Organic LETTERS

Letter

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Palladium-Catalyzed Synthesis of Alkynes via a Tandem Decarboxylation/Elimination of (*E*)-Enol Triflates

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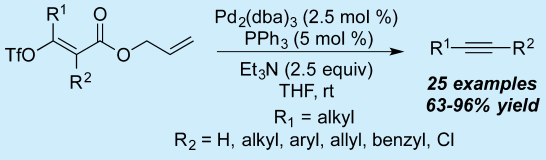
Supporting Information

ABSTRACT: A mild catalytic synthesis of alkynes via a tandem Pd-catalyzed decarboxylation/elimination of enol triflates is described. Key attributes of the method include readily available starting materials, broad functional group tolerance, and the ability to access terminal, internal, and halogenated alkynes. The preliminary scope of the reaction is demonstrated on 25 different examples with yields ranging from 63% to 96%.

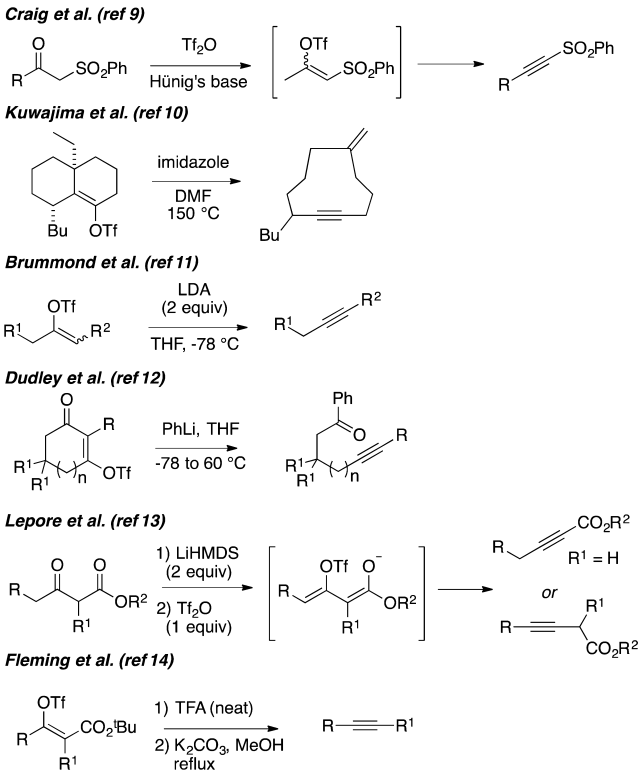


Alkynes represent one of the most fundamental building blocks in synthetic chemistry. The ubiquitous roles they play as substrates in various catalytic methodologies, as key pharmacophores in biologically active molecules, in bioconjugation, and in material science have solidified this functional group as an indispensable tool in the synthetic chemist's toolbox.[1,2] In response, the synthetic community has devoted significant effort to devise new approaches to alkynes with an ever-evolving goal of practicality and robustness pertinent to both academic and industrial applications.

Despite these efforts, gaps remain in the syntheses of alkynes, in particular with respect to methodologies capable of accessing multiple classes of alkynes (i.e., terminal, internal, halogenated) from a common precursor that would complement more traditional unilateral approaches. Perhaps more importantly, the discovery and development of catalytic methodologies that obviate the requirement of stoichiometric strong bases commonly employed in alkyne syntheses would broaden functional group tolerance and expand application to more structurally complex alkynes. Nonetheless, progress has been made in this area, particularly in the synthesis of internal alkynes where modern catalytic cross-coupling strategies between terminal alkynes and various partners have expanded the scope beyond the classical Sonagashira reaction.[3] This includes the recent seminal work of Fu,[4] Li,[5] Yu,[6] Wang,[7] and others[8] where nontraditional transition-metal-catalyzed modalities have allowed access to a wide array of functionalized internal alkynes. The only caveat of these approaches is the requirement of the corresponding starting terminal alkyne that may be nontrivial to acquire synthetically.

One substrate class that has been exploited successfully toward the synthesis of alkynes has been vinyl and/or enol triflates (Scheme 1). Early work by Craig demonstrated the feasibility of base-mediated elimination of triflic acid from *in situ* generated vinyl triflates as a convenient approach to alkynyl sulfones.[9] This was subsequently followed by work from the groups of Kuwajima,[10] Brummond,[11] Dudley,[12] Lepore,[13] and Fleming[14] where the elimination of triflic acid from either vinyl or enol triflates led to the corresponding alkynes. In spite of these successes, a catalytic elimination of triflic acid (or its equivalent) from either vinyl or enol triflates has yet to be reported.

