

Synthesis of Highly Functionalized Tri- and Tetrasubstituted Alkenes via Pd-Catalyzed 1,2-Hydrovinylation of Terminal 1,3-Dienes

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S Supporting Information

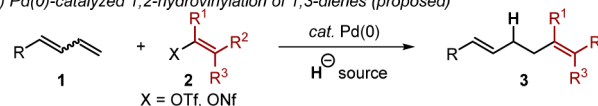
ABSTRACT: An efficient method for the construction of Csp²–Csp³ bond in a regio- and stereoselective fashion involving 1,3-terminal dienes, enol triflates/nonaflates, and sodium formate under Pd(0)-catalysis is described. The three component assembly allows trapping of a π -allyl intermediate, after the initial migratory insertion of the diene, by a hydride source that leads to structurally complex and synthetically challenging tri- and tetrasubstituted alkene building blocks.

Tri- and tetrasubstituted alkenes are important synthetic targets since they are a common structural motifs in many biologically active molecules^{1,2} and natural products^{3–5} as well as substrates for complexity generating reactions.^{6–12} However, the synthesis of such alkenes in a well-defined manner remains a great challenge. As our group is interested in accessing substrates of this type in another context,¹³ we reflected on the methods available to access tri- and tetrasubstituted alkenes. The most general methods, which we have deployed, involve carbometalation of alkynes using pyrophoric organometallic reagents (i.e., trialkylaluminum, lithium dialkylcopper, and alkyl lithium), followed by trapping of the resultant alkenyl–metal bond with various different processes such as addition of electrophiles, cross-coupling, or oxidative coupling.¹⁴ Despite significant advances in these protocols, the reactions often suffer from major drawbacks limiting their utility including poor functional group tolerance as a result of the use of highly nucleophilic organometallic reagents and difficult to control regioselective carbometalation of disubstituted alkynes.^{14,15}

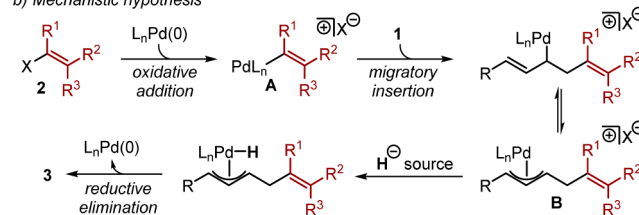
On the basis of our desire to access more diverse, stereo-defined alkenes, we envisioned an alternative strategy for their synthesis by performing a Pd-catalyzed 1,2-hydrovinylation of a 1,3-diene (Scheme 1a) with a vinyl electrophile. Recent progress in the synthesis of well-defined vinyl electrophiles, mainly the access to triflate derivatives, may allow for a compellingly broad scope.^{16–19} Specifically, we hypothesized that initiating catalysis by oxidative addition of a well-defined vinyl triflate **2** would allow for subsequent migratory insertion of a 1,3-diene **1** into the cationic vinyl Pd-intermediate **A** to yield a π -allyl intermediate **B** (Scheme 1b). Introduction of a hydride source would allow for reduction of this intermediate, likely site-selectivity based on an incorporated steric and electronic bias on the 1,3-diene.^{20,21a} By utilizing a cationic Pd-system, migratory insertion should be significantly faster than direct reduction of **A** with a hydride^{21,22} or β -hydride elimination²³ in the case of acyclic electrophiles to form allenes. The reductive coupling of a vinyl triflate with a

Scheme 1. Proposed Pd(0)-Catalyzed 1,2-Hydrovinylation of 1,3-Dienes with Enol Triflates/Nonaflates and a Hydride Source

a) Pd(0)-catalyzed 1,2-hydrovinylation of 1,3-dienes (proposed)



b) Mechanistic hypothesis

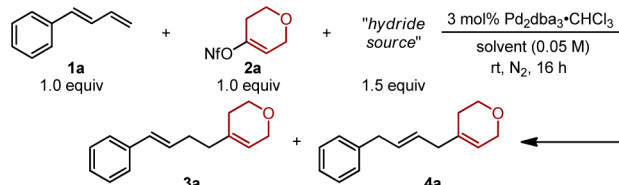


diene could be considered a reductive Heck-type reaction installing a Csp²–Csp³ bond. It should be noted that in practice reductive intermolecular Heck-type reactions have been limited to norbornene-like alkenes preventing the complexity incurred through β -hydrogen elimination processes. Furthermore, reductive Heck approaches using vinyl electrophiles have mainly been explored in an intramolecular fashion.^{24,25} Herein, we present a Pd-catalyzed intermolecular 1,2-hydrovinylation of 1,3-dienes²⁶ and vinyl triflates with sodium formate as the reductant, wherein mild conditions are applied to the synthesis of a vast array of well-defined, highly functionalized tri- and tetrasubstituted alkenes.

