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One-Pot Catalysis Using a Chiral Iridium Complex/Brønsted Base: Catalytic Asymmetric Synthesis of Catalponol

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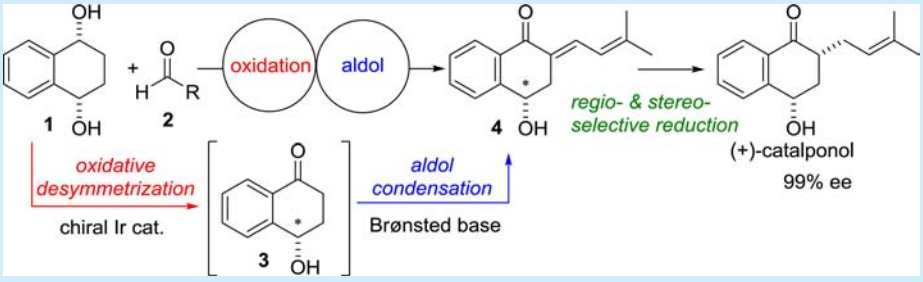
Supporting Information



ABSTRACT: Tandem asymmetric hydrogen transfer oxidation/aldol condensation under relay catalysis of a chiral iridium complex/achiral Brønsted base binary system is described for the synthesis of α-benzylidene-γ-hydroxytetralones with high ee's. A two-step synthesis of catalponol was achieved using this sequential methodology together with regio- and stereoselective hydroboration.

The development of enantioselective one-pot processes that enable many reactions to proceed in a single flask is now mainstream in modern organic synthesis.[1] A one-pot strategy avoids the time, labor, and yield losses incurred during the isolation and purification of synthetic intermediates in multistep sequences. Moreover, a multicatalysis system can drive an equilibrium reaction to completion. The hydrogen-transfer reaction is a powerful tool, yet there are only a few examples of its use in asymmetric multicatalysis systems.[2] One of the most representative examples is dynamic kinetic resolution using enzyme and metal catalysis,[3] in which enzymatic resolutions are combined with racemization by transition-metal catalysts. Other examples are one-pot processes based on a transition-metal-catalyzed reaction and chiral phosphoric acid catalyzed transfer hydrogenation with Hantsch esters.[4] Gong et al. reported a consecutive hydroamination/asymmetric transfer hydrogenation using relay catalysis of an achiral gold complex/chiral phosphoric acid binary system for the direct transformation of 2-(2-propynyl)aniline derivatives into tetrahydroquinolines with high enantiomeric purity.[4i] They also reported Friedländer condensation/asymmetric transfer hydrogenation using Mg(OTf)$_2$ and a chiral phosphoric acid for the synthesis of trisubstituted tetrahydroquinolines.[4d] Patil et al. reported a three-catalyst system using Au(I)/amine/chiral phosphoric acid catalysts for the synthesis of 2-substituted tetrahydroquinolines.[4b] Che et al. reported tandem intermolecular hydroamination/asymmetric transfer hydrogenation of alkynes using a gold(I) complex and chiral phosphoric acid for the synthesis of secondary amines, and obtained excellent ee's.[4g] Terada et al. reported carbonyl ylide formation/asymmetric transfer hydrogenation using $Rh_2(OAc)_4$ and a chiral phosphoric acid for the synthesis of isochromenecarboxylate derivatives.[4c] Regardless, there remains much room for improving synthetic variations.

We have reported the efficient oxidative desymmetrization of *meso*-diols by a chiral iridium complex used for the synthesis of natural products.[5] Recently, we applied this method to one-pot reactions, and our initial studies on dual catalysis were particularly effective for the synthesis of α-benzyl-β-hydroxyindanones.[6] Herein, we describe a dual catalyst system that produces highly enantioenriched α-benzylidene-γ-hydroxytetralones and its application to the catalytic asymmetric synthesis of (+)-catalponol.

Our target reaction comprises an oxidative desymmetrization and aldol condensation (Scheme 1). We envisioned that the first oxidative desymmetrization of *meso*-1,4-tetralinediol **1**[7] will proceed to give a chiral hydroxyl ketone **3** in the presence of chiral iridium complex. We previously described using this reaction with cyclohexanone as an oxidant;[5c] here, aromatic aldehyde **2** was used instead of cyclohexanone to prevent the competing cross aldol reaction of cyclohexanone and aldehyde **2** under basic conditions. The second step, base-catalyzed aldol condensation, utilized the ketone moiety produced by the first step.

