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Asymmetric Hydrogenation of Racemic 6-Aryl 1,4-Dioxaspiro[4.5]decan-7-ones to Functionalized Chiral β-Aryl Cyclohexanols via a Dynamic Kinetic Resolution

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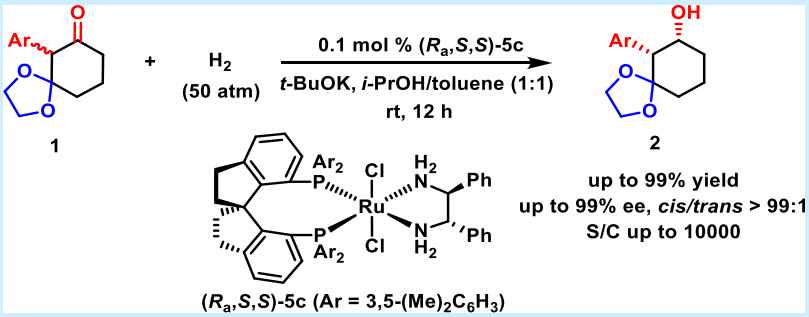

ABSTRACT: A ruthenium-catalyzed asymmetric hydrogenation method for the synthesis of functionalized β-aryl cyclohexanols is described. With chiral spiro ruthenium catalyst (R_a,*S*,*S*)-**5c**, a series of racemic α-aryl cyclohexanones bearing a β-monoethylene ketal group were hydrogenated to the corresponding functionalized β-aryl cyclohexanols in high yields with enantioselectivity of up to 99% ee via a dynamic kinetic resolution. This protocol can be conducted on a decagram scale and provide potential approaches for the synthesis of optically active and densely functionalized aryl cyclohexanols.

Chiral β-aryl-substituted cycloalkanols are ubiquitous and valuable structural motifs in numerous natural products, bioactive molecules, and pharmaceuticals.[1] Many synthetic methods for the synthesis of optically active chiral β-aryl-substituted cycloalkanols have been reported so far.[2] One of the most direct and facile methods is the asymmetric hydrogenation of racemic α-aryl cycloalkanones via a dynamic kinetic resolution (DKR) due to their operational simplicity, high atom economy, and environmental benefit.[3] Despite the great progress that has been made in the past few decades, a catalytic asymmetric hydrogenation of racemic α-aryl cycloalkanones to optically active chiral β-aryl substituted cycloalkanols via DKR is still difficult to fulfill the requirements of synthetic applications.[4]

The frequent natural occurrence of highly oxygenated carbocycles containing β-aryl cyclohexanol motifs, coupled with their wide range of interesting biological activities, have made these compounds of considerable interest to pharmacologists and synthetic chemists.[1] Typical examples include amaryllidaceae alkaloids, most notably (+)-pancratistatin,[5] (+)-7-deoxypancratistatin,[6] and (+)-lycorine[7] (Figure 1). These compounds exhibited significant bioactivities, in particular, cytotoxicity against tumor cell lines.[8] Considerable efforts have been devoted to their syntheses, but enantioselective synthesis by employing asymmetric catalysis is still scarce due to the lack of efficient and reliable asymmetric catalytic methods to install the chiral β-aryl cyclohexanol motifs.[9]

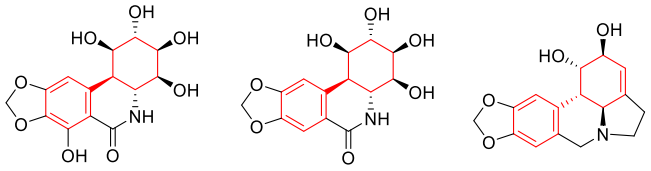

Figure 1. Examples of highly oxygenated natural products containing chiral β-aryl cyclohexanol motifs.

