A density functional theory study on the mechanism of simultaneous trifluoromethylation and oximation of aryl-substituted ethylenes

Sen Wang¹, Wenlu Song²,², Xiaowei Lan¹, Xuan Meng¹, Nan Li¹, Xianfu Wei¹, Wenjie Jing¹, Kui Lu¹ and Yujie Dai¹

Abstract
The effects of different substituents, located at the para position of the aromatic ring and at the β-carbon atom of styrenes, on difunctionalizations involving trifluoromethylation and oxime formation are investigated, showing that the difunctionalization reaction has a good adaptability to such reactants containing a range of substituents. This is important in the actual production process. It was found that proton transfer in the final tautomerism step involving transformation of a nitroso intermediate into an oxime is the rate-limiting step. The solvent effect did not influence the rate-limiting step significantly. Compared with direct proton transfer in a vacuum, the energy barrier of the final tautomerism step decreased from 57.80 kcal mol⁻¹ in vacuum to 12.98 kcal mol⁻¹ in water occurring via mediated proton transfer, which declines by 77.5%. When water participates in the rate-limiting step in organic solvents, the energy barrier also decreases significantly, which indicates that a small amount of water in the organic solvent is conducive to the reaction.

Keywords
density functional theory, difunctionalization, free radical reaction, oximation, trifluoromethylation

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1Tianjin Key Laboratory of Industrial Microbiology, Tianjin University of Science and Technology, Tianjin, P.R. China
2Jining University, Qufu, P.R. China
*W.S. has equal contribution with the first author.

Corresponding author:
Yujie Dai, Tianjin Key Laboratory of Industrial Microbiology, Tianjin University of Science and Technology, No. 29 of 13th Street, TEDA, Tianjin 300457, P.R. China.
Email: yjdai@126.com
Highlights

- The simultaneous trifluoromethylation and oximation of styrene was studied.
- The solvent effect has little impact on the overall reaction.
- The effect of substituents on rate-limiting steps is relatively small.
- The energy barrier of the tautomerism decreased by \( \text{H}_2\text{O} \)-mediated proton transfer.

Introduction

Fluorine is a substance with high electronegativity and activity. Introducing fluorine into organic molecules can dramatically change their physical, chemical, and biological properties. At present, there are mainly two types of methods for introducing a fluorine atom to an organic compound: direct C–F bond formation and the fluorinated building block method. The first method can be divided into three subtypes according to the electrical property of the reagent: electrophilic-fluorination, nucleophilic-fluorination, and radical-fluorination reactions. Generally, most of these reactions are harsh and difficult to control. The fluorinated building block route is an important method for synthesizing fluorinated organic compounds. It uses different fluorinated organic intermediates as fluorinating building blocks to synthesize fluorine-containing target molecules through appropriate reaction pathways. Compounds containing a trifluoromethyl group are often used as fluorinating building blocks in modern chemistry. The introduction of a trifluoromethyl moiety into a substrate can significantly improve its biological activity. Some organic compounds containing trifluoromethyl groups play very important roles in pharmaceuticals, agrochemicals, and in organic materials. Reactions involving the fluorinated building block method generally do not involve the breakdown and formation of a C–F bond, and benefit from mild reaction conditions, good selectivity, and high yields.

The oxime structural motif is widespread in natural products and in many biologically active compounds. It is an important synthon for the syntheses of amines, amides, nitriles, and heterocyclic compounds. Although there are a variety of synthetic methods that have been developed for the preparation of oximes, they usually require the presence of a carbonyl or a nitro group in the substrate. Simultaneously introducing two functional groups to an aryl olefin can significantly simplify the reaction steps and shorten the preparation time, thus improving the atom economy and reducing waste. It has been reported that \( \alpha \)-sulfonyl ketoximes can be prepared via the 1,2-difunctionalization of styrenes with sodium aryldisulfonates and tert-butyl nitrite (TBN). Our group previously investigated the bifunctionalization reaction of aryl-substituted ethylenes with the Langlois reagent (CF\textsubscript{3}SO\textsubscript{2}Na) as trifluoromethylation reagent and TBN as the oxidant and oxime source, which introduced a trifluoromethyl and an oxime simultaneously at the double bond position. Based on nuclear magnetic resonance (NMR) and isotope-tracking experiments, the putative reaction mechanism shown in Scheme 1 was proposed.

For novel chemical pathways, only when the reaction energy barrier, the reaction rate, the enthalpy change of each step, and the rate-limiting step of the whole reaction process are clearly known can new methods be readily applied to synthesis of other compounds. It is well known that substituents have a significant influence on reaction sites and reactivity. This is bad news for synthetic chemists in some circumstances. First, because of the influence of the existing substituents, it is difficult to determine where the subsequent substituents attack. Second, the rate at which a substituent attacks the desired reaction site changes significantly as the surrounding substituents change. Shen et al. investigated the activities of the electrophilic sites on the benzene ring of 4-substituted anilines and their acyl compounds through quantum chemical computations and chemical synthesis. Shiraz et al. used NICS (negative nucleus-independent chemical shift) calculations and energy barriers (\( \Delta E \)) to predict the most reactive site in azulene. It is common in chemistry to study the effects of substituents on reaction sites and reactivities by quantum chemistry computation. Solvent effects also have a great influence on chemical synthesis and the energy barrier and reaction rate constant of each step in a synthetic process. In this study, quantum chemistry calculations were employed to examine the transition state, the energy change of each step of the reaction and the rate-limiting step. The impacts of substituents and solvent effects on the reactivity and reaction sites of aryl ethylenes during trifluoromethylation and oxime formation were also investigated, so as to predict the effects of different substituents and solvents on the reactivities of the radical reactions during simultaneous trifluoromethylation and oximation of aryl-substituted styrene derivatives, and to provide theoretical guidance for related reactions.

