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Mechanism of Silver-Mediated Geminal Difluorination of Styrenes with a Fluoroiodane Reagent: Insights into Lewis-Acid-Activation Model

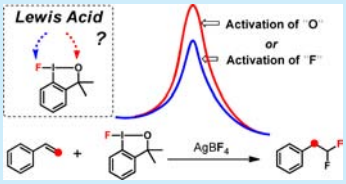
Biying Zhou,[†] Taishan Yan,[†] Xiao-Song Xue,*[,†,‡] and Jin-Pei Cheng[†,‡,§]

[†]State Key Laboratory of Elemento-Organic Chemistry and [‡]Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Tianjin 300071, China

[§]Center of Basic Molecular Science, Department of Chemistry, Tsinghua University, Beijing 100084, China

Supporting Information

ABSTRACT: Fluorination mediated by the cyclic hypervalent fluoroiodane reagent (**1**) often requires an exogenous Lewis acid. The widely accepted Lewis-acid-activation model is that a given Lewis acid binds to the oxygen atom of **1** (O-coordination) to polarize the I−O bond. Computational studies of silver-mediated geminal difluorination of styrenes with **1** reveal a new "F-coordination" model that is energetically much preferred over the commonly accepted "O-coordination" model. The calculations rationalize the regioselective formation of the geminal difluorination product.

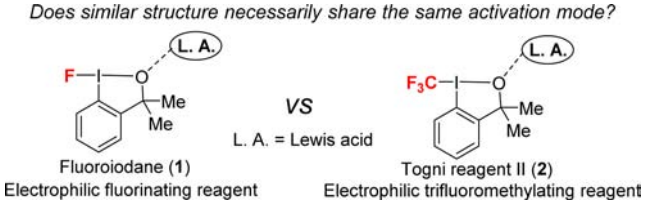


The growing appreciation of the unique physical and chemical properties of organofluorine compounds has led to their increasingly broad application in medicines,[1] agrochemicals,[2] functional materials,[3] and many other areas of research.[4] As is known, however, only a handful of organofluorine compounds occur in nature,[5] and almost all target fluorinated molecules have to be manmade. Consequently, the development of practical and efficient methods for selective introduction of fluorine and fluorine-containing groups into organic molecules for biologically active and other useful materials has become one of the hottest areas of organic chemistry.[6]

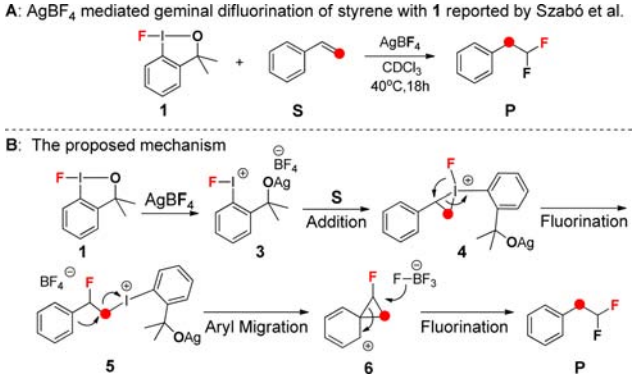
Very recently, development of novel fluorination reactions by use of hypervalent iodine reagents has attracted growing attention.[7] In particular, the air- and moisture-stable cyclic hypervalent fluoroiodane reagent (**1**: Scheme 1),[8] a structural analogue of the famous Togni reagent II (**2**),[9] is garnering an ever-increasing research interest because of its completely new reactivity and ease of handling.[10] Similar to Togni reagents,[9b] fluorination mediated by fluoroiodane **1** typically requires activation by an exogenous Lewis acid,[7c,d] and the widely accepted Lewis-acid-activation model for reagent **1** is that a given Lewis acid binds to the oxygen atom of **1** to polarize the I−O bond to facilitate the fluorine transfer (Scheme 1).[7c,d] However, in contrast with extensive mechanistic studies on Togni reagents,[9b,11] the activation model for hypervalent fluoroiodane reagent **1** has so far escaped experimental or computational scrutiny. Moreover, although fluoroiodane **1** has emerged as one of the privileged efficient and versatile fluorinating reagents,[7c−g] it has remained poorly understood with respect to the fluorination mechanism. A better understanding of its working activation model and the mechanism of its fluorine transfer would, for certain, greatly facilitate the development of practical strategies in exploring new applications of this reagent.

In 2014, Szabó et al. demonstrated that fluoroiodane **1**, in the presence of $AgBF_4$, was suitable for selective geminal difluorination of styrenes to obtain a variety of products bearing CHF_2 unit (Scheme 2A),[10a] a group that combines the properties

Scheme 1. Widely Accepted Lewis-Acid-Activation Model for Fluoroiodane and Togni Reagent II



Scheme 2. Silver-Mediated Geminal Difluorination of Styrene with Reagent 1 and the Proposed Mechanism by Szabó et al.



