Continuous Flow Oxidation of Alcohols and Aldehydes Utilizing Bleach and Catalytic Tetrabutylammonium Bromide

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Continuous Flow Oxidation of Alcohols and Aldehydes Utilizing Bleach and Catalytic Tetrabutylammonium Bromide

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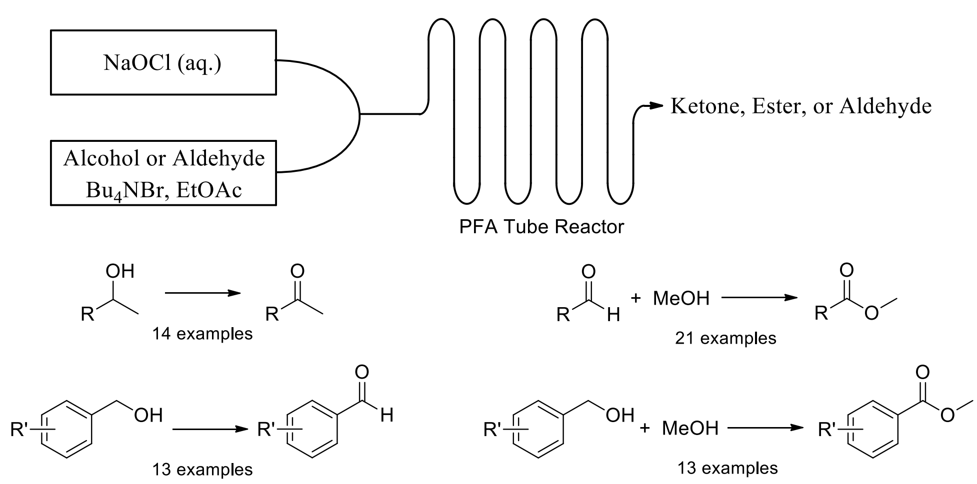
Table of contents graphic



Abstract. We report a method for the oxidation of a range of alcohols and aldehydes utilizing a simple flow system of alcohols in EtOAc with a stream of 12.5% NaOCl and catalytic Bu_4NBr. Secondary alcohols are oxidized to ketones, aldehydes directly to methyl esters in the presence of methanol, and benzylic alcohols to either benzaldehydes or methyl esters depending on the conditions used. The reaction conditions are mild and generally provide complete conversion in 5-30 min.

KEYWORDS. Flow, Oxidation, Catalytic, Bleach, Ketones, Aldehydes, Esters

Introduction. There exist numerous and varied methods for oxidation of alcohols including methods utilizing stoichiometric[1] (Jones, Collins, PCC, PDC, and others) and catalytic[2] (TPAP and others) metal species, hypervalent iodine reagents[3] (IBX, Dess-Martin periodinane and derivatives), stable N-oxyl radicals[4] (TEMPO and derivatives) or proceeding by way of alkoxysulfonium intermediates[5] (Moffatt-Swern, Moffatt-Pfitzner, Corey-Kim, Parikh-Doering), hydride transfer from metal alkoxides[6] (Oppenauer, Mukaiyama) and the Stevens oxidation,[7] which utilizes a concentrated solution of NaOCl as oxidant and acetic acid as solvent and generally oxidizes secondary alcohols in preference to primary. Variations of the Stevens method have also been reported utilizing co-solvents such as acetonitrile.[8] The use of PTC has also been investigated[9] though we have only found one example utilizing ethyl acetate and TBAB as the sole catalyst[9a] with limited examples and only secondary alcohols investigated.

The majority of the oxidations mentioned above possess limitations affecting their practicality. In recent years continuous flow methods for organic synthesis have increased in popularity and variety.[10] Key advantages include the precise control of reaction time and temperature. The very high surface-area-to-volume ratio results in exceptional heat transfer, which in turn enables very fast heating and cooling and reduces the occurrence of uncontrolled exothermic reactions. The small reaction volumes employed provide both significant leverage – a small reactor can produce large amounts of desired material over time – and more importantly, greatly enhanced safety. Recent demonstrations of this last point include publications by our group,[11] and others,[12] demonstrating the ability to utilize sodium azide or hydrazoic acid at high temperatures in flow.

In batch, scaling of multiphasic reactions presents significant challenges as varying reactor size, shape, and stirring rate can all have an effect on the rate and reproducibility of reactions. On small scale thorough mixing can be readily achieved by magnetic or overhead stirrers, but on larger scales this becomes harder to accomplish and often requires further optimization. Performing biphasic reactions in flow could be extremely beneficial as efficient mixing and small reactor inner diameters ensure consistent high surface-area-to-volume ratios between solvent plugs. Scalability thus becomes an issue of increasing reactor length and flow rates to increase throughput while maintaining the necessary contact between reagents. With these benefits in mind we endeavored to develop an environmentally friendly flow method utilizing the Stevens oxidation as inspiration.

Oxidations carried out in flow have been performed utilizing a wide variety of reagents including $KMnO_4$,[13a] ozone,[13b] DMSO/trifluoroacetic anhydride[13c] and immobilized ruthenium complexes.[13d-f] Oxidation methods have also been developed utilizing immobilized versions of TEMPO,[14] the stationary phase typically being silica- or polystyrene-based. Utilizing these immobilized reagents poses several possible disadvantages in flow. The primary concern with polymer immobilized reagents involves the swelling/shrinking properties of the stationary phase, which can lead to clogging and high system pressures. Although essentially immune to swelling, silica can lead to chromatographic effects, resulting in not only increased residence times, but also increased residence time distribution.

Results and Discussion. Using these flow reactions as inspiration we began to investigate the use of other traditional oxidants catalytically via re-oxidation by a stoichiometric oxidant. Ideally, we wished to perform the oxidations in the presence of an immobilized catalyst to ease purification as well as prevent leaching of metals in certain cases; however, leaching was often unavoidable.

