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Kinetic Evidence for the Formation of Oxazolidinones in the Stereogenic Step of Proline-Catalyzed Reactions**

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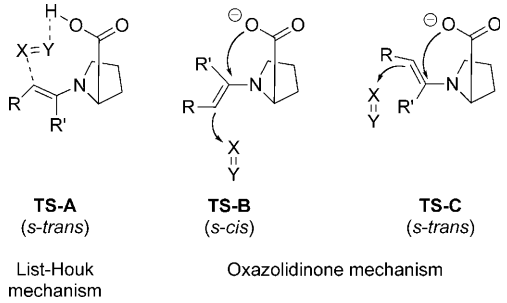
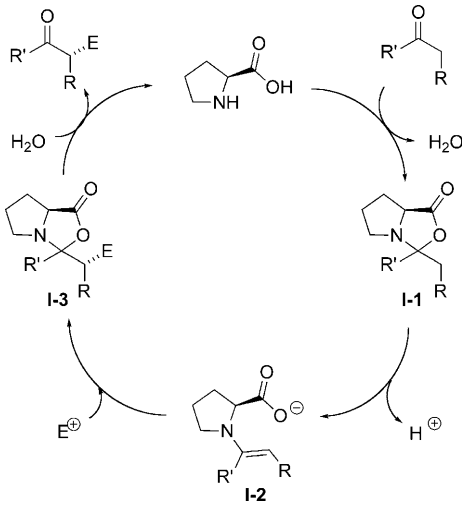
The stereoselectivity of proline-catalyzed reactions of aldehydes or ketones with electrophiles[1] is usually rationalized by the activation of the electrophile through the proton of the carboxy group as depicted in the List–Houk transition state (**TS-A**) in Scheme 1.[2] Oxazolidinone formation was generally considered an unproductive dead end of the reaction cascade[2g] until Seebach, Eschenmoser et al. suggested that oxazolidinones, rather than being "parasitic species", may also play a decisive role in determining the stereochemical course of proline-catalyzed reactions.[3] In this mechanism (Scheme 2) proline and the carbonyl compound combine with formation of the oxazolidinone **I-1**, which undergoes ring opening to furnish the *s-cis* and/or *s-trans* conformer of the enaminocarboxylate **I-2**. In order to account for the observed stereoselectivities, it was assumed that **TS-B** (Scheme 1), which yields the more stable oxazolidinone, is favored over the stereoelectronically preferred **TS-C**.[3]



Scheme 1. Transition-state models for the proline-catalyzed reactions of carbonyl compounds with electrophiles.



Scheme 2. The crucial role of oxazolidinones in proline-catalyzed reactions according to Seebach, Eschenmoser et al.[3]

Support for the involvement of the enamine carboxylate **I-2** has recently been provided by Blackmond, Armstrong et al., who reported that the enantioselectivity of proline-catalyzed reactions of aliphatic aldehydes with azodicarboxylates is reversed in the presence of tertiary amines.[4] This reversal was explained by a change from **TS-A** to **TS-C** in the presence of amines, where the attack of the electrophile occurs at the *s-trans* isomer of the enamine carboxylate. The role of the carboxylate group could not be clarified, however, and it was suggested that CO_2^- either acts as a steric blocking group, or in accordance with Seebach, Eschenmoser et al., participates in the addition step.[4]

Traditionally, anchimeric assistance (neighboring-group participation) has been derived from stereochemical as well as kinetic investigations in a variety of reactions, e.g., solvolytic displacement reactions, electrophilic additions, and eliminations.[5] Owing to the conformational flexibility of the intermediate enamines stereochemical investigations did not provide unequivocal evidence for or against the formation of oxazolidinones in the stereogenic step.[1e] Therefore, we approached this problem with kinetic methods.

