

Diastereoselective Ruthenium–Cp Complexation of Enantiopure Arene Compounds Possessing Stereogenic Benzylic Alcohol Functionalities

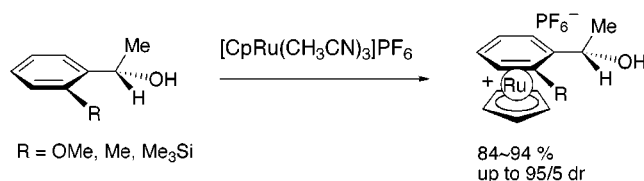
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ABSTRACT



Enantiopure (arene)ruthenium compounds possessing a stereogenic benzylic alcohol functionality were stereoselectively synthesized by diastereoselective ruthenium–Cp complexation to a distinct arene face. This diastereoselective ruthenium–Cp complexation was further extended to biaryl compounds linked with a six-membered lactone bridge for the synthesis of enantiomerically pure, axially chiral biaryls.

(η^6 -Arene)transition metal complexes are well-recognized as versatile intermediates in organic synthesis as a consequence of their electron-withdrawing ability and steric bulkiness of the transition metal. Particularly, η^6 -arene chromium complexes have been most extensively studied in organic reactions.¹ In contrast to the arene chromium complexes, isoelectronic (η^6 -arene)ruthenium Cp⁺ complexes have received comparatively little attention despite the mild conditions for their preparation and air stability.² Furthermore, η^6 -

arene transition metal complexes exist in two enantiomeric forms based on a planar chirality when the arene ring is substituted with different substituents at the 1,2- or 1,3-positions. Although the synthesis of planar chiral Ru complexes with unsymmetrically substituted cyclopentadienyl ligand has been studied,³ there are only few efforts for the preparation of planar chiral enantiomerically pure (η^6 -arene)-ruthenium complexes with different substituents on the arene ring.⁴ As part of our program on asymmetric syntheses

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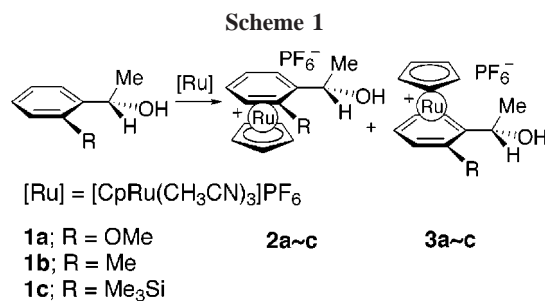
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utilizing the planar chiral arene transition metal complexes, we herein report on the stereoselective synthesis of planar chiral (arene)ruthenium Cp⁺ complexes of 2-substituted benzyl alcohol derivatives and their synthetic application to axially chiral biaryls.

We initially studied a diastereoselective ruthenium complexation of 2-substituted secondary benzyl alcohols. 1-(2-Methoxyphenyl)ethanol (**1a**, Scheme 1) was heated to reflux



with [CpRu(CH₃CN)₃]PF₆ in dichloroethane to give a (*S*_p^{*}, *S*_r^{*})-Ru complex **2a** in 93% yield with 92/8 dr (Table 1,

Table 1. Diastereoselective Ruthenium Complexation Reaction of 2-Substituted Secondary Benzyl Alcohols **1**

entry	compd	R	ratio (2 : 3)	yield (%)
1	1a	OMe	92:8	93
2	1b	Me	94:6	84
3	1c	SiMe ₃	95:5	86

entry 1). With more bulky, methyl- or trimethylsilyl-substituted phenylethanols, the diastereoselectivities of CpRu⁺ complexation increased slightly (entries 2 and 3). The relative configuration of **2a** was determined by X-ray crystallography after acetylation.⁵ This diastereoselective ruthenium complexation to the distinct arene face occurs via an interaction of the ruthenium to the benzylic oxygen atom.

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(5) Crystal structure data of acetylation of **2a**: experimental formula = C₁₆H₁₉O₃RuPF₆, FW = 505.36, orthorhombic, space group P2₁2₁2₁ (No. 19), *a* = 14.600(3) Å, *b* = 17.926(2) Å, *c* = 7.136(2) Å, *V* = 1867.7(5) Å³, *Z* = 4, *D*_{calcd} = 1.797 g cm⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC-165780. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax (+44) 1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

Among two proposed transition states **A** and **B**, the conformation **B** is minimized for nonbonded interaction between the *ortho*-substituent and the methyl groups (Figure 1).⁶

