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Effects of Silver Carbonate and *p*-Nitrobenzoic Acid for Accelerating Palladium-Catalyzed Allylic C−H Acyloxylation

Aymen Skhiri, Haruki Nagae, Hayato Tsurugi,* Masahiko Seki,* and Kazushi Mashima*

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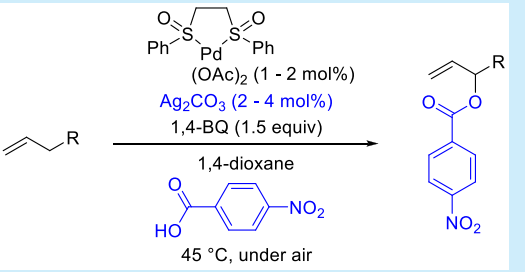
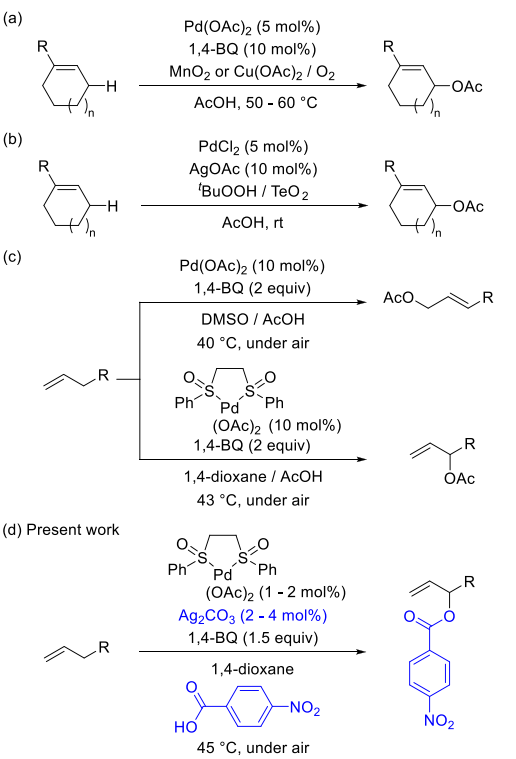
ABSTRACT: An allylic C−H acyloxylation of terminal alkenes with 4-nitrobenzoic acid was assisted by a bidentate-sulfoxide-ligated palladium catalyst combined with 1,4-benzoquinone and Ag_2CO_3 under mild reaction conditions. The catalytic activity was remarkably enhanced by Ag_2CO_3 as an additive and 4-nitrobenzoic acid as a carboxylate source; both components were essential to exhibiting high catalytic activity, high branch selectivity, and a wide substrate scope with low loading of the palladium catalyst. Branch-selective allylic acyloxylation of ethyl 7-octenoate (**1a**) gave the product which was led to ethyl 6,8-dihydroxyoctanoate (**5**), a useful synthetic intermediate of (*R*)-α-lipoic acid.



Oxidative allylic C(sp^3)−H bond functionalization of simple alkenes with carboxylic acids, i.e., allylic C-(sp^3)−H acyloxylation, is a powerful tool for preparing synthetically useful allyl esters.[1−3] Various methodologies have been developed to date to oxidize the allylic C(sp^3)−H bond using peracids and high-valent metal complexes as stoichiometric oxidants;[4] however, owing to the high reactivity of those oxidants, the functional group tolerance is narrow, and stoichiometric amounts of metal wastes are produced as byproducts. Aiming to overcome the narrow substrate scope and environmental unfriendliness for allylic C(sp^3)−H acyloxylation, Heumann and Åkermark et al. developed palladium-catalyzed allylic C(sp^3)−H acyloxylation of cyclic alkenes in the presence of a catalytic amount of 1,4-benzoquinone (1,4-BQ) together with more than stoichiometric amounts of MnO_2 or a catalytic amount of $Cu(OAc)_2$ with O_2 as the oxidants in acetic acid, giving allyl acetates in good yield without overoxidized products (Scheme 1(a)).[5,6] Uemura et al. demonstrated that a combination of *tert*-butyl hydroperoxide and TeO_2 was effective for acyloxylation of the allylic C(sp^3)−H bond of cyclic alkenes catalyzed by $PdCl_2$/AgOAc (Scheme 1(b)),[7] although terminal alkenes were not applied in this palladium-catalyzed allylic oxidation due to the facile isomerization of the alkene moiety. Later, White et al. developed a palladium-catalyzed linear-selective allylic C-(sp^3)−H bond acyloxylation of terminal alkenes in DMSO aided by 1,4-BQ as the oxidant under aerobic conditions. In addition, they successfully achieved branch-selective allylic acyloxylation of terminal alkenes with acetic acid using a bidentate sulfoxide-ligated palladium catalyst, i.e., the White catalyst, in combination with 1,4-BQ (Scheme 1(c)).[8,9] The branch/linear selectivity of the allylic C(sp^3)−H acyloxylation of terminal alkenes is controlled by the supporting ligands, monodentate (DMSO) vs a bidentate sulfoxide; the high catalyst loading (over 5 mol %) and longer reaction time of the

