Studies on Novel Aspects of the Transition Metal-Catalyzed Coupling Reactions of Organostannanes

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Contents

Introduction and General Summary

Transition Metal-Catalyzed Cross-Coupling Reaction

The transition metal-catalyzed cross-coupling reaction of organic electrophiles with organometallics is an extremely powerful tool in organic synthesis, and various kinds of electrophiles (R^1–X), organometallics (R^2–m), and transition metal catalysts are now available (eq 1).[1]

$$R^1\text{–}X \quad + \quad R^2\text{–}m \xrightarrow{\text{transition metal catalyst}} R^1\text{–}R^2 \qquad (1)$$

m = Mg, Li, Zn, Zr, Al, B, Sn, Si,...

The R^1 group of the electrophile in Equation 1 is usually an unsaturated moiety, and X represents halogen or a leaving group containing an oxygen[2] or nitrogen[3] atom. Both unsaturated and saturated moieties are available for R^2.

Historically, the prosperity of the cross-coupling reaction began with the independent studies by the Tamao-Kumada group[4] and the Corriu-Masse group.[5] They used nickel catalysts and Grignard reagents. Later, the reaction was extended to the organometallic reagents of Li,[6] Zn,[7] Zr,[8] Al,[9] B,[10] Sn,[11] and Si.[12]

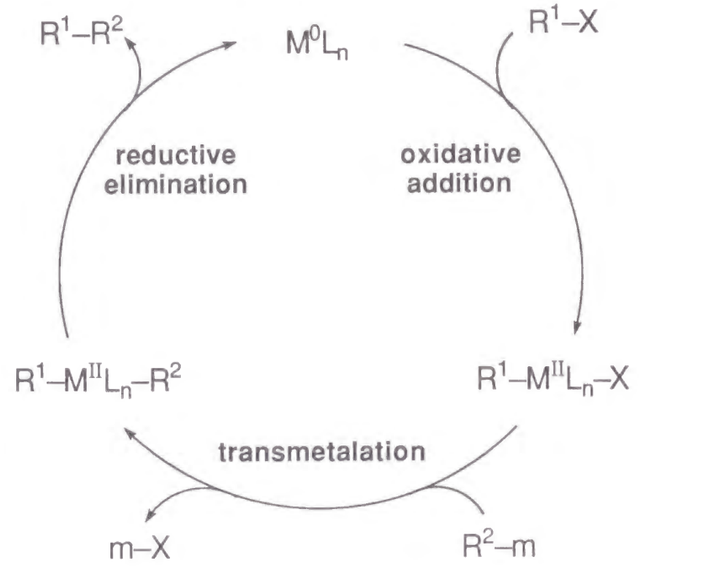
These organometallics are classified into three groups on the basis of reactivity. The first group involves organolithium and Grignard reagents and is characterized by high reactivity. Because of low chemoselectivity of these reagents, their application to multi-functional substrates encounters great difficulties. The second group includes the organometallic reagents of zinc, zirconium, aluminum, and boron, and exhibits medium reactivity and selectivity. The third group, consisting of organostannanes and organosilicons, shows high chemoselectivity and stability to allow us to effect the reaction without protection and any careful handling. The major drawback of these reagents is low reactivity. Therefore the reagent of the third group should

find wide applicability if an appropriate method for activation is available.

The transition metal catalysts used regularly in the cross-coupling reaction are palladium and nickel complexes. Most of examples employ either of the two catalysts often in conjunction with a ligand which allows the formation of reactive species and stabilizes them.

Their catalytic cycle is understood in terms of three distinct steps (Scheme 1): oxidative addition, transmetalation, and reductive elimination. Not all the reactions have been thoroughly investigated on the basis of well-defined homogeneous catalysis,[13] but they are considered to proceed via similar mechanisms and share a number of key features in common, as summarized in Scheme 1.

Scheme 1



M = transition metal
R^2–m = organometallic reagent
L = ligand

Palladium-Catalyzed Cross-Coupling Reaction of Organostannanes with Aryl Halides

The palladium-catalyzed coupling of organostannanes with aryl halides is the most commonly used cross-coupling reaction (eq 2).[14,15]

$$R^1\text{–}X \quad + \quad R^2\text{–}SnR^3_3 \xrightarrow{Pd(0)} R^1\text{–}R^2 \quad + \quad X\text{–}SnR^3_3 \qquad (2)$$

R^1 = aryl, alkenyl, alkynyl, allyl, heteroaryl, acyl,...

X = I, Br, OTf,...

R^2 = alkynyl, alkenyl, allyl, aryl, heteroaryl, alkyl,...

R^3 = butyl, methyl,...

Organostannanes, which belong to the third group as described above, have several characteristic features that distinguish them from the other organometallics. First, they are storable at room temperature, and usually prepared and purified in a separate step prior to the coupling reaction. Second, they are readily available by various synthetic methods; this availability makes them one of the most frequently used reagents especially in laboratory organic syntheses. Third, the reagents have moderate reactivity to attain C–C bond formation chemoselectively. These features mean that sometimes drastic conditions are required and unexpected side reactions accompany.

Chronologically speaking, the coupling reaction of organostannanes was first recorded by Kosugi and Migita in 1977. They reported that both acyl chlorides[16,17] and aryl iodides[11] coupled with organostannanes under palladium(0) or rhodium(I) catalysis. In 1978, Milstein and Stille reported the acylation of organotin compounds, using palladium catalysts,[18] and this work was followed by a series of papers describing a broad scope of the palladium-

catalyzed coupling of organic electrophiles with organostannanes; the reaction being called simply as the Stille reaction.

Almost all classes of organostannanes can couple with most of unsaturated halides in synthetically meaningful yields. The reactivity order of the organic moiety in organostannanes is generally considered to be alkynyl > vinyl > allyl > aryl, heteroaryl >> alkyl,[13c] and consequently, alkyl groups are typically used as innocent groups. Among various alkyl groups, butyl is preferred because of the low toxicity and low cost of the synthetic precursors.

Although aryl iodides and bromides were initially used as the coupling partner, vinyl trifluoromethanesulfonate (triflates)[19] and aryl triflates[20] were later introduced as novel electrophiles for the coupling, and thus the scope of the Stille reaction has expanded enormously. Among aryl halides, the reactivity scale is considered to be I > Br > OTf >> Cl, but the order between triflate and bromide may be reversed in the presence of a halogen ion.[21] For the coupling of aryl chlorides, an electron-withdrawing substituent such as a nitro group is needed for successful coupling.[11]

As described above, the Stille coupling is featured by high chemoselectivity. Almost all functional groups both on electrophiles and on organotin reagents are tolerated. Thus protection of these functional groups is not necessary.

Although rhodium was initially used as a catalyst in a series of the pioneering works by the Kosugi-Migita group,[16] palladium later grew to be the exclusive catalyst. In particular, palladium(0) or palladium(II) complexes have been employed because palladium(II) is rapidly reduced in situ to an active palladium(0) species, and a proper choice of a ligand and a solvent is often critical for the success of the reaction.

In spite of many synthetic applications, there are few reports on the mechanistic aspects of the Stille reaction. Although the reaction is considered

to follow the general pathway suggested for the cross-coupling reactions of boron and magnesium reagents (Scheme 1), little piece of evidence is available yet particularly for the Stille reaction. Mechanistic work on the Stille reaction has targeted mainly the oxidative addition step[21,22] and the reductive elimination step.[23] Vedejs and his co-workers have provided an elegant support for the nucleophilic assistance at the departing tin during the transmetalation step[24] as is the case of organosilicon reagents.[12b]

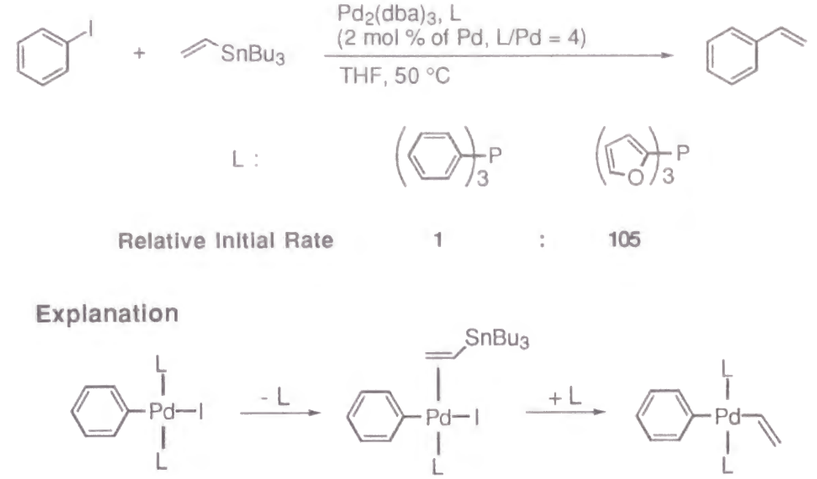
Improvement of the Catalytic Activity in the Palladium-Catalyzed Coupling of Organostannanes with Aryl Halides

Several attempts have been made to improve the utility of the Stille reaction, focusing on a ligand for palladium and an additive.[25]

An example of the ligand effect was demonstrated by Beletskaya[26] and her co-workers, who observed that the reaction was accelerated by orders of magnitude when the palladium catalyst lacked a phosphine ligand. The drawbacks of this "ligandless" procedure are poor stability of the catalyst, a rather narrow scope, and coproduction of considerable amounts of by-products.

A survey of ligands for the Stille reaction was carried out by Farina and his co-workers and revealed that this coupling reaction was accelerated by up to three orders of magnitude with modest donor ligands such as tri(2-furyl)phosphine and triphenylarsine compared with triphenylphosphine (Scheme 2).[27] According to their explanation, the dissociation of a ligand from the palladium(II) intermediate to make a vacant coordination site for an organostannane reagent is critical in the rate-determining transmetalation step, and the modest donor ligands behave ideally for high catalytic activity. This working hypothesis rationalizes an inhibitory effect of a free ligand and the slow rates observed with a stronger donor like triphenylphosphine.

Scheme 2



Although nitrogen-based bidentate ligands also are used for the cross-coupling reaction,[28,29] these sometimes induce troublesome side reactions such as homocoupling of organostannanes.

To accelerate the reaction, a co-catalyst or an additive is shown to be highly effective in the Stille reaction. These are likely to activate an organostannane rather than a catalyst. Accordingly, attention should be paid to the possibility that the activation of organostannanes may decrease the chemoselectivity.

Zinc chloride is a common additive introduced by Stille and his co-workers, and in some cases this particular salt induces the coupling even in the absence of palladium.[30] Organozinc intermediates may be involved in some of these cases.[31]

Another useful device for accelerating the reaction is use of a catalytic amount of a copper(I) salt,[32] which may lead to the corresponding reactive organocopper species. This procedure, due to its simplicity and economy, is finding considerable applications. Silver salts also have been used as the promoter.[33]

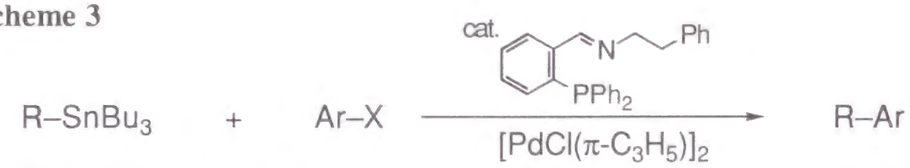
Novel Aspects of the Transition metal-Catalyzed Coupling Reactions of Organostannanes

Present Thesis, as a whole, describes the followings. First, active catalysts for the coupling of organostannanes with aryl halides were studied. Next, the reaction mechanism, especially the catalytic cycle, of the palladium-catalyzed coupling of organostannanes with aryl halides was investigated. On the basis of the reaction mechanism, a synthetically useful reaction was developed.

Novel iminophosphine ligands, *N*-(2-diphenylphosphinobenzylidene)-alkylamines or -arylamine, are highlighted first of all. Although iminophosphine ligands of this type together with transition metals were previously used as catalysts for alkylation of allylic carboxylates, hydrogenation of olefins and hydrosilation of ketones,[34] these studies were directed to asymmetric induction using chiral iminophosphines rather than the pursuit of the catalytic activity. The author expected that a palladium complex coordinated by this type of iminophosphine should be a good catalyst for the palladium-catalyzed cross-coupling reaction for the following reason. An imino group as a ligand seems to have a π-acceptor character which makes palladium(II) complex electrophilic and consequently accelerates the reaction of palladium(II) with nucleophilic organometallic reagents. In contrast, a phosphino group, which generally has strong affinity to palladium(0), will assist the metal to react with an electrophile. Thus, each of the coordinating groups may play their own role cooperatively in a catalytic cycle. Actually, novel aspects of the palladium-catalyzed coupling have been disclosed by iminophosphine ligands.

In Chapter 1, the author shows that a palladium complex coordinated by

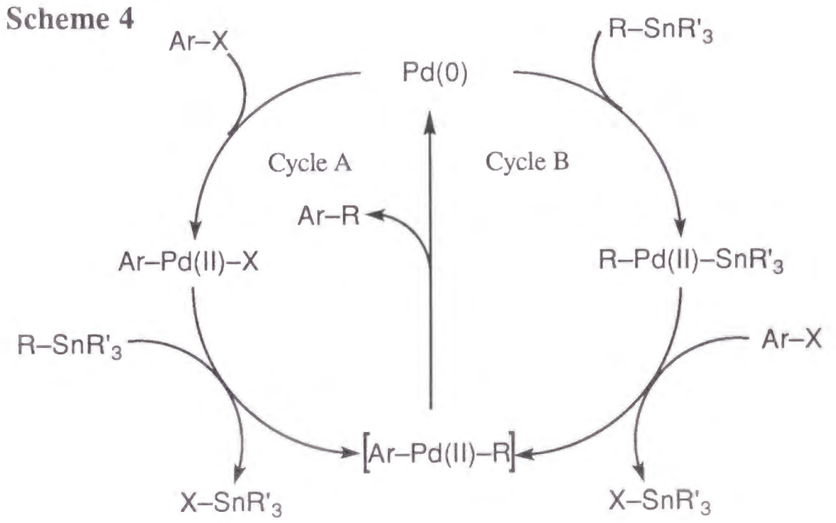
Scheme 3



N-(2-diphenylphosphinobenzylidene)-2-phenylethylamine is an efficient catalyst for the cross-coupling of organostannanes with aryl halides (Scheme 3). This catalyst features high rate, wide applicability and sufficient stability.

Chapter 2 deals with the elucidation of the reaction mechanism of the palladium-catalyzed coupling of organostannanes with aryl halides. The catalytic cycle shown as Cycle A in Scheme 4 is a well accepted one, but no convincing experimental proof has been disclosed about the mechanism.[35] The basis for Cycle A is that palladium(0) complex is an electron rich species to react with an aryl halide electrophile. The author has found that a palladium(0) complex coordinated by a bidentate ligand can react not only with an aryl halide but also with an organostannane nucleophile[36] and that the

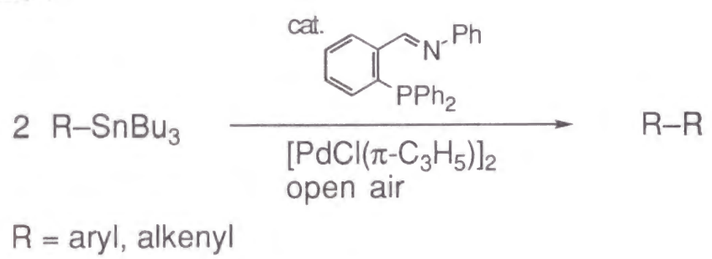
Scheme 4



resulting Pd(II) species is involved in the coupling reaction in some cases. Thus, the author proposes that the reaction should proceed via Cycle B in Scheme 4 in certain cases.[37]

Chapter 3 describes the homocoupling reaction of organostannanes catalyzed by an iminophosphine–palladium complex. The transition metal-catalyzed homocoupling of organostannanes[38,39] is less common than the corresponding cross-coupling reaction, though both of them will enjoy the merits of organostannanes. This may be due partly to the inconvenience in use of a reactive oxidant. The author found, in the course of the investigation of the reaction mechanism of the palladium-catalyzed cross-coupling reaction (Chapter 2), that an iminophosphine–palladium complex efficiently catalyzed the homocoupling of aryl- and alkenylstannanes by using air as a mild but sufficient oxidant (Scheme 5).

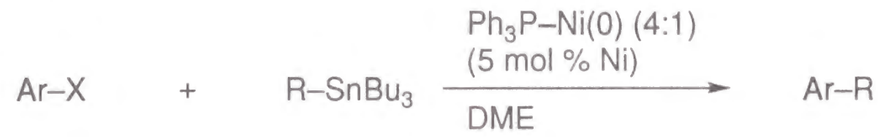
Scheme 5



The nickel-catalyzed coupling of aryl halides with organostannanes is discussed in Chapter 4. Nickel catalyst has never been used in the Stille reaction,[40,41] except for the coupling of an aryl mesylate with tributyl(phenyl)tin reported by Percec and his co-workers.[42] In this case, however, the homo-coupled biaryl derived from the mesylate predominated (45–64%), and the yield of the cross-coupled product (23–24%) was not high enough. The author found that a triphenylphosphine–nickel complex is a

highly active catalyst for the coupling of aryl halides, including aryl chlorides, with organostannanes (Scheme 6). This is the first example that unactivated aryl chlorides were shown to be applicable to this coupling.[43,44] From an industrial view point, it is noteworthy that even unactivated aryl chlorides are applicable to the Stille reaction because they are inexpensive and easily available in bulk quantities compared with aryl bromides and iodides.

Scheme 6



The author also discusses the reaction mechanism of the nickel-catalyzed coupling reaction. The mechanism was found to be strikingly different from that using a palladium catalyst. The difference seems to stem from the radical character of the nickel catalyst.

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Abbreviations

Following abbreviations and acronyms are used throughout this Thesis without any explanation.

acac	acetylacetonate(-*O*)	*F*	Faraday constant
bp	boiling point	h	hour(s)
brs	broad singlet (spectral)	IR	infrared
		J	coupling constant (in NMR)
Bu	butyl		
ca.	*circa* (about)	M	moles per liter
calcd	calculated	Me	methyl
dba	dibenzylideneacetone	min	minute(s)
dec	decomposition	mmol	milimole(s)
DME	1,2-dimethoxyethane	mp	melting point
DMF	*N*,*N*-dimethylform-amide	NMR	nuclear magnetic resonance
δ	scale (NMR)	Ph	phenyl
eq	equation	temp	temperature
equiv	equivalent(s)	THF	tetrahydrofuran

Chapter 1

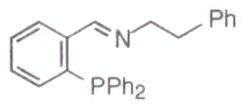
Cross-Coupling Reaction of Organostannanes with Aryl Halides Catalyzed by an Iminophosphine–Palladium Complex

Abstract

A palladium complex bearing an iminophosphine ligand, *N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine, was found to be a catalyst more active than conventional ones for the cross-coupling reaction of alkynyl-, alkenyl- and arylstannanes with various types of aryl halides to give the corresponding coupling products in high yields.

Introduction

Because of the availability and stability of organostannanes, the palladium-catalyzed coupling reaction of aryl halides with organostannanes is a powerful tool in organic synthesis.[1,2,3] On the other hand, the intrinsic low reactivity of organostannanes requires rather drastic conditions. In this Chapter, the author describes that a palladium complex coordinated with *N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine (**1**) is an efficient catalyst for the cross-coupling reaction of organostannanes with aryl halides.[4] This catalyst features high rate, wide applicability and sufficient stability.



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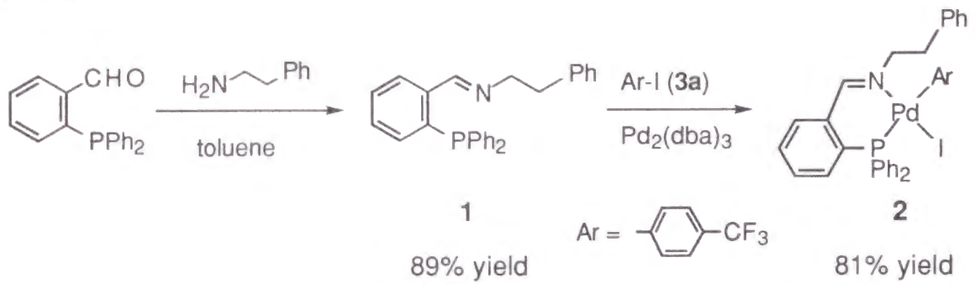
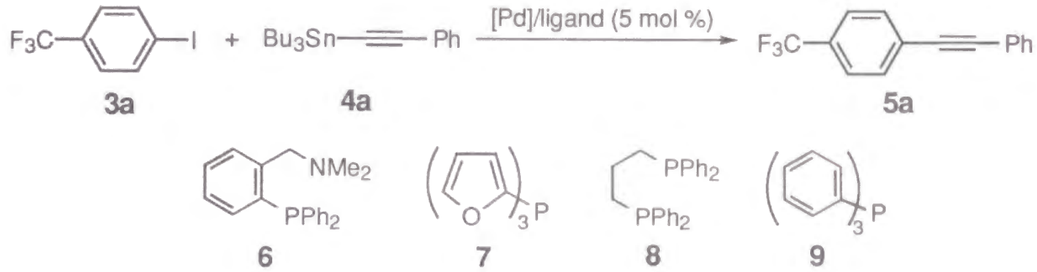
Results and Discussion

Iminophosphine **1** was readily prepared by condensation of 2-diphenylphosphinobenzaldehyde with 2-phenylethylamine (Scheme 1). Reaction of **1** with $Pd_2(dba)_3$ and 4-(trifluoromethyl)iodobenzene (**3a**) gave stable palladium(II) complex **2**, where both phosphorus and nitrogen atoms coordinate to palladium to form a six-membered ring.[5]

Scheme 1



Scheme 2



The catalytic activities of palladium complex **2** and some other palladium catalysts were compared in the coupling reaction of 4-(trifluoromethyl)-iodobenzene (**3a**) with tributyl(phenylethynyl)tin (**4a**) (Scheme 2). The conversion was readily monitored by ^{19}F NMR of the reaction mixture.[6] Yields of phenyl[4-(trifluoromethyl)phenyl]ethyne (**5a**) obtained by the reaction carried out for 24 h are summarized in Table 1. Iminophosphine–palladium complex **2** was found to show higher reaction rate than any other palladium complexes with phosphine ligands **6**–**9**. Thus, the reaction of **3a** with **4a** in THF in the presence of 5 mol % of palladium complex **2** at 25 °C gave 90% yield of cross-coupling product **5a** (entry 1). A palladium catalyst generated in situ from iminophosphine **1** and $[PdCl(\pi\text{-}C_3H_5)]_2$ (ligand/Pd = 1) was as effective as the preformed palladium catalyst (entry 2). In toluene or dioxane, the cross-coupling of **3a** with **4a** proceeded well as in THF by use of **1** as a ligand of palladium (entries 3 and 4). A palladium complex coordinated by aminophosphine **6**, where the imino moiety in **1** is replaced by an amino group, was slightly less active, giving 79% of **5a** (entry 6). Under the same reaction conditions, the palladium complex of tri(2-furyl)phosphine (**7**) (ligand/Pd = 2) gave only 57% yield (entry 7).

It is noteworthy that P–N ligands **1** and **6** are more effective than tri(2-furyl)phosphine (**7**), which has been reported by Farina and his co-workers to be the best phosphine ligand for the palladium-catalyzed coupling of

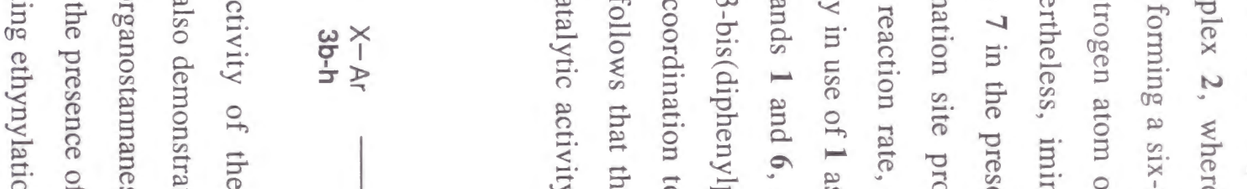
Table 1. Palladium-Catalyzed Coupling of 4-(Trifluoromethyl)iodobenzene (**3a**) with Tributyl(phenylethynyl)tin (**4a**)[a]

entry	ligand	ligand/Pd	solvent	yield of **5a** (%)[b]
1	**1**[c]	1	THF	90
2	**1**	1	THF	89 (83)[d]
3	**1**	1	toluene	87
4	**1**	1	dioxane	87
5	**1**	1	$CHCl_3$	71
6	**6**	1	THF	79
7	**7** ((2-furyl)$_3$P)	2	THF	57
8	**8** (dppp)	1	THF	34
9	**9** (Ph_3P)	2	THF	1

[a] The reaction was carried out in a solvent (5 mL) at 25 °C for 24 h using 4-(trifluoromethyl)iodobenzene (**3a**) (0.437 mmol), tributyl(phenylethynyl)tin (**4a**) (0.481 mmol), $[PdCl(\pi\text{-}C_3H_5)]_2$ (0.0109 mmol) and a ligand. [b] Determined by ^{19}F NMR. [c] Palladium complex **2** was used. [d] Isolated yield is given in the parenthesis.

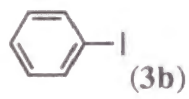
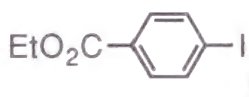
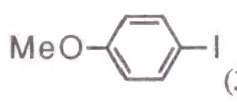
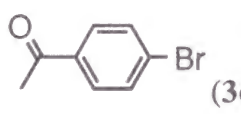
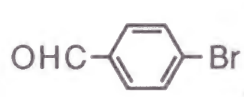
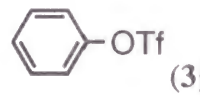
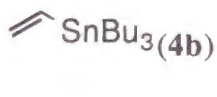
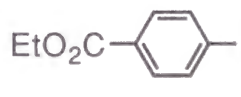
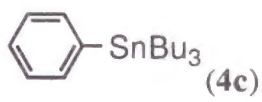
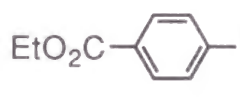
iodobenzene with tributyl(vinyl)tin.[3,7] Their kinetic study has shown that the dissociation of a ligand from the palladium(II) intermediate to make a vacant coordination site for vinyltin is responsible for the high catalytic activity. In the reaction with iminophosphine ligand **1**, the expected intermediate in the catalytic cycle is complex **2**, where both phosphino and imino groups coordinate to palladium forming a six-membered chelate. The dissociation of either phosphorus or nitrogen atom on **2** is unlikely because of the chelate coordination.[8,9] Nevertheless, iminophosphine **1** is more effective than monodentate phosphine **7** in the present cross-coupling reaction, suggesting that the vacant coordination site proposed by Farina may not always be necessary for the high reaction rate, or alternatively the reaction proceeds along a different pathway in use of **1** as a ligand.[10] Contrary to the high yields observed with P–N ligands **1** and **6**, the yield of **5a** was low (34%) with a diphosphine ligand, 1,3-bis(diphenylphosphino)propane (**8**), which forms a six-membered ring on coordination to a metal in a manner similar to P–N ligand **1** (entry 8). It follows that the coordination of the nitrogen atom is essential for the high catalytic activity, though its role in the reaction is not clear at present.

