JOC*Note*

The Photochemical Addition of 2,2,2-Trifluoroethanol to Methoxy-Substituted Stilbenes

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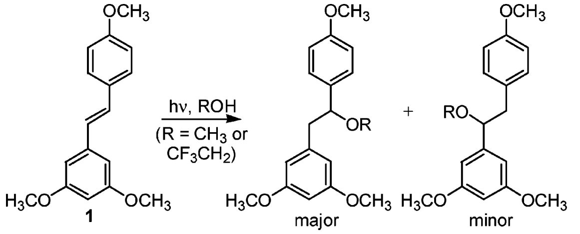
Abstract: The excited-state lifetime of the *trans*-stilbene chromophore in acetonitrile is prolonged by methoxy substituents in the meta positions. The long-lived singlet excited state of *trans*-3,5-dimethoxystilbene (*trans*-**2d**) is quenched upon the addition of 2,2,2-trifluoroethanol (TFE), and the Markovnikov ether is observed as the major product from steady-state irradiations. The results indicate that the reaction pathway proceeds through a carbocation intermediate.

Recently, during an investigation of benzylic ester photochemistry, we observed the photochemical addition of methanol and 2,2,2-trifluoroethanol (TFE) to *trans*-3,4′,5-trimethoxystilbene **1**, eq 1.[1] This reaction occurred more

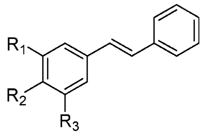


(1)

rapidly in TFE, suggesting that the greater ionizing ability and effective acidity of this solvent play an important role in the addition process. Furthermore, the preference for the Markovnikov product hinted at a pathway involving carbocation intermediates. A review of the literature revealed that the photochemical addition of methanol to unconstrained stilbene derivatives was originally reported by Laarhoven and co-workers,[2] although they concluded that carbocation intermediates were not involved in the reaction. This apparent disagreement prompted us to investigate the addition of TFE to methoxy-substituted stilbene derivatives in greater detail.

One significant structural motif that is present in **1** but not in the substrates investigated by Laarhoven is the 3,5-dimethoxyphenyl substitution pattern. Previous work in our laboratory[3] and others[4,5] has indicated that such a pattern gives rise to the well-studied "meta-effect" in benzylic ester photochemistry, where (1) C−O bond cleavage is more rapid than for other substitution patterns and (2) cation- (not radical-) derived products are observed in high yield. Recent work by Lewis and co-workers[6] has clearly shown that amino-substituted stilbene derivatives display a meta-effect that leads to significantly longer singlet lifetimes (τ_S for *trans*-4-aminostilbene = 0.1 ns; τ_S for *trans*-3-aminostilbene = 15 ns). Moreover, the photochemical addition of methanol to 2-(3-aminostyryl)naphthalene was observed, in contrast to the para isomer, which was unreactive.[6a] Finally, very recent publications by Lewis[7] and Arai[8] have investigated the photochemistry of hydroxystilbenes in water, and in the latter paper the addition of water to *trans*-3-hydroxystilbene was reported. We were intrigued by the possibility of (1) observing a similar effect for methoxy-substituted stilbenes and (2) observing photochemical reactivities that correlate with their photophysical properties. This note describes our success in both of these areas.

TABLE 1. Photophysical Characterization of *trans*-2a−e



2a: $R_1 = R_2 = R_3 = H$
2b: $R_1 = R_3 = H, R_2 = OCH_3$
2c: $R_1 = OCH_3, R_2 = R_3 = H$
2d: $R_1 = R_3 = OCH_3, R_2 = H$
2e: $R_1 = R_2 = OCH_3, R_3 = H$

	λ_{abs} (nm)	ϵ_{max} ($M^{-1}\,cm^{-1}$)	λ_{fl}[a] (nm)	$\lambda_{0,0}$[a] (nm)	τ_S[a,b] (ns)	Φ_{fl}[a,c]
2a	295, 307	28500, 27600	350	328	0.07[d]	0.016[c]
2b	302, 317	28700, 27700	381	344	<0.5[e]	0.007
2c	295	25800	357	336	0.93	0.096
2d	299, 306	30100, 29800	389	341	16.9	0.200
2e	301, 321	20600, 24700	389	353	<0.5[e]	0.018

[a] Measured by using degassed acetonitrile solutions (3 freeze−pump−thaw cycles) with absorbance of 0.25 at 295 nm (excitation wavelength). [b] Measured by single photon counting. [c] Measured by comparing the integrated area under the fluorescence curve to a standard (*trans*-stilbene **2a** in acetonitrile, ref 12). [d] In methanol, ref 11. [e] Shorter than the time resolution of the instrument.

