Asymmetric Reduction. The general procedure for the reduction of ketones with the cyclodextrin inclusion complexes of the amine–boranes was as follows. About 1.5 g wet weight or 1 mmol of the cyclodextrin complex was suspended and stirred in 2 mL of water containing 1 mmol of a ketone at 0 °C for the specified time. All the reaction mixtures were heterogeneous under such condition even for 3 weeks. The reduction of some water-insoluble ketones such as 2-chloro- and 2-bromo-1-phenylethanones did not proceed in water, but in carbon tetrachloride in the presence of the crystalline β-cyclodextrin complexes of pyridine– and trimethylamine–boranes. After the reaction, 0.1 M aqueous HCl solution was added to hydrolyze the unreacted amine–boranes, and then water was added to dissolve the complexes. The aqueous solution was extracted with diethyl ether. The combined ether extracts were washed with an aqueous sodium chloride solution, dried, and evaporated in vacuo. The residue (90–95% recovery) was purified by column chromatography on silica gel (Wakogel C-300) using dichloromethane as a eluent. The isolated products were identified by comparison of their NMR and IR spectra with those of authentic samples, and the optical rotations were measured at 25 °C in a suitable solvent. The absolute configuration and the enantiomeric excess were determined from the known values of optical rotation given in the literature.

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Effect of Phase-Transfer Catalysis on the Selectivity of Hydrogen Peroxide Oxidation of Aniline

Gabriela Barak and Yoel Sasson*

Casali Institute of Applied Chemistry, School of Applied Science and Technology, The Hebrew University of Jerusalem, 91904 Jerusalem, Israel

Received December 28, 1988

Several methods for the oxidation of aniline are reported in the literature. Classical stoichiometric oxidants as MnO_2[1] are used in order to obtain azobenzene.[1] Aqueous peracids oxidize ortho-substituted anilines to nitrobenzene[2] and nonsubstituted anilines to azo- and azoxybenzene[3] while anhydric peracids oxidize even unsubstituted aniline to nitrobenzene.[4] Catalytic systems as t-BuO_2H–Mo(VI), V(V),[5] or t-BuO_2H–Ti(IV)[6] are applied to produce nitrobenzene or azoxybenzene, respectively, in a selective manner. These oxidants are expensive and produce serious environmental problems.

Diluted hydrogen peroxide being cheap and nonpolluting can be an answer to these problems. Indeed an H_2O_2–WO_4^{-2} oxidation of aniline to mixtures of nitroso- and azoxybenzene[7] and the oxidation of *p*-chloroaniline to dichloroazobenzene in the presence of H_2O_2–boric acid[8] were reported.

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We made an interesting observation that while H_2O_2 oxidizes aniline selectively to azoxybenzene and the addition of either $RuCl_3$ or quaternary ammonium chlorides do not affect the selectivity at all, a ternary system of H_2O_2–$RuCl_3$ quaternary ammonium chloride (R_4NCl) or a binary system H_2O_2–quaternary ammonium bromide (R_4NBr) produce mixtures of nitro and azobenzene. Nitrobenzene becomes the main product when a H_2O_2–$RuCl_3$–quaternary ammonium bromide system is employed. Scheme I presents these alternatives.

Scheme I

$$2PhNH_2 + 3H_2O_2 \xrightarrow[\text{or no catalyst}]{RuCl_3 \text{ or } R_4NCl} PhN(O)=NPh + 5H_2O \quad (1)$$

$$3PhNH_2 + 6H_2O_2 \xrightarrow[\text{or } R_4NBr]{RuCl_3 + R_4NCl} PhN(O)=NPh + PhNO_2 + 9H_2O \quad (2)$$

$$PhNH_2 + 3H_2O_2 \xrightarrow{RuCl_3 + R_4NBr} PhNO_2 + 4H_2O \quad (3)$$

We have investigated the nature of this reaction and studied the effect of various parameters such as amount of hydrogen peroxide and amount and structure of the phase-transfer and metal catalysts on the selectivity of the process.

