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Article

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Nucleophilicity Parameters of Stabilized Iodonium Ylides for Characterizing their Synthetic Potential

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Abstract

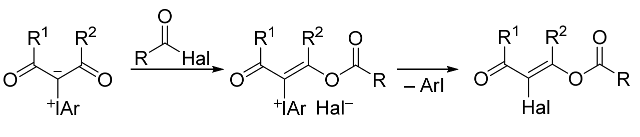
Kinetics and mechanisms of the reactions of the β-dicarbonyl-substituted iodonium ylides **1**(**a–d**) with several π-conjugated carbenium and iminium ions have been investigated. All reactions proceed with rate-determining attack of the electrophile at the nucleophilic carbon center of the ylides to give iodonium ions, which rapidly expel iodobenzene and undergo different subsequent reactions. The second-order rate constants k_2 for the reactions of the iodonium ylides with benzhydrylium ions correlate linearly with the electrophilicity parameters E of the benzhydrylium ions, and thus follow the linear free energy relationship $\log k(20°\mathrm{C}) = s_\mathrm{N}(N + E)$ (eq 1), where electrophiles are characterized by one parameter (E), while nucleophiles are characterized by two parameters: the nucleophilicity N and the susceptibility s_N. The nucleophilicity parameters $4 < N < 8$ for iodonium ylides **1**(**a–d**) derived from these correlations show that substituting hydrogen for Ph-I$^+$ at the carbanionic center of Meldrum's acid or dimedone, respectively, reduces the nucleophilicity by approximately ten orders of magnitude. The iodonium ylides **1**(**a-d**) thus have similar nucleophilicities as pyrroles, indoles, and silylated enol ethers, and therefore should be suitable substrates in iminium-activated reactions. Good agreement of the measured rate constant for the cyclopropanation of the imidazolidinone-derived iminium ion **10a** with the iodonium ylide **1a** with the rate constant calculated by eq 1 suggests a stepwise mechanism, in which the initial nucleophilic attack of the iodonium ylide at the iminium ion is rate-determining. The reaction of cinnamaldehyde with iodonium ylide **1a** catalyzed by (5*S*)-5-benzyl-2,2,3-trimethyl-imidazolidin-4-one (**11a**, MacMillan's first generation catalyst) gives the corresponding cyclopropane with an enantiomeric ratio of 70/30 and, thus, provides proof of principle that iodonium ylides are suitable substrates for iminium-activated cyclopropanations.

Introduction

Polyvalent iodine compounds have attracted significant interest in the last decades due to their great synthetic potential and easy accessibility.[1,2] An important class of synthetically useful polyvalent iodine derivatives are iodonium ylides, which have been applied as precursors for carbenes or metal carbenoids[3] as well as for transformations in which they act as electrophiles or nucleophiles. Aryl iodonium ylides were found to undergo metal-catalyzed as well as uncatalyzed reactions with alkenes,[4,5] ketenes,[6] alkynes,[7] nitriles,[8] isocyanates,[9] thiols,[10] and carbodiimides.[11] The uncatalyzed reactions with substituted ethylenes were postulated to be initiated by attack of the electrophilic iodine center at the CC-double bond followed by cyclization of the resulting betaine and extrusion of the iodoarene accompanied by ring contraction or expansion.[4,5,6a]

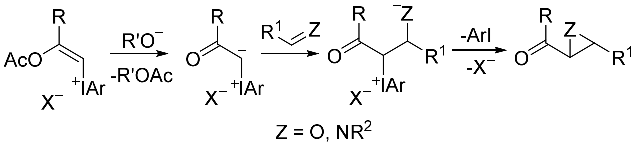
In the reactions with acyl halides, on the other hand, β-dicarbonyl aryliodonium ylides were reported to act as nucleophiles, which are attacked at the enolate oxygen of the carbonyl groups to give the corresponding iodonium ions;[6a,12] subsequent nucleophilic substitution of iodobenzene by halide anions often results in the corresponding β-carbonyl-α-haloenol esters[6a] (Scheme 1). Analogous reactions have been observed with alkylating agents such as trialkyloxonium salts or dialkyl sulfates.[12]

Scheme 1. Reactions of β-Dicarbonyl Aryliodonium Ylides with Acyl Halides



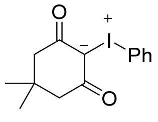
Iodonium ylides stabilized by only one acyl group, which can be generated in situ by treatment of (β-acetoxyvinyl)iodonium salts with alkoxide anions, were reported to react with aldehydes and activated imines at the ylide carbon.[13,14] Cyclization of the intermediate zwitterions with expulsion of iodoarene yields the corresponding epoxides[13] or aziridines[14] (Scheme 2).

Scheme 2. Synthesis of Epoxides and Aziridines *via* Monoacyl Iodonium Ylides[13,14]

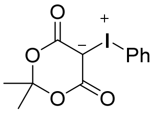


Though the possibility of attack of carbon electrophiles at the nucleophilic carbon center of isolable *β*-dicarbonyl iodonium ylides has been considered in the literature,[15] examples of such reactions have, to our knowledge, not yet been reported. In fact, an electrophilic attack at the ylide carbon was not even taken into consideration as a possible reaction pathway to account for the regioselectivity of the reactions of *β*-dicarbonyl iodonium ylides with diphenylketene.[6a]

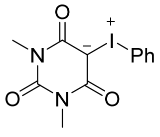
Benzhydrylium ions have previously been used as reference electrophiles[16a] in investigations of the reactivities of various nucleophiles, including phosphonium,[17] sulfonium,[18] and pyridinium ylides.[19] In order to explore the possibility of electrophilic attack at the carbon center of iodonium ylides, we have now studied kinetics and mechanisms of the reactions of four *β*-dicarbonyliodonium ylides **1(a-d)** with benzhydrylium ions of variable electrophilicity (Table 1).



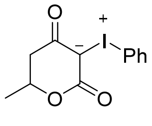
1a



1b



1c

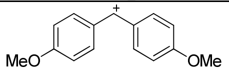
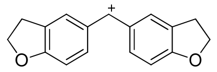
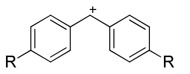
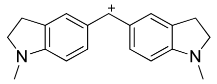
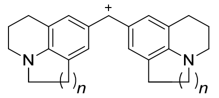


1d

Substitution of the measured rate constants into the linear free energy relationship (eq 1), where E is an electrophilicity parameter, N is a nucleophilicity parameter, and s_N is a nucleophile-specific susceptibility parameter, yields N and s_N for **1(a-d)**, the parameters which are needed to predict potential electrophilic reaction partners.

$$\log k_{20°C} = s_N(N + E) \qquad (1)$$

Table 1. Reference Electrophiles **2(a–k)** and Their Electrophilicity Parameters E

Electrophile	R		E^a
		**2a**	0.00
		**2b**	–1.36
	N(Ph)CH_2CF_3	**2c**	–3.14
	N(Me)CH_2CF_3	**2d**	–3.85
	NPh_2	**2e**	–4.72
	N-morpholino	**2f**	–5.53
	N(Ph)Me	**2g**	–5.89
	NMe_2	**2h**	–7.02
		**2i**	–8.76
	n = 2	**2j**	–9.45
	n = 1	**2k**	–10.04

