

Nucleophilic Reactivities of Ketene Acetals

Takahiro Tokuyasu^[a] and Herbert Mayr^{*[b]}*Dedicated to Professor Gottfried Märkl on the occasion of his 75th birthday***Keywords:** Carbocations / C–C coupling / Kinetics / Linear free energy relationship / Substituent effects

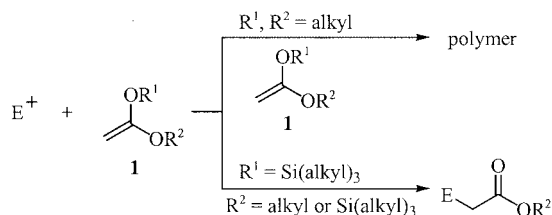
The kinetics of the reactions of ketene acetals with benzhydrylium ions have been followed photometrically. The reactions proceed with rate-determining C–C bond formation that is considerably faster than expected for outer-sphere electron transfer processes. Structure–reactivity relationships are discussed. The excellent correlations between the observed second-order rate constants ($\log k_2$) and the previ-

ously reported electrophilicity parameters (E) of benzhydrylium ions suggest that several of the compounds investigated in this work can be used as reference nucleophiles for the development of electrophilicity scales.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2004)

Introduction

Ketene acetals have electron-rich C=C double bonds, and react readily with many electrophiles under moderate conditions. Because of their high reactivity and ease of preparation, these compounds are often employed as building blocks in organic synthesis.^[1–4] Their reactions with carbon electrophiles in aldol,^[1] Michael,^[2] and Mannich reactions^[3] have been investigated extensively with respect to diastereoselective and enantioselective synthesis.^[4] While 1,1-dialkoxyalkenes **1** ($R^1, R^2 = \text{alkyl}$) readily polymerize when treated with electrophiles,^[5] the corresponding siloxy derivatives **1** [R^1 and/or $R^2 = \text{Si}(\text{alkyl})_3$] usually give the corresponding carboxylic acids or esters in high yield, because the electrophilic attack at the C=C double bond is followed by a rapid desilylation reaction (Scheme 1).^[6] For



Scheme 1. General difference in the reactions of siloxy- and alkoxy-alkenes with electrophiles

^[a] Department of Materials Chemistry & Frontier Research Center, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

^[b] Department Chemie der Ludwig-Maximilians-Universität München, Butenandtstr. 5–13 (Haus F), 81377 München, Germany
E-mail: herbert.mayr@cup.uni-muenchen.de

Supporting information for this article is available on the WWW under <http://www.eurjoc.org> or from the author.

the same reason, silylated enol ethers are more widely used in organic synthesis than are alkyl enol ethers.

In this present study, we have determined the nucleophilic reactivities of ketene acetals **1** from the kinetics of their reactions with benzhydrylium ions **2** (Table 1), which have recently been recommended as reference electrophiles for the construction of a comprehensive nucleophilicity scale.^[7,8]

Table 1. Benzhydrylium ions **2** used as reference electrophiles in this work

Ar_2CH^+			E
$(\text{mfa})_2\text{CH}^+$	2a	$X = \text{N}(\text{CH}_3)\text{CH}_2\text{CF}_3$	–3.85
$(\text{dpa})_2\text{CH}^+$	2b	$X = \text{NPh}_2$	–4.72
$(\text{mpa})_2\text{CH}^+$	2c	$X = \text{N}(\text{Ph})\text{CH}_3$	–5.89
$(\text{dma})_2\text{CH}^+$	2d	$X = \text{N}(\text{CH}_3)_2$	–7.02
$(\text{pyr})_2\text{CH}^+$	2e	$X = \text{N}(\text{CH}_2)_4$	–7.69
$(\text{thq})_2\text{CH}^+$	2f		–8.22
$(\text{jul})_2\text{CH}^+$	2g		–9.45
$(\text{lil})_2\text{CH}^+$	2h		–10.04

The nucleophilicity parameter N , defined by Equation (1), should provide a comparison of the activating effect of alkoxy and silyloxy groups on C=C double bonds and give information about potential electrophilic reaction partners of ketene acetals.^[8]

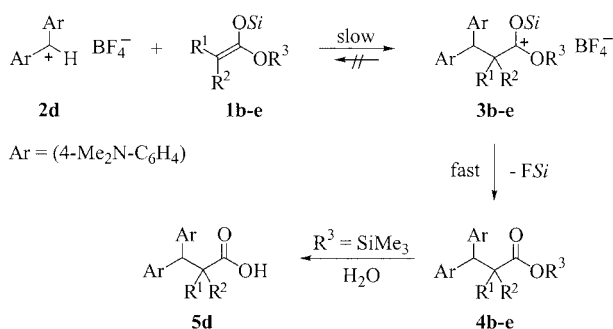
$$\log k = s(N + E) \quad (1)$$

k in $\text{M}^{-1}\cdot\text{s}^{-1}$ at 20 °C, s = nucleophile-specific slope parameter, N = nucleophilicity parameter, E = electrophilicity parameter.

In view of a shortage of reference nucleophiles having $N > 9$ in the previously published nucleophilicity scales,^[7–9] we hoped, furthermore, that some of the ketene acetals investigated in this work might prove to be suitable reference nucleophiles for the characterization of new electrophiles.

