Estimation of the rate constants for the radical addition of a trifluoromethyl radical to aryl-substituted vinyl triflates

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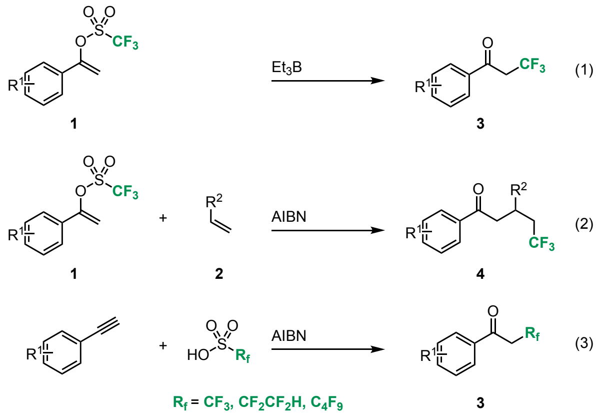
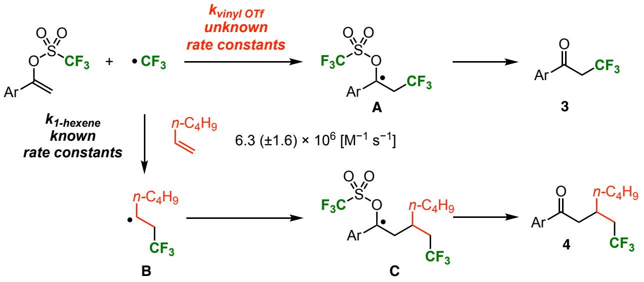
ABSTRACT: The rate constants for the radical addition of a trifluoromethyl radical to aryl-substituted vinyl triflates have been determined by applying competition kinetics at a single concentration point. The rate constants range from 4.1×10^6 to 5.6×10^6 M^{-1} s^{-1} and depend on the electronic properties of the benzene rings on the aryl-substituted vinyl triflates.

By virtue of the unusual characteristics of the fluorine atom, molecules that contain the trifluoromethyl group exhibit considerably improved binding selectivity, metabolic stability, and lipophilicity.[1–3] Therefore, trifluoromethyl substituents have attracted particular attention from organic and medicinal chemists, and several drugs containing trifluoromethyl groups have been developed. Recently, our[4–8] and other groups[9–13] have developed radical trifluoromethylation reactions in which aryl-substituted vinyl triflates act as both the source of trifluoromethyl radicals and as the radical acceptor. For example, the reaction of aryl-substituted vinyl triflates with a radical initiator gives α-trifluoromethylated ketones (Scheme 1, eq. 1),[4,6] while the reaction of aryl-substituted vinyl triflates in the presence of alkenes affords γ-trifluoromethylated ketones (Scheme 1, eq. 2).[7] We have also developed a one-shot trifluoromethylation from alkynes and trifluoromethane sulfonic acid (TfOH) and related perfluoroalkylated sulfonic acids (R_fSO_3H) (Scheme 1, eq. 3).[6] In these processes, TfOH is indirectly acting as the trifluoromethylating reagent. To use aryl-substituted vinyl triflates in trifluoromethylation reactions, the addition of trifluoromethyl radicals to the vinyl triflate must be prevented. Moreover, clarifying the rate constants for the reaction of aryl-substituted vinyl triflates with a trifluoromethyl radical can be expected to help the development of aryl-substituted vinyl triflates as a new type of trifluoromethylating reagent. In this work, we have estimated the rate constants for the addition of trifluoromethyl radicals to aryl-substituted vinyl triflates using competition experiments[14] relative to the addition of trifluoromethyl radicals to alkenes.[15]



Scheme 1. Radical trifluoromethylation of aryl-substituted vinyl triflates or aryl-substituted alkynes.

We selected the radical reaction of aryl-substituted vinyl triflates (**1**) with 1-hexene (**2**) as a model reaction to estimate the rate constants. The generated trifluoromethyl radicals exhibit two types of reactivity. One is the addition of aryl-substituted vinyl triflates to give radical **A** (Scheme 2); however, according to our previous theoretical calculations at the ROBHandHLYP/aug-cc-pVDZ//BHandHLYP/cc-pVDZ level,[6] this step is highly exothermic (185 kJ mol^{-1}), and the activation energy of the reverse reaction is 196.6 kJ mol^{-1}; accordingly, the generation of radical **A** should be irreversible. Irrespective, radical **A** could undergo β-cleavage to give α-trifluoromethylated ketones **3** and a trifluoromethane sulfonyl radical ($CF_3SO_2^{\bullet}$), whose α-cleavage would regenerate the trifluoromethyl radical. The other reactivity of the trifluoromethyl radical is the addition to 1-hexene (**2**) to give alkyl radical **B** (Scheme 2), which could then add to the vinyl triflate followed by β-cleavage to afford the corresponding γ-trifluoromethylated ketones (**4**). If the addition of the alkene is highly exothermic and the addition of alkyl radical **B** to aryl-substituted vinyl triflates is not a slow step, the rate constant can be estimated from the product ratio. Li and coworkers have reported that this is an exothermic reaction (105 kJ mol^{-1}; 25.2 kcal mol^{-1}) in methanol and that the activation energy of the reverse reaction is 140.5 kJ mol^{-1} (33.6 kcal mol^{-1}) at the B3LYP/6-31+G**/SDD/Aug-cc-PVTZ level.[16] The latter suggests that there is no problem given that compounds **4** are produced in sufficient yield.[7]



