$$Ar^1M + Ar^2X \longrightarrow Ar^1Ar^2$$

III.2.5 Palladium-Catalyzed Aryl–Aryl Coupling

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A. INTRODUCTION

The ability of late transition metals to induce carbon–carbon bond formation between two C_{sp^2} atoms via reductive elimination has been exploited in the synthesis of both symmetrical and unsymmetrical biaryls.[1] Earlier methods relied heavily on the use of Cu,[2] and organocoppers were used mostly as stoichiometric "nucleophilic" reagents. Some other late transition metals, Ni[3] in particular, were also used as formal nucleophiles. As methods for the synthesis of unsymmetrical biaryls, these reactions were of limited scope and low selectivity.

As in many other cases of cross-coupling, the discovery of the Ni-catalyzed reactions of Grignard reagents (*Kumada–Corriu reaction*)[4]–[6] provided a major breakthrough in the development of general and selective aryl–aryl coupling reactions. Specifically, the reaction of arylmagnesium halides with aryl iodides, bromides, and related electrophiles in the presence of Ni–phosphine complexes provided a high-yielding and "pair"-selective, or copuloselective (*copulo* in Latin = to pair) hereafter, method for the synthesis of unsymmetrical biaryls.[7] Some of the prototypical examples are shown in **Table 1**. In all of the examples shown in **Table 1**, Ni catalysts were used, and the metal countercation in the arylmetals was Mg. In 1976 a paper describing the Pd-catalyzed reaction of arylmagnesium halides with aryl halides was reported by Sekiya and Ishikawa.[8]

The discovery of the Ni- or Pd-catalyzed aryl–aryl coupling with arylzinc derivatives (*Negishi coupling*)[9] in 1977 was the second major breakthrough in this area. This study demonstrated that the countercation in the arylmetal could be metals other than Mg, such as Zn and Al, and that not only Ni but also Pd could serve as catalysts. In particular, the Zn–Ni and Zn–Pd reactions have been proved to display a combination of higher reactivity and superior chemoselectivity than the corresponding Mg–Ni and Mg–Pd reactions. Thus, the scope of the aryl–aryl coupling catalyzed by late transition metals was significantly expanded in the mid-1970s. Some prototypical examples of the Ni- or Pd-catalyzed reaction of arylzincs are shown in **Table 2**. The synthesis of an antitumor agent steganone[10] appears to represent the first successful application of the Ni- or Pd-catalyzed aryl–aryl coupling to the synthesis of complex natural products (**Scheme 1**).

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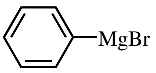
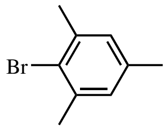
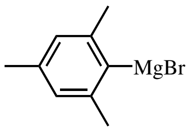
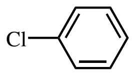
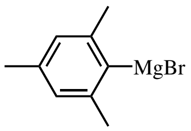
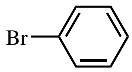
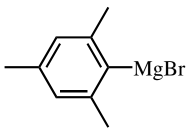
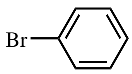
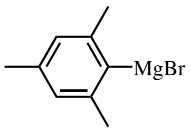
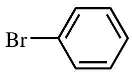
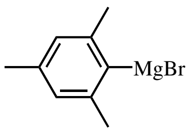
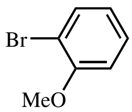
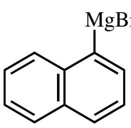
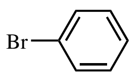
TABLE 1. Some Prototypical Examples of Ni-Catayzed Aryl–Aryl Coupling Reactions

$$\text{ArMgBr} + \text{ArX} \xrightarrow{\text{Cat.}} \text{Ar–Ar}'$$

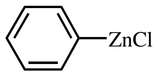
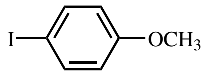
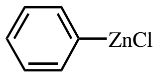
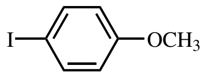
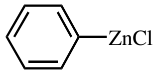
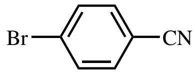
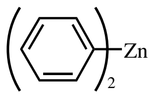
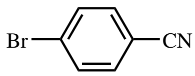
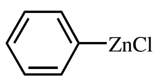
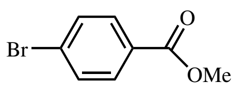
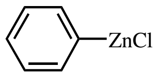
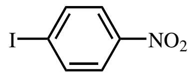
Entry	ArMgBr	ArX	Catalyst[a]	Yield (%)	Reference
1			Ni(dppp)Cl_2	48	[7]
2			Ni(dppp)Cl_2	6	[7]
3			Ni(dppp)Cl_2	78	[7]
4			Ni(dmpe)Cl_2	85	[7]
5			Ni$(PPh_3)_2Cl_2$	96	[7]
6			Ni(dppp)Cl_2	74	[7]
7			Ni(dppe)Cl_2	98	[7]

[a]dppp = 1,2-bis(diphenylphosphino)propane; dmpe = 1,2-bis(dimethylphosphino)ethane; dppe = 1,2-bis(diphenylphosphino)ethane.

Despite the general superiority of Zn over Mg, it is important to retain Mg as an option, especially in those cases where arylzincs are generated via arylmagnesium derivatives, and the use of Zn as the second metal countercation must be experimentally justified. It is also important to consider both Ni and Pd as catalyst components. Despite its shortcomings, Ni is significantly less expensive than Pd. So, it is very desirable to experimentally justify the use of Pd in preference to Ni.

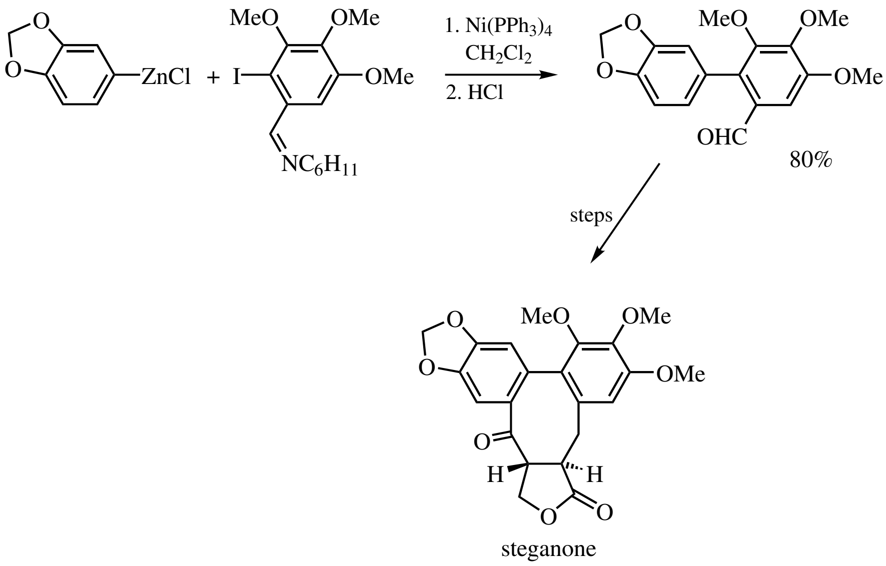
TABLE 2. Preparation of Biaryls by the Ni- or Pd-Catalyzed Reaction of Organizinc Reagents with Aryl Halides

$$ArZnX + ArX \xrightarrow{Cat.} Ar{-}Ar'$$

Entry	ArZnX	ArX	Catalyst	Yield (%)	Reference
1			$Ni(PPh_3)_4$	85	[11]
2			$Cl_2Pd(PPh_3)_2$ + DIBAH (1:2)	87	[11]
3			$Ni(PPh_3)_4$	90	[11]
4			$Ni(PPh_3)_4$	85	[11]
5			$Ni(PPh_3)_4$	70	[11]
6			$Cl_2Pd(PPh_3)_2$ + DIBAH (1:2)	90	[11]

