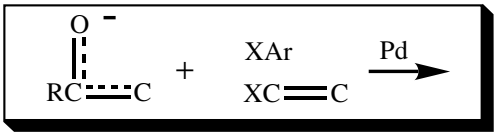

III.2.14 Palladium-Catalyzed Cross-Coupling Involving β-Hetero-Substituted Compounds

III.2.14.1 Palladium-Catalyzed α-Substitution Reactions of Enolates and Related Derivatives Other than the Tsuji–Trost Allylation Reaction

EI-ICHI NEGISHI

1. INTRODUCTION AND BACKGROUND

α-Substitution of carbonyl compounds with a carbon group, as exemplified by enolate alkylation,[1],[2] is a fundamentally important organic transformation. While there are many favorable cases of enolate alkylation, it has also been plagued with some serious limitations and difficulties. Thus, the scope of α-substitution of alkali and alkaline earth metal enolates under the usual thermal conditions is essentially limited to introduction of certain types of alkyl groups, such as Me, primary alkyl, allyl, and benzyl. Although its scope was expanded so as to include α-arylation through the development of radical processes ($S_{RN}1$),[3] its application to α-alkenylation and α-alkynylation remains largely unexplored. Among other methods for α-substitution, α-alkenylation and α-alkynylation of β-keto ester with alkenyl- and alkynylleads[4]–[6] are noteworthy. In view of their somewhat circuitous nature and the use of $Pb(OAc)_4$ as a stoichiometric reagent, however, the development of alternate and potentially more favorable procedures would be desirable. Some other indirect methods for α-alkenylation of carbonyl compounds[7]–[9] should also be noted.

Despite these numerous developments, it is fair to state that none has emerged as a general synthetic method for α-substitution of carbonyl compounds with various types of C_{sp^3}, C_{sp^2}, and C_{sp} groups. Concurrently, several different versions of Ni- and Pd-catalyzed methods for α-substitution of carbonyl compounds have been developed over the past few decades. They are, in fact, discussed in several sections spread over Parts III–V, as indicated below. Several representative methods are shown in **Scheme 1**.

Currently, the most extensively developed and general α-substitution methodology consists of several mutually related indirect protocols using α,β-unsaturated enones as

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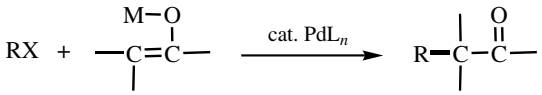
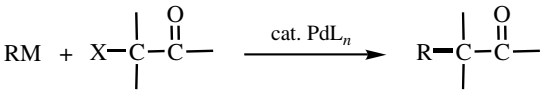
Several Pd-catalyzed methods for the synthesis of α-substituted carbonyl compounds

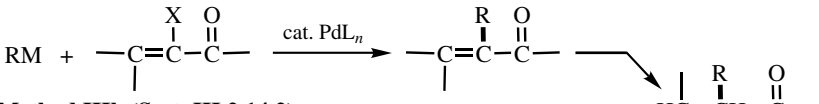
Method I (this section, i.e., **Sect. III.2.14.1**, and **Sect. V.2.1** (the Tsuji–Trost reaction))



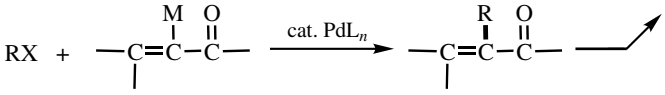
Method II (this section, i.e., **Sect. III.2.14.1**, and **Sect. III.2.14.2**)



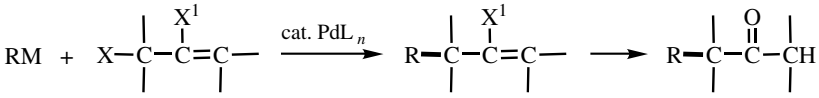
Method IIIa (**Sect. III.2.14.2**)



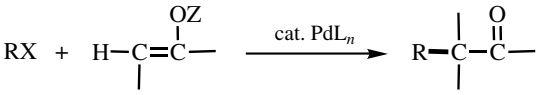
Method IIIb (**Sect. III.2.14.2**)



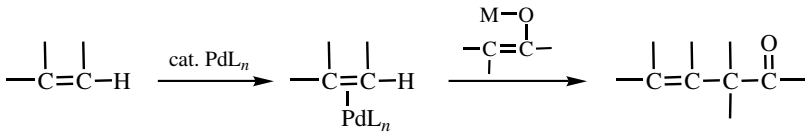
Method IV (**Sect. III.2.14.2**, see also **Sect. III.2.9**)



Method V (**Sect. IV.2.1**, the Heck reaction)



Method VI (**Sect. V.3.4**, Wacker-type C—C bond formation)

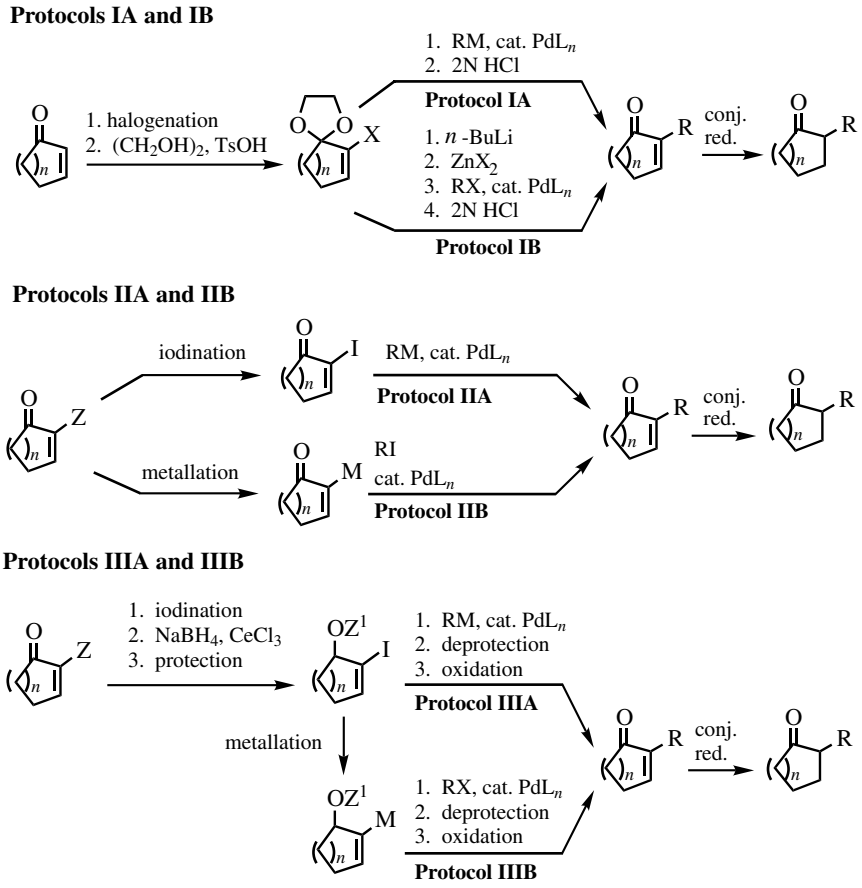


R = C groups. M = Metal or metal groups. X = Heteroatom groups (e.g., halogen, O).

Scheme 1

carbonyl compounds represented by Methods I and II in **Scheme 2**, which are discussed in **Sect. III.2.14.2**. Although indirect, it is applicable to the introduction of a wide range of carbon groups including alkenyl, aryl, alkynyl, as well as alkyl and benzyl groups in a highly stereo- and regio-controlled manner. α-Substituted enones thus obtained can be converted to the corresponding saturated derivatives via conjugate reduction in cases where such a transformation is desirable.

Interestingly, attempts to allylate α-iodoenones with allylmetals containing Zn under the influence of a Pd catalyst led only to the carbonyl addition products,[10] even though the Pd-catalyzed reaction of α-stannylenone with allylic electrophiles proceeds well.[11]



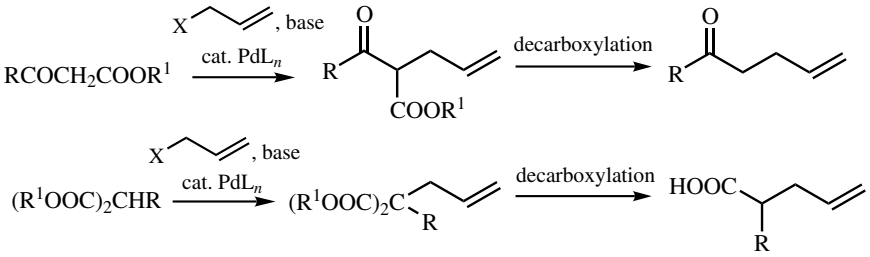
n = 1 or 2. M = Zn, Sn, Cu, B, and other metals. R = C group. Z = H, Si, or Sn group. X = I, Br, or Cl. Z^1 = Si or another protecting group.

Scheme 2

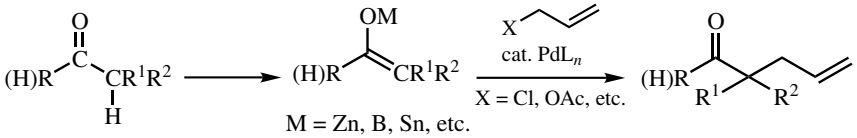
For α-allylation and α-propargylation of carbonyl compounds, however, the Tsuji–Trost reaction and related reactions discussed extensively in **Part V** (**Sect. V.2.1**) provide a wide range of very satisfactory procedures. Although the Tsuji–Trost reaction has mostly been carried out by using extrastabilized enolates, such as acetoacetates and malonates, subsequent decarboxylation provides more usual α-substituted ketones (**Scheme 3**).

With the use of Zn, B, and Sn as enolate countercations, even "ordinary" ketones, aldehydes, and carboxylic acid derivatives, such as esters and amides, can be satisfactorily and selectively α-allylated in the presence of Pd catalysts (**Scheme 4**), as discussed in **Sect. V.2.1.4**.

There are other more indirect and hence less obvious methods for the preparation of α-substituted carbonyl compounds via Pd-catalyzed or Pd-promoted C—C bond formation at a carbon center α to the carbonyl group. In Method IV in **Scheme 1**, β-hetero-substituted allylic electrophiles serve as masked carbonyl compounds. After Pd-catalyzed cross-coupling with organometals, the hetero-substituted alkenes may be converted to the desired α-substituted carbonyl compounds, as discussed in **Sect. III.2.14.2** (**Subsect. F.i**). For a more general discussion of Pd-catalyzed allylation of organometals, **Sect. III.2.9** should be consulted.

