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Enantioselective Synthesis of Chiral β-Aryloxy Alcohols by Ruthenium-Catalyzed Ketone Hydrogenation *via* Dynamic Kinetic Resolution (DKR)

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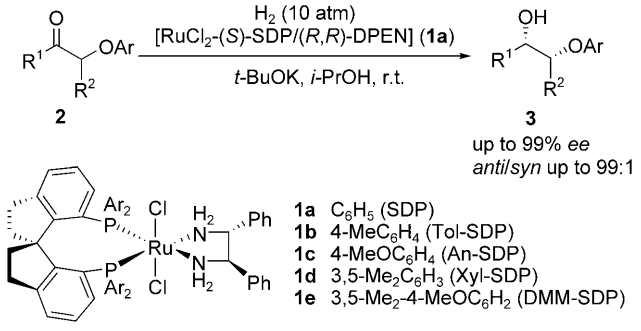
Abstract: A highly efficient enantioselective synthesis of chiral β-aryloxy alcohols by the {$RuCl_2$[(*S*)-SDP][(*R*,*R*)-DPEN]} [(S_a,*R*,*R*)-**1a**; SDP = 7,7′-bis-(diarylphosphino)-1,1′-spirobiindane; DPEN = *trans*-1,2-diphenylethylenediamine] complex-catalyzed asymmetric hydrogenation of *racemic* α-aryloxydialkyl ketones *via* dynamic kinetic resolution (DKR) has been developed. Enantioselectivities of up to 99% *ee* with good to high *cis*/*anti*-selectivities (up to > 99:1) were achieved.

Keywords: β-aryloxy alcohols; asymmetric hydrogenation; dynamic kinetic resolution; ketones; ruthenium

Optically active β-aryloxy alcohols are popular units occurring in the structures of various pharmaceutics and natural products.[1] The importance of these chiral building blocks continues to stimulate the development of new effective methods for the synthesis of this type of chiral alcohols in enantiomerically pure form.[2] The transition metal-catalyzed asymmetric hydrogenation of α-aryloxy ketones has provided an efficient approach to the synthesis of chiral β-aryloxy alcohols. For example, Rh- or Ru-catalyzed asymmetric hydrogenation of 3-(aryloxy)-2-oxo-1-propylamines (up to 97% *ee*)[3] and 1-phenoxypropan-2-one (80% *ee*)[4] produced the corresponding β-aryloxy alcohols in good to high enantioselecivities. However, only one stereogenic center was generated in these asymmetric hydrogenation reactions. By using $RuCl_2$-BINAP/diamine [BINAP = 2,2′-bis(diphenylphosphosphino)-1,1′-binaphthyl] catalysts Matsumoto[5] and Ohkuma[6] prepared β-methoxy alcohols with two stereogenic centers from the asymmetric hydrogenation of *racemic* 2-methoxylcyclohexanone (99% *ee*, 99% *de*) and 2-methoxyl-1,2-diphenylethanone (98% *ee*, 93% *de*) with high enantio- and diastereoselectivities. However, to the best of our knowledge, the synthesis of chiral β-aryloxy alcohols with two vicinal stereogenic centers by asymmetric hydrogenation of *racemic* α-aryloxy ketones has not been documented.

Recently, we developed a highly efficient method for the synthesis of chiral β-aryloxy primary alcohols by the $RuCl_2$-SDPs/diamine-catalyzed asymmetric hydrogenation of α-aryloxy aldehydes *via* dynamic kinetic resolution (DKR).[7] This success promoted us to explore efficient methods for the synthesis of chiral β-aryloxy secondary alcohols with two adjacent chiral centers. Herein we report the first example of the asymmetric hydrogenation of *racemic* α-aryloxydialkyl ketones with high enantioselectivities (up to 99.1% *ee*) and diastereoselectivities (*cis*/*trans* or *anti*/*syn* > 99:1) *via* DKR (Scheme 1).

