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Hydrosilane and bismuth-accelerated palladium catalyzed aerobic oxidative esterification of benzylic alcohols with air[†]

Xing-Feng Bai,^a Fei Ye,^a Long-Sheng Zheng,^a Guo-Qiao Lai,^a Chun-Gu Xia^b and Li-Wen Xu^{*ab}

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In a palladium-catalyzed oxidative esterification, hydrosilane can serve as an activator of palladium catalyst with bismuth, thus leading to a novel ligand- and silver-free palladium catalyst system for facile oxidative esterification of a variety of benzylic alcohols in good yields.

In recent years, the development of palladium-catalyzed oxidations that apply molecular oxygen has become a hot topic in organic synthesis and homogeneous catalysis.¹ Apart from direct oxidation of alcohols to aldehydes or ketones, transition metal complex-catalyzed oxidative esterification of alcohols remains of high interest to academic and industrial chemists.² Although palladium-catalyzed oxidation reactions using oxygen as the terminal oxidant have been widely investigated, so far relatively few works has been reported on palladium-catalyzed aerobic oxidative esterification from two different alcohols.³ In 2011, Beller's^{3a} and Lei's^{3b} groups demonstrated at the same time the utility of a palladium complex (Pd-phosphine) for the catalytic oxidative esterifications of primary alcohols with O₂ in the presence of silver hexafluorophosphate $(AgPF_6)$ or silver tetrafluoroborate $(AgBF_4)$ respectively. These works constructed an important milestone in the palladium-catalyzed oxidative esterification of alcohols. However, the present synthetic methods still suffered from one or more disadvantages, including slow rates with a long reaction time and expensive silver salts (about 830 RMB or 132 USD g^{-1} for AgPF₆ and 280 RMB or 45 USD g^{-1} for AgBF₄). Therefore the development of new palladium-based oxidation chemistry and novel palladium-based catalytic systems with higher reaction efficiency, shorter reaction times and good selectivity remains a challenging task in this reaction, especially using an air atmosphere directly as the terminal oxidant and silver-free reaction conditions. Herein, we report

a simple and selective catalytic oxidative esterification of benzylic alcohols promoted by palladium under mild conditions with air. This procedure is rapid and highly efficient and operates with a silver-free activator at ambient temperature and pressure.

In palladium-catalyzed oxidation, it is well known that this procedure involves reduction of a Pd(II) species to a Pd(0) species, and then the oxidative addition of substrates oxidizes palladium to regenerate a palladium species in catalytic cycle.⁴ Inspired by previous studies on palladium catalysis, we assumed that the two-electron reduction of Pd(II) to Pd(0) through a hydridopalladium intermediate is crucial to the palladium-catalyzed oxidative esterification, therefore we supposed that the addition of hydrosilanes could promote and accelerate the reduction of Pd(II) to Pd(0), which would be useful in the enhancement of catalytic efficiency of palladiumcatalyzed oxidative esterification. Hydrosilanes are present in many widely used compounds and used as an indispensable reagent in the field of organosilicon chemistry and organic synthesis. In the past decades, much effort has been given to their synthetic application in the addition of the Si-H bond in hydrosilanes across a C=C, C=O, C=N, or triple bond, also named hydrosilylation of olefins, carbonyl compounds, imines, or alkynes accordingly.⁵ Hydrosilanes are also stable reducing⁶ and silvlation agents⁷ and a transition metal or strong Lewis acid catalyst is required to drive this reaction. Their reaction by-products are safer and more easily handled than other organometallic-based reducing agents. To the best of our knowledge, no reports on the use of hydrosilanes in oxidative esterification and similar oxidative transformations of alcohols are known to date.

Upon the hypothesis that hydrosilanes could improve and accelerate the palladium-catalyzed oxidation of alcohols, the palladium-catalyzed oxidation of benzylic alcohol was performed with reaction conditions similar to Beller's work (Pd(OAc)₂ in methanol)^{3a} employing various hydrosilanes in the absence of any ligands and additives. Interestingly, a methanol solution containing benzylic alcohol (**1a**) and triethylsilane in a 1 : 1.5 molar ratio was heated at 40 °C for 24 h in the presence of a catalytic amount of Pd(OAc)₂ and Na₂CO₃ (2 eq.), causing the formation of mixtures of benzyloxytriethylsilane (**2a**), benzaldehyde (**2b**), and methyl benzoate (**2d**). However, the reaction proceeded in a nonselective manner and

