

# Enantioselective Baeyer–Villiger Oxidation: Desymmetrization of Meso Cyclic Ketones and Kinetic Resolution of Racemic 2-Arylcyclohexanones

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**S** Supporting Information

**ABSTRACT:** Catalytic enantioselective Baeyer–Villiger (BV) oxidations of racemic and meso cyclic ketones were achieved in the presence of chiral  $N,N'$ -dioxide–Sc<sup>III</sup> complex catalysts. The BV oxidations of prochiral cyclohexanones and cyclobutanones afforded series of optically active  $\epsilon$ - and  $\gamma$ -lactones, respectively, in up to 99% yield and 95% ee. Meanwhile, the kinetic resolution of racemic 2-arylcyclohexanones was also realized via an abnormal BV oxidation. Enantioenriched 3-aryloxepan-2-ones, whose formation is counter to the migratory aptitude, were obtained preferentially. Both the lactones and the unreacted ketones were obtained with high ee values.

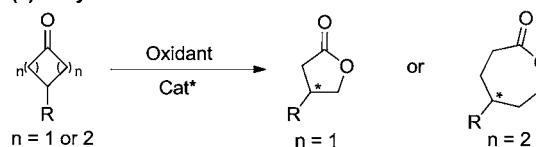
The Baeyer–Villiger (BV) oxidation<sup>1</sup> is highly valuable for the synthesis of esters or lactones. Especially, the asymmetric BV oxidation of racemic or prochiral cyclic ketones provides a simple and attractive route for the synthesis of optically active lactones.<sup>2</sup> Impressive results have been achieved for the BV oxidation of racemic cyclic ketones and 3-substituted cyclobutanones with biocatalysts, chiral metal complexes, or organocatalysts.<sup>3,4</sup> As is often the case, ring-strained cyclobutanones are more reactive in BV oxidations than other cyclic ketones, and they have been well-studied. For example, the BV oxidation of *meso*-cyclobutanones was successfully realized by the Ding group using a chiral Brønsted acid catalyst.<sup>4i</sup> Though biocatalysts have shown excellent enantiocontrol in the BV oxidation of 4-alkylcyclohexanones,<sup>5</sup> the desymmetrization of *meso*-cyclohexanones is less explored at present (Scheme 1a). To date, only one nonenzymatic catalytic system has been shown to afford the BV products in low yields or moderate ee values.<sup>6</sup>

In regard to the kinetic resolution of racemic cyclic ketones through BV oxidation, the stereochemistry is affected not only by stereoelectronic control but also by chiral recognition. The first two examples of BV oxidation of racemic cyclic ketones were independently reported by the groups of Bolm<sup>3a</sup> and Strukul.<sup>3b</sup> In general, the normal CHR-group-migrated product [i.e., the “normal” lactone (NL)] distribution, which depends on the migratory aptitude (tertiary > secondary > primary), was observed (Scheme 1b).<sup>1d,e</sup>

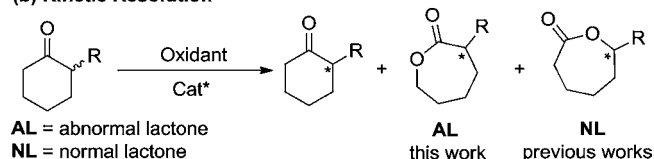
As far as we know, it is still difficult to perform a highly sophisticated catalysis for both the desymmetrization of meso cyclic ketones and the kinetic resolution of racemic cyclic

