VIP Carbonylation

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Domino Catalysis: Palladium-Catalyzed Carbonylation of Allylic Alcohols to β,γ-Unsaturated Esters**

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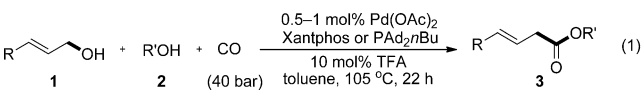
Palladium-catalyzed carbonylations of organic (pseudo)halides are of broad interest for both academic and industrial research.[1] In the last two decades, the majority of the work in this area focused on the application of new ligand systems and the extension of the range of nucleophiles for the carbonylation of aryl and vinyl halides (or related pseudohalides). Consequently, the development of general catalytic protocols for more challenging substrates remains an important but challenging goal. Based on our continuous interest in transition-metal-catalyzed reactions with CO,[1b] recently we became attracted by carbonylation of allylic compounds, which represents a straightforward and economic method for the synthesis of versatile building blocks, β,γ-unsaturated carbonyl compounds.[2] In spite of the tremendous progress in nucleophilic allylic substitution reactions,[3] carbonylation of allylic compounds has received much less attention. Most of the reported examples demand preinstalled leaving groups, such as chlorides,[4] carbonates,[5] acetates,[6] or phosphates.[6b,e,7] Obviously, this creates inherent problems such as significant waste generation and requires less efficient multistep sequences. Moreover, side reactions were observed for carbonylation of allylic halides owing to the accumulation of hydrogen halides in this reaction. However, by adding base to quench the acid, direct reaction with allylic halides is possible.[5a] In general, the resulting β,γ-unsaturated carbonyl compounds are highly susceptible to base-catalyzed isomerization, affording α,β-unsaturated carbonyl isomers.[4e] In the well-established carbonylation of allyl alkyl carbonates it is difficult to introduce various nucleophiles owing to the preferred reaction of the alkoxides from the substrates. Besides, allylic carbonates are usually prepared from allylic alcohols and toxic chloroformates. Thus, the overall process is also not really halide-free. Notably, carbonylation reactions of allylic acetates, which are commonly used as electrophiles in Pd-catalyzed allylic substitution reactions, are much less effective. For example, high CO pressure or halide additives are needed. This inefficiency is explained by the formation of π-allylpalladium acetates, which readily undergo reductive elimination to give the starting acetates rather than CO insertion.[8]

An ideal way to streamline carbonylation of allylic compounds from an economic and environmental point of view is to use of allylic alcohols directly as substrates. Alcohols are more widely available and represent more environmentally benign reagents, generating water as the sole by-product. Advantageously, the whole synthetic route is shortened because most of the above-mentioned substrates are obtained from the corresponding alcohols. Unfortunately, the poor leaving ability of the hydroxy group, combined with the possible side reactions caused by the released water, have hindered the application of allylic alcohols in carbonylation reactions.[3d] As a result, only very few examples were reported in this field and these protocols generally suffer from limitations, such as harsh reaction conditions, low yields, high metal catalyst and ligand loadings, and/or a limited substrate scope.[9] In fact, to the best of our knowledge, only carbonylations of allylic alcohols with specific nucleophlic substrates, for example, thiols[9g] and one example with phenol, are known.[9f,10]

In line with our previous work on the direct amination of allylic alcohols,[11] we turned our attention to respective carbonylation processes. Herein, we present the first general and efficient catalyst system for the direct carbonylation of allylic alcohols with a variety of aliphatic alcohols. Our protocol proceeds through domino catalysis and is atom economic and environmentally benign (salt free), and proceeds with excellent linear/branched regioselectivity [Eq. (1); Ad = adamantyl, TFA = trifluoroacetic acid, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene].



(1)

We started our investigation by examining the Pd-catalyzed carbonylation of cinnamyl alcohol **1a** with *n*-butanol **2a** (see the Supporting Information, Scheme S1 and Tables S1 and S2). Representative catalyst precursors, phosphine ligands, acidic additives, and solvents were studied to improve the efficiency of this transformation. An optimal yield (determined by GC) of 75% for product **3aa** was obtained using 1 mol% of $Pd(OAc)_2$, 1.1 mol% of Xantphos, 10 mol% of TFA, 1.2 equivalents of *n*-butanol **2a**, with toluene as the solvent at 105°C under 40 bar CO pressure. The reaction yield was improved to 85% when the reaction scale was increased from 1 mmol to 10 mmol with only

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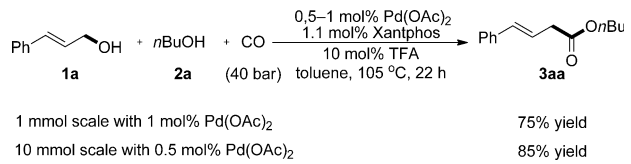
0.5 mol% Pd catalyst loading (Scheme 1). To the best our knowledge, this is the lowest palladium catalyst loading for any carbonylation of allylic compounds reported so far.



