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A Mild and Efficient Method for the Stereoselective Formation of C–O Bonds: Palladium-Catalyzed Allylic Etherification Using Zinc(II) Alkoxides

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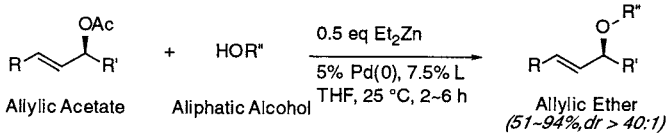
ABSTRACT



A highly chemo- and stereoselective palladium-catalyzed allylic etherification reaction is described. The use of zinc(II) alkoxides proved effective in promoting the addition of the oxygen nucleophile derived from aliphatic alcohols to η^3-allylpalladium complexes. Using diethylzinc (0.5 equiv), 5 mol % of $Pd(OAc)_2$, and 7.5 mol % of 2-di(*tert*-butyl)phosphinobiphenyl in THF, the cross-coupling reaction between various aliphatic alcohols and allylic acetates proceeded at ambient temperature to furnish allylic ethers with high stereoselectivity.

Ether linkages conjoining stereogenic carbon(s) are structural motifs in many natural products of biological importance,[1] and access to them has been a topic of considerable synthetic interest.[2] However, construction of C−O bonds via a direct S_N2 type *O*-alkylation as exemplified by the Williamson ether synthesis is impractical due to complications associated with the strong basicity of an alkoxide anion. With the exception of a few facile cyclization reactions, displacements with alkoxide nucleophiles at stereogenic carbon centers are prone to elimination and loss of stereochemical integrity.[3] The addition of an oxygen nucleophile to an η^3-allylmetal intermediate represents an attractive alternative approach because the C−O bond forming event may occur under mild conditions with stereocontrol.[4] However, in contrast to the widespread use of carbon and nitrogen nucleophiles, transition metal-catalyzed *O*-allylation remains largely limited to carboxylate and phenolic nucleophiles. Far less success has been achieved using aliphatic alcohols as nucleophiles due to their poor nucleophilicity.[5] Scattered literature precedents rely on an intramolecular setting or a large excess of alcohol

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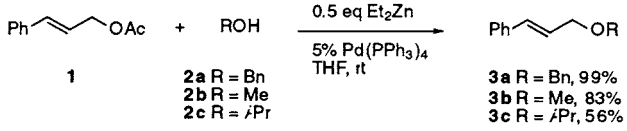
to effect catalysis.[6,7] In particular, these examples have mainly employed primary alcohols because of the difficulties associated with the reactions of structurally complex alcohols.[8] Therefore, a general and reliable protocol for this cross-coupling reaction would be of significant synthetic utility.

We hoped to address the reactivity mismatch between the hard alkoxide anions and soft η^3-allylmetal cations by modulating the apparent "hardness" of an alkoxide nucleophile. In this regard, we noted the "zinc effect" in metalloenzymes which leads to a dramatic increase in the acidity of the hydroxylic proton of a coordinated alcohol.[9] We contemplated that this might reflect a "softening" of the alkoxide anion by the Zn(II) center. Thus, it was intriguing to test whether zinc-bound alkoxides possess attenuated basicity while retaining sufficient nucleophilicity toward a metal-bound allylic cation.[10] Herein we report our investigations of Pd-catalyzed allylic etherification using zinc alkoxides as nucleophiles. Our results provide a solution to one of the long-standing problems in η^3-allylmetal chemistry.

