Catalytic *atropo*-Enantioselective Preparation of Axially Chiral Biaryl Compounds

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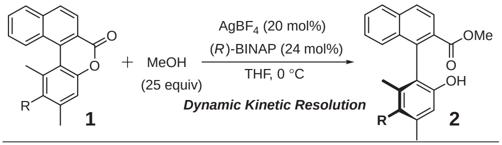
The *atropo*-enantioselective ring-opening of biaryl lactones with methanol was catalyzed by an optically active $AgBF_4$–phosphine complex to afford axially chiral biaryl compounds. The addition of triisobutylamine provided a dramatic rate acceleration in the reaction. Various types of axially chiral biaryl compounds were obtained with high enantioselectivity.

Axially chiral biaryl compounds are important building blocks in various biologically active natural products[1] and are effective ligands for various enantioselective syntheses.[2–4] In view of their increasing importance, various synthetic methods for axially chiral biaryl compounds have been reported to date.[5] Bringmann et al. have developed an efficient synthetic method for axially chiral biaryl compounds[6] from biaryl lactones, which are easily prepared by intramolecular aryl coupling. The biaryl axis in these lactones is configurationally unstable and provides *atropo*-enantiomers in equilibrium. Subsequent ring-opening of these configurationally unstable biaryl lactones can be performed stereoselectively, leading to axially chiral biaryl compounds.

Various metal-assisted ring-opening reactions of biaryl lactones have been reported[6b] and applied to the total synthesis of numerous axially chiral natural products.[6a,7] Considering the effectiveness of this lactone method, the catalytic *atropo*-enantioselective ring-opening of biaryl lactones is an ideal reaction to prepare axially chiral biaryl compounds. Seebach et al. have reported the first *atropo*-enantioselective ring-opening of biaryl lactones catalyzed by $(i\text{-PrO})_2$Ti-TADDOLate, which can work both as an optically active Lewis acid and as an O-nucleophile.[8] Recently, the catalytic *atropo*-enantioselective reductive ring-opening of various biaryl lactones using an optically active β-ketoiminatocobalt(II) complex was disclosed by our group.[9] Inspired by these studies, we have explored the catalytic *atropo*-enantioselective ring-opening of biaryl lactones with a simple alcohol. We report here an optically active $AgBF_4$–phosphine complex[10]-catalyzed *atropo*-enantioselective ring-opening of biaryl lactones with methanol, providing various axially chiral biaryl compounds in high yields and high enantioselectivities.



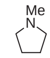
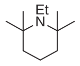
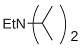
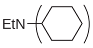
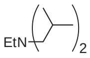
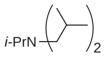
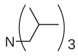
Product		Additive	Time/h	Yield/%	ee/%
R = H	**2a**	none	24	quant.	72
R = TBDMSO	**2g**	none	163	NR	—
R = TBDMSO	**2g**	Et_3N (1.0 equiv)	5	93	57

Scheme 1. Catalytic *atropo*-enantioselective ring-opening.

We initially selected methanol as a simple nucleophile and examined the catalytic *atropo*-enantioselective ring-opening of biaryl lactone **1a** in the presence of a variety of optically active $AgBF_4$–phosphine complexes. These studies indicated that the $AgBF_4$–(*R*)-BINAP complex is a desirable catalyst. Such conditions delivered the corresponding biaryl compound **2a** in quantitative yield with 72% ee. With the catalytic *atropo*-enantioselective ring-opening of biaryl lactone **1a** with methanol in hand, the biaryl lactone **1g** was subjected to *atropo*-enantioselective ring-opening catalyzed by the $AgBF_4$–(*R*)-BINAP complex, but the corresponding biaryl compound **2g** was not obtained. The possibility is to assume that the biaryl lactone **1g** can not be effectively activated by the $AgBF_4$–(*R*)-BINAP complex, because a bulky siloxy group of the biaryl lactone **1g** could lead to steric interactions with the ligand. Interestingly, the addition of triethylamine drove the reaction to afford the corresponding biaryl compound **2g** in high yield with moderate enantioselectivity (Scheme 1).

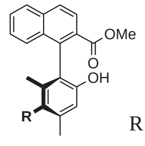
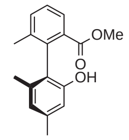
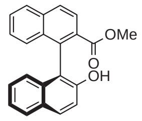
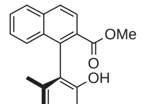
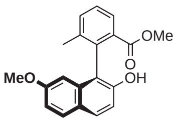
Intrigued by this finding, we hypothesized that triethylamine served as a base for the activation of methanol, and thus investigated the effect of other bases on the reaction (Table 1). Although the addition of carbonate salts **3a** and **3b** provided high yields, low enantioselectivity was observed (Entries 1 and 2). When DMAP (**3c**) and *N*-methylpyrrolidine (**3d**) were employed, the corresponding biaryl compound **2g** was obtained in low yield and low enantioselectivity after a long reaction time (Entries 3 and 4). Bulky amine bases were effective additives for the reaction (Entries 5–11). The addition of the most bulky

