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Catalytic *atropo*-Enantioselective Reduction of Biaryl Lactones to Axially Chiral Biaryl Compounds

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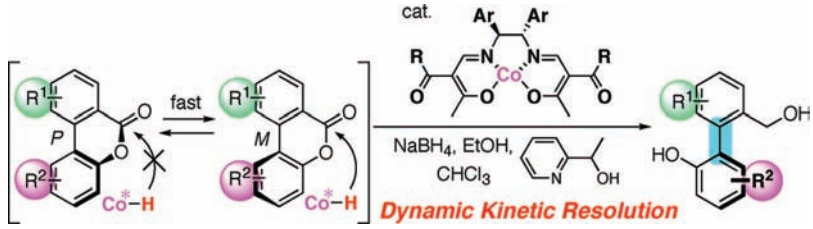
ABSTRACT



The *atropo*-enantioselective borohydride reduction with dynamic kinetic resolution of biaryl lactones was catalyzed by an optically active *β*-ketoiminatocobalt(II) complex to afford optically active biaryl compounds. Chiral HPLC analysis of the starting biaryl lactones was performed at various temperatures to determine suitable reaction conditions for dynamic kinetic resolution. Various types of axially chiral biaryl compounds were obtained with high enantioselectivity.

Axially chiral biaryl compounds are important building blocks present in various biologically active natural products. The absolute configuration of the biaryl axis is the predominant factor in their pharmacological properties.[1] These compounds have also been employed as effective chiral ligands for various enantioselective syntheses, e.g., BINOL[2] for aluminum hydride reduction, BINAP[3] as a reliable ligand for various transition-metal complex catalysts, and binaphthyl phosphoric acid[4] as a chiral organocatalyst. Although several preparative methods for these axially chiral biaryl compounds have been proposed, almost all are based on enantioselective aryl−aryl coupling reactions.[5] For instance, the enantioselective oxidative coupling of *β*-naphthol derivatives was reported using a cuprous[6] or vanadium[7] complex catalyst, although this was limited to only the homocoupling reaction to afford the corresponding BINOL derivatives. Direct coupling including the Suzuki−Miyaura coupling catalyzed by palladium complexes has been reported,[8] although these reactions are sensitive to sterically demanding substituents on the 2-positions of the precursors and consequently require severe reaction conditions, such as high temperature and high concentration, which results in poor selectivity. These drawbacks hamper their wide-range application to the reliable preparation of axially chiral biaryl compounds. An alternative strategy involving dynamic kinetic resolution has been

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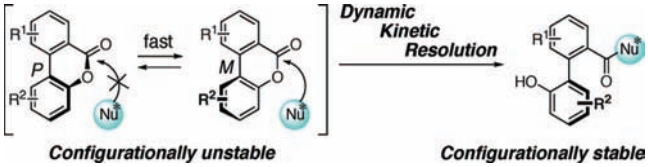
introduced by Bringmann.[9] The first step involves the intramolecular aryl-coupling of aromatics prefixed by an ester junction. The biaryl axis in the obtained lactone remains configurationally unstable and produces *atropo*-enantiomers in equilibrium. A chiral nucleophile could recognize one of these *atropo*-enantiomers and selectively attack it to afford the corresponding axially chiral biaryl compounds, which are configurationally stable (Scheme 1).

Scheme 1. Lactone Strategy Involving Dynamic Kinetic Resolution



Various chiral nucleophiles have been employed to demonstrate the effectiveness of this lactone strategy involving dynamic kinetic resolution. This strategy has been applied to the total synthesis of numerous axially chiral natural products.[9a,10] Though it is an efficient method for the synthesis of axially chiral biaryl compounds, almost all are based on diastereomeric selective reactions using a stoichiometric chiral nucleophile, including BINAL-H[11] and CBS reagent.[12] Only one example for the *atropo*-enantioselective reduction of biaryl lactones with a catalytic amount (10 mol %) of the CBS reagent has been reported.[12b] An efficient catalytic method, which can be applied to the *atropo*-enantioselective synthesis of a broad range of axially chiral biaryl compounds, is an important challenge. In the presence of a catalytic amount of an optically active β-ketoiminatocobalt(II) complex, dynamic kinetic resolution was effectively achieved for the enantioselective borohydride reduction of 2-alkyl-3-ketocarboxylates into the corresponding optically active *anti*-2-alkyl-3-hydroxycarboxylates.[13] In this Letter, we describe a versatile catalytic *atropo*-enantioselective reduction with dynamic kinetic resolution of biaryl lactones employing an enantioselective borohydride reduction catalyzed by a cobalt(II) complex to afford optically active biaryl compounds with high enantioselectivity.

