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Conjugate Addition of Allyl Stannanes with Concomitant Triflation

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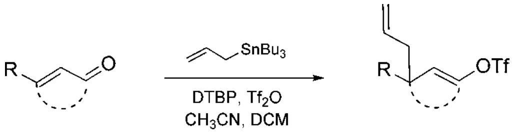
ABSTRACT



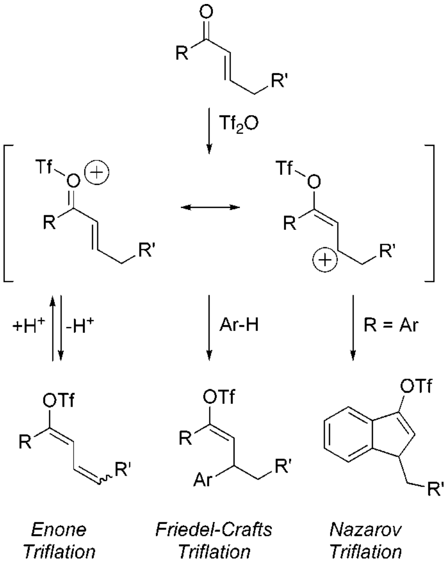
17 examples, 40-92% yield

A new method for the conjugate addition of allyltributylstannane with concomitant triflation is described. This reaction works with functionalized enones, enals, enoates, and vinylogous esters. The resulting vinyl triflates can be used for intramolecular Heck reactions to afford the products of 5-exo-trig cyclization.

Multicomponent C−C bond-forming reactions are becoming more common in synthetic chemistry as the desire for step economy increases.[1] The design of these reactions requires a careful balance between reactivity and compatibility of the components while aiming to generate complexity without prefunctionalization. In our continuing interest in the reactivity of the allylic trifloxy cation, we have developed a new multicomponent reaction that yields allylated vinyl triflates from enones under mild conditions.

Triflic anhydride is a valuable reagent for the electrophilic activation of simple carbonyl compounds.[2] Recently, we demonstrated that the activation of enones with triflic anhydride can produce an allylic trifloxy cation, which can subsequently undergo several new transformations (Scheme 1).[3] If this reactive intermediate is generated in the absence of a suitable nucleophile, deprotonation will afford a mixture of dienes.[3b] If instead it is generated in the presence of an electron-rich arene, nucleophilic attack of the arene is competitive with deprotonation, and Friedel−Crafts triflation adducts can be isolated in good yield.[3a,b] The treatment of aryl vinyl ketones with triflic anhydride can afford a trifloxy pentadienyl cation capable of undergoing a Nazarov triflation.[3c]

Scheme 1. Reactions Involving Allyl Trifloxy Cations



To expand the scope of C−C bond-forming triflations, we investigated alternative nucleophiles. Suitable candidates would exhibit comparable nucleophilicity to electron-rich arenes, which are viable nucleophiles for intermolecular Friedel−Crafts triflations.[3b] Furthermore, the nucleophile should exhibit low basicity such that the nucleophilic addition is competitive with deprotonation. It also must selectively

