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Review

Metal-catalyzed asymmetric oxidations mediated by optically pure furyl hydroperoxides

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Abstract

Metal-catalyzed asymmetric oxidations which rely on the use of commercially available *t*-butyl (TBHP) or cumyl hydroperoxides (CHP) and enantiopure ligands represent the majority of protocols reported to obtain enantiomerically enriched valuable compounds such as epoxides, sulfoxides, diols, etc. Herein, we review our recent results on the complementary and less studied oxidative approach based on the use of optically pure alkyl hydroperoxides as oxygen and chirality source. The synthetic sequence to enantiopure furyl hydroperoxides, easily accessible from ketones of the chiral pool is firstly described. Examples of metal-catalyzed asymmetric oxidations using these compounds for the production of enantiomerically enriched sulfoxides and epoxy alcohols are shown. The entire protocol is made more advantageous by recovering the optically pure alcohols during the purification procedure and recycling them for the one-step synthesis of the hydroperoxides.

Keywords: Optically pure alkyl hydroperoxides; Metal-catalyzed oxidations; Kinetic resolution; Enantiomerically enriched sulfoxides; Enantiomerically enriched epoxy alcohols; Diastereoselective oxidations

Contents

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1. Introduction

Metal-catalyzed asymmetric oxidations hold a prominent place in organic synthesis, since optically pure epoxides and sulfoxides are important building blocks and pharmaceutical targets [1]. The most widely employed approach for the synthesis of these enantiomerically enriched products requires the use of commercially available alkyl hydroperoxides (TBHP and CHP) or H_2O_2, and some representative optically pure ligands such as: (a) tartrate esters (L-/D-DET) [2], 1,2-diols [3], (b) 2,2′-binaphthol derivatives (*R*/*S*-BINOL) [4], (c) hydroxamic acids [5], (d) salicylidenimines [6], (e) C_3-symmetric alkanolamines [7] in the presence of metal complexes as Ti(O*i*-Pr)$_4$, VO(O*i*-Pr)$_3$, VO(acac)$_2$ (Fig. 1). Another important protocol for the production of enantioenriched unfunctionalized epoxides [1c,8] and sulfoxides [9] is based on Mn-Salen complexes (f).

The enantioselectivity observed in these processes was satisfactory and in many examples high ees (>90%) were achieved for the final compounds. Although the characterization of the labile metal species involved in the enantioselective oxidations is generally extremely difficult, the mechanistic proposal reported for some of the oxidative transformations has been supported by spectroscopic investigations [2c,10].

The alternative methodology that makes use of optically pure alkyl hydroperoxides and metal complexes has been more recently investigated. This complementary route can give important hint on the relevant structural requirements of the hydroperoxides in modulating the stereocontrol, a topic which was marginally investigated in the classical approach, where the source of asymmetric induction resides on the enantiopure ligand. The major limitation associated to this route is related to the synthesis of the oxidants. In fact, no general approach is available to prepare these compounds in optically pure form and in satisfactory yields. Moreover, it is worth noting that this class of substrates needs to show a good chemical stability [11] especially in the presence of metal complexes, which are generally required to activate them for the oxidation. The most useful and general synthesis of secondary optically pure alkyl hydroperoxides has been proposed by Adam [12], via the kinetic resolution of racemic hydroperoxides by horseradish peroxidase (Fig. 2). Although up to 50% yield of the optically pure hydroperoxides can be obtained in the best case, the procedure led to the resolution of a wide variety of compounds. Unfortunately, racemic tertiary alkyl hydroperoxides failed to be kinetically resolved by this system. Secondary optically pure hydroperoxides were satisfactorily obtained, as anomeric mixtures, by using sugars as starting chiral source (Fig. 2) [13]. The first example of a tertiary enantiopure hydroperoxide was recently reported by Seebach [14]. This compound (TADOOH) was efficiently synthesized in two steps starting from commercially available (−)-TADDOL (Fig. 2).

These hydroperoxides have been used as stereoselective oxygen donors in the Ti-catalyzed epoxidation of allylic alcohols [13a,13b,15] and sulfoxidation [13,14,16], in the nucleophilic epoxidation of α,β-unsaturated ketones [13c,13d,14], Baeyer–Villiger oxidation of ketones [14]. The level of asymmetric induction achieved ranged from 5% to 90% ee as a function of the structure of starting substrates, when using secondary enantiopure alkyl hydropeperoxides. The best values of ee (up to 97% ee) were observed performing the oxidations with TADOOH. At

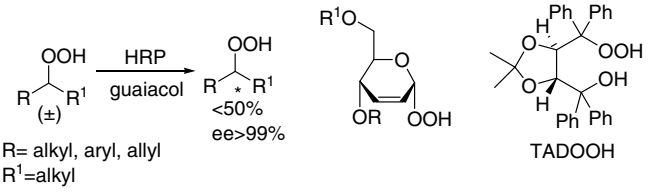


Fig. 2. Most successful examples of enantiopure hydroperoxides used as oxygen donors.

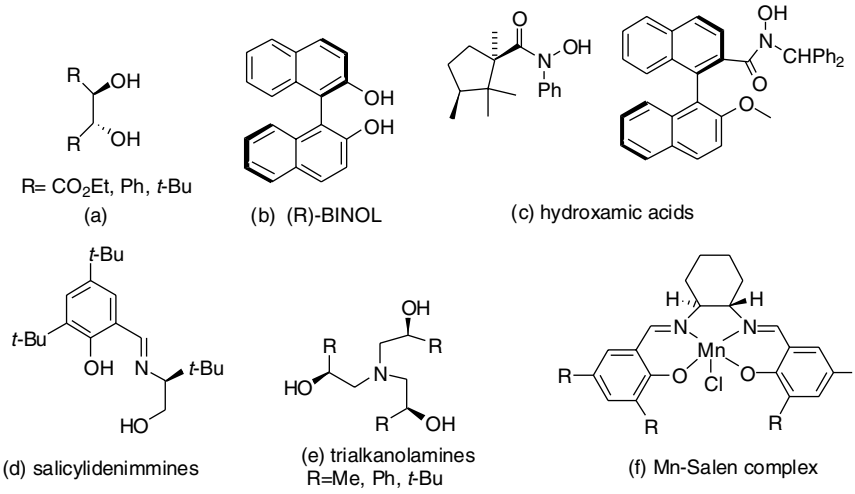


Fig. 1. Optically pure ligands and complex for the asymmetric epoxidation and sulfoxidation reactions.

