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Enantioselectivity and Chemoselectivity in Palladium-Catalyzed Grignard Cross-Coupling of Aryl Triflates

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CONTENTS

General Introduction

Carbon-carbon bond forming reactions are indispensable for construction of the carbon skeletons in synthetic organic chemistry. Recently, dramatic progress in organometallic chemistry has made a significant contribution to development of the carbon-carbon bond formation.[1] The reactions catalyzed by transition metal complexes play an essential role on synthesis of complicated compounds such as natural products, and more complicated and highly substituted building blocks are needed to synthesize various chemical products like medical compounds. The importance of optically active molecules stems from the central role of enantiomer recognition in biological activity. Of the various methods to obtain the optically active compounds in chemical reactions, catalytic asymmetric synthesis using transition metal complexes is an ideal and practical method, because a large amount of chiral product can be produced enantioselectively from achiral material and a small amount of chiral catalyst.[2]

One of the most general methods for the carbon-carbon bond formation is the cross-coupling reaction of organic halides or pseudo-halides with organometallic reagents catalyzed by transition metal complexes (Scheme 1).[1] Above all, Grignard cross-coupling reaction, discovered by Kumada[3] and Corriu[4] in 1972, is a powerful method and widely used for carbon-carbon bond formation because of its high reactivity and simplicity to prepare the reagents. The reaction has been also applied to asymmetric synthesis.[5,6] Hayashi et al. succeeded in synthesizing optically active biaryls by the Grignard cross-coupling by use of nickel catalyst coordinated with a chiral ligand.[7]

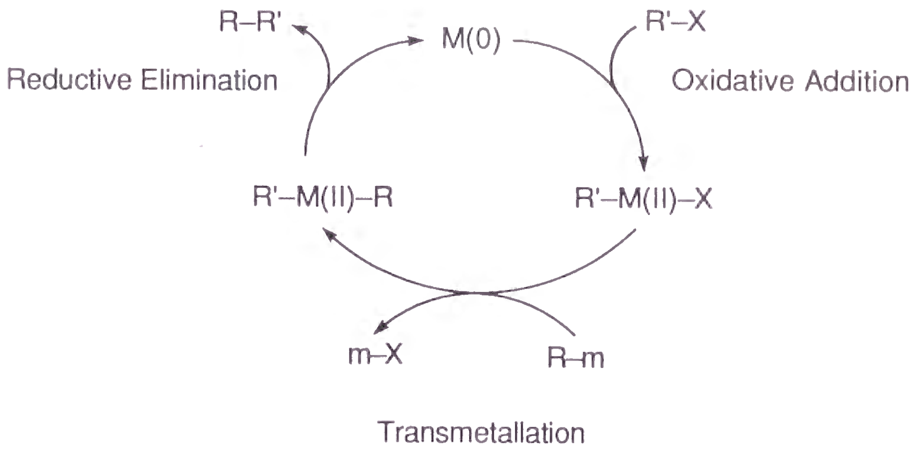
Scheme 1

$$\mathrm{R{-}m} \quad + \quad \mathrm{R'{-}X} \quad \xrightarrow{\mathrm{ML_n}\text{ (catalyst)}} \quad \mathrm{R{-}R'} \quad + \quad \mathrm{m{-}X}$$

M = Ni, Pd
m = Mg, Zn, Al, B, Si
X = Cl, Br, I, OTf

In general, the catalytic cycle of the cross-coupling reaction using transition metal complexes involves 3 steps, that is, 1) oxidative addition step, 2) transmetallation step, 3) reductive elimination step (Scheme 2).[1] At the oxidative addition step, carbon-metal bond is formed on the transition metal catalyst. Therefore, the enantioselectivity or chemoselectivity in the catalytic cross-coupling is determined at this oxidative addition step, the subsequent transmetallation and reductive elimination steps not affecting the overall selectivity. If one can control the enantioselectivity at the oxidative addition, asymmetric synthesis can be achieved not only in the cross-coupling but also in Heck reaction and carbonylation that proceed through a similar catalytic cycle. There have been no catalytic asymmetric reactions which control the enantioselectivity at the oxdative addition step and

Scheme 2

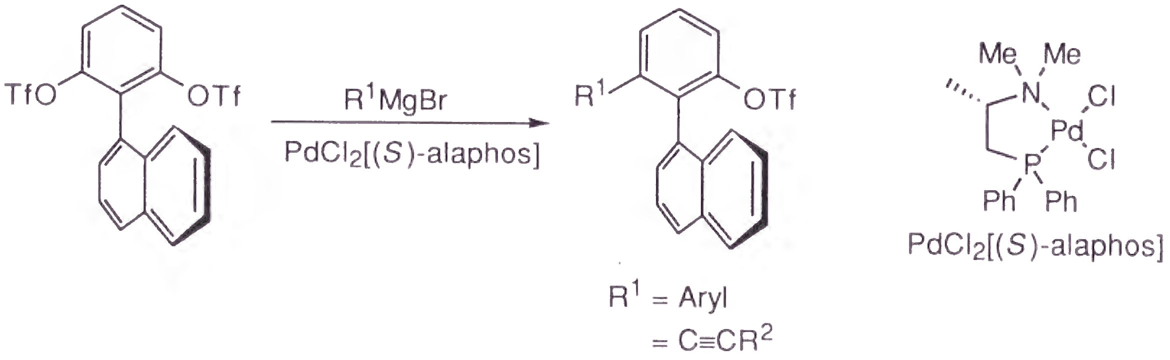


only a few examples have been known where the chemoselective cross-coupling reaction of aromatic compounds containing two different leaving groups is achieved.[8]

From these viewpoints, attention was focused on developing novel methods to control the enantioselectivity and chemoselectivity in the Grignard cross-coupling reactions. Axially chiral biaryls were chosen for the target compounds, because optically active biaryls, such as BINAP[9] and MOP[10], are very useful as chiral ligands for transition metal catalysts which induce high enantioselectivity in asymmetric synthesis. It would be useful to synthesize novel optically active biaryls which could not be obtained by other conventional methods.[11] In this thesis, the enantioselective Grignard cross-coupling reactions of pro-chiral biaryls containing two identical leaving groups at enantiotopic positions in the presence of transition metal catalyst are discussed. The Grignard cross-coupling reaction of several aromatic compounds containing both bromide and trifluoromethanesulfonyloxy group was also studied in order to achieve the chemoselective reactions.

The first two chapters are related to the enantioposition-selective Grignard cross-coupling of achiral symmetric biaryls containing two trifluoromethanesulfonyloxy groups at ortho-positions.

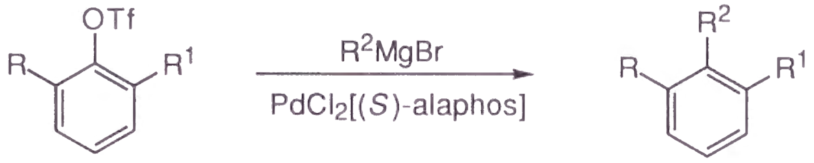
In Chapter 1, is described an enantioposition-selective Grignard cross-coupling with the aryl Grignard reagents. Optically active monoarylated biaryls were obtained high enantioselectivity in high yields in the presence of palladium catalyst $PdCl_2[(S)$-alaphos], where alaphos stands for 2-



dimethylamino-1-diphenylphosphino-3-methylpropane.

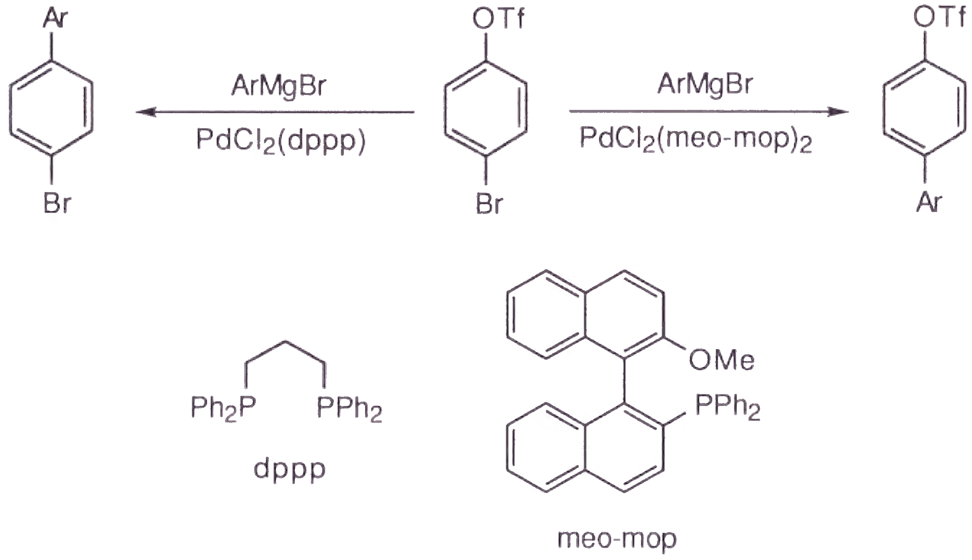
Chapter 2 is concerned with enantioposition-selective Grignard cross-coupling with alkynyl Grignard reagents, where alkynyl groups were introduced with higher enantioselectivity to give monoalkynylated products of up to > 99% ee.

Chapter 3 is concerned with the effect of phosphine ligands on the catalytic activity of the palladium-catalyzed cross-coupling of sterically congested aryl triflates with aryl Grignard reagents. Dichloro[1,3-bis(diphenylphosphino)propane]palladium ($PdCl_2(dppp)$) and $PdCl_2$-(alaphos) were found to be much more effective catalysts than other palladium complexes.

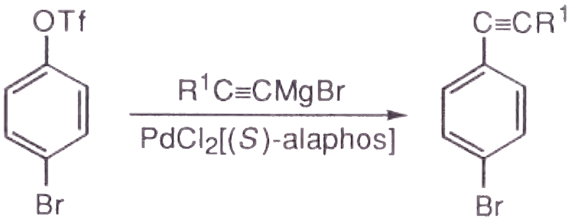


The last two chapters are related to the chemoselective Grignard cross-coupling of aromatic compounds containing both bromide and trifluoromethanesulfonyloxy group, which are known to have almost the same reactivity towards cross-coupling type reactions.

Chapter 4 deals with chemoselective Grignard cross-coupling reactions of bromoaryl triflates with aryl Grignard reagents. Reactive site of the cross-coupling depended on the phosphine ligands in palladium catalysts. It was revealed that only trifluoromethanesulfonyloxy group reacted chemoselectively in the presence of $PdCl_2(dppp)$. On the other hand, bromide was substituted with the aryl Grignard reagent selectively by use of $PdCl_2(meo\text{-}mop)_2$. The selective substitution was demonstrated to take place at the oxidative addition step to a palladium(0) species in a stoichiometric reaction of a bromophenyl triflate with palladium(0) phosphine complexes.



Chapter 5 is concerned with Grignard cross-coupling reaction of bromoaryl triflates with alkynyl Grignard reagents. $PdCl_2$(alaphos) was found to be much more effective as catalyst than other palladium complexes for the cross-coupling of aryl triflates. Alkynylarene bromides were formed by selective replacement of triflate in bromoaryl triflates by alkynyl group in the presence of $PdCl_2$(alaphos).



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Chapter 1

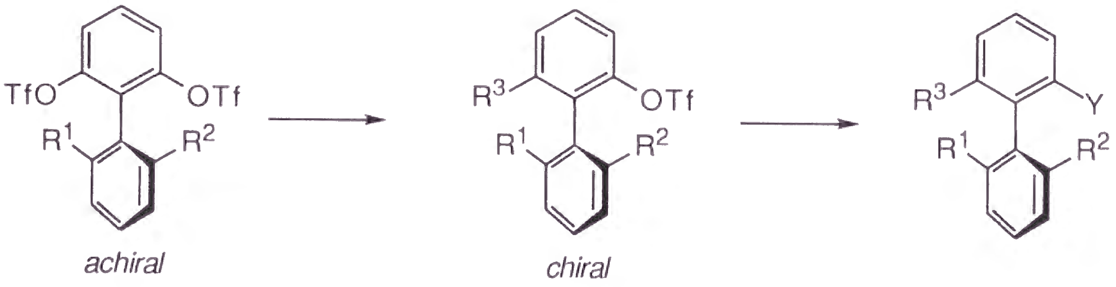
Enantioposition-Selective Arylation of Biaryl Ditriflates by Palladium-Catalyzed Asymmetric Grignard Cross-Coupling

Abstract: Asymmetric cross-coupling of achiral biaryl ditriflates with aryl Grignard reagents in the presence of 1 equiv of lithium bromide and 5 mol % of palladium complex $PdCl_2[(S)$-alaphos], where alaphos stands for 2-dimethylamino-1-diphenylphosphino-3-methylpropane, gave axially chiral monophenylated biaryl with high enantioposition-selectivity. The remained triflate group in the monophenylated biaryl was substituted with carboxyl and diphenylphosphino groups through palladium-catalyzed carbonylation and diphenylphosphinylation, respectively.

Introduction

Optically active biaryls represented by 1,1'-binaphthyls have found extensive use in chiral auxiliaries for a variety of synthetic asymmetric reactions including catalytic ones,[1,2] and considerable attention has been paid to their preparation by asymmetric synthesis. In most of the asymmetric syntheses so far reported, the axial chirality of biaryls has been generated at the coupling of two aryl units.[3] In this chapter, is described a new catalytic method for the preparation of axially chiral biaryls which is realized by an enantioposition-selective substitution reaction of one of the two enantiotopic triflate groups on achiral biaryl ditriflates (Scheme 1). The monoalkylated biaryls obtained here are very useful as axially chiral building blocks because the remaining triflate group can be readily substituted with some other functional groups by transition-metal-catalyzed coupling-type reactions.

Scheme 1

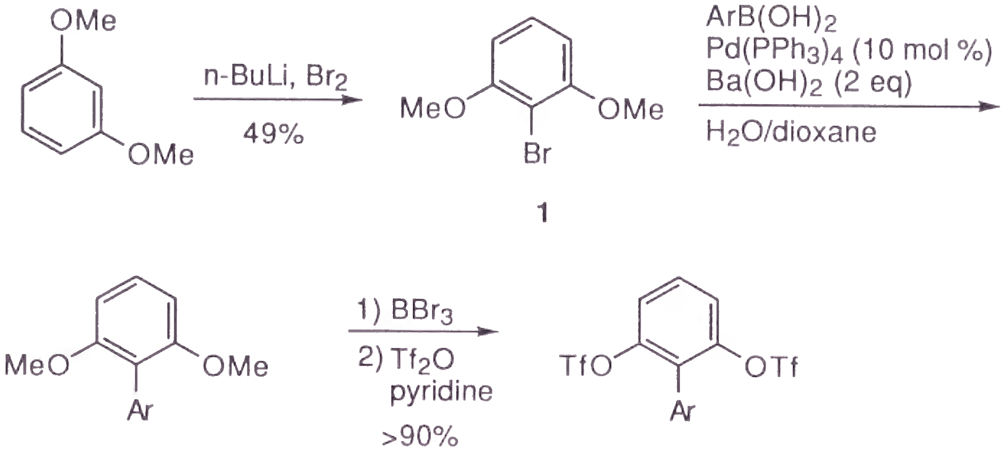


Results and Discussion

Ditriflates **5**, **6**, and **7** as substrates for the cross-coupling were prepared according to Scheme 2. Lithiation of *m*-dimethoxybenzene followed by bromination gave 2,6-

dimethoxyphenyl bromide (**1**). Suzuki coupling of **1** with arylboronic acids in the presence of $Ba(OH)_2$ and 10 mol % of $Pd(PPh_3)_4$ in dioxane/H_2O gave biaryl products **2**, **3**, and **4**. Ditriflates **5**, **6**, and **7** were obtained by demethylation using BBr_3 followed by ditriflation of the resulting phenols with trifluoromethanesufonic anhydride.

Scheme 2

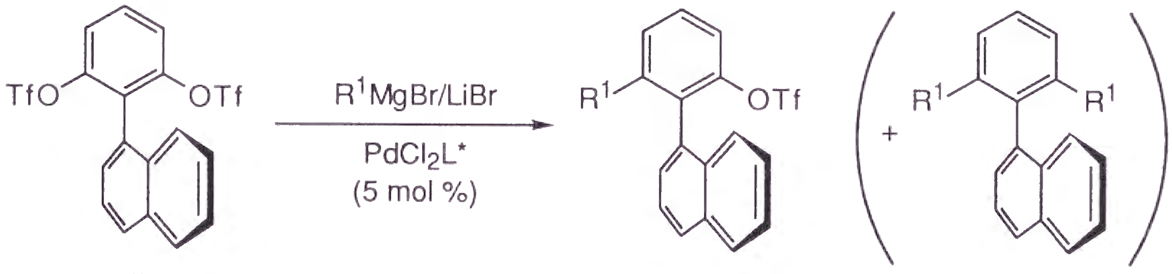


2: Ar = 1-naphthyl 93%
3: Ar = 2-MeC_6H_4 94%
4: Ar = 2-PhC_6H_4 63%

5: Ar = 1-naphthyl
6: Ar = 2-MeC_6H_4
7: Ar = 2-PhC_6H_4

For the cross-coupling of 1-[2,6-bis(trifluoromethanesulfonyloxy)phenyl]naphthalene (**5**) with phenylmagnesium bromide, several chiral phosphine-palladium complexes were examined for their catalytic activity and enantioselectivity (Scheme 3). The results are summarized in Table 1.

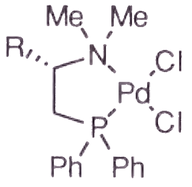
Scheme 3



5

8a: R^1 = Ph

9a



R = CH_3: $PdCl_2[(S)$-alaphos]
R = $PhCH_2$: $PdCl_2[(S)$-phephos]
R = $(CH_3)_2CH$: $PdCl_2[(S)$-valphos]
R = $(CH_3)_3C$: $PdCl_2[(S)$-*t*-leuphos]

Table 1. Effects of Phosphine Ligands on the Cross-Coupling of Ditriflate **5a** with Phenylmagnesium Bromide[a]

entry	catalyst	recovered ditriflate (%)[b]	yield of **8** (%)[b]	yield of **9** (%)[b]	% ee of **8**[c]
1	$PdCl_2$[(*S*)-alaphos]	0	84 (**8a**)	10 (**9a**)	90 (*S*)
2	$PdCl_2$[(*S*)-phephos]	0	87 (**8a**)	12 (**9a**)	86 (*S*)
3	$PdCl_2$[(*S*)-valphos]	28	56 (**8a**)	9 (**9a**)	78 (*S*)
4	$PdCl_2$[(*S*)-*t*-leuphos]	64	24 (**8a**)	0 (**9a**)	49 (*S*)
5	$PdCl_2$[(*S*)-*i*-Pr-PHOX]	47	26 (**8a**)	11 (**9a**)	52 (*S*)
6	$PdCl_2$[(*S*)-(*R*)-PPFA]	69	27 (**8a**)	3 (**9a**)	0
7	$PdCl_2$[(+)-DIOP]	82	6 (**8a**)	0 (**9a**)	46 (*R*)
8	$PdCl_2$[(*S*)-BINAP]	92	2 (**8a**)	0 (**9a**)	0
9	$PdCl_2$[(*R*)-MeO-MOP$]_2$	85	7 (**8a**)	0 (**9a**)	40 (*R*)

[a] The cross-coupling was carried out with 2 equiv of Grignard reagent in the presence of 1 equiv of LiBr and 5 mol % palladium catalyst in ether/toluene (1:1) at –20 °C for 48 h. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis of phenol obtained by alkaline hydrolysis of triflate **8**: Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1).

The reaction was carried out with 2 equiv of phenylmagnesium bromide in the presence of 1 equiv of LiBr and 5 mol % of phosphine-palladium complex in ether/toluene (1:1) at –20 °C for 48 h. The enantiomeric purity of a chiral monophenylated biaryl **8a** was determined by HPLC analysis of phenol obtained by alkaline hydrolysis of **8a** using a chiral stationary phase column. It was found that the palladium complexes coordinated with β-(dimethylamino)alkyldiphenylphosphines are highly effective as catalysts.[4] The reactivity was highest in the reaction with alaphos and phephos ligand, which gave **8a** of 84% yield and 87% yield, respectively (entries 1 and 2). The highest enantioselectivity was observed in the reaction with alaphos ligand, which gave **8a** of 90% ee (entry 1). It was found that the phosphine ligand with the smaller substituent at the chiral carbon atom induced the higher stereoselectivity, that is the order of efficiency for asymmetric induction is alaphos > phephos > valphos > *t*-leuphos (entries 1-4).

The reaction also took place with oxazoline-phosphine ligand *i*-Pr-PHOX[5] giving 26% yield of **8a**, whose enantiometric excess was 52% ee (entry 5). A palladium complex of ferrocenylphosphine, (*S*)-(*R*)-PPFA,[3e] was as catalytically active as that of *i*-Pr-PHOX, but **8a** was racemic (entry 6). The reaction was very slow with palladium complexes coordinated with bisphosphine ligands, DIOP[6] or 2,2'-bis(diphenylphosphino)-1,1'-binapthyl (BINAP)[2] (entries 7, 8). The palladium complex coordinated with monodentate phosphine ligand, 2-(diphenylphosphino)-2'-methoxy-1,1'-binapthyl (MeO-MOP) was much less catalytically active, which gave **8a** of 7%

Table 2. Effects of Metal Salts on the Cross-Coupling of Ditriflate **5a** with Phenylmagnesium Bromide Catalyzed by $PdCl_2$[(*S*)-alaphos][a]

entry	metal salts (eq)	recovered ditriflate (%)[b]	yield of **8** (%)[b]	yield of **9** (%)[b]	% ee of **8**[c]
1	none	69	21 (**8a**)	3 (**9a**)	53 (*S*)
2	LiCl (1)	58	33 (**8a**)	3 (**9a**)	71 (*S*)
3	LiBr (1)	0	84 (**8a**)	10 (**9a**)	90 (*S*)
4	LiI (1)	22	70 (**8a**)	2 (**9a**)	93 (*S*)
5	LiBr (1)[d]	0	87 (**8a**)	10 (**9a**)	86 (*S*)
6	LiI (1)[d]	53	35 (**8a**)	2 (**9a**)	88 (*S*)
7	LiBr (2)	52	39 (**8a**)	5 (**9a**)	87 (*S*)
8	LiBr (0.5)	26	66 (**8a**)	5 (**9a**)	87 (*S*)
9	LiBr (0.1)	37	45 (**8a**)	7 (**9a**)	77 (*S*)
10	LiI (2)	92	4 (**8a**)	0 (**9a**)	88 (*S*)
11	LiI (0.5)	21	71 (**8a**)	3 (**9a**)	94 (*S*)
12	LiI (0.25)	28	61 (**8a**)	3 (**9a**)	92 (*S*)
13	LiI (0.1)	40	48 (**8a**)	3 (**9a**)	90 (*S*)
14	Bu_4NI (1)	72	23 (**8a**)	5 (**9a**)	76 (*S*)
15	$MgBr_2$ (1)	69	20 (**8a**)	2 (**9a**)	63 (*S*)

[a] The cross-coupling was carried out with 2 equiv of Grignard reagent in the presence of 1 equiv of metal salts and 5 mol % palladium catalyst in ether/toluene (1:1) at –20 °C for 48 h. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis of phenol obtained by alkaline hydrolysis of triflate **8**: Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1). [d] The reaction was carried out in the presence of 5 mol % of $PdCl_2$[(*S*)-phephos].

yield, though the enantiomerically excess of **8a** was 40% (entry 9).

