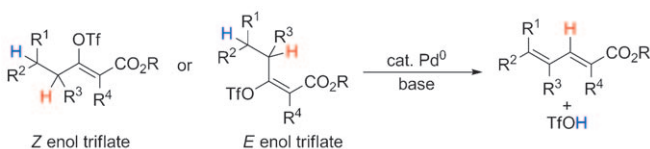


Palladium-Catalyzed Elimination/Isomerization of Enol Triflates into 1,3-Dienes**

Ian T. Crouch, Timothy Dreier, and Doug E. Frantz*

The prevalence of 1,3-dienes as substrates in some of the most important transformations in organic synthesis (e.g. Diels–Alder reactions) engenders this class of compounds as highly sought after raw materials for carbon–carbon bond construction. In addition, nature has incorporated 1,3-dienes into a multitude of biologically active natural products, thus further solidifying the broad interest of this functional group beyond simple methodology development. Nonetheless, despite their pervasiveness and significant efforts from the synthetic community, the stereoselective synthesis of functionalized, highly substituted 1,3-dienes remains a formidable challenge.^[1–4]

Our venture into the synthesis of 1,3-dienes began with a program to identify nontraditional reaction manifolds of stereodefined enol triflates because of their ability to act as pluripotent substrates with various catalysts and nucleophiles. In addition, our ability to readily access enol triflates with precise control of the acyclic stereochemistry provides the opportunity to exploit the unique reactivity differences between stereoisomeric starting materials.^[5] Herein, we report a conceptually new and mechanistically distinct catalytic reaction of enol triflates that is mediated by a commercially available palladium(0) catalyst en route to substituted 1,3-dienes (Scheme 1).



Scheme 1. Catalytic elimination/isomerization of enol triflates into 1,3-dienes. Tf = trifluoromethanesulfonyl.

Our initial experiments for the tandem elimination/isomerization of enol triflates were guided by a rational decision to use $[\text{Pd}(\text{P}t\text{Bu}_3)_2]$ as our catalyst of choice. This

decision was driven by two prevailing ideas. First, we were committed to identify a commercially available palladium catalyst for utmost simplicity and practicality in the implementation of this method. Second, we needed a catalyst that could rapidly undergo facile reductive elimination of triflic acid from a $[\text{L}_n\text{PdH}(\text{OTf})]$ intermediate to regenerate the active palladium(0) catalyst, thus minimizing the lifetime of the palladium-hydride intermediates. The elegant studies of Fu and co-workers showed that the reductive elimination of HX from a $[\text{L}_n\text{PdHX}]$ species can be a kinetically and thermodynamically favored process when $\text{L} = \text{P}(t\text{Bu})_3$, and therefore simplified our decision to use this catalyst.^[6] In addition to catalyst choice, from the outset it was not clear whether we would encounter differential activity between the Z and E enol triflates given the fact that their internal chelation environments are significantly different (on the assumption that a stereospecific oxidative addition of palla-

Table 1: Survey of the reaction conditions.^[a]

Entry	Enol Triflate ^[b]	Solvent	Base	Additive	Yield [%] ^[c]
1	(E)-1	DMSO	Hünig's	–	9
2	(E)-1	DCE	Hünig's	–	51
3	(E)-1	CH ₃ CN	Hünig's	–	66
4	(E)-1	THF	Hünig's	–	65
5	(E)-1	EtOAc	Hünig's	–	54
6	(E)-1	DMF	Hünig's	–	47
7	(E)-1	toluene	Hünig's	–	82
8	(E)-1	toluene	Et ₃ N	–	24
9	(E)-1	toluene	DIPA	–	14
10	(E)-1	toluene	PMP	–	65
11	(E)-1	toluene	Cy ₂ NMe	–	43
12	(E)-1	toluene	Na ₂ CO ₃	H ₂ O ^[d]	80 ^[e]
13 ^[f]	(E)-1	toluene	Na ₂ CO ₃	P(<i>t</i> Bu) ₃ ^[g]	0
14	(Z)-1	toluene	Na ₂ CO ₃	H ₂ O ^[h]	0
15	(Z)-1	toluene	Hünig's	TMSOTf ^[i]	82 ^[h]
16 ^[f]	(Z)-1	toluene	Hünig's	P(<i>t</i> Bu) ₃ ^[g] + TMSOTf ^[i]	0

