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Renewable camphor-derived hydroperoxide: synthesis and use in the asymmetric epoxidation of allylic alcohols†

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Renewable enantiopure tertiary furyl hydroperoxide has been easily synthesized in two steps starting from low cost (+)-(1*R*)-camphor and it has been used in the asymmetric epoxidation and kinetic resolution of allylic alcohols (enantioselectivities up to 46%).

In the last decade, there has been an increasing interest in the synthesis of optically pure alkyl hydroperoxides to be used as stereoselective oxidizing reagents, but only recently has some progress has been achieved in this field. Optically active hydroperoxides were obtained by $^1O_2$ photo-oxidation of thiazolidine derivatives[1] and allylstannanes,[2] by oxidation of unsaturated glycosides.[3] A broadly applicable approach has been realized by horseradish peroxidase (HRP) mediated kinetic resolution of secondary racemic hydroperoxides.[4] HRP does not catalyze kinetic resolution of tertiary hydroperoxides, which are not accessible in enantiopure form. The only example of optically pure tertiary hydroperoxide was reported by Seebach *et al.*, who used TADDOL as starting chiral source. TADOOH (Fig. 1) furnished the highest values of enantioselectivities yet observed with an enantiopure hydroperoxide in asymmetric oxidations.[5]

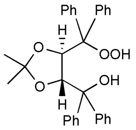
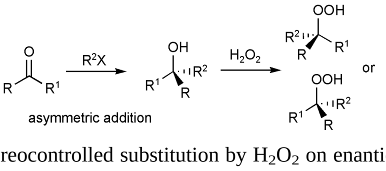


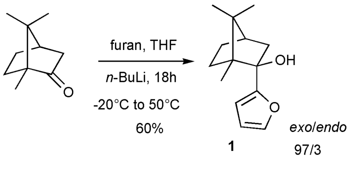
Fig. 1 TADOOH hydroperoxide.

We report here the first successful approach to a tertiary enantiopure hydroperoxide *via* stereospecific nucleophilic substitution of the OH group bound to the asymmetric carbon centre of the alcohol by H_2O_2. This route, unlike TADOOH, affords an optically pure tertiary hydroperoxide, having the reactive OOH group directly bound to the stereogenic carbon centre. Until now, the preparation of enantiopure hydroperoxides using this way, although being the simplest and shortest approach, has met with poor success.[6] On the other hand, it is a very difficult goal, since it requires the occurrence of a stereocontrolled substitution by H_2O_2 on the stereogenic carbon centre (Scheme 1). We exploited this two steps route for the synthesis of racemic furyl hydroperoxides that were used as renewable oxygen donors in asymmetric oxidations.[7]

In consideration of the well-known *endo*/*exo* discrimination in (+)-(1*R*)-camphor bicyclic system,[8] our choice was directed toward it, as cheap chiral source, to perform the sequence depicted in Scheme 1. (+)-(1*R*)-Camphor was treated with 2-furyl lithium in THF, according to general procedures[9] reported for aryl and heteroaryl lithium additions to this ketone. As predictable, *exo* furyl alcohol **1** was obtained almost exclusively, as judged from ^1H NMR (*exo*/*endo* 97/3), in good yield (Scheme 2). The *exo* configuration for the prevalent alcohol **1** was unambiguously assigned by NOESY experiment (see ESI†). On the basis of our previous studies,[7] diastereoisomerically pure *exo*-**1** was treated with *p*-toluensulfonic acid (PTSA) and 30% aqueous H_2O_2 in dimethoxyethane (DME) (Table 1, entry 1). Elimination product **3** and traces of hydroperoxide **2** were the only compounds detected (Scheme 3). Although this attempt was unsuccessful, by-products derived from tertiary 2-norbornyl cation skeletal rearrangements, namely Wagner–Meerwein and Nametkin rearrangements,[10] were not observed. Numerous investigations on the reactivity of 2-borneol systems under acid conditions showed that the relative tendency of 2-norbornyl cations to rearrange was affected by the substitution pattern of the cation and the reaction conditions.[11] Data in favor of classical structure for tertiary 2-norbornyl cations and their successful trapping have been reported.[11c] The electron-rich furan substituent should have reasonably stabilized the initially formed cation enabling its trapping by H_2O_2. Urea/hydrogen peroxide adduct (UHP) was then used as anhydrous source of H_2O_2 (entry 2), but the yield of **2** was only slightly improved. Forced reaction



Scheme 1 Stereocontrolled substitution by H_2O_2 on enantiopure alcohol.