Racemic α-aryloxydialkyl ketones **2** can be easily prepared by substitution of α-chloro cyclic ketones or α-bromo acyclic ketones with phenols.[8] For example, 2-chlorocyclohexanone reacted with phenol in gently



Scheme 1. {$RuCl_2$-[(*S*)-SDPs][(*R*,*R*)-DPEN]}-catalyzed hydrogenation of racemic α-aryloxydialkyl ketones *via* DKR.

refluxing acetone containing anhydrous K_2CO_3 for 30 h to provide 2-phenoxycyclohexanone (**2a**) in 75% yield. By using this procedure, a variety of *racemic* α-aryloxy cyclic and acyclic dialkyl ketones were prepared with moderate yields (see Supporting Information).

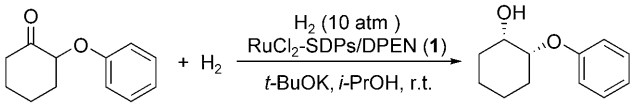
Primary experiments on the asymmetric hydrogenation of α-phenoxycyclohexanone (**2a**) were performed with the catalyst {$RuCl_2$[(*S*)-SDP][(*R*,*R*)-DPEN]} [(S_a,*R*,*R*)-**1a**] [SDP = 7,7′-bis(diarylphosphino)-1,1′-spirobiindane; DPEN = *trans*-1,2-diphenylethylenediamine] under the conditions of *S*/*C* = 1000 at 10 atm H_2 pressure. The hydrogenation product (1*S*,2*R*)-**3a** was obtained in excellent enantioselectivity and *cis*-selectivity (99% *ee*, *cis*/*trans* 99:1) (Table 1, entry 1). Systematic ligand screening showed that most of (*S*)-SDPs ligands, combined with (*R*,*R*)-DPEN were competent to hydrogenate α-phenoxycyclohexanone with high enantioselectivities and *cis*-selectivities, with the ligands (*S*)-SDP (**1a**) and (*S*)-Tol-SDP (**1b**) being the most efficient (entries 1–5). The complex {$RuCl_2$[(*S*)-SDP][(*S*,*S*)-DPEN]} [(S_a,*S*,*S*)-**1a**] was found to be a mismatched catalyst, which gave the product (1*S*,2*R*)-**3a** with only a moderate enantioselectivity (78% *ee*) (entry 6). Both catalysts (S_a,*R*,*R*)-**1a** and (S_a,*S*,*S*)-**1a** gave the product (1*S*,2*R*)-**3a** with the same configuration, indicating that the configuration of the hydrogenation product was mainly determined by SDPs ligands, instead of DPEN in $RuCl_2$-SDPs/diamine catalysts. The BINAP-based ruthenium catalyst {$RuCl_2$[(*R*)-BINAP][(*R*,*R*)-DPEN]} (R_a,*R*,*R*)-**4** was also evaluated under the same reaction conditions, and the hydrogenation product **3a** was obtained with slightly lower enantioselectivity (95% *ee*) (entry 7).

The reactivity of catalyst (S_a,*R*,*R*)-**1a** was remarkable. It can hydrogenate *racemic* α-aryloxydialkyl ketone **2a** at 5 atm hydrogen pressure (entry 8). When the catalyst loading was reduced from 0.1 mol% (*S*/*C* = 1000) to 0.01 mol% (*S*/*C* = 10,000) the selectivities of the reaction were maintained (entry 9). The hydrogenation reaction can even be carried out with 0.001 mol% (*S*/*C* = 100,000) catalyst, albeit the enantioselectivity (91% *ee*) and the *cis*/*trans* selectivity (*cis*/*trans* 85:15) were diminished and the reaction became slow (entry 10). These results demonstrate that the {$RuCl_2$[(*S*)-SDP][(*R*,*R*)-DPEN]} [(S_a,*R*,*R*)-**1a**] is a highly efficient catalyst for the asymmetric hydrogenation of *racemic* α-aryloxycyclohexanones *via* DKR.