Scheme 3



High catalytic activity of the palladium complex coordinated by iminophosphine **1** was also demonstrated in the cross-coupling of a variety of aryl halides **3b-g** with organostannanes **4a-c** (Scheme 3). The reaction of aryl iodides **3b-d** with **4a** in the presence of 5 mol % of the catalyst gave over 86% yields of the corresponding ethynylation products, irrespective of the electron-withdrawing or electron-donating characters of the substituents on the phenyl

Table 2. Cross-Coupling of Aryl Halides with Organostannanes Catalyzed by Iminophosphine (**1**)–Palladium[a]

	$RSnR'_3$	Ar–X	solvent	temp (°C)	time (h)	yield of **5**[b] (%)
1	Ph—≡—$SnBu_3$ **(4a)**	 **(3b)**	THF	50	24	93
2		 **(3c)**	THF	50	18	86
3		 **(3d)**	THF	50	29	91
4		 **(3e)**	toluene	90	72	90
5		 **(3f)**	toluene	90	48	84
6[c]		 **(3g)**	toluene	80	48	93
7[d]	 **(4b)**	 **(3c)**	toluene	90	43	90
8[e]	 **(4c)**	 **(3c)**	toluene	90	140	84

[a] The reaction was carried out in a solvent (5 mL) using an aryl halide (**3**) (0.437 mmol), an organostannane (**4**) (0.481 mmol), $[PdCl(\pi\text{-}C_3H_5)]_2$ (0.0109 mmol) and iminophosphine **1** (0.0219 mmol). [b] Isolated yield based on aryl halide. [c] The reaction was carried out in the presence of tetrabutylammonium bromide (1.31 mmol) using tributyl(phenylethynyl)tin (0.656 mmol). [d] Tributyl(vinyl)tin (0.656 mmol) was used. [e] Tributyl(phenyl)tin (0.874 mmol) was used.

group (entries 1–3 in Table 2). Aryl bromides **3e**, **3f** and triflate **3g** also underwent the cross-coupling, though a prolonged reaction time was required (entries 4–6). Acetyl and formyl groups were tolerated. Vinylation and phenylation of aryl iodide **3c** were also successful by use of tributyl(vinyl)tin (**4b**) and tributyl(phenyl)tin (**4c**), respectively, in the presence of the iminophosphine–palladium catalyst (entries 7 and 8).

Conclusion

The author has found that the *N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine–palladium complex is an efficient catalyst for the coupling reaction of organostannanes with aryl halides. This catalyst allows one to achieve the organostannane-based cross-coupling reaction highly efficiently in high yields, using a variety of structures of organostannanes and aryl halides.

Experimental Section

The description in General Remarks, Apparatus, and Chemicals applies to all Chapters of the present Thesis.

General Remarks. All manipulations of oxygen- and moisture-sensitive materials were conducted with the standard Schlenk techniques under a purified argon atmosphere (deoxygenated by passing through BASF-Catalyst R3-11 column at 80 °C). Silica-gel column chromatography was performed using Wakogel C-200.

Apparatus. Nuclear magnetic resonance spectra were taken on a JEOL EX-270 (^{1}H, 270 MHz; ^{19}F, 254 MHz; ^{31}P, 109 MHz; ^{119}Sn, 101 MHz) spectrometer or a Varian Mercury 200 (^{1}H, 200 MHz; ^{19}F, 188 MHz; ^{31}P, 81 MHz) spectrometer using tetramethylsilane (^{1}H) as an internal standard, and 20% trifluoroacetic acid (^{19}F), 85% phosphoric acid (^{31}P), and tetramethyltin (^{119}Sn) as external standards. COSY and NOESY nuclear magnetic resonance spectra were taken on a Bruker ARX-400 (^{1}H, 400 MHz) spectrometer using tetramethylsilane (^{1}H) as an internal standard. The preparative recycling gel permeation chromatography was performed with JAI LC-908 equipped with JAIGEL-1H and -2H columns (chloroform as an eluent). All melting points measured with a Yanagimoto-Seisakusho Micro Melting Point apparatus were not corrected. Elemental analyses were performed at the Microanalytical Center, Kyoto University.

Chemicals. Most of reagents were obtained from Wako Pure Chemical Industries Ltd. and, unless otherwise noted, used as delivered. Solvents were purified by distillation under argon after drying over a suitable drying reagent as follows: sodium benzophenone ketyl for toluene, ether, and

THF; phosphorus pentoxide for chloroform and dichloromethane. Chloroform-*d* and THF-d_8 for NMR spectroscopy of oxygen- and moisture-sensitive materials were distilled after drying over phosphorus pentoxide and Na–K alloy, respectively, and were vacuum-transferred into an NMR tube prior to use.

The following compounds were prepared according to literature procedures: tributyl(phenylethynyl)tin (**4a**),[11] tributyl(vinyl)tin (**4b**),[12] *N,N*-dimethyl-2-(diphenylphosphino)phenylmethylamine (**6**),[13] tri(2-furyl)-phosphine (**7**).[14]

***N*-(2-Diphenylphosphinobenzylidene)-2-phenylethylamine (1).** A mixture of 2-diphenylphosphinobenzaldehyde[15] (881 mg, 3.03 mmol) and 2-phenylethylamine (386 mg, 3.19 mmol) in toluene (35 mL) was stirred at a reflux temperature for 6 h. The mixture was concentrated under a reduced pressure, and the residue was treated with hexane (20 mL). Filtration of insoluble material gave **1** (1.07 g, 89% yield) as a light yellow solid: mp 87–89 °C; ^{1}H NMR ($CDCl_3$) δ 2.75 (t, J = 7.8 Hz, 2 H), 3.70 (t, J = 7.8 Hz, 2 H), 6.85–6.91 (m, 1 H), 7.11–7.42 (m, 17 H), 7.92–7.98 (m, 1 H), 8.82 (d, J = 4.6 Hz, 1 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ -13.2; Anal. Calcd for $C_{27}H_{24}NP$: C, 82.42; H, 6.15; N, 3.56. Found: C, 82.25; H, 6.19; N, 3.56.

Iodo[4-(trifluoromethyl)phenyl][*N*-(2-diphenylphosphino-benzylidene)-2-phenylethylamine]palladium(II) (2). To a solution of **1** (17.2 mg, 0.0437 mmol) and 4-(trifluoromethyl)iodobenzene (11.9 mg, 0.0437 mmol) in dichloromethane (1.0 mL) was added $Pd_2(dba)_3$ (20.0 mg, 0.0218 mmol) and the mixture was stirred for 10 min at room temperature. Evaporation of the solvent followed by gel permeation chromatography gave complex **2** (27.4 mg, 81% yield) as a brown solid: mp 108–111 °C; ^{1}H NMR

($CDCl_3$) δ 3.03 (t, J = 8.1 Hz, 2 H), 4.65 (t, J = 8.1 Hz, 2 H), 6.78–6.83 (m, 2 H), 7.17–7.53 (m, 20 H), 7.61–7.66 (m, 1 H), 8.01 (s, 1 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ 24.0; ^{19}F NMR ($CDCl_3$) δ 13.6; Anal. Calcd for $C_{34}H_{28}NPF_3IPd$: C, 52.91; H, 3.66; N, 1.81. Found: C, 52.92; H, 3.71; N, 1.82.

Coupling Reaction of 4-(Trifluoromethyl)iodobenzene with Tributyl(phenylethynyl)tin. A solution (5 mL) of 4-(trifluoromethyl)iodobenzene (119 mg, 0.437 mmol), $[PdCl(\pi\text{-}C_3H_5)]_2$ (4.0 mg, 0.0109 mmol) and a ligand was degassed by three freeze-thaw cycles. To this solution was added tributyl(phenylethynyl)tin (188 mg, 0.481 mmol), and the mixture was stirred at 25 °C for 24 h. Small part of the reaction mixture was sampled and diluted with chloroform-*d*. The yield based on the aryl iodide was determined by ^{19}F NMR. The results are summarized in Table 1.

Coupling Reaction of Aryl Halides with Organostannanes. A solution (5 mL) of *N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine (8.6 mg, 0.0219 mmol), an aryl halide (0.437 mmol), and $[PdCl(\pi\text{-}C_3H_5)]_2$ (4.0 mg, 0.0109 mmol) was degassed by three freeze-thaw cycles. To this solution was added an organostannane (0.481 mmol) and the mixture was stirred at the temperature indicated in Table 2. After the time specified in Table 2, a 1 M KF aqueous solution (2 mL) was added, and the reaction mixture was stirred at room temperature for 30 min. Filtration through a Celite plug was followed by extraction with ethyl acetate (50 mL). The organic layer was washed successively with water and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by gel permeation chromatography gave the corresponding coupling product. Yields are listed in Table 2.

Phenyl[4-(ethoxycarbonyl)phenyl]ethyne. A colorless solid: mp 79–81 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 7.5 Hz, 3 H), 4.38 (t, J = 7.5 Hz, 2 H), 7.35–7.39 (m, 2 H), 7.53–7.60 (m, 5 H), 8.01–8.05 (m, 2 H). Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.68; H, 5.79.

Other coupling products **5** in Table 1 and 2 have already been reported in the literature. Their spectroscopic data are as follows.

Phenyl[4-(trifluoromethyl)phenyl]ethyne.[16] ^{1}H NMR ($CDCl_3$) δ 7.35–7.68 (m, 9 H).

Diphenylethyne. ^{1}H NMR ($CDCl_3$) δ 7.30–7.55 (m, 10 H).

Phenyl(4-methoxyphenyl)ethyne.[17] ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3 H), 6.86–6.90 (m, 2 H), 7.31–7.54 (m, 7 H).

Phenyl(4-acetylphenyl)ethyne.[18] ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3 H), 7.34–7.39 (m, 3 H), 7.52–7.63 (m, 4 H), 7.91–7.96 (m, 2 H).

4-(Phenylethynyl)benzaldehyde.[19] ^{1}H NMR ($CDCl_3$) δ 7.26–7.40 (m, 3 H), 7.54–7.59 (m, 2 H), 7.66–7.70 (m, 2 H), 7.85–7.89 (m, 2 H), 10.03 (s, 1 H).

Ethyl 4-ethenylbenzoate.[20] ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 7.5 Hz, 3 H), 4.38 (t, J = 7.5 Hz, 2 H), 5.37 (d, J = 12.1 Hz, 1 H), 5.85 (d, J = 18.1 Hz, 1 H), 6.76 (dd, J = 18.1, 12.1 Hz, 1 H), 7.43–7.48 (m, 2 H), 8.00–8.04 (m, 2 H).

Ethyl 4-phenylbenzoate.[21] ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J = 7.5 Hz, 3 H), 4.40 (t, J = 7.5 Hz, 2 H), 7.36–7.51 (m, 3 H), 7.60–7.68 (m, 4 H), 8.08–8.12 (m, 2 H).

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(5) The cis geometry of the imino and aryl groups was assigned by a crosspeak in the NOESY spectra between PhCH_2 and ortho protons (to Pd) of $CF_3C_6H_4Pd$. Chapter 2 describes this assignment in detail.

(6) ^{19}F NMR ($CDCl_3$) for **3a**: δ 12.64; **5a**: δ 12.85.

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(8) The chelate coordination of P–N ligands to palladium(II) complexes is confirmed by X-ray diffraction studies. (a) For the palladium(II) complexes coordinated by *N*-(2-diphenylphosphinobenzylidene)-(*S*)-1-phenylethylamine, see: Ankersmit, H. A.; Løken, B. H.; Kooijman, H.; Spek, A. L.; Vrieze, K.; van Koten, G. *Inorg. Chim. Acta* **1996**, *252*, 141. (b) For the complexes of aminophosphine **2** and palladium(II), see: de Graaf, W.; Harder, S.; Boersma, J.; van Koten, G.; Kanters, J. A. *J. Organomet. Chem.* **1988**, *358*, 545.

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Chapter 2

On the Catalytic Cycle of the Palladium-Catalyzed Cross-Coupling Reaction of Organostannanes with Aryl Halides

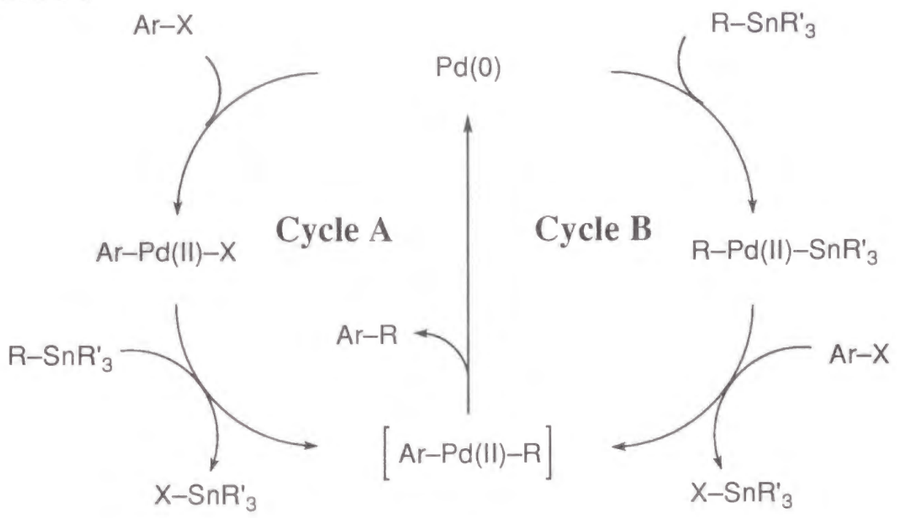
Abstract

The coupling reaction of tributyl(phenylethynyl)tin with 4-(trifluoromethyl)iodobenzene catalyzed by a Pd(0) complex having *N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine as a ligand was found to start with oxidative addition of the tin reagent to the Pd(0) complex. In contrast, the use of 1,3-bis(diphenylphosphino)propane as the ligand switched the catalytic cycle to the well-accepted one initiated by oxidative addition of the aryl iodide to the Pd(0) complex. The influence of the ligand and organostannane on the catalytic cycle was examined.

Introduction

A wide variety of organometallics undergo the coupling reaction with aryl halides with the aid of a palladium catalyst. Among all, the coupling reaction of organostannanes is widely used particularly in laboratories.[1,2] However, little is known about its reaction mechanism. For example, it still remains uncertain which of the electrophile or organometallic reagent reacts with a palladium(0) complex. The currently accepted catalytic cycle involves three distinct steps: (1) oxidative addition of an aryl halide to an electron-rich palladium(0) complex, (2) transmetalation of the resulting electrophilic palladium(II) complex with a nucleophilic organostannane, and (3) reductive elimination to give a cross-coupled product and regenerate the palladium(0) complex (Scheme 1, Cycle A).[3] Herein, the author shows that, besides the currently accepted cycle, the cross-coupling reaction in some cases takes place according to Cycle B (Scheme 1) which is initiated by oxidative addition of an organostannane to a palladium(0) complex.[4,5] He has examined how the ligand and substrate affect the catalytic cycle.

Scheme 1



Results

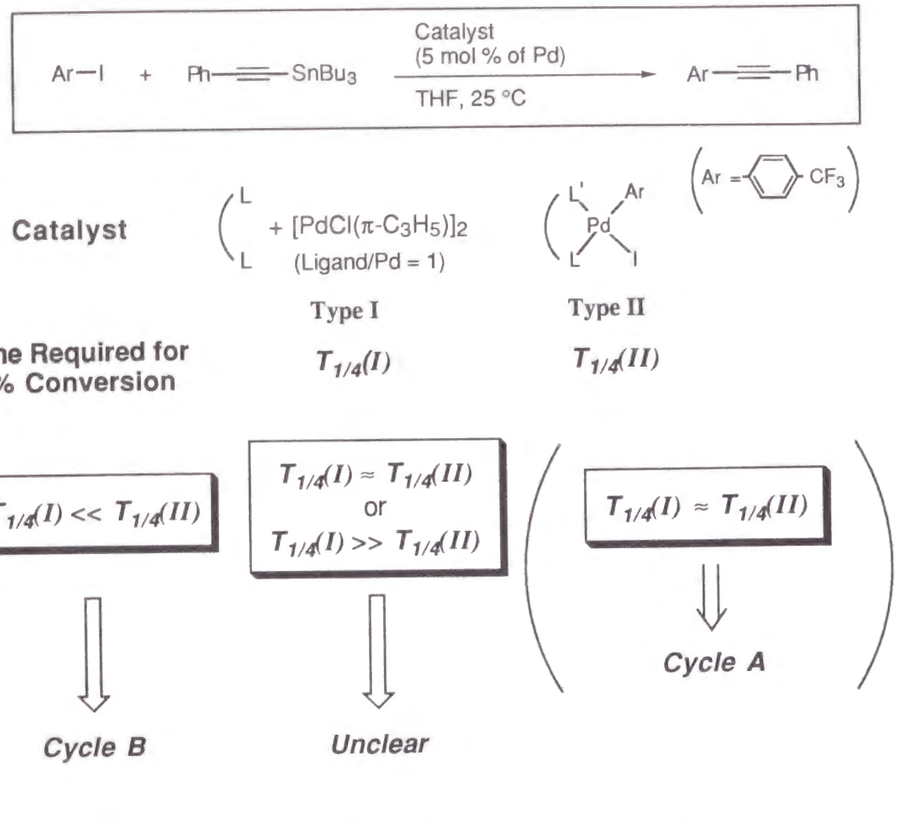
Effect of the Catalyst on the Reaction Rate.

First, the author examined the reaction rate of the palladium-catalyzed coupling of tributyl(phenylethynyl)tin with 4-(trifluoromethyl)iodobenzene (Ar–I), using *N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine (**1a**), 1,3-bis(diphenylphosphino)propane (**1b**), *N*,*N*-dimethyl-*N'*-(2-diphenylphosphinobenzylidene)ethylenediamine (**1c**) or *N*,*N*-dimethyl-2-(diphenylphosphino)phenylmethylamine (**1d**) as a ligand (Scheme 2, Figure 1).[6] The catalyst prepared in situ from $[PdCl(\pi\text{-}C_3H_5)]_2$ and the ligand was named Type I. The author prepared the complexes called Type II (**2a**, **2b**, **2c** and **2d**)[7] by the reaction of Ar–I with the corresponding palladium(0) complexes. The Type II complexes are the expected intermediates of Cycle A.

The author assumed that, if the reaction might take place according to Cycle A, no induction period should be observed with the preformed Type II catalyst and that the rate in an early stage of the reaction should be similar to or higher than that with the corresponding catalyst prepared in situ (Type I). If this is not the case, another catalytic cycle, Cycle B, must be working. To investigate the rate in an early stage of the reaction, the author measured time ($T_{1/4}$) required for 25% conversion. Conversion was monitored on the basis of consumed Ar–I by ^{19}F NMR of the reaction mixture. When the complex of Type II was used, the product derived from the complex also was counted in conversion. The results are summarized in Figure 1.

The author found that $T_{1/4}$ with preformed catalyst **2a** was 440 min, much larger than $T_{1/4}$ (= 72 min) obtained with the catalyst prepared in situ from **1a** and $[PdCl(\pi\text{-}C_3H_5)]_2$.[8] This means that the catalyst of **1a**–$[PdCl(\pi\text{-}C_3H_5)]_2$ did not mediate the coupling reaction according to Cycle A. The use of **1c** or **1d** gave the similar results: the Type I catalysts promoted the reaction

Scheme 2



faster than the Type II catalysts. Thus, it is likely that Cycle B is working in these cases, though further confirmation is required.

In contrast, the catalysts prepared from diphosphine **1b**, both Type I and Type II, promoted the reaction at almost the equal rates, $T_{1/4}$ being 1260 and 1270 min, respectively. These results suggest that in these cases Cycle A is involved.

The author is now in a position to say that the reaction is likely to proceed according to Cycle B when ligand **1a**, **1c** or **1d** is used. In the case of **1b**, there was not sufficient evidence that allowed us to decide which cycle was working. To gain more insight into the reaction mechanism, the author investigated how these Pd(0) complexes interacted with organostannanes and behaved in the coupling reaction.

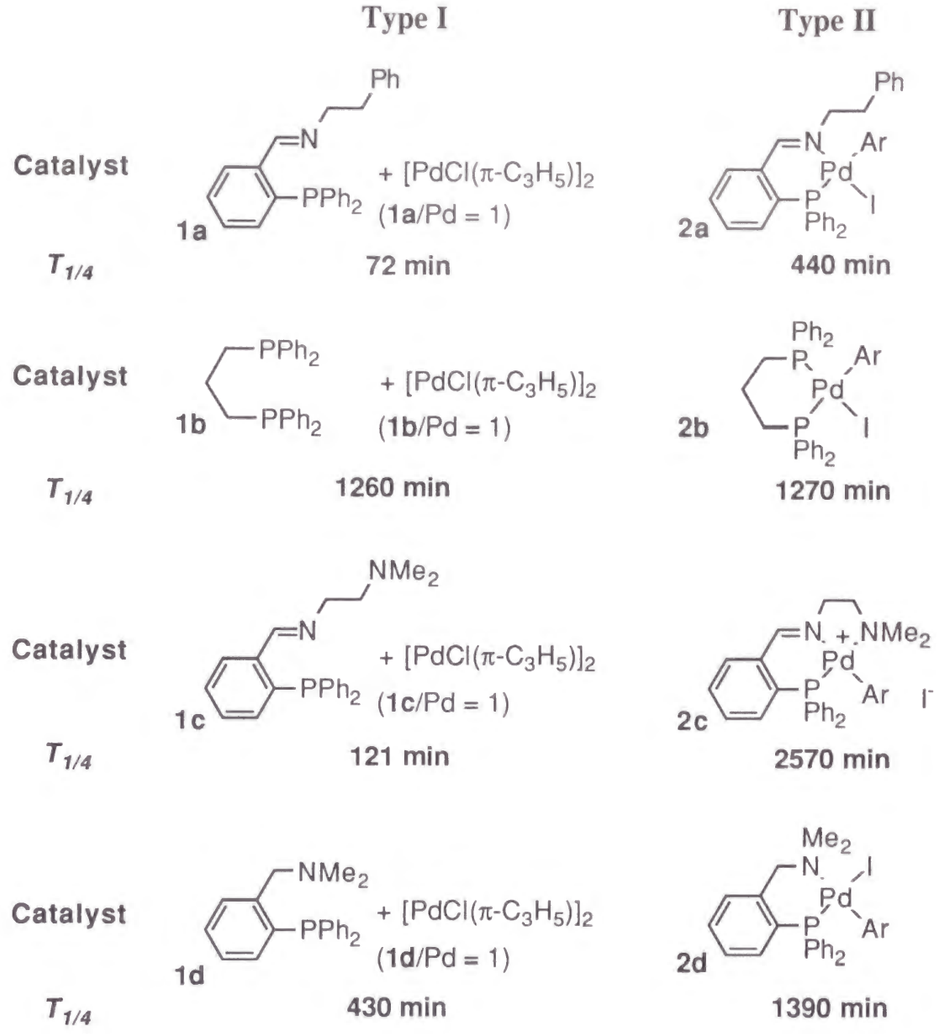


Figure 1. Reaction rates in an early stage of the coupling reaction of tributyl(phenylethynyl)tin with Ar–I by the catalyst prepared in situ (Type I) and the preformed catalyst (Type II).

Oxidative Addition of Organostannanes to Pd(0) Complexes.

The interaction of the Pd(0) complex coordinated by **1a**, **1b**, **1c** or **1d** with tributyl(phenylethynyl)tin or tributyltin iodide was examined by NMR spectroscopy (Figures 2–5). The Pd(0) complex was prepared by reduction of $[PdCl(\pi\text{-}C_3H_5)]_2$ in the presence of the corresponding ligand with sodium dimethyl malonate.[9]

Iminophosphine 1a–Pd(0) Complex.

It was found that tributyl(phenylethynyl)tin and tributyltin iodide added oxidatively to the iminophosphine **1a**–Pd(0) complex, giving **3a** and **4a**, respectively (Figure 2). Each of the complexes was characterized in a following way: (1) formation of a Pd–Sn bond was confirmed by a large shift in ^{119}Sn resonance, (2) coordination of the nitrogen atom was evidenced by a downfield shift (*ca.* 0.8 ppm) of the methylene protons adjacent to the nitrogen atom, and (3) the *cis*-configuration of the phosphino and stannyl groups was assigned on the basis of small coupling constants between phosphorus and tin atoms.[4a,4b,4d]

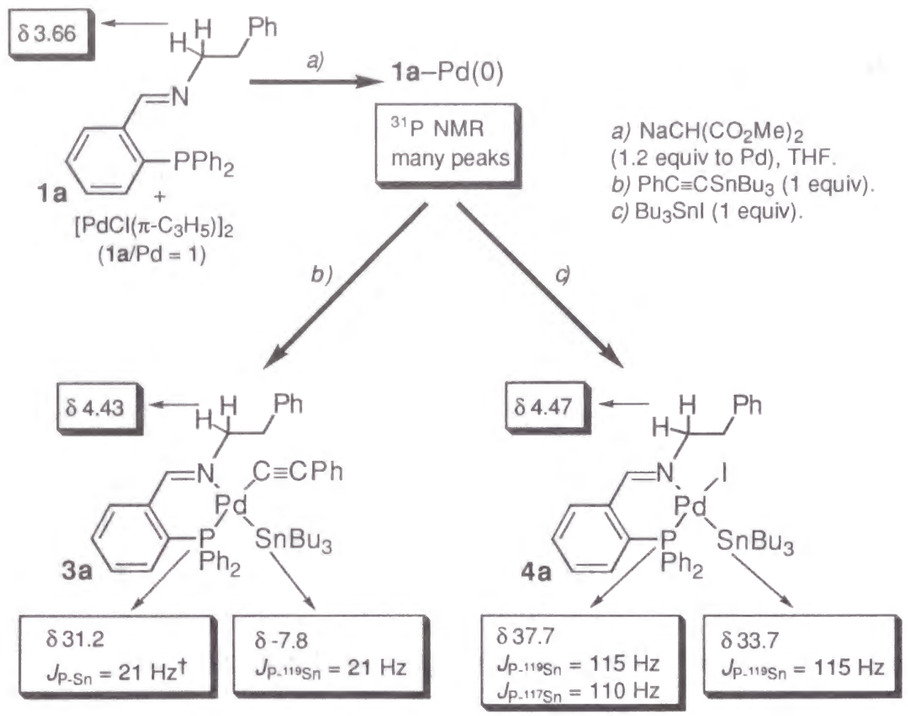


Figure 2. ^{31}P{^{1}H}, ^{119}Sn{^{1}H} and ^{1}H NMR (THF-d_8) parameters (chemical shift and $J_{Sn\text{-}P}$) of Pd(0)/**1a** and its reaction products with PhC≡CSnBu$_3$ or Bu$_3$SnI.