To address the challenges of an asymmetric synthesis of chiral β-aryl cyclohexanols containing contiguous stereocenters, we developed a ruthenium-catalyzed asymmetric hydrogenation of racemic α-aryl cyclohexanones modified with a monoethylene ketal group via DKR and successfully applied them for the enantioselective synthesis of the potent

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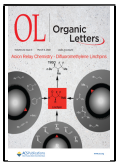

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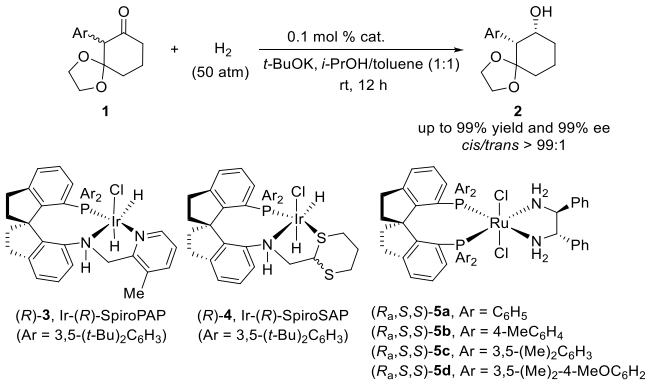
nonselective cannabinoid receptor (−)-CP-55940[10] and natural products (−)-Δ^9-THC[11] and (−)-α-lycorane.[12] Inspired by the structures of pancratistatin and analogues, we envisioned the asymmetric hydrogenation of racemic α-aryl cyclohexanones **1** with a β-monoethylene ketal group via DKR for the enantioselective synthesis of functionalized chiral β-aryl cyclohexanols **2**, in view of the fact that compound **2** could serve as potential intermediates to densely substituted and oxygenated carbocycles including amaryllidaceae alkaloids containing aryl cyclohexane motifs with contiguous stereocenters (Scheme 1). In this paper, we report our results of an

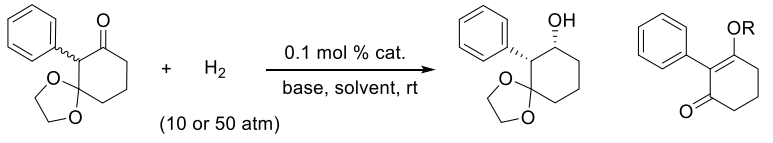
Scheme 1. Asymmetric Hydrogenation of Racemic α-Aryl Cyclohexanones to Chiral β-Aryl Cyclohexanols via DKR



asymmetric hydrogenation of racemic α-aryl cyclohexanones **1** via DKR for the enantioselective synthesis of new type of monoethylene ketal-functionalized chiral β-aryl cyclohexanols.

The study commenced with the evaluation of the chiral catalysts in the hydrogenation of the racemic 6-phenyl-1,4-dioxaspiro[4.5]decan-7-one (**1a**). We initially evaluated the chiral spiro iridium catalyst Ir-(*R*)-SpiroPAP ((*R*)-**3**), an extremely efficient chiral catalyst for an asymmetric hydrogenation of simple ketones.[13] Under the general conditions (2 mol % *t*-BuOK, EtOH, 10 atm H_2), we found it gave **2a** in 47% yield and 43% ee along with a 52% yield of byproduct **6a** (R = Et) (Table 1, entry 1). Under the same conditions, no desired product **2a** was observed for the chiral spiro iridium catalyst Ir-(*R*)-SpiroSAP ((*R*)-**4**)[14] (entry 2). Thus, we further evaluated the chiral spiro diphosphine-ruthenium-diamine catalyst (R_a,*S*,*S*)-**5c**[15] under the general conditions (5 mol % *t*-BuOK, *i*-PrOH, 50 atm H_2) for such chiral spiro ruthenium catalysts[3c] and found it provided **2a** in 89% yield and 96% ee along with a small amount of **6a** (R = *i*-Pr, 9% yield) (entry 3). With EtOH and *n*-PrOH instead of *i*-PrOH as solvents, catalyst (R_a,*S*,*S*)-**5c** also provided high enantioselectivity (88% ee and 90% ee, respectively) but with a significant amount of byproduct **6a** (entries 4 and 5). The formation of byproduct **6a** is due to the cyclohexanone **1a** with an β-ethylene ketal group being very sensitive to bases.[16] The poor solubility of **1a** in alcoholic solvents such as EtOH, *n*-PrOH, and *i*-PrOH slows the reaction rate of hydrogenation. At the same time the base-sensitive ketone **1a** was converted to byproduct **6a**. Although a higher reaction rate was observed for (R_a,*S*,*S*)-**5c** in *i*-PrOH, byproduct **6a** was still isolated in a 9% yield. Accordingly, to increase the solubility of **1a**, the hydrogenation of **1a** with (R_a,*S*,*S*)-**5c** was further performed in a mixture of the solvents *i*-PrOH and toluene (entries 6 and 7). The results showed that the yield of **2a** was increased significantly (up to 98%), together with a slight improvement in enantioselectivity (up to 98% ee). We then tested other chiral spiro diphosphine-ruthenium-diamine catalysts and found that the catalysts (R_a,*S*,*S*)-**5a**, (R_a,*S*,*S*)-**5b**, and (R_a,*S*,*S*)-**5d** provided comparable yields and enantioselectivities for the hydrogenation of **1a** in a

