Ambident Reactivity

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Ambident Reactivities of Formaldehyde *N*,*N*-Dialkylhydrazones**

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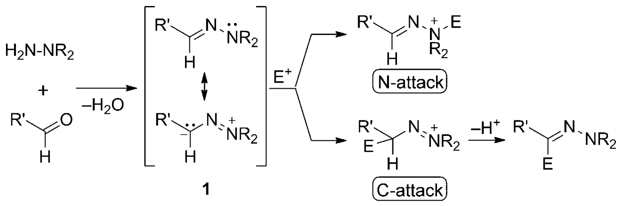
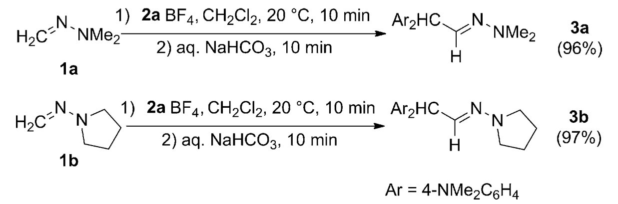
Dedicated to Professor Wolfgang Steglich on the occasion of his 80th birthday

N,*N*-Dialkylhydrazones **1**, which can be considered as 2-aza-enamines, have been employed as synthetically useful nucleophiles in a variety of C–C bond-forming reactions (Scheme 1).[1] Like enamines, hydrazones **1** are ambident nucleophiles[2] that react with electrophiles either at the terminal nitrogen or at the azomethine carbon, which adopts nucleophilic character from conjugation of the lone pair on the terminal nitrogen with the C=N double bond (Scheme 1).[1b] Electrophilic alkylation at nitrogen yields *N*,*N*,*N*-trialkylhydrazonium salts, the synthetic utility of which has already been explored.[3] When electrophilic addition occurs at the azomethine carbon, hydrazones **1** behave as acyl anion equivalents. This form of umpolung[4] of the carbonyl reactivity (Scheme 1)[1a–d] has been extensively applied in chiral auxiliary based strategy[3c,5] and in asymmetric organocatalyzed reactions.[6]



Scheme 1. Ambident nucleophilic reactivity of *N*,*N*-dialkylhydrazones **1**.

Despite their extensive use in organic synthesis, the ambident nucleophilicity of hydrazones has not been investigated quantitatively to date. In previous work, we have shown that the HSAB model[7] as well as the related Klopman–Salem concept of charge- and orbital-controlled reactions[8] cannot even explain the ambident behavior of the prototype ambident nucleophiles, for example cyanide, nitrite, cyanate, thiocyanate, or nitronate anions.[2] For that reason, an alternative approach to ambident reactivity based on Marcus theory[9] was suggested.[2] We now report on kinetic and quantum chemical investigations of the ambident nucleophilicities of two representative formaldehyde *N*,*N*-dialkylhydrazones, **1a** and **1b** (for structures see Scheme 2), and provide a rationalization of the regioselectivities of their reactions with electrophiles.



Scheme 2. Products from the reactions of **1a,b** with **2a** BF_4.

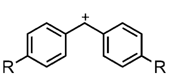
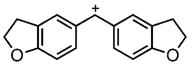
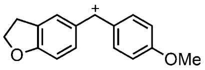
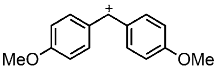
In numerous investigations, benzhydrylium ions **2** with variable *para*- and *meta*-substituents have been used as reference electrophiles for the construction of a comprehensive nucleophilicity scale on the basis of Equation (1), which characterizes nucleophiles by two solvent-dependent parameters (nucleophilicity N and sensitivity parameter s_N) and electrophiles by one solvent-independent parameter (electrophilicity E).[10]

$$\lg k(20\,^{\circ}\mathrm{C}) = s_N(N + E) \qquad (1)$$

We now used the benzhydrylium ions **2**, depicted in Table 1, as reference electrophiles to investigate the ambident nucleophilicities of the hydrazones **1a** and **1b**.

Addition of the hydrazones **1a,b** to dichloromethane solutions of bis(4-(dimethylamino)phenyl)methylium tetrafluoroborate (**2a** BF_4) at 20 °C followed by workup with

Table 1: Benzhydrylium ions Ar_2CH^+ employed as reference electrophiles in this work.

