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Unified Approach to Substituted Allenoates via Pd-Catalyzed β-Hydride Elimination of (*E*)-Enol Triflates

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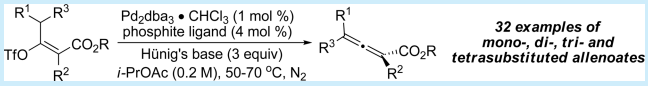
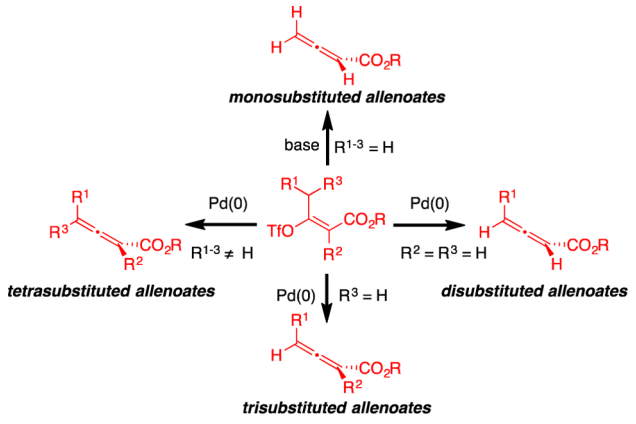
Supporting Information

ABSTRACT: A robust synthesis of allenoates via a Pd-catalyzed β-hydride elimination of (*E*)-enol triflates is presented. Salient features of this method include low catalyst loadings, mild reaction conditions, and the ability to access all four patterns of substituted allenoates from a single substrate class.



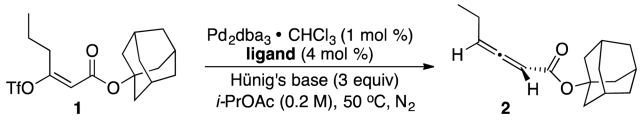
Allenes have become the bricks and mortar of several modern synthetic strategies to build complexity rapidly from relatively simple starting materials.[1,2] In this regard, the manipulation of two adjacent π-systems differentiated by orthogonality has led to elegant methods that allow selective reaction with one C=C bond over the other with exquisite control. In many cases, this selectivity in the allene is based on the electronic bias of one π-system (i.e., electron-poor or electron-rich) over the other that dictates chemoselectivity between two neighboring olefins. Allenoates are perhaps the most exploited in this context.[3] Countless methods have emerged utilizing allenoates that take advantage of the differential reactivity of the conjugated electron-deficient C=C bond compared to its next-door neighbor.[4] Yet, despite cementing their place in organic architecture, a unifying synthetic approach to access four different substitution patterns of allenoates (i.e., mono-, di-, tri-, and tetrasubstituted) from a single substrate class has not emerged.[5] We report here an approach to substituted allenoates from (*E*)-enol triflates using a simple Pd(0)/phosphite catalytic system that addresses this unmet synthetic need (Scheme 1).

Scheme 1. Unified Approach to Substituted Allenoates from (*E*)-Enol Triflates



We began our investigations with (*E*)-enol triflate **1** to serve as a model substrate for the synthesis of disubstituted allenoates (Table 1). Our initial experiments were guided by our previous success in the asymmetric synthesis of disubstituted allenoates via a Pd-catalyzed asymmetric β-hydride elimination using newly designed chiral phosphite ligands.[6] While these ligands worked well to access enantioenriched disubstituted allenoates, they completely failed with tri- and tetrasubstituted substrates. Furthermore, racemic disubstituted allenoates have synthetic utility in their own right, prompting us to identify simple, commercially available, achiral phosphite ligands to access this product class.[7] A selected survey of our results is presented in Table 1. We were pleased to find that as little as 1 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 4 mol % of $P(O^iPr)_3$ with excess Hünig's base (3 equiv) in isopropyl acetate were effective in providing the corresponding allenoate **2** in 94% HPLC assay yield (entry 2).

Table 1. Ligand Screen for Disubstituted Allenoates



entry[a]	ligand	assay yield (%) of **2**[b]
1	$P(OEt)_3$	84 (65)[c]
2	$P(O^iPr)_3$	94 (75)[c]
3	$P(OPh)_3$	78
4	$P(OC_6H_4\text{-}3,5\text{-}tBu)_3$	13
5	$P(OC_6H_4\text{-}4\text{-}Cl)_3$	13
6	$P(OC_6H_4\text{-}3\text{-}OMe)_3$	48

[a]Reactions were performed on a 1 mmol scale. [b]Determined by quantitative HPLC analysis. [c]Isolated yields.

