

Aminofluorination: Transition-metal-free N–F Bond Insertion into Diazocarbonyl Compounds

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Abstract

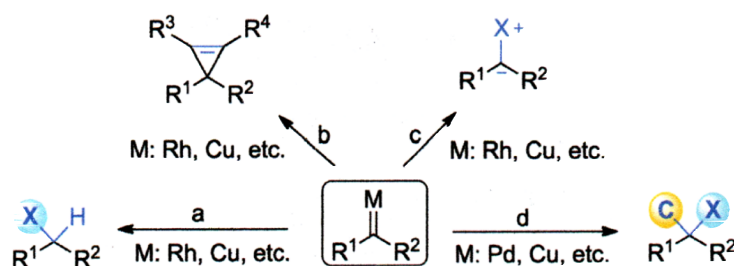
Gem-aminofluorination of diazocarbonyl compounds has been achieved for the first time. This reaction proceeds under mild conditions and does not require any transition-metal promoter or catalyst. Treatment of diazoesters with N-fluorobenzenesulfonimide (NFSI), which serves as both a fluorine and nitrogen source, results in the facile construction of C–N and C–F bonds, providing aminofluorination products in moderate to excellent yields. Kinetic studies and DFT calculations have provided valuable insight into the potential mechanism for this novel N–F bond insertion.

Keywords: Diazoacetate, Carbenoid Intermediates, Difunctionalization, Carbene, Aminofluorination, Bronsed Acids, Benzenesulfonimide

Introduction

Diazoacetate derivatives play an important role in the synthetic community. Over the past century, significant advances have been made towards the generation of carbenoid intermediates triggered by transition-metals. The resulting reactive species can undergo valuable transformations, such as threemembered ring (cyclopropane, cyclopropene) formation, X–H bond insertion (X = C, N, O, S, etc.) and ylide generation (Scheme 1a-c) ¹. van Vranken, Barluenga, Many others have developed palladium- or copper-catalysed multiple component reactions of diazo compounds, which allow the installation of two separated functional moieties on the carbenic carbon via a single operation (Scheme 1d) ². Despite these important advances, the direct introduction of two functional groups to the same carbon center, namely gem-difunctionalization of donor/acceptor (D/A) carbenes, is still far from well developed ^{3,4}. It is of note that these processes at least involve one C–C bond formation⁵. Thus the studies on the gem difunctionalization of D/A carbenes, which involves two distinct carbon heteroatom bond formations, would greatly enhance the synthetic applications of diazo compounds.

Scheme 1: Representative Reaction Modes of a Transition-metal Carbenoid

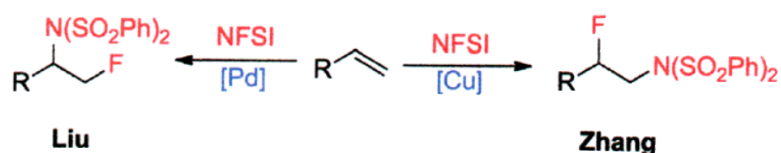


Single substitution of hydrogen with fluorine may alter the chemical and physical properties of a potential drug candidate by blocking undesired metabolism at a specific site ⁶. In contrast to the

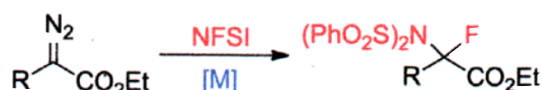
relatively large number of reports on the catalytic insertion of N–H bonds to α -diazocarbonyl compounds⁷, a simple yet appealing concept for the transition-metal catalysed N–F bond insertion has not been realized thus far. N-Fluorobenzenesulfonimide (NFSI) is inexpensive and shelf stable, and is often employed as a mild electrophilic fluorinating or aminating reagent^{8,9}. It has been demonstrated that NFSI could serve as both an amino and fluorine source for the transition-metal-catalysed amino-fluorination of alkenes (Scheme 2a). Inspired by these seminal works, we envisioned that NFSI might be an ideal candidate for the transition-metal catalysed N–F bond insertion into D/A carbenes (Scheme 2b). Although procedures for the amination^{7,12} or fluorination^{13,14} of diazo compounds are known, to my knowledge, direct amino-fluorination of diazo compounds remains unexplored. Herein, I present my primary results on gem-aminofluorination of diazocarbonyl compounds under mild conditions. Kinetic studies and DFT calculations shed light on the mechanism of the current N–F bond insertion.