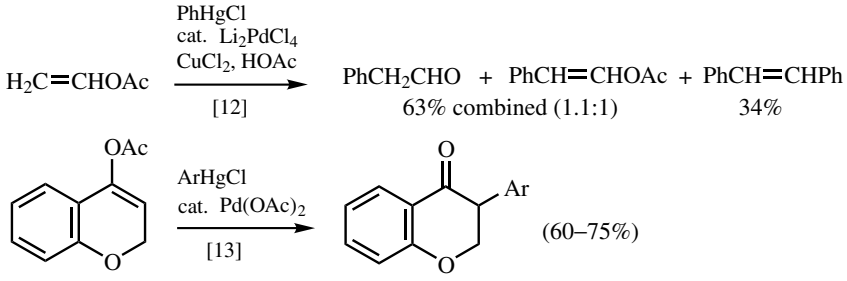


Scheme 3



Scheme 4

The Heck reaction of hetero-substituted alkenes (Method V in **Scheme 1**) can also serve as an indirect method for the preparation of α-substituted carbonyl compounds, as discussed in **Sect. IV.2.1**. Some of the earliest examples are shown in **Scheme 5**. One largely unsolved difficulty is the general lack of regiospecificity. If and when its satisfactory solution is achieved, the method would provide a potentially general and useful route to α-substituted carbonyl compounds.

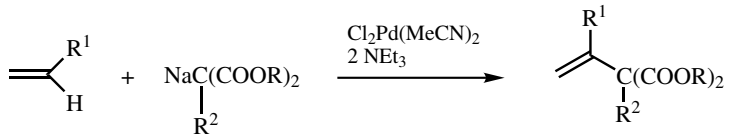


Scheme 5

Finally, the C—C bond formation by the reaction of π-complexes of Pd derived from alkenes, dienes, and other π-compounds with enolates and related carbon nucleophiles *à la* Wacker reaction (Method VI in **Scheme 1**) provides yet another alternative, as exemplified by the results shown in **Scheme 6**.[14] For a more general discussion of the C—C bond formation via Wacker-type reaction of Pd π-complexes with carbanions, the reader is referred to **Sect. V.3.4**.

In this section, attention is focused on the Pd-catalyzed α-substitution reactions of enolates and related derivatives represented by Method I in **Scheme 1**, other than Tsuji–Trost allylation and propargylation. Additionally, its charge-affinity inverted version represented by Method II in **Scheme 1** is also discussed. In general, it is advisable to consider simultaneously various other alternatives including those shown in **Scheme 1**, especially Method III. Indeed, Method III discussed in the following section provides the currently most

rigorous method for the synthesis of α-substituted carbonyl compounds, often permitting strict control of most of the selectivity aspects including regiochemistry, stereochemistry, and the degree of substitution. Nonetheless, the direct α-substitution of carbonyl compounds discussed in this section would be the ultimately satisfactory method provided that all crucial requirements, such as yields and selectivity levels, are satisfied.

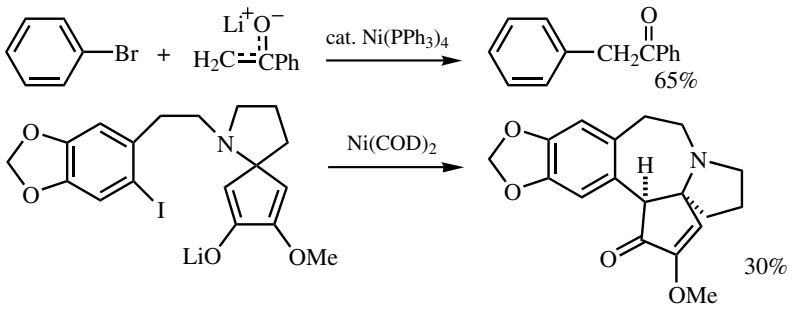


R^1	R^2	R	Yield (%)
H	H	Me	53
Me	H	Me	58
H	Me	Et	93
Me	Me	Et	90

Scheme 6

B. Pd- OR Ni-CATALYZED INTERMOLECULAR α-SUBSTITUTION OF CARBONYL AND RELATED DERIVATIVES

This area of research most probably began when Semmelhack and co-workers reported both inter- and intramolecular versions of Ni-catalyzed arylation of lithium enolates derived from ketones shown in **Scheme 7**.[15],[16] This work, however, was not developed further perhaps due, at least in part, to the fact that the same organic transformation was achieved much more satisfactorily by resorting to the $S_{RN}1$ reaction.[3]



Scheme 7

In 1977 a couple of independent papers by Fauvarque and Jutand,[17] and by Millard and Rathke[18] reported Ni- or Pd-catalyzed α-arylation and α-alkenylation of esters. These studies have been slowly but steadily followed by a series of investigations on Pd-catalyzed α-substitution of ester enolates, nitriles, and other related derivatives in the late 1970s and 1980s, as detailed in **Sect. B.i**.

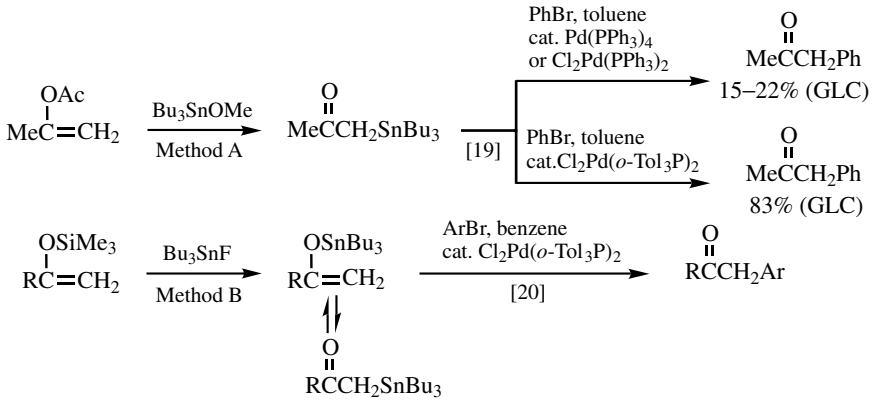
In the meantime, Kosugi et al.[19] and Kuwajima and Urabe[20] independently reported what appears to be the first Pd-catalyzed α-arylation of ketones by using their

trialkylstannyl derivatives. Despite further investigations mainly by Kosugi in the early 1980s,[21]–[24] however, the scope and synthetic utility of the reaction remained rather limited. Thus, for example, the scope of satisfactory α-arylation was largely limited to those of methyl ketones, and no reaction of aldehydes was investigated.

More recently, however, Pd-catalyzed α-arylation of ketones has been reinvestigated mostly by Buchwald,[25]–[27] Hartwig,[28]–[30] and Miura.[31]–[36] It now appears that the reaction is of considerable synthetic value, which is satisfactorily applicable to α-substitution of ketones other than methyl ketones as well as to that of phenols,[31] even though the critical issue of regiochemical control in nonobvious cases still remains largely uninvestigated. These more recent studies are discussed in **Sect. B.ii**.

B.i. Early Studies

B.i.a. ***Pd-Catalyzed α-Substitution of Ketones.*** As mentioned above, the first Pd-catalyzed α-substitution of ketones was most probably that reported independently in 1982 by Kosugi et al.[19] and by Kuwajima and Urabe[20] (**Scheme 8**). In both studies, the nucleophilic reagents derived from ketones were tin enolates that could be generated either by treating enol acetates with trialkyltin methoxides[19] or by treating silyl enol ethers with trialkyltin fluorides.[20] It also appears reasonable to assume that, under most of the cross-coupling conditions, tin enolates are in equilibrium with the corresponding α-stannyl ketones. The use of $Pd(PPh_3)_4$ or $Cl_2Pd(PPh_3)_2$ was ineffective, but $Cl_2Pd(o\text{-}Tol_3P)_2$ was a satisfactory catalyst[19] (**Scheme 8**).



Scheme 8

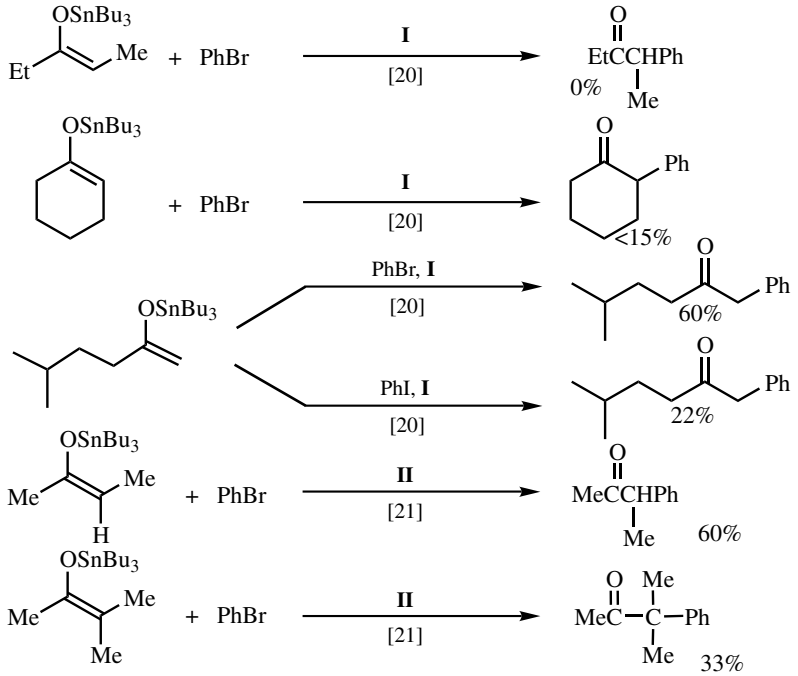
Some representative results are summarized in **Table 1**. These results indicate the following. First, as long as the steric requirements of R are not excessive, α-arylation can be achieved in moderate-to-excellent yields by using the conditions indicated in **Scheme 8**. However, the scope is practically limited to α-substitution of methyl ketones. The yields of α-phenylation observed with 3-pentanone and cyclohexanone were 0% and $<15\%$, respectively,[20] although more favorable results have also been reported in similar cases[21] (**Scheme 9**). Also disappointing is the yield of α-phenylation of pinacolone (29%). Second, various substituents in Ar, such as Me, *p*-MeO, *p*-Me_2N, and *p*-Cl, can be accommodated and little electronic effects are noticeable. Curiously, the use of aryl iodides appears to be much less desirable than that of aryl bromides,[20] as indicated by the results shown in **Scheme 9**.

TABLE 1. Pd-Catalyzed α-Arylation of Tin Enolates Derived from Methyl Ketones with Aryl Bromides in the Presence of $Cl_2Pd(o\text{-}Tol_3P)_2$ (cf. Scheme 8)

R of RCOMe	Ar of ArBr	Method[a]	Solvent	Temperature (°C)	Yield[b] of $RCOCH_2Ar$ (%)	Reference
Me	Ph	A	Toluene	100	78	[19]
Me	*o*-Tol	A	Toluene	100	91	[19]
Me	*m*-Tol	A	Toluene	100	88	[19]
Me	*p*-Tol	A	Toluene	100	80	[19]
Me	*p*-$Me_2NC_6H_4$	A	Toluene	100	71	[19]
Me	*p*-Anisyl	A	Toluene	100	51	[19]
Me	*p*-ClC_6H_4	A	Toluene	100	73	[19]
Me	*p*-$MeCOC_6H_4$	A	Toluene	100	64	[19]
n-C_7H_{15}	Ph	B	Benzene	reflux	61	[20]
n-C_7H_{15}	*p*-Anisyl	B	Benzene	reflux	62	[20]
$Me_2CH(CH_2)_2$	Ph	B	Benzene	reflux	60(84)	[20]
$Me_2CH(CH_2)_2$	*o*-Tol	B	Benzene	reflux	59	[20]
$Me_2CH(CH_2)_2$	*p*-Anisyl	B	Benzene	reflux	58(86)	[20]
$Me_2CH(CH_2)_2$	*p*-$MeCOC_6H_4$	B	Benzene	reflux	—(70)	[20]
s-Bu	Ph	B	Benzene	reflux	47	[20]
t-Bu	Ph	B	Benzene	reflux	29	[20]
$Me_2C{=}CH$	Ph	B	Benzene	reflux	—(56)	[20]

[a] See **Scheme 8** for A and B.

