ORGANIC
REACTIONS

CHAPTER 1

CATELLANI-TYPE REACTIONS: PALLADIUM-CATALYZED C−H FUNCTIONALIZATIONS MEDIATED BY NORBORNENES

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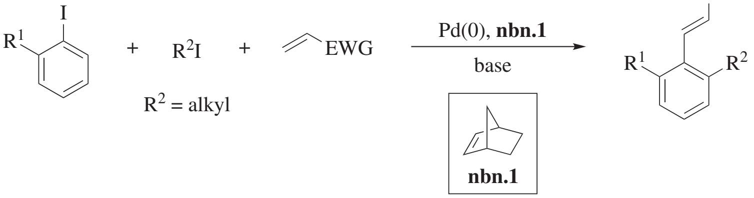
INTRODUCTION

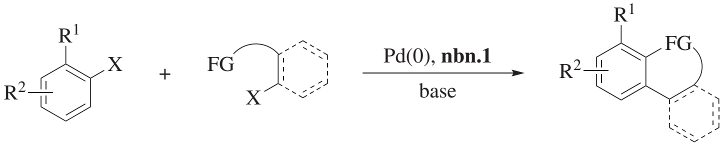
In 1997, Catellani and co-workers utilized norbornene (**nbn.1**), a strained bicyclic alkene, as a transient mediator to effect palladium-catalyzed *ortho*-C–H alkylation of iodoarenes, followed by functionalization at the *ipso* position with a Heck acceptor (Scheme 1).[1] The process provides 1,2,3-trisubstituted arenes, which are



Scheme 1

otherwise difficult to prepare, in a highly efficient and site-selective manner. The following features of the reaction are particularly noteworthy: (1) both the *ortho* and *ipso* positions of iodoarenes are simultaneously functionalized in a single transformation, (2) the C−H alkylation and carbon−carbon bond-forming events take place efficiently and predictably to afford high yields of the products even in the presence of many synthons with similar reactivities (e.g., aryl and alkyl iodides, norbornene, and olefins), (3) rigorous control of site-selectivity in arene C−H functionalization is possible without using a traditional heteroatom-containing directing group, and (4) for *ortho*-unsubstituted iodoarenes (R^1 = H), dialkylation occurs to deliver vinylarenes with two identical *ortho* substituents.

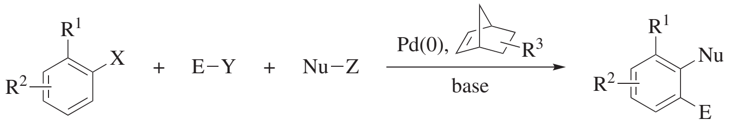
Inspired by the pioneering work of Catellani, Lautens and coworkers developed a semi-intramolecular variant of the Catellani reaction by using alkene-tethered alkyl bromides as bifunctional alkylating reagents.[2] This strategy was later extended to access a variety of polycyclic compounds (Scheme 2).[3–8]



X = I, Br, Cl
FG = alkene, heteroaryl, amide, amine,
alcohol, aldehyde, ester, ketone, imine, etc.

Scheme 2

The seminal work by Catellani and Lautens on palladium/norbornene joint catalysis has developed significantly over the last two decades.[9] In addition to alkylating reagents, various aryl, acyl, nitrogen, and sulfur electrophiles (E−Y) have been used to form carbon–carbon, carbon–nitrogen, and carbon–sulfur bonds *ortho* to the initial site of palladium insertion. The terminating reagents (Nu−Z) have also been expanded to include hydride-transfer reagents (e.g., benzyl and isopropyl alcohol); terminal and internal alkynes; arylboronic acids and bis(pinacolato)diboron; carbon nucleophiles (e.g., cyanides, enolates, carbenes); oxygen-, nitrogen-, sulfur-, and selenium-containing nucleophiles; and various arenes and heteroarenes (Scheme 3). Many new methods employ alkenyl halides and pseudohalides, which were first utilized by Lautens.[10]

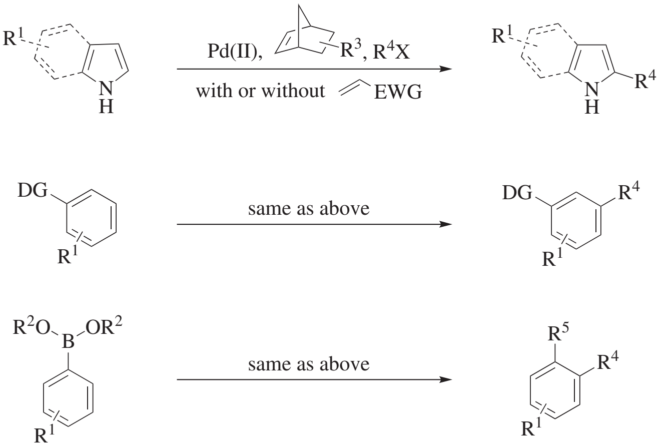


X = I, Br, Cl

Nu = H, aryl, alkenyl, alkynyl, alkyl, –CN,
NR^4R^5, OR^6, BR^7R^8, SR^9, SeR^{10}
E = alkyl, aryl, NR^4R^5, SR^9

Scheme 3

While early studies focused mainly on palladium(0)-catalyzed reactions of aryl halides and pseudohalides, Bach and coworkers developed a palladium(II)-catalyzed, norbornene-mediated reaction that enables C2-alkylation of indoles (Scheme 4, top reaction).[11] This work in turn inspired the groups of Yu,[12,13] Dong,[14] Zhang,[15] Zhou,[16] and others to further extend the strategy to the functionalization of arenes bearing a directing group (DG) (Scheme 4, middle reaction), thereby avoiding the requirement of an aryl halide substrate, and also to arylboron compounds (Scheme 4, bottom reaction).[17] Because the initially discovered palladium(0)-catalyzed reactions are commonly referred to as the Catellani reaction, the term "Catellani-type reaction" will be used throughout this chapter to describe both the palladium(0)- and palladium(II)-catalyzed reactions.



R^4 = alkyl, aryl, alkynyl, NR^6R^7, ArC(O), Cl

R^5 = EWG, H

Scheme 4

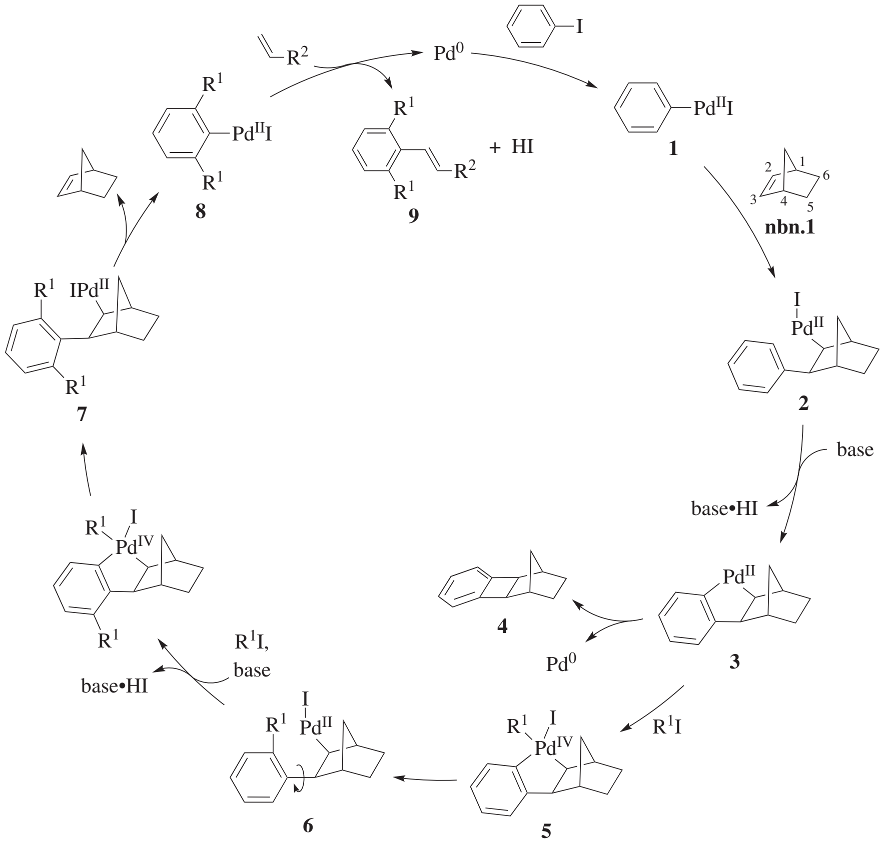
This chapter presents an overview of Catellani-type reactions described in the literature through December 2021, with a focus on both the initial discoveries and the current state of the art. The chapter is organized by the oxidation state of the palladium catalyst (i.e., palladium(0) and palladium(II)) and, within each category, by the electrophiles used for the reaction. Several reviews covering various aspects of this topic have been published, and readers are encouraged to refer to them for specific applications.[9,17–24]

MECHANISM AND STEREOCHEMISTRY

Mechanistic Considerations

Depending on the substrates and palladium catalyst used, a Catellani-type process may involve a palladium(0)/palladium(II)/palladium(IV) or a palladium(II)/palladium(IV) catalytic cycle.

Palladium(0)-Catalyzed Reactions. Scheme 5 depicts the catalytic cycle originally proposed by Catellani that explains the uniqueness of norbornene (**nbn.1**) for this chemistry.[1] Oxidative addition of an aryl iodide with palladium(0) affords arylpalladium(II) species **1**. If a palladium(II) catalyst is employed, the palladium(0) typically originates from reduction of palladium(II) by sacrificial quantities of phosphine ligand or by a solvent such as DMF. Arylpalladium(II) species **1** then undergoes preferential intermolecular carbopalladation with norbornene (**nbn.1**) in the presence of a Heck acceptor. This striking selectivity is largely due to the high strain energy of norbornene (**nbn.1**) (21.6 kcal/mol) that is released upon carbopalladation. The rigidity of the norbornyl moiety precludes the norbornylpalladium species **2** from undergoing a *syn*-β-hydride elimination. Since the metal is in close proximity to the *ortho* aromatic hydrogen atom, an electrophilic palladation takes place instead, leading to the formation of the key five-membered arylnorbornylpalladacycle (ANP) **3**. Direct reductive elimination of palladacycle **3** generates benzocyclobutene **4**, which is sometimes observed in Catellani-type reactions. Reaction of palladacycle **3** with an alkyl iodide to form the palladium(IV) species **5** is followed by reductive elimination



Scheme 5

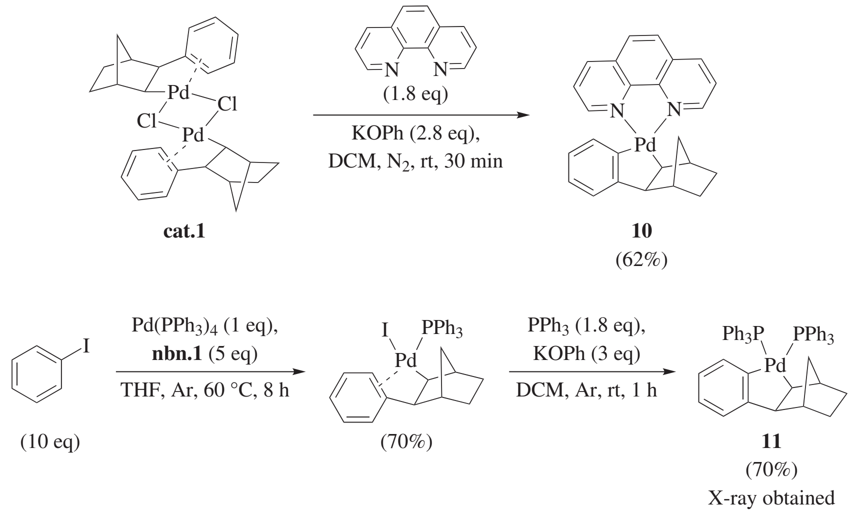
to provide the *ortho*-alkylated intermediate **6**. If another *ortho*-C–H bond is available, the alkylation sequence is repeated to afford the *ortho*,*ortho*-dialkylated norbornylpalladium species **7**, which then undergoes β-carbon elimination to form arylpalladium(II) species **8** due to the increased steric hindrance between the newly installed *ortho* substituents and the palladium center. The last step of the sequence—or, the terminating event—is a traditional Mizoroki–Heck reaction, which provides the final *ortho*,*ortho*-disubstituted vinylarene product **9** and regenerates the palladium(0) catalyst. Because the olefin product is formed via a Heck reaction, the carbon–carbon double bond of the vinylarene is generally (*E*)-configured.

Several aspects of the catalytic cycle are noteworthy. First, norbornene can be regarded as a transient directing group that places palladium in close proximity to the *ortho*-C–H bonds of iodoarenes, thereby facilitating the subsequent C–H functionalizations (Scheme 5). Second, while norbornene is a cocatalyst for the reaction, it is generally used in stoichiometric amounts to minimize undesired direct *ipso* functionalization of aryl halides. Third, the strained and rigid [2.2.1] bicyclic scaffold of norbornene is crucial for the entire catalytic cycle. For some reactions that will be discussed in the following section, structural modifications to norbornene are required to achieve higher reactivity and/or to inhibit side reactions. For example, introduction of a substituent at the bridgehead (C1) position can inhibit the second C–H palladation of intermediate **6** and promote the subsequent norbornene extrusion step, thereby achieving an otherwise challenging mono-*ortho*-functionalization of *ortho*-unsubstituted aryl halides. Installing an electron-withdrawing substituent at the C2 position of norbornene can also suppress premature reductive elimination of palladacycle **3**. Finally, enantioenriched norbornene derivatives enable enantioselective Catellani-type reactions, which further increases the synthetic utility of this chemistry. We refer the readers to a recent review on structurally modified norbornenes for thorough discussions on norbornene substituent effects.[25]

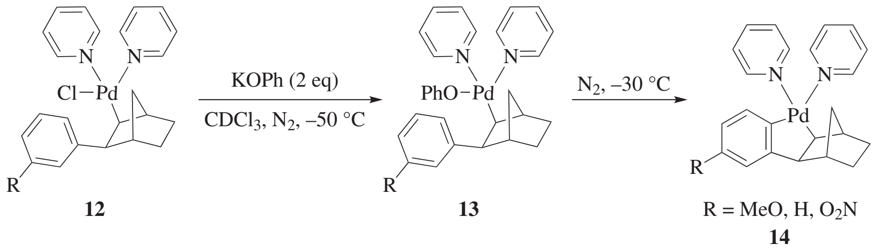
The aforementioned mechanism is supported by several studies. For example, key palladacycles **10**[26] and **11**[27] have been isolated and characterized (Scheme 6), lending support to the formation of palladacycle **3** (see Scheme 5). Although palladacycles **10** and **11** have not been evaluated in the Catellani reaction, diminished catalytic efficiencies are anticipated due to the stabilizing effects of the ligands.

