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Asymmetric Organocatalysis (2)

Organocatalytic Asymmetric Aziridination of Enones**

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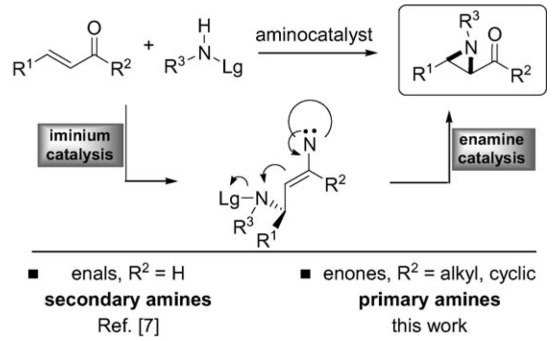
The development of novel and efficient catalytic methodologies for the stereoselective preparation of chiral aziridines is an important synthetic target.[1] Aziridines constitute a key structural feature of several classes of natural products and are extremely versatile building blocks that can undergo synthetically useful transformations.[2] The catalytic asymmetric aziridinations of olefins provide direct and useful access to such a valuable scaffold, and great efforts and progress have been made in this field.[3] However, to our knowledge, a general and highly stereoselective aziridination of simple α,β-unsaturated enones is still lacking.[4,5] Herein, we report an organocatalytic solution to this synthetic problem that is founded upon the use of a readily available chiral primary amine catalyst salt as well as on a rationally designed N-centered nucleophile.

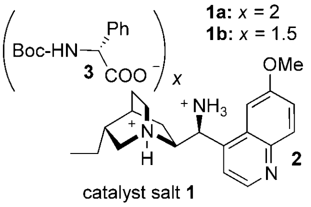
Previously reported asymmetric aziridinations of enones have severe restrictions in scope, as only chalcones are suitable substrates: metal-based systems[4] can provide highly enantioenriched compounds protected as *N*-tosyl derivatives, a protecting group that can prove to be difficult to remove, whereas two ingenious organocatalytic entries to nonprotected aziridines, showing moderate enantioselectivity (up to 67% *ee*), were recently reported through the use of chiral tertiary amines.[5]

Recently, the spectacular advances achieved in the field of chiral secondary amine catalysis[6] have set the conditions for the development of a highly chemo- and stereoselective aziridination of α,β-unsaturated aldehydes.[7] Central to the success of this approach was the ability of the organocatalyst to integrate orthogonal activation modes (iminium ion and enamine catalysis) into a more elaborate reaction sequence,[8] thus promoting first the nucleophilic addition of a N-centered nucleophile followed by an intramolecular cyclization (Scheme 1). We sought to extend this organocatalytic strategy to α,β-unsaturated ketones, an idea that was mainly triggered by the recent applications of chiral primary amine salts as efficient activators of enones through iminium catalysis.[9] The reduced steric constraints of primary amines offers the unique possibility of catalyzing processes between sterically demanding partners, overcoming the inherent difficulties of chiral secondary amine catalysis.



Scheme 1. Iminium–enamine sequential approach to aziridines. Lg = leaving group.

In particular, we recently introduced the catalyst primary amine salt **1**,[10] which is made by combining the easily available 9-amino(9-deoxy)*epi*-hydroquinine **2** with D-*N*-Boc phenylglycine (**3**; Boc = *tert*-butyloxycarbonyl). Salt **1** exhibits its high reactivity and selectivity in the enantioselective conjugate additions of carbon-,[10a] oxygen-,[10b] and sulfur-centered[10c] nucleophiles to α,β-unsaturated ketones.



catalyst salt **1**

To consolidate salt **1** as a general and selective iminium catalyst for enones, we questioned whether this catalytic system might be successfully extended to the highly enantioselective amine conjugate addition, a primary strategy for C–N bond construction.[11] Prompted by the synthetic value of asymmetric catalytic aza-Michael processes, we focused on the use of the commercially available N-protected hydroxylamines **4** as the nucleophilic components (Table 1). In analogy with the recently reported secondary amine catalyzed addition of **4** to enals,[12] the process involving enones and catalyzed by salt **1a** proceeded through a domino Michael addition–intramolecular aldol sequence, thus providing direct access to 5-hydroxyisoxazolidines **6**—useful chiral building blocks[13]—in high yield and with very high stereocontrol (*ee* values ranging from 93 to 99%). As highlighted in Table 1,

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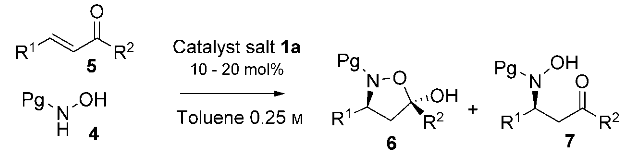
Table 1: Scope of the enantioselective amine conjugate addition to enones.[a]

