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A Pd(0)-Catalyzed Direct Dehydrative Coupling of Terminal Alkynes with Allylic Alcohols To Access 1,4-Enynes

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Supporting Information

ABSTRACT: A direct dehydrative coupling of terminal alkynes with allylic alcohols catalyzed by $Pd(PPh_3)_4$ with an N,P-ligand assisted by $Ti(OiPr)_4$ has been developed. The coupling reaction tolerates various functional groups, providing a valuable synthetic tool to access 1,4-enynes.

The Pd-catalyzed allylation of carbon nucleophiles with allylic compounds via π-allylpalladium intermediates (the Trost−Tsuji reaction) represents one of the most important developments in modern synthetic chemistry[1] and has a broad range of applications in the synthesis of natural products and bioactive compounds such as (+)-nigellamine A and aeruginosin 98B.[1e−h] In general, the leaving groups of functionalized allylic compounds include halides, acetates, ethers, sulfones, carbamates, and phosphates. However, there are very few examples of the use of allylic alcohols in the Trost−Tsuji reaction because of the very poor leaving ability of the hydroxyl group.[2] On the other hand, the reaction is also very sensitive to the acidity of the C−H bond of the pronucleophile;[1,3] thus, terminal alkynes have never been successfully used as pronucleophiles under the standard conditions of the Trost−Tsuji reaction.[4] In fact, the reaction of terminal alkynes with allylic electrophiles catalyzed by palladium generally affords 1,4-diene products, and the 1,4-enyne product has never been observed.[5−7]

1,4-Enynes are versatile reagents in organic synthesis and important structural motif in natural products and biologically active compounds.[8] Stoichiometric syntheses of 1,4-enynes from functionalized allylic compounds with terminal alkynes involving metalated species have been described.[9] It is noteworthy that the stable and readily available allyl substrates for transition-metal-catalyzed allylic substitutions are usually prepared from the corresponding allylic alcohols. For synthetic efficiency, it would be much more desirable to generate the 1,4-enynes directly from allylic alcohols and terminal alkynes.[10] It was reported that Ni(0) could catalyze the coupling of allyl esters with terminal alkynes to give 1,4-enynes through a different mechanism from the Pd-catalyzed coupling reaction.[7a−c] Although in limited cases dehydrative coupling of some active allylic alcohols with terminal alkynes can proceed under the catalysis of a Lewis acid such as $Cu(OTf)_2$ via a carbocation mechanism,[11] the Pd(0)-catalyzed direct coupling reaction of allylic alcohols with terminal alkynes has not been demonstrated to date. How to access diverse 1,4-enyne derivatives directly from allylic alcohols and terminal alkynes under transition-metal catalysis is still a challenging task.

Herein we report a direct dehydrative coupling reaction of terminal alkynes with allylic alcohols catalyzed by $Pd(PPh_3)_4$ with an N,P-ligand assisted by $Ti(OiPr)_4$ to access 1,4-enynes (Figure 1), which significantly extends the scope of the Trost−Tsuji reaction.

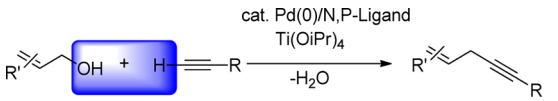
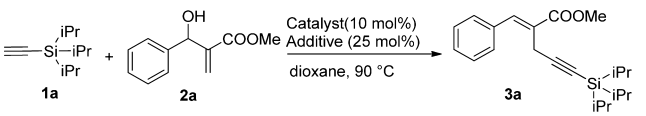


Figure 1. Pd-catalyzed dehydrative coupling of allylic alcohols with terminal alkynes.

We began our study by using the reaction of (triisopropylsilyl)acetylene (**1a**) with Morita−Baylis−Hillman (MBH) alcohol **2a** in the presence of $Pd(PPh_3)_4$ (10 mol %) as a catalyst (Table 1). No desired product **3a** was detected, and only mostly dimerized **1a** was obtained. The direct activation of allylic alcohols to generate π-allyl species is a key challenge in transition-metal-catalyzed nucleophilic allylic substitution, which can be facilitated by a Lewis acid.[2] However, the addition of $Cu(OMe)_2$ or $Al(OiPr)_3$ did not improve the yield of **3a** at all. It was reported that in the Pd-catalyzed amination

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	additive	yield (%)[b]
1	$Pd(PPh_3)_4$	none	0
2	$Pd(PPh_3)_4$	$Cu(OMe)_2$	0
3	$Pd(PPh_3)_4$	$Al(OiPr)_3$	0
4	$Pd(PPh_3)_4$	$Ti(OiPr)_4$	91
5[c]	$Pd(PPh_3)_4$	$Ti(OiPr)_4$	6
6	none	$Ti(OiPr)_4$	0

[a]Conditions: **1a** (0.5 mmol), **2a** (0.2 mmol), catalyst (10 mol %), additive (25 mol %), dioxane, N_2, 90 °C. [b]Isolated yields [c]$Pd(PPh_3)_4$ (5 mol %).

