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VIP *Very Important Paper*

2-Methylene-1,2-dihydropyridines (2-pyNHOs): Highly Nucleophilic Enamines

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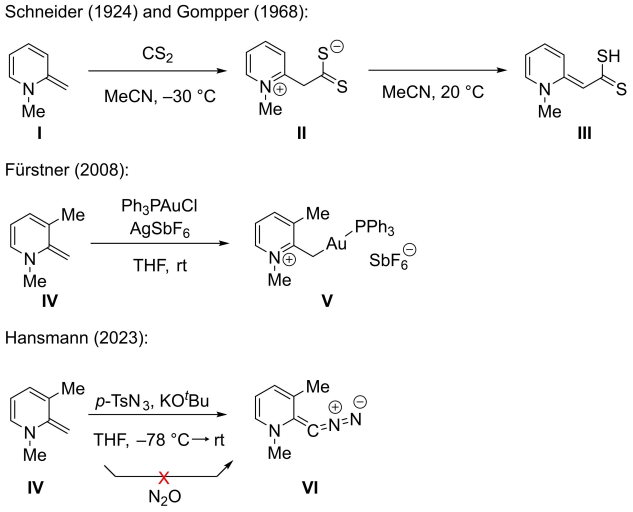
The high reactivity of 2-methylene-1,2-dihydropyridines also known as 2-methylpyridinium derived *N*-heterocyclic olefins (2-pyNHOs) has been recognized in organic synthesis, yet a quantification of their nucleophilicity is lacking. Herein we used stopped-flow photometry to determine the nucleophilicity of a series of 2-pyNHOs from the kinetics of their reactions with quinone methides and benzhydrylium ions as reference electrophiles in four organic solvents at 20 °C. The kinetic data was evaluated by using the Mayr-Patz equation, $\lg k(20\,^{\circ}C) = s_N(N + E)$, which gave nucleophilicity parameters N (and s_N). With N in the range of 19.4–21.2 (in DMSO), 2-pyNHOs exceed the reactivity of classical enamines, such as pyrrolidino-cyclopent-1-ene. The addition of 2-pyNHOs to quinone methides resulted in the formation of zwitterionic adducts with pyridinium and phenolate moieties. Subsequent tautomerization yielded entirely neutral pyridine-2(1*H*)-ylidene-phenol species in several cases. Formation of the zwitterionic adducts from 2-pyNHOs and neutral electrophiles was almost equally fast in the polar solvents acetonitrile and DMSO, but proceeded one to two orders of magnitude slower in the less polar solvents dichloromethane or THF.

Introduction

Enamines constitute key intermediates in organic synthesis[1] and organocatalysis.[2] One special class of enamines are 2-methylene-1,2-dihydropyridines, in which the amino group is part of an unsaturated six-membered heterocycle (Scheme 1).

Several groups reported that 1-methyl-2-methylene-1,2-dihydropyridine **I** added, as expected for the reactivity of enamines, via the exocyclic methylene unit to sufficiently reactive electrophilic heterocumulenes. For example, **I** reacts with carbon disulfide, followed by proton migration forming the colored product **III** (Scheme 1). Analogous addition reactions to phenyl iso(thio)cyanate have also been described.[3,4]

In 2008, Fürstner *et al.* investigated 2-methylene-1,2-dihydropyridines as C-centered ligands in the coordination sphere of Au(I) complexes, as depicted for the reaction of **IV** to give **V** in Scheme 1.[5] Recently the Hansmann group utilized **IV** to access the pyridine-derived diazoalkene **VI** via diazo transfer from *p*-tosylazide.[6] Interestingly, however, **IV** was not sufficiently reactive to add to N_2O directly to give the diazoalkene **VI**, as it was previously observed with mesoionic *N*-heterocyclic olefins (mNHOs).[7]



Scheme 1. Reactions of 2-methylene-1,2-dihydropyridines (2-pyNHOs).

We recently quantified the nucleophilicities of highly reactive mNHOs derived from 1,2,3-triazolium salts ($N = 21$–32),[8] as well as the nucleophilicities of mesoionic NHOs derived from 3-methylpyridinium salts (e.g. py-mNHO with N~26, Figure 1).[9] Owing to the lack of reactivity of 2-pyNHO **IV** with N_2O, we suspected a lower nucleophilicity of 2-methylene-1,2-dihydropyridines (2-pyNHOs) than for mNHOs. However, it

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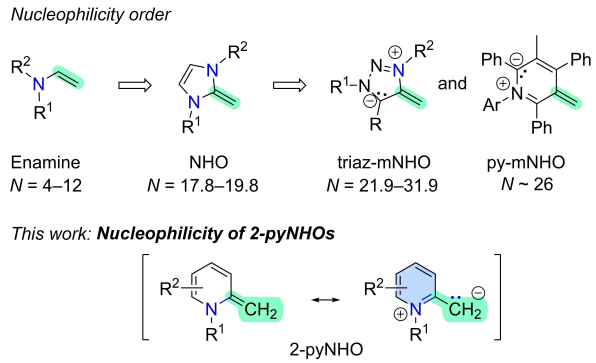

Figure 1. Enamines and various types of nucleophilic NHOs (ordered by their Mayr nucleophilicity parameter *N*).

remained unclear whether 2-pyNHOs are located in the reactivity range of classical enamines or reach the level of cyclic ketene aminals (1,1-enediamines),[10] which have more recently been termed *N*-heterocyclic olefins (NHOs, Figure 1).[11]

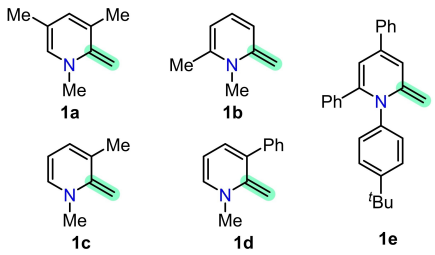

Figure 2. Structures of 2-methylene-1,2-dihydropyridines (2-pyNHOs) **1 a**–**1 e** investigated in this work.

