Ti(IV)-amino triphenolate complexes as effective catalysts for sulfoxidation†

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Received 30th March 2010, Accepted 26th May 2010
First published as an Advance Article on the web 8th July 2010
DOI: 10.1039/c0dt00228c

C_3-symmetric Ti (IV) amino triphenolate complexes efficiently catalyze, without previous activation and in excellent yields, the oxidation of sulfides at room temperature, using both CHP and the more environment friendly aqueous hydrogen peroxide as terminal oxidants, with catalyst loadings down to 0.01%. The Ti(IV) catalysts and the intermediate Ti(IV)-peroxo complexes have been characterized in solution by ^{1}H NMR and ESI-MS techniques and *via* density functional studies.

Introduction

One of the current trends in catalyst design is the use of multidentate ligands for complexation of metal ions.[1] Two main advantages of this strategy are the high thermodynamic stability of the metal complexes, which allows low catalyst concentrations without loss of catalyst integrity, and the inhibited formation of multimeric metal species under turnover conditions. This important feature is obtained by the nearly complete filling of all vacant sites of the metal by a single ligand. In addition, the presence of single mononuclear species greatly facilitates mechanistic studies and catalyst optimization, especially in stereoselective processes. While C_2 symmetric bidentate ligands have been extensively used, the C_3 symmetric ligands[2] have attracted less attention in spite of their advantages when octahedral complexes are involved in the catalytic process.[2a] In recent years, their successful application has been demonstrated in a significant number of reactions.[3]

Our interest in this topic comes from the use of chiral C_3-symmetric Ti(IV)-trialkanolamine complexes **1** (Fig. 1) as oxidation catalysts.[3b,c,e,4] In the complexes the tetradentate coordination occurs through three alkoxides and a tertiary amine. This arrangement results in a high thermodynamic stability of the complex. In the presence of alkyl hydroperoxides these complexes are able to catalyze the stereoselective oxidation of alkyl aryl sulfides with enantiomeric purity up to 93% and turnover numbers (TON) up to 1000.[3b,j] We also showed that secondary amines are effectively oxidized to nitrones with high chemoselectivities, quantitative yields and TONs reaching 700.[3e] In addition, we have shown that the high thermodynamic stability of **1** allows their incorporation in polyvinylidene fluoride membranes without affecting their performance, even after five recycles of the catalytic membrane.[5] More recently, we have been interested in the structural analogous Ti(IV) amino triphenolate complexes **2** (Fig. 1).

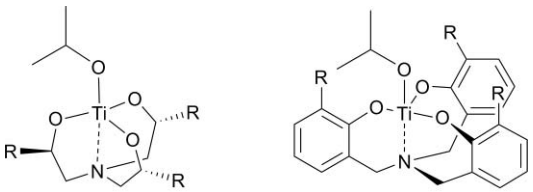

Fig. 1 Ti(IV) mononuclear complexes **1** and **2**.

These are very similar to **1** with respect to the trigonal-bipyramidal coordination geometry of Ti(IV), and to the number and type of donor atoms. On the other hand, because of the higher acidity of phenol compared to alcohol, we can expect a beneficial effect on the stability which allows for lower catalyst concentrations and loadings.

A substantial number of publications have appeared regarding the synthesis and complexation behaviour of amino triphenolate ligands **3** with transition metals.[6] Taking advantage of the high stability of these complexes, their applications are increasing rapidly. Among these metals, Ti(IV) amino triphenolate complexes **2** have been used successfully as polymerization catalysts.[7,8] In other organic transformations the variants of **2** have been reported to be poor Lewis acid catalysts and that activity is only observed after exchange of the apical isopropoxy ligand for a more labile triflate anion.[9] Recently, we found that Ti(IV) complexes **2** are efficient sulfoxidation[10] and N-oxidation[11] catalysts without the need of prior activation using aqueous hydrogen peroxide as oxidant.[12] Bull and co-workers have achieved ee's up to 47% in the benzyl phenyl sulfide oxidation by cumyl hydroperoxide using an enantiopure pseudo-C_3 Ti(IV) complex.[13] Herein we report a more detailed and complete study on the use of these catalytic systems in sulfoxidations using peroxides as primary oxidants. The speciation of the catalysts in solution has been done by NMR and ESI-MS techniques and the X-ray structure of complex **2c**, the most effective catalyst in these processes, has been determined.

We have also explored the nature of the Ti(IV) peroxo intermediates in these reactions using NMR and ESI-MS techniques and, with the aid of computational methods, structures for the metal peroxo intermediates are proposed.

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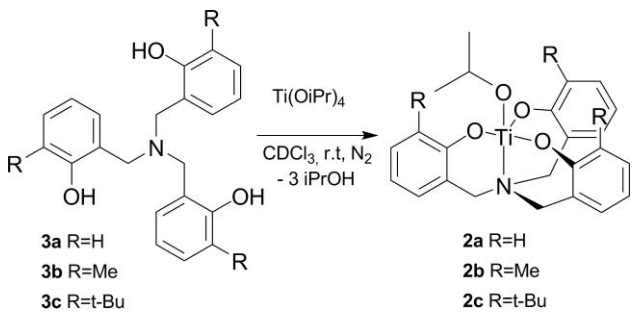
† Electronic supplementary information (ESI) available: ESI-MS and ^{1}H NMR spectra. CCDC reference number 756168. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0dt00228c

Results and discussion

Synthesis and characterization of complexes 2a–c

The nature of the substituent R in *ortho* position has been found to be very important to the stability of aminotriphenolate Ti(IV) complexes.[10,14] In the case of small substituents, for instance R = CH_3, the formation of aggregates, in particular μ-oxo dinuclear complexes, have been observed after exposure of the solid crystalline compounds to wet air.[14,15] This phenomenon was not observed when bulky substituents such as *tert*-butyl were present. In order to test whether the peripheral substituents R might have an effect on the catalytic activity of **2**, we prepared complexes **2a–c** carrying substituents of increasing size (R = H, CH_3 and *t*-Bu, respectively, Scheme 1). The complexes were obtained by mixing the appropriate ligand **3a–c** with an equimolar amount of Ti(O*i*-Pr)$_4$ in $CDCl_3$ under nitrogen atmosphere. Ligands **3a–c** were synthesized using a procedure developed in our group, based on a threefold reductive amination of the corresponding substituted salicylic aldehydes.[16] The ^{1}H NMR spectra of the *in situ* formed complexes in $CDCl_3$ show a single set of signals for each aromatic proton, for the methine proton of the coordinated isopropoxy apical ligand and for the Me and *t*-Bu *ortho* substituents in complexes **2b** and **2c**, respectively.



