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Enantioselective synthesis of aziridines from imines and alkyl halides using a camphor-derived chiral sulfide mediator via the imino Corey–Chaykovsky reaction

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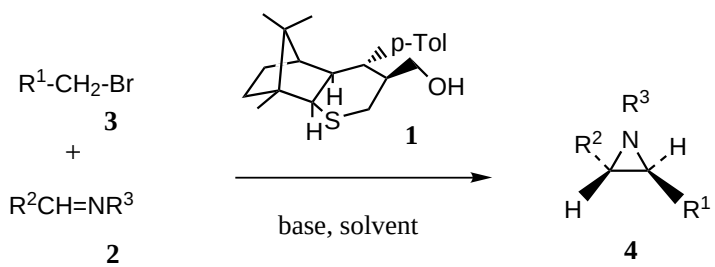
Abstract—Asymmetric one-pot aziridination of imines with alkyl bromides via the imino Corey–Chaykovsky reaction mediated by chiral sulfide is described. The desired aziridines are obtained in good yields with up to 98% ee of the *trans* isomer.

Aziridines, particularly optically active aziridines, are useful and versatile intermediates for the synthesis of a variety of nitrogen-containing compounds, and various new synthetic methods for aziridines have been developed.[1,2] The synthetic methods can conceptually be represented by several approaches,[1,2] e.g. the β-amine ring closure starting from β-amino alcohol or its equivalent (including the Gabriel–Cromwell method), the replacement of an epoxy oxygen by a nitrogen, the addition of a nitrogen source (including a nitrene species) to an olefin, the addition of a carbenoid to an imine, the aza Darzens type reaction, the imino Corey–Chaykovsky type aziridination, and so on. In most of these cases, metal complexes have been used not only to promote (catalyze) the reaction but also to control the regio- and stereo-selectivities as well as in the cases of epoxides synthesis. Recently, the enantiomeric aziridination of imines with sulfonium ylides derived from diazomethanes and sulfides and from sulfonium salts has been independently reported by Aggarwal's and Dai's groups, respectively.[3] In these cases the stereochemical outcome of the aziridination seems to be significantly dependent upon the substrates substituents, reaction conditions and chiral sulfides, and high enantioselectivity is obtained in very limited cases. Moreover, chiral sulfonium ylide-mediated, enantiomeric aziridination via a one-pot salt method has not extensively been investigated.[1–3]

We have previously demonstrated asymmetric epoxidation via the Corey–Chaykovsky reaction using a *d*-camphor-derived chiral sulfide to show fairly good *trans*/*cis* and enantioselectivities.[4] In order to develop highly enantioselective aziridination and to gain further insight into the potentiality (applicability) of this chiral sulfide, we carried out the related imino Corey–Chaykovsky aziridination (Scheme 1). We report here our results in this regard.



Scheme 1. Enantioselective aziridination via imino Corey–Chaykovsky reaction.

Keywords: asymmetric synthesis; aziridines; aziridination; chiral sulfide.

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The aziridination was performed in one-pot simply by stirring a mixture of *N*-sulfonylimine **2**, arylmethyl bromide **3**, chiral sulfide **1**,[4] and a base in an appropriate solvent at room temperature (Table 1). A model reaction (run 1) using powdered K_2CO_3 as a base in MeCN as a solvent afforded the desired aziridine (**4**) quantitatively in a *trans:cis* ratio of 75:25 with 92% ee of the *trans* isomer. The use of Cs_2CO_3 as a base in the reaction gave **4** with comparable high stereoselectivities [*trans:cis* = 76:24 and 94% ee (*trans*)] albeit in a lower yield (53%) (run 2). The reactions employing other bases such as KOH and NaH in MeCN failed. Screening of several solvents revealed that dry acetonitrile is the solvent of choice (runs 1, 3 and 4).[5] When the amount of the chiral sulfide (**1**) added was reduced (runs 5, 6 and 7 versus run 1), the reaction became extremely slow (low yield) in each case though high levels of both selectivities (*trans:cis* = 75:25, 90–92% ee of *trans* isomer) were still maintained. When the reaction was carried out at a higher temperature of 82°C in refluxing MeCN (run 8), the reaction was accelerated (2 h) as expected while the yield (94%) and the stereoselectivities (72:28, 84% ee) were not so markedly decreased. Table 1 suggests that an electron-withdrawing substituent R^3 such as RSO_2-groups (R = *p*-Tol, Ph, and Me) on the imine nitrogen is necessary to activate the C=N double bond for the nucleophilic attack by the sulfonium ylide formed from **1**+**3** and the base.[6] The *N*-sulfonyl group-substituted aziridines can be deprotected to provide the corresponding *N*-unsubstituted aziridines without concomitant ring opening.[7] Both electron-donating and electron-withdrawing substituents on aromatic groups in either R^1 or R^2 were tolerated (runs 9–15).

Dai et al. reported aziridination of sulfonylimines with some allylic sulfonium ylides (from salts) to give *C*-vinylaziridines with moderate *trans*:*cis* selectivity, in which only one example of the enantiomeric version was included but its enantiomeric excess was not shown.[8] So, we investigated asymmetric aziridination by applying our chiral sulfide to obtain optically active styrylaziridine (Scheme 2). The results are summarized in Table 2. Disappointingly, after efforts, we only found moderate to low *trans*:*cis* ratios and ee's of both the *trans* and *cis* isomers of **7** albeit in good yield. It is noteworthy that in MeCN/H_2O (run 4), the *cis* isomer of **7** is formed selectively (*trans*:*cis* = 10:90) in contrast to the other cases of varied solvents (runs 1–3).

In contrast to the above disappointing results, high enantiomeric induction for both the *trans* and *cis* isomers was attained to obtain the same styrylaziridine (**7**) when the styrylimine **8** and benzyl bromide (**9**) were used (Scheme 3, Table 3). In the presence of even a catalytic amount of the sulfide **1** (run 5), the reaction in MeCN still kept up the better high levels of stereoselectivity. To our knowledge, this is the first example of the catalytic, highly enantioselective one-pot synthesis of *C*-vinylaziridine[9] in the imino Corey–Chaykovsky aziridination.

Table 1. Chiral sulfide-induced enantioselective aziridination from imines and arylmethyl bromides[a]

Run	R^1	R^2	R^3	Yield (%)[b]	*trans*:*cis*[c]	*trans* ee (%)[c]
1	Ph	Ph	Ts (tosyl)	>99	75:25	92
2[d]				53	76:24	94
3[e]				>99	70:30	89
4[f]				99	75:25	85
5[g]				91	75:25	92
6[h]				61	75:25	90
7[i]				<10	75:25	91
8[j]				94	72:28	84
9	*p*-Tol	Ph	Ts	87	74:26	89
10	*p*-$NO_2C_6H_4$	Ph	Ts	>99	65:35	98
11	Ph	*p*-Tol	Ts	>99	79:21	89
12	Ph	*p*-$MeOC_6H_4$	Ts	94	63:37	86
13	Ph	*p*-ClC_6H_4	Ts	86	78:22	92
14	Ph	Ph	$PhSO_2$	84	76:24	92
15	Ph	Ph	$MeSO_2$	79	67:33	92

[a] Reactions were run using imine **2** (0.1 mmol), bromide **3** (0.3 mmol), sulfide **1** (0.1 mmol) and K_2CO_3 (0.3 mmol) in MeCN (5 cm^3) at room temperature for 1–2 days unless otherwise specified.

[b] Isolated yield.

[c] Determined by HPLC [Chiralcel OD, ethanol-hexane (1:20)]. The aziridines had a negative optical rotation (in $CHCl_3$) and the absolute configuration was assumed as [*S*,*S*] by correlation to epoxidation.

[d] Cs_2CO_3 was used as a base.

[e] CH_2Cl_2 was used as a solvent, time being for 4 days.

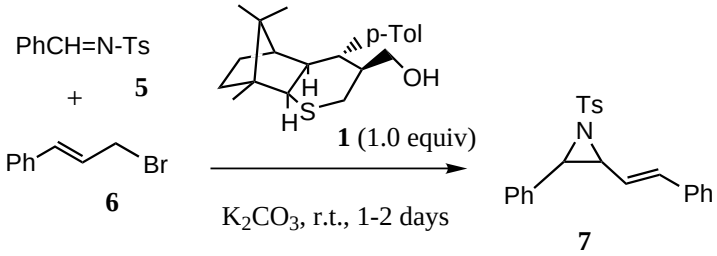
[f] *t*-BuOH was used as a solvent, time being for 3 days.

[g] 0.5 equiv. sulfide **1** was used.

[h] 0.2 equiv. sulfide **1** was used, time being for 4 days.

[i] 0.1 equiv. sulfide **1** was used, time being for 1 week.

[j] At 82°C for 2 h.

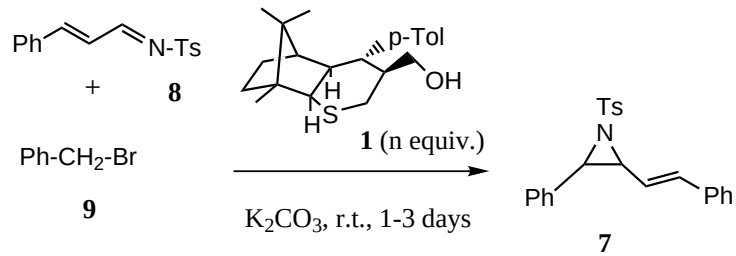


Scheme 2. Enantioselective aziridination of *N*-tosylimine with cinnamyl bromide.

Table 2. Aziridination of *N*-tosylimine with cinnamyl bromide to afford styrylaziridine

Run	Solvent	Yield[a] (%)	*trans*:*cis*[a]	ee (%)[a]	
				trans	*cis*
1	CH_2Cl_2	99	52:48	38	17
2	*t*-BuOH	77	42:58	32	8
3	MeCN	99	54:46	42	21
4	MeCN/H_2O[b]	52	10:90	21	7

[a] See corresponding footnotes in Table 1.
[b] Ratio v/v 9:1, time for 6 h.



Scheme 3. Enantioselective aziridination of cinnamylidene-*N*-tosylimine with benzyl bromide.

Table 3. Aziridination of cinnamylidene-*N*-tosylamine with benzyl bromide to afford styrylaziridine

Run	Solvent	*n* (equiv.)	Yield[a] (%)	*trans*:*cis* [a]	ee (%)[a]	
					trans	*cis*
1	CH_2Cl_2	1.0	69	63:37	85	91
2	*t*-BuOH	1.0	50	48:52	78	75
3	MeCN	1.0	99	75:25	94	84
4		0.5	73	80:20	93	88
5[b]		0.1	52	74:26	93	87

[a] See corresponding footnotes in Table 1.
[b] Time being for a week.

In conclusion, we have demonstrated stereoselective imino Corey–Chaykovsky reaction by solid–liquid phase transfer one-pot procedure to give optically active aziridines with high enantiomeric excess. Moreover, the chiral sulfide was recovered optically pure almost quantitatively after the reaction, and could be reused repeatedly. Further studies on the scope and limitation of this process are in progress.

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