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New aerobic oxidation of benzylic compounds: efficient catalysis by *N*-hydroxy-3,4,5,6-tetraphenylphthalimide (NHTPPI)/CuCl under mild conditions and low catalyst loading†

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Efficient aerobic oxidation of benzylic compounds using NHTPPI, a new NHPI analogue, as a key catalyst combined with CuCl, have been achieved under mild conditions and using as little as 1 mol% catalyst.

In recent years *N*-hydroxyphthalimide (NHPI, **1a**) has been recognized as a valuable catalyst for the aerobic oxidation of various organic compounds under mild conditions.[1] These oxidations proceed *via* intermediate phthalimide *N*-oxyl (PINO, **1b**) radical, able to abstract a hydrogen atom from the organic substrate.[2] The newly formed carbon centered radical then readily reacts with dioxygen, to give ultimately oxygenated compounds. PINO, however, is not indefinitely stable: its self-decomposition obeys second-order kinetics and has been studied by Masui[3] and, more recently, by Espenson.[2c,e] Self-decomposition of PINO makes it necessary to use quite large amounts of NHPI (generally 10 mol%) to achieved good conversions in the oxidation processes. Recently, various NHPI analogues have been prepared with the aim of tuning the catalyst performances,[2e,4] or of developing asymmetric versions.[5] These analogues, however, have mostly been used at catalyst loading ranging from 5 to 10 mol%.

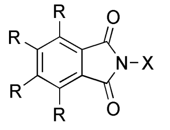
Herein, we report a new development in NHPI type catalysis, allowing highly efficient benzylic oxidation at mild temperature, with low catalyst loading. In a first series of experiments, we have investigated the aerobic oxidation of indan, chosen as a model substrate, under various experimental conditions but limiting the amount of NHPI to 1 mol%. CuCl‡[6] has been found to be, by far, the most active co-catalyst among a large variety of metal salts tested (Co(acac)$_2$, Mn(acac)$_2$, Mn(acac)$_3$, V(acac)$_2$, V(acac)$_3$, Mn(OAc)$_3$, CoCl$_2$, MnCl$_2$, CuCl, CuCl$_2$): 62% of indan-1-one was obtained in acetonitrile at 35 °C after 6 h, using 5 mol% of CuCl. We have next replaced **1a** by several analogues (Table 1).§

Compared to **1a** (run 1), analogues bearing electron donating or electron withdrawing substituents (**2–5**)[4b,7] were less effective (runs 2–5). Lower effectiveness was also observed for tetrachloro- and naphthalenic analogues **6** and **7**[7] (runs 6 and 7). Our previously described chiral *N*-hydroxyimides **8** and **9**,[5] both gave poorer results than **1a** (runs 8 and 9). Finally, *N*-hydroxy-3,4,5,6-tetraphenylphthalimide (**10a**, NHTPPI) revealed a very good catalytic activity (run 10), yielding 80% of indan-1-one after 6 h.

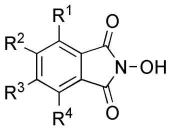
Table 1 Aerobic oxidation of indan using various NHPI analogues (1 mol%) as catalysts in acetonitrile at 35 °C

Run	Catalyst	Yield[a] (%)
1	**1a**	62
2	**2**	45
3	**3**	46
4	**4**	30
5	**5**	11
6	**6**	34
7	**7**	48
8	**8**	38
9	**9**	15
10	**10a**	80

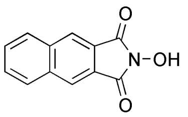
[a] Determined by GC after 6h



1 a R = H, X = OH (NHPI)
1 b R = H, X = O• (PINO)
10 a R = Ph, X = OH (NHTPPI)
10 b R = Ph, X = O•



2 R^2 = OMe, R^1, R^3, R^4 = H
3 R^2 = Cl, R^1, R^3, R^4 = H
4 R^2 = NO$_2$, R^1, R^3, R^4 = H
5 R^1 = NO$_2$, R^2, R^3, R^4 = H
6 R^1, R^2, R^3, R^4 = Cl



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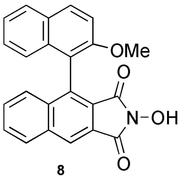

