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Direct, Copper-Catalyzed Oxidation of Aromatic C-H Bonds with Hydrogen Peroxide under Acid-Free Conditions

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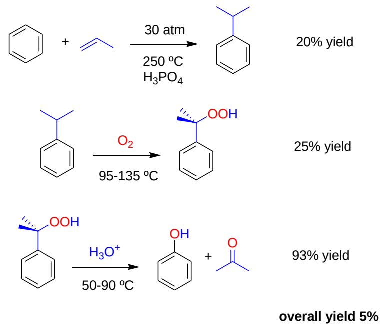
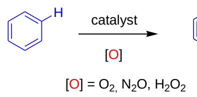
The direct oxidation of benzene into phenol using hydrogen peroxide has been achieved in the absence of any acid with $Tp^xCu(NCMe)$ complexes as the catalysts. In the case of anthracenes as the substrate, valuable anthraquinones have been quantitatively obtained in the same manner.

One of the most important intermediates of the chemical industry is phenol that is mainly prepared (95 % of worldwide production) by the cumene hydroperoxide process.[1,2] This process displays several drawbacks, the main being the overall yield in phenol that barely reaches 5% relative to benzene. It also involves a potentially hazardous cumyl hydroperoxide intermediate and furthermore generates acetone as a byproduct (Scheme 1). Because of this, the search for a one-step process for the direct conversion of benzene into phenol constitutes an area of permanent interest. Efforts toward this end have usually been defeated by the fact that oxidation of benzene is usually affected by a poor selectivity, since phenol is more reactive toward oxidation that the initial benzene and therefore over-oxidation products are usually formed decreasing the selectivity.[3]



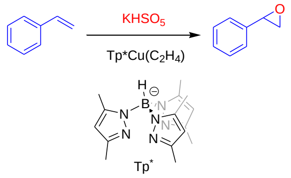
Scheme 1 The cumene process for phenol production

Several oxidation agents have been employed for such that reaction (eqn (1)) such as O_2, N_2O and H_2O_2. The direct hydroxylation of benzene with molecular oxygen would meet economical as well as environmental criteria for an ideal process. Unfortunately, the early described[4] systems took place with very low selectivity to hydroxylated products, and complete oxidation of benzene was observed with carbon dioxide and water formation. The use of palladium membranes,[5] or the activation of oxygen with carbon monoxide and metal heteropolyacids[6] resulted in some improvement of the conversions. The use of N_2O as the oxidant in a process developed by Solutia employing a [Fe-ZSM-5] zeolite as the catalyst ended in the Alphox™ process.[7]



(1)

In contrast, hydrogen peroxide as oxidant is highly desirable since water is the common byproduct and is relatively unexpensive compared with other organic peroxides and peracids.[8] An array of chemical systems have been described for the oxidation of benzene with H_2O_2,[9,10] most of them requiring a strong acid reaction medium. In fact, the majority of reported examples do not improve the results early reported in the so-called Fenton-chemistry,[11] the Fe(II)/H_2O_2 system in water at pH = 2, that in addition to the conversion of benzene into phenol provides mixtures of other oxidation products, due to the involvement of the hydroxyl radical. The best results reported to date, described by Bianchi, Vignola and co-workers[12] corresponds with a water-soluble iron catalyst, that afforded phenol through benzene oxidation with hydrogen peroxide with a phenol selectivity of 97% at a benzene conversion of 8-10%. Importantly, this iron catalyst also required trifluoroacetic acid as the co-catalyst.



(2)

Earlier work from our laboratory showed[13] that the complex Tp*Cu(NCMe) (Tp* = hydrotris(3,5-dimethylpyrazolylborate) catalyzed the oxidation of styrene with oxone® (potassium peroxosulfate) to give the corresponding oxirane (eqn (2)). On the basis of those results and with the aim of developing an *acid-free* catalytic system that would promote the direct oxidation of benzene with H_2O_2, we decided to investigate the potential of that complex for such transformation. Therefore, a solution of this copper complex in acetonitrile was charged with benzene and hydrogen peroxide, and heated for several hours. After the corresponding analysis‡, phenol was detected as the major product in the reaction mixture, with some 1,4-benzoquinone as the sole byproduct, as a consequence of overoxidation of the phenol produced. The latter was confirmed using phenol as the reactant and employing the same reaction conditions and catalyst. Table 1 shows the reaction conditions screening, that indicates that shorter reaction times, higher temperatures than ambient and a 1:1.5 [C_6H_6]:[H_2O_2] ratio provided the conversions as well as higher selectivities to phenol. The use of CuCl (Table 1, entry 5) gave lower conversions, benzoquinone being the main product. Methylene chloride as co-solvent was also tested, but conversions lowered considerably. It is interesting to note that blank experiments carried out in the absence of benzene showed that the copper complex also induced the slow decomposition of hydrogen peroxide, therefore phenol conversions based in the oxidant could not be determined.