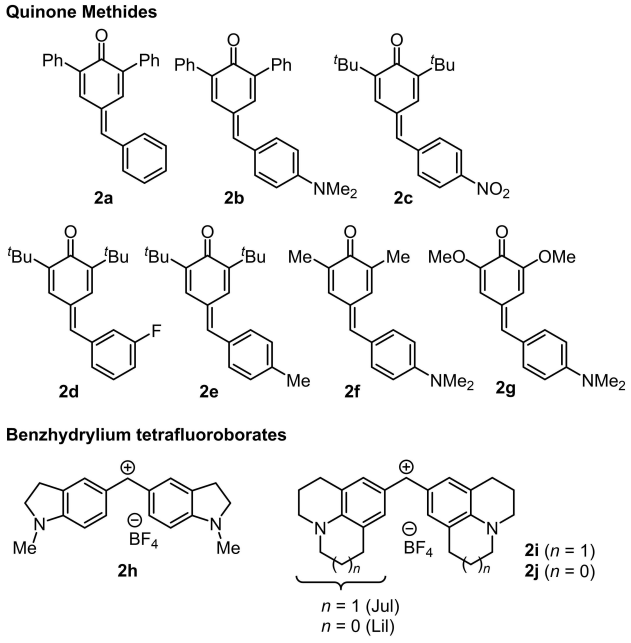

Figure 3. Reference electrophiles **2** used in this work (Jul = julolidin-9-yl, Lil = lilolidin-8-yl).

To further explore the scope and limitations of 2-pyNHOs as nucleophiles in organic synthesis, we set out to study their reactivity towards cationic and neutral electrophiles in more detail. In order to quantify the nucleophilicity of the 2-pyNHOs **1 a**–**1 e** (Figure 2) and facilitate the comparison with other types of enamines, NHOs, mNHOs, as well as with entirely different types of nucleophiles in general, we evaluated the kinetics of 2-pyNHO reactions with the well-established reference electrophiles **2** (Figure 3) within the comprehensive reactivity scales that were established by H. Mayr.[12–14]

By using the framework of the benzhydrylium methodology,[12d] following the kinetics of the reactions of 2-pyNHOs **1** with a series of reference electrophiles (**2**) yields second-order rate constants k_2 for carbon-carbon bond-forming reactions under defined conditions, that is, in a given solvent at a certain temperature. In Equation (1), the rate constants k_2 of the 2-pyNHOs/reference electrophile reactions can then be used along with reported electrophilicity parameters *E* of **2** to calculate the solvent-dependent nucleophilicity parameters *N* (and s_N) of **1**.

$$\lg k_2(20\,^{\circ}\mathrm{C}) = s_N(N + E) \tag{1}$$

Our product studies showed that the carbon-carbon bond-forming reactions of **1** with **2** yielded zwitterionic adducts in many cases. To accommodate solvent effects on the rates of the adduct formation, we investigated the **1** + **2** reactions in four different solvents (DMSO, CH_3CN, THF, and CH_2Cl_2).

Owing to the fact that currently > 1290 nucleophiles have been classified on the Mayr reactivity scale,[14] the 2-pyNHOs **1** can be comprehensively compared with other, structurally diverse types of nucleophiles. Furthermore, Equation (1) enables to predict novel reactions of 2-pyNHOs with electrophiles. Thus, in this work, we also demonstrate how Equation (1) can be used as a tool to widen the applications of 2-pyNHOs in organic synthesis.

Results and Discussion

Synthesis of 2-pyNHOs and Characterization of 2-pyNHOs/Electrophile Adducts

A series of differently substituted 2-methyl pyridinium salts **3 a**–**3 d** (Scheme 2, route A) as well as one *N*-aryl pyridinium salt (**3 e**) (Scheme 2, route B) were synthesized in one or two synthetic steps. The deprotonation of the respective 2-pyNHO precursors with potassium hydride in diethyl ether furnished **1 a**–**1 c** in excellent yields (88–91 %).[6] The methyl-substituted 2-pyNHOs **1 a**–**1 c** are relatively volatile and air sensitive yellow liquids at room temperature. The novel aryl-substituted 2-pyNHOs **1 d** and **1 e** were obtained by deprotonation of the 2-methyl pyridinium salts precursors with a slight excess of KHMDS (1.1 equiv.) in THF and isolated as orange solids in excellent yields (**1 d**: 98 %, **1 e**: 99 %).

The donor properties of a variety of NHOs was previously determined utilizing the Tolman electronic parameter (TEP).[15]

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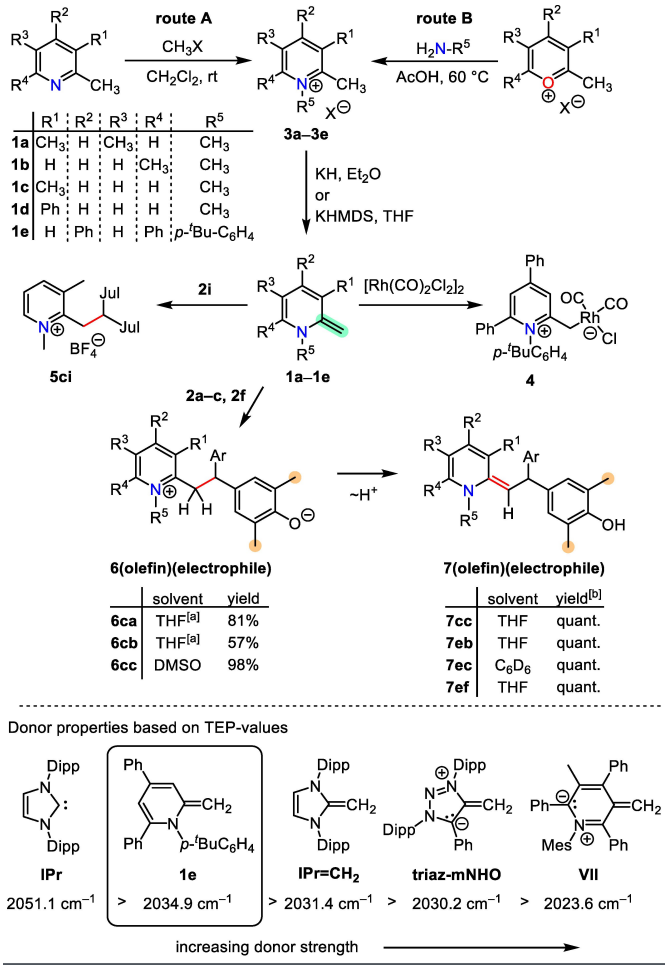


	R1	R2	R3	R4	R5
1a	CH3	H	CH3	H	CH3
1b	H	H	H	CH3	CH3
1c	CH3	H	H	H	CH3
1d	Ph	H	H	H	CH3
1e	H	Ph	H	Ph	p-tBu-C6H4

	solvent	yield
6ca	THF[a]	81%
6cb	THF[a]	57%
6cc	DMSO	98%

	solvent	yield[b]
7cc	THF	quant.
7eb	THF	quant.
7ec	C6D6	quant.
7ef	THF	quant.

