Electronic Supplementary Material (ESI) for Green Chemistry

Supporting Information

Nanocatalysis in Continuous Flow: Supported Iron Oxide Nanoparticles for the Heterogeneous Aerobic Oxidation of Benzyl Alcohol

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1. Preliminary Microwave-Batch Experiments using H_2O_2 or TBHP (*t*-Butyl Hydroperoxide) as Oxidant

Table S1. Aluminosilicate-supported Fe-nanoparticle catalysts.

Fe/Al-MCM-MW	Iron oxide NPs supported on Al-MCM-41 using MW ~ 0.5 wt% Fe
Fe/Al-SBA-MW	Iron oxide NPs supported on Al-SBA-15 using MW ~ 0.5 wt% Fe

1.1 Blank Runs (Substrate + Oxidant). A time-temperature matrix ranging from 70 to 130 °C and 2 to 16 min using 1 mmol of benzyl alcohol in 1 mL of acetonitrile and 2 equiv of either 50% H_2O_2 or TBHP (5-6 M in *n*-decane) was used to show the low oxidative activity of H_2O_2 and TBHP in the absence of catalyst. 1 mmol of *o*-xylene was added to all runs as internal standard.

Microwave batch experiments were performed in an Initiator (Biotage AB, Sweden) single-mode microwave reactor using 0.5-2 mL conical Pyrex vials and magnetic stirring. After cooling to room temperature, approximately 0.1 mL of the reaction mixture was removed with a syringe and 10 µL were subjected to HPLC analysis at 215 nm. The reaction mixture was heated for further 2 and then 12 min and the sampling procedure repeated as described above.

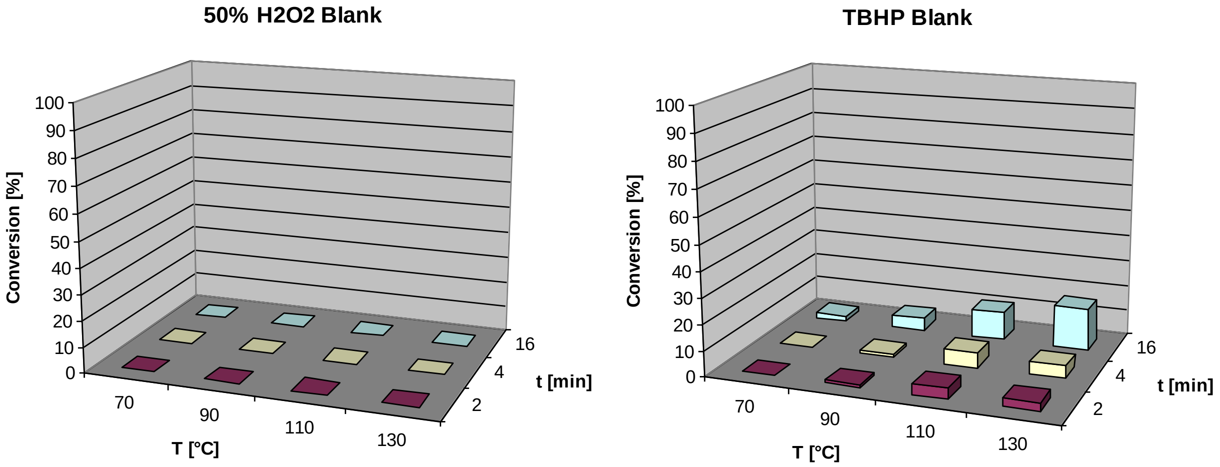


Figure S1. Blank runs using either 50% H_2O_2 (left diagram) or TBHP (right diagram) as oxidant.

Table S2. Conversions obtained in blank runs using either 50% H_2O_2 or TBHP as oxidant.

	50% H_2O_2 Blank			TBHP Blank		
T [°C]	**2 min**	**4 min**	**16 min**	**2 min[a]**	**4 min[a]**	**16 min [a]**
70	0	0	0	0	0	2
90	0	0	0	1	1	5
110	0	0	0	4	6	11
130	0	0	0	3	5	16

[a] benzaldehyde selectivity >99%.

1.2 Catalytic Activity of Support. The same time-temperature matrix was applied to test the catalytic activity of the supports with 50% H_2O_2 as oxidant and 25 mg mmol^{-1} support under otherwise identical conditions (1 mL MeCN, 1 mmol benzyl alcohol and 1 mmol *o*-xylene as internal standard).