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of fluorine with specific steric and electronic features that are important for fine-tuning the biological properties of drug molecules.[12,13] Although this reaction is a landmark discovery in the hypervalent fluoroiodane reagent mediated fluorinations, the detailed mechanism is not fully understood. Clearly, crucial to the development of new reactions based on fluoroiodane reagent **1** should be a thorough understanding of its activation model and fluorination mechanism. To this end, as part of our continued interest in understanding the reactivities and mechanisms of fluorinating and fluoroalkylating reagents,[14] we present herein the first computational study on the detailed mechanism of silver-mediated geminal difluorination of styrene with fluoroiodane reagent **1**. We uncover a new Lewis-acid-activation model that is energetically much favored over the generally accepted model for this reagent.

For the convenience of calculation, $AgBF_4$-mediated geminal difluorination of styrene with fluoroiodane reagent **1** was chosen as the model reaction (Scheme 2A).[10a] Geometry optimizations and frequency calculations were carried out in solution phase with the M06 functional[15,16] and the LANL2DZ[17] pseudopotential for I and Ag and the 6-31+G(d) basis set for all other atoms. The SMD model[18] was used to account for the solvation effects of chloroform. Single-point energy calculations were performed at the M06/6-311++G(d, p)+SDD(I, Ag)[19]-SMD-($CHCl_3$), B3LYP-D3(BJ)[20]/6-311++G(d, p)+SDD(I, Ag)-SMD($CHCl_3$), and MN12L[21]/6-311++G(d, p)+aug-cc-PVDZ-pp(I, Ag)[22]-SMD($CHCl_3$) levels with the optimized structures, and the same trends were observed for all methods (see Figures S1 and S2). The Gibbs free energies obtained at the M06/6-311++G(d, p)+SDD(I, Ag)-SMD($CHCl_3$)//M06/6-31+G(d)+LANL2DZ(I, Ag)-SMD($CHCl_3$) method are presented in the main text. All of the calculations were performed using Gaussian 09[23] and the structures were generated by CYLview.[24]

Inspired by the activation of Togni reagents by Lewis acids,[9b] Szabó et al. proposed a complex addition/fluorination/1,2-aryl migration/fluorination four-step mechanism for the titled reaction (Scheme 2B). In the first step, the $AgBF_4$ coordinates to the oxygen atom of **1** (O-coordination) to form activation complex **3**, which undergoes an electrophilic addition to the alkene in styrene to give the cyclic iodonium intermediate **4**. The calculation predicted that the formation of activation complex **3** from $AgBF_4$ and fluoroiodane **1** through Ag−O interaction is exoergic by 3.9 kcal mol^{-1} (Figure 1). Unexpectedly, the attack of the activated fluoroiodane **1** by the olefinic double bond via "O-coordination" transition state **TS1** requires a relatively high activation energy barrier of 30.2 kcal mol^{-1} (Figure 1), which is inconsistent with mild reaction conditions.[9b] We thus turned to an alternative pathway for the formation of the cyclic iodonium intermediate **4**. Both Mulliken and natural population analysis of reagent **1** showed that the F and O atoms are rich in negative charges (Figure 1 top right corner), indicating that, in addition to the O atom, the F atom can be an alternative activation site. Indeed, the activation complex **3′** formed through Ag−F interaction (F-coordination) displays a similar stability to **3** (3.0 vs 3.9 kcal mol^{-1}, Figure 1). Most importantly, the activation free energy barrier for the addition step via "F-coordination" transition state **TS1′** is now significantly reduced: **TS1′** is 9.3 kcal mol^{-1} more stable than **TS1**, meaning that the F atom of reagent **1** is the preferred activation site for the addition step. This may be a result of a more efficient polarization of the I−F bond when the activator $AgBF_4$ directly binds to the F atom, as indicated by a longer I−F bond in **TS1′** than in **TS1** (2.543 vs 2.310 Å, Figure 1). Similar results were obtained for other substituted styrenes

