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Efficient Synthesis of Hybrid (Hydroquinone–Schiff base)cobalt Oxidation Catalysts

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Hybrid catalysts **A** and **B** have recently been found to efficiently transfer electrons from a metal catalyst to molecular oxygen in biomimetic oxidations. In the present work hybrid catalysts **A** and **B** were synthesized in high yield from inexpensive starting materials. The key step is an efficient Suzuki cross-coupling, which allows the use of unprotected aldehyde **5**. The new synthesis of the title hybrid catalysts is easy to carry out and can be scaled up.

Introduction

Oxidation reactions are of fundamental importance in Nature, and they are key transformations in organic synthesis.[1] During the past decade numerous oxidation methods have been developed, and in particular bioinspired oxidations have attracted considerable interest.[2–4] Despite the development, traditional oxidation methods that employ stoichiometric amounts of high-oxidation-state metal reagents are still often used in the production of a large number of organic compounds.[5] These oxidations lead to considerable amounts of toxic metal waste, and therefore there is a need for development of more efficient and environmentally more friendly catalytic oxidation methods in industrial chemistry.

To meet the need of high efficiency and the requirement of a minimum of effluents, processes that employ transition metals as substrate-selective catalysts, and use environmentally friendly and cheap oxidants, such as molecular oxygen, have been developed ("green chemistry").[2,6,7] In these oxidations the substrate is oxidized by molecular oxygen, which in turn is converted to water. The catalyst is essential, because direct oxidations of organic substrates by molecular oxygen are unselective, and have high energy barriers for electron transfer from the substrate to oxygen. Reoxidation of the substrate-selective catalyst by direct interaction with molecular oxygen can occur[7] but is often difficult because of an unfavored electron transfer between the catalyst and O_2. By mimicking Nature's respiratory chain, and employing coupled redox catalysts as electron-transfer mediators (ETMs), this obstacle can be overcome.[2] An illustrative example of the principle of the use of an ETM is provided by the Wacker oxidation, where ethylene is oxidized to acetaldehyde by air (O_2) in the presence of a $PdCl_2$ and $CuCl_2$ catalytic system.[8] In more recent coupled systems an oxygen-activating catalyst, e.g. (salophen)cobalt, and a quinone/hydroquinone redox couple are used as electron-transfer mediators, operating together to perform the reoxidation of a palladium or ruthenium catalyst by molecular oxygen (Scheme 1). The coupled system leads to lower barriers for electron transfer, analogous to the processes occurring in biological systems (cf. the respiratory chain).[9]

Results and Discussion

Our research group has recently been able to significantly increase the efficiency of these reactions by covalently linking two ETMs into one catalyst, thus enhancing the rate of the electron transfer.[9] This new hybrid catalyst consists of a Schiff base unit with pendant hydroquinone groups (Scheme 1) and offers an efficient aerobic reoxidation of both palladium and ruthenium in oxidation reactions. The salen-type Schiff base unit was chosen as the oxygen-activating component because of its demonstrated efficiency in coupled aerobic oxidation, and the simple and modular synthesis of this complex.[10,11] The oxidized form of hydroquinone, benzoquinone, was chosen as the second ETM since it is a very versatile reoxidant for a variety of transition-metal catalysts.[2,12] Molecular modeling shows that in this design the hydroquinones are only 7 Å away from the cobalt atom,[13] a distance across which electron transfer is known to be facile.[14]

In the previously reported synthesis, the (hydroquinone–Schiff base)cobalt complex was prepared in a multistep synthetic sequence by using expensive methoxy-protected start-