Scheme 1 *In situ* synthesis of complexes **2a–c**.

The behaviour of complexes **2a–c** in solution was investigated by the combined use of ^{1}H NMR and ESI-MS techniques. Complexes **2** are obtained as a racemic mixture, resulting from the helical wrapping of the ligand around the metal ion. The chirality of the complexes is reflected on the diastereotopicity of the benzylic methylene protons. For these protons, an interesting difference is observed between complexes **2a** and **2b** on one hand and complex **2c** on the other. For complexes **2a** and **2b** a single broad signal is observed at 28 °C for the methylene protons, indicating that the exchange between the two enantiomers is occurring on the ^{1}H NMR time scale. In contrast, complex **2c** showed two doublets at 3.94 and 2.89 ppm, as a consequence of a much slower racemization rate.[17]

Accordingly to the previous results,[6,14] the presence of peripheral bulky *t*-Bu groups increases the activation barrier for racemization.

The stability of the complexes is also affected by the size of the substituents. Upon standing in solution (18 days), complexes **2a** and **2b** slowly convert into other species in which the apical isopropoxy ligand is released in solution as free isopropanol. In the case of complex **2b** a single signal is observed for the methyl group in *ortho* position, consistent with the formation of another highly symmetric species. In contrast, complex **2c** remains stable in solution showing no variations in the ^{1}H NMR spectrum. No changes occur even after solvent removal under vacuum and re-dissolution in $CDCl_3$ (except for the disappearance of free isopropanol).

Table 1 ESI-MS-TOF data for complexes **2a–c**[a]

Entry	Complex	Ion (*m*/*z* most abundant isotopic peak, rel. % intensity)
1	**2a**	**Ia** (412, 10); **IIa** (434, 22); **IIIa** (791, 34); **IVa** (845, 100)
2	**2b**	**Ib** (454, 100); **IIb** (476, 40); **IIIb** (875, 37); **IVb** (929, 32)
3	**2c**	**Ic** (580, 100)

[a] Methanol as mobile phase, [**2a–c**] = 2×10^{-5}.

In methanol, the solvent used in the oxidation with H_2O_2,[10] the ^{1}H NMR of complex **2c** shows a single, highly symmetrical species in which the apical isopropoxy ligand has been displaced (one equivalent of isopropanol is released) by a methoxy group. Complexes **2a** and **2b** show a similar behaviour.

The speciation in solution of complexes **2** was also investigated using ESI-MS spectrometry. Solutions of complexes **2a–c** using methanol as mobile phase (15 μM) were studied. The high stability of complexes **2a–c** was confirmed by the fact that, even working in a coordinating solvent like methanol and under electrospray conditions, the main signals in the spectra are related to the complexes, while signals corresponding to the free ligands are present only in trace amounts (Table 1, and Fig. 2 and 3).

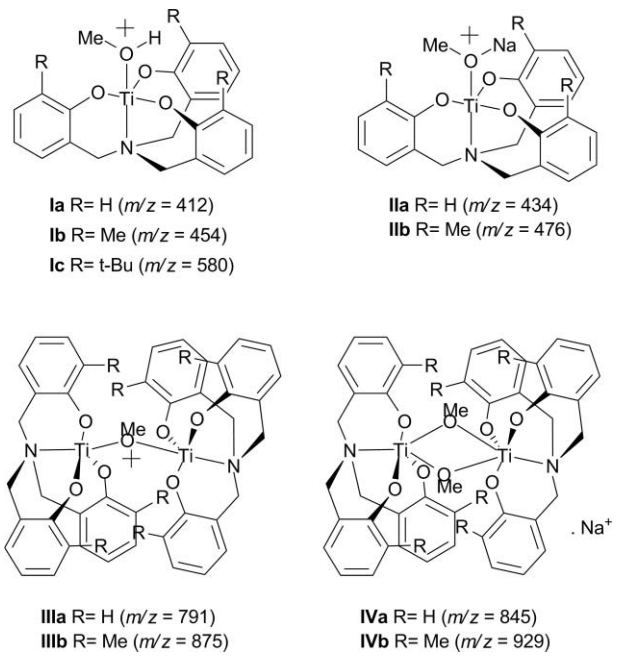


Fig. 2 Ions **Ia–c**, **IIa–c**, **IIIa–c**, **IVa–c** detected in ESI-MS experiments on complexes **2a–c** in methanol.

In all the cases ions corresponding to the protonated mononuclear complexes bearing a methoxy group as apical ligand (**I** or **II**) were detected (Fig. 3). For complexes **2a** and **2b** signals

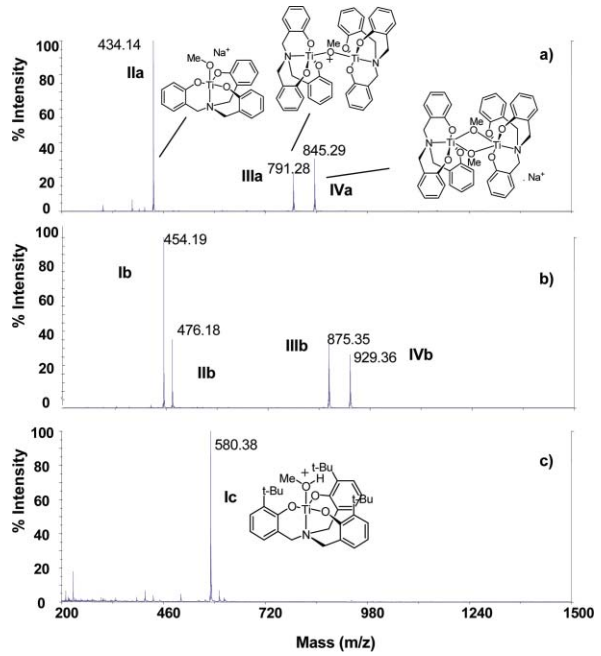


Fig. 3 ESI-MS spectra of the *in situ* formed complexes **2a** (a), **2b** (b) and **2c** (c) in methanol as mobile phase: [**2a–c**] = $(2.0 \times 10^{-5}$M).

corresponding to dinuclear complexes **IIIa**, **IIIb**, **IVa** and **IVb** were also present (Table 1, entries 1 and 2 and Fig. 3, spectra a and b).

