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Effective Oxidation of Secondary Amines to Nitrones with Alkyl Hydroperoxides Catalysed by (Trialkanolaminato)titanium(IV) Complexes

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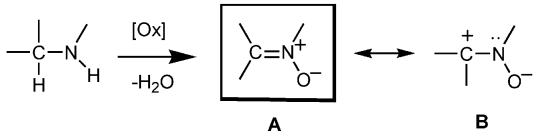
The effective catalytic oxidation of secondary amines to nitrones with alkyl hydroperoxides as the primary oxidants is described. The titanium alkoxide catalysts are protected from the water co-product by the combined use of a tightly binding trialkanolamine ligand and molecular sieves. Nitrones can be obtained in high yields (up to 98 %) under homogeneous, anhydrous conditions and even in the absence of solvent. The reactions are fast (2–7 h) and good selectivity and complete conversion can be achieved with as little as 1 % catalyst.

Introduction

Nitrones (*N*-alkylidenealkylamine *N*-oxides)[1] have the general structure described by the two limit resonance forms **A** and **B** and can be regarded as products originating from a double oxygen transfer to secondary amines, followed by loss of water.[2]



The nitrone function resembles the carbonyl group in its facilitation of the removal of a proton from an adjacent carbon under basic conditions, as well as in the addition of organometallic compounds to the unsaturated carbon.[2,3] The resonance structure **B** accounts for the reactivity towards nucleophiles.[4] Moreover, another form of reaction behaviour characteristic of nitrones arises from the carbon–nitrogen double bond and *N*-oxide functionality (structure **A**): as a result of their 1,3-dipolar electronic distribution of this kind, nitrones readily undergo cycloaddition reactions.[5] A variety of heterocycles and natural products have been synthesized[3,5,6] by exploitation of each of these modes of reactivity. Cyclic nitrones in particular are of fundamental importance for synthetic purposes. Also noteworthy is the use of nitrones either as spin trap reagents in EPR spectroscopy[7] or as therapeutic agents.[8]

The synthesis of nitrones is commonly achieved through condensation of carbonyl compounds with *N*-monosubstituted hydroxylamines, *N*-alkylation of oximes or zinc-mediated reduction of nitroalkanes or nitroarenes in the presence of aldehydes.[9] Another important synthetic procedure consists of the oxidation of secondary amines,[10] hydroxylamines[11] or imines.[12]

In principle, the catalytic oxidative approach provides the most direct and general method of synthesis.[13] Hydrogen peroxide (2–7 equiv.), for example, has been employed as a stoichiometric oxidant in the presence of catalysts (1–10 mol-%) such as Na_2MoO_4 or Na_2WO_4,[10,14] $MeReO_3$,[15] SeO_2,[14] Pt^{II}[16] or Ti^{IV}.[17] Moreover, dioxygen has been employed as primary oxidant in the presence of cyclohexanone monooxygenase as catalyst.[18]

Such oxidations often afford nitrones in high yields. In some cases, however, the reaction suffers from limited selectivity: for some substrates a significant amount of hydroxylamine is recovered. On the other hand, over-oxidation and hydrolysis can be a significant problem with highly reactive nitrones.[19] These problems might be addressable through the development of a catalytic system that uses a milder and more selective primary oxidant, such as an alkyl hydroperoxide. In this regard we were attracted to the possibility of a catalyst system based on titanium. Titanium complexes are inexpensive and non-toxic and are known to activate alkyl hydroperoxides. However, a challenge in the current application is that a stoichiometric amount of water is produced during the course of the oxidation and many titanium complexes are sensitive toward hydrolysis.

In a preliminary communication we reported that the titanatranes **2**[20] (Scheme 1) are able to catalyse the oxidation of secondary amines to nitrones by alkyl hydroperoxides.[21,22] In the presence of catalyst **2c** (1.0 %), for example, amine oxidations can be carried out in chloroform at 60 °C in nearly quantitative yields in as little as 1 hour.

The ability of a trialkanolamine ligand such as **1c** to stabilize titanium in the presence of water may well have utility beyond the current application. However, a limitation that needs to be overcome is the use of a homochiral ligand

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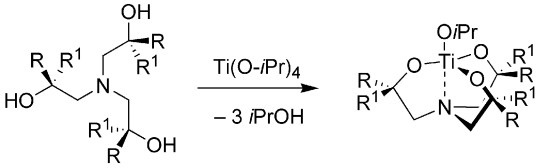


1a: R = R^1 = H
(*S*,*S*,*S*)-**1b**: R = Me, R^1 = H
(*R*,*R*,*R*)-**1c**: R = H, R^1 = Ph
1d: R = R^1 = Me

2a: R = R^1 = H
(*S*,*S*,*S*)-**2b**: R = Me, R^1 = H
(*R*,*R*,*R*)-**2c**: R = H, R^1 = Ph
2d: R = R^1 = Me

Scheme 1. Synthesis of titanatranes **2a**–**d** from the corresponding trialkanolamines **1a**–**d**.

prepared from a relatively expensive enantiopure epoxide. Consequently, this study had two principal objectives. We first explored the effect of parameters such as solvent, the type of molecular sieves and catalyst loading on catalytic efficiency. Secondly, we extended our studies to the use of alternative trialkanolamines such as achiral **1d** and, especially, the mixed-ligand system obtained from ammonia and *racemic* styrene oxide. Individual diastereomeric and regioisomeric components from this mixed-ligand system were prepared and tested, revealing unexpected trends in the reactivities of the corresponding catalysts.

Results and Discussion

Effect of Key Reaction Parameters

Encouraged by the results reported in our preliminary communication, we undertook an investigation of six critical parameters that would be expected to affect the rate and selectivity of the reaction. These factors include the choice of ligand, alkyl hydroperoxide, molecular sieves and solvent, as well as the substrate/catalyst and oxidant/substrate ratios.

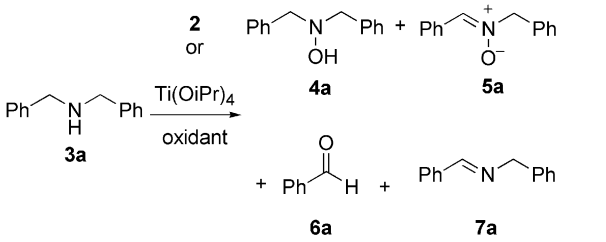
Influence of the Trialkanolamine Ligand

A series of reactions were performed with either Ti(O*i*Pr)$_4$ or titanatranes **2** as catalyst and either *tert*-butyl hydroperoxide (TBHP) or cumyl hydroperoxide (CHP) as primary oxidant. A standard set of reaction conditions was utilized (solvent chloroform, 60 °C, oxidant/substrate/catalyst = 40:10:1). Results are summarized in Table 1 and include several noteworthy observations.

