Communication

Enantioselective Palladium-Catalyzed Alkenylation of Trisubstituted Alkenols to form Allylic Quaternary Centers

Harshkumar H. Patel, and Matthew S Sigman

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Enantioselective Palladium-Catalyzed Alkenylation of Trisubstituted Alkenols to form Allylic Quaternary Centers

Harshkumar H. Patel and Matthew S. Sigman*

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

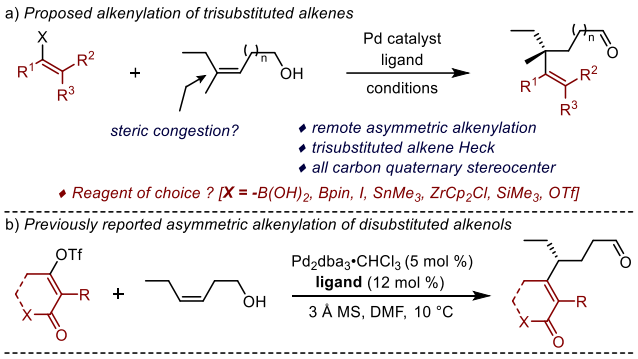
Supporting Information Placeholder

ABSTRACT: In this report, we describe the generation of remote allylic quaternary stereocenters β, γ, and δ relative to a carbonyl in high enantioselectivity. We utilize a redox-relay Heck reaction between alkenyl triflates and acyclic trisubstituted alkenols of varying chain-lengths. A wide array of terminal (*E*)-alkenyl triflates are suitable for this process. The utility of this functionalization is validated further by conversion of the products, via simple organic processes to access remotely functionalized chiral tertiary acid, amine and alcohol products.

Generation of enantiomerically enriched quaternary centers adjacent to an alkenyl moiety in acyclic systems has recently received considerable attention.[1] This is in part due to the unique structural features of quaternary centers for applications in synthesis, which is further enabled by the resultant synthetic flexibility of the allylic functional group.[2] Existing approaches to access an allylic quaternary center utilize the precise proximity of a pre-existing functional group or pre-installed stereocenter in the substrate of interest to enable the reactivity profile.[3] Although many excellent methods have been reported that allow for enantioselective installation of alkenyl groups α[4] or β[5,6] to a functional group, approaches outlining such a strategy to a quaternary chiral center γ or δ (or more remotely) directly have not been reported.[7-9]

To address this challenge, we envisioned applying our recently reported enantioselective redox-relay Heck tactic for functionalization of trisubstituted alkenols containing various chain-lengths between the alkene and alcohol with an alkenyl reagent (Figure 1a).[10,11] Successful development of such a method would provide direct access to the desired functionalized alkenyl quaternary stereocenter at remote positions (β, γ and δ) to a carbonyl group expanding the methods by which to access these highly desirable chiral building blocks. Additionally, such a reaction can be considered a surrogate to the unresolved enantioselective alkylative Heck reaction, since hydrogenation of the resultant double bond will furnish the desired aliphatic Heck-type products.[12] Compounds of this nature are difficult to access using traditional approaches.[13] Unfortunately, while we have reported the arylation of trisubstituted alkenols to establish quaternary stereocenters in high enantioselectivity, initial efforts to promote the corresponding reaction using alkenyl triflates was met with failure. Herein, we present the identification and application of a class of electron rich alkenyl triflates to the redox-relay Heck reaction, to forge quaternary stereocenters containing an alkene in high enantioselectivity.

