DOI: 10.1002/ejoc.200600902

CuCl-Catalyzed Regio- and Stereoselective Aminohalogenation of α,β-Unsaturated Nitriles

Jian-Lin Han,[a] San-Jun Zhi,[a] Le-Yong Wang,[a] Yi Pan,*[a] and Guigen Li*[b]

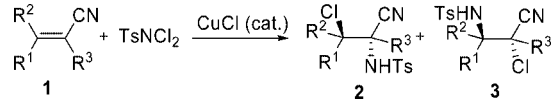
Keywords: Aminohalogenation / α,β-Unsaturated nitriles / Copper chloride

α,β-Unsaturated nitriles were found to be suitable substrates for aminochlorination with *N*,*N*-dichloro-*p*-toluenesulfonamide (4-$TsNCl_2$) in the presence of CuCl as the catalyst (10 mol-%) and 4 Å molecular sieves. The reaction is very convenient to carry out at room temperature without the protection of inert gases, and this method provides an easy route to vicinal haloamino nitriles with excellent regio- and stereoselectivities and in good chemical yields. The stereochemistry has been unambiguously confirmed by X-ray structural analysis.

Introduction

Aminohalogenation and related reactions of multiply functionalized alkenes have become an interesting topic in organic synthesis because the resulting vicinal haloamines are important building blocks in organic and medicinal chemistry.[1–5] The products resulting from these processes can readily be converted into numerous other derivatives by replacement of the halogen in both intramolecular and intermolecular reactions. In the past few years, we and other groups have developed the catalytic aminohalogenation of alkenes with the aid of several nitrogen/halogen sources such as 4-$TsNCl_2$,[6a,6b] 2-NsNNsCl (2-Ns: 2-nitrophenylsulfonyl), a combination of 2-$NsNCl_2$ and 2-NsNHNa,[6c,6d] and a combination of NBS and $TsNH_2$ in the presence of metal catalysts.[6e] The processes are believed to proceed according to a mechanism that involves aziridinium ion intermediates, which could explain the stereo- and regioselectivities of the resulting haloamine and diamine products.[6–9]

Although several synthetic approaches to vicinal haloamine functionalities have been developed,[6–8,10] the catalytic aminohalogenation of a series of functionalized alkenes has not been well documented. So far, there have been few substrates, including α,β-unsaturated ketones,[7b] α,β-unsaturated esters,[6a,11] methylenecyclopropanes, and vinylidenecyclopropanes[12] that have been subjected to the aminohalogenation reaction. In our ongoing investigation of this reaction we have now turned our attention to the aminohalogenation of α,β-unsaturated nitriles, which could have great potential in pharmaceutical chemistry.[13] In this work we report the preliminary results of our investigation of aminohalogenation with these substrates under new catalytic conditions (Scheme 1). The new method provides an easy route to vicinal haloamino nitriles and represents an important extension of the substrate scope of our original aminohalogenation.



Scheme 1.

Results and Discussion

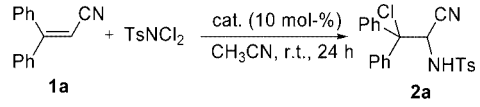
Initially, a readily available starting material – 3,3-diphenylacrylonitrile (**1a**) – was subjected to the reaction under our previous catalytic conditions. The reaction was performed in acetonitrile and catalyzed by use of CuOTf as the catalyst in the presence of molecular sieves (4 Å) to give the corresponding aminochlorinated product **2a** in a chemical yield of 67%. To improve the yield, a variety of other catalysts, such as CuCl, $CuCl_2$, $PdCl_2$, $Pd(OAc)_2$, $ZnCl_2$, AgOTf, and (salen)Mn^{III} {[*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine]manganese(III) chloride} were then utilized for this reaction. The results are listed in Table 1.

As indicated in Table 1, CuCl was found to catalyze the reaction to completion within 24 h and generated the vicinal haloamino nitrile **2a** in the highest chemical yield (79%). The reaction with copper(II) chloride catalyst also gave the haloamine product, but in a slightly lower yield

[a] School of Chemistry and Chemical Engineering, Nanjing University, and State Key Laboratory of Coordination, Nanjing University,
Nanjing 210093, P. R. China
E-mail: yipan@nju.edu.cn
[b] Department of Chemistry and Biochemistry, Texas Tech University,
Lubbock, Texas 79409-106, USA
E-mail: guigen.li@ttu.edu

(75%, Entry 3, Table 1). Surprisingly, when CuOTf, the most effective catalyst for α,β-unsaturated ketones and esters, was employed as the catalyst, a lower yield (67%) of product **2a** was obtained within the same period of time (Entry 1, Table 1).

