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Organocatalytic Enantioselective Aziridination of α-Substituted α,β-Unsaturated Aldehydes: Asymmetric Synthesis of Terminal Aziridines

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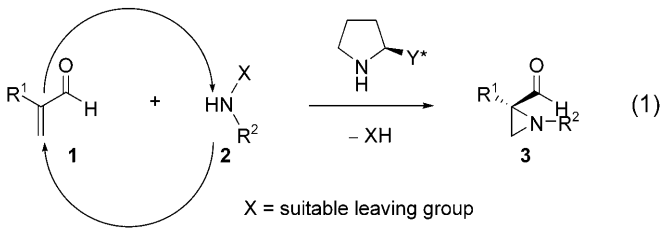
Abstract: The first example of a highly enantioselective organocatalytic aziridination of α-substituted α,β-unsaturated aldehydes is presented. The reaction is catalyzed by simple chiral amines and gives access to highly functional terminal azirdines containing an α-tertiary amine stereocenter in high yields and enantiomeric ratios (95.5:4.5–98:2).

Keywords: asymmetric catalysis; domino reactions; organocatalysis; α-substituted α,β-unsaturated aldehydes; terminal aziridines

Aziridines are valuable compounds, which can be used as versatile chiral building blocks, ligands and auxiliaries for organic synthesis.[1] They are also present in several natural products and can exhibit important biologically activities.[1,2] It is therefore highly desirable to develop catalytic asymmetric methods for the stereoselective synthesis of chiral aziridines. To date, a number of catalytic protocols have been developed for the enantioselective synthesis of aziridines.[3–12] This includes the pioneering works by Evans,[5a–c] Jacobsen,[5d–f] Wulf[10] and Aggarwal,[11] among others.

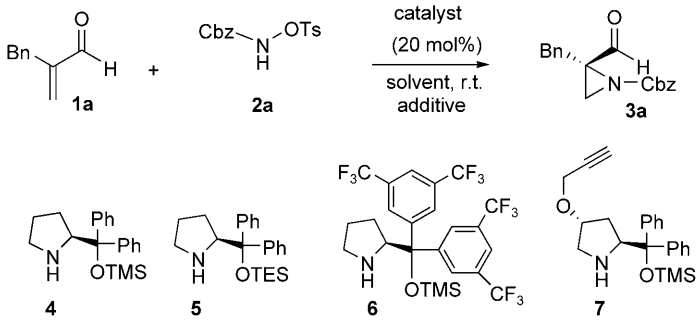
In particular, terminal aziridines are, arguably, the most useful aziridines and represent a particular challenging target. For example, they can be considered as a potential two carbon atoms and one nitrogen atom source due to the fact that they readily undergo regioselective ring-opening with various nucleophiles.[1a] In addition, there is no general method for the synthesis of highly enantioenriched 2-substituted (particularly 2-alkyl-substituted) terminal aziridines in an efficient manner.[13,14] There are a few direct atom economic catalytic enantioselective methods for the direct enantioselective synthesis of terminal azirdines as described above.[15] However, they are not yet applicable to the synthesis of 2-alkyl-substituted aziridines. Moreover, terminal 2-alkyl-substituted aziridines containing an α-tertiary amine stereocenter are also important as precursors for the synthesis of α,α-amino acid derivatives.[16]

In 2006, we disclosed the chiral amine-catalyzed asymmetric aziridination of simple linear enals.[17] This has led to the development of aziridinations of α,β-unsaturated aldehydes and ketones.[18,19] However, the aziridination of α-substituted acryl aldehydes **1** is still lacking in spite of the fact that this reaction would give a direct access to highly functional terminal aziridines **3**, which are valuable precursors for the synthesis of optically active nitrogen containing compounds.[16,19c,d] Thus, we envisioned a novel direct



(1)