In order to separate steric and electronic effects, we studied the kinetics of the reactions of the proline, pyrrolidine, and proline methyl ester derived enamines $\mathbf{1}^-$, **2**, and **3** with the benzhydrylium ions **4a–4f** and the quinone methides **4g–j** (Table 1). As shown previously, their electrophilicities

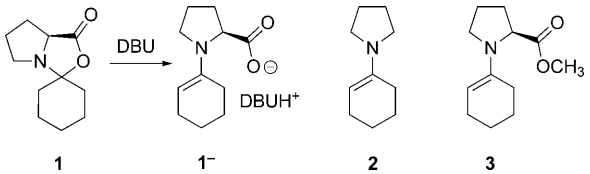


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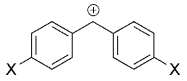
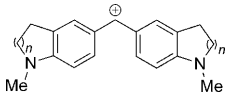
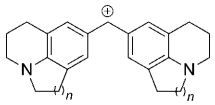
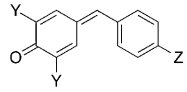
Table 1: Benzhydrylium ions **4a–f** and quinone methides **4g–j** employed as reference electrophiles.

Electrophile			E[a]
4a		X = NMe_2	−7.02
4b		X = $N(CH_2)_4$	−7.69
4c		n = 2	−8.22
4d		n = 1	−8.76
4e		n = 2	−9.45
4f		n = 1	−10.04
4g		Y = Ph; Z = OMe	−12.18
4h		Y = Ph; Z = NMe_2	−13.39
4i		Y = *t*Bu; Z = NO_2	−14.36
4j		Y = *t*Bu; Z = Me	−15.83

[a] Empirical electrophilicity parameter E for **4a–f** from Ref. [6]; E for **4g–j** from Ref. [7].

can be fine-tuned by variation of the *para* and *meta* substituents, while the steric surroundings of the reaction centers are kept constant.[6] The empirical electrophilicity parameters listed in Table 1 show a continuous decrease of reactivity from top to bottom by 8 orders of magnitude.

The prolinium trifluoroacetate catalyzed reaction of cyclohexanone with 4,4′-bis(dimethylamino)benzhydrol (**4a**-OH) was recently reported by Cheng et al. to yield (*S*)-**5a** with 16% *ee*.[8] Under the same conditions we obtained (*S*)-**5a** with an enantioselectivity of 24% *ee*(Scheme 3). The corresponding reaction of the benzhydrylium salt **4a**-[BF_4] with the enaminocarboxylate **1**$^-$, which was obtained by treatment of the oxazolidinone **1** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), gave (*R*)-**5a** with 25% *ee*. The reaction of the quinone methide **4j** with **1**$^-$ yielded the α-substituted cyclohexanone **5j** with 81% *de*. While the enantiomeric excess of the major diastereomer could not be determined, an *ee* value of 53% was found for the minor diastereoisomer. The reaction of **4a**-[BF_4] with the proline ester **3** yielded **5a** almost in racemic form (0.7% *ee*).

The rates of the reactions of **1**$^-$, **2**, and **3** with the electrophiles **4** were determined photometrically in CH_3CN at 20 °C by following the decrease of the absorbances of the colored electrophiles **4**. Reactions with $k_2 < 10^6\,M^{-1}s^{-1}$ were studied with stopped-flow techniques, while the laser-flash-photolytic generation of benzhydrylium ions was employed for determining rate constants $k_2 > 10^6\,M^{-1}s^{-1}$ as described previously.[9] By using the enamines **1**$^-$, **2**, and **3** in high excess relative to the electrophiles **4**, first-order conditions were achieved, and the first-order rate constants k_{obs} were obtained from the observed mono-exponential decays (Figure 1). From the linear plots of k_{obs} versus the concentrations [**1**$^-$], [**2**], or [**3**] the second-order rate constants k_2 were obtained which are listed in Table 2.

