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Developing a Modern Approach to Account for Steric Effects in Hammett-type Correlations

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Supporting Information Placeholder

ABSTRACT: The effects of aryl ring *ortho*-, *meta*-, and *para*-substitution on site selectivity and enantioselectivity were investigated in the following reactions: 1) enantioselective Pd-catalyzed redox-relay Heck reaction of arylboronic acids, 2) Pd-catalyzed β-aryl elimination of triarylmethanols, and 3) benzoylformate decarboxylase-catalyzed enantioselective benzoin condensation of benzaldehydes. Through these studies, it is demonstrated that the electronic and steric effects of various substituents on selectivities obtained in these reactions can be described by NBO charges, the IR carbonyl stretching frequency, and Sterimol values of various substituted benzoic acids. An extended compilation of NBO charges and IR carbonyl stretching frequencies of various substituted benzoic acids was used as an alternative to Hammett values. These parameters provide a correlative tool that allows for the analysis of a much greater range of substituent effects because they can also account for proximal and remote steric effects.

INTRODUCTION

Linear free energy relationships (LFERs) are an essential physical organic experimental tool, which allowed the shift from qualitative analogy to quantitative analysis in understanding how structural changes affect reaction outcomes.[1] The work of Hammett is the quintessential example of LFERs, wherein the pK_a of benzoic acid derivatives was related to various reaction rates (Figure 1a).[2] This parameter, known as the Hammett value (σ), has provided insight into the relationship between chemical structure and reactivity in systems containing aromatic rings.[3] Despite the Hammett parameter's widespread use, it is exclusively applied to electronic effects of *meta*- and *para*-substituted aromatic rings.[3a] This restriction is often attributed to steric effects at the *ortho*-position[2c], which cause the benzoic acid carbonyl group to twist out of the aromatic ring plane resulting in disruption of the conjugation between the carbonyl group and the arene.[3b] Thus, substitution at the *ortho* position introduces changes to steric, inductive, and, through altered conjugation, resonance effects.[4]

The inability of σ to describe *ortho* effects has been historically addressed and analyzed. As an early example, Taft generated *ortho*-substituent constants (σ_o*) through a method that eliminates steric effects by applying the variable $E°_s$ (Figure 1b).[5] Taft demonstrated that the acid-catalyzed hydrolysis of *ortho*-substituted benzoate esters is governed by steric effects, while in base-catalyzed hydrolysis both steric and electronic effects play a role. A significant drawback of the relationship developed by Taft was the limited scope of *ortho*-substituents. For example, its inapplicability to fluoro, amino, and even hydrogen at the *ortho* position is noteworthy.[1] Following this effort, two separate groups developed equations derived by multiple linear regression analysis to account for electronic effects as well as steric effects in *ortho*-substitution. Charton reported an *ortho*-substituent constant (Q_X) (Figure 1c), where $\sigma_{I,X}$ is the inductive field effect and $\sigma_{R,X}$ is the resonance effect.[6] However, bulky substituents (e.g., *t*-Bu) and substituents capable of resonance (e.g., NO_2, Ph, and MeO) were excluded from the set, which again leaves only a small range of descriptor sets for *ortho*-substituents. Subsequently, in 1975, Fujita and Nishioka described a general equation to account for *meta*-, *para*-, as well as *ortho*-substitutions in aromatic rings, where E_s is the Taft-Kutter-Hansch steric parameter,[5a,5c,7] F is the Swain-Lupton inductive-field effect,[8] and σ_p is used as σ_o (Figure 1d).[9] While the model has been applied to several hydrolysis reactions[9-10] and was recently reported to characterize a Ag-catalyzed decarboxylation of benzoic acids,[11] it has been historically criticized for its small selection of substituents[12] and non-systematic choice of σ^+, σ^-, and σ during model development.[13]

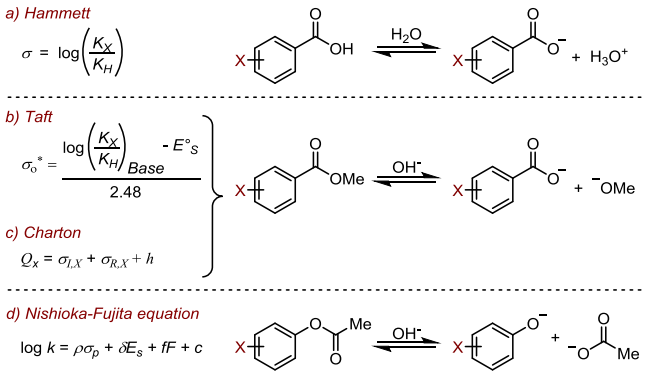


Figure 1. Earlier examples of aryl substituent effect descriptors.