Scheme 2. Synthetic route to yield the 2-pyNHOs **1**. Reactions of 2-pyNHOs **1** with electrophiles **2** led to zwitterionic adducts **6** (or cationic adduct **5 ci**). Some zwitterions **6** subsequently underwent proton transfer to furnish the entirely neutral tautomers **7**. [a] Low solubility in THF leads to precipitation of **6**, preventing a follow-up reaction to **7**. [b] Determined by NMR spectroscopy. Bottom: Summary of TEP values obtained from the corresponding $LRh(CO)_2Cl$ complexes in dichloromethane solution (Dipp = 2,6-diisopropylphenyl; Mes = mesityl).

The TEP is determined by IR-spectroscopy of the $[LRh(CO)_2Cl]$ complex in CH_2Cl_2 solution and calculated from the relationship $TEP = 0.8001\nu_{av} + 420\ cm^{-1}$.[16] A decreasing TEP value indicates increasing overall (σ-donor and π-backbonding) donor strength. The rhodium complex **4** was synthesized from 2-pyNHO **1 e** (Scheme 2). As expected **1 e** ($\nu_{av} = 2018.3\ cm^{-1}$, $TEP = 2034.9\ cm^{-1}$) is a significantly weaker donor than the mesoionic py-mNHO **VII** ($TEP = 2023.6\ cm^{-1}$)[9] as well as the NHO **IPr = CH$_2$** ($TEP = 2031.4\ cm^{-1}$)[7a,15] but an overall stronger donor than NHCs, such as **IPr** ($TEP = 2051.1\ cm^{-1}$) (Scheme 2).[16] However, it has been shown for mNHOs that relative nucleophilicities cannot be derived from the ordering of TEP values.[8]

To gain a first insight into the reactivity of **1** with electrophiles, **1 c** was reacted with the benzhydrylium tetrafluoroborate **2 i** in DMSO, which quantitatively yielded the pyridinium tetrafluoroborate **5 ci** (Scheme 2).[17] Furthermore, we conducted more extensive product studies of the reactions of 2-pyNHOs with the neutral quinone methide electrophiles **2 a–c** and **2 f**. While the reactions of the 2-pyNHO **1 c** with the quinone methides **2 a** and **2 b** in THF yielded zwitterionic adducts **6 ca** and **6 cb** at room temperature,[17] analogous zwitterions could not be observed for reactions of **1 e** with **2 b** (in THF), **2 c** (in benzene), and **2 f** (in THF), where the initial addition was followed by a fast proton transfer from the exocyclic methylene group to the basic phenolate oxygen to give the entirely neutral tautomers **7**.

To investigate the solvent effect on the equilibrium between the tautomers **6** and **7**, we first isolated **6 cc** as a violet, microcrystalline solid from the reaction of **1 c** with **2 c** in DMSO. A solution of **6 cc** in d_6-DMSO proved stable over at least four days at room temperature. However, upon exchanging the solvent to THF, a color change within a few seconds from dark blue to intense yellow was observed. Reaction monitoring by low temperature UV-vis spectroscopy (Figure 4) as well as NMR studies of the reaction product in d_8-THF (Figures S8–S12, Supporting Information) indicate the formation of a mixture of (*E*)- and (*Z*)-**7 cc** double bond isomers ((*E*)/(*Z*) = 4/3, Scheme 3), which slowly decomposes at room temperature.

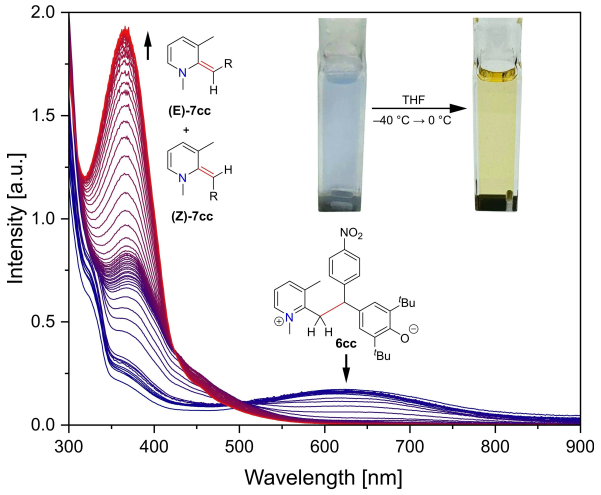
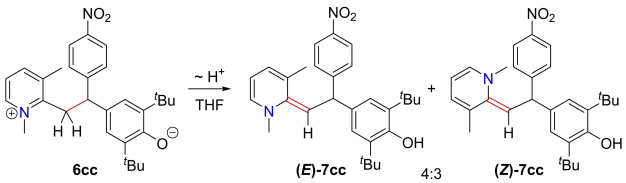


Figure 4. UV-vis spectra (4 spectra/min) in course of the conversion of **6 cc** to a mixture of (*E*)- and (*Z*)-**7 cc** in THF, measured in a 1.0 cm quartz cuvette upon warming from −40 °C (dark blue) to −20 °C (violet) to 0 °C (red); Datapoints during temperature changes were omitted (1.25 min). Complete structures of (*E*)-**7 cc**, and (*Z*)-**7 cc** are shown in Scheme 3. Insert: Photographs of solutions of **6 cc** in THF at −40 °C and (*E*)/(*Z*)-**7 cc** in THF at room temperature.



Scheme 3. Tautomerization of **6 cc** in THF to give a mixture of (*E*)- and (*Z*)-**7 cc**.

