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ABSTRACT

The relative rates of alkenyl alcohols in the Pd-catalyzed redox-relay Heck reaction were measured in order to examine the effect of their steric and electronic properties on the rate-determining step. Competition experiments between an allylic alkenyl alcohol and two substrates with differing chain lengths revealed that the allylic alcohol reacts 3-4 times faster in either case. Competition between di- and trisubstituted alkenyl alcohols provided an interesting scenario, in which the disubstituted alkene was consumed first followed by reaction of the trisubstituted alkene. Consistent with this observation, the transition structures for the migratory insertion of the aryl group into the di- and trisubstituted alkenes were calculated with a lower barrier for the former. An internal competition between a substrate containing two alcohols with differing chain lengths demonstrated the catalyst's preference for migrating towards the closest alcohol. Additionally, it was observed that increasing the electron density in the arene boronic acid promotes a faster reaction, which correlates with Hammett σ_p values to give a ρ of -0.87.

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1. Introduction

In recent years, we have reported¹⁻³ a redox-relay strategy⁴⁻⁷ in the context of a Heck reaction⁸ with alkenyl alcohols, wherein an enantioselective arylation occurs and the alkene unsaturation is relayed to the chain-terminating alcohol (Figure 1).^{9,10} Both tertiary^{1,2} and quaternary centers³ may be established in high enantioselectivity while a new functional group, a ketone or aldehyde, is concomitantly formed during the process at various distances from the original alkene.

Due to this reaction's robust ability to impart high enantioselectivity with a diverse set of alkenes and its interesting trends in site selectivity, it has been the focus of a number of mechanistic studies,¹¹⁻¹³ which support a rate-determining arylation step followed by successive β -hydride elimination and migratory insertion steps until the carbonyl product is released (Figure 1). Computational analysis^{12,13} of the reaction coordinate reveals a relatively flat energy surface after the initial migratory insertion of the aryl group, which is the site and enantioselectivity-determining step. Enantioselectivity is controlled by repulsion between the alkenol and the *t*Bu group on the oxazoline of *Ligand* and by a stabilizing C-H π interaction between the aryl group and the pyridyl ring. The electronic and steric nature of the arene and the alkene do not have a notable effect on enantioselectivity, yet significantly affect the site selection, as was described using Hammett σ values,² IR vibrations¹⁴, and NBO charges.¹² We hypothesize that polarization during the migratory insertion transition state, leading to subtle electronic differences in the alkene carbons, controls the site selectivity. Consequently, site selectivity increases with decreasing electron-density in the arene, increasing steric bulk on the alkene, and decreasing chain length in the alkenol. Examination of these factors on the rate of the reaction would provide further insight for future catalyst design and substrate compatibility, improving reaction rates, carrying out cascade reactions, and selectively functionalizing complex starting materials. Specifically, investigating whether the rate of reaction is more dependent on steric or electronic effects will allow for reaction designs which account for these influences.¹⁵

Figure 1. Enantioselective redox-relay Heck arylation

2. Results and Discussion

Herein, we report kinetic data to delineate the effect of substituents on the boronic acid and of the chain length between the alcohol and alkene on the reaction rate. Rates were measured by observing the formation of products by gas chromatography. In general, we observed overall zero order kinetics through multiple half lives. This suggests that transmetalation of the boronic acid is fast prior to rapid alkene binding, leading to a saturated catalyst, which then undergoes a rate limiting migratory

insertion (Figure 2a). The saturated complex depicted is based on previous computations.¹²). To further probe this hypothesis, several electronically differentiated boronic acid derivatives were evaluated under the same reaction conditions (Figure 2a,b). The rate of product formation is dependent on the nature of the boronic acid, which is consistent with rate limiting migratory insertion.¹⁶ More nucleophilic arenes react faster than their electron-poor counterparts, which correlates with Hammett σ_p values with a ρ of -0.87 (Figure 2c). In comparison, electron-rich boronic acids result in poor site selectivity with the same substrate **1**. For example, 4-OMePh boronic acid favors the major insertion product in a ratio of about 2:1 while 4-CO₂MePh boronic acid provides a ratio of 19:1.² Additionally, site selectivity ratios were related to Hammett σ_p values with a ρ of 1.42,² suggesting a greater electronic influence on site selection than the rate of the reaction.

