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Unexpected copper-catalyzed aminohalogenation reaction of olefins using *N*-halo-*N*-metallo-sulfonamide as the nitrogen and halogen sources

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Abstract—*N*-Chloro-*N*-sodium-sulfonamide was found to react with olefins in the presence of copper catalyst to give vicinal haloamine derivatives instead of aziridines. The resulting regio and stereochemistry indicates that this unexpected reaction could proceed through the formation of unprecedented *N*-chloro-*N*-copper-2-nitrobenzenesulfonyl aziridinium intermediates, which can increase the successful chance to render the asymmetric version of the aminohalogenation reaction. In addition, this finding provides a more convenient protocol by the use of solely pure NsNClNa for the aminohalogenation reaction as compared to the mixed nitrogen and chlorine sources consisting of $NsNCl_2$ and NsNHNa as previously reported by us. Two new simple olefin substrates, *trans*-stilbene and styrene, were also found to be effective for this new reaction system.

It is well known that transition metal copper can deliver *N*-halo-*N*-metallo-sulfonamides onto olefins to afford aziridine derivatives.[1–4] This delivery is believed to proceed through the formation of metal-nitrenoid intermediates as the crucial catalytic species.[1] These intermediates can also be generated by reacting *N*-halo-*N*-metallo-sulfonamides with other transition metals such as rhodium (II),[5] Fe(III)[6] and Mn(salen) complexes.[7] Recently, we have developed several new olefin addition reactions using *N*-*N*-dichloro-sulfonamides and their derivatives.[8–10] During the continuing study of these systems, we have now surprisingly found that *N*-halo-*N*-metallo-sulfonamides can react with olefins to give 1,2 vicinal haloamines in highly stereo and regioselective manners in the presence of copper catalysts under new conditions. In this communication, we report this discovery which is represented in Scheme 1 and the results collected in Table 1.

The current study was initiated by searching for reactive species of the previous aminohalogenation system where the combination of $NsNCl_2$ and NsNHNa was utilized as the nitrogen and chlorine sources.[8c] The former can react with olefins to form novel *N*-(2-nosyl), *N*-chloroaziridinium intermediates (Scheme 2), the latter generates a favorable ionic environment for aminohalogenation[8c] instead of diamination.[8b]

The model reaction was carried out by treating methyl cinnamate with an excess amount of 2-NsNClNa in acetonitrile solution (case 1 of Table 1) in the presence of 10 mol% of copper(I) triflate. Concurrently, three other copper catalysts, $Cu(OTf)_2$, CuCl and $CuCl_2$, were also examined as the catalysts under similar conditions. At first, CuOTf was found to catalyze the reaction to completion within 24 h at room temperature to give *anti* methyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-phenylpropionate in 74% chemical yield. The other three copper compounds can also catalyze the reaction to completion, but relatively low yields were obtained ($< 50\%$). Although the above copper compounds are regarded as typical aziridination catalysts in the reactions of *N*-halogeno-*N*-metallo-sulfonamides with olefins, no aziridine products were detected under the current conditions. This observation suggests that the aminohalogenation products might not be formed from aziridines. This assumption has been further confirmed by subjecting the synthesized *N*-*o*-nitrobenzenesulfonyl-2-carbomethoxy-3-phenylaziridine[11] to the reaction with chloride salts, KCl, NaCl, R_4NCl and 2-NsNClNa in the presence of copper catalyst, and no vicinal chloroamine products were observed, when the reaction was carried out overnight.

Cinnamic esters were chosen as the substrates not only because they are the most synthetically useful substrate classes for olefinic reactions[2] but also because they result in known haloamine products, which makes it convenient to compare with the previous system.[8c] The careful examination of the results listed in Table 1 reveals that cinnamic esters with either electron-donating or electron-withdrawing

Keywords: catalysis; aminohalogenation; vicinal chloroamine; *N*-chloro-*N*-metal-nitrobenzenesulfonamide.