Scheme 2. General reaction and mechanism of the addition of trifluoromethyl radicals to aryl-substituted vinyl triflates.

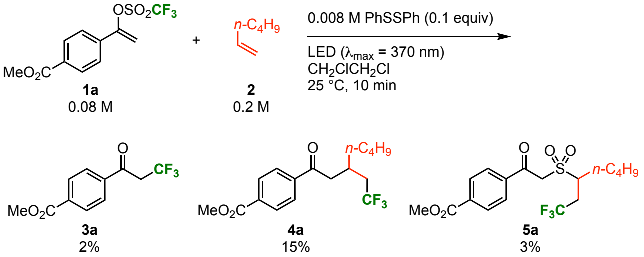
Generally, competition reactions are performed using a large excess of substrate so that the concentration of substrate can be considered constant throughout the reaction (pseudo-first order conditions). However, in this case, the vinyl triflate acts as a CF$_3$ radical source *and* as a radical acceptor. Furthermore, the use of a large excess of **2** furnished the α-trifluoromethylated ketones in low yield. Therefore, the reaction was stopped after a short time and low conversion. The last concentrations of aryl-substituted vinyl triflates and 1-hexene were calculated from the amount of vinyl triflate recovered and the yield of γ-trifluoromethylated ketones, respectively. The concentration was determined by taking the average of the initial and last concentrations.

Knowing the rate constant for the reaction of **2** with the CF$_3$ radical, the rate constant for the CF$_3$ radical to the vinyl triflate can be calculated from the product ratio of α-trifluoromethylated ketones (**3**) and γ-trifluoromethylated ketones (**4**), which can be easily determined from the ^{19}F NMR spectra of the crude reaction mixture. The addition-reaction rate constant ($k_{\mathrm{vinyl\ OTf}}$) can be calculated from the concentrations of vinyl triflate **1** and **2** and the known rate constant for the addition to **2** using equation (2), which is derived from the kinetic equation (1):

$$\frac{\mathbf{3}}{\mathbf{4}} = \frac{k_{\mathrm{vinyl\ OTf}} \cdot [\mathrm{CF_3}\,\bullet] \cdot [\mathbf{1}]}{[\mathrm{CF_3}\,\bullet] \cdot [\mathbf{2}] \cdot k_{\mathrm{alkene}}} \qquad (1)$$

$$k_{\mathrm{vinyl\ OTf}} = \frac{\mathbf{3}}{\mathbf{4}} \cdot \frac{[\mathbf{2}] \cdot 6.3\ \times\ 10^{6}\ \mathrm{M^{-1}s^{-1}}}{[\mathbf{1}]} \qquad (2)$$

For the determination of the rate constant using eq. 2, the solvent and the temperature are important factors. However, using THF as the reaction solvent resulted in a substantial decrease in the mass balance, probably due to a chain-transfer reaction.[17] We have previously conducted the reactions of aryl-substituted vinyl triflates with alkenes under heating conditions using AIBN as the radical initiator. Recently, we have furthermore discovered that PhSSPh acts as a good radical initiator under UV-light irradiation, which permits access to a broader temperature window. Thus, we performed the reaction of vinyl triflate **1a** with **2** in the presence of PhSSPh (0.1 equiv) in CH$_2$ClCH$_2$Cl at 25 °C for 10 min under irradiation from UV LEDs (Scheme 3). The expected α-trifluoromethylated ketone (**3a**) and γ-trifluoromethylated ketone (**4a**) were obtained in 2% and 15% yield, respectively, together with 3% yield of the corresponding trifluoromethylated β-keto sulfone (**5a**). To reduce the yield of **5a,** we conducted the reaction in the presence of various bases. However, only NaOH prevented the formation of **5a**, even though **3a** slightly decomposed. Given that **5a** is generated via the addition of the CF$_3$ radical to **2** followed by trapping of SO$_2$, the rate constant was calculated using the ratio of **3a** to **4a** + **5a** instead of the ratio of **3a** to **4a**.