## Scheme 1. Baeyer–Villiger (BV) Oxidation: Desymmetrization and Kinetic Resolution

### (a) Desymmetrization



### (b) Kinetic Resolution

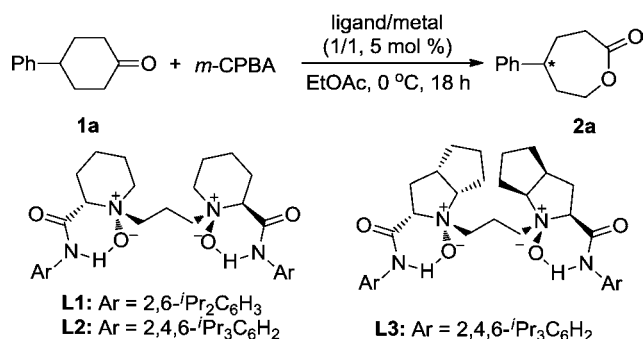


ketones using molecular catalysts. The excellent catalytic performance of chiral  $N,N'$ -dioxide–metal complex catalysts is attributed to the appropriate adjustment of the stereo-environment for lots of asymmetric transformations<sup>7a–d</sup> and the efficient chiral recognition of enantiomers.<sup>7e</sup> Thus, we expected that they could serve as good catalysts for asymmetric BV oxidations. Herein we describe asymmetric BV oxidations of prochiral cyclohexanones and cyclobutanones (desymmetrization process) as well as racemic cyclohexanones (kinetic resolution process). In the presence of a chiral  $N,N'$ -dioxide–Sc<sup>III</sup> complex catalyst, series of optically active  $\epsilon$ - and  $\gamma$ -lactones were obtained with excellent outcomes. Especially, the latter reaction gave the “abnormal” lactone (AL) from a preferential migration of a CH<sub>2</sub> group with high enantioselectivity (Scheme 1b); such reactivity has not been reported hitherto.

In the initial study, 4-phenylcyclohexanone (**1a**) and *m*-chloroperoxybenzoic acid (*m*-CPBA) were chosen as the model substrate and oxidant,<sup>8</sup> respectively. When the reaction was performed in EtOAc at 0 °C without a catalyst, the racemic  $\epsilon$ -lactone **2a** was isolated in 19% yield (Table 1, entry 1). Next, various complex catalysts prepared in situ from a metal salt and the chiral  $N,N'$ -dioxide **L1** were surveyed. The complex catalysts formed from **L1** and Cu(OTf)<sub>2</sub>, Mg(OTf)<sub>2</sub>, and Ni(OTf)<sub>2</sub> afforded **2a** in low yields (entries 2–4). A good yield was obtained in the presence of the **L1**–In(OTf)<sub>3</sub> complex but with only 6% ee (entry 5). We were delighted to find that the

Received: September 18, 2012

Published: September 29, 2012

Table 1. Optimization of the Reaction Conditions<sup>a</sup>

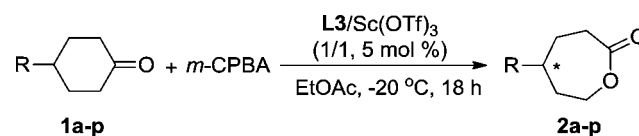
entry	L	metal	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	—	—	19	0
2	L1	Cu(OTf) <sub>2</sub>	42	0
3	L1	Mg(OTf) <sub>2</sub>	39	0
4	L1	Ni(OTf) <sub>2</sub>	42	0
5	L1	In(OTf) <sub>3</sub>	91	6
6	L1	Sc(OTf) <sub>3</sub>	84	68
7	L2	Sc(OTf) <sub>3</sub>	91	86
8	L3	Sc(OTf) <sub>3</sub>	86	88
9 <sup>d</sup>	L3	Sc(OTf) <sub>3</sub>	86	95

<sup>a</sup>Unless otherwise noted, the reactions were performed with L/metal (5 mol %) and **1a** (0.10 mmol) in EtOAc (0.5 mL) at 35 °C for 30 min followed by addition of *m*-CPBA (0.12 mmol) at 0 °C. <sup>b</sup>Isolated yields. <sup>c</sup>Determined by chiral HPLC. <sup>d</sup>The reaction was performed at -20 °C in 2.0 mL of EtOAc.

