Anthrone-derived NHPI analogues as catalysts in reactions using oxygen as an oxidant†

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An enantioselective synthesis of anthrone-derived NHPI analogues has been developed. One of these analogues, in combination with Co salts, was employed to catalyse the aerobic oxidation of benzylic compounds and diols. Exploratory studies using a racemic version of the catalyst were also conducted. Radical addition of dioxolanes or alcohols to activated alkenes with molecular oxygen as the terminal oxidant was also shown to be catalysed with NHPI analogues.

In recent years, *N*-hydroxyphthalimide (NHPI, Fig. 1) has been recognized as a valuable catalyst for the aerobic oxidation of organic compounds under mild conditions.[1] Molecular oxygen, which is environmentally benign and economical, would be an ideal oxidant for the oxygenation of hydrocarbons. These oxidations proceed *via* a phthalimide *N*-oxyl (PINO) radical intermediate which is able to abstract hydrogen atoms from organic compounds.[2] The newly formed carbon centered radical then readily reacts with molecular oxygen to give oxygenated compounds. However, PINO is not stable under aerobic oxidation conditions.[2c,e]

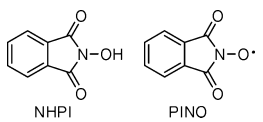
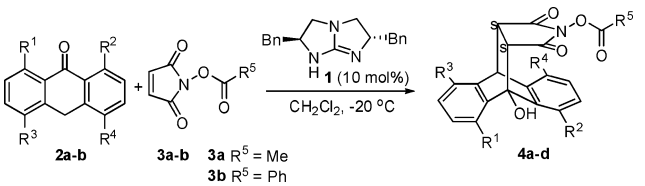


Fig. 1 *N*-Hydroxyphthalimide (NHPI) and phthalimide *N*-oxyl (PINO) radical intermediate.

It is likely that a suitably designed chiral analogue of NHPI should be of value for asymmetric catalysis. Einhorn *et al.* reported the synthesis of axially chiral analogues of NHPI.[3a] These analogues gave oxygenated products with moderate enantioselectivities in several catalytic asymmetric oxidation reactions, such as the desymmetrisation of 2-substituted indanes and the kinetic resolution of racemic acetals. A second generation of C_2-symmetrical NHPI analogues based on diphenol was subsequently developed and demonstrated to give moderate to high enantioselectivities for the oxidative ring opening reactions of various *N*-acyl oxazolidines.[3b] The enantioselectivities were highly dependent on the substitution pattern of the catalysts. Such catalysts could be useful for the synthesis of highly enantiomerically enriched oxazolidines. These experiments represent the first examples of chiral NHPI analogues catalysing enantioselective aerobic oxidations. Herein, we report a new class of NHPI analogues **4a–d** (Table 1), which were derived from anthrones. They were investigated as catalysts for the asymmetric aerobic oxidation of various organic compounds.

Table 1 Chiral bicyclic guanidine-catalysed Diels–Alder reactions between substituted anthrones and maleimides

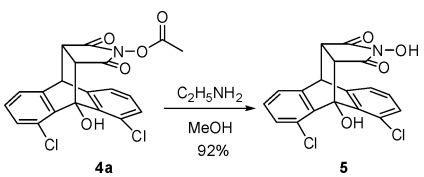


2a-b 3a-b **3a** R^5 = Me **3b** R^5 = Ph 4a-d

Entry	**2** [R^1, R^2, R^3, R^4]	R^5	**4**	Yield (%)[a]	ee (%)[b]
1	**2a** [Cl, Cl, H, H]	Me	**4a**	86	92
2	**2a** [Cl, Cl, H, H]	Ph	**4b**	85	12
3	**2b** [H, H, Cl, Cl]	Me	**4c**	83	64
4	**2b** [H, H, Cl, Cl]	Ph	**4d**	84	87

[a] Isolated yield. [b] Chiral HPLC.

The Brønsted-basic bicyclic guanidine **1** has been reported by our group to be an efficient catalyst for enantioselective Diels–Alder reactions between various anthrones and activated olefins.[4] It led us to evaluate **1** as a catalyst for the reactions of substituted anthrones **2a–b** with protected *N*-hydroxymaleimides **3a–b**. High enantioselectivity and high yield were achieved for adduct **4a** (Table 1, entry 1). Substituted anthrones **2a–b** were prepared from the reduction of their corresponding anthracenediones[5] while the *N*-hydroxymaleimides **3a–b** were prepared from the retro-Diels–Alder reaction of *N*-hydroxy-3,6-epoxy-1,2,3,6-tetrahydrophthalimide.[6] The subsequent cleavage of the protecting group from **4a** was carried out by treatment with ethylamine in MeOH to yield the anthrone-derived NHPI analogue **5** (Scheme 1).



