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Co(II), a catalyst for selective conversion of phenyl rings to carboxylic acid groups.

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An inexpensive protocol for the conversion of $-C_6H_4R$ into $-COOH$ groups using Co(II)-Oxone mixture as the catalytic system is described. A series of substrates containing substituted and non-substituted phenyl groups could be selectively converted into carboxylic acids. Initial mechanistic data have been provided.

Aqueous Co(II) salts catalyze the decomposition of potassium peroxymonosulfate (Oxone),[1] and the Co(II)-Oxone combination has been used extensively for water treatment and the complete oxidative degradation of phenols, surfactants and dyes.[2] Its potential in synthetic oxidation does not yet seem to have been explored, however. Development of mild and selective catalysts for the functionalization of C-H bonds remains a major challenge in modern chemistry and finds important implications in organic synthesis.[3] During studies of the Co(II)-Oxone system for the selective oxidation of C-H bonds, we found an unexpected conversion of phenyl rings into carboxylic acid groups. This type of transformation makes the phenyl group a masked carboxylic acid equivalent and, therefore, has significance in synthetic organic chemistry. Indeed oxidative degradation of arene rings to –COOH groups has seen extensive use, but the classic cases involve the much more reactive 2-furyl groups as the arene to be degraded.[4] Even so, previous work has usually involved harsh reagents and conditions as well as expensive materials such as ruthenium salts.[5,6] We have now achieved this transformation with high selectivity under mild conditions in water with inexpensive Co(II) as the catalyst. Moreover, instead of the 2-furyl groups usually employed, the present system is effective with the much more widely available phenyl derivatives.

Our work started with the aim of seeing C—H oxidation reactions from the Co(II)-Oxone system. The oxidation of ethylbenzene to acetophenone is a useful initial screen for identifying catalysts for such C-H bond oxidation reactions, but since our initial catalyst was the water-soluble Co(II) ion, we chose a water-soluble version of ethylbenzene, EBS (EBS = sodium 4-ethylbenzene sulphonate, **1**), as our initial substrate. If water proved a viable solvent for a wider range of substrates, it would be environmentally advantageous. Prior work on Co catalysts for the selective oxidation of organic compounds includes a number of

homogeneous and heterogeneous catalysts,[7] usually involving various Co-ligand combinations, not simple Co(II) ions as here.
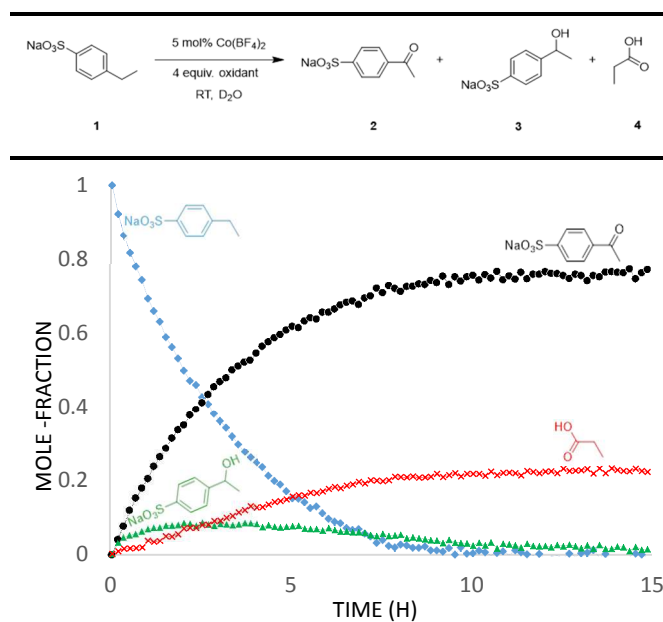

Figure 1. Oxidation of ethyl benzene sulphonate at room temperature in the presence of Co (II)/Oxone. Reactions carried out in air; similar results are obtained under nitrogen.

