


 Cite this: *Chem. Commun.*, 2026, 62, 5041

 Received 12th January 2026,
 Accepted 2nd February 2026

DOI: 10.1039/d6cc00190d

rsc.li/chemcomm

Analyzing the kinetics of the reactions of α -aryl-substituted vinyl azides (VA) with benzhydrylium ions by using the relationship $\lg k_2(20\text{ }^\circ\text{C}) = s_N(N + E)$ quantified the nucleophilic reactivity of VA in dichloromethane and CyreneTM. The nucleophilicities N of VA and of further styrenes correlate linearly with DFT-calculated methyl cation affinities, which facilitates the design of styrenes with predictable reactivity.

The nucleophilic reactivity of vinyl azides (VA)¹ is often described to be ‘enamine-type’ owing to the fact that the α -nitrogen facilitates the attack of an electrophile at the terminal carbon of the π -system (Fig. 1a).^{2–5} Subsequent extrusion of molecular nitrogen is accompanied by rearrangement to nitrilium ions, which usually furnish amides upon aqueous workup.⁶

In this work, we carried out a systematic study on the nucleophilic reactivity of a series of nine α -aryl-substituted VA to embed them in the currently most comprehensive reactivity scale, that is, the benzhydrylium-based Mayr scale (BBMS).⁷ We show that the positioning of VA in BBMS makes it for the first time possible to compare the nucleophilic reactivity of VA with those of structurally related α -substituted ‘styrene-type’ π -systems including analogues with α -alkyl, α -(trialkylsiloxy)-, α -amido, or α -amino groups. Quantum-chemical calculations indicate that methyl cation affinities (MCA)⁸ are highly competent and substance-class encompassing descriptors for the nucleophilic reactivity of such π -nucleophiles.

We first analyzed the general electronic properties of VA by quantum-chemical calculations. MO energies of the parent 1-(azidovinyl)benzene were calculated at the r²SCAN-3c/SMD(DCM) level of theory using ORCA 6.0.1 and ChimeraX 1.9 for visualization (SI, Section 7.2).⁹ Fig. 1b illustrates that the HOMO of this VA is centered around the π -system of the C–C double bond with participation of the adjacent azido α -nitrogen in accord with the anticipated general reactivity as enamine-type nucleophile.

Quantifying the enamine-type nucleophilic reactivity of α -aryl vinyl azides

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Encouraged by this insight, a series of nine VA (**1a–1i**, Fig. 2a) were synthesized from the respective alkenes by iodine azide addition and subsequent base-induced HI elimination.¹⁰ Subsequently, we set out to determine the VA nucleophilicity by using Mayr’s benzhydrylium methodology and the Mayr-Patz equation (MPE, Fig. 2b), which is a linear free energy relationship.^{7,11,12} In the MPE, E represents the electrophilicity of the (reference) electrophile, while a nucleophile is characterized by two solvent-dependent parameters N and s_N .^{7,11} The MPE has already been used to successfully quantify the nucleophilicities of a huge variety of π -nucleophiles, e.g., vinyl silanes, olefins, allyl silanes, silyl enol ethers, and enamides.^{11,12} This reliable framework makes it possible to straightforwardly compare VA reactivities with those of other nucleophilic species, also comprising enamines, which occur in many, more commonly used reactions with electrophiles.^{13,14}

A series of electrophilic benzhydrylium ions (**2**) serve as the backbone of MPE-based nucleophilicity scales.⁷ Ions **2** (with BF₄[–] or GaCl₄[–] counterions) give deeply colored solutions when dissolved in dichloromethane. We planned, therefore, to follow the kinetics of the reactions of **2** with VA (**1**) by using photometric methods. Owing to the variable reactivity of the VA **1a–1i**, a series of benzhydrylium ions **2** with electrophilicities in the range from $E = +0.61$ (**2a**) to -5.53 (**2g**) was used (Fig. 2c).^{11b} Benzhydrylium ions **2c** ($E = -1.36$) and **2e** ($E = -3.85$) were