Figure 2. Effect of arene electronic nature on reaction rate. a) reaction scheme b) product formation over time (see Figure S1 for linear fits) c) Hammett correlation of log(rate) to σ_p values.

An interesting feature of this reaction is that similar enantioselectivity but different site selectivity is observed as a function of the distance between the alkene and the alcohol. This raises the question of the relative reactivity of different alkenes. Understanding these differences may allow for strategic reaction designs, wherein two unique alkenes undergo selective functionalizations. Therefore, the effect of chain length on the reaction rate was examined through competition experiments. As allylic and homoallylic alcohols have been the main focus of previous reports including scope and computational analysis, we initially evaluated the relative rates of **1** and **2** (Figure 3a). In this experiment, the allylic alcohol reacts 4.4 times faster than the homoallylic alcohol. Independent rate measurements of **1** show that the overall rate is retarded by ~ 5 times in the presence of **2** (Figure S2). These results suggest that reversible binding of the alkene occurs and that the allylic alcohol reacts faster in a Curtin-Hammett controlled reaction.

Figure 3. Effect of chain length on rate. Competition experiments with 4-CO₂MePh boronic acid between a) homoallylic **1** and allylic **2**, b) trishomoallylic **3** and allylic **2**, and c) homoallylic **1** and trishomoallylic **3** alkenols.

To further explore this, the competitive rates between **2** and **3**, a trishomoallylic alcohol, were measured (Figure 3b). Again, the allylic alkenol reacted faster (3.6 times) than the substrate with a longer chain. Similar competitive rates were observed for **1** and **3**, which suggests that the homoallylic and trishomoallylic alcohols react similarly under these conditions. To test this, a competitive reaction of the two (**1** and **3**) was performed. As anticipated, these alkenes have nearly identical relative rates (Figure 3c).

An interesting consequence of these studies is that the allylic alcohol substrate reacts faster than other alkenols. The origin of this modest difference is unclear with the calculated energy difference for the migratory insertion for an allylic alcohol being ~0.5 kcal/mol higher than for a homoallylic alkenol.¹³ This is clearly within the error limits of the computations. Yet, a possible explanation is a lower contribution to entropy-driven preorganization of the allylic substrate, and as a result, the catalyst promotes a faster reaction, compared to substrates with longer chains.¹⁷

Figure 4. Competition between di- and trisubstituted alkenes

As the reaction operates on both di- and trisubstituted alkenols, we were also interested in determining their relative

rates. Empirically, trisubstituted alkenols were found to require more time to react. However, trisubstituted alkenes are more electron rich and, thus, determining the relative rates would delineate whether the empirical observations are governed by a steric effect of alkene substitutions. Consistent with our previous observations, the homoallylic disubstituted alkene **1** reacts significantly faster than the homoallylic trisubstituted alkene **4** (Figure 4). An interesting aspect of this competitive scenario is that **1** is consumed before any reaction of the trisubstituted alkene. In other words, there was no simultaneous reaction of **1** and **4**. However, the rate of consumption of the disubstituted homoallylic alcohol is slightly inhibited (1.3 times), again suggesting the reaction is under Curtin-Hammett control (Figure S2).

Figure 5. Computed transition states for migratory insertion of an aryl group into a) a disubstituted and b) a trisubstituted alkene.

To further investigate the origin of this chemoselectivity, we calculated the relevant transition structures. We reported previously^{11,12} that the selectivity determining step is migratory insertion through **TS1** for the disubstituted homoallylic alcohol (Figure 5a). We have now computed the analogous transition structure **TS2** for the corresponding trisubstituted olefin (Figure 5b). The $\Delta\Delta G^\ddagger$ is 4.9 kcal/mol in preference for the disubstituted alkene, which is in agreement with the experimentally measured relative rates. For the disubstituted alkene, the closest distances between hydrogens in the computed transition structure are relatively long (2.30 and 2.24 Å), and the dihedral angle during the insertion step is 8.9°. In comparison, the distances are shorter (2.13 and 2.20 Å) for the trisubstituted alkene (**TS2**), inducing more steric repulsion and greater distortion during the transition (dihedral angle: 16.2°). This suggests the main determinant of this chemoselectivity is steric in nature.

