Palladium Catalyzed Coupling Reaction of an Enol Nonaflate with (Vinyl)tributylstannanes and Acetylenes

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Abstract: A novel method for a stereoselective synthesis of trienes and dienynes was developed by palladium catalyzed cross coupling reactions of an enol nonaflate with (vinyl)tributylstannanes and acetylenes in good to excellent yields. Here, the enol nonaflate exhibited a higher reactivity compared with the corresponding enol triflate in the coupling reactions.

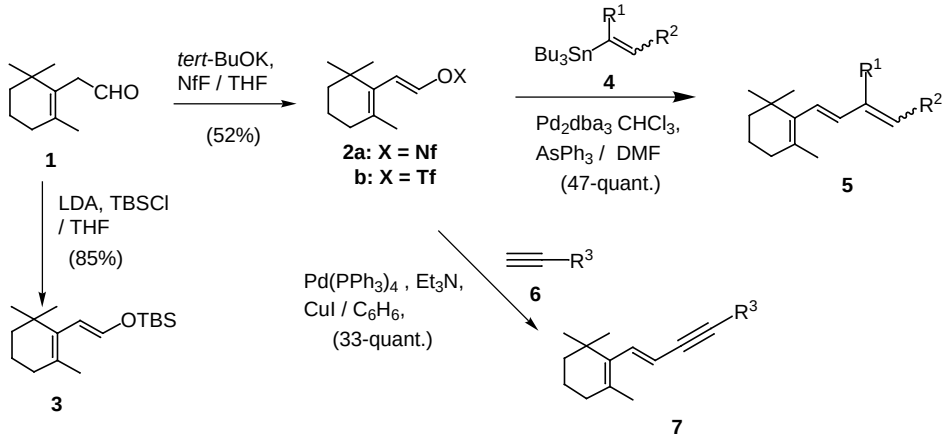
Key words: enol nonaflate, palladium catalyst, coupling reaction, alkenyl stannane, acetylene

Enol trifluoromethanesulfonates (triflates, Tf) are very useful components in the coupling reactions such as the Heck, Stille, Suzuki, and Sonogashira reactions for the preparation of olefinic compounds,[1] and have been widely used in the synthesis of natural products and related compounds.[2] However, the reports dealing with enol nonafluorobutanesulfonates (nonaflates, Nf) in a coupling reaction are only limited in the case of the Heck reaction.[3,4] In connection with our studies on a palladium catalyzed coupling reaction for retinoid synthesis,[5] we describe the results of the Stille and Sonogashira coupling reactions of the enol nonaflate derived from (2,6,6-trimethyl-1-cyclohexen-1-yl)acetaldehyde and the difference of its reactivity compared with that of the corresponding enol triflate (Scheme).

Enol nonaflate **2a** was prepared by treatment of (2,6,6-trimethyl-1-cyclohexen-1-yl)acetaldehyde **1**[6] with nonafluorobutanesulfonyl fluoride (NfF) using potassium *tert*-butoxide as a base in THF under reflux[7] for 1 h in a 52% yield.[8] An alternative approach to **2a** by the reaction of silyl enol ether **3** derived from **1** with NfF in the presence of a catalytic amount of tetrabutylammonium fluoride[3a] was unsuccessful. Enol triflate **2b** was obtained by our reported method.[5a]

At first we tested the coupling reactions of **2a** with various (vinyl)tributylstannanes **4** using 2.5 mol% of tris(dibenzylideneacetone)dipalladium-chloroform adduct (Pd_2dba_3-$CHCl_3$) and triphenylarsine ($AsPh_3$) as a ligand[9] in *N*,*N*-dimethylformamide, and these results are summarized in Table 1.[10] In all cases studied, only one product was obtained and it was found that this coupling reaction proceeded stereospecifically with retention of the configuration of the double bonds. The stereochemistry of the coupling product was determined on the basis of its ^1H NMR spectrum.[11] When the (vinyl)tributylstannanes having an electron withdrawing group were used, it required a high temperature and a long reaction time to complete the coupling reaction (entries 8 and 9).