[a] Reactions performed at 0.2 M using 1.0 equiv of enol triflate and 2.0 equiv of base. [b] Isomeric purity is > 99% as determined by LC/MS. [c] HPLC assay yields for the 2E,4E stereoisomer using an analytical standard of the product. [d] Used 2 equiv. [e] Isolated in 80% yield as a 10:1 ratio of (2E,4E)/(2E:4Z) stereoisomers. [f] No catalyst. [g] Used 20 mol %. [h] Isolated in 80% yield as a 10:1 ratio of (2E,4E)/(2E:4Z) stereoisomers. [i] Used 1 equiv. Bn = benzyl, Cy = cyclohexyl, DCE = 1,2-dichloroethane, DIPA = diisopropylamine, DMF = *N,N'*-dimethylformamide, DMSO = dimethyl sulfoxide, Hünig's = diisopropylethylamine, PMP = 1,2,2,6,6-pentamethylpiperidine, THF = tetrahydrofuran, TMS = trimethylsilyl.

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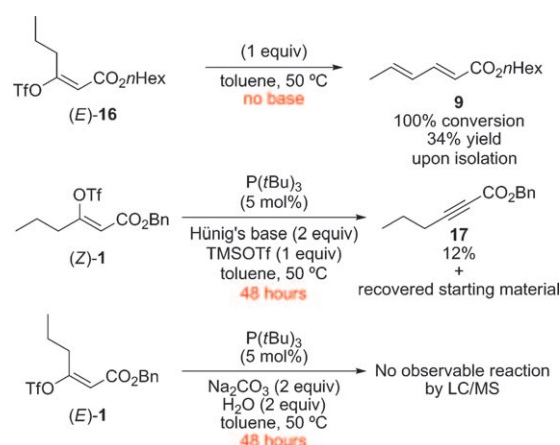
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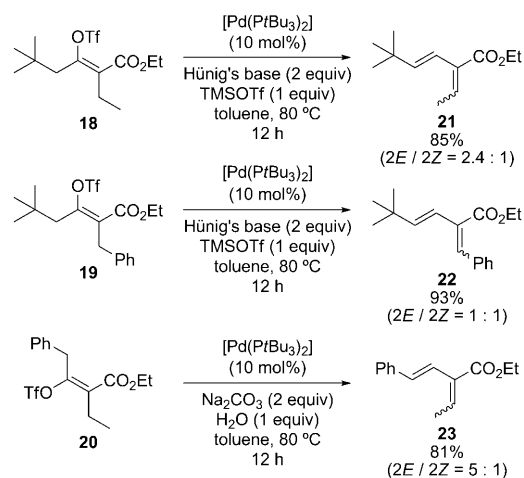
dium(0) takes place in the first step). Thus, we judiciously screened both *Z* and *E* stereoisomers of enol triflate **1** during the development phase of our investigations. The results of our optimization screen are shown in Table 1.

Two separate sets of reaction conditions have been identified based on the starting olefin geometry of the enol triflate. For the *E*-enol triflate **1**, various solvent and Brønsted base combinations provide the corresponding diene **2** in good yield in the presence of 2.5 mol % of $[\text{Pd}(\text{PrBu}_3)_2]$.^[7] However, the optimal reaction conditions we chose for the *E* enol triflates were toluene, Na_2CO_3 (2 equiv), and H_2O (2 equiv) at 50 °C with 2.5 mol % catalyst (Table 1, entry 12). Interestingly, (*Z*)-**1** completely failed to provide any observable product by LC/MS regardless of the base or solvent employed. Nonetheless, we discovered that the addition of a strong Lewis acid such as trimethylsilyl triflate (TMSOTf) along with Hünig's base restored the catalytic activity, thus providing **2** in comparable yield to its stereoisomer (Table 1, entry 15). Notably, without a source of palladium(0) the reactions of both stereoisomers did not provide any product (**2**), even in the presence of a phosphine ligand and/or a Lewis acid (Table 1, entries 13 and 16).

