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Recent Development of Regio- and Stereoselective Aminohalogenation Reaction of Alkenes

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Keywords: Aminohalogenation / Haloamidation / Cinnamate / Aziridinium ion / Ionic liquid

This microreview presents the development of the catalytic aminohalogenation of olefins. The olefin substrates include electron-deficient and functionalized ones, such as α,β-unsaturated esters, α,β-unsaturated ketones and α,β-unsaturated nitriles. In addition, the first asymmetric aminohalogenation by the use of Evans chiral auxiliaries is also discussed. The convincing evidence is provided to support the aziridinium mechanism of aminohalogenation reaction. The applications of this reaction are described by converting vicinal haloamines into other important synthetic building blocks.

1. Introduction

The aminohalogenation (or haloamidation) reaction converts common petroleum olefins into vicinal haloamine products by the addition of amine and halogen moieties onto carbon–carbon double bonds.[1] The haloamines can serve as versatile building blocks for chemical synthesis and medicinal sciences, it makes this reaction an increasingly important and active topic in modern organic chemistry.[2] Although the aminohalogenation reaction has been known for nearly 40 years,[3–5] it has not been well studied until recently when our laboratories were involved in its investigation.[6] This situation is probably due to the factor that

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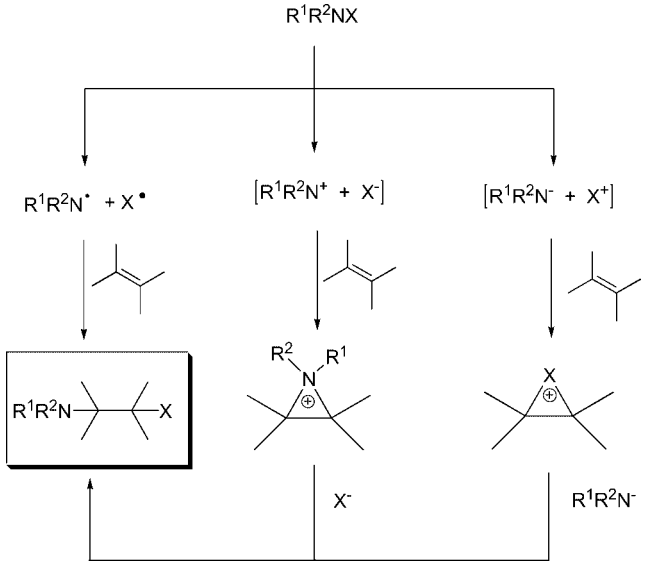
Cody Timmons was born in Texas, USA, in 1978. He graduated from Motley County High School in Matador, Texas, in 1997. From there, he entered West Texas A&M University in Canyon, Texas, graduating with B.S. and MS degrees in Chemistry in the years 2000 and 2002, respectively. His MS thesis dealt with experimental and computational studies on the degradation of explosives. He then moved to Texas Tech University in the fall of 2002 and joined the group of Professor Guigen Li, where he studied novel olefin addition and carbon-carbon bond formation methodologies. He completed his Ph.D. in May 2006 and is currently a postdoctoral research associate in the laboratory of Professor Peter Wipf at the University of Pittsburgh.

the substrate scope of the original aminohalogenation was strictly limited to the use of a very few alkenes. Meanwhile, the difficulty in the control of regio- and stereoselectivity and the confusing mechanism hypothesis of the original aminohalogenation may also have attributed to this situation.

Aminohalogenation reaction employs various nitrogen/halogen sources that are derived from amines, amides, sulfonamides, carbamates, and imides (R_1R_2NX or RNX_2).[1,3–4] These nitrogen/halogen sources are subjected to addition reactions with alkenes through either homolytic or heterolytic cleavage of their N–X bonds. The homolytic cleavage of N–X bond typically requires the use of peroxides, light or heat. The heterolytic cleavage of this bond is often accelerated by Lewis acid promoters or catalysts. The aziridinium or halonium intermediates resulting from the electrophilic species of N^+ or X^+ are proposed to exist in the aminohalogenation process as shown in Scheme 1.



Scheme 1.

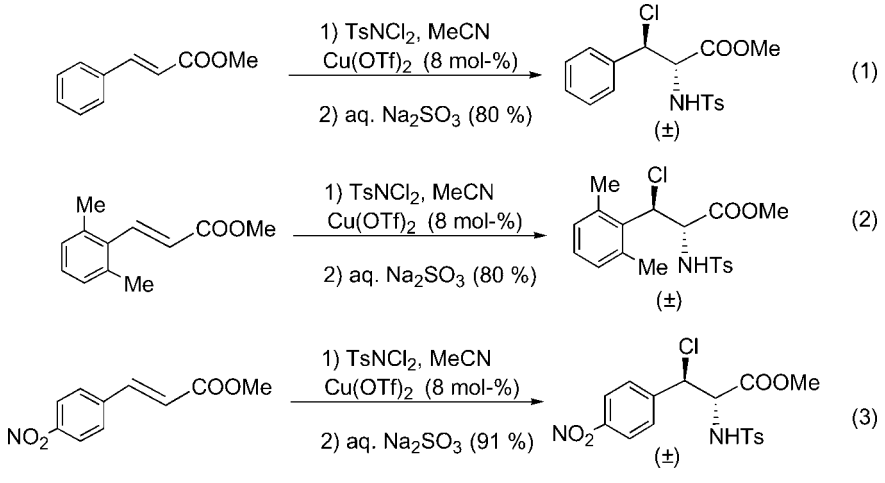
As indicated in Scheme 1, during the aminohalogenation process a nitrogen/halogen source can be reacted with alkenes via different mechanisms under different conditions. In addition to this reaction, the reactions of *p*-toluenesulfonyl chloride with different reactants also showed a similar behavior, i.e., *p*-toluenesulfonyl chloride acts as the chlorine anion source when it reacts with nucleophiles, such as amine and hydroxy compounds,[7] but acts as the chlorine cation source when it reacts with lithium enolates.[8] Another example is shown by the behaviors of 1,2,3-benzotriazole derivatives which can be either ionized into benzotriazole anion or *N*-substituted benzotriazole cations.[9]

This article will summarize the recent progress of the aminohalogenation reaction that was made mainly by our laboratories and a few others in the past several years. The work on intramolecular aminohalogenation reaction is not covered in this mini-review due to the space limitation.[10]

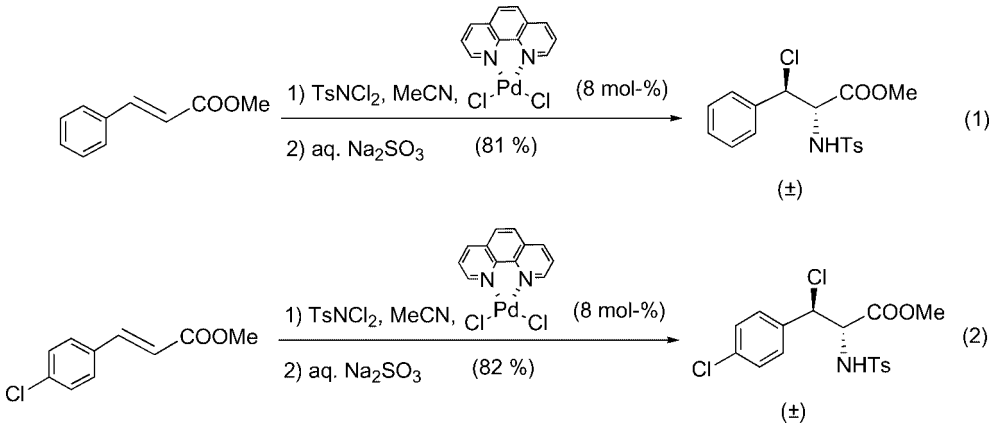
2. Aminohalogenation of α,β-Unsaturated Esters

(1) *N*,*N*-Dichloro-*p*-toluenesulfonamide as the Nitrogen/Halogen Source

Cinnamic esters are believed to be the most synthetically useful substrate classes[11] for olefinic oxidations that include catalytic asymmetric dihydroxylation,[12] epoxidation,[13] aziridination,[14] aminohydroxylation,[15] etc. However, when these substrates were subjected to the aminochlorination reaction with *N*,*N*-dichloro-*p*-toluenesulfonamides ($TsNCl_2$) or dichlorocarbamates[4] and the $CrCl_2$-promoted addition with *N*-chlorocarbamates[5] there were no haloamine products generated under the original known conditions. The screening of catalysts and catalytic conditions revealed that the combination of $ZnCl_2$–MeCN and $Cu(OTf)_2$–MeCN (metal as the catalyst and acetonitrile as the solvent) resulted in the successful aminohalogenation of α,β-unsaturated esters with *N*,*N*-dichloro-*p*-toluenesulfonamide (Scheme 2).[6a] Interestingly, a difficult substrate for olefinic oxidations, methyl *trans*-*p*-nitrocinnamate gave an excellent chemical yield of 91%, albeit an excess amount of $TsNCl_2$ (2 equiv.) and the prolonged period (48 h) were required for complete conversion.