the end of the oxidations the corresponding (−)-TADDOL was isolated during the purification and conveniently recycled for the two-step synthesis of the oxidant. These results confirmed previous data concerning the reactivity of alkyl hydroperoxides in metal-catalyzed asymmetric epoxidation (e.g., Sharpless asymmetric epoxidation of allylic alcohols) [2a,2b] and sulfoxidation [2c,2d]. In fact, the most stable and efficient oxidants in terms of asymmetric induction are tertiary alkyl hydroperoxides.

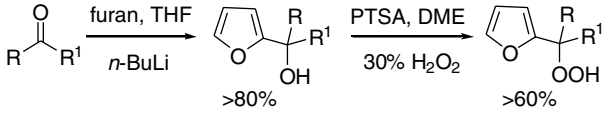
In the last years, we have been interested in asymmetric epoxidation [17] and sulfoxidation [18] mediated by racemic secondary and tertiary furyl hydroperoxides. They were easily synthesized [19] by a simple two-step approach starting from aldehydes or ketones in good to high overall yields (Scheme 1). They showed a satisfactory chemical stability, which allowed their employment as alternative oxygen donors to commercial TBHP or CHP.

When using the heteroaromatic equivalent of CHP (R=R^1=CH$_3$, Scheme 1)) in the asymmetric epoxidation of allylic alcohols [17] and sulfoxidation [18], under Sharpless-modified conditions, comparable level of ees for the epoxy alcohols or sulfoxides (>90%) were observed with respect to the reported methodologies which made use of TBHP or CHP. Unlike cumyl alcohol, which is a side-product in the asymmetric oxidations, the equivalent tertiary furyl alcohol could be recovered by flash chromatography and recycled for the one-step synthesis of the hydroperoxide according to Scheme 1. These results prompted us to direct our investigation to the more challenging goal of synthesizing furyl hydroperoxides in optically pure form and consequently check them as stereoselective oxygen donors.

2. Synthetic approach to enantiopure tertiary furyl hydroperoxides

2.1. (R)-Camphor-derived furyl hydroperoxide

We questioned if the straightforward and simple approach to alkyl hydroperoxides reported in Scheme 1 could be exploited for the synthesis of tertiary enantiopure furyl hydroperoxides, employing commercially or easily available optically pure ketones from the chiral pool. Turning to Scheme 1, a stereospecific nucleophilic substitution of the OH group bound to the stereogenic carbon centre of an enantiopure alcohol should have occurred in the second hydroperoxidation step. Previous reports on the preparation of enantiopure alkyl hydroperoxides following this way has met with poor success [20]. In fact, the nucleophilic substitution (S_N2) of secondary optically pure alcohols by H_2O_2 proceeded with inversion of configuration, but accompanied with a high degree of racemization and the final hydroperoxides were obtained in only up to 30% ee.



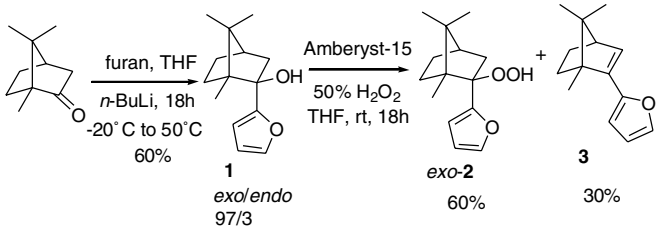
Scheme 1. Two-step route to racemic furyl hydroperoxides.

We succeeded in achieving the first preparation of a tertiary furyl hydroperoxide via stereospecific nucleophilic substitution (S_N1) (Scheme 2) [21]. In consideration of the well-known *endo*/*exo* discrimination in (*R*)-camphor bicyclic system [22], our choice was directed toward it, as cheap chiral source, to perform the synthetic sequence in Scheme 1. The furyl lithium addition furnished almost exclusively the *exo*-**1** alcohol in satisfactory yield. The alcohol *exo*-**1** was treated with 50% aqueous H_2O_2 with the heterogeneous acid catalyst Amberlyst-15 providing as single diastereoisomer the *exo* furyl hydroperoxide **2** in satisfactory yield and the alkene **3** in lower amount.

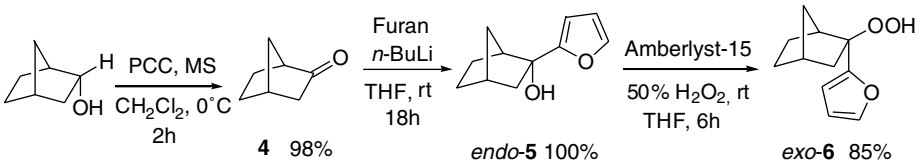
Surprisingly, by-products deriving from the well-known Wagner–Meerwein rearrangement of the intermediate tertiary 2-norbornyl carbocation were not detected [23]. The electron-rich furan can stabilize the tertiary carbocation by charge-delocalizing ability of furyl ring [24], thus enabling the attack of the nucleophile H_2O_2 exclusively from the *exo*-face of the carbocation. As expected, the alcohol *endo*-**1**, when treated under the same conditions furnished exclusively the same hydroperoxide *exo*-**2**, with the practical advantage that the diastereoisomeric mixture of the alcohols **1** were conveniently used without separation. It is interesting to note that the optically pure hydroperoxide *exo*-**2**, unlike TADOOH (Fig. 2) has the reactive OOH group directly bound to the newly generated stereogenic carbon centre, whose absolute configuration was established by NOESY experiment on the corresponding alcohol obtained after the reduction of *exo*-**2**. Moreover, the absolute configuration of *exo*-**2** was confirmed by TDDFT calculation of the optical rotation [25], which represents the first example of a direct determination without the need of the generally required chemical derivatization of the hydroperoxide [26].