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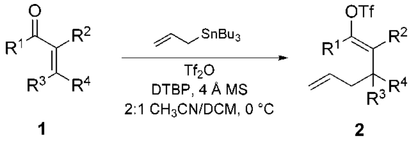
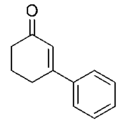
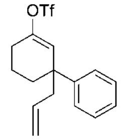
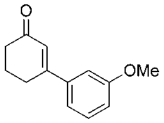
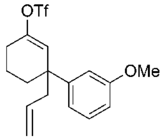
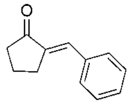
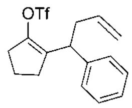
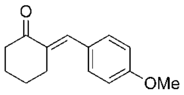
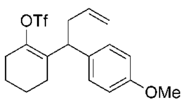
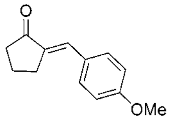
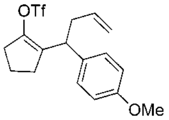
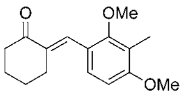
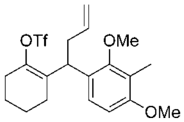
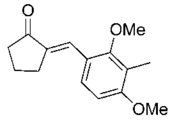
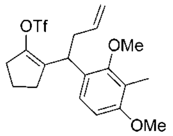
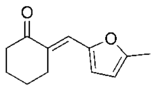
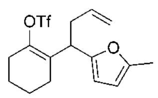
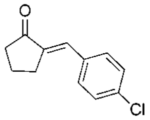
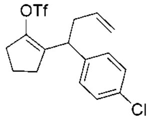
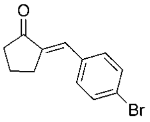
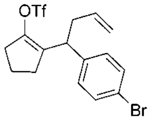
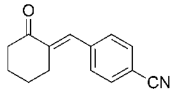
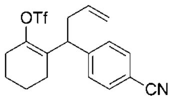
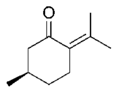
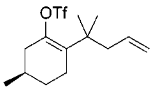
[1] *Multicomponent Reactions*; Zhu, J., Bienyamé, H., Eds.; Wiley VCH: Weinheim, 2005.
[2] Barazenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077−3119.
[3] (a) Grundl, M. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 23−25. (b) Grundl, M. A.; Kaster, A.; Beaulieu, E. D.; Trauner, D. *Org. Lett.* **2006**, *8*, 5429−5432. (c) Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022−11023.

10.1021/ol702996t CCC: $40.75

Table 1. α,β-Unsaturated Ketones Employed[a]



entry	substrate		product[b]	
1		**1a**		**2a** 80%
2		**1b**		**2b** 87%
3		**1c**		**2c** 65%
4		**1d**		**2d** 87%
5		**1e**		**2e** 91%
6		**1f**		**2f** 77%
7		**1g**		**2g** 92%
8		**1h**		**2h** 77%
9		**1i**		**2i** 64%
10		**1j**		**2j** 77%
11		**1k**		**2k** 60%
12		**1l**		**2l** 68%

[a] Reagents and reaction conditions: enone (1 equiv), DTBP (1.5 equiv), stannane (1.2 equiv), 4 Å molecular sieves (100 mg/mmol enone), and triflic anhydride (1.2 equiv) in a 2:1 acetonitrile/methylene chloride mixture at 0 °C. [b] Yields are given for isolated products.

react with the allylic trifloxy cation in the presence of other electrophiles such as triflic anhydride. With these considerations in mind, we selected allyltributylstannane. The Mayr scales for nucleophilicity indicated that this reagent exhibits comparable nucleophilicity to electron-rich arenes.[4] Also, previous studies illustrated that this nucleophile was compatible with silyl triflate activation of enones,[5] making allyltributylstannane an attractive candidate for use with triflic anhydride activation.

To develop our new method, we selected enone **1a** as the model substrate. Enone **1a** possess a phenyl group in the β-position capable of resonance stabilization of the carbocation, an advantageous characteristic in triflic anhydride activation. After screening a number of solvents, additives, and workup procedures, standard conditions were determined.[6] All reactions were run in a 2:1 mixture of acetonitrile/methylene chloride in the presence of 2,6-di-*tert*-butylpyridine (DTBP) and 4 Å molecular sieves at 0 °C.

One problematic aspect of this reaction concerned the sequestration of tin residues upon workup. Among a host of papers concerning the removal of tin residues,[7] we found that alkaline workups prior to column chromatography were critical to the facile separation of tin byproducts.[8] Treatment of the reaction mixture with aqueous sodium hydroxide hydrolyzed residual triflic anhydride, neutralized triflic acid, sequestered tin residues, and was crucial to the isolation of triflation adducts in high yield.

