Organic LETTERS

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Synergistic Pd/Enamine Catalysis: A Strategy for the C−H/C−H Oxidative Coupling of Allylarenes with Unactivated Ketones

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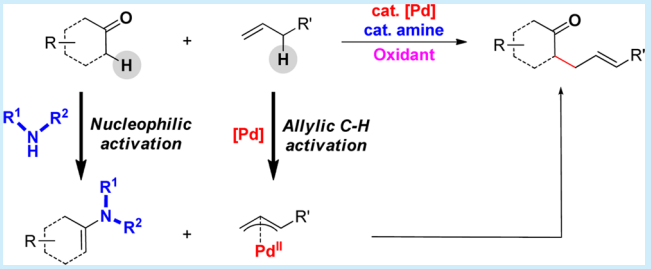
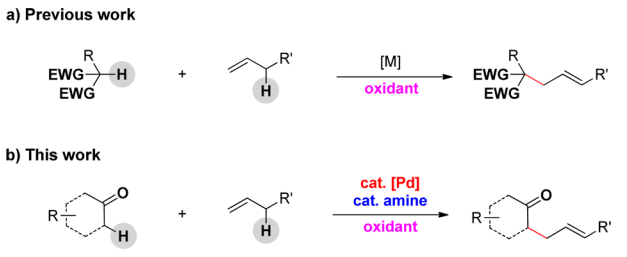
Supporting Information

ABSTRACT: By combining catalytic nucleophilic enamine activation with Pd-catalyzed C−H activation of allylarenes, the first oxidative allylic alkylation of unactivated ketones was achieved. Mechanistically, the Pd-catalyzed allylic C−H activation and proline-catalyzed ketone nucleophilic activation worked synergistically for the oxidative cross-coupling between allylarenes and unactivated ketones.



The Pd-catalyzed allylic alkylation (Tsuji−Trost allylic alkylation) is an important and efficient strategy for $C(sp^3)-C(sp^3)$ bond formation.[1] Along with its development, continuous efforts have been devoted to improve the efficiency and expand the scope in this transformation.[2] Most of the efforts are focused on prefunctionalized allylic substrates in which a reactive leaving group is installed for facile ionization to form the π-allyl palladium intermediate. Echoing the pursuit of atom-economic and sustainable chemistry, C−H activation and functionalization have become the forefront of organic synthesis.[3] In this regard, oxidative Tsuji−Trost allylic alkylation, which directly utilizes allylic hydrocarbons for $C(sp^3)-C(sp^3)$ coupling, has been developed over the recent years.[4] However, the carbon nucleophiles employed in these studies are confined to those stabilized carbon anions wherein two strong electron-withdrawing groups are adjacent to the center atom (Scheme 1a). Unactivated nucleophilic hydrocarbons, such as simple ketones, have not been realized in oxidative Tsuji−Trost allylic alkylation until now. Mechanistically, the key step for the successful Tsuji−Trost allylic alkylation is the nucleophilic attack by carbon nucleophile to the in situ generated π-allyl Pd intermediate.[4b,e] Since it is difficult for unactivated ketones to achieve α-allylation due to their low α-C-H acidity, harsh reactions in typical enolate-allylation processes are required.[5] In this regard, new strategies need to be developed for the oxidative cross-coupling between allylic hydrocarbons and unactivated ketones.

Scheme 1. Oxidative Tsuji−Trost Allylic Alkylation



Over the past few years, organocatalysis has grown spectacularly successfully to become one of the most exciting research areas in modern organic synthetic chemistry.[6] Compared with the well-established transition metal catalysis, organocatalysis can promote organic transformations through distinct activation modes.[7] Therefore, the combination of transition metal catalysts with organocatalysis represents a powerful catalytic approach for developing new reactions.[8] Among the developed dual catalysis systems, synergistic combination of enamine activation catalysis with transition metal catalysis has emerged and been proved to be a significant strategy for the direct functionalization of unactivated ketones/aldehydes.[9] In 2006, Córdova and co-workers demonstrated the first example of combining enamine activation catalysis with Pd catalysis.[10] This synergistic catalysis strategy promoted the intermolecular α-allylic alkylation of unactivated ketones and aldehydes with allylic acetates.[11] Since then, efforts have been taken to expand this synergistic strategy to other activated allylic substrates such as allylic halides, allylic alcohols, allylic amines, and allylic ethers.[12] Nevertheless, synergistic catalysis for alkenes without leaving groups has not yet been established until now.

