ORGANIC LETTERS

2010
Vol. 12, No. 3
504−507

One-Pot Highly Diastereoselective Synthesis of *cis*-Vinylaziridines via the Sulfur Ylide-Mediated Aziridination and Palladium(0)-Catalyzed Isomerization

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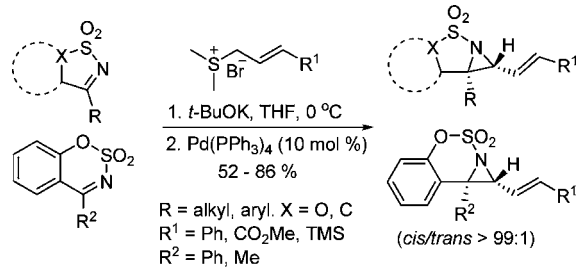
Received November 24, 2009

ABSTRACT



Highly diastereoselective synthesis of *cis*-trisubstituted vinylaziridines containing a quaternary carbon center is realized by a one-pot protocol in which the combination of sulfur ylide-mediated aziridination of cyclic ketimines and Pd(0)-catalyzed isomerization is employed successfully.

Vinylaziridines are important subunits in a number of biologically active compounds[1] and useful building blocks in organic synthesis.[2] Carbene[3,4] and nitrene[4] approaches are recognized as two of the most efficient methods for the preparation of aziridines, but generally they are less effective for vinyl-type aziridines due to the difficulty associated with the regioselectivity control. Although a Darzens-type reaction[5] is also well-documented to prepare aziridines, few direct syntheses involved vinylaziridines in the literature. Thus, the development of synthetic protocols for the preparation of vinylaziridines from readily available materials is especially attractive. The reaction between allylic ylide and imines

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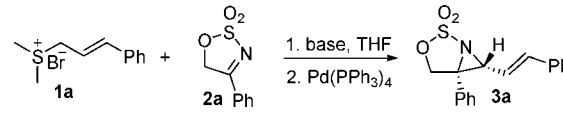
10.1021/ol9027072
Published on Web 12/23/2009

provides a facile way as it involves the regioselective construction of vinylaziridine unit with a concomitant formation of a carbon−carbon bond.[6] For the preparation of vinylaziridine via ylide routes, much attention has been focused on reactions using aldimines as substrates, and the continuous effort is rewarded by a series of elegant works in the synthesis of 1,2-disubstituted vinylaziridines.[7] However, the corresponding aziridination of ketimines, especially unsymmetric ketimines, is seldom explored,[7k,8] probably due to their lower reactivity and issues related to distereoselectivity.

During our research on ylide aziridination,[9] we noticed *trans*-vinylaziridine can be transformed into thermodynamically more stable *cis*-vinylaziridine via Pd(0)-catalyzed isomerization.[10] We surmised that the combination of ylide aziridination and Pd(0)-catalyzed isomerization would offer a facile route to *cis*-vinylaziridine. Herein, we wish to report a one-pot highly diastereoselective synthesis of *cis*-trisubstituted vinylaziridines containing a quaternary carbon center via sulfur ylide-mediated aziridination of ketimines and Pd(0)-catalyzed isomerization.

We started this project with the reaction between sulfonium salt **1a** and cyclic sulfamidates **2a**.[11] The challenge here is that the produced sulfide during the aziridination might posion the palladium catalyst, leading to suppressing the isomerization. To our delight, this reaction proceeded well to give the desired trisubstituted vinylaziridine **3a** with an excellent *cis*/*trans* ratio. As shown in Table 1, to a stirred mixture of sulfonium salt **1a** and imine **2a** in THF was added anhydrous K_2CO_3 in one portion at room temperature, and then $Pd(PPh_3)_4$ was added after imine **2a** totally disappeared. It was found that the desired *cis*-vinylaziridine **3a** could be obtained exclusively (*cis*/*trans* > 99/1) in 59% yield (entry 1). The yield was improved to good when *t*-BuOK or NaHMDS was used as base instead of K_2CO_3 (entries 3 and 5), and the reaction time was cut at least by half in the presence of strong bases (entries 3−5) due to the substantial speeding up of the ylide aziridination step. Among all the bases screened, *t*-BuOK was the best in terms of reaction time, yield, and diastereoselectivity.

Table 1. Effect of Base on the Aziridination[a]



entry	time (h)	base	yield[b] (%)	cis/trans[c]
1	75	K_2CO_3	59	>99/1
2	75	Cs_2CO_3	59	>99/1
3	29	*t*-BuOK	80	>99/1[d]
4	24	LiHMDS	38	>99/1
5	24	NaHMDS	72	>99/1

[a] **1a** (0.24 mmol) and **2a** (0.2 mmol) were mixed in THF (2.0 mL), rt, 15 min, and then base (0.24 mmol) was added. When **2a** disappeared, $Pd(PPh_3)_4$ (10 mol %) was added. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Cis/trans of the ylide aziridination process was 1/3.3.

