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PALLADIUM-CATALYSED STEREOSELECTIVE HYDROVINYLATION OF DISUBSTITUTED ACETYLENES: PREPARATION OF FUNCTIONALIZED 1,2,4-TRISUBSTITUTED-1,3-DIENES

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Summary - Vinyl halides react with disubstituted acetylenes in the presence of the palladium-formate reducing system to give stereoselective formation of functionalized 1,2,4-trisubstituted-1,3-dienes in good to high yield. With arylethynyl,dialkylcarbinols this reaction provides a convenient entry into conjugated dienes containing an oxygen atom at the allylic position. *The nature of the base* (Et_3N, *n*-Bu_3N, $NaHCO_3$) *and the temperature affect* the regiochemical outcome of the reaction. A high degree of regioselectivity is observed in the hydrovinylation of carbomethoxyethynyl,dialkylcarbinols. In these case the hydrovinylation step is followed by an in situ cyclization to 3-alkenyl-spirobutenolides.

Conjugated diene systems are of considerable importance both as building blocks in Diels-Alder reactions and as structural features of many naturally occurring products.[1] A variety of methods for the regio- and stereoselective synthesis of this class of compounds has been developed. One of the approaches investigated more thoroughly in the last years is based on the palladium-catalysed coupling of two vinyl moieties, i.e., the reaction of vinyl halides[2] and triflates[3] with 1-alkenes (scheme 1,a) and 1-alkenyl metals (scheme 1,b).[4]

$$\text{R-CH=CX} \xrightarrow[\text{b) } L_nMC=CHR^1\text{, Pd(0)}]{\text{a) } CH_2=CHR^1\text{, Pd(0)}} \text{R-CH=CH-CH=CH-R}^1$$

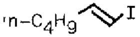
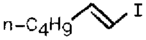
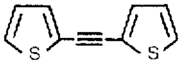
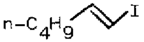
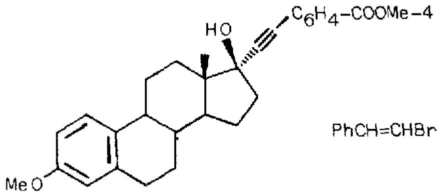
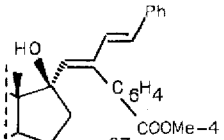
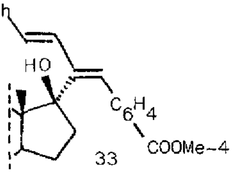
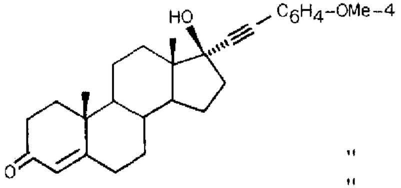
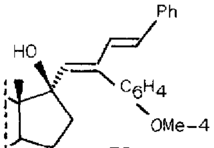
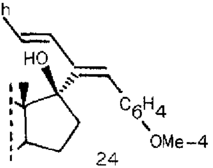
X = Br, I, OTf; ML_n = ZnCl; $B(OR)_2$; MgBr; AlR_2; $ZrCp_2Cl$; Cu,MgX_2; SnR_3; $SiMe_2F$

Scheme 1

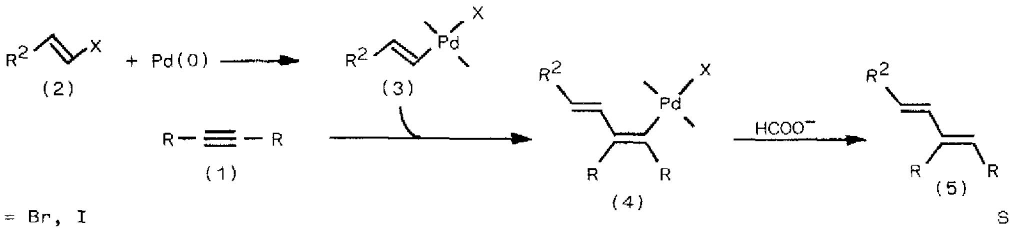
These methods allow the preparation of a large number of conjugated dienes in a variety of experimental conditions. However, the scope of many of these procedures is limited. Some of them require reagents incompatible with various common functional groups (strong bases or reducing agents) and the Heck reaction (scheme 1,a), which could tolerate a wide range of functionalities, can be best utilized in the presence of 1-alkenes, thus preventing internal ramification. Therefore it appeared to us of interest to explore the use of vinyl halides and disubstituted acetylenes in the presence of the palladium-formate reducing system to develop a new and selective synthesis of functionalized 1,2,4-trisubstituted-1,3-dienes. Now we report that disubstituted acetylenes (1) can be easily converted into internal conjugated dienes (5) through a palladium-catalysed hydrovinylation according to the scheme 2.