In the course of studying the oxidation of secondary alcohols to ketones utilizing various immobilized catalysts we performed a control experiment in the absence of the catalyst and only the stoichiometric re-oxidant, a 12.6% solution of sodium hypochlorite, present with a catalytic amount of phase transfer catalyst (PTC), tetrabutylammonium bromide (TBAB). The conditions utilized in the control experiment proved more than capable of oxidizing secondary alcohols without the need for an additional catalyst. The literature contains few examples of similar oxidations under batch conditions,[7,9] the Stevens oxidation[7] being among the most well-known.

Our initial investigations in batch translated well into flow utilizing simple and readily available equipment including a single syringe pump, 10 ml glass syringes, and a coil of 0.5 mm id PFA tubing (Figure 1)[15] and the reaction was optimized utilizing 2-octanol. All reactions were screened by offline GC analysis. Residence times (t_R) were varied by adjusting flow rates and optimal times were determined based on the GC conversion and yield data obtained from run samples. Early criteria for the reaction were set so as to ensure complete conversion within 30 min.

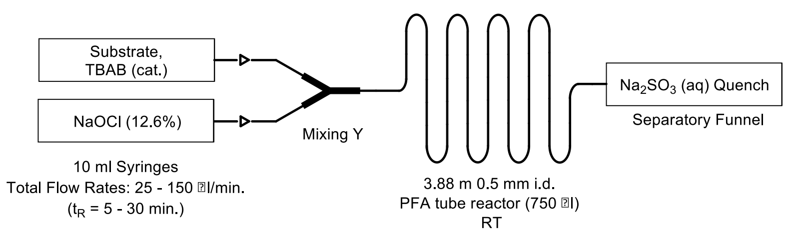
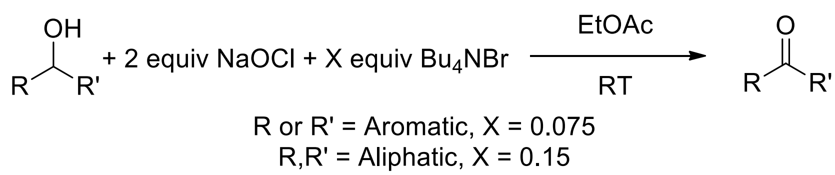


Figure 1: Schematic representation of the flow apparatus utilized for the oxidation of alcohols and aldehydes

An initial investigation of catalysts for this oxidation demonstrated that neither an alternative PTC, tetrabutylammonium acetate, nor a simple bromide salt, NaBr, was capable of catalyzing the reaction under our conditions; however, the addition of both reagents rescued the reaction and produced the expected products. Optimal catalyst loading for the oxidation of secondary aliphatic alcohols was 15 mol% TBAB. As expected, the oxidation of benzylic secondary alcohols was faster and thus could be performed with lower loading of the catalytic bromide, generally requiring 7.5 mol%. The use of two equivalents of bleach was optimal, and the reaction was best performed at an initial substrate concentration of approximately 0.8 M. Heating the reaction was not beneficial and the above optimized conditions thus constitute our continuous oxidation system.

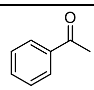
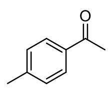
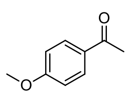
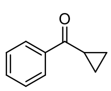
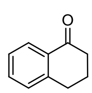
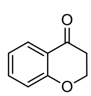
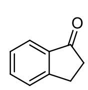
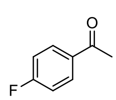
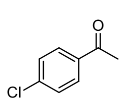
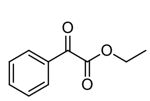
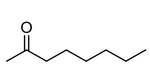
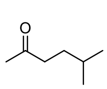
With the reaction thus optimized (Scheme 1) we began to examine the scope of the oxidation (Table 1). Initial screening focused on the substitution of the aromatic portion of the benzylic alcohols. Electron-donating and moderately withdrawing groups were well tolerated. Cyclic benzylic alcohols were also suitable substrates for reaction. Entry 4 is notable as the somewhat sensitive cyclopropyl ketone generated is stable to the reaction conditions. The presence of olefins or alkynes was not tolerated in any substrate that was investigated.

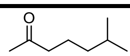
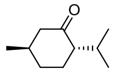


Scheme 1. Optimized reaction conditions for the oxidation of benzylic and aliphatic secondary alcohols.

We next examined the oxidation of a series of aliphatic alcohols and found that most provided good to excellent conversion. With regards to the presence of tertiary centers 6-methyl-2-heptanol (entry 13) was readily oxidized; however 5-methyl-2-hexanol (entry 12) was not efficiently oxidized. It would appear that the catalyst is less effective in this case, producing only low conversion. Upon oxidation of menthol only one diastereomer was observed, with no sign of epimerization to isomenthone, indicating that base induced epimerization was not occurring. Isomenthol was also subjected to the reaction conditions; however the oxidation was very sluggish and only low conversion (~5%) was obtained. The product observed by GC analysis of the reaction mixture, nevertheless, was isomenthone with no sign of epimerization to menthone. Overall, isolated yields agreed well with yields obtained by GC analysis with an internal standard, the exceptions being ketone products of appreciable vapor pressure and thus subject to loss of material during purification.

Table 1. The oxidation of secondary benzylic and aliphatic alcohols to ketones

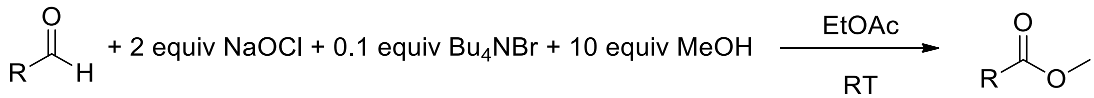
#	Product[a]	t_R[b] (min)	Conv. (%)[c]	Yield (%)[c] (isolated)
1		30	98	>95 (76)
2		30	93	>95 (92)
3		20	-	- (81)
4		30	95	>95 (88)
5		30	93	>95 (95)
6		30	99	- (>95)
7		30	54	36 (41)
8		30	93	>95 (79)
9		30	72	76 (77)
10		20	94	>95 (91)
11			86	81 (44)
12		30	58	40 (-)

13		30	100	>95 (-)
14		30	84	>95 (43)

[a] Reactions were run as outlined in Figure 1: A 0.818 M solution of alcohol containing 0.075 equivalents of TBAB (benzylic alcohols) or 0.15 equivalents of TBAB (aliphatic alcohols) was mixed with a 1.64 M solution of NaOCl at a mixing Y and flowed through a reactor coil for the indicated time. Products were isolated by flash chromatography
[b] Residence times (t_R) were obtained by variation of the total flow rates using a 750 μl reactor loop
[c] Conversion and Yield were obtained by offline GC analysis of aliquots of reaction mixture standardized with dodecane.