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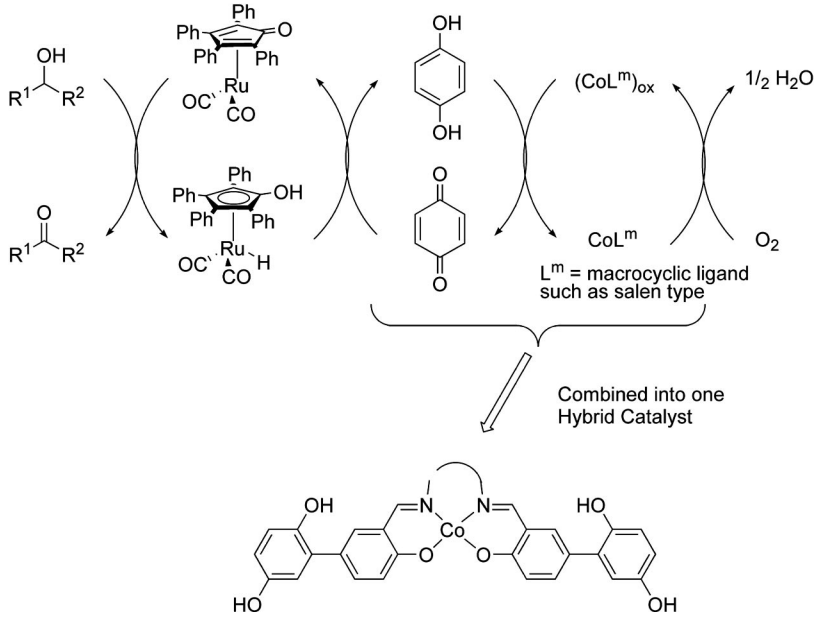
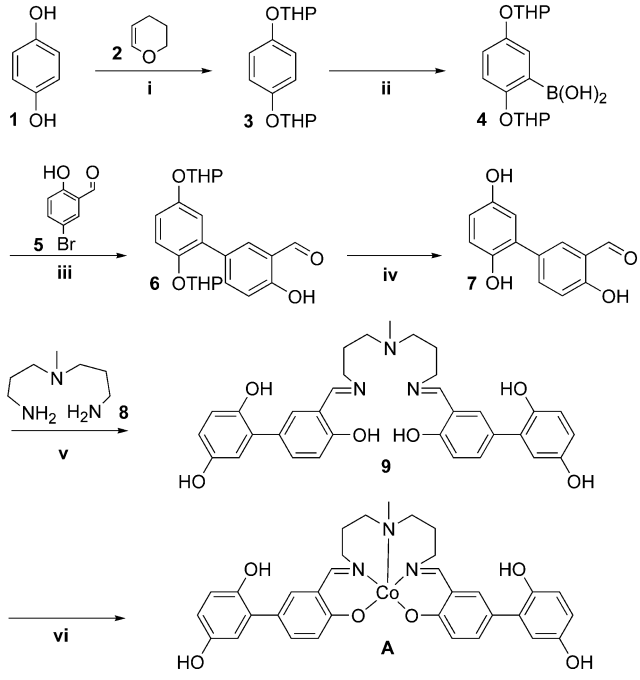


Scheme 1. In biomimetic aerobic oxidation the use of ETMs allows for low-energy electron transfer from substrate to molecular oxygen. Merging of two ETMs facilitates the electron transfer.

ing materials, which required the expensive and hazardous reagent BBr_3 for deprotection. Furthermore, the target molecule was obtained in a modest overall yield of 22%.[9] One reason for the low overall yield was that deprotection of the methyl-protected hydroquinone (dimethyl ether) by BBr_3 late in the synthesis gave a moderate yield. Therefore, alternative protective groups were investigated, and in the present synthesis THP was used as protective groups for the hydroquinone moiety. A second problematic step was the low yield of the Suzuki-coupling between 1-bromo-2,5-dimethoxybenzene and (3-formyl-4-methoxyphenyl)boronic acid, performed in DMF with $Pd(OAc)_2$ and PPh_3 as catalyst. After studying different alternatives, we finally settled on the synthetic route presented in Scheme 1, which gave complex **A** in a high overall yield (Scheme 2). Simple hydroquinone is used as starting material, and in all steps inexpensive reagents are employed.

The new route to the hybrid catalyst commenced with THP protection of hydroquinone with 3,4-dihydro-2*H*-pyran (**2**) and pyridinium *p*-toluenesulfonate (PPTS) to give **3** in excellent yield (97%). In the next step, the THP as a protective group facilitates the *ortho*-lithiation by coordinating to *n*BuLi. Addition of triisopropyl borate at –78 °C, followed by warming to room temperature yielded the boronic acid **4** (80–90%) after aqueous workup. The crude product **4** was subsequently used in a Suzuki cross-coupling, performed under phase-transfer conditions with commercially available 5-bromosalicylaldehyde (**5**), together with catalytic amounts of $Pd(OAc)_2$ and PPh_3 to yield the biphenyl building block **6** in an excellent yield of 94% after purification by flash chromatography. It is interesting to note that completely unprotected hydroxy aldehyde **5** can be used in the reaction with **4**.