Table 1 shows the results from reactions with a number of substituted enones. Substrates **1a**,**b** were prepared from

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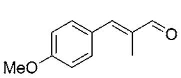
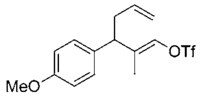
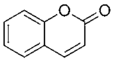
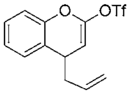
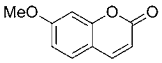
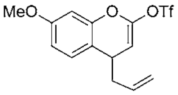
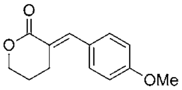
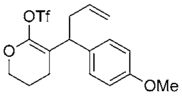
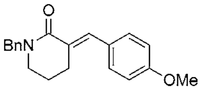
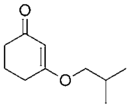
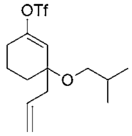
(4) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

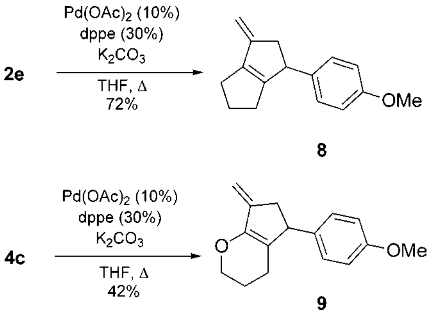
(5) (a) Kim, S.; Lee, J. M. *Synth. Commun.* **1991**, *21*, 25−29. (b) Kamenecka, T. M.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 4279−4282. (c) Paterson, I.; Steven, A.; Luckhurst, C. A. *Org. Biomol. Chem.* **2004**, *2*, 3026−3038. (d) Gotchev, D. B.; Comins, D. L. *J. Org. Chem.* **2006**, *71*, 9393−9402. (e) Miller, K. A.; Martin, S. F. *Org. Lett.* **2007**, *9*, 1113−1116.

Table 2. Employing Alternative α,*β*-Unsaturated Carbonyl Compounds[a]

entry	substrate		product[b]	
1		**1m**		**2m**, 77%
2		**3a**		**4a**, 44%
3		**3b**		**4b**, 68%
4		**3c**		**4c**, 71%
5		**5**	–	
6		**6**		**7**, 40%

[a] Reagents and reaction conditions: enone (1 equiv), DTBP (1.5 equiv), stannane (1.2 equiv), 4 Å molecular sieves (100 mg/mmol enone), and triflic anhydride (1.2 equiv) in a 2:1 acetonitrile/methylene chloride mixture at 0 °C. [b] Yields are given for isolated products.

Scheme 2. Intramolecular Heck Cyclizations of Allylated Vinyl Triflates



the corresponding vinylogous ester.[9] Substrates **1c**−**k** were prepared according to a procedure developed by Strauss and co-workers for ionic liquid-mediated aldol condensation.[10]

From Table 1, it is apparent that *β*-aryl-substituted enones undergo the reaction in good to excellent yields. These are robust substrates presumably due to their ability to stabilize the developing positive charge in the allylic tifloxy cation. This stabilization can be enhanced by the introduction of electron-donating substituents on the aromatic ring (substrates **1b**, **1d**,**e**) which lend modest increases in yield. Ortho substitution is tolerated (substrates **1f**,**g**). Other electron-rich arenes such as the substituted furan in enone **1h** also are suited for charge stabilization and perform well in the reaction. Gratifyingly, electron-deficient arenes also exhibit adequate stabilization without a severe decrease in yield. Electron-withdrawing substituents in the para position (substrates **1i**−**k**) are compatible. The reaction also proceeds in the absence of resonance stabilization. When pulegone (**1l**) was subjected to the reaction, vinyl triflate **2l** possessing an all carbon quaternary center was isolated in good yield.

