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Ru-Catalyzed Asymmetric Hydrogenative/Transfer Hydrogenative Desymmetrization of Meso-Epoxy Diketones

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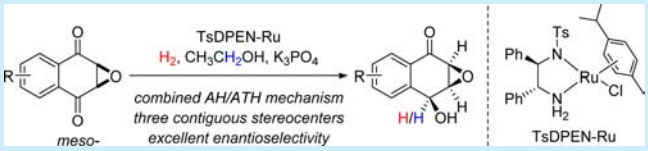
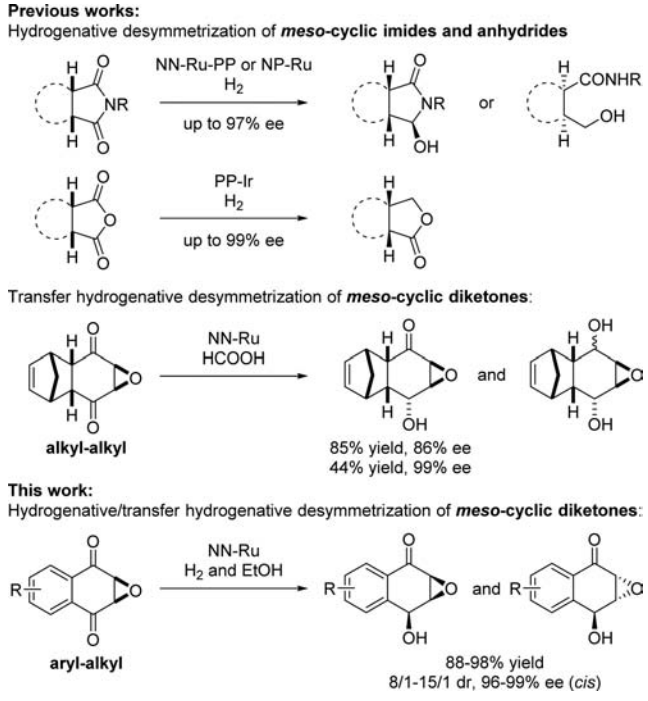
Supporting Information

ABSTRACT: Via a strategy of asymmetric reductive desymmetrization, chiral *cis*-epoxy naphthoquinols with multiple contiguous stereocenters and functional groups were synthesized with excellent enantioselectivities (96−99% ee) and diastereoselectivities (8/1−15/1). A combined asymmetric hydrogenation/transfer hydrogenation mechanism was proposed based on experimental results.



In the field of asymmetric catalysis, transition-metal-catalyzed enantioselective hydrogenation/transfer hydrogenation is considered to be one of the most efficient and practical reduction methodologies.[1] Most chiral compounds, including cyclic and acyclic chiral amines, alcohols, carboxylic derivatives, and alkanes can be prepared via a simple reduction of related C═C, C═N, and C═O bonds.[2] However, normally, enantioselective hydrogenation/transfer hydrogenation only generates one or at most two stereocenters; the preparation of compounds bearing multiple and contiguous stereocenters using this methodology is difficult. Such reactions are of particular interest because structural motifs bearing contiguous stereocenters are abundant in natural products and pharmaceuticals.[3] To overcome this drawback, a strategy of asymmetric desymmetrization of *meso*-substrates can be employed,[4] although this methodology has been insufficiently studied. Some impressive research has been reported independently by Ikariya, Zhang, and Bergens on the enantioselective hydrogenative desymmetrization of *meso*-cyclic imides and anhydrides for the preparation of chiral products bearing two or more stereocenters.[5] On the other hand, only one example concerning the enantioselective transfer hydrogenative desymmetrization of *meso*-cyclic diketones has been realized, even though the hydroxyl ketones are considered to be more versatile products. Using HCOOH as a hydrogen source, a sole alkyl−alkyl diketone substrate was reduced with a high enantioselectivity of 99% ee but a low yield of 44%.[6] Related hydrogenative methodology using H_2 as the hydrogen source still remains elusive, and a more efficient process with a wider substrate scope is highly desired. Herein, we present an asymmetric desymmetrization of *meso*-cyclic aryl−alkyl diketones utilizing a combined hydrogenation/transfer hydrogenation process. Using H_2 and EtOH as the hydrogen source, several *meso*-epoxy naphthoquinones with different substituents were desymmetrized via an effective asymmetric reduction (Scheme 1). The *cis*-epoxy naphthoquinol products, the structural motifs of which are found in various bioactive compounds,[7] can be simply derivatized via manipulation of both the epoxy and carbonyl groups for the synthesis of other polyfunctional compounds with multiple stereocenters.

