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Relative reactivity of alkenyl alcohols in the Palladium-catalyzed redox-relay Heck reaction

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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 about three times faster in both cases. Competition between a di- and trisubstituted alkenyl alcohols provided an interesting scenario, in which the disubstituted alkene was consumed first followed by consumption of the trisubstituted alkene. Consistent with this observation, the transition state structures for the migratory insertion of the aryl group into the di- and trisubstituted alkenes were calculated with a reduced barrier for the di-substituted alkene. 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 $\sigma_p$ values where $\rho = -0.87$. 2009 Elsevier Ltd. All rights reserved.

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1. Introduction

In recent years, we have reported a redox-relay strategy\textsuperscript{1-3} in the context of a Heck reaction\textsuperscript{4} with alkynyl alcohols, wherein an enantioselective arylation occurs on the alkene unsaturation is relayed to the chain-terminating alcohol (Figure 1).\textsuperscript{5,7} Both tertiary\textsuperscript{8,9} and quaternary centers\textsuperscript{10} 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 reactions robust ability to impart high enantioselectivity and its interesting trends in site selectivity, it has been the focus of a number of mechanistic studies,\textsuperscript{8-10} 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\textsuperscript{9,10} 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 βBu group on the oxazoline Ligand and the alkene 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

![Figure 1. Enantioselective redox-relay Heck arylation](image)

significantly affect the site selection, as was described using Hammett σ values\textsuperscript{6}, IR vibrations\textsuperscript{11}, and NBO charges.\textsuperscript{9} 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 alkene. 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.

2. Results and Discussion

Herein, we report kinetic data to delineate the effect on reaction rate of substituents on the boronic acid and of the chain length between the alcohol and alkene on the substrate. The kinetics were measured by observing the formation of the 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 undergoes a rate limiting migratory insertion. This is consistent with the computational results. To further probe this hypothesis, several electronically differentiated boronic acid derivatives were evaluated under the same reaction conditions. The rate of product formation is dependent on the nature of the boronic acid, which is consistent with rate limiting migratory insertion. More nucleophilic electron-rich arenes react faster than their electron-poor counterparts, which correlates with Hammett σ values with a ρ = -0.87 (Figure 2).

![Figure 2. Effect of arene electronic nature on reaction rate](image)
A surprising aspect of these results is the enhanced reactivity of the allylic alcohol, since the computed barrier for migratory insertion of the aryl group into a homoallylic alkenol has a lower activation energy of 0.5 kcal/mol. However, the complexity of the outersphere of the metal coordination environment may not be accounted for in the computations, wherein hydrogen bonding, counterion effects and solvent organization likely impact the reaction. Therefore, a possible explanation is a lower contribution to entropy-driven preorganization of the allylic substrate and the catalyst promotes a faster reaction, compared to substrates with longer chains.

As this reaction operates on both di- and trisubstituted alkenes, we were interested in determining their relative rates. Empirically, trisubstituted alkenes were found to take more time to be consumed. However, trisubstituted alkenes are more electron rich and, thus, determining the relative rates would delineate whether the empirical results were a function of a steric effect. Consistent with our previous observations, the homoallylic disubstituted alkene 1 reacts significantly faster than the homoallylic trisubstituted alkene 4 (Figure 4). An interesting feature of this competitive scenario is that 1 is consumed before any reaction of the trisubstituted alkene.

Figure 4. Competition between di- and trisubstituted alkenes
To further investigate the origin of this observation, we calculated the relevant transition structures. We reported previously that the selectivity determining and turnover limiting step is the migratory insertion through TS1 (Figure 5a). We have now computed the analogous transition structure TS2 for the trisubstituted olefin (Figure 5a). The ΔG‡ is 1.1 kcal/mol in preference for the disubstituted alkene, which is in agreement with the experimentally measured relative rates. For the disubstituted alkene, the closest H–H bond distances are relatively long (2.22 and 2.30 Å), and the dihedral angle for the insertion step is 8.8°. In comparison, the distances become shorter (2.20 and 2.13 Å) for the trisubstituted alkene (TS2), inducing more steric repulsion and a greater distorted dihedral angle (16.2°). This is in agreement with the main rate controlling factor being steric in nature.
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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. Studies are ongoing to understand this observation. In addition, di- and trisubstituted alkenes are non-competitive in the rate limiting step, although competitive alkene binding is observed. Of practical note, this result indicates that selective functionalization of disubstituted alkenes in the presence of trisubstituted alkenes could be a viable option for late stage introduction in complex molecules. 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.

4. Experimental section

General Methods

Dry dimethylformamide (DMF) was stored over activated 3 Å molecular sieves. Pd(CH$_2$CN)$_2$(OTs)$_2$, and Ligand were synthesized according to literature procedures. All starting materials were commercially available, and were used without further purification. All products except 1’ and X have been previously characterized. Spectra of the products from this study were in agreement with the previously characterized materials. $^1$H-NMR spectra were obtained at 500 MHz; chemical shifts are reported in ppm, and referenced to the CHC$_3$ singlet at 7.26 ppm. $^1$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 M06 functional implemented in Gaussian09. 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 confirm 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 Pd(CH$_2$CN)$_2$(OTs)$_2$, Cu(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. 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.

<table>
<thead>
<tr>
<th>R</th>
<th>Hammett $\rho$</th>
<th>Rate (mM/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBN</td>
<td>-0.27</td>
<td>3.71</td>
</tr>
<tr>
<td>Me</td>
<td>-0.17</td>
<td>2.77</td>
</tr>
<tr>
<td>Cl</td>
<td>+0.23</td>
<td>1.22</td>
</tr>
<tr>
<td>CO2Me</td>
<td>+0.45</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Note: plots of product formation over time can be found in the supplementary material (Figure S1)
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(CH₂CN)₂(OTs) (6.4 mg, 6 mol%), and Cu(OTf)₂ (2.1 mg, 3 mol%) were also dissolved in DMF (2 ml). Powdered molecular sieves (25 mg) and 4-methylphenyl 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 the aldehyde 1' (17.0 mg, 45%, colorless oil) as mixture of regioisomers (3.7:1). Rf (20% EtOAc/Hexanes) 0.74; FT-IR (neat) 2923.8, 1722.1, 1513.9, 1456.6, 815.9, 668.2, 547.8 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; ¹³C¹H¹NMR (125 MHz, CDCl₃) 202.8, 141.4, 136.0, 129.4, 127.8, 115.1, 70.3, 30.0, 28.8, 28.7, 12.4 ppm; HRMS (TOF ES⁺): MNa⁺, found 213.1249. C₁₅H₁₉O₂Na requires 213.1255.

4-(4-(Benzoyloxy)phenyl)hexanal (X)

Prepared in an identical manner to 1' described above employing 4-benzoyloxyphenyl boronic acid (xx mg, xx mmol), afforded the aldehyde X (32.1 mg, 57%, white semi-solid) as a mixture of regioisomers (3.2:1). Rf (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; ¹³C¹H¹NMR (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. C₁₉H₁₉O₂Na requires 305.1517.

Acknowledgments

BRB would like to thank Loughborough University for study leave funding.

5. References


Supplementary Material

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


**Frisch, M. J. et al. Gaussian09; Gaussian: Wallingford, CT, 2009.**