Organocatalysis

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Electrophilic Reactivities of α,β-Unsaturated Iminium Ions**

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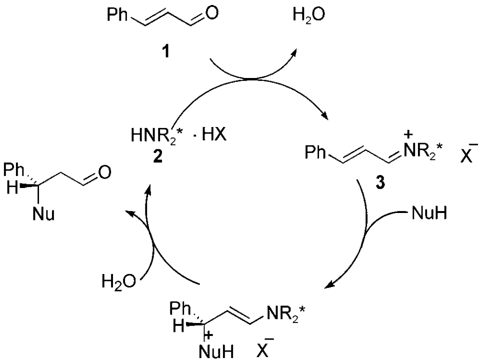
Dedicated to Professor Manfred T. Reetz on the occasion of his 65th birthday

During the last decade organocatalysis has become an important branch of organic chemistry.[1] Secondary amines have been demonstrated to activate carbonyl compounds towards attack by electrophiles (enamine[2]) and nucleophiles (iminium catalysis[3]). Scheme 1 illustrates the catalytic cycle for amine-catalyzed additions of nucleophiles to cinnamaldehyde (**1**). The cycle is initiated by the condensation of the catalyst **2** with the aldehyde **1** to produce the reactive iminium ion intermediate **3**, which is attacked by the nucleophile in the second step. In the final step, the product is released, and the catalyst is regenerated. Despite numerous applications of the iminium ion catalysis in organic syntheses, mechanistic data, which are needed to systematically optimize known processes and explore the scope and limitations, are rare. During the preparation of this manuscript, Platts, Tomkinson et al. reported kinetic and theoretical investigations of the iminium ion catalyzed Diels–Alder reaction of cinnamaldehyde with cyclopentadiene, using 2-(trifluoromethyl)pyrrolidine as the catalyst.[4] By studying the first two steps of the organocatalytic cycle separately, they concluded that the cycloaddition step is rate-determining under the specific reaction conditions used.

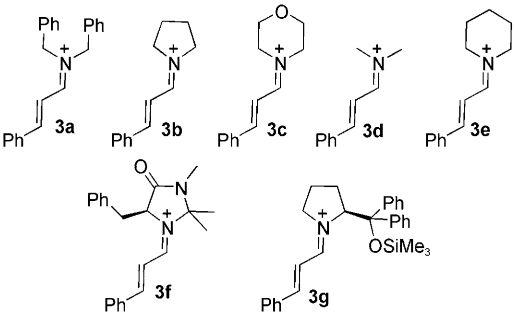


Scheme 1. Iminium catalysis in nucleophilic additions to cinnamaldehyde (**1**).

The key step in Scheme 1, as in related organocatalytic cycles employing iminium catalysis, is the reaction of an iminium ion with a nucleophile. Because reactions of carbocations and Michael acceptors with C, N, O, and P nucleophiles have previously been reported to follow Equation (1),[5] where electrophiles are characterized by one

$$\log k(20\,°\mathrm{C}) = s(N + E) \tag{1}$$

parameter (electrophilicity E) and nucleophiles are characterized by two parameters (slope s and nucleophilicity N), we assumed that the reactions of the iminium ions **3** with nucleophiles also followed this correlation. We therefore determined the electrophilicities of various iminium ions **3** (Scheme 2) derived from cinnamaldehyde (**1**) and secondary amines by studying the kinetics of their reactions with the silyl ketene acetals 2-(trimethylsiloxy)-5,6-dihydro-4*H*-pyran (**4a**) and 2-(trimethylsiloxy)-4,5-dihydrofuran (**4b**), whose N and s parameters are known.[5]



Scheme 2. Cinnamaldehyde-derived iminium ions **3a**–**g**.

