$$R^1M + R^2X \xrightarrow{Pd} \text{Natl. Prod.}$$

III.2.18 Synthesis of Natural Products via Palladium-Catalyzed Cross-Coupling

ZE TAN and EI-ICHI NEGISHI

A. INTRODUCTION

Since the discovery of Pd-catalyzed cross-coupling in the mid-1970s, it has been increasingly applied to the synthesis of essentially all types of organic compounds. Together with more conventional cross-coupling methodologies involving the use of Mg, Li, and Cu, Pd-catalyzed cross-coupling reactions and related Ni-catalyzed reactions have firmly occupied one of the most central positions in the organic synthetic methodology. Especially noteworthy are their applications in the area of complex natural products as well as oligomeric and polymeric materials. Many of their applications to the syntheses of natural products are indeed discussed throughout the preceding sections in this part, mainly from the viewpoint of synthetic methodology.

In recognition of the special significance and high level of interest among synthetic chemists, their applications to the synthesis of natural products are systematically catalogued in this section primarily in the form of a series of tables, which are arranged in the order of some of the preceding and pertinent sections, as listed below. Even in those cases where some specific examples are discussed in preceding sections, they are listed again in this section for the purpose of cataloguing all examples of natural products synthesis via Pd-catalyzed cross-coupling.

Subsection	Type of Cross-Coupling	Table Number	Pertinent Section Number
B	Aryl–aryl coupling	1	**III.2.5**
C	Alkenyl–aryl, aryl–alkenyl, and alkenyl–alkenyl couplings	2, 3	**III.2.6**

(*Continued*)

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D	Heteroaromatics	4	**III.2.7**
E	Alkyne synthesis	5, 6	**III.2.8**
F	Synthesis of diarylmethanes, allylated and propargylated arenes, and 1,4-dienes and 1,4-enynes	7	**III.2.9**
G	Alkylation, homoallylation, homopropargylation, and homobenzylation	8	**III.2.11**
H	Cross-coupling involving α-hetero-substituted organic electrophiles	9	**III.2.12**
I	Cross-coupling involving α-hetero-substituted organometals	10	**III.2.13**
J	Cross-coupling involving β-hetero-substituted compounds	11	**III.2.14**
K	Conjugate substitution	12	**III.2.15**

B. SYNTHESIS OF NATURAL PRODUCTS VIA Pd-CATALYZED ARYL–ARYL COUPLING

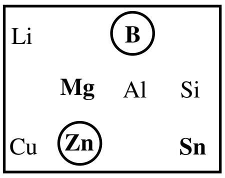
Pd- or Ni-catalyzed aryl–aryl coupling has emerged over the past two to three decades as one of the most general and satisfactory methods for the synthesis of biaryls. Various fundamental and synthetic aspects of Pd-catalyzed aryl–aryl coupling are discussed in **Sect. III.2.5**, and some detailed aspects of the synthesis of magnolol and (−)-monoterpenylmagnolol along with that of steganone via Ni-catalyzed aryl–aryl coupling are also presented in the same section.

The following rational procedure for finding the optimal protocol for a given biaryl synthesis with respect to metal countercations and catalysts is once again presented below as a reminder.

1. In cases where arylmagnesium derivatives are more conveniently available than the others, as is often the case, their Ni- or Pd-catalyzed reaction with aryl halides and related electrophiles should be considered first. It should also be reminded that, in aryl–aryl coupling, Ni catalysts are often satisfactory and competitive with Pd catalysts.

2. If the Mg–Ni and Mg–Pd combinations prove to be less than satisfactory, the simplest and generally most dependable modification has been to add 0.5–1 equiv of dry $ZnCl_2$ or $ZnBr_2$. The Zn–Ni and Zn–Pd combinations have often been two of the most satisfactory ones in terms of (i) fast reaction rate, (ii) high product yield, and (iii) selectivity features including chemoselectivity.

3. Although several other metals including Al, Si, Sn, and Cu have served as satisfactory countercations in less demanding cases, the B–Pd combination appears to be currently the only one that rivals or possibly even surpasses the Zn–Ni and Zn–Pd combinations, even though the preparation of arylboron derivatives via aryllithiums or arylmagnesium halides is more involved than the *in situ* generation of arylzincs. Although aryltins have been widely used and satisfactory in less demanding cases, they have been shown to be inferior to Zn and B in more demanding cases. So, the current scope of Pd- or Ni-catalyzed aryl–aryl coupling with respect to metal cations may be represented by **Scheme 1**.



- The metals in bold are widely used in the Pd-catalyzed Ar-Ar coupling in general,
- Those in a circle are generally most satisfactory.

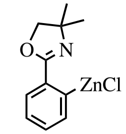
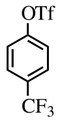
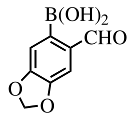
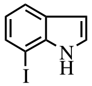
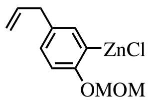
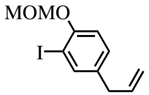
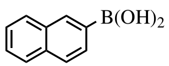
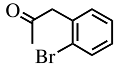
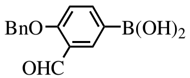
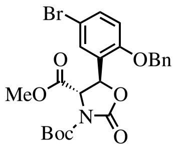
Scheme 1

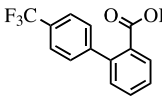
The examples summarized in **Table 1** represent most of the currently known syntheses of natural products involving Pd-catalyzed aryl–aryl coupling, which clearly indicate that Zn and B are indeed the two most frequently used metals.

C. SYNTHESIS OF NATURAL PRODUCTS VIA Pd-CATALYZED ALKENYL–ARYL, ARYL–ALKENYL, AND ALKENYL–ALKENYL COUPLING

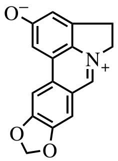
As detailed in **Sect. III.2.6**, Pd-catalyzed alkenyl–alkenyl coupling is probably the most general, selective, and satisfactory route to conjugated dienes of various types. Similarly, Pd-catalyzed alkenyl–aryl or aryl–alkenyl coupling provides a highly satisfactory route to arylated alkenes, although these compounds are often readily accessible via a wide range of more conventional reactions including carbonyl olefinations.

TABLE 1. Aryl–Aryl Coupling (cf. Sect. III.2.5)

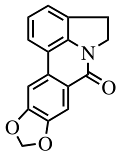
C_n	Name	ArM	ArX	Catalyst	Additive	Yield (%)	Reference
14	xenalepin			$Pd(PPh_3)_4$		78	[1]
16	ungerimine hippadine			$Pd(PPh_3)_4$	Na_2CO_3	40–49	[2]
18	magnolol			$Cl_2Pd(PPh_3)_2$	DIBAH	68	[3]
19	5-methylchrysene			$Pd(PPh_3)_4$	CsF	55–60	[4]
23	biphenomycin A			$Pd(PPh_3)_4$	Na_2CO_3	50	[5]



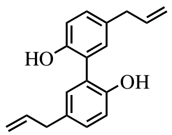
xenalepin



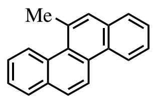
ungerimine



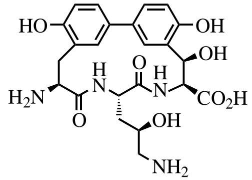
hippadine



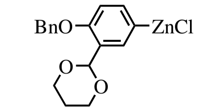
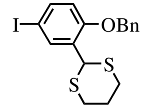
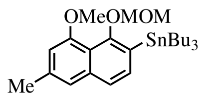
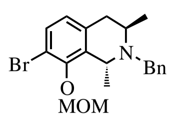
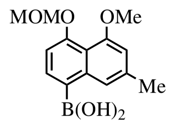
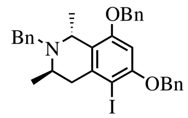
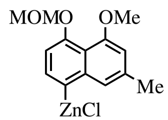
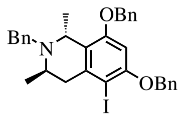
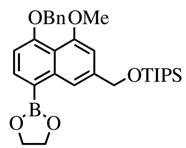
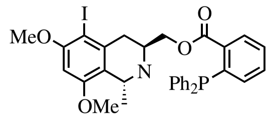
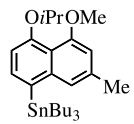
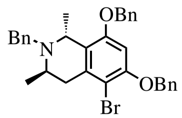
magnolol



5-methylchrysene

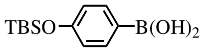
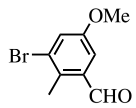
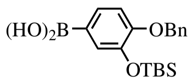
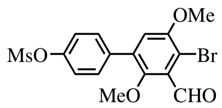
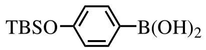
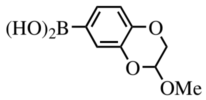
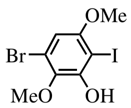
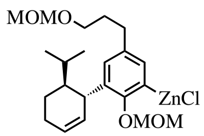
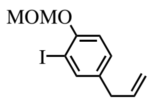


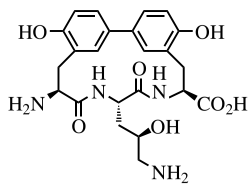
biphenomycin A

23	biphenomycin B (cf. below)			$Cl_2Pd(PPh_3)_2$	DIBAH	79	[6]
23	dioncophylline (cf. below)			$Cl_2Pd(PPh_3)_2$	LiCl CuBr BHT	31	[7]
23	korupensamine A korupensamine B (cf. [8])			$Pd(PPh_3)_4$	$NaHCO_3$	65–85	[8]
				$Pd(PPh_3)_4$		53	[8]
23	korupensamine A (cf. [9])			Cl$_2$Pd(dppf)	K_3PO_4 BHT	81	[9]
23	korupensamine A korupensamine B (cf. [10])			$Cl_2Pd(PPh_3)_2$	PPh_3 LiCl CuBr	15	[10] [11]

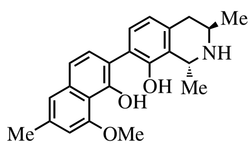
(*Continued*)

TABLE 1. (*Continued*)

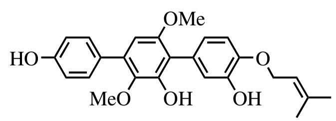
C_n	Name	ArM	ArX	Catalyst	Additive	Yield (%)	Reference
25	terprenin			$Pd(PPh_3)_4$	Na_2CO_3	100	[12]
				$Pd(PPh_3)_4$	Na_2CO_3	68	[12]
		 		$Pd_2(dba)_3$ $Pd(PPh_3)_4$	Na_2CO_3	70	[12]
28	(–)-monoterpenyl magnolol			$Cl_2Pd(PPh_3)_2$	DIBAH	37	[3]



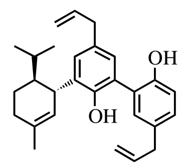
biphenomycin B



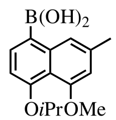
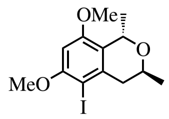
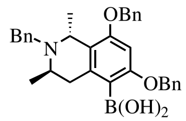
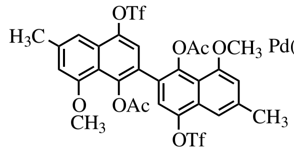
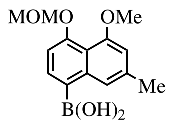
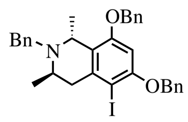
dioncophylline

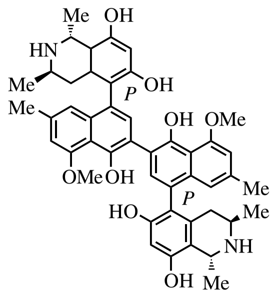


terprenin

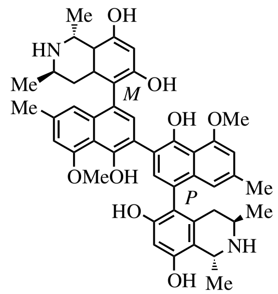


(–)-monoterpenyl-magnolol

46	michellamines			$Pd(PPh_3)_4$	K_3PO_4	85	[13]
46	michellamine A michellamine B			$Pd(PPh_3)_4$	$Ba(OH)_2$	74	[14]
46	michellamine A michellamine B			$Pd(PPh_3)_4$	$NaHCO_3$	40–53	[15]



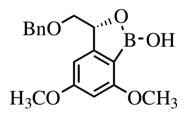
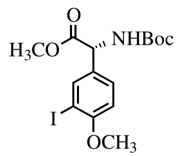
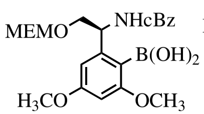
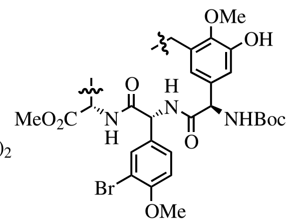
michellamine A



michellamine B

(*Continued*)

TABLE 1. (*Continued*)

C_n	Name	ArM	ArX	Catalyst	Additive	Yield (%)	Reference
53	vancomycin aglycon (cf. [19])			$Pd(PPh_3)_4$	Na_2CO_3	84	[16]–[19]
53	vancomycin aglycon (cf. [19])	same as above					[20]–[23]
53	vancomycin aglycon (cf. [24])			$Pd_2(dba)_3$	$(o\text{-tolyl})_3P$ Na_2CO_3	88	[24]

At present, Mg, Zn, B, Al, Sn, and Zr represent the six widely used metals, although Cu and Si have also been shown to be very promising. In more demanding cases where some of the above-mentioned metals are compared, Zn has often been shown to be superior to the others in terms of reactivity, product yield, and stereoselectivity. However, the ability of B, Al, and Zr as well as Zn to participate in facile and stereoselective hydrometallation and carbometallation makes B, Al, and Zr viable and attractive alternatives to Zn. It should also be recalled that the Pd-catalyzed coupling reactions of alkenylalanes and alkenylzirconiums can often be significantly accelerated by the addition of Zn salts (**Sect. III.2.6**).

Although alkenylstannanes are often somewhat less readily available than those containing B, Al, or Zr, they have nonetheless been very widely used. In fact, they may have been the most widely used alkenylmetals. However, some of the critical issues associated with them, such as their general toxicity, difficulty in the complete removal of toxic tin-containing by-products, and their lower and often inferior reactivity in more demanding cases relative to Zn and B (**Sect. III.2.6**), must not be overlooked. Despite these critical shortcomings, Pd-catalyzed alkenyl–alkenyl coupling using alkenylstannanes has widely been employed, especially in the synthesis of an impressive array of complex natural products including (±)-amijtrienol,[25] leinamycin,[26] (±)-8,15-diisocyano-11(20)-amphilectene,[27],[28] (+)-macrolactin E,[29] (−)-macrolactin A,[29],[30] (+)-mycotrienol,[31] rapamycin,[32]–[35] and saglifehrin A.[36] As satisfactory as the results reported in these syntheses are, data comparing various available metal countercations are very scarce at best. In view of the above-mentioned problems and difficulties associated with Sn, its comparison with some others, such as Zn, B, Al, Zr, and even Si, appears to be desirable.