Scheme 1. Representative Examples for Allylic C(sp^3)−H Acyloxylation by Palladium Catalysts and This Work



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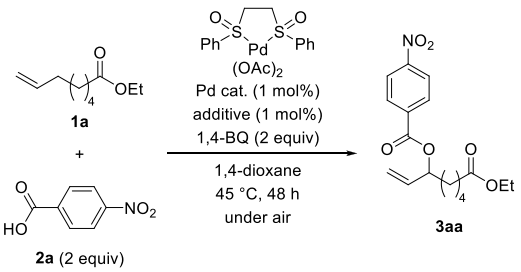
White catalyst system, however, remain serious issues. As a part of our continuous studies on synthesizing allylic-functionalized compounds using transition metal catalysts,[10] we herein report a significant improvement of the catalytic activity by *p*-nitrobenzoic acid as a carboxylate source and Ag_2CO_3 as a cocatalyst in the branch-selective allylic C(sp^3)−H acyloxylation of terminal alkenes with unprecedentedly low loadings of the palladium catalyst (Scheme 1(d)). Various mono- and disubstituted terminal and internal alkenes, including cyclic alkenes, were converted to the corresponding allyl esters in good to excellent yields. Furthermore, we found that this branch-selective allylic acyloxylation of terminal alkenes was applicable to a key step in the synthesis of (*R*)-α-lipoic acid.

We started by searching for the best additive for allylic acyloxylation of ethyl 7-octenoate (**1a**) as a model substrate and 4-nitrobenzoic acid (**2a**) as a carboxylate source using commercially available White catalyst (1 mol %) in the presence of 2 equiv of 1,4-BQ in 1,4-dioxane (0.50 mL) under aerobic conditions at 45 °C for 48 h, and the results are shown in Table 1. Under the standard conditions without any additive, the corresponding allylic carboxylate **3aa** was obtained in 23% yield (entry 1). The yield was remarkably

Table 1. Screening of Additives and Optimization for Allylic Acyloxylation of 1a with 2a[a]



entry	additive	time (h)	conv. of **1a** (%)	yield of **3aa** (%)	L/B ratio
1	-	48	26	23	1/99
2	Ag_2CO_3	48	93	91	1/99
3	$AgNO_3$	48	42	38	1/99
4	Ag_2O	48	34	32	3/97
5	AgOTf	48	46	45	<1/>99
6	AgOAc	48	23	18	1/99
7	AgCl	48	21	16	2/98
8	$CuCO_3$	48	24	22	<1/>99
9	$MnCO_3$	48	42	41	<1/>99
10	$Ce_2(CO_3)_3$	48	<5	trace	-
11	Na_2CO_3	48	10	trace	-
12	Ag_2CO_3	24	76	74	3/97
13[b]	Ag_2CO_3	48	30	29	1/99
14[c,d,e]	Ag_2CO_3	24	>99	98 (89)	<1/>99
15[f]	Ag_2CO_3	48	<5	trace	-
16[g]	Ag_2CO_3	48	<1	n.d.	-
17[h]	AgOTf	48	39	37	<1/>99

[a]Conditions: **1a** (0.30 mmol), **2a** (0.60 mmol, 2.0 equiv), Pd cat. (1 mol %), additive (1 mol %), 1,4-BQ (2.0 equiv) in 1,4-dioxane (0.50 mL) at 45 °C for 48 h. [b]1,4-Dioxane (2.0 mL). [c]1,4-BQ (1.5 equiv). Yield in parentheses is isolated yield. [d]**2a** (0.30 mmol, 1.0 equiv). [e]1 mmol scale reaction gave **3aa** in 84% isolated yield. Details were shown in the Supporting Information. [f]$Pd(OAc)_2$ instead of White catalyst. [g]Without Pd cat. n.d. = not detected. [h]AgOTf (2 mol %) was used as the additive.