Results and Discussion

Oxidations were carried out at 90 °C with 30% H_2O_2 (640 mmol), which was added to the following mixture: aniline (54 mmol), PT catalyst (3 mmol), $RuCl_3 \cdot 3H_2O$ (0.077 mmol), and 10 mL of 1,2-dichloroethane as solvent.

In the absence of both PT and metal catalysts, the main product is azoxybenzene (90% yield). When quaternary ammonium chloride (e.g. didecyldimethylammonium chloride, DDACl) or ruthenium chloride were separately added to the system, no significant changes were observed. Note that $RuCl_3$ is totaly extracted by aniline into the organic phase.

The combination of both DDACl and $RuCl_3$ produces an interesting and surprising change in products distribution: in addition to azoxybenzene 35% nitrobenzene was found in the reaction mixture. The nitrobenzene is evidently produced via a parallel pathway since when azoxybenzene was exposed to the same conditions no reaction occurred.

A possible interpretation of this phenomenon is that once extracted into the organic phase by either DDACl or aniline, $RuCl_3$ and H_2O_2 form together a more active oxidant specie[9] capable of oxidizing aniline to nitrobenzene. Based on our observation that indicated significant difference in catalytic activity between ammonium salts possessing similar lipophilicity but different symetry (see later), we tend to believe that the PT catalyst not only has a role in the extraction process but also participates in the formation of the active oxidation complex. A similar result is obtained in the presence of DDABr alone, suggesting the existence of an alternative pathway for the oxidation of aniline to nitrobenzene in which the oxidant species seems to be bromide anion. In fact, when the quaternary ammonium bromide is replaced by NaBr (9 mmol), the same amount of nitrobenzene is obtained. A higher amount of nitrobenzene (60% yield) is produced when a combination of the two systems (DDABr and $RuCl_3$) is employed. Analyzing this system, we found a strong de-

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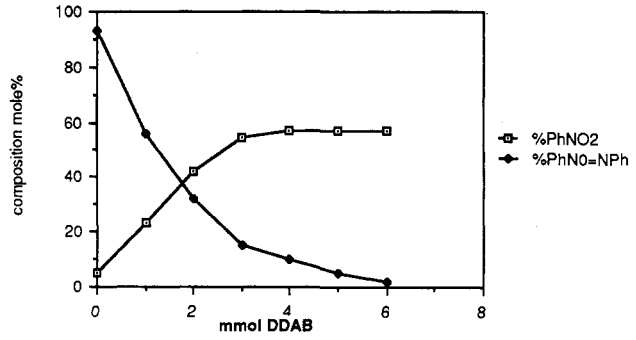

Figure 1.

Table I. Influence of the Size and Structure of the PT Cation on Product Distribution in the Oxidation of Aniline[a]

R_4NBr	no. of C atoms	% $PhNO_2$	% PhNO=NPh
tetraethyl	8	24	60
tetrapropyl	12	25	62
tetrabutyl	16	28	55
tetrapentyl	20	48	33
tetrahexyl	24	44	35
tetraheptyl	28	45	32
dodecyltrimethyl	15	42	41
didecyldimethyl	22	60	15
tricaprylmethyl	25	55	25

[a] Reaction conditions: aniline 54 mmol, $RuCl_3$ 0.077 mmol, R_4NBr 3 mmol, H_2O_2 640 mmol, dichloroethane 10 mL, 90 °C, 24 h. The mass balance to 100% is made up by a constant 5% azobenzene together with bromo and hydroxylation products.

pendence of the production of nitrobenzene on the amount of the DDABr, as presented in Figure 1.

