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Chemoselective Nucleophilic Arylation and Single-Step Oxidative Esterification of Aldehydes Using Siloxanes and a Palladium−Phosphinous Acid as a Reaction Switch

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Since Hiyama reported that arylfluorosilanes undergo transition metal-catalyzed coupling reactions this method has found multiple synthetic applications.[1,2] We have recently demonstrated that palladium−phosphinous acids are effective catalysts for Hiyama cross-coupling reactions of aryl halides in both organic solvents and water.[3,4] Our promising results with palladium−phosphinous acid-catalyzed Hiyama cross-couplings encouraged us to explore the possibility of palladium-catalyzed reactions between aldehydes and arylsiloxanes. Nucleophilic additions of arylstannanes and arylboronic acids to aldehydes have been reported to afford secondary alcohols,[5] whereas few examples with aryl- or alkenyl-silicon reagents are known.[6]

Initially, we screened the reaction between phenyltrimethoxysilane, **1**, and benzaldehyde, **2**, in the presence of TBAF and various palladium−phosphinous acid catalysts. Employing 2.5 mol % of $(t\text{-Bu}_2\text{POH})_2\text{PdCl}_2$, POPd, and 1.3 equiv of TBAF in refluxing acetonitrile, we were surprised to observe formation of 68% of methyl benzoate, **3**, and 28% of the expected 1,2-addition product diphenylmethanol, **4**. Conversion of aldehyde **2** to its ester was also the prevailing reaction when POPd and TBAF were employed in refluxing isopropyl alcohol, water, or THF. We found that addition of a palladium catalyst is not necessary for the 1,2-addition of **1** to aldehyde **2** while the use of TBAF is crucial. By contrast, formation of ester **3** did not proceed in the absence of a palladium catalyst, and POPd proved to effectively catalyze oxidative esterification of **2** at room temperature. Using 2.5 mol % of the Pd catalyst and stoichiometric amounts of TBAF, we obtained methyl benzoate **3** in a single step in 91% yield (Scheme 1). The divergent reaction pathways of benzaldehyde shown in Scheme 1 require the same solvent, reagent, and fluoride additive while a palladium−phosphinous acid complex serves as the reaction switch between nucleophilic 1,2-addition and oxidative esterification.

We then decided to extend the scope of these reactions to other aldehydes. Since the esterification does not use the aryl moiety of siloxane **1**, it was replaced with inexpensive tetramethyl orthosilicate, Si(OMe)_4, which gave **3** in 93% yield under the same conditions. The fine-tuning of reaction conditions showed that microwave irradiation assists arylation with phenyltrimethoxysilane while a general oxidative esterification procedure applicable to substrates that are less reactive than benzaldehyde requires slightly elevated temperatures. Under these conditions, TBAF-promoted arylation and POPd-catalyzed oxidative esterification of both electron-rich and electron-deficient aromatic aldehydes exhibiting various functional groups produced the corresponding alcohols and esters in 99% and 97%, respectively (Table 1). Best results were obtained with electron-poor aromatic aldehydes, whereas arylation and oxidative esterification of cyclohexanecarboxaldehyde and 4-methoxybenzaldehyde gave lower yields (entries 7 and 11).

Scheme 1. Divergent Transformations of Benzaldehyde Using POPd as a Reaction Switch

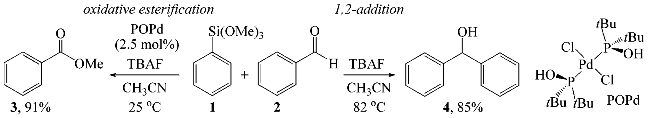
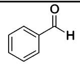
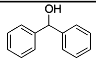
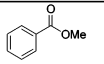
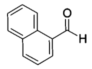
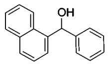
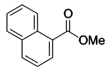
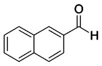
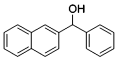
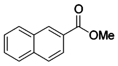
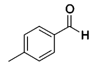
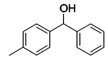
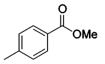
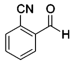
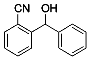
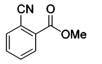
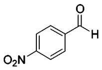
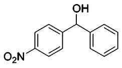
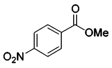
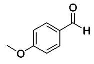
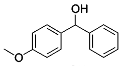
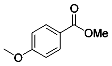
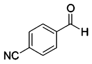
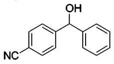
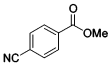
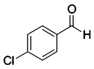
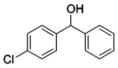
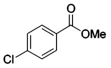
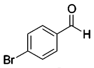
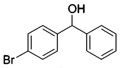
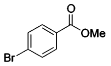
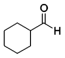
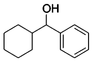
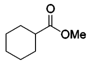


Table 1. TBAF-Promoted Arylation and POPd-Catalyzed Oxidative Esterification of Aldehydes

entry	aldehyde	1,2-addition	(%)[a]	oxidative esterification	(%)
1			95		97
2			99		87
3			98		92
4			94		89
5			87		78
6			96		97
7			73		61
8			93		79
9			86		90
10			79		93
11			67		75