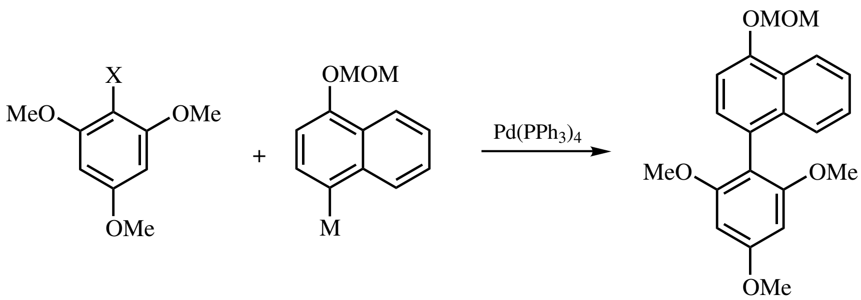
The discovery and development of the Pd-catalyzed aryl–aryl coupling with organometals containing B[12],[13] (*Suzuki coupling*), Sn[14]–[16] (*Stille coupling*), and other relatively electronegative metals in the 1980s represent a third major breakthrough. Curiously, little appears to be known about the Ni-catalyzed versions of these reactions. As discussed in **Sects. III.1** and **III.2.1**, the intrinsic reactivity of the C—B and C—Sn bonds in the Pd-catalyzed cross-coupling may be judged to be considerably lower than that of the C—Zn and C—Mg bonds. Moreover, the preparation of the requisite arylboronic acids and arylstannanes is chemically and technically more involved than the *in situ* generation of arylmetals containing Mg and Zn. Also, arylmetals containing B and Sn are generally more expensive than those containing Mg or even Zn. On these bases, the use of B and Sn must be reserved for those cases where their advantages over Mg and Zn outweigh their shortcomings.

Some of the potential advantages associated with B and Sn include the following. First, they generally display higher levels of chemoselectivity than Mg or even Zn, although Zn can, in fact, tolerate various carbonyl and other functional groups. Second, the C—B and C—Sn bonds are thermally and chemically more stable than the C—Mg and C—Zn bonds. This must, in fact, be one of the major reasons why they are intrinsically of lower reactivity. However, this does not immediately mean that their reactions are lower yielding or inferior to Zn or Mg in an overall sense. Indeed, there are indications that some Pd-catalyzed aryl–aryl coupling reactions of arylboron derivatives can be carried out under forcing conditions at high temperatures (>100 °C) to produce highly hindered unsymmetrical biaryls[17] (**Scheme 2**). In this reaction, the B—Pd reaction is



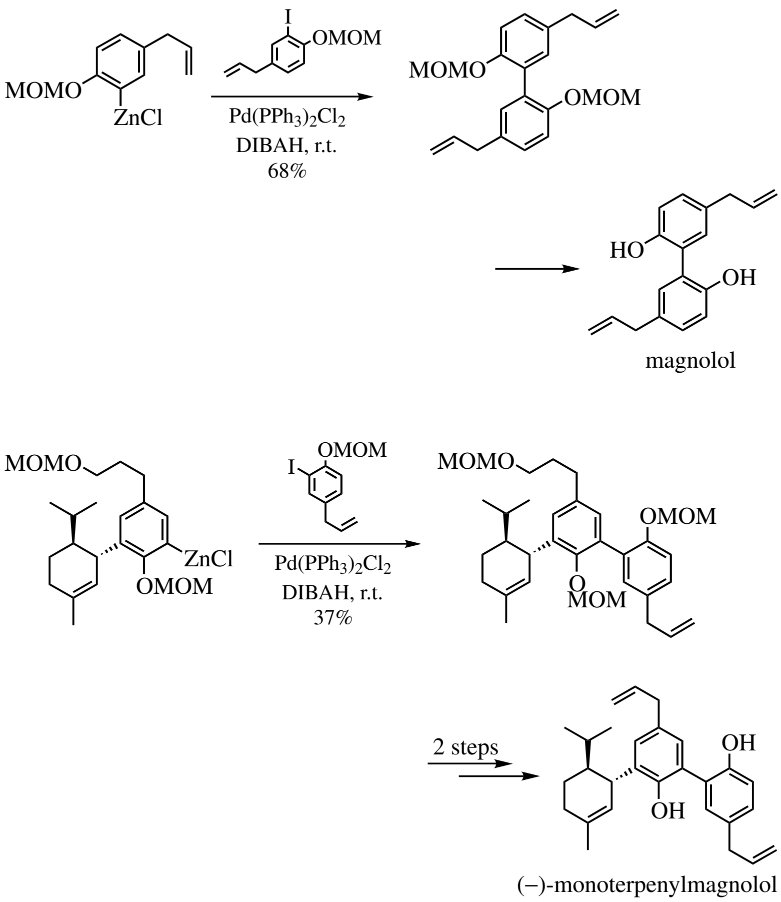
Scheme 1

even somewhat superior to the Zn—Pd reaction, although the Sn—Pd reaction was not at all effective. The lower reactivity of C—B and C—Sn bonds can, however, lead to various undesirable side reactions. For example, the synthesis of magnolol via Pd-catalyzed reaction of allyl-substituted arylstannanes is accompanied by extensive double bond migration, whereas a faster reacting arylzinc reagent avoids this undesirable side reaction.[18] The Zn–Pd reaction has also been successfully applied to the synthesis of (−)-monoterpenylmagnolol[18] (**Scheme 3**).



X	M	Temperature (°C)	Solvent	Yield (%)
I	$SnBu_3$	110	Toluene	0
I	ZnCl	65	THF	50
I	$B(OH)_2$	110	Toluene	79
Br	$SnBu_3$	110	Toluene	0
Br	ZnCl	65	THF	16
Br	$B(OH)_2$	110	Toluene	56

Scheme 2



Scheme 3

Since each metal or each protocol must have its own set of optimal conditions, it is, in fact, rather difficult and often dangerous to rank various protocols. This matter is further complicated by other factors and influences exerted by protective groups and other optional parameters. Thus, for example, chelating groups, such as $MeOCH_2O$ (MOMO), have significantly retarded the Pd-catalyzed cross-coupling involving strongly Lewis-acidic organometals, such as organozincs and organoalanes. In such cases, optimization of the desired cross-coupling should also include optimization of protecting groups and other optional parameters as well. Despite these complicating factors, it may still be useful to tentatively summarize the relative merits and demerits of various metal countercations and hence various cross-coupling protocols as follows.

In less demanding cases of aryl–aryl coupling, several metals including Mg, Zn, B, Al, Si, and Sn have often led to highly satisfactory and comparable results, as indicated by some examples discussed in **Sect. B**. In more demanding cases, however, Zn and B have been the two metals that have often been shown to be superior to the others. These two metals become even more attractive in an overall sense, when other important factors, such as chemoselectivity, ease of preparation of the required arylmetals, operational simplicity, and toxicity, are taken into consideration.

