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Selective oxidation of alcohols by combinatorial catalysis

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Abstract

High-throughput synthesis and screening of polyoxometalate (POM) and supported-metal libraries have been developed for the selective aerobic oxidation of alcohols to the corresponding aldehydes/ketones in the liquid phase. Libraries consisting of 96 catalysts were prepared in multi-well reactors and screened for catalytic activity using TLC, GC and NMR detection methods. Promising hits identified in the high-throughput primary screens were successfully scaled up and optimized in conventional laboratory test units. Isolated yields confirm high selectivities of more than 90% with quantitative conversions. Substrates tested include primary and secondary alcohols. Specific results will be presented for hydroxymethyl-substituted heterocycles and bicyclo-octanols.

Keywords: Catalysis; Alcohol oxidation; Formylimidazole; Bicyclo-octanone

1. Introduction

The selective liquid-phase oxidation of alcohols to the corresponding aldehydes/ketones is a desirable transformation of significant commercial interest in the fine chemicals and pharmaceutical industries. Many alcohol substrates are still oxidized by stoichiometric amounts of strong oxidants like $KMnO_4$ or CrO_3. These processes accumulate large inorganic salt rich waste streams and also use toxic metals. Nevertheless, the yields of the aldehydes/ketones are often low [1–7]. A catalytic process, that operates under mild reaction conditions and allows for high selectivities, is therefore highly desirable. New developments in catalytic alcohol oxidation have been recently reviewed [8].

We have developed a combinatorial approach to the discovery and optimization of catalysts for selective aerobic alcohol oxidation. High-throughput robotic synthesis and screening of polyoxometalate (POM) and supported-metal libraries have enabled the discovery of highly selective catalysts for the oxidation of various diverse alcohol substrates. Libraries consisting of 96 catalysts were prepared in multi-well reactors and screened for catalytic activity using various analytical methods. Hits identified in the high-throughput primary screens were successfully scaled up and optimized in conventional laboratory test units (Parr bombs for pressure reactions and refluxers for ambient pressure). The application of combinatorial approaches to various types of screening including organic liquid-phase transformations has been reviewed [9].

In this paper, we report the selective oxidation of 2-butyl-5-hydroxymethyl-imidazole to the corresponding aldehyde, a pharmaceutically important intermediate. Two heterogeneous catalyst systems (POM and supported metals) were used for

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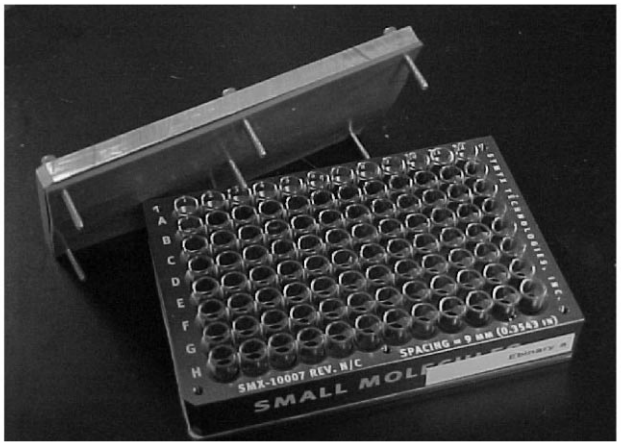
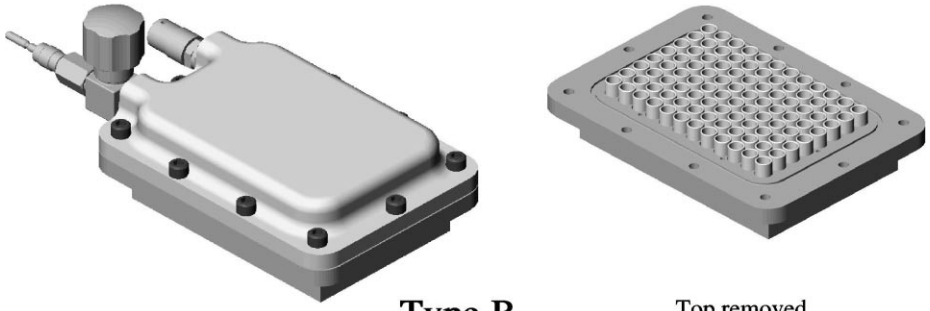
this reaction. The diversity and universality of the supported-metal platforms were also tested by its usage for the oxidation of a number of primary and secondary alcohols. While homogeneous catalysts often enable higher rates of reaction to be obtained, heterogeneous catalysts are preferred because these catalysts are more easily isolated from the product and lend themselves more favorably to recycling.

