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An Efficient Asymmetric Synthesis of Atropisomeric 1,1'-Binaphthyls via Nucleophilic Aromatic Substitution Reaction

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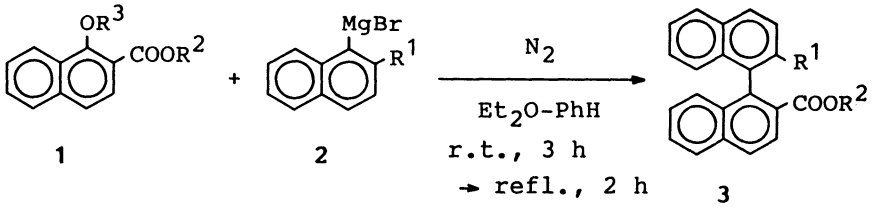
High levels of asymmetric induction (up to 98% optical yield) were achieved in the joining of two naphthalene rings by the nucleophilic displacement of 1-menthoxyl group of 1-(-)-menthoxy-2-naphthoates (**1**) with 1-naphthyl Grignard reagnts. Also reported is a convenient preparation of the prerequisite **1** via treatment of methyl 1-methoxy-2-naphthoate with sodium (-)-menthoxide in DMF.

Recently asymmetric synthesis of binaphthyl atropisomers has intensively been studied.[1] In previous paper, we have described the facile construction of 1,1'-binaphthyl skeleton via nucleophilic aromatic substitution of 1-methoxyl group of 1-methoxy-2-naphthoates (**1**, R^3 = Me) with 1-naphthyl Grignard reagents (Scheme 1).[2] Introduction of C-centro-chirality in the R^2 moiety caused bias in the formation of binaphthyl atropisomers, while the levels of the asymmetric induction were low to moderate (up to 51% optical yield), apparently due to rather remote location of the chiral center from the coupling site.[2]

The aryl-coupling reaction is very unique in that it is a nucleophilic aromatic substitution (S_NAr) of an alkoxyl group from substrate (**1**) which lacks highly electron-withdrawing substituents to activate aromatic nucleus for nucleophilic attack.[3] However, the Grignard substitution reminds us

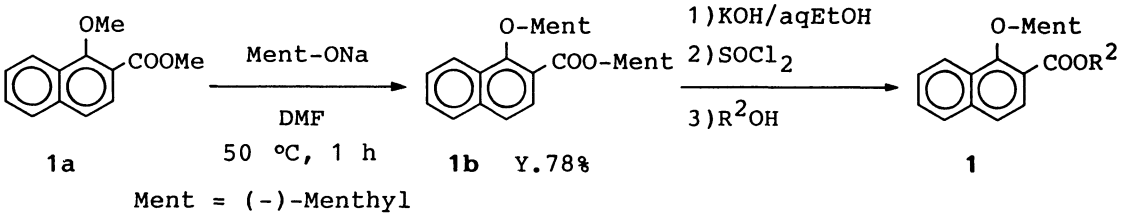


1 **2** **3**

Scheme 1.

of the Meyers reaction, in which 1-alkoxyl group is activated by an oxazoline group on the 2-position.[4] On the other hand, Wilson and Cram had reported highly stereoselective asymmetric coupling by leaving chiral 1-alkoxyl group in the Meyers reaction,[5] which strongly tempted us to try the reaction in Scheme 1 by using chiral R^3 substituent. Herein we wish to report a facile synthesis of 1-(-)-menthoxy-2-naphthoic esters and highly efficient asymmetric coupling of them with naphthyl Grignard reagents to give 1,1'-binaphthyl-2-carboxylates of high atropisomeric purity.