Optimization was initiated using a simplified goal of accessing trisubstituted alkenes by employing a cyclic vinyl electrophile coupling partner. The reaction system of *trans*-1-phenyl-1,3-butadiene (**1a**), 3,6-dihydro-2H-pyran-4-yl nonaflate (**2a**), and ammonium formate was subjected to conditions similar to those reported by our group for the vinylarylation of dienes (Table 1, entry 1).^{21a} Low yield of the hydrovinylation product was obtained with 47% of the enol nonaflate remaining. The probable reason for the higher levels of conversion as compared to the product yield could be attributed to the direct reduction of **2a**. Evaluation of various other metal formates revealed that simply employing sodium formate, which is sparingly soluble, afforded the product in good yield and excellent selectivity (entries 2–4). Introducing silanes gave the desired product in modest yields and lower regioselectivity (entries 5 and 6). Therefore, sodium formate was selected for further optimization due to the

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Table 1. Optimization for the 1,2-Hydrovinylation of 1,3-Diene with a Cyclic Enol Nonaflate


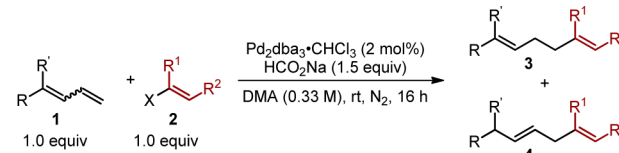
entry	solvent	hydride source	% conv. 2a ^a	% yield (3a/4a) ^{a,b}
1	DMA	HCO ₂ NH ₄	53	5 (nd)
2 ^c	DMA	(HCO ₂) ₂ Zn	69	52 (15.4:1)
3	DMA	HCO ₂ Li·H ₂ O	57	46 (16:1)
4	DMA	HCO ₂ Na	>95	62 (16:1)
5	DMA	Et ₃ SiH	93	59 (9.6:1)
6	DMA	(EtO) ₃ SiH	84	27 (8.8:1)
7	THF	HCO ₂ Na	28	4 (nd)
8	<i>t</i> -AmOH	HCO ₂ Na	48	10 (>20:1)
9 ^d	DMA	HCO ₂ Na	>95	79 (15:1)
10 ^{d,e}	DMA	HCO ₂ Na	>95	78 (15:1)

^aDetermined by NMR using an internal standard on 0.2 mmol scale. ^bYields are a combination of both 3a and 4a. ^cReaction performed with 0.75 equiv of zinc formate. ^dReaction performed in a concentration of 0.33 M 2a. ^eReaction performed using 2 mol % Pd₂dba₃·CHCl₃. Reaction performed on 0.5 mmol scale gave 75% yield (both 3a and 4a) and 15:1 regioselectivity (3a/4a).

promising results and clear economic advantages. Changing the solvents to either ethereal or alcoholic solvents, such as THF and *tert*-amyl alcohol, afforded lower yields of 3a (entries 7 and 8). Further improvement was obtained by increasing the concentration of 2a to 0.33 M (entry 9). Comparable results were obtained when the catalyst loading was reduced to 2 mol % of Pd₂dba₃·CHCl₃ (entry 10).

The scope of cyclic enol nonaflates and triflates with various aryl dienes were explored (Table 2). Besides the dihydropyran derived nonaflate used to optimize the reaction (3a), various protected tetrahydropyridine nonaflates gave the desired product in good yields and generally high selectivity for the styrenyl products (3b–3d). Six-membered carbocyclic electrophiles with substitution at the 4-position, such as a phenyl (3e) and ketal (3f) group, were equally compatible. Additionally, simple cyclic enol nonaflates with different ring sizes were successfully incorporated (3g and 3h). Next, we turned our attention toward the functionalization of natural product derived vinyl triflates. For example, enol triflates obtained from (1S)-(-)-camphor and cholesterol yielded 3i and 3j, respectively, in excellent yields and selectivity. Furthermore, the 1,1-disubstituted alkene in a (+)-nootkatone derivative remained intact and gave the 1,2-hydrovinylation product 3k in 86% yield with good site selectivity. The insensitivity of this reaction to the nature of the vinyl electrophile was highlighted by the use of a sterically hindered and biologically relevant estrone derivative, which gave the desired compound 3l in 70% yield.

