Pinacol Coupling of 2,2′-Biaryldiketone: An Application for the Synthesis of Enantiopure 3,4-Dihydrodibenzo[*c*,*g*]phenanthrene-3,4-diol Derivatives

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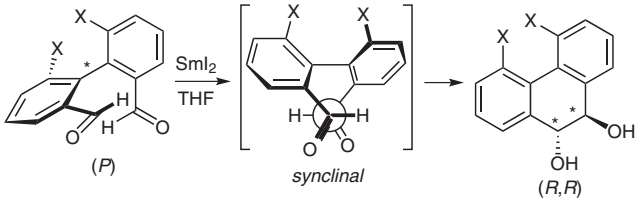
Received 11 March 2010

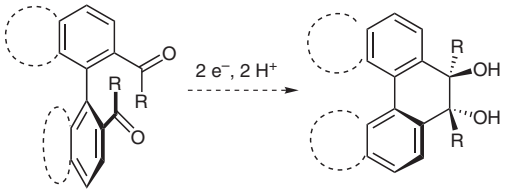
Abstract: Pinacol coupling of 2,2′-biaryldiketone gave *trans*-diol selectively. In the reaction of axially chiral diketones, enantiomerically pure diols were obtained. Various enantiopure 3,4-dihydrodibenzo[*c*,*g*]phenanthrene-3,4-diol could be synthesized by the pinacol coupling of optically active 2,2′-diacyl-1,1′-binaphthalene derived from (*P*)-1,1′-bi-2-naphthol [(*S*)-BINOL].

Key words: biaryls, diastereoselective reactions, diols, optically active compounds, pinacol coupling

Previously, we reported that the SmI_2-mediated pinacol cyclization of 2,2′-biaryldicarbaldehyde gives a *trans*-diol selectively (Equation 1).[1,2] In this reaction, the coupling proceeds in the synclinal mode, and the axial chirality of the dialdehyde (in cases where the starting biphenyl is configurationally stable) is stereospecifically transmitted onto two stereogenic centers of the product. Recently various efficient methods for the synthesis of optically active biaryl compounds are avairable,[3] and some enantiomerically pure biaryls are commercially available. We expected that various optically active 1,2-diols which would be utilized for asymmetric reactions[4] could be synthesized by the pinacol coupling of optically active 2,2′-biaryldiketone if the coupling proceeds stereospecifically similar to the reaction of 2,2′-biaryldicarbaldehyde (Equation 2).



Equation 1



Equation 2

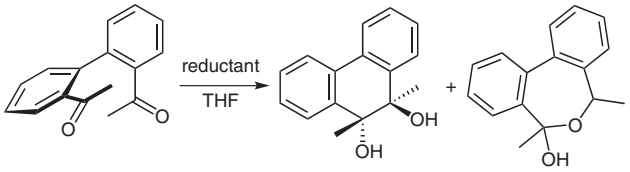
There are few reports on the pinacol coupling of 2,2′-biaryldiketone.[5] Blum et al. reported the pinacol coupling of 2,2′-dibenzoylbiphenyl through use of Mg and MgI_2 to afford a 3:5 mixture of *cis*- and *trans*-9,10-diphenylphenanthrene-9,10-diol.[5b] Neumann et al. reported the photolytic pinacol coupling of 2,2′-diacetylbiphenyl using a special distannane, $Me_2(PhS)Sn–Sn(SPh)Me_2$, to give *trans*-9,10-dimethylphenanthrene-9,10-diol.[5a] However, the relationship of the axial chirality of 2,2′-diacylbiphenyl with the stereochemistry of the coupling product was not investigated because the starting biphenyl is configurationally unstable. Therefore, we examined the pinacol coupling of 2,2′-diacylbiphenyl with particular focus on the stereochemistry of the reactant and the product. In this letter, we describe the outcome of the investigation.

