Highly Enantioselective Aziridination of N-Protected Imines: Comparison of the Phosphazene EtP_2 and Sodium Hydride as Bases

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Abstract: Asymmetric synthesis of 2,3-disubstituted *N*-Boc, *N*-SES, and *N*-Ts aziridines starting from N-protected imines, using sulfonium salt derived from Eliel's oxathiane, is reported. Sodium hydride was successfully used as a substitute for the phosphazene base EtP_2 without any loss of yield, enantioselectivity, or diastereoselectivity.

Key words: asymmetric synthesis, aziridines, enantioselectivity, imine, ylide

Chiral aziridines are highly valuable synthetic intermediates because of their ability to undergo different transformations, especially ring opening, to afford versatile optically active nitrogen-containing compounds. Amongst different methods for asymmetric aziridinations[1] the large area belongs to imine aziridinations and includes aza-Darzens reactions,[2] and reactions of imines with carbenes[3] or sulfur ylides.[4]

Recently, Solladié-Cavallo reported an asymmetric synthesis of 2,3-disubstituted *N*-tosyl aziridines[5] from *N*-tosylimines, using sulfonium salt **1** derived from Eliel's oxathiane.[6] A phosphazene base EtP_2 ($[Me_2N]_3P{=}NP(=NEt)[NMe_2]_2$) was used to generate the ylide.[7] The two-step synthesis provided in most cases *cis*/*trans* mixtures of aziridines; very high enantiomeric purities were reported (98.7–99.9% ee). Even though this method is amenable to gram-quantity synthesis, and the chiral auxiliary can easily be recovered and reused, the practicality of this procedure is limited by the use of sensitive and expensive phosphazene base. Herein, we present an application of this method for the asymmetric synthesis of *N*-SES-, *N*-Boc-, and *N*-Ts-disubstituted aziridines [SES = 2-(trimethylsilyl)ethanesulfonyl] with the use of sodium hydride as the base.

In our preliminary studies, the influence of the base on reaction yield, diastereo- and enantioselectivity in aziridination of *N*-Ts imines was examined. The sulfonium salt **1** was prepared from (*R*,*R*,*R*)-(+)-oxathiane **2**[8] and benzyl alcohol, using Vedejs's triflate method.[9] The salt **1** was isolated as a single diastereomer having R,R,R,S_S-(+)-configuration.[10] In contrast to Solladié-Cavallo's aziridinations, which were performed in CH_2Cl_2, we have chosen THF as the reaction solvent, because the reaction with NaH in CH_2Cl_2 required much longer time and resulted in low yields (<10%). The *N*-Ts aziridines **8**–**12** were prepared from corresponding *N*-Ts imines **3**–**7**[11] and sulfonium salt **1**, using EtP_2 or NaH as a base to generate the ylide (Table 1). Reactions with NaH were carried out overnight at –40 °C. Reactions with EtP_2 were carried out for 4 hours at –78 °C. Even though reaction with NaH required longer reaction time, it was found that the choice of base had almost no effect on the reaction diastereo- and enantioselectivity. Reaction yields are comparable in most cases.

Encouraged by results with *N*-Ts aziridines we decided to synthesize also the aziridines with Boc and SES protecting groups on nitrogen atom. It is well known that tosyl deprotection requires vigorous reaction conditions, whilst Boc and SES groups can easily be removed[12] before or after further transformations of aziridines into target compounds. The *N*-SES imines **13**–**15** and *N*-Boc imines **16**–**18** were prepared according to literature procedures,[13] and are known compounds except for *N*-(1-naphthylidene)-2-trimethylsilylethanesulfonamide (**15**).[14] The same procedure as for *N*-Ts aziridines was also used to prepare *N*-SES aziridines **19**–**21** with phenyl, 4-methoxyphenyl, and 1-naphthyl substituents on C-3 ring atom, as well as *N*-Boc aziridines **22**–**24** with the same substituents (Table 2).[15] Asymmetric syntheses of **19**, **20**, and **22** were already reported; some investigations on the effect of N-protecting groups were conducted, but the ee's obtained were lower.[4a–4c]

Reaction yields are comparable to those of *N*-Ts aziridines, except for 2-phenyl-3-(4-methoxyphenyl)-1-(*tert*-butoxycarbonyl)-aziridine (**23**, Table 2, entries 7 and 8). Even though conversion of the corresponding *N*-Boc imine to aziridine **23** was complete (confirmed by ^{1}H NMR of the crude reaction mixture), due to the presence of the electron-donating aromatic substituent, which enhanced its instability, the compound partially ring-opened during purification step. Ring opening was minimized, but still observed, using chromatography on neutral aluminium oxide.