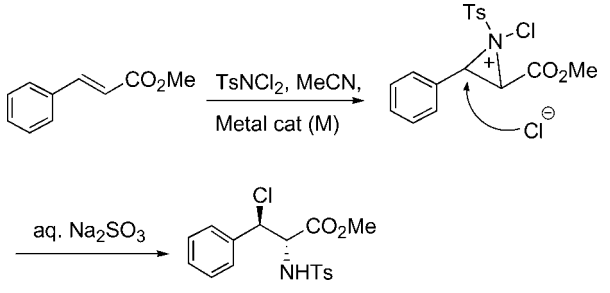
Scheme 2.



Scheme 3.

It was also found that the transition-metal-ligand complex, dichloro(1,10-phenanthroline)palladium(II), can serve as an effective catalyst for the aminohalogenation of cinnamic esters with the same nitrogen/chlorine source (Scheme 3).[16] This catalyst showed an advantage over $ZnCl_2$ and $Cu(OTf)_2$ in which dichloro(1,10-phenanthroline)palladium(II) can be handled very conveniently because it is less hygroscopic than that of the previous two catalysts. Similar to the previous catalytic systems,[6] this reaction can be performed simply by mixing three components, olefin substrates, *N*,*N*-dichloro-*p*-toluenesulfonamide and dichloro(1,10-phenanthroline)palladium(II) in acetonitrile in a vial of appropriate size. There is no need to use inert atmosphere protection.

These aminohalogenation processes are suggested to proceed though a mechanism involving the formation of *N*-chloro-*N*-tosylaziridinium intermediate at the initial rate-limiting-step (Scheme 4).[6,16] The catalysts help to remove the chlorine anion from *N*,*N*-dichloro-*p*-toluenesulfonamide, and also facilitate the formation of "Ts–N^+–Cl" species for the electrophilic addition. The nearby metal-associated "Cl^-" around the aziridinium intermediate acts as the nucleophile to open the three-membered ring. The S_N2 mechanism of this ring opening accounts for the excellent *anti* stereoselectivty. The regioselectivity can be explained by the fact that the β position of the aziridinium intermediate is loaded by more positive charge related to its α position because of the stabilization effect from the phenyl ring.

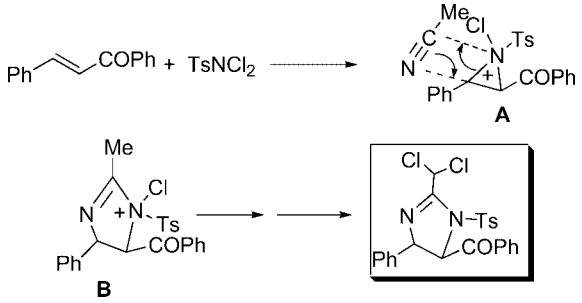


Scheme 4.

The latter aminohalogenation catalyzed by the transition-metal–ligand complex should be beneficial to the efforts on the asymmetric aminohalogenation assuming the complex is associated with the transition state during the formation of aziridinium intermediate at the rate-limiting step. Some encouraging results have been obtained and shown in section 5.

(2) Evidence for an Aziridinium-Based Mechanism

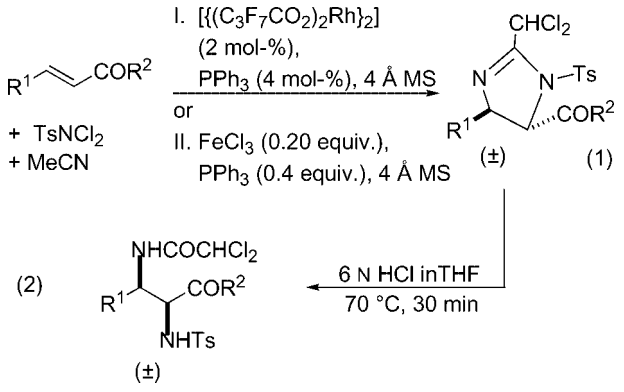
So far, attempts to isolate or directly detect the aziridinium intermediates during aminohalogenation process have been unsuccessful. However, the electrophilic diamination (or imidazolination) reaction under similar conditions of aminohalogenation can unambiguously support the hypothesis of aziridinium-based mechanism.[17–19] For example, when α,β-unsaturated ketones were subjected to the reaction with *N*,*N*-dichloro-*p*-toluenesulfonamide in acetonitrile at room temperature in the absence of any metal catalysts the vicinal diamine products were obtained predominantly (Scheme 5, for ester substrates, catalysts are necessary for this reaction[17]). The resulting regioselectivity and *syn* addition indicated that at the key step the aziridinium ring opening proceeded through [2+3] cyclic addition reaction between acetonitrile and the *N*-(*p*-tosyl)aziridinium intermediate (**A**) to form 1-*N*-(*p*-tosyl)imidazolinium (**B**). The following steps involved repeated deprotonation, chlorination, and an S_N2'-type displacement to afford 2,2-dichloromethyl-4-phenyl-5-phenylcarbonyl-1-*p*-tosyl-imidazoline as the final product.



Scheme 5.

The above diamination reaction was proven to be accelerated by several catalysts, such as rhodium(II) hep-

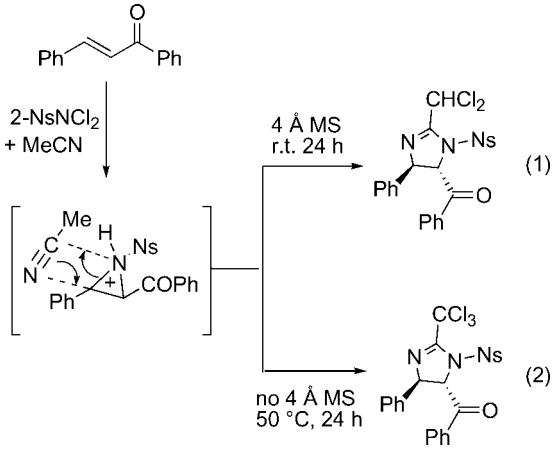
tafluorobutyrate, $FeCl_3{\cdot}PPh_3$ complex and manganese(IV) oxide that help to generate the aziridinium intermediate through the coordination with one of the chlorine atoms of *N*,*N*-dichloro-*p*-toluenesulfonamide (Scheme 6).[17] The reaction is usually aided by dried 4-Å molecular sieves.



Scheme 6.

As shown in Scheme 6, this reaction provides an easy synthesis of α,β-diamino derivatives that can mimic both α- and β-amino acids, and therefore, is important for peptidomimetic and protein research.

In addition to the *N*-chloro,*N*-(*p*-tosyl)aziridinium intermediate, several similar aziridinium species, such as *N*-(*p*-nosyl)aziridinium,[20] *N*-(*p*-tosyl)aziridinium,[19b] and *N*-chloro-*N*-(*p*-nosyl)aziridinium[6b] intermediates, could also exist during the diamination processes. For example, when the combination of 2-$NsNH_2$/NCS was treated with α,β-unsaturated ketones, the regio- and stereoselective imidazolines were obtained (Scheme 7).[20] The reaction is also very convenient to carry out simply by mixing olefin, 2-$NsNH_2$, NCS and 4-Å molecular sieves in freshly distilled acetonitrile at room temperature.

