The cinnamate-based aminohalogenation provides an easy access to *anti* methyl 3-aryl-*N*-*p*-tosyl- and *N*-*o*-nosyl-aziridine-2-carboxylates

Dianjun Chen, Sun Hee Kim, Brian Hodges†, and Guigen Li*

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061
E-mail: Guigen.Li@ttu.edu

Dedicated to Professor Henry J. Shine on the occasion of his 80th birthday
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Abstract
The first application of *trans*-alkyl cinnamate-based aminohalogenation to the synthesis of *anti* methyl 3-aryl-*N*-(*p*-toluene)sulfonylaziridine-2-carboxylates and *anti* methyl 3-aryl-*N*-(*o*-nitrobenzene)sulfonylaziridine-2-carboxylates was described. The synthesis was easily carried out by mixing alkyl cinnamate-derived haloamines with potassium carbonate in acetonitrile at room temperature. Good to excellent yields (83-97 % for *N*-*p*-Ts and 75-94 % for *N*-*o*-Ns *trans*-aziridine-2-carboxylates, respectively) have been achieved for 11 examples.

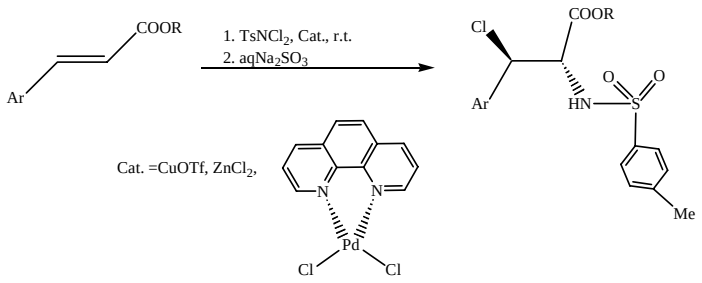
Keywords: Aminohalogenation, aziridine, cinnamate, haloamine

Introduction

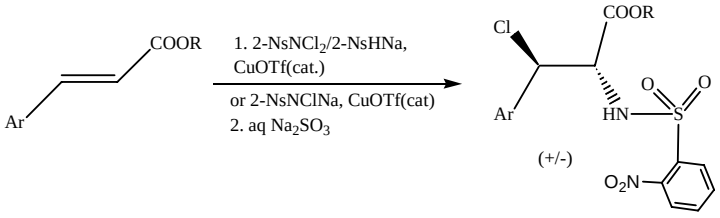
Aziridines are valuable building blocks for the synthesis of a variety of nitrogen-containing compounds which are biologically important.[1-3] Among aziridine derivatives, alkyl *N*-*p*-Ts- and *N*-*o*-Ns-aziridine-2-carboxylates are particularly useful because they can undergo regioselective ring openings to afford α- and β-amino esters by treatment with various nucleophiles.[4-6]

Several olefin-based aziridinations have been reported,[2-3] which are practical because readily available and inexpensive olefins can be used as the starting materials. One of these aziridination methods involved the use of [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) as the nitrogen source and transition metals or metal-ligand complexes as catalysts. A few other alternatives were also reported for olefin aziridinations under various catalytic conditions.[1d, 2-3] These nitrogen sources include chloramine-T, sulfamates and carbamates. In addition, 1,2-vicinal aminoalcohols, which are also derived from olefins have been used for aziridine synthesis by protection of their hydroxyl groups followed by intramolecular S_{N2} substitutions.[7] However, to the best of our knowledge, the application of 1,2-vicinal haloamines for the synthesis of aziridine carboxylates has not been well documented so far. This is probably due to the fact that

