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Dual Palladium- and Proline-Catalyzed Allylic Alkylation of Enolizable Ketones and Aldehydes with Allylic Alcohols

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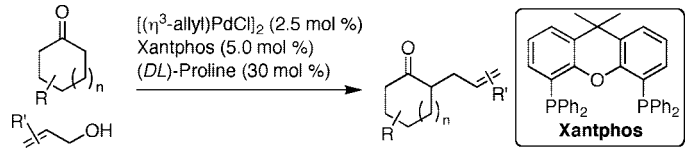
ABSTRACT



The dual Pd/proline-catalyzed α-allylation reaction of a variety of enolizable ketones and aldehydes with allylic alcohols is described. In this reaction, the choice of a large-bite angle ligand Xantphos and proline as the organocatalyst was essential for generation of the crucial π-allyl Pd intermediate from allylic alcohol, followed by nucleophilic attack of the enamine formed in situ from the corresponding enolizable carbonyl substrate and proline.

During the last two decades, palladium-catalyzed allylic alkylation has become an attractive and mature synthetic method.[1] Typical substrates are acetates and carbonates derived from allylic alcohols and acetic acid, and alcohols are formed as the concomitant byproduct stoichiometrically. In this respect, the use of allylic alcohols as substrates would be highly attractive since the extra step for allylic eletrophile preparation could be circumvented with water being the only byproduct (Figure 1).[2] An interesting synthetic application is the α-allylic alkylation of enolizable ketones and aldehydes. Such a transformation has been realized previously by employing preformed allylic enol carbonates or allylic β-ketoester substrates.[3] The alternative intermolecular direct ketone allylation is more difficult but has been achieved recently, combining enamine organocatalysis with palladium catalysis.[4] The role of the secondary amine catalyst is to in situ generate the enamine nucleophile which undergoes nucleophilic attack at an in situ generated π-allyl palladium complex. In these cases, allylic acetates were employed as substrates. A related study employed a dual Brønsted acid and palladium catalyst for the enantioselective allylic alkylation of simple aldehydes. In this case, allylic amines had to be used as substrates.[4b] Furthermore, allylic alkylation in high yield and high enantiomeric excess has been achieved without a transition-metal catalyst based on organo-SOMO catalysis.[5]

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(4) (a) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1952. Ibrahem, I.; Córdova, A. *Angew. Chem.* **2006**, *118*, 1986. (b) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (c) Bihelovic, F.; Matovic, R.; Vulovic, B.; Saicic, R. N. *Org. Lett.* **2007**, *9*, 5063.

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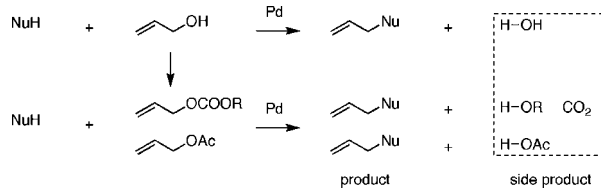
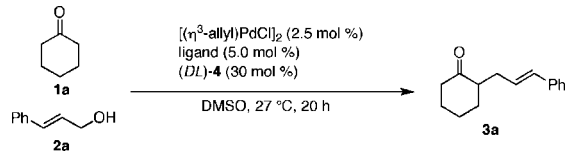


Figure 1. Allylic alkylation with allylic alcohol.

We recently achieved the allylic substitution by employing allylic alcohols in the presence of a palladium catalyst with self-assembling ligands developed in our laboratory[6] and made attempts to access α-alkylation of ketones and aldehydes with these systems as well. In the course of a catalyst screening, we discovered the Pd−Xantphos system as an effective catalyst for this transformation. In this paper, we report on a dual palladium- and proline-catalyzed allylic alkylation that allows for a direct α-allylation of enolizable ketones and aldehydes employing allylic alcohols as electrophiles.