Of course, the considerations made above do not point to the conclusion that one should consider Zn or B for all cases. They instead point to the following rational procedure for selecting the optimal countercation and the metal in the catalyst.

1. In cases where arylmagnesium derivatives are the most convenient sources of the arylmetal reagent, as are often the case, both Ni-catalyzed and Pd-catalyzed Grignard cross-couplings should be considered first, since they are the simplest options of all.

2. In cases where improvements in product yield, chemoselectivity, and so on are desirable in the Mg–Ni and Mg–Pd reactions, consider next *in situ* conversion of the arylic Grignard reagents into arylzincs for the Zn–Pd and Zn–Ni aryl–aryl coupling reactions. These combinations should also be considered in cases where either aryllithiums or arylzincs are the most readily available arylmetals. As readily and widely available as aryllithiums are, their direct use in aryl–aryl coupling has not generally been a viable option. This point may be experimentally verified in cases where aryllithiums are used as the first-generation organometals.

3. In cases where all of the options mentioned above leave some room for improvement, the B–Pd combination may prove to be a superior alternative. As discussed earlier, the generally greater stability of arylboronic acids may lead to superior results under forcing conditions. Although similar benefits may be expected from the SI–Pd reaction, Sn does not appear to share this advantage with B.

4. The selection of Al, Si, Sn, and others over Mg, Zn, and B will have to be well-justified on a rational basis, since their reactions are generally more involved and operationally cumbersome, and since the results observed with them are, in most cases, at best comparable and often inferior to those observable with Zn and B.

In the following subsections, various classes of the Pd-catalyzed aryl–aryl coupling along with some Ni–catalyzed analogs are classified into the following three categories, and they are discussed in the indicated order. Heteroarene-containing biaryls are mostly excluded from this section, as they are discussed in **Sect. III.2.7**.

1. Synthesis of biaryls without an ortho substituent (**Sect. B**).

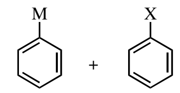
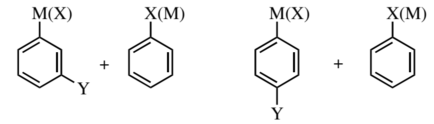
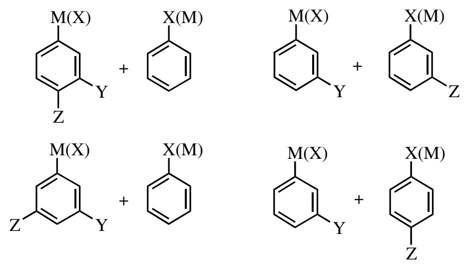
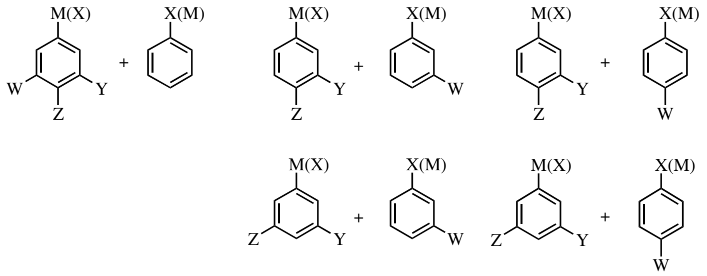
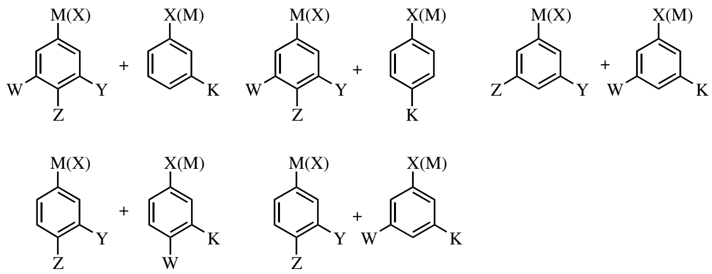
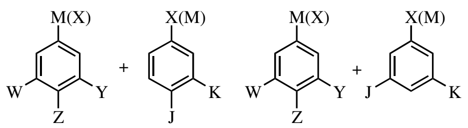
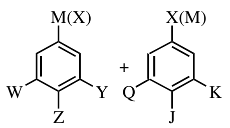
This general category includes 20 structural types and 39 different combinations of arylmetals and aryl halides shown in **Table 3**, and the entries in the subsequent tables are arranged in the indicated order. These classes of aryl–aryl coupling reactions may be considered to be relatively free from serious steric hindrance and may therefore be well suited for probing electronic and other effects. These are also generally less demanding cases, and various metals may serve as satisfactory countercations.

2. Synthesis of biaryls containing one or two ortho substituents (**Sect. C**).
3. Synthesis of chiral atropisomeric biaryls containing three or four ortho substituents (**Sect. D**).

As readily expected, ortho substituents including fused rings have been shown to exert steric hindrance to aryl–aryl coupling, which should increase, as the number of ortho

TABLE 3. Classification of Pd- of Ni-Catalyzed Aryl–Aryl Coupling Not Involving Ortho Substituents

$$\mathrm{ArM} + \mathrm{Ar'X} \xrightarrow{\text{Cat.}} \mathrm{Ar{-}Ar'}$$

Number of Substituents	Number of Possible Types	
0	1	
1	4	
2	8	
3	10	
4	10	
5	4	
6	2	

substituents increases. The syntheses of biaryls containing three or four ortho substituents are not only highly demanding from the synthetic point of view but also complicated by the formation of persistent atropisomers. The latter also provides an attractive opportunity for synthesizing chiral biaryls by cross-coupling. For these reasons, the syntheses of biaryls containing one or two ortho substituents and the syntheses of those containing three or four ortho substituents are discussed separately in **Sects. C** and **D**, respectively.

The discussion of the Pd-catalyzed aryl–aryl coupling presented in this section may be further supplemented by some recent reviews on the subject.[19]

B. SYNTHESIS OF BIARYLS WITHOUT ORTHO SUBSTITUENTS VIA Pd- OR Ni-CATALYZED ARYL–ARYL COUPLING

Biaryls without ortho substituents may contain 0 to 6 meta and/or para substituents, and there are 20 different structural types for such compounds and 39 reagent combinations (*i.e.*, ArM + Ar′X), leading to their formation, as shown in **Table 3**. Some of their representative examples are summarized in **Tables 4–7**. These results indicate that, regardless of the substitution patterns, the product yields can be consistently high, ranging from 70% to 100% with only a relatively small number of exceptions.

Thus, the electronic effects of the meta and para substituents on the eventual outcome reflected in the product yields appear to be relatively minor.

