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Catalytic Asymmetric β-Peroxidation of Nitroalkenes

Alessio Russo[a] and Alessandra Lattanzi[a,*]

[a] Dipartimento di Chimica, Università di Salerno, Via Ponte don Melillo, 84084 Fisciano, Italy
Fax: (+39)-089-969-603; e-mail: lattanzi@unisa.it

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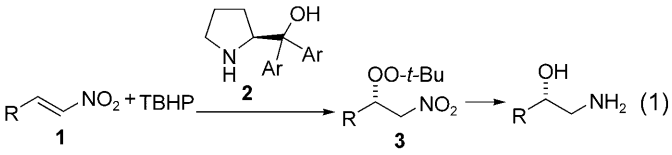
Abstract: The first example of an asymmetric β-peroxidation of nitroalkenes is disclosed. The reaction is promoted by catalytic loadings of a commercially available diaryl-2-pyrrolidinemethanol derivative and *tert*-butyl hydroperoxide as the oxidant. A synthetically useful class of peroxides is obtained in good yield and enantioselectivity (up to 84% *ee*).

Keywords: asymmetric catalysis; Michael addition; nitroalkenes; organocatalysis; peroxides

Catalytic asymmetric conjugate additions are fundamental reactions in organic synthesis, widely used to form carbon-carbon and carbon-heteroatom bonds.[1] An impressive number of Michael addition reactions, either using metal-based chiral complex catalysis[2] or small chiral molecules as organocatalysts[3] have been developed. Among the different acceptors, easily accessible nitroalkenes have been intensively investigated as being compounds of a highly reactive nature.[4] Moreover, the nitro group can undergo a number of further transformations, after the addition, giving rise to a variety of enantioenriched compounds.[5] In this context, organocatalysts such as *Cinchona* alkaloids and thioureas, besides enamine activation of ketones and aldehydes as donors,[6] can promote efficient asymmetric conjugate additions of different acidic pronucleophiles to nitroalkenes.[7] In these examples, a bifunctional type of catalysis has been proposed, that involves activation of the acceptor *via* hydrogen bonding between the nitro moiety and a Brønsted acid functionality of the catalyst, whereas the pronucleophile is deprotonated by a basic group of the catalyst. Hence, a synergic network of hydrogen bonding and ion pairing interactions engaged between the reactants and the active sites of the chiral promoter assure a well-organized transition state leading to high stereocontrol.

Despite the synthetic importance of epoxides or β-hydroxy compounds, achievable through asymmetric conjugate addition to nitroalkenes, the strong basicity and poor nucleophilicity of oxygen nucleophiles render this approach problematic. Indeed, only a few examples of stereoselective oxa-Michael reactions were reported by the groups of Enders,[8] Dixon[9] and Jørgensen.[10]

We have recently developed a simple methodology for the highly enantioselective epoxidation of α,β-enones catalyzed by diaryl-2-pyrrolidinemethanol compounds and *tert*-butyl hydroperoxide (TBHP) as the oxidant.[11] The same organocatalysts were found to be effective in the Michael addition of malonate esters to nitroalkenes although with only a moderate degree of asymmetric induction.[12] Encouraged by these results and the small number of asymmetric approaches based on oxa-Michael addition to nitroalkenes, we envisaged to exploit our organocatalytic system for their epoxidation.[13] Interestingly, peroxides **3** were formed as the result of the addition [Eq. (1)]. To the best of our knowledge, compounds **3**



have been previously suggested as intermediates in the oxidation of *trans*-β-nitrostyrenes to α-nitroacetophenones using TBHP and *n*-BuLi and one example (**3a**) was isolated.[14] Herein we report on the development of the first asymmetric variant of this relatively unexplored reaction, which represents a straightforward entry to functionalized enantioenriched acyclic peroxides. Indeed, chiral non-racemic acyclic peroxides are extremely difficult to obtain and the rare examples reported are based on a modified version of the asymmetric metal-catalyzed Kharasch–Sosnovsky

oxidation.[15] Moreover, the great potential of compounds **3** can be recognized as synthetic precursors of enantioenriched β-amino alcohols, which are products of pharmaceutical interest[16] as well as widely employed chiral building blocks and ligands for asymmetric synthesis.[17]

Based on our earlier work,[11,12] we initially investigated commercially available L-α,α-diphenylprolinol **2a**, in catalytic amounts, as promoter of the reaction of *trans*-β-nitrostyrene **1a** and TBHP in different solvents at room temperature (Table 1).