2. Experimental

Ninety-six-well high-throughput high-pressure batch reactors were designed and built. Two reactor types are shown in Fig. 1. Catalyst libraries for primary screening were synthesized in-situ by using Library Studio™ and Impressionist™ software (Symyx Technologies, Santa Clara, CA). The metal precursor solutions were dispensed automatically by Cavro™ robots and the catalysts were prepared by subsequent drying and calcination steps. Wet-impregnation techniques of pre-loaded carriers, freeze-drying methods, and slurry-dispensing of preformed solid catalysts were also employed. The reactor vials were then filled with calculated amounts of reagents/solvent and the reactor block was pressurized, either by sealing and heating to the required temperature to generate high pressure in the sealed vials or by pressurizing with reactants or inert gas through the common headspace, depending on which



Type A



Type B

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Fig. 1. Ninety-six-well parallel batch reactors. Type A: aluminum microplate contains 96 wells with 1 ml disposable glass liners that are sealed by teflon-faced silicone seal. The reactor is compatible to organic reagents/solvents that can tolerate reaction temperatures up to about 200°C. Type B: an 8×12 array of 1 ml vials is assembled in a reactor with common headspace. The reactor can tolerate temperature up to 200°C and pressures up to 1000 psi (60 bar). Patent pending.

Table 1
Supported-metal catalyzed aerobic oxidation of 2-butyl-5-hydroxymethyl-imidazole

Catalyst	Amount of catalyst (mg)	Alcohol (mg)	Solvent	Air pressure (psi)	Time (h)	Temperature (°C)	Conversion (%)	Selectivity (%)
C1	700	310	EtOAc	200	8	150	100	>95
C2	200	160	EtOAc	200	4	150	>95	>95
C3	200	160	EtOAc	200	4	150	>95	>95
C4	200	160	EtOAc	200	4	150	100	>95

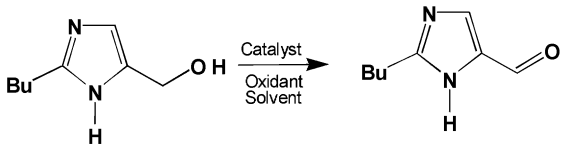
reactor type was employed. Following the reaction, the reactor block was cooled and the reaction products were analyzed by a modified TLC procedure, fast serial GC, and NMR.

A typical experimental procedure for the scale-up experiments was as follows: 100 and 300 ml commercial stainless steel reactors were loaded with the ingredients and the amounts are shown in Tables 1 and 3, respectively. The reactor was sealed, pressurized with air, and was heated at the temperature for the required number of hours. The oxidized product was recovered by filtering out the solid catalyst residue, washing the catalyst residue and the reaction vessel with a suitable solvent (e.g. methanol), and concentrating the combined filtrate and washings under vacuum.

3. Results and discussion

3.1. Oxidation of 2-butyl-5-hydroxymethyl-imidazole to 2-butyl-5-formyl-imidazole

2-Butyl-5-formyl-imidazole is an important intermediate in synthesis sequences of certain diuretic and antihypertensive compounds (Scheme 1). Recently, this transformation was reported by two different



2-butyl-5-hydroxymethylimidazole 2-butyl-5-formylimidazole

Scheme 1. Oxidation of 2-butyl-5-hydroxymethyl-imidazole to 2-butyl-5-formylimidazole.

research groups in the presence of Pt/Bi catalyst systems using H_2O_2 [10] or air [11] as the oxidant. High yields of ~90% were achieved. However, the use of noble metals suffers from disadvantages like Pt leaching, the requirement of alkaline conditions (1 equivalent of NaOH usually added), higher cost, and elaborate regeneration. Therefore, a need existed for highly selective, low-cost, and easy to reuse catalyst systems that do not require alkaline conditions.

We investigated the imidazole alcohol oxidation using non-noble metal-based libraries. We screened 5000 samples in 4 weeks encompassing two of our oxidation platforms (POM and supported metal). Trends observed in the primary screen were reproduced in the secondary screen. Information gained from one platform (catalyst composition, reaction conditions, solvents, additives, etc.) was used to guide experiments in the other platform. Two classes of proprietary catalysts were identified which give >90% yield.

3.1.1. Polyoxometalates

POMs represent a general class of oxidation catalysts and the methods have been disclosed for the oxidation of alcohols wherein the reaction is stopped at the aldehyde or ketone, thus avoiding over oxidation to the carboxylic acid [12–15].

