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Electrophilic aromatic substitution of electron-rich arenes with *N*-fluorobenzenesulfonimide (NFSI) as an electrophile†

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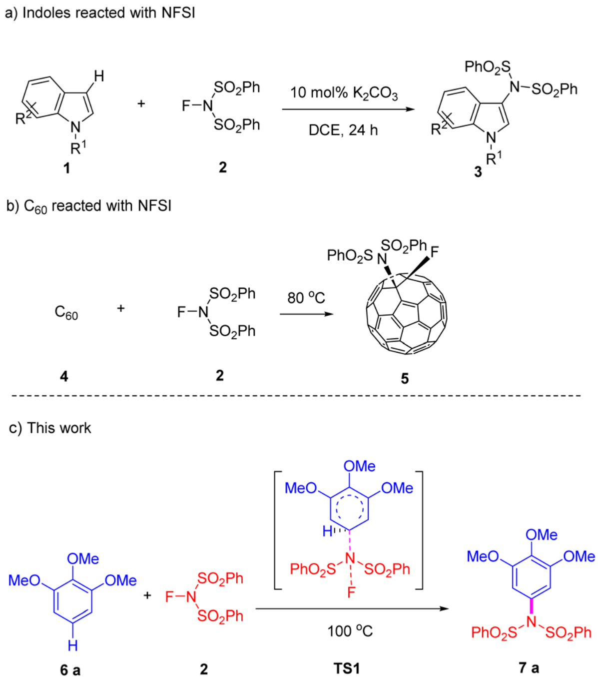
An efficient amidation of electron-rich arenes using NFSI as a nitrogen source has been successfully disclosed. This amidation process can be easily conducted at elevated temperatures, without the need for catalysts or additives. A wide range of arenes substituted with hydroxy, alkoxy, or carbonyl groups were found to be compatible, yielding the desired amination products. Computational study shows that the amidation proceeds *via* an electrophilic aromatic substitution pathway, comprising a three-step process that includes substitution, addition, and elimination, which differs slightly from the classical mechanism.

Introduction

N-Fluorobenzenesulfonimide (NFSI)[1–4] is a readily available, stable, and highly soluble crystalline powder that is widely utilized as a fluorinating reagent[5–14] or oxidant in organic reactions.[15–29] Additionally, NFSI has proven to be an efficient source of nitrogen for the C–H bond amidation of aromatic, heteroaromatic, benzyl, allyl, and aldehyde groups.[30–36] In the amidation reactions, NFSI acts as a source of nitrogen radicals[37] or as a nucleophilic nitrogen in various metal-catalyzed transformations of aromatic and aliphatic compounds.[38–67] In this context, we describe a different type of amidation reaction in which NFSI serves as a source of electrophilic nitrogen, while the arene functions as a nucleophile.

Several research groups have reported the regioselective amidation reactions of indoles, pyrroles, quinolones, and imidazoheterocycles, which were mediated solely by a base or the hypervalent iodine reagents under mild conditions without using any metallic catalyst or oxidant.[68–71] These groups hypothesized that the amidation reaction likely proceeds *via* a free radical mechanism (Scheme 1a).[70] Additionally, it has been documented that the fluorinating reagent NFSI can be added to C_{60}, yielding adduct 5 with over 90% efficiency on a large scale, again without the necessity for a metal catalyst or base. A concerted (2 + 2) cycloaddition mechanism has been proposed for the formation of this adduct (Scheme 1b).[72]

Following the established literature procedures for metal-free amidation of heterocycles, we initially treated electron-rich arenes with NFSI. We were pleased to find that the mixture of 1,2,3-trimethoxybenzene (TMB) and NFSI could efficiently yield product **7a** under elevated temperature conditions, without the need for any catalyst or additive (Scheme 1c). Furthermore, through density functional theory (DFT) calculations, we proposed a three-step mechanism characterized by the



Scheme 1 Reactions of arenes with NFSI without the need for catalysts.