The effects of the addition of metal salts on the reactivity and the enantioselectivity are summarized in Table 2. The reactions were carried out with 5 mol % of $PdCl_2$[(*S*)-alaphos] at –20 °C. In the presence of 1 equiv of LiBr or LiI, the reactivity and enantioselectivity were higher than those in the absence of metal salts (entries 3 and 4).[7] The highest reactivity was observed with LiBr, while the highest enantioselectivity was achieved by use of LiI. The same tendency of effect of Li salts was observed with (*S*)-phephos ligand (entries 5 and 6). When 2 equiv of LiBr was used, enantioselectivity (87% ee) was somewhat lower, but the chemical yield was extremely low (39%) (entries 3 and 7). Drops in reactivity and in enantioselectivity were observed when decreasing the amount of LiBr (entries 8 and 9). The same phenomenon was also observed with LiI (entries 10-13). The addition of Bu_4NI or $MgBr_2$ raised slightly the enantiomeric purity of

Table 3. Effects of Reaction Temperature on the Cross-Coupling of Ditriflate **5a** with Phenylmagnesium Bromide Catalyzed by $PdCl_2[(S)\text{-alaphos}]^a$

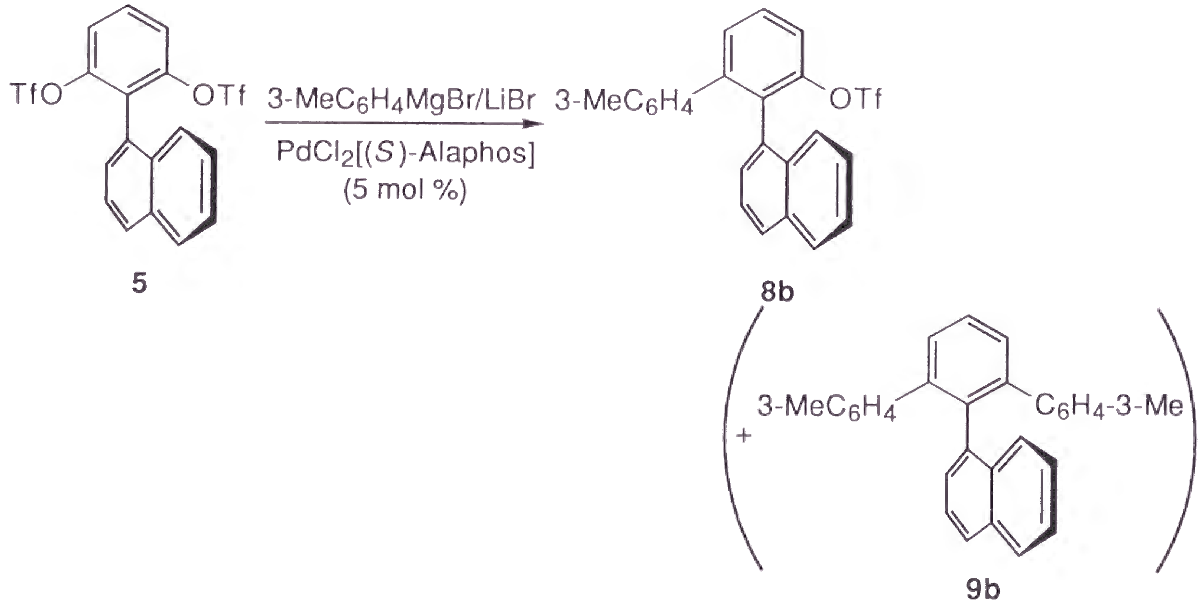
entry	reaction temp (°C)	reaction time (h)	recovered ditriflate (%)[b]	yield of **8** (%)[b]	yield of **9** (%)[b]	% ee of **8**[c]
1	–20	48	22	70 (**8a**)	2 (**9a**)	93 (*S*)
2	–10	48	0	92 (**8a**)	6 (**9a**)	94 (*S*)
3	0	20	0	78 (**8a**)	18 (**9a**)	91 (*S*)

[a] The cross-coupling was carried out with 2 equiv of Grignard reagent in the presence of 1 equiv of LiI and 5 mol % palladium catalyst in ether/toluene (1:1). [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis of phenol obtained by alkaline hydrolysis of triflate **8**: Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1).

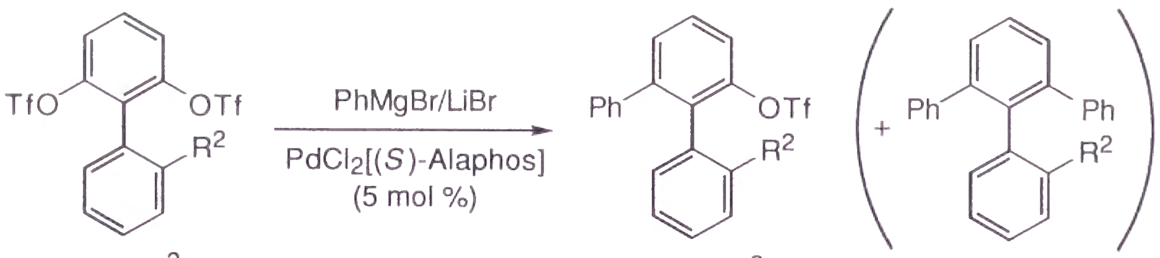
8a, but did not affect the chemical yield (entries 14 and 15). It has been observed that only LiBr was completely soluble during the course of reaction. Thus, acceleration of reactivity by addition of LiBr may be due to the solubility of the salt. As shown in Table 2, addition of LiI is effective for the induction of higher enantioselectivity. In order to optimize the reaction conditions, the effect of reaction temperature was examined. The results are summarized in Table 3. The reaction was completed at –10 °C in 48 h, which gave 92% yield of **8a** in 95% ee.

High enantioselectivity was also observed in the reaction of **5** with *m*-tolylmagnesium bromide under the same conditions, which gave 90% yield of the corresponding monoarylation product **8b** in 95% ee (Scheme 4, Table 4, entry 1) . The asymmetric phenylation was also successful for 1-[2,6-bis(trifluoromethanesulfonyloxy)phenyl]-2-methylbenzene (**6**) and 2-

Scheme 4



Scheme 4 (continued)



6: R^2 = Me
7: R^2 = Ph

8c: R^2 = Me
8d: R^2 = Ph

9c-d

phenylbenzene analog **7**. The reaction of **6** with phenylmagnesium bromide in the presence of 1 equiv of LiI at −10 °C gave 85% yield of **8c** in 95% ee (entry 7). The reaction of **7** with phenylmagnesium bromide in the presence of 1 equiv of LiI at −10 °C gave 80% yield of **8d** in 94% ee (entry 8).

Table 4. Asymmetric Cross-Coupling of Ditriflates **5**-**7** with Grignard Reagents Catalyzed by $PdCl_2[(S)$-alaphos$]$[a]

entry	ditriflate	Grignard reagent	reaction temp (°C)	reaction time (h)	recovered ditriflate (%)[b]	yield of **8** (%)[b]	yield of **9** (%)[b]	%ee of **8**[c]
1	**5**	$3\text{-}MeC_6H_4MgBr$	−10	72	22	90 (**8b**)	2 (**9b**)	95 (*S*)
2	**5**	$3\text{-}MeC_6H_4MgBr$	0	48	12	73 (**8b**)	10 (**9b**)	92 (*S*)
3	**5**	$2\text{-}MeC_6H_4MgBr$	−10	48		NR		
4	**5**	$4\text{-}MeC_6H_4MgBr$	−10	48		NR		
5	**5**	$4\text{-}ClC_6H_4MgBr$	−10	48		NR		
6	**5**	*i*-BuMgBr	−10	48		NR		
7[d]	**6**	PhMgBr	−10	72	0	85 (**8c**)	15 (**9c**)	95
8[d]	**7**	PhMgBr	−10	72	11	80 (**8d**)	8 (**9d**)	94

[a] The cross-coupling was carried out with 2 equiv of Grignard reagent in the presence of 1 equiv of LiI and 5 mol % palladium catalyst in ether/toluene (1:1) for 48 h. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis of phenol obtained by alkaline hydrolysis of triflate **8**: For entries 1-6, Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1); for entries 7, Chiralcel OD-H (hexane/2-propanol = 95/5); for entries 8, Chiralcel AD (hexane/2-propanol = 95/5). [d] The cross-coupling was carried out with 3 equiv of Grignard reagent in the presence of 1 equiv of LiI.

Table 5. Relationship between Conversion and Enantiomeric Exess in the Cross-Coupling Ditriflate **5a** with Phenylmagnesium Bromide[a]

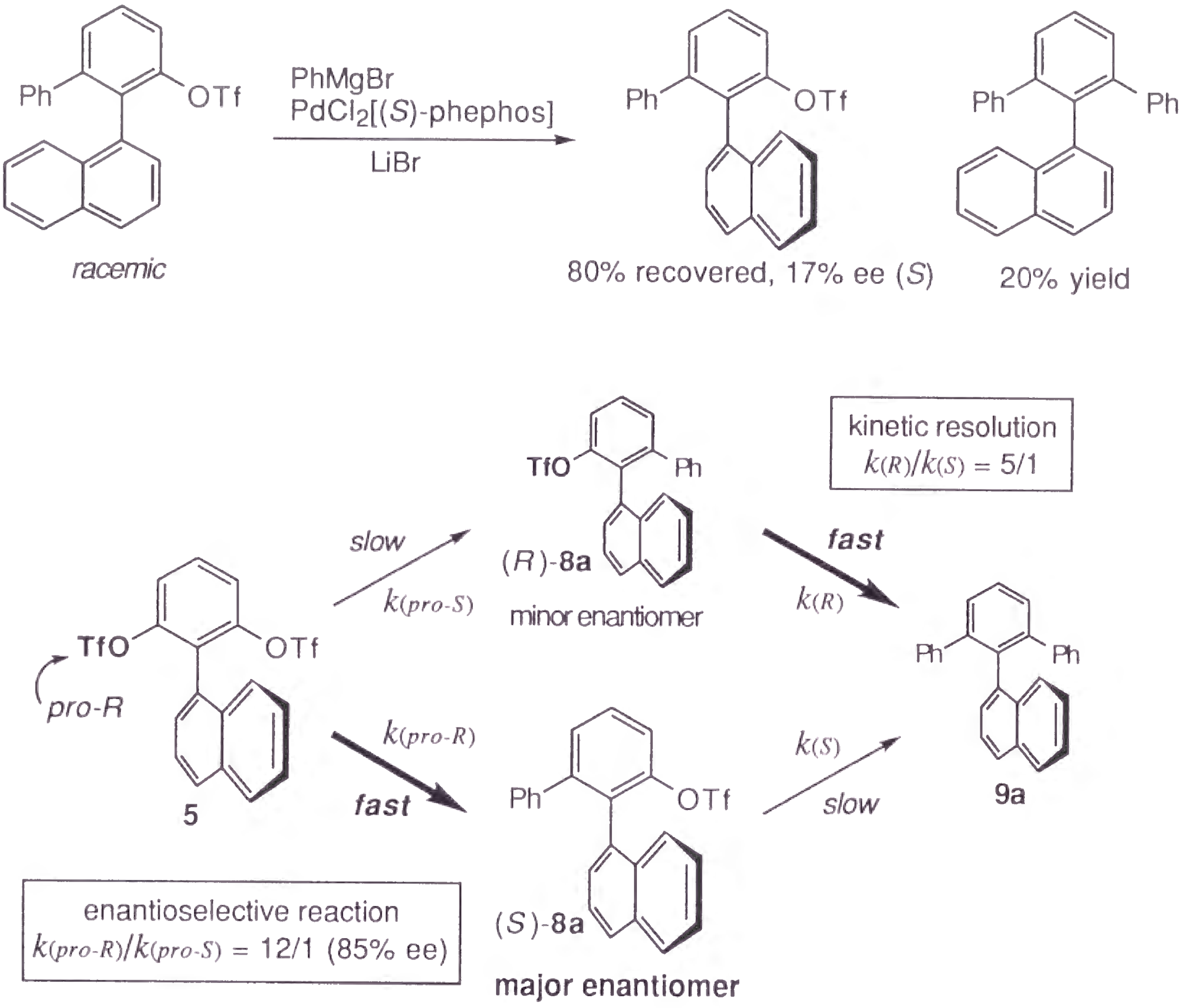
entry	catalyst	Li salt	reaction temp (°C)	reaction time (h)	recovered ditriflate (%)[b]	yield of **8** (%)[b]	yield of **9** (%)[b]	%ee of **8**[c]
1[d]	$PdCl_2$[(*S*)-phephos]	LiBr	–30	16	60	39 (**8a**)	0 (**9a**)	85 (*S*)
2	$PdCl_2$[(*S*)-phephos]	LiBr	–30	48	0	87 (**8a**)	13 (**9a**)	93 (*S*)
3	$PdCl_2$[(*S*)-alaphos]	LiBr	–20	12	57	40 (**8a**)	1 (**9a**)	87 (*S*)
4	$PdCl_2$[(*S*)-alaphos]	LiBr	–20	48	0	84 (**8a**)	10 (**9a**)	90 (*S*)
5	$PdCl_2$[(*S*)-alaphos]	LiBr	–20	72	0	75 (**8a**)	25 (**9a**)	90 (*S*)
6	$PdCl_2$[(*S*)-alaphos]	LiI	–10	12	69	30 (**8a**)	0 (**9a**)	94 (*S*)
7	$PdCl_2$[(*S*)-alaphos]	LiI	–10	48	0	92 (**8a**)	6 (**9a**)	94 (*S*)

[a] The cross-coupling was carried out with 2 equiv of Grignard reagent in the presence of 1 equiv of LiBr or LiI and 5 mol % palladium catalyst in ether/toluene (1:1) . [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis of phenol obtained by alkaline hydrolysis of triflate **8**: Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1). [d] The cross-coupling was carried out with 1.1 equiv of Grignard reagent.

It was found in the asymmetric cross-coupling of ditriflate **5** with PhMgBr that the enantiomeric purity of **8a** was dependent on the yield of diphenylation product **9a**. Thus, in entry 2 (Table 5), where the reaction was accompanied by the formation of 13% yield of diphenylation product **9a** in the presence of 1 equiv of LiBr and 5 mol % of $PdCl_2$[(*S*)-phephos] at –30 °C, the enantiomeric purity of **8a** was 93% ee, higher than that of **8a** obtained in entry 1 where the reaction was quenched before **9a** was formed. That is, in this asymmetric cross-coupling of ditriflate **5**, the enantiomeric purity of **8a** was dependent on the yield of **9a**.

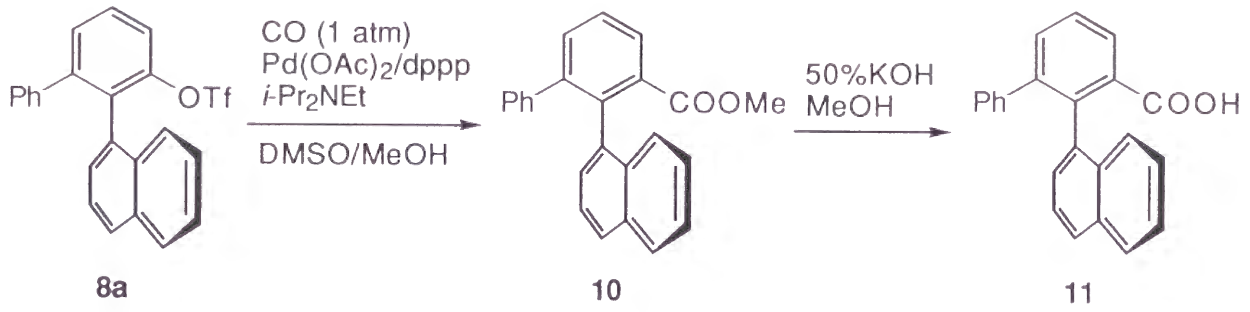
A kinetic resolution at the second cross-coupling was demonstrated by a control experiment using racemic **8a** (Scheme 5). At 20% conversion to diphenylation product **9a**, the recovered **8a** was an (*S*)-isomer with 17% ee, indicating that the (*R*)-isomer of **8a** undergoes the phenylation about 5 times faster than its (*S*)-isomer ($k(R)/k(S) = 5/1$). It follows that the minor enantiomer of **8a** formed at the first asymmetric cross-coupling is consumed preferentially at the second asymmetric cross-coupling, which causes an increase of enantiomeric purity of **8a** as the amount of diphenylation product **9a** increases.[8] The kinetic resolution was also observed in the reaction with alaphos/LiBr (entries 3-5), but not observed in a combination of alaphos with LiI (entries 6 and 7).

Scheme 5

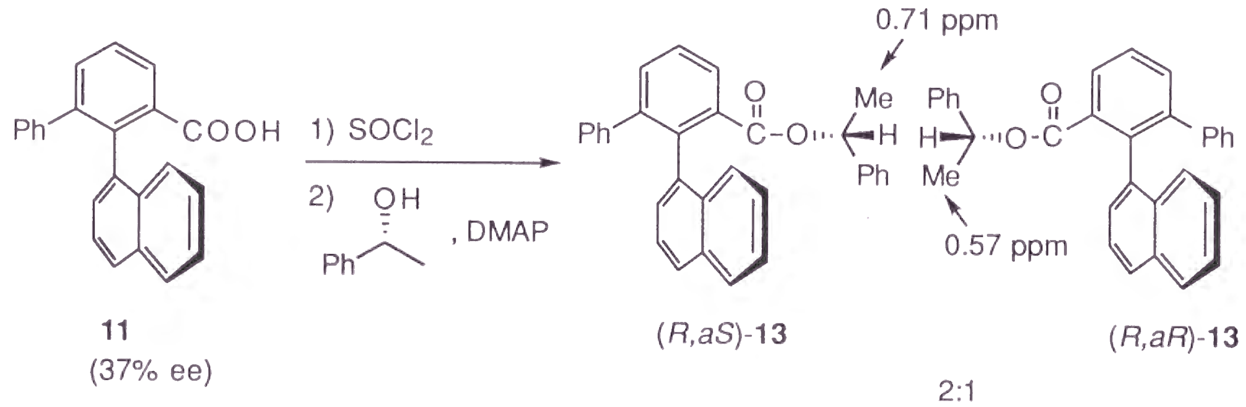


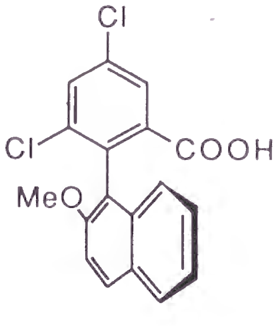
The monoalkylated biaryls **8** obtained here are very useful as axially chiral building blocks because the remaining triflate group can be readily substituted with some other functional groups by transition-metal-catalyzed coupling-type reactions.[9] For example, enantiomerically pure mono-triflate (*S*)-**8a** was converted into methyl ester (*S*)-**10** and carboxylic acid (*S*)-**11** in high yields by palladium-catalyzed carbonylation.[10] The carboxylic acid (*S*)-**11** is a useful alternative for Fukushi's biarenecarboxylic acid **12** that has been successfully used for the determination of absolute configuration of secondary alkyl alcohols by NMR spectroscopy.[11] It has been reported that, for example, the methyl NMR signals of (*aR*)-**12** and (*aS*)-**12** of (*R*)-1-phenylethanol appear upfield (0.68 ppm, 0.50 ppm, respectively) relative to that of the original alcohols (0.91 ppm). Then **11** (37% ee) was esterified with (*R*)-1-phenylethanol to give two diastereomers **13**. The NMR spectrum showed two doublets in 2:1 ratio which are derived from methyl groups of phenylethyl moiety. These signals appeared upfield (0.71 ppm, 0.57 ppm, respectively) relative to that of the original alcohol, similar to the case of **12**. Thus, the absolute configuration of the major diastereoisomer whose methyl signal appears downfield should be (*R*,*aS*), and the other minor

Scheme 6



Scheme 7



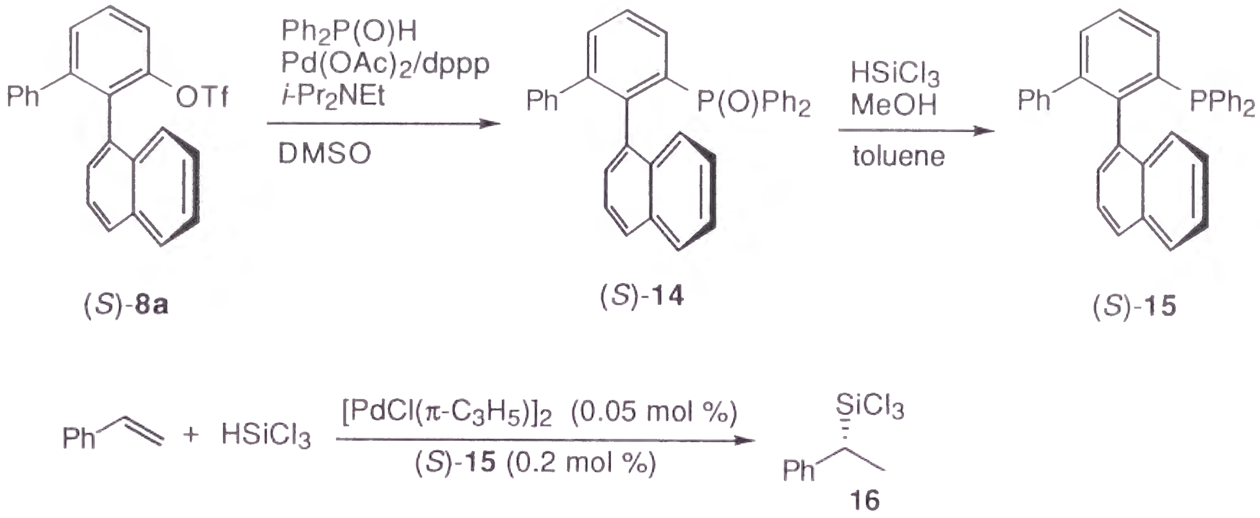


(*S*)-**12**

isomer whose methyl signal appears upfield should be (*R*,*aR*). Therefore, the axially chirality of **11** was assigned to be *S*.