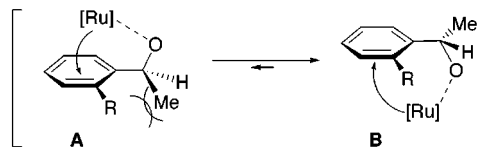


Figure 1. Proposed Transition State

The diastereoselective ruthenium Cp complexation of the secondary benzyl alcohols was further extended to biaryl compounds linked with a six-membered lactone bridge. One of us already reported that the related biaryls connected with δ -lactone bridge gave the corresponding chromium or ruthenium complexation products.⁷ However, these transition metal-coordinated biaryls were obtained as axially equilibrated compounds without distinction of the arene face in *racemic* form. Furthermore, most of δ -lactone bridged biaryls without the transition metal coordination to the arene ring are configurationally unstable at the biaryl axis.⁸ However, these nonchiral axially equilibrated compounds are useful intermediates for asymmetric synthesis of axially chiral biaryls. Thus, the δ -lactone rings of axially equilibrated biaryls were opened with *chiral O*-nucleophiles via dynamic kinetic resolution to give optically active biaryls developed by the Würzburg group.⁸ To prepare the optically active RuCp⁺ complexes of the biaryls connected with δ -lactone by using diastereoselective complexation with the distinct arene face, δ -lactone bridged biaryls with an enantiomerically active secondary benzyl alcohol function were initially prepared (Scheme 2). Catalytic asymmetric reduction⁹ of acetophenone derivative **4a** with a chiral (*S*)-oxazaborolidine and BH₃·Me₂S gave the (*R*)-alcohol **5a** with 97% ee in a quantitative yield, and subsequent palladium-catalyzed intramolecular coupling with a combination of Pd(OAc)₂ and 2-di-*tert*-butylphosphinobiphenyl¹⁰ produced the desired diastereomeric biaryl δ -lactones **6a** and **6a'** as an inseparable 2:1 atropisomeric mixture in 69% yield. The atropisomerization barrier of these two diastereomers was measured by

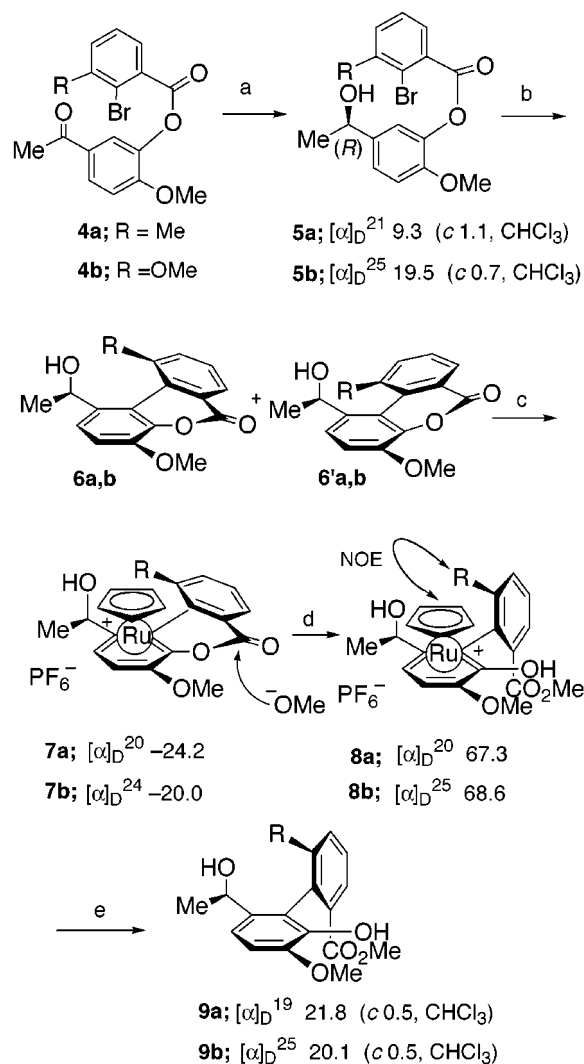
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Scheme 2^a