Scheme 3. Initial study of the addition of the trifluoromethyl radical to aryl-substituted vinyl triflate 1a.

$$k_{\mathrm{vinyl\ OTf}\,\mathbf{1a}} = \frac{\mathbf{3}}{(\mathbf{4}+\mathbf{5})} \cdot \frac{k_{\mathrm{alkene}} \cdot [\mathbf{2}]}{[\mathbf{1}]} \qquad (3)$$

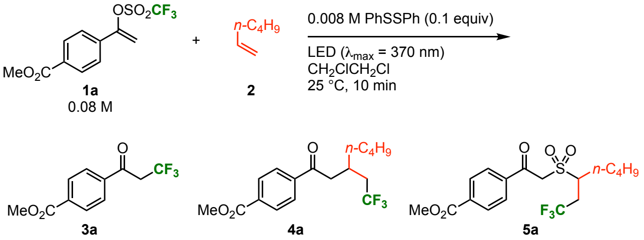
Next, we performed a series of experiments using different concentrations of **2** while keeping the concentration of the vinyl triflate fixed, which afforded a mixture of **3a**, **4a**, and **5a**. From the slope of plot of the (**4a**+**5a**)/**3a** ratio as a function of the concentration of **2**, which should theoretically furnish a straight line, the relative rate constants can be calculated as shown in equation (5):

$$\frac{(\mathbf{4a}+\mathbf{5a})}{\mathbf{3a}} = \frac{k_{\mathrm{alkene}} \cdot [\mathbf{2}]}{k_{\mathrm{vinyl\ OTf}} \cdot [\mathbf{1a}]} \qquad (4)$$

$$slope = \frac{k_{\mathrm{alkene}}}{k_{\mathrm{vinyl\ OTf}} \cdot [\mathbf{1a}]} \qquad (5)$$

As shown in **Figure 1**, the **4a** + **5a**/**3a** ratio relative to the concentration of **2** (Table 1) showed a linear relationship. A linear regression of the data yielded $k_{alkene}/(k_{vinyl\ OTf}[\mathbf{1a}])$ = 20.6 M^{-1}, from which the rate constant $k_{vinyl\ OTf}$ for the addition of the CF$_3$ radical to the vinyl triflate was estimated to be 4.64 × 10^6 M^{-1} s^{-1} at 25 °C.

Table 1. Competition experiments



1a [M]	**2** [M]	(**4a** + **5a**)/**3a**^{a}
0.08	0.39	8.17
0.08	0.19	4.03
0.08	0.12	2.04
0.08	0.08	1.41

[a] Calculated from the average of three results of the ^{19}F NMR monitoring using $PhCF_3$ as the internal standard.

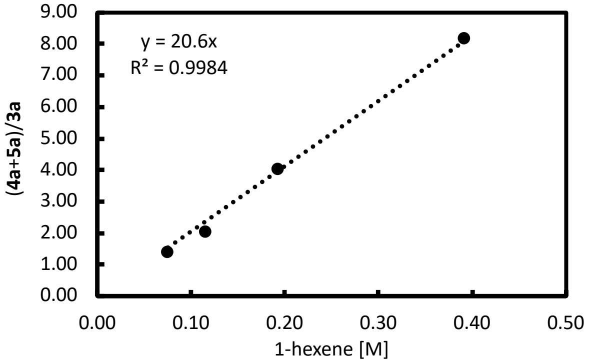


Figure 1. Product ratios (**4a**+**5a**)/**3a** as a function of the concentration of 1-hexene (**2**) in the presence of vinyl triflate **1a** (0.08 M); determination of the rate constant $k_{\text{vinyl OTf}}$ at 25 °C

Next, using equation 3, we estimated the rate constants with various aryl-substituted vinyl triflates (**1**) while fixing the concentration of 1-hexene to 0.2 M for simplicity. The thus obtained rate constants and Hammett's *para*-substitution parameters (σ_p^-) are summarized in Table 2. Since the CF_3 radical is an electrophilic radical, substrates with electron-deficient groups exhibit lower reaction-rate constants. Fluorine-substituted vinyl triflate **1b** and simple vinyl triflate **1c** did not result in a linear relationship, which can most likely be attributed to the triflate-elimination reactions to which slightly electron-rich aryl-substituted vinyl triflates are susceptible to. Therefore, we constructed the corresponding Hammett plots excluding aryl-substituted vinyl triflates **1b** and **1c** (**Figure 2**). Good correlations were observed between the Hammett parameters and the rate constants. According to the results, cyano-substituted vinyl triflate **1g** shows promising potential as a source of trifluoromethyl radicals.