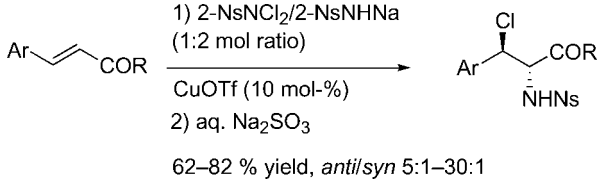


Scheme 7.

The aziridinium-based mechanism has been further supported by the results of the aminohalogenation of unfunctionalized alkenes which is described in section 4.[21]

(3) *N*,*N*-Dichloro-*o*-nitrobenzenesulfonamide as the Nitrogen/Halogen Source

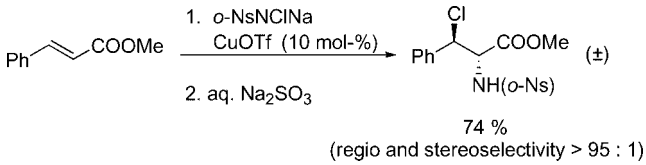
The haloamino compounds with a *N*-nosyl protecting group showed an advantage over their *N*-tosyl-protected counterparts because the former can be readily cleaved under different mild condition ($PhSH/K_2CO_3$ in DMF at room temperature).[22] When the analogous nitrogen source, *N*,*N*-dichloro-*o*-nitrobenzenesulfonamide (*o*-$NsNCl_2$), was allowed to react with α,β-unsaturated esters under the previous aminohalogenation conditions, it failed to give the desired haloamine product. Instead, the *anti* methyl 3-chloro-2-(*o*-nitrophenylsulfonamido)-3-phenylpropionate was determined to be the predominant product.[6b] However, when the combinational nitrogen and chlorine source, $NsNCl_2$/NsNHNa (1:2, mol ratio), was used to react with α,β-unsaturated esters in the presence of copper(I) triflate as the catalyst, the haloamino products were obtained in good yields and up to excellent stereoselectivity (Scheme 8). Furthermore, there was no minor regio isomers detected under this condition.



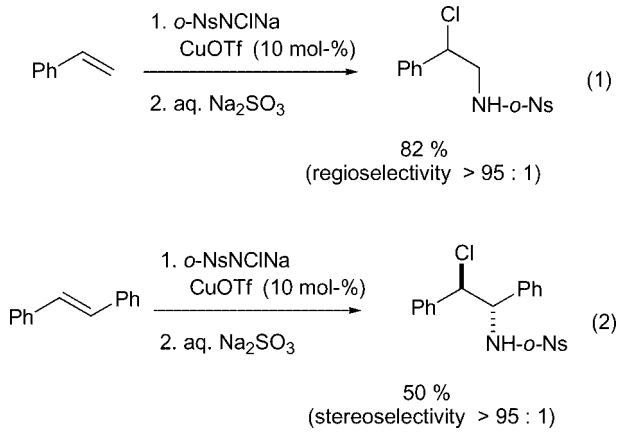
Scheme 8.

In addition to copper(I) triflate and copper(II) triflate, copper(I) chloride can also be used for this reaction to give similar results. 2-$NsNCl_2$ can be readily prepared by treating 2-nitrobenzenesulfonamide with commercial bleach and followed by CH_3COOH acidification. As compared to *p*$TsNCl_2$, 2-$NsNCl_2$ was shown to be more stable and can be stored at room temperature for a few months without inert gas protection. The 2-NsNHNa salt was obtained by performing the deprotonation of 2-$NsNH_2$ with sodium hydroxide in methanol/water solution, and subsequently, by drying overnight under vacuum prior to use.

The second 2-$NsNCl_2$-based aminohalogenation was developed by using *N*-chloro-*N*-sodiumsulfonamide as the nitrogen/chlorine source and copper(I) triflate as the catalyst (Scheme 9).[23] This reaction provides a more convenient protocol by the use of solely pure NsNClNa for the aminohalogenation reaction as compared to the above mixed nitrogen and chlorine sources. In addition to α,β-unsaturated esters, two simple olefin substrates, *trans*-stilbene and styrene, were also found to be effective for the reaction (Scheme 10).



Scheme 9.



Scheme 10.

The possible catalytic pathway is shown in Scheme 11. At the initial stage, 2-NsNClNa reacts with Cu^{I} triflate to give *N*-chloro-2-nitrobenzenesulfonamide copper compound **B**. The subsequent electrophilic addition of **B** onto the olefin substrate affords the aziridinium intermediate **C** in which the copper ion is associated with the nitrogen of three-membered ring or concurrently with the oxygen of the sulfonyl group. The chlorine anion reacts with intermediate **C** in a three-membered ring opening by the S_N2 mechanism. The S_N2 opening is responsible for the high *anti* stereoselectivity. Intermediate **D** could coexist with **E** in equilibrium before the reaction is quenched. An excess amount of 2-NsNClNa was proven to be necessary to drive the reaction toward the formation of intermediate **E**. At the final stage, the *N*-chloro-2-nitrobenzenesulfonamide copper compound, the actual catalytic species, is regenerated from intermediate **E** for the continuing catalytic cycles. It seems that the strong electron-withdrawing ability of 2-nitrophenylsulfonyl (nosyl) group is important for the formation of the active species **C**.

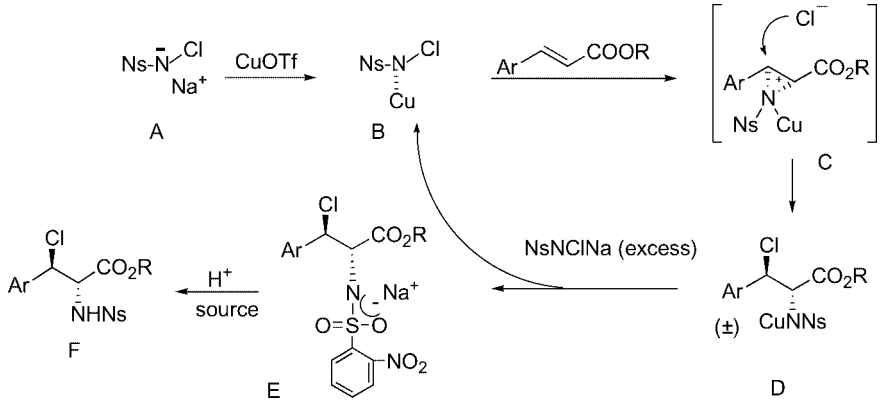
The successful aminohalogenation of above two simple olefin substrates, *trans*-stilbene and styrene, can exclude the possibility for the reaction to go through the α,β-unsaturated addition mechanism.