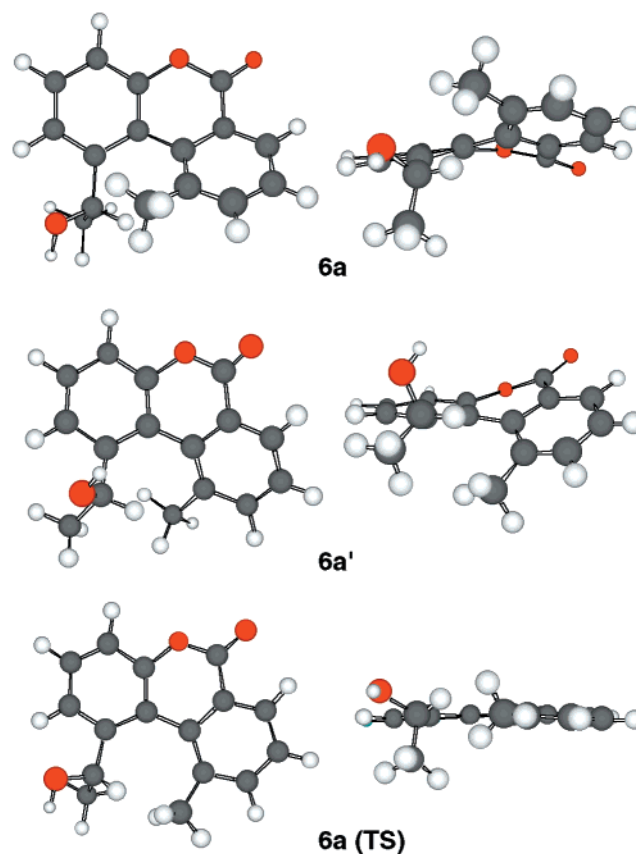
^a Reagents and conditions: (a) BH₃·Me₂S, (*S*)-oxazaborolidine (20 mol %), THF, rt (99%, 97% ee from **4a**; 99%, 98% ee from **4b**), (b) Pd(OAc)₂, (10 mol %), 2-(di-*tert*-butylphosphino)biphenyl (20 mol %), NaOAc, DMA, 100 °C (69% from **5a**; 60% from **5b**), (c) [CpRu(CH₃CN)₃]PF₆, (CH₂Cl)₂, reflux, (51% from **6a** and **6a'**; 48% from **6b** or **6b'**), (d) NaOMe, MeOH, (98% from **7a**; 99% from **7b**), (e) *hν*, CH₃CN, (95% from **8a**; 98% from **8b**).

dynamic ¹H NMR studies of coalescence of two independent signals at 110 °C. The activation free energy was calculated as 17.01 kcal mol⁻¹ on the basis of the Eyring equation.¹¹ Theoretical calculations¹² showed that the diastereomer **6a** was 1.12 kcal mol⁻¹ more stable than **6a'** in total energy, and the atropisomerization barrier was estimated as 17.77 kcal mol⁻¹ (Table 2), in a good agreement with the experimental value. Thus, these two axial diastereomers can be observed at room temperature. With the optically active δ -lactone-bridged biaryl in hand, we next studied the

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(12) Geometry optimizations were carried out with B3LYP hybrid density functional theory on using 6-31G* (C, H, O) and LACVP (Ru) basis sets with the Gaussian 98 and Jaguar V3.5 suite of programs.

Table 2. Summary of ab Initio Calculations of Biaryl Lactone



entry	compd	total energy (H)	zero point energy (H)	enthalpy corr ⁿ (H) at 298 K	free energy corr ⁿ (H) at 298 K
1	6a	-843.80850	0.26407	0.28077	0.22204
2	6a'	-843.81005	0.26383	0.28056	0.22168
3	6a (TS)	-843.78257	0.26439	0.28018	0.22253

Ru(II)⁺Cp complexation of the diastereomeric mixture **6a** and **6a'**. Surprisingly, ruthenium complex **7a** was obtained as a single axially chiral diastereomer in 51% yield¹³ without formation of any stereo- and regioisomers by treatment with [CpRu(CH₃CN)₃]PF₆ under the same conditions.¹⁴ The formation as a single diastereomer is in sharp contrast to the previous report^{7b,c} that the related δ -lactone-linked biaryl compound gave an inseparable mixture of chromium complexes. The configuration of **7a** was determined by X-ray analysis.¹⁵ The Cp ruthenium fragment was coordinated to the arene ring substituted with the electron-donating hydroxymethyl and methoxy groups via an interaction of the ruthenium with the benzylic oxygen. The axial chirality of

(13) The described values are purified yields of crude products (~70%) after a recrystallization for a removal of contaminant ruthenium reagent along with 10% yield of the starting materials. The diastereoselectivity of the ruthenium complexation products was determined of the crude products by NMR spectra, and the stereo- and regioisomers were not observed by ¹H NMR spectra of the crude products of **7a** and **7b**.

