

Aerobic Oxidation of Diverse Primary Alcohols to Methyl Esters with a Readily Accessible Heterogeneous Pd/Bi/Te Catalyst

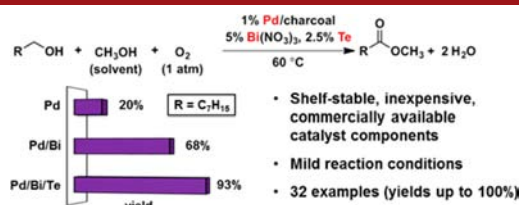
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ABSTRACT



Efficient aerobic oxidative methyl esterification of primary alcohols has been achieved with a heterogeneous catalyst consisting of 1 mol % Pd/charcoal (5 wt %) in combination with bismuth(III) nitrate and tellurium metal. The Bi and Te additives significantly increase the reaction rate, selectivity, and overall product yields. This readily accessible catalyst system exhibits a broad substrate scope and is effective with both activated (benzylic) and unactivated (aliphatic) alcohols bearing diverse functional groups.

Heterogeneous Pd catalysts are widely used in organic chemistry for the reduction of organic compounds. Prominent examples include simple supported catalysts such as Pd/C and Pd/Al₂O₃, as well as more complex variants such as Lindlar's catalyst, in which Pd/CaCO₃ is modified by Pb(OAc)₂ and quinoline.¹ Similar catalysts for selective oxidation of organic molecules would be appealing, but effective examples are rare. Adam's catalyst (PtO₂) is typically used as a hydrogenation catalyst,² but it also mediates aerobic oxidation of primary alcohols to carboxylic acids.³ A high catalyst loading is often required in the latter application (e.g., 0.6 equiv of Pt^{3b}), and other

reagents, such as the Jones reagent (CrO₃/H₂SO₄) or bleach/TEMPO,⁴ tend to be more synthetically reliable.

Homogeneous⁵ and heterogeneous⁶ Pd catalysts have been widely studied for aerobic alcohol oxidation. The majority of this work has focused on conversion of alcohols to aldehydes and ketones. Methods for oxidation of primary alcohols to carboxylic acids and esters (Scheme 1) tend to be more limited with respect to substrate scope (e.g., benzylic alcohols)⁷ and/or catalyst accessibility.^{8,9} Here, we describe a readily accessible Pd/charcoal-based

(1) (a) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446–450. (b) Lindlar, H.; Dubuis, R. *Org. Synth. Coll.* **1973**, *5*, 880–882.

(2) King, A. O.; Shinkai, I. *e-EROS* **2001**10.1002/047084289X.rp181.

(3) See, for example: (a) Heyns, K.; Blazejwicz, L. *Tetrahedron* **1960**, *9*, 67–75. (b) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095–1098.

(4) Zhao, M. M.; Li, J.; Mano, E.; Song, Z. J.; Tschäen, D. M. *Org. Synth.* **2005**, *81*, 195–203.

(5) For reviews: (a) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijkstra, A. *Acc. Chem. Res.* **2002**, *35*, 774–781. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (c) Schultz, M. J.; Sigman, M. S. *Tetrahedron* **2006**, *62*, 8227–8241. (d) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221–229. (e) Karimi, B.; Zamani, A. *J. Iran. Chem. Soc.* **2008**, *5*, S1–S20.

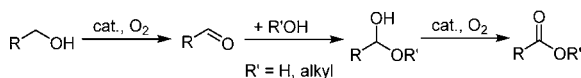
(6) (a) Zhan, B.-Z.; Thompson, A. *Tetrahedron* **2004**, *60*, 2917–2935. (b) Mallat, T.; Baiker, A. *Chem. Rev.* **2004**, *104*, 3037–3058. (c) Matsumoto, T.; Ueno, M.; Wang, N.; Kobayashi, S. *Chem.—Asian J.* **2008**, *3*, 196–214. (d) Parmeggiani, C.; Cardona, F. *Green Chem.* **2012**, *14*, 547–564.

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catalyst system that promotes efficient aerobic oxidation of primary alcohols, including benzylic and aliphatic examples, to the corresponding methyl esters. Use of Bi and Te cocatalysts significantly improves the activity and selectivity of the reactions and enables the broadest substrate scope and functional-group compatibility reported to date for this transformation.

