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Guanidinium Ylide Mediated Aziridination: Identification of a Spiro Imidazolidine-Oxazolidine Intermediate

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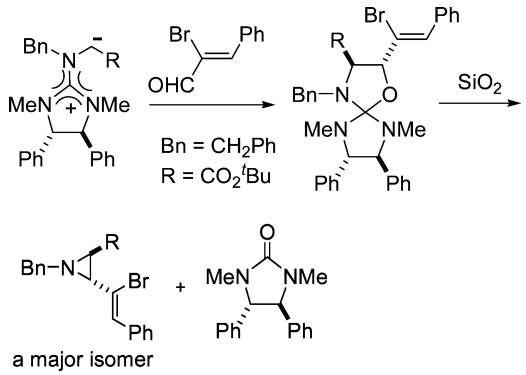

We successfully isolated a spiro imidazolidine-oxazolidine intermediate in the reaction of guanidinium ylide mediated aziridination using α-bromocinnamaldehyde. X-ray crystallographic analysis unambiguously revealed that the stereogenic centers of the spiro intermediate were in a *trans* configuration. The role of the spiro compound as an intermediate in the aziridination reaction was confirmed by observation of its smooth chemical conversion into aziridine products.

Aziridine-2-carboxylates are very versatile intermediates[1−3] in the synthesis of biologically active nitrogen-containing compounds because they can be converted into α- or *β*-amino acid derivatives, including unnatural amino acids, via regioselective ring-opening reactions.[1,4,5] We have shown that guanidinium salts react with aryl or α,*β*-unsaturated aldehydes to stereospecifically afford aziridine products and urea, which can be reused by conversion back to the starting guanidinium salt, and that effective asymmetric induction occurs when chiral guanidinium salts are used.[6−8] For this aziridine synthesis, the following reaction profiles are proposed (Scheme 1). Guanidinium ylide is produced from guanidinium salt **1** under basic conditions and acts as a nucleophile for C−C bond formation with aldehyde **2** to give the zwitterionic species **3a**. Spontaneous cyclization to the spiro imidazolidine-oxazolidine compound **3b** then occurs. The spiro intermediate is subsequently fragmented to aziridine **4** and urea **5** by treatment with silica gel (SiO_2) or acetic anhydride. Previous attempts to isolate the spiro compound **3b** in a pure form have failed in all but one of the reactions examined. The exception was the reaction with α-bromocinnamaldehyde, which successfully afforded the intended spiro intermediate as a crystalline product; this product was then smoothly converted into the corresponding aziridine and urea. In this paper, we present the unambiguous identification of the spiro imidazolidine-oxazolidine formed by the reaction with α-bromocinnamaldehyde using X-ray crystallographic analysis and evidence that this compound acts as an intermediate for the guanidinium ylide mediated aziridination.

According to the previously reported guanidinium ylide mediated vinyl aziridination,[8] we carried out the reaction of diphenylguanidinium salt **6** and (*Z*)-α-bromocinnamaldehyde (**7**) (Table 1). Standard two-step treatment afforded the expected aziridine products **9** as a diastereomeric mixture in moderate yields (39−45%) together with urea **10.** The *trans*-aziridine *trans*-**9** was obtained as the major isomer, independent of the conditions used (entries 1 and 2). However, an undefined product was isolated in 1% yield from the crude product mixture obtained under the conditions in entry 2; ^{1}H NMR spectral data suggested that it was the spiro imidazolidine-oxazolidine compound **8**, a possible precursor for aziridines **9** and urea **10**. Identification of this potential precursor in the crude product mixture prompted us to attempt to isolate this species before treatment of step 2 (entries 3 and 4). Hence, the guanidinium salt **6** and aldehyde **7** were stirred with tetramethylguanidine (TMG) in tetrahydrofuran (THF) at −40 °C for 2.5 h and then at −10 °C for 3.5 h. After evaporation of the solvent, the crude product obtained was purified using NH-silica gel chromatography (NH−SiO_2). The purified compound was identified by ^{1}H NMR as the intended spiro compound **8**, mp 150−153 °C, in 73% yield (entry 3). Extending the stirring time at −40 °C from 2.5 to 18 h did not improve the yield of **8**; rather**,** the aziridine product was increasingly formed (entry 4).