The mechanism of the cyclopalladation step has been examined by ^{1}H NMR spectroscopy (Scheme 7).[28] Complex **13**, which is formed from complex **12** and potassium phenoxide, is stable at –50 °C but undergoes cyclization at –30 °C. Half conversion of **13** to **14** takes approximately 10, 100, and 240 minutes for R = MeO, H, and O_2N, respectively, indicating that an electrophilic aromatic substitution (S_EAr) mechanism is most likely involved for the ring-closure step. However, recent experimental and computational studies suggest that a concerted metalation–deprotonation (CMD) pathway is also possible.[27,29–31]

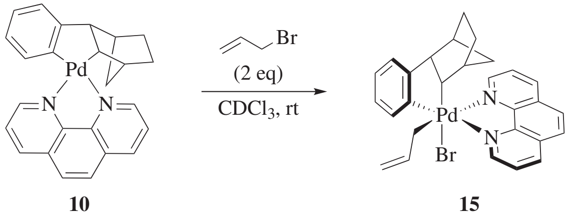
The reactivity of palladacycle **10** was further examined by Catellani and Mann.[32] Using allyl bromide as the electrophile, palladium(IV) complex **15** is formed at room temperature but also slowly degrades at this temperature. Characterization by ^{1}H NMR spectroscopy at –20 °C reveals that *cis* oxidative addition of allyl bromide occurs from the less sterically hindered side of complex **10** (Scheme 8).[32]



Scheme 6

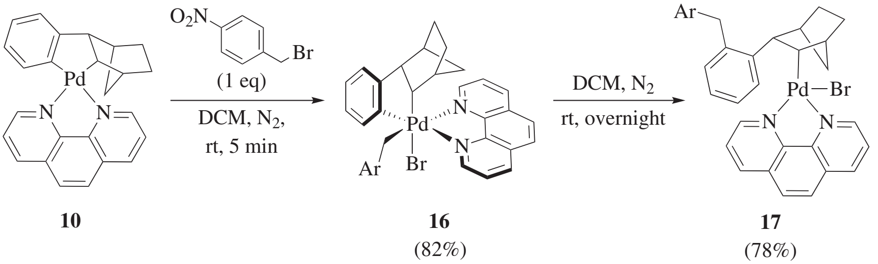


Scheme 7



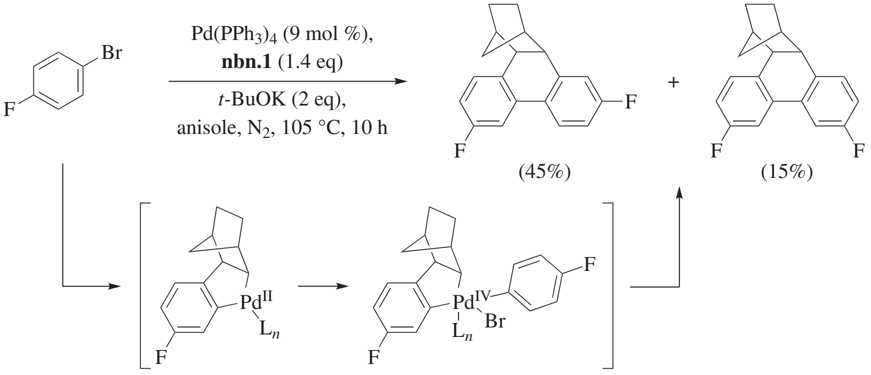
Scheme 8

Treatment of complex **10** with 4-nitrobenzyl bromide at room temperature for five minutes affords a similar palladium(IV) complex **16** (Scheme 9).[33] When kept overnight at room temperature, **16** undergoes selective C(sp^2)–C(sp^3) bond-forming reductive elimination to yield palladium(II) complex **17**. Taken together, these observations support the transformation of palladacycle **3** into intermediate **6** (see Scheme 5).



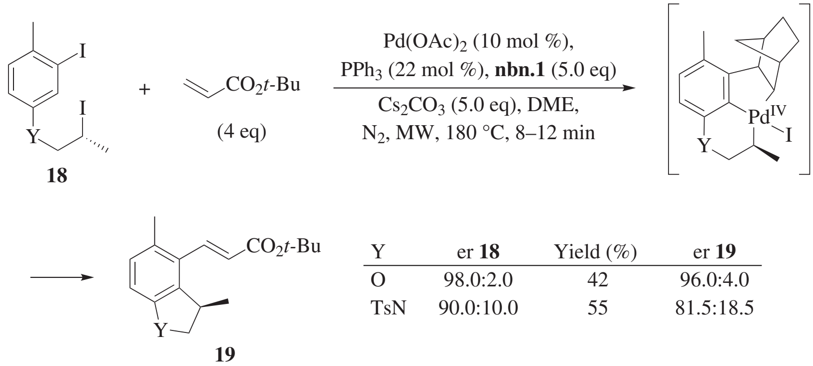
Scheme 9

The reaction of the ANP with an aryl halide would form a similar palladium(IV) species, but the subsequent reductive elimination step is more complicated: undesired aryl–norbornyl C(sp^2)–C(sp^3) bond formation can compete with the desired aryl–aryl C(sp^2)–C(sp^2) bond formation, although the latter is usually faster. For example, in the absence of a terminating reagent, the reaction of 1-bromo-4-fluorobenzene under typical reaction conditions affords a mixture of regioisomeric products. The undesired product, obtained in 15% yield, is formed when C(sp^2)–C(sp^3) reductive elimination occurs first, followed by palladium insertion into the nearby aryl C–H bond and subsequent reductive elimination to form the aryl–aryl bond (Scheme 10).[34] This problem can be circumvented by using the "*ortho* effect" (vide infra).



Scheme 10

The stereochemistry of the oxidative addition to the palladacycle has been studied by employing enantioenriched substrates such as **18** (Scheme 11).[35,36] While erosion of the enantiomeric ratio is observed for an aniline-tethered secondary iodide, (probably due to anchimeric assistance of the nitrogen atom), a phenol-tethered substrate provides the corresponding product **19** without a significant decrease in the enantiomeric ratio. The absolute configurations of the substrates and products were determined by X-ray crystallography, which indicates that the annulation proceeds with overall inversion of configuration at the chiral center. Given that reductive elimination from a palladium(IV) species has been reported to proceed with retention of configuration,[26] oxidative addition of the secondary alkyl iodide to the palladacycle most likely occurs with inversion of stereochemistry, which is consistent with an S_N2 mechanism.



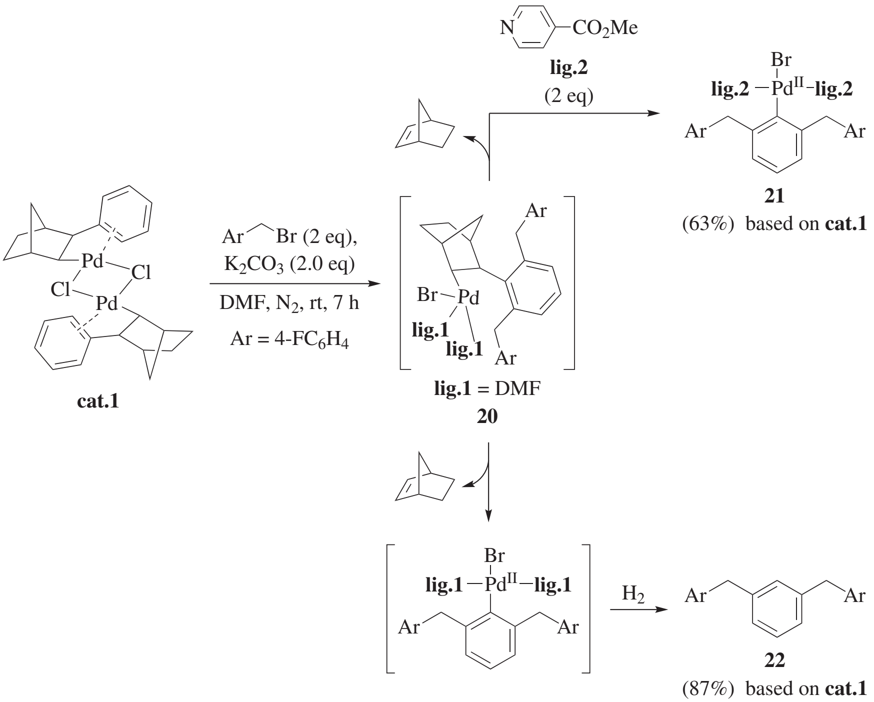
Y	er **18**	Yield (%)	er **19**
O	98.0:2.0	42	96.0:4.0
TsN	90.0:10.0	55	81.5:18.5

Scheme 11

The norbornene (**nbn.1**) extrusion step was investigated using the *ortho*,*ortho*-dialkylated norbornylpalladium species **20**, which in turn is formed from the palladium dimer **cat.1** and 4-fluorobenzyl bromide (Scheme 12).[37] When treated with methyl isonicotinate (**lig.2**), compound **20** undergoes norbornene (**nbn.1**) elimination to afford aryl palladium species **21**, which is stable enough to be isolated. On the other hand, dialkylated arene **22** is obtained in high yield in the presence of hydrogen gas via hydrogenolysis of the analogous DMF–palladium complex. These experiments support the norbornene-extrusion step shown in Scheme 5.

Based on the catalytic cycle shown in Scheme 5 and the aforementioned mechanistic studies, various types of *ortho*/*ipso* difunctionalizations of aryl halides have been achieved, simply by using different combinations of electrophiles and terminating reagents. The generality and modularity of Catellani-type reactions can be attributed to the fact that palladium(0) preferentially reacts with aryl halides whereas the arylnorbornylpalladacycle (a palladium(II) species) reacts faster with electrophiles such as alkyl halides.[9] As observed in many palladium-catalyzed coupling reactions, aryl iodides are more reactive than aryl bromides, and aryl chlorides have only seldom been used. Both electron-rich and electron-deficient aryl iodides are suitable substrates, as long as an *ortho* substituent is present to prevent bis-alkylation.

Palladium(II)-Catalyzed Reactions. Since the key five-membered palladacycle **3** is formed from an arylpalladium(II) species and norbornene (**nbn.1**), it is conceivable that a palladium(II) salt could be used to access a similar intermediate from substrates other than aryl (pseudo)halides. In practice, two

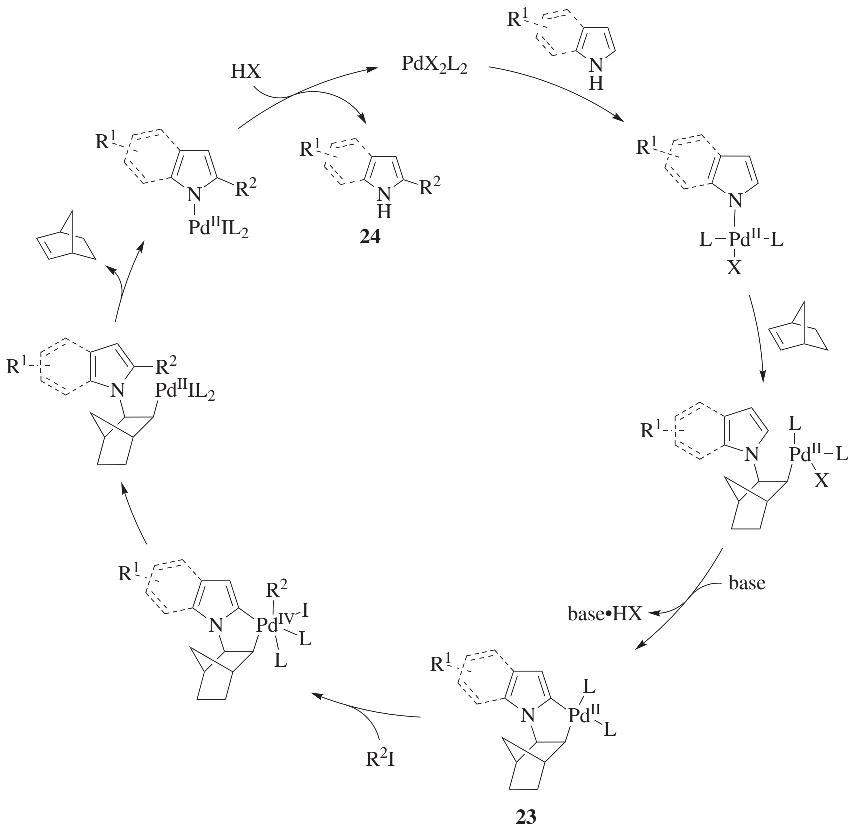


Scheme 12

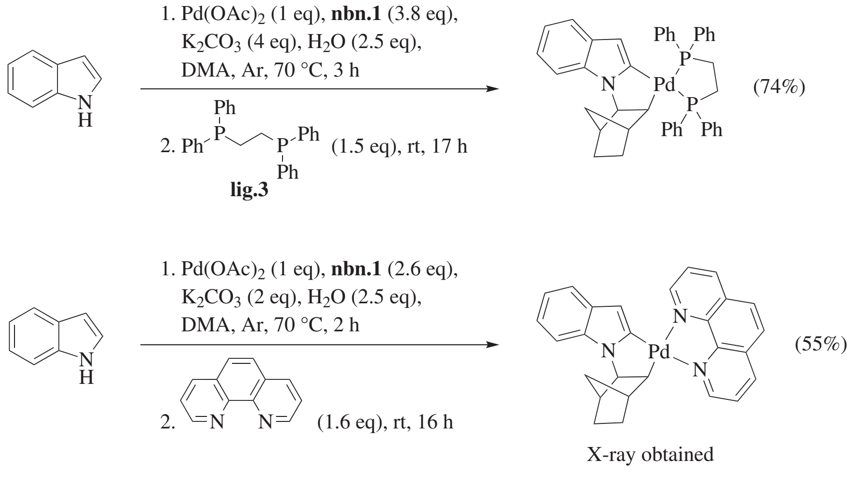
strategies have been developed to achieve palladium(II)-catalyzed Catellani-type reactions: electrophilic palladation of arenes and transmetallation with arylboron species.[17] A brief discussion of representative catalytic cycles is presented below.

C2-Functionalization of NH-Indoles.[38] In lieu of the oxidative addition event that initiates the palladium(0)-catalyzed reactions, the proposed catalytic cycle commences with *N*-palladation of the indole to provide the equivalent palladium(II) species (Scheme 13). *Syn*-aminopalladation of norbornene (**nbn.1**) and *ortho*-C−H palladation generate the key five-membered palladacycle **23**, which can be isolated and fully characterized when a stabilizing ligand such as 1,2-bis (diphenylphosphino)ethane (**lig.3**) or 1,10-phenanthroline is added (Scheme 14).[38] The next three steps—oxidative addition, reductive elimination, and β-carbon elimination—mirror the palladium(0)-catalyzed process. Final protodemetallation affords product **24** and regenerates the palladium(II) catalyst.

