

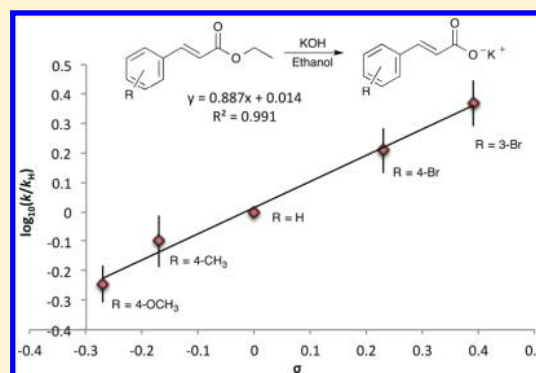
A Robust, “One-Pot” Method for Acquiring Kinetic Data for Hammett Plots Used To Demonstrate Transmission of Substituent Effects in Reactions of Aromatic Ethyl Esters

Hon Man Yau,[†] Ronald S. Haines,* and Jason B. Harper*

School of Chemistry, University of New South Wales, UNSW, Sydney, NSW 2052, Australia

S Supporting Information

ABSTRACT: A “one-pot” method for acquiring kinetic data for the reactions of a series of substituted aromatic esters with potassium hydroxide using ¹³C NMR spectroscopy is described, which provides an efficient way to obtain sufficient data to demonstrate the Hammett equation in undergraduate laboratories. The method is time-efficient and robust, and lends itself to group work. The high throughput nature of the method allows collection of sufficient data to explore the transmission of electronic effects between the aromatic moiety and the ester functionality with varying chain lengths.



KEYWORDS: Upper-Division Undergraduate, Organic Chemistry, Physical Chemistry, Kinetics, NMR Spectroscopy, Laboratory Instruction

INTRODUCTION

The Hammett equation¹ bridges the concepts of equilibrium and kinetics in an empirical but insightful way such that it is desirable to include it in senior undergraduate courses, particularly those involving the determination of reaction mechanisms of organic processes.² For the dissociation constants of *m*- and *p*-substituted benzene derivatives such as benzoic acids and protonated anilines (K_X , where X denotes the substituent) and the rate constants for reactions of similar compounds (k_X , where X is the substituent), the Hammett equation allows the separation of a ‘substituent constant’ (σ), which is a measure of the electron-donating or -withdrawing nature of the substituent, from a ‘reaction constant’ (ρ), which is a measure of the susceptibility of a given reaction to the nature of the substituents (eqs 1a, 1b).

$$\log\left(\frac{K_X}{K_H}\right) = \rho\sigma \quad (1a)$$

$$\log\left(\frac{k_X}{k_H}\right) = \rho\sigma \quad (1b)$$

The reaction constant for the ionization of benzoic acid is arbitrarily defined as +1, and hence, the magnitude of the reaction coefficient for other processes allows comparison as to whether they are either more or less sensitive to the electronic nature of the substituents than is the ionization of benzoic acid. The sign of the reaction constant in the kinetic form (eq 1b) can provide information about the mechanism; a positive

reaction constant indicates that the process is favored by electron withdrawal from the aromatic ring by substituents and a negative reaction constant indicates that the process is favored by electron-donating groups.¹ Applications of the Hammett equation now encompass correlations of Hammett parameters with NMR chemical shifts³ and gas-phase ionization energies from ab initio calculations.⁴

Previous papers^{3,5–10} in this *Journal* have used between four and 11 substituents (in addition to the unsubstituted parent compound) to demonstrate the Hammett relationship, with many using parallel collection of data by allocating students to work with a particular substituted compound, then pooling data from the whole class.^{5,8,9} This approach is vulnerable to variations in the quality of data across the class due to differing skill levels of students, or variations in conditions, in particular temperature variations for kinetic experiments. These issues, in particular the consequences of temperature variation across multiple experiments, are eliminated when data for all substrates are recorded in a single reaction mixture (‘one pot’).

