Contrasteric Regioselectivity of Palladium(0) Catalyzed Couplings of Alkynes with a Bis(enoltriflate).
Novel Syntheses of *E*-Configurated Dienediynes

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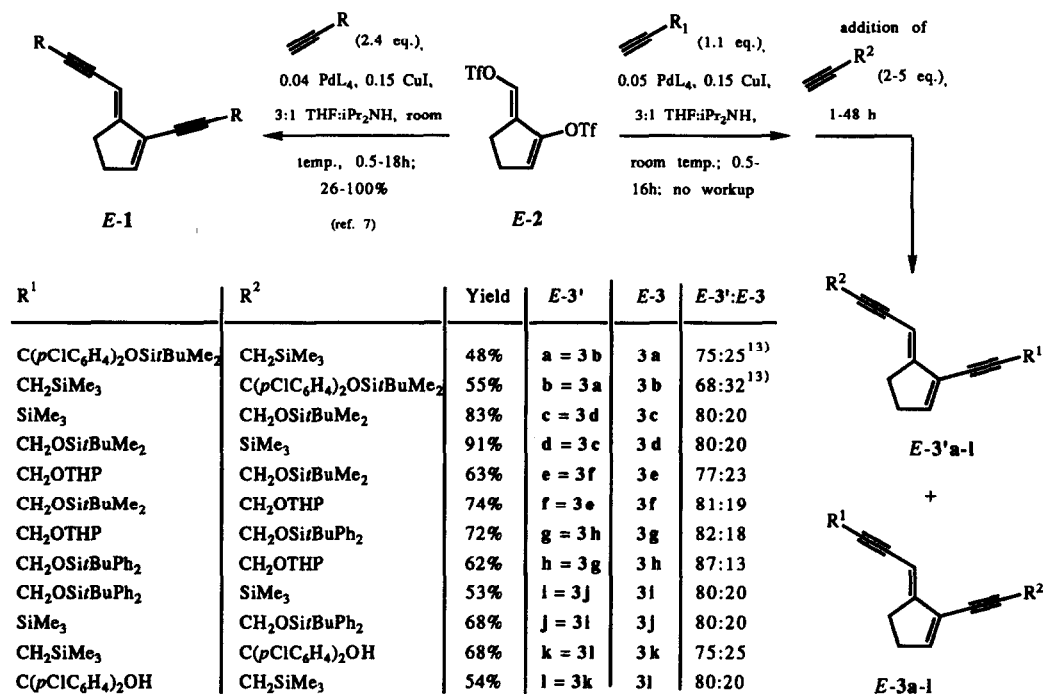Tammannstr. 2, D-3400 Göttingen, Germany;
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Abstract: Two consecutive PdCl$_2$(PPh$_3$)$_2$ catalyzed couplings of the bis(enoltriflate) *E*-2 with two different alkynes were performed as one-pot reactions; they provided 3:1-7:1 mixtures of dienediynes *E*-3a'-1' and *E*-3a-1 in 48-91% yield. *Selective* syntheses of such dienediynes were achieved by Pd mediated couplings of enolnonaflate *E*-6 with an alkyne followed by addition of a lithium acetylide and by dehydration.