3. Aminohalogenation of α,β-Unsaturated Ketones and Nitriles

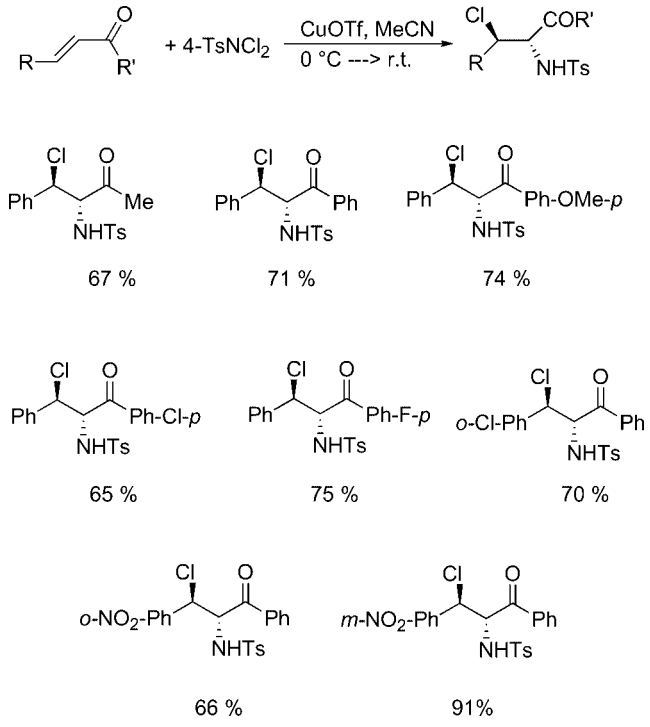
The α,β-unsaturated ketones behaved differently from α,β-unsaturated esters in aminohalogenation reaction.[24] When zinc dichloride was employed as the catalyst only a small amount of haloamine product was produced even after 48 h with most of the olefin starting materials remaining. When rhodium(II) heptafluorobutyrate or the complex derived from iron(III) chloride and triphenylphosphane was used as the catalyst, diamine products were predominantly produced. The reaction of *trans*-4-phenyl-3-buten-2-one with 4-$TsNCl_2$ occurred smoothly only when copper(I) triflate was used as the catalyst, under the previous condition and gave a promising chemical yield at first (<40%). Further operational modifications resulted in up to 91% yields, where the modifications are to perform the reaction at 0 °C for 2 h, and then at room temperature for an additional 10 h. At the same time, 4-$TsNCl_2$ is added slowly into reaction mixture via a syringe pump (Scheme 12). Similar to the situation of the previous α,β-unsaturated ester-based system, the use of 4-Å molecular sieves together with the catalysts further improved the yield. The reaction was found to proceed faster than the aminohalogenation of cinnamate esters, which generally required up to 24 h for the completion.

Interestingly, when aliphatic enones were subjected to the reaction under the same condition, the opposite regioselectivity was obtained for the major isomeric products (Scheme 13). In addition, the aliphatic enones showed faster reaction rates and can be completely consumed within 2 h. Since the aliphatic enones are volatile liquids, an excess amount of these starting materials can be removed simply by distillation after the reaction. When 1.0 equiv. of 4-$TsNCl_2$ was slowly added into the reaction system containing 2 equiv. of methyl vinyl ketone, nearly quantitative yields were obtained. In fact, the crude products were almost pure as revealed by crude ^{1}H NMR analysis.

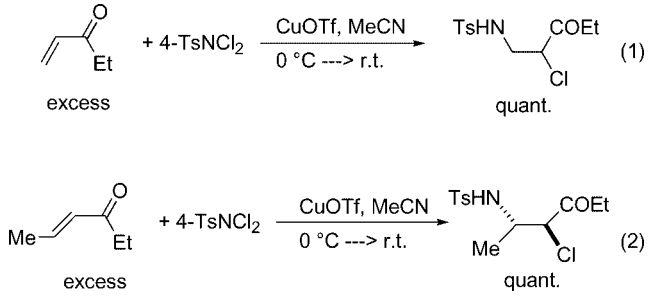
The 2-nitrobenzenesulfonamide-based aminohalogenation of α,β-unsaturated ketones has also been achieved by



Scheme 11.

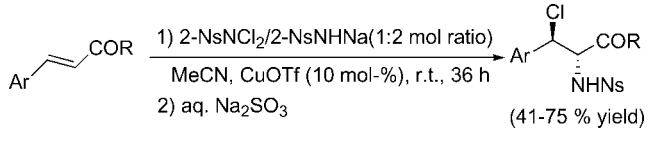


Scheme 12.



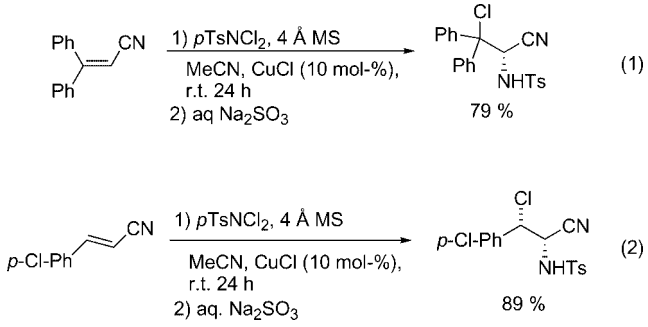
Scheme 13.

using the combinational nitrogen and chlorine source, 2-$NsNCl_2$/2-NsNHNa, in the presence of copper(I) triflate as the catalyst (Scheme 14).[25] For this reaction, there were no regioisomers observed and the stereoselectivity was ranged between 7:1 and 20:1, albeit the chemical yields (41–75%) are lower than those of α,β-unsaturated esters. Interestingly, the pure 2-NsNClNa which worked well with α,β-unsaturated esters did not work well for α,β-unsaturated ketones with only a very small amount of the haloamine product observed.[23]



Scheme 14.

Similar to the aminohalogenation of α,β-unsaturated ketones, α,β-unsaturated nitriles also showed a different performance from α,β-unsaturated ester-based aminohalogenation process (Scheme 15).[26] The reaction of 3,3-diphenylacrylonitrile with 4-$TsNCl_2$ under the previous condition in the presence of zinc(II) dichloride catalyst did not result in any vicinal haloamine product. However, the reaction catalyzed by Cu^I triflate did occur smoothly to give a chemical yield of 67%. Furthermore, when the catalyst was changed to Cu^ICl together with 4-Å molecular sieves, the yield was enhanced to 79%. The use of 4-Å molecular sieves was proven to be crucial for this catalytic system. If there were no 4-Å molecular sieves present in the system, the yield was decreased to 41%. In contrast to the previous α,β-unsaturated ketone and ester-based systems where 4 Å molecular sieves can only improve the chemical yields by about 5–10%.

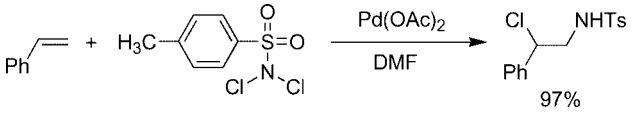


Scheme 15.

4. Aminohalogenation of Unfunctionalized Alkenes

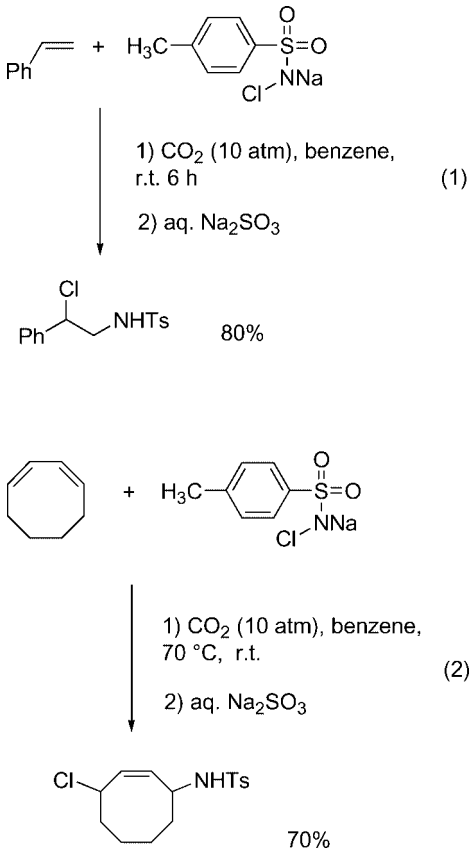
(1) Aminochlorination

The aminohalogenation of unfunctionalized alkenes was re-examined very recently. It was found that palladium acetate was able to catalyze the reaction.[27] The reaction was conducted in DMF at room temperature, and the product was readily transferred into aziridines in the presence of K_2CO_3. When styrene was used as substrate, a nearly quantitative yield of 97% was achieved before it was subjected to cyclization to aziridine in a one-pot operation (Scheme 16).



Scheme 16.

Carbon dioxide was found to promote aminohalogenation of normal alkenes when chloramine-T was used as the nitrogen/halogen source by Komatsu and co-workers (Scheme 17).[28] The reaction was performed at room temperature under CO_2 pressure at 10 atm, in benzene as solvent. The reaction proceeded to completion within 6–9 h without the use of any catalysts to give up to 80% yields and excellent regioselectivity. Besides the normal alkenes as the substrates, dienes can also be employed as the substrates to give 1,4-haloamine products, albeit higher pressure of CO_2 and a prolonged period (24 h) were needed for a complete conversion.