In view of these limitations to previously reported *ortho*-substituent parameter sets and models, we sought to apply multivariate analysis tools[14] to identify descriptors sets that account for variations at all sites on an aromatic ring. Success would allow for one to analyze a much greater substituent effect range and also delineate the structural/mechanistic origin for observed correlations. Within this study, we compare these modern parameters to the aforementioned historical techniques. To accomplish this, we conducted two case studies to understand *ortho*-substituent effects (Figure 2): a) site selectivity in the enantioselective Pd-catalyzed redox-relay Heck reaction of alkenols developed in our laborato-

ry,[15] and b) site selectivity in a Pd-catalyzed β-aryl elimination of triarylmethanol reported by the Johnson group.[16] In addition to proximal steric effects from *ortho*-substituents, a secondary aim is to study remote steric effects, which can also be present at the *meta*-position as reported in a benzoylformate decarboxylase-catalyzed enantioselective benzoin condensation from Pohl, Müller, and coworkers (Figure 2c).[17] Herein we describe the correlation of computationally derived general parameter sets to reaction outcomes with a broad range of aromatic substitution patterns.

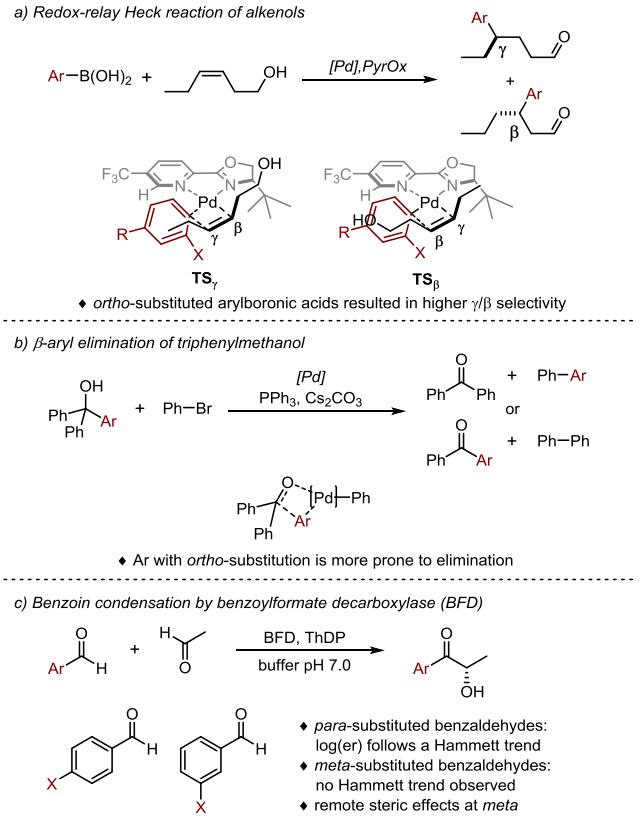


Figure 2. Processes under study in this report: a) enantioselective Pd-catalyzed redox-relay Heck reaction, b) Pd-catalyzed β-aryl elimination of triarylmethanols, and c) benzoin condensation by benzoylformate decarboxylase.

RESULTS AND DISCUSSION

Univariate Parameter Analysis. In line with this objective, we computationally acquired and analyzed steric and electronic parameters for a set of 46 functional groups in all three aryl positions: *ortho*, *meta*, and *para* of a benzoic acid (total of 139 molecules including the unsubstituted benzoic acid). These include: the infrared (IR) carbonyl stretching ($\nu_{C=O}$) and COH bending (ν_{COH}) frequencies and intensities,[14] natural bond orbital (*NBO*) charges[18] of each atom in the carboxylic acid moiety, Sterimol[19] B_1, B_5, and L of the substituent, and the torsion angle between the carbonyl group and the aromatic ring plane (see Tables S1 to S6 in SI).

Our initial goal was to identify alternatives to the Hammett value (σ) in order to remove the dependence on empirically derived parameters. Previous work by Jones et al.[20] revealed a linear relationship between experimentally derived IR carbonyl stretching frequencies ($\nu_{C=O}$) of *meta*- and *para*-substituted acetophenone derivatives to the Hammett value, σ_m and σ_p, respectively. Additionally, Seybold and coworkers[21] demonstrated that a linear correlation exists between σ_p and the computationally derived NBO charges of the carboxylic acid group in *meta*- and *para*-substituted benzoic acids.

