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$FeCl_3$-Catalyzed Aminohalogenation of Arylmethylenecyclopropanes and Arylvinylidenecyclopropanes and Corresponding Mechanistic Studies

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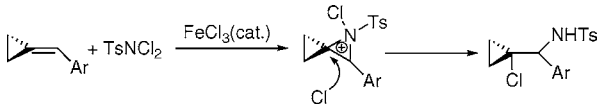
ABSTRACT



The aminochlorination of methylenecyclopropanes (MCPs) 1 and vinylidenecyclopropanes (VCPs) has been explored with use of $FeCl_3$ (20 mol %) as a Lewis acid catalyst in acetonitrile under convenient mild conditions. The stereochemistry has been unambiguously confirmed by X-ray structural analysis. The aziridinium-based mechanism, accounting for both regio- and stereoselectivity, has been carefully studied. A linear free-energy relationship study of this reaction confirms consistency with the Hammet equation.

The aminohalogenation reaction has become an active topic in organic synthesis because the resulting vicinal haloamines are important building blocks in organic and medicinal chemistry.[1−4] Recently, we and others have successfully established the aminohalogenation of α,β-unsaturated carboxylic esters and ketones under various catalytic systems.[3,4] This work can overcome the shortcomings of original aminohalogenation which showed a narrow scope of substrates and controversal mechanism hypothesis of radical-based and bridged chloronium ion-based processes.[1,2] In the new aminohalogenation reaction the aziridinium-based mechanism was proposed to explain the resulting regio- and stereoselectivity of the vicinal haloamino products.[3−5] Surprisingly, when some trisubstituted unfunctionalized olefins such as methylenecyclopropanes and vinylidenecyclopropanes were subjected to this reaction under known catalytic conditions, poor yields were obtained. However, the resulting vicinal haloamine products from these substrates are useful for medicinal chemistry and pharmaceutical research.[6] Herein we report the preliminary results of the aminohalogenation reaction of these special alkenes

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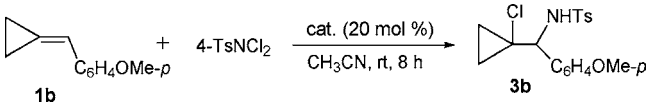
with *N*,*N*-dichlorotoluenesulfonamine ($TsNCl_2$) as the halogen and nitrogen source in the presence of $FeCl_3$ as a Lewis acid catalyst. Meanwhile, the linear free-energy relationship study of this reaction has also been studied for the first time.

Initially, we performed the reaction of MCP **1b** with $TsNCl_2$ in acetonitrile to give the corresponding aminochlorinated product **3b** in 40% yield. In contrast, no reaction occurred in other solvents, such as toluene, tetrahydrofuran (THF), and dichloromethane (DCM). When the solvent was changed to *N*,*N*-dimethylformamide (DMF) or ethanol, a trace amount of **3b** was formed. To improve the yield of **3b**, we screened a variety of Lewis acid promoters such as $ZrCl_4$, $BF_3{\cdot}OEt_2$, $Mn_2(OAc)_3$, $FeCl_3$, and $Yb(OTf)_3$ (20 mol %) for this reaction. The results are listed in Table 1, which indicates

Table 1. Addition of *N*,*N*-Dichlorotoluenesulfonamine to MCP **1b**



1b **3b**

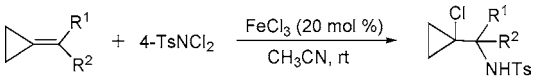
entry	catalyst	yield (%)[a]
1	CuOTf	23
2	$ZrCl_4$	42
3	$BF_3{\cdot}OEt_2$	73
4	$Mn_2(OAc)_3$	64
5	$PdCl_2$	N.R.[b]
6	$FeCl_2$	N.R.[b]
7	**$FeCl_3$**	**77**
8	$Yb(OTf)_3$	48
9	$SnCl_4$	complex mixture

[a] Isolated yields. [b] No reaction.

that $FeCl_3$ showed the best catalytic ability for this reaction and gave **3b** in 77% yield within 8 h (Table 1, entries 1−9).