This behavior can be explained in terms of the concentration of hydrogen peroxide in the organic phase and stoichiometry of the reaction. From equations 1–3 it can be seen that the formation of nitrobenzene requires an amount of hydrogen peroxide twice as big as for the formation of azoxybenzene. As Dehmlow[10] has shown, the concentration of H_2O_2 in the organic phase is directly proportional to the amount of PT catalyst present in the system. It is consequently expected that increasing the amount of DDABr more nitrobenzene will be produced. It should be mentioned, however, that with large amounts of DDABr (more than 3 mmol) ring bromination and hydroxylation byproducts become quite disturbing (more than 25%), so a limit of 3 mmol of DDAB is recommended.

The effect of the nature of the quaternary ammonium catalyst on the selectivity of the process was then examined. The results are summarized in Table I.

The results in Table I concerning the symmetric cations can be explained by the fact that the more lipophylic the cation, the greater its H_2O_2 extraction capability.[10] Higher concentration of hydrogen peroxide results in higher selectivity to nitrobenzene. The superiority of the asymmetric cations over the symmetrics with a similar number of carbon atoms in nitrobenzene production is unexpected when extraction phenomena only are considered. Symmetric cations extract the hydrogen peroxide into the organic phase better than the asymmetric ones. We suggest that the PT catalyst is involved in the active oxidation complex together with $RuCl_3$ and H_2O_2. An asymmetric lipophylic cation enables the approach to the metal and at the same time allows a good extraction of the hydrogen

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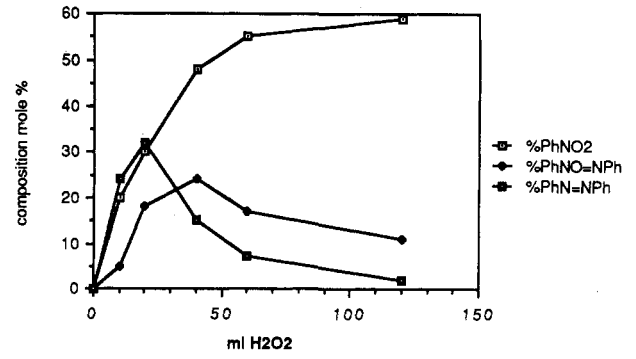

Figure 2.

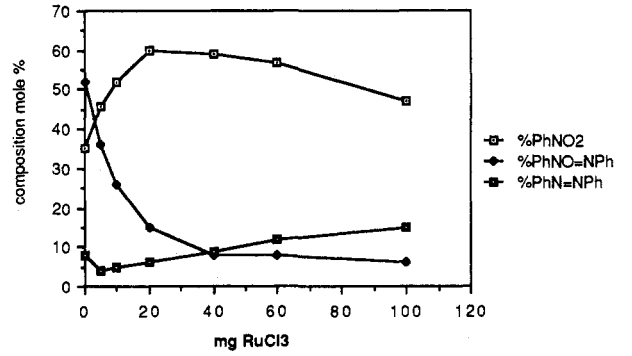

Figure 3.

peroxide. All these assumptions and the mechanism of this process are under investigation in our laboratory.

The importance of the amount of hydrogen peroxide in the production of nitrobenzene is illustrated in Figure 2.

It can be seen that at stoichiometric amounts of hydrogen peroxide, azobenzene, which is the lowest oxidation product of aniline, become the main product, testifying for a lack of oxidant in the organic phase. The large excess of hydrogen peroxide is required only in order to keep a high enough concentration in the organic phase, enabling in this way the formation of the higher oxidation state product, nitrobenzene.

The amount of $RuCl_3$ also influences the product distribution, as presented in Figure 3.

There is an optimal amount of $RuCl_3$ for the production of nitrobenzene. At lower amounts of $RuCl_3$, azoxybenzene is produced in high quantities while higher amounts encourage the formation of azobenzene.

From all other metal catalysts checked only $CoCl_2$ shows a tendency to produce nitrobenzene in addition to azoxybenzene. In the presence of $PdCl_2$ and $RhCl_3$ only azoxybenzene is produced. Finally it is important to mention that in the presence of aniline, the well-known decomposition of the hydrogen peroxide over $RuCl_3$[11] is totally avoided.