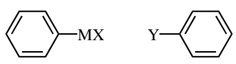
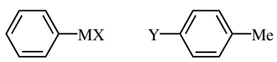
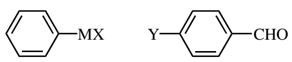
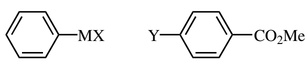
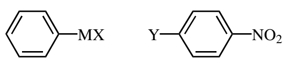
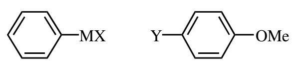
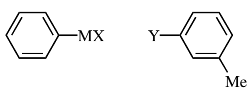
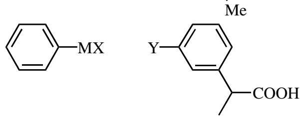
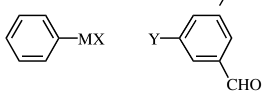
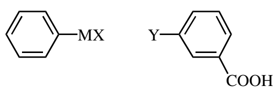
Metal Countercations. It is reasonable to state that biaryls without ortho substituents can be prepared in comparably high yields by using Mg, Zn, B, Al, Si, and Sn as the countercations in many cases. Of these, Mg, Zn, B, and Sn have been the four most widely used metals. The relative merits and demerits of these metals and a rational procedure for selecting the most appropriate countercation in a given case are discussed in **Sect. A**. In a nutshell, the procedure must take into consideration various factors, such as (i) accessibility of arylmetals (Mg > Zn > B or Sn, where > indicates "generally more favorable than"), (ii) intrinsic catalytic reactivity (Zn > Mg > B or Sn), (iii) stability of the Ar—M bonds (B ≃ Sn > Zn ≃ Mg), (iv) ease of experimental manipulation including workup and purification (Mg ≃ Zn > B > Sn), (v) chemoselectivity (Sn ≃ B > Zn > Mg), and (vi) toxicity (Mg, Zn, and B > Sn). In general, Zn and B emerge as the two most satisfactory metals, and they have indeed been the two most widely used metals.

Arylzincs are invariably generated *in situ* and used directly in the subsequent cross-coupling, and the yields of biaryls are based on one or both of the starting aryl electrophiles before metallation. On the other hand, arylmetals containing B or Sn are usually prepared from the corresponding Grignard reagents or aryllithiums and isolated as pure compounds. The yields of biaryls are usually based on purified arylmetals containing B or Sn and/or aryl electrophiles used as the cross-coupling partners. The isolation and purification steps in the use of arylmetals containing B or Sn make the overall synthetic operation more involved. This complication, however, may be more than offset by being able to use pure arylmetals, which can be critically important in polymerization (**Sect. III.2.17.2**) and other processes.

Aryl Electrophiles. Although aryl iodides are the most reactive and most widely used aryl electrophiles, the corresponding bromides are also often satisfactory especially in those cases where aryl bromides are activated toward oxidative addition to Pd or Ni by the presence of one or more electron-withdrawing groups, such as CHO, COOH, COOMe, CN, NO_2, and halogens. Various sulfonates, such as those containing OSO_2F[20] and OSO_2CF_3,[21]–[23] have also been successfully used. The reactivity of aryl triflates appears to be roughly comparable with that of the corresponding bromides. Although less frequently employed than aryl iodides and bromides, aryl chlorides have been increasingly used in recent years.[24]–[29]

TABLE 4. Pd-, Ni-, or Cu-Catalyzed Phenyl–Aryl Coupling with *p*- or *m*-Substituted Aryl Electrophiles[a]

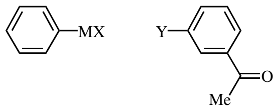
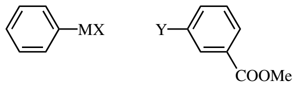
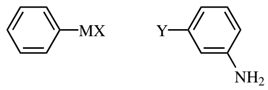
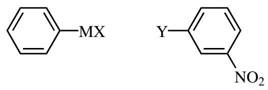
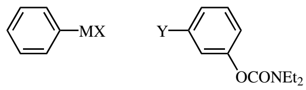
$$\text{PhMX} + \text{ArY} \xrightarrow{\text{Cat.}} \text{Ph–Ar}'$$

Entry	Substrates	MX	Y	Catalyst	Yield (%)	Reference
1		$B(OH)_2$	Br	$BnPd(PPh_3)_2Cl$	83	[22]
		ZnCl	OSO_2F	$Pd(PPh_3)_4$	95	[20]
		$SnPh_3$	Tf	$Pd(PPh_3)_4$	78	[30]
	p-Mono					
2		$SiMe_2(OMe)$	I	CuI	72	[31]
3		ZnCl	Br	$Pd(PPh_2)Cl_2$	92	[32]
		$B(OH)_2$	Br	$Pd/C + PPh_3$	96	[33]
4		ZnCl	Br	$Ni(PPh_3)_4$	70	[9]
		$B(OH)_2$	Br	$Pd(PPh_3)_4$	94	[12]
5		ZnCl	I	$Pd(PPh_3)_2Cl_2$/DIBAH	90	[9]
		SnR_3	Br	$Pd(PPh_3)_2Cl_2$, LiCl	85	[34]
6		ZnCl	I	$Ni(PPh_3)_4$	85	[9]
		$B(O(CH_2)_3O)_2$	I	$Pd(dppe)Cl_2$	82	[35]
		$Al(i\text{-}Bu)_2$	I	$Cl_2Pd(PPh_3)_2$	72	[11]
		$AlPh_2$	I	$Cl_2Pd(PPh_3)_2$	95	[36]
		ZnCl	OSO_2F	$Pd(PPh_3)_4$	56	[20]
	m-Mono					
7		BPh_3	Br	$Pd(PPh_3)_4$	98	[37]
		$SnBu_3$	Br	$Pd(PPh_3)_4$	80	[38]
8		ZnCl	I	$PdCl_2(PPh_3)_2$	74	[39]
9		$B(OH)_2$	Br	$Pd(PPh_3)_4$	95	[40]
10		$B(OH)_2$	I	$PdCl_2(dppf)$	93	[41]
		$SnBu_3$	I	$Cl_2Ni(NEt_3)_2$	89	[42]
		MgBr	Br	$PdCl_2$	90	[43]
		$B(OH)_2$	Br	$Pd(PPh_3)_4$	62	[44]
		BPh_3Na	Br	$Pd(OAc)_2$	96	[45]
		$B(OH)_2$	Br	$Pd(PPh_3)_4$	90	[46]
		$SnBu_3$	Br	CuI	94	[47]

(*Continued*)

TABLE 4. (*Continued*)

$$\text{PhMX} + \text{ArY} \xrightarrow{\text{Cat.}} \text{Ph–Ar}'$$

Entry	Substrates	MX	Y	Catalyst	Yield (%)	Reference
11		ZnCl	Br	$PdCl_2(PPh_3)_2$	79	[32]
12		$B(OH)_2$	Cl	$Cl_2Ni(dppf)$	96	[25]
13		$B(OH)_2$	I	$Pd(OAc)_2$	82	[48]
14		BPh_3	I	$Pd(PPh_3)_4$	98	[49]
		$B(OH)_2$	Br	$Pd(OAc)_2$	94	[50]
15		ZnCl	OTf	Ni(acac), DIBAH	92	[21]

[a]Arranged according to the following order of substitution pattern in aryl electrophiles: Ph > *p*-monosubstituted aryl > *m*-monosubstitued arly. In cases where the substituent pattern in the same, the substituents are arranged according to increasing order of priority determined by the Cahn–Ingold–Prelog rule.