1,3-Bis(diphenylphosphino)propane 1b–Pd(0) Complex.

The diphosphine **1b**–Pd(0) complex also reacted with tributyl(phenylethynyl)tin and tributyltin iodide, giving Pd(II) complex **3b** and **4b**, respectively (Figure 3). The assignment of each complex is based on a large shift of ^{119}Sn resonance and three sets of coupling between phosphorus and tin atoms.

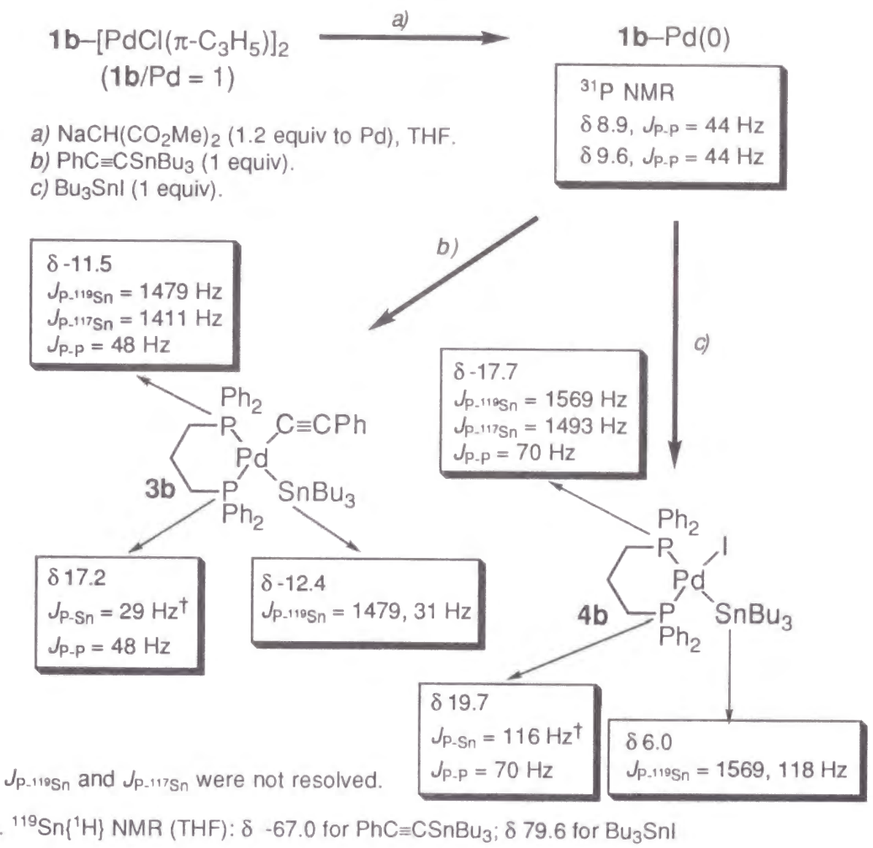


Figure 3. ^{31}P{^{1}H} and ^{119}Sn{^{1}H} NMR (THF) parameters (chemical shift, $J_{Sn\text{-}P}$ and $J_{P\text{-}P}$) of Pd(0)/**1b** and its reaction products with PhC≡CSnBu$_3$ or Bu$_3$SnI.

Amino(imino)phosphine 1c–Pd(0) Complex.

The reaction of amino(imino)phosphine **1c**–Pd(0) with tributyl(phenylethynyl)tin gave oxidative addition product **3c** (Figure 4). Formation of a Pd–

Sn bond was confirmed by a large downfield shift of ^{119}Sn resonance and the coupling between phosphorus and tin. The downfield shift of the adjacent methylene protons shows coordination of the nitrogen atom of the imino group. The reaction of the Pd(0) complex with tributyltin iodide gave two major species, where the coupling between phosphorus and tin was not observed in $^{31}P\{^1H\}$ NMR spectra. Thus, at present, formation of **4c** is not confirmed.

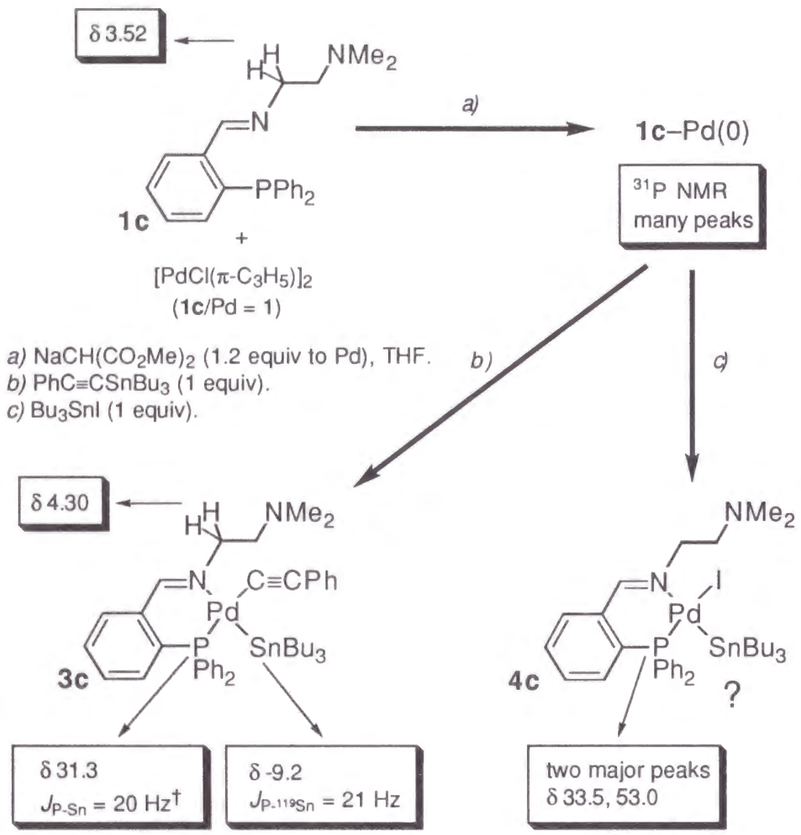


Figure 4. $^{31}P\{^1H\}$, $^{119}Sn\{^1H\}$ and ^1H NMR (THF-d_8) parameters (chemical shift and $J_{Sn\text{-}P}$) of Pd(0)/**1c** and its reaction products with $PhC{\equiv}CSnBu_3$ or Bu_3SnI.

*Aminophosphine **1d**–Pd(0) Complex.*

The aminophosphine **1d**–Pd(0) complex reacted with tributyl(phenylethynyl)tin and tributyltin iodide in a manner similar to the iminophosphine **1a**–Pd(0) complex, giving the corresponding oxidative addition products **3d** and **4d**, respectively (Figure 5). The assignment also was accomplished similarly.

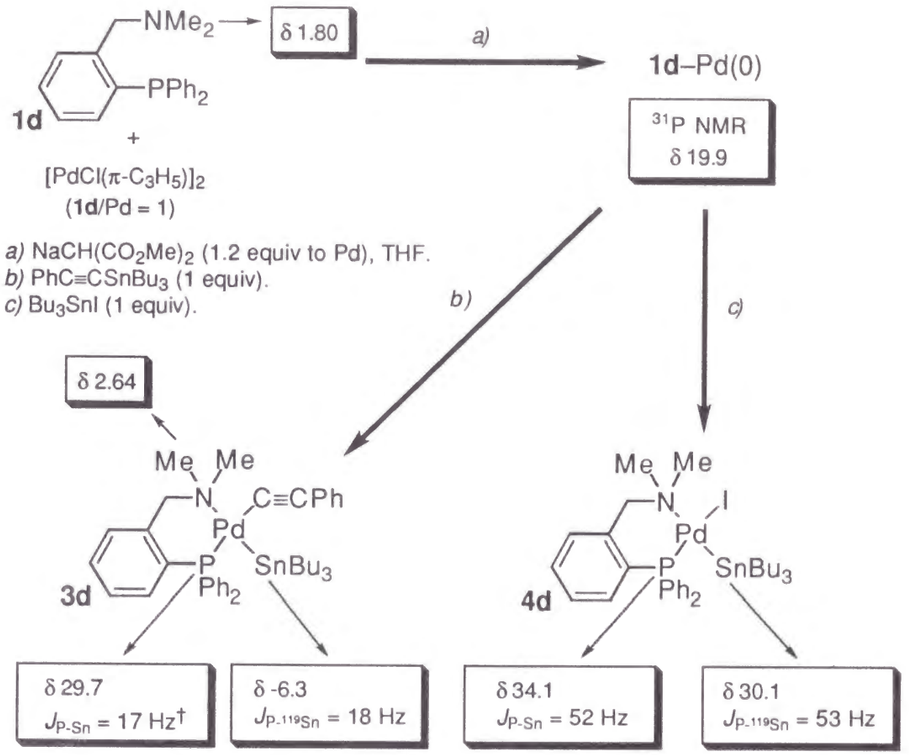
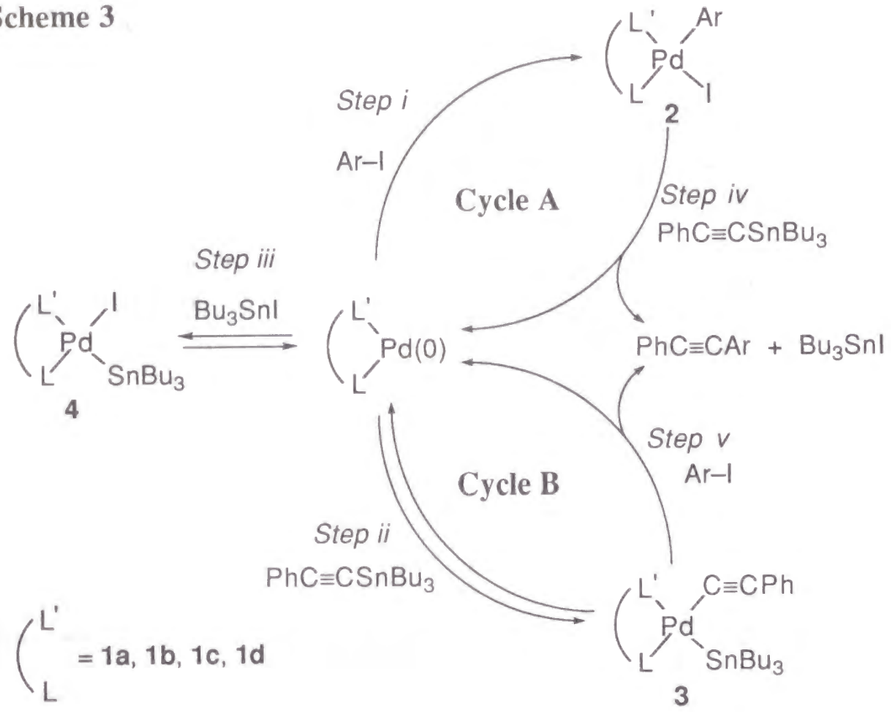


Figure 5. $^{31}P\{^1H\}$, $^{119}Sn\{^1H\}$ and ^1H NMR (THF-d_8) parameters (chemical shift and $J_{Sn\text{-}P}$) of Pd(0)/**1d** and its reaction products with $PhC{\equiv}CSnBu_3$ or Bu_3SnI.

Reversibility of the Reaction of the Pd(0) Complexes with Ar–I, Tributyl(phenylethynyl)tin and Tributyltin Iodide.

All the Pd(0) complexes coordinated by bidentate ligand **1a**, **1b**, **1c** or **1d** may react with all of the species present in the reaction mixture, except for the coupled product. Namely, Ar–I, tributyl(phenylethynyl)tin and tributyltin iodide can react with the Pd(0) complex coordinated by each of the bidentate ligands (*Step i*, *ii* and *iii* in Scheme 3, respectively). The reversibility of the reaction of the Pd(0) complexes with these species was next examined.

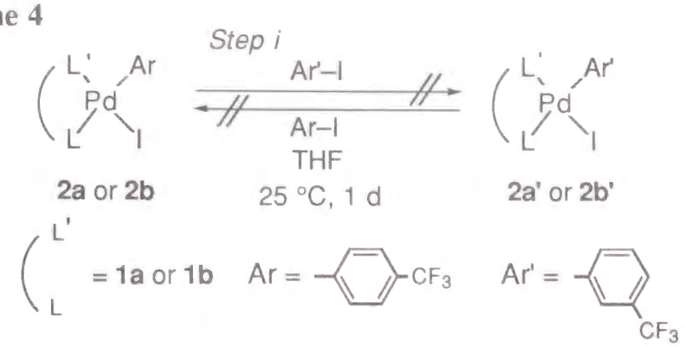
Scheme 3



Reaction with Ar–I (Step i).

The author found that oxidative addition of Ar–I to the Pd(0) complex coordinated by **1a** or **1b** was irreversible, confirming that the intermolecular exchange of an Ar group shown in Scheme 4 was not observed at 25 °C within 1 d. This observation implies that complex **2a** and **2b** (and probably **2c** and **2d**), once produced, cannot but get into Cycle A.

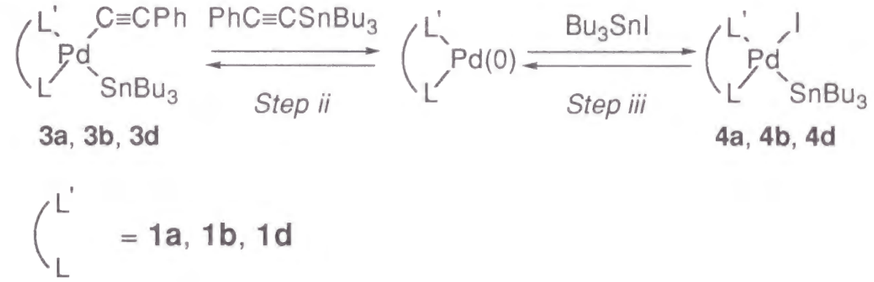
Scheme 4



Reaction with Organostannanes (Steps ii and iii).

Next, the reversibility of oxidative addition of organostannanes, tributyl(phenylethynyl)tin or tributyltin iodide, was examined. The ratio of complexes **3** and **4** was found to depend on the concentration of tributyl(phenylethynyl)tin and tributyltin iodide. Namely, when tributyltin iodide was added to complex **3**, complex **4** was generated proportionally, and *vice versa*. These results are rationalized by the equilibrium among **3**, **4** and the Pd(0) complex as shown in Scheme 5.

Scheme 5



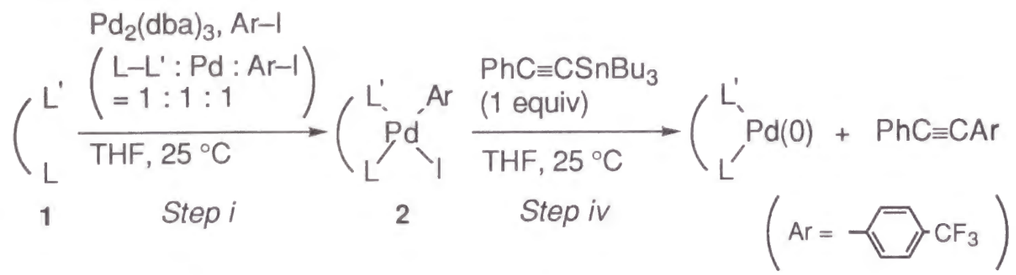
Reaction Rate of the Individual Step.

The reaction rates of *Steps i*, *ii*, *iv* and *v* in Scheme 3 were estimated by ^{19}F NMR.

Steps i and iv in Cycle A.

Examination under the stoichiometric conditions using bidentate ligand **1a**, **1b**, **1c** or **1d** revealed that transmetalation of **2** was the rate-determining-step of Cycle A, as shown by the data in Scheme 6.

Scheme 6



	Step i	*Step iv*
1a	<10 min, 100% conv.	15 h, 60% conv.
1b	<10 min, 100% conv.†	15 h, 32% conv.
1c	<10 min, 100% conv.	25 h, 24% conv.
1d	<10 min, 100% conv.	22 h, 23% conv.

†The Pd(0) complex was prepared by reduction of $[PdCl(\pi\text{-}C_3H_5)]_2$–**1b** (**1b**/Pd = 1) by $NaCH(CO_2Me)_2$ (1.2 equiv) in THF.

Steps ii and v in Cycle B.

Due to instability of **3**, isolation of **3** was unsuccessful, and thus the author could not measure the rate of *Step v*. The results that oxidative addition of tributyl(phenylethynyl)tin to a Pd(0) complex coordinated by **1a**, **1b**, **1c** or **1d** (*Step ii* in Scheme 3) was fast enough have been already described in earlier Section of this Chapter. It seems appropriate to consider that *Step v* is the rate-determining-step of Cycle B.

Behavior of the Pd Complexes in the Cross-Coupling Reaction.

The author next studied, by $^{31}P\{^1H\}$ NMR, the behavior of the palladium complex coordinated by **1a**, **1b**, **1c** or **1d** (ligand/Pd = 1) during the palladium-catalyzed cross-coupling reaction of tributyl(phenylethynyl)tin with Ar–I in THF at 25 °C.

*Iminophosphine **1a** as a Ligand.*

The oxidative addition products (**3a** and **4a**) of tributyl(phenylethynyl)-tin and tributyltin iodide to Pd(0)/**1a**, respectively, were observed as two major species along with a small amount of complex **2a** in the reaction catalyzed by **1a**–$[PdCl(\pi\text{-}C_3H_5)]_2$ (Figure 6). If the reaction proceeded along Cycle A, complex **2a** must be the dominant species since the rate-determining-step should be transmetalation, but this is not the case.

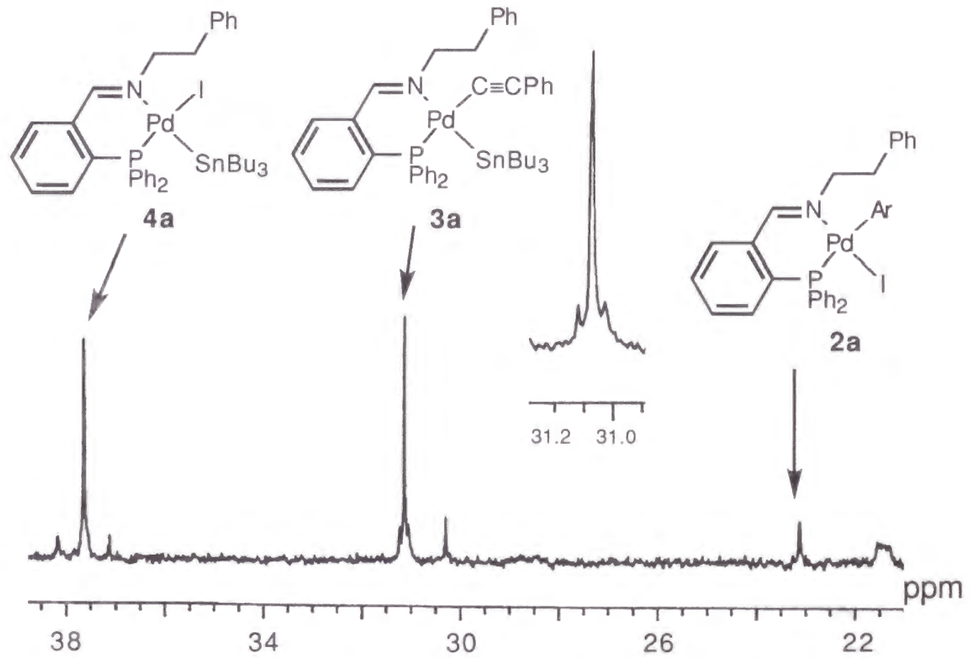


Figure 6. $^{31}P\{^1H\}$ NMR (109 MHz) spectrum of the reaction mixture (at *ca.* 18% conversion) of **1a**–$[PdCl(\pi\text{-}C_3H_5)]_2$-catalyzed coupling of tributyl(phenylethynyl)tin with Ar–I in THF at 25 °C.

This result suggests that the coupling reaction of tributyl(phenylethynyl)-tin with Ar–I using **1a**–$[PdCl(\pi\text{-}C_3H_5)]_2$ as a catalyst proceeded through oxidative addition of a C–Sn bond of the organostannane to the Pd(0) complex. This observation is consistent with the earlier observations. Namely, Cycle B in Scheme 1 accounts for all of these results.

*Diphosphine **1b** as a Ligand.*

The reaction catalyzed by **1b**–$[PdCl(\pi\text{-}C_3H_5)]_2$ afforded complex **2b** (Figure 7), showing that the reaction proceeded according to Cycle A and that transmetalation was the rate-determining-step. This spectroscopic experiment agrees well with the kinetic experiment discussed earlier.

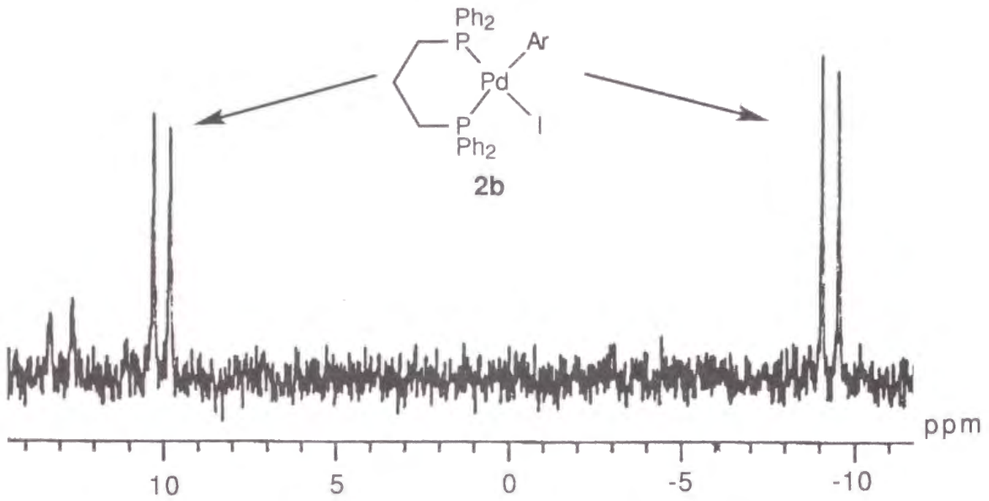


Figure 7. $^{31}P\{^1H\}$ NMR (109 MHz) spectrum of the reaction mixture (at *ca.* 38% conversion) of **1b**–$[PdCl(\pi\text{-}C_3H_5)]_2$-catalyzed coupling of tributyl(phenylethynyl)tin with Ar–I in THF at 25 °C.

*Amino(imino)phosphine **1c** as a Ligand.*

Spectroscopic study by $^{31}P\{^1H\}$ NMR revealed that the Pd complex coordinated by amino(imino)phosphine **1c** produced, under the coupling reaction conditions of tributyl(phenylethynyl)tin with Ar–I, a single species

identical with that observed in the stoichiometric reaction of Pd(0)/**1c** with tributyltin iodide (cf. Figures 4 and 8). Although the signal of $^{31}P\{^1H\}$ NMR corresponds to that of **2c**, ^{19}F signal attributed to **2c**[10] was not observed. This means that Pd(0)/**1c** catalyst is not involved in Cycle A. Although **3c** was not detected, above observation does not necessarily contradict the outcome of the kinetic experiment which suggested that Cycle B was plausible when **1c** was used as a ligand.

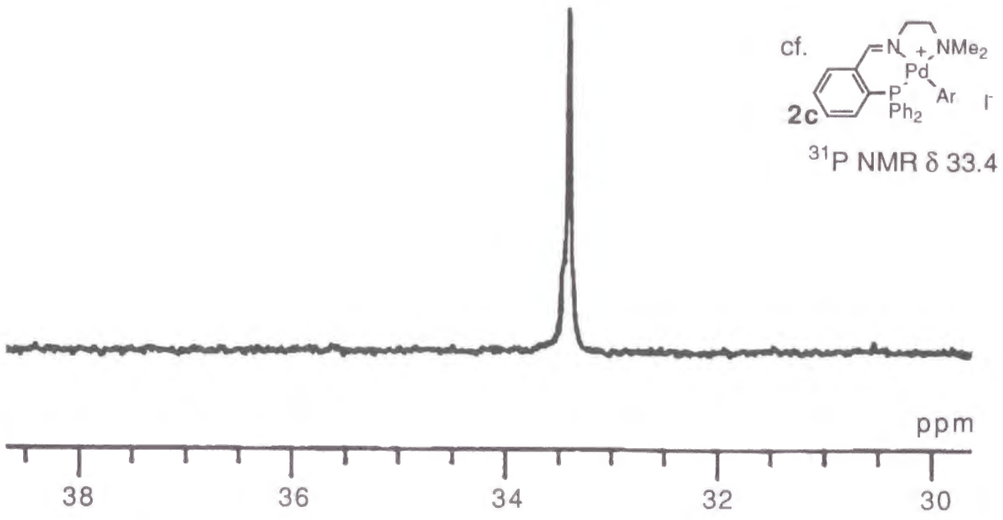


Figure 8. $^{31}P\{^1H\}$ NMR (109 MHz) spectrum of the reaction mixture (at *ca.* 20% conversion) of **1c**–$[PdCl(\pi\text{-}C_3H_5)]_2$-catalyzed coupling of tributyl(phenylethynyl)tin with Ar–I in THF at 25 °C.

*Aminophosphine **1d** as a Ligand.*

Two oxidative addition products (**3d** and **4d**) of tributyl(phenylethynyl)-tin and tributyltin iodide to Pd(0)/**1d** were observed by $^{31}P\{^1H\}$ NMR (Figure 9), and no trace of complex **2d** was detected. This observation together with the kinetic experiment clearly shows that the coupling reaction using **1d** as a ligand proceeds along Cycle B.

