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Discovery of Multicomponent Heterogeneous Catalysts via Admixture Screening: PdBiTe Catalysts for Aerobic Oxidative Esterification of Primary Alcohols

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Abstract.

In the present study, we demonstrate the utility of "admixture screening" for the discovery of new multicomponent heterogeneous Pd catalyst compositions that are highly effective for aerobic oxidative methyl esterification of primary alcohols. The identification of possible catalysts for this reaction was initiated by the screening of simple binary and ternary admixtures of Pd/charcoal in combination with one or two metal and/or metalloid components as the catalyst. This approach permitted rapid evaluation of over 400 admixture combinations for the oxidative methyl esterification of 1-octanol at 60 °C in methanol. Product yields from these reactions varied widely, ranging from 2–88%. The highest yields were observed with Bi-, Te and Pb-based additives, and particularly from those containing both Bi and Te. Validation of the results was achieved by preparing specific PdBiTe catalyst formulations via a wet-impregnation method, followed by application of response surface methodology to identify the optimal Pd-Bi-Te catalyst stoichiometry. This approach revealed two very effective catalyst compositions: $PdBi_{0.47}Te_{0.09}/C$ (PBT-1) and $PdBi_{0.35}Te_{0.23}/C$ (PBT-2). The former catalyst was used in batch aerobic oxidation reactions with different primary alcohols and shown to be compatible with substrates bearing heterocycle and halide substituents. The methyl ester products were obtained in >90% yield in nearly all cases. Implementation of the PBT-2 catalyst in a continuous-flow packed-bed reactor achieved nearly 60,000 turnovers with no apparent loss of catalytic activity.

Introduction.

Heterogeneous catalysts offer numerous potential advantages over homogeneous catalysts for the industrial synthesis of organic chemicals.[1] Their thermal stability and ease of catalyst immobilization (e.g., in fixed-bed or other reactor configurations) are particularly advantageous for high-temperature, gas-phase and large-volume continuous processes in the commodity chemical industry. Contemporary heterogeneous catalyst development efforts are especially focused on such applications. Heterogeneous catalysts also have benefits for lower-volume production of pharmaceuticals and fine chemicals; however, the development of catalysts that exhibit the broad functional group tolerance needed in applications of this type has been the focus of much less attention. One potential barrier to progress in this area is that the synthetic organic and organometallic chemistry background of many researchers within the pharmaceutical and related industries provides little or no training in the synthesis or characterization of heterogeneous catalysts and materials. Experimental strategies that lower the barrier to heterogeneous catalyst discovery and development could significantly expand the application of heterogeneous catalysts in these industries.

Heterogeneous catalysts for organic chemical processes are commonly composed of an active metal dispersed on a support material, such as high-surface-area carbon, a metal oxide, or other inorganic material. Many catalysts also feature "promoters" that modulate the activity or selectivity of the metal catalyst.[2] A prominent example is Lindlar's catalyst for partial reduction of alkynes to alkenes, which consists of $CaCO_3$-supported Pd in combination with Pb and quinoline as selective modifiers or poisons to prevent full reduction of the alkyne to the saturated C–C bond.[3] Heterogeneous catalysts are commonly prepared through the deposition of the active metal and promoters onto a support via one of numerous possible methods, including impregnation, adsorption, precipitation, or ion exchange.[4] Additional washing, drying, and calcination steps are typically incorporated as intermediate or final steps to prepare the ultimate catalyst. The diverse methods for heterogeneous catalyst preparation can be labor- and/or time-intensive,[5-7] but even more relevant to the present context, the protocols are outside of the experimental vernacular of organic chemists and related users of heterogeneous catalysts.

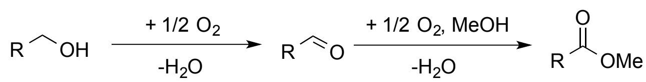
The present study takes inspiration from the field of homogeneous catalysis to demonstrate a method for discovery and development of heterogeneous catalysts that could facilitate the contribution of non-specialists to this field. In the field of homogeneous catalysis, many catalysts are prepared in situ via simple combination of different catalyst components, such as a metal salt, ancillary ligand, and an acid, base or other additive. This approach is commonly employed both for the discovery of new homogeneous catalysts and catalytic reactions and as a user-friendly method for performance of catalytic reactions in organic chemistry. We anticipated that certain heterogeneous catalyst compositions could be generated in a similar manner. An important precedent for this concept is evident in the use of heterogeneous Ni (Raney Nickel), Pd, or Pt catalysts for asymmetric hydrogenation of carbonyl compounds, whereby the catalyst is modified in situ by inclusion of tartaric acid or cinchona alkaloids in the reaction mixture.[8,9]

The present study addresses the development of heterogeneous catalysts for selective aerobic oxidation of alcohols, specifically, the oxidative methyl esterification of primary alcohols. Heterogeneous Pd and Pt catalysts have been studied extensively for aerobic oxidation of primary and secondary alcohols to carboxylic acids, ketones, and aldehydes.[10] The incorporation of one or more promoters derived from the early transition metals, lanthanides, and/or main group elements often enhances the catalyst activity and selectivity.[11] The origin of the promoter effects is often not fully understood, but previous studies implicate contributions ranging from selective blocking of catalyst sites that promote side reactions[13a,k-m] to the formation of synergistic catalyst/promoter active sites that enhance catalyst performance.[13c,h,i] Promoters may form surface alloys or intermetallic structures that exhibit different activity relative to the pure-metal catalyst or hinder agglomeration of metal nanoparticles.[13d,g,p] In addition, some promoters are believed to mediate adsorption and dissociation of O_2, thereby protecting the catalytic metal surface from over-oxidation.[13f,k-m] The diverse roles of individual promoters and the potential for synergistic interactions between promoters complicate the rational design of new heterogeneous catalysts of this type, but they also represent an important modular feature of the catalysts that may be altered to optimize catalyst performance, similar to the manner in which ancillary ligands or acid/base additives may be used to modulate the activity and/or selectivity of homogeneous catalysts. Here, we describe a readily accessible "admixture screening" method that streamlines the assessment and identification of effective heterogeneous catalyst/promoter combinations. We further show that catalysts discovered by this method serve as useful starting points for the development of robust multicomponent catalysts suitable for implementation in a continuous flow process relevant to pharmaceutical or other specialty chemical applications. These principles are illustrated in the development of heterogeneous Pd/Bi/Te catalysts for oxidative methyl esterification of primary alcohols, including those bearing heterocycles and halide substituents.