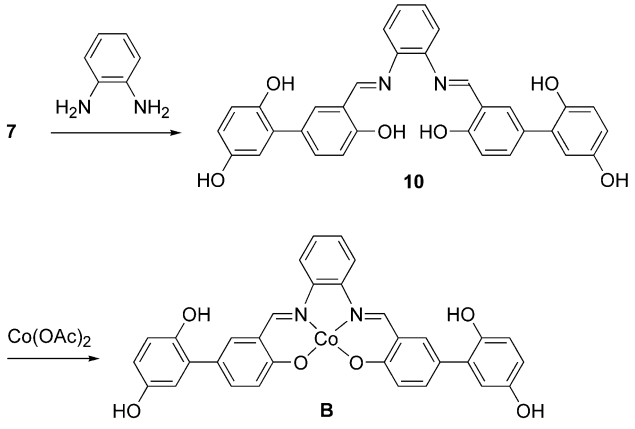
Scheme 2. (i). **2**, PPTS, DCM, room temp., 97%; (ii) 1. *n*BuLi, room temp.; 2. $B(OiPr)_3$, –78 °C to room temp.; 3. H_2O; (iii) $Pd(OAc)_2$, PPh_3, Na_2CO_3, $BnEt_3NCl$, toluene, EtOH, H_2O, 100 °C, 94%; (iv) PPTS, EtOH, H_2O, 60 °C, 98%; (v) **8**, EtOH, room temp., 94%; (vi) $Co(OAc)_2{\cdot}4H_2O$, MeOH, 62 °C, 95%.

The hydroquinone part of compound **6** makes it rather sensitive to acid and elevated temperatures, but the cleavage of the THP groups went smoothly when the reaction was performed at 60 °C in ethanol/water (9:1) with a catalytic amount of PPTS (2 mol-%). To prevent degradation and

side reactions the reaction mixture was quenched with pyridine prior to concentration, followed by precipitation with chloroform. In this way very pure crystalline material was obtained without any additional purification by e.g. column chromatography. In the subsequent step 2 equiv. of salicylaldehyde–hydroquinone **7** were allowed to react with *N*-(3-aminopropyl)-*N*-methylpropane-1,3-diamine (**8**) in ethanol resulting in a hydroquinone–salen ligand **9**, which could be used without further purification. Heating of **9** with cobalt(II) acetate in methanol resulted in the formation of the corresponding hybrid catalyst **A**, after washing with water to remove excess cobalt acetate.

The reactions shown in Scheme 2 for the synthesis of key compound **7** [i.e. steps (i) to (iv)] are scalable and were carried out routinely on a 20 mmol to 0.5 mol scale.

Compound **7** can be condensed with a variety of diamines to give Schiff base compounds, and salophen ligand **10**[9] is now accessible on large scale by reaction with 1,2-diaminobenzene. The cobalt complex **B** is a useful co-catalyst in palladium-catalyzed oxidations.[9]



The present protocol provides an efficient and versatile synthesis of the hybrid oxidation catalysts **A** and **B**. Two features of the synthesis are worth mentioning: (i) the efficient Suzuki coupling in which the hydroxy aldehyde can be used unprotected and (ii) the protection of the hydroquinone, which is accomplished without the use of fancy reagents, and both the protection and deprotection steps proceed with high yields under mild conditions. With this new synthesis, large amounts of **7** are readily accessible, and we have proved this by the preparation of 4.4 g of **7**.

Conclusions

We have reported on a new synthetic procedure for the synthesis of hybrid (hydroquinone–salen)cobalt catalysts **A** and **B**. By altering the protective groups of hydroquinone and optimizing the reaction conditions of the key Suzuki cross-coupling, an efficient and inexpensive synthetic route with very good overall yield was developed. The large-scale synthesis with this new approach allows screening and testing of various aerobic oxidation reactions, and this work is ongoing in our laboratory.

Experimental Section

1,4-Bis(tetrahydro-2*H*-pyran-2-yloxy)benzene (3): Hydroquinone (55.1 g, 0.5 mol) was suspended in dichloromethane (400 mL). 3,4-Dihydro-2*H*-pyran (136 mL, 1.5 mol) and PPTS (0.251 g, 1.0 mmol) were added, and the mixture was stirred at room temp. for 3 h. The reaction mixture was quenched by addition of anhydrous K_2CO_3 (1.0 g) and pyridine (1 mL). The reaction mixture was then washed with water (200 mL), dried with Na_2SO_4 and concentrated. The crude product was purified by recrystallization from ethyl acetate to afford white crystals (133.6 g, 96%, as a mixture of two diastereoisomers). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.97 (s, 4 H, Ar-*H*), 5.30 (m, 2 H, OC*H*O), 3.93 (m, 2 H, OC*H*H), 3.59 (m, 2 H, OCH*H*), 1.99 (m, 2 H, CH_2), 1.84 (m, 4 H, CH_2), 1.72–1.54 (m, 6 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 151.9, 151.8, 117.5, 117.5, 97.2, 97.1, 62.0, 30.5, 25.2, 18.9 ppm.