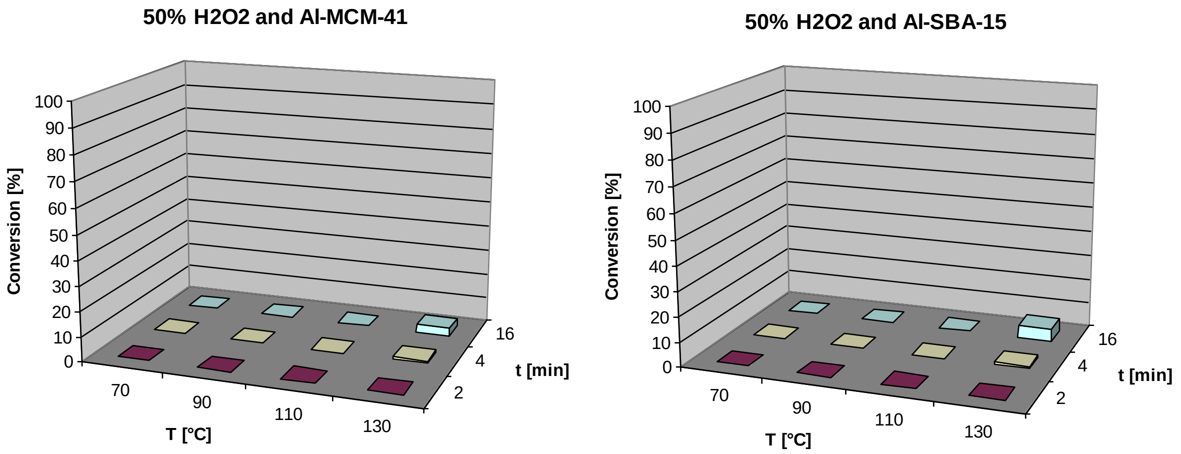


Figure 2. Conversions with Al-MCM-41 or Al-SBA-15 supports and 50% H_2O_2 as oxidant.

Table S3. Conversions obtained with either Al-MCM-41 or Al-SBA-15 / 50% H_2O_2.

	50% H_2O_2/ Al-MCM-41 support			50% H_2O_2/ Al-SBA-15 support		
T [°C]	**2 min**	**4 min[a]**	**16 min[a]**	**2 min**	**4 min[a]**	**16 min[a]**
70	0	0	0	0	0	0
90	0	0	0	0	0	0
110	0	0	0	0	0	0
130	0	1	3	0	1	5

[a] benzaldehyde selectivity >99%.

As can be seen from Figure 1, only a very small conversion (3-5%) to the benzaldehyde at higher temperatures >130 °C using the two supports was observed.

1.3 Catalytic Activty of Fe/Al-SBA-15. Catalytic oxidations of benzyl alcohol were performed in microwave batch with 25 mg mmol^{-1} Fe/Al-SBA-15 catalyst (~0.5 wt% Fe) under otherwise identical reaction conditions. Both 50% H_2O_2 and TBHP (5-6 M in *n*-decane) were used as oxidant.

1.3.1 Fe/Al-SBA15 with 50% H_2O_2 as Oxidant. Higher conversions were achieved at the expense of a lower benzaldehyde selectivity, with higher amounts of benzoic acid being formed in the reaction mixture.

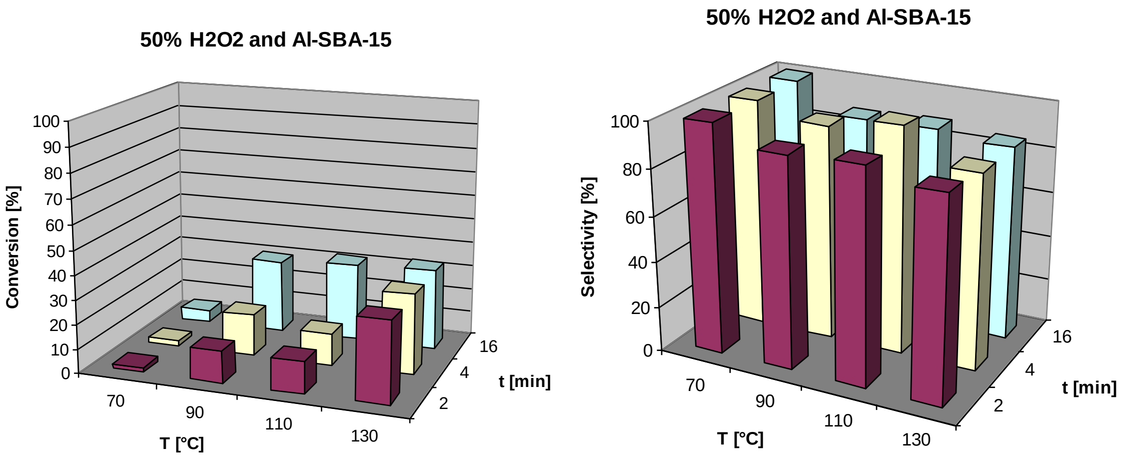


Figure 3. Conversions (left) and corresponding selectivities (right) obtained using 50% H_2O_2 and Fe/Al-SBA-15 (0.5 wt% Fe) as catalyst.

Furthermore it is evident from the obtained data that because of the low oxidizing efficiency (converted moles benzaldehyde per mole oxidant) of 50% H_2O_2 already at 130 °C and 2 min all the oxidant is obviously used up and the highest conversion achievable is 33 % at a selectivity of 88% (the H_2O_2 consumption can also be monitored by HPLC at 215 nm as peak at 1.0 min). The highest conversion achieved without causing a drop of selectivity below 90% was 17% at 90°C and 4 min reaction time.

Table S4. Conversions and corresponding selectivities obtained using 50% H_2O_2 and Fe/Al-SBA-15 (0.5 wt% Fe) as catalyst.