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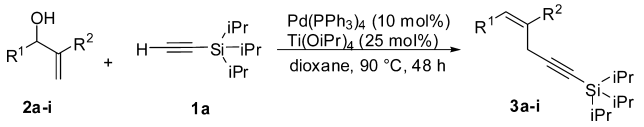
of allylic alcohols, $Ti(OiPr)_4$ as a Lewis acid helped to activate the allylic alcohol in generating a π-allylpalladium intermediate.[12] To our delight, the desired 1,4-enyne product **3a** was obtained in 91% yield directly from allylic alcohol **2a** and terminal alkyne **1a** with exclusive γ-regioselectivity in the $Pd(PPh_3)_4/Ti(OiPr)_4$ catalytic system. When the Pd(0) catalyst loading was decreased to 5 mol %, the yield of **3a** decreased sharply to 6%. No reaction was observed in the absence of $Pd(PPh_3)_4$ using $Ti(OiPr)_4$ alone. Thus, the combination of $Pd(PPh_3)_4$ and $Ti(OiPr)_4$ is essential and synergistically catalyzes the direct coupling of allylic alcohols with terminal alkynes.

Subsequently, under the standard conditions with the $Pd(PPh_3)_4/Ti(OiPr)_4$ catalyst, various allylic alcohols were reacted with terminal alkyne **1a** (Table 2). MBH alcohols **2a–d**

Table 2. Pd(0)-Catalyzed Allylation of 1a with 2a–i Assisted by Ti(IV)[a]



entry	2 (R^1, R^2)	product	yield (%)[b]
1	**2a** (C_6H_5, COOMe)	**3a**	91
2	**2b** (2-MeC_6H_4, COOMe)	**3b**	92
3	**2c** (3-MeC_6H_4, COOMe)	**3c**	84
4	**2d** (3-$MeOC_6H_4$, COOMe)	**3d**	93
5[c]	**2e** (C_6H_5, Me)	**3e**	99
6[c]	**2f** (4-MeC_6H_4, Me)	**3f**	98
7	**2ga** (C_6H_5, H)	**3g**	0, 18[d]
8	**2h** (4-MeC_6H_4, COOMe)	**3h**	0
9	**2i** (Me, H)	**3i**	13

[a]Conditions: **1a** (0.5 mmol), **2** (0.2 mmol), $Pd(PPh_3)_4$ (10 mol %), $Ti(OiPr)_4$ (25 mol %), dioxane, N_2, 90 °C. [b]Isolated yields. [c]Reaction time 10 h. [d]From cinnamyl alcohol (**2gb**).

reacted efficiently to give the corresponding 1,4-enyne products **3a–d** (entries 1–4). Allylic alcohols **2e** and **2f** also reacted smoothly to give the corresponding products **3e** and **3f** almost quantitatively (entries 5 and 6). The configuration of the newly generated double bond in the products was deduced to be *E* by nuclear Overhauser effect spectroscopy (NOESY) analysis, which suggested that the geometries of the π-allylpalladium complexes generated from MBH alcohols and normal allylic alcohols (e.g., **2e**) could be different.[13] However, the $Pd(PPh_3)_4/Ti(OiPr)_4$ catalyst system was very sensitive to the structure of the allylic alcohol: a minor change of the substituent from methyl to H derailed the reaction completely (reducing the yield of **3** to 0% from 99%; entry 5 vs 7), and MBH alcohol **2h** similarly failed to give any desired product **3h** (entry 8). In addition, the use of alkyl-substituted allylic alcohol **2i** resulted in a very low yield of the desired product **3i** (entry 9). In all cases of low yields of the coupling reaction, only dimerization of **1a** was observed.