Results and discussion

The formation of trifluoromethyl radicals in vacuum

The proposed reaction process for the simultaneous trifluoromethylation and oximation of aryl-substituted ethylenes is given in Scheme 1. The whole reaction proceeds via a free-radical chain process. The difunctionalization reaction can be divided into three processes involving seven steps: (1) The first process consists of three steps: 1, 2, and 3. TBN forms a tert-butoxy radical and a nitric oxide radical on heating. Radical transfer from the tert-butoxy radical to the Langlois reagent (CF\textsubscript{3}SO\textsubscript{2}Na) forms a trifluoromethylsulfinic radical, which is followed by homolysis to give the trifluoromethyl radical. (2) The second process also includes three steps: 4, 5, and 6. The aryl-substituted ethylene reacts with the trifluoromethyl radical and TBN to give the \( \alpha \)-trifluoromethylthethylketoxime. (3) The third process consists of only step 7, and involves termination of the reaction via radical combinations; this step is not discussed later. The formation of trifluoromethyl radicals includes three steps and the optimized structure parameters of the
Scheme 1. The reaction mechanism for the simultaneous trifluoromethylation and oximation of aryl ethylenes.
reactants (R), transition states (TS) and intermediates (IM) in vacuum and in the dimethyl sulfoxide (DMSO), ethanol, and water are shown in Figures 1 and 2. The potential energy surface for the formation of trifluoromethyl radicals in vacuum is given in Figure 3.

![Figure 1](image1.png)

**Figure 1.** Some optimized structural parameters of the reactant (R1) and transition state (TS) of TBN homolysis in vacuum (oxygen: red; nitrogen: blue; carbon: gray; hydrogen: white).

![Figure 2](image2.png)

**Figure 2.** The optimized initial and transition state structures (IM2 and TS(2)) during the homolysis of a trifluoromethyl sulfonate radical to form a trifluoromethyl radical in vacuum (oxygen: red; sulfur: yellow; carbon: gray; fluorine: cyan).

The bond length of N(6) to O(5) is 1.398 Å and the C(1)–O(5) distance is 1.481 Å in TBN (R1). The bond length of the nitrogen–oxygen double bond is 1.188 Å. The angle for O(7)–N(6)–O(5) is 110.909°. As the reaction proceeds, the N(6)–O(5) bond length increases leading to a transition state (TS) in which the aforementioned bond length is 1.654 Å while the length of the N(6)=O(7) bond became 1.196 Å. In addition, the bond angle for O(7)–N(6)–O(5) increased to 116.579° in TS(1), being larger by 5.67° compared with the reactant. As the reaction in step 1 progressed, the N(6)–O(7) bond distance increased further, and upon bond breaking, the NO radical (N=O is 1.158 Å) and tert-butoxy radical (C(1)–O(5) is 1.383 Å) were formed. Not only are the bond lengths shorter in the product of step 1, but the three dihedral angles in the tert-butyl group (112.034°, 109.988°, 109.993°) are smaller than those in the TBN (112.289°, 111.404°, 111.401°). The subsequent step is formation of the trifluoromethyl radical, which is an important process for the simultaneous trifluoromethylation and oximation of the aryl-substituted ethylene.

![Figure 3](image3.png)

**Figure 3.** The potential energy surface of the difunctionalization reaction of an aryl-substituted ethylene in vacuum.

The bond length of N(6) to O(5) is 1.398 Å and the C(1)–O(5) distance is 1.481 Å in TBN (R1). The bond length of the nitrogen–oxygen double bond is 1.188 Å. The angle for O(7)–N(6)–O(5) is 110.909°. As the reaction proceeds, the N(6)–O(5) bond length increases leading to a transition state (TS) in which the aforementioned bond length is 1.654 Å while the length of the N(6)=O(7) bond became 1.196 Å. In addition, the bond angle for O(7)–N(6)–O(5) increased to 116.579° in TS(1), being larger by 5.67° compared with the reactant. As the reaction in step 1 progressed, the N(6)–O(7) bond distance increased further, and upon bond breaking, the NO radical (N=O is 1.158 Å) and tert-butoxy radical (C(1)–O(5) is 1.383 Å) were formed. Not only are the bond lengths shorter in the product of step 1, but the three dihedral angles in the tert-butyl group (112.034°, 109.988°, 109.993°) are smaller than those in the TBN (112.289°, 111.404°, 111.401°). The subsequent step is formation of the trifluoromethyl radical, which is an important process for the simultaneous trifluoromethylation and oximation of the aryl-substituted ethylene. Step 2 is triggered by t-BuO·attacking the sodium atom to form a trifluoromethyl sulfonate radical and sodium.
Table 1. The energy barriers (\(\Delta E\)), reaction enthalpy changes (\(\Delta H_{298K}\)), Gibbs free energy changes (\(\Delta G_{298K}\)), tunneling correction factors (\(\kappa\)), and reaction rate constants (\(k\)) of the six reaction steps corresponding to those in Scheme 1.