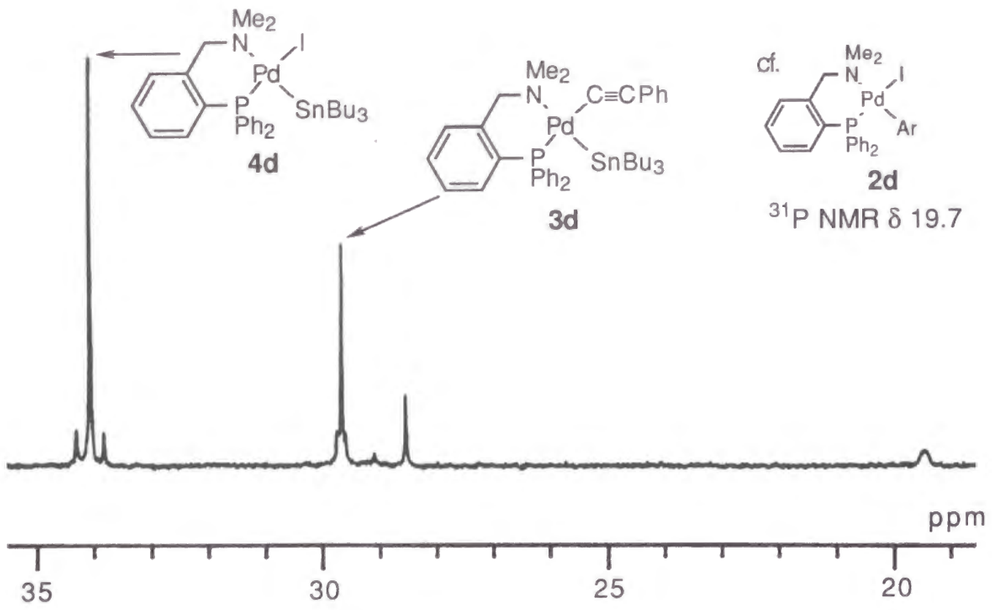


Figure 9. $^{31}P\{^{1}H\}$ NMR (109 MHz) spectrum of the reaction mixture (at *ca.* 15% conversion) of **1d**–$[PdCl(\pi\text{-}C_3H_5)]_2$-catalyzed coupling of tributyl(phenylethynyl)tin with Ar–I in THF at 25 °C.

Catalytic Cycle in the Iminophosphine–Pd(0)-Catalyzed Coupling Reaction of Other Organostannanes with Ar–I.

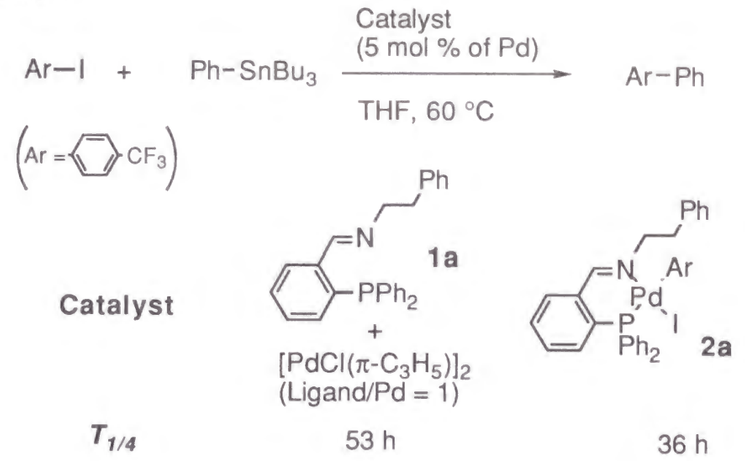
The author next applied the kinetic and spectroscopic methods to see how the coupling reaction of tributyl(phenyl)tin or tributyl(vinyl)tin with Ar–I proceeds in the presence of Pd(0)/**1a**. Generally, tributyl(phenyl)tin and tributyl(vinyl)tin are less reactive than tributyl(phenylethynyl)tin in the Stille reaction.[2a] These organostannanes did not oxidatively add to Pd(0)/**1a** under the conditions that tributyl(phenylethynyl)tin did.

Tributyl(phenyl)tin.

The coupling reaction carried out using the preformed catalyst (**2a**) or the catalyst prepared in situ from $[PdCl(\pi\text{-}C_3H_5)]_2$ and **1a** was observed to

take place in a comparable rate (Scheme 7). This result suggests that Cycle A was operating in each reaction.

Scheme 7



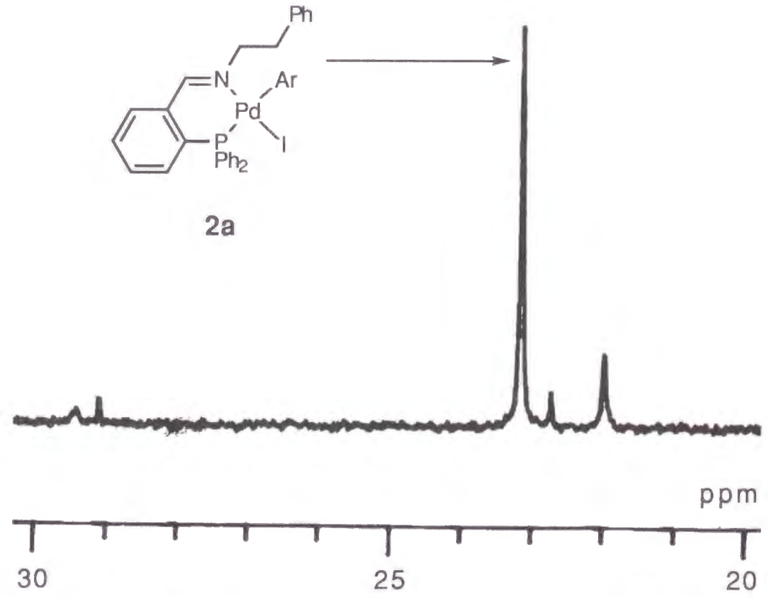


Figure 10. $^{31}P\{^{1}H\}$ NMR (109 MHz) spectrum of the reaction mixture (at *ca.* 52% conversion) of **1a**–$[PdCl(\pi\text{-}C_3H_5)]_2$-catalyzed coupling of tributyl(phenyl)tin with Ar–I in THF at 60 °C.

The monitoring experiment by $^{31}P\{^{1}H\}$ NMR showed that **2a** was the major species in the coupling of tributyl(phenyl)tin with Ar–I (Figure 10).

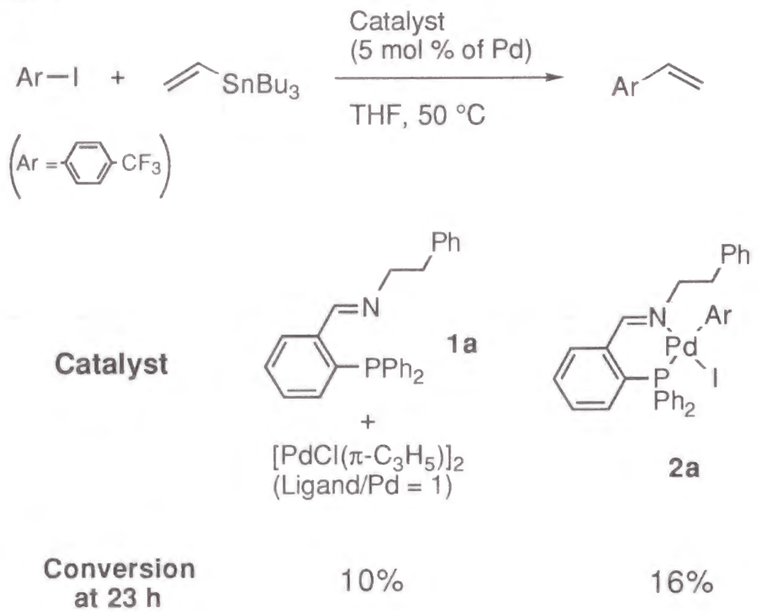
These two observations lead to the conclusion that the coupling reaction of tributyl(phenyl)tin undergoes via Cycle A.

Tributyl(vinyl)tin.

The catalysts prepared with iminophosphine **1a**, both prepared in situ and preformed, promoted the coupling reaction in comparable rates, as was revealed by the conversions after 23 h: 10% and 16%, respectively (Scheme 8).

Palladium complex **2a** was observed by $^{31}P\{^{1}H\}$ NMR as an almost exclusive species in the coupling reaction of tributyl(vinyl)tin with Ar–I catalyzed by iminophosphine **1a**–Pd(0) (Figure 11). Thus, the author may safely conclude that Cycle A is the mechanism of this reaction.

Scheme 8



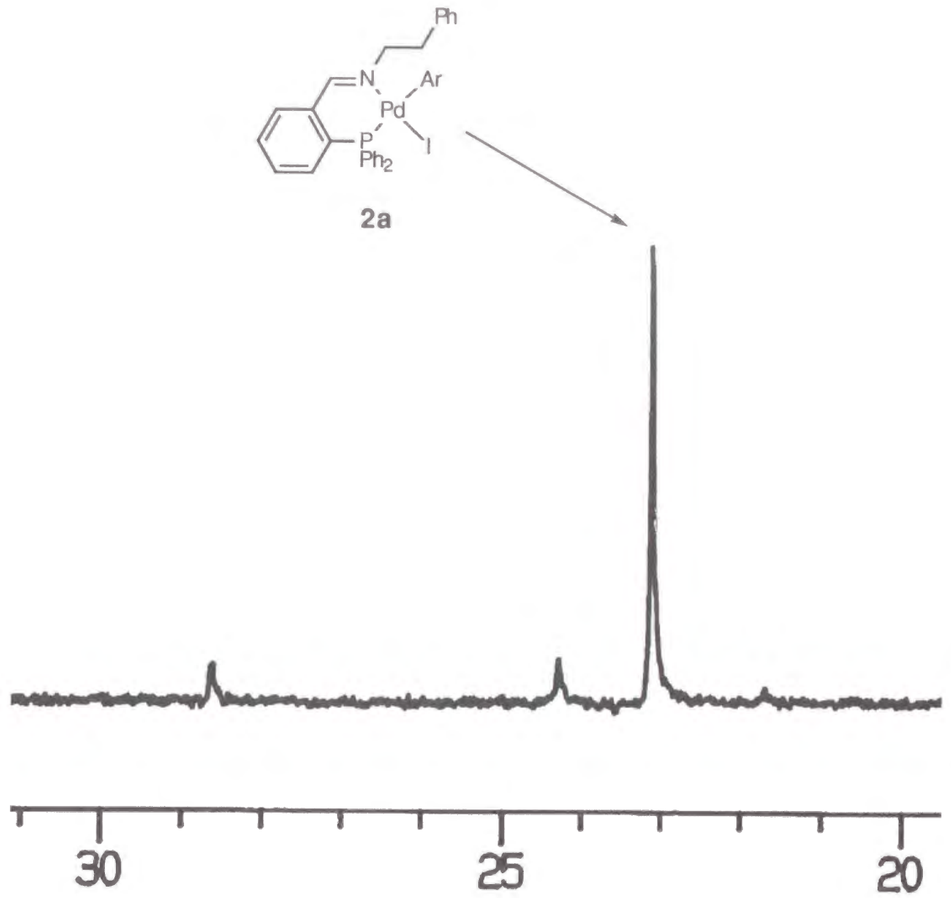
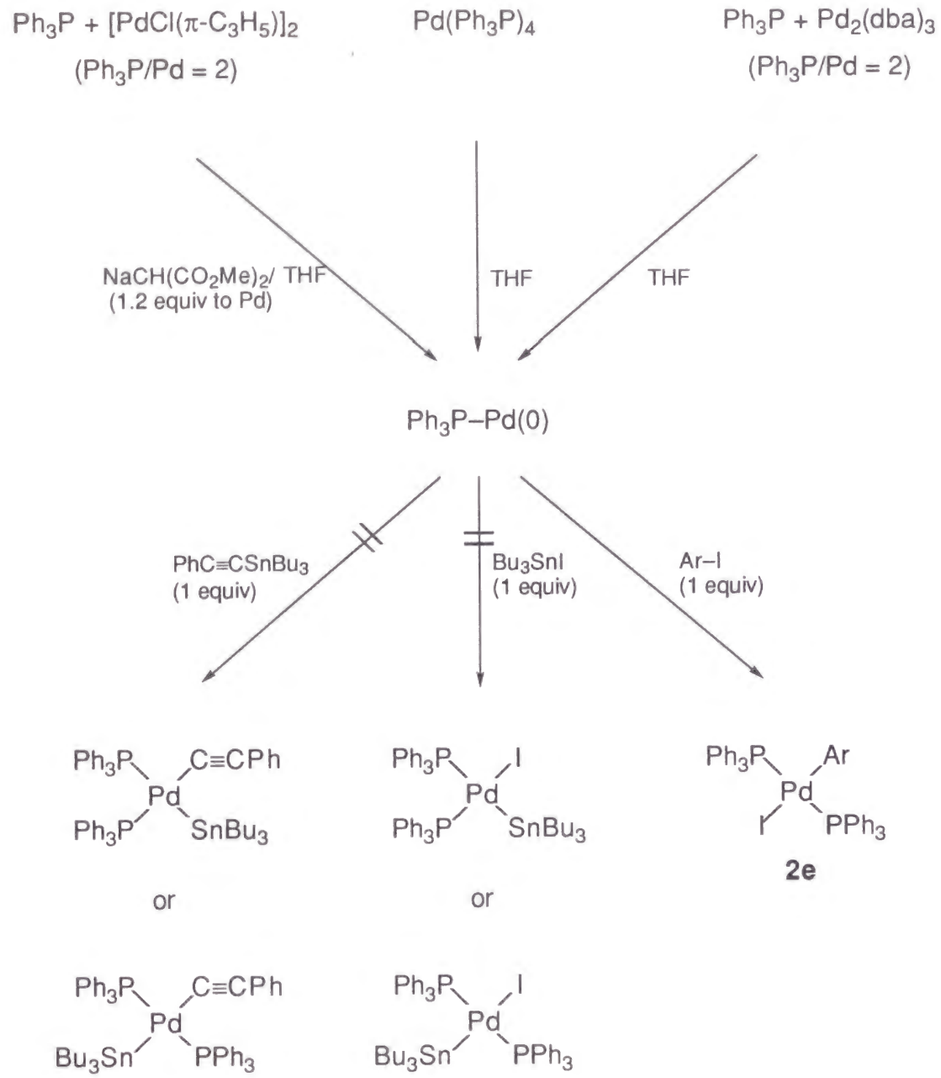


Figure 11. $^{31}P\{^{1}H\}$ NMR (109 MHz) spectrum of the reaction mixture (at *ca.* 13% conversion) of **1a**–$[PdCl(\pi\text{-}C_3H_5)]_2$-catalyzed coupling of tributyl(vinyl)tin with Ar–I in THF at 50 °C.

Catalytic Cycle in the Triphenylphosphine–Pd(0)-Catalyzed Coupling Reaction of Tributyl(phenylethynyl)tin with Ar–I.

As depicted in Scheme 9, tributyl(phenylethynyl)tin and tributyltin iodide did not oxidatively add to the triphenylphosphine–Pd(0) complex generated by any of three different ways.

Scheme 9



In the Ph_3P–Pd(0)-catalyzed coupling of tributyl(phenylethynyl)tin with Ar–I, the formation of **2e** was observed by $^{31}P\{^1H\}$ NMR (Figure 12). Thus, the reaction has proceeded according to Cycle A, transmetalation being the rate-determining-step.

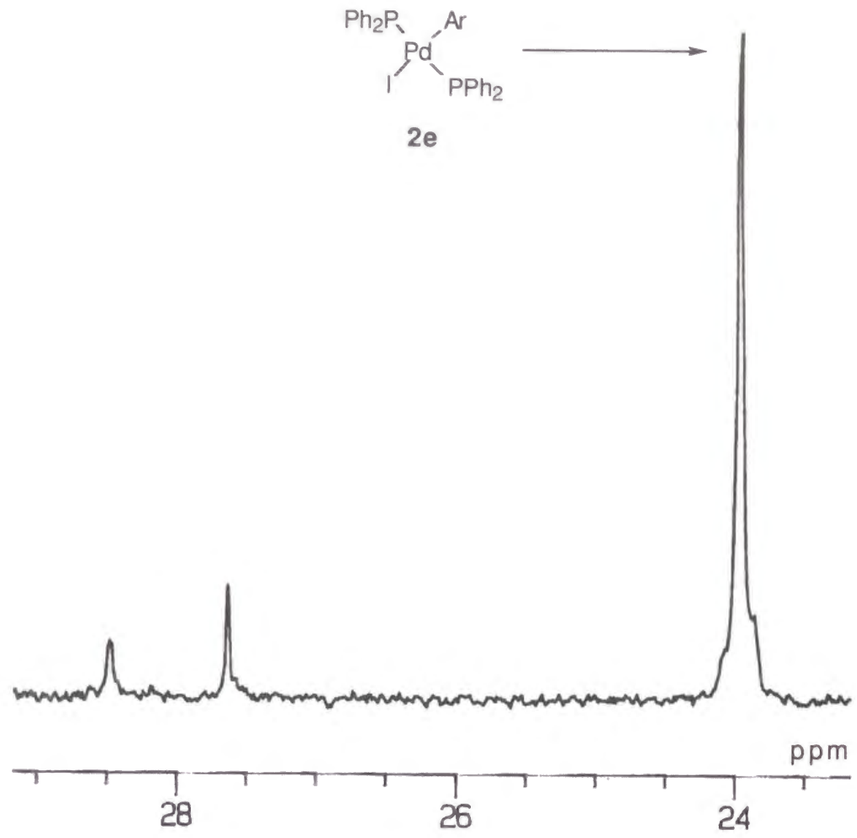


Figure 12. $^{31}P\{^1H\}$ NMR (109 MHz) spectrum of the reaction mixture (at *ca.* 75% conversion) of the coupling of tributyl(phenylethynyl)tin with Ar–I catalyzed by Ph_3P–$Pd_2(dba)_3$ (Ph_3P/Pd = 2) in THF at 50 °C.

Discussion

The author has found that oxidative addition of tributyl(phenylethynyl)-tin to a Pd(0) complex coordinated by a bidentate ligand readily takes place. By contrast, the tin reagent did not react with the Pd(0) complex coordinated by triphenylphosphine, the most common monodentate phosphine ligand, under the same reaction conditions. Although these results alone do not furnish a solution, it is likely that *cis*-coordination of donative atoms on palladium is important for the activation of a Sn–C bond, or alternatively a rigid chelate is

needed for the stabilization of complex (P–N)$Pd^{II}(SnBu_3)R$. Vinyl- or phenylstannane, in contrast, did not react even with the iminophosphine **1a**–Pd(0) complex. Thus, Pd(0) complexes contrast sharply with Pt(0) complexes. For example, a Ph_3P–Pt(0) complex, as reported, reacts with alkynyl-, alkenyl-, aryl-, and alkylstannanes to give the corresponding organoplatinum(II) complexes.[4]

The oxidative addition product (**3a** or **3d**) of tributyl(phenylethynyl)tin to the Pd(0) complex coordinated by iminophosphine **1a** or aminophosphine **1d** was detected invariably during the cross-coupling reaction, though oxidative addition of Ar–I to the Pd(0) complex is irreversible and the resulting complex (**2a**) is consumed very slowly. The observations demonstrate that Pd(0)/**1a** and Pd(0)/**1d** prefer alkynylstannane rather than Ar–I. On the other hand, the reaction of the diphosphine **1b**–Pd(0) complex takes place highly selectively with Ar–I in view of the exclusive formation of complex **2b** in a catalytic reaction. Although unclear at present, it appears reasonable to assume that the nitrogen moieties of **1a**, **1c**, and **1d** are appropriately labile to accelerate the reaction of the alkynylstannane with the Pd(0) complex coordinated by one of these amino- or iminophosphine ligands.

As the reaction proceeds, the coupling reaction of tributyl(phenylethynyl)tin with Ar–I catalyzed by the iminophosphine **1a**–Pd(0) complex became slower in a pace more than expected from the consumption of the starting material.[11] This observation is rationalized as follows: tributyltin iodide, which is coproduced and accumulated as the reaction proceeds, reacts with the active Pd(0) complex oxidatively. The observed increase of the ratio of (P–N)$Pd^{II}(SnBu_3)I$ to (P–N)$Pd^{II}(SnBu_3)(C{\equiv}CPh)$ implies the decrease of the active catalyst. Consequently, a proper removal of tributyltin iodide from the reaction mixture will maintain the activity of this catalytic system.

Conclusion

The palladium(0) complex coordinated by bidentate ligand **1a**, **1b**, **1c** or **1d** reacted with tributyl(phenylethynyl)tin and Ar–I, giving the corresponding oxidative addition products. (L–L')$Pd^{II}(C{\equiv}CPh)(SnBu_3)$ was involved in a catalytic cycle when **1a** or **1d** was used as a ligand, whereas (L–L')$Pd^{II}(Ar)I$ was shown to be a key species in the use of **1b**. The less reactive organostannanes, tributyl(phenyl)tin and tributyl(vinyl)tin, underwent the coupling reaction according to the catalytic cycle initiated by oxidative addition of Ar–I to the Pd(0) complex even when **1a** was used. The Pd(0) complex coordinated by conventional triphenylphosphine did not react with tributyl(phenylethynyl)tin, and $(Ph_3P)_2Pd^{II}(Ar)I$ was shown to be involved in a catalytic cycle. Although details, including the generality of Cycle B, remain yet to be studied, the findings discussed herein provide us with a novel clue for the elucidation of the reaction mechanism of the transition metal-catalyzed cross-coupling reactions.

Experimental Section

Chemicals. The following compounds were prepared according to literature procedures: tributyl(phenylethynyl)tin,[12] tributyl(vinyl)tin,[13] *N,N*-dimethyl-2-(diphenylphosphino)phenylmethylamine (**1d**).[14] *N*-(2-Diphenylphosphinobenzylidene)-2-phenylethylamine (**1a**) and iodo[4-(trifluoromethyl)phenyl][*N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine]palladium(II) (**2a**) were prepared as described in Chapter 1.

***N,N*-Dimethyl-*N'*-(2-diphenylphosphinobenzylidene)ethylenediamine (1c).** A mixture of 2-diphenylphosphinobenzaldehyde[15] (400 mg, 1.38 mmol) and *N,N*-dimethylethylenediamine (132 mg, 1.50 mmol) in toluene (20 mL) was heated to reflux for 3 h. Concentration *in vacuo* gave **1c** (491 mg, 99% yield) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 6 H), 2.37 (t, J = 7.3 Hz, 2 H), 3.59 (t, J = 7.3 Hz, 2 H), 6.83–6.89 (m, 1 H), 7.23–7.41 (m, 12 H), 7.94–8.00 (m, 1 H), 8.90 (d, J = 4.9 Hz, 1 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ -13.0; Anal. Calcd for $C_{23}H_{25}N_2P$: C, 76.64; H, 6.99; N, 7.77. Found: C, 76.34; H, 6.89; N, 7.54.

Iodo[3-(trifluoromethyl)phenyl][*N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine]palladium(II) (2a'). To a solution of *N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine (**1a**) (17.2 mg, 0.0437 mmol) and 3-(trifluoromethyl)iodobenzene (11.9 mg, 0.0437 mmol) in dichloromethane (1.0 mL) was added $Pd_2(dba)_3$ (20.0 mg, 0.0218 mmol), and the mixture was stirred for 10 min at room temperature. Evaporation of the solvent followed by gel permeation chromatography gave complex **2a'** (29.0 mg, 86% yield) as a light yellow solid: mp 106–109 °C; ^{1}H NMR ($CDCl_3$) δ 3.00–3.06 (m, 2 H), 4.61–4.68 (m, 2 H), 6.69–6.72 (m, 2 H), 7.13–7.52 (m, 22 H), 7.61–7.68 (m, 1 H), 7.99–8.01 (m, 1 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ 24.3; ^{19}F NMR ($CDCl_3$) δ 13.2. Anal. Calcd for $C_{34}H_{28}NPF_3IPd$: C, 52.91; H, 3.66; N, 1.81. Found: C, 52.98; H, 3.72; N, 1.75.

Iodo[4-(trifluoromethyl)phenyl][1,3-bis(diphenylphosphino)-propane]palladium(II) (2b). To a suspension of sodium hydride (60% in mineral oil, 10.3 mg, 0.258 mmol) in THF (2 mL) was added dimethyl malonate (36.9 mg, 0.279 mmol) at room temperature. The mixture was stirred for 20 min, and the resulting solution was added to a solution of 1,3-bis(diphenylphosphino)propane (**1b**) (88.5 mg, 0.215 mmol) and $[PdCl(\pi\text{-}C_3H_5)]_2$ (39.3 mg, 0.107 mmol) in THF (6 mL), and the mixture was stirred for 1 h. After addition of 4-(trifluoromethyl)iodobenzene (58.3 mg, 0.215 mmol), stirring was continued for 40 min. To the mixture was added diethyl ether (20 mL), and the organic layer was washed with water (3 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by gel permeation chromatography gave **2b** (104 mg, 61%) as a brown solid: mp 121–124 °C; ^{1}H NMR ($CDCl_3$) δ 1.6–2.7 (m, 6 H), 6.72–6.77 (m, 2 H), 7.0–7.5 (m, 16 H), 7.70–7.85 (m, 6 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ –9.7 (J = 54 Hz), 11.0 (J = 54 Hz); ^{19}F NMR ($CDCl_3$) δ 13.7. Anal. Calcd for $C_{34}H_{30}P_2F_3IPd$: C, 51.64; H, 3.82. Found: C, 51.48; H, 3.94.

Iodo[3-(trifluoromethyl)phenyl][1,3-bis(diphenylphosphino)-propane]palladium(II) (2b'). Complex **2b'** was prepared in 89% yield as a brown solid in a manner similar to **2b** and exhibited mp 134–136 °C; ^{1}H NMR ($CDCl_3$) δ 1.7–2.2 (m, 2 H), 2.3–2.7 (m, 4 H), 6.63–6.72 (m, 2 H), 7.06–7.52 (m, 17 H), 7.6–8.0 (m, 5 H), 7.99–8.01 (m, 1 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ -9.6 (J = 52 Hz), 11.1 (J = 52 Hz); ^{19}F NMR ($CDCl_3$) δ 13.2. Anal. Calcd for $C_{34}H_{30}P_2F_3IPd$: C, 51.64; H, 3.82. Found: C, 51.49; H, 3.69.

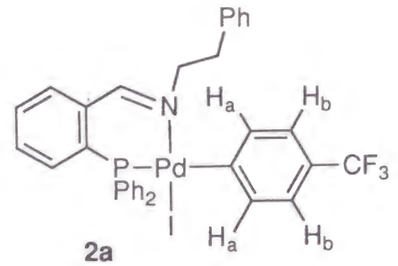
Iodo[4-(trifluoromethyl)phenyl][*N*,*N*-dimethyl-*N'*-(2-diphenylphosphinobenzylidene)ethylenediamine]palladium(II) (2c). Complex **2c** was prepared in 90% yield as an orange solid in a manner similar to **2a'** and exhibited mp 148–151 °C; ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3 H), 2.57 (s, 3 H), 3.06–3.12 (m, 2 H), 4.55–4.60 (m, 2 H), 6.93–6.97 (m, 2 H), 7.12–7.16 (m, 2 H), 7.26–7.68 (m, 13 H), 8.15–8.21 (m, 1 H), 9.53 (s, 1 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ 33.1; ^{19}F NMR ($CDCl_3$) δ 13.4. Anal. Calcd for $C_{30}H_{29}N_2PF_3IPd$: C, 48.77; H, 3.96; N, 3.79. Found: C, 48.51; H, 3.82; N, 3.62.

