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C_3-Symmetric Titanium(IV) Triphenolate Amino Complexes for a Fast and Effective Oxidation of Secondary Amines to Nitrones with Hydrogen Peroxide

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Abstract: The efficient catalytic oxidation of secondary amines to nitrones using hydrogen peroxide as primary oxidant is described. The titanium(IV) complex **2** bearing a C_3-symmetrical triphenolate amino ligand has proved to be an air- and water-tolerant complex that efficiently catalyzes secondary amine oxidations at 60 °C without previous activation [catalyst loading as low as 0.01%, yields up to 99%, turnover numbers (TONs) up to 8000 and turnover frequencies (TOFs) up to 11000 h^{-1}).

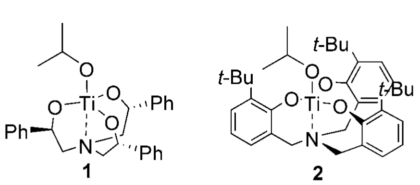
Keywords: homogeneous catalysis; hydrogen peroxide; nitrones; oxidation; secondary amines; titanium(IV)

Nitrones are valuable synthetic intermediates for the synthesis of biologically active compounds,[1] as effective spin trap reagents[2] and as therapeutic agents.[3] Usually, they are synthesized either *via* condensation of carbonyl compounds with *N*-monosubstituted hydroxylamines, *N*-alkylation of oximes and zinc-mediated reduction of nitroalkanes and nitroarenes, in the presence of aldehydes.[4] Another important synthetic procedure consists of the oxidation of secondary amines,[5] hydroxylamines[6] or imines.[7]

In principle, the oxidative approach, using hydrogen peroxide (or urea hydrogen peroxide) or alkyl hydroperoxide starting from corresponding secondary amines, provides the most direct and general method for preparing nitrones.[8,9] Hydrogen peroxide (2–7 equiv.) is used as primary oxidant in the presence of a catalyst (1–8% mol) such as Na_2MoO_4, Na_2WO_4, CH_3ReO_3 or SeO_2. Good 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 or overoxidation can be observed and hydrolysis of the products can be a significant problem.[5b,10]

Recently we have shown the possibility to use the titanium alkoxide catalyst **1** for this reaction using alkyl hydroperoxides as primary oxidants.[9] Nitrones are obtained in high yield (up to 98%) under homogeneous 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. The catalyst is protected from co-product water by the addition of molecular sieves. The high stability of **1** allows the incorporation of the catalysts in polyvinylidene difluoride (PVFD) membranes without affecting their performance even after 5-fold recycling of the catalytic membrane.[11]

More recently we have been interested in the study of coordination chemistry and catalytic activity of C_3-symmetrical triphenolate amino complexes of Ti(IV).[12] In particular we have shown that the *in situ* prepared Ti(IV) triphenolate amino complex **2** (Figure 1), is able to activate hydrogen peroxide and catalyze the oxidation of sulfides, with catalyst loadings down to 0.01%, TONs up to 8000 and TOFs up to 1700 h^{-1}.[12b] The Ti(IV)-tri(phenolate) amino complex **2** is structurally very similar to **1** when considering the trigonal bipyramidal coordination geometry of Ti(IV) and the number and type of donor atoms. The higher acidity of phenol compared to alcohol has a beneficial effect on the stability of **2** with respect to **1** and thus allows higher TONs on the oxidation of sulfides. Moreover, as shown in the previous works, the presence of the *tert*-butyl groups on the periphery (upper rim) of the ligand is essential for the stability of the complex in the presence of water.



1 **2**

Figure 1. Titanatranes from C_3-symmetrical tris(2-phenyl ethanolate amino (**1**) and triphenolate amino (**2**) ligands.

