Diastereoselectivity in Addition of Methylmagnesium Halide to Benzoylformate of Chiral 1,1′-Binaphthalene-2,2′-diol

Kaoru FUJI,* Kiyoshi TANAKA, Mija AHN, and Maki MIZUCHI

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan.
Received October 14, 1993; accepted December 2, 1993

The Grignard reactions of mono-benzoylformate ester of 1,1′-binaphthalene-2,2′-diol were examined to investigate the complex-induced proximity effect of the phenolic hydroxyl at C-2′ under different reaction conditions. This hydroxyl group exerted a significant neighboring group participation in the reaction. The nucleophilic addition reaction proceeded with higher diastereoselectivity than that of a series of sterically similarly sized binaphthyl esters recently reported. The halogen ligand in methyl Grignard reagents plays a crucial role in controlling the degree and sense of diastereoselectivity. A plausible mechanism is also proposed.

Keywords 1,1′-binaphthol; Grignard reaction; atrolactic acid; neighboring group participation; diastereoselectivity

In connection with Prelog's rule,[1] atrolactic acid (2-hydroxy-2-phenylpropanoic acid) synthesis was extensively studied in early investigations on asymmetric reactions.[2] In spite of the low 1,4-asymmetric induction, this transformation provided an empirical and useful investigative tool for determination of the absolute configuration of chiral alcohol present as an ester group of α-keto esters. This work has been extended by using compounds of axial chirality, such as 1,1′-binaphthalen-2-ol, from which optically active atrolactic acid was obtained with a high enantioselectivity of 85% ee.[3] In 1989, Miyano *et al.* reinvestigated the addition reaction of methylmagnesium iodide to the benzoylformate of enantiomerically pure 1,1′-binaphthalen-2-ol, and found that the *Ra*-enantiomer induced *S*-chirality with much lower levels of optical yield (3—17%) than that reported previously under almost the same experimental conditions.[4] Furthermore, they examined the inherent chiral induction ability of the axially chiral 1,1′-binaphthalene framework in Prelog's atrolactic acid synthesis by using a variety of benzoylformate esters of 2′-substituted 1,1′-binaphthalen-2-ol.[5] The sense of the diastereoselection was interpreted in terms of the steric bulkiness of the 2′-substituents with C5′—C8′ moieties of 1,1′-binaphthalene skeleton.

Recently, we have investigated diastereodifferentiating alkylations by utilizing chiral binaphthols as a chiral auxiliary and observed that the free hydroxy group at C2′ contributes to activation of the reaction as well as to the degree and course of the diastereoselection.[6] The reactive hydroxyl can play an important role in reactions through the complex-induced proximity effect (CIPE).[7] It was also shown that CIPE played an important role in the high diastereoselectivity of 1,4-addition of organocopper reagents to the chiral binaphthyl ester of α,β-unsaturated carboxylic acid.[8] Consequently, it was expected that the stereoselectivity of the Grignard reaction of the benzoylformate would be increased by utilizing chiral binaphthol without protection of the 2′-hydroxy group. We describe herein our results on methyl Grignard additions to the benzoylformate of 1,1′-binaphthalene-2,2′-diol.

Results and Discussion

Chiral 2′-hydroxyl-1,1′-binaphthalen-2-yl benzoylformate (**2**) was prepared by condensation of benzoylformic acid with chiral binaphthol (**1**) in the presence of a condensation agent as depicted in Chart 1. The Grignard reactions of **2** with methylmagnesium halides were carried out in ether or an appropriate solvent at −78 °C for 1 h and the products were analyzed by HPLC (Table I). The

