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The Effect of the Leaving Group in *N*-Heterocyclic Carbene-Catalyzed Nucleophilic Aromatic Substitution Reactions

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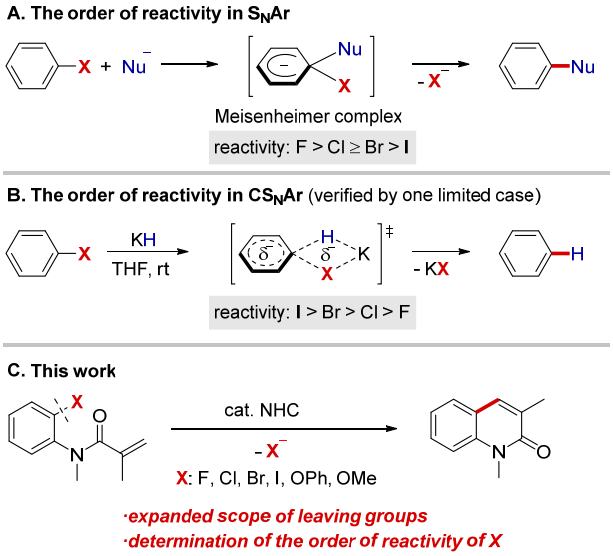
Abstract

We report here that the reactivity order of the leaving group is F > Cl ≥ Br > I in *N*-heterocyclic carbene-catalyzed CS$_N$Ar reactions of aryl halides bearing an α,β-unsaturated amide. Based on a qualitative Marcus analysis, the nature of the transition state in this catalytic CS$_N$Ar is primarily determined by the potential energy of the Meisenheimer complex, even though it is not involved as a discrete intermediate in the reaction pathway.

Keywords: *N*-heterocyclic carbene, Nucleophilic catalysis, Concerted nucleophilic aromatic substitution

1. Introduction

The nature of the leaving group is one of the key factors in determining various aspects of substitution reactions, encompassing rates, stereospecificity, substrate scope and various other outcomes. Therefore, establishing the order of reactivity of leaving groups for a given substitution reaction is of paramount importance, not only from the preparative perspective, but also from a fundamental viewpoint, in particular, for clarifying the mechanism for the reaction.[1] Nucleophilic aromatic substitution[2] represents one of the reaction categories that highlights the significant influence of a leaving group on the reaction mechanism. The conventionally accepted mechanism for nucleophilic aromatic substitution reactions involves the attack of a nucleophile to the *ipso* carbon of a leaving group to form an anionic intermediate, which is referred to as a Meisenheimer complex,[3] followed by the elimination of the leaving group (S$_N$Ar mechanism, Scheme 1A). In this mechanistic manifold, the order of reactivity of the leaving groups is F > Cl ≥ Br > I.[4,5,6] In contrast, the reverse order of reactivity (I > Br > Cl > F) was observed as early as 1980 by Pierre in the reduction of a series of aryl halides using KH, which implies the existence of an alternative mechanism that is distinct from a typical S$_N$Ar involving a Meisenheimer complex.[7] Recent theoretical studies revealed that the nucleophilic aromatic substitution by KH in THF proceeds in a concerted manner, in which an attack of a nucleophile and the dissociation of a leaving group occur simultaneously (CS$_N$Ar mechanism, Scheme 1B).[8] Although the origin of this reverse order of reactivity of halogen leaving groups remains unclear, one possible explanation is that C–X bond cleavage is involved in the rate-determining step under this mechanistic scenario, and therefore a weaker C–X bond would be expected to react more rapidly.[9] Since the seminal work by Ritter,[10-12] several new nucleophilic aromatic substitution reactions that proceed via a concerted mechanism have been reported.[13] Moreover, Jacobsen, based on DFT calculations, proposed that classical nucleophilic aromatic substitution reactions that were originally thought to proceed via a Meisenheimer complex basically favor a concerted pathway, except for aryl fluorides that contain a strong electron-withdrawing substituent, such as a nitro group.[14] Experimental mechanistic studies on CS$_N$Ar reactions have been dominated by investigations of the electronic effect of aryl halides, in which the lower sensitivity to the electronic nature of aryl halides provides a strong indication of the CS$_N$Ar mechanism.[15,16] In contrast, except for the Pierre's reduction reaction,[7,8] the order of reactivity of leaving groups has not been explored, although it is known that several unique leaving groups, such as OH,[10-12,17] OMe,[15,18] amide,[16,19] and SMe,[20] can participate in CS$_N$Ar reactions. Herein, we report on a detailed investigation of the effect of leaving groups in *N*-heterocyclic carbene (NHC)[21,22]-catalyzed intramolecular nucleophilic aromatic substitution reactions (Scheme 1C).