With these optimized reaction conditions in hand for both the *E* and *Z* enol triflates, we explored the initial scope and limitations of this new method for the synthesis of the corresponding 1,3-dienes. The culmination of our efforts thus far is highlighted in Table 2. Gratifyingly, a broad range of acyclic enol triflates were viable substrates and in each case provided the expected *2E,4E* dienoates as the major stereoisomeric products. In addition, the successful synthesis of (*2E,4Z*)-1,3-cyclooctadiene (**8**; Table 2, entry 7) from the corresponding cyclic enol triflate provides, as far as we are aware, the only known synthesis of this cyclic diene. Incorporation of a heteroatom-containing substituent on the enol triflate is highlighted in entries 3 and 11–13 in Table 2, and includes the synthesis of the dienyloboronate ester **14** as a highly versatile synthetic building block.^[8] The ability to convert either stereoisomer of the starting enol triflate into



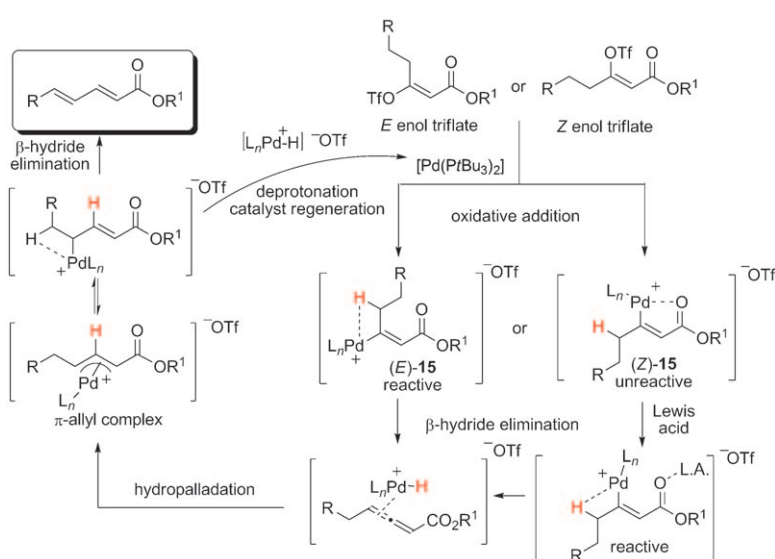
Scheme 3. Mechanistic studies.



Scheme 4. Additional studies.

the corresponding diene in comparable yields and stereoselectivity (Table 2, entries 4 and 5) should allow the utmost flexibility during strategic synthetic planning when only one stereoisomer of the enol triflate is synthetically accessible, or a mixture of stereoisomers is unavoidable.

Preliminary mechanistic investigations into these reactions have shed some light on a unifying reaction pathway that rationalizes the stark reactivity differences between the *E* and *Z* enol triflates. We propose that the reactions proceed through the catalytic pathway as outlined in Scheme 2. Following oxidative addition into the enol triflate, a β -hydride elimination from a cationic vinyl palladium(II) complex occurs to provide the corresponding allenolate.^[9] A subsequent hydropalladation followed by a second β -hydride elimination isomerizes the allene to give the corresponding diene.^[10] Catalyst regeneration occurs by a deprotonation of the resultant cationic palladium(II) hydride and completes the catalytic cycle.



Scheme 2. Proposed reaction pathway. L.A. = Lewis Acid.