Table 1. Aminochlorination of 3,3-diphenylacrylonitrile (**1a**).[a]



Entry	Catalyst	Yield (%)[b]
1	CuOTf	67
2	CuCl	79
3	$CuCl_2$	75
4	$PdCl_2$	59
5	$Pd(OAc)_2$	N.R.[c]
6	$ZnCl_2$	N.R.[c]
7	AgOTf	16
8	(salen)Mn^{III}	62

[a] Conditions: 1 mmol of nitrile and 2 mmol of $TsNCl_2$ in CH_3CN (4 mL) in the presence of molecular sieves (4 Å) (0.5 g) at room temperature for 24 h. [b] Isolated yields. [c] No reaction was observed.

To investigate this catalytic reaction further (Table 2), several other common solvents were also examined, but CH_3CN was found to be the only efficient choice for this reaction. Other solvents, such as CH_2Cl_2, toluene, DMF, and THF, afforded either none or only trace amounts of the corresponding vicinal haloamino nitriles (Entries 2–6, Table 2). As in our previous systems, molecular sieves (4 Å) were found to be essential for the reaction: the yield was decreased to 41% if molecular sieves (4 Å) were not added (Entry 7, Table 2). The role of molecular sieves (4 Å) could be to absorb some of the metal catalyst on their surfaces to enhance the catalytic activity further. It turned out that the reaction was not sensitive to temperature change: similar yields could be obtained either on raising the temperature to 50 °C or on decreasing it to 5 °C (71% yield for 50 °C and 78% yield for 5 °C). The reaction generally required 24 h for the complete consumption of the starting α,β-unsaturated nitriles. Shortening of the reaction time to 12 h resulted in a much lower yield of **2a** (41%). It was also found that at least 2 equiv. of $TsNCl_2$ was needed for the complete conversion, the yield being decreased from 79% to 51% when 1.2 equiv. of $TsNCl_2$ was used (Entry 12, Table 2).

After the reaction conditions had been optimized, a series of α,β-unsaturated nitriles were investigated carefully. As can be seen in Table 3, this reaction has a broad substrate range: cinnamonitriles (Entries 2 and 3, Table 3), a β-substituted cinnamonitrile (Entry 1, Table 3), and α-substituted cinnamonitriles (Entries 4–9, Table 3) can all be employed to give modest to very good chemical yields (55–89%). These substrates showed good to excellent stereoselectivities, with ratios ranging from 7:1 to >20:1. In two cases (Entries 3 and 9, Table 3), only the *anti* isomers were observed; only one regioisomer was observed for each of these cases. In the case of the aromatic substrate with a strongly electron-withdrawing group (NO_2) on the aromatic ring [3-(4-nitrophenyl)acrylonitrile], only a trace amount of aminochlorination product was observed even after the reaction time had been extended to 72 h at 50 °C.

In the cases of cinnamonitriles and β-substituted cinnamonitriles (Entries 1–3, Table 2), regioselectivities similar to those observed in aminohalogenation reactions of α,β-unsaturated esters and ketones were achieved. However, when α-substituted cinnamonitriles (Entries 4–9, Table 2) were employed for the reaction, the opposite regioselectivities were observed for the major isomeric products, which are β-amino nitriles (Scheme 2). These products can be readily converted into the useful β-amino acids.

The mechanism of this reaction is believed to be similar to that of our previously reported aminohalogenation of α,β-unsaturated esters and ketones. The first step would be the formation of the aziridinium intermediate, and this positively charged intermediate would be attacked by a chloride anion to give the aminohalogenation adducts. The regio- and stereoselectivity of this reaction can be explained well on the basis of this mechanistic hypothesis involving these key aziridinium intermediates.

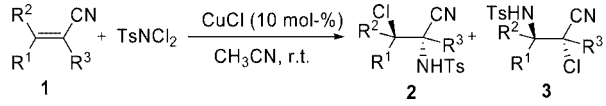
Of all the products shown in Table 3, only **3d** was successfully recrystallized suitably for X-ray crystallographic

Table 2. Aminochlorination of 3,3-diphenylacrylonitrile (**1a**).[a]

Entry	Solvent	Molecular sieves (4 Å) (g)	Substrate[b]	Time (h)	Temperature (°C)	Yield (%)[c]
1	CH_3CN	0.5	1:2	24	25	79
2	BnCN	0.5	1:2	24	25	20
3	CH_2Cl_2	0.5	1:2	24	25	0
4	toluene	0.5	1:2	24	25	15
5	DMF	0.5	1:2	24	25	0
6	THF	0.5	1:2	24	25	5
7	CH_3CN	0	1:2	24	25	41
8	CH_3CN	0.5	1:2	24	5	78
9	CH_3CN	0.5	1:2	24	50	71
10	CH_3CN	0.5	1:2	12	25	41
11	CH_3CN	0.5	1:2	48	25	79
12	CH_3CN	0.5	1:1.2	24	25	51

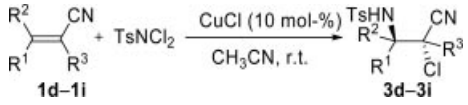
[a] Conditions: 1 mmol of **1a** and 4 mL of solvent in the presence of CuCl (0.1 mmol, 10 mol-%) were used. [b] Ratio of **1a**/$TsNCl_2$. [c] Isolated yields.

