Rhodium-Catalyzed C–H Amination: A Case Study of Selectivity in C–H Functionalization Reactions

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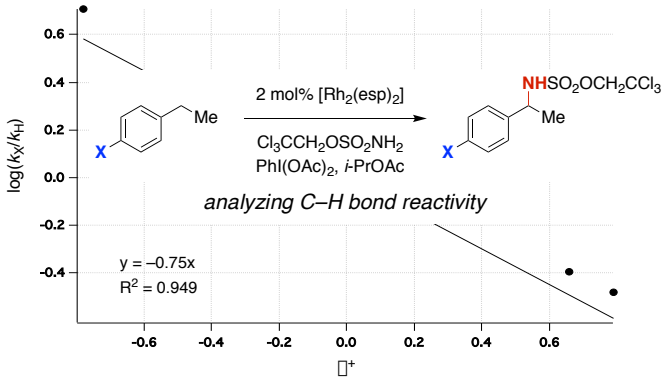
ABSTRACT

An advanced undergraduate organic chemistry laboratory experiment involving a rhodium-catalyzed intermolecular hydrocarbon C–H oxidation reaction is described. In the initial phase of this lab, students conduct a C–H amination reaction of ethylbenzene and isolate a benzylic amine product. In the second part of the lab, competition experiments are performed to compare the relative rates of C–H insertion with electronically disparate *para*-substituted ethylbenzene derivatives. Reaction progress is monitored by thin-layer chromatography and the outcome quantitatively assessed using ^{1}H NMR spectroscopy. Data from competition experiments form the basis for a discussion of reaction mechanism, including analysis of putative transition structures and relative potential energy barriers for C–H oxidation. Experiments have been designed such that instructors can tailor the level of detail and discussion from introductory to advanced.

GRAPHICAL ABSTRACT



KEYWORDS

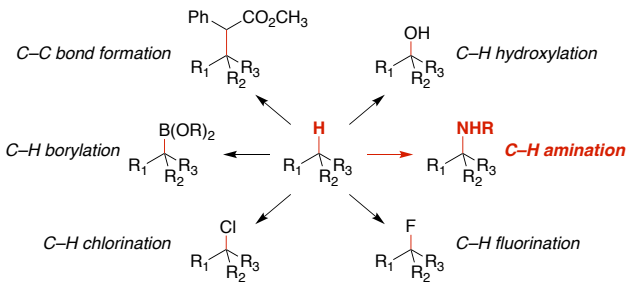
Organic Chemistry, C–H Oxidation, Catalysis, Transition metal, Kinetics, NMR Spectroscopy, Synthesis, Laboratory instruction, Hands-on learning/Manipulatives, Upper-division undergraduate

In research aimed at developing new tactics for assembling complex molecules, catalyst-mediated oxidation of saturated C–H bonds has emerged as a powerful method for the selective introduction of polar functional groups into hydrocarbon frameworks[1]. Addition of a polar substituent through C–H oxidation mitigates reliance on protecting groups and, thus, reduces the number of steps needed for molecular assembly. Such transformations, in effect, allow synthetic chemists to consider the C–H bond as a functional group with characteristic and predictable reactivity. Despite the rapid growth of this field in recent years, its inclusion in the undergraduate curriculum has been limited. Research in C–H functionalization offers a forum for teaching students about modern advances in organic chemistry and the concepts of catalysis, reaction kinetics, and reaction selectivity. Undergraduate laboratory experiments describing C–H functionalization have been previously highlighted in *this journal*; the majority, however, have focused on radical halogenation reactions[2]. Others include enzymatic steroid hydroxylation[3], stoichiometric cyclometallation with noble metals[4], and non-metal-mediated carbene C–H insertions[5]. This report is the first to describe a catalytic, metal-mediated C–H functionalization experiment for advanced undergraduate students. The primary pedagogical goals of this laboratory practical are: 1) to introduce students to catalytic C–H oxidation chemistry, 2) to underscore the concept of kinetically-controlled reaction selectivity, and 3) to demonstrate how reaction mechanisms are analyzed experimentally. In the course of this study, students will also gain familiarity with common laboratory techniques such as thin-layer chromatography (TLC), column chromatography, and ^{1}H NMR spectroscopy.