Scheme 2: Aminofluorination Catalysed by Transition-metals

(a) Aminofluorination of alkenes with NFSI



(b) Our initial design (M = Cu, Pd, etc.):

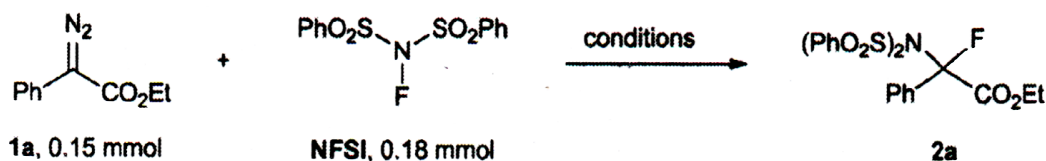


Results and Discussion

Optimization Studies and Substrate Scope

I initiated my studies using the reaction of ethyl diazophenyl acetate **1a**¹⁵ with NFSI using CuBr as a precatalyst and bathocuproine (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline; BC) as a ligand¹¹. Gratifyingly, in the presence of 5 mol% CuBr and 6 mol% BC, ethyl diazophenyl acetate **1a** was completely consumed after stirring in a reaction medium of 1,2 dichloroethane (DCE) at 60°C for 21 h, and the desired product **2a** was obtained in a 79% NMR yield (Table 1, entry 1). To my surprise, the reaction proceeded equally well in the absence of both CuBr and BC, giving **2a** in 89% yield (Table 1, entry 2). The reaction could complete in a comparably short time when the reaction was carried out at an elevated temperature (Table 1, entries 2–4 vs. entry 5). A brief examination of the solvent effects revealed that DCE was still the best choice (Table 1, entries 6–14). Notably, the reaction can also be performed in water, giving **2a** in a moderate yield, which indicates an environmentally benign perspective (Table 1, entry 15). Due to the similar polarity between **2a** and NFSI, a slight excess of **1a** (1.5 eq.) was necessary to make sure that NFSI reached full conversion. In this case, **2a** was isolated in a nearly quantitative yield (Table 1, entry 16).

Table 1: Optimization of the Reaction Conditions



Entry ^a	Solvent	Temp (°C)	Time (h)	Yield ^b (%)
1 ^c	DCE	60	21	79
2	DCE	60	21	89
3	DCE	80	7	7
4	DCE	100	4	73
5	DCE	RT	24	17
6	CH ₂ Cl ₂	60	24	81
7	ChCl ₃	60	24	70
8	Toluene	60	24	58
9	MeCN	60	24	69
10	THF	60	24	47
11	Dioxane	60	24	22
12	DMF	60	24	0
13	MeOH	60	24	0
14	H ₂ O	60	12	62
15 ^d	DCE	60	24	82
16 ^e	DCE	60	48	97 ^f

^a All reactions were carried out under an atmosphere of argon in 0.15 mmol scale, [1a] = 0.10 M, [NFSI] $\frac{1}{4}$ 0.12 M.

^b Yields were determined by ¹⁹F NMR, using 1-bromo-4-fluorobenzene as the internal standard.

^c In the presence of 5 mol% CuCl and 6 mol% BC.

^d Under air.

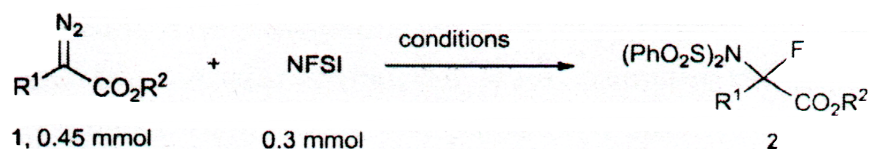
^e The reaction was carried out in 0.3 mmol scale, [1a] = 0.15 M, [NFSI] = 0.10 M.