Enantiomeric purities of all products were again very high, and as expected according to the proposed mechanism,[5] the choice of N-protecting group had no effect on reaction enantioselectivity. However, reaction diastereoselectivity was highly substrate dependent, and varied with the nature of the protecting group, substituent, and in the case of aziridine **21**, the base. The largest influence on

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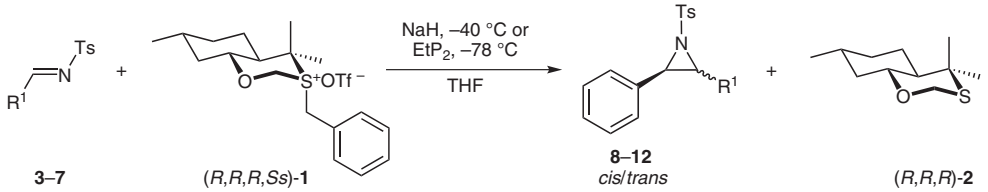
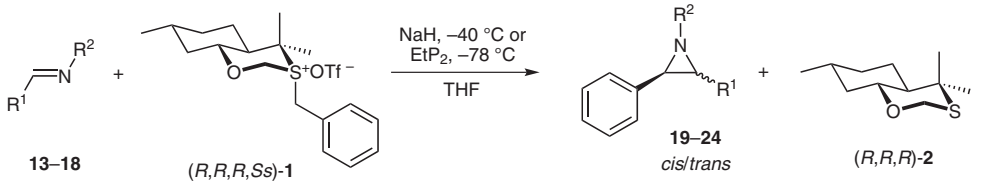
Table 1 Asymmetric Synthesis of *N*-Ts Aziridines



Entry	R^1	Base	Imine	Product	Yield (%)	*cis*/*trans*[a]	*cis*[b] ee (%)	*trans*[b] ee (%)
1	Ph	NaH	**3**	**8**	60	60:40	*meso*	98
2	Ph	EtP_2	**3**	**8**	73	64:36	*meso*	98
3	PMP	NaH	**4**	**9**	57	58:42	98	n.d.[c]
4	PMP	EtP_2	**4**	**9**	58	62:38	98	n.d.[c]
5	*t*-Bu	NaH	**5**	**10**	68	100:0	97	–
6	*t*-Bu	EtP_2	**5**	**10**	73	100:0	98[d]	–
7	1-naphthyl	NaH	**6**	**11**	60	31:69	96	96
8	1-naphthyl	EtP_2	**6**	**11**	69	32:68	96	96[e]
9	9-phenanthryl	NaH	**7**	**12**	76	45:55	95	96
10	9-phenanthryl	EtP_2	**7**	**12**	58	43:57	98	98

[a] The *cis*/*trans* ratios were determined by ^{1}H NMR spectroscopy of the crude product.
[b] Determined by chiral HPLC on the *cis*/*trans* mixture.
[c] Enantiomers were not separated on the following columns: Chiralcel AS, OJ, AD, and OB.
[d] 2*R*,3*S*-Configuration of *cis*-isomer determined by X-ray analysis.[5]
[e] 2*R*,3*R*-Configuration of *trans*-isomer determined by X-ray analysis.[5]

Table 2 Asymmetric Synthesis of *N*-SES and *N*-Boc Aziridines



Entry	R^1	R^2	Base	Imine	Product	Yield (%)	*cis*/*trans*[a]	*cis*[b] ee (%)	*trans*[b] ee (%)
1	Ph	SES	NaH	**13**	**19**	68	44:56	*meso*	>99
2	PMP	SES	NaH	**14**	**20**	47	63:37	>99	98
3	1-naphthyl	SES	NaH	**15**	**21**	63	24:76	97	98
4	1-naphthyl	SES	EtP_2	**15**	**21**	52	12:88	–	99
5	Ph	Boc	NaH	**16**	**22**	60	10:90	*meso*	97
6	Ph	Boc	EtP_2	**16**	**22**	59	8:92	*meso*	97
7	PMP	Boc	NaH	**17**	**23**	31	9:91	–	96
8	PMP	Boc	EtP_2	**17**	**23**	26	8:92	–	98
9	1-naphthyl	Boc	NaH	**18**	**24**	75	2:98	–	96
10	1-naphthyl	Boc	EtP_2	**18**	**24**	56	0:100	–	98

[a] The *cis*/*trans* ratios were determined by 1H NMR spectroscopy of the crude product.
[b] Determined by chiral HPLC on the *cis*/*trans* mixture.

diastereoselectivity was the nature of the N-protecting group, and in the case of aziridines **22**–**24**, very good or total *trans*-diastereoselectivities were achieved using Boc protecting group. For *N*-Boc aziridines, ring substituent showed no significant effect on diastereoselectivity. The *N*-SES aziridines **19** and **21** were obtained in the form of *cis*/*trans* mixtures with *trans* being the major isomer.