During the present dynamic kinetic resolution, a lower temperature enhanced the proper recognition of each absolute conformer, whereas a higher temperature caused a fast equilibrium between them. In order to achieve high enantioselectivity, the appropriate reaction temperature was examined. From chiral HPLC analysis of the axially chiral biaryl lactone **1a** at −20 °C, two peaks assigned to the corresponding *atropo*-isomers were clearly observed. At higher temperatures, less resolved peaks were observed. Eventually at 30 °C, a single sharp peak was detected (Figure 1).

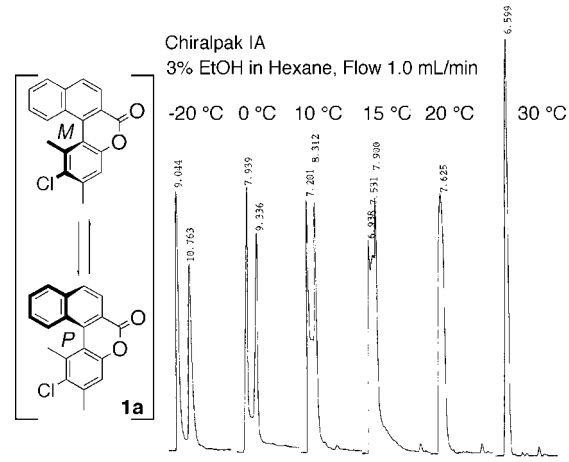
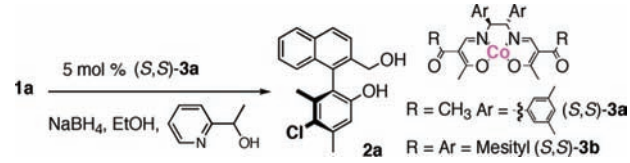


Figure 1. HPLC analysis of biaryl lactone **1a**.

These observations indicated that the equilibrium between the *atropo*-isomers at 30 °C would be so fast that an efficient dynamic kinetic resolution could be expected. In fact, when the reaction was carried out at −40 °C, after a long reaction time, the corresponding biaryls **2a** were obtained in moderate yield and moderate enantioselectivity (Table 1, entry 1). In the reactions at −20 and 0 °C, the reaction rate was

Table 1. Examination of Reaction Temperature[a]



entry	temp (°C)	time (h)	yield (%)	ee (%)[b]
1	−40	168	57	53
2	−20	43	81	49
3	0	5.3	86	54
4	10	6.3	88	62
5	15	7.5	72	73
6	20	4.0	71	71
7	30	6.2	74	85
8[c]	40	27	52	84

[a] Reaction conditions: 0.10 mmol of substrate, 0.0050 mmol of cobalt catalyst, and 0.30 mmol of modified $NaBH_4$ [0.30 mmol of $NaBH_4$, 0.30 mmol of EtOH, and 4.2 mmol of 1-(2-pyridinyl)ethanol] in $CHCl_3$. [b] Determined by HPLC analysis. [c] The reaction was stopped halfway because of decomposition of the borohydride.

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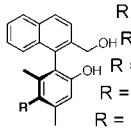
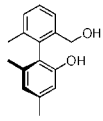
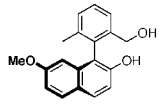
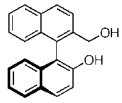
improved, but the enantioselectivites of the biaryls **2a** remained at 49% and 54% ee, respectively (entries 2 and 3). The reaction at 10 °C gave the biaryls **2a** in 62% ee and 88% yield (entry 4). At a higher reaction temperature, the enantioselectivity was improved with a slight decrease in the yield (entries 5−8). Finally, it was found that 30 °C was the best reaction temperature for the catalytic *atropo*-enantioselective reduction of the biaryl lactone **1a** to produce the corresponding biaryls **2a** in 85% ee with 74% yield (entry 7).

