Guanidinium Ylides as a New and Recyclable Source for Aziridines and Their Roles as Chiral Auxiliaries

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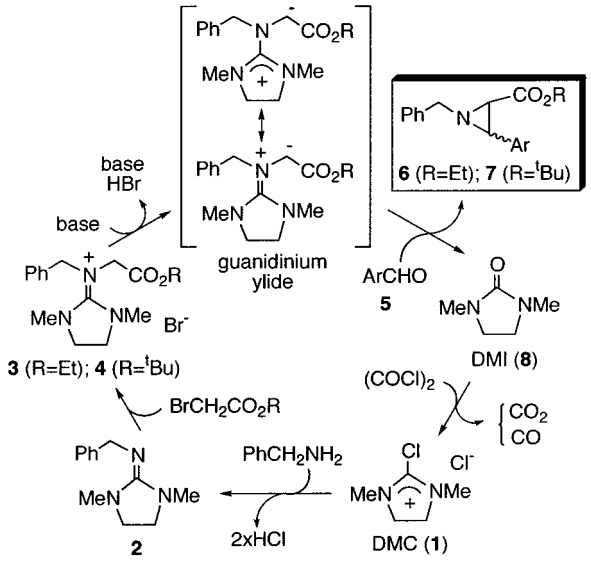
Aziridines are very important molecules not only as key components of biologically active natural products such as mitomycins, but also as reactive synthetic intermediates for nitrogen-containing compounds. Therefore, there have been many approaches to their preparation, including asymmetric synthesis, which could be classified into three types of reactions: (i) intramolecular substitution by nitrogen nucleophiles, (ii) addition of carbenes to imines, and (iii) addition of nitrenes to olefins.[1]

Guanidinium ylides have not hitherto been known to our knowledge; however, these would be expected to act as stabilized equivalents of azomethine ylides[2] (see Scheme 1). In our guanidine chemistry[3] we found that treatment of guanidinium bromides **3** (or **4**) with aryl aldehydes **5** in the presence of a base directly afforded 3-arylaziridine-2-carboxylates **6** (or **7**) in high yields with excellent to moderate *trans* diastereoselectivity. Furthermore, the introduction of chiral centers into the guanidinium template resulted in effective asymmetric induction on the aziridine formation. In this communication we present a new aziridine synthesis from guanidinium ylides and an application of the methodology to asymmetric synthesis.

Reaction of **3**, prepared from 2-chloro-1,3-dimethylimidazolinium chloride (DMC)[4] (**1**) according to the reported method[3a] (see Scheme 1), with benzaldehyde (**5a**) (0.9 equiv) in DMF in the presence of NaH (1.2 equiv) at −20 °C followed by SiO_2 treatment[5] afforded 3-phenylaziridine-2-carboxylate **6a** in 84% yield in a 27:73 ratio of *cis* and *trans* derivatives[6,7] ***c*-6a** and ***t*-6a** (entry 1, Table 1). Examination of the reaction conditions allowed us to use tetramethylguanidine (TMG) as a base and a solvent. Thus, stirring **3** and **5a** with TMG (1.1 equiv) at room temperature followed by SiO_2 treatment[5] similarly gave ***c*-6a** and ***t*-6a** in 28 and 41% yields, respectively (entry 2, Table 1).

This synthetic method was found to be applicable to a variety of aryl aldehydes, including heterocycles, as shown in Table 1, in which *trans* aziridines[8] ***t*-6** were preferentially formed. In particular, not only *trans* selectivity (ca. 90% de) but also satisfactory conversion (68−95%) were observed when electron-rich benzaldehydes **5b-d** and indolyl aldehydes **5h−i** (entries 3-6, 12, and 13, Table 1) were used. Cinnamaldehyde **5g** could also be converted to aziridines **6g** in total 70% yield, in which no 1,4-addition occurred (entry 11, Table 1). Interestingly, replacement of the ethyl ester function in **3** to a *tert*-butyl ester as in **4** led to a reversion of diastereoselectivity dependent upon the substituent of aldehydes used. Thus, *cis*-excess products were obtained in the cases of **5a** and **5e** (entries 15 and 18, Table 1). In these reactions 1,3-dimethylimidazolidin-2-one (DMI) (**8**), a synthetic precursor of **1**, was isolated as an alternative product. Thus, this reaction sequence could be regarded as an effective cycle reaction, because of no waste of any of the key components during reactions (see Scheme 1).