TABLE 5. Pd- or Ni-Catalyzed Aryl–Phenyl Coupling with *p*- or *m*-Substituted Arylmetals[a]

$$\text{ArMX} + \text{PhY} \xrightarrow{\text{Cat.}} \text{Ar–Ph}$$

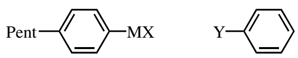
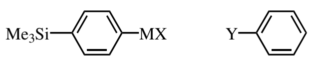
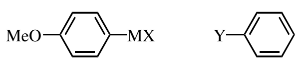
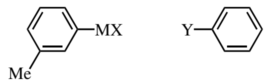
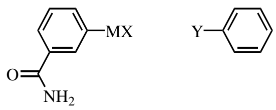
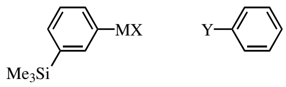
Entry	Substrates	MX	Y	Catalyst	Yield (%)	Reference
	p-Mono					
1		ZnCl	I	$Cl_2Pd(PPh_2Me)_2$	62	[51]
		$B(OH)_2$	I	Pd, Al_2O_3,KF	98	[52]
		MgBr	Br	$NiCl_2(PPh_3)_2$	88	[53]
		MgBr	Br	Ni(acac)	80	[54]
		$B(OH)_2$	Br	Pd/resin, KOH	82	[55]
		$B(OH)_2$	OTf	$Pd(PPh_3)_4$, K_3PO_4	83	[22]
2		SiF_2Et	I	$Cl_2Pd(allyl)_2$	94	[56]
3		$B(OH)_2$	I	$PdCl_2$, Ph_4PBr, K_2CO_3	90	[57]
4		$B(OH)_2$	Br	$Pd(PPh_3)_4$, Na_2CO_3	73	[58]
5		$B(OH)_2$	I	$PdCl_2$, Ph_4PBr, K_2CO_3	90	[57]
		SiR_2OH	I	$Pd(PPh_3)_4$	74	[59]
		SiR_2F	I	$Cl_2Pd(allyl)_2$	91	[60]
		$SnBu_3$	I	$PdCl_2$	78	[61]
		$Sn(CH_2CH_2(CF_2)_5CF_3)_3$	I	$PdCl_2(PPh_3)_2$	97	[62]
6		$B(OH)_2$	I	$Pd(OAc)_2$, Na_2CO_3	95	[63]
		$B(OH)_2$	I	$PdCl_2$	86	[64]
7		ZnBr	I	Pd(acac)(dppf)	92	[65]

TABLE 5. (*Continued*)

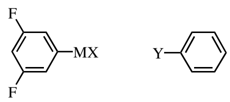
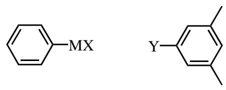
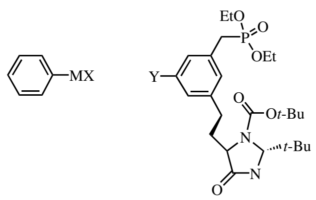
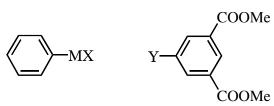
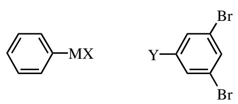
$$\mathrm{ArMX} + \mathrm{PhY} \xrightarrow{\text{Cat.}} \mathrm{Ar{-}Ph}$$

Entry	Substrates	MX	Y	Catalyst	Yield (%)	Reference
	m-Mono					
8		$SnBu_3$	Br	$Pd(PPh_3)_4$	75	[38]
9		$B(OR)_2$	I	$Pd(PPh_3)_4$	95	[66]
10		$B(OH)_2$	Br	$Pd(PPh_3)_4$	75	[59]

[a]Arranged according to the following order of substitution pattern in aryl electrophiles: *p*-monosubstitued arylmetal > *m*-monosubstituted arylmetal. In cases where the substituent pattern is the same, the substituents are arranged according to increasing order of priority determined by the Cahn–Ingold–Prelog rule.

TABLE 6 Pd- or Ni-Catalyzed Aryl–Aryl Coupling Using 3,5- Substituted Arylmetals or Aryl Electrophiles[a]

$$\mathrm{ArMX} + \mathrm{Ar'Y} \xrightarrow{\text{Cat.}} \mathrm{Ar{-}Ar'}$$

Entry	Substrates	MX	Y	Catalyst	Yield (%)	Reference
1		$B(OH)_2$	I	$PdCl_2$	65	[57]
2		$B(OH)_2$	Br	$Pd(OAc)_2$	92	[67]
		$B(OH)_2$	Cl	$Pd(dba)_2$ + Ligand[b]	94	[28]
3		$B(OH)_2$	Br	$Pd(OAc)_2$, PPh_3	86	[68]
4		$B(OH)_2$	Br	$Pd(OAc)_2$	66	[69]
5		$B(OH)_2$	Br	$Pd(PPh_3)_4$	67	[70]

[a]Aryl electrophiles are arranged according to increasing order of priority determined by the Cahn–Ingold–Prelog rule.

[b]Ligand =

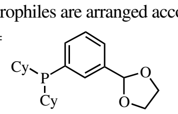
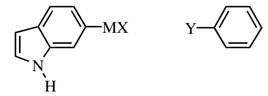
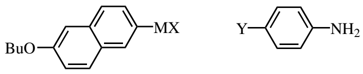
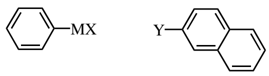
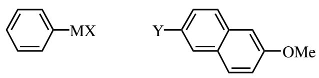
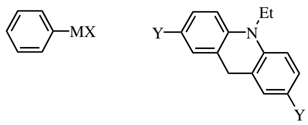
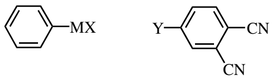
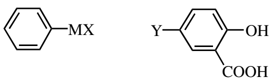
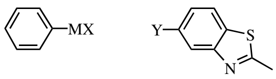
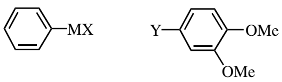


TABLE 7. Pd- or Ni-Catalyzed Aryl–Aryl Coupling Using 3,4-Substituted Arylmetals or Aryl Electrophiles[a]

$$\text{ArMX} + \text{Ar}'\text{Y} \xrightarrow{\text{Cat.}} \text{Ar–Ar}'$$

Entry	Substrates	MX	Y	Catalyst	Yield (%)	Reference
1		$B(OH)_2$	Br	$Pd(PPh_3)_4$	87	[71]
2		$B(OH)_2$	I	$Pd(PPh_3)_4$	52	[72]
3		$B(OH)_2$ MgBr	Br OMe	$Pd(DIPHOS)_2$ $NiCl_2(PPh_3)_2$	95 99	[73] [74]
4		MgBr $B(OH)_2$ $B(OH)_2$	Br Br Br	$Ph_2(dba)_3$ + IPrHCl[b] $Pd(OAc)_2$ $Pd(PPh_3)_4$	98 99 95	[27] [75] [76]
5		MgBr	Br	$NiCl_2(dppp)$	75	[77]
6		$SnBu_3$	I	$Pd_2(dba)_3 \cdot CHCl_3$	72	[23]
7		MgBr $B(OEt)_2$	Br Br	$Cl_2Pd(dppf)$ $Pd(OAc)_2$	87 99	[43] [78]
8		ZnCl $B(OH)_2$	Br Br	$PdCl_2$, K_2CO_3, H_2O $Pd(PPh_3)_4$	100 98	[79] [80]
9		MgBr	Br	$NiCl_2(PPh_3)_2$	99	[74]

