Reaction of phosphinoyl-activated imines: stereocontrolled synthesis of either *trans*- or *cis*-vinylaziridines

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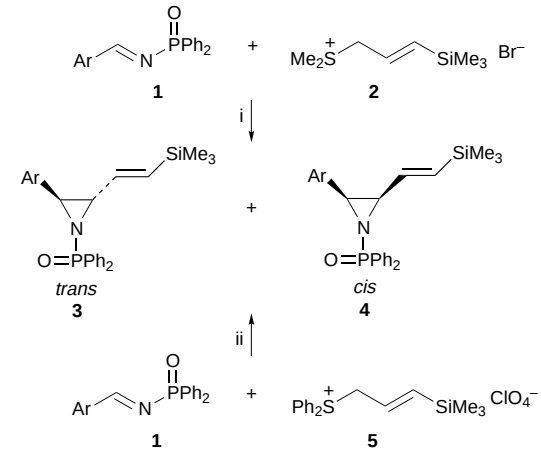
Phosphinoyl imines react with allylsulfonium ylide to provide *trans*-aziridines at room temperature and *cis*-aziridines at low temperature, in high yields and good to excellent stereoselectivities.

Aziridines are versatile building blocks that have found many uses in organic synthesis.[1] They are also an important subunit in many natural products.[2] All these factors make the synthesis of aziridines an active field of research, and recently, a number of methods have appeared in the literature for the preparation of these useful compounds. Among them the direct approach to ring formation *via* a carbene or nitrene route is more attractive because of its efficiency.[3] Similar to the carbene approach, ylide attack at a C=N bond is another useful possibility,[1b] however, the synthesis of substituted aziridines *via* an ylide route is less well explored. For example, only a few procedures have been reported for the synthesis of vinyl-substituted aziridines,[4] although the versatility in synthesis of this kind of aziridine is well documented.[5] As part of a programme aimed at the application of imines to organic synthesis, we studied the aziridination reaction using normal and *N*-tosyl-activated imines as starting materials and semi-stabilized and stabilized sulfonium ylides as reagents,[3a,b,6] and found that the ylide route is a convenient way to prepare aziridine derivatives.

In the presence of Lewis acids, aldimines reacted with allyl- and prop-2-ynyl-sulfonium ylides to deliver the corresponding *cis*-aziridines as the sole products when the substituent at nitrogen was an aryl group.[6] On the other hand, the reaction of *N*-tosyl imines with allyl- and prop-2-ynyl-sulfonium ylides also provided the corresponding aziridines, but high stereoselectivities were obtained only in the case of prop-2-ynylsulfonium ylides;[3b] *cis*- and *trans*-aziridines were afforded with lower selectivity when trimethylsilylallylsulfonium ylide was used as the starting material.[3a] Unlike the ylide epoxidation reaction, where the *trans* isomer is usually the preferred configuration, the former reaction afforded the *cis*-isomer exclusively. In order to improve the stereoselectivity of the latter reaction another imine activation group was sought. It was found that when phosphinoyl-activated imines reacted with allylsulfonium ylides, both *cis*- and *trans*-aziridines were formed with high stereoselectivity. Here we disclose the results of our studies on the stereocontrolled aziridination of phosphinoyl-activated imines *via* the ylide route.

N-Phosphinoyl imines **1**[7] reacted with [3-(trimethylsilyl)-allyl]dimethylsulfonium bromide **2** in the presence of base at room temperature to provide *trans*-vinylaziridines **3** predominantly. On the other hand, *cis*-vinylaziridines **4** were the main products when the preformed ylide prepared from [3-(trimethylsilyl)allyl]diphenylsulfonium perchlorate **5** reacted with the same imines **1** (Scheme 1, Table 1). The operation was simple and the yields of both reactions were excellent.‡

From Table 1, it can be seen that all reactions furnished the desired aziridines in satisfactory yields. Stereocontrol is realized *via* simply changing the ligands on the sulfur atom (that is, Ph or Me) and the reaction conditions. Reaction at room

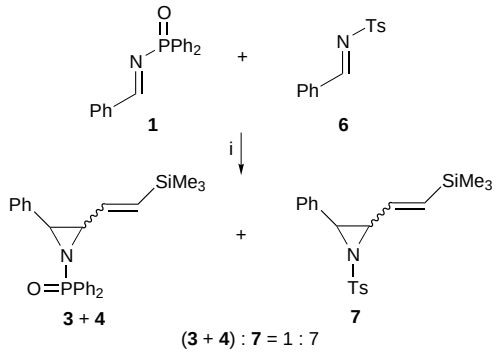


Scheme 1 *Reagents and conditions*: i, base, CH_2Cl_2, room temp.; ii, base, THF, the **1**, −100 °C