During our initial batch experiments we had discovered that the oxidation of primary alcohols produced very little aldehyde, but did produce significant amounts of an ester obtained from two molecules of the original alcohol, likely via formation of a hemiacetal that was then further oxidized.[16] While the oxidation of aldehydes directly to esters is known[17] it is frequently substrate-specific and, in practice, it is much more common to oxidize to the acid under various conditions followed by esterification. With this point and our previous results in hand, we set out to determine whether it would be possible to develop a general continuous processing method for the oxidation of an aldehyde, in the presence of an appropriate alcohol, to an ester without requiring the intermediacy of the acid. An initial experiment with benzaldehyde and EtOH demonstrated that this reaction was possible, although only moderate conversion and low yield were observed in initial experiments. Increasing the amount of EtOH utilized from 2 to 10 equivalents while using 10 mol% of tetrabutylammonium bromide was found to be optimal.

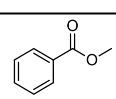
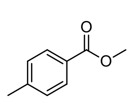
While our initial experiments utilized ethanol, it was discovered that the reaction was more prone to the formation of reactor-clogging precipitates when 10 or more equivalents, relative to aldehyde, were used. This problem could be mitigated through the use of a diluted solution of aldehyde; though decreasing the concentration below ~0.5 M slowed the reaction and led to incomplete conversion within our desired 30 min. target reaction time. Ultimately, this problem was overcome by switching to MeOH. Thus, the optimized reaction conditions (Scheme 2) utilize 10 eq. of MeOH and 10 mol% TBAB, and were found to be appropriate for the majority of benzaldehydes (Entry 4-17) which were moderately to highly electron deficient and aliphatic aldehydes (Entry 18-21).

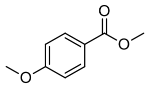
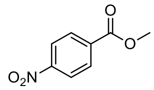
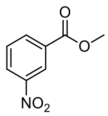
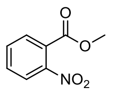
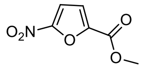
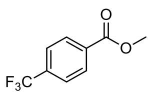
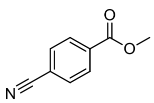
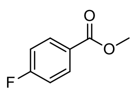
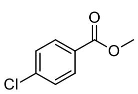
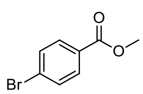
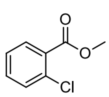
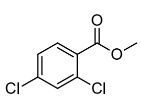
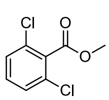
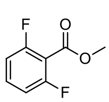
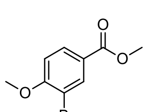


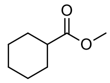
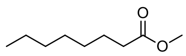
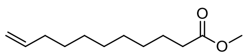
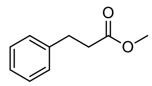
Scheme 2. Optimized reaction conditions for the oxidation of benzaldehydes and aliphatic aldehydes to methyl esters.

Electron-rich benzaldehydes (Entry 1-3), however, were more resistant to oxidation. This result would seem to indicate that it is the electrophilicity of the aldehyde that is most important with regard to the rate of oxidation. At least one electron poor heteroaromatic aldehyde was also a suitable substrate for oxidation (Entry 7). While the reaction appears to be quite general, substitution *ortho*- to the aldehyde moiety generally decreased the rate of oxidation, the exception being when a suitably strong electron withdrawing group is present. This effect, while pronounced when a single *ortho*- substituent is present, can drastically slow oxidation to the ester when both *ortho*- positions are substituted (Entry 15). The smaller, more electron deficient fluorine equivalent (Entry 16) did however undergo oxidation, albeit with low conversion. Interestingly, while secondary alcohols containing an olefin did not undergo oxidation, 10-undecenal was oxidized quite smoothly under these conditions, providing a 75% isolated yield of methyl 10-undecenoate (Entry 20).

Table 2. Oxidation of aromatic and aliphatic aldehydes to esters

#	Product[a]	t_R[b] (min)	Conv. (%)[c]	Yield (%)[c] (isolated)
1		10	58	51 (44)
2		20	56	45 (23)

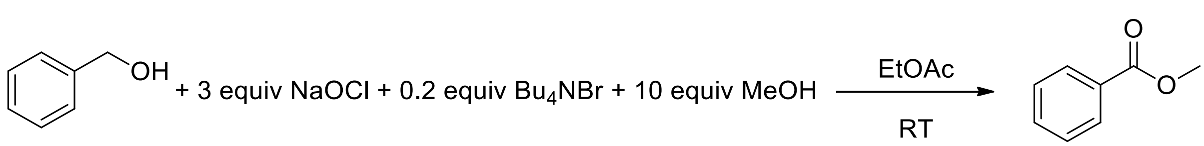
3		20	57	8 (-)
4		10	100	>95 (91)
5		5	100	>95 (92)
6		20	100	>95 (94)
7		5	100	93 (84)
8		20	100	>95 (99)
9		5	100	>95 (90)
10		20	93	- (47)
11		20	97	93 (80)
12		10	85	81 (92)
13		20	57	52 (34)
14		10	88	- (80)
15		20	0	0 (-)
16		10	38	- (9)
17		20	69	49 (53)

18		5	93	80 (19)
19		5	93	55 (38)
20		20	97	62 (75)
21		10	96	41 (41)

[a] Reactions were run as outlined in Figure 1: A 0.818 M solution of alcohol containing 0.1 equivalents of TBAB and 10 equivalents of methanol was mixed with a 1.64 M solution of NaOCl at a mixing Y and flowed through a reactor coil for the indicated time. Products were isolated by flash chromatography
[b] Residence times (t_R) were obtained by variation of the total flow rates using a 750 μl reactor loop
[c] Conversion and Yield were obtained by offline GC analysis of aliquots of reaction mixture standardized with dodecane.

