Organocatalysis

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How Does Electrostatic Activation Control Iminium-Catalyzed Cyclopropanations?**

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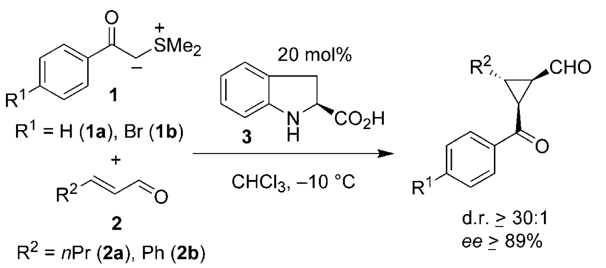
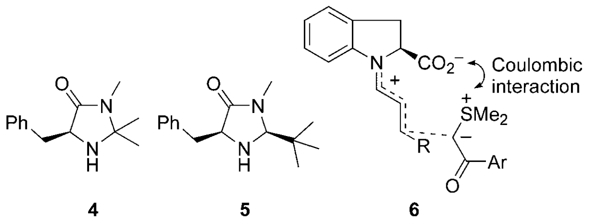
Dedicated to Professor Hans-Ulrich Reißig on the occasion of his 60th birthday

Three-membered carbocycles are versatile building blocks in organic chemistry and are found in numerous natural products.[1] The use of sulfur ylides for their syntheses from α,β-unsaturated carbonyl compounds was introduced in the 1960s by Corey and Chaykovsky.[2] Since then, numerous syntheses of cyclopropanes have emerged that often provide excellent levels of both enantio- and diastereocontrol.[3,4] In 2005 MacMillan and Kunz reported an enantioselective cyclopropanation reaction by using chiral indoline-2-carboxylic acid (**3**) as a catalyst (Scheme 1).[5]



Scheme 1. Diastereo- and enantioselective organocatalytic ylide cyclopropanation with indoline-2-carboxylic acid (**3**) by MacMillan and Kunz.[5]



Scheme 2. Imidazolidinones **4** and **5** and transition state **6** for the cyclopropanation of iminium ions derived from **3** with sulfur ylides.

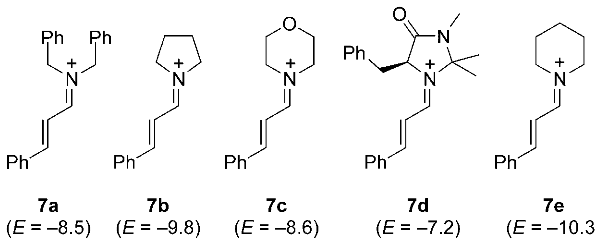
From the observation that the imidazolidinones **4**·TFA and **5**·TFA (Scheme 2, TFA = trifluoroacetic acid) did not catalyze the reaction of (*E*)-hex-2-enal (**2a**) with the sulfur ylide **1a** (0% conversion), MacMillan and Kunz concluded that the iminium ions derived from **2a** and **4** or **5** are inert to the ylides **1**. Electrostatic stabilization of the transition state **6** (Scheme 2), that is, Coulombic attraction between the negatively charged carboxylate group and the positively charged sulfonium fragment, was suggested to account for the high reactivity and selectivity of the iminium ions derived from **3**.[5,6] On the other hand, Cao et al. reported the highly diastereoselective and enantioselective cyclopropanation of cinnamaldehyde (**2b**) with the triphenylarsonium analogue of **1a** when the diphenylprolinyl trimethylsilyl ether was used as the catalyst.[7]

In previous work we have shown that the rates of the reactions of carbocations and Michael acceptors with n, π, and σ nucleophiles can be described by Equation (1), where $k_{20^\circ\mathrm{C}}$

$$\lg k_{20^\circ\mathrm{C}} = s(N + E) \qquad (1)$$

is the second-order rate constant in $\mathrm{M}^{-1}\mathrm{s}^{-1}$, s is the nucleophile-specific slope parameter, N is the nucleophilicity parameter, and E is the electrophilicity parameter.[8] Based on unpublished reactivity parameters of sulfur ylides and the recently reported electrophilicity parameters of iminium ions (Scheme 3),[9] we had expected that in contrast to MacMillan's statement,[5] the reactions of cinnamaldehyde-derived iminium ions **7** with sulfur ylide **1b** should proceed readily, as predicted by Equation (1).