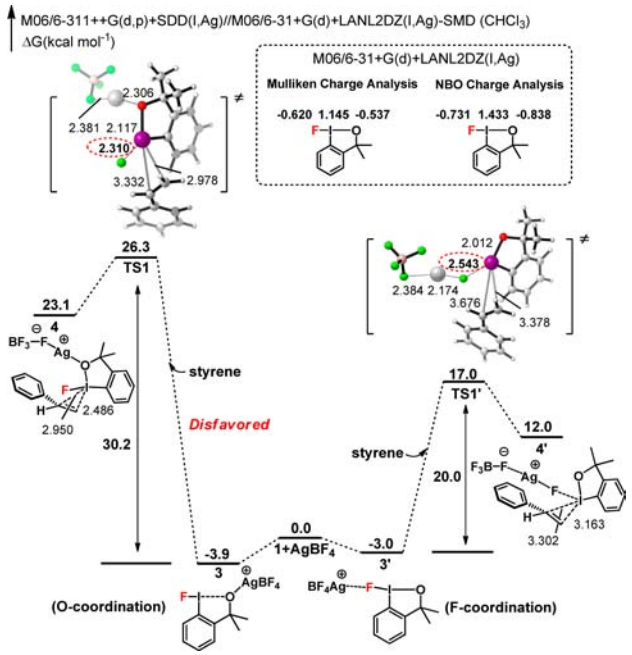
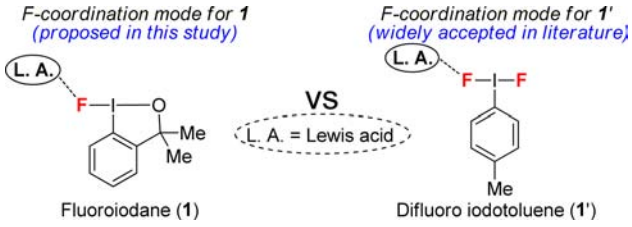


Figure 1. Calculated potential energy profile for silver-mediated addition of the fluoroiodane to the double bond of styrene.

(Figure S3), meaning that the conclusion drawn here is not substrate dependent. This result has an important implication for future reaction developments: the widely accepted Lewis-acid-activation model for Togni reagent **II** should not be directly transposed to fluoroiodane reagent **1**, despite the similarity in structure. It is worth emphasizing that the F atom acting as the activation site is not uncommon for Brönsted acids and Lewis acids activation of difluoro iodotoluene **1′**, the linear analogue of **1** (Scheme 3).[7a,25]

Scheme 3. F-Coordination Mode for 1 and Its Linear Analogue 1′



Having established that the F-coordination pathway is the preferred pathway, we next explored the detailed reaction mechanism to understand the origin of regioselective formation of the geminal difluorination product. Accordingly to the proposed mechanism (Scheme 2), the formation of the cyclic iodonium intermediate **4** is followed by an intramolecular 1,2-fluoro shift (fluorination) to give intermediate **5**. As shown in Figure 2, the Ag-assisted fluoro shift via **TS2** (yielding intermediate **5′** instead of **5**) is a kinetically feasible process with a barrier of 9.2 kcal mol^{-1} relative to intermediate **4′**. Intermediate **5′** would rapidly evolve to a more stable intermediate **5** due to the favorable Ag−O interaction. Subsequent displacement of the iodobenzene by nucleophilic attack of the aromatic ring (1,2-aryl migration) requires an activation free energy of 26.4 kcal mol^{-1} (Figure. 2). It should be noted that the displacement requires a very high barrier in the