Some detailed aspects of the syntheses of the following compounds are presented in **Sect. III.2.6**. The scheme numbers indicated in parentheses are those in **Sect. III.2.6**: methyl dimorphecolate (**Scheme 46**), xerulin (**Scheme 48**), papulacandin D (**Scheme 49**), vitamin A (**Scheme 60**), β- and γ-carotene (**Schemes 61** and **62**), vitamin D (**Scheme 65**), reveromycin B (**Scheme 67**), and nakienone A (**Scheme 70**). In this section, attempts have been made to catalogue most of the currently known examples of the synthesis of natural products via Pd-catalyzed alkenyl–aryl or aryl–alkenyl coupling (**Table 2**) and alkenyl–alkenyl coupling (**Table 3**).

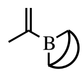
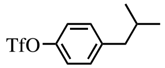
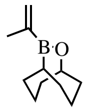
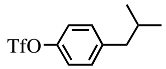
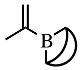
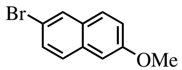
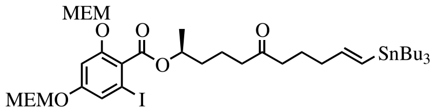
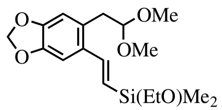
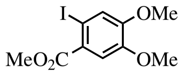
D. SYNTHESIS OF HETEROAROMATIC NATURAL PRODUCTS VIA Pd-CATALYZED CROSS-COUPLING

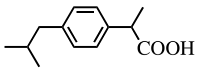
The construction of heteroaromatic compounds via Pd-catalyzed cross-coupling reactions is discussed in detail in **Sect. III.2.7**. Among all of the available methods, the use of Pd–Zn and Pd–B cross-coupling in the synthesis of natural products is particularly noteworthy. Some of the representative examples of natural product syntheses are shown in **Table 4**.

E. SYNTHESIS OF NATURAL PRODUCTS VIA Pd-CATALYZED ALKYNYLATION

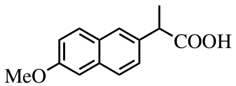
Pd-catalyzed alkyne cross-coupling has become one of the most satisfactory methods for the synthesis of alkynes. As discussed in **Sect. III.2.8**, there are two related but discrete protocols, that is, Sonogashira coupling, which does not involve formation of alkynylmetals as preformed and discrete reagents (**Sect. III.2.8.1**), and the general

TABLE 2. Aryl–Alkenyl and Alkenyl–Aryl Cross-Coupling (cf. Sect. III.2.6)

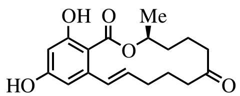
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
13	ibuprofen			$Pd(PPh_3)_4$	K_3PO_4	68	[37]
				$Pd(PPh_3)_4$	K_3PO_4	73	[37]
14	naproxen			$Pd(PPh_3)_4$	K_3PO_4	75	[37]
18	(*S*)-zearalenone			polymer-$Pd(PPh_3)_4$		54	[38]
21	nitidine			$((allyl)PdCl)_2$	$P(OEt)_3$ Bu_4NF	76	[39]



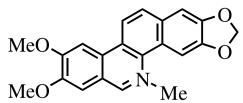
ibuprofen



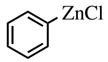
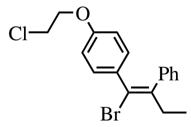
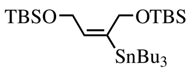
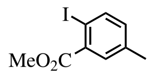
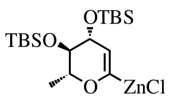
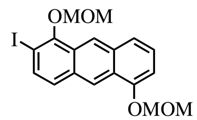
naproxen

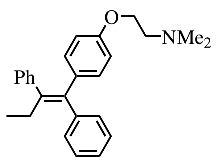


(*S*)-zearalenone

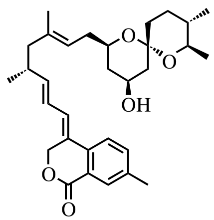


nitidine

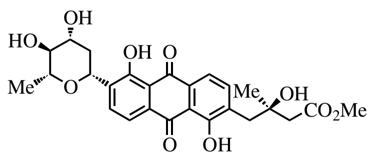
26	(*Z*)-tamoxifen			$Pd(PPh_3)_4$		99	[40]
31	lacrimin A			$Cl_2Pd(PPh_3)_2$	$ZnCl_2$ LiCl	43	[41]
26	vineomycinone B2 methyl ester			$Cl_2Pd(PPh_3)_2$	DIBAH	75	[42],[43]



(*Z*)-tamoxifen

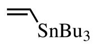
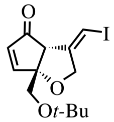
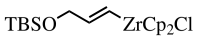
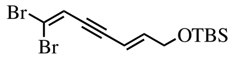
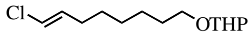
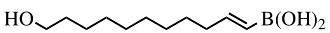
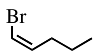


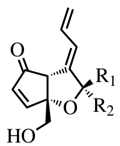
lacrimin A



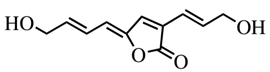
vineomycinone B2 methyl ester

TABLE 3. Alkenyl–Alkenyl Cross-Coupling (cf. Sect. III.2.6)

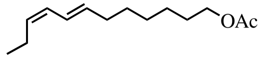
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
11	didemnenones A and B			$Cl_2Pd(PPh_3)_2$		68	[44],[45]
11	lissoclinolide			$Cl_2Pd(PPh_3)_2$	DIBAH	91	[46]
14	(7*E*,9*Z*)-dodecadien-1-yl acetate			$Pd(PPh_3)_4$		96	[47]
16	bombykol			$Pd(PPh_3)_4$	NaOEt	82	[48]



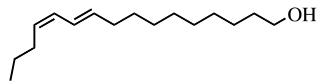
R_1 = H, R_2 = OH **didemnenone A**
R_1 = OH, R_2 = H **didemnenone B**



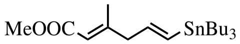
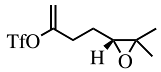
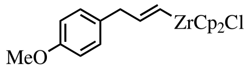
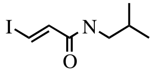
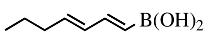
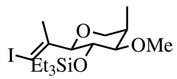
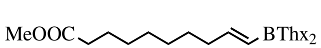
lissoclinolide

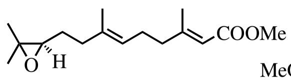


(7*E*,9*Z*)-dodecadien-1-yl acetate

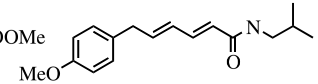


bombykol

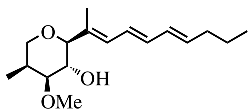
16	C_{16}-cecropia juvenile hormone			$Pd(PPh_3)_4$	CsF	58	[49]
17	piperovatine			Pd(0)		40	[50]
17	restrictinol			$Pd(PPh_3)_4$	TlOH	73	[51]
18	coriolic acid			$Cl_2Pd(PPh_3)_2$	NaOH	54	[52]



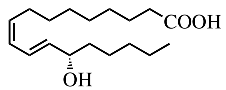
C_{16}-cecropia-juvenile hormone



piperovatine



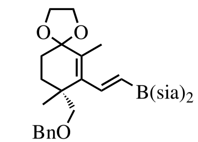
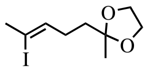
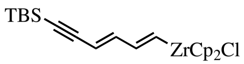
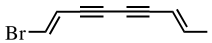
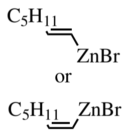
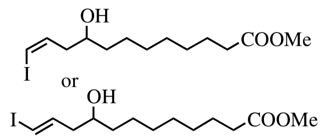
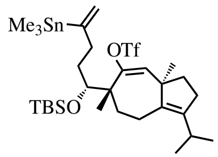
restrictinol

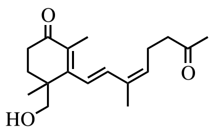


coriolic acid

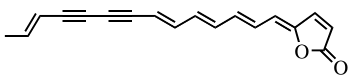
(*Continued*)

TABLE 3. (*Continued*)

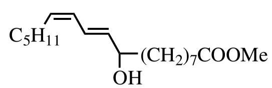
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
18	(±)-trispord B			$Pd(PPh_3)_4$	NaOEt	52	[53]
18	xerulin			$Cl_2Pd(PPh_3)_2$	DIBAH $ZnCl_2$	95	[54]
19	methyl dimorphecolate			$Pd(PPh_3)_4$		88–95	[55]
20	(±)-amijitrienol			$Pd(PPh_3)_4$	Et_3N	75	[25]



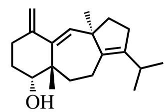
(±)-trispord B



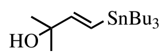
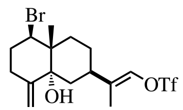
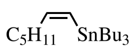
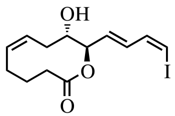
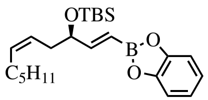
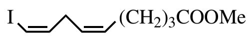
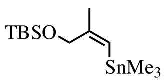
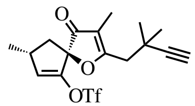
xerulin

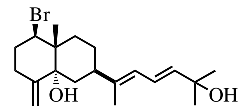


methyl dimorphecolate

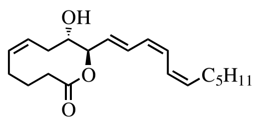


(±)-amijitrienol

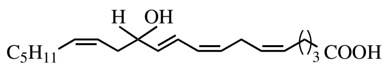
20	(±)-aplysiadiol			$Pd(PPh_3)_4$	CsF LiCl	31	[56]
20	ascidiatrienolide			$Cl_2Pd(CH_3CN)_2$	DMF	72	[57]
20	(12*R*)-HETE			$Pd(PPh_3)_4$	TlOH	55	[58]
20	(+)-jatraphone			$Pd(PPh_3)_4$	100		[59]



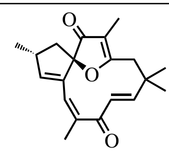
(±)-aplysiadiol



ascidiatrienolide



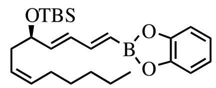
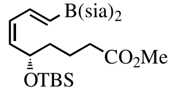
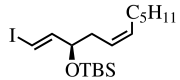
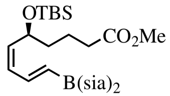
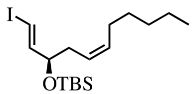
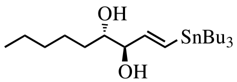
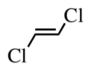
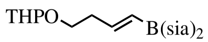
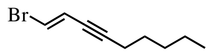
(12*R*)-HETE

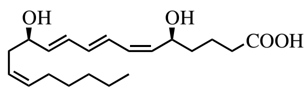


(+)-jatraphone

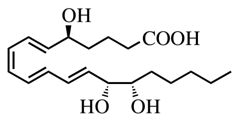
(*Continued*)

TABLE 3. (*Continued*)

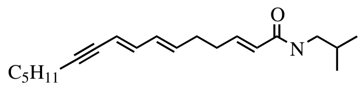
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
20	leukotriene B_4			$Pd(PPh_3)_4$	TlOH	62	[68]
				$Pd(PPh_3)_4$	LiOH	68–76	[69]
20	leukotriene B_4			$Pd(PPh_3)_4$	NaOH	70	[60]
20	lipoxin B			$Pd(PPh_3)_4$		61	[61]
20	(2*E*,6*E*,8*E*)-*N*-(2-methyl-propyl)-2,6,8-hexadecatrien-10-ynamide			$Pd(PPh_3)_4$	NaOH	23	[62]



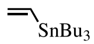
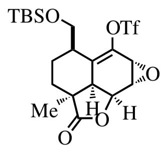
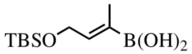
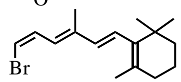
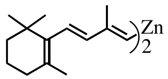
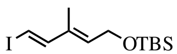
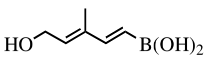
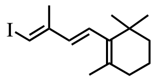
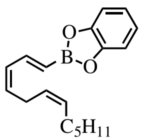
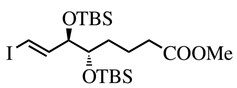
leukotriene B_4

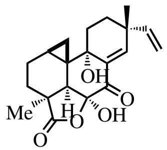


lipoxin B

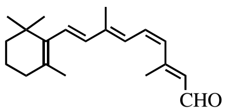


(2*E*,6*E*,8*E*)-*N*-(2-methyl-propyl)-2,6,8-hexadecatrien-10-ynamide

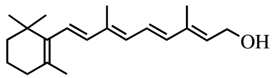
20	(±)-myrocin C			$Cl_2Pd(PPh_3)_2$	LiCl	54	[63]
20	(11*Z*)-retinal			$Pd(PPh_3)_4$	KOH Ag_2CO_3	86	[64]
20	vitamin A			$Pd(PPh_3)_4$		87	[65]
				$Pd(PPh_3)_4$	TlOH	83	[66]
20	(5*S*,6*R*)-DiHETE			$Pd(PPh_3)_4$	TlOH	70	[67]



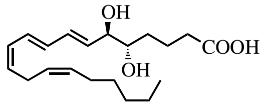
(±)-myrocin C



(11*Z*)-retinal



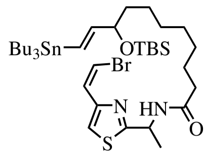
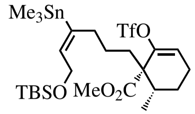
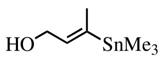
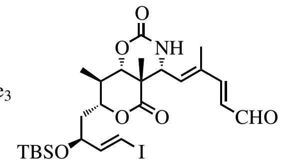
vitamin A

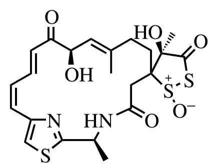


(5*S*,6*R*)-DiHETE

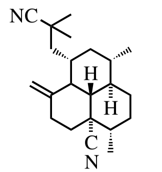
(*Continued*)

TABLE 3. (*Continued*)

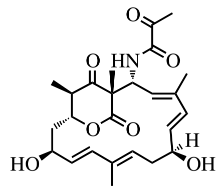
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
22	leinamycin			$Pd(PPh_3)_4$		65	[26]
22	(±)-8,15-diisocyano-11(20)-amphilectene			$Pd(PPh_3)_4$		86	[27],[28]
25	lankacidin C			$Cl_2Pd(CH_3CN)_2$		90	[70]



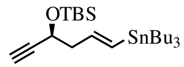
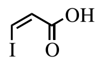
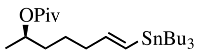
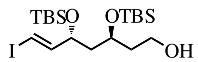
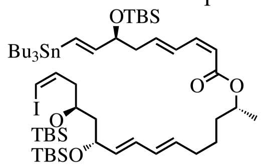
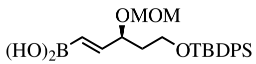
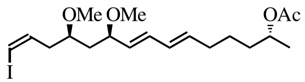
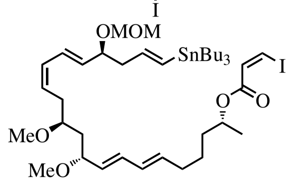
leinamycin