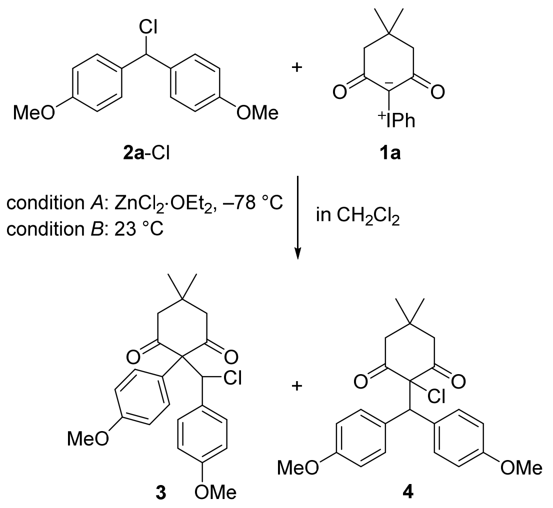
[a] From ref 16a.

Results and Discussion

Synthesis of the iodonium ylides. The ylides **1(a–d)** were prepared by condensation of the corresponding CH acids with diacetoxyiodobenzene under basic conditions following literature procedures.[20,21]

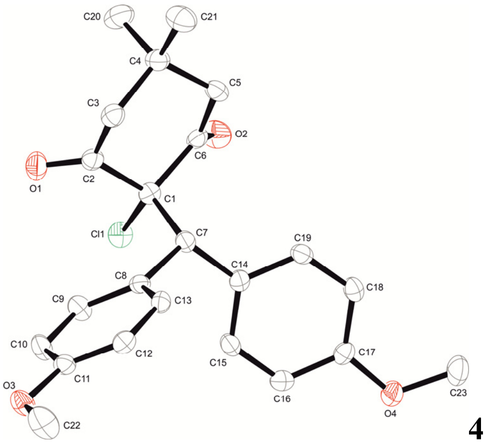
Product studies. To investigate the general course of the reactions of benzydrylium ions with the iodonium ylides **1**, the reaction of **1a** with **2a** was studied in detail. When the bis(p-methoxy)benzhydryl cation (**2a**) was generated *in situ* in dichloromethane at −78 °C by ionization of the benzhydryl chloride **2a**-Cl with $ZnCl_2·OEt_2$ in the presence of the iodonium ylide **1a** and tetra-*n*-butylammonium chloride (1 equiv with respect to $ZnCl_2$), compound **3** was obtained in 62% yield[22] (Scheme 3) and characterized by single crystal X-ray crystallography.[23] Combination of **2a**-Cl and **1a** in dichloromethane at ambient temperature without Lewis acid additive yielded compound **3**, accompanied by its isomer **4** (Scheme 3), which was also characterized by single crystal X-ray diffraction analysis (Figure 1).

Scheme 3. Reactions of the Benzhydryl Chloride **2a**-Cl with the Iodonium Ylide **1a** With or Without Added Lewis Acid.



	3	4
condition *A*:	62%[a]	-
condition *B*:	21%[b]	36%[b] (15%)[c]

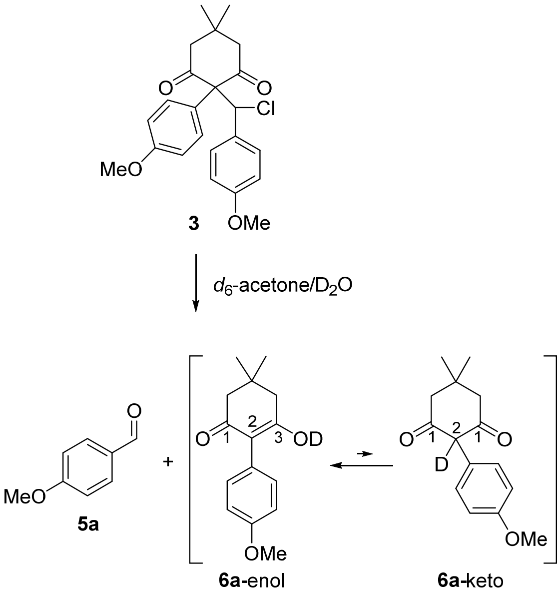
[a] Yield of isolated product after recrystallization.
[b] Based on the ^{1}H NMR spectrum of the crude mixture.
[c] Yield of isolated product after column chromatography.



4

Figure 1. ORTEP drawing (50% probability ellipsoids) of 2-(bis(4-methoxyphenyl)methyl)-2-chloro-5,5-dimethylcyclohexane-1,3-dione (**4**).

