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Study of the Regioselectivity of Palladium-catalyzed Monocouplings between Conjugated Bis(enoltriflates) and Trimethylsilylacetylene

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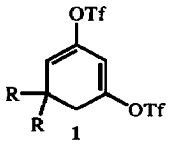
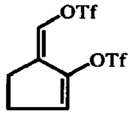
***Abstract*:** The Z-configurated bis(enoltriflates) 2 and 7 were treated at room temperature with TMS acetylene (1.25 equiv.) in the presence of CuI (0.17 equiv.) and various palladium catalysts (0.07 equiv.), solvents, and amines to afford monocoupling products. Surprisingly, opposite regioselectivities were observed starting from the five-membered (→8, n = 0) vs. the six-membered bis(enoltriflates) (→9, n = 1).

Palladium-catalyzed coupling reactions of alkenyl trifluoromethanesulfonates ("monotriflates") with nucleophiles offer a versatile access to functionalized olefins [1]. By this method, *inter alia*, 1,3-enynes can be synthesized as first reported by Cacchi et al.[2] and Chen and Yang [3]. *Bis*(enoltriflates) ("bistriflates"), on the other hand, have been scarcely described. The only ones known before ours were compounds **1** (R = H, Me) [4]; however, these were not coupled with nucleophiles.



1

R = H or Me



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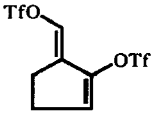

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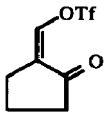

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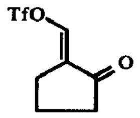
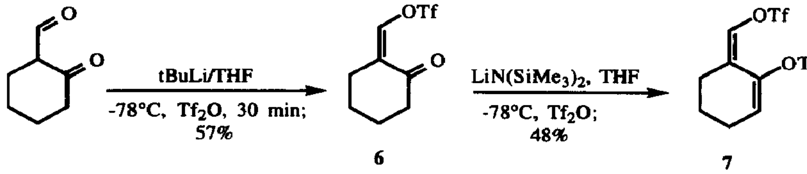


5

OTf = OSO_2CF_3

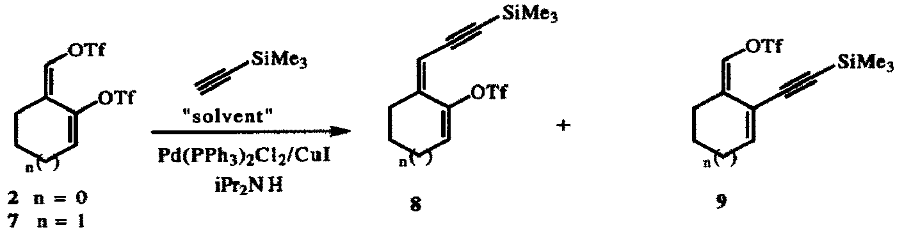


Three years ago we described stereoselective syntheses of the *Z*/*E* isomeric bistriflates **2** [5] and **3** [7]. In the presence of cat. $PdCl_2(PPh)_3$ and cat. CuI, the Z-configurated bistriflate **2** couples with terminal alkynes in THF/iPr_2NH (3:1) regioselectively at the exocyclic - i.e., less hindered - triflate moiety [5b]. Surprisingly, the isomeric *E*-bistriflate **3** couples under the same conditions preferentially at the semicyclic - i.e., more hindered - triflate site [8]. When in the meantime we found that the six-membered ring analogue **7** of *Z*-bistriflate **2** couples with the opposite regiochemical preference, too, we decided to study regiocontrol in these reactions more thoroughly. Accordingly, this communication describes the regioselectivity of palladium catalyzed monocouplings between Z-bistriflate **2** and its homologue **7**, respectively, with trimethylsilyl acetylene ("TMS acetylene") as a function of solvent, catalyst, and the added amine. The importance of some of these parameters for yield and rate of other enyne forming C,C-couplings is known [9].

Z-Bistriflate **7** [10] was prepared stereoselectively via the Z-configurated monotriflate **6** [11] according to the procedure which we used [5] in the five-membered ring series for the preparation of Z-bistriflate **2** from formylcyclopentanone via the Z-configurated monotriflate **4**.