The identification of robust reaction conditions led to the expansion of the substrate scope of this method (Figure 1). A wide variety of functional groups are tolerated under the

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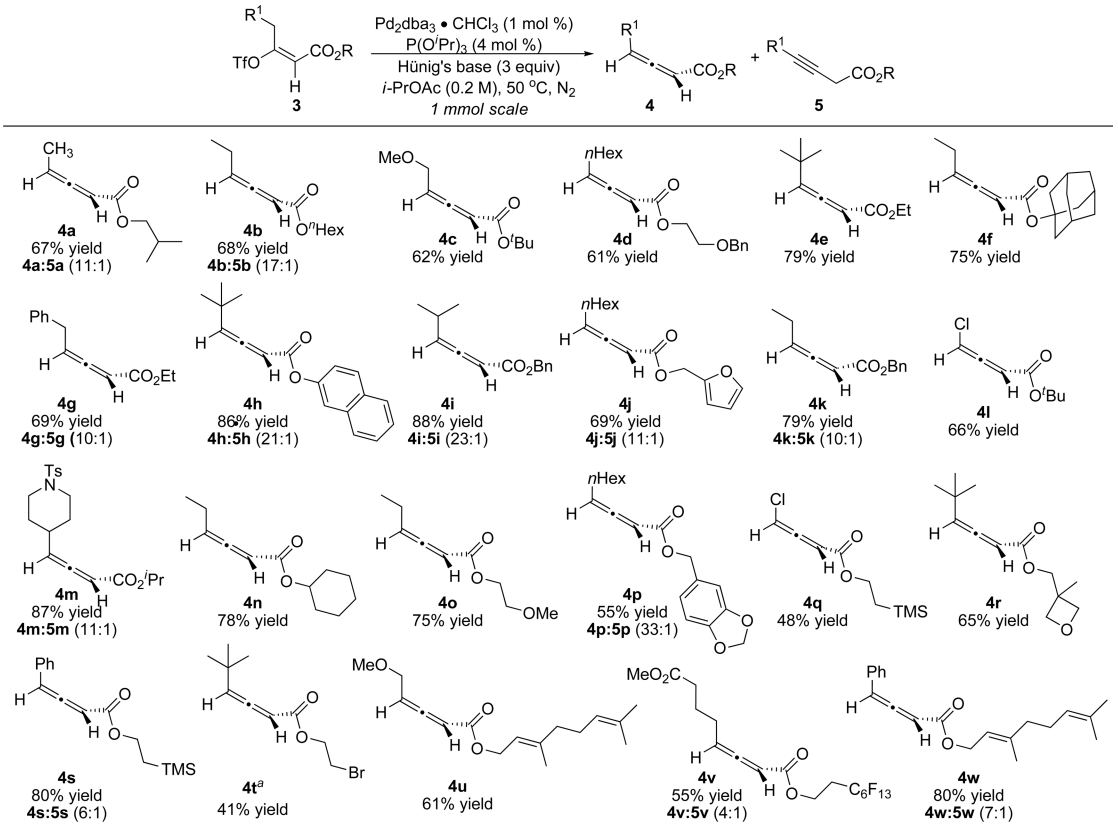


[a] 2 mol % $Pd_2dba_3 \bullet CHCl_3$ and 8 mol % $P(O^iPr)_3$ was used

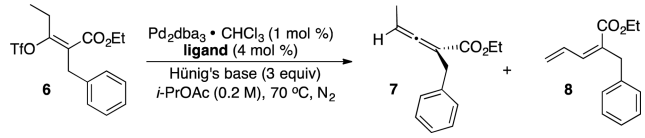
Figure 1. Substrate scope for the synthesis of disubstituted allenoates. Yields are isolated and represent an average of two experiments.

reaction conditions, including primary bromides (**4t**), silanes (**4q** and **4s**), ethers (**4c**, **4o**, and **4r**), and tosylated amines (**4m**), providing good yields of the corresponding allenoates. We would particularly like to highlight the ability to access chlorinated allenoates (as in **4l** and **4q**) that are otherwise difficult to obtain.[8] However, in a few of our examples, an inseparable mixture of the allenoate and the corresponding isomeric 3-alkynoate **5** is obtained. The amount of this byproduct appears dependent on the overall kinetics of the reaction, with those substrates requiring longer reaction times (>12 h) exhibiting higher amounts of **5**.

We next turned our attention to the application of this approach to the synthesis of trisubstituted allenoates using (*E*)-enol triflate **6**. Interestingly, the optimum ligand for disubstituted allenoates, $P(O^iPr)_3$, proved ineffective with trisubstituted substrates, giving a low overall yield of both the allenoate **7** and isomeric 1,3-dienoate **8** (Table 2, entry 4). Despite this, a quick screen revealed $P(OPh)_3$ to be superior with respect to yield and product selectivity (Table 2, entry 2) at slightly elevated temperatures (70 °C vs 50 °C). At this stage of development, the exact nature of this subtle ligand dependence is not clear, but efforts are ongoing to understand this phenomenon.

With the newly optimized conditions for trisubstituted allenoates, we probed the preliminary scope with a selected set of appropriately substituted (*E*)-enol triflates **9** (Figure 2). Additional functional group tolerance is demonstrated with this class of substrates, including internal alkynes (**10d**) and olefins (**10e**).

