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Vinyl Ketones to Allenes: Preparation of 1,3-Dien-2-yl Triflates and Their Application in Pd-Catalyzed Reactions with Soft Nucleophiles

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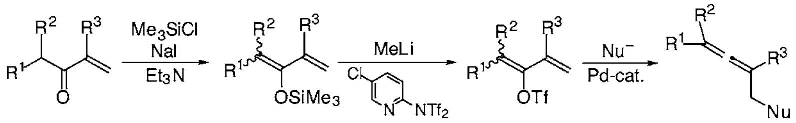
ABSTRACT

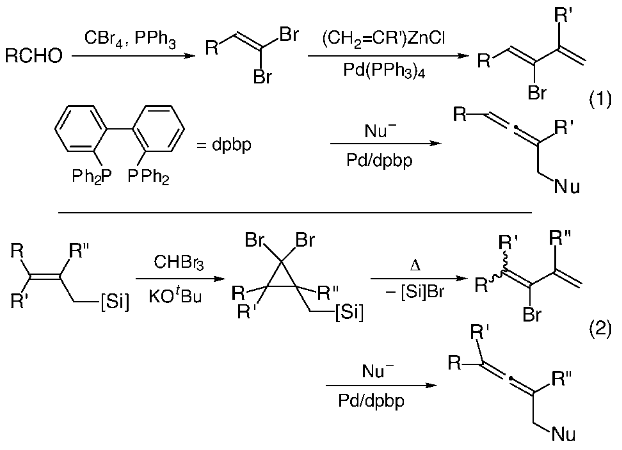


A general route of converting alkenyl ketones to functionalized allenes was developed. Substituted 1,3-dien-2-yl triflates, which were prepared from the alkenyl ketones via silyl dienol ethers, were excellent substrates for the palladium-catalyzed reaction with soft nucleophiles giving the multisubstituted allenes in high yields. Comparison between the dienyl triflates and analogous bromodienes in the Pd-catalyzed reaction was studied as well.

Alkenyl and aryl trifluoromethanesulfonates (triflates), usually prepared from the corresponding ketones[1,2] and phenols,[1] respectively, are widely used electrophiles for many transition-metal-catalyzed or -mediated reactions.[1b,2b]

Recently, we have developed two protocols of preparing functionalized allenes from either aldehydes (Scheme 1, eq 1)[3] or allylsilanes (Scheme 1, eq 2).[4] In both cases, the key intermediary compounds are 2-bromo-1,3-dienes, and Pd-catalyzed formal S_N2' substitution to the bromodienes affords the functionalized allenes in excellent yields. The Pd-catalyzed reaction proceeds through the catalytic cycle involving oxidative addition of the olefinic C−Br bond to a Pd(0). It was demonstrated that aryl triflates were slightly more reactive than the corresponding aryl bromide toward

Scheme 1



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[1] (a) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85. (b) Ritter, K. *Synthesis* **1993**, 735.

[2] (a) Stang, P. J. *Acc. Chem. Res.* **1978**, *11*, 107. (b) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47. (c) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979. (d) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

[3] (a) Ogasawara, M.; Ikeda, H.; Hayashi, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 1042. (b) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089. (c) Ogasawara, M.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764.

[4] (a) Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org. Lett.* **2003**, *5*, 217. (b) Ogasawara, M.; Ge, Y.; Uetake, K.; Fan, L.; Takahashi, T. *J. Org. Chem.* **2005**, *70*, 3871.

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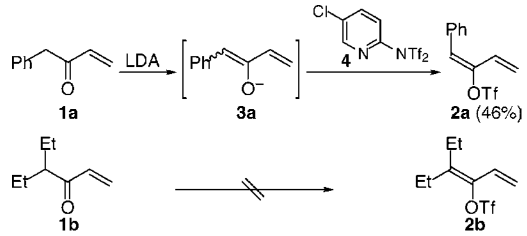
the oxidative addition to Pd(PPh$_3$)$_4$.[5,6] Since alkenyl triflates show some analogies to aryl triflates in their chemical reactivity,[7] we were interested in application of 1,3-butadien-2-yl triflate derivatives in the Pd-catalyzed reaction.[8] It should be noted that in many occasions alkenyl and aryl triflates are more easily accessible than the corresponding bromides because a variety of ketones and phenols are easily available either from commercial sources or by well-established synthetic methods.