Results and Discussion

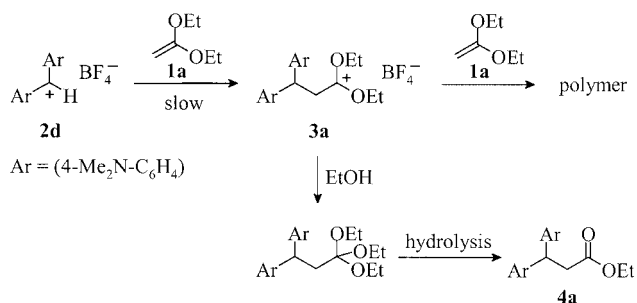
As illustrated in Scheme 2, we carried out product studies with the most readily available benzhydrylium salt, $(\text{dma})_2\text{CH}^+\text{BF}_4^-$. By analogy to previously described reactions of benzhydrylium tetrafluoroborates with silylated ketene acetals,^[6,7] compounds **1b**, **1c**, and **1e** reacted readily with $(\text{dma})_2\text{CH}^+\text{BF}_4^-$ in dichloromethane to yield the esters **4b** (= **4c**) and **4e** in high yields. The silyl ester **4d**, which was formed from $(\text{dma})_2\text{CH}^+\text{BF}_4^-$ and **1d**, was not isolated, but the initially obtained reaction product was hydrolyzed to give the carboxylic acid **5d**.



	R ¹	R ²	R ³	Si	isolated product	yield / %
b	H	H	<i>n</i> Bu	SiMe ₃	4b	96
c	H	H	<i>n</i> Bu	SiMe ₂ tBu	4c = 4b	97
d	H	Me	SiMe ₃	SiMe ₃	5d	69
e	Me	-CH ₂ CH ₂ -	SiMe ₃		4e	92

Scheme 2. Products of the reactions of $(\text{dma})_2\text{CH}^+\text{BF}_4^-$ (**2d**) with the silylated ketene acetals **1b–e**

In contrast, the reaction of 1,1-diethoxyethene (**1a**) with the benzhydrylium salt $(\text{dma})_2\text{CH}^+\text{BF}_4^-$ in CH₂Cl₂ produced only polymeric material (Scheme 3).



Scheme 3. Reaction of the ketene acetal **1a** with $(\text{dma})_2\text{CH}^+\text{BF}_4^-$ (**2d**)

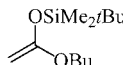
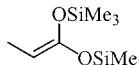
To avoid polymerization that arises from the reaction of cation **3a** with further units of ketene acetal **1a**, the reaction was conducted in EtOH/CH₃CN in the presence of 2,6-di-*tert*-butylpyridine. In agreement with the nucleophilicity parameters of $N = 9.81$ and $s = 0.81$ determined for **1a** in this work (see below), and a solvent nucleophilicity of $N_1 = 5.77$ and $s = 0.92$ obtained for a 20/80 (v/v) ethanol/acetonitrile mixture,^[10] benzhydrylium ions react faster with **1a** than with ethanol in a 0.36 M solution of **1a** in EtOH/CH₃CN (solvent nucleophilicities N_1 refer to first-order rate constants). On the other hand, a much smaller reactivity ratio k_{1a}/k_{EtOH} was expected in reactions with the dialkoxy-carbenium ion **3a**. Because of the anomeric stabilization^[11] of the resulting ortho ester (or of acetals), alkoxy-substituted carbenium ions react much faster with O-nucleophiles than predicted by the N parameters derived from reactions with benzhydrylium ions. 2,6-Di-*tert*-butylpyridine was added as a proton scavenger to prevent the acid-catalyzed reaction of 1,1-diethoxyethene (**1a**) with ethanol.^[12] Consistent with the preceding analysis, the ester **4a**, derived from the reaction of the cation **3a** with ethanol, could be trapped in 21% yield under these conditions.

The reactions of benzhydrylium ions **2** with the ketene acetals **1** (> 10 equiv.) were followed by UV–Vis spectroscopy in CH₂Cl₂ using the instrumentation described previously.^[13] From the exponential decays of the carbenium absorbances, we derived the pseudo-first-order rate constants, k_{obsd} (s^{-1}). Since, in all cases, k_{obsd} was proportional to the concentrations of the ketene acetals **1**, we calculated second-order rate constants k_2 (Table 2) from plots of k_{obsd} versus the concentrations of the nucleophiles (Figure 1).

The plots of the rate constants of the reactions of ketene acetals **1** with benzhydrylium ions **2** against the corresponding electrophilicity parameters E gave linear correlations (Figure 2), from which parameters N and s of the ketene acetals **1** were determined (Table 2) according to Equation 1.