Our initial attempt was focused on the reaction of 2,2′-diacetylbiphenyl **1** under several reduction conditions (Table 1). Upon treatment of **1** with SmI_2 at 0 °C, the only detectable product was hemiacetal **3** in 64% yield (entry 1).[6,7] At –78 °C, the formation of **3** was suppressed to 20%, and the *trans*-diol **2** was obtained in 66% yield (entry 2). The yield of the *trans*-diol **2** increased to 96% by the combination of SmI_2 and methanol (entry 3). Addition of hexamethyl phosphoramide (HMPA) to SmI_2 solution was not effective for the formation of the diol **2** (entry 4).[8] Further attempt with a low-valent titanium species generated from $TiCl_4$ and Zn[9] gave only the *trans*-diol **2** in 94% yield. The relative stereochemistry of **2** was determined by X-ray crystal structure analysis (Figure 1).[10]

Next, we examined pinacol coupling of optically active 2,2′-diacylbiphenyl which proved to be configurationally stable at room temperature to check the possibility of chiral transmission of axial chirality of biaryldiketone to new chiral centers of the diol. As optically active 2,2′-diacylbiphenyl compounds, 2,2′-diacyl-1,1′-binaphthalenes were selected because these compounds are configurationally stable[11] and easily prepared from commercially available1,1′-bi-2-naphthol (BINOL) in enantiomerically pure form. Various 2,2′-diacyl-1,1′-binaphthalenes were synthesized from (*P*)-1,1′-bi-2-naphthol [(*S*)-BINOL]. 2,2′-Dialkanoylbinaphthalenes were prepared from the known dialdehyde **4**[1] in two steps as shown in Scheme 1. 2,2′-Diaroylbinaphthalenes were prepared from the known triflate **5**[11] in two steps via oxidation of the benzylic position with *N*-hydroxyphthalimide (NHPI) (Scheme 2).[12,13]

SYNLETT 2010, No. 9, pp 1359–1362
Advanced online publication: 12.05.2010
DOI: 10.1055/s-0029-1219928; Art ID: U01610ST

Table 1 Reaction of 2,2′-Diacetylbiphenyl **1** under Several Reduction Conditions



1 **2** **3**

Entry	Reductant	Conditions	Yield	
			2 (%)	**3** (%)
1	SmI_2	0 °C, 5 min	0	64
2	SmI_2	–78 °C, 5 min	66	20
3	SmI_2, MeOH	–78 °C, 5 min	96	0
4	SmI_2, HMPA	–78 °C, 5 min	48	26
5[a]	$TiCl_4$, Zn	–10 °C, 30 min	94	0

[a] In THF–CH_2Cl_2.

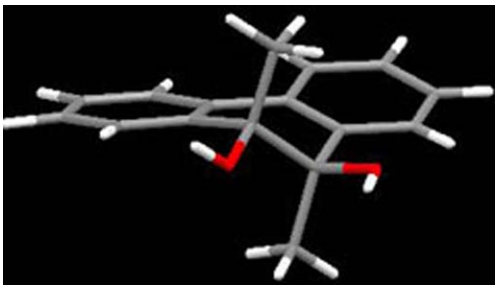
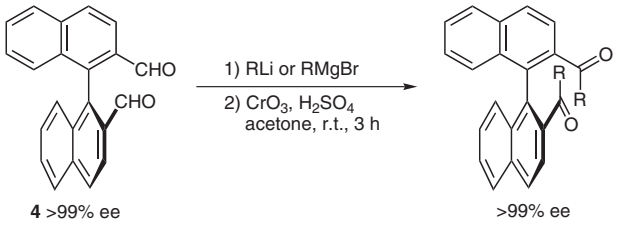
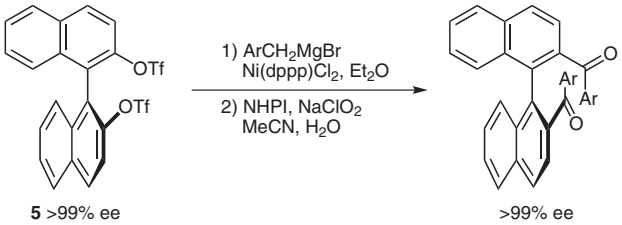


