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Novel 2,2,6,6-Tetramethylpiperidine 1-Oxyl–Iodobenzene Hybrid Catalyst for Oxidation of Primary Alcohols to Carboxylic Acids

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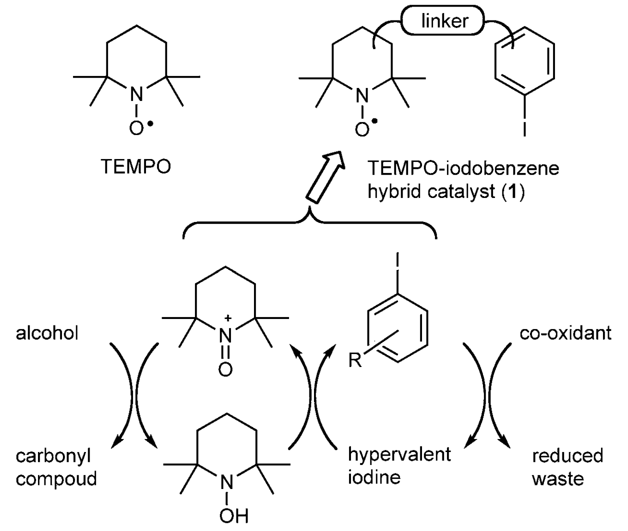
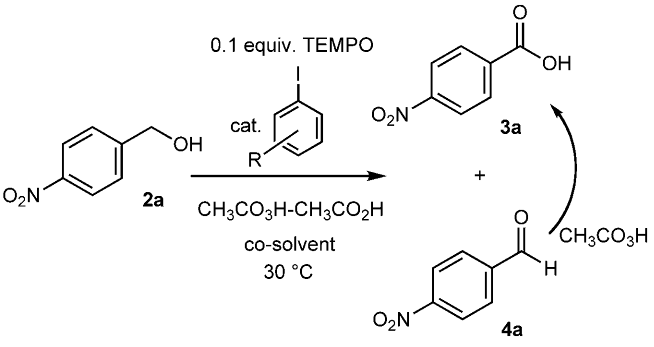
Abstract: Novel bifunctional hybrid-type catalysts bearing 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and iodobenzene moieties (**1a** and **1b**) were developed and used for the environmentally benign oxidation of primary alcohols to carboxylic acids. Reaction of primary alcohols **2** with a catalytic amount of **1** in the presence of peracetic acid as a co-oxidant under mild conditions gave the corresponding carboxylic acids **3** in excellent yields.

Keywords: carboxylic acids; hybrid catalysts; hypervalent iodine; oxidation; primary alcohols; 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)

The oxidation of primary alcohols to the corresponding carboxylic acids is one of the most important transformations in synthetic organic chemistry.[1,2] Environmentally benign procedures are strongly required especially for the production of pharmaceuticals, flavours and fragrances, and agrochemicals. 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO), a stable nitroxyl radical, and its derivatives in combination with a co-oxidant have received much attention; furthermore, they have been used as environmentally sensitive chemical reagents[3] to achieve this essential transformation. Some successful methods have been developed for the direct conversion to carboxylic acids using TEMPO with some co-oxidants such as NaOCl,[4] NaOCl/NaClO$_2$,[5] trichloroisocyanuric acid,[6] phenyliodine(III) diacetate (PIDA),[7] and Py·HBr$_3$.[8] A combination of TEMPO and a hypervalent iodine compound[9,10] has been widely used for the total syntheses of complex natural products because of the mild reaction conditions required and the reaction's chemoselectivity. However, hypervalent iodine reagents are expensive; moreover, stoichiometric amounts of iodine reagents are necessary during oxidation to produce equimolar amounts of organic iodine waste. In addition, some of the reagents are potentially explosive. To overcome these disadvantages, catalytic hypervalent iodine oxidations using catalytic amounts of an iodobenzene derivative and a co-oxidant have recently been developed and reported by several researchers,[11] including our group.[12] In 2006 Li and co-workers reported an oxidation of the primary alcohols to the aldehydes using catalytic amounts of both TEMPO and PIDA without a solvent.[13] However, reaction mixture had to be heated to 80 °C or a higher temperature. These results encouraged us to develop an efficient double-redox cycle system using both TEMPO and iodobenzene as catalysts under mild conditions, and to apply this system to a hybrid catalysis (Scheme 1). Hybridization of these two moieties should render the oxidation step of the TEMPO moiety by hypervalent iodine more efficient because the reaction would change to an intramolecular mode. Furthermore, it should make the recovery and reuse of the catalyst easier, because only one molecule of catalyst would be used. As a part of our studies for the development of practical and environmentally benign oxidation reactions,[12,14] we report herein a direct oxidation of primary alco-



Scheme 1. Double catalyst system and hybridization of TEMPO and iodobenzene.