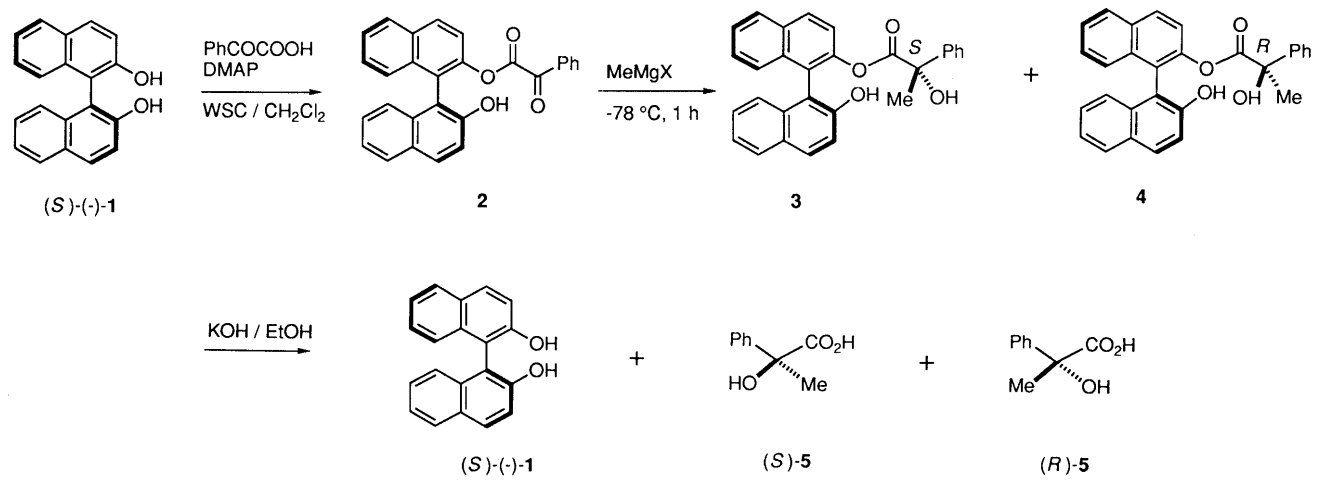

Chart 1

Table I. Results of Reactions

Entry	Grignard reaction[a]					Atrolactate			
	Reagent	eq	Add.[b]	Solvent	Additive	Product[c]	Chem. yield (%)[d]	Conf. at C2	de (%)[e]
1	MeMgCl[f]	2	A	Ether	—	**3**	48	*S*	51
2	MeMgCl[f]	4	A	Ether	—	**3**	73	*S*	39
3	MeMgCl[f]	4	A	Ether	$MgBr_2 \cdot Et_2O$ (3 eq)	**3**	69	*S*	48
4	MeMgCl[f]	2	A	THF	—	**3**	33	*S*	27
5	MeMgBr[g]	2	A	Ether	—	**3**	56	*S*	57
6	MeMgBr[g]	3	A	Ether	—	**3**	85	*S*	53
7	MeMgBr[g]	3	B	Ether	—	**3**	78	*S*	60
8	MeMgBr[g]	3	A	Ether	$MgBr_2 \cdot Et_2O$ (3 eq)	**3**	59	*S*	58
9	MeMgBr[h]	2	A	THF	—	**3**	26	*S*	48
10	MeMgI[i]	2	B	Ether	—	**4**	69	*R*	30
11	MeMgI[i]	2	A	Ether	—	**4**	74	*R*	44
12	MeMgI[i]	2	A	Ether	$ZnCl_2$ (2 eq)	**4**	45	*R*	14
13	MeMgI[i]	1.2	A	Ether	—	**4**	44	*R*	61
14	MeMgI[i]	1.2	A	Ether	$MgBr_2 \cdot Et_2O$ (1.2 eq)	**4**	35	*R*	39
15	MeMgI[i]	2	A	THF	—	**3**	27	*S*	28
16	MeMgI[i]	1.2	A	THF	$MgBr_2 \cdot Et_2O$ (1.2 eq)	**3**	7	*S*	39
17	MeMgI[i]	2	A	Toluene	—	**3**	87	*S*	18
18	MeMgI[i]	1.2	A	Toluene	$MgBr_2 \cdot Et_2O$ (1.2 eq)	**3**	49	*S*	17

a) Reactions were carried out at −78 °C for 1 h. *b*) Order of addition: A, addition of Grignard reagent to ester; B, addition of ester to reagent. *c*) Predominant product. *d*) Combined isolated yield. *e*) Determined by HPLC. *f*) 3 M in THF. *g*) 3 M in ether. *h*) 1 M in THF. *i*) 0.9 M in ether.

