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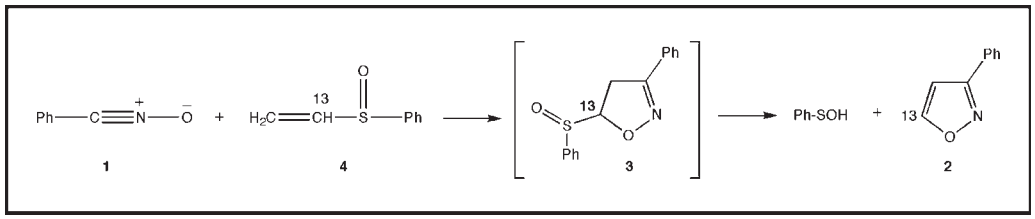

The regioselectivity of the 1,3-dipolar cycloaddition of benzonitrile *N*-oxide to phenyl vinyl sulfoxide is established by isotopic labeling and ^{13}C NMR analysis, and by DFT calculations.

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INTRODUCTION

The synthesis of 3-phenylisoxazoles is an active area because that structural unit is the core of many compounds with biological or agricultural activity [1]. One of the prominent routes to these molecules is the reaction of a benzonitrile *N*-oxide **1** with a substituted alkyne or alkene, a pathway first recognized as a 1,3-dipolar cycloaddition by Huisgen [2]. Several hundred examples of this process have been documented [3].

The parent compound **2** can be prepared by this procedure with acetylene as the dipolarophile [4], but more often a two-step sequence is used whereby a monosubstituted alkene serves as the dipolarophile, followed by an elimination process on the intermediate isoxazoline **3** (Scheme 1). In the latter case, two distinct isomeric intermediates are possible depending on whether the oxygen terminal of **1** adds to the substituted or the unsubstituted carbon of the alkene (paths **a** and **b**, respectively in Scheme 1). This reaction is known to be generally regioselective for the 5-substituted cycloadduct **3a** [5]. However, yields for the process are not quantitative, and rigorous analyses for the isomeric 4-substituted cycloadduct are seldom reported [6].

Phenyl vinyl sulfoxide **4** and its 2-substituted analogs (R—CH=CH—S(O)—Ph) are among the useful dipolarophiles in the synthesis of isoxazoles *via* 1,3-dipolar cycloaddition, particularly, because subsequent elimination of phenylsulfenous acid occurs spontaneously [7]. Maiorana and coworkers investigated the regioselectivity of the addition step in the 2-substituted systems based on the distribution of the final isomeric oxazole products using ^1H NMR spectroscopy and found that the regioselectivity ratio is dramatically altered (90:10 to 10:90) depending on R [7b]. Clearly, direct analysis of the product ratio cannot be used to determine the regioselectivity when R = H, as the two intermediates (**3a**/**3b**) yield the same product (**2a**/**2b**), although this case may easily be the most relevant to understanding the influence of the S(O)Ph group. Herein, we report the results for a simple isotope labeling experiment that solve this problem.

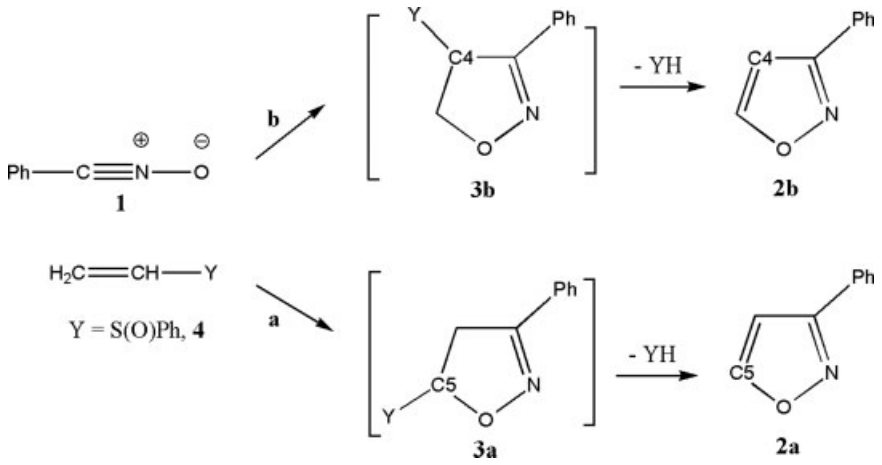
Our approach, summarized in Scheme 2, was to analyze product **2** by ^{13}C NMR spectroscopy following reaction of **1** with a sample of **4** selectively enriched with ^{13}C in the 1-position (C1). The results show that the ^{13}C label is incorporated largely at the 5-position of the isoxazole ring. We estimate a regioselectivity of 110:1 based on the integrated ^{13}C peak areas in the final product. These conclusions were then supported with DFT calculations.

