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A 'waterproof' catalyst for the oxidation of secondary amines to nitrones with alkyl hydroperoxides

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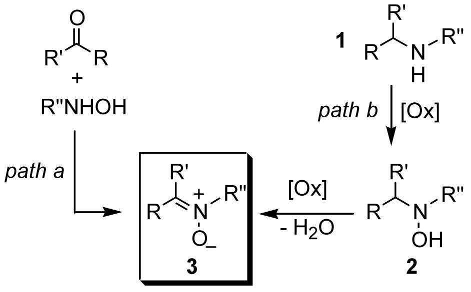
Abstract—Catalytic oxidation of secondary amines to nitrones using alkyl hydroperoxides as primary oxidant has been demonstrated for the first time. The titanium alkoxide catalyst is protected from co-product water by the combined use of a tightly binding trialkanolamine ligand and molecular sieves. Nitrones can be obtained in high yield (up to 98%) under homogeneous, anhydrous conditions and even in the absence of solvent. The reactions are fast (2–7 h) and good selectivity can be achieved with as little as 1% catalyst. © 2002 Elsevier Science Ltd. All rights reserved.

Nitrones are versatile and valuable synthetic intermediates for the synthesis of heterocycles[1] and natural products[2] and they are also effective spin trap reagents.[3] Usually, they are synthesized either via condensation of carbonyl compounds with *N*-monosubstituted hydroxylamines (Scheme 1, path a)[4] or by oxidation of secondary amines or the corresponding hydroxylamines (Scheme 1, path b).[5]

In principle, the oxidative approach provides the most direct and general method for preparing nitrones.[6] Stoichiometric oxidants used in these reactions include oxaziridines[7] or dioxirane.[8] Alternatively hydrogen peroxide (2–7 equiv.) is used as primary oxidant[9] in the presence of a catalyst (1–8% mol) such as Na_2MoO_4 or Na_2WO_4[5,6,10,11] $MeReO_3$[12] or SeO_2.[10,13] Excellent yields have been obtained for the catalytic oxidation of certain amines. However, other cases suffer from limited chemoselectivity such that a significant amount of hydroxylamine is recovered.[12] With highly reactive nitrones, over-oxidation and hydrolysis can be significant problems.[6,14] It occurred to us that these problems might be addressed by developing a catalytic system that uses an alkyl hydroperoxide rather than hydrogen peroxide as primary oxidant.



Scheme 1. Synthesis of nitrones via (a) condensation of carbonyl compounds with *N*-monosubstituted hydroxylamine or (b) the oxidation of secondary amines.

A literature report indicated that reaction of dibutylamine with *tert*-butyl hydroperoxide in the presence of 4% titanium(IV) isopropoxide produced 'trace amounts' of the corresponding nitrone.[15] One interpretation of this result is that the active titanium catalyst species is being destroyed by hydrolysis as the reaction proceeds. (Note that a molar equivalent of water is necessarily formed in the conversion of **2** to **3**.) We hoped to address this problem in two ways: (1) addition of molecular sieves to remove water from the system as it is generated, and (2) replacement of some of the isopropoxide ligands on the titanium catalyst with a chelating polydentate ligand. In particular, the C_3-symmetric trialkanolamines **4a–c** seemed attractive candidates as ligands for this application. We have previously utilized a catalyst generated from titanium(IV) isopropoxide and **4c**[16] in the enantioselective oxidation of alkyl aryl sulfides using cumyl hydroperoxide as primary oxidant.[17] The catalyst proved highly

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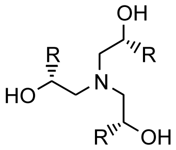
efficient, reaching enantiomeric excesses up to 84% and up to 1000 turnovers. Significantly, these catalysts were highly robust, maintaining their solution integrity and catalytic performance even in the presence of a large excess of alkyl hydroperoxide or alcohol.[18]

4a R=H
(*S,S,S*)-**4b** R=Me
(*R,R;R*)-**4c** R=Ph



In an initial study, dibenzylamine **1a** was used as model substrate and the optimized conditions from our sulfoxidation studies were utilized [10% catalyst generated from Ti(O^{i}Pr)$_4$ and **4c**].[17,18] An excess (4 equiv.) of cumyl hydroperoxide was used as oxidant and reactions were run in $CDCl_3$ and monitored by ^{1}H NMR.[19]