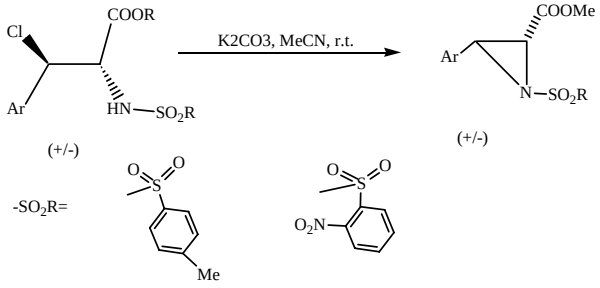
olefin-based synthesis of *anti* alkyl 3-halo-2-(*p*-toluenesulfonamido)-3-arylpropionates and *anti* alkyl 3-halo-2-(*o*-nitrobenzenesulfonamido)-3-arylpropionates have not been available until recently. We established several aminohalogenation processes of α,β–unsaturated esters (Scheme 1 and 2).[8-9] In this report, we describe the first application of aminohalogenation on the synthesis of alkyl *N*-*p*-Ts and *N*-*o*-Ns *trans*-aziridine-2-carboxylates, which is represented in Scheme 3 and the results summarized in Table 1.



Scheme 1



Scheme 2



Scheme 3

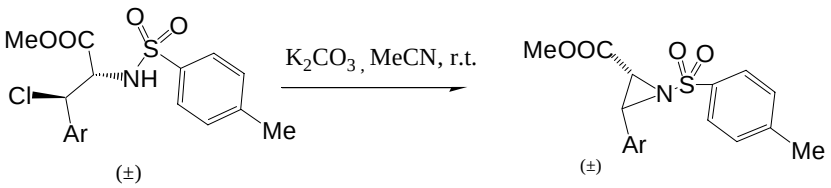
Results and Discussion

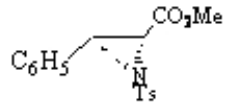
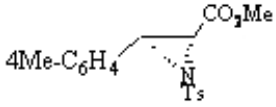
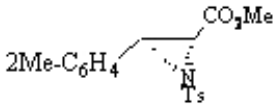
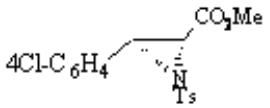
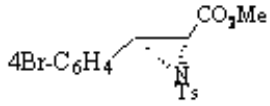
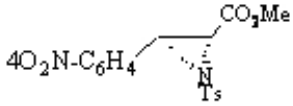
The intramolecular cyclization of haloamines has been performed by the use of potassium carbonate, sodium hydride or other bases in organic solvents or potassium hydroxide in aqueous solution as reported by several groups.[10] Considering the hydrolysis of the methyl ester group and possible side elimination reaction of hydrogen chloride, we chose the combination of potassium carbonate and acetonitrile for the present synthesis. Methyl 3-chloro-2-amino-3-

phenylpropionate was the first substrate used for the cyclization and resulted in nearly a quantitative yield (97%), which indicated there was no need to use other combinations. As revealed in Table 1, all methyl 3-chloro-2-(*N*-*p*-Ts-amino)-3-arylpropionates gave good to excellent yields, although optimization is still needed for the substrates of alkyl 3-chloro-2-(*N*-*o*-Ns-amino)-3-arylpropionate as shown in Table 2.

The synthesis for both *N*-*p*-tosyl and *N*-*o*-nosyl aziridines required the use of 2.0 equivalents of potassium carbonate in acetonitrile solution. The cyclization can also be finished at room temperature within a period of 3 hours. The reaction mixture was heterogeneous throughout the period due to the poor solubility of potassium carbonate in acetonitrile. The intramolecular S_N^2 chloride displacement ensures an *anti* stereochemistry of aziridine products. There was no epimerization observed under the current conditions.