In this paper, we report a general method of preparing 1,3-dien-2-yl triflates and their application in the palladium-catalyzed allene formation reaction. The overall process developed here provides a novel route to the allenes from vinyl ketones.

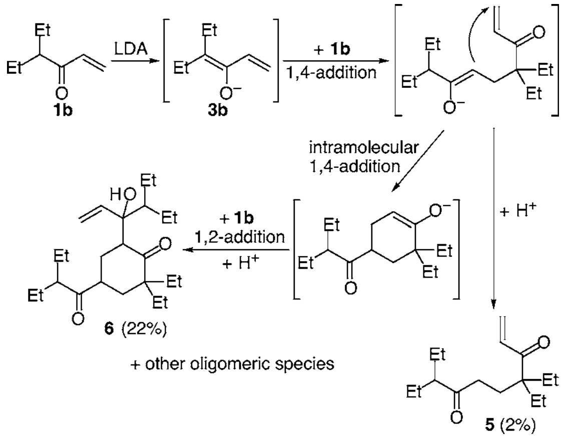
Conversion of vinyl ketones **1a** and **1b**, which were easily prepared in high yields from acryloyl chloride and benzyl- or 3-pentylzinc chloride,[9] into the corresponding 1,3-dien-2-yl triflates was examined under various conditions. As summarized in Scheme 2, **1a** afforded the triflate **2a** in 46% yield by the reaction of its enolate with *N*-(5-chloro-2-pyridyl)triflimide **4**.[2d] On the other hand, **1b** did not yield the desired triflate **2b** under the identical conditions, although the vinyl ketone **1b** could not be recovered from the reaction mixture.

Scheme 2



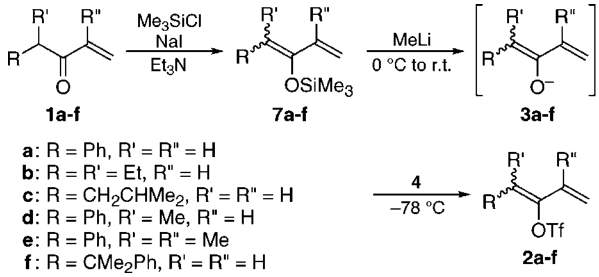
It was found that the vinyl ketone **1b** was consumed prior to the reaction with the triflating reagent **4**. Treatment of **1b** with equimolar LDA followed by aqueous workup gave a complex mixture with no remaining **1b**. After careful chromatographic separation of the product mixture, NMR and HRMS analyses clarified that a dimer **5** (2%) and a trimer **6**[10] (22%) were among the components of the mixture (Scheme 3). The formation of **5** and **6** could be rationalized as shown in Scheme 3. The vinyl ketone **1b** was a good Michael acceptor, and the generated enolate **3b** reacted with **1b** to give the oligomerized products **5**, **6**, and others. On the other hand, the enolate **3a**, derived from **1a**, was less nucleophilic due to the electron-withdrawing phenyl group, and thus it did not react with the vinyl ketone **1a** under the reaction conditions. These analysis indicated that formation of the undesirable oligomeric products could be ascribed to coexistence of the Michael acceptor **1b** and the nucleophile **3b**.