With these results in hand and the notion that a benzylic alcohol should be oxidized more quickly than methanol, we also investigated the possibility of oxidizing a benzylic alcohol in the presence of methanol directly to the methyl ester without the need to isolate an intermediate aldehyde. Lending credence to this idea, the one step oxidation of alcohols to methyl esters is known,[18] however, the conditions used typically involve either catalytic or stoichiometric metals or the use of elemental halogens. Certain examples, in a manner similar to our method, utilize a halide salt and stoichiometric oxidant to achieve the oxidation.[18a-c]

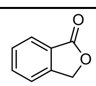
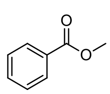
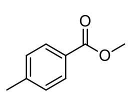
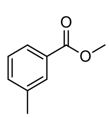
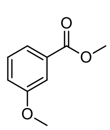
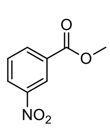
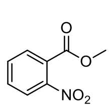
When utilizing 1,2-benzenedimethanol under the reaction conditions that were used previously in the oxidation of aldehydes omitting the added methanol, we were pleased to observe the formation of phthalide with full conversion and 90% isolated yield. Optimization of the general oxidation of benzylic alcohols to methyl esters simply required an increase to 3 equivalents of NaOCl and 20 mol% of catalyst (Scheme 3).

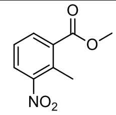
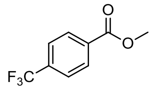
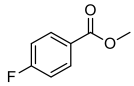
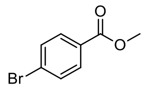
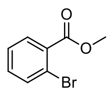
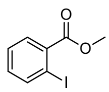


Scheme 3. Optimized reaction conditions for the oxidation of benzylic alcohols to methyl benzoates

Once again electron-deficient benzylic alcohols were the most suitable in this reaction (Table 3) as the second oxidation occurs much more quickly. Electron-rich benzylic alcohols would form the desired products, albeit in lower yield. While conversion of the electron rich benzylic alcohols was complete, the majority of the oxidized material stalled at the aldehyde oxidation state. Attempts were made to increase yield, but none provided consistent improvements. Interestingly, as in the Stevens oxidation, aliphatic primary alcohols appear to undergo oxidation more slowly than secondary and benzylic alcohols. This result explains why the oxidation of aldehydes and benzylic alcohols in the presence of vast excesses of methanol and ethanol is possible. It also implies that the reaction as described may be able to oxidize secondary and benzylic alcohols selectively in the presence of primary aliphatic alcohols in a similar manner to the Stevens oxidation.

Table 3. Oxidation of benzylic alcohols to esters.

#	Product[a]	t_R[b] (min)	Conv. (%)[c]	Yield (%)[c]
1[d]		20	100	90
2		20	100	47[e]
3		20	100	17[e]
4		30	100	42[e]
5		30	100	41[e]
6		10	100	81
7		30	100	89

8		30	100	85
9		20	100	78
10		30	100	76
11		20	100	73
12		30	100	25[e]
13		30	100	27[e]

[a] Reactions were run as outlined in Figure 1: A 0.55 M solution of alcohol containing 0.2 equivalents of TBAB and 10 equivalents of methanol was mixed with a 1.64 M solution of NaOCl at a mixing Y and flowed through a reactor coil for the indicated time

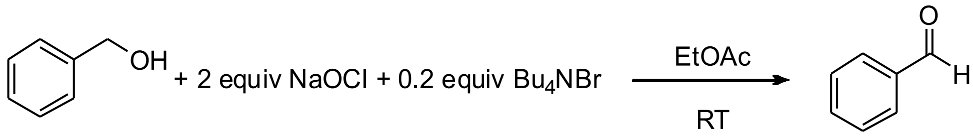
[b] Residence times (t_R) were obtained by variation of the total flow rates using a 750 μl reactor loop

[c] Conversion and Yield were obtained by offline GC analysis of aliquots of reaction mixture standardized with dodecane

[d] The formation of phthalide was performed with 2 equivalents of NaOCl and 0.1 equivalents of TBAB

[e] % Yield is representative only of the esters of interest. Low yield is the result of large amounts of product stalled at the aldehyde oxidation state and not due to side reactions or decomposition

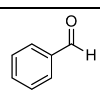
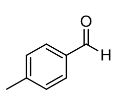
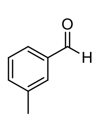
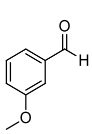
When we initially investigated the oxidation of benzylic alcohols to methyl esters, we envisioned that the second oxidation would be faster than the first, and the aldehyde would quickly form a hemiacetal with methanol, rather than with another molecule of benzylic alcohol as we had observed previously, and then oxidize to the methyl ester. Our early experiments with electron-deficient benzylic alcohols demonstrated this type of reactivity with only small amounts of aldehyde present at any given time; however, when we utilized electron-rich alcohols, we were intrigued by the formation of significant quantities of the benzaldehydes. In fact, the low yield of the esters obtained with electron rich benzylic alcohols is mostly attributable to the remainder of the reaction products being stalled at the aldehyde oxidation state. With this result in mind, and the apparent stability of the aldehydes used in the initial oxidations to methyl esters, we decided to examine the selective oxidation of benzylic alcohols to aldehydes selectively under the same conditions (Scheme 4).

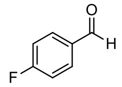
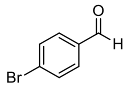
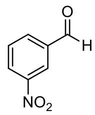
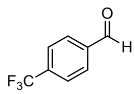
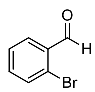
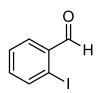
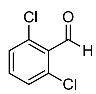
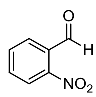
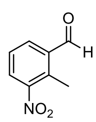


Scheme 4. Optimized reaction conditions for the oxidation of benzylic alcohols to aldehydes

Benzylic alcohols possessing strongly and weakly electron-donating groups were oxidized very quickly, providing the desired aldehydes in good yield (Table 4). In the case of benzylic alcohols with pendant electron-withdrawing groups (entry 5 - 8) the reactions produced only low to moderate yield of the desired aldehydes. These decreased yields are attributable to the high electrophilicity of the aldehydes produced. Their electrophilic nature likely leads to formation of hemiacetals with a second benzylic alcohol and subsequent oxidation to an ester. In these cases the ester products could be isolated, and in the case of entry 8, observed by GC. In an effort to prevent the over-oxidation to esters we attempted the oxidation of electron-poor benzylic alcohols bearing an *ortho*- substituent (entry 9 – 13). We hoped to utilize the decreased reactivity observed in the oxidation of aldehydes with an *ortho*-substituent that we had encountered previously.