EBS was selectively and efficiently oxidized using a simple cobalt salt with Oxone as the primary oxidant. Cobalt(II) tetrafluoroborate hexahydrate was chosen on account of its oxidatively stable counteranion. With 5 mol% catalyst loading and 4 equiv. of Oxone, sodium 4-acetylbenzene sulphonate (**2**) was formed in 76% yield after 11 h at 25 ºC. In control reactions under the same conditions, **2** was barely detectable with Oxone alone and entirely absent with Co(II) alone, so the combination of the two is needed. The course of the catalytic reaction was monitored by ^{1}H NMR spectroscopy (Figure 1). Phenylethyl alcohol sulphonate (**3**), derived from initial hydroxylation, was observed in small amounts (up to

10%) at intermediate reaction times, but it was further oxidized to the ketone during the later course of the reaction.

In a key observation, significant amounts (15-20%) of propionic acid (**4**), were also detected by ^{1}H NMR in the products, together with acetate and formate (Figure S1, see SI). The peak assignments were confirmed by the addition of authentic samples of these products to the NMR solutions. Propionic acid could only have plausibly been formed by oxidative degradation of the benzene sulphonate group to -COOH, but this would mean that the benzylic CH$_2$ group had resisted attack, an unexpected outcome. The other expected oxidation product from the degradation of the benzene ring upon the initial oxidation to **2**, would be pyruvic acid, but it was not

Table 1. Optimization of the reaction conditions

Entry	Cat. (%)	Oxidant[a]	T (°C)	t (h)	Yield[b]	M.B[c]	TON[b]
1	1	Oxone	50	18	22	44	21
2	2.5	Oxone	50	18	30	37	12
3	**5**	**Oxone**	**50**	**18**	**38**	**40**	**8**
4	10	Oxone	50	18	50	50	5
5	5	Oxone	25	24	25	51	-
6	5	Oxone	40	24	38	38	-
7	5	Oxone	50	24	41	41	-
8	5	Oxone	50	6	38	45	-
9	5	NaIO$_4$	50	18	0	>95	-
10	5	Na$_2$S$_2$O$_8$	50	18	0	>95	-
11	5	Na$_2$S$_2$O$_8$	50	24	3	82	-
12	5	H$_2$O$_2$ (aq.)	50	18	0	>95	-
13	5	NaOCl	50	18	0	>95	-
14	5	^{t}BuOOH (aq.)	50	18	0	>95	-
15[d]	5	Oxone	50	20	27	75	-
16[e]	5	Oxone	40	4	60	>95	-

Reaction conditions: 2-phenylpyridine (10 μL, 0.07 mmol), Oxone (516 mg, 0.84 mmol), Co(BF$_4$)$_2$ (1.2 mg, 0.0035 mmol), D$_2$O (1-2 mL). Reactions carried out in air. [a]12 equivalents of oxidant used unless otherwise specified. [b]Yield and TONs determined by ^{1}H NMR spectroscopy using 3-(Trimethylsilyl) propionic-2,2,3,3-d$_4$ acid sodium salt as an internal standard. [c]Mass Balance = ([Recovered Starting Material]+[Products])/[Initial Starting Material]. [d]Reaction carried out with RuCl$_3$ as the catalyst, and the product was the *N*-oxide of the 2-picolinic acid. [e]The substrate was 2-picolinic acid and the product was the *N*-oxide of the 2-picolinic acid; 8 equiv. oxidant used. All the reactions were done in D$_2$O for the ease of characterization of the species formed by ^{1}H NMR spectroscopy and avoid loss of product during workup; however, the reaction can be carried in water as the solvent too.

observed by ^{1}H NMR spectroscopy. In a separate experiment, it was seen that pyruvate is very readily converted to acetate under similar reaction conditions so we would not have seen it even if it had formed. Since EBS has a reactive benzylic position and an arene ring deactivated by the sulphonate group, the major oxidation product was still the ketone, **2**.