In conclusion, NaH was successfully used as a substitute for the expensive and sensitive base EtP_2, without any major influence on yield, enantioselectivity, or diastereoselectivity. This approach was applied to the synthesis of *N*-SES and *N*-Boc aziridines. Diastereoselectivities of the product aziridines varied with the N-protecting group, but the ring substituent also affected *cis*/*trans* ratio. Further investigations of the influence of ring substituent on diastereoselectivity are ongoing, and the results will be published in due course.

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(14) ***N*-(1-Naphthylidene)-2-trimethylsilylethanesulfonamide (15)**
A mixture of 1-naphthaldehyde (300 mg, 0.26 mL, 1.91 mmol, 1 equiv), 2-(trimethylsilyl)ethanesulfonamide (415 mg, 2.29 mmol, 1.2 equiv), and anhyd Et_3N (1.26 mL, 9.1 mmol, 4 equiv) in anhyd CH_2Cl_2 (15 mL), under argon, was cooled to 0 °C. A $TiCl_4$ solution in CH_2Cl_2 (1.9 mL of 1 M solution, 1 equiv) was carefully added, and reaction mixture was stirred at 0 °C for 1 h, and then at r.t. for 20 h. The reaction mixture was filtered trough Celite, concentrated, and toluene (20 mL) was added to the solid residue. After 10 min of stirring, the mixture was filtered, and the filtrate concentrated under vacuum. The NMR analysis of the crude product **15** showed that it containes 4% of the starting amide and 96% of the imine. The product was found to decompose on silica gel and was used in the next step without further purification (570 mg, w = 98%, yield 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 9 H), 1.09–1.15 (m, 2 H), 3.19–3.25 (m, 2 H), 7.59–7.65 (m, 2 H), 7.71 (td, 1 H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.96 (d, 1 H, J = 8.0 Hz), 8.15 (d, 1 H, J = 8.0 Hz), 8.19 (d, 1 H, J = 7.2 Hz), 9.04 (d, 1 H, J = 8.0 Hz), 9.59 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –2.09, 9.50, 49.01,

124.22, 125.08, 126.95, 127.48, 128.91, 129.03, 131.73, 133.76, 135.22, 136.14, 170.91.

(15) **2-Phenyl-3-(1-naphthyl)-1-(2-trimethylsilylethanesulfonyl)-aziridine (21)**

To a stirred solution of benzyl sulfonium salt **1** (352 mg, 0.80 mmol, 1 equiv) under argon in anhyd THF (10 mL), cooled to –40 °C, NaH dispersion in paraffin (64 mg, w = 60%, 1.6 mmol, 2 equiv) was added. After 1 h, a THF solution (2 mL) of *N*-(1-naphthylidene)-2-trimethylsilylethanesulfonamide (**15**, 270 mg, w = 98%, 0.80 mmol, 1 equiv) was dropwise added. The reaction mixture was stirred for 20 h at –40 °C. Cold H_2O (15 mL) was carefully added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was analyzed by ^{1}H NMR to determine the diastereomeric ratio and then was purified by column chromatography on silica gel. First fraction contained recovered (*R*,*R*,*R*)-oxathiane **2** (145 mg, 90%); R_f = 0.8 (PE–EtOAc, 8:2).The title compound **21** was isolated as colorless oil (201 mg, 63%); R_f = 0.47 (PE–EtOAc, 8:2). Isomers of **21** were separated by chiral HPLC; *trans*: ee >99% [Chiralcel OD, hexane–EtOAc (90:10), 254 nm, 1 mL/min, t_R(minor) = 11.5 min, t_R(major) = 14.4 min]; $[\alpha]_D^{25}$ +75 (*c* 1; CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.05 (s, 9 H), 1.05–1.09 (m, 2 H), 2.94–3.06 (m, 2 H), 4.32 (d, 1 H, *J* = 4.5 Hz), 4.80 (d, 1 H, *J* = 4.5 Hz), 7.40–7.56 (m, 5 H), 7.60 (td, 1 H, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 7.64 (d, 2 H, *J* = 8.1 Hz), 7.68 (d, 1 H, *J* = 7.1 Hz), 7.88 (d, 1 H, *J* = 8.1 Hz), 7.91 (d, 1 H, *J* = 8.1 Hz), 8.25 (d, 1 H, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –2.16, 9.63, 48.58, 49.49, 50.97, 123.55, 125.19, 125.22, 126.15, 126.70, 128.32, 128.72, 128.81, 128.93, 129.37, 129.60, 132.47, 133.28, 133.55. IR (KBr): 3057, 2950, 1325, 1250, 1145, 932, 843, 796 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO_2SSi$ (409.62): C, 67.44; H, 6.64; N, 3.42. Found: C, 67.36; H, 7.06; N, 3.50. *Cis*: ee >99% [Chiralcel OD, hexane–EtOH (90:10), 254 nm, 1 mL/min, t_R(minor) = 5.7 min, t_R(major) = 8.0 min], $[\alpha]_D^{25}$ +197 (*c* 0.35, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 9 H), 1.23–1.29 (m, 2 H), 3.25–3.31 (m, 2 H), 4.39 (d, 1 H, *J* = 7.2 Hz), 4.67 (d, 1 H, *J* = 7.2 Hz), 7.01–7.03 (m, 3 H), 7.12–7.17 (m, 2 H), 7.32–7.53 (m, 3 H), 7.58 (d, 1 H, *J* = 7.1 Hz), 7.70 (d, 1 H, *J* = 8.1 Hz), 7.77 (d, 1 H, *J* = 8.1 Hz), 8.04 (d, 1 H, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –2.11, 9.86, 46.02, 47.27, 49.17, 122.84, 124.84, 125.80, 125.98, 126.31, 127.27, 127.71, 127.78, 127.79, 128.36, 128.50, 131.26, 131.97, 133.08. IR (KBr): 3059, 2950, 1328, 1250, 1145, 911, 841, 804 cm^{-1}