Initial primary screening of diverse POM libraries showed that V-containing Keggin type POMs are highly selective for the above-mentioned oxidation. PVMo-based POMs with ammonium as the counter cation were found to be highly efficient. Optimization of the composition and scale up of the lead catalyst were carried out using commercially available autoclave reactors. The oxidation reaction was tested in various solvent systems like *t*-butanol, EtOAc, CH_3CN, MIBK, etc. The air pressure was varied between 200 and 400 psi, while the catalyst and

alcohol loading were varied between 200–700 mg and 160–340 mg, respectively. The reaction was also carried out at various temperatures depending upon the type of solvent used.

NH_4-PVMo gave ~100% conversion and ~100% selectivity (NMR data) at 150 and 120°C in EtOAc and MIBK, respectively. The time needed to achieve this conversion was 8 and 9 h for the reaction at 150 and 120°C, respectively. The air pressure in both the cases was 200 psi.

3.1.2. Supported metals

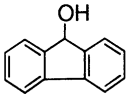
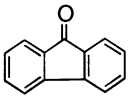
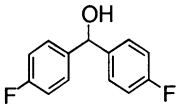
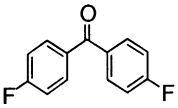
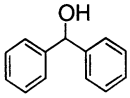
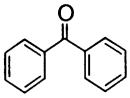
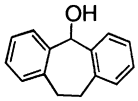
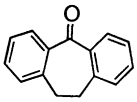
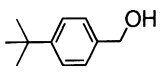
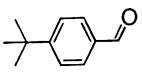
The oxidation of imidazole alcohol was also solved by high-throughput screening of the supported-metal platform. A few examples are given in Table 1. The conversion and selectivity were obtained by ^{1}H NMR analysis.

It is seen that complete conversion can be accomplished in less than 8 h reaction time at a moderate temperature of 150°C and air pressure of 200 psi. The amount of solvent used in all cases was 20 ml.

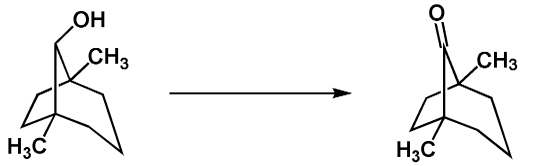
3.2. Oxidation of benzylic alcohols to the corresponding aldehydes and ketones

The above-mentioned supported-metal catalyst libraries were found to be a convenient and efficient platform for the general oxidation of benzylic alcohols to aldehydes and ketones under relatively mild conditions. Solvent screening identified MIBK as an efficient solvent. The typical experimental procedure involved heating the reaction mixture in MIBK solvent under an atmosphere of oxygen at ambient pressure. The desired aldehyde and ketone products were isolated in excellent yields by simple filtration of the reaction mixture followed by concentration under reduced pressure. Additional purification, if needed, was accomplished by flash column chromatography. Representative examples are listed in Table 2. The reaction times given in the table are the times required to achieve quantitative conversion as monitored by GC–MS. The results clearly show that high yields can be obtained for a number of diverse benzylic alcohol substrates. Because the benzylic protons are activated,

Table 2
Supported-metal catalyzed aerobic oxidation of alcohols to aldehydes and ketones[a]

Entry	Alcohol	Product	Yield (%)	Time (h)
1			91	8
2			92	36
3			91	24
4			92	8
5			70[b]	48

[a] Reaction conditions: temperature = 150°C, 1 atm O_2, MIBK solvent. Yields correspond to isolated material of >95% purity.
[b] Yield based on GC–MS, GC–MS selectivity = 100%.



1,5-dimethyl-bicyclo-
[3,2,1]-octan-8-ol

1,5-dimethyl-bicyclo-
[3,2,1]-octan-8-one

Scheme 2. Oxidation of 1,5-dimethyl-bicyclo-[3,2,1]-octan-8-ol to 1,5-dimethyl-bicyclo-[3,2,1]-octan-8-one.

a reaction temperature of only 105°C was sufficient for the transformation. Obviously, lower reaction temperatures of <100°C resulted in dramatically longer reaction times, whereas higher temperatures (∼140°C) led to more pronounced side-product formation as well as oxidative cleavage of the solvent. In addition, we have shown that these reactions can be carried out at ambient pressure, and therefore high-pressure equipment is not needed to accomplish the selective oxidation.

