

# Synthesis of $\alpha$ -Fluoroketones from Vinyl Azides and Mechanism Interrogation

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# **Supporting Information**

**ABSTRACT:** An efficient and mild fluorination of vinyl azides for the synthesis of  $\alpha$ -fluoroketones is described. The mechanistic studies indicated that a single-electron transfer (SET) and a subsequent fluorine atom transfer process could be involved in the reaction.



F luorine atoms prevail in pharmaceuticals, agrochemicals, and materials due to their unique biological, chemical, and physical properties.<sup>1</sup> Moreover, radiotracers labeled with <sup>18</sup>F are extensively used as positron emission tomography (PET) agents.<sup>2</sup> As a result, the development of new methods for efficient, selective, and mild incorporation of a fluorine atom into diverse molecules has received significant attention in organic synthesis. In particular, the emergence of bench-stable, safe, and easily accessible fluorinating reagents, such as 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) (Selectfluor), N-fluorobenzenesulfonimide (NFSI), 1-fluoropyridiniums, etc., has substantially advanced the progress of  $\hat{C}$ -F bond formation.<sup>1-3</sup>  $\alpha$ -Fluoroketones are versatile building blocks for the synthesis of a wide variety of fluorine-containing compounds.<sup>4</sup> Generally, ketones,<sup>5</sup> phenylethylenes,<sup>6</sup> and phenylacetylenes<sup>7</sup> were used as feedstocks for the preparation of  $\alpha$ -fluoroketones. However, despite significant advances, these methodologies generally remain limited due to complicated procedures, harsh reaction conditions, limited substrate scope, and/or the requirement of expensive noble metals.

Vinyl azides,<sup>8</sup> a class of unique functionalized alkenes with high intrinsic reactivity, have served as versatile synthons for numerous transformations.<sup>9</sup> As an enamine-type nucleophile, vinyl azide was readily subjected to the electrophile to generate an iminodiazonium ion **A**, followed by Schmidt-type rearrangement to form nitrilium ion **B**, which could be intercepted by water to yield the amide (Scheme 1).<sup>10</sup> Very recently, alcohols successfully interrupted the migration to produce  $\alpha$ -alkoxy- $\beta$ haloalkyl azides (Scheme 1).<sup>11</sup> We were drawn to the possibility that replacing alcohol with water could provide an approach to synthesis of  $\alpha$ -fluoroketones.

Although the traditional electrophilic addition process has been extensively accepted as the mechanism for these transformations of vinyl azides (Scheme 1),<sup>10,11</sup> we could not exclude the possibility that a charge transfer<sup>12</sup> between an electron donor (vinyl azide) and an electron acceptor (Selectfluor) took place in the reaction. Accordingly, the

# Scheme 1. Reactions of Vinyl Azides



association of an electron-rich substrate with an electrondeficient reagent to form an aggregate was referred to as an electron donor-acceptor (EDA) complex.<sup>13</sup> Herein, we report an efficient and mild method for the synthesis of various  $\alpha$ fluoroketones from the corresponding vinyl azides using Selectfluor as fluorine source as well as investigations on the fluorinating mechanism (Scheme 1).

We began our investigation on the reaction of the substrate **1a** with Selectfluor using acetonitrile as the solvent. To our delight, we observed the desired  $\alpha$ -fluoroketone **2a** in 12% yield (Table 1, entry 1). As might be expected, we identified that the use of an inorganic base (e.g., NaHCO<sub>3</sub>) and water was essential for the desired product formation in satisfactory yield. The screening of organic solvents showed acetonitrile was the best choice in terms of chemical yield and reaction time (entries 2–7). We next examined the influence of water in this fluorine incorporation protocol. The results showed that 2

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# Table 1. Optimization of Reaction Conditions<sup>a</sup>



<sup>a</sup>**1a** (0.20 mmol), Selectfluor (0.30 mmol), base (0.40 mmol),  $H_2O$  (0.40 mmol), and solvent (2 mL). <sup>b</sup>Isolated yield. <sup>c</sup>Cosolvent CH<sub>3</sub>CN/H<sub>2</sub>O (2:1). <sup>d</sup>NFSI (0.30 mmol). <sup>e</sup>2,4,6-Trimethyl-N-fluoropyridinium (0.30 mmol).

equiv of water gave the highest chemical yield and employing an excess amount of water diminished the reaction yields (entries 8-10). Furthermore, replacing NaHCO<sub>3</sub> with other base or Selectfluor with other fluorinating reagent did not improve the chemical yield (entries 11-13 and 14, 15).