Table 4: Oxidation of benzylic alcohols to aldehydes.

#	Product[a]	t_R[b] (min)	Conv. (%)[c]	Yield (%)[c] (isolated)
1		12.5	100	81 (-)
2		10	94	91 (66)
3		15	100	> 95 (71)
4		15	100	93 (83)

5		10	100	83 (34)
6		10	100	65 (28)
7		5	100	23 (10)
8		5	100	34 (-)
9		15	100	95 (82)
10		15	100	85 (74)
11		25	73	64 (46)
12		10	100	70 (55)
13		5	100	70 (50)

[a] Reactions were run as outlined in Figure 1: A 0.82 M solution of alcohol containing 0.2 equivalents of TBAB was mixed with a 1.64 M solution of NaOCl at a mixing Y and flowed through a reactor coil for the indicated time. Products were isolated by flash chromatography

[b] Residence times (t_R) were obtained by variation of the total flow rates using a 750 μl reactor loop

[c] Conversion and Yield were obtained by offline GC analysis of aliquots of reaction mixture standardized with dodecane.

As can be seen when comparing entry 7 to 12, moving the nitro group from the *meta*- to the *ortho*- position increases the yield from 10% to 55% and comparing entry 7 to 13 demonstrated that the addition of a methyl group in the *ortho*- position increases the yield from 10% to 50%. Clearly the presence of an *ortho*- substituent can be used to increase the yield of aldehyde in this reaction via suppression of over-oxidation in the case of electron poor benzylic alcohols.

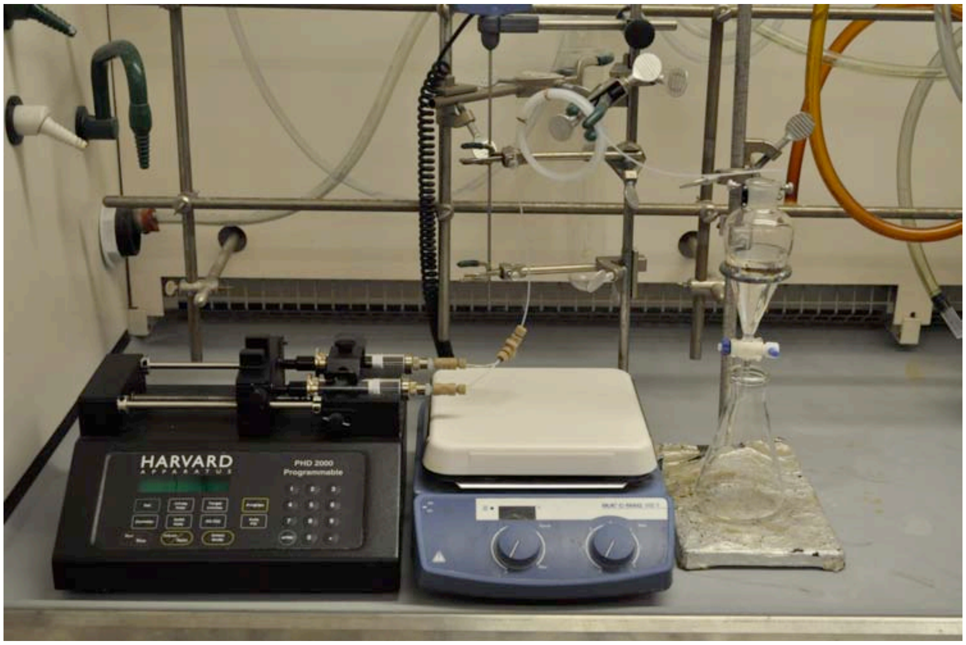
Scale up. Following the completion of the investigation of substrate scope, we sought to demonstrate the ability to easily scale up the reaction. Towards this end we utilized a Uniqsis FlowSyn commercial flow system fitted with a 14 ml reactor coil.[19] In order to avoid any risk associated with the use of concentrated bleach with stainless steel components and seals, the bleach solution was pumped utilizing two glass 50 ml syringes and a syringe pump plugged into the mixing T-joint. The experiment utilized 5-nitro-2-furaldehyde as substrate and prepared methyl 5-nitro-2-furoate in the same manner as on small scale. In total, the flow system was allowed to run for 75 minutes and generated 11.0 g (75% yield) of methyl 5-nitro-2-furoate. This rate of throughput translates to 211 g of product per day. This experiment represented a 20-fold increase in scale, utilized tubing with a different inner diameter, required no further optimization, and provided the desired product with only a slight decrease in isolated yield from previous experiments, a testament to the simplicity of scale up in flow systems.

Conclusion. We have developed a continuous flow oxidation method utilizing a 12.6% aqueous solution of sodium hypochlorite as stoichiometric oxidant. The process was found to be capable of oxidizing secondary alcohols to ketones, aldehydes directly to methyl esters, and benzylic alcohols to aldehydes and esters in moderate to high conversion and yield in most cases. The conditions utilized for oxidation have proven relatively mild and are well tolerated by a wide range of substrates. The use of continuous flow reactors greatly reduced the challenges inherent to performing biphasic reactions in batch, most notably the strict control of reaction time, the ability to continuously quench small volumes of bleach without the associated heating, and the ability to greatly increase scale and throughput without further optimization.

Experimental.