The convenient switching between arylation and oxidative esterification of aldehydes with siloxanes provides access to both secondary alcohols and esters using essentially the same reagent, additive, and solvent. To the best of our knowledge, nucleophilic additions of arylsiloxanes to aldehydes have only been accomplished with rhodium(I) and copper(I) complexes in the presence of a fluoride source.[6] Although our method requires elevated temperatures it affords better results than rhodium-catalyzed procedures, and it eliminates the need for a transition metal catalyst and arylfluorosilanes, which are not readily available and more difficult to handle than arylsiloxanes. The choice of fluoride source appears to be crucial. Employing benzaldehyde, phenyltrimethoxysilane, and potassium fluoride in THF at 60 °C, Oi et al. did not observe any sign of phenylation and therefore developed a rhodium(I)-catalyzed process.[6a] We made similar observations. In our hands, KF and

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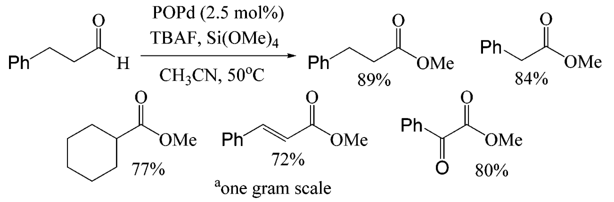
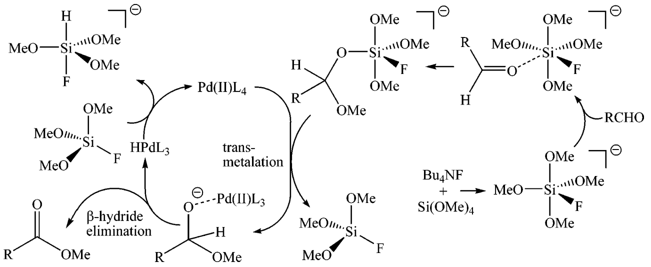
Scheme 2. Oxidative Esterification of Aliphatic Aldehydes[a]



[a] On a 1 g scale.

Scheme 3. Pd(II)-Catalyzed Oxidative Esterification of Aldehydes



CsF were ineffective additives; however, we found that the reaction proceeds with excellent yields in the presence of TBAF. Fluoride additives are known to activate arylsiloxanes through formation of pentavalent silicates, which are likely to play a key role during arylation. The phenyl transfer may be further facilitated by an increase of the electrophilicity of the aldehyde through coordination to the Lewis acidic countercation which would explain the different results obtained with metal and ammonium fluoride salts. In contrast to reactions with Grignard and organolithium reagents, our method is compatible with halides, cyano, and nitro groups (entries 5, 6, 8−10). As expected, other arylsiloxanes such as 3-furyl-, 2-thiophene-, and *p*-tolylsiloxane undergo 1,2-addition to benzaldehyde with up to 89%, whereas vinylsiloxane gave less than 40% yield (see SI).

The POPd-catalyzed conversion of aldehydes to the corresponding methyl esters incorporates an oxidation and an esterification step into a single process under mild reaction conditions. The procedure is also suitable for aliphatic aldehydes. Phenylacetaldehyde, 3-phenylpropanal, cinnamaldehyde, phenylglyoxal, and cyclohexanecarboxaldehyde were converted on a 1 g scale to the corresponding esters at 50 °C with up to 89% yield (Scheme 2). Other siloxanes such as tetraethyl and tetrabutyl orthosilicate give the corresponding esters in similar yields. While one-pot oxidative esterifications of aldehydes with hydrogen peroxide or oxone in alcoholic solution are known, few practical examples of transition metal-catalyzed processes can be found in the literature.[7] Our method might become particularly useful for oxidation of aldehyde groups in multifunctional compounds when carboxylic acid intermediates need to be avoided or when sensitive electron-rich heteroatoms that do not tolerate commonly used oxidizing reagents are present.[8]

A proposed mechanism for the palladium-catalyzed one-pot esterification of aldehydes is shown in Scheme 3. POPd appears to be the catalytically active species and is regenerated at the end of the catalytic cycle. We have been able to recover POPd after completion of the esterification of benzaldehyde and confirmed the structure by crystallographic analysis. Coordination of the aldehyde to the oxophilic pentavalent silicate generated in situ from TBAF and tetramethyl orthosilicate will increase its electrophilicity and facilitate transfer of a methoxide group.[9] Transmetalation from silicon to the palladium catalyst is then followed by *β*-hydride elimination and formation of the corresponding ester. The hydride might initially be bonded to the palladium catalyst but both proton and deuterium NMR studies with deuterated benzaldehyde showed that a siloxane functions as the hydride acceptor when acetonitrile is used as solvent (see Supporting Information). The reaction proceeds under both air and nitrogen atmosphere which is in agreement with the proposed catalytic cycle; that is, oxygen can be ruled out as the hydride acceptor. We found that during the course of the esterification the aldehyde signal disappears as a new NMR signal at 4.6 ppm is formed which corresponds to pentavalent $HSiF(OMe)_3$. The siloxane thus fulfills three important functions: it generates a Lewis-acidic silicate that activates the aldehyde and it serves as both the methoxy group donor and the hydride acceptor. It is likely that the hydride ultimately reacts with tetrabutylammonium via Hoffmann elimination or with the solvent, in particular when protic solvents such as isopropyl alcohol and water are used.

In conclusion, selective chemodivergent conversion of aldehydes toward esters and secondary alcohols has been realized using siloxanes and POPd as a reaction switch under otherwise almost identical conditions. Both reactions are applicable to a range of aldehydes. The palladium phosphinous acid-catalyzed oxidative esterification procedure generates esters in a single step in high yields under mild conditions. The TBAF-promoted arylation of aldehydes with arylsiloxanes provides the corresponding secondary alcohols in better yields than previously reported methods while avoiding the use of a transition metal catalyst and arylfluorosilanes.

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Supporting Information Available: All experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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