2.2. (S)-Norcamphor-derived furyl hydroperoxide

Structural modifications of the bicyclic system used as chiral source for the synthesis of this type of hydroperoxides lead to useful information on the factors affecting the reactivity and the asymmetric induction provided by these oxidants. Hence, we embarked on the synthesis of a less



Scheme 2. Two-step route to optically pure tertiary furyl hydroperoxide **2** derived from (*R*)-camphor.



Scheme 3. Route to optically pure tertiary furyl hydroperoxide **6** derived from (*S*)-norcamphor.

sterically demanding furyl hydroperoxide derived from the norcamphor framework [27]. Since the norcamphor is not commercially available in enantiomeric pure form, the synthetic sequence previously employed required an additional step (Scheme 3). Commercially available (+)-2-*endo*-norborneol was firstly oxidized to (*S*)-norcamphor **4** in high yield [28]. The addition of furyl lithium occurred to the less hindered *exo*-face of the ketone **4** [24], affording in quantitative yield the *endo*-alcohol **5** in stereospecific manner. The crucial hydroperoxidation was performed under previously optimised conditions. Pleasingly, the formation of the hydroperoxide proceeded in high yield and with complete epimerization at carbon 2, which gave the exclusive formation of *exo*-**6**, without any by-product. It is interesting to note that hydroperoxide *exo*-**6** was synthesized in overall 83% yield and in highly stereoselective manner.

2.3. (*S*)-Norcamphor-modified furyl hydroperoxides

One potential opportunity to increase the stereocontrol of (*S*)-norcamphor-based furyl hydroperoxides was envisaged by functionalization at position 3 of the norcamphor framework, which allowed the formation of an additional stereocentre close to the reactive site of the hydroperoxide. This sequence leads to oxidants having the same configuration at carbon 2 with respect to hydroperoxide **6** and an additional stereogenic centre. According to the literature the α-alkylation of norcamphor can be generally performed in stereocontrolled manner [29]. At first, (*S*)-norcamphor was methylated and the *exo*-methyl ketone **7** was isolated in high yield (Scheme 4) [30]. This compound was reacted with furyl lithium affording in good yield a diastereoisomeric mixture of the alcohols **8**, which was directly treated under previously optimized conditions for the hydroperoxidation.

As expected, the selective and exclusive formation of *exo*-hydroperoxide **9** occurred in satisfactory yield, thanks to the complete epimerization at carbon 2 in the oxidation, which allowed the convenient use of the unseparated mixture of **8** as starting material [31].

The synthetic approach reported in Scheme 4 is susceptible of being exploited to access a variety of α-alkylated (*S*)-norcamphor modified furyl hydroperoxides in predictable stereocontrolled manner.

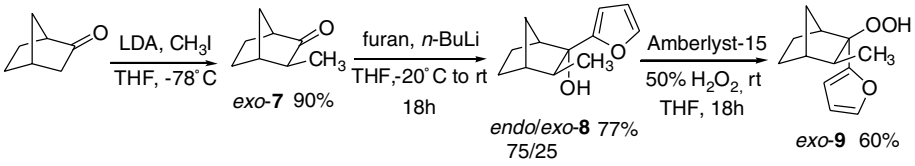
3. Metal-catalyzed asymmetric sulfoxidation and kinetic resolution of racemic sulfoxides

3.1. Asymmetric sulfoxidation and kinetic resolution mediated by (*R*)-camphor-derived furyl hydroperoxide

The most important and direct approach to optically pure sulfoxides is the asymmetric oxidation of prochiral sulfides [32]. Ti(O*i*-Pr)$_4$ proved to be the best metal catalyst for the electrophilic activation of the alkyl hydroperoxides in all the enantioselective protocols. Hence, this metal complex was used in our investigation on the asymmetric sulfoxidation mediated by hydroperoxide *exo*-**2** in absence of any ligand [33]. Through solvent screening it was found that the highest level of asymmetric induction was achieved when using toluene as the solvent.

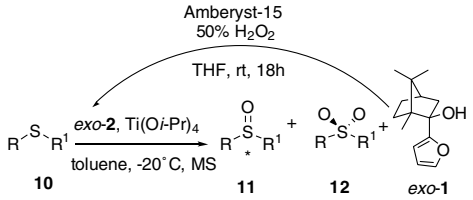
A preliminary screening led us to develop the optimized conditions (20% mol of Ti(O*i*-Pr)$_4$/1 equiv of *exo*-**2**/MS 4 Å, at −20 °C) for the sulfoxidation (Table 1).

Although the sterically demanding hydroperoxide *exo*-**2** was relatively low reactive, the sulfoxidation proceeded in highly chemoselective way under catalytic loadings of the metal catalyst, in fact, only traces of sulfone **12** were detected at the end of the reactions. The sulfoxides were isolated in moderate yields and enantioselectivity. The electronic properties of the substituent in the aryl group of the sulfides had noticeable effects on the asymmetric induction. Appreciable results have been observed in the sulfoxidation of the 2-phenyl dithiane and dithiolane, which were converted into the *trans*-(1*S*,2*S*)-monosulfoxide with complete chemo- and diastereoselectivity. A low discrimination was observed in the oxidation of a dialkyl sulfide (entry 7). In the last two entries the opposite enantiomer of sulfoxides was preferentially obtained when using the enantiomer of *exo*-**2**, easily obtained starting from commercially available (*S*)-camphor.