Thus, major efforts were made to further optimize the coupling reaction in order to extend its scope. Bidentate ligands are known to facilitate Pd(0)-catalyzed cross-coupling reactions.[14] Thus, several bidentate ligands (Figure 2) were examined using allylic alcohol **2ga** as the benchmark testing substrate. The use of diamine ligand **L1** together with the $Pd(PPh_3)_4/Ti(OiPr)_4$ catalyst system in the reaction of **2ga** with **1a** gave only a trace of the desired coupling product **3g**.

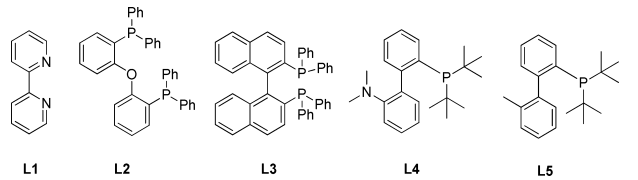
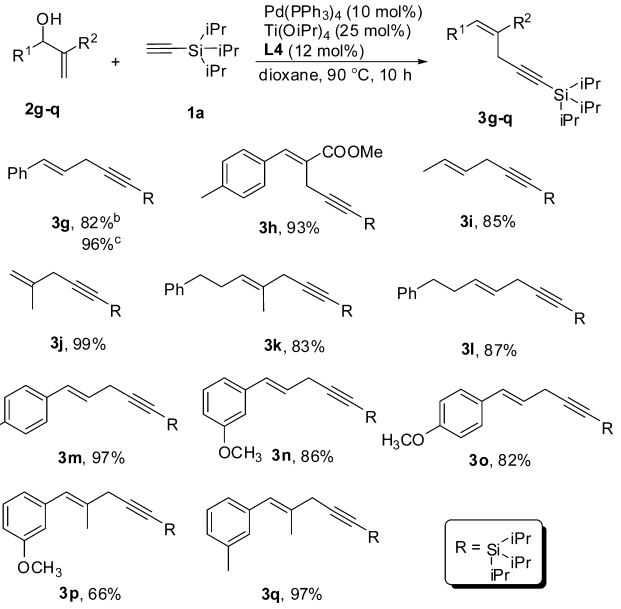


Figure 2. Bidentate ligands tested.

Using bisphosphine ligands **L2** and **L3** in the coupling reaction afforded the **3g** in yields of 61% and 0%, respectively. Surprisingly, the combination of N,P-ligand **L4** with PPh_3 led to a remarkable increase in the yield of **3g** up to 82%. When **L5** was used, the coupling reaction afforded **3g** in only 55% yield. Reducing the loadings of **L4** and $Pd(PPh_3)_4$ decreased the yield sharply. The use of **L4** together with $Pd_2(dba)_3$ led to a sharp decrease in the yield of **3g** to 13%.

With the further-optimized conditions in hand, various allylic alcohols **2g–q** (poor substrates under the previous conditions) were reacted with terminal alkyne **1a**, and the corresponding products **3g–q** were obtained in good to excellent yields (66–99%) (Scheme 1). The coupling constant (J_H = 15.7 Hz)

Scheme 1. Pd-Catalyzed Coupling of 1a with 2g–q[a]



[a]Conditions: see the Supporting Information. [b]From **2ga**. [c]From **2gb**.

indicated the *E* configuration of the newly formed double bond. The structural diversity of the 1,4-enyne cross-coupling products was greatly enhanced under the $Pd(PPh_3)$/**L4** conditions.

Notably, under the catalysis of Pd(0)/**L4**/$Ti(OiPr)_4$, **2ga** and its isomer **2gb** gave the same product **3g** in excellent yields with exclusive γ-regioselectivity, which indicated the generation of the same π-allylpalladium intermediate in the two palladium-catalyzed allylation reactions. In constrast, low yields of **3g** (0% or 18%, respectively) were obtained under the earlier conditions (Table 2, entry 7). Among allylic alcohol **2ga** derivatives, both para- and meta-substituted substrates gave the desired products **3m–o** in good yields. Interestingly, less reactive alkylallylic alcohols also provided the coupling products **3i–l** in excellent yields (83–99%).