Table 2: Preliminary substrate scope.^[a]

Entry	Enol Triflate ^[b]	Method, ^[c] Cat. [mol %]	t [h]	T [°C]	Product ^[d]	Yield [%] ^[e]
1		A, 2.5	12	50		3 87
2		A, 2.5	12	50		4 84
3		A, 2.5	12	25		5 59 ^[f]
4		A, 2.5	12	50		6 54
5		B, 2.5	12	50		6 72
6		B, 10	12	80		7 72
7		B, 10	12	80		8 92
8		A, 2.5	12	50		9 82 ^[g]
9		B, 10	12	80		10 64
10		B, 10	12	80		11 90 ^[h]
11		B, 2.5	12	50		12 74
12		B, 10	12	80		13 81
13		B, 2.5	12	50		14 41 ^[f]

[a] Reactions performed at 0.2 M in toluene under an inert atmosphere of N₂. [b] Isomeric purity > 99% as determined by LC/MS. [c] Method A: Na₂CO₃ (2 equiv) as base and H₂O (2 equiv); Method B: Hünig's base (2 equiv) and TMSOTf (1 equiv). [d] Diene stereochemistry (both major and minor isomers) confirmed by nOe analysis. [e] Yields of the isolated products are reported as an average of two separate experiments (< 10% difference between both runs). [f] Isolated as a 5:1 mixture of 4E/4Z stereoisomers. [g] Isolated as a 7:1 mixture of 4E/4Z stereoisomers. [h] Isolated as an 8:1 mixture of 2E/2Z stereoisomers.

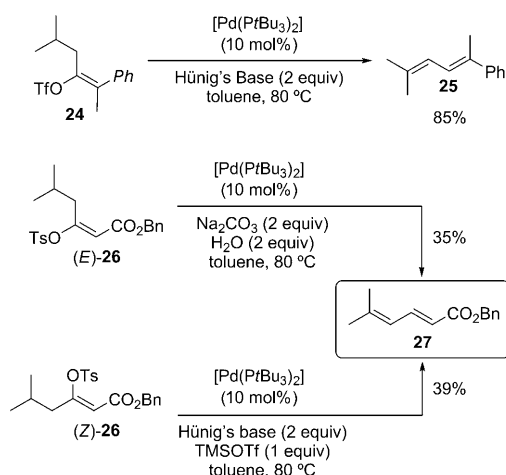
We believe that the significant reactivity differences between the *E* and *Z* enol triflates is due to the inherent intramolecular chelation environments, which dictate their relative reactivity after the oxidative addition. In the case of *E* enol triflates, a more facile β -hydride elimination from a cationic vinyl palladium(II) complex can be explained by the readily accessible open coordination site in these complexes ((*E*)-**15**). In contrast, we believe with *Z* enol triflates the carbonyl oxygen occupies the open coordination site in the cationic square-planar palladium(II) complex (*Z*)-**15** and this interaction attenuates the agostic interaction with the β -hydrogen atoms.

However, strong Lewis acids, such as TMSOTf, can effectively compete with the palladium center for coordination to the carbonyl oxygen atom, thus freeing a coordination site for a subsequent β -hydride elimination to occur.^[11] Nonetheless, despite these significant kinetic differences between *E* and *Z* enol triflates, current evidence supports the hypothesis that the products are under thermodynamic control.^[12]

Several experiments provide data consistent with our mechanistic proposal (Scheme 3). First, the reaction of enol triflate (*E*)-**16** performed with a stoichiometric amount of catalyst and in the absence of exogenous base provided the diene product **9** in reasonable yield. This is consistent with the pathway that occurs through an initial oxidative addition/ β -hydride elimination sequence rather than a Brønsted base mediated deprotonation/elimination pathway.^[13] Second, control reactions in the absence of a palladium catalyst with enol triflates (*Z*)-**1** or (*E*)-**1** provide little or no conversion into alkynoate **17** (or the corresponding allenolate) after 48 h. This result supports the critical involvement of palladium in the first step and is evidence against alkynoates (or allenolates) as kinetically viable entry points into the catalytic cycle by a base-mediated elimination of

triflic acid. Furthermore, to provide support of the intermediacy of a π -allyl complex, we subjected enol triflates **18–20** to the reaction conditions (Scheme 4). The success of these reactions, which provided isomeric dienes **21–23**, is consistent with the formation of a π -allyl palladium complex capable of β -hydride elimination from the α -carbon atom. More importantly, the difficulty of accessing substituted 1,3-butadienes such as **21–23** by using traditional methods highlights the unique capacity of this novel reaction of enol triflates.

