

Inverted Diastereoselectivity in Asymmetric Aziridine Synthesis via Aza-Darzens Reaction of (2*S*)-*N*-Bromoacyl Camphorsultam

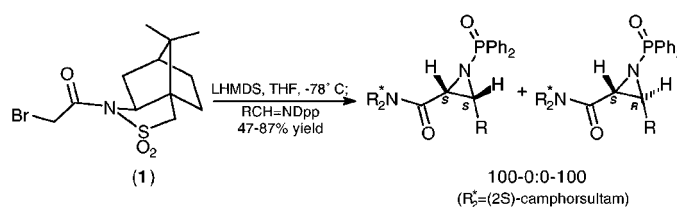
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Received July 28, 1999

ABSTRACT

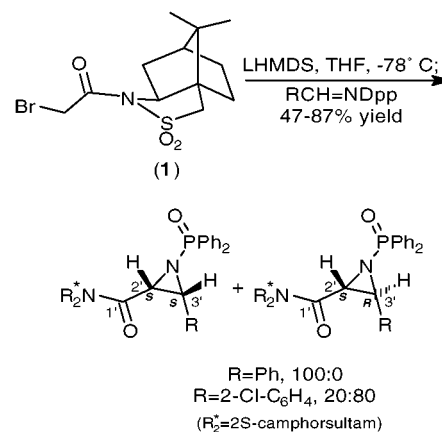


The *aza*-Darzens reaction of the chiral enolate derived from (2*S*)-bromoacetyl camphor sultam (1) with certain C-3-substituted *N*-diphenylphosphinyl imines gives mixtures of *trans*- and *cis*-aziridines. In some cases, only *trans* isomers are observed. A steric repulsion between the enolate halogen atom and this C-3-substituent is invoked to rationalize these observations.

There has been much attention of late on the synthesis and uses of chiral aziridines.¹ We recently reported the *aza*-Darzens reaction (ADZ) of *N*-bromoacyl (2*R*)-camphorsultam with *N*-diphenylphosphinylimines (“*N*-Dpp imines”) to be a useful method for preparation of enantiopure *cis*-2-carboxy aziridines.² We here report our recent findings that the presence of substituents in the C-3-position of certain imines leads to altered diastereocontrol in the ADZ reaction of bromoacyl (2*S*)-camphorsultam, in certain cases leading exclusively to *trans*-aziridines.

N-Dpp benzaldimine reacted with the enolate derived from (2*S*)-sultam (1) under the conditions outlined in Scheme 1 to give exclusively the *cis*-aziridine 2 ($R = \text{Ph}$) ($^3J = 6.2$, typical of such aziridines³) in 71% yield, but the corresponding imine derived from 2-chlorobenzaldehyde gave a mixture

Scheme 1. Variable Diastereocontrol in ADZ Reaction



of *cis*- and *trans*-aziridines 3 in 68% combined yield, with the *trans* isomer dominating (*cis:trans* = 1:4; $^3J_{\text{cis}} = 6.1$ Hz, $^3J_{\text{trans}} = 2.8$ Hz) (Scheme 1). The absolute configuration of the *cis*-aziridinyl sultam was deduced by comparison with

(1) Davis, F. A.; McCoull, W. *Tetrahedron Lett.* **1999**, *40*, 249. Sodergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, *38*, 6897. Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. Sodergren, M. J.; Alonso, D. A.; Andersson, P. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3563.

(2) Cantrill, A. A.; Hall, L. D.; Jarvis, A. N.; Osborn, H. M. I.; Raphy, J.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1996**, 2631.

the ^1H and ^{13}C NMR obtained for authentic phenylaziridine **2** (shown by X-ray analysis to be of $2R,2'R,3'R$ configuration), while that of the *trans*-aziridine was confirmed as $(2'S,3'R)$ by X-ray analysis of a single crystal (Figure 1).

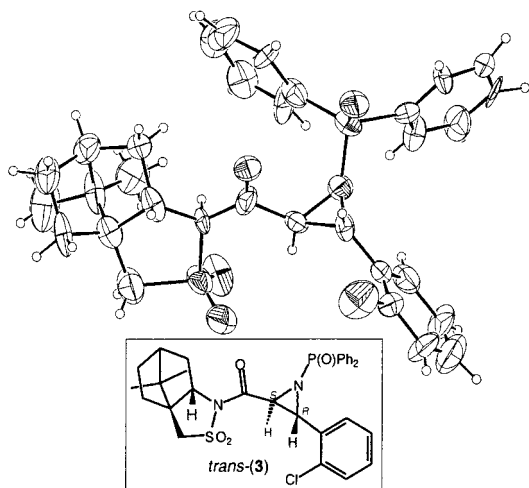


Figure 1. X-ray structure of *trans*-aziridine **3**.

