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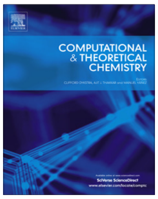

Persulfate-promoted benzylic mono- and difluorination: A mechanistic study

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ABSTRACT

A systematic investigation has been conducted into the mechanism for the persulfate-promoted benzylic mono- and difluorination with Selectfluor by using density functional theory (DFT). In the monofluorination, the role of $SO_4^{\cdot-}$ (from the substrate-assisted cleavage of $S_2O_8^{2-}$ in the initiation phase) is just to trigger fluorination by producing the initial benzyl radical. The cationic *N*-radical from the fluorine transfer between the benzyl radical and Selectfluor can abstract hydrogen from the substrate, generating the benzyl radical to complete the reaction cycle. The difluorination contains the monofluorination and the second fluorine transfer. The benzylic C—H activation in the monofluorination product can be achieved by cationic *N*-radical or $SO_4^{\cdot-}$. Whether in monofluorination or in difluorination, the rate-determining step is the generation of $SO_4^{\cdot-}$.

1. Introduction

Fluoromethylated arenes (e.g. mono- and difluoromethylation) are broadly applicable in the syntheses of pharmaceuticals and agrochemicals because the difluoromethyl group (CF_2H) is isosteric with the hydroxy group and it can act as a lipophilic hydrogen bond donor [1]. At the same time, compounds with a monofluoromethyl group (CFH_2) are very important with regard to the isostere-based drug design [2–4]. A lot of effort has been focused on the introduction of fluoromethyl group (CF_2H or CFH_2) onto arenes and some valuable methods have been successfully developed [5–7], containing functional group transformation, direct benzylic C—H fluorination and so on. Undoubtedly, the benzylic C—H fluorination is the best way to synthesize fluoromethylarenes without pre-functionalization. In this respect, significant progress has been made, including transition-metal-catalyzed benzylic C—H activation and transition-metal-free C—H oxidative activation via radical reaction. For example, silver/persulfate-catalyzed benzylic C—H activation /difluorination has been developed by Tang's group (Scheme 1a) [8]. Groves' group has presented a Mn/PhIO-catalyzed method for the direct transformation of benzylic C—H bond into C—F bond (Scheme 1b) [9]. As for the transition-metal-free benzylic C—H fluorination, Inoue et al. have reported the fluorination of benzylic C—H bond employing NDHPI/Selectfluor system (Scheme 1c) [10]. Chen's group has developed a photolytic method for direct benzylic C—H fluorination, in which the selectivity of mono- and difluorination products can be realized by catalyst control (Scheme 1d) [11].

Recently, Yi's group has reported persulfate-promoted benzylic C—H mono- and difluorination (Scheme 1e) [12], in which the amount of persulfate and Selectfluor can determine the selectivity of mono- and difluorination products. Interestingly, a comparison between Yi's and Tang's work (Scheme 1a vs. e) contributes to the discovery that persulfate can advance the benzylic C—H fluorination without the aid of silver. In Yi's design (Scheme 2), the benzylic C—H is activated by the hydrogen abstraction between the substrate and $SO_4^{\cdot-}$, which is derived from the homolytic cleavage of $S_2O_8^{2-}$. The resultant benzyl radical **A** abstracts a fluorine atom from Selectfluor to provide the monofluorination product. In addition, difluoromethylated arenes could be generated according to an analogous procedure through a fluorinated benzylic radical **C**.

Although a preliminary mechanism has been provided (Scheme 2) by Yi's group, some specific details of the reaction remain to be clarified. For example, the proposed active intermediates in Scheme 2, such as $SO_4^{\cdot-}$, benzyl radical **A**, **C**, cationic *N*-radical **B** (from Selectfluor) and so on, have not been directly captured and characterized so far due to the lag of modern analytical techniques. Especially the role of cationic *N*-radical **B** has not been clear, which may be relevant to the experimental fact that when Selectfluor is replaced by *N*-fluorobenzenesulfonimide (NFSI), only trace product is found. In addition, the reason why Ag(I) doesn't significantly improve the reaction remains largely

