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# 'One-Pot' Kinetic Profiling of $S_NAr$ Reactions via Sequential Addition Kinetic Elucidation (SAKE)

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**Abstract:** Efficient acquisition of high-quality kinetic data under synthetically relevant conditions remains a major bottleneck in reaction development and process optimisation. Here, we introduce Sequential Addition Kinetic Elucidation (SAKE), a one-pot methodology that generates multiple kinetic datasets within a single experiment through staged reagent dosing and continuous *in situ* monitoring. This approach minimises inter-experimental variability while maximising data density, enabling robust extraction of global rate laws using automated analysis tools. The SAKE protocol is demonstrated using nucleophilic aromatic substitution ( $S_NAr$ ) reactions between aryl phenyl ethers and secondary amines, a system featuring competing uncatalysed and base-catalysed pathways. Integration with Auto-VTNA and microkinetic modelling enables quantitative determination of rate parameters, including pathway-specific rate constants and reversible inhibition by phenol. By systematically varying temperature, electrophile electronics, amine basicity, and solvent, quantitative relationships between reaction conditions and kinetic behaviour, including correlations with solvent descriptors, can be established. Compared to conventional kinetic workflows requiring multiple independent experiments, SAKE significantly reduces experimental effort while providing mechanistically rich datasets under process-relevant conditions. This methodology offers a general framework for accelerating kinetic analysis, with potential applications in reaction optimisation, solvent selection, and data-driven process development.

## Introduction

Kinetic analysis underpins the rational development, optimisation, and scale-up of chemical reactions. Reliable rate laws and mechanistic insight are essential for reactor design, process safety, and the translation of laboratory chemistry to industrial manufacture.<sup>1–6</sup> At the heart of kinetic studies lies the ability to monitor how the composition of a reaction mixture evolves over time under carefully controlled initial conditions. Recent advances in process analytical technologies have enabled real-time, *in situ* monitoring of reactions under synthetically-relevant conditions (*in operando*).<sup>7–10</sup> Techniques such as reaction progress kinetic analysis (RPKA) and variable time normalization analysis (VTNA) have further enhanced mechanistic understanding by allowing rate laws to be extracted directly from reaction profiles.<sup>1,7,11,12</sup> In addition, the development of microkinetic models—built from elementary reaction steps—has been accelerated by the availability of ordinary differential equation (ODE) solvers<sup>13–16</sup> and machine learning algorithms.<sup>17–21</sup> Despite these advances, collecting high-quality kinetic data remains a labour-intensive and resource-demanding task. Traditional approaches often require multiple independent experiments, each with its own setup, monitoring, and analysis. Our previous work on automating VTNA via a Python-based platform (Auto-VTNA) revealed that systematic errors between experimental runs can introduce significant uncertainty in the derived reaction orders. By computationally scoring the degree of concentration profile overlay via the RMSE of fitting all profiles to the same flexible monotonic function, Auto-VTNA can algorithmically derive unbiased reaction orders which optimise overlay. The ability of Auto-VTNA to derive several orders in the same calculation also calls into question the conventional design of VTNA campaigns, in which the initial concentration of only one species is varied at a time.<sup>22</sup>

Sequential addition protocols have previously been used to investigate catalyst activation and deactivation, typically yielding qualitative insights.<sup>23–27</sup> More recently, Williams et al. introduced the Continuous Addition Kinetic Experiment (CAKE) protocol,<sup>28</sup> in which catalyst is added continuously while reaction progress is monitored, enabling quantitative determination of reaction orders and rate constants from a single experiment. While CAKE has been successfully applied to catalytic systems including those involving

catalyst decomposition, a complementary approach is needed for non-catalytic reactions where sequential additions of different reagents can probe concentration dependences and inhibition effects.

In this study, we present a new one-pot kinetic protocol—Sequential Addition Kinetic Elucidation (SAKE)—that combines staged reagent dosing with continuous monitoring to generate multiple reaction profiles from a single experiment. SAKE mimics the effect of running multiple reactions under different initial conditions, thereby minimizing inter-run variability.<sup>5,29,30</sup> The resulting datasets can be analysed using conventional microkinetic modelling tools and Auto-VTNA where appropriate.<sup>22,31</sup>

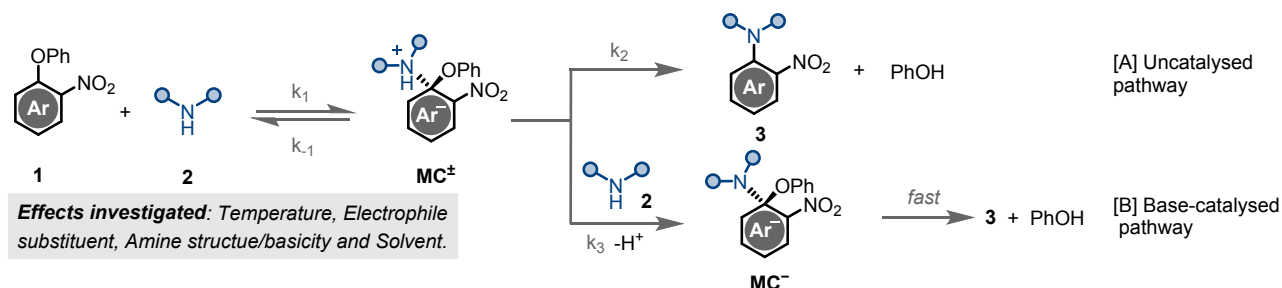
This study applies SAKE to partially base-catalysed nucleophilic aromatic substitution ( $S_NAr$ ) reactions of aryl phenyl ethers as it enables comparisons with earlier initial-rate studies, particularly those of Um and co-workers.<sup>32–43</sup>  $S_NAr$  is one of the most important transformations in organic synthesis, widely utilised to produce aniline derivatives for pharmaceuticals, agrochemicals, dyes, pigments and polymers.<sup>44–46</sup> Base catalysis, typically observed as a positive reaction order in added base or a greater than first-order dependence on amine concentration, has been reported in a range of  $S_NAr$  systems with substrates bearing fluoride, methoxy and phenoxy leaving groups. One of the objectives of the current work is to understand the extent of base catalysis with changes in substrates and reaction conditions, building on previous work to achieve a more holistic understanding of the phenomenon.<sup>46–49</sup>

## Results and Discussion

The  $S_NAr$  reaction between 2-nitro-1-(phenoxy)arenes, **1** ( $X = OPh$ ), and secondary amines **2** yields a substituted aniline **3** and phenol (Scheme 1). After the initial nucleophilic attack of the amine at C-1 to form a zwitterionic Meisenheimer complex ( $MC^\ddagger$ ), the reaction bifurcates into two kinetically distinct pathways:<sup>32–34,37–40,46,50–53</sup>

- i. Uncatalysed pathway (A): Direct expulsion of the leaving group and phenol by-product from  $MC^\ddagger$ .