Figure 6. Internal competition between alcohols of differing chain lengths

Finally, we interrogated selectivity during the relay process to uncover how the catalyst selects the hydrogen undergoing β -hydride elimination. As this process is post rate limiting, we designed two substrates which contain a branching point with two different distances to the chain-terminating alcohols (Figure 6). After initial migratory insertion, this internal competition presumably proceeds through relay to the branch point, where the catalyst must select to chain-walk towards either alcohol as highlighted in intermediate **A**. **Although migration towards the farther alcohol would result in Pd bound to a trisubstituted alkene, we have previously shown that the catalyst is able to relay through other branch points.**³ Additionally, our recent isotopic labeling studies suggest that chain-walking is likely to be unidirectional towards the alcohol **and that the catalyst relays to the carbinol position before releasing the carbonyl product.**¹¹ In the event, the product distribution of the resulting aldehydes from **5** (6.8:1) and **6** (6.9:1) reveals that the catalyst prefers to relay to the closer alcohol for each case. This is consistent with our previous isotopic labeling experiments and computational analysis, which reveals lower energetic Pd-intermediates as the catalyst migrates towards the alcohol. Thus, it is energetically favorable for the catalyst to prefer the shorter distance between the branching point and the alcohol in substrates **5** and **6**. These results should facilitate the design of more sophisticated applications of the enantioselective relay Heck reactions.

3. Conclusions

The relative reactivity of various alkenes in the redox-relay Heck reaction has provided valuable insight into the subtle effects on the migratory insertion step. The distance between the alkene and the alcohol does not significantly affect the rate of reaction, except in the case of allylic alcohols. In addition, di- and trisubstituted alkenes are not competitive in the rate limiting step, though Curtin Hammett pre-equilibrium binding of both alkenes occurs. Of practical note, this result indicates that selective functionalization of disubstituted alkenes in the presences of trisubstituted alkenes is a viable option for late-stage introduction of an aryl group in complex molecules containing both types of alkenes. Moreover, selective carbonyl formation from the redox-relay process is also possible, with preference for the alcohol that lies closer to the site of alkene addition. These results provide a foundation for developing chemoselective

variants of relay Heck reactions, which is a goal of current interest.

4. Experimental section

General Methods

Dry dimethylformamide (DMF) was stored over activated 3 Å molecular sieves. $\text{Pd}(\text{CH}_3\text{CN})_2(\text{OTf})_2$ and *Ligand* were synthesized according to literature procedures.^{1,18} All starting materials were commercially available and were used without further purification. All products except **1** and 4-(4-(Benzyloxy)phenyl)hexanal have been previously characterized.^{2,3} Spectra of the products from this study were in agreement with the previously characterized materials.^{2,3} ^1H -NMR spectra were obtained either at 300 or 500 MHz; chemical shifts are reported in ppm, and referenced to the CHCl_3 singlet at 7.26 ppm. ^{13}C -NMR spectra were obtained at 125 MHz and referenced to the center peak of the CDCl_3 signals at 77.0 ppm. The abbreviations s, d, t, q, and m stand for the resonance multiplicities singlet, doublet, triplet, and multiplet, respectively. Analysis by gas chromatography (GC) was performed using a Hewlett Packard HP 6890 series GC system fitted with an Agilent HP-5 column. Each kinetic experiment was carried out in a 10 mL round bottom flask equipped with a side arm and was repeated twice. Rates were determined by GC measurements of products (both regioisomers) relative to an internal standard of 2-methoxynaphthalene.

