Stereoselective Synthesis of (*Z*)-Enynes via Pd(II)/CuI(I)-Catalyzed Cross-Coupling Reaction of bis-Vinylic Tellurides with 1-Alkynes

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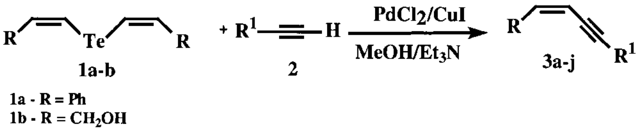
Abstract: (*Z*)-bis-Vinylic tellurides undergo direct coupling reaction with terminal alkynes in the presence of palladium (II) at room temperature to give (*Z*)-enyne systems in good yields.

Key words: cross-coupling, enynes, palladium, tellurium

Calicheamycins, esperamycins and dynemycins are a new class of antibiotic molecules recently emerged,[1,2] among the most potent antitumor agents known to date. All of these molecules exhibit a common moiety, a conjugated enediyne system able, upon DNA complexation and chemical initiation, to rearrange with concomitant formation of biradical species. Since it is complexed to the DNA minor groove, this biradical abstracts hydrogen atoms from the desoxyribose part of DNA. Oxidation then leads to DNA cleavage, and eventually to cell death.[1]

The synthesis of enynes has received special interest during the last 20 years and new methodologies using vinyl halides or vinyl organometallic compounds have been recently developed. The cross coupling of vinyl bromides, iodides, chlorides and triflates with monosubstituted acetylenes has been achieved in the presence of a Pd^0 or Pd^{II}/CuI catalyst using an amine as base.[3-7] The synthesis of enynes has been also performed using the coupling reaction of bromoalkynes with vinyl metals, like vinyl boron,[8] -copper,[9] -zinc,[10] -aluminum[11] or -magnesium reagents.[12] The use of vinylic tellurides[13] to obtain enyne and enediyne systems has been previously described using transmetalation with *n*-BuLi,[14] cyanocuprates[15] and directly with terminal alkynes.[16] In this paper we report the stereoespecific formation of (*Z*)-enyne systems by palladium catalyzed cross coupling reaction of (*Z*)-bis-vinylic tellurides with 1-alkynes (Scheme 1).[17]

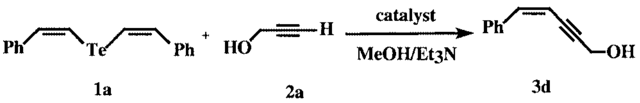


Scheme 1

In this way, (*Z*)-bis-vinylic tellurides were easily obtained from the reaction of the corresponding alkynes with elemental tellurium in alkaline media.[13] These compounds are stable to oxygen and can be chromatographed and stored in the dark at room temperature for several months.

Since our initial research efforts were dedicated to develop a good catalytic system, firstly we investigated the influence of the ligands in the palladium complex. Thus, (*Z*)-bis-vinylic telluride **1a** (1 equiv.) was treated in methanol at room temperature with 2-propyn-1-ol (2 equiv.) **2a** in the presence of different catalysts and Et_3N (1 equiv.) as base (Scheme 2). As shown in Table 1, $Pd(PPh_3)_4$ or $Pd(PPh_3)_4$/CuI did not exhibit catalytic activity in this reaction (entries 1 and 2) and Pd (II) catalysts such as $PdCl_2$/PPh_3, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $PdCl_2(PhCN)_2$ gave unsatisfactory yields of the desired enyne **3d** (entries 3-6).

The reaction was greatly enhanced by increasing the amount of $PdCl_2$/CuI from 1% to 10% (entries 7-10) and the enyne **3d** was obtained in 85% isolated yield (entry 10).

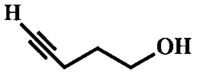
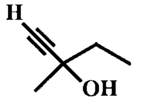
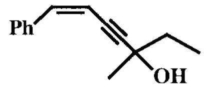
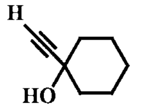
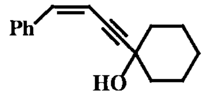
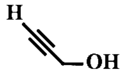
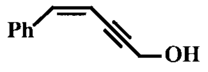
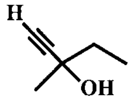
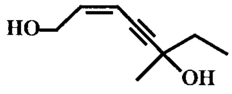
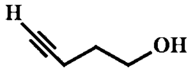
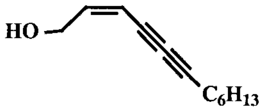
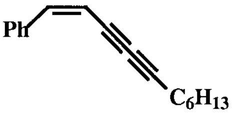
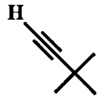
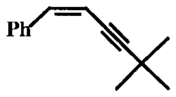
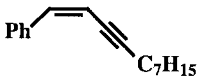
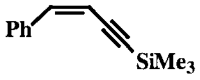
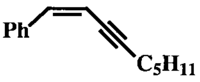


Scheme 2

Table 1 Influence of the Ligands in the Palladium Complex.