Scheme 4. Hydrolysis of **3** in a Mixture of d_6-Acetone and D_2O

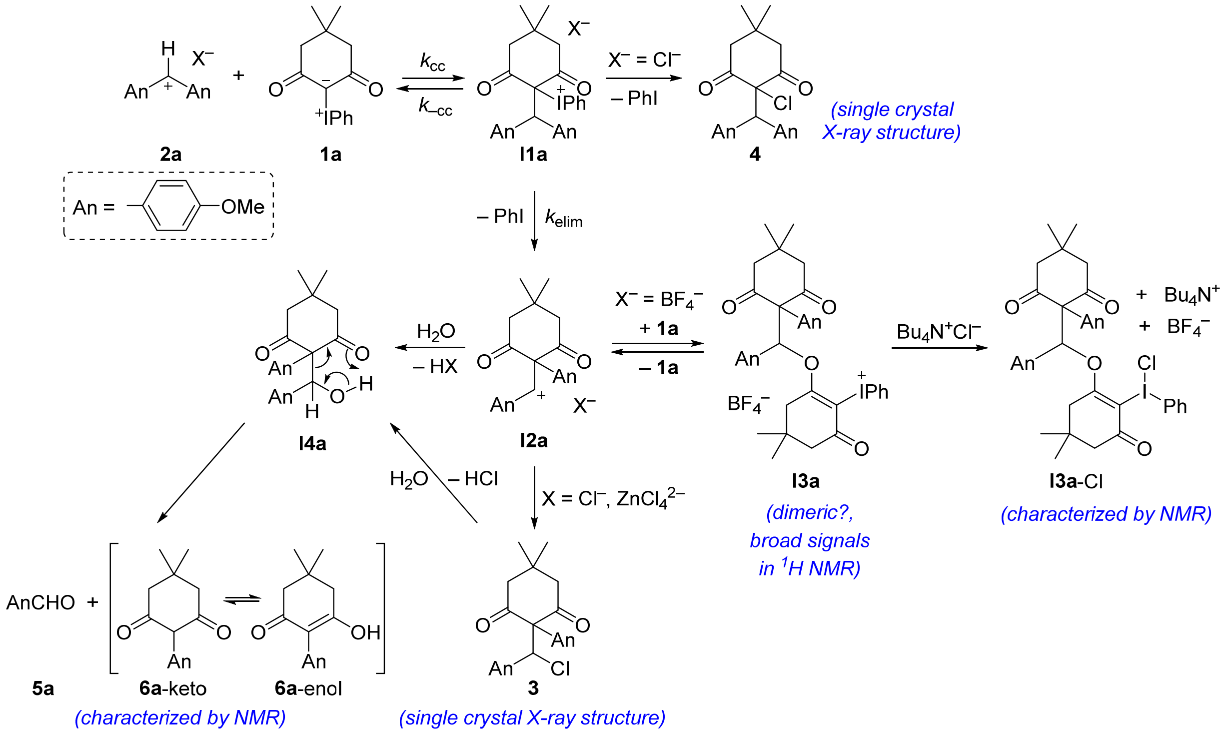


Hydrolysis of **3** in a d_6-acetone/D_2O mixture (2/1) led to the formation of *p*-anisaldehyde (**5a**) and 2-(*p*-anisyl)dimedone (**6a**), which were characterized without separation by NMR and HRMS (Scheme 4). The ^{1}H and ^{13}C NMR spectra of compound **6a** in d_6-acetone/D_2O (2/1) showed only one signal for the two geminal methyl groups and one signal for C-1 and C-3 (for numbering see Scheme 4). From the chemical shifts at δ 186.0 (C-1, C-3) and δ 116.0 (C-

2) one can derive that **6a** exists as a rapidly equilibrating mixture of two enols, as previously reported for unsubstituted dimedone in protic solvents.[24]

A mechanism, which accounts for these experimental observations, is presented in Scheme 5: In the first step, the adduct **I1a** is formed by attack of **2a** at the nucleophilic carbon of iodonium ylide **1a**. If a strong nucleophile, such as Cl^-, is present, it can substitute iodobenzene in **I1a** to give **4**. Concomitantly, iodobenzene is expelled from **I1a** (probably anchimerically assisted by the anisyl group which migrates through a *p*-methoxy-stabilized phenonium transition state) to give the benzyl cation **I2a**, which is trapped by Cl^- to yield **3**. Adducts analogous to **4** do not form in the absence of a strong nucleophile, for example, when the reaction of **1a** with **2a**-Cl is catalyzed by $ZnCl_2 \cdot OEt_2$ (i.e., conditions A in Scheme 3). In this case, **I1a** exclusively decomposes with formation of the benzyl cation **I2a**, which is intercepted by a chlorozincate anion to yield **3**. In the presence of water, hydrolysis of **I2a** or **3** results in the formation of the intermediate **I4a**, which fragments into aldehyde **5a** and the 2-arylated dimedone **6a**.

Scheme 5. Mechanism of the Reaction of the Iodonium Ylide **1a** with Benzhydryl Cation **2a**



A different scenario was observed in the corresponding reactions of the ylides with benzhydrylium ions with weakly nucleophilic counterions (BF_4^-) under anhydrous conditions. When **2a**-BF_4 was combined with 1 equiv. of the ylide **1a**, the intensities of the ^{1}H NMR signals of the benzhydrylium ion **2a** decreased to only 50% of the initial value. Complete consumption of the cation **2a** was observed, however, when **2a-**BF_4 was combined with 2 equiv. of **1a**. The ^{1}H and ^{13}C NMR spectra of the resulting mixture showed the formation of iodobenzene as well as of a product with broad signals, which was assigned to structure **I3a** by the following experiments: Mixing **2a-**BF_4 with 2 equiv of **1a** in CD_2Cl_2 at 20 °C and subsequent addition of tetrabutylammonium chloride (1 equiv) showed the formation of a species, which was assigned to the structure **I3a**-Cl by its ^{1}H, ^{13}C, and 2D NMR spectra (see Supporting Information for details). When Bu_4NBF_4 (instead of Bu_4NCl) was added to a mixture of **2a-**BF_4 and **1a**, the ^{1}H NMR spectrum showed the same broad signals as they were observed for the reaction without additives. This behavior can be rationalized on the basis of previous literature reports: X-ray structures of vinyliodonium tetrafluoroborates show the presence of dimers in the solid state, where two BF_4^- anions bridge the iodine atoms of two iodonium ions to give an eight-membered ring.[25] The broad NMR signals could be explained, therefore, by an analogous dimerization of **I3a-**BF_4 in solution. In line with previous reports on iodonium chlorides,[26] added chloride ions could effectively inhibit dimerization of **I3a** by coordination to the iodonium center, in accord with the sharper NMR signals.

As the iodonium salt **I3a**-Cl was the only species observed by ^{1}H NMR immediately after mixing **2a**-BF_4 with 2 equiv of **1a** in CD_2Cl_2 and subsequent addition of Bu_4NCl, it must be formed in less than a few seconds. **I3a**-Cl could not be isolated and was converted into **3** when the reaction mixture was stored for two days under anhydrous conditions (as analyzed by ^{1}H NMR spectroscopy).

Given that the benzyl cation **I2a** is more electrophilic than its benzhydrylium precursor **2a**, the ylide **1a** will react faster with **I2a** than with **2a**, in accord with the need for two equivalents of ylide **1a** to achieve full conversion of the benzhydrylium ion **2a**. Hydrolysis of the intermediate **I3a** during aqueous workup and chromatography on silica gel eventually gave rise to the formation of the aldehyde **5a**. As discussed below, two equivalents of ylides **1a**–**d** are also required for the quantitative conversion of other benzhydrylium tetrafluoroborates.

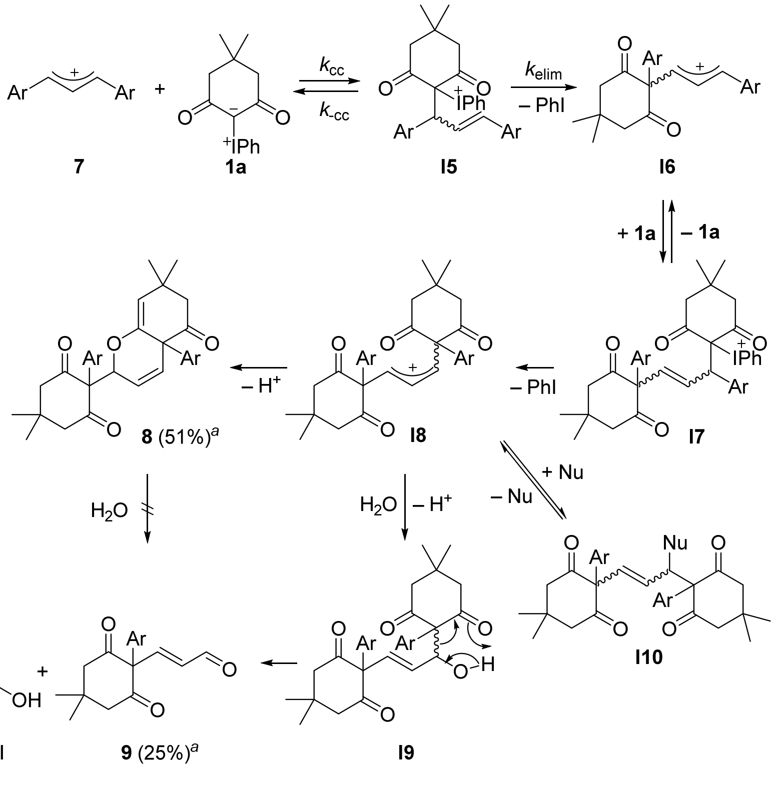
How can one explain the different regioselectivity in the reactions of the ylide **1a** with the carbocations **2a** and **I2a**? Why is **1a** attacked at carbon by **2a** and at oxygen by **I2a**? Probably, electrophilic attack at the enolate oxygen of ylide **1a** is generally faster than attack at carbon, as previously reported for the reactions of acyl stabilized iodonium ylides with acyl chlorides,[6a,12] trialkyloxonium ions,[12] or dialkyl sulfates.[12b] Because of the high stabilization of **2a**, intermediates arising from O-attack at **2a** are formed reversibly, and all isolated products **3**, **4**, **5a**, and **6a** are derived from the thermodynamically favored intermediate **I1a**, the result of C-attack. On the other hand, the steric bulk of the quaternary carbon adjacent to the carbocationic center of **I2a** may give rise to a high barrier for its C-attack at **1a** and favor O-attack.