Scheme 2.

hols to carboxylic acids using a novel bifunctionalized TEMPO–iodobenzene hybrid catalyst **1** and peracetic acid (PAA) as a co-oxidant.

We chose PAA as a co-oxidant of the double redox cycle system: PAA oxidizes iodoarenes to a hypervalent species,[15] although the combination of PAA and TEMPO was not found to give satisfactory results for the oxidation of alcohols.[5a] Also, PAA is known to be a safe and environmentally friendly oxidant that releases non-toxic acetic acid as the co-product and is commercially available in acetic acid solutions. We first investigated the double catalytic reaction of 4-nitrobenzyl alcohol (**2a**) as a substrate with a catalytic amount of TEMPO and several iodoarenes in a 9% acetic acid solution of PAA at 30 °C (Scheme 2). The results are summarized in Table 1. When **2a** was reacted with 0.1 equiv. of TEMPO and 0.1 equiv. of iodobenzene in the presence of 5 equiv. of PAA, the oxidation proceeded slowly to give 4-nitrobenzoic acid (**3a**) and the aldehyde **4a** in 57% and 9% yields, respectively, along with 29% of starting alcohol **2a** after 24 h (entry 1). Next, the substituent effects on the benzene ring of iodobenzene were examined (entries 2–5). Electron-withdrawing groups such as carboxy and acyloxy groups decreased the catalytic activity (entries 2 and 3), whereas electron-donating groups slightly increased the catalytic activity (entries 4 and 5). *p*-Iodotoluene gave the best result among all of them (entry 5). Using a fluoro alcohol such as 2,2,2-trifluoroethanol as a co-solvent resulted in a lower reactivity of the catalyst in contrast to Kita's report[15] (entry 6). When a similar reaction with 10 equiv. of PAA was performed, the reaction was completed within 24 h to afford **3a** in quantitative yield (entry 7). Using 0.5 equiv. of *p*-iodotoluene shortened the reaction time to 5 h (entry 8). Reactions without TEMPO (entry 9) and without iodoarene (entry 10) gave only trace amounts of the oxidized products. These results indicate that the two catalysts work together in this catalytic oxidation. When the aldehyde **4a** was reacted with only PAA, the carboxylic acid **3a** was obtained. This observation showed that PAA works as the main oxidant for the conversion of aldehyde into carboxylic acid.

Table 1. Oxidation of **2a** using double catalyst system.[a]

Entry	Iodoarene R (equiv.)	Equiv. of PAA	Co-solvent	Time [h]	Yield [%][b] 3a	4a	2a[c]
1	H (0.1)	5	none	24	57	9	29
2	*o*-CO_2H (0.1)	5	none	24	31	3	58
3	*p*-$OCOC_6H_4$ (0.1)	5	none	24	40	3	51
4	*p*-MeO (0.1)	5	none	24	55	9	27
5	*p*-Me (0.1)	5	none	24	60	10	25
6	*p*-Me (0.1)	5	CF_3CH_2OH	24	26	23	50
7	*p*-Me (0.1)	10	none	24	99	0	0
8	*p*-Me (0.5)	10	none	5	98	0	0
9[d]	*p*-Me (0.1)	10	none	24	trace		[e]
10	none	10	none	24	trace		[e]

[a] Reactions were carried out with 0.1 equiv of TEMPO at 30 °C.

