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Synthesis of Allyl and Alkyl Vinyl Ethers Using an in Situ Prepared Air-Stable Palladium Catalyst. Efficient Transfer Vinylation of Primary, Secondary, and Tertiary Alcohols

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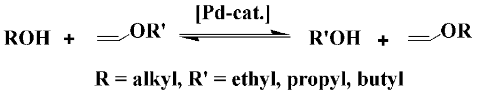
An air-stable palladium catalyst formed in situ from commercially available components efficiently catalyzed the transfer vinylation between butyl vinyl ether and various allyl and alkyl alcohols to give the corresponding allyl and alkyl vinyl ethers in 61−98% yield in a single step.

Introduction

Vinyl ethers are a highly valuable class of synthons with applications in polymer formulations, surfactants, and drug delivery systems as well as general organic synthesis.[1−3] Arguably even more valuable are allyl vinyl ethers, as they can undergo Claisen rearrangements,[4] which often constitute a key step in the synthesis of complex natural products or compounds used as flavors and fragrances.[5−7]

Simple vinyl ethers are produced on a technical scale by base-catalyzed addition of alkanols to acetylene,[8] while more complex vinyl ethers have been prepared by mercury-catalyzed transfer vinylations,[9] base- or metal-catalyzed isomerization of allyl ethers, or elimination reactions.[10] β-Oxa-γ,δ-enones, e.g., vinyl acetol, are accessible by the acid-catalyzed fragmentation of 4-methylene-1,3-dioxolane.[11] Recently Ishii and co-workers reported that $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadiene) is a highly effective catalyst for the vinylation of alkanols and phenols using vinyl acetate and Na_2CO_3 as the stoichiometric reagents under inert atmosphere.[12] Allyl vinyl ethers have been prepared from carbonyl precursors using the Tebbe reagent,[13] from silyl enol ethers,[14] and by aldol condensation of α,β-unsaturated esters.[15]

We successfully employed the palladium catalyst (L−L)$Pd(OAc)_2$; (L−L = 2,2′-bipyridyl or 1,10-phenanthroline chelate) for the transfer vinylation of protected sugars.[16] The catalyst had originally been described by McKeon and Fitton.[17,18] Prior to our work, its only other reported applications to vinyl ether synthesis were in the vinylation of steroids[19] and the synthesis of glycidol vinyl ether in moderate yield.[20] The palladium complex accelerates the equilibration of the reaction shown in eq 1, which can be driven by an excess of either vinyl ether or alcohol.



(1)

R = alkyl, R' = ethyl, propyl, butyl

The reactions are generally slow, e.g., 4−7 days for the sugar substrates in our previous report, and at such extended reaction times tend to generate acetals and ortho esters as side products.[16]

We now have reevaluated the Pd catalyst for a variety of primary, secondary, and tertiary alcohols and discovered that the utility of the reaction is greatly improved simply by changing the counterion ion from acetate to trifluoro acetate. Most significantly, the catalyst also effectively vinylates a representative selection of primary and secondary allyl alcohols leading to the corresponding allyl vinyl ethers in high yields. To our knowledge, this is the first direct catalytic route to this class of compounds.

Results and Discussion

The results of our study are summarized in Table 1. All reactions were carried out at 75 °C in air with a 0.5

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TABLE 1. Vinylation of Simple Primary, Secondary, Tertiary, and Allylic Alcohols (ROH) with *n*-Butyl Vinyl Ether (BVE) as the Reagent and Solvent (Molar Ratio ROH/BVE = 1:20) and (DPP)PdX$_2$ (DPP = 4,7-Diphenyl-1,10-phenanthroline; X = OAc$^-$, OOCCF$_3$$^-$) at 0.5 Mol % Catalyst Load and 75 °C Reaction Temperature (i.e., Refluxing BVE)

		% yield[a] of vinyl ether formed and time to equilibrium (h) with counterion X:[b]	
entry	alcohol vinylated	OAc^-	$OOCCF_3^-$
	primary alcohols		
1	benzyl alcohol	84 (23)	88 (4)
2	benzyl alcohol[c]	not det	98 (20)
3	1,6-hexanediol[d]	98 (5)	98 (2.5)
4	4-penten-1-ol	95 (8)	95 (1)
	secondary alcohols		
5	cyclopentanol	92 (24)	92 (3)
6	cyclohexanol	86 (33)	86 (4)
7	1-phenylethanol	77 (24)	79 (6)
8	menthol	82 (55)	83 (13)
9	isomenthol	not det	86 (6)
10	neomenthol	not det	86 (32)
	tertiary alcohols		
11	adamantanol	42 ($\gg$72)[e]	61 (48)
12	*tert*-butyl alcohol	47($\gg$32)[e]	72 (32)
	allylic alcohols		
13	allyl alcohol[f]	62 (24)	90 (7)
14	1-penten-3-ol	not det	81 (8)
15	(−)-carveol[g]	not det	80 (8)
16	2-cyclohexen-1-ol	not det	84 (3)
17	(*S*)-(−)-perillyl alcohol	not det	89 (2.5)
18	3-methyl-2-buten-1-ol	not det	96 (1)
19	linalool	not det	0 (>12)