From the mono-exponential decays of the UV/Vis-absorbances of **2** (see below) in the reactions of the benzhydrylium ions **2b**-**k** (of $E \leq -1$) with a large excess of the ylides **1**(**a**–**d**) (pseudo-first order conditions) one can derive that intermediates generated by attack of **2** at the enolate oxygen of **1**(**a**-**d**) do not accumulate at any time in the reaction mixtures.

The situation is different for the subsequent reaction of the intermediate **I2a**. Since the benzyl cation **I2a** is less stabilized than the benzhydryl cation **2a**, iodonium ion **I3a**, the adduct arising from the kinetically preferred O-attack of **I2a** at **1a**, persists as an NMR detectable species (see above) and undergoes only slow retroaddition (conversion of **I3a**-Cl into **3** takes two days).

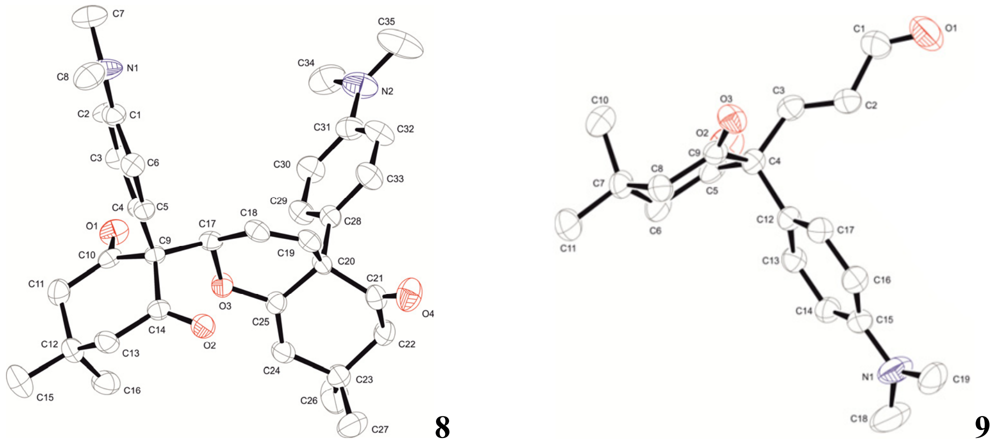
To examine the consistency of the reaction mechanism suggested in Scheme 5 we have also examined the reaction of the iodonium ylide **1a** with 1,3-bis(4-(dimethylamino)phenyl)allylium tetrafluoroborate **7**-BF_4 (Scheme 6). When **7**-BF_4 was combined with 4 equiv. of **1a** (in synthetic grade CH_2Cl_2, 24 h, ambient temperature), two products were isolated after aqueous workup and separation by column chromatography: the tetrahydrochromenyl-substituted cyclohexane-1,3-dione **8** (51%, single crystal X-ray structure shown in Figure 2, left) and the acrylaldehyde derivative **9** (25%, single crystal X-ray structure shown in Figure 2, right).

S**cheme 6.** Mechanism of the Reaction of the 1,3-Bis(4-dimethylaminophenyl)allylium Tetrafluoroborate **7**-BF_4 (Ar = 4-Me_2N-C_6H_4) with the Iodonium Ylide **1a**.



^{a} Yields of isolated products after aq workup and column chromatography.

In contrast, **9** was not observed in the ^{1}H spectrum of the crude mixture when the reaction of **7**-BF_4 with **1a** was carried out under rigorous anhydrous conditions (in the presence of molecular sieves) in dichloromethane at room temperature, while **8** was the major product. When the same reaction was carried out in CD_2Cl_2 (0.55 mL) containing one drop of D_2O (9 mg), the enal **9** formed as the major product (^{1}H NMR).



8

9

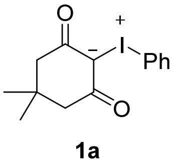
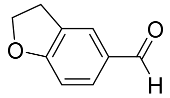
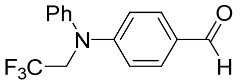
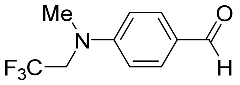
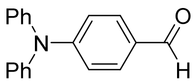
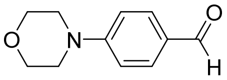
Figure 2. ORTEP drawings (50% probability ellipsoids) of 2-(4-(dimethylamino)phenyl)-2-(4a-(4-(dimethylamino)phenyl)-7,7-dimethyl-5-oxo-4a,5,6,7-tetrahydro-2H-chromen-2-yl)-5,5-dimethylcyclohexane-1,3-dione (**8**, left) and (*E*)-3-(1-(4-(dimethylamino)phenyl)-4,4-dimethyl-2,6-dioxocyclohexyl)acrylaldehyde (**9**, right, only one molecule of the asymmetric unit shown).

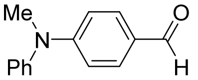
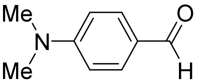
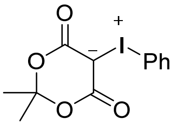
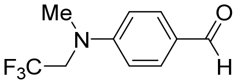
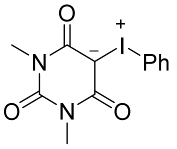
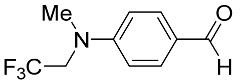
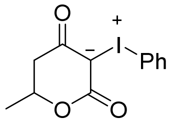
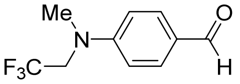
These results are in full analogy to the mechanism suggested for the benzhydryl systems in Scheme 5. According to Scheme 6, attack of the allyl cation **7** at the nucleophilic carbon of the ylide **1a** yields the intermediate **I5**. Expulsion of iodobenzene accompanied by aryl migration generates the allyl cation **I6**. Since **I6** is more electrophilic than **7**, it immediately reacts with a further molecule of ylide **1a** to yield the iodonium ion **I7**. As in the step before, expulsion of iodobenzene and aryl migration lead to the allyl cation **I8**, which undergoes intramolecular cyclization followed by loss of a proton to yield the isolated product **8**.