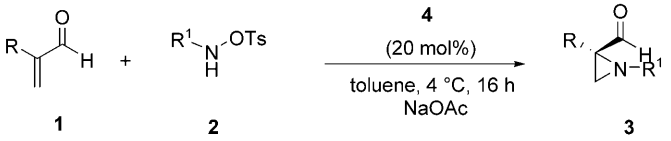
Table 1. Catalyst screen for the reaction between **1a** and **2a**.[a]



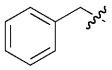
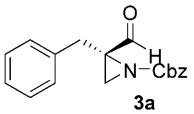
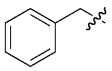
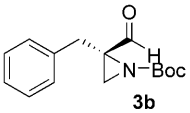
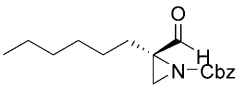
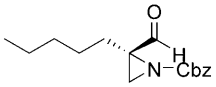
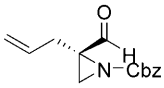
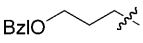
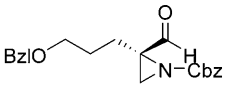
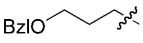
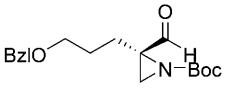
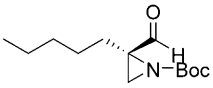
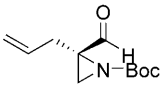
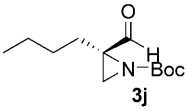
Entry	Catalyst	Solvent	Additive	Time [h]	Conversion [%][b]	*er*[c]
1	**4**	$CHCl_3$	NaOAc	17	69	94:6
2	**4**	$CHCl_3$	K_2CO_3	17	69	53.5:46.5
3	**4**	$CHCl_3$	Et_3N	16	66	62.5:37.5
4	**4**	$CHCl_3$	Na_2CO_3	16	46	57:43
5	**4**	toluene	NaOAc	17	100	97:3
6	**4**	CH_2Cl_2	NaOAc	19	54	92:8
7	**4**	EtOH	NaOAc	17	100	79.5:20.5
8	**4**	toluene	NaOAc	17	100 (68)[d]	96:4
9	**4**	toluene	NaOAc	20	100[e]	96.5:3.5[e]
10	**5**	toluene	NaOAc	16	100	96.5:3.5
11	**6**	toluene	NaOAc	16	43	86:14
12	**7**	toluene	NaOAc	20	100[f]	88:12[f]
13	–	toluene	NaOAc	17	0	–
14	–	toluene	NaOAc	17	0[g]	–
15	**4**	toluene	NaOAc	16	100 (88)[d,h]	97:3

[a] *Experimental conditions:* A mixture of **2a** (0.30 mmol), aldehyde **1a** (0.25 mmol), additive (0.75 mmol) and catalyst (20 mol%) in 1.0 mL solvent was stirred at the temperature and conditions displayed in the Table.
[b] Conversion of **1a** as determined by NMR analysis.
[c] Determined by chiral phase HPLC analysis.
[d] Reaction run in 0.5 mL solvent. Isolated yield in parenthesis.
[e] An excess of **1a** (0.3 mmol) to **2a** (0.25 mmol) was used.
[f] Catalyst **7** (10 mol%).
[g] **2b** was used instead of **2a**.
[h] Reaction run at 4 °C and 1.5 equiv. NaOAc were used. Bn = benzyl, Ts = *p*-toluenesulfonyl.

Table 2. Scope of the organocatalytic terminal enantioselective aziridine synthesis.[a]



1 2 3

Entry	R	R^1	Prod	Yield [%][b]	*er*[c]
1		Cbz	 **3a**	88	97:3
2		Boc	 **3b**	89	98:2
3	*n*-hexyl	Cbz	 **3c**	69	97.5:2.5
4	*n*-pentyl	Cbz	 **3d**	64	97.5:2.5
5		Cbz	 **3e**	65	95.5:4.5
6		Cbz	 **3f**	75[d]	96:4[d]
7		Boc	 **3g**	90	97:3
8	*n*-pentyl	Boc	 **3h**	67	97.5:2.5
9		Boc	 **3i**	73	96:4
10	*n*-butyl	Boc	 **3j**	81	98:2

[a] *Experimental conditions:* A mixture of aldehyde **1** (0.25 mmol), **2** (0.30 mmol), NaOAc (0.375 mmol) and catalyst **4** (20 mol%) in toluene (0.5 mL) was stirred at room temperature for the time shown in the Table. The crude product **3** was purified by column chromatography.