Entry	Catalyst (mol%)	Time (h)	Yield, **3d** (%)
1	$Pd(PPh_3)_4$/CuI (20)	48	0
2	$Pd(PPh_3)_4$ (20)	48	0
3	$PdCl_2/PPh_3$ (20)	20	8
4	$PdCl_2(PPh_3)_2$ (20)	20	5
5	$Pd(OAc)_2$ (20)	24	2
6	$PdCl_2(PhCN)_2$ (20)	20	5
7	$PdCl_2$/CuI (1)	24	23
8	$PdCl_2$/CuI (3)	24	30
9	$PdCl_2$/CuI (5)	24	47
10	$PdCl_2$/CuI (10)	6	85

Table 2 Enynes **3** Prepared According to Scheme 2

Entry	bis-Vinylic Telluride (**1**)	Alkyne (**2**)	Enyne (**3**)	Time(h)	Yield(%)[a]
1	**1a**		 **3a**	4	82
2	**1a**		 **3b**	5	78
3	**1a**		 **3c**	4	83
4	**1a**		 **3d**	6	85
5	**1b**		 **3e**	5	70
6	**1b**		 **3f**	4	75
7	**1b**	$H-\equiv-\equiv-C_6H_{13}$	 **3g**	7	84
8	**1a**	$H-\equiv-\equiv-C_6H_{13}$	 **3h**	7	80
9	**1a**		 **3i**	5	85
10	**1a**	$H-\equiv-C_7H_{15}$	 **3j**	8	77
11	**1a**	$H-\equiv-SiMe_3$	 **3l**	5	73
12	**1a**	$H-\equiv-C_5H_{11}$	 **3m**	8	75

[a] yield of isolated pure product.

The nature of the amine was critical for the success of the coupling. When (*Z*)-bis-vinylic telluride **1a** (1 equiv.) was treated at room temperature with 2-propyn-1-ol (2 equiv.) **2a** and $PdCl_2$ (10%)/CuI (10%) in MeOH (10 mL) using pyrrolidine, piperidine or morpholine (1 equiv.) as base, no reaction was observed. By using Et_2NH, *n*-$PrNH_2$ or *n*-$BuNH_2$, moderated yields were observed (15% to 28%). However, by using Et_3N, the enyne **3d** was obtained in 85% isolated yield and the reaction was completed within 6 h.

Thus, the optimum condition for the coupling in Scheme 1 was found to be the use of PdCl$_2$(10 mol%)/CuI (10 mol%), MeOH (10 mL), (*Z*)-bis-vinylic telluride **1** (1 mmol), the appropriate alkyne **2** (2 mmol) and Et$_3$N (1 mmol) at 25 °C.[17] Extending the coupling reaction to other alkynes, various *Z*-enynes **3** were obtained in good yields (Table 2). Although in all cases an excess of alkyne was used, the transfer of only one vinylic group was observed.

The formation of the enynes was confirmed by the analysis of the ^{1}H NMR spectrum. The stereoisomeric purities of the enynes **3a-j** were similar to that of starting bis-vinylic tellurides **1**,[18] due to a complete retention of configuration in this type of reaction. The stereochemistry of the obtained enynes was easily established. As an example, the ^{1}H NMR spectrum of compound **3d**, showed a double triplet at 5.75 ppm with coupling constants of 12 Hz and 2 Hz, typical of *cis* positioned hydrogen (hydrogen at carbon 4). The hydrogen at carbon 5 resonates at 6.63 ppm as a doublet with coupling constant of 12 Hz.

In summary, we have explored the Pd(II)/CuI catalyzed cross-coupling reaction of the (*Z*)-bis-vinylic tellurides with alkynes and established a new stereoselective route to (*Z*)-enynes in good yields. Our approach is improved compared to described methodologies, avoiding the preparation of vinyl metals, haloalkynes or protection of hydroxyl group in propargylic alcohol. In comparison to our previously described methodology the procedure has the advantage of easy access and great stability of (*Z*)-bis-vinylic tellurides. The use of this methodology for the synthesis of polyacetylenic compounds is under study in our laboratory. [19,20]

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(17) **Pd(II) Catalyzed Cross-Coupling Reaction of (*Z*)-Bis-Vinylic Tellurides with Alkynes: General Procedure:** To a solution of PdCl$_2$ (10 mol%, 0.018 g), CuI (10 mol%, 0.02 g) in MeOH (10 mL) at 25 °C. under an argon atmosphere, were added (*Z*)-bis-vinylic telluride **1** (1 mmol, 0.33 g) and the appropriate alkyne (2 mmol). The mixture was stirred at room temperature for the time indicated in Table 1, treated with NH$_4$Cl saturated solution (5 mL), extracted with ethyl acetate. The organic layer was washed with brine and dried over MgSO$_4$. The solvent were evaporated and the residue was purified by flash silica-gel chromatography eluting with hexane (products **3h**−**m)** or hexane/ethyl acetate 7:3 (products **3a**−**g)** to give the product **3**. **Selected spectral and analytical data for 3d**: Yield 0.13 g (85%); 200 MHz ^{1}H NMR (CDCl$_3$) δ = 7.83-7.27 (m, 5H), 6.63 (d, *J* = 12 Hz, 1H), 5.75 (dt, *J* = 12.0, 2.0 Hz, 1H), 4.46 (d, *J* = 2 Hz, 2H), 2.10 (s, 1H); 50 MHz ^{13}C NMR (CDCl$_3$) δ = 139.10, 136.15, 132.55, 128.55, 128.25, 106.70, 93.80, 84.00, 51.70; IR (neat, cm^{-1}) ν 3370, 3060, 2200, 1660, 786; LRMS (rel. int.) m/z 158 (15), 140 (19), 102 (100), 77 (30).

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