Tetrahedron Letters 54 (2013) 3586–3590

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A convenient synthesis of chiral vinyl aziridines via aza-Barbier–Darzen type reaction

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ARTICLE INFO

Article history:
Received 17 March 2013
Revised 8 April 2013
Accepted 15 April 2013
Available online 20 April 2013

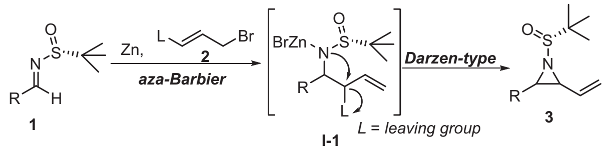
Keywords:
Aza-Barbier–Darzen type reaction
1,3-Dibromoprop-1-ene
(*R*)-*N*-*tert*-Butanesulfinyl imine
Vinyl aziridine

ABSTRACT

A facile and efficient approach for the synthesis of chiral vinyl aziridines has been developed in moderate yields and high diastereoselectivities via Zn-promoted aza-Barbier–Darzen type reaction of (*R*)-*N*-*tert*-butanesulfinyl imines with 1,3-dibromoprop-1-ene.

Vinyl aziridines have gained much attention in the past two decades primarily due to their versatile reactivity for synthesizing numbers of natural and non-natural products undergoing ring opening[1] or ring-expansion.[2] They are also very important subunits in a huge amount of biologically active compounds.[3] Conversion of vinyl epoxides[4], addition of nitrenoids to 1,3-dienes[5], and ylides addition to activated imines[6] are popular ways for the construction of vinyl aziridines. However, literatures on effective synthesis of enantiomerically pure vinyl aziridines are less reported. To the best of our knowledge, the reaction between ylide and *N*-*tert*-butanesulfinyl imines proved to be one of the most powerful protocols. Stockman and co-workers presented the reaction of allyl sulfur ylides with chiral *N*-*tert*-butanesulfinyl imines achieving a series of chiral vinyl aziridines in moderate to good yields (44–82%) with high stereoselectivities (*cis*/*trans* up to 1/4.8) and excellent diastereoselectivities (85 to 95% de)[6g] by employing the approach developed by Hou and Dai.[6a–e] Deng and co-workers described the synthesis of optically active vinyl aziridines via *N*-*tert*-butanesulfinyl imines with telluronium allylides in good to excellent yields (56–98%) with excellent diastereoselectivities (up to >98% de, *cis*/*trans* up to 30/1).[6h] Despite these considerable contributions, a more efficient and convenient route to synthesize vinyl aziridines is particularly appealing.

In the past several years, we have been interested in the asymmetric synthesis of various chiral amines via aza-Barbier reaction.[7] For example, we successfully presented a highly diastereoselective synthesis of chiral homoallylic amines by Zn-mediated allylation of *N*-*tert*-butanesulfinyl imines developed by Ellman et al.[8] at room temperature. By simply changing the solvent, a surprisingly remarkable opposite stereocontrol was achieved with both up to 98% de as well as in good yields.[7a] Moreover, if 3-benzoyloxyallyl bromide or 3-arylallyl bromide was employed, α-hydroxyallylation or cinnamylation of *N*-*tert*-butanesulfinyl imines would be gained also in excellent diastereoselectivities.[7b–d] Furthermore, when β,γ-disubstituted allyl bromide was used and followed by cyclization, chiral α-methylene-γ-lactams would be obtained.[7e] In the meantime, it is revealed that DMF with the additive LiCl could replace the unpleasant HMPA on stereocontrol.[7d] Encouraged by the successful allylation above, we further envisioned that an aza-Barbier reaction between imine **1** and allyl bromide **2** possessing a leaving group in γ-position might be carried out to give the corresponding homoallylic amine intermediate **I-1**. Accordingly, nitrogen in **I-1** might nucleophilically attack the carbon adjacent to the leaving group (the former γ-position of the allyl bromide), and subsequently underwent a S_N2-like reaction in a diastereoslective manner to form the desired vinyl aziridines (Scheme 1). Herein, we wish to report our development of a new and efficient approach to chiral vinyl aziridine via Zn-mediated aza-Barbier–Darzen type reaction.



Scheme 1. Reaction proposal.