- ii. Base-catalysed pathway (B): a second molecule of amine deprotonates  $\text{MC}^+$  to promote the expulsion of PhOH from  $\text{MC}^-$ . If the deprotonation step ( $k_3$ ) is slow, it is known as a rate-limiting proton transfer (RLPT) mechanism.



**Scheme 1.** Competing kinetic pathways A and B for the  $\text{S}_{\text{N}}\text{Ar}$  reaction between 2-nitro-1-(phenoxy)arenes, **1**, and secondary amines **2**.<sup>54</sup>

Assuming  $k_1 \gg k_2 + k_3[\mathbf{2}]$ , the steady-state approximation may be applied to the overall system, from which a simplified rate equation can be derived (Eq. 1); *i.e.* if both pathways A and B operate, a partial amine order between **1** and **2** is expected to be observed, and their relative rates represented by  $Kk_2$  and  $Kk_3$ .

$$\frac{d}{dt}[\mathbf{3}] = Kk_2[\mathbf{1}][\mathbf{2}] + Kk_3[\mathbf{1}][\mathbf{2}]^2 \quad (\text{Eq. 1})$$

$$\text{where } K = \frac{k_1}{k_{-1}}$$

Previous kinetic studies of similar reactions were performed under pseudo-first order ('flooding') conditions deploying an excess of the amine, and the kinetic parameters  $Kk_2$  and  $Kk_3$  were extracted from a combination of initial rate experiments and linear plots.<sup>32–34,40,43</sup> In this paper, the  $\text{S}_{\text{N}}\text{Ar}$  reaction between 2-nitro-1-(phenoxy)arenes, **1**, and secondary amines **2** was reassessed using the SAKE methodology under synthetically relevant conditions, *i.e.* using no more than 2.5 equivalents of amine. Kinetic parameters were derived using Auto-VTNA and microkinetic modelling, shedding light on the effect of amine basicity and electrophile substituents on the competition between pathways A and B, concluding with a study of solvent effects.

### General Description of the Sequential Addition Kinetic Elucidation (SAKE) Protocol

Sequential addition kinetic elucidation (SAKE) is a protocol for kinetic experimentation in batch reactors where portions of reaction components are added sequentially to generate distinct periods, with varying initial concentrations and mass balances. The number of additions per reaction species can be chosen analogously to the number of different excess experiments in a standard VTNA campaign and, for complex systems, can be spread out over more than one SAKE experiment. SAKE requires reaction monitoring with sufficient temporal resolution within each period. This is most effectively achieved using *in situ* analytical techniques, although the protocol is also compatible with offline methods such as HPLC, GC, and NMR.

### SAKE Design for S<sub>N</sub>Ar Case Study

In this work, the reaction progress is tracked in real time using *in situ* IR spectroscopy, calibrated against HPLC analysis of extracted aliquots. The following dosing schedule was utilised to collect data on the effect of amine and phenol on the reaction rate:

- i. Period 1: Reaction is initiated by adding a sub-stoichiometric amount of amine **2** (*ca.* 0.33 equivalent with respect to electrophile **1**), generating the first reaction profile.
- ii. Period 2: When the first portion of amine is near the expected endpoint (*ca.* 33% conversion), a second dose of amine (*ca.* 0.66 equivalent) is added.
- iii. Period 3: At ~ 50% conversion, the phenol by-product (*ca.* 1 equivalent) is introduced to probe its inhibitory effect.
- iv. Finally, once the reaction rate is lowered significantly as the concentrations of **1** and **2** deplete, another portion of **2** was added (*ca.* 1.33 eq. with respect to **1**) to drive the reaction to completion (Period 4).

Thus, each SAKE experiment generates a reaction profile containing a kinetic dataset with 4 'Periods' simulating different initial conditions (Table 1 and Fig. 1).

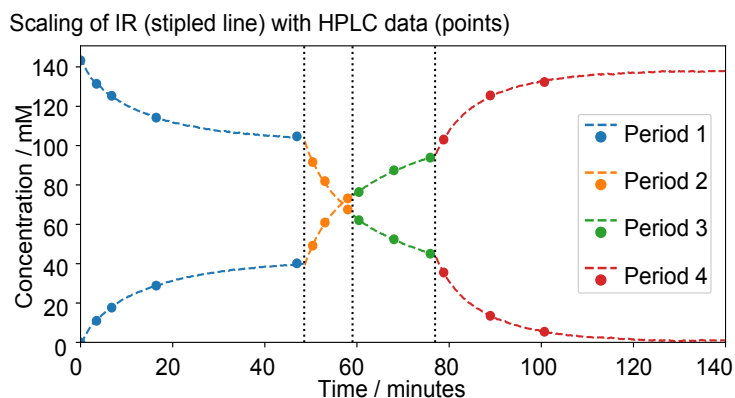


**Figure 1.** A typical reaction profile generated using the SAKE protocol consisting of 4 periods, initial conditions are described in Table 1. Data points were recorded using *in situ* IR spectroscopy (dashed lines) and quantitative HPLC analysis of extracted reaction aliquots (discrete data points). The decreasing and increasing reaction trends correspond to the conversion of **1** and the formation of **3**, respectively. Corresponding IR/HPLC plots for all experiments are provided in Figures SA35–66 of the ESI.