Initial studies centered on a model system in which cinnamyl acetate **1** was used as substrate and Et_2Zn served as the source of base and counterion (Scheme 1). Exposing

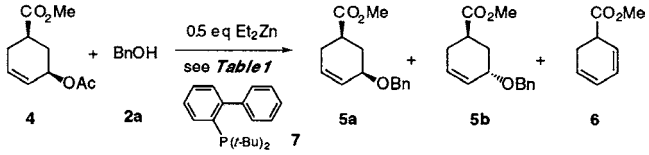
Scheme 1



1 to a preformed solution of benzyl alcohol (**2a**, 1 equiv) and Et_2Zn (0.5 equiv) in THF at 25 °C for 2 h in the presence of 5 mol % of $Pd(PPh_3)_4$ led to the smooth formation of allylic ether **3a** in nearly quantitative yield. Control experiments established that both the Pd and Zn were required for this reaction and that alkali metal benzyloxides induced an instantaneous transacylation. The use of Me_2Zn also provided a comparable result. Decreasing the loading of Et_2Zn to 0.25 equiv gave **3a** in 48% yield with a 50% recovery of unreacted **1** and **2a**, indicating that a 1:2 ratio of Et_2Zn to alcohol is required for the completion of the reaction. Ethers **3b** and **3c** were obtained from the reactions of methanol and 2-propanol in 83% and 56% yield, respectively. In these cases, cinnamyl alcohol (**3d**, R = H) and bis(cinnamyl) ether (**3e**, R = *trans*-cinnamyl) were also isolated in low yields (<5%), presumably via an acetyl transfer reaction. In contrast, transacylation predominates in the reaction of *tert*-butyl alcohol, where only cinnamyl alcohol and bis(cinnamyl) ether were obtained.

The stereochemical course of the reaction was next examined in the context of a disubstituted allylic system (Table 1).[11] It was anticipated that due to the propensity of the cyclic substrate **4** to epimerization and β-H elimination, the alkylation of **4** would present a more challenging testing ground for the reaction.[5f] Indeed, under the same conditions as initial studies the reaction gave a mixture of **5a** and **5b** in low yields, along with a large amount of diene **6** (entry 1). Despite the low yields, the strong dependence of the diastereomeric ratio of **5** on the catalyst and ligand was noteworthy. Whereas using $Pd(PPh_3)_4$ as catalyst gave the anti isomer **5b** as the major product, the addition of a bidentate ligand favored the formation of the syn isomer **5a** (entries 1 vs 2−4). Significant improvements came from the use of biphenyl-derived ligand **7**,[12] which produced only **5a** with a decreased yield of diene **6** (entry 5). Interestingly, the formation of diene **6** could be further diminished by running the reaction in the presence of 10% NH_4OAc (entry

Table 1. Stereoselectivity of Pd-Catalyzed *O*-Allylation of Zinc(II) Benzyloxide with Allylic Acetate **4**[a]



entry	Pd/ligand	yield **5**,[b] %	yield **6**,[b] %	**5a**:**5b**[c]
1	$Pd(PPh_3)_4$	20	65	1:2
2	$Pd(PPh_3)_4$/dppb	48	35	2:1
3	$Pd(PPh_3)_4$/dppf	28	58	4.5:1
4	$Pd(PPh_3)_4$/BINAP	22	60	10:1
5	$Pd(OAc)_2$/**7**	52	20	>40:1
6[d]	$Pd(OAc)_2$/**7**	70	<10	>40:1

[a] All reactions were carried out in THF (1.0 M) with 1.1 equiv of benzyl alcohol at 25 °C in the presence of 5 mol % of Pd and 7.5 mol % of ligand except for entry 1 where 5 mol % of $Pd(Ph_3P)_4$ was used as catalyst. [b] Isolated yields. [c] Diastereomeric ratio of the crude product mixture determined by ^{1}H NMR. [d] NH_4OAc (10 mol %) was added.

