

# Dynamic Kinetic Resolution of Phthalides via Asymmetric Transfer Hydrogenation: A Strategy Constructs 1,3-Distereocentered 3-(2-Hydroxy-2-arylethyl)isobenzofuran-1(3*H*)-one

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**Supporting Information** 



**ABSTRACT:** Dynamic kinetic resolution of phthalides through asymmetric transfer hydrogenation for the construction of 3-(2-hydroxy-2-arylethyl)isobenzofuran-1(3*H*)-one with 1,3-distereocenters has been developed. This procedure is carried out under a mild condition at 40 °C catalyzed with RuCl[(*S*,*S*)-TsDPEN](mesitylene) using HCOOH/Et<sub>3</sub>N (5:2) as a hydrogen source. A variety of phthalides are smoothly transferred to provide optically pure phthalides with high yields, excellent enantioselectivities, and acceptable diastereomeric ratios.

D ynamic kinetic resolution through asymmetric transfer hydrogenation (DKR-ATH) as a powerful methodology can construct two stereocenters for the preparation of various optically active compounds. To date, most successful examples use  $\alpha$ -substituted ketones as substrates, where well-established DKR-ATH has led to the formation of various functionalized alcohols with 1,2-distereocenters such as  $\alpha$ -halo alcohols (Lassaletta's work, Scheme 1A<sub>1</sub>),<sup>1</sup>  $\alpha$ -substituted  $\beta$ -hydroxy ketones/esters/amides,<sup>2</sup>  $\beta$ -amino- $\alpha$ -hydroxy esters,<sup>3</sup> and so on.<sup>4,5</sup> In some cases, 1,2-distereocenters can be further inducted to produce three stereocenters under DKR-ATH process. One prominent example reported by Johnson and colleagues<sup>6</sup> can provide chiral  $\gamma$ -butyrolactones with three stereocenters (Johnson's work, Scheme 1A<sub>2</sub>).

Despite significant efforts made in the development of DKR-ATH, it is obvious that DKR-ATH biases to construct chiral molecule with 1,2-distereocenters. Direct construction of chiral molecule with 1,3-distereocenters is still difficult to be realized in DKR-ATH process. Main limitation is due to rapid substrate racemization at remote  $\beta$ -position of a carbonyl functionality. A remarkable breakthrough is based on a biocatalytic strategy developed by Peng's group,<sup>7</sup> where the enzyme ATA-036 as the efficient catalyst enables an organic transformation of racemic  $\beta$ -substituted ketone to optically pure molecules with 1,3distereocenters. Therefore, learning from biocatalysis in biochemical processes, developing a DKR-ATH process to realize an efficient construction of 1,3-distereocenters is highly desirable; especially, construction of chiral phthalides with 1,3-

### Scheme 1. DKR-ATH of Substituted Ketones

A) DKR-ATH of  $\,\alpha\text{-substituted ketones}$ 

A<sub>1</sub>: Lassaletta's work





### B) DKR-ATH of β-substituted ketones

This work (undeveloped)



distereocenters could be applied potentially to synthesize a wide range of biologically active compounds, such as  $\gamma$ -amino alcohols,<sup>8</sup> chromanols,<sup>9</sup> flavanol<sup>9a</sup> and so on.<sup>10</sup> Phthalides and their analogues have been reported as showing a wide range of biological active against several illnesses and physiological

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conditions, bronchitis, diarrhea, pneumonia, viral infections, and tuberculosis.<sup>11</sup> Therefore, constructing phthalides and developing their analogues are meaningful work.

On the basis of typically efficient catalyst on various asymmetric transfer hydrogenation,<sup>12,13</sup> some chiral N-sulfonylated diamine-based (TsDPEN-based) organometallic complexes have been explored for construction of chiral molecules with 1,2-distereocenters in DKR-ATH process.<sup>6</sup> Recently, we also find that chiral RuCl[(S,S)-TsDPEN](mesitylene) displays excellent catalytic efficiency in asymmetric transfer hydrogenation of  $\beta$ -keto sulfones,<sup>14</sup>  $\alpha$ -halomethyl ketones,<sup>15</sup> and  $\alpha$ trifluoromethylimines.<sup>16</sup> In this contribution, by utilizing the benefit of RuCl[(S,S)-TsDPEN](mesitylene) on asymmetric transfer hydrogenation, we realize a DKR-ATH of phthalides to construct optically pure phthalides with 1,3-distereocenters. As we envisaged, RuCl[(S,S)-TsDPEN](mesitylene) enables an efficient DKR-ATH to afford various chiral phthalides with high yields and excellent enantioselectivities under mild reaction conditions.