RESULTS AND DISCUSSION

Synthesis. Standard procedures were used to convert 1-^{13}C-ethyl iodide to phenyl 1-^{13}C-vinyl sulfoxide **4*** (see Experimental Section). A mixture consisting of ~80% unlabeled **4** and 20 % labeled **4** (*i.e.* **4***) was then reacted with benzonitrile *N*-oxide **1** under conditions [7] that directly produced 3-phenyl-5-isoxazole **2** (Scheme 2). The crude product of this reaction was contaminated only with by-products resulting from the phenylsulfenous acid elimination (*i.e.* Ph_2S_2); purification by flash column chromatography produced pure **2**.

^{13}C NMR analysis. Initial chemical shift assignment of the isoxazole carbons in the ^{13}C NMR spectrum of **2** was straightforward (see Experimental Section). In

Scheme 1



earlier work, we definitively assigned the signal at δ 161.48 to C3 by preparing **2** selectively ^{13}C-labeled at this position [8]. This was accomplished by using the synthetic approach summarized in Scheme 2 beginning with benzaldehyde oxime ^{13}C-labeled at the oxime carbon. C4 and C5 (δ 102.42 and 158.85, respectively) were assigned by comparison with data from the NMR literature [9].

The first row in Table 1 gives the integrated peak areas observed in a natural abundance sample of **2**. In this case, the areas of C4 and C5 are roughly equal (C5/C4 = 1.12), and each is about three times the C3 peak area. The second row gives ^{13}C data observed when **2** is prepared from a mixture that was ∼20% ^{13}C1-enriched phenyl 1-vinyl sulfoxide (**4***) and 80% natural abundance **4**. As expected, the enrichment causes significant