| Step | \(\Delta E\) (kcal mol\(^{-1}\)) | \(\Delta H_{298K}\) (kcal mol\(^{-1}\)) | \(\Delta G_{298K}\) (kcal mol\(^{-1}\)) | \(\kappa\) | \(K\) |
|------|-------------------------------|--------------------------------|--------------------------------|--------|--------|
| 1\(^\circ\) | 47.42 | 35.32 | 24.41 | 1.177 | 7.699 \(\times 10^{-24}\) s\(^{-1}\) |
| 1\(^\circ\) | 47.88 | 35.10 | 24.21 | 1.184 | 3.558 \(\times 10^{-24}\) s\(^{-1}\) |
| 1\(^\circ\) | 47.86 | 35.11 | 24.13 | 1.184 | 3.680 \(\times 10^{-24}\) s\(^{-1}\) |
| 1\(^\circ\) | 47.88 | 35.10 | 24.21 | 1.184 | 3.558 \(\times 10^{-24}\) s\(^{-1}\) |
| 2\(^\circ\) | – | 29.78 | 28.69 | – | – |
| 2\(^\circ\) | – | 27.35 | 26.96 | – | – |
| 2\(^\circ\) | – | 27.27 | 25.77 | – | – |
| 2\(^\circ\) | – | 27.36 | 27.21 | – | – |
| 3\(^\circ\) | 5.68 | 4.24 | –7.07 | 1.006 | 2.973 \(\times 10^{7}\) s\(^{-1}\) |
| 3\(^\circ\) | 4.97 | 3.20 | –7.95 | 1.004 | 9.859 \(\times 10^{7}\) s\(^{-1}\) |
| 3\(^\circ\) | 4.99 | 3.22 | –7.93 | 1.004 | 9.531 \(\times 10^{7}\) s\(^{-1}\) |
| 3\(^\circ\) | 4.96 | 3.19 | –7.84 | 1.004 | 1.002 \(\times 10^{8}\) s\(^{-1}\) |
| 4\(^\circ\) | 24.84 | –39.96 | –27.97 | 1.006 | 1.952 \(\times 10^{12}\) s\(^{-1}\) M\(^{-1}\) |
| 4\(^\circ\) | 25.59 | –40.53 | –28.91 | 1.003 | 5.477 \(\times 10^{13}\) s\(^{-1}\) M\(^{-1}\) |
| 4\(^\circ\) | 25.58 | –40.51 | –28.88 | 1.003 | 5.569 \(\times 10^{13}\) s\(^{-1}\) M\(^{-1}\) |
| 4\(^\circ\) | 33.64 | –40.53 | –28.93 | 1.003 | 6.704 \(\times 10^{19}\) s\(^{-1}\) M\(^{-1}\) |
| 5\(^\circ\) | 14.98 | 14.95 | 16.06 | 1.004 | 8.073 \(\times 10^{9}\) s\(^{-1}\) M\(^{-1}\) |
| 5\(^\circ\) | 16.29 | 14.42 | 14.98 | 1.003 | 4.750 \(\times 10^{9}\) s\(^{-1}\) M\(^{-1}\) |
| 5\(^\circ\) | 16.29 | 14.46 | 14.99 | 1.003 | 4.830 \(\times 10^{9}\) s\(^{-1}\) M\(^{-1}\) |
| 5\(^\circ\) | 16.31 | 14.40 | 14.97 | 1.003 | 4.718 \(\times 10^{9}\) s\(^{-1}\) M\(^{-1}\) |
| 6\(^\circ\) | 57.80 | –13.98 | –11.72 | 6.170 | 9.607 \(\times 10^{31}\) s\(^{-1}\) |
| 6\(^\circ\) | 58.36 | –14.95 | –12.73 | 6.244 | 3.771 \(\times 10^{31}\) s\(^{-1}\) |
| 6\(^\circ\) | 58.36 | –14.93 | –12.71 | 6.244 | 3.771 \(\times 10^{31}\) s\(^{-1}\) |
| 6\(^\circ\) | 58.36 | –14.96 | –12.74 | 6.244 | 3.771 \(\times 10^{31}\) s\(^{-1}\) |

\(^\circ\): in vacuum; \(^\circ\): DMSO (dimethyl sulfoxide); \(^\circ\): ethanol; \(^\circ\): water; –: not obtained.

The process of the trifluoromethyl radical attacking styrene to produce an \(\alpha\)-trifluoromethylketoxime in vacuum.

tert-butyl nitrite has a transition state to dissociation and did not follow a Morse curve-type dissociation, which may be due to the reduction of energy caused by the conformational adjustment of the product of step 1. The energy barrier of the homolysis of TBN was 47.42 kcal mol\(^{-1}\), which was obtained from the relative energy difference between the transition state \(TS(2)\) and the reactant TBN (R). Step 1 is endothermic and the amount of heat absorbed is 35.32 kcal mol\(^{-1}\) depending on the relative energy difference between the intermediate of \(IM(1)\) and TBN (R1). The reaction rate constant of the homolysis of TBN is 7.699 \(\times 10^{-24}\) s\(^{-1}\). This step represents a decrease in the Gibbs free energy. As shown in Table 1, the energy barrier for breaking the C–S bond in CF\(_3\)SO\(_2\) is 5.68 kcal mol\(^{-1}\) and the reaction rate constant of this step is 2.973 \(\times 10^{7}\) s\(^{-1}\). The low energy barriers and high reaction rate constants of this step indicate that this step occurs very easily under normal temperature. As a whole, the generation of CF\(_3\) initiated by \(t\)-BuO\(^{-}\) can be carried out readily at room temperature. The products of this process are trifluoromethyl radical and nitric oxide (NO), and they continue to act as intermediates in reactions with aryl-substituted ethylenes. It can be seen from Table 1 that cleavage of the C–S bond is an endothermic process and the reaction enthalpy change is 4.24 kcal mol\(^{-1}\). In sum, the reactions involving steps 1, 2, and 3 in the first process are all endothermic.