Scheme 1. Pd-catalyzed carbonylation of cinnamyl alcohol **1a** with *n*-butanol **2a**.

The progress of the carbonylation of cinnamyl alcohol **1a** with *n*-butanol **2a** was examined under the optimized reaction conditions (Figure 1). Surprisingly, GC analysis of samples taken from the reaction mixture showed that **1a** was initially converted into the C–O coupling product **4a** within 15 min. Then, the carbonylative product **3aa** is generated at lower rate along with the consumption of the reaction intermediate **4a**.

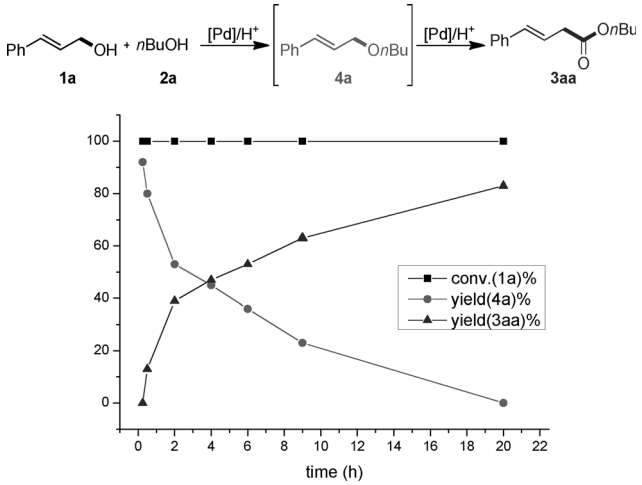
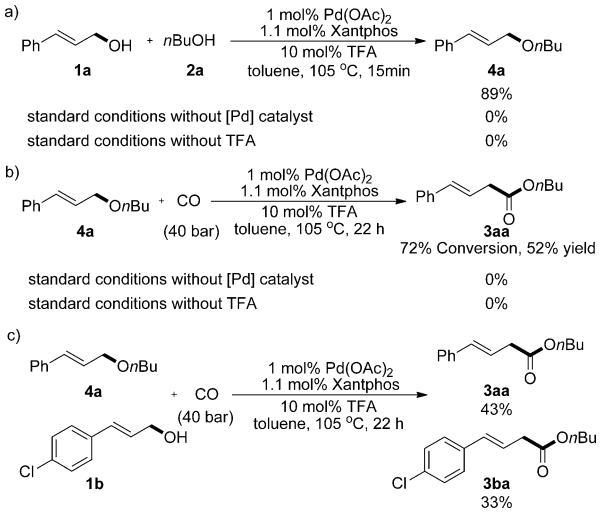


Figure 1. Domino C–O coupling/carbonylation reaction process.

To gain further insights into this interesting new domino reaction, stepwise reactions were investigated separately (Scheme 2). In the absence of CO gas, the C–O coupling reaction proceeded smoothly and produced **4a** in 89% yield after 15 min. Meanwhile, carbonylation of **4a** could also be accomplished under the standard conditions without additional **2a**. Both C–O coupling and carbonylation steps do not proceed without the presence of either Pd catalyst or TFA (Scheme 2a and 2b). Additionally, the reaction of a 1:1 mixture of **4a** and (*E*)-4-chlorocinnamyl alcohol **1b** yielded a mixture of carbonylated products **3aa** and **3ba** (Scheme 2c). These results clearly reveal that the carbonylation of cinnamyl alcohol **1a** with *n*-butanol **2a** occurred through a sequential C–O coupling and carbonylation process and the reaction rate of the carbonylation step is much slower.



Scheme 2. Investigation of stepwise C–O coupling and carbonylation reactions.