Ar_2CH^+			E[a]
	R = $N(CH_3)_2$	**2a**	−7.02
	R = $N(CH_3)Ph$	**2b**	−5.89
	R = $N(CH_2CH_2)_2O$	**2c**	−5.53
	R = NPh_2	**2d**	−4.72
	R = $N(CH_3)CH_2CF_3$	**2e**	−3.85
	R = $N(Ph)CH_2CF_3$	**2f**	−3.14
		**2g**	−1.36
		**2h**	−0.81
		**2i**	0

[a] Electrophilicity parameters E for **2a–i** from Ref. [10c,11].

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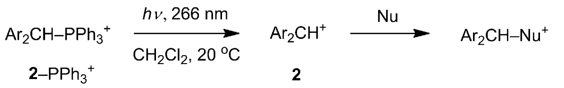
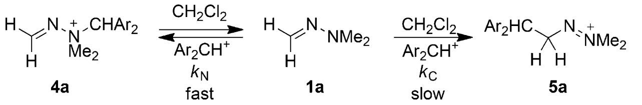
aqueous $NaHCO_3$ solution led to the formation of the benzhydryl-substituted hydrazones **3** (Scheme 2) that were isolated in nearly quantitative yields and characterized as specified in the Supporting Information.

The rates of the reactions of the *N*,*N*-dialkylhydrazones **1a**,**b** with the carbenium ions **2** were measured spectrophotometrically in dichloromethane at 20 °C by monitoring the disappearance of the absorbances of the benzhydrylium ions **2**, using conventional or stopped-flow techniques as described elsewhere.[10] For the fast reactions ($k > 10^6\,\mathrm{L\,mol^{-1}\,s^{-1}}$), laser flash photolytic techniques were employed:[12] The benzhydrylium ions **2** were generated by laser flash irradiation (7 ns pulse, 266 nm, 40–60 mJ pulse^{-1}) of the corresponding benzhydryltriphenylphosphonium tetrafluoroborates **2**-PPh_3BF_4 in the presence of the nucleophiles **1** (Scheme 3). The intermediate benzhydrylium ions **2** were identified by their UV/Vis spectra. In all cases, hydrazones were used in excess (> 8 equivalents), resulting in pseudo first-order kinetics.



Scheme 3. Generation of the benzhydrylium ions **2** by laser flash irradiation of the phosphonium salts **2**-PPh_3BF_4 (in CH_2Cl_2).

Depending on the nature of the carbenium ions and the concentrations of the hydrazones **1a**,**b**, different concentration/time correlations were observed, which can be explained by the fast and reversible formation of **4a** being in competition with the slower and more quantitative formation of **5a** (Scheme 4).



Scheme 4. Ambident nucleophilicity of **1a**.

For the reactions of **1a** with the highly stabilized carbenium ions **2b–f**, we observed mono-exponential decays (as exemplified in the Supporting Information, Figure S1, for the reaction of **1a** with **2c**), which correspond to the attack of these carbocations at the azomethine carbon of the hydrazones (Scheme 4, right). The first-order rate constants k_{obs} ($\mathrm{s^{-1}}$) were obtained by fitting the function $A = A_0 e^{-k_{\mathrm{obs}}t} + C$ to the time-dependent absorbances of **2**. The second-order rate constants were obtained from the slopes of the k_{obs} versus [**1a**] plots, as depicted in the inset of Figure S1 of the Supporting Information, and assigned to carbon attack (k_C in Table 2) for the reasons discussed below.

For the reaction of **1a** (0.67 mM) with the less-stabilized carbenium ion **2g** (11 μM), we observed a double-exponential decay of the absorbance of **2g** (Figure 1a), indicating the occurrence of two processes (k_C for carbon attack, k_N for nitrogen attack), which can separately be enhanced or suppressed by adjusting the concentrations of **1a**. As shown in Figure 1b, the absorbance of **2g**, which was generated by laser flash photolysis of the phosphonium tetrafluoroborate **2g**-PPh_3BF_4 in CH_2Cl_2 at 20 °C, decreases mono-exponentially to approximately 50 % of the initial value in a 2.3 mM solution of **1a** within 3 μs (formation of **4a**, Scheme 4), whereas the consumption of the remaining **2g** required almost 50 ms (formation of **5a**, not shown in Figure 1b). From the linear correlation of k_{obs} with [**1a**], the second-order rate constant $k_N = 1.63\times10^8\,\mathrm{L\,mol^{-1}\,s^{-1}}$ (Table 2) can be derived.