2-Phenyl-3-(4-methoxyphenyl)-1-(*tert*-butoxycarbonyl)-aziridine (23)

Compound **23** was prepared as above starting from *N*-(*tert*-butoxycarbonyl)-4-methoxybenzaldimine (**17**, 100 mg, 0.42 mmol, 1 equiv), and was isolated as colorless oil after workup and chromatography on neutral alumina, activity I (42 mg, 31%); R_f = 0.55 (hexane–EtOAc, 9:1). Product **23** is a *cis*/*trans* mixture (9:91), and the assignments are of the major *trans*-isomer. *Trans*: ee = 96% [Chiralpak AD, hexane–2-PrOH (92:8), 229 nm, 1 mL/min, t_R(major) = 25.7 min, t_R(minor) = 28.8 min]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 3.71 (d, 1 H, *J* = 3.3 Hz), 3.76 (d, 1 H, *J* = 3.3 Hz), 3.81 (s, 3 H), 6.89 (d, 2 H, *J* = 9.1 Hz), 7.27 (d, 2 H, *J* = 9.1 Hz), 7.32–7.35 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.67, 47.09, 47.73, 55.35, 81.34, 113.91, 126.93, 127.40, 127.98, 128.33, 128.47, 135.87, 159.54, 160.56. IR (KBr): 2926, 1752, 1720, 1608, 1519, 1255, 990, 831 cm^{-1}.

2-Phenyl-3-(1-naphthyl)-1-(*tert*-butoxycarbonyl)-aziridine (24)

Compound **24** was prepared as above starting from *N*-(*tert*-butoxycarbonyl)-1-naphthaldimine (**18**, 100 mg, 0.39 mmol, 1 equiv), and was isolated as viscous colorless oil after workup (101 mg, 75%); R_f = 0.22 (hexane–EtOAc, 8:2). Even though the crude mixture contained mixture of *trans*/*cis* isomers (98:2), after chromatography, only *trans*-isomer was isolated. *Trans*: ee = 96% (Chiralcel OJ, hexane–EtOH (95:5), 254 nm, 1 mL/min, t_R(minor) = 9.9 min, t_R(major) = 12.5 min]. $[\alpha]_D^{25}$ +89 (*c* 2.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 9 H), 3.85 (d, 1 H, *J* = 3.5 Hz), 4.47 (d, 1 H, *J* = 3.5 Hz), 7.37–7.54 (m, 8 H), 7.61 (d, 1 H, *J* = 6.8 Hz), 7.83 (d, 1 H, *J* = 8.5 Hz), 7.87–7.89 (m, 1 H), 8.22–8.25 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.42, 44.66, 47.18, 81.32, 123.95, 124.18, 125.39, 125.63, 125.97, 126.42, 127.51, 128.33, 128.53, 128.65, 132.01, 132.55, 133.42, 135.04, 160.11. IR (KBr): 3052, 2976, 2926, 1711, 1295, 1148, 779 cm^{-1}. Anal. Calcd for $C_{23}H_{23}NO_2$ (345.43): C, 79.97; H, 6.71; N, 4.05. Found: C, 79.90; H, 6.50; N, 3.89.