Scheme 1. Pd-Catalyzed Aerobic Oxidation of 1° Alcohols to Carboxylic Acids and Esters



The intrinsic challenge of oxidizing aliphatic alcohols relative to benzylic alcohols prompted us to use 1-octanol as a substrate in our catalyst development efforts. A variety of commercially available heterogeneous and homogeneous Pd sources were tested as catalysts at a 1 mol % Pd loading for the oxidative esterification of octanol to methyl octanoate under 1 atm of O₂ in methanol (Table 1).¹⁰ Only poor conversions and yields were obtained, with a maximum of a 20% yield using 1 wt % Pd/C.¹¹ Main-group elements and other additives have found widespread use as promoters in heterogeneous catalysis with platinum group metals, and bismuth has been used frequently in alcohol oxidation.^{6b,12} Inclusion of 1 mol % Bi(NO₃)₃ in the reactions led to significantly increased yields of methyl octanoate, and a 60% yield was achieved with 1 mol % Pd/Char and Bi(NO₃)₃ (Table 1, entry 5).

The beneficial effect of Bi(NO₃)₃ prompted us to examine other additives in the reaction. The majority of these additives, such as Cu, Ag, Pb and Sb, had a negligible or only slightly beneficial effect on the catalytic yield relative to the reaction in the absence of additives. TeO₂, however, exhibited a beneficial effect that surpassed even Bi(NO₃)₃ (Figure 1). The best result was obtained with the intermetallic material Bi₂Te₃ (87% yield of methyl octanoate).

(9) Transfer- and acceptorless-dehydrogenation methods provide an alternative approach to the conversion of primary alcohols to carboxylic acids and esters: (a) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2005**, *127*, 10840–10841. (b) Owston, N. A.; Nixon, T. D.; Parker, A. J.; Whittlesey, M. K.; Williams, J. M. J. *Synthesis* **2009**, 1578–1581. (c) Yamamoto, N.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2011**, *76*, 2937–2941. (d) Balaraman, E.; Khaskin, E.; Leitus, G.; Milstein, D. *Nat. Chem.* **2013**, *5*, 122–125.

(10) CAUTION: The use of pure O₂ in combination with organic solvents is a flammability hazard and should be limited to small scale applications.

(11) Similarly poor yields for aliphatic alcohol oxidation have been noted in the literature: (a) Mallat, T.; Baiker, A. *Appl. Catal. A: Gen.* **1991**, *79*, 41–58. (b) Keresztesi, C.; Mallat, T.; Grunwaldt, J.-D.; Baiker, A. *J. Catal.* **2004**, *138*, 138–146.

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This observation prompted us to explore the synergistic effect of Bi(NO₃)₃ in combination with Te metal and with TeO₂ (Figures 2 and S2, respectively).¹³ The two-dimensional array in Figure 2 highlights the optimal additive composition of 5 mol % Bi(NO₃)₃ and 2.5 mol % Te, which led to a 94% yield of methyl octanoate.

Table 1. Screening of Pd Sources for the Oxidative Esterification of 1-Octanol

entry	catalyst	yield (conv) ^a	
		no Bi(NO ₃) ₃	Bi(NO ₃) ₃ ^b
1	1 wt % Pd/C	20 (22)	45 (54)
2	1 wt % Pd/Al ₂ O ₃	6 (17)	49 (65)
3	2.5 wt % Pd/C	7 (40)	57 (58)
4	5 wt % Pd/C	10 (11)	45 (61)
5	5 wt % Pd/Char^c	16 (20)	60 (60)
6	30 wt % Pd/C	5 (9)	30 (39)
7	PdCl ₂ ^d	0 (0)	0 (0)
8	Pd(OAc) ₂ ^d	0 (0)	15 (17)

^a Reactions performed on 1 mmol scale; [RCH₂OH] = 1 M. ¹H NMR yields; int. std. = trimethoxybenzene. ^b Bi(NO₃)₃·5H₂O = Bi(NO₃)₃ unless otherwise noted. ^c Char = activated charcoal. ^d 20 mg of activated carbon.