This inversion of the diastereopreference previously seen was even more pronounced in the reaction of the *N*-Dpp imine derived from 2-bromobenzaldehyde: in this reaction *only* a *trans*-aziridine was observed (67% yield, $^3J = 2.6$ Hz), an observation also made when *N*-Dpp-2-iodobenzaldimine was employed in the reaction. When *N*-Dpp-2-fluorobenzaldimine was reacted under the same conditions, lower stereoselectivity was observed, as might be expected, with the *cis*:*trans* ratio being unity ($^3J_{\text{cis}} = 6.2$ Hz, $^3J_{\text{trans}} = 2.8$ Hz), although the yield of aziridine was good.

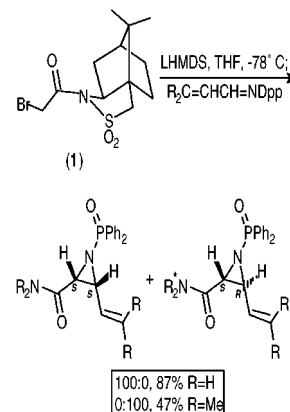
At first sight, these data seem to suggest that the bulk of the 2-substituent is intimately related to the diastereoselectivity of the reaction; to further probe the structural influences, *N*-Dpp-3-bromobenzaldimine was next subjected to the reaction conditions. In this case, only a *cis*-aziridine ($^3J = 6.2$ Hz) was isolated from the reaction. We then turned our attention to nonhalogenated 2-substituted benzaldimines. *N*-Dpp-2-methylbenzalimine showed diastereoselectivity similar to that of the analogous 2-fluoro imine, giving a 1:1 mixture of *cis*- and *trans*-aziridines ($^3J_{\text{cis}} = 6.0$ Hz, $^3J_{\text{trans}} = 2.8$ Hz), while the corresponding 2- and 4-methoxy imines reacted to give only one diastereoisomer in each case (a *trans*-aziridine ($^3J = 3.1$ Hz) from the 2-isomer and a *cis*-aziridine from the 4-isomer). A 2-nitro substituent favored exclusive formation of a *cis*-aziridine, perhaps due to lower steric demand of this planar substituent. Once again, these data do not point conclusively to a convincing rationalization of the phenomena inducing this stereocontrol. These preliminary data are collected in Table 1.

Table 1. Variation in Diastereoselectivity in ADZ of *N*-Dpp Imines

R	yield/%	<i>cis</i> : <i>trans</i>	$^3J_{\text{cis/trans}}$ /Hz
Ph (2)	71	100:0	6.2
2-F-C ₆ H ₄	84	50:50	6.2/2.8
2-Cl-C ₆ H ₄ (3)	68	20:80	6.1/2.8
2-Br-C ₆ H ₄	67	0:100	2.6
2-I-C ₆ H ₄	73	0:100	2.8
3-Br-C ₆ H ₄	60	100:0	6.2
4-Br-C ₆ H ₄	65	100:0	6.2
2-Me-C ₆ H ₄	87	50:50	6.0/2.8
2-OMe-C ₆ H ₄	65	0:100	3.1
4-OMe-C ₆ H ₄	74	100:0	6.2
2-NO ₂ -C ₆ H ₄	72	100:0	5.8
4-NO ₂ -C ₆ H ₄	77	100:0	6.4
2-pyridyl	67	100:0	6.6

Interestingly, when the *N*-Dpp imines derived from acrolein and 3,3-dimethylacrolein were used in the ADZ reaction, a similar variable diastereoselectivity was observed (Scheme 2). Thus, the unsubstituted vinyl imine

Scheme 2. Variable Diastereocontrol in ADZ Reaction of Vinylimines



reacted in the “usual” fashion to give exclusively *cis* aziridine, whereas the 3,3-dimethyl analogue gave *trans*-configured aziridine.