A typycal procedure is as follows: diphenylacetylene (0.249 g, 1.40 mmol) was added to

Table - Palladium-Catalysed Hydrovinylation of Disubstituted Acetylenes.[a]

Entry	Alkyne (1)	Vinyl halide (2)	Base/Phosphine/ Temperature(°C)/Time(h)	% Yield of (5)[b,c]	Relative percentages i	ii
a	Ph-≡-Ph		Et_3N/PPh_3/80/4	64		
b	4-MeCO-C_6H_4-≡-C_6H_4-COMe-4	"	" / " /60/4.5	58		
c	" "		" / " /60/3	72		
d	4-MeO-C_6H_4-≡-C_6H_4-OMe-4		$n-Bu_3N/PPh_3$/60/1.5	55		
e	n-C_3H_7-≡-C_3H_7-n	PhCH=CHBr[d]	Et_3N/PPh_3/50/1	40		
f			" / " /60/2	57		
g		PhCH=CHBr[d]	$Et_3N/P(o-Tol)_3$/60/0.25	60(31)	 67	 33
h	" "	"	Et_3N/DPPF[e]/60/24	57(31)	60	40
i	" "	"	$n-Bu_3N/P(o-Tol)_3$/60/6	76(18)	46	54
l	" "	"	$NaHCO_3$[f]/-/25/48	71(12)	52	48
m	" "	"	" /-/60/1.5	81	40	60
n	" "	"	" /-/90/0.25	86	31	69
o		"	Et_3N/PPh_3/60/0.25	45(43)	 76	 24
p		"	$Et_3N/P(o-Tol)_3$/60/0.25	80	56	44

a) Reaction conditions are not optimized. b) Yields (calculated on the starting alkyne) are for pure, isolated products. All new products had satisfactory elemental analysis and spectral data in agreement with the proposed structures. c) Figures in parentheses refer to the recovered starting material. d) As an E/Z mixture. However, only the styryl derivative from the E isomer was isolated.[12] e) DPPF refers to 1,1'-bis(diphenylphosphino)ferrocene. f) In the presence of $n-Bu_4NCl$ [(1):$n-Bu_4NCl$ = 1:1].



X = Br, I

Scheme 2

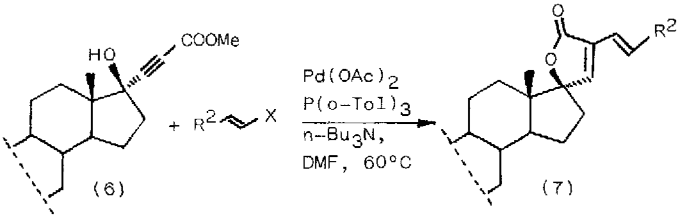
a mixture of Z-1-iodohexene (0.706 g, 3.36 mmol) and triethylamine (0.68 ml, 4.90 mmol).

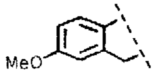
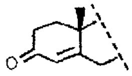
Then, $Pd(OAc)_2(PPh_3)_2$ (0.031 g, 0.042 mmol) and DMF (1 ml) were added. The mixture was purged with argon and formic acid (0.14 ml, 3.64 mmol) was added all at once. The mixture was stirred at 80 °C under an argon atmosphere for 4 h, diethylether and water were added, the organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by preparative HPLC on silica gel 20-45 µ (Amicon Co.). Elution with n-hexane gave the conjugated diene (5a) (0.237 g, 64% yield): mp 46-48 °C; IR (KBr) 1598, 785, 753, 705, 695 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.67-6.80 (m,10H), 6.53 (s,1H), 6.46 (d,J=15.7 Hz, 1H), 5.37 (dt,J= 7.5 Hz,J=15.7 Hz,1H), 2.3-1.9 (m,2H), 1.6-1.1 (m,4H), 0.85 (t,3H); MS (m/e) = 262 (M^+), 205.