Vicinal Difunctionalization of Thiophenes. Electron-rich thiophenes are also amenable to palladium(II)/norbornene (**nbn.1**) joint catalysis (Scheme 15).[39] Electrophilic palladation at the 5-position of 2-substituted thiophenes affords an aryl palladium(II) species, which undergoes carbopalladation with norbornene derivative **nbn.2** to form the key palladacycle. Subsequent reaction with an alkyl iodide and a terminating reagent delivers the final 4,5-difunctionalized products. As will be discussed in the next section, the presence of a secondary amide moiety at the C2

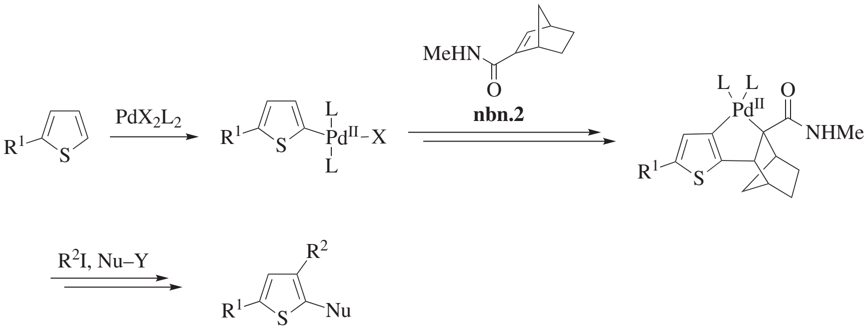


Scheme 13



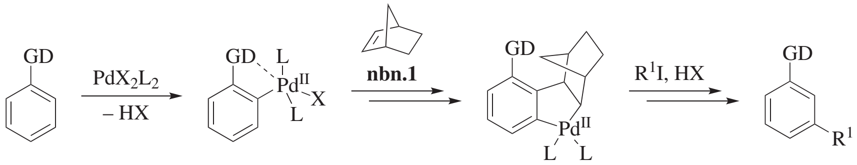
Scheme 14

position on the norbornene mediator is beneficial for many Catellani-type reactions, presumably due to hydrogen bonding with substrates and/or ligands.[25]



Scheme 15

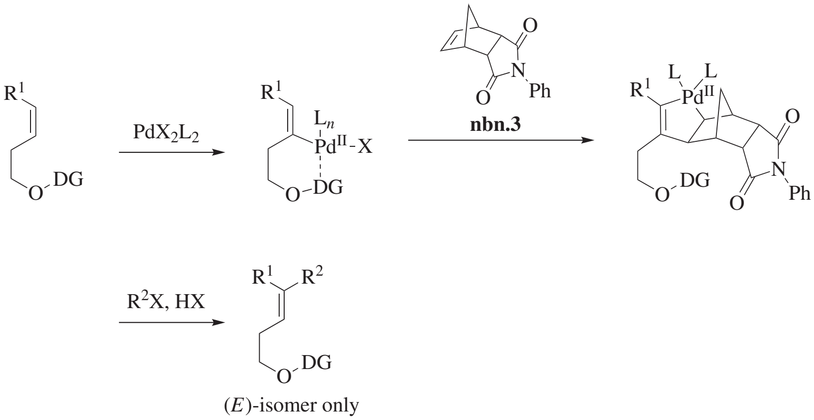
Meta-Functionalization of Arenes with a Directing Group. The well-established, palladium(II)-catalyzed, directed *ortho*-C–H palladation strategy can be exploited to access a palladacycle similar to the key ANP intermediate **3** in the classical catalytic cycle. The palladacycle is generated via *ortho*-C–H palladation, norbornene insertion, and *meta*-C–H palladation. This species then reacts with an electrophile to achieve a formal *meta*-functionalization of the arenes (Scheme 16).[12–14]



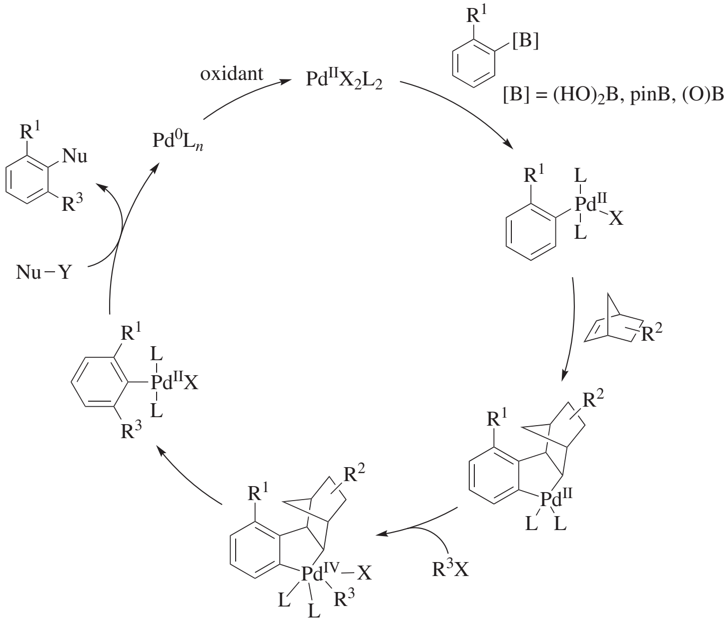
Scheme 16

Distal Functionalization of Alkenes with a Directing Group. Alkenes tethered to a directing group have been functionalized using palladium(II) catalysis (Scheme 17).[40] Directed C–H palladation at the proximal alkene position is followed by insertion of norbornene and C–H palladation at the distal position to form an alkenylnorbornylpalladacycle, which then reacts with an electrophile to afford the final trisubstituted alkene products. Again, the thermodynamically more stable (*E*)-alkene products are obtained in most cases. In this study, an imide-based norbornene derivative **nbn.3** is chosen for its superior reactivity.

Ortho-Functionalization of Arylboron Species. Starting from an arylboron species, transmetallation can be used to form the arylpalladium(II) species necessary for a Catellani-type reaction (Scheme 18).[15,16,41,42] The subsequent steps are essentially the same as those of the palladium(0)-catalyzed reactions except that a stoichiometric amount of oxidant is required to regenerate the catalytically active palladium(II) species from the in situ formed palladium(0) species.



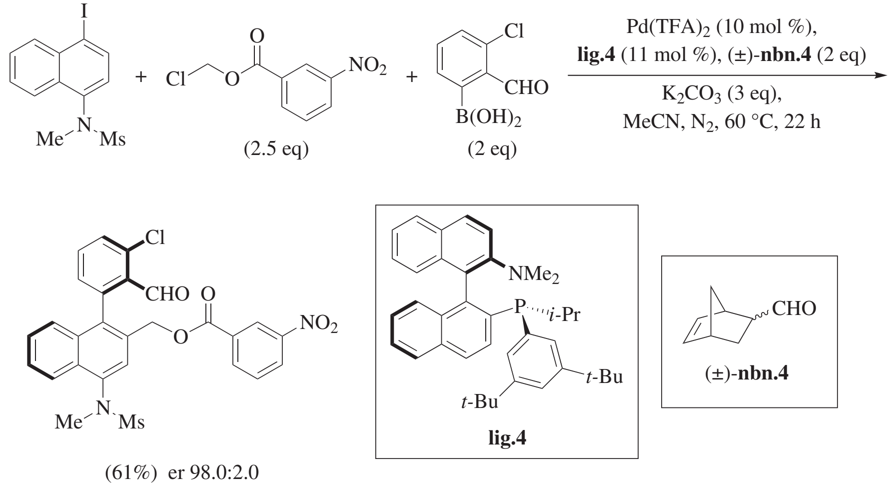
Scheme 17



Scheme 18

Stereochemical Control in Catellani-Type Reactions. Although Catellani-type reactions are well understood and widely utilized, stereochemical control remains a formidable challenge. To date, only a handful of examples using chiral phosphine ligands, chiral norbornene derivatives, or chiral amines to construct axial or central chirality have been documented. Four examples of asymmetric Catellani-type reactions with distinct modes of asymmetric induction are discussed in this section.

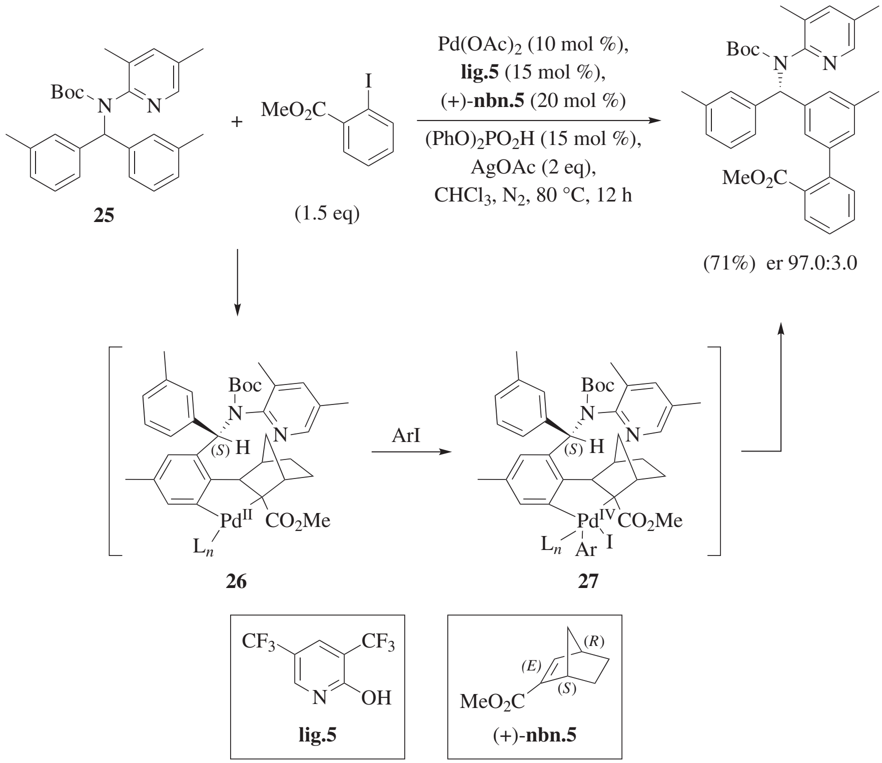
When aryl–aryl bonds are formed in the Catellani reaction, the biaryl products may exist as atropisomers with axial chirality, and catalytic asymmetric transformations can be achieved in the presence of chiral ligands. The first example involves an *ortho*-alkylation/*ipso*-Suzuki coupling sequence and relies on the chiral phosphine ligand **lig.4**, which contains both axial chirality and *P*-center chirality. Synthetically useful biaryl aldehydes are obtained in moderate-to-excellent yields and with up to 98.0:2.0 er (Scheme 19).[43]



Scheme 19

In addition to chiral phosphine ligands, enantioenriched norbornene derivatives can also impart stereocontrol in Catellani-type reactions. For example, in the presence of enantioenriched norbornene derivative (+)-**nbn.5**, prochiral diarylmethylamine derivative **25** undergoes enantioselective remote *meta*-C–H arylation via desymmetrization.[44] Mechanistically, directed and reversible *ortho*-C−H activation is followed by norbornene insertion and *meta*-C−H activation to form the palladacycle **26**, which then undergoes oxidative addition with an aryl iodide to generate **27** (Scheme 20).[44] The enantiodifferentiating step is thought to be either norbornene insertion or *meta*-C–H activation.

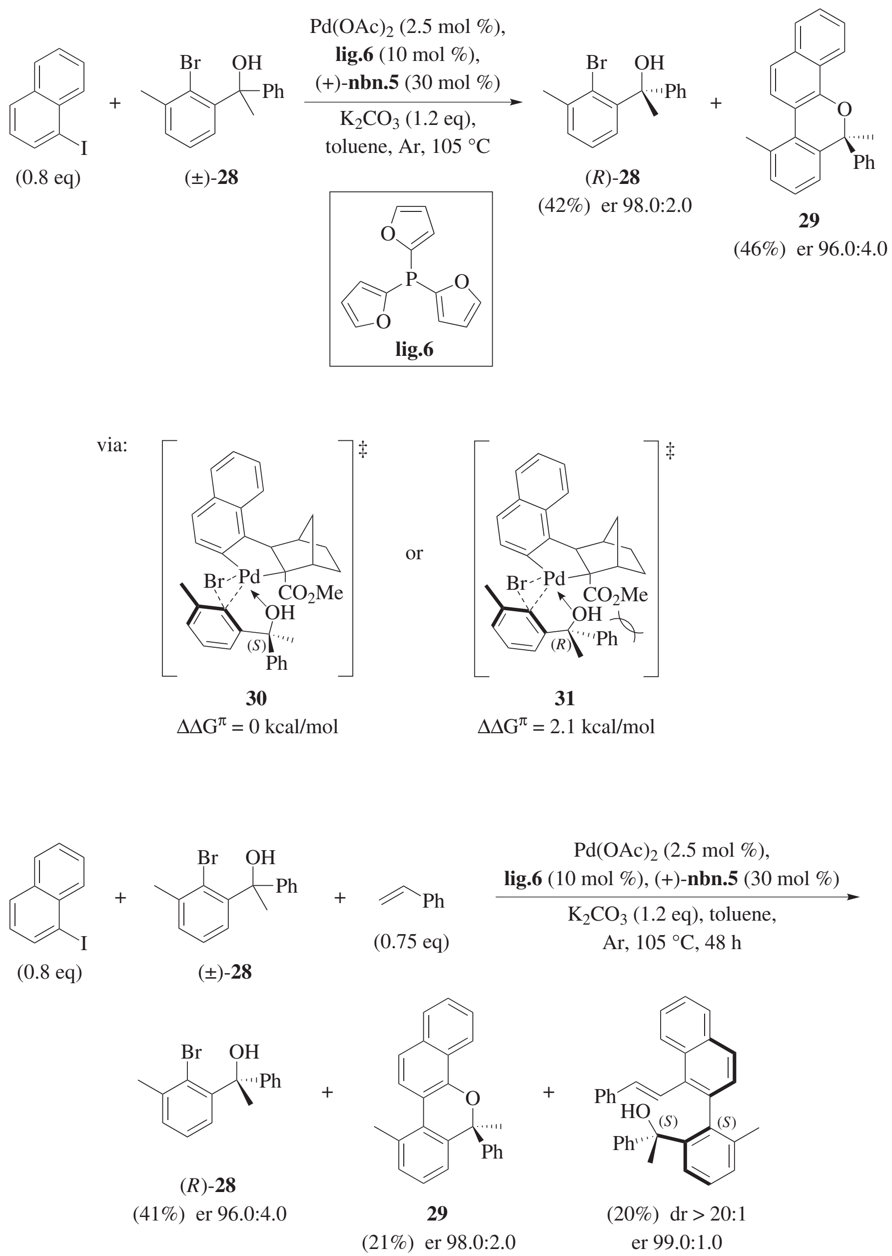
When the bifunctional arylating agent contains a tertiary benzyl alcohol moiety, the Catellani reaction can be used to effect kinetic resolutions. The chiral ANP generated from (+)-**nbn.5** preferentially reacts with (*S*)-**28**, affording both the cyclized product (i.e., benzo[*c*]chromene **29**) and unreacted (*R*)-**28** with high enantiomeric ratios (Scheme 21).[45] These kinetic resolutions typically exhibit a selectivity factor (*s*-factor) ranging from 26 to 544. Based on DFT calculations, oxidative addition of the aryl bromide to the chiral palladacycle is the enantiodiscriminating step, with an energy difference of 2.1 kcal/mol between the two competing transition states **30** and **31**. A control experiment involving intermolecular termination reveals that transient axial chirality is generated during the oxidative addition and is then