Experimental Section

Materials. All chemicals were standard laboratory chemicals from commercial companies (Aldrich, Fluka, BDH, and Abic).

Oxidation Procedure. The oxidations were performed in a 100-mL three-neck flask equipped with a well-cooled condenser. The reaction vessel was charged with 5 mL of aniline (54 mmol), 10 mL of 1,2-dichloroethane, 1.2 g of DDAB (3 mmol), and 0.02 g of $RuCl_3$ (0.077 mmol). The mixture was heated to 90 °C for 10 min with stirring and then 60 mL of H_2O_2 (30%, 640 mmol) was added in one portion. The reaction mixture was refluxed for 24 h, and then the organic phase was separated. The aqueous phase was washed twice with ethylene chloride, and then all the

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organic phases were dried over Na_2SO_4. The organic phases were combined and fractionally distilled under high vacuum. Nitrobenzene (4 g) was obtained, which is a 60% yield. Azo- and azoxybenzene as well as the byproducts were separated by liquid chromatography on silica gel with benzene as eluent. The retention times are as follows: azobenzene 0.66, azoxybenzene 0.50, byproducts 0-0.3.

Analysis. The reactions were followed up by GLC analysis. Dichlorobenzene was used as internal standard. The products were identified by comparison with standards and by gas chromatograph-mass spectra (GCMS) analysis. The column used was 15% OV 101 on Chromosorb W with the following program: 100 °C (3 min), 25 °C/min, 250 °C (10 min). The detector was FID. **Caution!** Avoid contamination with metals. Such contamination may cause rapid decomposition, generation of large quantities of oxygen gas, and high pressures.

Acknowledgment. We are grateful to Abic Ltd. Ramat-Gan for the donation of DDAB.

Registry No. $PhNO_2$, 98-95-3; PhNO=NPh, 495-48-7; $RuCl_3$, 10049-08-8; H_2O_2, 7722-84-1; aniline, 62-53-3; tetraethylammonium bromide, 71-91-0; tetrapropylammonium bromide, 1941-30-6; tetrabutylammonium bromide, 1643-19-2; tetrapentylammonium bromide, 866-97-7; tetrahexylammonium bromide, 4328-13-6; tetraheptylammonium bromide, 4368-51-8; didecyltrimethylammonium bromide, 1119-94-4; didecyldimethylammonium bromide, 2390-68-3; tricaprylmethylammonium bromide, 26305-24-8.

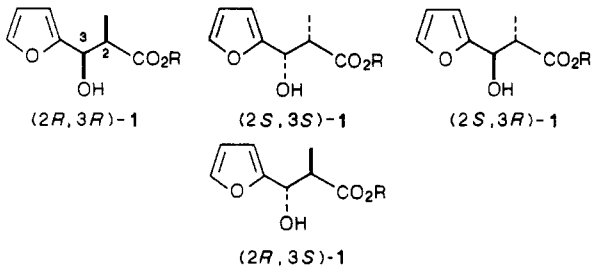
A New and Practical Synthesis of Four Possible Stereoisomers of 3-(2-Furyl)-3-hydroxy-2-methylpropionate

Masato Kusakabe and Fumie Sato*

Department of Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

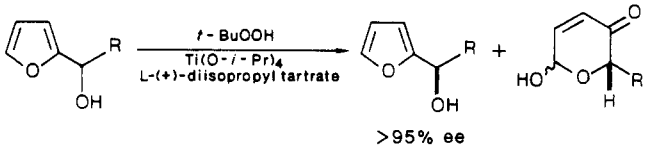
Received December 20, 1988

Optically active 3-(2-furyl)-3-hydroxy-2-methylpropionate (1) has been utilized as a key intermediate for the synthesis of several natural compounds,[1] and thus the synthesis of four possible stereoisomers of 1 has attracted much interest in recent years. Procedures currently



available for their preparation include asymmetric aldol reaction of furfural and chiral enolate,[1a,b] asymmetric reduction of 3-(2-furyl)-2-methyl-3-oxopropionate using yeast,[2] and enantioselective enzymatic hydrolysis of the corresponding acetate of 1 using lipase.[3] There is, however, no single methodology that allows the highly stereoselective synthesis of all the four possible stereoisomers of 1.