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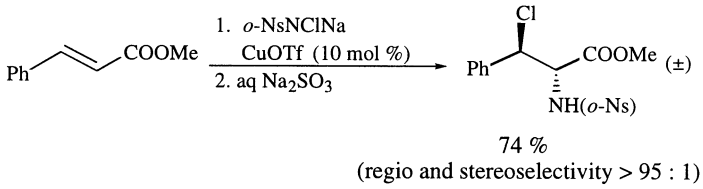
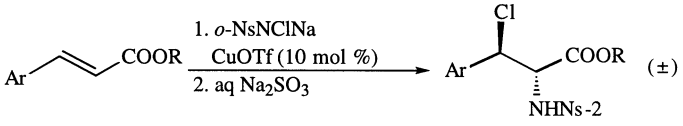
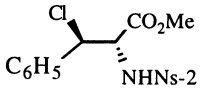
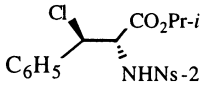
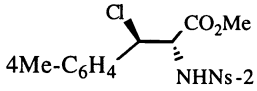
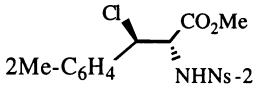
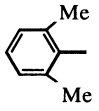
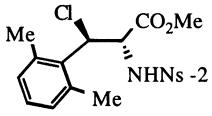
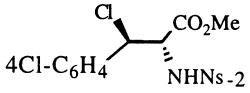
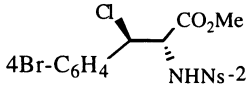
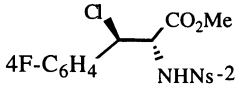
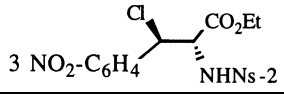


Scheme 1.

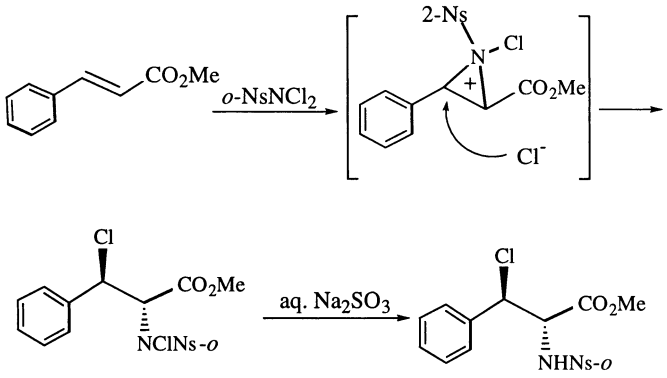
groups on their aromatic rings can be subjected to this reaction. For all of these cases which we examined, the regioselectivity has been completely controlled as revealed by the crude ^{1}H NMR analysis. Meanwhile, excellent *anti*/*syn* stereoselectivity was also obtained for most of the cases. Only in cases **5** and **9**, modest stereoselectivity was obtained (*anti*/*syn*=5:1 and 9:1, respectively). For cases **1** and **6**, the *anti*/*syn* stereoselectivity was found to be superior to that generated under the previous system. Besides the cinnamate substrates, two simple olefins also showed their effectiveness in regard to yields, and regio and stereoselectivity (Scheme 3). In the case of styrene, excellent regioselectivity (> 95 : 1) and yields (82%) were achieved. Complete *anti*/*syn* stereoselectivity, albeit in a modest yield (50%), was obtained using *trans*-stilbene as the substrate. In contrast, these simple olefins resulted in very complex products and diminished yields in the previous $NsNCl_2$/NsNHNa-based system. The successful utility of the simple olefins can

Table 1. Results of CuOTf-catalyzed aminochlorination of cinnamic esters

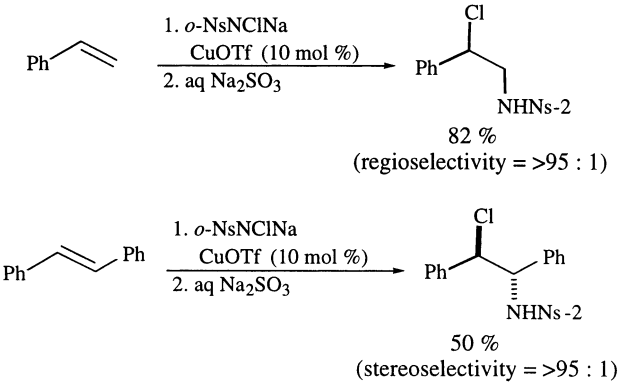


Entry	Ar	R	Product (±)[a]	Stereoselectivty[b] (*anti*/*syn*)[a]	Yield (%)[c]
1	C_6H_5	Me		>95:1	74
2[d]	C_6H_5	*i*-Pr		16:1	76
3	4-Me–C_6H_4	Me		24:1	72
4	2-Me–C_6H_4	Me		32:1	72
5[d]		Me		5:1	70
6	4-Cl–C_6H_4	Me		>95:1	66
7	4-Br–C_6H_4	Me		24:1	76
8	4-F–C_6H_4	Me		19:1	74
9	3-NO_2–C_6H_4	Et		9:1	63