Computational Methods

All calculations were performed using M06¹⁹ functional implemented in Gaussian09.²⁰ The LanL2DZ and 6-31+G(d) basis sets were used for Pd and all other atoms, respectively. Single point calculations using the SDD basis set for Pd and the 6-311++G(d, p) basis set for all other atoms and the SMD solvent model with the parameters for DMF were used to account for solvent effects. Frequency calculations at the same level of theory at the optimized geometries were carried out to conform the stationary points as minima (no imaginary frequency) or transition state (one imaginary frequency) and provided the thermal corrections to the single point energies.

Competition Experiments

Standard solutions of $\text{Pd}(\text{CH}_3\text{CN})_2(\text{OTf})_2$, $\text{Cu}(\text{OTf})_2$, *Ligand*, and alkene were prepared in DMF for each set of experiments. The appropriate amounts were added to individual reactions to give 0.05 M concentration with equimolar amounts of competing alkene (totaling 0.3 mmol), palladium catalyst (6 mol%), copper co-catalyst (3 mol%), and *Ligand* (9 mol%). The solutions containing palladium, copper, and ligand were mixed, and then the alkene was added. Boronic acid (3 equiv) and powdered molecular sieves (45 mg, 150 mg/mmol) were added to the reaction flask, which was subsequently purged with O_2 . Once the reaction mixture was added to the reaction flask, aliquots (~100 μL) were removed periodically and passed through a silica plug eluting with ethyl acetate for GC analysis.

Effect of Boronic Acid

The same general procedure as described for the competition experiments was followed using *cis*-5-hexen-1-ol (**1**). Conditions were maintained in each experiment, yet the substitution (R) at the *para*-position of the boronic acid was changed, according to the Hammett series below.

R	Hammett σ_p	Rate (mM/h)
OBn	-0.27	3.71
Me	-0.17	2.77

Cl	+0.23	1.22
CO ₂ Me	+0.45	0.88

Note: plots of product formation over time can be found in the supplementary material (Figure S1)

4-(*p*-Tolyl)hexanal (**1'**)

cis-5-hexen-1-ol (20.0 mg, 0.2 mmol) was dissolved in DMF (2 mL), and in a separate vial *Ligand* (4.9 mg, 9 mol%), Pd(CH₃CN)₂(OTs)₂ (6.4 mg, 6 mol%), and Cu(OTf)₂ (2.1 mg, 3 mol%) were dissolved in DMF (2 mL). Powdered molecular sieves (25 mg) and 4-tolyl boronic acid (81.6 mg, 3 equiv) were added to a 10 mL round bottom flask, which was subsequently purged with oxygen. The solutions were mixed and added to the reaction flask. The reaction was allowed to stir for 18 hours at room temperature and was quenched by addition of brine and diluted with diethyl ether. The aqueous layer was extracted with diethyl ether (2 x 10 mL), and the combined organic layers were washed with brine (2 x 10 mL). The organic layer was dried over magnesium sulfate, and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (1-5% EtOAc/Hexanes) to afford aldehyde **1'** (17.0 mg, 45%, colorless oil) as mixture of regioisomers (3.7:1). *R_f* (20% EtOAc/Hexanes) 0.74; FT-IR (neat) 2923.8, 1722.1, 1513.9, 1456.6, 815.9, 668.2, 548.7 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 9.65 (1H, t, *J* 1.5 Hz), 7.11 (2H, d, *J* 8.0 Hz), 7.00 (2H, d, *J* 8.0 Hz), 2.41-2.35 (1H, m), 2.32 (3H, s), 2.30-2.24 (2H, m), 2.04-1.98 (1H, m), 1.83-1.76 (1H, m), 1.72-1.64 (1H, m), 1.62-1.56 (1H, m), 0.78 (3H, t, *J* 7.5 Hz) ppm; ¹³C{¹H}-NMR (125 MHz, CDCl₃) 202.8, 141.4, 136.0, 129.4, 127.8, 47.0, 39.1, 30.0, 28.8, 20.7, 12.4 ppm; HRMS (TOF ES⁺): MNa⁺, found 213.1249. C₁₃H₁₈ONa requires 213.1255.