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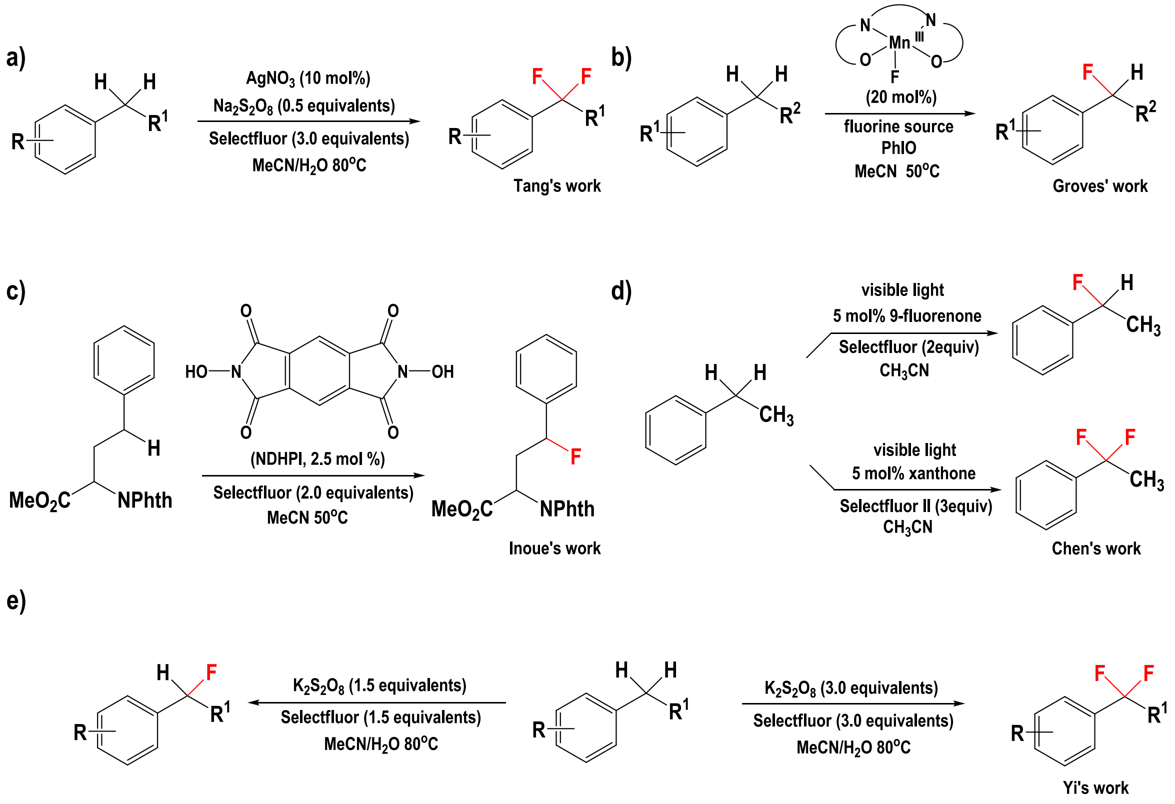
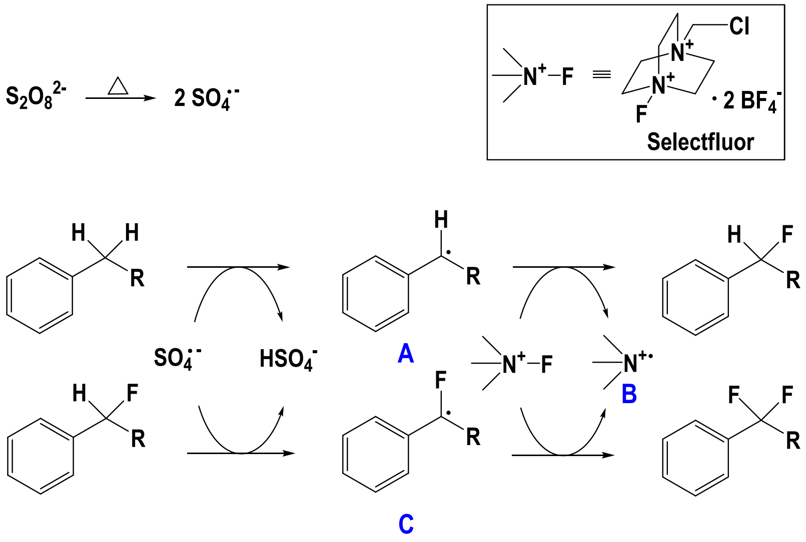


Scheme 1. Representative reports about the benzylic C—H activation/fluorination.



Scheme 2. Proposed mechanism for the persulfate-promoted benzylic C—H mono- and difluorination reported by Yi's group.

unknown. Generally, Ag(I) can catalyze the dissociation of $S_2O_8^{2-}$ to give $SO_4^{\cdot-}$ on the basis of literature [13,14].

To explain these problems, evidently we need to have a comprehensive understanding of the reaction mechanism for the persulfate-promoted benzylic C—H fluorination (Scheme 1e). Quantum-chemical calculations of the potential energy surface (PES) of the target reaction by density functional theory (DFT), provides an effective means to study the reaction mechanism [15–17]. The mechanisms of Ag(I)-catalyzed decarboxylative fluorination of aliphatic carboxylic acids and aminofluorination of unactivated alkenes have been studied by using DFT in our group [18,19]. As a continuation of the theoretical research work on the radical fluorination, here we shall carry out a systematic theoretical investigation into the mechanism of the persulfate-promoted benzylic C—H bond activation/fluorination. The goal of the work is to explore the nature of the reactivity and to explain the above-mentioned problems.

2. Computational methods

All calculations were carried out with the Gaussian 09 software [20]. Geometry optimizations and frequency analysis were