Materials and Methods. ^{1}H NMR spectra were obtained at 500 MHz. All spectra were obtained in deuterated chloroform and referenced to residual chloroform at 7.26 ppm. Solvents and starting materials were used as received from the supplier without further purification. Flash chromatography was performed using 230-400 mesh silica gel obtained from SiliCycle. Reactions were monitored off-line by GC. GC samples were prepared by collecting a 40 μl sample of the reaction mixture (20 μl organic and 20 μl aqueous) which was diluted to 5 ml in a volumetric flask with EtOAc and a known amount of dodecane as an internal standard. 1 μl injections of sample were run according to one of the following methods. GC Method A: Samples were run on an Agilent DB-WAX column (30 m x 0.32 mm i.d., 25 μm film thickness) with a flow rate of 1 ml/min. Oven temperature was held at 50 °C for 10 minutes and then increased linearly to 250 °C over 10 minutes with a final hold of two minutes. GC Method B: Samples were run on an Agilent HP-5 column (30 m x 0.32 mm i.d., 25 μm film thickness) with a flow rate of 1 ml/min. Oven temperature was held at 50 °C for 10 minutes and then increased linearly to 250 °C over 10 minutes with a final hold of two minutes. GC yields and conversions were determined using standard curves generated form a series of known standards referenced to the internal standard dodecane.

Flow Apparatus. Syringes of reagents were loaded into a syringe pump and connected to a Y-mixer and the reaction coil using Upchurch Super Flangeless fittings and Luer lock adapters. The reaction coil was comprised of a 750 μl (3.88 m) piece of 0.02” (0.5 mm) inner diameter PFA tubing connected to the Y-mixer using Upchurch Super Flangeless fittings. Reactions were run at appropriate flow rates to obtain the desired retention time which had been previously determined. The effluent was collected in a separating funnel containing a saturated aqueous solution of sodium sulfite. Upon completion of the reaction the organic layer was separated and the aqueous layer washed twice with EtOAc. Purification was performed via flash column chromatography.



General Procedure for the Oxidation of Secondary Alcohols to Ketones. A secondary alcohol and TBAB (100 mg, 0.075 eq. for benzylic alcohols, 200 mg, 0.15 eq. for aliphatic alcohols) were dissolved in a minimal amount of EtOAc in a 5 ml volumetric flask. Upon complete dissolution the volume was brought to 5 ml with EtOAc to obtain a final concentration of 0.818 M. This solution was then added to a glass airtight syringe. An equal volume of an approximately 1.64 M solution of sodium hypochlorite was taken up in a second syringe.

Acetophenone: 500 mg of 1-phenylethanol was dissolved and processed as described in the general procedure for the oxidation of secondary alcohols to ketones. The solutions of reagents flowed for 165 minutes at a total flow rate of 25 μl/min with a retention time of 30 minutes. A total volume of 2.06 ml of organic phase was collected providing a theoretical yield of 202 mg of acetophenone. Purification was accomplished via flash column chromatography with 5% EtOAc in hexanes. 153 mg of pure acetophenone (76% yield) was obtained. GC (Method A): Standard: T_R = 17.079', Reaction: T_R =

17.071’; ^{1}H NMR (500 MHz): 7.97 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 2.61 (s, 3H).

General Procedure for the Oxidation of Aldehydes to Methyl Esters. An aldehyde and TBAB (132 mg, 0.1 eq.) were dissolved in 1.65 ml of methanol (10 eq.) in a 5 ml volumetric flask. Upon complete dissolution the volume was brought to 5 ml with EtOAc to obtain a final concentration of 0.818 M. This solution was then added to a glass airtight syringe. An equal volume of an approximately 1.64 M solution of sodium hypochlorite was taken up in a second syringe.

Methyl benzoate: 435 mg of benzaldehyde was dissolved and processed as described in the general procedure for the oxidation of aldehydes to methyl esters. The solutions of reagents flowed for 91 minutes at a total flow rate of 75 μl/min with a residence time of 10 minutes. A total volume of 3.41 ml of organic phase was collected providing a theoretical yield of 379 mg of methyl benzoate. Purification was accomplished by flash column chromatography with 2% EtOAc in hexanes. 175 mg of pure methyl benzoate (44% yield) was obtained. GC (Method A): Standard: T_R = 16.258`, Reaction: $T_R$ = 16.259`; ^{1}H NMR (500 MHz): 8.04 (m, 2H), 7.56 (m, 2H), 7.44 (m, 2H), 3.92 (s, 3H).

General Procedure for the Oxidation of Benzylic Alcohols to Methyl Esters. A benzylic alcohol and TBAB (175 mg, 0.2 eq.) were dissolved in 1.10 ml of methanol (10 eq.) in a 5 ml volumetric flask. Upon complete dissolution the volume was brought to 5 ml with EtOAc to obtain a final concentration of 0.547 M. This solution was then added to a glass airtight syringe. An equal volume of an approximately 1.64 M solution of sodium hypochlorite was taken up in a second syringe.

Methyl 3-nitro-2-methylbenzoate: 455 mg of 3-nitro-2-methylbenzyl alcohol was dissolved and processed as described in the general procedure for the oxidation of benzylic alcohols to methyl esters. The solutions of reagents flowed for 166 minutes at a total flow rate of 25 μl/min with a residence time of 30 minutes. A total volume of 2.08 ml of organic phase was collected providing a theoretical yield of 223 mg of methyl 3-nitro-2-methylbenzoate. Purification was accomplished via flash column chromatography with 2.5% EtOAc in hexanes. 168 mg of pure methyl 3-nitro-2-methylbenzoate (75% yield) was obtained. GC (Method B): Reaction: T_R = 18.255'; ^{1}H NMR (500 MHz): 8.00 (dd, J = 8 Hz, 1 Hz, 1H), 7.85 (dd, J = 8 Hz, 1 Hz, 1H), 7.39 (t, J = 8Hz, 1H), 3.94 (s, 3H), 2.63 (s, 3H).

General Procedure for the Oxidation of Benzylic Alcohols to Aldehydes. A benzylic alcohol and TBAB (265 mg, 0.2 eq.) were dissolved in a minimal amount of EtOAc in a 5 ml volumetric flask. Upon complete dissolution the volume was brought to 5 ml with EtOAc to obtain a final concentration of 0.818 M. This solution was then added to a glass airtight syringe. An equal volume of an approximately 1.64 M solution of sodium hypochlorite was taken up in a second syringe.

