Palladium-catalysed Reaction of Vinylic Halides with Allylic Alcohols: A Highly Chemo-, Regio- and Stereo-controlled Synthesis of Conjugated Dienols

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A new, direct, highly chemo-, regio- and stereo-controlled method for the construction of (*E,E*) and (*E,Z*) conjugated dienols from vinylic halides and allylic alcohols is described.

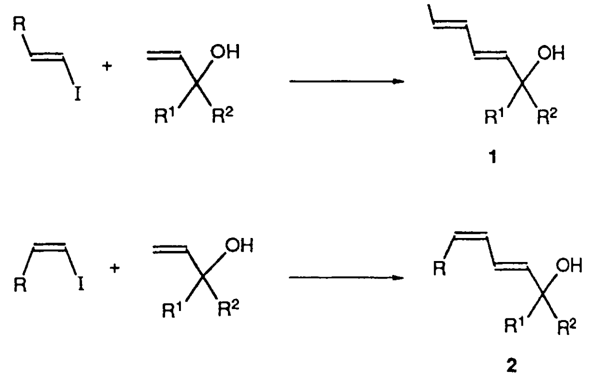
Palladium-catalysed coupling of aromatic halides with allylic alcohols is well known to give aryl substituted carbonyl compounds.[1–4] This type of reaction can be performed under very mild conditions upon addition of a tetraalkylammonium salt.[5] Reactions of vinylic halides with allylic alcohols still remain a challenge, from a synthetic point of view. They can proceed in the presence of secondary amines, but result in isomeric mixtures of carbonyl compounds and amino alcohols; only small amounts of dienols are obtained.[3,4,6]

We recently reported a selective formation of 4-enals from

Table 1 Palladium-catalysed chemo-, regio- and stereo-controlled synthesis of conjugated dienols from vinylic halides and allylic alcohols[a] (Scheme 1; R = C_6H_{13})

Vinylic halide	R^1	R^2	Silver salt	Conjugated dienol[b]	Yield[c] (%)
(*E*)	H	H	$AgNO_3$	(*E,E*) **1a**	(traces)
(*E*)	H	H	AgOAc	(*E,E*) **1a**	(60)
(*E*)	H	H	Ag_2CO_3	(*E,E*) **1a**	(60)
(*Z*)	H	H	AgOAc	(*E,Z*) **2a**	(61)
(*E*)	H	Et	AgOAc	(*E,E*) **1b**	70 (78)
(*Z*)	H	Et	AgOAc	(*E,Z*) **2b**	69
(*E*)	H	C_5H_{11}	AgOAc	(*E,E*) **1c**	80
(*Z*)	H	C_5H_{11}	AgOAc	(*E,Z*) **2c**	75
(*Z*)	H	C_5H_{11}	Ag_2CO_3	(*E,Z*) **2c**	76
(*E*)	Me	Me	AgOAc	(*E,E*) **1d**	82[d]
(*Z*)	Me	Me	AgOAc	(*E,Z*) **2d**	82[d]

[a] A suspension in DMF of vinylic halide (1 equiv.), allylic alcohol (3 equiv.), $AgNO_3$ (1.1 equiv), or AgOAc (1.1 equiv) or Ag_2CO_3 (0.55 equiv.) and $Pd(OAc)_2$ (0.03–0.05 equiv.) was stirred overnight at room temperature and then heated at 50–60 °C for 3–8 h unless otherwise noted. After cooling to room temperature, diethyl ether was added and the precipitate filtered off. The organic phase was washed (H_2O) and dried ($MgSO_4$). Evaporation under reduced pressure followed by silica gel column chromatography gave **1a**–**1d** or **2a**–**2d**. [b] All compounds were characterized by mass spectrometry, and IR, ^1H NMR and ^{13}C NMR spectroscopy. [c] Non-optimized yields of isolated compounds; GLC yields are in parentheses. [d] The reaction mixture was stirred at 60 °C for 24 h.



a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = Et$
c; $R^1 = H$, $R^2 = C_5H_{11}$
d; $R^1 = R^2 = Me$

Scheme 1 (R = C_6H_{13}) *Conditions*: Cat. $Pd(OAc)_2$, AgOAc or Ag_2CO_3, DMF

vinylic halides and primary allylic alcohols.[7] We now report that conjugated dienols can be efficiently prepared from vinylic halides and allylic alcohols; a highly chemo-, regio- and stereo-controlled formation of a conjugated dienic alcohol is achieved when a vinylic halide is treated with an allylic alcohol, in the presence of silver acetate (or silver carbonate) and a catalytic amount of palladium acetate, in *N,N*-dimethylformamide (DMF; Scheme 1).

Appropriate silver salts have been useful in several Heck-type reactions. Silver nitrate has suppressed the desilylation and has enhanced the reaction rate of the arylation and vinylation of vinyl and allyl trimethylsilanes.[8] Silver carbonate has permitted double bond isomerisation to be avoided in intramolecular and intermolecular arylation and vinylation of alkenes.[9,10] A combination of tetra-n-butylammonium hydrogen sulphate and silver carbonate has directed the coupling of vinylic halides with primary allylic alcohols towards the formation of 4-enals.[7]

The formation of conjugated dienic alcohols described herein is highly dependent not only on the nature of the silver salt but also on the nature of the solvent. In acetonitrile, none of the silver salts (nitrate, carbonate or acetate) was successful; low conversions were observed with silver nitrate and low yields and selectivities were obtained with silver carbonate or silver acetate. In DMF, silver nitrate remained inefficient but silver acetate or silver carbonate was effective (Table 1).

The coupling described is highly regioselective with respect to the addition of the vinylic group which only occurs at the terminal carbon. It is also highly stereoselective with respect to the formation of the two conjugated double bonds; the geometry of the organic halide double bond is retained and only an (*E*) type double bond is formed α to the alcohol functional group (Scheme 1). The process appears general as it is applicable to primary, secondary as well as tertiary allylic alcohols (Table 1).

This highly chemo-, regio- and stereo-selective construction of (*E,E*) and (*E,Z*) conjugated dienol functionalities, which is equivalent to a highly controlled vinylic hydrogen substitution of allylic alcohols by vinylic halides, is particularly attractive as it requires only one functionalized alkene reactant, in contrast to the cross-coupling between a vinylic halide and a preformed vinylic organometallic compound.[4]

The reaction described should find a broad synthetic applicability as conjugated (*E,E*) and (*E,Z*) dienol moieties often appear as a partial structure in numerous biologically active compounds such as the leucomycins,[11] the oxazolomycins[12] or many of the lipoxygenase metabolites of arachidonic acid (HETEs,[13] diHETEs,[13] leukotrienes[13] and lipoxins[14]) or other unsaturated hydroxy compounds.[15]

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