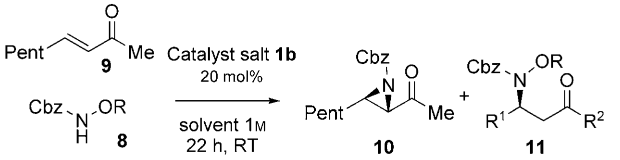


4a: Pg = Cbz; **4b**: Pg = Boc
4c: Pg = CO_2Et

Entry	4	R^1	R^2	*T* [°C], *t* [h]	**6**:**7**[b]	Yield [%][c]	*ee* [%][d]
1	**a**	pentyl	Me	RT, 72	8:1	(**a**) 85	99
2	**b**	pentyl	Me	RT, 72	9.5:1	(**b**) 77	99
3	**c**	pentyl	Me	RT, 72	6:1	(**c**) 43	99
4	**a**	Me	Me	RT, 72	3:1	(**d**) 63	95
5[e]	**a**	Ph	Me	30, 72	7.5:1	(**e**) 78	94
6[e]	**a**	*p*-Cl-C_6H_4	Me	30, 72	5.5:1	(**f**) 68	93
7[e]	**a**	Ph	Ph	50, 96	1:3	(**g**) 51	95
8[e]	**a**	CO_2Et	Me	30, 72	9.5:1	(**h**) 65	95
9	**a**	$(CH_2)_3$		0, 40	0:100	(**i**) 85	95

[a] Reactions carried out on a 0.2 mmol scale with 1.2 equiv of **4** and 10 mol% of the catalyst salt **1a**, unless otherwise noted. [b] Determined by ^{1}H NMR analysis. [c] Overall yield of isolated products (sum of **6** and **7**). [d] Determined by chiral HPLC analysis. [e] 20 mol% of the catalyst **1a**.

Table 2: Selected screening results for the aziridination of enones.[a]



8a: R = Ac; **8b**: R = Mesyl
8c: R = Tosyl

Entry	8	Solvent	Additive (2 equiv)	Conv.[b]	**10**:**11**[b]	d.r.[b]	*ee* [%][c]
1	**a**	toluene	–	21	1:99	–	77[d]
2	**b**	toluene	–	67	1.1:1	–	86
3	**c**	toluene	–	78	4.3:1	4:1	81
4	**c**	H_2O	–	57	4:1	7:3	79
5	**c**	THF	–	58	2:1	5.6:1	82
6	**c**	$CHCl_3$	–	65	7.3:1	7.5:1	89
7[e]	**c**	$CHCl_3$	–	56	9:1	9:1	95
8[e]	**c**	$CHCl_3$	$K_2CO_{3\,(s)}$	<10	$>99:1$	–	–
9[e]	**c**	$CHCl_3$	$NaHCO_{3\,(aq)}$	45	$>99:1$	$>19:1$	80
10[e]	**c**	$CHCl_3$	$NaHCO_{3\,(s)}$	>95	$>99:1$	19:1	96

[a] Unless otherwise noted, the reactions were carried out on a 0.1 mmol scale with 2 equiv of **9** and $[\mathbf{8}]_0 = 1$ M for 22 h in the presence of 20 mol% of the catalyst salt combination **1b** (30 mol% of **3** and 20 mol% of **2**). [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by chiral HPLC analysis. [d] *ee* value of compound **11**. [e] $[\mathbf{9}]_0 = 0.25$ M and 1.2 equiv of **8c** were employed.

variation of the carbamate protecting group from benzyloxycarbonyl (Cbz) to Boc or CO_2Et can be realized without loss in enantiocontrol (Table 1, entries 1–3). Importantly, a wide variety of different unsaturated ketones can be efficiently activated by catalyst **1a**: both linear compounds, including chalcone (Table 1, entry 7), a particularly challenging class of substrates for iminium catalysis, and a cyclic enone (Table 1, entry 9) afforded the expected products in high optical purity. The partitioning between the tandem or the conjugate addition products **6** and **7**, respectively, is strongly dependent on the electronic as well as the steric contribution of the R^2 substituent of enone **5**.

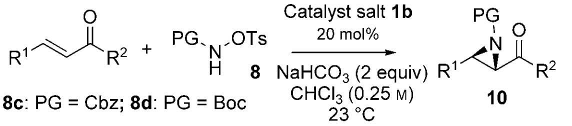
Next, we moved toward the principal aim of our investigations, the development of a domino conjugate-cyclization sequence, leading to chiral aziridines. From the outset, we recognized the choice of the nitrogen-atom source as the crucial parameter for developing an efficient aziridination methodology. As planned in Scheme 1, a suitable compound should first act as a nucleophile under iminium catalysis by **1**, affording a stereoselective heteroatom addition step, and then should become electrophilic to facilitate the enamine-catalyzed cyclization step.