We were pleased to know that ester function activates o-alkoxyl group for nucleophilic displacement by not only carbanions (e.g. Scheme 1) but also alkoxides,[6] a process without precedent.[3] Thus, treatment of methyl 1-methoxy-2-naphthoate (**1a**) with an excess amount of sodium (-)-menthoxide in dimethylformamide under mild conditions (50 °C, 1 h) caused facile exchange of both the methoxyl groups to give (-)-menthyl 1-(-)-menthoxy-2-naphthoate (**1b**)[7] in high yield (Scheme 2).[8] Conversion of **1b** into other alkyl naphthoates is simple and straightforward.[7]



1a **1b** Y.78% **1**

Ment = (-)-Menthyl

Scheme 2.

The 1-(-)-menthoxy-2-naphthoates (**1b–1d**) were then treated with naphthyl Grignard reagents in ether–benzene at ambient temperature for 3 h followed by heating at gentle reflux for 2 h under a nitrogen atmosphere as before (Scheme 1).[2] Results listed in Table 1 show that chiral 1-(-)-menthoxyl leaving group induces highly efficient asymmetric coupling of the two naphthalene units to give 1,1'-binaphthyl structure in excellent yields.[9] Especially noteworthy is the asymmetric synthesis of 2'-methoxy-1,1'-binaphthyl-2-carboxylate (**3a**) of high atropisomeric purity (98%) (Fig. 1); axially homochiral acid from **3a** is useful as chiral derivatizing agent for discrimination of enantiomeric alcohols and amines,[10] and convenient obtention of it is highly desirable.[11] Considering the previous results,[2] it is con-

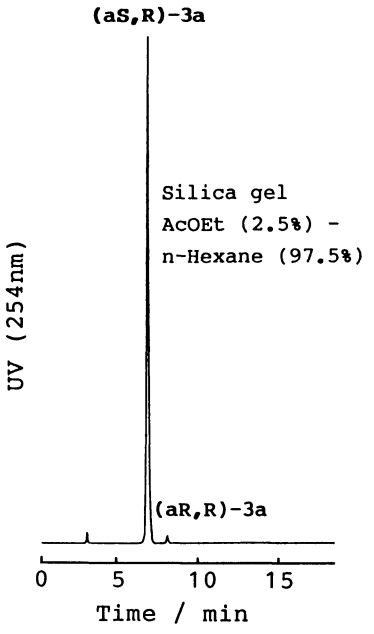
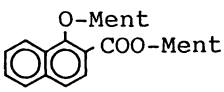
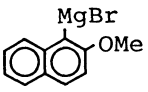
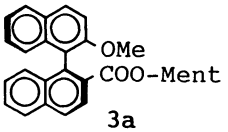
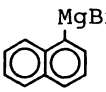
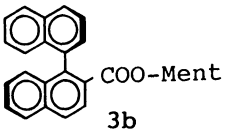
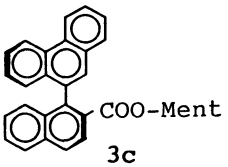
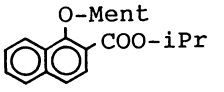
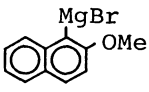
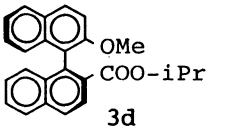
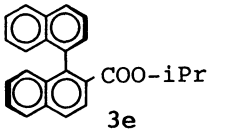
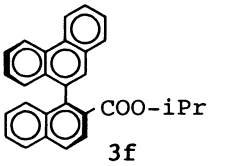
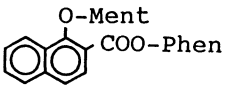
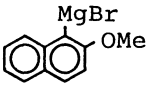
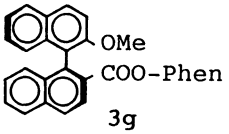
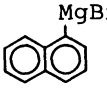
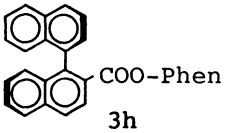


Fig. 1. HPLC of the products from **1b** and **2a**.