All of the ketene acetals **1** studied in this work have nucleophilicity parameters N that range from 9.8 to 11.5, which are approximately five orders of magnitude greater than those of structurally related enol ethers.^[6–8] Comparable results have been reported for acid-catalyzed hydrolyses of enol ethers and ketene acetals: the protonation of 1,1-

Table 2. Second-order rate constants for the reactions of benzhydrylium tetrafluoroborates **2** with ketene acetals **1** (CH₂Cl₂, 20 °C) and calculated nucleophilicity (*N*) and slope (*s*) parameters for ketene acetals **1**

Ketene Acetal	<i>N</i>	<i>s</i>	Ar ₂ CH ⁺	<i>k</i> ₂ / M ⁻¹ s ⁻¹	
	1a	9.81	0.81	(mfa) ₂ CH ⁺	7.02 × 10 ⁴
				(dpa) ₂ CH ⁺	1.29 × 10 ⁴
				(mpa) ₂ CH ⁺	1.45 × 10 ³
				(dma) ₂ CH ⁺	1.79 × 10 ² [a]
				(jul) ₂ CH ⁺	1.99
	1b	10.21	0.82	(mfa) ₂ CH ⁺	1.90 × 10 ⁵
				(dpa) ₂ CH ⁺	2.86 × 10 ⁴
				(dma) ₂ CH ⁺	4.40 × 10 ²
				(thq) ₂ CH ⁺	4.57 × 10 ¹
				(lil) ₂ CH ⁺	1.33
	1c	10.32	0.79	(mfa) ₂ CH ⁺	1.34 × 10 ⁵
				(dpa) ₂ CH ⁺	2.36 × 10 ⁴
				(dma) ₂ CH ⁺	4.62 × 10 ²
				(thq) ₂ CH ⁺	4.94 × 10 ¹
				(lil) ₂ CH ⁺	1.53
	1d	10.38	0.87	(dpa) ₂ CH ⁺	7.90 × 10 ⁴
				(mpa) ₂ CH ⁺	7.71 × 10 ³
				(dma) ₂ CH ⁺	8.40 × 10 ²
				(thq) ₂ CH ⁺	7.17 × 10 ¹
				(lil) ₂ CH ⁺	1.97
	1e	11.50	0.91	(mpa) ₂ CH ⁺	1.13 × 10 ⁵
				(dma) ₂ CH ⁺	1.39 × 10 ⁴
				(pyr) ₂ CH ⁺	3.06 × 10 ³
				(thq) ₂ CH ⁺	9.99 × 10 ²
				(jul) ₂ CH ⁺	7.70 × 10 ¹
				(lil) ₂ CH ⁺	1.95 × 10 ¹

[a] Calculated from rate constants obtained at lower temperatures by using the Eyring activation parameters $\Delta H^\ddagger = 38.3 \text{ kJ}\cdot\text{mol}^{-1}$ and $\Delta S^\ddagger = -70.9 \text{ J}\cdot\text{mol}^{-1} \text{ K}^{-1}$

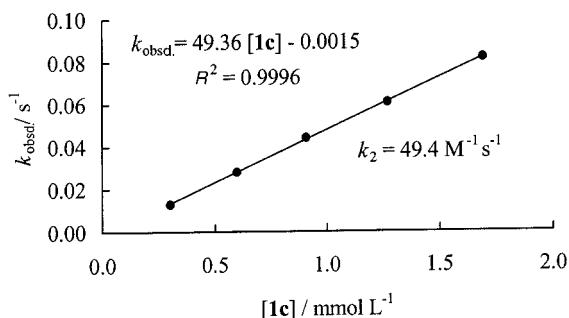


Figure 1. Determination of the second-order rate constant *k*₂ (M⁻¹ s⁻¹, 20 °C, CH₂Cl₂) of the reaction of (thq)₂CH⁺ with **1c** from the slope of the linear correlation of *k*_{obsd.} with the nucleophile concentration

dimethoxyethene is a million times faster than that of methoxyethene (Table 3).^[14]

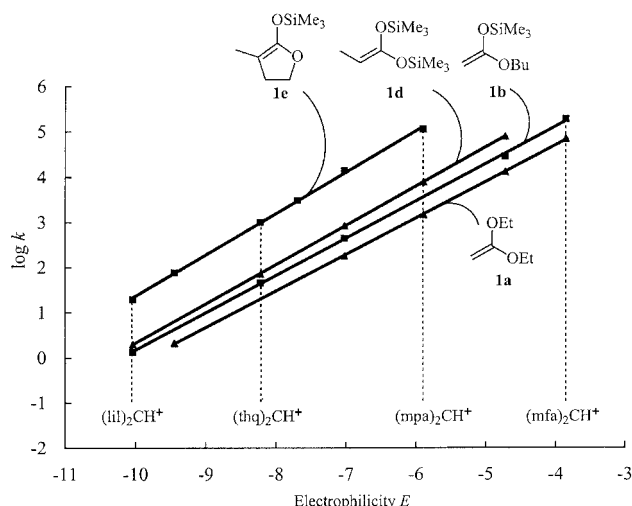


Figure 2. Correlation of the rate constants (log *k*₂, at 20 °C, in CH₂Cl₂) for the reactions of ketene acetals (**1**) with the benzhydrylium ions (**2**) versus their electrophilicity parameters *E* (correlation for **1c** is not shown)

Table 3. Relative reactivities of vinyl ethers and ketene acetals toward benzhydrylium ions and protons

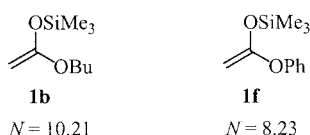
	OR	<i>T</i> / °C			Rate enhancement ^[a]
<i>k</i> (2d) / M ⁻¹ s ⁻¹	OEt	20	1.62 × 10 ⁻³ [b]	1.79 × 10 ²	1.10 × 10 ⁵
<i>k</i> (H ₃ O ⁺) / s ⁻¹	OMe	25	7.60 × 10 ⁻¹ [c]	7.20 × 10 ⁵ [c]	9.47 × 10 ⁵

[a] $k[\text{H}_2\text{C}=\text{C}(\text{OR})_2]/k[\text{H}_2\text{C}=\text{CH}(\text{OR})]$. [b] Calculated from Equation (1) by using *E* = -7.02 for **2d** and *N* = 3.92 and *s* = 0.90 for ethoxyethene (from ref.^[8]). [c] From ref.^[14].