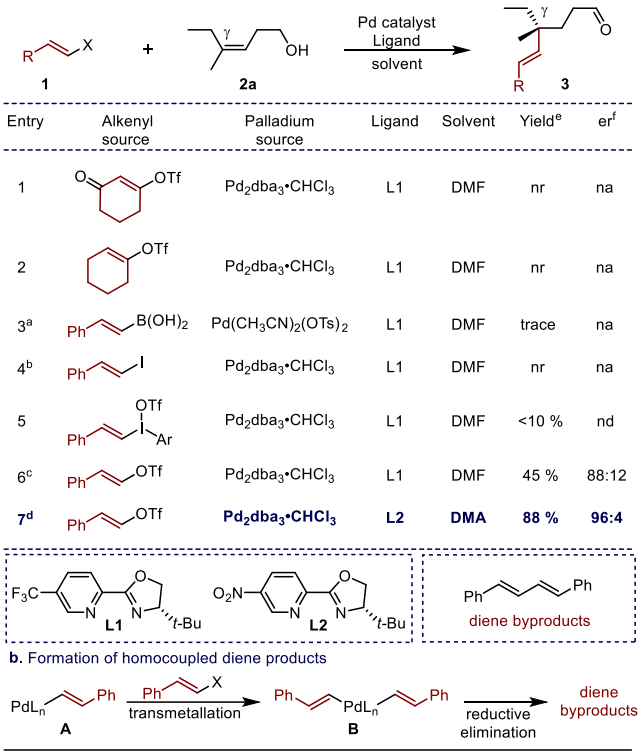
Figure 1. Proposed enantioselective redox-relay Heck alkenylation of trisubstituted alkenols



At the outset of this project, a search for a suitable alkenyl coupling partner was undertaken considering that electron deficient alkenyl triflates, while successful in the reaction of disubstituted alkenols (Figure 1b), were unreactive with the corresponding trisubstituted alkenols.[14] Initially, it was hypothesized that slow migratory insertion of the electron-poor alkenyl triflate (Table 1, entry 1) into the more hindered system was responsible for the failure to observe product, which is consistent with previous report of reduced yields with electron-poor aryl boronic acids using hindered alkenols.[15] Considering this, an electron rich alkenyl triflate (Table 1, entry 2) containing a cyclohexenyl group, was submitted to the reaction with trisubstituted alkenol **2a**. Unfortunately, complete recovery of starting material resulted. Presumably, the cyclohexenyl unit prevents migratory insertion of the trisubstituted alkene due to its size. This hypothesis is consistent with poorer yields observed previously with *ortho*-substituted arenes with trisubstituted alkenes.[10] Therefore, a range of less hindered electron-rich reagents were evaluated. Initially, alkenyl boronic acids were investigated due to their commercial availability, stability, and the ease with which one can vary the electronic nature of the alkenyl substituent. Unfortunately, an alkenyl boronic acid (Table 1, entry 3) was an ineffective coupling partner with alkenol **2a**. Further, submission of alternative coupling partners such as an alkenyl iodide (Table 1, entry 4), and an alkenyl iodonium salt (Table 1, entry 5) were unsuccessful. The main byproduct observed in this reaction is a diene resulting from a homocoupling event. Apparently, after initial transmetallation, palladium alkenyl species **A** does not undergo the desired migratory insertion with the hindered alkenol but instead a second transmetallation event competitively occurs to form palladium bis-alkenyl species **B** (Table 1b). This intermediate can undergo subsequent reductive elimination resulting in the formation

of the diene, which has deleterious effects on the reaction (vide infra).

Table 1. Alkenyl coupling partner evaluation and reaction optimization.



Entry	Alkenyl source	Palladium source	Ligand	Solvent	Yield[e]	er[f]
1		Pd_2dba_3•$CHCl_3$	L1	DMF	nr	na
2		Pd_2dba_3•$CHCl_3$	L1	DMF	nr	na
3[a]		$Pd(CH_3CN)_2(OTs)_2$	L1	DMF	trace	na
4[b]		Pd_2dba_3•$CHCl_3$	L1	DMF	nr	na
5		Pd_2dba_3•$CHCl_3$	L1	DMF	<10 %	nd
6[c]		Pd_2dba_3•$CHCl_3$	L1	DMF	45 %	88:12
7[d]		**Pd_2dba_3•$CHCl_3$**	**L2**	**DMA**	**88 %**	**96:4**