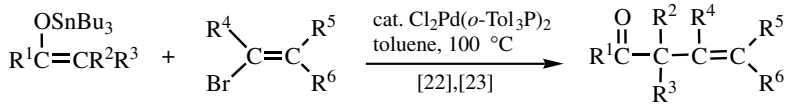
[b] The numbers in parentheses are the yields observed with 1.5 equiv of ArBr.



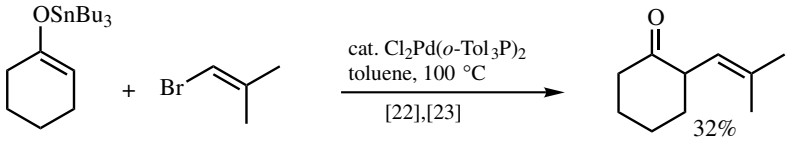
I = 3 mol % $Cl_2Pd(o\text{-}Tol_3P)_2$, benzene, reflux.
II = 0.7 mol % $Cl_2Pd(o\text{-}Tol_3P)_2$, toluene, 100 °C.

Scheme 9

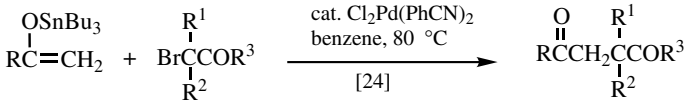
This method is also applicable to α-alkenylation[22],[23] (**Scheme 10**) and the synthesis of 1,4-diketones[24] and γ-ketoesters[37] (**Scheme 11**). As in α-arylation, favorable results are largely limited to the α-substitution of methyl ketones.



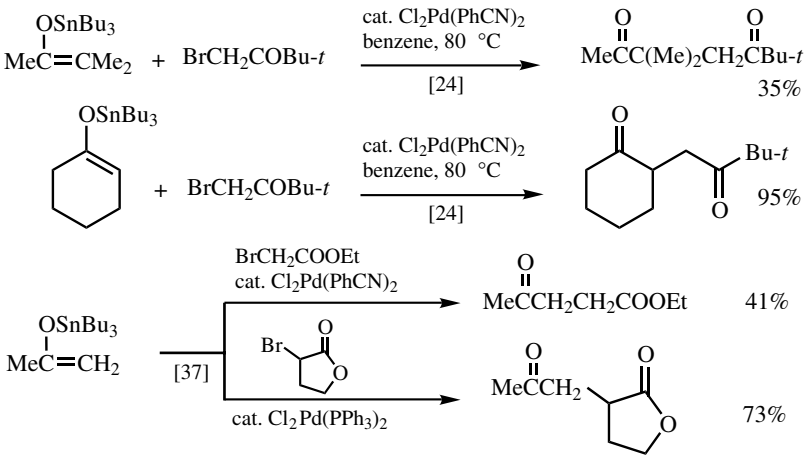
R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)
t-Bu	H	H	Me	H	H	53
t-Bu	H	H	H	Me	Me	81
t-Bu	H	H	Me	Me	Me	86
t-Bu	H	H	Me	Me	H	76
t-Bu	H	H	Me	H	Me	90
Me	Me	H	H	Me	Me	35
Me	Me	Me	H	Me	Me	8



Scheme 10



R	R^1	R^2	R^3	Yield (%)
Me	H	H	*t*-Bu	83
Me	Me	H	Et	70
Me	Me	H	*t*-Bu	73
Me	Me	Me	Me	0
Me	H	H	*n*-Hex	66
t-Bu	H	H	*t*-Bu	97

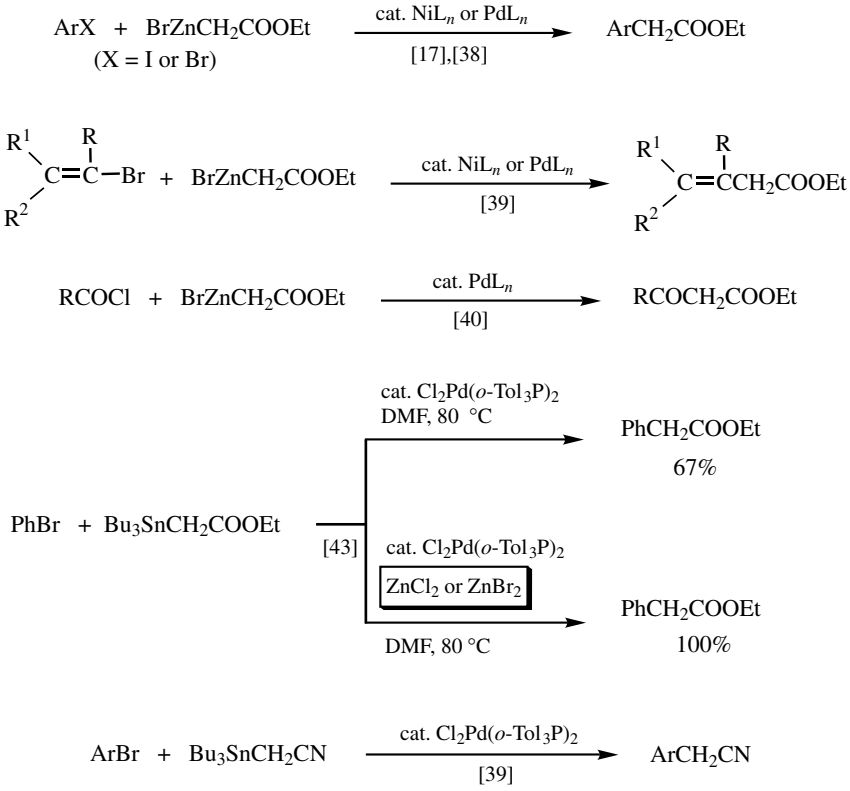


Scheme 11

B.i.b. ***Pd-Catalyzed α-Substitution of Esters, Nitriles, and Other Related Derivatives.*** Following the pioneering work of Fauvarque and Jutand,[17],[38] Pd-catalyzed α-substitution of esters using Reformatsky reagents has been applied not only to α-arylation but also to α-alkenylation[39] and α-acylation.[40] More recent studies reported the use of aryl and alkenyl triflates as electrophiles.[41],[42]

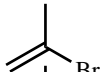
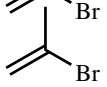
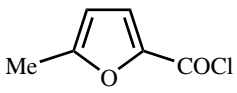
A variant of Pd-catalyzed α-substitution reactions of Reformatsky reagents is the use of the corresponding tin reagents,[43] for example, Bu_3SnCH_2COOEt. The use of Bu_3SnCH_2CN in place of esters was also reported.[44] In α-arylation of Bu_3SnCH_2COOEt, however, the most favorable results were obtained by using $ZnBr_2$ or $ZnCl_2$ (1.3 equiv) as an added reagent. The Sn-to-Zn transmetallation to *in situ* generate the Reformatsky reagent was judged to be unlikely by the authors. Regardless of mechanistic details, however, its synthetic merits relative to the direct use of Reformatsky reagents are rather questionable. Another variant involves the use of silyl enol ethers and TlOAc.[45],[46] Here again, its merits relative to the reaction of Reformatsky reagents are not clear.

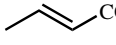
Some of the representative results are summarized in **Scheme 12** and **Tables 2** and **3**. It should be noted that α-alkenylation of ester enolates is prone to regioisomerization to produce α,β-unsaturated esters (**Table 2**) and that this tendency is more pronounced with Ni than Pd.

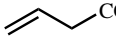
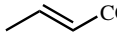
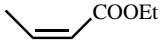


Scheme 12

TABLE 2. Pd- or Ni-Catalyzed α-Arylation and α-Alkenylation of $BrZnCH_2COOEt$ (cf. Scheme 12)

RX	Catalyst	Other Conditions	Product Yield (%)	Reference
PhI	$PhPdI(PPh_3)_2$	HMPA	90	[38]
PhI	$Ni(PPh_3)_4$	HMPA	85	[38]
PhBr	$Ni(PPh_3)_4$	HMPA	67	[38]
PhCl	$Ni(PPh_3)_4$	HMPA	65	[38]
PhF	$Ni(PPh_3)_4$	HMPA	0	[38]
PhI	$Ni(PPh_3)_4$	NMP	86	[38]
PhCl	$Ni(PPh_3)_4$	NMP	86	[38]
PhI	$Ni(PPh_3)_4$	DMF	72	[38]
PhCl	$Ni(PPh_3)_4$	DMF	23	[38]
1-NaphBr	$Ni(PPh_3)_4$	HMPA	69	[38]
1-NaphCl	$Ni(PPh_3)_4$	HMPA	24	[38]
	$Ni(PPh_3)_4$	HMPA	88[a]	[39]
	$Pd(PPh_3)_4$	HMPA	64[b]	[39]
	$Ni(PPh_3)_4$	HMPA	91	[39]
	$Pd(PPh_3)_4$	HMPA	86	[39]
(*E*)-PhCH=CHBr E/Z = 94:6	$Pd(PPh_3)_4$	HMPA	96[c]	[39]
(*Z*)-PhCH=CHBr 100% Z	$Pd(PPh_3)_4$	HMPA	86[d]	[39]
PhCOCl	$Pd(PPh_3)_4$	DME	80	[40]
m-ClC_6H_4COCl	$Pd(PPh_3)_4$	DME	83	[40]
p-MeC_6H_4COCl	$Pd(PPh_3)_4$	DME	84	[40]
p-$MeOC_6H_4COCl$	$Pd(PPh_3)_4$	DME	51	[40]
p-$NO_2C_6H_4COCl$	$Pd(PPh_3)_4$	DME	41	[40]
(*E*)-MeCH=CHCOCl	$Pd(PPh_3)_4$	DME	72	[40]
	$Pd(PPh_3)_4$	DME	89	[40]
n-OctCOCl	$Pd(PPh_3)_4$	DME	30	[40]

[a]  COOEt (100%).

[b]  COOEt (63%),  COOEt (25%), and  (12%).