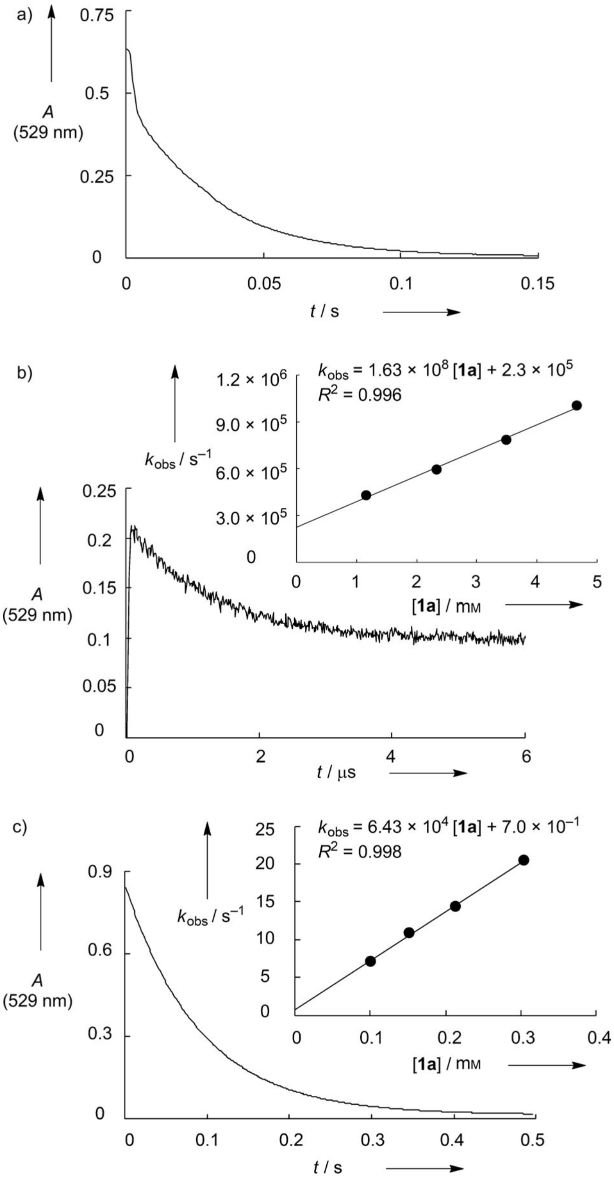
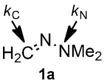
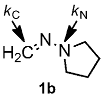


Figure 1. a) Double-exponential decay of the absorbance during the reaction of **2g** ([**2g** OTf] = 1.05×10^{-5} M) with **1a** ([**1a**] = 6.71×10^{-4} M; b) fast exponential decay of the absorbance during the reaction of **2g** (generated from [**2g**-PPh_3BF_4] = 3.00×10^{-5} M) with **1a** ([**1a**] = 2.33×10^{-3} M; $k_{\mathrm{obs}} = 5.95\times10^5\,\mathrm{s^{-1}}$). Inset: Plot of k_{obs} versus [**1a**] yields the second-order rate constant $k_N = 1.63\times10^8\,\mathrm{L\,mol^{-1}\,s^{-1}}$ and c) slow exponential decay of the absorbance during the reaction of **2g** ([**2g** OTf] = 1.05×10^{-5} M) with **1a** ([**1a**] = 1.53×10^{-4} M; $k_{\mathrm{obs}} = 10.9\,\mathrm{s^{-1}}$. Inset: Plot of k_{obs} versus [**1a**] yields the second-order rate constant $k_C = 6.43\times10^4\,\mathrm{L\,mol^{-1}\,s^{-1}}$.

Table 2: Second-order rate constants k_C (C attack) and k_N (N attack) as well as equilibrium constants K_N (N-attack) for the reactions of the *N*,*N*-dialkylhydrazones **1 a**,**b** with the reference electrophiles Ar_2CH^+ **2** (CH_2Cl_2, 20°C).