**Table 1.** Initial concentrations corresponding to each period of the SAKE protocol for the reaction system in Scheme 2 at 115

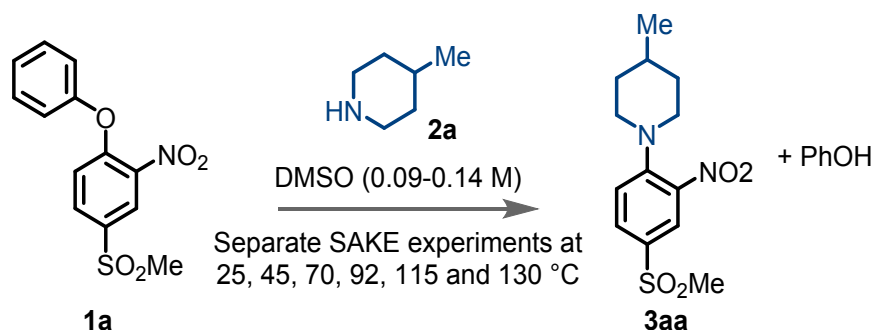
| °C.Period | [ <b>1</b> ] / mM | [ <b>2</b> ] / mM | [ <b>3</b> ] / mM | [PhOH] /mM |
|-----------|-------------------|-------------------|-------------------|------------|
| 1         | 132.8             | 48.9              | 0                 | 0          |
| 2         | 94.8              | 86.3              | 36.3              | 36.3       |
| 3         | 60.4              | 51.9              | 69.7              | 169.9      |
| 4         | 40.3              | 164.1             | 88.1              | 186.7      |

Subsequently, reaction orders for **1**, **2** and phenol can be readily derived from the application of Auto-VTNA to the datasets.

### Temperature Effects

To investigate the influence of temperature on the  $S_NAr$  reaction kinetics, we applied the SAKE protocol to the reaction between 4-(methylsulfonyl)-2-nitro-1-phenoxybenzene (**1a**) and 4-methylpiperidine (**2a**) to

afford substituted product **3aa**. Seven isothermal SAKE experiments were conducted across six temperatures from 25–130 °C (Scheme 2 and Fig. 2).



**Scheme 2.** The  $S_NAr$  reaction between **1a** and **2a** in DMSO at different temperatures.

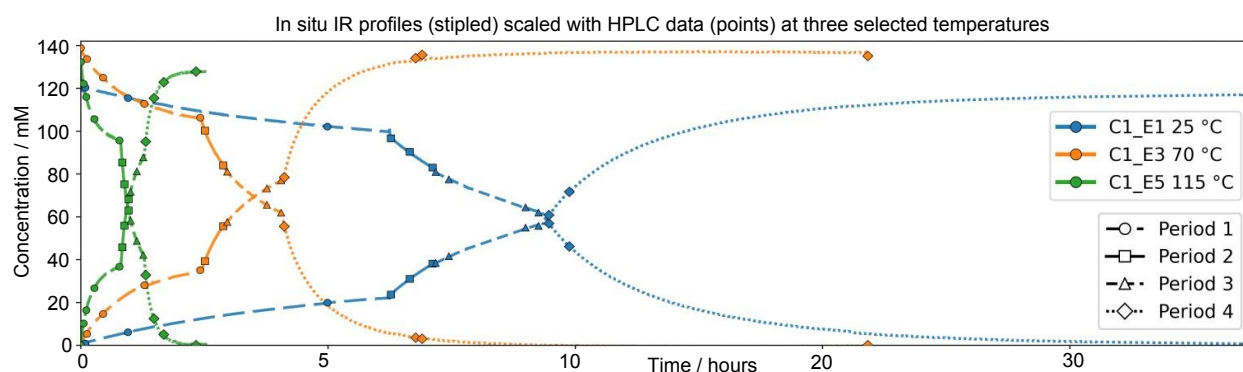


**Figure 2.** Kinetic profiles obtained by *in situ* IR spectroscopy (broken lines) and calibrated against HPLC data (discrete data points) for three of the six temperatures studied, illustrating the increase in  $Kk_2$  and  $Kk_3$  with temperature.

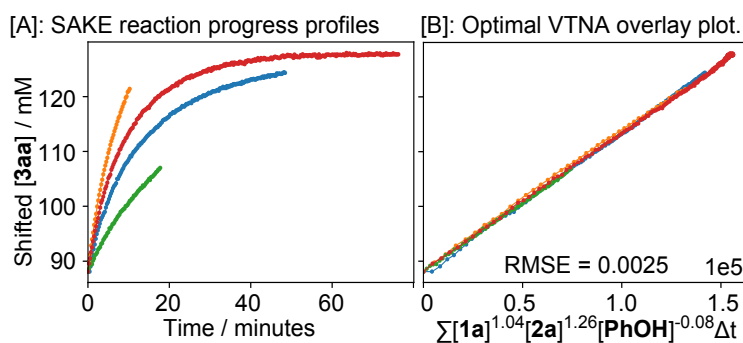


**Figure 3.** Auto-VTNA analysis of the reaction system depicted in Scheme 2 at 115 °C. [A] Selected time-shifted reaction profiles obtained at 115 °C using the SAKE protocol. [B] Overlay plot using reaction orders extracted by Auto-VTNA. Auto-VTNA results for all experiments are provided in Figures SA102–133 of the ESI.

As shown in Table 2, the reaction order in amine **2a** decreased progressively from 1.64 to 1.20 with increasing temperature. This suggests a shift in the dominant mechanism from base-catalysed pathway B toward the uncatalysed pathway A. In contrast, the reaction order in electrophile **1a** remained consistently close to 1 across all temperatures, serving as a reliable internal benchmark (See Fig. 3). Indeed, fixing the order in **1a** to 1 only has a minor impact on the calculated orders of **2a** and PhOH ( $\pm 0.05$ ). The phenol by-product exhibited a slight inhibitory effect, with a reaction order of approximately  $-0.1$ . Given the significant pKa difference between phenol (18.0) and piperidine **2a** (10.9) in DMSO,<sup>55,56</sup> this is attributed to reversible hydrogen bonding between phenol and amine **2a**, forming an inactive complex.<sup>57</sup>

Microkinetic modelling using a three-parameter rate law (incorporating  $Kk_2$ ,  $Kk_3$ , and  $K_i$ , as shown in Fig. 4) provided excellent fits to the experimental data, with root mean square errors (RMSE) ranging from 0.28 to 0.67 mM (Table 2). Notably, the ratio  $k_3/k_2$ , representing the relative contribution of the base-catalysed pathway, correlated linearly with the amine reaction order ( $R^2 = 0.994$ ), reinforcing the mechanistic interpretation (Fig. 5).