Table 1. Asymmetric Hydrogenation of 1a. Optimizing the Reaction Conditions[a]



entry	cat	base (mol %)	solvent	conv[c] (%)	yield[b] (%) 2a	yield[b] (%) 6a	ee[d] (%)
1	(*R*)-**3**	*t*-BuOK (2)	EtOH	100	47	52	43
2	(*R*)-**4**	*t*-BuOK (2)	EtOH	100		96	
3	(R_a,*S*,*S*)-**5c**	*t*-BuOK (5)	*i*-PrOH	100	89	9	96
4	(R_a,*S*,*S*)-**5c**	*t*-BuOK (5)	EtOH	100	64	33	88
5	(R_a,*S*,*S*)-**5c**	*t*-BuOK (5)	*n*-PrOH	100	68	26	90
6	(R_a,*S*,*S*)-**5c**	*t*-BuOK (5)	*i*-PrOH/toluene (1:1)	100	98		98
7	(R_a,*S*,*S*)-**5c**	*t*-BuOK (5)	*i*-PrOH/toluene (2:1)	100	96		97
8	(R_a,*S*,*S*)-**5a**	*t*-BuOK (5)	*i*-PrOH/toluene (1:1)	100	98		95
9	(R_a,*S*,*S*)-**5b**	*t*-BuOK (5)	*i*-PrOH/toluene (1:1)	100	99		93
10	(R_a,*S*,*S*)-**5d**	*t*-BuOK (5)	*i*-PrOH/toluene (1:1)	100	98		93
11	(R_a,*S*,*S*)-**5c**	*t*-BuOLi (5)	*i*-PrOH/toluene (1:1)	55	36	15	92
12	(R_a,*S*,*S*)-**5c**	*t*-BuONa (5)	*i*-PrOH/toluene (1:1)	60	46	12	96
13	(R_a,*S*,*S*)-**5c**	*t*-BuOK (2)	*i*-PrOH/toluene (1:1)	100	99		98
14[e]	(R_a,*S*,*S*)-**5c**	*t*-BuOK (2)	*i*-PrOH/toluene (1:1)	100	94	4	94

[a]Reaction conditions: 1.0 mmol of **1a**, 0.1 mol % of catalyst, solvent (4 mL), 10 atm H_2 (for catalysts (*R*)-**3** and **4**) or 50 atm H_2 (for catalysts (R_a,*S*,*S*)-**5**), room temperature (25−30 °C), 12 h. The *cis*/*trans* selectivity of the product **2a** for all reactions was greater than 99:1 as determined by ^{1}H NMR spectroscopy. [b]Isolated yield. [c]Determined by ^{1}H NMR spectroscopy. [d]The ee value of product **2a** was determined by high-performance liquid chromatography using a chiral column. [e]0.01 mol % (R_a,*S*,*S*)-**5c**, 80 atm H_2 (initial), 40 h.