Table 1 Stereoselective preparation of aziridines

Entry	Ar	Ylide	Base	*T*/°C	Yield (%)[a]	*cis*:*trans*[b]
1	Ph	**2**	NaH	room temp.	92	10 : 90
2	Ph	**2**	KOH	room temp.	78	24 : 76
3	*p*-ClC_6H_4	**2**	NaH	room temp.	93	12 : 88
4	*p*-$MeOC_6H_4$	**2**	NaH	room temp.	95	20 : 80
5	1-Naphthyl	**2**	NaH	room temp.	86	22 : 78
6	Ph	**5**	NaHMDS[c]	−100	93	91 : 9
7	*p*-$MeOC_6H_4$	**5**	NaHMDS[c]	−100	90	99 : < 1
8	*p*-MeC_6H_4	**5**	NaHMDS[c]	−100	94	99 : < 1
9	*p*-ClC_6H_4	**5**	NaHMDS[c]	−100	84	85 : 15
10	2-Furyl	**5**	NaHMDS[c]	−100	90	99 : < 1
11	*p*-$CF_3C_6H_4$	**5**	NaHMDS[c]	−100	72	85 : 15
12	Ph	**5**	NaHMDS[c]	−78	91	87 : 13
13	Ph	**5**	NaHMDS	−78	93	85 : 15

[a] Isolated yield. [b] Determined by 300 MHz ^{1}H NMR spectroscopy. [c] 1 equiv. of LiBr was added.



Scheme 2 *Reagents and conditions*: i, **2**, NaH, CH_2Cl_2, room temp.

temperature with the dimethylsulfonium salt provided *trans*-aziridines **3** (*trans* : *cis* = 78 : 22 to 90 : 10), even though *cis*-aziridines are considered thermodynamically more stable.[8] In this reaction, the selection of base is important. High stereoselectivity is obtained when NaH is used (entry 1), but it is lowered if KOH is used (entry 2). This might be because the use of NaH avoids the formation of water in the reaction. It was also observed that the stereoselectivity of the reaction in CH_2Cl_2 was better than that in MeCN or benzene. At low temperature, reaction of the ylide preformed from diphenyl sulfide with imines **1** gave rise to *cis*-aziridines with high stereoselectivity. Lower temperatures favored the *cis*-isomers (entries 6 and 12). In some cases the reaction furnished the *cis*-products almost exclusively (entries 7, 8 and 10). Unlike epoxidation and cyclopropanation reactions,[9] the presence of LiBr is not crucial and the stereochemistry of this reaction does not depend on whether LiBr is present or not (entries 12 and 13).

The improvement of stereoselectivity in the case of the *N*-diphenylphosphinoyl imines as compared with the *N*-tosyl imines is probably due to their different reactivity toward the attack of the allylsulfonium ylide. A competition reaction involving phosphinoylimine, tosylimine and allylsulfonium ylide shows that phosphinoylimine is less reactive than tosylimine (Scheme 2).

In summary, the $Ph_2P(O)$ moiety is a good activating group of imines for the reaction with sulfonium ylides. The advantages are (i) the stereochemistry can be greatly improved and tuned to either the *cis*- or *trans*-isomer, (ii) the *cis*- and *trans*-aziridines are easily separated by simple chromatography and (iii) the $Ph_2P(O)$ group is easily removed using acid.[10] Further investigations on the reaction mechanism and asymmetric synthesis of aziridines using *N*-phosphinoyl imines are underway.

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Notes and References

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‡ *General experimental procedure* for room temperature reaction: To a solution of sulfonium salt **2** (0.44 mmol) and phosphinoyl imine **1** (0.4 mmol) in CH_2Cl_2 (4 ml) was added NaH (15 mg, 0.6 mmol) at room temp. The resulting mixture was stirred at room temp. until the starting material **1** disappeared (monitored by TLC). Water (10 ml) was added and the mixture was extracted with CH_2Cl_2 (15 ml × 3). The organic solutions were combined and dried ($MgSO_4$). Removal of solvent under reduced pressure and chromatography (silica gel, light petroleum–EtOAc 5 : 1) afforded pure *trans*-aziridine **3** and *cis*-aziridine **4**.