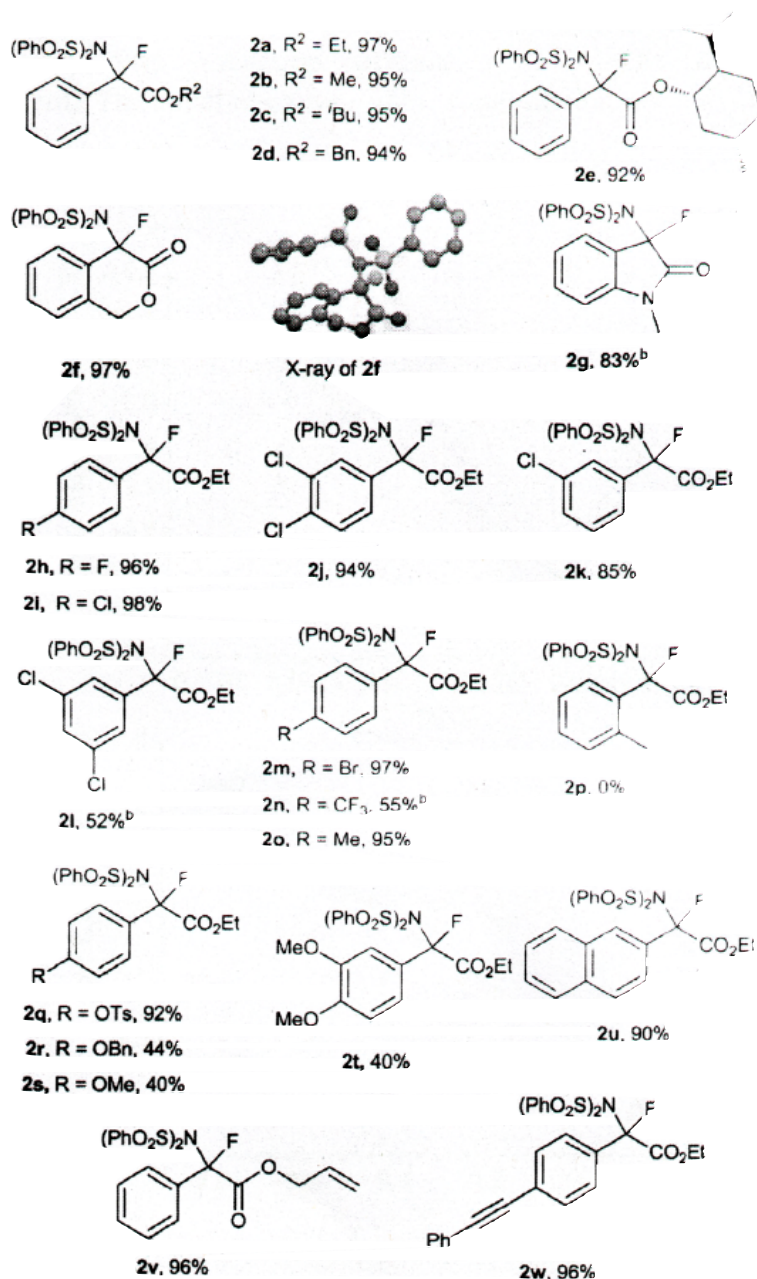
^f Isolated yield.

With the optimized reaction conditions in hand (Table 1, entry 16), the generality and limitations of this metal-free N–F bond insertion were investigated. The results are summarized in Table 2. Most of the α -diazoacetates reacted with NFSI smoothly to give the corresponding products in moderate to excellent yields. When changing the ester group (R²) from methyl to isobutyl, or benzyl, no significant decrease of the product yields was observed (Table 2, 2a–d). When the diazo compound contained a chiral auxiliary, an ester derived from (+)-menthol, a pair of diastereoisomers 2e were obtained in a ratio of 1:1. Interestingly, diazo compounds derived from cyclic esters and amides were proven to be viable substrates. N–F bond insertion of 1f and 1g gave the corresponding products 2f and 2g in 97% and 83% yields, respectively. The structure of 2f was confirmed by X-ray crystallographic analysis ¹⁶. The effects of substituents on the phenyl ring were also examined. Both electron-withdrawing and electron-donating