Using $FeCl_3$ (20 mol %) as the catalyst, we next investigated the scope and limitations of this reaction by use of a variety of MCPs **1** under the above conditions. The results are summarized in Table 2. The corresponding adducts **3** were formed in moderate to high yields. As can be seen from Table 2, for those MCPs **1** bearing electron-donating groups on the aromatic rings, the addition reaction proceeded smoothly to give the corresponding adducts **3** in higher yields than those without these groups (Table 2, entries 1−9). When MCP **1i** was used as substrate, in which both aromatic rings have the strong electron-donating group MeO, the corresponding ad-

Table 2. Addition of *N*,*N*-Dichlorotoluesulfonamine to MCPs **1**[7]



1 **3**

entry	MCP	R^1	R^2	yield (%)[a]
1	**1a**	H	C_6H_5	**3a**, 48
2	**1b**	H	4-MeC_6H_4	**3b**, 53
3	**1c**	H	4-$MeOC_6H_4$	**3c**, 77
4	**1d**	H	2,4-$(MeO)_2C_6H_3$	**3d**, 72
5	**1e**	H	3,4,5-$(MeO)_3C_6H_2$	**3e**, 70
6	**1f**	H	$C_{10}H_7$	**3f**, 44
7	**1g**	C_6H_5	C_6H_5	**3g**, 54
8	**1h**	4-MeC_6H_4	4-MeC_6H_4	**3h**, 75
9	**1i**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**3i**, 99

[a] Isolated yields.

duct **3i** was obtained in quantitative yield (Table 2, entry 9). As anticipated for MCPs **1** bearing electron-withdrawing groups such as Cl or NO_2 on the aromatic ring, the reaction is sluggish and gave the corresponding adduct in lower yields under the same conditions (see Table SI-1 in the Supporting Information).

To better study the influence of the electronic character of the aromatic and the cyclopropane ring on this reaction, the Hammet effect was examined in this system. A set of parallel reactions of MCPs **1** bearing various substituents on the benzene ring with $TsNCl_2$ were carried out under identical conditions (see Table S-1 in the Supporting Information). The reaction was quenched simultaneously when some starting materials, MCPs **1**, still remained. Therefore, a set of comparable reaction rate could be obtained. We plotted the $\log(k/k_0)$ (k_0 is the reaction rate of MCP **1a**) vs σ to figure out the linear free-energy relationship of this reaction.[8] A straight line was obtained with an ρ value of −1.35, which implies the existence of a positive ion intermediate in this reaction (Figure 1). Furthermore, we noticed that the σ constants fitted the line much better than those of $\sigma^{\bullet}$ or σ^{+}, which deviated from a straight line (see Figure S-1 in the Supporting Information). This might serve as a substantial proof of the existence of a bridged positive ion intermediate, otherwise the other two kinds of σ constants should stand for a radical or a resonance-stabilized carboca-

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(7) **Typical Reaction Procedure for Aminohalogenation.** A dry vial was loaded with MCPs **1** (0.5 mmol) and acetonitrile (1.5 mL). Anhydrous $FeCl_3$ (0.1 mmol) was next added to the solution, followed by the addition of $TsNCl_2$ (0.75 mmol). The resulting solution was stirred at room temperature (25 °C) for about 8 h until the starting materials were consumed (monitored by TLC). The reaction was quenched by addition of 1.0 mL of saturated aqueous Na_2SO_3 solution. The two phases were separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, and purification by flash chromatography (EtOAc/petroleum ether, v/v, 1/7) to provide the pure product. When vinylidenecyclopropanes were used as substrates to react with $TsNCl_2$ instead of MCPs, the reaction temperature was decreased to −15 °C because some of the products are not stable at room temperature.

(8) σ and σ^{+} values are given by: (a) Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 323. (b) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207−1216.