It should be noted that the cyclization leading to **8** requires one of the allylic CC bonds in **I8** to adopt (*Z*)-configuration. Though allyl cations with the dimedone group in (*Z*)-position may be formed during the aryl migration **I5** → **I6** or **I7** → **I8**, it is likely that the (*E,E*)-configuration of **I8** is preferred. However, reversible addition of a nucleophile to (*E,E*)-**I8** (→**I10**, Scheme 6) and subsequent elimination may give rise to a small equilibrium concentration of (*E,Z*)-**I8**, which can undergo cyclization. Trapping of **I8** by water gives the intermediate **I9**, which fragments (analogous to **I4a**, Scheme 5) to give the 2-aryl substituted dimedone **6h** and the isolated propenal derivative **9**. Generation of **9** by hydrolysis of **8** can be excluded, as only trace amounts of **9** formed when D_2O was added to a solution of crude **8** (Supporting Information, p S13).

In line with these mechanistic schemes, the 4-(dimethylamino)benzaldehyde **5h** was obtained as the major product along with iodobenzene, when a drop of D_2O (9 mg) was added immediately after combining **1a** (100 µmol) and **2h** (30 µmol) in CD_2Cl_2 (0.55 mL, ^{1}H NMR analysis). In accord with the mechanism proposed in Scheme 5, all combinations of 3 equiv of the iodonium ylides **1(a–d)** with the benzhydrylium tetrafluoroborates or triflates **2(b–h)**-X (under anhydrous conditions) yielded the corresponding benzaldehydes **5(b–h)** after aqueous workup and column chromatography (Table 2). In contrast, a complex mixture of products containing only traces of the aldehyde **5h** formed, when equimolar amounts of **1a** and **2h** were mixed in CD_2Cl_2 under anhydrous conditions (^{1}H NMR spectrum recorded after 2 h).

Table 2. Reactions of Benzhydrylium Tetrafluoroborates **2(b–h)**-BF_4 with Iodonium Ylides **1(a–d)** in Dichloromethane[a]

Nucleophile	Electrophile	Product		Yield[b] (%)
 **1a**	**2b**[c]		**5b**	65
	2c		**5c**	68
	2d		**5d**	88
	2e		**5e**	68
	2f		**5f**	64

	2g		**5g**	69
	2h		**5h**	65
 **1b**	**2d**		**5d**	88
 **1c**	**2d**		**5d**	65
 **1d**	**2d**		**5d**	53

[a] Reaction conditions: Iodonium ylide **1** (3 equiv.) reacted with **2**-X (1 equiv., X = TfO^- for **2b**, X = BF_4^- for **2c-h**,) in CH_2Cl_2 at ambient temperature. [b] Yields refer to isolated products after aq workup and purification by column chromatography (for details see Supporting Information). [c] **2b**-OTf was generated in situ from **2b**-Cl and trimethylsilyl triflate.

Kinetic Investigations

All reactions of the nucleophiles **1(a-d)** with the reference electrophiles **2(a-f)** were performed in dichloromethane at 20°C and monitored by UV−Vis spectroscopy at or close to the absorption maxima of the electrophiles. In order to achieve pseudo-first-order conditions, the ylides were used in excess (>10 equivalents) over the benzhydrylium ions. In each kinetic run, a monoexponential decay of the absorbance of the benzhydrylium ion with complete disappearance of the corresponding band was observed. First-order rate constants k_{obs} (s^{-1}) were determined by fitting a function $A_t = A_0 e^{-k_{\mathrm{obs}} t} + C$ to the experimental time-dependent absorbances (Figure 3). These k_{obs} were found to correlate linearly with the concentrations of the ylides, which allowed us to derive the second-order rate constants k_2 (M^{-1} s^{-1}) listed in Table 3 as the slopes of the k_{obs} vs [**1**] plots (inset of Figure 3).

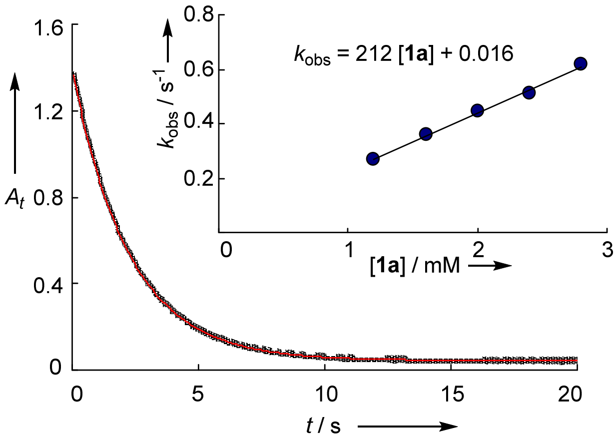


Figure 3. Exponential decay of the absorbance A_t (λ = 601 nm) in the reaction of **1a** (2.00×10^{-3} M) with the benzhydrylium ion **2c** (1.98×10^{-5} M) in CH_2Cl_2 at 20 °C. Inset: Correlation between the first-order rate constants k_{obs} (s^{-1}) and the concentration of **1a**.

Figure 4 shows that the experimental second-order rate constants k_2 correlate linearly with electrophilicity parameters E of the corresponding benzhydryl cations, i.e., the gross rate constants of the reactions of **1** with **2** follow eq 1.

Table 3. Second-Order Rate Constants (k_2) for the Reactions of Iodonium Ylides **1(a–d)** with the Benzhydrylium Ions **2(a–f)** in CH_2Cl_2 at 20 °C

Ylide	Electrophile	k_2 (M^{-1} s^{-1})	N, s_{N}[a]
1a	**2b**	1.07×10^{4}	6.18, 0.81
1a	**2c**	2.12×10^{2}	
1a	**2d**	6.69×10^{1}	
1a	**2f**	4.29	
1b	**2a**	3.32×10^{4}	4.36, 1.06
1b	**2b**	2.21×10^{3}	
1b	**2c**	1.40×10^{1}	
1b	**2d**	3.95	
1c	**2c**	3.04×10^{3}	7.98, 0.71
1c	**2d**	6.25×10^{2}	
1c	**2e**	2.27×10^{2}	
1d	**2c**	2.60×10^{1}	4.67, 0.92
1d	**2d**	7.54	
1d	**2e**	4.94×10^{-1}	
1d	**2f**	2.18×10^{-1}	

[a] The nucleophile-specific parameters s_N and N were derived from the slopes and the intercepts on the abscissa of the correlations between log k_2 (this table) and the electrophilicity parameters E of the benzhydryl cations (from Table 1). For details see text.