^a Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University,

Hangzhou 310012, P. R. China. E-mail: liwenxu@hznu.edu.cn; Fax: +86 2886 5135; Tel: +86 2886 5135

^b State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, P. R. China. E-mail: licpxulw@yahoo.com

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(он 1а	Pd(OAc) ₂ (5 mol%) Na ₂ CO ₃ (2 eq.) Et ₃ SiH (x eq.) MeOH, 40°C, 24 h air	2a OMe OMe 2c	2b OMe C 2d
Entry	Base	Silane (x eq.)	Conversion ^a (%)	2a/2b/2c/2d ^b
1	Na ₂ CO ₃	Et ₃ SiH (1.5)	91	18/60/0/13
2	c		14	0/2/12/0
3	Na ₂ CO ₃	<i>c</i>	29	0/21/0/8
4	C	Et ₃ SiH (1.5)	56	1/11/43/1
5	c	Et ₃ SiH (0.2)	84	0/23/60/1
6	c	$PhMe_2SiH$ (0.2)	78	0/20/58/0
7	Na ₂ CO ₃	TEOS (0.1)	9	0/9/0/0
8	Na ₂ CO ₃	$Et_3SiH(1.0)$	92	12/57/0/16
9	Na ₂ CO ₃	$Et_3SiH(0.1)$	> 99	4/16/0/80
10	Na ₂ CO ₃	$(EtO)_2$ SiHMe (0.2)	>99	0/6/0/94
11	Na ₂ CO ₃	PMHS (0.2)	>99	0/0/0/100
12	Na ₂ CO ₃	PMHS (0.1)	> 99	0/30/0/70
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 Table 1
 Silane-initiated ligand-free palladium catalyzed oxidation of benzylic alcohol in methanol

^{*a*} Reaction conditions: 0.5 mmol of benzylic alcohol, 5 mol% Pd(OAc)₂, 2 eq. Na₂CO₃, 2 mL of MeOH, 40 °C, in air, for 24 h. ^{*b*} The selectivities were determined by GC analysis. ^{*c*} No addition of silanes or any additives.

the aldehyde was a major product while the ester was detected with by-product in a promising yield. In the absence of hydrosilanes and ligands, poor conversions of alcohol were determined by GC (Entries 2 and 3, Table 1), which prompted us to investigate the effect of hydrosilanes on the palladiumcatalyzed oxidation of alcohols. As shown in Table 1, different hydrosilanes were tested in the absence or presence of base, and consequently, these hydrosilanes exhibited promising activation in the palladium-catalyzed oxidative transformation of benzylic alcohol. The anticipated ester 2d was not formed in the absence of base while the aldehyde 2b and corresponding acetal product **2c** were obtained in good yields (Entries 4–6, Table 1). In this reaction, when tetraethoxysilane without a Si-H moiety was used as an additive, poor conversion of benzylic alcohol was detected. Fortunately, the selectivity of oxidation with respect to the ester product increased from 16 to 100% in the four mixtures (Entries 8-12). To our delight, a highly chemoselective oxidation took place in the presence of diethoxy(methyl)silane or polymethylhydrosiloxane (PMHS) (Entries 10 and 11). Control experiments proved that a catalytic amount of polymethylhydrosiloxane (PMHS) was enough to guarantee the activation of the palladium catalyst in the oxidative esterification of benzylic alcohol.

Therefore, these facts in the model reaction suggest that PMHS accelerated the reduction of Pd(II) to Pd(0) and then formed polysiloxane-stabilized palladium colloids (Pd@polysiloxane),⁸ which generated a highly efficient palladium catalyst with high selectivity.⁹ As shown in Scheme 1, on the basis of previous studies^{3,10} and this work, we propose that the palladium-catalyzed oxidative esterification proceeds through a two step catalytic cycle: 1) oxidative addition and alcoholysis of Pd(0) intermediate (**II**) with alcohol subsequently to generate intermediate (**IV**) and then afford the aldehyde *via* β -hydride elimination; and 2) insertion-elimination of β -hydride of hemiacetal (**V**) to generate the



Scheme 1 Proposed mechanism of palladium-catalyzed oxidative esterification of benzyl alcohol in the presence of PMHS.

ester and the palladium hydride intermediate (I) which undergoes reductive elimination to regenerate the Pd(0) species.