Kinetics of 2-pyNHO Reactions with Reference Electrophiles

The kinetics of reactions of **1** with electrophiles **2** (structures are shown in Figure 3) in DMSO, acetonitrile, THF, or dichloromethane were monitored by stopped-flow UV/vis spectrophotometry under (pseudo)-first-order conditions, that is, by using one of the reactants in an at least 5-fold excess over the reaction partner. The temperature of the drive syringes, the flow circuit, and the observation cell of the stopped-flow instrument was maintained constant at 20 °C (±0.2 °C) by use of a circulating bath cryostat. To hamper degradation of nucleophiles and electrophiles by oxidation or reactions with trace water, all solutions were prepared in dry glassware under an atmosphere of dry argon. In the majority of the kinetic measurements, either the decrease of the absorption of the nucleophilic 2-pyNHOs **1** or that of the electrophile was followed at or close to their absorption maximum (λ_{max}).[17]

Under these conditions, the (pseudo)-first-order rate constants k_{obs} (s^{-1}) were derived from a least squares fit of the function $A_t = A_0 \exp(-k_{obs}t) + C$ to the time-dependent absorbance of the decaying colored species, as exemplified for the reaction of **1a** with **2b** to give the zwitterionic adduct **6ab** in Figure 5. The linear increase of k_{obs} with the concentration of the 2-pyNHOs (as shown in Figure 5c) made it possible to determine the second-order rate constants k_2 ($M^{-1}s^{-1}$) from the slopes of the linear relationships.

Kinetics of reactions of **1a–1d** with the *p*-NO_2-substituted quinone methide **2c** in DMSO (and acetonitrile) were monitored by following the increase of absorption at 575 nm, that is, by following the formation of the respective zwitterions **6**. The rate constants k_{obs} (s^{-1}) were then derived from a least squares fit of the function $A_t = A_0\{1-\exp(-k_{obs}t)\} + C$ to the time-dependent absorbances of the colored species. Second-order rate constants k_2 ($M^{-1}s^{-1}$) were calculated as described above from the slope of the linear correlation of k_{obs} with the concentration of the excess compound.

Table 1 lists the second-order rate constants k_2 for reactions in DMSO. Details of the individual kinetic measurements are given in the Supporting Information.

With the same number of methyl groups at the heterocycle, **1b** and **1c** are almost equally reactive towards cationic and neutral reference electrophiles. However, the 1,3-dimethyl substitution pattern introduces a slightly stronger steric shielding of the reactive exocyclic methylene group at C-2 of **1c** than at the C-2 of **1b**, which gives rise to 1.7- to 4-fold higher second-order rate constants for the reactions of the 1,6-dimethyl-substituted 2-pyNHO **1b** with the same set of electrophiles. Introducing a third methyl substituent, as in 2-pyNHO **1a**, generates a nucleophile which is at average two-fold as reactive as **1b**.

Attachment of a phenyl ring at C-3, that is, in the vicinity of the reactive C-2 methylene position, as in 2-pyNHO **1d**, further reduces the nucleophilicity in comparison to the C-3 methylated 2-pyNHO **1c** presumably due to the slightly electron-withdrawing property ($\sigma_m = +0.06$) and the enhanced steric demand of the phenyl group. Finally, the 1,4,6-triaryl-substituted 2-pyNHO **1e** shows roughly the same reactivity towards the reference electrophiles as the 1,3-dimethyl-substituted 2-pyNHO **1c**.

Evaluating the second-order rate constants from Table 1 according to the Mayr-Patz Equation (1) by correlating the logarithmic second-order rate constants (lg k_2) with the electrophilicity parameters *E* of the reference electrophiles as shown in Figure 6 furnished the nucleophilicity descriptors *N* (and s_N) of the 2-pyNHOs **1a–1d**, which are listed in the bottom line of Table 1. The analogous graph for **1e** is shown in the Supporting Information (Figure S89).

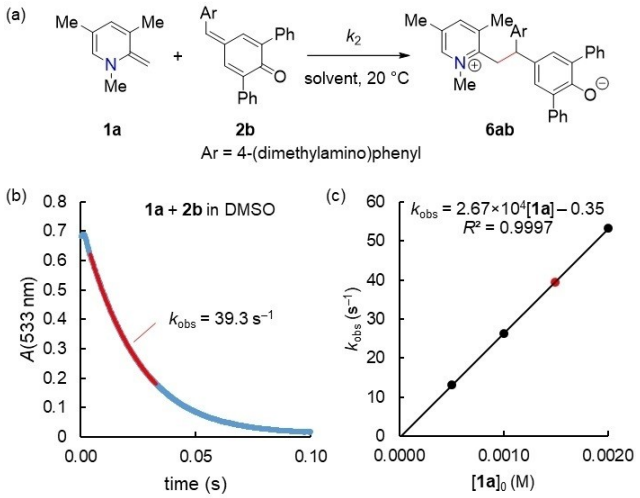


Figure 5. (a) Reaction of the 2-pyNHO **1a** with the reference electrophile **2b** to give the zwitterionic adduct **6ab**. (b) Exponential decay of the absorbance *A* at 533 nm for the reaction of **1a** ($c_0 = 1.50\times10^{-3}$ M) with **2b** ($c_0 = 2.00\times10^{-5}$ M) in DMSO at 20 °C. (c) Determination of the second-order rate constant k_2 for **1a** with **2b** from the slope of the linear correlation between k_{obs} and [**1a**].

Solvent Effects

To assess the reactivity of 2-pyNHOs in typical organic solvents, the kinetics of the reactions of the 2-pyNHO **1c** with electrophiles **2** were also determined in acetonitrile, dichloromethane, and THF solution. As shown in Table 2, 2-pyNHO **1c** reacts by a factor of two slower in acetonitrile than in DMSO. The relatively constant offset between the **1c** reactivities in DMSO and MeCN over the entire reactivity range, comprising of neutral and cationic electrophiles, enables one to mutually convert the second-order rate constants k_2 for reactions in these two solvents by Equation (2), which is graphically depicted in Figure 7a.

$$\lg k_2(\mathrm{MeCN}) = \lg k_2(\mathrm{DMSO}) - 0.275 \qquad (2)$$

Furthermore, the rate constants for reactions of 2-pyNHO **1c** with electrophiles in acetonitrile from Table 2 were evaluated by Equation (1) to calculate $N = 19.69$ (and $s_N = 0.61$) as reactivity descriptors for **1c** in MeCN, which can be used to predict reaction rates of **1c** with both neutral and cationic electrophiles (Figure 7b).

