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Enantioselective Redox-Relay Oxidative Heck Arylations of Acyclic Alkenyl Alcohols using Boronic Acids

Tian-Sheng Mei, Erik W. Werner, Alexander J. Burckle, and Matthew S. Sigman*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112, United States

Supporting Information

ABSTRACT: A general, highly selective asymmetric redox-relay oxidative Heck reaction using achiral or racemic acyclic alkenols and boronic acid derivatives is reported. This reaction delivers remotely functionalized arylated carbonyl products from acyclic alkenol substrates, with excellent enantioselectivity under mild conditions, bearing a range of useful functionality. A preliminary mechanistic investigation suggests that the regioselectivity of the initial migratory insertion is highly dependent on the electronic nature of the boronic acid and more subtle electronic effects of the alkenyl alcohol.

An existing challenge in synthetic chemistry is setting chiral centers via carbon−carbon bond formation remote to functional groups.[1] Besides directly functionalizing specific C−H bonds in an enantioselective manner, addition of carbon nucleophiles to alkenes using a metal catalyst is an especially attractive approach as the alkene is an easily accessible, robust functional group. This strategy requires addition of the carbon nucleophile−metal species to the alkene, which is often electronically biased toward site-selective addition (e.g., a conjugated alkene). The resultant metal−alkyl complex needs to be efficiently transformed to avoid deleterious reaction pathways available to metal−alkyls. One successful tactic is the metal-catalyzed conjugate addition of carbon-nucleophiles to α,β-unsaturated carbonyls wherein the metal−enolate formed in the process is hydrolyzed to reform the active catalyst for a subsequent catalytic cycle (Figure 1a).[2] These methods allow for the formation of a wide range of β-substituted carbonyl products in high enantiomeric excess.

We have recently reported an alternative conceptual approach to setting remote chiral centers using an alkenyl substrate.[3] Specifically, we have developed an enantioselective Heck-type reaction[4−6] of racemic acyclic alkenol substrates using aryl diazonium salts as the coupling partners, which delivers β-aryl carbonyl products similarly to conjugate addition methods (Figure 1b).[3] The approach also allows direct access to γ- or δ-substituted aryl carbonyl products in high enantioselectivity by using a redox-relay strategy[7] wherein the unsaturation in the alkene is migrated toward the alcohol.[8] This transformation occurs presumably through an iterative β-hydride elimination/migratory insertion process to ultimately be trapped by formal oxidation of the alcohol resulting in a carbonyl product (Figure 1c).[9]

While this method leads to high enantioselectivity for a range of alkenol substrates (mainly allylic and homoallylic alcohols), a significant question arises as to why preferential insertion is observed at the site distal from the alkyl alcohol.[10] Additionally, the use of aryl diazonium salts limits both the scope and potentially the practical application of this method. Therefore, we became interested in developing an oxidative variant of the enantioselective redox-relay Heck reaction using ubiquitous aryl boronic acid derivatives[11] as the aryl source to improve the synthetic utility and also to begin to probe the origin of site selective migratory insertion. Herein, we report an enantioselective redox-relay oxidative Heck reaction with acyclic alkenols and aryl boronic acids, delivering remotely functionalized carbonyl products in high enantioselectivity and generally high site selectivity.

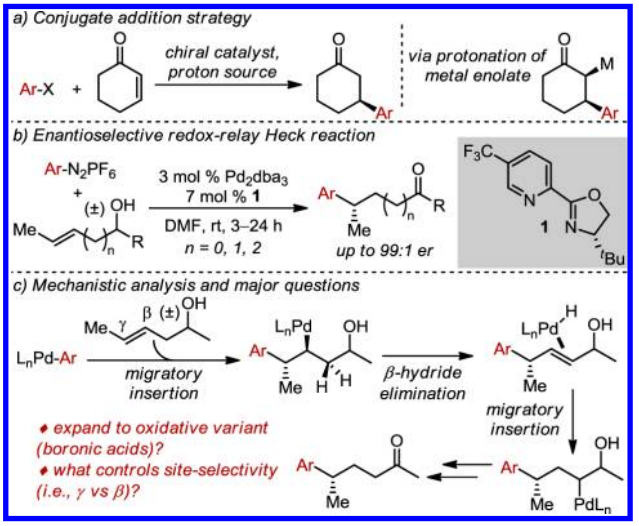

Figure 1. (a) Enantioselective β-functionalization reactions. (b) Enantioselective redox-relay Heck reactions. (c) Mechanistic analysis.