Scheme 4. Route to (*S*)-norcamphor-modified tertiary furyl hydroperoxide *exo*-**9**.

Table 1
Asymmetric sulfoxidation by Ti(O*i*-Pr)$_4$/*exo*-**2**/MS



Entry	Sulfide (R, R)[1]	t (h)	Yield **11**%(**12**)%	Ee **11**%
1	Me, *p*-Tol	22	64(4)	47(*S*)
2	Me, Ph	22	52(6)	46(*S*)
3	Me, *p*-MeO-C$_6$H$_4$	23	54(9)	36(*S*)
4	Me, *p*-Cl-C$_6$H$_4$	26	39(4)	20(*S*)
5		44	52	24(*S*,*S*)
6		5	50	33(*S*,*S*)
7	Me, Bn	24	68(8)	5(*R*)
8	Me, *p*-Tol	22	57(5)	51(*R*)
9	Me, *p*-MeO-C$_6$H$_4$	23	56(8)	37(*R*)

The asymmetric induction might be dictated by noncovalent aromatic interactions of the chiral *exo*-**2**/Ti complex with the sulfide, as the methyl aryl substituted sulfides are oxidized with higher enantioselectivity than the dialkyl sulfides, where only steric effects of the substituents can account for the chiral molecular recognition, thus allowing a lower stereochemical bias. We have proposed two hypothetical transition states **A** and **B** to account for the observed sense of enantioselectivity, assuming that under catalytic loadings of Ti(O*i*-Pr)$_4$, a mononuclear Ti/*exo*-**2** complex should form. The hydroperoxide is electrophilically activated for the oxygen transfer by further coordination of the remote oxygen atom of peroxide bond to the metal centre (Fig. 3).

When the sulfide approaches the O–O bond according to pathway **A**, a significantly strong steric interaction should be expected for the tolyl substituent facing the C$_{10}$-camphor methyl of the hydroperoxide with respect to

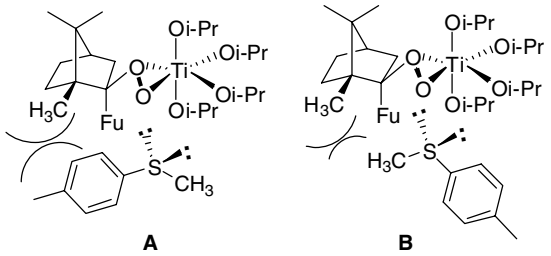


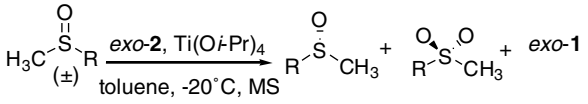
Fig. 3. Proposed transition states for the Ti/*exo*-**2** promoted sulfoxidation. Fu = 2-furyl.

the steric interaction of the two methyl groups in **B**. Consequently, the preferential formation of the (*S*)-**11** through pathway **B** is envisaged, which is in agreement with experimental results (Table 1). A smaller discrimination between the two proposed pathways is predictable and accordingly a lower enantioselectivity observed in the oxidation of dialkyl sulfides. During the chromatographic process the optically pure alcohol *exo*-**1** can be isolated in 70–80% yield and recycled for the one-step synthesis of the hydroperoxide, thus making the entire process an example of chiral resource saving protocol.

Although the asymmetric sulfoxidation proceeded with high chemoselectivity, the oxidation of sulfoxides to sulfones was investigated in order to check if the kinetic resolution of sulfoxides could occur (Table 2). This pathway can be a valuable approach to optically enriched sulfoxides [7a,34] even though, in the best case, half of the starting material is lost in the process. In most of the examples reported, the kinetic resolution showed to be stereoconvergent with the sulfoxidation, when using the same reaction conditions, and the cooperative effect of the kinetic resolution was conveniently exploited to enhance the final enantiomeric excess of the sulfoxides [32].

Under catalytic loadings of the metal catalyst, the kinetic resolution was a negligible process (entry 1, Table 2), but when using stoichiometric amounts of the Ti(O*i*-Pr)$_4$ enantiomerically enriched (*R*)-sulfoxides were preferentially recovered (entries 2–5). Although small stereoselectivity factors **S** [35] were calculated in entries 2–5, these results showed an unprecedented opposite sense of

Table 2
Kinetic resolution of racemic sulfoxides by Ti(O*i*-Pr)$_4$/*exo*-**2**/MS



Entry	Ti(O*i*-Pr)$_4$ (mol%)	Sulfoxide (*R*,*R*^{1})	*t* (h)	Yield **11**′%	ee **11**′%	**S**
1	20	Me, *p*-Tol	44	93	0	1.0
2	100	Me, *p*-Tol	22	56	18(*R*)	1.8
3	100	Me, Ph	28	20	39(*R*)	1.7
4	100	Me, *p*-MeO–C$_6$H$_4$	16	39	25(*R*)	1.7
5	100	Me, *p*-Cl–C$_6$H$_4$	23	23	49(*R*)	2.0

enantioselectivity in the asymmetric oxidation of sulfides and kinetic resolution of sulfoxides mediated by the same chiral oxidative system.

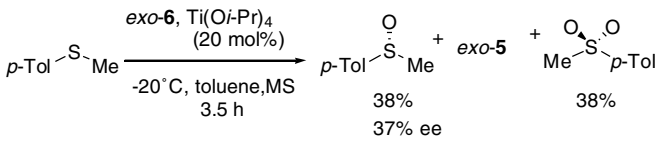
The opposite sense of enantioselectivity observed during the kinetic resolution might be explained by invoking a different steric control in the second oxidation step. In fact, sulfoxides are known to coordinate to the titanium [2c,36], and in this case, the oxygen could be delivered intramolecularly by the chelated hydroperoxide to the sulfoxide. Although this result prevented the well-documented synergic use of stereoconvergent kinetic resolution to improve the final enantiomeric excess of sulfoxides, the process is nonetheless suitable of application for the preparation of enantioenriched sulfoxides of opposite absolute configuration by means of the same chiral promoter.

