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Stereoselective synthesis of (*E*)-chloroenynes or (*E*,*E*)-chlorodienes starting from a stereoisomeric mixture of 1,2-dichloroethylenes

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Abstract—Under palladium or nickel catalysis, a stereomeric mixture 1:1 of (*Z*) and (*E*)-1,2-dichloroethylene readily reacts with 1-alkynes, vinyl alanes or vinyl boranes to afford selectively the corresponding (*E*)-coupling product in good to excellent isolated yields. The selectivity of this coupling reaction is discussed. © 2002 Elsevier Science Ltd. All rights reserved.

Chloroenynes are quite interesting intermediates which undergo a variety of synthetically useful transformations to give unsaturated compounds (e.g. enynes, 1,3-diynes, chloropolyenes, enediynes and polyenes).[1] By far, the most convenient and simple method for the synthesis of (*E*)- and (*Z*)-chloroenynes is the stereospecific palladium-copper catalyzed cross-coupling reaction of terminal alkynes with (*E*)- and (*Z*)-1,2-dichloroethylene.[2] This procedure is of great interest since the preparation of organometallic acetylide species is not required and it allows a huge range of functionalized 1-alkynes to couple chemoselectively under very mild conditions.

During our studies on this palladium-catalyzed coupling reaction, it was observed that the reactivity of (*E*)-1,2-dichloroethylene was higher than with the corresponding (*Z*)-isomer when the reaction was performed in piperidine, whereas in the presence of butylamine, the (*Z*)-1,2-dichloroethylene was more reactive than the corresponding (*E*)-isomer.[3] These results show that when a stereomeric mixture of 1,2-dichloroethylenes is reacted, the expected selectivity of the coupling reaction may be a function of the amine used. Moreover, it was also reported that in the presence of $Pd(PPh_3)_4$, the rate constant of the oxidative step for (*Z*)-1,2-dichloroethylene was ca. four times larger than the (*E*)-isomer ($k^Z/k^E = 3.6$).[4] It appeared therefore interesting to attempt a stereoselective synthesis of chloroenynes by coupling the easily available mixture of (*Z*)- and (*E*)-1,2-dichloroethylene with terminal alkynes in less than molar amounts. The results of this study are reported now.

As expected, it was found that under suitable conditions,[3] the reaction of the commercially available stereomeric mixture (*E*/*Z*:1/1) of 1,2-dichloroethylenes with hept-1-yne **1a** in the presence of $Pd(PPh_3)_4$, CuI and piperidine in benzene afforded selectively the desired (*E*)-chloroenyne **2a** in good yield (90%) together with a small amount of the (*Z*)-isomer ($E/Z = 90/10$). In order to favour the selective obtention of the (*E*)-isomer and to avoid the formation of the disubstituted products, an excess of (*Z*,*E*)-1,2-dichloroethylenes is needed (5 equiv.). It should be noted that this selectivity was enhanced in favour of the (*E*)-isomer when diethylether was used instead of benzene (Table 1, entry 1: *E*/*Z*, 98/2 in Et_2O instead of C_6H_6/*E*/*Z*, 90/10). The results presented in Table 1 show that under similar conditions, various 1-alkynes have been used successfully. In most cases, good yields of (*E*)-chloroenynes **2** were obtained and the reaction was highly stereoselective: the *E*-stereomeric purity was higher than 95%, except in the case of alkyne **1b** (entry 2).

Next, the cross-coupling reaction of alkyne **1** and a mixture of (*E*)- and (*Z*)-1,2-dichloroethylenes in the presence of *n*-butylamine was studied. Under these conditions, (*Z*)-1,2-dichloroethylene is expected to be more reactive than the (*E*)-isomer[3] and therefore the coupling should produce selectively (*Z*)-chloroenynes **2**.

Keywords: palladium; copper; alkynes; chloroenynes; chlorodienes.