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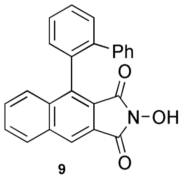

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To our knowledge NHTPPI has not been described previously. It can be prepared in a single step from commercially available tetraphenylphtalic anhydride (ESI†). It is more soluble than NHPI in most of the classical organic solvents. The main features of the NHTPPI/CuCl catalysed oxidation system are as follows: acetonitrile is the solvent of choice, benzonitrile, trifluoromethylbenzene, acetic acid or ethyl acetate being less appropriate (probably due to a lack of solubility of CuCl). The optimum amount of CuCl has been found to be around 5 mol%. Larger amounts resulted in no improvement of the reaction rate or of the final yield of indan-1-one. Smaller amounts reduce the reaction rate: if the quantity of CuCl was diminished to 0.5 mol%, 45% indan-1-one was formed after 6 h but the reaction then became exceedingly sluggish. The effect of temperature on the oxidation of indan using 1 mol% NHTPPI and 5 mol% CuCl is outlined in Fig. 1.

At 20 °C, 24 h are necessary to get 78% yield of indan-1-one, with a very slow further evolution. At 35 °C a 80% yield was obtained after only 6 h with no further evolution. At 50 °C the

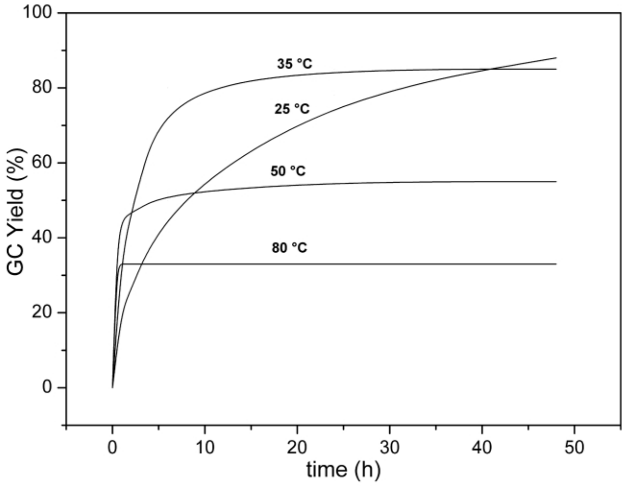

Fig. 1 Oxidation of indan catalysed by NHTPPI (1 mol%)/CuCl (5 mol%) at various temperatures.

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b4/b403004d/

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reaction stopped at 55% yield in less than 6 h. At 80 °C it stopped at 33% yield in less than 1 h. These results clearly indicate that catalysis by NHTPPI is more rapid at higher temperature, but that better turnover numbers of the catalyst are obtained at lower temperature.

A series of benzylic compounds has next been oxidized using 1 or 2 mol% NHTPPI and 5 mol% CuCl (Table 2). Indan-1-one or 2-methylindan-1-one have been obtained in 77 and 65% isolated yields, which represent more than 90% yields based on indan or 2-methylindan reacted (runs 1 and 2). Tetralin was similarly oxidized to tetralone with 74% isolated yield (run 3). In the same conditions, the oxidation of indan-1-ol was very slow, yielding only 15% of indan-1-one after 24 h. Therefore, a direct pathway leading from indan to indan-1-one seem likely (run 4).[8] 4-Methoxy-1-ethylbenzene and fluorene gave 60% and 42% conversions after 6 h and 24 h oxidation. An additional 1 mol% NHTPPI raised the conversions to 79 and 84% and allowed isolation of 70% of 4-methoxyacetophenone and of 79% fluorenone (runs 5 and 6). Oxidation of a methyl substituent was less efficient: 4-methylanisol gave 25% of *p*-anisaldehyde, accompanied by 9% of *p*-anisic acid after 48 h reaction (run 7). Selective oxidation of one ethyl group of 1,4-diethylbenzene was observed, resulting in the isolation of 52% 4-ethylacetophenone using 1 mol% NHTPPI (run 8). This results, clearly indicates that a carbonyl substituent deactivates benzylic sites to oxidation. Finally, xanthone and isochromanone were obtained with excellent 96 and 86% isolated yields from xanthene and isochroman with only 1 mol% NHTPPI (run 9 and 10). In each case the main oxidation compound was accompanied by only small amounts (1–3%) of the corresponding alcohol.