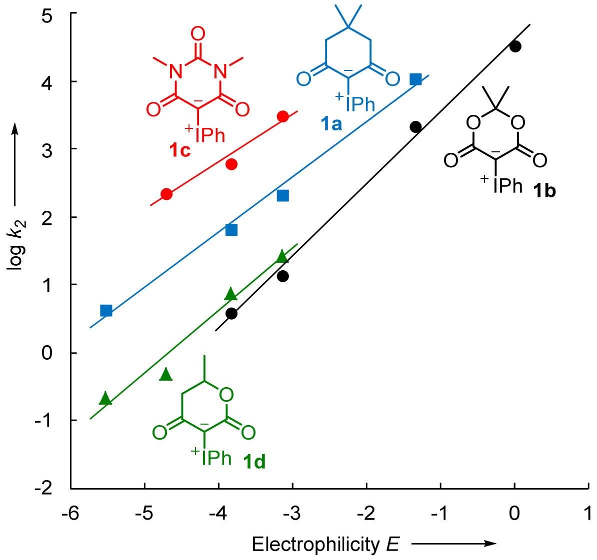


Figure 4: Correlation of log k_2 for the reactions of the iodonium ylides **1(a-d)** with the benzhydryl cations **2(a-f)** versus the electrophilicity parameters E of the corresponding carbenium ions.

Let us now analyze how the kinetic data can be interpreted in terms of the mechanism presented in Scheme 5. In the following general analysis, which refers to different benzhydrylium ions, specifying labels a,b,c etc. in the formula numbers in Scheme 5 are omitted. As the expulsion of iodobenzene during the transformation of **I1** into **I2** must be irreversible, the overall rate of disappearance of the electrophiles **2** (k_2), which is experimentally accessible by the kinetic experiments, will depend on the rates of the two first steps of the reaction (k_{CC}, k_{-CC}, and k_{elim}, Scheme 5; formation of **4** does not occur with the BF_4^- salts).

The rate law for the consumption of **2** can be formulated as follows:

$$\frac{d[\mathbf{2}]}{dt} = -k_{CC}[\mathbf{1}][\mathbf{2}] + k_{-CC}[\mathbf{I1}] \qquad (2)$$

$$\frac{d[\mathbf{I1}]}{dt} = k_{\mathrm{CC}}[\mathbf{1}][\mathbf{2}] - k_{-\mathrm{CC}}[\mathbf{I1}] - k_{\mathrm{elim}}[\mathbf{I1}] \qquad (3)$$

As the experimental observations described above do not give evidence for an observable concentration of **I1**, the steady-state approximation, $d[\mathbf{I1}]/\mathrm{d}t = 0$, applies and we arrive at eq 4.

$$\frac{d[\mathbf{2}]}{dt} = -k_2[\mathbf{1}][\mathbf{2}] = -k_{\mathrm{CC}}\,\frac{k_{\mathrm{elim}}}{k_{-\mathrm{CC}} + k_{\mathrm{elim}}}[\mathbf{1}][\mathbf{2}] \qquad (4)$$

The linear correlations depicted in Figure 4 either imply that $k_2 = k_{\mathrm{CC}}$ (for $k_{\mathrm{elim}} >> k_{\mathrm{CC}}$) or that substituent variation in the benzhydrylium ions affects the second term of eq 4, i.e., the quotient $k_{\mathrm{elim}}/(k_{-\mathrm{CC}} + k_{\mathrm{elim}})$ proportionally to k_{CC}. As this coincidence is highly unlikely for reactions of four different iodonium ylides with benzhydrylium ions of widely differing electrophilic reactivities, we conclude $k_{\mathrm{elim}} >> k_{-\mathrm{CC}}$, equivalent to the conclusion that iodobenzene is a better nucleofuge than the iodonium ylides **1(a-d)**. The second term of eq 4 thus becomes 1, leading to $k_2 = k_{\mathrm{CC}}$. Monoexponential decays of the benzhydrylium concentrations, would also be found if $k_{\mathrm{elim}} << k_{-\mathrm{CC}}$. In this case eq. 5 would hold with $K = k_{\mathrm{CC}}/k_{-\mathrm{CC}}$

$$\frac{d[\mathbf{2}]}{dt} = -k_2[\mathbf{1}][\mathbf{2}] = -k_{\mathrm{elim}}K[\mathbf{1}][\mathbf{2}] \qquad (4)$$

Since $k_{\mathrm{elim}}K$ cannot be expected to be linearly correlated with the electrophilic reactivities E of the benzhydrylium ions (Figure 4), this possibility was also eliminated.

Additional support for rate-determining CC-bond formation ($k_2 = k_{\mathrm{CC}}$) comes from the observation that the reactivity parameters N and s_{N} derived in this way correctly reproduce the rate constants of the reactions of iodonium ylides with iminium ions, for which the subsequent reaction steps are completely different (see next paragraph). One thus can conclude that the nucleophilicity parameters s_{N} and N given in Table 3 allow one to calculate the reactivities of the carbon centers of the iodonium ylides **1(a-d)** towards any C(sp^2)-centered electrophile with a known value of *E*.

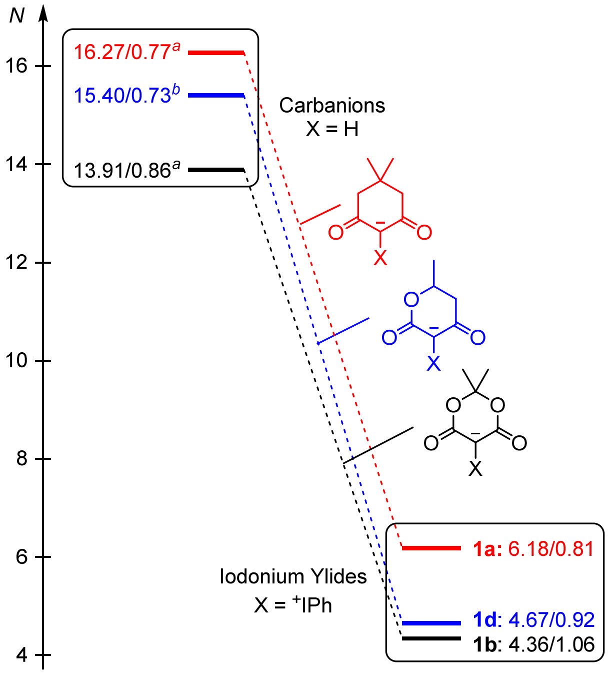


Figure 5. Comparison of the nucleophilicity parameters N/s_N (in CH_2Cl_2) of the iodonium ylides **1a**, **1b**, and **1d** with those of the corresponding carbanions (in DMSO). [a] From ref 27. [b] This work, kinetics of the reactions of electrophiles **2i-k** with 6-methyl-2,4-dioxotetrahydro-2H-pyran-3-ide were used for the determination of N/s_N in DMSO (see Supporting Information).

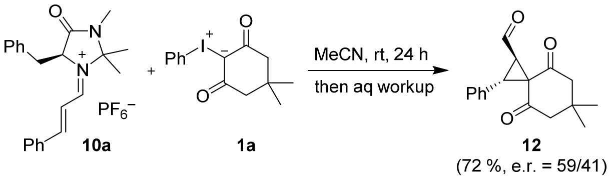
Figure 5 illustrates that replacement of the hydrogen at the reaction center of carbanions (X = H, Figure 5, left) by $^+$IPh reduces the nucleophilic reactivity by approximately ten orders of magnitude.