Consistent with these observations, analyzing the parameters for the 47 *para*-substituted benzoic acids, we have determined linear relationships between the IR carbonyl stretching frequency ($\nu_{C=O}$) and the Hammett value (σ_p) (Figure 3a) as well as the NBO charge of the benzoic acid moiety ($NBO_{=O}$) to σ_p (Figure 3b). These correlations indicate that $\nu_{C=O}$ and $NBO_{=O}$ can be used as computed alternatives to σ_p. This compelling result extends the correlations that Jones and Seybold initially reported and eliminates the dependence on experimental parameters. In contrast, *ortho*-substituted benzoic acid $\nu_{C=O}$ and $NBO_{=O}$ descriptors gave only qualitative trends with σ_p. These unsurprising results support the long held understanding that the electronic effects exerted by *para*-substitution are not equivalent to those observed for *ortho*-substitution presumably due to additional effects resulting from the proximity of the *ortho*-substituent to the reaction site (vide supra).

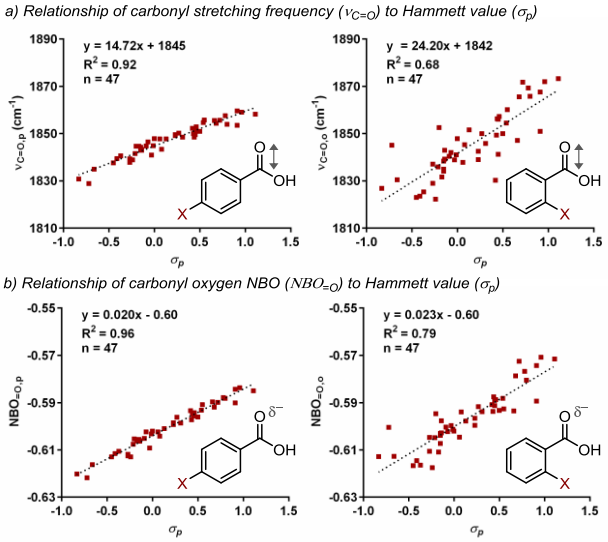
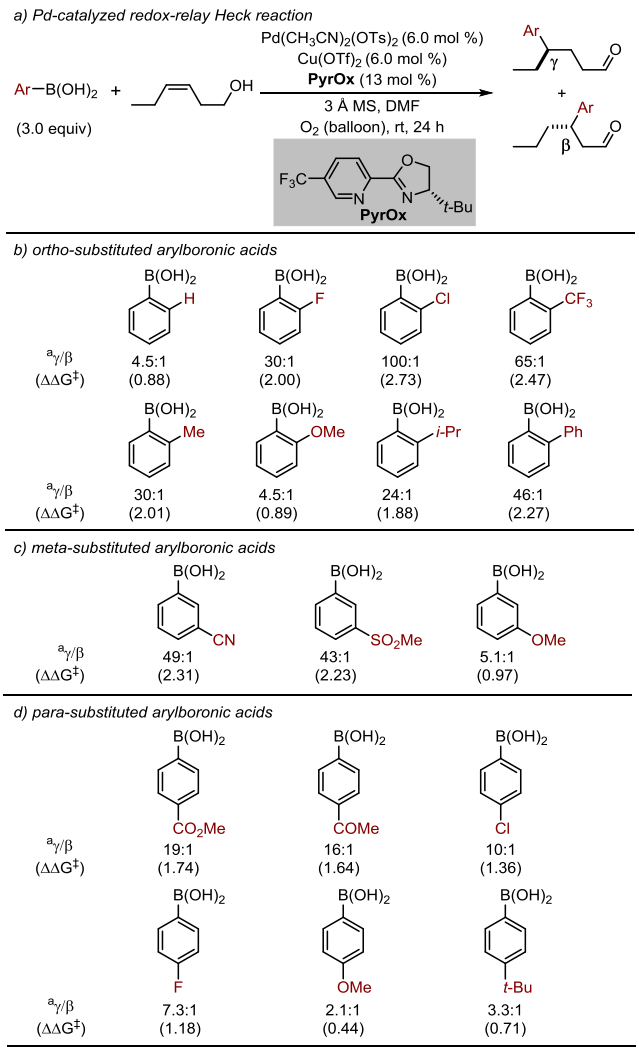


Figure 3. Comparison between *para*- and *ortho*-substituted benzoic acids through Hammett value (σ_p) correlations with a) carbonyl stretching frequency ($\nu_{C=O}$) and b) carbonyl oxygen NBO ($NBO_{=O}$).