4-(4-(Benzyloxy)phenyl)hexanal

Prepared in an identical manner to **1'** described above, employing 4-benzyloxyphenyl boronic acid (136.8 mg, 0.6 mmol), afforded the aldehyde (32.1 mg, 57%, white semi-solid) as a mixture of regioisomers (3.2:1). *R_f* (20% EtOAc/Hexanes) 0.58; FT-IR (neat) 2930.7, 2022.7, 1723.3, 1652.9, 1558.7, 1455.8, 836.5, 750.0, 667.9 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 9.66 (1H, t, *J* 1.5 Hz), 7.44 (2H, d, *J* 7.5 Hz), 7.39 (2H, t, *J* 7.5 Hz), 7.33 (1H, t, *J* 8.0 Hz), 7.04 (2H, d, *J* 9.0 Hz), 6.93 (2H, d, *J* 9.0 Hz), 5.04 (2H, s), 2.41-2.35 (1H, m), 2.33-2.22 (2H, m), 2.04-1.98 (1H, m), 1.82-1.75 (1H, m), 1.72-1.64 (1H, m), 1.62-1.52 (1H, m), 0.79 (3H, t, *J* 7.5 Hz) ppm; ¹³C{¹H}-NMR (125 MHz, CDCl₃) 202.8, 157.6, 137.4, 136.8, 128.8, 128.6, 128.2, 127.8, 115.1, 70.3, 46.6, 42.5, 30.0, 29.0, 12.4 ppm; HRMS (TOF ES⁺): MNa⁺, found 305.1522. C₁₉H₂₂O₂Na requires 305.1517.

General procedure A: preparation of the diol substrates **5** and **6**

To a solution of lithium diisopropyl amine (LDA), which was prepared from *n*-BuLi (2.5 M, 10.5 mL, 26.3 mmol) and *i*-Pr₂NH (4.2 mL, 30 mmol) in dry THF (60 mL) at -78 °C for 15 min, was added ε-Caprolactone (2.0 g, 18 mmol) dropwise. After the reaction mixture was stirred at -78 °C for 30 min, 1-bromo-3-

methyl-2-butene (3.3 mL, 28 mmol) was added dropwise. The resultant mixture was stirred for another 30 min, quenched with saturated aqueous NH₄Cl solution and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated to give a residue, which was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 10:1) to afford **S1** (1.82 g, 57%) as a colorless oil.

To a solution of **S1** (142 mg, 0.779 mmol) in DCM (8 mL) at -78 °C, DIBAL-H (25% wt. in toluene, 2.34 mmol) was added dropwise. The resultant mixture was stirred for 30 min at -78 °C, quenched with HCl (1 M), and extracted with DCM. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated to give a residue, which was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 3:1) to afford diol **5** (117 mg, 81%) as a colorless oil. *R_f* (petroleum ether/EtOAc, 1:1) 0.2; ¹H-NMR (500 MHz, CDCl₃) 5.16-5.14 (m, 1 H), 3.68-3.62 (m, 2 H), 3.57-3.52 (m, 2 H), 2.04-2.02 (m, 2 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.59-1.53 (m, 3 H), 1.45-1.28 (m, 4 H) ppm. ¹³C{¹H}-NMR (75 MHz, CDCl₃) 132.5, 122.5, 65.0, 62.2, 60.4, 41.1, 32.7, 30.2, 29.6, 25.7, 22.8, 17.7, 17.0 ppm. IR (neat): 3322, 2922, 2852, 1456, 1035 cm⁻¹. HRMS (TOF ES⁺): MNa⁺, found 217.1521. C₁₁H₂₂O₂Na requires 209.1517.

Compound **6** was prepared according to the general procedure **A** as a colorless oil, in 63% yield for the first step and 74% yield for the second step. *R_f* (petroleum ether/EtOAc, 1:1) = 0.2. ¹H-NMR (500 MHz, CDCl₃) 5.12-5.10 (m, 1 H), 3.58-3.55 (m, 2 H), 3.47-3.45 (m, 2 H), 2.33 (br s, 2 H), 1.99-1.96 (m, 2 H), 1.66 (s, 3 H), 1.58 (s, 3 H), 1.54-1.46 (m, 3 H), 1.31-1.19 (m, 14 H) ppm. ¹³C{¹H}-NMR (125 MHz, CDCl₃) 132.5, 122.6, 65.6, 62.7, 41.2, 32.6, 30.7, 29.9, 29.6, 29.5, 29.4, 29.3, 26.9, 25.7, 25.7, 17.7 ppm. IR (neat): 3322, 2925, 2860, 1457, 1040 cm⁻¹. HRMS (TOF ES⁺): MNa⁺, found 279.2301. C₁₆H₃₂O₂Na requires 279.2300.