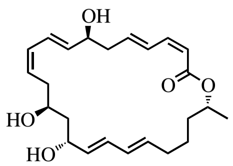


(±)-8,15-diisocyano-11(20)-amphilectene

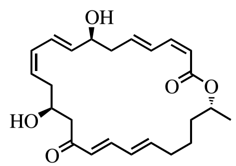


lankacidin C

24	(−)-macrolactin A			$Cl_2Pd(CH_3CN)_2$	$Ph_2PO_2NBu_4$	64	[29]
	(+)-macrolactin E			$Cl_2Pd(CH_3CN)_2$	$Ph_2PO_2NBu_4$	82	[29]
				$Pd_2(dba)_3$	NMP DIPEA	42	[29]
24	macrolactin A			$Pd(OAc)_2$	PPh_3 TlOH	78	[30]
				Pd(0)	$AsPh_3$	58	[30]



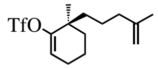
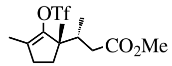
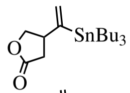
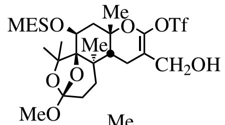
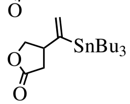
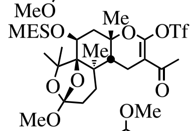
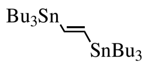
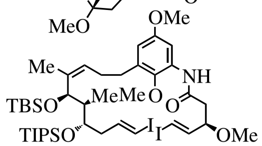
(−)-macrolactin A

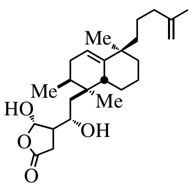


(+)-macrolactin E

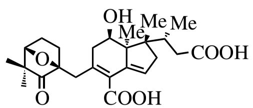
(*Continued*)

TABLE 3. (*Continued*)

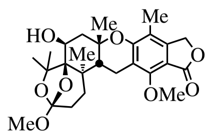
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
25	dysidiolide			$Pd(PPh_3)_4$	LiCl	80	[71]
25	glycinoclepin A			$Pd(PPh_3)_4$	LiCl	87	[72]
26	(−)-austalide B			$Pd_2(dba)_3$	TFP LiCl	71	[73]
26	(−)-austalide B			$Pd_2(dba)_3$	TFP LiCl	71	[74]
26	(+)-mycotrienol			$Cl_2Pd(CH_3CN)_2$		54	[31]



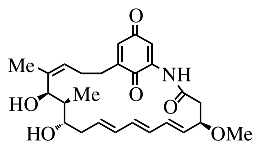
dysidiolide



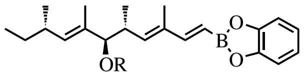
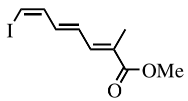
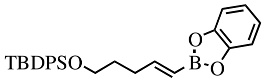
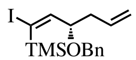
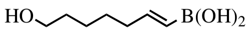
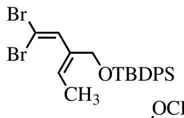
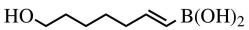
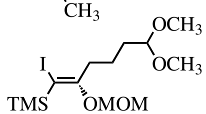
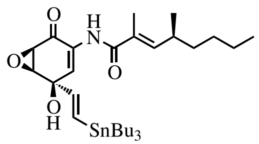
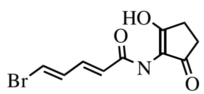
glycinoclepin A

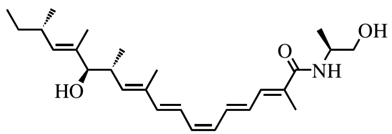


(−)-austalide B

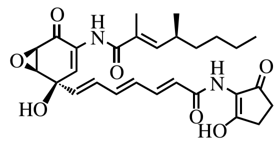


(+)-mycotrienol

26	myxalamide A			$Pd(OAc)_2$	TPPTS *i*-Pr_2NH	44	[75]
28	(−)-chlorothricolide (cf. [77])			$Pd(PPh_3)_4$	TlOH	74	[76],[77]
28	(−)-chlorothricolide (cf. [78])			$Pd(PPh_3)_4$	TlOH	72	[78]
28	(−)-chlorothricolide (cf. [79])			$Pd(PPh_3)_4$	TlOH	86	[79],[80]
28	(−)-manumycin B			$Cl_2Pd(PPh_3)_2$	DIBAH	71	[81]



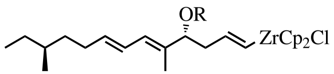
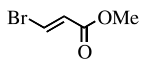
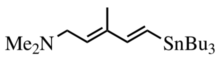
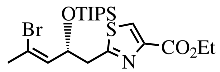
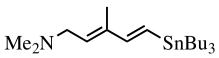
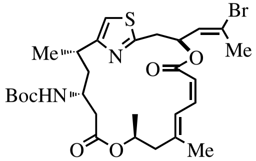
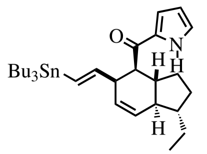
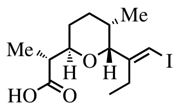
myxalamide A

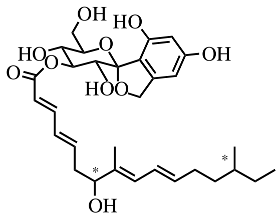


(−)-manumycin B

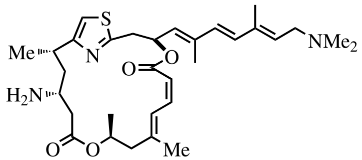
(*Continued*)

TABLE 3. (*Continued*)

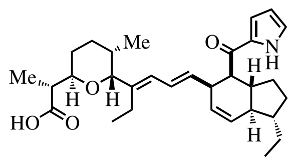
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
31	papulacandin D			$Cl_2Pd(PPh_3)_2$	DIBAH	82	[82],[83]
31	(−)-pateamine A			$Pd_2(dba)_3$	TFP	46 69	[84]
31	(−)-pateamine A			$Pd_2(dba)_3{\cdot}CHCl_3$	$AsPh_3$	27 57	[85],[86]
31	indanomycin			$Pd(PPh_3)_4$		61	[87]



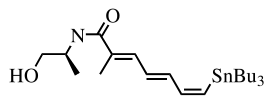
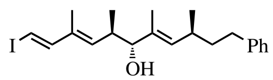
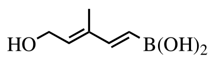
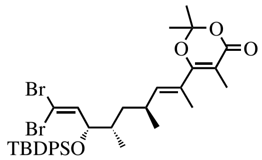
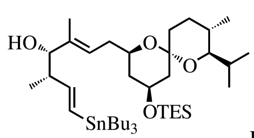
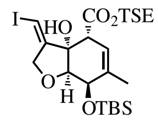
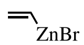
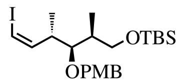
papulacandin D

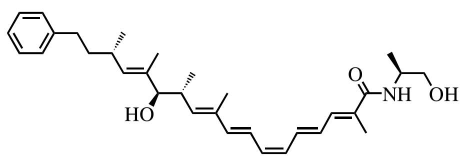


(−)-pateamine A

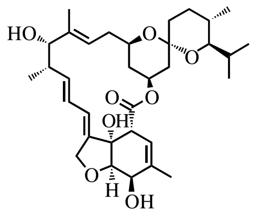


indanomycin

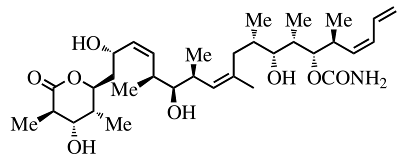
32	stipiamide			$PdCl_2(CH_3CN)_2$	NMP	78	[89],[90]
33	kijanolide (cf. [88])			$Pd(PPh_3)_4$	TlOH	77–86	[88]
33	22,23-dihydroavermectin B_{1b} aglycon			$Cl_2Pd(CH_3CN)_2$	DMF	40	[91]
33	discodermolides			$Pd(PPh_3)_4$		NA	[92]



stipiamide



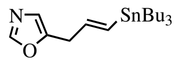
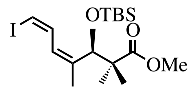
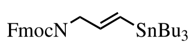
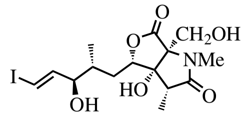
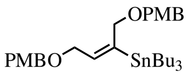
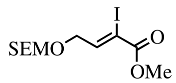
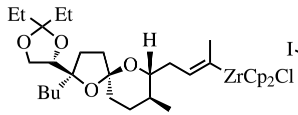
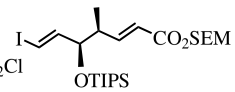
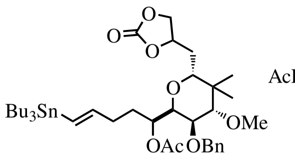
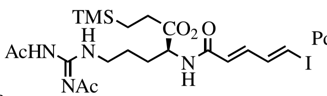
22,23-dihydroavermectin B_{1b} aglycon

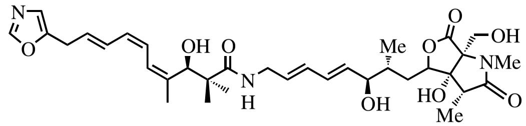


discodermolides

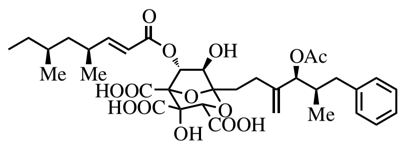
(*Continued*)

TABLE 3. (*Continued*)

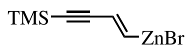
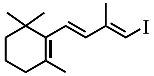
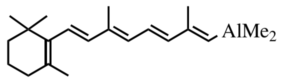
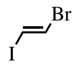
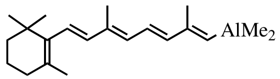
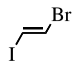
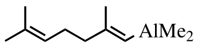
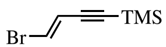
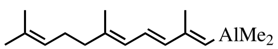
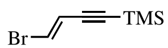
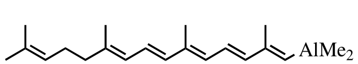
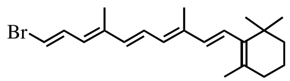
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
34	neooxazolomycin			$PdCl_2(CH_3CN)_2$	DMF	79	[93]
				$PdCl_2(CH_3CN)_2$		84	[93]
35	(+)-zaragozic acid A			$Cl_2Pd(CH_3CN)_2$		70	[94]–[97]
36	reveromycin B (cf. below)			$Pd(PPh_3)_4$	$ZnCl_2$	84	[98]
38	onnamide A (cf. below)			$Pd(PPh_3)_4$		51	[99]

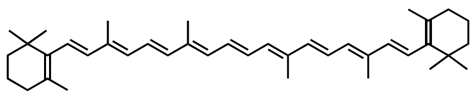


neooxazolomycin

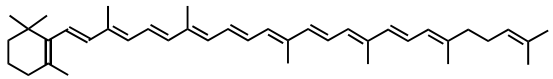


(+)-zaragozic acid A

40	β-carotene			$Pd_2(dba)_3$	TFP $ZnBr_2$	100	[100]
				$Cl_2Pd(PPh_3)_2$	DIBAH $ZnBr_2$	68	[100]
40	γ-carotene			$Pd(PPh_3)_4$	$ZnBr_2$	85	[100]
				$Pd_2(dba)_3$	TFP $ZnBr_2$	82	[100]
				$Pd_2(dba)_3$	TFP $ZnBr_2$	74	[100]
				$Pd_2(dba)_3$	TFP $ZnBr_2$	53	[100]



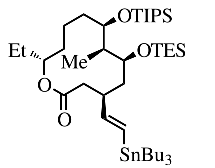
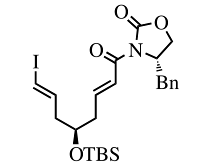
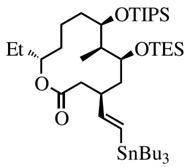
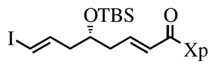
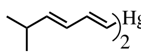
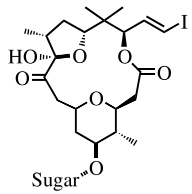
β-carotene

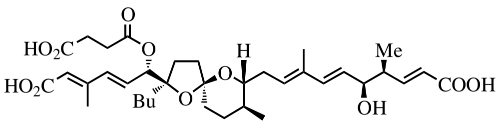


γ-carotene

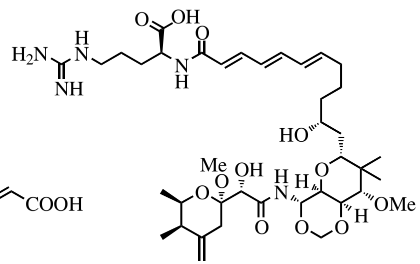
(*Continued*)

TABLE 3. (*Continued*)

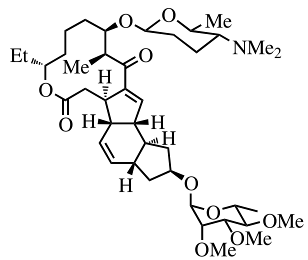
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
41	(+)-lepicidin A			$Pd_2(dba)_3 \cdot CHCl_3$	DIPEA NMP	69	[101]
41	macrolide (+)-A83543A (lepicidin) aglycon			$Pd_2(dba)_3 \cdot CHCl_3$	NMP DIPEA	65	[102]
43	polycavernoside (cf. below)			$Pd(PPh_3)_4$		75	[103]



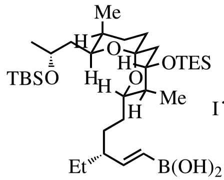
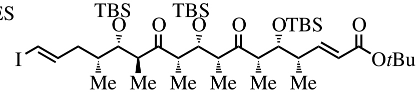
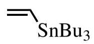
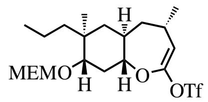
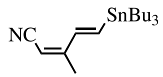
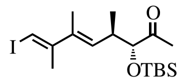
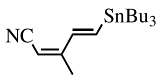
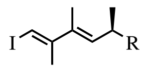
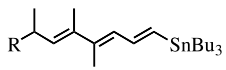
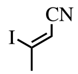
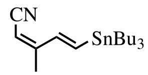
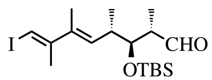
reveromycin B



onnamide A

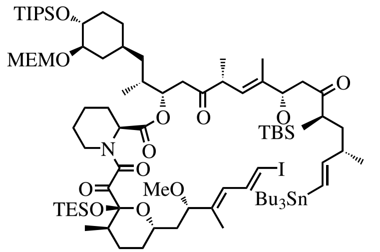
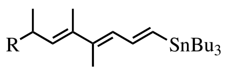
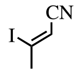


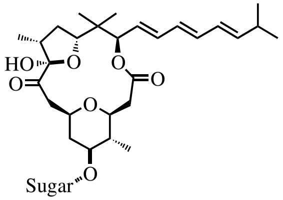
(+)-lepicidin A

44	rutamycin B			$Pd(PPh_3)_4$	75	[104]
49	brevetoxin A (cf. [105])			$Pd(PPh_3)_4$ LiCl	82	[105]–[109]
50	calyculins (cf. below)			$PdCl_2(CH_3CN)_2$	88	[110]
50	(−)-calyculin A (cf. below)			$Cl_2Pd(PPh_3)_2$	67	[111]
50	(+)-calyculin A (cf. below)			$Cl_2Pd(PPh_3)_2$	59	[112],[113]
50	calyculin A (cf. below)			$Cl_2Pd(PPh_3)_2$	75	[114]