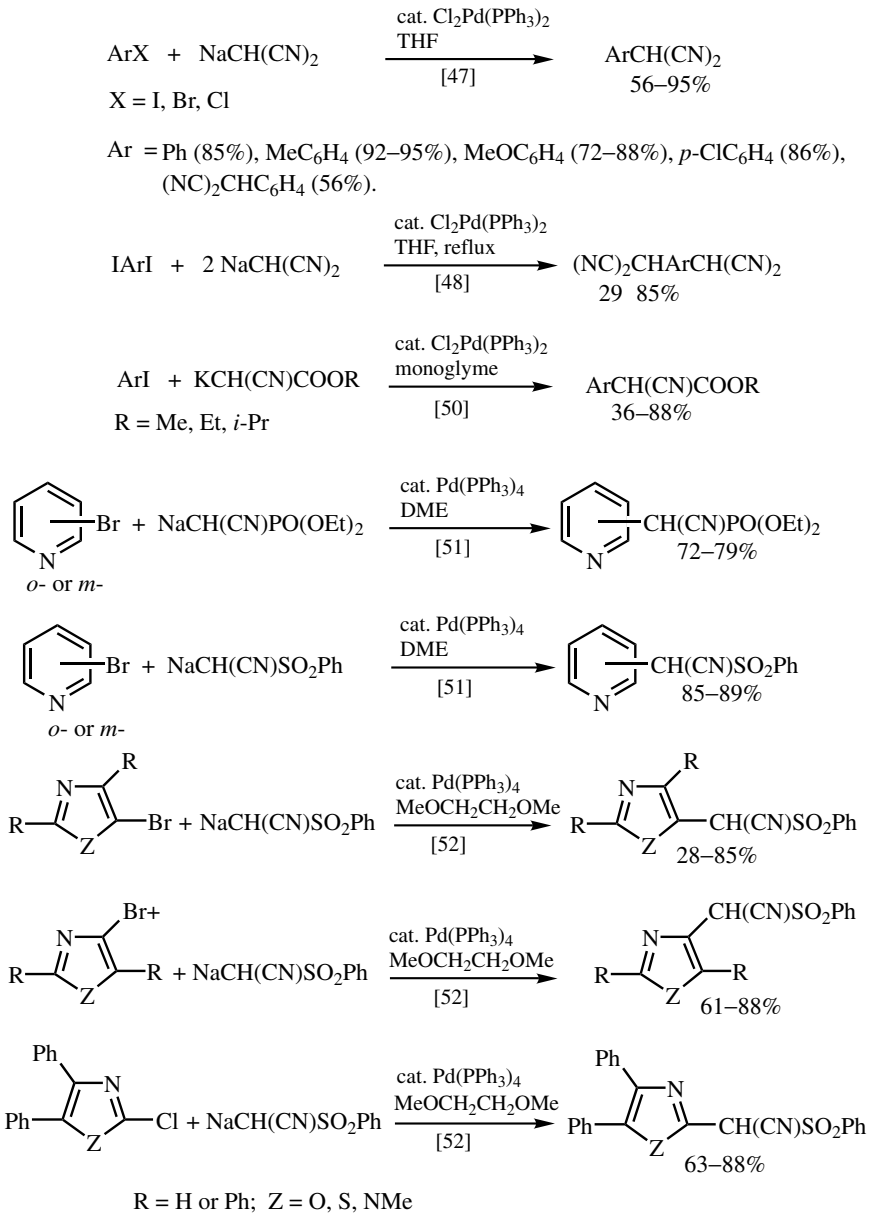
[c] E/Z = 88:12.

[d] E/Z = 46:54.

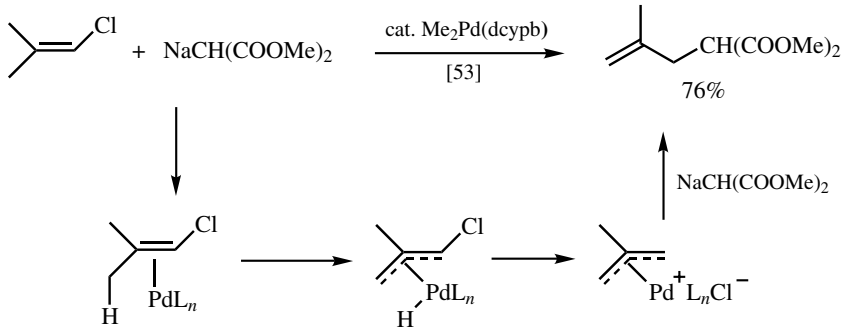
TABLE 3. Pd-Catalyzed Arylation of Bu_3SnCH_2COOEt and Bu_3SnCH_2CN (cf. Scheme 12)

Ar of ArBr	Bu_3SnCH_2COOEt or Bu_3SnCH_2CN	Catalyst	Other Conditions	Product Yield(%)	Reference
Ph	Bu_3SnCH_2COOEt	$Pd(PPh_3)_4$	HMPA	25	[43]
Ph	Bu_3SnCH_2COOEt	$Cl_2Pd(PhCN)_2$	HMPA	Trace	[43]
Ph	Bu_3SnCH_2COOEt	$Cl_2Pd(PPh_3)_2$	HMPA	36	[43]
Ph	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	HMPA	59	[43]
Ph	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	DMF	67	[43]
Ph	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)$	$ZnBr_2$ or $ZnCl_2$, DMF	100	[43]
Ph	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	Benzene	25	[43]
Ph	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	THF	34	[43]
p-MeC_6H_4	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	$ZnBr_2$, DMF	93	[43]
m-MeC_6H_4	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	$ZnBr_2$, DMF	60	[43]
o-MeC_6H_4	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	$ZnBr_2$, DMF	71	[43]
p-ClC_6H_4	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	$ZnBr_2$, DMF	89	[43]
o-$MeOC_6H_4$	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	$ZnBr_2$, DMF	82	[43]
p-$MeCOC_6H_4$	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	$ZnBr_2$, DMF	22	[43]
p-NCC_6H_4	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	$ZnBr_2$, DMF	67	[43]
p-$O_2NC_6H_4$	Bu_3SnCH_2COOEt	$Cl_2Pd(o\text{-}Tol_3P)_2$	$ZnBr_2$, DMF	34	[43]
Ph	Bu_3SnCH_2CN	$Cl_2Pd(o\text{-}Tol_3P)_2$	m-Xylene	72	[44]
$Me_2C_6H_4$	Bu_3SnCH_2CN	$Cl_2Pd(o\text{-}Tol_3P)_2$	m-Xylene	74–78	[44]
o- or p-$MeOC_6H_4$	Bu_3SnCH_2CN	$Cl_2Pd(o\text{-}Tol_3P)_2$	m-Xylene	70–77	[44]
o- or p-ClC_6H_4	Bu_3SnCH_2CN	$Cl_2Pd(o\text{-}Tol_3P)_2$	m-Xylene	66–67	[44]

The scope of Pd-catalyzed α-arylation of enolates has been further expanded so as to include amides,[29] malononitrile,[47]–[49] α-cyanoesters,[50] α-cyanophosphates, and α-cyanosulfones.[51],[52] The metal countercations in these reactions are mostly alkali metals, such as Li, Na, K, and Cs. Some representative examples of these reactions are shown in **Scheme 13**. The Pd-catalyzed reaction of 2-methyl-1-propenyl chloride with $NaCH(COOMe)_2$ in the presence of 2 mol% of $Me_2Pd(dcypb)$, where dcypb is $Cy_2P(CH_2)_3PCy_2$, led to 2-methylallylation[53] (**Scheme 14**).



Scheme 13



Scheme 14

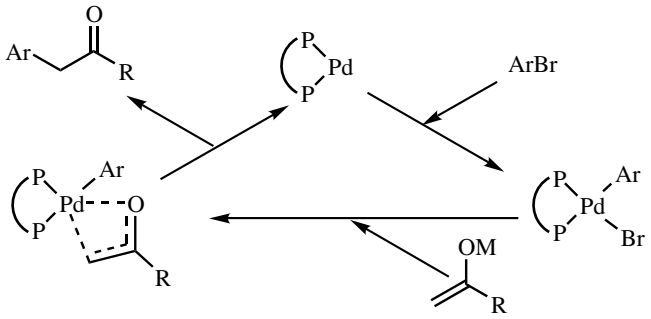
B.ii. Recent Reinvestigations of Pd-Catalyzed α-Arylation of Ketones

The Pd-catalyzed α-arylation of ketones developed in the 1970s and 1980s (*vide supra*) was of rather limited synthetic scope. In most of the early studies, tin enolates (or α-stannyl ketones) were used. In this connection, however, it should be pointed out that ketone enolates containing Zn and B have been used successfully in Pd-catalyzed α-allylation (**Sect. V.2.1.4**),[54],[55] although their applicability to α-arylation and other α-substitution reactions has not been explored.

In 1997, Palucki and Buchwald[25] and Hamann and Hartwig[28] independently reported improved procedures for Pd-catalyzed α-arylation of ketones that involve three readily noticeable changes from the previously known Sn-based method. First, chelating ligands, such as BINAP, Tol-BINAP, and dppf, are used in place of monodentate phosphines, such as *o*-Tol_3P. Second, alkali metals, such as Na and K, are used in place of Sn-containing groups. Third, THF is used in place of benzene, toluene, and so on. Although it is not very clear which of the above-mentioned three factors are critically responsible, the results are generally noticeably superior to those reported earlier. Significantly, the recently developed procedures are applicable to high-yielding α-arylation of even ketones other than methyl ketones.

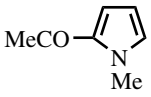
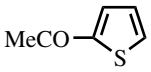
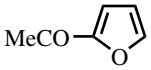
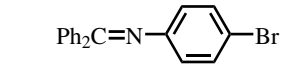
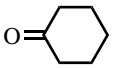
An adaptation of the widely accepted three-step catalytic cycle shown in **Scheme 15** has been proposed for the reaction.[25],[28]

Some representative results are shown in **Table 4**. These results indicate that the yields of the desired products range from about 50% to 95% and are mostly good to excellent.



Scheme 15

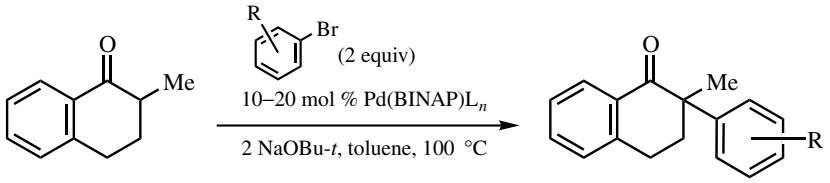
TABLE 4. Pd-Catalyzed α-Arylation of Ketone Enolates Containing Na or K in THF

ArBr	Ketone	Catalyst[a]	Base	Product Yield (%)	Reference
PhBr	MeCOPh	A	$KN(SiMe_3)_2$	84	[28]
o-MeC_6H_4Br	MeCOPh	A	$KN(SiMe_3)_2$	94	[28]
p-(t-Bu)C_6H_4Br	MeCOPh	A	$KN(SiMe_3)_2$	85	[28]
m-NCC_6H_4Br	MeCOPh	A	NaOBu-*t*	73	[28]
p-$MeOC_6H_4Br$	MeCOPh	A	$KN(SiMe_3)_2$	69	[28]
PhBr		A	$KN(SiMe_3)_2$	79	[28]
PhBr		A	$KN(SiMe_3)_2$	68	[28]
PhBr		A	$KN(SiMe_3)_2$	57	[28]
PhBr	MeCOBu-*t*	A	$KN(SiMe_3)_2$	51	[28]
	MeCOBu-*n*	B	NaOBu-*t*	64[b]	[25]
3,5-$Me_2C_6H_3Br$	MeCOBu-*t*	C	NaOBu-*t*	93	[25]
p-ClC_6H_4Br	$MeCOCH_2$Bu-*t*	C	NaOBu-*t*	71[c]	[25]
p-$Et_2NCOC_6H_4Br$	$MeCOCHPh_2$	C	NaOBu-*t*	69	[25]
PhBr	EtCOPh	A	$KN(SiMe_3)_2$	71	[28]
PhBr	*i*-PrCOPh	A	$KN(SiMe_3)_2$	55	[28]
p-PhC_6H_4Br	EtCOPr-*i*	B	NaOBu-*t*	93	[25]
m-$MeOC_6H_4Br$	EtCOPh	C	NaOBu-*t*	91	[25]
p-(t-Bu)C_6H_4Br		C	NaOBu-*t*	67	[25]

[a] A = $Pd(dba)_2$ + dtpf (= 1,1′-bis(di-o-tolylphosphino)ferrocene).
B = $Pd_2(dba)_3$ + BINAP. C = $Pd_2(dba)_3$ + Tol-BINAP.
[b] A 20:1 mixture of regioisomers. Mono/di = 10:1.
[c] Mono/di = 7:1.