To explore the effect of the diene coupling partner, three aliphatic 1,3-dienes were subjected to the reaction. A simple cyclohexyl-substituted substrate performed well in the reaction with high site selectivity in the reduction resulting in >20:1 of the 1,2-hydrovinylation product (3m). However, using a substrate derived from 4,4-dimethyl-1-vinylcyclohexene gave modest site selectivity and yield (3n). The origin of this observation may be attributed to the preferential formation of thermodynamically more stable internal alkene product. Finally, a geraniol derived

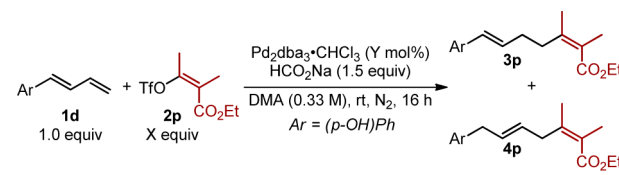
Table 2. Scope of the Pd(0)-Catalyzed 1,2-Hydrovinylation of 1,3-Dienes with Cyclic Enol Electrophiles


entry	Yield (%)	Ratio (3:4)
3a	75%	(15:1) ^a
3b	82%	(10:1)
3c	64%	(9.1:1)
R = (<i>p</i> -OMe)Ph		
3d	78%	(13.6:1)
3e	69%	(10.8:1)
3f	66%	(12:1)
R = (<i>p</i> -OH)Ph		
3g	74%	(12.6:1)
3h	67%	(9.7:1)
3i	81%	(>20:1)
R = (1S)-(-)-camphor		
3j	84%	(17.6:1)
R = cholesterol		
3k	86%	(11.5:1)
R = (+)-nootkatone		
3l	70%	(>20:1)
R = estrone		
Y = Boc		
3m	61%	(>20:1)
3n	58%	(5.4:1)
3o	51%	(1.8:1)

^aThe bracket represents the ratios of 3:4. All yields are a combination of both 3 and 4. All yields represent an average of two experiments. Note: For 3a–3h and 3m–3o, enol nonaflates were used; for 3i–3l, enol triflates were used.

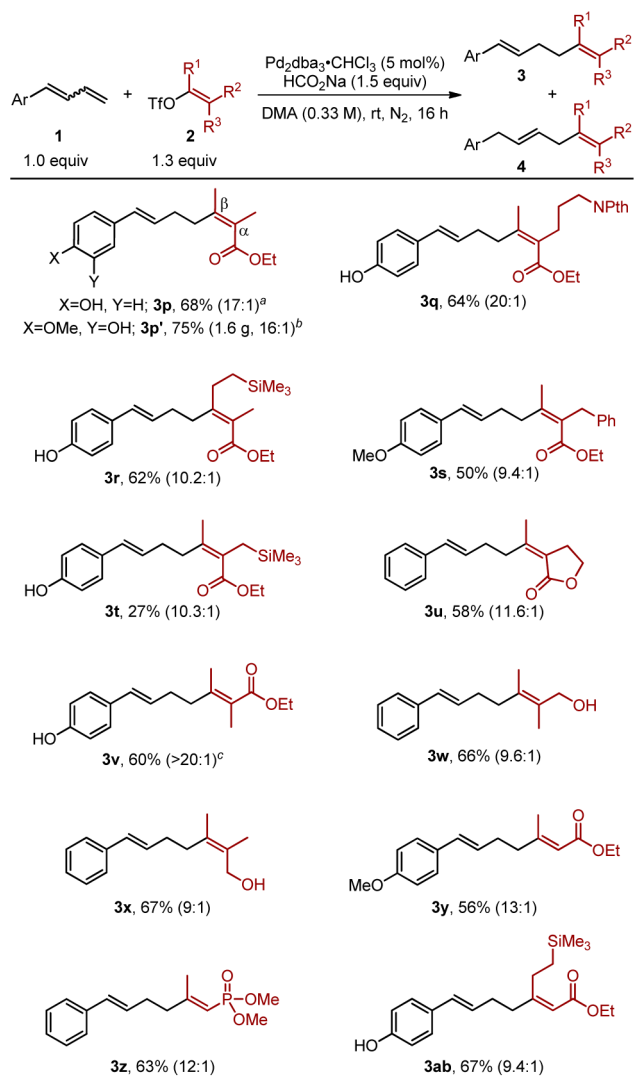
diene lead to significantly lower site selectivity (3o). While the cause of this latter result is unclear at this time, a general observation is that a steric bias is required for high selectivity.

After proof of concept, we wished to expand the system to synthetically more diverse electrophiles by investigating the use of acyclic enol triflates derived from β -keto esters (Table 3). The stereoselective synthesis of these enol triflates has been

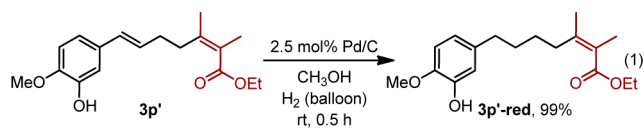
Table 3. Optimization for the 1,2-Hydrovinylation of 1,3-Diene with β -Keto Ester Derived Enol Triflate


entry	X	Y	% conv. 1d	% yield (3p/4p) ^a
1	1.0	2	80	45 (>20:1)
2	1.3	2	83	55 (>20:1)
3	1.3	5	95	68 (17:1)

^aDetermined by NMR using an internal standard on 0.2 mmol scale. Yields are a combination of both 3p and 4p.