In all monocoupling experiments, the bistriflate (**2** or **7**, 0.045 mol/l) was treated at room temperature with TMS acetylene (1.25 equiv.), palladium catalyst (7 mol-%), and CuI (17 mol-%) in a mixture (3:1, v:v) of solvent and amine. The reaction was monitored by thin layer chromatography either until it was complete or until we saw no further progress towards completion. Workup through extraction with brine/Et_2O, drying over Na_2SO_4, decoloration with charcoal, and flash chromatography on silicagel [13] provided the "exocyclic coupling product" **8** and the "semicyclic coupling product" **9** as non-separated mixtures. The former was identified by 200 or 300 MHz ^1H-NMR spectroscopy in $CDCl_3$ through a pair of olefinic signals at $\delta = 5.49$ (br. s) / 6.23 (br. s; **8**, n = 0) and 5.50 (br. s) / 5.99 (td, $^3J = 4.6$ Hz, $^5J = 1.1$ Hz; **8**, n = 1), the latter through similar sets of peaks at $\delta = 6.49$ (br. s) / 6.59 (br. s; **9**, n = 0) and 6.40 (br. s) / 6.47 (td, $^3J = 4.3$ Hz, $^5J = 1.5$ Hz; **9**, n = 1), respectively [14]. The isomer ratio **8**:**9** was determined from the integral ratio of these resonances. In duplicate runs which were performed for the majority of the coupling reactions, these ratios were reproducible within the error limits of the method. The average ratios along with the best isolated yields are compiled in Table 1 with respect to variation of the solvent, in Table 2 with respect to variation of the catalyst, and in Table 3 with respect to variation of the amine.

Table 1. *Solvent effects upon the regioselectivity of Pd-catalyzed monocouplings of bistriflates **2** and **7***

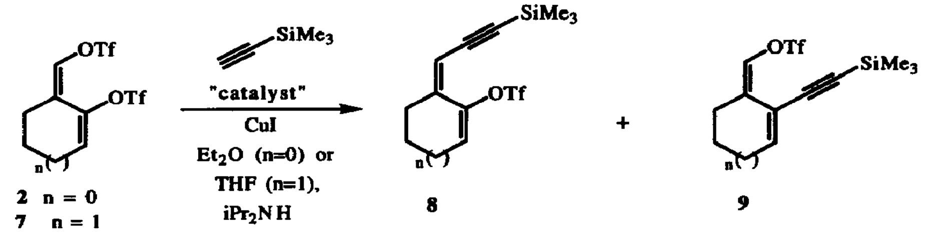


Solvent	E_T[12] of solvent	n = 0 Time	n = 0 % Yield (**8** + **9**)	n = 0 Isomer ratio **8** : **9**	n = 1 Time	n = 1 % Yield (**8** + **9**)	n = 1 Isomer ratio **8** : **9**
C_6H_{12}	31.2	50 min	73	85:15	30 min	75	4:96
Toluene	33.9	25 min	70	84:16	30 min	66	4:96
C_6H_6	34.5	20 min	93	84:16	25 min	64	6:94
Et_2O	34.6	30 min	67	83:17	25 min	71	3:97
THF	37.4	1 h	76	80:20	30 min	73	9:91
CH_2Cl_2	41.1	1 h 15 min	64	67:33	1 h 30 min	63	17:83[a]
DMF	43.8	1 h 30 min	62	47:53	50 min	56	13:87
DMSO	45.0	2 h	46	78:22	5 h 30 min	54	18:82
CH_3CN	46.0	1 h 20 min	55	79:21	1 h 10 min	61	17:83
iPrOH	48.6	1 h 40 min	77	81:19	2 h 30 min	70	11:89

a) 2 equiv. of TMS acetylene were used.

The result of our study is that semicyclic monocoupling in the six-membered ring series (**8**:**9** ratios 14:86 - 1:>99 in those reactions which gave >40% yield) is more preferred than exocycyclic monocoupling in the five-membered ring series (**8**:**9** ratios 37:63 - 85:15 in those reactions which gave >40% yield). Each of the parameters solvent, catalyst, and amine influenced the regioselectivity; however, the effects were usually different in the two series. Best for obtaining the exocyclic coupling product **8** (n = 0) selectively and in reasonable yield are cyclohexane, $Pd(PPh_3)_3Cl_2$, and iPr_2NH. Conversely, the semicyclic coupling product **9** (n = 1) is best obtained in the presence of Et_2O, $Pd(PPh_3)_4$, and a primary amine.

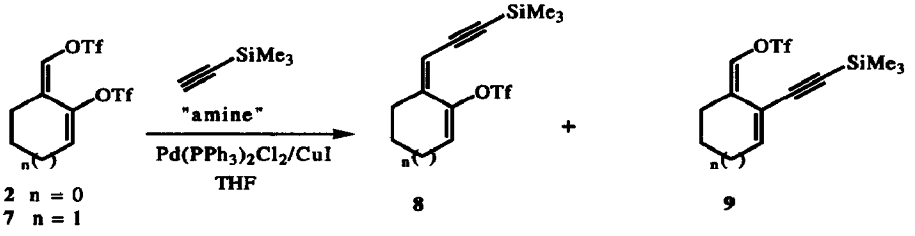
Table 2. *Catalyst effects upon the regioselectivity of Pd-catalyzed monocouplings of bistriflates 2 and 7*