Under the standard conditions, Ti(O*i*Pr)$_4$ proved to be a reasonably effective catalyst (Entries 1, 2). However the reaction is not completely selective and nitrone is obtained in high yield (91%) only with CHP as stoichiometric oxidant (Entry 2). Interestingly, a titanium complex bearing the parent triethanolamine ligand **1a** (Entries 3, 4) proved to be a less effective catalyst than Ti(O*i*Pr)$_4$ itself. Reactions proceeded very slowly, resulting in low levels of conversion (10% or less after 21 h).[23]

With regard to the titanatrane complexes **2b** and **2c** (Entries 5–10), it is evident that α-substitution of the hydroxy-bearing C atom provides much more effective catalysts. Catalyst **2c** (R = Ph) appears somewhat more effective than **2b** (R = Me). It is unclear whether this is due to electronic effects (enhanced Lewis acidity) or steric effects (improved hydrolytic stability) or to some combination of both.

Table 1. Effect of the catalyst, alkyl hydroperoxide and molecular sieves (MS) on the oxidation of dibenzylamine (**3a**).



	Cat/ROOH/MS [a]	Time / h	Conv.[b] / %	**5a**[b] / %	**6a**[b] / %
1	Ti(O*i*Pr)$_4$/TBHP/5 Å	9.0	66	60	3
2	Ti(O*i*Pr)$_4$/CHP/5 Å	8.0	100	91	9
3	**2a**/TBHP/5 Å	21.0	6	6	–
4	**2a**/CHP/5 Å	21.0	10	10	–
5	**2b**/TBHP/5 Å	105.0	100	91	6
6	**2b**/CHP/5 Å	6.0	>99	>99	nd
7	**2c**/TBHP/5 Å	8.0	100	98	2
8	**2c**/CHP/5 Å	2.5	>99	>99	nd
9	**2c**/CHP/4 Å	2.0	100	99	1
10	**2c**/CHP/3 Å	1.5	100	>99	–
11	**2d**/TBHP/4 Å	8.0	100	98	2
12	**2d**/CHP/4 Å	2.0	100	99	1
13	**2c-mix**[c]/CHP/4 Å	1.0	100	98	2

[a] Conditions: [ROOH]$_0$ = 0.4 M, [Ti^{IV}]$_0$ = 0.01 M, [**3a**]$_0$ = 0.10 M, in $CDCl_3$ at 60 °C, molecular sieves (250 mg mmol^{-1}). [b] Determined by ^{1}H NMR with DCE as internal standard. [c] Ligand prepared from racemic styrene oxide; see text.

Effect of the Alkyl Hydroperoxide

In all cases in Table 1, CHP is superior to TBHP as stoichiometric oxidant. This is somewhat unfortunate for large-scale synthetic applications in terms of separating side-product alcohol from the nitrone product (*tert*-butyl alcohol is volatile whereas cumyl alcohol frequently requires chromatographic separation). The difference between CHP and TBHP, however, is small when the best catalysts – **2c** and **2d** – are used. Therefore, from the standpoint of practicality, TBHP may be the better oxidant for larger-scale applications.

With the best combination of ligand and alkyl hydroperoxide (CHP/**2c**), complete conversion of **3a** into **5a** could be achieved in only 1.5 h (Entry 10). Consequently, we focused on this system in our subsequent studies.

Effect of Molecular Sieves

A set of experiments was carried out in the presence of 5 Å, 4 Å and 3 Å molecular sieves (250 mg per mmol of substrate) under the standard conditions (Figure 1 and Table 1, Entries 8–10).

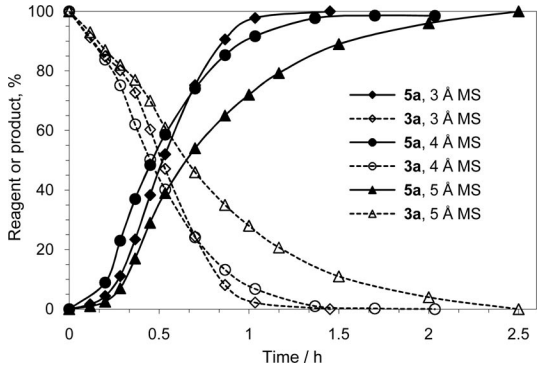


Figure 1. Time-dependence (h) of formation of the nitrone **5a** through the oxidation of dibenzylamine (**3a**) by CHP catalysed by (*R*,*R*,*R*)-**2c** (0.01 M) in $CDCl_3$, at 60 °C in the presence of molecular sieves (3 Å, 4 Å and 5 Å, 250 mg mmol^{-1}). $[\mathbf{3a}]_0$ = 0.10 M; $[CHP]_0$ = 0.40 M.

The reaction proceeds more rapidly in the presence of 3 Å or 4 Å molecular sieves than it does with 5 Å sieves: complete conversion into nitrone **5a** is observed in 1.0–1.5 h in the first two cases, in comparison with 2.5 h in the last. A much less substantial difference is observed with 3 Å instead of 4 Å molecular sieves and either may be employed.

In addition, a control experiment was carried out under otherwise identical conditions but with omission of molecular sieves. The reaction was significantly slower, requiring 4 h for completion; nevertheless, complete conversion of **3a** to **5a** had been achieved after that time. In contrast, when the reaction was run with 4 Å sieves but with omission of the titanium catalyst, no reaction occurred.

Solvent

The use of solvents other than $CDCl_3$ was briefly investigated. In particular, reactions in the apolar solvent [D_6]benzene and in the more polar protic solvent [D_4]MeOH were carried out (Figure 2). Quantitative yields of nitrone were obtained with all three solvents, although significant differences in reaction rate were observed. In benzene the reaction is almost twice as fast [$t_{1/2(benzene)}$ = 16 min vs. $t_{1/2(chloroform)}$ = 27 min] whereas in methanol it is four times slower [$t_{1/2(methanol)}$ = 105 min]. A major contribution to the decreased reactivity in methanol is likely to be the competition between the alcoholic solvent and the alkyl hydroperoxide for coordination to the catalyst, which should lower the concentration of the active Ti^{IV}-peroxo complex.

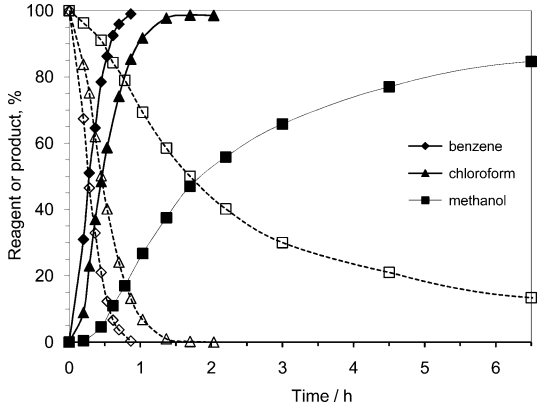


Figure 2. Solvent-dependence ($[\mathbf{3a}]_0$ = 0.10 M) of the rate of oxidation of amine **3a** (dashed lines) to nitrone **5a** (solid lines) by CHP ($[CHP]_0$ = 0.40 M) catalysed by (*R*,*R*,*R*)-**2c** (0.01 M) at 60 °C and in the presence of molecular sieves (4 Å, 250 mg mmol^{-1}).