[a] All pure products have been proven to be identical to those obtained from our previously aminohalogenation system.
[b] Estimated by crude ^{1}H NMR determination. >95% means only one isomer was observed.
[c] The yeilds after purification via column chromatography.
[d] The combined yield of two isomers which were difficult to separate by column chromatography.



Scheme 2.

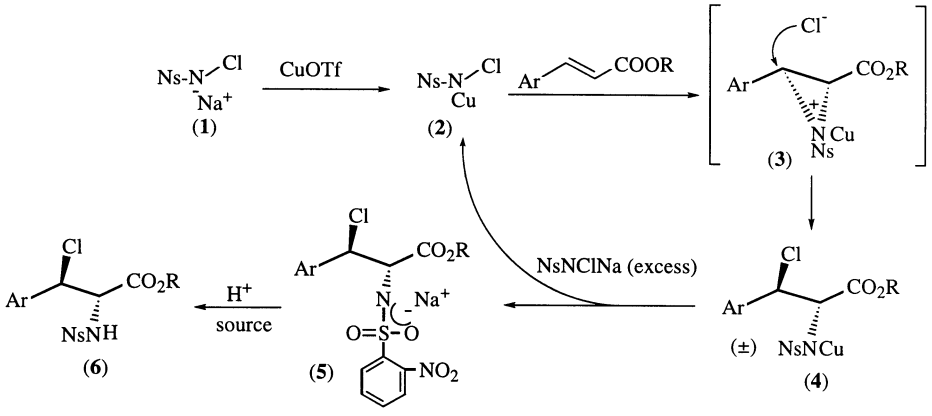


Scheme 3.

exclude the possible mechanism involving the copper-mediated Michael-type addition of nitrogen source onto cinnamates.

To explain the regio and stereoselectivity of the resulting haloamine products, a detailed catalytic pathway is proposed as shown in Scheme 4. At the initial stage, 2-NsNClNa reacts with Cu(I) triflate to give *N*-chloro-*N*-copper-2-nitrobenzenesulfonamide **2**. The subsequent electrophilic addition of **2** onto the olefin substrate affords the aziridinium intermediate **3** 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 generated near the carbonium active sites of intermediate **3** undergoes the three-membered ring opening via the S_N2 mechanism. The S_N2 opening is responsible for the high *anti* stereoselectivity. The observed regioselectivity can be readily explained based on the fact that β-position of the aziridinium intermediate is loaded with more positive charge than its α-position due to the stabilization effect from β-aromatic ring. Intermediate **4** could coexist with **5** in equilibrium before the reaction is quenched. Obviously, an excess amount of 2-NsNClNa is necessary to drive the reaction toward the formation of intermediates **5**. At the final stage, *N*-chloro-*N*-copper-2-nitrobenzenesulfonamide, the actual catalytic species, is regenerated from intermediate **5** for the continuing catalytic cycles. It seems that the strong electron-withdrawing ability of 2-nitrobenzenesulfonyl (nosyl) group is important for the formation of the active species **3**.

In addition, medium effects proved to be critical for this catalytic system. Only acetonitrile showed effectiveness while other solvents, such as CH_2Cl_2, $CHCl_3$, THF, benzene, toluene, etc. resulted in either a tiny amount of product or no haloamine at all. An excess amount of 2-NsNClNa (3.0 equiv.) is necessary for the complete consumption of olefin starting materials, which helps to generate the actual catalytic species (**2**) as well as intermediate (**5**) as indicated in Scheme 4. In fact, a stoichiometric amount or 2.0 equiv. of 2-NsNClNa resulted in only $< 50\%$ conversion even in a



Scheme 4.

prolonged reaction period. It should also be noticed that no aziridine products were detected even in incomplete experiments. After reductive hydrolysis quenching of the reaction mixture with saturated aqueous Na_2SO_3 solution, the unreacted 2-NsNClNa is converted to its sulfonamide form. It is easy to recover 2-$NsNH_2$ for reuse because of its low solubility in several common solvents including $CHCl_3$ and CH_2Cl_2. In addition to the solvent effects, the concentrations of reactants and the catalyst proved to be critical for this reaction as well. When the reaction mixture was diluted to 1/2 of the concentration shown in the typical procedure, only a trace amount of haloamine product was detected after the reaction was carried out over 24 h as revealed by the crude ^{1}H NMR or TLC analysis.