Application in Organocatalysis: Reactions with *α,β*-Unsaturated Iminium Ions.[28]

In previous work we have discussed that iminium-activation of *α,β*-unsaturated carbonyl compounds is restricted to reactions with nucleophiles of $2 < N < 14$, because more reactive nucleophiles may undergo direct reactions with the carbonyl precursors, while less reactive nucleophiles do not react readily with typical iminium ions.[29] Given that the iodonium ylides **1(a–d)** have now been found to have nucleophilicity parameters in this range ($4 < N < 8$, Table 3) we selected iodonium ylide **1a** to test whether iodonium ylides are suitable substrates in iminium-activated reactions.

As illustrated in Scheme 7, the reaction of **1a** with the iminium ion **10a**, derived from cinnamaldehyde and MacMillan's first generation catalyst (5*S*)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone (**11a**),[30] provided the cyclopropanation product **12** in 72% yield with an enantiomeric ratio (e.r.) of 59/41 after purification by column chromatography. The substituted spiro[2.5]octane **12** was crystallized from an ethyl acetate/*n*-pentane mixture (1:3) and subsequently analyzed by single crystal X-ray diffraction.[31,32]

Scheme 7. Reaction of the Iminium Hexafluorophosphate **10a**-PF_6 with the Iodonium Ylide **1a** in Acetonitrile at Room Temperature.



The experimental second-order rate constant of the reaction of **1a** with **10a** ($k_{\mathrm{exp}} = 0.232$ M^{-1} s^{-1} in CH_2Cl_2 at 20 °C, Supporting Information) deviates only by a factor of 2 from the rate constant $k_{\mathrm{calc}} = 0.108$ M^{-1} s^{-1} calculated by eq 1 using the N and s_N parameters of **1a** in Table 3 and the previously published[33] electrophilicity parameter of **10a** ($E = -7.37$). This good agreement indicates a rate-determining step similar to that of the reactions of the iodonium ylides **1** with benzhydrylium ions **2** (see above), i.e., rate-determining nucleophilic attack of the ylide **1a** at the iminium ion **10a**, followed by intramolecular nucleophilic attack of the resulting enamine moiety in **13** at the iodonium-substituted carbon (Scheme 8).

Scheme 8. Reaction Mechanism for the Reaction of the Iminium Ion **10a** with the Iodonium Ylide **1a**.

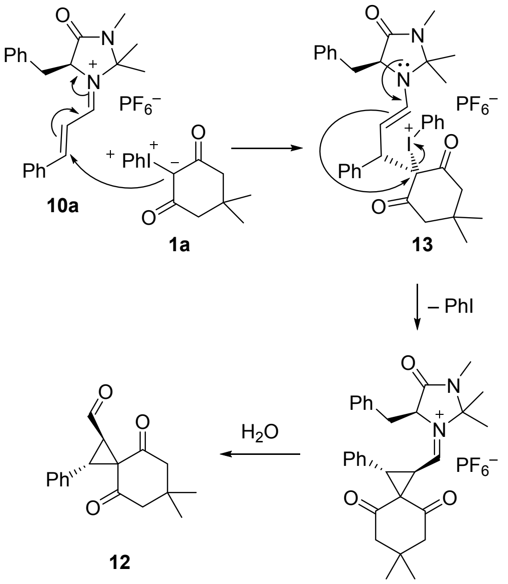
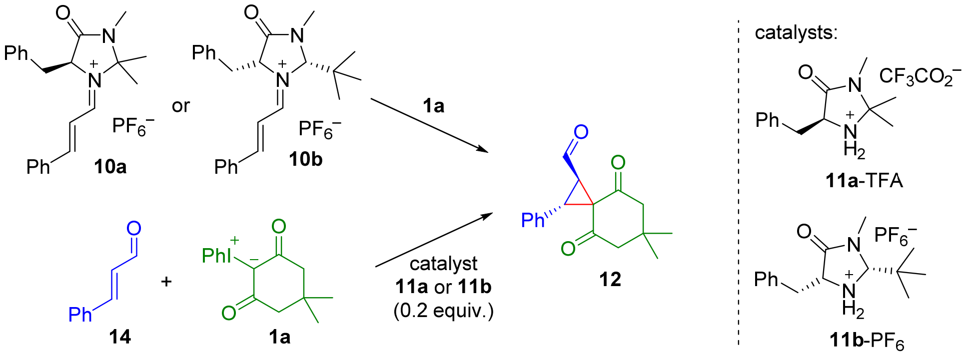


Table 4. Yields and Enantioselectivities of the Reactions of Iodonium Ylide **1a** with Either Iminium Ions **10a,b** or a Combination of Cinnamaldehyde (**14**) and Catalysts **11a,b** (in MeCN).



entry	Electrophile	Catalyst (0.2 equiv.)	AN/W[a]	T (°C)	t (h)	Yield (%)	e.r.[b]
1	**10a**-PF_6	none	100/0	20	24	72	59/41
2	**14**	**11a**-TFA	100/0	20	12	66	61/39
3	**14**	**11a**-TFA	95/5	20	12	46	69/31
4	**14**	**11a**-TFA	90/10	20	12	[c]	71/29
5	**14**	**11a**-TFA	80/20	20	12	[c,d]	72/28
6	**14**	**11a**-TFA	100/0	–30	12	43	69/31
7	**14**	**11a**-TFA	95/5	0	12	[c]	70/30

8	**14**	**11a**-TFA	95/5	–30	12	48	69/31
9	**14**	**11a**-TFA	95/5[e]	20	68	50	70/30
10	**10b**-PF$_6$	none	100/0	20	2	32	38/62[f]
11	**10b**-PF$_6$	none	100/0	20	0.1	[c]	38/62[f]
12	**10b**-PF$_6$	none	100/0	–30	12	[c]	32/68[f]
13	**14**	**11b**-PF$_6$	100/0	20	12	[c]	47/53[f]
14	**14**	**11b**-PF$_6$	95/5	20	12	[c]	46/54[f]

[a] AN/W = acetonitrile-water mixture (v/v). [b] Enantiomeric ratio (e.r.) from HPLC analysis (Supporting Information). [c] Yield was not determined. [d] Significant amount of **1a** insoluble in diethyl ether was detected after dissolving of the crude mixture in this solvent, which indicates a low degree of conversion. [e] Acetone-water mixture (v/v). [f] The major enantiomer obtained with **10b** or **11b** has the opposite configuration to that formed by **11a**.