Table 3. Results of CuCl-catalyzed aminochlorination of α,β-unsaturated nitriles.[a]



Entry	R^1	R^2	R^3	Product (±)	Stereoselectivity[b] (*anti*/*syn*)	Yield[c] (%)
1	Ph	Ph	H	**2a**	N/A	79
2	*p*-MeC_6H_4	H	H	**2b**	10:1	76
3	*p*-ClC_6H_4	H	H	**2c**	>20:1	55
4	H	Ph	Ph	**3d**	9:1	76
5	H	*p*-ClC_6H_4	Ph	**3e**	10:1	89
6	H	*o*-ClC_6H_4	Ph	**3f**	10:1	69
7	H	Ph	*p*-ClC_6H_4	**3g**	8:1	67
8	H	*p*-ClC_6H_4	*p*-ClC_6H_4	**3h**	7:1	85
9	H	*o*-ClC_6H_4	*p*-ClC_6H_4	**3i**	>20:1	61

[a] Conditions: 1 mmol of nitrile and 2 mmol of $TsNCl_2$ in CH_3CN (4 mL) in the presence of CuCl (0.1 mmol, 10 mol-%) and molecular sieves (4 Å) (0.5 g) at room temperature for 24 h. [b] Estimated by crude ^1H NMR determinations; ">20:1" means no minor isomer was detected. [c] The yields after purification by preparative TLC.



Scheme 2.

analysis. As shown by the ORTEP drawing of **3d** in Figure 1, the stereochemistry was unambiguously confirmed. In Entries 1–3 in Table 3 the positively charged aziridinium ion should be better stabilized on the β-position of each substrate, and the subsequent S_N2 ring-opening by the chloride anion would thus be direced onto this position. In the α,α-disubstituted cases (Entries 3–9 in Table 3), however, in which there is only one substituent on their β-positions, the aziridinium stabilization situation would be reversed and the subsequent attack of the chloride anion would be directed onto their α-positions to give the opposite regioselectivity.

Finally, attempts to employ aliphatic nitriles such as acrylonitrile and cyclohexylideneacetonitrile for this reaction have not been successful. Both Cu^I and Cu^{II} chloride, and also Cu^I triflate, failed to give any aminohalogenation adducts, even after the temperature was enhanced with extension of the reaction time. The poorer stabilization ability of aliphatic groups in relation to their aromatic counterparts could be responsible for this observation. Further study of the use of these substrates for aminohalogenation with the aid of ionic liquids will be continued in our laboratories in the future.

Conclusions

A regio- and stereoselective aminochlorination of α,β-unsaturated nitriles under convenient catalytic conditions has been developed. The synthesis is convenient to carry out without the protection with an inert gas at room tem-

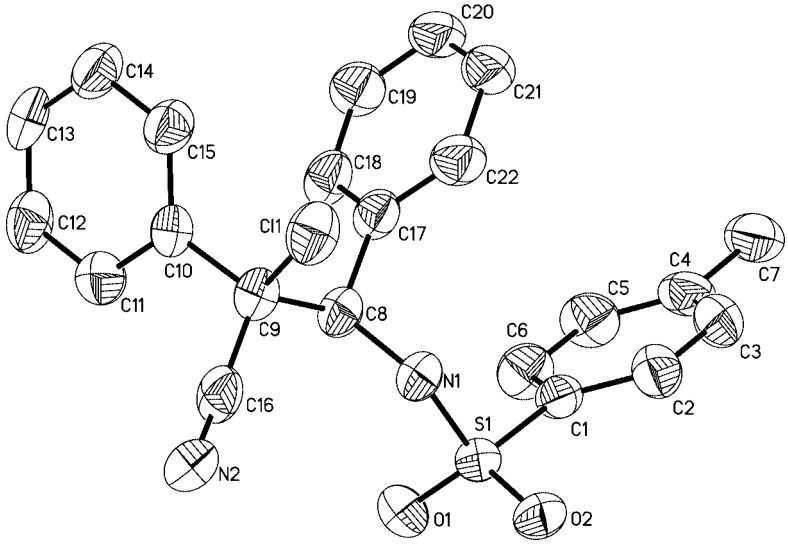


Figure 1. ORTEP diagram showing **3d**.

perature and the new method provides an easy route to vicinal haloamino nitriles. Good chemical yields and excellent regio- and stereoselectivities have been achieved with nine different nitriles. Opposite regioselectivities were observed with α,α-disubstituted β-monosubstituted cinnamonitriles. The stereochemistry was unambiguously confirmed by X-ray analysis.