INTRODUCTION

The promise of C–H oxidation technologies to transform the practice of chemical synthesis relies on the ability to control product selectivity with substrates possessing disparate C–H bond types. Modern reaction methods for C–H oxidation largely rely on the generation of transient electrophilic species that are sufficiently reactive to convert C–H bonds to C–X bonds[6] (Scheme 1). In practice, both steric and electronic factors have been found to influence the rate of C–H bond oxidation towards different electrophiles. These data provide an empirical set of guidelines for predicting reaction outcomes, in much the same way that the identity of a nucleophile-electrophile pair can be used to gauge the feasibility of an S_N2 reaction. Detailed mechanistic studies of specific oxidation reactions have given deeper insight into factors that conspire to favor C–H oxidation at a particular site in a complex molecule.

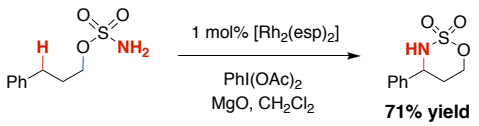
Scheme 1. Catalytic C–H functionalization



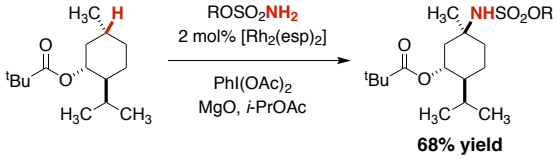
Transition metal-catalyzed C–H amination reactions have emerged as efficient and selective technologies for generating amines and amine derivatives[7]. Examples of both intra- and intermolecular reaction processes can be found in the literature and are promoted by a variety of metal complexes, including those derived from Mn, Fe, Co, Cu, Ru, Rh, Pd, and Ag.[8] For intermolecular C–H amination, dirhodium tetracarboxylate catalysts, in particular [Rh_2(esp)$_2$] (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate), have proven exemplary when used in combination with sulfamate starting materials and an inexpensive bulk oxidant. Reactions of this type, as highlighted in Scheme 2, proceed in high yield and with excellent selectivity for benzylic and 3° C–H bonds. How do we begin to understand and rationalize the characteristic selectivity trends in these amination reactions? This is the central question that frames the set of experiments described below.

Scheme 2. C–H functionalization under Rh-catalysis.

A. *Intramolecular C–H Amination*



B. *Intermolecular C–H Amination*



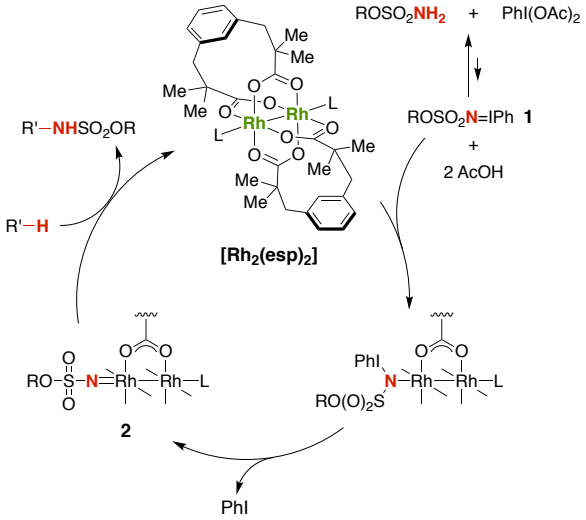
BACKGROUND

Early reports of successful rhodium-catalyzed C–H amination reactions describe the use of alkoxysulfonamide starting materials, which can be made to undergo oxidative cyclization to give 6-membered ring products (Scheme 2A). Analogous, intermolecular processes have typically employed an alkoxy- or aryloxysulfonamide as a nitrogen source (e.g., 2,2,2-trichloroethoxysulfonyl amine ($TcesNH_2$)) along with [Rh_2(esp)$_2$], a dirhodium tetracarboxylate catalyst, and diacetoxyiodobenzene ($PhI(OAc)_2$) as the stoichiometric oxidant. When these reagents are combined with a hydrocarbon substrate, efficient C–H bond oxidation affords the *N*-alkylsulfonamide product (Scheme 2B).

Mechanistic studies[9] have established that C–H amination proceeds through the intermediacy of TcesN=IPh **1**, which results from condensation between $TcesNH_2$ and $PhI(OAc)_2$ (Scheme 3). TcesN=IPh **1** engages the dirhodium catalyst liberating PhI to afford electrophilic Rh-nitrene **2** as the active oxidant. This high-energy intermediate has a fleeting lifetime under the reaction conditions and rapidly reacts with substrate to give an alkoxysulfonamide product and to release $[Rh_2(esp)_2]$, thus completing one catalytic turnover. As noted above, this method shows a clear preference for oxidation of certain types of C–H bonds, favoring benzylic and 3° over 2° and 1° sites. In addition, amination of stereogenic 3° C–H centers occurs with absolute retention of stereochemistry (Scheme 2B).