We began our investigation by exploring our previously developed catalytic system for oxidative Heck reactions of electronically nonbiased olefins.[12] These conditions employ a cationic Pd salt ligated with an *N*-heterocyclic carbene and catalytic $Cu(OTf)_2$ under an O_2 atmosphere. To initiate the optimization, the *N*-heterocyclic carbene was replaced with the chiral pyridine oxazoline ligand **1**,[3,13] resulting in poor conversion of a *cis*-homoallylic alcohol **3**, albeit with good mass balance for the desired product (entry 1, Table 1). Poor conversion in Pd-catalyzed aerobic oxidations is often attributed to catalyst deactivation through aggregation of Pd

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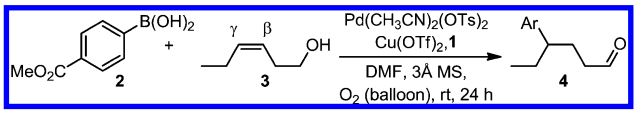
Table 1. Reaction Optimization



entry	Pd/Cu/ligand (mol %)	2 (equiv)	3 Å MS (mg/mmol)	conv. (%)[a]	yield (%)[a]
1	5/5/11	2	–	17	15
2	5/5/11	2	40	58	50
3	5/5/11	2	150	80	70
4	5/5/11	2	400	78	67
5	5/5/11	3	150	>90	82[b] (99:1 er)[c]

[a]Determined by GC analysis using an internal standard. [b]Isolated yield. [c]er value was determined with SFC after reducing the aldehyde to the primary alcohol.

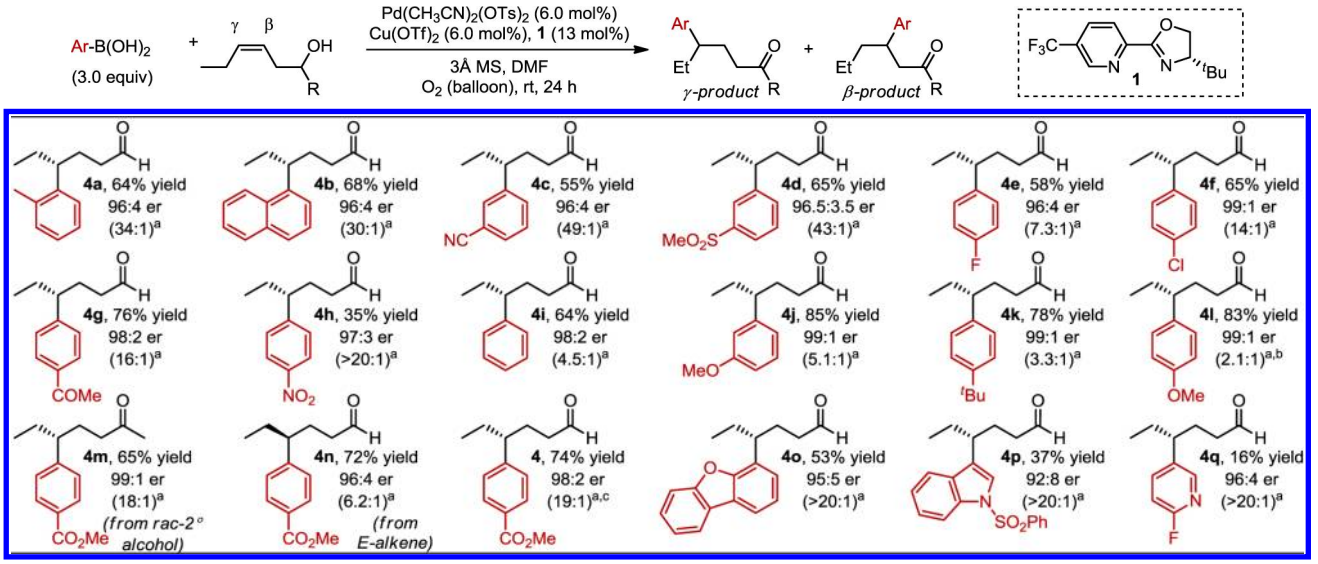
metal during the process. This is a result of retarded oxidation of Pd(0) to Pd(II) with O_2 (or Cu(II)), which can be circumvented by the addition of molecular sieves (MS).[14] Indeed, the addition of 3 Å MS significantly improved the reaction outcome with enhanced yields of the desired product (entries 2–4). Increasing the boronic acid and catalyst loadings gave complete conversion in 82% yield (entry 5), 19:1 regioselectivity (γ:β), and excellent enantioselectivity (er: 99:1). Of note, removing $Cu(OTf)_2$ significantly reduces the yield, and in the absence of Pd, no significant reaction is observed.