		Conversion			Benzaldehyde-Selectivity	
T [°C]	**2 min**	**4 min**	**16 min**	**2 min**	**4 min**	**16 min**
70	2	2	5	>99	>99	>99
90	13	**17**	30	92	**94**	87
110	13	13	32	93	99	88
130	33	33	33	88	85	85

1.3.2 Fe/Al-SBA-15 with t-Butyl Hydroperoxide (TBHP) as oxidant. The use of TBHP led to a much higher oxidizing efficiency than 50% H_2O_2 as can be seen in Figure 4 where the highest conversion obtained was 49 % at 59% benzaldehyde selectivity, although the same excess was used (2 equiv). The highest conversion achievable without causing a drop of selectivity below 90% was 16% at 90 °C and 4 min reaction time, which is almost the same reaction rate as observed with 50% H_2O_2.

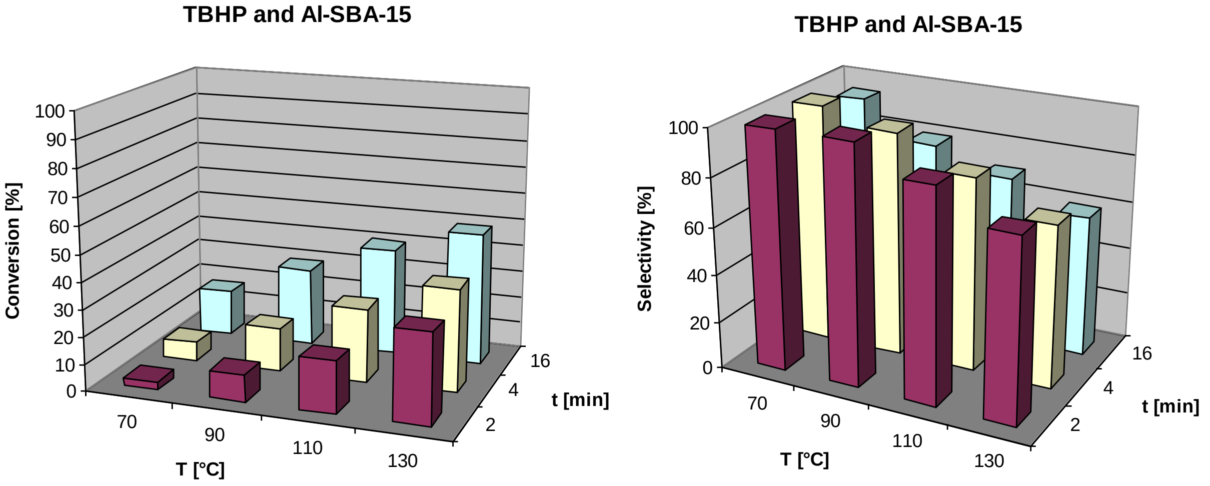
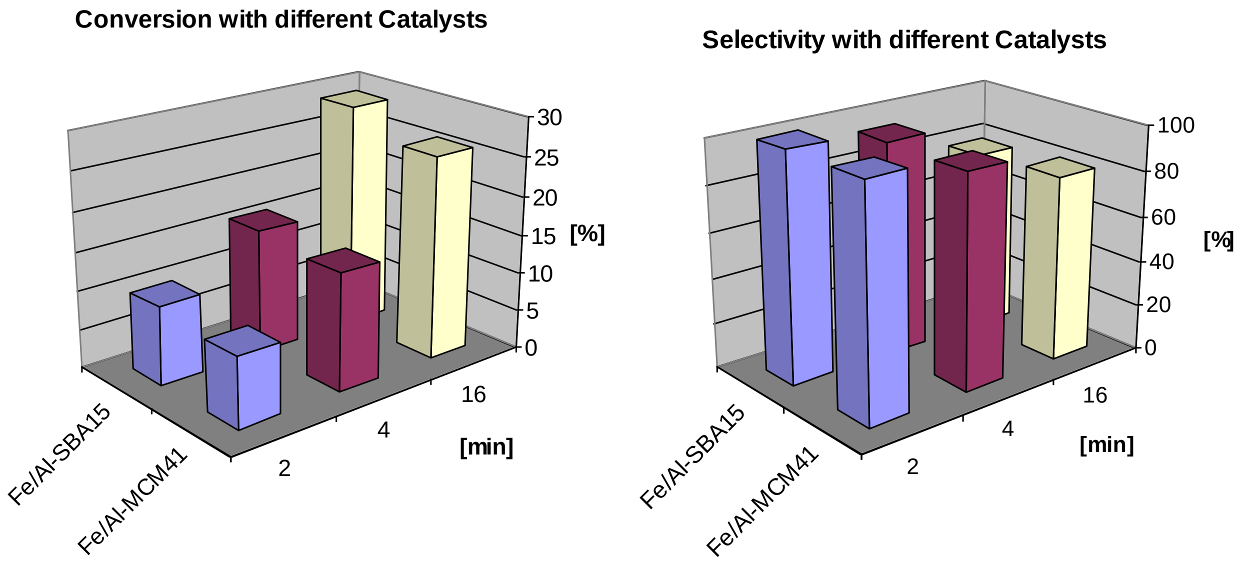


Figure S4. Conversions and corresponding selectivities obtained using TBHP and Fe/Al-SBA-15 (0.5 wt% Fe) as catalyst.