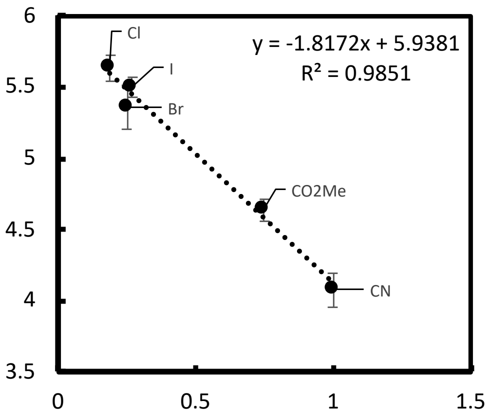
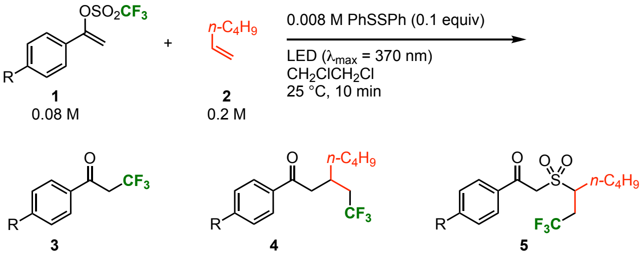


Table 2. Rate constants and Hammett's *para*-substitution parameters (σ_p^-) for the addition of trifluoromethyl radicals to aryl-substituted vinyl triflates.



entry	R	**1**	σ_p^-	*k* [10^6 M^{-1} s^{-1}]
1	F	**1b**	−0.03	4.83±0.03
2	H	**1c**	0	5.60±0.08
3	Cl	**1d**	0.19	5.64±0.09
4	Br	**1e**	0.25	5.36±0.16
5	I	**1f**	0.27	5.50±0.07
6	CO_2Me	**1a**	0.75	4.64±0.08
7	CN	**1g**	1.00	4.08±0.12

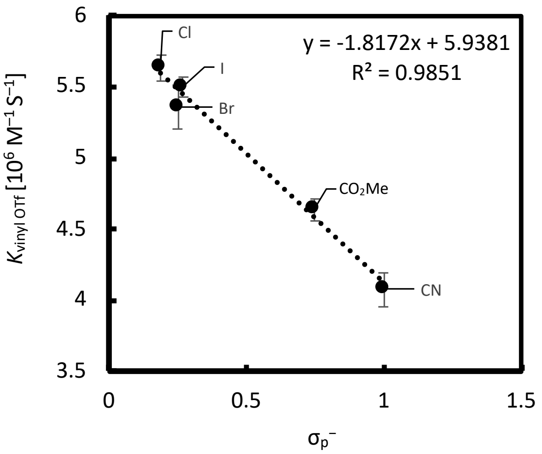


Figure 2. Hammett plot of the rate constants (**1a**, **1d**–**1g**) as a function of the Hammett constant for the *para*-substituent aryl moiety in the vinyl triflates (σ_p^-).

In summary, we have carried out kinetic competition experiments using 1-hexene and aryl-substituted vinyl triflates to determine the rate constants for the addition of a CF_3 radical to aryl-substituted vinyl triflates, which allowed us to establish guidelines for the use of aryl-substituted vinyl triflates as a source of CF_3. In particular, aryl-substituted vinyl triflates that contain cyano groups show promising potential for various trifluoromethylation reactions because their direct addition reaction is sluggish. Currently, we are developing new reactions in this area.

EXPERIMENTAL SECTION

General Information. All reagents were purchased from common commercial suppliers and used without further purification unless otherwise stated. ^{19}F NMR spectra were recorded on JEOL JNM-ECA500 or ECZ500 (^{19}F 470 MHz) spectrometers. Aryl-substituted vinyl triflates were prepared from the corresponding ketones and trifluoromethanesulfonic anhydride (Tf_2O) with 2-fluoropyridne according to a previously reported method.[18]

To perform the experiments, aliquots of 0.5, 0.25, 0.15, and 0.1 mL of a 0.1 M stock solution of 1-hexene (**2**) in CH_2ClCH_2Cl were transferred to separate 10 mL flasks. Vinyl triflates **1** (0.5 mL of a 0.2 M solution in CH_2ClCH_2Cl) and PhSSPh (0.25 mL of a 0.04 M solution in CH_2ClCH_2Cl) were added to each flask. Each flask was then filled up to 1.25 mL with CH_2ClCH_2Cl, and the resulting mixture was placed in a constant-temperature water bath under irradiation from UV LEDs for 10 min. The product ratios were determined by ^{19}F NMR analysis using $PhCF_3$ as the internal standard.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of spectra (PDF)

Funding Sources

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