With this catalytic system in hand, we initially investigated a wide array of arylboronic acids with homoallylic alcohols substrates (Table 2), which deliver γ-aryl carbonyl chiral building blocks in uniformly high enantioselectivity (er up to 99:1) with moderate to good yields. In general, the observed site selectivity (γ vs β) for alkene functionalization is good to excellent. High site- and enantioselectivity is observed for ortho-substituted aryl boronic acids (**4a**, **4b**). In the case of meta- or para-substituted aryl boronic acids, electron-deficient examples afford high site selectivity (**4c**–**h**). In contrast, electron-rich arylboronic acids give considerably lower levels of site selectivity, although in high enantioselectivity (**4j**–**l**). Interestingly, the minor isomeric product is also formed in high enantioselectivity (**4l**), which has several important mechanistic implications, as discussed below. A racemic secondary alkenyl alcohol (**4m**) performs similarly as does an *E*-alkene, which yields the other enantiomer as the major product (**4n**). Scaling of this method from 0.5 to 10 mmol resulted in very similar results (**4**). Finally, several heteroaromatic boronic acid derivatives were evaluated (**4o**–**q**). In all cases, excellent site and enantioselectivity is observed although the conversion of the alkene is poor possibly due to observed higher levels of homocoupling and phenol formation for these boronic acids.

A series of both primary and racemic secondary substituted alkenyl alcohols were selected as substrates to probe whether a steric effect can influence the site and enantioselectivities (Table 3, **5a**–**e**). Excellent enantioselectivity is observed in all cases, although an apparent steric effect influences site selectivity, with smaller groups leading to more of the β-insertion product (compare **5a** (-Me), **4l** (-Et), **5d** (-^{i}Pr)). Of note, this minor product is formed in similar enantioselectivity to that of the major product. Next, the effect of chain-length (i.e., the distance from the alcohol to alkene) was probed by systematically evaluating ethyl-substituted alkenyl alcohols (Table 3, **5f**–**j**). Again, the enantioselectivity is consistently high for all substrates evaluated, suggesting that the alcohol is not involved directly in face selection. This is also supported by the successful use of racemic alcohol substrates (**5d**, **5e**, **5j**). A clear trend emerges in terms of site selectivity for alkene insertion: as the alcohol is further removed from the alkene the selectivity is diminished. As an important synthetic note, many of these enantiomerically enriched products would be very cumbersome to synthesize using conventional approaches as the chiral centers are quite remote from the carbonyl.

In many asymmetric catalytic reactions, enantioselectivity is highly sensitive to the nature of the substrates used in the reaction.[15] In this case, enantioselectivity is essentially independent of the nature of both reaction partners. In contrast, the site selectivity of the alkene insertion is controlled

Table 2. Scope of the Enantioselective Redox-Relay Heck Reaction of Homoallylic Alcohols and Aryl Boronic Acids



[a]Yields are reported as a combination of isomers and reaction performed on 0.5 mmol scale. Enantioselectivity determined by SFC equipped with a chiral column. Ratio of γ to β-product as determined by either ^{1}H NMR or gas chromatography. [b]Enantioselectivity of β-product is 99:1 er. [c]Reaction performed on 10 mmol scale.