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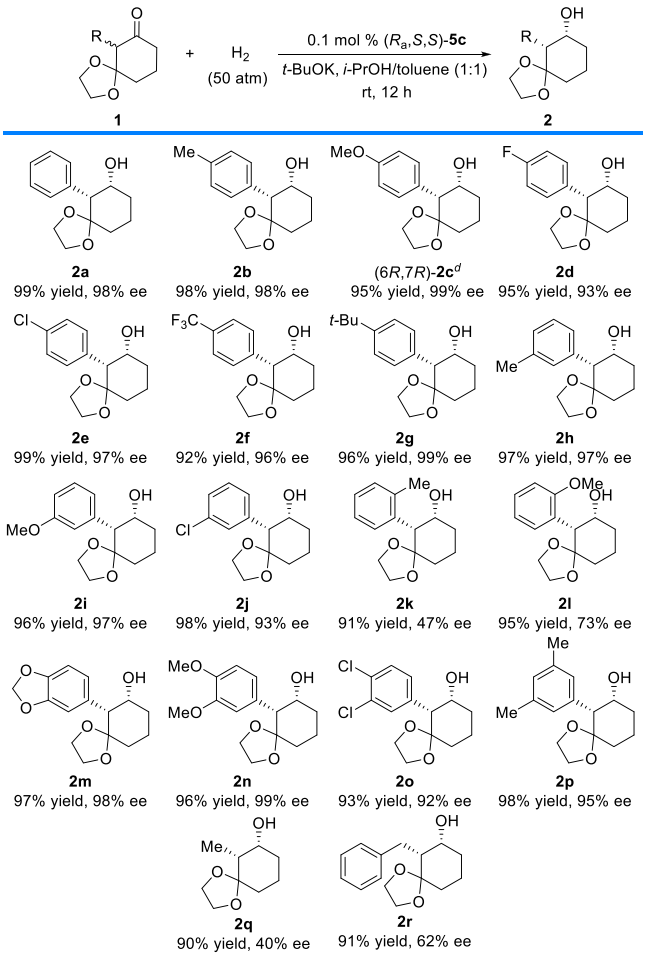
mixed solvent of *i*-PrOH and toluene (v/v = 1:1) (entries 8–10). Other bases, such as *t*-BuOLi and *t*-BuONa, could not promote the full conversion of **1a** because of their poor solubility in a mixed solvent (entries 11 and 12). The reduction of the amount of base from 0.05 to 0.02 equiv gave a slight increase in yield (entry 13). It is worth noting that, when the catalyst loading was reduced to 0.01 mol % (S/C = 10 000), the hydrogenation can still be performed smoothly, providing **2a** in 94% yield and 94% ee (entry 14).

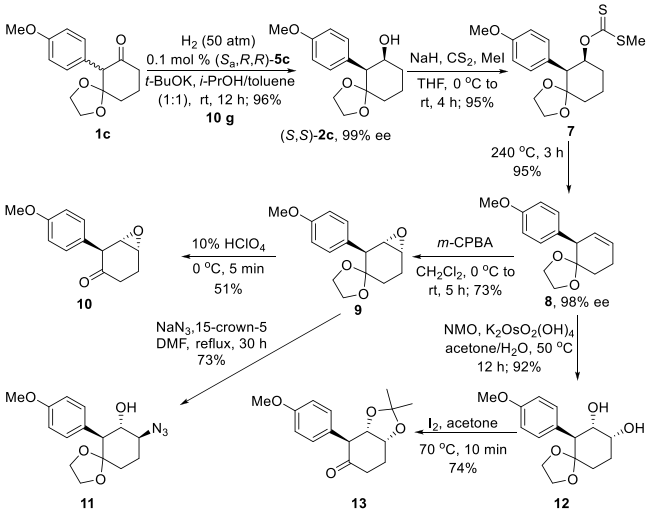
With the optimal reaction conditions in hand, we examined the substrate scope of this hydrogenation by using catalyst (R_a,*S*,*S*)-**5c**. As shown in Scheme 2, the electronic property and position of the substituents on the phenyl ring of the substrates have an obvious effect on the enantioselectivity. Generally, the substrates with electron-donating substituents (**1c**, 4-MeO, 99% ee) gave a higher enantioselectivity than the substrates with electron-withdrawing substituents (**1d**, 4-F, 93% ee); the substrates with *para*/*meta*-substituents (**1b**, 4-Me, 98% ee; **1h**, 3-Me, 97% ee) on the phenyl ring gave a significantly higher enantioselectivity than the substrates with *ortho*-substituents (**1k**, 2-Me, 47% ee; **1l**, 2-OMe, 73% ee). When the aryl group was replaced by an alkyl group such as methyl (**1q**) and benzyl (**1r**) high yields with low to moderate enantioselectivities were observed. However, the hydrogenation of the five-membered ring substrates such as 6-methyl substituted 1,4-dioxaspiro[4.4]nonan-7-one gave no desired product due to its highly base-sensitive property.[17] In addition, the hydrogenation can be easily upscaled as demonstrated in the decagram synthesis of **2c** with erosions neither in the yield nor ee (Scheme 3). Finally, the absolute configurations of the hydrogenation products were determined as (*R*,*R*) through the single-crystal X-ray diffraction analysis of product **2c** (see the Supporting Information).