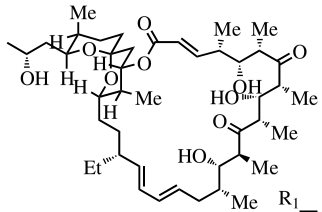
(*Continued*)

TABLE 3. (*Continued*)

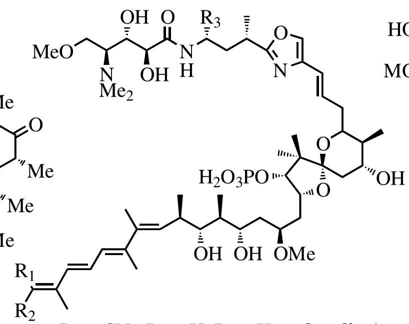
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
50	demethoxyrapamycin			$Cl_2Pd(TFP)_2$	DIPEA	65	[33]
51	calyculin C			$Cl_2Pd(PPh_3)_2$		59	[115]



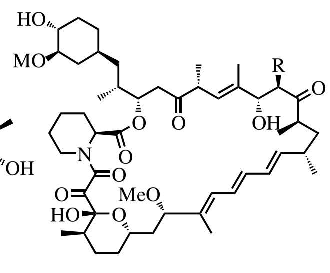
polycavernoside



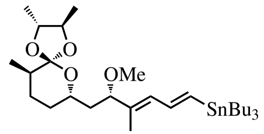
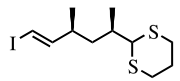
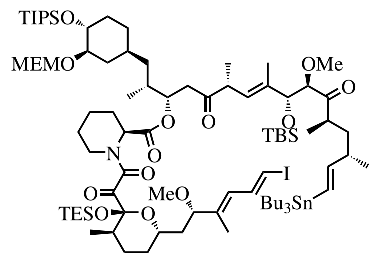
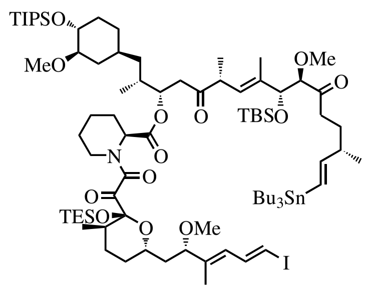
rutamycin B



R_1 = CN, R_2 = H, R_3 = H **calyculin A**
R_1 = CN, R_2 = H, R_3 = CH_3 **calyculin C**

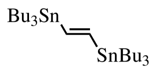
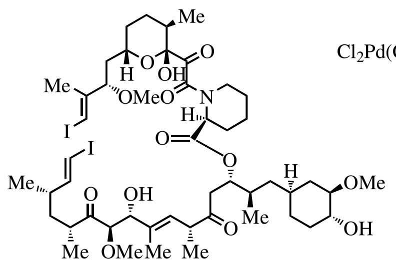
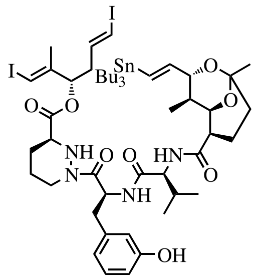
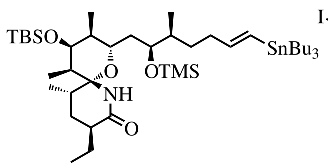
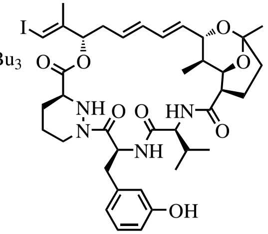


R = H **demethoxyrapamycin**
R = OMe **rapamycin**

51	rapamycin (cf. above)			$Cl_2Pd(CH_3CN)_2$	DMF	42	[32]
51	rapamycin (cf. above)			$Cl_2Pd(TFP)_2$	DIPEA	74	[33]
51	rapamycin (cf. above)			$Cl_2Pd(TFP)_2$		74	[33]

(*Continued*)

TABLE 3. (*Continued*)

C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
51	rapamycin (cf. above)			$Cl_2Pd(CH_3CN)_2$	DIPEA	27	[34],[35]
60	sanglifehrin A (cf. below)			$Pd_2(dba)_3{\cdot}CHCl_3$	$AsPh_3$ DIPEA	40	[36]
				$Pd_2(dba)_3{\cdot}CHCl_3$	$AsPh_3$ DIPEA	40	[36]

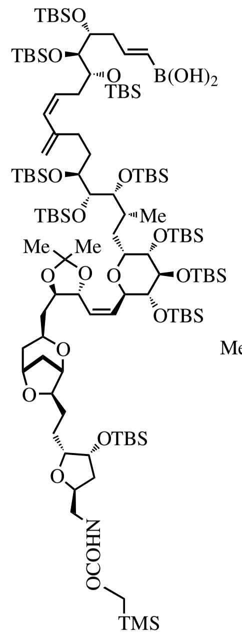
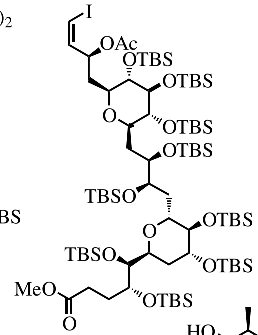
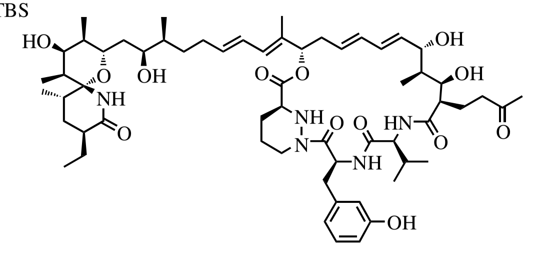
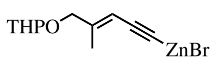
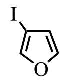
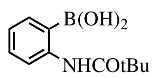
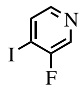
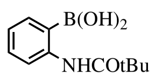
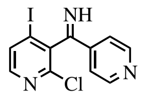
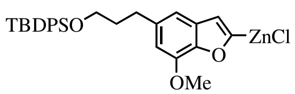
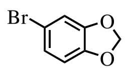
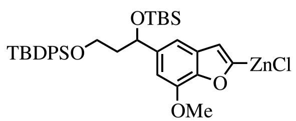
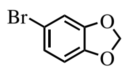
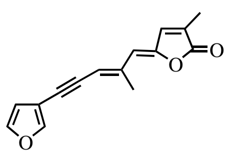
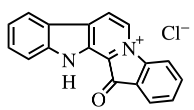
123	palytoxin (cf. [116])	same as the acid					[116]
	palytoxin carboxylic acid (cf. [119])			$Pd(PPh_3)_4$	TlOH	70	[117]–[119]
	 **sanglifehrin A**						

TABLE 4. Heteroaromatics (cf. Sect. III.2.7)

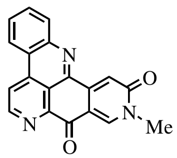
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
15	freelingyne			$Pd(PPh_3)_4$		82	[120]
18	fascaplysin			$Pd(PPh_3)_4$	K_2CO_3	98	[121]
19	amphimedine			$Pd(PPh_3)_4$	$Ba(OH)_2$	82	[122]
19	egonol			$Pd(PPh_3)_4$		19	[123]
19	(±)-machicendiol			$Pd(PPh_3)_4$		15	[123]



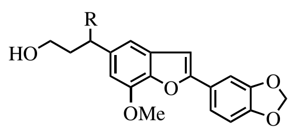
freelingyne



fascaplysin



amphimedine



R = H **egonol**
R = OH **(+)-machicendiol**

protocol developed by Negishi[124] with Zn, B, and Sn as well as that involving the use of haloalkynes (**Sect. III.2.8.2**). Although not yet widely known, it should be noted that the scope of Sonogashira coupling is more limited than the latter. Thus, terminal alkynes cannot be directly and selectively synthesized without protection and deprotection of one of the acetylene carbon atoms. The reaction also is sluggish or it may altogether fail in cases where alkynes contain electron-withdrawing substituents. Despite these limitations, Sonogashira coupling has thus far been the much more widely employed of the two, probably because it is operationally somewhat simpler. It should also be recalled that there are other intricate differences between the two protocols, as discussed in **Sect. III.2.8**.

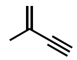
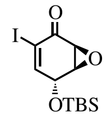
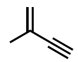
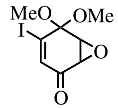
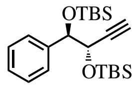
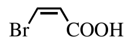
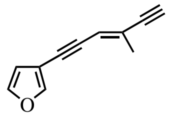
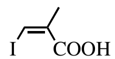
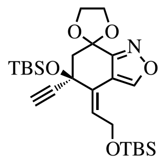
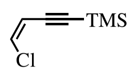
In cases where alkynylmetals are generated either *in situ* or in a separate step as discrete reagents, Mg, Zn, B, and Sn have been the four widely used metals. Comparative studies have shown that Zn is generally the most favorable among them (**Sect. III.2.8.2**). Here again, however, Sn has been the most frequently used metal. Similar comments on Sn as those made in **Sect. D** are also applicable to these cases. Particularly noteworthy are examples of the intramolecular cyclization of alkynyltins, as in the synthesis of neocarzinostatin,[125]–[128] cyclization via double alkynylation with haloalkynes, as in the synthesis of calicheamicinone[129] and dynemicin A,[130]–[132] and the carbopalladation–cross-coupling tandem cyclization, as in the synthesis of neocarzinostatin.[133],[134]

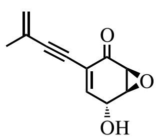
F. SYNTHESIS OF NATURAL PRODUCTS VIA Pd-CATALYZED CROSS-COUPLING INVOLVING ALLYL, BENZYL, AND PROPARGYL REAGENTS

Pd-catalyzed cross-coupling has been shown to be particularly well suited for the synthesis of diarylmethanes, allylated arenes, 1,4-dienes, 1,4-enynes, and related derivatives, as discussed in **Sect. III.2.9**. It should be recalled that this favorable characteristic does not extend to the coupling of two allylic, propargylic, and benzylic reagents to produce 1,5-dienes, 1,5-enynes, bibenzyl, and related compounds (**Sect. III.2.10**). Also to be recalled is that the use of propargyl reagents often leads to the formation of allenes, and this tendency of Pd is in contrast with that of Cu in dealing with propargyl(allenyl) reagents. As in many other cases of Pd-catalyzed cross-coupling, Zn, B, Al, and Sn have been used most frequently, although it is likely that Cu, Zr, and Si are also satisfactory in some cases.

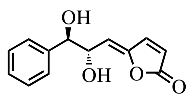
Following a very satisfactory synthesis of α-farnesene via alkenyl–allyl coupling[174] as the first example of natural product syntheses of this class, some other natural products containing 1,4-dienes and allylated arenes have been synthesized, as indicated by the results summarized in **Table 7**. The synthesis of humulene via intramolecular alkenyl–allyl coupling is noteworthy, even though the cyclization was achieved only in 32% yield.[175] Also noteworthy is the Ni- or Pd-catalyzed synthesis of allylated quinones, such as menaquinone-3 and coenzymes Q_n ($n = 3$ or 10).[176],[177],[194] Both Ni and Pd appear to be highly satisfactory and roughly comparative with each other[194] despite the claim that Ni is superior to Pd.[176] Many additional satisfactory examples may be expected. At present, however, no natural products appear to have been synthesized by using propargylic reagents in Pd-catalyzed cross-coupling.

TABLE 5. Alkyne Synthesis Via Sonogashira Cross-Coupling (cf. Sect. III.2.8.1)

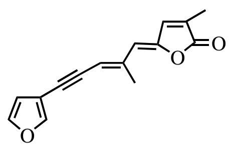
C_n	Name	RC≡CH	R′X	Catalyst	Additive	Yield (%)	Reference
11	(+)-harveynone			$Cl_2Pd(PPh_3)_2$	CuI i-Pr_2NH	52	[135]
11	(±)-harveynone			$Pd(OAc)_2$	CuI Et_3N	62	[136]
13	goniobutenolide A			$Cl_2Pd(PPh_3)_2$	CuI Et_3N PPh_3	55	[137]
15	freelingyne			$Pd(PPh_3)_4$	CuI Et_3N	50	[120]
18	(−)-calicheamicinone			$Pd(OAc)_2$	CuI n-$BuNH_2$ PPh_3	76	[138]



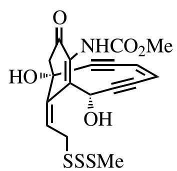
(+)-harveynone



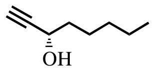
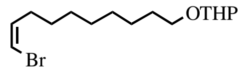
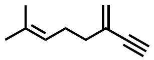
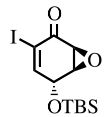
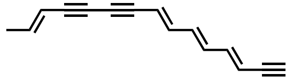
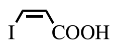
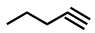
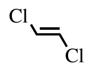
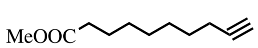
goniobutenolide A

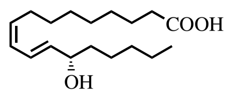


freelingyne

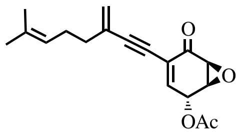


(−)-calicheamicinone

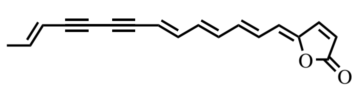
18	coriolic acid			$Cl_2Pd(PPh_3)_2$	CuI *n*-$PrNH_2$	96	[52]
18	(−)-tricholomenyn A			$Cl_2Pd(PPh_3)_2$	CuI *i*-Pr_2NH	54	[135]
18	xerulin			$Pd(PPh_3)_4$	CuI Et_3N BHT	70	[54]
19	methyl eleostearate			$Pd(PPh_3)_4$	CuI *n*-$BuNH_2$	98	[139]
				$Pd(PPh_3)_4$	CuI *n*-$BuNH_2$	80	[139]



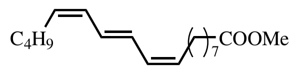
coriolic acid



(−)-tricholomenyn A



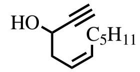
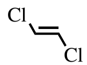
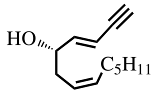
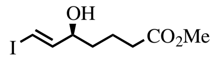
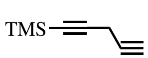
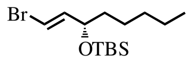
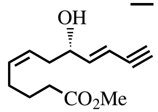
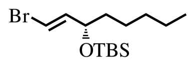
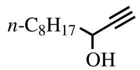
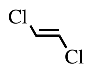
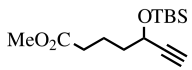
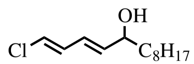
xerulin

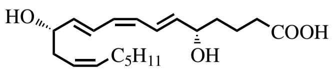


methyl eleostearate

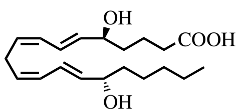
(*Continued*)