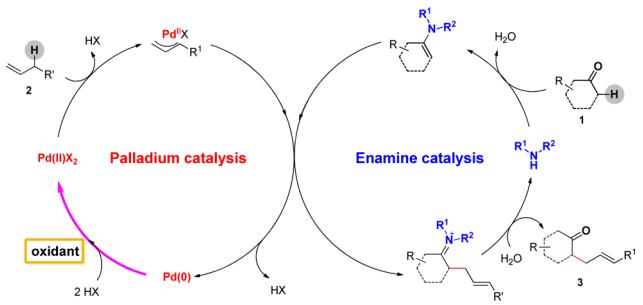
Considering that transition metal (especially palladium)-catalyzed allylic C−H activation has been established,[13] we assume that the combination of the nucleophilic activation by enamine activation catalysis and allylic C−H activation by Pd

Received: June 2, 2014

dx.doi.org/10.1021/ol501584d | Org. Lett. XXXX, XXX, XXX−XXX

catalysis might provide a chance to deal with the oxidative Tsuji–Trost allylic alkylation for unactivated ketones (Scheme 1b). Based on the widely accepted mechanism of enamine activation catalysis and palladium catalysis,[7i,10] the oxidative cross-coupling between allylic hydrocarbons and unactivated ketones can be assumed to proceed through combined Pd/enamine catalytic cycles shown in Scheme 2. Pd(II) has the

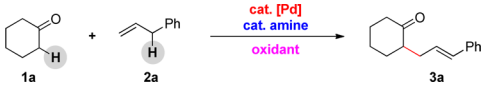
Scheme 2. Mechanistical Assumption for the Oxidative Cross-Coupling between Allylic Hydrocarbons and Unactivated Ketones



ability to activate the allylic C–H bond, which will afford an electrophilic π-allylpalladium intermediate.[1a,b,4e] Meanwhile, the amine catalyst could react with the unactivated ketone to generate an enamine intermediate. Then, the formation of enamine increases nucleophilicity of the ketone substrate, which might allow it to undergo nucleophilic attack to the *in situ* generated π-allylpalladium.[10,11b,12a] This would lead to the formation of an iminium intermediate that could afford the final $C(sp^3)–C(sp^3)$ bond formation product through a hydrolysis process. Importantly, an oxidant is required for the oxidation of Pd(0) to regenerated Pd(II), which will lead to the completion of the Pd catalytic cycle.[13b] During all of these processes, the compatibility of the oxidative condition will be the major challenge for applying synergistic strategy to the cross-coupling between allylic hydrocarbons and unactivated ketones.[9,14] It is worthy of noticing that rare methods have been successful in the area of combining transition metal catalysis with organocatalysis.[15] Therefore, discovering suitable combination of catalysts and oxidants will be the key for achieving the oxidative Tsuji–Trost allylic alkylation with unactivated ketones.

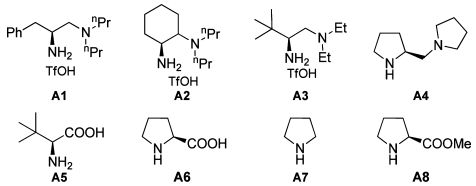
We initiated our study on the direct oxidative coupling of cyclohexanone (**1a**) with allylbenzene (**2a**) by applying $Pd(PPh_3)_4$ as the catalyst and *p*-benzoquinone as the oxidant. First, we tried primary amine catalysts, which showed good nucleophilic activation capacity in our previous study.[16] However, only trace amount of the desired product could be observed (Table 1, entries 1–3). Further investigation showed that secondary amine and primary amino acids exhibited better reactivity (Table 1, entries 4 and 5). To our delight, the simple secondary amino acid L-proline exhibited good reactivity and furnished the desired product in 30% yield (Table 1, entry 6). However, Pd(II) catalyst precursors such as $[(\eta^3\text{-allyl})PdCl]_2$ and $PdCl_2(PPh_3)_2$ showed poor reactivities in this transformation, which indicated the importance of choosing a suitable Pd complex (Table 1, entries 7 and 8).[17] We were pleased to find that the combination of $Pd(OAc)_2$ with PPh_3 showed an excellent reactivity, which afforded the desired product in 72% yield (Table 1, entry 9). It is worthy of noting that only the linear product was observed. Regretfully, racemic