Iodo[4-(trifluoromethyl)phenyl][*N*,*N*-dimethyl-2-(diphenylphosphino)phenylmethylamine]palladium(II) (2d). Complex **2d** was prepared in 75% yield as a light brown solid in a manner similar to **2a'** and exhibited mp 180 °C (dec); ^{1}H NMR ($CDCl_3$) δ 2.90 (brs, 3 H), 3.2–3.7 (m, 2 H), 6.65–6.70 (m, 2 H), 7.07–7.20 (m, 2 H), 7.2–7.7 (m, 14 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ 20.8; ^{19}F NMR ($CDCl_3$) δ 13.5. Anal. Calcd for $C_{28}H_{26}NPF_3IPd$: C, 48.19; H, 3.76; N, 2.01. Found: C, 48.42; H, 3.95; N, 2.13.

Coupling of 4-(Trifluoromethyl)iodobenzene with Tributyl-(phenylethynyl)tin Catalyzed by the Catalyst Prepared in situ. A solution of 4-(trifluoromethyl)iodobenzene (119 mg, 0.437 mmol), a ligand (0.0218 mmol), and $[PdCl(\pi\text{-}C_3H_5)]_2$ (4.0 mg, 0.0109 mmol) in THF (5 mL) was degassed by three freeze-thaw cycles. To this solution was added tributyl(phenylethynyl)tin (188 mg, 0.481 mmol), and the resulting mixture was stirred at 25 °C. An aliquot of the reaction mixture was sampled and diluted with chloroform-*d*. Then the yield based on the consumed aryl iodide was determined by ^{19}F NMR. The results are shown in Figure 1.

Coupling of 4-(Trifluoromethyl)iodobenzene with Tributyl-(phenylethynyl)tin Catalyzed by a Preformed Catalyst. A solution of complex **2** (0.0218 mmol) and 4-(trifluoromethyl)iodobenzene (119 mg, 0.437 mmol) in THF (5 mL) was degassed by three freeze-thaw cycles. To this solution was added tributyl(phenylethynyl)tin (188 mg, 0.481 mmol), and the resulting mixture was stirred at 25 °C. An aliquot of the reaction mixture was sampled and diluted with chloroform-*d*. Then the yield based on the aryl iodide was determined by ^{19}F NMR. The results are summarized in Figure 1.

Generation of a Pd(0) Complex Coordinated by a Bidentate Ligand and its Reaction with an Organostannane. Dimethyl malonate (9.66 mg, 0.0732 mmol) was added to a suspension of sodium hydride (60% in oil, 2.80 mg, 0.07 mmol) in THF (or THF-d_8) (0.6 mL). This solution was added to a solution of a bidentate ligand (0.0636 mmol) and $[PdCl(\pi\text{-}C_3H_5)]_2$ (11.6 mg, 0.0318 mmol) in THF (or THF-d_8) (0.3 mL). After 5 min, an organostannane (0.0636 mmol) was added, NMR spectra were recorded immediately.



2a

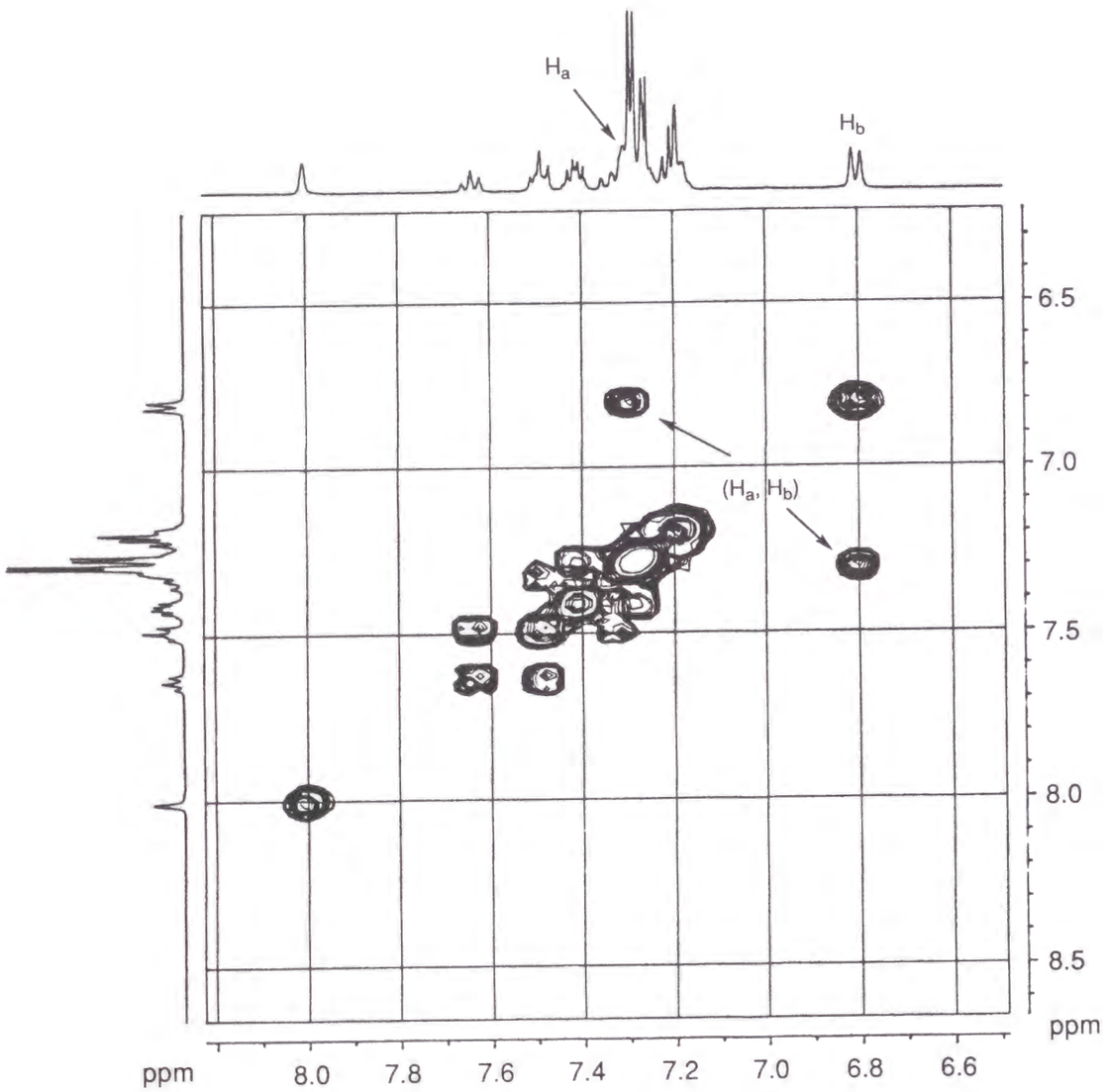
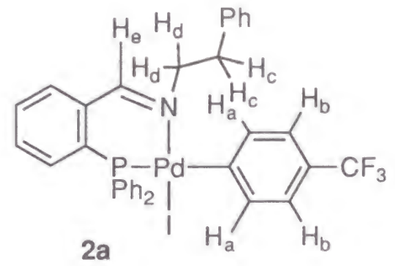


Figure 13. Section of the COSY spectrum of Pd(II) complex **2a**.



2a

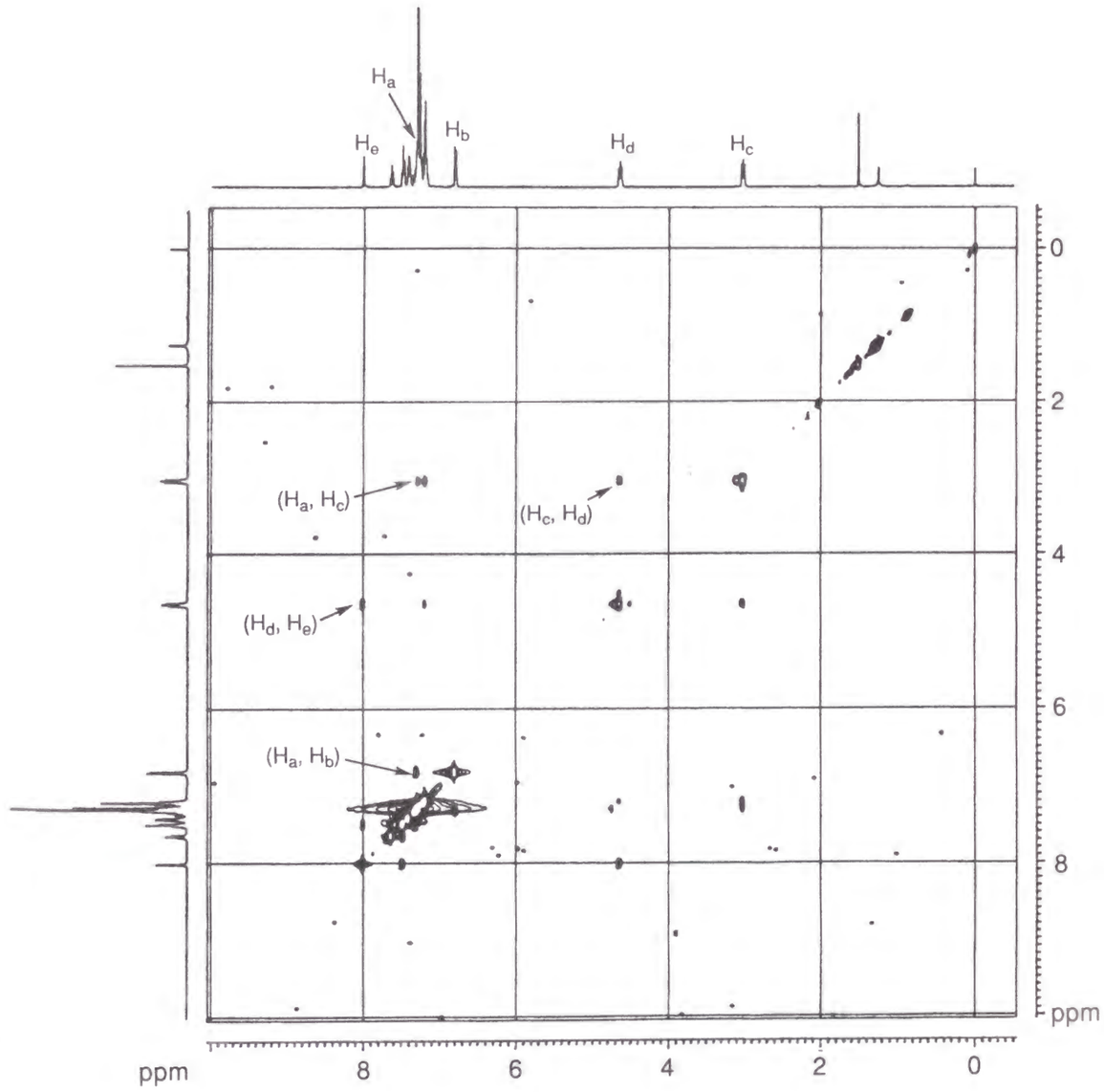
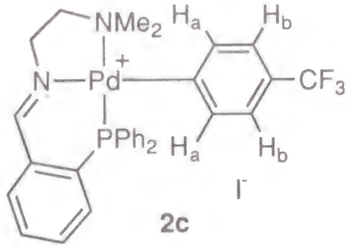


Figure 14. NOESY spectrum of Pd(II) complex **2a**.



2c

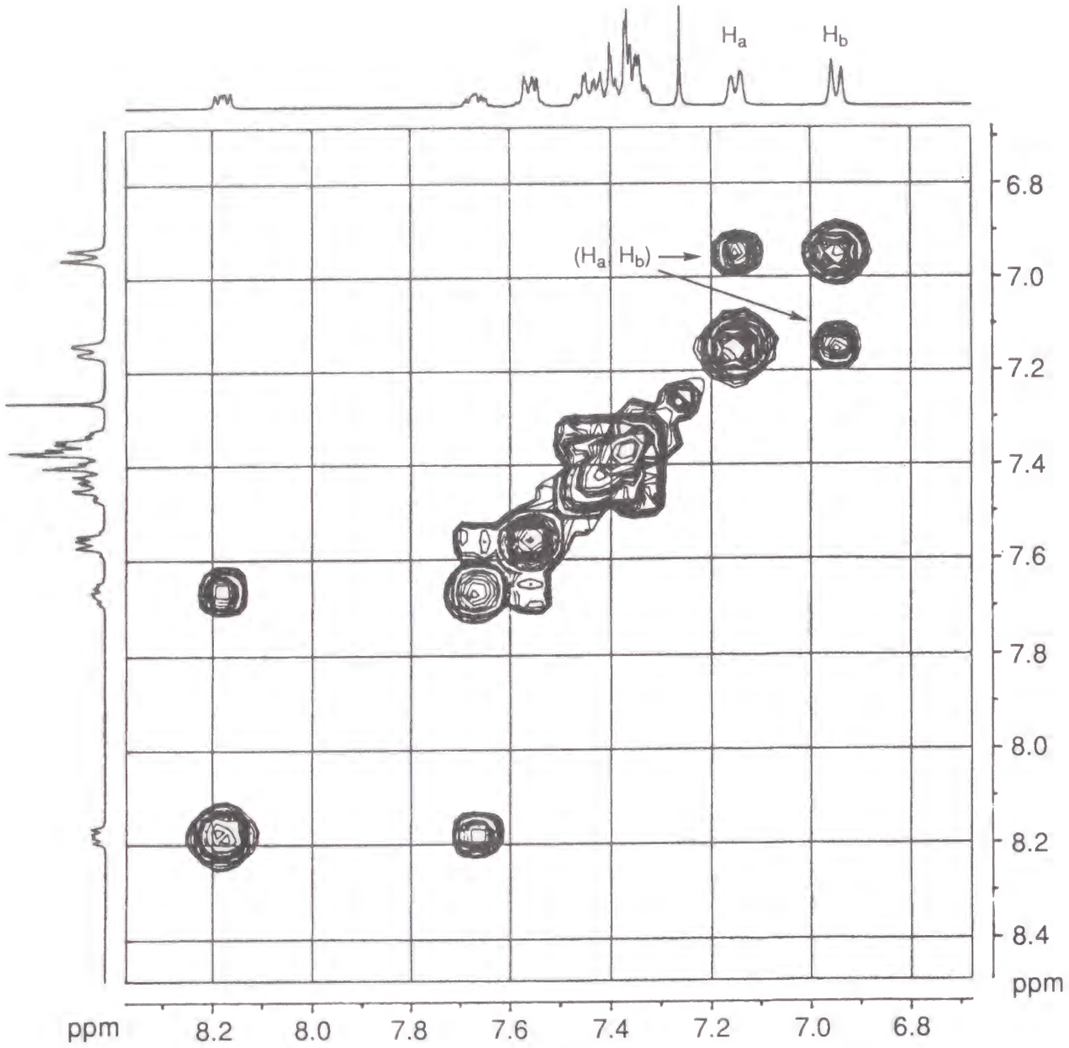
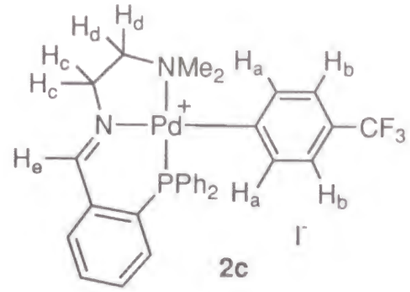


Figure 15. Section of the COSY spectrum of Pd(II) complex **2c**.



2c

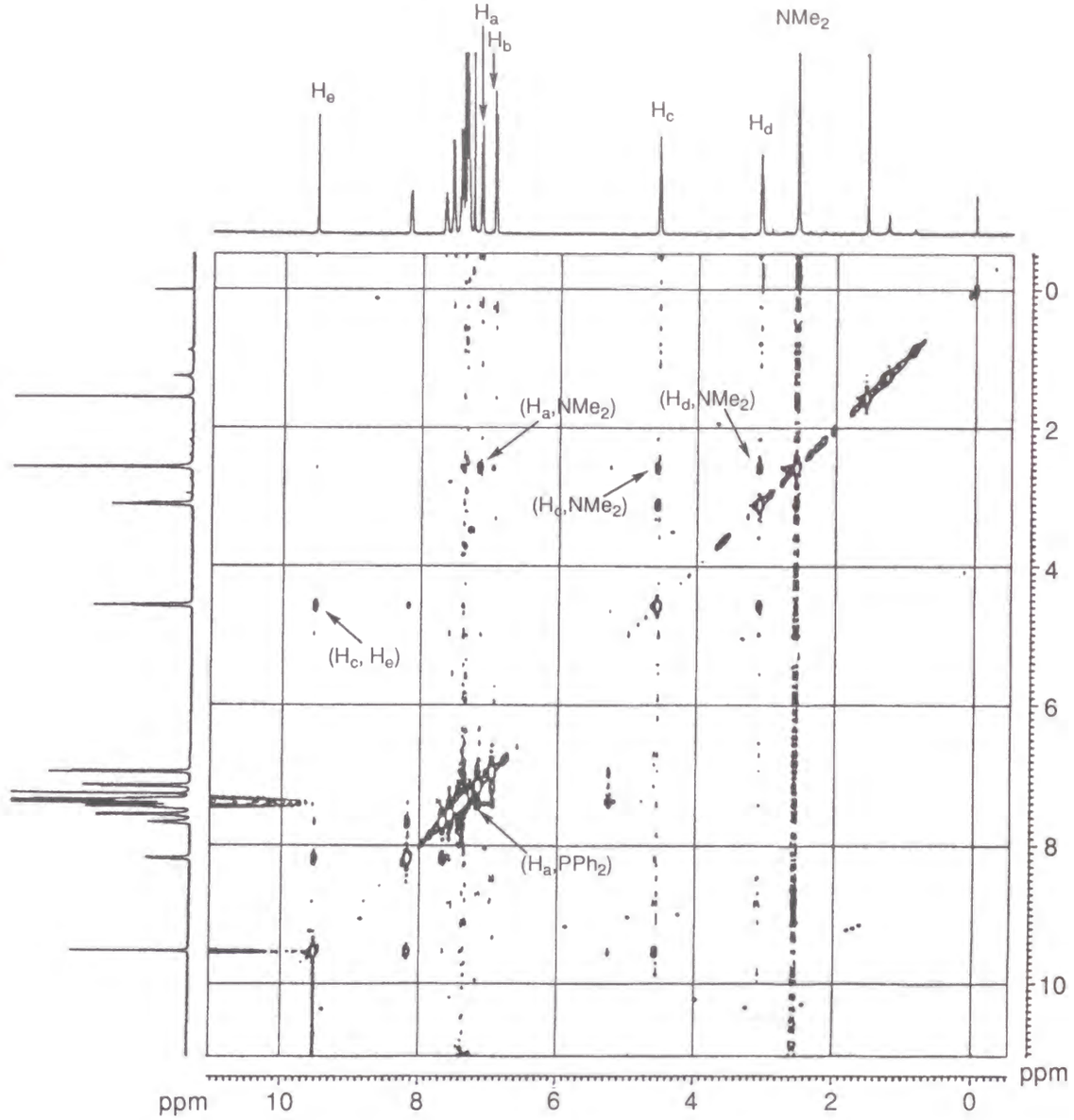
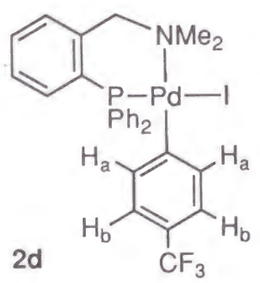


Figure 16. NOESY spectrum of Pd(II) complex **2c**.



2d

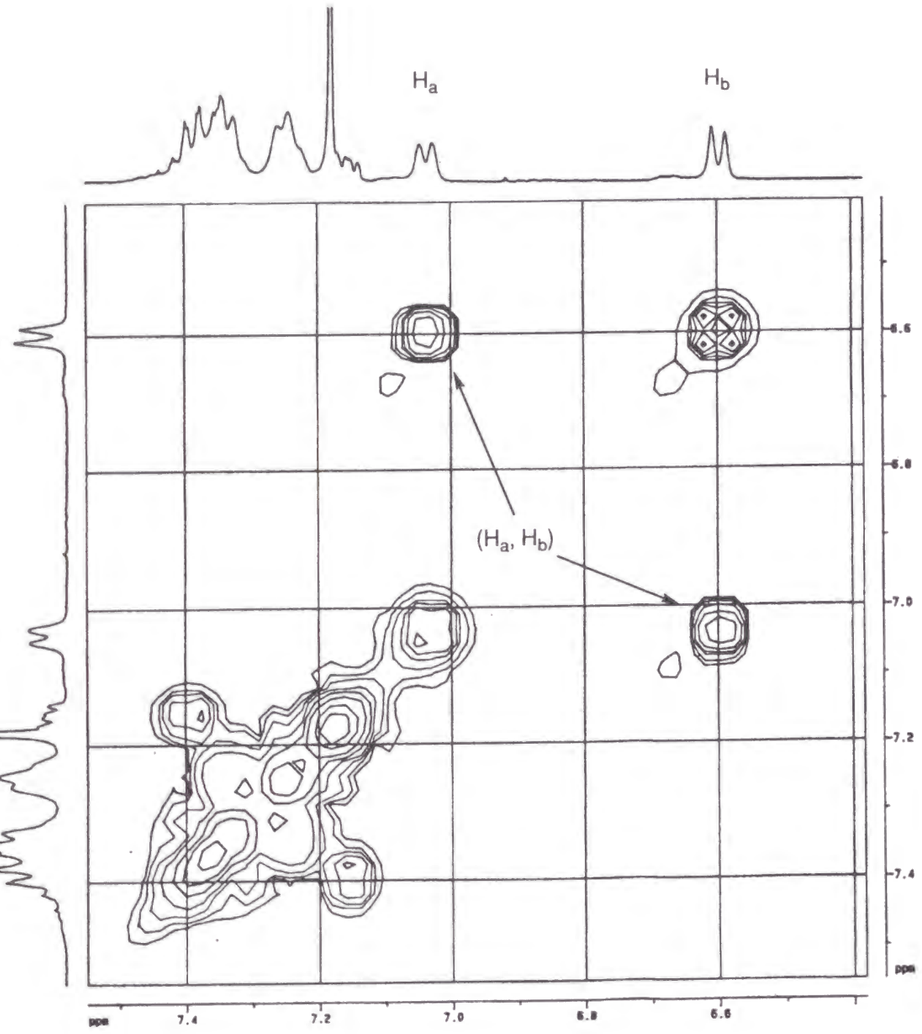
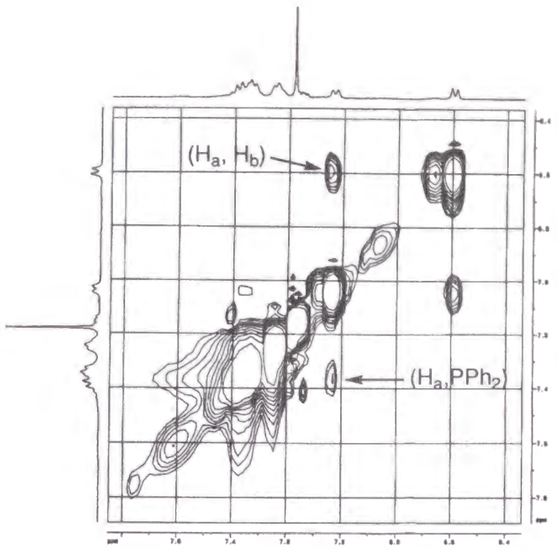
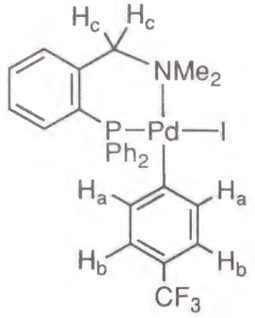


Figure 17. Section of the COSY spectrum of Pd(II) complex **2d**.





2d

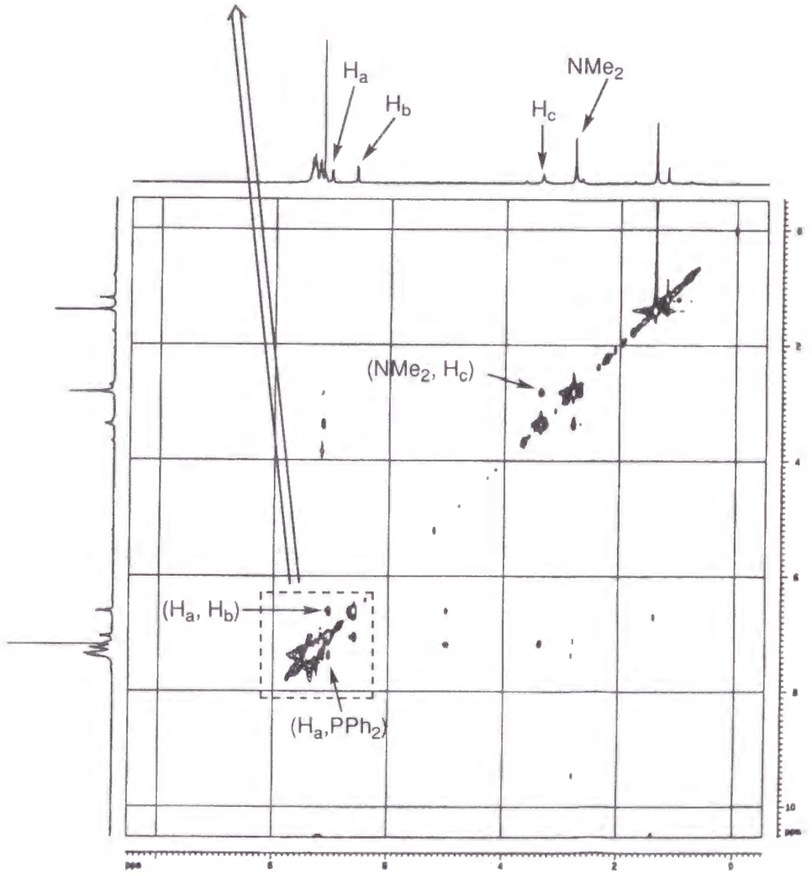


Figure 18. NOESY spectrum of Pd(II) complex **2d**.

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(2) For reviews, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Mitchell, T. N. *Synthesis* **1992**, 803. (c) Farina, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Ed.; Pergamon Press: New York, 1995; Vol. 12, Chapter 3.4; p 200.