Experimental Section

General: All moisture-sensitive reactions were performed under nitrogen or argon in glassware that had been flame-dried. Solvents were dried and distilled prior to use. Melting points are uncorrected. IR spectra were collected with a Bruker Vector 22 instrument (KBr pellets). ^{1}H and ^{13}C NMR (TMS used as internal standard) spectra were recorded with a Bruker ARX 300 spectrometer and $CDCl_3$ or CD_3COCD_3 were used as solvents. Elemental analyses were performed with a Perkin–Elmer 240 elemental analysis instrument. Mass spectra of the new compounds were measured with a Finnigan LCQ Electrospray Mass Spectrometer. Thin layer chromatography was carried out on silica gel 60 (F-254) TLC plates. Gel 60 (F-254) TLC plates (20 cm × 20 cm) were used for isolation.

Starting Materials: 2,2-Diphenylacrylonitrile (**1a**),[14] (*E*)-4-methylcinnamonitrile (**1b**),[15] (*E*)-4-chlorocinnamonitrile (**1c**),[15] and (*Z*)-2,3-diphenylacrylonitrile (**1d**)[16] were prepared according to the reported methods. Starting materials **1e**–**1i** were prepared according to the reported method with modifications.[16]

(*Z*)-3-(4-Chlorophenyl)-2-phenylacrylonitrile (1e): A mixture of 4-chlorobenzaldehyde (14.1 g, 0.1 mol) and purified dry benzyl cyanide (11.7 g, 0.1 mol) in ethanol (95%, 65 mL) was placed in a 200 mL beaker, and a solution of sodium ethoxide (1.0 g) in absolute ethanol (7 mL) was added dropwise, with vigorous stirring. After the addition, the mixture had turned cloudy. Vigorous stirring was continued for another 2 h, then the mixture was cooled in an ice bath and the product was separated by filtration. The white mass was washed first with distilled water (50 mL) and then with cold ethanol (95%, 10 mL) to remove unchanged reagents. Recrystallization from 95% ethanol afforded 20.3 g of product as a white solid (85%). M.p. 97–99 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.5 Hz, 2 H), 7.66–7.69 (m, 2 H), 7.49 (s, 1 H), 7.39–7.48 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.0, 136.8, 134.5, 132.5, 130.8, 129.8, 129.6, 129.5, 126.4, 118.1, 112.6 ppm.

(*Z*)-3-(2-Chlorophenyl)-2-phenylacrylonitrile (1f): This compound was isolated from the reaction between 2-chlorobenzaldehyde (14.1 g, 0.1 mol) and benzyl cyanide (11.7 g, 0.1 mol) as a white solid (19.1 g, 80% yield) with m.p. 102–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12–8.15 (m, 1 H), 7.92 (s, 1 H), 7.72–7.76 (m, 2 H), 7.38–7.53 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 135.2, 134.2, 132.6, 131.7, 130.2, 130.1, 129.8, 129.5, 127.6, 126.7, 117.7, 115.2 ppm.

(*Z*)-2-(4-Chlorophenyl)-3-phenylacrylonitrile (1g): This compound was isolated from the reaction between benzaldehyde (10.6 g, 0.1 mol) and (4-chlorophenyl)acetonitrile (15.2 g, 0.1 mol) as a white solid (16.7 g, 70% yield) with m.p. 108–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.92 (m, 2 H), 7.62 (d, J = 8.6 Hz, 2 H), 7.42–7.53 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.9, 135.6, 133.8, 133.7, 131.2, 129.7, 129.6, 129.4, 127.6, 118.0, 110.9 ppm.

(*Z*)-2,3-Bis(4-chlorophenyl)acrylonitrile (1h): This compound was isolated from the reaction between 4-chlorobenzaldehyde (14.1 g. 0.1 mol) and (4-chlorophenyl)acetonitrile (15.2 g, 0.1 mol) as a light yellow solid (20.5 g, 75% yield) with m.p. 109–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, J = 8.6 Hz, 2 H), 7.60 (d, J = 8.6 Hz, 2 H), 7.43–7.48 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.9, 141.8, 135.3, 133.5, 131.1, 130.1, 129.8, 129.6, 127.5, 118.3, 109.5 ppm.

(*Z*)-3-(2-Chlorophenyl)-2-(4-chlorophenyl)acrylonitrile (1i): This compound was isolated from the reaction between 2-chlorobenzaldehyde (14.1 g. 0.1 mol) and (4-chlorophenyl)acetonitrile (15.2 g, 0.1 mol) as a light yellow solid (20.5 g, 75% yield) with m.p. 109–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.14 (m, 1 H), 7.89 (s, 1 H), 7.60–7.68 (m, 2 H), 7.40–7.52 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.2, 136.1, 135.2, 132.7, 132.3, 131.9, 130.3, 129.7, 127.8, 127.7, 117.3, 114.0 ppm.