From these data, one may make a tentative suggestion as to the sequence of events responsible for the variation in

(3) All previously unreported compounds exhibited satisfactory physical data. The following procedure is representative: *N*-bromoacetyl-(2*S*)-bornane-10,2-sultam (336 mg, 1.0 mmol) was dissolved in 20 mL of dry THF under a nitrogen atmosphere and cooled to -78 °C. Lithium (hexamethyldisilyl)amide (1.1 mL, 1.0 M, 1.1 mmol) was added dropwise and the resulting yellow solution stirred for approximately 30 min. After this time, *N*-diphenylphosphinyl 2'-chlorobenzaldimine (340 mg, 1.0 mmol) was added as a solution in THF (15 mL) to the reaction mixture. The reaction mixture was then left stirring at -78 °C for approximately 3–4 h and followed by TLC. After this time the reaction was quenched via addition of a saturated ammonium chloride solution (20 mL). The aqueous layer was then extracted with diethyl ether (3×20 mL), the organic layers were combined, washed with brine, dried (MgSO_4), and filtered, and the solvent was removed in vacuo to afford *cis*- and *trans*-(2*S*,2'*S*,3'*S*)-*N*-[(1-diphenylphosphinyl-3-(2-chlorophenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam

diastereoselectivity in this ADZ reaction (Scheme 3). Thus, although there is a paucity of empirical data concerning transition-state preferences in the reaction of imines with enolates,⁴ we suggest a closed transition state along Zimmerman–Traxler guidelines.⁵ Since the aziridine C2 is indubitably of (*S*)-absolute configuration, the reaction must involve attack of the *si*-face of the *Z*-enolate⁶ upon the imine. Where there is no imine C-3 substituent, we suggest a pseudoequatorial positioning of the imine C-1 substituent (i.e., an *E*-configured imine) and attack upon the *si*-face. When there is C-3 substitution, we postulate a repulsive interaction between this group and the Br atom of the chiral sultam enolate, leading to a preference for a transition state in which the imine substituent adopts a pseudoaxial locus (a *Z*-imine⁷), leading to *re*-face attack. This arrangement leads inevitably to a (*2'S,3'R*)-*trans*-aziridine, as shown in Scheme 3. One may rationalize the lower selectivity shown for *trans*-aziridine in the reaction of 2-methylbenzalimine (whose C-3 substituent should engender at least as much steric demand as a bromo substituent⁸ [which leads to an exclusively *trans*-

3 as a very pale yellow solid. From ¹H NMR, the mixture was adjudged to be approximately a 20:80 mixture of *cis:trans* isomers. After flash chromatography (light petroleum ether:ethyl acetate (1:9)) *cis-3* was obtained as a colorless solid (81 mg, 0.13 mmol, 13%); *R*_f 0.63 (EtOAc); [α]_D²⁰ = +28.7 (*c* = 1, CH₂Cl₂); ν_{max}(CCl₄)/cm⁻¹ 3057, 2964, 1703, 1440, 1341, 1128, 1266, 1169, 745, 705, 644; δ_H (400 MHz, CDCl₃) 0.78–0.83 (6H, m), 1.12–1.20 and 1.72–1.97 (7H, m), 3.22 and 3.30 (2H, 2 × d, *J* = 13.9 Hz), 3.57–3.60 (1H, m), 4.11–4.50 (2H, 2 × dd, *J* = 6.1 Hz, 15.9 Hz), 7.10–7.57 and 7.85–8.03 (14H, m); δ_C (100 MHz, CDCl₃) 19.72, 20.55, 26.29, 32.49, 38.12, 40.69, 42.31 (2 × CH, *J* = 5.6 Hz), 44.56, 47.70, 48.95, 52.46, 64.58, 126.01, 128.44, 128.57, 128.68, 129.07, 129.18, 129.58, 130.62, 130.82, 131.55, 131.68, 131.74, 131.77, 131.83, 131.94, 132.10, 132.27, 134.61, 163.74; *m/z* (CI) 595 ([MH]⁺, 66), 531 (60), 419 (100), 313 (43), 201 (91), 77 (32) (found: [MH]⁺, 595.1594, C₃₁H₃₃ClN₂O₄-PS requires [MH]⁺, 595.1588). Similarly, *trans-3* was obtained as a colorless solid (325 mg, 0.55 mmol, 55%); *R*_f 0.56 (EtOAc); [α]_D²⁰ = +59.4 (*c* = 1, CH₂Cl₂); ν_{max}(CCl₄)/cm⁻¹ 3056, 2985, 1705, 1440, 1338, 1168, 1266, 1126, 738, 706, 623 (Ar); δ_H (400 MHz, CDCl₃) 0.75 (3H, s), 0.80 (3H, s), 1.01–1.29 and 1.65–1.89 (7H, m), 3.23 (1H, d, *J* = 13.6 Hz), 3.28 (1H, d, *J* = 13.6 Hz), 3.72 (1H, m), 4.16 (1H, dd, *J* = 2.8 Hz, 13.3 Hz), 4.30 (1H, dd, *J* = 2.8 Hz, 13.3 Hz), 7.03–7.10 and 7.19–7.34 (10H, m), 7.63–7.67 and 7.79–7.83 (4H, m); δ_C (100 MHz, CDCl₃) 19.65, 20.64, 26.29, 32.52, 37.75, 41.27 (aziridine CH, *d*, *J* = 5.5 Hz), 43.96 (aziridine CH, *d*, *J* = 5.5 Hz), 44.37, 47.59, 48.76, 52.71, 65.11, 126.52, 127.95, 128.08, 128.12, 128.24, 128.41, 128.94, 129.41, 131.19, 131.55, 131.65, 132.45, 133.00, 134.32, 135.49, 164.92 (CO, *d*, *J* = 5.6 Hz); *m/z* (CI) 594 ([M]⁺, 19), 559 (49), 219 (68), 201 (100), 77 (27) (found: [M]⁺, 594.1559, C₃₁H₃₂-ClN₂O₄PS requires [M]⁺, 594.1508).

