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ARTICLE TYPE

Potassium formate as a small molecule switch: controlling oxidation/reduction behaviour in a two-step sequence

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A one-pot reaction sequence is described in which the addition of one compound allowed switching between simultaneously occurring oxidation and reduction reactions.

In the past decade, multi-step one-pot procedures have attracted an increasing interest of the chemical community.¹ Combining multiple transformations in one reaction vessel renders sequences more cost-effective as fewer work-up and purification steps are required. Multistep one-pot procedures are therefore considered to contribute to a more sustainable way of producing chemicals. A major challenge in the design of multi-step sequences is the compatibility of the involved substrates, intermediates and reagents or catalysts.

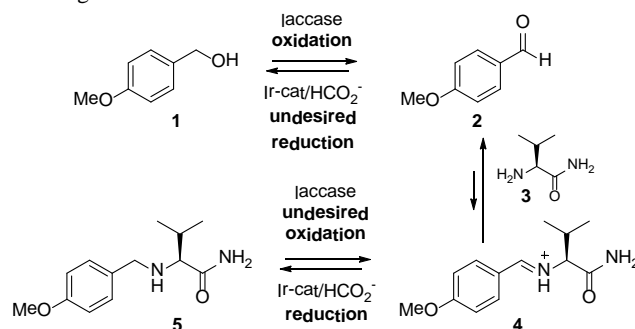
A particular challenge is seen in reactions in which opposing or counteracting reagents or catalysts (acid/base, oxidator/reductor) are used simultaneously.² Incompatibilities between opposing catalysts have been resolved by immobilization on insoluble polymers³ or encapsulation in sol-gels.⁴ Such behaviour is advantageously used in for example dynamic kinetic resolutions and related procedures⁵ in which secondary alcohols are racemised via the corresponding ketone through a redox equilibrium induced by a single catalyst. A remarkable case has been described by Kroutil et al., in which racemisation and reduction were performed stepwise by a single alcohol dehydrogenase (ADH). Switching between non-selective oxidation and enantioselective reduction occurred by removal of the co-substrate acetone and addition of *i*-propanol.⁶

In a different strategy, enantioselectivity has been achieved via chemical oxidation by a metal-catalyst, and simultaneous reduction by ADH in the same reaction vessel.⁷ As shown in this approach, performing multistep reactions in a consecutive manner does not per se require the adaptation of the catalysts or reactants used.

In this paper, we describe a model one-pot reaction system with counteracting catalysts, in which the oxidant acts on the starting compound and the final product, while the reductant acts on the intermediate product leading to both starting material and

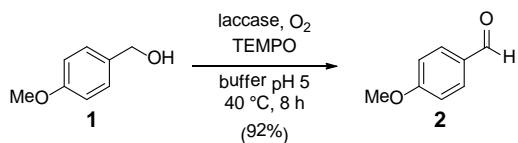
final product. We have shown that by introducing a specific reagent, the reaction can be efficiently steered into one direction by 'switching-off' the oxidation and simultaneously 'switching on' the reduction, with all catalysts present from the start of the reaction. This is the first example of a reagent-mediated switch between two counteracting catalytic systems, which can now be efficiently performed in one pot in the desired sense.

The two-step sequence involves the aqueous enzymatic oxidation of *p*-methoxybenzyl alcohol (**1**) to anisaldehyde (**2**), which in the presence of valinamide (**3**) is in equilibrium with iminium intermediate **4** (Scheme 1). For the enzymatic oxidation laccase was selected because of its outstanding oxidative performance on benzylic systems and its broad substrate selectivity.⁸ The iminium ion **4** reacts further in an iridium-catalyzed reductive amination with formate as the hydride source to yield amine **5**. However, since the latter product is readily oxidized by laccase, and benzaldehyde is also prone to reduction by the iridium catalyst, this process does not lead to any product formation when carried out in a single vessel. The major challenge therefore was to limit the undesired reverse reactions.



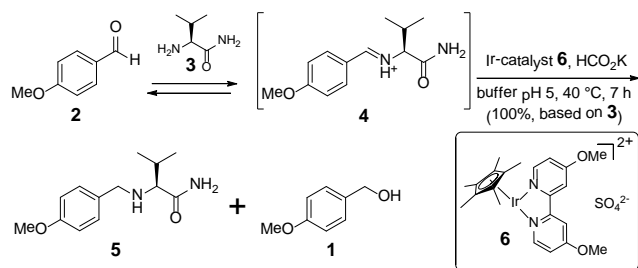
Scheme 1 One-pot oxidation/reduction sequence.

In order to tackle the problem, we initially analysed the partial reactions involved in more detail. Laccase belongs to the class of oxidoreductases and is capable of performing oxidations at the expense of O₂ with water as the only byproduct. Because of its stability and non-toxic waste, laccase is also widely applied in industry.⁹ Laccase readily oxidised anisyl alcohol (**1**) to aldehyde **2** in oxygenated citric acid buffer at pH 5 in 92% yield (Scheme 2). We selected an activated alcohol¹⁰ to keep reactions short. In addition, 0.3 equivalents of TEMPO were used as electron carrier, which appeared crucial for the oxidation to proceed.^{10,11}



Scheme 2 Laccase-mediated oxidation of anisyl alcohol (**1**).