Table 1. Additive effects on the catalytic *atropo*-enantioselective ring-opening of biaryl lactone **1g**[a]

Entry	Base (1.0 equiv)		Time/h	Yield/%	ee/%[b]
1	Cs_2CO_3	**3a**	13	81	0
2[c]	K_2CO_3	**3b**	5	92	28
3	DMAP	**3c**	42	27	35
4	 Me N	**3d**	47	38	29
5	 Et N	**3e**	17	88	45
6	 EtN 2	**3f**	24	77	53
7	 EtN 2	**3g**	23	81	54
8	Et_3N	**3h**	5	93	57
9	 EtN 2	**3i**	23	92	60
10	 *i*-PrN 2	**3j**	14	89	66
11	 N 3	**3k**	29	84	70

[a]Reaction conditions: 0.10 mmol of substrate **1g**, 2.5 mmol of MeOH, 0.020 mmol of $AgBF_4$, and 0.024 mmol of (*R*)-BINAP. All reactions were carried out in THF at 0 °C. [b]Determined by HPLC analysis. [c]K_2CO_3 (0.5 equiv) was added.

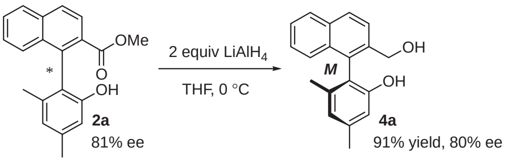
Table 2. Catalytic *atropo*-enantioselective ring-opening of various axially biaryl lactones[a]

Entry	Product		Temp /°C	Time /h	Yield /%	ee /%[b]
1[c]	 R = H	**2a**	–20	93	92	82
2	R = Cl	**2b**	20	47	84	70
3[d]	R = Me	**2c**	20	71	97	64
4[d]	R = MeO	**2d**	–20	74	79	84
5		**2e**	–20	73	89	84
6		**2f**	40–50	42	49	50
7[e]		**2f**	40	42	77	46
8[d,e]	 R = TBDMSO	**2g**	–20	139	82	80
9[d,e]	R = *i*-PrMe$_2$SiO	**2h**	–20	115	55	76
10		**2i**	–20–rt	187	21	63
11[e]		**2i**	–20	66	96	81

[a]Reaction conditions: 0.10 mmol of substrate, 2.5 mmol of MeOH, 0.020 mmol of AgBF$_4$, and 0.024 mmol of (*R*)-BINAP. All reactions were carried out in THF. [b]Determined by HPLC analysis. [c](*S*)-H$_8$-BINAP was used instead of (*R*)-BINAP. [d](*R*)-H$_8$-BINAP was used instead of (*R*)-BINAP. [e]Triisobutylamine (1.0 equiv) was added.

cyclic amine **3e** gave the product **2g** in high yield, but enantioselectivity remained low at 45% (Entry 5). The enantioselectivities were improved with bulky acyclic amine bases such as isobutylamine derivatives **3i**–**3k** (Entries 9–11). Specifically, the addition of triisobutylamine **3k** provided the product **2g** in 84% yield and 70% ee (Entry 11).

Encouraged by these studies, the generality and scope of this *atropo*-enantioselective reaction were investigated (Table 2). From biaryl lactones **1a**, **1b**, and **1c**, the corresponding biaryl methyl esters were obtained in high yields with good-to-high enantioselectivity (Entries 1–3). The biaryl lactone **1d** with a methoxy group also afforded the axially chiral biaryl compound **2d** in high yield with 84% ee (Entry 4). Enantioenriched biphenyl compound **2e** can also be produced from the corresponding biaryl lactone **1e** (Entry 5). The binaphthyl compound **2f** was obtained in high yield with moderate enantioselectivity by the addition of triisobutylamine (Entry 7). In the reaction of the biaryl lactones with bulky siloxy groups, it is crucial to activate methanol with the triisobutylamine additive. In the presence of triisobutylamine, biaryl lactones **1g** and **1h** afforded products **2g** and **2h** in good-to-high yields with 80% ee and 76% ee, respectively (Entries 8 and 9). The reaction of the biaryl lactone **1i** was also accelerated by the addition of triisobutylamine to produce the axially chiral biaryl compound **2i** in 96% yield with 81% ee (Entry 11).



Scheme 2. Reduction of the axially chiral biaryl compound **2a**.

To determine the absolute configuration of **2a** corresponding to the AgBF$_4$–(*R*)-BINAP complex, the axially chiral biaryl compound **2a** with 81% ee was reduced by LiAlH$_4$ (Scheme 2). The corresponding reduced product **4a** was obtained in 91% yield with 80% ee. The absolute configuration of the diol **4a** was revealed to be the M form by comparing its optical rotation sign and HPLC retention time with reported values (see Supporting Information).[11] Therefore, the axially chiral biaryl methyl ester **2a** with the M configuration was assumed to correspond to the AgBF$_4$–(*R*)-BINAP complex. The mechanistic investigation and the examination of various nucleophiles are currently underway.

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References and Notes

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11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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