As shown in Figure 1, complete conversion of the amine into the nitrone was observed in all cases and no hydroxylamine **2a** was observed. At 25°C (Fig. 1A) the reaction was slow and required 143 h for completion; however, an identical run in the presence of 5 Å molecular sieves was complete in 45 h. An identical pair of runs at 60°C (Fig. 1B) showed a further reduction in reaction time to 4 h in the absence of additive and 2.5 h in presence of molecular sieves. Thus increasing the reaction temperature accelerates the reaction without a loss of selectivity while molecular sieves apparently extend catalyst life, presumably by removal of the water produced during the reaction.[20]

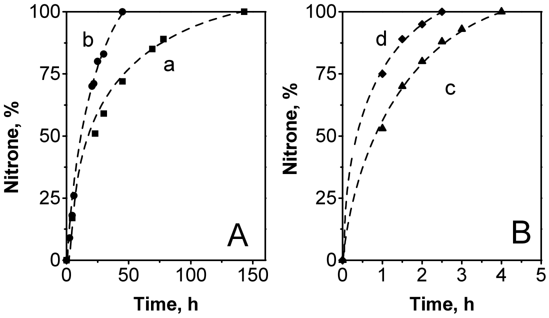


Figure 1. Dependence of the yields of nitrone **3a** on the time (h) for the oxidation of dibenzyl amine **1a** [0.1 M] with CHP [0.4 M] catalyzed by Ti(IV)/(*R,R,R*)-**4c** [0.01 M] in $CDCl_3$. (A) $T = 25$°C (■, curve a) and with 5 Å molecular sieves (250 mg/mmol) (●, curve b). (B): at 60°C (▲, curve c) and with 5 Å molecular sieves (250 mg/mmol) (◆, curve d).

The nature of the ligand and the hydroperoxide both significantly impact the rate and selectivity of the reaction as shown in Table 1. These reactions were run at 60°C in the presence of 10% catalyst and 5 Å molecular sieves.

Interestingly, at this rather high catalyst loading and in the presence of molecular sieves, complete conversion of the amine could be achieved using inexpensive Ti(O^{i}Pr)$_4$ in combination with cumyl hydroperoxide. However, the chemoselectivity was somewhat low (91%) in this case. Reactions using the achiral titanatrane derived from **4a** (commercially available as TYZOR® TE) proceeded only slowly; even after 21 h, conversions were <15%.[21]

In contrast, chiral catalysts prepared from Ti(O^{i}Pr)$_4$ and (*S,S,S*)-**4b** or (*R,R,R*)-**4c** afforded nitrone **3a** in high yield, with complete conversion of the reagent and excellent chemoselectivity. Reaction rates for ligand **4c** were consistently faster than those for **4b**. For both ligands, cumyl hydroperoxide was superior to *t*-butyl hydroperoxide in terms of both rate and chemoselectivity. Under the best conditions (ligand **4c**/cumyl hydroperoxide) complete conversion of the amine to **3a** could be achieved in 2.5 h.

It was subsequently determined that reactions proceeded somewhat faster in the presence of 4 Å versus 5 Å molecular sieves and consequently 4 Å sieves were used in the remainder of our studies.Table 2 shows the effect of increasing the substrate to catalyst ratio on the oxidation of dibenzylamine with cumyl hydroperoxide. Using a catalyst prepared from Ti(O^{i}Pr)$_4$ and **4c**, complete conversion of the dibenzylamine with 100% selectivity for the nitrone was observed in 1 h, even at a substrate to catalyst ration $s/c = 100$. It is noteworthy that, in order to maintain the catalyst concentration at 0.01M, this reaction was performed neat. However, further increasing the ratio to $s/c = 1000$ (which necessarily dropped the catalyst concentration to 0.001 M) resulted in a severe deterioration of chemoselectivity.