Initially, **1** was reacted with *Cp[(*R*,*R*)-Tsdpen]Ir **5**[8] (10 mol %), KOH (0.5 molar equiv), and benzaldehyde **2a** (6 molar equiv) in THF at 30 °C for 22 h, providing the desired **4a** in 57% yield with 98% ee (entry 1). As shown in Table 1, the use of 1 molar equiv of base increased the chemical yield (entry 2). Inspired by this result, we screened several bases and found that

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Scheme 1. Asymmetric Tandem Oxidation/Aldol Condensation

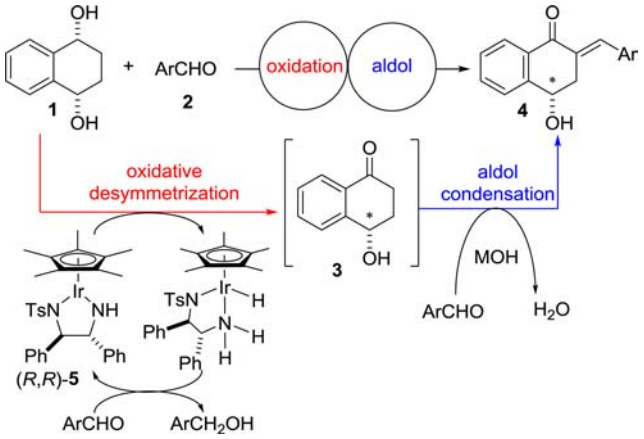
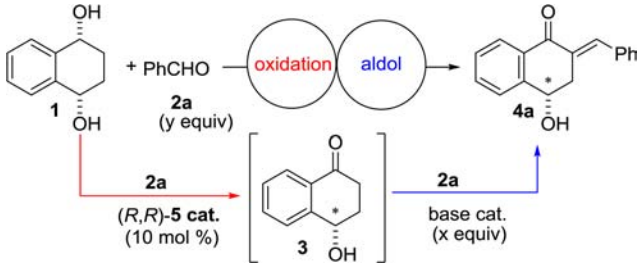


Table 1. Optimization of Reaction Conditions for Asymmetric Tandem Oxidation/Aldol Condensation[a]



entry	base	*x* (equiv)	*y* (equiv)	yield[b] (%)	ee[c] (%)
1	KOH	0.5	6	57	98
2	KOH	1.0	6	79	97
3	KOH	1.0	3	15	ND
4	NaOH	1.0	6	79	97
5	KO^{t}Bu	1.0	6	0	
6	CsOH·H_2O	1.0	6	82	96

[a]Unless noted otherwise, the reactions were carried out on a 0.0762 mmol scale of **1** with **2a**, 10 mol % of **5** in THF at 30 °C for 22 h. [b]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c]Determined by chiral HPLC analysis.

other metal hydroxides such as NaOH and CsOH·H_2O similarly promoted the cascade reaction with iridium catalyst **5** (entries 4 and 6), whereas KO^{t}Bu afforded a complex mixture under the same conditions (entry 5). It should be noted that the yield of **4a** is decreased to 15% with 3 equiv of aldehyde (entry 3) due to the formation of α-benzyl-γ-hydroxytetralone **6** in 62% yield (*cis*/*trans* = 2:1). This result indicates that an asymmetric borrowing hydrogen reaction proceeded when a lower concentration of benzaldehyde was used as an oxidant (Scheme 2). The diastereoselectivity of **6** might be thermodynamically controlled under this basic condition. Thus, an excess amount of aldehyde is required to obtain the enone **4** in high yield.

With the optimized reaction conditions for the relay catalysis in hand, we next investigated the scope of the reaction using CsOH·H_2O as a base catalyst (Table 2). The reaction of **1** with 1-naphthaldehydes **2b** similarly proceeded under the optimized conditions, giving enone **4b** in 82% yield with 98% ee (entry 2). Aromatic aldehydes **2c**−**e** bearing an electron-withdrawing group also gave the enones **4c**−**e** in good yield with high ee's (entries 3−5). Aldehydes **2f**,**g** containing an electron-donating