Scheme 2

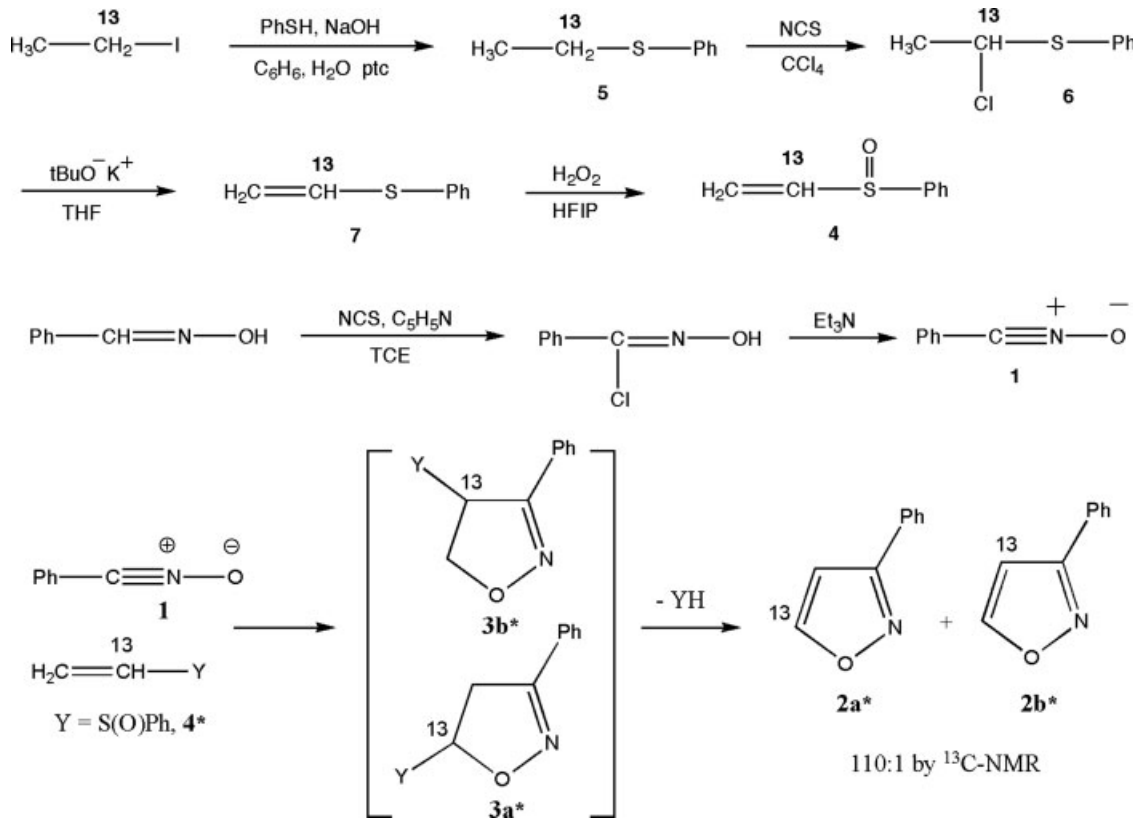


Table 1
Data from ^{13}C NMR analysis of **2**.

	Integrated peak area ratio		
	C5/C3	C4/C3	C5/C4
Natural abundance	3.53	3.15	1.12
^{13}C-Enriched[a]	53.59	3.56	15.05
^{13}C 1st adjustment[b]	50.66	0.95	
^{13}C 2nd adjustment[c]	50.66	0.41	
^{13}C Final adjustment[d]	50.66	0.46	

[a] Observed areas when 2 is prepared from 4* with 17% ^{13}C label at the 1-position.
[b] Adjusted peak areas in the ^{13}C-enriched experiment; obtained by subtracting the contribution from natural abundance component (83% of the area in row 1) from the observed area (row 2).
[c] Estimated distribution of the ^{13}C label originating from 4* onto C5 and C4 before scaling (see Discussion).
[d] Scaled for C5/C4 relative sensitivity (1.12).

increase in the C5 and C4 peak areas relative to C3. From the total amount of this increase, we can, in fact, determine that a total of 17% of the product obtained in the enriched experiment comes from labeled **4***. The distribution of ^{13}C from C1 of this component onto the C5 and C4 positions in **2** (**2a*/2b*** in Scheme 2) provides the measure of regioselectivity in our reaction. When the natural abundance ^{13}C contributions from the C1 and C2 carbons of the **4**(83%)/**4***(17%) mixture are subtracted from the areas in row 2, the resulting data (third row in Table 1) clearly show that in the reaction of **4*** with **1**, the ^{13}C label at C1 has been deposited largely at the 5-position of the isoxazole ring. This implies that C4 in **2** originates mostly from the C2 carbon of **4***, which is not labeled. If the reaction were 100% regioselective, the natural ^{13}C abundance at C2 in **4*** (1.108%) should produce a net peak area of 0.54 for C4 in row 3 (*i.e.* 17% of the respective C4 value in row 1). As the observed area, 0.95, is larger by 0.41, this excess area must have come from a small fraction of the ^{13}C label at C1 in **4***, and this can now be used to make a quantitative estimate of the regioselectivity. To do this, we first scale the excess area by 1.12 to account for the inherently greater sensitivity of C5 toward integration (*i.e.* C5/C4 = 1.12 in row 1). Thus, our analysis, based on the final, adjusted integrated ^{13}C data (row 5), affords an overall regioselectivity of 50.66:0.46, or 110:1, for the reaction between **1** and **4** (in dichloroethane at 50°C).

It should be noted that, because of differences in relaxation times (T1) and NOE effects between protonated (*i.e.* C4, C5) and non-protonated carbons (*i.e.* C3), integrated peak areas from Fourier-Transform ^{13}C NMR spectra acquired with standard pulse sequences cannot be used to obtain accurate values for relative numbers of carbons in the same molecule (in contrast to the common integration practice in ^{1}H NMR spectroscopy). In this study, however, as we are comparing relative peak areas for the same carbon atoms in isotopically-distinct isomers, this limitation does not apply.