In this work, styrene was used as an initial representative of an aryl-substituted ethylene. It is synthetic resin monomer and an important industrial raw material for preparing ion exchange resins and synthetic rubber in industry. In addition, styrene can be used in pharmaceuticals, dyes, pesticides, and mineral-processing industries. The trifluoromethyl group is often used as a bioisostere in place of chlorine or methyl for the preparation of various derivatives. It can be used to regulate the configuration and electronic properties of lead compounds or to protect active methyl groups from metabolic oxidation.
The process of trifluoromethyl radical attack on styrene (Scheme 1) mainly has three steps: steps 4, 5, and 6. Step 4 involves attack of the trifluoromethyl radical (IM(3)) on styrene to generate the (3,3,3-trifluoropropyl) benzene radical intermediate (IM(4)). As shown in Figure 5, before the trifluoromethyl radical attacks styrene, the length of the C(2)=C(8) bond was 1.341 Å, while in TS(3) it is 1.348 Å. In intermediate IM(4), the newly formed bond (C(8)=C(9)) is 1.514 Å, the previous (C(2)=C(8)) bond becomes C(2)–C(8) with a bond length of 1.499 Å, and the single bond between C(2) and C(1) is shortened to 1.415 Å. Steps 5 and 6 involve reaction of the (3,3,3-trifluoropropyl)benzene radical intermediate (IM(4)) with TBN to generate 3,3,3-trifluoro-1-phenylpropan-1-nitric oxide (IM(5)) and t-BuO·; the former is converted into α-trifluoromethylethyl ketoxime (P) through tautomerism and the latter enters a radical chain process. In the transition state TS(4), the C(1)–C(2) bond length changes from 1.415 Å in IM(4) to 1.446 Å, and the C(2)–N(21) bond length is 2.033 Å. The new bond C(2)–N(21) in IM(5) has a bond length of 1.526 Å. Subsequently, an isomerization reaction took place, which involved transfer of H(13) from C(2) to O(22). With the H(13) atom of C(2) approaching the O(22) atom of nitric oxide, the α-trifluoromethylethyl ketoxime (P) is formed. From the transition state structure of the reaction in step 6 (Figure 5), it can be seen that a four-atom cyclic transition state (TS(5)) with C(2), H(13), O(22), and N(21) is formed via H(13) transfer between C(2) and O(22). As reaction of step 6 proceed, the distance between N(21) and O(22) lengths from 1.283 Å in IM(5) to 1.396 Å in α-trifluoromethylethyl ketoxime (P), while the single bond between N(21) and C(2) is reduced in length from 1.391 to 1.288 Å. The new bond O(22)–H(13) in α-trifluoromethylethyl ketoxime (P) has a length of 0.967 Å. This is where the reaction is complete. It can be seen from Table 1, that step 4 (trifluoromethyl radical attack on the styrene to generate (3,3,3-trifluoropropyl) benzene radical (IM(4))) is an exothermic reaction and the reaction heat (ΔH°298K) is −39.96 kcal mol⁻¹. The energy barrier of step 4 is 24.84 kcal mol⁻¹ and the reaction rate constant is 1.952 × 10⁻¹² s⁻¹ M⁻¹. Subsequently, in step 5, IM(4) undergoes an addition reaction with TBN. The energy barrier of the fifth step is the smallest in the second process, which is 14.98 kcal mol⁻¹ and the reaction rate constant is 8.073 × 10³ s⁻¹ M⁻¹. Also, the fifth step is an endothermic reaction and the enthalpy change of the reaction is 14.95 kcal mol⁻¹. As shown in Table 1, the energy barrier for H(13) transferring from C(2) to O(22) was 57.80 kcal mol⁻¹. Compared with the other steps, step 6 has the highest energy barrier and is the rate-limiting step for the whole reaction process. It can be seen from Table 1 that the rate constant for this rate-limiting step is 9.607 × 10⁻³¹ s⁻¹. Step 6 is also an exothermic process and the enthalpy change is −13.98 kcal mol⁻¹.

Effect of the para substituents of the aryl ring and the β-C substituents of styrene on the difunctionalization reaction in vacuum

The substituents on the aromatic ring of styrene can affect the electron density distribution on the benzene ring and the conjugated vinyl bond, and further may affect the difunctionalization reaction. Grainger et al. reported that ortho substituents close to the reaction sites may have some influence on the formation of transition states. Electron-donating and the electron-withdrawing substituents have different effects on the electron distribution of the reactants and the transition states, and further influence the energy barrier of the reaction. To examine the effect of
para substituents on the aryl ring on the difunctionalization reaction, the difunctionalizations of the para-substituted styrene with electron-donating methoxy and methyl groups and an electron-withdrawing of fluorine group were examined in this study. To further explore the effects of substituents on the difunctionalization reaction, the native of the β-C. Since the first process only produces a trifluoromethyl radical and does not involve the subsequent reaction of styrene, the substituents only affect the second process. Hence, steps 4, 5, and 6 of the difunctionalization reaction with the substituted styrene were examined. Tables 2 and 3 list the methoxy and fluorine as representatives of electron-donating and electron-withdrawing groups, respectively, on the β-C. Since the first process only produces a trifluoromethyl radical and does not involve the subsequent reaction of styrene, the substituents only affect the second process. Hence, steps 4, 5, and 6 of the difunctionalization reaction with the substituted styrene were examined. Tables 2 and 3 list the
energy barriers that needed to be overcome and the reaction rate constants for steps of 4, 5, and 6. Figure 6 shows the optimized structures and some main parameters of the intermediates, transition states and products of steps 4, 5, and 6 of the difunctionalization reaction of para-substituted styrenes in vacuum and in different solvents: dimethyl sulfoxide (DMSO), ethanol (EtOH), and water (H2O).