Previous work¹¹ has described a general ‘one-pot’ approach to obtaining relative rates using the Menshutkin reaction between substituted benzyl bromides and pyridine, and the sodium borohydride reduction of substituted acetophenones. The present work applies this approach to the reaction of substituted esters with potassium hydroxide, a reaction previously used to demonstrate the Hammett relationship.^{5,10}

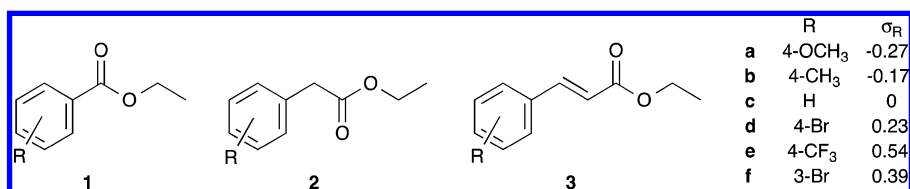


Figure 1. Esters used in this experiment and the associated Hammett substituent constants (σ).¹⁶

Consider a series of competing reactions between a single species, N , and multiple reactants x_i . The relative rate constants for two competing reactions can be obtained from the fractions of the starting materials remaining at an arbitrary time after initiating the reaction¹¹ (eq 2).

$$\frac{k_1}{k_2} = \frac{\ln\left(\frac{x_1}{x_{1,t=0}}\right)}{\ln\left(\frac{x_2}{x_{2,t=0}}\right)} \quad (2)$$

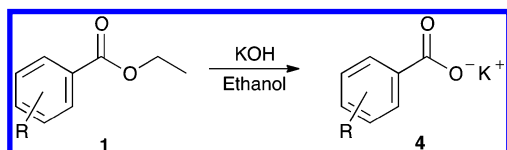
The k_i are the rate constants for the two competing reactions; and $x_{i,t=0}$ and x_i are the concentrations of reactant i at the start of the reaction and later at a time when all the concentrations are determined together, respectively. Unlike previous work published in this *Journal*^{9,12} and elsewhere,^{13–15} this formulation removes the need for starting with equimolar amounts of reactants, leaving only the requirement that the extent of reaction can be determined for all species by whatever analytical method is used at a single point in time after initiating the reaction; that is, at the time of measurement, the residual amount of the fastest-reacting species must be detectable along with a measurable decrease in the amount of the slowest-reacting species. In principle, even this constraint could be relaxed by sampling the reactants more than once after the reaction was initiated.

Only one paper dealing with experimental demonstration of the Hammett equation previously published in this *Journal* has used NMR spectroscopy to acquire kinetic data.⁹ The ‘one-pot’ approach described herein minimizes spectrometer time by requiring only two spectra: one of the mixture of the competing reagents prior to addition of a common reagent and one at some point after the addition of the common reagent.

EXPERIMENTAL OVERVIEW

In this laboratory experiment, students compare the ρ values from Hammett plots for the reaction, with potassium hydroxide, of ethyl benzoates **1a–d**, ethyl phenylacetates **2a–e**, and ethyl *trans*-cinnamates **3a–d,f** (Figure 1). The reaction is exemplified by the conversion of ethyl benzoates **1a–d** to potassium salts **4a–f** (Scheme 1). The outcome is that the students learn how modification of the carbon chain between the carbonyl moiety and the aromatic ring affects the communication of electronic effects between the *para*- or *meta*-substituent on the ring and the reaction center; these changes

Scheme 1. Reaction of the Ethyl Benzoates **1a–d** with Potassium Hydroxide in Ethanol



are observed as changes in the ρ value as determined from the slope of the corresponding Hammett plot.

EXPERIMENT

Students carry out the experiment individually and subsequently pool their data. Two 3-h periods over consecutive days are used to complete the experiment. Students prepare mixtures in ethanol containing approximately equimolar amounts of either benzoates **1a–d**, phenylacetates **2a–e** or cinnamates **3a–d,f**, with the total concentration of esters being ca. 0.4 mol L⁻¹. A ¹³C NMR spectrum is recorded of an aliquot of the reaction mixture prior to reaction. While having the species present at approximately equal concentrations simplifies analysis, this is not a requirement for the subsequent calculations with the formulation shown in eq 2, unlike methods previously reported,^{9,12–15} and therefore reduces the impact of student error on the experiment outcome. The only other reagent required for the reaction is ethanolic potassium hydroxide (ca. 0.1 mol L⁻¹), which is added to initiate the reaction. Full experimental details are provided in the Supporting Information.

After the reaction mixture is heated at reflux overnight, the solvent is removed and the extent of conversion of the ethyl esters is determined by dissolving the residue in deuterated acetone and analyzed using ¹³C NMR spectroscopy. Once again, the procedure is robust as the nature of the calculations means that the absolute extent of conversion of the ethyl esters to the corresponding salts is irrelevant, while the quantity of potassium hydroxide used is chosen such that consumption gives straightforward analysis. Variations from this still allow the subsequent calculations to be carried out, and neither this exact concentration nor complete reaction of the hydroxide are necessary for the experiment to be successful.