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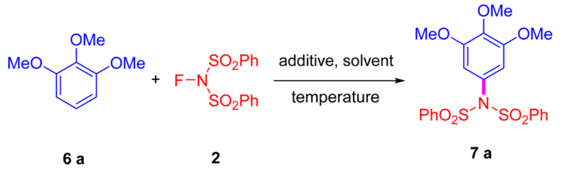
formation of adduct intermediates, which differs slightly from the classic electrophilic aromatic substitution mechanism.[73]

Our investigations started with the reaction between TMB and NFSI in various solvents at their respective refluxing temperatures. Unfortunately, only a poor yield of the desired product was isolated in dichloromethane after an extended reaction time. Even worse, only traces of product **7a** were detected when the reaction was conducted in diethyl ether, which has a lower boiling point; a significant amount of starting material remained in the reaction mixture (Table 1, entries 1 and 2). Using high boiling point solvents, moderate yields of the desired product have been obtained (entries 3 and 4). Through detailed investigation, we believed that the reaction temperature plays a crucial role in the progression of the reaction. A nearly quantitative yield of the desired product was obtained when the reaction mixture was refluxed in DCE (entry 7). Conversely, minimal amounts of the desired product were produced when the reaction temperature was lowered down to 40 °C, with a substantial quantity of starting materials remaining (entry 5). The quantity of NFSI has also been assessed. Notably, some TMB remained when an equivalent amount of NFSI was used in this reaction, and a significantly larger excess of NFSI did not enhance the yield (entries 8 and 9). Notably, an excellent yield of the desired product was also achieved when the reaction mixture was stirred at its melting temperature without any solvent (entry 10). Consequently, we began to explore the role of solvents in this reaction, discovering that it could be effectively performed in various solvents, particularly in water (entries 11 and 12).

Table 1 Conditions optimization[a]

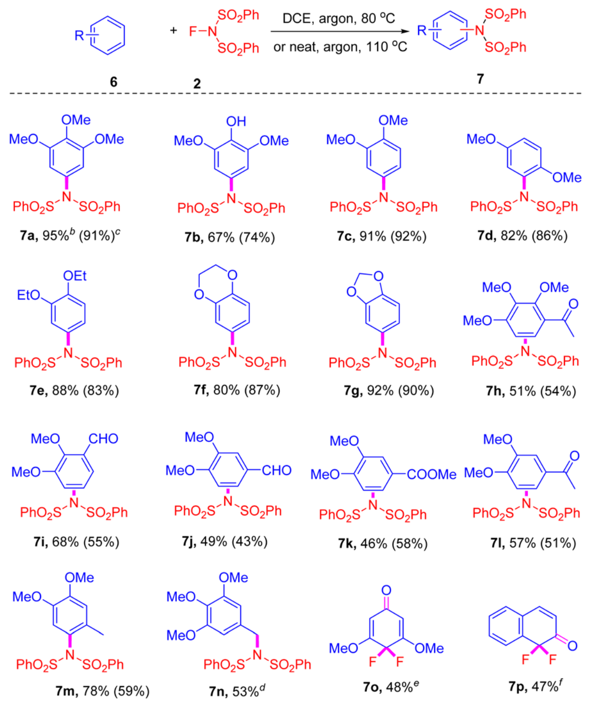


Entry	Solvent	Additive	Temp [°C]	Yield[b] [%]
1	Et_2O	—	35	<5
2	CH_2Cl_2	—	40	<10
3	CCl_4	—	75	79
4	Toluene	—	110	62
5	DCE	—	40	<10
6	DCE	—	60	18
7	DCE	—	80	>95
8	DCE	—	80	68[c]
9	DCE	—	80	92[d]
10	Neat	—	110	91
11	MeOH	—	65	<5
12	H_2O	—	100	31
13	DCE	TEMPO	80	68
14	Neat	TEMPO	110	64

[a] Reaction condition: **6a** (1.0 mmol), **2** (2.0 mmol), additives (1.0 mmol) in solvent (5 mL) under argon. [b] Isolated yield of **7a**. [c] NFSI was used in 1.0 equivalent. [d] NFSI was used in 3.0 equivalent.

Inspired by these results, we hypothesized that the formation of the desired product resembles an electrophilic aromatic substitution process rather than a radical mechanism,[74–77] despite NFSI generally undergoing homolysis at elevated temperatures.[78–81] To test our hypothesis, the radical scavenger TEMPO was selected.[82] Upon the addition of an equivalent of TEMPO, we observed no significant change in the reaction outcome, with only a slight decrease in yield compared to the original reaction, regardless of whether the reaction was conducted in a solvent or in neat conditions (Table 1, entries 13 and 14).

