Asymmetric Catalysis

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Organocatalytic Enantioselective Aziridination of α,β-Unsaturated Aldehydes**

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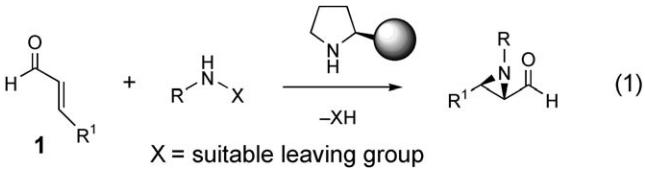
Aziridines are three-membered nitrogen-containing heterocycles of great importance as versatile chiral building blocks in organic synthesis.[1] They can also be found in natural products, such as mitomycin, porfiromycin, and mitiromycin, which are potent antitumor and antibiotic agents.[2] Asymmetric protocols that involve chiral substrates or the utilization of chiral auxiliaries[3] have been developed for the synthesis of aziridines.[1a] Catalytic asymmetric methods have also been developed.[1b,4] Organometallic catalysts with Cu,[5] Rh,[6] Ru,[7] Mn,[8] and Ag[9] have been employed in asymmetric aziridination reactions. In this context, Evans and co-workers reported the first Cu-catalyzed asymmetric nitrene transfer to olefins. Jacobsen and co-workers have developed metal-catalyzed enantioselective aziridinations of *cis* olefins and an enantioselective aziridination of imines.[5f] Lewis acid catalysis has also been employed for the asymmetric aziridination of imines.[1b,4] For example, Antilla and Wulff reported an efficient method for the asymmetric aziridination of *N*-benzhydrylimines.[10] Aggarwal and co-workers reported the asymmetric generation of aziridines from sulfur ylides and imines by diazo decomposition.[11]

In the field of organocatalysis, reactions that involve a combination of catalytic iminium and enamine intermediates have been developed recently.[12–14] On the basis of this research and our previous experience in the combination of catalytic cycles,[15] we envisaged that a reaction between a "nitrene" equivalent and an enal would occur under the catalysis of a chiral amine by iminium and enamine activation to provide simple asymmetric access to 2-formylaziridines [Eq. (1)].

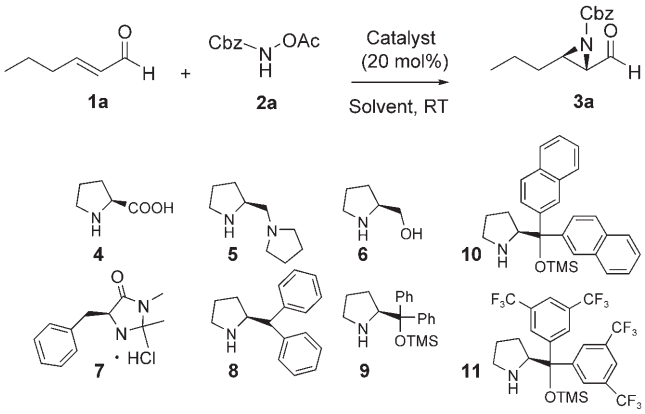
Thus, we would need to develop a reaction in which the nitrogen-atom source would first act as a nucleophile and at a later stage become electrophilic. MacMillan and co-workers recently described the initial amine-catalyzed conjugate attack on enals.[16a] Herein we report the first example of a highly enantioselective catalytic asymmetric aziridination of α,β-unsaturated aldehydes in which 2-formylaziridines are formed in good to high yields and with 87–99% *ee*.



(1)

After extensive screening of catalysts and different suitable nitrogen-atom sources for the asymmetric aziridination of 2-hexenal (**1a**), we found that acylated hydroxycarbamates **2** had the right properties to promote product formation.[16–17] The results of the screening of reaction conditions for the enantioselective transformation between enal **1a** and acetyl hydroxycarbamate **2a** are displayed in Table 1.

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



Entry	Catalyst	Solvent	*t* [h]	Conv. [%][b]	d.r.[c]	*ee* [%][d]
1	**4**	$CHCl_3$	24	0	–	–
2	**5**	$CHCl_3$	4	15	1:1	n.d.
3	**6**	$CHCl_3$	16	>5	n.d.	n.d.
4	**7**	$CHCl_3$	24	0	–	–
5	**8**	$CHCl_3$	4	45	1:1	57
6	**9**	$CHCl_3$	3	86	9:1	99
7	**10**	$CHCl_3$	4	76	5:1	90
8	**11**	$CHCl_3$	24	20	>19:1	98
9[e]	**9**	$CHCl_3$	0.5	100	5:1	96
10[e]	**9**	CH_3CN	0.5	66	>19:1	90
11[e]	**9**	DMF	0.5	100	>19:1	88

[a] Experimental conditions: A mixture of **2a** (0.30 mmol), **1a** (0.25 mmol), and the catalyst (20 mol%) in the solvent (1.0 mL) was stirred at room temperature for the time given. Cbz = benzyloxycarbonyl, DMF = *N*,*N*-dimethylformamide, n.d. = not determined, TMS = trimethylsilyl. [b] Conversion to the product **3a**, as determined by NMR spectroscopic analysis [c] Determined by NMR spectroscopy. [d] Determined by HPLC analysis on a chiral phase. [e] The reaction was performed at 40°C.