Table 1. Optimization of the oxa-Michael addition of TBHP to **1a**.[a]

Entry	2	Solvent	Time [h]	Yield [%][b]	*ee* [%][c]
1	**2a**	toluene	16	38	51
2	**2a**	*p*-xylene	17	38	55
3	**2a**	hexane	15	58	44
4[d]	**2a**	hexane	18	30	18
5	**2b**	hexane	18	52	-6
6	**2c**	hexane	46	5	7
7[e]	**2d**	hexane	17	37	48
8[e]	**2e**	hexane	19	60	45
9[e]	**2f**	hexane	16	trace	n.d.[f]
10[e]	**2g**	hexane	16	60	64
11[e]	**2h**	hexane	20	10	54
12[e,g]	**2g**	hexane	26	58	78
13[e]	**2g**	methylcyclohexane	6	53	68
14[e,g,h]	**2g**	methylcyclohexane	60	72	84

[a] Molar ratios: **1a**/TBHP/**2** = 1.0/1.5/0.3. Reaction carried out at $c = 0.5$ M of **1a**.
[b] Yield of isolated product after flash chromatography.
[c] Determined by HPLC analysis on a Daicel Chiralcel OD-H column.
[d] Cumene hydroperoxide as the oxidant.
[e] Reaction carried out at $c = 0.2$ M of **1a**.
[f] Not determined.
[g] At −18 °C.
[h] Using 20 mol% of **2g**.

In toluene or *p*-xylene, peroxide **3a** was isolated in moderate yield and encouraging *ee* values (entries 1 and 2). In hexane, the conversion increased, although the enantioselectivity slightly decreased (entry 3). Moreover, polymeric by-products were observed. Reactions carried out in hexane with more hindered cumene hydroperoxide led to the corresponding product **3b** in low yield and 18% *ee* (entry 4). Hence, TBHP was chosen for further optimization of the reaction in hexane as the solvent. *Cinchona* alkaloids such as quinine, quinidine, cinchonine and cinchonidine gave disappointing results.[18] The reaction carried out with the *O*-methylated catalyst **2b** (Figure 1) yielded the product in poor enantioselectivity (entry 5).

This proved the key role exerted by the hydroxy group in the control of the asymmetric induction, likely *via* hydrogen bonding with the nitro group of the alkene. The tertiary *N*-methylated catalyst **2c** proved to be ineffective, thus demonstrating that the secondary amine is crucial for the reaction to succeed (entry 6). Different readily accessible diaryl-2-pyrrolidinemethanols were then screened for their catalytic ability to promote the reaction (entries 7–11). Commercially available compound **2g** turned out to be the most effective and to our delight, a significant improvement of the *ee* was observed (entries 10 and 12). A better solubilization of the nitroalkene was achieved using methylcyclohexane as the solvent (entry 13). The rate of conversion increased, which helped to reduce catalyst loading and when the reaction was performed at −18 °C, **3a** was isolated in good yield and 84% *ee* (entry 14).

Having estabilished an optimal reaction protocol, we explored the scope and limitations of our system for the β-peroxidation of *trans*-nitroalkenes (Table 2).

We first studied the influence of steric hindrance in the β-nitrostyrenes (entries 2–5). Both *para* and *meta* substitution with alkyl substituents were well tolerated and the corresponding peroxides were recovered in good yields and fairly good *ee* values. The introduc-

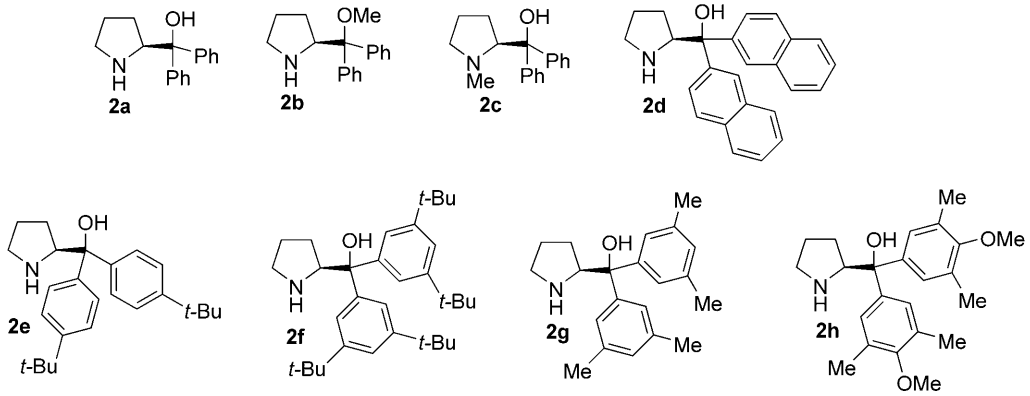
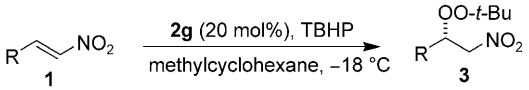


Figure 1. Various diaryl-2-pyrrolidinemethanol derivatives tested.