Table 1. Ligand Effects on Cyclohexanone Allylation with Cinnamyl Alcohol

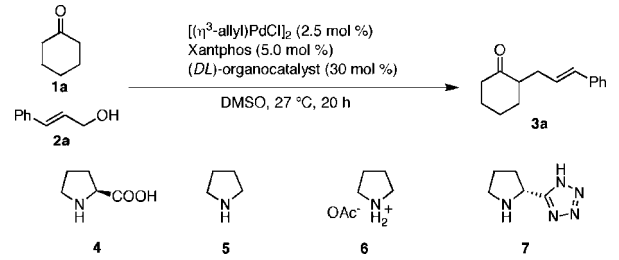


entry	ligand	convn[b] (%)	bite angle[c] (°)
1	Xantphos	50	111
2	PPh_3[d]	0	
3	Dppe	0	86
4	Dppf	4	101
5	DPEphos	27	102
6[e]	Xantphos	0	111

[a] The solution of ketone (1.5 mmol) and cinnamyl alcohol (0.5 mmol) in DMSO (2 mL) was stirred in the presence of 2.5 mol % of [(η^3-allyl)PdCl]$_2$, 5 mol % of ligand, and 30 mol % of (DL)-proline at 70 °C for 20 h. [b] dppe: bis(diphenylphosphanyl)ethane. dppf: 1,1′-bis(diphenylphosphino)ferrocene. DPEphos: bis(2-diphenylphosphinophenyl) ether. Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. [c] Conversion estimated by ^{1}H NMR. [d] Reference 6. [e] 10 mol %. [f] [(η^3-allyl)Pd (cod)]BF_4 was employed.

We began our investigations by looking at the α-allylation of cyclohexanone with cinnamyl alcohol (Table 1). As the organocatalyst we selected proline since its potential for reversible enamine/immonium ion formation on reaction with an enolizable ketone or aldehyde in polar aprotic solvents such as DMSO is well established.[7] π-Allyl palladium chloride dimer was employed as the palladium source, and a screening of monodentate and bidentate phosphine ligands with differing bite angles was undertaken. While triphenylphosphine and dppe were not effective at all, when dppf or DPEphos was used a moderate conversion toward the desired allylation product **3a** was observed (Table 1, entries 2−5). Best results were obtained with the large bite angle diphosphine Xantphos (entry 1). Hence, this reaction shows a correlation between catalyst activity and the size of the natural bite angle of the diphosphine ligand employed, with larger bite angle diphosphines furnishing the more active catalyst.[8] Interestingly, when the catalyst precursor was switched to [(η^3-allyl)Pd(cod)]BF_4, which was the most effective catalyst precursor in the case of Pd/self-assembling ligands, no reaction took place.[5]

Table 2. Screening for the Optimal Organocatalyst



entry[a]	catalyst	yield[b] (%)
1	L-**4**	50[c]
2	**5**	0
3	**6**	0
4	**7**	20[c]
5	(*DL*)-**4**	89[d]

[a] The solution of ketone (1.5 mmol) and cinnamyl alcohol (0.5 mmol) in DMSO (2 mL) was stirred in the presence of 2.5 mol % of [(η^3-allyl)Pd Cl]$_2$, 5 mol % of xantphos, and 30 mol % of organocatalyst at 27 °C for 20 h. [b] Isolated yield. [c] Racemic **3a** was obtained when enantiomerically pure organocatalyst was used. [d] At 70 °C. Isolated yield.

Next, we examined the combination of organocatalyst and Pd/Xantphos. Thus, the most active organocatalyst was proline, which allowed for 50% conversion at 27 °C and gave a synthetically useful yield of 89% at 70 °C (Table 2, entries 1 and 5). Unfortunately, employing enantiomerically pure L-proline **4** (Table 2, entry 1) furnished essentially racemic allylation product **3a**. On the other hand, when pyrrolidine **5** was used as a potential enamine-forming organocatalyst, the desired allylation product could not be observed at all (entry 2). In order to probe the need for the presence of a carboxylic acid function pyrrolidinium acetate was employed. However, no reaction was observed (entry 3). Conversely, when proline-derived tetrazole **7** was used, a 20% yield of product was obtained.

Obviously, the presence of both a secondary amine function and an acidic function with a pK_a in the range of a carboxylic acid within the same organocatalyst molecule are essential prerequisites for the title reaction to proceed.