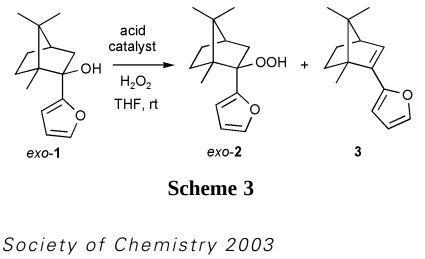


Scheme 2

Table 1 Acid-catalyzed addition of 30% aqueous H_2O_2 to *exo*-**1**

Entry	Acid catalyst (equiv)	H_2O_2 source (equiv)	*t* (h)	Yield *exo*-**2**%[a]	Yield **3**%[a]
1[b]	PTSA (0.5)	H_2O_2 (2)	2	6	94
2[b]	″	UHP (4)	48	14	11
3[b]	PTSA (1)	UHP (30)	24	5	10
4	Amberlyst-15 (100%wt/**1**)	UHP (20)	″	48	33
5	Amberlyst-15 (200%wt/**1**)	UHP (50)	19	79(52)	15(10)
6[c]	Amberlyst-15 (100%wt/**1**)	H_2O_2 (10)	18	63(60)	37(30)

[a] Determined by ^1H NMR analysis. Numbers in parentheses refer to isolated products after flash chromatography. [b] DME was used as solvent. [c] H_2O_2 was used as 50% water solution.



Scheme 3

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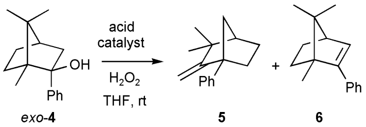
† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b303904h/

conditions (entry 3) did not favor the formation of the hydroperoxide. When using the heterogeneous Amberlyst-15 in THF (entry 4), we were pleased to observe a satisfactory conversion to **2**, which was further improved in the presence of a large excess of UHP by doubling the amount of catalyst (entry 5). In order to check if the lower isolated yield of **2** was due to its inherent chemical instability or to partial decomposition during the tedious workup required to remove urea, 50% aqueous H_2O_2 was employed. A complete recovery of **2** (entry 6), indicated the good chemical stability of this compound. The assessment of the *exo* configuration was accomplished by reducing **2** with Ph_3P to the alcohol, whose spectroscopic data and specific optical rotation perfectly matched with those of *exo*-**1**. Furyl alcohol *endo*-**1** should have furnished the same carbocation intermediate and hence *exo*-**2**. To support this hypothesis *endo*-**1** was treated under optimized conditions. Although in 35% isolated yield, *exo*-**2** was indeed obtained. All the results confirmed the expectations of H_2O_2 attack exclusively from the *exo*-side of the carbocation, since *endo*-**2** was not detected. As a practical consequence, the diastereoisomeric mixture of alcohols **1** can be conveniently used without separation.

In order to gain an insight into the stabilization of the tertiary 2-norbornyl cation, provided by the furan substituent, *exo*-**4** (Scheme 4) was treated under previously optimized conditions (Table 2, entry 1), but it proved to be unreactive. When performing the reaction at 45 °C (entry 2), olefin **5**, derived by Wagner–Meerwein rearrangement of the 2-norbornyl cation, was the major product together with a small amount of olefin **6**. Similar results were obtained carrying out the reaction with UHP or using PTSA (entries 3 and 4). In this case, the rearrangement of the cation was a fast process, confirming how the nature of substitution affects the evolution of the intermediate.[11]