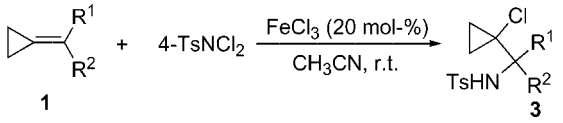


Scheme 17.

Interestingly, when methylenecyclopropanes (MCPs) **1** and vinylidenecyclopropanes (VCPs) were employed as the substrates, the catalyst had to be changed to ion(III) chloride in a loading of 20 mol-% in order to obtain good chemical yields (Table 1).[29] The reaction can be finished at room temperature within 8 hours.

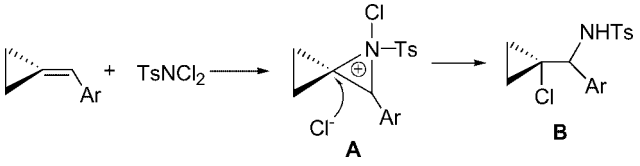
A series of methylidenecyclopropanes were next subjected to this reaction by using $FeCl_3$ as the catalyst. For these substrates, two regioisomers were obtained, and can be easily separated via silica gel flash chromatography to give moderate to good combined yields (Table 2). As can be seen from Table 2, adduct **a** was proven to be the major product.

Table 1. Results of aminohalogenation of methylidenecyclopropanes.



Entry	MCP	R^1	R^2	Yield of **3** (%)
1	**1a**	H	C_6H_5	**3a** (48)
2	**1b**	H	4-Me-C_6H_4	**3b** (53)
3	**1c**	H	4-MeO-C_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-Me-C_6H_4	4-Me-C_6H_4	**3h** (75)
9	**1i**	4-MeO-C_6H_4	4-MeO-C_6H_4	**3i** (99)

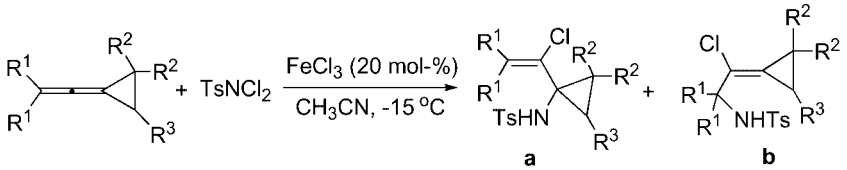
Again, the aziridinium-based mechanism is suggested for this reaction as shown in Scheme 18. In the initial step, the electrophilic addition of $TsNCl_2$ to MCPs forms the corresponding *N*-chloro-*N*-(*p*-tosyl)aziridinium intermediate **A**, which is believed to be the rate-limiting step. The second step is the ring opening of aziridinium by chlorine anion (Cl^-) The C–C hyperconjugation effect enhanced by the strain in the spiro ring bonds could be important in stabilizing the positively charged aziridinium intermediate and in controlling the regioselectivity. The excellent regioselectivity of the product shows the much stronger ability of cyclopropane to stabilize the positive ion as opposed to the aromatic ring. This effect was observed regardless of the position of attachment for the electron-donating group.



Scheme 18.

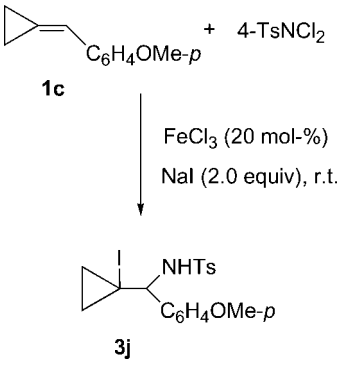
To rule out the possibility of bridged chloronium ion mechanism, the control experiments were also performed as shown in Scheme 19. The aminoiodination product **3j** was

Table 2. Results of aminohalogenation of vinylidenecyclopropanes.



Entry	R^1	R^2	R^3	Yield (%), product **a**	Yield (%), product **b**
1	C_6H_5	H	C_6H_5	**4a** (59)	**5a** (26)
2	C_6H_5	H	*p*-CH_3O-C_6H_4	**4b** (51)	**5b** (21)
3	C_6H_5	*p*-CH_3O-C_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	**4e** (86)	trace

exclusively produced in the presence of NaI, presumably by the attack of iodide anion on the aziridinium ring. This observation can further confirm that the aziridinium intermediates exist during the reaction process.



Scheme 19.

The $\log(k/k_0)$, where k_0 is the reaction rate of MCP **1a**, vs. σ was plotted to figure out the linear free-energy relationship of this reaction. [σ and σ^+ values are obtained from the literature[49a,49b]]. A straight line was obtained with a ρ value of –1.35, which implies the existence of a positive ion intermediate in this reaction (Figure 1). The σ constants fitted the line much better than those of $\sigma^\cdot$ or σ^+, which deviated from a straight line. This determination may also indicate the existence of a bridged aziridinium ion. Further proof against the involvement of a carbocation intermediate lies in the difference between the ρ^+ values reported before, which can be as negative as –4.1, and the ρ value acquired: When 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 through a metal–carbenoid species (M=NTs).[30]

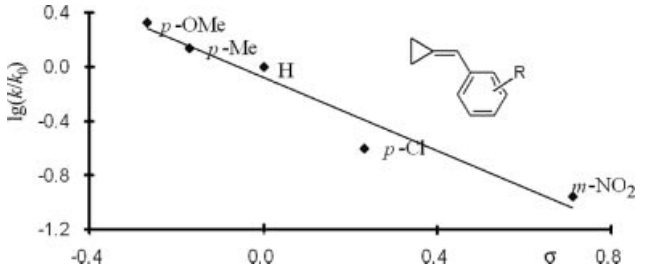


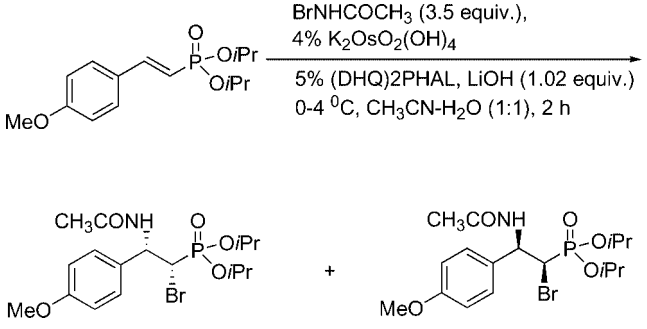
Figure 1. Linear free energy relationship of the aminohalogenation of MCPs.

(2) Aminobromination or Bromoamidation

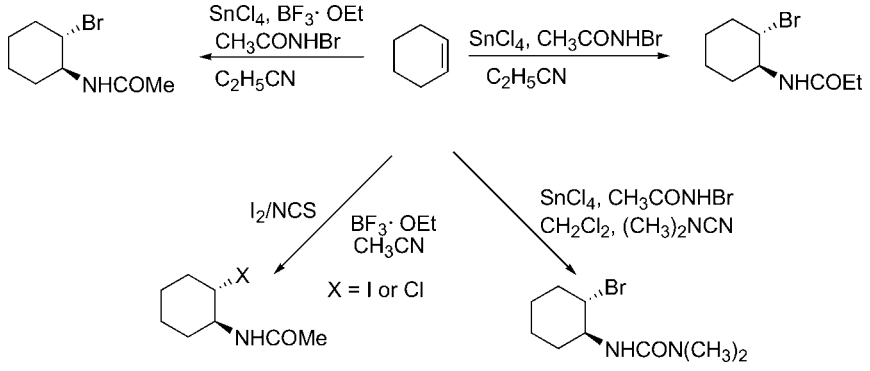
Very recently, Corey and co-workers established the haloamidation reaction of alkenes by using *N*-bromoacetamide, NCS, and I_2 as halogen sources, and various nitriles and *N*,*N*-dimethylcyanamide as nitrogen sources. The reaction is efficiently catalyzed by Lewis acids, such as $SnCl_4$, $SnBr_4$ and $BF_3{\cdot}Et_2O$ (Scheme 20).[2a] Interestingly, the reaction occurred more efficiently when ca. 1 equiv. of H_2O was added into the reaction system. The reaction is believed to go through the formation of bromonium intermediate, which was accelerated by Lewis acids. The resulting bromonium intermediate is then opened by nitriles and cyanamide nucleophiles, which is analogous to the Ritter reaction process.[31]

This reaction has shown a broad substrate scope, and can serve as a general approach to a variety of important synthetic building blocks, such as *N*-acylaziridines, oxazolines, 1,2-amino alcohols, etc. In fact, Corey has already applied this reaction to the challenging total synthesis of anti-influenza neuramidase inhibitor, oseltamivir,[32] with an impressive overall yield of 30%.