Stilbenes **2a**−**e** were selected for this study. While *cis*- and *trans*-**2a** are commercially available, the remaining eight compounds were synthesized by traditional Wittig chemistry. The photophysical characterization of **2a**−**e** is given in Table 1 for the trans isomers only. The values for the absorption maxima and extinction coefficients are similar to those of other substituted *trans*-stilbenes. For the cis isomers, the absorption maxima are approximately 20 nm shorter than their trans counterparts, and the extinction coefficients are on the order of 10000−16000 $M^{-1}\,cm^{-1}$. Furthermore, while all of the trans isomers demonstrate measurable fluorescence, none of the five *cis*-stilbenes fluoresce appreciably.[9]

The data in Table 1 show substantial variations depending on the position of the methoxy substituent.[10]

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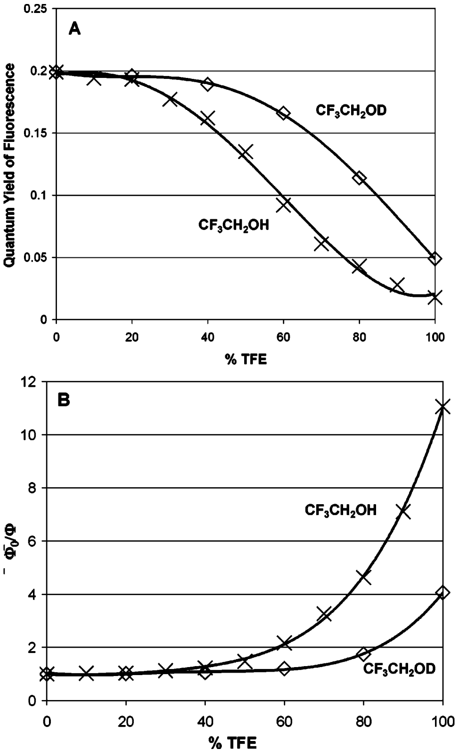
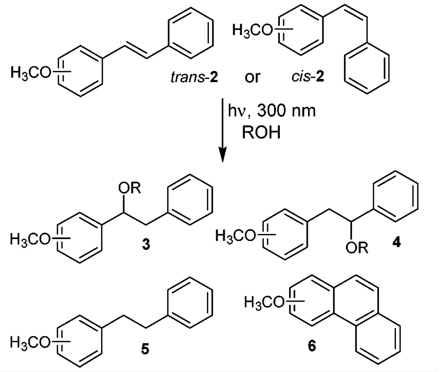


FIGURE 1. Quenching of the fluorescence of *trans*-**2d** by either TFE (crosses) or TFE-OD (diamonds). (A, top) Plot of the quantum yield of fluorescence versus the percentage of TFE in acetonitrile; (B, bottom) the same data presented as a Stern−Volmer plot.

Most notably, the singlet lifetimes and fluorescence quantum yields of the substrates are increased significantly by *m*-methoxy substitutents. Indeed, both the singlet lifetime and fluorescence quantum yield of the 3,5-dimethoxy compound *trans*-**2d** in acetonitrile ($\tau_S = 16.8$ ns, $\Phi_{fl} = 0.200$) are much greater than those observed for *trans*-stilbene itself ($\tau_S = 0.07$ ns,[11] $\Phi_{fl} = 0.016$[12]), and even greater than the diamino analogue studied by Lewis and co-workers ($\tau_S = 16.1$ ns, $\Phi_{fl} = 0.100$[6e]).

