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Nickel-Catalyzed Asymmetric Grignard Cross-Coupling of Dinaphthothiophene Giving Axially Chiral 1,1′-Binaphthyls

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Axially chiral biaryls represented by 1,1′-binaphthyls are known to create effective chiral environments for asymmetric reactions,[1] and growing attention has been paid to their synthesis by means of asymmetric catalysis. One of the most promising methods is the nickel- or palladium-catalyzed asymmetric cross-coupling,[2] which can be grouped into two types according to the mode of generation of the axial chirality. One is the cross-coupling of arylmagnesium[3] or -boron reagents[4] with aryl halides, where the axial chirality is generated at the formation of the biaryl skeleton. The other is the enantioposition-selective cross-coupling of achiral biaryl ditriflates, where one of the enantiotopic triflates participates in the cross-coupling.[5] Here we wish to report the third type of catalytic asymmetric cross-coupling, that is, the nickel-catalyzed reaction of dinaphtho[2,1-*b*:1′,2′-*d*]thiophene (**1**) with the Grignard reagents giving axially chiral 1,1′-binaphthyls (Scheme 1), where the axial chirality is generated at the cleavage of the carbon−sulfur bond in the thiophene ring.

It has been reported that the carbon−sulfur bond cleavage takes place in thiophene and benzothiophene in the reaction with the Grignard reagents under the catalysis by a nickel complex to give the cross-coupling products.[6] On the other hand, the dinaphthothiophene **1**, readily accessible from binaphthol,[7] is regarded as an achiral molecule because of the rapid flipping at ambient temperature,[8] and it is expected to become an axially chiral molecule once the thiophene ring undergoes the ring opening. We examined several reaction conditions, mainly chiral ligands of the nickel catalyst, for high catalytic activity and high enantioselectivity in the asymmetric cross-coupling of dinaphthothiophene **1** with 4-methylphenylmagnesium bromide (**2a**). It was found that the oxazoline-phosphine (*S*)-**4** containing an isopropyl substituent[9] is the most enantioselective of the ligands examined (Table 1). Thus, the reaction of **1** with 2 equiv of the Grignard reagent **2a** in the presence of 3 mol % of a nickel catalyst generated from $Ni(cod)_2$ [10] and ligand **4** in THF[11] at 20 °C for 120 h gave, after aqueous workup, 77% isolated yield of (*S*)-2-mercapto-2′-(4-methylphenyl)-1,1′-binaphthyl (**3a**), whose enantiomeric purity was determined to be 95% ee by HPLC analysis with a chiral stationary phase column (entry 1 in Table 1). Use of a large excess (10 equiv) of the Grignard reagent **2a** gave 97% yield of (*S*)-**3a** within 24 h (entry 2). The phenyl-substituted oxazoline-phosphine (*R*)-**5** was the second best, giving (*R*)-**3a** of 86% ee (entry 3). Other chiral phosphine ligands **6**−**9** including those used successfully for other types of asymmetric cross-coupling[3−5] were much less enantioselective than the oxazoline-phosphine ligands for the present reaction (entries 4−7). The reaction with the phenyl (**2b**) and 4-methoxyphenyl (**2c**) Grignard reagents also proceeded with high enantioselectivity in the presence of the nickel catalyst of (*S*)-**4** to give the corresponding binaphthylthiols **3b** and **3c** with over 93% enantioselectivity (entries 8 and 9). For the introduction of the methyl group, MOP ligand (*S*)-**8**[12] was more effective than the oxazoline-phosphine (*S*)-**4** in terms of both catalytic activity and enantioselectivity (entries 10 and 11).

According to the catalytic cycle generally accepted for the nickel-catalyzed cross-coupling,[13] the present reaction involves nickelacycle **10** which is formed by oxidative addition of dinaphthothiophene **1** to a nickel(0) species[14] (Scheme 2). Transmetalation of the aryl or alkyl group from the Grignard reagent to **10** leads to

Scheme 1

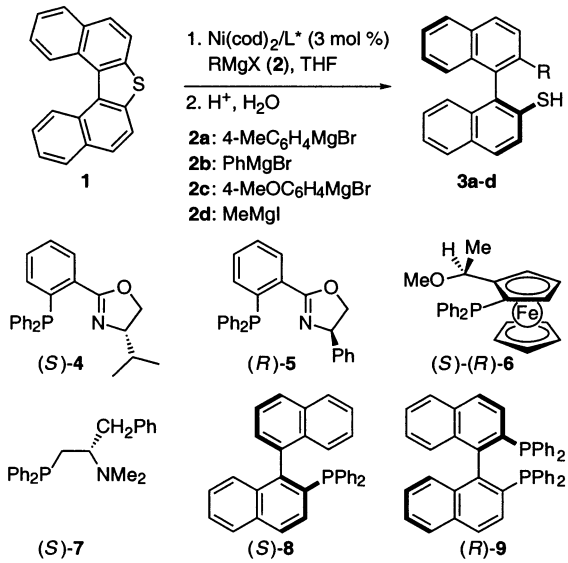

Table 1. Nickel-Catalyzed Asymmetric Cross-Coupling of **1** with the Grignard Reagents **2**[a]