Scheme 1 Synthesis of chiral anthrone-derived NHPI analogues.

A variety of benzylic compounds can be oxidised to their corresponding oxygenated derivatives by molecular oxygen in the presence of NHPI.[7] When NHPI was replaced by racemic **5** in some preliminary oxidation experiments, very similar results were obtained. This indicated that **5** has the desired catalytic properties. With optically pure **5** in hand, we attempted several asymmetric

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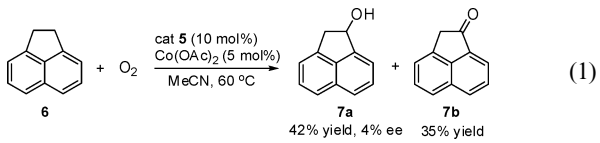
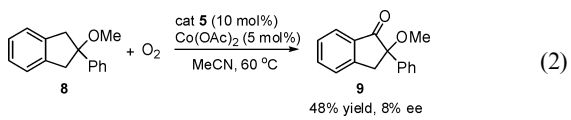
oxidation reactions of benzylic compounds and a diol with **5** and cobalt acetate as the co-catalyst.

The aerobic oxidation of 0.2 M of acenaphthene **6** in CH_3CN at 60 °C in the presence of 10 mol% of optically enriched **5** (92% ee) and $Co(OAc)_2$ (1 mol%) gave alcohol **7a** in 42% yield. Asymmetric induction was negligible (4% ee) (eqn (1)) and significant over-oxidation was observed, leading to 35% yield of acenaphthylen-1(2*H*)-one **7b**. Indane is readily oxidised to 1-indanone in good yield by NHPI-mediated oxidation.[3,7] Indanes bearing two different substituents on C2 are interesting substrates for asymmetric oxidations as they have two enantiotopic benzylic carbons. Using similar reaction conditions, 2-methoxy-2-phenylindane **8** was oxidised to ketone **9** in 48% yield and 8% ee (eqn (2)). A slightly better result was observed with ethylbenzene **10**. It was oxidised to 1-phenylethanol **11a** in good yield and 13% ee (eqn (3)). Over-oxidation was also appreciable and 30% of acetophenone **11b** was obtained.

The proposed mechanism for the NHPI–O_2–Co(II) oxidation system suggests that the oxidation of NHPI to PINO is achieved with a Co(III)peroxy-radical specie that was generated from the Co(II) and O_2.[8] The PINO is responsible for abstracting the benzylic hydrogen before the insertion of another molecule of O_2 at that position. A non-zero enantioselectivity for the reactions discussed above (eqn (1)–(4)) may indicate the formation of relatively tight complexes between chiral NHPI–PINO derivatives and the benzylic radical specie, possibly through non-covalent interactions; the insertion of O_2 should also be a rapid process.



(1)



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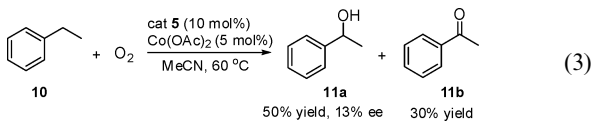
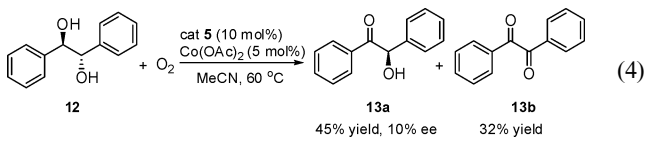


(3)



(4)

It has been shown that NHPI in combination with Co(II) salts is also an efficient method for the oxidation of alcohols to their corresponding carbonyl compounds.[9] Our experiments with compounds **6**, **8** and **10** also demonstrated that the **5**–Co(II) catalyst system is able to oxidise alcohols with ease under mild conditions. 1,2-Diphenylethanediol **12** was oxidised to benzoin **13a** in 45% yield and 10% ee with 32% of the over-oxidised product, benzil **13b** (eqn (4)). Optimisation of the reaction may be possible through the variation of reaction temperature and reaction time.