Results and Discussion.

Context and Preliminary Results. Previous studies by us[12] and others[13] have investigated homogeneous Pd catalysts for aerobic oxidation of alcohols to aldehydes and ketones. Whereas numerous useful catalysts have been identified for these two-electron oxidation reactions, development of analogous homogeneous catalysts for four-electron oxidation of primary alcohols to carboxylic acids and esters has been less successful.[14] In contrast, heterogeneous catalysts show significant promise for the latter applications.[5] The oxidative cross-coupling of primary alcohols with methanol is a particularly useful transformation that provides a means to reverse the polarity of nucleophilic primary alcohols into electrophilic methyl esters (Scheme 1).

Scheme 1. Generic Pathway for the Aerobic Oxidation of Alcohols to Methyl Esters.



Gas-phase oxidative methyl esterification of aliphatic alcohols has been demonstrated with Au-based catalysts,[15] and liquid-phase precedents have been achieved with supported Ag[16] and Au,[17] polymer-incarcerated mixed noble-metal nanoparticles,[18] and heterogeneous cobalt catalysts.[19] Precedents for heterogeneous Pd catalysts for the oxidation of primary alcohols to carboxylic acids[11d-g,i,j,n-p] suggested to us that related catalysts could be highly effective for oxidative methyl esterification and may show good compatibility with alcohols bearing diverse functional groups. These catalysts often incorporate main-group promoters that enhance the catalytic performance. For example, Wedemeyer and coworkers demonstrated that $Bi(NO_3)_3$ could be added to Pd- and Pt-on-charcoal catalysts to increase the yields of phenoxyacetic acids in the aerobic oxidation of the 2-phenoxyethanol.[20] In a recent preliminary study, we found that Pd/charcoal (5 wt. %) is an effective catalyst for methyl esterification of a variety of primary alcohols when $Bi(NO_3)_3$ (5 mol %) and Te metal (2.5 mol %) are included as co-catalysts in the batch reaction mixtures.[21] This admixture catalyst system exhibited excellent activity and functional-group compatibility.

Admixture Screening Studies. The heterogeneous catalyst system just noted is poorly defined: the sources of promoters, $Bi(NO_3)_3$ and Te, exhibit poor solubility in the methanol solvent, no reduction or calcination steps were included to promote formation of a robust catalyst, and the nature of the interactions between the promoters and the heterogeneous Pd catalyst was not characterized. In spite of these complexities and uncertainties, the promising results raised the possibility that simple catalyst admixtures could be used in primary screening studies in liquid phase to discover new heterogeneous catalysts.

In order to test the utility of admixture screening, we selected 28 different additives as possible promoters, consisting of main-group, transition-metal and rare-earth sources in elemental, oxide, or salt formulations. In several cases, different forms of an element were tested [e.g., Bi, $Bi(NO_3)_3$, and Bi_2O_3]. Pd/charcoal (5 wt. %) was combined with one or two of these components in a 1:1 or 1:1:1 molar ratio, respectively, and the diverse admixtures were tested as catalysts for aerobic oxidative methyl esterification of 1-octanol in methanol at 60 °C. 1-Octanol was selected for testing because aliphatic alcohols tend to be significantly more difficult to oxidize relative to benzylic alcohols. Overall, 406 unique admixtures, with 231 different elemental combinations, were tested as catalysts for the reaction, and the results are depicted in Figure 1.