Neocarzinostatin chromophore ("NCS") is a highly strained and exceedingly labile bicyclic dienediyne [1]. Its most noteworthy property is the capability to cleave DNA [2]. This initiated an intensive search for more stable and hopefully equally DNA-cleaving dienediyne models. Wender et al. were the first to obtain iso- and heterocyclic *bicyclic* dienediyne models of NCS [3]. A stream of related reports has emerged since then [4]. One interesting contribution was the first synthesis of NCS-related *monocyclic* dienediynes by Terashima and coworkers [5] who prepared an *E*-dienediyne *E*-3 and its isomer *Z*-3. A shorter synthesis of related *Z*-diene- diynes *Z*-1 was developed in our laboratories; it was based on the Pd catalyzed of the bis(enoltriflate) ("bistriflate") *Z*-3 with two equivalents of *one* alkyne [6]. An equally straightforward procedure starting from the *E*-configurated bistriflate *E*-2 led to the isomeric *E*-dienediynes *E*-1 [7]. A report by Terashima et al. about identical approaches to *Z*- and *E*-1 appeared thereafter [8]. Extending this strategy, we prepared dienediynes *Z*-3 by submitting the bistriflate *Z*-2 to two consecutive Pd-mediated couplings with two *different* alkynes [9]; as expected, the less hindered semicyclic C=C bond is attached to the first alkyne and the endocyclic C=C bond to the second. Again, Terashima's group was on our heels [10].
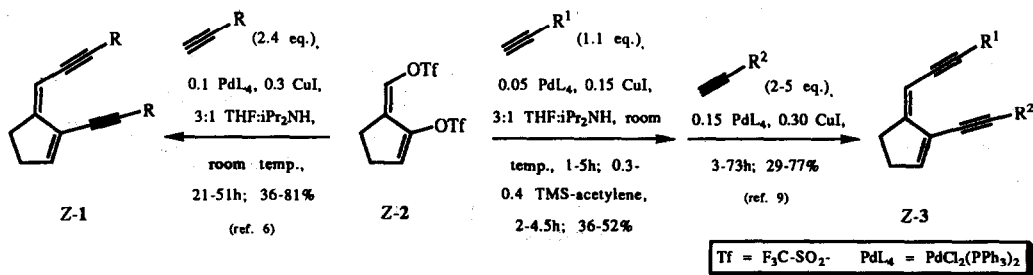
The present investigation concerned consecutive Pd-mediated couplings of the E-configurated bistriflate E-2 (0.08 M) with two different alkynes. Because of the faster reaction of exo- vs. endocyclic triflate group in the Z-series, we were surprised that E-2 couples preferentially at the *endocyclic* position. Consecutive additions - in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI - of $C≡C-R^1$ and $C≡C-R^2$ to E-2 furnished the dienediynes E-3'a-l/E-3a-l [11] as 87:13 - 75:25 mixtures in 48-91% yield after flash chromatography on silica [12]. When the order of the addition was reversed, we isolated the same dienediynes as before but in (almost) opposite ratios. The previous major constituent became the minor component, and *vice versa*. Three pairs of compounds 3d (vs. 3c), 3j (vs. 3i), and 3l (vs. 3k) were assigned structurally because of a 2 Hz ^5J H,H-coupling between the highlighted protons of the group $(=)CH\text{-}C≡C\text{-}CH_2\text{-}R$: The occurrence of this coupling indicates the alkyne which has replaced the exocyclic triflate moiety. The assignment of 3c vs. d was corroborated by and the distinction of 3a vs. b and of 3e vs. f founded upon $\delta(sp^2\text{-}H)$ comparisons with independently synthesized material (*vide infra*). The structures of isomers 3g vs. h followed from correlating their $\delta(sp^2\text{-}H)$ values with those of the closely related compounds 3e,f.

R^1	R^2	Yield	E-3'	E-3	E-3':E-3
$C(pClC_6H_4)_2OSitBuMe_2$	CH_2SiMe_3	48%	a = 3b	3a	75:25 [13]
CH_2SiMe_3	$C(pClC_6H_4)_2OSitBuMe_2$	55%	b = 3a	3b	68:32 [13]
$SiMe_3$	$CH_2OSitBuMe_2$	83%	c = 3d	3c	80:20
$CH_2OSitBuMe_2$	$SiMe_3$	91%	d = 3c	3d	80:20
CH_2OTHP	$CH_2OSitBuMe_2$	63%	e = 3f	3e	77:23
$CH_2OSitBuMe_2$	CH_2OTHP	74%	f = 3e	3f	81:19
CH_2OTHP	$CH_2OSitBuPh_2$	72%	g = 3h	3g	82:18
$CH_2OSitBuPh_2$	CH_2OTHP	62%	h = 3g	3h	87:13
$CH_2OSitBuPh_2$	$SiMe_3$	53%	i = 3j	3i	80:20
$SiMe_3$	$CH_2OSitBuPh_2$	68%	j = 3i	3j	80:20
CH_2SiMe_3	$C(pClC_6H_4)_2OH$	68%	k = 3l	3k	75:25
$C(pClC_6H_4)_2OH$	CH_2SiMe_3	54%	l = 3k	3l	80:20