Scheme 1. Enantioselective Hydrogenative/Transfer Hydrogenative Desymmetrization of *meso*-Substrates



Inspired by some excellent research concerning the asymmetric hydrogenation of ketones (especially that of 1-tetralone and its analogues),[8] we envisaged that the asymmetric hydrogenative desymmetrization of *meso*-2,3-epoxy-tetrahydronaphthalene-1,4-diones could be realized using a similar

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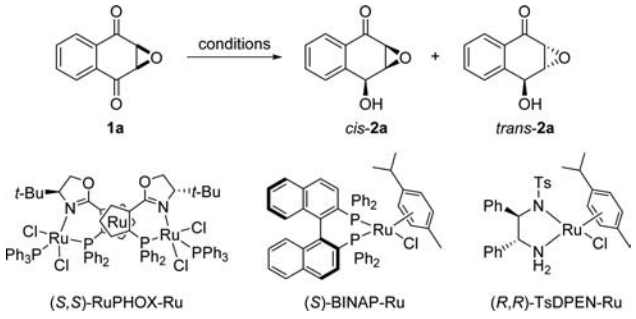
ruthenium catalyst. First, a unique RuPHOX−Ru complex with a C_2 symmetric phosphine/oxazoline ligand, developed within our group and successfully applied to the asymmetric hydrogenation and transfer hydrogenation of aryl−alkyl ketones,[8j,9] was used for the hydrogenation of the model substrate **1a**. No reaction occurred under the reported conditions[8j] or under normal hydrogenation conditions (Table 1, entries 1−2). The well-known catalyst, BINAP-Ru, used often for the hydrogenation of ketones, also showed no activity in this reaction (entry 3). Finally, the TsDPEN−Ru complex, which is commercially available and widely used for both hydrogenation and transfer hydrogenation of aryl−alkyl ketones,[8c,d,10] was examined in this reaction using normal hydrogenation conditions. The desired product was obtained in 52% conversion and 92% ee, together with 5% of its diastereoisomer (entry 4). Other solvents were examined (entries 5−11). The conversions in the protic solvents were much higher than those in nonprotic solvents. EtOH was discovered to be the best solvent with regards to both conversion (63% for product with 5% for its diastereoisomer) and enantioselectivity (96% ee) (entry 5). To improve the activity, a cationic catalyst Ru(OTf)((*R*,*R*)-TsDPEN), preprepared from RuCl((*R*,*R*)-TsDPEN) and AgOTf, was used in the hydrogenation. The substrate was completely converted to give the desired product only in 46% conversion with excellent diastereo- and enantioselectivity. However, byproducts **2aa** (40%) and **2ab** (14%), which are produced by further hydrogenation of **2a**, were detected with the structures being determined via NMR spectroscopy (entry 12).[11] When the H_2 pressure was increased, conversion increased but with a slight decrease in ee (entries 13−14 vs 5). Elevating the temperature from rt to 50 °C reduced both the conversion and enantioselectivity (entry 15). A large amount of starting material was recovered (55%), and a small amount of open loop epoxy propane byproducts **2ac** (16%) and **2ad** (12%) were observed in the NMR spectra.[11] When the reaction was conducted in the absence of H_2, no product was detected (entry 16).