entry	ligand (eq to Ni)	R in RMgX (**2**)	temp (°C)	time (h)	yield of **3** (%)[b]	% ee of **3**[c] (config)
1[d]	(*S*)-**4** (1.5)	4-MeC_6H_4	20	120	77	95 (*S*)
2	(*S*)-**4** (1.5)	4-MeC_6H_4	20	24	97	95 (*S*)
3	(*R*)-**5** (1.5)	4-MeC_6H_4	20	30	90	86 (*R*)
4	(*S*)-(*R*)-**6** (3.0)	4-MeC_6H_4	20	12	88	3 (*S*)
5	(*S*)-**7** (1.5)	4-MeC_6H_4	20	8	86	1 (*S*)
6	(*S*)-**8** (3.0)	4-MeC_6H_4	20	10	93	14 (*S*)
7	(*R*)-**9** (1.5)	4-MeC_6H_4	20	10	72	2 (*S*)
8	(*S*)-**4** (1.5)	Ph	20	24	92	95 (*S*)
9	(*S*)-**4** (1.5)	4-$MeOC_6H_4$	20	30	96	93 (*S*)
10	(*S*)-**4** (1.5)	Me	0	24	54	54 (*R*)
11	(*S*)-**8** (3.0)	Me	10	24	97	68 (*R*)

[a] The reaction was carried out with 10 equiv of Grignard reagent in the presence of 3 mol % of $Ni(cod)_2$/ligand in THF unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis of the phenylcarbamate ester of thiol **3** with chiral stationary phase columns: Chiralpak AD (**3a**, **3c**, **3d**) (hexane/2-propanol = 90/10) and Chiralcel OD-H (**3b**) (hexane/2-propanol = 90/10). [d] Reaction with 2 equiv of **2a**.

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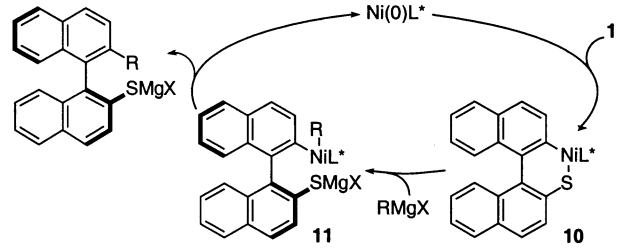
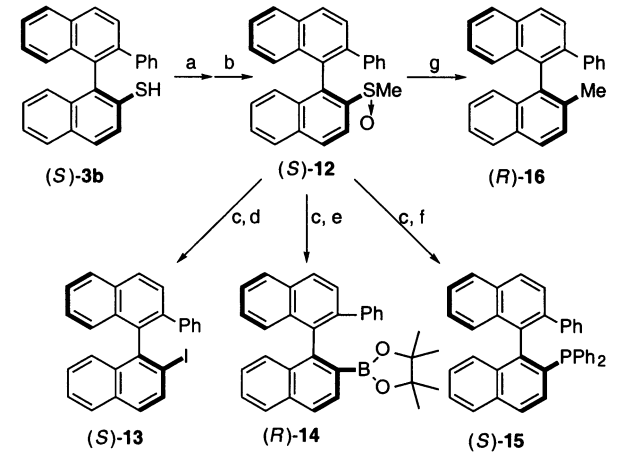
Scheme 2



Scheme 3 [a]



[a] Reaction conditions: (a) MeI, K_2CO_3, acetone, room temperature, 99%; (b) *m*CPBA, CH_2Cl_2, 0 °C, 92%; (c) EtMgBr, THF, room temperature; (d) I_2, room temperature, 67%; (e) (i) $B(OMe)_3$, (ii) 10% HCl, (iii) pinacol, benzene, reflux 48%; (f) Ph_2PCl, room temperature, 62%; (g) $Ni(acac)_2$, MeMgI, THF, 50 °C, 76%.

diorganonickel intermediate **11**, the reductive elimination from which gives the cross-coupling product. The dependency of the enantioselectivity on the Grignard reagent observed here may indicate that the stereochemical outcome is determined at or after the transmetalation step.

The axially chiral cross-coupling products **3** are versatile intermediates for further transformation, the mercapto group being replaced by some functional groups by way of the methylsulfinyl group. Thus, the 2-methylsulfinylbinaphthyl **12**, obtained by methylation of the mercapto group in (*S*)-**3b**[15] (95% ee) followed by oxidation of the sulfide with peracid, was allowed to react with ethylmagnesium bromide in THF[16] to generate a binaphthylmagnesium bromide, treatment of which with electrophiles gave iodide (*S*)-**13**, boronate (*R*)-**14**, and phosphine (*S*)-**15**[15,17] without racemization (Scheme 3). The substitution of the methylsulfinyl group with an alkyl group is also possible by nickel-catalyzed cross-coupling. For example, the cross-coupling of **12** with the methyl Grignard reagent proceeded in refluxing THF to give a high yield of the methylation product **16**.

In conclusion, we have described a new efficient route to axially chiral 1,1′-binaphthyls, which has been realized by nickel-catalyzed asymmetric cross-coupling of dinaphthothiophene **1** with the Grignard reagents. This asymmetric reaction is formally classified as a dynamic kinetic resolution of the starting chiral substrate.[18] The dinaphthothiophene **1** is a chiral molecule but undergoes racemization much faster than the catalytic cross-coupling reaction, and, after the asymmetric carbon−carbon bond formation, the racemization does not take place. Studies on catalytic asymmetric synthesis of various kinds of axially chiral biaryls using this type of methodology are in progress.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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