Table 1. Results of cyclization of methyl 3-chloro-2-(*p*-toluenesulfonamido)-3-arylpropionates

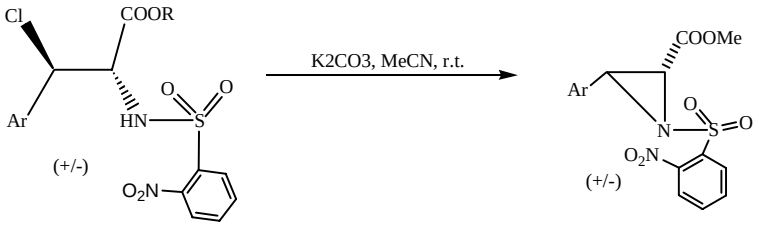


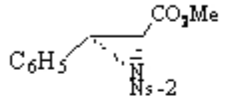
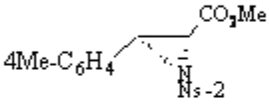
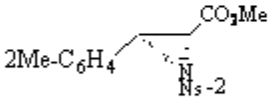
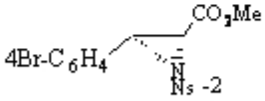
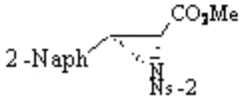
Entry	Ar	Product (±)		Yield (%) [a]
1	C_6H_5		**1**	97
2	4-Me-C_6H_4		**2**	94
3	2-Me-C_6H_4		**3** [b]	89
4	4-Cl-C_6H_4		**4**	89
5	4-Br-C_6H_4		**5** [b]	88
6	4-NO_2-C_6H_4		**6**	83

[a] Purified yields. [b]HRMS (MALDI-FTMS) *m/z* (M^++1) was obtained.

After the efficient synthesis of *anti* methyl 3-phenyl-*N*-(*p*-toluene)sulfonylaziridine-2-carboxylates, we turned our attention to the synthesis of *anti* methyl 3-phenyl-*N*-(*o*-nitrobenzene)sulfonylaziridine-2-carboxylates. An attractive aspect of the latter analogues is revealed by the fact that the nosyl groups of these compounds can be readily deprotected under mild conditions simply by treating with thiophenol and potassium carbonate in DMF solution at 0 °C to room temperature.[11]

Table 2. Results of cyclization of methyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-arylpropionates



Entry	Ar	Product (±)		Yield (%) [a]
1	C_6H_5		**7** [b]	94
2	4-Me-C_6H_4		**8** [b]	78
3	2-Me-C_6H_4		**9**	75
4	4-Br-C_6H_4		**10**	76
5	2-Naph		**11**	85

[a] Purified yields. [b]HRMS (MALDI-FTMS) *m/z* (M^++1) was obtained.

Similar to the case 1 of Table 1, the cyclization of *anti* alkyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-phenylpropionate proceeded nearly quantitatively (entry 1, Table 2, 94 % yield) without any epimerization on the α-position of methyl 3-phenyl-*N*-(*o*-nitrobenzene)sulfonylaziridine-2-carboxylate. The resulting crude product was also determined to be pure by ^{1}H-NMR analysis. However, the other four substrates (entries 2 - 4 of Table 2)

gave lower yields than the first case (75 - 85 %). Further improvement will be made to increase the chemical yields.

In summary, the aminohalogenation of alkyl cinnamates have been utilized for the synthesis of *anti* alkyl 3-aryl-*N*-(*p*-toluene)sulfonylaziridine-2-carboxylates and *anti* alkyl 3-aryl-*N*-(*o*-nitrobenzene)sulfonylaziridine-2-carboxylates for the first time. The synthesis was easily carried out under mild conditions at room temperature without special protection from inert gases. The present synthesis can complement known aziridinations which have some scope limitations.