3.3. Oxidation of 1,5-dimethyl-bicyclo-[3,2,1]-octan-8-ol to the ketone

1,5-Dimethyl-bicyclo-[3,2,1]-octan-8-one and the corresponding ketals are intermediates in the fragrance industry and are being used as perfume additives [16,17]. The precursor alcohol was synthesized from readily available 1,5-dimethyl-cyclo-octadiene according to a literature procedure [18]. The bicyclo-octanol alcohol oxidation was reported to give 73% conversion using 10% Pt/coal, dioxane, O_2, 80°C, 18 h [16] (Scheme 2).

Supported-metal libraries were found to be efficient catalyst systems for this reaction. Several hits were identified within the supported-metal platform. The high-throughput screening protocol encompassed 14 redox metals, various supports, as well as 15 solvents. The lead catalyst was scaled-up and optimized. Catalytic test results are given in Table 3. The conversion and selectivity were obtained by GC–MS analysis.

Toluene (150°C/500 psi air/20 h) gave 100% alcohol conversion and 90% selectivity, and MIBK (150°C/500 psi/7 h) gave 100% alcohol conversion and 95% selectivity. However, both solvents were partly decomposed (oxidized) under these reaction conditions. Bicyclo-octanol is a non-activated secondary alcohol and requires higher temperatures to achieve complete conversions within acceptable reaction times. The absence of alpha-protons makes the oxidative decomposition and cleavage more difficult. However, overoxidation to the Bayer–Villiger product could occur and is drastically favored once all the alcohol has been consumed. Therefore, termination of the reaction at the stage of complete conversion is essential for high selectivities.

Chlorobenzene was found to be the best solvent that converted all the alcohol in 34 h at 140°C/500 psi air with a selectivity >90%. The conversion as a function of reaction time is given in Fig. 2. *N*-octane was found to be a viable and advantageously

Table 3
Supported-metal catalyzed aerobic oxidation of 1,5-dimethyl-bicyclo-[3,2,1]-octan-8-ol to 1,5-dimethyl-bicyclo-[3,2,1]-octan-8-one

Catalyst	Amount of catalyst (mg)	Alcohol (mg)	Solvent (ml)	Air pressure (psi)	Time (h)	Temperature (°C)	Conversion (%)	Selectivity (%)
C1	600	320	MIBK 30	400	7	150	90	90
C1	600	320	MIBK 30	500	7	150	100	95
C5	1200	320	Toluene 30	500	20	150	100	90
C5	1200	320	Chlorobenzene 30	500	32	140	95	>90
C5	1200	320	Chlorobenzene 30	500	34	140	100	>90
C5	3600	960	Chlorobenzene 30	500	57	140	95	>90
C5	1200	320	*n*-Octane 30	500	38	140	100	>90
C5	3600	1200	*n*-Octane 30	500	42	140	100	>80
C5	1200	1200	*n*-Octane 30	500	42	140	100	>80
C5	1200	1200	*n*-Octane 30	500	40	135	100	>80
C5	1200	1200	*n*-Octane 30	500	40	130	100	>80
C5	1200	1200	*n*-Octane 30	500	40	125	100	>80
C5	1200	1200	*n*-Octane 30	500	75	120	>90	>90

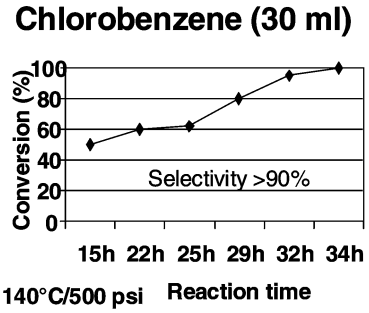


Fig. 2. Supported-metal catalyzed aerobic oxidation of 1,5-dimethyl-bicyclo-[3,2,1]-octan-8-ol to 1,5-dimethyl-bicyclo-[3,2,1]-octan-8-one in chlorobenzene solvent, catalyst 1.2 g and alcohol 0.32 g.

non-chlorinated alternative solvent but longer reaction times are required when compared to chlorobenzene (125–140°C/500 psi/40 h gives 100% conversion and >80% selectivity).

4. Conclusion

Combinatorial synthesis and screening of heterogeneous catalysts for liquid-phase alcohol oxidation have been developed. The workflow for platform development and lead discovery has been established. We found that POMs and supported-metals are highly useful platforms for the (aerobic) selective oxidation of broad classes of aromatic carbocyclic and heterocyclic benzylic alcohols as well as secondary aliphatic alcohols that contain no reactive alpha-protons. High-throughput synthesis and screening allowed ∼5000 samples to be screened in less than 1 month. Numerous hits identified in the primary screen were scaled and quickly optimized in conventional lab test units. The developed leads are simple, robust, low-cost, reusable/regenerable and therefore have potential application in general oxidation processes.

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