The extent of conversion of the ethyl esters is determined by comparing the integration of a signal due to the esters relative to the signal due to benzophenone standard (δ ca. 197) in a ¹³C NMR spectrum of the reaction mixture prior to addition of the potassium hydroxide and at completion of the reaction. A relaxation agent (chromium(III) acetylacetonate) is required to ensure rapid relaxation of all the ¹³C nuclei, coupled with an appropriate pulse sequence (see Supporting Information) to allow integration of the signals. Benzoates **1a–d** are quantified using the signals due to the methylene carbon of the ethyl functionality (δ ca. 62); phenylacetates **2a–e** using the signals due to the carbonyl carbon (δ ca. 172) and cinnamates **3a–d,f** using the signals of the carbonyl carbon (δ ca. 167). In each mixture, the rate of reaction of each substituted species is determined relative to the unsubstituted case using eq 2 and a Hammett plot constructed from the resulting data.

HAZARDS

Students must wear gloves, safety glasses and lab coats at all times during the experiments. Potassium hydroxide is corrosive and ethanolic solutions of such should be handled with care.

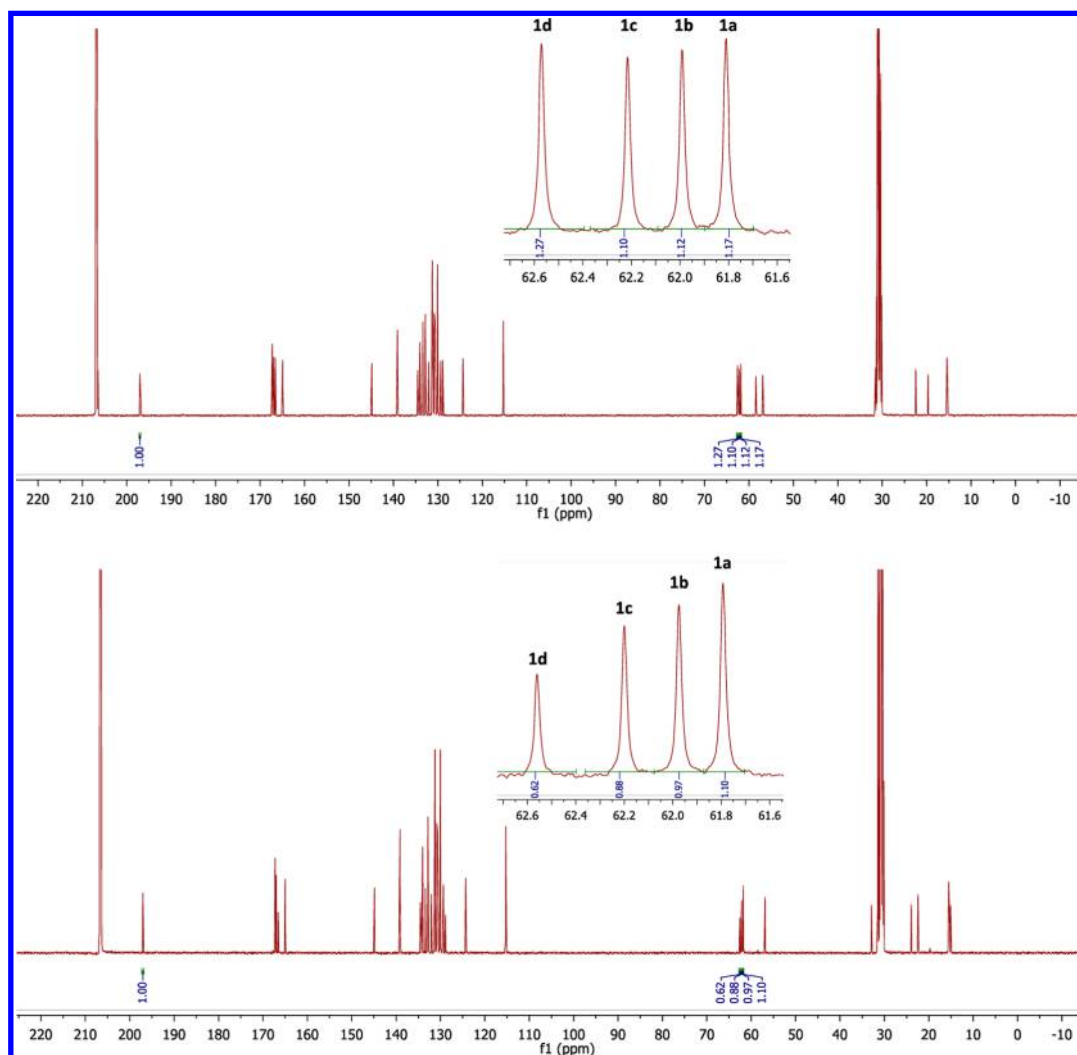


Figure 2. Representative ^{13}C NMR spectra (100 MHz) at 25 $^{\circ}\text{C}$ of a solution containing a mixture of the ethyl benzoates **1a–d** before (top) and after (bottom) reaction with potassium hydroxide in ethanol at reflux. Signals shown in the inset correspond to the methylene carbon of the ester functionality of benzoates **1a–d**.

Ethanol and acetone- d_6 are flammable. While of low toxicity, care should also be taken with chromium(III) acetylacetonate (a serious irritant), benzophenone and esters **1a–d**, **2a–e** and **3a–d,f**, along with the mixtures containing the corresponding potassium salts.

RESULTS AND DISCUSSION

Second-year undergraduate students (16 students) readily completed the experiment with one set of esters, and third-year undergraduate students (12 students) with two sets of esters. There was no significant difference in performing the experiment based on experience, with the exception of the efficiency that having spent more time in the laboratory brings. Thus, this experiment is demonstrated as robust, and functions well for students with a range of abilities. Students were provided with the NMR spectra from their samples, along with a spreadsheet (with instructions) to work through in the following week (see Supporting Information).