The majority of the examples involve α-arylation of methyl ketones. However, several examples at the bottom of **Table 4** clearly indicate that high product yields may be observed also in other cases. Although high regioselectivity can be observed in more obvious cases, the regiochemistry of more delicate cases where the two CO-bound carbon groups are very similar remains to be investigated. In this connection, it should be pointed out that the α-haloenone-based methodology discussed in **Sect. III.2.14.2** provides a strictly regiospecific, if somewhat more indirect, alternative.

Many additional data may also be found in the corresponding full papers.[27],[30] It is noteworthy that enantioselective α-arylation can be achieved in up to 88% ee, as shown in **Scheme 16**.[26]



R	Yield (%)	ee (%)
H	66	73
p-(*t*-Bu)	73	88
m-	74	84
p-CN	40	61

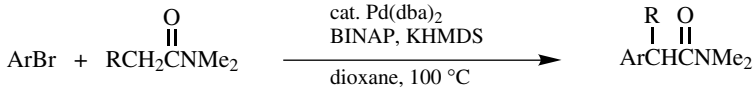
Scheme 16

B.iii. Recent Investigations of Pd-Catalyzed *α*-Arylation of Other Carbonyl and Related Compounds

Amides. Despite many investigations in the 1970s and 1980s on Pd-catalyzed α-arylation of carboxylic acid derivatives, that of amides had not been studied until recently. In 1998, the reaction of potassium enolates of *N*,*N*-dimethylacetamide (DMA) and other amides with aryl bromides in the presence of catalytic amounts of $Pd(dba)_2$ and bidentate phosphines, such as BINAP and dppf, was shown to provide the desired *α*-arylated products in up to roughly 70% yields, as shown in **Table 5**.[29] Diarylation competed with monoarylation to the extent of up to 18%. Under the conditions used, the intermolecular reactions of amides other than acetamides were rather disappointing, as indicated by the last two entries in **Table 5**. Clearly, additional development is desirable. Its intramolecular cyclic version, however, is considerably more favorable, as discussed in the following subsection.

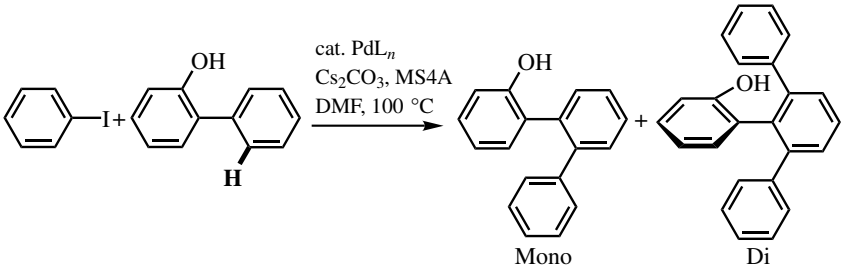
Phenols. Pd-Catalyzed α-arylation of phenols or phenolates was studied first within the context of intramolecular cyclization,[56] as discussed in the following subsection. A more

TABLE 5. Pd-Catalyzed *α*-Arylation of Amides

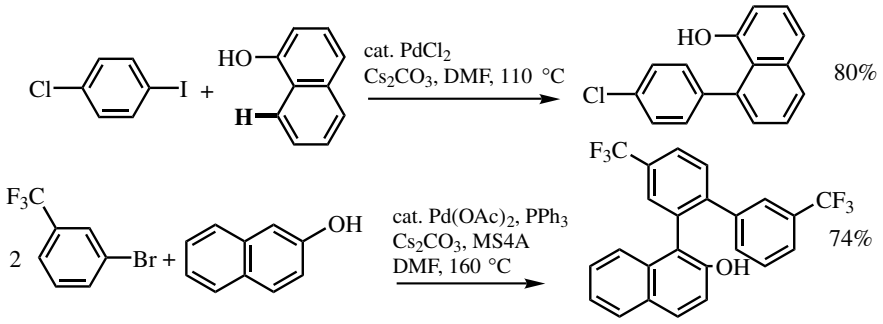


ArBr	R	Time (h)	Yield (%) Monoarylated	Yield (%) Diarylated
o-MeC$_6$H$_4$Br	H	1.5	72	4
p-MeC$_6$H$_4$Br	H	1.5	72	10
p-MeOC$_6$H$_4$Br	H	4	48	18
p-PhC$_6$H$_4$Br	H	2	66	13
β-NaphBr	H	2	70	9
p-BuC$_6$H$_4$Br	Me	3	16	—

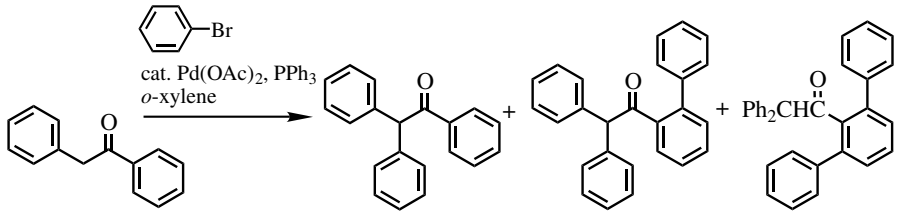
recent investigation of the intermolecular version of Pd-catalyzed α-arylation of phenolates has indicated that, in addition to or in place of the desired α-arylation, arylation in some other positions in phenols can occur. Some representative examples are shown in **Scheme 17**.[31],[33] Similar arylation reactions of benzyl aryl ketones have also been recently reported, as shown in **Scheme 18**.[35] These results indicate that appropriately positioned arene C—H bonds can be intramolecularly activated and metallated by Pd. Similar intramolecular arene C—H activations by Pd are also discussed in **Sects. IV.6.2** and **VI.4.1.2**.



PhI/ArOH	PdL$_n$	Time (h)	Yield % Mono	Yield % Di
2:1	$Pd(OAc)_2$	22	[80]	12
4:1	$PdCl_2$	44	14	[70]



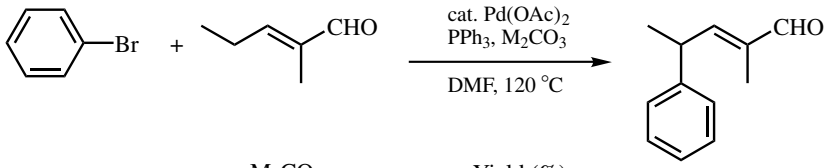
Scheme 17



M_2CO_3	Time (h)	Yield (%) Mono	Yield (%) Di	Yield (%) Tri
K_2CO_3	24	[96]	3	0
Cs_2CO_3	5	47	[35]	9
Cs_2CO_3	22	1	5	[54]

Scheme 18

α,β-Unsaturated Aldehydes. Whereas Pd-catalyzed α-arylation of ordinary aldehydes remains elusive, an interesting and potentially useful γ-arylation of α,β-unsaturated aldehydes has recently been reported[32] (**Scheme 19**). Here again, the superiority of Cs_2CO_3 relative to K_2CO_3 or Na_2CO_3 is evident. Although multiple arylation is possible and has in fact been observed, the desired monoarylation products can be obtained generally in high yields[32] (**Table 6**).

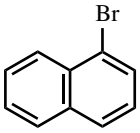
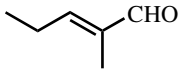
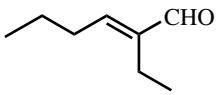
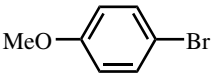
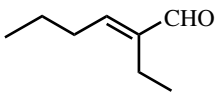
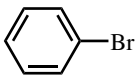
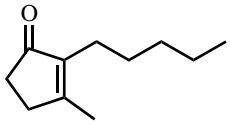
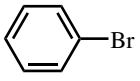
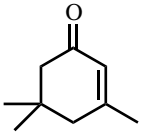


M_2CO_3	Yield (%)
Cs_2CO_3	84
K_2CO_3	69
Na_2CO_3	12
Cs_2CO_3 (PhI)	34[a]

[a] PhI was used in place of PhBr, and the reaction temperature was 60 °C.

Scheme 19

TABLE 6. Pd-Catalyzed γ-Arylation of α,β-Unsaturated Aldehydes

ArBr	Aldehyde	Temperature (°C)	Time (h)	Yield[a] (%)
		60	4	94 (67)
		60	4	82 (64)
		60	2	92 (60)
		60	21	58 (47)[b]
		60	6	71 (56)[b]

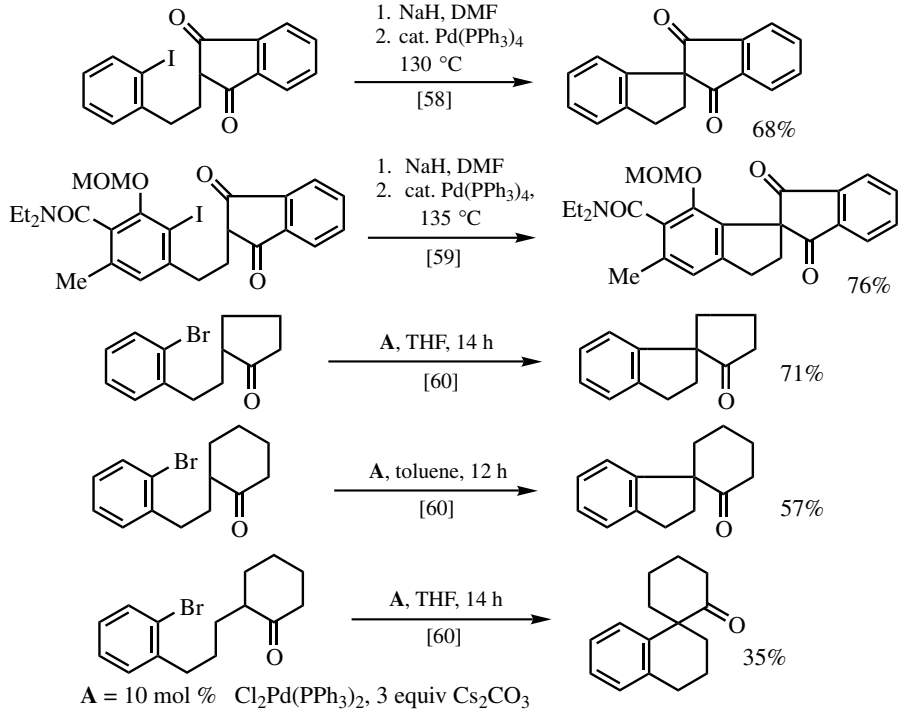
[a] GLC yield. The numbers in parentheses are isolated yields.
[b] Minor amounts (<10%) of diarylated products were formed.