Multivariate Parameter Analysis. On the basis of the poor correlation of *ortho*-substituents to various single parameters, we employed a multivariate linear regression strategy[14,19b,22] of relating physical organic descriptors to reaction outcomes. As the first case study, we examined the enantioselective Pd-catalyzed redox-relay Heck reaction reported by our lab (Table 1).[15] We selected this reaction due to familiarity, ability to evaluate an expanded scope, and more importantly, its wide range of observed site selectivity (at which site the aryl group is delivered to the alkene). This Pd-catalyzed reaction between arylboronic acids and *cis*-hexenol produces constitutional isomers of remotely functionalized, arylated carbonyl products. The site of migratory insertion is highly sensitive to electronic modifications on the aryl ring of the boronic acid leading to formation of γ and β products. In our earlier studies such electronic effects were quantitatively correlated using Hammett σ values but only for *meta*- and *para*-substituents with electron-withdrawing substituents resulting in enhanced γ/β site selectivity. Importantly, while not used in this correlation, the

reaction was determined to be compatible with *ortho*-substituted arylboronic acids.

Table 1. Scope of arylboronic acids in redox-relay Heck reaction.



Reaction was run at 0.5 mmol scale of **2**. [a]Product ratios (γ/β) were determined by GC/MS. The site selectivity data for *meta*- and *para*-substituted arylboronic acids were obtained from Mei et al.[15] ΔΔG‡ was reported in kcal/mol.

Therefore, to study the effect of varying the substituents at the *ortho*-position of the arylboronic acid in the redox-relay Heck reaction, several additional *ortho*-substituted arylboronic acids were subjected to the same reaction conditions. These new examples were designed with the intention to distribute σ_p and Sterimol B_1 (Figure 4). Sterimol values[19a] describe the size of a substituent using three different measurements: 1) *L*, the length measured along the axis of the bond between the substituent and the parent molecule, 2) B_1, the minimal radius measured perpendicular to the bond axis used to measure *L*, and 3) B_5, the maximal radius measured perpendicular to the same bond axis.[19a] The considerations taken into account when selecting the set of *ortho*-substituted arylboronic acids were: 1) covering a wide range of electronic and steric features to better represent the reaction tolerance to substituent variation, 2) spreading the data evenly across the chosen chemical space for statistical purposes, and 3) creating a diverse set with practical utility, while keeping it synthetically viable, by selecting common functional groups.[23]

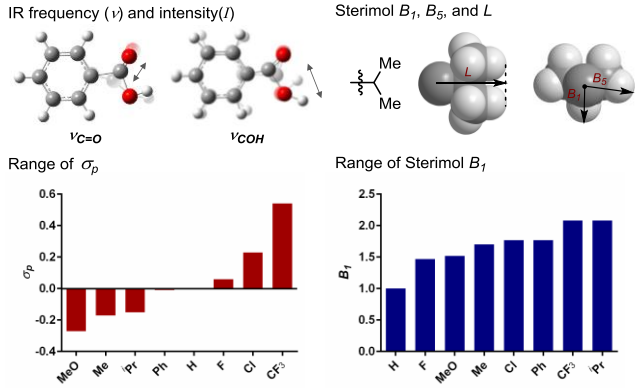


Figure 4. Parameters used to assess the spread of steric and electronic effects from *ortho*-substituents in benzoic acids.

The results of these new examples are depicted in Table 1b and in general, correlate well with the trend observed when using *meta*- and *para*-substituted arylboronic acids; electron-withdrawing groups resulted in higher γ/β site selectivity. Surprisingly, *ortho*-fluorophenylboronic acid (Table 1b) and *ortho*-chlorophenylboronic acid resulted in significantly higher γ/β site selectivity in comparison to their *para* counterparts. This suggests that an inductive field effect might be contributing to the observed selectivity, since the *ortho*-substituent is closer to the reaction site. As the aryl group becomes more electron-poor, palladium becomes inclined to migrate to the β carbon, as it is more electronegative than the γ carbon on the basis of NBO charge calculations of the transition states.[24]

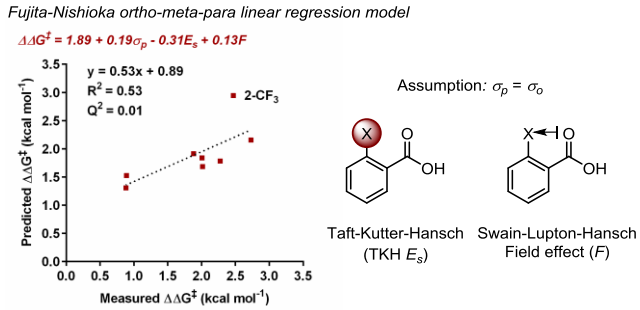


Figure 5. Multivariate linear regression model of *ortho*-substituted arylboronic acids based on the Fujita-Nishioka equation.