MM3[6] and DFT[7a] calculations indicate the E isomer of iminium ion **3f** to be the more stable species because it avoids nonbonding interactions between the geminal methyl groups and the styryl group. This conclusion has so far not been tested experimentally, because the reaction of **1** and **2f**-HCl in CD_3OD at room temperature gives **3f**-Cl in only low conversion.[3f] As **3f**-OTf was synthesized as a pure crystalline material in this work, NOE experiments could be performed which showed strong correlations between the hydrogens as indicated in Scheme 3 (see the Supporting Information). Weak correlations between the benzylic phenyl group and one of the geminal methyl groups as well as the β-styryl proton (dotted lines in structure (E)-**3f**, Scheme 3) indicate

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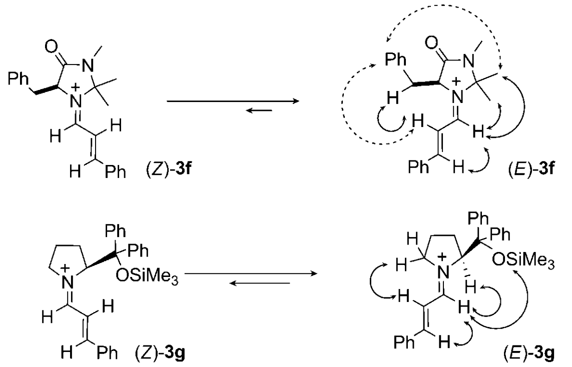
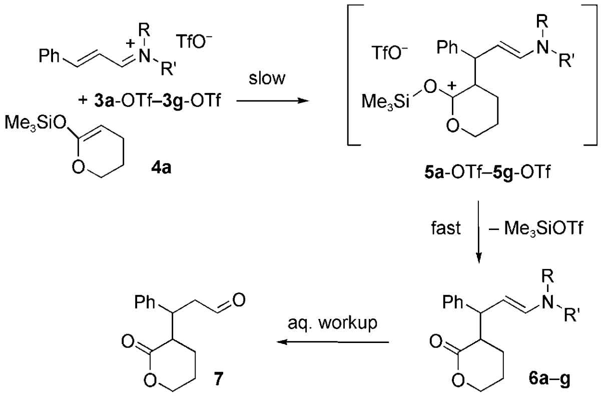


Scheme 3. Assignment of the conformations of **3f**-OTf and **3g**-OTf in $CDCl_3$ solution by NOESY spectroscopy.

the existence of at least two conformers of (*E*)-**3f**, in line with calculations by Houk et al.[7a,b] The iminium triflate **3g**-OTf was isolated as a 10:1 mixture of two stereoisomers. The NOESY spectra indicated that (*E*)-**3g**-OTf (Scheme 3) is the major component in this mixture of stereoisomers, in agreement with recent DFT calculations.[7c,d]

Treatment of **3a**-OTf–**3f**-OTf with 1.5 equivalents of ketene acetal **4a** in CH_2Cl_2 gave **7** in 22–66% yield after aqueous workup (Scheme 4). The iminium salts **3a**-OTf (d.r. 4:1) and **3f**-OTf (d.r. 9:1) reacted with higher diastereoselectivity than **3b**-OTf (d.r. 3:1), **3c**-OTf (d.r. 2:1), **3d**-OTf (d.r. 2:1), and **3e**-OTf (d.r. 3:1). When the reactions of **3b**, **3c**, and **3f** with two equivalents of **4a** were monitored by ^{1}H NMR spectroscopy in CD_2Cl_2, the quantitative formation of the enamines **6b**,**c**,**f** was observed, confirming their intermediacy in the organocatalytic cycle (Scheme 1). Compound **3g** reacted analogously; because impure material was used for the product studies a d.r. value and yield cannot be provided. The corresponding products with **4b** have not been isolated.



Scheme 4. Products of the reactions of iminium triflates **3**-OTf with silyl ketene acetal **4a**.

The kinetics of the reactions of **3a**–**g** with the ketene acetals **4a** and **4b** were determined photometrically by following the disappearance of the absorbances of the iminium ions at 340–370 nm. All kinetic experiments were performed under first-order conditions using a high excess of the nucleophiles **4a**,**b**. From the exponential decays of the UV/Vis absorbances of the electrophiles **3a**–**g**, the first-order rate constants k_{obs} were obtained. Plots of k_{obs} [s^{-1}] versus the concentration of the nucleophiles **4** were linear with negligible intercepts as required by the relation $k_{obs} = k_2[\mathbf{4}]$ (Figure 1). The slopes of these plots gave the second-order rate constants k_2 [$M^{-1}s^{-1}$], which are summarized in Table 1. The dihydrofuran **4b** was 16–40 times more reactive than the dihydropyran **4a**, in agreement with earlier investigations on **4a** and **4b**.[5] Substitution of the k_2 values (Table 1) and the known *N* and *s* parameters of **4a** and **4b**, respectively, into Equation (1) gave the electrophilicity parameters *E* by a least-squares minimization.