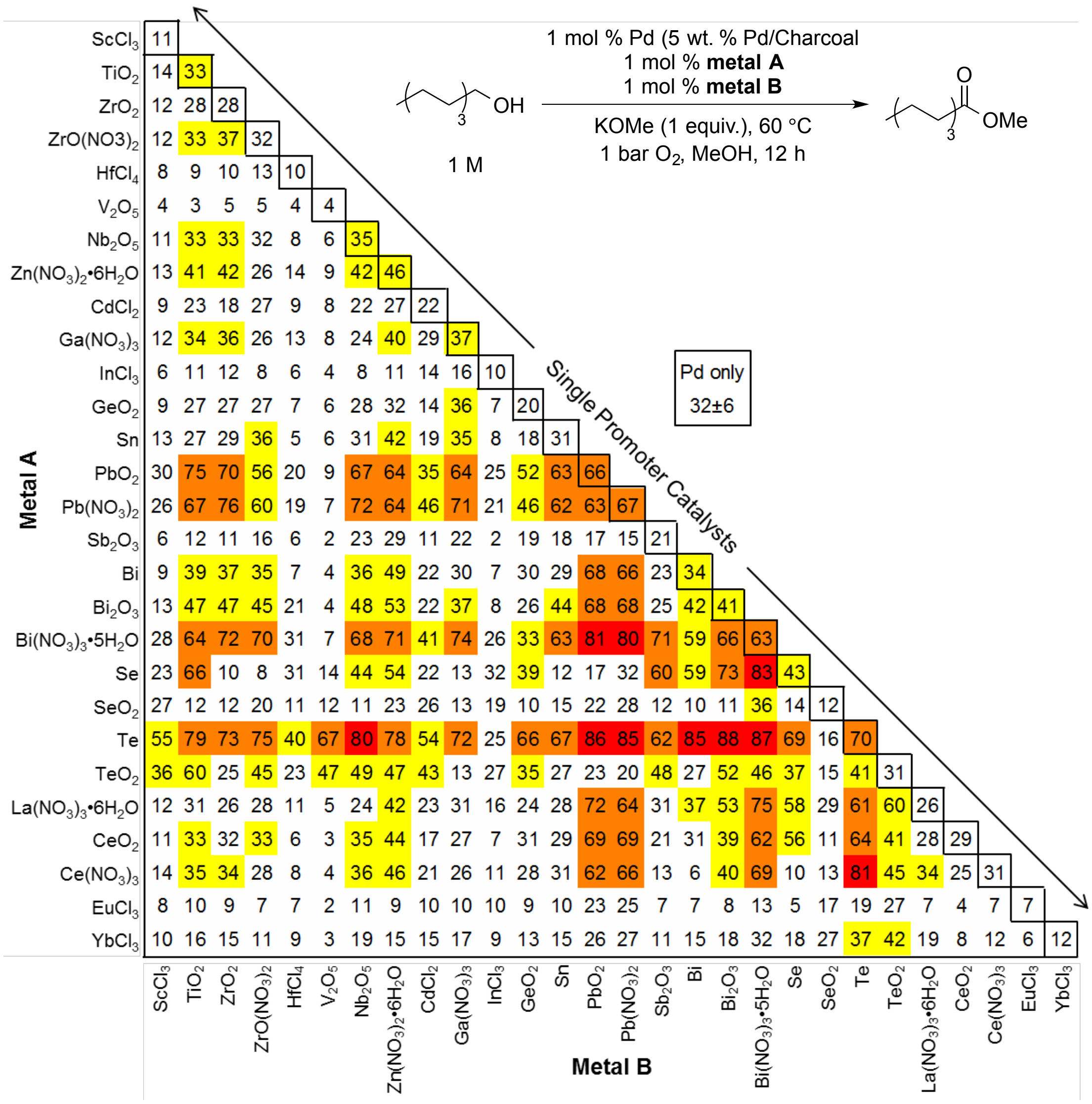


Figure 1. Admixture screening data (methyl octanoate yields) obtained from the aerobic oxidation of 1-octanol with heterogeneous catalysts composed of Pd/charcaol in combination with one or two additives. Color code reflects methyl octanoate yields: below that obtained with Pd alone (white), above Pd alone (yellow), > 60% (orange), and ≥ 80% (red).

Pd/charcoal itself shows modest activity for oxidation of 1-octanol under the reaction conditions, affording methyl octanoate in 32% yield, and the additives exhibit both poisoning and promoting effects on the catalyst, with yields ranging from 2–88%. The most effective single-component promoters observed in these studies (diagonal edge of Figure 1) derive from sources of the main-group elements, Bi, Pb, and Te. Two-promoter combinations containing these elements exhibit even higher yields (orange and red entries in Figure 1). Some of the additives inhibit catalytic activity (e.g. $HfCl_4$ and V_2O_5), while a number of others have little or no effect on the reaction (e.g. Sn, CeO_2). Overall, the highest yields were observed when Bi- or Pb-based additives were combined with elemental Te as a second additive.

It is reasonable to expect that the "admixture screening" approach used here, like many other primary screening approaches, exhibits false-negatives. For example, the lack of effort to prepare specific catalyst formulations could miss active compositions among additives that are too insoluble to interact chemically with Pd in an admixture suspension. This limitation is offset, however, by the simplicity/accessibility of the method and, more importantly, by the number of successful "hits" observed from the method. Many of the component mixtures exhibit significantly enhanced activity relative to the Pd/charcoal benchmark. The successful admixtures represent convenient catalyst systems that may be use in laboratory-scale synthetic applications, but they also serve as important starting points for development of robust catalyst formulations for large-scale applications. As catalysts composed of Pd, Bi and Te were the most effective admixtures, these elements were selected to pursue the latter goal, as elaborated below.

Synthesis and Optimization of $PdBi_xTe_y/C$ Heterogeneous Catalysts. Catalysts containing well-defined elemental compositions were prepared via wet-impregnation of Pd/C with Bi and Te precursors. $Bi(NO_3)_3$ and $TeCl_4$ were dissolved in an aqueous solution of dilute HCl and HNO_3 and added to a suspension of Pd/C in water. Excess formaldehyde (37 wt. % in water) was added to this mixture to reduce the promoters that had adsorbed onto the Pd/C catalyst. The catalysts were then filtered, washed with excess water, and dried in a vacuum oven prior to use.

ICP-AES analysis of the catalysts indicated that all of the Bi and Te used in the impregnation step were retained in the final catalyst, and SEM-EDX analysis showed that the promoters were predominantly co-localized with Pd on the carbon support (see Supporting Information).

PdBiTe catalysts prepared by this method were tested in the oxidative methyl esterification of 1-octanol with K_2CO_3 as the base,[22] and response surface methodology[23,24] was used to optimize the Bi and Te stoichiometry in the catalyst. A catalyst composed of a Pd:Bi:Te ratio of 1:1:1 was used as a starting point, and four surrounding compositions were used to determine the gradient associated with Bi and Te mole fraction leading to improved activity (Figure 2A). The path of steepest ascent was followed over four iterations to a catalyst consisting of $PdBi_{0.33}Te_{0.15}$, after which a number of compositions in this region were prepared to identify the best catalyst(s).[25] The results did not show a sharp peak for the optimal catalyst; rather, a relatively broad of range of catalyst compositions led to high yields of methyl octanoate (Figure 2B). Two of the best catalyst compositions, $PdBi_{0.47}Te_{0.09}$ (PBT-1) and $PdBi_{0.35}Te_{0.23}$ (PBT-2) were carried forward for further investigation.

Reaction time-courses for the oxidative methyl esterification of 1-octanol were monitored to assess the activity of the PBT-1 and PBT-2 catalysts relative to the previously reported admixture catalyst, which consists of 1 mol % Pd/charcoal (5 wt %), 5 mol % $Bi(NO_3)_3$, 2.5 mol % Te. Catalysts incorporating only Bi or Te (in the mole-fractions associated with PBT-2), as well as Pd/C alone, were tested for comparison (Figure 3). Pd/C shows negligible activity under the reaction conditions (Figure 3, purple diamonds), while incorporation of Bi or Te leads to