Exo-**2** was then employed as oxidant in the asymmetric epoxidation of allylic alcohols using Ti(O*i*-Pr)$_4$ as metal catalyst (Scheme 5, Table 3). Geraniol was regioselectively (entry 1) converted into the (2*S*,3*S*)-epoxy alcohol **8a** in satisfactory yield and with moderate 42% ee. Nerol, was epoxidized in good yield, but with somewhat smaller enantioselectivity (entry 2). The best value of ee was achieved in the epoxidation of **7c** (entry 3). Primary cyclo epoxy alcohol **8d** (entry 4) was obtained with appreciable ee, while α-methyl cinnamyl alcohol **7e** reacted sluggishly and was epoxidized with the lowest ee (entry 5). Enantiomeric excesses shown in Table 3, although moderate, were generally better or in some cases comparable (except for **8e**) with the ones previously achieved[3,5,12] using an enantiopure hydroperoxide. When catalytic loadings of Ti(O*i*-Pr)$_4$ (30 mol%) were employed in the epoxidation of **7a** and **7c**, the enantioselectivity was almost maintained (40% ee, not shown in Table 3). Interestingly, the epoxidation of **7f** (entry 6) afforded the *syn* epoxy alcohol with complete diastereoselectivity and 38% ee, while, unreactive (*R*)-**7f** was isolated in 37% yield and 35% ee. This is a promising first example of kinetic resolution of secondary allylic alcohols mediated by an enantiopure hydroperoxide.[13] At the end of the reactions, *exo*-**1** was usually recovered in 70–80% yields by flash chromatography, without loss of optical purity and it can be reconverted into *exo*-**2** (Scheme 3), rendering the process a valuable chiral resource-saving protocol.

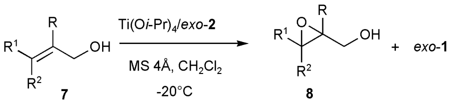


Scheme 4

Table 2 Acid-catalyzed addition of 50% aqueous H_2O_2 to *exo*-**4**

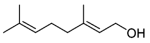
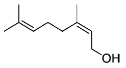
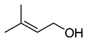
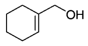
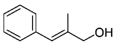
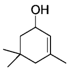
Entry	Acid catalyst (equiv)	H_2O_2 source (equiv)	*t* (h)	Yield **4**%[a]	Yield **5**%[a]	Yield **6**%[a]
1	Amberlyst-15 (200%wt/**4**)	H_2O_2 (10)	17	100	—	—
2[b]	″	″	7	10	74	16
3[b]	Amberlyst-15 (100%wt/**4**)	UHP (20)	66	80	15	5
4[c]	PTSA (2)	H_2O_2 (8)	48	35	55	10

[a] Determined by ^1H NMR analysis. [b] Reaction performed at 45 °C. [c] DME was used as solvent.



Scheme 5

Table 3 Asymmetric epoxidation of allylic alcohols by *exo*-**2**/Ti(O*i*-Pr)$_4$/MS 4Å[a]

Entry	Allylic alcohol	**7**	*t* (h)	Yield **8**%[b]	Ee **8**%[c]	Config.[f]
1		**7a**	5	54	42	(2*S*,3*S*)
2		**7b**	7	59	31[d]	(2*S*,3*R*)
3		**7c**	5	45	46	(2*S*)
4		**7d**	6	48	36	(1*R*)
5		**7e**	45	30	24[e]	(2*R*,3*R*)
6		**7f**	20	48	38[d]	(1*S*, 2*S*, 6*R*)

[a] Molar ratios: *exo*-**2**/**7**/ Ti(O*i*-Pr)$_4$ 1.3–1.5/1/1. [b] Isolated products after flash chromatography. [c] Determined by ^1H NMR shift experiments on the acetylated epoxide with Eu(hfc)$_3$. [d] Determined by ^1H NMR analysis of the derived MTPA ester in C_6D_6. [e] Determined by HPLC analysis on chiral column (Daicel Chiralcel OD). [f] Assigned by comparison of measured $[\alpha]_D$ with the literature value or by Mosher's esters method.

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