Table 2. Asymmetric β-peroxidation of *trans*-nitroalkenes catalyzed by **2g**/TBHP system.[a]



Entry	R	3	Yield [%][b]	*ee* [%][c]
1	Ph	**3a**	72	84
2[d]	4-MeC_6H_4	**3c**	59	83
3	3,4-$Me_2C_6H_3$	**3d**	70	83
4	4-*t*BuC_6H_4	**3e**	83	83
5	2-MeC_6H_4	**3f**	62	43
6	4-$CF_3C_6H_4$	**3g**	60	78
7[d]	4-BrC_6H_4	**3h**	41	82
8[d]	4-ClC_6H_4	**3i**	80	84
9[d,e]	3-$MeOC_6H_4$	**3j**	40	80
10[d,e]	2-naphthyl	**3k**	38	80
11[d,e]	2-furyl	**3l**	37	81
12[d,e]	3-furyl	**3m**	45	83
13	cyclohexyl	**3n**	73	72
14	pentyl	**3o**	20	n.d.[f]

[a] Molar ratio: **1**/TBHP/**2g** = 1.0/1.5/0.2. Reaction carried out at $c = 0.15$ M of **1** at 0.15 mmol scale for 48–130 h.
[b] Yield of isolated product after flash chromatography.
[c] Determined by HPLC analysis on chiral columns.
[d] Using a 3:1 (v/v) mixture of methylcyclohexane and toluene.
[e] Using 30 mol% of **2g**.
[f] Not determined.

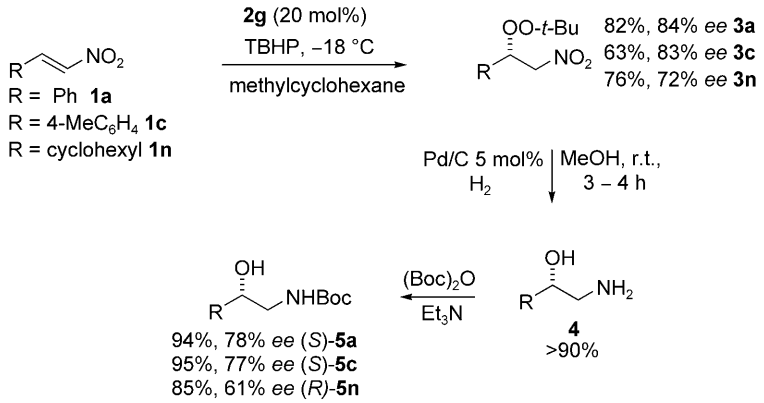
tion of an *ortho*-methyl group significantly decreased the enantioselectivity, presumably on steric grounds, although a good conversion was observed (entry 5). β-Nitrostyrenes having electron-withdrawing groups afforded the products in fairly good enantioselectivity and in some examples slightly reduced yields, which can be ascribed to the lower solubility of the starting materials in the reaction mixture (entries 6–9). 2-Naphthyl and heteroaromatic derivatives furnished the peroxides in moderate yields, but the asymmetric induction was maintained (entries 10–12).[19] Interestingly, the aliphatic cyclohexyl nitroalkene **3n** was converted into the peroxide in good yield and 72% *ee* (entry 13). Unfortunately, the acyclic derivative **3o** gave the product in low yield (entry 14).

To demonstrate the synthetic utility of peroxides **3**, we studied their transformation into 1,2-amino alcohols. The β-peroxidation, carried out on model nitroalkenes **1a**, **1c** and **1n** at a 1.5-mmol scale, afforded compounds **3** with comparable or improved yields (Scheme 1).