The presence of the catalytic amount of TFA is essential to achieve both steps of this domino reaction process. To assess the role of TFA, **1a** and **4a** were mixed with TFA in [D_8]toluene at room temperature, and NMR studies were performed (Figure 2). The formation of trifluoroacetate **5a** from **1a** was observed after 6 h. In contrast, **4a** was not converted into **5a** upon treatment with TFA under the same conditions.

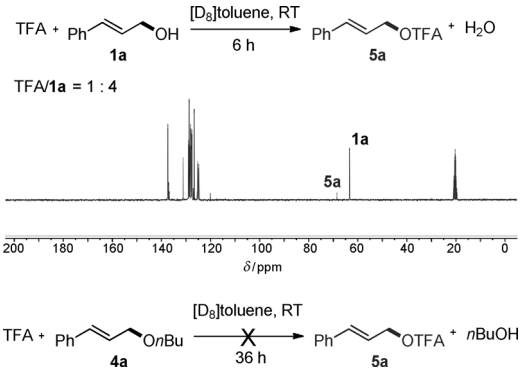
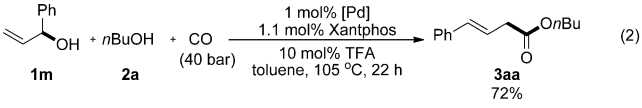
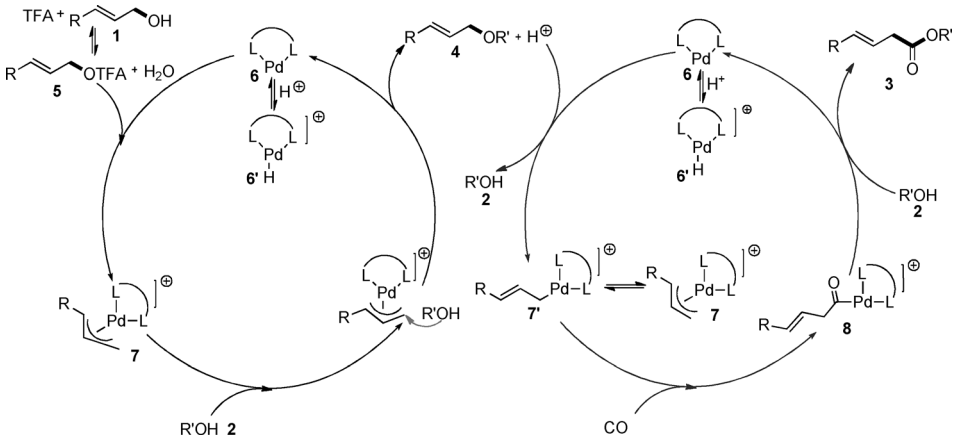


Figure 2. Influence of TFA in the reactions of **1a** and **4a**.

We suspected that the carbonylation step should proceed via typical π-allyl/Pd intermediates because the same product **3aa** was obtained when 1-phenylprop-2-en-1-ol **1m**, the isomer of **1a**, was employed as the starting material under the same reaction conditions [Eq. (2)].



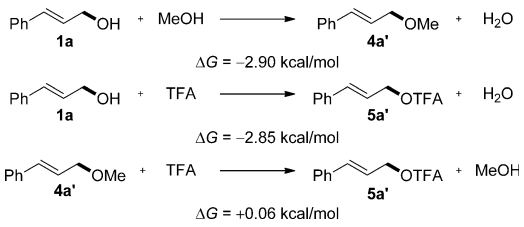
On the basis of our experimental findings, a domino palladium-catalyzed sequence is proposed for the formation of **3aa** (Scheme 3).[12] It is known that $Pd(OAc)_2$ can be



Scheme 3. Proposed mechanism.

reduced in situ to Pd^0 species **6** in the presence of phosphine ligands and CO.[13] Oxidative addition of trifluoroacetate **5** or the protonated allylic alcohol **1** with Pd^0 complex **6** gives the π-allyl/Pd intermediate **7**. This intermediate undergoes a fast nucleophilic substitution by the aliphatic alcohol **2** at the less sterically hindered terminal position to afford the C–O coupling product **4** and regenerates Pd^0 species **6**. Subsequently, oxidative addition of protonated allylic ether **4** leads to π-allyl/Pd complex **7**, followed by CO coordination and insertion to give the acyl Pd complex **8**. Finally, alcoholysis of intermediate **8** generates the desired carbonylative product **3** and Pd hydride species **6′**, which is in an equilibrium with the Pd^0 complex **6** under acidic condition.