Significantly, in the case of **2a**, ions **IIIa** and **IVa** are the most abundant peaks in the spectrum (Table 1, entry 1 and Fig. 3). These species have isotopic clusters and m/z ratio consistent with dinuclear complexes containing one (**III**) or two methoxy residues (**IV**), likely bridging between the two Ti(IV) nuclei. Importantly, these dinuclear species were not detected for complex **2c** (Table 1, entry 3 and Fig. 3, spectrum c), confirming the extreme stability of the mononuclear complex and its resistance to aggregation.[18] Therefore, we can conclude that two analytical techniques, ^{1}H NMR and ESI-MS, provide useful information for the speciation in solution of titanatrane complexes **2a–c**, clarifying the nature of the species present in solution and their relative stability.

Suitable crystals (methanol–dichloromethane) for X-ray diffraction have been obtained for complex **2c′**, bearing the methoxy apical ligand (Fig. 4).

The X-ray determined structure of complex **2c′** presents a propeller-like conformation around the Ti(IV) atom, a classical arrangement in such types of metal complexes. At the molecular level, no significant structural differences with respect to the X-ray structure of analogous Ti(IV) complex with additional *para tert*-butyl substituents[18] were observed, whereas the packing is clearly affected by the lack of such voluminous groups. In addition, a slight disorder for the apical methoxy carbon was found out.

Catalytic sulfoxidations

Ti(IV)-trialkanolamine complexes **1** are known to efficiently catalyse the oxidation of sulfides using alkyl hydroperoxides as primary oxidants.[3b,j,4] Because of the structural similarities, we tested the catalytic activity of complexes **2a–c** in the same reaction under similar conditions. The catalytic activity of complexes

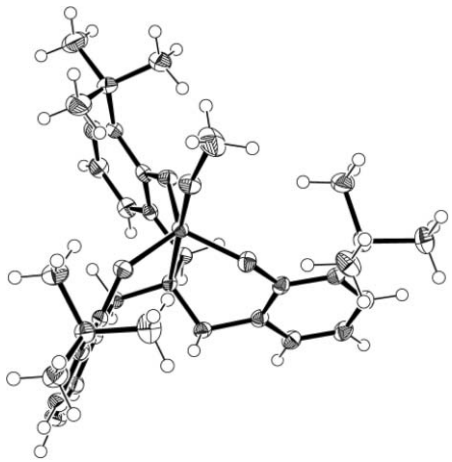
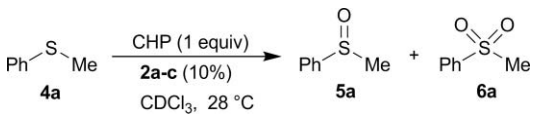


Fig. 4 Molecular structure of **2c′** in the solid state (ORTEP plot, 50% probability ellipsoids). The disorder of the methoxy carbon is removed for clarity.

2a–c was tested by mixing each complex, prepared *in situ*, with 10 equivalents of cumyl hydroperoxide (CHP) and 10 equivalents of thioanisole **4a** in $CDCl_3$ (69 mM) (Scheme 2).



Scheme 2 Oxidation of methyl phenyl sulfide (**4a**) with CHP catalyzed by complexes **2a–c**.

Reactions were carried out at 28 °C and monitored by ^{1}H NMR. The kinetic profiles (Fig. 5) clearly evidenced the formation of the oxidation products phenyl methyl sulfoxide **5a** and phenyl methyl sulfone **6a** (Table 2). While in the case of transesterification and Diels–Alder reactions these complexes have been reported to need the substitution of the apical ligand,[9] in oxygen-transfer reactions we found that all complexes are very effective Lewis acid catalysts without the need of prior activation. This is illustrated by the time for the half consumption of the reagent ($t_{1/2}$) in the order of 30–60 min and by the complete consumption of the oxidant. The high reactivity of these catalysts is evident from

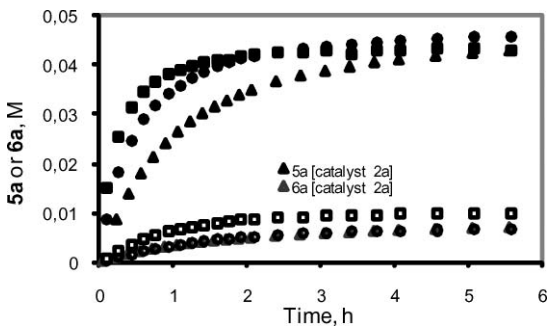
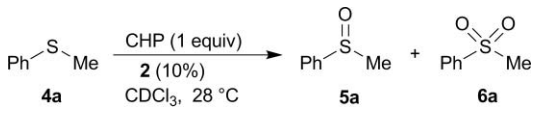


Fig. 5 Oxidation of thioanisole (**4a**) to methyl phenyl sulfoxide (**5a**) and methyl phenyl sulfone (**6a**) with CHP in $CDCl_3$ at 28 °C catalyzed by complexes **2a–c** (10%). $[\mathbf{4a}]_0 = [\mathrm{CHP}]_0 = 69.0$ mM. Reaction catalyzed by **2a**: **5a** (●), **6a** (○). Reaction catalyzed by **2b**: **5a** (▲), **6a** (△). Reaction catalyzed by **2c**: **5a** (■), **6a** (□). Concentrations were determined by ^{1}H NMR, internal standard 1,2-dichloroethane.

Table 2 Oxidation of thioanisole (**4a**) by cumene hydroperoxide (CHP) to methyl phenyl sulfoxide (**5a**) and methyl phenyl sulfone (**6a**) catalyzed by complexes **2a–c**[a]



4a **5a** **6a**

Entry	Catalyst	$t_{1/2}$[b]/h	**5a**[c] (%)	**5a** : **6a**[c]
1	**2a**	1.1	80	89 : 11
2	**2b**	0.9	78	88 : 12
3	**2c**	0.5	65	84 : 16

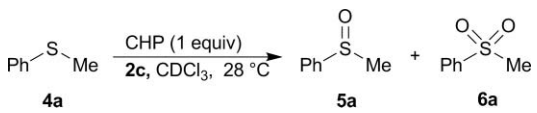
[a] Reactions were carried out in $CDCl_3$ at 28 °C using a molar ratio substrate/CHP 1 : 1 and 10% of catalyst: $[\mathbf{4a}]_0 = [CHP]_0 = 69.0$ mM. [b] Time required for a 50% decrease of the initial concentration of oxidant. [c] Determined by ^1H NMR ($CDCl_3$, 300 MHz) using DCE as internal standard and quantitative GC analysis of the crude reaction mixture after total oxidant consumption (iodometric test).