To investigate the interaction of the long-lived excited state of *trans*-**2d** with alcohols, the fluorescence quantum yield of this substrate was determined in various mixtures of acetonitrile and TFE or TFE-OD. Figure 1A shows the plot of Φ_{fl} versus percent alcohol. There appear to be two plateau regions in Figure 1A: a low quenching region (0−20% TFE), where $\Phi \approx 0.20$, and a high quenching region (80−100% TFE) where $\Phi \approx 0.02$. The fluorescence of *trans*-**2d** shows only a slight decrease in methanol ($\Phi_{fl} = 0.19$), but preliminary experiments do show quenching by solutions of anhydrous HCl in methanol or acetonitrile. Such behavior is reminiscent of the fluorescence quenching observed by Yates and co-workers[13] for substituted styrene derivatives in acidic solution. Assuming a concentration of 13.7 M for pure TFE, the quenching ratio of $k_{TFE}/k_{TFE-OD} = 3.3{:}1$ also indicates rate-determining proton transfer. Figure 1B shows the same data plotted as a Stern−Volmer plot of $\Phi_{fl}/\Phi_{fl}{}^{\circ}$ versus % TFE in acetonitrile.[14] Even at very low concentrations of TFE (i.e., 0−30%), the upward curvature is still obvious. The curvature of this plot emphasizes that the quenching of fluorescence by TFE is unlikely to be the result of a simple bimolecular interaction. A likely explanation for this effect is that higher concentrations of TFE not only increase the number of available quenching molecules, but also create a highly ionizing environment that enhances the quenching mechanism (vide infra).

SCHEME 1. Products from Irradiation of *trans*- or *cis*-2



	Methanol (1 hour)[a]					TFE (10 minutes)[b]				
	% conv.	**3**[a]	**4**[a]	**5**	**6**[c]	% conv.	**3**[b]	**4**[b]	**5**	**6**[c]
trans-**2a**	14	76	-	0	24	21	84	-	0	16
trans-**2b**	9	79	0	1	19	22	83	0	1	16
trans-**2c**	29	12	31	8	49	69	13	74	1	12
trans-**2d**	56	2	17	8	73	100	14	82	1	2
trans-**2e**	15	52	4	0	43	33	57	34	0	9

[a] $R = CH_3$. [b] $R = CH_2CF_3$. [c] For **6c** and **6e**, the yield given is the sum of the two possible isomers.

Irradiation of the five substrates (either cis or trans isomer) in methanol or TFE resulted in the formation of several products, Scheme 1. The isomeric ethers **3** and **4** are easily differentiated by the masses (GC-MS) of the two benzylic carbocations that are produced following fragmentation of each compound.[15] The product yields obtained following irradiation of *trans*-**2a**−**e** in methanol (1 h) and TFE (10 min) are also shown in Scheme 1. Particularly noteworthy points are (1) the higher percent conversions in TFE, (2) the high yields of Markovnikov ethers in TFE, and (3) the very high reactivity of *trans*-**2d**.

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(9) Lewis has investigated the fluorescence behavior of the three monosubstituted *cis*-aminostilbenes (Lewis, F. D.; Kalgutkar, R. S. *J. Phys. Chem. A* **2001**, *105*, 285), although fluorescence was only observed for the meta isomer ($\tau_S = 17.4$ ns at 77 K). We observe weak fluorescence from *cis*-**2d** in room temperature acetonitrile ($\Phi_{fl} = 0.006$ at 284 nm), but this signal could also be attributed to as little as 2.4% impurity of *trans*-**2d** in the sample.

(10) During the preparation of this paper, Majima and co-workers published an investigation of the photophysical behavior of some of these same methoxy-substituted stilbenes, Hara, M.; Tojo, S.; Majima, T. *J. Photochem. Photobiol. A*: *Chem.* **2004**, *162*, 121. Surprisingly, several of the quantum yields and fluorescence lifetimes reported are much lower than our values. For example, in the case of *trans*-**2d** $\Phi_{fl} = 0.023$ and $\tau_S = 4$ ns. In light of this discrepancy, we have repeated our measurements and calculations, but find essentially no change from our original values in Table 1.

(11) Kim, S. K.; Courney, S. H.; Fleming, G. R. *Chem. Phys. Lett.* **1989**, *159*, 543.

(12) Mazzucato, U. *Pure Appl. Chem.* **1982**, *54*, 1705.

(13) (a) Wan, P.; Culshaw, S.; Yates, K. *J. Am. Chem. Soc.* **1982**, *104*, 2509. (b) McEwen, J.; Yates, K. *J. Am. Chem. Soc.* **1987**, *109*, 5800.

(14) A reviewer pointed out that a true Stern−Volmer plot should show $\Phi_{fl}/\Phi_{fl}{}^{\circ}$ versus the molarity of the quencher rather than the percentage in TFE.