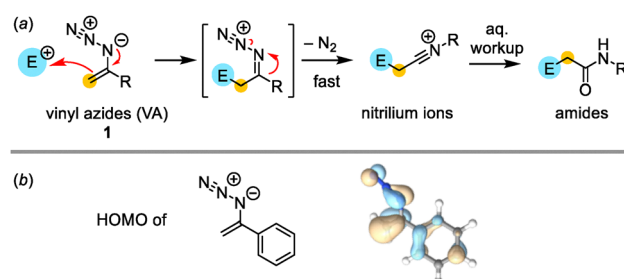


Fig. 1 (a) Reactions of vinyl azides (VA) with cationic electrophiles and subsequent aqueous workup furnishes amides. (b) Representation of the HOMO of 1-(azidovinyl)benzene.

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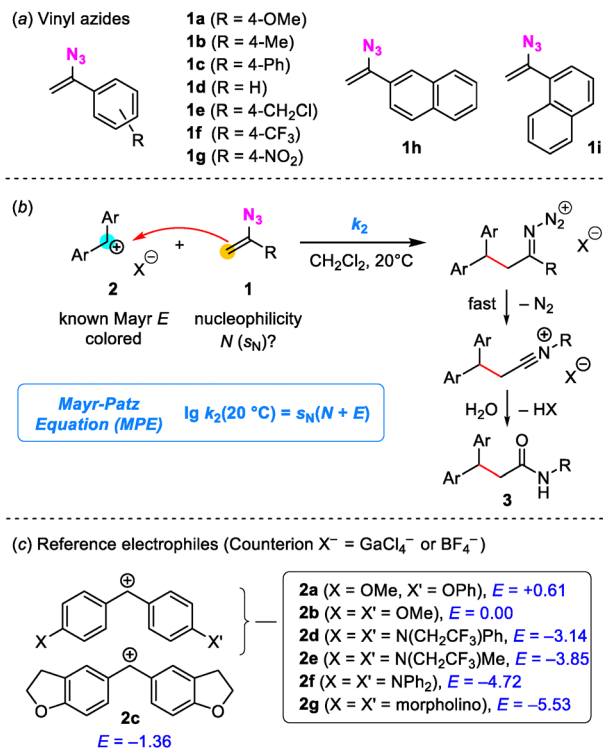


Fig. 2 (a) Structures of investigated vinyl azides (VA). (b) Reactions of VA **1** with benzhydrylium ions **2** furnish nitrilium ions, which can be hydrolyzed to amides **3**. (c) Structures of reference electrophiles **2a–2g** and their electrophilicity parameters *E* (from ref. 11b; counterions: GaCl₄⁻ for **2a–2c** and BF₄⁻ for **2d–2g**).

selected to characterize typical reaction products of the kinetically investigated carbon–carbon bond forming reactions of VA **1** and benzhydrylium ions **2** (Fig. 2b). The reactions of **1a** + **2c**, **1d** + **2e**, and **1h** + **2e** led, after aqueous workup, to secondary amides **3** (SI, Section 4). Amide formation from the combination of **1** and **2** is rationalized by the initial formation of an iminodiazolium ion, followed by a Schmidt-type rearrangement to a nitrilium ion, which finally yields the isolated secondary amide by aqueous workup. Analogous amide formations were reported by Chiba and co-workers.⁶

Second-order rate constants *k*₂ for the reactions of VA **1** with colored benzhydrylium ions **2a–2g** were determined from the kinetics of their reactions in CH₂Cl₂ at 20 °C. The **1** + **2** reactions were monitored at or close to the absorbance maxima of the colored benzhydrylium ions by using stopped-flow or conventional UV-Vis spectroscopy. The VA nucleophiles were used in excess over the benzhydrylium ions (that is, [2]₀ << [1]₀) which ensured pseudo-first order reaction conditions. Least squares-fitting of the mono-exponential decay functions $A = A_0 \exp(-k_{\text{obs}}t) + C$ to the time-dependent experimental absorbances allowed us to determine the first-order rate constants *k*_{obs} (s⁻¹) at a given VA concentration. After carrying out analogous kinetic measurements with the same benzhydrylium ion **2** at four to five different VA concentrations, the second-order rate constant *k*₂ (M⁻¹ s⁻¹) of the bimolecular **1** + **2** reaction was calculated as the slope of the linear correlation of *k*_{obs} with [VA]₀. It should be noted that the

second-order rate constants *k*₂ for the reactions of **1c** and **1f** with **2c** were determined from only three *k*_{obs} values. Furthermore, our attempts to determine the kinetics of the reactions of VA **1g** (*p*-NO₂) with **2** did not give rise to mono-exponential decay curves and were discarded therefore. The second-order rate constants *k*₂ of all kinetically investigated **1** + **2** reactions in dichloromethane are listed in Table S1 (SI). DFT calculated Gibbs activation energies [Δ*G*[‡] at the r²SCAN-3c/SMD(DCM) level of theory, SI, Section 7.5] for the adduct formation of the parent VA **1d** with the electrophiles **2c–2g** correlate linearly with the experimental Δ*G*[‡] indicating that the determined second-order rate constants *k*₂ reflect the C–C bond-formation process.

Next, the MPE-defined nucleophilic reactivity parameters *N* (and *s_N*) of the individual VAs **1a–1i** were calculated from linear correlations of lg *k*₂ vs. the electrophilicity *E* of **2**.^{11b} Fig. 3 depicts such correlations for vinyl azides **1a** (*p*-OMe), **1d** (H), **1f** (*p*-CF₃), and **1i** (naphth-1-yl). The slopes of the linear correlations reflect the nucleophiles' sensitivity parameter *s_N*, while the intercepts with the abscissa (that is, lg *k*₂ = 0) correspond to the VA nucleophilicity parameters *N* (= -*E*). Individual correlations of VA **1a–1i** are shown in the SI (Section 1), and the calculated *N* (and *s_N*) are embedded in Fig. 4.

The relative reactivities of VA **1** can roughly be expressed solely by their *N* parameters when the slight variability in the sensitivity factors *s_N* (from 0.79 to 0.99) is neglected. The nucleophilicities *N* of the parent α-azidostyrene **1d** and its *p*-X-substituted analogues correlate excellently with the Hammett substituent parameter σ_p of the X group.¹⁵ The correlation $N = -3.738\sigma_p + 4.869$ (*R*² = 0.9474, *n* = 6, Fig. S10 in SI) can thus be used to predict the nucleophilic reactivities of further ring-substituted α-azido-styrene derivatives. The Hammett system, however, does not allow us to include both naphthyl compounds **1h** and **1i** in the correlation. Yet, the nucleophilicity scale in Fig. 4 shows that the β-naphthyl VA **1h** is located considerably above the parent VA **1d**, close to the *p*-Me VA **1b**, in accord with the expected positioning for an electron-rich π-system. The α-naphthyl VA **1i** is by two orders of magnitude less nucleophilic

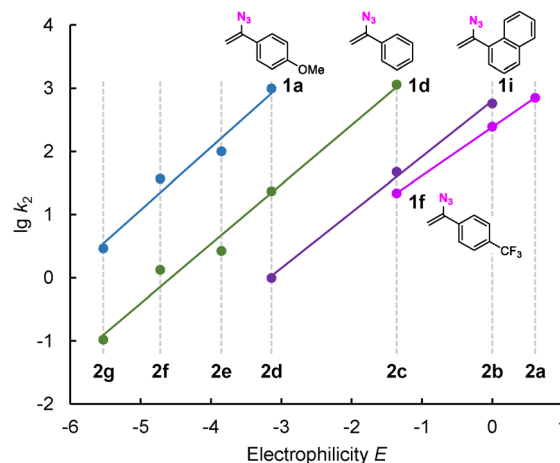


Fig. 3 Correlations of lg *k*₂ for reactions of vinyl azides **1** with benzhydrylium ions **2** with the electrophilicities *E* of **2** (all data from Table S1, SI).



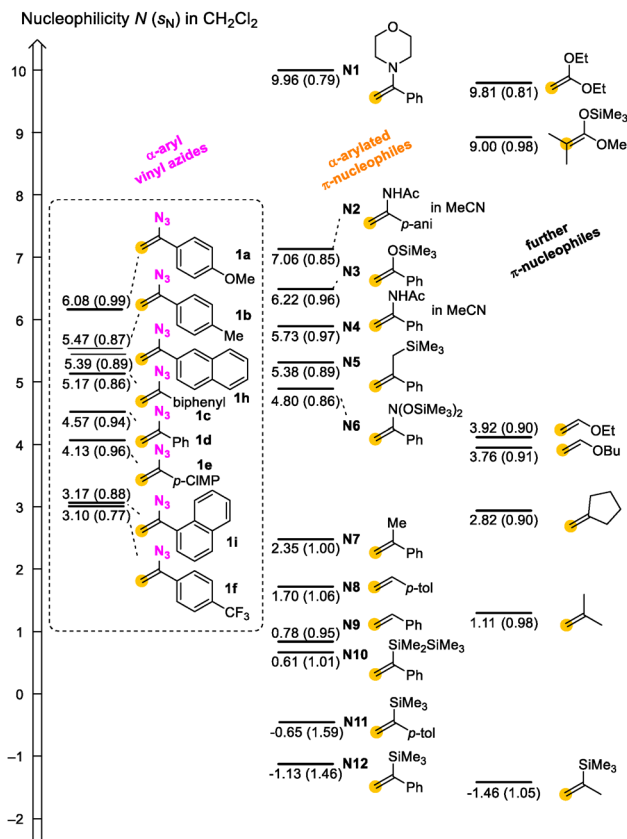


Fig. 4 Comparison of nucleophilic reactivities of α -aryl VAs with those of structurally analogous π -nucleophiles. N and s_N for all nucleophiles, except the VAs (this work), are from sources quoted in ref. 12 (p -ani = 4-MeO-C₆H₄-; biphenyl = 4-Ph-C₆H₄-; p -ClMP = 4-ClCH₂-C₆H₄-; p -tol: 4-Me-C₆H₄-).

than **1h**, which may be rationalized by unfavorable *peri*-interactions¹⁶ that cause a twist of the vinylic π -system out of the plane of the aromatic system (SI, Section 7.3).

Usually, second-order rate constants $k_2(20\text{ }^\circ\text{C}) > 10^{-5}\text{ M}^{-1}\text{ s}^{-1}$ are required for efficient and productive bimolecular reactions between electrophiles and nucleophiles. It may be surprising, therefore, that nucleophilic attack of VA at relatively weak electrophiles, such as p -quinone methides (p -QM),¹⁷ dialkyl arylidenemalonates,¹⁸ or N -tosyl imines^{6a} with $E < -10$ ¹⁹ have been reported. For example, the reaction of VA **1d** ($N = 4.57$, $s_N = 0.94$) with the p -QM 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one ($E = -15.58$)^{19a} is predicted by the MPE to proceed unproductively slow ($k_2^{\text{MPE}} = 4.5 \times 10^{-11}\text{ M}^{-1}\text{ s}^{-1}$ at 20 $^\circ\text{C}$). A significant enhancement of the electrophiles' reactivity can be achieved by Lewis acid activation. Thus, complexation of p -QMs and N -tosyl imines with BF₃·OEt₂ and of arylidenemalonates with TiCl₄ were the optimum strategies used in reported reactions of these electrophiles with VA.^{6a,17,18} Stronger electrophiles, such as Selectfluor ($E = -5.20$)²⁰ undergo reactions with VA without the need of catalysts or promoters.¹⁰ Furthermore, acidic conditions were used by Chiba *et al.* to generate cationic electrophiles from alcohol precursors.⁶ Slowly added VA **1d** attacked thus generated tritylium ions Ph₃C⁺ ($E = +0.51$),²¹ 1,3-diphenylallylium ions

($E = +2.70$),²² or parent benzhydrylium ions Ph₂CH⁺ ($E = +5.47$)²³ under mild reaction conditions (at -40 $^\circ\text{C}$ in CH₂Cl₂)^{6a} in accord with predictions by using the MPE.

Fig. 4 gives a comprehensive overview of further π -systems with reported nucleophilic reactivities N . Obviously, α -azidostyrene **1d** ($N = 4.57$) is by more than three orders of magnitude a stronger nucleophile than the parent styrene **N9** ($N = 0.78$). Though the N₃ group is classified as an electron-accepting group according to its Hammett parameters $\sigma_p = +0.08$ and $\sigma_m = +0.37$,¹⁵ VAs indeed benefit in reactivity from the assumed 'enamine-type' electron-pair donating effect of the nitrogen at the π -system. Classical enamines, such as the α -morpholino-styrene **N1**, are considerably stronger nucleophiles though. Yet, VA **1d** reaches almost the reactivity level of the analogous enamide **N4** ($N = 5.73$ in MeCN). A difference of $\Delta N \approx +1$ is consistently kept between VA and enamides when the ring-substituents at the styrene unit are varied (p -OMe: $\Delta N = +0.98$ for **1a** vs. **N2**, p -Me: $\Delta N = +1.10$ for **1b** vs. **N14**, naphth-2-yl: $\Delta N = +0.89$ for **1h** vs. **N13**, see below for structures of **N13** and **N14**).

Refining organic synthesis protocols to use sustainable-by-design solvents based on renewable, plant-based raw materials requires reactivity studies in such solvents. Therefore, Table 1 lists second-order rate constants k_2 , which were determined for the reactions of **2d–2g** with the VA **1h** in Cyrene™ (= dihydrolevoglucosenon), a biorenewable solvent for which Reichardt's normalized solvent parameter $E_T^N = 0.333$ indicates slightly higher polarity than for the standard solvent dichloromethane ($E_T^N = 0.309$).^{24,25}

The individual second-order rate constants k_2 of comparable reactions of **1h** with **2** were determined to be higher in Cyrene™ than in dichloromethane. Though the correlation of $\lg k_2$ with E is only moderate ($R^2 = 0.8338$), the nucleophile-specific parameters $N = 6.00$ and $s_N = 0.90$ for **1h** in Cyrene can be tentatively determined, highlighting that biorenewable solvents are compatible with conditions for carbocation-nucleophile reactions and enable reaction rates at the same or even higher level than fossil-sourced, classical solvents.

Methyl cation affinities (MCA), calculated as the negative Gibbs free energies (ΔG_R) of the addition of the methyl cation (⁺CH₃) to the vinylic double bond (Fig. 5a), reflect the intrinsic Lewis basicities of styrene-type π -systems. Nucleophilicities of the differently α -activated styrene-type π -nucleophiles **N1–N15** without *ortho*-substituents at the aryl ring were collected from the current version of Mayr's Reactivity Database.¹² The quantum-chemically calculated MCA values of **1a–1i** and **N1–N15** are listed in Fig. 5b (see SI for details). The data of 22 nucleophiles in Fig. 5c show a strong linear correlation of their nucleophilicity parameter N with the thermodynamic driving force for the C–C bond formation as expressed by MCA. This linear free energy relationship is extensive, as it

Table 1 Second-order rate constants $k_2(20\text{ }^\circ\text{C})$ for the reactions of the VA **1h** with the benzhydrylium ions **2d–2g** in Cyrene

Electrophiles	2d	2e	2f	2g
$k_2\text{ (M}^{-1}\text{ s}^{-1}\text{)}$	583	28.3	42.6	1.81



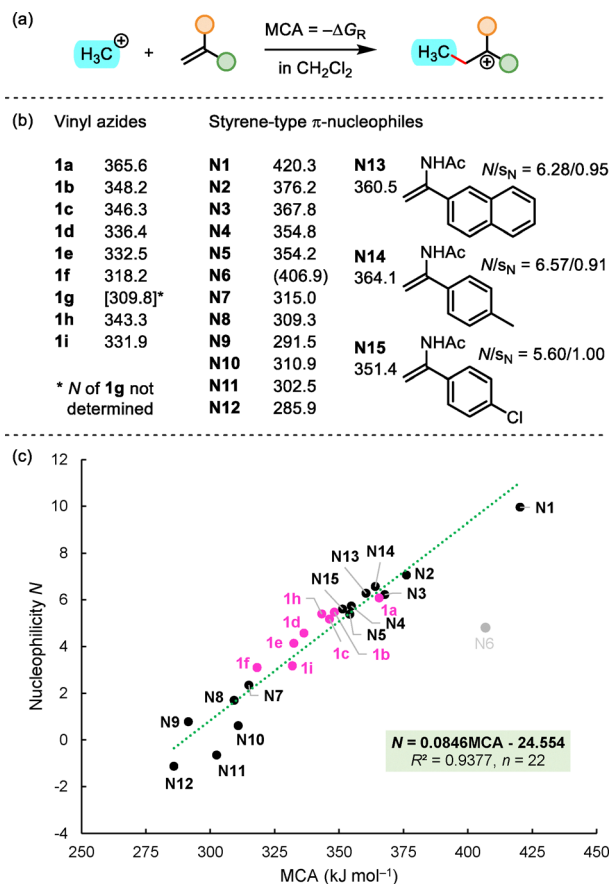


Fig. 5 (a) Definition of methyl cation affinities (MCA) of α,α' -disubstituted π -systems in dichloromethane. (b) MCA values (in kJ mol⁻¹) of **1a-1i** and **N1-N15** (calculated at the r²SCAN-3c/SMD(DCM) level of theory). (c) Correlation of nucleophilicity *N* with MCA of variously α -functionalized styrenes (data of **N6** not used for the construction of the correlation line).

ranges over 12 units along the *N* scale and covers π -systems from various classes of compounds (vinyl silanes, alkenes, allyl silanes, silyl enol ethers, enamides, and enamines) whose MCA values differ by 134 kJ mol⁻¹. The *N,N*-bis(silyloxy)enamine **N6** is an outlier for unknown reasons, however.

In summary, this work provides for the first time a quantitative fundament for the understanding of the scope of organic reactions with nucleophilic vinyl azides (VA) by embedding them in Mayr's comprehensive reactivity scales, in which VA had previously not been considered. The reliable and far-reaching correlation of π -nucleophilicity with quantum-chemically calculated methyl cation affinity (MCA) facilitates the future design of styrene-like nucleophiles with foreseeable reactivity. This work also underscores that MCA is a molecular property that should not be missed as a fitting parameter in multi-variate regression analysis²⁶ or automated quantum-chemical approaches to predict polar reactivity.^{27,28}

Project conceptualization was done jointly by C. G. and A. R. O. Experimental methodology development and kinetic investigations were carried out by C. G. and P. T. Results of the kinetic measurements were formally analyzed and visualized by C. G., P. T., and A. R. O. Quantum-chemical investigations,

supervised by H. Z., were performed, analyzed, and visualized by J. B. The manuscript was written jointly with input from all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

Data for this article, including raw and evaluated data of kinetic measurements and NMR data (FID files) are available at Open Data LMU at <https://doi.org/10.5282/ubm/data.761>. Further data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d6cc00190d>.

Acknowledgements

We thank the Department Chemie, LMU München for financial support. This project has received funding from the European Union's Horizon Europe research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 101106557 "ResolveByBio" (MSCA-2022-PF to P. T.). C. G. and A. R. O. thank for funding by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – project number 530072453 (OF 120/3-1). J. B. and H. Z. acknowledge financial support by the Deutsche Forschungsgemeinschaft (RTG 2620 Ion Pair Effects in Molecular Reactivity, project number 426795949). We gratefully acknowledge the computational and data resources provided by the Leibniz Supercomputing Centre (<https://www.lrz.de>).

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