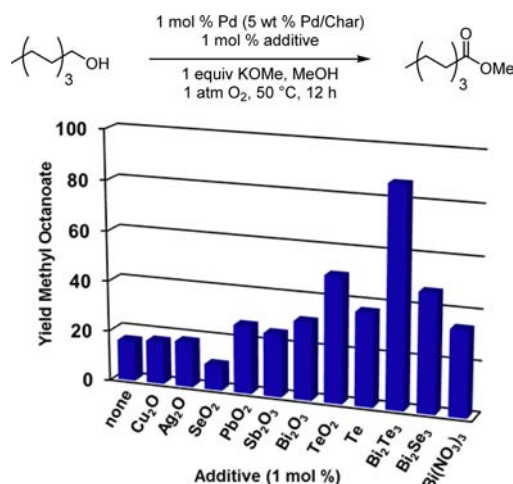


Figure 1. Screening of main-group additives for Pd-catalyzed oxidative esterification of 1-octanol. Reactions carried out on 1 mmol scale. ¹H NMR yields with trimethoxybenzene as internal standard. Loading of additive based on mol % of cation.

The beneficial effect of the Bi(NO₃)₃ and Te is clearly evident from reaction time courses with representative benzylic and aliphatic alcohol substrates (Figure 3). Independent reactions were performed in the absence and

(13) For previous observations of the beneficial effect of Te promoters in palladium catalyzed alcohol oxidation, see refs 12c and 12g.

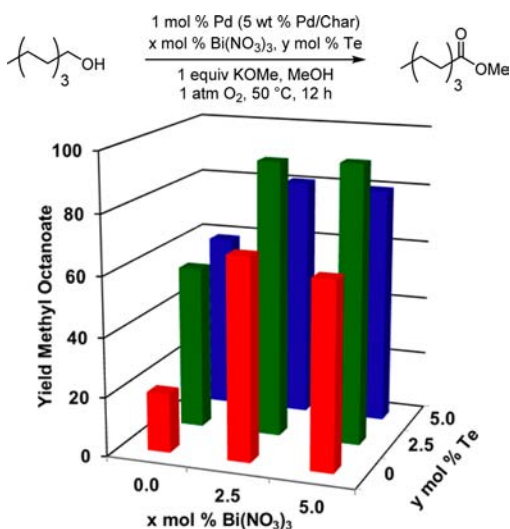


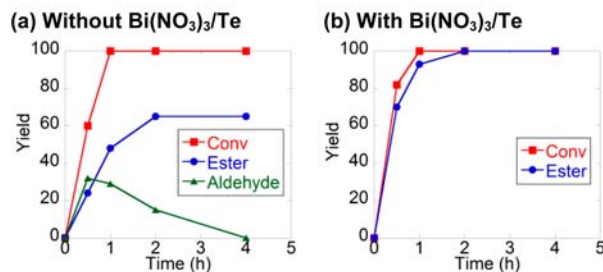
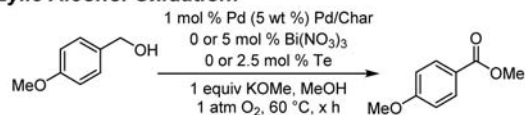
Figure 2. Effect of 1-octanol oxidative esterification with $\text{Bi}(\text{NO}_3)_3$ and Te metal. Reactions carried out on 1 mmol scale. ^1H NMR yields with trimethoxybenzene as internal standard.

presence of the Bi/Te additives. In the oxidation of 4-methoxybenzyl alcohol without additives (Figure 3a), all of the substrate was consumed within 1 h, and a significant quantity of aldehyde (32%) intermediate was detected. The aldehyde gradually disappeared and was completely consumed within 4 h. The yield of methyl ester maximized at 63%. A significant quantity of anisole ($\geq 15\%$ yield) was detected in the final reaction mixture, suggesting that decarbonylation of the aldehyde is a significant side reaction (Figure S3).¹⁴ When the reaction was carried out in the presence of $\text{Bi}(\text{NO}_3)_3$ and Te, full conversion of the substrate occurred within 1 h (Figure 3b). In this case, no aldehyde intermediate was observed and the reaction exhibited excellent mass balance. The ester product was formed in near-quantitative yield ($>98\%$) after 2 h and remained stable under the reaction conditions.

Consistent with the catalyst-development data presented above, oxidative esterification of 1-octanol showed poor conversion and yield in the absence of the Bi/Te additives (Figure 3c). Only a 20% yield of the ester was observed after 2 h and slowly increased to $\sim 40\%$ after 12 h. In contrast to the reaction of the benzylic alcohol, no aldehyde intermediate was observed during the reaction. In the presence of the Bi/Te additives, faster rates were observed together with higher conversion and yield (Figure 3d). A 90% yield of methyl octanoate was obtained after 12 h with excellent mass balance, and again, no aldehyde intermediate was detected.