First, to gain more insight about the mechanism of this reaction, a series of control experiments was conducted (Scheme 2, eqs 1-4). In the presence of radical scavenger TEMPO, no fluorine-containing products were obtained, but the TEMPO adducts 3a and 3b were found in the reaction mixture. To rule out the possibility that TEMPO could be involved in the initiation step, the reaction of 1a without Selectfluor was carried out. As might be expected, TEMPO only acted as the radical scavenger (Scheme 2, eqs 1 and 2). On the other hand, when the reaction of 1a was conducted under standard conditions in the presence of radical scavenger 1,1diphenylethene, we did not find any adduct products except 2a (Scheme 2, eq 3). To exclude the influence of natural light, we also conducted the reaction of 1a under the standard reaction conditions in the dark. The reaction proceeded smoothly to afford the desired  $\alpha$ -fluoroketone 2a in 85% yield (Scheme 2, eq 4). To provide further evidence, (Z)-4-(1-azido-2-cyclopropylvinyl)-1,1'-biphenyl (1z) was prepared as a radical probe.<sup>14</sup> However, the reaction of 1z only gave  $\alpha$ -fluoroketone 2z in 80% yield, without the formation of ring-opening product (Scheme 2, eq 5).

In order to confirm the fact that the oxygen of  $\alpha$ -fluoroketones was from H<sub>2</sub>O, an isotopic-labeling experiment using H<sub>2</sub>O<sup>18</sup> was performed (Scheme 3, eqs 1 and 2). As expected, the results indicated that water could catch the iminodiazonium ion D before migration (Schemes 1, 3, and 4). In addition, because of the generation of H<sub>2</sub>O from the reaction of the released HN<sub>3</sub> with NaHCO<sub>3</sub>, we also detected 23% of the <sup>16</sup>O product under the standard reaction conditions (Scheme 3, eq 1).









Scheme 3. Further Experiments



Having established above optimal reaction conditions, we aimed to define the scope of this new C-F bond forming protocol. As shown in Figure 1, a series of differentially substituted  $\alpha$ -fluoroketones were readily obtained in moderate to good yields. Although we found that o-bromide (2k) was provided only in 41% yield accompanied by  $\alpha$ -fluoroamide as the competitive product<sup>15</sup> probably due to steric hindrance, this protocol could accommodate a wide range of substituents on arenes regardless of their electronic properties (2a-m). For example, both the electron-rich p-methoxyl group (2f) and the electron-deficient *p*-nitro group (2h) gave the corresponding products in good yields. It is of note that vinyl azides containing alkynyl (2n) or alkenyl (2o) groups were compatible with the reaction conditions, providing the desired products in useful yields. This protocol could also be extended to nonterminal vinyl azides (2p-r), including cyclic substrate (2p), quickly generating the desired  $\alpha$ -fluoroketones in high yields (less than 10 min). Not only aryl but alkyl substrates could be subject to

# Scheme 4. Proposed Mechanism



Figure 1. Scope of vinyl azides.

the fluorination, furnishing the corresponding  $\alpha$ -fluoroketones in satisfactory yields (2s-y). Moreover, the chemical yields were not compromised when a series of functionalized groups were installed (2s-x vs 2y). In particular, in the examples of 2tand 2u, the formyl group and the benzyl alcohol unit were not affected in the process of fluorination.

On the basis of the above results, we can deduce that direct electrophilic fluorination of vinyl azide<sup>10</sup> is disfavored in this case. Thus, a plausible radical mechanism for this fluorine-incorporated reaction is proposed in Scheme 4. The initial step involves a single-electron transfer (SET) process,<sup>11,12</sup> converting the vinyl azide 1 into the radical cation C. The subsequent step is a fluorine atom transfer to generate the intermediate D, followed by a reaction with H<sub>2</sub>O to give the intermediate E, which undergoes an elimination of HN<sub>3</sub> to furnish  $\alpha$ -fluoroketone **2**.

In conclusion, we have developed a transition-metal-free and efficient protocol for the synthesis of  $\alpha$ -fluoroketones from vinyl azides under mild reaction conditions. The mechanistic studies indicated that a fluorine atom transfer process could be involved. This protocol, in the presence of commercially available Selectfluor, readily provided a variety of desired products in moderate to good yields. Moreover, this transformation showed excellent functional group tolerance and demonstrated its potential for further applications in medicinal and agrochemical research. Further applications of radical cation of vinyl azides in organic synthesis are ongoing in our group.

## ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.6b01691.

Experimental details, characterization data, and <sup>1</sup>H, <sup>19</sup>F, and <sup>13</sup>C NMR spectra for all compounds (PDF)

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# Notes

The authors declare no competing financial interest.

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