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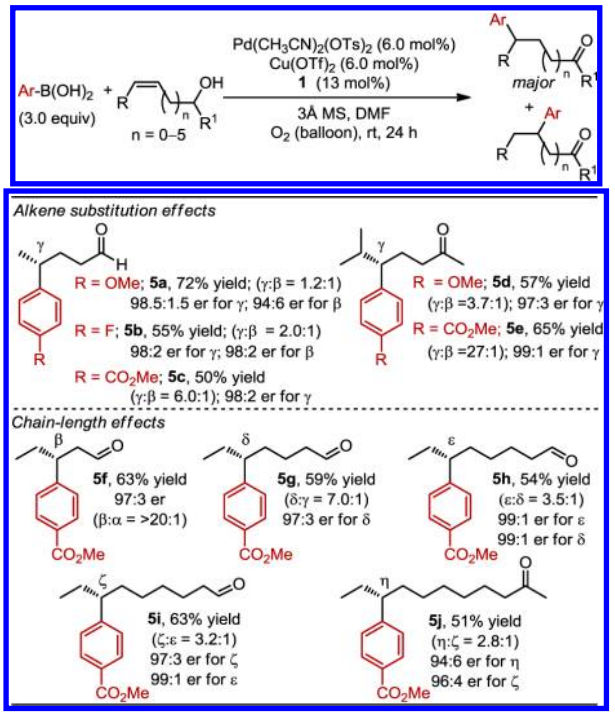
Table 3. Evaluation of Various Alkenol Substrates



[a]Yields are reported as a combination of isomers. Enantioselectivity determined by SFC equipped with a chiral column. Ratio of γ to β-product as determined by either ^{1}H NMR or gas chromatography.

both by the nature of the arylboronic acid and the substitution and chain length of the alkenyl alcohol. To quantify the electronic effect of aryl boronic acids on the site selection, a linear free energy relationship was identified using Hammett σ-values of both meta- and para-substituted boronic acids versus the log of the ratio of site selectivity, which is proportional to relative rates of isomer formation (Figure 2).[16] The resultant

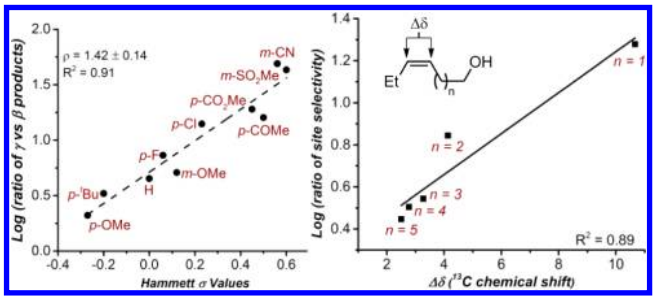
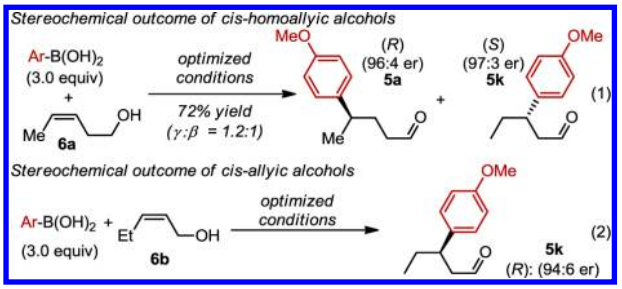


Figure 2. (Left) Plot of Log of site-selectivity versus Hammett σ-values derived from the scope presented in Table 2. (Right) Plot of Log of site-selectivity versus $\Delta\delta$ ^{13}C chemical shift.

Hammett plot has a ρ-value of 1.42, suggesting that the orientation of insertion is sensitive to the electronic nature of the Pd–Ar species formed (vide infra). In conjunction with this correlation is the trend of site selectivity as a function of chain-length (Table 3). To probe the origin of this interesting observation, the relative ^{13}C chemical shifts for each alkene carbon were compared.[17] For all cases, the most downfield-shifted carbon is distal from the alcohol. Interestingly, correlating the $\Delta\delta$ ^{13}C chemical shifts versus the log of the ratio of site selectivity reveals a clear trend. Although various scenarios cannot be ruled out, this observation is also suggestive of electronic effects governing site selectivity.