Consistent with previous observations in the enol ether series,^[6] compounds **1b** and **1c** have similar nucleophilic reactivities (*N* = 10.21 and 10.32, respectively), suggesting that C–C bond formation is the rate-determining step. If the initial step of Scheme 2 would be reversible, i.e., if desilylation would be rate-determining, compound **1c** should be considerably less reactive, because the desilylation of the trimethylsiloxy-substituted carbocation **3b** is much faster than attack at the sterically hindered *tert*-butyldimethylsilyl group in the cation **3c** (Scheme 2).

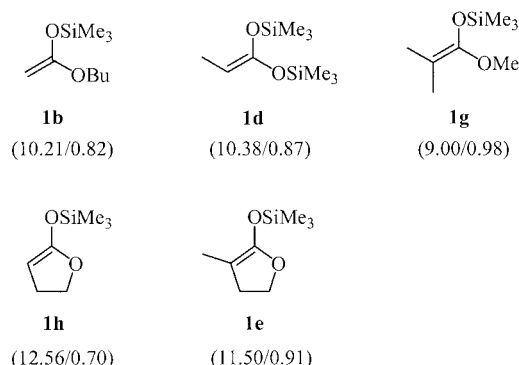
Comparison of the nucleophilicities of compounds **1a** and **1b** shows that the activating effect of a trimethylsiloxy group is similar to that of an alkoxy group. A similar relationship has previously been observed in the enol ether series.^[6] Possibly, the slightly more shielded C-2 atom in 1,1-dialkoxyethenes (**1a**, $\delta_{\text{C}} = 55.6 \text{ ppm}$), relative to the corresponding siloxy compounds (**1c**, $\delta_{\text{C}} = 60.4 \text{ ppm}$), indicates a higher electron donating ability of the alkoxy unit, relative to the siloxy unit, in the ground states of the ketene acetals. This ground state effect may be compensated, however, by the more effective hyperconjugative stabilization of the siloxy-substituted carbenium ions **3b,c** relative to **3a**, which, thus, gives rise to the comparable reactivities of 1,1-dialkoxyalkenes and the corresponding siloxy derivatives.

A comparison of the reactivity parameters of ketene acetals **1b** and **1f**^[7,8] shows that a phenoxy group activates the C=C double bond considerably less than does a butoxy group (Scheme 4).



Scheme 4. Substituent effects on the nucleophilic reactivity of ketene acetals

It has been noticed repeatedly that the slope parameter s for π -systems is largely dependent on the number of alkyl groups at the nucleophilic center.^[8] In line with previous observations in the alkene and allylsilane series, compounds **1a**, **1b**, and **1c** (terminal double bond) have similar slope parameters (0.79–0.82; Table 2). The slope parameters increase, however, from **1b** to **1d** to **1g** as the number of methyl groups at the position of electrophilic attack increases (Scheme 5). Consistent with this trend, the s parameter of **1e** is considerably larger than that of **1h**.



Scheme 5. Effect of methyl substituents at the position of electrophilic attack (N/s). Nucleophilicity parameters for **1h** and **1g** were taken from ref.^[7]

Although a rationalization for the decrease in N and the increase in s by the number of methyl groups at the position of electrophilic attack (as shown in Scheme 5) has been attempted,^[15] a conclusive explanation for this phenomenon is still missing.

Two possible pathways for the combinations of electrophiles with nucleophiles, namely electron transfer and polar reactions, have been discussed.^[16–18] While Lewis acid-promoted Mukaiyama–Michael reactions of ketene acetals have been proposed to proceed not only by the simple polar reaction pathways but also by electron transfer,^[17a] outer-sphere electron transfer processes have been excluded for the reactions of trityl cations with ketene acetals.^[17b] Recently, we have examined combination reactions of our reference electrophiles **2** with a large variety of nucleophiles, and have found that outer-sphere electron transfer processes

do not occur in any of the reactions so far investigated.^[18] To examine whether electron transfer takes place in the reactions examined in this work, the actually observed activation free energies, $\Delta G_{\text{obsd.}}^{\ddagger}$, were compared with the free energies of electron transfer, $\Delta G_{\text{ET}}^{\circ}$.

From the linear correlation between the one-electron reduction potentials of benzhydrylium ions and their empirical electrophilicity parameters, E , we derived Equation (2), which relates the free energy of one-electron transfer ($\text{kJ}\cdot\text{mol}^{-1}$) with the oxidation potential of the corresponding nucleophile (E°_{ox} vs. SCE) and the empirical electrophilicity parameter E of the benzhydrylium ion.^[18]

$$\Delta G_{\text{ET}}^{\circ} = 96.5E^{\circ}_{\text{ox}} - 1.91 - 6.85E \quad (2)$$

When $\Delta G_{\text{ET}}^{\circ}$, as calculated by Equation (2), is plotted against the electrophilicity parameters E of benzhydrylium ions (Figure 3)^[19,20], we see that over the whole range in which Equation (1) is applicable ($10^{-5} < k < 10^8 \text{ M}^{-1} \text{ s}^{-1}$), $\Delta G_{\text{ET}}^{\circ}$ is considerably larger than the experimentally observed activation free energy for the electrophile nucleophile combinations. Consequently, outer-sphere electron transfer can be ruled out for the reactions studied in this work.

