Alkenyl Carbonyl Derivatives in Enantioselective Redox Relay Heck Reactions: Accessing α,β-Unsaturated Systems

Chun Zhang, Celine B. Santiago, Lei Kou, 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 highly enantioselective and site-selective Pd-catalyzed arylation of alkenes linked to carbonyl derivatives to yield α,β-unsaturated systems is reported. The high site selectivity is attributed to both a solvent effect and the polarized nature of the carbonyl group, both of which have been analyzed through multidimensional analysis tools. The reaction can be performed in an iterative fashion allowing for a diastereoselective installation of two aryl groups along an alkyl chain.

Developing methods for site selective migratory insertion into relatively unbiased multisubstituted alkenes would be an enabling approach to synthesis.[1] Of specific interest is precisely functionalizing internal alkenes with enantiocontrol and site control for remotely installing groups in molecules.[2−6] However, this prospect is difficult to achieve, as alkenes of this sort are distantly located from a discriminating functional group, which removes obvious innate factors for governing site selectivity.[1] In this regard, our discovery that alkenes positioned at various distances from an alcohol undergo site selective addition of an aryl-Pd intermediate is unique (Figure 1a).[7] The origin of this site selectivity has been investigated through empirical exploration of the scope in combination with computational,[8] labeling,[8c] and correlative studies.[8d] While the detailed origin of selectivity for the addition of the organo-

metallic at the carbon distal to the alcohol is still under investigation, the vast majority of the studies point to a remote electronic effect that is modestly influenced by alkene substituent size. The electronic effect is thought to arise from reducing the dipole during the formation of the C−C bond through the orientation of the alcohol and the arene (compare TS **A** and **B**). Therefore, changing the substituent on the arene and the distance between the alcohol and alkene influences site selectivity.

This hypothesis provides the impetus for further exploration of the substrate scope in terms of replacing the alcohol with an alternative functional group. We were attracted to carbonyls due to three factors. First, the products of the enantioselective relay Heck reaction are remotely functionalized α,β-unsaturated carbonyls, which are envisioned to be useful for further elaboration and would be difficult to access using conventional strategies (Figure 1b). Second, the diversity of carbonyls would presumably allow for a wider range of observed site selectivity as a function of such groups, providing the basis for additional mechanistic understanding and enhancing selectivity.[8] Finally, reduction of the resultant α,β-unsaturated carbonyl provides an allylic alcohol, which would be suitable for an iterative relay Heck reaction (Figure 1b).[7a] However, we also envisioned many potential issues including further reaction of the α,β-unsaturated carbonyl products under the reaction conditions, isomerization of the alkenes into conjugation since Pd-hydrides are formed in these reactions, and the potential deleterious effect of these new functional groups on enantioselectivity and yield. Herein, we present the successful development of an enantioselective relay Heck reaction of alkenes linked to carbonyl derivatives, which allows access to an array of α,β-unsaturated carbonyl products with remotely installed aryl groups. Of particular interest, these arylations have enhanced site selectivity compared to the previous variants using alkenols and provide an opportunity for further interrogation of site selective migratory insertion of unbiased alkenes.

Based on our previous reports,[7] our study commenced with the reaction of phenylboronic acid (**1a**) and (Z)-dec-4-enal (**2a**) catalyzed by Pd ligated with PyrOx under oxidative Heck-type conditions (Table 1, entry 1). To our delight, the reaction performed well yielding the product in 73% and a 98:2 er without the need for a copper cocatalyst, thus allowing a reduction in the overall ligand loading. Under these conditions, the site selectivity was modest favoring the δ product in a 5.8:1 ratio. No reaction of the α,β-unsaturated aldehyde product is
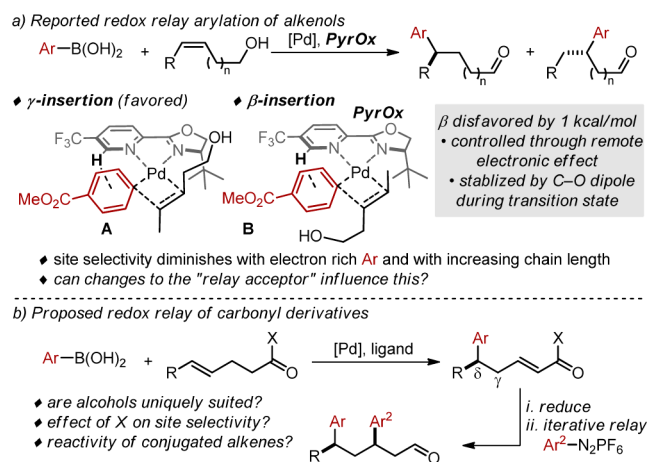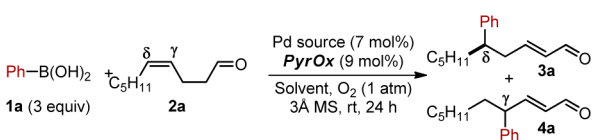

Figure 1. (a) Previously reported enantioselective relay Heck reactions of alkenols including mechanistic analysis. (b) Proposed new enantioselective relay Heck reaction of alkenes linked to carbonyl derivatives and resultant iterative Heck reaction.