DFT calculations and analysis. 1,3-Dipolar addition reactions have been the subject of numerous electronic structure investigations [10]. Among the earlier studies in this area is work by Houk [11], which analyzed the frontier MO interactions in cycloaddition reactions. Subsequent studies used increasingly more sophisticated theoretical tools to obtain more accurate activation and reactions energies. However, elucidation and interpretation of the factors that control reactivity and regioselectivity in 1,3-dipolar addition reactions remains debatable and an active topic of research. For instance, Although Schleyer searched for a role for the in plane aromaticity in the cyclic transition states of 1,3-dipolar addition reactions [12], Ponti and Molteni advocated a possible role for the reactivity indices of the separate reactants in driving the reactions in the context of hard-soft acid-base theory [13]. More recently, Ess and Houk showed that the reactivities of different 1,3-dipoles correlate with the energy needed to distort the dipole and the dipolarophile to the transition state geometries ($E_d^{\ddagger}$) [14]. Because none of the prior theoretical studies had considered any dipolar reactions of a vinyl sulfoxide, we became interested in investigating the reaction we studied experimentally (**1** + **4**) using density functional theory. For this purpose, we used the B3LYP and B3P86/6-31+G(d,p) levels of theory to study the transition states (TS), and products of the actual molecules used in the experiments. To present the results in perspective, we also calculated the reactions between **1** and each of ethylene and propene. Relevant geometrical parameters and energies of the reaction of **4** are presented in Figure 1, and Table 2 compares the results for the three alkenes considered.

Figure 1 shows that the TS in which the oxygen atom adds to the substituted carbon of **4** (**TS3a**) is 2.8 kcal/mol lower in energy than the alternative TS where oxygen adds to the terminal carbon (**TS3b**) ($\Delta\Delta G^{\circ\ddagger}$, at 298 K and 1 atm). A nearly identical $\Delta\Delta G^{\circ\ddagger}$ is obtained at the B3P86 level, and this value remains largely unchanged when the energies are calculated in a dichloroethane solvent continuum. The computed regioselectivity agrees well with the estimated experimental regioselectivity of 110:1, which affords and experimental $\Delta\Delta G^{\ddagger}$ = 2.6 kcal/mol at 323 K. The calculations reveal that the kinetic product (**3a**) is also the thermodynamic product in the given reaction, with $\Delta\Delta G^{\circ}$ = 5.5 kcal/mol in favor of the isomer in which the S(O)Ph substituent is attached at the 5-position before loss of phenylsulfenous acid to give the isoxazole ring (Fig. 1).

In light of the recent studies by Ess and Houk [14], we analyzed the calculated regioselectivity in reactions

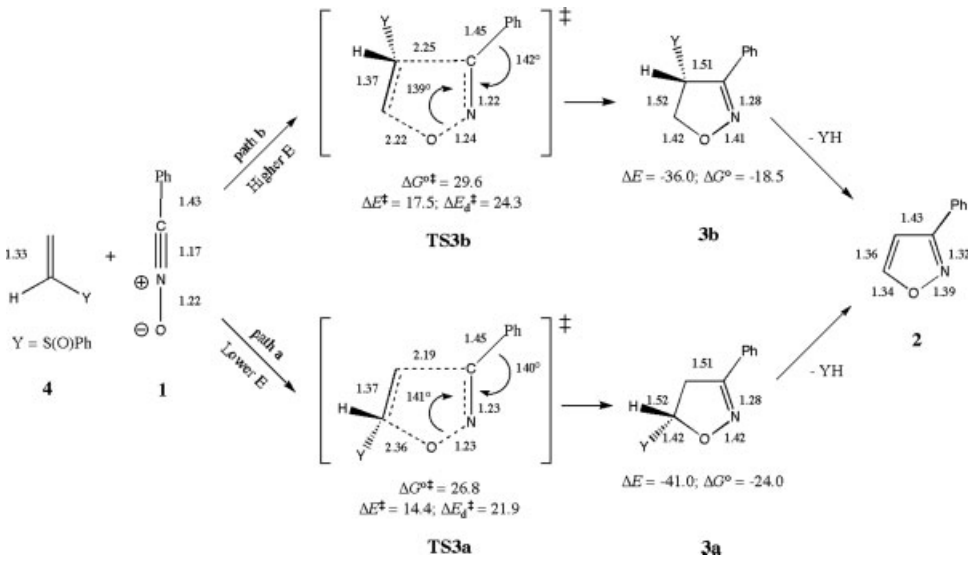


Figure 1. Selected B3LYP geometric parameters and energies of the transition states and products in the reaction between 4 and 1 (in Å and kcal/mol).