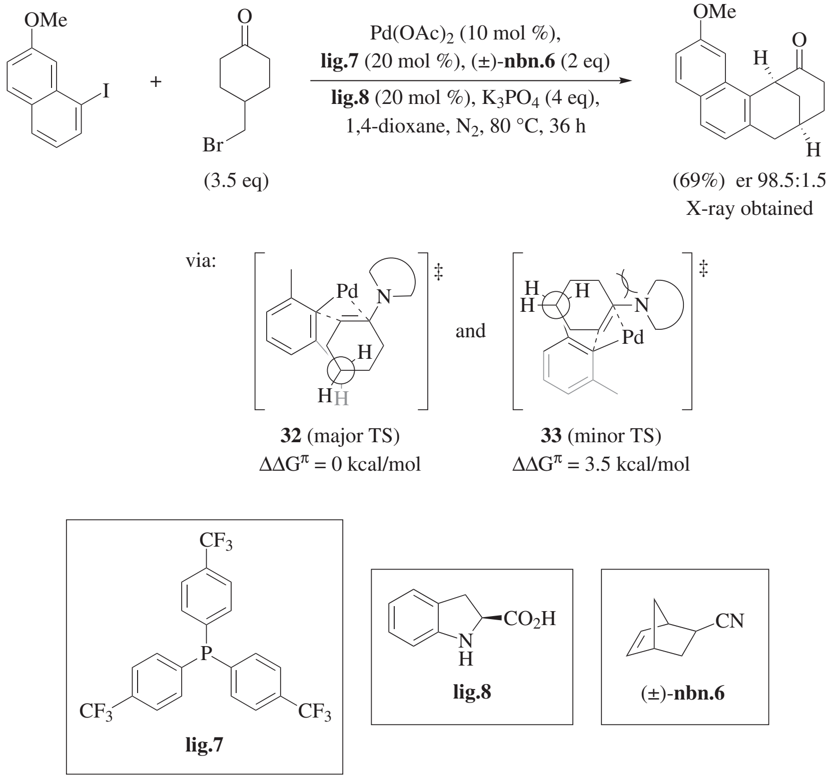
Scheme 20

converted to central chirality during the cyclization step (Scheme 21, bottom reaction).

Another mechanistically distinct example of stereocontrol in Catellani-type reactions involves enamine catalysis (Scheme 22).[46] The terminating agent, a chiral enamine, is generated in situ from the condensation of a ketone with a chiral secondary amine organocatalyst (e.g., indoline-2-carboxylic acid (**lig.8**)). 4-(Bromomethyl)cyclohexanone acts as a bifunctional reagent, and the method furnishes an all-carbon bridged-ring system via *ortho*- and *ipso*-bisalkylation of an iodoarene in a highly efficient and enantioselective manner. Alkenyl triflates and conjugated vinyl iodides are also viable substrates. DFT calculations suggest that *ipso*-alkylation occurs via an enamine insertion pathway, which is also the enantiodetermining step. The transition state leading to the observed enantiomer **32** was calculated by DFT to be 3.5 kcal/mol lower in energy than the transition state leading to the minor enantiomer **33** due to increased steric interactions between the indoline and cyclohexene moieties in **33**.


(0.8 eq)
(±)-**28**
Pd(OAc)$_2$ (2.5 mol %),
lig.6 (10 mol %),
(+)-**nbn.5** (30 mol %)
K$_2$CO$_3$ (1.2 eq),
toluene, Ar, 105 °C
lig.6
(*R*)-**28**
(42%) er 98.0:2.0
29
(46%) er 96.0:4.0
via:
or
30
ΔΔG$^\pi$ = 0 kcal/mol
31
ΔΔG$^\pi$ = 2.1 kcal/mol
(0.8 eq)
(±)-**28**
(0.75 eq)
Pd(OAc)$_2$ (2.5 mol %),
lig.6 (10 mol %), (+)-**nbn.5** (30 mol %)
K$_2$CO$_3$ (1.2 eq), toluene,
Ar, 105 °C, 48 h
(*R*)-**28**
(41%) er 96.0:4.0
29
(21%) er 98.0:2.0
(20%) dr > 20:1
er 99.0:1.0

Scheme 21



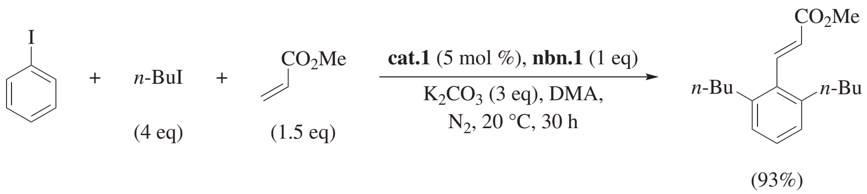
Scheme 22

SCOPE AND LIMITATIONS

Palladium(0)-Catalyzed Reactions

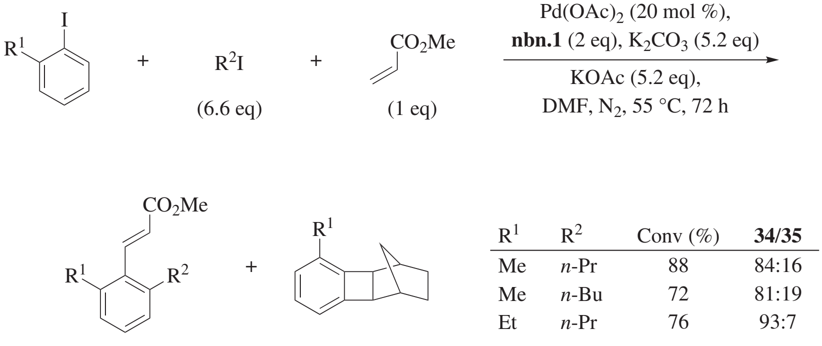
***Ortho*-Alkylation of Aryl (Pseudo)Halides.** In Catellani's seminal work, a preformed phenylnorbornylpalladium(II) (PNP) dimer **cat.1** is used as the precatalyst to convert iodobenzene into methyl (*E*)-2,6-di-*n*-butylcinnamate in 93% yield in the presence of norbornene (**nbn.1**), *n*-butyl iodide, methyl acrylate, and potassium carbonate (Scheme 23).[1] Remarkably, this single-step transformation involves cleavage of two carbon−hydrogen bonds and formation of three carbon−carbon bonds (at the *ipso* and two *ortho* positions of iodobenzene).

While this methodology provides straightforward access to 2,6-disubstituted vinylarenes from simple aryl iodides, the preformed palladacycle catalyst limits the practicality of the method and also generates palladacycle-derived byproducts when substituted iodoarenes are employed. Moreover, *ortho*-substituted iodoarenes are unreactive. These issues are circumvented by using palladium(II) acetate as



Scheme 23

the catalyst and a combination of potassium acetate and potassium carbonate as the base, although conversion and selectivity are still moderate (Scheme 24).[47] This procedure requires both an elevated reaction temperature (55 °C) and slow addition of the alkyl iodide and alkene via syringe pump. The major byproducts are benzocyclobutene derivatives **35**, which result from the initially formed palladacycle undergoing reductive elimination rather than oxidative addition with the alkyl iodide (cf. Scheme 5).

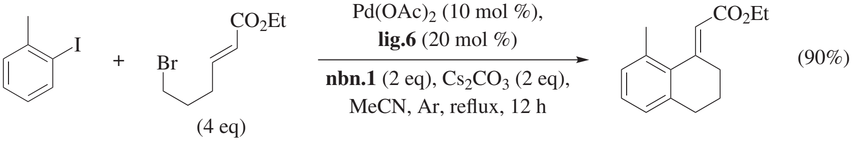


34 **35**

R^1	R^2	Conv (%)	**34/35**
Me	n-Pr	88	84:16
Me	n-Bu	72	81:19
Et	n-Pr	76	93:7

Scheme 24

A modified catalytic system consisting of a palladium(II) salt and a phosphine ligand (e.g., palladium(II) acetate and tri(2-furyl)phosphine (**lig.6**)) is more effective for this chemistry. For example, by using alkene-tethered alkyl bromides as bifunctional alkylating reagents, benzo-fused carbocycles are prepared in one step from 2-substituted iodoarenes (Scheme 25).[2] Optimization studies identified cesium carbonate and acetonitrile as the best base and solvent, respectively. This set of modified conditions significantly improves the efficiency of the reaction and has been applied

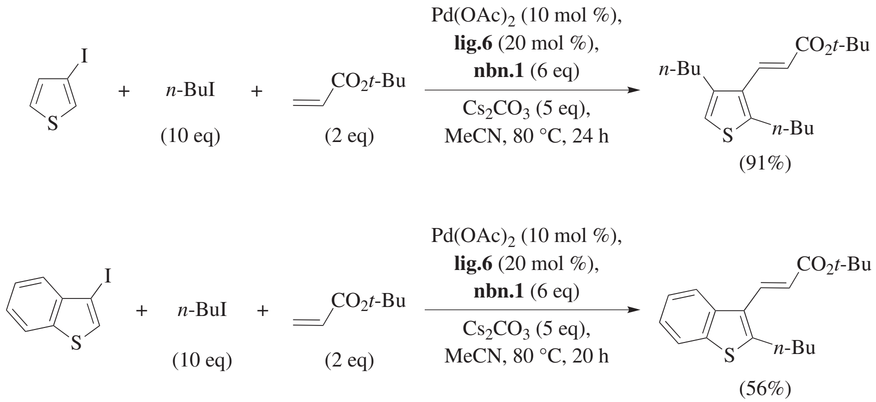


Scheme 25

to a variety of Catellani reactions involving both inter- and intramolecular termination steps (vide infra).

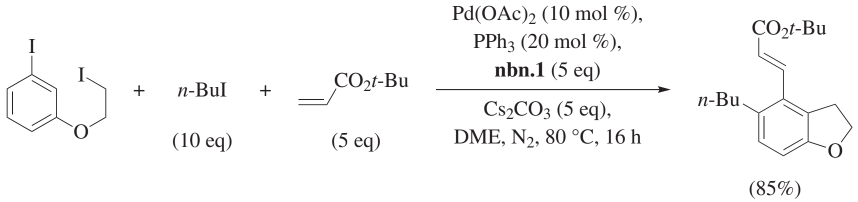
Since these early efforts, the scope of the Catellani reaction has expanded significantly, and a wide range of alkylating reagents has been employed. The following discussion will be divided into sections on simple and bifunctional alkylating reagents. Simple alkylating agents contain only an electrophilic functionality and are usually employed in combination with a separate terminating agent that effects an intermolecular termination step. Bifunctional alkylating reagents are tethered to a terminating functionality, and the termination step is intramolecular.

With Simple Alkylating Reagents. Unlike many reactions that rely on palladium catalysis, the Catellani reaction is compatible with simple alkyl halides as alkylating agents. Treatment of 3-iodothiophene or 3-iodobenzo[*b*]thiophene with iodobutane and a Heck acceptor affords the desired *ortho*-alkylation/*ipso*-olefination products in moderate-to-good yields (Scheme 26).[48]



Scheme 26

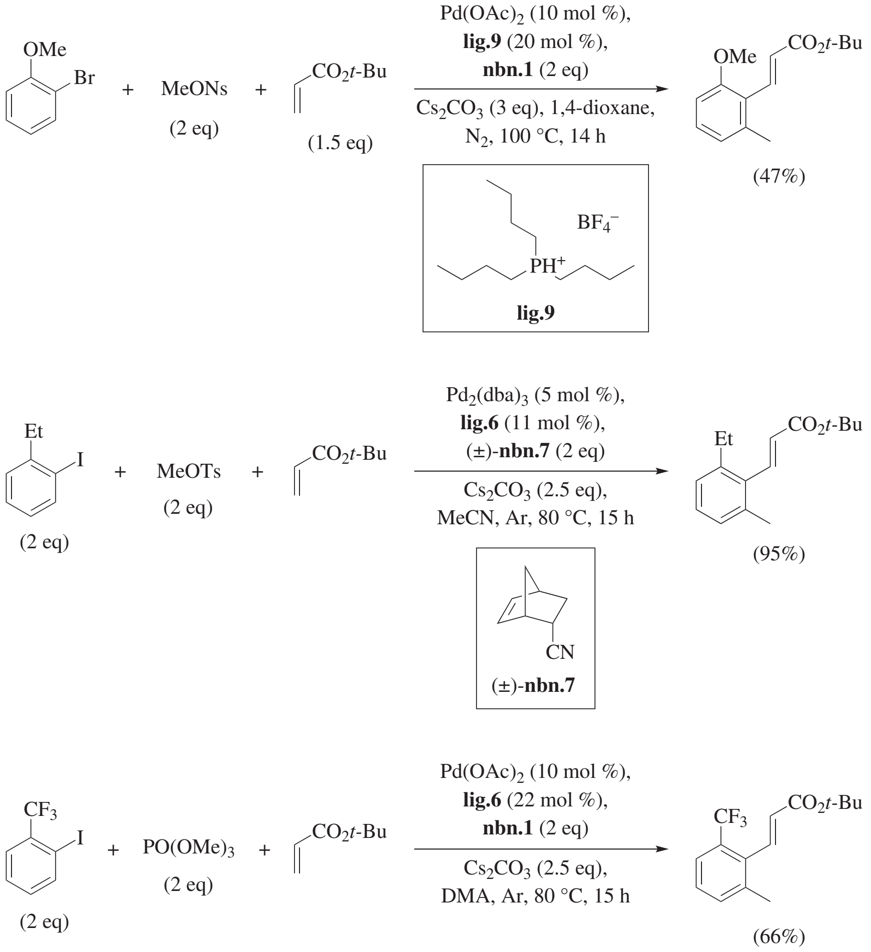
When iodoarenes lacking a 2-substituent are used in the Catellani alkylation reaction, two identical alkyl groups are introduced into the two *ortho* positions (see Scheme 23). However, by using iodoarenes tethered to an alkyl iodide moiety in the presence of a separate alkyl iodide, the reaction generates polysubstituted five- and six-membered oxabicycles (Scheme 27).[49] Based on steric considerations, the