Under the optimized reaction conditions, a series of *racemic* α-aryloxy cyclic ketones were hydrogenated to the corresponding β-aryloxy alcohols with excellent enantioselectivities and high *cis*/*trans* selectivities. As showed in Table 2, the substituents on the phenyl ring of the α-aryloxycyclohexanones **2a–h** have little effect on the enantioselectivity and *cis*/*trans* selectivity of the reaction (Table 2, entries 1–8). A pyridin-2-yl group in α-(pyridin-2-yloxy)cyclohexanone (**2i**) could be tolerated by this catalytic system and the hydrogenated product **3i** was obtained in 91% *ee* for enantioselectivity and 97:3 for *cis*/*trans* selectivity (entry 9). The ring size of the cyclic ketones imposed a significant effect on the enantioselectivity of the reaction. When the size of the cyclic ketone substrate was changed from a six-membered to five-membered ring, the *ee* value of the hydrogenation product was decreased dramatically from 99% to 78% (entry 10 *vs.* entry 1). Enlarging the size from a six-membered to seven-membered ring in the substrate also led to a drop in both enantioselectivity and *cis*/*trans* selectivity (entry 11 *vs.* entry 1).

Conformationally flexible substrates such as *racemic* α-aryloxy acyclic dialkyl ketones **2l–p** have also been examined under similar reaction conditions. The hydrogenation products **3l–o** were obtained with high *ee* values (94–96% *ee*) and high *anti*-selectivities (entries 12–15). However, the acyclic dialkyl ketone substrates with R^1 = ethyl instead of methyl gave a lower enantioselectivity. For example, the hydrogenation of ethyl ketones such as 2-phenoxypentan-3-one (**2p**) and 1-phenoxy-1-phenylbutan-2-one (**2q**) yielded the corresponding β-aryloxy alcohols **3p** and **3q** with only 80% *ee* and 84% *ee*, respectively (entries 16 and 17).

Table 1. Optimizing the asymmetric hydrogenation conditions.[a]



2a **3a**

Entry	Catalyst	Time [h]	*cis*/*trans*[b]	*ee* [%][c]
1	(S_a,*R*,*R*)-**1a**	1	>99/1	99
2	(S_a,*R*,*R*)-**1b**	1	>99/1	99
3	(S_a,*R*,*R*)-**1c**	1	>99/1	98
4	(S_a,*R*,*R*)-**1d**	1	97:3	95
5	(S_a,*R*,*R*)-**1e**	1	98:2	98
6	(S_a,*S*,*S*)-**1d**	2	99:1	78
7	(R_a,*R*,*R*)-**4**	1	98:2	95
8[d]	(S_a,*R*,*R*)-**1a**	2	99/1	98
9[e]	(S_a,*R*,*R*)-**1a**	3	>99/1	99
10[f]	(S_a,*R*,*R*)-**1a**	88	85:15	91

[a] The reactions were performed at 0.2 M of **2a**, under 10 atm of H_2, at room temperature (25–30 °C) in *i*-POH containing (S_a,*R*,*R*)-**1a** (*S*/*C* = 1000) and *t*-BuOK ([*t*-BuOK] = 0.04 M) unless otherwise stated. The conversion is 100%.

[b] Determined by GC, HPLC or SFC.

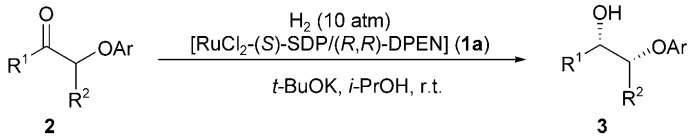
[c] *ee* value for *cis*-isomer, which was determined by HPLC or SFC, the configuration of the product is (1*S*,2*R*).

[d] 5 atm.

[e] *S*/*C* = 10,000, under 25 atm H_2.

[f] *S*/*C* = 100,000, under 60 atm of H_2, at 35 °C.

