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

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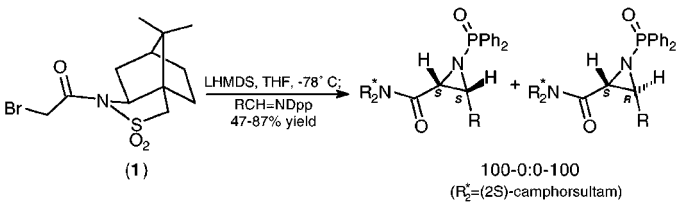
## ABSTRACT

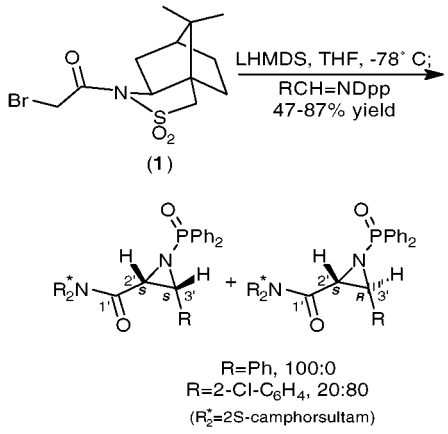



**The *aza*-Darzens reaction of the chiral enolate derived from (2*S*)-bromoacetyl camphor sultam (1) with certain C-3-substituted *N*-diphenylphosphinyl imines gives mixtures of *trans*- and *cis*-aziridines. In some cases, only *trans* isomers are observed. A steric repulsion between the enolate halogen 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 = Ph) ($^3J$ = 6.2, typical of such aziridines[3]) in 71% yield, but the corresponding imine derived from 2-chlorobenzaldehyde gave a mixture of *cis*- and *trans*-aziridines **3** in 68% combined yield, with the *trans* isomer dominating (*cis*:*trans* = 1:4; $^3J_{cis}$ = 6.1 Hz, $^3J_{trans}$ = 2.8 Hz) (Scheme 1). The absolute configuration of the *cis*-aziridinyl sultam was deduced by comparison with

**Scheme 1.** Variable Diastereocontrol in ADZ Reaction




(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.

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the $^1$H and $^{13}$C NMR obtained for authentic phenylaziridine **2** (shown by X-ray analysis to be of 2*R*,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).

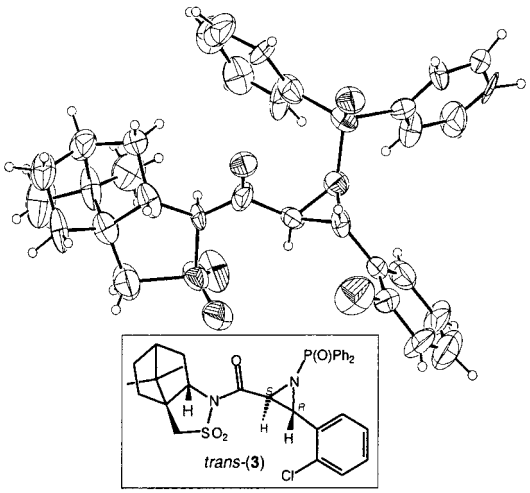



**Figure 1.** X-ray structure of *trans*-aziridine **3**.

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 ($^3J_{cis}$ = 6.2 Hz, $^3J_{trans}$ = 2.8 Hz), although the yield of aziridine was good.

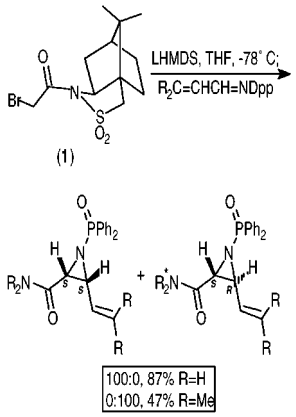
At first sight, these data seem to suggest that the bulk of the 2-substituent is intimately related to the diastereoselectivity of the reaction; to further probe the structural influences, *N*-Dpp-3-bromobenzaldimine was next subjected to the reaction conditions. In this case, only a *cis*-aziridine ($^3J$ = 6.2 Hz) was isolated from the reaction. We then turned our attention to nonhalogenated 2-substituted benzaldimines. *N*-Dpp-2-methylbenzaldimine showed diastereoselectivity similar to that of the analogous 2-fluoro imine, giving a 1:1 mixture of *cis*- and *trans*-aziridines ($^3J_{cis}$ = 6.0 Hz, $^3J_{trans}$ = 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/% | *cis*:*trans* | $^3J_{cis/trans}$/Hz |
|---|---|---|---|
| Ph (**2**) | 71 | 100:0 | 6.2 |
| 2-F-$C_6H_4$ | 84 | 50:50 | 6.2/2.8 |
| 2-Cl-$C_6H_4$ (**3**) | 68 | 20:80 | 6.1/2.8 |
| 2-Br-$C_6H_4$ | 67 | 0:100 | 2.6 |
| 2-I-$C_6H_4$ | 73 | 0:100 | 2.8 |
| 3-Br-$C_6H_4$ | 60 | 100:0 | 6.2 |
| 4-Br-$C_6H_4$ | 65 | 100:0 | 6.2 |
| 2-Me-$C_6H_4$ | 87 | 50:50 | 6.0/2.8 |
| 2-OMe-$C_6H_4$ | 65 | 0:100 | 3.1 |
| 4-OMe-$C_6H_4$ | 74 | 100:0 | 6.2 |
| 2-$NO_2$-$C_6H_4$ | 72 | 100:0 | 5.8 |
| 4-$NO_2$-$C_6H_4$ | 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