Subsequently, in order to compare the reactivity, the coupling reactions of enol triflate **2b** were carried out and the results were listed in Table 1. It was noteworthy that



Scheme

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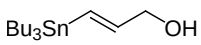
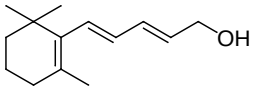
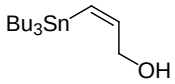
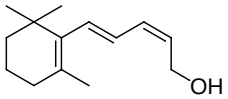
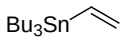
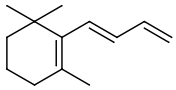
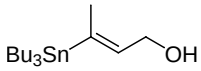
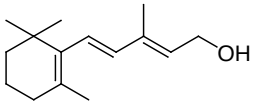
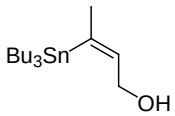
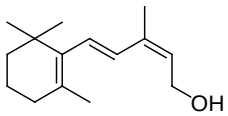
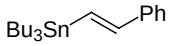
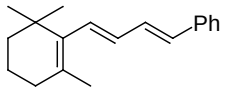
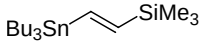
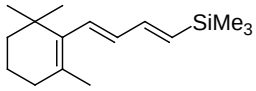
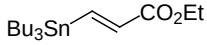
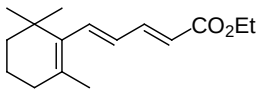
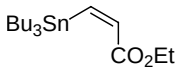
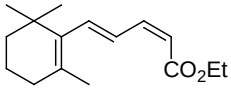
Table 1 Cross Coupling of Enol Perfluorosulfonate **2** with Various (Vinyl)tributylstannanes **4**

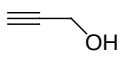
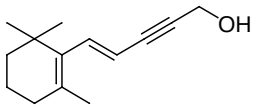
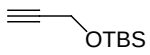
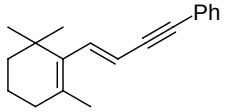
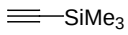
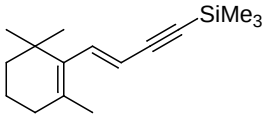
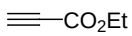
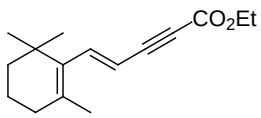
Entry	Stannane **4**	Reaction time (h)	Temp.	Product **5**	Yield (%)[a]	
					From **2a**	From **2b**
1	 **4a**	3	r.t.	 **5a**	quant.	63
2	 **4b**	3	r.t.	 **5b**	quant.	62
3	 **4c**	3	r.t.	 **5c**	quant.	75
4	 **4d**	2	r.t.	 **5d**	quant.	69
5	 **4e**	2	r.t.	 **5e**	92	87
6	 **4f**	0.5	r.t.	 **5f**	91	73
7	 **4g**	14	r.t.	 **5g**	47	45
8	 **4h**	5	80 °C	 **5h**	57	61
9	 **4i**	3	80 °C	 **5i**	62	63

[a] Isolated yield.

the enol nonaflate **2a** had displayed a slightly higher reactivity than that of the corresponding enol triflate **2b**, except for the cases in the olefins having an electron with drawing group. This finding is in accordance with the previously reported results in the coupling reaction of an aryl nonaflate or an aryl triflate with an arylzinc bromide.[4a]

As all our attempts to couple **2a** with tributylstannylacetylenes were unsuccessful, we focused our attention on a Sonogashira reaction. Using palladium tetrakistriphenylphosphine ($Pd(PPh_3)_4$) as a catalyst in the presence of triethylamine and cupper(I) iodide, the reactions of **2a** with various acetylenes **6** in benzene smoothly afforded the coupled products **7** in moderate to excellent yields, and these results are compiled in Table 2.[12] The protected

Table 2 Cross Coupling of Enol Perfluorosulfonate **2** with Various Acetylenes **6**

Entry	Acetylene **6**	Reaction time (h)	Temp.	Product **7**	Yield (%)[b] From **2a**	Yield (%)[b] From **2b**
1	 **6a**	14	r.t.	 **7a**	33	-[b]
2	 **6b**	2	r.t.		82[c]	70[c]
3	 **6c**	2	r.t.	 **7c**	70	58
4	 **6d**	2	r.t.	 **7d**	quant.	78
5	 **6e**	3	r.t.	 **7e**	64	21

[a] Isolated yield.
[b] Not performed.
[c] After treatment with TBAF (2 steps).

propalgyl alcohol **6b** gave a good yield compared to the free alcohol **6a** (entries 1 and 2). When ethyl propiolate **6e** (acetylene having an electron withdrawing group) was used, it required a high reaction temperature and a long time to complete the coupling reaction, which was the same as the case in the Stille reaction (entry 5). In addition, the enol nonaflate **2a** was more reactive than the corresponding enol triflate **2b** to produce good results in all cases.

In summary, we have developed a novel method for the preparation of polyolefinic compounds by the palladium catalyzed coupling of an enol nonaflate with (vinyl)tributylstannanes and acetylenes. Also, it was shown that the reactivity of enol nonaflate is higher than that of enol triflate. Due to not only the high cost of the triflating reagent, but also the troublesome preparation of triflate in some case,[13] using enol nonaflate would be very efficient for giving an alternative vinylic component in a coupling reaction. Further studies on the application of this novel coupling for a preparation of retinoids and related compounds are currently in progress.