The ^{1}H NMR spectral data of compound **8** were consistent with a 1-oxa-4,6,9-triazaspiro[4.4]nonane derivative. The *trans*-stereochemistry of the oxazolidine ring system was suggested by the coupling constant (J = 7.9 Hz) between the C_2- and C_3-methine protons at δ 4.91 and δ 3.83, respectively, in the ^{1}H NMR spectrum. Fortunately, a single crystalline sample of **8** could be prepared by recrystallization from *n*-hexane−ethyl acetate. X-ray crystallographic analysis of this sample unambiguously indicated that it was (2*R**,3*R**,7*S**,8*S**)-4-benzyl-3-

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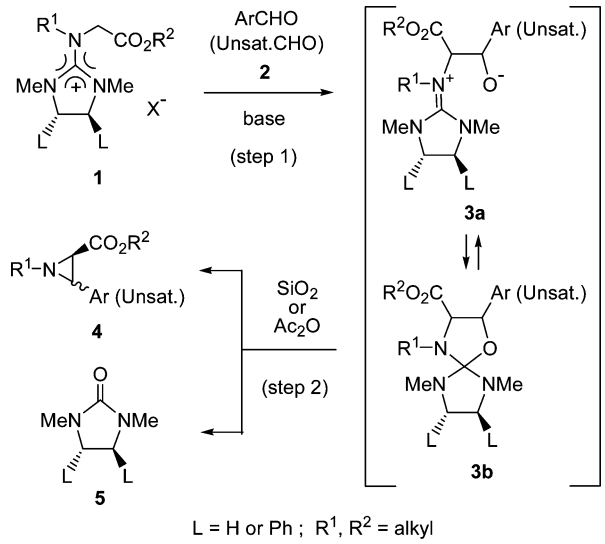
SCHEME 1. Guanidinium Ylide Mediated Aryl (or Unsaturated) Aziridination



tert-butoxycarbonyl-6,9-dimethyl-7,8-diphenyl-2-[(*Z*)-(1-bromo-2-phenyl)vinyl]-1-oxa-4,6,9-triazaspiro[4.4]nonane, as shown in Figure 1.[9]

Next, we examined the spiro intermediate formation reaction under chiral conditions using the (*S*,*S*)-diphenylguanidinium salt (*S*,*S*)-**6**. Treatment of (*S*,*S*)-**6** and **7** with TMG in THF according to the conditions in entry 3 of Table 1, followed by purification using NH-SiO_2 chromatography, afforded the optically active spiro imidazolidine-oxazolidine intermediate (−)-**8** in 74% yield as colorless plates (mp 65−68 °C).[10] The spiro compound (−)-**8** was then subjected to fragmentation in chloroform ($CHCl_3$) triggered by SiO_2 to smoothly yield the *trans*-(+)-aziridine *trans*-(+)-**9** and the *cis*-(+)-aziridine *cis*-(+)-**9** in 63% and 12% yields, respectively, as well as the recyclable chiral urea (*S*,*S*)-**10** in 97% yield (Scheme 2).

The enantiomeric excess (ee) of the *trans*-(+)-**9** and *cis*-(+)-**9** products was estimated to be 98% and 94% ee, respectively, indicating that high asymmetric induction occurred throughout steps 1 and 2. In addition, the major formation of *trans*-(+)-**9** from the (−)-1-oxa-4,6,9-triazaspiro[4.4]nonane intermediate (−)-**8** with a *trans*-oxazolidine ring system indicated that the stereochemistry at the C_2 allylic position is retained during this conversion. On the basis of these characteristics, we sought to delineate the reaction mechanism of this aziridination reaction.

We have reported that the (*S*,*S*)-diphenylguanidinium salt (*S*,*S*)-**6** induces the (2*R*)-configuration of aziridine-2-carboxylates.[6] Thus, given that (*S*,*S*)-**6** was used as the ylide source in the present work, the absolute configurations of the aziridine products can be reasonably deduced to be a (2*R*,3*S*)-configuration for *trans*-(+)-**9** and a (2*R*,3*R*)-configuration for *cis*-(+)-**9**.