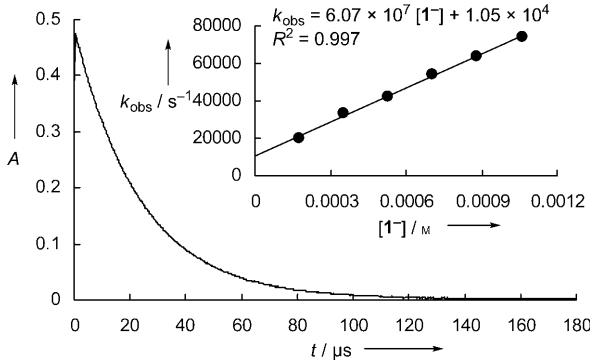
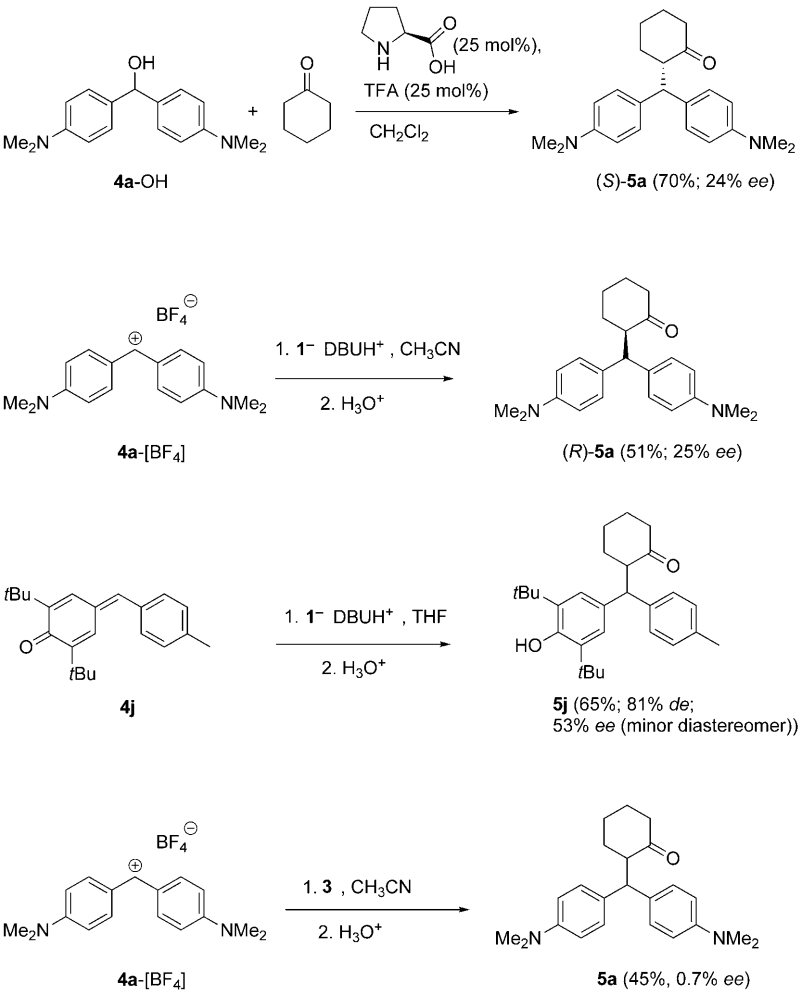


Figure 1. Exponential decay of the absorbance A at 611 nm during the reaction of **1**$^-$ (5.27×10^{-4} M) with laser-flash-photolytically generated **4b** at 20 °C in acetonitrile ($k_{obs} = 4.25\times10^4\,s^{-1}$). Inset: Determination of the second-order rate constant ($k_2 = 6.07\times10^7\,M^{-1}s^{-1}$) as the slope of the correlation between the first-order rate constant k_{obs} and the concentration of the enamine **1**$^-$.



Scheme 3. Stereoselectivities of the reactions of cyclohexanone-derived enamines with the reference electrophiles **4a** and **4j** (TFA = trifluoroacetic acid).

Table 2: Second-order rate constants for the reactions of $\mathbf{1}^-$, **2**, and **3** with reference electrophiles **4** in acetonitrile at 20 °C.