TABLE 5. (*Continued*)

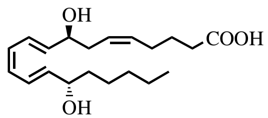
C_n	Name	RC≡CH	R′X	Catalyst	Additive	Yield (%)	Reference
20	(5*S*,12*S*)-DiHETE			$Pd(PPh_3)_4$	CuI piperidine	85	[140]
				$Pd(PPh_3)_4$	CuI piperidine	62	[140]
20	5,15-DiHETE			$Pd(PPh_3)_4$	CuI n-$PrNH_2$	82	[141]
20	8,15-DiHETE			$Pd(PPh_3)_4$	CuI n-$PrNH_2$	80	[141]
20	14,15-dihydro leukotriene B_4			$Pd(PPh_3)_4$	CuI n-$BuNH_2$	70	[142]
				$Pd(PPh_3)_4$	CuI n-$BuNH_2$	33	[142]



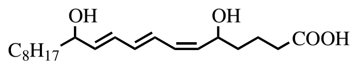
(5*S*,12*S*)-DiHETE



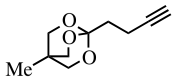
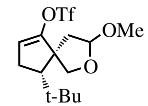
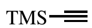
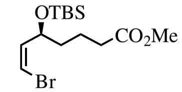
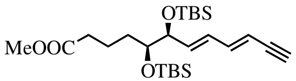
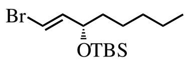
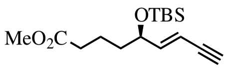
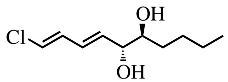
5,15-DiHETE

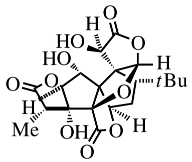


8,15-DiHETE

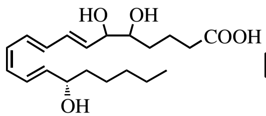


14,15-dihydro leukotriene B_4

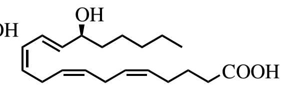
20	(+)-ginkgolide B			$Pd(PPh_3)_4$	CuI n-$PrNH_2$	76-84	[143]
20	leukotriene B_4 (cf. **Table 3**)			$Pd(PPh_3)_4$	CuI n-$PrNH_2$	94	[60]
20	leukotriene B_4 (cf. **Table 3**)			same as above		100	[69]
20	lipoxin A			$Pd(PPh_3)_4$	CuI n-$PrNH_2$	96	[144]
20	lipoxin B (cf. **Table 3**)			$Pd(PPh_3)_4$	CuI n-$PrNH_2$	70	[61]



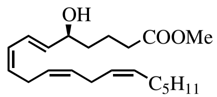
(+)-ginkgolide B



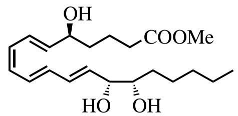
lipoxin A



15-(*S*)-HETE



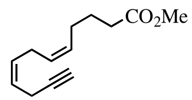
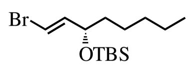
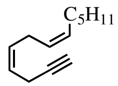
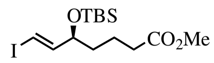
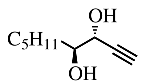
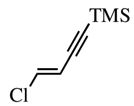
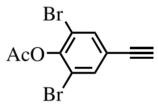
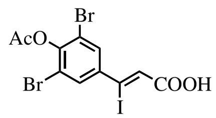
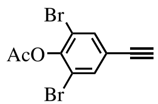
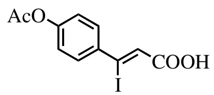
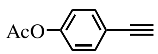
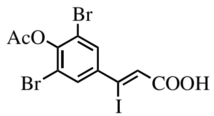
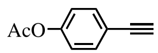
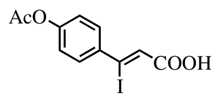
5-(*S*)-HETE

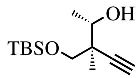
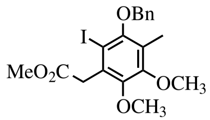
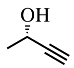
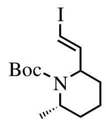


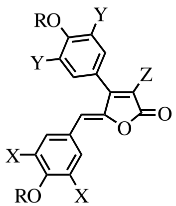
lipoxin B_4

(*Continued*)

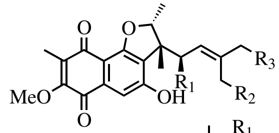
TABLE 5. (*Continued*)

C_n	Name	RC≡CH	R′X	Catalyst	Additive	Yield (%)	Reference
20	15-(*S*)-HETE (cf. above)			$Pd(PPh_3)_4$	CuI n-$PrNH_2$	92	[145]
21	5-(*S*)-HETE (cf. above)			$Pd(PPh_3)_4$	CuI piperidine	83	[146]
21	lipoxin B_4 (cf. above)			$Cl_2Pd(PhCN)_2$	CuI piperidine	75	[147]
21	rubrolide A (cf. below)			$Cl_2Pd(PPh_3)_2$	CuI Et_3N	70	[148]
	rubrolide C (cf. below)			$Cl_2Pd(PPh_3)_2$	CuI Et_3N	54	[148]
	rubrolide D (cf. below)			$Cl_2Pd(PPh_3)_2$	CuI Et_3N	54	[148]
	rubrolide E (cf. below)			$Cl_2Pd(PPh_3)_2$	CuI Et_3N	50	[148]

22	furaquinone A			$Pd(OAc)_2$	CuI Et_2NH PPh_3	98	[149]
22	furaquinone B						
22	furaquinone H						
22	himbacine			$Cl_2Pd(PhCN)_2$	CuI piperidine	81	[150]

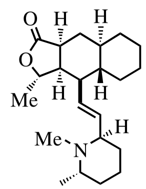


Rubrolides diacetates	R	X	Y	Z
A	Ac	Br	Br	H
C	Ac	Br	H	H
D	Ac	H	Br	H
E	Ac	H	H	H



furaquinone

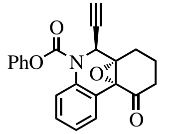
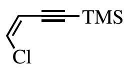
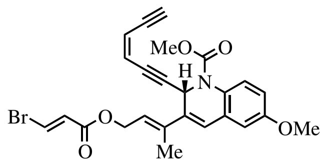
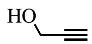
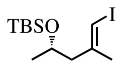
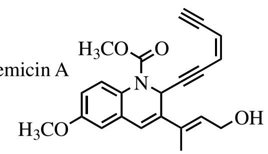
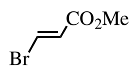
	R_1	R_2	R_3
A	OH	H	OH
B	OH	OH	H
H	OH	OH	OH

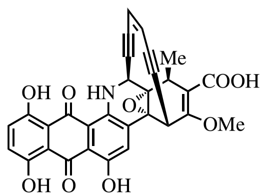


himbacine

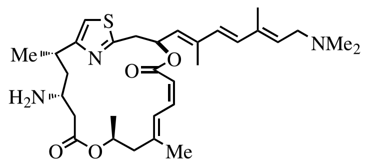
(*Continued*)

TABLE 5. (*Continued*)

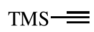
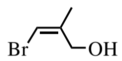
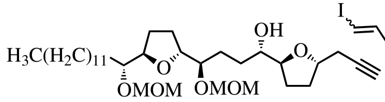
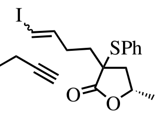
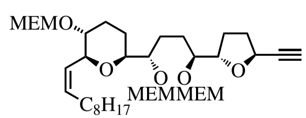
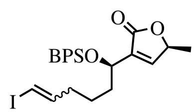
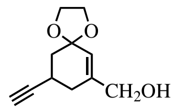
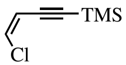
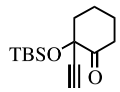
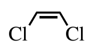
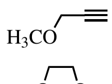
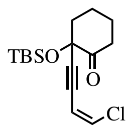
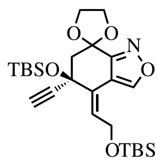
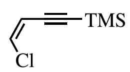
C_n	Name	RC≡CH	R′X	Catalyst	Additive	Yield (%)	Reference
30	dynemicin A models			$Pd(OAc)_2$	CuI n-$PrNH_2$ PPh_3	88	[151]
				$Pd(OAc)_2$	CuI n-$BuNH_2$ PPh_3	86	[152]
30	dynemicin A related			$Pd(PPh_3)_4$	CuI	25	[153]
31	(−)-pateamine A			$Pd(PPh_3)_4$	CuI n-$PrNH_2$	91	[86]
32	tri-*O*-methyl dynemicin A methyl ester			$Pd(PPh_3)_4$	CuI	12	[154]



dynemicin A

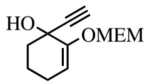
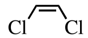
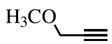
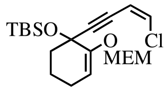
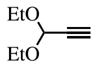
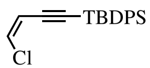
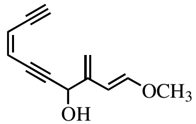
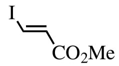
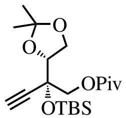
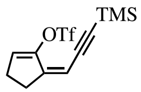
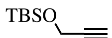
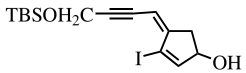


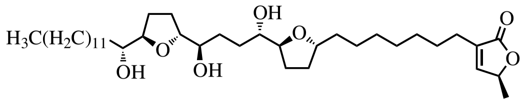
(−)-pateamine A

34	neooxazolomycin (cf. [93])			$Pd(PPh_3)_4$	CuI n-$BuNH_2$	NA	[93]
37	(+)-4-deoxy-gigantecin (cf. below)			$Pd(PPh_3)_4$	CuI Et_3N	60	[155]
37	mucocin (cf. below)			$Cl_2Pd(PPh_3)_2$	TEA CuI	55	[156]
52	calicheamicin γ′1 related (cf. [157])			$Cl_2Pd(PPh_3)_2$	CuI n-$BuNH_2$	59	[157]
	calicheamicin esperamicin related (cf. [158])			$Pd(PPh_3)_4$	CuI n-$PrNH_2$	79	[158]
				$Pd(PPh_3)_4$	CuI n-$BuNH_2$	53	[158]
52	calicheamicin γ′1 (cf. [162])			$Pd(OAc)_2$	CuI n-$BuNH_2$ PPh_3	76	[159]–[162]

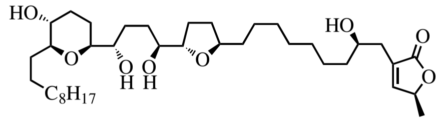
(*Continued*)

TABLE 5. (*Continued*)

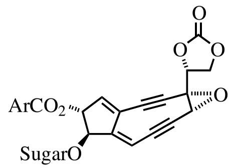
C_n	Name	RC≡CH	R′X	Catalyst	Additive	Yield (%)	Reference
	calicheamicin esperamicin related (cf. [163])			$Pd(PPh_3)_4$	CuI n-$BuNH_2$	80	[163]
				$Pd(PPh_3)_4$	CuI n-$BuNH_2$	88	[163]
	calicheamicin esperamicin related (cf. [164])			$Pd(PPh_3)_4$	CuI n-$PrNH_2$	91	[164]
				$Pd(PPh_3)_4$	CuI n-$PrNH_2$	84	[164]
				$Pd(PPh_3)_4$	CuI Et_3N	87	[164]
	neocarzinostatin chromophore (cf. below)			$Pd(PPh_3)_4$	CuI Et_2NH	73	[165]
	neocarzinostatin chromophore (cf. below)			$Cl_2Pd(PPh_3)_2$	CuI Et_2NH	70–75	[133]



(+)-4-deoxygigantecin

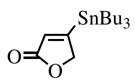
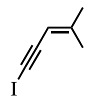
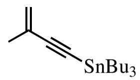
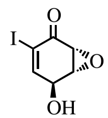
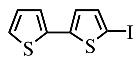


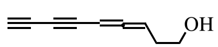
mucocin



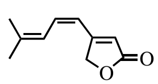
neocarzinostatin chromophore

TABLE 6. Alkyne Synthesis Involving Alkynylmetals or Alkynylhalides (cf. Sect. III.2.8.2)

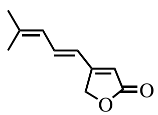
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
9	marasin	ClZnHC=C=CHCH$_2$CH$_2$O(CH$_3$)CHOEt	Br—≡—≡—TMS	$Cl_2Pd(PhCN)_2$		75	[166]
10 10 10	(*Z*)-scobinolide (*E*)-scobinolide cleviolide			$Cl_2Pd(PPh_3)_2$	DMF	37	[167]
11	(±)-harveynone (cf. Table 5)			$Cl_2Pd(PPh_3)_2$	CuI	74	[136]
14	5-(3-buten-1-ynyl)-2,2′-bithienyl	TMS—≡—MgBr		$Pd(PPh_3)_4$		65	[168]



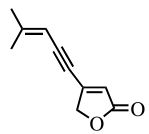
marasin



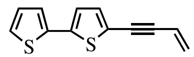
(*Z*)-scobinolide



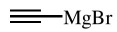
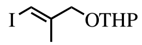
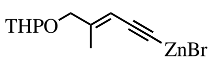
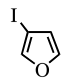
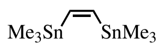
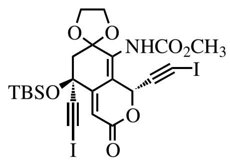
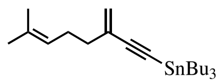
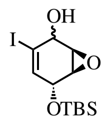
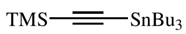
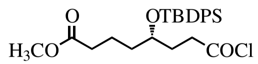
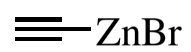
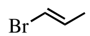
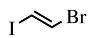
(*E*)-scobinolide



cleviolide

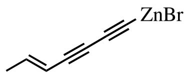
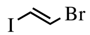
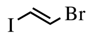
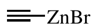
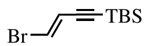
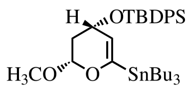
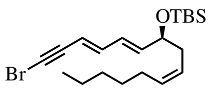
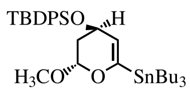
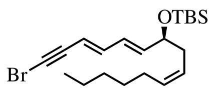
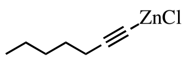
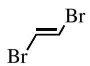


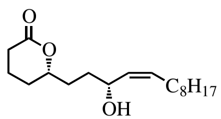
5-(3-buten-1-ynyl)-2,2′-bithienyl

15	freelingyne (cf. **Table 5**)			$Pd(PPh_3)_4$		94	[120]
				$Pd(PPh_3)_4$		82	[120]
16	(±)-calicheamicinone (cf. **Table 5**)			$Pd(PPh_3)_4$	DMF	72	[129]
18	(−)-tricholomenyn A (cf. **Table 5**)			$Cl_2Pd(PPh_3)_2$	CuI Et_3N	98	[169]
18	PsiAβ (cf. below)			$Cl_2Pd(PPh_3)_2$		80	[170]
18	xerulin (cf. **Table 5**)						
			 one step	$Pd(PPh_3)_4$		72	[54]