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0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.04.046

As bromo group is an ideal leaving group for many reactions and, most importantly, 1,3-dibromoprop-1-ene **2a** is commercially available, it was chosen as the allyl bromide reagent. Initially, we examined the reaction of (*R*)-*N*-*tert*-butanesulfinyl imine **1a** and 3 equiv of 1,3-dibromoprop-1-ene **2a** (purchased from Aldrich® with the proportion of 60% (*E*)-isomer and 40% (*Z*)-isomer) in THF in the presence of 3 equiv of zinc at room temperature to check the potential of our hypothesis, yet desperately, no reaction happened (Table 1, entry 1). When the temperature was raised to 50 °C, to our delight, the reaction proceeds smoothly as we expected that the desired vinyl aziridine product **3a** was indeed isolated in 54% yield and confirmed by NMR spectra. It is noteworthy that the tandem aza-Babier–Daezen type reaction of (*R*)-*N*-*tert*-butanesulfinyl imine (**1a**) with 1,3-dibromoprop-1-ene **2a** occurred in a region and stereoselective fashion to give a single vinyl aziridine diastereomer. The absolute stereochemistry of the obtained product was identified unambiguously through X-ray crystallographic analysis of vinyl aziridine **3a**,[11] of which newly generated stereocenters were determined to be (*R*, *R*), and a *trans* configuration was found (Fig. 1).

When the reaction temperature was raised to 60 °C, a slightly lower yield of 48% was obtained (entry 8). Under similar reaction conditions, the amount and ratio of zinc and 1,3-dibromoprop-1-ene **2a** was examined at 50 °C. Three equivalents of zinc and three equivalents of 1,3-dibromoprop-1-ene **2a** were found to be the best (Table 1, entries 4–7). Furthermore, it was noticeable that the rotation speed made an important role in this reaction that the yields increased with the increasing stir rate until it reached a platform which once mentioned by Jacobsen and co-workers [9] and that 1000 r/min was the suitable rate (Table 1, entries 3, 9–12).

With the optimal condition established, we set out to explore the scope of *N*-*tert*-butanesulfinyl imines. Thus, a wide range of (*R*)-*N*-*tert*-butanesulfinyl imines **1** were examined to react with 1,3-dibromoprop-1-ene **2a** (3 equiv) in the presence of zinc (3 equiv) in anhydrous THF with the rotation speed of 1000 r/min at 50 °C for 2 h as summarized in Table 2. Inspiringly, all the reactions went smoothly and afforded the desired vinyl aziridines in moderate yields. Better yields were observed when electron-withdrawing groups were on the phenyl ring in both *para*- and *ortho*-positions or the phenyl ring only existed (Table 2, entries 1–7, 11). Whereas phenyl group bearing electron-donating group, fused cyclyl group, and heterocyclyl group gave the unsatisfactory results (Table 2, entries 8–10).

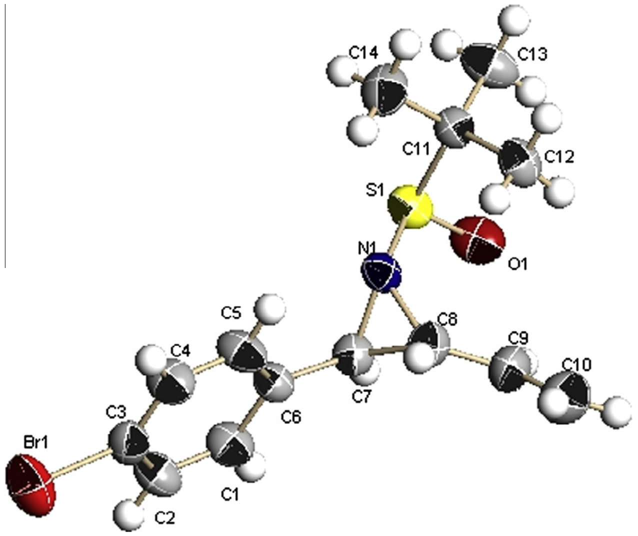
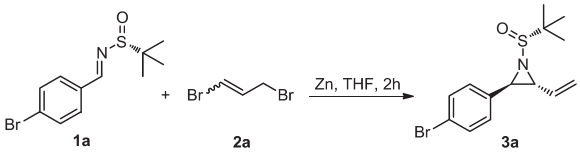


Figure 1. X-ray crystal structure of **3a**.