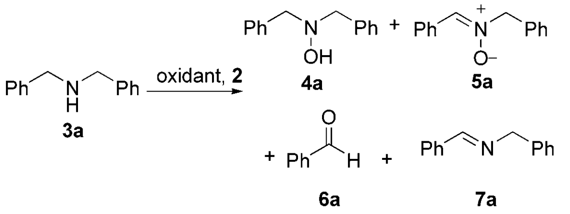
Herein we report that the *in situ* prepared Ti(IV) triphenolate amino complex **2** is a very stable and highly efficient catalyst for the oxidation of secondary amines to nitrones. The catalyst is highly active in the competitive solvent MeOH using aqueous hydrogen peroxide as the primary oxidant. These reaction conditions are unprecedented for these kinds of catalysts and make them far superior to the titanatrane **1**.

Triphenolamine has been prepared with a new synthetic strategy, recently developed by us, based on a three-fold reductive amination of the corresponding substituted salicyl aldehyde,[12a] followed by a reaction of the triphenolamine with Ti(O-*i*-Pr)$_4$ in $CHCl_3$ under nitrogen furnishing the corresponding mononuclear, C_3-symmetric Ti(IV) complex **2**. The formation of the complexes is fast and quantitative, as confirmed by ^{1}H NMR spectra recorded a few minutes after mixing of the reagents.[12b]

Stimulated by the remarkable stability of complex **2** even in the presence of large excesses of water, we decided to study also the catalytic activity of **2** in the oxidation of secondary amines using aqueous hydrogen peroxide as oxidant. The use of hydrogen peroxide is highly advantageous, since it is non-toxic and environmentally friendly, producing only water as by-product.

In an initial study, dibenzylamine **3a** was used as model substrate and the optimized conditions from our previous studies with catalyst **1** were utilized [1% catalyst , 4 equiv. of cumyl hydroperoxide (CHP), in $CDCl_3$). However, under these reaction conditions a rather slow conversion of the reagent occurred and the corresponding imine **7a** was obtained as main product. (Table 1, entry 1).

Table 1. Oxidation of dibenzylamine **3a** catalyzed by **2** at 60 °C. Effect of the oxidant and solvent.[a]



	ROOH	Solvent	Time [h]	Conv.[b] [%]	**4a:5a:6a:7a**
1	CHP	$CDCl_3$	24	76	3:0:21:76
2	TBHP	$CDCl_3$	12	36	0:25:20:55
3	H_2O_2	CD_3CN	18	83	16:75:9:0
4	H_2O_2	CD_3OD	8	98	1:92:7:0
5	H_2O_2[c]	CD_3OD	8	>99	0:96:4:0

[a] *Reaction conditions:* [**3a**]$_0$ = 0.1 M; **3a**:oxidant:**2** = 1:4:0.01, 60 °C.

[b] Based on the substrate, determined *via* ^{1}H NMR using DCE as internal standard.

[c] Reaction carried out using multiple additions of hydrogen peroxide: one equivalent every half hour.

The preferential imine **7a** formation could originate from the degradation of CHP which initiates radical processes under the reaction conditions.[13] The use of *tert*-butyl hydroperoxide as primary oxidant did not improve significantly the system, allowing the recover of only 20% of nitrone **5a** (Table 1, entry 2) .

Despite the modest results in chloroform with alkyl hydroperoxides, we decided to investigate the catalytic activity of the complex using aqueous hydrogen peroxide (70%) in methanol or acetonitrile (Table 1, entries 3–5). Interestingly, in both cases complete conversion of the amine **3a** in few hours with high yields in nitrone **5a** was observed. Among the two solvents that allow us to work under homogeneous conditions, methanol gave the best result in terms of reactivity and selectivity (Table 1, entry 4). The detailed analysis of the reaction course clearly showed the formation of the hydroxylamine intermediate **4a** that is subsequently oxidized to the corresponding nitrone **5a** (Figure 2).