Typical Procedure for Aminochlorination of Nitriles: The nitrile (1.0 mmol), molecular sieves (4 Å) (0.5 g), CuCl (10 mg, 0.1 mmol, 10 mol-%), and freshly distilled acetonitrile (2.0 mL) were placed in a dry vial. A solution of 4-$TsNCl_2$ (480 mg, 2.0 mmol) in freshly distilled acetonitrile (2.0 mL) was then slowly added under argon to the above mixture by syringe over 5 min. The resulting solution was stirred without argon protection at room temperature for 24 h and the reaction was then quenched with saturated aqueous Na_2SO_3 (5.0 mL) solution. The two phases were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine and dried with anhydrous sodium sulfate. Purification by TLC (EtOAc/petroleum ether, 1:4 v/v) provided the pure product.

3-Chloro-3,3-diphenyl-2-(tosylamino)propionitrile (2a): This compound was isolated as a white solid (324 mg, 79% yield) from the reaction between **1a** (205 mg, 1.0 mmol) and $TsNCl_2$ (480 mg, 2 mmol) in the presence of CuCl (10 mg, 0.1 mmol, 10 mol-%) in acetonitrile (4.0 mL). M.p. 159–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.3 Hz, 2 H), 7.47–7.52 (m, 4 H), 7.31–7.39 (m, 8 H), 5.41 (d, J = 10.4 Hz, 1 H), 5.20 (d, J = 10.3 Hz, 1 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.2, 139.6, 139.5, 136.0, 130.4, 129.5, 129.3, 129.1, 129.0, 128.3, 128.0, 127.7, 115.3, 77.5, 55.1, 22.0 ppm. IR (KBr): ν = 3256, 2933, 1596, 1493, 1333, 1163, 1090 cm^{-1}. MS (ESMS/[M + Na]$^+$): calcd. for $C_{22}H_{19}ClN_2O_2SNa$ 433.1; found 432.9. $C_{22}H_{19}ClN_2O_2S$ (410.92): calcd. C 64.30, H 4.66, N 6.82; found C 64.38, H 4.73, N 6.91.

3-Chloro-3-(4-methylphenyl)-2-(tosylamino)propionitrile (2b): This compound was isolated as a white solid (265 mg, 76% yield) from the reaction between **1b** (143 mg, 1.0 mmol) and $TsNCl_2$ (480 mg, 2 mmol) in the presence of CuCl (10 mg, 0.1 mmol, 10 mol-%) in acetonitrile (4.0 mL). M.p. 140–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.3 Hz, 2 H), 7.35–7.37 (m, 4 H), 7.20 (d, J = 8.1 Hz, 2 H), 5.38 (d, J = 10.4 Hz, 1 H), 5.11 (d, J = 3.8 Hz, 1 H), 4.63 (dd, J = 10.4, 3.8 Hz, 1 H), 2.45 (s, 3 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 144.2, 139.7, 137.6, 133.1, 130.0, 129.6, 128.1, 127.4, 116.2, 62.0, 52.2, 20.9, 20.6 ppm. IR (KBr): ν = 3210, 2919, 1594, 1469, 1323, 1150, 1085 cm^{-1}. MS (ESMS/[M + Na]$^+$): calcd. for $C_{17}H_{17}ClN_2O_2SNa$ 371.1; found 371.0. $C_{17}H_{17}ClN_2O_2S$ (348.85): calcd. C 58.53, H 4.91, N 8.03; found C 58.43, H 5.12, N 7.94.

3-Chloro-3-(4-chlorophenyl)-2-(tosylamino)propionitrile (2c): This compound was isolated as a white solid (203 mg, 55% yield) from the reaction between **1c** (164 mg, 1.0 mmol) and $TsNCl_2$ (480 mg, 2 mmol) in the presence of CuCl (10 mg, 0.1 mmol, 10 mol-%) in acetonitrile (4.0 mL). M.p. 142–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.3 Hz, 2 H), 7.35–7.44 (m, 6 H), 5.40 (d,

J = 10.5 Hz, 1 H), 5.12 (d, J = 3.9 Hz, 1 H), 4.64 (dd, J = 10.5, 3.9 Hz, 1 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 144.3, 137.5, 135.1, 135.0, 130.1, 130.0, 129.0, 127.3, 116.2, 60.8, 51.8, 21.0 ppm. IR (KBr): ν = 3209, 2914, 1595, 1471, 1319, 1150, 1084 cm^{-1}. MS (ESMS/[M + Na]$^+$): calcd. for $C_{16}H_{14}Cl_2N_2O_2SNa$ 391.0; found 391.1. $C_{16}H_{14}Cl_2N_2O_2S$ (369.27): calcd. C 52.04, H 3.82, N 7.59; found C 52.17, H 3.96, N 7.64.