Table 1. Optimization of the Catalysts and Oxidant Combination[a]



entry	[Pd] cat.	amine cat.	oxidant	yield (%)[b]
1	$Pd(PPh_3)_4$	**A1**	BQ	trace
2	$Pd(PPh_3)_4$	**A2**	BQ	trace
3	$Pd(PPh_3)_4$	**A3**	BQ	trace
4[c]	$Pd(PPh_3)_4$	**A4**	BQ	12
5	$Pd(PPh_3)_4$	**A5**	BQ	10
6	$Pd(PPh_3)_4$	**A6**	BQ	30
7	$[(\eta^3\text{-allyl})PdCl]_2$	**A6**	BQ	trace
8	$PdCl_2(PPh_3)_2$	**A6**	BQ	trace
9	$Pd(OAc)_2/2PPh_3$	**A6**	BQ	72
10[c]	$Pd(OAc)_2/2PPh_3$	**A7**	BQ	trace
11[c]	$Pd(OAc)_2/2PPh_3$	**A8**	BQ	trace
12	$Pd(OAc)_2/2PPh_3$	**A6**	DMBQ	24
13	$Pd(OAc)_2/2PPh_3$	**A6**	DDQ	nd
14	$Pd(OAc)_2/2PPh_3$	**A6**	Cl_4-BQ	nd
15	$Pd(OAc)_2/2PPh_3$	**A6**	O_2 (1 atm)	nd
16		**A6**	BQ	nd
17	$Pd(OAc)_2/2PPh_3$		BQ	nd
18	$Pd(OAc)_2/2PPh_3$	**A6**	BQ	nd

[a]Reaction conditions: **1a** (0.50 mmol), **2a** (1.0 mmol), [Pd] catalyst (10 mol %), amine catalyst (20 mol %), and *p*-benzoquinone (1.5 equiv) in toluene (1.0 mL), 100 °C, 10 h. [b]Yields shown were determined by GC analysis with byphenyl as the internal standard, nd = not detected. [c]PhCOOH (20 mol %) was added.

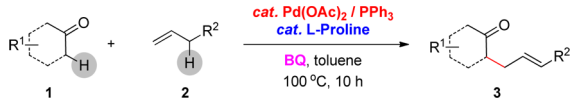


product was obtained though optically pure L-proline was used in this system.[18] When simple pyrrolidine (**A7**) and methyl pyrrolidine-2-carboxylate (**A8**) were applied as the amine catalyst in the reaction system, the yield of the desired product dropped dramatically (Table 1, entries 10 and 11).[12a] This strict demand on the structure of the amine catalyst is due to the fact that primary amine catalysts and simple pyrrolidine could react with the oxidant BQ directly.[19] As for the selection of oxidant, a decreased yield of the coupling product was obtained in the case of 2,6-dimethylbenzoquinone (DMBQ), which demonstrated excellent reactivity for the oxidative Tsuji–Trost allylic alkylation with activated ketones (Table 1, entry 12).[4e,f] Other oxidants such as 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ), tetrachlorobenzoquinone (Cl_4-BQ), and oxygen failed to give the coupling product (Table 1, entries 13–15). Control experiments showed that Pd catalyst, amine catalyst, and oxidant were all crucial for the successful oxidative coupling (Table 1, entries 16–18). These results supported the synergistic feature of this reaction system. Thus, the standard condition was obtained as $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), L-proline (20 mol %), and *p*-benzoquinone (BQ, 1.5 equiv) in toluene (1.0 mL) at 100 °C with stirring for 10 h.[20]

Subsequently, we applied the optimized reaction conditions to examine the functional group tolerance of allylarenes. To our delight, *para* substituents on the phenyl ring afforded the coupling products in good yields (Table 2, entries 1–4).

dx.doi.org/10.1021/ol501584d | Org. Lett. XXXX, XXX, XXX–XXX

Table 2. Substrate Scope for the Synergistic Oxidative Tsuji–Trost Allylic Alkylation[a]