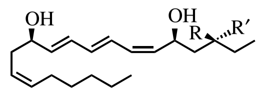
(*Continued*)

TABLE 6. (*Continued*)

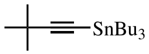
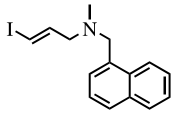
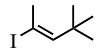
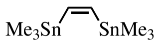
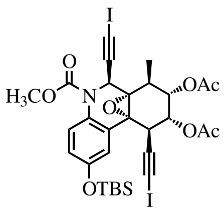
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
18	xerulin (cf. **Table 5**)			$Pd(PPh_3)_4$		65	[54]
				$Pd(PPh_3)_4$		70	[54]
				$Pd(PPh_3)_4$		77	[54]
20	3-(*R*)-OH-LTB4			$Pd(PPh_3)_4$		61–71	[171]
	3-(*S*)-OH-LTB4			$Pd(PPh_3)_4$		61–71	[171]
20	(2*E*,6*E*,8*E*)-*N*-(2-methyl-propyl)-2,6,8-hexadeca trien-10-ynamide (cf. **Table 3**)			$Pd(PPh_3)_4$		58	[62]

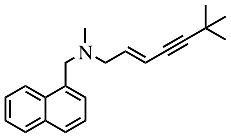


PsiAβ

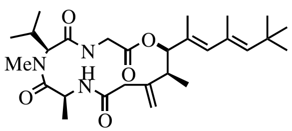


R = OH, R′ = H **3-(*R*)-OH-LTB4**
R = H, R′ = OH **3-(*S*)-OH-LTB4**

21	terbinafine			$Cl_2Pd(CH_3CN)_2$	87	[172]
28	epiantillatoxin	$H_3CC{\equiv}CMgBr$		$Pd(PPh_3)_4$	68	[173]
30	(±)-dynemicin A (cf. **Table 5**)			$Pd(PPh_3)_4$	80	[130]–[132]



terbinafine



epiantillatoxin

(*Continued*)

TABLE 6. (*Continued*)

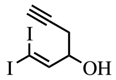
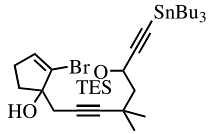
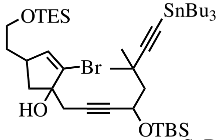
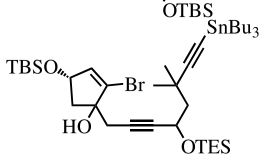
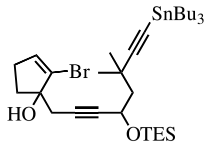
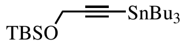
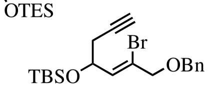
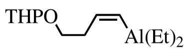
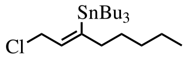
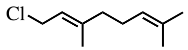
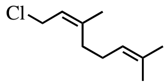
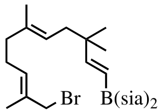
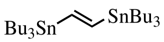
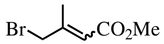
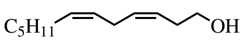
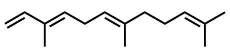
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
	neocarzinostatin chromophore (cf. **Table 5**)	$TBSOH_2C{-}{\equiv}{-}SnBu$		$Pd(PPh_3)_4$		70–80	[133]
	neocarzinostatin chromophore (cf. **Table 5**)			$Pd(PPh_3)_4$		32	[125]
	neocarzinostatin related (cf. **Table 5**)			$Pd(PPh_3)_4$		62	[126]
				$Pd(PPh_3)_4$		60	[127]
				$Pd(PPh_3)_4$		72	[128]
				$Pd(PPh_3)_4$		75	[134]

TABLE 7. Allylation, Benzylation, and Propargylation (cf. Sect. III.2.9)

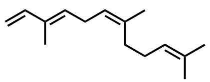
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
12	(3*Z*,6*Z*)-dodeca-3,6-dien-1-ol			$Pd(PPh_3)_4$		51	[178]
15	α-farnesene			$Pd(PPh_3)_4$		86	[174]
15	(*Z*)-α-farnesene			$Pd(PPh_3)_4$		77	[174]
15	humulene			$Pd(PPh_3)_4$	NaOH	32	[175]
16	C_{16}-cecropia juvenile hormone			$Cl_2Pd(CH_3CN)_2$		72	[49]



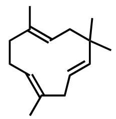
(3Z,6Z)-dodeca-3,6-dien-1-ol



α-farnesene



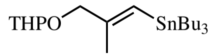
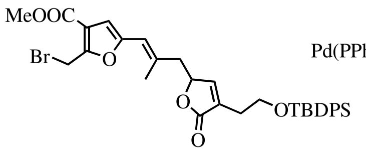
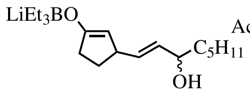
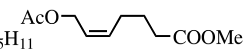
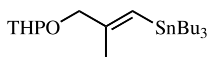
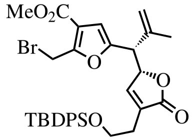
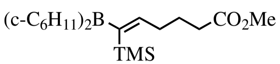
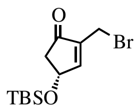
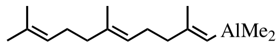
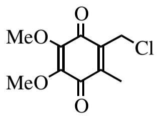
(Z)-α-farnesene

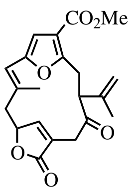


humulene

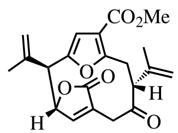
(*Continued*)

TABLE 7. (*Continued*)

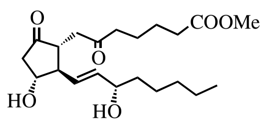
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
21	(±)-acerosolide			$Pd(PPh_3)_4$		50–60	[179],[180]
21	(±)-11-deoxypro-taglandin E_2 methyl ester (cf. [181])			$Pd(PPh_3)_4$		74	[181]
21	gorgiacerone			$Pd(PPh_3)_4$		NA	[182]
21	6-keto-PGs			$Pd(PPh_3)_4$	NaOH	81	[183]
24	coenzyme Q_3			$Pd(PPh_3)_4$		82	[177]



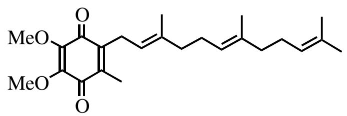
(±)-acerosolide



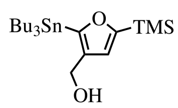
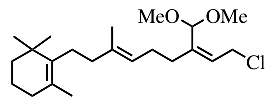
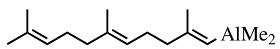
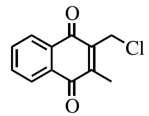
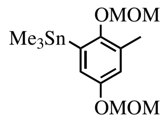
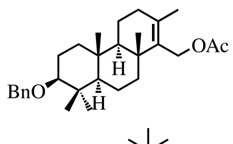
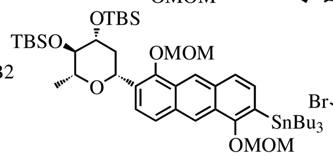
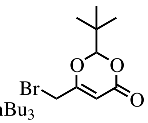
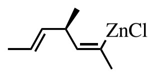
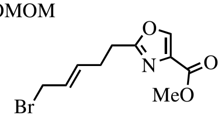
gorgiacerone

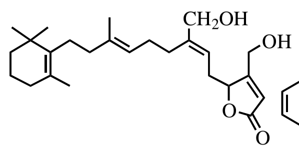


6-keto-PGs

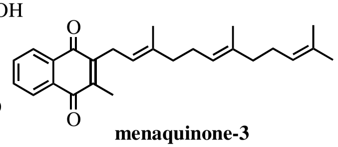


coenzyme Q_3

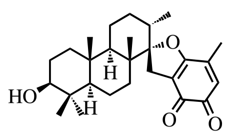
25	(*E*)-neomanoalide			$Pd(dba)_2$	PPh_3	66	[184]
26	menaquinone-3			$Pd(PPh_3)_4$		89	[177]
27	(−)-stypoldione			$Pd(dba)_2$	LiCl	100	[185]
27	vineomycinone B2 methyl ester			$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	45–50	[42]
29	hennoxazole (cf. below)			$Pd_2(dba)_3{\cdot}CHCl_3$	$AsPh_3$	68	[186]



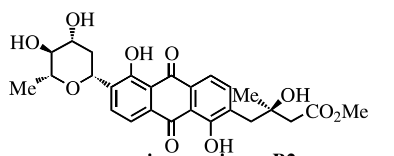
(*E*)-neomanoalide



menaquinone-3



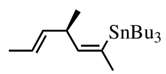
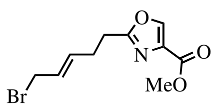
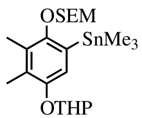
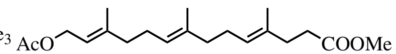
(−)-stypoldione

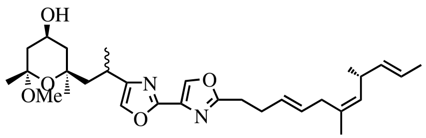


vineomycinone B2 methyl ester

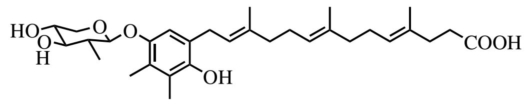
(*Continued*)

TABLE 7. (*Continued*)

C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
29	hennoxazole			$Pd_2(dba)_3 \cdot CHCl_3$	$AsPh_3$	47	[187]
31	lurlene (lurlenic acid)			$Pd_2(dba)_3$	LiCl	98	[188],[189]



hennoxazole



lurlene
(lurlenic acid)

G. SYNTHESIS OF NATURAL PRODUCTS VIA Pd-CATALYZED ALKYLATION, HOMOALLYLATION, HOMOPROPARGYLATION, AND HOMOBENZYLATION

Until recently, cross-coupling between alkylmetals and aryl, alkenyl, and alkynyl halides was achieved mostly with alkylcoppers. Over the past two decades, however, the Ni- or Pd-catalyzed reaction of alkylmetals with the unsaturated organic halides mentioned above has been developed as a viable alternative, as detailed in **Sect. III.2.11**. The Cu-based methodology still remains highly competitive. So, it is advisable to consider both options for finding the method for a given case.

Unlike the cases discussed earlier in this section, the current range of metal countercations in Pd-catalyzed alkylation is practically limited to Zn and B, although Mg has been satisfactory in some cases. The scope of Pd-catalyzed alkylation with alkylmetals containing other metals, such as Al, Si, Sn, and Zr, is severely limited at present. Of the two widely used metals, that is, Zn and B, Zn is significantly more reactive than B, and less elaborate and less vigorous reaction conditions are required. However, in those cases where alkylboranes are readily available via hydroboration, this and the higher level of chemoselectivity make B an attractive and competitive alternative. Here again, the general lack of comparative data does not permit a critical comparison of the two metals. As a crude guideline, it is not unreasonable to consider Zn in cases where alkylmetals containing Li, Mg, or Zn are some of the most readily available alkylmetals. In cases where alkenes are to be covnerted to alkylmetals, however, B may be considered first.

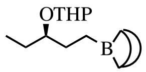
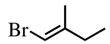
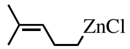
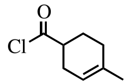
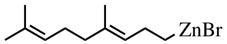
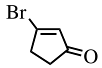
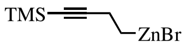
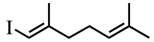
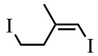
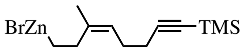
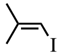
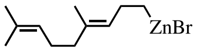
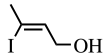
The currently available results of the synthesis of natural products via Pd-catalyzed alkylation are shown in **Table 8**, which is indeed dominated by the reactions of alkylzincs and alkylboranes. It is noteworthy that homoallyl-, homopropargyl-, and homobenzylzincs are readily generated by (i) indirect zincation, (ii) oxidative magnesiation followed by metathetical zincation, and, most cleanly, (iii) lithiation of primary alkyl iodides followed by zincation, and that the resultant alkylzincs very cleanly and selectively undergo Pd- or Ni-catalyzed cross-coupling with unsaturated organic electrophiles. The synthesis of 1,5-dienes via Pd-catalyzed reaction of homoallyl- and homopropargylzincs detailed in **Sect. III.2.11.2** is particularly noteworthy.

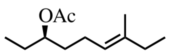
The currently available examples of the synthesis of natural products via Pd-catalyzed alkylation are summarized in **Table 8**.

H. SYNTHESIS OF NATURAL PRODUCTS VIA Pd-CATALYZED CROSS-COUPLING INVOLVING α-HETERO-SUBSTITUTED ORGANIC ELECTROPHILES

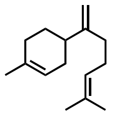
Of various types of Pd-catalyzed cross-coupling reactions involving α-hetero-substituted organic electrophiles discussed in **Sect. III.2.12**, the Pd-catalyzed carbonylative and noncarbonylative acylation as well as selective alkenylation with 1,1-dihaloalkenes have attracted the special attention of synthetic chemists. Along with several other organometallic reactions with acyl halides and related electrophiles involving Cu, Mg, Al, and Mn, Pd-catalyzed acylation with organometals containing Zn and Sn has emerged as a competitive and complementary alternative. It should be noted that the high reactivity of organozincs does not readily permit the desired

TABLE 8. Alkylation, Homoallylation, Homopropargylation, and Homobenzylation (cf. III.2.11)

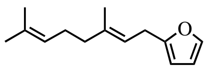
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
12	(*E*)-1-ethyl-5-methyl-4-heptenyl acetate (quadrilure)			$Cl_2Pd(dppf)$	K_3PO_4	58	[190]
15	β-bisabolene			$Pd(PPh_3)_4$		75	[191]
15	dendrolasin			$Cl_2Pd(PPh_3)_2$	DIBAH	55	[192]
15	(2*E*,6*E*)-farnesol			$Pd(PPh_3)_4$		90	[193]
15	(2*E*,6*Z*)-farnesol			$Cl_2Pd(dppf)$		84	[194]
15	(2*Z*,6*Z*)-farnesol			$Pd_2(dba)_3$	TFP	78	[194]
15	(2*Z*,6*E*)-farnesol			$Pd(PPh_3)_4$		86	[194]



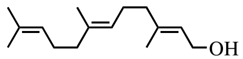
quadrilure



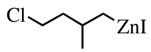
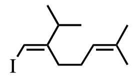
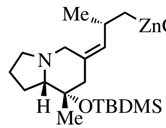
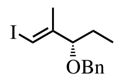
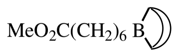
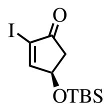
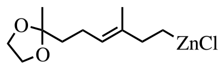
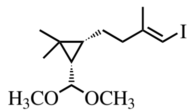
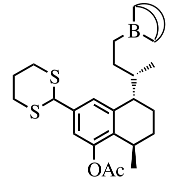
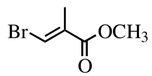
β-bisabolene