The reducing agent in our sequence was iridium complex **6** (Scheme 3), which has been successfully applied in aqueous reductive amination reactions.¹² The catalyst is based on related iridium complexes which catalyse transfer hydrogenation reactions as has been documented by Fukuzumi et al.¹³ The reductive amination of **2** with (*S*)-valinamide (**3**) to the stable product **5** proceeded in 92% yield under similar conditions in 10 buffer pH 5 at 40 °C (Scheme 3). Thus, iridium complex **6** was capable of reducing the intermediate iminium ion **4** in the presence of HCO₂K as the hydride source. An excess of anisaldehyde (**2**) was used, because it was partially reduced to anisyl alcohol (**1**) in a competing reaction.



Scheme 3 Aqueous reductive amination of anisaldehyde (**2**).

Next, the compatibility of the oxidation conditions with each of the reactants of the reductive amination was examined (Table 1). The presence of either valinamide (**3**, entry 2) or iridium complex **6** (entry 3) was tolerated. Contrarily, a 64 mM concentration of HCO₂K (1 equiv) almost completely inhibited the enzymatic activity, while 32 mM HCO₂K (0.5 equiv) resulted in only a small decrease in yield. To investigate whether this inhibition is reversible, we removed the HCO₂K by filtration over a spin-filter, after which the recovered laccase was tested in the oxidation of alcohol **1**. Formation of aldehyde **2** was indeed observed, showing that laccase is only reversibly inactivated by HCO₂K.

Table 1 Compatibility of the enzymatic oxidation with the reactants of the reductive amination.^a

Entry	Additive	Conversion after 8 h (%) ^b
1	–	92
2	valinamide (3) (0.66 equiv)	91
3	iridium complex 6 (5 mol%)	96
4	HCO ₂ K (64 mM)	2
5	HCO ₂ K (32 mM)	84

^a Conditions: 25 U Laccase, 0.3 equiv. TEMPO.^b Conversions determined by RP-HPLC.

The same approach was used for the reductive amination (Table 2), which revealed that the reaction was not hampered by TEMPO (entry 2). The presence of laccase (entry 3) did have a tolerable negative influence on the yield. Work of Arends et al. revealed that the rhodium analogue of complex **6** shows a significant decrease in activity in the presence of various

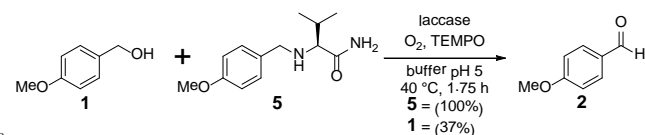
enzymes due to complexation of the metal center.¹⁴ In our hands the activity loss was limited, because a higher complex/enzyme ratio was used. In the presence of both laccase and TEMPO (entry 4), an initial yield of 8% was observed after 4 h, which gradually decreased to provide only traces of product **5** after 7 h, indicating that the product had reacted to another compound.

Table 2 Compatibility of the reductive amination with the reactants of the oxidation.^a

Entry	Additive	Conversion after 8 h (%) ^a
1	–	100
2	TEMPO (0.3 equiv)	100
3	laccase (25.0 U)	64
4	laccase (25 U) + TEMPO (0.3 equiv)	3

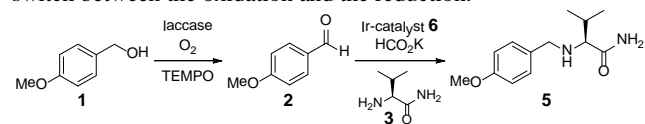
^a Conditions: 5 equiv. **2**, 10 equiv. HCO₂K, 0.05 equiv. **6**.^b Conversions determined by RP-HPLC.

Fabbrini and coworkers showed that benzylic amines can be oxidized to iminium ions by the oxidized TEMPO species, resulting in the corresponding aldehydes in aqueous media.¹² Likewise, the alkylated valinamide **5** may be rapidly oxidized via the iminium intermediate to aldehyde **2** and valinamide **3** in the presence of laccase and TEMPO. A competition experiment with alcohol **1** and amine **5** confirmed that the amine is more easily oxidised at pH 5.0 to aldehyde **2** than anisyl alcohol (**1**) (Scheme 4). At the time that amine **5** was fully oxidised to aldehyde **2**, 63% of anisyl alcohol (**1**) was still left. Competitive experiments at lower pH also gave a higher rate for the amine oxidation (pH 4.5–3.5) or resulted in laccase inactivation (pH 3.0–2.5).[‡]



Scheme 4 Competitive oxidation of amine **5** and alcohol **1**.

