DOI: 10.1002/adsc.201400341

Chiral *N,N′*-Dioxide–Scandium(III)-Catalyzed Asymmetric Epoxidation of 2-Arylidene-1,3-diketones with Hydrogen Peroxide

Yangyang Chu,[a] Xiaoyu Hao,[a] Lili Lin,[a] Weiliang Chen,[a] Wei Li,[a] Fei Tan,[a]
Xiaohua Liu,[a] and Xiaoming Feng[a,]*

[a] Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China
Fax: (+86) 28-8541-8249; e-mail: xmfeng@scu.edu.cn

Received: April 4, 2014; Published online: ■■ ■■, 0000

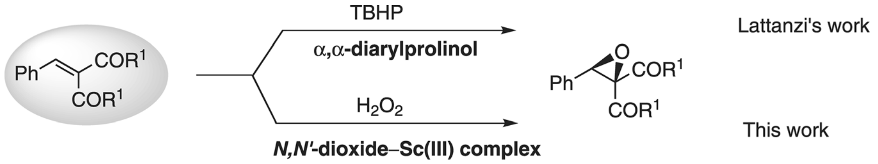
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400341.

Abstract: The catalytic asymmetric epoxidation of 2-arylidene-1,3-diketones using aqueous 30% H_2O_2 as oxidant has been successfully realized by an *N,N′*-dioxide–scandium(III) triflate [$Sc(OTf)_3$] complex, giving the corresponding products in moderate to good yields (up to 85%) with excellent enantioselectivities (up to 99% *ee*) under mild reaction conditions without extra additives.

Keywords: 2-arylidene-1,3-diketones; asymmetric catalysis; epoxidation; hydrogen peroxide; *N,N′*-dioxide–scandium(III) complexes

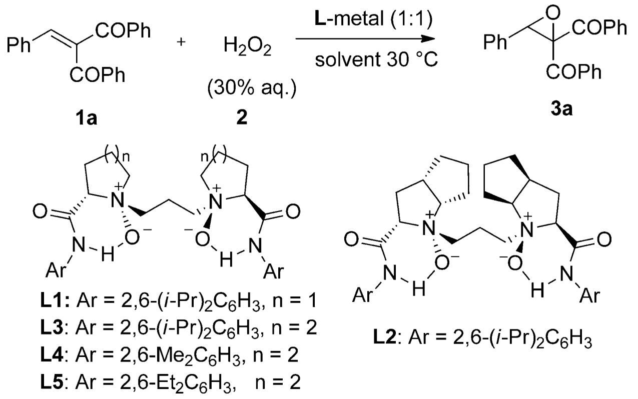
The asymmetric epoxidation of olefins[1] is a very practical method for synthesizing chiral epoxide compounds, which are versatile intermediates and building blocks for the synthesis of useful natural products[2] and drugs.[3] A milestone achievement was obtained by Sharpless for the asymmetric epoxidation of allylic alcohols in the early 1980s. In recent years, asymmetric epoxidation reactions have been accomplished with various oxidants using a wide range of catalysts, such as polypeptides,[5a] chiral ketone,[5b–f] phase-transfer catalyst,[5g] and metal complexes.[5h,i,j] Among these oxidants, aqueous hydrogen peroxide is probably the most competitive for its advantages of cheapness, high atom efficiency and generating water as the sole by-product. Although great progress has been made in H_2O_2-efficient epoxidations,[6] the epoxidations of unfunctionalized[7] and trisubstituted olefins[8] using H_2O_2 as oxidant are still challenging. For the latter, the greater steric hindrance makes the oxidation process more difficult. Recently, one type of trisubstituted olefin, 2-arylidene-1,3-diketone, has been applied in asymmetric [3+2] cycloaddition reactions.[9] In 2010, Lattanzi et al. reported the first enantioselective epoxidation of 2-arylidene-1,3-diketones using α,α-diarylprolinol as organocatalyst and TBHP as oxidant, giving the corresponding epoxides in moderate to good *ee* values (64–85%) within 3–7 days.[10] However, a highly efficient catalytic system for the catalytic asymmetric epoxidation of 2-arylidene-1,3-diketones with environmentally benign H_2O_2 as oxidant is still desirable. The chiral *N,N′*-dioxide–metal complexes developed by our group have shown powerful catalytic ability in a variety of asymmetric reactions owing to their tunable electronic and steric chiral scaffolds, including the asymmetric epoxidation of α,β-unsaturated carbonyl compounds with hydrogen peroxide.[12] As part of our continuing efforts in the epoxidation reaction of olefins, we disclose here an efficient epoxidation reaction of 2-arylidene-1,3-diketones with hydrogen peroxide catalyzed by an *N,N′*-dioxide-$Sc(OTf)_3$ complex under mild reaction conditions (Scheme 1).