Accordingly, treatment of the iminium triflates (**7a–e**)-OTf with the sulfur ylide **1b** yielded cyclopropane derivatives in 42–77% yield. However, in contrast to MacMillan's



Scheme 3. Iminium ions **7** derived from cinnamaldehyde (**2b**) and their electrophilicity parameters *E* (from Ref. [9]).

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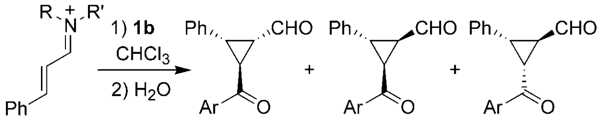
conditions,[5] which gave only two diastereomers in a ratio of 33:1 and high enantioselectivity, no significant stereoselectivity was observed (Scheme 4). None of the diastereoisomers obtained with **7d** was formed with high enantioselectivity.

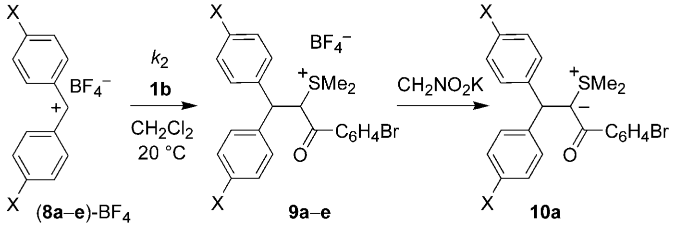


7a	1.0	:	1.0	:	2.6
7b	1.5	:	1.7	:	1.0
7c	1.1	:	1.0	:	2.6
7d	1.0 (*ee* = 10 %)	:	1.6 (*ee* = 15 %)	:	1.0 (*ee* = 50 %)
7e	1.0	:	1.4	:	4.1

Scheme 4. Reactions of iminium triflates **7** with the sulfur ylide **1b** (Ar = *p*-Br-C_6H_4).

To elucidate whether electrostatic activation really accounts for the catalytic activity of **3** in cyclopropanation reactions with sulfur ylides, we determined the nucleophilicity parameter of **1b** as well as the electrophilicity parameter of the zwitterion **7f**$^{\pm}$ derived from chiral **3** and cinnamaldehyde (**2b**).

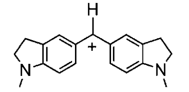
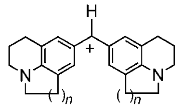
The nucleophile-specific parameters *N* and *s* of the sulfur ylide **1b** were derived from the second-order rate constants k_2 of the reactions of **1b** with the reference electrophiles **8a–e** (see Table 1),[8b] which gave the addition products **9a–e** as confirmed by the isolation and characterization of the ylide **10a** (Scheme 5, for details see the Supporting Information). The kinetics were monitored photometrically by following the disappearance of the colored benzhydrylium ions **8** as described previously[8,10] and specified in the Supporting Information.



Scheme 5. Reactions of the sulfur ylide **1b** with the reference electrophiles **8** in CH_2Cl_2 at 20 °C.

As required by Equation (1), lgk_2 for the reactions of **1b** with **8a–e** correlated linearly with the electrophilicity parameters *E* of **8a–e** (Table 1) and yielded the nucleophile-specific parameters $N(\mathbf{1b}) = 11.95$ and $s(\mathbf{1b}) = 0.76$ (Figure 1). The nucleophilicity of sulfur ylide **1b** is thus similar to that of an alkoxycarbonyl- or cyano-stabilized triphenylphosphonium ylide,[10] and **1b** is more nucleophilic than indoles,[8e] pyrroles,[8g] and dihydropyridines,[8h] which have previously been employed as substrates in iminium-catalyzed reactions.

Table 1: Second-order rate constants for the reactions of the benzhydrylium ions **8a–e** with the sulfur ylide **1b** (20 °C, CH_2Cl_2).

Electrophile		$E^{[a]}$	k_2 [$M^{-1}s^{-1}$]
8a	X = N(Me)$_2$	−7.02	5.82×10^3
8b	X = N(CH$_2$)$_4$	−7.69	1.84×10^3
8c		−8.76	2.45×10^2
8d (*n* = 2)		−9.45	8.40×10^1
8e (*n* = 1)		−10.04	2.91×10^1

[a] *E* from Ref. [8b].