Table S5. Conversions and corresponding selectivities obtained using TBHP and Fe/Al-SBA-15 (0.5 wt% Fe) as catalyst.

		Conversion			Benzaldehyde-Selectivity	
T [°C]	**2 min**	**4 min**	**16 min**	**2 min**	**4 min**	**16 min**
70	3	7	17	>99	>99	94
90	10	**16**	29	>99	**94**	79
110	19	27	40	89	81	70
130	33	38	49	76	68	59

1.4 Catalyst Tests. A comparison of iron oxide supported on two different supports was performed in microwave batch in the already described manner. TBHP in *n*-decane was used instead of H_2O_2 because of the observed higher oxidation economy/ efficiency. All experiments were done in MeCN as solvent, 90 °C and the conversion/selectivity monitored using a calibrated HPLC method after 2, 4, 16 min reaction time. These comparison runs did however show, that there are virtually no differences in yield or selectivity, when switching between these two supports.


Conversion with different Catalysts

Selectivity with different Catalysts

Figure S5. Conversions and corresponding selectivities obtained using TBHP as oxidant and 2 different catalysts (~ 0.5 wt% Fe) in MeCN at 90 °C.

Table S6. Comparison of the conversion/ selectivity obtained with four different types of catalysts using TBHP (see conditions from table S1) as oxidant at 90 °C.

90 °C	Fe/Al-SBA15		Fe/Al-MCM41	
Time [min]	Conv [%]	Sel [%]	Conv [%]	Conv [%]
2	10	>99	9	>99
4	16	94	15	93
16	29	79	26	81

1.5 Solvent Screenings. A screening of 4 different sufficiently oxidation resistant solvents (MeCN, acetone, toluene, dioxane) was performed in a similar manner as for the catalysts. As catalyst Fe/Al-SBA15 was used. The reaction rate achieved using acetonitrile as solvent exceeded all other solvents significantly.

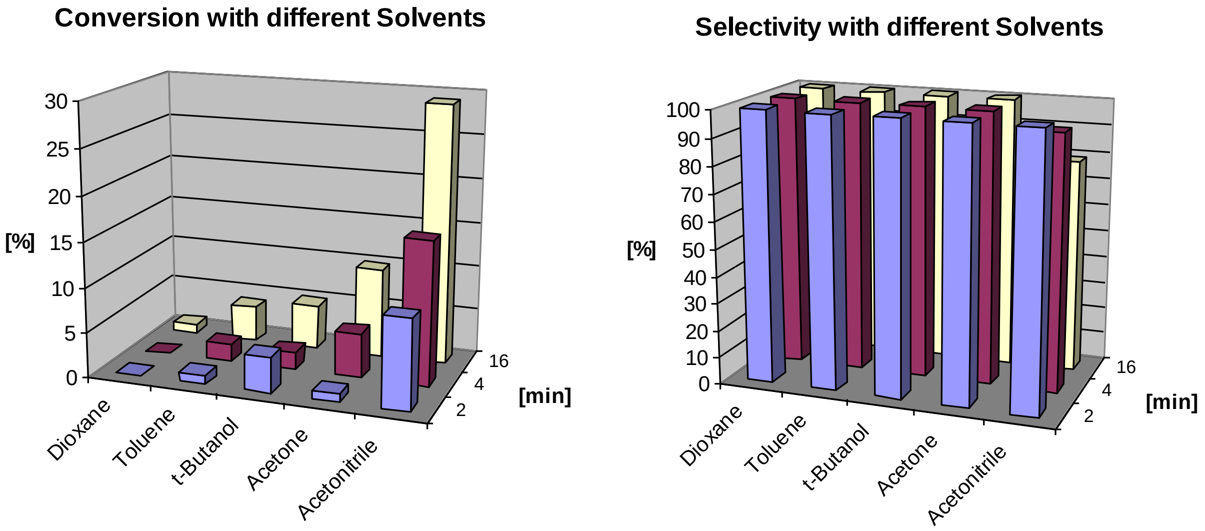


Figure S6. Conversions and corresponding selectivities obtained using TBHP as oxidant and five different solvents with Fe/Al-SBA15 (0.5 wt% Fe) at 90 °C.

Table S7. Optimization study using TBHP (see conditions from Table S1)as oxidant and showing the influence of the solvent on the reaction at 90 °C.

90 °C	Acetonitrile		Acetone		Toluene		t-Butanol		Dioxane	
Time [min]	Conv [%]	Sel [%]	Conv [%]	Conv [%]	Conv [%]	Sel [%]	Conv [%]	Sel [%]	Conv [%]	Sel [%]
2	10	>99	1	4	4	>99	4	>99	0	>99
4	16	94	5	2	2	>99	2	>99	0	>99
16	29	79	10	5	5	>99	5	>99	1	>99

2. Aerobic Oxidation in Continuous Flow

Selected HPLC chromatograms presenting volume-dependent conversion data as well as purity profiles obtained during the optimization work outlined in the main part of the paper. In addition, ICP-MS data collected in leaching tests is available.