In order to further increase the conversion and enantioselectivity, additives, especially bases which have been frequently used in Ru-catalyzed asymmetric hydrogenation and transfer hydrogenation of ketones, were applied to the reactions (Table 2). Addition of Cs_2CO_3 (10 mol %) resulted complete conversion to the desired product (dr = 90/10) with a reduced enantioselectivity of 88% (entry 1). Interestingly, when reducing the hydrogenation time to 8 and 3 h, the reaction proceeds well with an increase in ee (entries 2−3). Further reducing the reaction time to 1 h resulted in incomplete conversion but similar enantioselectivity (98%) and an even higher diastereoselectivity (81/6) (entry 4). The conversion and enantioselectivity were dramatically reduced in the absence of H_2 when the same reaction time of 1 h was used (entry 5). No product was detected when the Cs_2CO_3 additive was removed (entry 6). Based on the above-mentioned results, a combined hydrogenation/transfer hydrogenation mechanism can be proposed.[8c,d] The product *cis*-

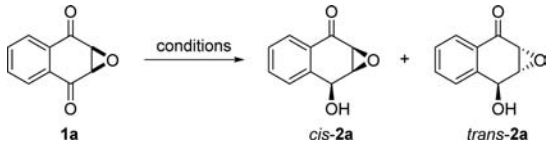
Table 1. Ligand and Solvent Screening[a]



entry	ligand	solvent	conv/% (*cis*/*trans*)[b]	ee/% (*cis*)[c]
1[d]	RuPHOX	*i*PrOH	0	–
2	RuPHOX	MeOH	0	–
3	BINAP	MeOH	0	–
4	TsDPEN	MeOH	52/5	92
5	TsDPEN	EtOH	63/5	96
6	TsDPEN	*i*PrOH	48/5	92
7	TsDPEN	acetone	32/3	91
8	TsDPEN	DCM	30/3	89
9	TsDPEN	THF	10/1	86
10	TsDPEN	EtOAc	9/1	87
11	TsDPEN	toluene	5/0	82
12[e]	TsDPEN	EtOH	46/0	99
13[f]	TsDPEN	EtOH	80/7	95
14[g]	TsDPEN	EtOH	88/8	95
15[h]	TsDPEN	EtOH	15/2	92
16[i]	TsDPEN	EtOH	0	–

[a]Conditions: **1a** (0.1 mmol), ligand-Ru (1 mol %), H_2 (5 atm), solvent (1.5 mL), rt (20−25 °C), 24 h, unless otherwise noted. [b]The conversions of *cis*-**2a** and *trans*-**2a** were calculated from ^{1}H NMR spectra. [c]The ee values of *cis*-**2a** were determined by HPLC using a chiral column. [d]*t*BuOK (10 mol %). [e]Cl is replaced by OTf in the catalyst. [f]H_2 (10 atm). [g]H_2 (20 atm). [h]50 °C. [i]In the absence of H_2.

Table 2. Base Screening[a]



entry	base	temp/°C	time/h	conv/% (*cis*/*trans*)[b]	ee/% (*cis*)[c]
1	Cs_2CO_3	rt	24	90/10	88
2	Cs_2CO_3	rt	8	91/9	97
3	Cs_2CO_3	rt	3	92/8	98
4	Cs_2CO_3	rt	1	81/6	98
5[d]	Cs_2CO_3	rt	1	48/4	95
6[d,e]	–	rt	1	0	–
7[d,f]	Cs_2CO_3	rt	1	21/3	97
8[d,g]	Cs_2CO_3	rt	1	0	–
9	K_2CO_3	rt	3	93/7	96
10	Na_2CO_3	rt	3	89/11	98
11	Li_2CO_3	rt	3	83/7	96
12	$KHCO_3$	rt	3	60/6	97
13	$NaHCO_3$	rt	3	92/8	98
14	K_2HPO_4	rt	3	91/9	98
15	K_3PO_4	rt	3	91/9	99
16	K_3PO_4	0	3	92/8	>99
17[h]	K_3PO_4	0	3	92/8	>99
18[i]	K_3PO_4	0	3	91/9	>99