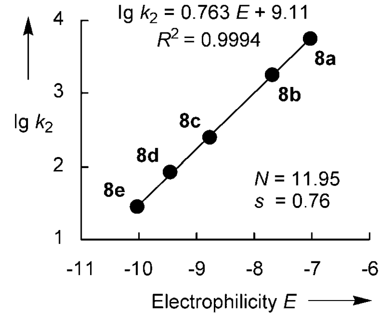
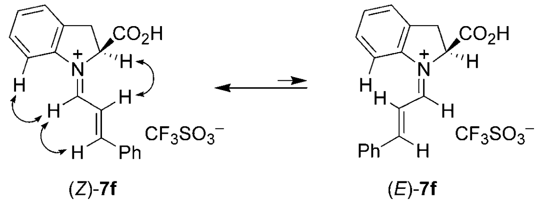


Figure 1. Plot of lgk_2 for the reactions of the sulfur ylide **1b** with the benzhydrylium ions **8a–e** in CH_2Cl_2 at 20 °C versus the electrophilicity parameters *E* of **8a–e**.

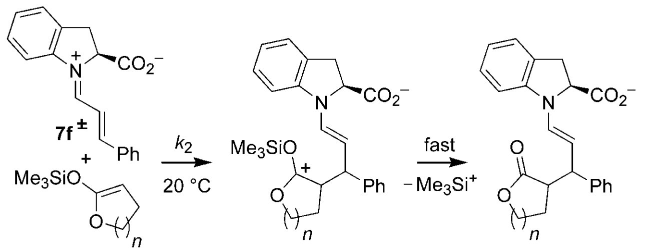
The observation made by MacMillan and Kunz that **4**-H$^+$ fails to catalyze the reaction of **1** with **2** thus cannot be explained by the low nucleophilicity of sulfur ylides. Instead it can be rationalized by the high basicity of sulfur ylides, which inhibits the formation of iminium ions; this is in line with the observation that the sulfur ylide **1b** is quantitatively protonated in $CHCl_3$ solution when treated with **4**·TFA. Because of the poor solubility of **3**, sulfur ylide **1b** was not protonated when **3** was added to a solution of **1b** in $CHCl_3$.

For the determination of its electrophilicity parameter, the zwitterion **7f**$^{\pm}$ was synthesized by treatment of **3** with cinnamaldehyde (**2b**) in methanol at room temperature. When this reaction was carried out in the presence of triflic acid, the corresponding iminium triflate **7f**-OTf was obtained. NOESY experiments showed strong correlations between the protons marked in Scheme 6, indicating (*Z*)-**7f** as the favored conformation. Analogous NMR experiments with the zwitterion **7f**$^{\pm}$ were less conclusive because of the slow decomposition of **7f**$^{\pm}$ in CD_3OD.



Scheme 6. Assignment of the conformations of iminium ion **7f** by NOESY experiments (CD_3OD, 20 °C).

In analogy to the previously reported determination of the electrophilicity parameters for the iminium ions **7a**–**e**,[9] E of **7f**$^{\pm}$ was derived from the second-order rate constants of the reactions of **7f**$^{\pm}$ with the reference nucleophiles **11** and **12** (Scheme 7). The zwitterion **7f**$^{\pm}$ reacts about 10^2 times more slowly with the ketene acetals **11** and **12** than the iminium ion **7d** derived from MacMillan's catalyst **4**.[9] Substitution of the N and s parameters for the reference nucleophiles **11** and **12** and of the second-order rate constants from Scheme 7 into Equation (1) gave $E(\mathbf{7f}^{\pm}) = -9.5$ by least-squares minimization. A comparison with the iminium ions **7a**–**e** (Scheme 3) shows that **7f**$^{\pm}$ is one of the weakest electrophiles derived from cinnamaldehyde. Yet, **3** was reported to be the most effective catalyst for the organocatalytic cyclopropanation reactions of unsaturated aldehydes with sulfur ylides **1**.[5] In order to rationalize this discrepancy, we have investigated the kinetics of the reactions of the sulfur ylide **1b** with the iminium ions **7a**–**e** and the zwitterion **7f**$^{\pm}$.



