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Telluronium Salts Mediated Aziridination of Chiral *N-tert*-Butylsulfinylimines: Highly Stereoselective Synthesis of Optically Active Vinylaziridines

Jun-Cheng Zheng,[†] Wei-Wei Liao,[†] Xiao-Xia Sun,[‡] Xiu-Li Sun,[†] Yong Tang,*,[†] Li-Xin Dai,[†] and Jin-Geng Deng*,[‡]

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu,
Shanghai 200032, P. R. China, and Chengdu Institute of Organic Chemistry,
Chinese Academy of Sciences, No. 9 Section 4, Renmin Nan Lu, Chengdu, P. R. China

tangy@mail.sioc.ac.cn

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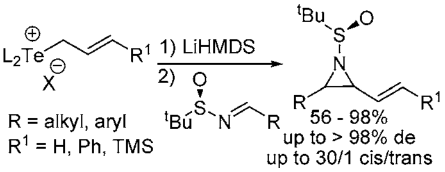
ABSTRACT



Optically active *cis*-2-substituted vinylaziridines are synthesized by the reaction of *N-tert*-butylsulfinylimines with telluronium ylides with excellent diastereoselectivity in good to excellent yields.

Vinylaziridines are important subunits in a number of biologically active compounds[1] and versatile intermediates for the synthesis of nitrogen-containing compounds, such as alkaloids, amino acids, amino alcohols, and β-lactamic antibiotics.[2] Although carbene[3,4] and nitrene[4] approaches are recognized as two of the most efficient methods for the preparation of aziridines, they are generally less effective for vinyl-type aziridines due to the difficulty associated with the regioselectivity control. Darzens-type reaction is also well-documented to prepare aziridines,[5] but few direct synthesis involved vinylaziridines in the literature. Of the synthetic methods developed for vinylaziridines, the reaction between ylide and imines proved to be one of the most convenient ways.[6] By an ylide approach, to access optically active vinylaziridines, Aggarwal et al. reported that silylated chiral sulfur allylide could react with *N*-SES phenylimine to afford *trans*-phenylvinylaziridine in 94% ee with moderate

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[†] Shanghai Institute of Organic Chemistry.

[‡] Chengdu Institute of Organic Chemistry.

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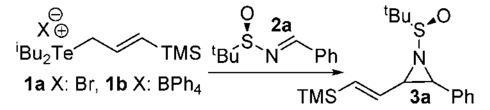
cis/*trans* selectivity (*cis/trans* = 22/78),[7a] and Saito et al. also described the synthesis of nonracemic chiral vinylaziridines via a chiral ylide route, but the enantioselectivity was poor (enantiomeric excess up to 42%).[7b] Very recently, Stockman et al. documented the reaction of *tert*-butylsulfinylimines[8] with sulfur ylide and found that the desired optically active vinylaziridines could be obtained with high diastereoselectivity (85−95% de, *cis/trans* up to 1/4.8, *trans* favored) in moderate to good yield (44−82%).[9] As described above, although the reaction of imines with ylide provided a good access to vinylaziridines, the stereoselectivity, in particular, the *cis/trans* selectivity, is generally not good.[6,7,9] Furthermore, few reports appeared in the literature on the preparation of optically active *cis*-disubstituted aziridines via an ylide route.[10] In this paper, we wish to report a highly efficient protocol for the synthesis of optically active 2-substituted vinylaziridines with high *cis*-selectivity and excellent diastereoselectivity via telluronium allylides.

In a previous study on ylide chemistry,[11] we found that the nature of ylide influenced the stereochemistry in ylide cyclopropanation.[12] Considering that the match of ylide and substrate is very important for achieving good stereoselectivity in ylide reaction,[6−12] we tried the aziridination of telluronium allylide with chiral *N*-*tert*-butylsulfinylimines.[13] Fortunately, it was found that this reaction proceeded well to give the desired *cis*-2-substituted vinylaziridines. As shown in Table 1, telluronium salt **1a**, after deprotonation by LDA, reacted with enantiopure imine **2a** at −78 °C in THF to afford the desired aziridine with high *cis*-selectivity and excellent diastereoselectivity (>99/1) in 55% yield (entry 1). The yield was improved to good when NaHMDS or KHMDS was used as a base instead of LDA (entries 3 and 4), however, the stereoselectivity deteriorated greatly. In our screened conditions, the best base was LiHMDS. In this case, the desired product was obtained in good yield (83%) with a good *cis/trans* ratio and excellent diastereoselectivity. Toluene as a solvent instead of THF also gave the similar yield and stereoselectivity (entry 7). The anion of the telluronium salt was also found to influence both the yield and stereoselectivity. Tetraphenylborate decreased the yield as well as the diastereoselectivity greatly under the same conditions (entry 8, Table 1).

