Homogeneous Catalysis

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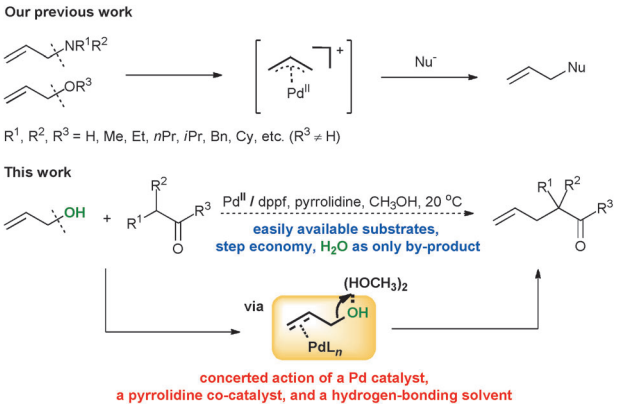
Palladium-Catalyzed Allylic Alkylation of Simple Ketones with Allylic Alcohols and Its Mechanistic Study**

Xiaohong Huo, Guoqiang Yang, Delong Liu, Yangang Liu, Ilya D. Gridnev, and Wanbin Zhang**

Abstract: *Allylic alcohols were directly used in Pd-catalyzed allylic alkylations of simple ketones under mild reaction conditions. The reaction proceeded smoothly at 20°C by the concerted action of a Pd catalyst, a pyrrolidine co-catalyst, and a hydrogen-bonding solvent, and does not require any additional reagents. A computational study suggested that methanol plays a crucial role in the formation of the π-allylpalladium complex by lowering the activation barrier.*

The palladium-catalyzed allylic alkylation is a powerful synthetic tool for C–C bond formation and has a broad range of applications in the synthesis of biologically important molecules.[1,2] One of the general features of this transformation is that substrates with a wide range of activated leaving groups (acetates, carbonates, etc.) can be utilized to form π-allylpalladium complexes.[3] However, the direct use of the accessible allylic alcohols in Pd-catalyzed allylic alkylations remains a challenge. It is worth noting that the use of allylic alcohols as substrates would help to avoid the additional steps required for the preparation of the corresponding activated substrates and the formation of at least stoichiometric amounts of waste both in the preparation and substitution steps. Therefore, allylic alcohols are gaining increasing attention as ideal substrates for palladium-catalyzed allylic alkylation reactions[4–7] with regard to waste minimization and sustainability.[8] While there have been some reports of Pd-catalyzed allylic alkylations using allylic alcohols, most of these methods required activators[4,6] or special ligands.[7] Therefore, a simple and convenient method for the direct use of allylic alcohols is highly desired.

We have demonstrated that allylic amines and allylic alkyl ethers possessing challenging leaving groups have been successfully utilized to form π-allylpalladium complexes through hydrogen-bond activation (Scheme 1).[9] Just before the submission of this manuscript, Ohshima and co-workers reported an interesting platinum- and pyrrolidine-catalyzed direct allylic alkylation of β-keto carbonyl compounds with allylic alcohols using acetic acid as an additive under high temperature and microwave conditions.[5h,10] We herein report a simple method for the direct use of allylic alcohols in Pd-catalyzed allylic alkylations of simple ketones in the presence of a pyrrolidine co-catalyst in alcohol solvents under mild conditions, and a mechanistic study of this reaction (Scheme 1).



Scheme 1. Reactions of allylic substrates with challenging leaving groups. Bn = benzyl, Cy = cyclohexyl, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, Nu = nucleophile.