As a first step toward identifying the origin of the site selectivity trends observed for this data set and developing general *ortho* descriptors, we assessed a regression model using the parameters disclosed by Fujita and coworkers.[9] The ratios of γ/β site selectivity from the redox-relay Heck reaction of *ortho*-substituted arylboronic acids were used to calculate the measured $\Delta\Delta G^{\ddagger}$. The resulting correlation of the predicted versus the measured site selectivity is fair as quantified by the slope of 0.53 and the low Q^2 value (Figure 5). One of the outliers in the Fujita-Nishioka model is the *ortho*-trifluoromethyl group, which was also found to be an outlier in a previous report.[11] The inability of the Fujita-Nishioka descriptors to model all *ortho*-substituents prompted us to evaluate other parameters that more effectively describe the *ortho* effect.

As a preliminary step to identify additional parameters that can describe the *ortho* effect, all monochloro-substituted benzoic acids were analyzed (Figure 6). Torsion angle measurements in geometry-optimized conformations of *meta*- and *para*-

chlorobenzoic acids show that the carbonyl group was unsurprisingly planar to the aryl ring, due to the stabilization afforded by extended conjugation. Furthermore, since the *meta*- and *para*-substitutions are distal from the carboxylic acid group, the effects at these positions are likely only electronic in nature. In contrast, the carbonyl group in *ortho*-chlorobenzoic acid is twisted out of plane from the aryl ring, with a torsion angle of 26° due to steric effects between the *ortho*-chloro substituent and the carbonyl group. Furthermore, pK_a values[25] of substituted benzoic acids show a trend of p$K_{a(para)}$ > p$K_{a(meta)}$ > p$K_{a(ortho)}$, supporting the assertion that inductive effects, due to proximity, also play a major role in acidity determination.

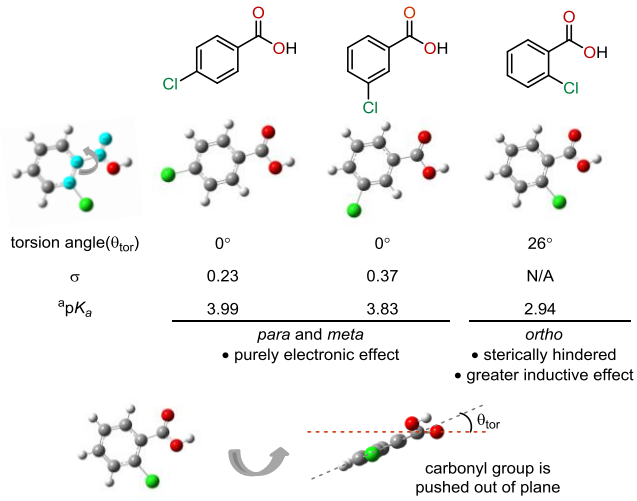


Figure 6. Comparison of steric and electronic effects between *ortho*-, *meta*-, and *para*-substitutions in benzoic acids. $^{a}pK_a$ values were obtained from Jencks and Regenstein's compilation.[25]

With various steric and electronic parameters in hand (see Tables S1 to S6 in SI), we set out to develop a mathematical model correlating the results of the redox-relay Heck reaction. After stepwise linear regression, to determine which parameters contributed to the site selectivity of the reaction, a significant correlation was revealed using Sterimol L_o, $\nu_{C=O,o}$, and σ_p (Figure 7a). Concerning L_o, it is reasonable to consider that the length of the substituent at the *ortho*-position, could be impacting the selectivity in the proposed transition state. This can be better visualized using the proposed transition state of this reaction on the basis of DFT calculations performed by Wiest et al (Figure 7c).[24] A longer *ortho*-substituent, in terms of Sterimol L, could presumably orient the alkenol in a similar fashion as TSγ to minimize steric interactions between the alcohol moiety and the *ortho*-substituent. This will then lead the palladium to migrate to the β position resulting in increased γ product. In terms of electronic effects, the carbonyl stretching frequency, which presumably reflects the disruption of conjugation due the steric effect at the *ortho* position, serves as an electronic correction to σ_p.

