Allylation of Aliphatic Aldehydes

Pd-Catalyzed Nucleophilic Alkylation of Aliphatic Aldehydes with Allyl Alcohols: Allyl, 2-Tetrahydrofuryl, and 2-Tetrahydropyranyl Ethers as Useful C_3, C_4, and C_5 Sources**

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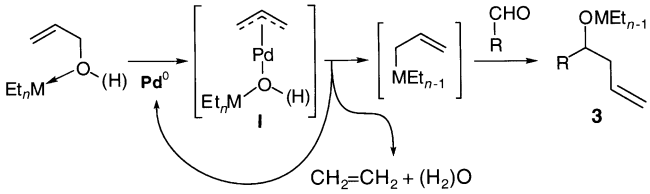
The allylation of aldehydes at both the carbonyl carbon atom and at the carbon atom α to the carbonyl group is among the most fundamental and useful methods for elaborating molecules. These reactions, in general, have been performed by using the activated forms of allyl alcohols, such as carboxylic acid esters and other organic and inorganic acid esters. A possible reason why allyl halides have been used most widely for alkylation is because of their ready conversion into a variety of allylmetallic species (Metal = Mg, Li, Si, Sn, etc.).

Recently, we disclosed that nucleophilic alkylation of an aromatic aldehyde can be successfully performed by using allyl alcohol itself. This is possible by virtue of the ability of palladium(0) species to catalytically activate allyl alcohol as its π-allylpalladium species in the presence of Et_3B through an allyl–ethyl exchange reaction between the π-allylpalladium and Et_3B species (Scheme 1).[1]



Scheme 1. Pd-catalyzed alkylation of aliphatic aldehydes ($Et_nM = Et_3B$ or Et_2Zn). For the reaction with Et_2Zn, the hydrogen atom(s) in parenthesis should be either ignored or replaced with Zn^{II} arising as a result of the hydrolysis of Et_2Zn.

Unfortunately, the reaction is not applicable to aliphatic aldehydes; aliphatic aldehydes undergo competitive nucleophilic and electrophilic alkylations under similar conditions. For example, the reaction of cyclohexanecarboxaldehyde (**1a**) and cinnamyl alcohol (**2a**) provided a mixture of **3a** and **4a** in almost equal amounts [Eq. 1 and Table 1, entry 1]. The nucleophilic alkylation giving rise to **3a** could be obviated by

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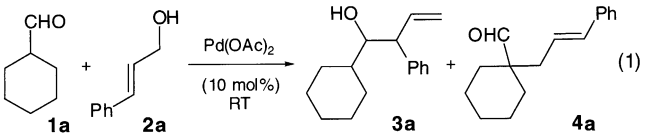


Table 1: Effects of organometallic compounds and ligands (**1a** = 1.1 mmol, **2a** = 1.0 mmol) in the Pd-catalyzed ambiphilic allylation of aliphatic aldehydes with allyl alcohols.

Entry	RM[a] (equiv)	Phosphane (equiv)	Solvent (mL)	Time [h]	% isolated **3a**[b]	% isolated **4a**
1	Et_3B (2.4)	PPh_3 (0.2)	THF (5.0)	4	39	30[c]
2	Et_2Zn (3.6)	PPh_3 (0.2)	THF (5.0)	30[d]	18	0
3	Et_2Zn (3.6)	PBu_3 (0.2)	THF (5.0)	10	53	0
4	Et_2Zn (3.6)	PBu_3 (0.2)	tol[e] (0.5)	30	79	0[c]
5	Et_2Zn (3.6)	PBu_3 (0.4)	tol[e] (0.5)	6	75	0

[a] A 1 M solution of Et_2Zn or Et_3B in *n*-hexane was used. [b] *syn*:*anti* = 1:14 to ca. 1:18. [c] 1,4-Diphenyl-1,5-hexadiene was obtained in 20% (entry 1) and 3% yields (entry 3). [d] 45% Conversion. tol = toluene.

using LiCl and Et_3N as additives. This resulted in the selective α-alkylation of aliphatic aldehydes to give **4a**.[2]

Here we report that nucleophilic alkylation of aliphatic aldehydes with allyl alcohols proceeds selectively just by substituting Et_3B for Et_2Zn.[3]

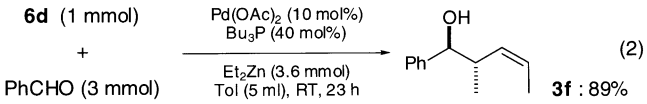
Our working hypothesis (Scheme 1)[2] suggested that organometallic species of higher migratory aptitude might promote the allyl–alkyl exchange process more readily and hence facilitate generation of an allylmetal species. Accordingly, we reexamined the reaction of **1a** and **2a** (Table 1) using Et_2Zn in place of Et_3B. As was expected, **4a** was not produced at all; however, the reaction was very sluggish and provided the expected **3a,** albeit in low yield (Table 1, entry 2). Application of nBu_3P, in place of Ph_3P, dramatically increased the yield of **3a** and the reaction rate (entry 3, Table 1). Interestingly, nonpolar solvents seem to give the best results (Table 1, entries 4 and 5). The solvent system in these reactions is rather unique: it consists of toluene (0.5 mL) and *n*-hexane (3.6 mL) for a 1 mmol scale reaction. The amount of toluene is set to make the initial reaction mixture homogeneous at 0°C (Scheme 2, see also the Experimental Section).

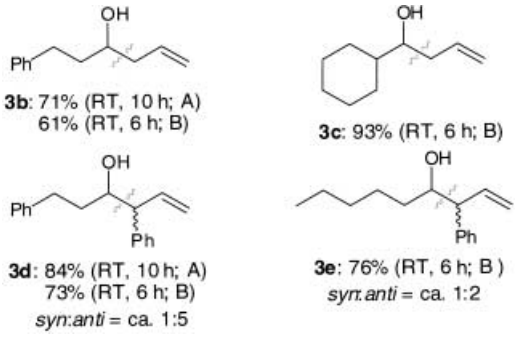
The utility and generality of the present nucleophilic alkylation of aliphatic aldehydes with allyl alcohols are apparent from the results summarized in Scheme 2. The diastereoselectivity found for the reactions carried out with cinnamyl alcohol is modest and seems to depend on the steric bulk of the alkyl chain of the aldehydes and ranges from *syn*:*anti* = 1:18 (cyclo-$C_6H_{11}CHO$) to 1:2 (*n*-$C_5H_{11}CHO$). It is worth noting that, despite in situ formation of zinc alkoxides, no aldol-, Cannizzaro-, or Tischchenko-type products were detected at all in these reactions.

We envisaged that the reaction conditions that were successful for the activation of allyl alcohols should be applicable to the activation of allyl ethers because an ether group is a much better leaving group than a hydroxy group.[4] Indeed, allyl 2-tetrahydrofuryl (THF) ethers **5** and allyl 2-tetrahydropyranyl (THP) ethers **6**[5] turned out to readily effect nucleophilic allylation of ω-formylalkanolates formed in situ to furnish 1,4-dihydroxy-6-heptenes **7** and 1,5-dihydroxy-7-octenes **8**, respectively, in excellent yields (Table 2).[6] Except for highly branched allylic substrates, most of the reactions were completed within a few hours at room temperature.

The regioselectivity is in accord with that displayed by structurally fluctuant allylmetallic species of main-group elements, which give rise exclusively to the most highly branched isomers. In particular, the clean transformation of **6e** to **8e** and **6f** to **8f** is notable. These observations suggest that allylzinc species are reactive intermediates in these reactions. However, the poor stereoselectivity of **8d** (Table 2, entry 6) is quite different from that reported previously by us; the allylation of aldehydes by umpolung of 1,3-dimethylallyl benzoates provides *Z-anti* adducts exclusively.[7]

We thus examined the reaction of **6d** in the presence of three equivalents of benzaldehyde under otherwise identical conditions and found that (*Z*)-*anti*-2-methyl-1-phenyl-3-pentenol (**3f**) was produced exclusively in excellent yield [Eq. 2].



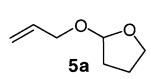
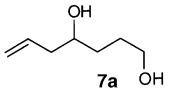
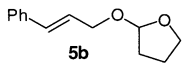
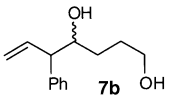
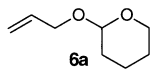
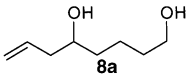
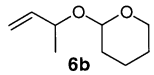
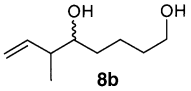
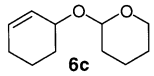
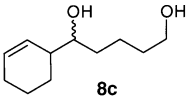
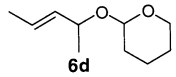
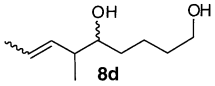
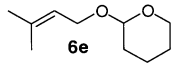
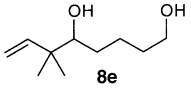
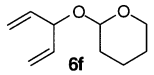
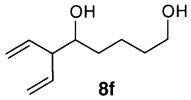


Scheme 2. Nucleophilic allylation of aliphatic aldehydes undertaken using conditions A (Table 1, entry 3) and/or B (Table 1, entry 5).

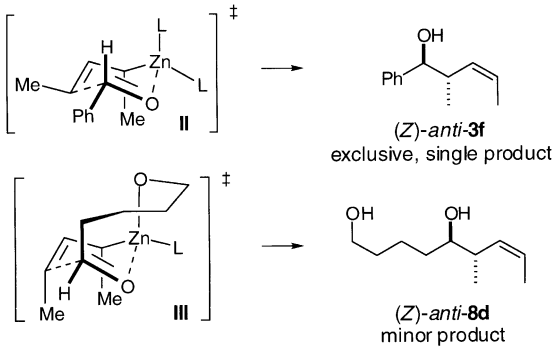
This result clearly indicates that allylzinc species generated from different sources (benzoate and **6d**) are identical and react with benzaldehyde via a transition state **II** (Scheme 3). The methyl group α to the Zn atom occupies a quasi-axial position in this six-membered chairlike transition state so as to minimize the steric repulsion with the two ligands on the Zn^{II} center. Thus, a quasi-equatorial conformation of the methyl group γ to the Zn^{II} center is rendered the most likely one.[8]

The poor stereoselectivity of **8d** may be attributed to the formation of a cyclic zinc ω-formylalkanolate species through coordination of the aldehyde oxygen atom to the Zn^{II} center, which makes approach of the aldehyde with its substituent in

Table 2: Pd-catalyzed, Et_2Zn-promoted alkylation of hemiacetals generated from allyl 2-THF **5** and allyl 2-tetrahydropyran (THP) ethers **6**.[a]

Entry	Allyl ether	Reaction time [h]	Product	Yield (diastereomer ratio)
1	 **5a**	1	 **7a**	87
2	 **5b**	1	 **7b**	88 (*syn*/*anti* = 1:3)
3	 **6a**	2	 **8a**	91
4	 **6b**	0.5	 **8b**	97 (*syn*/*anti* = 1:2)
5	 **6c**	17	 **8c**	78 (1:2)[b]
6	 **6d**	27	 **8d**	89 (*Z*:*E*:*E* = 2:1.5:1)[b]
7	 **6e**	9	 **8e**	73
8	 **6f**	1	 **8f**	92

[a] Reaction conditions: **5** or **6** (1 mmol), $Pd(OAc)_2$ (0.1 mmol), $P(n\text{Bu})_3$ (0.4 mmol), and Et_2Zn (3.6 mmol, 1 M *n*-hexane) in toluene (0.5 mL) at room temperature under N_2. [b] The stereochemistry (*syn* or *anti*) is unknown.



Scheme 3. Transition states **II** and **III** leading to *Z*-anti isomers in the reactions of benzaldehydes and ω-formylalkanolates, respectively, with 1,3-dimethylallylzinc.

a quasi-equatorial position impossible. For example, transition state **III**, which leads to a *Z-anti* isomer, apparently suffers from 1,3-diaxial Me···Me repulsion and is unfavorable.

The allyl,[9] 2-tetrahydrofuryl, and 2-tetrahydropyranyl groups have been recognized as useful protecting groups of hydroxy groups.[10] They can be easily introduced and removed selectively under a wide variety of mild conditions, under which other functional groups remain intact. In contrast, the results in Table 2 indicate that these protecting groups could be utilized as useful C_3, C_4, and C_5 sources and provide unsaturated diols **7** and **8**, which are of significant importance as synthetic intermediates.

In conclusion, we have shown that allyl alcohols and their 2-THF and 2-THP ether derivatives are good substrates for performing the nucleophilic allylation of aliphatic aldehydes. The reaction proceeds at room temperature in the presence of a catalytic amount of a Pd^0 species and a stoichiometric amount of Et_2Zn. The reaction contrasts the electrophilic allylation at the α-position of aliphatic aldehydes, which proceeds in the presence of a catalytic amount of a Pd^0 species and a stoichiometric amount of Et_3B together with Et_3N and LiCl.[2]

Further studies to demonstrate the utility of the present umpolung methodology are in progress, for example, modification of carbohydrates that possess five- and six-membered hemiacetal structures such as **5** and **6** as a common structural motif.

Experimental Section

General procedure (Table 2, entry 3): Diethylzinc (3.2 mmol, 1.0 M *n*-hexane solution) and **6a** (142.2 mg, 1.0 mmol) were added successively by syringe to a homogeneous solution of $Pd(OAc)_2$ (22.6 mg, 0.1 mmol) and $n\text{Bu}_3\text{P}$ (80.9 mg, 0.4 mmol) in toluene (0.5 mL, dried over Na/benzophenone ketyl) at 0 °C under N_2. After completion of the addition, the mixture was allowed to warm to room temperature and stirred for an additional 2 h, during which time a copious amount of a white precipitate appeared and the reaction mixture became sludgy. The mixture was diluted with EtOAc and washed with HCl (0.2 M), sat. $NaHCO_3$, and brine and then the organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil, which was purified by column chromatography over silica gel (AcOEt/hexane, 1/4 v/v) to give **8a** (230.6 mg, 91 %, $R_f = 0.48$; AcOEt/hexane, 1/4 v/v). **8a**: IR (neat) $\tilde{\nu} = 3331$ (s), 3076 (m), 1641 (m), 1435 (m), 1340 (m), 914 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, tetramethylsilane (TMS)) $\delta = 1.40$–1.64 (m, 6H), 2.17 (dt, $J = 14.1$, 7.3 Hz, 1H), 2.29 (br dt, $J = 14.1$, 7.3 Hz, 1H), 2.55 (br s, 2H), 3.64 (m, 1H), 3.63 (t, $J = 6.2$ Hz, 2H), 5.11 (d, $J = 11.7$ Hz, 1H), 5.12 (dm, $J = 15.8$ Hz, 1H), 5.83 ppm (ddt, $J = 15.8$, 11.7, 7.7 Hz 1H); ^{13}C NMR (100 MHz, $CDCl_3$, tetramethylsilane) $\delta = 21.8$, 32.4, 36.3, 42.0, 62.3, 70.7, 117.6, 135.0 ppm; HRMS calcd for $C_8H_{16}O_2$: 144.1150; found *m*/*z* (relative intensity): 144.1098 (1), 126 (4), 116 (2), 71(100).

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