absolute structures of the atrolactates **3** and **4** were determined by hydrolytic transformation to atrolactic acid, whose specific rotation was reported.[9]

As can be seen in Table I, the degree of diastereoselectivity is relatively high compared with the reported values in additions to sterically similar benzoylformates. For example, Miyano *et al.*[5] described predominant formation of the **3** type product with 4 and 6% diastereomeric excess's (de's) for 2′-unsubstituted and 2′-methoxy compounds, respectively, from the addition of MeMgI. A 16% de was observed with the 2′-methyl compound in preferential formation of the **4** type product. Our present results strongly suggest the existence of some participation by the phenolic 2′-hydroxyl in the addition reaction with Grignard reagent. It is noteworthy that the sense of asymmetric induction with methylmagnesium iodide is opposite to that with the corresponding bromide and chloride in ether as a solvent. Although the crystal structures of typical Grignard reagents were elucidated by X-ray diffraction,[10] the structures of the actual reactive species in solution are still unclear. The three methyl Grignard reagents employed in the present study differ in the steric bulk of the halogen ligand and its bonding strength to magnesium atom, if aggregation states are not taken into account. It is feasible that complexation between organometallics and the phenolic hydroxyl at C-2′ dictates the diastereofacial differentiation. Thus, the (*S*)-product **3** with methylmagnesium chloride or bromide could be deduced from the ligation as depicted in the figure, since the transition state imposes intramolecular attack of the methyl group from the *re*-face of the carbonyl. The absolute stereochemistry of atrolactic acid obtained from methylmagnesium iodide in ether (entries 10—14) is the same as that obtained from 1,1′-binaphthalen-2-yl benzoylformates with a bulky substituent at C-2′ in the binaphthyl moiety.[5] Intramolecular addition was suppressed somehow in this case and the 2′-hydroxy group complexed with the Grignard reagent as a bulky group to facilitate the intermolecular approach from the opposite site of the carbonyl, leading to the (*R*)-alcohol **4**.

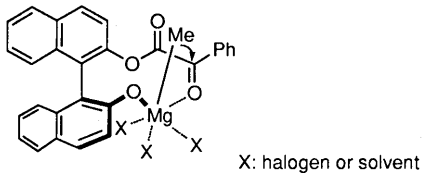

Fig. 1

A significant solvent effect was observed in the addition reaction with methylmagnesium iodide. Both tetrahydrofuran (THF) and toluene, with more and less ligating ability than ether, respectively, alter the sense of diastereoselectivity observed in ether. It is likely that the change of solvent to one with greater ligating ability causes ligand exchange resulting in a difference of aggregation or a reduction of the electronic repulsion between the reagent and substrate. In order to examine the reaction mechanism, the Grignard reactions in the presence of metallic additives were carried out, but the results were not informative.

In conclusion, the present study has demonstrated that the phenolic hydroxyl at C-2′ on the binaphthalene ring is indispensable for diastereoselectivity and increases it to 61% de, which is rather high compared to precedent examples in atrolactic acid synthesis. Although detailed mechanistic elucidation is still required, the present results indicate that the choice of the Grignard reagent can alter the sense of diastereoselection. Reaction design utilizing such neighboring group participation is in progress.