3.2. Asymmetric sulfoxidation and kinetic resolution mediated by (*S*)-norcamphor-derived furyl hydroperoxide

The asymmetric sulfoxidation promoted by hydroperoxide *exo*-**2** represented an important preliminary text to evaluate the efficiency of this type of optically pure oxidants. It was observed that moderate reactivity and level of asymmetric induction could be achieved in the reaction. Hence, our goal was to employ a new oxidant which should have been easily accessible, more reactive than compound *exo*-**2** and at the same time to investigate the impact of the structural modifications on the asymmetric induction. Hydroperoxide *exo*-**6** derived from (*S*)-norcamphor, which possessed those requirements, was then employed in the Ti-catalyzed asymmetric sulfoxidation [27].

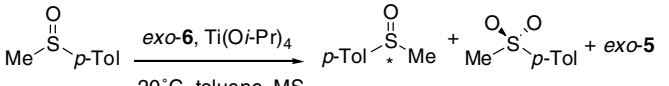
As expected, this compound reacted faster than reagent **2** in the oxidation of model methyl *p*-tolyl sulfide (Scheme 5). Moreover, the oxidation was not chemoselective, in fact, a significant amount of sulfone was isolated. The enantiosectivity was lower than the result obtained with *exo*-**2** (Table 1, entry 1).

To clarify the influence of the kinetic resolution on the enantioselectivity observed, the same reaction was carried out at different degrees of conversion. When quenching the oxidation after 1 h, the sulfoxide was recovered in 35% yield and 23% ee, while the amount of the sulfone was comparatively reduced (10%). This analysis showed an enhancement of the ee for the (*R*)-sulfoxide when increasing the conversion to sulfone, which clearly indicated that a stereoconvergent process of kinetic resolution was in act during the over-oxidation. In order to confirm the stereoselectivity of the kinetic resolution a set of experiments was performed on racemic methyl *p*-tolyl sulfoxide under different reaction conditions (Table 3).



Scheme 5.

Table 3
Kinetic resolution of racemic methyl *p*-tolyl sulfoxide by Ti(O*i*-Pr)$_4$/*exo*-**6**



Entry	*t* (h)	Ti(O*i*-Pr)$_4$ (mol%)	Yield 11′**a**%	ee 11′**a**%	**S**
1	1	100	38	28(*S*)	1.8
2	3.5	50	62	8(*R*)	1.4
3	21	20	63	7(*R*)	1.4

When using stoichiometric loadings of Ti(O*i*-Pr)$_4$ (entry 1) enantioenriched (*S*)-**11′a** was isolated, whereas 50% mol or 20% mol of catalyst (entries 2–3) afforded enantioenriched (*R*)-**11′a** with comparable selectivity.

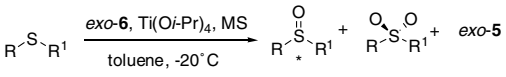
Although the calculated stereoselectivity factors **S** were small, indicating a poorly efficient kinetic resolution under substoichiometric amounts of catalyst, the process was stereoconvergent with the sulfoxidation step confirming our expectations. The stereochemical preference in the kinetic resolution was dependent on the Ti/*exo*-**6** ratio. The inversion of enantioselection could be ascribed to the difference in structures of the titanium complexes generated by different ratios of metal catalyst/chiral oxidant. An analogous observation was reported in the asymmetric epoxidation of homoallylic alcohols by Zr(O*t*-Bu)$_4$/enantiopure tartrate derivatives/TBHP, where the enantiofacial preference has been observed to be dependent on Zr complex/tartrate esters ratio [37].

Less sterically hindered hydroperoxide *exo*-**6** proved to be more reactive than *exo*-**2**, but the asymmetric induction displayed in the course of the sulfoxidation step was lower (23% against 47% ee for methyl *p*-tolyl sulfoxide). Being the kinetic resolution under substoichiometric loadings of Ti(O*i*-Pr)$_4$ stereoconvergent with the sulfoxidation, the reaction conditions were chosen to exploit the positive contribution of the kinetic resolution to enhance the ee of sulfoxides (Table 4).

After short reaction times, preferentially enriched methyl aryl (*R*)-sulfoxides were isolated in moderate enantiomeric excess (entries 1–3), which are comparable to the values obtained by the use of *exo*-**2**. 2-Phenyl-dithiane and dithiolane were chemoselectively oxidized in high yield exclusively to *trans* (1*S*,2*S*)-mono-sulfoxides with enantioselectivity comparable to that observed when using *exo*-**2**. At the end of the oxidations *exo*-**5** could be isolated by flash chromatography in 95% yield and efficiently recycled to access *exo*-**6**. The speculative models proposed to explain the preferred formation of (*R*)-sulfoxides in Ti/*exo*-**2** catalyzed oxygen-transfer process (Fig. 3), would seem to account for the results achieved even when using *exo*-**6** in the oxidation of sulfides to sulfoxides (Fig. 4).