increased by adding Ag_2CO_3: treatment of the reaction mixture with Ag_2CO_3 (1 mol %) afforded **3aa** in 91% yield with an exclusive branch selectivity (entry 2). We further tested the allylic acyloxylation using several silver salts as listed in entries 3−7. Although $AgNO_3$, Ag_2O, and AgOTf exhibited better catalytic activity compared with the standard conditions (entry 1), the yields of **3aa** were much lower than the case using Ag_2CO_3 (entries 3−5 vs entry 2). Silver salts such as AgOAc and AgCl exhibited almost no additive effects (entries 6 and 7). The unprecedented high positive effects of Ag_2CO_3 led us to further investigate other carbonate salts such as Cu, Mn, Ce, and Na under the standard reaction conditions: copper and manganese carbonate salts were previously used for allylic acyloxylation of cyclic alkenes with $Pd(OAc)_2$;[5] however, we observed no significant improvement of the catalytic activity when using these carbonates (entries 8 and 9), and the use of $Ce_2(CO_3)_3$ and Na_2CO_3 suppressed the catalytic reaction (entries 10 and 11), suggesting that both the silver cation and carbonate anion were essential for efficiently improving the catalytic performance. The specific role of additional metal ions in Pd-catalyzed C−H bond functionalization was reported for the formation of Pd−Ag and Pd−Na aggregates in the reaction mixture.[11] Using Ag_2CO_3 as the additive, we checked the reaction conditions by shortening the reaction time to 24 h, which produced **3aa** in a slightly lower yield (entry 12), and by diluting the reaction solution concentration, **3aa** was obtained in lower yield (entry 13). By changing the amount of 1,4-BQ to 1.5 equiv and **2a** to 1.0 equiv with respect to **1a**, the yield of **3aa** reached 98% in 24 h with perfect branch selectivity (entry 14). When the White catalyst was replaced with $Pd(OAc)_2$ under the same reaction conditions as in entry 2, **3aa** was detected in only a trace amount (entry 15), indicating the importance of the bidentate sulfoxide ligand for the reaction. No product was obtained without the palladium catalyst (entry 16), and to double the amount of AgOTf (2 mol %) was not effective for the acyloxylation (entry 17). The importance of the *para*-nitro substituent was significant: other electron-withdrawing and -donating substituents on the benzoic acid derivatives resulted in much lower yields for the acyloxylation (below 40%).[12] In addition, typical carboxylic acids for the acyloxylation such as acetic acid and pivalic acid were ineffective under the optimized reaction conditions.[12]

We next evaluated the substrate scope of mono- and disubstituted terminal alkenes (Table 2). Allylic acyloxylation with simple terminal alkenes such as 1-hexene (**1b**), 1-octene (**1c**), and 1-decene (**1d**) gave the branch-selective allylic acyloxylation products in excellent yields. The size of the alkyl group adjacent to the allylic position affected the reactivity: the yield gradually decreased with increasing bulkiness of the secondary (**1e**, Cy) to a tertiary counterpart (**1f**, ^{t}Bu), though the branch-selective products were obtained exclusively. When allylbenzene (**1g**) was used as the substrate, the branch product **3ga** was obtained with the corresponding linear one in 1.0:1.2 ratio in a moderate yield with the catalyst loading of 2 mol %. Interestingly, allyl ester **1h** was applicable under the reaction conditions without its degradation to afford **3ha** in a moderate yield. Alkyl bromide **1i** was tolerant under the reaction conditions to form **3ia** without dehalogenation. Similar to the model substrate **1a**, allylic acyloxylation of the related carboxylic acid derivatives, methyl ester (**1j**) and tertiary amide (**1k**), afforded **3ja** and **3ka**, respectively in good yields. In addition, the ketal moiety in **1l** remained intact during the catalytic reaction to form **3la** in a good yield,