Scheme 3



Generation of the enone-free dienolate **3b** was achieved by a two-step protocol. As shown in Table 1, **1b** was converted to the corresponding silyl dienol ether **7b** by a reaction with Me$_3$SiCl, NaI, and Et$_3$N.[11] After removal of the unreacted vinyl ketone **1b** by distillation, treatment of **7b** with equimolar MeLi generated **3b** without coexisting

Table 1. Preparation of Dienyl Triflates **2** from Vinyl Ketones **1**



a: R = Ph, R' = R" = H
b: R = R' = Et, R" = H
c: R = CH$_2$CHMe$_2$, R' = R" = H
d: R = Ph, R' = Me, R" = H
e: R = Ph, R' = R" = Me
f: R = CMe$_2$Ph, R' = R" = H

entry	vinyl ketone **1**	yield of **7**[a] (%)	*E*/*Z* in **7**[b,c]	yield of **2**[d] (%)	*E*/*Z* in **2**[b,c]
1	**1a**	56 (**7a**)	<0/99<	54[e] (**2a**)	28/72[e]
2	**1b**	57 (**7b**)		70 (**2b**)	
3	**1c**	35[f] (**7c**)	28/72	79 (**2c**)	31/69
4	**1d**	51 (**7d**)	79/21	81 (**2e**)	86/14
5	**1e**	72 (**7e**)	62/38	69 (**2d**)	73/27
6	**1f**	69[g] (**7f**)	22/78	70 (**2f**)	24/76

[a] Isolated yield by vacuum distillation. [b] The *E*/*Z* ratios were determined by ^{1}H NMR analysis. [c] The geometry of the products was determined by ^{1}H NMR NOE experiments. [d] Isolated yield by silica gel chromatography. [e] Triflation was performed at room temperature. [f] The relative low yield was due to high volatility of the product. [g] Due to low volatility, **7f** could not be purified. The yield was calculated from the ^{1}H NMR spectrum of the crude mixture.

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[5] Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810.

[6] Kamikawa, T.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 7087.

[7] Representative examples for the use of alkenyl triflates in Pd-catalyzed reactions. See: (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (b) Willis, M. C.; Brace, G. N. *Tetrahedron Lett.* **2002**, *43*, 9085. (c) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749.

[8] It was reported previously that 1-phenyl-1,3-butadien-2-yl acetate was not reactive to the Pd-catalyzed reaction. See ref 3a.

[9] Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.

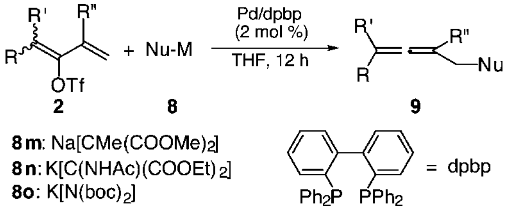
[10] Although the product **6** was isolated as a single isomer, its stereochemistry has not been determined yet.

1b. The generated dienolate was reacted with **4** to give the dienyl triflate **2b** in a moderate yield (Table 1, entry 2). The scope of the present method was broad, and dienyl triflates of a wide range of substitution patterns could be prepared. It should be noted that all of the dienyl triflates except **2a** could not be prepared by direct deprotonation of the vinyl ketones **1** (the route shown in Scheme 2).[12]

In most of the cases, silyl dienol ethers **7** were obtained as mixtures of (*E*)- and (*Z*)-isomers. The (*E*)/(*Z*) ratios in **7c**−**f** were nearly retained during the transformation to **2c**−**f** via **3c**−**f** (Table 1, entries 3−6). The triflate **2a** prepared by the method shown in Scheme 2 was (*E*)-isomer exclusively. On the other hand, **2a** obtained via the silyl dienol ether **7a** was a mixture of the two isomers with the (*Z*)-isomer as the major component (Table 1, entry 1).

The 1,3-dien-2-yl triflates **2** obtained here were applied in the Pd-catalyzed reaction with soft nucleophiles. As expected, **2** were found to be excellent substrates for a variety of multisubstituted functionalized allenes. The results of the Pd-catalyzed reaction are summarized in Table 2. The triflate (*E*)-**2a** was reacted with $Na[CMe(COOMe)_2]$ (**8m**) in THF in the presence of a Pd catalyst (2 mol %) generated in situ from $[PdCl(\pi\text{-allyl})]_2$ and dpbp[13] to give the corresponding allene **9am** in 97% yields (Table 2, entry 1). Multisubstituted allenes could be prepared with appropriate triflates **2**. For example, the Pd-catalyzed reactions of 1,1-disubstituted 1,3-butadien-2-yl triflates, such as **2b** or **2d**, afforded trisubstituted allenes in excellent yields (Table 2, entries 2−5, 7, and 8). Similarly, tetrasubstituted allenes **9em**−**9eo** were obtained from the 1,1,3-trihydrocarbyl-1,3-butadien-2-yl triflate **2e** in >90% isolated yields (Table 2, entries 9−11). A variety of soft nucleophiles, such as stabilized carbanions (**8m** and **8n**) and an *N*-nucleophile (**8o**), could be used for the reactions with the triflates (Table 2, entries 4, 5, 10, and 11). In all cases, the reactions proceeded cleanly, and no appreciable byproducts were detected in the reaction mixtures.