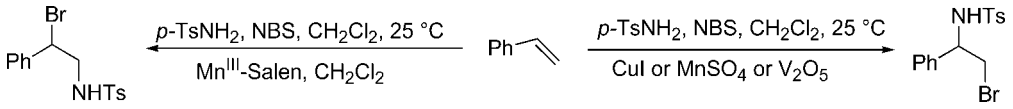
Recently, Lee and co-workers reported the aminobromination of α, β- unsaturated phosphonates under the Sharpless AA conditions by using an excess amount of *N*-



Scheme 21.



Scheme 20.

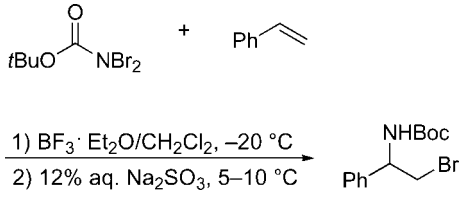


Scheme 22.

bromoacetamide as the nitrogen/halogen source.[33] Four α,β-unsaturated phosphonates were examined and converted into *syn* β-acetylamino-α-bromophosphonates in chemical yields ranging from 21% to 35%. The reaction yielded only *syn* products, unfortunately, no enantiomeric excess was observed (Scheme 21). The mechanism was proposed to be similar to the catalytic pathway of the Sharpless AA reaction, but the catalytic cycle II dominates the process in which the osmium(VI) bis(azaglycolate) is attacked by *N*-bromoacetamide anion. At the same time, the bromine anion attacks at the α position of glycolates from the osmium side to give the final product.

Sudalai and co-workers reported the aminobromination reaction by using the combination of pTsNH$_2$ and NBS as the halogen/nitrogen source.[34] They found that regioselectivity heavily depends on the types of metal catalysts. When CuI, V_2O_5 or $MnSO_4$, were used as the catalysts, an α-amino, β-bromo product was generated. However, when the catalyst was changed to Mn^{III}–salen, an α-bromo, β-amino product was obtained instead (Scheme 22).

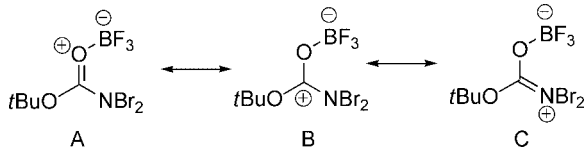
This ionic addition was further extended to the use of carbamate-based nitrogen/halogen source, *tert*-butyl-*N*,*N*-dibromocarbamate (BBC) for aminobromination together with BF_3·OEt_2 as reported by Zwierzak and Sliwinska[35–36] Similar regioselectivity was observed with the final products being *tert*-Boc-protected amines (Scheme 23).



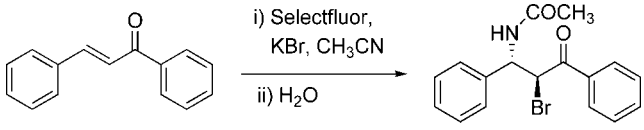
Scheme 23.

The ionic mechanism was proposed based on the fact that the BBC–BF_3·OEt_2 complex has a different IR spectrum from that of the pure BBC. The shifting of C=O bond stretch from 1724 cm^{-1} to 1655 cm^{-1} and 1630 cm^{-1} suggested the diminishing bond order of the carbonyl moiety. The contributing structures that are shown in Scheme 24 (A, B and C) and the IR frequencies were consistent with the assigned structure. The interaction of the boron atom with the carbonyl group of BBC sufficiently ionizes the N–Br bond towards dissociation to form the Br^+ ion.[36]

Selectfluor, since its inception 1980s has been used extensively to introduce fluorine into a variety of compounds under mild conditions. It has also been used in the presence of other halogen species such as Cl^+, Br^+, SCN^+ and NO_2^+.



Scheme 24.



Scheme 25.

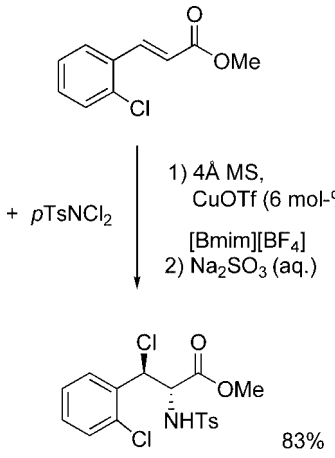
Interestingly, when acetonitrile was used as solvent and KBr as an additive, the reaction of selectfluor with olefins led to a vicinal haloamine product (Scheme 25).[37]

5. Ionic Liquid Media for Aminohalogenation and Asymmetric Aminohalogenation

Since the aminohalogenation reaction is believed to go through the formation of aziridinium ion intermediate, ionic liquids[38–39] should be able to play an important role on this reaction through ionic solvation effects. They can help the chlorine atom to leave the nitrogen source (4-TsNCl$_2$) based on the fact that the partial negative charge on chlorine is surrounded by positively charged 1,3-dialkylimidazolium ion of the ionic liquid. In addition, ionic liquids can also make the resulting aziridinium ion and chlorine anion intermediates more stable.

It has been found that an ionic liquid, [bmim][BF_4], is an effective reaction media for the aminohalogenation of cinnamates to improve the chemical yields (Scheme 26).[40] The reaction occurred at a faster rate, and was finished within 6 h with a reduced amount of catalyst (6 mol-%). More importantly, the scope is expected be extended under the ionic liquid-based catalytic system. For example, methyl *o*-chlorocinnamate worked more efficiently in [bmim][BF_4] to give an yield of 83% and excellent regio- and stereoselectivities.

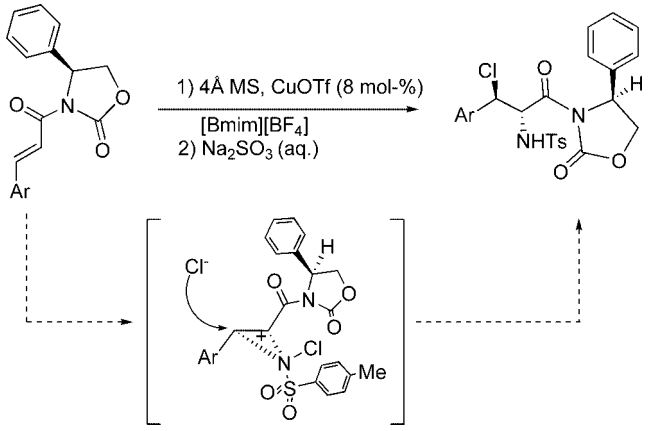
Very recently, the 2-Ns-based aminohalogenation of α,β-unsaturated ketones was achieved in another ionic liquid media, 1-*n*-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][N(SO_2CF_3)$_2$]).[41] This ionic liquid resulted in the first aminohalogenation of electron-deficient alkenes without the use of any catalysts. Interestingly, [Bmim][N(SO_2CF_3)$_2$] was found to be superior not only to classical organic solvents but also to [bmim][BF_4]. Although [bmim][BF_4] was proven to be successful in the



Scheme 26.