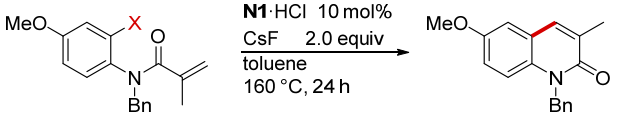
Scheme 1. Order of the Reactivity of Leaving Groups in Nucleophilic Aromatic Substitution

2. Results and Discussion

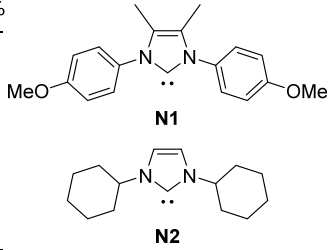
We started our study by reinvestigating the scope of leaving groups in an attempt to improve the preparative utility of the catalytic nucleophilic aromatic substitution. In our previous study, we identified *N*-heterocyclic carbene **N1** as the most effective catalyst for the cyclization of a range of aryl fluorides bearing an α,β-unsaturated amide moiety at the *ortho* position.[23] Although the corresponding aryl chlorides and bromides were unreactive under the identical conditions when they contained no additional substituents, they were reactive when a weak electron-withdrawing group was introduced (Scheme 2A). For example, the introduction of a methoxy group at the *meta* position to the leaving group, which would be predicted to slightly reduce the electron density of the carbon *ipso* to the leaving group, allowed not only fluoride **1a** (entry 1) but also chloride **1b** (entry 2) and bromide **1c** (entry 3) to successfully participate in the catalytic cyclization. Even the corresponding iodide **1d** underwent this catalytic substitution, albeit in a lower efficiency (entry 4). In view of several examples of stoichiometric base-mediated CS_NAr reactions using phenol-based electrophiles,[10-12,17,18,20] we next examined the reactivity of phenol derivatives in our catalytic aromatic substitution reaction. We were pleased to observe that a reaction using a substrate bearing a phenoxy group **1e** underwent the desired substitution to form **2** in 80% yield (entry 5). Even more surprising was that a methoxy group can also serve as a leaving group under these conditions (entry 6). With this specific substrate, the cyclohexyl-substituted NHC **N2** was found to be optimal for delivering the cyclized product **2** in 87% yield (entry 7). Catalytic reactions of inert but readily available phenol derivatives, such as aryl ethers and esters[24-28] basically require transition-metal catalysts, such as nickel[24-28] and rhodium[29] complexes. Therefore, the use of an organocatalyst, instead of transition metal catalysts, to transform such strong C–O bonds would be highly desirable. Although there are sporadic examples of the substitution of inert phenol derivatives using an organocatalyst, such as phosphazene bases,[30,31] TfOH,[32] and organic photoredox catalysts,[33,34] the substrates are limited to those with a strong electron-withdrawing groups or π-extended aromatics.