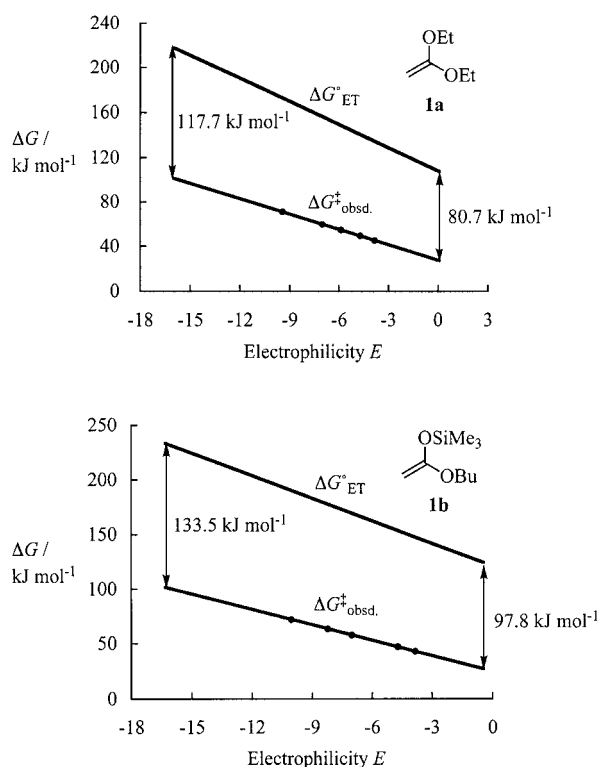


Figure 3. Comparison of the calculated free energies for electron transfer $\Delta G_{\text{ET}}^{\circ}$ [from Equation (2)] and experimental activation free energies $\Delta G_{\text{obsd.}}^{\ddagger}$ (20 °C) for the reactions of ketene acetals (**1**) with benzhydrylium ions (**2**) in the range of $100 > \Delta G_{\text{obsd.}}^{\ddagger} > 27 \text{ kJ}\cdot\text{mol}^{-1}$ corresponding to $-5 < \log k_2 < 8$; $E^{\circ}_{\text{ox}}(\text{1a}) = +1.14 \text{ V}$ (vs SCE, from ref.^[19]); $E^{\circ}_{\text{ox}}(\text{1b}) \approx E^{\circ}_{\text{ox}}$ [1-ethoxy-1-(trimethylsilyloxy)ethene] = 1.28 V (vs SCE, from ref.^[20])

Conclusion

The substituent effects on the nucleophilic reactivities of ketene acetals are in close analogy to those previously observed for other C=C double bond systems.^[8] The good accessibility of compounds **1b–1d**, their ease of handling, and their clean reactions with electrophiles suggest that these compounds are suitable as reference nucleophiles, although the rate constants of their reactions with benzhydrylium ions were not employed for the determination of the parameters *E*, *N*, and *s* of the reference compounds. Actually, this proposal deviates from our previous strategy that no further reference compounds in the range $-6 < N < 12$ should be defined.^[7] It should be noted, however, that the consideration of these reactions in the original correlation analysis,^[7] which included the full set of reference compounds, would not have affected any of the other reactivity parameters, because the excellent correlations of $\log k_2$ vs. *E* observed in this work indicate a perfect match with the previously determined electrophilicity parameters.

Experimental Section

General Remarks: The benzhydrylium cations used in this work were prepared by the methods described in ref.^[7]. 1,1-Diethoxyethene (**1a**) was purchased (Fluka), and silyl ketene acetals **1b**,^[21] **1c**,^[21] **1d**,^[22] and **1e**^[23] were prepared by the reported methods. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were obtained in CDCl₃ solutions (25 °C) using tetramethylsilane as the internal standard.

Kinetics: The kinetics of ketene acetals **1** with benzhydrylium ions **2** were followed by UV–Vis spectroscopy in CH₂Cl₂. Solutions of Ar₂CH⁺BF₄[−] were combined with an excess amount (> 10 equivalents) of the ketene acetal solutions, and then the decay of the carbenium absorbance at 590–640 nm was monitored as a function of time to give pseudo-first-order kinetics.

Slow reactions ($\tau_{1/2} > 10$ s) were measured using a J&M TIDAS diode array spectrophotometer that was connected to a Hellma 661.502-QX quartz Suprasil immersion probe (5 mm light path) through fiber optic cables using standard SMA connectors. All kinetic measurements were conducted in Schlenk flasks with the exclusion of moisture, and the temperature of the solutions during the kinetic measurements was maintained by circulating bath cryostats within ± 0.1 °C (water/glycol bath for $T > -10$ °C; ethanol bath for $T < -10$ °C) and monitored using a thermocouple probe that was inserted into the reaction mixture. When kinetic experiments were conducted at variable temperatures, second-order rate constants k_2 were calculated at 20 °C from the Eyring equation.