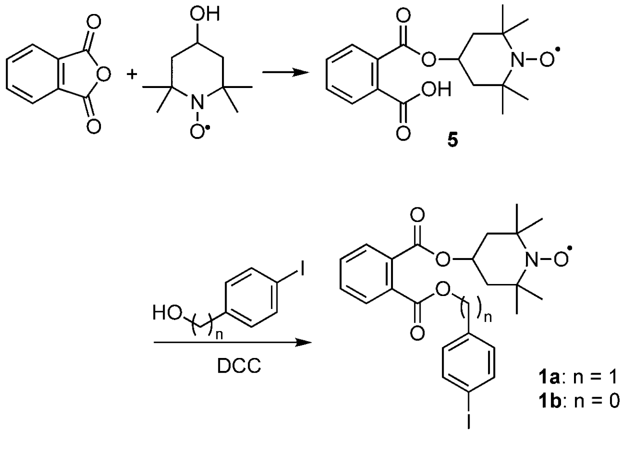
[b] Isolated yields.

[c] Recovery of unreacted starting alcohol **2a**.

[d] The reaction was carried out without TEMPO.

[e] No attempt to recover **2a** was made.

After the double redox cycle system using catalytic amounts of TEMPO and iodoarene had been achieved, we next attempted to design and synthesize a novel bifunctionalized hybrid-type catalyst **1** that incorporates both TEMPO and *p*-substituted iodobenzene moieties (Scheme 3). Phthalic acid was chosen as a linking unit to reduce the distance between the two catalyst sites, which are required to react with each other. Reaction of 4-hydroxy-TEMPO with phthalic anhydride in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) gave mono ester **5** which was coupled with 4-iodobenzyl alcohol by using *N*,*N*-dicyclohexylcarbodiimide (DCC) to afford the diester **1a** in 76% yield in two steps. Esterification of **5** with 4-iodophenol gave **1b** in 70% yield in two steps. When **2a** was reacted with 0.1 equiv. of **1a** in the presence of



Scheme 3. Synthesis of hybrid catalysts **1a** and **1b**.

Table 2. Catalytic oxidation of primary alcohols to carboxylic acids with **1**.[a]

Entry	Primary alcohol	Catalyst	Time [h]	Yield [%][b]
1	4-nitrobenzyl alcohol (**2a**)	**1a**	24	99
2	**2a**	**1b**	24	94 (4)
3	benzyl alcohol (**2b**)	**1a**	24	59 (28)
4	4-methylbenzyl alcohol (**2c**)	**1a**	24	37 (55)
5[c]	2-nitrobenzyl alcohol (**2d**)	**1a**	48	92 (5)
6[c]	**2d**	**1b**	48	86 (8)
7[c]	3-nitrobenzyl alcohol (**2e**)	**1a**	48	94
8[c]	**2e**	**1b**	48	quant
9[c]	4-chlorobenzyl alcohol (**2f**)	**1a**	48	56 (20)
10[c]	4-fluorobenzyl alcohol (**2g**)	**1a**	48	67 (19)
11[c]	2,4-dichlorobenzyl alcohol (**2h**)	**1a**	48	78 (13)
12[c]	3,4-difluorobenzyl alcohol (**2i**)	**1a**	48	62 (18)
13[d]	3-phenyl-1-propanol (**2j**)	**1a**	17	96
14[d]	**2j**	**1b**	20	96
15[d]	1-tetradecanol (**2k**)	**1a**	48	75[e]
16[d]	cyclohexylmethanol (**2l**)	**1a**	24	quant.
17[d]	**2l**	**1b**	26	97

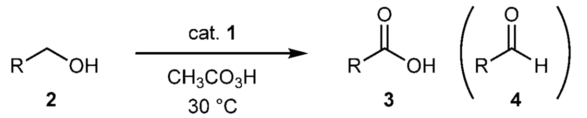
[a] Reactions were carried out with 0.1 equiv. of catalyst in the presence of 10 equiv. of PAA (9% acetic acid solution) at 30 °C.

[b] Figures in parentheses are the yields of aldehydes **4**.

[c] 15 equiv. of PAA were used.

[d] 0.3 equiv. of catalyst was used.

[e] After esterification with CH_2N_2.



Scheme 4.

Table 3. Catalytic oxidation of secondary alcohols to ketones with **1a**.[a]

Entry	Secondary alcohol	Time [h]	Yield [%]
1	1-phenylethanol (**6a**)	19	92
2	diphenylmethanol (**6b**)	28	95
3[b]	3-pheny-2-butanol (**6c**)	48	39 [56][c]

[a] Reactions were carried out with 0.1 equiv. of **1a** in the presence of 10 equiv. of PAA (9% acetic acid solution) at 30 °C.