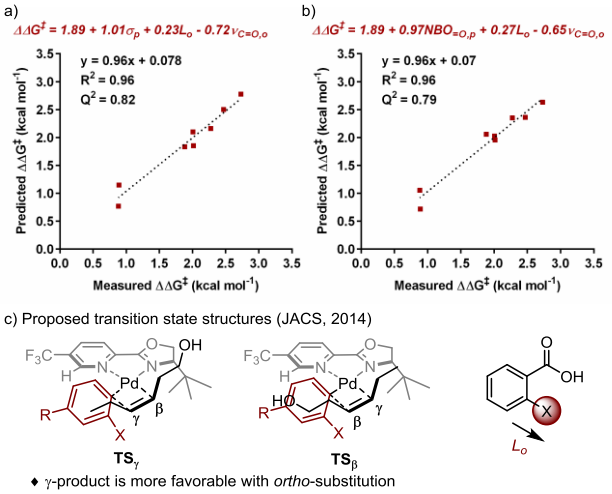


Figure 7. Multivariate linear regression model for *ortho*-substituted arylboronic acids in redox-relay Heck reaction.

In order to view the *ortho* results in a broader context of the product determining step(s) of this reaction, a comprehensive model including *ortho*-, *meta*-, and *para*-substituted arenes was desired. Therefore, a series of *meta*- and *para*-substituted arylboronic acids (Tables 1c and 1d) previously reported by Mei et al.[15] were included in an extensive sample set. Using the same equation as the *ortho* regression model, wherein parameters to predict ΔΔG‡ include Sterimol L_o, $\nu_{C=O}$, and using $\sigma_o = \sigma_p$ for *ortho*-substituents, a good correlation was achieved for the comprehensive model (Figure 8a). The Sterimol L_o is a steric parameter accounting only for *ortho*-substitution, wherein a hydrogen atom is accounted for in *meta*- and *para*-substituted arylboronic acids. Additionally, in the *ortho* model as well as the comprehensive model of the redox-relay Heck reaction, the σ_p and σ_m can be easily replaced with computationally derived NBO charges on the carbonyl oxygen of the corresponding benzoic acid ($NBO_{=O}$) (Figures 7b and 8b). This is more desirable since all of the predictor variables in the multivariate linear regression model can be

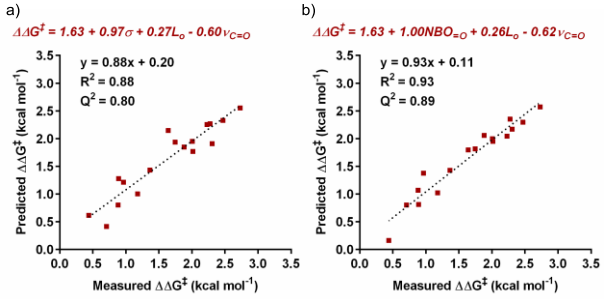
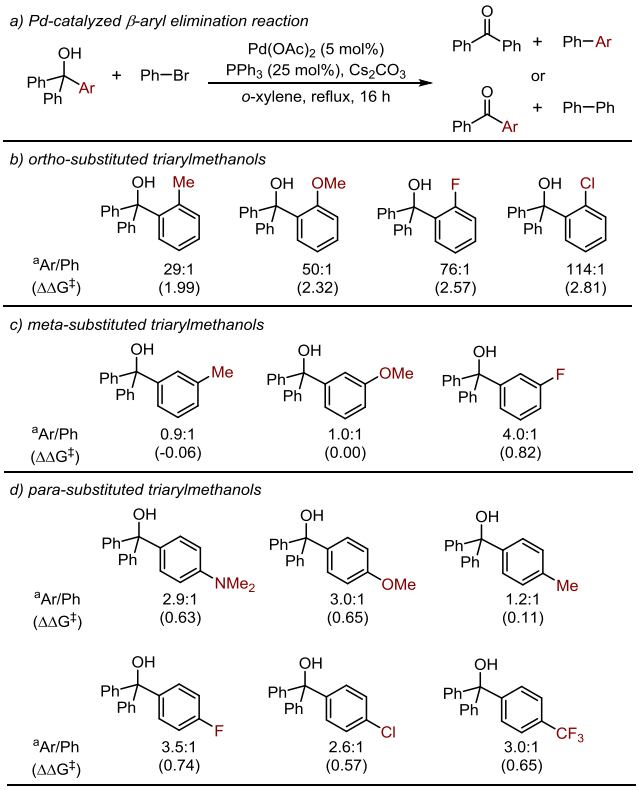


Figure 8. Comprehensive multivariate linear regression models for *ortho*-, *meta*-, and *para*-substituted arylboronic acids in redox-relay Heck reaction.

derived computationally, eliminating the dependence on empirically obtained parameters, wherein some are not reported. In other words, this modern variant of a Hammett plot, with easily accessible parameters, now incorporates *ortho*-substituents.