groups on the aromatic ring of 1 were tolerated under the reaction conditions. The reaction of diazo acetates bearing mild electron-withdrawing or electron-donating groups (fluoro, chloro, bromo and methyl) at the para position of the phenyl ring gave the corresponding products in excellent yields (Table 2, 2h, 2i, 2m and 2o). Incorporation of one chloro group to the meta position had no obvious impact on the yields of the products (Table 2, 2i and 2k). Interestingly, the yield of 2l bearing two meta chloro substituents was decreased to 52%. While the diazo acetate bearing an ortho substituted group was not compatible to the current conditions (Table 2 and 2p), probably due to the steric hindrance effect. Similarly, strong electron-donating or -withdrawing substituents on the aromatic ring were amenable for the current amino fluorination, albeit giving moderate yields (Table 2, 2n, 2r-t). Of note, vinyl and alkyl moieties remained intact (Table 2, 2v and 2w), indicating that the involvement of a free carbene intermediate is less likely (vide infra). Notably, the reaction could be scaled up to gram scale without sacrificing the yield of 2a (5 mmol scale, 2.39 g 2a was obtained with a 97% yield). It is worthwhile to mention that the current conditions are not applicable to alkyl or heteroaryl acetate derived diazo compounds¹⁷.

Table 2: Geminal Aminofluorination of Various Diazocompoundsa





^a All reactions were carried out in 0.30 mmol scale under argon at 60° C, [1a] = 0.15 M, [NFSI] = 0.10 M, isolated yield.

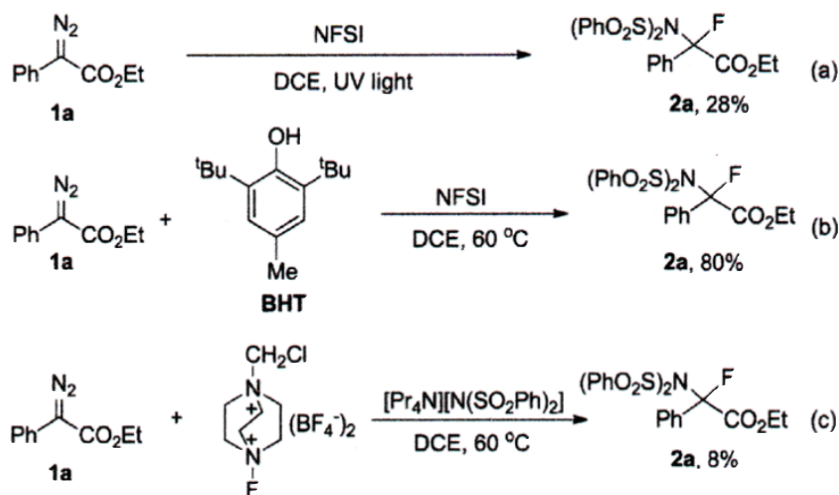
^b Reaction was carried out at 80° C.

Mechanistic Studies

Having uncovered an efficient method for N–F bond insertion, I sought to gain more insight into the reaction mechanism. Thus a series of additional experiments were subsequently carried out. Performing the reaction under irradiation by UV light, 2a was obtained in a much lower yield (Scheme 3a). Furthermore, evolution of N₂ was significantly slow in the absence of NFSI under otherwise identical conditions (Figure S1†). These experiments also suggest that a pathway via a free carbene intermediate is unfavourable. Addition of the radical scavenger 2,6-di-tert-butyl-4-methylphenol (BHT) had no obvious influence on the reaction efficiency (Scheme 3b), which indicates that a mechanism that involves free radical species is also less likely. Additionally, considering the diazo carbon atom is mildly nucleophilic and might be trapped by the electrophilic fluorine atom, a subsequent displacement of