These experiments mean that bistriflate E-2 undergoes the Pd catalyzed C-C bond formation at the sterically more hindered endocyclic sp^2 center (to which no H is attached) in preference to the exocyclic sp^2 center (bearing one H). This finding contrasts with the behavior of the isomeric bistriflate Z-2 and cannot presently be explained.
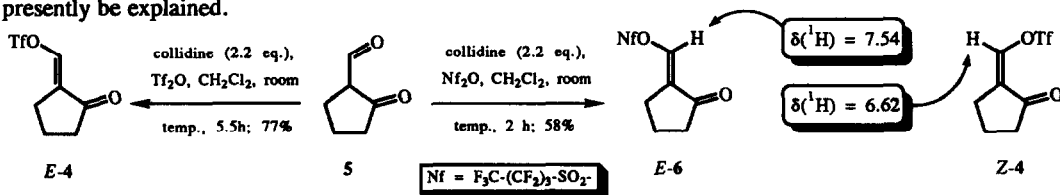
In order to safely assign the structures of dienediynes **3a-f** we synthesized them on an independent route. It started from monotriflate *E*-4 - now more efficiently and less expensively accessible from formylcyclopentanone **(5)** [14] than previously described due to replacement of 2,6-di-*tert*-butylpyridine through collidine - or from the similarly prepared nonaflate *E*-6. The latter's *E*-configuration followed from its $\delta(sp^2\text{-H}) = 7.54$ which is close to 7.49 of *E*-4 [7] and different from 6.62 of *Z*-4 [6].
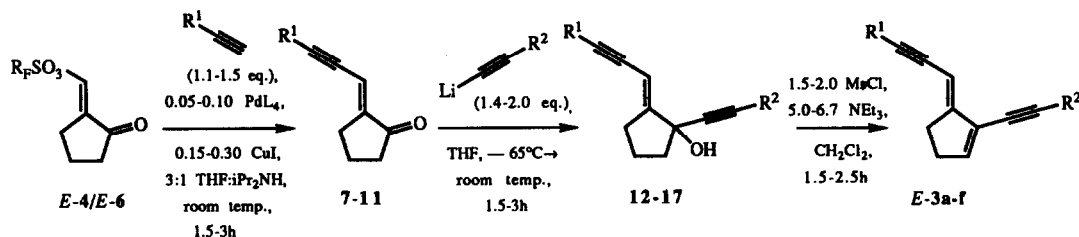
R_F	R^1	Yield 7-11	R^2	Yield 12-17	Yield *E*-3a-f
Nf	C(pClC$_6$H$_4$)$_2$OSitBuMe$_2$	66% **7**	CH$_2$SiMe$_3$	49% **12**	75% **3a**
Tf	CH$_2$SiMe$_3$	73% **8**	C(pClC$_6$H$_4$)$_2$OSitBuMe$_2$	80% **13**	46% **3b**
Nf	SiMe$_3$	60% **9**	CH$_2$OSitBuMe$_2$	73% **14**[15)	65% **3c**
Nf	CH$_2$OSitBuMe$_2$	72% **10**	SiMe$_3$	72% **15**	54% **3d**
Nf	CH$_2$OTHP	57% **11**	CH$_2$OSitBuMe$_2$	78% **16**	63% **3e**
Nf	CH$_2$OSitBuMe$_2$	72% **10**	CH$_2$OTHP	43% **17**	49% **3f**