Because of safety considerations, benzene itself is an inappropriate choice of solvent for synthetic applications. However, these results suggest that other non-polar solvents such as toluene may prove advantageous for this oxidation.

Oxidant/Substrate Ratio

The stoichiometry of the oxidation of a secondary amine to a nitrone requires a minimum of two molar equivalents of oxidant for complete conversion. In fact, most of the reported catalytic methods employ an excess of hydrogen peroxide (up to 7 equiv.). However, an excess of oxidant can in some cases have a negative effect on the reaction outcome. In particular, nitrones formed by oxidation of cyclic amines tend to be unstable under oxidative conditions and often undergo further oxidation. In view of the high levels of conversion achieved with four molar equivalents of alkyl hydroperoxide, we investigated whether the use of an excess of oxidant was actually necessary to the process.

A set of reactions was carried out under the standard catalytic conditions, but with reductions in the amounts of oxidant to 3 equiv. or 2 equiv. In both cases neither unreacted hydroxylamine **4a** nor over-oxidation or decomposition products were detected, indicating that selectivity is not influenced by the relative amount of alkyl hydroperoxide. As shown by the kinetic profiles in Figure 3, the reactions were slower, but nearly complete conversion of dibenzylamine into nitrone **5a** was achieved even at an oxidant/substrate ratio of 2:1.

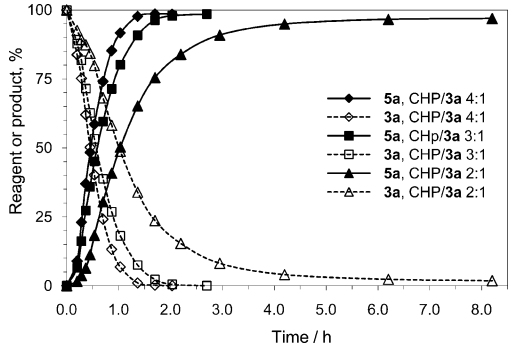


Figure 3. Time-dependence of the yields of amine **3a** and nitrone **5a** in the oxidation of **3a** ($[\mathbf{3a}]_0$ = 0.10 M) by CHP (2–4 equiv.) catalysed by (*R*,*R*,*R*)-**2c** (0.01 M) in $CDCl_3$, at 60 °C in the presence of molecular sieves (4 Å, 250 mg mmol^{-1}).

Substrate/Catalyst Ratio

Catalyst loading is an important consideration for catalytic systems, because it can affect both raw materials cost and ease of product isolation. The results reported in Table 2 and Table 3 show the effect of increasing the sub-

strate/catalyst ratio on the oxidation of dibenzylamine **3c** with CHP. With (*R*,*R*,*R*)-**2c** as catalyst, 20:1, 100:1 and 1000:1 ratios were used.

Table 2. Oxidation of dibenzylamine (**3a**) with CHP (4 equiv.) catalysed by (*R*,*R*,*R*)-**2c** (0.01 M) in $CDCl_3$, at 60 °C and in the presence of molecular sieves (4 Å, 250 mg mmol^{-1} substrate).

	[**3a**]$_0$ / M	**3a**:(*R*,*R*,*R*)-**2c**	Time / h	**5a**[a] / %
1	0.1	10:1	2.5	100
2	0.2	20:1	1.5	100
3	1.0	100:1	1.0	100
4	1.0	1000:1	100.0	68 [b]

[a] Determined by ^{1}H NMR with DCE as internal standard. [b] 100% conversion; other products including benzaldehyde (**6a**, 22%) and *N*-benzylidenebenzylamine (**7a**, 10%) were detected.

Table 3. Oxidation of dibenzylamine **3a** ([**3a**]$_0$ = 0.10 M) with CHP ([CHP]$_0$ = 0.40 M) catalysed by (*R*,*R*,*R*)-**2c** in $CDCl_3$, at 60 °C and in the presence of molecular sieves (4 Å, 250 mg mmol^{-1} substrate).

	3a/(*R*,*R*,*R*)-**2c**	[**2c**] / mM	Time / h	**5a**[a] / %
1	10:1	10.0	2.5	100
2	20:1	5.0	4.0	100
3	100:1	1.0	21.0	100
4	1000:1	0.1	71.0	60[b]

[a] Determined by ^{1}H NMR with DCE as internal standard. [b] 83% conversion; other products including *N*,*N*-dibenzylhydroxylamine (**4a**, 5%), benzaldehyde (**6a**, 9%) and *N*-benzylidenebenzylamine (**7a**, 9%) were detected.

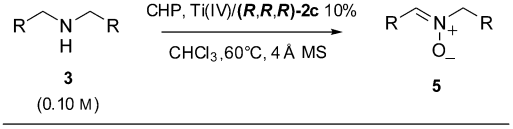
In the first case (Table 2) the catalyst loading was decreased by increasing the substrate concentration (up to 1.0 M), and the CHP concentration accordingly, whereas the concentration of the catalyst was kept constant ([**2c**]$_0$ = 0.01 M). In the second set of experiments (Table 3) catalyst concentration was decreased (0.01–0.0001 M) with a constant substrate concentration ([**3a**]$_0$ = 0.10 M).

The results reported in Table 2 and Table 3 show that complete conversion of dibenzylamine and 100% selectivity for the nitrone could be achieved in the presence of 1% of catalyst (Entries 3). Faster reaction times were obtained in the first set of experiments (Table 2) as a result of the increased reactant concentration: it is noteworthy that in order to maintain the catalyst concentration at 0.01 M the reaction corresponding to a substrate/catalyst ratio of 100:1 (Table 2, Entry 3) was performed under essentially neat conditions. Such high efficiency in the neat reaction would be a prerequisite for the development of a solvent-free protocol for a high-performance synthesis of nitrones. Because the yields of nitrone were quantitative in both cases, 100 turnovers could likewise be obtained under higher-dilution conditions. When the substrate/catalyst ratio was further increased to 1000:1, which necessarily dropped the catalyst concentration to 0.001 M in the case of Table 3, a substantial decrease in chemical yield as a result of significantly diminished selectivity was observed (Entries 4). Yields of nitrone of up to 68%, corresponding to 680 catalytic cycles, were obtained.