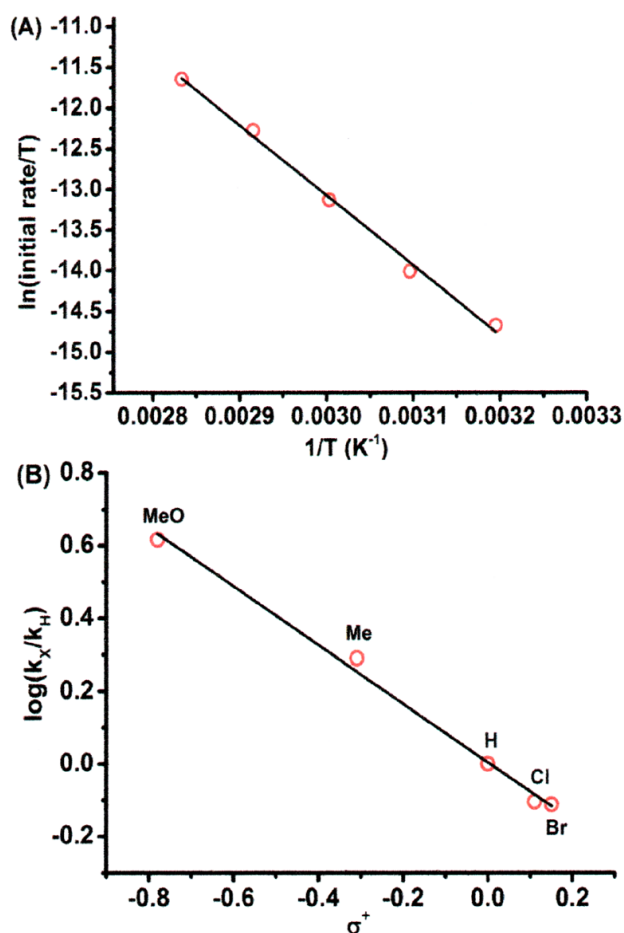
dinitrogen by the imide moiety of NFSI would give 2a. With this consideration in mind, the following control experiment was carried out immediately. The combination of selectfluor, a reactive electrophilic fluorinating reagent, with tetrapropyl ammonium benzenesulfonimide did afford 2a in 8% yield (Scheme 3c).

Scheme 3: Preliminary Mechanistic Studies



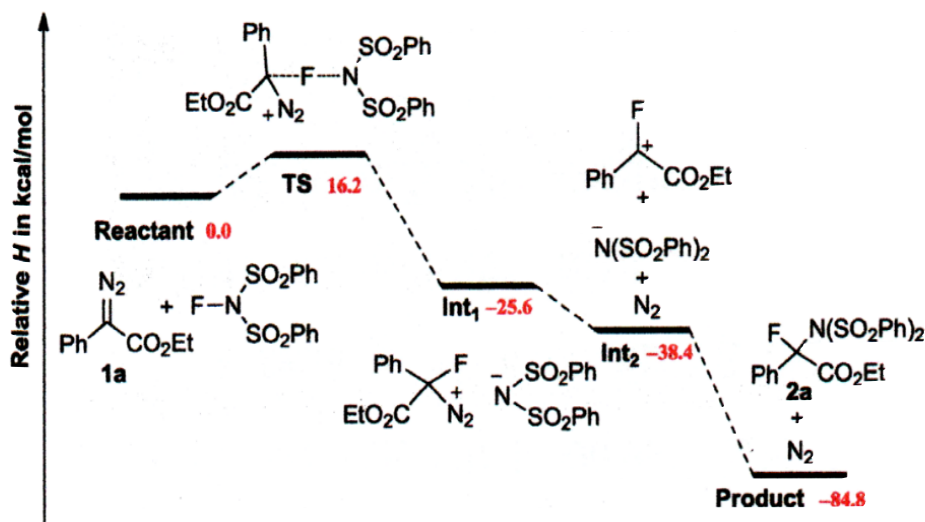
Kinetic studies for the reaction of 1a with NFSI were further performed to get a deeper understanding of the reaction mechanism. The reaction was found to be first-order in both 1a and NFSI (Figures S2–S5[†]). The activation parameters $\text{DH}^\ddagger = 17.1 \text{ kcal mol}^{-1}$ and $\text{DS}^\ddagger = -13.0 \text{ cal mol}^{-1} \text{ K}^{-1}$ were obtained from Eyring plots by varying the temperature from 313 to 353 K (Figure 1A, top). The negative DS^\ddagger value may suggest the generation of a bimolecular transition state involving NFSI and 1a. Similar kinetic behaviours were observed for the reactions of various para-substituted diazo phenyl acetates 1 with NFSI. A fairly linear Hammett correlation between $\log(k_X/k_H)$ and σ^+ was obtained with a reaction constant of $\rho = -0.81$ (Figure 1B, bottom). The small negative ρ value suggests that the transition state is weakly polarized with a positive charge at the reaction center.^{18, 1.}