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Table 1. Second-order rate constants k_2(20 °C) for the reactions of 2-pyNHOs **1a–1e** with the reference electrophiles **2** in DMSO.

Electrophiles	E[a]	k_2 ($M^{-1}s^{-1}$)				
		1a	**1b**	**1c**	**1d**	**1e**
2a	−11.87	–	–	–	–	1.02×10^5
2b	−13.39	2.67×10^4	2.02×10^4	9.81×10^3	2.47×10^3	9.67×10^3
2c	−14.36	1.64×10^4	9.33×10^3	3.49×10^3	1.32×10^3	3.11×10^3
2f	−16.36	8.13×10^2	4.59×10^2	1.61×10^2	9.59×10^1	–
2g	−17.18	2.01×10^2	1.16×10^2	–	2.49×10^1	–
2i	−9.45	–	–	–	–	7.23×10^6
2j	−10.04	4.34×10^6	2.47×10^6	1.46×10^6	7.59×10^5	1.70×10^6
N (s_N)		21.16 (0.59)	20.76 (0.60)	19.91 (0.62)	19.41 (0.61)	19.36 (0.68)

[a] With electrophilicity parameters E from Ref. [14].

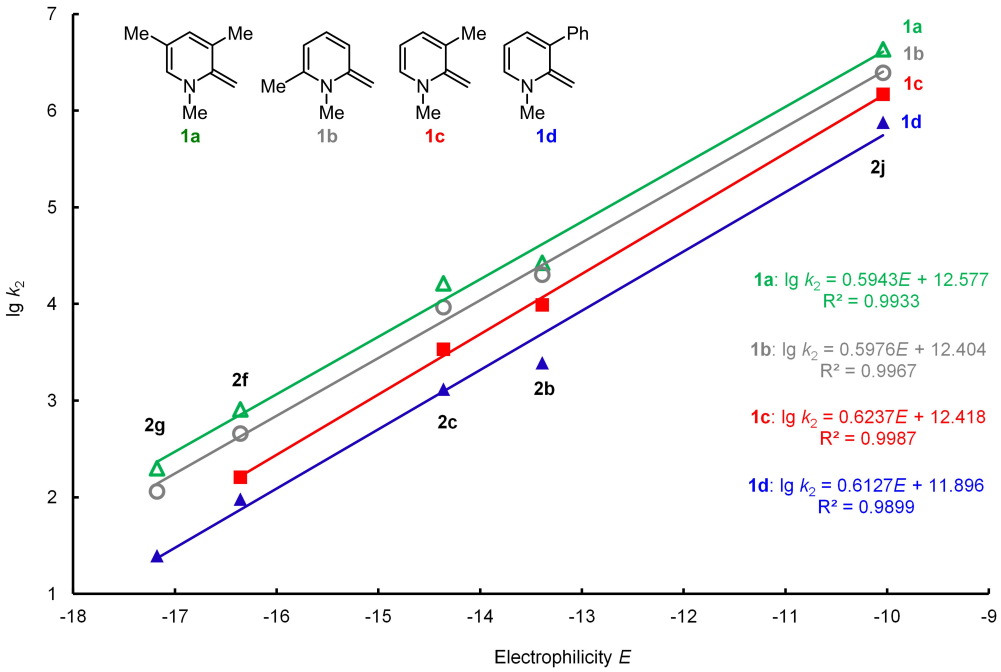

Figure 6. Plot of lg k_2 (DMSO, 20 °C) against the electrophilicity parameters E of the reference electrophiles **2** (with data from Table 1).

The reported addition reactions of 2-pyNHOs, such as **I** (see Scheme 1), to the electrophilic heterocumulene carbon disulfide (CS_2: $E=-17.70$)[18] under mild conditions[3] is in perfect agreement with an estimated second-order rate constant of k_2(20 °C) = 10–100 $M^{-1}s^{-1}$ for this electrophile-nucleophile combination.[19] Analogous addition reactions of 2-pyNHO **I** with phenyl isocyanate ($E=-15.38$)[18] and phenyl isothiocyanate ($E=-18.15$)[18] further corroborate the high reactivity level of the exocyclic π-bond of 2-pyNHOs.[3]

As can be expected for reactions of a neutral substrate with a cationic reaction partner yielding a positively charged product, the reactions of **1c** with the benzhydrylium ion **2j** are almost insensitive towards solvent variation. As a consequence, the k_2-values for the **1c**+**2j** adduct formation are all found within one order of magnitude when comparing the solvents DMSO, acetonitrile, dichloromethane, and THF (Table 2).

The combination of neutral reactants to furnish zwitterionic products occurs slower in the less polar solvents dichloromethane and THF than in MeCN or DMSO. Thus, reactions of 2-pyNHO **1c** with the neutral *p*-quinone methides **2b** are by a factor of 78 faster in DMSO than in THF (by factor of 11 in dichloromethane).

The superimposition of absorption spectra of the reactants prevented us from following the kinetics of consumption of the starting materials of reactions of **1c** with **2c–2e** by photometry. Rate constants k_2 of **1c**+**2** reactions in THF, which were determined by following the increase of absorption (λ = 575–650 nm) during formation of colored adducts **6**, were only weakly correlated with the electrophilicities E of the *p*-quinone methides **2**, however. This loss of correlation was even more obvious for the analogous reactions of **1c** with **2c–2e** in dichloromethane, which occurred at rates that were almost

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Table 2. Second-order rate constants k_2(20 °C) for the reactions of 1,2-dihydro-1,3-dimethyl-2-methylenepyridine (**1 c**) with the reference electrophiles **2** in DMSO, acetonitrile (MeCN), dichloromethane (DCM), and THF.