Both the triflate *E*-4 (0.44 M) and the nonaflate *E*-6 (0.06-0.35 M) coupled smoothly with alkynes giving the enynones in 57-73% yield. **7-11** were *E*-configurated because of the 6.34-6.50 range of their $\delta(sp^2\text{-H})$ values and the identity of $\delta(sp^2\text{-H})_9$ with the literature value 6.36 [5]. Subsequent addition of a second alkyne as the lithium acetylide gave the moderately stable carbinols **12-17** (43-80%). They were converted into the desired dienediynes *E*-**3a-f** in 46-75% yield by treatment with mesylchloride/triethylamine. The virtue of *this* route is that the dienedynes are obtained isomerically pure.
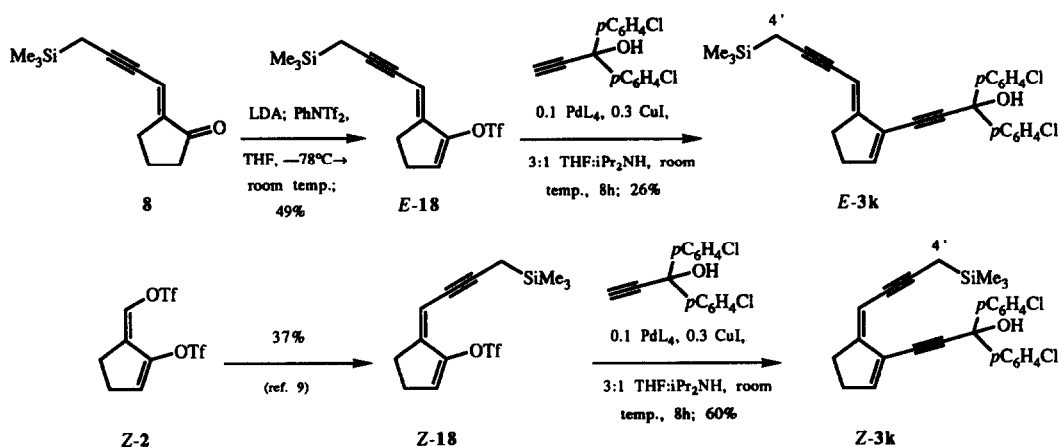
The *E*-configuration of the newly prepared dienediynes *E*-**3** was expected under the plausible assumption that the *established E*-configuration of their precursors **2, 4, 6,** and **7-11** was preserved during the

subsequent manipulations. In addition, we sought *definitive* confirmation in the exemplary case of dienediyne 3k. On the one hand, it was obtained with the E configuration following Terashima's strategy [5] by converting enynone 8 into triflate E-18 and coupling it with the required alkyne. On the other hand, Z-configurated 3k was obtained from the known triflate Z-18 following our already described procedure [9]. While the ^{1}H and ^{13}C NMR-spectra of E- and Z-3k were very similar in general, a conspicuous difference is the chemical shift value for 4'-H_2: It is 1.69 (d, $^5J = 2.4$ Hz) in the E and 1.15 (m_c) in the Z isomer. The main constituent in the E-3'l ($\approx$3k) / E-3l mixture described above had δ(4'-H_2) 1.70. This means, it possesses indeed the E geometry.

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11. Compounds E-3a-f, E-3k, E-6, and 7-17 gave satisfactory 250, 300 or 500 MHz ^{1}H-NMR spectra [15], combustion analyses, and/or high resolution mass spectra. The dienediyne mixtures E-3'a-l/E-3a-l [13], Z-3k, and E-18 were only characterized by 200 MHz ^{1}H- and 50 MHz ^{13}C-NMR spectra.

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13. The mixtures E-3'a/E-3a and E-3'b/E-3b were contaminated with 31 and 45%, respectively, of the dienediyne E-3 [$R^1 = R^2 = C(pClC_6H_4)_2OSitBuMe_2$].

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15. Compound 14 gave some elimination product 3c during ^{1}H-NMR spectroscopy.