Imines and Enamines. Imines and enamines can also be α-arylated. Since this reaction is currently limited to intramolecular cyclization to produce indoles,[57] it is discussed in the following subsection.

C. Pd-CATALYZED INTRAMOLECULAR CYCLIZATION VIA α-SUBSTITUTION OF CARBONYL AND RELATED DERIVATIVES

In view of the various types of Pd-catalyzed intermolecular α-substitution of carbonyl compounds discussed above, it might readily be expected that their intramolecular versions can proceed satisfactorily to produce cyclic compounds, provided that there is not an excessive ring strain in the cyclic structure to be formed. Indeed, ketones, esters, amides, nitriles, imines, enamines, and phenols containing haloaryl, haloalkenyl, and related electrophilic groups have been converted to the corresponding cyclic compounds under the influence of Pd catalysts, as detailed below.

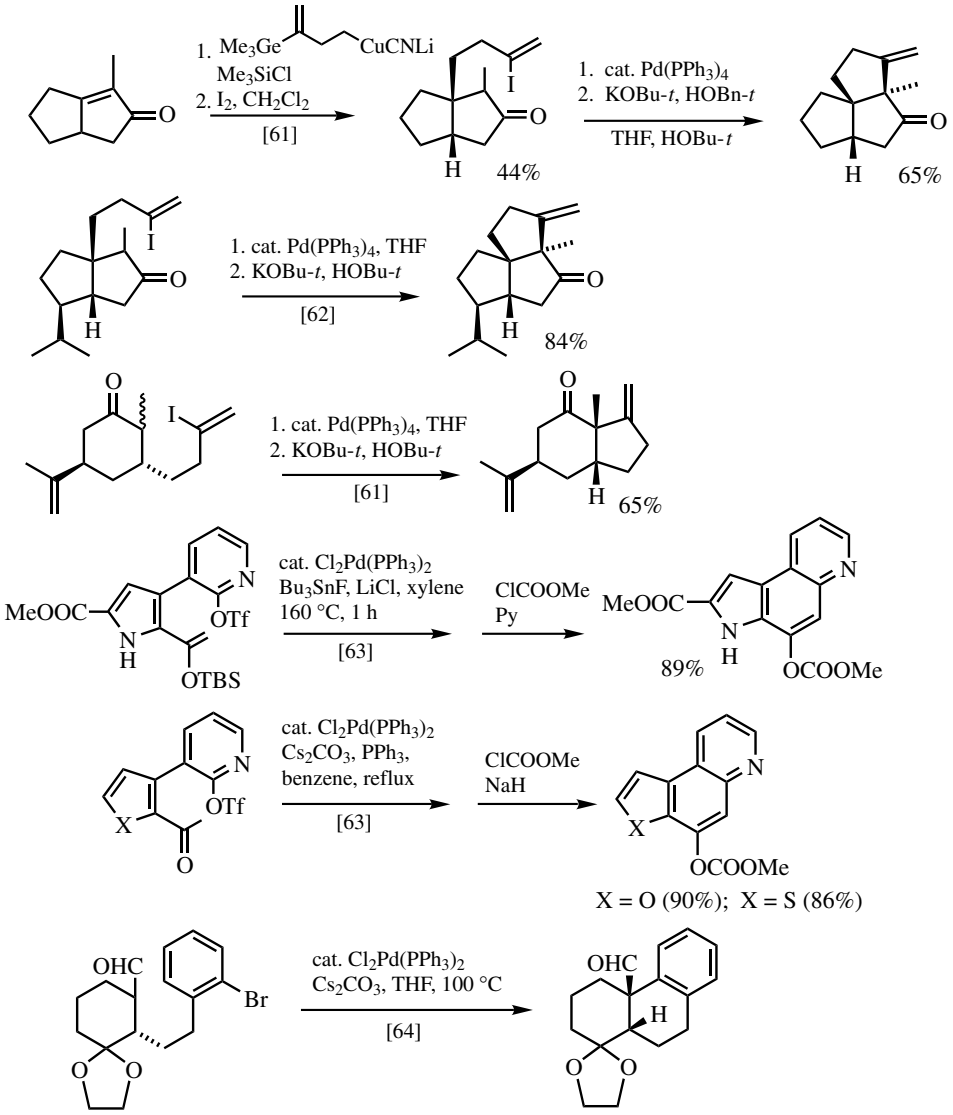
Ketones. Although Ni-catalyzed cyclization of iodoaryl-containing lithium enolates shown in **Scheme 7**[16] might represent the first example of this class of reactions, subsequent studies have been performed mainly with Pd catalysts. The syntheses of spiro-fused oligocyclic models for fredericamycin A by Ciufolini and co-workers[58],[59] provided some prototypical examples of Pd-catalyzed cyclization via intramolecular α-arylation of ketones **(Scheme 20)**. Under appropriate conditions, bromoaryl-containing monoketones can also be converted to spiro-fused bicycles and oligocycles[60] (**Scheme 20**).



Scheme 20

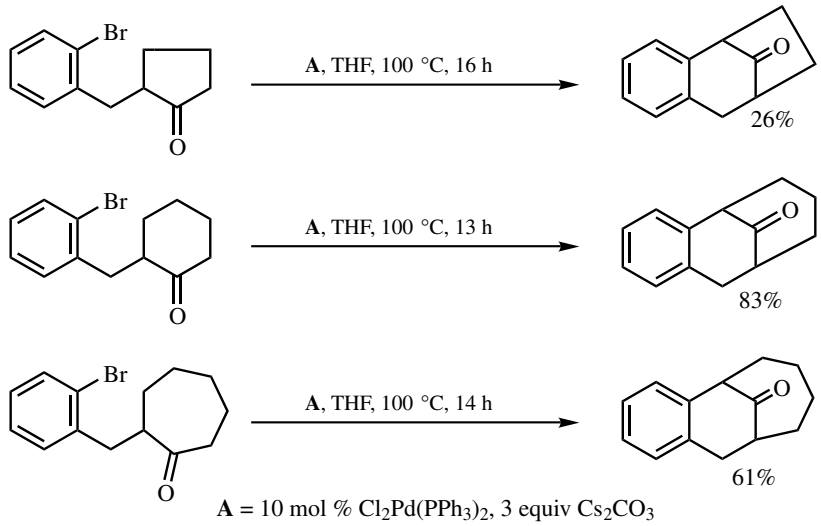
Most of the other currently known examples deal with the formation of fused bicycles and oligocycles, as summarized in **Scheme 21**.

Some examples of the formation of bridge-fused bicycles and oligocycles are also known, as shown in **Scheme 22**.[60]



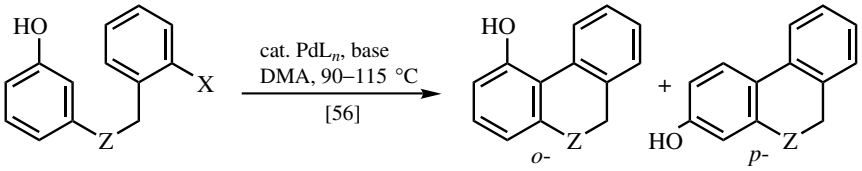
Scheme 21

Phenols. The Pd-catalyzed intramolecular cyclization reaction of haloaryl-containing phenols, in which the haloaryl-containing substitutents are *meta* to OH, proceeds readily to give fused bicycles and oligocycles in high yields.[56] The use of K- or Cs-containing bases, for example, KOBu-*t*, K_2CO_3, and Cs_2CO_3, is advantageous. The high *o/p* ratio is noteworthy (**Scheme 23**).[56]

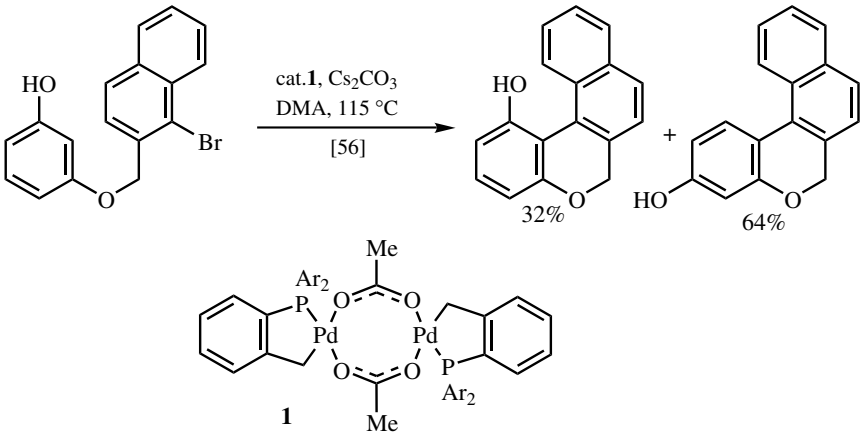


A = 10 mol % $Cl_2Pd(PPh_3)_2$, 3 equiv Cs_2CO_3

Scheme 22

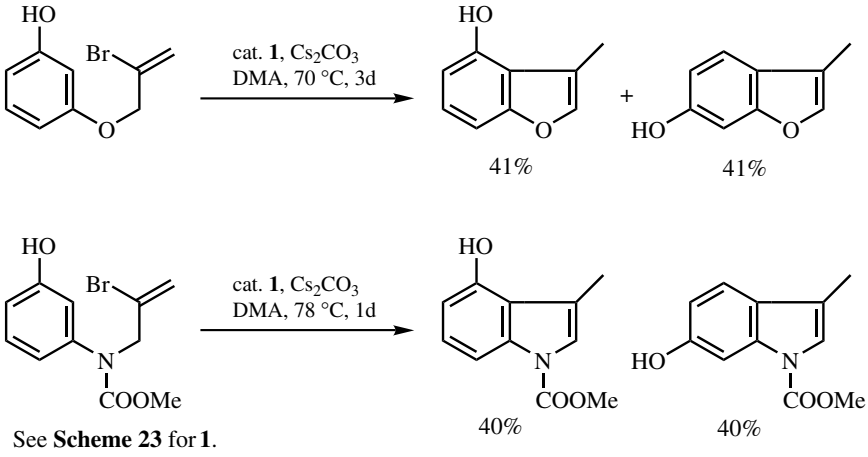


X	Z	Catalyst	Base	Yield (%) *o*-	Yield (%) *p*-
Br	O	$Pd(PPh_3)_4$	KOBu-*t*	87	2–5
Br	CH_2	**1**	Cs_2CO_3	75	Very minor
I	NCOOMe	**1**	Cs_2CO_3	76	Very minor



Scheme 23

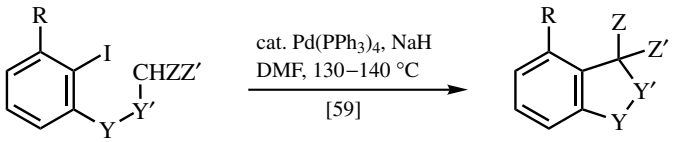
The scope of the cyclization reaction has been extended so as to permit the synthesis of five-membered rings, such as benzofurans and indoles, by using Herrmann's catalyst (**1**).[65] Unfortunately, however, the regioselectivity observed in the formation of benzo-fused five-membered rings has been uniformly low (**Scheme 24**).[66]



See **Scheme 23** for **1**.