We have proposed that the aziridination reaction proceeds via one of two mechanisms, depending on the substituent on the aromatic ring of the aryl aldehyde used for the guanidinium ylide mediated aryl aziridination reaction.[7] If the substituent is an electron-donating group, an S_Ni type reaction occurs in which the C_2 allylic stereochemistry of the oxazolidine ring system is retained; whereas if the substituent is an electron-withdrawing group, an S_N2 type reaction occurs in which the C_2 allylic stereochemistry of the oxazolidine ring system is lost as a result of inversion. In the present work, however, the C_2 allylic stereochemistry of the oxazolidine ring system was preferentially retained during the fragmentation of the spiro imidazolidine-oxazolidine intermediate **8** to aziridine products **9**, despite the presence of an electron-withdrawing bromine atom on the aldehyde unit **7**. Although this result appears to contradict the general rule outlined above, it can be explained by considering that a halogen atom can stabilize the cationic character of a neighboring position by the formation of a cyclic halonium ion.[11] Thus, the present observation, that the spiro imidazolidine-oxazolidine intermediate **8** undergoes fragmentation with retention of the C_2 allylic stereochemistry of the oxazolidine ring system to give the *trans*-aziridine *trans*-**9** as a major aziridine product, can be explained in terms of stabilization[12] by the bromine atom on the aldehyde **7**, as shown in Scheme 3.

In conclusion, we have presented evidence that, in the two-step guanidinium ylide mediated azidirination reaction, a thermodynamically stable spiro imidazolidine-oxazolidine intermediate with a *trans*-configuration is formed in step 1 and then this spiro intermediate is smoothly converted to aziridine products and urea in a stereochemically controlled manner in step 2.

Experimental Section

Isolation of Spiro Intermediate 8. A solution of **6** (151 mg, 0.27 mmol, 1.26 equiv) in THF (0.75 mL) at room temperature was added to TMG (0.04 mL, 0.32 mmol, 1.5 equiv) under argon. After stirring at the same temperature for 5 min, the reaction mixture was cooled to −40 °C, and a solution of **7** (48 mg, 95% purity, 0.22 mmol, 1.00 equiv) in THF (0.5 mL) was added. The reaction mixture was stirred at −40 °C for 2.5 h and then at −10 °C for 3.5 h. After evaporation of the solvent under reduced pressure the residue was purified by column chromatography (NH-silica gel, *n*-hexane/AcOEt = 50:1 to 5:1) to afford **8** as a colorless solid (108 mg, 73%, mp 150−153 °C), together with the *trans*-aziridine *trans*-**9** as a pale yellow oil (8 mg, 9%). A part of **8** was recrystallized from *n*-hexane/AcOEt for X-ray crystallographic analysis to give colorless prisms (mp 160−161 °C).

(2*R,3*R**,7*S**,8*S**)-4-Benzyl-3-*tert*-butoxycarbonyl-6,9-dimethyl-7,8-diphenyl-2-[(*Z*)-(1-bromo-2-phenyl)vinyl]-1-oxa-4,6,9-triazaspiro[4.4]nonane (8).** IR (ATR): ν_{max} 1724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.18 (s, 9H), 2.38 (s, 3H), 2.50 (s, 3H), 3.83 (d, J = 7.9 Hz, 1H), 3.95 (d, J = 15.0 Hz, 1H), 4.02 (d, J = 7.9 Hz, 1H), 4.03 (d, J = 7.9 Hz, 1H), 4.50 (d, J = 15.0 Hz, 1H), 4.91 (d, J = 7.9 Hz, 1H), 7.01 (m, 2H), 7.20−7.40 (m, 15H), 7.46 (d, J = 7.9 Hz, 2H), 7.64 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 27.5, 30.9, 31.0, 51.0, 69.7, 72.8, 74.1, 81.5, 81.6, 122.3, 124.1, 126.7, 127.38, 127.43, 127.5, 128.1,

(9) X-ray data were collected on a Bruker SMART 1000 CCD detector. The crystal structure was solved by direct methods (SHELXS-97) (Sheldrick, 1997) and refined by full-matrix least-squares (SHELXL-97) (Sheldrick, 1997). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included at their calculated positions. Crystal data for **8**: $C_{39}H_{42}BrN_3O_3$; M = 680.67 g mol^{-1}, triclinic, *P*-1, colorless block measuring 0.40 × 0.35 × 0.30 mm, T = 150 K, a = 9.1682(14) Å, b = 13.934(2) Å, c = 14.818(2) Å, α = 103.742(2)°, β = 102.728(2)°, γ = 103.863(2)°, V = 1706.3(4) $Å^3$, Z = 2, D_{calcd} = 1.325 Mg m^{-3}, μ = 1.246 mm^{-1}, T_{max} = 0.7062, T_{min} = 0.6356, GOF on F^2 = 1.027, R1 = 0.0468, wR2 = 0.1162 [$I > 2\sigma(I)$], R1 = 0.0684, and wR2 = 0.1279 (all data). CCDC-299422.