2-iodobenzaldehyde: 955 mg of 2-iodobenzyl alcohol was dissolved and processed as described in the general procedure for the oxidation of benzylic alcohols to aldehydes. The solutions of reagents flowed for 180 minutes at a total flow rate of 16.67 □l/min with a retention time of 15 minutes. A total volume of 1.50 ml of organic phase was collected providing a theoretical yield of 324 mg of 2-iodobenzaldehyde. Purification was accomplished by filtration through a plug of silica with EtOAc. 241 mg of pure 2-iodobenzaldehyde (74% yield) was obtained. GC (Method B): Reaction: T_R = 17.096'; ^{1}H NMR (500 MHz): 10.07 (s, 1H), 7.96 (ddd, J = 8 Hz, 1 Hz, 0.5 Hz, 1H), 7.88 (ddd, J = 7.5 Hz, 1.5 Hz, 0.5 Hz, 1H), 7.47 (m, 1H), 7.29 (ddd, J = 7.5 Hz, 7 Hz, 2 Hz, 1H).

Large Scale Synthesis of Methyl 5-nitro-2-furoate: 23 g of 5-nitro-2-furaldehyde, 66 ml of MeOH and 5.2 g of TBAB were dissolved in EtOAc and brought to a final volume of 200 ml. The solution of reagents and ~12.5% NaOCl flowed for 75 minutes at a total flow rate of 2.8 ml/min and a residence time of 5 minutes and was stopped once the syringes of bleach were exhausted. Unlike previous examples, the reaction was flowed through a 14 ml coil of 0.04" (1 mm) inner diameter PTFE tubing using a Uniqsis FlowSyn commercial flow unit. As a preventative measure to protect the valves and pumps of the unit the bleach solution was delivered via a syringe pump outfitted with two 50 ml syringes. A total volume of 105 ml of organic phase was collected providing a theoretical yield of 14.7

g of methyl 5-nitro-2-furoate. Purification was accomplished via filtration through a plug of silica with EtOAc. A total of 11.0 g of pure methyl 5-nitro-2-furoate (75% yield) was obtained.

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Supporting Information Available. The contents of the Supporting Information include the following: (1) General procedures for oxidation reactions and (2) Experimental details, analytical data and spectra for synthesized compounds. This material is available free of charge via the internet at http://pubs.acs.org.

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[1] For reviews of Cr(VI) based oxidations see: a) Patel, S.; Mishra, B. K. *Tetrahedron*, **2007**, *63*, 4367; b) Freeman, F. (Eds.: Mijs, W. J., De Jonge, C. R. H. I.); *Org. Synth. Oxid. Met. Compd.* **1986**, 41; c) Ley, S. V.; Madin, A. *Comp. Org. Synth.* *7*, 251-289 (Eds.: Trost, B. M., Fleming, I.); Pergamon Press: Oxford, 1991.

[2] For a review of TPAP oxidations see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis,* **1994**, *7*, 639.

[3] For reviews of hypervalent iodine based oxidations see: a) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086; b) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185; c) Zhdankin, V. V. *Current Organic Synthesis*, **2005**, *2*, 121; d) Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111; e) Satam, V.; Harad, A.; Rajule, R.; Pati, H. *Tetrahedron* **2010**, *66*, 7659.

[4] For recent reviews of TEMPO and Nitroxyl radical catalyzed oxidations see: a) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346,* 1051; b) Vogler, T.; Studer, A. *Synthesis*, **2008**, 1979. For a review of the use of TEMPO and derivatives in industrial synthesis see: c) Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2010**, *14*, 245.

[5] For reviews of oxidations mediated by alkoxysulfonium intermediates see: a) Mancuso, A. J.; Swern, D. *Synthesis*, **1981**, 165; b) Tidwell, T. T. *Synthesis*, **1990**, 857. c) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.

[6] For reviews of the Oppenauer oxidation see: a) Creyghton, E. J.; Van der Waal, J. C. *Fine Chemicals Through Heterogenous Catalysis* (Eds.: Sheldon, R. A., Bekkum, H. v.); Wiley-VCH: Weinheim; New York, 2001; b) Jerome, J. E.; Sergent, R. H. *Chem. Ind.* **2003**, *89*, 97; c) Graves, C. R.; Campbell, E. J.; Nguyen, S. B. T. *Tetrahedron: Asymmetry*, **2005**, *16*, 3460; d) Fuchter, M. J. *Name Reactions for Functional Group Transformations* (Eds.: Li, J. J., Corey, E. J.); John Wiley & Sons: Hoboken, 2007. For the Mukaiyama oxidation see: e) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773. For reviews of other metal catalyzed hydride transfer reaction see: f) Fujita, K. –i.; Yamaguchi, R. *Synlett.* **2005**, 560; g) Bäckvall, J. –E. *J. Organomet. Chem.* **2002**, *652*, 105.

[7] a) Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 2030; b) Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* **1982**, *23*, 4647.

[8] a) McDonald, C. E.; Nice, L. E.; Shaw, A. W.; Nestor, N. B. *Tetrahedron Lett.* **1993**, *34*, 2741; b) Nwaukwa, S. O.; Keehn, P. M. *Tetrahedron Lett.* **1982**, *23*, 35;

[9] a) Mirafzal, G. A.; Lozeva, A. M. *Tetrahedron Lett.* **1998**, *39*, 7263; b) Lee, G. A.; Freedman, H. H. *Tetrahedron Lett.* **1976**, *20*, 1641; c) Meyers, C. Y. *J. Org. Chem.* **1961**, *26*, 1046.