Another synthetic application is the preparation of a new chiral phosphine ligand. Thus, the triflate group in (*S*)-**8a** was replaced by the diphenylphosphino group by the palladium-catalyzed diphenylphosphinylation[12] followed by reduction of diphenylphosphine oxide in (*S*)-**14** with trichlorosilane and triethylamine, which gave axially chiral triarylmonophosphine (*S*)-**15**. This new monodentate chiral phosphine ligand (*S*)-**15** was found to be effective for the palladium-catalyzed asymmetric hydrosilylation. The hydrosilylation of styrene was carried out without solvent with 1.2 equiv of trichlorosilane[13] in the presence of 0.1 mol % palladium catalyst generated from $[PdCl(\pi\text{-}C_3H_5)]_2$ and (*S*)-**15** (Pd/**15** = 1/2) at 0 °C for 24 h, which gave 85% yield of (*R*)-1-(trichlorosilyl)-1-phenylethane (**16**) (91% ee).[14] The enantioselecivity attained here

Scheme 8



is much higher than that reported with other chiral phosphine ligands including MeO-MOP whose basic skeleton is analogous to that of the new ligand **15**.[13,15]

Experimental Section

General. All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5 (Merck, SICAPENT). Optical rotations were measured with a JASCO DIP-370 polarimeter. NMR spectra were recorded on a JEOL JNM-EX270 (270 MHz for ^1H and 109 MHz for ^{31}P) or JEOL JNM LA500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^1H NMR, and to an external 85% H_3PO_4 standard for ^{31}P NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR. HPLC analysis was performed on a Shimazu LC-9A liquid chromatograph system with chiral stationary phase columns, Sumitomo Chemical Co. Ltd., Sumipax OA series and Daicel Chemical Co. Ltd., Chiralpak OD-H and AD.

Materials. PPh_3, dppb, (+)-DIOP, and (*S*)-BINAP from Aldrich Chemical Company, Inc. are commercially available. Palladium complexes $PdCl_2$[(*S*)-alaphos],[4] $PdCl_2$[(*S*)-valphos],[4] $PdCl_2$[(*S*)-phephos],[4] $PdCl_2$[(*S*)-*t*-leuphos],[4] $PdCl_2$[(*S*)-(*R*)-PPFA], $PdCl_2$[(+)-DIOP], $PdCl_2$-[(*S*)-BINAP],[15] and $PdCl_2[(R)\text{-MeO-MOP}]_2$[16] were prepared in a similar manner to the reported procedures. THF, benzene, ether, and toluene were distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane and DMSO were distilled from calcium hydride under nitrogen.

Synthesis of Ditriflates. Ditriflates **5**, **6**, and **7** were prepared by palladium-catalyzed cross-coupling of **1** with arylboronic acid followed by demethylation and ditriflation. Naphthaleneboronic acid (Lancaster) and *o*-tolylboronic acid (Aldrich) were commercially available. Biphenyboronic acid were prepared in a similar manner to the reported procedures.

Typical procedures for the preparation of ditriflates are shown below.

2-Bromo-1,3-dimethoxybenzene (1). To a solution of 1,3-dimethoxybenzene (5.52 g, 40.0 mmol) in 200 mL of ether was added dropwise at room temperature *n*-butyllithium (1.5 M hexane solution, 27 mL, 42 mmol). The reaction mixture was refluxed for 3 h, cooled to room temperature, then cooled to –50 °C, and Br_2 (2.0 mL, 39 mmol) was added at –50 °C. The mixture was slowly warmed up to room temperature and stirred at room temperature for 1 h and quenched with saturated sodium thiosulfate solution. The mixture was extracted with 500 mL of ether. Ether extracts were washed with brine (2 × 50 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from hexane to give 4.15g (49% yield) of **1**: mp 91 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.90 (s, 6H), 6.58 (d, J = 8.3 Hz, 2H), 7.23 (t, J = 8.3 Hz, 1H).

1-(2,6-Dimethoxyphenyl)naphthalene (2). To a mixture of **1** (822 mg, 3.79 mmol), naphthaleneboronic acid (980 mg, 5.68 mmol), tetrakis(triphenylphosphine)palladium (440 mg, 0.381 mmol), and $Ba(OH)_2 \cdot 8H_2O$ (2.69 g, 8.52 mmol) was added 100 mL of 1,3-dioxane and 10 mL of water, and the mixture was refluxed for 2 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was diluted with 200 mL of ethyl acetate, washed with water (2 × 50 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to give 920 mg (92% yield) of **2**: mp 147 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.64 (s, 6H), 6.72 (d, J = 8.3 Hz, 2H), 7.30–7.57 (m, 6H), 7.83–7.89 (m, 2H); IR (KBr) 3055, 3010, 2962, 1589, 1506, 1430, 1392 cm^{-1}; EI-MS m/z, 264 (M$^+$, base), 249, 205. Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.66; H, 6.07.

In a similar manner, **1-(2,6-Dimethoxyphenyl)-2-methylbenzene (3)** and **1-(2,6-Dimethoxyphenyl)-2-phenylbenzene (4)** were prepared by the cross-coupling with *o*–tolyl boronic acid and biphenyl boronic acid, respectively.

1-(2,6-Dimethoxyphenyl)-2-methylbenzene (3). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.07 (s, 3H), 3.71 (s, 6H), 6.69 (d, J = 8.3 Hz, 2H), 7.11–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.66, 55.77, 103.96, 118.93, 125.14, 127.14, 128.59, 129.46, 130.70, 134.18, 137.29, and 157.66; EI-MS m/z, 228 (M$^+$, 100), 213 (23), 197 (44), 152 (23). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.46; H, 6.90. **1-(2,6-Dimethoxyphenyl)-2-phenylbenzene (4).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.52 (s, 6H), 6.45 (d, J = 8.3 Hz, 2H), 7.10–7.17 (m, 6H), 7.30–7.46 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.54, 103.68, 118.89, 126.12, 126.76, 127.11, 127.37, 128.64, 129.31, 131.62, 132.82, 142.24, 142.47, and 157.56; EI-MS m/z, 290 (M$^+$, 100), 243 (16), 215 (31). Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.56; H, 6.20.

1-[2,6-Bis(trifluoromethanesulfonyloxy)phenyl]naphthalene (5). To a solution of **2** (4.67 g, 17.7 mmol) in 70 mL of dichloromethane was added dropwise BBr_3 (3.8 mL, 40 mmol) at –78 °C. The mixture was stirred at –78 °C for 1 h, slowly warmed up to room temperature, and stirred at room temperature for 3 h. The mixture was cooled to 0 °C, quenched with water, and extracted with 500 mL of dichloromethane. The organic layer was washed with water (2 × 70 mL), dried over magnesium sulfate, and concentrated under reduced pressure. To a solution of the residue, pyridine (5.7 mL, 70 mmol) in dichloromethane (40 mL) was added trifluoromethanesulfonic anhydride (8.9 mL, 53 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h, then quenched with water, and extracted with 500 mL of dichloromethane. The organic layer was washed with water (2 × 70 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to give 8.1 g (92% yield) of **5**: mp 105 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.32 (d, J = 8.2 Hz, 1H), 7.43–7.70 (m, 7H), 7.93 (d, J = 7.9 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 118.05 (q, J = 320.0 Hz), 121.86, 124.63, 124.83, 125.62, 126.26, 126.84, 127.75, 128.49, 129.33, 129.50, 130.25, 130.34, 131.42, 133.45, 134.42, and 148.35; IR (KBr) 1452, 1232, 1215, 1165, 972 cm^{-1}; EI-MS m/z 500 (M^+, 35), 234 (100), 205 (19). Anal. Calcd for $C_{18}H_{10}O_6F_6S_2$: C, 43.21; H, 2.01. Found: C, 43.50; H, 1.83.

In a similar manner, **1-2,6-Bis(trifluoromethanesulfonyloxy)phenyl]-2-methylbenzene (6)** and **1-[2,6-Bis(trifluoromethanesulfonyloxy)phenyl]-2-phenylbenzene (7)** were prepared.

1-2,6-Bis(trifluoromethanesulfonyloxy)phenyl]-2-methylbenzene (6). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.13 (s, 3H), 7.19 (d, J = 7.9 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.58 (t, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.38, 118.22 (q, J = 318.8 Hz), 121.83, 125.70, 127.67, 129.84, 130.32, 130.65, 130.98, 137.41, and 147.69; EI-MS m/z, 464 (M^+, 16), 198 (100), 115 (23). Anal. Calcd for $C_{15}H_{10}O_6F_6S_2$: C, 38.80; H, 2.17. Found: C, 38.54; H, 2.27. **1-[2,6-Bis(trifluoromethanesulfonyloxy)phenyl]-2-phenylbenzene (7).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (m, 2H), 7.20 (m, 3H), 7.28 (s, 1H), 7.29 (s, 1H), 7.39–7.58 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 118.22 (q, J = 318.8 Hz), 121.48, 126.56, 127.17, 128.82, 129.68, 130.07, 130.22, 130.42, 131.72, 140.29, 142.55, and 147.54; EI-MS m/z, 526 (M^+, 26), 260 (45), 244 (100), 215 (51). Anal. Calcd for $C_{20}H_{12}O_6F_6S_2$: C, 45.63; H, 2.30. Found: C, 45.59; H, 2.40.

Asymmetric Grignard Cross-Coupling of Ditriflates with Aryl Grignard Reagents Catalyzed by $PdCl_2$[(*S*)-alaphos]. Typical Procedure. To a mixture of ditriflate **5** (50 mg, 0.1 mmol), dichloro[(2-dimethylamino)propyldiphenylphosphine]palladium ($PdCl_2$[(*S*)-alaphos]) (2.2 mg, 0.005 mmol), and lithium bromide (13 mg, 0.1 mmol) in 200 μL of toluene was added phenylmagnesium bromide (1 M, 200 μL, 0.2 mmol) in ether at –20 °C, and the mixture was stirred at –10 °C for 48 h. The mixture was quenched with water and extracted with 70 mL of ether. The organic layer was washed with brine (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/ethyl acetate = 10/1) to give 39 mg (92% yield) of **8a** and 2 mg (6% yield) of **9a**. The reaction conditions and results are summarized in Table 4, 5.

Determination of the Enantiomeric Excess of 8. Enantiomeric purities of **8** were determined by HPLC analysis of phenols obtained by alkaline hydrolysis of triflate **8** by the following procedure. To a solution of **8** (0.3 mg) in 300 μL of methanol and 300 μL of 1,3-dioxane was added 2N (300 μL). The mixture was stirred at room temperature for 12 h, acidified with 10% HCl at 0°C, and extracted with 10 mL of ether. The organic layer was evaporated, and filtered. The filtrate was analyzed by HPLC with a chiral stationary phase column. for **8a**, **8b**, Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1); for **8c**, Chiralcel OD-H (hexane/2-propanol = 95/5); for **8d**, Chiralcel AD (hexane/2-propanol = 95/5). The data for HPLC analysis are reported below, together with the spectroscopic and optical rotation data.

(*S*)-1-[2-Phenyl-6-(trifluoromethanesulfonyloxy)phenyl]naphthalene (8a) (>99% ee). mp 142 °C; $[\alpha]^{20}_D$ –145 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.97-7.06 (m, 5H), 7.19–7.21 (m, 1H), 7.31–7.64 (m, 7H), 7.78–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 118.08 (q, *J* = 320.0 Hz), 120.23, 124.80, 125.33, 125.74, 126.30, 127.12, 127.68, 128.28, 128.65, 128.84, 129.30, 129.46, 130.17, 131.47, 132.25, 132.73, 133.20, 139.61, 145.33, and 148.02; IR (KBr) 3057, 1423, 1221, 1203, 910 cm^{-1}; EI-MS m/z, 428 (M$^+$, 100), 295 (78), 277 (59). Anal. Calcd for $C_{23}H_{15}O_3F_3S$: C, 64.48; H, 3.53. Found: C, 64.35; H, 3.37. **1-(2,6-Diphenylphenyl)naphthalene (9a).** mp 146 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.04 (m, 10H), 7.05–7.29 (m, 4H), 7.47–7.63 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 124.48, 125.09, 125.36, 126.15, 126.35, 126.99, 127.20, 127.70, 127.80, 129.07, 129.36, 129.73, 132.58, 132.87, 137.23, 137.42, 141.81, and 142.96; IR (KBr) 3052, 1498, 1448, 1387, 762 cm^{-1}; EI-MS m/z, 356 (M$^+$, 100), 276 (14). Anal. Calcd for $C_{28}H_{20}$: C, 94.34; H, 5.66. Found: C, 94.51; H, 5.44. **1-[2-(3-Methylphenyl)-6-(trifluoromethanesulfonyloxy)phenyl]naphthalene (8b) (95% ee).** $[\alpha]^{20}_D$ –149 (*c* 1.4, chloroform); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.07 (s, 3H), 6.69-6.73 (m, 1H), 6.84-6.85 (m, 3H), 7.18–7.25 (m, 2H), 7.31–7.47 (m, 4H), 7.52-7.61 (m, 2H), 7.76-7.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.08, 118.07 (q, *J* = 316.3 Hz), 120.05, 124.75, 125.33, 125.64, 125.84, 126.17, 127.42, 127.78, 128.16, 128.56, 129.17, 129.33, 129.68, 130.06, 131.56, 132.28, 132.68, 133.15, 137.19, 139.45, 145.43, and 147.99; EI-MS m/z, 442 (M$^+$, 100), 309 (61), 265 (38). Anal. Calcd for $C_{24}H_{17}O_3F_3S$: C, 65.15; H, 3.87. Found: C, 64.84; H, 3.92. **1-[2,6-Di(3-methylphenyl)phenyl]naphthalene (9b).** mp 97-98 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.71 (s, 18H), 7.25–7.51 (m, 8H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.11, 124.42, 125.01, 125.19, 126.15, 126.48, 126.84, 126.97, 127.57, 127.68, 129.17, 129.59, 130.01, 132.74, 132.87, 136.58, 137.27, 137.64, 141.72, and 142.99; EI-MS m/z, 384 (M$^+$, 100), 369 (18). Anal. Calcd for $C_{30}H_{24}$: C, 93.70; H, 6.30. Found: C, 93.30; H, 6.40. **1-[2-Phenyl-6-(trifluoromethanesulfonyloxy)-phenyl]-2-methylbenzene (95% ee) (8c).** mp 73-76 °C; $[\alpha]^{20}_D$ –15.5 (*c* 1.5, chloroform); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.94 (s, 3H), 7.06–7.21 (m, 9H), 7.35–7.39 (m, 1H), 7.46–7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.63, 118.27 (q, *J* = 317.5 Hz), 120.22, 125.24, 127.17, 127.80, 128.29, 128.93, 129.23, 129.87, 130.01, 131.36, 133.17, 133.96, 136.83, 139.60, 144.36, and 147.51; EI-MS m/z, 392 (M^+, 100), 259 (86), 244 (79), 215 (56). Anal. Calcd $C_{20}H_{15}O_3F_3S$: C, 61.22; H,3.85. Found: C, 61.40; H, 3.86. **1-(2,6-Diphenylphenyl)-2-methylbenzene (9c).** mp 104-105 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.80 (s, 3H), 6.86 (m, 4H), 6.95 (m, 1H), 7.05-7.17 (m, 10H), 7.90 (d, *J* = 1.5 Hz, 1H), 7.44 (s, 1H), 7.49 (dd, *J* = 6.9, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 124.60, 126.23, 126.68, 127.39, 129.28, 129.35, 129.50, 132.03, 136.35, 139.02, 141.81, and 142.00; EI-MS m/z 320 (M^+, 100), 305 (21), 145 (19). Anal. Calcd for $C_{25}H_{20}$: C, 93.71; H, 6.29. Found: C, 93.47; H, 6.44. **1-[2-Phenyl-6-(trifluoromethanesulfonyloxy)phenyl]-2-phenylbenzene (94% ee) (8d).** mp 91-93 °C; $[\alpha]^{20}_D$ −26.7 (*c* 1.1, chloroform); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.73 (d, *J* = 6.9 Hz, 2H), 6.78 (d, *J* = 6.9 Hz, 2H), 7.04–7.14 (m, 6H), 7.26–7.33 (m, 5H), 7.36–7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 118.23 (q, *J* = 320.0 Hz), 120.17, 126.50, 126.73, 126.87, 127.63, 128.70, 128.89, 129.31, 129.99, 130.24, 131.70, 132.45, 133.43, 139.30, 140.49, 141.81, 144.28, and 147.64; EI-MS m/z, 454 (M^+, 85), 321 (25), 303 (100), 215 (41). Anal. Calcd for $C_{25}H_{17}O_3F_3S$: C, 66.07; H, 3.77. Found: C, 65.79; H, 3.86. **1-(2,6-Diphenylphenyl)-2-phenylbenzene (9d).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.67 (d, *J* = 6.5 Hz, 2H), 6.82-6.84 (m, 4H), 6.97-7.17 (m, 13H), 7.30 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 125.93, 126.02, 126.23, 127.20, 127.35, 127.43, 127.58, 128.87, 129.56, 129.69, 129.74, 133.35, 137.42, 137.92, 140.80, 141.10, 141.61, and 141.87; EI-MS m/z 382 (M^+, 100), 303 (19), 289 (28). Anal. Calcd for $C_{30}H_{22}$: C, 94.20; H, 5.80. Found: C, 92.90; H, 5.84.

(*S*)-1-(2-Methoxycarbonyl-6-phenylphenyl)naphthalene (10) (>99% ee). To a solution of (*S*)-**8a** (0.21 g, 0.50 mmol), palladium diacetate (90 mg, 0.40 mmol), and 1,3-bis-(diphenylphosphino)propane (0.16 g, 0.40 mmol) in mixture of DMSO (11 mL) and methanol (4 mL) was added 1.5 mL of triethylamine. The mixture was stirred under carbon monoxide (1 atm) at 80 °C for 15 h. After being cooled to room temperature, it was concentrated under reduced pressure. The residue was dissolved in 100 mL of ether and washed with water (2 × 20 mL). The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to give 0.14 g (82% yield) of (*S*)-**10**: mp 81 °C; $[\alpha]^{20}_D$ −147 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$, 270MHz) δ 3.37 (s, 3H), 7.03–7.08 (m, 5H), 7.19–7.22 (m, 1H), 7.33–7.49 (m, 3H), 7.55–7.58 (m, 1H), 7.63–7.74 (m, 2H), 7.76–7.79 (m, 1H), 7.84–7.87 (m, 1H), 8.01–8.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.72, 124.67, 125.28, 125.56, 125.74, 126.50, 127.24, 127.32, 127.60, 127.67, 128.03, 128.54, 128.93, 132.64, 132.87, 133.15, 133.43, 137.26, 138.71, 140.75, 143.41, and 168.39; IR (KBr) 3057, 3006, 2949, 1705, 1308, 1279, 773 cm^{-1}. Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.15; H, 5.36. Found: C, 85.25; H, 5.28.

(*S*)-2-(1-Naphthyl)-3-phenylbenzoic Acid (11) (>99% ee). To a solution of (*S*)-**10** (139 mg, 0.411 mmol) in 5 mL of methanol was added 1 mL of 50% KOH solution and the mixture was refluxed for 8 h. The reaction mixture was acidified by addition of conc. HCl at 0 °C and extracted with 200 mL of ethyl acetate. The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1) to give 116 mg (87% yield) of (*S*)-**11**: mp 207-209 °C; $[\alpha]^{20}{}_D$ –155 (*c* 0.5, chloroform); ^1H NMR ($CDCl_3$, 270MHz) δ 3.5 (broad, 1H), 6.88-6.98 (m, 5H), 7.09–7.12 (m, 1H), 7.24–7.43 (m, 5H), 7.53–7.69 (m, 3H), 7.74–7.77 (m, 1H), 7.98–8.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 124.67, 125.26, 125.51, 125.74, 126.51, 127.27, 127.39, 127.58, 127.67, 128.03, 128.90, 129.43, 131.59, 132.63, 132.89, 134.18, 136.86, 139.37, 140.64, 143.69, 171.92; IR (KBr) 3321, 3055, 1726, 1691, 1142, 779 cm^{-1}. Anal. Calcd for $C_{23}H_{16}O_2$: C, 85.19; H, 4.97. Found: C, 84.91; H, 5.07.

1-Phenylethyl 2-(1-naphthyl)-3-phenylbenzoate (13). To a mixture of **11** (37% ee, 43.5 mg, 0.134 mmol) and thionyl chloride (1 mL) was added DMF (10 μL), and the mixture was heated with stirring at 90 °C for 8 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure. To the residue benzene (10 mL) was added, the reaction mixture was concentrated under reduced pressure. To a solution of the residue, (R)-1-phenylethanol (17.8 mg, 0.146 mmol) in pyridine (1 mL) was added 4-(N,N-dimethylamino)-pyridine (18.1 mg, 0.148 mmol), the mixture was stirred at ambient temperature for 24 h, then quenched with 10% hydrochlorolic acid, and extracted with 100 mL of ether. The organic layer was washed with (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1) to give 39.1 mg (68% yield) of **13** as a mixture of diastereomers. The diastereomers ratio was determined from NMR spectrum ((*R*, *aS*)-**13**/(*R*, *aR*)-**13** = 2/1). ^1H NMR ($CDCl_3$, 270 MHz) δ 0.57 (d, *J* = 6.6 Hz, 1/3H), 0.71 (d, *J* = 6.6 Hz, 2/3H, 5.50-5.59 (m, 1H), 6.55–8.00 (m, 20H).

(*S*)-1-[2-(Diphenylphosphinyl)-6-phenylphenyl]naphthalene (14) (>99% ee). To a mixture of (*S*)-**8a** (108 mg, 0.252 mmol), diphenylphosphine oxide (106 mg, 0.522 mmol), palladium diacetate (2.9 mg, 0.013 mmol), and 1,4-bis(diphenyphosphino)butane (dppb, 5.6 mg, 0.013 mmol) was added 1 mL of DMSO and diisopropylethylamine (108 μL, 0.620 mmol), and the mixture was heated with stirring at 100 °C for 12 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was diluted with 100 mL of ethyl acetate, washed with water (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1) to give 120 mg (99% yield) of (*S*)-**14**: mp 179 °C; $[\alpha]^{20}{}_D$ +49.2 (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$, 270MHz) δ 6.73–6.80 (m, 2H), 6.84–6.87 (m, 4H), 6.95–6.99 (m, 4H), 7.04–7.10 (m, 1H), 7.18–7.39 (m, 8H), 7.49–7.55 (m, 1H), 7.60–7.69 (m, 5H); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 28.0 (s); IR (KBr) 3055, 1631, 1439, 1113, 723, 698 cm^{-1}. Anal. Calcd for $C_{34}H_{25}OP$: C, 84.98; H, 5.24. Found: C, 85.01; H, 5.05.

(*S*)-1-[2-(Diphenylphosphino)-6-phenylphenyl]naphthalene (15) (>99% ee). To a mixture of (*S*)-**13** (120 mg, 0.250 mmol) and triethylamine (1 mL) in toluene (6 mL) was added trichlorosilane (300 μL, 0.297 mmol) at 0 °C. The reaction mixture was refluxed for 12 h. After being cooled to room temperature, the mixture was diluted with 100 mL of ether and quenched with a small amount of saturated $NaHCO_3$. The resulting suspension was filtered through celite and the filter cake was washed with ether. The combined organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1) to give 85 mg (73% yield) of (*S*)-**15**: mp 194-197 °C; $[\alpha]^{20}_D$ +15.3 (*c* 0.5, chloroform); ^1H NMR ($CDCl_3$, 270MHz) δ 6.84–7.03 (m, 6H), 7.06–7.39 (m, 15H), 7.44–7.54 (m, 2H), 7.58–7.69 (m, 2H); $^{31}P\{^1H\}$ NMR ($CDCl_3$) d –12.5 (s); IR (KBr) 3053, 1633, 1437, 746, 698 cm^{-1}. *m/e* calcd for $C_{34}H_{25}P$: 464.1694, found 464.1708.