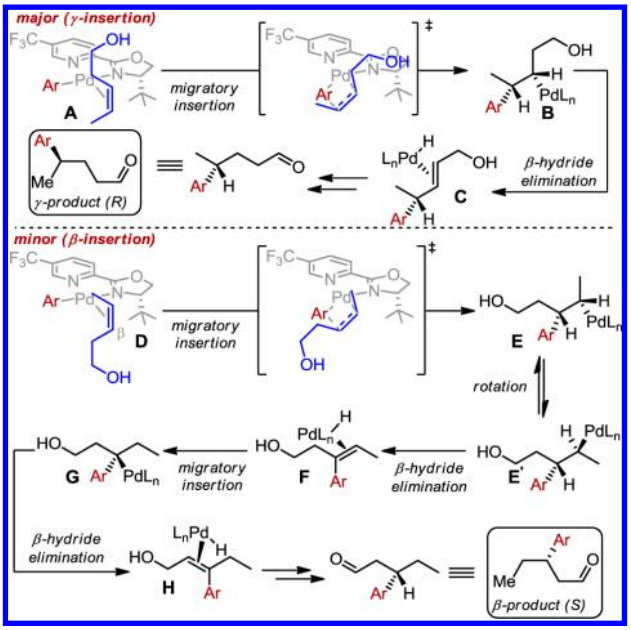
Considering the above discussion, an important question concerning the relationship of site selection to face selection arises as high enantiomeric excess is also observed for minor isomers analyzed (eq 1). Therefore, the absolute configuration



was determined for addition to *cis*-homoallylic alcohol **6a**, revealing that the enantiomer formed from γ-insertion product **5a** is (*R*) whereas the β-insertion product **5k** is (*S*) (see Supporting Information for details). Addition to an allylic alcohol **6b** also yields product **5k** as the only product in high enantioselectivity (eq 2). In this case, though, the opposite enantiomer is observed to that of **5k** formed from a homoallylic substrate.[3]

Taken together, these data suggest that, as the opposite faces of the alkene are presented to the catalyst, a highly enantioselective insertion takes place but at different alkene carbons (Scheme 1). For the major pathway, the alkene

Scheme 1. Mechanistic Analysis of Stereochemical Course



presumably undergoes migratory insertion in the orientation as depicted in the transformation of **A**→**B** to account for the observed enantioselectivity. Of particular note, the site selectivity is decreased as the Pd–aryl species becomes less electrophilic (i.e., when the aryl group is more electron-rich). This is coupled to diminished site selectivity as a function of a less electronically biased alkene, which suggests that an electronic bias is required for enhanced site-selectivity and that this is a highly sensitive event considering the magnitude of

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the ρ-value. An interesting feature of the minor insertion pathway is that the redox-relay product is formed even though this would formally require translation of the metal through the initially fashioned C−C bond. As this product is also formed in high enantioselectivity as the opposite enantiomer, the initial migratory insertion likely proceeds with the opposite orientation of the alkene as depicted in **D**→**E**. To form the aldehyde product, β-hydride elimination should yield the trisubstituted alkene in **F** followed by insertion of the resultant Pd−H to deliver **G**. Subsequent repetitive events ultimately will yield the aldehyde. The high level of enantioselection suggests that the Pd−H does not dissociate from the alkene, which may be attributed to the electrophilic nature of the catalyst. At this stage, simple stereochemical models cannot account for the excellent enantioselectivity observed as well as why the site selection operates in concert with face selection. These issues will require significant mechanistic investigations, which are currently underway.

In conclusion, we report a highly enantioselective oxidative Heck reaction of alkenyl alcohols that operates through a redox-relay process. The products formed using this method would be difficult to access rapidly using traditional approaches. Preliminary efforts to understand the origin of site selectivity in this process are reported, wherein Hammett and other correlative techniques suggest that electronic effects play a major role in controlling site selection. Understanding the rules governing migratory insertion of relatively unbiased alkenes has not been extensively defined. Research is underway to probe this important organometallic mechanistic question, apply this method to synthetic endeavors, and expand the concept of redox-relay Heck reactions to new substrate and reaction types.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for new substances. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

sigman@chem.utah.edu

Notes

The authors declare no competing financial interest.

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