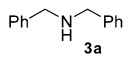
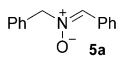
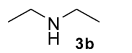
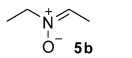
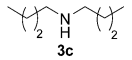
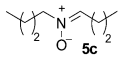
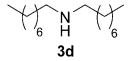
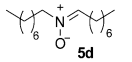
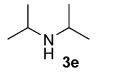
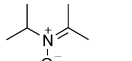
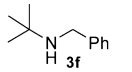
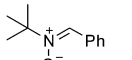
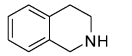
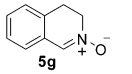
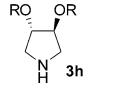
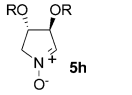
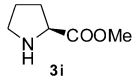
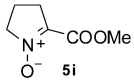
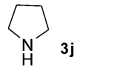
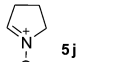
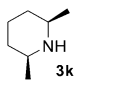
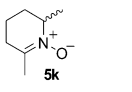
Scope of the Reaction

A standard protocol based on the above studies was selected to explore the scope of the reaction. These standard conditions involved the use of a 10% loading of catalyst **2c** with four molar equivalents of cumyl hydroperoxide relative to the secondary amine substrate. Unless otherwise indicated, the results in Table 4 were obtained in chloroform as solvent at 60 °C in the presence of molecular sieves (4 Å).

Table 4. Oxidation of the secondary amines **3a**–**g** by CHP (80% in cumene) catalysed by (*R*,*R*,*R*)-**2c** (10%) at 60 °C.[a]



3 (0.10 M) → **5**

	Substrate	Product	Time / h	Yield[b] / %
1	 **3a**	 **5a**	3.0	91
			24[c]	70[c]
2	 **3b**	 **5b**	3.0	90
3	 **3c**	 **5c**	3.0	70
4	 **3d**	 **5d**	3.0	95
5	 **3e**	 **5e**	5.0	98
6	 **3f**	 **5f**	2.0	92
7	 **3g**	 **5g**	6.0	65
8	 **3h** R = TBDMS	 **5h** R = TBDMS	8.0	63
9	 **3i**	 **5i**	2.0	73
10	 **3j**	 **5j**	5.0	–[d]
			2.5	45[e]
			7.0	39
11	 **3k**	 **5k**	18.0	90[f]
			3.0	85[e]

[a] Reaction conditions: [**2a**]$_0$ = 0.1 M; **3**/CHP/Cat = 1:4:0.1, 60 °C. [b] Based on products isolated after chromatography. Reactions were carried out on mmol scale. [c] Reaction performed neat ([**3a**]$_0$ = 1.00 M) in the presence of **2a** TYZOR®TE (10%) as catalyst. [d] Only decomposition products were observed. [e] Reaction was carried out in the presence of only two equivalents of CHP. [f] Reaction was carried out at 30 °C.

The acyclic and cyclic secondary amines **3a**–**i** (Entries 1–9) afforded the corresponding nitrones **5a**–**i** in synthetically useful yields (63–98%). In the cases of **3g** and **3i** the systems proved to be completely regioselective, with exclusive formation of the regioisomers **5e**, originating from benzylic oxidation, and **5i**, originating from the tertiary carbon oxidation, being observed. The *C*-aldonitrones **5a**, **5b**, **5d** and **5f** and the keto nitrone **5e** were found to be quite stable in the oxidative environment and could be isolated in yields of 90% or higher.

Worthy of note is the synthesis of the enantiopure (*R*,*R*)-nitrone **5h**, a valuable intermediate for the synthesis of glycosidase inhibitors and many other natural products,[13] which could be obtained in good yields without decomposition or removal of the *tert*-butyldimethylsilyl protecting groups (Table 4, Entry 8). This results is superior to those previously reported in the literature, in which the corresponding hydroxylamine was oxidized to the nitrone with SeO_2 as catalyst.[24] The directed oxidation of the secondary amine bearing *O*-MOM protecting groups has been reported as well, but in this case stoichiometric amounts of the much less "green" HgO were used.[25]

Another cyclic nitrone **5i**, originating from oxidation of (*S*)-proline methyl ester (**3i**), was obtained with complete regiocontrol and in high yield, much higher than that previously reported (73% vs. 45%; Table 4, Entry 9).[10a] The presence of the ester function proved to be totally compatible with the oxidizing system.

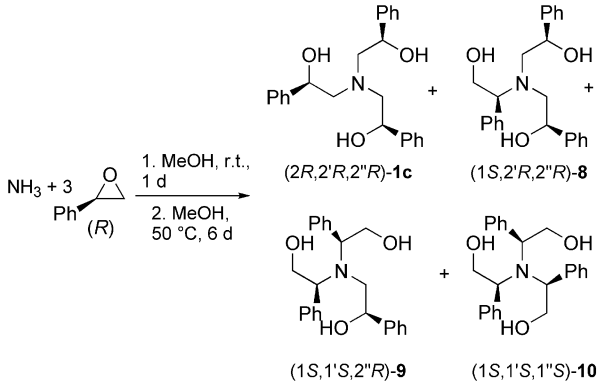
Also shown in Entry 1 is an attempt to oxidize dibenzylamine (**3a**) in the presence of the triethanolamine catalyst **2a** (10%) carried out under almost neat conditions ($[\mathbf{3a}]_0$ = 1.0 M, $[CHP]_0$ = 4.0 M). This resulted in 100% conversion of the amine after 24 h and a 70% yield of the isolated nitrone **5a**, although the achiral titanatrane **2a** had previously been shown to be far less active than the C_α-substituted titanatranes **2b**–**d** under dilute conditions (see Table 1 and discussion thereafter). This example is significant because it suggests that running these reactions at higher concentrations may similarly prove beneficial for other catalysts and substrates.

Under the standard conditions (4 equiv. CHP) the more reactive cyclic amines **3j** and **3k** afforded little or none of the corresponding nitrones (Entries 10 and 11). Such low yields are a common trend observed in the synthesis of cyclic nitrones by oxidation: cyclic nitrones do not survive in the presence of excess oxidant and are easily further oxidized to oximes or carbonyl compounds.[10,15a] In order to improve the yields for the oxidation of the cyclic amines **3j** and **3k** it proved advantageous to modify the reaction conditions. With only 2 equiv. of oxidant the yields of the corresponding nitrones were significantly increased, to 45% for **5j** and 85% for **5k**. A high yield of **5k** (90%) could be also obtained with 4 equiv. of CHP but with oxidation at 30 °C. It may be noted that nitrone **5k** is a chiral molecule and could in principle be formed stereoselectively with use of an enantiopure catalyst such as (*R*,*R*,*R*)-**2c**. However ^1H NMR analysis in the presence of (*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol as chiral solvating agent showed that **5k** was obtained as a racemic mixture.