**L1**-Sc(OTf)<sub>3</sub> complex gave **2a** in 84% yield with 68% ee (entry 6). Next, the efficiency of other *N,N'*-dioxide ligands with Sc(OTf)<sub>3</sub> was explored. When ligand **L2** containing bulkier isopropyl groups at the ortho and para positions of the aniline moiety was employed, 86% ee and 91% yield were achieved (entry 7). As for the chiral backbone moiety, the *N,N'*-dioxide **L3** derived from (*S*)-ramipril exhibited a slight superiority in enantiocontrol toward this reaction compared with ligand **L2** derived from (*S*)-pipercolic acid (entry 8 vs 7). Performing the reaction at -20 °C and lowering the reaction concentration benefited the enantioselectivity (entry 9).

Under the optimal conditions (Table 1, entry 9), various *meso*-cyclohexanones **1** afforded the corresponding  $\epsilon$ -lactones with excellent enantioselectivities. As shown in Table 2, the enantiocontrol of the reaction was sensitive to neither the electronic properties nor the steric hindrance of substituents on the phenyl ring of 4-aryl-substituted cyclohexanones. Generally, the desired chiral 5-aryl-substituted  $\epsilon$ -lactones **2** were isolated with excellent enantioselectivities (up to 95% ee) in good yields (up to 90%) (Table 2, entries 1–10). Moreover, fused-ring-substituted cyclohexanones **2k** and **2l** were also tolerated, giving the desired products with 95% and 94% ee, respectively (entries 11 and 12). 4-Alkyl-substituted cyclohexanones also gave good enantioselectivities (84%–94% ee; entries 13–16). The enantioselectivity increased gradually along with the improvement of the steric hindrance of the alkyl group, implying that the stable conformation of the prochiral cyclohexanone could probably benefit the enantiocontrol. Additionally, treatment of 5.0 mmol of **1a** under the optimal reaction conditions smoothly produced **2a** in 78% yield (0.74 g) with 93% ee in the scaled-up version (entry 17).

The synthetic importance of this desymmetrization was exemplified by a transformation of one of the optically active  $\epsilon$ -lactone products. Product **2m** was easily converted into  $\beta$ -

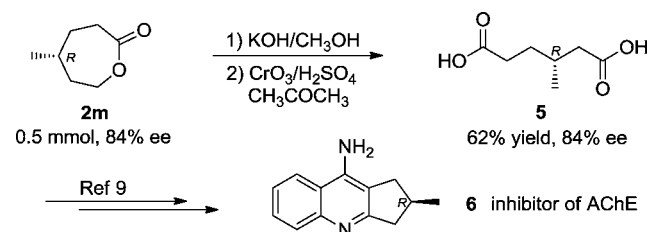
Table 2. Substrate Scope for the Desymmetrization of *meso*-Cyclohexanones<sup>a</sup>

entry	R	product	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	Ph	<b>2a</b>	86	95
2	4-MeC <sub>6</sub> H <sub>4</sub>	<b>2b</b>	90	95
3	3-MeC <sub>6</sub> H <sub>4</sub>	<b>2c</b>	84	94
4	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>2d</b>	81	95
5	3-MeOC <sub>6</sub> H <sub>4</sub>	<b>2e</b>	87	94
6	4-FC <sub>6</sub> H <sub>4</sub>	<b>2f</b>	71	92
7	3-FC <sub>6</sub> H <sub>4</sub>	<b>2g</b>	84	94
8	4-ClC <sub>6</sub> H <sub>4</sub>	<b>2h</b>	82	94
9	3-ClC <sub>6</sub> H <sub>4</sub>	<b>2i</b>	81	94
10	4-PhC <sub>6</sub> H <sub>4</sub>	<b>2j</b>	80	94
11	1-naphthyl	<b>2k</b>	84	95
12	2-naphthyl	<b>2l</b>	87	94
13	Me	<b>2m</b>	76	84 (R) <sup>d</sup>
14	Et	<b>2n</b>	72	85 (R) <sup>d</sup>
15	<i>i</i> Pr	<b>2o</b>	75	92 (R) <sup>d</sup>
16	<i>t</i> Bu	<b>2p</b>	81	94 (R) <sup>d</sup>
17 <sup>e</sup>	Ph	<b>2a</b>	78	93