Palladium-Catalyzed Asymmetric Hydrosiliylation of styrene with (*S*)-15. To a mixture of $[PdCl(\pi\text{-}C_3H_5)]_2$ (0.54 mg, 1.5 μmol), (*S*)-**15** (2.5 mg, 5.4 mmol), and styrene (264 mg, 2.54 mmol) was added trichlorosilane (300 μL, 3 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 24 h. The crude mixture was purified by bulb-to-bulb distillation under reduced pressure to give 518 mg (85%) of **16**. ^1H NMR ($CDCl_3$, 270MHz) δ 1.62 (d, *J* = 7.6 Hz, 3H), 2.90 (q, *J* = 7.6 Hz, 1H), 7.21-7.37 (m, 5H).

Determination of the Enantiomeric Excess of 16. Enantiomeric purities of **16** was determined by HPLC analysis of (3,5-dinitrophenyl)carbamate ester obtained by Tamao's oxidation and esterifition by the following procedure. To a suspension of KF (764 mg, 29.4 mmol) and $KHCO_3$ (2.61 g, 26.0 mmol) in 100 mL of THF/MeOH (1:1) was added **16**. To the suspension was added 2.2 mL of 30% H_2O_2 at ambient temperature. Then the reaction mixture was vigorously stirred for 12 h. To this reaction mixture was added 4 g of $Na_2S_2O_3 \cdot 5H_2O$ and then entire mixture was stirred for 1 h. The mixture was filtered through a Celite plug, and the filter cake was rinsed with Et_2O. The filtrate was concentrated in vacuo and the resulting residue was dissolved in CH_2Cl_2. After drying over $MgSO_4$, organic solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1) to give 196 mg (74% yield) of 1-phenylethanol. A mixture of alcohol (2 mg), 3,5-dinitrophenyl isocyanate (5 mg), and pyridine (5 μL) in toluene (0.5 mL) was stirred at ambient temperature for 30 min. The mixture was evaporated, diluted with chloroform, and filtered. The filtrate was analyzed by HPLC with a chiral stationary phase column Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 50/15/1). The enantiomeric excess of the (3,5-dinitrophenyl)carbamate ester was determined to be 91% ee.

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Chapter 2

Enantioposition-Selective Alkynylation of Biaryl Ditriflates by Palladium-Catalyzed Asymmetric Cross-Coupling

Abstract: Asymmetric cross-coupling of achiral biaryl ditriflates with alkynyl Grignard reagents in the presence of 1 equiv of lithium bromide and 5 mol % of palladium complex $PdCl_2$[(*S*)-alaphos], where alaphos stands for 2-dimethylamino-1-diphenylphosphino-3-methylpropane, gave axially chiral mono-alkynylated biaryl with high enantioposition-selectivity

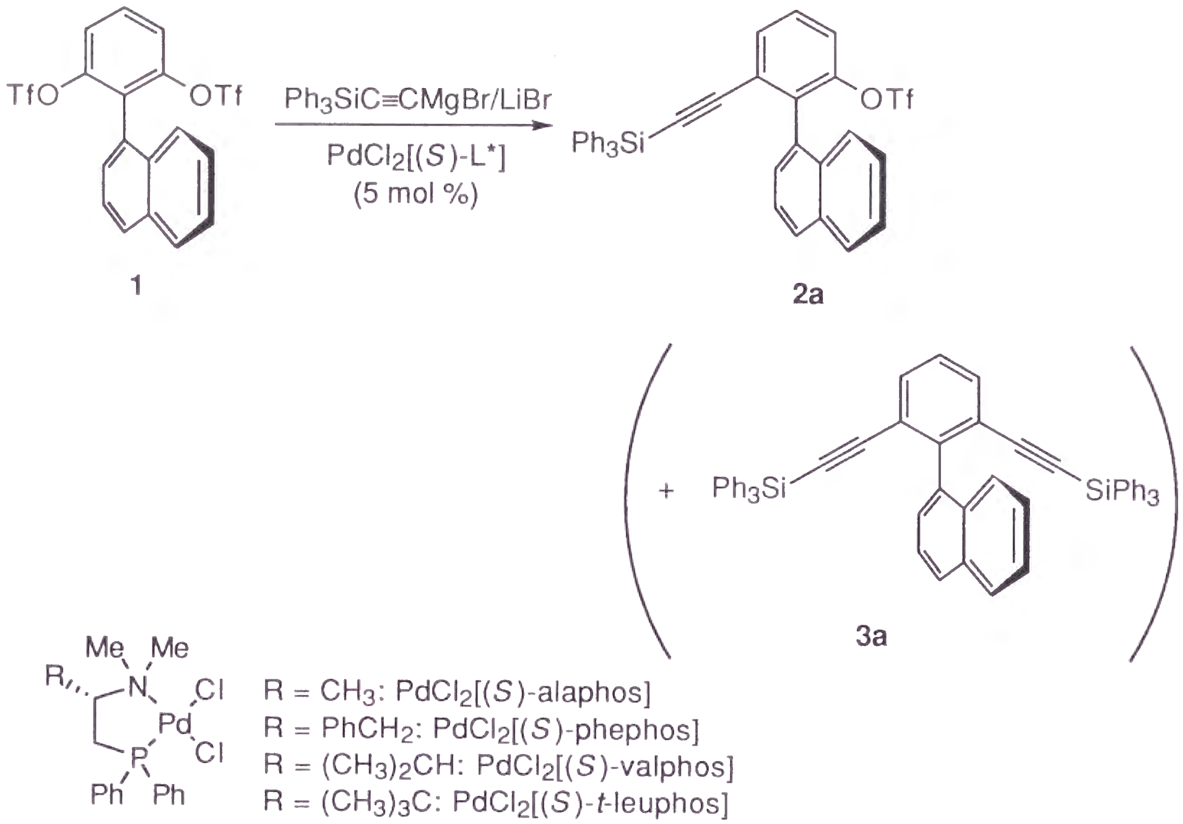
Introduction

In Chapter 1, it was reported that, a new type of catalytic asymmetric synthesis of axially chiral biaryls could be realized by enantioposition-selective monoarylation of achiral ditriflates with aryl Grignard reagents in the presence of palladium catalyst coordinated with a chiral β-aminoalkylphosphine ligand. Biaryl molecules of high enantiomeric purities were conveniently obtained by a kinetic resolution of monoarylation product at the second arylation step forming bisarylation product, though the enantioselectivity in the monoarylation step is not higher than 85%.[1] In this chapter, is described introduction of the alkynyl groups to the biaryl ditriflates with higher enantioposition-selectivity by using of alkynyl Grignard reagents.

Results and Discussion

For the asymmetric monosubstitution of enantiotopic ditriflates in 1-[2,6-bis[(trifluoromethane)sulfonyloxy]phenyl]naphthalene (**1**) with an alkynyl group, several reaction conditions were examined (Sheme 1). Attempts to use Sonogashira method[2] were not successful. The highest enantioselectivity was merely 20%, which was obtained with 1-heptyne, cuprous iodide, diisopropylamine, and 5 mol % of $PdCl_2$[(*S*)-phephos][3] in THF at 40 °C. The alkynylation of **1** with triphenylsilylacetylene did not take place under similar conditions. The substitution was found to proceed with much higher enantioselectivity by use of alkynyl Grignard reagents. The results are summarized in Table 1. The reaction of **1** with 2 equiv of triphenylsilylethynylmagnesium bromide, which was generated from triphenylsilylethyne and ethylmagnesium bromide, in the presence of 1 equiv of LiBr and 5 mol % of $PdCl_2$[(*S*)-alaphos][3] in ether/toluene (1:1) at 20 °C for 2 h gave 88 % yield of axially chiral monoalkynylated biaryl **2a** and 10% yield of dialkynylated biaryl **3a** (entry 2 in Table1). Removal of triphenysilyl group in **2a** with tetrabutylammonium fluoride followed by alkaline hydrolysis of triflate gave phenol, whose enantiomeric purity was determined to be 92% ee by HPLC analysis with chiral stationary phase column, Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1). The absolute

Scheme 1



R = CH_3: $PdCl_2$[(*S*)-alaphos]
R = $PhCH_2$: $PdCl_2$[(*S*)-phephos]
R = $(CH_3)_2CH$: $PdCl_2$[(*S*)-valphos]
R = $(CH_3)_3C$: $PdCl_2$[(*S*)-*t*-leuphos]

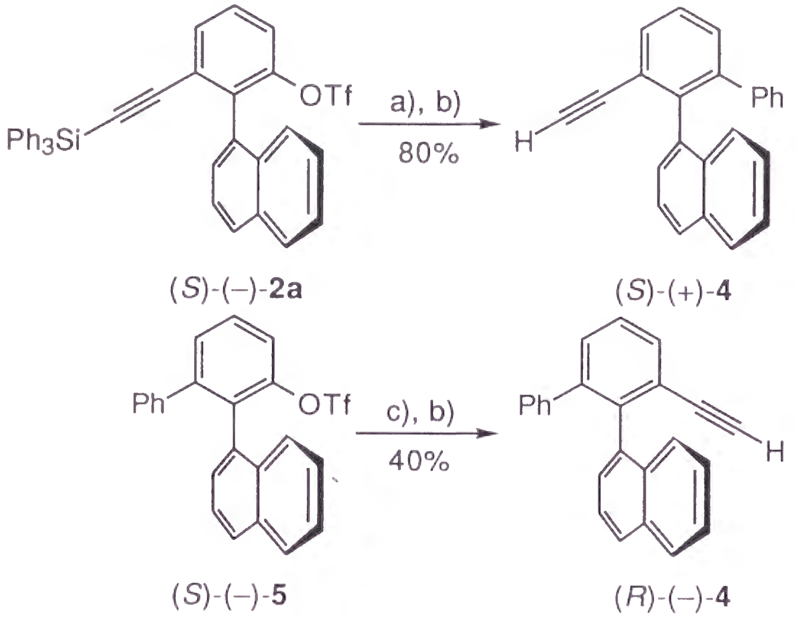
Table 1. Effects of Phosphine Ligands on the Cross-Coupling of Ditriflate **1** with Triphenylsilylethynylmagnesium Bromide[a]

entry	catalyst	reaction time (h)	recovered ditriflate (%)[b]	yield of **2** (%)[b]	yield of **3** (%)[b]	%ee of **2**[c]
1	$PdCl_2$[(*S*)-alaphos]	4	4	91 (**2a**)	0 (**3a**)	88 (*S*)
2	$PdCl_2$[(*S*)-alaphos]	6	0	88 (**2a**)	10 (**3a**)	92 (*S*)
3	$PdCl_2$[(*S*)-alaphos]	10	0	83 (**2a**)	13 (**3a**)	92 (*S*)
4	$PdCl_2$[(*S*)-alaphos]	17	0	53 (**2a**)	43 (**3a**)	>99 (*S*)
5	$PdCl_2$[(*S*)-phephos]	4	7	89 (**2a**)	0 (**3a**)	82 (*S*)
6	$PdCl_2$[(*S*)-phephos]	17	0	60 (**2a**)	38 (**3a**)	92 (*S*)
7	$PdCl_2$[(*S*)-valphos]	17	0	86 (**2a**)	7 (**3a**)	86 (*S*)
8	$PdCl_2$[(*S*)-*t*-leuphos]	17	48	54 (**2a**)	0 (**3a**)	4 (*S*)

[a] The cross-coupling was carried out with 2 equiv of Grignard reagent in the presence of 1 equiv of LiBr and 5 mol % palladium catalyst in ether/toluene (1:1) at 20 °C. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis of phenols obtained by alkaline hydrolysis of triflate **2a**: Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1).

configuration of (–)-**2a** was assigned to be (S) by comparison of the optical rotation value of 1-(3-ethynylbiphenyl-2-yl)naphthalene (**4**) obtained by palladium-catalyzed phenylation of the remained triflate on **2a** with that obtained by palladium-catalyzed ethynylation of 1-[3-(trifluoromethanesulfonyloxy)biphenyl-2-yl]naphthalene (**5**) whose absolute configuration is known to be (*S*)-(–) (Scheme 2).[1]

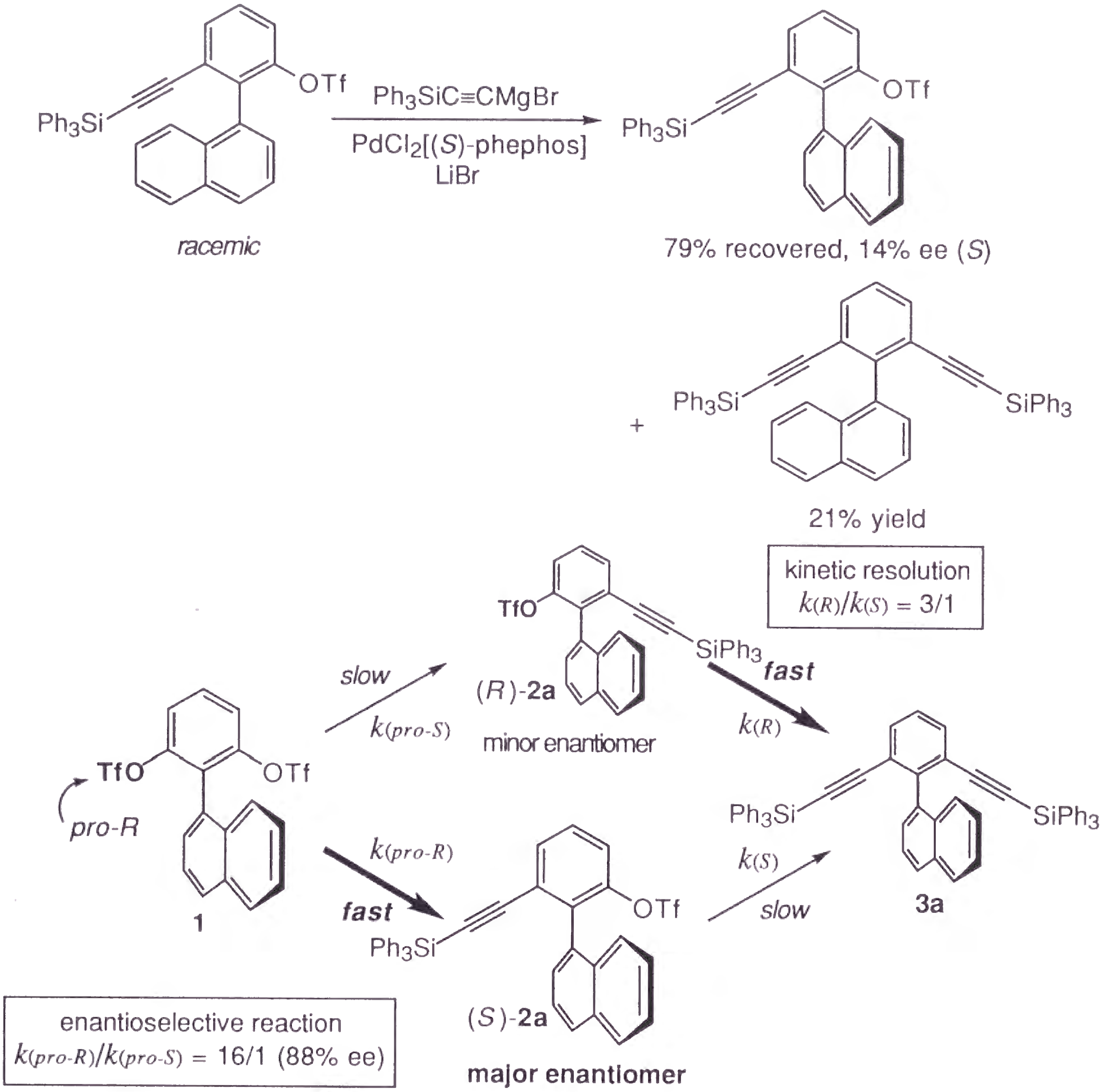
Scheme 2



a) PhMgBr, LiBr, $PdCl_2[Ph_2P(CH_2)_2NMe_2]$ (5 mol %). b) Bu_4NF. c) $Ph_3SiC{\equiv}CH$, CuI, $PdCl_2(PPh_3)_2$ (5 mol %).

A little lower enantioselectivity was observed in the reaction with Phephos[3] and Valphos[3] lignad, which gave **2a** of 82% ee and 86% ee, respectively (entries 5-7). The palladium complex cooridinated with *t*-Leuphos[3] which is one of the most effective ligands for the nickel-catalyzed asymmetric cross-coupling of 1-phenylethylmagnesium chloride, was much less catalytically active and less enantioselective (entry 8).[3] It is noteworthy that other palladium or nickel complexes were all much less catalytically active than palladium complexes coordinated with β-(dimethylamino)-alkyldiphenylphosphines. Higher eantiomeric purity of monoalkynylation product **2a** was observed in the reaction forming higher yield of bisalkynylation product **3a** (entries 1-4). Enantiomerically pure **2a** was obtained in the reaction carried out with $PdCl_2$[(*S*)-alaphos] catalyst for a prolonged reaction time, where 43% yield of **3a** was formed together with 53% yield of **2a** (entry 4). The higher enantiomeric purity of **2a** at the higher conversion to **3a** can be accounted for by a kinetic resolution at the second cross-coupling forming **3a**.[1] Thus, the minor enantiomar, that is (*R*)-**2a**, formed at the first asymmetric alkynylation is consumed preferentially at the second asymmetric alkynylation, which causes an increase of enantiomeric purity of (*S*)-**2a** as the amount of bisalkynylation product **3a** increases. The kinetic resolution was confirmed by the asymmetric alkynylation of racemic **2a** under similar reaction conditions. At 21% conversion to bisalkynylation product **3a**, the recovered **2a** was an (*S*)-isomer with 14% ee, indicating that the (*R*)-**2a** undergoes the second alkynylation about 3 times faster than (*S*)-**2a** ($k(R)/k(S) = 3/1$) (Scheme 3).

Scheme 3



In the present asymmetric alkynylation, the reaction rate of cross-coupling was not strongly affected by the addition of lithium salts (Table 2). Thus, the reaction in the presence of lithium chloride, lithium bromide, or lithium iodide gave 94% yield of monoalkynylation products **2a**, the yield being only a little higher than that (89%) in the reaction without any lithium salts. It is noted that the enantiomeric purity of **2a** was all the same (91% ee) irrespective of the addition of lithium salts.

Table 2. Effects of Li Salts on the Cross-Coupling of Ditriflate **1** with Triphenylsilylethynylmagnesium Bromide[a]

entry	Li salts	recovered ditriflate (%)[b]	yield of **2** (%)[b]	yield of **3** (%)[b]	%ee of **2**[c]
1	none	3	89 (**2a**)	7 (**3a**)	91 (*S*)
2	LiCl	3	94 (**2a**)	2 (**3a**)	91 (*S*)
3	LiBr	0	94 (**2a**)	4 (**3a**)	91 (*S*)
4	LiI	0	94 (**2a**)	5 (**3a**)	91 (*S*)

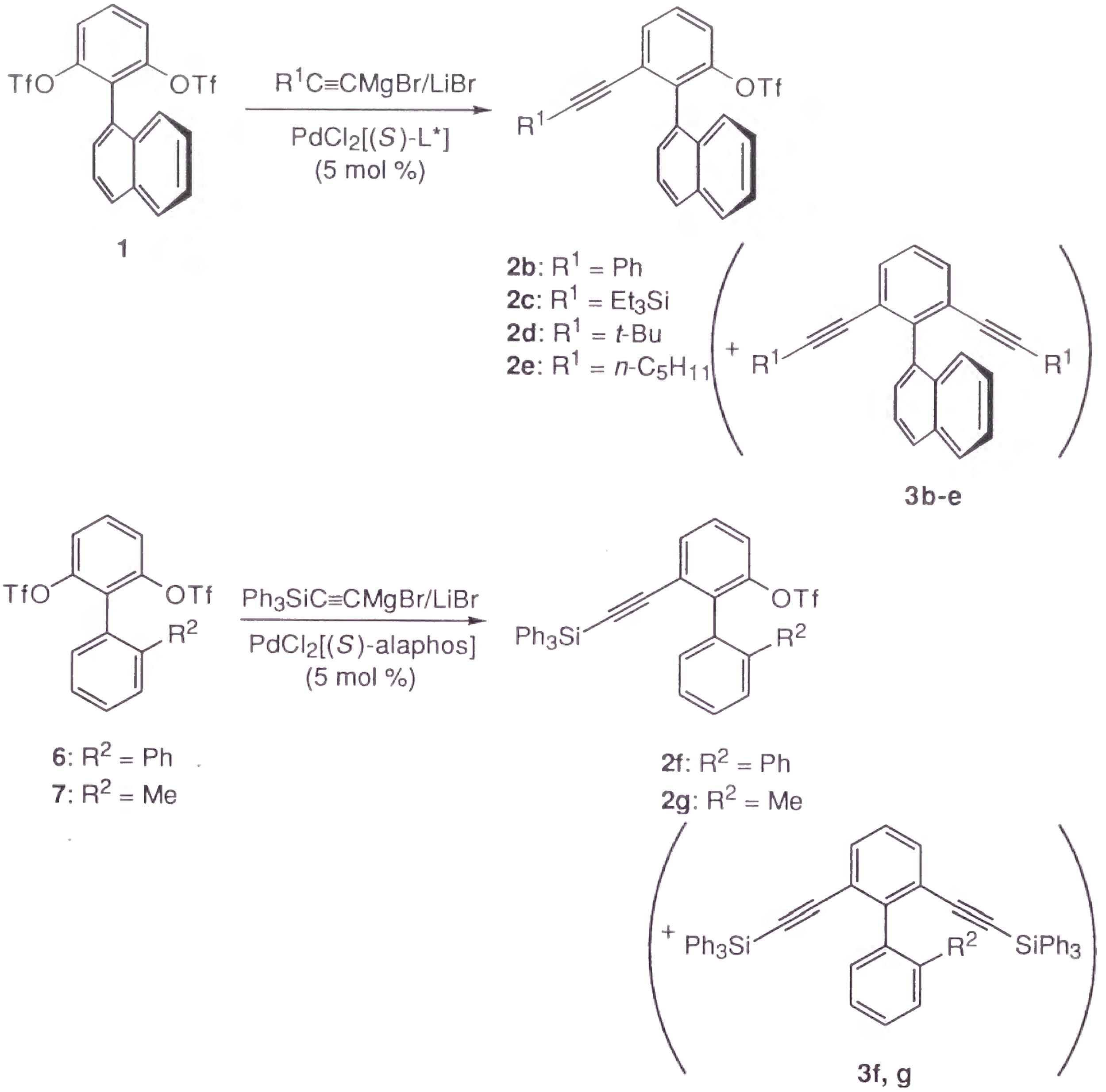
[a] The cross-coupling was carried out with 2 equiv of Grignard reagent in the presence of 5 mol % palladium catalyst in ether/toluene (1:1) at 20 °C for 2 h. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis of phenols obtained by alkaline hydrolysis of triflate **2a**: Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1).

