^3J_{PC}$ = 3.5 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 24.0; MS (CI) m/z 274 (M$^+$ + 1, 100); HRMS (EI) m/z calcd for $C_{12}H_{20}NO_4P$ [M$^+$] 273.1130, found [M$^+$] 273.1135.

General Procedure for the Reaction of Phosphorated Nitroso Alkenes 1 with Cyclohexa-1,3-diene 2b. To a stirred solution of α-bromooxime[10] (1.0 mmol) in CH_2Cl_2 (5 mL) were added 1,3-cyclohexa-1,3-diene **2b** (1.2 mmol) and triethylamine (1.2 mmol) at room temperature and under a nitrogen atmosphere. The reaction was allowed to stir at room temperature for 30 min. The solvent was removed by rotary evaporation, and the residue was stirred with diethyl ether. The triethyl amine hydrobromic salt was filtered through a sintered glass vacuum filtration funnel with Celite. The filtrate was concentrated to dryness in vacuum, and the crude cycloadducts **10** were characterized without further purification steps.

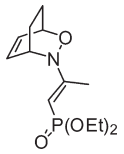
(1*R,4*S**)-3-((*E*)-1-(Diphenylphosphoryl)prop-1-en-2-yl)-2-oxa-3-azabicyclo [2.2.2]oct-5-ene(10a)**



Obtained as colorless oil (337 mg, 96%) from 1-bromo-1-(diphenylphosphoryl) propan-2-one oxime[10] (351 mg, 1.0 mmol), Et_3N (168 μL, 1.2 mmol), and cyclohexa-1,3-diene **2b** (114 μL, 1.2 mmol) as described in the general procedure. IR (NaCl) ν_{max} 3423, 2975, 1721, 1601, 1251, 1193 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.62−7.46 (m, 10H), 6.62−6.57 (m, 1H), 6.41−6.37 (m, 1H), 5.08 (d, $^2J_{PH}$ = 21.6 Hz, 1H), 4.77−4.74 (m, 1H), 4.60−4.59 (m, 1H), 1.99 (s, 3H), 1.45−1.11 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0 (d, $^2J_{PC}$ = 11.0 Hz), 137.0 (d, $^1J_{PC}$ = 103.2 Hz), 136.8 (d, $^1J_{PC}$ = 103.6 Hz), 130.9, 130.3, 130.2, 129.2, 128.6, 128.4, 91.1 (d, $^1J_{PC}$ = 118.7 Hz), 69.9, 50.8, 23.8, 20.6, 16.3 (d, $^3J_{PC}$ = 5.5 Hz); ^{31}P NMR (120 MHz, d_6-DMSO) δ 21.8; MS (CI) m/z 352 (M$^+$ + 1, 18), 201 (100); HRMS (EI) m/z calcd for $C_{21}H_{22}NO_2P$ [M$^+$] 351.1388, found [M$^+$] 351.1391.

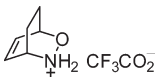
dx.doi.org/10.1021/jo201116u |J. Org. Chem. 2011, 76, 6715–6725

Diethyl (*E*)-2-((1*R,4*S**)-2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)prop-1-enylphosphonate(10b)**



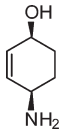
Obtained as brown oil (273 mg, 95%) from 1-bromo-2-hydroxyiminopropyl phosphonic acid diethyl ester[10] (287 mg, 1.0 mmol), Et_3N (168 μL, 1.2 mmol), and cyclohexa-1,3-diene **2b** (114 μL, 1.2 mmol) as described in the general procedure. IR (NaCl) ν_{max} 3423, 2978, 1716, 1598, 1254, 1025, 951, 797 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.14−6.10 (m, 1H), 5.89−5.84 (m, 1H), 4.32 (d, $^2J_{PH}$ = 13.8 Hz, 1H), 4.29−4.25 (m, 1H), 4.10−4.04 (m, 1H), 3.79−3.50 (m, 4H), 1.71 (s, 3H), 1.18−0.82 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3 (d, $^2J_{PC}$ = 19.6 Hz), 130.0, 127.4, 86.3 (d, $^1J_{PC}$ = 203.3 Hz), 69.5, 59.8 (d, $^2J_{PC}$ = 5.6 Hz), 50.3, 23.1, 19.9, 15.3 (d, $^3J_{PC}$ = 7.0 Hz), 7.7; ^{31}P NMR (120 MHz, $CDCl_3$) δ 24.9; HRMS (EI) *m*/*z* calcd for $C_{13}H_{22}NO_4P$ [M^+] 287.1286, found [M^+] 287.1289.