Alternatives to Enantiopure Trialkanolamines

Significance of C_3 Symmetry

In this study the C_3 enantiopure trialkanolamines **2b** and **2c** were used in reactions in which enantioselectivity was not an issue. This fact deserves some comment. First of all, the presence of at least one substituent on each oxygen-linked trialkanolamine C atom has a crucial role in affording mononuclear titanatranes, which appear to be better catalysts for oxidation reactions.[20] In fact, the unsubstituted titanatrane **2a** is known to form polynuclear aggregates in solution and the corresponding peroxo complexes are very reactive and unstable, resulting in extensive decomposition of the oxidant over time.[20,26] Furthermore, the enantiopure trialkanolamines are synthetically much easier to prepare as pure compounds: the synthesis of (*R*,*R*,*R*)-**1c** carried out by addition of ammonia to enantiopure (*R*)-styrene oxide affords (*R*,*R*,*R*)-**1c** as the main component in 80% yield, although a smaller amount of (1*S*,2′*R*,2′′*R*)-**8** is formed as well, due to incomplete regiocontrol of the nucleophilic attack on the epoxide. (Scheme 2).[27] Two other regioisomers – (1*S*,1′*S*,2′′*R*)-**9** and (1*S*,1′*S*,1′′*S*)-**10** – could in principle also be formed, although, presumably as a result of the steric congestion around the nitrogen atom, their formation is not observed (Scheme 2).



Scheme 2. Synthesis of (*R*,*R*,*R*)-**1c** through a threefold ring-opening of (*R*)-styrene oxide with ammonia.

Despite these attractive features of the C_3 ligand **1c**, its preparation from the relatively expensive optically pure styrene oxide and the need for chromatographic purification of the ligand both represent disadvantages. As an alternative, we have noted that useful reaction rates can be achieved with titanium isopropoxide (Table 1, Entry 2) or the triethanolamine complex **2a** (Table 4, Entry 1) as catalysts under highly concentrated conditions. However, selectivity in nitrone formation, relative to catalyst **2c**, is diminished in both cases. For this reason we investigated additional alternatives as described below.

Catalysis with an Achiral Trialkanolamine

The achiral ligand **1d** is readily prepared from isobutylene oxide and ammonia. As shown in Table 1, Entry 12, the corresponding titanium complex **2d**[28] affords the nitrone **5a** in nearly quantitative yield after 2.0 h with CHP as pri-

mary oxidant. At least at this relatively high (10%) catalyst loading, the performances of catalysts **2c** and **2d** were virtually indistinguishable. This excellent reactivity may in part reflect the high stability of titanatrane **2d** toward hydrolysis. In fact, a hydrolysis half-life of more than one year has been determined for the corresponding silatrane under conditions in which hydrolysis of the unsubstituted silatrane exhibits a half-life of only six minutes.[29]

Ligand Preparation from Racemic Styrene Oxide

The ligands (*S*,*S*,*S*)-**1b** and (*R*,*R*,*R*)-**1c** both possess C_3 symmetry and as such are homochiral. We initially assumed that such homochirality would enhance catalytic efficiency. We reasoned that this would promote the formation of a single catalytic species in the system and avoid destabilizing interactions between the ligand arms with opposite chirality in the case of the undesired diastereomers. In order to test this premise we carried out the addition of ammonia to racemic styrene oxide in propan-2-ol solution, using a MW-assisted technique. In contrast with the synthesis of ligand **1c** shown in Scheme 2, the analogous reaction carried out with racemic styrene oxide can also yield diastereomers of the possible four regioisomers, in particular the diastereomeric trialkanolamine (2*R**,2′*R**,2′′*S**)-**1c**′ (Scheme 3).

An ammonia solution in propan-2-ol (2.0 M) was used in this synthesis in order to avoid the formation of the solvolysis products that had previously been observed in reactions carried out in methanol.[25] After 4 h at 130 °C (300 W), 68% conversion was observed (determined on the crude product by ^{1}H NMR). The trialkanolamines were obtained as a mixture of regio- and diastereoisomers in 62% total yield after separation from unreacted epoxide by filtration through silica gel.

The regioisomeric ratio was estimated by ^{1}H NMR to be approximately (**1c** + **1c**′)/(**8** + **8**′ + **8**′′) = 92:8. No significant amounts of the regioisomers **9** and **10** were detected. On the other hand, the diastereomers (2*R**,2′*R**,2′′*R**)-**1c** and (2*R**,2′*R**,2′′*S**)-**1c**′ were obtained in a 1:2 ratio. The mixture of ligands **1c-mix** was treated with a stoichiometric amount of Ti(O*i*Pr)$_4$, yielding **2c-mix**. ^{1}H NMR analysis of the mixed Ti^{IV} complexes proved particularly diagnostic for determining the ratio of the different trialkanolamines, due to the downfield shift of the benzylic proton upon coordination to the metal centre.[30]

The Ti^{IV} complex mixture **2c-mix** was used in the oxidation of dibenzylamine (**3a**) by CHP, under the standard reaction conditions for the oxidation protocol (Table 1, Entry 13). The resulting kinetic profile is shown in Figure 4 (curve symbol: black diamond). For comparison, the kinetic profile obtained with (2*R*,2′*R*,2′′*R*)-**2c** as catalyst under identical conditions is also reported. We were quite surprised to discover that the catalyst **2c-mix** (curve symbol: black diamond) shows a significantly higher activity than the homochiral enantiopure (2*R*,2′*R*,2′′*R*)-**2c** (curve symbol: filled circle).

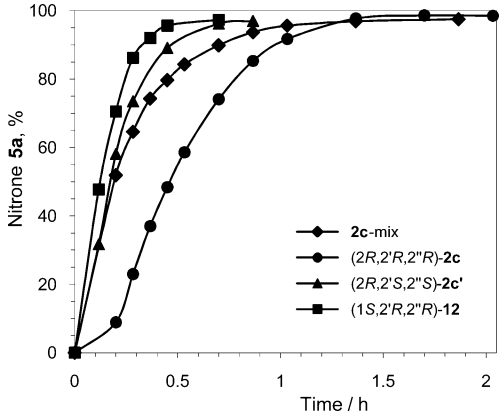
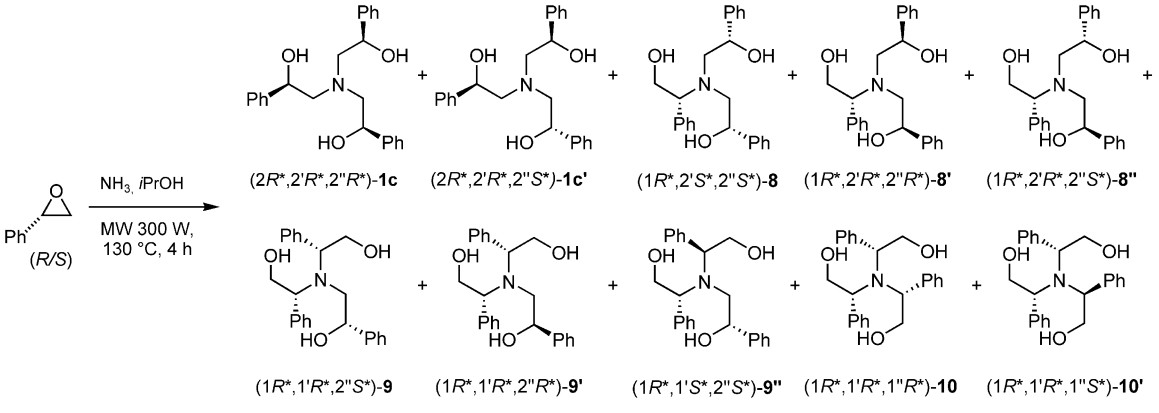