A stopped-flow spectrophotometer system (Hi-Tech SF-61DX2 controlled by Hi-Tech KinetAsyst2 software) was used to investigate rapid reactions ($\tau_{1/2} < 10$ s), and pseudo-first-order rate constants k_{obsd} (s^{−1}) were obtained by least-square fitting of the single exponential $A_t = A_0 \exp(-k_{\text{obsd}}t) + C$ to the absorbance data (averaged from at least four kinetic runs at each nucleophile concentration).

The detailed kinetic data (concentrations and rate constants of the individual kinetic experiments) are given in the Supporting Information (see also the footnote on the first page of this article).

Ethyl 3,3-Bis[4-(dimethylamino)phenyl]propionate (4a): Ethanol (1.5 mL) was added to a solution of (dma)₂CH⁺BF₄[−] (**2d**; 165 mg, 0.485 mmol) in CH₃CN (7.5 mL) at -40 °C. Immediately afterwards, a solution of 2,6-di-*tert*-butylpyridine (810 mg, 4.23 mmol) and ketene acetal **1a** (482 mg, 4.15 mmol) in CH₃CN (1.0 mL) was added. The reaction mixture was warmed to room temperature over 20 min, and then poured into 0.1 M KOH solution (20 mL). After extraction with CH₂Cl₂ (2 × 20 mL), the combined organic phases were washed with brine and dried (MgSO₄). The solvent was evaporated under reduced pressure, and the components were separated by column chromatography on silica gel (toluene/diethyl ether, 97:3) to give **4a** as an oil that contained small amounts of inseparable impurities (35 mg, ca. 21%). ¹H NMR: δ = 1.12 (t, *J* = 7.1 Hz, 3 H, OCH₂CH₃), 2.88 (s, 12 H, NMe₂), 2.96 (d, *J* = 8.1 Hz, 2 H, 2-H), 4.02 (q, *J* = 7.1 Hz, 2 H, OCH₂CH₃), 4.37 (t, *J* = 8.1 Hz, 1 H, Ar₂CH), 6.65, 7.09 (2 d, AA'BB' system with *J*_{AB} = 8.7 Hz, 2 × 4 H, ArH) ppm. ¹³C NMR: δ = 14.1 (q, OCH₂CH₃), 40.7 (q, NMe₂), 41.43 (t, C-2), 45.3 (d, Ar₂CH), 60.2 (t, OCH₂CH₃), 112.8, 128.2 (2 d, Ar), 132.5, 149.2 (2 s, Ar), 172.3 (s, C-1) ppm. HRMS (EI): calcd. *m/z* for C₂₁H₂₈N₂O₂, 340.2151; found, 340.2145.

Butyl 3,3-Bis[4-(dimethylamino)phenyl]propionate (4b): **A:** 1-Butoxy-1-(trimethylsiloxy)ethene (**1b**; 368 mg, 1.95 mmol) was added to a solution of (dma)₂CH⁺BF₄[−] (**2d**; 340 mg, 1.00 mmol) in CH₂Cl₂ (20 mL) under nitrogen. After stirring for 20 min, the reaction mixture was poured into 1.5 M aq. NH₃ solution (20 mL) and then the organic phase was separated. The aqueous phase was extracted with CH₂Cl₂ (20 mL). The combined organic phases were washed with brine and dried (MgSO₄). After evaporation of the solvent under reduced pressure, the product was purified by column chromatography on silica gel (toluene/diethyl ether, 97:3) to give **4b** (354 mg, 96%); m.p. 60–61 °C (hexane). ¹H NMR: δ = 0.85 (t, *J* = 7.3 Hz, 3 H, CH₃), 1.18–1.28, 1.42–1.50 (2 m, 2 × 2 H, CH₂CH₂), 2.88 (s, 12 H, NMe₂), 2.96 (d, *J* = 8.1 Hz, 2 H, 2-H), 3.97 (t, *J* = 6.7 Hz, 2 H, OCH₂), 4.37 (t, *J* = 8.0 Hz, 1 H, Ar₂CH), 6.65, 7.09 (2 d, AA'BB' system with *J*_{AB} = 8.7 Hz, 2 × 4 H, ArH) ppm. ¹³C NMR: δ = 13.7 (q, CH₃), 19.0 (t, CH₂), 30.6 (t, CH₂), 40.7 (q, NMe₂), 41.4 (t, C-2), 45.3 (d, Ar₂CH), 64.1 (t, OCH₂), 112.8, 128.2 (2 d, Ar), 132.5, 149.2 (2 s, Ar), 172.4 (s, C-1) ppm. C₂₃H₃₂N₂O₂ (368.51): calcd. C 74.96, H 8.75, N 7.60; found C 74.84, H 8.72, N 7.55.

B: 1-Butoxy-1-(*tert*-butyldimethylsiloxy)ethene (**1c**; 190 mg, 0.825 mmol) was added to a solution of (dma)₂CH⁺BF₄[−] (**2d**; 177 mg, 0.520 mmol) in CH₂Cl₂ (10 mL) under nitrogen. After stirring for 3 min, the reaction mixture was treated as described for the reaction with **1b**. Purification of the crude product by column chromatography on silica gel (toluene/diethyl ether, 96:4) gave **4b** (185 mg, 97%).