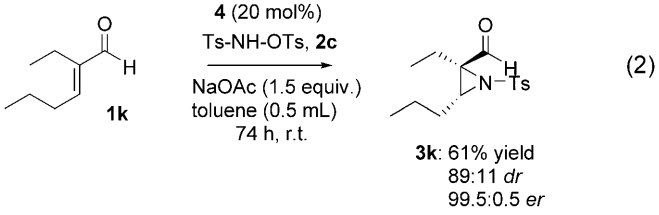
[b] Isolated yield of pure product **3** after silica gel column chromatography.

[c] Determined by chiral phase HPLC analysis.

[d] Reaction run at room temperature. Bzl = benzoyl, Ts = *p*-toluenesulfonyl.

route to highly functional terminal aziridines **3** containing an α-tertiary amine stereocenter *via* a chiral amine-catalyzed reaction between α-substituted acryl aldehydes **1** and a suitable nitrogen source **2**, which could first act as a nucleophile and at a later stage become an electrophile [Eq. (1)].

Here we report the first example of a highly enantioselective catalytic asymmetric aziridination of α-substituted α,β-unsaturated aldehydes **1**, which gives 2-alkyl-2-formylaziridines in high yields and *er* (95.5:4.5–98:2).



(2)

The key results from an initial catalyst and solvent screen are summarized in Table 1. We found to our delight that protected diarylprolinols **4**–**7**[20] catalyzed the asymmetric aziridination reaction between aldehyde **1a** and **2a** to give terminal aziridine **3a** in high enantiomeric ratios. This is noteworthy since the development of aminocatalytic enantioselective reactions using α-substituted α,β-unsaturated aldehydes is challenging.[21,22]

Several bases were screened as additives and we found that the employment of NaOAc is preferred (entries 1–4). The highest enantiomeric ratio of **3a** was accomplished in toluene using chiral amines **4** or **5** as the catalysts. The reaction does not give product **3a** if the amine catalyst is not present (entries 13 and 14). Our present conditions differ from our first pub-