Figure 1



- Figure 1 (A) (top) Plot of $\ln(\text{initial rate}/T)$ vs. $1/T$ for the reaction between 1a and NFSI in DCE, $[1a] = 0.15$ M, $[NFSI] = 0.1$ M, slope = -8.61×10^3 , y-intercept = 1.27×10 , $r^2 = 0.996$.
- Figure 1 (B) (bottom) Hammett plot of $\log(k_X/k_H)$ vs. σ^+ for the reaction of NFSI with para substituted diazo phenyl acetates 1 in DCE at 50° C, $[1] = 0.15$ M, $[NFSI] = 0.1$ M, slope = -0.81 , y-intercept = 0.4×10^{-2} , $r^2 = 0.995$

Scheme 4: Mechanistic Rationale Supported by DFT Calculations



DFT calculations were carried out to provide more details on the potential mechanism (Scheme 4) ²⁰. The reaction of 1a with NFSI encounters an activation enthalpy of 16.2 kcal mol⁻¹ with a slight loss of entropy ($DS^\ddagger = -9.0 \text{ cal mol}^{-1} \text{ K}^{-1}$), which matches well with the experimental values (vide supra). According to the downhill energy profile, the following steps are rather facile. The weakly polarized TS further collapses to an ion pair Int1 with an energy change of -41.8 kcal mol⁻¹. Releasing N₂ from Int1 has been proven to be an exothermic process. Finally, an S_N1 like reaction takes place to give 2a, with a total enthalpy change of -84.8 kcal mol⁻¹. It is of note, that the formation of a procarbonium ion through the reaction of diazo carbon with Cl⁺, Br⁺ and I⁺ has been reported recently ²¹. However, in our case, the replacement of NFSI by NXS (X = Cl, Br, I) results in no formation of the aminohalogenated product. It is well known that diazo compounds are not stable in the presence of a strong acid. Indeed, addition of strong Brønsted acids (CCl₃CO₂H or CF₃CO₂H) led to the rapid decomposition of 1a. However, the addition of acetic acid had no influence on the current N–F bond insertion ^{22, 23}.

Conclusions

In conclusion, I have developed an unprecedented N–F bond insertion into diazocarbonyl compounds. The current method represents a facile approach to construct C–N and C–F bonds on the same carbon without any transition-metal as a catalyst or promoter. Mechanistic studies, including kinetic experiments and DFT calculations, revealed that a reaction sequence of electrophilic activation of 1 by NFSI, followed by an S_N1 like displacement of dinitrogen by benzenesulfonimide is preferred. Further study on the asymmetric variant as well as the difunctionalization of the metal carbene is ongoing in our laboratory study.

Acknowledgements

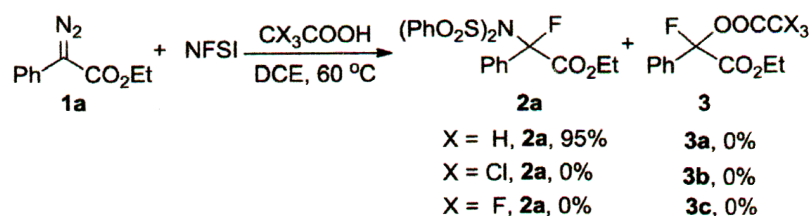
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