Scheme 2. Asymmetric Borrowing Hydrogen Reaction

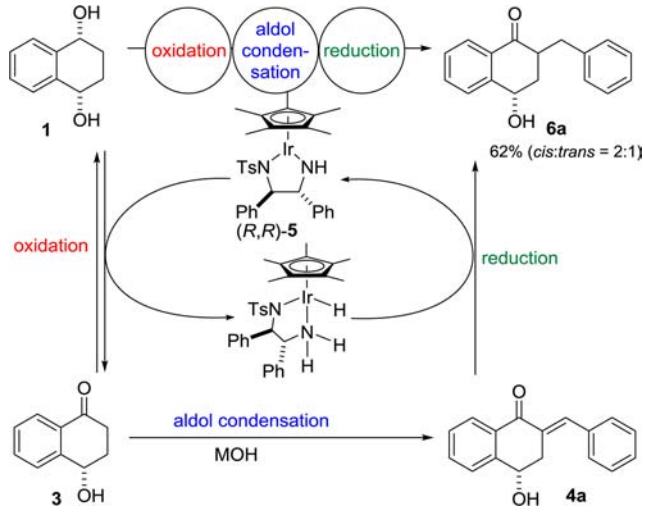
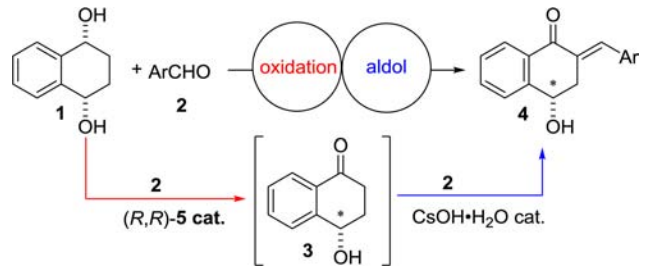


Table 2. Asymmetric Tandem Oxidation/Aldol Condensation of 1 with Aromatic Aldehydes[a]



entry	**2**	Ar	temp (°C)	yield[b] (%)	ee[c] (%)
1	**2a**	Ph	30	82	96
2	**2b**	1-naphthyl	30	82	98
3	**2c**	4-FC_6H_4	20	92	98
4	**2d**	4-ClC_6H_4	30	62	92
5	**2e**	4-BrC_6H_4	30	82	96
6	**2f**	4-MeC_6H_4	20	69	>99
7	**2g**	3,5-$Me_2C_6H_3$	20	79	>99

[a]Unless noted otherwise, the reactions were carried out on a 0.0762 mmol scale of **1** with **2**, 10 mol % of **5**, and 1 equiv of CsOH·H_2O in THF for 22 h. [b]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c]Determined by chiral HPLC analysis.

group also afforded the desired products with excellent ee's (entries 6 and 7). The structure and stereochemistry of **4d** were unambiguously determined by single-crystal X-ray crystallographic analysis, as depicted in Figure 1. The absolute configuration of **4a** was determined by comparison with an authentic sample obtained by aldol condensation of (*S*)-**3** (Scheme 3).

Next, we applied our method to the synthesis of catalponol.[9] Catalponol was first isolated in 1971 by Inoue et al. from *Catalpa ovata* (Japanese name "Kisasage") wood.[9a] Catalponol has attracted much attention as it exhibits prominent biological properties, such as antitermitic activity, reported by McDaniel,[9c] and the enhancement of dopamine biosynthesis and protection against L-DOPA-induced cytotoxicity in PC12 cells, reported by Lee.[9d] Kündig's group accomplished the first enantioselective total synthesis of catalponol using Cr(arene) $(CO)_3$ chemistry (Figure 2).[9e]

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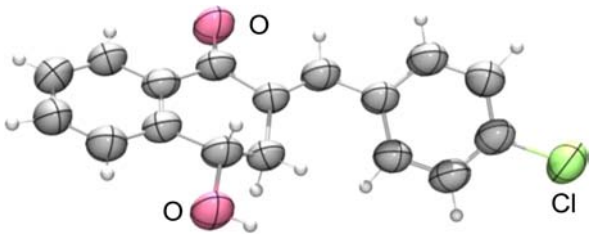
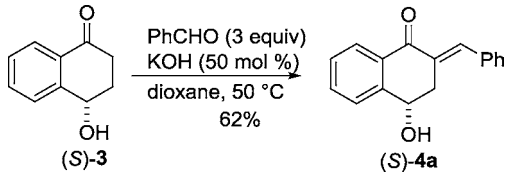


Figure 1. POV-ray drawing of (±)-**4d** with probability ellipsoids drawn at the 50% level.