Table 1. Optimization of the Enantioselective Relay Heck Reaction of 2a[a]

entry	Pd source	solvent	yield of 3a (%)[b]	er (3a)[c]	δ:γ[d]
1	Pd(MeCN)$_2$(OTs)$_2$	DMF	73	98:2	5.8
2	none	DMF	–	–	–
3	Pd(MeCN)$_2$(OTs)$_2$[e]	DMF	trace	–	–
4	Pd(MeCN)$_2$(OTs)$_2$[f]	DMF	trace	–	–
5	Pd(MeCN)$_2$(OTs)$_2$[g]	DMF	65	98:2	5.2
6	Pd(MeCN)$_2$(OTs)$_2$	DMA	78	99:1	15
7	Pd(MeCN)$_2$(OTs)$_2$	1,4-dioxane	73	98:2	7.8
8	Pd(MeCN)$_2$(OTs)$_2$	THF	38	98:2	9.3

[a]Conditions: **1a** (0.75 mmol, 3.0 equiv), **2a** (0.25 mmol, 1.0 equiv), [Pd] (0.01875 mmol, 7.5 mol %), ligand (0.0225 mmol, 9 mol %), solvent (3 mL), O$_2$ (1 atm), rt, 24 h. [b]Reported yields are of isolated **3a** as a >20:1 ratio of the *E*-alkene isomer. [c]Determined by SFC equipped with a chiral stationary phase. [d]Determined by NMR. [e]In the absence of 3 Å MS. [f]In the absence of ligand. [g]Using air (1 atm). DMF = *N,N*-dimethylformamide; DMA = *N,N*-dimethylacetamide; THF = tetrahydrofuran.
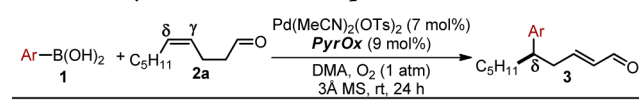
observed suggesting that the catalyst prefers reaction with electron-rich alkenes.[9] Control experiments confirmed the requirement of Pd (Table 1, entry 2), molecular sieves (entry 3), and PyrOx (entry 4). Slightly reduced yields are observed using air instead of pure O$_2$ as the terminal oxidant albeit in excellent enantioselectivity (entry 5). As a significant goal of this project was to increase site selectivity, we further explored the choice of solvent. Interestingly, when DMA was used as solvent, the site selectivity significantly increased favoring the δ product in a 15:1 ratio with modestly enhanced yield and er (entry 6). Other solvents were also competent but did not improve the results further (entries 7−8).
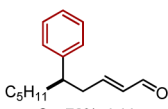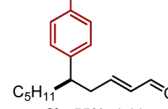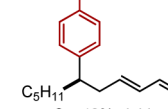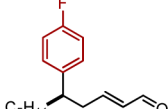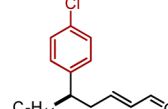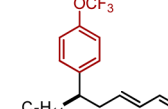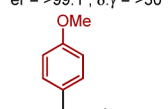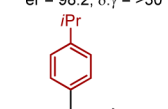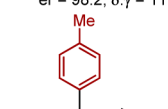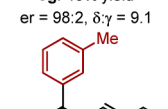
This observed improvement in site selectivity is notable and inspired us to investigate the potential origin of the solvent effect.[10] Therefore, an array of various substituted amide solvents were evaluated in the reaction (Figure 2). To correlate these results, we performed multidimensional analysis relating the measured $\Delta\Delta G^{\ddagger}$ for site selectivity to various parameters describing the different amide solvents (see Supporting Information for details). An excellent correlation was achieved relating the IR intensity of the carbonyl stretch ($I_{C=O}$) and
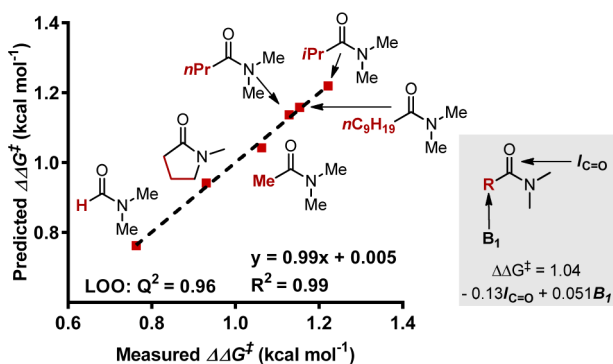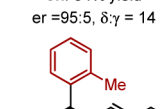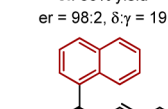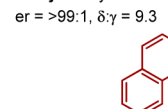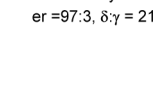

Figure 2. Multidimensional correlation of solvent parameters with site selectivity.