a comparison with the Ti(IV)-trialkanolamine catalysts **1** which exhibit similar reactivities.[3b,4b] Noteworthy, the increase of the steric bulk on the periphery of the catalyst leads to an increased catalytic activity. This might be related to the tendency of the catalysts with smaller *ortho* substituents to form aggregates, which may have no or lower catalytic activity. Ti(IV)-amino triphenolate catalysts **2a–c** give sulfoxide : sulfone ratios from 89 : 11 to 84 : 16 and clearly outperform the Ti(IV)-trialkanolamine catalysts **1**, which generally yield sulfoxides and sulfones in a ratio of about 60 : 40 when the same oxidant : substrate ratio is used.[3b,4b,19] Blank reactions (no catalyst) did not afford significant conversion into the products under comparable reaction times, as well as the reactions performed in the presence of triphenolamines **3a–c**.

On the basis of these preliminary results, the catalytic activity of complex **2c**, which results in the best results as far as the reactivity is concerned, was explored in detail (Table 3).

The system remains active after decreasing the catalyst loading down to 0.1% (Table 3, entries 2 and 3). In this case, even if the reaction becomes extremely slow, a yield of 94% was obtained

Table 3 Oxidation of thioanisole (**4a**) by CHP to methyl phenyl sulfoxide (**5a**) and methyl phenyl sulfone (**6a**) catalyzed by **2c**.[a] Effect of concentration and catalyst loading



4a **5a** **6a**

Entry	**2c** (%)	$[\mathbf{4a}]_0$/M	*t*/h	**5a**[c] (%)	**5a** : **6a**[b]
1	10	0.069	2	65	84 : 16
2	1	0.069	30	90	95 : 5
3	0.1	0.069	380	94	99 : 1
4	1	0.50	3	81	90 : 10
5	0.1	0.50	42	> 99	99 : 1
6	—	0.50	18	5	> 99 : 1
7	—[c]	0.50	18	5	> 99 : 1
8	—[d]	0.50	18	72	83 : 17

[a] Reactions were carried out in $CDCl_3$ at 28 °C using a molar ratio **4a**/CHP = 1 : 1. [b] Determined by ^1H NMR ($CDCl_3$, 300 MHz) using DCE as internal standard and quantitative GC analysis of the crude reaction mixture after total oxidant consumption (iodometric test). [c] Reaction performed in the presence of 1% of ligand **3c**. [d] Reaction performed in the presence of 1% of Ti(O*i*-Pr)$_4$.

after two weeks (Table 3, entry 3). The fact that at even at very low concentrations (0.07 mM) and in the presence of a large excess of competing ligands (cumyl alcohol and CHP) catalyst **2c** retains its activity indicating a very high stability of the catalyst under turnover conditions. In the second series of experiments, performed at much higher substrate concentrations (0.5 M), the reactions occurred much faster and, when performed with 0.1% of catalyst, afforded a complete conversion into products after 42 h. An interesting concomitant effect is that lowering catalyst loading yields to a significant increase of chemoselectivity in favour of sulfoxide (Table 3, entries 3 and 5). Moreover, in all reactions, at the end of the oxidation signals corresponding to the catalyst **2c** were still detected in the reaction mixture.

Reactions carried out using 1% of Ti(O*i*Pr)$_4$ afforded the sulfoxide in lower yields (72%) and after much longer reaction times (Table 3, entry 8) and with lower chemoselectivities (**5a** : **6a** = 83 : 17).

Stimulated by the elevated catalytic activity of the **2c**/CHP system and the high stability of complex **2c** under turnover conditions, the activity of complex **2c** using hydrogen peroxide as terminal oxidant was explored as well.[10] The development of catalytic systems that use hydrogen peroxide as terminal oxidant has been the focus of intense research since this is a cheap, easy to handle, and much more environment benign oxidant.[20] It is important to note that the Ti(IV) trialkanolamine complexes **1** are absolutely not active under these conditions and they do not afford significant amounts of oxidized products. Only few Ti(IV) complexes have been reported to be able to activate H_2O_2 or its urea complex in the oxidation of sulfides or olefins, mainly based in salen, salan and salalen ligands.[21,22]

As we have previously communicated, complex **2c** resulted an excellent catalysts in sulfide oxidations using hydrogen peroxide as terminal oxidant.[10] The reactions were carried out in homogeneous conditions (methanol as solvent) and sulfoxides were obtained in high yields and selectivities.

The system **2c**/H_2O_2 was found to be more active than the system **2c**/CHP. TOFs up to 1700 h^{-1} were obtained and catalyst loadings could be decreased down to 0.01% (8000 TON).[10] The **2c**/H_2O_2 system shows better chemoselectivities favouring the sulfoxide formation with comparable catalyst loadings. Indeed, under these conditions, sulfone **6a** forms only in very small amounts and at the end of the reaction, in contrast to the **2c**/CHP system where it is formed from the very beginning and in much larger amounts (Fig. 5 and Table 2). Catalyst **2c** was revealed to be stable under turnover conditions also in this case and the ^1H NMR signals relative to **2c** were detected unchanged at the end of the reactions.

The scope of the reaction has been explored working at millimolar scale. A series of sulfides was oxidized with CHP and H_2O_2 (Table 4)[10] in the presence of **2c** at 10 and 1% loading, respectively.

Included in the series are aryl/alkyl and dialkyl sulfides. In all cases, fast reactions and complete consumption of the oxidant were observed. In analogy with thioanisole **4a**, also with the other substrates the oxidation with H_2O_2 shows a higher reactivity and selectivity for the formation of the corresponding sulfoxides in comparison to CHP. In the aryl-methyl series, the effect of electron-donating and withdrawing groups present in the aromatic group was examined (**4a**, **4e**, **4f**). A significant

Table 4 Oxidation of sulfides **4a–f** by CHP [a] and H_2O_2 [b] catalyzed by **2c**. Scope of the reaction