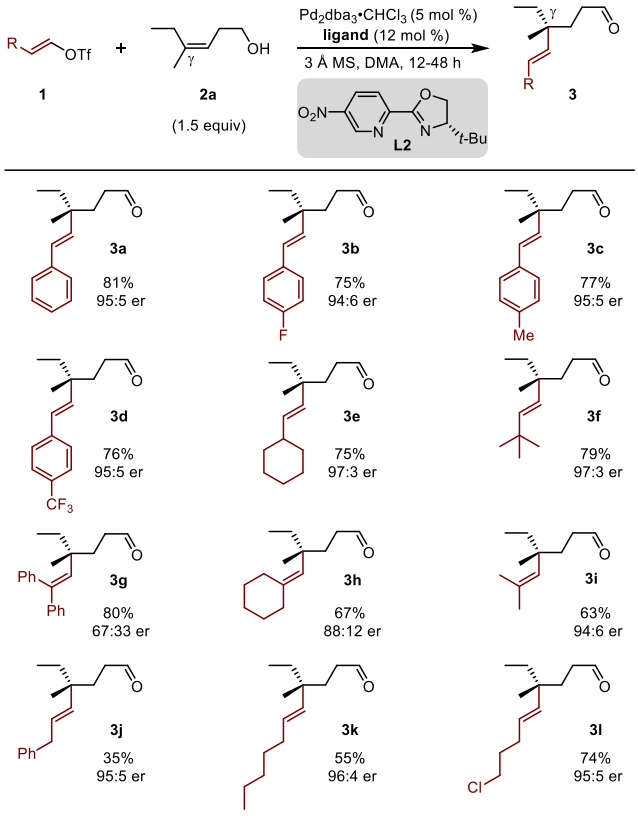
b. Formation of homocoupled diene products

nr: no reaction; na: not applicable; nd: not determinded; [a]Diene byproducts were observed. [b]AgOTf (1.0 equiv) was used as an additive.[c]1:1 equiv of the alkenol and triflate**.** [d]DMA (0.5 M) and 1.5 equiv of alkenol. [e]Isolated yields. [f]Enantioselectivity determined by SFC equipped with a chiral column. All reaction carried out on 0.1 mmol scale.

These unfortunate results suggested that a Pd(0) path might be a more prudent approach to avoid a second transmetallation. Therefore, we reconsidered a less hindered *E*-alkenyl triflate (Table 1, entry 6), which was synthesized from the appropriate alkenyl iodonium salt, using Gaunt's procedure.[16] Submitting this reagent and trisubstituted alkenol **2a** to Pd(0) and a chiral pyridine oxazoline ligand resulted in the formation of desired γ-substituted alkenylated carbonyl product **3a** in 45% yield and 88:12 enantiomeric ratio (er). Surprisingly, approximately 20% yield of the diene product was also observed. We surmised that the diene byproduct in this case may arise from bimetallic transmetallation between two palladium alkenyl species.[17] To prevent such a process, excess alkenol was used and further optimization of the solvent, concentration, and chiral PyrOx ligand culminated in the formation of the desired γ-alkenylated carbonyl product in high yield and enantioselectivity (Table 1, entry 7). Of particular note, a more electrophilic catalyst is introduced, replacing the CF_3 with NO_2 on the pyridine moiety, which leads to significantly higher yields. Presumably, this change enhances both the binding of the hindered alkene and rates of migratory insertion.[18]

Using these optimized conditions, the scope of the alkenyl electrophile was evaluated. A wide variety of β-substituted alkenyl triflates were synthesized and reacted with acyclic trisubstituted alkenol **2a** under the optimal conditions. Electron-rich and poor

Table 2. Scope of alkenyl triflate in the redox-relay Heck asymmetric alkenylation of trisubstituted alkenol.



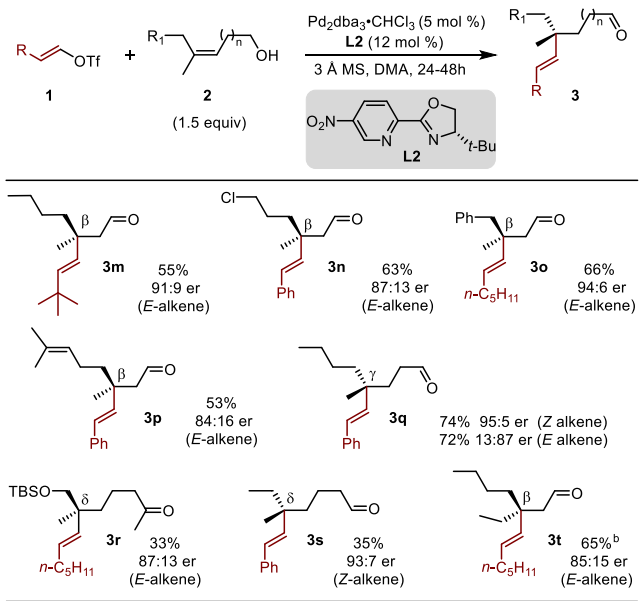
Yields are reported as an average of two parallel experiments. Enantioselectivity determined by SFC equipped with a chiral column. Reaction performed on 0.5 mmol scale. Absolute configuration determined to be *(R)* for a synthetic derivative of **3i** arising from the (*Z*)-alkene. All other products were assigned by analogy.