(3) For example, see: Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(4) There have been many reports concerning oxidative addition of organostannanes to platinum(0) complexes, which often show the reactivities similar to palladium(0) complexes. (a) Eaborn, C.; Kundu, K.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* **1981**, 1223. (b) Butler, G.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1979**, *181*, 47. (c) Butler, G.; Eaborn, C.; Pidcock, A. *ibid.* **1978**, *144*, C23. (d) Eaborn, C.; Pidcock, A.; Steele, B. R. *J. Chem. Soc., Dalton Trans.* **1976**, 767. (e) Cetinkaya, B.; Lappert, M. F.; McMeeking, J.; Palmer, D. E. *ibid.* **1973**, 1202.

(5) This type of catalytic cycle was referred to without any evidence by Stille and his co-workers in the palladium-catalyzed coupling of acyl chlorides with organostannanes. Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129.

(6) For the catalytic activity of the Pd complex coordinated by **1a**, **1b** or **1d**, in the Stille reaction, see Chapter 1.

(7) The configurations of complexes **2a**, **2c** and **2d** were determined by NOESY NMR spectra. See the Experimental Section of this Chapter.

(8) The conversion after 24 h using preformed catalyst **2a** was the same as that with the catalyst prepared in situ. See Chapter 1.

(9) The procedure for the generation of a Pd(0) complex was kindly communicated by Professor Tamio Hayashi, Kyoto University.

(10) ^{19}F NMR (THF) for **2c**: δ 13.2.

(11) At 25 °C in THF in the presence of 5 mol % of the catalyst, the yield for 72 min: 25% (Figure 1 of this Chapter); for 24 h: 89% (Table 1 of Chapter 1).

(12) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.

(13) Seyferth, D.; Stone, F. G. A. *J. Am. Chem. Soc.* **1957**, *79*, 515.

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Chapter 3

Homocoupling Reaction of Organostannanes Catalyzed by an Iminophosphine–Palladium Complex

Abstract

An iminophosphine–Palladium complex has been successfully utilized as a catalyst for oxidative homocoupling reaction of organostannanes using air as an oxidant.

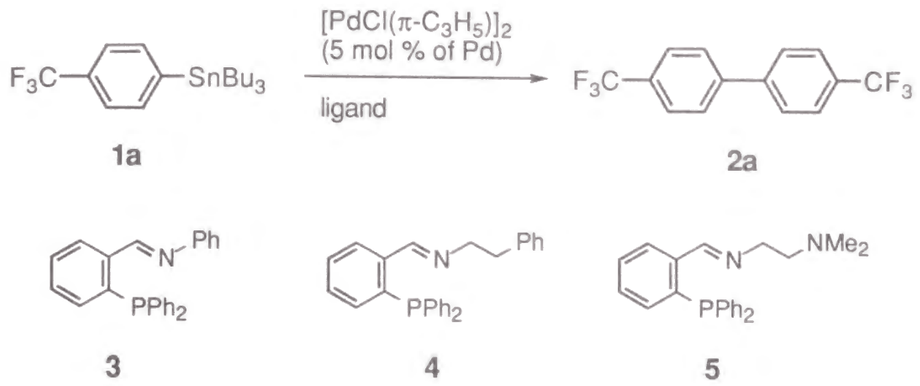
Introduction

Because of the high availability, stability and chemoselectivity of organostannanes, the palladium-catalyzed cross-coupling of organostannanes with aryl halides is now a useful synthetic tool.[1,2] On the other hand, the palladium-catalyzed homocoupling of organostannanes is less familiar, even though both of them will enjoy the merits of organostannanes. All the examples of the palladium-catalyzed[3] homocoupling of organostannanes reported in the literature focusing on the synthetic utility[4] employ such an oxidant as *t*-BuOOH,[5] benzoquinone[6] or 1,2-dichloroethane,[7] except for the homocoupling of alkenylstannanes catalyzed by bis(acetonitrile)dichloro-palladium(II).[8] In the course of the investigation of the reaction mechanism of the palladium-catalyzed cross-coupling reaction (Chapter 2), the author found that an iminophosphine–palladium complex efficiently catalyzed the homocoupling of aryl- and alkenylstannanes by use of air as a mild oxidant.

Results and Discussion

The catalytic activities of palladium complexes coordinated by phosphine-based ligands were compared in the homocoupling reaction of tributyl[4-(trifluoromethyl)phenyl]tin (**1a**) (Scheme 1). The conversion was readily monitored by ^{19}F NMR of the reaction mixture. Yields of 4,4'-bis(trifluoromethyl)biphenyl (**2a**) obtained by the reaction carried out for 4 h are summarized in Table 1. A palladium complex coordinated by *N*-(2-diphenylphosphinobenzylidene)aniline (**3**) was found to show higher reaction rate than any other palladium complexes examined. Thus, the reaction of **1a** in DMF in the presence of 5 mol % of **3**–Pd at 40 °C for 4 h in an open air gave over 95% yield of homocoupled product **2a** (entry 1). A palladium complex coordinated by iminophosphine **4** or **5**, where the substituent on the imino moiety in **3** is replaced by 2-phenylethyl or 2-(dimetylamino)ethyl

Scheme 1



group, respectively, was less potent, giving **2a** in 83% (entry 2) or 35% yield (entry 3), respectively. Under the same reaction conditions, the palladium complex of triphenylphosphine (ligand/Pd = 2) gave **2a** in 64% yield (entry 4). A palladium catalyst without any ligand was much less active, giving only 15% yield of **2a** (entry 5). The reaction of **1a** catalyzed by **3**–Pd under a strictly prepared argon atmosphere gave **2a** in <5% yield, indicating that oxygen is essential for the homocoupling reaction (entry 6).[4a] Kinetic experiments in various solvents show that DMF is the best solvent examined (entries 1 and 7–9).[9]

The iminophosphine **3**–Pd catalyst was applied to the homocoupling of a variety of aryl-, alkenyl- and alkynylstannanes (Scheme 2 and Table 2). In particular, arylstannanes reacted smoothly in the presence of 2 mol % of the catalyst to give the corresponding biaryls in moderate to good yields, irrespective of the electron-withdrawing or electron-donating characters of the substituents on the phenyl ring (entries 1–6). In use of an organostannane that has a hydroxyl group, the reaction underwent without protection (entry 6). Heteroarylstannanes also gave homocoupled products in moderate to good

Table 1. Palladium-Catalyzed Homocoupling of Tributyl[4-(trifluoromethyl)phenyl]tin[a]

entry	ligand	solvent	yield (%)[b]
1	**3**	DMF	>95 (87)[c]
2	**4**	DMF	83
3	**5**	DMF	35
4	Ph_3P[d]	DMF	64
5	none	DMF	15
6[e]	**3**	DMF	<5
7	**3**	THF	30
8	**3**	toluene	20
9	**3**	$CHCl_3$	16

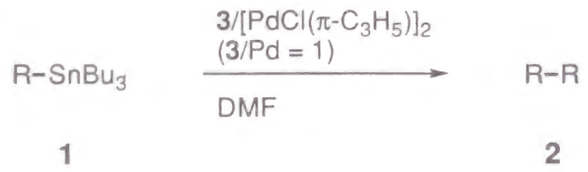
[a] The reaction was carried out at 40 °C for 4 h in a solvent (2 mL) in an open air using tributyl[4-(trifluoromethyl)phenyl]tin (0.32 mmol) in the presence of $[PdCl(\pi\text{-}C_3H_5)]_2$ (0.008 mmol) and a ligand (0.016 mmol). [b] Determined by ^{19}F NMR. [c] Isolated yield is given in the parenthesis. [d] Triphenylphosphine (0.032 mmol) was used. [e] Under an argon atmosphere prepared through three freeze-thaw cycles.

Table 2. Homocoupling of Organostannanes Catalyzed by Iminophosphine–Palladium[a]

entry	R in **1**	temp (°C)	time (h)	yield of **2**[b] (%)
1	Ph	70	4	66
2	4-O_2N-C_6H_4	50	5	84
3	4-OHC-C_6H_4	50	36	76
4	4-MeO-C_6H_4	70	102	81
5	2-NC-C_6H_4	50	44	80
6	4-$HOCH_2$-C_6H_4	70	10	75
7	2-thienyl	50	53	60
8	2-pyridyl	70	72	79
9[c]	(*E*)-PhCH=CH	50	4	68
10	PhC≡C	50	6	31
11	BuC≡C	50	11	34

[a] The reaction was carried out in DMF (2 mL) in an open air using an organostannane (0.8 mmol) in the presence of $[PdCl(\pi\text{-}C_3H_5)]_2$ (0.008 mmol) and *N*-(2-diphenylphosphinobenzylidene)aniline (0.016 mmol). [b] Isolated yield based on organostannane. [c] (*E*,*E*)-1,4-Diphenylbutadiene was obtained.

Scheme 2



yields (entries 7 and 8). (*E*)-Tributyl(2-phenylethenyl)tin also underwent the oxidative dimerization in the presence of the iminophosphine–palladium catalyst to give (*E*,*E*)-1,4-diphenyl-1,3-butadiene in 68% yield (entry 9). Although alkynylstannanes reacted very fast, the expected products, 1,3-diynes, were isolated in yields less than 34%, probably due to the instability of the products under the reaction conditions (entries 10 and 11).

Conclusion

An iminophosphine–palladium complex was demonstrated to be an efficient catalyst for the homocoupling of aryl- and alkenylstannanes under an aerial atmosphere. Oxygen was proved to be essential for the reaction.

Experimental Section

Chemicals. Following compounds were prepared according to literature procedures: tributyl[4-(trifluoromethyl)phenyl]tin,[10] tributyl(4-nitrophenyl)tin,[11] tributyl(4-formylphenyl)tin,[12] tributyl(4-methoxyphenyl)-tin,[13] tributyl[4-(hydroxymethyl)phenyl]tin,[4a] 2-(tributylstannyl)thiophene,[14] 2-(tributylstannyl)pyridine,[15] (*E*)-tributyl(2-phenylethenyl)tin,[16] tributyl(phenyl-ethynyl)tin,[17] tributyl(1-hexyn-1-yl)tin.[18] *N*-(2-Diphenylphosphino-benzylidene)-2-phenylethylamine and *N*,*N*-dimethyl-*N*′-(2-diphenylphosphino-benzylidene)ethylenediamine were prepared as described in Chapter 1 and Chapter 2, respectively.

***N*-(2-Diphenylphosphinobenzylidene)aniline.**[19] A mixture of 2-diphenylphosphinobenzaldehyde[20] (500 mg, 1.72 mmol) and aniline (166 mg, 1.78 mmol) in toluene (15 mL) was stirred at a reflux temperature for 19 h. The mixture was concentrated under a reduced pressure, and the residue was treated with hexane (20 mL). Filtration of insoluble material gave **3** (624 mg, 99% yield) as a light yellow solid: mp 109–112 °C; ^{1}H NMR ($CDCl_3$) δ 6.86–6.98 (m, 3 H), 7.10–7.50 (m, 15 H), 8.16–8.25 (m, 1 H), 9.07 (d, J = 5.2 Hz, 1 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ -12.7; Anal. Calcd for $C_{25}H_{20}NP$: C, 82.17; H, 5.52; N, 3.83. Found: C, 82.07; H, 5.69; N, 3.58.

Tributyl(2-cyanophenyl)tin. A 1.67 M hexane solution of BuLi (20 mL, 33.4 mmol) was added dropwise to a solution of 2-bromobenzonitrile (6.59 g, 36.2 mmol) in THF (30 mL) at -78 °C, and the mixture was stirred at -78 °C for 1 h. To the mixture was added tributyltin chloride (9.06 g, 27.8 mmol) at -78 °C and the temperature was allowed to rise gradually up to room temperature. After 12 h, the mixture was poured into water (50 mL) and extracted with diethyl ether (150 mL x 2). The combined organic layer was

washed successively with water (50 mL) and brine (50 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent was followed by silica gel column chromatography (hexane/ethyl acetate = 98/2) to give tributyl(2-cyanophenyl)tin (2.98 g, 27% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.82–1.78 (m, 27 H), 7.31–7.42 (m, 1 H), 7.43–7.58 (m, 2 H), 7.59–7.71 (m, 1 H). Anal. Calcd for $C_{19}H_{31}NSn$: C, 58.19; H, 7.97; N, 3.57. Found: C, 58.00; H, 8.02; N, 3.43.

Palladium-Catalyzed Homocoupling Reaction of Tributyl[4-(trifluoromethyl)phenyl]tin. Tributyl[4-(trifluoromethyl)phenyl]tin (142 mg, 0.326 mmol) was added to a solution of a ligand and $[PdCl(\pi\text{-}C_3H_5)]_2$ (3.0 mg, 0.008 mmol) in a solvent (2 mL). After stirring at 40 °C for 4 h on exposure to air, a small part of the reaction mixture was sampled and diluted with chloroform-*d*. The yield based on tributyl[4-(trifluoromethyl)-phenyl]tin was determined by ^{19}F NMR. The results are summarized in Table 1.

Homocoupling of Organostannanes Catalyzed by Iminophosphine 3–Pd. An organostannane (0.8 mmol) was added to a solution of *N*-(2-diphenylphosphinobenzylidene)aniline (6.0 mg, 0.016 mmol) and $[PdCl(\pi\text{-}C_3H_5)]_2$ (3.0 mg, 0.008 mmol) in DMF (2 mL), and the resulting mixture was stirred at the temperature for the time both indicated in Table 2. Quenching with water (10 mL), extraction with ethyl acetate (30 mL x 2), washing the combined organic layer with water (10 mL) and brine (10 mL), drying the organic layer over anhydrous magnesium sulfate, and evaporation, followed by gel permeation chromatography, gave the corresponding coupling product. The yields are listed in Table 2.

All of the products listed in Table 2 have already been reported in the literature. Their spectroscopic data are as follows.

Biphenyl. ^{1}H NMR ($CDCl_3$) δ 7.29–7.51 (m, 6 H), 7.55–7.65 (m, 4 H).

4,4'-Dinitrobiphenyl. mp 238–240 °C (lit.,[21] 241–244 °C); ^{1}H NMR ($CDCl_3$) δ 7.72–7.83 (m, 4 H), 8.30–8.42 (m, 4 H).

4,4'-Diformylbiphenyl. mp 144–146 °C (lit.,[22] 145 °C); ^{1}H NMR ($CDCl_3$) δ 7.78–7.84 (m, 4 H), 7.98–8.03 (m, 4 H), 10.10 (s, 2 H).

4,4'-Dimethoxybiphenyl.[23] ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 6 H), 6.91–7.02 (m, 4 H), 7.42–7.54 (m, 4 H).

2,2'-Dicyanobiphenyl.[24] ^{1}H NMR ($CDCl_3$) δ 7.53–7.62 (m, 4 H), 7.69–7.77 (m, 2 H), 7.81–7.87 (m, 2 H).

4,4'-Bis(hydroxymethyl)biphenyl. mp 193–194 °C (lit.,[25] 188–189 °C); ^{1}H NMR ($CDCl_3$) δ 4.75 (brs, 4 H), 7.41–7.51 (m, 4 H), 7.56–7.65 (m, 4 H).

2,2'-Bithiophene.[7] ^{1}H NMR ($CDCl_3$) δ 6.96–7.06 (m, 2 H), 7.14–7.28 (m, 4 H).

2,2'-Bipyridine. ^{1}H NMR ($CDCl_3$) δ 7.27–7.37 (m, 2 H), 7.77–7.89 (m, 2 H), 8.36–8.45 (m, 2 H), 8.66–8.74 (m, 2 H).

(*E*,*E*)-1,4-Diphenylbutadiene. ^{1}H NMR ($CDCl_3$) δ 6.52–6.75 (m, 2 H), 6.80–7.05 (m, 2 H), 7.15–7.52 (m, 10 H).

1,4-Diphenylbutadiyne.[4] ^{1}H NMR ($CDCl_3$) δ 7.30–7.40 (m, 6 H), 7.49–7.58 (m, 4 H).

5,7-Dodecadiyne.[4] ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7.0 Hz, 6 H), 1.20–1.85 (m, 8 H), 2.52 (t, J = 6.3 Hz, 4 H).

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Chapter 4

Nickel-Catalyzed Cross-Coupling Reaction of Organostannanes with Aryl Halides

Abstract

A nickel complex used in combination with lithium bromide or triphenylphosphine was found to be an active catalyst for the cross-coupling reaction of aryl halides with organostannanes. Of these, the Ni(0)–LiBr system was shown to enhance the rate of the coupling of an aryl iodide, whereas the Ni(0)–Ph_3P catalyst was applicable to a wide variety of aryl halides including aryl chlorides.

Introduction

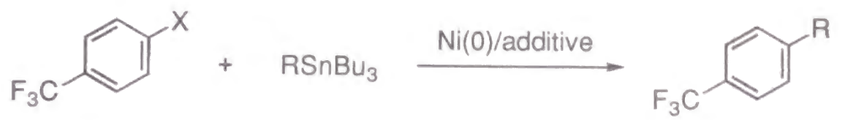
The transition metal-catalyzed cross-coupling reactions are now powerful tools of organic synthesis.[1] Among these, the coupling reaction of organostannanes with aryl halides using a palladium catalyst has gained increasing popularity.[2] Much attention has been paid to the design of an active catalyst with the aim of the expansion of the utility of this already useful reaction.[3] There are, however, few examples that utilize transition metals other than palladium particularly in the coupling of aryl halides (or pseudohalides) with organostannanes.[4] Nickel catalysts have never been used for this reaction,[5] except for the coupling of an aryl methanesulfonate (mesylate) with tributyl(phenyl)tin reported by Percec and his co-workers, who observed that the homocoupling of the aryl mesylates predominated (45–64%) and the yields of the cross-coupled product were low (23–24%).[6] The author has found that a nickel complex in the presence of either lithium bromide or triphenylphosphine is a highly active catalyst for the coupling of aryl halides with organostannanes. Compared to palladium catalysts, the nickel catalysts have salient features: Ni(0)–LiBr shows large rate-enhancement in the coupling of aryl iodides, whereas Ni(0)–Ph_3P can be applied to a wide variety of aryl halides including aryl chlorides. This is the first demonstration that even unactivated aryl chlorides can be used as substrates of the coupling reaction.[7] From an industrial point of view, it is noteworthy that aryl chlorides are applicable to the coupling reaction[8] because they are inexpensive and easily available in bulk quantities compared with aryl bromides or iodides.

Results and Discussion

The catalytic activity of nickel complexes was first examined for the reaction of 4-(trifluoromethyl)iodobenzene (**1a**) with tributyl(vinyl)tin (**2a**) (Scheme 1). The conversion was readily monitored by ^{19}F NMR studies of the

reaction mixture.[9] Yields of 4-(trifluoromethyl)styrene (**3a**) obtained in the reaction carried out for 3 h are summarized in Table 1.

Scheme 1



1a: X = I
1b: X = Br
1c: X = Cl
1d: X = OTf

2a: R = vinyl
2b: R = allyl
2c: R = PhC≡C

3a: R = vinyl
3b: R = allyl
3c: R = PhC≡C

The author found that nickel(0) alone can catalyze the reaction to some extent. Thus, the coupling of **1a** with **2a** in the presence of 5 mol % of a nickel(0) catalyst generated in situ from $Ni(acac)_2$ and diisobutylaluminum hydride (1:2 ratio) in 1,2-dimethoxyethane at 50 °C for 3 h gave **3a** in 62% yield (entry 1), whereas the use of other solvents resulted in lower yields (entries 2–4).

The effect of additives was examined using 1,2-dimethoxyethane as the solvent. Addition of lithium bromide increased the yield (entries 5–7), and the maximum yield reached 91% when the additive-nickel ratio was 20 (entry 6). Under the same reaction conditions, the nickel(0) catalyst in combination with 2 equivalents of triphenylphosphine gave **3a** only in 62% yield. However, prolonged reaction time (20 h) raised the yield to 96% (entry 8). The reaction using 4 equivalents of triphenylphosphine was slower than that with 2 equivalents, but the yield after 20 h was equally high (entry 9). These additives were also effective in THF as a solvent (entries 10 and 11). Lithium iodide was found to be as effective as lithium bromide in THF (entries 10 and 12).

In order to clarify the character of each catalyst discussed above, the reaction in an early stage was monitored, and the results are shown in Figure 1

Table 1. Nickel-Catalyzed Coupling of 4-(Trifluoromethyl)iodobenzene (**1a**) with Tributyl(vinyl)tin (**2a**)[a]

entry	solvent	additive	additive/Ni	yield of **3a**[b]
1	DME	—	—	62
2	THF	—	—	19
3	dioxane	—	—	30
4	DMF	—	—	3
5	DME	LiBr	4	84
6	DME	LiBr	20	91
7	DME	LiBr	40	81
8	DME	Ph_3P	2	62 (96)[c]
9	DME	Ph_3P	4	35 (89)[c]
10	THF	LiBr	60	69
11	THF	Ph_3P	4	61 (90)[c]
12	THF	LiI	60	78

Table 1. Footnotes.

[a] The reaction was carried out in a solvent (2 mL) at 50 °C for 3 h using 4-(trifluoromethyl)iodobenzene (**1a**) (0.761 mmol), tributyl(vinyl)tin (**2a**) (0.801 mmol) and an additive in the presence of a Ni(0) catalyst prepared in situ from $Ni(acac)_2$ (0.038 mmol) and of a 1.5 M toluene solution of diisobutylaluminum hydride (0.076 mmol). [b] Determined by ^{19}F NMR. [c] Yield after 20 h is given in parentheses.

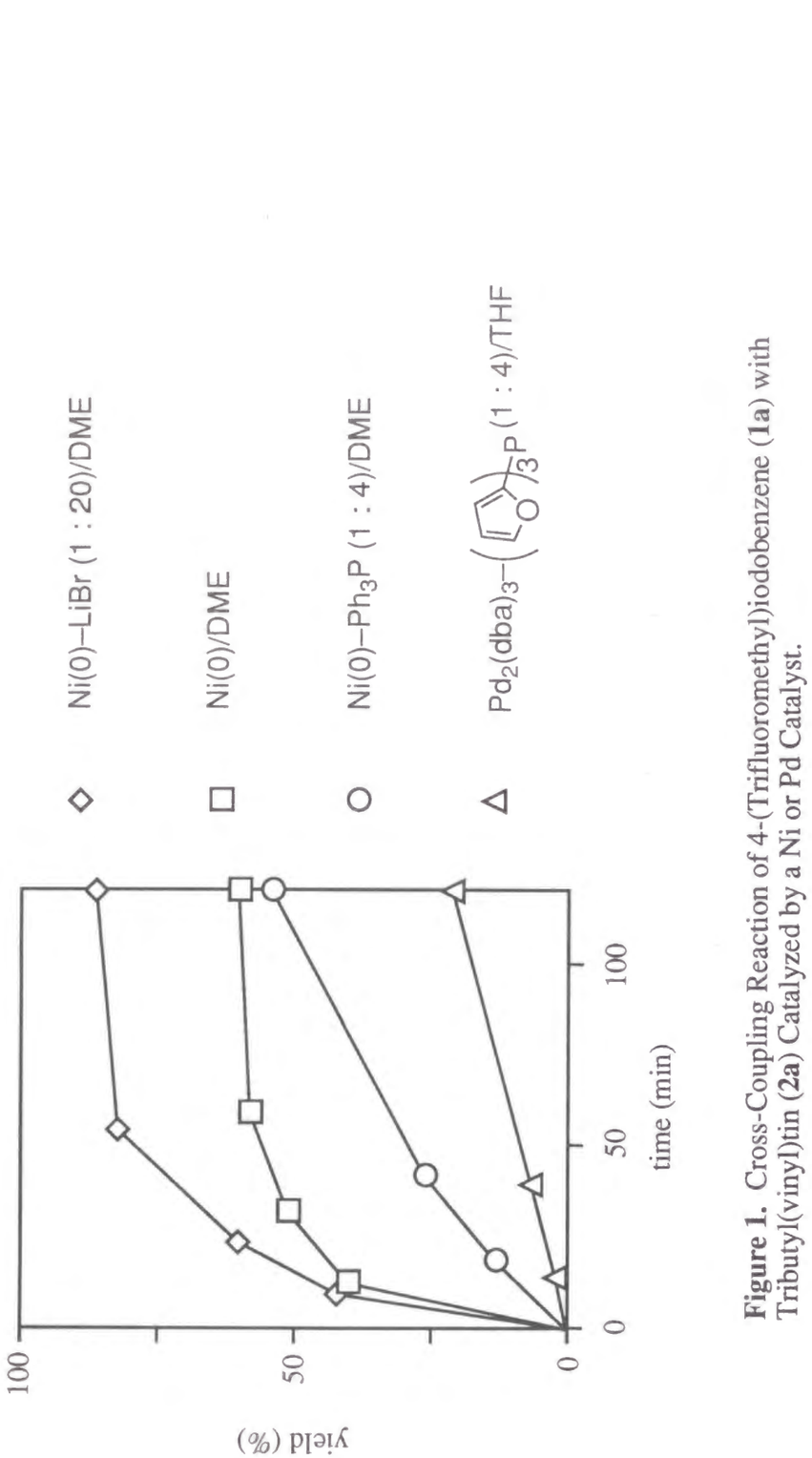


Figure 1. Cross-Coupling Reaction of 4-(Trifluoromethyl)iodobenzene (**1a**) with Tributyl(vinyl)tin (**2a**) Catalyzed by a Ni or Pd Catalyst.

together with that of a tri(2-furyl)phosphine–palladium(0) complex, which has been reported by Farina and his co-workers to be one of the most effective phosphine–palladium catalysts in the coupling of iodobenzene with tributyl(vinyl)tin.[10] All the nickel catalysts examined including the Ni(0)–Ph_3P complex afforded much higher initial rate than the tri(2-furyl)phosphine–Pd(0) complex. Furthermore, Figure 1 clearly shows that lithium bromide maintains the catalyst active without decreasing the rate, whereas the stabilization of the nickel(0) species by triphenylphosphine is accompanied by the slowdown of the reaction.[11]

The scope of the nickel-catalyzed coupling was investigated using various aryl halides and organostannanes. The results are summarized in Table 2.[12] The reaction of 4-(trifluoromethyl)iodobenzene catalyzed by the Ni(0)–Ph_3P complex gave the corresponding coupling products with tributyl(vinyl)tin, allyltributyltin and tributyl(phenylethynyl)tin in high yields (≥75%) (entries 1–3). This particular catalyst was applied to the reaction of 4-(trifluoromethyl)phenyl bromide or chloride, giving the respective coupling product in 86% or 58% yield (entries 4 and 5). On the other hand, the Ni(0)–LiBr catalyst was less effective for the reaction of the aryl bromide or chloride, giving 51% or 0% yield of the coupling product, respectively (entries 4 and 5). The corresponding triflate was proved to be a poor substrate for the nickel catalysts (entry 6).