To further improve the yield, the effects of solvent, temperature, and loading amount of $Pd(PPh_3)_4$ were next investigated. As summarized in Table 2, the *cis*/*trans* ratio of product **3a** was consistently excellent as long as the loading amount of $Pd(PPh_3)_4$ was kept at 10 mol %. When the reaction was carried out in toluene, CH_2Cl_2, or CH_3CN, high diastereocontrol could be maintained, but the yield of the *cis*-vinylaziridine decreased substantially (entries 1−3). MeOH as a solvent did not work for this reaction (entry 4). The yield was improved to 85% when the reaction was run in THF at 0 °C (entry 6). As revealed in entries 7 and 8, the loading amount of $Pd(PPh_3)_4$ was pivotal to secure good diastereoselectivity. For example, the *cis*/*trans* ratio deteriorated significantly when reducing the loading amount of $Pd(PPh_3)_4$ from 10 mol % to 2 mol % or 5 mol %, and

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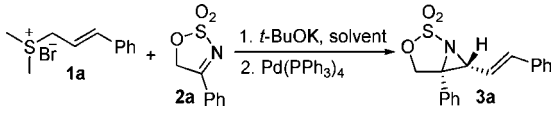
prolonged reaction time did not help at all. Under the optimal conditions, the desired *cis*-vinylaziridine **3a** was isolated in 86% yield with excellent diastereoselectivity (*cis*/*trans* > 99/1) (entry 9).

Table 2. Effects of Solvent, Temperature, and Loading Amount of $Pd(PPh_3)_4$ on the Aziridination[a]



entry	time (h)	t (°C)	solvent	$Pd(PPh_3)_4$ (mol %)	yield (%)[b]	cis/trans[c]
1	18	25	toluene	10	50	>99/1
2	18	25	CH_2Cl_2	10	73	>99/1
3	18	25	CH_3CN	10	43	>99/1
4	18	25	MeOH	10	trace	
5	29	25	THF	10	80	>99/1
6	27	0	THF	10	85	>99/1
7	67	0	THF	5	83	4.8/1
8	67	0	THF	2	89	2.4/1
9[d]	27	0	THF	10	86	>99/1

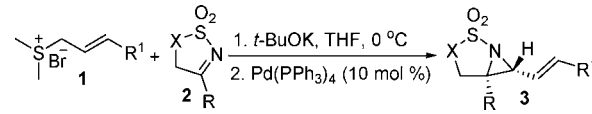
[a] **1a** (0.24 mmol) and **2a** (0.2 mmol) mixed in solvent (2.0 mL), 15 min, then *t*-BuOK (0.24 mmol) was added. When **2a** disappeared, $Pd(PPh_3)_4$ was added. [b] Isolated yield. [c] Determined by ^1H NMR. [d] **2a** was used on a 0.5 mmol scale.

Having established optimal conditions for the synthesis of trisubstituted *cis*-vinylaziridines, we examined the scope and limitation of the one-pot reaction by employing various cyclic ketimines. As summarized in Table 3, the reaction displayed good generality with respect to the substituents of cyclic ketimines. Various aryl substituents with different electronic and steric characteristics (entries 1−7) as well as alkyl substituent (entry 8) all proved to be suitable substrates to afford the desired products with excellent diastereoselectivity in moderate to good yields, providing an easy access to *cis*-trisubstituted vinylaziridines. Furthermore, the reaction of other allylic ylides such as (*E*)-dimethyl(3-(methoxycarbonyl)allyl) sulfonium bromide **1b** and (*E*)-dimethyl(3-(trimethylsilyl)allyl)sulfonium bromide **1c** were also tested. Under the optimal conditions, both of them worked well with imine **2a** to furnish the corresponding *cis*-vinylaziridines exclusively in 65% and 64% yield, respectively (entries 9 and 10). The relative configuration of the aziridines were determined by ^1H NMR, IR and Mass spectra. The structure of **3g** was further determind by X-ray analysis.[12]

In addition to the five-membered ring ketimines **2**, we also explored the reactivity of benzo-fused ketimines **4**, **6a** and **6b** (Scheme 1). As expected, the one-pot protocol also fitted well for those imines. For example, benzobicyclo[3.1.0]vinylaziridine **5** could be accomplished in 82% yield with *cis*/*trans* ratio >99/1 (Scheme 1, eq 1). Similarly, benzobicyclo[4.1.0]vinylaziridine **7a** and **7b** were delivered in 70% and 67% yield, respectively, with only *cis*-isomer (Scheme 1, eq 2).

(12) For details, see the Supporting Information.