To obtain the highly efficient DKR-ATH of phthalides to various optically pure phthalides with 1,3-distereocenters, the optimization of the reaction conditions were performed using DKR-ATH of 3-(2-0x0-2-phenylethyl) isobenzofuran-1(3H)one 1a as a model reaction. On the basis of those extensively studied chiral TsDPEN-based organometallic complexes in ATH reaction, four representative organometallic complexes, AreneRuTsDPEN (Arene = mesitylene and p-cymene, 4a and 4b) and Cp\*MTsDPEN (Cp\* = pentamethylcyclopentadiene, M = Rh and Ir, 4c and 4d), were screened to compare their catalytic performances at first, where the DKR-ATH of 3-(2oxo-2-phenylethyl)isobenzofuran-1(3H)-one 1a was carried out through the use of CH<sub>2</sub>Cl<sub>2</sub> as solvent and HCOOH/Et<sub>3</sub>N (5:2) as hydrogen source according to the reported method.<sup>4b</sup> As shown in Table 1, it was found that, in the case of 4a as a catalyst, DKR-ATH of 1a could afford the chiral products of 2a and 3a with 97% total yield, 99% ee value for 2a, and good dr value. Such a result was better than that obtained with the catalysts 4b-4d (Table 1, entry 1 versus entries 2-4), demonstrating that 4a was the best catalyst in this catalysis system. Furthermore, the optimization of the polar solvents confirmed that CH<sub>2</sub>Cl<sub>2</sub> was the optimal reaction solvent (Table 1, entry 1 versus entries 5-10). Moreover, through the further optimization of amount of 4a and reaction temperature, it was found that the increased amount of 4a and the enhanced reaction temperature did not affect the reaction results (Table 1, entries 11 and 13), while the decreased amount of 4a and the low reaction temperature reduced the total yields (Table 1, entries 12 and 14). As a result, in the presence of 0.20 mol % of (S,S)-TsPDEN/[RuCl<sub>2</sub>(mesitylene)]<sub>2</sub> 4a, an optimal reaction condition in this DKR-ATH was the use of HCOOH/Et<sub>3</sub>N (5:2) as a hydrogen resource,  $CH_2Cl_2$  as a solvent at 40 °C of reaction temperature.

Having established the efficient DKR-ATH of  $3-(2-\infty - 2-phenylethyl)$  isobenzofuran-1(3H)-one, we further investigated its general applicability with a series of analogues of 1a. As shown in Table 2, various phthalides 1a-1p could be transformed into corresponding chiral alcohols 2 and 3 in high yields (more than 90%) with excellent enantioselectivity (more than 99% ee) and good diastereomeric ratios (up to 90/10 dr) under above optimal reaction condition. It was also found that electronic and steric properties of substituents at the Ar group did not affect their enantioselectivities, regardless of the electro-donating or -withdrawing substituents at 2-3-4-





cat.	solvent	yield of $2 + 3 (\%)^{b}$	ee (%) of $2^c$	dr of $2/3^{\circ}$
4a	$CH_2Cl_2$	97	99	82/18
4b	$CH_2Cl_2$	92	97	80/20
4c	$CH_2Cl_2$	90	90	72/28
4d	$CH_2Cl_2$	82	76	60/40
4a	CH <sub>3</sub> CN	90	47	60/40
4a	i-PrOH	85	90	76/24
4a	MeOH	trace	-	-
4a	DMF	96	98	58/42
4a	1,4-dioxane	82	99	53/47
4a	THF	90	97	50/50
4a <sup>d</sup>	$CH_2Cl_2$	97	99	83/17
4a <sup>e</sup>	$CH_2Cl_2$	92	99	80/20
4a <sup>f</sup>	$CH_2Cl_2$	98	99	80/20
4a <sup>g</sup>	$CH_2Cl_2$	73	88	72/28
	cat. 4a 4b 4c 4d 4a 4a 4a 4a 4a 4a 4a <sup>d</sup> 4a <sup>c</sup> 4a <sup>f</sup> 4a <sup>g</sup>	cat.       solvent         4a $CH_2Cl_2$ 4b $CH_2Cl_2$ 4c $CH_2Cl_2$ 4d $CH_2Cl_2$ 4a $CH_3CN$ 4a $i$ -PrOH         4a       DMF         4a       1,4-dioxane         4a       THF         4a <sup>d</sup> CH_2Cl_2         4a <sup>e</sup> CH_2Cl_2         4a <sup>f</sup> CH_2Cl_2	cat.         solvent         yield of $2 + 3 (\%)^b$ 4a $CH_2Cl_2$ 97           4b $CH_2Cl_2$ 92           4c $CH_2Cl_2$ 90           4d $CH_2Cl_2$ 90           4d $CH_2Cl_2$ 82           4a $CH_2Cl_2$ 82           4a $DHF$ 90           4a $DMF$ 96           4a $1,4$ -dioxane         82           4a $THF$ 90           4a <sup>d</sup> $CH_2Cl_2$ 97           4a <sup>d</sup> $CH_2Cl_2$ 92           4a <sup>d</sup> $CH_2Cl_2$ 92           4a <sup>d</sup> $CH_2Cl_2$ 92           4a <sup>d</sup> $CH_2Cl_2$ 92           4a <sup>d</sup> $CH_2Cl_2$ 98           4a <sup>g</sup> $CH_2Cl_2$ 73	cat.solventyield of $2 + 3 (\%)^b$ ee $(\%)$ of $2^c$ 4a $CH_2Cl_2$ 97994b $CH_2Cl_2$ 92974c $CH_2Cl_2$ 90904d $CH_2Cl_2$ 82764a $CH_3CN$ 90474a $i$ -PrOH85904a $MeOH$ trace-4a $DMF$ 96984a $THF$ 90974a^d $CH_2Cl_2$ 97994a^c $CH_2Cl_2$ 92994a^f $CH_2Cl_2$ 98994a^g $CH_2Cl_2$ 7388