Comparing the data in Table 3 with that in Table 1, when a methoxy group is located at the β-carbon, the reaction energy barrier of step 4, 5, and 6 is increased by 3.11 kcal mol−1, 0.03 kcal mol−1, and 0.45 kcal mol−1, respectively, in vacuum. Fluorine, as the β-C substituent, has a greater effect on the energy barrier, increasing the energy barriers of step 4 by 6.43 kcal mol−1 and reducing the barrier of step 5 by 2.39 kcal mol−1. For the rate-limiting step, an F substituent located at the β-carbon reduces the reaction barrier by only 0.80 kcal mol−1. We know that the rate-limiting step of the reaction plays a decisive role in the reaction. As a whole, for para and β-C substituents, neither the electron-withdrawing nor the electron-donating substituent has much effect on step 6, indicating
Figure 6. The optimized structures and some of the main parameters of the intermediates (IM), transition states (TS) and products (P) in steps 4, 5, and 6 of the difunctionalization of para-substituted styrenes in vacuum. (Substituents marked as superscripts; oxygen: red; nitrogen: blue; carbon: gray; fluorine: cyan; hydrogen: white).
that the difunctionalization reaction has good applicability for substituted styrene derivatives with different substituents at the \( \text{para} \) and \( \beta \)-carbon positions, and thus can be applied to the synthesis of many differently substituted styrene derivatives.

**The effect of different solvents on the difunctionalization reaction**

Methods for controlling chemical reactions have always been a goal in chemistry. The solvent effect is a very important aspect in chemical reactions and is usually used to control the speed and selectivity of a reaction.\(^{42,43}\) Therefore, it is necessary to obtain the theoretical data of a reaction in different solvents so as to guide experiments. To examine the solvent effect on the difunctionalization of substituted styrenes, the reaction processes in DMSO, ethanol, and water as the solvents were examined at the B3LYP/6-31+G(d,p) level with the CPCM (Conductor Polarized Continuum Model) solvent model. For unsubstituted styrene, the energy barriers for the homolysis of TBN in DMSO, ethanol, and water were 47.88 kcal mol\(^{-1}\), 47.86 kcal mol\(^{-1}\), and 47.88 kcal mol\(^{-1}\), respectively (given in Table 1), which were 0.46 kcal mol\(^{-1}\), 0.44 kcal mol\(^{-1}\), and 0.46 kcal mol\(^{-1}\) higher than that in vacuum. The reaction rate constants for the homolysis of TBN are \(3.558 \times 10^{-24}\) s\(^{-1}\), \(3.680 \times 10^{-24}\) s\(^{-1}\), and \(3.558 \times 10^{-24}\) s\(^{-1}\), respectively. In this section, the subsequent value orders given

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**Figure 7.** The optimized structures and some of the main parameters of the intermediates (**IM**), transition states (**TS**) and products (**P**) in steps 4, 5, and 6 of the difunctionalization of \( \beta \)-C substituted styrenes in vacuum. (Substituents marked as superscripts; oxygen: red; nitrogen: blue; carbon: gray; fluorine: cyan; hydrogen: white).
correspond one-to-one to the solvent order with the former in DMSO, the middle in ethanol, and the latter in water. The optimized structures of the reactants, transition states, and intermediates of the first process are similar to the data presented in vacuum. It was found that the presence of a solvent was not conducive to the homolysis of TBN because the energy barriers only changed marginally. Step 2 is still a barrierless process in the solvent (potential energy surface scans are not provided), and their reaction enthalpy changes are 27.35 kcal mol\(^{-1}\), 27.27 kcal mol\(^{-1}\), and 27.36 kcal mol\(^{-1}\), respectively. Subsequently, the generated CF\(_3\)SO\(_2\) radicals were homolyzed to give \(\cdot\text{CF}_3\) and SO\(_2\). The energy barriers for the breakage of the C–S bond are 4.97 kcal mol\(^{-1}\), 4.99 kcal mol\(^{-1}\), and 4.96 kcal mol\(^{-1}\), respectively. The energy barriers in the third step are 0.71 kcal mol\(^{-1}\), 0.69 kcal mol\(^{-1}\), and 0.72 kcal mol\(^{-1}\) lower than that in vacuum. In the solvents, the reaction rate constants are 9.859 \(\times\) 10\(^{10}\) s\(^{-1}\), 9.531 \(\times\) 10\(^{10}\) s\(^{-1}\), and 1.002 \(\times\) 10\(^{10}\) s\(^{-1}\), respectively. The optimized structures of the intermediates, transition states, and products in the second reaction process of the difunctionalization of styrene are very similar, so only the structure diagrams in DMSO are given in Figure 8. By comparing the energy barrier of step 4 in vacuum with those in solvents, we found that the barriers in DMSO and ethanol are 0.75 kcal mol\(^{-1}\) and 0.74 kcal mol\(^{-1}\) lower than that in vacuum. However, in water, the energy barrier increases by 8.80 kcal mol\(^{-1}\). In the presence of solvents, the reaction energy barriers in step 5 are increased by 1.31 kcal mol\(^{-1}\), 1.27 kcal mol\(^{-1}\), and 1.33 kcal mol\(^{-1}\), respectively. The energy barriers of the rate-limiting step (step 6) in the solvents are all 58.36 kcal mol\(^{-1}\) and the rate constants are all 3.771 \(\times\) 10\(^{-31}\) s\(^{-1}\). From the Gibbs free energy change (\(\Delta G_{298K}\)) in Table 1, we can see that the Gibbs free energy changes for all the steps in solvent are decreased, except for those of the first and the second steps.

The solvent effect on the reactions with substituted styrenes as reactants was also examined. Figures 9 and 10 show the optimized structures of the transition states of the substituted styrenes in the second reaction process of the difunctionalization in DMSO as the solvent. In other solvents, the optimized structures of the transition states are very similar to that in DMSO and are not listed here. The energy barriers and reaction rate constants of all the steps in the solvents are listed in Tables 2 and 3. It can be seen that the solvents slightly increase the energy barriers of steps 4 and 6 and decrease that of step 5. This trend did not change with the position and type of substituents on the styrene.