4a-f **5a-f** **6a-f**

Entry	Substrate	R^1	R^2	Oxidant	**5** [c,d] (%)	**5** : **6** [c]
1	**4a**	Ph	Me	CHP	72 (70)	84 : 16
2				H_2O_2	97 (93)	98 : 2
3	**4b**	*p*-Me	*n*-Bu	CHP	80 (75)	89 : 11
4				H_2O_2	95 (89)	95 : 5
5	**4c**	PhC_6H_4	CH_2Ph	CHP	69 (65)	82 : 18
6				H_2O_2	91 (84)	93 : 7
7	**4d**	*n*-Bu	*n*-Bu	CHP	75 (70)	86 : 14
8				H_2O_2	92 (83)	93 : 7
9	**4e**	*p*-$MeOC_6H_4$	Me	CHP	85 (81)	92 : 8
10				H_2O_2	94 (86)	94 : 6
11	**4f**	*p*-$NO_2C_6H_4$	Me	CHP	49 (46)	66 : 34
12				H_2O_2	77 (61)	85 : 15

[a] Reactions were carried out at 0.5 mmol scale in $CHCl_3$ at 28 °C using $[\mathbf{4a}]_0 = [CHP]_0 = 0.5$ M, $[\mathbf{2c}]_0 = 0.005$ M. [b] Reactions were carried out at 0.5 mmol scale in MeOH at 28 °C using $[\mathbf{4a–f}]_0 = [CHP]_0 = 0.5$ M, $[\mathbf{2c}]_0 = 0.005$ M. [c] Determined by ^{1}H NMR (CD_3OD, 300 MHz) and quantitative GC analysis of the crude reaction mixture after total oxidant consumption (iodometric test). [d] Isolated yields are given in parentheses.

Table 5 ^{1}H NMR chemical shifts (δ, ppm) from $PhCH_2$ and *t*-Bu protons of complex **2c**: $[\mathbf{2c}] = 0.008$ M, after H_2O_2 addition (10 equivalents) in different deuterated solvents

	δ ($PhCH_2$)		δ (*t*-Bu)	
Solvent	**2c**	$+H_2O_2$	**2c**	$+H_2O_2$
CD_3OD [b]	3.49	3.64	1.43	1.35
CD_2Cl_2	3.91, 2.93	nd [a]	1.47	1.41
$CDCl_3$	2.89, 3.95	nd [a]	1.45	1.41
CD_3COCD_3	3.50	3.60	1.47	1.40
CD_3CN	3.43	3.54	1.45	1.38

[a] Not detected due to the overlapping of H_2O signals. [b] 1000 equivalents of H_2O_2 were added.

effect of the *para* substituents (H, OMe and NO_2) was found, especially in the oxidation with CHP (Table 5, entries 1, 9–11). Although with both substrates a quantitative consumption of the oxidant was observed, the sulfoxide : sulfone ratio is much different (92 : 8 for the electron-rich *p*-methoxyphenyl methyl sulfide **4e**, 84 : 14 for phenyl methyl sulfide **4a** and 66 : 34 for the electron poor *p*-nitrophenyl methyl sulfide **4f**). A similar behaviour was previously observed with the Ti(IV)-trialkanolamine **1** catalyzed sulfoxidations in which the formation of high amounts of sulfone was found to originate from the biphilic nature of the Ti(IV) peroxo complex.[19] The fact that a comparable behaviour is observed for the Ti(IV)-amino triphenolate complexes **2c** is indicative that a similar mechanistic pathway could be occurring. Currently, we are examining this aspect in more detail.

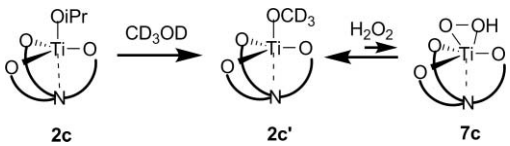
Characterization of the peroxo-titanium complexes

Ti(IV) catalyzed sulfoxidations and allylic alcohol oxidations usually occur by *in situ* activation of peroxides *via* formation of Ti(IV) peroxo complexes which are the active species in the oxygen transfer process.[23] The identification and characterization of the peroxo intermediates in these catalytic reactions is an important task. In the case of the Katsuki–Sharpless system for the asymmetric epoxidation of allylic alcohols, studies on the formation of the titanium peroxo species have been performed *via* IR measurements,[24] while with the Ti(IV) trialkanolamine complexes **1**, Ti(IV)-peroxo species have been characterized *via* single-crystal diffractometric analysis,[25] ^{1}H NMR, ESI-MS experiments and computational methods.[3j,26] Recently Katsuki and co-workers reported the X-ray crystal structure of a peroxo Ti(IV) salan complex which is thought to be part of the catalytic cycle in the epoxidation reaction.[21i,27,28] Peroxo species of Ti(IV)-amino triphenolate complexes **2** have not been isolated and characterized so far.

In order to obtain more information on the nature of the active species in the oxygen transfer process, we decided to investigate more in detail the behaviour of catalyst **2c** in the presence of CHP and H_2O_2.

2c and CHP. The addition of increasing amounts of cumyl hydroperoxide (1–100 equiv) to a chloroform-d_3 solution of complex **2c** (both formed *in situ* or after removal of the excess of isopropanol) did not allow the detection of any new species *via* ^{1}H NMR the formation, even though a change in the colour of the solution was observed. A similar behaviour was observed for the addition of increasing amounts of cumyl alcohol. This observation is in agreement with the kinetic experiments monitored *via* ^{1}H NMR, where the signals of the catalyst are detected during the course of the reaction. The peroxo-complex could not be detected of any new species by ESI-MS (CH_3CN, 2×10^{-5} M), even in the presence of a large excess of CHP (100–1000 equivalents). The inertness of the isopropoxy apical ligand has been already evidenced by other authors showing that it can be exchanged only with more acidic ligands such as trifluoroacetic or triflic acid,[9,18] bidentate derivatives.[29] or in alcoholic solution (methanol). In the reaction with CHP it seems that the equilibrium toward the reactive peroxo complex allows its formation only in very low concentrations (not detectable *via* ^{1}H NMR) and once formed it reacts immediately in the presence of a nucleophile (sulfide).

2a–c and H_2O_2. The **2a–c**–hydrogen peroxide systems were investigated *via* ^{1}H NMR in methanol-d_4. Initially, after dissolving in CD_3OD a concentrated chloroform solution of the *in situ* formed complex **2c**, the complete displacement of the apical isopropoxy ligand by CD_3OD was observed. The characteristic ^{1}H NMR signals for the apical isopropoxy ligand disappeared and only signals deriving from free isopropanol were observed at 3.91 (1H, q, $J = 6.3$ Hz) and 1.12 (6H, d, $J = 6.3$ Hz) ppm (Scheme 3 and Fig. 6, spectrum a).