Scheme 27

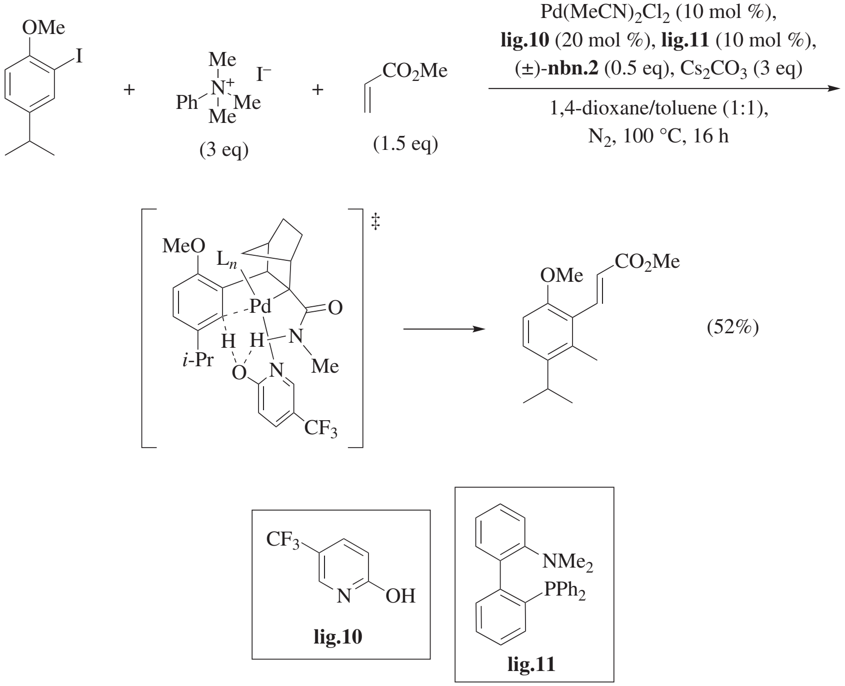
intermolecular alkylation is thought to occur first, followed by an intramolecular alkylation and a Heck reaction.

Ortho-methylation using the Catellani strategy is challenging due to the high volatility and reactivity of methyl halides.[50] This issue can be addressed by using methyl 4-nitrobenzenesulfonate (MeONs),[51] methyl 4-methylbenzenesulfonate (MeOTs), or trimethylphosphate[52] as the alkylating reagent (Scheme 28). The latter two reagents are particularly efficient and general and have been used in the presence of six types of terminating reagents, including Heck acceptors, terminal alkynes, $Zn(CN)_2$, and bis(pinacolato)diboron.[52]



Scheme 28

When phenyltrimethylammonium iodide is used as the methylating reagent (Scheme 29),[53] *N*-methyl amide-substituted norbornene **nbn.2** proves to be the optimal mediator in the presence of 5-trifluoromethyl-2-pyridinol. The latter reagent promotes concerted metalation–deprotonation of the *ortho*-C−H bond,[54] presumably via the intermediate shown.[53] Experimental and computational studies reveal that the additional steric bulk of the amide substituent in **nbn.2** serves to accelerate the norbornene insertion step and to inhibit formation of the benzocyclobutene side product. Moreover, a hydrogen bond between the N−H moiety and the oxygen of **lig.10** accelerates the *ortho*-C−H metalation step, which is turnover-limiting.

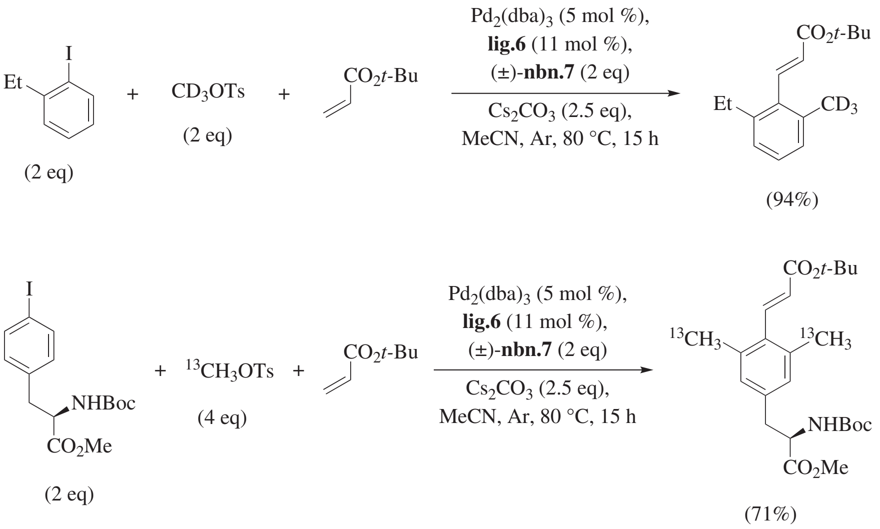


Scheme 29

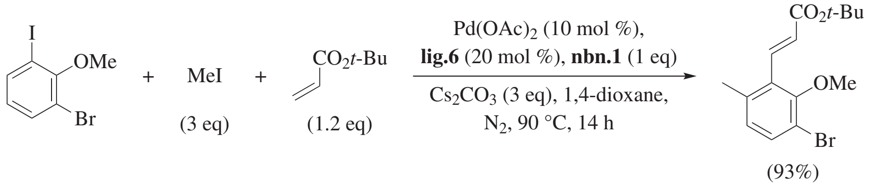
By employing CD_3OTs or $^{13}CH_3OTs$ as the alkylating reagent, this method can be used to generate isotope-labeled methylation products, as shown in Scheme 30.[52]

The differential reactivity of aryl iodides and bromides can be exploited to access densely functionalized aryl bromide derivatives from 2-bromo-6-iodoanisoles (Scheme 31).[51] Because C(aryl)−Br bonds exhibit lower reactivity than C(aryl)−I bonds under the conventional Catellani alkylation conditions, the dominant reaction pathway involves methylation *ortho* to the iodine and subsequent *ipso*-olefination to provide a 1,2,3,4-tetrasubstituted aryl bromide.

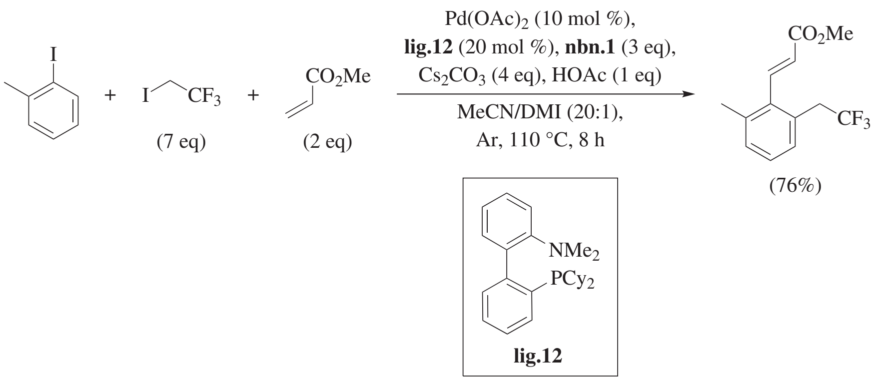
Fluorinated alkyl halides are challenging alkylating reagents for the Catellani reaction because both oxidative addition to the palladacycle and reductive elimination of the resulting palladium(IV) complex are disfavored. However, using the electron-rich phosphine ligand DavePhos (**lig.12**) 1,1,1-trifluoro-2-iodoethane can be employed as an alkylating reagent, and *ortho*-trifluoroethylated vinylarenes are obtained in moderate-to-good yields (Scheme 32).[55]



Scheme 30

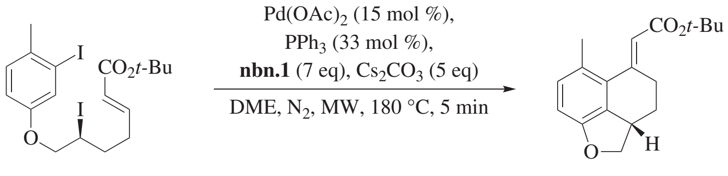


Scheme 31



Scheme 32

Secondary alkyl iodides are another class of challenging alkylating reagents: oxidative addition to the key palladacycle is slower than the competing β-hydrogen elimination.[47] By tethering a secondary alkyl halide moiety to an iodoarene, intramolecular *ortho*-alkylation and subsequent *ipso*-Heck reaction afford bicyclic heterocycles under microwave-irradiation conditions. Phenol-derived enantioenriched substrates provide the corresponding products without significant decrease in the enantiomeric ratios (Scheme 33).[35]

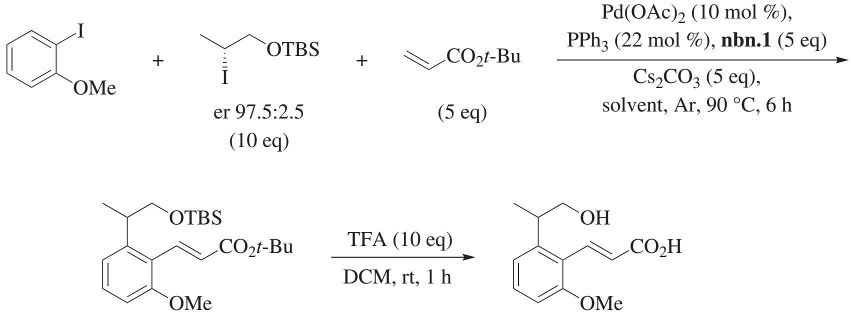


er 91.0:9.0

(78%) er 90.0:10.0

Scheme 33

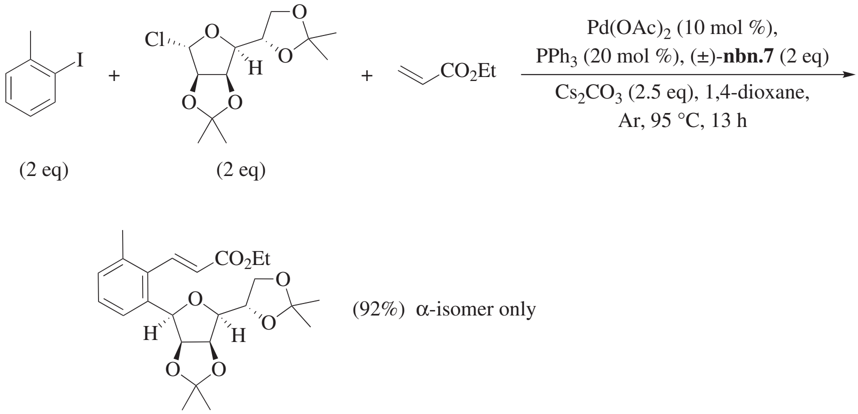
Similar reaction conditions can be used to effect the intermolecular version of this reaction, albeit with a large excess of the secondary alkyl iodide (Scheme 34).[56] Nearly complete retention of enantiopurity is observed when the reaction is carried out in acetonitrile, although the absolute configuration of the product has not been determined. Interestingly, significant erosion of the enantiomeric ratio occurs in dimethylformamide, but the reasons behind the solvent-specific results are not known.



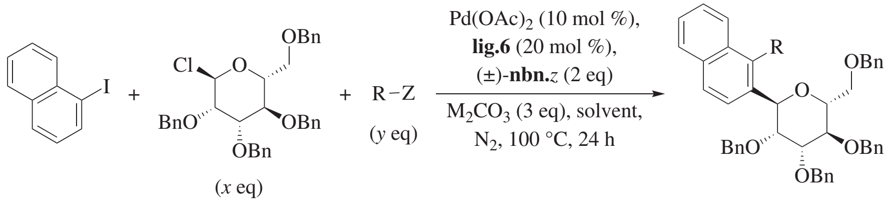
Solvent	Yield (%)	er
MeCN	53	97.0:3.0
DMF	65	70.0:30.0

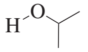
Scheme 34

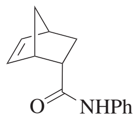
When activated secondary alkyl chlorides, such as glycosyl chlorides, are used as the alkylating reagents, *C*-aryl glycosides are obtained in moderate-to-good yields using cyano-substituted norbornene derivative **nbn.7** as the mediator (Scheme 35).[57] Amide-substituted norbornene derivatives **nbn.8** and **nbn.9** also effect this reaction and have been demonstrated in the context of other types of terminating agents, including isopropyl alcohol, methyl and arylboronic acids, and terminal alkynes (Scheme 36).[58]



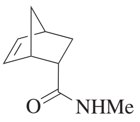
Scheme 35



R−Z	R	*x*	*y*	*z*	M	Solvent	Yield (%)	α/β
	H	1.5	2	**8**	Cs	THF	70	>20:1
Me–B(OH)$_2$	Me	1.5	2	**8**	Cs	THF	66	>20:1
TIPS—≡	TIPS—≡—⌇	1	0.75	**9**	K	MeCN	48	>20:1