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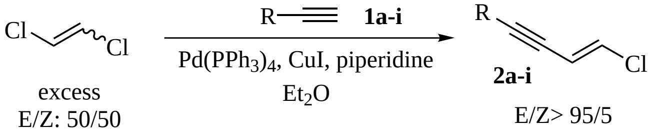
Table 1. Stereoselective synthesis of (*E*)-chloroenynes **2** from a mixture of (*Z*) and (*E*)-1,2-dichloroethylenes[a]



Entry	R	Yields[b] of **2** (%)	*E*/*Z*[c]
1	**a**: C_5H_{11}	90	98/2[d]
2	**b**: C_6H_5	80	90/10
3	**c**: $HO(CH_2)_9$	85	97/3
4	**d**: $HO(Me)_2C$	90	98/2
5	**e**: $C_5H_{11}CH(OH)$	70	95/5
6	**f**: Me_2NCH_2	75	95/5
7	**g**: $HO(C_5H_{11})CHCH_2$	71	98/2
8	**h**: $HOCH_2CH_2$	88	95/5
9	**i**: $HO(C_6H_5)CH$	78	95/5

[a] All reactions were performed in the presence of 5 mol% of $Pd(PPh_3)_4$, 10 mol% of CuI, 1,2-dichloroethylene (5 equiv., *E*/*Z*:1/1), piperidine (2 equiv.) in Et_2O at room temperature. All of the reported compounds exhibited spectral data in full accord with assigned structures.

[b] Yields are given for pure isolated products.

[c] Ratios were determined by ^1H NMR spectra in the crude reaction mixture.

[d] A 90/10 ratio was obtained when the reaction was performed in C_6H_6.

Thus, when performing the coupling with oct-1-yn-3-ol **1e** in diethylether in the presence of *n*-butylamine and $Pd(PPh_3)_4$–CuI, a mixture of (*E*)- and (*Z*)-chloroenynes **2e** was obtained in which the (*E*)-isomer is predominating (entry 10, Table 2). Attempts to improve this selectivity by using other palladium catalysts including $Pd(OAc)_2$, $Pd(dba)_2$, $PdCl_2(PPh_3)_2$ either with or without added triphenylphosphine met with no success. The effect of various amines was also studied and had no significant change on the selectivity of this reaction as summarized in Table 2. These results clearly demonstrate that, whatever the conditions used (nature of the amine or the catalyst), the (*E*)-isomer is remarkably more reactive than the (*Z*)-isomer. Such trends in selectivity have been already observed in the case of transition metal-catalyzed coupling reaction of bromoolefins or 1,2-dibromoethylenes with organometallic reagents.[5]

Table 2. Effects of amines on selectivity of the coupling of **1e** with stereoisomeric mixture (1/1) of 1,2-dichloroethylene[a]

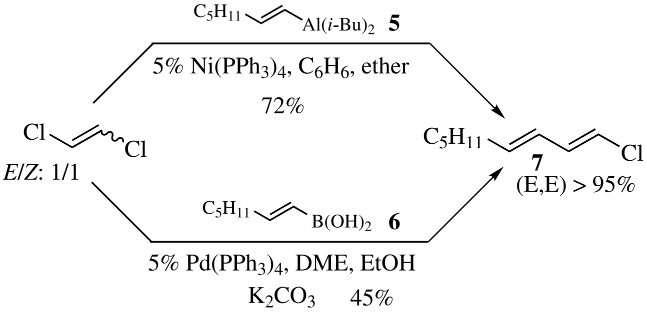
Entry	Amine	Yield (%)[b]	*E*/*Z*[c]
10	$BuNH_2$	90	85/15
11	Et_3N	84	82/18
12	Et_2NH	73	76/24
13	$i\mathrm{Pr}_2NH$	32	95/5
14	Pyrrolidine	65	92/8

[a] All reactions were performed in the presence of 5 mol% of $Pd(PPh_3)_4$, 10 mol% of CuI, 1,2-dichloroethylene (5 equiv., *E*/*Z*:1/1), amine (2 equiv.) in diethylether at room temperature.

[b] Yields of isolated product.

[c] Ratios were determined by ^1H NMR spectra in the crude reaction mixture.