Electrophiles	E[a]	k_2 ($M^{-1}s^{-1}$)			
		DMSO	MeCN	DCM	THF
2 h	−8.76	–[b]	–[b]	2.66×10^{6}	5.08×10^{6}
2 i	−9.45	–[b]	–[b]	2.32×10^{6}	–
2 j	−10.04	1.46×10^{6}	8.90×10^{5}	6.39×10^{5}	1.15×10^{6}
2 b	−13.39	9.81×10^{3}	4.63×10^{3}	8.92×10^{2}	1.25×10^{2}
2 c	−14.36	3.49×10^{3}	1.85×10^{3}	–[c]	–[c]
2 d	−15.03	–[b]	–[b]	–[b]	–[c]
2 e	−15.83	–[b]	–[b]	–[c]	–[c]
2 f	−16.36	1.61×10^{2}	9.72×10^{1}	4.41×10^{1}	2.04
2 g	−17.18	–[b]	4.19×10^{1}	2.15×10^{1}	4.97×10^{-1}

[a] With electrophilicity parameters E from Ref. [14]. [b] Not determined. [c] Only gross rate constants could be determined by following the increase of absorption, which was assigned to the rate of product **6** formation. Owing to concomitant tautomerization from the initial adduct **6** to **7**, these rate constants do not reflect a simple carbon-carbon bond-forming reaction but more complex kinetics.

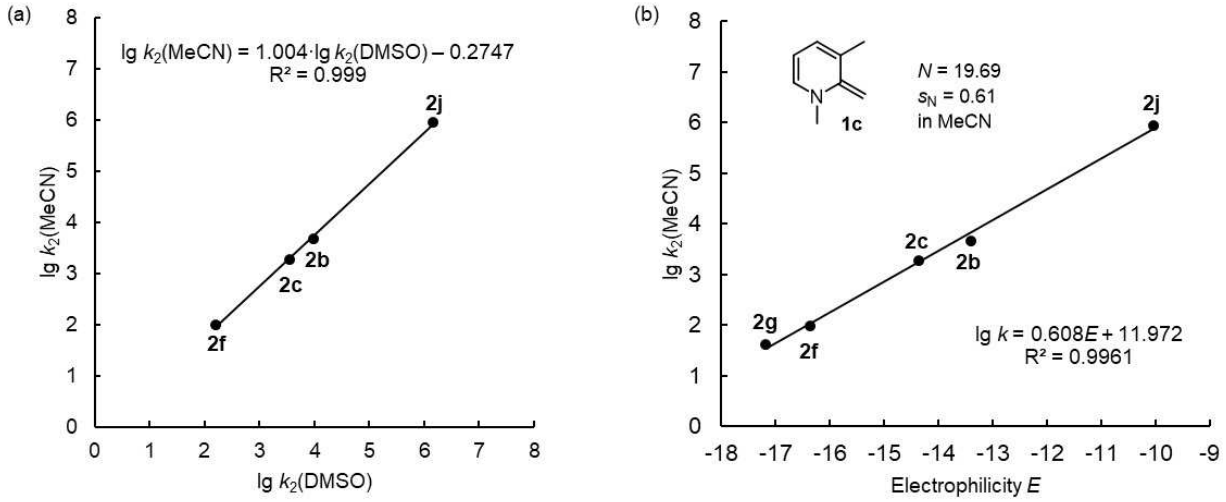

Figure 7. (a) Comparison of the reactivity of **1 c** towards electrophiles **2 b**, **2 c**, **2 f**, and **2 j** in MeCN with that in DMSO. (b) Linear correlation of second-order rate constants (lg k_2) with electrophilicity descriptors E for reactions of **1 c** with neutral and positively charged reference electrophiles in acetonitrile (20 °C).

unrelated to the E parameter of the *p*-quinone methides **2**. We rationalize this observation by tautomerization of the initially formed (colored) zwitterionic adduct **6** to give species **7** (cf. Figure 4). Owing to this subsequent reaction, a part of **6** is consumed even at the millisecond and seconds time scale of the kinetic measurements at 20 °C. Following the increase of the absorption of **6**, thus, gave too low values for rate constants owing to the tautomerization which rapidly converted **6** to **7** (see Figure 4). We could, therefore, only measure gross rate constants for reactions of **1 c** with **2 c**–**2 e** in dichloromethane and THF, and nucleophilicity parameters N (and s_N) for **1 c** in dichloromethane and THF could not be determined.

Reactivity Comparison of 2-pyNHOs with Other 1,1-Disubstituted Olefins

By positioning 2-pyNHOs on Mayr's nucleophilicity scales, the reactivities of the 2-pyNHOs **1 a**–**1 e** become comparable with those of other enamines that are derived from various secondary amines and ketones or aldehydes.[20]

The nucleophilicity scale in Figure 8 illustrates that classical 1-alkyl or 1-aryl substituted enamides or enamines are located at a reactivity range from $4 < N < 12$. Introduction of alkyl substituents at the 2-position of the π-bond further increases the electron density and gives rise to enhanced nucleophilic reactivities ($13 < N < 17$) for enamines derived from cyclopentanone or cyclohexanone.[21]

The addition of an electrophile to the carbon-carbon double bond of an enamine yields iminium ions. In contrast, electro-