Obviously, the use of solely pure *N*-chloro-*N*-sodium-2-nitrobenzenesulfonamide provides a more convenient protocol for the aminohalogenation reaction as compared to the mixed nitrogen and chlorine sources consisting of $NsNCl_2$ and NsNHNa. This study suggests that other analogous nitrogen/halogen sources, such as *N*-halo-*N*-metal fluorinated carbamates (e.g. $CF_3OCONClLi$) and amides, should also be tested for the aminohalogenation reaction. The novel *N*-chloro-*N*-copper-2-nitrobenzenesulfonyl aziridinium intermediates can increase the successful chance to render the asymmetric version of the aminohalogenation reaction by screening variety of transition metal–ligand complexes.[12]

In summary, the novel copper-catalyzed aminohalogenation reaction using 2-NsNClNa as the nitrogen/chlorine source has been established without the formation of aziridine derivatives. This reaction occurs under mild and convenient conditions in highly regioselective and stereoselective manners. More work by employing new substrates, such as cyclic α,β-unsaturated esters and ketones for this new catalytic system and by using *N*-copper-*N*-(2-nosyl)aziridinium in asymmetric synthesis will be carried out in the future.

1. Experimental

Into a dry vial was added methyl cinnamate (162 mg, 1.00 mmol) and freshly distilled acetonitrile (3 mL). The reaction vial was immersed in a room temperature bath, and 2-NsNClNa (755 mg, 3.0 mmol) and copper(I) trifluoromethanesulfonate benzene complex (50.3 mg, 0.10 mmol, 10 mol%) was added. The resulting dark brown solution in the capped vial was stirred at room temperature for 24 h without argon protection. As the reaction proceeded to completion over the course of 24 h, the color of the solution changed from dark brown to greenish brown and finally to light green. The reaction was quenched by dropwise addition of saturated aqueous Na_2SO_3 solution (2 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness. Purification by flash chromatography (EtOAc/hexane, 3/7 v/v) provided colorless oil *anti* methyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-phenylpropionate **1** (295 mg, 76% yield) which has been unambiguously confirmed by the conversion to a known sample.[8c] ^{1}H NMR (200 MHz, $CDCl_3$), δ 8.04–7.87 (m, 2H), 7.92–7.87 (m, 1H), 7.74–7.69 (m, 2H), 7.35–7.29 (m, 5H), 6.12 (d, *J*=9.61 Hz, 1H), 5.28 (d, *J*=6.12 Hz, 1H), 4.74 (dd, *J*=6.12, 9.61 Hz, 1H), 3.62 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ 168.3, 147.4, 135.5, 134.1, 133.7, 133.0, 130.5, 129.4, 128.8, 127.6, 125.6, 63.1, 61.3, 52.8.

^{1}H and ^{13}C NMR spectra of compounds **2**–**9** of Table 1 have been confirmed to be identical to those of known samples.[8c]

Acknowledgements

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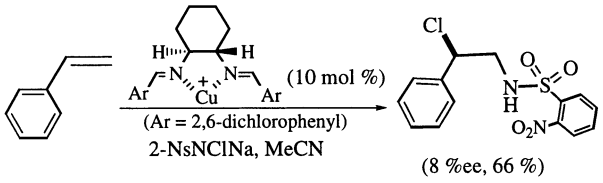
11. *N-o*-Nitrobenzenesulfonyl-2-carbomethoxy-3-phenylaziridine was synthesized via the deprotonation of *anti* methyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-phenylpropionate with K_2CO_3 in DMF followed by cyclization.
12. Our latest results indicate that the asymmetric catalytic aminohalogenation reaction can be achieved, although only 8% ee was observed for the reaction of styrene with 2-NsNClNa when the complex of bis[(2,6-dichlorobenzylidene)diimino]-cyclohexane-CuOTf was used as the catalyst (HPLC analysis: Chiralcel AD, PrOH/hexane (15/85), 0.5 mL min^{-1}).



(8 %ee, 66 %)