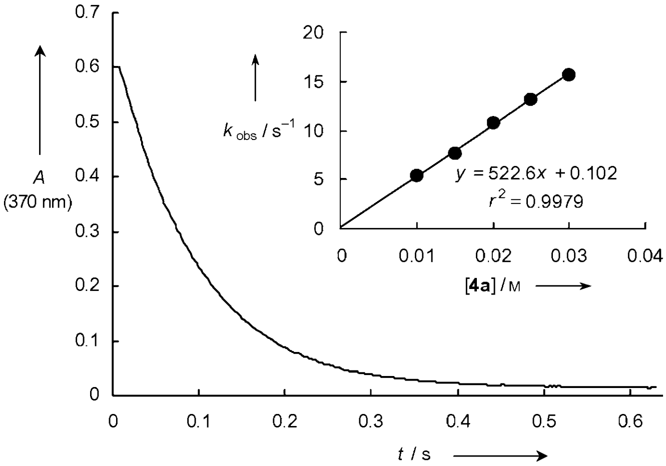


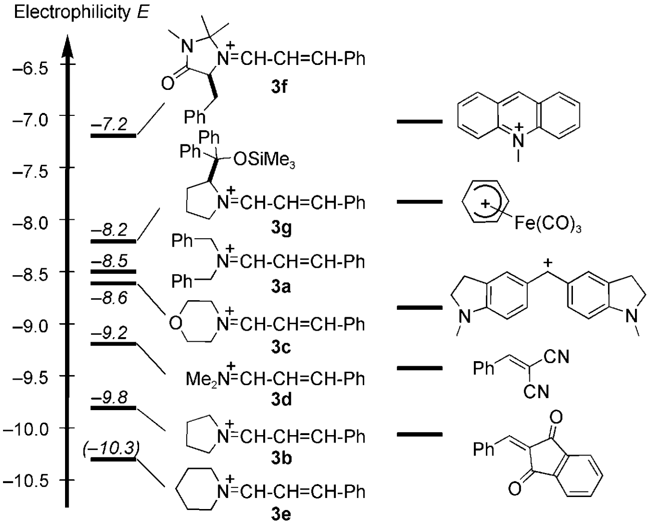
Figure 1. Exponential decay of the absorbance at 370 nm during the reaction of **3f**-OTf (4.5×10^{-5} M) with **4a** (2.0×10^{-2} M). Inset: Determination of the second-order rate constant k_2 from the dependence of the first-order rate constant k_{obs} for the reaction of **3f**-OTf with **4a** on the concentration of ketene acetal **4a** (20 °C in CH_2Cl_2).

Scheme 5 compares the electrophilicities of the iminium ions **3a**–**g** with those of other electrophiles and shows that they are comparable to (tricarbonyliron)dienylium complex-

Table 1: Second-order rate constants k_2 for the reactions of the iminium ions **3** with the ketene acetals **4** (20 °C, CH_2Cl_2, counterion: TfO^-).

3	λ_{max} [nm][a]	k_2(**4a**) [$M^{-1}s^{-1}$]	k_2(**4b**) [$M^{-1}s^{-1}$]	E[b]
3a	360	5.26×10^1	9.04×10^2	−8.5
3b	348	3.49	1.30×10^2	−9.8
3c	349	4.32×10^1	7.42×10^2	−8.6
3d	342[c]	1.50×10^1	2.81×10^2	−9.2
3e	342	2.22	(3.6×10^1)[d]	(−10.3)
3f	370	5.23×10^2	9.06×10^3	−7.2
3g	365	6.70×10^1	2.68×10^3	−8.2