styrenyl triflates (**3a**-**3d**) furnished the desired γ-alkenylated carbonyl products in good yields and high enantioselectivity. Simple alkyl substituted alkenyl triflates **1e** and **1f** provided the desired compounds **3e** and **3f** in excellent enantiomeric ratio of 97:3 and 75% and 79% yield, respectively. Notably, use of (*E*)-stereodefined alkenyl triflates is required since, a mixture of (*E*)- and (*Z*)-**1f** (ratio of *E*/*Z* was 1:2.2) provides only 32% yield of **3f** with a reduction of er from 97:3 to 92:8. This suggests that the migratory insertion is slowed with (*Z*)-alkenyl triflates due to increased steric effects. Next, larger substrates such as β-disubstituted alkenyl triflates were subjected to this reaction. Although, yields of the desired γ-alkenylated products are generally good, the enantioselectivity observed was highly dependent on the nature of the coupling partner. For example, product **3g** containing a β-disubstituted diphenyl group was formed in excellent yield and significantly reduced er (67:33). Similarly, the formation of **3h** follows the same trend, good yield and a modest 88:12 er. However, a reduction in size of the alkenyl coupling partner to a β-disubstituted dimethyl group, proved to be an excellent reagent with an enhanced er of 94:6 (**3i**). Linear alkenyl groups containing simple aliphatic substituents including a primary alkyl halide (**3j**-**3l**) are viable reagents especially in terms of enantioselectivity albeit the incorporation of a remote arene (**3j**) does cause a reduction in yield.

To explore the limits of the alkenol counterpart in this enantioselective alkenylation of trisubstituted alkenols, various (*E*)- and (*Z*)-stereodefined alkenols were synthesized and subjected to the Heck

conditions with a range of alkenyl triflates. The (*E*)-allylic trisubstituted alkenols gave the desired product in moderate to good yields (**3m**-**3o**). While **3o** was formed in good enantiomeric ratio of 94:6, **3m** and **3n** showed slightly lower er of 91:9 and 87:13 respectively. Additionally, geraniol underwent migratory insertion at the allylic position to provide **3p** in moderate yield but an 84:16 er. These results collectively suggest that the enantioselectivity is not only affected by the nature of the alkenyl triflate, but also mitigated by the stereochemistry of the alkenol substrate. To probe this, (*E*)- and (*Z*)-4-methyloct-3-en-1-ol (**2q**) were subjected to the reaction with styrenyl triflate **1a**, providing **3q** in high yields. However, reaction of (*Z*)-alkenol led to aldehyde **3q** in significantly higher er (95:5 as compared to 13:87 for (*E*)-alkene). This suggests that (*Z*)-alkenols are superior to their (*E*)-counterparts. An alkene bearing another oxygen substituent and having a secondary alcohol is also tolerable, enabling the delivery of alkenyl group to a more remote δ position with respect to the carbonyl (**3r**). A bis-homoallylic alcohol gave the desired δ-alkenylated product **3s** in good er, albeit in modest yield. Lastly, a more demanding trisubstituted alkenol bearing butyl and ethyl substituents required slightly higher catalyst loading and reaction times to provide the aldehyde **3t** in 65% yield and a moderate enantiomeric ratio.