2.1 Solvent and Oxygen-Pressure Effects on Selectivity and Catalyst Lifetime. Striving to reduce the initially observed high backpressure generated by the mesoporous silica supported iron catalyst (Fe/Al-SBA15), *n*-heptane doped with dioxane was tested as improved solvent system for the aerobic oxidation of benzyl alcohol. This experiment indicated a high initial activity of the catalyst, followed by a very rapid decrease in catalyst activity, using a very high oxygen pressure (50 bar) and a maximal oxygen flow-rate (50 bar, 98 mL min^{-1}). Under these conditions, dibenzyl ether formation was the main reaction to convert benzyl alcohol.

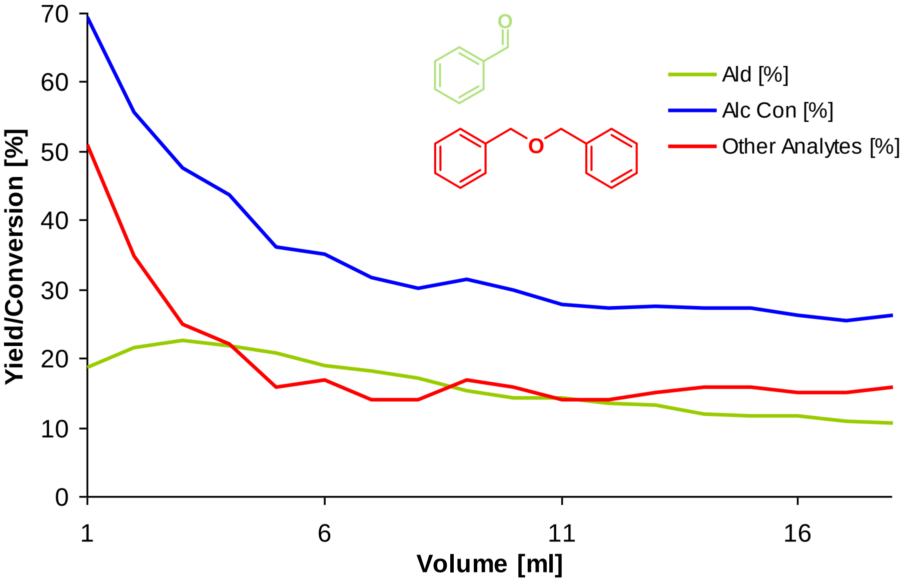


Figure S7. Decrease of catalyst activity in the oxidation of benzyl alcohol on Fe/Al-SBA15 0.1 M in *n*-heptane/dioxane 9:1 at 120 °C, 5 mol% TEMPO, 0.22 mL min^{-1}, 50 bar O_2 at 98 ml min^{-1}. Conversions at different volumes were calculated from HPLC areas using 1 equiv o-xylene as internal standard, added prior to the reaction. The amount of dibenzyl ether was calculated as gap to 100%; GC-MS analysis shows that there are no other relevant analytes in the mixture).

Moreover, the conversion rate of benzyl alcohol to benzaldehyde vs volume was examined under slightly modified conditions using a 0.1 M solution in *n*-heptane/dioxane 2:1 at 140 °C, 0.22 mL min^{-1}, 25 bar O_2 at 5 mL min^{-1} and 5 mol% TEMPO as co-catalyst.

Despite the low leaching tendency of the catalyst (see Table S8), prolonged operation of the iron oxide catalyst resulted in a constantly decreasing conversion rate. We believe that deactivation/poisoning phenomena are responsible for this decrease (see Figure S8).

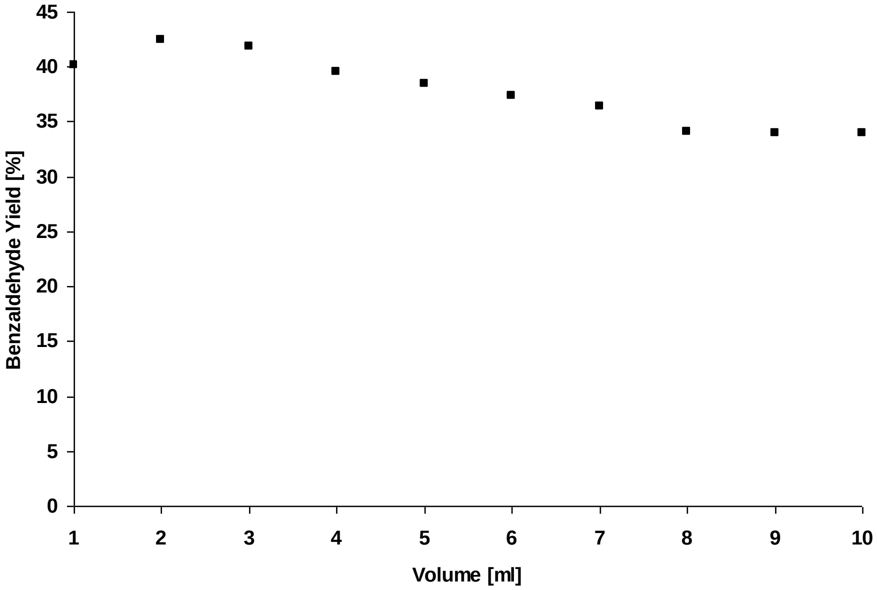


Figure S8. Decrease of catalyst activity using an optimized solvent mixture of *n*-heptane/dioxane 2:1 at 140 °C, 0.22 mL min^{-1}, 25 bar O_2 at 5 mL min^{-1}, 0.1 M, 5 mol% TEMPO, Fe/Al-SBA15 (1 wt% Fe)