To obtain some information on the cause of enhanced catalytic properties of NHTPPI compared to NHPI, we investigated generation and self decomposition of the corresponding radical **10b** in acetonitrile at 35 °C in the absence of substrate, measuring the absorbance changes by UV-vis spectrophotometry. Ammonium hexanitratocerate(IV) (CAN)[9] has been found to be the most convenient oxidant to generate **10b** in CH_3CN: when CAN was added progressively to a solution of **10a** a new absorption band with a maximum at 425 nm appeared. It increased until 1 equiv. of CAN had been added.

This band has been attributed to radical **10b**, as its fast appearance was followed by slower decreasing accounting for self-decomposition of the radical. The absorbance change was monitored at 425 nm (ESI†). Second-order kinetics fitting[2c] gave second-order rate constant $k_d = 0.162$ L mol^{-1} s^{-1} at 35 °C. For $[\mathbf{10b}]_0 = 0.5$ mmol L^{-1}, the half life ($t_{1/2}$) of **10b** is 205 min.

Table 2 Oxidation of various substrate catalysed by NHTPPI/CuCl[a]

Run	Substrate	Time/h	Conv.[b] (%)	Yield[c] (%)
1	Indan	6	83	77 (93)
2	2-Methylindan	27	73	65 (90)
3	Tetralin	18	84	74 (88)
4	Indan-1-ol	24	15	15 (100)
5	4-Methoxy-1-ethylbenzene	23	79	70 (88)[d]
6	Fluorene	48	84	79 (94)[d]
7	4-Methylanisol	48	34	25 (70)[e]
8	1,4-Diethylbenzene	8	69	52 (75)
9	Xanthene	18	98	96 (98)
10	Isochroman	7	93	86 (92)

[a] Standard procedure: 1 mmol of substrate, 0.01 mmol of NHTPPI, 0.05 mmol of CuCl in 10 ml of acetonitrile with O_2 at atmospheric pressure and at 35 °C. [b] Determined by GC. [c] Yield of pure oxidation product after column chromatographic purification. Numbers in parentheses give the yield based on the substrate reacted. [d] 0.02 mmol of NHTPPI were used. [e] In addition to 25% of *p*-anisaldehyde, 9% of *p*-anisic acid was also obtained.

For a comparison, self-decomposition of **1b** (PINO) in the same conditions of temperature and concentration, monitored at 380 nm gave $k_d = 0.777$ L mol^{-1} s^{-1} and $t_{1/2} = 43$ min (ESI†). So, the half life of **10b** was found to be 4.7 times longer than that of PINO at 35 °C. This result has to be compared with recent results of Espenson: he showed that PINO radicals substituted either by electron donating or by electron withdrawing substituents have lower kinetic stabilities than unsubstituted PINO, accounting for lower efficiency of the corresponding NHPI catalysts.[2e] In our case indeed, enhanced kinetic stability of the radical species is accompanied by enhanced catalytic activity of NHTPPI.

In conclusion we have developed a new catalytic system for aerobic oxidation using NHTPPI/CuCl. Enhanced kinetic stability of the corresponding radicals allows efficient catalysis with low catalyst loading. Further extention of this approach is underway.

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Notes and references

‡ To our knowledge the use of CuCl in association with *N*-hydroxyimides for catalytic oxidations has been restricted to our own work on NHPI chiral analogues.[5] Its precise role has not yet been established. However, this role can tentatively be related to the formation of μ-oxocopper(II) species by reaction of CuCl with dioxygen in acetonitrile.[6] These species may generate PINO or **10b** radicals from NHPI or NHTPPI. Further investigations concerning this point are underway.

§ Valuable NHPI analogues have been described by Ishii, bearing several *N*-hydroxyimide functionalities in the same molecule,[4d,f] or a masked *N*-hydroxyimide functionality.[4e] In the present study, we have restricted our choice to NHPI analogues with a single free *N*-hydroxyimide moiety.

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