Table 2. Scope of triarylmethanols in β-aryl elimination reaction.



Reaction was run at 0.5 mmol scale of **3**. [a]Product ratios (Ar/Ph) were determined by GC/MS. The site selectivity data were obtained from Bour et al.[16] ΔΔG‡ was reported in kcal/mol.

Case Study 2. To further test the validity of this approach, a similar mathematical modeling strategy was applied to a Pd-catalyzed β-aryl elimination reaction of triarylmethanols. This β-aryl elimination reaction was initially developed by Miura and coworkers[26] and was investigated mechanistically by Johnson and coworkers (Table 2).[16] In this reaction, *ortho*-substituted aryl groups have a greater propensity to cleave the C–C_{Ar} bond compared to the C–C_{Ph} bond. As hypothesized by Johnson et al.[16], the selective cleavage arising from *ortho*-substitution is presumably due to the slight lengthening of the C–C_{Ar} bond as a result of minimizing the interaction of the *ortho* group with the phosphine ligands and the additional phenyl rings. This facilitates the coordination of the β-aryl group bearing *ortho*-substitution to the metal center, preceding β-aryl elimination. The $\Delta\Delta G^{\ddagger}$ for this reaction is calculated based on the logarithmic value of the transfer ratio between the two possible biphenyl ketone products (Ar/Ph). To our delight, the multivariate linear regression model used in the first case study: $\Delta\Delta G^{\ddagger} = \alpha NBO_{=O,p} + \beta L_o + \gamma \nu_{C=O}$ produced a significant correlation in this system of various *ortho*-, *meta*-, and *para*-substituted triarylmethanols (Figure 9a). In addition, an improved model was identified using the same library of parameters described above (Tables S1-S6 in SI). This model includes Sterimol $B_{1,o}$, describing the size of the *ortho*-substituent, and IR C–O–H bend frequency (ν_{COH}), representing the steric and electronic perturbation of the *ortho*-substituent to the IR C–O–H bending (Figure 9b). While multiple models can be revealed through these multivariate linear regression techniques, interpretation is a main criteria by which a model can be selected as well as statistical evaluation. In all, the success of developing a site selectivity model that accounts for each of these distinct Pd-catalyzed systems (redox-relay Heck and β-aryl elimination) supports our hypothesis that *ortho*-substitution does not need to be excluded from Hammett-type analysis.

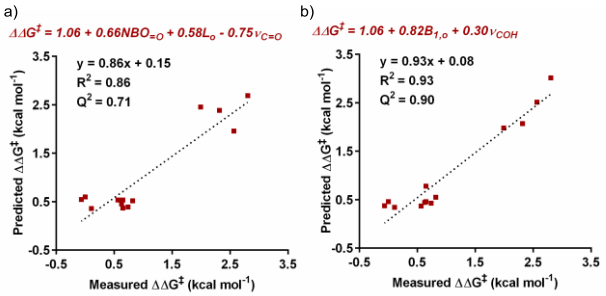
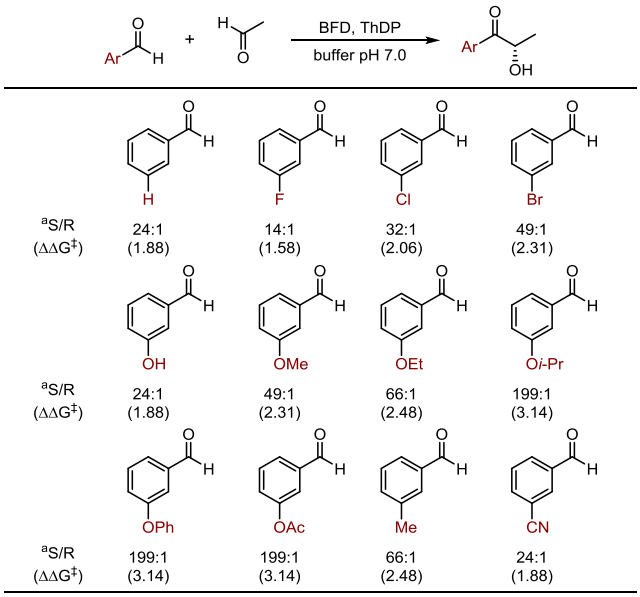


Figure 9. Comprehensive multivariate linear regression model of β-aryl elimination reaction of *ortho*-, *meta*-, and *para*-substituted triarylmethanols.