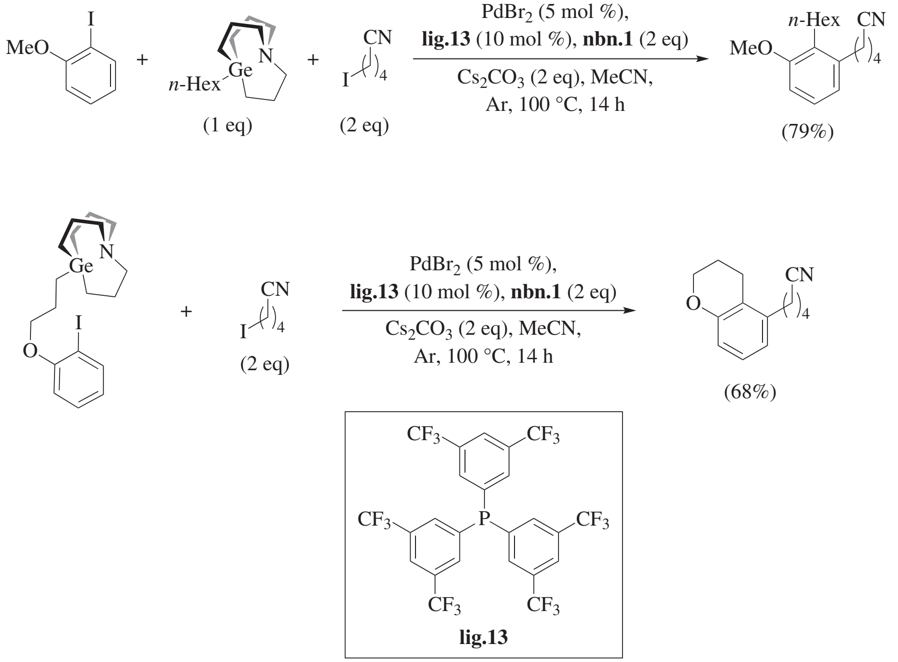
(±)-**nbn.8**



(±)-**nbn.9**

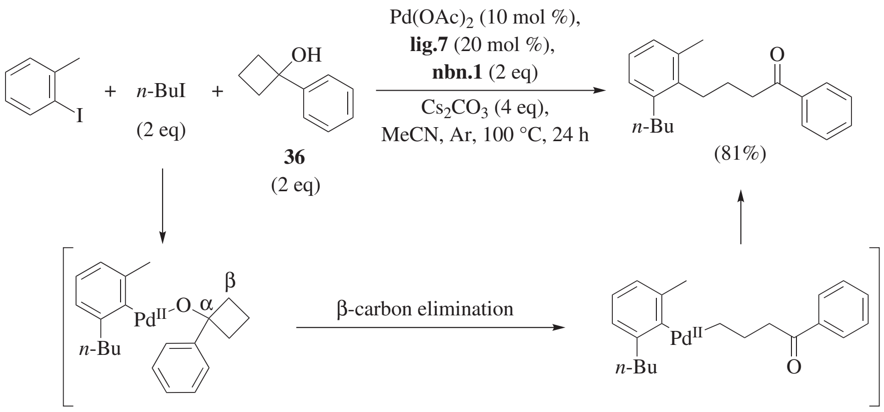
Scheme 36

Although *ortho*-alkylation has been studied extensively since Catellani's initial discovery, reactions terminated by *ipso*-alkylation are unusual. Air- and moisture-stable alkyl carbagermatranes, which can be synthesized from the corresponding germanium bromide and alkyl Grignard or alkylzinc reagents,[59] facilitate *ipso*-termination and provide access to 1,2,3-trisubstituted arenes that are otherwise difficult to prepare (Scheme 37).[60]



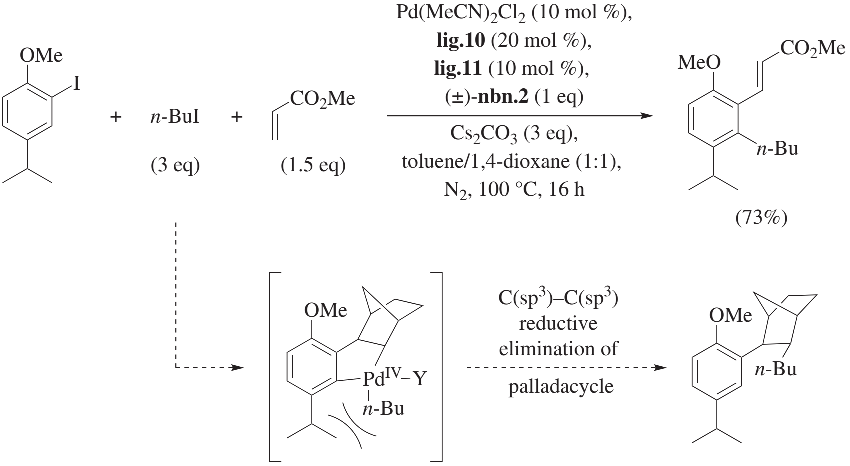
Scheme 37

Cyclobutanol **36** can also afford *ipso*-alkylated products, where the key step is the strain-promoted β-carbon elimination (Scheme 38).[61]



Scheme 38

For most Catellani reactions, the efficiency diminishes significantly when the aryl halide is substituted at the *meta* position, unless the substituent is very small (e.g., F and MeO). This limitation, known as the "*meta* constraint", is largely due to slower norbornene insertion and slower oxidative addition of the alkyl iodide to the palladacycle, which is sterically more hindered because of the *meta* substituent (*ortho* to the palladacycle). As a consequence, an undesired direct Heck reaction or C(sp^3)–C(sp^3) reductive elimination of the palladacycle may occur. However, this side reaction can be avoided by using amide-substituted **nbn.2** as the mediator under carefully optimized conditions. This protocol provides 1,2,3,4-tetrasubstituted arenes, which are otherwise difficult to access, in an efficient and modular fashion (Scheme 39).[53]

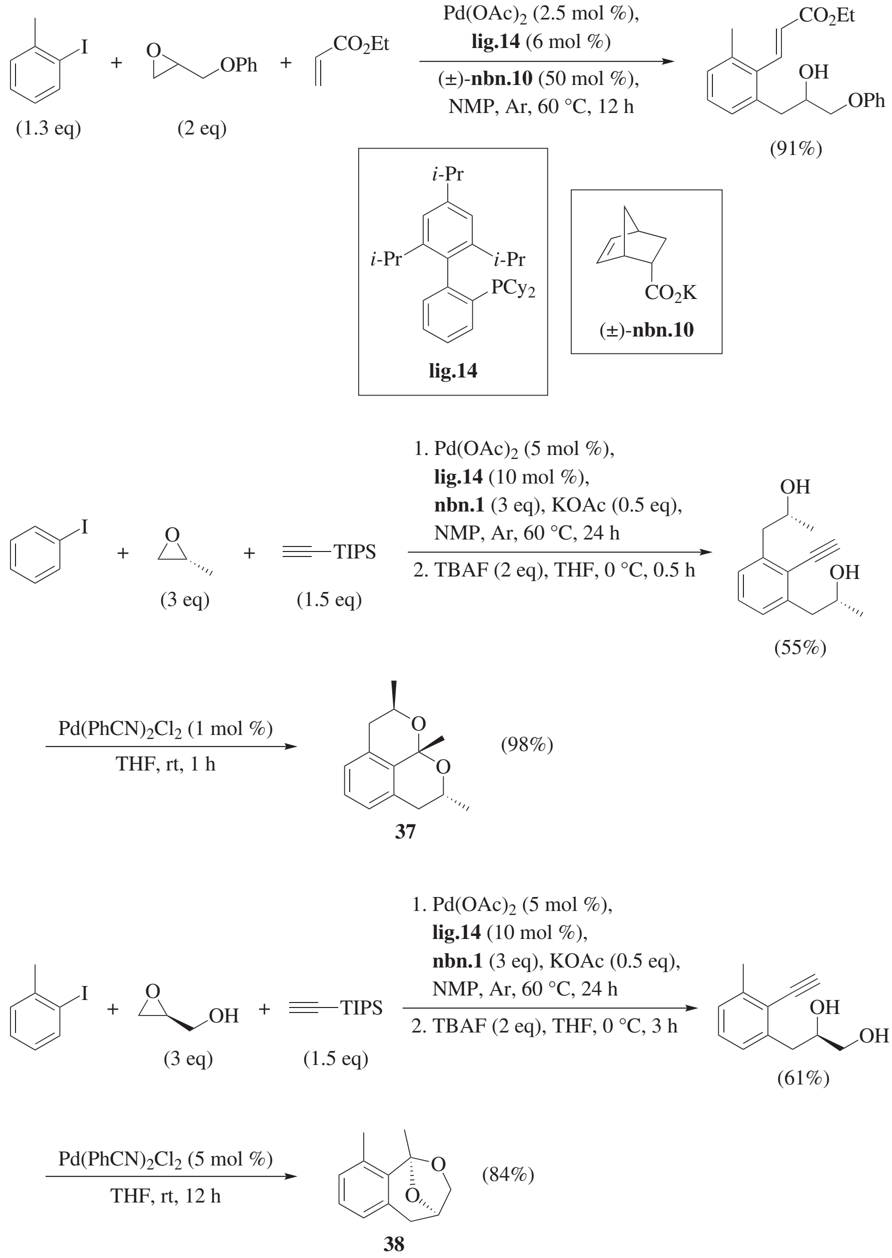


Scheme 39

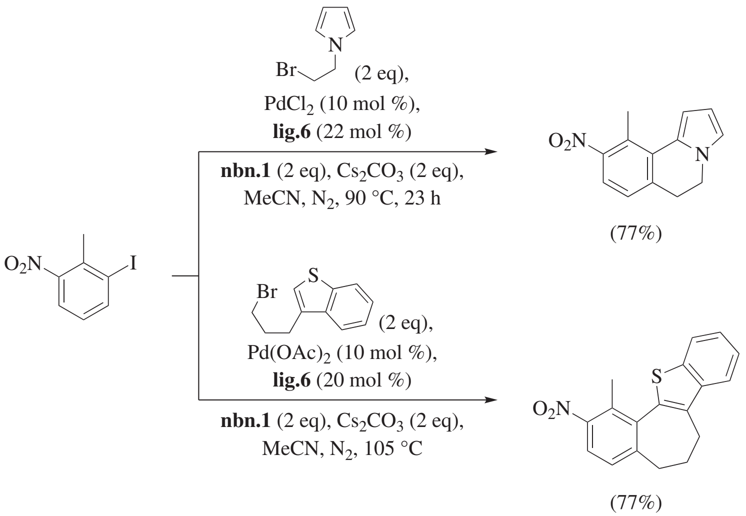
Epoxides can also function as simple alkylation reagents (Scheme 40).[62] For example, using epoxides as the alkylating agents and terminal alkynes as the terminating reagents, mono- or dialkylation of iodoarenes occurs to give phenylacetylenes with an *ortho*-(2′-hydroxyalkyl) substituent. Treatment with a palladium catalyst then effects an oxacyclization reaction to generate benzofused dioxabicycle scaffolds such as 2*H*-pyrano[4,3,2-*ij*]isochromene derivative **37** and 1,4-epoxybenzo[*c*]oxepine derivative **38**.[63]

With Bifunctional Alkylating Reagents. Since the first report featuring bifunctional alkylating reagents in the Catellani reaction (see Scheme 25),[2] a wide variety of fused rings have been prepared via this strategy. For instance, when alkyl bromides linked to an electron-rich heteroarene (e.g., indole,[64] pyrrole,[10] pyrazole,[10] thiophene,[65] or furan[4]) serve as the bifunctional reagents, *ortho*-alkylation is followed by *ipso*-heteroarylation to deliver structurally diverse fused heterocycles in a single step (Scheme 41).

In addition to heteroarenes, other types of nucleophilic functionalities have been tethered to alkyl bromides to form bifunctional alkylating reagents. For example,

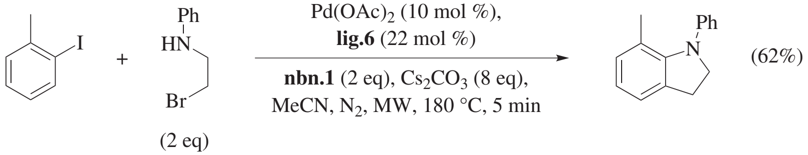

I
(1.3 eq)
O
OPh
(2 eq)
CO2Et
Pd(OAc)2 (2.5 mol %),
lig.14 (6 mol %)
(±)-nbn.10 (50 mol %),
NMP, Ar, 60 °C, 12 h
CO2Et
OH
OPh
(91%)
i-Pr
i-Pr
i-Pr
PCy2
lig.14
CO2K
(±)-nbn.10
I
O
(3 eq)
TIPS
(1.5 eq)
1. Pd(OAc)2 (5 mol %),
lig.14 (10 mol %),
nbn.1 (3 eq), KOAc (0.5 eq),
NMP, Ar, 60 °C, 24 h
2. TBAF (2 eq), THF, 0 °C, 0.5 h
OH
OH
(55%)
Pd(PhCN)2Cl2 (1 mol %)
THF, rt, 1 h
O
O
(98%)
37
I
O
OH
(3 eq)
TIPS
(1.5 eq)
1. Pd(OAc)2 (5 mol %),
lig.14 (10 mol %),
nbn.1 (3 eq), KOAc (0.5 eq),
NMP, Ar, 60 °C, 24 h
2. TBAF (2 eq), THF, 0 °C, 3 h
OH
OH
(61%)
Pd(PhCN)2Cl2 (5 mol %)
THF, rt, 12 h
O
O
(84%)
38

Scheme 40

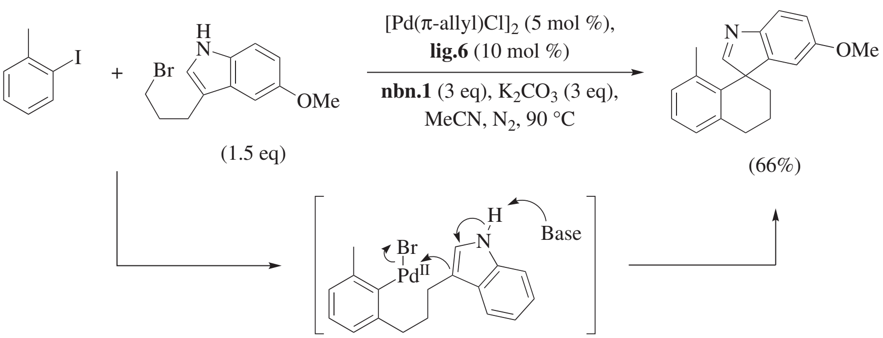


Scheme 41

bromoalkylamines enable the preparation of indolines and tetrahydroquinolines (Scheme 42).[66] Similarly, indole-containing alkyl bromides can be employed to access spiroindolenine derivatives (Scheme 43).[64] Interestingly, this reaction is terminated with an *ipso*-dearomatization event, rather than the aforementioned *ipso*-amination process.