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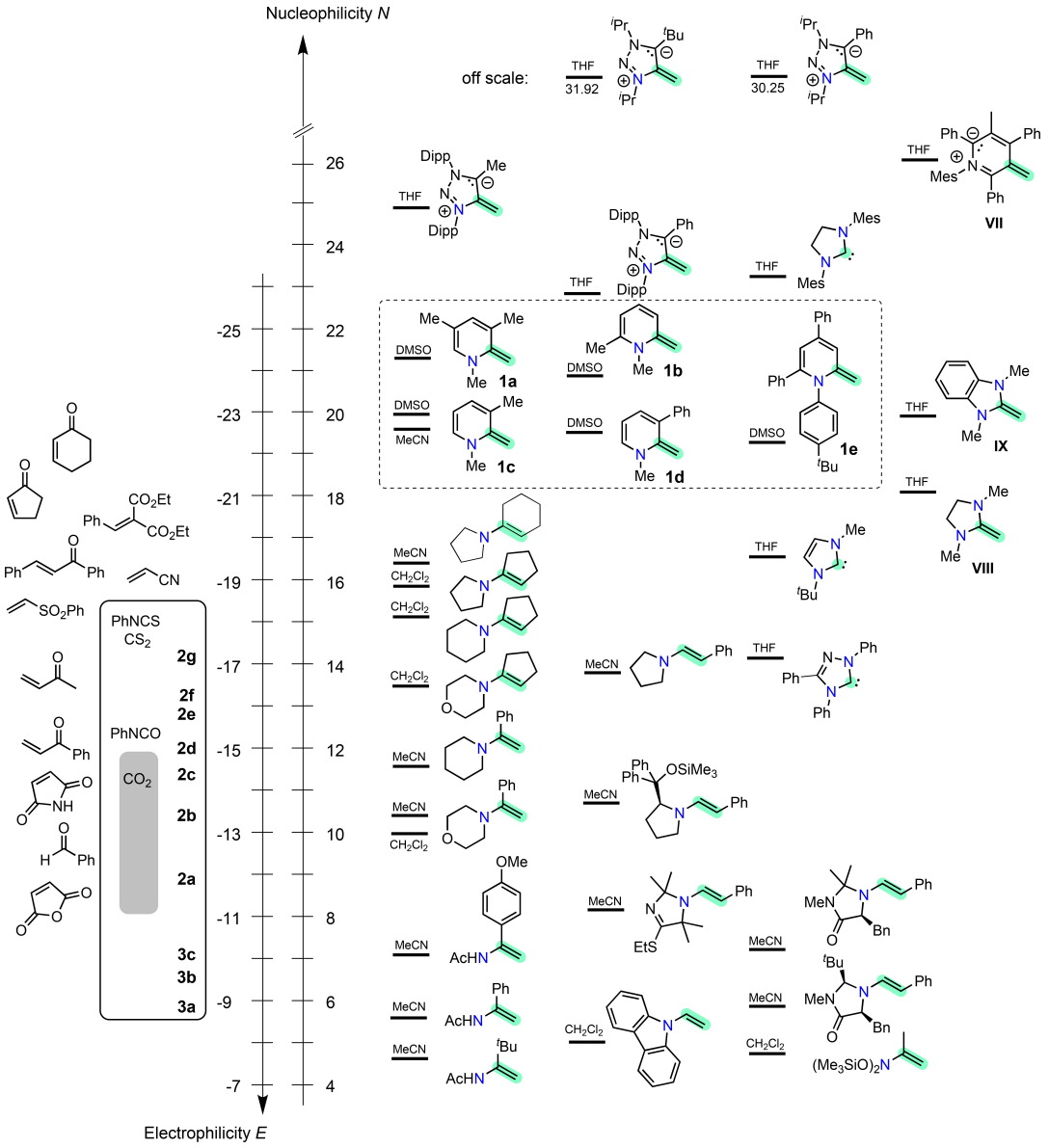

Figure 8. Comparison of the 2-pyNHOs **1a**–**1e** (in the dashed frame) with structurally related nucleophiles (enamides, enamines, NHOs, mNHOs or NHCs) on the nucleophilicity scale (Dipp = 2,6-diisopropylphenyl, Mes = mesityl) combined with the reactivity scale of selected, potential carbon-centered electrophilic reaction partners (electrophiles in the frame have already been shown to react successfully with 2-pyNHOs **1**).

phile additions to the 1,2-dihydropyridine-derived enamines (2-pyNHOs) studied in this work, generate better stabilized pyridinium ions. Thus, the reactions of 2-pyNHOs benefit from the incipient aromatic character in the cationic part of the adducts which form via lower barriers than for structurally analogous classical enamines.[22a] As a consequence, the 2-pyNHOs are located at a level ($19.4 < N < 21.2$) on the nucleophilicity scale which is similar or even slightly higher than that of NHOs.[22b] Currently, only mesoionic compounds, such as the triaz-mNHOs or the py-mNHOs (e.g., **VII**) allowed for an even stronger π-bond polarization and higher nucleophilicities of 1,1-disubstituted olefins.

Conclusions

In conclusion, we used stopped-flow techniques to determine the nucleophilicities of methyl- and aryl-substituted 2-pyNHOs by following the kinetics of their reactions with reference electrophiles. The kinetic investigations were supported by product studies. The experimentally determined nucleophilicity values *N* in DMSO and acetonitrile are in the range of $N = 19.4$–21.2 (s_N ca. 0.6) on the Mayr reactivity scale, indicating significantly higher nucleophilic reactivity than observed for typical enamines that are utilized in organocatalysis. Yet, the 2-pyNHOs are clearly less reactive than mesoionic NHOs (mNHOs), which feature an even more pronounced carbon-carbon bond polarization that induces partial charge separation in the

exocyclic π-bond.[7a] This ranking is additionally supported by the Tolman electronic parameters.

Arranging the electrophilicity scale relative to the nucleophilicity scale in a way that at each horizontal level $E+N=-3$, as in Figure 8, enables one to predict new electrophilic reaction partners for 2-pyNHOs. With s_N parameters for 2-pyNHOs from 0.60 to 0.68, reactions of electrophile/2-pyNHO pairs at the same horizontal level will proceed with second-order rate constants of $k_2=10^{-2}\,M^{-1}s^{-1}$ at 20 °C, which corresponds to half-reactions times of 1000 seconds when 0.1 molar solutions of reactants are used. Even faster reactions can be expected if electrophiles with higher electrophilicities *E* are used, that is, if they are located at positions below the level of the 2-pyNHOs in Figure 8. The knowledge of nucleophilicities will be helpful in rationalizing and predicting the synthetic scope of the pyridine-derived olefins. Furthermore, the herein determined reactivities will facilitate the development of novel applications of 2-pyNHOs in organocatalysis. As we benefit from the improved precision of predictions for novel transformations, we are currently exploring further applications of 2-pyNHOs.

Supporting Information

The authors have cited additional references within the Supporting Information.[23–25]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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[1] a) P. W. Hickmott, *Tetrahedron* **1982**, *38*, 1975–2050; b) P. W. Hickmott, *Tetrahedron* **1982**, *38*, 3363–3446; c) G. H. Alt, A. G. Cook, in *Enamines: Synthesis, Structure, and Reactions* (Ed: A. G. Cook), Marcel Dekker Inc., New York **1988**, Ch. 4.
[2] a) For selected reviews on enamine catalysis, see: B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557; b) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; d) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; e) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; f) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; g) P. M. Pihko, I. Majander, A. Erkillä, *Asymmetric Organocatalysis* (Ed: B. List), *Topics in Current Chemistry*, Vol. 291. Springer, Berlin **2010**, 145–200; h) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632–649; i) R. C. Wende, P. R. Schreiner, *Green Chem.* **2012**, *14*, 1821–1849; j) J. Alemán, S. Cabrera, *Chem. Soc. Rev.* **2013**, *42*, 774–793; k) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 13860–13874; l) M. H. Aukland, B. List, *Pure Appl. Chem.* **2021**, *93*, 1371–1381.
[3] a) W. Schneider, K. Gaertner, A. Jordan, *Ber. Dtsch. Chem. Ges.* **1924**, *57*, 522–532; b) R. Gompper, B. Wetzel, W. Elser, *Tetrahedron Lett.* **1968**, *9*, 5519–5522; c) X. Zhang, L. Wang, Q. Wang, F. Ge, X. Wang, *ChemistrySelect* **2019**, *4*, 8655–8660.
[4] In addition, a slow and low yielding reaction of compound **I** with the Michael acceptor 5-ethoxymethylene-2,2-dimethyl-1,3-dioxan-4,6-dione has been reported (2 weeks at r.t., 5% yield): H.-G. Henning, L. H. Thanh, J. Laue, B. Urban, G. Reck, *Monatsh. Chem.* **1994**, *125*, 95–105.
[5] A. Fürstner, M. Alcarazo, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 3210–3214.
[6] J. Reitz, P. W. Antoni, J. J. Holstein, M. M. Hansmann, *Angew. Chem. Int. Ed.* **2023**, *62*, e202301486.
[7] a) M. M. Hansmann, P. W. Antoni, H. Pesch, *Angew. Chem. Int. Ed.* **2020**, *59*, 5782–5787; b) P. W. Antoni, C. Golz, J. J. Holstein, D. A. Pantazis, M. M. Hansmann, *Nat. Chem.* **2021**, *13*, 587–593; c) P. Varava, Z. Dong, R. Scopelliti, F. Fadaei-Tirani, K. Severin, *Nat. Chem.* **2021**, *13*, 1055–1060; d) M. M. Hansmann, *Angew. Chem. Int. Ed.* **2023**, *62*, e202304574.
[8] A. Eitzinger, J. Reitz, P. W. Antoni, H. Mayr, A. R. Ofial, M. M. Hansmann, *Angew. Chem. Int. Ed.* **2023**, *62*, e202309790.
[9] Q. Sun, A. Eitzinger, R. Esken, P. W. Antoni, R. J. Mayer, A. R. Ofial, M. M. Hansmann, *Angew. Chem. Int. Ed.* **2024**, *63*, e202318283.
[10] P. W. Hickmott, *Tetrahedron* **1984**, *40*, 2989–3051.
[11] a) For reviews on N-heterocyclic olefins (NHOs), see: R. D. Crocker, T. V. Nguyen, *Chem. Eur. J.* **2016**, *22*, 2208–2213; b) R. S. Ghadwal, *Dalton Trans.* **2016**, *45*, 16081–16095; c) M. M. D. Roy, E. Rivard, *Acc. Chem. Res.* **2017**, *50*, 2017–2025; d) S. Naumann, *Chem. Commun.* **2019**, *55*, 11658–11670.
[12] a) H. Mayr, M. Patz, *Angew. Chem. Int. Ed.* **1994**, *33*, 938–957; b) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77; c) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807–1821; d) H. Mayr, *Tetrahedron* **2015**, *71*, 5095–5111.
[13] a) For p-quinone methides as reference electrophiles: R. Lucius, R. Loos, H. Mayr, *Angew. Chem. Int. Ed.* **2002**, *41*, 91–95; b) D. Richter, N. Hampel, T. Singer, A. R. Ofial, H. Mayr, *Eur. J. Org. Chem.* **2009**, *2009*, 3203–3211.
[14] For a freely accessible database of reactivity parameters *N*, s_N, and *E*, see: https://www.cup.lmu.de/oc/mayr/reaktionsdatenbank2/(accessed: 28 March 2024).
[15] K. Powers, C. Hering-Junghans, R. McDonald, M. J. Ferguson, E. Rivard, *Polyhedron* **2016**, *108*, 8–14.
[16] H. V. Huynh, *Chem. Rev.* **2018**, *118*, 9457–9492.
[17] For details see Supporting Information.
[18] Z. Li, R. J. Mayer, A. R. Ofial, H. Mayr, *J. Am. Chem. Soc.* **2020**, *142*, 8383–8402.
[19] Calculated by using Equation (1) and assuming a nucleophilicity of $N=20$ ($s_N=0.60$) for the 2-pyNHO **I** in acetonitrile.
[20] a) B. Kempf, N. Hampel, A. R. Ofial, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 2209–2218; b) S. Lakhdar, B. Maji, H. Mayr, *Angew. Chem. Int. Ed.* **2012**, *51*, 5739–5742; c) H. Mayr, S. Lakhdar, B. Maji, A. R. Ofial, *Beilstein J. Org. Chem.* **2012**, *8*, 1458–1478; d) H. Erdmann, F. An, P. Mayer, A. R. Ofial, S. Lakhdar, H. Mayr, *J. Am. Chem. Soc.* **2014**, *136*, 14263–14269; e) D. S. Timofeeva, R. J. Mayer, P. Mayer, A. R. Ofial, H. Mayr, *Chem. Eur. J.* **2018**,

24, 5901–5910; f) M. J. Hensinger, A. Eitzinger, O. Trapp, A. R. Ofial, *Chem. Eur. J.* **2024**, *30*, e202302764.
[21] a) Anchimeric assistance, as observed in enaminocarboxylates in Ref. [21b], may further increase the nucleophilicity of enamines but the activating effect depends somewhat on the type of the electrophilic reaction partner; b) T. Kanzian, S. Lakhdar, H. Mayr, *Angew. Chem. Int. Ed.* **2010**, *49*, 9526–9529.
[22] a) The same effect may rationalize the reactivity order **VIII** < **IX** in the NHO series that was reported in Ref. [22b]; b) Z. Li, P. Ji, J.-P. Cheng, *J. Org. Chem.* **2021**, *86*, 2974–2985.
[23] P. W. Antoni, T. Bruckhoff, M. M. Hansmann, *J. Am. Chem. Soc.* **2019**, *141*, 9701–9711.
[24] X. Wang, Y. He, M. Ren, S. Liu, H. Liu, G. Huang, *J. Org. Chem.* **2016**, *81*, 7958–7962.
[25] I. M. Resta, J. F. Miravet, M. Yamaji, F. Galindo, *J. Mater. Chem. C* **2020**, *8*, 14348–14352.

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