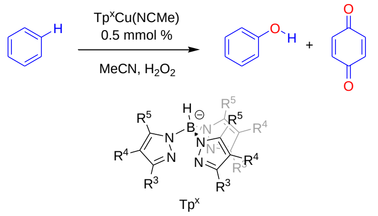
Table 1. Oxidation of benzene with H_2O_2 using $Tp^*Cu(NCMe)$ as the catalyst.[a]

Entry	mmol C_6H_6/ mmol H_20_2	temp (ºC)	rxn time	%Benzene Conv[b,c]	%Selectivity to PhOH[b,d]
1	1:5	60	4 h	15	73
2	1:1.5	60	4 h	19	79
3	1:1.5	80	2 h	21	81
4	3:4.5	80	2 h	17	80
5[e]	1:5	60	4h	6	<5

[a]Reactions conditions: catalyst, 0.01 mmol, 3 mL of CH_3CN. [b]Values determined by ^1H NMR spectroscopy (see Supporting Information). [c]As percentage of initial benzene consumed. [d]Selectivity to phenol = [mmol phenol/(mmol of all oxidation products detected]x100. [e]CuCl as catalyst.

Aimed by these results, we investigated a series of twelve complexes of general formula $Tp^xCu(NCMe)$ (Tp^x = hydrotrispyrazolylborate,[14] Scheme 2) as potential catalysts for this reaction. As shown in Table 2, in all cases the partial conversion of benzene into a mixture of phenol and 1,4-benzoquinone was observed, no other products being observed either by GC or NMR studies. The conversions were found within the range 14-30 %, whereas the selectivity toward phenol remained in the interval 67-85% (benzoquinone accounting for the residual of the benzene reacted). As mentioned above, one of the drawbacks of the direct oxidation of benzene is that the phenol produced is more reactive than the starting arene, therefore reacting further with the oxidant. Because of this, a large benzene:hydrogen peroxide ratio is commonly employed, 10:1 in the case of the aforementioned iron system, that also employed a slow addition device to inject the oxidant.[12] In our system, we have employed a 1:1.5 ratio of [C_6H_6]:[H_2O_2], and have added the oxidant in one portion at the beginning of the reaction, to afford conversion and selectivities at least comparable to that iron-based system.[15]

In order to avoid over-oxidation of phenol, Bianchi *et al.*[16] have also observed a certain improvement of the selectivity by using tetramethylene sulfone (sulfolane) as a co-solvent, a effect explained as the result of the interaction of phenol and sulfolane by means of hydrogen bonding, in a heterogeneous system using TS-1 as the catalyst. We have applied this strategy to our copper-based system, adding a four-fold excess of sulfolane referred to benzene, as co-solvent. The effect of the additive is shown in Table 2, with a slight decrease in the benzene conversion but a substantial increase in phenol selectivity. The best results were again found with the complex $Tp^{*,Br}Cu(NCMe)$ that gave a 92% selectivity at a 25% benzene conversion. Again, these values improve those of the iron system.[15,17]



Scheme 2 Oxidation of benzene with hydrogen peroxide using hydrotrispyrazolylboratecopper complexes as catalysts

Once demonstrated the capabilities of these copper complexes to catalyze the oxidation of C-H bonds of benzene, we focussed our attention into anthracenes as the substrates. Current synthetic methods for anthraquinone at the industrial scale are not based in anthracene.[18-19] On the contrary, methodologies based in the metal-catalyzed oxidation of the latter into 9,10-anthraquinone require a strong acidic medium to promote the direct oxidation.[20] The substituted 2-ethylanthracene is also of interest for its oxidation into

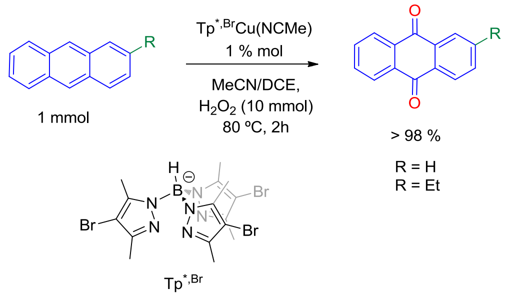
Table 2. Evaluation of Catalyst Effect.[a,b]