(15) For example, the base peak in the mass spectrum of **3d** (TFE) is *m*/*z* 249, while the isomer **4d** (TFE) has a base peak of *m*/*z* 189. Both ions are diagnostic for the regiochemistry of the TFE addition reaction.

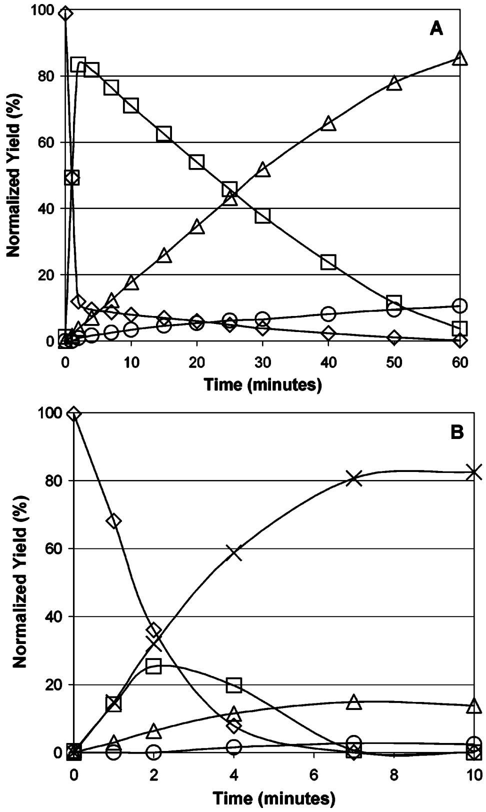

FIGURE 2. (A, top) Yield versus time plot for the irradiation of the unsubstituted stilbene *trans*-**2a** in TFE for 1 h. Products are labeled as follows: *trans*-**2a** (diamonds), *cis*-**2a** (squares), **3a** (triangles), **6a** (circles). (B, bottom) Yield versus time plot for the irradiation of the 3,5-dimethoxy compound *trans*-**2d** in TFE for 10 min. Products are labeled as follows: *trans*-**2d** (diamonds), *cis*-**2d** (squares), **3d** (triangles), **4d** (crosses), and **6d** (circles). Product **5** (<2% yield in all cases) has been omitted for clarity.

The most rapid reaction for any of the five substrates is trans–cis isomerization, which leads to a photostationary state of the two isomers within 2 min of starting the irradiation. For this reason, the table shows the percent conversion of *the mixture of stilbene isomers*, which provides a much better indication of the reactivity of each substrate. This issue is best considered by examining Figure 2, which shows the change in the photolysis mixture as a function of time for *trans*-**2a** (A) and *trans*-**2d** (B) upon irradiation in TFE. In both cases, the starting trans isomer is >90% consumed within 5 min. However, for the unsubstituted *trans*-**2a**, isomerization is the major reaction pathway, while *trans*-**2d** demonstrates significant formation of the ether **4d**. Furthermore, the observation that the concentration of the cis isomer decreases over time does not necessarily mean that the cis isomer gives rise to addition products. Given that a photostationary state is attained very early in these irradiation experiments, determining which isomer leads to product formation is not possible from these data. Indeed, irradiation of *cis*-**2a**–**e** in TFE leads to essentially the same product yields as shown in Scheme 1 (Supporting Information).

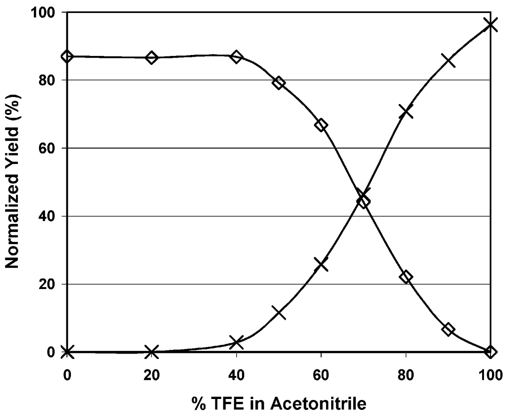

FIGURE 3. Combined yields of *cis*- and *trans*-**2d** (diamonds) and combined yields of ethers **3d** and **4d** (crosses) as a function of percent TFE in acetonitrile.