Sterimol B$_1$ value of the substituent R to the measured site selectivity.[11] This relationship was validated using Leave-One-Out analysis with a $Q^2 = 0.96$. As illustrated by the coefficients in the regression model, decreasing the $I_{C=O}$ and increasing the Sterimol B$_1$ of the R group of the solvent result in higher site selectivity. This suggests that the polarization model for site selectivity described in the introduction is impacted by both the dipole and orientation of the solvent. It should be noted that improved site selectivity does not necessary lead to higher yields and DMA was found to balance both of these requirements.

Using DMA as solvent under the optimal conditions, the scope of aryl substituted boronic acid (**1**) was probed in the formation of various δ-aryl substituted α,β-unsaturated aldehydes (Table 2). In general, modest to good yields using either electron-rich or -deficient aryl substituted boronic acids is observed as a single geometrical alkene isomer. In all cases, the enantiomeric ratios are excellent. Previously, we found a significant reduction in site selectivity when electron-rich aryl boronic acids were employed. In fact, the best site selectivity previously observed for the formation of a δ-aryl product was

Table 2. Aryl Boronic Acid Scope[a]

3a: 78% yield
er = 99:1, δ:γ = 15

3b: 55% yield
er = 97:3, δ:γ = >30

3c: 48% yield
er = 95:5, δ:γ = >30

3d: 71% yield
er = >99:1 , δ:γ = >30

3e: 64% yield
er = 98:2, δ:γ = >30

3f:[b] 60% yield
er = 98:2, δ:γ = 11

3g: 43% yield
er = 98:2, δ:γ = 9.1

3h: 54% yield
er =95:5, δ:γ = 14

3i: 80% yield
er = 98:2, δ:γ = 19

3j: 65% yield
er = >99:1, δ:γ = 9.3

3k: 60% yield
er =97:3, δ:γ = 21

3l:[b] 56% yield
er = 96:4, δ:γ = >30

3m:[b] 50% yield
er = 98:2, δ:γ = 14

3n:[b] 50% yield
er = >99:1, δ:γ = >30

[a]Standard reaction conditions: **1** (0.75 mmol, 3.0 equiv), **2a** (0.25 mmol, 1.0 equiv), Pd(MeCN)$_2$(OTs)$_2$ (0.019 mmol, 7.5 mol%), ligand (0.023 mmol, 9 mol %), DMA (3 mL), 3 Å Ms (50 mg), O$_2$ (1 atm), rt, 24 h. Yields are of isolated **3**, >20:1 *E*-alkene product. Enantioselectivity determined by SFC equipped with a chiral stationary phase. [b]Cu(OTf)$_2$ (0.013 mmol, 5 mol %), ligand (0.035 mmol, 14 mol%) were used.

7:1 with an electron-poor boronic acid. In this system, the site selectivity is >9:1 favoring the δ-product for both electron-rich and -poor partners with electron-poor coupling partners providing even higher levels of control (often >30:1). Of note, some yields were improved by the addition of Cu(OTf)$_2$ (see Table 2).[12,13]

The second stage of scope evaluation was focused on the nature of the carbonyl linked to the alkene (Table 3). As

Table 3. Evaluation of Functional Group Tolerance of the Alkene Substituent[a]

[a]Standard reaction conditions: **1a** (0.75 mmol, 3.0 equiv), **2** (0.25 mmol, 1.0 equiv), Pd(MeCN)$_2$(OTs)$_2$ (0.019 mmol, 7.5 mol%), ligand (0.023 mmol, 9 mol%), DMA (3 mL), 3 Å Ms (50 mg), O$_2$ (1 atm), rt, 24 h. Yields of isolated **3**, >20:1 E-alkene product Enantioselectivty determined by SFC equipped with a chiral stationary phase. [b]Yields are a combination of **3** and **4**, >20:1 E-alkene product.