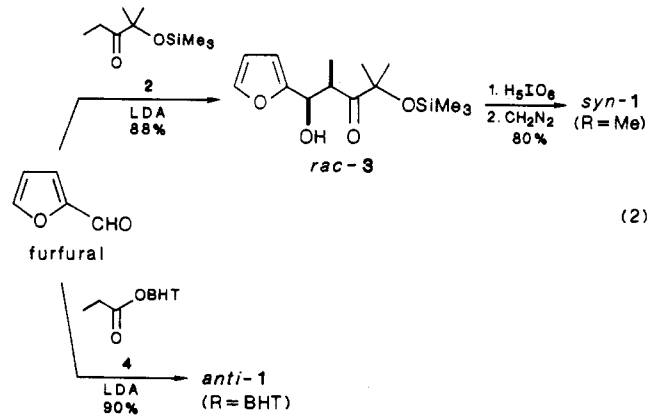
Recently we have reported that the kinetic resolution of 2-furylcarbinols using the Sharpless reagent proceeds highly efficiently to provide a practical method for the synthesis of homochiral 2-furylcarbinols (eq 1).[4] Herein



(1)

we report that the kinetic resolution of racemic 1 with syn and anti configuration, both of which can be readily prepared by Heathcock's aldol methodology, provides a convenient access to all the stereoisomers of 1.

The aldol reaction of furfural and α-[(trimethylsilyl)oxy] ketone 2[5] afforded racemic 3 predominantly in 88% yield, which was converted into racemic *syn*-1 (R = Me) in 80% overall yield by oxidative cleavage (H_5IO_6) followed by esterification (CH_2N_2) (eq 2). On the other hand, the reaction of furfural and 2,6-di-*tert*-butyl-4-methylphenyl propionate (BHT propionate, 4)[6] afforded racemic *anti*-1 (R = BHT) predominantly in 90% yield (eq 2).



(2)

The kinetic resolution of *syn*-1 (R = Me) using 0.6 equiv of *tert*-butyl hydroperoxide (TBHP) and a catalytic amount (20 mol %) of Ti(O-*i*-Pr)$_4$/L-(+)-diisopropyl tartrate (L-(+)-DIPT) proceeded highly efficiently to provide (2*R*,3*R*)-1 (R = Me) in 45% yield (based on racemic 1), which can be readily separated from the corresponding oxidation product and L-(+)-DIPT by column chromatography on silica gel (eq 1). The optical purity of (2*R*,3*R*)-1 (R = Me) thus obtained was found to be more than 99% ee by ^{1}H NMR analysis of the corresponding acetate in the presence of (+)-Pr(dppm)$_3$ (dppm = di(perfluoro-2-propoxypropionyl)methanato). Spectral data and optical rotation of (2*R*,3*R*)-1 (R = Me) were in good agreement with the reported values,[1a] $[\alpha]^{25}_D$ +14.7° (*c* 1.64, $CHCl_3$) [lit.[1a] $[\alpha]_D$ +14.75° (*c* 1.8, $CHCl_3$)]. The kinetic resolution of *anti*-1 (R = BHT) under the same reaction conditions also proceeded highly efficiently to afford (2*S*,3*R*)-1 (R = BHT) of more than 99% ee in 49% yield.[7] Needless to say, two other isomers of 1, i.e., (2*S*,3*S*)- and (2*R*,3*S*)-1, can be prepared by the kinetic resolution using D-(−)-DIPT as a chiral source instead of L-(+)-DIPT.

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(6) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087.

(7) Compound 3 was found to be a poor kinetic resolution substrate. Thus, the optical purity of the remaining 3 after ca. 60% conversion was only 63% ee.

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