[a]Conditions: **1a** (0.1 mmol), (*R*,*R*)-TsDPEN-Ru (1 mol %), H_2 (5 atm), base (10 mol %), EtOH (1.5 mL), rt (20−25 °C), unless otherwise noted. [b]The conversions of *cis*-**2a** and *trans*-**2a** were calculated from ^{1}H NMR spectra. [c]The ee values of *cis*-**2a** were determined by HPLC using chiral column. [d]In the absence of H_2. [e]In the absence of base. [f]*i*PrOH as solvent. [g]MeOH as solvent. [h]K_3PO_4 (5 mol %). [i]K_3PO_4 (1 mol %).

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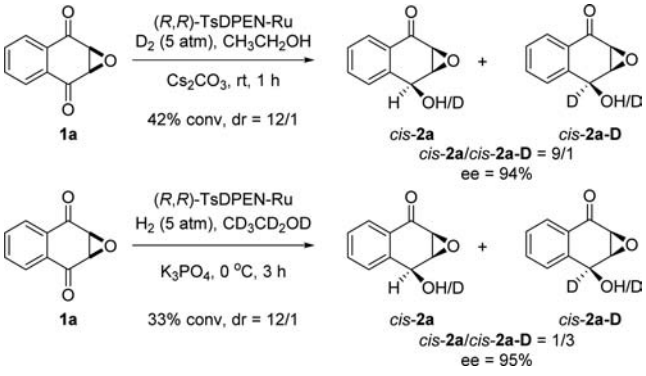
2a was obtained with low conversion (21%) and 97% ee using *i*-PrOH as the hydrogen resource and solvent in the absence of H_2, while no reaction occurred using MeOH (entries 7−8). Other weak bases were tested, with K_3PO_4 providing slightly better enantioselectivity (entries 9−15). Further reducing the temperature to 0 °C increased the enantioselectivity of the product to above 99% ee (entry 16). Changing the loading amount of K_3PO_4 made no obvious difference (entries 17−18).

To gain a better understanding of the reaction mechanism, deuterium labeling experiments using D_2 and ethanol-D_6 were performed (Scheme 2). When the reaction was conducted with

Scheme 2. Deuterium Labeling Experiments

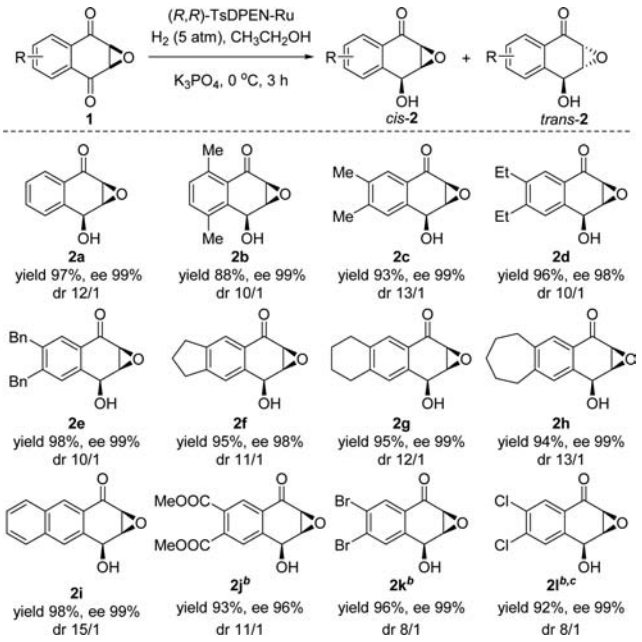


D_2 and normal ethanol, **1a** was converted to **2a** in 42% conversion and 12/1 dr. The main product *cis*-**2a** was obtained in 94% ee with a H/D ratio of 9/1. When the reductants were changed to H_2 and ethanol-D_6, the conversion was 33% with an identical dr of 12/1. Compound *cis*-**2a** was produced in 95% ee and with a H/D ratio of 1/3. Based on these results, it can be envisaged that this transformation proceeds via a combined asymmetric hydrogenation/transfer hydrogenation mode both catalyzed by TsDPEN−Ru and transfer hydrogenation plays a dominant role.