Table 1. Asymmetric Synthesis of Binaphthyls via S_NAr Reaction[a)]

Run	1[b)]	2	3		
			Struct.[b)]	Yield/%	Opt.yield/%[c)]
1	 1b	 2a	 3a	81	98
2		 2b	 3b	93	76
3		 2c	 3c	78	59
4	 1c	 2a	 3d	92	97
5		 2b	 3e	95	80
6		 2c	 3f	55	65
7	 1d	 2a	 3g	85	91
8		 2b	 3h	74	91

a) Reaction conditions: **1**, ca. 1.8 mmol; **2**/**1** = 1.8 (mol/mol); Et_2O (10-15 ml) - PhH (15 ml); room temp (3 h) and reflux (2 h). Recovered **3**s were substantiated by IR and ^{1}H-NMR spectroscopy. b) Ment = (-)-Menthyl; Phen = (R)-1-Phenylethyl. c) Determined by HPLC on silica gel or ^{1}H-NMR.

cluded that the 1-(-)-menthoxyl group rather than the chiral ester moiety on the 2-position determines configurational bias of the binaphthyl structure. It should be noted, however, that the preferential binaphthyl axis was also governed by the Grignard reagent used; 1-naphthyl Grignard reagent (**2b**) induced chiral binaphthyl axis opposite to that induced by 2-methoxy-1-naphthyl (**2a**) and 9-phenanthryl Grignard reagent (**2c**). Although 2-methyl-1-naphthylmagnesium bromide reacted with 1-methoxy-2-naphthoates to give the corresponding binaphthyls in excellent yields,[2] steric bulk of the reagent seemed to prevent the reaction with 1-(-)-menthoxy-2-naphthoates. Further work is in progress to provide rational explanation for the steric course of the asymmetric coupling.

References

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2) H. Hotta, T. Suzuki, and S. Miyano, Chem. Lett., **1990**, 143.
3) For general overview of S_NAr reaction, see, J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, New York (1968).
4) A. I. Meyers and K. A. Lutomski, J. Am. Chem. Soc., **104**, 879 (1982).
5) J. M. Wilson and D. J. Cram, J. Org. Chem., **49**, 4930 (1984).
6) o-Alkoxybenzoic esters also undergo similar S_NAr reactions, details of which will be reported in future.
7) **1b**: $[\alpha]_D^{25}$ -97° (c 1.03, $CHCl_3$). **1c**: $[\alpha]_D^{25}$ -55° (c 0.945, $CHCl_3$). **1d**: $[\alpha]_D^{25}$ -27° (c 0.935, $CHCl_3$).
8) See Ref. 5 for the introduction of (-)-menthoxyl group into the 1-position of 2-oxazoline-activated 1-bromo or 1-methoxynaphthalene.
9) The absolute configuration of (+)-1-(9-phenanthryl)-2-naphthoic acid (**4**) was assigned to R by ^1H NMR study based on the fact that the methyl protons of (S)-1-phenylethyl ester resonate at lower field (δ = 0.59, d, J = 6.5 Hz) than those of (-)-acid ester (δ = 0.46, d, J = 6.5 Hz).[10b] (R)-**4** (65% ee): $[\alpha]_D^{25}$ +30° (c 1.05, THF). Generality of the NMR assignment of the axial chirality of 1,1'-binaphthyl-2-carboxylic acids as 1-phenylethyl esters will be published elsewhere. Absolute configurations of the other two binaphthylcarboxylic acids are known.[5]
10) a) S. Miyano, S. Okada, H. Hotta, M. Takeda, T. Suzuki, C. Kabuto, and F. Yasuhara, Bull. Chem. Soc. Jpn., **62**, 3886 (1989); b) S. Miyano, S. Okada, M. Takeda, C. Kabuto, and H. Hashimoto, ibid., **62**, 1528 (1989).
11) H. Hotta, T. Suzuki, S. Miyano, and Y. Inoue, J. Mol. Cat., **54**, L5 (1989).

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