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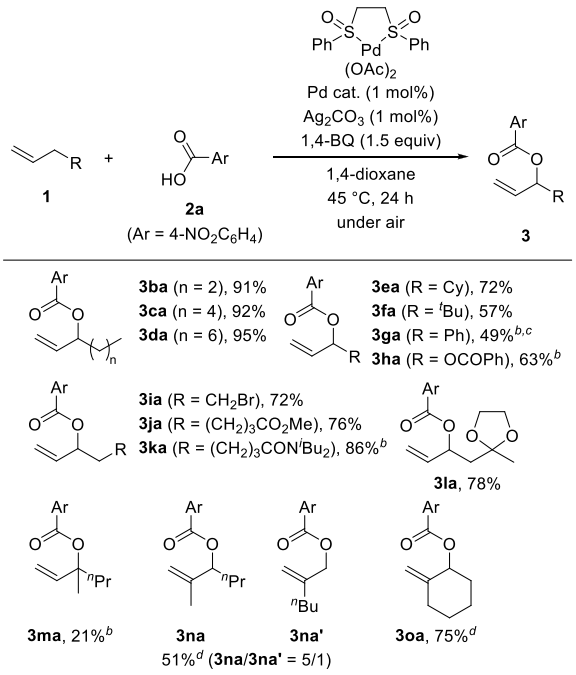
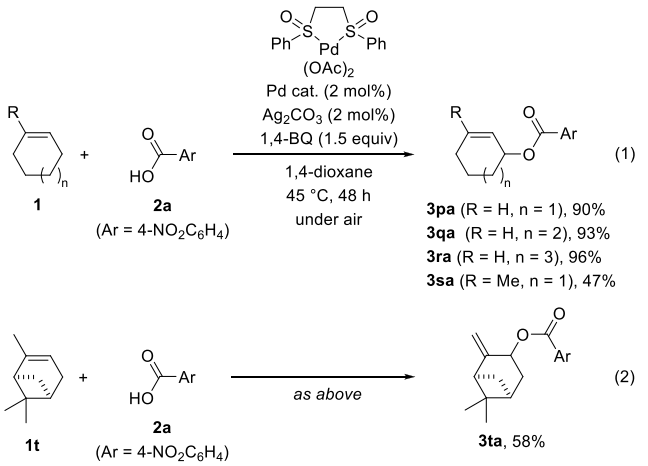
Table 2. Substrate Scope for Terminal Alkenes[a]



[a]Conditions: **1** (0.30 mmol), **2a** (0.30 mmol, 1.0 equiv), Pd cat. (1 mol %), Ag_2CO_3 (1 mol %), 1,4-BQ (1.5 equiv) in 1,4-dioxane (0.50 mL) at 45 °C for 24 h. [b]Pd cat. (2 mol %) and Ag_2CO_3 (2 mol %) were used for 24 h. [c]Branch and linear ratio, 1.0:1.2. [d]Pd cat. (2 mol %) and Ag_2CO_3 (2 mol %) were used for 48 h.

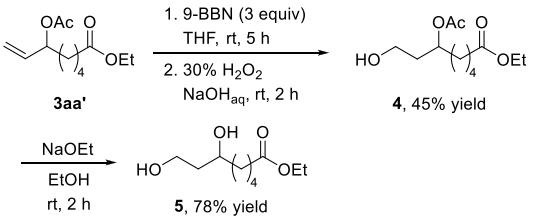
whereas 5-hexene-2-one, the ketone variant of **1l**, was not applicable in this reaction. 3-Methyl-1-hexene (**1m**) was less reactive under these catalytic conditions due to the steric congestion by methyl and *n*-propyl groups at the allylic position. The reactivity of 1,1-disubstituted alkenes **1n,o** was next evaluated under the reaction conditions. When 2-methyl-1-hexene (**1n**) was used, C−H acyloxylation occurred preferentially at the *n*-butyl chain over the methyl group to produce a mixture of **3na** and **3na′** with 5:1 ratio in a moderate yield, in which the *n*-alkyl chain was preferentially functionalized over the methyl group. Methylenecyclohexane (**1o**) was oxidized at the *α*-position of the cyclohexane ring to give acyloxylation product **3oa** without isomerization of the C=C moiety into the six-membered ring.