2.2 Leaching Tests. Samples from selected optimization runs were subjected to ICPMS analysis. 5 ml fractions of the reactions were collected and the solvent evaporated. The samples were collected at three sets of different conditions, listed in Table S8-S9. The residues were quantitatively transferred with 1 mL nitric acid/fraction into 12 mL polystyrene tubes and measured directly with an Agilent 7500ce inductively coupled plasma mass spectrometer. Fe was quantitatively determined at m/z 56 using He as collision gas. A calibration was performed with an external calibration curve established from 1.000 g Fe L^{-1} standard. Indium was used as an internal standard.

A first set of experiments refers to operation of the catalyst without substrate (benzyl alcohol) at optimum conditions, under single-pass operation of the reactor in a *n*-heptane/dioxane 2:1 mixture at 140 °C, 25 bar oxygen, 5 mL min^{-1} oxygen flow, 0.22 mL min^{-1} liquid flow rate and 5 mol% TEMPO (also see Table 2, entry 3 and Figure S9).

Table S8. ICP-MS data from leaching tests without benzyl alcohol at optimized conditions.

Sample	T [°C]	Fraction	Solvent	TEMPO	Benzyl alcohol	Oxygen addition	Fe [µg]
W-S-B	rt.	flushing blank	*n*-heptane/dioxane 2:1	none	none	none	0.41
W-S 1	140	1	*n*-heptane/dioxane 2:1	yes	none	yes	1.05
W-S 2	140	2	*n*-heptane/dioxane 2:1	yes	none	yes	0.19
W-S 3	140	3	*n*-heptane/dioxane 2:1	yes	none	yes	0.37

A second set of conditions was set up to investigate iron leaching at optimum conditions for single-pass operation of the reactor in a *n*-heptane/dioxane 2:1 mixture at 140 °C, 25 bar oxygen, 5 ml min^{-1} oxygen flow, 0.22 mL min^{-1} liquid flow rate and 5 mol% TEMPO (also see Table 2, entry 3 and Figure S9). A blank sample was collected in the form of a “process blank” at target temperature and with oxygen addition, to see possible effects on leaching caused by oxygen at higher temperatures.

Table S9. ICP-MS data from leaching tests with benzyl alcohol at optimized conditions.

Sample	T [°C]	Fraction	Solvent	TEMPO	Benzyl alcohol	Oxygen addition	Fe [µg]
S-B-O2	140	process blank	*n*-heptane/dioxane 2:1	none	none	yes	0.22
S-1	140	1	*n*-heptane/dioxane 2:1	yes	yes	yes	0.16
S-2	140	2	*n*-heptane/dioxane 2:1	yes	yes	yes	0.18
S-3	140	3	*n*-heptane/dioxane 2:1	yes	yes	yes	0.17

Both sets of experiments showed only minor differences in iron content of the samples as compared to the collected blanks and seem to be within an experimental error. It would be expected that operation of a heterogeneous catalyst with homogeneous reaction mechanism should result in an analytical iron value at least magnitudes higher than the blank value, which is not the case in these experiments.

In order to complement the results from the above leaching studies at optimum conditions, the previously used optimized solvent mixture (*n*-heptane/dioxane 2:1) was substituted with pure *n*-heptane. Also in these tests, no iron leaching could be observed.

Table S10. ICP-MS data from leaching tests under non-optimized conditions using *n*-heptane as solvent.

Sample	T [°C]	Fraction	Solvent	TEMPO	Benzyl alcohol	Oxygen addition	Fe [µg]
H-B	rt.	flushing blank	*n*-heptane	none	none	none	0.11
H-B-O2	140	process blank	*n*-heptane	none	none	yes	0.18
H 1	140	1	*n*-heptane	yes	yes	yes	0.14
H 2	140	2	*n*-heptane	yes	yes	yes	0.05
H 3	140	3	*n*-heptane	yes	yes	yes	0.26

2.3 Solvent Effects on Catalyst Selectivity. A switch between coordinating (dioxane) and non-coordinating (*n*-heptane) reaction solvent was found to alter selectivity of the reaction, as can be seen in the chromatogram overlay of the reaction performed either in one of the pure solvents, or in an optimized mixture of the two. Whereas the use of dioxane leads to a relatively pure conversion at low conversion rate, *n*-heptane leads to a high catalyst activity, but also channels the reaction towards alkylation products. The 2:1 mixture of *n*-heptane and dioxane significantly improved both conversion rate and selectivity to benzaldehyde. Benzyl formate, in later recirculation experiments identified as side-product possibly indicative of catalyst deactivation by fouling, was found in traces.