Scheme 1. Vinyl/Enol Triflates as Alkyne Precursors



Our group has exploited enol triflates[15] in a number of Pd-catalyzed transformations to obtain 1,3-dienoates,[16] substituted pyrazoles,[17] and enantioenriched chiral allenes.[18] During the

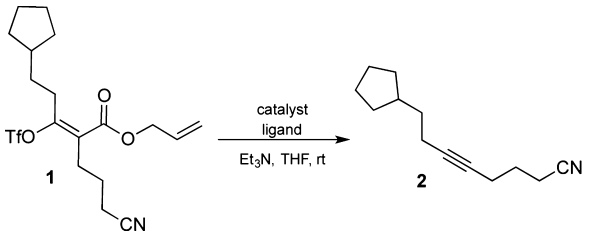
Received: June 30, 2016

DOI: 10.1021/acs.orglett.6b01904
Org. Lett. XXXX, XXX, XXX−XXX

course of these studies, we consistently found that enol triflates containing an allylic ester functionality were incompatible in all of these methodologies. In hindsight, this outcome is not surprising given the multitude of Pd-catalyzed reactions that allylic esters serve as substrates.[19] Upon closer inspection, we were able to determine that enol triflates with allylic esters were undergoing a tandem decarboxylation/elimination sequence to yield the corresponding alkyne. With this knowledge in hand, we set out to optimize this approach as a practical and robust synthesis of alkynes.

Our initial optimization studies utilized (*E*)-enol triflate **1** along with various combinations of Pd(0) sources, phosphorus-based ligands, and triethylamine. The culmination of our efforts is summarized in Table 1. Gratifyingly, we found that several

Table 1. Selected Optimization Studies for the Tandem Pd-Catalyzed Decarboxylation/Elimination of 1 to 2



entry[a]	catalyst (mol %)	ligand (mol %)	time	yield (%)[b]
1	Pd_2dba_3 (2.5)	none	24 h	7
2	none	PPh_3 (5)	24 h	0
3	Pd_2dba_3 (2.5)	PPh_3 (5)	20 min	91
4		PPh_3 (50)	10 min	85
5		P(2-furyl)$_3$ (5)	20 min	9
6		$PPh(Et)_2$ (5)	24 h	39
7		$P(OPh)_3$ (5)	20 min	91
8		dcpb[c] (2.5)	24 h	8
9		dppb[d] (2.5)	24 h	13
10	$Pd(PCy_3)_2$ (5)	–	3 h	92
11	$Pd(PPh_3)_4$ (5)	–	20 min	92
12	$Pd(P^tBu_3)_2$ (5)	–	45 min	92

[a]All reactions were performed at 0.25 M in THF using 2.5 equiv of Et_3N. [b]Isolated yields. [c]dcpb = 2-(dicyclohexylphosphino)biphenyl. [d]dppb = 1,4-bis(diphenylphosphino)butane.

Pd-catalyst systems provide high yields of the corresponding internal alkyne **2**. However, it is important to note that the reaction requires both ligand and a Pd-source to be successful (entries 1 and 2). Interestingly, excess ligand (entry 4) does not seem to inhibit the reaction. We ultimately chose the combination of Pd_2dba_3 (2.5 mol %) and PPh_3 (5 mol %) as our catalyst system of choice (entry 3) for our preliminary substrate scope although we believe other catalysts would be equally effective at promoting this reaction across a broad range of substrates.

Figure 1 highlights the scope of the method in its current state of development for the synthesis of internal alkynes. Overall, isolated yields are generally high with reaction times of less than 1 h in most cases. In addition, the reaction displays high functional group tolerance that includes terminal and internal olefins (as in **6** and **19**), ketones (**14**), acetals (**18**), protected amines (**21**), ethers and esters (**24**).

We also wish to report several highlights as well as limitations of this method. First, the reaction performs equally well on large scale (20 mmol) providing alkyne **2** in 92% yield (Scheme 2). We were also pleased to find that the catalyst loading can be reduced down to 0.05 mol % (using $Pd(PPh_3)_4$) with no detriment to yield (93%) albeit with longer reaction times (70 h). Furthermore, the method is applicable to the synthesis of terminal alkynes but with slightly lower yields due to competing simultaneous Sonogashira cross-coupling with the starting enol triflate. Finally, halogenated terminal alkynes such as **28** can also be accessed in good overall yield.