As in the case of the titanatranes **1**, along the course of the reaction we observe the formation of the benzaldehyde **6a**. This product is arising from the hydrolysis/overoxidation of nitrone **5a**. In order to improve the yields we decided to perform multiple additions of hydrogen peroxide at time intervals. Indeed, the addition of one equivalent of hydrogen peroxide every 30 min effected a decrease of the aldehyde **6a** formation in favour of the corresponding nitrone **5a** (96% in 8 h).

The effect of substrate concentration and catalyst loading was further studied to determine the catalytic efficiency of the system. Table 2 shows the effect of increasing the substrate to catalyst ratio on the oxidation of dibenzyl amine **3a**. Good substrate conversion with high selectivity for the nitrone **5a** were obtained even at a substrate to catalyst ratio up to 10,000 for total 8000 TONs and a very high TOF (11,000 h^{-1}) (table 2, entry 4). Interestingly, further decreasing the catalyst loading (0.01%), which necessarily drops the catalyst concentration to 0.01 mM, did not affect sensibly the chemoselectivity and slow down the reaction.

The scope of the reaction was explored under the conditions reported in Table 2, entry 1, catalyst loading 5%. Table 3 reports isolated yields for a series of nitrones prepared under these conditions on a 1.0-mmol scale . The nitrones were readily isolated *via* removal of the solvent under vacuum followed by chromatography over silica gel.

All the nitrones were obtained in synthetically useful yields (73–98%). In the case of less hindered amines (**3a**, **b**, **e**, **f**) the oxidation occurs in short reaction times while more hindered amines (**3c**, **d**) require longer reaction times, up to 45 h. Interestingly the chemoselectivity of the reaction remains high because of the high stability of the catalyst under turnover

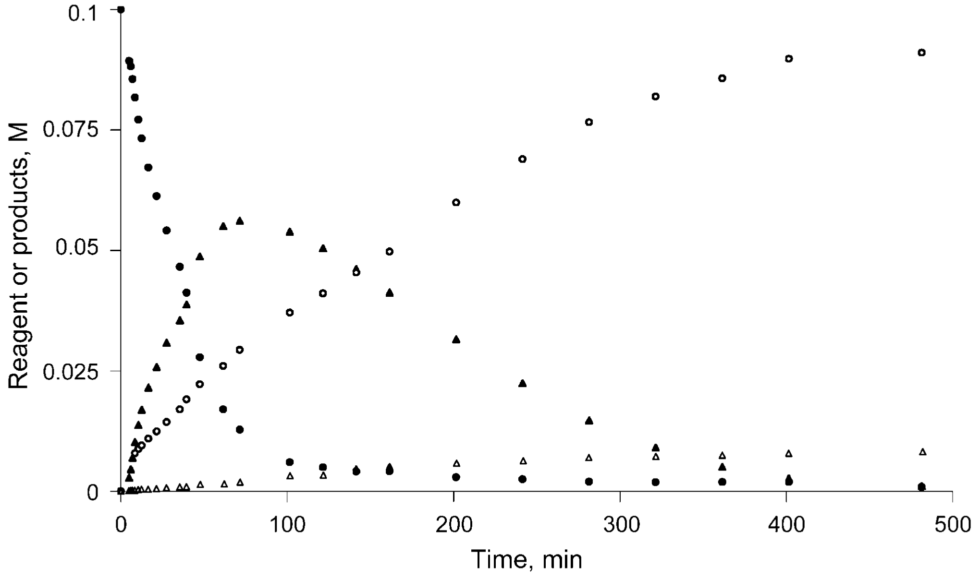


Figure 2. Dependence of the yields of nitrone (○, **5a**), hydroxylamine (▲, **4a**) and benzaldehyde (△, **6a**) on the time (min) for the oxidation of dibenzylamine (●, **3a**) [0.1 M] with aqueous H_2O_2 (70%) [0.4 M] catalyzed by **2** [0.001 M] in CD_3OD at 60 °C.