3,3-Bis[4-(dimethylamino)phenyl]-2-methylpropionic Acid (5d): Bis(silylated) ketene acetal **1d** (162 mg, 0.742 mmol) was added to a solution of (dma)₂CH⁺BF₄[−] (**2d**; 114 mg, 0.335 mmol) in CH₂Cl₂ (20 mL) under a nitrogen atmosphere. After stirring for 3 min, the reaction mixture was poured into water (20 mL) buffered at pH 5. The organic phase was separated and the aqueous phase was extracted with CH₂Cl₂ (15 mL). The combined organic phases were washed with brine and dried (MgSO₄) and then the solvent was evaporated under reduced pressure. The crude product (95 mg), which contained colored contaminants, was dissolved in diethyl ether and basified to pH 13 with aqueous KOH solution and then the phases were separated. The aqueous phase was acidified to pH 5 by adding 2 M HCl. After extraction with CH₂Cl₂, the organic phase was dried (MgSO₄). Evaporation of the solvent gave **5d**

(75 mg, 69%) as a colorless solid material; m.p. 199–200 °C (CH₂Cl₂/cyclohexane). ¹H NMR (CD₂Cl₂): δ = 1.09 (d, *J* = 6.8 Hz, 3 H, 2-Me), 2.84, 2.86 (2 s, 2 × 6 H, NMe₂), 3.22 (dq, *J* = 11.7, 6.8 Hz, 1 H, 2-H), 3.84 (d, *J* = 11.5 Hz, 1 H, Ar₂CH), 6.62, 6.65, 7.07, 7.12 (4 d, 2 AA'BB' systems with *J*_{AB} = 8.8 Hz, 4 × 2 H, ArH) ppm. ¹³C NMR (CD₂Cl₂): δ = 17.2 (q, 2-Me), 40.62, 40.63 (2 q, NMe₂), 44.4 (d, C-2), 53.1 (d, Ar₂CH), 113.0, 113.1, 128.0, 128.6 (4 d, Ar), 131.3, 132.4, 149.4, 149.5 (4 s, Ar), 180.4 (s, CO₂H) ppm. HRMS (FAB): calcd. *m/z* for C₂₀H₂₇N₂O₂ ([M + H]) 327.2073; found *m/z*, 327.2070.

3-{Bis[4-(dimethylamino)phenyl]methyl}-3-methyldihydrofuran-2-one (4e): The cyclic ketene acetal **1e** (320 mg, 1.86 mmol) was added to a solution of (dma)₂CH⁺BF₄[−] (**2d**; 345 mg, 1.01 mmol) in CH₂Cl₂ (20 mL) under nitrogen. After stirring for 5 min, the reaction mixture was treated in the same way as described for **1b**. The crude product was purified by column chromatography on silica gel (toluene/diethyl ether, 96:4) to give **4e** (328 mg, 92%); m.p. 141–142 °C (CH₂Cl₂/pentane). ¹H NMR: δ = 1.24 (s, 3 H, 3-Me), 2.11 (ddd, *J* = 13.0, 8.1, 4.9 Hz, 1 H), 2.73–2.80 (m, 1 H), 2.85, 2.91 (2 s, 2 × 6 H, NMe₂), 3.61 (td, *J* = 8.9, 5.0 Hz, 1 H), 4.02–4.08 (m, 1 H), 4.32 (s, 1 H, Ar₂CH), 6.59 (d, AA'BB' system with *J*_{AB} = 8.9 Hz, 2 H, Ar), 6.69 (d, AA'BB' system with *J*_{AB} = 8.7 Hz, 2 H, Ar), 7.13 (d, AA'BB' system with *J*_{AB} = 8.9 Hz, 2 H, Ar), 7.17 (d, AA'BB' system with *J*_{AB} = 8.7 Hz, 2 H, Ar) ppm. ¹³C NMR: δ = 24.7 (q, 3-Me), 31.7 (t, C-4), 40.40, 40.44 (2 q, NMe₂), 47.7 (s, C-3), 55.1 (d, Ar₂CH), 65.0 (t, C-5), 112.3, 112.5 (2 d, Ar), 128.5, 129.1 (2 s, Ar), 129.9, 130.0 (2 d, Ar), 149.0, 149.1 (2 s, Ar), 182.7 (s, C-2) ppm. C₂₂H₂₈N₂O₂ (352.47): calcd. C 74.97, H 8.01, N 7.95; found C 74.87, H 8.02, N 7.86.

Acknowledgments

We thank the Fonds der Chemischen Industrie for financial support, the Deutsche Akademische Austauschdienst for a scholarship to T. T., Dr. Armin R. Ofial for discussions, and Dr. Holger Schimmel for preliminary experiments with compound **1a**.

- [1] [1a] H. Gröger, E. M. Vogl, M. Shibasaki, *Chem. Eur. J.* **1998**, *4*, 1137–1141. [1b] S. G. Nelson, *Tetrahedron: Asymmetry* **1998**, *9*, 357–389. [1c] R. Mahrwald, *Chem. Rev.* **1999**, *99*, 1095–1120. [1d] E. M. Carreira, in *Comprehensive Asymmetric Catalysis I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 997–1065. [1e] T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406–1430; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352–1375. [1f] I. R. Corrêa Jr., R. A. Pilli, *Quim. Nova* **2003**, *26*, 531–541. [1g] M. Abe, M. Ikeda, M. Nojima, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3261–3266. [1h] S.-I. Murahashi, Y. Imada, T. Kawakami, K. Harada, Y. Yonemushi, N. Tomita, *J. Am. Chem. Soc.* **2002**, *124*, 2888–2889. [1i] S. E. Denmark, T. Wynn, G. L. Beutner, *J. Am. Chem. Soc.* **2002**, *124*, 13405–13407. [1j] K. Oisaki, Y. Suto, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 5644–5645.
- [2] [2a] D. A. Evans, K. A. Scheidt, J. N. Johnston, M. C. Willis, *J. Am. Chem. Soc.* **2001**, *123*, 4480–4491. [2b] M. Miyashita, T. Yanami, T. Kumazawa, A. Yoshikoshi, *J. Am. Chem. Soc.* **1984**, *106*, 2149–2156. [2c] R. Gnaneshwar, P. P. Wadgaonkar, S. Sivaram, *Tetrahedron Lett.* **2003**, *44*, 6047–6049. [2d] Y. Fujita, S. Fukuzumi, J. Otera, *Tetrahedron Lett.* **1997**, *38*, 2117–2120.