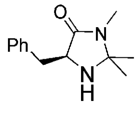
[a] In CH_2Cl_2. [b] The *E* parameter for each iminium ion results from a least-squares minimization of $\Delta^2 = \Sigma(\log k_2 - s(E+N))^2$ which uses the second-order rate constants k_2 (this table) and the nucleophile parameters *N* and *s* (for **4a**: $N = 10.61$, $s = 0.86$; for **4b**: $N = 12.56$, $s = 0.70$) from Ref. [5b]. [c] Counterion: BF_4^-, from Ref. [8]. [d] The kinetic traces for the determination of k_{obs} showed relatively large deviations from monoexponential behavior during the first half-life. Therefore, only an approximate value is given for the second-order rate constant k_2 for this electrophile–nucleophile combination.



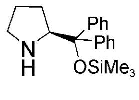
Scheme 5. Comparison of the electrophilicities of iminium ions **3a**–**g** with those of other types of neutral and positively charged electrophiles.

es[5c] and highly electron-deficient Michael acceptors such as benzylidene malononitriles[9] and 2-benzylidenindan-1,3-diones.[10] The electrophilicities of the iminium ions studied in this work differ by three units of *E*, corresponding to relative reactivities of 10^2 to 10^3 depending on the *s* value of the corresponding nucleophile. Though we do not find a very good correlation between electrophilicity *E* and $\lambda_{\max}$ of the iminium ions (see the Supporting Information), Table 1 shows that the most electrophilic iminium ion, **3f**, also has the absorption maximum at the longest wavelengths, indicating a particularly small HOMO–LUMO gap for this species.

It is apparent that the iminium ion **3f**, which is derived from MacMillan's catalyst **2f**, is the most active compound of this series, in line with the observation that **2f** is particularly suitable for iminium ion catalyzed reactions employing weak nucleophiles, e.g., for Diels–Alder reactions[3a,11] of unsaturated aldehydes with cyclopentadiene or 2-methylbuta-1,3-diene (isoprene), or Friedel–Crafts reactions with heterocyclic arenes (indoles, pyrroles, furans).[12]



2f



2g

Most likely it is the inductive electron-withdrawing effect of the trimethylsiloxy and the two phenyl groups in **2g**, which make the iminium ion **3g** 20 times more electrophilic than the corresponding parent compound **3b**. The high electrophilicity of **3g** rendered its use in many types of reactions, such as Michael reactions,[13] aziridinations,[14] 1,3-dipolar cycloadditions,[15] asymmetric triple domino Michael/Michael/aldol condensations,[16] and asymmetric tandem Michael/Morita–Baylis–Hillman reactions.[17] The relatively high electrophilicities of the iminium ions **3a** and **3c**, which can be explained by the inductive effect of the phenyl groups (in **3a**) and of oxygen (in **3c**), rationalize the findings of List et al. that dibenzylamine and morpholine are particularly suitable catalysts for iminium ion catalyzed hydrogenations.[18]

In organocatalytic nucleophilic additions to α,β-unsaturated carbonyl compounds, the intermediate iminium ions are formed in only low concentrations. It is, therefore, not only the reactivity of the iminium ions which controls the rates of the overall processes, but also the rates of their formation as well as their equilibrium concentrations, which have to be considered for optimizing the catalytic cycles. Systematic studies of these factors are currently under investigation.

Experimental Section

Following a protocol for the generation of iminium triflates by Schroth and Jahn,[19] we obtained yellowish crystals of **3a**-OTf–**3e**-OTf by treating cinnamaldehyde (**1**) with a mixture of the corresponding N-trimethylsilylated secondary amines (1 equiv) and trimethylsilyl triflate (1 equiv) in diethyl ether. Iminium triflates **3f**-OTf and **3g**-OTf were obtained from a mixture of cinnamaldehyde (**1**) and **2f** or **2g**, respectively, in diethyl ether upon addition of an aqueous solution of trifluoromethanesulfonic acid. The salts **3a**-OTf–**3g**-OTf are stable at room temperature in ordinary laboratory atmosphere and were characterized by NMR spectroscopy and HRMS (see the Supporting Information).

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