Table 3. Cross-Coupling of Ditriflate with Alkynyl Grignard Reagents Catalyzed by $PdCl_2[(S)$-alaphos][a]

entry	ditriflate	Grignard reagent	reaction temp (°C)	reaction time (h)	recovered **1** (%)[b]	yield of **2** (%)[b]	yield of **3** (%)[b]	% ee of **2**[c]
1	**1**	$PhC{\equiv}CMgBr$	20	6	0	95 (**2b**)	5	84 (*S*)
2	**1**	$Et_3SiC{\equiv}CMgBr$	20	3	0	86 (**2c**)	9	52 (*S*)
3	**1**	t-$BuC{\equiv}CMgBr$	20	4	12	79 (**2d**)	6	43 (*S*)
4	**1**	n-$C_5H_{11}C{\equiv}CMgBr$	20	20	0	80 (**2e**)	15	26 (*S*)
5	**6**	$Ph_3SiC{\equiv}CMgBr$	20	24	31	60 (**2f**)	0	96
6	**6**	$Ph_3SiC{\equiv}CMgBr$	20	48	0	88 (**2f**)	4	99
7	**7**	$Ph_3SiC{\equiv}CMgBr$	20	10	3	87 (**2g**)	4	85

[a] The cross-coupling was carried out with 2 equiv of Grignard reagent in the presence of 1 equiv of LiI and 5 mol % palladium catalyst in ether/toluene (1:1). [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis of phenols obtained by alkaline hydrolysis of triflate **2**: For entries 1-4, Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1); For entries 5-6, Chiralcel OD-H (hexane/2-propanol = 95/5); For entry 7, Chiralcel OD-H (hexane/2-propanol = 95/5)

Scheme 4



The results obtained for the asymmetric cross-coupling reactions of ditriflates with various kinds of alkynyl Grignard reagents (Scheme 4) are summarized in Table 3. Asymmetric substitution of ditriflate **1** with phenylethynyl group also proceeded with high enantioselectivity. Monoalkynylation product **2b** of 84% ee was obtained under the conditions where a small amount of bisalkynylation product was formed (entry 1). The reaction carried out with triethylsilylethynylmagnesium bromide, *t*-butylethynylmagnesium bromide, and 1-heptynylmagnesium bromide gave **2c** of 52% ee, **2d** of 43% ee, and **2e** of 26% ee, respectively (entries 2-4). The enantioselectivities were much lower in the reactions with these Grignard reagents, especially with 1-heptynylmagnesium bromide (entry 4). It is interesting that the enantioselectivity is strongly dependent on the substituents on the ethynyl Grignard reagents. If the stereochemistry in the present asymmetric substitution were determined at attack of a chiral palladium(0) species on one of the enantiotopic triflate groups on aryl ditriflate **1**, the total stereochemical outcome would be all the same irrespective of the Grignard reagents used.

The asymmertic substitution with an alkynyl group was also successful for 1,3-bis[[(trifluoromethyl)sulfonyl]oxy]-2-(biphenyl-2-yl)benzene (**6**) and its 2-methyphenyl analog **7** (entries 5-7). The highest enantioselectivity, was observed in the reaction of **6** with triphenylsilylethynylmagnesium bromide catalyzed by $PdCl_2[(S)$-alaphos]. Monoalkynylation product **2f** of 96% ee was formed in the reaction where the formation of bisalkynylation product **3f** was not observed (entry 5), indicating that the enantioposition-selectivity at the first alkynylation step is 96%. In the reaction which is accompanied by a small amount (4%) of **3f**, the enantiomeric purity of **2f** was significantly increased by the kinetic resolution at the second alkynylation to give **2f** of 99% ee in 88% yield (entry 6). These results show that the reactivity of ditriflates with the alkynyl Grignard reagent is dependent on the steric bulkiness of the C-2 substituent between two trifluoromethanesulfonyloxy groups, that is, the order of reactivity is **1** (naphthyl) > **7** (*o*-Me-C_6H_4) > **6** (*o*-Ph-C_6H_4).

Experimental Section

General. All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5 (Merck, SICAPENT). Optical rotations were measured with a JASCO DIP-370 polarimeter. NMR spectra were recorded on a JEOL JNM-EX270 (270 MHz for ^1H and 109 MHz for ^{31}P) or JEOL JNM LA500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^1H NMR, and to an external 85% H_3PO_4 standard for ^{31}P NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR. HPLC analysis was performed on a Shimazu LC-9A liquid chromatograph system with chiral stationary phase columns, Sumitomo Chemical Co. Ltd., Sumipax OA series and Daicel Chemical Co. Ltd., Chiralpak OD-H and AD.

Materials. PPh_3 from Aldrich Chemical Company, Inc. were commercially available. Palladium complexes $PdCl_2[(S)$-alaphos], $PdCl_2[(S)$-valphos], $PdCl_2[(S)$-phephos], $PdCl_2[(S)$-*t*-phephos] were prepared in a similar manner to the reported procedures.[3] Ether and toluene were distilled from sodium benzophenone ketyl under nitrogen.

Preparation of Ethynylmagnesium Bromide. Typical Procedure. To a solution of triphenylsilylacetylene (600 mg, 2.11 mmol) in 900 µL of toluene was added ethylmagnesium bromide (1M ether solution, 2.22 mL). The mixture was heated at 50 °C for 30 min.

Asymmetric Grignard Cross-Coupling of Ditriflates with Ethynyl Grignard Reagents Catalyzed by $PdCl_2[(S)$-alaphos]. Typical Procedure. To a mixture of ditriflate **1** (50.0 mg, 0.100 mmol), dichloro[(2-dimethylamino)propyldiphenylphosphine]-palladium ($PdCl_2[(S)$-alaphos]) (2.2 mg, 0.0050 mmol), and lithium bromide (8.6 mg, 0.10 mmol) in 200 µL of toluene was added triphenylsilylethynylmagnesium bromide (1 M, 2.0 mmol) in ether at 20 °C, and the mixture was stirred at –10 °C until **1** was not detected by silica gel TLC (hexane/benzene = 3/1). The reaction mixture was quenched with water and extracted with 70 mL of ether. Combined ether extracts were washed with brine (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/benzene = 3/1) to give 59.6 mg (94% yield) of **2a** and 3 mg of **3a** (4% yield). The reaction conditions and results are summarized in Tables 1 and 3.

Determination of the Enantiomeric Excess of 2. Enantiomeric purities of **2a**, **2c**, **2f**, and **2g** were determined by HPLC analysis of phenols obtained by desilylation followed by alkaline hydrolysis of triflate **2a**, **2c**, **2f**, and **2g**, respectively. (In case of **2b**, **2d**, and **2e**, phenols were obtained by alkaline hydrolysis of triflate.) To a solution of **2** (0.3 mg) in THF (0.5 mL) was addded tetrabutylammonium fluoride aq (0.5 mL) and stirred at room temperature for 30 min. To the mixtucre was added 300 μL of methanol, 300 μL of 1,3-dioxane, and 300 μL of 2 N NaOH. The mixture was stirred at room temperature for 12 h, acidified with 10% HCl at 0°C, and extracted with 10 mL of ether. The organic layer was evaporated, and filtered. The filtrate was analyzed by HPLC with a chiral stationary phase column. For **2a**, **2f-i**, Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1); for **2d**, Chiralcel OD-H (hexane/2-propanol = 95/5); for **2e**, Chiralcel OB-H (hexane/2-propanol = 95/5). The data for HPLC are reported below, together with the spectroscopic and optical rotation data.

(*S*)-1-[2-Trifluoromethanesulfonyloxy-6-(triphenylsilylethynyl)phenyl]naphthalene (2a) (>99% ee). mp 117-120 °C; $[\alpha]^{20}_D$ –90.0 (*c* 1.1, chloroform); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (dd, *J* = 1.5, 7.9 Hz, 6H), 7.21 (t, *J* = 7.9 Hz, 6H), 7.32–7.52 (m, 10H), 7.76 (dd, *J* = 1.5, 7.9 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 95.06, 105.99, 118.09 (q, *J* = 317.5 Hz), 122.21, 124.96, 125.28, 125.92, 126.40, 126.79, 127.76, 128.29, 128.54, 129.18, 129.28, 129.73, 131.04, 131.64, 132.56, 132.76, 133.48, 135.20, 137.23, and 147.69. Anal. Calcd for $C_{37}H_{25}O_3F_3SSi$: C, 70.01; H, 3.97. Found: C, 70.22; H, 3.84. **1-[2,6-Bis(triphenylsilylethynyl)phenyl]-naphthalene (3a).** mp 191-192 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16–7.46 (m, 34H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H) 7.72 (d, *J* = 7.9 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 93.12, 107.56, 124.20, 125.18, 125.64, 125.90, 126.08, 127.40, 127.63, 127.72, 128.26, 128.26, 129.58, 131.87, 133.15, 133.55, 135.26, 136.88, and 146.74. Anal. Calcd for $C_{54}H_{40}Si_2 \cdot 0.2C_4H_8O$: C, 86.30; H, 5.50. Found: C, 86.16; H, 5.47. **(*S*)-1-[2-Phenylethynyl-6-(trifluoromethanesulfonyloxy)phenyl]naphthalene (2b).** $[\alpha]^{20}_D$ –202 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.74 (d, *J* = 8.3 Hz, 2H), 7.08–7.20 (m, 3H), 7.38–7.72 (m, 8H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.97 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 87.07, 94.90, 118.13 (q, *J* = 320.0 Hz), 121.40, 121.96, 124.93, 125.52, 125.89, 126.28, 127.39, 128.03, 128.24, 128.46, 128.57, 129.17, 131.28, 131.42, 131.59, 131.70, 133.45, 136.52, and 147.74; EI-MS m/z, 452 (M^+, 48), 391 (70), 291 (100), 242 (30). Anal. Calcd for $C_{25}H_{15}O_3F_3SSi$: C, 66.37; H, 3.34. Found: C, 66.17; H, 3.32. **1-[2,6-Di(phenylethynyl)phenyl]naphthalene**

(3b). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.77 (d, J = 1.5 Hz, 2H), 6.78 (s, 2H), 7.08–7.17 (m, 6H), 7.38–7.67 (m, 8H), 7.95 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 88.50, 93.33, 122.89, 124.55, 125.04, 125.54, 125.82, 126.30, 127.48, 127.85, 127.96, 128.01, 128.04, 128.32, 131.23, 131.57, 131.95, 133.45, 137.41, and 145.38. Anal. Calcd for $C_{32}H_{20}$: C, 95.02; H, 4.98. Found: C, 94.72; H, 5.00. **(*S*)-1-[2-Triethylsilylethynyl-6-(trifluoromethanesulfonyloxy)phenyl]naphthalene (2c).** $[\alpha]^{20}_D$ –75.6 (*c* 1.86, chloroform); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.19 (q, J = 7.8 Hz, 6H), 0.58 (t, J = 7.8 Hz, 9H), 7.38 (d, J = 3.5 Hz, 2H), 7.41–7.49 (m, 5H), 7.53 (t, J = 7.9 Hz, 1H), 7.63 (dd, J = 1.0, 7.9 Hz, 2H), 7.88 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.80, 6.97, 98.26, 102.94, 118.12 (q, J = 317.5 Hz), 121.58, 124.88, 125.44, 125.75, 126.13, 127.43, 128.14, 128.23, 129.02, 129.07, 131.36, 131.74, 132.08, 133.57, 137.13, and 147.71; EI-MS m/z, 490 (M^+, 79), 461 (100), 433 (79), 405 (50), 271 (68), 242 (76). Anal. Calcd for $C_{25}H_{25}O_3F_3SSi$: C, 61.20; H, 5.14. Found: C, 61.46; H, 5.04. **1-[2,6-Bis(triethylsilylethynyl)phenyl]naphthalene (3c).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.19 (q, J = 7.5 Hz, 12H), 0.56 (t, J = 7.5 Hz, 18H), 7.37–7.47 (m, 4H), 7.57 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.94, 6.98, 95.92, 104.56, 124.50, 124.96, 125.23, 125.54, 125.92, 127.12, 127.19, 127.72, 127.80, 131.90, 132.03, 133.63, 137.44, and 146.67; EI-MS m/z, 480 (M^+, 82), 451 (100), 423 (53), 395 (24), 279 (33). Anal. Calcd for $C_{32}H_{40}Si_2$: C, 79.93; H, 8.39. Found: C, 79.66; H, 8.50. **(*S*)-1-[2-*t*-Butylethynyl-6-(trifluoromethanesulfonyloxy)phenyl]naphthalene (2d).** $[\alpha]^{20}_D$ –64.5 (*c* 1.64, chloroform); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.66 (s, 9H), 7.36–7.55 (m, 8H), 7.88 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.50, 29.89, 78.90, 104.74, 118.16 (q, J = 316.6 Hz), 120.69, 124.90, 125.69, 125.77, 126.36, 128.11, 128.23, 128.79, 128.90, 131.13, 131.82, 131.87, 133.47, 136.73, and 147.67; EI-MS m/z, 432 (M^+, 97), 299 (50), 284 (73), 269 (100), 239 (53). Anal. Calcd for $C_{23}H_{19}O_3F_3S$: C, 63.88; H, 4.43. Found: C, 63.98; H, 4.60. **1-[2,6-Di(*t*-butylethynyl)phenyl]naphthalene (3d).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.71 (m, 18H), 7.24–7.50 (m, 8H), 7.82 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.49, 30.17, 78.24, 102.51, 124.85, 124.91, 125.09, 125.24, 126.38, 127.04, 127.17, 127.25, 127.70, 130.34, 132.03, 133.38, 138.28, and 145.83; EI-MS m/z, 364 (M^+, 100), 295 (46), 277 (31), 263 (23). Anal. Calcd for $C_{28}H_{28}$: C, 92.26; H, 7.74. Found: C, 91.99; H, 7.95. **(*S*)-1-[2-Heptynyl-6-(trifluoromethanesulfonyloxy)phenyl]naphthalene (2e).** $[\alpha]^{20}_D$ –12.5 (*c* 1.43, chloroform); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.68–1.04 (m, 9H), 1.93 (t, J = 6.9 Hz, 2H), 7.35–7.58 (m, 8H), 7.89 (d, J = 7.3 Hz, 1H), 7.91 (d, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.71, 18.98, 21.93, 27.50, 30.70, 78.30, 96.53, 118.11 (q, J = 321.2 Hz), 120.63, 124.88, 125.49, 125.74, 126.05, 128.16, 128.31, 128.93, 131.65, 131.77, 133.43, 136.37, 144.16, and 147.72; EI-MS m/z, 446 (M^+, 100), 313 (45), 242 (83), 231 (86). Anal. Calcd for $C_{24}H_{21}O_3F_3SSi$: C, 64.56; H, 4.72. Found: C, 64.27; H, 4.82. **1-[2,6-Di(heptynyl)phenyl]naphthalene (3e).** ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.61–0.96 (m, 18H), 1.86 (t, J =

6.6 Hz, 4H), 7.20–7.46 (m, 8H), 7.75 (d, *J* = 7.3 Hz, 1H), 7.78 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.73, 18.98, 21.97, 27.62, 30.24, 79.16, 95.29, 125.16, 125.49, 125.64, 125.97, 127.07, 128.01, 128.14, 128.61, 130.81, 131.79, 133.45, 138.38, and 143.27. Anal. Calcd for $C_{30}H_{32}$: C, 91.78; H, 8.95. Found: C, 91.66; H, 8.93. **1-[2-Trifluoromethanesulfonyloxy-6-(triphenylsilylethynyl)phenyl]-2-methylbenzene (85% ee) (2f).** mp 98-99 °C; $[\alpha]^{20}_{D}$ –23.5 (*c* 1.4, chloroform); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.09 (s, 3H), 7.23-7.41 (m, 21H), 7.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.54, 94.57, 106.09, 118.26 (q, *J* = 315.0 MHz), 122.18, 125.56, 126.00, 127.90, 128.79, 128.85, 129.87, 130.12, 130.29, 132.53, 132.96, 133.02, 135.41, 136.94, 138.56, and 147.11. Anal. Calcd $C_{34}H_{25}O_3F_3SSi$: C, 68.21; H,4.21. Found: C, 68.24; H, 4.08. **1-[2,6-Bis(triphenylsilylethynyl)phenyl]-2-methylbenzene (3f).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.55 (s, 3H), 7.16–7.46 (m, 35H) 7.65 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.66, 92.67, 107.59, 123.28, 125.54, 127.01, 127.83, 128.31, 129.71, 129.86, 133.09, 133.35, 135.45, 136.30, 138.84, and 148.09. Anal. Calcd for $C_{53}H_{40}Si_2$: C, 86.84; H, 5.50. Found: C, 86.81; H, 5.54. **1-[2-Trifluoromethanesulfonyloxy-6-(triphenylsilylethynyl)phenyl]-2-phenybenzene (99% ee) (2g).** $[\alpha]^{20}_{D}$ –77.0 (*c* 1.1, chloroform); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.06-7.14 (m, 6H), 7.26-7.34 (m, 7H), 7.35-7.46 (m, 1H), 7.49 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.60 (dd, *J* = 1.0, 7.8 Hz, 1H), 7.64 (dd, *J* = 1.5, 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 95.21, 106.55, 118.18 (q, *J* = 321.3 MHz), 121.78, 126.23, 126.76, 127.02, 127.68, 127.93, 128.03, 128.65, 129.05, 129.89, 131.62, 131.97, 132.31, 132.96, 135.46, 138.53, 140.72, 142.21, and 146.74. Anal. Calcd $C_{39}H_{27}O_3F_3SSi$: C, 70.89; H,4.12. Found: C,70.44; H, 4.30. **1-[2,6-Bis(triphenylsilylethynyl)phenyl]-2-phenylbenzene (3g).** mp 181-183 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88 (t, *J* = 7.9 Hz, 2H), 6.95 (d, *J* = 1.5 Hz, 1H), 6.96 (s, 1H), 7.04 (t, *J* = 7,4 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.22–7.50 (m, 36H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 92.99, 107.97, 123.73, 126.25, 126.84, 126.94, 127.29, 127.63, 127.88, 128.04, 129.46, 129.76, 130.07, 130.63, 132.96, 133.34, 135.51, 137.65, 141.03, 141.89, and 147.99. Anal. Calcd for $C_{58}H_{42}Si_2$: C, 87.61; H, 5.32. Found: C, 87.34; H, 5.34.

(*S*)-1-(2-Ethynyl-6-phenylphenyl)naphthalene (4). To a mixture of **2a** (20.0 mg, 0.0315 mmol), dichloro[(2-dimethylamino)ethyldiphenylphosphine]palladium (0.7 mg, 0.002 mmol), and lithium bromide (1.0 mmol) in 50 μL of toluene was added phenylmagnesium bromide (1 M, 0.1 mmol) in ether, and the mixture was stirred at 40 °C. The reaction mixture was quenched with water and extracted with 50 mL of ether. Combined ether extracts were washed with brine (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. Tetrabutylammonium fluoride was added to the residue, and the reaction mixture was stirred at room temperature for 1 h. The mixture was evaporated and extracted with 50 mL of ether. Combined ether extracts were washed with water (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/ethyl acetate = 20/1 to give 10.8 mg (61% yield) of **4**. $[\alpha]^{20}_D$ +88 (*c* 0.91, chloroform); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.64 (s, 1H), 6.98 (s, 5H), 7.18-7.53 (m, 6H), 7.67 (dd, *J* = 2.6, 6.6 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 80.28, 82.72, 123.66, 124.88, 125.39, 125.77, 126.08, 126.54, 127.43, 127.57, 127.60, 128.04, 128.21, 128.85, 130.67, 131.97, 132.49, 133.07, 137.23, 140.83, 141.72, and 142.78; EI-MS m/z, 304 (M^+, 100), 289 (30), 276 (16), 150 (39). Anal. Calcd $C_{24}H_{16}$: C, 94.70; H, 5.30. Found: C, 94.56; H, 5.02.

(*R*)-1-(2-Ethynyl-6-phenylphenyl)naphthalene (4). To a mixture of **5** (21.0mg, 0.0490 mmol), $PdCl_2(PPh_3)_2$ (1.8 mg, 0.0026 mmol), CuI (0.5 mg, 0.003 mmol), and di-isoproplyamine (25 μL) in 65 μL of DMF was added triphenylsilylethyne (28 mg, 0.098 mmol) and the mixture was stirred at 40 °C for 48 h. The reaction mixture was evaporatied, diluted with 50 mL of ether and washed with brine (2 × 20 mL). The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. Tetrabutylammonium fluoride was added to the residue, and the reaction mixture was stirred at room temperature for 1 h. The mixture was evaporatied and extracted with 50 mL of ether. Combined ether extracts were washed with water (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/ethyl acetate = 20/1) to give 11.0 mg (40% yield) of **4**. $[\alpha]^{20}_D$ –104 (*c* 0.23, chloroform); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.64 (s, 1H), 6.98 (s, 5H), 7.18-7.53 (m, 6H), 7.67 (dd, *J* = 2.6, 6.6 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H). Anal. Calcd $C_{24}H_{16}$: C, 94.70; H, 5.30. Found: C, 94.56; H, 5.02.

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Chapter 3

Palladium Catalysts for Cross-Coupling of Ortho-Substituted Aryl Triflates with Grignard Reagents

Abstract: Dichloro[(2-dimethylamino)propyldiphenylphosphine]palladium ($PdCl_2$(alaphos)) and dichloro[1,3-bis(diphenylphosphino)propane]palladium ($PdCl_2$(dppp)) were found to be much more effective catalysts than $PdCl_2(PPh_3)_2$ and other palladium complexes for cross-coupling of sterically congested aryl triflates with aryl Grignard reagents.

Introduction

The cross-coupling reaction of organic triflates with organometallic reagents has provided an efficient method for carbon-carbon bond formation since Snieckus first reported nickel-catalyzed cross-coupling reaction of aryl or vinyl triflates with Grignard reagents in 1992.[1] However, there have been few works concerning the effects of phosphine ligands on the catalytic activity in the palladium-catalyzed cross-coupling of aryl triflatas with Grignard reagents. As described in Chapter 1, during the investigation of the enantioposition-selective cross-coupling of aryl ditriflates with the Grignard reagents, it was found that the palladium complexes coordinated with β-(dimethylamino)alkyldiphenylphosphines are highly effective as catalysts for the Grignard cross-coupling of aryl triflates containing sterically bulky groups at ortho-position.

In this chapter, are described the effects of phosphine ligands on the catalytic activity of the palladium-catalyzed cross-coupling of sterically congested aryl triflates with aryl Grignard reagents. The ligand effects were different from those observed for the cross-coupling of non-congested aryl halides or triflates,[2,3] that is, dichloro[(2-dimethylamino)propyldiphenylphoshine] palladium ($PdCl_2$(alaphos)) and dichloro-[1,3-bis(diphenylphosphino)propane]palladium ($PdCl_2$-(dppp)) were much more effective catalysts than $PdCl_2(PPh_3)_2$ and other palladium complexes for the cross-coupling of sterically congested aryl triflates.

