Organocatalysis

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Imidazolidinone-Derived Enamines: Nucleophiles with Low Reactivity**

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Dedicated to Professor Wolfgang Beck on the occasion of his 80th birthday

During the last decade the concept of enamine activation has become a powerful tool in asymmetric synthesis. It uses chiral secondary amines as catalysts to activate saturated carbonyl compounds by conversion into enamines.[1] Among various catalysts tested, diarylprolinol silyl ether **1b** was found to be particularly useful for the stereoselective introduction of different functionalities to the α-position of aldehydes.[2,3]

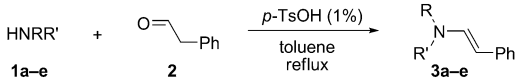
Imidazolidinones **1c–e** (Table 1), which have been used extensively in iminium catalysis,[4] are less effective in enamine-activated processes unless strong electrophiles are employed. Typical examples are enantioselective α-halogenations[5] and α-alkylations of aldehydes with stabilized carbocations which were in situ generated by treatment of alcohols with acids.[6] Mechanistic investigations, focusing on the characterization and reactivities of the intermediate enamines, are rare.[7–9]

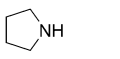
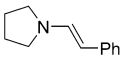
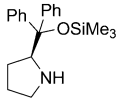
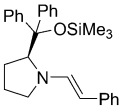
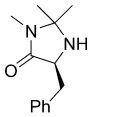
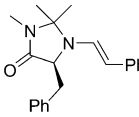
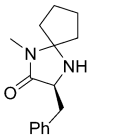
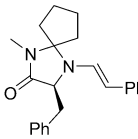
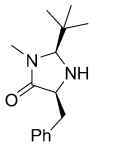
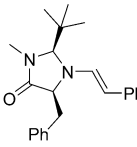
While the synthesis and the X-ray structure of the enamine **3b** have previously been described by Seebach et al.,[8] we are not aware of any X-ray structures of enamines derived from imidazolidinones. Gellman et al. used ^{1}H NMR spectroscopy to characterize the enamine generated from imidazolidinone **1c** and 3-phenylpropanal in DMSO solution and reported its reaction with methyl vinyl ketone catalyzed by 4-ethoxycarbonylcatechol.[9]

In order to elucidate the relationships between structure and reactivities of enamines derived from **1a–e**, we have now synthesized the enamines **3a–e**, performed X-ray analyses of **3d** and **3e**, and measured the kinetics of their reactions with the stabilized benzhydrylium ions **4a–h** (Table 2).

Enamines **3c–e**, which had not been isolated previously, were obtained by refluxing phenylacetaldehyde (**2**) and the amines **1c–e** in the presence of 1 mol% of *p*-toluenesulfonic acid in toluene under argon using a Dean–Stark apparatus filled with molecular sieves (4 Å) to remove the generated water.[10] After evaporation of the solvent, **3e** was immediately obtained as a crystalline material in 87% yield, while column chromatography was employed to separate the enamines **3c** and **3d** from the nonreacted imidazolidinones **1c** and **1d**, respectively.

Table 1: Amines **1a–e** and the corresponding phenylacetaldehyde-derived enamines **3a–e**.



Amine		Product		Yield [%]
	**1a**		**3a**	86[a]
	**1b**		**3b**	35[b]
	**1c**		**3c**	44[c]
	**1d**		**3d**	32[c]
	**1e**		**3e**	87[d]

[a] After distillation. [b] **3b** was prepared by heating **1b** and **2** in benzene at reflux following a procedure described by Seebach (Ref. [8]). After solvent removal and crystallization from Et_2O, **3b** was obtained as a pure material. [c] After column chromatography. [d] After crystallization.

Crystals of **3d** and **3e** suitable for X-ray analysis were grown by the vapor diffusion crystallization method in diethyl ether/*n*-pentane mixtures. As shown in Figure 1,[11] the C–N bond between the heterocyclic ring and the *E*-configurated C=C bond has *s*-trans conformation in both enamines **3d** and **3e**. Whereas the benzylic phenyl group is located over the imidazolidinone ring in **3d**, possibly because of stabilizing CH–π interactions (London dispersion interaction between the phenyl ring and the cyclopentane ring),[12] the benzyl group is located over the C=C bond in the enamine **3e** and thus directs electrophiles to the *Si* face of the C=C bond.[5] NMR spectroscopy showed that the conformations of **3d** and **3e**, which were observed in the crystals, also dominate in $CDCl_3$ solution (see the Supporting Information).