2-Chloro-2,3-diphenyl-3-(tosylamino)propionitrile (3d): This compound was isolated as a white solid (312 mg, 76% yield) from the reaction between **1d** (205 mg, 1.0 mmol) and $TsNCl_2$ (480 mg, 2 mmol) in the presence of CuCl (10 mg, 0.1 mmol, 10 mol-%) in acetonitrile (4.0 mL). M.p. 154–156 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.44 (m 7 H), 7.18–7.23 (m, 1 H), 7.00–7.11 (m, 4 H), 6.82 (d, J = 7.6 Hz, 2 H), 5.57 (d, J = 10.0 Hz, 1 H), 5.00 (d, J = 10.0 Hz, 1 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 143.1, 138.3, 134.9, 134.1, 130.2, 129.5, 129.3, 128.9, 128.7, 127.8, 127.5, 127.1, 117.7, 67.2, 67.0, 20.7 ppm. IR (KBr): ν = 3248, 1597, 1450, 1336, 1166, 1089 cm^{-1}. MS (ESMS/[M + Na]$^+$): calcd. for $C_{22}H_{19}ClN_2O_2SNa$ 433.1; found 433.1. $C_{22}H_{19}ClN_2O_2S$ (410.92): calcd. C 64.30, H 4.66, N 6.82; found C 64.21, H 4.78, N 6.96.

2-Chloro-3-(4-chlorophenyl)-2-phenyl-3-(tosylamino)propionitrile (3e): This compound was isolated as a white solid (396 mg, 89% yield) from the reaction between **1e** (240 mg, 1.0 mmol) and $TsNCl_2$ (480 mg, 2 mmol) in the presence of CuCl (10 mg, 0.1 mmol, 10 mol-%) in acetonitrile (4.0 mL). M.p. 177–179 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.46 (m, 7 H), 7.05–7.27 (m, 4 H), 6.75 (d, J = 8.5 Hz, 2 H), 5.75 (d, J = 9.3 Hz, 1 H), 4.98 (d, J = 9.8 Hz, 1 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 143.4, 138.1, 134.6, 134.4, 132.9, 131.2, 130.4, 129.4, 129.0, 127.9, 127.5, 127.2, 117.5, 66.9, 66.3, 20.7 ppm. IR (KBr): ν = 3251, 2935, 1598, 1444, 1325, 1163, 1092 cm^{-1}. MS (ESMS/[M + Na]$^+$): calcd. for $C_{22}H_{18}Cl_2N_2O_2SNa$ 467.0; found 467.1. $C_{22}H_{18}Cl_2N_2O_2S$ (445.36): calcd. C 59.33, H 4.07, N 6.29; found C 59.15, H 4.11, N 6.30.

2-Chloro-3-(2-chlorophenyl)-2-phenyl-3-(tosylamino)propionitrile (3f): This compound was isolated as a white solid (307 mg, 69% yield) from the reaction between **1f** (240 mg, 1.0 mmol) and $TsNCl_2$ (480 mg, 2 mmol) in the presence of CuCl (10 mg, 0.1 mmol, 10 mol-%) in acetonitrile (4.0 mL). M.p. 198–201 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.52 (m, 8 H), 7.11–7.17 (m, 3 H), 7.01 (d, J = 7.9 Hz, 2 H), 5.72 (d, J = 10.2 Hz, 1 H), 5.63 (d, J = 10.2 Hz, 1 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 143.4, 137.7, 135.3, 134.6, 132.5, 130.5, 129.7, 129.4, 129.2, 129.0, 128.8, 127.5, 127.3, 127.0, 117.2, 66.9, 61.5, 20.7 ppm. IR (KBr): ν = 3257, 1595, 1435, 1339, 1164, 1077 cm^{-1}. MS (ESMS/[M + Na]$^+$): calcd. for $C_{22}H_{18}Cl_2N_2O_2SNa$: 467.0; found 467.0. $C_{22}H_{18}Cl_2N_2O_2S$ (445.36): calcd. C 59.33, H 4.07, N 6.29; found C 59.49, H 4.00, N 6.25.