Entry	Catalyst	R^3	R^4	R^5	% Benzene Conversion[c,d]	% Selectivity to PhOH[c,e]	Sulfolane added[e] % Benzene Conversion[c,d]	Sulfolane added[e] % Selectivity to PhOH[c,e]
1	$Tp^*Cu(NCMe)$	Me	H	Me	21	81	23	83
2	$Tp^{iPr2}Cu(NCMe)$	iPr	H	iPr	21	67	18	78
3	$Tp^{cbu}Cu(NCMe)$	Cyclobutyl	H	H	14	78	15	93
4	$Tp^{Ph}Cu(NCMe)$	Ph	H	H	27	85	24	92
5	$Tp^{Ph,4Et}Cu(NCMe)$	Ph	Et	H	23	78	18	93
6	$Tp^{p\text{-}tol}Cu(NCMe)$	p-MeC_6H_4	H	H	20	75	18	89
7	$Tp^{Ms}Cu(NCMe)$	2,4,6-$Me_3C_6H_2$	H	H	27	78	23	83
8	$Tp^{*,Br}Cu(NCMe)$	Me	Br	Me	30	83	25	92
9	$Tp^{Ph,Me,Br}Cu(NCMe)$	Ph	Br	Me	18	85	23	90
10	$Tp^{Br,Ph,Br}Cu(NCMe)$	Br	Br	Ph	19	79	21	91
11	$Tp^{Br,p\text{-}tol,Br}Cu(NCMe)$	Br	Br	p-MeC_6H_4	20	70	17	90
12	$Tp^{Br3}Cu(NCMe)$	Br	Br	Br	27	77	25	91

[a] Reactions conditions: catalyst, 0.005 mmol; C_6H_6, 1mmol, H_2O_2, 1.5 mmol; temp = 80 ºC, time = 2h, 2 mL of CH_3CN. [b]R^3-R^5 correspond to pyrazolyl substituents according to Scheme 2. [c]Values determined by 1H NMR spectroscopy (see Supporting Information). [d]As percentage of initial benzene consumed. [e]Selectivity to phenol = [mmol phenol/(mmol of all oxidation products detected]x100.

quinone, given the well-known role capabilities of 2-ethyl-9,10-anthraquinone in the industrial synthesis of hydrogen peroxide. Its preparation[21] is frequently claimed as a drawback in terms of costs. The direct, metal induced oxidation of 2-ethylanthracene has already been reported but always using a strong acidic reaction medium.[20c]

On the basis of the above, we have studied the oxidation of both anthracene (AN) and 2-ethylanthracene (2EAN) with hydrogen peroxide. When a series of copper complexes bearing Tp^x ligands were employed as catalysts in those reactions, nearly quantitative conversions into 9,10-anthraquinone (AQ) or 2-ethyl-9,10-anthraquinone (2EAQ) were observed for an array of catalysts upon heating at 80 ºC for 2 h (eqn (3)). The best results were obtained with the complex $Tp^{*,Br}Cu(NCMe)$ as the catalyst, that provided 98% isolated yields of both quinones. Yields were significantly lower below that temperature, or longer reaction times were required to enhance conversion values, although selectivity into the quinones was not dependent of the temperature (optimization conditions are given in the ESI). At variance with the benzene system, in this case a large excess of H_2O_2 was employed to assess the desired oxidation. Attempts to obtain intermediate oxidation products failed, probably due to their instability under the reaction conditions. It is worth mentioning that this transformation lacks of the formation of other products derived from the oxidation of either other aromatic C-H bonds or, more importantly, the available aliphatic C-H bonds of the ethyl groups. Therefore, this system operates under a complete selectivity toward the formers.[22] Both the yields and the selectivities observed with this copper-based catalyst are unprecedented for acid-free catalytic systems in this oxidation reactions.[20c]



Scheme 3. Oxidation of anthracene and 2-ethylanthracene into

In conclusion, we have found that complexes of general formula $Tp^xCu(NCMe)$ catalyze the oxidation of benzene into phenol and of anthracenes into quinones with conversions that challenge other systems reported in the literature. Particularly, this system does not require the presence of an acidic medium and operates at somewhat mild conditions. Studies to ascertain the mechanism that governs these transformations are currently underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: full experimental details. See DOI:10.1039/b000000x/

‡ **General Catalytic Procedure.** The oxidations reactions were performed in a 25 mL round bottomed flask equipped with a reflux condenser and a magnetic stirrer bar. In a typical experiment, 0.005 mmol of catalyst were dissolved in 2 mL of acetonitrile and 1 mmol (88 µL) of benzene and 1.5 mmol (0.15 mL) of an aqueous solution of hydrogen peroxide (30% v/v) were added in one portion. The mixture was stirred for 2 hours at 80 ºC. After cooling at room temperature, the phases were separated and the aqueous phase was extracted with $CDCl_3$ (1-2 mL). An exactly weighted amount of diethyl malonate was added as internal standard and the mass balance in the organic phase was then determined by ^1H NMR. In the case of anthracene, a similar procedure was employed with the following reactants: anthracene (0.25 mmol), H_2O_2 (10 mmol), catalyst (1 mmol), MeCN (3 mL) and DCE (3 mL). The anthraquinone was extracted and isolated as a orange solid at the end of the reaction. See ESI for detailed procedures.

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