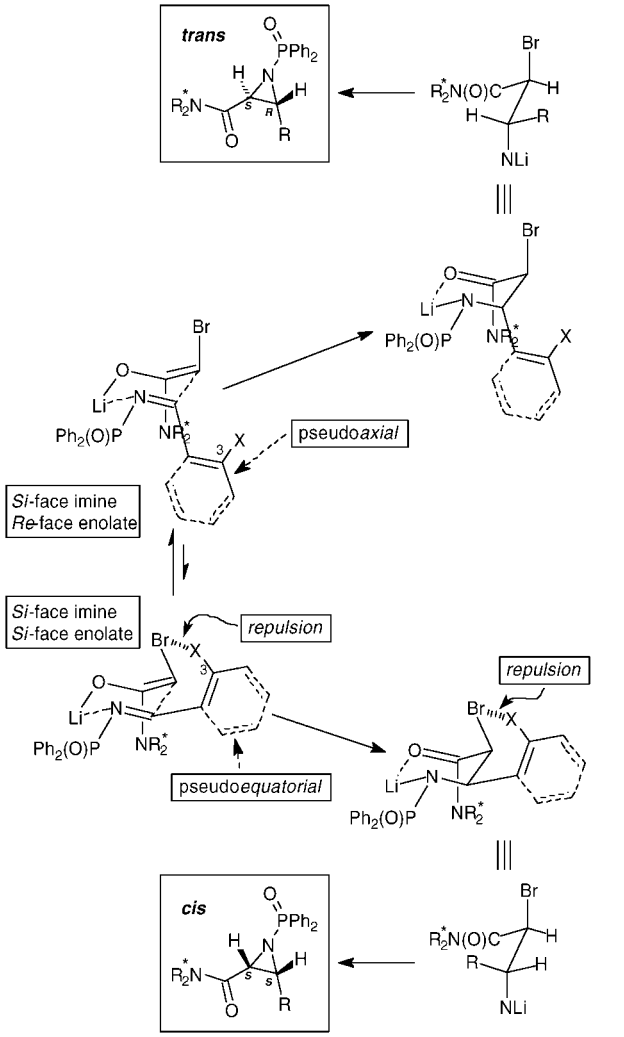

reacted in the "usual" fashion to give exclusively *cis* aziridine, whereas the 3,3-dimethyl analogue gave *trans*-configured aziridine.

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*-enolate[6] 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*-imine[7]), 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-methylbenzaldimine (whose C-3 substituent should engender at least as much steric demand as a bromo substituent[8] [which leads to an exclusively *trans*-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.

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

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**3** as a very pale yellow solid. From $^1$H 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); $[\alpha]^{20}_D$ = +28.7 ($c$ = 1, $CH_2Cl_2$); $\nu_{max}(CCl_4)/cm^{-1}$ 3057, 2964, 1703, 1440, 1341, 1128, 1266, 1169, 745, 705, 644; $\delta_H$ (400 MHz, $CDCl_3$) 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); $\delta_C$ (100 MHz, $CDCl_3$) 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, $C_{31}H_{33}ClN_2O_4PS$ requires [MH]$^+$, 595.1588). Similarly, *trans*-**3** was obtained as a colorless solid (325 mg, 0.55 mmol, 55%); $R_f$ 0.56 (EtOAc); $[\alpha]^{20}_D$ = +59.4 ($c$ = 1, $CH_2Cl_2$); $\nu_{max}(CCl_4)/cm^{-1}$ 3056, 2985, 1705, 1440, 1338, 1168, 1266, 1126, 738, 706, 623 (Ar); $\delta_H$ (400 MHz, $CDCl_3$) 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); $\delta_C$ (100 MHz, $CDCl_3$) 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, $C_{31}H_{32}ClN_2O_4PS$ requires [M]$^+$, 594.1508).

(4) Asymmetric *aza*-Darzens and Darzens-like reactions: Gennari, C.; Pain, G. *Tetrahedron Lett.* **1996**, *37*, 3747. Fujisawa, T.; Hayakawa, R.; Shimizu, M. *Tetrahedron Lett.* **1992**, *33*, 7903. Davis, F. A.; Zhou P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243. Davis, F. A.; Zhou, P.; Liang, C. H.; Reddy, R. E. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1511. Florio, S.; Troisi L.; Capriati, V. *J. Org. Chem.* **1995**, *60*, 2279.

(5) Zimmerman, H. E. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(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. 1* **1974**, 757.

(8) Streitwieser, A.; Heathcock, C. H.; Kosower, E. M. *Introduction to Organic Chemistry*; Macmillian Publishing Company: New York, 1992.