<sup>a</sup>Unless otherwise noted, the reactions were performed with **L3**/Sc(OTf)<sub>3</sub> (5 mol %) and **1** (0.1 mmol) in EtOAc (1.0 mL) at 35 °C for 30 min followed by addition of *m*-CPBA (0.12 mmol in 1.0 mL of EtOAc) at -20 °C. <sup>b</sup>Isolated yields. <sup>c</sup>Determined by chiral HPLC and chiral GC. <sup>d</sup>The absolute configuration was confirmed by comparison of the optical rotation with the literature value.<sup>5a</sup> <sup>e</sup>**1a** (5.0 mmol), *m*-CPBA (6.0 mmol), 36 h.

methyl-substituted adipic acid **5** (Scheme 2), which is an important intermediate in the synthesis of **6**, an effective inhibitor of acetylcholinesterase.<sup>9</sup>

## Scheme 2. Synthesis of Adipic Acid 5



Next, the use of this catalytic system for BV oxidation of a variety of *meso*-cyclobutanones was explored, and the desired  $\gamma$ -lactones were obtained in good yields (up to 99%) with good enantioselectivities (up to 91% ee). As shown in Table 3, the electronic nature of the substituents in cyclobutanones **3** had nearly no effect on the efficiency and enantioselectivity of the reaction (entries 1–6). For 3-alkyl-substituted substrates **3g** and **3h**, the reaction using ligand **L1** instead of **L3** at -40 °C generated the desired products in quantitative yields with 80% ee (entries 7 and 8).

Another challenge to the catalytic enantioselective BV oxidation is its application to the kinetic resolution of racemic cyclic ketones. It was thus significant that the BV oxidation of racemic 2-phenylcyclohexanone [(±)-**7a**] catalyzed by the chiral *N,N'*-dioxide-Sc(OTf)<sub>3</sub> complex was exemplified. Only a

**Table 3. Substrate Scope for the Desymmetrization of *meso*-Cyclobutanones<sup>a</sup>**

entry	R	product	yield (%) <sup>b</sup>	ee (%) <sup>c,d</sup>
1	Ph	<b>4a</b>	82	91 ( <i>S</i> )
2	4-MeC <sub>6</sub> H <sub>4</sub>	<b>4b</b>	84	90 ( <i>S</i> )
3	3-MeC <sub>6</sub> H <sub>4</sub>	<b>4c</b>	80	91
4	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>4d</b>	78	91 ( <i>S</i> )
5	4-FC <sub>6</sub> H <sub>4</sub>	<b>4e</b>	71	87 ( <i>S</i> )
6	4-ClC <sub>6</sub> H <sub>4</sub>	<b>4f</b>	83	87 ( <i>S</i> )
7 <sup>e</sup>	3-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>4g</b>	99	80 ( <i>R</i> )
8 <sup>e</sup>		<b>4h</b>	99	80 ( <i>R</i> )

<sup>a</sup>The procedure was similar to that in Table 2 except the reaction temperature was  $-60$  °C. <sup>b</sup>Isolated yields. <sup>c</sup>Determined by chiral HPLC. <sup>d</sup>The absolute configurations were confirmed by comparison of the optical rotations with the literature values. <sup>e</sup>Using ligand L1 (5 mol %) at  $-40$  °C.

trace amount of product (*R*)-**8a** was observed under the optimal conditions shown in Table 1, entry 9. It is worth pointing out that this product was generated from the migration of the less-substituted group, which is contrast to the previous reports.<sup>3</sup> Further prolonging the reaction time did not improve the yield. Fortunately, the ee value of the abnormal lactone **AL-8a** was excellent (Table 4, entry 1). To improve the conversion of this reaction, the efficiency of additives was then examined [see the Supporting Information (SI) for details]. Interestingly, when the reaction was performed with 20.0 mg of