To better understand the reaction pathway as well as the observed relative stereochemistry, we further conducted a supporting experiment. When the reaction between (*R*)-*N*-*tert*-butanesulfinyl imine **1d** with 2 equiv of both allyl bromide reagent **2a** and zinc was tested, three products were found as fellows: the desired vinyl aziridine **3d**, the homoallylic amine **4d**, and the diamine compound **5d**. However, the imaginary intermediate homoallylic amine **6d** did not appear (Fig. 2a). It might indicate that the intermediate **I-1** and zinc might generate another allylic zinc reagent which could react with (*R*)-*N*-*tert*-butanesulfinyl imine **1d** or be protonated by water. Although the detailed mechanistic pathway is not clear, Figure 2b could account for the selectivity of the tandem reaction. As described in our studies[7a] of simple allylation of *N*-sulfinyl imines with allyl bromide, in a THF system a six-membered cyclic chair transition state model was believed to be preferred and the allylzinc was thought to coordinate both to the imine nitrogen and to sulfinyl oxygen (Fig. 2b).

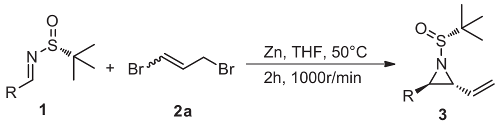
Table 1
Screening and optimization of the reaction conditions



Entry[a]	2 (equiv)	Zn (equiv)	Temperature (°C)	Rotation Speed[b] (r/min)	Yield[c] (%)
1	3	3	rt	1000	NR
2	3	3	40	1000	NR
3	3	3	50	1000	54
4	2	2	50	1000	29
5	4	4	50	1000	52
6	3	4.5	50	1000	51
7	3	2	50	1000	38
8	3	3	60	1000	48
9	3	3	50	300	32
10	3	3	50	500	45
11	3	3	50	700	50
12	3	3	50	1200	54

[a] The reaction was performed with imine **1a** (0.25 mmol), 1,3-dibromoprop-1-ene **2a**, and Zn in 1 mL dry THF.
[b] The reactions were operated on IKA® (MST Digital).
[c] Isolated yield.

Table 2
Diastereoselective synthesis of vinyl aziridines[10]



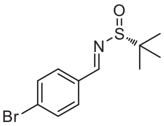
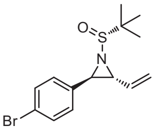
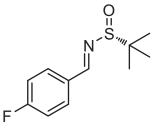
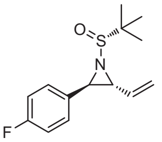
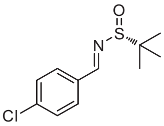
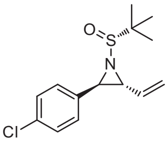
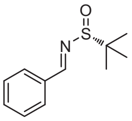
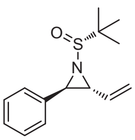
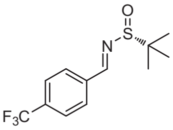
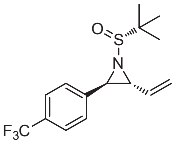
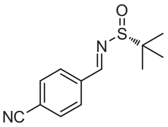
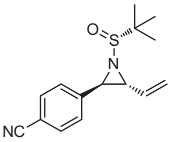
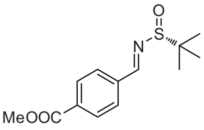
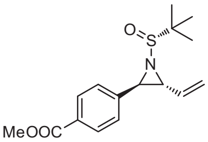
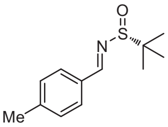
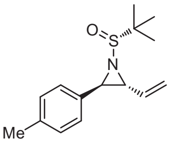
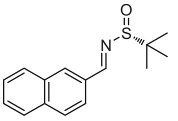
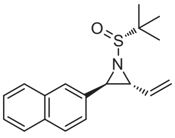
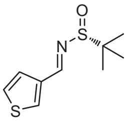
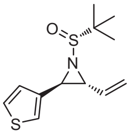
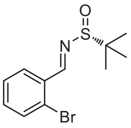
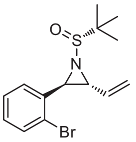
Entry[a]	1	3	Yield[b] (%)	dr[c]
1	 **1a**	 **3a**	54	>20:1
2	 **1b**	 **3b**	42	>20:1
3	 **1c**	 **3c**	48	>20:1
4	 **1d**	 **3d**	52	>20:1
5	 **1e**	 **3e**	63	>20:1
6	 **1f**	 **3f**	55	>20:1
7	 **1g**	 **3g**	45	>20:1
8	 **1h**	 **3h**	27	>20:1

Table 2 (*continued*)

Entry[a]	1	3	Yield[b] (%)	dr[c]
9	 **1i**	 **3i**	37	>20:1
10	 **1j**	 **3j**	25	>20:1
11	 **1k**	 **3k**	48	>20:1

[a] Reaction was performed with imine **1** (0.25 mmol), Zn (0.75 mmol) and 1,3-dibromoprop-1-ene **2a** (0.75 mmol) in 1 mL dry THF at 50 °C.