General Procedure and Spectral Data of (1*R,4*S**)-2-Oxa-3-azoniabicyclo[2.2.2]oct-5-ene 2,2,2-trifluoroacetate (12)**



To a stirred solution of cycloadduct **10b** freshly prepared (287 mg, 1.0 mmol) in MeOH (5 mL) was added some drops of trifluoroacetic acid at room temperature. The reaction was allowed to stir at room temperature for 2 h. The solvent was removed by rotary evaporation, and the residue was purified by flash chromatography (SiO_2, AcOEt/MeOH 98:2) to afford **10** (50 mg, 22% from α-bromoketone[10]) as colorless oil. IR (NaCl) ν_{max} 3417, 1670, 1197, 1145 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.90 (ddd, *J* = 7.8 Hz, *J* = 5.8 Hz, *J* = 1.2 Hz, 1H), 6.64 (ddd, *J* = 7.8 Hz, *J* = 6.3 Hz, *J* = 1.2 Hz, 1H), 4.95−5.00 (m, 1H), 4.55−4.50 (m, 1H), 2.30−2.15 (m, 2H), 1.62−1.56 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 163.2 (q, $^2J_{FC}$ = 32.6 Hz), 137.3, 130.0, 118.4 (q, $^1J_{FC}$ = 294.0 Hz), 72.3, 50.2, 23.1, 18.4; ^{19}F RMN (282 MHz, CD_3OD) δ −76.4; MS (CI) *m*/*z* 111 ($M^+ - CF_3CO_2$, 100); HRMS (EI) *m*/*z* calcd for $C_8H_{10}F_3NO_3$ [M^+] 225.0613, found [M^+] 225.0617.

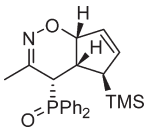
General Procedure and Spectral Data of (1*S,4*R**)-4-Aminocyclohex-2-enol (13)**



To a stirred solution of cycloadduct **10b** freshly prepared (287 mg, 1.0 mmol) in dry MeOH (5 mL) was added a solution of $ZnCl_2$ (134 mg, 1.0 mmol) at 0 °C. The reaction was allowed to stir from 0 °C to room temperature and was kept for an additional 2 h at room temperature. The crude reaction mixture was filtered through a sintered glass vacuum filtration funnel with Celite, the solvent was removed to dryness in vacuum, and the crude compound was purified by flash chromatography (SiO_2, AcOEt) to afford amino alcohol **13** (19 mg, 17% from α-bromooxime[10]) as colorless oil. Spectral data are in agreement with those reported in the literature.[30]

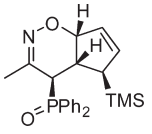
General Procedure for the Reaction of Phosphorated Nitroso Alkenes 1 with 5-(Trimethylsilyl)cyclopenta-1,3-diene 2c. To a stirred solution of α-bromooxime[10] (1.0 mmol) in CH_2Cl_2 (5 mL) were added 5-(trimethylsilyl)cyclopenta-1,3-diene **2c** (1.2 mmol) and triethylamine (1.2 mmol) at room temperature and under a nitrogen atmosphere. The reaction was allowed to stir at room temperature for 30 min. The solvent was removed by rotary evaporation, and the residue was stirred with diethyl ether. The triethyl amine hydrobromic salt was filtered through a sintered glass vacuum filtration funnel with Celite. The solvent was removed by rotary evaporation, and the crude compounds were purified by flash chromatography to afford a mixture of oxazines in a ratio of 50:50 for compounds **14a**/**15a** and 92:8 for compounds **14b**/**15b**. The in situ heating of these mixtures of cycloadducts **14**/**15** in refluxing chloroform afforded 1,2-oxazines **14**.

(4*S,4a*R**,5*R**,7a*R**)-4-(Diphenylphosphoryl)-3-methyl-5-(trimethylsilyl)-4,4a,5,7a-tetrahydrocyclopenta[*e*][1,2]oxazine (15a)**



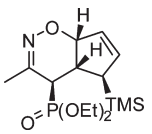
Obtained as colorless solid from 1-bromo-1-(diphenylphosphoryl) propan-2-one oxime[10] (351 mg, 1.0 mmol), Et_3N (168 μL, 1.2 mmol), and 5-(trimethylsilyl) cyclopenta-1,3-diene **2c** (199 μL, 1.2 mmol) as described in the general procedure before heating in refluxing chloroform. The crude product was purified by flash chromatography (SiO_2, AcOEt/pentane 50:50) to get oxazine **15a**.^1H NMR (300 MHz, $CDCl_3$) δ 7.94−7.39 (m, 10H), 5.94−5.91 (m, 1H), 5.53−5.50 (m, 1H), 5.48−5.46 (m, 1H), 3.73−3.69 (m, 1H), 3.39−3.32 (m, 1H), 2.77−2.75 (m, 1H), 2.01 (s, 3H),− 0.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 140.2, 131.9, 131.9, 131.8, 131.7, 131.6, 131.6, 131.5, 130.7, 130.6, 130.1, 130.0, 129.1, 129.0, 129.0, 128.9, 128.9, 128.8, 128.7, 128.5, 128.4, 124.5, 88.5 (d, $^2J_{PC}$ = 10.2 Hz), 42.9, 37.6, 36.0 (d, $^1J_{PC}$ = 79.7 Hz), 20.8 (d, $^3J_{PC}$ = 2.6 Hz), − 3.0; ^{31}P NMR (120 MHz, $CDCl_3$) δ 24.3.