Initially, we investigated the Pd-catalyzed allylic alkylation of cyclohexanone with cinnamyl alcohol in several solvents, using a $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/dppf catalyst system and 1.0 equivalent of pyrrolidine at 20°C.[11] We found that the reaction proceeded well in alcohol solvents and that methanol showed the most promising results. The reaction temperature and the amounts of cyclohexanone and pyrrolidine were also screened and the optimal reaction conditions were: cinnamyl alcohol/ketone = 1.1:1, 20 mol% pyrrolidine, and 2.5 mol% $[Pd(\eta^3\text{-allyl})Cl]_2$/dppf as a catalyst in methanol at 20°C. The effect of an acid as a co-catalyst was also explored, as it can catalyze both the formation of the enamine and the ionization of the leaving group.[5h,6b–d] The results suggested that our

[*] X. Huo, Prof. D. Liu, Prof. Y. Liu, Prof. W. Zhang
School of Pharmacy, Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240 (China)
E-mail: wanbin@sjtu.edu.cn
Homepage: http://wanbin.sjtu.edu.cn
Dr. G. Yang, Prof. W. Zhang
School of Chemistry and Chemical Engineering
Shanghai Jiao Tong University (China)
Prof. I. D. Gridnev
Department of Chemistry, Graduate School of Science
Tohoku University
Aramaki 3-6, Aoba-ku, Sendai 9808578 (Japan)
E-mail: igridnev@m.tohoku.ac.jp

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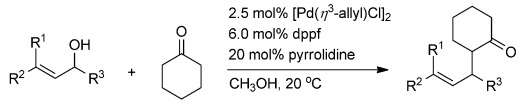
catalytic system was more effective in the absence of such an acid co-catalyst.[11]

A number of allylic alcohols were examined (Table 1). The reaction of allyl alcohol and crotyl alcohol with cyclohexanone proceeded smoothly in high yields (Table 1, entries 1 and 2). The allylic alkylation using cyclic or disubstituted allylic alcohol gave the desired products in moderate to high yields, when the reaction was carried out using 40 mol% pyrrolidine at 40 °C. No 1,3-diene product was formed (Table 1, entries 3–5).[12] Additionally, various cinnamyl alcohols with an electron-donating group or an electron-withdrawing group on the phenyl ring (Table 1, entries 6–10) and a 1,3-diphenyl-substituted substrate (Table 1, entry 11) all gave the desired products in excellent yields.

Table 1: Substrate scope of allylic alcohols.[a]

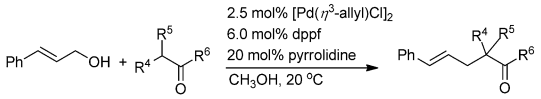


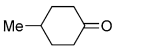
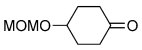
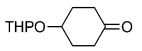
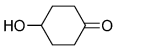
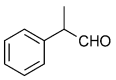
Entry	R^1	R^2	R^3	t [h]	Yield [%][b]
1	H	H	H	8	93
2[c]	H	Me	H	12	94 (E/Z = 11/1)
3[c]	H	$-(CH_2)_3-$		24	57
4[c]	Me	Me	H	24	54
5[c]	H	Ph	Me	24	82
6	H	Ph	H	12	97
7	H	3-Me-C_6H_4	H	12	98
8	H	4-Me-C_6H_4	H	12	99
9	H	4-MeO-C_6H_4	H	12	99
10	H	4-Cl-C_6H_4	H	12	98
11	H	Ph	Ph	18	98

[a] 0.50 mmol of cyclohexanone, 0.55 mmol of allylic alcohols; [b] yields of isolated products; [c] 40 mol% pyrrolidine, 40 °C.

The scope of a series of ketones was investigated next (Table 2). The reaction of cyclic ketones with cinnamyl alcohol occurred rapidly with high yields. For example, the reactions with cyclopentanone and cyclohexanone proceeded smoothly with high activities and yields (Table 2, entries 1 and 2). However, a higher temperature and an excess ketone were required for the reaction when cycloheptanone was used as a substrate (Table 2, entry 3). 4-Substituted cyclohexanones also furnished the allylated products in excellent yields (Table 2, entries 4–7). Ketones that possess acid-labile groups were compatible with our catalytic system (Table 2, entries 5 and 6). In addition, a free hydroxy group in the ketone substrate did not affect the reaction (Table 2, entry 7). The product was obtained in an excellent yield when aromatic ketones such as indanone were used (Table 2, entry 8). To our delight, phenyl acetaldehyde could be subjected to the reaction conditions, affording the desired products in 66% yield and several unidentified by-products (Table 2, entry 9). Butyraldehyde could also be used in the allylic alkylation reaction, providing the desired product in 70% yield (Table 2, entry 10). When an α-branched aldehyde, 2-phenylpropionaldehyde, was utilized in the reaction, the desired product was obtained in excellent yield (Table 2, entry 11).