Table 1. Effects of Base, Solvent, and Telluronium Salt on the Aziridination of *tert*-Butylsulfinylimines (ref 14)[a]

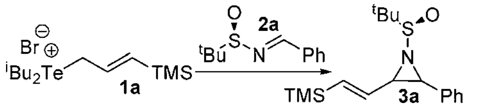


entry	solvent	base	yield (%)[b]	*cis*/*trans*[c]	de (%)[c]
1	THF	LDA	55	20/1	>98
2	THF	^{t}BuOK	trace		
3	THF	NaHMDS	85	2.5/1	78
4	THF	KHMDS	85	1/2.5	5
5	THF	LiTMP	55	6/1	95
6	THF	LiHMDS	83	17/1	97
7	PhMe	LiHMDS	84	16/1	97
8[d]	PhMe	LiHMDS	82	1/4	9

[a] **2a**/**1**/base = 1.0/1.5/1.5. [b] Isolated yield. [c] Determined by ^{1}H NMR, and de was assigned for the *cis*-isomer. [d] **1b** was used instead of **1a**.

Additives also proved to influence the aziridination. As shown in Table 2, the addition of TMEDA or HMPA deteriorated both the yield and the diastereoselectivity (entries 1 and 2). In the presence of LiBr or $MgBr_2$, high *cis/trans* selectivity was achieved and the diastereoselectivity maintained. The best result was obtained when Lewis acid $Ti(OEt)_4$ was used. In this case, the desired aziridine **3a** was isolated in 98% yield with a good *cis/trans* selectivity

Table 2. Effects of Addition Sequence and Additives on the Aziridination of *tert*-Butylsulfimines[14]



entry	additive	sequence[a]	yield (%)[b]	*cis*/*trans*[c]	de (%)[c]
1[d]	TMEDA[e]	A	57	12/1	95
2[d]	HMPA[e]	A	52	1/2.6	56
3[d]	LiBr[f]	A	68	20/1	>98
4[d]	LiBr[f]	B	75	20/1	>98
5[g]	$MgBr_2$[f]	B	85	20/1	>98
6[h]	$Ti(OEt)_4$[f]	B	98	20/1	>98

[a] A: additive was added after the addition of base (LiHMDS). B: additive was added before the addition of base. [b] Isolated yield. [c] Determined by ^{1}H NMR, and de was assigned for the *cis*-isomer. [d] With 1.5 equiv of base used. [e] With 3 equiv used. [f] With 2 equiv used. [g] With 1.9 equiv of base used. [h] With 4 equiv of base used.

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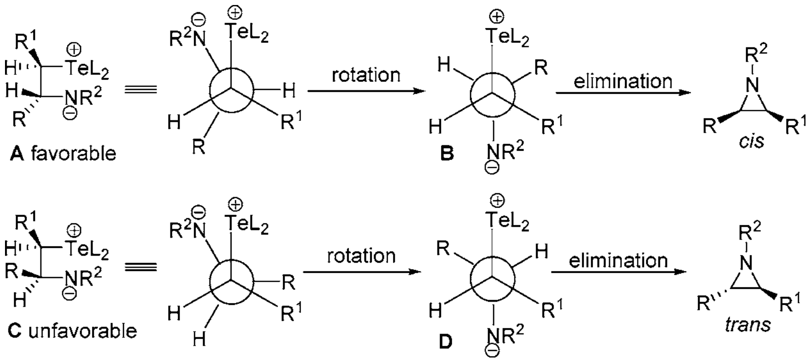
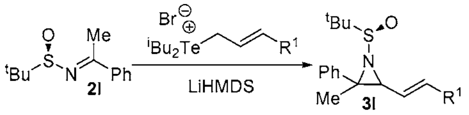


Figure 1. Proposed mechanism for the aziridination mediated by telluronium salt.

(*cis/trans* = 20/1) and excellent diastereoselectivity (dr > 99/1, entry 6).

Having established optimal conditions, a survey of the scope of imines suitable for this aziridination was carried out. As summarized in Table 3, the reaction displayed good generality with respect to the substituents of imines. Various aryl and heteroaryl aldimines (entries 1−7) as well as alkyl and α,*β*-unsaturated aldimines (entries 8−12) all worked well to afford the desired products with high diastereoselectivity in good to excellent yields, providing an easy access to optically active *cis*-2-substituted vinylaziridines. Furthermore, ketimines, usually less active than aldimines in ylide reactions,[15] worked well in this aziridination. For example, phenylmethylketimine **2l** could react with silylated telluronium allylide to afford the corresponding aziridine in 76% yield with excellent diastereoselectivity (*cis/trans* > 30/1 and >98% de, Scheme 1).