Table 2. Ligand Screen for Trisubstituted Allenoates



entry[a]	ligand	isolated yield (%) of 7	7/8 ratio
1	$P(OEt)_3$	58	8:1
2	$P(OPh)_3$	56	N/A
3	$P(OBu)_3$	25	12:1
4	$P(O^iPr)_3$	44	1:1
5	$P(O\text{-}o\text{-}tol)_3$	52	N/A
6[b]	$P(OC_6H_4\text{-}2,4\text{-}t\text{-}Bu)_3)_3$	0	N/A

[a]Reactions were performed on a 1 mmol scale. [b]No conversion of the starting triflate was observed.

We report several highlights of this method as shown in Scheme 2. First, we have observed that, with (*E*)-enol triflates such as **11**, monosubstituted allenoates are obtained by simple base-mediated elimination of triflic acid without the need of a Pd-catalyst.[9] In addition, tetrasubstituted allenoates are accessible in excellent yield, as demonstrated with (*E*)-enol triflate **13**, making this the first method to access all four substitution patterns of allenoates from a single substrate class. We have also demonstrated this method on moderate scale (15 mmol) where the isolated yield parallels that obtained on a 1 mmol scale (see Figure 1).

Finally, Scheme 3 provides the known limitations of our method. As in our previous work,[6] we observe that (*Z*)-enol triflates fail to react under these reaction conditions. In

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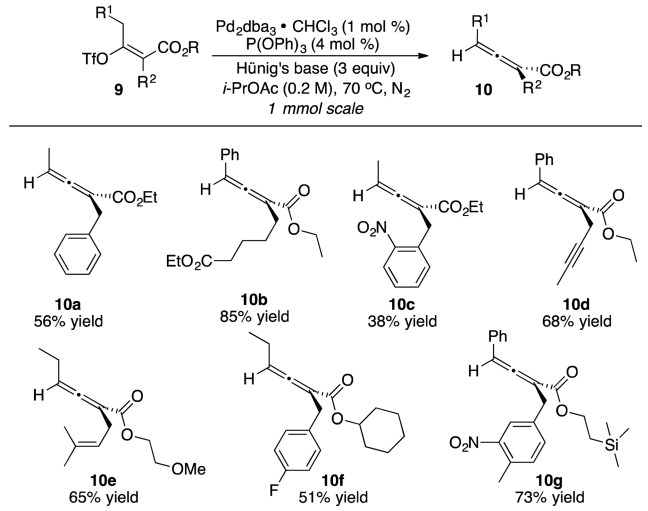
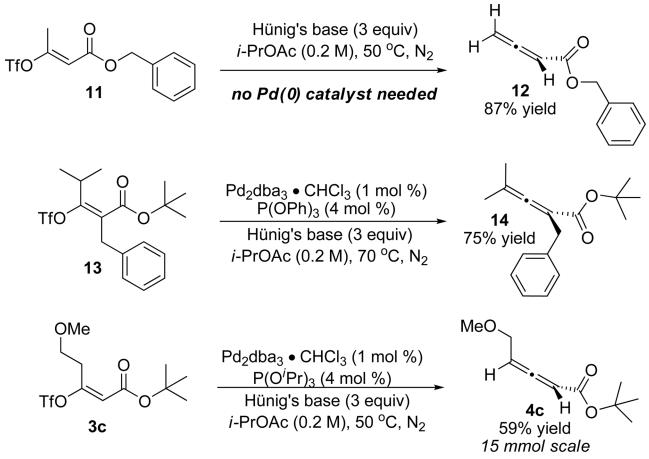
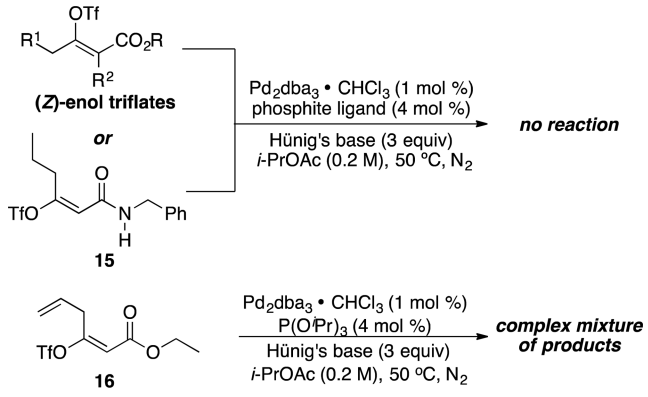


Figure 2. Substrate scope for the synthesis of trisubstituted allenoates. Yields are isolated and represent an average of two experiments.

Scheme 2. Highlights of the Method



Scheme 3. Limitations of the Method



addition, the corresponding (*E*)-amide triflates (as in **15**) also fail to yield any of the desired allenoates. Furthermore, we have found that terminal olefins (as in **16**) appear to be reactive under these Heck-type reaction conditions to give a complex mixture of unsaturated products.

In conclusion, we have developed a general method to access mono-, di-, tri-, and tetrasubstituted allenoates via a Pd-catalyzed β-hydride elimination of (*E*)-enol triflates in good yields with excellent functional group tolerance. Current efforts are focused on a deeper mechanistic understanding of this chemistry to elucidate the subtle ligand dependence between substrate classes and the lack of reactivity of others.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02736.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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