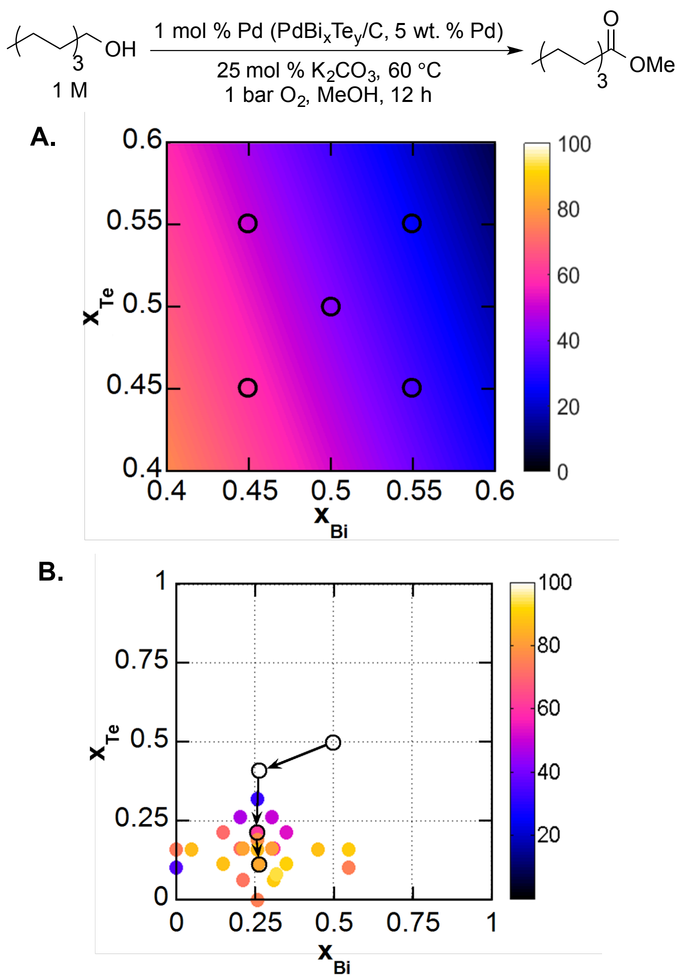


Figure 2. Response-surface-methodology data for PdBiTe catalyst optimization in the oxidative methyl esterification of 1-octanol, with a color gradient reflecting the yield of methyl octanoate under the conditions indicated in the equation. (A) Catalyst composition starting points for determination of the path of steepest ascent towards higher yields. (B) Iterative path followed over three steps of catalyst optimization, starting at a 1:1:1 Pd:Bi:Te ratio (open circles), and catalyst activity data for PdBiTe compositions in the region of highest activity (colored circles).

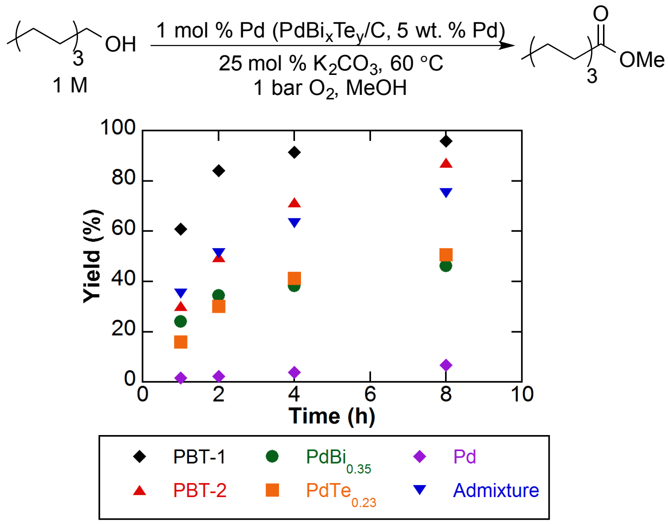


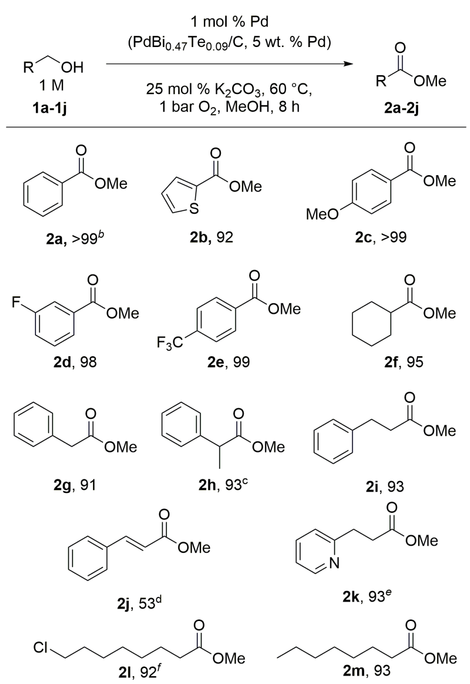
Figure 3. Reaction time-courses comparing the activity of the different catalysts for the oxidative methyl esterification of 1-octanol. PBT-1 = $PdBi_{0.47}Te_{0.09}$; PBT-2 = $PdBi_{0.35}Te_{0.23}$; Admixture = 1 mol % Pd/charcoal (5 wt %), 5 mol % $Bi(NO_3)_3$, 2.5 mol % Te.

considerable improvement in performance (Figure 3, green circles and orange squares, respectively). Catalysts incorporating both Bi and Te, including PBT-1, PBT-2 and the admixture (Figure 3, black diamonds, red triangles, and inverted blue triangles, respectively), show further improvement in activity over the single-promoter catalysts, with PBT-1 giving the best results. The synergy evident between Bi and Te was confirmed by showing that simply increasing the quantity of Bi or Te in single-promoter catalyst did not improve the catalyst performance (see Table S4 in the Supporting Information).

Batch Reaction Data with PdBiTe Catalysts. The previously reported PdBiTe admixture catalyst tolerates a wide range of functional groups,[21] and in order to compare the performance of the newly formulated PBT-1 catalyst, thirteen representative primary alcohols, including those with heterocycles and halide-containing functional groups, were tested in batch reactions at 1 mol % Pd loading (Scheme 2). The majority of substrates underwent oxidation to the corresponding methyl ester in >90% yield within 8 h. One exception is cinnamyl alcohol **2j**, which undergoes competive hydrogen-transfer reduction of the alkene, resembling previously reported observations.[9c,21] Benzylic alcohols are considerably more reactive than aliphatic alcohols, and benzyl alcohol **1a** afforded the methyl ester in near-quantitative yield (>99%) in 2 h with only 0.1 mol % PBT-1. The data show that PBT-1 exhibits a scope that closely resembles the admixture catalyst, while improving the product yields (up to 16%) and reactions rates (approx. two-fold) under comparable conditions for a number of the alcohols.

Both PBT-1 and PBT-2 retained good activity upon recycling in the oxidation of benzyl alcohol and 1-octanol (Figure 4). The reactions were stopped at incomplete conversion in order to increase the sensitivity of the tests to changes in catalyst activity. PBT-1 showed a small

Scheme 2. Scope of Aerobic Alcohol Esterification System with PBT-1.[a]



[a]Reactions carried out on 1 mmol scale; ^{1}H NMR yields with trimethoxybenzene as internal standard. [b]0.1 mol% Pd, 2 h. [c]16 h. [d]25 °C. [e]2 mol% Pd. [f]5 mol% Pd.