Scheme 3 Peroxo-Ti(IV) formation by reaction of **2c** with H_2O_2 in CD_3OD.

Addition of hydrogen peroxide to **2c′** affords the formation of a new species in amounts which depend on the excess of H_2O_2 employed. Up to 100 equivalents no significant changes in the

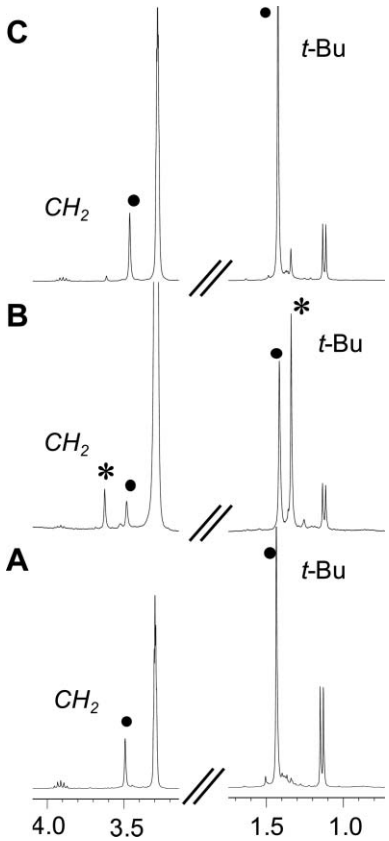


Fig. 6 ^{1}H NMR spectra (CD_3OD, 300 MHz) in the region from 0 to 4.3 ppm of (a) complex **2c** (0.8×10^{-3} M). (b) after the addition of hydrogen peroxide (35%, 0.8 M) and (c) after addition of thioanisole **4a** (0.8 M). Signals correspond to complex **2c** (•), newly formed species (*) and methyl groups from **4a**, **5a** and **6a**.

^{1}H NMR spectrum were observed. Only in the presence of a larger excess of hydrogen peroxide (1000 equivalents) the yellow solution became brighter and a new species was detected in the ^{1}H NMR spectrum, characterized by an upfield shift of the *tert*-butyl signal (from 1.43 to 1.35 ppm) and a downfield shift of the methylene signal (from 3.49 to 3.64 pm) (Fig. 6, spectrum b). Upon standing for one week no evident signs of decomposition were observed. On the other hand, addition of stoichiometric amounts of sulfide **4a** to the solution, led to the formation of sulfoxide **5a** and sulfone **6a**. Contemporaneously, the disappearance of the newly formed species was observed with the rebuilding of the initial catalyst **2c′** (Fig. 6, spectrum c). This experimental evidence is consistent with the occurrence of a ligand exchange process in which the solvent (CD_3OD) and the bidentate peroxide compete for coordination to the metal center (Scheme 3).

The formation of the peroxo-complex **7c** was also monitored by ^{1}H NMR in other, less coordinating, solvents like CD_2Cl_2, $CDCl_3$, acetone-d_6 and CD_3CN (Table 5).

The addition of hydrogen peroxide in chlorinated solvents led to a change of colour from yellow to dark orange and in acetonitrile or acetone from yellow to dark green. These variations are indicative of a change in the coordination sphere of the metal ion (Table 5). In all cases the ^{1}H NMR spectra showed the decreasing of the signals corresponding to the apical isopropoxy ligand just after addition of one equivalent of H_2O_2 with the parallel appearance of the free isopropanol and a shift of the methylene and *t*-Bu signals (Table 5). This phenomenon is consistent with the formation of a new species *via* apical isopropoxy/peroxy exchange, which leads to the peroxo complex **7c**. In all these systems, in contrast with what was observed in methanol-d_4, the complete formation of complex **7c** was evidenced after addition of only a ten-fold excess of hydrogen peroxide. On the other hand, extensive decomposition of the peroxo species happened in 24 h. This observation can be correlated to the low conversions obtained in the reactions carried out in acetonitrile (52%) or acetone (44%) associated with H_2O_2 decomposition.[10,30]

Further evidence on the nature of the peroxo Ti(IV) complex could be achieved *via* ESI-MS experiments. Spectra obtained in negative mode, with $[\mathbf{2c}] = 1 \times 10^{-5}$ M in methanol in the presence of a large excess of hydrogen peroxide (1000 equiv.) showed the presence of a single peak at $m/z = 580$ (**Vc**) (Fig. 7 and 8), whose isotopic cluster corresponds to the monomeric anionic peroxo specie originating from **7c** (Scheme 3).[31] The same species was obtained when perdeuterated methanol or acetonitrile were used as solvent.

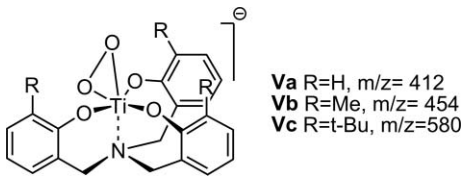


Fig. 7 Ti(IV) peroxo anions **Va–c**, from ESI-MS experiments on complexes **2a–c** in the presence of H_2O_2 and using methanol as mobile phase.

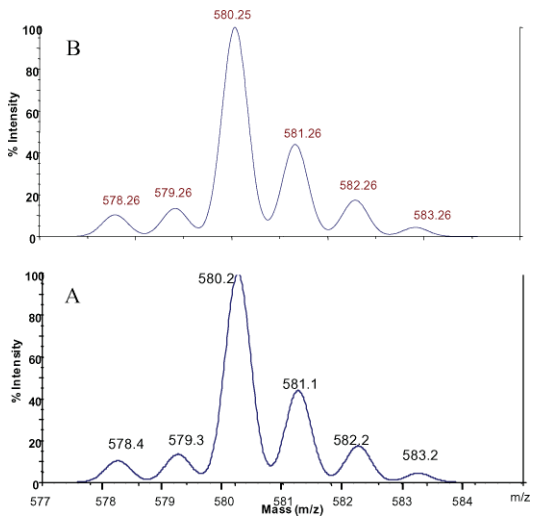


Fig. 8 Experimental (A) and calculated (B) isotopic distribution of anion **Vc** (R = *t*-Bu), $m/z = 580$.

The formation of the peroxo complexes deriving from **2a** and **2b** was also explored (Fig. 7). In both cases addition of aqueous hydrogen peroxide to a solution of **2a** and **2b** in methanol-d_4 led to the formation of systems with complex ^{1}H NMR spectra, referable to the formation of aggregates. Nevertheless, ESI-MS analysis of the resulting mixtures allowed the detection of ion **Vb** ($m/z = 454$) (Fig. 9), even if in small amounts, while for complex **2a** no peroxo species could be detected at all.