The rate constants for the **N1**-catalyzed cyclization at 130 °C were determined for substrates **1a-f**. The reactions for the examined substrates followed first-order kinetics based on the concentration of the α,β-unsaturated amide, and the obtained rate constants (k_{obs}) are listed in Scheme 2B. The rate for aryl fluoride **1a** was higher by 10 tmes than that for chloride analogue **1b**, whereas the difference in rate between chloride **1b** and bromide **1c** was not quite large (k_{Cl}/k_{Br} = 1.1). Aryl iodide **1d** underwent this catalytic cyclization but the rate was slower by 0.4 times compared with bromide **1c**. Interestingly, a OPh group was found to serve as a better leaving group than Cl, Br and I in terms of the reaction rate (k_{OPh}/k_{Br} = 4.5), which indicates that the electronegativity of the atom to be dissociated is the primary factor for reactivity rather than the strength of the C–X bond.[35] Although a OMe group was a much less reactive leaving group (k_{OMe}/k_{Br} = 0.18) under these conditions. These kinetic studies revealed that the order of reactivity of halogen-based leaving groups in the NHC-catalyzed aromatic substitution follows the same the order as was observed in a typical S_NAr reaction, yet are different from the order observed in Pierre's reduction reaction that proceeds via a CS_NAr mechanism.

A Scope of the leaving group



entry	X	yield of **2** / %
1	F (**1a**)	95
2	Cl (**1b**)	77
3	Br (**1c**)	77
4	I (**1d**)	48
5	OPh (**1e**)	80[a]
6	OMe (**1f**)	56
7	OMe (**1f**)	87[b]

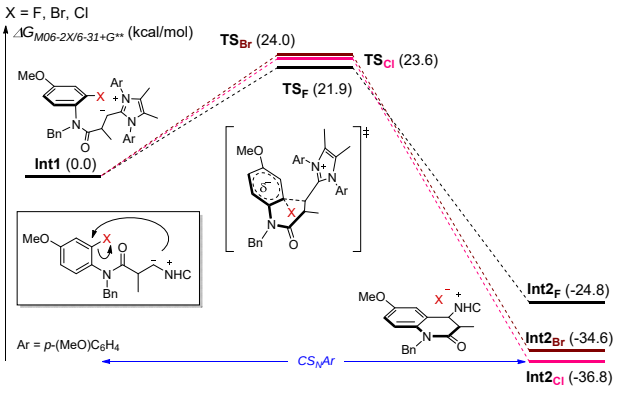


B Rate constrants at 130 °C using catalyst **N1**

X	k_{obs} / s^{-1}	k_{rel}
F (**1a**)	$1.77\pm0.21 \times 10^{-4}$	11.8
Cl (**1b**)	$1.66\pm0.11 \times 10^{-5}$	1.1
Br (**1c**)	$1.50\pm0.20 \times 10^{-5}$	1.0
I (**1d**)	$6.16\pm0.46 \times 10^{-6}$	0.4
OPh (**1e**)	$6.77\pm0.44 \times 10^{-5}$	4.5
OMe (**1f**)	$2.65\pm0.18 \times 10^{-6}$	0.2

Scheme 2. Comparison of the Leaving group in **N1**-Catalyzed Cyclization of **1**. [a]With 20 mol% NHC catalyst for 48 h, [b]With **N2** at 140 °C for 48 h

Computational analyses (M06-2X/6-31+G(d,p) with Polarizable Continuum Model (toluene)) of reactions with substrates bearing halogen leaving groups (i.e., **1a-1c**) revealed that the CS_NAr mechanism is operative and there was no evidence for a Meisenheimer intermediate either on their energy surfaces or intrinsic reaction coordinates in all cases (Scheme 3).[36] The activation barriers for these aromatic substitution processes of **1a-1c** are 21.9 (X = F), 23.6 (X = Cl) and 24.0 (X = Br) kcal/mol, which is consistent with the order of reactivity of halogen groups determined in experimental studies (Scheme 2). The activation barrier of more than 20 kcal/mol indicates that the step from **Int1**x to **Int2**x (X = F, Cl, Br) is likely the rate-determining step in these catalytic reactions, because the addition of an NHC catalyst to an α,β-unsaturated carbonyl compound and the β-elimination of an NHC catalyst were reported to proceed more facilely with the activation barriers of approximately 12.0 and 14.3 kcal/mol, respectively.[36]



Scheme 3. Calculated Energy Diagrams for **N1**-Catalyzed Cyclization of Aryl Halides **1a-c**