Scheme 1



Ar: a=Ph, b=3,4-OCH_2OPh, c=4-MeOPh, d=2-MeOPh, e=4-ClPh, f=4-NO_2Ph, g=PhCH=CH, h=3-[(1-Boc)indolyl], i=2-[(1-Boc)indolyl], j=3-Pyridyl

Next, this aziridine synthesis was applied to asymmetric synthesis, because of the easy availability of chiral templates (Table 2). Smooth reaction was observed when the guanidinium bromide **9** (or **ent-9**)[9] with a *tert*-butyl ester function was treated with piperonal **5b** under the same conditions on achiral salts, in which TMG (entry 2, Table 2) was more effective in both chemical yield and stereoselectivity than NaH in DMF (entry 1, Table 2). Thus, optically active *trans* derivative ***t*-7b** was obtained in 82% yield and with 97% ee in the former reaction, whereas in 75% yield and with 72% ee in the latter case. In this reaction sequence a chiral urea **10** was, as expected, recovered as a reuseable source for **9** (or **ent-9**).

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(4) Isobe, T.; Ishikawa, T. *J. Org. Chem*. **1999**, *64*, 5832−5835; 6984−6988; 6989−6992.

(5) Incomplete coversion of high polar substances into less polar ones during SiO_2 column chromatography of crude products made us modify the isolation work. Thus, the solvent used was evaporated after the aldehyde disappeared on TLC. The residue was stirred in $CHCl_3$ with SiO_2 and then the SiO_2 was removed. Evaporation of the filtrate followed by purification (SiO_2) afforded aziridines.

(6) No isomerization was observed when each isomer was independently treated under the conditions used in the reaction.

(7) In general, methine protons of *cis* derivatives were observed with larger coupling constant ($J = \sim 7$ Hz) than those of *trans* one ($J = \sim 4$ Hz) in ^{1}H NMR spectra of 2,3-disubstituted aziridine systems. In our case ***c*-6a** showed the ring protons as doublets ($J = 6.7$ Hz), whereas ***t*-6a** as either broad singlets or doublets ($J = \sim 2$ Hz) (For example, see Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem*. **1999**, *64*, 518−521).

(8) Some aziridines showed the presence of invertomers at the nitrogen atom in the ^{1}H NMR spectra (See, Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* **2001**, *57*, 1801−1812 and references therein).

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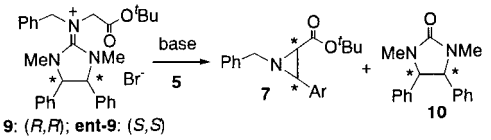
Table 1. Reaction of Guanidinium Bromides **3** or **4** with Aryl Aldehydes **5** Giving Aziridine Derivatives **6** or **7**

	3 or **4** + **5**			base → **6** or **7** + **8**					
						yield[b] (%) of **6** or **7**			
entry	**3** or **4**	**5**	base[a]	time (h)		*cis*	*trans*	*cis*/*trans*	**8** (%)
1	**3**	**5a**	A	24	**6a**	23	61	27/73	78
2	**3**	**5a**	B	24	**6a**	28	41	41/59	77
3	**3**	**5b**	A	24	**6b**	8	69	10/90	71
4	**3**	**5b**	B	24	**6b**	4	64	6/94	83
5	**3**	**5c**	A	9	**6c**	7	78	8/92	-[c]
6	**3**	**5d**	A	8	**6d**	2	93[d]	2/98	-[c]
7	**3**	**5e**	A	24	**6e**	17	48	26/74	93
8	**3**	**5e**	B	24	**6e**	16	45	26/74	94
9	**3**	**5f**	A	24	**6f**	2	45	4/96	-[c]
10	**3**	**5f**	B	2	**6f**	3	43	7/93	72
11	**3**	**5g**	A	24	**6g**	17	53[d]	24/76	-[c]
12	**3**	**5h**	A	24	**6h**	4	72[d]	5/95	88
13	**3**	**5i**	A	24	**6i**	4	75[d]	5/95	88
14	**3**	**5j**	A	7	**6j**	8	58	12/88	72
15	**4**	**5a**	B	19	**7a**	57	20	74/26	-[e]
16	**4**	**5b**	A	7	**7b**	2	64	3/97	84
17	**4**	**5b**	B	25	**7b**	3	60	5/95	74
18	**4**	**5e**	B	24	**7e**	32	25	56/44	-[c]
19[e]	**4**	**5h**	B	24	**7h**	2	21	9/91	-[c]
20[e]	**4**	**5i**	B	6	**7i**	2	57	3/97	-[c]
21	**4**	**5j**	B	4	**7j**	2	29	6/94	-[c]

[a] A: NaH. The reaction was carried out in DMF at −20 °C. B: TMG. The reaction was carried out without solvent at rt. [b] Isolated, nonoptimized yield [c] Isolation was not attempted. [d] A mixture of two invertomers at the nitrogen atom. [e] Deprotection of the Boc group was observed during the reaction.