With the optimized reaction conditions in hand, the *meso*-epoxy naphthoquinone substrate scope was investigated (Scheme 3). The substrates **1b** and **1c** bearing the methyl groups substituted at different positions gave their corresponding products with an identical enantioselectivity of 99% ee and with 10/1 and 13/1 dr, respectively. The substrates **1d**−**1h** bearing electron-donating alkyl groups with acyclic or cyclic structures were all converted to their related products with excellent enantioselectivities (98−99%) and diastereoselectivities (10/1−13/1). Substrate **1i** with a naphthyl skeleton also gave its corresponding product with 99% ee and a better dr of 15/1. However, reductions of other substrates **1j**, **1k**, and **1l** bearing electron-withdrawing COOMe, Br, and Cl groups were less reactive. Complete conversions were obtained under a high temperature and/or high H_2 pressure. The methoxycarbonyl group substituted **1j** was converted to **2j** with the lowest enantioselectivity (96% ee) and with a dr of 11/1. The remaining two substrates **1k** and **1l** were converted to their respective products both with 99% ee and 8/1 dr.

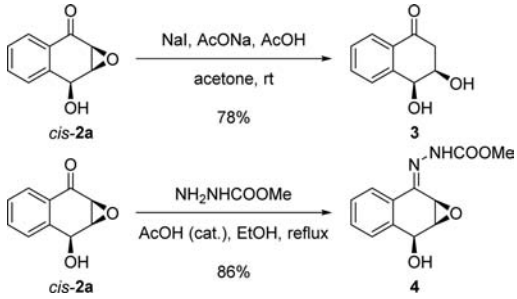
To demonstrate the practicality of this methodology, the epoxy and carbonyl groups were converted to other functionalities according to the reported conditions involving similar transformations (Scheme 4).[12,13] The epoxy ring of *cis*-**2a** underwent a reductive opening to give the hydroxyl-substituted ketone **3** in 78% yield. The carbonyl group was simply converted to hydrozone **4** in 86% yield.

Scheme 3. Substrate Scope[a]



[a]Conditions: **1** (0.10 mmol), (*R*,*R*)-TsDPEN-Ru (1 mol %), K_3PO_4 (5 mol %), H_2 (5 atm), EtOH (1.5 mL), 0 °C. The yields were for the mixture of *cis*/*trans*-isomers isolated by flash chromatography. The dr values were calculated from ^{1}H NMR spectra. The ee values were determined by HPLC using a chiral column. [b]Reacted at room temperature. [c]Reacted under 10 atm of H_2.

Scheme 4. Derivatizations on Epoxy and Carbonyl Groups



In conclusion, we have described the first Ru-catalyzed asymmetric reductive desymmetrization of *meso*-epoxy naphthoquinones for the synthesis of a series of chiral *cis*-epoxy naphthoquinols with three contiguous stereocenters. Excellent enantioselectivities (96−99% ee) and diastereoselectivities (8/1−15/1) were obtained, and a combined asymmetric hydrogenation/transfer hydrogenation mechanism was proposed based on experimental results. This methodology was further applied to the synthesis of several multifunctionalized compounds via simple derivatizations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01073.

Synthetic details for substrates, procedures for hydrogenation reactions, spectra of NMR and HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

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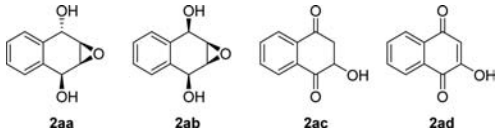

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