Table 4. Scope of the Pd(0)-Catalyzed 1,2-Hydrovinylation of 1,3-Dienes with β -Keto Ester Derived Enol Triflates

^aThe bracket represents the ratios of 3/4. All yields are a combination of both 3 and 4. All yields represent an average of two experiments. ^bThe reaction was performed on 7.0 mmol scale and 1.0 M conc. of diene. ^cMixture of (*E*) and (*Z*) isomers were observed (3v/3p', 6.6:1).



extensively reported.^{16–18} Recently, Frantz and co-workers have developed a practical approach that allows access to di- and trisubstituted enol triflates in a highly stereodefined and scalable fashion.¹⁹ On the basis of the effective formation of 3l from the oxidative addition of a sterically congested vinyl electrophile, we were hopeful that the use of this type of triflate to access tetrasubstituted alkenes would be successful. However, the use of acyclic electrophiles of this sort was anticipated to be particularly challenging, especially under Pd(0)-catalysis, since they have the inherent ability to undergo β -hydride elimination after the initial oxidative addition, to form allenenes as demonstrated in the synthesis of various useful compounds such as dienes,²⁷ heteroaromatics,²⁸ and chiral allenenes.²³ Also, E₂ elimination of acyclic

enol triflates in the presence of a base is an established method for alkynyl ester synthesis.²⁹ Therefore, we were initially concerned that these issues may impede our ability to develop reactions using these reagents.

Submitting (*Z*)-enol triflate (2p) to the previous reaction conditions furnished the desired (*Z*)-tetrasubstituted alkene 3p in 45% yield without measurable degradation of alkene stereochemical integrity (Table 3, entry 1). Slight adjustments to the reaction conditions, such as increasing the catalyst loading and stoichiometry of the vinyl triflate, improved the yield (entries 2 and 3). We hypothesize that the mild reaction conditions employed, such as the absence of basic coordinating ligands and strong exogenous bases, leads to a faster rate of migratory insertion relative to β -hydride elimination avoiding previously reported deleterious processes.

As many configurationally defined (*Z*)-enol triflates are readily synthesized from cheap and easily accessible β -keto esters, the scope is broad (Table 4). The reaction was successfully scaled to 7.0 mmol (3p') allowing access to these compounds on a gram scale. Installation of various functional groups, which provide handles for further elaboration, is highlighted by the successful incorporation of an *N*-phthalimide protected amine (3q) and an alkyl silane at the β -position (3r). Substitution at the α -position, such as a benzyl group (3s) and an alkyl silane (3t), underwent hydrovinylation albeit in lower yields. An enol triflate bearing a lactone reacted smoothly under the reaction conditions (3u). Unfortunately, the reaction with (*E*)-enol triflate yielded a mixture of (*E*)- and (*Z*)-tetrasubstituted alkenes (3v). The reactivity difference between (*E*)- and (*Z*)-enol triflates has previously been observed, but the exact reason for this result is unclear at this time.²⁸ However, the reaction of the reduced variant produced by treatment with DIBAL-H¹⁶ lead to (*E*)-tetrasubstituted alkene (3w) with no loss of stereochemical integrity. Similarly, the use of (*Z*)-hydroxymethylene enol triflate gave 67% yield of a single stereoisomer as determined by comparing the ¹H and ¹³C NMR of both the stereoisomers (i.e., 3w and 3x), whereas the (*E*)- and (*Z*)-stereochemistry was confirmed using NOE experiments. Conversely, (*E*)-enol triflates containing hydrogen at the α -position afforded (*E*)-trisubstituted alkenes as illustrated in the successful synthesis of 3y–3ab. Finally, the disubstituted alkene present in 3p' can be reduced selectively in the presence of the electron-deficient tetrasubstituted alkene using 2.5 mol % of Pd/C to give quantitative yield (eq 1). Thus, this reductive Heck approach can also be considered as a two-step alkylation of stereodefined trisubstituted enol triflates.

In conclusion, we have developed a simple and mild reductive Heck approach for the coupling of terminal 1,3-dienes with cyclic as well as acyclic enol triflates and nonaflates. This method allows rapid access to a variety of structurally diverse and functionalized alkenes including stereodefined (*E*)- and (*Z*)-tri- and tetrasubstituted alkenes starting from easily accessible β -keto ester derived enol triflates. These alkenes will be versatile building blocks for applications in enantioselective relay Heck reactions under study in our lab.¹³ Additional studies are also directed toward the expansion of this reductive Heck approach to other dienes and terminal alkenes.

■ 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>.

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Notes

The authors declare no competing financial interest.

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