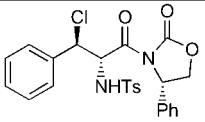
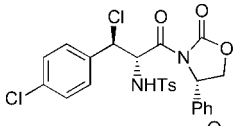
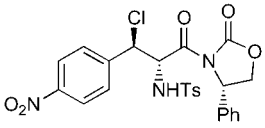
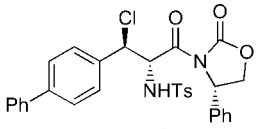
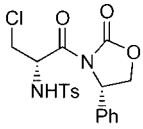
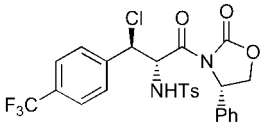
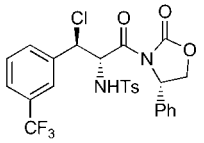
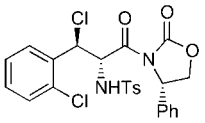
$TsNCl_2$-based aminohalogenation, it failed to give any product for this α,β-unsaturated ketone-based aminohalogenation in the absence of catalyst.

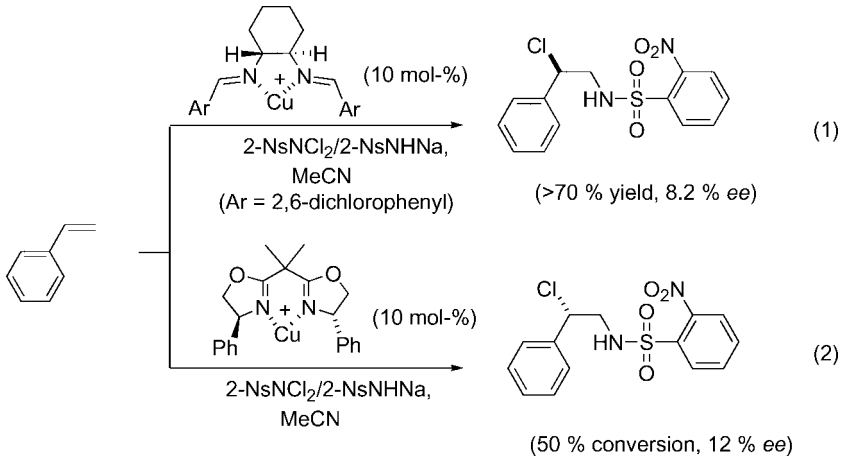
The first asymmetric aminohalogenation of alkenes has also been established by taking advantage of the ionic liquid, [bmim][BF_4] (Scheme 27).[42] Good chemical yields (60–72%) and diastereoselectivities (up to 75% *de*, 7:1 for



Scheme 27.

Table 3. Results of asymmetric aminohalogenation in [bmim][BF_4].

Entry	Product	*dr*	Yield (%)	$[\alpha]_D^{25}$	M.p. /°C
1		3:1	63	+89.2, *c* = 0.9 (+94.1, *c* = 0.21)	81–83 (244, dec.)
2		7:1	70	+67.5, *c* = 0.52 (+68.0, *c* = 0.54)	78–80 (275, dec.)
3		6:1	65	+65.4, *c* = 0.42 (+17.0, *c* = 0.21)	190–192 (263–265)
4		3:1	72	+85.9, *c* = 0.34 (+25.1, *c* = 0.21)	92–94 (210–212)
5		3:1	65	+53.9, *c* = 0.92 (+95.5, *c* = 1.96)	60–62 (172–174)
6		3:1	64	+81.5, *c* = 0.46 (+73.0, *c* = 0.14)	90–92 (249–251)
7		4:1	60	+66.3, *c* = 0.4	65–67
8		4:1	65	+68.8, *c* = 0.64 (+160.0, *c* =0.08)	163–165 (245–247)



Scheme 28.

Entry 2 of Table 3) have been obtained with a good scope of substrates (Table 3). The resulting individual diastereomers have been cleanly separated by column chromatography.

As anticipated the success of this asymmetric aminohalogenation is largely attributed to the high polarity of ionic liquids by solvation effects to decrease the energy of resulting aziridinium intermediate. The diastereochemistry is controlled by non-chelating template (Scheme 27). The electrophilic species approaches the substrate from the less hindered side of the oxazolidinone ring. The ring opening of aziridinium intermediate through S_N2 substitution has to proceed through the more bulky side of the phenyl ring of the oxazolidinone to give the *anti* stereochemistry.

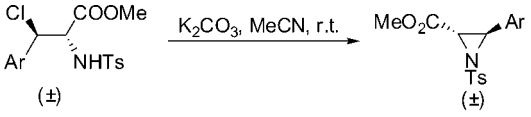
The asymmetric catalytic aminohalogenation controlled by ligand-metal complexes has not been successful. However, encouraging preliminary results of this asymmetric reaction have been obtained in our laboratories as shown in Scheme 28. This reaction took an advantage of the catalytic complexes of metal copper and chiral diimine ligand (*S*,*S*) which was initially established by Jacobsen for the asymmetric aziridination reaction.[14a] The $NsNCl_2$/NsNHNa combination was used as the nitrogen/halogen source in acetonitrile. Good yield (70%) and 8.2% *ee* were determined with styrene as the substrate. Evans (*S*)-bis(oxazoline)copper complex[14b] was also applied to this reaction and led to enantiomeric excess of 12% *ee*, although incomplete conversion (≈ 50%) was observed. These results indicate that the Lewis acidic metal center of the catalyst can be associated with the transition-state during the formation of aziridinium intermediate, which is necessary to generate the enantioselectivity.

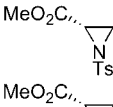
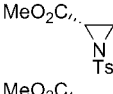
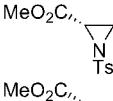
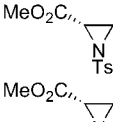
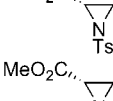
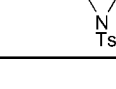
6. Applications of Vicinal Haloamine Products

The first application of aminohalogenation was conducted by synthesizing aziridinecarboxylates via intramolecular cyclization of vicinal haloamine products.[43] It is well known that aziridinecarboxylates are very useful building blocks for the synthesis of a variety of nitrogen-containing compounds that are biologically important.[14,44] Among aziridine derivatives, alkyl *N*-*p*Ts- and *N*-*o*-Ns-aziridine-2-carboxylates are particularly useful because they can undergo regioselective ring openings to afford α- and β-amino esters when treated with various nucleophiles.[14] Thus far, the application of 1,2-vicinal haloamines for the synthesis of aziridinecarboxylates has not been well documented. This is probably due to the fact that olefin-based synthesis of *anti* alkyl 3-halo-2-(*p*-tolylsulfonamido)-3-arylpropionates and *anti* alkyl 3-halo-2-(*o*-nitrophenylsulfonamido)-3-arylpropionates have not been available until now.

The synthesis of *N*-*p*-tosyl- and *N*-*o*-nosylaziridines required the use of 2.0 equiv. of potassium carbonate in acetonitrile solution.[45a] The cyclization can be finished at room temperature within 3 h to give up to 97% yields (Table 4). Under this condition, there was no epimerization

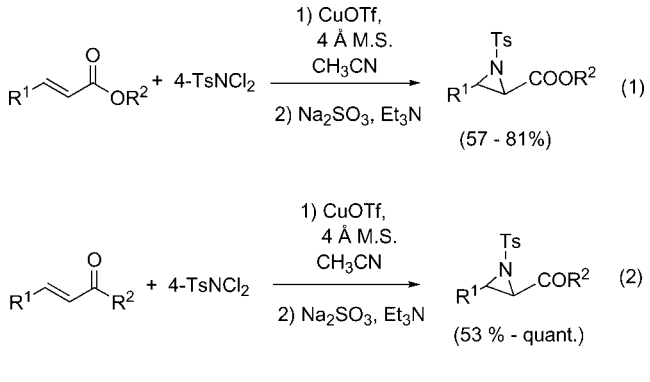
Table 4. Results of cyclization of methyl 3-chloro-2-(*p*-tolylsulfonamido)-3-arylpropionates.