11 ($n = 1$) $k_2 = 95.2\ \text{M}^{-1}\,\text{s}^{-1}$
12 ($n = 2$) $k_2 = 10.6\ \text{M}^{-1}\,\text{s}^{-1}$

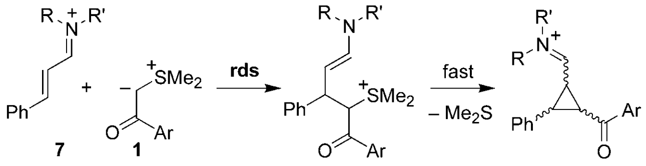
Scheme 7. Reactions of the zwitterion **7f**$^{\pm}$ with the ketene acetals **11** and **12** in CH_2Cl_2/MeOH (9:1, v/v) at 20°C.

Table 2 shows that the experimental rate constants for the reactions of iminium ions **7a**–**e** with the sulfur ylide **1b** agree within a factor of 3 to 32 with those calculated by Equation (1) from $E(\mathbf{7a})$–$E(\mathbf{7e})$[9] and the nucleophile-specific parameters N and s for **1b** given in Figure 1. This agreement is quite remarkable in view of the simplicity of Equation (1) and the reactivity range of 40 orders of magnitude covered by this correlation, and it demonstrates the applicability of our nucleophilicity parameters N/s for exploring the scope of iminium-catalyzed reactions.[11] The similarity of calculated and experimental rate constants suggests, moreover, that the cyclopropanation reactions between iminium ions **7a**–**e** and the sulfur ylide **1b** proceed by a stepwise mechanism, in which the formation of the first C–C bond is rate-determining (Scheme 8).

Table 2: Experimental and calculated second-order rate constants (in $\text{M}^{-1}\,\text{s}^{-1}$) for the reactions of the sulfur ylide **1b** with the iminium ions **7a**–**e** and with **7f**$^{\pm}$ in CH_2Cl_2 at 20°C.

Iminium ion	k_2^{exp}	$k_2^{\text{calcd[a]}}$	$k_2^{\text{exp}}/k_2^{\text{calcd}}$
7a	1.08×10^4	4.19×10^2	26
7b	1.19×10^2	4.31×10^1	2.8
7c	4.01×10^3	3.52×10^2	11
7d	1.31×10^5	4.07×10^3	32
7e	1.22×10^2	1.79×10^1	6.8
7f$^{\pm}$	$\gg 10^7$[b]	7.15×10^1	$\gg 10^5$

[a] Calculated by Equation (1) by using the electrophilicity parameters E for **7a**–**e** (from Ref. [9]) and **7f**$^{\pm}$ ($E = -9.5$, see above) as well as the N and s values for **1b** (from Figure 1). [b] Too fast for our instrumentation.



Scheme 8. Stepwise mechanism for the cyclopropanation of iminium ions **7** with sulfur ylides **1**. rds = rate-determining step.

While good agreement between observed and calculated rate constants has also been observed for the reactions of **7d** with pyrroles, indoles, and furans,[12] the situation changes dramatically for the reaction of the ylide **1b** with the zwitterion **7f**$^{\pm}$. Now, the observed rate constant is more than 10^5 times (!) higher than predicted by Equation (1) (last entry in Table 2). Obviously, the reaction of **7f**$^{\pm}$ with **1b** is accelerated by a special factor which is not taken into account when we parametrized the nucleophilicity of **1b** through its reactions with the reference electrophiles **8a**–**e** and when we parametrized the electrophilicity of **7f**$^{\pm}$ through its reactions with the reference nucleophiles **11** and **12**. Electrostatic interaction between the carboxyl group of **7f**$^{\pm}$ and the sulfonium group of **1b**, as depicted in transition state **6** (Scheme 2), may account for this more than 10^5-fold acceleration. The remarkable magnitude of this electrostatic activation moreover rationalizes the high stereoselectivity of the cyclopropanation reaction depicted in Scheme 1. As described in Scheme 4, only low diastereoselectivity and enantioselectivity were observed in the reaction of **7d** with **1b** where this electrostatic activation is absent.

In conclusion, we have shown that electrostatic activation is, indeed, responsible for the more than 10^5-fold acceleration of the reaction of the zwitterion **7f**$^{\pm}$ with the sulfur ylide **1b** and the high stereoselectivity of this reaction. However, in contrast to previous statements,[5] also iminium ions **7a**–**e** react readily with the benzoyl-stabilized sulfur ylide **1b**, though with low stereoselectivity. The previously reported failure of **4**-H$^+$ to catalyze the cyclopropanation of α,β-unsaturated aldehydes with sulfur ylides thus is not a result of the low rate of the reaction **7d** + **1b** but because of the high basicity of sulfur ylides, which inhibits the formation of iminium ions.

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