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Activator-free and one-pot C-allylation by simple palladium catalyst in water

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ABSTRACT

For atom economic and green chemistry concepts, we develop a reaction that involves one-pot and one step to construct the C–C bond without the help of any activating reagents for allylic alcohols in water. The palladium-catalyzed allylation of cyclic 1,3-diones using allylic alcohols directly gave the corresponding allylated products in 8–99% yields.

Allylic substitution is a fundamental transformation in organic synthesis and also is one of the most powerful tools for the formation of carbon–carbon and carbon–heteroatom bonds.[1] Transition-metal-mediated C- and N-allylation reactions are very constructive for further investigating because of their broad substrate scope. For instance, Tsuji–Trost reaction has served as a pivotal reaction to construct C–C bonds by using a (π-allyl)metal intermediate in this regard.[2] Palladium-catalyzed conversion of allylic alcohols directly into allylation products are highly beneficial, especially from the standpoint of the atom economy.[3] We have reported our attempts and some successful applications of a process involving the C–O bond cleavage by palladium complexes in the presence of $Ti(OPr^i)_4$ in benzene.[4] Due to inherent low aptitude of the hydroxy group, the precedent protocols require stoichiometric or catalytic activators for allyl alcohols.[3b,5] Recently, more and more particular catalysts or ligands have been developed for enabling such conversion without the aid of activators.[3a,5g,6] Furthermore, water has become as a highly recommended solvent for organic reactions in terms of cost, safety, availability, and environmental concerns.[7] We have recently disclosed a new catalytic system for palladium/carboxylic acid-catalyzed allylation of cyclic 1,3-diones with allylic alcohols using water as the solvent.[7a] However, it gave only moderate yields of products without the presence of carboxylic acid as an activator. Oshima's report provided an incentive for further studies of reactions under 'no-activator' condition.[8] In this Letter, we display a reaction which was taken place in distilled water without any other activators involved.

To determine the optimal reaction conditions, the palladium-catalyzed allylation of 1,3-cyclohexadione (**1a**) with cinnamyl alcohol (**2a**) was investigated under various conditions. Initially, using $Pd(acac)_2$ instead of $Pd(OAc)_2$ under the same conditions gave nearly the same total yields (entry 1 in Table 1). The yields were increased when we prolonged the reaction time to 30 min (entry 2). Providing increasing the **2a** stoichiometry to 1.2 mmol in conjunction with $Pd(acac)_2$ (0.05 mmol) and PPh_3 (0.2 mmol) in water (5 mL) refluxed for 30 min, it gave excellent yields of products **3a** and **4a** to 56% and 40%, respectively (entry 3). However, it was observed that lower reaction temperature would decrease the yield of the products (entry 4). The reaction did not occur in the absence of the palladium species (entry 5), phosphine ligand (entry 6), or water (entry 7). The effect of water may activate allyl alcohol via hydration of the hydroxy group and stabilize the resulting hydroxide ion by strong solvation with water. In water, the hydroxide ion can leave with hydrating water molecules and the negative charge can be delocalized in the water cluster.[7b] As expected, increasing the relative amount of cinnamyl alcohol would favor the formation of the desired diallylated product **4a** (entry 8). Using MeOH as solvent gave only moderate yields of products (entry 9). Then, all of Pd reagents in our lab were investigated (entries 3 and 10–16). However, using Pd(0) complex $Pd_2(dba)_3$ with extra PPh_3 as catalyst has increased the yield of products (entries 16). $PdCl_2(PhCN)_2$ was employed as the palladium source, and a screening of monodentate (entries 17–22) and bidentate phosphine ligands (entries 23–25) was undertaken.

To explore the scope of this novel system, allylation of a series of cyclic 1,3-diones (**1b–h**) with cinnamyl alcohol (**2a**) using $PdCl_2(PhCN)_2$ and PPh_3 in water is summarized in Table 2. Dimedone (**1b**) has been extensively used as precursors of potential

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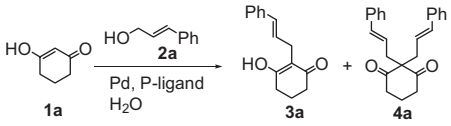
Table 1
Allylation of 1,3-cyclohexadione (**1a**) with cinnamyl alcohol (**2a**)[a]



1a 3a 4a

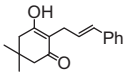
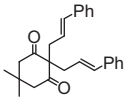
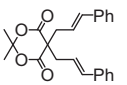
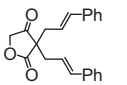
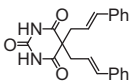
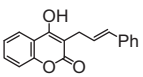
Entry	Palladium	Ligand	Yield[b] (%) (**3a**:**4a**)
1[c,d]	$Pd(acac)_2$	PPh_3	63 (11:89)
2[c]	$Pd(acac)_2$	PPh_3	74 (95:5)
3	$Pd(acac)_2$	PPh_3	96 (58:42)
4[e]	$Pd(acac)_2$	PPh_3	56 (16:84)
5	—	PPh_3	0
6	$Pd(acac)_2$	—	0
7[f]	$Pd(acac)_2$	PPh_3	0
8[g]	$Pd(acac)_2$	PPh_3	99 (5:95)
9[h]	$Pd(acac)_2$	PPh_3	55 (58:42)
10	$Pd(OAc)_2$	PPh_3	68 (24:76)
11	$PdCl_2$(1,10-phen)	PPh_3	95 (17:83)
12	$PdCl_2(MeCN)_2$	PPh_3	90 (26:74)
13	$PdCl_2(PhCN)_2$	PPh_3	99 (41:59)
14	$Pd(propionate)_2$	PPh_3	90 (38:62)
15	$Pd_2(dba)_3$	—	14 (0:100)
16	$Pd_2(dba)_3$	PPh_3	89 (8:92)
17	$PdCl_2(PhCN)_2$	$(2\text{-furyl})_3P$	97 (38:62)
18	$PdCl_2(PhCN)_2$	$(2\text{-pyridyl})Ph_2P$	85 (9:91)
19	$PdCl_2(PhCN)_2$	$(3\text{-}MeC_6H_4)_3P$	99 (28:72)
20	$PdCl_2(PhCN)_2$	$(4\text{-}MeC_6H_4)_3P$	91 (40:60)
21	$PdCl_2(PhCN)_2$	$(4\text{-}MeOC_6H_4)_3P$	90 (41:59)
22	$PdCl_2(PhCN)_2$	$(4\text{-}FC_6H_4)_3P$	95 (18:82)
23	$PdCl_2(PhCN)_2$	Dppp[i]	0
24	$PdCl_2(PhCN)_2$	Dppb[j]	98 (41:59)
25	$PdCl_2(PhCN)_2$	Dpph[k]	84 (71:29)

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), Pd catalyst (0.05 mmol), and ligand (0.2 mmol) in water (5 mL) were refluxed for 30 min.
[b] Isolated yield.
[c] Compound **2a** (0.8 mmol) was used.
[d] Reflux for 15 min.
[e] Stirred at 70 °C.
[f] Without water.
[g] Compound **2a** (2 mmol) was used.
[h] Using MeOH as solvent.
[i] 1,3-Bis(diphenylphosphino)propane.
[j] 1,4-Bis(diphenylphosphino)butane.
[k] 1,6-Bis(diphenylphosphino)hexane.

antidiabetic drugs[9] and tyrosinase inhibitor,[10] and it would undergo mono- and di-allylation while providing excellent yields of products **3b** and **4b** in 55% and 44%, respectively (entry 1). When the relative amount of **2a** was increased, the selective diallylation product **4b** could be obtained in a 95% yield (entry 2). Based on our observation, there were given only diallylated products when the ring contained heteroatoms. Such as 1,3-dioxane-4,6-dione **1c**, furan-2,4-dione **1d**, and pyrimidine-2,4,6-trione **1e**. Compound **1c**, the core of phospholipase A_2 inhibitors,[11] it gave product **4c** in a 77% yield (entry 3), and compound **1d** afforded moderate yields of **4d** (entry 4), and **1e**, a novel chemical scaffold for amyotrophic lateral sclerosis (ALS),[12] also gave only diallylated product **4e** in high yields (entry 5). The approach of 'no activator' is more selective than previous report,[7a] especially for compound **1e**. Then, we chose the coumarin derivatives to treat this reaction because of their anticoagulantic, spasmolytic, antifungal, and anti-HIV activities.[13] 4-Hydroxycoumarin (**1f**) gave monoallylated products **3f** and **5** in 55% and 30% yields, respectively (entry 6). Compound **5** may be produced via diallylated product **4f**, which was hydrolyzed and then decarboxylated to compound **5**.[7a] 6-Chloro-4-hydroxycoumarin (**1g**) reacted as **1f**, affording the corresponding products **3g** and **6** in 49% and 39% yields, respectively (entry 7). The solubility of the cyclic 1,3-diones **1d**–**h** can be problematic. It can be alleviated by using a 2:3 methanol/H_2O mixture as the solvent (entries 4–8). 2,4-Quinolinediol (**1h**) gave the desired products in rare yields, but using $(3\text{-}MeC_6H_4)_3P$ instead of PPh_3 as ligand would give moderate results (entry 8). Compound **1h** is a major core of the anti-HCV reagent.[13,14]

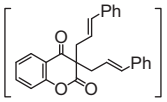
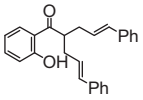
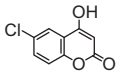
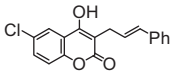
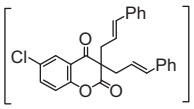
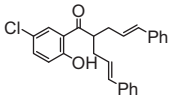
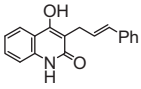
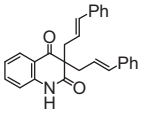
The results for allylation of 1,3-cyclohexadione (**1a**) with both aromatic and aliphatic alcohols **2b**–**j** in the presence of a catalytic amount of $PdCl_2(PhCN)_2$ associated with $(3\text{-}MeC_6H_4)_3P$ in water are summarized in Table 3. In addition to the parent cinnamyl alcohol (**2a**), the regioisomer **2b** also reacted to give the same products **3a** and **4a** in excellent yields of 51% and 48%, respectively (entry 1). (*E*)-2-Methyl-3-phenylprop-2-en-1-ol (**2c**) reacted to give the allylating product **7** in moderate yields (entry 2). Allylation of 1,3-cyclohexadione (**1a**) worked well with cinnamyl alcohols containing electron donating groups, giving generally high yields of the corresponding allylic products. (*E*)-3-(4-Methoxyphenyl)prop-

Table 2
Allylation of cyclic 1,3-diones (**1b-h**) with cinnamyl alcohol (**2a**)[a]

Entry	**1**		*h*	Product		Yields[b] (%)
1		**1b**	0.5		**3b**	55
					**4b**	44
2[c]		**1b**	0.5		**4b**	95
3		**1c**	1		**4c**	77
4[d]		**1d**	2		**4d**	53
5[d]		**1e**	2		**4e**	84
6[d]		**1f**	2		**3f**	55

(*continued on next page*)

Table 2 (*continued*)

Entry	1		h	Product		Yields[b] (%)
					**4f**	Not obtained
					**5**	30
7[d]		**1g**	2		**3g**	49
					**4g**	Not obtained
					**6**	39
8[d,e]		**1h**	2		**3h**	23
					**4h**	37

[a] Reaction conditions: **1** (1 mmol), **2a** (1.2 mmol), $PdCl_2(PhCN)_2$ (0.05 mmol), and PPh_3 (0.2 mmol) were refluxed in water (5 mL).
[b] Isolated yields.
[c] Compound **2a** (2 mmol) was used.
[d] Water (3 mL) and MeOH (2 mL) were used.
[e] Ligand $(3\text{-}MeC_6H_4)_3P$ (0.2 mmol) was used.

Table 3
Reaction of 1,3-cyclohexadione (**1a**) with allylic alcohols **2**[a]

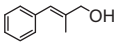
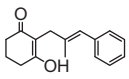
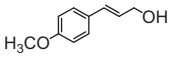
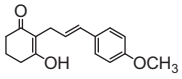
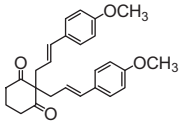
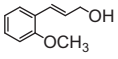
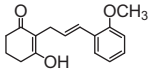
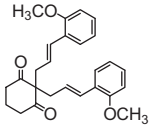
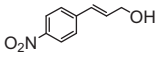
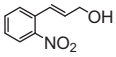
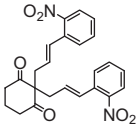
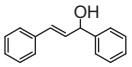
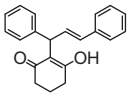
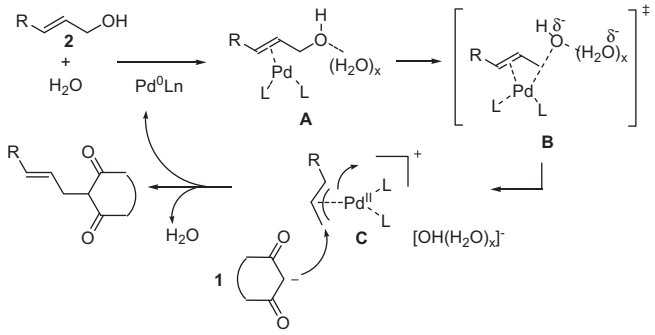
Entry	2		h	Product		Yields[b] (%)
1		**2b**	1		**3a**	51
					4a	48
2		**2c**	2		**7**	47
3		**2d**	0.5		**8**	56
					**9**	37
4		**2e**	0.5		**10**	23
					**11**	74
5		**2f**	24	—		

Table 3 (*continued*)

Entry	2		h	Product		Yields[b] (%)
6		**2g**	15		**12**	53
7		**2h**	2		**13**	42
8		**2i**	2		**14**	40
9		**2j**	2		**15**	8(*E*/*Z* = 80/20)[c]

[a] Reaction conditions: **1** (1 mmol), **2a** (1.2 mmol), $PdCl_2(PhCN)_2$ (0.05 mmol), and $(3\text{-}MeC_6H_4)_3P$ (0.2 mmol) were refluxed in water (5 mL).
[b] Isolated yields.
[c] Determined by GC.



Scheme 1. Proposed mechanism of the allylation of cyclic 1,3-diones **1** with allylic alcohols **2**.

2-en-1-ol (**2d**) gave mono- and diallylated products **8** and **9** in the yields of 56% and 37%, respectively (entry 3). (*E*)-3-(2-Methoxyphenyl)prop-2-en-1-ol (**2e**) also gave the corresponding products in overall 97% yield (entry 4). Using cinnamyl alcohol containing electron-withdrawing groups gave lower yields. (*E*)-3-(4-Nitrophenyl) prop-2-en-1-ol (**2f**) did not conduct under reflux condition for 24 h (entry 5). (*E*)-3-(2-Nitrophenyl) prop-2-en-1-ol (**2g**) gave only diallylated product in a 53% yield under reflux for 15 h (entry 6). The secondary alcohols **2h** and **2i** gave 42% and 40% yields, respectively (entries 7 and 8). Steric factors affected the yield. Treatment of **1a** with crotyl alcohol (**2j**) gave only stereoisomeric product **15** in the yield of 8%, and the formation of regioisomeric product was not observed (entry 9). As our observation, the reactivity of aromatic alcohols was better than aliphatic alcohols.

We speculated reaction mechanism in which water activates allyl alcohol via hydration of the hydroxy group and stabilizes the resulting hydroxide ion by strong solvation with water (**A**→**B**), since Oshima et al. reported that the hydroxide ion of water can leave with hydrating water molecules and the negative charge can be delocalized in the water cluster. (Scheme 1)[8] Intermolecular nucleophilic substitution of nucleophiles **1** takes place at the π-allyl system (**C**) to produce 2-allylated-1,3-diones.[15]

In conclusion, we have developed that aqueous reaction media enables the direct use of allylic alcohols as the allyl source without the help of any activating reagents for C–C bond formation. Moreover, this method gives potential industrial significance because of its simplicity in operation, economical, and environmentally advantages, air-stable, and economical viable. The alkylation of aromatic allylic alcohol worked well with cyclic 1,3-diones, giving generally good to high yields of the corresponding allylic 1,3-diones. However, the results of acyclic diketones such as acetylacetone were unsatisfied. Further investigations on other applications are in progress.

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Supplementary data

Supplementary data (experimental procedures and data for products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.022.

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