Finally, ongoing experiments to explore the extended scope of this reaction with respect to other enol sulfonate substrates are shown in Scheme 5. For example, unactivated



Scheme 5. Preliminary studies with other substrates.

vinyl triflate **24** readily participated in the palladium-catalyzed elimination/isomerization reaction to provide the tetrasubstituted 1,3-diene **25** in excellent yield upon isolation. Furthermore, although acetoacetate-derived enol triflates are both readily available, and easily handled, less costly enol sulfonate derivatives may be more amenable to large-scale syntheses. In this regard, enol tosylates provide a viable alternative.^[14] Thus, in preliminary experiments, we subjected enol tosylates (*E*)-**26** and (*Z*)-**26** to the palladium-catalyzed elimination/isomerization. While the reaction conditions are harsher and the yields somewhat lower than their enol triflate counterparts, the viability of enol tosylates to provide the corresponding 1,3-dienes shows significant promise.

In conclusion, we have discovered a new catalytic elimination/isomerization pathway of stereodefined enol triflates capable of providing the corresponding functionalized, highly substituted 1,3-dienes in synthetically useful yields. Preliminary mechanistic studies support a distinct catalytic pathway that rationalizes the stark reactivity differences between *E* and *Z* enol triflates through stereoisomeric cationic vinyl palladium(II) complexes. In addition to providing a practical approach to 1,3-dienes, we believe that this new mechanism also opens the opportunity to selectively intercept allenes and π -allyl complexes through tunable cationic vinyl palladium(II) species. A full report on the further development of this approach to additional substrates and a detailed mechanistic study is forthcoming.