In general, the solvent has little effect on the overall reaction process. Zhao et al.\(^{44}\) found that the solvent also had little effect on the yields of the trifluoromethylselenolation of indole and the trifluoromethylthiolation of 4-aminobenzamide.\(^{45}\) However, in solution, the molecules of the reactants can be dissolved and are in sufficient contact to allow the reactions to proceed smoothly. DMSO has good solubility for most of the organic reactants and it is helpful that the reactants are sufficiently mixed for the reaction to occur. On the contrary, the energy barrier of the final step of the reaction in this study is as high as 57.80 kcal mol\(^{-1}\) and the energy barrier of step 1 is 47.42 kcal mol\(^{-1}\) in vacuum, indicating that this reaction should be carried out at a higher temperature, and the high boiling point of DMSO can provide a higher temperature environment to facilitate this reaction. Therefore, the actual reaction is chosen to be carried out in DMSO as the solvent.\(^{29}\)

**Water-mediated proton transfer in the oximation reaction**

In the final step (step 6), the oxime product was formed via tautomerism of the nitro compound (such as IM(S)), and occurs through hydrogen transfer. According to the homomolecular hydrogen transfer mechanism calculated previously (step 6, the hydrogen transfer from \(\alpha\)-C to O(22) directly to form the final oxime product), it is the rate-limiting step with the highest energy barrier. From the mechanism calculations above, we found that neither substituents nor solvents had a significant effect on this rate-limiting step. However, there are many reports on the severe decrease of the energy barrier by water-facilitated proton transfer. For example, Chuchev and Belbruno\(^{46}\) and Cheng et al.\(^{47}\) reported that water molecules facilitate proton transfer in decarboxylation reactions. Many commonly used organic solvents also contain small amounts of water, which can be used to facilitate proton transfer during the reaction. Thus, we calculated the water-facilitated proton transfer in the tautomerism of the nitro compound. When there is no water in vacuum, the proton is transferred through a C(2)–H(13)–O(22)–N(21) tautomerized (as shown in Figure 5). The energy barrier for this transition state is 57.80 kcal mol\(^{-1}\) in vacuum and it seriously slows down the overall reaction rate. When two water molecules are involved in the proton transfer in water as shown in Figure 11(a), the transition state includes a seven-membered (C(2)–H(13)–O(24)–H(28)–O(26)–H(23)–O(22)) ring. Transfer of H(13) from C(2) to O(24) of the water molecule is accompanied by H(28) of the water molecule approaching O(26), and meanwhile H(23) of the water molecule approaches O(22) of nitric oxide. With the aid of the two water molecules, proton transfer from C(2) to the O(22) of nitric oxide occurs easily. (C(2) gives a proton to water but O(22) obtains a proton from water). Gao et al.\(^{48}\) found that when a water molecule facilitates H transfer from a carboxyl group to the \(\alpha\)-C of a benzene ring, the energy barrier was lowered by 14.2 kcal mol\(^{-1}\).

In this study, the energy barrier of step 6 occurring via proton transfer mediated by two water molecules is 12.98 kcal mol\(^{-1}\) (shown in Figure 11(a)), which is 44.82 kcal mol\(^{-1}\) lower than that in vacuum. In aqueous solvent, the energy barrier of the proton transfer mediated with water in the final step is 45.38 kcal mol\(^{-1}\) lower than that without water (also see Figure 12). It can be seen that the energy barrier was significantly reduced by 77.8% when water was involved in the final step. However, in the actual experimental process, organic solvents are usually used for their better solubility toward organic reactants. The organic solvents used in the actual experimental process basically contain a small amount of water and some organic reagents are mutually soluble with water. Thus, we calculated the
energy barriers of the changes of water-mediated proton transfer in the final step in the organic solvents DMSO and ethanol. In DMSO, the energy barrier decreases from 58.36 kcal mol\(^{-1}\) to 12.98 kcal mol\(^{-1}\) when water molecules participate in proton transfer. In ethanol, the energy barrier is reduced from 58.36 kcal mol\(^{-1}\) to 12.97 kcal mol\(^{-1}\) when water is involved in the proton transfer in step 6. These results show that the energy barrier of the final step was significantly reduced when water was present in the organic solvent, indicating that adding a small amount of water to DMSO with better solubility for the reactants was conducive to the difunctionalization reaction. Langlois et al.\(^{49}\) proved that this conjecture was correct through experiments. Using mixed solvents

**Figure 8.** The optimized structures and of the some main parameters of the intermediates (IM), transition states (TS), and products (P) in steps of 4, 5, and 6 of the difunctionalization of styrene in DMSO (oxygen: red; nitrogen: blue; carbon: gray; fluorine: cyan; hydrogen: white).
Figure 9. The optimized structures and some of the main parameters of the transition states (TS) in steps 4, 5, and 6 of the difunctionalization reaction for para-substituted styrene in DMSO (oxygen: red; nitrogen: blue; carbon: gray; fluorine: cyan; hydrogen: white).
(organic solvents and water), the trifluoromethylation yield with an aromatic compound was 52%, but that of the organic solvent was 29%.