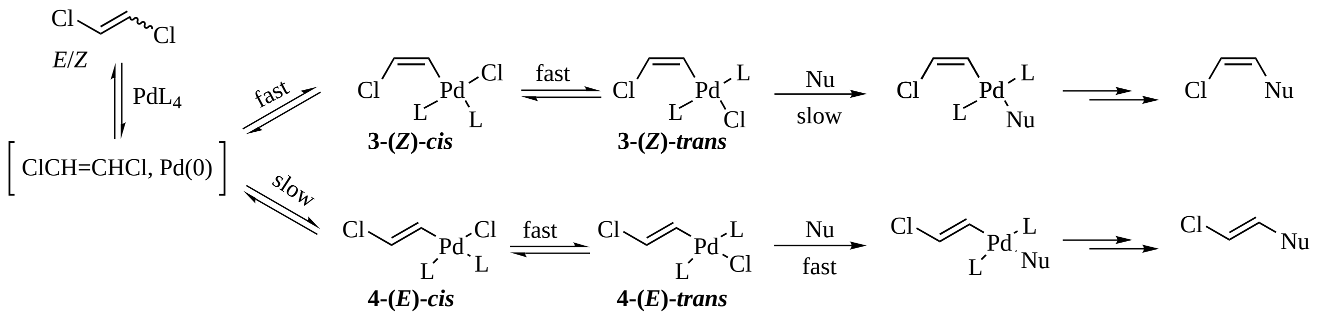
Finally, it should be noted that the selectivity observed in the case of 1,2-dichloroethylenes is not dependent on the nature of nucleophiles.[4] Thus, selective nickel- or palladium-catalyzed cross-coupling of vinyl alane **5** or vinyl borane **6** with a mixture of (*Z*)- and (*E*)-1,2-dichloroethylene according to the procedure developed by Linstrumelle[6] and Millar,[7] respectively resulted in the formation of (*E*,*E*)-chlorodiene **7** having a stereomeric purity higher than 95%[8].



The initial step of the mechanism of this reaction is presumably a coordination step followed by oxidative addition of (*E*)- and (*Z*)-1,2-dichloroethylene to the low-ligated Pd(0) complex to afford a mixture of σ-vinyl palladium species **3** and **4** (Scheme 1). Despite the higher reactivity of (*Z*)-1,2-dichloroethylene than of the (*E*)-isomer in the oxidative addition step,[4] the overall coupling reaction is the selective formation of (*E*)-chloroenynes **2**. It seems reasonable to conclude that the high selectivity of the reaction is due to the fact that the resulting σ-vinyl palladium species **3** and **4** exhibit different reactivity toward nucleophiles and that therefore the **4**-(*E*)-*trans* probably undergoes the transmetallation step much faster than **3**-(***Z***)-*trans* in the catalytic cycle.

In summary, we have shown that the coupling reaction of an excess of stereomeric mixture of (*Z*)- and (*E*)-1,2-dichloroethylenes with a terminal alkyne under appropriate conditions affords selectively (*E*)-chloroenynes in good yields. Moreover, when a vinyl alane or vinyl borane was used instead of 1-alkyne, the (*E*,*E*)-chlorodiene was obtained with a high stereomeric purity. These results show that although the coupling reaction is cleaner with the pure *trans* dichloroethylene (available commercially at Lancaster at a reasonable price), it can nevertheless be very well carried out with the usual *cis*–*trans* mixture. The observed selectivity may be assumed to be controlled by the rate of the transmetallation step in the catalytic cycle.

Typical procedure for the preparation of 2c: CuI (20 mmol, 40 mg) was added at room temperature to a solution of dichloroethylenes (*E*/*Z*:1/1, 10 mmol, 670 μL), alkyne **1c** (2 mmol, 334 mg), piperidine (4 mmol, 396 μL), and $Pd(PPh_3)_4$, (0.1 mmol, 116 mg) in Et_2O (5 mL). After consumption of the starting material (4 to 6



Scheme 1.

h), the dark brown reaction mixture is concentrated in vacuo. The ratio E/Z is determined by ^1H NMR spectra in the crude reaction mixture. Purification by flash chromatography on silica gel (AcOEt/cyclohexane: 40/60) gave 390 mg (85%) of **2c** (E/Z: 97/3). ^1H NMR (200 MHz, $CDCl_3$): δ 6.42 (d, $J=13.4$ Hz, 1H), 5.90 (dt, $J=13.4$ and 2.2 Hz, 1H), 3.63 (t, $J=6.7$ Hz, 2H), 2.28 (td, $J=6.9$ and 2.2 Hz, 2H), 1.56–1.49 (m, 4H), 1.30 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 128.6, 114.3, 93.5, 75.6, 63.0, 32.7, 29.3 (×2), 29.0, 28.8, 28.4, 25.7, 19.3.

Acknowledgements

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