- [3] [3a] M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096–1122; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070. [3b] S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094. [3c] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.
- [4] For general reviews, see: [4a] T. Mukaiyama, M. Murakami, *Synthesis* **1987**, 1043–1054. [4b] I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, *97*, 2063–2192. [4c] S. Kobayashi, K. Manabe, H. Ishitani, J.-I. Matsuo, in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, **2002**, *4*, 317–369. [4d] A. D. Dilman, S. L. Ioffe, *Chem. Rev.* **2003**, *103*, 733–772.
- [5] [5a] P. R. Johnson, H. M. Barnes, S. M. McElvain, *J. Am. Chem. Soc.* **1940**, *62*, 964–972. [5b] J. V. Crivello, Y.-L. Lai, R. Malik, *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 3103–3120. [5c] Z. Wu, L. Cao, C. U. Pittmann Jr., *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 861–871. [5d] Z. Wu, C. U. Pittmann Jr., *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 873–881.
- [6] J. Burfeindt, M. Patz, M. Müller, H. Mayr, *J. Am. Chem. Soc.* **1998**, *120*, 3629–3634.
- [7] H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512.
- [8] H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77.
- [9] For a collection of reactivity data: <http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html>.
- [10] S. Minegishi, S. Kobayashi, H. Mayr, *J. Am. Chem. Soc.* **2004**, *126*, 5174–5181.
- [11] [11a] C. Scott, F. Grein, *Can. J. Chem.* **1996**, *74*, 1221–1228. [11b] K. Rakus, S. P. Verevkin, W.-H. Peng, H.-D. Beckhaus, C. Rüchardt, *Liebigs Ann.* **1995**, 2059–2067. [11c] C. J. Cramer, *J. Org. Chem.* **1992**, *57*, 7034–7043. [11d] F. Grein, P. Deslongchamps, *Can. J. Chem.* **1992**, *70*, 1562–1572. [11e] P. v. R. Schleyer, E. D. Jemmis, G. W. Spitznagel, *J. Am. Chem. Soc.* **1985**, *107*, 6393–6394.
- [12] H. M. Barnes, D. Kundiger, S. M. McElvain, *J. Am. Chem. Soc.* **1940**, *62*, 1281–1287.
- [13] [13a] A. D. Dilman, S. L. Ioffe, H. Mayr, *J. Org. Chem.* **2001**, *66*, 3196–3200. [13b] S. Minegishi, H. Mayr, *J. Am. Chem. Soc.* **2003**, *125*, 286–295.
- [14] A. J. Kresge, M. Leibovitch, *J. Am. Chem. Soc.* **1992**, *114*, 3099–3102.
- [15] [15a] G. Hagen, H. Mayr, *J. Am. Chem. Soc.* **1991**, *113*, 4954–4961. [15b] J. Bartl, S. Steenken, H. Mayr, *J. Am. Chem. Soc.* **1991**, *113*, 7710–7716.
- [16] [16a] M. Patz, S. Fukuzumi, *J. Phys. Org. Chem.* **1997**, *10*, 129–137. [16b] S. Shaik, A. Shurki, *Angew. Chem.* **1999**, *111*, 616–657; *Angew. Chem. Int. Ed.* **1999**, *38*, 586–625.
- [17] [17a] J. Otera, Y. Fujita, N. Sakuta, M. Fujita, S. Fukuzumi, *J. Org. Chem.* **1996**, *61*, 2951–2962. [17b] S. Fukuzumi, K. Ohkubo, J. Otera, *J. Org. Chem.* **2001**, *66*, 1450–1454.
- [18] A. R. Ofial, K. Ohkubo, S. Fukuzumi, R. Lucius, H. Mayr, *J. Am. Chem. Soc.* **2003**, *125*, 10906–10912.
- [19] J. Gersdorf, J. Mattay, H. Görner, *J. Am. Chem. Soc.* **1987**, *109*, 1203–1209.
- [20] S. Fukuzumi, M. Fujita, J. Otera, Y. Fujita, *J. Am. Chem. Soc.* **1992**, *114*, 10271–10278.
- [21] K. Miura, Y. Takeyama, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542–1553.
- [22] C. Ainsworth, Y.-N. Kuo, *J. Organomet. Chem.* **1972**, *46*, 73–87.
- [23] G. M. Rubottom, J. M. Gruber, R. Marrero, H. D. Juve, C. W. Kim, *J. Org. Chem.* **1983**, *48*, 4940–4944.

Received February 25, 2004