Figure 1 X-ray crystal structure of diol **2**



4 >99% ee >99% ee

Scheme 1

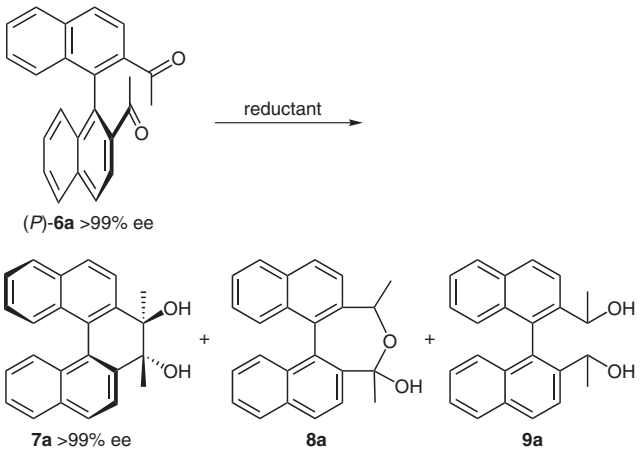


5 >99% ee >99% ee

Scheme 2

Pinacol cyclization was examined using (*P*)-2,2′-diacetyl-1,1′-binaphthalene (**6a**, Table 2). First, the coupling was examined by treatment of SmI_2 in the presence of methanol in THF (entry 1). However, anticipated pinacol product **7a** was not obtained, and the hemiacetal **8a** and diol **9a** were obtained in 10% and 32% yields, respectively. In contrast, we observed that the reaction of the diketone **6a** with low-valent titanium reagents gave the *trans*-diol **7a**, which proved to be diastereo- and enantiomerically pure.[14] Relative stereochemistry of the pinacol coupling product **7a** was determined by X-ray crystal structure analysis (Figure 2).[15] The absolute stereochemistry of two chiral centers in **7a** were assigned as *R* and *R* from the X-ray crystal structure, because the 1,1′-bi-2-naphthyl derivative and 3,4-dihydrodibenzo[*c*,*g*]phenanthrene are configurationally stable at room temperature.[16] Furthermore, the diol **7a** was diequatorial, which suggested that the pinacol coupling proceeded by the synclinal mode, as shown in Scheme 3.

Table 2 Pinacol Cyclization with (*P*)-2,2′-Diacetyl-1,1′-binaphthalene (**6a**)



(*P*)-**6a** >99% ee **7a** >99% ee **8a** **9a**

Entry	Reductant	Conditions	Yield		
			7a (%)	**8a** (%)	**9a** (%)
1	SmI_2, MeOH	THF, –78 °C, 5 min	0	10	32
2	$TiCl_4$, Zn	THF, CH_2Cl_2, –10 °C, 3 h	96	0	0

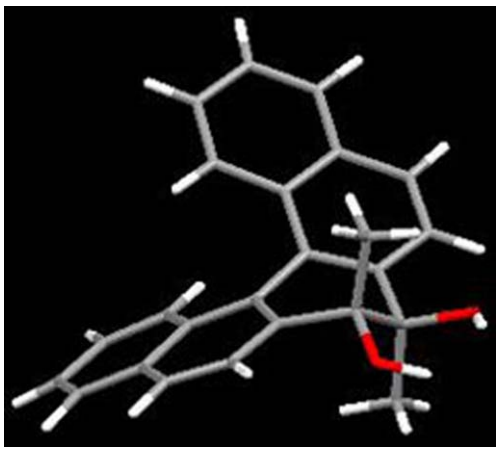
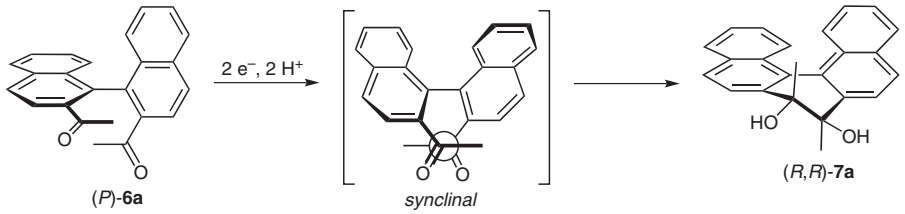


Figure 2 X-ray crystal structure of **7a**

Various enantiomerically pure *trans*-diols **7** have been synthesized by the pinacol cyclization of 2,2′-diacyl-1,1′-binaphthalenes **6** (Table 3).

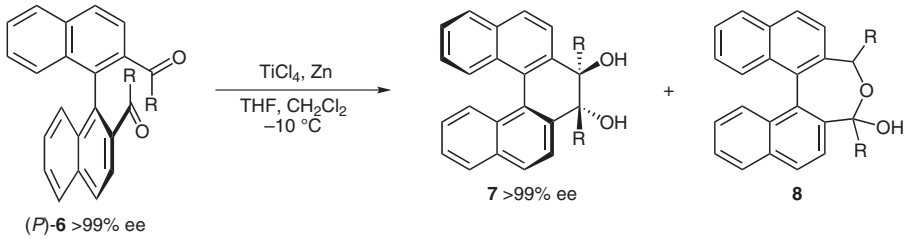
As can be seen from the result of 2,2′-dialkanoyl-1,1′-binaphthalene (R = Alk in **6**), the reaction was sensitive to the steric effect of the substituent R (entries 1–3). As the substituent R became bulkier (Me → *n*-Bu → *c*-Hex), the yields of the coupling product **7** decreased (96% → 68% → 30%).