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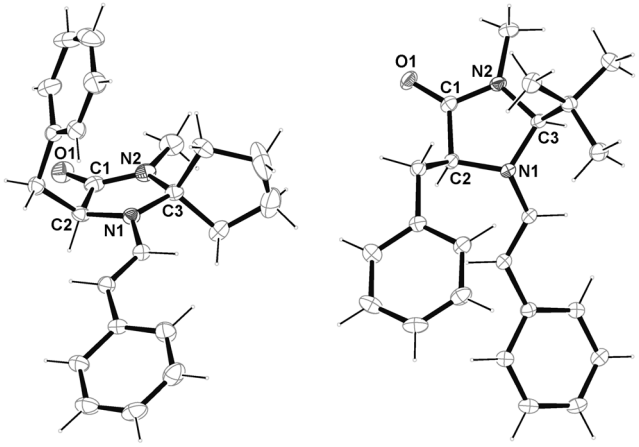


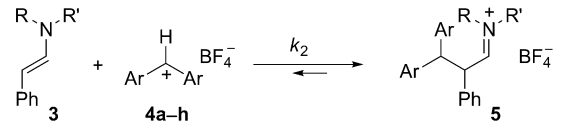
Figure 1. Crystal structures of the enamines **3d** (left) and **3e** (right).

From the pyramidalization parameter Δ, defined by Dunitz as the distance between the N atom and the plane formed by the three attached carbon atoms,[13] one can derive that the almost planar sp^2-hybridized nitrogen in **3b** ($\Delta =$ 0.037 Å)[8] adopts more and more sp^3 character as one moves to **3d** ($\Delta = 0.155$ Å) and eventually to **3e** ($\Delta =$ 0.293 Å).

In order to quantify the nucleophilic reactivities of **3a–e** we have studied the kinetics of their reactions with the benzhydrylium ions **4a–h** (Table 2), which have been used as reference electrophiles for the construction of comprehensive nucleophilicity scales on the basis of Equation (1). Herein, nucleophiles are characterized by two parameters (nucleophilicity N and sensitivity parameter s_N) and electrophiles by one parameter (electrophilicity E).[14]

$$\lg k_2(20\,^{\circ}\mathrm{C}) = s_N(N + E) \qquad (1)$$

As described previously,[14b] the rates of the reactions of carbocations **4** with the enamines **3a–e** were measured photometrically by following the disappearance of the UV/Vis absorbances of the diarylcarbenium ions **4** (Scheme 1), using conventional and stopped-flow instruments. All kinetic experiments were performed at 20 °C in acetonitrile with a large excess of the enamines **3a–e** in order to achieve conditions for first-order kinetics.



Scheme 1. Reactions of the enamines **3** with the carbocations **4** in acetonitrile at 20 °C.

The first-order rate constants k_{obs} were obtained by least-squares fitting of the function $A_t = A_0 \exp(-k_{obs}t) + C$ to the time-dependent absorbances of the electrophiles. Plots of k_{obs} versus the concentrations of the nucleophiles [**3**] were linear, as exemplified in Figure 2. The slopes of these plots gave the second-order rate constants k_2 (in $M^{-1}s^{-1}$), which are summarized in Table 3.

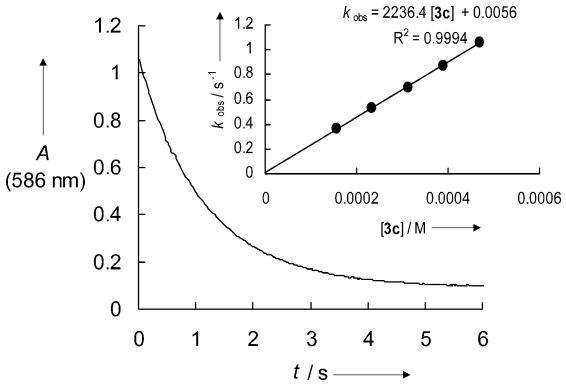
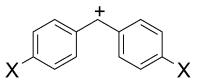
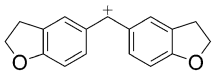
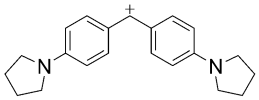
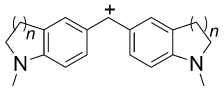


Figure 2. Exponential decay of the absorbance at 586 nm during the reaction of **4c**-BF_4^- (1.60×10^{-5} M) with **3c** (3.90×10^{-4} M). Inset: Plot of the rate constants k_{obs} versus [**3c**] (20 °C in CH_3CN).

Table 2: Reference electrophiles **4a–h**.

		E[a]
		
	**4a**	−1.36
X = N(Ph)CH_2CF_3	**4b**	−3.14
X = N(Me)CH_2CF_3	**4c**	−3.85
X = N$(CH_2CH_2)_2$O	**4d**	−5.53
X = NMe_2	**4e**	−7.02
	**4f**	−7.69
	**4g** ($n=2$)	−8.22
	4h ($n=1$)	−8.76

[a] Electrophilicity parameters E from Ref. [14b].

Plots of $\lg k_2$ versus the empirical electrophilicity parameters E are linear for all reactions studied in this investigation (Figure 3), indicating that Equation (1) can be used to determine N and s_N parameters for the enamines **3a–e** (Table 3).

One can see that the enamine **3b**, which is derived from the Hayashi–Jørgensen catalyst **1b**, is almost two orders of magnitude less reactive than **3a**, the parent compound of this series. As one of the diastereotopic faces of **3b** is completely open for electrophilic attack, the reduction of reactivity must predominantly be due to the electron-withdrawing inductive effect of the trimethylsiloxybenzhydryl group in **3b**.

The inductive electron-withdrawing effect of the extra endocyclic amido group in the imidazolidinone derivatives **3c** and **3d**, the pyramidalization of the enamine nitrogen, and the steric shielding of both faces of the C=C bond by the two alkyl groups at the 2-position of the imidazolidinone ring reduce

Table 3: Second-order rate constants k_2 for the reactions of the carbocations **4a–h** with the enamines **3a–e** (acetonitrile, 20 °C).

Enamine	R^+	k_2 [$M^{-1}s^{-1}$]	N, s_N
3a	**4e**	1.38×10^5	12.25, 0.99
	4f	3.48×10^4	
	4g	9.94×10^3	
	4h	2.64×10^3	
3b	**4d**	1.48×10^5	10.56, 1.01
	4e	2.33×10^3	
	4h	7.94×10^1	
3c	**4a**	4.73×10^6	7.20, 1.14
	4b	7.80×10^4	
	4c	2.24×10^3	
	4d	1.15×10^2	
3d	**4b**	2.77×10^5	7.92, 1.07
	4c	7.26×10^3	
	4d	4.93×10^2	
3e	**4b**	3.46×10^2	5.80, 0.87
	4c	2.56×10^1	
	4d	2.13	

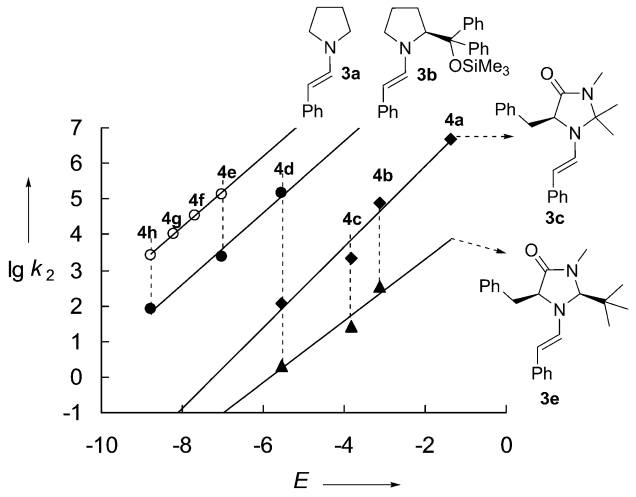


Figure 3. Plots of $\lg k_2$ for the reactions of **3a–c**, and **3e** with the benzhydrylium ions **4** in CH_3CN at 20 °C versus the corresponding electrophilicity parameters E. (Correlation for **3d** is omitted for the sake of clarity; it is shown on page S19 of the Supporting Information).

the nucleophilicities of these enamines by another two to three orders of magnitude relative to **3b**.