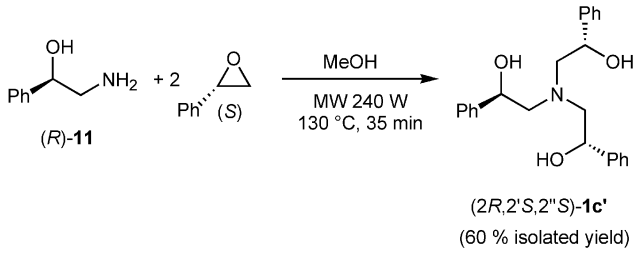
Figure 4. Dependence of reaction rate on the nature of the catalyst (0.01 M) in the oxidation of **3a** ([**3a**]$_0$ = 0.10 M) by CHP ([CHP]$_0$ = 0.40 M) in $CDCl_3$ at 60 °C and in the presence of molecular sieves (4 Å, 250 mg mmol^{-1}).

The substrate half-conversion time was 10 min in the former case and 30 min in the latter. Moreover, the typical induction period observed when **2c** is used as catalyst (ca. 10 min) appears to be absent in the reaction profile for **2c-mix**. Evidently at least one of the catalysts derived from Ti(O*i*Pr)$_4$ and the various constituents of **1c-mix** is a more active catalyst than **2c** itself.



Scheme 3. MW-assisted synthesis of the trialkanolamine **1c-mix** from racemic styrene oxide.

In order to test this premise, the behaviour of the individual trialkanolamines comprising **1c-mix** was examined separately. The diastereoisomer (2*R*,2′*S*,2′′*S*)-**1c**′ was prepared by the procedure shown in Scheme 4.



Scheme 4. Synthesis of (2*R*,2′*S*,2′′*S*)-**1c** through a double ring-opening of (*S*)-styrene oxide with (*R*)-**11**.

(*R*)-2-Amino-1-phenylethanol [(*R*)-**11**] was treated with enantiopure (*S*)-styrene oxide (2 equiv.) in methanol, under microwave irradiation conditions at 130 °C. The compound (2*R*,2′*S*,2′′*S*)-**1c**′ was obtained after chromatographic purification in good yield (60%). The regioisomer (1*S*,2′*R*,2′′*R*)-**8** was already available as a co-product of the synthesis of (*R*,*R*,*R*)-tris(2-phenylethanol)amine (**1c**) (Scheme 2).

The Ti^{IV} complexes **2c**′ and **12** (Figure 5) were prepared by the usual protocol and their reactivities were examined in the oxidation of dibenzylamine [curve symbol ▲ for (2*R*,2′*S*,2′′*S*)-**2c**′, curve symbol ■ for (1*S*,2′*R*,2′′*R*)-**12** (Figure 4)]. Both new Ti^{IV} complexes proved to be more active than **2c**, consistently with the observed increased activity of **2c-mix**. At least three of the possible isomeric titanatranes – (2*R*,2′*S*,2′′*S*)-**2c**′, (*1R*,2′*S*,2′′*S*)-**12** and (2*R*,2′*R*,2′′*R*)-**2c** – present in **2c-mix** thus promote catalytic activation of alkyl hydroperoxide for the fast and effective oxidation of secondary amines. In fact, we subsequently showed that the mixture of trialkanolamines obtained directly by addition of ammonia to inexpensive racemic styrene oxide *without chromatographic purification* of the single region- and stereoisomers can be used to prepare an effective Ti^{IV} catalyst for oxidation of secondary amines to nitrones.

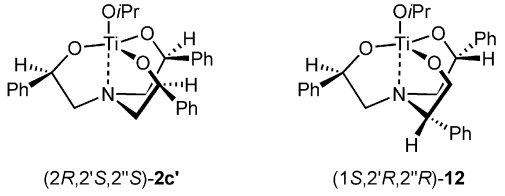


Figure 5. Titanatranes (2*R*,2′*S*,2′′*S*)-**2c**′ and (1*S*,2′*R*,2′′*R*)-**12** obtained from the corresponding trialkanolamines (2*R*,2′*S*,2′′*S*)-**1c**′ and (1*S*,2′*R*,2′′*R*)-**8**.

Conclusions

We have developed an effective and selective titanium-catalysed oxidation of secondary amines to nitrones. Several nitrones were prepared in synthetically useful yields and reaction times with the use of 10% of titanium catalyst. Even oxidatively sensitive nitrones could be prepared by limiting the amount of primary oxidant to the two molar equivalents required for the transformation. At least in the case of dibenzylamine, we have demonstrated that catalyst loading can be diminished to 1% and also that CHP can be replaced by the more attractive oxidant TBHP, in each case without significant loss of selectivity. Moreover, the excellent results obtained with catalysts **2d** and **2c-mix** demonstrate that this synthetic approach can be used without resorting to relatively expensive enantiopure ligands or ligand purification by chromatography.

An ideal protocol for the synthesis of sensitive nitrones such as **5f** should proceed rapidly under mild conditions with only the two molar equivalents of oxidant required by the stoichiometry. The desire for a high reaction rate is not merely a matter of convenience; rapid consumption of the primary oxidant minimizes the exposure of the product nitrone to the oxidative environment. We have not yet achieved this ideal situation; however, several observations during the course of these studies bode well for further progress toward this goal. The significantly faster reaction observed with catalyst **12** than with our standard catalyst **2c** is noteworthy in this regard and suggests that further improvements in catalyst efficiency are achievable. Furthermore, our results indicate that additional increases in the reaction rates should be attainable either by use of a nonpolar solvent or by running the reaction under highly concentrated or neat conditions.

Titanium is an especially attractive transition metal for applications in organic synthesis because of its low cost and nontoxic nature; however, hydrolytic instability is a general problem for many catalytic applications. A remarkable feature of this chemistry is that a *catalytic* amount of titanium complex is utilized in a reaction that produces a *stoichiometric* amount of water. This was accomplished through the combined use of molecular sieves and a tightly coordinating trialkanolamine ligand. In that regard, this study appears to have broader implications beyond its specific application to nitrone synthesis.