In the aromatic series, the steric effect of the substituent R was also observed. In the case of the dibenzoyl derivative **6d** (R = Ph), the pinacol-coupling product **7d** was obtained in 69% yield, accompanied by the hemiacetal **8d** in 18% yield (entry 4).[17] The results of the *p*- and *m*-tolyl ketones (**6e** and **6f**) were almost the same as **6d**. In contrast, the coupling product was not obtained from the *o*-tolyl ketone **6g** (entry 7), probably because of the steric hindrance around the carbonyl groups. This reaction is tolerant to the substituent on the 3-position of the phenyl ring in R (en-



Scheme 3

Table 3 Synthesis of Various Enantiomerically Pure *trans*-Diols **7**



Entry	R	6	Time (h)	Products			
				7	Yield (%)	8	Yield (%)
1	Me	**6a**	3	**7a**	96	**8a**	0
2	*n*-Bu	**6b**	6	**7b**	68	**8b**	0
3	*c*-Hex	**6c**	3	**7c**	30	**8c**	0
4	Ph	**6d**	3	**7d**[a]	69	**8d**	18
5	4-MeC_6H_4	**6e**	3	**7e**[b]	69	**8e**	28
6	3-MeC_6H_4	**6f**	5	**7f**[c]	62	**8f**	17
7	2-MeC_6H_4	**6g**	6	**7g**	0[d]	**8g**	0
8	3,5-$Me_2C_6H_3$	**6h**	11	**7h**	42	**8h**	30
9	3-$MeOC_6H_4$	**6i**	4	**7i**[e]	46	**8i**	39
10	3-$F_3CC_6H_4$	**6j**	12	**7j**[f]	61	**8j**	20
11	3-PhC_6H_4	**6k**	6	**7k**	40	**8k**	20
12	2-FC_6H_4	**6l**	6	**7l**	0[g]	**8l**	0

[a] $[\alpha]_D^{19}$ +471 (*c* 1.02, $CHCl_3$).
[b] $[\alpha]_D^{20}$ +410 (*c* 1.00, $CHCl_3$).
[c] $[\alpha]_D^{19}$ +426 (*c* 1.02, $CHCl_3$).
[d] Compound **6g** was recovered in 90%.
[e] $[\alpha]_D^{20}$ +357 (*c* 1.03, $CHCl_3$).
[f] $[\alpha]_D^{20}$ +355 (*c* 1.03, $CHCl_3$).
[g] Diol **9l** was obtained in 72%.

tries 8–11). The 2-fluorophenyl ketone **6l** gave only the diol **9l** in 72% yield (entry 12).

In conclusion, we found that the pinacol coupling of enantiomerically pure axially chiral 2,2′-biaryldiketones proceeds to give *trans*-diols in the enantiomerically pure form. By this method, various enantiopure 3,4-dihydrodibenzo[*c*,*g*]phenanthrene-3,4-diols could be synthesized. Currently asymmetric reactions using the diol **6** are under investigation.

Acknowledgment

This research was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture. We thank Dr. T. Moriguchi (Department of Applied Chemistry, Kyushu Institute of Technology) and Dr. T. Matsumoto (Institute for Materials Chemistry and Engineering, Kyushu University) for assistance in X-ray crystallographic analysis.

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(10) CCDC 768807 contains the supplementary crystallographic data for compound **2**.

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(14) Compound **7a** and the enantiomer of **7a** derived from (*M*)-BINOL proved to have an ee value of greater than 99% by HPLC with chiral column (DAICEL OD-H).

(15) CCDC 623903 contains the supplementary crystallographic data for compound **7a**.

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(17) **Typical Procedure is Described for the Synthesis of 7d**
To a solution of diketone (*P*)-**6d** (415 mg, 0.897 mmol) in THF (7 mL) was added 1 M $TiCl_4$ in CH_2Cl_2 (2 mL) and Zn (0.260 g, 3.98 mmol) at –10 °C. After stirring for 6 h at –10 °C, the reaction was quenched by adding 10 wt% K_2CO_3 solution. The mixture was filtered through a Celite pad (washed with EtOAc). The resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc = 8:2) to afford the diol **7d** (239 mg, 69% yield, >99% ee) and acetal **8d** (62 mg, 18% yield).