Table 2. Asymmetric hydrogenation of *racemic* α-aryloxydialkyl ketones catalyzed by (S_a,*R*,*R*)-**1a**.[a]



Entry	Ar	R^1	R^2	3	Time [h]	Selectivity[b]	*ee* [%][c]
1	C_6H_5	$(CH_2)_4$		**3a**	1	>99:1	99
2	4-MeC_6H_4	$(CH_2)_4$		**3b**	1	>99:1	99
3	4-MeOC_6H_4	$(CH_2)_4$		**3c**	2.5	>99:1	99
4	4-ClC_6H_4	$(CH_2)_4$		**3d**	2	>99:1	98
5[d]	4-BrC_6H_4	$(CH_2)_4$		**3e**	6	>99:1	99
6	3-MeC_6H_4	$(CH_2)_4$		**3f**	2	>99:1	99
7	2-MeC_6H_4	$(CH_2)_4$		**3g**	2	>99:1	98
8	2-Np	$(CH_2)_4$		**3h**	7	>99:1	99.1
9	2-Py	$(CH_2)_4$		**3i**	2	93:7	91
10	C_6H_5	$(CH_2)_3$		**3j**	1	99:1	78
11	C_6H_5	$(CH_2)_5$		**3k**	3	96:4	93
12	C_6H_5	Me	Me	**3l**	2	89:11	96
13	C_6H_5	Me	Ph	**3m**	12	98:2	94
14[d]	4-MeOC_6H_4	Me	Ph	**3n**	11	98:2	95
15	4-BrC_6H_4	Me	Ph	**3o**	6	96:4	95
16	C_6H_5	Et	Me	**3p**	7	87:13	80
17	C_6H_5	Et	Ph	**3q**	8	97:3	84

[a] The reaction conditions were the same as those in Table 1, entry 1, 100% conversion and 89–99% yields.
[b] Determined by GC, HPLC or SFC.
[c] Determined by HPLC or SFC.
[d] The configurations of the product **3e** and **3n** are (1*S*,2*R*) and (1*R*,2*S*) as determined by X-ray diffraction analysis of single crystals[12] (see Supporting Information).

Furthermore, the *anti*/*syn* selectivity in the hydrogenation of ketone **2p** decreased to 87:13. This result showed the need for a large difference in sizes between two alkyl groups of the ketone to achieve high enantio- and diastereoselectivity.

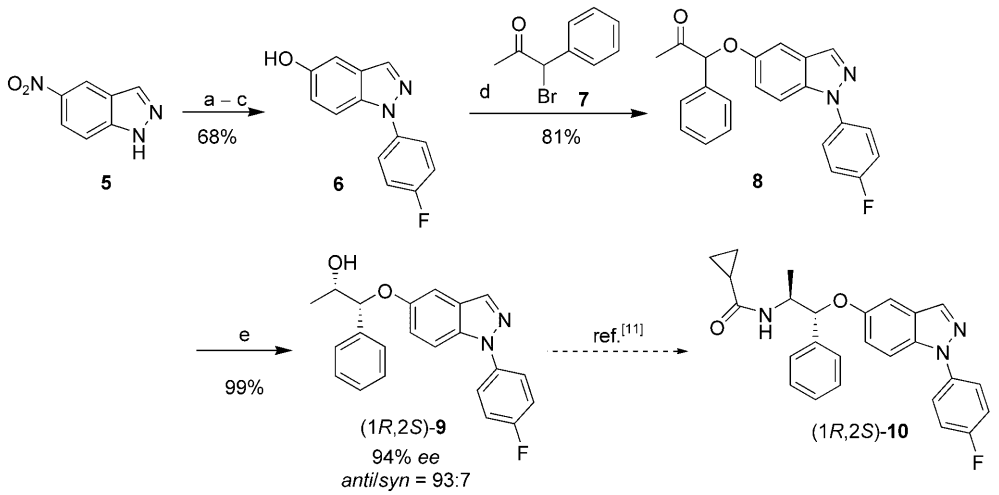
To demonstrate a potential for the application of the $RuCl_2$-SDPs/DPEN-catalyzed asymmetric hydrogenation of *racemic* α-aryloxy dialkyketones *via* DKR in the synthesis of pharmaceuticals and biologically active compounds, the hydrogenation of *racemic* 1-aryl-1-indazolyloxypropan-2-one was carried out (Scheme 2). The product of this reaction, a chiral 1-aryl-1-indazolyloxypropan-2-ol, can serve as a key intermediate for the synthesis of 1-aryl-1-indazolyloxypropan-2-amine (1*R*,2*S*)-**10**, which was reported to be a new type of non-steroidal glucocorticoid modulator.[9] We thus prepared 1-[1-(4-fluorophenyl)-1*H*-indazol-5-yloxy]-1-phenylpropan-2-one (**8**) from the easily available 5-nitroindazole (**5**) in 4 steps including copper-catalyzed coupling reaction[10] in 55% yield. The *racemic* α-indazolyloxy ketone **8** was hydrogenated by catalyst (S_a,*R*,*R*)-**1a** to the chiral α-indazolyloxy alcohol (1*R*,2*S*)-**9** in 99% yield with 94% *ee* and 93:7 *anti*/*syn* selectivity. The α-indazolyloxy alcohol (1*R*,2*S*)-**9** can be conveniently converted to target molecule (1*R*,2*S*)-**10** and other 1-aryl-1-indazolyloxypropan-2-amine derivatives by the literature method.[11] This investigation provides a highly efficient method for the enantioselective synthesis of the potential non-steroidal glucocorticoid modulators.