Experimental

Methods and Materials Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. Infrared

spectra (IR) were recorded on a JASCO A-202 spectrophotometer in chloroform. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken with a Varian Gemini 200 (200 MHz) in $CDCl_3$ with chemical shifts being reported in δ ppm from tetramethylsilane as an internal standard. Coupling constants are expressed in hertz. Mass spectra (MS) were obtained with a JEOL JMS-DX300 mass spectrometer. Optical rotations were determined on a Horiba SEPA-200 polarimeter. Column chromatography was carried out with Silica gel 60 spherical. High-performance liquid chromatography (HPLC) was conducted with a Shimadzu LC10-A using the hexane/2-propanol solvent system on a Chiralpak AS chiral column (Daicel Chemical Co.) for binaphthols or a Shimpak Silica prepacked column (Shimadzu Co.) for determination of diastereoselectivity of Grignard reactions. THF, ether and toluene were distilled from sodium metal-benzophenone ketyl and methylene chloride was distilled from calcium hydride. Optically pure binaphthols employed in this study were prepared by enzymatic transformation from racemic binaphthol monoacetate according to the reported procedure[11] and their optical purities were checked by HPLC before use.

2'-Hydroxy-1,1'-binaphthalen-2-yl Benzoylformate (2) 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (WSC, 1.44 g, 7.5 mmol) was added to a stirred solution of (*S*)-(−)-binaphthol (1.43 g, 5 mmol), 4-dimethylaminopyridine (61.1 mg, 0.5 mmol) and benzoylformic acid (1.5 g, 0.01 mol) in methylene chloride (30 ml), and the whole was refluxed for 1 h with stirring under nitrogen. After cooling, the mixture was poured into ice-cold 5% HCl and extracted with methylene chloride. The extract was washed with water, dried over sodium sulfate and evaporated under reduced pressure to leave the residue. Purification of the residue by column chromatography on silica gel with a solvent system of hexane–methylene chloride–ethyl acetate (6 : 3 : 1) provided **2** (1.69 g) as prisms of mp 136—137 °C (from hexane–ether) in 81% yield. $[\alpha]_D^{20}$ −57.8 (c = 1.02, $CHCl_3$). IR ν cm^{-1}: 3550, 3050, 1760, 1690, 1200. ^{1}H-NMR δ: 5.24 (s, 1H), 7.09—8.18 (m, 17H). MS *m/z*: 418 (M^+), 390, 286, 105, 77. *Anal.* Calcd for $C_{28}H_{18}O_4$: C, 80.37; H, 4.34. Found: C, 80.11; H, 4.36.

The Grignard Reaction of 2'-Hydroxy-1,1'-binaphthalen-2-yl Benzoylformate (2) with Methylmagnesium Halide: General Procedure A solution of methylmagnesium halide (0.36—1.2 mmol) in an appropriate solvent was added to a solution of 2'-hydroxy-1,1'-binaphthalen-2-yl benzoylformate (**2**, 0.3 mmol) at −78°C under a nitrogen atmosphere, and the mixture was stirred for 1 h at the same temperature. The mixture was quenched by the addition of saturated ammonium chloride solution and extracted with ethyl acetate. The extract was washed successively with sodium bicarbonate solution and water, and then dried over magnesium sulfate. Evaporation of the extract under reduced pressure left an oily residue, which was subjected to HPLC analysis and then to column chromatography on silica gel to give a mixture of **3** and **4**. The separation of the mixture was performed by column chromatography on silica gel with a solvent system of hexane–methylene chloride–ethyl acetate (3 : 3 : 1) to afford pure **3** and **4**.

3: mp 157—158 °C. $[\alpha]_D^{20}$ −23.3 (c = 1.01, $CHCl_3$). IR ν cm^{-1}: 3550, 3060—2940, 1750, 1150. ^{1}H-NMR δ: 1.38 (s, 3H), 3.28 (s, 1H), 5.11 (s, 1H), 6.99—8.08 (m, 17H). MS *m/z*: 434 (M^+), 286, 268, 105, 77. HRMS Calcd for $C_{29}H_{22}O_4$: 434.1519. Found: 434.1525. *Anal.* Calcd for $C_{29}H_{22}O_4$: C, 80.16; H, 5.10. Found: C, 79.77; H, 5.11.