We further evaluated the reactivity of this C(sp^3)−H acyloxylation for internal alkenes, as depicted in eqs 1 and 2. Allylic acyloxylation of cyclic alkenes **1p−1r** afforded the corresponding products in excellent yields without contamination by doubly C−H acyloxylation products. When using 1-methyl-1-cyclohexene (**1s**) as the substrate, C(sp^3)−H acyloxylation occurred at the less sterically congested methylene position, giving **3sa** in a moderate yield without isomerization of the C=C moiety as well as no formation of the linear acyloxylation product at the methyl group (eq 1). In contrast, (1*R*)-(+)-*α*-pinene (**1t**), a naturally occurring 1-methyl-1-cyclohexene motif, was converted to the corresponding acyloxylation product **3ta** in a moderate yield. It was noteworthy that **1t** was initially isomerized to methylenecyclohexane, and the methylene position adjacent to the C=C moiety was acyloxylated, which was different from the reaction with **1s**, probably due to the steric hindrance at the allylic position of the cyclohexene ring of **1t**.

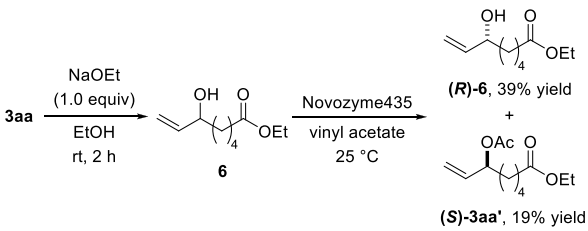


The compound **3aa′** obtained by allylic acyloxylation of ethyl 7-octenoate (**1a**) is a useful starting material for synthesizing ethyl 6,8-dihydroxyoctanoate **5**, a key synthetic intermediate for a biologically active *α*-lipoic acid.[13,14] Under hydroboration−oxidation conditions employing 9-BBN and H_2O_2, hydroxylated compound **4** was obtained in 45% yield without decomposition of the ester functionality. Subsequent hydrolysis in the presence of sodium ethoxide afforded ethyl 6,8-dihydroxyoctanoate **5** in 78% yield (Scheme 2). The allylic carboxylate **3aa** thus-obtained was further transformed to chiral allyl acetate (*S*)-**3aa′** by kinetic resolution (Scheme 3).

Scheme 2. Synthesis of Ethyl 6,8-Dihydroxyoctanoate 5 from 3aa′



Scheme 3. Kinetic Resolution for Synthesizing (*S*)-Acetoxy Compound (*S*)-3aa′



After hydrolysis of **3aa** by following a similar procedure from **4** to **5**, racemic allylic alcohol **6** was obtained. Subsequent enzymatic kinetic resolution[15] using Novozyme435 in vinyl acetate gave the (*S*)-acetoxylated compound (*S*)-**3aa′** in 19% isolated yield with 98% ee along with recovering 39% of (*R*)-**6** (88% ee). Combined with the diol synthesis shown in Scheme 3, this palladium-catalyzed allylic oxidation became an effective synthetic pathway to obtain chiral (*R*)-*α*-lipoic acid.

In summary, we achieved a remarkable reaction rate and yield acceleration for branch-selective allylic acyloxylation of alkenes catalyzed by a disulfoxide-ligated palladium catalyst

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(White catalyst) using 4-nitrobenzoic acid as the carboxylate source and Ag_2CO_3 as the additive. This reaction system was widely applicable to various terminal mono- and disubstituted alkenes and internal alkenes while maintaining high branch selectivity. One of the allylic acyloxylation products, **3aa**, was a good source for the synthesis of ethyl 6,8-dihydroxyoctanoate **5**, a synthetic key intermediate for (*R*)-α-lipoic acid. Further elaboration to clarify the effect of Ag_2CO_3 is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02406.

Detailed experimental procedures for Pd-catalyzed C−H acyloxylation, characterization data for the acyloxylation products, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Kazushi Mashima − *Department of Chemistry, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka, Japan*; orcid.org/0000-0002-1316-2995; Email: mashima@chem.es.osaka-u.ac.jp

Hayato Tsurugi − *Department of Chemistry, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka, Japan*; orcid.org/0000-0003-2942-7705; Email: tsurugi@chem.es.osaka-u.ac.jp

Masahiko Seki − *Tokuyama Corporation, Tsukuba, Ibaraki, Japan*; orcid.org/0000-0002-9942-377X; Email: maseki@tokuyama.co.jp

Authors

Aymen Skhiri − *Department of Chemistry, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka, Japan*

Haruki Nagae − *Department of Chemistry, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka, Japan*; orcid.org/0000-0002-5589-7375

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02406

Notes

The authors declare no competing financial interest.

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