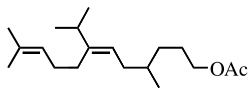


dendrolasin

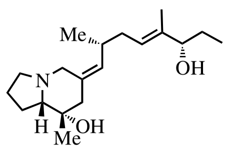


(2*E*,6*E*)-farnesol

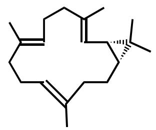
17	yellow seale pheromone			$Pd(PPh_3)_4$		NA	[195]
19	(+)-pumiliotoxin A			$Pd(PPh_3)_4$		60	[196]
20	PGE_1 (cf. [197])			$Cl_2Pd(dppf)$	$AsPh_3$ Cs_2CO_3	70–80	[197]
20	(+)-casbene			$Pd(PPh_3)_4$		70	[198]
20	(±)-dihydroxy-serrulatic acid			$Cl_2Pd(dppf)$	K_2CO_3	77	[199],[200]



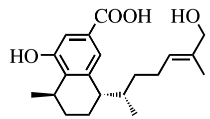
yellow seale pheromone



(+)-pumiliotoxin A



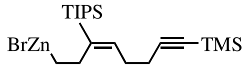
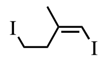
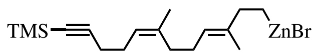
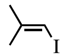
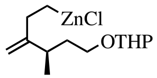
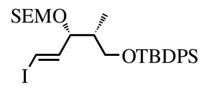
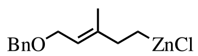
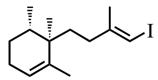
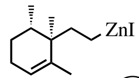
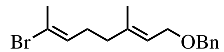
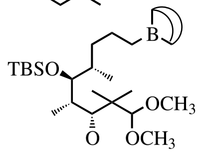
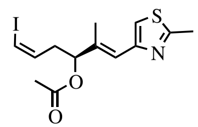
(+)-casbene

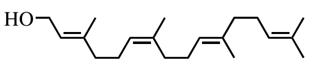


(±)-dihydroxy-serrulatic acid

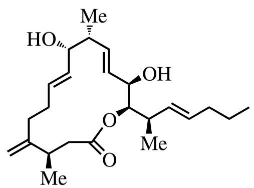
(*Continued*)

TABLE 8. (*Continued*)

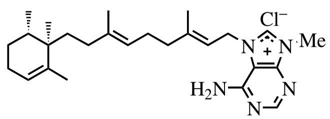
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
20	(2*E*,6*Z*,10*E*)-geranylgeraniol			$Cl_2Pd(dppf)$	DIBAH	81	[194],[204]
				$Cl_2Pd(dppf)$	DIBAH	67	[194],[204]
24	(+)-amphidinolide J			$Pd(PPh_3)_4$		84	[201]
26	(±)-ageline A			$Cl_2Pd(dppf)$		68	[202]
26	(±)-ageline A			$Cl_2Pd(dppf)$		66	[202]
26	epothilone A			$Cl_2Pd(dppf)$	Cs_2CO_3 $AsPh_3$	64	[203]



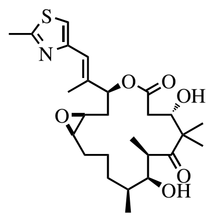
(2*E*,6*Z*,10*E*)-geranylgeraniol



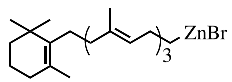
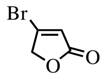
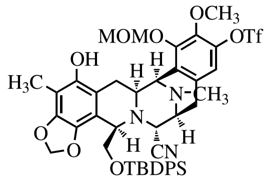
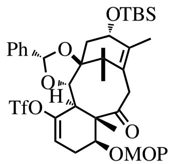
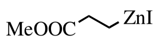
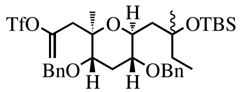
(+)-amphidinolide J

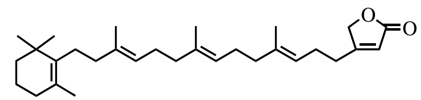


(±)-ageline A



epothilone A

30	mokupalide			$Cl_2Pd(PPh_3)_2$		62	[192]
39	ecteinascidin (cf. [205])	Me_4Sn		$Cl_2Pd(PPh_3)_2$	LiCl	83	[205]
47	taxol (cf. [206])	$TMSCH_2MgCl$		$Pd(PPh_3)_4$		91	[206]
49	brevetoxin A (cf. [105])			$Pd(PPh_3)_4$		94	[105]–[109]



mokupalide

oxidative addition–CO insertion–reductive elimination cascade, since they tend to cross-couple without incorporation of CO.

The *trans*-selective cross-coupling of 1,1-dihaloalkenes exhibiting ≥98% stereoselectivity has found various interesting and attractive applications in natural products synthesis, as represented by those of lissoclinolide,[46] (−)-chlorothricolide,[78] and kijanolide.[88] These and other examples are summarized in **Table 9**.

I. SYNTHESIS OF NATURAL PRODUCTS VIA Pd-CATALYZED CROSS-COUPLING OF α-HETERO-SUBSTITUTED ORGANOMETALS

Pd-catalyzed cross-coupling of α-hetero-substituted organometals with various types of electrophiles is discussed in detail in **Sect. III.2.13**. Several representative examples of natural product syntheses are shown in **Table 10**.

J. SYNTHESIS OF NATURAL PRODUCTS VIA Pd-CATALYZED CROSS-COUPLING INVOLVING β-HETERO-SUBSTITUTED COMPOUNDS

Pd-catalyzed cross-coupling of β-hetero-substituted organometals and/or electrophiles is wide-ranging, as discussed in **Sect. III.2.14.2**. However, the following four topics are particularly noteworthy from the viewpoint of their applications to natural product syntheses:

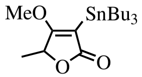
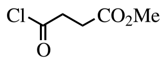
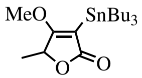
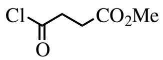
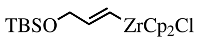
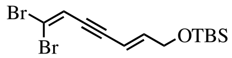
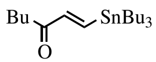
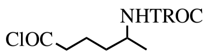
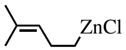
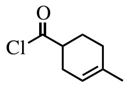
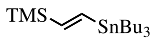
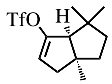
1. Use of 1,2-dihaloethylenes as (*E*)- or (*Z*)-ethylene and ethyne synthons.
2. α-Substitution of carbonyl compounds by use of α-haloenones and related derivatives.
3. Use of aryl electrophiles hetero-substituted in a position that is β to the leaving group for the synthesis of heterocycles including pyrroles, indoles, furans, thiofurans, lactones, and lactams.
4. Use of β-hetero-substituted allylic electrophiles for the synthesis of ketones and other functional derivatives.

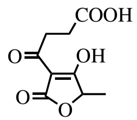
Most of the six possible 1,2-dihaloethylenes, especially the (*E*)-isomers, containing I, Br, and/or Cl have been used in the synthesis of natural products via Pd-catalyzed cross-coupling. Some details of the synthesis of lipoxin B (**Scheme 6**) and xerulin (**Scheme 11**) are presented in **Sect. III.2.14.2**. The scheme numbers above correspond to those in **Sect. III.2.14.2**.

α-Substitution of α-haloenones catalyzed by Pd complexes has also been widely applied to natural product syntheses. Some details of the syntheses of (−)-methyl shikimate (**Scheme 23**), (±)-tricholomenyn A (**Scheme 24**), prostaglandins (**Scheme 28**), savinin (**Scheme 43**), gadain (**Scheme 43**), and strobilurin A (**Scheme 49**) are presented in **Sect. III.2.14.2**. The scheme numbers indicated in parentheses are those in **Sect. III.2.14.2**. Some related examples including the syntheses of nakienones A and B (**Scheme 33**) and carbacyclin (**Scheme 34**) are also discussed in some detail.

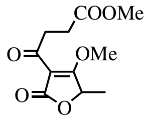
Some representative examples of natural product syntheses are shown in **Table 11**.

TABLE 9. Cross-Coupling Involving α-Hetero-Substituted Organic Electrophiles (cf. Sect. III.2.12)

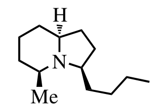
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
9	(±)-carolinic acid			*trans*-Bn(Cl)Pd(PPh_3)$_2$		62	[207]
11	dimethyl (±)-carolinate			*trans*-Bn(Cl)Pd(PPh_3)$_2$	CO	56	[208]
11	lissoclinolide (cf. Table 3)			$Cl_2Pd(PPh_3)_2$	DIBAH	91	[46]
13	(+)-monomorine I			$Pd(PPh_3)_4$		45	[209]
15	β-bisabolene (cf. Table 8)			$Pd(PPh_3)_4$		75	[191]
15	(±)-$\Delta^{9(12)}$-capnellene			$Pd(PPh_3)_4$	CO LiCl	86	[210]



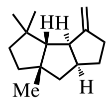
(±)-carolinic acid



dimethyl (±)-carolinate



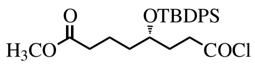
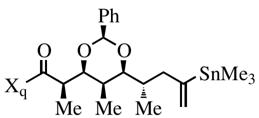
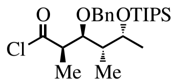
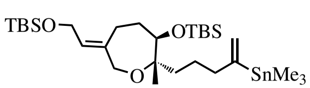
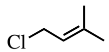
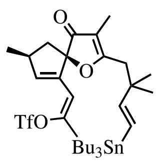
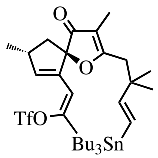
(+)-monomorine I

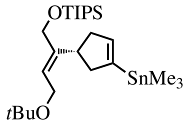
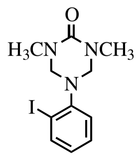
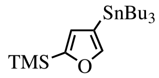
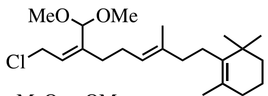
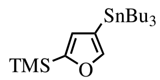
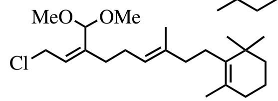


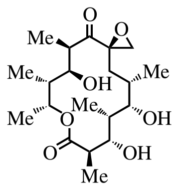
(±)-$\Delta^{9(12)}$-capnellene

(*Continued*)

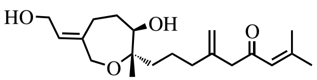
TABLE 9. (*Continued*)

C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
18	PsiAβ (cf. **Table 6**)	TMS—≡—$SnBu_3$		$Cl_2Pd(PPh_3)_2$		80	[170]
20	oleandolide (cf. below)			$Pd_2(dba)_3$	*i*-Pr_2NEt	85	[211]
20	(+)-(2′*S*,3*R*)-zoapatanol (cf. below)			$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3 CO	76	[212]
20	(±)-*epi*-jatrophone (cf. below)			$Cl_2Pd(CH_3CN)_2$	CO LiCl	53	[213]
	(±)-jatrophone (cf. below)			$Cl_2Pd(CH_3CN)_2$	CO LiCl	24	[213]

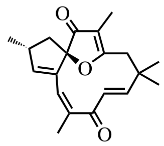
21	(−)-strychnine			$Pd_2(dba)_3$	CO LiCl NMP $AsPh_3$	80	[214]
25	manoalide			$Pd_2(dba)_3$	PPh_3 CO	94	[215]
25	*seco*-manoalide			$Pd_2(dba)_3$	PPh_3 CO	94	[215]



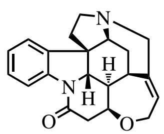
oleandolide



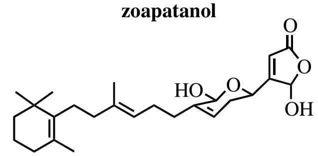
(+)-(2′*S*,3*R*)-zoapatanol



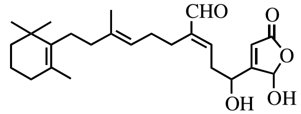
(±)-jatrophone



(−)-strychnine



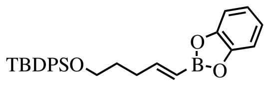
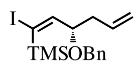
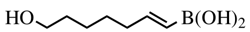
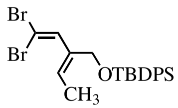
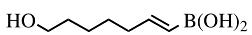
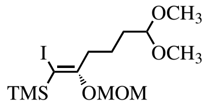
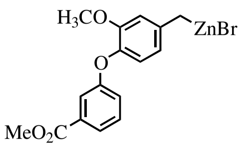
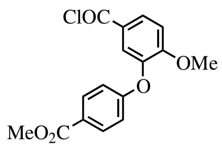
manoalide

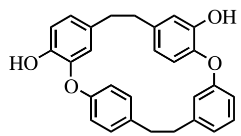


***seco*-manoalide**

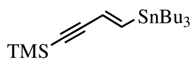
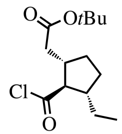
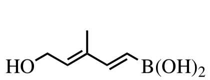
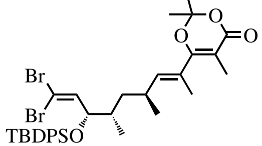
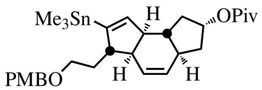
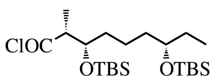
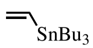
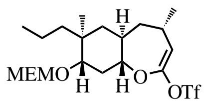
(*Continued*)

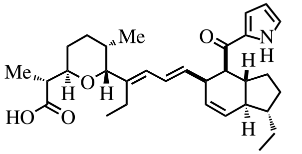
TABLE 9. (*Continued*)

C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
28	(−)-chlorothricolide (cf. [76])			$Pd(PPh_3)_4$	TlOH	74	[76],[77]
28	(−)-chlorothricolide			$Pd(PPh_3)_4$	TlOH	72	[78]
28	(−)-chlorothricolide			$Pd(PPh_3)_4$	TlOH	86	[79],[80]
28	riccardin B			$Cl_2Pd(PPh_3)_2$		50	[216]

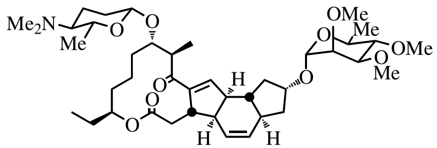


riccardin B

31	indanomycin			$PhCH_2PdCl(PPh_3)_2$		76	[87]
33	kijanolide (cf. [88])			$Pd(PPh_3)_4$	TlOH	77–86	[88]
41	spinosyn A			$Pd_2(dba)_3 \cdot CHCl_3$	*i*-Pr_2NEt	83	[217],[218]
49	brevetoxin A (cf. [105])			$Pd(PPh_3)_4$	LiCl	82	[105]–[109]

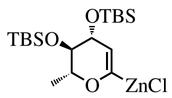
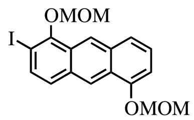
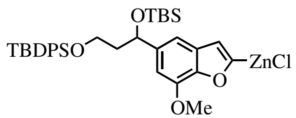
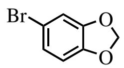
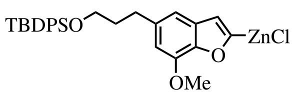
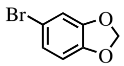