The reaction proceeds with a high degree of stereospecificity, i.e., at least with the examples we have been testing, the configuration of the vinyl partner is retained (^1H-NMR analysis). Furthermore, addition of the in situ formed vinylpalladium intermediate (3) to the carbon-carbon triple bond and next formate reduction of the dienylpalladium intermediate (4) tends to produce only one stereoisomer. Control experiments carried out on (5d) revealed that the obtained 1,2,4-trisubstituted-1,3-diene do not undergo E/Z isomerization under reaction conditions. The stereochemistry of (5) has been assumed to derive from a syn-addition of vinyl palladium species to (1) on the ground of literature data,[5] the result of the X-ray analysis of 1,2,3-triphenyl-2-propen-1-ol obtained from the related palladium-catalysed reaction of phenyl iodide and 1,3-diphenyl-2-propyn-1-ol,[6] and a likely uniformity of the addition mechanism. With respect to the catalyst we have not thouroughly investigated this point. Tri-o-tolylphosphine was found to increase the yields (compare entry o with p). However, good results were also obtained by using triphenylphosphine and many entries in the Table employed triphenylphosphine as the ligand.

In order to evaluate the scope of this reaction as a convenient entry into stereodefined 1,3-dienes containing a center of chirality and an oxygen atom at the allylic position, a class of compounds reported to allow the control of diastereofacial selectivity in intermolecular Diels-Alder reactions,[7] we have studied the reactivity of steroidal arylethynyl,dialkylcarbinols (entries g-p). In the presence of Et_3N, the addition of the vinyl unit to the less crowded carbon atom was found to be favoured (entries g,h,o,p).[8] This result can be rationalized in terms of steric hinderance and hydroxyl coordination affecting the direction of addition of (3) to the carbon-carbon triple bond.[9] The regioisomeric ratio ranges from about 3.2 to about 1.3 depending on the nature of the ligand. Interestingly, a tendency to favour the reverse addition of (3) to the tertiary propargylic sistem, as well as higher overall yields,[10] were observed substituting $n-Bu_3N$ for Et_3N (compare entry i with g) or, even more, $NaHCO_3/n-Bu_4NCl$ for Et_3N (compare entry m with g and i). The regiochemistry was found to depend on the reaction temperature as well. Increasing it from 25°C to 90°C, the yield of the regioisomer with the added vinyl unit near the hydroxy group increases up to 59% (entries l-n).

A high degree of regioselectivity was observed in the hydrovinylation of steroidal carbomethoxyethynyl,dialkylcarbinols (6), very likely as the result of convergent steric, coordinating, and electronic effects.[9,11] In these cases the new carbon-carbon bond is formed quite exclusively on the carbon atom near the carbonyl group. However, the usual acyclic 1,3-dienes were not isolated since the addition step is followed by an in situ cyclization reaction and 3-alkenyl-spirobutenolides (7) are instead obtained in high yield (Scheme 3).



Yield	Substituents
72 %	 ;R^2 = $n\text{-}C_4H_9$; X = I
80 %	 ;R^2 = Ph; X = Br

Scheme 3

In conclusion, the palladium-catalysed hydrovinylation of disubstituted alkynes described here provides a useful and selective entry into stereodefined functionalized 1,2,4-trisubstituted-1,3-dienes not easily available by using established procedures. Further work along this line is in progress.

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References and notes

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7) Fisher, M.J.; Hehre, W.J.; Kahn, S.D.; Overman, L.E. J. Am. Chem. Soc. (1988) 110, 4625 and references therein

8) The structure of the regioisomers was assigned on the ground of ^{1}H-NMR spectra in the presence of variable amounts of the paramagnetic shift reagent $Eu(dpm)_3$. The olefinic proton of the 1,3-diene system appearing as a singlet was shifted the greater in all of the major isomers of entries g,h,l,o,p and in all of the minor isomers of entries i,m,n. Since the olefinic proton α to the allylic position is closer to the coordination site, the structure i was conceivably assigned to all of the above mentioned isomers.

9) Arcadi, A.; Cacchi, S.; Marinelli, F. Tetrahedron (1985) 41, 5121; Arcadi, A.; Cacchi, S.; Marinelli, F. Tetrahedron Lett. (1986) 27, 6397

10) In some cases, reactions were stopped because of disappearance of the starting vinyl halide (entries g,o). Changing from $Et_3N/P(o\text{-}Tol)_3$ to $n\text{-}Bu_3N/P(o\text{-}Tol)_3$ and to $NaHCO_3$/ /$n\text{-}Bu_4NCl$ proved to prolong the presence of the vinyl halide in the reaction medium. The same result can be obtained by using DPPF as the ligand. However, the use of DPPF slows down the hydrovinylation step as well (entry h).

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