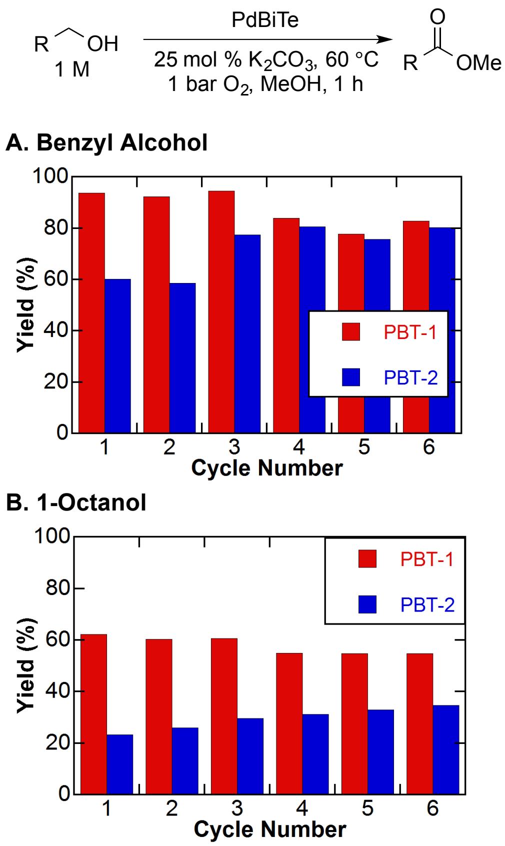
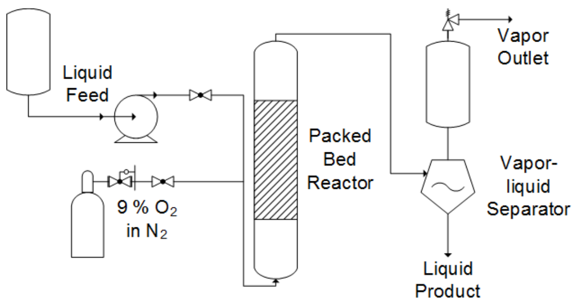


Figure 4. Batch recycling of PBT-1 and PBT-2 catalysts in the oxidative methyl esterification of benzyl alcohol (A) and 1-octanol (B). Catalyst loading: 0.1 mol % Pd for benzyl alcohol; 1 mol % Pd for 1-octanol.

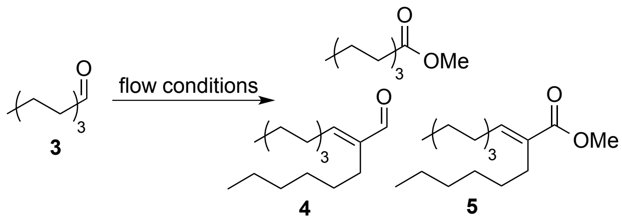
decrease in yield for cycles 4-6 relative to cycles 1-3, but otherwise showed steady performance. PBT-2 exhibited modest improvement in performance during the recycle tests. Possible complications associated with these types of experiments (e.g., mechanical losses in catalyst recovery) make us hesitant to draw definitive conclusions from the small changes, however, and in order to carry out a more rigorous assessment of the catalyst stability, we investigated the performance of PBT-1 and PBT-2 under continuous process conditions.

Continuous Process Data with PdBiTe Catalysts. The performance of the PdBiTe catalysts under continuous process conditions was assessed by incorporating the catalyst into a packed-bed reactor (Scheme 3).[26] A solution of the primary alcohol was mixed with a diluted O_2/N_2 gas stream at a tee junction, and the gas-liquid mixture was fed into a packed bed reactor containing the catalyst. After exiting the reactor, the gas and liquids were separated and the product was collected. The progress of the reaction was monitored by taking aliquots from a sample collection port and performing GC analysis.

Scheme 3. Schematic Diagram of the Flow Reactor.



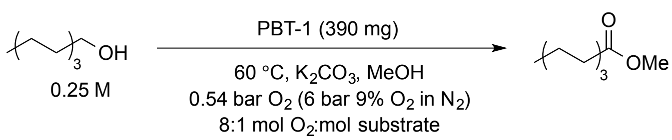
Initial testing of 1-octanol oxidation with the PdBiTe catalysts revealed a complication that was not evident from the batch reactions. The yield of methyl octanoate reached a plateau at ~80%, and no improvement was realized by varying the liquid and gas flow rates, O_2 pressure, and 1-octanol concentration. These results prompted us to search for potential catalyst poisons. Octyl aldehyde (**3**) is an expected intermediate in the esterification reaction, and when it was tested as a substrate, the reaction led to complete conversion of the aldehyde but only ~50% selectivity for methyl octanoate. Aldol condensation products **4** and **5** were identified as by-products and accounted for the remaining mass balance (eq 1). Subsequent studies showed that these aldol products strongly inhibit oxidation of 1-octanol.[27]



(1)

While both alcohol oxidation and aldol condensation are promoted by Brønsted bases, we speculated that the aldol reaction could be minimized by using a lower concentration of K_2CO_3. This hypothesis was validated, as shown in Table 1, by using a four-fold lower K_2CO_3 concentration. Under these conditions, an excellent yield of methyl octanoate (96%) could be obtained.[28]

Table 1. Optimization of Flow Conditions to Achieve High Steady-State Yields in the Aerobic Oxidation of 1-Octanol.



Entry	$[K_2CO_3]$ (mM)	WHSV[a] (h^{-1})	Yield (%)[b]
1	62.5	10.6	79
2	31.3	10.6	82
3	15.6	10.6	72
4	**15.6**	**2.66**	**96**

[a] Weight hourly space velocity = mg alcohol/(mg Pd·hr). [b] Determined by GC vs an internal standard.

Background oxidation of the methanol solvent to methyl formate is a possible side-reaction of the methanol solvent, but only minimal methyl formate was observed during of 1-octanol in the flow reactor. Over 350 mg of the PBT-1 catalyst at a WHSV of 12 h^{-1} (0.25 M 1-octanol, 0.015 M K_2CO_3, 0.54 bar O_2 (9% O_2 in N_2), 8:1 mol O_2:mol substrate, 60 °C), the [HCOOMe] was found to be ≤2 mM. We are currently exploring the mechanistic basis for the low reactivity of methanol in the oxidative homocoupling reaction.