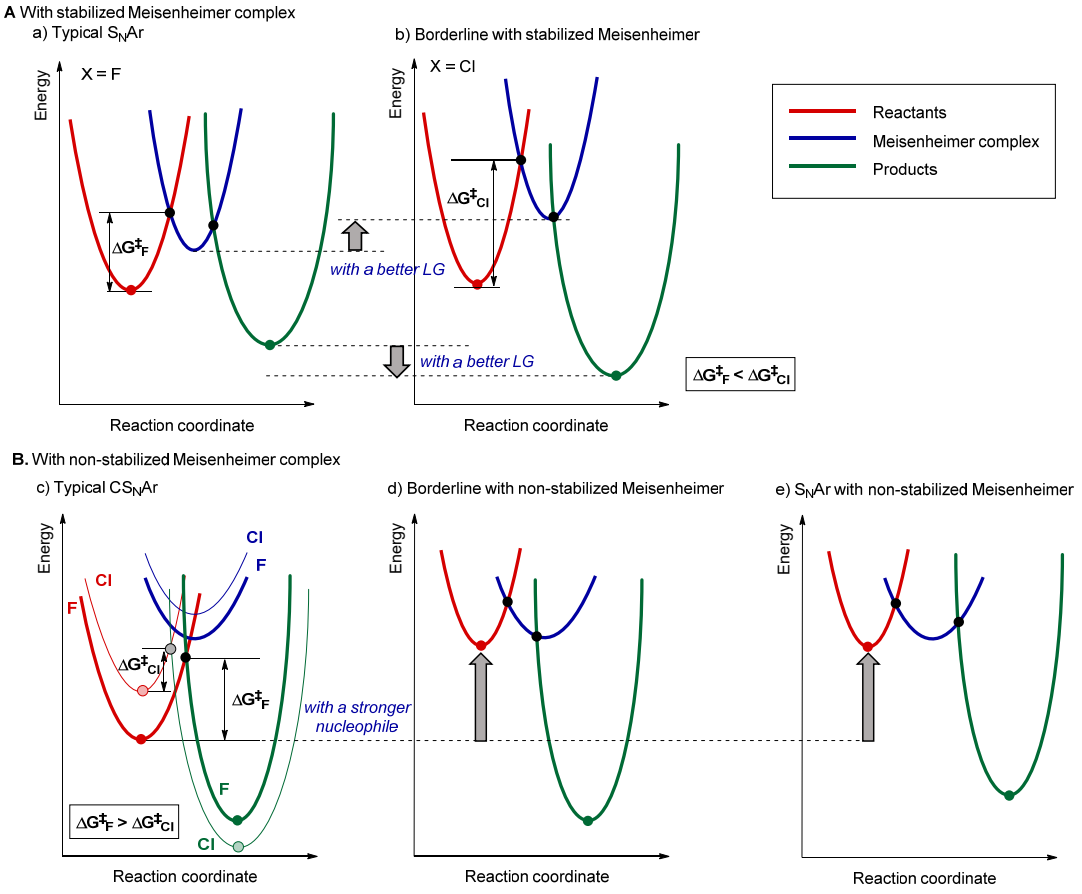
An analysis based on the qualitative Marcus theory[37-39] is helpful for developing a unified understanding of the effect of the leaving group on nucleophilic aromatic substitution reactions.[14] In this analysis, the favored reaction pathway is determined by the relative energy of the Meisenheimer complex in comparison to the intersection of the potential energy surfaces of the reactants and products. In a typical S_NAr reaction, the Meisenheimer complex is lower in energy and has intersections with the potential energy surfaces of the reactants and products (Scheme 4a, red: reactants; blue: Meisenheimer complex; green: products). According to Hammond's postulate,[40] the structure of the transition state resembles a Meisenheimer complex, and therefore the energy potential of the Meisenheimer complex would affect the stability of the transition state more significantly than that of the reactants (i.e., C–X bond strength) or products (i.e, the stability of X^-). Therefore, among halogen derivatives, fluorides are the most reactive, since they can stabilize the Meisenheimer complex the most. When the fluoride is replaced with a better leaving group, such as chloride, in reactions involving a stabilized Meisenheimer complex, the product surface becomes lower in energy. This change decreases the second energy hill determined by the Meisenheimer complex and the product curves, thus allowing the reaction to proceed in a concerted-like pathway, rather than a two-step mechanism involving a discrete intermediate (Scheme 4b, Borderline with a stabilized Meisenheimer). This type of borderline reactivity was observed in the fluorination of 1-chloro-2,4-dinitrobenzene, which proceeds through an energy surface with a shallow minimum.[14] The activation barrier for this borderline case should be larger than that for a typical S_NAr, because the use of a better leaving group (i.e., lower electronegativity in a halogen family) would lead to a Meisenheimer curve higher in energy. Therefore, the order of reactivity of the reported S_NAr could be interpreted by the energy diagrams shown in Schemes 4a and 4b.

