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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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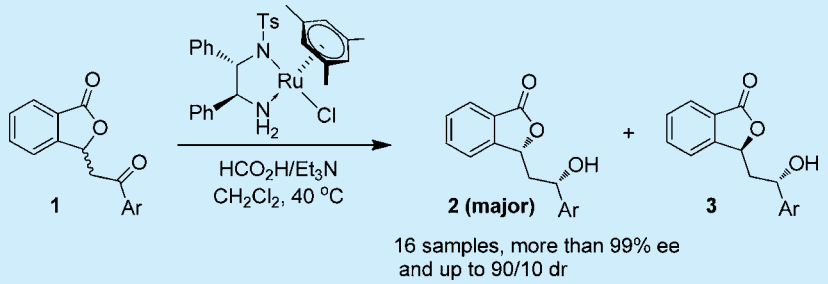
Supporting Information

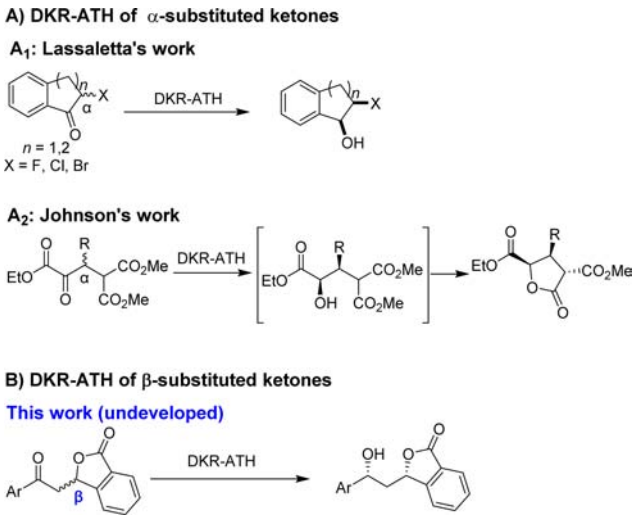


ABSTRACT: Dynamic kinetic resolution of phthalides through asymmetric transfer hydrogenation for the construction of 3-(2-hydroxy-2-arylethyl)isobenzofuran-1(3*H*)-one with 1,3-distereocenters has been developed. This procedure is carried out under a mild condition at 40 °C catalyzed with RuCl[(*S*,*S*)-TsDPEN](mesitylene) using HCOOH/Et_3N (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.

Dynamic 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 α-substituted ketones as substrates, where well-established DKR-ATH has led to the formation of various functionalized alcohols with 1,2-distereocenters such as α-halo alcohols (Lassaletta's work, Scheme 1A_1),[1] α-substituted β-hydroxy ketones/esters/amides,[2] β-amino-α-hydroxy esters,[3] and so on.[4,5] 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[6] can provide chiral γ-butyrolactones with three stereocenters (Johnson's work, Scheme 1A_2).

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 β-position of a carbonyl functionality. A remarkable breakthrough is based on a biocatalytic strategy developed by Peng's group,[7] where the enzyme ATA-036 as the efficient catalyst enables an organic transformation of racemic β-substituted ketone to optically pure molecules with 1,3-distereocenters. 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-distereocenters could be applied potentially to synthesize a wide range of biologically active compounds, such as γ-amino alcohols,[8] chromanols,[9] flavanol[9a] and so on.[10] Phthalides and their analogues have been reported as showing a wide range of biological active against several illnesses and physiological

Scheme 1. DKR-ATH of Substituted Ketones



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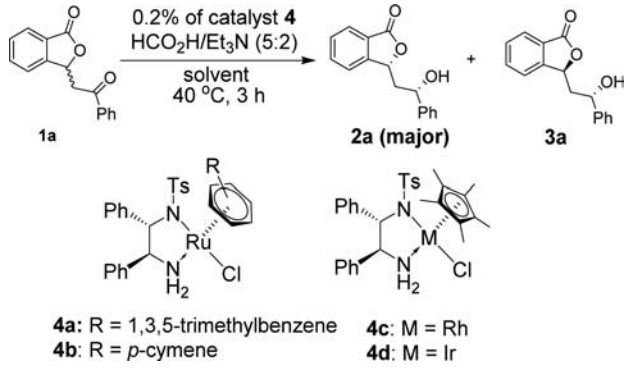
conditions, bronchitis, diarrhea, pneumonia, viral infections, and tuberculosis.[11] Therefore, constructing phthalides and developing their analogues are meaningful work.