The following three-part experiment is intended to introduce advanced undergraduate students to dirhodium-catalyzed, intermolecular C–H amination chemistry. *Para*-substituted ethylbenzene derivatives are utilized as substrates for the purpose of comparing relative reaction rates of the oxidation event. In this way, students will be able to examine how electronic factors influence reactivity and selectivity and, if desired, to quantify these effects. Through this course of study, students will become familiar with methods for analyzing reaction kinetics and complex reaction mechanisms. The ensuing discussion emphasizes the basic precepts of nucleophilicity and electrophilicity to rationalize the reactivity of key reaction partners. Students are asked to 1) consider how each reactive partner in this amination process is best classified; and 2) how, apropos to this analysis, structural changes to the hydrocarbon starting material can alter reaction rate. For interested practitioners, a quantitative evaluation of free energy of activation and plausible transition structures that describe C–N bond formation are also provided.

Scheme 3. A postulated mechanism for $[Rh_2(esp)_2]$-catalyzed C–H amination proceeding through a Rh-nitrene **2** intermediate. R = CH_2CCl_3, R' = alkyl, L = solvent.



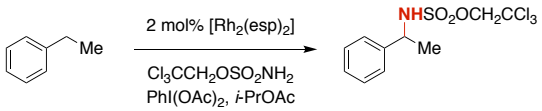
EXPERIMENT

This laboratory exercise consists of three parts (Box 1). In piloting this project, students were paired in groups of two or three, and used three, four-hour lab periods to complete all experimental and analytical work. Initially, each student (or student group) will perform a reaction with ethylbenzene as substrate. Following completion of the reaction, the product can be isolated by silica gel chromatography and characterized. In this portion of the lab, students are familiarized with protocols for reaction set-up, thin-layer chromatography monitoring of reaction progress, and chromatographic methods of product purification. Characterization of the isolated material by ^{1}H NMR spectroscopy offers experience with structure assignment (data provided in Supporting Information). If desired, the experiment can be ended at this point, with concepts of catalysis and C–H oxidation serving as the principle talking points for discussion (see Discussion Section).

In part 2, each student will conduct an experiment in which equimolar quantities of ethylbenzene and one of five possible *para*-substituted ethylbenzene derivatives are combined and subjected to the amination reaction. Upon completion of the reaction, the mixture is analyzed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of the pure product from ethylbenzene oxidation (part 1) can be used to deconvolve the more complex spectrum of the reaction mixture from the competition experiment and to determine the ratio of the two products. The product ratio provides a relative measure of the rates at which the two substrates undergo oxidation.[9a] This information can be used to calculate the approximate difference in free energy of activation for the C–N bond-forming event between the two starting materials (see Discussion Section).

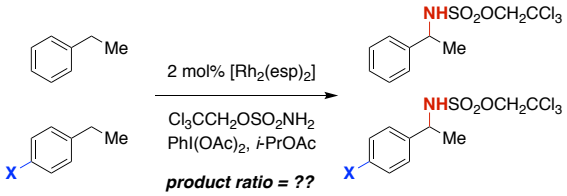
Box 1. Overview of the three-part amination experiment.

Part 1. Amination of ethylbenzene



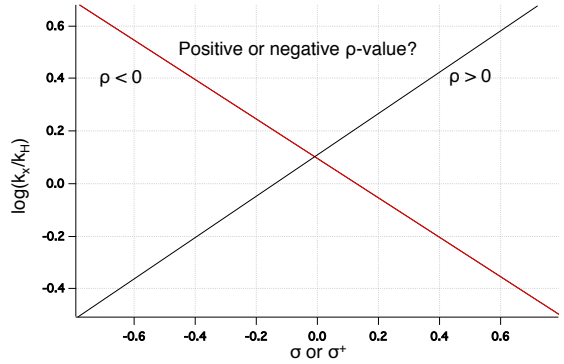
- Perform amination reaction, isolate and characterize sulfonamide product

Part 2. Competition experiment



- Perform competition reaction to measure relative rate of C–H amination

Part 3. Hammett Analysis



- Plot data from competition experiments against σ-parameters
- Determine σ-parameter that provides best fit of data
- Analyze reaction mechanism and transition state for C–N bond formation