We next explored the potential of the Co(II)-Oxone system for the selective oxidative conversion of –Ph groups to -COOH. We chose 2-phenylpyridine as our substrate for optimization because of its water solubility and the oxidative resistance of its protonated pyridine ring, formed in the acidic environment (typical pH range = 1-2). Our optimization results on its reaction to form 2-picolinic acid are summarized in Table 1. Oxone was the best oxidant (entries 1-8) among all the other oxidants tested (entries 9-14). With 12 equiv. versus substrate, we saw complete oxidation (Figure S2). Again, no oxidation took place in the absence of either Co(II) or Oxone. A catalyst loading of 5 mol% was chosen for further screening (bold entry in Table 1) to strike a balance between yield and turnover number (TON) (entries 1-4). The role of temperature was also analyzed (entries 5-8). The rate of the reaction increased considerably on going from 25°C to 50°C (Figure S4) without an excessive reduction in the mass balance and all further screening was done at 50°C. Since, ruthenium salts[6] also catalyze the oxidation of phenyl rings to carboxylic acids with Oxone, we carried out the same reaction using RuCl$_3$-Oxone for the sake of comparison. The reaction was slow and the *N*-oxide form of the 2-picolinic acid was obtained as the main product in 27% yield after 20 h under otherwise identical conditions, showing the selectivity advantage of the Co(II) system for the title conversion. When 2-picolinic acid itself was subjected to the Co(II)-Oxone system, it exhibited resistance to oxidative degradation (entry 16) with the *N*-oxide of the 2-picolinic acid being the only observed product (yield 60%). The mass balance of was around 50% in most of the cases (Table 1), measured with reference to an internal standard in a capillary tube; the observation of values <100% is attributed to the overoxidation of the starting material. Besides, variable amounts of formate and acetate were observed by ^{1}H NMR spectroscopy in all cases, no doubt due to the oxidation of –Ph group.

After optimizing reaction conditions, we explored the substrate scope (Table 2). The three positional isomers for phenylpyridine were each selectively oxidized affording the corresponding isomeric carboxylic acids in modest yields (entries 1-3). Next, the functional group oxidation resistance of substituents on the phenyl ring was tested. Substrates containing both electron-donating and withdrawing groups (entries 4-7) were transformed into their carboxylic acid derivatives in similar yields. As expected, the oxidation-sensitive aldehyde group in 6-(4-fluorophenyl) picolinaldehyde was readily oxidized to the corresponding acid to yield dipicolinic acid (entry 8). In the case of amino group substitution (entry 9), total oxidation of both rings resulted in formate being the only product (^{1}H NMR data). The highly electron-donating character of the amino group no doubt makes the substituted pyridine ring much more prone to oxidation. For 2-methylpyridine (entry 10, 11), the reaction, although slow, gave the expected oxidation product, 2-picolinic acid, albeit in low yields even at elevated temperatures and with a higher Oxone:substrate ratio. This was surprising because Ar-Me groups are usually much more easily converted to –COOH groups than is the case for –C$_6$H$_5$ groups, so we have a very unexpected case of easier oxidation of Ar-C$_6$H$_5$ groups over Ar-Me groups.

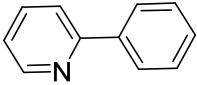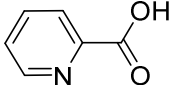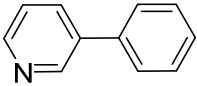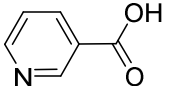This observation prompted us to check for similar selectivity in other cases. Indeed, methyl substituents on the heteroarene were able to survive the oxidation. With 3-methyl-2-

Table 2. Screening of substrates

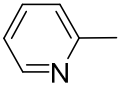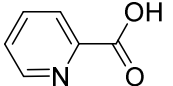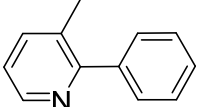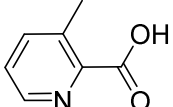| Entry	Substrate	Product	Time (h)	Yield[a] (%)	Mass Balance (%)
1	2-phenylpyridine	pyridine-2-carboxylic acid (OH, O)	6	38	45
2	3-phenylpyridine	pyridine-3-carboxylic acid (OH, O)	3	45	51
3	4-phenylpyridine	pyridine-4-carboxylic acid (OH, O)	3	53	61
4	2-(4-methylphenyl)pyridine	pyridine-2-carboxylic acid (OH, O)	3	38	65
5	2-(4-methoxyphenyl)pyridine (O–)	pyridine-2-carboxylic acid (OH, O)	3	37	37
6	2-(4-CHO-phenyl)pyridine (CHO)	pyridine-2-carboxylic acid (OH, O)	4	44	58
7	3-(3-aminophenyl)pyridine (NH$_2$)	pyridine-3-carboxylic acid (OH, O)	4	43	47
8	substrate (F, OHC)	product (COOH, HOOC)	3	30	30
9	2-amino-5-phenylpyridine (H$_2$N)	formic acid (H, O, O)	2	-	-
10[b]	2-methylpyridine	pyridine-2-carboxylic acid (OH, O)	3	10	69
11[c]	2-methylpyridine	pyridine-2-carboxylic acid (OH, O)	4	16	44
12	3-methyl-2-phenylpyridine	3-methylpyridine-2-carboxylic acid (OH, O)	2	37	50