Table 1. Effect of the ligand and oxidant on the Ti-catalyzed oxidation of dibenzylamine[a]

Catalyst/oxidant	Time (h)	Conv. (%)[a]	**2a** (%)[a]	**3a** (%)[a]	PhCHO (%)[b]
Ti(^{i}PrO)$_4$/TBHP	8.0	66	3	60	3
Ti(^{i}PrO)$_4$/CHP	8.0	100	–	91	9
Ti(IV)/**4a**/TBHP	21.0	13	–	13	–
Ti(IV)/**4a**/CHP	21.0	14	–	14	–
Ti(IV)/**4b**/TBHP	105.0	>99	3	91	6
Ti(IV)/**4b**/CHP	6.0	>99	–	>99	–
Ti(IV)/**4c**/TBHP	8.0	>99	–	98	2
Ti(IV)/**4c**/CHP	2.5	>99	–	>99	–

[a] Conditions: hydroperoxide (0.4 M), Ti(IV) (0.01 M) and dibenzylamine (0.10 M) in $CDCl_3$ at 60°C with 5 Å molecular sieves (250 mg/mmol).
[b] Yields of dibenzylhydroxylamine **2a**, *N*-benzylidene benzylamine *N*-oxide **3a** and benzaldehyde determined via ^{1}H NMR using DCE as internal standard.

Table 2. Effect of substrate/catalyst ratio on oxidation of dibenzylamine[a]

$[Bn_2NH]_0$, M	Substrate/ catalyst	Time (h)	Yield (**3a**) (%)[b]
0.1	10:1	3.0	100
0.2	20:1	1.5	100
1.0	100:1	1.0	100
1.0	1000:1	100.0	68[c]

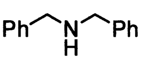
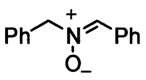
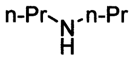
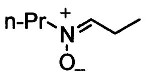
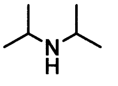
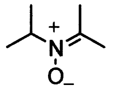
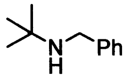
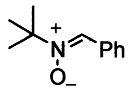
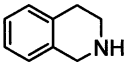
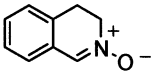
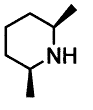
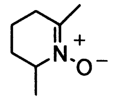
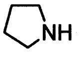
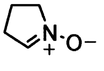
[a] Conditions: $Ti(O^iPr)_4 = \mathbf{4c} = 0.01$ M, dibenzylamine **1a**, cumyl hydroperoxide (4 equiv.) and 4 Å sieves in $CDCl_3$ at 60°C.

[b] Determined via ^1H NMR using DCE as internal standard.

[c] 100% conversion; other products: *N*-benzylidene benzylamine (10%), PhCHO (22%).

The conditions for the highest catalyst loading (10%) from Table 2 were adopted to explore the scope of the reaction with other secondary amines. Table 3 reports isolated yields for a series of pure nitrones prepared under these conditions. The nitrones were readily isolated via removal of the solvent under vacuum followed by chromatography over silica gel.[22]

Table 3. Catalytic oxidation of secondary amines by CHP[a]

Substrate		Product		Time, h	Yield, %[b]
	**1a**		**3a**	3.0	91
	**1b**		**3b**	3.0	70
	**1c**		**3c**	5.0	98
	**1d**		**3d**	2.0	92
	**1e**		**3e**	6.0	65
	**1f**		**3f**	7.0 3.0	39[c] 85[d]
	**1g**		**3g**	5.0 2.5	-- 45[d]

a. Reaction Conditions: $[substrate]_0$=0.10 M, $[CHP]_0$=0.40 M; $[Ti(IV)/\mathbf{4c}]_0$= 0.01 M, 4A ms, $CHCl_3$ at 60°C.

b. Based on isolated product after chromatography. Reactions werecarried out on mmol scale .

c. 6-(Hydroxyimino)-heptan-2-one was also detected via ^1H NMR and gc-mass (25%).

d. Only two equiv of CHP were used $[CHP]_0$=0.20M.

Linear secondary amines (**1a**–**d**) and the cyclic *N*-benzyl derivative **1e** afforded the corresponding nitrones in synthetically useful yields (70–98%) in 2–6 h. In the case of 1,2,3,4-tetrahydroisoquinoline **1e**, exclusive formation of the regioisomer originating from benzylic oxidation was observed.