For interested students and instructors, data obtained in part 2 can be combined and used to quantitatively assess structure-activity relationships, which constitutes the third section of this laboratory experiment[10]. This analysis requires some familiarity with transition state theory and physical organic chemistry[11] (sample slides discussing Hammett analysis are provided in Supporting Information). Product ratios can be correlated with relative rate constants for oxidation of *para*-substituted ethylbenzenes vs. ethylbenzene itself (please see discussion in Part 2 below for notes on this analysis). These data are plotted against the corresponding σ-constant for a given *para*-substituent. Students will evaluate both σ and σ^+ to determine which σ-parameter affords the best goodness-of-fit of the data to a regression line (R^2 value). The choice of σ-constant and the slope of the regression line provides insight into the charge distribution in the transition structure of the C–N bond-forming event. A discussion of how these data inform a more general understanding of the differential reactivity of different C–H bond types follows from this analysis.

HAZARDS

All manipulations of chemicals are performed in a fume hood and require the use of appropriate personal protective equipment (goggles, gloves, lab coats). Diacetoxyiodobenzene ($PhI(OAc)_2$) and potassium permanganate are oxidants that cause irritation to eyes, skin and mucus membranes upon exposure. Ethyl acetate, isopropyl acetate, and hexanes are flammable solvents. As *n*-hexane is a known neurotoxin and is present in commercial hexanes, alternative solvents including pentane or cyclohexane may be used instead for column chromatography. 4-Ethylanisole, 4-ethylchlorobenzene, 4-ethylbromobenzene, 4-ethylbenzonitrile, and 4-ethylnitrobenzene are volatile aromatic compounds and potential irritants. Ethylbenzene is an irritant and a potential carcinogen. Deuterated chloroform, $CDCl_3$, is volatile and a known carcinogen/mutagen, and should be handled exclusively in a fume hood. Magnesium oxide, silica gel, and Celite are irritating to mucus membranes if inhaled and should be handled in a fume hood. $[Rh_2(esp)_2]$ and $TcesNH_2$ are non-hazardous substances. Please note, ethylbenzene-derived C–H amination products have not been tested for safety and thus should be handled with care.

DISCUSSION

Classroom Testing

This laboratory experiment has been incorporated into the curriculum of the advanced organic chemistry laboratory at Stanford University (CHEM 132), and has been successfully conducted for five consecutive years. The pedagogy of this series of experiments and the supporting materials were assessed through graded oral presentations given by each student at the end of the sequence. This presentation was also accompanied by a lab write-up that included pre- and post-lab questions (see Supporting Information) as well as an analysis of the reaction protocol and data obtained. For the amination reaction of ethylbenzene, students typically isolated product in yields ranging from 30–40%. Analysis of the competition experiment data has been particularly successful, producing a Hammett plot with an R^2 value of 0.98 or greater when fit against σ^+ parameters.

Overview

This lab has been designed to be modular in order to cater to undergraduate audiences of different backgrounds. For some, a complete discussion of σ-parameters and Hammett analysis, as outlined in part 3, may be beyond the desired scope of an advanced organic chemistry lab. Performing part 1 of this experiment should suffice to familiarize students with basic concepts of catalysis and C–H functionalization while emphasizing reaction set-up, purification and analytical skills. Part 2 offers a more in-depth discussion of reaction mechanism and transition state theory, even if the Hammett analysis is not included as part of the overall experiment. To simplify work for instructors, all necessary ^1H NMR spectra have been provided. In addition to these data,

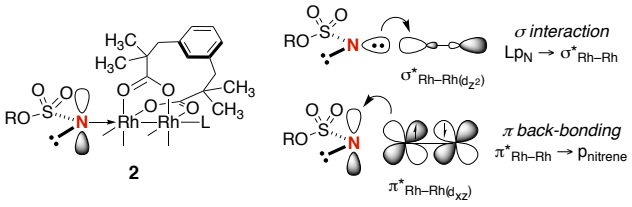
detailed experimental procedures (including pictures), lecture slides, and key discussion materials can be found in the Supporting Information.

Part 1: C–H Amination of Ethylbenzene

Students performing part 1 of this lab are encouraged to draw and to discuss the mechanism for generation of the rhodium-bound nitrene (**2,** Scheme 3). In principle, all steps preceding the extrusion of iodobenzene are reversible. Magnesium oxide (MgO) is hypothesized to function as a base for scavenging acetic acid (AcOH) in this process. Given this information, students should recognize that a base additive can influence the position of the equilibrium between $TcesNH_2$ + $PhI(OAc)_2$ ⇆ PhI=NTces + 2 AcOH.