The steric interactions of model sulfide approaching the electrophilically activated hydroperoxide in chiral Ti/*exo*-**6** complex, via pathways **A** and **B**, are inferior with

Table 4
Asymmetric sulfoxidation by Ti(O*i*-Pr)$_4$/*exo*-**6**/MS



Entry	Sulfide (R, R^1)	t (h)	Yield **11**%(**12**)%	ee **11**%
1	Me, *p*-Tol	4	34(55)	42(*R*)
2	Me, Ph	5	30(54)	38(*R*)
3	Me, *p*-MeO-C$_6$H$_4$	4	31(63)	53(*R*)
4	Me, *p*-Cl-C$_6$H$_4$	3	52(23)	5(*R*)
5		2	95	32(*S*,*S*)
6		1.5	90	18(*S*,*S*)

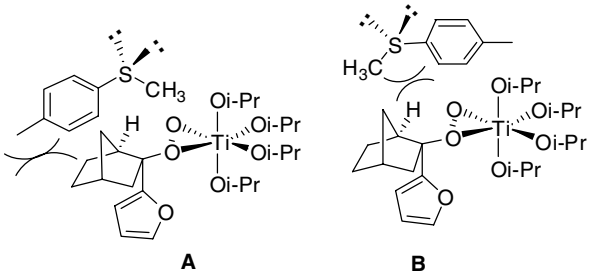


Fig. 4. Hypothetical transition states for the Ti/*exo*-**6** promoted sulfoxidation.

respect to chiral Ti/*exo*-**2** complex (Fig. 3). When the sulfide attacks with the *pro*-(*S*) lone pair along the O-O bond axis in the Ti complex **A**, the tolyl group will face the hydrogen substituent at C$_1$ of the bicyclic system, instead of C$_{10}$ methyl group of the camphor skeleton in *exo*-**2**. The sulfide, approaching with the *pro*-(*R*) lone pair along the O–O bond axis in the Ti complex **B**, will experience a lower steric interaction of methyl group facing the hydrogen at the C$_1$ position. A decreased preference for one of the two pathways, hence a lower enantioselectivity is envisaged when using *exo*-**6**, although pathway **B** should be slightly favoured leading to enantioenriched (*R*)-sulfoxides. The stereochemical outcome of the kinetic resolution is more difficult to rationalize, even in consideration that species having different selectivities are involved in the process as a function of the modified stoichiometric Ti/hydroperoxide ratios.

3.3. Asymmetric sulfoxidation and kinetic resolution mediated by (*S*)-norcamphor-modified furyl hydroperoxide

The bicyclic framework of the norcamphor offered the possibility to introduce structural modifications via stereoselective α-alkylation. The new stereocentre, being close to the hydroperoxy group should have reasonably influenced the asymmetric induction.

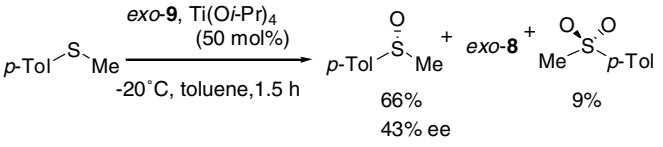
The asymmetric sulfoxidation of the model sulfide with the α-methylated hydroperoxide *exo*-**9** proceeded in highly chemoselective way (Scheme 6), leading to the formation of the enantioenriched (*R*)-sulfoxide in good yield and improved ee with respect to oxidant *exo*-**6** (Scheme 6) [31].

Since previous investigation pointed out the occurence of the kinetic resolution accompanying the asymmetric sulfoxidation by *exo*-**6**, racemic methyl *p*-tolyl sulfoxide was oxidized in the presence of 50 mol% of Ti(O*i*-Pr)$_4$ (Scheme 7).

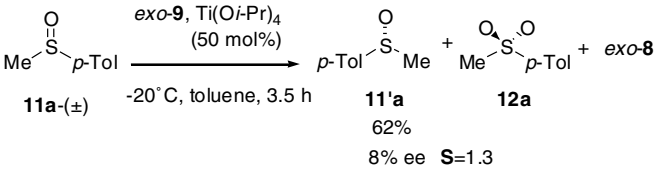
The process was found to be stereoconvergent with the sulfoxidation step since the (*R*)-sulfoxide was isolated as prevalent enantiomer, although the kinetic resolution was poorly efficient. This process plays a negligible role in affecting the asymmetric induction reported in Scheme 6, since the amount of sulfone is small and, consequently, the enantioselectivity originates exclusively from the oxidation of the sulfide to sulfoxide.

The sulfoxidation using hydroperoxide *exo*-**9** was then thoroughly studied (Table 5) under catalytic loading of the metal catalyst (20 mol%).

Methyl aryl sulfoxides were obtained in good yield and high chemoselectivity after short reaction times (entries 1–5). The level of asymmetric induction was moderate, but much better than the one observed (~20% ee) when using oxidant *exo*-**6** without exploiting the positive contribution of the kinetic resolution. Interestingly, 2-phenyl dithianes and dithiolane were chemoselectively oxidized to give exclusively the *trans* mono-sulfoxides in high yields (entries 6–10) and comparable enantioselectivity. The level of asymmetric induction was improved when compared to that achieved with *exo*-**6** and *exo*-**2** for the mono-sulfoxides in entries 6 and 7. In this case, the alcohol *exo*-**8** could be recovered in 65–75% yield and recycled for the synthesis of the oxidant.

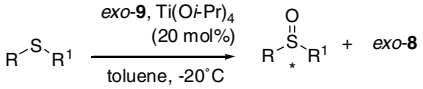


Scheme 6.



Scheme 7.

Table 5
Asymmetric sulfoxidation by Ti(O*i*-Pr)$_4$/*exo*-**9**



10 **11**

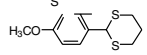
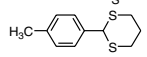
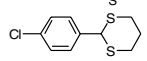
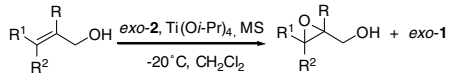
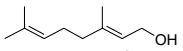
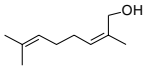
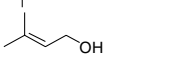
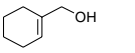
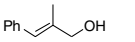
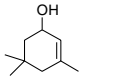
Entry	Sulfide (R, R^1)	t(h)	Yield **11**%(**12**)%	ee **11**%
1	Me, *p*-Tol	1.5	63(3)	44(*R*)
2	Me, Ph	1	60(3)	44(*R*)
3	Me, *p*-MeO-C$_6$H$_4$	0.5	73(6)	40(*R*)
4	Me, *p*-Cl-C$_6$H$_4$	1	56(4)	30(*R*)
5	Me, β-naphthyl	1	60(5)	41(*R*)
6		3	80	50(*S*,*S*)
7		2	74	21(*R*,*R*)
8		3	82	44(*S*,*S*)
9		2.5	80	37(*S*,*S*)
10		3	90	41(*S*,*S*)