| T /<br>°C | Orders Obtained via Auto-VTNA |                          |                            | Overlay Score | Fitted Kinetic Parameters                      |                                                |                            |                           | RMSE /<br>mM |
|-----------|-------------------------------|--------------------------|----------------------------|---------------|------------------------------------------------|------------------------------------------------|----------------------------|---------------------------|--------------|
|           | 1a                            | 2a                       | PhOH                       |               | $Kk_2 / 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ | $Kk_3 / 10^{-3} \text{ M}^{-2} \text{ s}^{-1}$ | $k_3/k_2 / \text{ M}^{-1}$ | $K_i / 10^{-6} \text{ M}$ |              |
| 25        | 0.84                          | 1.58 / 1.64 <sup>a</sup> | -0.08 / -0.07 <sup>a</sup> | 0.0029        | 0.183                                          | 3.60                                           | 19.7                       | 0.529                     | 0.283        |
| 45        | 0.92                          | 1.41 / 1.45 <sup>a</sup> | -0.12 / -0.10 <sup>a</sup> | 0.0029        | 0.569                                          | 6.75                                           | 11.9                       | 0.804                     | 0.412        |
| 70        | 1.04                          | 1.36 / 1.34 <sup>a</sup> | -0.07 / -0.07 <sup>a</sup> | 0.0045        | 1.61                                           | 13.9                                           | 8.61                       | 0.591                     | 0.666        |
| 92        | 1.05                          | 1.28 / 1.25 <sup>a</sup> | -0.06 / -0.08 <sup>a</sup> | 0.0047        | 3.63                                           | 24.8                                           | 6.82                       | 1.07                      | 0.402        |
| 92        | 1.04                          | 1.27 / 1.27 <sup>a</sup> | -0.07 / -0.08 <sup>a</sup> | 0.0032        | 3.68                                           | 29.0                                           | 7.87                       | 1.16                      | 0.334        |
| 115       | 1.04                          | 1.26 / 1.24 <sup>a</sup> | -0.08 / -0.09 <sup>a</sup> | 0.0025        | 8.58                                           | 46.3                                           | 5.39                       | 1.34                      | 0.636        |
| 130       | 1.11                          | 1.26 / 1.20 <sup>a</sup> | -0.07 / -0.08 <sup>a</sup> | 0.0026        | 15.4                                           | 55.5                                           | 3.62                       | 1.65                      | 0.515        |

<sup>a</sup> Order values obtained by fixing the order of **1a** to the expected value of 1.

**Table 2.** Order values and rate constants extracted from SAKE experiments at different temperatures.

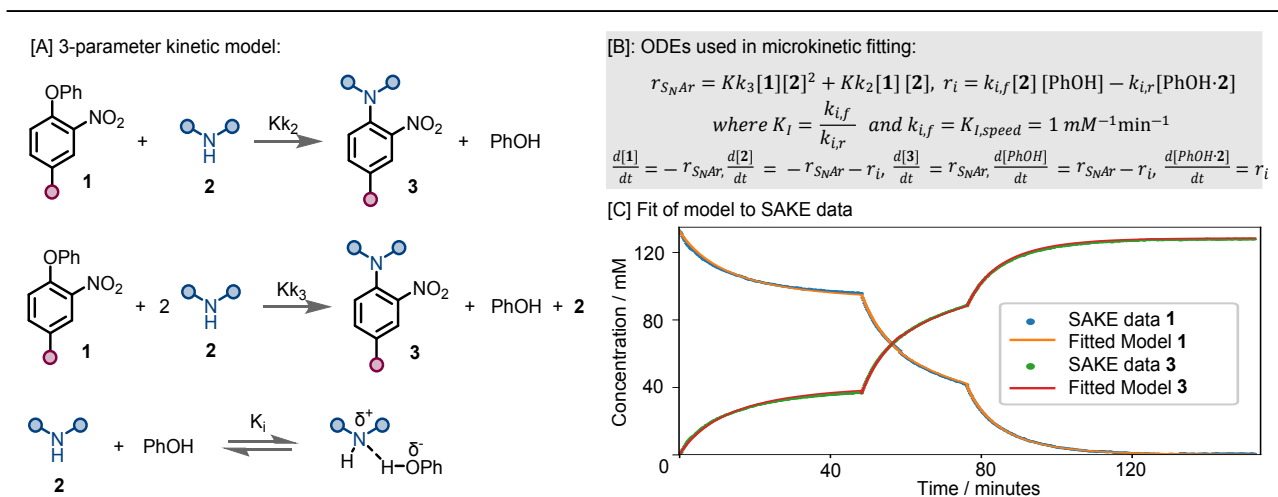


**Figure 4.** [A] The three-parameter kinetic model. [B] Ordinary differential equations (ODEs) used in the kinetic fitting. [C] Fitting of the kinetic model to the SAKE reaction profiles for the  $S_{NAr}$  reaction of **1a** and **2a** at 115 °C (Scheme 2).

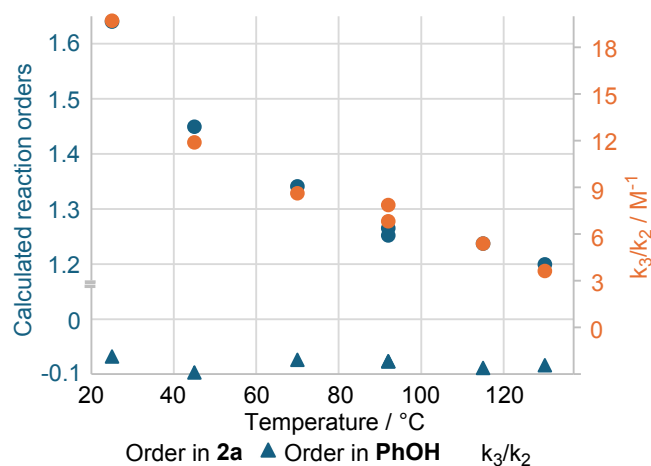


**Figure 5.** Orders in **2a** and **PhOH**, and the  $k_3/k_2$  ratio, against reaction temperature.

Eyring plots derived from fitted  $Kk_2$  and  $Kk_3$  parameters yielded activation entropies ( $\Delta S^\ddagger$ ) of  $-188 \pm 2$  and  $-211 \pm 2$  J/mol/K and activation enthalpies ( $\Delta H^\ddagger$ ) of  $38.3 \pm 0.7$  and  $24.0 \pm 0.8$  kJ/mol, respectively (Fig. 6). The lower entropic barrier of pathway B is likely due to the participation of a second amine in the rate limiting transition state (RLTS), consistent with the RLPT mechanism.