(14) For similar observations with related catalysts and mechanistic insights into the promotion effect of Bi on Pd-catalyzed alcohol oxidation, see: (a) Ferri, D.; Mondelli, C.; Krumeich, F.; Baiker, A. *J. Phys. Chem. B* **2006**, *110*, 22982–22986. (b) Burgener, M.; Wirz, R.; Mallat, T.; Baiker, A. *J. Catal.* **2004**, 152–161.

Benzylic Alcohol Oxidation:



Aliphatic Alcohol Oxidation:

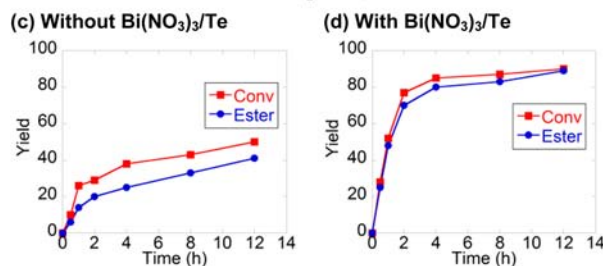
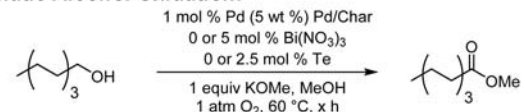


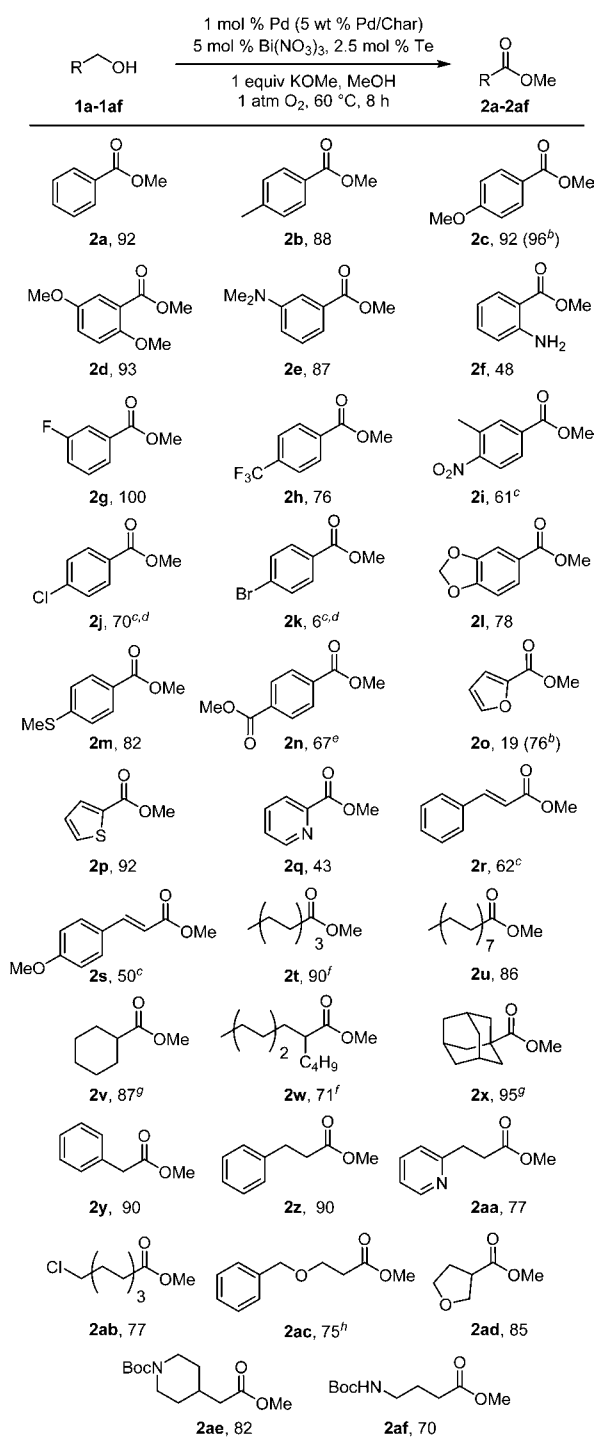
Figure 3. Time courses of Pd/Char-catalyzed oxidative esterification of (a) 4-methoxybenzyl alcohol without additives; (b) 4-methoxybenzyl alcohol with additives; (c) 1-octanol without additives; and (d) 1-octanol with additives. ^1H NMR yields with trimethoxybenzene as internal standard (std. dev. $\pm 3\%$).