To demonstrate the generality and efficiency of this method, a diverse array of electron-rich arenes was screened (Scheme 2). Benzenes bearing two or more alkyloxy groups proved to be suitable substrates for this transformation, yielding the desired products in good to excellent yields (**7a–m**). Notably, these amidation reactions proceeded smoothly in both DEC and neat conditions, regioselectively furnishing the final product as a single isomer. Moreover, the presence of phenolic hydroxyl (**7b**) and carbonyl groups (**7h–l**) was fully tolerated in this transformation, particularly the aldehyde substituent, which is an exceptionally reactive functional group in substitution reactions (**7i** and **7j**). Other substituted benzenes were also examined; however, no reaction occurred with anisole or trimethylbenzene, and a complex mixture was obtained with aniline or naphthylamine. Interestingly, the reaction of 1,2,3-trimethoxy-5-methylbenzene with NFSI yielded a different type



Scheme 2 Scope of reaction between NFSI and electron-rich arenes. [a] Reaction conditions: **6** (1.0 mmol) and **2** (2.0 mmol) in DCE (5 mL) or in neat under argon atmosphere. [b] Isolated yields in DCE. [c] Isolated yields in neat. [d] Using 1,2,3-trimethoxy-5-methylbenzene as substrate. [e] Using 1,3,5-trimethoxybenzene as substrate. [f] Using 2-methoxy naphthalene as substrate.

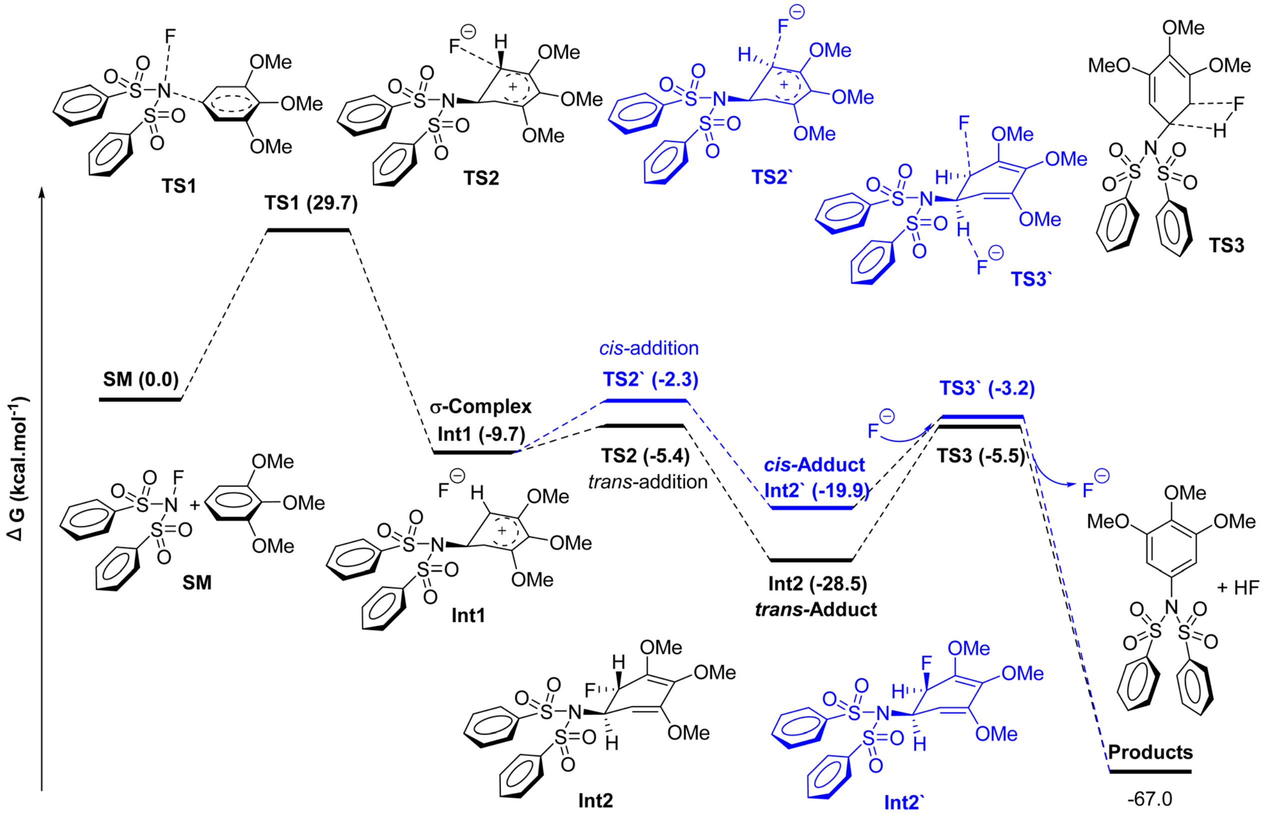
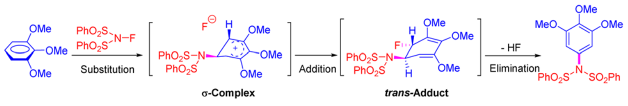