As observed under batch reaction conditions, the PdBiTe catalysts exhibit much higher activity for the oxidation of benzyl alcohol to methyl benzoate than for the oxidation of 1-octanol. These faster rates facilitated testing of the catalyst performance during extended use. Long-term assessment of the PBT-1 catalyst for benzyl alcohol oxidation revealed a steady decrease in catalyst activity during a 33 h test at a WHSV of 760 h^{-1} (Figure 5, blue circles). In contrast, the PBT-2 catalyst showed excellent long-term stability over 43 h at a WHSV of 700 h^{-1} (Figure 5, red diamonds). Further testing was therefore carried out with PBT-2, and a scan of different flow rates showed that methyl benzoate reached near quantitative yields at a WHSV of 500 h^{-1} (Figure 6A). With these conditions, no decrease in the product yield was observed after nearly 60,000 catalytic turnovers (Figure 6B).

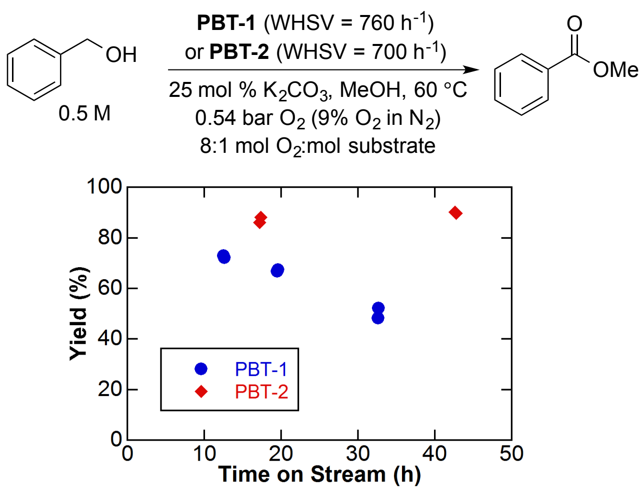


Figure 5. Long-term testing of PBT-1 and PBT-2 catalysts under continuous conditions for the oxidative methyl esterification of benzyl alcohol.

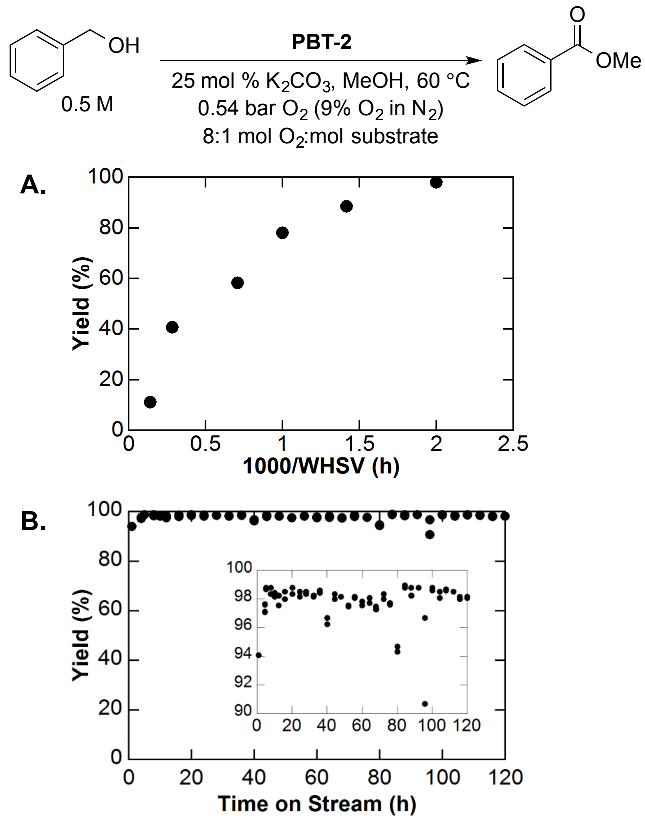


Figure 6. Oxidative methyl esterification of benzyl alcohol under continuous-flow conditions with the PBT-2 catalyst. (A) Assessment of different flow rates to identify the optimal WHSV and (B) long-term testing of the PBT-2 catalyst at a WHSV of 500 h^{-1}.

The reactor effluent from the extended run with the PBT-2 catalyst was analyzed by ICP-AES to determine the extent of leaching of the different catalyst components: Pd, Bi, and Te (Table S3), and the final product solution contained less than one part-per-million of the three elements: 0.025, 0.20, and 0.10 ppm of Pd, Bi and Te, respectively. Even with this low level of leaching, the high turnover numbers led to modest changes in the catalyst composition during the course of the reaction (Figure 7A). During the experiment shown in Figure 6B, the leaching resulted in a change of the PBT-2 catalyst from a stoichiometry of $PdBi_{0.35}Te_{0.21}$ to $PdBi_{0.21}Te_{0.12}$, on the basis of ICP-AES analysis of the catalyst before and after the reaction (Figure 7B, black circles). A similar analysis of the PBT-1 catalyst used in the long-term flow run revealed no detectable levels of Te remaining in the catalyst after the reaction (Figure 7B, blue circles). These observations account for the different performance of PBT-1 and PBT-2 during continuous operation. PBT-2 starts with higher mole-fraction of Te, and the catalyst composition remains in the region of high activity, despite partial leaching, whereas a similar leaching rate with PBT-1 results in complete depletion of the Te component.

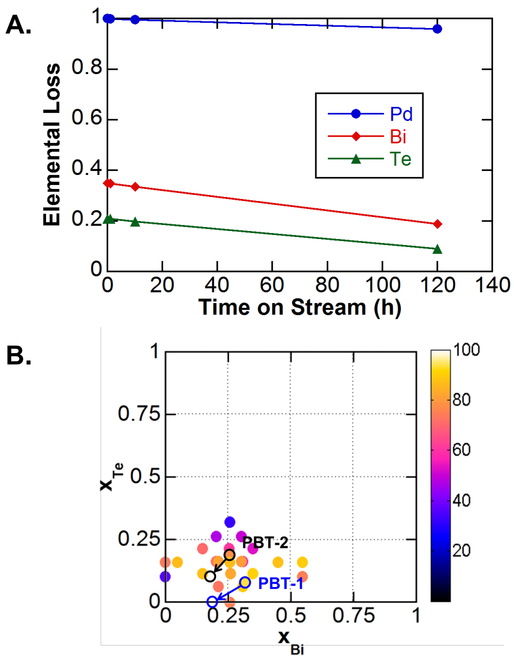


Figure 7. Elemental leaching studies: (A) Loss of Pd, Bi and Te from the PBT-2 catalyst during continuous oxidative methyl esterification of benzyl alcohol (cf. Figure 6B). (B) Change in PBT-1 and PBT-2 catalyst compositions during long-term oxidation of benzyl alcohol, mapped onto the catalyst activity plot shown in Figure 2B.