The salient features of the Ni(0)–LiBr and Ni(0)–Ph_3P catalysts are summarized as follows. The Ni(0)–LiBr complex accelerates the coupling of an aryl iodide with organostannanes, but the corresponding bromide and chloride are not accelerated. The Ni(0)–Ph_3P catalyst renders sufficiently high rates to the reaction of the aryl iodide, bromide and even chloride. It is noteworthy that an aryl chloride can be a substrate for this reaction because the activation of less reactive Cl–C bond of aryl chlorides has been one of the

Table 2. Nickel-Catalyzed Coupling of 4-(Trifluoromethyl)halobenzene (**1**) with Organostannanes (**2**)[a]

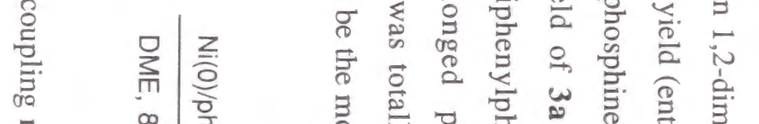
	X in	R in		Ni(0)–Ph_3P[b]		Ni(0)–LiBr[c]	
entry	**1**	**2**	temp (°C)	time (h)	yield of **3**[d]	time (h)	yield of **3**[d]
1	I	vinyl	50	20	96	3	91
2	I	allyl	80	3	78	16	71
3	I	PhC≡C	50	3	75	6	—[e]
4	Br	vinyl	50	76	86	4	51
5	Cl	vinyl	80	23	58[f]	7	0
6	OTf	vinyl	80	6	37	3	0

[a] The reaction was carried out in 1,2-dimethoxyethane (2 mL) using 4-(trifluoromethyl)halobenzene (**1**) (0.761 mmol), an organostannane (**2**) (0.801 mmol) in the presence of a Ni(0) catalyst prepared in situ from $Ni(acac)_2$ (0.038 mmol) and a 1.5 M toluene solution of diisobutylaluminum hydride (0.076 mmol). [b] The reaction was carried out in the presence of triphenylphosphine (0.0759 mmol). [c] The reaction was carried out in the presence of lithium bromide (0.762 mmol). [d] Determined by ^{19}F NMR. [e] The reaction gave a complex mixture. [f] Triphenylphosphine (0.152 mmol) was used.

most challenging problems in modern organic synthesis with organometallic reagents.[8]

To find a more effective ligand for the coupling of aryl chlorides, the catalytic activity of nickel catalysts coordinated by various phosphine ligands was examined for the reaction of 2-chloronaphthalene (**1e**) with tributyl(vinyl)tin (**2a**) (Scheme 2 and entries 1–6 of Table 3). The coupling of **1e** with **2a** in the presence of the nickel(0) catalyst (5 mol %) and triphenylphosphine (20 mol %) in 1,2-dimethoxyethane at 80 °C for 9 h gave 2-vinylnaphthalene (**3d**) in 86% yield (entry 1). Use of tri(*o*-tolyl)phosphine, tri(2-furyl)phosphine or tributylphosphine in liue of triphenylphosphine was less effective, giving lower yield of **3a** (entries 2–4). Among bidentate phosphine ligands, 1,1'-bis(triphenylphosphino)ferrocene[13] gave **3d** in a moderate yield after a prolonged period (entry 5), whereas 1,3-bis(triphenylphosphino)propane was totally ineffective (entry 6). After all, triphenylphosphine was proved to be the most effective ligand among these.

Scheme 2



The Ni(0)–Ph_3P-catalyzed coupling reaction was applied to various aryl halides with organostannanes (Scheme 2 and entries 7–12 of Table 3). The coupling reaction of tributyl(vinyl)tin with aryl chlorides having an electron-withdrawing group, such as a formyl or acetyl group, gave the corresponding vinylarenes in yields over 80% (entries 7–10). Alkynylstannanes also coupled with 2-chloronaphthalene in high yields (entries 11 and 12).

It is noteworthy that a substituent at the *ortho* position neither retarded the reaction nor reduced the yields (entries 8 and 9). This tendency was further confirmed by a competitive experiment described in Scheme 3.

Table 3. Nickel(0)-Catalyzed Coupling of Aryl Chlorides with Organostannanes[a]

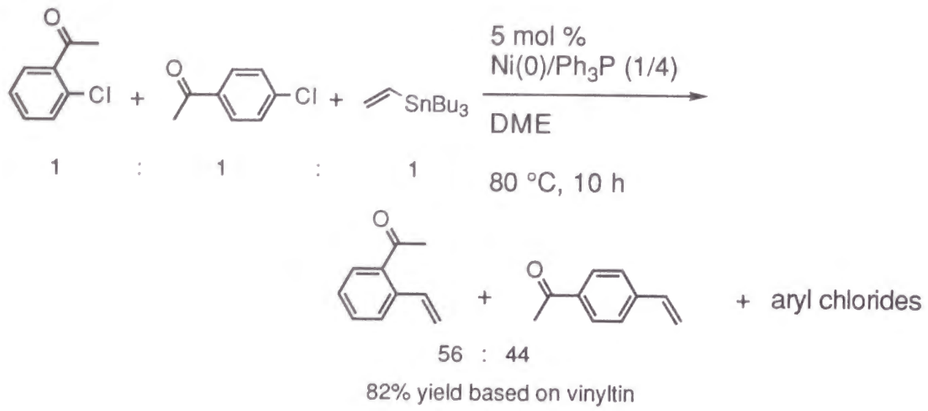
entry	ligand (ligand/Ni)	**1** Ar	**2** R	time (h)	yield (%)[b] of **3**
1	Ph_3P (4)	2-naphthyl	vinyl	9	86
2	(*o*-tolyl)$_3$P (4)	2-naphthyl	vinyl	18	<5[c]
3	(2-furyl)$_3$P (4)	2-naphthyl	vinyl	41	64
4	Bu_3P (4)	2-naphthyl	vinyl	17	<5[c]
5	dppf[d] (2)	2-naphthyl	vinyl	31	65
6	dppp[e] (2)	2-naphthyl	vinyl	20	<5[c]
7	Ph_3P (4)	4-CHO-C_6H_4	vinyl	9	86
8	Ph_3P (4)	4-MeCO-C_6H_4	vinyl	24	88
9	Ph_3P (4)	2-MeCO-C_6H_4	vinyl	16	81
10	Ph_3P (4)	2-PhCO-C_6H_4	vinyl	23	80
11	Ph_3P (4)	2-naphthyl	PhC≡C	70	79
12	Ph_3P (4)	2-naphthyl	BuC≡C	38	81

Table 3. Footnotes.

[a] The reaction was carried out at 80 °C in 1,2-dimethoxyethane (2 mL) using an aryl chloride (0.756 mmol) and an organostannane (0.911 mmol) in the presence of 5 mol % of a Ni(0) complex. The Ni(0) complex was prepared in situ from Ni(acac)$_2$ (0.038 mmol) and a 0.95 M hexane solution of diisobutylaluminum hydride (0.076 mmol) in the presence of a ligand. [b] Isolated yield based on aryl halide. [c] Determined by ^{1}H NMR. [d] 1,1'-Bis(diphenylphosphino)ferrocene. [e] 1,3-Bis(diphenylphosphino)propane.

Thus, in the Ni(0)–Ph_3P-catalyzed coupling reaction of tributyl(vinyl)tin, *o*-chloroacetophenone was the more preferred electrophile compared to the *p*-chloro derivative.

Scheme 3



82% yield based on vinyltin

To gain an insight into the reaction mechanism, the author examined the reaction of Ni(0) complexes with 4-(trifluoromethyl)iodobenzene (**1a**) under the stoichiometric conditions (Scheme 4 and Table 4). It was found that the reaction of the Ni(0) species in the absence of an additive ceased within 5 min, giving reduction product **4** (22%) together with recovered **1a** (78%) (entries 1 and 2). Under the same conditions, the reaction of the Ni(0)–LiI catalyst, which was as effective as Ni(0)–LiBr for the coupling of **1a** with tributyl(vinyl)tin (*vide supra*), completed within 5 min, providing **4** (59%) and homocoupled product **5** (41%) (entries 3 and 4). The reaction of Ni(0)–Ph_3P with **1a** was very slow (entries 5 and 6). These observations show that the character of each complex correlates closely with the one seen in the cross-coupling reaction, and that the reaction of the Ni(0) species with aryl halides is likely to be the key step in the cross-coupling reaction. Formation of Ar–Ni^{II}–I was not observed in all of the experiments under the stoichiometric conditions. The generation of an aryl radical (Ar•) intermediate seems to

Table 4. Reaction of a Ni(0) Complex with 4-(Trifluoromethyl)iodobenzene (**1a**) under the Stoichiometric Conditions[a]

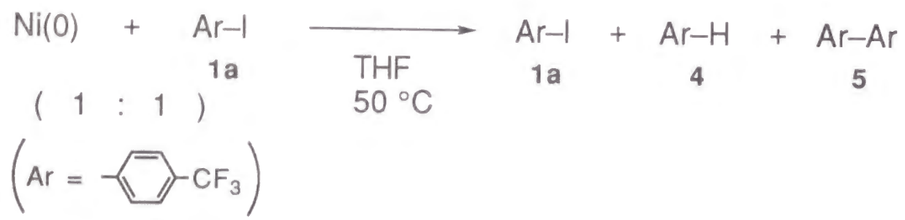
entry	additive (ratio of additive/Ni)	time (min)	ratio[b] **1a**	**4**	**5**
1	—	5	78	22	0
2	—	300	78	22	0
3	LiI (4)	5	0	59	41
4	LiI (4)	300	0	59	41
5	Ph_3P (4)	5	67	33	0
6	Ph_3P (4)	300	4	78	13

[a] The reaction was carried out at 50 °C in THF (2 mL) using 4-(trifluoromethyl)-iodobenzene (0.076 mmol) and a Ni(0) complex (0.076 mmol) in the presence or absence of an additive. The Ni(0) complex was prepared in situ from $Ni(acac)_2$ (0.076 mmol) and a 0.95 M hexane solution of diisobutylaluminum hydride (0.152 mmol).

[b] Determined by ^{19}F NMR.

account for both the absence of Ar–Ni^{II}–I and the production of **4** and **5**. Kochi and his co-workers reported that the reaction of a Ni(0) complex with an aryl halide involves an aryl radical which then gives the corresponding arene by proton abstraction.[14] Thus, it appears to be plausible that an aryl radical intermediate is involved in the cross-coupling reaction. Anyway, the reaction mechanism of the cross-coupling reaction in use of a nickel catalyst must be totally different from the one with a palladium catalyst.

Scheme 4



Conclusion

The cross-coupling reaction of 4-(trifluoromethyl)iodobenzene with tributyl(vinyl)tin using the Ni(0)–LiBr catalyst proceeded in high rate, whereas the Ni(0)–Ph_3P system was found to be applicable to the coupling of various aryl halides including less reactive aryl chlorides with vinyl-, allyl- and alkynyltin. Although the details of the reaction mechanism remain yet to be studied, the reaction of the Ni(0) species with an aryl halide seems to be the rate-determining-step.

Experimental Section

Chemicals. Following compounds were prepared according to the literature methods: tri(2-furyl)phosphine,[15] tributyl(vinyl)tin,[16] tributyl-(phenylethynyl)tin,[17] tributyl(1-hexyn-1-yl)tin.[18]

4-(Trifluoromethyl)phenyl trifluoromethanesulfonate (1d). To a solution of 4-(trifluoromethyl)phenol (4.85 g, 29.9 mmol) in pyridine (20 mL) was added trifluoromethanesulfonic anhydride (10.1 g, 35.9 mmol) at 0 °C. After stirring at 0 °C for 3 h, the mixture was poured into water (70 mL) and extracted with ether (100 mL). The organic layer was washed successively with a 1 N HCl aqueous solution (70 mL x 3), a saturated $NaHCO_3$ aqueous solution (70 mL), water (50 mL), and brine (50 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent was followed by distillation under the reduced pressure gave **1d** (7.48 g, 85% yield) as a colorless liquid: bp 73 °C/11 mmHg; ^{1}H NMR ($CDCl_3$) δ 7.36–7.48 (m, 2 H), 7.69–7.81 (m, 2 H); ^{19}F NMR ($CDCl_3$) δ 2.95, 12.99. Anal. Calcd for $C_8H_4O_3SF_6$: C, 32.66; H, 1.37. Found: C, 32.73; H, 1.30.

Nickel-Catalyzed Coupling of 4-(Trifluoromethyl)iodobenzene with Tributyl(vinyl)tin. A 1.5 M hexane solution of diisobutylaluminum hydride (0.05 mL, 0.075 mmol) and an additive were added successively to a solution (2 mL) of 4-(trifluoromethyl)iodobenzene (207 mg, 0.761 mmol), tributyl(vinyl)tin (254 mg, 0.801 mmol) and $Ni(acac)_2$ (9.8 mg, 0.038 mmol). After stirring at 50 °C for 3 h, an aliquot of the reaction mixture was sampled and diluted with chloroform-*d*. By ^{19}F NMR, the yield based on the aryl iodide was estimated. The results are summarized in Table 1. The results depicted in Figure 1, Table 2 and Table 4 also were obtained similarly.

Nickel-Catalyzed Coupling of Aryl Chlorides with Organostannanes. A 0.95 M hexane solution of diisobutylaluminum hydride (0.08 mL, 0.076 mmol) was added to a solution of an aryl chloride (0.756 mmol), an organostannane (0.911 mmol), a phosphine ligand and $Ni(acac)_2$ (9.8 mg, 0.038 mmol) in 1,2-dimethoxyethane (2 mL), and the mixture was stirred at 80 °C. After the reaction time indicated in Table 3, a 1 M KF aqueous solution (2 mL) was added, and the mixture was stirred at room temperature for 30 min. Filtration through a Celite pad was followed by addition of ethyl acetate (30 mL). The aqueous layer was separated, and the organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by gel permeation chromatography gave the corresponding coupled product. Yields are listed in Table 3. The result depicted in Scheme 3 also was obtained similarly.

2-(Hexyn-1-yl)naphthalene. A colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7.0 Hz, 3 H), 1.41–1.72 (m, 4 H), 2.46 (t, J = 6.8 Hz, 2 H), 7.39–7.52 (m, 4 H), 7.69–7.96 (m, 3 H). Anal. Calcd for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.48; H, 7.70.

Other coupling products listed in Table 3 are the compounds already reported in literature. Their spectroscopic data are as follows.

2-Vinylnaphthalene. ^{1}H NMR ($CDCl_3$) δ 5.34 (dd, J = 10.9, 0.7 Hz, 1 H), 5.88 (dd, J = 17.7, 0.7 Hz, 1 H), 6.89 (dd, J = 17.7, 10.9 Hz, 1 H), 7.40–7.50 (m, 2 H), 7.61–7.67 (m, 1 H), 7.72–7.86 (m, 4 H).

4-Vinylbenzaldehyde.[19] ^{1}H NMR ($CDCl_3$) δ 5.44 (d, J = 10.9 Hz, 1 H), 5.91 (d, J = 17.7 Hz, 1 H), 6.77 (dd, J = 17.7, 10.9 Hz, 1 H), 7.52–7.58 (m, 2 H), 7.82–7.87 (m, 2 H), 9.99 (s, 1 H).

4-Vinylacetophenone.[20] ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3 H), 5.39 (dd, J = 11.0, 0.7 Hz, 1 H), 5.87 (dd, J = 17.6, 0.7 Hz, 1 H), 6.75 (dd, J = 17.6, 11.0 Hz, 1 H), 7.41–7.56 (m, 2 H), 7.84–8.00 (m, 2 H).

2-Vinylacetophenone.[21] ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3 H), 5.34 (dd, J = 10.9, 1.3 Hz, 1 H), 5.64 (dd, J = 17.4, 1.3 Hz, 1 H), 7.20 (dd, J = 17.4, 10.9 Hz, 1 H), 7.28–7.68 (m, 4 H).

2-Vinylbenzophenone.[22] ^{1}H NMR ($CDCl_3$) δ 5.22 (dd, J = 11.0, 1.0 Hz, 1 H), 5.70 (dd, J = 17.4, 11.0 Hz, 1 H), 6.78 (dd, J = 17.4, 1.0 Hz, 1 H), 7.31–7.84 (m, 8 H).

2-(Phenylethynyl)naphthalene.[23] ^{1}H NMR ($CDCl_3$) δ 7.20–7.71 (m, 8 H), 7.73–7.96 (m, 3 H), 8.06 (s, 1 H).

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Appendix

Electroreductive Synthesis of Chiral Piperazines and Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of the Chiral Piperazines

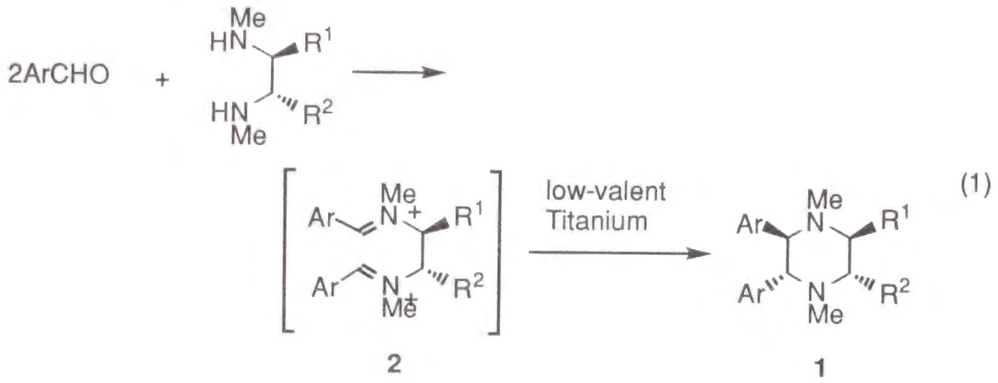
Abstract

Electroreduction of diimines, prepared from 1,2-diamines and aromatic aldehydes, in acidic media gave intramolecularly coupled products, 2,3-diarylpiperazines, stereoselectively. Chiral tri- and tetrasubstituted piperazines were synthesized effectively from chiral 1,2-diamines by the same electroreductive method. Chiral piperazines, prepared from (1*R*,2*R*)-diaminocyclohexane were effective chiral ligands of catalysts for the enantioselective addition of diethylzinc to aldehydes.

Introduction

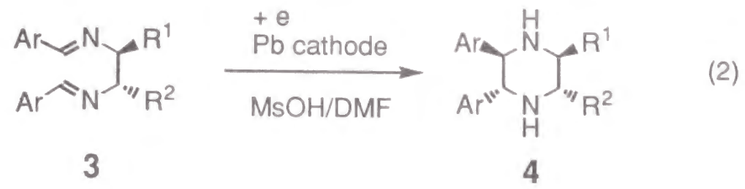
Chiral 1,2-diamines have been known to be effective ligands of catalysts for enantioselective synthesis of some chiral compounds.[1] The methods of synthesis of chiral 1,2-diamines were, however, rather limited. Reductive intermolecular coupling of imines promoted by metal reducing agents has been reported as one of the methods,[2] though complete stereoselectivity was not always achievable.

On the other hand, chiral piperazines also seem to be effective chiral ligands. The electroreduction of *N,N'*-dibenzylideneethylenediamine leading to the formation of *trans*-2,3-diphenylpiperazine **1** ($R^1 = R^2 = H$, 42% yield),[3,4] for instance, has been reported to be a typical stereoselective method for synthesis of 2,3-diphenylpiperazine. Recently, it was also reported that reductive intramolecular coupling of diiminium salts **2** using low-valent titanium as the reducing agent gave *N,N'*-dimethyl-2,3-diarylpiperazines **1** stereoselectively (eq 1; $R^1 = R^2 = H$, 42%; R^1 = alkyl, $R^2 = H$, 7–30%; $R^1 = R^2 = -(CH_2)_4-$, 8–19%).[2f] Chiral piperazines were obtained by using chiral 1,2-diamines as the starting materials. In these two types of methods, however, the yields of **1** were



unsatisfactory and the piperazines obtained by these methods were limited to *N,N'*-dimethylated piperazines. *N,N'*-Unsubstituted piperazines seem to be more

useful materials for the creation of chiral catalysts than *N,N'*-dimethylated compounds, since the former are able to be easily modified by introducing appropriate substituents on the nitrogen atoms. The stereoselective synthesis of chiral *N,N'*-unsubstituted piperazines is, however, hitherto unknown.



In this Chapter, the electroreductive intramolecular coupling of aromatic diimines **3** is discussed to be an effective method leading to the formation of *N,N'*-unsubstituted 2,3-diarylpiperazines **4** (eq 2). This method is remarkably effective for the stereoselective synthesis of chiral tri- and tetrasubstituted piperazines. It is also found that chiral piperazines derived from **4** are effective ligands of catalysts for the enantioselective addition of diethylzinc to aldehydes.

Results and Discussion

The author scrutinized the reaction condition of electroreduction, using *N,N'*-dibenzylideneethylenediamine (**3a**) as a typical substrate. Intramolecular coupling product, *trans*-2,3-diphenylpiperazine (**4a**), was obtained in very high yield (95%) when the electroreduction was carried out with a lead cathode in dry DMF containing methanesulfonic acid (MsOH). The reaction gave similar results in dry acetonitrile. Use of other cathode materials (Zn, Sn, and Pt) resulted in somewhat lower yields (80–90%).

The presence of a strong protic acid such as MsOH was essential to promote the intramolecular coupling. When the reaction was carried out in the absence of MsOH, **4a** was not formed but *N,N'*-dibenzylethylenediamine was

Table 1. Electroreductive Intramolecular Coupling of Diimines to Piperazines

entry		Ar of **3**	R^1 of **4**	R^2 of **4**		yield[a] (%)
1	**3a**	C_6H_5	H	H	**4a**	95
2	**3b**	4-MeO-C_6H_4	H	H	**4b**	82
3	**3c**	3-BnO-C_6H_4	H	H	**4c**	80
4	**3d**	4-Cl-C_6H_4	H	H	**4d**	75
5	**3e**	2-HO-C_6H_4	H	H	**4e**	42
6	**3f**	4-MeO_2C-C_6H_4	H	H	**4f**	50
7	**3g**	1-naphthyl	H	H	**4g**	62
8	**3h**	C_6H_5	Me[b]	H	**4h**	82
9	**3i**	C_6H_5	C_6H_5 (*R*)	H	**4i**	92
10	**3j**	C_6H_5	*i*-Bu (*S*)	H	**4j**	87
11	**3k**	2-HO-C_6H_4	*i*-Bu (*S*)	H	**4k**	38
12	**3l**	C_6H_5	$-(CH_2)_4-$[c]		**4l**	59
13	**3m**	2-HO-C_6H_4	$-(CH_2)_4-$[c]		**4m**	78
14	**3n**	2-MeO-C_6H_4	$-(CH_2)_4-$[c]		**4m**	72

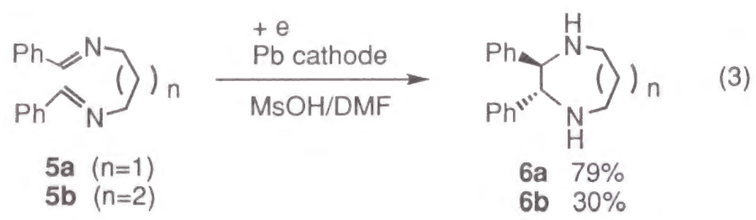
[a] Isolated yield. Each of all products was obtained as a single stereoisomer. See reference 6.

[b] Prepared from racemic 1,2-diaminopropane. [c] Prepared from (1*R*,2*R*)-diaminocyclohexane.

obtained as the main product (>60%). Trifluoroacetic acid was also effective whereas acetic acid brought about considerable decrease in the yield of **4a** (~30%).

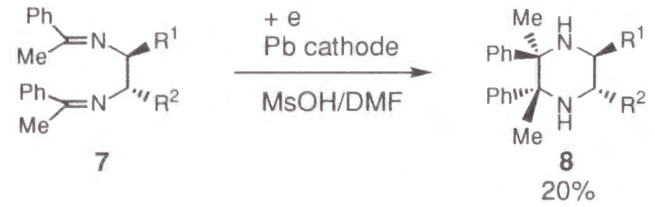
The results obtained with other diimines are summarized in Table 1. The electroreduction of diimines **3b–g** prepared from ethylenediamine and aromatic aldehydes gave *trans*-2,3-diarylpiperazines **4b–g** exclusively (entries 2–7). Tri- and tetrasubstituted piperazines **4h–n** were also obtained stereoselectively from diimines **3h–n** in reasonable yields (entries 8–14). Optically active piperazines were synthesized from optically active 1,2-diamines (entries 9–14). The protection of hydroxyl group on the aryl was not always necessary (entries 5, 11, and 13).

Seven- and eight-membered cyclic compounds **6a,b**[8] were also obtained stereoselectively from **5a,b** by the same method. The yields decreased with increasing the ring size (eq 3).



(3)

Diketoimines **7** also gave the corresponding intramolecularly coupled product **8**[9] stereoselectively, though the yield was relatively low (eq 4).



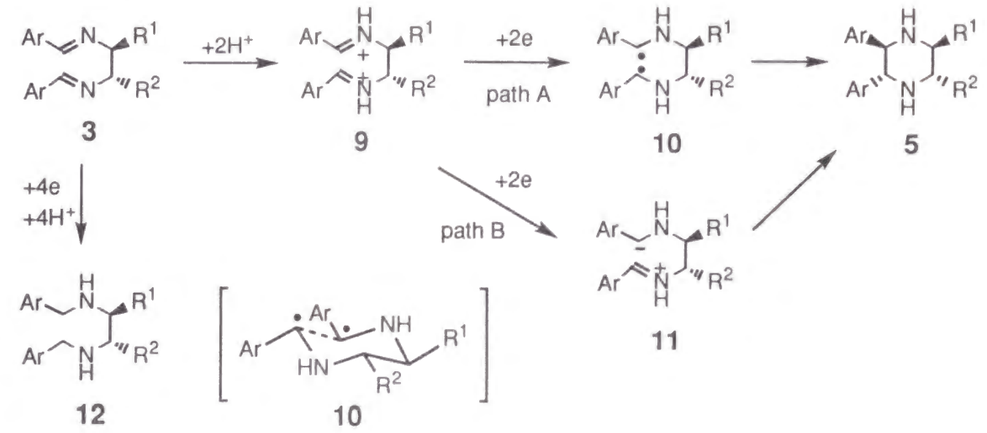
(4)

Reaction Mechanism.