(10) The *trans*-aziridine was concomitantly formed in 11% yield.

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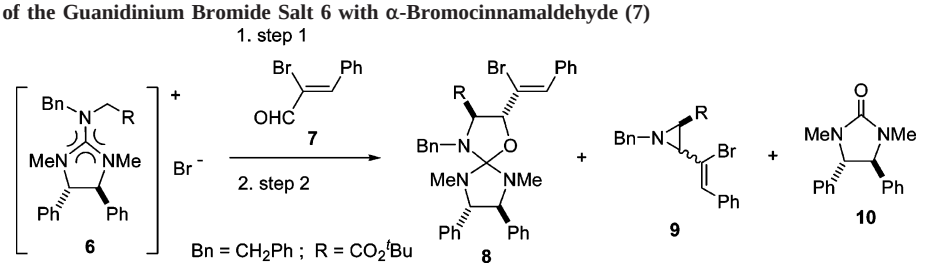
TABLE 1. Reaction of the Guanidinium Bromide Salt 6 with α-Bromocinnamaldehyde (7)



	conditions[a]		yield (%)[b]			
entry	step 1	step 2	**8**	*cis*-**9**	*trans*-**9**	**10**
1	TMG[c]/THF; (1) −40 °C, 3 h; (2) rt, 3.5 h	$Ac_2O/CHCl_3$; (1) 0 °C, 0.5 h; (2) rt, 16 h	0	8	31	82
2	NaH[d]/DMF; −40 °C, 5 h	SiO_2/MeCN; rt, 30 h	1	10	25	64
3	TMG[e]/THF; (1) −40 °C, 2.5 h; (2) −10 °C, 3.5 h	NT[f]	73	0	9	NI[g]
4	TMG[e]/THF; (1) −40 °C, 18 h; (2) rt, 1.5 h	NT[f]	64	0	21	NI[g]

[a] rt = room temperature. [b] Isolated yield. [c] 1.6 equiv. [d] 2.0 equiv. [e] 1.5 equiv. [f] Not treated. [g] Not isolated.

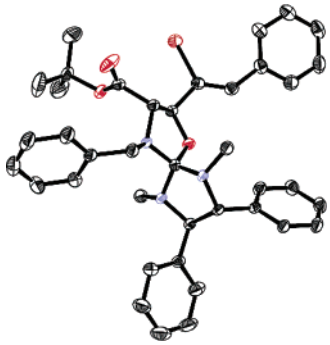
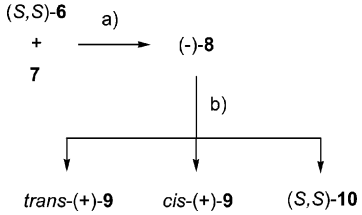


FIGURE 1. ORTEP drawing of 1-oxa-4,6,9-triazaspiro[4.4]nonane intermediate **8**. Hydrogens are omitted for clarity.

SCHEME 2. Two-Step Aziridination Using (*S,S*)-Guanidinium Bromide Salt (*S,S*)-6 and (*Z*)-α-Bromocinnamaldehyde (7)



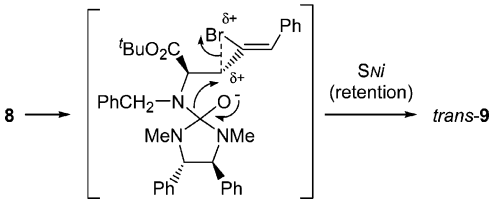
[a] Reagents and conditions: (a) TMG (1.4 equiv)/THF, −20 to 0 °C, 2 h [(−)-**8**, 74%]; (b) $SiO_2/CHCl_3$, rt, 20 h [*trans*-(+)-**9**, 63% (98% ee); *cis*-(+)-**9**, 12% (94% ee); (*S,S*)-**10**, 97%].

128.187, 128.194, 128.2, 128.45, 128.52, 128.6, 129.1, 135.0, 139.8, 134.0, 140.2, 170.3. HRFABMS *m/z*: 682.2458 (calcd for $C_{39}H_{43}{}^{81}BrN_3O_3$ 682.2467), 680.2443 (calcd for $C_{39}H_{43}{}^{79}BrN_3O_3$ 680.2488).