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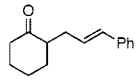
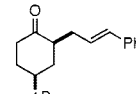
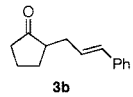
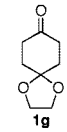
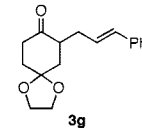
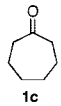
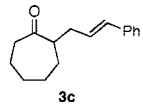
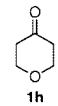
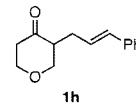
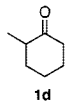
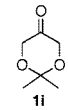
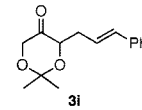
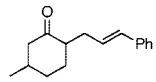
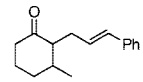
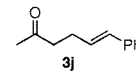
(6) Usui, I.; Schmidt, S.; Keller, M.; Breit, B. *Org. Lett.* **2008**, *10*, 1207.
(7) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
(8) Van Haaren, R. J.; Goubitz, K.; Fraanje, J.; van Strijdonck, G. P. F.; Coussens, B.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Inorg. Chem.* **2001**, *40*, 3363.

Table 3. Scope of Ketone[a]

entry	ketone	product	yield[b] (%)	entry	ketone	product	yield[b] (%)
1	 1a	 3a	89	6	 1f	 3f	96 (cis/trans = 10:1)
2	 1b	 3b	75	7	 1g	 3g	96
3	 1c	 3c	32	8	 1h	 1h	96
4	 1d		0	9	 1i	 3i	85
5	 1e	 3d  3e	55 33	10	 1j	 3j	44

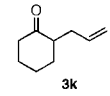
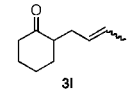
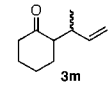
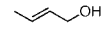
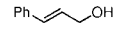
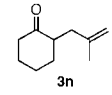
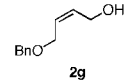
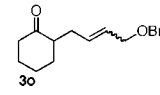
[a] The solution of ketone (1.5 mmol) and cinnamyl alcohol (0.5 mmol) in DMSO (2 mL) was stirred in the presence of 2.5 mol % of $[(\eta^3\text{-allyl})PdCl]_2$, 5 mol % of xantphos, and 30 mol % of (DL)-proline at 70 °C for 20 h. [b] Isolated yield.

The allylation reaction with cinnamyl alcohol proceeds well with unsubstituted cyclic ketones to furnish the corresponding allylation products **3a**−**c** (Table 3, entries 1−3). When 2-methylcyclohexanone **1d**was used, no reaction took place (Table 3, entry 4). Such a lack of reactivity for **1d** has been observed before in the case of organocatalytic attempts for α-oxygenation of this ketone.[9] 3-Substituted methylcyclohexanone **1e** gave a mixture of the two regioisomers **3d** and **3e** (Table 3, entry 5). 4-Substituted cyclohexanones **1f** also furnished the allylation product in excellent yield (Table 3, entries 6 and 7) as well as oxygen-containing heterocyclic ketones (Table 3, entries 8 and 9). Acyclic ketones were considerably less reactive than cyclic substrates. Only with acetone could the corresponding allylation product be obtained in acceptable yield (Table 3, entry 10), though a considerable amount of the bis(cinammyl) ether was formed as a byproduct.

The reaction is not restricted to the use of cinnamyl alcohol but can be transferred to a range of simple allylic alcohols. Thus, allylation of cyclohexanone employing the parent allylic alcohol **2b** furnished **3k** in excellent yield (Table 4, entry 1). Using either 3-buten-2-ol (**2c**) or the isomeric crotyl alcohol (**2d**) gave a mixture of the α- and γ-allylation product in similar ratios and good yields. Also, starting either from cinnamyl alcohol (**2a**) or 1-phenyl 2-propenol (**2e**), the same allylation product **3a** was obtained in similar yields. These observations are in accord with a π-allyl intermediate involved in the reaction mechanism. In addition, excellent yields of the corresponding allylation product **3n** could be

(9) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966.