Remote steric analysis. To assess the applicability of this mathematical modeling approach across a broad range of systems, an enzyme-catalyzed reaction was selected as the third case study. In particular, the *Pseudomonas putida* benzoylformate decarboxylase-catalyzed enantioselective condensation reaction between benzaldehydes and acetaldehyde yielding 2-(S)-hydroxypropanone derivatives was analyzed due to the identification of a significant effect on enantioselectivity as a function of substitution pattern (Table 3).[17] For example, electron-donating *para*-substituents resulted in an increase of enantioselectivity, which according to Pohl and coworkers[17b] can be attributed to the stabilization achieved from edge-to-face interactions of the phenyl moiety of the benzaldehyde substrate with the aromatic side chain of benzoylformate decarboxylase residues Phe464 and Phe397 located in the active site. Additionally, as compared to the former two case studies where steric effects at the *ortho*-position need to be accounted for in determining reactivity, only one *ortho*-substituted benzaldehyde was successfully employed as a substrate for this reaction due to incompatibility of such substrates in the reaction. Intriguingly, a good correlation between the enantioselectivity of *para*-substituted benzaldehydes and σ_p was observed, but no correlation of *meta*-substituted benzaldehydes with the σ_m was observed (Figure 10a). This is presumably due to remote steric contributions present at the *meta*-position in this biological system.[17b]

Table 3. Scope of *meta*-substituted benzaldehydes in the studied enzymatic benzoin condensation.



Reaction was run at 10 mmol/L concentration of **5**. [a]Enantioselectivity was determined by chiral-phase HPLC. BFD = benzoylformate decarboxylase. ThDP = thiamine diphosphate. The enantioselectivity data were obtained from Dünnwald et al.[17a] $\Delta\Delta G^{\ddagger}$ was reported in kcal/mol.

As an example, for a series of *meta*-alkoxy substituents, the σ_m values remain similar while the enantioselectivity increases (Table 3). The enhancement in measured $\Delta\Delta G^{\ddagger}$ could be mainly attributed to the increase in size of alkoxy substituents (OH < OMe < OEt < O*i*-Pr). This result prompted application of the parameter library previously described, wherein an improved model was identified using the NBO charge of the *para*-substituted benzoic acids ($NBO_{=O,p}$), the IR carbonyl stretching frequency ($\nu_{C=O,m}$) and intensity ($I_{C=O,m}$) of the *meta*-substituted benzoic acid (Figure 10b). Electronic contributions are reflected by the inclusion of $NBO_{=O,p}$ and $\nu_{C=O,m}$ in the linear regression model while the combination of steric and electronic effects at the *meta* position are described by the IR carbonyl stretching vibration intensity, $I_{C=O,m}$, which represents the change in dipole moment during the vibration.

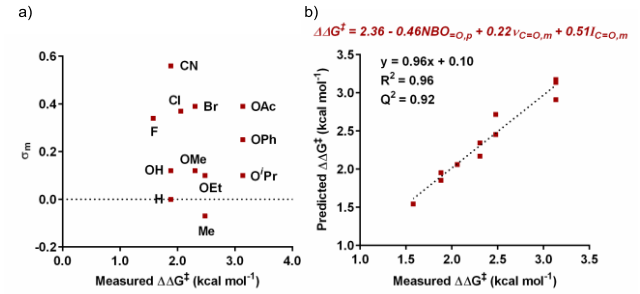


Figure 10. a) Hammett linear free energy relationship. b) Multivariate linear regression model of enantioselectivities obtained from various *meta*-substituted benzaldehydes.

CONCLUSION

In summary, a mathematical modeling approach has been successfully applied in three unique case studies to now incorporate proximal and remote steric effects in Hammett-type correlations. Computationally derived parameters, carbonyl oxygen NBO charge and the IR carbonyl stretching frequency of *para*-substituted benzoic acids, were utilized as alternatives to Hammett σ values. Additionally, a table of values was established as a generalizable set of descriptors for *ortho*-, *meta*-, and *para*-substituents in aryl rings. This new correlative tool allows for the analysis of a much greater range of substituent effects and provides a strategy to identify proximal and remote steric effects in aromatic systems. Further applications of this parameter library and determination of aryl ring multi-substituent descriptors are future goals in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data, NMR spectra, and computational methods. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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SYNOPSIS TOC.