discussed above, we believed that this would be an opportunity to further probe the origin of site selectivity. In general, a wide range of functional groups are compatible with the reaction including a ketone (**3p**) and a carboxylic acid (**3q**). Various esters are excellent substrates for the reaction (**3r**–**t**) including the highly versatile and sensitive *p*-nitrophenol derived substrate (**3u**). Both a nitrile (**3v**) and amide (**3w**) perform well in the reaction although a 5:1 mixture of alkene geometrical isomers is observed using the smaller nitrile. Finally, a substrate containing an α,β-unsaturated aldehyde yields the conjugated product **3x** with a ζ-aryl substitution in excellent enantioselectivity and site selectivity. Unfortunately, site selectivity and yield diminish significantly as the chain length is extended between the alkene and the aldehyde (**3y**–**z**) similar to our previous report.[7b]

On the basis of the range of selectivity observed as a function of the substrate carbonyl, we explored how the carbonyl may be impacting site selectivity. To accomplish this, the substrates containing only the C$_5$H$_{11}$ group with different carbonyls were submitted for geometry minimizations and IR frequency calculations.[8d] Various parameters were compiled including

point charges on a number of atoms and IR frequencies and intensities of the functional groups. A good correlation was found between the NBO charge of the carbonyl oxygen (Figure 3)[14] and the measured site selectivity. The aldehyde substrate
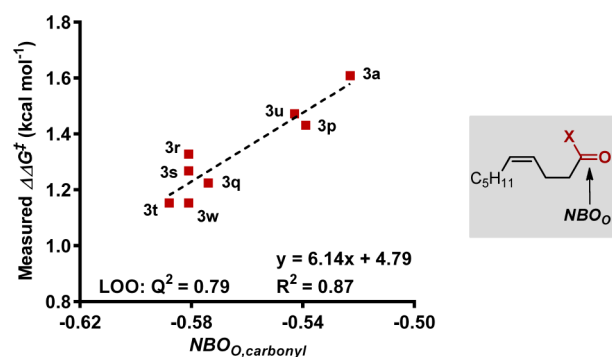

Figure 3. Correlation of observed site selectivity to the NBO charge of the carbonyl oxygen.

corresponding to product **3a** with the least negative NBO charge on the carbonyl oxygen resulted in the highest site selectivity, while the ester substrate corresponding to product **3t**, which has the greatest negative NBO charge on the carbonyl oxygen, resulted in the lowest site selectivity. Despite the distance of the functional group from the alkene, the optimized geometries of the substrates illustrate bending of the substrate to allow alignment of the carbonyl with the alkene (see Supporting Information). Additionally, the greatest NBO charge difference between the alkene carbons (C$_δ$=C$_γ$) was observed for the substrate that provided the highest site selectivity (**2a**), illustrating the remote effect of alkene polarization on the migratory insertion step.

As this method provides direct access to highly enantiomerically enriched α,β-unsaturated aldehydes, we envisioned exploiting these products in iterative relay Heck reactions. This three-step approach would facilitate the 1,3 difunctionalization of a simple alkyl chain in a modular fashion. To test this possibility, the carbonyl of product **3a** was reduced to yield an allylic alcohol (**5**), which upon treatment with an aryl diazonium salt under conditions from our previously reported relay Heck reaction[7a] forms product **6** in high diastereoselectivity (eq 1). Using the enantiomer of the ligand provides
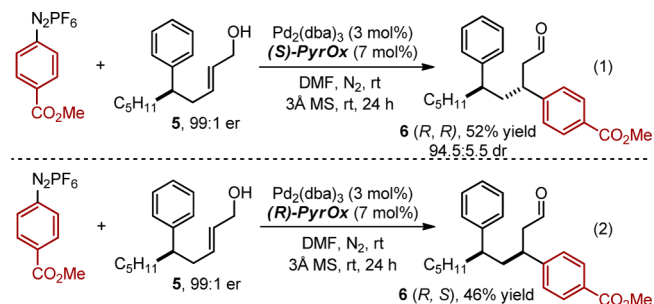
access to the other diastereomer in good albeit modestly reduced diastereoselectivity (eq 2), suggesting mainly catalyst controlled addition.

In conclusion, we have reported a unique method to produce α,β-unsaturated carbonyls containing an aryl group δ to the carbonyl in high enantioselectivity. The scope of the reaction is broad in both the aryl coupling partners and the carbonyl

derivatives. Of particular interest is the evolving understanding of substrate substituent effects on site selective migratory insertion. The subtle influence of the remote carbonyl has been studied through correlative tools providing further evidence that polarization of the substrate during migratory insertion is essential for effective site control. This important finding should allow us to design more versatile catalysts and systems to achieve greater site selection at even more remote sites. Exploring this goal in the context of further expansion of the enantioselective relay Heck reaction is underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, analytical data for products, NMR spectra of products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04289.

■ AUTHOR INFORMATION

Corresponding Author

*sigman@chem.utah.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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