<sup>*a*</sup>1.0 mmol 1a, 2.0  $\mu$ mol catalyst and 0.5 mL HCOOH/Et<sub>3</sub>N (5:2) were added into CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) and the mixture was stirred at 40 °C for 3 h. <sup>*b*</sup>Isolated yield. <sup>*c*</sup>Determined by HPLC analysis using a chiral stationary phase. <sup>*d*</sup>Data was obtained by the use of 0.4 mol % of 4a. <sup>*f*</sup>Data was obtained by the use of 0.1 mol % of 4a. <sup>*f*</sup>The reaction temperature was at 50 °C. <sup>*g*</sup>The reaction temperature was at 30 °C.

postions of Ar group (Table 2, entries 1–13). Moreover, other Ar groups at 3-position of phthalides (such as naphthyl, thienyl, and furyl groups) also could be transformed into the corresponding chiral products with desirable results in this DKR-ATH process (Table 2, entries 14–16). These observations indicate that this DKR-ATH was suitable for constructing a wide scope of chiral phthalides with 1,3-distereocenters.

To determine the synthetic utility and the stereochemistry of chiral products, the DKR-ATH of 1d was performed on gramscale level (Figure 1), where 1.0 g of 1d could be transferred to 4-((S)-1-hydroxy-2-((R)-3-oxo-1,3-dihydroisobenzofuran-1-yl)-ethyl)benzonitrile 2d with 99% ee (70/30 dr), where its recrystallization could afford the enantiomerically pure 2d in 68% yield under the above reaction condition. More importantly, the absolute stereochemistry of 2d could also be determined as (*S*,*R*)-isomer configuration proved by its X-ray crystallographic analysis as shown in Figure 1. Several works are studying the catalytic mechanism of the asymmetric hydrogenation for acetophenone,<sup>17</sup> a simple aromatic ketone, with the catalyst 4b. Herein, we propose that this DKR-ATH appears to proceed through that similar catalytic cycle (see the Supporting Information, proposed mechanism).

In summary, we find that the further exploration of RuCl[(S,S)-TsDPEN](mesitylene) enables a highly efficient DKR-ATH of phthalides for the synthesis of 3-(2-hydroxy-2-arylethyl)isobenzofuran-1(3H)-ones with 1,3-distereocenters,

1	O A Ar	0.2% of cata HCO <sub>2</sub> H/Et <sub>3</sub> I CH <sub>2</sub> Cl 40 °C,	N (5:2) 3h 2 (majo	) + () ,OH År r)	O ,OH Ar 3
entry	2	Ar	yield of $2 + 3 (\%)^{b}$	ee (%) of $2^c$	dr of $2/3^{c}$
1	2a	Ph	97	99	82/18
2	2b	4-FPh	96	99	77/23
3	2c	4-ClPh	96	99	77/23
4	2d	4-CNPh	90	99	74/26
5	2e	4-MePh	95	99	69/31
6	2f	4-iPrPh	96	99	78/22
7	2g	4-MeOPh	94	99	80/20
8	2h	3-FPh	94	99	71/29
9	2i	3-ClPh	95	99	73/27
10	2j	3-BrPh	97	99	71/29
11	2k	3-MeOPh	97	99	77/23
12	21	2-MeOPh	93	99	73/27
13	2m	2,4-Me <sub>2</sub> Ph	93	99	90/10
14	2n	2-naphthyl	96	99	77/23
15	20	2-thienyl	94	99	78/22
16	2p	2-furyl	91	99	70/30

Table 2. DKR-ATH of 3-Substituted Phthalides Catalyzed by  $4a^a$ 

<sup>*a*</sup>1.0 mmol 1, 2.0  $\mu$ mol catalyst and 0.5 mL HCOOH/Et<sub>3</sub>N (5:2) were added into CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) and the mixture was stirred at 40 °C for 3 h. <sup>*b*</sup>Isolated yield. <sup>*c*</sup>Determined by HPLC analysis using a chiral stationary phase.



Figure 1. X-ray structure of 2d.

where various phthalides can be smoothly transferred into desired products in high yields with excellent enantioselectivities and good diasteromeric ratio. Furthermore, such a DKR-ATH strategy under mild reaction conditions makes this catalyst an attractive feature in the practical preparation of a wide scope of biologically active phthalides.

# ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.5b02394.

General information, typical experimental procedures, characterization, HPLC spectra of compounds (PDF)

Crystallographic data of compound 2d (CIF)

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#### Notes

The authors declare no competing financial interest.

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