[b] 0.3 equiv. of catalyst was used.

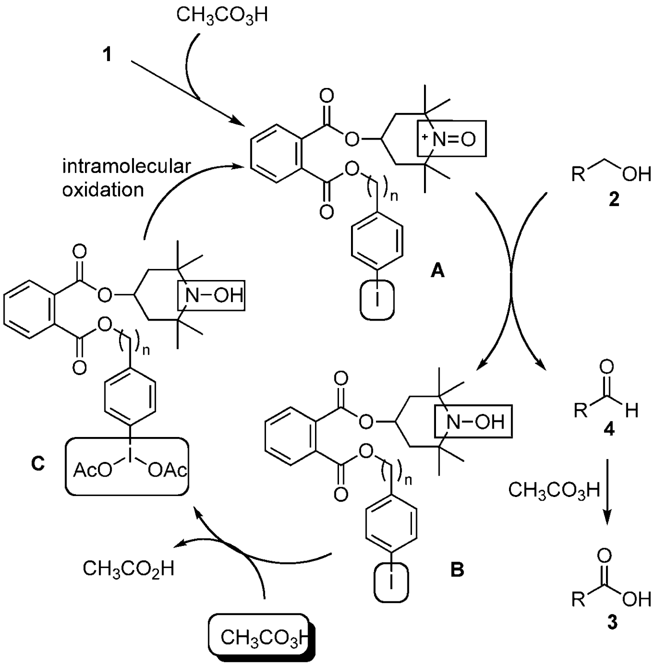
[c] Figure in parenthesis is the yield of recovered **6c**.

10 equiv. of PAA at 30 °C for 24 h, almost the same result was observed as that using TEMPO and *p*-iodotoluene giving carboxylic acid **3a** in 99% yield. In this reaction, **1a** was recovered in 70% yield (Table 2, entry 1). By contrast, a similar reaction of **2a** with 0.1 equiv. of **1b**, that has the less reactive *p*-benzoyloxy group on the iodobenzene moiety (see, Table 1, entry 3),[16] showed an enhancement of the catalytic activity to afford **3a** in 94% yield along with 4% of aldehyde **4a** after 24 h and 77% recovery of **1b** (Table 2, entry 2).

Various primary alcohols (**2b–l**) were oxidized with a catalytic amount of the unique catalyst **1** and PAA (Scheme 4). The results are summarized in Table 2. When benzyl alcohol **2b** and 4-methylbenzyl alcohol **2c** were reacted with **1a** and PAA, both **2b** and **2c** were consumed within 10 h, but the second oxidation step from the aldehyde to the carboxylic acid required a longer reaction time. The carboxylic acid **3b** was obtained in 59% yield along with **4b** in 28% yield after 24 h (entry 3), while the carboxylic acid **3c** was obtained in 37% yield along with **4c** in 55% yield after 24 h (entry 4). The oxidation of other benzylic alcohols gave the carboxylic acids as the major products in good yields (entries 5–12). In all cases, the first oxidation step was more rapid than the second step. Aliphatic primary alcohols were readily oxidized to give the corresponding carboxylic acids in good yields (entries 13–17). The catalyst **1b** showed slightly lower reactivity than that of **1a** (entries 6, 14, and 17). Secondary alcohols (**6a–c**) were also reacted with **1a** under the same conditions to afford the corresponding ketones (Table 3). Benzylic secondary alcohols reacted smoothly (entries 1 and 2); by contrast, an aliphatic secondary alcohol reacted slowly even with 0.3 equiv. of **1a** (entry 3). The catalyst was recovered in 60–80% yield in all cases.

A possible reaction mechanism is shown in Scheme 5. The oxoammonium cation **A** formed from **1** is most likely the active oxidant in this reaction.[17] Primary alcohol **2** is oxidized with **A** to produce **B** and aldehyde **4**, which would then be converted into the carboxylic acid **3** by a Baeyer–Villiger-type reaction with PAA. The iodoarene moiety of **B** is reacted with PAA to form the hypervalent iodine species **C**, which should intramolecularly oxidize the hydroxylamine moiety to **A** for reuse in the next oxidation. In the case of a benzylic alcohol bearing an electron-donating group, the Baeyer–Villiger-type reaction of the resulting aldehyde may be relatively slow leading to a longer reaction time.