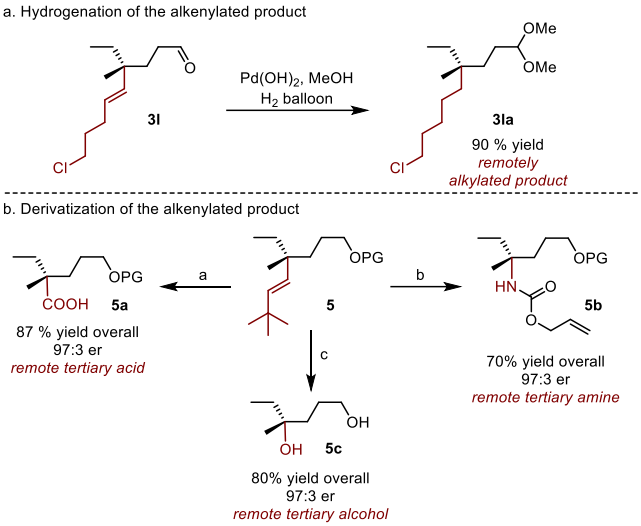
Table 3. Evaluation of trisubstituted alkenols



[a] Yields are reported as an average of two parallel experiments. Enantioselectivity determined by SFC or GC equipped with a chiral column. Reaction performed on 0.25 mmol scale. [b] 7.5 mol % of Pd_2dba_3•$CHCl_3$, 16 mol % **L2**, 2 equivalents of alkenol added and the reaction stirred for 56 hours.

To take advantage of the alkenyl functional group in this unique transformation, the resulting products were processed to various attractive building blocks. As envisioned, this alkenylation reaction can be a surrogate for the long-standing challenge of intermolecular enantioselective alkyl Heck reactions as showcased by a hydrogenation of **3l** to furnish **3la** in excellent yield (Scheme 1a). Indeed, products of this sort would be difficult to access using traditional strategies. Additionally, the aldehyde group in product **3f** was reduced to the alcohol and appropriately protected to provide **5** (not shown). Ozonolysis of alkene **5** followed by treatment with the Jones reagent provided enantiomerically enriched acid **5a** (Scheme 1b).[5c] This carboxylic acid was subjected to a Curtius rearrangement[19] yielding an isocyanate, which was trapped insitu by the addition of allyl alcohol to provide chiral tertiary protected amine **5b**. Similarly, ozonolysis of **5**, followed by treatment with triphenylphosphine furnished tertiary aldehyde (not shown), and subsequent Baeyer-Villiger oxidation[20] and hydrolysis of the formate ester yielded chiral tertiary alcohol **5c**. The enantioselectivity was effectively preserved in all of these functional group transformations. Thus, from a simple alkenylated product, one can access a diverse range of remote tertiary functionalized alkyl products.[21]

Scheme 1. Derivatization of alkenylated products.



a) **5** (PG = TBDPS), acetone, –78 °C, O_3, CrO_3. **b**) i. **5** (PG = OTBDPS), acetone, –78 °C, O_3, CrO_3. ii. DPPA, Et_3N, toluene, reflux, 12 h, then add allyl alcohol (5 equiv), 80 °C. **c**) i. **5** (PG = 3,5-dinitrobenzoicacid ester), dichloromethane, O_3, –78 °C, PPh_3, ii. *m*-CPBA, dichloromethane, KOH.

In conclusion, we have reported a new method to form quaternary chiral centers remotely from a carbonyl in high enantioselectivity. This process utilizes simple to access starting materials, a conveniently prepared chiral ligand, and is performed under mild conditions. High enantioselectivity is predicated on using a (*Z*)-trisubstituted alkene and a relatively unhindered alkenyl triflate. The olefin introduced in the products offers a flexible handle for further synthetic manipulations as highlighted by the transformation of the alkene to an alcohol, protected amine, and a carboxylic acid – all remote from the carbonyl in the product. Finally, hydrogenation of the alkenylated products provides access to a quaternary center bearing four unique alkyl groups. Further efforts are focused on expanding the scope to other coupling partners as well as applying this method in synthetic endeavors.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for new compounds. 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 interests.

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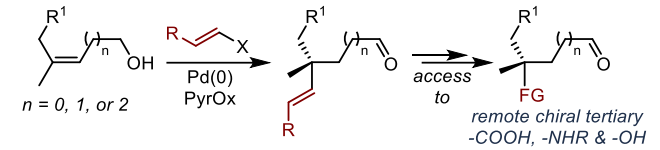
TOC Graphic



remote chiral tertiary
-COOH, -NHR & -OH
and
alkyl Heck-type products

- *Trisubstituted alkene Heck*
- *Remote quaternary alkenyl stereocenter*