Experimental Section

General Procedures. Typical experiment is represented by entry 1 of Table 1. Into a dry vial, methyl 3-chloro-2-(*N*-*p*-Ts-amino)-3-phenylpropionate (36.8 mg, 0.10 mmol) was loaded with dried potassium carbonate (27.6 mg, 0.20 mmol) and acetonitrile (3.0 mL). The resulting reaction mixture was stirred at room temperature for 3 h. The reaction was finally quenched by 3 mL of water. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 x 5.0 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate. Concentration to dryness afforded the crude *anti* methyl 3-phenyl-*N*-(*p*-toluene)sulfonylaziridine-2-carboxylate which was almost pure as determined by ^{1}H-NMR analysis (32.1 mg, 97 % yield). A small amount of the crude product was further purified for analytical purposes. The analytical data were proven to be identical to those of the same known sample. M.p. 44-45 °C (Lit., 44.2-44.6 °C). IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1747 (C=O), 1214 (C-O) cm^{-1}. ^{1}H NMR (300 MHZ, $CDCl_3$) δ 7.78 (J = 6.60 Hz, 2H), 7.33-7.25 (m, 7H), 4.44 (J = 3.77 Hz, 1H), 3.87 (s, 3H), 3.53 (J = 3.77 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 144.4, 137.0, 132.5, 129.6, 128.9, 128.6, 127.5, 127.4, 53.2, 47.7, 46.8, 21.6.

Methyl 3-(*p*-tolyl)-*N*-(*p*-toluene)sulfonylaziridine-2-carboxylate (2) was obtained in 94% yield. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1748 (C=O), 1213 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) d 7.77 (d, J = 6.61 Hz, 2H), 7.28 (d, J = 6.61 Hz, 2H), 7.17-7.10 (m, 4H), 4.39 (d, J = 4.01 Hz, 1H), 3.85 (s, 3H), 3.56 (d, J = 4.01 Hz, 1H), 2.42 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 144.3, 138.9, 137.1, 129.5, 129.3, 127.5, 127.4, 53.1, 47.9, 46.4, 21.6, 21.2.

Methyl 3-(*o*-tolyl)-*N*-(*p*-toluene)sulfonylaziridine-2-carboxylate (3) was obtained in 89% yield. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1747 (C=O), 1211 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, J = 1.75, 6.59 Hz, 2H), 7.31-7.04 (m, 6H), 4.44 (d, J = 4.22 Hz, 1H), 3.87 (s, 3H), 3.55 (d, J = 4.22 Hz, 1H), 2.44 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 144.5, 138.0, 136.6, 130.5, 130.1, 129.6, 128.8, 127.8, 126.5, 125.9, 53.2, 46.8, 45.3, 21.6, 19.2. HRMS (MALDI-FTMS) *m/z* (M^++1) found 346.1104, calcd. for $C_{18}H_{19}NO_4S$ 345.1107.

Methyl 3-(*o*-chlorophenyl)-*N*-(*p*-toluene)sulfonylaziridine-2-carboxylate (4) was obtained in 89% yield. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1748 (C=O), 1213 (C-O) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.83 (d, J = 8.36 Hz, 2H), 7.35-7.09 (m, 6H), 4.68 (d, J = 3.97 Hz, 1H), 3.89 (s, 3H), 3.45 (d, J = 3.97 Hz, 1H), 2.45 (s, 3H).

Methyl 3-(*p*-bromophenyl)-*N*-(*p*-toluene)sulfonylaziridine-2-carboxylate (5) was obtained in 88% yield. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1747 (C=O), 1214 (C-O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.17 Hz, 2H), 7.44 (d, J = 8.42 Hz, 2H), 7.30 (d, J = 8.17 Hz, 2H), 7.13 (d, J = 8.42 Hz, 2H), 4.38 (d, J = 3.90 Hz, 1H), 3.86 (s, 3H), 3.49 (d, J=3.90 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 144.6, 136.8, 131.8, 131.7, 129.7, 129.0, 127.5, 123.1, 53.2, 46.9, 46.8, 21.6. HRMS (MALDI-FTMS) *m/z* (M^++1) found 410.0054, calcd. for $C_{17}H_{16}NO_4BrS$ 410.0054.