On the other hand, the reaction proceeds in a concerted manner when the Meisenheimer curve is higher in energy than the intersection between the energy surfaces of the reactants and products (Scheme 4c). In this mechanistic scenario, the transition state is stabilized either by destabilizing the reactants or by stabilizing the products. The order of reactivity of I > Br > Cl > F observed in Pierre's work is in agreement with this view, since a C–X bond becomes weaker and X^- is stabilized more in this order. The situation regarding our NHC-catalyzed CS_NAr reaction should be different from that depicted in Scheme 4c, since the reactants involve a transient unstable yet highly nucleophilic ylide. This circumstance should increase the energy potential of the reactants so as to have an intersection with the non-stabilized Meisenheimer curve, resulting in the two subclasses depending on the relative position of the intersection between the Meisenheimer and product surfaces. When the intersection is on the left side of the minimum of the Meisenheimer curve, the substitution process should proceed without a discrete intermediate (Scheme 4d, Borderline with a non-stabilized Meisenheimer). When the intersection is on right side of the minimum, the reaction can be viewed as an S_NAr reaction with the Meisenheimer intermediate (Scheme 4e). In both cases, the reactivity of the halogen leaving groups would be expected to follow the same order as that in a typical S_NAr reactions, since the activation barrier is primarily determined by the energy level of the Meisenheimer curve, irrespective of whether or not a Meisenheimer complex is involved as a discrete intermediate along the reaction pathway. Our NHC-catalyzed reactions are best described as the energy diagram shown in Scheme 4d.

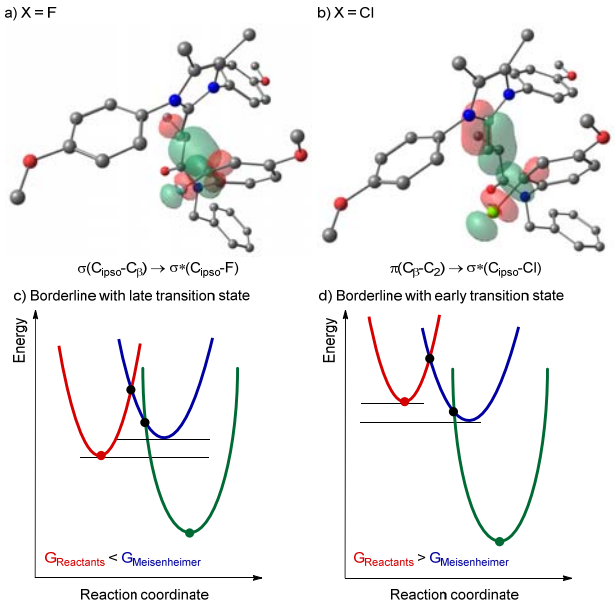
Natural bond orbital (NBO) analyses[41] of the transition states with **1a** revealed a noncovalent stereoelectronic interaction between the σ* (C_{ipso}–C_β) bond orbital and the σ (C_{ipso}–F) antibonding orbital, which indicates that the transition state structurally resembles the Meisenheimer complex rather than the reactant (Scheme 5a).[40] On the other hand, a different type of noncovalent stereoelectronic interaction was observed in the transition state with **1b** and **1c**. The π orbital lying on the bond between the β carbon and C2 of the dihydroimidazole (C_β–C2), instead of the σ (C_{ipso}–C_β) bond orbital, constitute an interaction with the σ* (C_{ipso}–X) antibonding orbital, which indicates that the transition state structurally resembles the ylide reactant (Scheme 5b, X = Cl).[42] The difference in the nature of the transition states between fluoride and other halogens can be rationalized by assuming the different geometric relationship between the energy potentials of the reactants and the Meisenheimer complex in the Marcus diagram. Thus, in the case of fluoride, the transition state should resemble the Meisenheimer complex, although it is not involved as an intermediate. This indicates that the minimum in the Meisenheimer curve should be higher than the minimum of the reactant surface, as in Scheme 5c, as is the case for the diagram of typical S_NAr reactions. In the cases of other halogens, the minimum of the Meisenheimer curve should be located lower in energy than the minimum of the reactant surface (Scheme 5d), due to the lability of C–X (X = Cl, Br, I) bonds, which makes the transition state structurally similar to the reactants.