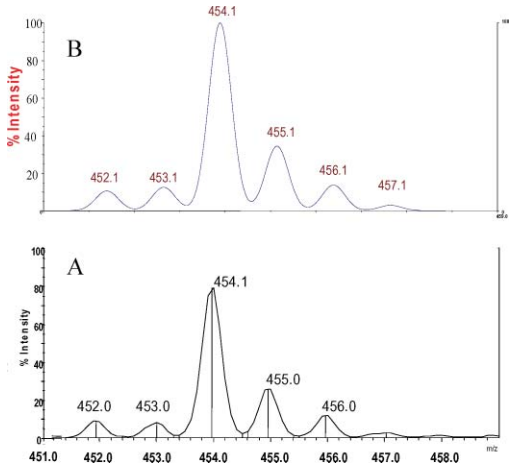


Fig. 9 Experimental (A) and calculated (B) isotopic distribution of ion **Vb** (R = Me), $m/z = 454$.

Theoretical studies

In order to obtain more insight on the nature of the peroxo species under study, the structures of the peroxo species obtained by reaction with CHP and hydrogen peroxide were optimized by means of density functional calculations (B3LYP) using the LANL2DZ basis set (Fig. 10). It is largely accepted that in the hydrogen peroxide (or alkyl hydroperoxide) activation by early transition d_0 metals, such as Ti(IV), the active species originates from exchange of one of the alkoxo ligands by the oxidant. The new resulting hydroperoxo (or alkylperoxo) metal complex becomes active for the oxygen transfer process when the peroxo moiety is η^2-coordinated.[32]

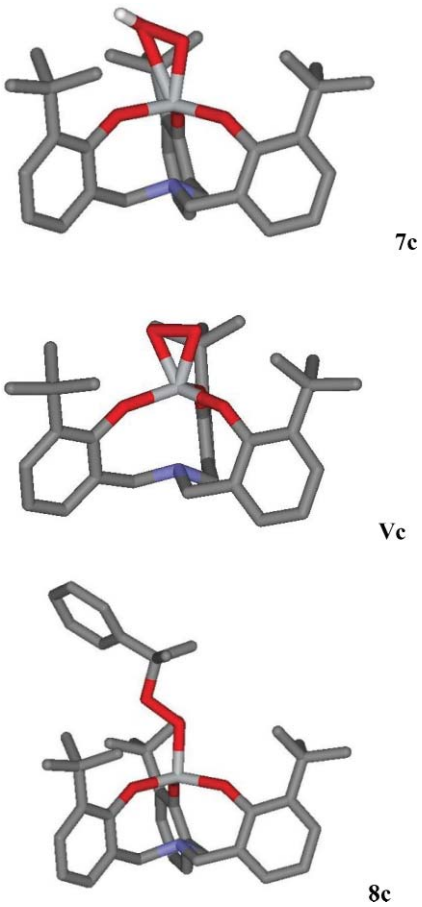


Fig. 10 Optimized geometries of peroxo-complexes **7c**, **Vc** and **8c** (B3LYP LANL2DZ). Hydrogen atoms have been omitted for clarity.

The peroxo complexes detected experimentally are the hydroperoxo **7c** (^{1}H NMR) and the corresponding anionic peroxo species **Vc** (ESI-MS). In both cases the optimization afforded structures with distorted bipyramidal geometries, in which the peroxo moieties are η^2-coordinated and occupy the upper part of the complex, *trans* to the nitrogen atom. In all cases the aminotriphenoxide ligand maintains a propeller like conformation, in analogy with what we observe in the X-ray structure of catalyst **2c** (Fig. 4)

The neutral adduct with hydrogen peroxide **7c** displays peroxidic Ti–O, Ti–O(H) and O–O bonds of 1.904, 2.517 and 1.515 Å, respectively, while the anionic **Vc** has a more symmetric η^2-peroxo group (Ti–O = 1.872 Å and O–O = 1.520 Å). In both cases attempts to force the peroxo structure in an octahedral conformation failed.

We also considered the possible geometries of the cumylperoxo complex **8c**, species that we could not observe experimentally. It is interesting to note that in the most stable structure the peroxo moiety presents an end-on coordination mode (Ti–O, Ti–OCum and O–O bonds of 1.864, 2.927 and 1.487 Å, respectively) Very likely the steric hindrance between the *tert*-butyl substituents and the cumyl group disfavours the peroxo η^2-coordination mode.

Conclusion

In summary, we have synthesized and characterized a series of mononuclear titanium(IV) complexes able to catalyze the oxidation of sulfides to sulfoxides in high yields and chemoselectivities and, thanks to their intrinsic stability to hydrolysis, high turnovers and turnover frequencies. The best catalyst **2c** is able to activate both alkyl and hydrogen peroxides as terminal oxidants with catalyst loadings down to 0.01% and TONs up to 8000. Spectroscopic evidence (^{1}H NMR and ESI-MS), supported by DFT calculation, indicate that the active species in the process are monoperoxo-Ti(IV) complexes.

Experimental

General procedures

All synthetic operations for catalyst preparation were carried out under nitrogen atmosphere in a MBraun MB 200MOD glovebox, equipped with a MB 150 G-I gas recycling system (nitrogen working pressure: 6 bar). 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 4 Å molecular sieves and degassed prior to use. Deuterated solvents were purchased from Aldrich and stored over 4 Å molecular sieves. All chemicals were purchased from Aldrich and Fluka as high-purity products (>95%) and used without further purification. Cumyl hydroperoxide (Fluka, 80% solution in cumene) was stored at 4 °C over 4 Å molecular sieves. Ti(IV) tetraisopropoxide, thioanisole, dibutyl sulfide, benzyl phenyl sulfide, *n*-butyl

p-tolyl sulfide, *p*-methoxy thioanisole, *p*-nitro thioanisole and 35% aqueous hydrogen peroxide from Aldrich. Ligands **3a–c** were synthesized as previously reported.[16] Ti(IV) complexes, prepared as previously reported,[10] were always handled and stored in a glovebox, with the exception of complex **2c** which could be handled in open air.