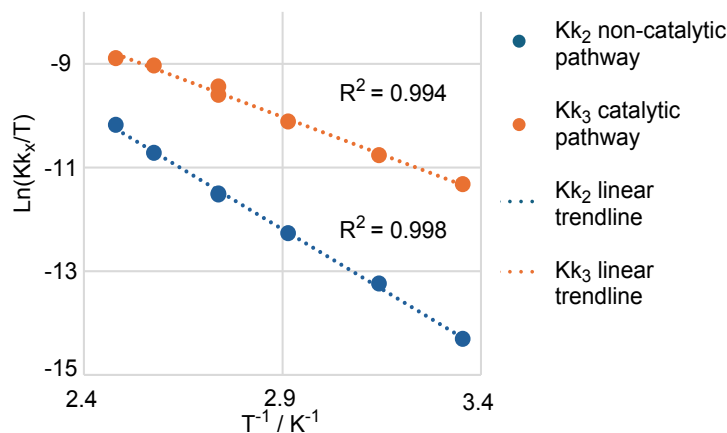
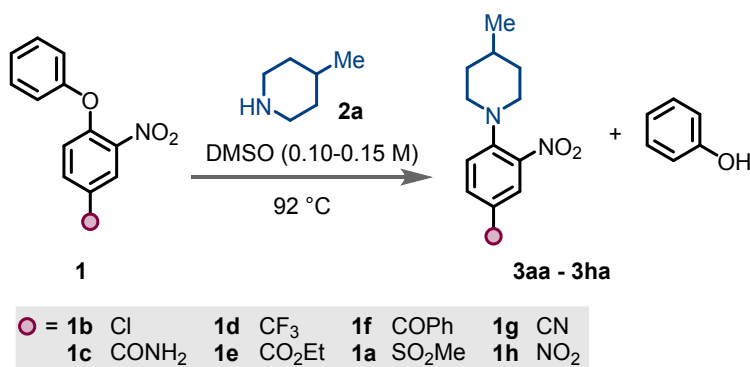


**Figure 6.** Eyring plots for pathways A and B for the reaction between **1a** and **2a**.

### Substituent Effect (Hammett Analysis)

To probe the electronic effects exerted by the electrophile, a series of *para*-substituted 2-nitroaryl phenyl ethers (**1a–h**) were reacted with 4-methylpiperidine (**2a**) using the SAKE protocol (Scheme 3, and Tables

SA17 and SA22 in the ESI). The reactions proceeded cleanly to the corresponding tertiary aniline products (**3aa–3ha**), with reaction times varying significantly depending on the substituent; from full conversion after 30 minutes (**1h**) to only 70% conversion after 2 days (**1b**) (Fig. 7).



**Scheme 3.** Reactions studied using the SAKE protocol to investigate how the electronic nature of the electrophile affects pathways A and B.

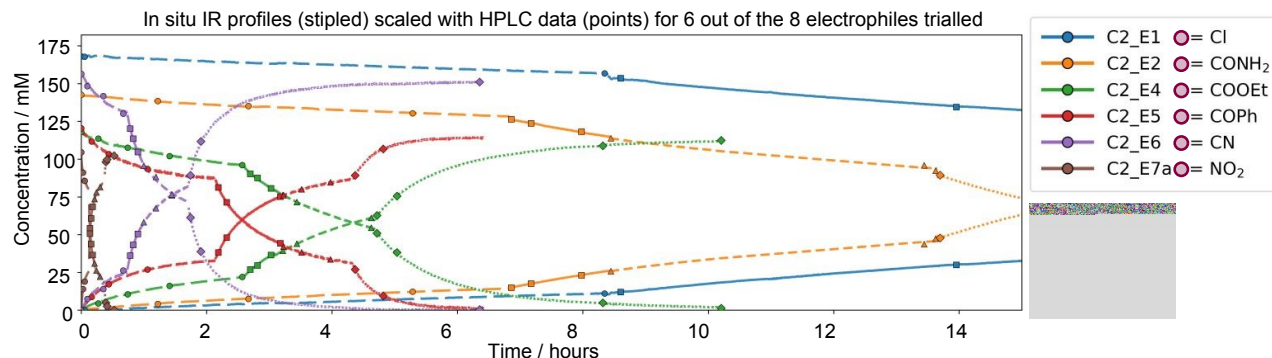


**Figure 7.** Kinetic profiles obtained by *in situ* IR spectroscopy (broken lines) and calibrated against HPLC data (discrete data points) for six of the eight electrophiles studied (**1b**, **1c**, **1e**, **1f**, **1g** and **1h**), illustrating the increase in  $Kk_2$  and  $Kk_3$  with the electron-withdrawing power of the para substituent. For the least reactive electrophiles, only part of the full SAKE profiles is shown to better visualise the faster experiments.

Kinetic analysis revealed a clear trend: from the dominance of pathway A for moderately electron-withdrawing groups to increasing base catalysis for more strongly withdrawing groups. For example, the nitro-substituted electrophile **1h** exhibited strong base catalysis with a high amine order (1.80) and a large  $k_3/k_2$  ratio (58). In contrast, the chloro-substituted **1b** showed the opposite ( $k_3/k_2 < 1$ ) and an amine order

close to 1. In all cases, the inhibitory effect of phenol remained modest (ca.  $-0.08$ ). As expected, the order of the electrophile **1** remained close to 1 in all cases except **1b** (See Section S5.3 in ESI).