The time courses in Figure 3 highlight the intrinsically slower rates and more challenging reactivity of aliphatic alcohols relative to benzylic alcohols. They further reveal that inclusion of $\text{Bi}(\text{NO}_3)_3$ and Te enhances both reaction selectivity and catalyst activity, enabling high yields to be obtained with both classes of substrates.

This Pd/Bi/Te catalyst system exhibits the broadest substrate scope reported to date for the oxidative esterification of alcohols (Scheme 2). Diverse benzylic alcohol substrates (**1a–1n**), including heterocyclic examples (**1o–1q**), were subjected to the optimized catalyst conditions. High yields of methyl esters were obtained for the majority of examples, including products bearing ether (**2c**, **2d**, **2l**), tertiary amine (**2e**), and thioether (**2m**, **2p**) functional groups. Electron-deficient benzylic alcohols (**1g–1i**) react more slowly and undergo side reactions, but good-to-excellent yields (61–100%) could still be obtained. Halogenated benzyl alcohols (**1j–1k**) are susceptible to

(15) For additional examples of allylic alcohol oxidation by heterogeneous Pd catalysts, see: (a) Enache, D. I.; Edwards, J. K.; Landon, P.; Solsona-Espriu, B.; Carley, A. F.; Herzing, A. A.; Watanabe, M.; Kiely, C. J.; Knight, D. W.; Hutchings, G. J. *Science* **2006**, *311*, 362–365. (b) Parlett, C. M. A.; Bruce, D. W.; Hondow, N. S.; Newton, M. A.; Lee, A. F.; Wilson, K. *ChemCatChem* **2013**, *5*, 939–950.

Scheme 2. Scope of Aerobic Alcohol Esterification with Pd/Char, Bi(NO₃)₃, Te Catalyst System^a



^a Reactions carried out on 1 mmol scale; [RCH₂OH] = 1 M; isolated yields. ^b Aldehyde starting material. ^c 25 °C. ^d Isolated with methyl benzoate. ^e 1,4-Bis(hydroxymethyl)benzene starting material. ^f 60 °C for 15 h. ^g 70 °C. ^h 50 °C for 12 h.

dehydrohalogenation, although a good yield of the chlorinated substrate **1j** could be obtained by lowering the

reaction temperature to 25 °C. Esterification of allylic alcohol derivatives **1r** and **1s** proceed with high conversions, but the yields are reduced owing to the alkene hydrogenation side product. Again, the best yields were obtained by running the reaction at 25 °C.¹⁵ This catalyst system is not well suited for recycling. For example, the yield of **2d** dropped from 98% to 85% (NMR yield) after filtering the used catalyst and reusing it in a second reaction of **1d** in methanol with 1 equiv of KOMe. Ongoing studies are focused on developing a more robust catalyst formulation better suited for reuse and large-scale applications.

The significant scope enhancement enabled by the Bi/Te cocatalysts is evident in reactions of aliphatic alcohols (**1t–1af**). Excellent yields were obtained with diverse substrates bearing simple hydrocarbon side chains (**1t–1z**), including those with considerable steric hindrance adjacent to the alcohol (**1v–1x**). Pyridine substituents often poison homogeneous Pd oxidation catalysts, but substrate **1aa**, with a remote pyridyl group, afforded the methyl ester in good yield. A primary alkyl chloride **2ab** was well tolerated in the reaction. Good mass balance was observed (77% yield; 82% conversion); unlike the reaction of the aryl chloride substrate **1j**, dehydrohalogenation did not occur. Ether-containing substrates were effective, including the benzylether substrate **1ac**, which could be susceptible to cleavage of the benzylic C–O bond in the presence of heterogeneous Pd catalysts. Finally, the Boc-protected secondary and primary amine-containing substrates **1ae** and **1af** reacted successfully, affording the corresponding methyl esters in good yields.

In summary, 1 mol % Pd/charcoal, together with Bi(NO₃)₃ and Te, represents a highly effective catalyst system for aerobic oxidation of primary alcohols to methyl esters. Successful substrates include aliphatic examples and those bearing diverse functional groups. Each of the components of this catalyst system is shelf-stable, commercially available, and inexpensive, offering advantages over homogeneous catalysts, which typically require a higher catalyst loading and/or expensive ligands.

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Supporting Information Available. Experimental procedures, catalyst screening and reaction optimization data, full characterization for all new compounds, and NMR spectra for all reported products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare the following competing financial interest(s): This work is currently being considered by our tech transfer office for a possible patent application.