Catalyst	n = 0 Time	n = 0 % Yield (8 + 9)	n = 0 Isomer ratio 8 : 9	n = 1 Time	n = 1 % Yield (8 + 9)	n = 1 Isomer ratio 8 : 9
$Pd(PPh_3)_4$	7 h	58	82:18	21 h	78	5:95
$Pd(PPh_3)_2Cl_2$	30 min	67	83:17	30 min	73	9:91
$Pd(AsPh_3)_2Cl_2$	24 h	44	57:43	3 h 45 mn	77	14:86
$Pd(dppe)_2Cl_2$	7 h	58	58:42	10 h 30 mn	37	19:81
$Pd(PPh_3)_2(OAc)_2$	5 h 30 min	50	65:35	20 h	65	14:86
$Pd(OAc)_2$, 2 PPh_3	24 h	43	80:20	25 min	64	6:94
$Pd(PhCN)_2Cl_2$	6 h	44	37:63	20 h	<11	31:69
$Pd(CH_3CN)_2Cl_2$	5 h	47	37:63	24 h	10	29:71

An interpretation of these results seems premature. Nonetheless, they offer the possibility to access isomerically pure monocoupling products **9** (n = 1) in a more convenient way than the one previously developed [5b] for the obtention of isomerically pure monocoupling products **8** (n = 0).

Table 3. *Amine effects upon the regioselectivity of Pd-catalyzed monocouplings of bistriflates 2 and 7*



Amine	n = 0 Time	n = 0 % Yield (8 + 9)	n = 0 Isomer ratio 8 : 9	n = 1 Time	n = 1 % Yield (8 + 9)	n = 1 Isomer ratio 8 : 9
$PrNH_2$	no reaction	-	-	22 h 30 min	49	1:>99
$PhCH_2NH_2$	no reaction	-	-	22 h	66	2:98
iPr_2NH	3 h	67	80:20	30 min	73	9:91
Piperidine	3 h	37	100:0	1 h	75	4:96
Pyrrolidine	decomposition	-	-	3 h	54	2:98
Morpholine	24 h	23	85:15	24 h	64	5:95
NEt_3	2 h	71	80:20	50 min	62	6:94

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10. Bistriflate **7** is Z because its olefinic ^{1}H-NMR resonances (δ = 6.09, 6.52) resemble those of Z-bistriflate **2** (δ = 6.23, 6.54) [5a]; conversely, the olefinic ^{1}H-NMR resonances of the *E*-isomer of **7** (δ = 6.11, 6.88) resemble those of *E*-bistriflate **3** (δ = 6.20, 6.80) [6b].
11. The Z-configuration of monotriflate **6** was deduced from its olefinic $\delta(^1H)$ = 6.46 which is similarly shifted upfield compared with $\delta(^1H)$ = 7.42 in the *E*-isomer as established for the olefinic resonances of the Z- (**4**: δ = 6.62) vs. the *E*-configurated five-membered ring analogues (**5**: δ = 7.49) [7].
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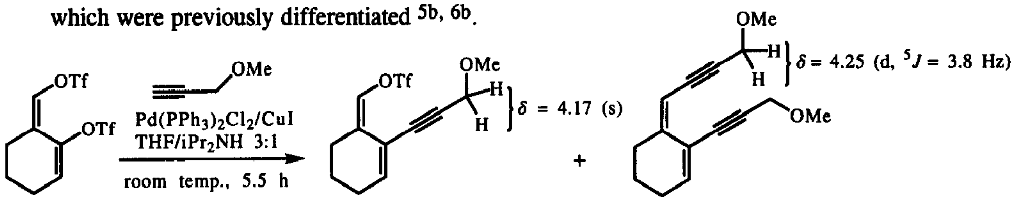
14. Monocoupling product **8** (n = 1) was distinguished from its isomer **9** (n = 1) because of the indicated similarities with the olefinic $\delta(^1H)$ values of the five-membered ring analogues **8**/**9** (n = 0) which were previously differentiated [5b, 6b].



7 **10** 25% **11** 35%

Further evidence that in bistriflate **7** coupling occurs preferentially at the semicyclic triflate moiety was gathered from an incomplete biscoupling between **7** and 3-methoxy-1-propyne. It delivered 25% of monocoupling product **10** and 35% of biscoupling product **11**. In compound **11**, the constitutionally heterotopic propargylic CH_2 groups exhibit a singlet and a doublet in the ^{1}H-NMR spectrum. The doublet splitting is due to a $^5J_{H,H}$ coupling (3.8 Hz) in the substructure $C{=}CH\text{-}C{\equiv}C\text{-}CH_2\text{-}OMe$; the existence of this coupling was corroborated by an appropriate crosspeak in the COSY spectrum. Since the ^{1}H-NMR resonance of the propargylic CH_2 group of monocoupling product **10** was a singlet, i.e., devoid of such a $^5J_{H,H}$ coupling, compound **10** must be devoid of the substructure $C{=}CH\text{-}C{\equiv}C\text{-}CH_2\text{-}OMe$ as specified in the formula.

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