On the basis of typically efficient catalyst on various asymmetric transfer hydrogenation,[12,13] 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.[6] Recently, we also find that chiral RuCl[(*S*,*S*)-TsDPEN](mesitylene) displays excellent catalytic efficiency in asymmetric transfer hydrogenation of *β*-keto sulfones,[14] *α*-halomethyl ketones,[15] and *α*-trifluoromethylimines.[16] 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-oxo-2-phenylethyl)isobenzofuran-1(3*H*)-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-(2-oxo-2-phenylethyl)isobenzofuran-1(3*H*)-one **1a** was carried out through the use of CH_2Cl_2 as solvent and HCOOH/Et_3N (5:2) as hydrogen source according to the reported method.[4b] 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_2Cl_2 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/[$RuCl_2$(mesitylene)]$_2$ **4a**, an optimal reaction condition in this DKR-ATH was the use of HCOOH/Et_3N (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-oxo-2-phenylethyl)isobenzofuran-1(3*H*)-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-

Table 1. Optimization of Reaction Conditions for DKR-ATH of 3-(2-Oxo-2-phenylethyl)isobenzofuran-1(3*H*)-one[a]



entry	cat.	solvent	yield of **2** + **3** (%)[b]	ee (%) of **2**[c]	dr of **2**/**3**[c]
1	**4a**	CH_2Cl_2	97	99	82/18
2	**4b**	CH_2Cl_2	92	97	80/20
3	**4c**	CH_2Cl_2	90	90	72/28
4	**4d**	CH_2Cl_2	82	76	60/40
5	**4a**	CH_3CN	90	47	60/40
6	**4a**	i-PrOH	85	90	76/24
7	**4a**	MeOH	trace	-	-
8	**4a**	DMF	96	98	58/42
9	**4a**	1,4-dioxane	82	99	53/47
10	**4a**	THF	90	97	50/50
11	**4a**[d]	CH_2Cl_2	97	99	83/17
12	**4a**[e]	CH_2Cl_2	92	99	80/20
13	**4a**[f]	CH_2Cl_2	98	99	80/20
14	**4a**[g]	CH_2Cl_2	73	88	72/28

[a]1.0 mmol **1a**, 2.0 *μ*mol catalyst and 0.5 mL HCOOH/Et_3N (5:2) were added into CH_2Cl_2 (2.0 mL) and the mixture was stirred at 40 °C for 3 h. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase. [d]Data was obtained by the use of 0.4 mol % of **4a**. [e]Data was obtained by the use of 0.1 mol % of **4a**. [f]The reaction temperature was at 50 °C. [g]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 gram-scale 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,[17] 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(3*H*)-ones with 1,3-distereocenters,

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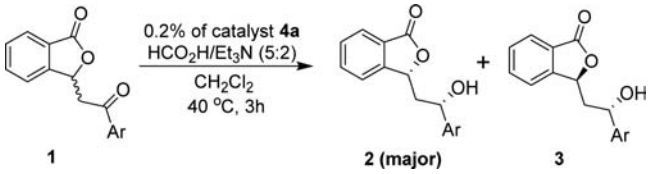
Table 2. DKR-ATH of 3-Substituted Phthalides Catalyzed by 4a[a]



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	2l	2-MeOPh	93	99	73/27
13	2m	2,4-Me_2Ph	93	99	90/10
14	2n	2-naphthyl	96	99	77/23
15	2o	2-thienyl	94	99	78/22
16	2p	2-furyl	91	99	70/30

[a]1.0 mmol **1**, 2.0 μmol catalyst and 0.5 mL HCOOH/Et_3N (5:2) were added into CH_2Cl_2 (2.0 mL) and the mixture was stirred at 40 °C for 3 h. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase.

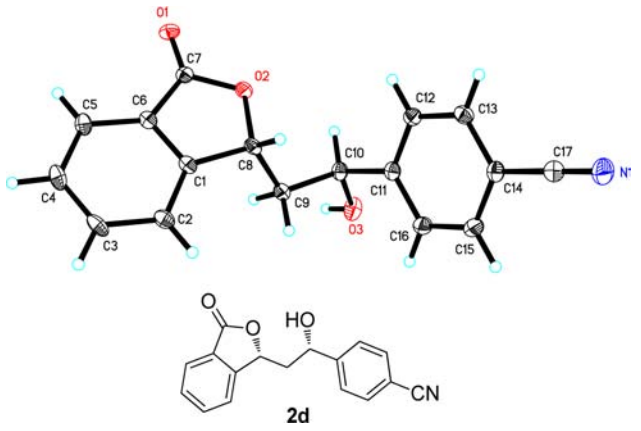


Figure 1. X-ray structure of **2d**.

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.orglett.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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