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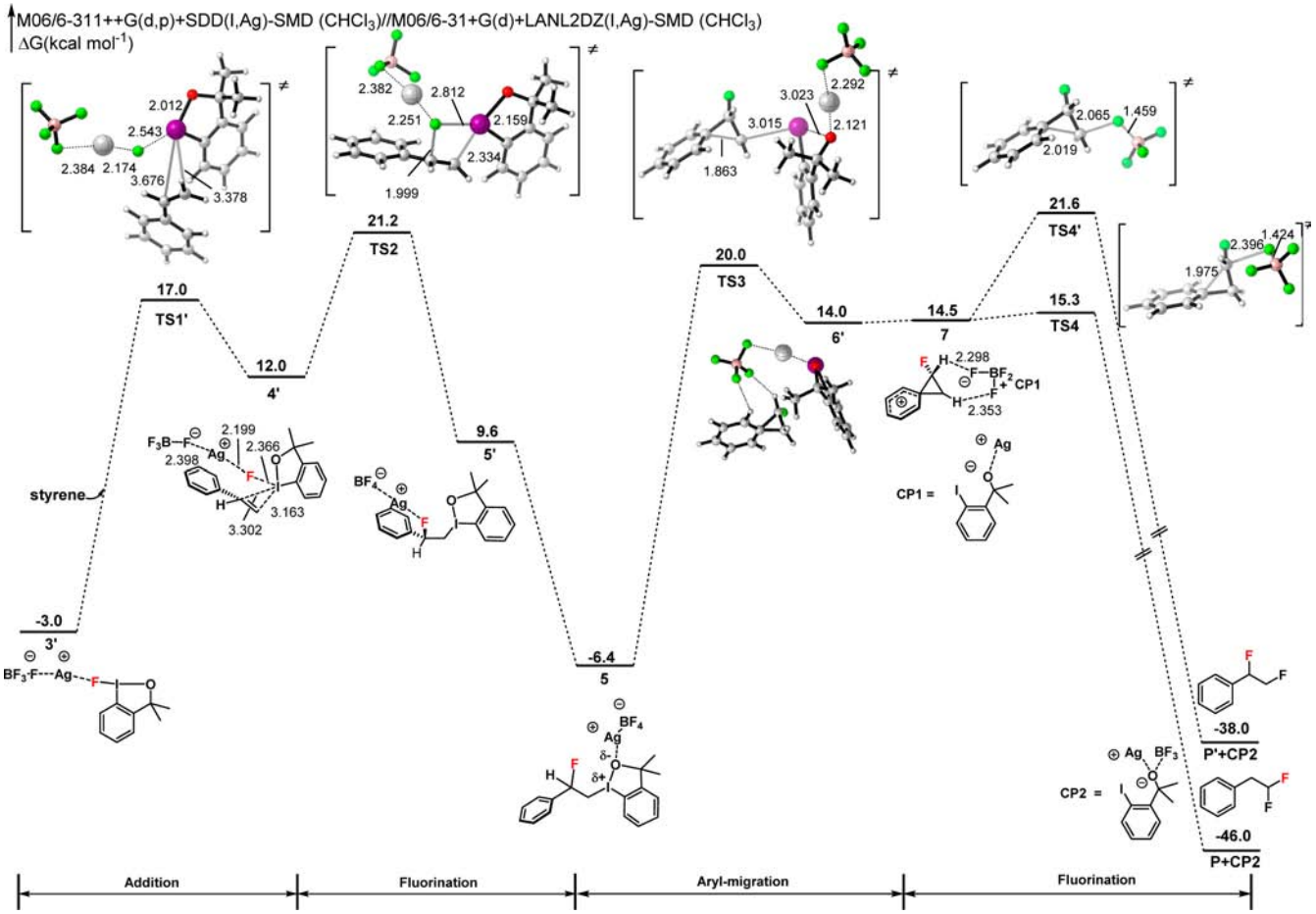

Figure 2. Calculated potential energy profile for $AgBF_4$-mediated germinal difluorination reaction with the fluoroiodane **1**.

absence of $AgBF_4$ (Figure S4), indicating a significant enhancement of the nucleofugality of the iodoarene moiety by $AgBF_4$. Finally, the phenonium ion undergoes a second fluorination at the F-bearing carbon atom by a nucleophilic fluorine arising from the unexpected but not unusual BF_4^- anion,[26] affording the germinal difluorination product **P** (Scheme 2). In principle, the nucleophilic attack of BF_4^- can occur at either the fluorinated carbon or the unsubstituted methylene of cyclopropyl. It can be seen from Figure 2 that attacking at the F-bearing carbon atom (**TS4**) is preferred over at the unsubstituted carbon (**TS4′**) by 6.3 kcal mol^{-1}, thus explaining experimental observation that only geminal difluorination products **P** were obtained in these transformations.

Reviewing the computed energy profile of the overall reaction pathway, the 1,2-aryl migration is the rate-limiting step, with an activation free energy of 26.4 kcal mol^{-1} in chloroform. The identification of aryl migration being the rate-limiting step would open up exciting possibilities for developing asymmetric version of this kind of transformation. Indeed, most recently, Jacobsen et al. have developed a highly enantioselective conversion of styrenes to versatile chiral building blocks containing difluoromethyl groups based on stereospecific aryl migration process.[27]

In summary, as the hypervalent fluoroiodane reagent is a structural analogue of the Togni reagent **II**, the well-established "O-coordination" Lewis acid-activation model for the latter has been generally postulated for the former in literature. Indeed, the Lewis acid $AgBF_4$ coordination to the oxygen atom is preferred over coordination to the fluorine atom of the fluoroiodane reagent in the ground state. However, the "F-coordination" transition state is energetically much favored over the "O-coordination" transition state for the first electrophilic attacking step. Therefore, the Lewis-acid-activation model for Togni reagent **II** should not be directly transposed to the fluoroiodane reagent, despite the similarity in structure. The results presented herein are expected to have broad mechanistic implications for other Lewis acid-mediated fluorinations employing the fluoroiodane reagent and would facilitate the development of new strategies involving this reagent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03134.

Figures S1−S4 and optimized geometries of all computed species (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xuexs@nankai.edu.cn.

ORCID

Xiao-Song Xue: 0000-0003-4541-8702

Notes

The authors declare no competing financial interest.

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