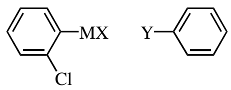
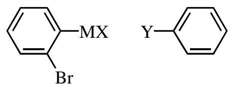
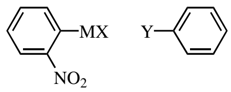
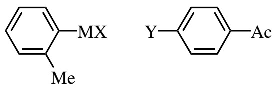
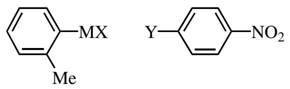
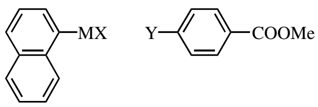
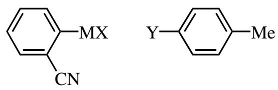
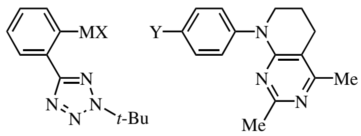
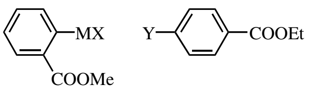
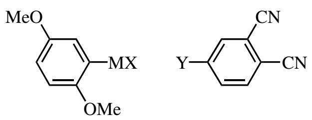
[a]Aryl electrophiles are arranged according to increasing order of priority determined by the Cahn–Ingold–Prelog rule.
[b]IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

C. SYNTHESIS OF BIARYLS CONTAINING ONE OR TWO ORTHO SUBSTITUENTS VIA Pd- OR Ni-CATALYZED ARYL–ARYL COUPLING

Some representative examples of the synthesis of biaryls containing just one ortho substituent are shown in **Table 8**. The product yields are generally in the range of 70–100%, and Mg, Zn, B, and Sn are commonly used. Thus, one ortho substituent does not generally exert significant steric effects detrimental to the desired cross-coupling. Somewhat surprisingly, even those substituents that can chelate metals, such as COOMe[81] and CN,[26] have been successfully employed. All in all, the synthesis of biaryls containing only one ortho substituent appears to be closely analogous to those cases discussed in the preceding subsection.

TABLE 8. Pd- or Ni-Catalyzed Aryl–Aryl Coupling Providing Biaryls Containing One Ortho Substituent[a]

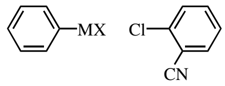
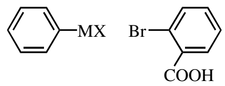
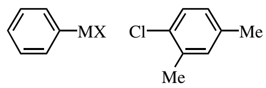
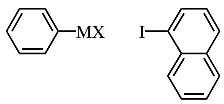
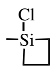
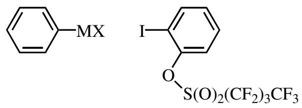
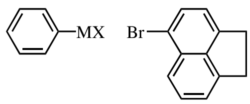
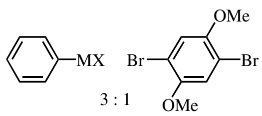
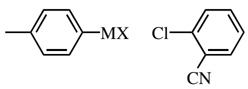
$$\mathrm{ArMX} + \mathrm{Ar'Y} \xrightarrow{\text{Cat.}} \mathrm{Ar{-}Ar'}$$

Entry	Substrates	MX	Y	Catalyst	Yield (%)	Reference
1		MgBr	Cl	Ni(triphos)$ClPF_6$	53	[82]
		MgCl	Cl	Pd(dppf)Cl_2	79	[83]
2		MgBr	Br	Pd(dppb)Cl_2	75	[84]
3		$B(OH)_2$	Br	$Pd(PPh_3)_4/Na_2CO_3$	98	[85]
		$B(OH)_2$	OTf	$Pd(PPh_3)_4$	98	[86]
		$SnMe_3$	OTf	$Pd_2dba_3 \cdot CHCl_3$	93	[87]
4		$B(OH)_2$	Br	Pd_2dba_3	98	[87]
5		ZnCl	Br	$PdCl_2(PPh_3)_2$/DIBAH	70	[9]
6		$B(OH)_2$	I	$Pd(OAc)_2$, K_2CO_3, H_2O	98	[87]
7		ZnBr	Cl	$NiCl_2(PPh_3)_2$	75	[26]
8		ZnCl	Br	$PdCl_2(PPh_3)_2$	78	[88]
9		ZnI	Br	$Pd(PPh_3)_4$	100	[81]
10		$SnMe_3$	I	$Pd_2dba_3 \cdot CHCl_3$	75	[23]

(*Continued*)

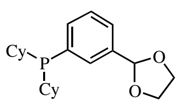
TABLE 8. (*Continued*)

$$\text{ArMX} + \text{Ar}'\text{Y} \xrightarrow{\text{Cat.}} \text{Ar}-\text{Ar}'$$

Entry	Substrates	MX	Y	Catalyst	Yield (%)	Reference
11		ZnCl		Ni(acac)$_2$, dppf	86	[26]
12		Sn(Bu)$_3$		Pd(PPh$_3$)$_4$	95	[47]
13		MgBr		Pd(dba)$_2$ + Ligand[b]	85	[84]
14				TBAF, (allylPdCl)$_2$/(t-Bu)$_3$P	85	[60]
15		ZnBr		Pd(dba)$_2$, tfp[c]	76	[89]
16		MgBr		Ni(acac)$_2$	72	[90]
17		ZnCl		Pd(PPh$_3$)$_4$	76	[89]
18		MgCl		Ni(acac)$_2$, (i-PrO)$_3$P ZnCl$_2$	82	[91]

[a]Aryl electrophiles are arranged according to increasing order of priority determined by the Cahn–Ingold–Prelog rule.

[b]Ligand =

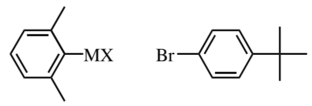
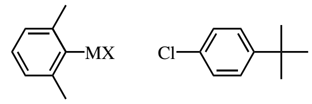
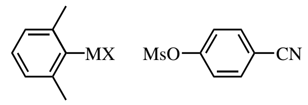
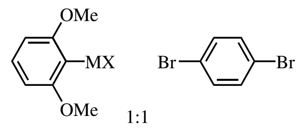
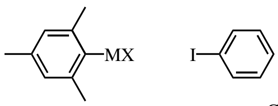
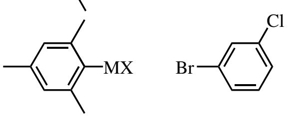
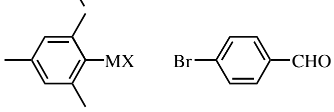
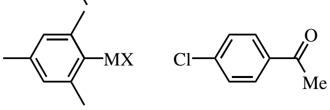
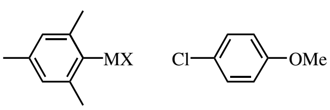


[c]tfp = tris(o-furyl)phosphine.

The Pd- or Ni-catalyzed reaction of 2,6-disubstituted arylmetals or aryl electrophiles appears to represent a point of deviation in that low product yields of <50% have been frequently reported, as indicated by the results shown in **Table 9**. Despite this unmistakable trend, the currently available data on this class of reactions are still limited and seemingly erratic or inconsistent. Consequently, they do not lend themselves to providing a reliable and useful set of generalizations. With the understanding that these cases share some critical features with the synthesis of biaryls containing three or four ortho substituents, it is recommended one consult the following subsection (**Sect. D**) for probing critical factors, such as metal countercations, leaving groups, and catalysts.