Results and Discussion

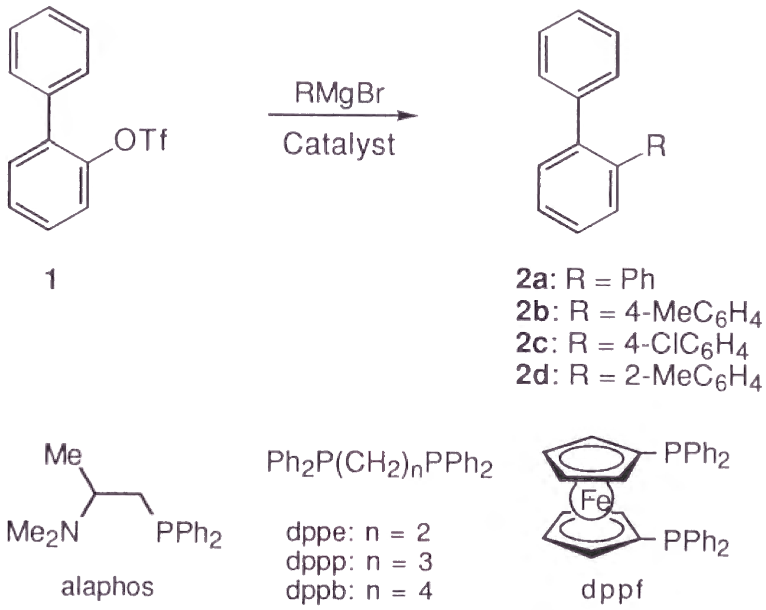
Various types of phosphine ligands were examined for the palladium-catalyzed cross-coupling of 2-phenylphenyl triflates (**1**) which is a sterically congested aryl triflate (Scheme 1). In a typical experiment, to a mixture of 2-phenylphenyl triflate (**1**) (1.0 mmol), dichloro[(2-dimethylamino)propyldiphenylphosphine]palladium ($PdCl_2$(alaphos)) (0.05 mmol), and lithium bromide (1.0 mmol) in ether was added phenylmagnesium bromide (2.0 mmol) in ether at 0 °C, and the mixture was stirred at 30 °C for 3 h. Acidic hydrolysis and preparative TLC on silica gel gave 95% yield of 1,2-diphenylbenzene (**2a**) (entry 1 in Table 1). The reaction was much slower with the palladium catalysts coordinated with triphenylphosphine ligands, $PdCl_2(PPh_3)_2$ and

Table 1. Effects of Phosphine Ligands on the Cross-Coupling of Aryl Triflate **1** with Grignard Reagents[a]

entry	catalyst	Grignard	time (h)	yield (%) of **2**[b]
1	$PdCl_2$(alaphos)	PhMgBr	3	95 (**2a**)
2	$PdCl_2(PPh_3)_2$	PhMgBr	24	25 (**2a**)
3	$Pd(PPh_3)_4$	PhMgBr	24	2 (**2a**)
4	$PdCl_2$(dppf)	PhMgBr	24	10 (**2a**)
5	$PdCl_2$(dppe)	PhMgBr	14	93 (**2a**)
6	$PdCl_2$(dppp)	PhMgBr	1	97 (**2a**)
7	$PdCl_2$(dppb)	PhMgBr	3	95 (**2a**)
8	$NiCl_2(PPh_3)_2$	PhMgBr	24	97 (**2a**)
9[c]	$Pd(PPh_3)_4$	$PhB(OH)_2$	24	67 (**2a**)

[a] The cross-coupling was carried out with 2 equiv of Grignard reagent in the presence of 1 equiv. of LiBr and 5 mol % palladium catalyst in ether at 30 °C. [b] Isolated yield by silica gel chromatography. [c] In the presence of K_3PO_4 in refluxing dioxane/H_2O (10/1)

Scheme 1



1

2a: R = Ph
2b: R = 4-MeC_6H_4
2c: R = 4-ClC_6H_4
2d: R = 2-MeC_6H_4

alaphos

$Ph_2P(CH_2)_nPPh_2$

dppe: n = 2
dppp: n = 3
dppb: n = 4

dppf

$Pd(PPh_3)_4$, which gave **2a** in low yields after a prolonged reaction time (entries 2 and 3), though the triphenylphosphine-palladium complexes have been often used for the cross-coupling of aryl halides with several organometallic reagents.[2] The cross-coupling was also slow with dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium ($PdCl_2$(dppf)), which is one of the most effective catalysts for the Grignard cross-coupling of aryl bromides and related reactions (entry 4).[4]

Table 2. Cross-Coupling of Aryl Triflates with Grignard Reagents[a]

entry	triflate	R in RMgBr	catalyst	time (h)	yield (%)[b]
1	**1**	4-MeC_6H_4	$PdCl_2$(alaphos)	4	93 (**2b**)
2	**1**	4-MeC_6H_4	$PdCl_2$(dppp)	1	92 (**2b**)
3	**1**	4-ClC_6H_4	$PdCl_2$(alaphos)	2	92 (**2c**)
4	**1**	4-ClC_6H_4	$PdCl_2$(dppp)	1	91 (**2c**)
5	**1**	4-ClC_6H_4	$NiBr_2(PPh_3)_2$	1	5 (**2c**)
6	**1**	2-MeC_6H_4	$PdCl_2$(alaphos)	3	92 (**2d**)
7	**1**	2-MeC_6H_4	$PdCl_2$(dppp)	1	93 (**2d**)
8	**3**	2-MeC_6H_4	$PdCl_2$(alaphos)	2	92 (**7**)[c]
9	**3**	2-MeC_6H_4	$PdCl_2$(dppp)	1	91 (**7**)[c]
10	**3**	2-MeC_6H_4	$NiBr_2(PPh_3)_2$	1	5 (**7**)[c]
11	**4**	Ph	$PdCl_2$(alaphos)	5	95 (**8**)
12	**4**	Ph	$PdCl_2$(dppp)	1	97 (**8**)
13	**4**	Ph	$NiBr_2(PPh_3)_2$	24	12 (**8**)
14	**5**	Ph	$PdCl_2$(dppp)	14	94 (**9a**)[d]
15	**5**	2-MeC_6H_4	$PdCl_2$(dppp)	18	65 (**9b**)[d]
16	**6**	Ph	$PdCl_2$(dppp)	1	97 (**10**)

[a] The cross-coupling was carried out with 2 equiv of Grignard reagents in ether in the presence of 1 equiv of LiBr and 5 mol % palladium catalyst at 30 °C. [b] Isolated yield by silica gel chromatography. [c] Contaminated with a small amount of 2,2'-dimethylbiphenyl and the yield was calibrated by ^{1}H NMR. [d] GLC yield.

Of the palladium catalysts containing α,ω-bis(diphenylphosphino)-alkanes (entries 5-7), dichloro[1,3-bis(diphenylphosphino)propane]palladium ($PdCl_2$(dppp)) was most catalytically active, a little more active than $PdCl_2$(alaphos), in the reaction with the phenyl Grignard reagent to give **2a** in 97% yield. The chemical yield of **2a** obtained with $PdCl_2$(alaphos) or $PdCl_2$(dppp) shown above is higher than that obtained by the reaction of **1** with phenylboronic acid in the presence of $Pd(PPh_3)_4$ (entry 9).[5]

The high catalytic activity observed here for $PdCl_2$(alaphos) is ascribed, at least partly, to the high basicity of the alaphos ligand which is a chelating ligand with a trialkylamino group and an alkyldiphenylphosphino group. The high basicity will accelerate the oxidative addition of sterically congested aryl triflates to the palladium(0) species. The oxidative addition is one of the key steps in the catalytic cycle of the transition metal-catalyzed cross-coupling reactions.[2] Higher basicity of α,ω-bis(diphenylphosphino)alkanes than PPh_3 or dppf may be also related to the higher catalytic

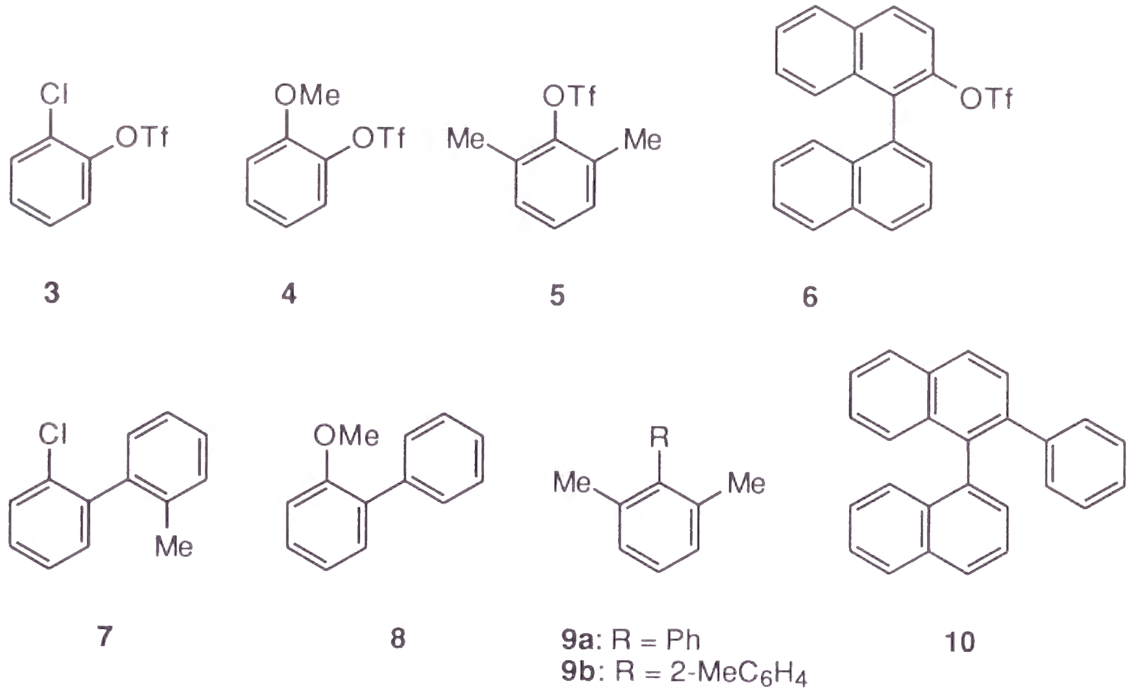


Figure 1. The Chemical Structures of Compounds Shown in Table 2.

activity of the palladium complexes of dppe, dppp, and dppb than those of triarylphosphines.

The palladium catalysts, $PdCl_2$(alaphos) and $PdCl_2$(dppp), were also effective for the reaction of 2-phenylphenyl triflates (**1**) with some other aryl Grignard reagents (entries 1-7, in Table 2). The triflate group in **1** was successfully substituted with 4-methylphenyl, 4-chlorophenyl, and 2-methylphenyl groups by use of these palladium catalysts. On the other hand, the nickel complex $NiBr_2(PPh_3)_2$, which have been reported to be effective catalyst for the cross-coupling of aryl triflates,[5] can not be used for the cross-coupling of aryl triflates and Grignard reagents containing chloride on the aromatic ring, the chloride being reactive towards the nickel-catalyzed cross-coupling leading to polymeric products (entries 5, 10). Other sterically congested aryl triflates **3-6** (Figure 1), which contain substituents at ortho-position(s) also underwent the cross-coupling with phenyl, and 2-methylphenyl Grignard reagents to give the corresponding cross-coupling products in high yields by use of $PdCl_2$(alaphos) or $PdCl_2$(dppp) catalyst (entries 8-16 in Table 2).

Experimental

General. All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5 (Merck, SICAPENT). NMR spectra were recorded on a JEOL JNM-EX270 spectrometer (270 MHz for ^1H) or a JEOL JNM LA500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal TMS standard for ^{1}H NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR.

Materials. PPh_3, dppe, dppp, dppb, and dppf from Aldrich Chemical Company, Inc. were commercially available. Palladium complex $PdCl_2$(alaphos) was prepared according to the reported procedures.[6] Aryl triflates were prepared by triflation of phenols with triflluoromethanesulfonic anhydride and pyridine. Ether and toluene were distilled from sodium benzophenone ketyl under nitrogen.

Grignard Cross-Coupling. Typical procedure. To a mixture of 2-phenylphenyl triflate (**1**) (60.4 mg, 0.20 mmol), dichloro[1,3-bis(diphenylphosphino)propane]palladium (5.9 mg, 0.01 mmol) and lithium bromide (17.3 mg, 0.20 mmol) in 400 mL of ether was added phenylmagnesium bromide (2 M ether solution, 200 mL, 0.4 mmol) at 0 °C, and stirred at 30 °C for 1 h. The mixture was hydrolyzed with 10% hydrochloric acid and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC (elution with hexane/benzene = 20/1) to give 44.7 mg (97% yield) of 1,1':2'-1"-terphenyl (**2a**). **1,1':2'-1"-Terphenyl (2a).** ^{1}H-NMR ($CDCl_3$) δ 7.13-7.44 (m, 14H). **4-Methyl-1,1':2'-1"-terphenyl (2b).** ^{1}H-NMR ($CDCl_3$) δ 2.30 (s, 3H), 7.02 (s, 4H), 7.13-7.24 (m, 5H), 7.40 (s, 4H). **4-Chloro-1,1':2'-1"-terphenyl (2c).** ^{1}H-NMR ($CDCl_3$) δ 7.03-7.43 (m, 13H). **2-Methyl-1,1':2'-1"-terphenyl (2d).** ^{1}H-NMR ($CDCl_3$) δ 1.89 (s, 3H), 7.05-7.14 (m, 9H), 7.23-7.46 (m, 4H). **2-Chloro-2'-methyl-1,1'-biphenyl (7).** ^{1}H-NMR ($CDCl_3$) δ 2.06 (s, 3H), 7.14 (d, J = 7.0 Hz, 1H), 7.22-7.31 (m, 6H), 7.46 (m, 1H). **2-Methoxy-1,1'-biphenyl (8).** ^{1}H-NMR ($CDCl_3$) δ 3.80 (s, 3H), 6.97-7.06 (m, 2H), 7.29-7.42 (m, 5H), 7.51 (s, 1H), 7.54 (d, J = 1.7 Hz, 1H). **2,6-Dimethyl-1,1'-biphenyl (9a).** ^{1}H-NMR ($CDCl_3$) δ 2.02 (s, 6H), 7.09-7.60 (m, 8H). **2-Methyl-2',6'-dimethyl-1,1'-biphenyl (9b).** ^{1}H-NMR ($CDCl_3$) δ 2.02 (s, 6H), 2.00 (s, 3H), 7.09-7.60 (m, 7H). **2-Phenyl-1,1'-binaphthyl (10).** ^{1}H-NMR ($CDCl_3$) δ 6.99-7.09 (m, 5H), 7.22-7.49 (m, 8H), 7.66 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H). Anal. Calcd for $C_{26}H_{18}$: C, 94.51; H, 5.49. Found: C, 94.33; H, 5.60.

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Chapter 4

Control of Reactive Site in Palladium-Catalyzed Grignard Cross-Coupling of Arenes Containing both Bromide and Triflate

Abstract: In Chapter 4, is described the chemo-selectivity of the palladium-catalyzed Grignard cross-coupling of arenes containing both bromide and triflate. Reactive site depended on the ligands in palladium catalysts. That is, reaction of 4-bromophenyl triflate (**1**) with phenylmagnesium bromide in the presence of 5 mol % of $PdCl_2$(dppp) gave 97% yield of 4-bromobiphenyl (**2a**), which was formed by selective replacement of triflate in **1** by phenyl. On the other hand, bromide in **1** was substituted with the phenyl Grignard reagent selectively by use of $PdCl_2$(meo-mop)$_2$ to give 4-biphenyl triflate (**3a**) in high yield. The selective substitution was demonstrated to take place at the oxidative addition step to a palladium(0) species in a stoichiometric reaction of **1** with palladium(0) phosphine complexes.

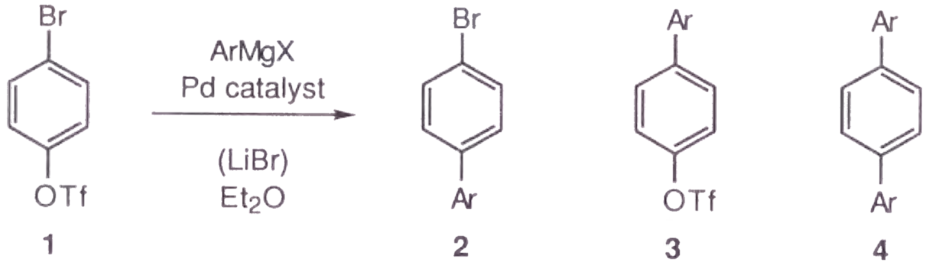
Introduction

The transition metal-catalyzed cross-coupling of aromatic electrophiles with organometallic reagents is recognized to be a versatile method for the construction of aromatic molecules.[1] In the palladium-catalyzed cross-coupling, aromatic iodides are generally more reactive than the corresponding bromides or triflates, iodides undergoing the substitution preferentially.[1] On the other hand, it is difficult to control the reactivity of aryl bromides and triflates in the palladium-catalyzed cross-coupling reactions.[2] One successful example is the reaction of 4-bromophenyl triflate with tributyl(vinyl)tin where the coordination number of phosphine ligand in a palladium-triphenylphosphine catalyst controls the selectivity.[3,4,5] In this Chapter, effects of phosphine ligands on the reactivity and selectivity were examined in the palladium-catalyzed cross-coupling, and it was found that selective replacement of either triflate or bromide by Grignard reagents is achieved by use of 1,3-bis(diphenylphosphino)propane (dppp) or 2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl (meo-mop) as a ligand.[6]

Results and Discussion

Effects of phosphine ligands on the reactivity and selectivity were examined in the palladium-catalyzed Grignard cross-coupling reaction of 4-bromophenyl triflate (**1**) with phenylmagnesium bromide (Scheme 1). The results are shown in Table 1. It was found that the triflate group in **1** is selectively substituted with phenyl group in the presence of palladium catalysts coordinated with bisphosphines. Of the bisphosphine complexes, $PdCl_2$(dppp) was most selective and catalytically active.[7] Thus, the reaction of **1** (1.0 mmol) with

Scheme 1



a: Ar = Ph. **b**: Ar = 2-MeC_6H_4. **c**: Ar = 4-ClC_6H_4

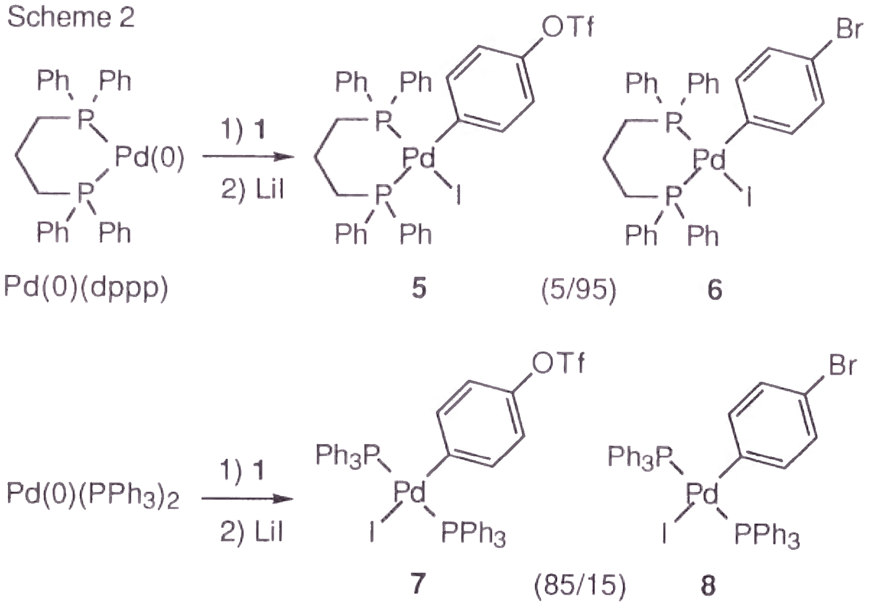
Table 1. Cross-coupling of 4-Bromophenyl Triflate (**1**) with Phenylmagnesium Bromide in the Presence of Palladium-phosphine Complexes[a]

		conditions			yield (%)[b] of			
entry	catalyst	additive	temp (•C)	time (h)	rec **1**	**2a**	**3a**	**4a**
1	$PdCl_2$(dppp)	LiBr	0	0.5	0	97	0	3
2	$PdCl_2$(dppp)	-	0	2	24	74	0	1
3	$PdCl_2$(dppe)	LiBr	0	2	40	59	0	0
4	$PdCl_2$(dppb)	LiBr	0	2	5	96	1	0
5	$PdCl_2$(dppf)	LiBr	0	2	40	46	4	7
6	$PdCl_2(PPh_3)_2$	LiBr	0	2	81	5	14	2
7	$PdCl_2(PPh_3)_2$[c]	LiBr	0	2	30	16	35	7
8	$PdCl_2(PPh_3)_2$[c]	–	0	2	3	9	43	11
9	$PdCl_2$(P(*o*-tol)3)2[c]	–	20	2	55	0	23	2
10	$PdCl_2$(meo-mop)2[c]	LiBr	20	2	19	2	62	10
11	$PdCl_2$(meo-mop)2[c]	–	20	2	6	0	68	4

[a] The cross-coupling was carried out with 1.2 equiv of the Grignard reagent in the presence or absence of 1 equiv of lithium bromide and 5 mol % of catalyst in ether unless otherwise noted. [b] Isolated yield by silica gel preparative TLC. 4-Bromobiphenyl (**2a**) was obtained as a mixture with a small amount of biphenyl, and the yield of **2a** was calculated on the basis of GLC and ^1H NMR analyses of the mixture. [c] With 2.0 equiv of the Grignard reagent.

phenylmagnesium bromide (1.2 mmol) in the presence of lithium bromide (1.0 mmol) and $PdCl_2$(dppp) (0.05 mmol) in ether (0.4 mL) at 0 °C for 30 min gave 97% yield of 4-bromobiphenyl (**2a**) together with a small amount (3%) of *p*-terphenyl (**4a**) (entry 1 in Table 1). None of the 4-biphenyl triflate (**3a**), which would be formed by phenylation of bromide in **1**, was detected. In the absence of lithium bromide, the cross-coupling was slower but the selectivity in forming **2a** was still high[8,9,10] (entry 2), indicating that lithium bromide is not responsible for the high triflate-selectivity. Palladium complexes coordinated with 1,2-bis(diphenylphosphino)ethane (dppe) and 1,4-bis(diphenylphosphino)butane (dppb) also catalyzed the substitution of triflate forming **2a** with high selectivity, though the reaction is slower than that catalyzed by $PdCl_2$(dppp) (entries 3 and 4). On the other hands, use of monodentate phosphine ligands reversed the selectivity, **1** undergoing the cross-coupling at bromide site to give 4-biphenyl triflate (**3a**) preferentially. The selectivity forming **3a** is not so high with triphenylphosphine complex, which gave 43% of **3a** together with 9% of **2a** at highest selectivity (entries 6–8). The selectivity and catalytic activity were improved by use of sterically more bulky phosphine ligands. Highest yield forming **3a** was 68%, which was observed in the reaction catalyzed by $PdCl_2$(meo-mop)$_2$[11,12] (entry 11).