The chiral induction in the previous oxidation reactions was moderate. However, these results clearly indicate that asymmetric catalysis mediated by optically active **5** is possible. We intend to develop several other aerobic oxidation reactions using our anthrone-derived NHPI analogues as catalysts. Subsequent exploratory work was carried out using racemic catalyst **14** (Fig. 2).

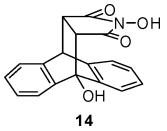
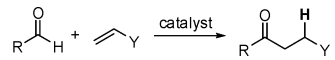


Fig. 2 Racemic anthrone-derived NHPI catalyst **14**.

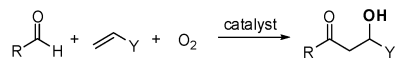
Addition of aldehydes to terminal alkenes is an unique method for the preparation of ketones.[10] Direct hydroacylation of terminal alkenes with aldehydes by transition-metal catalysts has been reported (eqn (5)).[10] The concomitant introduction of acyl or hydroxy moieties to alkenes, referred to as hydroxyacylation, can be achieved by a cascade reaction (eqn (6)). This provides a novel route to β-hydroxy carbonyl compounds. Acyl radicals[11] can easily decarbonylate and react with O_2 leading to carboxylic acids and other undesired products.[12] To overcome these drawbacks, 1,3-dioxolanes were often employed as masked aldehydes and as the source of the acyl group.[13,14] Deprotection of the product, a β-hydroxy ketal, under acidic conditions will provide the β-hydroxy carbonyl compounds.

***Hydro**acylation*



(5)

***Hydroxy**acylation*

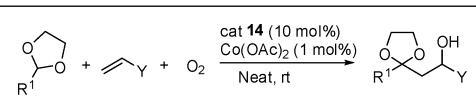


(6)

A mixture of 1,3-dioxolane **15a** and methyl acrylate **16a** was allowed to react under O_2 (1 atm) in the presence of catalyst **14** (10 mol%) and a small amount of $Co(OAc)_2$ (1 mol%) at room temperature for 5 h (Table 2, entry 1). The β-hydroxy ketal **17a** was obtained in 60% yield. Acrylonitrile **16b** was also found to serve as a good acceptor for **15a**, giving cyanohydrin **17b** in good yield (entry 2). 2-Methyl-1,3-dioxolane **15b**, also provided the corresponding hydroxy-acylated products **17c–d** in good yields (entries 3 and 4).

α-Hydroxy-γ-lactones are valuable synthetic precursors to compounds such as α,β-butenolides, which have potent biological activities.[15] They are also useful as monomers of biodegradable polymers and as fine chemicals. Ishii *et al.* reported the catalytic generation of an α-hydroxy carbon radical using NHPI in

Table 2 Hydroxyacylation of alkenes using 1,3-dioxolanes and dioxygen

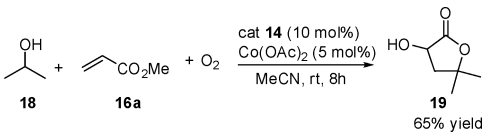


Entry	**10** [R^1]	Y	**4**	Yield (%)[a]
1	**15a** [H]	**16a** [CO_2Me]	**17a**	60
2	**15a** [H]	**16b** [CN]	**17b**	56
3	**15b** [Me]	**16a** [CO_2Me]	**17c**	58
4	**15b** [Me]	**16b** [CN]	**17d**	52

[a] isolated yield.

combination with cobalt acetate under O_2 (1 atm).[16] Trapping the generated radicals with α,β-unsaturated esters leads to α-hydroxy-γ-lactones which are difficult to obtain by conventional methods. This new method for the construction of α-hydroxy-γ-lactones is general for a variety of alcohols and α,β-unsaturated esters.

Catalyst **14**–$Co(OAc)_2$ was employed in the radical reaction between isopropyl alcohol **18** and methyl acrylate **16a** under O_2 (1 atm). This reaction occurred at room temperature to give **19** in 65% yield in 8 h (eqn (7)).



(7)

In conclusion, we have developed an enantioselective synthesis of anthrone-derived NHPI analogues. One of these analogues, in combination with Co salts, was employed to catalyse the aerobic oxidation of benzylic compounds and diols. However, low enantioselectivities were observed. Exploratory studies using a racemic version of the catalyst were also conducted. Radical addition of dioxolanes or alcohols to activated alkenes with molecular oxygen as the terminal oxidant was shown to be catalysed with the NHPI analogues. Asymmetric versions of these reactions will be investigated.

Acknowledgements

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