2-Chloro-2-(4-chlorophenyl)-3-phenyl-3-(tosylamino)propionitrile (3g): This compound was isolated as a white solid (298 mg, 67% yield) from the reaction between **1g** (240 mg, 1.0 mmol) and $TsNCl_2$ (480 mg, 2 mmol) in the presence of CuCl (10 mg, 0.1 mmol, 10 mol-%) in acetonitrile (4.0 mL). M.p. 192–194 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.40 (m, 4 H), 7.24–7.29 (m, 3 H), 7.15–7.19 (m, 2 H) 7.03 (d, J = 8.1 Hz, 2 H), 6.96 (d, J = 7.4 Hz, 2 H), 5.40 (d, J = 9.9 Hz, 1 H), 4.95 (d, J = 10.2 Hz, 1 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 143.2, 138.2, 135.8, 134.4, 134.0, 129.4, 129.3, 129.0, 128.9, 128.0, 127.1, 117.2, 66.9, 66.2, 20.7 ppm. IR (KBr): ν = 3256, 1595, 1491, 1416, 1334, 1164, 1094 cm^{-1}. MS (ESMS/[M + Na]$^+$): calcd. for $C_{22}H_{18}Cl_2N_2O_2SNa$ 467.0; found 467.1. $C_{22}H_{18}Cl_2N_2O_2S$ (445.36): calcd. C 59.33, H 4.07, N 6.29; found C 59.18, H 4.17, N 6.13.

2-Chloro-2,3-bis(4-chlorophenyl)-3-(tosylamino)propionitrile (3h): This compound was isolated as a white solid (407 mg, 85% yield) from the reaction between **1h** (274 mg, 1.0 mmol) and $TsNCl_2$ (480 mg, 2 mmol) in the presence of CuCl (10 mg, 0.1 mmol, 10 mol-%) in acetonitrile (4.0 mL). M.p. 141–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.41 (m, 6 H), 7.12 (d, J = 8.4 Hz, 2 H), 7.06 (d, J = 7.9 Hz, 2 H), 6.89 (d, J = 8.3 Hz, 2 H), 5.56 (d, J = 9.9 Hz, 1 H), 4.93 (d, J = 10.0 Hz, 1 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 143.5, 138.0, 136.0, 134.6, 133.7, 133.2, 131.2, 129.4, 129.3, 129.1, 128.1, 127.2, 117.0, 78.6, 66.0, 20.7 ppm. IR (KBr): ν = 3241, 2952, 1597, 1492, 1435, 1328, 1169, 1094 cm^{-1}. MS (ESMS/[M + Na]$^+$): calcd. for $C_{22}H_{17}Cl_3N_2O_2SNa$ 500.9; found 501.0. $C_{22}H_{17}Cl_3N_2O_2S$ (479.81): calcd. C 55.07, H 3.57, N 5.84; found C 55.21, H 3.47, N 5.76.

2-Chloro-3-(2-chlorophenyl)-2-(4-chlorophenyl)-3-(tosylamino)-propionitrile (3i): This compound was isolated as a white solid (293 mg, 61% yield) from the reaction between **1i** (274 mg, 1.0 mmol) and $TsNCl_2$ (480 mg, 2 mmol) in the presence of CuCl (10 mg, 0.1 mmol, 10 mol-%) in acetonitrile (4.0 mL). M.p. 198–201 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.49 (m, 5 H), 7.16–7.25 (m, 5 H), 7.03 (d, J = 8.1 Hz, 2 H), 5.67 (d, J = 10.5 Hz, 1 H), 5.59 (d, J = 10.4 Hz, 1 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 143.5, 137.6, 136.1, 135.3, 133.7, 132.5, 130.7, 129.5, 129.4, 129.4, 129.3, 129.1, 127.5, 126.9, 116.8, 66.0, 61.5, 20.79 ppm. IR (KBr): ν = 3260, 2980, 1596, 1493, 1437, 1338, 1164, 1096 cm^{-1}. MS (ESMS/[M + Na]$^+$): calcd. for $C_{22}H_{17}Cl_3N_2O_2SNa$ 500.9; found 501.0. $C_{22}H_{17}Cl_3N_2O_2S$ (479.81): calcd. C 55.07, H 3.57, N 5.84; found C 55.05, H 3.46, N 5.86.

Crystal Data for 3d: $C_{22}H_{21}ClN_2O_3S$ (428.92); monoclinic, space group $C2/c$; a = 17.8838(16), b = 14.3201(16), c = 18.4191(18) Å; β = 110.153(2)°; V = 4428.3(8) Å^3; Z = 8; $D_{calcd.}$ = 1.287 g cm^{-3}; $F(000)$ = 1792; crystal size 0.22 × 0.24 × 0.28 mm; $2\theta_{max}$ = 52.0°; reflections collected: 11914; unique: 4342 (R_{int} = 0.034); parameters: 272; $R1$ = 0.0529; $wR2$ = 0.1351; GOF = 1.03. CCDC-612351 (for **3d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

We gratefully acknowledge the 863 High Technology Program (to Y. P., P. R. China) and the Welch Foundation (D-1361) (to G. L., USA) for the generous financial support. The research funds for Y. P. from the Qing-Lan program of Jiangsu Province and the Kua-Shi-Ji program of the Education Ministry of China are also acknowledged.