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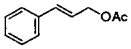
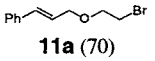
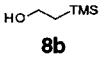
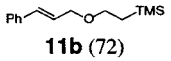
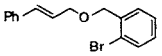
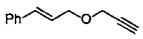
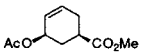
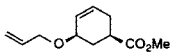
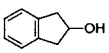
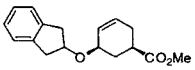
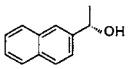
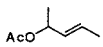
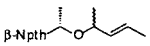
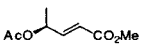
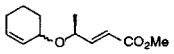
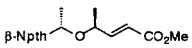
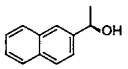
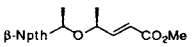
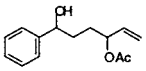
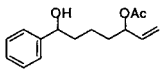
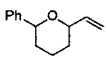
Table 2. Pd-Catalyzed Etherification of Aliphatic Alcohols with Allylic Acetates

entry	alcohol	allylic acetate	ether (% yield)
1[a]	 **8a**	 **1**	 **11a** (70)
2[a]	 **8b**	**1**	 **11b** (72)
3[a]	 **8c**	**1**	 **11c** (76)
4[a]	 **8d**	**1**	 **11d** (69)
5[b]	 **8e**	 **4**	 **11e** (62)
6[b]	 **8f**	**4**	 **11f** (54)
7[b,c]	 **8g**	 **9**	 **11g** (62)
8[b,c]	 **8h**	 **10**	 **11h** (51)
9[b,d]	**8g**	**10**	 **12** (57, 86[f])
10[b,d]	 **8i**	**10**	 **13** (60, 84[f])
11[a,c]	 **8j**		 **14** (92)
12[a,c]	 **8k**		 **15** (94)

[a] Condition A: 1 equiv of alcohol, 1 equiv of allylic acetate, 0.5 equiv of Et_2Zn, 5 mol % of $Pd(PPh_3)_4$, THF (1.0 M), rt, 2 h. [b] Condition B: 1 equiv of alcohol, 1.5 equiv of allylic acetate, 0.5 equiv of Et_2Zn, 5 mol % of $Pd(OAc)_2$, 7.5 mol % of **7**, 10 mol % of NH_4OAc, THF (0.5 M), rt, 6−12 h. [c] The product was obtained as a 1:1 mixture of diastereomers. [d] Only a single isomer was detected by GC and ^1H NMR. [e] Isolated yield. [f] The reaction was carried out with 2.2 equiv of alcohol and 1.1 equiv of Et_2Zn under condition B.

6). Thus, these conditions were subsequently employed for the reactions of 1,3-disubstituted allylic acetates (vide infra, condition B in Table 2). While the origin of **5b** and the role of NH_4OAc are unclear at the moment, the results indicate that the Pd-catalyzed allylic etherification can be performed with high stereoselectivity.

As summarized in Table 2, a variety of acyclic and cyclic substrates participate in inter- and intramolecular allylic etherification. In general, primary alcohols gave higher yields than more sterically hindered secondary alcohols. The remarkably mild nature of the present method is manifest in the facile and selective *O*-alkylation of 2-bromo- and 2-silyl-ethanols in preference to oxirane formation or Peterson-type elimination (entries 1 and 2). Also of interest is entry 3 in which a substrate susceptible to metal−halogen exchange or oxidative addition undergoes uneventful allylic alkylation. When the alcohol and allylic acetate both are used in enantiomerically enriched forms, an ether linkage flanked by α,α′-stereogenic centers could be established with complete stereochemical fidelity (entries 9 and 10). In these cases, higher yields could be easily attained by using 2 equiv of nucleophile while a 1−1.5:1 ratio of the two reaction partners is generally sufficient to obtain serviceable yields. Finally, using an internal hydroxyl group as a nucleophile, five- and six-membered oxacycles are formed in excellent yields (entries 11 and 12). It is noteworthy that unlike previous reports which required a 2,6-dichlorobenzoate[5c] or a tin alkoxide for cyclization,[6a] preactivation of the leaving group or the nucleophile was unnecessary.

In summary, we have described a mild and efficient method for stereoselective allylic etherification. The use of a zinc alkoxide based nucleophile is critical for promoting the Pd-catalyzed *O*-allylation of aliphatic alcohols. The high level of functional group tolerance, high generality, and operational simplicity are important features of the present method. Our protocol greatly expands the current scope of this important cross-coupling process and will undoubtedly form the basis for further development. Extensions of these findings including the development of a bimetallic catalytic system are currently in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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