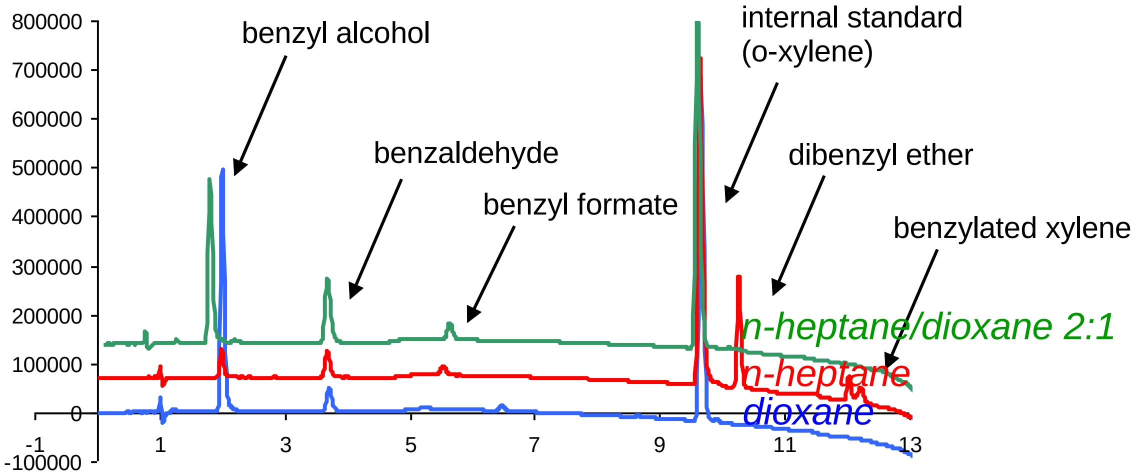


Figure S9. HPLC at 215 nm showing the occurrence of undesired alkylation reactions depending on solvent composition (140°C, 0.22 mL min^{-1}, 5 mol% TEMPO, 25 bar O_2 at 5 mL min^{-1}). The identity of the peaks was confirmed by referencing against genuine samples of the compounds and GC/MS analysis of the product mixture.

2.4 Catalyst Deactivation during Recirculation. Recirculation was performed at 120 and 140 °C for 7 h at 0.22 mL min^{-1}, 5 mol% TEMPO, 25 bar O_2 at 5 mL min^{-1}. Using *n*-heptane/dioxane 2:1 as solvent of choice for the previously performed single-pass optimizations, conversions were coming to a halt at 30-50 % conversion of benzyl alcohol to benzaldehyde, indicating catalyst deactivation. Inspection of the corresponding chromatograms at 215 nm for different reaction times revealed that benzyl formate, which is constantly accumulating during the reaction, is formed in increasing amounts towards the point of complete deactivation of the catalyst, until no benzyl alcohol is converted any more, and thus also formation of benzyl formate stops. Figure S10 shows a sample chromatogram taken after 7 h at 120 and 140 °C, showing the large amount of benzyl formate accumulated at full catalyst deactivation. The catalyst also appears to be deactivated more quickly at 140 °C, as compared to 120 °C.

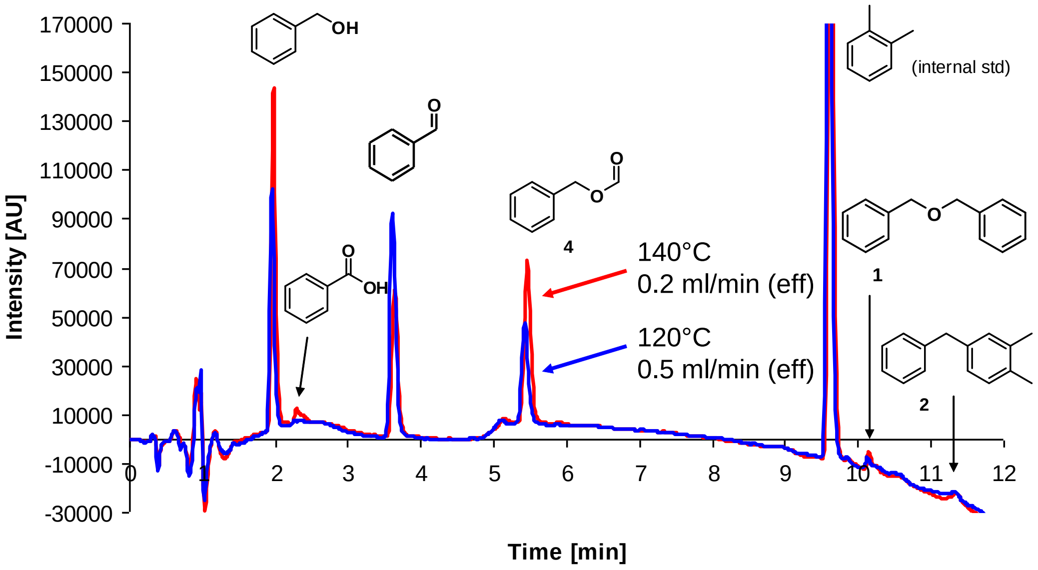


Figure S10. HPLC chromatogram at 215 nm of the recirculation runs at 120 (blue) and 140 °C (red) after 7 h at 0.22 mL min^{-1}, 5 mol% TEMPO, 25 bar O_2 at 5 mL min^{-1} (50 and 30%

converted to benzaldehyde). The identity of the peaks was confirmed by referencing against genuine samples of the compounds and GC/MS analysis of the product mixture.