Table 6
Asymmetric epoxidation of allylic alcohols by *exo*-**2**/Ti(O*i*-Pr)$_4$/MS



13 **14**

Entry	Allylic alcohol	t (h)	Yield **14**%	ee **14**%
1		5	54	42(2*S*,3*S*)
2		7	59	31(2*S*,3*R*)
3		5	45	46(2*S*)
4		6	48	36(1*R*)
5		45	30	24(2*R*,3*R*)
6		20	48	38(1*S*,2*S*,6*R*)

These data clearly indicated that the presence of the new stereocentre close to the reactive site of the norcamphor-based hydroperoxide *exo*-**6** had a positive influence in affecting the enantioselectivity of the asymmetric sulfoxidation. Since the introduction of the α-methyl group was the minimal structural modification to investigate, it is predictable that more efficient (*S*)-norcamphor-modified hydroperoxides will be accessible by a proper choice of the α-group.

4. Metal-catalyzed asymmetric epoxidation of allylic alcohols

4.1. Ti(Oi-Pr)$_4$-Catalyzed epoxidation mediated by (R)-camphor-derived furyl hydroperoxide

Our study on the use of optically pure furyl hydroperoxides was enlarged to the epoxidation of allylic alcohols using, at first, oxidant *exo*-**2** in the presence of stoichiometric amounts of Ti(O*i*-Pr)$_4$ [21] (Table 6).

Geraniol and nerol were regioselectively converted into the 2,3-epoxy alcohols in moderate yields and enantioselectivity (entries 1–2). Similar results were obtained for a variety of substituted allylic alcohols (entries 3–5). In some examples (entries 1–3), the levels of asymmetric induction, although modest, represent the highest values achieved up to now for these epoxy alcohols when using optically pure alkyl hydroperoxides as stereoselective oxygen donors.

Catalytic loadings of the metal catalyst (30 mol%) led to the formation of the products in longer reaction times, but with the same level of enantioselectivity. The epoxidation of the racemic secondary allylic alcohol in the last entry was carried out using an excess of the alcohol, in order to contemporarily study the kinetic resolution. Interestingly, the *erythro* epoxy alcohol was obtained with complete diastereoselectivity and 38% ee, while, the corresponding recovered (*R*)-**13** was isolated in 37% yield and 35% ee. This represents a promising result, since cyclohexenols are the poorest substrates in the kinetic resolution of secondary allylic alcohols mediated by Ti(O*i*-Pr)$_4$/L-DIPT/TBHP system [38], which is the most efficient protocol to resolve racemic secondary allylic alcohols.

4.2. Vanadium-catalyzed epoxidation mediated by (S)-norcamphor-derived furyl hydroperoxide

A less developed methodology for the asymmetric epoxidation of allylic alcohols involves the use of a vanadium catalyst (VO(O*i*-Pr)$_3$ or VO(acac)$_2$) an optically pure hydroxamic acid as the ligand and an alkyl hydroperoxide (TBHP, CHP) [5]. This protocol has seen a renewed interest in the last years, since the first example reported by Sharpless et al. [5a].

Recently, a complementary methodology has been proposed, employing the enantiopure tertiary hydroperoxide TADOOH/VO(O*i*-Pr)$_3$ and a sterically demanding achiral hydroxamic acid. [39] The epoxy alcohols were obtained in satisfactory yields and with up to 72% ee. In the Ti(O*i*-Pr)$_4$ catalyzed epoxidation of allylic alcohols, mediated by enantiopure alkyl hydroperoxides, the addition of achiral diols slightly influenced the asymmetric induction with respect to the enantiomeric excesses obtained in absence of the diols [15a].

Sharpless et al. [5a] suggested that the control of the complexation mode of vanadium/ligand is important in

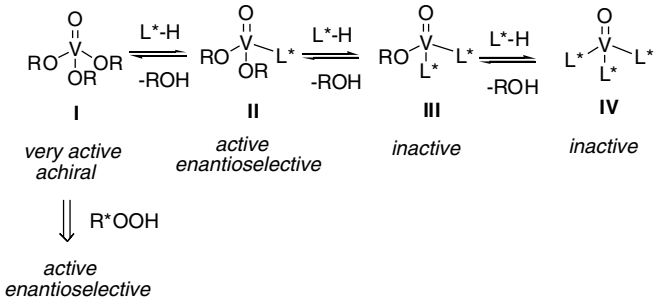


Fig. 5. Vanadium/ligand complexes.

the epoxidation, as different species can equilibrate (Fig. 5). Confirmation of this proposal was recently reported by NMR studies [10c].

When using an enantiopure hydroperoxide and an achiral ligand, enantioselective epoxidations can occur via complexes **I** and **II**, unlike the classical methodology making use of enantiopure ligand and achiral hydroperoxide, where the asymmetric epoxidation takes place only via complex **II**.

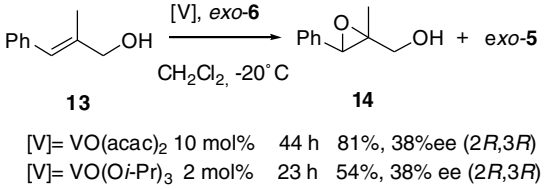
We have reported the first analysis of the competitive enantioselective epoxidation by species **I** on a model compound using an optically pure hydroperoxide (Scheme 8) [40].