Al(O<sup>*i*</sup>Pr)<sub>3</sub> as an additive, the conversion reached 50.0% (entry 2). In this case, an abnormal lactone distribution was also observed, with the CH<sub>2</sub> group migrating preferentially. The abnormal/normal lactone ratio was **AL-8a/NL-9a** = 17/1. Both **AL-(R)-8a** and unreacted (*S*)-**7a** were obtained with 94% ee and a high *s* value (entry 2). It is premature to provide a clear rationalization of the role of Al(O<sup>*i*</sup>Pr)<sub>3</sub> and the unprecedented regioselectivity using this catalyst system. Al(O<sup>*i*</sup>Pr)<sub>3</sub> might benefit the release of the product from the chiral catalyst and then accelerate the catalytic cycle. The steric nature of the catalyst has a critical effect on the migratory aptitude. Because of the particular environment generated by the chiral *N,N'*-dioxide–Sc(OTf)<sub>3</sub> catalyst, the less-hindered CH<sub>2</sub> group can achieve the antiperiplanar migration more easily than the bulkier CHR group, resulting in generation of **AL-(R)-8a** from (*R*)-**7a** prior to the other isomer.

The kinetic resolution of a series of racemic 2-aryl-cyclohexanones **7** was then examined<sup>11</sup> (see the SI for details about the experimental procedure). As shown in Table 4, compounds **AL-8** were obtained as the major products. Generally, lactones **AL-(R)-8** and unreacted ketones (*S*)-**7** were isolated with high conversion and *s* values and good to excellent **AL-(R)-8/NL-9** ratios (5.6/1 to >19/1) (entries 2–7). The reaction efficiency and enantiocontrol were sensitive to the electronic properties of the substituent on the phenyl group of the substrate (entries 3–6). Substrates with an electron-withdrawing substituent (Cl, Br) gave the unreacted ketone (*S*)-**7** and lactone **AL-(R)-8** with higher ee values than those with electron-donating ones (Me, OMe) (entries 3 and 4 vs 5 and 6). Moreover, 2-fused-ring-substituted ketones **7** were also tolerated, giving the products and unreacted ketones with good ee values (entries 8–10). Especially, 2-(naphthalen-1-yl)-cyclohexanone [(±)-**7g**] achieved the best results of the kinetic resolution via BV oxidation, affording unreacted ketone (*S*)-**7g** in 99% ee and **AL-(R)-8g** in 98% ee with 50.3% conversion. A

**Table 4. Substrate Scope for the Kinetic Resolution of Racemic 2-Aryl-Substituted Cyclohexanones<sup>a</sup>**

entry	7: R	<i>T</i> (°C)	<i>t</i> (h)	conv. (%) <sup>b</sup>	ee (%) <sup>c</sup>		yield (%) <sup>d</sup>		8/9 <sup>e</sup>	<i>s</i> <sup>f</sup>
					7	8	7	8 + 9		
1 <sup>g</sup>	7a: Ph	$-20$	18	8.3	9	99 ( <i>R</i> )	–	trace	18/1	–
2	7a: Ph	$-40$	36	50.0	94 ( <i>S</i> )	94 ( <i>R</i> )	46	51	17/1	115
3	7b: 4-ClC <sub>6</sub> H <sub>4</sub>	$-40$	41	51.1	97 ( <i>S</i> )	93 ( <i>R</i> )	47	53	>19/1	113
4	7c: 4-BrC <sub>6</sub> H <sub>4</sub>	$-40$	41	51.3	97 ( <i>S</i> )	92 ( <i>R</i> ) <sup>h</sup>	47	53	>19/1	102
5	7d: 4-MeC <sub>6</sub> H <sub>4</sub>	$-40$	43	49.4	89 ( <i>S</i> )	91 ( <i>R</i> )	51	48	12/1	114
6	7e: 4-MeOC <sub>6</sub> H <sub>4</sub>	$-40$	48	47.7	82 ( <i>S</i> )	90 ( <i>R</i> )	44	56	5.6/1	48
7	7f: 4-PhC <sub>6</sub> H <sub>4</sub>	$-40$	48	50.0	90 ( <i>S</i> )	90 ( <i>R</i> )	44	53	16.5/1	58
8	7g: 1-naphthyl	$-20$	27	50.3	99	98	49	51	>19/1	481
9	7h: 2-naphthyl	$-20$	15	52.3	90	82	45	54	9/1	17
10	7h: 2-naphthyl	$-20$	27	57.6	98	72	39	61	6.5/1	27
11 <sup>i</sup>	7g: 1-naphthyl	$-20$	48	47.9	91	99	53	47	>19/1	624