Firstly, the complexes of chiral *N,N′*-dioxide **L3** derived from (*S*)-pipecolic acid with various metal salts were investigated with 2-arylidene-1,3-diketone **1a** as the model substrate. Except for the complexes of lanthanide metals, the complexes of other metals could not catalyze the reaction (see the Supporting Information for details). For example, when the **L3**-Cu($OTf)_2$ complex was applied, no product was detected (Table 1, entry 1). The use of the **L3**-La($OTf)_3$ complex did afford the desired product in 24% yield with 34% *ee* (Table 1, entry 2). Encouraged by this result, other lanthanide metals were tested and it was found that the **L3**-Sc($OTf)_3$ complex could give 96% *ee* and 57% yield (Table 1, entry 4 *vs.* entry 3). Next, the structure of the chiral *N,N′*-dioxide was explored. When **L1** which is derived from L-proline and **L2**



Scheme 1. Catalytic asymmetric epoxidation reaction.

Table 1. Optimization of the reaction conditions.[a]



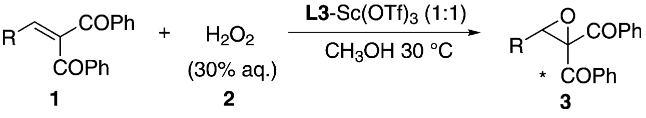
Entry	Ligand	Metal	Solvent	Yield [%][b]	*ee* [%][c]
1	**L3**	$Cu(OTf)_2$	THF	n.r.[d]	–
2	**L3**	$La(OTf)_3$	THF	24	34
3	**L3**	$Y(OTf)_3$	THF	16	95
4	**L3**	$Sc(OTf)_3$	THF	57	96
5	**L1**	$Sc(OTf)_3$	THF	trace	70
6	**L2**	$Sc(OTf)_3$	THF	39	83
7	**L4**	$Sc(OTf)_3$	THF	38	56
8	**L5**	$Sc(OTf)_3$	THF	52	78
9	**L3**	$Sc(OTf)_3$	H_2O	n.r.	–
10	**L3**	$Sc(OTf)_3$	CH_2Cl_2	11	92
11	**L3**	$Sc(OTf)_3$	t-C_4H_9OH	61	98
12	**L3**	$Sc(OTf)_3$	CH_3OH	74	98

[a] Unless otherwise noted, all reactions were performed with **1a** (0.10 mmol), **2** (0.30 mmol), and catalyst (10 mol%) in solvent (0.5 mL) at 30 °C for 48 h.
[b] Isolated yield.
[c] Determined by HPLC.
[d] No reaction.

which is derived from L-rapipril acid were tested, the yields decreased sharply (Table 1, entries 5 and 6). The substituent at the amide moiety of the *N,N'*-dioxide ligands also affected the reaction obviously. With greater steric hindrance, better results were obtained (Table 1, entries 4, 7 and 8). Then, the effect of solvents was investigated. When H_2O was introduced as solvent, unfortunately, no product was detected (Table 1, entry 9). If CH_2Cl_2 was used, a high enantioselectivity could be obtained albeit with 11% yield (Table 1, entry 10). To our delight, when using *tert*-butyl alcohol as the solvent, the yield increased to 61% while the enantioselectivity was maintained (Table 1, entry 11). Encouraged by the result, alcohol solvents were examined carefully. Gratifyingly, CH_3OH was the best solvent candidate which can afford the product in 74% yield with 98% *ee* (Table 1, entry 12). Other conditions such as temperature and other metal salts were also surveyed, but no superior results were obtained (see the Supporting Information).