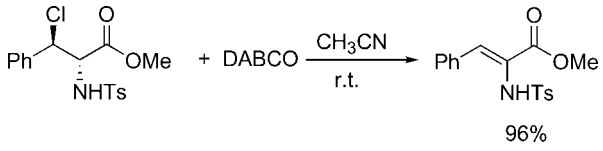
Entry	Ar	Product (±)	Yield (%)
1	C_6H_5		97
2	4-Me-C_6H_4		94
3	2-Me-C_6H_4		89
4	4-Cl-C_6H_4		89
5	4-Br-C_6H_4		88
6	4-NO_2-C_6H_4		83

observed on the α position of 2-methoxycarbonyl-3-phenyl-*N*-(*o*-nitrophenyl)sulfonylaziridine as revealed by quick ^{1}H NMR analysis.

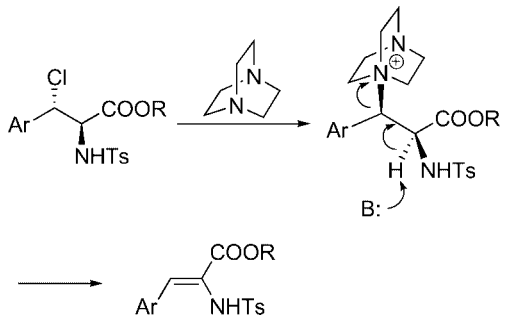
In a later study, a simple one-pot procedure for the stereoselective synthesis of *anti* 3-alkyl and 3-aryl-*N*-(*p*-tosyl)aziridine-2-carboxylates and ketones was also developed (Scheme 29).[45b] The one-pot procedure consists of the



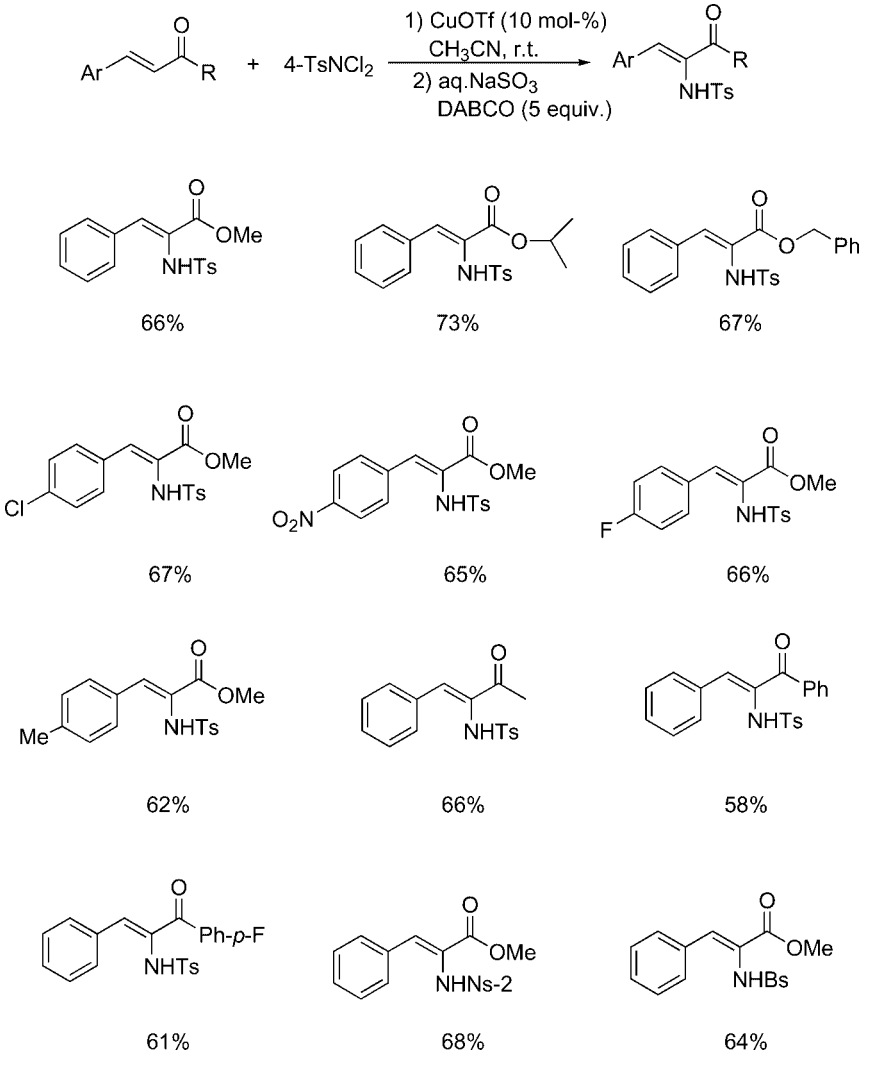
Scheme 29.



Scheme 30.



Scheme 31.



Scheme 32.

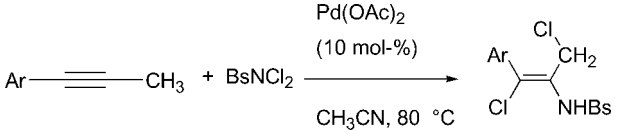
aminohalogenation reaction and in situ intramolecular S_N2 substitution by using triethylamine as the base. For several enone cases, a slightly modified procedure is used in which 1.0 equiv. of *p*$TsNCl_2$ was slowly added into 2.0 equiv. of enone for the aminohalogenation reaction followed by quenching with aqueous Na_2SO_3. This procedure resulted in crude aziridines that were nearly pure as revealed by quick ^1H NMR analysis. Moderate to excellent yields and high *anti* stereoselectivity have been achieved for 21 examples.

The second application of aminohalogenation reaction was represented by the synthesis of *N*-protected α,β-dehydroamino acid derivatives that are important building blocks for organic and medicinal research. Much work on the asymmetric hydrogenation has been strongly dependent on the use of these compounds to give enantiomerically pure amino acids.[46–47] In addition, α,β-dehydroamino acid derivatives have been found to be the structural units in many biologically active natural products. The known synthetic approaches to *N*-protected dehydroamino acids can be used for this synthesis, but they suffer from a few shortcomings, such as multiple-step synthesis, harsh conditions, expensive reagents, and unsatisfactory yields. The vicinal haloamines derived from the aminohalogenation reaction of α,β-unsaturated esters and ketones were found to undergo the elimination by treatment with 2.0 equiv. of DABCO to give α,β-dehydroamino acid and ketone derivatives (Scheme 30). Interestingly, other organic bases that were examined did not result in dehydroamino products.

The tentative reaction mechanism is given in Scheme 31. The first step involves a typical S_N2 substitution reaction between the vicinal haloamine and DABCO to give quaternary amine salt with *syn* stereoselectivity. The *syn* diamino intermediate is subjected to the following elimination reaction by the extra amount of base. The *syn* stereoselectivity of the first step accounts for the complete control of the geometry of the resulting dehydroamino acid after the E2 elimination (Scheme 31).

The one-pot in situ operation for this transformation was achieved by quenching with aqueous Na_2SO_3 at first, and then followed by adding a larger excess amount of DABCO (5.0 equiv.) into the quenched reaction mixture. This one-pot transformation proceeded to completion within 30 min (Scheme 32).

The halogen-functionalized *N*-tosyl-α,β-dehydroamino derivatives have been successfully synthesized through the aminohalogenation of alkynes (Scheme 33). This reaction was conducted by treating alkynes with *N*,*N*-dichlorobenzenesulfonamide at 80 °C in the presence of palladium acetate catalyst. The reaction was suggested to go through the formation of β-halovinyl palladium and π-allylpalladium species.[48]



Scheme 33.

7. Conclusion

The aminohalogenation reaction of olefins (aminobromination and aminochlorination) has become a powerful synthetic tool for organic chemistry. More applications of this reaction will be explored in the near future. The new aziridinium mechanism of this reaction has been strongly supported by the physical organic chemistry determinations and the electrophilic diamination results. Finally, the asymmetric aminohalogenation will become an increasingly important and interesting topic in organic chemistry and will attract more synthetic chemists.

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