Scheme 2



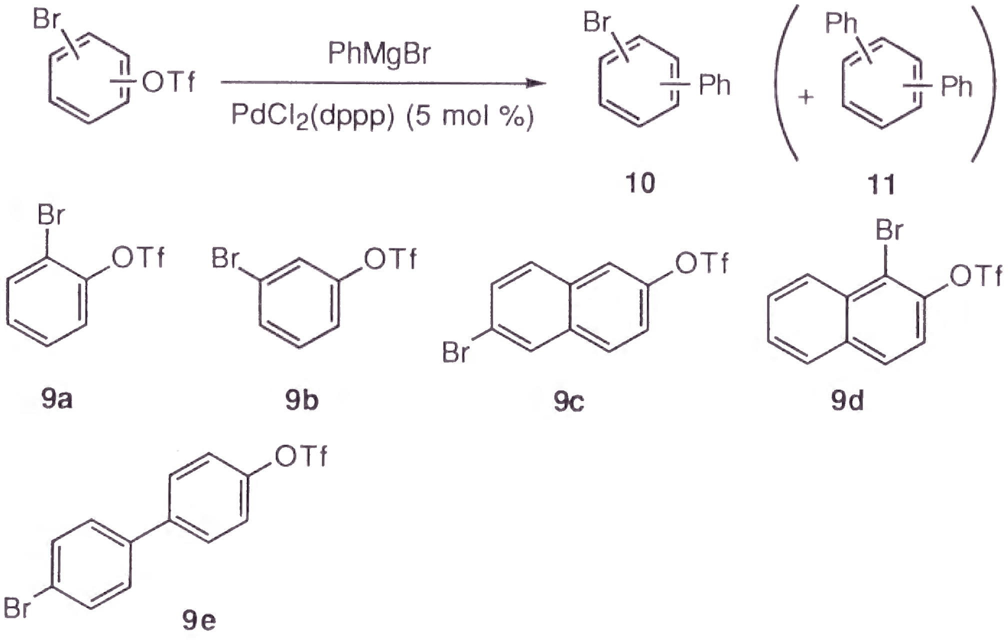
The selective substitution of either triflate or bromide in the Grignard cross-coupling should be determined at oxidative addition step in the catalytic cycle. The effects of phosphine ligands on the selectivity at the oxidative addition step were demonstrated in a stoichiometric reaction of palladium(0) phosphine complexes with 4-bromophenyl triflate (**1**) (Scheme 2). Thus, a palladium(0) species coordinated with bisphosphine dppp, which was generated by treatment of a mixture of $[PdCl(\pi\text{-}C_3H_5)]_2$ and dppp (1 equiv to Pd) with one equiv of dimethyl sodiomalonate in THF, was allowed to react with **1** at 0 °C for 1 h. Anion exchange by addition of excess lithium iodide to the reaction mixture gave 60% yield of the palladium(II) complexes, PdI(Ar)(dppp), where Ar group consists of 4-trifluoromethylsulfonyloxyphenyl (**5**) and 4-bromophenyl (**6**) in a ratio of 5 to 95, indicating that triflate group participated in the oxidative addition preferentially. Structures of **5** and **6** were assigned by comparison with authentic samples prepared by reaction of the Pd(0)–dppp with 4-iodophenyl triflate and 4-iodophenyl bromide, respectively. Reverse selectivity was observed in the oxidative addition of **1** to a palladium(0) complex coordinated with triphenylphosphine, which gave palladium(II) complexes (69% yield) containing

Table 2. Cross-coupling of Bromoaryl Triflates **1** and **9** with Grignard Reagents in the Presence of $PdCl_2$(dppp)[a]

entry	triflate	Ar in ArMgBr (equiv)	conditions temp (°C)	time	yield (%) of coupling products[c]	
1	**1**	2-MeC_6H_4 (1.5)	0	2	91 (**2b**)	3 (**4b**)
2	**1**	4-ClC_6H_4 (1.3)	0	2	95 (**2c**)	3 (**4c**)
3	**9a**	Ph (1.5)	20	12	82 (**10a**)	2 (**11a**)
4	**9b**	Ph (1.3)	0	2	91 (**10b**)	4 (**11b**)
5	**9c**	Ph (1.3)	0	2	91 (**10c**)	3 (**11c**)
6	**9d**	Ph (2.0)	30	24	91 (**10d**)	2 (**11d**)
7	**9e**	Ph (1.5)	0	1	91 (**10e**)	0 (**11e**)

[a] All reactions were carried out in the presence of 1 equiv of lithium bromide and 5 mol % of $PdCl_2$(dppp). [b] Isolated yield by silica gel preparative TLC. In entries 1-6, cross-coupling products **2** and **10** were obtained as a mixture with a small amount of biphenyls formed by homocoupling of the Grignard reagents, and the yields were calculated on the basis of GLC and ^1H NMR analyses of the mixture. [c] No arylated triflates, which would result from monosubstitution of bromide, were detected.

Scheme 3



4-trifluoromethylsulfonyloxyphenyl (**7**) and 4-bromophenyl (**8**) in a ratio of 85 to 15. The oxidative addition shown above is the first example of successful control of the leaving group-selectivity by a proper choice of phosphine ligand on palladium.

The selective substitution of triflate group on **1** was also observed in the cross-coupling with 2-methylphenyl and 4-chlorophenyl Grignard reagents in the presence of $PdCl_2(dppp)$ as a catalyst to give over 90% yield of the corresponding monoarylation products, **2b** and **2c**, respectively (Table 2, entries 1 and 2). Aromatic compounds **9a-e**, which contain both triflate and bromide on benzene, naphthalene, or biphenyl skeleton, also underwent the selective substitution of the triflate group (Scheme 3). Replacement of triflate by phenyl took place with high selectivity in the reaction with phenylmagnesium bromide in the presence of $PdCl_2(dppp)$, bromide remaining intact (entries 3–7).

Experimental

General. All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5 (Merck, SICAPENT). NMR spectra were recorded on a JEOL JNM-EX270 spectrometer (270 MHz for ^{1}H) or a JEOL JNM LA500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal TMS standard for ^{1}H NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR.

Materials. PPh_3, dppe, dppp, dppb, and dppf from Aldrich Chemical Company, Inc. were commercially available. Palladium complex $PdCl_2$(alaphos) was prepared according to the reported procedures.[13] Aryl triflates were prepared by triflation of phenols with trifluoromethanesulfonic anhydride and pyridine. Ether and toluene were distilled from sodium benzophenone ketyl under nitrogen.

Grignard Cross-Coupling of Aryl Triflates with Aryl Grignard Reagents Catalyzed by $PdCl_2$(alaphos). Typical Procedure. To a mixture of 4-bromophenyl triflate (**1**) (60.4 mg, 0.2 mmol), dichloro[(2-dimethylamino)propyldiphenylphosphine]palladium ($PdCl_2$(alaphos)) (4.4 mg, 0.01 mmol), and lithium bromide (17.2 mg, 0.2 mmol) in 100 μL of ether was added phenylmagnesium bromide (290 μL, 1.4 M, 0.4 mmol) in ether/toulene (2/1) at room temperature, and the mixture was stirred at 30 °C until **1** was not detected by silica gel TLC (hexane/benzene = 3/1). The reaction mixture was quenched with water and extracted with 100 mL of ether. Combined ether extracts were washed with brine (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/benzene = 3/1) to give 44.6 mg (93% yield) of **2a** . The reaction conditions and results are summarized in Table 1.

4-Bromobiphenyl (2a). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.34–7.48 (m, 5H), 7.55-7.62 (m, 4H). **1-Phenyl-4-trifluoromethanesulfonyloxybenzene (3a).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.40 (t, *J* = 8.5 Hz, 1H), 7.47 (t, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H). **1,1':4',1''-Terphenyl (4a).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (t, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 4H), 7.65 (t, *J* = 7.5 Hz, 4H), 7.68 (s, 4H). **1-Bromo-4-(2-methylphenyl)benzene (2b).** ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.25 (s, 3H), 7.19-7.36 (m, 6H), 7.54 (d, *J* = 8.5 Hz, 2H). **1,4-Di(2-methylphenyl)benzene (4b).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.35 (s, 6H), 7.25-7.31 (m, 8H), 7.37 (d, *J* = 1.0 Hz, 4H). **1-Bromo-4-(4-chlorophenyl)benzene (2c).** ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H). **1,4-Di(4-chlorophenyl)benzene (4c).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21–7.49 (m, 12H). **1-Bromo-2-phenylbenzene (10a).** ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.18-7.45 (m, 8H), 7.67 (dd, *J* = 7.9, 1.0 Hz, 1H). **1,1':2',1''-Terphenyl (11a).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13-7.45 (m, 14H). **1-Bromo-3-phenylbenzene (10b).** ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.25–7.49 (m, 11H), 7.63-7.68 (m, 3 H). **1,1':3',1''-Terphenyl (11b).** ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.35-7.80 (m, 14H). **6-Bromo-2-phenylnaphthalene (10c).** ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.42-7.49 (m, 6H), 7.53-7.68 (m, 2H), 7.87 (t, *J* = 8.6 Hz, 2H), 8.43 (d, *J* = 8.6 Hz, 1H). **2,6-Diphenylnaphthalene (11c).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21-8.08 (m, 16H). **1-Bromo-2-phenylnaphthalene (10d).** ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.42–7.67 (m, 8H), 7.87 (t, *J* = 7.7 Hz, 2H), 8.42 (d, *J* = 7.7 Hz, 1H). **1,2-Diphenylnaphthalene (11d).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.12-7.31 (m, 10H), 7.40 (t, *J* = 8.3 Hz, 1H), 7.49 (t, *J* = 6.9 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 1H). **4-Bromo-4'-phenylbiphenyl (10e).** ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.18-7.51 (m, 13H)

Oxidative Addition of Bromophenyl Triflate to a Pd(0)-dppp Complex. To a mixture of $[PdCl(\pi\text{-}C_3H_5)]_2$ (73.2 mg, 0.2 mmol) and dppp (168.4 mg, 0.4 mmol) in 2.5 mL of THF was added dimethyl sodiomalonate (820 μL, 0.5 M, 0.41 mmol) in THF at 0 °C. After 10 min, 4-bromophenyl triflate (244 mg, 0.8 mmol) was added to the mixture, and stirring was continued for 1 h. Then LiI (106 mg, 0.8 mmol) was added to the mixture at rt. After stirring for 30 min, the mixture was diluted with 100 mL of chloroform and washed with water (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1) to give 193.3 mg of a mixture of $PdI(4\text{-}TfOC_6H_4)(dppp)$ (**5**) and $PdI(4\text{-}BrC_6H_4)(dppp)$ (**6**) in a ratio of 5 to 95. **PdI(4-TfOC$_6$H$_4$)(dppp) (5).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.91 (m, 2H), 2.42 (m, 2H), 2.55 (m, 2H), 6.49 (dd, *J*(H,H) = 8.3, *J*(H,P) = 1.5 Hz, 2H), 6.98 (ddd, *J*(H,H) = 8.3, *J*(H,P) = 7.8, *J*(H,P) = 2.0 Hz, 2H), 7.16-7.46 (m, 16H), 7.78 (m, 4H); ^{31}P NMR ($CDCl_3$, 109 MHz) δ –9.59 (d, *J* = 52.5 Hz, 1P), 10.85 (d, *J* = 52.5 Hz, 1P). **PdI(4-BrC$_6$H$_4$)(dppp) (6).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.90 (m, 2H), 2.41 (m, 2H), 2.53 (m, 2H), 6.66 (dd, *J*(H,H) = 8.4, *J*(H,P) = 2.0 Hz, 2H), 6.76 (ddd, *J*(H,H) = 8.4, *J*(H,P) = 7.8, *J*(H,P) = 2.0 Hz, 2H), 7.16-7.45 (m, 16H), 7.79 (m, 4H); ^{31}P NMR ($CDCl_3$, 109 MHz) δ –9.40 (d, *J* = 52.5 Hz, 1P), 11.17 (d, *J*

= 52.5 Hz, 1P).

Oxidative Addition of Bromophenyl Triflate to a Pd(0)(PPh_3)$_2$ complex. To a mixture of [PdCl(π-C_3H_5)]$_2$ (73.2 mg, 0.2 mmol) and triphenylphosphine (215.1 mg, 0.82 mmol) in 2.5 mL of THF was added dimethyl sodiomalonate (820 μL, 0.5 M, 0.41 mmol) in THF at 0 °C. After 10 min, 4-bromophenyl triflate (244 mg, 0.8 mmol) was added to the mixture, and stirring was continued for 1 h. LiI (106 mg, 0.8 mmol) was added to the mixture at rt. After stirring for 30 min, the mixture was diluted with 100 mL of chloroform and washed with water (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/benzene = 1/3) to give 268.5 mg of mixture of trans-PdI(4-TfOC_6H_4)(PPh_3)$_2$ (**7**) and trans-PdI(4-BrC_6H_4)(PPh_3)$_2$ (**8**) in a ratio 85 to 15. **trans-PdI(4-TfOC_6H_4)(PPh_3)$_2$ (7).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.16 (d, *J*(H,H) = 8.5 Hz, 2H), 6.68 (dt, *J*(H,H) = 8.5, *J*(H,P) = 1.5 Hz, 2H), 7.25-7.37 (m, 18H), 7.49-7.54 (m, 12H); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 23.26 (s). **trans-PdI(4-BrC_6H_4)(PPh_3)$_2$. (8)** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.33 (d, *J*(H,H) = 8.3 Hz, 2H), 6.42 (dt, *J*(H,H) = 8.3, *J*(H,P) = 2.0 Hz, 2H), 7.25-7.36 (m, 18H), 7.49-7.53 (m, 12H); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 23.32 (s).

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Chapter 5

Palladium-Catalyzed Cross-Coupling of Aryl Triflates with Alkynyl Grignard Reagents

Abstract: Dichloro[(2-dimethylamino)propyldiphenylphosphine]palladium ($PdCl_2$(alaphos)) was found to be much more effective as catalyst than other palladium complexes for cross-coupling of aryl triflates with alkynyl Grignard reagents. Reaction of bromoaryl triflates with alkynyl Grignard reagents in the presence of 5 mol % of $PdCl_2$(alaphos) gave high yields of alkynyl arene bromides formed by selective replacement of triflate by alkynyl group.

Introduction

Alkynyl arenes are very useful materials for π-conjugated polymers, liquid crystals, and dehydrobenzoannulenes, etc.[1] Sonogashira method is well known to be effective synthetic method for alkynyl arenes.[2] Although the Grignard cross-coupling of aryl electrophiles is generally recognized to be a versatile method for the construction of aromatic compounds, to our knowledge, no reports have appeared concerning the Grignard cross-coupling of aryl triflates with alkynylmagnesium halides.[3] Furthermore, there are no examples of chemoselective alkynylation of bromoaryl triflates by transition metal-catalyzed cross-coupling, because of the difficulty in controlling the reactivity of bromide and trifluoromethanesulfonyl group in the palladium-catalyzed cross-coupling reactions.[4,5] In Chapter 2 which is concerned with enantioposition-selective cross-coupling of aryl triflates with alkynyl Grignard reagents, it was described that palladium complexes coordinated with β-(dimethylamino)alkyldiphenylphosphines are highly effective as catalysts for the Grignard cross-coupling.[6] In this chapter, it is described that $PdCl_2$(alaphos),[7] where alaphos stands for (2-dimethylamino)propyldiphenylphosphine, is a unique catalyst which efficiently catalyzes the Grignard cross-coupling of aryl triflates with alkynyl Grignard reagents. Moreover it was found that selective replacement of triflate occurred in the reaction of bromoaryl triflates with alkynyl Grignard reagents catalyzed by $PdCl_2$(alaphos) to give alkynyl arene bromides in high yields.

Results and Discussion

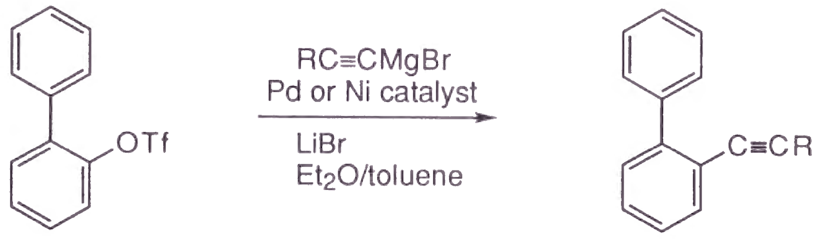
Effects of phosphine ligands on the reactivity in the palladium-catalyzed cross-coupling of 2-phenylphenyl triflate (**1**) with phenylethynylmagnesium bromide, which was generated by the reaction of phenylethyne with ethylmagnesium bromide, are summarized in Table 1. The cross-coupling was carried out with 2 equiv of the Grignard reagent in the presence of 1 equiv of LiBr and 5 mol % of palladium catalyst at 30 °C. It was found that $PdCl_2$(alaphos) is by far the most

Table 1. Effects of Phosphine Ligands on the Cross-Coupling of Aryl Triflate **1** with Grignard Reagents[a]

entry	catalyst	Grignard	time (h)	yield (%) of **2**[b]
1	$\mathrm{PdCl_2}$(alaphos)	PhC≡CMgBr	6	93 (**2a**)
2	$\mathrm{PdCl_2(PPh_3)_2}$	PhC≡CMgBr	24	30 (**2a**)
3	$\mathrm{PdCl_2}$(dppp)	PhC≡CMgBr	6	0 (**2a**)
4	$\mathrm{PdCl_2}$(dppf)	PhC≡CMgBr	24	3 (**2a**)
5	$\mathrm{NiCl_2(PPh_3)_2}$	PhC≡CMgBr	6	0 (**2a**)
6	$\mathrm{PdCl_2}$(alaphos)	$\mathrm{Ph_3Si}$C≡CMgBr	10	99 (**2b**)

[a] The cross-coupling was carried out with 2 equiv of Grignard reagent in the presence of 1 equiv of LiBr and 5 mol % palladium catalyst in ether/toluene (3:1) at 30 °C. [b] Isolated yield by silica gel chromatography.

Scheme 1



1

2a: R = Ph
2b: R = $\mathrm{Ph_3Si}$

effective of the palladium and nickel catalysts examined to give 93% yield of 2-phenylethynylbiphenyl (**2a**) in the reaction carried out for 6 h (entry 1). The second best catalyst was $\mathrm{PdCl_2(PPh_3)_2}$, but the reaction was much slower, 30% of **2a** being formed after 24 h (entry 2). $\mathrm{PdCl_2}$(dppp), $\mathrm{PdCl_2}$(dppf), and $\mathrm{NiCl_2(PPh_3)_2}$ were all much less catalytically active than $\mathrm{PdCl_2}$(alaphos) for the alkynylation (entries 3-5). The reaction with triphenylsilylethynylmagnesium bromide also proceeded smoothly to give 2-(triphenylsilylethynyl)biphenyl (**2b**) in 99% yield (entry 6).

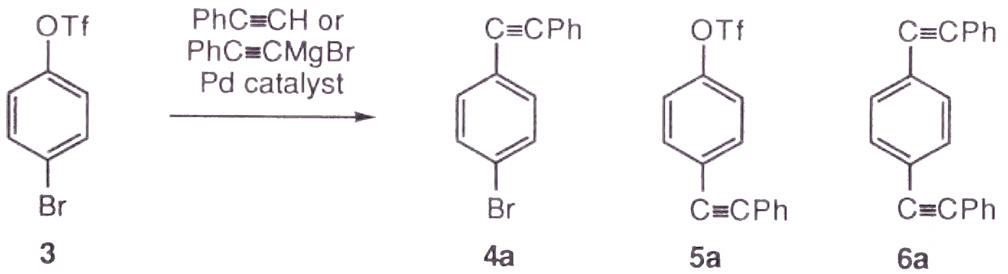
In the Grignard cross-coupling of arenes bearing both triflate and bromide using $\mathrm{PdCl_2}$(alaphos), triflate group was selectively substituted with phenylethynyl group. Thus, the reaction of 4-bromophenyl triflate (**3**) with 2 equiv of phenyethynylmagnesium bromide in the presence of 1 equiv of LiBr and 5 mol % of $\mathrm{PdCl_2}$(alaphos) at 20 °C for 3 h gave 96 % yield of 1-bromo-4-(phenylethynyl)benzene (**4a**) together with a small amount (2%) of 1,4-di(phenylethynyl)benzene (**6a**) (Table 2, entry 1). None of 1-phenylethynyl-4-trifluoromethanesulfonyloxybenzene (**5a**) was detected. In the absence of lithium bromide, the cross-coupling

Table 2 Cross-Coupling of 4-Bromophenyl Triflate **3** with Phenylethynylmagnesium Bromide Catalyzed by $PdCl_2[(S)\text{-alaphos}]$

entry	catalyst	reagent (eq)	reaction temp (°C)	reaction time (h)	recovered **3** (%)[a]	yield of **4** (%)[a]	yield of **5** (%)[a]	yield of **6** (%)[a]
1[b]	$PdCl_2$(alaphos)	PhC≡CMgBr (2)	20	3	0	96 (**4a**)	0	2 (**6a**)
2[b, c]	$PdCl_2$(alaphos)	PhC≡CMgBr (2)	20	3	5	92 (**4a**)	0	2 (**6a**)
3[d]	$PdCl_2(PPh_3)_2$	PhC≡CH (2)	20	40	10	8 (**4a**)	73 (**5a**)	8 (**6a**)

[a] Isolated yield by silica gel chromatography. [b] The reaction was carried out in the presence of 1 equiv of LiBr and 5 mol % palladium catalyst in ether/toluene (3:1). [c] The reaction was carried out in the absence of LiBr. [d] The reaction was carried out in the presence of 10 mol % of CuI and 10 mol % palladium catalyst in THF/Et_3N (4:1).

Scheme 2



reaction proceeded more slowly but the chemoselectivity in forming **4a** was kept in the high level (entry 2), indicating that lithium bromide is not responsible for the high triflate-selectivity.[6,8,9] On the contrary, preferential substitution of bromide occurred in Sonogashira method. The Sonogashira reaction of **3** carried out with 2 equiv of phenylacetylene in the presence of 10 mol % of $PdCl_2(PPh_3)_2$ at 40 °C for 24 h gave 8% yield of **4a**, 73% yield of **5a**, and 8% yield of **6a** (entry 3).