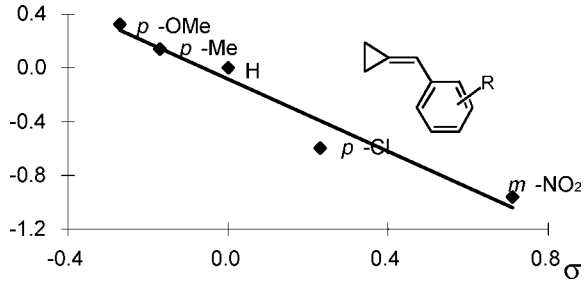
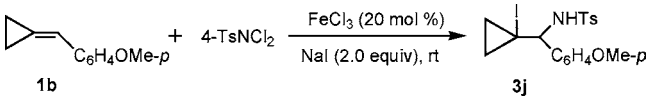


Figure 1. Linear free-energy relationships of the aminohalogenation reaction.[8]

tion intermediate, respectively.[9] Further proof against the involvement of carbocation intermediate lies in the difference between the ρ^+ values reported before,[10] which can be as negative as −4.1, and the ρ value acquired by us. Another noteworthy factor is that this Hammet equation is in sharp contrast with that reported by Pérez and Che on the aziridination reaction of olefin with PhI═NTs, which is believed to proceed via a metal carbenoid species (M═NTs).[11] To the best of our knowledge, the present work serves as the first measurement of ρ values in aziridium-mediated reactions.

To rule out the possibility of the bridged chloronium ion mechanism, we also performed the control experiments as shown in Scheme 1. The aminoiodination product **3j** was

Scheme 1

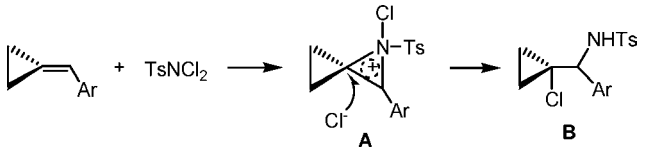


1b 3j

exclusively produced in the presence of NaI, presumably via the attack of iodide anion to the aziridinium ring. This observation can confirm that the aziridinium intermediates exist during the reaction process. In fact, the diamination reaction of α,β-unsaturated carboxylic esters and ketones has also previously supported this aziridinium-based hypothesis.[5]

The aziridinium-based mechanism of this reaction is shown in Scheme 2. The first step, the electrophilic addition of $TsNCl_2$ to MCPs **1**, forms the corresponding *N*-*p*-tosyl-*N*-chloroaziridinium intermediate **A**, and is believed to be the rate-limiting step.[3,4] The second step is the ring opening of aziridinium by the chlorine anion (Cl^-). The carbon−carbon hyperconjugation effect enhanced by the strain in the spiro

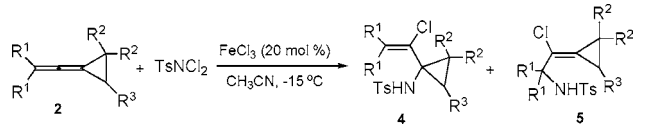
Scheme 2



ring bonds[12] could be important in stabilizing the positively charged aziridinium intermediate and in controlling the regioselectivity of the attack of the chlorine anion. The excellent regioselectivity of the product shows the much stronger ability of cyclopropane to stabilize the positive ion as opposed to the aromatic ring, regardless of the position of attachment for the electron-donating group.[11]

To validate our proposed effect of the cyclopropyl ring, we prepared another series of cyclopropane-containing substrates, vinylidenecyclopropanes **2**,[13] to be subjected to this reaction under similar conditions. Two separable products **4** and **5** were isolated by silica gel flash chromatography in moderate to good combined yields. The results are summarized in Table 3. As can be seen from Table 3,