Experimental Section

General: All synthetic operations for catalyst preparation were carried out under nitrogen in an MBraun MB 200MOD glove-box, equipped with a MB 150 G-I gas recycling system (nitrogen working pressure: 6 bar). ^{1}H NMR kinetics were run by use of the *multi_zgvd (vdlist)* sequence on a Bruker Avance DRX 300 instrument. The working temperature was achieved by appropriate adjustment of the temperature control units. Molecular sieves (3 Å, 4 Å and 5 Å) both in pellet and in powder form were purchased from Aldrich and activated before use by overnight heating at 200–250 °C and cooling under nitrogen. Unless otherwise noted, Fluka dry-quality solvents were used (water <0.005–0.010%, stored over molecular sieves). When necessary, solvents were further purified or dried by standard techniques, stored over molecular sieves (4 Å) and degassed prior to use. Distilled water was filtered with a Millipore MILLI-Q system. Microwave-assisted reactions were performed with a Milestone MW Ethos-1600 lab station. Reaction

mixtures were prepared in 2- or 100-mL reactors (HPR-1000/10S, Milestone) fitted with pressure and temperature control units. Deuterated solvents were purchased from Aldrich ($CDCl_3$, 99.8% D; [D_4]MeOH, 99.8% D; [D_6]benzene, 99.6% D) and stored over molecular sieves (4 Å). All chemicals were purchased from Aldrich and Fluka as high-purity products (>95%) and were used without further purification. Ammonia was purchased as solutions (2.0 M) in dry methanol or propan-2-ol. (Triethanolaminato)titanium(IV) isopropoxide (Aldrich, 80 wt.-% solution in 2-propanol) was dried prior to use. (*R*)-(–)-2-Amino-1-phenylethanol (Aldrich, 90%) was stripped with dry toluene and dried prior to use. (*S*,*S*,*S*)-Tris-2-propanolamine (**1b**), (*R*,*R*,*R*)-tris-2-phenylethanolamine (**1c**), and tris(2-methyl-propan-2-ol)amine (**1d**) were prepared by literature procedures.[25,28] *tert*-Butyl hydroperoxide (Fluka, 80% solution in di-*tert*-butyl peroxide) was distilled under vacuum (bp = 33 °C/16 Torr) and stored at 4 °C over molecular sieves (4 Å). Cumyl hydroperoxide (Fluka, 80% solution in cumene) was stored at 4 °C over molecular sieves (4 Å). (3*S*,4*S*)-3,4-Bis[(*tert*-butyl)dimethylsilyloxy]pyrrolidine (**3h**) was prepared by a literature method.[30]

Analysis: Melting points are uncorrected and were determined with a Reichert Austria apparatus (1 °C precision). ^{1}H NMR spectra were recorded with a Bruker AC 200 instrument operating at 200.13 MHz or with a Bruker AC 250 (250.18 MHz) or Bruker Avance DRX 300 (300.13 MHz) instrument, with use of the partially deuterated solvent or TMS as internal references; TMS δ = 0 ppm, C*H*Cl_3 δ = 7.26 ppm, C*H*$_3$OH δ = 4.78, 3.35 ppm. ^{1}H NMR kinetics (at 28 °C or 60 °C) were recorded with Bruker AC 250 (250.18 MHz) and Bruker Avance DRX 300 (300.13 MHz) spectrometers fitted with probe temperature control units. ^{13}C NMR spectra were recorded with Bruker AC 250 (62.9 MHz) or Bruker Avance DRX 300 (75.5 MHz) spectrometers in H-decoupled mode, with use of the solvent carbon resonance as the internal standard: *C*HCl_3 δ = 77.0 ppm (t). Enantiomeric excesses were determined by ^{1}H NMR in the presence of (*R*)-(–)-(9-anthryl)-2,2,2-trifluoroethanol (Fluka, 98%).

Synthesis of (2*R*,2′*S*,2′′*S*)-Tris(2-phenylethanol)amine (1c′): (*R*)-(–)-2-Amino-1-phenylethanol (500 mg, 3.28 mmol) in dry methanol (0.80 mL) was placed in a 2 mL screw-cap Teflon® vial. (*S*)-Styrene oxide (0.845 mL, 7.24 mmol) was then added and the reaction mixture was irradiated in the microwave apparatus with the following program: initial power 300 W, target temp. 130 °C, 5 min; working power 240 W, T_{max} = 130 °C, 35 min, after which the reaction mixture was allowed to cool to room temperature. Complete conversion of the starting reagents was observed by TLC [silica gel, toluene/EtOAc (8:2) with triethylamine (5%)]. The volatile solvent was evaporated and purification by radial chromatography over silica gel (dichloromethane/ethyl acetate mixtures) afforded (2*R*,2′*S*,2′′*S*)-**1c′** (743 mg, 1.97 mmol, 60% yield) as a low-melting, yellowish product. m.p. 35–38 °C. $[\alpha]_D^{25}$ = +12.8 (*c* = 1.02, ethanol). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.57–7.20 (m, 15 H), 4.85 (dd, *J* = 9.3, 5.0 Hz, 1 H, CH), 4.79 (dd, *J* = 9.3, 4.0 Hz, 2 H, 2 × CH), 4.09 (br s, 3 H, 3 × OH), 2.97–2.83 (m, 6 H, 3 × CH_2) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 142.1, 141.9, 128.5, 127.7, 126.0, 125.9, 74.2, 72.3, 65.8, 65.6 ppm. $C_{24}H_{27}NO_3$ (377.48): calcd. C 76.36, H 7.21, N 3.71; found C 76.06, H 7.26, N 3.54.

Synthesis of 1c-mix: Racemic styrene oxide (2.820 mL, 24.0 mmol) was placed in a 100 mL Teflon®-coated vial and ammonia (2.0 M solution in dry propan-2-ol, 4.0 mL, 8.0 mmol) was added. The vial was capped and placed in the cavity of a Micro-Wave lab-station. A heating program was started with the following parameters: initial power 300 W, target temperature 130 °C, 5 min; working power 240 W, T_{max} = 130 °C, 60 min. After four irradiation cycles, the mixture was allowed to cool to room temperature and a 68% conversion of the starting epoxide was obtained. Solvent was then evaporated and crude **1c-mix** was separated from unreacted epoxide by radial chromatography (silica gel, petroleum ether/ethyl acetate 95:5), to provide **1c-mix** (1.872 g, 4.96 mmol, 62% yield) as a white solid. The **1c**/**8** regioisomeric composition in **1c-mix** was determined by ^{1}H NMR to be approximately 92:8, by integration of the peaks in the regions δ = 4.95–4.73 ppm (3 H of **1c** and 2 H of **8**) and 4.23–3.59 ppm (3 H of **8**).