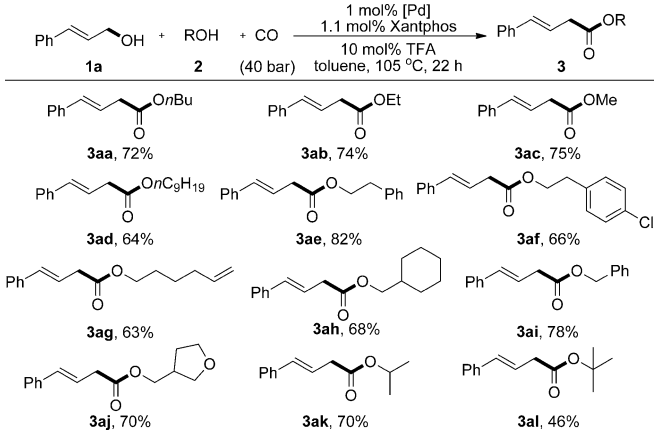
To understand the C–O coupling process in more detail (Scheme 2a and Figure 2), DFT investigations (see the Supporting Information for details) were carried out. In our calculations, we used real-size substrates, but methanol instead of *n*-butanol as model. Both the reaction free energy of ether formation and exchange were calculated. Scheme 4 shows clearly that ether formation (**4a′**) is favored



Scheme 4. BP86 free energies for the substitution reactions.

($\Delta G = -2.90$ kcal mol^{-1}) thermodynamically. Hence, it reveals that the transformation of **1a** into **4a′** under the same reaction conditions without either Pd catalyst or TFA is kinetically hindered. This conclusion is supported by the fast formation of **4a** under the catalytic conditions (Figure 1). The noncatalytic formation of **5a′** is feasible, because the formation of **5a′** is also favored ($\Delta G = -2.85$ kcal mol^{-1}) thermodynamically. According to the calculated Gibbs free energy ($\Delta G = 0.06$ kcal mol^{-1}), the exchange of **4a′** and **5a′** will be in fair equilibrium, but such equilibrium (**4a** and **5a′**) was not observed under the noncatalytic condition, and this reveals once again the kinetic influence.

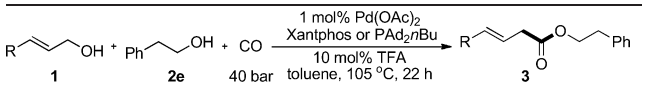
With the optimized reaction conditions established, we examined the generality and limitation of this novel domino process with respect to aliphatic alcohols (Scheme 5). A variety of substituted primary aliphatic alcohols gave the corresponding carbonylative products in synthetically useful yields with excellent regioselectivity. Notably, the branched products were never observed in any transformation of the shown substrates. A broad range of functional groups were tolerated, including reactive chloro (**3af**), alkene (**3ag**), benzyl (**3ai**), and tetrahydrofuran groups (**3aj**), which provide useful handles for further synthetic transformations. Notably, secondary and tertiary alcohols underwent this transformation smoothly in moderate to good yields (**3ak** and **3al**).

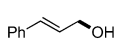
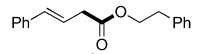
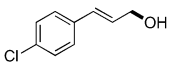
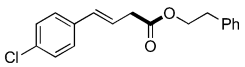
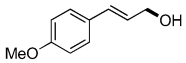
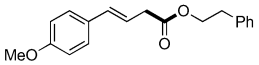
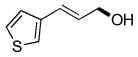
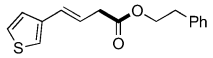
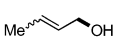
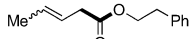
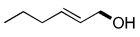
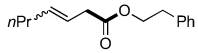
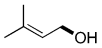
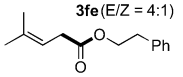
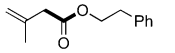
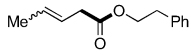
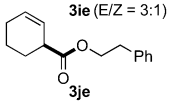
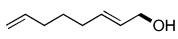
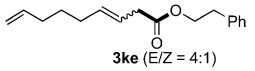
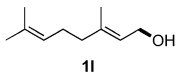
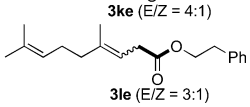


Scheme 5. Carbonylation of **1a** with a variety of aliphatic alcohols. Reaction conditions: **1a** (1 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (1 mol%), Xantphos (1.1 mol%), TFA (10 mol%) in toluene (2 mL) under 40 bar CO at 105 °C. Yields of the isolated products are shown.