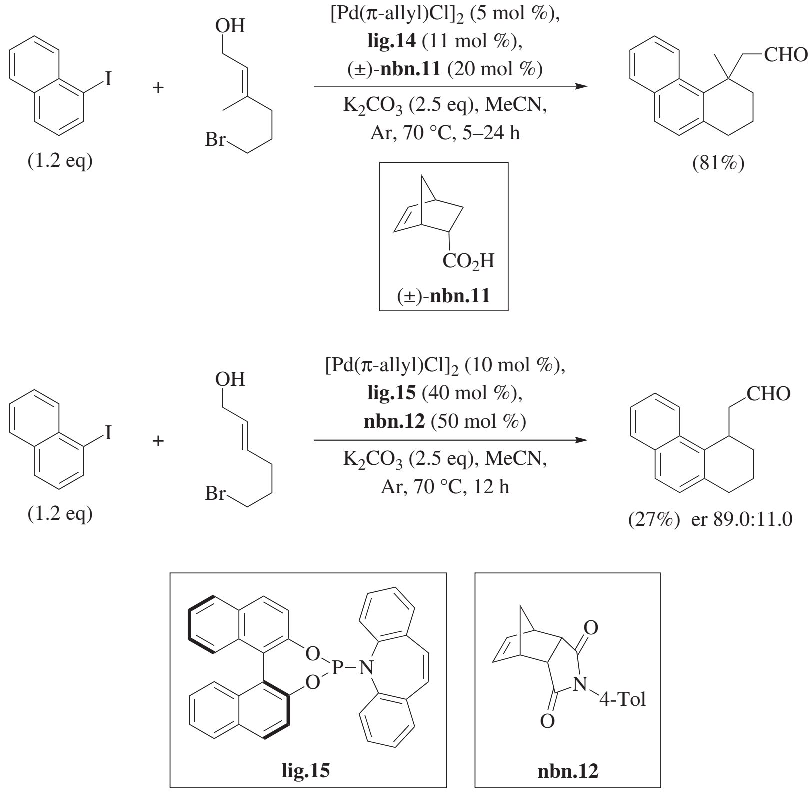


Scheme 42



Scheme 43

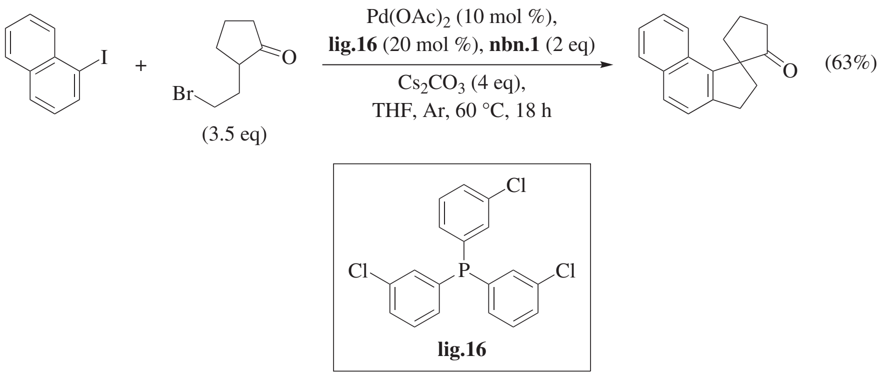
When the alkyl bromide or iodide is tethered to an allyl alcohol, *ortho*-alkylation is followed by a redox-relay Heck reaction[67–69] to furnish tetrahydronaphthalene and indane derivatives bearing a synthetically useful aldehyde moiety (Scheme 44).[7]



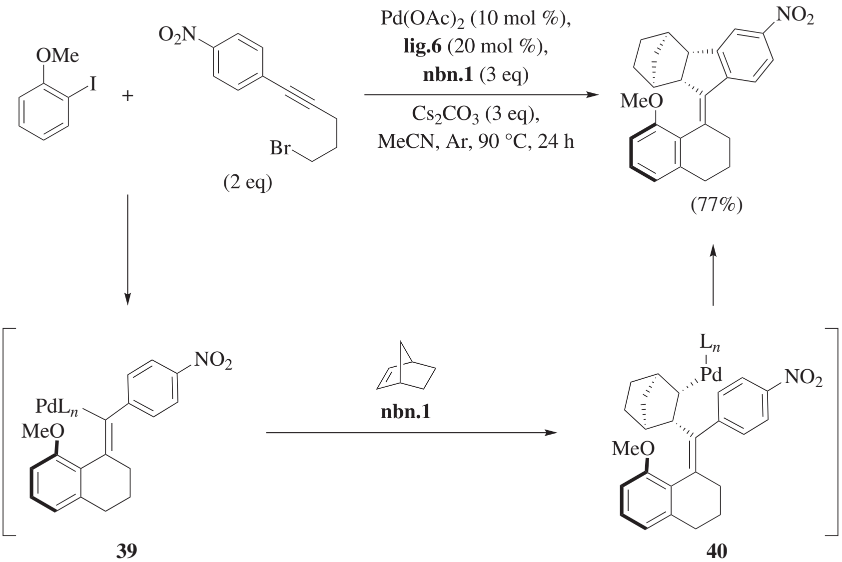
Scheme 44

Spirodihydroindenone derivatives are obtained in moderate yields when cyclopentanone-containing alkyl bromides are used as the alkylating reagents (Scheme 45).[5] In this case, the *ortho*-alkylation is followed by an *ipso*-enolate coupling.

Alkyne-tethered alkyl bromides are another class of bifunctional reagents widely used for the expedient synthesis of complex fused polycyclic compounds. However, when simple bromoalkyl aryl alkynes are subjected to typical Catellani reaction conditions, norbornene does not function as a reaction mediator. Rather, the reagent is incorporated into the product, producing helical alkenes in a single step. Mechanistically, *ortho*-alkylation and intramolecular carbopalladation afford the vinyl palladium species **39**, which then undergoes intermolecular carbopalladation with norbornene (**nbn.1**) to form **40** (Scheme 46).[3] Subsequent arene C−H functionalization provides the final product. Enantioenriched bromoalkyl aryl alkynes undergo this reaction to yield enantioenriched helical alkenes with almost complete retention



Scheme 45

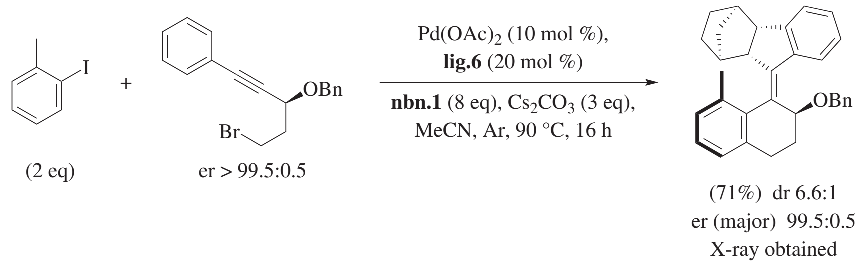


Scheme 46

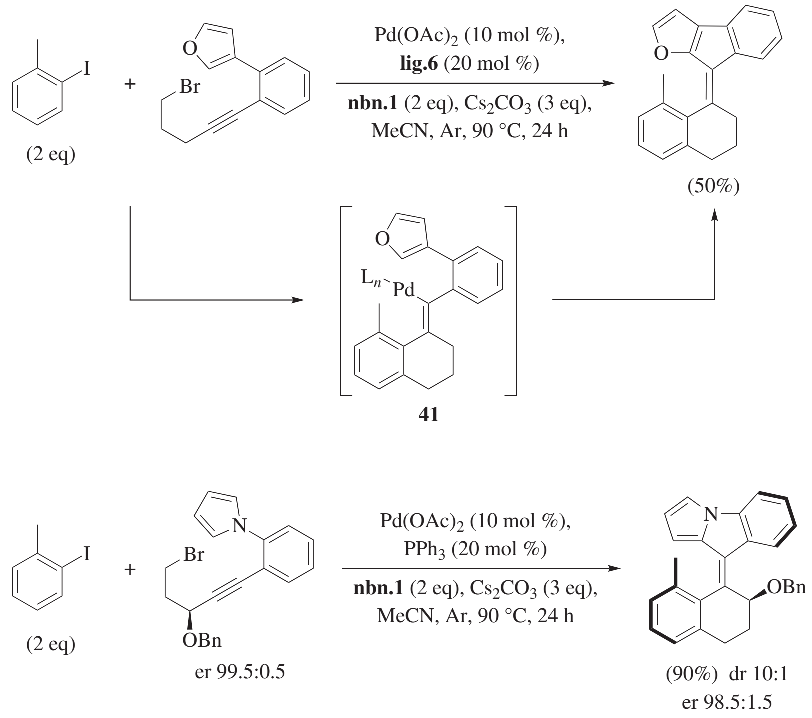
of central chirality, moderate induction of helical chirality, and exclusive *exo*-facial selectivity (Scheme 47).[70]

When the bifunctional reagent contains an additional aryl or heteroaryl group, the vinylpalladium species **41** undergoes intramolecular C–H functionalization in preference to the aforementioned intermolecular norbornene (**nbn.1**) insertion. The use of enantiomerically enriched alkyl bromides affords sterically crowded tetrasubstituted helical alkenes, which are otherwise difficult to access, with complete retention of central chirality and good induction of helical chirality (Scheme 48).[4]

Treatment of iodoarenes bearing a pyrrole at the *ortho* position with alkyne-tethered alkyl bromides results in intermolecular alkylation followed



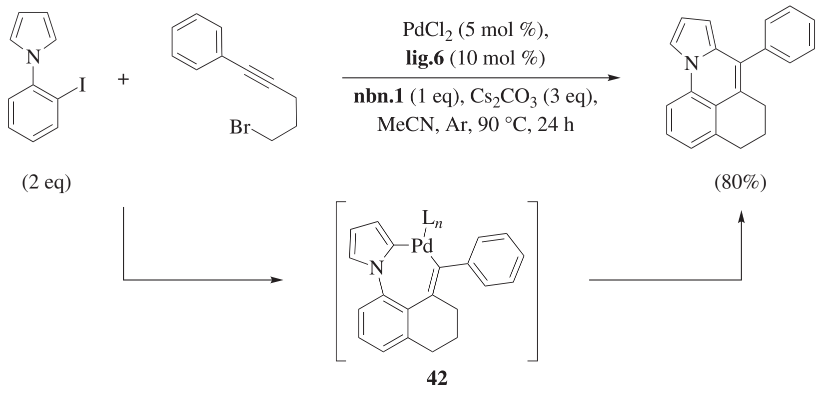
Scheme 47



Scheme 48

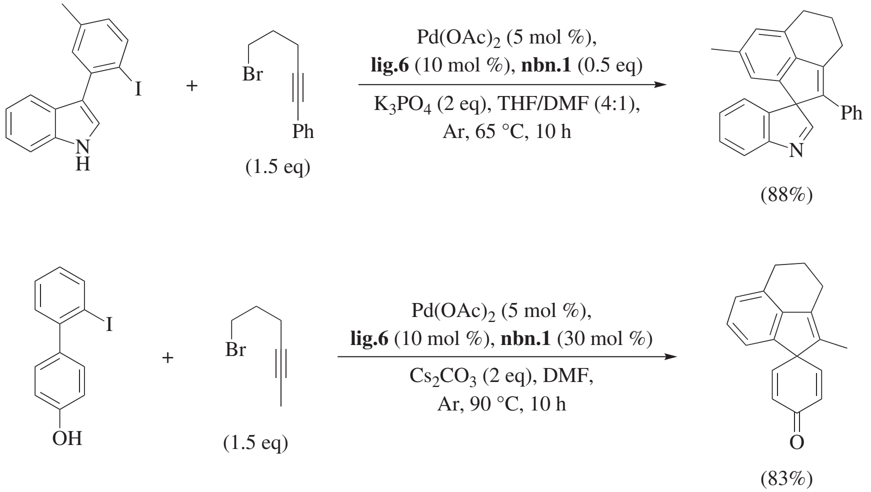
by intramolecular carbopalladation. The resulting vinyl palladium species **42** undergoes reductive elimination to generate tetracyclic fused pyrroles (Scheme 49).[71] Similarly, 1-(2-iodobenzyl)-1*H*-pyrroles and -indoles can be utilized to prepare seven-membered-ring fused heterocycles.[72]

By using indole-based biaryl iodides, this strategy is applicable to the synthesis of spiroindolenine-containing pentacyclic products (Scheme 50, top reaction).[6] In this case, the intermediate vinylpalladium species reacts with the indole moiety via a dearomatization process, leading to pentacyclic spiroindolenines in good yields. This arene dearomatization strategy can also be extended to the synthesis



Scheme 49

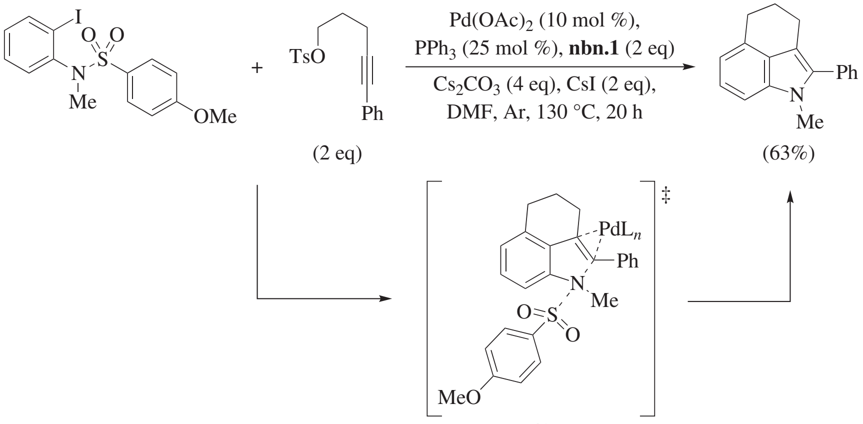
of spiro[4,5]decane-embedded polycyclic molecules from phenol-containing biaryl iodides (Scheme 50, bottom reaction).[8]



Scheme 50

Tricyclic indole derivatives are produced when alkyne-tethered tosylates are used to alkylate 4-methoxybenzenesulfonyl-protected 2-iodoanilines. DFT calculations suggest that the reaction proceeds via TS **43**, wherein the coordination of nitrogen to palladium induces simultaneous nitrogen–sulfur bond scission and carbon–nitrogen bond formation (Scheme 51).[73]

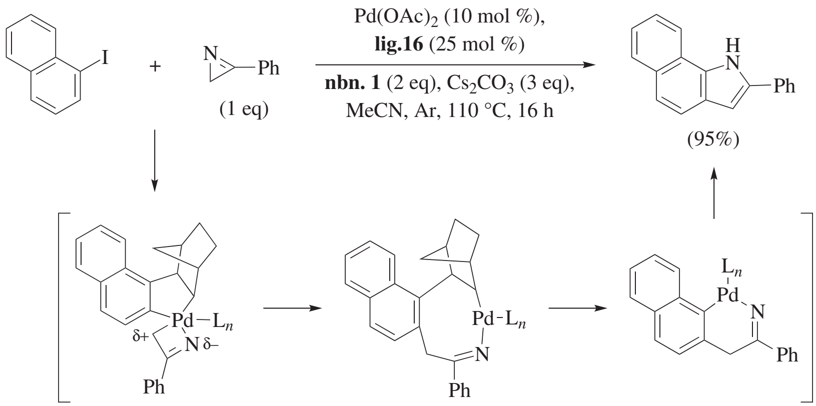
Strained three-membered heterocycles such as 2*H*-azirines,[74] *N*-substituted aziridines,[75,76] and epoxides[76,77] are a distinct class of bifunctional alkylating reagents that provide an alternative to alkyl-halide-tethered Heck acceptors. For example, aryl-substituted 2*H*-azirines have been used to prepare indoles via



43

Scheme 51

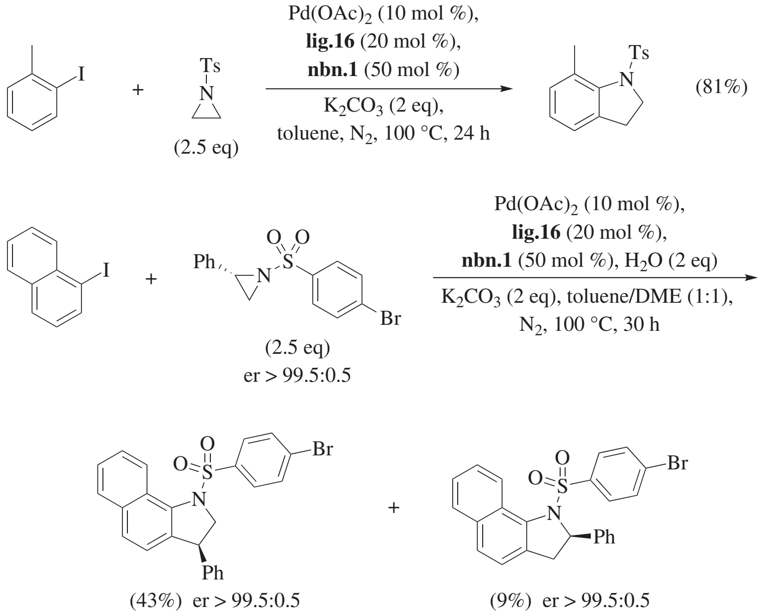
Catellani-type reactions (Scheme 52).[74] Mechanistically, oxidative addition of the nitrogen−carbon single bond to the palladacycle affords the palladium(IV) intermediate **44**, which then undergoes reductive elimination to form intermediate **45**. Norbornene (**nbn.1**) extrusion, reductive elimination, and tautomerization deliver the indole product.