A pair of representative ^{13}C spectra of mixtures of the benzoate esters **1a–d** before and after reaction with potassium hydroxide are shown in Figure 2; equivalent spectra for the phenylacetate and cinnamate cases are given in the Supporting Information. While the spectra are complex, in each case the

signals due to the esters are readily identified. The ^{13}C spectra presented were obtained at a resonance frequency of 100 MHz, which is not prohibitively high for teaching use, though clearly a greater magnetic field would increase dispersion further. While the inherent insensitivity of the method (due to the low natural abundance of ^{13}C and its low magnetogyric ratio) does mean that the acquisition time for each spectrum is *ca.* 90 min (full details in Supporting Information), only two spectra are needed to complete an entire Hammett plot and the process can be automated. The data shown in Figure 2 from one student sufficed to generate the Hammett plot shown in Figure 3.

Independent of the level of the student, approximately 90% of students obtained a linear relationship in their Hammett plots (representative examples are provided in Supporting Information). In cases where a linear relationship was not observed, often one signal in the NMR spectrum was much smaller than anticipated, suggesting incomplete dissolution (either in the NMR sample or on addition of the standard solution).

Subsequent to analysis of their own data, students were provided with data from the remainder of the class (in each class this meant between 5 and 8 data sets for each ester). This allowed determination of reaction constants from averaged

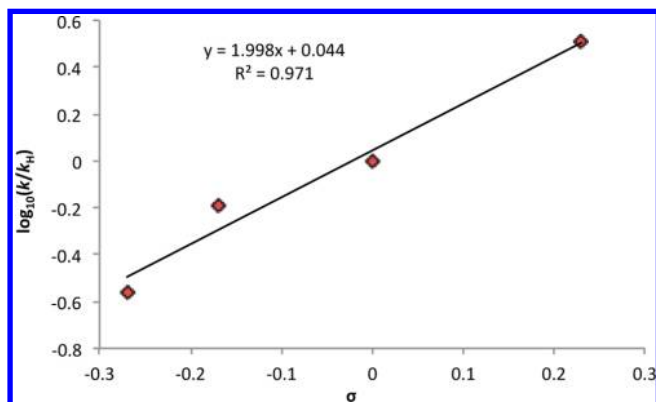


Figure 3. Representative Hammett plot constructed from the data presented in Figure 2 for the reaction of ethyl benzoates **1a–d** with potassium hydroxide in ethanol at reflux.

relative rate data for each set of esters. When the class data were pooled, the uncertainties in the averaged rate data were small enough to allow clear discrimination between the electronic effects for each class of ester (see Figure 4 and Figures S10–12 in the Supporting Information).