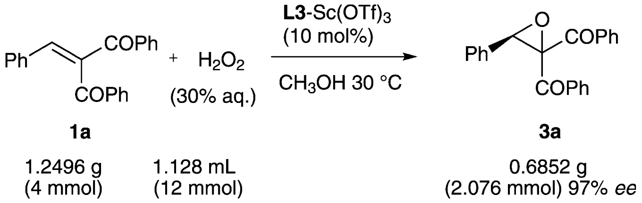
Under the optimized reaction conditions (Table 1, entry 12), the substrate scope was investigated. As summarized in Table 2, the enantioselectivity of the reaction was influenced little by substitution at the *meta-* and *para*-positions of the aromatic ring (Table 2, entries 5–10, 12 and 13). Most of the substrates provided the corresponding chiral epoxides in

Table 2. Substrate scope for the asymmetric epoxidation reaction of 2-arylidene-1,3-diketones compounds with hydrogen peroxide.[a]



Entry	R	Product	Yield [%][b]	*ee* [%][c]
1	Ph	**3a**	74	98 (*R*)
2	$4\text{-}NCC_6H_4$	**3b**	71	93 (*R*)
3	$3\text{-}O_2NC_6H_4$	**3c**	58	98 (*R*)
4	$4\text{-}O_2NC_6H_4$	**3d**	79	82 (*R*)
5	$3\text{-}F_3CC_6H_4$	**3e**	53	99 (*R*)
6	$4\text{-}F_3CC_6H_4$	**3f**	55	99 (*R*)
7	$3\text{-}FC_6H_4$	**3g**	58	99 (*R*)
8	$4\text{-}FC_6H_4$	**3h**	50	98 (*R*)
9	$3\text{-}ClC_6H_4$	**3i**	64	99 (*R*)[d]
10	$4\text{-}ClC_6H_4$	**3g**	60	99 (*R*)
11	$3,4\text{-}Cl_2C_6H_3$	**3k**	85	99 (*R*)
12	$3\text{-}BrC_6H_4$	**3l**	54	98 (*R*)
13	$4\text{-}BrC_6H_4$	**3m**	59	97 (*R*)
14	$3\text{-}PhOC_6H_4$	**3n**	63	99 (*R*)
15	$3\text{-}MeOC_6H_4$	**3o**	62	99 (*R*)
16	$3\text{-}MeC_6H_4$	**3p**	63	98 (*R*)
17	$4\text{-}MeC_6H_4$	**3q**	69	97 (*R*)

[a] Unless otherwise noted, all reactions were conducted with **1** (0.10 mmol), **2** (0.30 mmol), **L3** (10 mol%) and $Sc(OTf)_3$ (10 mol%) in CH_3OH (0.5 mL) at 30 °C for 48 h.
[b] Isolated yield.
[c] Determined by HPLC.
[d] The absolute configuration of adduct **3i** was determined to be *R* by X-ray crystallographic analysis, other products were determined to be *R* from CD spectra in comparison with the spectrum of **3i**.



Scheme 2. Scale-up version of the reaction.

good yields (53–85%) and excellent enantioselectivities (93–99% *ee*), but use of **3d** led to some loss of enantioselectivity (Table 2, entries 2 and 3 *vs.* entry 4). The best result was obtained when a trisubstituted olefin with two chlorine substituents on the aromatic ring was applied as the substrate (85% yield and 99% *ee*, Table 2, entry 11). The olefins with electron-donating groups on the aromatic ring were also good substrates and afforded the corresponding products in 97–99% *ee* (Table 2, entries 14–17). The relatively low yields are probably caused by the steric hindrance and the poor solubility of the 2-arylidene-1,3-diketones in the solvent. The alkyl substrate (**1r**) was also tested under the optimized reaction conditions, unfortunately, the desired epoxide product was not detected (see the Supporting Information for details). The absolute configuration of adduct **3i** was determined to be *R* by X-ray crystallographic analysis,[13] and the others were determined to be *R* by comparing their CD spectra with the spectrum of **3i**.