As the C=C bond of **3e** has one open face, its low nucleophilicity (10^2 times less than that of **3c** and **3d**) must be due to the enhanced pyramidalization of the enamine nitrogen in **3e** (X-ray structure, Figure 1), which strongly reduces the electron density in the C=C bond.[15]

While the interpretation of the NMR chemical shifts of the β-protons in **3a–e** is problematic because of the anisotropy of the phenyl groups, the ^{13}C NMR chemical shifts show the lower electron densities at the β carbon of the imidazolidinone-derived enamines **3c–e** (Table 4).

Table 4: NMR chemical shifts ($CDCl_3$) of the enamines **3a–e**.

enamine	$\delta(C^\beta$–$H)$ [ppm]	$\delta(C^\beta)$ [ppm]
3a	5.18	97.4
3b	5.02[a]	97.2[a]
3c	5.47	101.9
3d	5.47	102.1
3e	4.76	102.9

[a] From Ref. [8b].

The fact that **3b** has significantly higher nucleophilicity than **3c–e** may explain why **1b** is a more suitable catalyst than **1c–e** for most enamine-activated reactions.

By using the N and s_N values of **3b** (Table 3) and the E values of Michael acceptors,[14f] Equation (1) allows one to predict whether a reaction may take place at room temperature. Hayashi's observation that **1b** catalyzes Michael additions of aldehydes to β-nitrostyrenes[16] is in line with a calculated second-order rate constant ($k_{calcd} = 4.8\times10^{-4}\,M^{-1}s^{-1}$) for the reaction of **3b** with β-nitrostyrene ($E = -13.85$).[17] It has been shown, however, that the initially generated zwitterions from the enamines and nitrostyrene collapse with formation of cyclobutanes, the ring opening of which is the rate-determining step of the catalytic cycle.[7e,18] For that reason, a sufficiently fast reaction of the enamine with the Michael acceptor is only one of the criteria that have to be fulfilled for a catalytic cycle to proceed.

The more than 100 times higher nucleophilicity of **3b** compared with **3c**,**d** may also rationalize the fact that **1b** and not **1c–e** are usually employed as catalysts for Mannich-type reactions of imines with aldehydes.[19] In line with the low nucleophilicity of **3c–e** Gellman et al reported that **1c**-catalyzed conjugate additions of aldehydes to enones require Brønsted acids as cocatalysts to activate the enones.[9]

In summary, we have described the first X-ray structures of enamines derived from imidazolidinones. Nucleophilic reactivities of these enamines have been determined from the kinetics of their reactions with diarylcarbenium ions **4**, which showed that the enamine **3b**, derived from the Hayashi–Jørgensen catalyst, is 10^3 to 10^5 times more nucleophilic than the enamines derived from the imidazolidinones **1c–e**.

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Communications

Organocatalysis

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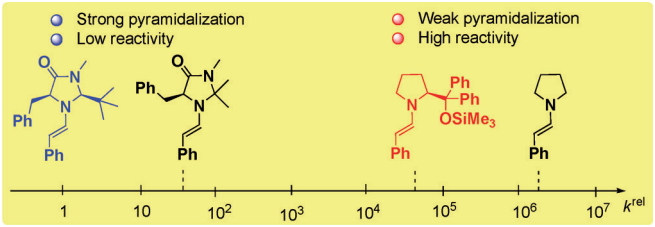
Imidazolidinone-Derived Enamines: Nucleophiles with Low Reactivity



Extraordinarily weak nucleophiles: Enamines derived from imidazolidinones are 10^3–10^5 times less reactive than those derived from the Hayashi–Jørgensen catalyst. This finding explains the lower activity of MacMillan catalysts for enamine-activated reactions.