Nucleophile	Ar_2CH^+	k_C/L mol^{-1} s^{-1}	k_N/L mol^{-1} s^{-1}	K_N/L mol^{-1}
 **1a**	**2b**	8.50		
	2c	1.76×10^1		
	2d	8.30×10^1		
	2e	4.97×10^2		
	2f	1.82×10^3		
	2g	6.43×10^4	1.63×10^8	3.08×10^2
	2h		2.91×10^8	1.40×10^3
	2i		5.68×10^8	1.16×10^4
 **1b**	**2b**	4.14×10^1		
	2c	1.18×10^2		
	2d	9.22×10^2		
	2e	4.50×10^3		
	2f	1.15×10^4		
	2g		8.46×10^7	9.46×10^2
	2h		1.96×10^8	7.71×10^3
	2i		3.93×10^8	

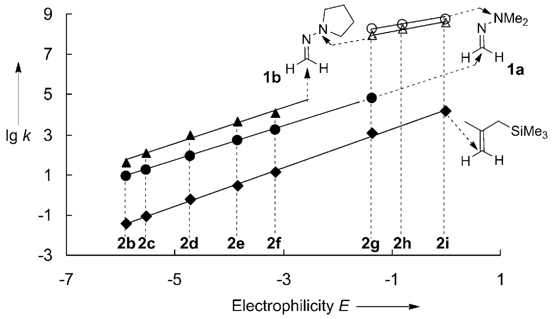


Figure 2. Dependence of the second-order rate constants (lg k_C and lg k_N) for the reactions of the *N*,*N*-dialkyl hydrazones **1 a**,**b** with the benzhydrylium ions **2 b**–**i** in CH_2Cl_2 at 20°C (electrophilicity parameters *E* for Ar_2CH^+ from Table 1; data for trimethyl(2-methylallyl)silane from Ref. [10a] are added for comparison).

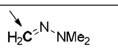
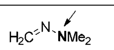
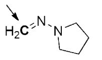
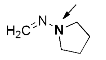
For smaller concentrations of **1a** (< 0.3 mM), the equilibrium for the fast reaction (N attack; Scheme 4, left) is on the side of the reactants, and only the slow process (C attack; Scheme 4, right) is observable on a longer timescale. Figure 1 c shows the mono-exponential decay of **2g** in a 0.15 mM solution of **1a** observed by using a stopped-flow technique. The first-order rate constants k_{obs} were again obtained by least-squares fitting of the function $A_t = A_0 e^{-k_{obs}t} + C$ to the time-dependent absorbances of the electrophiles, and the second-order rate constant $k_C = 6.43\times10^4$ L mol^{-1} s^{-1} (Table 2) for the slow reaction was obtained from the slope of the k_{obs} *vs* [**1a**] plot, which is shown in the insert of Figure 1 c.

The more Lewis acidic carbenium ions **2h**,**i** react almost quantitatively at nitrogen (Scheme 4, left), even at lower concentrations of **1a**, and the corresponding rate constants k_N are reported in Table 2. In these cases, the rate constants k_C for carbon attack (Scheme 4, right) cannot be measured directly.

Similar observations were made for the reactions of **1b** with the benzhydrylium ions **2**: With the better-stabilized carbenium ions **2b**–**f**, we exclusively observed the slow reactions at the carbon center, and with the less-stabilized benzhydrylium ions **2g**–**i**, the fast reactions at the tertiary nitrogen atom were monitored (Table 2).

From the absorbances of **2g**–**i** immediately after irradiation and after reaching the stationary state (the plateau shown in Figure 1 b), that is, when the equilibrium $\mathbf{1} + \mathbf{2} \rightleftharpoons \mathbf{4}$ is fully established but the benzhydrylium ions are not yet consumed by C-attack at the hydrazones, the equilibrium constants can also be derived for N-attack, which are listed in the right column of Table 2 (for details see pp. S14–S16 of the Supporting Information).

These interpretations are in line with the existence of two distinct correlation lines for **1a** as well as for **1b** in Figure 2. As the rate constants for carbon attack (lg k_C) and nitrogen attack (lg k_N) of the benzhydrylium ions **2** at **1a** and **1b** correlate linearly with the empirical electrophilicity parameters *E* of the benzhydrylium ions **2**, Equation (1) is applicable and can be used to determine the *N* and s_N parameters for the C- and N-positions of the aza-enamines **1a**,**b**, which are shown in Scheme 5. Figure 2 and Table 2 show that the nitrogen termini of the hydrazones **1a**,**b** are about three orders of magnitude more nucleophilic than the carbon termini.