Analysis of the reaction rate at different temperatures (50–80 °C) under flow conditions provided the basis for Arrhenius analysis of PBT-2-catalyzed oxidation of benzyl alcohol (Figure 8), which revealed that the reaction exhibits an activation energy of 79 kJ/mol and a pre-exponential of 1.1 x 10^{12} s^{-1}. These values correspond to a turnover frequency of 1,600 h^{-1} at the reaction temperature of 60 °C typically used in our study. The large pre-exponential term is consistent with a surface-mediated rate-limiting step involving bound substrate.[29] More thorough mechanistic studies are the focus of ongoing work, but the Arrhenius parameters may be compared to data obtained with a AuPd/TiO_2 catalyst, which is one of the most active known heterogeneous catalysts for alcohol oxidation.[30] The activation energy for the oxidation of benzyl alcohol with the AuPd/TiO_2 catalyst is 56 kJ/mol and has a pre-exponential of 1.5 x 10^8 s^{-1}. The AuPd catalyst was only investigated at elevated temperatures (100–160 °C); however, at a benchmark temperature of 100 °C for both catalysts, the calculated TOFs correspond to 33,000 h^{-1} for PdBiTe (PBT-2) and 8000 h^{-1} for AuPd (TOF values reflect the rate on a per Pd and Au+Pd atom basis, respectively).

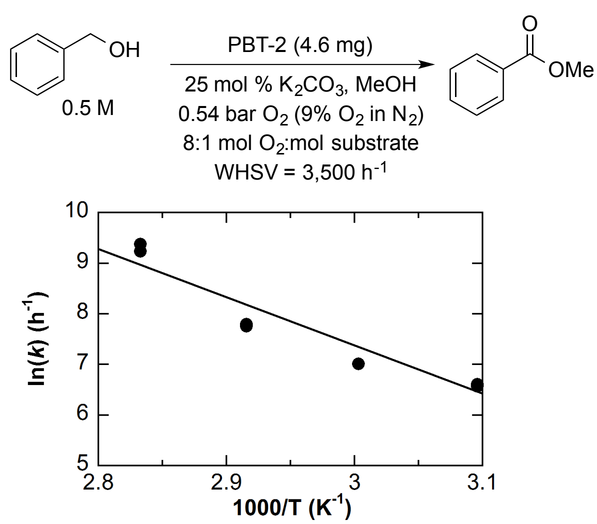


Figure 8. Arrhenius plot of ln(*k*) vs 1000/T. Fitted parameters: A = 1.1 x 10^{12} s^{-1}, E_a = 79 ± 8.3 kJ/mol.

Conclusion

In summary, this study demonstrates a promising new approach for the discovery of novel heterogeneous catalysts. New Pd-based catalyst compositions were identified via the liquid-phase screening of simple admixtures of commercially available components, including Pd/charcoal and various possible promoters in their elemental, oxide, or salt formulations. The screening data revealed a number of highly promising compositions that provided a foundation for subsequent development and optimization of more-precise heterogeneous catalyst formulations. These efforts led to two highly effective PdBiTe catalysts that show excellent activity for the oxidative methyl esterification of diverse primary alcohols. One of these, with a composition of $PdBi_{0.35}Te_{0.21}/C$ (PBT-2), was shown to have good stability and excellent performance under continuous flow conditions in a packed-bed reactor, and it represents the most active liquid-phase oxidative esterification catalyst reported to date. More-rigorous characterization of the catalysts described herein, together with mechanistic analysis of the reactions, are the focus of ongoing work and will be reported in due course.

The admixture screening method used here resembles methods commonly used for the discovery and optimization of homogeneous catalysts. For example, use of unmodified Pd/C as a starting point is analogous to the use of a homogeneous transition-metal salt, such as $Pd(OAc)_2$ or $PdCl_2$, which is known or expected to have some baseline catalytic activity for a reaction of interest. Addition of Bi, Te, and other potential promoter sources is analogous to the screening of ancillary ligands and other additives in homogeneous catalytic reaction mixtures in an effort to modulate the activity, selectivity, and/or stability of the transition-metal salt. The effectiveness of admixture screening for heterogeneous catalyst discovery will undoubtedly vary for different metal catalysts and/or classes of promoters. Nevertheless, the results of the present study suggest that similar tactics could be used to streamline the discovery of heterogeneous catalysts for many other applications. Representative reactions of interest in our ongoing studies include the oxidative coupling of alcohols and amines to prepare nitriles and carboxamides. Moreover, the admixture screening method elaborated herein should be accessible to researchers with varied backgrounds, including those with no training or expertise in heterogeneous catalyst synthesis and formulation. This feature has potential to enable many organic chemists and other non-specialist researchers to contribute to the field of heterogeneous catalysis.

Methods

General Considerations. Commercially available reagents and solvent were obtained from commercial sources and used as received. No precautions were taken to exclude air or water from the solvent or reaction mixtures. ^{1}H NMR spectra were recorded on a Varian MercuryPlus 300 MHz spectrometer. SEM-EDX particle images and elemental analyses were performed using a LEO SUPRA 55 VP scanning electron microscope (SEM) coupled with a Thermo-Fischer Noran System 7 energy dispersive X-ray spectroscopy (EDX) detector.