To assess the feasibility of such an organocatalytic aziridination strategy, we examined the reaction of enone **9** with different nitrogen-based reagents **8**. Selected results of the extensive screening of the reaction conditions by using the catalyst salt combination **1b** (1.5 equiv of **3** relative to **2**) are reported in Table 2.[14] The acylated hydroxycarbamate **8a**, which was employed in the aziridination of enals under secondary amine catalysis,[7] provided only the conjugate addition product **11** (Table 2, entry 1). Gratifyingly, installing a better leaving group such as a tosyl moiety (**8c**; Table 2, entry 3) allowed selective partitioning of the reaction manifold toward the tandem sequence, leading to the desired aziridine **10** as the major product. Further optimization of the standard reaction parameters revealed that the choice of solvent (compare Table 2, entries 3–6), the reagent concentration, and the stoichiometric ratio of the reagents (Table 2, entry 7) were important factors in the efficiency and generality of the catalytic system. Finally, we envisaged that the *p*-toluenesulfonic acid, generated during the enamine-induced ring-closing step when using **8c**, may affect the activity of the catalyst. We reasoned that the presence of an inorganic base could have a beneficial effect on both the reaction rate and the selectivity of the aziridination. Carrying out the aziridination in $CHCl_3$ with $[\mathbf{9}]_0 = 0.25$ M, 1.2 equivalents of **8c**, and 2 equivalents of solid $NaHCO_3$ induced higher chemo-, diastereo-, and enantioselectivity (Table 2, entry 10). These catalytic conditions were selected for further exploration aimed at expanding the scope of this transformation.

As highlighted in Table 3, the method proved to be successful for the synthesis of a wide range of *N*-Cbz as well as *N*-Boc ketoaziridines **10** in good yield and with high levels of stereoselectivity (single diastereoisomer and very high *ee* values, up to 99%). By adjusting the reaction time, it was also possible to decrease the catalyst loading to 5 mol% without affecting the efficiency of the system (Table 3, entry 4).

Importantly, there appears to be significant tolerance toward steric and electronic demands of the β-olefin substituent to enable access to a broad variety of both aliphatic (Table 3, entries 1–6) and aromatic aziridines (Table 3, entries 7 and 8). Moreover, the presented protocol is also effective with cyclohexenone, affording the desired cyclic aziridine **10h** in very high optical purity (Table 3, entry 9). This result has significant consequences from a synthetic

Table 3: Asymmetric organocatalytic aziridination of enones.[a]

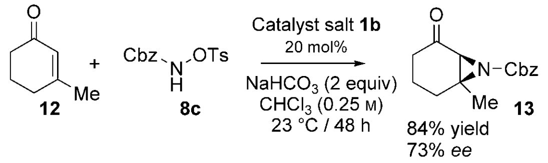


Entry	R^1	R^2	PG	**10**	*t* [h]	Yield[b]	d.r.[c]	*ee* [%][d]
1	pentyl	Me	Cbz	**a**	24	93	19:1	96
2	pentyl	Me	Boc	**b**	24	82	>19:1	99
3	Me	Me	Cbz	**c**	16	96	>19:1	93
4[e]	Me	Me	Cbz	**c**	72	79	>19:1	93
5	Me	Et	Cbz	**d**	48	94	19:1	98
6	CO_2Et	Me	Cbz	**e**	48	74	>19:1	95
7	Ph	Me	Cbz	**f**	72	85	>19:1	73
8	*p*-NO_2-C_6H_4	Me	Cbz	**g**	72	92	>19:1	99[f]
9	$(CH_2)_3$		Cbz	**h**	20	86	>19:1	98

[a] The reactions were carried out on a 0.2 mmol (0.25 M) scale with 1.2 equiv of **8** and 20 mol% of the catalyst salt combination **1b** at room temperature in $CHCl_3$. [b] Yield of isolated product. [c] Determined by ^1H NMR analysis of the crude mixture. [d] Determined by chiral HPLC analysis. [e] 5 mol% of the catalyst salt **1b** was employed. [f] The absolute configuration of **10g** was determined to be 2*S*,3*R* by means of TD-DFT calculations of the electronic circular dichroism spectra; see the Supporting Information for details.

standpoint since, to our knowledge, a highly enantioselective aziridination of cyclic enones has not yet been described.

Along this line, we investigated the aziridination of β-substituted cyclohexenone **12** [Eq. (1)], leading to product **13**



(1)

having a quaternary stereocenter with interesting enantioselectivity.[15] Although the catalytic system needs further optimization to enhance the level of enantioselectivity for such a class of substrates, the extension to cyclic enones opens up new opportunities to expand the synthetic potential of this asymmetric aziridination strategy.

In summary, we have reported an asymmetric amine conjugate addition to enones that provides a suitable platform for developing an unprecedented example of highly chemo- and stereoselective aziridinations of both linear and cyclic α,β-unsaturated ketones. The method, which affords valuable N-Cbz- as well as N-Boc-protected aziridines with almost complete diastereocontrol and very high enantioselectivity (up to 99% *ee*), exploits the ability of the readily available chiral primary amine catalyst salt **1** to promote a domino iminium–enamine intramolecular sequence. Our current studies focus on expanding the catalytic system to more elaborated multicomponent, domino transformations.

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