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InterScience

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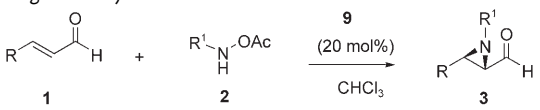
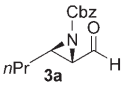
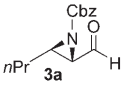
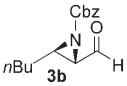
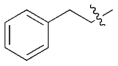
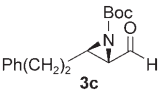
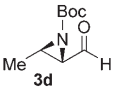
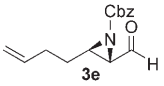
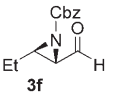
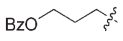
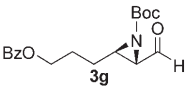
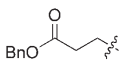
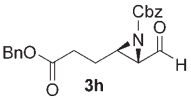
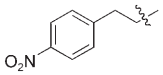
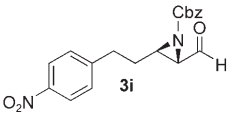
We found that the chiral amines **8**–**11** catalyzed the asymmetric formation of the 2-formylaziridine **3a** with up to d.r. > 19:1 (*trans*/*cis*) and with 57–99% *ee*. The chiral amine **9**[18] was the most efficient catalyst under our reaction conditions and mediated the formation of **3a** with high chemo-, diastereo-, and enantioselectivity (Table 1, entry 6). We found that the reaction was accelerated significantly at 40°C with little change in the enantioselectivity (Table 1, entry 9). Moreover, the chiral amine **9** catalyzed the asymmetric formation of **3a** in polar aprotic solvents, such as DMF and CH_3CN. On the basis of our initial results, we decided to investigate the enantioselective aziridination of enals **1** with acetylated hydroxylamines **2** under the catalysis of amine **9** (Table 2).

Table 2: Scope of the organocatalytic aziridination.[a]



Entry	R	R^1	Product	*T* [°C]	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	*n*Pr	Cbz	 **3a**	RT	3	62	10:1	99
2	*n*Pr	Cbz	 **3a**	40	0.5	78 (68)[e]	4:1 (4:1)[e]	96 (90)[e]
3	*n*Bu	Cbz	 **3b**	40	0.5	70	5:1	96
4		Boc	 **3c**	40	0.4	68	5:1	92
5	Me	Boc	 **3d**	RT	5	54	5:1 (6:1)[f]	90 (94)[f]
6		Cbz	 **3e**	40	0.5	68	6:1	96
7	Et	Cbz	 **3f**	40	0.6	60	5:1	97
8		Boc	 **3g**	40	0.4	60	5:1	98
9		Cbz	 **3h**	40	0.5	62	5:1	84
10		Cbz	 **3i**	40	0.4	66	7:1	92

[a] Experimental conditions: A mixture of **1** (0.30 mmol), **2** (0.25 mmol), and **9** (20 mol%) in $CHCl_3$ (1.0 mL) was stirred at the temperature and for the time shown. The crude product **3** was purified by column chromatography. Bz = benzoyl, Bn = benzyl, Boc = *tert*-butoxycarbonyl. [b] Yield of the pure product **3** after silica-gel column chromatography. [c] Determined by NMR spectroscopy or GC analysis. [d] Determined by HPLC on a chiral phase or GC analysis. [e] Catalyst loading: 10 mol%. [f] Determined after 0.5 h.

The organocatalytic enantioselective aziridination reactions were highly chemo- and enantioselective, and the corresponding Boc- or Cbz-protected 2-formylaziridines **3** were isolated in good to high yields with 84–99% *ee*. The reactions proceeded with even higher diastereo- and enantioselectivity (up to d.r. > 19:1 and 99% *ee*) at room temperature. However, we observed that the aziridine product started to decompose during prolonged reaction times, possibly as a result of the high reactivity of the 2-formylaziridines **3**.[19] Hence, short reaction times (20–40 min) and a temperature of 40°C were superior conditions for most substrates with respect to the yield of **3**. The reaction between acetylated Fmoc-protected hydroxyamine and 2-hexenal (**1a**) gave the corresponding Fmoc-protected 2-formylaziridines in 63% yield and with d.r. 5:1, but with only 46% *ee* (Fmoc = 9-fluorenylmethoxycarbonyl).