1 2 3

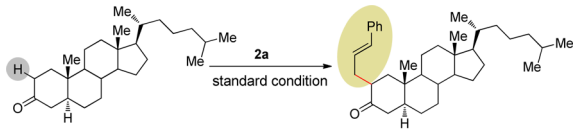
entry	1	2	3	yield (%)[b]
1	1a	2a, R = H	3a, R = H	75
2	1a	2b, R = F	3b, R = F	70
3	1a	2c, R = OMe	3c, R = OMe	78
4	1a	2d, R = CF_3	3d, R = CF_3	55
5	1a	2e	3e	54
6	1b	2a	3f (3:1 dr)	68
7	1c	2a	3g	86
8	1d	2a	3h (5:1 dr) & 3h' (3:1 dr)	80 (3h:3h' = 1.6:1)
9	1e	2a	3i	71
10	1f	2a	3j	48
11	1g	2a	3k	36
12[c]	1h	2a	3l	21

[a]Reaction condition: **1** (0.50 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.050 mmol), PPh_3 (0.10 mmol), L-proline (0.10 mmol), and *p*-benzoquinone (0.75 mmol) in toluene (1.0 mL), 100 °C, 10 h. [b]Yields shown are of isolated yields. [c]Acetone (0.5 mL) in toluene (0.5 mL).

Allybenzene with a strong electron-withdrawing CF_3 substituent was less reactive than that with a strong electron-donating OMe substituent in this transformation (Table 2, entries 3 and 4). In addition, allylthiophene was also tested and afforded the desired product in a good yield (Table 2, entry 5). Afterward, we decided to apply the synergistic Pd/Enamine catalysis strategy on a set of unactivated ketones. The oxidative allylic alkylation reaction with allylbenzene proceeded well for six-membered cyclic ketones to furnish the corresponding allylation products (Table 2, entries 1, 6–9). Simple cyclohexanone and 4-methyl cyclohexanone afforded the allylation products in good yields (Table 2, entries 1 and 6). Delightfully, 1,4-cyclohexanedione monoethylene acetal gave the desired product in an excellent yield of 86% (Table 2, entry 7). As for 3-methyl cyclohexanone, a mixture of two regioisomers was obtained since there were two reactive sites (Table 2, entry 8). Moreover, 4-oxacyclohexanone was also suitable in this transformation, which afforded the desired product in 71% yield (Table 2, entry 9). Finally, efforts were taken to expand this synergistic oxidative coupling reaction to other cyclic and acyclic ketones. The reaction with cyclopentanone and cycloheptanone did proceed to afford the desired product, but with reduced efficiency in our synergistic catalysis system (Table 2, entries 10 and 11).[12a,21] Furthermore, acyclic ketones showed poor reactivity in this system when compared with the cyclic ketones. A promising result was obtained when an excess amount of acetone was used, affording the desired product in 21% yield (Table 2, entriy 12).

To demonstrate the synthetic utility of this synergistic oxidative coupling reaction, a steroid 5α-cholestan-3-one (**4**), which contains a six-membered cyclic ketone moiety, was tested under the standard condition with allylbenzene. Delightfully, direct α-alkylation product could be obtained in a satisfactory 50% yield with a good regioselectivity (Scheme 3). Overall, this report, to the best of our knowledge, is the first example for achieving C–H/C–H oxidative coupling of unactivated ketones with allylarenes.

Scheme 3. Oxidative Tsuji–Trost Allylic Alkylation with 5α-cholestan-3-one



4: 5α-cholestan-3-one **5:** 50%, *dr* > 20:1

In conclusion, a Pd/proline co-catalyzed oxidative cross-coupling of unactivated ketones with allylic hydrocarbons was achieved for the first time. The introduction of nucleophilic activation through enamine activation catalysis enabled the oxidative allylic alkylation with unactivated cyclic ketones. In this transformation, palladium catalyst, amine catalyst, and *p*-benzoquinone were all crucial for the direct oxidative coupling. Importantly, this reaction provides an example for employing synergistic catalysis in developing new oxidative coupling reactions[22] that are difficult to achieve through traditional monocatalysis methods. Detailed mechanistic investigations and improvement of this system into an asymmetric version are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of ^1H, ^{13}C, and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the 973 Program (2011CB808600, 2012CB725302), the National Natural Science Foundation of China (21390400, 21025206, 21272180, and 21302148), the Research Fund for the Doctoral Program of Higher Education of China (20120141130002), and the Program for Changjiang Scholars and Innovative Research Team in University

(IRT1030). The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated.

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(20) In Supporting Information, we have presented the detailed optimization of catalyst ratio and temperature from the standard reaction system.

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dx.doi.org/10.1021/ol501584d | *Org. Lett.* XXXX, XXX, XXX−XXX