(*R*,*R*)-Bis(2-phenylethanol)-(*S*)-(1-phenyl-2-ethanol)amine (8): Compound (1*S*,2′*R*,2′′*R*)-**8** was obtained by treatment of ammonia with (*R*)-styrene oxide by the literature procedure.[27] m.p. 52–53 °C. $[\alpha]_D^{25}$ = –63.5 (*c* = 1.02, ethanol). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.46–7.14 (m, 15 H, H_{Ar}), 4.76 (dd, *J* = 9.3, 3.5 Hz, 2 H, 2 × CH), 4.17–3.73 (m, 3 H, 1 × CH, 1 × CH_2), 2.97 (dd, *J* = 14.3 and 3.5 Hz, 2 H, 2 × diastereotopic C*H*H–), 2.77 (dd, *J* = 14.3 and 3.5 Hz, 2 H, 2 × diastereotopic CH*H*) ppm. ^{13}C NMR ($CDCl_3$, 250 MHz): δ = 142.3, 137.5, 128.6, 128.5, 128.3, 127.9, 127.7, 125.9, 72.9, 69.0, 62.7, 61.5 ppm. $C_{24}H_{27}NO_3$ (377.48): calcd. C 76.36, H 7.21, N 3.71; found C 76.12, H 7.24, N 3.62.

In Situ Preparation of Titanatranes 2a–d, 2c-mix, 2c′ and 12: For the NMR studies, Ti^{IV}/trialkanolamine complexes were prepared in situ from commercially available Ti(O*i*Pr)$_4$ in $CDCl_3$ as solvent by the literature procedure.[22,26] The resulting solutions (additionally containing 3 equiv. of 2-propanol released during preparation of the catalyst) were used directly without purification.

Compound 2d: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 4.55 (sept, *J* = 5.8 Hz, 1 H, CH), 3.13 (s, 6 H, 3 × CH_2), 1.32 (d, *J* = 5.8 Hz, 6 H, 2 × CH_3), 1.31 (s, 18 H, 6 × CH_3) ppm.

Compound (2*R*,2′*S*,2′′*S*)-2c′: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.48–6.99 (m, 15 H, H_{Ar}), 5.97–5.89 (dd, *J* = 8.8, 5.3 Hz, 1 H, CH), 5.67 (d, *J* = 7.0 Hz, 1 H, CH), 5.63–5.55 (dd, *J* = 10.0, 4.3 Hz, 1 H, CH), 4.77 (sept, *J* = 6.0 Hz, 1 H, $CHMe_2$), 3.43 (dd, *J* = 12.8, 1.3 Hz, 1 H, 1 × diastereotopic C*H*H), 3.35–3.16 (br m, 3 H), 2.81 (dd, *J* = 12.3, 4.3 Hz, 1 H, 3 diastereotopic C*H*H), 2.69 (dd, *J* = 12.5, 10.3 Hz, 1 H, 1 × diastereotopic C*H*H), 1.46 (d, *J* = 6.0 Hz, 6 H, 2 × CH_3) ppm.

Compound (1*S*,2′*R*,2′′*R*)-12: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.40–7.12 (m, 15 H, H_{Ar}), 6.33 (br m, 1 H, CH), 5.56 (t, *J* = 5.8 Hz, 1 H, CH), 5.17 (t, *J* = 5.8 Hz, 1 H, diastereotopic C*H*H), 4.96 (dd, *J* = 11.3, 7.5 Hz, 1 H, 1 × diastereotopic C*H*H), 4.80 (sept, *J* = 6.3 Hz, 1 H, $CHMe_2$), 4.48 (dd, *J* = 11.8, 5.3 Hz, 1 H, 1 × diastereotopic C*H*H), 4.11 (t, *J* = 7.8 Hz, 1 H, 1 × diastereotopic C*H*H), 3.72 (dd, *J* = 13.3, 5.6 Hz, 1 H, 1 × diastereotopic C*H*H), 3.23 (d, *J* = 5.8 Hz, 1 H, CH), 2.90 (dd, *J* = 11.8, 5.3 Hz, 1 H, 1 × diastereotopic C*H*H), 1.46 (d, *J* = 6.0 Hz, 6 H, 2 × CH_3) ppm.

Procedure for Ti^{IV}-Catalysed Oxidation of Dibenzylamine with TBHP/CHP, Monitored by ^{1}H NMR: The correct amount of Ti^{IV} catalyst (formed in situ, 0.1 M solution in $CDCl_3$) was placed in a screw-cap NMR tube containing powdered molecular sieves (3 Å, 4 Å or 5 Å, 13 mg). Alkyl hydroperoxide (from a 1.0 M solution in $CDCl_3$) was then added. After 30 min at room temperature the amine (from a 0.2 M solution in $CDCl_3$) was added at 0 °C. Solvent was added up to a 1.00 mL volume. The consumption of **3a** and formation of **5a** were monitored by recording proton NMR spectra at fixed times with use of 1,2-dichloroethane as internal standard.

Typical Procedure for Ti^{IV}-Catalysed Oxidation of Secondary Amines 3a–g with CHP/(*R*,*R*,*R*)-2c (mmol Scale): A 25 mL screw-cap vial containing a magnetic stirring bar was charged under nitrogen with powdered molecular sieves (4 Å, 250 mg), (*R*,*R*,*R*)-**2c** (0.10 mmol), dry chloroform (10 mL) and cumyl hydroperoxide

(2.00 or 4.00 mmol). The solution was stirred under nitrogen at room temperature for 30 min and was then cooled to 0 °C, after which one of the amines **3a**–**g** (1.00 mmol) was added. The vial was capped and the reaction mixture was warmed to 30 °C or 60 °C. The reaction course was monitored by TLC, GC–MS and ^{1}H NMR spectroscopy. After disappearance of starting material, the solution was allowed to cool to room temperature and filtered. The solids were washed with dichloromethane and the solvent was removed under vacuum. The crude product was purified by radial chromatography over silica gel (gradient: diethyl ether/petroleum ether). Yields were calculated on the isolated products, which were identified by comparison with melting points and ^{1}H NMR, ^{13}C NMR and MS spectroscopic data reported in the literature.[10,15a,24,31–34]

Oxidation of Dibenzylamine with CHP/2a: A 25 mL screw-cap vial containing a magnetic stirring bar was charged under nitrogen with molecular sieves (4 Å, 500 mg), **2a** (TYZOR® TE, 0.300 mL, 1.03 mmol) and cumyl hydroperoxide (7.15 mL, 40.3 mmol) and the reaction mixture was stirred at room temperature for 30 min. Dibenzylamine (2.00 mL, 10.1 mmol) was added at 0 °C and the reaction mixture was stirred overnight at 60 °C. After 18 h quantitative consumption of the substrate was observed by ^{1}H NMR spectroscopy. Molecular sieves were then filtered from the reaction mixture. Concentration and chromatographic purification (silica gel, petroleum ether/diethyl ether 1:1) afforded nitrone **5a** (1.486 g, 7.03 mmol, 70% yield) as a white solid.

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