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(2) (a) Yasuda, N.; Xavier, L.; Rieger, D. L.; Li, Y.; DeCamp, A. E.; Dolling, U.-H. *Tetrahedron Lett.* **1993**, *34*, 3211. (b) Nicolaou, K. C.; Sato, M.; Miller, N. D.; Gunzner, J. L.; Renaud, J.; Untersteller, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 889. (c) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027.
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(7) Subramanian, L. R.; Bentz, H.; Hanack, M. *Synthesis* **1973**, 293.
(8) ^{1}H NMR data of enol nonaflate **2a** are as follows: (300 MHz, $CDCl_3$) δ: 0.97 (6 H, s, Me × 2), 1.42–1.50 (2 H, m, CH_2), 1.56–1.62 (2 H, m, CH_2), 1.68 (3 H, s), 2.02 (2 H, t, *J* = 7 Hz), 6.21 (1 H, d, *J* = 12 Hz, =CH), 6.46 (1 H, d, *J* = 16 Hz, =CH).
(9) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
(10) **Typical coupling procedure**: To a stirred solution of enol nonaflate (**2a**, 1 mmol),(vinyl)tributylstannane (**4**, 1.5 mmol), and $AsPh_3$ (20 mol%, 60 mg) in DMF (2 mL) was added Pd_2dba_3-$CHCl_3$ adduct (2.5 mol%, 26 mg) all at once under nitrogen. After stirring for an indicated period in Table 1, the reaction was quenched with saturated aqueous NH_4Cl solution (3 mL) and extracted with diethyl ether (10 mL × 3). The extracts were washed with saturated aqueous NaCl solution (10 mL) and then dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the coupled product **5**.
5a: IR ($CHCl_3$) cm^{-1}: 3610, 3446, 2969, 1647; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.00 (6 H, s, Me × 2), 1.40–1.46 (2 H, m, CH_2), 1.56–1.62 (3 H, m, CH_2 and OH), 1.69 (3 H, s, Me), 2.02 (2 H, t, *J* = 7 Hz, CH_2), 4.19 (2 H, t, *J* = 7 Hz, CH_2), 5.78 (1 H, dt, *J* = 15, 6 Hz, =CH), 6.03 (1 H, dd, *J* = 16, 10 Hz, =CH), 6.14 (1 H, d, *J* = 16 Hz, =CH), 6.31 (1 H, ddt, *J* = 15, 10, 1 Hz, =CH); HRMS (EI) $C_{14}H_{22}O$: requires 206.1669, found 206.1667.
(11) In the case of trisubstituted olefins **5d** and **5e**, its stereochemistry was determined after conversion to the corresponding aldehyde by oxidation, respectively. See: Wada, A.; Hiraishi, S.; Takamura, N.; Date, T.; Aoe, K.; Ito, M. *J. Org. Chem.* **1997**, *62*, 4343.
(12) **Typical coupling procedure**: To a stirred solution of enol nonaflate (**2a**, 0.5 mmol), acetylene (**6**, 1 mmol), diisopropylamine (2 mmol, 200 mg), and CuI (15 mol%, 35 mg) in benzene (3 mL) was added $Pd(PPh_3)_4$ (10 mol%, 58 mg) all at once under nitrogen. After stirring for an indicated period in Table 2, the reaction was quenched with saturated aqueous NH_4Cl solution (3 mL) and extracted with ether (10 mL × 3). The extracts were washed with saturated aqueous NaCl solution (10 mL) and then dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on a silica gel to produce the coupled product **7**.
7a: IR ($CHCl_3$) cm^{-1}: 3608, 3450, 2932, 2209, 1604; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.00 (6 H, s, Me × 2), 1.40–1.47 (2 H, m, CH_2), 1.56–1.61 (3 H, m, CH_2 and OH), 1.70 (3 H, s, Me), 1.99 (2 H, t, *J* = 6 Hz, CH_2), 4.41 (2 H, d, *J* = 4 Hz, CH_2), 5.47 (1 H, dt, *J* = 16.5, 2 Hz, =CH), 6.59 (1 H, d, *J* = 16 Hz, =CH); HRMS (EI) $C_{14}H_{20}O$: requires 204.1513, found 204.1520.
(13) In the case of ^{13}C-labeled aldehyde **1**, there was no reappearance of the peak for the conversion to the corresponding enol triflate. On the contrary, there was no trouble in preparation of the enol nonaflate.