Scheme 3. Determination of the Absolute Configuration of 4a



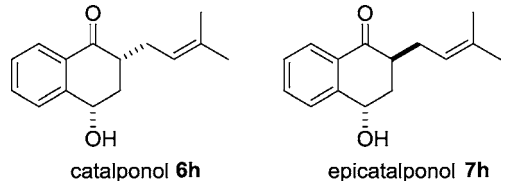
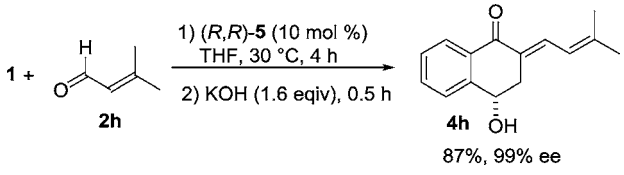


Figure 2. Structures of catalponol and epicatalponol.

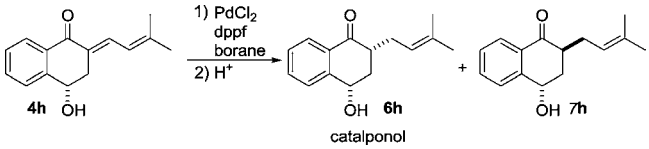
As depicted in Scheme 4, we anticipated the synthesis of key intermediate **4h** by oxidative desymmetrization/aldol condensation. Treatment of **1** with 3-methyl-2-butenal **2h** in the presence of (*R*,*R*)-**5** for 3 h, followed by KOH addition, resulted in the desired dienone **4h** in 87% yield with 99% ee. In contrast, application of the aforementioned relay catalysis method gave a lower chemical yield of 55%, probably due to competing homoaldol condensation of enolizable aldehyde **2h**.

Scheme 4. Sequential Asymmetric Reaction of 1 and 2h



With **4h** in hand, the final goal of our effort was to attain the regio- and stereoselective reduction of the dienone.[10] We tried several methods for the achiral conjugated reduction of unsaturated carbonyl compounds. Although Stryker's reagent,[10b] $NaBH_4$ using $InCl_3$ catalyst,[10f] transfer hydrogenation[10e,i] using an Ir catalyst, and hydrosilylation using Cu[10d,g] or Rh[10h] catalysts gave unsatisfactory results, we were pleased to find that catalponol was obtained by the Pd-catalyzed hydroboration developed by Hoshino et al.[10c] The results are shown in Table 3. The reaction using catecholborane gave the catalponol in 78% yield and epicatalponol in 8% yield (entry 1). Although pinacolborane also promoted the reaction, the yield was low (entry 2). Interestingly, 9-BBN, the best borane in the original procedure,[10c] gave complex mixtures (entry 3). The observed stereoselectivity can be explained if the boron enolate is

Table 3. Regio- and Stereoselective Hydroboration of 4h[a]



entry	borane	yield[b] (%) 6h	7h	ratio 6h:7h
1	catecholborane	78	8	8:1
2	pinacolborane	55	16	2.4:1
3	9-BBN	0	0	

[a]Unless noted otherwise, the reactions were carried out on a 0.0636 mmol scale of **4h** with 2.2 molar equiv of borane and 10 mol % of $PdCl_2$(dppf) in THF at 0−30 °C. [b]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

protonated from the opposite site of the other borate moiety, as shown in Figure 3.[11]

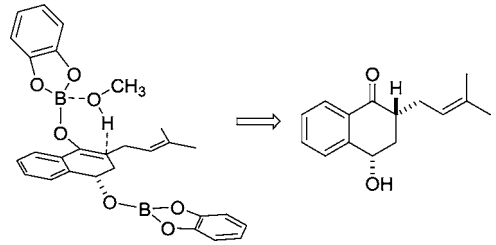


Figure 3. Transition-state model.

In conclusion, we have demonstrated a one-pot synthesis of α-benzylidene γ-hydroxytetralones from *meso*-diols using a tandem oxidation/aldol condensation reaction. This reaction can be extended to the catalytic asymmetric synthesis of a natural product. (+)-Catalponol was prepared in 68% overall yield over two steps from the *meso*-diol **1**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02480.

Crystallographic data for (±)-**4d** (CIF)
Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra and HPLC charts (PDF)

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Notes

The authors declare no competing financial interest.

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