Analysis

Melting points are uncorrected and were determined by a Reichert Austria apparatus, 1 °C precision. ^{1}H NMR spectra were recorded on a Bruker AC 250 (250.18 MHz) or Bruker Avance DRX 300 (300.13 MHz) spectrometer, using the partially deuterated solvent or TMS as internal references (TMS $\delta = 0$ ppm, C*H*Cl$_3$ $\delta =$ 7.26 ppm, C*H*$_3$OH $\delta = 4.78$, 3.35 ppm). ^{1}H NMR kinetics (at 28 °C) were recorded on a Bruker Avance DRX 300 (300.13 MHz) spectrometers equipped with probe temperature control units. ^{13}C NMR spectra were recorded on Bruker AC 250 (62.9 MHz) or Bruker Avance DRX 300 (75.5 MHz) spectrometers in H-decoupled mode, using the solvent carbon resonance as the internal standard: CHCl$_3$ $\delta = 77.0$ ppm (t). ESI-MS experiments of complexes **2a–c** were performed in a ESI-TOF Mariner™ Biospectrometry™ Workstation, Applied Biosystems by flow injection analysis using methanol as mobile phase. ESI-MS experiments of peroxo complexes **Va–c** were performed in a Agilent LC/MSD Trap serie SL by flow injection analysis using methanol as mobile phase. GC analysis were performed using a Shimadzu GC-2010 gas chromatograph with a FID detector and a capillary column EQUITYTM-5 using dodecane as external standard.

General procedure for monitoring the sulfoxidation reactions catalyzed by 2a–c with CHP as oxidant (Table 2). A screw-cap NMR tube was charged with a solution of the corresponding *in situ* formed Ti(IV)-catalyst **2** in CDCl$_3$ (0.00414 mmol), the internal standard (1,2-dichloroethane, DCE), 35% aqueous H_2O_2 (0.0414 mmol) and thioanisole (0.0414 mmol) were added up to a final volume of 0.6 mL. Concentrations of sulfide, sulfoxide and sulfone were monitored by integration of the methyl group signals by ^{1}H NMR: PhS*Me* (2.4 ppm), PhSO*Me* (2.8 ppm) and PhSO$_2$*Me* (3.1 ppm) with respect to the internal standard, DCE (3.78 ppm).

General procedure for monitoring the sulfoxidation reactions catalyzed by 2c with CHP as oxidant (Table 3). A screw-cap NMR tube was charged with the correct amount of a solution of the *in situ* formed complex **2c** in CDCl$_3$. The internal standard (1,2-dichloroethane), 35% aqueous H_2O_2 and thioanisole (**4a**) were added with final concentrations as reported in Table 3 to a final volume of 0.6 mL. Concentrations of sulfide, sulfoxide and sulfone were monitored by integration of the methyl group signals in ^{1}H NMR: PhS*Me* (2.4 ppm), PhSO*Me* (2.8 ppm) and PhSO$_2$*Me* (3.1 ppm) with respect to the internal standard, DCE (3.78 ppm). Final yields were determined by quantitative GC analysis after complete CHP consumption (iodometric test).

General procedure for sulfoxidation reactions catalyzed by 2c using CHP or aqueous H_2O_2 as oxidant (Table 4). To a solution of the corresponding sulfide **4a–f** (0.5 mmol) and catalyst **2c** (0.005 mmol) in CHCl$_3$ (1 mL) or MeOH (1 mL) was added CHP (80% in cumene, 0.5 mmol) or H_2O_2 (35%, 0.5 mmol). The mixture was stirred at rt until all the oxidant has been consumed (iodometric test). CHCl$_3$ was added and the mixture was washed with 5% sodium metabisulfite aqueous solution, the layers were separated and the aqueous one extracted twice with chloroform. The organic layers were washed with brine, dried over MgSO$_4$ and the solvent was removed under reduce pressure. Sulfoxide : sulfone ratios were determined by quantitative GC analysis and by ^{1}H NMR (CDCl$_3$, 300 MHz) of the crude reaction mixtures. Yields were determined on the isolated products after flash chromatography on silica gel, eluent petroleum ether–ethyl acetate. All analytical data of sulfoxides **5a–f** and sulfones **6a–f** match those already reported in the literature.[33]

X-Ray crystal analysis of 2c′

Colourless crystals of **2c′** for single-crystal X-ray diffraction analysis were obtained from methanol. The obtained single crystals were mounted on a Nylon loop sample holder with perfluoro polyether and the data collected at 123.0(2) K using Bruker-Nonius KappaCCD diffractometer with APEX-II detector and graphite-monochromatized Mo-Kα ($\lambda = 0.71073$ Å) radiation. COLLECT[34] software was used for the data collection (θ and ω scans) and DENZO-SMN[35] for the processing. The structure was solved by direct methods with SIR2004[36] and refined by full-matrix least-squares methods with WinGX-software,[37] which utilizes the SHELXL-97 module[38] Lorentzian polarization correction and multi-scan absorption correction (SADABS[39]) were applied on all data. All C–H hydrogen positions were calculated and refined as riding atom model with 1.2 and 1.5 times of the thermal parameter of the C-atoms, respectively.

Crystal data for 2c′. $C_{34}H_{45}NO_4Ti$, $M_r = 579.61$, crystal size $0.30 \times 0.23 \times 0.20$ mm, orthorhombic, space group $Pna2_1$ (no. 33), $a = 11.8776(2)$, $b = 23.2811(3)$, $c = 11.4274(2)$ Å, $V = 3159.95(9)$ Å^3, $Z = 4$, $D_c = 1.218$ Mg m^{-3}, $\mu = 0.307$ mm^{-1}, $F(000) = 1240$, 30406 collected reflections ($2\theta_{max} = 25.00°$) of which 5547 independent ($R_{int} = 0.0649$), $T_{max} = 0.9411$, $T_{min} = 0.9134$, full-matrix least-squares on F^2 with 8 restraints and 372 parameters, GOF $= 1.021$, $R_1 = 0.0384$ [$I > 2\sigma(I)$], wR_2 (all data) $= 0.0823$, largest peak/hole $= 0.180/-0.275$ e$^-$Å^{-3}, Flack[40] parameter $= 0.10(2)$.

Acknowledgements

We acknowledge support of the University of Padova - Assegni di Ricerca di Ateneo 2006 (M. M.) and COST, Action D40 'Innovative Catalysis - New Processes and Selectivities'

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$$\Delta G^{\ddagger}\ (\text{kcal mol}^{-1}) = 4.57 \times 10^{-3} T_c(10.32 + \log(\sqrt{2}T_c/\pi\Delta\nu))$$

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