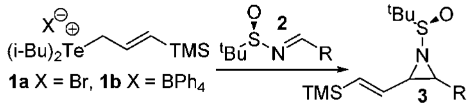
Scheme 1. Stereoselective Aziridination of Ketimine **2l**[14]

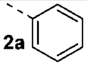
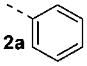
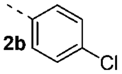
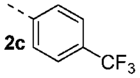
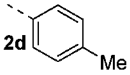
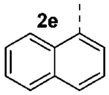
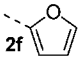
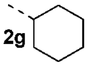
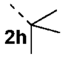
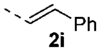
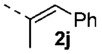
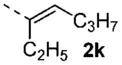


R^1 = TMS 76% yield, 30/1 trans/cis, >98% de

Further study showed that the reaction of the simple allylic telluronium salt **1c** with imine **2a** also proceeded well to give the desired *cis*-vinylaziridine with high diastereoselectivity in high yield (*cis/trans* = 14/1, 95% de, entries 1 and 2 in Table 4), completely different from *cis/trans* selectivity in the reaction of the corresponding sulfur ylide in which a *trans*-isomer was favored. This result demonstrated that telluronium ylide, compared with the corresponding sulfur ylide,[9] was unique. Noticeably, although cinnamyl sulfonium ylide was reported to be inert to *tert*-butylsulfinylimines,[6e] the corresponding telluronium ylide worked well to afford the desired cinnamyl aziridine with excellent selectivity in high yield (entry 3, Table 4), suggesting that telluronium ylide is more active than the corresponding sulfur ylide.

Table 3. Stereoselective Aziridination of Enantiopure *N*-*tert*-Butylsulfinylimines[14]



entry	2, R	method[a]	yield (%)[b]	*cis/trans*[c]	de (%)[c]
1	 2a	A	83	17/1	97
2	 2a	B	98	20/1	>98
3	 2b	B	96	20/1	>98
4	 2c	B	98	20/1	>98
5	 2d	B	98	20/1	97
6	 2e	B	98	22/1	>98
7	 2f	B	93	19/1	94
8[d]	 2g	A	83	9/1	>98
9[d]	 2h	A	53	>30/1	>98
10	 2i	B	88	10/1	88
11	 2j	B	98	25/1	87
12	 2k	B	91	12/1	86

[a] A: **2**/**1**/LiHMDS = 1.0/1.5/1.5. B: $Ti(OEt)_4$ was added, **2**/**1**/$Ti(OEt)_4$/LiHMDS = 1.0/1.5/2/4. [b] Isolated yield. [c] Determined by ^1H NMR, and de was assigned for the *cis*-isomer. [d] Salt **1b** was used instead of **1a**.

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(14) For detailed procedure, please see Supporting Information.

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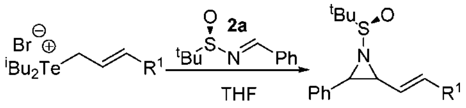
Table 4. Aziridination of **2a** Mediated by Different Telluronium Salts[14]



entry	**1** (R^1)	method[a]	yield (%)[b]	*cis*/*trans*[c]	de (%)[c]
1	**1c** (H)	A	75	9/1	95
2	**1c** (H)	B	91	14/1	96
3	**1d** (Ph)	B	89	>30/1	>98

[a] A: **2a/1**/LiHMDS = 1.0/1.5/1.5. B: Ti(OEt)$_4$ was added, **2a/1**/Ti(OEt)$_4$/LiHMDS = 1.0/1.5/2.0/4.0. [b] Isolated yield. [c] Determined by ^{1}H NMR, and de was assigned for the *cis*-isomer.

In the literature, the ylide aziridination is regarded as a two-step reaction.[6e,16] Although the detailed mechanistic pathway is not clear, Figure 1 could account for the selectivity of the aziridination. The telluronium ylide attacks the imine to form intermediates **A** and **C**. Transformation of intermediates **A** and **C** into the corresponding **B** and **D** by rotation was followed by an intramolecular *anti*-elimination to afford the vinylaziridine. Obviously, intermediate **A** is favored over **C** due to steric hindrance and thus, *cis*-aziridine formed preferably.

In conclusion, on the basis of the reaction of enantiopure *N*-*tert*-butylsufinylimines with various allylic telluronium ylides, a highly stereoselective and efficient ylide aziridination has been developed. This aziridination provided an easy access to optically active *cis*-2-substituted vinylaziridines and 2,2-disubstituted vinylaziridines directly from imines. The excellent diastereoselectivity, good *cis/trans* selectivity, as well as high yield make this reaction potentially useful in organic synthesis.

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Supporting Information Available: General synthetic procedures and characterization and spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051921N

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