The epoxy alcohol was obtained in 38% ee in both the experiments employing differently active vanadium catalysts. It is interesting to note that reactions in Scheme 8 represent the first asymmetric example of the well-known system reported by Sharpless et al. [41] for the regio- and diastereoselective epoxidation of allylic alcohols (VO(acac)$_2$/TBHP/allylic alcohol).

In order to suppress the pathway involving species **I**, the equilibria had to be shifted toward complexes **II**, **III** and **IV** in the presence of an achiral hydroxamic acid as the ligand. Hence, an excess of the ligand (up to 1.5 equiv.) with respect to the metal had to be used to observe asymmetric epoxidation pathway provided only by complex **II**.

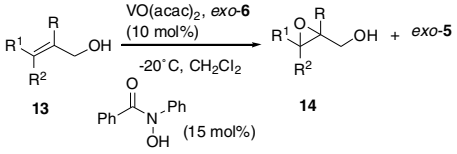
After a screening of various achiral hydroxamic acids, synthesized according to known procedures, commercially available *N*-hydroxy-*N*-phenylbenzamide was found to be the best ligand for the epoxidation carried out under catalytic conditions (10 mol% of the VO(acac)$_2$) (Table 7).

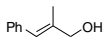
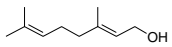
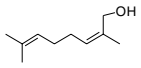
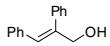
In the presence of the achiral hydroxamic acid the enantioselectivity significantly increased (entry 1) to 61% ee (compare with data in Scheme 8), which could be furtherly improved performing the reaction at −40 °C (up to 67% ee). The sterically encumbered oxidant *exo*-**2** gave negligible conversion to the product. Differently substituted epoxy alcohols were obtained in good yields and moderate ees when using *exo*-**6**.



Scheme 8.

Table 7
Asymmetric epoxidation of primary allylic alcohols by VO(acac)$_2$/*exo*-**6**/*N*-hydroxy-*N*-phenylbenzamide



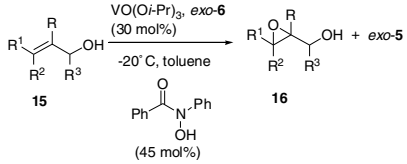
Entry	Allylic alcohol	t (h)	Yield **14**%	ee **14**%
1		48	70	61 (2*R*,3*R*)
2		45	64	40 (2*R*,3*R*)
3		72	61	41 (2*R*,3*S*)
4		42	98	44 (2*R*)
5[a]		23	88	44 (2*R*,3*R*)
6		23	76	45 (2*R*,3*R*)

[a] The reaction was carried out in toluene using VO(O*i*-Pr)$_3$.

The epoxidation of less reactive racemic secondary allylic alcohols and their kinetic resolution was investigated under modified conditions requiring more active VO(O*i*-Pr)$_3$ as the catalyst (Table 8).

The allylic alcohol **15a** was converted in low yield and ee exclusively into the *erythro* epoxy alcohol (entry 1) and the

Table 8
Asymmetric epoxidation of secondary allylic alcohols by VO(O*i*-Pr)$_3$/*exo*-**6**/*N*-hydroxy-*N*-phenylbenzamide



Entry	Allylic alcohol	t (h)	Yield **16**%	Dr (E/T) **16**%	ee **16**%	Yield **15**%	ee **15**%
1	 **15a**	90	29	>99/<1	13 (1*S*,2*S*,3*R*)	70	5(1*R*)
2	 **15b**	90	52	>99/<1	17 (2*S*,3*S*,4*S*)	43	23(2*R*)
3[a]	 **15b**	12	58	>99/<1	11(2*S*,3*S*,4*S*)	40	15(2*R*)

[a] The reaction was carried out in absence of the ligand.

kinetic resolution of the corresponding alcohol was a negligible process. A comparable level of asymmetric induction and efficiency of the kinetic resolution was observed in the epoxidation of compound **15b**, whose corresponding product was obtained as single *erythro* isomer. This level of stereoselectivity was better than the one observed when using common systems [38] as Ti(O*i*-Pr)$_4$/L-DET/TBHP, Ti(O*i*-Pr)$_4$/TBHP and most of all VO(acac)$_2$/TBHP which furnished the epoxy alcohol **16b** in E/T 91/9. Interestingly, the experiment performed in absence of ligand (entry 3) afforded, in shorter reaction time, exclusively the *erythro* epoxy alcohol, with marginal influence on the asymmetric induction. This result clearly pointed out that the structure of the hydroperoxide can be crucial by itself in controlling the level of diastereoselectivity during the reaction.

5. Conclusions

Metal-catalyzed asymmetric oxidations are fundamental processes in organic synthesis and the development of alternative methodologies to the pre-existing methods is highly desirable. Up to now, oxidations mediated by optically pure alkyl hydroperoxides have received limited attention, mainly due to the difficulty in their preparation.

Recently, we have developed an easy and simple approach to optically pure tertiary furyl hydroperoxides. The synthetic route allows the formation of the oxidants in predictable stereocontrolled manner and in good overall yields by using enantiopure commercial sources, furthermore it is susceptible of further elaboration to access new enantiopure compounds. Investigations on their reactivity in Ti-catalyzed sulfoxidation showed that moderate level of asymmetric induction can be achieved for the sulfoxides. Nevertheless, it is likely that improvements in the control of the enantioselectivity will be achieved in the future by synthesizing novel (*S*)-norcamphor-modified hydroperoxides and exploiting the positive contribution of the stereoconvergent kinetic resolution. In the vanadium-catalyzed epoxidation of allylic alcohols promising results have been obtained, although still far from the excellent levels of Sharpless and related methodologies. Interestingly, all the oxidations proceeded in highly diastereoselective manner, giving evidence that structural requirements of the alkyl hydroperoxides play an important role in affecting the stereoselectivity even in absence of any ligand. Finally, optically pure furyl hydroperoxides can be easily regenerated in one step, recycling the corresponding alcohols during the purification procedure, which makes the entire process more convenient.

Acknowledgements

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