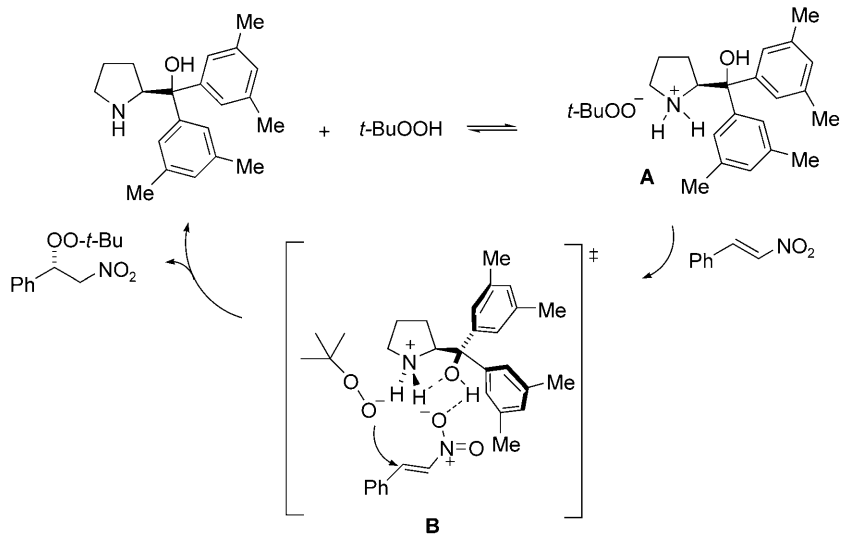
One-pot cleavage of the O–O bond and reduction of the nitro group could be easily accomplished by hydrogenation. 1,2-Amino alcohols **4** were obtained in quantitative yield and only a slight erosion of the enantioselectivity was observed. The *S* absolute configuration of the stereogenic centre and *ee* values of compounds **4a,c** were determined on the corresponding *N*-Boc derivatives **5a,c** (Boc = *tert*-butylcarboxy) by comparison of their optical rotations and HPLC data with those reported in the literature.[20] Aliphatic compound **5n** showed to be enriched in the *R*-enantiomer.[20c] The optical purity of 1,2-amino alcohols **4** can be eventually improved to high levels by a single crystallization as demonstrated for compound **4a** whose derivative **5a** was isolated in 93% *ee*. Hence, the synthetic sequence illustrated in Scheme 1 served also to establish the absolute configuration of peroxides **3**.[21]

Upon analysis of the data and in agreement with our previous reports,[11,12] we suggest a bifunctional type of catalysis with the formation of the contact ion pair **A**,[22] after deprotonation of TBHP by amino alcohol **2g** (Scheme 2).

In transition state **B**, the intermolecular hydrogen bonding between the catalyst OH group and the nitro moiety appears to preferentially orientate the approach of the nitroalkene, favoring the attack of *tert*-butyl peroxy anion to its *Si* face. Finally, protonation



Scheme 1. Synthetic elaboration of peroxides **3** to 1,2-amino alcohols.



Scheme 2. Proposed catalytic cycle for the β-peroxidation of nitroalkenes.

of the anionic intermediate forms the product and catalyst **2g** is regenerated.

In conclusion, we have developed the first example of an asymmetric β-peroxidation of nitroalkenes, which gives access to optically active peroxides **3** in moderate to good yields and synthetically useful levels of enantioselectivity. This reaction is noteworthy for its simplicity, easy access of starting compounds and more importantly, commercial availability in both enantiomeric forms, of diaryl-2-pyrrolidinemethanol **2g** as the catalyst. The utility of the asymmetric β-peroxidation was demonstrated by a straightforward and efficient conversion of peroxides into 1,2-amino alcohols, showing an interesting development of TBHP as a synthon for the hydroxy group. Further investigations on the full scope of the β-peroxidation and applications of ion pair catalysis provided by diaryl 2-pyrrolidinemethanol derivatives are underway.

Experimental Section

General Procedure for the Asymmetric β-Peroxidation of Nitroalkenes

A sample vial was charged with nitroalkene (0.15 mmol), catalyst **2g** (9.3 mg, 0.03 mmol) and methylcyclohexane (or methylcyclohexane/toluene, 3/1 v/v) (1.0 mL). TBHP (5–6 M decane solution, 40 μL, 0.23 mmol) was then added to the stirred solution at −18 °C. The reaction was monitored by TLC. Unsoluble polymeric by-products were additionally formed during the reaction. The solvent was removed under reduced pressure and the crude reaction mixture was directly purified by flash chromatography on silica gel eluting with mixtures of PE and PE/diethyl ether 98/2 to provide peroxide **3**. Residual nitroalkene isolated with the peroxide **3** (which is in general slightly more mobile on TLC than the corresponding nitroalkene) could be removed by precipitation in hexane at low temperature.

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