Having examined the stepwise details of formation of the rhodium-bound nitrene **2**, students should then consider the intrinsic reactivity of this transient intermediate. A Lewis structure of the sulfonylnitrene, TcesN, provides a starting point for this discussion. The nitrogen atom in TcesN has an incomplete octet, and is therefore extremely reactive as an electrophile (Figure 1). Although a free sulfonylnitrene is an unlikely intermediate on the reaction coordinate, the Rh-bound form (**2**) shares analogous electrophilic properties. Binding of TcesN to $[Rh_2(esp)_2]$ attenuates the reactivity of this species and makes possible selective C–H bond oxidation.

Figure 1. Depiction of a Rh-bound sulfonylnitrene stabilized through σ-bonding and π-backbonding interactions. R = CH_2CCl_3.



The presentation of reaction mechanism and Rh-nitrene reactivity notwithstanding, an important question remains unanswered: for substrates possessing multiple C–H bonds, how is product selectivity determined? As highlighted in Scheme 2, high yields of single oxidation products are generally obtained from reactions of substrates bearing many disparate C–H bonds. Part 2 of this lab provides an analysis of reactivity-selectivity principles by examining relative rates of C–H bond oxidation.

Part 2: Competition Experiments

In part 2, students perform a competition experiment using equimolar amounts of ethylbenzene and one of five possible *para*-substituted derivatives. The goal of these competition experiments is to determine the extent to which the *para*-substituent group influences the rate of C–H bond amination. In this analysis, the product ratio, as measured by ^1H NMR integration, is used as an estimate of the relative reaction rates of substituted versus unsubstituted ethylbenzene. It should be noted, however, that the accuracy of this measurement necessitates

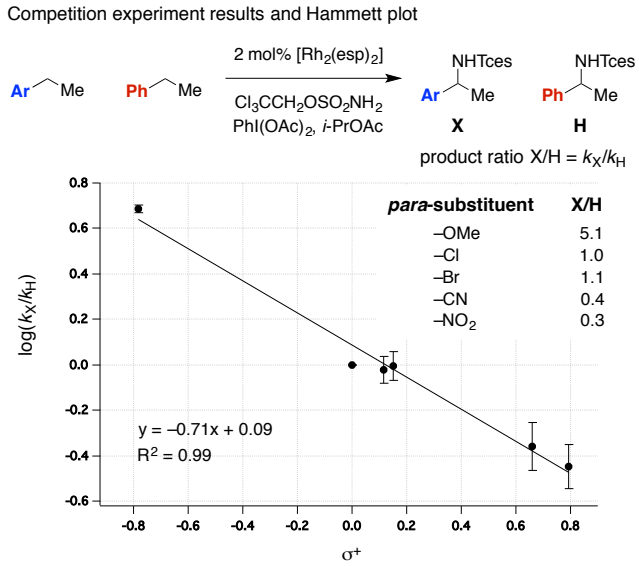
recording the product ratio at low substrate conversion; this can be accomplished either by halting the reaction shortly after initiation or by using a large excess of the competing substrates relative to the oxidant and/or nitrogen source, $TcesNH_2$. For this part of the amination experiment, both substrates are used in two-fold excess of the $TcesNH_2$ limiting reagent. Our prior work shows that the product ratios in these competition reactions do not differ even if 10 equivalents of each starting material is employed.[9a] Thus, a decision was made in formulating this lab practical to conserve materials and to minimize waste.[12]

A more accurate method for quantifying relative reaction rates in competition experiments measures consumption of the two starting materials (see Notes to Instructors in Supporting Information).[13] Such an analysis is problematic for this lab due to the volatility of certain ethylarenes, particularly ethylbenzene. Fortunately, the error introduced by product ratio analysis manifests principally in the extreme data points of the Hammett plot (e.g., –OMe, $–NO_2$). This error results in a calculated ρ that differs in magnitude by ~10–15% from the value obtained by estimating the relative consumption of starting material. Most importantly for the purpose of this lab, the sign of ρ is negative, consistent with *para*-electron-donating groups accelerating the rate of C–H amination. The absolute value of ρ is not a point of discussion.

A recorded ^1H NMR spectrum of the unpurified reaction mixture provides a quantitative measure of the product ratio in the competition experiment (sample NMR spectra are provided in Supporting Information). The methylene unit of the Tces group and the N–H of the alkoxysulfonamide are the most convenient ^1H NMR signals to integrate in order to determine the ratio of the two products (see Supporting Information for details). Comparing the data from all five competition experiments shows an obvious trend: the oxidation reaction is accelerated for substrates bearing *para*-electron-donating groups (Figure 2). A rationalization of these data follows from the mechanistic discussion in part 1. Electron-rich substrates display enhanced nucleophilicity and react faster with the electron deficient Rh-nitrene **2**.