Procedure for the Admixture Screening of Catalysts in Batch. 2 M KOMe in MeOH (0.5 mL) was added to 20 x 150 mm culture tube containing 21.3 mg of 5 wt. % Pd/Charcoal (1 mol % Pd) and 1 mol % of Metal A and Metal B (cf. Figure 1). The culture tube was then placed on a 48 well orbital shaker and agitated under 1 atm O_2 for 30 min while heating to 60 °C. Once the reaction temperature was reached, the headspace was purged with O_2, and the substrate was added as a 2 M solution in MeOH (0.5 mL) containing 0.2 M mesitylene as an internal standard (I.S.). After 12 hours, the post reaction solution was injected onto a GC to determine product and reactant concentrations. 48 reactions were carried out in parallel on the same orbital shaker, and each set of 48 had one reaction tube containing just Pd/Charcoal as a control.

Catalyst Preparation. 500 mg of 5 wt. % Pd/C (obtained from Sigma Aldrich: product number 276707) was mixed with 15 mL of DI water. $Bi(NO_3)_3{\bullet}5H_2O$ and $[TeCl_4]_4$ were dissolved in a mixture of 1 M HCl (1 mL) and conc. HNO_3 (0.1 mL) and added to the catalyst suspension. The Pd/C and dissolved Bi and Te salts were mixed at 50 °C for 3 h. After 3 h, 500 μL of a 30 % NaOH solution was added to make the mixture alkaline. 200 μL of 37 % formaldehyde was then added and the mixture was heated to 80 °C under N_2 for 16 h. The catalyst was then filtered and washed with water (~500 mL) until neutral. The catalyst was then dried under vacuum at 70 °C for 20 hours to afford the final catalyst.

GC Method and Retention Times. GC analyses were performed using a DB-Wax column (Length = 30 m, i.d. = 0.25 mm) installed in a Shimadzu GC-17A equipped with a flame-ionization detector. An 11 min GC method was used consisting of a 1 min hold at 70 °C, ramp at 20 °C/min from 70 °C to 200 °C (6.5 min), and a 3.5 min hold at 200 °C. The injector and detector were held at 225 °C and the column flow was 1.5 mL/min of He with a split ratio of 20. Retention times were as follows: benzyl alcohol (7.7 min), benzaldehyde (5.7 min), methyl benzoate (6.3 min), 1-octanol (5.7 min), octyl aldehyde (4.0 min), methyl octanoate (4.7 min), and mesitylene (3.7 min).

Procedure for the Batch Reaction Oxidation of Alcohols. MeOH (0.5 mL) was added to 20 x 150 mm culture tube containing 21.3 mg of PBT-2 (1 mol % Pd) and 34.6 mg K_2CO_3 (25 mol %) and was then placed on a 48 well orbital shaker and agitated under 1 atm O_2 for 30 min while heating to 60 °C. Once the reaction temperature was reached, the headspace was purged with O_2, and the substrate was added as a 2 M solution in MeOH (0.5 mL) containing 0.2 M mesitylene as an internal standard (I.S.). The post reaction solution was injected onto a GC to determine product and reactant concentrations. The catalyst was recovered by filtration or centrifugation.

Procedure for the Batch Recycling of the Catalyst. Upon completion of a reaction cycle, the test tube containing the reaction mixture was centrifuged at 1000 rpm for 5 min. The supernatant was decanted and the solid material was rinsed with fresh MeOH by resuspending the catalyst, centrifuging the mixture at 1000 rpm for 5 min, followed by decanting the supernatant. Fresh K_2CO_3 was added and a new reaction was performed by using the procedure for the batch reaction oxidation of alcohols described above.

Preparation of the Packed-Bed Reactor. The packed bed reactor was made from a stainless steel tube 0.25” o.d. x 3” with 1 cm of glass wool inside a Swagelok fitting with a 200 mesh stainless steel screen. Powdered catalyst (0.4 g PBT-2) was added, leaving 1 cm of open space for more glass wool to be retained by another 200-mesh stainless steel screen and a Swagelok fitting.

Procedure for Alcohol Oxidation under Flow Conditions. A solution of 5 M benzyl alcohol and 1 M mesitylene in MeOH was added to a 260 mL syringe pump (Teledyne ISCO 260D), and 0.138 M K_2CO_3 in MeOH was added to a second 260 mL syringe pump. The flow rate of the second pump was set to 9 times that of the pump containing alcohol to afford a final liquid solution of 0.5 M benzyl alcohol, 0.1 M mesitylene, and 0.125 M K_2CO_3 in MeOH. A cylinder of 9 % O_2 in N_2 was regulated down to 15 bar and the gas flow rate was controlled by a mass flow controller with a O_2 to substrate molar ratio of 8:1. The gas and liquids were mixed in two 1/8” tees and sent through a heated zone, after which they passed through the packed bed reactor (PBR) in an up-flow configuration. The preheated zone and packed-bed reactor were submerged in ethylene glycol heat transfer fluid maintained at 60 °C. The weight hourly space velocity (WHSV) was controlled by adjusting the gas and liquid flow rates to the appropriate level. Aliquots of the reaction mixture (100-500 μL) could be removed through a small tee for GC analysis, and the remaining liquid and gas were separated using a large tee with the liquids collected out the bottom using a level gauge and the gases vented out the top through a pressure relief valve. The pressure relief valve controls the reaction pressure and was maintained at 6 bar.

ICP-AES Analysis of the Catalyst. The catalyst (25 mg PBT-2) was added to a crucible and heated at 450 °C/min to 900 °C and held at this temperature for 2 hours. After cooling, the crucible was filled with aqua regia and heated on a hot plate to the boiling point. After 3 hours, the aqua regia was collected in a 100 mL volumetric flask and diluted up to 100 mL using 9 % HCl. The solution was analyzed on a Perkin Elmer Instruments Optima 2000 DV ICP AES.

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Supporting Information Available. Additional screening tables and catalyst characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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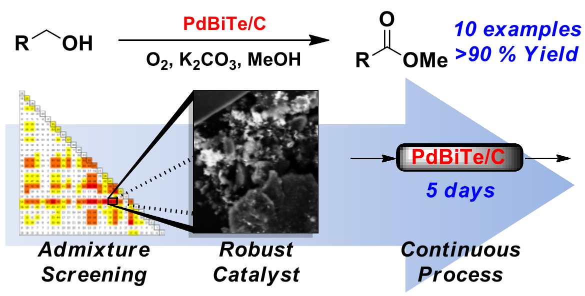
TOC Graphic


PdBiTe/C
O2, K2CO3, MeOH
10 examples
>90 % Yield
PdBiTe/C
5 days
Admixture Screening
Robust Catalyst
Continuous Process