<sup>a</sup>Unless otherwise noted, the reactions were performed with L3/Sc(OTf)<sub>3</sub> (5 mol %), **7** (0.1 mmol), and Al(O<sup>*i*</sup>Pr)<sub>3</sub> (20.0 mg) in EtOAc (1.0 mL), to which *m*-CPBA (0.10 mmol in 1.0 mL of EtOAc) was added. <sup>b</sup>Conv. = (ee<sub>7</sub>)/(ee<sub>7</sub> + ee<sub>8</sub>). <sup>c</sup>Determined by chiral HPLC. <sup>d</sup>Isolated yields. <sup>e</sup>Determined by <sup>1</sup>H NMR analysis. <sup>f</sup>*s* = ln[(1 – conv.)(1 – ee<sub>7</sub>)]/ln[(1 – conv.)(1 + ee<sub>7</sub>)]. <sup>g</sup>Reaction without Al(O<sup>*i*</sup>Pr)<sub>3</sub>. <sup>h</sup>The absolute configuration of **8c** was determined to be *R* by X-ray analysis<sup>10</sup> (for details about the absolute configurations of the other compounds, see the SI). <sup>i</sup>Using 5.0 mmol of **7g** as the substrate.



sufficiently high *s* value (up to 481) and **8g/9g** ratio (>19/1) were obtained (entry 8). Furthermore, treatment of 5.0 mmol of ( $\pm$ )-**7g** smoothly afforded the product **8g** in 47% yield (0.564 g) with 99% ee, and the unreacted ketone was recovered in 53% yield (0.593 g) with 91% ee (entry 11).

In summary, we have successfully developed highly enantioselective BV oxidations of both meso and racemic cyclic ketones using chiral *N,N'*-dioxide–Sc<sup>III</sup> complex catalysts in a common solvent (ethyl acetate). The desymmetrization of both prochiral cyclohexanones and cyclobutanones afforded the corresponding lactones in up to 99% yield with up to 95% ee. Moreover, unlike the system described previously, kinetic resolution of racemic 2-aryl cyclohexanones was realized via an abnormal BV oxidation, giving  $\epsilon$ -lactones with a reversal of migratory aptitude and high levels of enantioselection. To the best of our knowledge, there is no precedent for the asymmetric BV oxidation with an unusually broad array of cyclic ketones. This work also represents the first example of asymmetric BV oxidation catalyzed by rare-earth metal complexes. Additional research on the mechanism of these processes, extension of the methodology to inert cyclic ketones,<sup>11</sup> and the switch of selectivity for normal and abnormal lactones is underway in our laboratory.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Experimental details and analytical data (NMR, HPLC and HR-ESI-MS). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21021001 and 21172151), the Ministry of Education (20110181130014), and the National Basic Research Program of China (973 Program; 2010CB833300) for financial support.

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(10) CCDC 897036 (**8c**) 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](http://www.ccdc.cam.ac.uk/data_request/cif).

(11) Under the optimal reaction conditions, only a trace amount of BV product was observed for 2-phenylcyclopentanone, and no BV products were observed for 2-alkylcyclohexanones and 2-phenylcycloheptanone.