**Conclusion**

In this paper, the free-radical reaction mechanism of the difunctionalization of aryl-substituted ethylenes has been investigated by using the Gaussian09 package at the B3LYP/6-31+(d,p) level in vacuum and the solvent effects of DMSO, ethanol, and water were examined with the CPCM solvent model. It was found that step 2 involving formation of CF₃SO₂⁺(IM₂) from reaction of CF₃SO₂Na with t-BuO⁻ was a barrierless step, which can be carried out easily. The tautomerism of 3,3,3-trifluoro-1-phenylpropan-1-nitric oxide (IM(5)) to the final product, α-trifluoromethyl ketoxime (P) is the rate-limiting step (step 6). Generally, substituents have a significant influence on the structure, stability, and electronic properties of the reactant’s main skeleton, thus changing the reaction results.50–52 However, this work has revealed that the substituents have little effect on the radical difunctionalizations of aryl ethylenes represented by styrene, indicating that this kind of reaction can be applied to the difunctionalization of styrenes with multiple substituents. Based on our calculations, although the solvent effect does not influence the energy barrier of the tautomerism of step 6 significantly, the existence of water changes the reaction.

![Figure 10. The optimized structures and some of the main parameters of the transition states (TS) in steps 4, 5, and 6 of the difunctionalization reaction for β-C substituted styrene in DMSO (oxygen: red; nitrogen: blue; carbon: gray; fluorine: cyan; hydrogen: white).](image-url)
mechanism during step 6 and significantly reduces its energy barrier. The energy barrier of step 6, proton transfer mediated by two water molecules in the solvent (water) is 12.98 kcal mol\(^{-1}\), which is 44.82 kcal mol\(^{-1}\) lower than that in vacuum (i.e. lower by 77.5%). When water participated in the proton transfer in DMSO and ethanol, the energy barrier was also significantly reduced and declined by 77.7% and 77.8%, respectively, indicating that the presence of a small amount of water in the organic solvent was conducive to the reaction. This study is of some significance for the application of difunctionalization reactions for the synthesis of organo fluorine compounds with different substituents.

**Computational methods**

All of the quantum chemistry computations and structure optimizations of the reactants, products, and the transition states are based on the density functional theory (DFT).\(^5\) All the computations were performed with the Gaussian09 package.\(^5\) All molecular geometries including those of the reactants, intermediates, and products in the reactions in vacuum and in solvents (DMSO, ethanol, and water) were

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**Figure 11.** The structural parameters and energy barriers of the transition states (TS) in step 6 with proton transfer mediated by two water molecules in the solvent: (a) water, (b) DMSO, and (c) ethanol (oxygen: red; nitrogen: blue; carbon: gray; fluorine: cyan; hydrogen: white).

**Figure 12.** The potential energy surface for the proton transfer mediated by two water molecules in the solvent (water).
optimized at the B3LYP/6-31+G(d,p) level. The solvent effects were simulated using the CPCM model.\textsuperscript{55} Unrestricted spin calculations were used for all the open-shell systems. The TS and QST\textsubscript{2} methods were used to find the transition states when the structures of the reactant and the product in the reaction were fully optimized. Frequency analyses were conducted to determine whether a given structure is a minimum or a transition state. Calculations of intrinsic reaction coordinates (IRC) were employed to confirm the located transition states, which connect with the expected minima. All initial states, stable intermediates, and final products were confirmed to have only real harmonic frequencies and each transition state was confirmed to have one single imaginary vibrational frequency.\textsuperscript{48} The energy barrier of the reaction was obtained from the energy difference between the transition states and the corresponding reactants. Transition state theory is often used to calculate the chemical reaction rate constants (\(k\))\textsuperscript{56} and in this paper, we calculated the reaction rate constant using the following equation:\textsuperscript{57,58}  
\[
k = \frac{k_b \cdot k_h \cdot T}{h \cdot Q_A} \cdot \frac{Q_{\text{TS}}}{Q_A} \cdot e^{-\frac{\Delta E}{RT\cdot T_{000}}} \tag{1}
\]
\[
k = 1 + \left(\frac{h}{k_b \cdot T \cdot \zeta_{\text{hin}}} \cdot 3 \times 10^{-10}\right)^{2/3} \tag{2}
\]
\[
k = \frac{k_b \cdot k_h \cdot T}{h} \cdot \frac{k_g \cdot T}{P} \cdot \frac{Q_{\text{TS}}}{Q_A} \cdot \frac{Q_B}{Q_A} \cdot e^{-\frac{\Delta E}{RT\cdot T_{000}}} \tag{3}
\]
In the above equation, \(k_b\), \(h\), \(R\), \(P\), and \(T\) are physical constants; \(k_b\) is the Boltzmann constant (1.38 \times 10^{-23} \text{ J K}^{-1}); \(h\) is Planck’s constant (6.63 \times 10^{-34} \text{ J s}); \(R\) is the molar gas constant (8.314 J (mol K)^{-1}); \(P\) is the pressure (bar); \(T\) is the reaction temperature (298 K); \(\sigma\) is the degree of degeneracy of the reaction path (the value is 1 in this study); \(\Delta E\) is the static potential threshold on the minimum energy response path (MEEP); \(Q_A\) and \(Q_B\) are the partition functions of the reactants; and \(Q_{\text{TS}}\) is the partition function for the transition state;\textsuperscript{59} \(\zeta_{\text{hin}}\) is the imaginary frequencies of the transition state. Equation (1) is used to calculate the monomolecular reaction rate. \(k\) is the tunnel effect correction factor, which can be calculated by equation (2). Equation (3) is used to calculate the bimolecular reaction rate. In equation (3), we multiply \(N_A \times 0.001\) when converting \(\text{s}^{-1}\) (molecules cm\textsuperscript{-3})\textsuperscript{-1} to unit \(\text{s}^{-1}\) M\textsuperscript{-1}. \(N_A\) is Avogadro’s constant. All the three-dimensional (3D) molecular structures were prepared using GaussView 5.0.\textsuperscript{60}