Table 2: Scope of different ketones and aldehydes.[a]

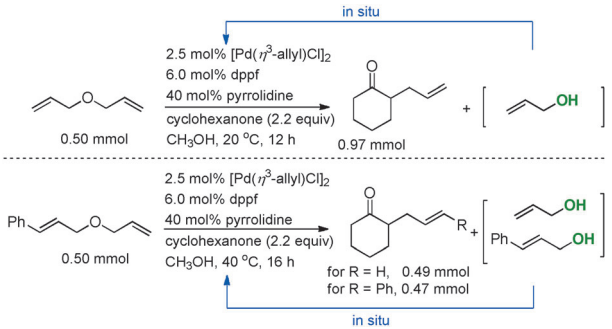


Entry	Ketones/Aldehydes	t [h]	Yield [%][b]
1		10	92
2		12	97
3[c]		24/12[d]	52/97[d]
4		12	98
5		12	95
6		12	98
7		12	97
8[c]		24	92
9[c]		24	66
10[c]		24	70
11[c]		18	92

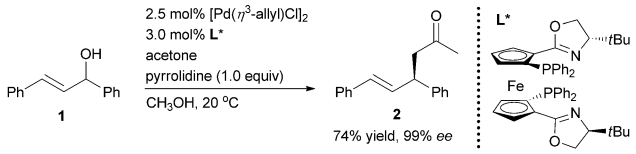
[a] 0.50 mmol of ketones or aldehydes, 0.55 mmol of cinnamyl alcohol; [b] yields of isolated products; [c] 40 mol% pyrrolidine, 40 °C; [d] 0.50 mmol of cinnamyl alcohol, 1.50 mmol of cycloheptanone, 40 °C, the yield is based on cinnamyl alcohol. MOM = methoxymethyl, THP = tetrahydropyranyl.

Our methodology can be easily extended to bisallyl ethers (Scheme 2). These substrates gave the desired products and the corresponding allylic alcohols.[9b] The in situ generated allylic alcohol was subsequently utilized in the reaction to give another equivalent of the desired product.

To extend the applicability of this methodology, we applied our catalytic system to an asymmetric synthesis using a chiral ferrocene-based phosphinooxazoline ligand (Scheme 3).[13] Allylic alcohol **1** was utilized in the Pd-catalyzed asymmetric allylic alkylation of acetone, affording the desired product in high yield and excellent enantioselec-



Scheme 2. Reactions of in situ generated allylic alcohols.



Scheme 3. Asymmetric transformation.

tivity. The product **2** could be easily transformed into chiral 4-oxo-2-phenylpentanoic acid **3**,[9b] which is an important intermediate for the synthesis of various therapeutic agents, peptides, and bioactive natural products.[14]

From the results above, it is obvious that allylic alcohols can be directly used in Pd-catalyzed allylic alkylation of carbonyl compounds under mild conditions employing our methodology. The synthetic importance of this process prompted us to investigate the reaction mechanism.[15] We carried out DFT calculations[16] for the C–O bond cleavage of allyl alcohol with the help of methanol (Figure 1). The results

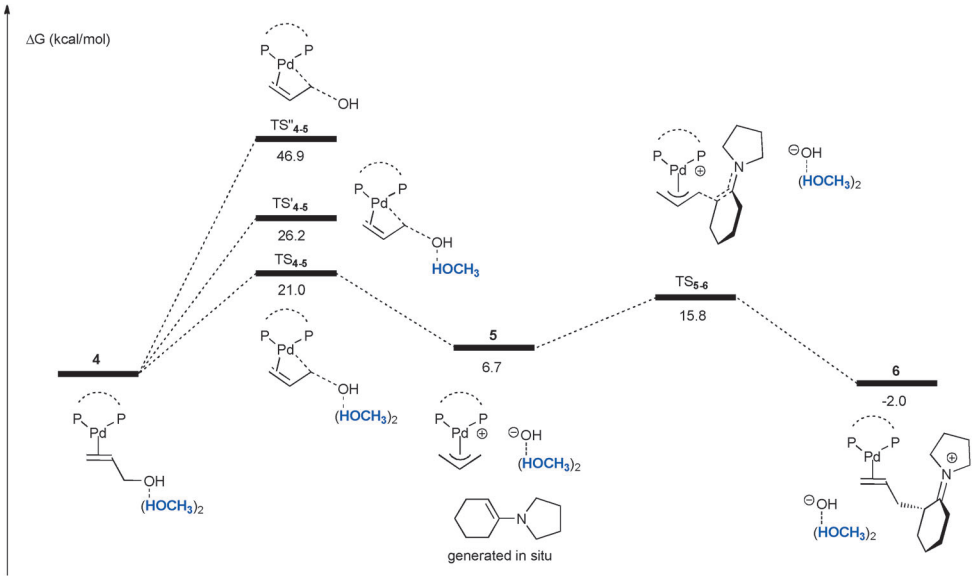


Figure 1. Free energy profile of the Pd-catalyzed allylic alkylation of cyclohexanone with allyl alcohol. The ligand was 1,2-bis(diphenylphosphino)ethane (dppe). TS = transition state.

suggest that the cleavage of the stable C–O bond can be easily achieved in methanol through hydrogen-bond activation. For the same process in the absence of methanol, a much higher activation barrier was obtained. The calculated results suggest that methanol plays a crucial role in the formation of the π-allylpalladium complex by lowering the activation energy and stabilizing the resulting hydroxide.

To compare the reactivities of allyl substrates with different leaving groups (OH, OEt, and OAc), the kinetics of these reactions were measured by ^{1}H NMR spectroscopy and GC–MS. As shown in Figure 2, the rate of the reactions changed in the order OEt > OH ⩾ OAc. These results indicate that the nature of the leaving group has an important effect on the rate of the reaction. The reaction utilizing allyl alcohol was similar to that with allyl ether.[9b] When allyl alcohol was used, *N*-allylpyrrolidine was also detected by GC–MS during the reaction. As the reaction proceeds, *N*-allylpyrrolidine is completely converted into the desired product. However, allyl acetate, the most common substrate in allylic alkylations, provided only 20% of the desired product (Figure 2) and 80% *N*-allylpyrrolidine after 3 h, in contrast to the reactions involving allyl ether and allyl alcohol.

The calculated energies of the ionization step demonstrate that the easy ionization characteristic for the allyl acetate is not beneficial for the formation of the desired product (Figure 3). Apparently, the facile ionization promotes the allylation of pyrrolidine rather than the ketone and slows down the allylation of the ketone. We hypothesize that the in situ generated acetic acid protonates the pyrrolidine, thus subsequently inhibiting the formation of the enamine. Indeed, when the reaction of allyl acetate was conducted with 2.0 equivalents of pyrrolidine, the desired product was obtained with 100% conversion in 3 h.

Further calculations for the catalytic cycle were conducted. As shown in Figure 1, the first step is the ionization of the OH group on the allylic moiety to give a transient π-allylpalladium complex **5** via $TS_{4\text{-}5}$ (Figure 4a). The in situ generated enamine then attacks the π-allylpalladium complex **5**, forming the imine-palladium complex **6** via $TS_{5\text{-}6}$ (Figure 4b). Our calculations also showed that the regeneration of the Pd catalyst from catalyst–product complex **6** does not require the dissociation of the product to give a 14-valence-electron Pd complex, as has been suggested previously.[15c] We have thus discovered a mild process ($\Delta G = 16.3$ kcal mol^{-1}; at 298 K) for the sub-

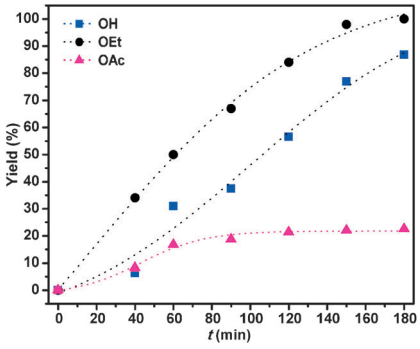


Figure 2. Effect of leaving groups (OH, OEt, and OAc) on the reaction yields. Reaction conditions: 0.50 mmol of substrates, 1.50 mmol of cyclohexanone, 1.0 equiv of pyrrolidine, 6.0 mol% dppf, 2.5 mol% $[Pd(\eta^3\text{-allyl})Cl]_2$ in CD_3OD (2 mL).