Next, we attempted to expand the scope of the reaction by varying the type of carbonyl compound employed. To this end, we treated enals, enoates, enamides, and vinylogous esters to the optimized reaction conditions with varying degrees of success (Table 2). Enal **1m**[11] underwent allylative triflation in high yield. Vinyl triflate **2m** was isolated as a single olefin isomer, as assessed by NOESY correlation data (see Supporting Information). Commercially available coumarins **3a**,**b** also performed well in the reaction.[12]

While linear enoates such as methyl α-methylcinnamate yielded a complex mixture of products, the conformationally restricted enoate **3c**[13] proved a viable substrate for our method. By contrast, no products from enamides such as **5** were isolable. Perhaps the most unusual result in this series was the successful allylation of vinylogous ester **6** to generate the *β*-alkoxy vinyl triflate **7**. Such allylation with concomitant regioselective installation of the vinyl triflate would be challenging via conventional cuprate chemsitry due to facile *β*-elimination of the alkoxy substituent. The use of triflic anhydride circumvents the formation of the problematic metallo enolate intermediate.

Vinyl triflates can be used in a host of transition metal-mediated reactions.[14] Indeed, vinyl triflates **2c**−**l** and **4c** represent viable substrates for an intramolecular Heck reaction. Treatment of **2e** with Pd(OAc)$_2$ in the presence of

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(6) Full details of reaction optimization can be found in the Supporting Information.

(7) Davies, A. G. Organic Synthesis: Tin/Lithium Transmetallation, the Stille Reaction, and the Removal of Tin Residues. In *Organotin Chemistry*, 2nd ed.; Wiley-VCH: Weinheim, 2004; pp 373−382 and the references therein.

(8) Renaud, P.; Lacôte, E.; Quaranta, L. *Tetrahedron Lett.* **1998**, *39*, 2123−2126.

(9) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797−6798.

(10) Kreher, U. P.; Rosamilia, A. E.; Raston, C. L.; Scott, J. L.; Strauss, C. R. *Org. Lett.* **2003**, *5*, 3107−3110.

(11) Desmond, R.; Mills, S. G.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 3895−3898.

(12) These compounds were isolated using a fluoride workup as described in the Supporting Information.

(13) (a) Jackson, J. A.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750−5754. (b) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811−4814.

(14) Ritter, K. *Synthesis* **1993**, 735−762.

(15) For recent examples of ketene acetal triflates in cross-coupling reactions, see: Stille: (a) Nicolaou, K. C.; Pihko, P. M.; Bernal, F.; Frederick, M. O.; Qian, W.; Uesaka, N.; Diedrichs, N.; Hinrichs, J.; Koftis, T. V.; Loizidou, E.; Petrovic, G.; Rodriquez, M.; Sarlah, D.; Zou, N. *J. Am. Chem. Soc.* **2006**, *128*, 2244−2257. Suzuki: (b) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027−9030. (c) Bartali, L.; Larini, P.; Guarna, A.; Occhiato, E. G. *Synthesis* **2007**, 1733−1737. Negishi: (d) Kadota, I.; Takamura, H.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 4729−4731. (e) Kadota, I.; Kadowaki, C.; Takamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6199−6202. (f) Kadota, I.; Takamura, H.; Sato, K.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 3494−3498.

K_2CO_3 and 1,2-bis(diphenylphosphino)ethane (dppe) afforded the product of 5-exo-trig cyclization, **8**, in good yield (Scheme 2). While triflates formed from ester carbonyl compounds have been utilized in a variety of transition metal-mediated cross-coupling reactions,[15] they have been underutilized in Heck-type reactions. Treatment of **4c** under the same reaction conditions afforded the product of 5-exo-trig cyclization, **9**, in good yield.

In summary, we have presented an operationally simple conjugate allyl addition with concomitant triflation. The reaction proceeds under essentialy neutral conditions and works well with certain substrates that would perform poorly with conventional cuprate chemistry. Extension of this chemistry to alternative classes of nucleophiles and a more detailed study of the operative mechanisms in triflic anhydride activation are areas of ongoing investigation.

Acknowledgment. Financial support by Novartis and the Alfred P. Sloan Foundation is gratefully acknowledged. E.D.B. thanks the National Science Foundation for a Graduate Research Fellowship.

Supporting Information Available: Spectroscopic and analytical data for compounds **1f−h**, **k**, **2a−m**, **3c**, **4a−c**, **5, 7−9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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