[1] J. E.G. Kemp in: *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, vol. 3, pp. 471–513.
[2] a) D. A. Griffith, S. J. Danishefsky, *J. Am. Chem. Soc.* **1991**, *113*, 5863–5870; b) H. Driguez, J. P. Vermes, J. Lessard, *Can. J. Chem.* **1978**, *56*, 119–130; c) J. Lessard, H. Driguez, J. P. Vermes, *Tetrahedron Lett.* **1970**, *11*, 4887–4891.
[3] a) F. A. Daniher, P. E. Butler, *J. Org. Chem.* **1968**, *33*, 4336–4340; b) F. A. Daniher, P. E. Butler, *J. Org. Chem.* **1968**, *33*, 2637–2642; c) F. A. Daniher, M. T. Melchior, P. E. Butler, *Chem. Commun. (London)* **1968**, 931–932.
[4] B. S. Orlek, G. Stemp, *Tetrahedron Lett.* **1991**, *32*, 4045–4048.

[5] J. Qui, R. B. Silverman, *J. Med. Chem.* **2000**, *43*, 706–720.
[6] a) G. Li, H. X. Wei, S. H. Kim, M. Neighbors, *Org. Lett.* **1999**, *1*, 395–397; b) H. X. Wei, S. H. Kim, G. Li, *Tetrahedron* **2001**, *57*, 3869–3973; c) G. Li, H. X. Wei, S. H. Kim, *Org. Lett.* **2000**, *2*, 2249–2252; d) J. Y. Liu, Y.-N. Wang, G. Li, *Eur. J. Org. Chem.* **2006**, *14*, 3112–3115; e) , V. V. Thakur, S. K. Talluri, A. Sudalai, *Org. Lett.* **2003**, *5*, 861–864.
[7] For recent aminohalogenations, see: a) X. Xin, S. R. S. S. Kotti, Y.-Y. Liu, J. F. Cannon, A. D. Headley, G. Li, *Org. Lett.* **2005**, *6*, 4881–4884; b) D. Chen, C. Timmons, S. Chao, G. Li, *Eur. J. Org. Chem.* **2004**, 3097–3101.
[8] For recent aminohalogenations, see: a) X. Qi, S. H. Lee, J. Y. Kwon, Y. Kim, S. J. Kim, Y. S. Lee, J. Yoon, *J. Org. Chem.* **2003**, *68*, 9140–9143; b) A. Volonterio, P. Bravo, W. Panzeri, C. Pesenti, M. Zanda, *Eur. J. Org. Chem.* **2002**, 3336–3340; c) S. Raghavan, S. R. Reddy, K. A. Tony, C. N. Kumar, S. Nanda, *Synlett* **2001**, *6*, 851–853; d) M. R. Manzoni, T. P. Zabawa, D. Kasi, S. R. Chemler, *Organometallics* **2004**, *23*, 5618–5621.
[9] For recent diaminations, see: a) G. Li, H.-X. Wei, S. H. Kim, M. D. Carducci, *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4277–4280; b) H.-X. Wei, S. H. Kim, G. Li, *J. Org. Chem.* **2002**, *67*, 4777–4781; c) K. I. Brooker-Milburn, D. J. Guly, B. Cox, P. A. Procopiou, *Org. Lett.* **2003**, *5*, 3313–3315; d) K. Muniz, M. Nieger, *Synlett* **2003**, 211–214; e) D. Chen, C. Timmons, H.-X. Wei, G. Li, *J. Org. Chem.* **2003**, *68*, 5742–5745; f) C. Timmons, D. Chen, X. Xu, G. Li, *Eur. J. Org. Chem.* **2003**, 3850–3854; g) W. Pei, H.-X. Wei, A. D. Headley, G. Li, *J. Org. Chem.* **2003**, *68*, 8404–8408.
[10] S. Karur, S. R. S. S. Kotti, X. Xu, J. F. Cannon, A. D. Headley, G. Li, *J. Am. Chem. Soc.* **2003**, *125*, 13340–13341.
[11] a) G. Li, H. X. Wei, S. H. Kim, *Tetrahedron* **2001**, *57*, 8407–8411; b) G. Li, S. H. Kim, H. X. Wei, *Tetrahedron Lett.* **2000**, *41*, 8699–8703.
[12] Q. Li, M. Shi, C. Timmons, G. Li, *Org. Lett.* **2006**, *8*, 625–628.
[13] V. K. Kansal, A. P. Bhaduri, *Indian J. Chem., Sect. B* **1981**, *20*, 885–890.
[14] S. A. Dibiase, B. A. Lipisko, A. Haag, R. A. Wolak, G. W. Gokel, *J. Org. Chem.* **1979**, *44*, 4660–4669.
[15] H. Zhao, M. Z. Cai, C. Y. Peng, *Synth. Commun.* **2002**, *32*, 3419–3423.
[16] S. Wawzonek, E. M. Smolin, *Org. Synth.* **1949**, *29*, 83–84.

Received: October 14, 2006
Published Online: January 17, 2007