2.5 Influence of TEMPO Loading on Purity Profiles in Recirculation. A reinvestigation on the effects of TEMPO-loading on purity profiles, with emphasis on recirculation operation led to the unexpected result that all observed side-reactions including all alkylation reactions such as dibenzylether formation and Friedel-Crafts alkylation reactions, as well as benzyl formate formation, indicative of catalyst deactivation, can be suppressed by simply increasing the TEMPO loading beyond a critical concentration of 10 mol%. Moreover, it should be noted, that despite the use of pure *n*-heptane as solvent, the formation of alkylation products was not taking place.

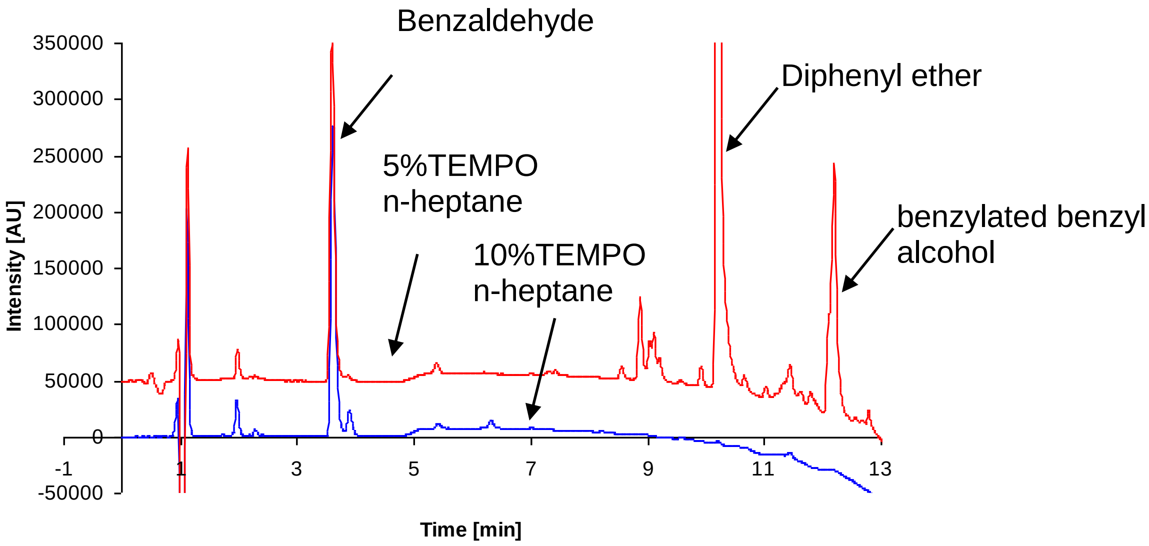
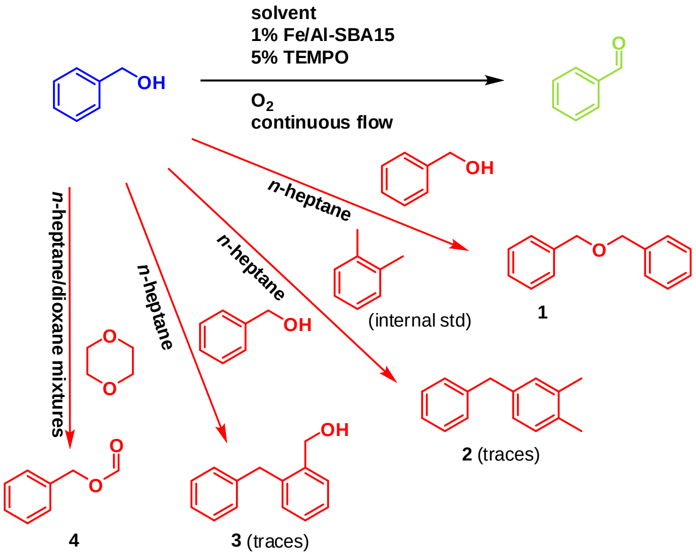


Figure S11. HPLC at 215 nm of benzyl alcohol oxidation performed at 120 °C after 3 h of continuous recirculation using 5 or 10 mol% TEMPO and 0.22 mL min^{-1}, 35 bar O_2 at 5 mL min^{-1}. The identity of the peaks was confirmed by referencing against genuine samples of the compounds and GC/MS analysis of the product mixture.

2.6 Summary of Side-Reactions in Different Solvents.



Scheme S12. Dependence of byproduct formation on reaction conditions.