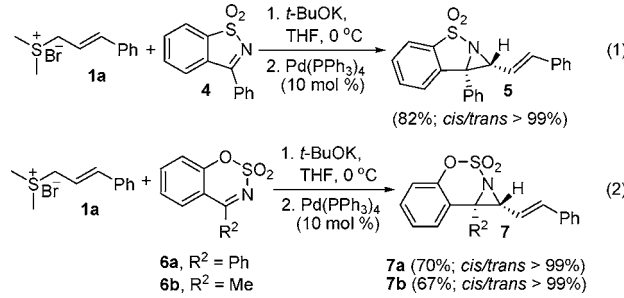
Table 3. Stereoselective Aziridination of cyclic imines[a]



entry	R^1	R	X	yield (%)[b]	cis/trans[c]
1	Ph	Ph (**2a**)	O	86	>99/1
2	Ph	*p*-F-C_6H_4 (**2b**)	O	52	>99/1
3	Ph	*p*-Br-C_6H_4 (**2c**)	O	73	>99/1
4	Ph	*p*-Me-C_6H_4 (**2d**)	O	75	>99/1
5	Ph	*p*-MeO-C_6H_4 (**2e**)	O	76	>99/1
6	Ph	*o*-Me-C_6H_4 (**2f**)	O	82	>99/1
7	Ph	Ph (**2g**)	C	84	>99/1
8	Ph	*n*-C_6H_{13} (**2h**)	C	78	>99/1
9	CO_2Me	Ph (**2a**)	O	65	>99/1
10	TMS	Ph (**2a**)	O	64	>99/1

[a] **1** (0.60 mmol) and **2** (0.50 mmol) were mixed in THF (5.0 mL), 15 min, and then *t*-BuOK (0.60 mmol) was added. When **2** disappeared, $Pd(PPh_3)_4$ (10 mol %) was added. [b] Isolated yield. [c] Determined by ^1H NMR.

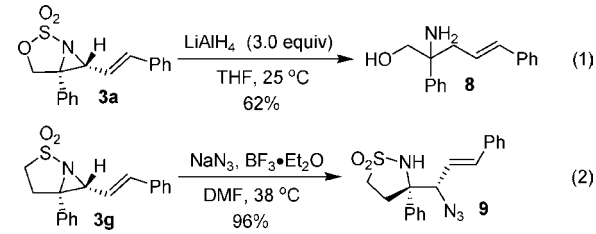
Scheme 1. Aziridination of Cyclic Imines **4**, **6a**, and **6b**



The functionalized vinylaziridines prepared by the current method are potentially useful. For example, as shown in Scheme 2, the sulfone group in **3a** can be removed in the presence of $LiAlH_4$ with concomitant ring-opening of aziridine, giving rise to β-amino alcohol **8** in 62% yield (Scheme 2, eq 1). In addition, the aziridine moiety can also react with other nucleophile like NaN_3 stereospecifically, and the desired compound **9** was obtained as the only product in 96% yield.

A mechanism is proposed to account for the observed diastereoselectivity of the one-pot methodology, although the

Scheme 2. Product Elaboration



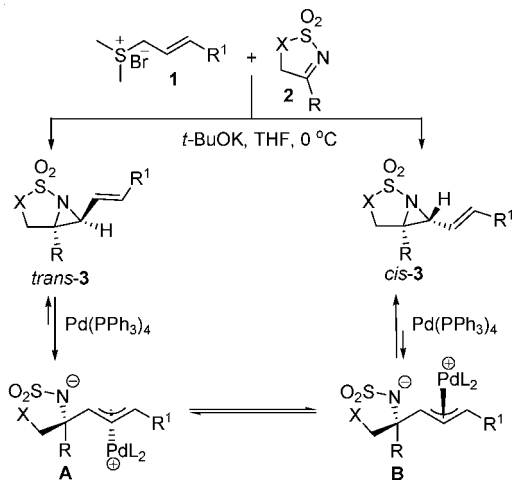


Figure 1. Proposed mechanism for observed diastereoselectivity of the aziridination.

detailed mechanistic pathway is not clear. As depicted in Figure 1, the first step involving the reaction of sulfur ylide and imine leads to *trans*/*cis* mixture of vinylaziridine **3**. In the following Pd(0) catalyzed isomerization,[10] the equilibrium between *trans*-**3** and *cis*-**3** is established through π-allyl palladium complexes[13] **A** and **B**, in which *cis*-configured aziridine *cis*-**3** dominates because of its higher thermodynamical stability.

In conclusion, we developed a one-pot protocol to construct *cis*-vinylaziridine by combining allylic ylide aziridination and Pd(0)-catalyzed isomerization reaction of vinylaziridine. Following this protocol, a series of *cis*-trisubstituted vinylaziridines containing a quaternary carbon center were achieved with exclusive *cis*-selectivity (*cis*/*trans* > 99/1) in moderate to good yields starting with allylic sulfur ylide and cyclic ketimines. We are now working on the asymmetric version of above reaction, and progress will be reported in due course.

Acknowledgment. We are grateful for the financial support from the National Natural Sciences Foundation of China (No. 20821002 and 20672131), the Major State Basic Research Development Program (Grant No. 2006CB806105), and the Chinese Academy of Sciences.

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

OL9027072

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