TABLE 9. Pd- or Ni-Catalyzed Aryl–Aryl Coupling Providing Biaryls Containing Two Ortho Substituents[a]

$$\text{ArMX} + \text{Ar}'\text{Y} \xrightarrow{\text{Cat.}} \text{Ar–Ar}'$$

Entry	Substrates	MX	Catalyst	Yield (%)	Reference
2,4-Di-					
1		$B(OH)_2$	$Pd(OAc)_2$, K_3PO_4	97	[92]
2		$B(OH)_2$	$NiCl_2(PPh_2Et)_2$/ zinc metal	94	[29]
3		$B(OH)_2$	$NiCl_2$(dppf)	56	[93]
4	 1:1	$B(OH)_2$	$Pd(PPh_3)_4$, Cs_2CO_3	50	[94]
2,4,6-Tri-					
5		$B(OH)_2$	$Pd(PPh_3)_4$	92	[95]
6		MgBr	Ni complex	41	[96]
7		$B(OH)_2$	$Pd(PPh_3)_4$	45	[40]
8		$B(OH)_2$	$NiCl_2$(dppf)	78	[25]
9		MgBr	$Pd_2(dba)_3 \cdot HCl$	95	[27]

(*Continued*)

TABLE 9. **(*Continued*)**

$$\text{ArMX} + \text{Ar}'\text{Y} \xrightarrow{\text{Cat.}} \text{Ar}{-}\text{Ar}'$$

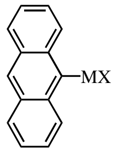
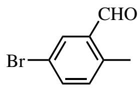
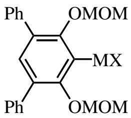
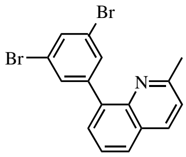
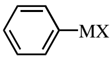
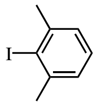
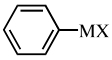
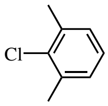
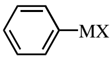
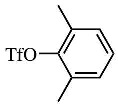
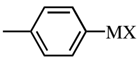
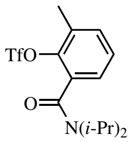
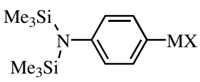
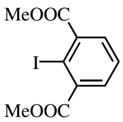
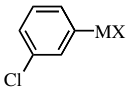
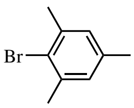
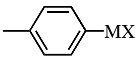
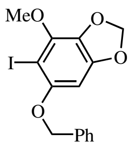
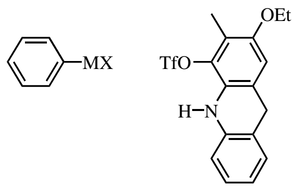
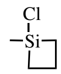
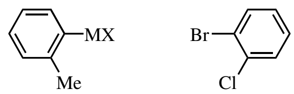
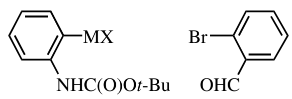
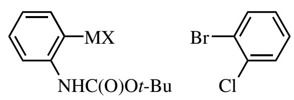
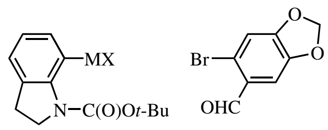
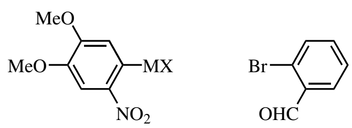
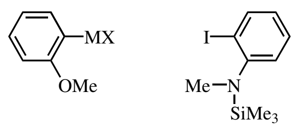
Entry	Substrates		MX	Catalyst	Yield (%)	Reference
2,4,5,6-Tetra-						
10			$SnBu_3$	$Pd(PPh_3)_2Cl_2$	62	[97]
11			ZnCl	$Ni(PPh_3)Cl_2$	49	[98]
12			$B(OH)_2$	$Pd(OAc)_2$, PPh_3	92	[92]
13			MgBr	$Pd_2(dba)_3 \cdot CHCl_3$	87	[27]
14			MgBr	$Cl_2Pd(dppp)$	94	[99]
15			MgBr	Ni(acac)	47	[53]
16			ZnCl	$Ni(PPh_3)_4$	20	[100]
17			$SnBu_3$	$Pd(PPh_3)_4$	58	[38]
18			$B(OH)_2$	$Pd(OAc)_2$, K_2CO_3	100	[101]

TABLE 9. (*Continued*)

$$\text{ArMX} + \text{Ar}'\text{Y} \xrightarrow{\text{Cat.}} \text{Ar–Ar}'$$

Entry	Substrates	MX	Catalyst	Yield (%)	Reference
19		$B(OH)_2$	$Pd(PPh_3)_4$	96	[102]
20			TBAF, $(allylPdCl)_2/(t\text{-}Bu)_3P$	70	[103]
21		MgBr	$NiCl_2$	49	[104]
22		$SnBu_3$	$PdBnCl(PPh_3)_2$	95	[105]
23		$SnBu_3$	$Pd(PPh_3)Cl_2$	74	[106]
24		$SnBu_3$	$Pd(OAc)_2$	63	[107]
25		$SnMe_3$	$Pd(PPh_3)_4$, CuBr	70	[103]
26		MgBr	$Pd(PPh_3)_4$	66	[108]

[a]Aryl electrophiles are arranged according to increasing order of priority determined by the Cahn–Ingold–Prelog rule.

Examples of the synthesis of biaryls containing two aryl groups, each of which contains one ortho substituent, seem to be rather rare. In the synthesis of magnolol and (−)-monoterpenylmagnolol shown in **Scheme 3**,[18] Zn was reported to be more satisfactory than Sn. The latter reaction was reported to be accompanied by double bond migration to significant extents.

D. SYNTHESIS OF BIARYLS CONTAINING THREE OR FOUR ORTHO SUBSTITUENTS

Biaryls containing three or four ortho substituents are discrete from the others in that they can exist as persistent atropisomers that are chiral. There are even a number of natural products containing such chiral biaryl moieties including michellamines A and B [109],[110] and vancomycin.[111] These compounds provide some of the ultimately challenging synthetic tasks. Specifically, two synthetic issues separate them from most of the other biaryls. One is dealing with three or four ortho substituents that exert strong steric hindrance to cross-coupling. Their electronic effects may also be significant in some cases. The other is controlling the absolute and relative stereochemistry of the atropisomers. Some noteworthy progress have been made recently along these lines. In recent synthesis of michellamines A and B,[17] Zn, B, and Sn were compared by using some model compounds. As the results shown in **Scheme 2** indicate, both 1-iodo and 1-bromo derivatives of 2,4,6-tris(methoxy)benzenes are satisfactory cross-coupling partners in the Pd-catalyzed reaction with the 1-naphthylboronic acid derivative, whereas only the iodo derivative is satisfactory in the reaction of the 1-naphthylzinc derivative. Noteworthy is the complete failure observed with the 1-naphthyltin derivative.[17] Although these results represent just one study, the inferior reactivity of Sn as compared with Zn and/or B has been recorded in a growing number of more demanding cases of the Pd-catalyzed cross-coupling reactions, as discussed also in the following dozen or so sections in this part.

As indicated by the results shown in **Tables 10** and **11**, successful syntheses of biaryls containing three or four ortho substituents have indeed been reported by the use of Zn, B, and Mg. Although it is still premature to draw firm conclusions, areneboronic acids appear to lead to at least comparable and possibly even higher yields of the desired biaryls than arylmetals containing Zn or Mg, despite their significantly lower intrinsic reactivity. If true, this might stem from the facts that biaryls generally unassociated with delicate regio- and/or stereochemical issues are thermally stable compounds and that areneboronic acids are much more thermally stable than the corresponding arylmetals containing Zn or Mg. These stability features must permit the formation of sterically hindered biaryls under forcing conditions with minimal complications arising from competitive side reactions including reagent decomposition.