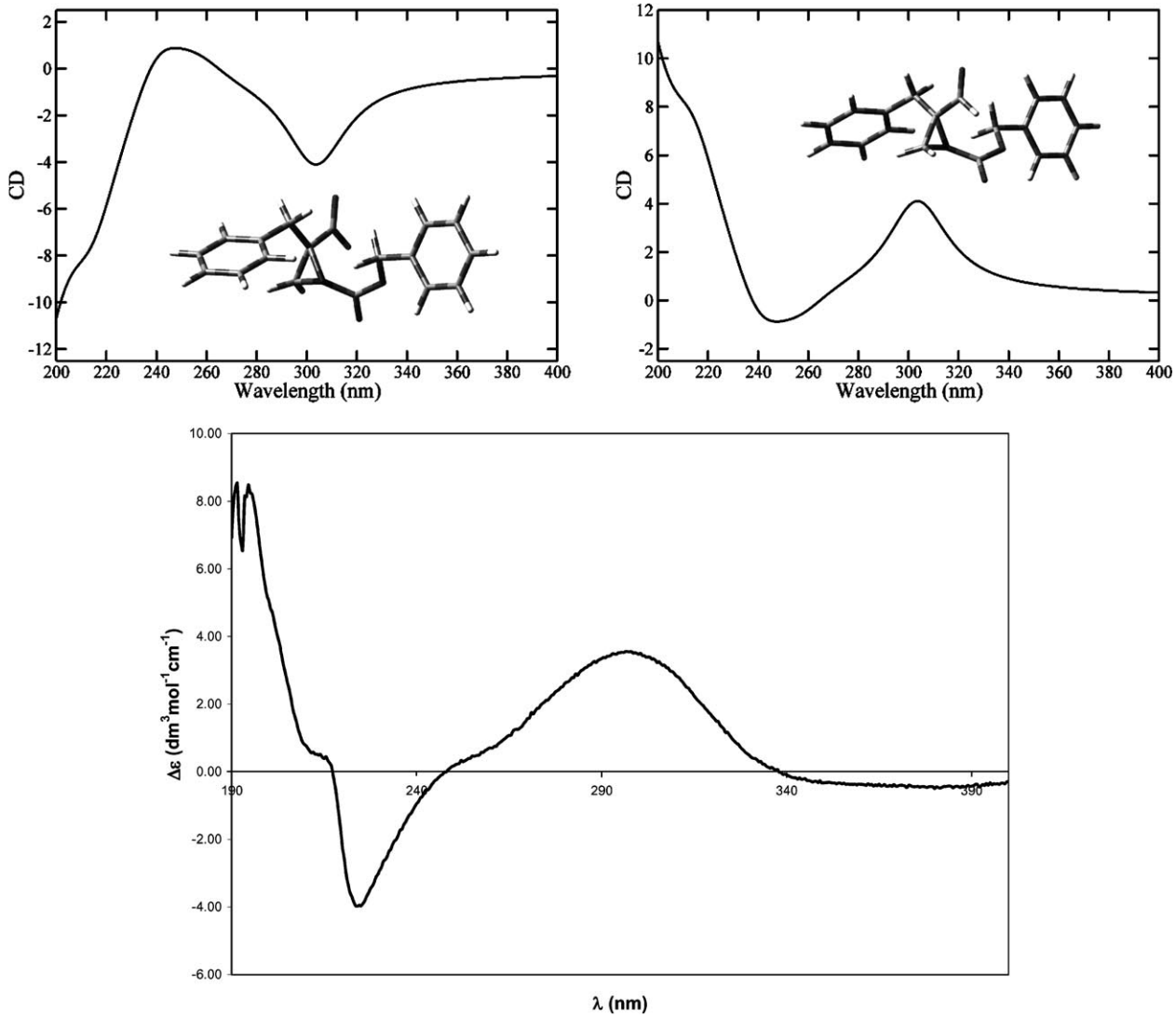


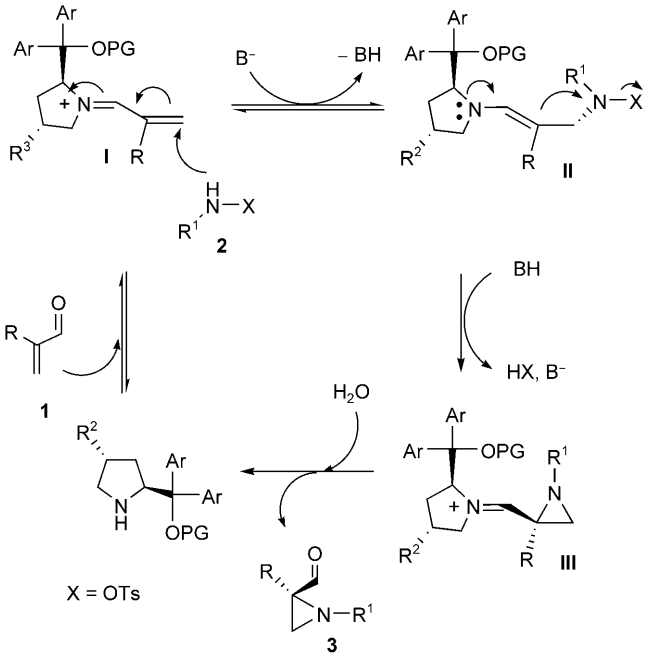
Figure 1. *Top left:* ECD spectra calculated for the (2*R*)-**2a** and the optimized geometry. *Top right:* ECD spectra calculated for the (2*S*)-**2a** and the optimized geometry. *Lower picture:* Experimental (full trace) ECD spectra of compound **2a**.

lished aziridination protocol where no base was added and heating was used instead to accelerate the reaction.[17] With these results in hand, we decided to probe the scope of the catalytic aziridination of α-substituted aldehydes **1** with "nitrene" equivalent **2** using **4** as the amine catalyst and NaOAc as the additive in the optimal solvent toluene (Table 2).