[10] a) *Microreactors* (Eds.: Ehrfield, W., Hessel, V., Löwe, H.); Wiley-VCH: Weinheim, 2000; b) *Chemical Micro Process Engineering* (Eds.: Hessel, V., Hardt, S., Löwe, H.); Wiley-VCH: Weinheim, 2004; c) *Microreactors in Organic Synthesis* (Ed.: Wirth, T.); Wiley-VCH: Weinheim, 2008; d) *Flash Chemistry: Fast Organic Synthesis in Microsystems* (Ed.: Yoshida, J.); Wiley-Blackwell: Oxford, 2008; e) *Micro Process Engineering* (Eds.: Hessel, V., Renken, A., Schouten, J. C., Yoshida, J.); Wiley-Blackwell: Oxford, 2009; f) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem.* **2004**, *116*, 410; *Angew. Chem. Int. Ed.* **2004**, 43, 406; g) Doku, G. N.; Verboom, W.; Reinhoudt, D. N.; van den Berg, A. *Tetrahedron*, **2005**, *61*, 2733; h) Geyer, K.; Codée, D. C.; Seeberger, P. H. *Chem. Eur. J.* **2006**, *12*, 8434; i) Mason, P. B.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300; j) Watts, P.; Wiles, C. *Org. Biomol. Chem.* **2007**, *5*, 727; k) Ahmed-Omer, B.; Brandt, J. C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5*, 733; l) Wiles, C.; Watts, P. *Eur. J. Org. Chem.* **2008**, 1655; m) Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. *Synlett.* **2008**, 151; n) Yoshida, J.; Nagaki, A.; Yamada, T. *Chem. Eur. J.* **2008**, *14*, 7450; o) Hartman, R. L.; Jensen, K. F. *Lab Chip*, **2009**, *9*, 2495; p) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675.

[11] Palde, P. B.; Jamison, T. F. *Angew. Chem.* **2011**, *123*, 3587; *Angew. Chem. Int. Ed.* **2011**, *50*, 3525.

[12] Gutmann, B.; Roduit, J. -P.; Roberge, D.; Kappe, C. O. *Angew. Chem.* **2010**, *122*, 7255; *Angew. Chem. Int. Ed.* **2010**, *49*, 7101.

[13] a) Sedelmeier, J.; Ley, S. V.; Baxendale, I. R.; Baumann, M. *Org. Lett.* **2010**, *12*, 2618; b) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596; c) Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J. –i. *Angew. Chem.* **2005**, *117*, 2465; *Angew. Chem. Int. Ed.* **2005**, *44*, 2413; d) Kobayashi, S.; Miyamura, H.; Akiyama, R.; Ishida, T. *J. Am. Chem. Soc.* **2005**, *127*, 9251; e) Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *Chem. Commun.* **2006**, 2566; f) Zotova, N.; Hellgardt, K.; Kelsall, G. H.; Jessiman, A. S.; Hii, K. K. *Green Chem.* **2010**, *12*, 2157.

[14] a) Tanaka, H.; Chou, J.; Mine, M.; Kuroboshi, M. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1745; b) Subhani, M. A.; Beigi, M.; Eilbracht, P. *Adv. Synth. Catal.* **2008**, *350*, 2903; c) Bogdan, A.; McQuade, D. T. *Beilstein Journal of Organic Chemistry*, **2009**, *5*, 17.

[15] Photographs of the actual apparatus utilized and of plug flow in the tube reactor are contained in the supporting information.

[16] The oxidation of hemiacetals to esters has been proposed in numerous oxidation systems. For specific examples related to halogen based oxidations see: a) McDonald, C. E.; Holcomb, H. L.; Leathers, T. W.; Kennedy, K. E. *Microchem. J.* **1992**, *47*, 115; b) McDonald, C. E.; Nice, L. E.; Shaw, A. W.; Nestor, N. B. *Tetrahedron Lett.* **1993**, *34*, 2741; c) Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29*, 5087.

[17] a) Le Paih, J.; Frison, J. –C.; Bolm, C. *Modern Oxidation Methods* (Eds.; Baeckvall, J. –E.); Wiley-VCH: Weinheim, 2004. For select examples see: b) Corey, E. J.; Gilman, N. M.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616; c) O'Connor, B.; Just, G. *Tetrahedron Lett.* **1987**, *28*, 3235; d) Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29*, 5087; e) Schmidt, A.; Habeck, T.; Snovydovych, B; Eisfeld, W. *Org. Lett.* **2007**, *9*, 3515; f) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron*, **2009**, *65*, 3102.

[18] For oxidations utilizing halide reagents see: a) Tohma, H.; Maegawa, T.; Kita, Y. *Synlett.* **2003**, 723; b) Shaikh, T. M. A.; Emmanuvel, L.; Sudalai, A. *Synth. Commun.* **2007**, *37*, 2641; c) Reddy, K. R.; Venkateshwar, M; Maheswari, C. U.; Prashanthi, S. *Synth. Commun.* **2010**, *40*, 186; d) Mori, N.; Togo, H. *Synlett.* **2004**, 880; e) Mori, N.; Togo, H. *Tetrahedron*, **2005**, *61*, 5915; f) Karade, N. N.; Tiwari, G. B.; Huple, D. B. *Synlett.* **2005**, 2039. For oxidations with Ru catalysis see: g) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Chem. Commun.* **2008**, 624; h) Owston, N. A.; Nixon, T. D.; Parker, A. J.; Whittlesey, M. K.; Williams, J. M. J. *Synthesis*, **2009**, 1578; i) Zweifel, T.; Naubron, J. –V.; Grützmacher, H. *Angew. Chem.* **2009**, *121*, 567; *Angew. Chem. Int. Ed.* **2009**, *48*, 559. For the aerobic oxidation of alcohols with heterogenous gold catalysis see: j) Nielsen, I. S.; Taarning, E.; Egeblad, K.; Madsen, R.; Christensen, C. H. *Catal. Lett.* **2007**, *116*, 35; k) Su, F. –Z.; Ni, J.; Sun, H.; Cao, Y.; He, H. –Y.; Fan, K. –N. *Chem. Eur. J.* **2008**, *14*, 7131; l) Klitgaard, S. K.; DeLa Riva, A. T.; Helveg, S.; Werchmeister, R. M.; Christensen, C. H. *Catal. Lett.* **2008**, *126*, 213. For oxidations

utilizing MnO_2 see: m) Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synlett*. **2002**, 1293; n) Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis*, **2003**, 1055.

[19] http://www.uniqsis.com/