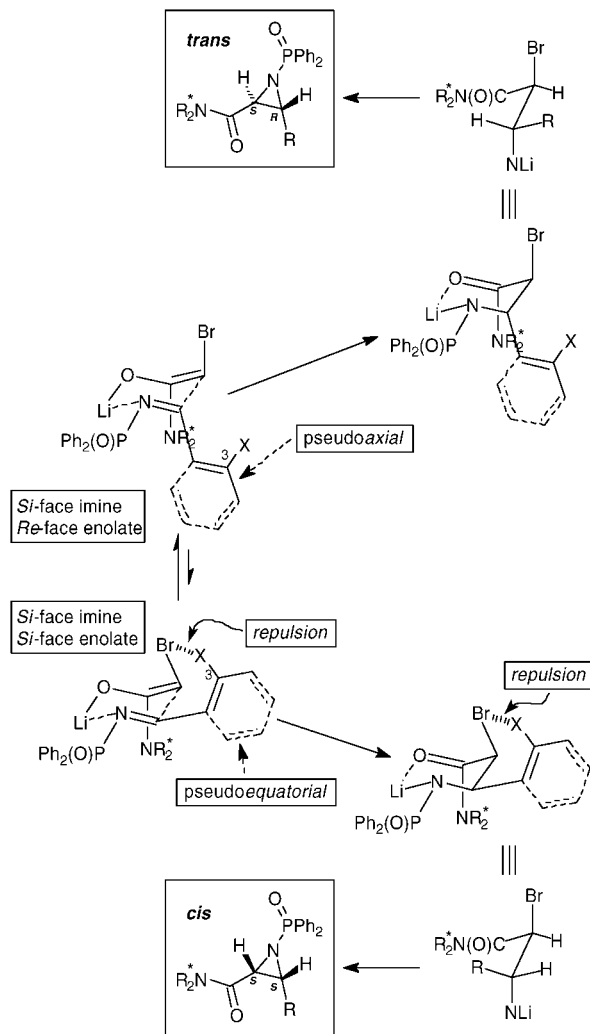
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(6) Calculations (UFF, Rapper, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard, W. A., III; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, 114, 10024) show the *Z*-enolate to be more stable than the *E*-enolate by 4.1 kcal/mol.

(7) Although all imines used were of (*E*)-configuration (³J_{P-H} = 32 Hz) in the pure state, (*E*)-(Z)-isomerism of imines under the influence of metal ions is well-known; see, for example: Alshalaan, A. M.; Alshowiman, S. S.; Alnajjar, I. M. *Inorg. Chim. Acta* **1986**, 121, 127–129. For a discussion of the factors underlying (*E*)/(Z)-preferences in imines, see: Bjørgo, J.; Boyd, D. R.; Watson, C. G.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. I* **1974**, 757.

Scheme 3. Mechanistic Possibilities in ADZ Reaction of C-3-Substituted *N*-Dpp Imines



configured aziridine]) by supposing that a Br–Br repulsion (involving lone-pair:lone-pair interaction) is greater than a Br–CH repulsion (involving a lone-pair:bonding-electron repulsion). The *precise* details of the mechanism responsible for these phenomena are at present under investigation in our laboratory.

Acknowledgment. We acknowledge the financial support of the EPSRC (studentship to A.B.McL.). J.B.S. thanks ZENECA for an award from the Strategic Research Fund and Mr. Glen Buchman for valuable advice.

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