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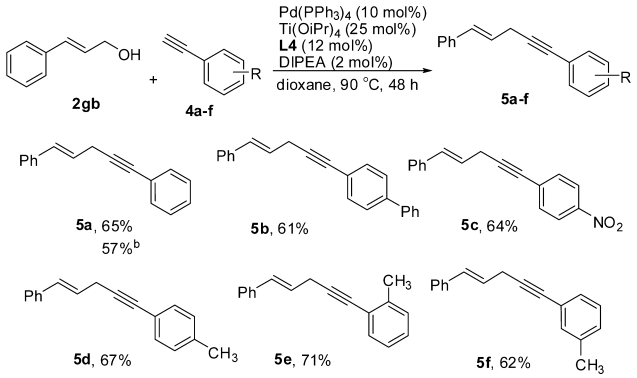
Subsequently, we examined the coupling of arylacetylenes **4** with cinnamyl alcohol **2gb** (Scheme 2). In these cases, a

Scheme 2. Pd(0)-Catalyzed Coupling of 4 with 2gb[a]

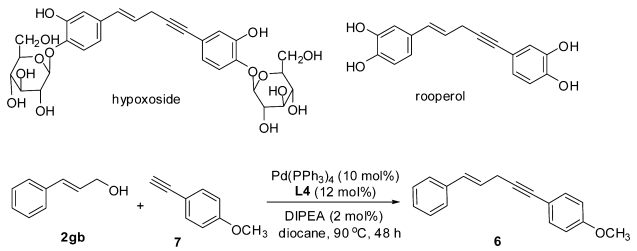


[a]Conditions: see the Supporting Information. [b]From **2ga**.

catalytic amount of diisopropylethylamine (DIPEA) (2 mol %) was found to be beneficial to activate the alkynyl C−H bond. Various substituted phenylacetylenes **4a−f** (R = H, Ph, NO_2, *p*-CH_3, *o*-CH_3, *m*-CH_3) were successfully transformed into the desired products **5a−f** in 57−71% isolated yield.

Hypoxoside is a norlignan diglucoside isolated from the corms of *Hypoxis* plants [African potato (AP)].[9,15] The inactive hypoxoside is deglucosylated by *β*-glucosidase to form rooperol (Scheme 3). In pharmacological studies, the derivatives of

Scheme 3. Synthesis of Compound 6



rooperol exhibited good anticancer bioactivities.[15] Among them, compound **6** showed the best anticancer activity for the inhibition of human esophageal carcinoma cell growth (IC_{50} = 10 μg/mL; 2.5 times more active than rooperol).[16] To illustrate the potential synthetic application of this novel coupling, **6** was efficiently synthesized through the direct reaction of 4-methoxyphenylacetylene (**7**) with **2gb** in 58% yield under the conditions of Pd(0)/**L4**/DIPEA catalysis. Both substrates are commercially available, and the synthetic protocol is very convenient.

The proposed mechanism for this novel coupling is shown in Figure 3. The hydroxyl group of the allylic alcohol is activated by Ti(O*i*Pr)$_4$ to generate allylic titanate **A**, which reacts with the Pd(0)/**L4** species to form a *π*-allylpalladium intermediate **B**. The amino group of the N,P-ligand in **B** can help to deprotonate the terminal alkyne intramolecularly to form intermediate **C**. Subsequently, **C** can be transformed into the 1,4-enyne via the formation of intermediate **D** followed by reductive elimination.

In conclusion, a palladium-catalyzed direct dehydrative coupling of terminal alkynes with allylic alcohols to give 1,4-enynes has been developed. The reaction is catalyzed by

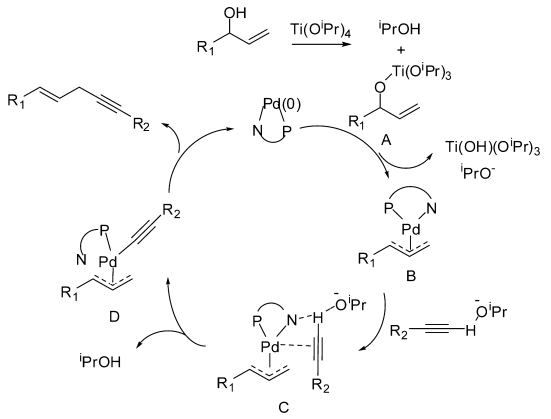


Figure 3. Tentative mechanism for the Pd-catalyzed catalytic coupling of terminal alkynes with allylic alcohols.

Pd(PPh$_3$)$_4$ assisted by Ti(O*i*Pr)$_4$, and the scope of the coupling is further extended by using a N,P-ligand. The coupling reaction tolerates various functional groups, providing a valuable synthetic tool to access 1,4-enynes readily. The scope, mechanism, and synthetic applications of this novel coupling are under further investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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