For the more reactive cyclic secondary amines **1f** and **1g**, it proved advantageous to modify the reaction conditions. When we attempted to oxidize *cis*-2,6-dimethylpiperidine **1f**, using 4 equiv. of hydroperoxide, the over-oxidation product 6-(hydroxyimino)-heptan-2-one was found in the reaction mixture (25%, determined via ^1H NMR), together with higher amounts of nitrone **3f** (39%). When the amount of hydroperoxide was decreased to 2 equiv., the yield of **3f** increased dramatically to 85%. It should be noted that nitrone **3f** is a chiral molecule, and in principle could be formed enantioselectively using our enantiopure catalyst. However, ^1H NMR analysis in the presence of a chiral solvating agent indicated that **3f** was generated in racemic form.[23]

The use of homochiral trialkanolamines in a reaction where enantioselectivity is not an issue deserves some comment. Synthesis of the trialkanolamine by reaction of ammonia with an enantiopure epoxide in the ligand synthesis avoids the formation of diastereomeric (*R*,*S*,*S*) and (*R*,*R*,*S*) co-products. We initially assumed that use of the pure homochiral ligand would be important to avoid destabilizing interactions between the ligand arms in the case of the undesired diastereomers. Interestingly, we have recently tested this premise using the crude mixture of trialkanolamines generated from racemic styrene oxide and ammonia, which contains a mixture of both diastereomers and regioisomers derived from attack of ammonia at the benzylic position. We were somewhat surprised to discover that this catalyst shows comparable activity to that prepared from fully purified (*R*,*R*,*R*)-**4c**. This observation will be followed up in our future studies.

We feel that the prospects for further improvements in this reaction are excellent and plan to pursue this research. However, the current study has broader implications beyond the issue of nitrone synthesis. Hydrolytic instability is a general problem when using early transition metal catalysts. Among the early transition metals, titanium is especially attractive because of its low cost and non-toxic nature. In this paper we have demonstrated that, with the proper choice of ligands and reaction conditions, a *catalytic* quantity of titanium can function in a reaction which produces a *stoichiometric* amount of water.

Acknowledgements

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19. Typical oxidation procedure with Ti(IV) catalysis: in a 1.0 ml volumetric flask Ti(IV)-based catalyst (0.01 mmol) was dissolved in $CDCl_3$. Activated molecular sieves (25 mg), the hydroperoxide (0.4 mmol) and, after 30 min, the substrate were added. The solution was transferred in a screw cap NMR tube, warmed to the reaction temperature and the course of the reaction was monitored by ^1H NMR. For a detailed procedure for the synthesis of Ti(IV)/**4a**–**c** complexes see Refs. 17 and 18.
20. A reaction containing molecular sieves but no titanium catalyst resulted in no significant conversion of the amine into products.
21. The oxidation of diethylamine with the achiral dimer $((\eta^2\text{-}t\text{-butylperoxo})\text{titanatrane})_2$ as stoichiometric oxidant was reported by Boche et al. Et_2NOH was formed and recovered as the insoluble hydroxyldiethylamine titanatrane complex: Boche, G.; Möbus, K.; Harms, K; Marsh, A. *J. Am. Chem. Soc.* **1996**, *118*, 2770.
22. Typical oxidation procedure with Ti(IV)/**4c** catalysis: in a 25 ml screw-cap vial, under nitrogen, the preformed catalyst (0.1 mmol) was dissolved in 10 ml of $CHCl_3$. 250 mg of 4 Å activated molecular sieves were added, followed by CHP (4.0 mmol, 80% in cumene) and, after 30 min, by the substrate (1.0 mmol). The solution was heated at 60°C and the reaction course has been monitored via TLC. After the disappearance of the reagent, the solvent was removed under vacuum and the reaction mixture was purified directly via radial chromatography over silica gel (gradient: ethyl ether, petroleum ether). For a detailed procedure for the synthesis of Ti(IV)/**4c** complex see Refs. 17 and 18.
23. The enantiomeric excess of the product was determined via ^1H NMR in $CDCl_3$ in the presence of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol.