



Rate Profiling the Impact of Remote Functional Groups on the **Redox-Relay Heck Reaction**

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ABSTRACT: The redox-relay Heck reaction is a powerful method for the construction of enantioenriched quaternary stereocenters remote from existing functional groups. However, there has been little success in the design of site-selective alkene functionalization based on these methods. Herein, we show that experimentally determined rates can be used to train a multivariate linear regression model capable of predicting the rate of a specific relay Heck reaction, allowing for the site-selective functionalization of diene substrates

 $\bigwedge Te^1$ and others² have developed an array of enantioselective Pd-catalyzed alkene functionalization reactions wherein a remote functional group impacts both the reactivity and the selectivity of these processes. In particular, a range of redox-relay Heck reactions of both di- and trisubstituted alkenes have been reported wherein tertiary or quaternary stereocenters are set using a chiral catalyst. The remote functional group attached to the alkene can vary widely and includes alcohols, arenes,^{1h} electron-withdrawing groups (mainly carbonyl derivatives),^{1g} and protected amines.¹¹ However, in considering the application of these reactions to more complex systems that contain more than one similar alkene in the substrate, it is difficult to anticipate which alkene would be most reactive.³ Thus, we found that a significant advancement in this context would be to build an analysis tool that provided the ability to predict which alkene in a polyene substrate would react on the basis of the structural environment. Herein, we interrogate the role of the remote functional group in the relative rates of redox-relay Heck reactions using a combination of experimental rate measurements, computational chemistry, and multivariate linear regression. This analysis allowed us to design diene substrates capable of undergoing selective functionalization of a specific alkene based solely on the basis of the identity of the remote functional group. Our group has previously carried out extensive mechanistic studies of the redox-relay Heck reaction with a focus on understanding the nature of the chain-walking process and the impact of the chain length between the alkene and terminal group on the site selectivity, enantioselectivity, and rate of the reaction.⁴

The turnover-limiting step is proposed to be the migratory insertion of the aryl-palladium species into the alkene. Of particular interest, allylic alcohols were found to react ~4 times



faster than homoallylic alcohols and disubstituted alkenes significantly outcompete trisubstituted alkenes in the reaction (Figure 1a).^{4c} Taken together, we hypothesized that the nature of the remote functional group (G) could have a considerable impact on the reaction rate and perhaps could be used to



Ŕ Ŕ k ArB(OH) Figure 1. Inspiration and goals of this study. (a) Previous studies

reveal the impact of proximity on the rate of ene-ols. (b) How does the nature of the terminal group impact rate? (c) Application of this approach to site-selective polyene functionalization.

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Figure 2. Independently measured relative rates. (a) Standard reaction conditions used. (b) Products formed from the relay Heck reaction. (c) Relative rates of the terminal groups investigated.

modulate the site of reaction in substrates containing multiple alkenes. Specifically, it was reasoned that G could impact the rate by modulating either the binding affinity for the alkene (concentration of the reactive species) or the barrier of the migratory insertion (the rate constant).⁵ To explore this possibility, we sought to measure the relative rates of a training set of alkene substrates that were decorated with a broad array of functional groups. We would then use these rates to build a predictive model through correlation with various molecular features derived from mechanistically relevant DFT structures. This statistical model then could be used to predict unseen substrates and applied to more complex scenarios.

To begin this study, we chose a representative subset of synthetically useful terminal groups related to those that have been previously shown to efficiently engage in the relay Heck reaction.1c,g,i The rates of the relay Heck reaction were determined by measuring the initial rates using ex situ reaction monitoring under a standard set of conditions (Figure 2a). We chose to focus on utilizing the same trisubstituted alkene core for all of the terminal groups studied to isolate the effect the terminal group has on the system. We also sought to investigate the impact that the proximity of the terminal group (either allylic or homoallylic) has on the rate of the reaction. Therefore, we chose a set of 8 allylic and 15 homoallylic imides, amides, sulfonamides, carbamates, nitriles, ketones, and alcohols that give rise to a wide array of products (Figure 2b). The independently measured rates are compared to one another (k_{rel}) by referencing each rate to that of homoallylic phthalimide 2k (Figure 2c). Our initial hypothesis was that the rate would be dependent on the electronics of the alkene (with electron-rich alkenes reacting faster) and the steric environment of the alkene (with large groups reacting slower). To test the impact of subtle electronic perturbations on the reaction rate, we deployed para-substituted benzamide (2a-c and 2f) and sulfonamide substrates (2e, 2g, and 2p). The sulfonamides followed the expected reactivity based on the Hammett electronic parameters, with the most electronwithdrawing sulfonamide 2g reacting the slowest and the most electron-rich 2p reacting the fastest. However, the substituted benzamide series did not follow a similar Hammett response, with electron-donating and -withdrawing groups reacting slower than unsubstituted benzamide 2c. Additional qualitative

trends can be perceived on the basis of the relative size of the terminal group. For example, the relative rate of every allylic substrate other than the alcohol is slower when compared to that of its homoallylic counterpart. However, the same trend is not as apparent in the homoallylic series, with relatively small terminal groups such as a nitrile (2h) or an alcohol (2i) reacting slower than the phthalimide (2k). These initial conflicting trends suggested that there are subtler substrate features impacting the reaction rate.

We next carried out intermolecular competition experiments to determine if these independently measured relative rates can be translated to a competitive scenario (Figure 3). These



Figure 3. Intermolecular competition reactions. ^aPredicted ratio based on independently measured relative rates.

competition reactions were performed using an equimolar excess of two alkenes relative to phenylboronic acid and comparing the amount of product formed.⁶ In general, the independently measured rates were able to accurately predict the major product (cf., measured vs predicted); however, the observed ratios were typically higher than predicted. One notable exception is entry 2, where homoallylic nitrile **2h** was predicted to be slower than homoallylic trifluoroacetamide **2d**. This suggests that the independent rate data for **2h** are likely artificially low due to the ability of the nitrile to serve as a ligand for the aryl–palladium intermediate (see the Supporting Information for details). On the basis of this observation, the competitive rate data for the nitrile substrate were used to generate a predictive model.

With these data in hand, we turned our attention to determining if the relative rates could be predicted using multivariate linear regression techniques (Figure 4). This was



Figure 4. Multivariable linear regression reveals the steric and electronic parameters that impact the rate of the relay Heck reaction.

accomplished by relating structural features of the alkene and alkene–Pd complex to the log of the relative rates $[log(k_{rel})]$.⁷ The geometries used for the acquisition of the DFT-derived parameter set for the alkene substrates were calculated at the M06-2x/def2-TZVP level of theory, and those of the alkene–Pd complexes were calculated at the M06/SDD-6-31+G(d) level of theory (see the Supporting Information for details). By using an iterative MLR process, we were able to determine that the impact of the terminal group on the rate of the reaction can be described using three quantitative descriptors (in order of decreasing impact): the Boltzmann-weighted percent buried volume of the disubstituted carbon atom, the energy of the antibonding π -bond of the alkene, and the calculated ¹³C NMR chemical shift of the Pd–alkene complex (for a full list of parameters used for model development, see the Supporting

Information). The performance of this model was determined using both leave-one-out (LOO) and external validation in which the data set was pseudorandomly divided into a training and validation set (approximately 80:20 split). This model not only can predict the rate of a specific terminal group with reasonable accuracy but also provides some insight into the factors that govern the rate. For example, the $%V_{bur-BW}$ was found to be the most dominant factor impacting the relative rate, which indicates that the rate is largely guided by the proximal steric environment of the alkene.

A consistent outlier in all of the models generated is homoallylic biscarbamate 2j (Figure 4, gray box). To rationalize why this substrate was consistently predicted to have a significantly slower rate than measured, we performed transition state (TS) calculations on a subset of the substrates (Figure 5b). The calculated transition state 2j-TS was found to



Figure 5. Transition state analysis. (a) Calculated transition state geometries for 2j and 2k. (b) Comparison of relative rates and calculated transition state energies.

be lower than 2k-TS, consistent with the experimentally observed faster rate of 2j. The low transition state barrier for 2j-TS can be rationalized by the presence of an attractive noncovalent interaction (NCI) between the benzyl group of the benzyl carbamate and the pyridine of the ligand (2j-TS, a). A similar orientation is observed in the case of 2k-TS; however, the longer distance between the phthalimide and pyridine ring systems (3.55 Å vs 3.37 Å) suggests that this interaction is less favorable (see the Supporting Information for additional TS calculations). This perhaps suggests that the more electron-rich nature of the benzyl ring leads to a stronger noncovalent interaction with the electron-deficient pyridine ring than with the phthalimide.⁸ Additionally, the key bond distances for the forming C–Pd and C–Ph bonds (b and c, respectively) are similar between the two, suggesting the difference resulting in **2j-TS** being lower in energy is the presence of the stabilizing NCI. Overall, these data suggest that the inability of **2j** to be predicted accurately by this model is due to the presence of this unique NCI.

This provoked us to calculate the transition state energies for a subset of the substrates studied to determine if the rate is directly related to the migratory insertion barrier. However, we did not observe a correlation between the rate and the calculated barrier across a wide range of substrates (Figure 5b). For example, the calculated barrier of 2a ($k_{\rm rel} = 0.14$) was found to be lower than that of $2k (k_{rel} = 1.00)$. The lack of a direct correlation between the observed rates and the calculated transition state barriers suggests that the migratory insertion is not always the rate-limiting step. This implies that other factors such as the relative binding propensity and/or the rate of the chain-walking process (e.g., subsequent β -hydride elimination and migratory insertion steps) can influence the overall rate. The statistical model is consistent with this hypothesis (for additional discussion, see section 7a of the Supporting Information).

Lastly, using this predictive model, we designed substrates bearing two alkenes that could be functionalized in an alkeneselective manner (Scheme 1). On the basis of the relative rate

Scheme 1. Site-Selective Functionalization of Dienes 5a and 5b



data, we paired an allylic alcohol with either an allylic phthalimide (5a) or biscarbamate (5b). Subjecting these substrates to the standard reaction conditions resulted in a 6:1-10:1 ratio of the expected monofunctionalized adduct 6 and the 2:1 adduct 7, with no observable amount of the isomeric monosubstituted product. This result shows that it is possible to design a highly site-selective relay Heck reaction based solely on the nature of the terminal group, which could facilitate design possibilities for more complex situations.

In conclusion, we have demonstrated that the rate of the relay Heck reaction can vary by approximately an order of magnitude solely on the basis of the identity and proximity of the terminal group relative to the alkene. Using the collected relative rate data, we were able to construct a statistical model that can predict the rate of a specific terminal group. We also carried out transition state calculations to rationalize these results and found that the migratory insertion step may not always be the rate-limiting step for each of the terminal groups studied. Lastly, we were able to use this predictive model to design diene substrates that can undergo site-selective functionalization. We expect the insights garnered through this study will guide the design of site-selective Heck transformations in more complex scenarios.

ASSOCIATED CONTENT

3 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00450.

List of relevant DFT-derived parameters used for the modeling process (XLSX)

Experimental procedures for all reactions, a detailed explanation of the methods used for rate determination, spectroscopic characterization data for all new compounds, detailed computational methods, copies of ¹H and ¹³C NMR spectra, and copies of SFC chromatograms (PDF)

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The authors declare no competing financial interest.

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