The reactions were efficient and proceeded with high enantioselectivity to give the corresponding terminal aziridine products **3a**–**3j** in good to high yields and high enantiomeric ratios (entries 1–10). The reaction tolerated several enals **1** with different functional groups at their α-alkyl substituent.[23] For example, highly stereoselective aziridination of aldehyde **1e** at its less electron-rich olefin can be accomplished using our methodology to give the corresponding Boc-protected terminal azirdine **3e** in 73% yield and a 96:4 *er* (entry 9). It is noteworthy that the scope of the reaction can be broadened to α,β-disubstituted enals **1** [Eq. (2)]. As exemplified in the highly diastereo- and enantioselective aziridination of disubstituted enal **1k** to give the corresponding product **3k** in 61% yield with 89:11 *dr* and 99.5:05 *er*.

The absolute stereochemistry of terminal aziridines **3** was assigned by means of TD-DFT calculations of the electronic dichroism (ECD) spectra of **3a** (Figure 1).[24] The density functional theory (DFT) calculations of the *S*-enantiomer of **3a** matched with the experimental CD spectra of **3a** (Figure 1). Thus, the absolute configuration of **3a** at C-2 is assigned as *S*. The mechanistic proposal for our aminocatalytic enantioselective synthesis of terminal aziridines **3** is shown in Scheme 1. The efficient shielding of the chiral iminium intermediate **I** by the bulky aryl groups of catalysts **4**–**7** leads to stereoselective nucleophilic *Re*-facial conjugate attack on the β-carbon by the amino group of **2** (Scheme 1). Next, the generated chiral enamine intermediate **II** performs a stereoselective 3-*exo*-tet nucleophilic attack from its less sterically hindered *Si*-face on the now electrophilic nitrogen and leaving group X is released (Scheme 1). The intramolecular ring closure pushes the equilibrium forward and makes this step irreversible. Subsequent hydrolysis of the iminium intermediate **III** gives the corresponding terminal azirdine **3** and releases the amine catalyst.

In summary, we report the first example of a highly enantioselective organocatalytic aziridination of α-substituted α,β-unsaturated aldehydes. The reaction is efficiently catalyzed by simple chiral pyrrolidine derivatives and gives the corresponding 2-alkyl substituted terminal aziridines containing an α-tertiary amine stereocenter in high yields and *er* (95.5:4.5–97.5:2.5). We are currently performing mechanistic studies and synthetic applications of this transformation as well as development of other enantioselective aziridinations based on this concept.



Scheme 1. The proposed reaction pathway for a chiral amine-catalyzed enantioselective aziridination of α-substituted enals **1**.

Experimental Section

Representative Procedure for the Aziridination between Benzyl *N*-tosyloxycarbamate 2a or *tert*-butyl *N*-tosyloxycarbamates 2b and α-Substituted α,β-Unsaturated Aldehyde 1

To a stirred solution of catalyst **4** (20 mol%) in toluene (0.5 mL) were added α-substituted-α,β-unsaturated aldehyde **1** (1.0 equiv., 0.25 mmol), benzyl *N*-tosyloxycarbamate **2a** or *tert*-butyl *N*-tosyloxycarbamate **2b** (1.2 equiv., 0.30 mmol) and NaOAc (0.375 mmol, 1.5 equiv.) at 0 °C and the resulting reaction mixture was vigorously stirred for the reported time at 4 °C. Next, the reaction mixture was directly loaded upon a silica gel column and immediate chromatography (pentane:EtOAc-mixtures) furnished the aziridine product **3**.

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