(14) The corresponding Cr(CO)₃ complex was not formed by treatment of **6** with Cr(CO)₆ or (naphthalene)Cr(CO)₃.

the complex **7a** was found to be the (*S*)-configuration. The complex **7a** is by 2.1 kcal mol⁻¹ more stable than the corresponding (*R*)-configured diastereomer **7a'** by ab initio calculations (Table 3).¹² This value is larger than the

Table 3. Summary of ab Initio Calculation of Ruthenium Complex

entry	compd	total	zero point	enthalpy	free energy
		energy (H)	energy (H)	corr (H) at 298 K	corr (H) at 298 K
1	7a	-1131.03520	0.37604	0.39619	0.32953
2	7a'	-1131.03916	0.37649	0.39754	0.32776

difference (1.12 kcal mol⁻¹) of the total energies between the pre-ruthenium complexation diastereomers **6a** and **6a'**. Although a precise mechanism for the formation of ruthenium complex **7a** as a single axial diastereomer is not clear at the present time, complex **7a** might be formed as a thermodynamically stable compound via axial isomerization of the diastereomeric (*R*)-axial ruthenium complex derived from the diastereomer **6a'** under the reaction conditions. An alternative mechanism may also be considered: the ruthenium complexation takes place from a distinct face of only diastereomer **6a** via a dynamic kinetic resolution of the axially equilibrated diastereomers **6a** and **6a'**. We further examined the diastereoselective ruthenium complexation of a sterically less substituted biaryl lactone, the methoxy analogue **6b**. The palladium-catalyzed coupling of optically active alcohol **5b** produced the desired biaryl as a single diastereomer in 60% yield without detection of any stereoisomers. A rapid interconversion between **6b** and **6b'** is considered feasible by decreasing a steric demand.¹⁶ Similarly, the ruthenium complexation of the diastereomeric mixture of **6b** and **6b'** gave the single axially chiral ruthenium

complex **7b** without the formation of any stereo- and regioisomers in 48% yield¹³ under the same conditions. In this way, the equilibrated axially diastereomeric biaryls linked with the δ -lactone ring bridge gave a thermodynamically stable atropisomeric compound as a single isomer by ruthenium complexation to the distinct arene face.¹⁷

With the axially chiral ruthenium-complexed δ -lactone biaryls in hand, we next focused on the ring opening of δ -lactones **7a** and **7b** with *nonchiral* reagents. The ruthenium complexes **7a** and **7b** were treated with NaOMe in methanol at room temperature to give a single diastereomer¹⁸ of axially chiral *ortho*-tetra-substituted biaryl ruthenium complexes **8a** and **8b** in 98% and 99% yields, respectively. The relative configuration was elucidated by differential NOE experiments and an opposite face attack of nucleophile to the transition metal fragment. Thus, a 7% NOE was observed between the methyl group on the ruthenium-free arene ring and the Cp ring of **8a**. Finally, demetalation of the complexes **8a** and **8b** gave axially chiral biaryls **9a** and **9b** in good yields. Furthermore, stereoselective reduction of the lactone ring of **7b** with LiAlH₄ gave the corresponding axially chiral biaryl as a single diastereomer in 99% yield.¹⁹

In conclusion, we have developed a diastereoselective ruthenium complexation of 2-substituted secondary benzyl alcohol derivatives to the distinct arene face and asymmetric synthesis of enantiomerically pure axially chiral biaryls.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) Exploitation of Multi-Element Cyclic Molecules from the the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and characterization data of products. This material is available free of charge via Internet at <http://pus.acs.org>.

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(15) Crystal structure data of **7a**: experimental formula = C₂₂H₂₁O₄-PF₆Ru, FW = 595.44, orthorhombic, space group *Pbcn* (No. 60), *a* = 16.953(3) Å, *b* = 15.441(2) Å, *c* = 20.454(2) Å, *V* = 5354(2) Å³, *Z* = 8, *D*_{calcd} = 1.477 g cm⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC-165781.

(16) Theoretical calculations (B3LYP/6-31*) showed that the atropisomerization barrier between axial diastereomers **6b** and **6b'** is estimated at 8.68 kcalmol⁻¹.

(17) A naphthyltetrahydroisoquinoline skeleton with a chiral center having sterically bulky substituents and specific nitrogen substitution could also fix the axial axis of δ -lactone-bridged biaryls by palladium-catalyzed cyclization: see ref 8c.

(18) The δ -lactone ring opening of the ruthenium-uncomplexed biaryls **6** with NaOMe gave the diastereomeric mixture of axially atropisomeric biaryls (*dr* = 7:3 for **6a**; 1:1 for **6b**) on the basis of the axially equilibrated ratio of **6a** and **6b**.

(19) Interestingly, a related ruthenium complex biaryl lactone ring could be opened only with *O*-nucleophiles: see ref 7b. We are now investigating the reason for these different reactivities with hydride reduction between the related ruthenium complexes.