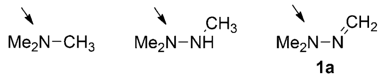
		N, s_N [a]		*N*, s_N [a]
1a		6.98, 0.85		19.31, 0.46
1b		7.84, 0.89		17.90, 0.48

[a] *N* and s_N as defined by Equation (1).

Scheme 5. *N* and s_N parameters for the hydrazones **1 a**,**b** in CH_2Cl_2.

As in the enamine series,[13] the C-nucleophilicity of the pyrrolidino derivative **1b** is one order of magnitude greater than that of the corresponding dimethylamino derivative **1a** because of the more efficient $n\rightarrow\pi$ electron donating ability of the pyrrolidine ring.[1b]

In previous work, we have shown that the reactions of benzhydrylium ions with tertiary amines proceed with almost equal rates in acetonitrile and in dichloromethane.[14] Therefore, it is possible to directly compare the rate constants in Scheme 6, even though the values for trimethylamine and trimethylhydrazine refer to acetonitrile and that for **1a** refers to CH_2Cl_2. As discussed previously, trimethylamine is more nucleophilic than the tertiary nitrogen in trimethylhydrazine,[14c] which implies that the retarding inductive effect of the H_3CNH group compared to CH_3 is more important than the



			1a
k_{rel} (**2g**) =	13 [a,b]	1.0 [a]	0.36

Scheme 6. Relative nucleophilicities of trimethylamine, trimethylhydrazine, and the tertiary nitrogen of **1 a**. [a] Data in MeCN from Ref. [14]. [b] Calculated by using *N* and s_N from Ref. [10a] and *E* from Table 1.

activation by H_3CNH through the α-effect. We now find that replacement of a methyl group in trimethylhydrazine by a methylene group (→**1a**) reduces the nucleophilicity only by a factor of 2.8 (Scheme 6).

The smallness of this effect can be explained by the fact that the terminal nitrogen of **1a** is pyramidally coordinated such that its lone pair interacts only weakly with the π_{NC} system, as demonstrated by the quantum chemically calculated structures of **1a** and related molecules (Supporting Information, page S17).

While nucleophilicity parameters for ordinary enamines with terminal double bonds are not available, Figure 3 shows that the 2-aza-enamines **1a** and **1b** are significantly less nucleophilic than common enamines[13,15] and possess C-nucleophilicities comparable to those of enamides.[16]

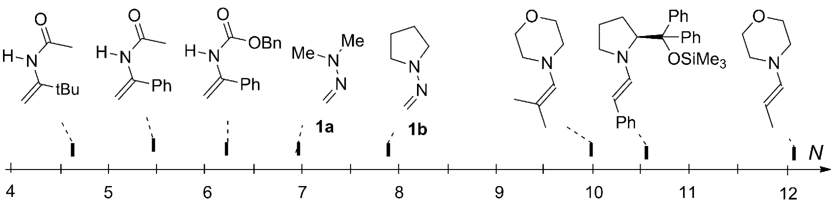
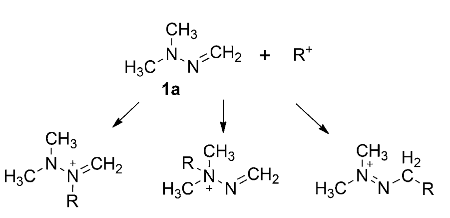


Figure 3. Comparison of the nucleophilicity parameters *N* of the hydrazones **1a**,**b** with those of enamines and enamides (*N* values from Scheme 5 and Refs. [13,15,16]).

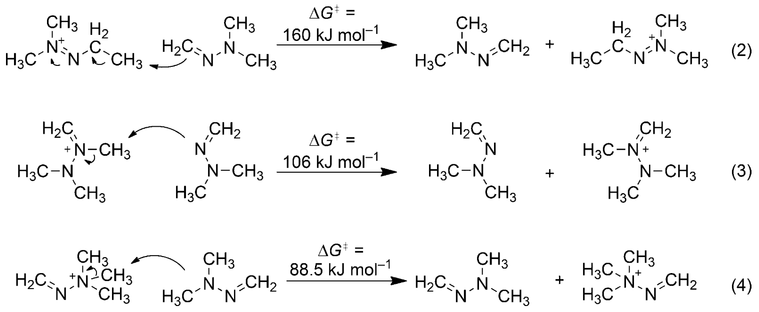
In previous work,[2] we have rationalized ambident reactivity by Marcus theory,[9] which describes activation free energies $\Delta G^{\neq}$ by a combination of reaction free energies ΔG^0 and intrinsic barriers $\Delta G_0^{\neq}$, the latter of which correspond to the barriers of identity reactions. Following this approach, we have now calculated the Gibbs free energies for the addition of methyl and benzhydryl cations to the three different nucleophilic centers of the hydrazone **1a** (Scheme 7) and the free energies of activation for the degenerate methyl transfer reactions (Scheme 8).