Table 2. Oxidation of dibenzylamine **3a** catalyzed by **2** at 60 °C with aqueous H_2O_2 (70%). Effect of concentration and catalyst loading.[a,b]

	$[\mathbf{3a}]_0$ [M]	**2** [%]	$t_{1/2}$[c] [min]	**5a**[d] [%][c]	TON	TOF[e] [h^{-1}]
1	0.1	5	10	92	18	80
2	0.1	1	31	90	90	3180
3	1	0.1	17	84	840	3200
4	1	0.01	26	80	8000	11000

[a] *Reaction conditions:* **3a**: oxidant = 1:4, aqueous H_2O_2 (70%), 60 °C in CD_3OD.

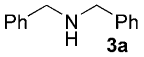
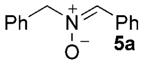
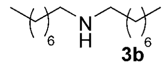
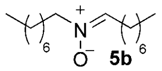
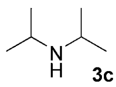
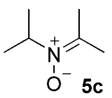
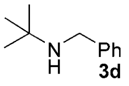
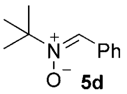
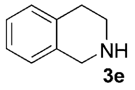
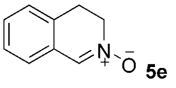
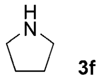
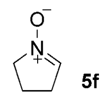
[b] Uncatalyzed reaction yields 25% of **5a** after 15 h.

[c] Time for 50% decrease of $[\mathbf{3a}]_0$.

[d] Based on the substrate, determined *via* ^1H NMR using DCE as internal standard. In the final reaction mixture unreacted **3a** and **4a** intermediates are the other compounds present.

[e] Determined at 20% conversion.

Table 3. Oxidation of secondary amines **3a–f** by aqueous H_2O_2 (70%) catalyzed by **2** (5%) at 60 °C.[a]

	Substrate	Product	Time [h]	Yield[b] [%]
1	 **3a**	 **5a**	2.0	92
2	 **3b**	 **5b**	3.5	97
3	 **3c**	 **5c**	45.0	73
4	 **3d**	 **5d**	45.0	92
5	 **3e**	 **5e**	0.5	99
6	 **3f**	 **5f**	3.0	76

[a] *Reaction conditions:* $[\mathbf{3a}]_0 = 1\,M$; **3a**: H_2O_2: **2** = 1:4:0.05, 60 °C.

[b] Based on the substrate, determined *via* ^1H NMR.

conditions and of hydrogen peroxide, that does not decompose. In the case of substrate **3e** (Table 3, entry 5) a single nitrone was obtained, consistent with the regioselectivity already observed with other oxidizing systems.[8,9]

In summary, we have reported that the C_3-symmetrical Ti(IV) complex **2** is an effective catalyst for the oxidation of secondary amines to nitrones. Thanks to the high stability of the complex **2**, the inexpensive and *'green'* aqueous hydrogen peroxide can be used as primary oxidant, with catalyst loadings down to 0.01%, high selectivity for the nitrone production, reaching TONs up to 8000 and fast reactions (TOFs up to 11,000). More detailed studies on the use of different oxidants and on the mechanism of the reaction and the characterization of the species involved in the process are currently in progress.

Experimental Section

Typical Oxidation Procedure with Ti(IV)/2 Catalysis

In a 25-mL screw-cap vial, under nitrogen, the *in situ* formed complex in $CDCl_3$ catalyst (0.05 mmol) was dissolved in 10 mL of MeOH, followed by H_2O_2 (4.0 mmol, 70% in water) and, after 30 min, by the substrate (1.0 mmol). The solution was heated at 60 °C and the reaction course was monitored *via* TLC, GC-MS and ^{1}H NMR. 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). Products were identified by comparison of ^{1}H NMR and mass spectral data with those reported in literature.[5b,14] For a detailed procedure for the synthesis of Ti(IV) complex **2** see Ref.[14]

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