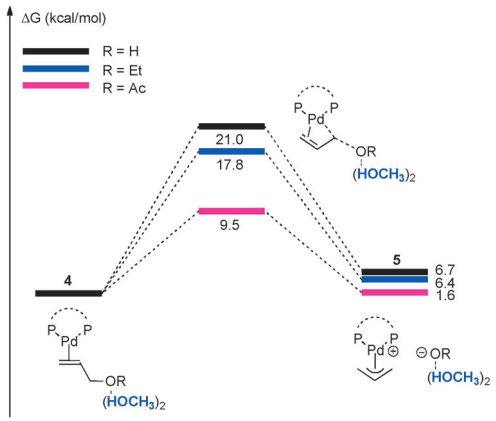


Figure 3. Free energy of the ionization step of allyl alcohol, allyl ether, and allyl acetate.

stitution of the product with allyl alcohol via $TS_{6\text{-}4}$ (Figure 4c), directly giving **4**.[15c]

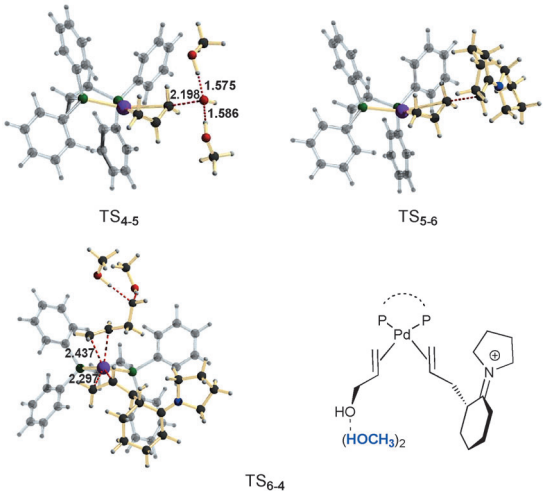


Figure 4. Optimized geometries of transition states $TS_{4\text{-}5}$, $TS_{5\text{-}6}$, $TS_{6\text{-}4}$; bond lengths are given in Å.

In summary, we have developed a palladium-catalyzed allylic alkylation of simple ketones with allylic alcohols, proceeding by the concerted action of a Pd catalyst, a pyrrolidine co-catalyst, and a hydrogen-bonding solvent. The procedure does not require any additional reagents. In a preliminary study, the Pd-catalyzed asymmetric allylic alkylation of acetone was carried out with high yield and excellent enantioselectivity. A computational study suggested that methanol plays a crucial role in the formation of the π-allylpalladium complex, by lowering the activation energy and stabilizing the resulting hydroxide. Finally, a catalytic cycle for the reaction under investigation has been proposed using DFT calculations.

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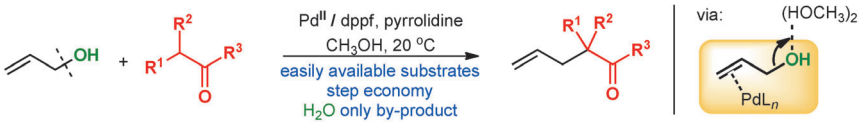
Communications

Homogeneous Catalysis

X. Huo, G. Yang, D. Liu, Y. Liu,
I. D. Gridnev,*
W. Zhang* _____ ■■■■–■■■■

Palladium-Catalyzed Allylic Alkylation of Simple Ketones with Allylic Alcohols and Its Mechanistic Study



Concerted action: Allylic alcohols were directly used in the title reaction under mild conditions. The reaction smoothly proceeds by the concerted action of a Pd catalyst, a pyrrolidine co-catalyst, and a hydrogen-bonding solvent, and does not require any additional reagents. A computational study suggested that methanol plays a crucial role in the formation of the π-allylpalladium complex by lowering the activation barrier.