(4*R,4a*R**,5*R**,7a*R**)-4-(Diphenylphosphoryl)-3-methyl-5-(trimethylsilyl)-4,4a,5,7a-tetrahydrocyclopenta[*e*][1,2]oxazine (14a)**



Obtained as colorless solid (360 mg, 88%) from 1-bromo-1-(diphenylphosphoryl) propan-2-one oxime[10] (351 mg, 1.0 mmol), Et_3N (168 μL, 1.2 mmol), and 5-(trimethylsilyl) cyclopenta-1,3-diene **2c** (199 μL, 1.2 mmol) as described in the general procedure. The crude product was purified by flash chromatography (SiO_2, AcOEt/pentane 50:50). Mp 131−133 °C; IR (KBr) ν_{max} 3052, 2949, 2909, 1636, 1436, 1191, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97−7.43 (m, 10H), 5.87−5.84 (m, 1H), 5.55−5.51 (m, 1H), 5.15−5.12 (m, 1H), 3.47 (dddd, *J* = 12.9 Hz, *J* = 9.3 Hz, *J* = 3.9 Hz, *J* = 1.2 Hz, 1H), 3.08 (d, $^2J_{PH}$ = 13.5 Hz, 1H), 1.75 (d, $^4J_{PH}$ = 2.1 Hz, 3H), 1.66−1.62 (m, 1H), − 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0 (d, $^2J_{PC}$ = 5.0 Hz), 137.1, 132.3, 132.3, 132.2, 132.2, 131.9, 131.8, 131.7, 131.6, 131.5, 130.7, 130.3, 129.1, 129.0, 128.8, 128.7, 128.5, 128.3, 127.7, 83.4, 47.6 (d, $^1J_{PC}$ = 61.1 Hz), 45.2 (d, $^2J_{PC}$ = 9.5 Hz), 39.4 (d, $^3J_{PC}$ = 2.5 Hz), 24.0 (d, $^3J_{PC}$ = 1.0 Hz), − 3.4; ^{31}P NMR (120 MHz, $CDCl_3$) δ 27.1; HRMS (EI) *m*/*z* calcd for $C_{23}H_{28}NO_2PSi$ [M^+] 409.1627, found [M^+] 409.1629.

Diethyl (4*R,4a*R**,5*R**,7a*R**)-3-Methyl-5-(trimethylsilyl)-4,4a,5,7a-tetrahydrocyclopenta[*e*][1,2]oxazin-4-ylphosphonate (14b)**



Obtained as colorless oil (300 mg, 87%) from 1-bromo-2-hydroxyiminopropyl phosphonic acid diethyl ester[10] (287 mg, 1.0 mmol), Et_3N

(168 μL, 1.2 mmol), and 5-(trimethylsilyl)cyclopenta-1,3-diene **2c** (199 μL, 1.2 mmol) as described in the general procedure. The crude product was purified by flash chromatography (SiO_2, AcOEt/pentane 50:50) affording a mixture of diastereoisomers in a ratio of 92:8. Major diastereoisomer: IR (NaCl) ν_{max} 2984, 2949, 1630, 1242, 1025, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89−5.85 (m, 1H), 5.56−5.52 (m, 1Hm), 5.23−5.20 (m, 1H), 4.22−4.02 (m, 4H), 3.35−3.25 (m, 1H), 2.54 (d, $^2J_{PH}$ = 24.9 Hz, 1H), 2.12 (d, $^4J_{PH}$ = 2.4 Hz, 3H), 1.61−1.57 (m, 1H), 1.31 (td, $^3J_{HH}$ = 7.2 Hz, $^4J_{PH}$ = 1.2 Hz, 6H), − 0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (d, $^2J_{PC}$ = 6.4 Hz), 137.4, 127.3, 83.0, 63.1 (d, $^2J_{PC}$ = 6.5 Hz), 62.4 (d, $^2J_{PC}$ = 7.0 Hz), 45.2 (d, $^2J_{PC}$ = 13.0 Hz), 42.2 (d, $^1J_{PC}$ = 135.2 Hz), 39.2 (d, $^3J_{PC}$ = 5.0 Hz), 23.6 (d, $^3J_{PC}$ = 1.9 Hz), 16.4 (d, $^3J_{PC}$ = 6.0 Hz), 16.3 (d, $^3J_{PC}$ = 6.5 Hz), − 3.5; ^{31}P NMR (120 MHz, $CDCl_3$) δ 23.7_{minor}, 21.6_{major}; HRMS (EI) *m/z* calcd for $C_{15}H_{28}NO_4PSi$ [M^+] 345.1525, found [M^+] 345.1526.

■ ASSOCIATED CONTENT

Supporting Information. Spectra data for all new compounds; computational methods; Cartesian coordinates, harmonic analysis data, and energies for all the stationary points discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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