The electroreduction of **3a** in the absence of MsOH afforded the corresponding reduced amine (**12**) as described previously. In acidic media,

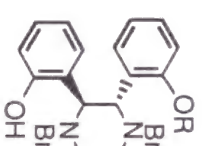
however, diimines **3** were protonated to form diiminium salts **9** and the salts were electrochemically reduced. Two reaction pathways, namely, intramolecular radical coupling of a diradical intermediate **10** (path A) and nucleophilic addition of an anionic moiety of **11** to the intramolecular C=N bond (path B) may be depicted for the intramolecular coupling of **9** as shown in Scheme 1. As the electrochemical reduction of imines has been known to exhibit two one-electron waves under acidic conditions,[10] the reduction of an iminium salt seems to proceed stepwise with forming a radical species as the first intermediate and an anion as the second intermediate. In addition, the observation of ESR spectra of the intermediate radicals has been reported in the electroreductive intermolecular coupling of iminium salts.[11] Hence, it is reasonable that one-electron reduction of the second iminium salt moiety of **9** will take place prior to reduction of the radical species formed by one-electron reduction of the first iminium salt moiety of **9**. Thus, the diradical species **10** is likely to be formed as the intermediate and the intramolecular coupling proceeds according to path A. The complete stereoselectivity may be explained by the assumption that intermediate **10** may be most stable when it adopts a chair conformation in which all the substituents are located in equatorial positions.

Scheme 1



Chiral tri- and tetrasubstituted piperazines were easily synthesized from chiral 1,2-diamines by this electroreductive method (Table 1, entries 9–14). These chiral piperazines are expected to be effective ligands of catalysts for the enantioselective synthesis of some chiral compounds. Chiral piperazines **13** prepared from **4m** (Scheme 2), for example, were studied as chiral ligands in the reaction of aldehydes with diethylzinc (eq 5).[12] Bifunctional piperazine **13a** showed only moderate enantioselectivity, whereas monofunctional ligand **13b** derived by mono-*O*-benzylation of **13a** gave chiral secondary alcohols with high enantioselectivity (Table 2).

Scheme 2



13a R=H
13b R=Bn

(a) (1) TMSCl (2 equiv)/Et_3N/toluene, reflux, 1 h.
(2) BnBr (2 equiv), reflux, 2 h.
(b) NaH (1.1 equiv)/BnBr (1.2 equiv)/THF, reflux, 2 h.

(5)

Table 2. Enantioselective Addition of Diethylzinc to Aldehydes

entry	aldehyde	catalyst	yield[a] (%)	% ee (configuration)[b]	$[\alpha]^{25}_D$ (*c*, solvent)
1	PhCHO	**13a**	64	64[c] (*S*)	-28.8 (1.4, $CHCl_3$)
2	PhCHO	**13b**	85	>99[c] (*S*)	-46.8 (2.5, $CHCl_3$)
3	4-$MeOC_6H_4CHO$	**13b**	95	>99[c] (*S*)	-36.0 (5.1, benzene)
4	PhCH=CHCHO	**13b**	90	88[c] (*S*)	-7.2 (2.4, $CHCl_3$)
5	*n*-$C_6H_{13}CHO$	**13b**	91	81[d] (*S*)	+7.8 (5.0, $CHCl_3$)

[a] Isolated yield. [b] Determined by the optical rotation. Reported values are as follows: $[\alpha]_D$ -45.45 (*c* 5.15, $CHCl_3$) for (*S*)-1-phenylpropanol,[13] $[\alpha]_D$ -17.2 (*c* 5, benzene) for (*S*)-1-(4-methoxyphenyl)propanol in 51% ee,[14] $[\alpha]^{23}_D$ -6.6 (*c* 3.2, $CHCl_3$) for (*S*)-1-phenylpent-1-en-3-ol in 75% ee,[15] $[a]^{24}_D$ +9.6 (*c* 8.3, $CHCl_3$) for (*S*)-3-nonanol.[16] [c] Determined by ^1H NMR of the corresponding acetate using $Eu(hfc)_3$. [d] Based on the optical rotation.

Conclusion

The electroreductive intramolecular coupling of diimines which were prepared from ethylenediamine gave the corresponding piperazines in high yields with high diastereoselectivity. The coupling provided seven- and eight-membered cyclic diamines also with high *trans*-selectivity. Furthermore, chiral piperazines derived from optically active diimines were shown to be applicable to the enantioselective addition of diethylzinc to various aldehydes.

Experimental Section

Apparatus. Nuclear magnetic resonance spectra of the compounds prepared in this Chapter were taken on a Varian Gemini-200 (^{1}H, 200 MHz; ^{13}C, 50 MHz) spectrometer or on a JEOL JNM-GX400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi 260-10 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Cathodic reduction was carried out using DC Power Supply (GP 050-2) of Takasago Seisakusyo, Ltd.

Chemicals. Diimines **3**, **5** and **7** were prepared from aromatic aldehydes or acetophenone and 1,n-diamines by refluxing the mixture in benzene.[17] (*R*)-1,2-Diamino-1-phenylethane and (*S*)-1,2-diamino-4-methylpentane were prepared from (*R*)-phenylglycine and (*S*)-leucine, respectively, according to the reported method.[18]

General Procedure of Electroreduction. A solution of tetrabutylammonium 4-toluenesulfonate (4 g) in DMF (40 mL) was put into a divided cell (50 mL beaker) equipped with a lead cathode (5 x 10 cm^2), a carbon rod anode, and a ceramic diaphragm. To the catholyte were added a diimine **3** (10 mmol) and methanesulfonic acid (30 mmol). After electricity was passed with a constant current of 0.5 A (2.2 *F*/mol), the catholyte was poured into water (200 mL) and adjusted to pH 8 by addition of $NaHCO_3$. The product **4** was extracted with dichloromethane and isolated by recrystallization from hexane-AcOEt or column chromatography on Al_2O_3 (Activity III, hexane-AcOEt).

4a: mp 96–98 °C; IR (KBr) 3320, 3280, 2820, 1605, 1495, 860, 760, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.95 (brs, 2 H), 3.15 (s, 4 H), 3.72 (s, 2 H), 7.10 (s, 10 H); ^{13}C NMR ($CDCl_3$) δ 46.98 (t), 68.18 (d), 127.30 (d), 127.88 (d), 128.13 (d),

141.53 (s). Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.67; H, 7.71 ; N, 11.62.

4b: mp 100–101 °C; IR (KBr) 3275, 2820, 1615, 1515, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77 (brs, 2 H), 3.13 (s, 4 H), 3.63 (s, 2 H), 3.72 (s, 6 H), 6.62–6.73 (m, 4 H), 6.96–7.07 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 47.08 (t), 54.98 (q), 67.50 (d), 113.21 (d), 129.12 (d), 134.00 (s), 158.73 (s). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.54; H, 7.47; N, 9.35.

4c: A colorless paste; IR (neat) 3500–3000 (broad), 1740, 1590, 780, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50 (brs, 2 H), 3.13 (s, 4 H), 3.68 (s, 2 H), 4.88 (d, J = 11.8 Hz, 2H), 4.92 (d, J = 11.8 Hz, 2 H), 6.63 (dd, J = 7.5, 1.2 Hz, 2 H), 6.70–6.80 (m, 4 H), 7.02 (dt, J = 7.5, 1.2 Hz, 2 H), 7.25–7.50 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 46.56 (t), 67.73 (d), 69.80 (t), 114.25 (d), 114.43 (d), 120.91 (d), 127.55 (s), 127.96 (d), 128.64 (d), 128.97 (d), 137.24 (s), 142.51 (s), 158.64 (s). Anal. Calcd for $C_{30}H_{30}N_2O_2$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.71; H, 6.65; N, 5.92.

4d: mp 122–125 °C; IR (KBr) 3325, 2800, 1595, 1490, 845, 825, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 (brs, 2 H), 3.11 (s, 4 H), 3.60 (s, 2 H), 6.96–7.03 (m, 4 H), 7.06–7.14 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 46.79 (t), 67.57 (d), 128.21 (d), 129.43 (d), 133.09 (s), 139.78 (s). Anal. Calcd for $C_{16}H_{16}N_2Cl_2$: C, 62.55; H, 5.25; N, 9.12; Cl, 23.08. Found: C, 62.45; H, 5.16; N, 8.99; Cl, 23.26.

4e: mp 177 °C; IR (KBr) 3300, 3500–2000 (broad), 1615, 1590, 1480, 765, 760, 745, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09–3.28 (m, 4 H), 4.06 (s, 2 H), 6.13 (dd, J = 7.6, 1.5 Hz, 2 H), 6.42 (dt, J = 7.6, 1.0 Hz, 2 H), 6.84 (dd, J = 7.6, 1.0 Hz, 2 H), 7.08 (dt, J = 7.6, 1.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 45.02 (t), 63.13

(d), 116.64 (d), 118.64 (d), 123.33 (s), 129.12 (d), 130.20 (d), 157.15 (s). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.37. Found: C, 70.91; H, 6.69; N, 10.31.

4f: mp 102–105 °C; IR (KBr) 3600–3100 (broad), 1715, 1610, 765, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, 2 H), 3.20 (s, 4 H), 3.84 (s, 2 H), 3.86 (s, 6 H), 7.16 (d, J = 8.2 Hz, 4 H), 7.77 (d, J = 8.2 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 46.14 (t), 51.92 (q), 67.35 (d), 128.18 (d), 129.46 (d), 129.62 (s), 145.21 (s), 167.01 (s). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.69; H, 6.08; N, 7.87.

4g: mp 100–101 °C; IR (KBr) 3600, 3450, 3250, 2825, 1600, 1515, 795, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (brs, 2 H), 3.22–3.40 (m, 4 H), 4.99 (s, 2 H), 7.08–8.20 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 47.63 (t), 60.26 (d), 122.50 (d), 125.07 (d), 125.20 (d), 125.56 (d), 127.78 (d), 128.57 (d), 131.59 (s), 133.65 (s), 137.44 (s). Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.00; H, 6.54; N, 8.26.

4h: mp 76–78 °C; IR (KBr) 3275, 2810, 1600, 1495, 805, 755, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, J = 6.4 Hz, 3 H), 1.82 (brs, 2 H), 2.71 (t, J = 11.0 Hz, 1 H), 3.12 (dd, J = 11.0, 2.7 Hz, 1 H), 3.11–3.23 (m, 1 H), 3.68 (d, J = 9.0 Hz, 1 H), 3.79 (d, J = 9.0 Hz, 1 H), 7.11 (s, 10 H); ^{13}C NMR ($CDCl_3$) δ 19.90 (q), 51.91 (d), 54.21 (t), 67.64 (d), 68.38 (d), 127.12 (d), 127.75 (d), 128.02 (d), 141.28 (s), 141.44 (s). Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.79; H, 8.03; N, 11.14.

4i: mp 141–144 °C; $[\alpha]_D^{20}$ -121 (*c* 1.2, $CHCl_3$); IR (KBr) 3275, 2810, 1600, 1495, 800, 755, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (brs, 2 H), 2.99 (dd, J =

11.2, 10.4 Hz, 1 H), 3.22 (dd, *J* = 11.2, 2.9 Hz, 1 H), 3.74 (d, *J* = 8.9 Hz, 1 H), 3.92 (d, *J* = 8.9 Hz, 1 H), 4.19 (dd, *J* = 10.4, 2.9 Hz, 1 H), 7.08–7.56 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 54.89 (t), 61.40 (d), 67.86 (d), 68.29 (d), 127.02 (d), 127.17 (d), 127.23 (d), 127.39 (d), 127.64 (d), 127.78 (d), 128.04 (d), 128.14 (d), 128.29 (d), 141.06 (s), 141.47 (s), 142.76 (s). Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.05; H, 7.05; N, 8.91. Found: C, 83.75; H, 7.15; N, 8.74.

4j: mp 73–76 °C; $[\alpha]_D^{20}$ +83 (*c* 1.0, $CHCl_3$); IR (KBr) 3275, 2810, 1600, 1495, 795, 755, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, *J* = 6.5 Hz, 3 H), 0.95 (d, *J* = 6.5 Hz, 3 H), 1.27–1.38 (m, 2 H), 1.57–1.76 (m, 1 H), 1.84 (brs, 2 H), 2.71 (t, *J* = 10.7 Hz, 1 H), 3.03–3.18 (m, 2 H), 3.68 (d, *J* = 8.9 Hz, 1 H), 3.78 (d, *J* = 8.9 Hz, 1 H), 7.11 (s, 10 H); ^{13}C NMR ($CDCl_3$) δ 22.38 (q), 23.10 (q), 24.16 (d), 43.44 (t), 53.09 (t), 54.25 (d), 68.08 (d), 68.38 (d), 127.30 (d), 127.92 (d), 128.25 (d), 141.49 (s). Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.49; H, 8.87; N, 9.31.

4k: mp 182–183 °C; $[\alpha]_D^{20}$ +20 (*c* 2.7, $CHCl_3$); IR (KBr) 3260, 3500–2000 (broad), 1610, 1585, 1470, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (d, *J* = 6.4 Hz, 3 H), 0.97 (d, *J* = 6.4 Hz, 3 H), 1.38 (t, *J* = 6.4 Hz, 2 H), 1.40–1.80 (m, 3 H), 2.73 (t, *J* = 10.5 Hz, 1 H), 3.05–3.25 (m, 2 H), 4.03 (d, *J* = 9.8 Hz, 1 H), 4.13 (d, *J* = 9.8 Hz, 1 H), 6.14 (d, *J* = 7.5 Hz, 2 H), 6.43 (t, *J* = 7.5 Hz, 2 H), 6.84 (d, *J* = 7.5 Hz, 2 H), 7.09 (t, *J* = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.13 (q), 23.00 (q), 23.98 (d), 42.95 (t), 50.91 (t), 52.81 (d), 62.96 (d), 63.25 (d), 116.65 (d), 118.70 (d), 123.18 (s), 123.38 (s), 129.13 (d), 130.22 (d), 157.09 (s). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.58; H, 8.03; N, 8.58. Found: C, 73.25; H, 8.21; N, 8.58.

4l: mp 108–110 °C; $[\alpha]_D^{20}$ -70 (*c* 1.7, $CHCl_3$); IR (KBr) 3300, 3600–2000 (broad), 1615, 1585, 1475, 765, 760, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30–1.50

(m, 4 H), 1.65–1.80 (m, 4 H), 1.70 (brs, 2 H), 2.57–2.65 (m, 2 H), 3.82 (s, 2 H), 7.10 (s, 10 H); ^{13}C NMR ($CDCl_3$) δ 24.71 (t), 31.61 (t), 61.45 (d), 68.41 (d), 127.19 (d), 127.88 (d), 128.17 (d), 141.56 (s). Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27; N, 9.58. Found: C, 82.01; H, 8.19; N, 9.42.

4m: mp 215 °C; $[\alpha]_D^{20}$ -7.2 (*c* 1.7, $CHCl_3$); IR (KBr) 3300, 3600–2000 (broad), 1615, 1585, 1475, 765, 760, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20–1.90 (m, 8 H), 2.42 (brs, 2 H), 2.65–2.75 (m, 2 H), 4.17 (s, 2 H), 6.13 (dd, *J* = 7.6, 1.4 Hz, 2 H), 6.43 (dt, *J* = 7.6, 1.0 Hz, 2 H), 6.84 (dd, *J* = 7.6, 1.4 Hz, 2 H), 7.08 (dt, *J* = 7.6, 1.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.10 (t), 31.33 (t), 59.58 (d), 63.27 (d), 116.58 (d), 119.61 (d), 123.27 (s), 129.01 (d), 130.22 (d), 157.06 (s). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.84; H, 7.56; N, 8.50.

4n: mp 110–111 °C; $[\alpha]_D^{20}$ +6.1 (*c* 3.3, $CHCl_3$); IR (KBr) 3700–3100 (broad), 1600, 1500, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15–1.40 (m, 4 H), 1.60–1.80 (m, 6H), 2.72 (brs, 2 H), 3.69 (s, 6 H), 4.71 (brs, 2 H), 6.60–7.14 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 24.30 (t), 30.16 (t), 55.17 (d), 60.04 (d), 110.30 (d), 120.36 (d), 125.91 (s), 128.89 (d), 129.63 (d), 157.17 (s). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.96; H, 8.01; N, 7.95. Found: C, 74.75; H, 7.89; N, 7.87.

6a: mp 90 °C; IR (KBr) 3380, 3350, 3050, 1600, 770, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80–2.00 (m, 2 H), 2.90–3.10 (m, 2 H), 3.20–3.40 (m, 2 H), 4.22 (s, 2 H), 6.90–7.10 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 36.60 (t), 48.32 (t), 68.34 (d), 126.95 (d), 128.05 (d), 142.67 (s). Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.76; H, 8.11; N, 10.64.

6b: mp 105 °C; IR (KBr) 3600–3100 (broad), 1610, 800, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.50 (m, 4 H), 2.70–2.90 (m, 2 H), 3.10–3.31 (m, 2 H), 4.09 (S, 2 H), 6.90–7.10 (M, 10 H); ^{13}C NMR ($CDCl_3$) δ 29.53 (t), 47.88 (t), 64.85 (d), 127.04 (d), 127.98 (d), 128.31 (d), 142.25 (s). Anal. Calcd for $C_{18}H_{22}N_2$: H, 8.33; N, 10.52. Found: C, 81.18; H, 8.37; N, 10.33.

8: mp 130 °C; IR (KBr) 3325, 1605, 1495, 840, 780, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 6 H), 2.96 (d, J = 7.3 Hz, 2 H), 3.50 (d, J = 7.3 Hz, 2 H), 7.22 (s, 10 H); ^{13}C NMR ($CDCl_3$) δ 21.19 (q), 41.32 (t), 61.30 (s), 127,25 (d), 128.86 (d), 133.90 (d), 146.25 (s). Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.33; N, 10.52. Found: C, 81.17; H, 804.; N, 10.44.

Synthesis of 13. Compound **13a** was obtained from **4m** by usual *O*-protection with chlorotrimethylsilane and subsequent *N*-alkylation with benzyl bromide in toluene as shown in Scheme 2 (73% yield). *O*-Benzylation of **13a** with sodium hydride (1.1 equiv) and benzyl bromide (1.2 equiv) in THF gave **13b** (79% yield).

13a: mp 78–80°C; $[\alpha]_D^{20}$ +26 (*c* 1.2, $CHCl_3$); IR (KBr) 3500–2000 (broad), 1585, 745, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.48 (m, 4 H), 1.70–1.90 (m, 2 H), 2.40–2.65 (m, 4 H), 3.67 (d, J = 16.0 Hz, 2 H), 3.86 (s, 2 H), 4.15 (d, J = 16.0 Hz, 2 H), 5.98 (d, J = 7.4 Hz, 2 H), 6.41 (t, J = 7.4 Hz, 2 H), 6.77 (d, J = 7.4 Hz, 2 H), 6.90–7.35 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 24.72 (t), 30.92 (t), 53.11 (t), 62.98 (d), 67.41 (d), 116.67 (d), 119.13 (d), 124.32 (s), 127.89 (d), 128.76 (d), 129.20 (d), 130.12 (d), 131.82 (d), 135.50 (s), 157.08 (s). Anal. Calcd for $C_{34}H_{36}N_2O_2$: C, 80.92; H, 7.19; N, 5.55. Found: C, 80.93: H, 7.17: N, 5.33.

13b: mp 75 °C; $[\alpha]_D^{20}$ -50 (*c* 1.0, $CHCl_3$); IR (KBr) 3500–2000 (broad), 1595, 1500, 760, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–2.00 (m, 8 H), 2.50–2.70 (m, 2 H), 3.35 (d, J = 16 Hz, 1 H), 3.60–3.80 (m, 3 H), 4.22 (d, J = 10.6 Hz, 1 H), 4.24 (d, J = 14.6 Hz, 1 H), 4.54–4.64 (m, 2 H), 5.98 (d, J = 7.5 Hz, 1 H), 6.36 (t, J = 7.5 Hz, 1 H), 6.48 (d, J = 7.5 Hz, 1 H), 6.60 (d, J = 7.5 Hz, 1 H), 6.70–7.50 (m, 19 H), 7.60 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.83 (t), 25.26 (t), 30.51 (t), 32.04 (t), 51.34 (t), 56.56 (t), 60.98 (d), 61.78 (d), 68.20 (d), 69.93 (t), 70.75 (d), 111.90 (d), 116.70 (d), 118.29 (d), 120.96 (d), 123.89 (s), 126.13 (d), 126.24 (d), 127.18 (d), 127.80 (d), 127.91 (d), 128.16 (d), 128.36 (d), 128.50 (d), 128.68 (d), 129.85 (d), 129.44 (d), 130.89 (d), 130.96 (d), 134.78 (s), 138.06 (s), 142.61 (s), 143.02 (s), 157.75 (s), 158.77 (s). Anal. Calcd for $C_{41}H_{42}N_2O_2$: C, 82.79; H, 7.12; N, 4.71. Found: C, 82.64: H, 7.06: N, 4.61.

General Procedure for Enantioselective Addition of Diethylzinc to Aldehydes. A mixture of a 1 M hexane solution of diethylzinc (0.32 mL, 0.32 mmol) and a chiral piperazine **13** (0.16 mmol) in toluene (5 mL) was stirred at reflux temperature for 30 min. A 1 M hexane solution of diethylzinc (4.8 mL, 4.8 mmol) and an aldehyde (3.2 mmol) were added to the mixture at 0 °C. The mixture was stirred for 15–24 h at room temperature. After a 1 N HCl aqueous solution (20 mL) was added, the mixture was extracted with dichloromethane. The product, a secondary alcohol, was isolated by preparative thin layer chromatography (silica gel, hexane-AcOEt).

References and Notes

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(2) (a) Smith, J. G. *Can. J. Chem.* **1966**, *44*, 59. (b) Smith, J. G.; Veach, C. D. *ibid.* **1966**, *44*, 2497. (c) Smith, J. G.; Ho, I. J. *J. Org. Chem.* **1972**, *37*, 653. (d) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152. (e) Mangeneg, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255. (f) Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999.

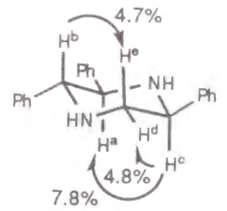
(3) Koch, R. W.; Dessy, R. E. *J. Org. Chem.* **1982**, *47*, 4452.

(4) The author have also found that the electroreduction of diisoquinolinium salt **i** gave corresponding coupling product **ii** stereoselectively.[5]

i **ii** 80 %

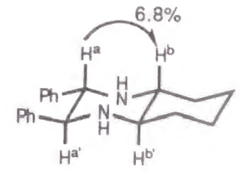
(5) Shono, T.; Kise, N.; Shirakawa, E. 56th Annual Meeting of the Chemical Society of Japan, April 1988, Abstr., p. 1493.

(6) Stereochemistry of **4a** was determined through its *N,N'*-dimethylation and subsequent comparison of the ^{1}H NMR spectrum with the reported data.[7] Stereochemistries of **4i** and **4l** were deduced on the basis of reasonable coupling constants and NOE enhancements in their ^{1}H NMR (400 MHz).



4 i

H^a δ 3.92 (d) J_{ab} = 8.9 Hz
H^b δ 3.74 (d) J_{cd} = 2.9 Hz
H^c δ 4.19 (dd) J_{de} = 11.2 Hz
H^d δ 3.22 (dd) J_{ce} = 10.4 Hz
H^e δ 2.99 (dd)



4 l

H^a δ 3.82 (s)
H^b δ 2.57–2.65 (m)

It seems reasonable that other coupling products **4b–h**, **4j**, **4k**, **4m**, and **4n** have the same configurations with **4a**, **4i**, and **4l**.

(7) Beugelmans, R.; Iguertsira, L. B.; Chastanet, J.; Negron, G.; Roussi, G. *Can. J. Chem.* **1985**, *63*, 725.

(8) The stereoconfigurations of **6a,b** were assigned to be trans by comparison with the samples prepared from *dl*-1,2-diamino-1,2-diphenylethane and 1,n-dibromoalkanes.

(9) Although the structure of **8** was not comfirmed, it seems likely that it is trans.

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Conclusion and Prospect

In closing this Thesis, the author concludes his contribution to modern organic synthesis as follows: First, he discovered active catalysts for the transition metal-catalyzed cross-coupling reaction of organostannanes with aryl halides and demonstrated their synthetic potential. Second, he disclosed a new catalytic cycle for the cross-coupling reaction. Third, he applied the active catalyst to the homocoupling of organostannanes.

The findings discussed herein will provide us with clues to further investigation concerning not only the coupling reaction of organostannanes but also the cross-coupling reaction of other organometallic reagents. The catalytic cycle demonstrated here should be pursued in terms of generality, including the cross-coupling reaction of other organometallic reagents. The elucidation of the reaction mechanism will lead us to the creation of more active catalysts for the cross-coupling reactions of various organometallic reagents.

Furthermore, an active species $(L\text{–}L')Pd^{II}(R)(SnR'_3)$, the new type of nucleophile that was first demonstrated in this Thesis, will find wide applications leading to novel methodology for C–C bond forming reactions.

List of Publications

I. Parts of the present Thesis have been, or are to be, published in the following journals.

Chapter 1

(1) An Iminophosphine–Palladium Catalyst for Cross-Coupling of Aryl Halides with Organostannanes. Shirakawa, E.; Yoshida, H.; Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 3759–3762.

Chapter 2

(2) On the Catalytic Cycle of the Palladium-Catalyzed Cross-Coupling Reaction of Alkynylstannane with Aryl Iodide. Shirakawa, E.; Yoshida, H.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 5177–5180.

Chapter 3

(3) Homocoupling of Organostannanes Catalyzed by Iminophosphine–Palladium. Shirakawa, E.; Murota, Y.; Nakao, Y.; Hiyama, T. *Synlett*, in press.

Chapter 4

(4) Nickel-Catalysed Cross-Coupling Reactions of Aryl Halides with Organostannanes. Shirakawa, E.; Yamasaki, K.; Hiyama, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2449–2450.

Appendix

(5) Electroorganic Chemistry. 129. Electroreductive Synthesis of Chiral Piperazines and Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of the Chiral Piperazines. Shono, T.; Kise, N.; Shirakawa, E.; Matsumoto, H.; Okazaki, E. *J. Org. Chem.* **1991**, *56*, 3063–3067.

II. Other publications not included in this Thesis.

(1) Asymmetric Aldol Reaction of α-Isocyanocarboxylates with Paraformaldehyde Catalyzed by Chiral Ferrocenylphosphine-Gold(I) Complexes: Catalytic Asymmetric Synthesis of α-Alkylserines. Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tterahedron Lett.* **1988**, *29*, 235–238.

(2) Asymmetric Synthesis of β-Hydroxy-α-alkylamino Acids by Asymmetric Aldol Reaction of α-Isocyanocarboxylates Catalyzed by Chiral Ferrocenylphosphine-Gold(I) Complexes. Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253–5262.

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