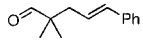
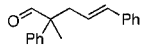
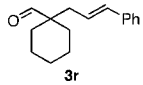
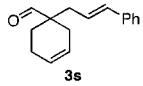
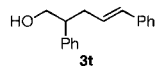
Table 4. Scope of Allylic Alcohol

entry	allyl alcohol	product	yield[b] (%)
1	 2b	 3k	91
2	 2c	 3l	74 (E:Z = 67:33)
		 3m	12 (syn:anti = 64:36)
3	 2d	3l	84 (E:Z = 67:33)
		3m	12 (syn:anti = 69:31)
4	 2a	3a	89
5	 2e	3a	85
6	 2f	 3n	91
7	 2g	 3o	67 (E:Z = 33:67)

[a] The solution of cyclohexanone (1.5 mmol) and allylic alcohol (0.5 mmol) in DMSO (2 mL) was stirred in the presence of 2.5 mol % of $[(\eta^3\text{-allyl})\ PdCl]_2$, 5 mol % of xantphos, and 30 mol % of proline at 70 °C for 20 h. [b] Isolated yield. [c] At 80 °C.

obtained with β-methallyl alcohol (**2f**). On the other hand, with α,α- and γ,γ-dimethylallyl alcohol, the allylation reaction did not proceed at all. In this case, the common π-allyl Pd intermediate might be sterically to hindered to allow for reaction with the enamine. Further, using (*Z*)-4-(benzyloxy)but-2-en-1-ol (**2g**) led to formation of **3o**. Interestingly, the linear product was formed exclusively as an *E*/*Z* mixture of 1:2, which implies that $\sigma-\pi-\sigma$ isomerization is faster than nucleophilic attack to the Pd intermediate.

Table 5. Scope of Aldehyde

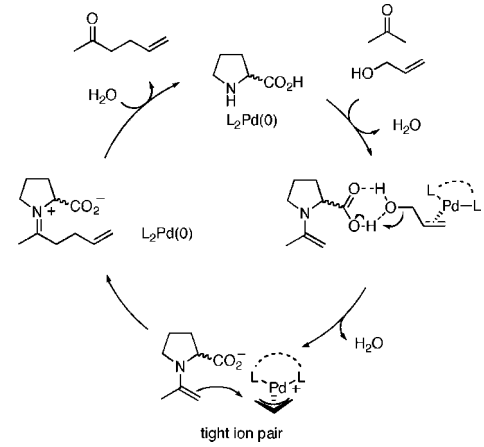
entry	aldehyde	product	yield[b] (%)
1	 **1j**	 **3p**	78
2	 **1k**	 **3q**	81
3	 **1l**	 **3r**	84
4	 **1m**	 **3s**	73
5	 **1n**	 **3t**	77[c]

[a] The solution of aldehyde (1.5 mmol) and cinnamyl alcohol (0.5 mmol) in DMSO (2 mL) was stirred in the presence of 2.5 mol % of [(η^3-allyl)PdCl]$_2$, 5 mol % of xantphos, and 30 mol % of (DL)-proline at 70 °C for 20 h. [b] Isolated yield. [c] Isolated yield after reduction with $NaBH_4$ as alcohol.

We also briefly looked into enolizable aldehydes, which turned out to be excellent substrates for the title reaction (Table 5). Thus, starting from α-disubstituted aldehydes **1j**−**m** the efficient construction of quaternary carbon centers could be achieved through allylation (Table 5, entries 1−4). Also an α-monosubstituted aldehyde was employed which gave the corresponding monoallylation product selectively (entry 5). Due to stability problems with this aldehyde it was isolated as the corresponding alcohol after reduction with sodium borohydride.

A mechanistic rationale taking into account all experimental observations is given in Scheme 2. Thus, the carboxylic acid function of proline may be involved in the ionization step of the palladium olefin complex of allylic alcohol through hydrogen bonding and protonation of the hydroxy leaving group. This would result in the formation of a tight ion pair between enamine nucleophile and π-allyl palladium electrophile which should allow for a rapid allylation. An external carboxylic acid would preclude the formation of such an ion pair, which may be the reason for its failure (Table 2, entry 3).

Scheme 2. Proposed Mechanism



In conclusion, a dual transition metal and organocatalytic α-allylation of enolizable ketones and aldehydes employing simple allylic alcohols as electrophiles has been developed. The combination of a palladium wide bite angle diphosphine ligand (Xantphos) and proline as the organocatalyst proved essential for the title reaction to proceed. Control experiments show the importance of the presence of a carboxylic acid function in the secondary amine catalyst. Unfortunately, employing enantiomerically pure proline did not allow thus far for efficient enantioinduction during this allylation reaction. Hence, future studies will address the problem of enantioselectivity control.

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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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