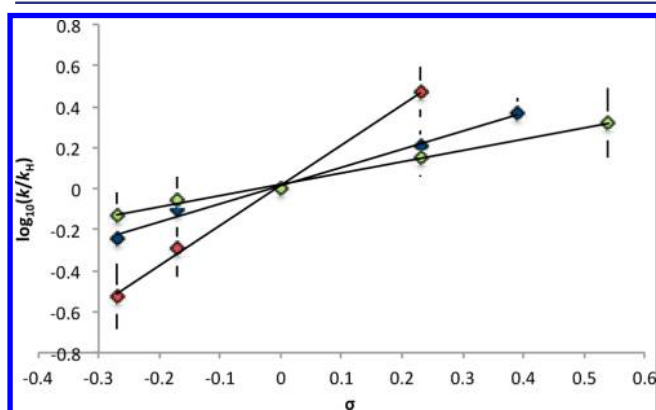


Figure 4. Representative Hammett plot constructed from the relative rate information from an undergraduate class for the reaction of either ethyl benzoates **1a–d** (red diamonds, $R^2 = 0.998$), ethyl phenylacetates **2a–e** (green diamonds, $R^2 = 0.994$), or cinnamates **3a–d,f** (blue diamonds, $R^2 = 0.991$) with potassium hydroxide in ethanol at reflux. Each data point and the associated errors shown were calculated from the relative rate of the corresponding substituent from at least six separate experiments.

The ρ value for the reaction of ethyl benzoates **1a–d** with potassium hydroxide in ethanol at reflux from combined data was typically found to be ca. 2, with individual student values being in the range 1.5–2.5. This was in good agreement with values in the literature for the same reaction carried out in a range of solvents and at different temperatures ($\rho = 1.8$ – 2.5^{17}). Using the ρ value obtained, students were required to describe the electronic demands in the transition state of the hydrolysis of ethyl benzoates, based on the mechanism of the reaction, and make comparisons with the ρ values of the other two reactions subsequently.

Similarly, a ρ value of ca. 0.5 for the combined data (with individual student values in the range 0.25–0.75) was observed for the reaction of phenylacetates **2a–e** with potassium hydroxide in ethanol at reflux, which is in reasonable agreement, particularly given the temperature difference, with

literature values for the same reaction carried out in 88% ethanol–water at 30 °C ($\rho = 0.82^{17}$). For the reaction of ethyl cinnamates **3a–d,f** with potassium hydroxide in ethanol at reflux, combined student data gave a reaction constant of ca. 0.9, with individual student data being in the range 0.6–1.2. This value can be compared with the literature value for the same reaction carried out in 88% ethanol–water at 30 °C ($\rho = 1.27^{17}$), noting the temperature and solvent differences.

Students compared the relative electronic effects on the reaction across the three classes of ester. This was done both by simply combining all the data on a single plot (a representative example is shown in Figure 4) to allow a visual interpretation and also by comparing the reaction constants. Students then calculated the attenuation factor (f) for a methylene unit and a vinyl unit; these are simply the quotient of the reaction constant for phenylacetates **2a–e** and cinnamates **3a–d,f**, respectively, with the reaction constant for benzoates **1a–d** (eqs 3a, 3b). Typical attenuation factors determined were ca. 0.25 for the methylene unit (lower but comparable to the literature value of 0.43 ± 0.06^{18}) and ca. 0.45 for the vinyl unit (in agreement with the literature value of 0.48 ± 0.07^{18}). A comparison of the two attenuation factors led to a discussion by the students of the role of conjugation in transmitting electronic effects. Feedback from the students confirmed the efficacy of the experiment in communicating the importance of structure in the magnitude of substituent effects.

$$f_{\text{CH}_2} = \frac{\rho_{\text{phenylacetates}}}{\rho_{\text{benzoates}}} \quad (3a)$$

$$f_{\text{CH=CH}} = \frac{\rho_{\text{cinnamates}}}{\rho_{\text{benzoates}}} \quad (3b)$$

SUMMARY

A fast and robust method to generate data for Hammett plots, which can be used to introduce electronic effects in organic reactions at the undergraduate level, has been described. The combination of NMR spectroscopy to acquire kinetic data, a simple method for processing that data, and a choice of reaction and substrates that allows demonstration of the attenuating effects of different groups, made this a very comprehensive and engaging experiment. The experiment can be structured as a group experiment by sharing the results for the different ester systems between students without risking the quality of the kinetic data used in the Hammett plots.

ASSOCIATED CONTENT

Supporting Information

Student experimental procedure, risk assessment, student instructions for analysis, instructor's notes (including for NMR analysis), representative spectra and associated Hammett plots, representative Hammett plots from combined class data, Excel spreadsheets (instructor and student). This material is available via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: r.haines@unsw.edu.au.