Under the optimized conditions for each substrate, various axially chiral biaryl lactones were subjected to dynamic kinetic resolution during the *atropo*-enantioselective reduction catalyzed by the optically active cobalt(II) complex (Table 2). From biaryl lactones **1a**, **1b**, and **1c**, reducing

Table 2. Catalytic *atropo*-Enantioselective Reduction of Various Axially Biaryl Lactones[a]

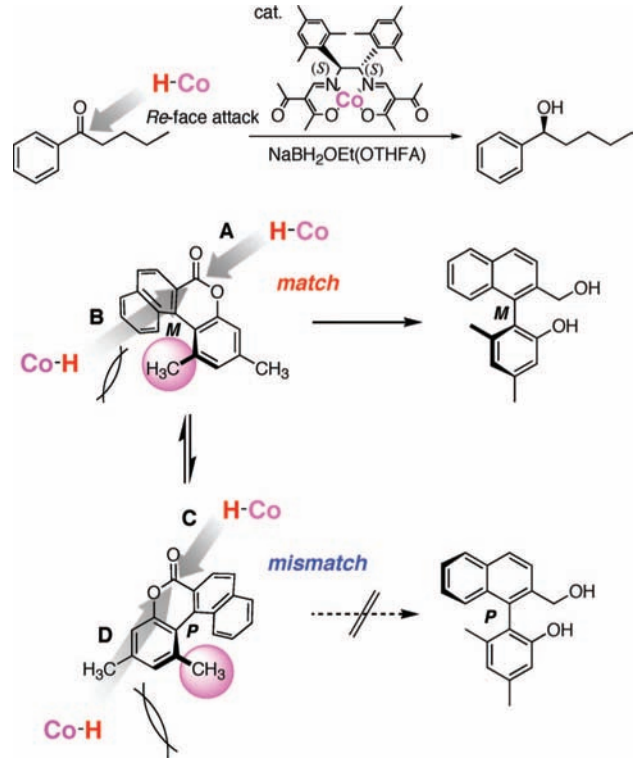
entry	product		temp (°C)	time (h)	yield (%)	ee (%)[b]
1	 R = Cl	**2a**	30	6	74	85
2[c]	R = H	**2b**	0	2	87	89
3	R = Me	**2c**	15	19	85	84
4	R = AcO	**2d**	15	21	85	89
5	R = MeO	**2e**	15	18	88	91
6	R = *i*-PrMe$_2$SiO	**2f**	15	7	89	93
7[d]	R = TBDMSO	**2g**	0	17	90	93
8		**2h**	0	4	64	89
9		**2i**	-5	2	96	83
10[e]		**2j**	50	6.5	87	80

[a] Reaction conditions: 0.10 mmol of substrate, 0.0050 mmol of cobalt catalyst, and 0.30 mmol of modified $NaBH_4$ in $CHCl_3$. [b] Determined by HPLC analysis. [c] 0.0055 mmol of (*S*,*S*)-**3a** was used. [d] 0.0056 mmol of (*S*,*S*)-**3a** and 0.33 mmol of modified $NaBH_4$ (see Supporting Information) in $CHCl_3$ were used. [e] 0.0050 mmol of (*S*,*S*)-**3b** and 0.30 mmol of modified $NaBH_4$ [0.30 M $NaBH_4$ in diglyme solution (1.0 mL) and 1.8 mmol of *t*-BuOH] in $CHCl_3$ were used.