$R^+ = CH_3^+$ [a]	–443	–455	–458
$R^+ = Ph_2CH^+$ [b]	–108	–110	–117
$R^+ = Ph_2CH^+$ [c]	–98.6	–101	–119

[a] In the gas phase [MP2/6-311+G(2d,p)]
[b] In the gas phase [MP2/6-311+G(2d,p)//B3LYP/6-31G(d,p)]
[c] In CH_2Cl_2 (IEFPCM) [MP2/6-311+G(2d,p)//B3LYP/6-31G(d,p)]

Scheme 7. Gibbs free energies (ΔG^0, kJ mol^{-1}) for methyl and benzhydryl cation additions to the three nucleophilic centers of 1,1-dimethyl-2-methylenehydrazine **1a** in the gas phase and in dichloromethane solution.



Scheme 8. Gibbs free energies of activation for the identity reactions (2)–(4) (MP2/6-311+G(2d,p) level of theory).

Scheme 7 shows that methyl cation as well as benzhydryl cation addition at carbon is thermodynamically favored over electrophilic attack at the nitrogen centers. The preference for carbon attack of $R^+ = Ph_2CH^+$ is calculated to be 7 kJ mol^{-1} in the gas phase and 18 kJ mol^{-1} in dichloromethane solution, in accord with the experimental observation that **3a** is formed exclusively under thermodynamically controlled conditions (Scheme 2).[12a]

The barriers of the identity methyl transfer reactions are calculated to increase significantly from Equation (4) ($N_{sp3} \rightarrow N_{sp3}$) over Equation (3) ($N_{sp2} \rightarrow N_{sp2}$) to Equation (2) ($C_{sp3} \rightarrow C_{sp2}$). It should be noted that the activation energies of the reactions (2) and (4) are comparable to those calculated for the corresponding identity reactions at the C- and N-terminus of vinylamine (149 and 99.2 kJ mol^{-1}, respectively),[2] the carbon analogue of **1a**. The ordering of $\Delta G^{\neq}$ of Equations (2)–(4) shows that electrophilic attack at the terminal nitrogen of **1a** is highly favored intrinsically, while electrophilic attack at carbon has the highest intrinsic barrier. As the calculated reaction free enthalpies in Scheme 7 and the intrinsic barriers in Scheme 8 can also be expected to reproduce the relative magnitudes of $\Delta\Delta G^0$ and $\Delta\Delta G_0^{\neq}$ for reactions in solution, it can now be qualitatively explained why hydrazones are attacked at the sp^3 nitrogen under kinetically controlled and at carbon under thermodynamically controlled conditions.

In conclusion, we have shown that the tertiary nitrogen centers in the *N*,*N*-dialkylformaldehyde hydrazones **1a** and **1b** are approximately three orders of magnitude more nucleophilic than the azomethine carbons. If the electrophilic attack at the tertiary nitrogen is reversible, the thermodynamically more stable products of carbon attack are formed. Following the rule of thumb that electrophile–nucleophile combinations take place at ambient temperature if $E + N$ (as defined by Eq. (1)) is greater than about -5,[10] the value of $N \approx 7$ for **1** derived in this work implies that electrophiles with $E > -12$ should be able to attack the carbon of **1** at room temperature. One can thus explain why Mannich salts ($E = -6.7$), Vilsmeier reagents ($E = -5.8$), and nitrostyrenes ($E \approx -12$) undergo uncatalyzed reactions with hydrazones,[1] whereas weaker electrophiles, for example, enones ($E \approx$

−18), aldehydes ($E \approx -19$), or weakly activated imines ($E \approx -14$) require Brønsted or Lewis acid activation for reactions with hydrazones.[5,6]

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