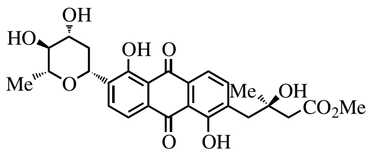
indanomycin



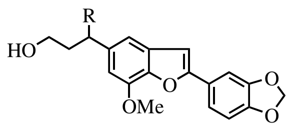
spinosyn A

TABLE 10. Cross-Coupling Involving α-Hetero-Substituted Organometals (cf. III.2.13)

C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
26	vineomycinone B2 methyl ester			$Cl_2Pd(PPh_3)_2$	DIBAH	75	[42],[43]
19	(±)-machicendiol			$Pd(PPh_3)_4$		15	[123]
19	egonol			$Pd(PPh_3)_4$		19	[123]

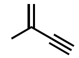
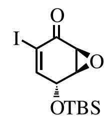
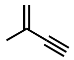
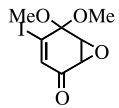
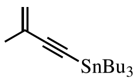
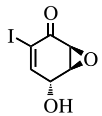
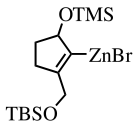
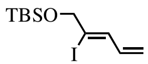
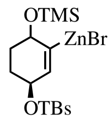
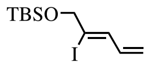


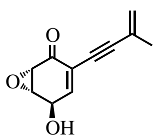
vineomycinone B2
methyl ester



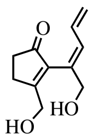
R = H **egonol**
R = OH **(±)-machicendiol**

TABLE 11. Cross-Coupling Involving β-Hetero-Substituted Compounds (cf. III.2.14)

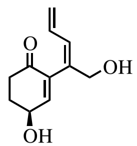
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
11	(+)-harveynone			$Cl_2Pd(PPh_3)_2$	CuI *i*-Pr_2NH	52	[135]
11	(±)-harveynone			$Pd(OAc)_2$	CuI Et_3N	62	[136]
11	(±)-harveynone			$Cl_2Pd(PPh_3)_2$	CuI	74	[136]
11	nakienone A			$Cl_2Pd(TFP)_2$	BuLi	95	[219]
11	nakienone B			$Pd(PPh_3)_4$		68	[220]



(+)-harveynone



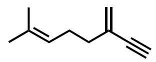
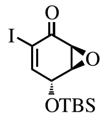
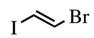
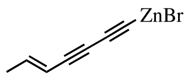
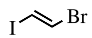
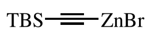
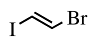
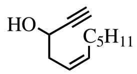
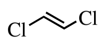
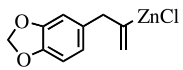
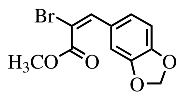
nakienone A

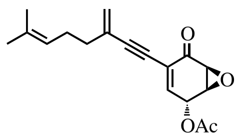


nakienone B

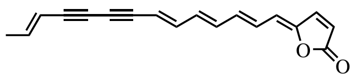
(*Continued*)

TABLE 11. (*Continued*)

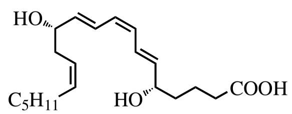
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
18	(−)-tricholomenyn A			$Cl_2Pd(PPh_3)_2$	CuI i-Pr_2NH	54	[135]
18	xerulin			$Pd(PPh_3)_4$		72	[54]
				$Pd(PPh_3)_4$		65	[54]
				$Pd(PPh_3)_4$		70	[54]
20	(5*S*,12*S*)-DiHETE			$Pd(PPh_3)_4$	CuI piperidine	94	[140]
20	gadain			$Pd(PPh_3)_4$		90	[221]



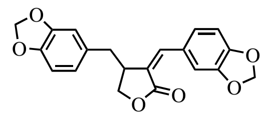
(−)-tricholomenyn A



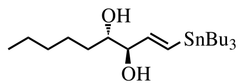
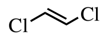
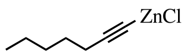
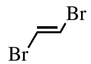
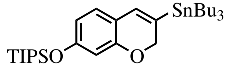
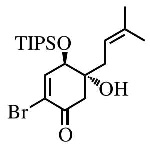
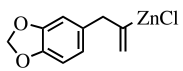
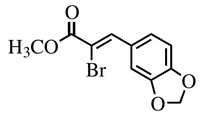
xerulin

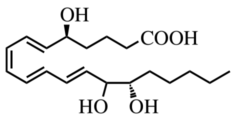


(5*S*,12*S*)-DiHETE

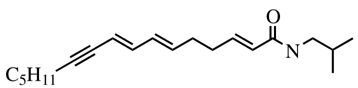


gadain

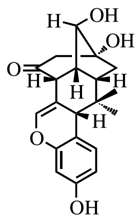
20	lipoxin B			$Pd(PPh_3)_4$	61	[61]
20	(2*E*,6*E*,8*E*)-*N*-(2-methyl-propyl)-2,6,8-hexadecatrien-10-ynamide			$Pd(PPh_3)_4$	58	[62]
20	miroestrol			$Pd(PPh_3)_4$	80	[222]
20	savinin			$Pd(PPh_3)_4$	81	[221]



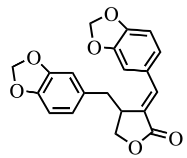
lipoxin B



(2*E*,6*E*,8*E*)-*N*-(2-methyl-propyl)-2,6,8-hexadecatrien-10-ynamide



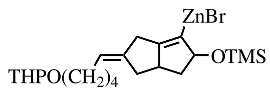
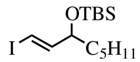
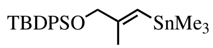
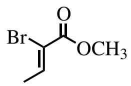
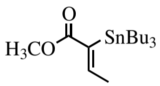
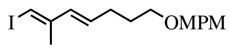
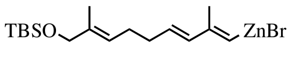
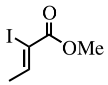
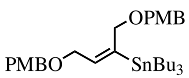
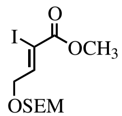
miroestrol

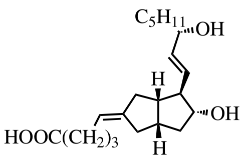


savinin

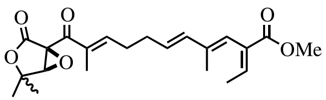
(*Continued*)

TABLE 11. (*Continued*)

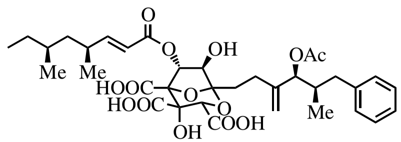
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
21	(±)-carbacyclin			$Cl_2Pd(TFP)_2$	BuLi	84	[223]
21	(+)-epolactaene			$Pd(PPh_3)_4$		47	[224],[225]
21	(+)-epolactaene			$Cl_2Pd(CH_3CN)_2$	CuI	91	[226]
21	(+)-epolactaene			$Pd_2(dba)_3$	TFP	62	[227]
35	(+)-zaragozic acid A			$Cl_2Pd(CH_3CN)_2$		70	[94]–[97]



(±)-carbacyclin

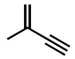
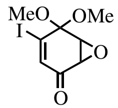
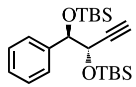
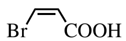
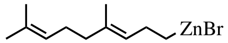
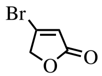
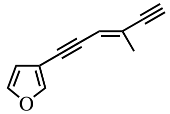
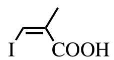
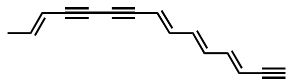
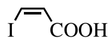


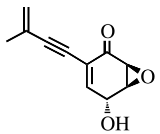
(+)-epolactaene



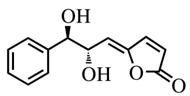
(+)-zaragozic acid A

TABLE 12. Conjugate Substitution (cf. III.2.15)

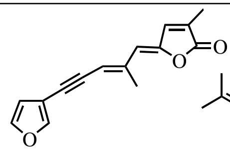
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
11	(±)-harveynone			$Pd(OAc)_2$	CuI Et_3N	62	[136]
13	goniobutenolide A			$Cl_2Pd(PPh_3)_2$	CuI Et_3N PPh_3	55	[137]
15	dendrolasin			$Cl_2Pd(PPh_3)_2$	DIBAH	55	[192]
15	freelingyne			$Pd(PPh_3)_4$	CuI Et_3N	50	[120]
18	xerulin			$Pd(PPh_3)_4$	CuI Et_3N BHT	70	[54]



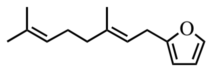
(+)-harveynone



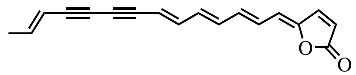
goniobutenolide A



freelingyne



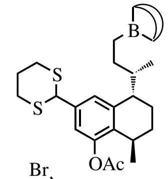
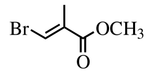
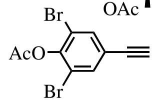
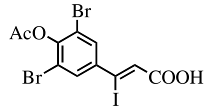
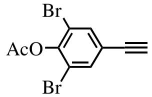
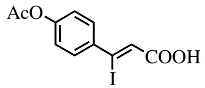
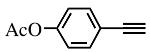
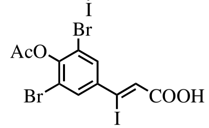
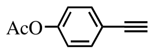
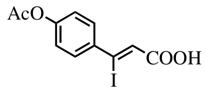
dendrolasin

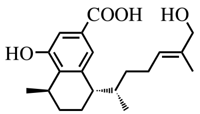


xerulin

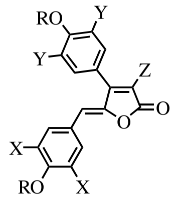
(*Continued*)

TABLE 12. (*Continued*)

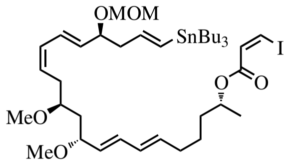
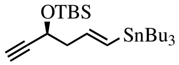
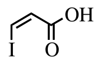
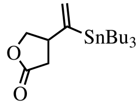
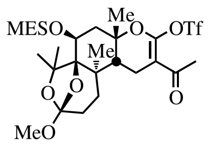
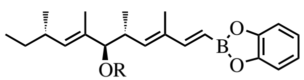
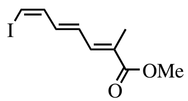
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
20	(±)-dihydroxy-serrulatic acid			$Cl_2Pd(dppf)$	K_2CO_3	77	[199],[200]
21	rubrolide A			$Cl_2Pd(PPh_3)_2$	CuI Et_3N	70	[148]
	rubrolide C			$Cl_2Pd(PPh_3)_2$	CuI Et_3N	54	[148]
	rubrolide D			$Cl_2Pd(PPh_3)_2$	CuI Et_3N	54	[148]
	rubrolide E			$Cl_2Pd(PPh_3)_2$	CuI Et_3N	50	[148]

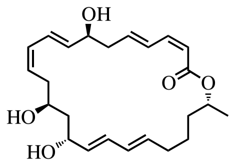


(±)-dihydroxy-serrulatic acid

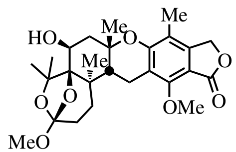


Rubrolides diacetates	R	X	Y	Z
A	Ac	Br	Br	H
C	Ac	Br	H	H
D	Ac	H	Br	H
E	Ac	H	H	H

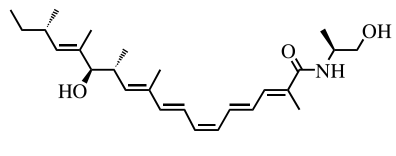
24	macrolactin A			Pd(0)	$AsPh_3$	58	[30]
24	(−)-macrolactin A			$Cl_2Pd(CH_3CN)_2$	$Ph_2PO_2NBu_4$	64	[29]
26	(−)-austalide B			$Pd_2(dba)_3$	TFP LiCl	71	[74]
26	myxalamide A			$Pd(OAc)_2$	TPPTS i-Pr_2NH	44	[75]



(−)-macrolactin A



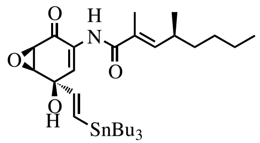
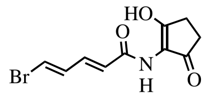
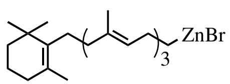
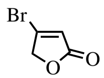
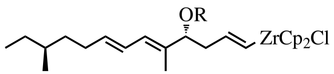
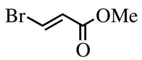
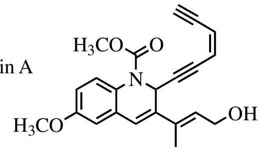
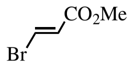
(−)-austalide B

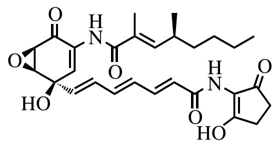


myxalamide A

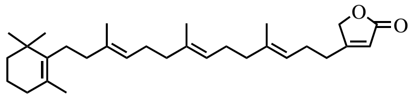
(*Continued*)

TABLE 12. (*Continued*)

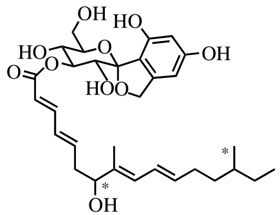
C_n	Name	RM	R′X	Catalyst	Additive	Yield (%)	Reference
28	(−)-manumycin B			$Cl_2Pd(PPh_3)_2$	DIBAH	71	[81]
30	mokupalide			$Cl_2Pd(PPh_3)_2$		62	[192]
31	papulacandin D			$Cl_2Pd(PPh_3)_2$	DIBAH	82	[82],[83]
32	tri-*O*-methyl dynemicin A methyl ester (cf. **Table 5**)			$Pd(PPh_3)_4$	CuI	12	[154]



(−)-manumycin B



mokupalide



papulacandin D

K. Pd-CATALYZED CONJUGATE SUBSTITUTION

Pd-catalyzed conjugate substitution, as defined in **Scheme 1** of **Sect. III.2.15**, is nothing more than Pd-catalyzed alkenylation with β-halo- or β-metallo-substituted α,β-unsaturated carbonyl compounds and related derivatives. Since the reaction is closely related to the widely known conjugate addition and since it can serve as the component of a novel and alternative conjugate addition protocol, their special discussion is warranted.

In cases where β-haloenones and related electrophiles are used, Pd-catalyzed conjugate alkenylation, arylation, alkynylation, and alkylation can readily be achieved. In fact, conjugate substitution generally proceeds more favorably than the corresponding reaction with ordinary alkenyl halides. As in the more usual alkenylation, organometals containing Zn, B, Al, Sn, and Zr have been shown to be generally satisfactory reagents. Grignard reagents are associated with the usual chemoselectivity problems, and organosilanes have thus far been rarely used.

Some details of the syntheses of natural products via Pd-catalyzed conjugate substitution, such as those of dendrolasin and mokuplalide (**Scheme 6** of **Sect. III.2.15**), are discussed in **Sect. III.2.15**. These and additional examples are presented in **Table 12**.

Pd-catalyzed conjugate substitution has also been carried out with β-metalloenones containing mostly Sn and, to a minor extent, Zn. Some examples of their applications to natural product syntheses are also shown in **Table 12**.

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