The results from the irradiation experiments compliment the photophysical properties in many respects. First, the substrates are much more reactive in TFE compared to methanol. This was expected based on the rapid quenching of excited *trans*-**2d** by TFE ($\Phi_{fl} = 0.018$) but not by methanol ($\Phi_{fl} = 0.190$). Second, substrates with *m*-methoxy substituents are more reactive than unsubstituted or para-substituted compounds. In methanol, where quenching by the solvent is quite slow, the more reactive substrates give high yields of phenanthrene product **6**;[16] in TFE, addition products **3** and **4** are favored. The correlation between the propensity toward TFE-adduct formation and excited-state lifetime is striking, with *trans*-**2d** having both the longest singlet lifetime ($\tau_S = 16.9$ ns) and the highest reactivity (100% conversion after 10 min in TFE, 96% total ether product formed). Obviously, a longer lived excited state allows more time for an intermolecular reaction to intercept the excited stilbene. To provide further evidence for the connection between the fluorescence quenching behavior shown in Figure 1 and the photochemical addition of TFE, the irradiation of *trans*-**2d** was repeated in a series of TFE–acetonitrile mixtures. Figure 3 shows a comparison of the combined yield of stilbenes (*cis*- and *trans*-**2d**) and the combined yield of the ethers (**3d** and **4d**) after 10 min of irradiation as a function of % TFE in acetonitrile. The lack of substantial ether formation for % TFE < 40% and the rapid increase in yield thereafter strongly suggests that the mechanism responsible for the quenching of *trans*-**2d** fluorescence leads to formation of the addition products. In addition, these results point to the excited state of the trans isomer being the species responsible for ether formation.

Importantly, Markovnikov ethers are preferred for all five substrates, keeping in mind that *m*-methoxy substituents are electron withdrawing with respect to the benzylic position. This preference provides further evidence for the presence of carbocation intermediates in the addition reaction, as indicated earlier by the quenching studies. A reviewer pointed out that, on the basis of a direct comparison with the meta-effect in benzylic ester chemistry, the expected major product from irradiation of *trans*-**2d** should be **3d** rather than **4d**. However, a significant difference between these two reactions is that the former involves an excited-state bond cleavage,

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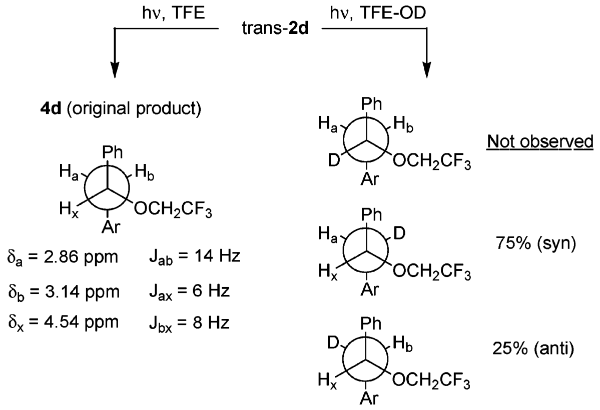
[16] The efficient cyclization of *m*-methoxy stilbenoid systems has been observed previously. Noller, K.; Dosteyn, F.; Meier, H. *Chem. Ber.* **1988**, *121*, 1609.

SCHEME 2. ^{1}H NMR Analysis of the Addition of TFE and TFE-OD to *trans*-2d



whereas the current work deals with an excited-state bond formation. The excited-state electron-donating ability of the *m*-methoxy substituents appears to effectively increase the basicity of the benzylic position, thereby leading to more rapid protonation by TFE. With this in mind, we believe that **4d** should be the expected product based on both excited-state transmission of electron density and relative stability of the two possible carbocation intermediates.

In the earlier studies by Laarhoven and co-workers,[2] the photochemical addition of methanol to unsubstituted *trans*-stilbene (**2a** in this study) was concluded to occur via two competing mechanisms: (1) direct addition across the central alkene unit and (2) rearrangement via a 1,2-hydride shift to give a carbene intermediate, followed by insertion into the O−H bond of the solvent. The presence of a carbene intermediate was suggested based on the observation (^{1}H NMR) that irradiation in CH_3OD led to deuterium incorporation on the same carbon as the nucleophile. The authors determined the carbene insertion:direct addition ratio to be 0.9 following irradiation at 300 nm. Furthermore, the fluorescence of *trans*-stilbene was not quenched in 6 M H_2SO_4, indicating that excited-state protonation is not an important decay pathway for the substrate.