Nucleophile	Electrophile	k_2 [$M^{-1}s^{-1}$]	Nucleophile	Electrophile	k_2 [$M^{-1}s^{-1}$]
$\mathbf{1}^-$	**4b**	6.07×10^7	**2**	**4d**	2.12×10^5
	4c	3.03×10^7		**4e**	7.62×10^4
	4d	1.31×10^7		**4f**	3.25×10^4
	4g	4.41×10^4	**3**	**4c**	3.74×10^4
	4h	1.35×10^4		**4d**	1.40×10^4
	4i	8.58×10^2		**4e**	5.98×10^3
2	**4c**	6.43×10^5		**4f**	2.02×10^3

While the enamines **2** and **3** were used as pure samples, solutions of $\mathbf{1}^-$ were freshly prepared by treatment of **1** with one equivalent of DBU.[3] The quantitative conversion of **1** to $\mathbf{1}^-$ under these conditions was demonstrated by kinetic investigations with solutions obtained from **1** with 0.95 or 1.3 equivalents of DBU.[10] Details are given in the Supporting Information.

The second-order rate constants for the reactions of **2** with **4c–f** in acetonitrile (Table 2) deviate from those previously measured in dichloromethane solution[11] by less than a factor of 3, in line with our previous observations that the rates of the reactions of carbocations with neutral π systems are only slightly affected by the nature of the solvent.[12] Plots of the logarithms of the second-order rate constants against the empirical electrophilicity parameters E of the reference electrophiles **4** are linear, showing that Equation (1)[13] is applicable (Figure 2). This allows us to calculate the nucleophilicity parameter N and the nucleophile-specific slope parameter s for the enamines $\mathbf{1}^-$ ($N=18.86$; $s=0.70$), **2** ($N=16.42$; $s=0.70$), and **3** ($N=14.96$; $s=0.68$) in acetonitrile.

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

The enamine ester **3** is about 15 times less reactive than the unsubstituted enamine **2**, which reflects the electron-withdrawing effect of the ester group. In contrast, the enamino carboxylate $\mathbf{1}^-$ is 50 to 60 times more reactive than **2** and even 800 to 900 times more reactive than **3** (Table 2, Figure 2). In line with earlier observations that the reactions of ordinary enamines with the quinone methides **4g–i** in dichloromethane solution are thermodynamically unfavorable, **2** was now found not to react with **4g–i**.[14]

Can one rule out that the second-order rate constants listed for $\mathbf{1}^-$ in Table 2 reflect the rates of addition of the carboxylate group to the electrophiles **4** while the isolated products **5** are the result of thermodynamic product control? This possibility can be rigorously excluded for the reactions of $\mathbf{1}^-$ with the quinone methides **4g–i**, as no decrease of absorbance was observed when these electrophiles were combined with carboxylate ions, for example tetrabutylammonium acetate in acetonitrile (thermodynamically unfavorable). The disappearance of the benzhydrylium ions **4b–d** in the reactions with $\mathbf{1}^-$ also cannot be explained by initial reactions of the carbocations with the carboxylate group, because previous studies on the kinetics of the reactions of the amino-substituted benzhydrylium ions **4a–f** with tetrabutylammonium acetate[15] have shown that the reactions with carboxylate anions are approximately 10 times slower than the reactions with $\mathbf{1}^-$, which are reported in Table 2.

Two reasons may account for the fact that $\mathbf{1}^-$ is by far the most reactive enamine of this series (Figure 2). One is anchimeric assistance of the electrophilic attack by the carboxylate group as shown in **TS-B/C** of Scheme 1. The second is electrostatic attraction between the cationic electrophiles and the anionic nucleophile $\mathbf{1}^-$, which may contribute in the reactions with the benzhydrylium ions **4b–d**. From the comparison of the rate constants for the reactions of **4a** with aniline ($k_2=7.16\times10^3\,M^{-1}s^{-1}$)[16] and the 3-aminobenzenesulfonate anion ($k_2=7.68\times10^4\,M^{-1}s^{-1}$) in acetonitrile, one can deduce that Coulombic attractions may be responsible for an acceleration of the cation–anion combinations in acetonitrile by a factor of approximately 10.[17] As a consequence, Coulomb attraction can only partially account for the high reactivity of $\mathbf{1}^-$ with **4b**, **4c**, and **4d**, and anchimeric assistance by the carboxylate group must play a significant role.