Next, we evaluated the scope of allylic alcohols by using 2-phenylethanol **2e** as a standard coupling partner (Table 1). Both 3-arylprop-2-en-1-ols (Table 1, entries 1–4) and 3-alkylprop-2-en-1-ols (Table 1, entries 5–12) furnished the corresponding products in good yields with Xantphos or PAd_2nBu as ligands, respectively. α,β-Unsaturated esters were not detected in these reactions despite the facile isomerization of β,γ-unsaturated esters to α,β-unsaturated esters.[4e] We demonstrated the utility of our carbonylation protocol in the reaction of 2,7-octadienol **1k**, a bulky feedstock and geraniol **1l**, an ingredient commonly used in perfumes and flavors (Table 1, entries 11 and 12). The loss of the stereochemistry of the double bonds can be explained by *syn*/*anti* isomerization of the π-allyl Pd intermediate.[7]

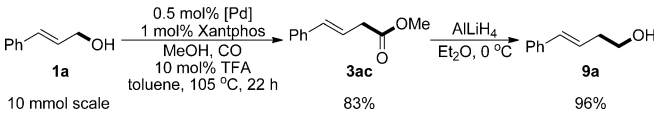
Table 1: Pd-catalyzed carbonylation of allylic alcohols with **2e**.[a]



entry	1	3	Yield [%][b]
1	 **1a**	 **3ae**	82
2	 **1b**	 **3be**	73
3	 **1c**	 **3ce**	63
4	 **1d**	 **3de**	60
5	 **1e**	 **3ee** (E/Z = 3:1)	68
6	 **1f**	 **3fe** (E/Z = 4:1)	63
7	 **1g**	 **3ge**	72
8	 **1h**	 **3he**	51
9	 **1i**	 **3ie** (E/Z = 3:1)	74
10	 **1j**	 **3je**	54
11	 **1k**	 **3ke** (E/Z = 4:1)	78
12	 **1l**	 **3le** (E/Z = 3:1)	70

[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (1 mol%), Xantphos (1.1 mol%) or PAd_2nBu (4 mol%), TFA (10 mol%) in toluene (2 mL) under 40 bar CO at 105 °C. [b] Yields of the isolated products.

Finally, to illustrate the synthetic potential of this method, we performed a gram-scale synthesis of the homoallylic alcohol **9a** from the widely available allylic alcohol **1a** in two



Scheme 6. Gram-scale synthesis of homoallylic alcohol **9a** from allylic alcohol **1a**.

steps with 80% overall yield upon isolation (Scheme 6). It should be noted that this sequence allows for a straightforward C1 extension of easily available allylic alcohols to the corresponding homoallylic alcohols.

In conclusion, we developed a general and benign carbonylation method of allylic alcohols with aliphatic alcohols to produce a variety of synthetically useful β,γ-unsaturated esters. Interestingly, this reaction proceeds through a novel sequential C-O coupling/carbonylation pathway. In view of the easy availability of the substrates, the efficiency, the excellent regioselectivity, and the salt-free conditions, this method is expected to complement the current methods for carbonylations in organic synthesis.

Experimental Section

General procedure for 1 mmol scale reactions: A 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (13.4 mg, 1 mol%), Xantphos (38.1 mg, 1.1 mol%) or PAd_2nBu (85.9 mg, 4 mol%), and toluene (12 mL). 2 mL of this clear yellow stock solution was transferred into each of the six vials (4 mL reaction volume) equipped with a stirring bar under the protection of argon. Then the allylic alcohol (1 mmol), the aliphatic alcohol (1.2 mmol), and TFA (8 μL, 10 mol%) were added into each vial sequentially. The vials were placed in an alloy plate, which was transferred to a 300 mL autoclave under argon atmosphere. After flushing the autoclave three times with N_2, the pressure was adjusted to 40 bar of CO at ambient temperature and the mixtures were stirred for 22 h at 105 °C. The reaction was cooled to room temperature and then the pressure was released. Evaporation of the solvent gave a residue that was purified by silica gel column chromatography using *n*-heptane and ethyl acetate as eluent.

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[10] Under the optimized conditions (3–5 mol% of $Pd(OAc)_2$, 12–20 mol% of PPh_3) reported in Ref. [9f] and [9g], the carbonylation reactions of allylic alcohols with aliphatic alchohols provide very low yields according to the results reported in Ref. [9f] and our own experimental results. Please see the Supporting information for details.

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