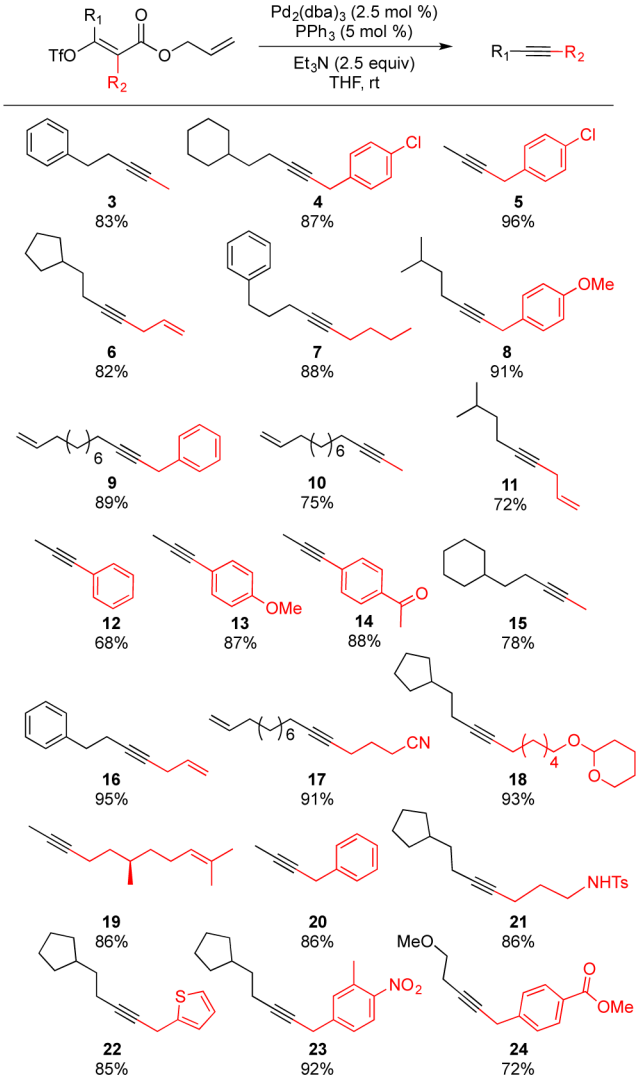
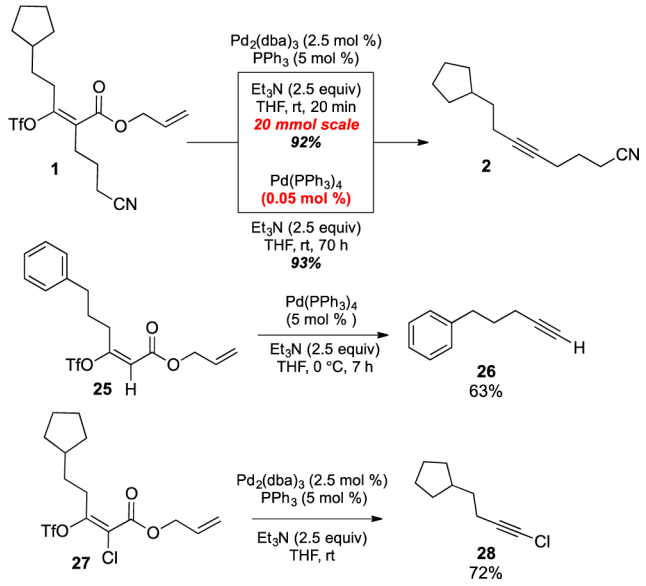


Figure 1. Substrate scope for the Pd-catalyzed decarboxylation/elimination of (*E*)-enol triflates. Isolated yields reported are an average of two separate runs.

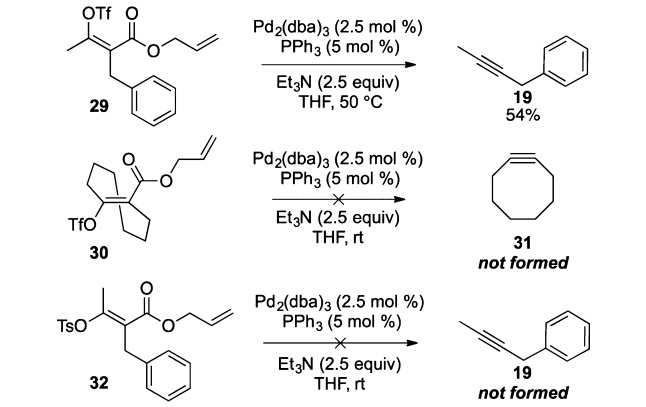
Nonetheless, there are several important limitations that we wish to divulge at this time. The corresponding (*Z*)-enol triflates (such as **29**) do participate in the tandem decarboxylation/elimination to yield alkynes but in much lower yields and at higher temperatures (Scheme 3). We believe this to be a direct reflection of the higher energy barrier associated with the required $E1_{cb}$-type mechanism that is likely occurring with these substrates. In addition, cyclic (*E*)-enol triflates fail to react under our standard conditions to provide cyclic alkynes (i.e., **30** to **31**). Lastly, we have also attempted to utilize (*E*)-enol tosylates,[20] for example **32**, in this chemistry but have failed to identify reaction conditions that would lead to productive formation of alkynes.

DOI: 10.1021/acs.orglett.6b01904
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Highlights of the Method



Scheme 3. Limitations of the Method



In conclusion, we have discovered and developed a Pd-catalyzed tandem decarboxylation/elimination of (*E*)-enol triflates to the corresponding alkynes. Salient features of this method include high functional group tolerance, low catalyst loadings, and the ability to access terminal, internal, and halogenated alkynes. Work continues in our laboratories to identify additional nontraditional catalytic pathways of enol triflates and related substrates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01904.

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.

■ ACKNOWLEDGMENTS

We would like to thank the National Science Foundation (CHE-1362953) for supporting this work. High-resolution mass spectrometry data were obtained through the support from the National Institute of Minority Health and Health Disparities (G12MD007591) within the NIH.

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DOI: 10.1021/acs.orglett.6b01904
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