In the presence of $PdCl_2$(alaphos) catalyst, other benzene or naphthalene derivatives bearing both triflate and bromide (**7**-**10**) also underwent the selective substitution of triflate group with several alkynyl Grignard reagents (Table 3). Various alkynyl groups, substituted with alkyl, aryl, and silyl groups, were introduced efficiently into the phenyl or naphthyl ring in higher than 90% yield. Replacement of triflate by alkynyl groups also took place with perfect selectivity, bromide being remained intact. The cross-coupling product 1-bromo-4-(triethylsilylethynyl)benzene (**5c**), obtained by the reaction with the triethylsilylethynyl Grignard reagent, was converted into terminal acetylene (**19**) by desilylation with tetrabutylammonium fluoride and it was submitted to the second cross-coupling. The alkynyl Grignard reagent generated from **19** was allowed to react

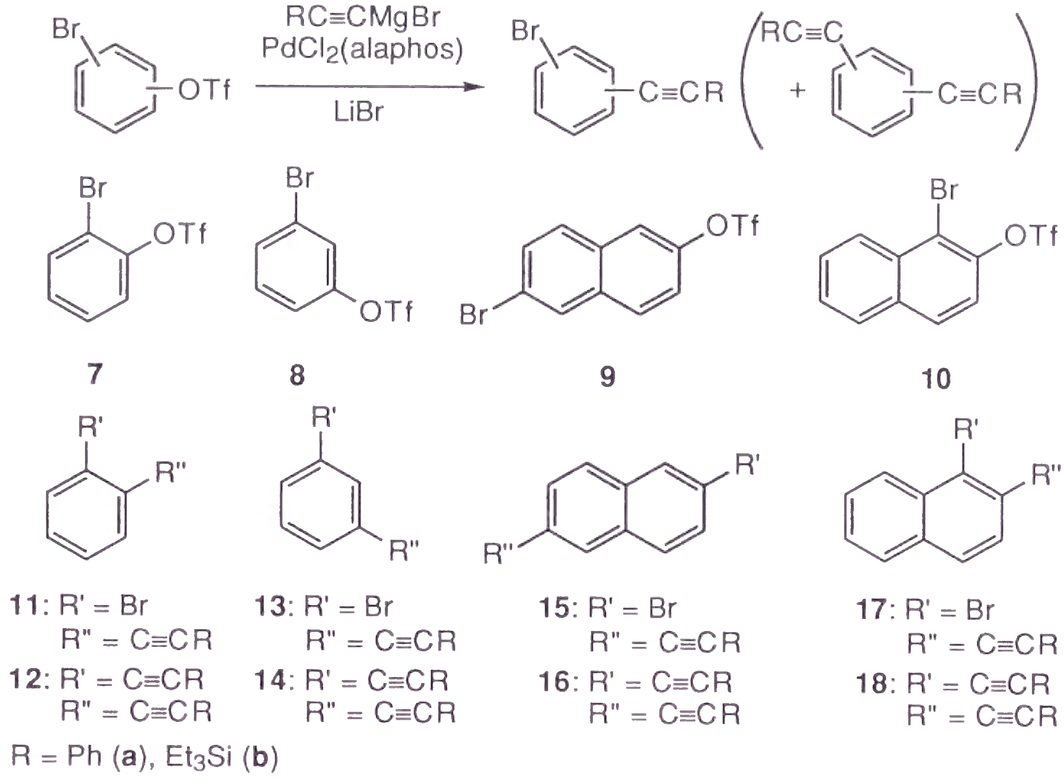
Table 3. Cross-Coupling of Bromoaryl Triflates with Alkynyl Grignard Reagents[a]

entry	triflate	R in RC≡CMgBr	reaction temp (°C)	reaction time (h)	yield of alkynyl-bromoarene (%)[b]	yield of di-alkynylarene (%)[b]
1	**1**	Et_3Si	20	1	99 (**4c**)	2 (**6c**)
2	**1**	n-C_5H_{11}	30	12	92 (**4d**)	5 (**6d**)
3	**1**	t-Bu	30	20	90 (**4e**)	8 (**6e**)
4	**7**	Ph	20	4	92 (**11a**)	2 (**12a**)
5	**7**	Et_3Si	30	4	91 (**11c**)	3 (**12c**)
6	**8**	Ph	20	1	99 (**13a**)	0
7	**8**	Et_3Si	20	1	93 (**13c**)	2 (**14c**)
8	**9**	Ph	20	12	95 (**15a**)	2 (**16a**)
9	**9**	Et_3Si	20	4	92 (**15c**)	5 (**16c**)
10	**10**	Ph	40	4	94 (**17a**)	0
11	**10**	Et_3Si	40	6	90 (**17c**)	5 (**18c**)

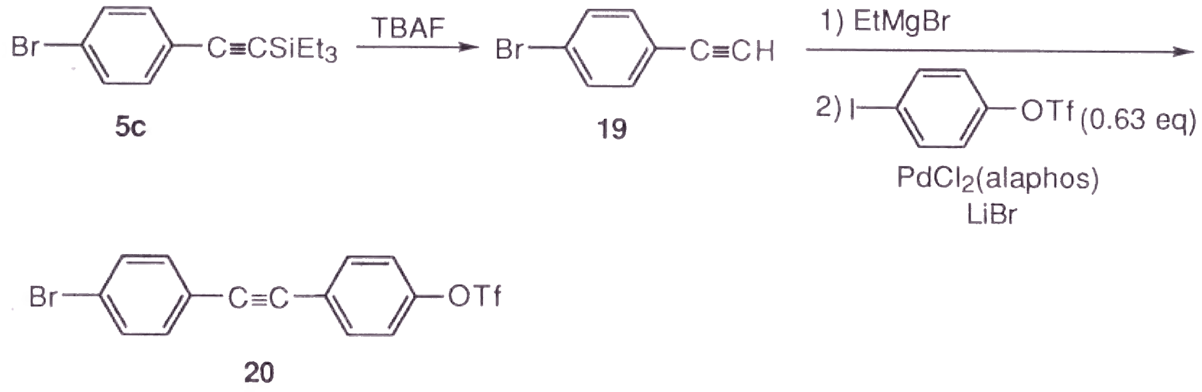
[a] The reaction was carried out with 2 equiv of Grignard reagent in the presence of 1 equiv of LiBr and 5 mol % palladium catalyst in ether/toluene (3:1). In any cases, no starting materials and alkynylarene triflates were detected. [b] Isolated yield by silica gel chromatography.

with 4-iodophenyl triflate by use of $PdCl_2$(alaphos) as a catalyst. Selective substitution of iodide took place to give 1-(4-bromophenyl)-2-[(4-trifluoromethylsulfonyloxy)phenyl]ethyne (**20**) with high selectivity. These results shows that the order of reactivity of the substituents on an aromatic ring is iodide > triflate > bromide in the alkynyl Grignard cross-coupling reaction catalyzed $PdCl_2$(alaphos). By using this selective catalytic alkynylation, highly conjugated aryl alkynyl compounds are expected to be synthesized efficiently.

Scheme 3



Scheme 4



Experimental

General. All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5 (Merck, SICAPENT). NMR spectra were recorded on a JEOL JNM-EX270 spectrometer (270 MHz for ^1H) or a JEOL JNM LA500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal TMS standard for ^1H NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR.

Materials. PPh_3, dppe, dppp, dppb, and dppf from Aldrich Chemical Company, Inc.

were commercially available. Palladium complex $PdCl_2$(alaphos) was prepared according to the reported procedures.[7] Aryl triflates were prepared by triflation of phenols with triflluoromethanesulfonic anhydride and pyridine. Ether and toluene were distilled from sodium benzophenone ketyl under nitrogen.

Synthesis of Alkynylmagnesium Bromide. Typical Procedure. To a solution of phenylacetylene (510 mg, 4.99 mmol) in 1.4 mL of toluene was added ethylmagnesium bromide (2.7 mL, 2 M ether solution, 5.5 mmol). The mixture was heated at 50 °C for 30 min. Other alkynylmagnesium bromides were prepared in the same manner.

Grignard Cross-Coupling of Aryl Triflates with Alkynyl Grignard Reagents Catalyzed by $PdCl_2$(alaphos). Typical Procedure. To a mixture of triflate **1** (60.4 mg, 0.2 mmol), dichloro[(2-dimethylamino)propyldiphenylphosphine]palladium ($PdCl_2$(alaphos)) (4.4 mg, 0.01 mmol), and lithium bromide (17.2 mg, 0.2 mmol) in 100 μL of ether was added phenylethynylmagnesium bromide (290 μL, 1.4 M, 0.4 mmol) in ether/toulene (2/1) at room temperature, and the mixture was stirred at 30 °C until **1** was not detected by silica gel TLC (hexane/benzene = 3/1). The reaction mixture was quenched with water and extracted with 100 mL of ether. Combined ether extracts were washed with brine (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/benzene = 3/1) to give 44.6 mg (93% yield) of **2a** . The reaction conditions and results are summarized in Table 1.

2-Phenylethynylbiphenyl (2a). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.25–7.49 (m, 11H), 7.63-7.68 (m, 3 H). **2-Triphenylsilylethynylbiphenyl (2b).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28–7.42 (m, 17 H), 7.53 (dd, J = 1.5, 7.8 Hz, 6H), 7.71 (d, J = 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 92.10, 109.09, 121.17, 126.92, 127.40, 127.86, 129.15, 129.35, 129.45, 129.74, 133.52, 133.70, 135.53, 135.96, 140.26, 144.74. Anal. Calcd for $C_{32}H_{24}Si$: C, 88.03 H, 5.54. Found: C, 87.83; H, 5.57.

Sonogashira Reaction of Bromophenyl Triflate (3) with Phenylacetylene Catalyzed by $PdCl_2(PPh_3)_2$. To a mixture of bromophenyl triflate (**3**) (60.4 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.020 mmol), copper(I) iodide (3.8 mg, 0.020 mmol), and 0.25 mL of triethylamine in 1 mL of THF was added phenylacetylene (32 μL, 0.29 mmol), and the mixture was stirred at 40 °C for 12 h. The mixture was quenched with 10% hydrochloric acid and extracted with 100 mL of ethyl acetate. The organic layer was washed with brine (2 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 47.6 mg (73% yield) of 4-trifluoromethanesulfonyloxy(phenylethynyl)benzene (**4a**), 4.1 mg (8% yield) of 4-phenylethynylbromobenzene (**5a**), and 4.4 mg (8% yield) of 1,4-di(phenylethynyl)benzene (**6a**). **4-Trifluoromethanesulfonyloxy-(phenylethynyl)benzene (4a).** mp 55°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27-7.61 (m, 9H). **4-Phenylethynylbromobenzene (5a).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (s, 7H), 7.39 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.52 (s, 2H). **1,4-Di(phenylethynyl)-benzene (6a).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.36 (m, 6H), 7.50–7.54 (m, 8H).

Grignard Cross-Coupling of Bromoaryl Triflates with Alkynyl Grignard Reagents Catalyzed by $PdCl_2$(alaphos). Grignard cross-coupling of bromoaryl triflates with alkynyl Grignard reagents catalyzed by $PdCl_2$(alaphos) was carried out in a similar manner to that of aryl triflates shown above.

4-(Triethylsilylethynyl)bromobenzene (5c). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.67 (q, *J* = 7.9 Hz, 6H), 1.04 (t, *J* = 7.9 Hz, 9H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.38, 7.46, 93.76, 104.86, 123.25, 131.79; EI-MS m/z, 296 (M^+, 11), 294 (11), 267 (99), 265 (98), 239 (85), 237 (84), 211 (83), 209 (100). Anal. Calcd for $C_{14}H_{19}BrSi$: C, 56.94; H, 6.49. Found: C, 57.11; H, 6.60. **1,4-Bis(triethylsilylethynyl)benzene (6c).** mp 36-38 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.67 (q, *J* = 8.3 Hz, 12H), 1.04 (t, *J* = 8.3 Hz, 18H), 7.38 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.38, 7.46, 93.76, 105.86, 123.25, 131.79; EI-MS m/z, 354 (M^+, 25), 325 (100), 297 (46), 269 (79). Anal. Calcd for $C_{22}H_{34}Si_2$: C, 74.50; H, 9.66. Found: C, 74.25; H, 9.92. **4-Heptynylbromobenzene (5d).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, *J* = 7.0 Hz, 3H), 1.37 (sextet, *J* = 7.0 Hz, 2H), 1.43 (tt, *J* = 7.0, 7.5 Hz, 2H), 1.60 (quint, *J* = 7.0 Hz, 2H), 2.40 (t, *J* = 7.5 Hz, 2H), 7.29 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.97, 19.40, 22.21, 28.33, 31.11, 79.55, 91.78, 121.50, 123.10, 131.39, 133.01; EI-MS m/z, 252 (M^++2, 26), 250 (M^+, 26), 223 (29), 221 (29), 195 (60), 142 (99), 129 (78), 116 (100). Anal. Calcd for $C_{13}H_{15}Br$: C, 62.17; H, 6.02. Found: C, 62.38; H, 6.07. **1,4-Diheptynylbenzene (6d).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, *J* = 7.0 Hz, 6H), 1.37 (sextet, *J* = 7.0 Hz, 4H), 1.43 (tt, *J* = 7.0, 7.5 Hz, 4H), 1.60 (quint, *J* = 7.0 Hz, 4H), 2.38 (t, *J* = 7.5 Hz, 4H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.97, 19.43, 22.21, 28.41, 31.11, 80.36, 91.92, 123.17, 131.31; EI-MS m/z, 266 (M^+, 85), 237 (34), 209 (37), 165 (77), 141 (100), 129 (82), 115 (38). Anal. Calcd for $C_{20}H_{26}$: C, 90.16; H, 9.84. Found: C, 90.33; H, 9.93. **4-(*t*-Butylethynyl)bromobenzene (5e).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (s, 9H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.95, 30.92, 78.07, 99.71, 121.42, 123.07, 131.29, 133.02; EI-MS m/z, 238 (M^++2, 30), 236 (M^+, 32), 223 (71), 221 (76), 157 (22), 142 (100), 115 (28). Anal. Calcd for $C_{12}H_{13}Br$: C, 60.78; H, 5.53. Found: C, 60.57; H, 5.53. **1,4-Di(*t*-Butylethynyl)benzene (6e).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (s, 18H), 7.28 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.97, 30.98, 78.90, 99.81, 123.05, 131.28; EI-MS m/z, 238 (M^+, 55), 223 (100), 208 (13), 193 (22). Anal. Calcd for $C_{18}H_{22}$: C, 90.70; H, 9.30. Found: C, 90.70; H, 9.53. **2-(Phenylethynyl)bromobenzene (11a).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.63 (m, 6H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 8.32 (d, *J* = 7.8 Hz, 1H). **1,2-Di(phenylethynyl)benzene (12a).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.37 (m, 7H), 7.51–7.54 (m, 7H). **2-(Triethylsilylethynyl)bromobenzene (11c).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (q, *J* = 8.0 Hz, 6H), 1.07 (t, *J* = 8.0 Hz, 9H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.38, 7.50, 97.26, 104.11, 125.46, 125.74, 126.82, 129.43, 132.33, 133.73; EI-MS m/z, 296 (M^++2, 6), 294 (M^+, 5), 267 (100), 265 (97), 239 (83), 237 (82), 211 (74), 209 (88). Anal. Calcd for $C_{14}H_{19}BrSi$: C, 56.94; H, 6.49. Found: C, 56.93; H, 6.42. **1,2-Bis(triethylsilylethynyl)benzene (12c).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.69 (q, J = 8.0 Hz, 12H), 1.06 (t, J = 8.0 Hz, 18H), 7.23 (dd, J = 2.5, 6.5 Hz, 2H), 7.47 (dd, J = 2.5, 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.43, 7.56, 95.86, 104.59, 125.75, 127.88, 132.89; EI-MS m/z, 354 (M^+, 28), 325 (27), 297 (100), 269 (83), 241 (86), 213 (54). Anal. Calcd for $C_{22}H_{34}Si_2$: C, 74.50; H, 9.66. Found: C, 74.44; H, 9.91. **3-(Phenylethynyl)bromobenzene (13a).** ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.02–7.53 (m, 8H), 7.69 (s, 1H). **3-(Triethylsilylethynyl)bromobenzene (13c).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.67 (q, J = 7.8 Hz, 6H), 1.04 (t, J = 7.8 Hz, 9H), 7.16 (t, J = 7.9 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.35, 7.45, 93.42, 104.54, 122.00, 125.33, 129.59, 130.53, 131.51, 134.74; EI-MS m/z, 296 (M^++2, 5), 294 (M^+, 5), 267 (75), 265 (77), 239 (78), 237 (77), 211 (67), 209 (74), 129 (100). Anal. Calcd for $C_{14}H_{19}BrSi$: C, 56.94; H, 6.49. Found: C, 57.17; H, 6.60. **1,3-Bis(triethylsilylethynyl)benzene (14c).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.67 (q, J = 7.8 Hz, 12H), 1.04 (t, J = 7.8 Hz, 18H), 7.23 (t, J = 8.0 Hz, 1H), 7.39 (dd, J = 1.5, 8.0 Hz, 2H), 7.57 (t, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.38, 7.48, 92.36, 105.35, 123.53, 128.13, 131.85, 135.40; EI-MS m/z, 354 (M^+, 11), 325 (100), 297 (39), 269 (39). Anal. Calcd for $C_{22}H_{34}Si_2$: C, 74.50; H, 9.66. Found: C, 74.51; H, 9.80. **2-Bromo-6-(phenylethynyl)naphthalene (15a).** mp 131-133 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.347.37 (m, 2H), 7.54–7.57 (m, 3H), 7.69 (d, J = 8.5 Hz, 1H), 7.72 (t, J = 8.5 Hz, 1H), 8.00 (d, J = 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 89.36, 90.35, 120.68, 121.12, 123.07, 127.06, 128.39, 128.44, 129.31, 129.48, 129.84, 129.96, 131.23, 131.41, 131.65, and 133.70; EI-MS m/z, 308 (M^++2, 100), 306 (M^+, 99), 226 (72), 113 (57). Anal. Calcd for $C_{18}H_{11}Br$: C, 70.38; H, 3.61. Found: C, 70.09; H, 3.39. **2,6-Di(phenylethynyl)naphthalene (16a).** mp 200-201 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.40 (m, 6H), 7.52-7.61 (m, 6H), 7.79 (d, J = 8.5 Hz, 2H), 8.03 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 89.63, 90.47, 121.44, 123.17, 127.83, 128.41, 129.17, 131.19, 131.69, 131.72, 132.38. Anal. Calcd for $C_{26}H_{16}$: C, 95.09; H, 4.91. Found: C, 94.69; H, 4.94. **2-Bromo-6-(triethylsilylethynyl)naphthalene (15c).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.71 (q, J = 8.0 Hz, 6H), 1.07 (t, J = 8.0 Hz, 8H), 7.53 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.96 (s, 1H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.43, 7.50, 92.86, 106.19, 120.71, 121.16, 126.87, 129.28, 129.81, 129.92, 131.28, 131.79, and 133.57; EI-MS m/z, 346 (M^++2, 27), 344 (M^+, 26), 317 (73), 315 (69), 289 (57), 287 (56), 261 (91), 259 (100), 130 (54). Anal. Calcd for $C_{18}H_{21}BrSi$: C, 62.60; H, 6.13. Found: C, 62.47; H, 6.10. **2,6-Bis(triethylsilylethynyl)naphthalene (16c).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.71 (q, J = 7.5 Hz, 12H), 1.07 (t, J = 7.5 Hz, 8H), 7.50 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.94 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.45, 7.51, 92.91, 106.44, 121.45, 127.62, 129.41, 131.70, and 132.28; EI-MS m/z 404 (M^+, 31), 375 (50), 319 (57), 145 (51), 131 (60), 117 (100). Anal. Calcd for $C_{26}H_{36}Si_2$: C, 77.16; H, 8.97. Found: C, 76.90; H, 9.09. **1-Bromo-2-(phenylethynyl)naphthalene (17a).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18–7.35 (m, 6H), 7.58 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 89.36, 90.35, 120.69, 121.16, 123.08, 127.07, 128.41, 128.46, 129.35, 129.51, 129.86, 129.99, 131.24, 131.44, 131.61, and 133.73; EI-MS m/z, 306 (M^++2, 98), 304 (M^+, 100), 226 (76), 113 (43). Anal. Calcd for $C_{18}H_{11}Br$: C, 70.38; H, 3.61. Found: C, 70.17; H, 3.38. **1-Bromo-2-(triethylsilylethynyl)naphthalene (17c).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.74 (q, J = 8.0 Hz, 6H), 1.09 (t, J = 8.0 Hz, 9H), 7.51 (t, J = 8.3 Hz, 1H), 7.52 (t, J = 8.3 Hz, 1H), 7.59 (t, J = 8.3 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 8.29 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.43, 7.56, 98.21, 105.40, 123.50, 126.71, 127.12, 127.29, 127.80, 127.90, 128.13, 129.35, 132.17, and 133.67; EI-MS m/z, 346 (M^++2, 27), 344 (M^+, 26), 317 (67), 315 (65), 289 (62), 287 (60), 261 (44), 259 (46), 179 (100). Anal. Calcd for $C_{18}H_{21}BrSi$: C, 62.60; H, 6.13. Found: C, 62.37; H, 6.09. **1,2-Bis(triethylsilylethynyl)naphthalene (18c).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.72 (q, J = 8.0 Hz, 6H), 0.78 (q, J = 8.0 Hz, 6H), 1.09 (t, J = 8.0 Hz, 9H), 1.13 (t, J = 8.0 Hz, 9H), 7.50 (t, J = 8.5 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.57 (t, J = 8.5 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.48, 4.56, 7.63, 7.71, 97.09, 102.23, 102.50, 105.60, 123.74, 124.39, 126.59, 126.87, 127.32, 128.06, 129.07, 132.40, and 133.42; EI-MS m/z, 404 (M^+, 100), 347 (66), 291 (72), 263 (73), 235 (74), 205 (55). Anal. Calcd for $C_{26}H_{36}Si_2$: C, 77.16; H, 8.97. Found: C, 76.93; H, 9.12.

4-Ethynylbromobenzene (19). To a solution of 4-(triethylsilylethynyl)bromobenzene (**5c**) (200 mg, 0.738 mmol) in 2 mL of THF was added tetrabutylammonium fluoride aq (0.5 mL) at room temperature. The reaction mixture was stirred for 30 min, then concentrated under reduced pressure, and extracted with 100 mL of ether. The organic layer was washed with water (2 × 50 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to give 75 mg (quantitative yield) of **19**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.12 (s, 1H), 7.35 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H).

1-(4-Bromophenyl)-2-[(4-trifluoromethanesulfonyloxy)phenyl]ethyne (20). To a solution of **19** (36.2 mg, 0.20 mmol) in 100 μL of ether and 100 μL of toluene was added ethylmagnesium bromide (1.6 M, 130 μL, 0.21 mmol) at room temperature, and the mixture was stirred at 50 °C for 30 min. To a mixture of 4-iodophenyl triflate (41 mg, 0.12 mmol), lithium bromide (10 mg, 0.12 mmol), and $PdCl_2$(alaphos) (2.4 mg, 0.006 mmol) was added the Grignard reagent. The mixture was stirred at 30 °C for 2 h, quenched with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to give 44.3 mg (91% yield) of **20**: mp 152-153 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 88.39, 90.15, 118.73 (q, J = 321.3 Hz), 121.57, 123.13, 123.66, 130.47, 131.75, 133.07, 133.40 and 149.06; EI-MS m/z 406 (M^++2, 20), 404 (M^+, 21), 273 (95), 271 (100), 163 (81). Anal. Calcd for $C_{24}H_{17}O_3$-BrF_3S: C, 44.46; H, 1.99. Found: C, 44.42; H, 1.91.

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