Table 2. Asymmetric Aziridine Synthesis Using Chiral Guanidinium Bromides **9** or **ent-9**[a]



9: (*R*,*R*); **ent-9**: (*S*,*S*)

	9 or **ent-9**			time (h)		yield[b] (%) of **7**[c]			
entry		**5**	base			*cis* (ee%)	*trans* (ee%)	*cis*/*trans* (%)	**10** (%)
1	**9**	**5b**	A	39	**7b**	7	75(72)	9/91	86
2	**ent-9**	**5b**	B	4	**7b**	6	82(97)	7/93	91
3	**9**	**5a**	B	5	**7a**	61(75)	32(73)	66/34	96
4	**ent-9**	**5a**	B	3	**7a**	60(79)	31(77)	66/34	88
5	**ent-9**	**5e**	B	4	**7e**	51	35(59)	59/41	-[d]
6	**ent-9**	**5h**	B	7	**7h**	6	70(95)	8/92	87
7	**ent-9**	**5i**	B	5.5	**7i**	9	87(76)	9/91	90

[a] The reaction was carried out under the same conditions shown in Table 1. [b] Isolated, nonoptimized yield. [c] See Supporting Information for the separation conditions of enantiomeric aziridines by chiral HPLC. [d] Isolation was not attempted.

We further examined the scope of this TMG-promoted asymmetric aziridine synthesis using some aryl aldehydes. Introduction of chiral units into the imidazolidine ring could cause rate acceleration of the reaction and effective product formation with satisfactory enantioselectivity, in which diastereoselectivites were also observed. In particular, both high diastereo- and enantioselectivities were observed in the cases of indolyl aldehydes **5h** and **5i** (entries 6 and 7, Table 2) in addition to **5b** mentioned above.

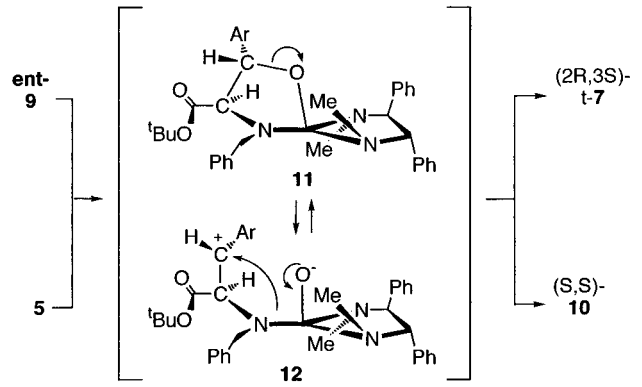


Figure 1. A possible reaction path for the enantioselective formation of (2*R*,3*S*)-*trans*-aziridine **t-7** from **ent-9** with **5**.

The absolute stereochemistries of aziridine products were determined by chemical correlation of 3-phenylaziridine-2-carboxylates (***c*-7a**: 79% ee; ***t*-7a**: 77% ee) obtained in entry 4 in Table 2 with commercially available *tert*-butyl (*S*)-phenylalaninate. Independent hydrogenation[10] of ***c*-7a** and ***t*-7a** with $Pd(OH)_2/C$ in the presence of $(Boc)_2O$ afforded an identical *N*-Boc-protected *tert*-butyl phenylalaninate, which was found to be an (*R*)-excess product (77% ee for each) compared to an authentic (*S*)-derivative (see **SI**), indicating that the (*S*,*S*)-guanidinium ylide mainly produced (2*R*,3*R*)-*cis* and (2*R*,3*S*)-*trans* aziridines. Production of (2*R*)-aziridines **7a** from **ent-9** suggested that the *re*-face of the ylide has to be attacked by an aldehyde function in the C−C bond formation to afford a spiro oxazolidine[11] **11** (see Figure 1). Enantioselectivity of *trans* aziridine may be recognized by assuming minimized steric replusion between the substituents of each component in the benzylic cation/hydroxide ion pair intermediate **12** derived from **11** as shown in Figure 1.

In conclusion, we have established an efficient preparation method of 3-arylaziridine-2-carboxylates from guanidinium ylides and aryl aldehydes applicable to asymmetric synthesis. It is known that ammonium, azomethine, and nitrile ylides are useful and reactive nitrogen ylides in organic synthesis.[12] Therefore, our results obtained here indicate a new entry of a guanidinium ylide as a synthetically versatile nitrogen ylide.

Supporting Information Available: Chiral conditions of HPLC (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) **9** and **ent-9** were prepared from the corresponding ureas by successive treatments with oxalyl chloride, *tert*-butyl glycinate, and benzyl bromide (Preparation of the urea: see, Isobe, T.; Fukuda, K.; Ishikawa, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1729−1735).

(10) Reductive ring opening of the related aziridine system was reported by Lee et al. (Chang, J. W.; Bae, J. H.; Shin, S. H.; Park, C. S.; Choi, D.; Lee, W. K. *Tetrahedron Lett.* **1998**, *39*, 9193−9196).

(11) The oxazolidine could be approached by two possible routes: (1) stepwise reactions of the C−C bond formation followed by nucleophilic addition or (2) direct connection by [2 + 3] cycloaddition.

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