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- [1] Isomerization of alkynoates into dienones: a) B. M. Trost, T. Schmidt, *J. Am. Chem. Soc.* **1988**, *110*, 2301; b) B. M. Trost, U. Kazmaier, *J. Am. Chem. Soc.* **1992**, *114*, 7933; c) D. Ma, Y. Yu, X. Lu, *J. Org. Chem.* **1989**, *54*, 1105.
- [2] Recent cross-coupling routes to dienes: a) H. Yu, W. Jin, C. Sun, J. Chen, W. Du, S. He, Z. Yu, *Angew. Chem.* **2010**, *122*, 5928; *Angew. Chem. Int. Ed.* **2010**, *49*, 5792; b) Y. H. Xu, J. Lu, T. P. Loh, *J. Am. Chem. Soc.* **2009**, *131*, 1372; c) J. P. Ebran, A. L. Hansen, T. M. Gøgsig, T. Skrydstrup, *J. Am. Chem. Soc.* **2007**, *129*, 6931; d) K. S. Yoo, C. H. Yoon, K. W. Jung, *J. Am. Chem. Soc.* **2006**, *128*, 16384; e) G. A. Molander, Y. Yokoyama, *J. Org. Chem.* **2006**, *71*, 2493; f) T. Kurahashi, H. Shinokubo, A. Osuka, *Angew. Chem.* **2006**, *118*, 6484; *Angew. Chem. Int. Ed.* **2006**, *45*, 6336; g) C. Fu, S. Ma, *Org. Lett.* **2005**, *7*, 1707; h) A. L. Hansen, J. P. Ebran, M. Ahlquist, P. O. Norrby, T. Skrydstrup, *Angew. Chem.* **2006**, *118*, 3427; *Angew. Chem. Int. Ed.* **2006**, *45*, 3349; i) Y. Hatamoto, S. Sakaguchi, Y. Ishii, *Org. Lett.* **2004**, *6*, 4623; j) J. Takagi, K. Takahashi, T. Ishiyama, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 8001.
- [3] Recent phosphine-mediated routes to dienes: a) D. J. Dong, H.-H. Li, S.-K. Tian, *J. Am. Chem. Soc.* **2010**, *132*, 5018; b) J. T. Markiewicz, D. J. Schauer, J. Löfstedt, S. J. Corden, O. Wiest, P. Helquist, *J. Org. Chem.* **2010**, *75*, 2061; c) S. Xu, W. Zou, G. Wu, H. Song, Z. He, *Org. Lett.* **2010**, *12*, 3556.
- [4] Metathesis approaches to dienes and dienones: a) W. Zhu, M. Jiménez, W.-H. Jung, D. P. Camarco, R. Balachandran, A. Vogt, B. W. Day, D. P. Curran, *J. Am. Chem. Soc.* **2010**, *132*, 9175; b) G. Moura-Letts, D. P. Curran, *Org. Lett.* **2007**, *9*, 5; c) R. P. Murelli, M. L. Snapper, *Org. Lett.* **2007**, *9*, 1749; d) T. W. Funk, J. Efskind, R. H. Grubbs, *Org. Lett.* **2005**, *7*, 187.
- [5] D. Babinski, O. Soltani, D. E. Frantz, *Org. Lett.* **2008**, *10*, 2901. Despite the prevailing notion that triflates are unstable and difficult to work with, our experiences with enol triflates derived from acetoacetates have been quite the contrary.
- [6] I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 13178. [Pd(*t*Bu₃P)₂] can be easily handled in air and weighed out on the benchtop, see: G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555.
- [7] A quick survey of other palladium catalysts including [Pd(PPh₃)₄], [Pd(PCy₃)₂], [Pd₂(dba)₃], and [Pd(PPh₃)₂Cl₂] did not provide any of the diene product in comparable yield.
- [8] N.-W. Tseng, M. Lautens, *J. Org. Chem.* **2009**, *74*, 2521.
- [9] We have yet to observe the intermediacy of the allene during the course of these reactions. Nonetheless, β -hydride eliminations from vinyl palladium(II) complexes to form allene intermediates have been proposed in other reactions although at much higher temperatures. L. M. Lutete, I. Kadota, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 1622.
- [10] For examples of isomerizations of allenes into dienes, see a) R. Hayashi, R. P. Hsung, J. B. Feltenberger, A. G. Lohse, *Org. Lett.* **2009**, *11*, 2125; b) M. Al-Masum, Y. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 3809.
- [11] An alternative explanation for the role of TMSOTf is the possibility that it promotes an unprecedented *Z* to *E* isomerization of the vinyl palladium(II) complex. In either case, however, the role of the carbonyl oxygen atom in attenuating reactivity remains the same.
- [12] In an effort to study the β -hydride elimination and hydro-palladation steps more closely reactions with deuterium-labelled enol triflates were performed, but were inconclusive because of deuterium scrambling in the diene π system as a result of

equilibrating Pd–H(D) intermediates. See the Supporting Information for more details.

- [13] The base-mediated elimination of triflic acid from enol triflates to provide the corresponding alkynoate (or allenolate) could serve as a potential pathway for these reactions that bypasses the initial oxidative addition and subsequent β -hydride elimination from a vinyl palladium(II) complex. The success of reactions in
- the absence of base, however, is evidence against this alternative pathway.
- [14] For the recent use of enol tosylates in cross-coupling reactions, see Ref [2h] and a) H. Nakatsuji, K. Ueno, T. Misaki, Y. Tanabe, *Org. Lett.* **2008**, *10*, 2131; b) J. M. Baxter, D. Steinhuebel, M. Palucki, I. W. Davies, *Org. Lett.* **2005**, *7*, 215; c) D. Steinhuebel, J. M. Baxter, M. Palucki, I. W. Davies, *J. Org. Chem.* **2005**, *70*, 10124.
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