In view of the significance of chiral biaryls, it may be predicted that many additional investigations along this line will be reported in the near future, and they should help provide a more definitive discussion of this topic.

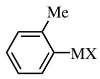
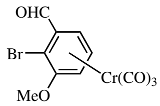
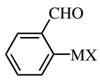
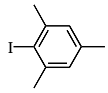
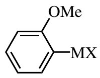
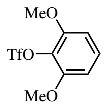
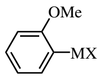
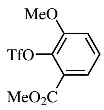
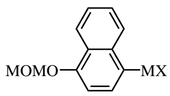
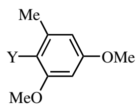
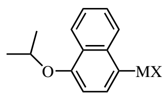
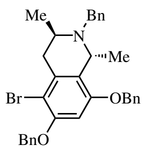
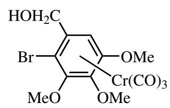
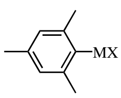
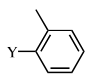
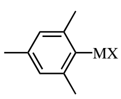
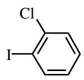
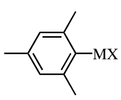
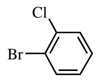
The other important issue of enantioselective synthesis of chiral biaryls is discussed in **Sect. III.2.16**, and it is therefore not duplicated here.

E. SYNTHETIC APPLICATIONS OF THE Pd- OR Ni-CATALYZED ARYL–ARYL COUPLING

Synthesis of biaryls via Pd- or Ni-catalyzed aryl–aryl coupling has found many attractive applications in the synthesis of oligo- and polyaryls and natural products containing biaryls. The former topic is discussed in **Sect. III.2.17.2**, and the latter is further supplemented in **Table 1** of **Sect. III.2.18**.

TABLE 10. Pd- or Ni-Catalyzed Aryl–Aryl Coupling Providing Biaryls Containing Three Ortho Substituents

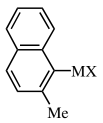
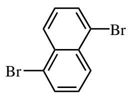
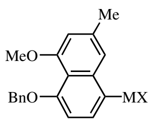
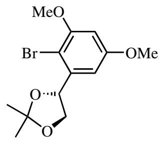
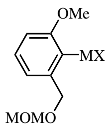
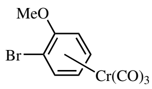
$$\text{ArMX} + \text{Ar}'\text{Y} \xrightarrow{\text{Cat.}} \text{Ar–Ar}'$$

Entry	Substrates	MX	Catalyst	Yield (%)	Reference
1	 	$B(OH)_2$ $B(OH)_2$	$Pd(PPh_3)_4$ $Pd(PPh_3)_4$	82 80	[112] [113]
2	 	$B(OH)_2$	$Pd(PPh_3)_4$	73	[114]
3	 	$B(OH)_2$	$Pd(PPh_3)_2Cl_2$	74	[115]
4	 	$B(OH)_2$	$Pd(PPh_3)_2Cl_2$	0	[116]
5	 	ZnCl Y = I $B(OH)_2$ Y = I $SnBu_3$ Y = I ZnCl Y = Br $B(OH)_2$ Y = Br $SnBu_3$ Y = Br	$Pd(PPh_3)_4$ $Pd(PPh_3)_4$ $Pd(PPh_3)_4$ $Pd(PPh_3)_4$ $Pd(PPh_3)_4$ $Pd(PPh_3)_4$	50 79 0 16 56 0	[17] [17] [17] [17] [17] [17]
6	 	$SnBu_3$ $SnBu_3$	$Cl_2Pd(PPh_3)_2$ $Cl_2Pd(PPh_3)_2$	15 21	[117] [118]
7	 	$B(OH)_2$	$Pd(PPh_3)_4$	67	[119]
8	 	ZnCl Y = I $B(OH)_2$ Y = Br $B(OH)_2$ Y = Cl	$Ni(PPh_3)_4$ $Pd_2(dba)_3$, P(*t*-Bu)$_3$ $Pd_2(dba)_3$, P(*t*-Bu)$_3$	93 97 93	[11] [87] [87]
9	 	$B(OH)_2$	$Pd(PPh_3)_4$, $Ba(OH)_2$	94	[114]
10	 	$B(OH)_2$	$Pd(PPh_3)_4$, $Ba(OH)_2$	56	[114]

(*Continued*)

TABLE 10. (*Continued*)

$$\text{ArMX} + \text{Ar}'\text{Y} \xrightarrow{\text{Cat.}} \text{Ar–Ar}'$$

Entry	Substrates		MX	Catalyst	Yield (%)	Reference
11			MgBr	$NiBr_2$, (*S*)-PPFOMe[b]	89	[120]
12			$B(OH)_2$	$Pd(PPh_3)_4$	90	[121]
13			$B(OH)_2$	$Pd(PPh_3)_4$	86	[122]

[a]Aryl electrophiles are arranged according to increasing order of priority determined by the Cahn–Ingold–Prelog rule.
[b]PPFOMe =

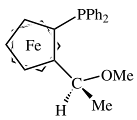


TABLE 11. Pd- or Ni-Catalyzed Aryl–Aryl Coupling Providing Biaryls Containing Four Ortho Substituents

$$\text{ArMX} + \text{Ar}'\text{Y} \xrightarrow{\text{Cat.}} \text{Ar–Ar}'$$

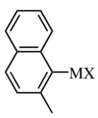
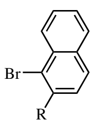
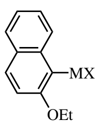
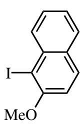
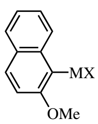
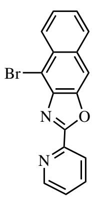
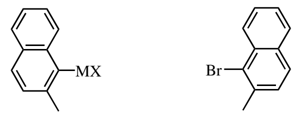
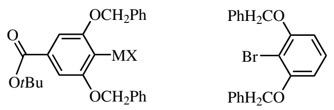
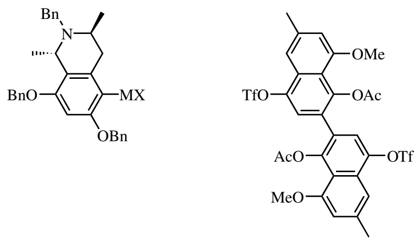
Entry	Substrates		MX	Catalyst	Yield (%)	Reference
1		 R = H, Me, OMe	MgBr	$Ni(PPh_3)Cl_2$	55–79	[123]
2			ZnCl	$Ni(PPh_3)Cl_2$	36	[124]
			ZnCl	$(CH_3CN)_2PdCl_2$	35	[124]
			$B(OH)_2$	$Pd(PPh_3)_4$	39	[124]
3			$B(OH)_2$	$Pd(PPh_3)_4$, Na_2CO_3	73	[125]

TABLE 11. (*Continued*)

ArMX + Ar′Y $\xrightarrow{\text{Cat.}}$ Ar–Ar′

Entry	Substrates	MX	Catalyst	Yield (%)	Reference
4		MgBr MgBr	Pd(acac)$_2$ $NiBr_2$, dppf	50 77	[126] [127]
5		$B(OH)_2$	$Pd(PPh_3)_4$, Na_2CO_3	12	[128]
6		$B(OH)_2$	$Pd(PPh_3)_4$, $Ba(OH)_2$	74	[129]

[a]Aryl electrophiles are arranged according to increasing order of priority determined by the Cahn–Ingold–Prelog rule.

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