[a] By GC. [b] If $X^- = OOCCF_3^-$ 30 mol % of NEt_3 were added to suppress acetal formation; see text. [c] *tert*-Butyl vinyl ether was used instead of butyl vinyl ether. [d] Reaction produces primarily divinyl ether; calculation is based on this product only. [e] Reaction abandoned before equilibrium was established. [f] Using propyl vinyl ether instead of butyl vinyl ether. [g] *p*-Mentha-6,8-dien-2-ol; mixture of two isomers. One isomer is initially vinylated faster than the other, but at equilibrium the ratio of vinylated isomers matches that of the starting alcohol.

mol % catalyst load with respect to alcohol. The catalyst is formed in situ from PdX$_2$, and the ligand at equimolar ratios. To drive the equilibrium, a 20-fold molar excess of commercially available butyl vinyl ether (BVE) was employed as both the solvent and vinyl source. At the end of the reaction, unreacted BVE can be recovered by passing the reaction mixture through activated charcoal to remove the catalyst followed by distillation. Propyl vinyl ether (PVE) was used for the vinylation of allyl alcohol (entry 13) due to separation problems between the product allyl vinyl ether and BVE. This substitution had no noticeable effect on the overall reaction. *tert*-Butyl vinyl ether (entry 2) was used for a direct comparison of the steric demands of the vinyl source on the reaction rate and equilibrium. 4,7-Diphenyl-1,10-phenanthroline (DPP) was chosen as the ligand in all cases as it resulted in optimum catalyst solubility in the vinyl ether reaction medium giving clear yellow reaction solutions. Other 2,2′-bipyridyl- and phenanthroline-derived ligands are also effective but were not further investigated.

Entries 1, 3−8, and 11−13 of Table 1 show that the exchange of acetate for trifluoroacetate substantially shortens the time until the reaction reaches equilibrium as indicated by invariant product concentrations beyond the reaction times listed in Table 1. The same entries in Table 1 also establish that the exchange of the counterion has no effect on the equilibrium position itself, as the achieved yields are the same within the error range of their determination.

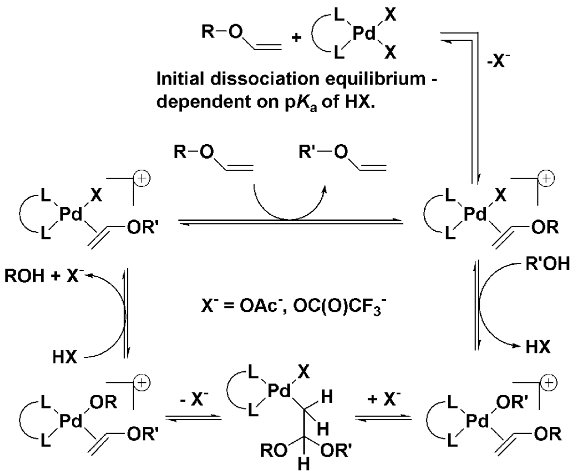

FIGURE 1. Proposed mechanism of the catalytic transfer vinylation.

The proposed mechanism for the transfer vinylation is shown in Figure 1. In the initial equilibrium, one of the counterions X$^-$ is displaced by η^2-coordination of vinyl ether. The coordinating ability of the counterion is related to the pK_a of the corresponding acid (4.75 for acetic acid vs 0.50 for trifluoro acetic acid on the aqueous scale). When the less coordinating trifluoro acetate is used, this equilibrium lies further to the right. Consequently, at equal catalyst precursor concentrations, more actually catalytically active centers are formed resulting in a faster reaction. At the same time, the use of trifluroacetate leads to the formation of acetals as a major byproduct catalyzed by the formation of the much stronger acid HOC(O)CF$_3$ in the catalytic cycle. Acetal formation is, however, completely suppressed when the free acid is scavenged by NEt$_3$ added in 10−15-fold excess with respect to palladium. No coordinative inhibition of the catalyst by the auxiliary base or change in product distributions is observed even at higher base concentrations.

No transfer vinylation was observed when 2,2:6,6-terpyridine was employed as the ligand. Monodentate ligands such as pyridine also fail to give active catalysts;[12,17,18] i.e., a cis chelation is a necessary condition for catalysis to occur. This suggests an intramolecular attack of a coordinated alkoxide on the activated double bond to give the palladium alkyl complex (bottom center of Figure 1) as the key intermediate.

The fact that the reaction is very sensitive to steric effects supports this model. Vinyl ethers with substituents other than hydrogen on the α-carbon of the vinyl group do not give any transfer vinylation because either the η^2-vinyl alkoxide intermediate cannot be formed at all or cannot assume the right conformation for the oxypalladation to occur. The method is thus limited to simple ethenyl ethers. Steric bulk on either one but not both of the two alcohol moieties involved in any given reaction is however well tolerated. Entries 1 and 2 in Table 1 demonstrate the effect of a bulky vinyl source on the reaction rate and equilibrium position while entries 11

TABLE 2. Comparison of the Palladium- and Iridium-Based Vinylation Catalysts for Allyl and Alkenyl Alcohols and Phenols

entry	alcohol	% yield with Pd catalyst	% yield with Ir catalyst[b]
1	4-pentenol	95	100
2	1,6-hexanediol	98	87
3	phenol	0	98
4	allyl alcohol	90	0
5	1-penten-3-ol	81	<5
6	(−)-carveol	80	49
7	2-cyclohexen-1-ol	84	33
8	(*S*)-(−)-perillyl alcohol	89	86
9	3-methyl-1-butenol	96	0
10	linalool	0	0

[a] GC yields. [b] Reaction conditions: alcohol/vinyl acetate/Na_2CO_3/Ir = 1.0:2.0:0.6:0.02; toluene, argon, 100 °C for 4 h; for comparison, some yields were taken from ref 12.

and 12 and the series of menthols (entries 8−10) illustrate the effect of steric bulk of the incoming alcohols on the reaction rate. While the yields at equilibrium under the given conditions are essentially the same for all three menthols, the vinylation of isomenthol, in which both alkyl substituents are oriented trans to the reacting hydroxyl reaches equilibrium in 6 h, while with neomenthol, in which the reacting hydroxyl group is oriented cis to the bulky isopropyl substituent, it requires 32 h to reach its equilibrium. If both the vinyl source and the incoming alcohol are sterically demanding, no reaction occurs. Also the catalyst fails to vinylate the sterically demanding tertiary allyl alcohol linalool. Other primary and secondary allyl alcohols are, however, cleanly vinylated in good to excellent yields (entries 13−18 in Table 1). Table 2 compares the results obtained with the iridium and the palladium system with allyl and alkenyl alcohols, showing their complementarity for different classes of substrates.

Both catalysts tolerate the presence of double bonds remote to the hydroxyl function to be vinylated and also vinylate diols, but the palladium system does not vinylate phenols, probably due to the lower nucleophilicity of phenoxide vs alkoxide,[21] which prevents the oxypalladation step from occurring. In turn, the iridum system vinylates phenols but completely fails for linear allyl alcohols, while for allyl alcohols in which the double bond is part of a ring system variable yields are obtained.

Cationic iridium complexes of the type [Ir(cod)(L)(L′)]X (L = phosphine, L′ = nitrile, X = noncoordinating counterion) are known to catalyze the enolization of allyl alcohols,[22,23] which can subsequently tautomerize to the corresponding carbonyl compounds. These are, however, not observed in the GC traces of the reactions, which suggests that in the absence of stabilizing ligands the iridium center is deactivated by an irreversible reaction with the enol, whose formation competes with the transfer vinylation. Thus, the transfer vinylation yields inversely correlate to the ease of formation and stability of the corresponding enols: e.g., perillyl alcohol, whose enolization would result in an exocyclic double bond is vinylated in high yield, while the kinetically and thermodynamically more easily enolized linear allyl alcohols instantly poison the catalyst and therefore give no vinyl ethers.

Finally, neither catalyst vinylates 2-propyn-ol, 2-butyn-1-ol, or other propargyl alcohols tested. Instead, immediate darkening of the reaction mixtures and formation of a brown precipitate is observed in both cases.

Conclusion

The complex (DPP)Pd($OOCCF_3$)$_2$ (DPP = 4,7-diphenyl-1,10-phenanthroline) is an optimized catalyst for the equilibrium transfer vinylation of various alcohols with butyl vinyl ether as the reactant and solvent and NEt_3 as an auxiliary base. The catalyst system is air-stable, does not generate acetal byproducts on the time scale of the reaction, tolerates remote carbon−carbon double bonds in the alcohol substrates, and vinylates allyl alcohols but not phenols. It is thus complementary to the iridium catalyst [Ir(cod)Cl]$_2$ (cod = 1,5-cyclooctadiene), which uses vinyl acetate under basic conditions as the vinyl source and does vinylate phenols, but not allyl alcohols.

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Supporting Information Available: Typical reaction protocol; extensive GC and GC−MS characterization data for all vinyl ethers synthesized; and $^1H/^{13}C$ NMR data and spectral images for new vinyl ethers synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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