In conclusion, we have designed and synthesized bifunctional hybrid-type catalysts bearing two catalyst sites, TEMPO and iodobenzene moieties (**1a** and **1b**). These catalysts proved to be efficient for the environmentally benign oxidation of primary alcohols to carboxylic acids. Reaction of primary alcohols with a catalytic amount of **1** in the presence of peracetic acid as a co-oxidant under mild conditions gave the corre-



Scheme 5. Possible catalytic cycle.

sponding carboxylic acids in excellent yields with recovery of catalyst **1**.

Experimental Section

Preparation of Compound 1a

To a solution of 4-hydroxy-TEMPO (517 mg, 3 mmol) in pyridine (10 mL), phthalic anhydride (2.132 g, 15 mmol) and DMAP (183 mg, 1.5 mmol) were added at room temperature. The mixture was stirred for 1 h and the reaction mixture was then concentrated. The residue was passed through a short pad of silica gel to give the crude mono ester **5**, which was used without further purification. The crude mono ester **5** was added to a solution of 4-iodobenzyl alcohol (772 mg, 3.3 mmol), DMAP (73 mg, 0.6 mmol), camphorsulfonic acid (CSA, 70 mg, 0.3 mmol), and DCC (1.237 g, 6 mmol) in benzene (70 mL). The mixture was stirred for 30 min and the reaction mixture was then concentrated. The residue was purified using silica gel column chromatography to give pure **1a** as orange crystals; yield: 1.216 g (76%); mp 127–129 °C (20% EtOAc in hexane); IR (KBr): ν = 1718, 1591, 1487, 1448, 1383, 1365, 1314, 1291, 1279 cm^{-1}; anal. calcd. for $C_{24}H_{27}INO_5$: C 53.74, N 2.61, H, 5.07; found: C 53.40, N 2.98, H 5.06; HR-MS (EI): *m/z* = 536.09520, calcd. for $C_{24}H_{27}INO_5$: 536.09342.

Preparation of Compound 1b

The crude mono ester **5** (160 mg, 0.5 mmol) was added to a solution of 4-iodophenol (140 mg, 0.64 mmol), DMAP (12 mg, 0.1 mmol), CSA (12 mg, 0.05 mmol), and DCC (206 mg, 1 mmol) in benzene (20 mL). The mixture was stirred for 30 min and the reaction mixture was then concentrated. The residue was purified using silica gel column chromatography to give pure **1b** as orange crystals; yield: 182 mg (70%); mp 142–144 °C (20% EtOAc in hexane); IR (KBr): ν = 1746, 1738, 1597, 1581, 1480, 1393, 1378, 1281, 1273, 1261, 1197 cm^{-1}; anal. calcd. for $C_{23}H_{25}INO_5$: C 52.88, N 2.68, H 4.82; found: C 52.75, N 3.16, H 4.68; HR-MS (EI): *m/z* = 522.0742, calcd. for $C_{23}H_{25}INO_5$: 522.0778.

Typical Experimental Procedure for the Oxidation of Primary Alcohols

In a typical experimental procedure for the oxidation of primary alcohols, to a solution of primary alcohol (0.5 mmol) in a 9% acetic acid solution of PAA (4.232 g, 5 mmol), the hybrid catalyst (0.05 mmol) was added at 30 °C and the resulting mixture was stirred at the same temperature. The mixture was diluted with ethyl acetate and extracted with 50% K_2CO_3 solution. The organic layer was then washed with an aqueous saturated $Na_2S_2O_3$ solution, dried, and concentrated to give the recovered catalyst which was purified by recrystallization from ethyl acetate-hexane. The alkaline solution was acidified by a 10% HCl solution and extracted with ethyl acetate. The organic layer was dried and concentrated to give the pure carboxylic acid. In all cases, except for the oxidation of 1-tetradecanol, the products were isolated directly in > 98% purity as determined by ^1H and ^{13}C NMR without the need for further purification. The carboxylic acid products were compared spectroscopically with their commercially available counterparts.

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[16] When **2a** was treated with 0.1 equiv. of TEMPO and 0.1 equiv. of *p*-benzoyloxyiodobenzene in the presence of 10 equiv. of PAA at 30 °C for 24 h, 48% of **3a** and 8% of **4a** were obtained along with 34% of unreacted **2a**.

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