4: mp 59—61 °C. $[\alpha]_D^{20}$ −89.3 (c = 1.01, $CHCl_3$). IR ν cm^{-1}: 3550, 3060—2940, 1750, 1140. ^{1}H-NMR δ: 1.00 (s, 3H), 3.40 (s, 1H), 5.13 (s, 1H), 7.02—8.05 (m, 17H). MS *m/z*: 434 (M^+), 286, 239, 105, 77. HRMS Calcd for $C_{29}H_{22}O_4$: 434.1519. Found: 434.1526. *Anal.* Calcd for $C_{29}H_{22}O_4$: C, 80.16; H, 5.10. Found: C, 79.81; H, 5.16.

Hydrolysis of Atrolactate 3 or 4 to Atrolactic Acid A mixture of **3** or **4** (116 mg, 0.27 mmol) and 20% KOH ethanol solution (10 ml) was refluxed with stirring for 3 h under nitrogen. After concentration under reduced pressure, the mixture was made acidic with 5% HCl and extracted with ethyl acetate. The extract was evaporated under reduced pressure to give the residue, which was subjected to column chromatography on silica gel. Binaphthol (75 mg, 98% yield) was recovered from the early fractions with hexane–ethyl acetate (3 : 1) without any loss of optical purity by HPLC analysis, and atrolactic acid (41 mg, 93% yield) was eluted with methanol.

(*S*)-**5**: mp 116—117 °C (needles from benzene–hexane). $[\alpha]_D^{20}$ 35.1 (c = 1.01, EtOH). IR ν cm^{-1}: 3520, 3100—2900, 1720, 1150—1060. ^{1}H-NMR δ: 1.82 (s, 3H), 7.33—7.59 (m, 5H). MS *m/z*: 166 (M^+), 121, 105, 77.

(*R*)-**5**: mp 108—109 °C (needles from benzene–hexane). $[\alpha]_D^{20}$ −32.6 (c = 1.02, EtOH). IR, ^{1}H-NMR, and MS; the same as those of (*S*)-**5**.

References

1) V. Prelog, *Helv. Chim. Acta*, **36**, 308, 320 (1953); J. C. Fiaud, "Determination of Configurations by Chemical Methods," ed. by H. B. Kagan, Georg Thieme Publishers, Stuttgart, 1977, pp. 19—49.
2) J. D. Morrison, H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Engelwood Cliffs, 1971, pp. 35—83.
3) J. A. Berson, M. A. Greenbaum, *J. Am. Chem. Soc.*, **80**, 445, 653 (1958).
4) Y. Tamai, T. Nakano, S. Koike, K. Kawahara, S. Miyano, *Chem. Lett.*, **1989**, 1135.
5) Y. Tamai, T. Nakano, S. Miyano, *Chem. Lett.*, **1992**, 807.
6) K. Fuji, M. Node, F. Tanaka, S. Hosoi, *Tetrahedron Lett.*, **30**, 2825 (1989); K. Fuji, F. Tanaka, M. Node, *ibid.*, **32**, 7281 (1991).
7) K. Fuji, M. Node, F. Tanaka, *Tetrahedron Lett.*, **31**, 6553 (1990).
8) K. Fuji, K. Tanaka, M. Mizuchi, S. Hosoi, *Tetrahedron Lett.*, **32**, 7277 (1991).
9) R. A. Barnes, B. R. Juliano, *J. Am. Chem. Soc.*, **81**, 6462 (1959); J. H. Brewster, *ibid.*, **78**, 4061 (1956); D. J. Cram, K. R. Kopecky, F. Hauck, A. Langemann, *ibid.*, **81**, 5754 (1959).
10) P. G. Williard, "Comprehensive Organic Synthesis," Vol. 1, ed. by B. M. Trost, I. Fleming, Pergamon Press, Oxford, 1991, pp. 1—42; E. Negishi, "Organometallics in Organic Synthesis," John Wiley & Sons, New York, 1980, pp. 92—94.
11) M. Inagaki, J. Hiratake, T. Nishioka, J. Oda, *Agric. Biol. Chem.*, **53**, 1879 (1989).