[2,5-Bis(tetrahydro-2*H*-pyran-2-yloxy)phenyl]boronic Acid (4): Compound **3** (13.92 g, 50 mmol) was dissolved partially in dry THF (100 mL) under argon. A 2.5 M solution of *n*-butyllithium in hexanes (20 mL, 50 mmol) was added dropwise by syringe at room temp. After stirring at room temp. for 1 h, the reaction mixture was cooled to –78 °C, and triisopropyl borate (23 mL, 100 mmol) was added dropwise. After stirring at –78 °C for 30 min, the reaction mixture was warmed to room temp. and was then stirred at room temp. for 1.5 h. The reaction mixture was quenched with water (100 mL). After stirring for 30 min, the reaction mixture was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were washed with brine (50 mL). The solution was dried with Na_2SO_4. The solvent was removed under vacuum, and the resulting crude product (17.5 g, pale yellow oil) was used directly without further purification in the Suzuki coupling.

5-[2,5-Bis(tetrahydro-2*H*-pyran-2-yloxy)phenyl]salicylaldehyde (6): Compound **4** (10.2 g, 31.7 mmol) and 5-bromo-2-methoxybenzaldehyde (4.24 g, 21.1 mmol) were dissolved in toluene (90 mL). To this mixture was added a solution of Na_2CO_3 (6.71 g, 63.3 mmol) and $BnEt_3NCl$ (0.24 g, 1.06 mmol) in water (30 mL). Ethanol (30 mL) was then added, followed by a solution of of $Pd(OAc)_2$ (0.024 g, 0.106 mmol) and PPh_3 (0.111 g, 0.422 mmol) in toluene (30 mL). The mixture was purged with argon for 10 min, and then stirred under argon at 100 °C for 3.5 h. After cooling to room temp., the mixture was filtered to remove the black precipitate. The layers were then separated, the aqueous layer was diluted with brine (70 mL) and extracted with ethyl acetate (3 × 70 mL). The combined organic layers were washed with brine (2 × 70 mL), dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (pentane/ethyl acetate, 9:1) to afford the product as a pale yellow oil (7.86 g, 94%, mixture of diastereoisomers). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.01 (s, 1 H, C*H*O), 9.93 (s, 1 H, O*H*), 7.78 (d, *J* = 2.3 Hz, 1 H, Ar-*H*), 7.78 (dd, *J* = 9.2, *J* = 2.3 Hz, 1 H, Ar-*H*), 7.16 (d, *J* = 8.9 Hz, 1 H, Ar-*H*), 7.05 (d, *J* = 3.0 Hz, 1 H, Ar-*H*), 7.03 (d, *J* = 9.2 Hz, 1 H, Ar-*H*), 7.00 (dd, *J* = 8.9, *J* = 3.0 Hz, 1 H, Ar-*H*), 5.38 (m, 1 H, OC*H*O), 5.27 (m, 1 H, OC*H*O), 3.95 (m, 1 H, OC*H*H), 3.78 (m, 1 H, OC*H*H), 3.58 (m, 2 H, OCH*H*), 2.07–1.48 (m, 12 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 196.7, 160.6, 152.1, 148.6, 148.6, 138.5, 134.5, 130.5, 130.5, 130.4, 120.3, 118.6, 118.5, 117.3, 117.0, 116.7, 116.5, 97.5, 97.1, 97.1, 62.0, 62.0, 30.4, 30.4, 25.2, 25.1, 18.8, 18.7 ppm. MS (ESI-TOF): calcd. for $C_{23}H_{26}O_6Na^+$ 421.1622; found 421.1629.

5-(2,5-Dihydroxyphenyl)salicylaldehyde (7): Compound **6** (7.82 g, 19.6 mmol) was dissolved in ethanol (90 mL), followed by addition of water (10 mL). Pyridinium *p*-toluenesulfonate (0.099 g, 0.393 mmol) was then added, and the mixture was stirred at 60 °C for 3 h. After cooling to room temp., the reaction mixture was