Fig. 1 Free energy profile for the amidation reaction at the wb97xd/6-311++ level of theory.

of amidated product (**7n**) as the major product. Conversely, 1,3,5-trimethoxybenzene (**7o**) and 2-methoxy naphthalene (**7p**) predominantly produced fluorinated compounds, with no amidation products detected.

Electrophilic aromatic substitution is a hallmark reaction in synthetic organic chemistry, typically understood as a two-step mechanism involving the formation of a σ-complex followed by the elimination of a small molecule.[83] Through a combination of computational and experimental investigations, we propose an alternative three-step mechanism characterized by substitution, addition, and elimination (Scheme 3).

Geometry optimizations and frequency calculations of all presented structures were performed at the wB97XD/6-311G** level of theory,[84] and the complete mechanism is illustrated in Fig. 1. TMB initially attacks the nitrogen atom of NFSI, resulting in the σ-complex (**Int1**) *via* **TS1**. This step presents an energy barrier of 29.7 kcal mol^{-1}, which can be regarded as the rate-determining step. Notably, the existence of **TS1** was further corroborated by Intrinsic Reaction Coordinate (IRC) calculations, confirming that the first-order saddle points identified represent genuine transition states connecting the starting materials and the σ-complex.



Scheme 3 Proposed mechanism for the amidation of TMB.

In light of the addition product of NFSI with C60, we propose that the resulting σ-complex does not undergo an elimination reaction directly but rather proceeds through an addition reaction.[72,85] Furthermore, extensive calculations indicate that this process occurs as a competition between *cis*- and *trans*-addition pathways. The fluorine anion of the σ-complex preferentially adds from the side opposite the nitrogen atom, resulting in the formation of the *trans*-adduct (**Int2**). This pathway requires overcoming a modest energy barrier of 4.3 kcal mol^{-1}. Conversely, the fluorine anion may also engage in a *cis*-addition reaction, yielding the *cis*-adduct. However, the energy barrier for the *cis*-addition (**Int2′**) is 7.4 kcal mol^{-1} higher than that for the *trans*-addition. Thus, based on these findings, we can conclude that the reaction proceeds through the kinetically favored *trans*-adduction pathway that leads to the corresponding *trans*-adduct.

The loss of aromaticity in both adducts leads to their immediate elimination. In the case of the *trans*-adduct, fluorine departs in conjunction with the adjacent hydrogen, resulting in the formation of the desired product, **7a**, which requires an energy input of 23.0 kcal mol^{-1}. Similarly, the *cis*-adduct undergoes elimination facilitated by another fluorine anion, yielding the same product.

Conclusions

In summary, we have developed a practical transition metal-free, regioselective amidation of electron-rich arenes using

NFSI as the commercially available amino source. This procedure can be conducted in both solvents and neat conditions, and it does not require any external oxidants or additives. The amidation process is compatible with a wide range of functional groups, including hydroxy, alkoxy, and carbonyl groups. DFT calculations support a three-step electrophilic aromatic substitution mechanism for this amidation reaction, wherein the σ-complex is formed first, followed by the production of two adduct isomers, and ultimately yielding the desired product through an elimination reaction. The formation of the σ-complex has been identified as the rate-determining step.

Data availability

The authors confirm that the data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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