Scheme 24

Esters, Nitriles, Amides, Imines, and Enamines. Pd-Catalyzed α-arylation of extrastabilized enolates and related derivatives containing esters and nitrile groups developed by Uno, Takahashi, and co-workers[47],[48],[50] (**Sect. B.i.b**.) has been applied to the synthesis of cyclic compounds with moderate success, as indicated by the results shown in **Scheme 25**.[59]



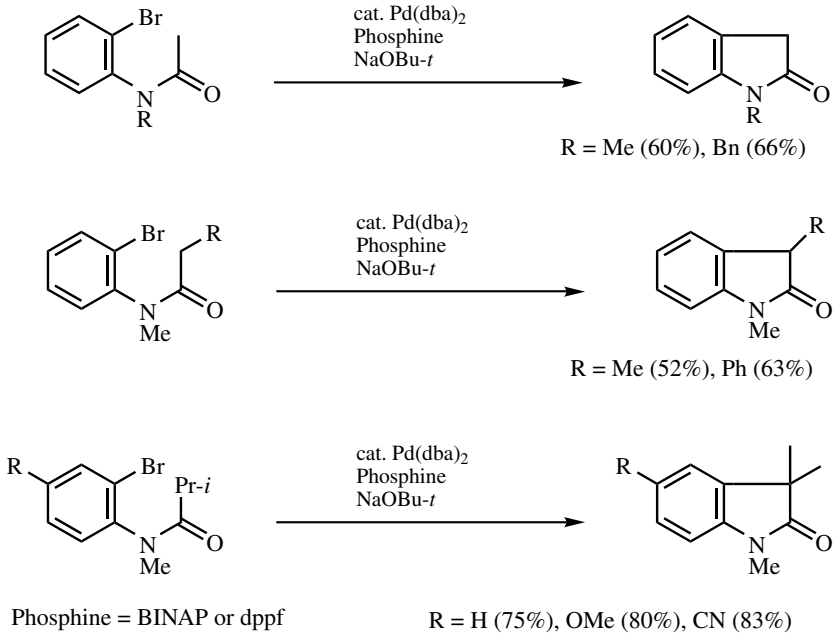
R	Y	Y′	Z	Z′	Yield (%)
H	CH_2	CH_2	COOEt	COOEt	62
Me	CH_2	CH_2	COOEt	COOEt	75
H	CH_2	CH_2	COMe	COOEt	53
H	CH_2	CH_2	CN	COOEt	38
H	CH_2	CH_2	CN	CN	54
H	CH_2	$(CH_2)_2$	CN	COOEt	49
H	NMe	CO	Me	COOEt	31
H	CH_2	CO	H	COOMe	0

Scheme 25

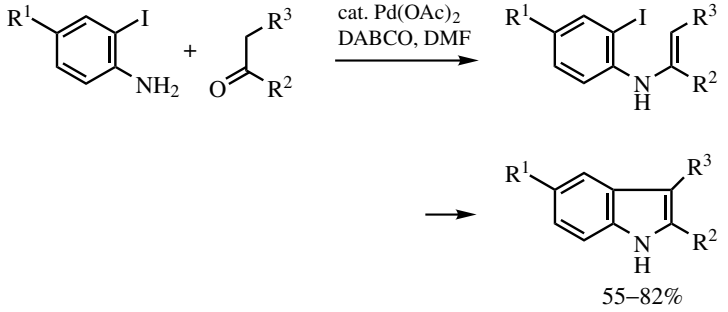
The intramolecular version of Pd-catalyzed α-arylation of amides is considerably more favorable than its intermolecular version[29] (**Scheme 26**).

Imines and enamines react similarly to give indoles generally in good yields[57] (**Scheme 27**).

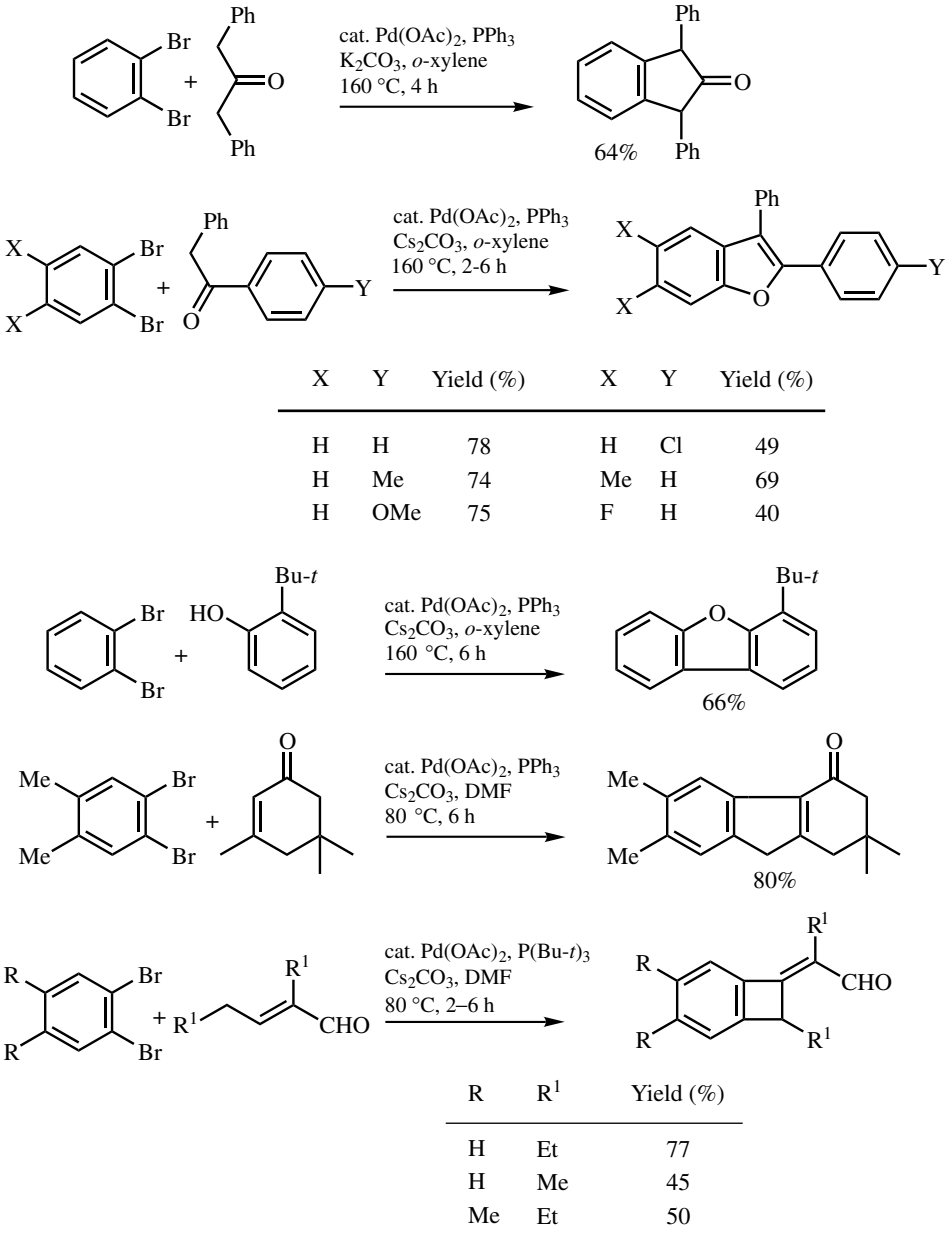
Inter–Intra Tandem Processes Involving Pd-Catalyzed α-Arylation of Carbonyl Compounds with 1,2-Dibromoarenes. 1,2-Dibromoarenes have been shown to undergo Pd-catalyzed inter–intra tandem processes leading to the formation of cyclic compounds, as summarized in **Scheme 28**.[34] In some examples, however, the cyclization process itself does not actually involve Pd-catalyzed α-arylation. It instead involves either an interesting diaryl ether formation (**Sect. III.3.3**) or intramolecular Heck reaction (**Sect. IV.2.2**).



Scheme 26



Scheme 27



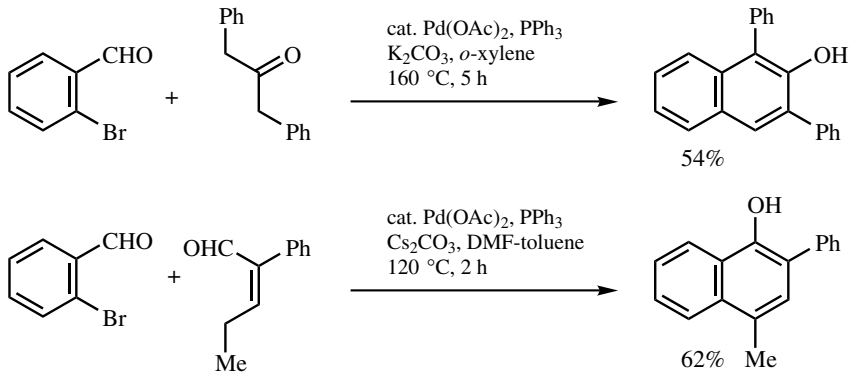
X	Y	Yield (%)	X	Y	Yield (%)
H	H	78	H	Cl	49
H	Me	74	Me	H	69
H	OMe	75	F	H	40

R	R^1	Yield (%)
H	Et	77
H	Me	45
Me	Et	50

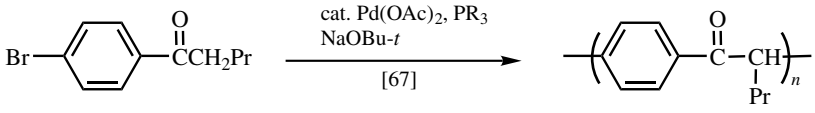
Scheme 28

Similar tandem cyclization reactions of *o*-bromobenzaldehydes have also been reported[36] (**Scheme 29**). In these reactions, either Br or formyl group may react first. However, their mechanistic details are not very clear.