Hammett analysis of the fitted rate constants ( $Kk_2$  and  $Kk_3$ ) against  $\sigma^-$  values revealed linear correlations (Fig. 8). Pathway B ( $Kk_3$ ) showed a particularly high sensitivity to substituent electronics ( $\rho = 4.34$ ,  $R^2 = 0.96$ ). The uncatalysed pathway ( $Kk_2$ ) exhibited a more modest electronic influence ( $\rho = 2.37$ ), and a worse linear trend ( $R^2 = 0.86$ ) implying that other effects may be in play for the rate limiting expulsion of phenoxide from  $\mathbf{MC}^\ddagger$ .

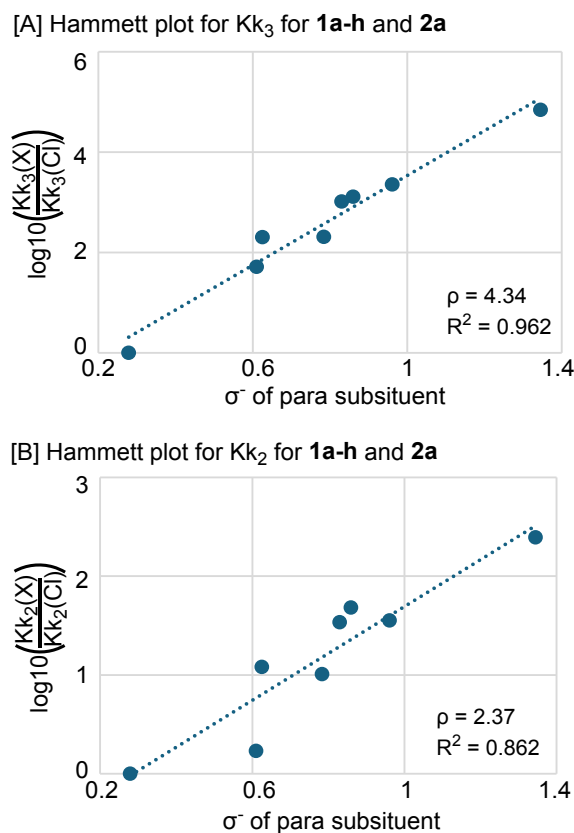


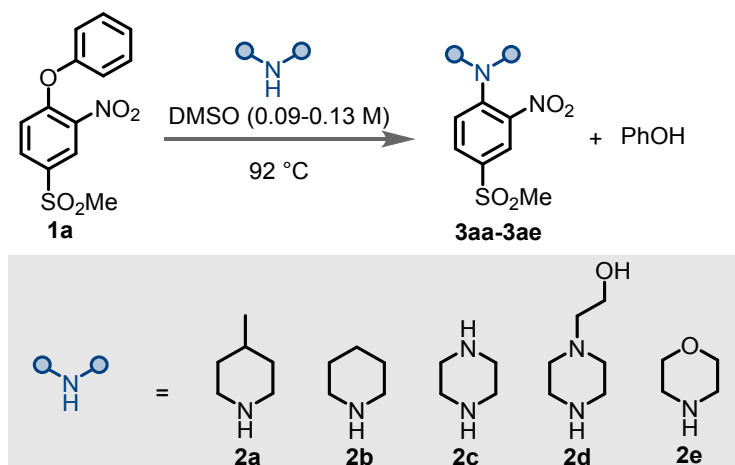
**Figure 8.** Hammett plots for the  $Kk_2$  (A) and  $Kk_3$  (B) parameters for the  $S_NAr$  reaction between electrophiles **1a-h** with 4-methylpiperidine **2a**.

The enhanced sensitivity of the rate limiting step of pathway B to the para-substituent can be rationalised by considering the effect of deprotonation of  $\mathbf{MC}^\ddagger$ , which converts the electron-withdrawing ammonium

group in  $\mathbf{MC}^{\pm}$  into the electron rich amino group of  $\mathbf{MC}^{-}$  (Scheme 1).<sup>58</sup> This increases the stabilising effect of electron-withdrawing substituents in pathway B compared to pathway A, where phenoxide departs without deprotonation of  $\mathbf{MC}^{\pm}$ .

### Amine Basicity

To elucidate the role of amine basicity on the relative rates of pathways A and B, we applied the SAKE protocol to a series of cyclic secondary amines **2a–2e** reacting with **1a** in DMSO at 92 °C (Scheme 4). Five amines with pKa values in DMSO ranging from 9.08 to 10.82 were trialled.<sup>32,56,59</sup> A modified experimental design was used for piperazine **2c** to avoid excess amounts of **1a** that can lead to diarylation, highlighting the versatility of SAKE (see Section S2.4.2). Amine orders from Auto-VTNA (1.25–1.38, Table SA23), and  $k_3/k_2$  ratios from kinetic modelling (2.5–5.5, Table SA18) did not change significantly with basicity, while phenol by-product inhibition remained modest (calculated order of –0.01 to –0.07).



**Scheme 4.** Reactions performed to study the effect of the amine basicity on reaction pathways A and B.

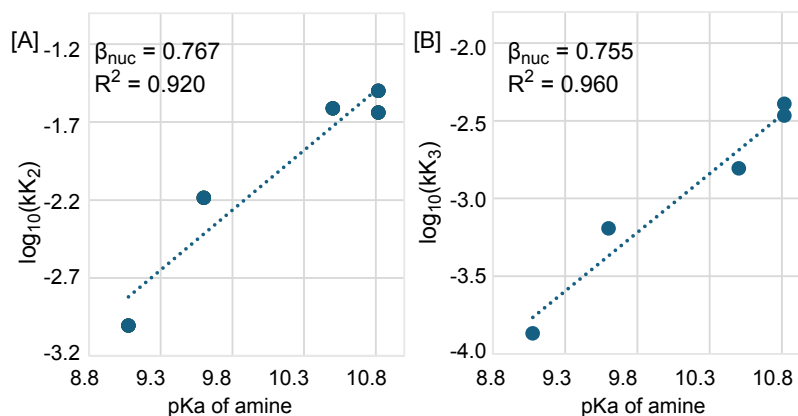


**Figure 9.** Brønsted plots for the S<sub>N</sub>Ar reaction between **1a** and cyclic amines **2a-e**.

The resultant Brønsted plot (Fig. 9) yielded  $\beta_{\text{nuc}}$  values of 0.76 and 0.77 for  $Kk_2$  and  $Kk_3$ , respectively, indicating comparable sensitivity of both pathways to nucleophile strength in DMSO. The similarity in  $\beta_{\text{nuc}}$  values is consistent with the RLPT mechanism, in which amine basicity affects  $K = k_1/k_{-1}$  but neither  $k_2$  nor  $k_3$ .<sup>32</sup>