Table 3. Results of Aminochlorination of Vinylidenecyclopropanes



entry	R^1	R^2	R^3	yield (%)[a]	yield (%)[a]
1	C_6H_5	H	C_6H_5	**4a**, 59	**5a**, 26
2	C_6H_5	H	*p*-$CH_3OC_6H_4$	**4b**, 51	**5b**, 21
3	C_6H_5	*p*-$CH_3OC_6H_4$	CH_3	**4c**, 69	trace
4	C_6H_5	C_6H_5	H	**4d**, 55	**5d**, 35
5	C_6H_5	C_6H_5	CH_3	**5e**, 86	trace

[a] Isolated yields.

identification of the two adducts showed that adducts **4** were the major products rather than adducts **5**.

The adduct **4a** was verified by X-ray diffraction. The ORTEP drawing of **4a** is shown in Figure 2. The addition of $TsNCl_2$ is predominantly directed on the double bond adjacent to the cyclopropyl ring, which is due to the role of cyclopropane in stabilizing the positively charged aziridinium ion. In addition, the steric effect turned out to play a major role in determining the subsequent attack position of the chlorine

(9) (a) Thomas, H. L.; Kathleen, S. R. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; Chapter II. (b) $\sigma^\bullet$ values are given by: (c) Dinctürk, S.; Jackson, R. A. *J. Chem. Soc., Perkin Trans. II* **1981**, 1127−1131.

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(11) (a) Diaz-Requejo, M. M.; Pérez, P. J.; Brookhart, M.; Templeton, J. L. *Organometallics* **1997**, *16*, 4399−4402. (b) Au, S.-M.; Huang, J.-S.; Yu, W.-Y.; Fung, W.-H.; Che, C.-M. *J. Am. Chem. Soc.* **1999**, *121*, 9120−9132.

(12) (a) Carey, F. A.; Sundbery, R. J. *Advanced Organic Chemistry*; Plenum Press: New York, 1990; Part A, Chapter V. (b) For reviews of Cyclopropylmethyl cations see: Richey, H. G., Jr. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1972; Vol. III, Chapter 25.

(13) Vinylidenecyclopropanes are prepared according to the synthetic method reported by Mizuno. (a) Maeda, H.; Hirai, T.; Sugimoto, A.; Mizuno, K. *J. Org. Chem.* **2003**, *68*, 7700−7706. (b) Isagawa, K.; Mizuno, K.; Sugita, H.; Otsuji, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2283−2285.

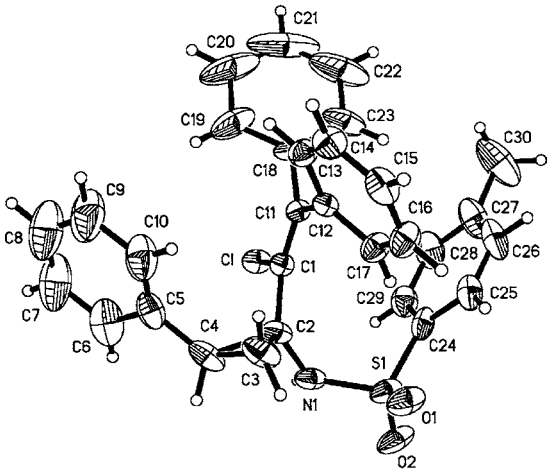

Figure 2. ORTEP diagram of **4a**.

anion to the positively charged aziridinium ring to give the adducts **4** and **5**.

In conclusion, the scope and limitations of aminohalogenation of olefins are expanded to the use of MCPs **1** and VCPs **2** to afford multisubstituted cyclopropanes, which can undergo cross coupling or S_N2 reactions to introduce cyclopropyl substituent to many natural products. The reaction proceeded smoothly without the use of any inert gas protection in the presence of a readily available $FeCl_3$ catalyst. The first linear free-energy relationships of aminohalogenation have been carefully studied by a series of plotted experiments.

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Supporting Information Available: The spectroscopic data and analytic data of the compounds shown in Tables 1−3 and Scheme 1 and a detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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