quenched with pyridine (0.32 mL, 3.93 mmol). The mixture was concentrated in vacuo below 30 °C to afford a yellow oil (if the product precipitates it should be redissolved by the addition of a minimal amount of ethanol). Chloroform was then added resulting in the formation of pale yellow crystals. The mixture was filtered, and the filter cake was washed with chloroform, and dried in vacuo at room temp. to give **7** (4.43 g, 98%). ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 10.72 (br. s, 1 H, C*H*O), 10.29 (s, 1 H, O*H*), 8.24 (br. s, 1 H, Ar-O*H*), 8.77 (br. s, 1 H, Ar-O*H*), 7.82 (d, *J* = 2 Hz, 1 H, Ar-*H*), 7.70 (dd, *J* = 8, *J* = 2 Hz, 1 H, Ar-*H*), 7.02 (d, *J* = 8 Hz, 1 H, Ar-*H*), 6.73 (d, *J* = 8 Hz, 1 H, Ar-*H*), 6.65 (d, *J* = 2 Hz, 1 H, Ar-*H*), 6.56 (dd, *J* = 8, *J* = 2 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 191.8, 159.5, 150.2, 146.7, 137.1, 130.0, 129.3, 126.7, 121.8, 116.8, 116.8, 115.9, 114.9 ppm. IR (KBr disc): $\tilde{\nu}$ = 3375 (br.), 1653, 1639, 1501, 1489, 1458, 1323, 1278, 1202, 1176, 892, 873, 807, 783, 743, 725, 712, 624, 610 cm^{-1}. MS (ESI-TOF): calcd. for $C_{13}H_9O_4^-$ 229.0506; found 229.0504.

Bis{3-[5-(2,5-dihydroxyphenyl)salicylidenimino]propyl}methylamine (9): Compound **7** (0.918 g, 3.98 mmol) was placed in a round-bottomed flask and *N*-(3-aminopropyl)-*N*-methylpropane-1,3-diamine (**8**, 0.269 g, 1.85 mmol) was added as a solution in ethanol (20 mL). The reaction mixture was stirred at room temp. for 14 h. The solvent was then removed by rotary evaporation. The crude product could be used without further purification (0.959 g, 91% yield). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 13.65 (br., s, 2 H, Ar-O*H*), 8.74 (br., s, 4 H, Ar-O*H*), 8.59 (s, 2 H, C*H*N), 7.57 (d, *J* = 2 Hz, 2 H, Ar-*H*), 7.47 (dd, *J* = 8, *J* = 2 Hz, 2 H, Ar-*H*), 6.87 (d, *J* = 8 Hz, 2 H, Ar-*H*), 6.71 (d, *J* = 8 Hz, 2 H, Ar-*H*), 6.64 (d, *J* = 2 Hz, 2 H, Ar-*H*), 6.53 (dd, *J* = 8, *J* = 2 Hz, 2 H, Ar-*H*), 3.63 (t, *J* = 6 Hz, 4 H, CH_2), 2.40 (t, *J* = 6 Hz, 4 H, CH_2), 1.79 (t, *J* = 6 Hz, 4 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 166.1, 159.8, 150.1, 146.6, 133.0, 131.8, 128.9, 127.4, 118.0, 116.7, 116.1, 116.1, 114.5, 56.2, 54.6, 41.9, 28.2 ppm. MS (ESI-TOF): calcd. for $C_{33}H_{36}N_3O_6^+$ 570.2599; found 570.2610.

(Bis{3-[5-(2,5-dihydroxyphenyl)salicylideniminato]propyl}methylamine)cobalt(II) (A): Compound **9** and cobalt(II) acetate tetrahydrate (0.533 g, 2.14 mmol) were placed in a round-bottomed flask, and dry methanol (20 mL) was added. The reaction mixture was degassed by briefly evacuating the flask and back-filling with argon. The reaction mixture was then heated at 62 °C for 1 h and cooled to room temp. The color had changed from orange to dark brown. A colour change to purple was observed when the product was exposed to air. The solvent was evaporated, and the crude product was dried in vacuo overnight. The resulting solid was suspended in water (10 mL), and the product was collected by filtration. The filter cake was washed with water to give complex **A** (1.02 g, 97%). IR (KBr disc): $\tilde{\nu}$ = 3431 (br.), 3043, 2927, 2858, 1649, 1596, 1563, 1521, 1475, 1389, 1374, 1355, 1316, 1254, 1134, 1091, 899, 848 cm^{-1}. MS (ESI-TOF): calcd. for $C_{33}H_{29}CoN_3O_6^+$ [oxidized bis(benzoquinone) form] 622.1388; found 622.1354.

Supporting Information (see footnote on the first page of this article): General methods and ^{1}H and ^{13}C NMR spectra of compounds **3** and **6**.

Acknowledgments

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