To develop a comprehensive understanding of the reaction mechanism for nucleophilic aromatic substitutions, an Albery-More O'Ferrall-Jencks diagram[43,44] was applied, which is a representation of potential energy surfaces in a two-dimensional reaction coordinate, in which the vertical axis refers to the progress of Ar–X bond breaking, while the horizontal axis refers to the progress of Ar–Nu bond formation (Nu = nucleophile) (Scheme 6). Based on this diagram, three limiting mechanisms, i.e., S_N1,[45] S_NAr and CS_NAr, can be clearly discriminated visually. In between the two extremes of S_NAr and CS_NAr lies the borderline area in which the degrees of Ar–Nu bond formation and Ar–X bond cleavage are intermediate between those in the two extreme cases. Unlike the CS_NAr extreme, borderline cases proceed through the energy potential of the Meisenheimer complex, although its minimum is outside the reaction pathway (borderline a) or immediately before the second transition state $\mathbf{TS_D}$ (borderline b), thereby making these pathways also distinct from the S_NAr extreme. Our NHC-catalyzed aromatic substitution reactions can be depicted as borderline a (X = halogen).

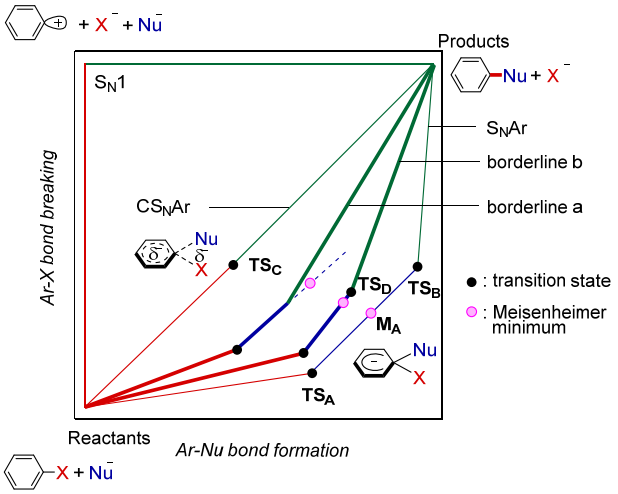
Expanding the scope of leaving groups in our NHC-catalyzed nucleophilic aromatic substitution allows for useful synthetic applications. For example, 3-aminopyridines bearing a fluoride substituent at the C2 or C4 position are not commercially available, and tedious preparation is required.[46,47] In contrast, the corresponding chlorides and bromides are readily available and are applicable to our catalytic CS_NAr reactions as shown Scheme 7a. DFT calculations revealed that the reaction with **1i** also proceeds in a concerted manner. Our organocatalytic method can also be used for the late-stage derivatization of densely functionalized bioactive molecules (Scheme 7b). Furthermore, a Bromhexine[48] derivative **1m**, which contains an aniline moiety bearing Br at the *ortho* and *para* positions, can also participate successfully in our NHC-catalyzed cyclization. It should be noted that palladium-catalyzed intramolecular Mizoroki-Heck cyclization of this type of substrates would not produce a six-membered product, not only because of the incompatibility of a pendant Br group but also because the palladium-catalyzed variant is known to favor a 5-exo cyclization mode.[49]