This interpretation is corroborated by comparing the reactivities of the enamines $\mathbf{1}^-$ and **2** toward the neutral electrophiles β-nitrostyrene (**6**) and di-*tert*-butyl azodicarboxylate (**7**), where Coulombic attractions cannot contribute (Scheme 4). The observation that enaminocarboxylate $\mathbf{1}^-$ reacts 107 times faster with β-nitrostyrene (**6**), but only 6 times faster with azodicarboxylate **7** than enamine **2** (Table 3) indicates that the magnitude of the anchimeric assistance is strongly dependent on the nature of the electrophiles.

The kinetic data presented herein thus provide clear evidence for anchimeric assistance by the carboxylate group in electrophilic additions to the enaminocarboxylate $\mathbf{1}^-$. In combination with the

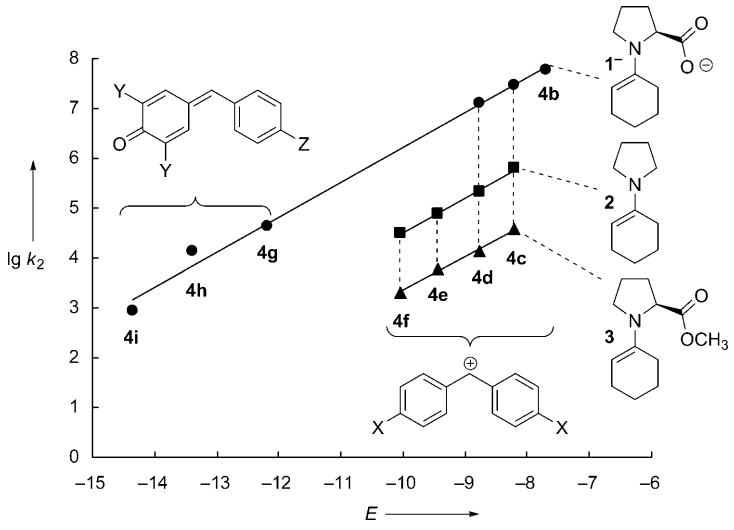
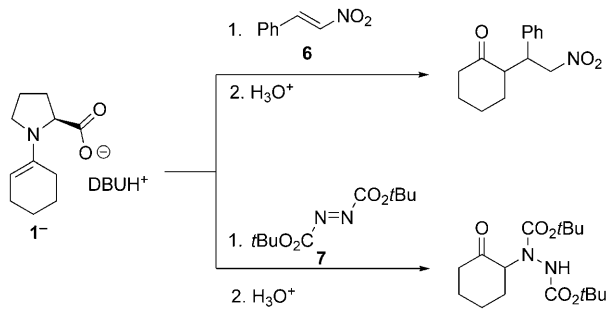


Figure 2. Plots of $\lg k_2$ for the reactions of the enamines $\mathbf{1}^-$, **2**, and **3** with the reference electrophiles **4b–i** at 20 °C in acetonitrile versus their electrophilicity parameter E.



Scheme 4. Reactions of **6** [3,18] and **7** with enamine **1**$^-$.

Table 3: Second-order rate constants for the reactions of **1**$^-$ and **2** with **6** and **7** in acetonitrile at 20 °C.

Electrophile	Nucleophile	k_2 [$M^{-1}\,s^{-1}$]
6	**1**$^-$	2.43×10^3
	2	2.27×10^1
7	**1**$^-$	1.80×10^3
	2	2.99×10^2[a]

[a] From Ref. [19].

results from the Blackmond and Armstrong groups[4] these data support the proposal that oxazolidinone formation may occur in the stereogenic step of proline-catalyzed reactions,[3] particulary in the presence of strong bases. Our results do not affect the rationalization of the stereoselectivities of a manifold of proline-catalyzed reactions by **TS-A** when the effective nucleophile is an enaminocarboxylic acid[1e,20] and not an enaminocarboxylate anion.

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