Table 4 compares the yields and selectivities for the reactions of cinnamaldehyde (**14**) with iodonium ylide **1a** under organocatalytic conditions using MacMillan's catalysts of first[34] and second[35] generation **11a** and **11b**, respectively. According to Scheme 7, the isolated iminium hexafluorophosphate **10a**-PF$_6$ reacted with **1a** in acetonitrile at 20 °C to give cyclopropane **12** in 72% yield (e.r. = 59/41) after aqueous workup (entry 1). When the reaction of cinnamaldehyde (**14**) with iodonium ylide **1a** was performed in the same solvent (MeCN, 20 °C) under organocatalytic conditions (20 mol-% of **11a**-TFA), the yield dropped slightly but the e.r. remained unchanged (entry 2). As in the **11a**-Cl-catalyzed Diels-Alder reaction of cinnamaldehyde with cyclopentadiene,[34] addition of water was found to increase the enantioselectivity of the catalyzed reactions (entries 2–5). While an increase of the e.r. from 61/39 to 69/31 was observed when the temperature was lowered from 20 to −30 °C for the **11a**-TFA-catalyzed reaction in pure acetonitrile (entries 2 and 6), variation of temperature did not affect the enantiomeric ratio in acetonitrile-water mixtures (entries 3, 7, 8). Almost the same stereoselectivity as in aq. acetonitrile was observed when 95 % aq acetone was employed (e.r. = 70/30, entry 9), but the reaction was much slower.

MacMillan's second generation catalyst, **11b**, was found to give slightly higher (inverse) enantiomeric ratios but considerably lower yields than **11a** when used under stoichiometric conditions (isolated iminium salts, entries 1 and 10). A slight increase of the e.r. was observed when the isolated iminium salt **10b**-PF_6 was combined with **1a** in acetonitrile at −30 °C (e.r. = 32/68, entry 12).

In contrast to the situation with **11a**, a change from stoichiometric to organocatalytic conditions caused a significant drop in e.r. from 38/62 to 47/53 when **11b** was employed (entries 10 and 13). Addition of water was found to have only a marginal effect on the selectivity of the organocatalytic reaction using **11b** (entries 13, 14).

The lower performance of **11b** in the reaction of **1a** with **14** can be explained by the different persistence of the different reaction products in the solutions obtained after aqueous workup. Chiral HPLC indicated that the concentrations of both enantiomers of **12** decreased significantly within several hours, when the crude mixtures were dissolved in dichloromethane or acetonitrile.

As the enantiomer initially formed in excess decomposed faster in the presence of **11b** than the minor enantiomer, the e.r. decreased from initially 32/68 to ca 50/50 within 3 h. This observation suggests that decomposition of **12** is induced by **11b** or some chiral byproducts that react with different rates with the two enantiomers, which explains the low performance of **11b** in terms of both yield and stereoselectivity. An attempt to increase the e.r. by decreasing the reaction time from 2 h to 0.1 h did not increase the enantioselectivity[36] (Table 4, entries 10–11).

Conclusions

While previous investigations of the reactions of stabilized *β*-dicarbonyl substituted iodonium ylides with acid chlorides and trialkyloxonium ions showed exclusive reactions at the enolate oxygens of the ylides, we have now found the first examples for electrophilic attack at the ylide carbon of **1(a-d)**. These were the only observable reactions, when the iodonium ylides **1(a-d)** were combined with stabilized carbenium or iminium ions, presumably because the competing O-attack of these electrophiles is highly reversible. In all investigated cases, the initial rate-determining CC-bond forming step was followed by fast expulsion of iodobenzene and rearrangements.

The reactions of **1(a-d)** with the benzhydrylium ions **2** followed second-order kinetics, and the resulting second-order rate constants correlated linearly with the electrophilicity parameters E of the benzhydrylium ions, which allowed us to derive the N and s_N parameters of the iodonium ylides **1(a-d)** according to eq (1). In this way, the nucleophilic reactivities of the iodonium ylides can directly be compared with those of other C-nucleophiles, e.g., allylsilanes and -stannanes, pyrroles and indoles, silylated enol ethers and enamides, as well as isonitriles and methyl hydrazones (Figure 6).[16]

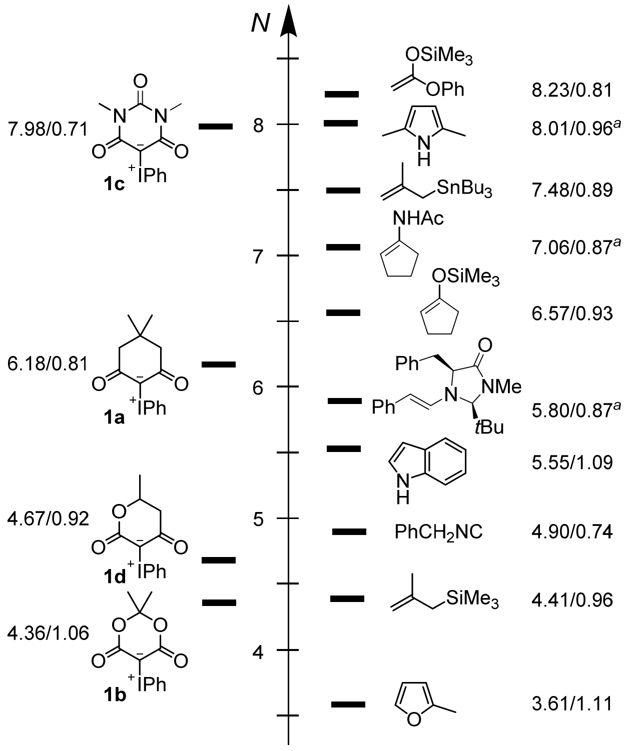


Figure 6. Nucleophile-specific parameters N/s_N of iodonium ylides **1(a-d)** compared with those of various C-nucleophiles in dichloromethane.[16] [a] In acetonitrile.

The fact that the rate constant for the cyclopropanation of the cinnamaldehyde-derived iminium ion **10a** by the iodonium ylide **1a** closely resembles that calculated from E, N, and s_N by eq 1 indicates that this reaction proceeds through rate-determining nucleophilic attack of the iodonium ylide at the electron-deficient CC-double bond. With nucleophilicity parameters $4 < N < 8$ (Table 3) the iodonium ylides **1(a-d)** are in the reactivity range suitable for iminium-activated reactions. Accordingly, imidazolidinone **11a** catalyzes the cyclopropanation of cinnamaldehyde (**14**) to produce an enantiomeric ratio of ca. 70/30. In spite of the moderate enantioselectivities observed so far, these results should trigger further investigations of iminium-activated reactions. From the rule of thumb that electrophiles are expected to react efficiently with nucleophiles if $E + N > –5$, one can predict that electrophiles with $E > –10$ should be able to attack at the carbon center of the iodonium ylides **1(a-d)**. From the formation of **I3a** (Scheme 5) one can expect, however, that highly reactive carbocations $E > (0 \text{ to } 4)$ will attack the intrinsically preferred O-position of **1** as previously observed for the reactions of **1(a-d)** with acyl chlorides and oxonium ions.[6a,12]

Acknowledgements.

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Supporting Information.

Detailed synthetic procedures and product characterization; details of kinetic measurements; crystallographic data for **4**, **8** and **9**; copies of ^{1}H and ^{13}C{^{1}H} NMR spectra for all isolated products. (PDF)

Crystallographic data (CIF)

CCDC 1474094 (**4**, rv305), CCDC 1445166 (**8**, po046), and CCDC 1445164 (**9**, qo065) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif

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