[b] Isolated yield.

[c] Determined by NMR.

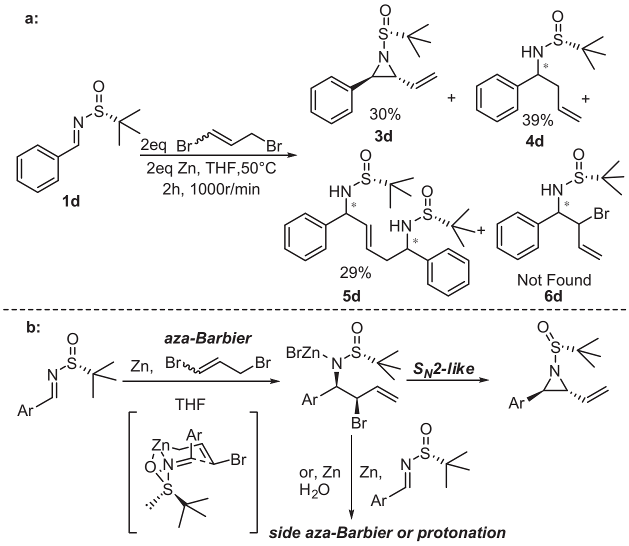


Figure 2. Mechanistic proposals relating to reaction stereocontrol.

In summary, we have developed a facile and efficient approach for the synthesis of chiral vinyl aziridines via zinc promoted aza-Barbier–Darzen type reaction of (*R*)-*N*-*tert*-butanesulfinyl imines with 1,3-dibromoprop-1-ene. This protocol provided an easy access to optically active *trans*-2-subtituted vinyl aziridines directly from imines and commercially available allyl bromide reagent. Mild condition, along with good yields and excellent stereoselectivities, makes this tandem approach attractive in the synthesis of vinyl aziridines.

Acknowledgments

Financial support from the National Nature Science Foundation of China (21072031 and 21103023) and the Shanghai Municipal Committee of Science and Technology (10ZR1404100) is gratefully acknowledged. The authors are also thankful to Dr. Xiao-Di Yang for her assistance with X-ray crystallography.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.046.

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10. *General procedure for the preparation of tert-butylsulfinyl-vinyl-aziridines:* Under Argon, 1,3-dibromoprop-1-ene **2a** (75 μL, 0.75 mmol) was added to a suspension of activated zinc powder (49 mg, 0.75 mmol) and (*R*)-*N-tert*-butanesulfinylimine (0.25 mmol) in anhydrous tetrahydrofuran (1 mL) with the rotation speed of 1000 r/min at 50 °C. Two hours later, the resultant mixture was diluted with 10 mL ethyl acetate, washed by saturated aqueous $NaHCO_3$, water, and brine and dried over anhydrous Na_2SO_4. Concentrated in vacuo, the residue was purified by flash column chromatography to afford the desired product.
11. *Crystallographic data for* ***4d*** *($C_{14}H_{18}BrNOS$):* CCDC 921102; $T = 296(2)$ K; wavelength: 0.71073 Å; formula weight: 328.26; crystal system: monoclinic; space group: $P2(1)$; unit cell dimensions: $a = 5.735(3)$ Å, $b = 10.136(6)$ Å, $c = 13.289(7)$ Å, $\alpha = 90°$, $\beta = 100.133(7)°$, $\gamma = 90°$, $V = 760.5(7)$ Å^3; Z value = 2; D_{calcd}: 1.434 Mg/m^3; absorption coefficient: 2.829 mm^{-1}; $F(000) = 336$; crystal size: 0.25 × 0.21 × 0.18 mm; θ range: 2.54–25.50°; limiting indices: $-6 \leqslant h \leqslant 6$, $-12 \leqslant k \leqslant 8$, $-16 \leqslant l \leqslant 16$; reflections collected/unique: 3785/2075 [$R(\text{int}) = 0.0321$]; completeness to $\theta = 25.50$: 98.8%; absorption correction: semi-empirical from equivalents; max. and min. transmission: 0.6260 and 0.5644; refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 2075/1/167; goodness-of-fit on F^2: 0.962; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0370$, $wR_2 = 0.0838$; R indices (all data): $R_1 = 0.0609$, $wR_2 = 0.0943$; absolute structure parameter: 0.006(14); extinction coefficient: 0.008(2); largest diff. peak and hole: 0.265 and −0.366 e.A^{-3}.