Finally, it is noteworthy that those haloaryl ketones in which the halogen and carbonyl groups are *para* to each other cannot cyclize but they can be led to linear polymers, as shown in **Scheme 30**.[67]



Scheme 29

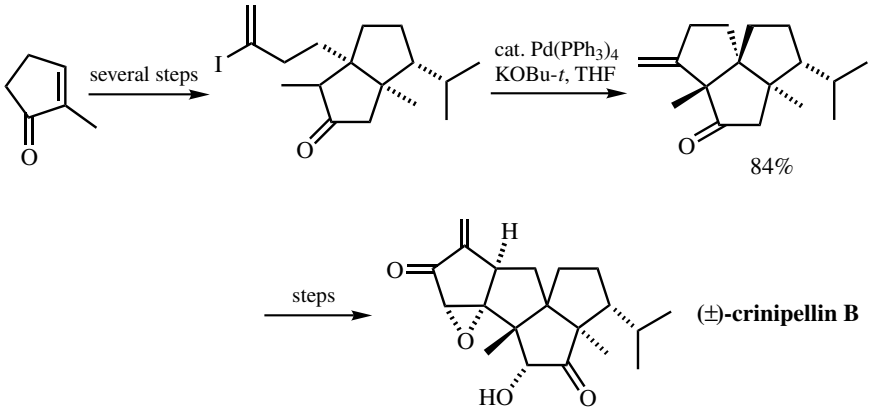


PR_3	Yield (%)	Mol. Wt.
P(Bu-*t*)$_3$	63	15200
P(*o*-Tol)$_3$	55	4600

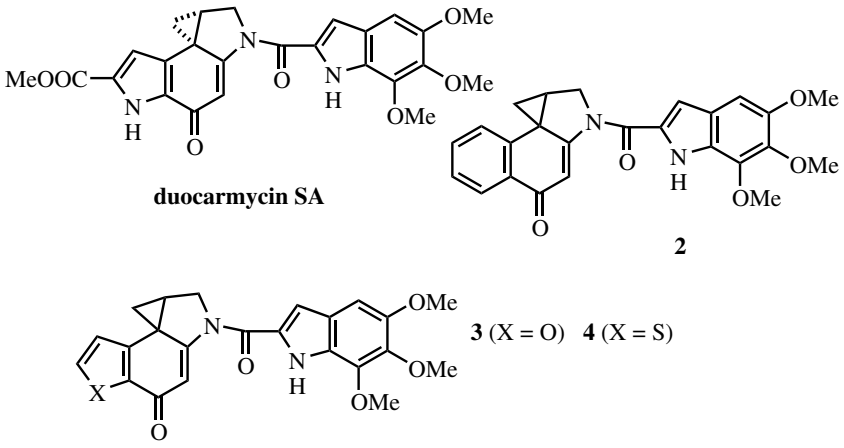
Scheme 30

D. APPLICATIONS TO NATURAL PRODUCT SYNTHESES

The number of examples of natural product syntheses involving Pd-catalyzed α-arylation or α-alkenylation of carbonyl and related compounds is still very small. The synthesis of ($\pm$)-crinipellin B by Piers and Renaud[62] shown in **Scheme 31** may well represent the only *bona fide* example of the total synthesis of natural products in which the methodology discussed in this section plays a crucial role.



Scheme 31



Scheme 32

Although not naturally occurring, benzene, furan, and thiophene analogs of CC-1065/duocarmycin pharmacophores (**2**–**4**) (**Scheme 32**) have been synthesized via Pd-catalyzed α-arylation,[63] as briefly presented in **Scheme 21**.

REFERENCES

[1] H. O. House, *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, Menlo Park, CA, 1972, Chap. 9.

[2] M. E. Jung, *Tetrahedron*, **1976**, *32*, 3–31.

[3] R. A. Rossi and J. F. Bunnett, *J. Am. Chem. Soc.*, **1972**, *94*, 683.

[4] M. G. Moloney and J. T. Pinhey, *J. Chem. Soc. Chem. Commun.*, **1984**, 965.

[5] S. Hashimoto, T. Shinoda, and S. Ikegami, *J. Chem. Soc. Chem. Commun.*, **1988**, 1137.

[6] S. Hashimoto, Y. Miyazaki, and S. Ikegami, *Synlett*, **1996**, *324*.

[7] T. C. T. Chang, M. Rosenblum, and S. B. Samuels, *J. Am. Chem. Soc.*, **1980**, *102*, 5931.

[8] P. F. Hudrlik and A. K. Kulkarni, *J. Am. Chem. Soc.*, **1981**, *103*, 6251.

[9] P. A. Wender, D. A. Holt, and S. M. Sieburth, *J. Am. Chem. Soc.*, **1983**, *105*, 3348.

[10] E. Negishi, Z. Tan, S. Y. Liou, and B. Liao, *Tetrahedron*, **2000**, *56*, 10197.

[11] W. Adam and P. Klug, *Synthesis*, **1994**, 557.

[12] R. F. Heck, *J. Am. Chem. Soc.*, **1968**, *90*, 5535.

[13] R. Saito, T. Izumi, and A. Kasahara, *Bull. Chem. Soc. Jpn.*, **1973**, *46*, 1776.

[14] L. S. Hegedus, R. E. Williams, M. A. McGuire, and T. Hayashi, *J. Am. Chem. Soc.*, **1980**, *102*, 4973.

[15] M. F. Semmelhack, R. D. Stauffer, and T. D. Rogerson, *Tetrahedron Lett.*, **1973**, 4519.

[16] M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *J. Am. Chem. Soc.*, **1975**, *97*, 2507.

[17] J. F. Fauvarque and A. Jutand, *J. Organomet. Chem.*, **1977**, *132*, C17.

[18] A. A. Millard and M. W. Rathke, *J. Am. Chem. Soc.*, **1977**, *99*, 4833.

[19] M. Kosugi, M. Suzuki, I. Hagiwara, K. Goto, K. Saitoh, and T. Migita, *Chem. Lett.*, **1982**, 939.

[20] I. Kuwajima and H. Urabe, *J. Am. Chem. Soc.*, **1982**, *104*, 6831.

[21] M. Kosugi, I. Hagiwara, T. Sumiya, and T. Migita, *J. Chem. Soc. Chem. Commun.*, **1983**, 344.

[22] M. Kosugi, I. Hagiwara, and T. Migita, *Chem. Lett.*, **1983**, 839.

[23] M. Kosugi, I. Hagiwara, T. Sumiya, and T. Migita, *Bull. Chem. Soc. Jpn.*, **1984**, *57*, 242.

[24] M. Kosugi, I. Takano, M. Sakurai, H. Sano, and T. Migita, *Chem. Lett.*, **1984**, 1221.

[25] M. Palucki and S. L. Buchwald, *J. Am. Chem. Soc.*, **1997**, *119*, 11108.

[26] J. Åhman, J. P. Wolfe, M. V. Troutman, M. Palucki, and S. L. Buchwald, *J. Am. Chem. Soc.*, **1998**, *120*, 1918.

[27] J. M. Fox, X. Huang, A. Chieffi, and S. L. Buchwald, *J. Am. Chem. Soc.*, **2000**, *122*, 1360.

[28] B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, **1997**, *119*, 12382.

[29] K. H. Shaughnessy, B. C. Hamann, and J. F. Hartwig, *J. Org. Chem.*, **1998**, *63*, 6546.

[30] M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, **1999**, *121*, 1473.

[31] T. Satoh, Y. Kawamura, M. Miura, and M. Nomura, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 1740.

[32] Y. Terao, T. Satoh, M. Miura, and M. Nomura, *Tetrahedron Lett.*, **1998**, *39*, 6203.

[33] T. Satoh, J. Inoh, Y. Kawamura, M. Miura, and M. Nomura, *Bull. Chem. Soc. Jpn.*, **1998**, *71*, 2239.

[34] Y. Terao, T. Satoh, M. Miura, and M. Nomura, *Bull. Chem. Soc. Jpn.*, **1999**, *72*, 2345.

[35] T. Satoh, Y. Kametani, Y. Terao, M. Miura, and M. Nomura, *Tetrahedron Lett.*, **1999**, *40*, 5345.

[36] Y. Terao, T. Satoh, M. Miura, and M. Nomura, *Tetrahedron*, **2000**, *56*, 1315.

[37] J. H. Simpson and J. K. Stille, *J. Org. Chem.*, **1985**, *50*, 1759.

[38] J. F. Fauvarque and A. Jutand, *J. Organomet. Chem.*, **1979**, *177*, 273.

[39] J. F. Fauvarque and A. Jutand, *J. Organomet. Chem.*, **1981**, *209*, 109.

[40] T. Sato, T. Itoh, and T. Fujisawa, *Chem. Lett.*, **1982**, 1559.

[41] F. Orsini and F. Pelizzoni, *Synth. Commun.*, **1987**, *17*, 1389.

[42] F. Orsini, F. Pelizzoni, and L. M. Vallarino, *J. Organomet. Chem.*, **1989**, *367*, 375.

[43] M. Kosugi, Y. Negishi, M. Kameyama, and T. Migita, *Bull. Chem. Soc. Jpn*., **1985**, *58*, 3383.

[44] M. Kosugi, M. Ishiguro, Y. Negishi, H. Sano, and T. Migita, *Chem. Lett.*, **1984**, 1511.

[45] C. Carfagna, A. Musco, G. Sallese, R. Santi, and T. Fiorani, *J. Org. Chem.*, **1991**, *56*, 261.

[46] R. Galarini, A. Musco, R. Pontellini, and R. Santi, *J. Mol. Catal.*, **1992**, *72*, L11.

[47] M. Uno, K. Seto, and S. Takahashi, *J. Chem. Soc. Chem. Commun.*, **1984**, 932.

[48] M. Uno, K. Seto, M. Masuda, W. Ueda, and S. Takahashi, *Tetrahedron Lett.*, **1985**, *26*, 1553.

[49] I. M. Blake, H. L. Anderson, D. Beljonne, J. L. Brédas, and W. Clegg, *J. Am. Chem. Soc.*, **1998**, *120*, 10764.

[50] M. Uno, K. Seto, W. Ueda, M. Masuda, and S. Takahashi, *Synthesis*, **1985**, 506.

[51] T. Sakamoto, E. Katoh, Y. Kondo, and H. Yamanaka, *Heterocycles*, **1988**, *27*, 1353.

[52] T. Sakamoto, Y. Kondo, T. Suginome, S. Ohba, and H. Yamanaka, *Synthesis*, **1991**, 552.

[53] M. T. Reetz, K. Wanninger, and M. Hermes, *Chem. Commun*., **1997**, 535.

[54] E. Negishi, H. Matsushita, S. Chatterjee, and R. A. John, *J. Org. Chem.*, **1982**, *47*, 3188.

[55] E. Negishi and R. A. John, *J. Org. Chem.*, **1983**, *48*, 4098.

[56] D. D. Hennings, S. Iwasa, and V. H. Rawal, *J. Org. Chem.*, **1997**, *62*, 2.

[57] C. Chen, D. R. Lieberman, R. D. Larsen, T. R. Verhoeven, and P. J. Reider, *J. Org. Chem.*, **1997**, *62*, 2676.

[58] M. A. Ciufolini and M. E. Browne, *Tetrahedron Lett.*, **1987**, *28*, 171.

[59] M. A. Ciufolini, H. B. Qi, and M. E. Browne, *J. Org. Chem.*, **1988**, *53*, 4149.
[60] H. Muratake and M. Natsume, *Tetrahedron Lett.*, **1997**, *38*, 7581.
[61] E. Piers and P. C. Marais, *J. Org. Chem.*, **1990**, *55*, 3454.
[62] E. Piers and J. Renaud, *J. Org. Chem.*, **1993**, *58*, 11.
[63] H. Muratake, A. Hayakawa, and M. Natsume, *Tetrahedron Lett.*, **1997**, *38*, 7577.
[64] H. Muratake and H. Nakai, *Tetrahedron Lett.*, **1999**, *40*, 2355.
[65] M. Beller, H. Fischer, W. A. Herrmann, K. Öfele, and C. Brossmer, *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 1848.
[66] D. D. Hennings, S. Iwasa, and V. H. Rawal, *Tetrahedron Lett.*, **1997**, *38*, 6379.
[67] D. Wang and Z. Wu, *Chem. Commun.*, **1999**, 529.