The α,β-aziridine aldehydes **3** could also be converted in one step into the corresponding Boc- or Cbz-protected β-amino acid esters in the presence of a thiazolium catalyst generated in situ (Scheme 1).[20] For example, the β-amino acid ester **12a** was formed in two steps from the inexpensive enal **1a** and the acetyl carbamate **2a**. Next, hydrogenolysis of the isolated compound **12a** with 10% Pd/C led to removal of the Cbz group to give quantitatively the corresponding β-amino acid ester **13a**. Comparison with literature data revealed that the β-amino acid derivative **13a** had the absolute configuration *R* at C3 ($[\alpha]_D^{25} = +10.9$ ($c = 0.5$, H_2O); Lit. (*S*-**13a**):[21] $[\alpha]_D^{25} = -10.7$ ($c = 2.1$, H_2O)). Thus, the reactions with the catalyst (*S*)-**9** provide access to (2*S*,3*R*)-2-formylaziridines **3**.

We propose that efficient shielding of the *Si* face of the chiral iminium intermediate by the bulky aryl groups of **9** leads to stereoselective *Re*-facial nucleophilic conjugate attack on the β carbon atom of the electrophile by the amino group of **2** (Scheme 2). Next, the chiral enamine intermediate generated performs a 3-*exo*-tet nucleophilic attack on the now electrophilic nitrogen atom, and acetic acid is released. The intramolecular ring closure pushes the equilibrium in the forward direction and makes this step irreversible. The same type of reaction mechanism has been

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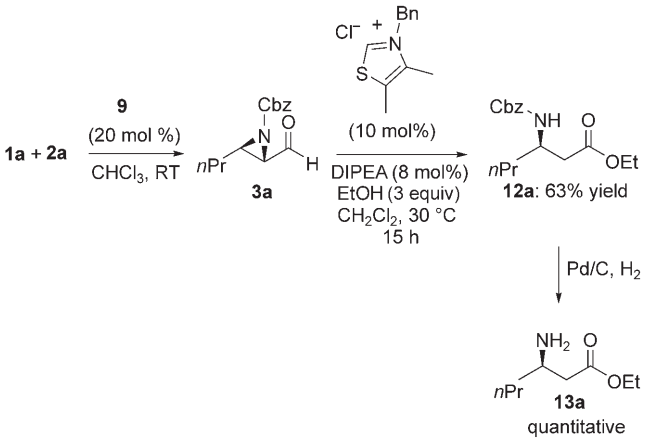
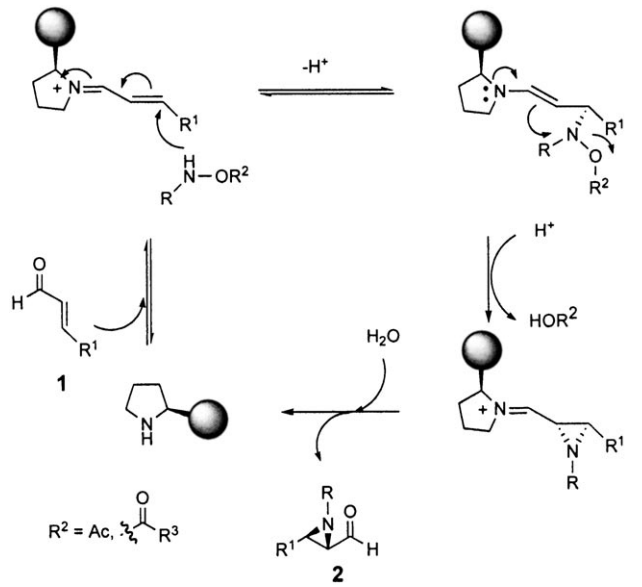


Scheme 1. Two-step asymmetric synthesis of the β-amino acid ester derivative **12a**. DIPEA = *N*,*N*′-diisopropylethylamine.



Scheme 2. A plausible reaction pathway for enantioselective aziridination catalyzed by a chiral amine.

observed in the organocatalytic asymmetric epoxidation of enals.[13g,j]

In summary, we have reported an unprecedented example of a highly chemo- and enantioselective organocatalytic aziridination of α,β-unsaturated aldehydes. The reaction is catalyzed efficiently by simple chiral pyrrolidine derivatives and gives the corresponding 2-formylaziridines in good to high yields with d.r. 4:1–19:1 and 84–99% *ee*. The synthetic utility of the novel catalytic enantioselective aziridination was exemplified in the two-step asymmetric synthesis of β-amino acid esters with readily removable protecting groups. Mechanistic studies, synthetic applications of this transformation, and the development of other enantioselective aziridination reactions based on this concept are ongoing in our laboratory.

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