Methyl 3-(*p*-nitrophenyl)-*N*-(*p*-toluene)sulfonylaziridine-2-carboxylate (6) was obtained in 83% yield. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1747 (C=O), 1215 (C-O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 6.87 Hz, 2H), 7.81 (d, J = 8.20 Hz, 2H), 7.44 (d, J = 6.87 Hz, 2H), 7.33 (d, J = 8.20 Hz, 2H), 4.53 (d, J = 3.81 Hz, 1H), 3.89 (s, 3H), 3.49 (d, J = 3.81 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 148.2, 144.9, 140.1, 136.6, 129.8, 128.2, 127.5, 123.9, 53.4, 47.5, 45.9, 21.6. HRMS (MALDI-FTMS) *m/z* (M^++1) found 377.0802, calcd. for $C_{17}H_{16}N_2O_6S$ 377.0812.

Methyl 3-phenyl-*N*-(*o*-nitrobenzene)sulfonylaziridine-2-carboxylate (7) was obtained in 94% yield. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1744 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.22-8.19 (m, 1H), 7.81-7.72 (m, 3H), 7.37-7.34 (m, 5H), 4.58 (d, J = 3.90 Hz, 1H), 3.89 (s, 3H), 3.69 (d, J = 3.90 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 147.7, 134.2, 132.6, 130.3, 129.1, 128.6, 127.1, 124.8, 53.2, 50.2, 48.3. HRMS (MALDI-FTMS) *m/z* (M^++1) found 363.0644, calcd. for $C_{16}H_{14}N_2O_6S$ 363.0645.

Methyl 3-(*p*-tolyl)-*N*-(*o*-nitrobenzene)sulfonylaziridine-2-carboxylate (8) was obtained in 78% yield. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1748 (C=O), 1215 (C-O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.19-8.15 (m, 1H), 7.76-7.69 (m, 3H), 7.26-7.21 (m, 2H), 7.15-7.12 (d, 2H), 4.52 (d, J = 3.98 Hz, 1H), 3.87 (s, 3H), 3.73 (d, J = 3.98 Hz, 1H), 2.32 (s, 3H). HRMS (MALDI-FTMS) *m/z* (M^++1) found 377.0808, calcd. for $C_{17}H_{16}N_2O_6S$ 377.0802.

Methyl 3-(*o*-tolyl)-*N*-(*o*-nitrobenzene)sulfonylaziridine-2-carboxylate (9) was obtained in 75% yield. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1747 (C=O), 1214 (C-O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.21-8.18 (m, 1H), 7.79-7.73 (m, 3H), 7.26-7.9 (m, 4H), 4.62 (d, J = 4.20 Hz, 1H), 3.89 (s, 3H), 3.75 (d, J = 4.20 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 144.5, 138.0, 136.6, 130.5, 130.1, 129.6, 128.8, 127.8, 126.5, 125.9, 53.2, 46.8, 45.3, 21.6, 19.2. HRMS (MALDI-FTMS) *m/z* (M^++1) found 377.0807, calcd. for $C_{17}H_{16}N_2O_6S$ 377.0802.

Methyl 3-(*p*-bromophenyl)-*N*-(*o*-nitrobenzene)sulfonylaziridine-2-carboxylate (10) was obtained in 76% yield. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1747 (C=O), 1215 (C-O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.21-8.18 (m, 1H), 7.80-7.73 (m, 3H), 7.47-7.44 (m, 2H), 7.21-7.18 (d, 2H), 4.54 (d, J = 3.86 Hz, 1H), 3.88 (s, 3H), 3.63 (d, J = 3.86 Hz, 1H).

Methyl 3-(2-naphthyl)-*N*-(*o*-nitrobenzene)sulfonylaziridine-2-carboxylate (11) was obtained in 85% yield. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1747 (C=O), 1213 (C-O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.19-8.16 (m, 1H), 7.85-7.64 (m, 7H), 7.48-7.45 (m, 2H), 7.36-7.32 (m, 1H), 4.73 (d, J = 3.90 Hz, 1H, 3.89 (s, 3H), 3.80 (d, J = 3.90 Hz, 1H).

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† Undergraduate participant.

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