To show the synthetic utility of the current method, a gram-scale synthesis of **3a** by using the **L3**-Sc(OTf)$_3$ complex was performed. As shown in Scheme 2, in the presence of 10 mol% of **L3**-Sc(OTf)$_3$, 4 mmol of the starting materials **1a** (1.2496 g) reacted with 3 equivalents of H_2O_2, and the corresponding product **3a** was obtained in 50% yield (0.6852 g) with 97% *ee* (Scheme 2).

Based on the previous work[14] and the absolute configuration of products, a possible catalytic activation model was proposed to elucidate the origin of the stereoselectivity. As outlined in Scheme 3, the alkene **1i** coordinated to the scandium(III) in a bidentate fashion to form a stable six-membered ring. The *Si* face of the alkene **1i** was shielded by the nearby isopropylphenyl group of the *N,N′*-dioxide **L3**. Thus, the peroxide attacked the β-carbon atom of the Michael acceptor **1i** preferably from the *Re* face, and the carbon-oxygen bond was formed. Then, the α-carbon attacked the peroxide molecule to form the corresponding *R*-configured product **3i** as determined by the X-ray crystallographic analysis.

In conclusion, we have developed an effective chiral *N,N′*-dioxide catalyst for the asymmetric epoxidation reaction of 2-arylidene-1,3-diketones with hydrogen peroxide. The corresponding chiral epoxides were furnished in moderate to good yields (up to 85%) with good to excellent enantioselectivities (up to 99% *ee*) under mild reaction conditions. This catalytic system is attractive for its air tolerance and performance without extra additives. Further investigations on the application of *N,N′*-dioxides to other reactions are in progress.

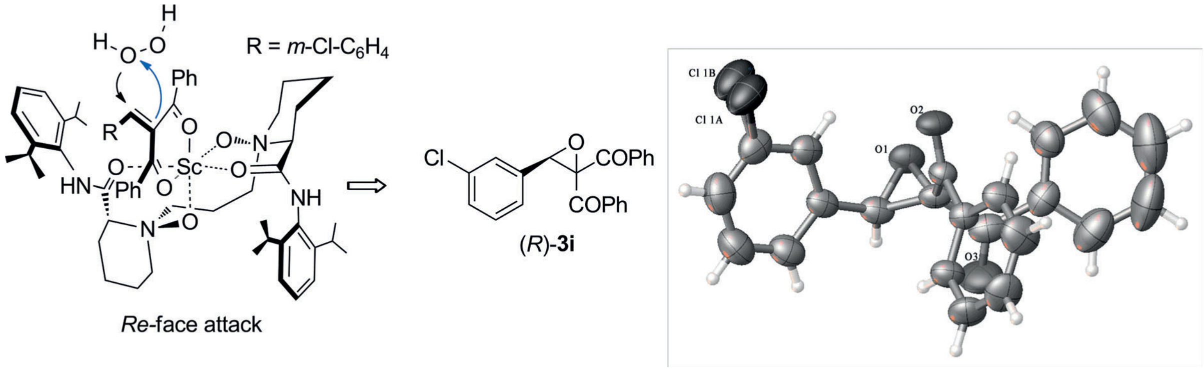
Experimental Section

Typical Procedure for the Asymmetric Epoxidation of 2-Arylidene-1,3-diketones

A mixture of *N,N′*-dioxide **L3** (6.6 mg, 0.01 mmol), Sc(OTf)$_3$ (5.0 mg, 0.01 mmol), and **1a** (31.2 mg, 0.1 mmol), was stirred in CH_3OH (0.5 mL) at 30 °C for 30 min. Then, H_2O_2 (28.2 μL, 0.3 mmol, 30% w/w in H_2O) was added. The reaction mixture was stirred at 30 °C for 48 h. After complete consumption of the starting materials, the mixture was purified directly by column chromatography on silica gel column (petroleum ether:ethyl acetate:CH_2Cl_2 = 50:1:1) to afford **3a** as a white solid; yield: 24.2 mg (74%).

Acknowledgements

We appreciate the National Natural Science Foundation of China (Nos. 21321061 and 21172151), and the Minstry of



Scheme 3. Proposed catalytic model and X-ray structure of the product (*R*)-**3i**.

Education of The People's Republic of China (No. NCET-11-0345) for financial support.

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[13] CCDC 994239 (**3i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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