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ORCID iD

Yujie Dai https://orcid.org/0000-0002-6484-4478

Supplemental material

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References

1. Gad SC, Anderson B, et al. Philip Wexler 2005, pp. 343–346.
2. Berger R, Resnati G, Metrangolo P, et al. Cheminform 2011; 40: 3496–3508.
3. Montserrat R-B, Olivier M, Myriam D, et al. J Am Chem Soc 2014; 136: 2637–2641.
4. Wang ZG and Hammond GB. J Org Chem 2000; 65: 6547–6552.
5. Okamura K. J Syn Org Chem Jpn 2010; 16: 446–453.
6. Liu G, Hu J and Unemoto T. 2017; 1: 35.
7. Denis A, Breitn F, Fromentin C, et al. Bioorg Med Chem Lett 2000; 10: 2019–2022.
8. Peng W and Zhu S. Synlett 2003; 34: 4395–4404.
9. Li M, Wang Y, Xue XS, et al. Asian J Org Chem 2017; 6: 235–240.
10. Qing S. PhD Thesis, Clemson University, Clemson, SC, 2017.
11. Ogawa Y, Tokunaga E, Kobayashi O, et al. iScience 2020; 23: 101467.
12. Inoue M, Sumii Y and Shibata N. ACS Omega 2020; 5: 10633–10640.
13. Lagu SB, Vejella RP, Bhandare RR, et al. Pharmaceuticals 2020; 13: 375.
14. Kang H, Zhou B, Li M, et al. Chinese J Chem 2020; 38: 130–134.
15. Xue XS, Zhang J, Yang JD, et al. Angew Chem Int Ed 2018; 57: 12690–12695.
16. Sera Y, Adachi K, Fujii K, et al. J Nat Prod 2003; 66: 719–721.
17. Duan XJ, Li XM and Wang BG. J Nat Prod 2018; 81: 130–134.
18. Bergstr MA, Andersson SI, Broo K, et al. J Med Chem 2003; 46: 3922–3925.
19. Qu H, Huang R, Yao G, et al. J Med Chem 2007; 50: 5004–5011.
20. Yang SH and Chang S. Org Lett 2001; 3: 4209–4211.
21. Dong X, Kita Y and Oestreich M. Angew Chem Int Ed 2018; 57: 10728–10731.
22. Wan PH, Iosub AV and Stahl SS. J Am Chem Soc 2014; 136: 13664–13667.
23. Yamaguchi K, Fujiwara H, Ogasawara Y, et al. Asian J Org Chem 2017; 6: 235–240.
24. Sukhorukov AY and Ioffe SL. Chem Rev 2011; 42: 5004–5041.
25. Knifton JF. *J Org Chem* 1973; 38: 3296–3301.
26. Zeynizadeh B and Karimkoshteh M. *J Nanostructure Chem* 2013; 3: 57.
27. Ji Y, Liu Y, Song R, et al. *Adv Synth Catal* 2016; 358: 2286–2292.
28. Chen F, Zhou NN, Zhan JL, et al. *Org Chem Front* 2016; 4: 135–139.
29. Lu K, Wei X, Li Q, et al. *Org Chem Front* 2019; 6: 3766–3770.
30. Zhang X and Nau WM. *J Phys Org Chem* 2000; 13: 634–639.
31. Ferene R. *J Mol Struct: THEOCHEM* 2002; 617: 31–45.
32. Rajalakshmi R, Palaniappanand AN and Srinivasan S. *Spectrochim Acta A* 2014; 117: 186–190.
33. Shen X, Huajun HE, Yang B, et al. *Chem Res Chin Univ* 2017; 33: 773–778.
34. Shiraz NZ, Sharifzadeh ES and Koosha N. *Acta Chim Slov* 2013; 60: 166–173.
35. Tercan M, Zdemir N, Ozdemir FA, et al. *J Mol Struct* 2020; 1209: 127980.
36. Zhao X, Wei X, Tian M, et al. *Tetrahedron Lett* 2019; 60: 1796–1799.
37. Zhao X, Zheng X, Tian M, et al. *Org Chem Front* 2018; 5: 2636–2640.
38. Chuchev K and Belbruno JJ. *J Mol Struct: THEOCHEM* 2007; 807: 1–9.
39. Cheng X, Wang J, Ke T, et al. *Chem Phys Lett* 2010; 496: 36–41.
40. Gao L, Hu Y, Zhang H, et al. *J Mol Struct* 2016; 1116: 56–61.
41. Langlois BR, Laurent E and Roidot N. *Tetrahedron Lett* 1991; 32: 7525–7528.
42. Abedini N and Kassaee MZ. *Silicon Neth* 2022; 14: 2089–2095.
43. Jagadeeshwar NM, Khanapurmath NI, Chougala LS, et al. *J Fluorese* 2021; 31: 1–11.
44. Siino G, Crespi S and Bonesi SM. *Photochem Photobiol* 2021; 97: 1298–1309.
45. Becke ADP. *Phys Rev A* 1988; 38: 3098–3100.
46. Firsch A, Nielsen AB and Holder AL. Pittsburgh, PA: Gaussian Inc., 2000.
47. Marenic AV, Cramer CJ and Truhlar DG. *J Phys Chem B* 2009; 113: 6378–6396.
48. Miller WH. *J Chem Phys* 1974; 61: 1823–1834.
49. Canneaux S, Bohr F and Henon E. *J Comput Chem* 2013; 35: 82–93.
50. Miransky VA and Shovkovy IA. *Phys Rep* 2015; 576: 1–209.
51. Liu YP, Lu DH, Gonzalez Lafont A, et al. *J Am Chem Soc* 1993; 115: 7806–7817.
52. Dennington R, Keith T and Millam J. *GaussView 5.0*. Wallingford, CT: Gaussian Inc., 2008.