General procedure for low temperature reaction: To a solution of sulfonium salt **5** (0.48 mmol) in THF (6 ml) under argon at −100 °C was added NaHMDS (2 M in THF, 0.24 ml, 0.48 mmol). The resulting mixture was stirred for 10 min. A solution of imine **1** (0.4 mmol) in THF (2 ml) was added and the stirring continued for another 1 h. The reaction temperature was then allowed to rise to room temp. Work up as above and chromatography provided pure *trans*-aziridine **3** and *cis*-aziridine **4**.

1 (*a*) D. Tanner, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 599; (*b*) A. H. Li, L. X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341.
2 For reviews, see: W. A. Remers and B. S. Iyengar, *Recent Progress in the Chemical Synthesis of Antibiotics*, ed. G. Lukacs and M. Ohno, Springer, Berlin, 1990, p. 415; F. E. Ziegler and M. Belema, *J. Org. Chem.*, 1997, **62**, 1083; T. Fukuyama, F. Nakatsubo, A. J. Cocuzza and Y. Kishi, *Tetrahedron Lett.*, 1977, 295.
3 For example: (*a*) A. H. Li, Y. G. Zhou, L. X. Dai, X. L. Hou, L. J. Xia and L. Lin, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1317; (*b*) A. H. Li, L. X. Dai, X. L. Hou and M. B. Chen, *J. Org. Chem.*, 1996, **61**, 4641; (*c*) Y. G. Zhou, A. H. Li, X. L. Hou and L. X. Dai, *Tetrahedron Lett.*, 1997, **38**, 7225; (*d*) V. K. Aggarwal, A. Thompson, R. V. H. Jones and M. C. H. Standen, *J. Org. Chem.*, 1996, **61**, 8368; (*e*) R. S. Atkinson, M. P. Coogan and I. S. T. Lochrie, *Chem. Commun.*, 1996, 789; (*f*) D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson and D. M. Barnes, *J. Am. Chem. Soc.*, 1993, **115**, 5328; (*g*) Z. Li, K. R. Conser and E. N. Jecobsen, *J. Am. Chem. Soc.*, 1993, **115**, 5326; (*h*) K. B. Hansen, N. S. Finney and E. N. Jacobsen, *Angew. Chem., Int. Ed. Engl*, 1995, **34**, 676; (*i*) L. Casarrubios, J. A. Pérez, M. Brookhart and J. L. Templeton, *J. Org. Chem.*, 1996, **61**, 8358; (*j*) J. M. Mohan, B. S. Uphade, V. R. Choudhary, T. Ravindranathan and A. Suddalai, *Chem. Commun.*, 1997, 1429; (*k*) K. G. Rasmussen and K. A. Jørgensen, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1287.
4 A. A. Cantrill, A. N. Jarvis, H. M. I. Osborn, O. A. Ouadi and J. B. Sweeney, *Synlett*, 1996, 847.
5 For example: U. M. Lindstrom and P. Somfai, *J. Am. Chem. Soc.*, 1997, **119**, 8385; J. Ahman, T. Jarevang and P. Somfai, *J. Org. Chem.*, 1996, **61**, 8148; I. Coldham, A. J. Collis, R. J. Mould and R. E. Rathmell, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2739.
6 D. K. Wang, L. X. Dai and X. L. Hou, *Chem. Commun.*, 1997, 1231.
7 B. Krzyzanowska and W. J. Stec, *Synthesis*, 1978, 521; B. Krzyanowska and W. J. Stec, *Synthesis*, 1982, 270; A. Zweierzak and A. Napieraj, *Tetrahedron*, 1996, **52**, 8789.
8 T. Ibuka, N. Mimura, H. Ohno, K. Nakai, M. Akaji, H. Habashita, H. Tamamura, Y. Miwa, T. Taga, N. Fuji and Y. Yamamoto, *J. Org. Chem.*, 1997, **62**, 2982 and references cited therein; A. A. Canttrill, L. D. Hall, A. N. Jarvis, H. M. I. Osborn, J. Rappy and J. B. Sweeney, *Chem. Commun.*, 1996, 2631.
9 T. Yong, Ph.D. Thesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 1995; Y. G. Zhou, A. H. Li, X. L. Hou and L. X. Dai, *Chem. Commun.*, 1996, 1353.
10 R. Ramage, D. Hopton and M. Parrott, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1357; G. W. Kenner, G. A. Noore and R. Ramage, *Tetrahedron Lett.*, 1976, 3623.

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