The latter results underline that it is impossible to conduct both transformations simultaneously, and that in a one-pot system the products revert to the starting materials. We then chose to adjust the procedure, prompted by the observed inhibition of laccase by HCO₂K (Table 1, entry 4). To test whether laccase could be inactivated and oxidation of amine **5** would be suppressed, the reductive amination was performed in the presence of laccase, TEMPO and 25 equivalents HCO₂K. Indeed, 88% of the desired product was formed, showing that HCO₂K could be used as a switch between the oxidation and the reduction.



Scheme 5 One-pot two-step sequence with opposing catalysts.

After establishing the possibility to switch between the two different reactions, we set out to optimize the one-pot oxidation/reduction process (Scheme 5). Reaction in the absence of laccase (Table 3, entry 1) did not lead to any product formation. Without inhibition of laccase – in the presence of small amounts of HCO₂K – no desired product was formed either (entry 2). If 100 equivalents of HCO₂K were added, laccase was successfully inhibited (entry 3) albeit that only 18% of the desired

[‡] Details on the competitive oxidation under various pH values can be found in the Electronic Supplementary Information (ESI)

Table 3 One-pot two-step sequence optimization.

entry	laccase (U)	Ir-cat (mol%)	HCO ₂ K (equiv)	time oxidation (h)	alcohol conversion (equiv) ^{a,b}	total reaction time (h)	conversion (%) ^d
1	0.0	5	10	10	0.00	10	0
2	25.0	5	0.5	24	5.00	24	0
3	25.0	5	100	12.5	4.46	20	18
4	25.0	5	25	12.5	4.61	20	29
5	2.50	5	10	13	4.44	20	32
6	2.50	5	2 × 2.5	16.5	4.32	65	64
7	2.50	1	10	22	3.67	50	80 (40) ^c
8	2.50	0.5	10	23	3.78	71	70
9	2.50	0.2	10	17	4.50	136	61
10	2.50	1	3 × 2.5	23	3.78	88	81
11 ^d	2.50	1	10	41	3.51	65	91(50) ^c
12 ^e	2.50	1	10	41	2.36	41	78 (62) ^c

^a Conversions determined by RP-HPLC ^b With respect to valinamide **3**. ^c Isolated yields between brackets. Isolated yields were lower due to losses during the extraction procedure. ^d Two times more concentrated. ^e Four times more concentrated.

5 compound was obtained. The low yield was the result of a second, fast competing reduction, being the aldehyde reduced to alcohol **2**. The iminium ion is formed in an unfavourable equilibrium reaction in water, and a fast reduction mainly results in aldehyde reduction. Decreasing the reduction rate should
10 afford more product **5** because more time is available to set the equilibrium. Indeed, when 25 equivalents HCO₂K were used (entry 4), the yields significantly increased. A further enhancement was achieved by using 10 equivalents of HCO₂K (entry 5). In this case, a ten-fold lower amount of laccase was
15 used as otherwise the enzyme would not be inhibited efficiently and oxidation of compound **5** would occur. Remarkably, the oxidation of the alcohol was only slightly slower in entry 5 compared to entries 2-4. When HCO₂K was added in two portions of 2.5 equivalents a yield of 64% was observed. To
20 summarize, by using the appropriate amount of the 'switching' compound, the yield was increased from traces to 64%.

We continued the optimisation by varying the amount of catalyst **6** (entries 7-9). The presence of 0.5 or 1 mol% catalyst gave high yields of 70 and 80%, respectively, while 0.2 mol%
25 catalyst led to a disagreeable reaction time of 136 h and a lower yield. In entry 10, both optimised amounts HCO₂K (2.5 equiv.) and iridium complex **6** (1 mol%) were used. However, a comparable yield was obtained to the example in which the HCO₂K was added in one batch (entry 7).

30 A last strategy involved using more concentrated reactions, thereby increasing the concentration of iminium ion **4**. Indeed, a high yield of 91% (entry 11) was obtained if the reaction was performed twice as concentrated. Contrarily, 78% (entry 12) was found with a four times more concentrated reaction mixture. In
35 the latter case, the enzymatic oxidation appeared to be slow and far from completion, explaining the lower yield. Probably the high concentration of reagents hampered the laccase activity.

Preliminary experiments to apply this switch concept to substituted benzylic alcohols indicated that in each of these cases
40 extensive experimentation was required, which is considered beyond the scope of this communication.

Conclusions

A successful two-step reaction sequence with counteracting catalysts in water was performed. An enzymatic oxidation was
45 combined with a reducing metal catalyst in one-pot. First, anisyl

alcohol (**2**) was oxidised to anisaldehyde (**3**), which reacted in a reductive amination with valinamide (**4**). The reaction sequence was performed subsequently in which it was crucial to inhibit the laccase with an excess of HCO₂K. At the same time, the
50 reductive amination started. The reaction conditions were fine-tuned and led to a maximum conversion of 91% and a maximum isolated yield of 62%. This is the first example in which a compound acts as switch between two opposing reactions in a one-pot procedure.

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