*E-mail: j.harper@unsw.edu.au.

Present Address

[†]Hon Man Yau: Schreiner Research Group, Institute of Organic Chemistry, Justus-Liebig University Giessen, Heinrich-Buff-Ring 58, 35392 Giessen, Germany.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge the support of Sharon Yu, Dominic Francis, and Nicholas Konstandaras in preparation of the ester starting materials and Bradley Butler for NMR analysis, along with the students who completed this laboratory. This work was supported in part by the University of New South Wales Goldstar Grants Programme and the Australian Research Council Discovery Project Funding Scheme (Project DP130102331).

REFERENCES

- (1) Hammett, L. P. The Effect of Structure upon the Reactions of Organic Compounds. Benzene Derivatives. *J. Am. Chem. Soc.* **1937**, *59*, 96–103.
- (2) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*, 2nd ed.; Oxford University Press: New York, 2012; pp 1041–1049.
- (3) Setliff, F. L.; Soman, N. G.; Toland, A. D. Hammett Correlations of Amide Proton Chemical-Shifts—An Organic or Spectroscopy Experiment. *J. Chem. Educ.* **1995**, *72*, 362–363.
- (4) Ziegler, B. E. Theoretical Hammett Plot for the Gas-Phase Ionization of Benzoic Acid versus Phenol: A Computational Chemistry Lab Exercise. *J. Chem. Educ.* **2013**, *90*, 665–668.
- (5) Leisten, J. A. A Group Experiment on the Hammett Sigma-Rho Relation. *J. Chem. Educ.* **1961**, *38*, 302–304.
- (6) Salmon, M.; Jimenez, A.; Salazar, I.; Zawadzki, R. NMR Hammett Correlation—Laboratory Experiment. *J. Chem. Educ.* **1973**, *50*, 370–371.
- (7) Hathaway, B. A.; Olesen, B. Determining Hammett Sigma and Rho Values—Improvements on a Published Student Experiment. *J. Chem. Educ.* **1993**, *70*, 953–955.
- (8) Marrs, P. S. Class Projects in Physical Organic Chemistry: The Hammett Equation. *J. Chem. Educ.* **2001**, *78*, 527–529.
- (9) Mullins, R. J.; Vedernikov, A.; Viswanathan, R. Competition Experiments as a Means of Evaluating Linear Free Energy Relationships. *J. Chem. Educ.* **2004**, *81*, 1357–1361.
- (10) Keenan, S. L.; Peterson, K. P.; Peterson, K.; Jacobson, K. Determination of Hammett Equation Rho Constant for the Hydrolysis of *p*-Nitrophenyl Benzoate Esters. *J. Chem. Educ.* **2008**, *85*, 558–560.
- (11) Yau, H. M.; Croft, A. K.; Harper, J. B. ‘One-Pot’ Hammett Plots: A General Method for the Rapid Acquisition of Relative Rate Data. *Chem. Commun.* **2012**, *48*, 8937–8939.
- (12) Mak, K. K. W.; Chan, W.-F.; Lung, K.-Y.; Lam, W.-Y.; Ng, W.-C.; Lee, S.-F. Probing the Rate-Determining Step of the Claisen-Schmidt Condensation by Competition Reactions. *J. Chem. Educ.* **2007**, *84*, 1819–1821.
- (13) Navarrini, W.; Russo, A.; Tortelli, V. Relative Rate Constants for the Reactions of CF₃OF with Olefins in Solution. *J. Org. Chem.* **1995**, *60*, 6441–6443.
- (14) Portal, C. F.; Bradley, M. High-Throughput Physical Organic Chemistry Hammett Parameter Evaluation. *Anal. Chem.* **2006**, *78*, 4931–4937.
- (15) Lorello, G. R.; Legault, M. C. B.; Rakić, B.; Bisgaard, K.; Pezacki, J. P. Synthesis and Bioorthogonal Coupling Chemistry of a Novel Cyclopentenone-Containing Unnatural Tyrosine Analogue. *Bioorg. Chem.* **2008**, *36*, 105–111.
- (16) Hansch, C.; Leo, A.; Taft, R. W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991**, *91*, 165–195.

(17) Jaffe, H. H. A Reexamination of the Hammett Equation. *Chem. Rev.* **1953**, *53*, 191–261.

(18) Hammett, L. P. *Physical Organic Chemistry*; McGraw-Hill: Tokyo, 1970; pp 366–367.