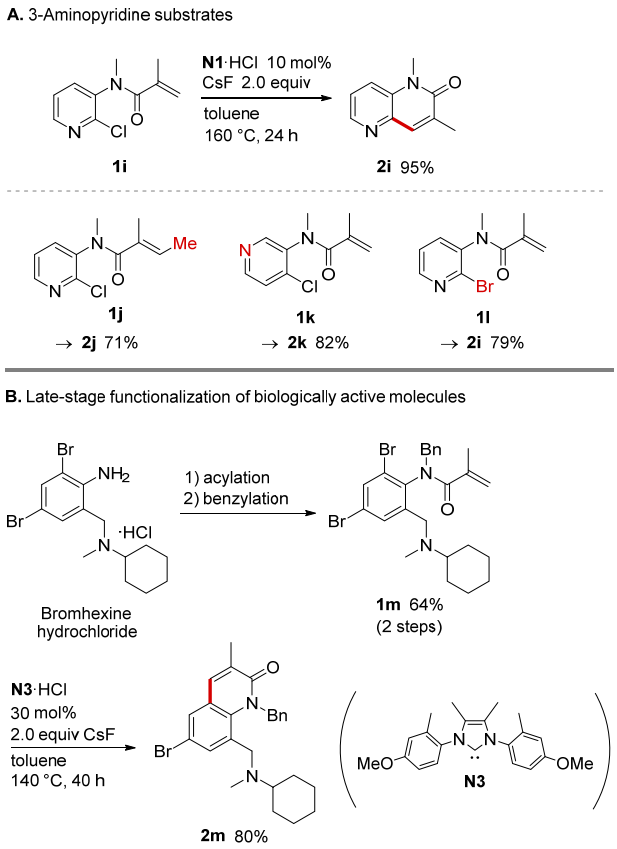
Scheme 4. Classification of Nucleophilic Aromatic Substitution Reactions by Qualitative Marcus Theory



Scheme 5. NBO Analysis for Transition States Generated from **1a** and **1b**



Scheme 6. Albery-More O'Ferrall-Jenks Plot for Nucleophilic Aromatic Substitutions



Scheme 7. Synthetic Applications

3. Conclusion

In summary, we show herein that the reactivity of the leaving group in NHC-catalyzed CS$_N$Ar reactions decreases in the order of F, Cl, Br to I. This order of reactivity is opposite to that observed in the CS$_N$Ar reaction reported by Pierre. This difference was shown to be rationalized by a qualitative Marcus analysis. Unlike the Pierre's reaction, our catalytic reactions involve a transient high energy reactant, which increases the energy potential to a sufficiently high level to cross the energy surface of the non-stabilized Meisenheimer complex. As a result, the energy of the transition state is primarily determined by the stability of the Meisenheimer intermediate, as is observed in typical S$_N$Ar reactions, even though it is not involved as a discrete intermediate during the course of the reaction. These results provide a revised perspective of the effect of the leaving group in nucleophilic aromatic substitution reactions and point out that the nature of the leaving group is one of the key factors that dictates the mechanism. Although the effect has been discussed in the context of two extreme mechanistic manifolds, *i.e.*, S$_N$Ar and CS$_N$Ar, the reactions in reality largely fall into borderline cases, which would require careful investigations to completely understand the nature of the transition state. As in the cases of nucleophilic aliphatic substitution (S$_N$1 vs S$_N$2) and the β-elimination of alkyl halides (E1, E2 and E1cb), a mechanistic continuity exists in nucleophilic aromatic substitution reactions, and that a subtle change in the structure of the substrate could lead to a different mechanism depending on the relative energy potentials of the reactants, the Meisenheimer complex, and the products.

Supporting Information

Detailed experimental procedures. Characterization of new compounds. Copies of ^{1}H and ^{13}C NMR spectra of products. Computational details. This material is available on *******.

Acknowledgement

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