of **4** using the activation strain model. This model is built on a thermodynamic cycle that gives the activation energy ($\Delta E^{\ddagger}$) as the sum of a distortion energy ($\Delta E^{\ddagger}_{d}$; defined as the energy needed to distort the equilibrium geometry of the reactants to the respective geometries in the TS) and an electronic interaction term ($\Delta E^{\ddagger}_{int}$, for the energy change that takes place when the distorted reactants are brought to the TS). In our system, $\Delta E^{\ddagger}_{d}$ has a term from the dipole ($\Delta E^{\ddagger}_{d1}$) and another from the alkene ($\Delta E^{\ddagger}_{d2}$, Table 2). Each of these terms is larger for the higher energy TS (**TS3b**). The net difference between the total $\Delta E^{\ddagger}_{d}$ in the two TSs ($\Delta\Delta E^{\ddagger}_{d} = 2.9$ kcal/mol) is very close to the difference between the actual activation energies ($\Delta\Delta E^{\ddagger} = 2.4$ kcal/mol). This behavior is in line with the general conclusions reached by Ess and Houk [14] on the reactivities of 1,3-dipole addition reactions.

Finally, to examine if S(O)Ph imparts any special substituent effects on the dipolarophilicity of ethylene, we calculated the reactions of ethylene and propene with **1**. The results are included in Table 2. In spite of the large electronic difference among the given three alkenes when the lower energy **TS3a** is considered, the activation energy appears to be rather invariant: $\Delta G^{\circ\ddagger} =$ 26.8, 27.2, and 25.8 kcal/mol, for Y = H, CH_3 or S(O)Ph, respectively. The same holds for the reaction energies: $\Delta G^{\circ}_{rxn} = -23.3$ (H), -22.7 (CH_3), and -24.0 (S(O)Ph). Similarly, the calculated regioselectivity is comparable for Y = CH_3 ($\Delta\Delta G^{\circ\ddagger} = 3.3$ kcal/mol) and S(O)Ph ($\Delta\Delta G^{\circ\ddagger} = 2.8$ kcal/mol). Noticeably, the small variations in the activation energies among the three substituents correlate with the variation in the respective distortion energies.

Table 2

B3LYP activation and reaction energies of addition of PhCNO (**1**) to substituted ethylene (CH_2=CHY).[a]

Y	O adds to	$\Delta E^{\ddagger}$	$\Delta G^{\circ\ddagger}$	$\Delta E^{\ddagger}_{d1}$	$\Delta E^{\ddagger}_{d2}$	ΔG°_{rxn}
S(O)Ph	C1	14.4	26.8	17.6	4.3	−24.0
S(O)Ph	C2	17.5	29.6	18.7	5.6	−18.9
CH_3	C1	14.9	27.2	17.6	3.7	−22.7
CH_3	C2	17.9	30.5	19.3	4.9	−18.3
H	C1 = C2	14.1	25.8	17.1	3.0	−23.3

$\Delta E^{\ddagger}$ is the raw electronic activation energy without ZPE correction. $\Delta G^{\circ\ddagger}$ and ΔG°_{rxn} are the standard state activation and reaction free energies, respectively, obtained at 298 K and 1 atm using unscaled harmonic vibrational frequencies. $\Delta E^{\ddagger}_{d1}$ and $\Delta E^{\ddagger}_{d2}$ are the energies needed to distort the geometries of **1** and the alkene, respectively, to their corresponding parameters in the transition state. When Y = S(O)Ph, the results are for the lowest energy conformer.

[a] Units are in kcal/mol, relative to the separated reactants.

Overall, the DFT calculations support the experimental quantification of the regioselectivity in the reaction between **1** and **4** made from the integrated ^{13}C areas of the final product (**2**). The calculations confirm that the observed regioselectivity is not the result of any special effects provided by the S(O)Ph group.