Reaction conditions: All reactions were carried out in 0.07 mmol scale in D$_2$O at 50°C with 5 mol% catalyst loading and 12 equivalents of Oxone unless otherwise mentioned. [a]Yields determined by ^{1}H NMR spectroscopy using 3-(Trimethylsilyl) propionic-2,2,3,3-d$_4$ acid sodium salt as an internal standard. [b]Reaction done at 40°C with 4 equivalents of Oxone. [c]Reaction done at 70°C with 8 equivalents of Oxone.

phenylpyridine, 3-methylpyridine-2-carboxylic acid was obtained, albeit in low yield (entry 12), again due to the selective oxidation of the phenyl ring over the methyl group. This constitutes a significant advantage of the present method since previous systems using ruthenium[8] or potassium permanganate[9] are known to oxidize aliphatic functionalities either along with (Ru) or in preference to (Mn) phenyl rings.

We have been able to obtain some initial insights into the mechanism. Cobalt ions have been reported previously to interact with Oxone, forming freely diffusing [SO$_4$][.-] radicals as the true oxidants.[1a,1b] However, the remarkable selectivity reported here towards the phenyl groups intrigued and motivated us to investigate the mechanism in some detail. In principle, the oxidation could proceed through a two- or one-electron process, and both radical[10] mechanisms and first-row transition metals[11] usually prefer the latter. Cyclobutanol oxidation has been discussed previously as a means to distinguish between one- and two-electron oxidative processes.[12]
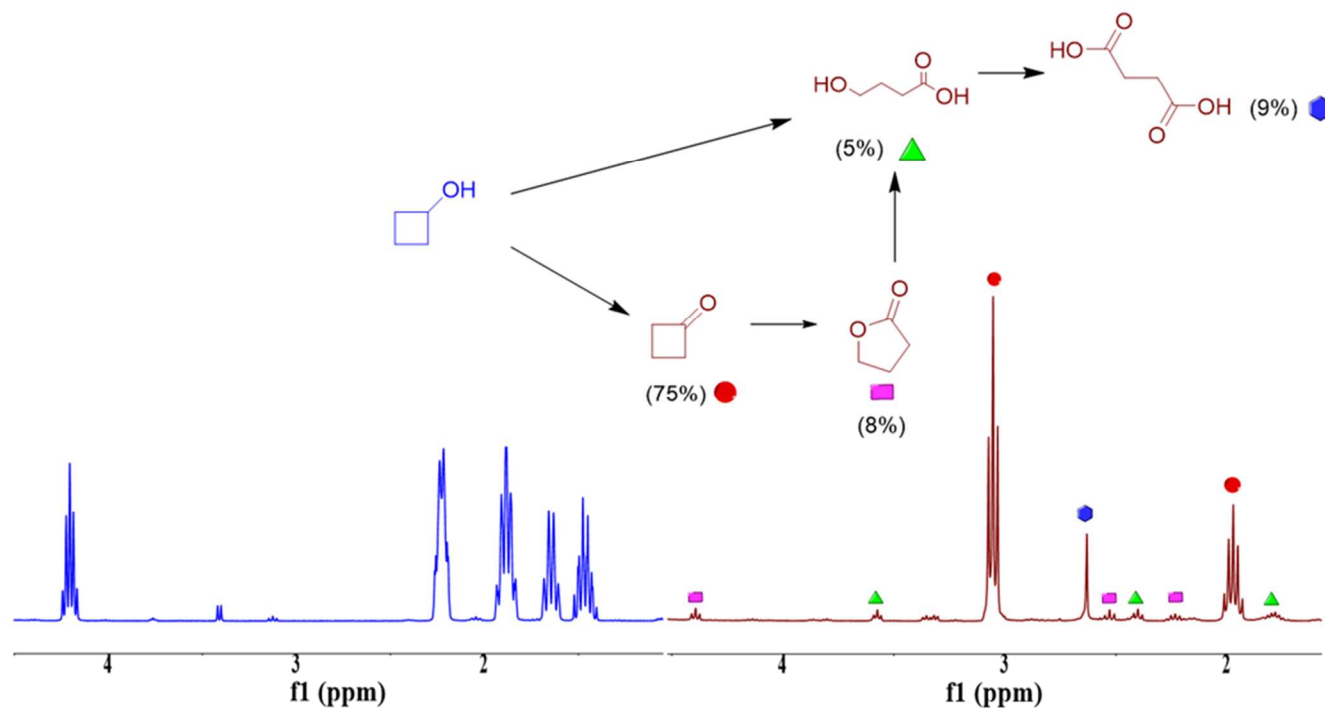
Figure 2. Conversion of cyclobutanol to cyclobutanone with the Co(II)-Oxone system, demonstrating the oxidation process is predominantly a two-electron process. Reaction conditions: 5 mol % catalyst, 2 equiv. of Oxone, room temperature for 40 min.