Scheme 2. Asymmetric Hydrogenation of Racemic α-Aryl Cyclohexanones 1[a,b,c]



[a]Reaction conditions: 1.0 mmol of **1**, 0.1 mol % (R_a,*S*,*S*)-**5c**, 2 mol % *t*-BuOK, *i*-PrOH/toluene (2/2 mL), 50 atm H_2, at room temperature (25–30 °C) for 12 h. The *cis*/*trans* selectivity of the product **2** for all reactions was greater than 99:1 as determined by ^{1}H NMR spectroscopy. [b]Isolated yield. [c]The ee value was determined by high-performance liquid chromatography using a chiral column. [d]The configuration of product **2c** was determined as the (*R*,*R*)-configuration by single-crystal X-ray diffraction analysis.

Scheme 3. Decagram-Scale Synthesis and Functional Group Interconversions of 2c



For instance, to further demonstrate the utility and versatility of our method to diverse oxygenated chiral β-aryl cyclohexanes, cyclohexanol (*S*,*S*)-**2c** was then transformed into a xanthate ester **7**, with which a concurrent Chugaev *syn*-elimination[18] could regioselectively afford a cyclohexene product **8** with no obvious erosion of enantiopurity (Scheme 3). Oxidation of cyclohexene **8** with *m*-chloroperbenzoic acid (*m*-CPBA) diastereroselectively yielded epoxide **9** in 73% yield. Subsequently, deketalization of **9** with 10% $HClO_4$ provided epoxide ketone **10** in 51% yield. Alternatively, opening the epoxide ring of **9** with sodium azide afforded azide alcohol **11** with 73% yield. In addition, the direct dihydroxylation of cyclohexene **8** with NMO/$K_2OsO_2(OH)_4$[19] yielded the corresponding *cis*-1,2-cyclohexanediol **12** as a single isomer with 92% yield. Impressively, a one-pot deketalization and diol protection of **12** uniquely in the condition of iodine and acetone cleanly provided the dihydroxy-protected ketone **13** in 74% yield.[20] The synthesized chiral compounds, in particular, **10** and **13** can serve as useful building blocks for the synthesis of amaryllidaceae constituents and unnatural derivatives[9b] such as the analogues of deoxypancratistatin.[21]

In conclusion, we have developed an efficient method for the synthesis of chiral β-aryl cyclohexanols by a ruthenium-catalyzed asymmetric hydrogenation of the corresponding racemic α-aryl cyclohexanones bearing a β-monoethylene ketal

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group via DKR. A series of functionalized β-aryl cyclohexanols bearing two contiguous stereocenters were obtained often with high yields and excellent enantioselectivities. This protocol could be performed at low catalyst loading (S/C = 10 000) and on a decagram scale without significant erosions in yield and enantioselectivity. The obtained β-aryl cyclohexanols could be readily converted into a wide variety of oxygenated arylcyclohexanes. Given the extensive availability of functionalized β-aryl cyclohexanols, we believe that this protocol will find widespread use as building blocks for the enantioselective synthesis of densely substituted and oxygenated aryl cyclohexanes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00044.

Synthesis and characterization of detailed experimental procedures (PDF)

Accession Codes

CCDC 2042516 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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