Having established the oxidative esterifcation of alcohol by palladium with PMHS, we turned to evaluate the scope of benzylic alcohols. Unfortunately, similar to previous reports, ^{3a,b} the oxidative esterification was very sensitive to the substituent on the phenyl ring of the benzylic alcohol (see Table S1, ESI⁺). For most substituted benzylic alcohols, the aldehyde was the major product and the yield of the ester was poor. For the example of o-tolylmethanol, a trace ester product was detected while 2-methylbenzaldehyde was observed in only 43% yield. In a hope to achieve better substrate conversion and selectivity. we examined other inorganic or organic bases when the palladium-catalyzed oxidation of o-tolylmethanol was used a model reaction. Gratifyingly, t-BuONa was found to be an effective base for the Pd-catalyzed oxidation. However, the selectivity of ester to aldehyde was low (24 : 70) and 2-methylbenzaldehyde was observed in 70% yield (Table S2, ESI†). Consistent with Lei and Beller's results,³ the present catalyst system still exhibited limited ability in the key step of β-hydride elimination of the hemiacetal intermediate while the corresponding 2-methylbenzaldehyde was obtained in high yield. Meanwhile, we found several silver salts showed poor selectivity in this reaction, and the desired ester was obtained in low yield under the PHMS-initiated Pd-catalyzed oxidation (see ESI[†]). Thus we investigated the effect of various metal salts on the palladium-catalyzed oxidative esterification of o-tolylmethanol. To our surprise, employing bismuth halides as cocatalyst resulted in completed conversion and the selectivity is excellent (>99% of ester). Notably, in fact almost no aldehyde was detected when BiCl₃ was used a cocatalyst. It should be noted that the short reaction time (2 hr) and milder conditions at room temperature also led to complete conversion (>99%) and excellent isolated yield (87%). Other bismuth salts, except Bil₃, were also effective for the Pd-catalyzed oxidative esterification of o-tolylmethanol (Table S3, ESI⁺). In comparison to the control experiments without PMHS, a decreased yield (73%) was obtained with longer reaction times (8 h), which suggests that PMHS accelerates the formation of the activated Pd(0) species and that bismuth promotes the formation of the hemiacetal or β-hydride elimination of intermediate IV or VI (Scheme 1) efficiently to corresponding aldehyde and ester respectively. Accordingly, BiCl₃ is one of



Scheme 2 Oxidative esterification of benzylic alcohols catalyzed by palladium/bismuth in the presence of PMHS.



Scheme 3 Synthesis of 3-aryl phthalides via oxidative esterification.

the cheapest metal salts (0.9 RMB or 0.0014 USD g^{-1}), which would make the present palladium catalyst system more practically useful in organic synthesis.

With the optimized conditions, a variety of benzylic alcohols were examined by using bimetallic Pd/Bi in the presence of PMHS. To our delight, the oxidative esterification of various benzylic alcohols proceeded with remarkably high yields and excellent selectivities in 2 hrs. The scope of the bismuth and PHMS-accelerated Pd-catalyzed oxidative esterification is depicted in Scheme 2. Unsubstituted benzylic alcohol gave the desired product 2d smoothly and excellent isolated yield was obtained (84%). No aldehdye was observed in this case. For electron-donating group substituted aromatic alcohols, all runs demonstrated complete oxidative esterification in excellent selectivities to provide the corresponding esters (up to 95%). For the strong electron-withdrawing groups, such as a nitro moiety, the conversion was incomplete in two hours and the isolated yield of the corresponding ester 3d was moderate (58%). In addition, halide-containing benzylic and allylic alcohols also resulted in complete conversion with excellent selectivities.

Phthalides are important building blocks in the field of medicinal chemistry and organic synthesis.¹¹ Thus we expanded the scope of this oxidative esterification to include diols that led to selective oxidation and intramolecular esterification. As shown in Scheme 2 (**3**) and Scheme 3, this palladium-catalyzed

oxidative esterification is also successful in an intramolecular manifold. The reaction provides a catalytic route toward the construction of 3-arylphthalides.

In summary, we have developed a novel palladium catalyst system for oxidative esterification reactions of primary benzylic alcohols that focus on the findings of catalytic activity of bismuth and PMHS in this reaction. This silver-free catalyst system for the oxidative esterification has several advantages of high yields, ligand-free, environmentally benign, direct use of air atmosphere as terminal oxidant or avoiding the use of oxygen balloon, and the reaction efficiency is high.

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