### Solvent Effect

While the kinetics of base-catalysed S<sub>N</sub>Ar reactions have been previously investigated in various solvent systems, including: DMSO<sup>35</sup>, 90% water–dioxane,<sup>33,34,60</sup> 80% water–DMSO,<sup>51</sup> methanol,<sup>37</sup> toluene,<sup>61</sup> benzene,<sup>40</sup> and acetonitrile,<sup>32,52,62</sup> a comprehensive and systematic study of various solvents on the competition between pathways A and B is lacking. In this part of the study, the reaction of **1a** with **2a** at 70 °C was studied using the SAKE protocol in twelve solvents spanning a broad dielectric range ( $\epsilon = 2.2$ –46.7), including both protic and aprotic media. This approach enables an unprecedented comparative analysis of pathway selectivity across solvents. As anticipated, polar aprotic solvents DMSO, DMF, NMP, and MeCN facilitated efficient conversion, consistent with their capacity to stabilize polar Meisenheimer intermediates and related transition states without stabilising the nucleophile by hydrogen bonding. In contrast, ethers (e.g., 1,4-dioxane, 2-methyl-THF) and alcohols (e.g., ethanol, isopropanol, tert-butanol)

yielded markedly reduced rate constants for both pathways (Table SA19 in the ESI). The extent of base catalysis, as quantified by the  $k_3/k_2$  ratio and order in **2a**, varied substantially with solvent. For instance, ethanol exhibited a modest  $k_3/k_2$  ratio of 2.71 with an amine order of 1.18, while 3-pentanone yielded a value of 139 with a higher amine order of 1.97, underscoring the profound influence of solvent on the competitive pathways A (order in **2** of 1) and B (order in **2** of 2).

To better understand these trends, we conducted a comprehensive multivariate analysis using a suite of solvent descriptors, including:

- (i) Dielectric constant ( $\epsilon$ ) and dipole moment ( $\mu$ );<sup>63,64</sup>
- (ii) Gutmann donor/acceptor numbers (AN/DN);<sup>65</sup>
- (iii) Hansen solubility parameters, including: dispersion ( $\delta_D$ ), polar ( $\delta_P$ ), and hydrogen bonding ( $\delta_H$ );<sup>66</sup>
- (iv) Catalán parameters: polarizability (SPP),<sup>67</sup> acidity (SA),<sup>68</sup> and basicity (SB);<sup>69</sup>
- (v) Kamlet-Taft parameters: hydrogen bond donating ability ( $\alpha$ ),<sup>70</sup> accepting ability ( $\beta$ ),<sup>71</sup> and dipolarity/polarizability ( $\pi^*$ );<sup>72</sup>
- (vi) Abraham's hydrogen bond acidity ( $\alpha_A$ ),<sup>73</sup> and basicity ( $\beta_A$ ).<sup>74</sup>

Pearson correlation analysis revealed that polarity-related descriptors strongly correlated with both  $Kk_2$  and  $Kk_3$ , while acidity and basicity parameters exhibited pathway-specific effects (Fig. 10). Notably,  $Kk_3$  was negatively correlated with solvent acidity, suggesting that protic solvents attenuate base catalysis by stabilizing the amine nucleophile via hydrogen bonding. Conversely,  $Kk_2$  showed moderate positive correlations with basicity descriptors, likely because relatively basic alcoholic solvents can facilitate phenolate expulsion via H-bond donation (Fig. 10). It is also possible that basic solvents stabilize **MC<sup>±</sup>** by hydrogen bonding to the ammonium group, thereby limiting its conversion to **MC<sup>-</sup>**. Notably, the fitted inhibition constant  $K_i$  across all solvents does not correlate with polarity and acidity, but is negatively correlated with basicity. This suggests that more basic solvents may compete with the amine for hydrogen bonding to phenol, thereby reducing phenol's inhibitory effect on amine activity. This finding strengthens the hypothesis that inhibition of **2** by PhOH is due to hydrogen bonding rather than protonation.

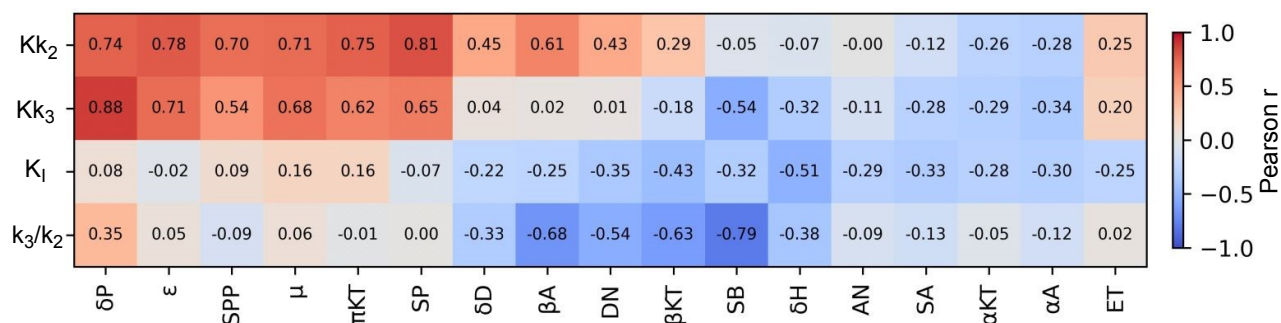


**Figure 10.** Pearson correlation heatmap for descriptors and the fitted parameters  $Kk_2$ ,  $Kk_3$  and  $K_i$  as well as  $k_3/k_2$  across the 12 selected solvents.