The more advanced student may recognize that the relative ratio of products is directly proportional to the relative rate constants for the C–N bond-forming event. This derivation is straightforward given that the oxidation step is concerted and involves only a single transition state. Accordingly, the Eyring equation can be used to correlate the rate of the C–H amination step with the rate constant. Although the experiment does not provide a measure of the absolute rate for an individual reaction, a reasonable approximation of the relative rate for the oxidation of two substrates is given by the product ratio. Students who work through this analysis will appreciate the elegant simplicity of these competition experiments for gaining insight into reaction kinetics of the product-determining step. Based on this analysis, students can calculate differences in free energies of activation ($\Delta\Delta G^{\ddagger}$) that give rise to different product ratios in any one of the competition experiments.

Figure 2. Product ratios from competition experiments used for Hammett analysis.



Part 3: Hammett Analysis

For those interested, a plot of log(k_X/k_H) can be correlated against available substituent constants known as σ-parameters. The purpose of this exercise is to gain deeper insight into the transition structure leading to C–N bond formation. σ-Values are experimentally determined constants that reflect the static electrical properties – resonance and inductive contributions – of a given functional group. Different σ-parameter scales have been tabulated by measuring the influence of substituent groups on reaction equilibrium or rate for a given set of model reactions. By empirically fitting log(k_X/k_H) against a particular set of σ-constants, it is possible to analyze the electronic distribution of a transition structure and the relative influence of resonance and inductive effects on TS‡ energies.

A plot of log(k_X/k_H) against either σ or σ⁺ can be generated using Excel or any other available graphing program (both plots have been included in Supporting Information). Fitting these data to a regression line shows that σ⁺ constants afford an R^2 value that is closer to unity. While a detailed discussion of σ and σ⁺ is beyond the scope of this lab, the key point to communicate to students is that the latter constant weighs the contribution of resonance effects on the transition state more heavily than the former. Based on this insight, the fact that electron-donating groups (i.e., –OMe) accelerate the rate of C–H amination, and that oxidation is stereospecific (Scheme 2B), students can infer possible transition state structures. A concerted, asynchronous transition state in which C–H cleavage is more advanced than C–N bond formation (resulting in localization of positive charge on the benzylic carbon) is consistent with these data.

With insight into the transition structure for C–H amination, students can begin to appreciate why C–H reactivity generally follows as benzylic ~ 3° > 2° > 1°. Carbon centers that are better suited to support partial positive charge formation in the transition structure are advantaged as substrates for this process. With benzylic substrates, electron-donating groups such as –OMe can act to stabilize the developing cationic carbon center, thereby lowering the free energy of activation and, accordingly, increasing the rate of the amination event. These conclusions are in accord with the role of the hydrocarbon substrate as the nucleophilic partner in C–H oxidation reactions. Students who complete this portion of the lab will realize the power of structure-activity relationship studies for exploring complex reaction mechanisms.

SUMMARY

Feedback from students regarding this laboratory exercise has indicated that it was operationally straightforward and that each part could be completed in a fixed 4-hour period. In addition to a standard laboratory report (including graded pre- and postlab questions), students were asked to give oral presentations discussing their results and mechanistic conclusions. Students gained an appreciation for a number of core concepts in reaction catalysis, foremost of which was the relationship between relative reaction rates and product selectivities in kinetically-controlled processes. Discussions relied on a simplified reaction coordinate that considered the product-determining step in the C–H amination reaction. Quantitative analysis of this reaction coordinate diagram underscored for students how small transition state energy differences markedly influence reaction outcomes. Correlating these data with σ^+ substituent parameters emphasized how electronic factors influence reaction rates and how kinetics experiments are used to challenge mechanistic hypotheses. Overall, we hope this three-part lab provides a forum for teaching select concepts and tools of physical organic chemistry while highlighting a modern reaction process in organic chemistry. Students should feel empowered to delve further into the different analytical methods used to interrogate reaction mechanisms and to question the data that supports textbook 'arrow-pushing' schemes.

ASSOCIATED CONTENT

Supporting Information

Copies of the laboratory procedure, suggested problems, instructor notes, relevant NMR spectra, pictures of the experimental set-up, and lecture slides are available on-line.

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Notes

The authors declare no competing financial interest.

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