Two-Step Aziridination under Chiral Conditions. A solution of (*S,S*)-**6** (151 mg, 0.27 mmol, 1.24 equiv) in THF (0.75 mL) was similarly treated with a solution of **7** (49 mg, 95% purity, 0.22 mmol, 1.00 equiv) in THF (0.5 mL) in the presence of TMG (0.04 mL, 0.32 mmol, 1.44 equiv). After stirring at −20 °C for 30 min and then at 0 °C for 1.5 h, the same workup afforded (−)-**8** as colorless plates [112 mg, 74%, mp 65−68 °C, $[\alpha]^{22}_D$ −3.0 (*c* 1.3, $CHCl_3$)].

The spiro intermediate (−)-**8** (101 mg, 0.15 mmol) was dissolved in $CHCl_3$ (2 mL), and the resulting solution was slowly added to a suspension of SiO_2 (2.98 g) in $CHCl_3$ (6 mL). The resulting mixture was stirred at room temperature for 20 h, filtered through a Celite pad, and washed with $CHCl_3$ (50 mL). After evaporation of the solvent, the residue was purified by column chromatography (NH-SiO_2, *n*-hexane/AcOEt = 50:1 to 4:1) to give the *trans*-(+)-aziridine *trans*-(+)-**9** as a pale yellow oil (38 mg, 63%), the *cis*-(+)-aziridine *cis*-(+)-**9** as a colorless solid (7 mg, 12%, mp 90−91 °C), and (*S,S*)-**10** as colorless solid (38 mg, 97%).

SCHEME 3. Proposed Mechanism for Preferential Formation of *trans*-Aziridine from the Spiro Imidazolidine-Oxazolidine Intermediate with a *trans*-Oxazolidine Ring System.



***tert*-Butyl (2*R*,3*S*)-*trans*-1-Benzyl-3-[(*Z*)-1-bromo-2-phenyl)-vinyl]aziridine-2-carboxylate [*trans*-(+)-9].** 98% ee by chiral HPLC (CHIRALCEL OD-H, 0.46 cm × 25 cm); *n*-hexane/2-propanol = 450:1; flow rate = 1.0 mL/min; detection wavelength = 254 nm; t_R (minor) = 10.3 min, t_R (major) = 12.3 min; $[\alpha]^{22}_D$ +40.1 (*c* 1.4, $CHCl_3$); R_f = 0.66 (*n*-hexane/AcOEt = 10:1); IR (ATR): ν_{max} 1720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.42 (s, 9H), 2.86 (br s, 1H), 3.15 (br s, 1H), 4.05 (d, *J* = 13.6 Hz, 1H), 4.20 (d, *J* = 13.6 Hz, 1H), 7.08 (s, 1H), 7.23−7.36 (m, 6H), 7.40 (d, *J* = 7.1 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 28.0, 43.9, 52.1, 54.4, 82.2, 122.5, 127.0, 128.06, 128.12, 128.3, 128.7, 129.0, 135.1, 138.8, 167.2. HREIMS *m/z*: 413.1018 (calcd for $C_{22}H_{24}{}^{79}BrNO_2$ 413.0990)

***tert*-Butyl (2*R*,3*R*)-*cis*-1-Benzyl-3-[(*Z*)-1-bromo-2-phenyl)vinyl]aziridine-2-carboxylate [*cis*-(+)-9].** 94% ee by chiral HPLC (CHIRALCEL OD-H, 0.46 cm × 25 cm); *n*-hexane/2-propanol = 800:1; flow rate = 1.0 mL/min; detection wavelength = 254 nm; t_R (major) = 34.1 min, t_R (minor) = 40.6 min; $[\alpha]_D{}^{23}$ +32.1 (*c* 0.3, $CHCl_3$); R_f = 0.38 (*n*-hexane/AcOEt = 10:1). IR (ATR): ν_{max} 1730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 9H), 2.56 (br s, 1H), 2.83 (br s, 1H), 3.56 (d, *J* = 13.6 Hz, 1H), 3.91 (d, *J* = 13.6 Hz, 1H), 7.25 (s, 1H), 7.26−7.37 (m, 6H), 7.43 (d, *J* = 7.1 Hz, 2H), 7.56 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 28.0, 46.5, 51.2, 62.7, 81.6, 117.56, 127.4, 127.9,

128.0, 128.1, 128.5, 129.0, 129.8, 135.1, 137.3, 166.3. HREIMS *m*/*z*: 413.0970 (calcd for $C_{22}H_{24}{}^{79}BrNO_2$ 413.0990).

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Supporting Information Available: General experimental procedures, NMR and HPLC charts of products, and X-ray data of **8** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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