Exhaustive linear regression modelling identified minimal descriptor sets capable of accurately predicting kinetic parameters (using scikit-learn in Python). Eventually, we opted for simple linear two-parameter models to avoid overfitting and ensure interpretability. For  $Kk_2$  (Fig. 11A) the best-performing two-parameter model ( $R^2 = 0.80$ ) included the Snyder polarity index (SP) and Abraham's solvent acidity ( $\alpha A$ ), consistent with a mechanism involving rate limiting phenolate expulsion from a partially charged transition state. For  $Kk_3$  (Fig. 11B), the optimal model ( $R^2 = 0.94$ ) incorporated the Hansen polar solubility parameter ( $\delta P$ ) and Catalán's solvent acidity (SA), highlighting the importance of dipolar stabilization, and the detrimental effect of solvent acidity on the rate limiting proton transfer step of Pathway B, likely due to stabilization of the nucleophilic lone pair of **2a** through hydrogen bonding. The relevance of Catalán's acidity scale is particularly appropriate, as it is derived from the bathochromic shift in the UV-vis spectrum of 4-nitroaniline, which is strongly correlated to the ability of solvents to stabilise the amine **2a** via hydrogen bonding.<sup>68</sup>

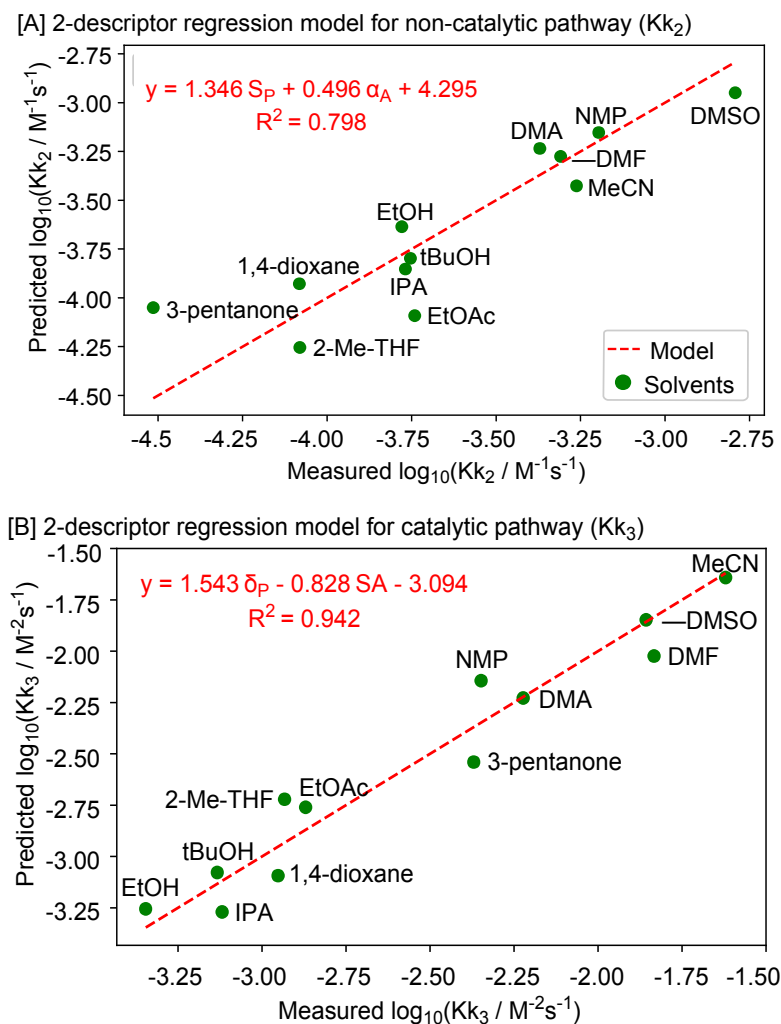


**Figure 11.** Linear regression model for the  $Kk_2$  (A) and  $Kk_3$  (B) data, using the two descriptors that provided the greatest  $R^2$  value. The solvent parameters were normalized from 0 to 1 to facilitate comparison of the different coefficients.

These observations indicate a profound solvent effect on both the overall reaction rate and the extent of base catalysis. Both pathways proceed via polar transition states, with their relative contributions determined by the solvent acidity. Although the best-fitting two-parameter models are consistent with the RLPT mechanism, more evidence is required to determine the true RLTS across solvents. Ongoing work aims to gain a more general understanding of the mechanism of base catalysis in  $S_NAr$  reactions, building on the studies of Um *et al.*, and will be reported in due course.<sup>32,51,75</sup>

## Conclusion

We have developed and demonstrated Sequential Addition Kinetic Elucidation (SAKE), a data-efficient experimental methodology for acquiring kinetically rich datasets under synthetically relevant conditions. By combining staged reagent dosing with continuous *in situ* monitoring, SAKE enables multiple kinetic regimes to be accessed within a single experiment, significantly reducing experimental workload and inter-run variability compared to conventional approaches.

Application of SAKE to nucleophilic aromatic substitution ( $S_NAr$ ) reactions of 2-nitroaryl phenyl ethers with secondary amines highlights its ability to resolve complex kinetic behaviour in systems featuring competing pathways and product inhibition. Integration with Auto-VTNA and microkinetic modelling enabled quantitative extraction of global rate laws and pathway-specific parameters, including the relative contributions of uncatalysed and base-catalysed pathways, as well as reversible inhibition by phenol. Systematic variation of temperature, substrate electronics, amine basicity, and solvent provided mechanistic insight while establishing quantitative relationships between reaction conditions and kinetic response.

While more complex reaction networks may still require complementary experiments, and further work is needed to integrate model-based experimental design, the present study establishes SAKE as a versatile and scalable approach for quantitative kinetic analysis. Its ability to generate reproducible, high-density datasets makes it well suited for integration into emerging data-driven and automated reaction engineering workflows.

## Author contributions

DD and KKH conceptualised the ideas within this work, with input from LS. DD developed the code, performed the experiments, and analysed the data. AA, KKH and LS offered advice during the work and

mentorship to DD. DD wrote the original draft of the manuscript, and all authors participating in the subsequent revisions.

### Conflicts of interest

There are no conflicts to declare.

### Data availability

All kinetic datasets generated in this project, and Python scripts for all data processing and analysis can be found at <https://github.com/ddalland/SAKE>.

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**Data Availability Statement**

All experimental kinetic datasets generated in this study, along with the Python scripts used for data processing, Auto-VTNA analysis, and microkinetic modelling, are openly available in a public repository at: <https://github.com/ddalland/SAKE>

Additional supporting data, including detailed experimental procedures, calibration methods, and extended datasets, are provided in the Electronic Supplementary Information (ESI) accompanying this article.