In contrast, *trans*-**2d** reacts with TFE-OD to give products that exclusively have the deuterium and the nucleophile on adjacent carbons, Scheme 2. These results are supported by the GC-MS spectrum of deuterated **4d** (TFE), which shows no enhancement of the M + 1 signals for the *m*/*z* 189 ion. Moreover, the ^{1}H NMR data indicate that the addition gives two diasteriomers[17] as expected for a reaction proceeding through a carbocation intermediate. Assuming that only the trans isomer reacts (due to the expected short excited-state lifetime of the cis isomer), the ratio of syn:anti addition is 3:1. The preference for syn addition suggests that the poorly stabilized intermediate ion pair undergoes rapid collapse to give the observed product.[18] In addition, the lack of deuterium incorporation on the nucleophile-bearing carbon indicates that the carbocation intermediate does not undergo rearrangement via a 1,2-hydride shift. This substantiates our earlier work,[1] which indicated that the rate of such rearrangements is low compared to the rates of nucleophile trapping (to yield the product ethers) or deprotonation (to re-form the stilbene substrates).

The results described in this report are summarized as follows: (1) The "meta effect" described by Lewis and co-workers for amino-substituted stilbene derivatives is also important for methoxy-substituted derivatives; *m*-methoxy substituents prolong the excited-state lifetime of the stilbene chromophore, and lead to high fluorescence quantum yields. (2) The meta effect also increases the reactivity of the substrate, leading to high yields of phenanthrene products in methanol, and high yields of solvent adduct in TFE. The higher reactivity of these substrates is likely due to the long singlet lifetimes, which in turn make subsequent reactions more probable. (3) The combination of the highly ionizing environment of TFE and the stabilization of a zwitterionic excited state appears to lead to rapid photoprotonation of *trans*-**2d**, the substrate for which the meta effect is the greatest. Further studies are required to identify any cationic intermediates that are formed on the reaction pathway, and to fully understand these results in relation to the investigations of Laarhoven and co-workers. This work is currently in progress, and we will report our findings in due course.

Experimental Section

Synthesis of Substrates 2b−e. Benzyltriphenylphosphonium bromide was produced by addition of triphenylphosphine (15.3 g, 0.058 mol) to a solution of benzyl bromide (10.0 g, 0.058 mol) in benzene (50 mL). The resulting mixture was stirred overnight at room temperature, and the precipitate (20.0 g, 80% yield) was isolated by suction filtration and washed with diethyl ether. The isolated bromide salt (10.0 g, 0.023 mol) was reacted with 1 equiv of sodium ethoxide, followed by an equimolar amount of the appropriate aldehyde. The reaction mixture was heated to 80 °C while stirring overnight, and the cooled reaction mixture was extracted with methylene chloride. The *trans*- and *cis*-stilbenes were separated by column chromatography, giving yields of 10−15% for each isomer.

Photolysis Procedure. A 1×10^{-3} M solution (50 mL) of the substrate of interest was thermostated at 25 °C in a quartz reaction vessel and purged with nitrogen for 30 min. Irradiations were performed in a Rayonet reactor with 10 low-pressure mercury lamps (300 nm emission). Aliquots taken during the reaction were analyzed by GC-FID to determine product yields. The mass balances were greater than 90% in all cases. The yields listed in Scheme 1 (and the yield versus time plots) have been normalized to the initial response of the starting materials **2a**−**e**. After the reaction was complete, the solvent was removed under reduced pressure, and the residue was taken up in methylene chloride for GC-MS analysis.

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Supporting Information Available: The ^{1}H, ^{13}C, and MS characterization of the eight synthesized starting materials, and the 500-MHz spectra used for the analysis of the addition of TFE and TFE-OD to *trans*-**2d**; also, the yield versus time plots for *trans*-**2b**, *trans*-**2c**, and *trans*-**2e** in TFE, *cis*-**2a**−**e** in TFE, and *trans*-**2a**−**e** in methanol. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] Kingsbury, C. A.; Thorton, W. B. *J. Org. Chem.* **1965**, *31*, 1000.

[18] Laser flash photolysis of styrene in TFE leads to a transient cation intermediate (λ_{max} = 315 nm), which decays with a rate constant greater than 5×10^7 s^{-1}. Cozens, F. L.; Kanagasabapathy, V. M.; McClelland, R. A.; Steenken, S. *Can. J. Chem.* **1999**, *77*, 2069.