EXPERIMENTAL

Melting points were determined on a MelTemp apparatus. Extracts were dried over Na_2SO_4, and solvents were removed by rotary evaporation at reduced pressure. Product purities were determined by gas chromatography-mass spectrometry analysis on a Hewlett Packard HP 6890 system equipped with a HP-5MS crosslinked diphenyl (5%) dimethyl (95%) polysiloxane capillary column (30 m × 0.25 mm × 0.25 μm film), a 5973 mass selective detector, and a HP Kayak XA computer. NMR spectra were measured at 298 K with a Brüker Avance DRX 500 MHz NMR spectrometer operating at frequencies of 500.630 (^1H) and 125.884 (^{13}C) using a standard 5 mm broadband multinuclear (PABBO) probehead (90° pulse widths: ^1H, 11.5 μs; ^{13}C, 6.0 μs). Chemical shifts (ppm) were measured relative to internal Me_4Si (^1H) or internal $CDCl_3$ (^{13}C). ^{13}C chemical shifts were measured using a standard power gated decoupling pulse sequence (zgpg30) from the Brüker pulse sequence library. Spectral windows for ^{13}C acquisitions were set at 240 ppm, and a total of *ca*. 300 scans of 32 k data points were collected and then zero-filled to 64 k points before Fourier transformation. The recycle delay (D1) was set at 2 s.

Phenyl 1-^{13}C-vinyl sulfoxide (4). The synthesis of phenyl vinyl sulfoxide selectively ^{13}C-labeled in the 1-position began with a sample of *ca*. 20% ^{13}C-enriched 1-^{13}C-ethyl iodide that was prepared by mixing 4 volumes of unlabeled ethyl iodide (Sigma–Aldrich, 17780) with 1 volume of 99% atom purity 1-^{13}C-ethyl iodide (Cambridge Isotope Laboratories, CLM-1025). As shown in Scheme 2, preparation of phenyl 1-^{13}C-vinyl sulfoxide **4** proceeded from labeled ethyl iodide *via* the sequence: 1-^{13}C-ethyl phenyl sulfide **5** [15] to 1-^{13}C-chloroethyl phenyl sulfide **6** [16] to phenyl 1-^{13}C-vinyl sulfide **7** [17] to **4** [18], following methods that have been reported previously. The crude product was used for the subsequent synthesis of **2**; GC-MS analysis of crude **4** showed that it was at least 94% pure.

3-Phenyl-5-^{13}C isoxazole (2). We have reported a general synthesis of unlabeled 3-phenyl-5-isoxazole beginning from benzaldehyde oxime previously [7a]. Adaptation of this method using phenyl 1-^{13}C-vinyl sulfoxide **4** afforded 3-phenyl-5-^{13}C isoxazole **2**, as follows. To a solution of *N*-chlorosuccinimide (0.119 g, 0.8913 mmol) and pyridine (4 μL, 0.124 mmol) in 1,1,2-trichloroethane (TCE) (1.0 mL) was added benzaldehyde oxime (0.098 g, 0.809 mmol; Aldrich 245674) and the solution was stirred at 50°C for 30 min. A solution of phenyl 1-^{13}C-vinyl sulfoxide **4** (0.138 g, 0.905 mmol) and triethylamine (0.12 mL, 0.86 mmol) in TCE (98 μL) was added dropwise *via* Pasteur pipet over 3 min. The solution was stirred at 50°C for 20 min and then heated to reflux for an additional 60 min. The reaction mixture was cooled to room temperature and evaporated to dryness, and the residue was treated with 2*M* NaOH (5 mL). The mixture was heated at reflux for 35 min, cooled to room temperature, neutralized with saturated NH_4Cl solution (3 mL), and extracted with CH_2Cl_2. The extract was washed with water (2 × 10 mL), dried (anhydrous Na_2SO_4), and evaporated to give 0.092 g of crude product **2**. Purification by flash liquid chromatography (4:1 hexane:ethyl acetate on flash silica gel) removed the Ph_2S_2 by-product and afforded **2** as a pale yellow oil in *ca*. 94% purity by GC-MS analysis. ^{13}C NMR (deuteriochloroform) δ 102.42 (C4), 126.86 (C2′/3′; assignments may be interchanged), 128.76 (C1′), 128.91 (C2′/3′; assignments may be interchanged), 130.00 (C4′), 158.85 (C5), 161.48 (C3).

Computational methods. All computations were carried out using Gaussian 03. [19]. The B3LYP [20] and B3P89 [21] levels of theory and the standard 6-31+G(d,p) basis set [22] were used to optimize the reactants, transition states, and products for normal mode vibrational analysis. Several conformers defined by rotation of the S(O)Ph group were considered for the transition state and products, but we report only the results for the lowest energy conformer. Solvent effects were calculated *via* single point calculations on the gas phase optimized geometries using the polarizable continuum model (PCM) [23].

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