products were obtained in good-to-high yields with a high enantioselectivity (entries 1−3). The biaryl lactones **1d** and **1e** with acetyl and methoxy groups also afforded the axially chiral biaryls **2d** and **2e** in high yields with excellent enantioselectivities (entries 4 and 5). The siloxy groups, such as the isopropyldimethylsiloxy group and *tert*-butyldimethylsiloxy group, were tolerated for this reaction to produce the corresponding biaryls **2f** and **2g** with excellent enantioselectivities (entries 6 and 7). This reduction system also allowed the synthetically applicable enantioselection for the biaryl lactones, **1h** and **1i**, which have never before been applied to *atropo*-enantioselective reduction (entries 8 and 9). These axially chiral binaphthyl compounds are structually important units of a steadily growing number of chiral ligands for asymmetric synthesis. HPLC analysis of binaphthyl lactone **1j** at 50 °C showed a single peak (see Supporting Information), indicating that a higher temperature is required to achieve fast equilibrium between the *atropo*-isomers. Indeed, the *atropo*-enantioselective reduction of the binaphthyl lactone **1j** was conducted at 50 °C. However, the corresponding binaphthyls **2j** was not obtained. It was reasonable that the modified borohydride that reacted at 50 °C with the modifier alcohols decomposed with hydrogen evolution. To suppress the decomposition, various solvents were examined for the *atropo*-enantioselective reduction with dynamic kinetic resolution of the binaphthyl lactone **1j** at 50 °C. It was found that in the presence of a catalytic amount of the (*S*,*S*)-cobalt(II) complex **3b**, the use of 0.3 M sodium borohydride in diglyme solution afforded the resulting binaphthyls **2j** in high yield and high enantioselectivity (entry 10).

The absolute configuration of **2b** corresponding to the (*S*,*S*)-cobalt(II) complex catalyst **3a** was revealed to be *M* by comparison of its CD spectrum and optical rotation with reported values. The CD spectra of biaryls **2a**−**g** also exhibited similar curves with that of **2b** (see Supporting Information). On the basis of these results, the axially chiral biaryl products with the *M* configuration were assumed to correspond to the (*S*,*S*)-cobalt(II) complex catalyst.

Scheme 2. Plausible Mechanism of Selectivity



The mechanistic course of the lactone cleavage with the chiral hydride nucleophile was investigated by Bringmann.[9a]

The rapidly *atropo*-isomerizing lactone can be attacked by the hydride nucleophile, leading to an intermediary hydroxy aldehyde, which can be further reduced to give the target biaryl compounds. The resulting intermediary hydroxy aldehyde was indeed configurationally unstable, for it isomerized via a lactolate intermediate, such that asymmetric induction initially achieved by the chiral hydride nucleophile was potentially lost. In the presence of a catalytic amount of optically active β-ketoiminatocobalt(II) complex, the borohydride reduction of the configurationally unstable hydroxy aldehyde proceeded rapidly to afford the racemic biaryl product. This result indicates that the high enantiomeric excess observed in the present reduction system cannot be caused by the second hydride attack on the configurationally unstable intermediary hydroxy aldehyde. Therefore, the initial hydride attack on the lactone is the stereochemically determining step and the intermediary hydroxy aldehyde is reduced immediately after its formation to give the configurationally stable biaryl diols with axial chirality. From this consideration and the absolute configuration of the axially chiral biaryl product, possible transition states of the present reduction were proposed as follows. Two possible transition states, which avoid steric repulsion of the methyl group of the biaryl lactones with the hydride nucleophile, are shown in Scheme 2. In one of the possible transition states (**A**, Scheme 2), the *M* configured biaryl lactone would approach the (*S*,*S*)-cobalt hydride complex, leading to the observed biaryls with the *M* absolute configuration at the biaryl axis. The enantioselective sense in the present reduction of the axially chiral biaryl lactones was in perfect accord with various examples of the cobalt(II) complex catalyzed reduction of carbonyl compounds reported by our group.[14]

In conclusion, we have developed a versatile catalytic *atropo*-enantioselective borohydride reduction with dynamic kinetic resolution of various biaryl lactones catalyzed by the optically active β-ketoiminatocobalt(II) complex. The axially chiral biaryls were obtained in high yield and with excellent enantioselectivity. A fast equilibrium between the *atropo*-isomers of the biaryl lactones was demonstrated from HPLC analysis. To achieve catalytic *atropo*-enantioselective reduction with dynamic kinetic resolution of binaphthyl lactones, the use of $NaBH_4$ in diglyme solution was essential.

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

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