It is known from those studies that the strained cyclobutanol system easily opens if free radical intermediates are formed; otherwise the ring remains intact to give cyclobutanone, indicating a 2e⁻ oxidation. When cyclobutanol was treated with Co(II)-Oxone under our conditions, cyclobutanone was formed in 80% yield along with other products (Figure 2). The peak assignments for the other oxidation products (γ-butyrolactone, γ- hydroxybutyric acid and succinic acid confirmed by the addition of authentic samples of these materials to the NMR solutions. If the published criteria hold in this case, the reaction would then appear to go through a mixed pathway involving both a one-electron and a two-electron process, with the preferential oxidation of cyclobutanol to cyclobutanone suggesting a predominant two-electron process. Pyridinium[13] ion is known to hinder radical mechanisms, by reacting with intermediate carbon-based radicals. In our case, however, the outcome of the reaction was not affected by the presence of pyridinium ion in the reaction mixture. These results are consistent with a two-electron process as the major pathway, where a cobalt oxo species[14] might be involved, giving a role to cobalt beyond just activating the Oxone. However, we cannot neglect the possibility of [SO₄]˙⁻ radicals playing a role since we observe to some extent ring opening products. The research in this direction is currently ongoing and we hope to look at these points in more detail in future.

Conclusions

We report an inexpensive and green protocol for the conversion of –C₆H₅ to –COOH groups. This oxidative conversion proceeds under mild conditions in air and with water as solvent.

Moreover, the reaction has a broad substrate scope and is selective for the oxidation of –C₆H₅ while leaving untouched aliphatic substituents on other rings. Yields are only modest but the wide availability of cheap phenyl derivatives of N-heterocycles could provide an easy access to their carboxylic acid derivatives. Initial mechanistic investigations suggest a predominant two-electron process, where a high valent cobalt oxo species could act as the true catalytically active species and hence a possible role for the cobalt ions beyond activating the Oxone.

Experimental

General Procedure for catalytic oxidation. A mixture of Oxone (516 mg, 0.84 mmol), the corresponding substrate (0.07 mmol) and the cobalt catalyst (1.2 mg, 5 mol%) were added to a NMR tube with a capillary containing 3-(Trimethylsilyl) propionic-2,2,3,3-d₄ acid sodium salt as the internal standard and dissolved in deuterium oxide (1-2mL). After collection of the initial ¹H NMR spectra, the NMR tube was placed in an oil bath preheated to the required temperature. The reaction was monitored by the ¹H NMR spectrum at different time intervals. In reactions where complete conversion was too rapid even at room temperature the initial ¹H NMR spectra were taken prior to addition of the cobalt catalyst or by keeping the NMR tube in an ice bath. The yield was determined by comparative integration of the product and starting material peaks to the internal standard in the ¹H NMR spectrum. 2-phenyl pyridine was used as a representative substrate, and isolated yield of 2-picolinic acid was

obtained (see SI for details).[15] Product identity in all the cases were determined by addition of authentic commercially available compounds.

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Notes and references

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We describe the use of Co(II) in the presence of Oxone to effectively catalyze the conversion of $-C_6H_5$ to $-COOH$ groups with a broad substrate scope, selectivity and under mild conditions.

- **Green solvent**
- **Inexpensive catalyst**
- **Mild conditions**

Heat