General procedure B: oxidative Heck reaction of **5** and **6**

A mixture of Pd(CH₃CN)₂(OTs)₂ (14.5 mg, 27.3 μmol, 10 mol%), Cu(OTf)₂ (4.4 mg, 12 μmol, 4.5 mol%), *ligand* (10.7 mg, 39.3 μmol, 14.5 mol%), 3 Å MS (42 mg) in DMF (2 mL) was stirred for 10 minutes. After the mixture was purged 3 times with O₂, a solution of **5** (50 mg, 0.27 mmol) and boronic acid (183 mg, 0.80 mmol, 300 mol%) in DMF (1 mL) was added. The resulting mixture was stirred for 24 h at room temperature. The mixture was quenched with water, diluted with EtOAc and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated to give a residue, which was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 4:1) to afford a mixture of **P1** and **P2** (73 mg, 74%) as a colorless oil. The ratio of **P1**:**P2** is about 6.8:1 according to the crude ¹H-NMR. *R_f* (petroleum ether/EtOAc, 3:1) = 0.6. **P1** ¹H-NMR (500 MHz, CDCl₃) 9.47-9.46 (m, 1 H), 7.47-7.31 (m, 5 H), 7.28-7.22 (m, 2 H), 6.95-6.92 (m, 2 H), 5.31 (s, 2 H), 3.61 (t, *J* = 6.0 Hz, 2 H), 2.20-2.10 (m, 1 H), 1.66-1.21 (m, 10 H), 1.29 (s, 6 H) ppm. ¹³C{¹H}-NMR (75 MHz, CDCl₃) 250.4, 156.6, 141.0, 137.1, 128.5, 127.9, 127.5, 126.7, 114.3, 70.0, 62.5, 52.2, 41.6, 37.0, 32.6, 29.0, 28.3, 23.9, 23.2 ppm. IR (neat): 2934, 2864, 1734, 1508, 1497 cm⁻¹. HRMS (TOF ES⁺): MNa⁺, found 391.2254. C₂₄H₃₂O₃Na requires 391.2249.

A mixture of **P3** and **P4** was prepared from **6** according to the general procedure **B** as a colorless oil in 78% yield. The ratio of **P3:P4** is about 6.9:1 according to the crude $^1\text{H-NMR}$. R_f (petroleum ether/EtOAc, 3:1) = 0.6. **P3** $^1\text{H-NMR}$ (500 MHz, CDCl_3) 9.44-9.43 (m, 1 H), 7.45-7.31 (m, 5 H), 7.22-7.21 (m, 2 H), 6.93-6.91 (m, 2 H), 5.04 (s, 2 H), 3.62 (t, J = 5.0 Hz, 2 H), 2.16-2.06 (m, 1 H), 1.66-1.50 (m, 6 H), 1.40-1.13 (m, 14 H), 1.27 (s, 6 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ -NMR (75 MHz, CDCl_3) 205.6, 156.6, 141.0, 137.1, 128.5, 127.8, 127.4, 126.7, 114.2, 114.2, 69.9, 62.9, 52.2, 41.5, 37.0, 32.7, 29.5, 29.4, 29.3, 29.2, 29.0, 28.6, 26.9, 25.6, 23.9 ppm. IR (neat): 2925, 2854, 1718, 1511, 1242 cm^{-1} . HRMS (TOF ES+): MNa^+ , found 461.3037. $\text{C}_{29}\text{H}_{42}\text{O}_3\text{Na}$ requires 461.3056.

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Supplementary Material

Kinetic plots not presented herein, NMR spectra, and details of the computational results can be found in the supplementary material.

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