Table 2. Palladium-Catalyzed Synthesis of Multisubstituted Allenes **9** from 1,3-Dien-2-yl Triflates **2** and Nucleophiles **8**[a]



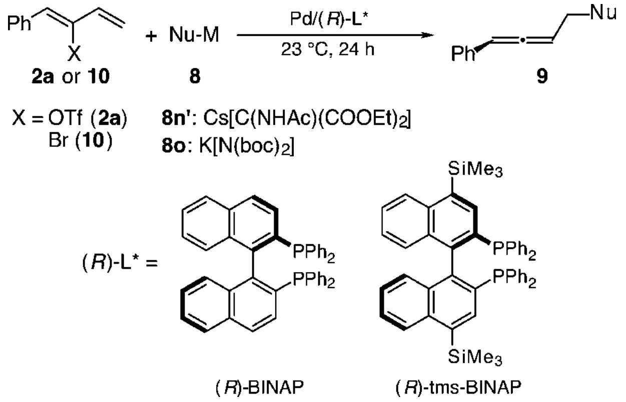
8m: $Na[CMe(COOMe)_2]$
8n: $K[C(NHAc)(COOEt)_2]$
8o: $K[N(boc)_2]$

entry	triflate **2**	nucleophile **8**	*T* (°C)	yield of **9**[b] (%)
1	(*E*)-**2a**	**8m**	23	97 (**9am**)
2	(*Z*)-**2a**	**8m**	23	92 (**9am**)
3	**2b**	**8m**	23	99 (**9bm**)
4	**2b**	**8n**	50	96 (**9bn**)
5	**2b**	**8o**	50	85 (**9bo**)
6	(*E*)- and (*Z*)-**2c**[c]	**8m**	23	87 (**9cm**)
7	(*E*)-**2d**	**8m**	23	96 (**9dm**)
8	(*Z*)-**2d**	**8m**	23	95 (**9dm**)
9	(*E*)- and (*Z*)-**2e**[c]	**8m**	23	93 (**9em**)
10	(*E*)- and (*Z*)-**2e**[c]	**8n**	50	95 (**9en**)
11	(*E*)- and (*Z*)-**2e**[c]	**8o**	50	90 (**9eo**)
12	(*E*)- and (*Z*)-**2f**[c]	**8m**	23	90 (**9fm**)

[a] Reaction was carried out with **2** (1.0 mmol) and **8** (1.1 mmol) in THF in the presence of the catalyst (2 mol %) generated from $[PdCl(\pi\text{-allyl})]_2$ and dpbp. [b] Isolated yield by silica gel chromatography. [c] As (*Z*)- and (*E*)-mixtures.

The (*E*)/(*Z*)-isomers of **2d** were separated by careful column chromatography of the mixture. Both isomers reacted with **8m** smoothly under the Pd catalysis and yielded the identical allene **9dm** in nearly quantitative yields (Table 2, entries 7 and 8). Apparently, the stereochemistry in **2** was not critical for the Pd-catalyzed reaction. Indeed, the allenic products were obtained in excellent yields even with the (*E*)/(*Z*)-mixtures of the triflates (Table 2, entries 6, 9−12).

Table 3. Pd-Catalyzed Asymmetric Synthesis of Axially Chiral Allenes from Dienyl Triflates **2** or Bromodienes **10**[a]



entry	diene	Nu−M	solvent	L*	yield[b] (%)	% ee[c]
1[d]	(*Z*)-**2a**	**8o**	THF	tms-BINAP	72 (**9ao**)	22
2[d,e]	(*Z*)-**10**	**8o**	THF	tms-BINAP	98 (**9ao**)	77
3[f]	(*Z*)-**2a**	**8n′**	CH_2Cl_2	BINAP	89 (**9an**)	79
4[f,g]	(*Z*)-**10**	**8n′**	CH_2Cl_2	BINAP	75 (**9an**)	89

[a] All of the reactions were carried out with **2a** or **10** (0.50 mmol) and **8** (0.55 mmol) in a given solvent (5.0 mL) for 24 h in the presence of a Pd catalyst generated from $Pd(dba)_2$ and (*R*)-L*. [b] Isolated yield by column chromatography. [c] Determined by chiral HPLC analysis (**9ao**: Chiralpak OD-H; **9an**: Chiralcel OJ-H). [d] With 5 mol % of the Pd catalyst. [e] Taken from ref 15. [f] With 10 mol % of the Pd catalyst. [g] Taken from ref 3b.

Since the dienyl triflates **2** were demonstrated as useful precursors to the allenic compounds, their application in

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(11) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2089.

(12) Several 1,3-dien-2-yl triflates have been reported so far. However, none of the reported procedures could be generally applicable for preparation of dienyl triflates. See:, (a) Luan, L.; Song, J.-S.; Bullock, R. M. *J. Org. Chem.* **1995**, *60*, 7170. (b) Wipf, P.; Xu, W. *J. Org. Chem.* **1996**, *61*, 6556. (c) Nicolaou, K. C.; Postema, M. H. D.; Miller, N. D.; Yang, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2821. (d) Alvarez, R.; Iglesias, B.; López, S.; de Lera, A. R. *Tetrahedron Lett.* **1998**, *39*, 5659. (e) Bio, M. M.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 2905. (f) Bio, M. M.; Leighton, J. L. *J. Org. Chem.* **2003**, *68*, 1693.

(13) dpbp = 2, 2′-bis(diphenylphosphino)-1, 1′-biphenyl. See: Ogasawara, M.; Yoshida, K.; Hayashi, T. *Organometallics* **2000**, *19*, 1567, and references therein.

asymmetric reactions giving axially chiral allenes was examined. Two nucleophiles (**8o** and **8n′**) were selected as representatives and the results of the asymmetric reactions were compared to those with the corresponding bromodiene **10** (Table 3). Reaction of (*Z*)-**2a** with **8o** in the presence of a Pd/(*R*)-tms-BINAP[14] catalyst (5 mol %) gave the axially chiral allene (*R*)-**9ao** of 22% ee in 72% yield (Table 3, entry 1). The enantioselectivity of the reaction was considerably lower than that of the analogous reaction with (*Z*)-**10** (Table 3, entry 2).[15] Likewise, (*R*)-**9an** obtained from (*Z*)-**2a** showed lower enantiopurity (79% ee, Table 3, entry 3) than that from (*Z*)-**10** (Table 3, entry 4).[3b]

In summary, we have developed a general method for the conversion of vinyl ketones to 1,3-dien-2-yl triflates. The dienyl triflates were demonstrated to be reactive substrates for the Pd-catalyzed reactions with soft nucleophiles producing a variety of functionalized allenes. Using alkenyl ketones with proper substituents at proper positions, multisubstituted allenes, including persubstituted allenes, could be made. Whereas the various alkenyl ketones are easily available, the overall protocol developed in this study provides a useful synthetic method of the allenic compounds.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] (a) Hu, A.; Ngo, H. L.; Lin, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2501. (b) Hu, A.; Ngo, H. L.; Lin, W. *Org. Lett.* **2004**, *6*, 2937. (c) Hu, A.; Lin, W. *Org. Lett.* **2005**, *7*, 455.

[15] Ogasawara, M.; Ngo, H. L.; Sakamoto, T.; Takahashi, T.; Lin, W. *Org. Lett.* **2005**, *7*, 2881.