In conclusion, we have developed a highly efficient method for the synthesis of chiral β-aryloxy alcohols with two adjacent stereogenic centers by chiral $RuCl_2$-SDPs/DPEN-catalyzed asymmetric hydrogenation of *racemic* α-aryloxydialkyl ketones *via* DKR. This catalytic asymmetric hydrogenation has also been applied to the enantioselective synthesis of the key chiral intermediate of non-steroidal glucocorticoid modulators, 1-aryl-1-indazolyloxypropan-2-amine derivatives.

Experimental Section

General Procedure for Asymmetric Hydrogenation

The catalyst [$RuCl_2$-(*S*)-SDP/(*R*,*R*)-DPEN] (S_a,*R*,*R*)-**1a**) (2.0 mg, 0.002 mmol) and anhydrous *i*-PrOH (8.0 mL) was placed in a 30-mL hydrogenation vessel. The vessel was placed in an autoclave and purged with hydrogen by pressurizing to 10 atm and releasing the pressure. The procedure was repeated three times and the solution was stirred under 10 atm of H_2 for 5 min. After releasing the pressure, the α-aryloxy ketone **2** (2 mmol) and a solution of *t*-BuOK in *i*-PrOH (0.2 mmol mL^{-1}, 2.0 mL, 0.4 mmol) were added. The



Scheme 2. Synthesis of the key intermediate of chiral 1-aryl-1-indazolyloxypropan-2-amines. *Regeants and conditions*: a) 5 mol% $Cu(OAc)_2$, 4-$FC_6H_4B(OH)_2$, pyridine, DCM, room temperature, 24 h; b) Raney-Ni, 3 atm H_2, acetone/THF/MeOH (1:1:2), 35 °C, 2 h, 75% yield for two steps; c) $NaNO_2$, H_2SO_4/H_2O, room temperature to 95 °C (3 h), 90% yield; d) K_2CO_3, 18-crown-6, dioxane, 75 °C, 2 h, 81% yield; e) 0.1 mol% (S_a,*R*,*R*)-**1a**, KO-*t*-Bu, *i*-PrOH, 10 atm H_2, 30 °C, 10 h, 99% yield.

autoclave was purged with hydrogen and pressurized to 10 atm. After stirring at room temperature for a certain number of hours, the reaction was stopped. The reaction mixture was filtered through a short silica gel column, and the filtrate was diluted with acetone and analyzed by GC, HPLC or SFC to determine the conversion and the selectivity. The enantioselectivity was determined by chiral HPLC or SFC (see Supporting Information).

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[12] CCDC 751289 [(1*S*,2*R*)-**3e**] and CCDC 751290 [(1*S*,2*R*)-**3n**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