44 **45**

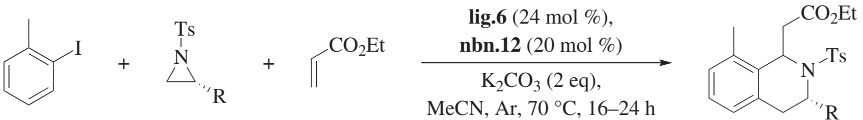
Scheme 52

In a similar fashion, the use of an aziridine as the alkylating agent provides access to indoline products (Scheme 53).[75] When an enantioenriched aziridine is employed, the product is obtained with no erosion of the enantiomeric ratio, albeit in low yield and as a mixture of regioisomers. Although not fully investigated, the low yield may be due to competing oxidative addition of the palladacycle to the carbon−bromine bond of the electron-deficient arene.



Scheme 53

In the presence of a Heck acceptor, the above alkylation reaction can be combined with an *ipso*-Heck termination and an aza-Michael addition to access tetrahydroisoquinoline derivatives (Scheme 54).[76] In this case, norbornene derivative **nbn.12** exhibits higher catalytic efficiency than norbornene (**nbn.1**), and again, enantioenriched aziridine substrates afford products with complete stereoretention. Product **46** (R = $MeOCH_2$) is obtained as a single diastereomer, indicating that the intramolecular aza-Michael addition is highly diastereoselective. The two-component reaction between the aryl iodide and aziridine shown in Scheme 53 may compete with the desired three-component reaction for some substrates.

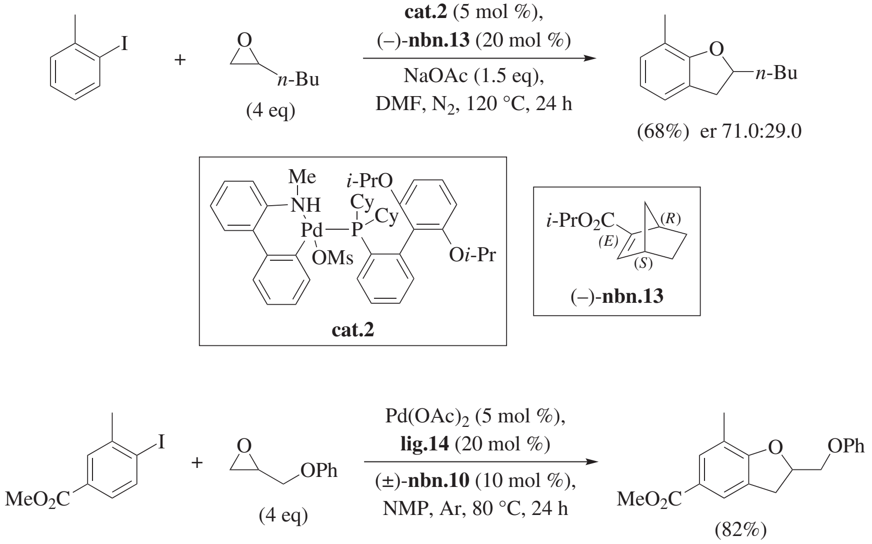


46

R	er (aziridine)	Yield (%)	dr	er **46**
H	—	81	—	—
$MeOCH_2$	99.5:0.5	53	>20:1	99.0:1.0

Scheme 54

Epoxides can also be utilized as bifunctional alkylating reagents to prepare 2,3-dihydrobenzofuran derivatives in the presence of Buchwald's Ruphos-Pd-G4 precatalyst **cat.2**. Use of the enantioenriched isopropyl-ester-substituted norbornene (−)-**nbn.13** mediator results in enantioenriched 2,3-dihydrobenzofurans with moderate enantiomeric ratios (up to 71.0:29.0 er) (Scheme 55, top reaction).[77,78] Alternatively, the same transformation can be achieved using palladium acetate, XPhos (**lig.14**), and the potassium salt of 5-norbornene-2-carboxylic acid (**nbn.10**) (Scheme 55, bottom reaction).[79] Notably, because **nbn.10** is basic, no additional base is needed in this protocol.



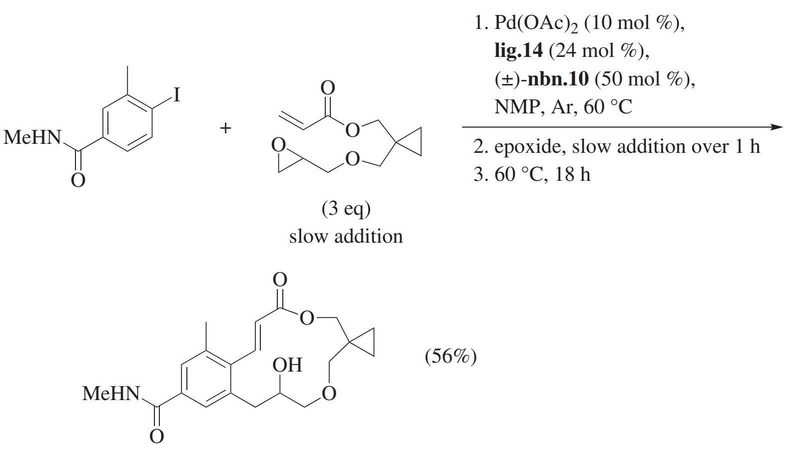
Scheme 55

When a Heck acceptor is present in the above reaction, *ortho*-alkylation and *ipso*-Heck coupling afford an alcohol product (Scheme 56),[62] which can be converted to an isochroman derivative via an oxa-Michael addition under basic conditions. By tethering the epoxide to the Heck acceptor, the Catellani reaction provides one-step access to macrocycles that are otherwise difficult to prepare.

Ortho-Arylation of Aryl (Pseudo)Halides.

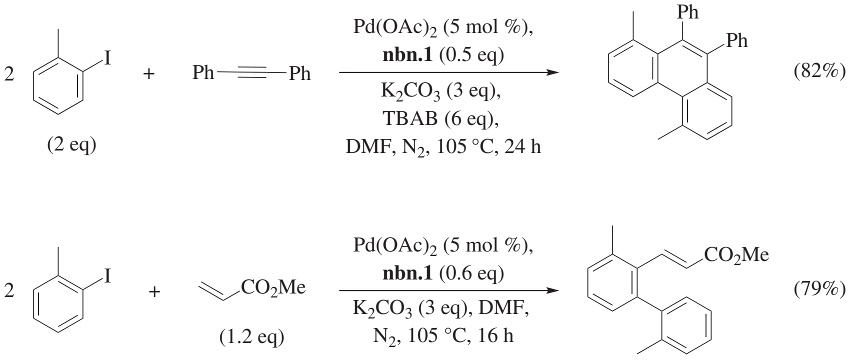
With Simple Arylating Reagents. *Ortho*-arylation reactions are more challenging than *ortho*-alkylation reactions under palladium/norbornene catalysis for two reasons: (1) reductive elimination of the palladium(IV) species may lead to undesired aryl−norbornyl ($C(sp^2)-C(sp^3)$) bond formation in addition to the desired aryl−aryl ($C(sp^2)-C(sp^2)$) bond formation, and (2) homocoupling and cross-coupling of aryl halides can be competing pathways.

The first issue is addressed by installing an *ortho* substituent on the aryl halide. The resulting "*ortho* effect" proves to be very general: an *ortho* substituent on the aryl halide favors aryl−aryl ($C(sp^2)-C(sp^2)$) reductive elimination over ($C(sp^2)-C(sp^3)$) bond formation by 4−12 kcal/mol.[80] In the initial report of an



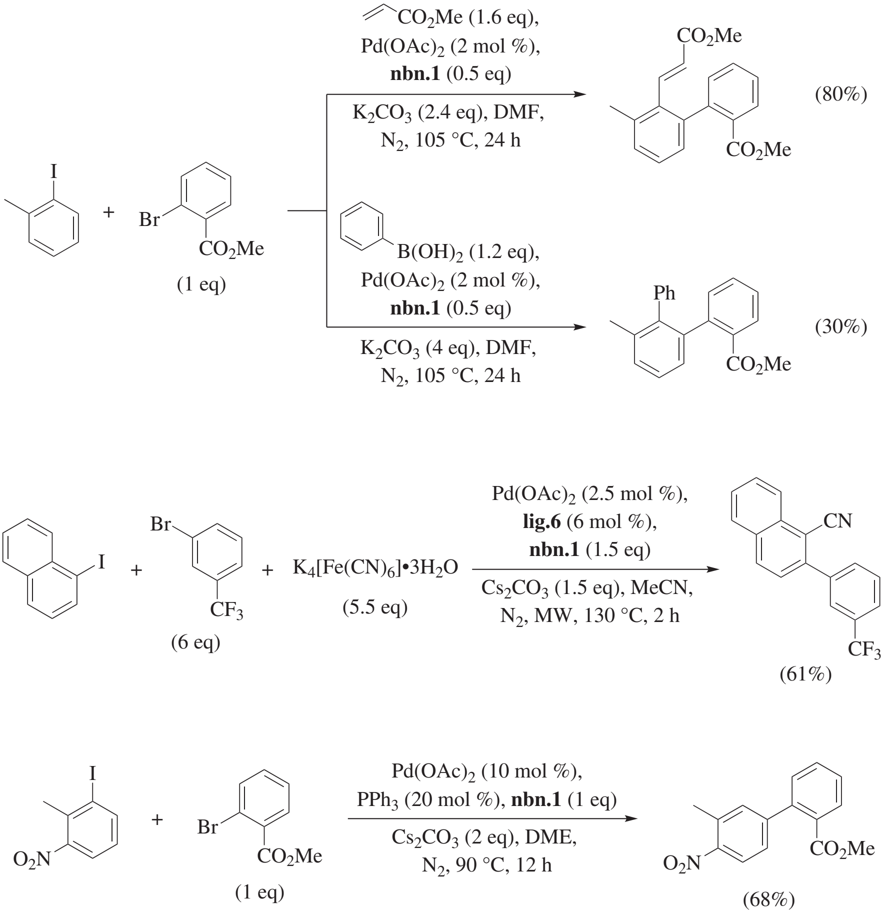
Scheme 56

ortho-arylation–homocoupling reaction, internal alkynes are used as the terminating reagents, ultimately generating phenanthrene derivatives from 2-substituted iodoarenes after migratory insertion and C–H vinylation (Scheme 57, top reaction).[81] Alkenes (Scheme 57, bottom reaction),[82] arylboronic acids,[83] benzyl alcohol,[84] ketones,[85] and heteroarenes[86] are also compatible terminating reagents for this reaction, furnishing a wide variety of biphenyls that are not easily accessible using other approaches.



Scheme 57

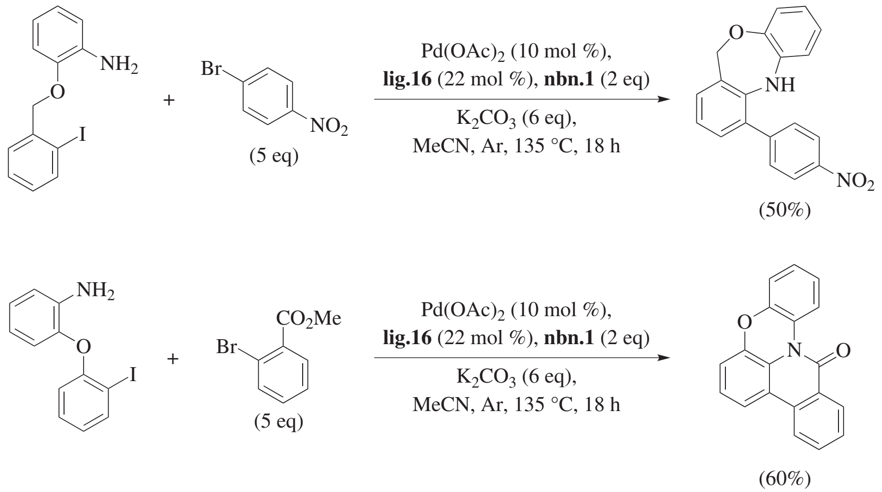
Employing two different aryl-halide starting materials (substrate and electrophile) presents formidable chemoselectivity issues and is considerably more challenging than the above homocoupling reactions. Cross-coupling is possible when one of the two aryl halides has much higher reactivity towards palladium(0) and the other reacts preferentially with the palladacycle. Indeed, highly selective cross-coupling reactions occur using an iodoarene with an *ortho* electron-donating group (EDG) and a bromoarene with an electron-withdrawing group. These reactions may be terminated with a variety of reagents (Scheme 58), including electron-deficient alkenes,[87] cyanide anion,[50] arylboronic acids,[88] and hydride donors (e.g., 1,2-dimethoxyethane mediated reduction).[20]



Scheme 58

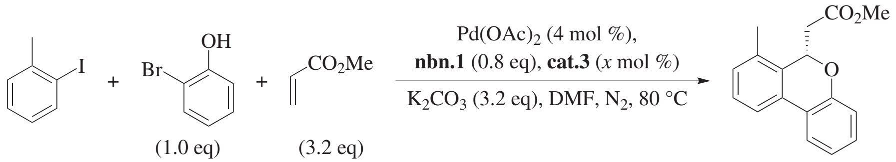
When aryl iodides containing a nucleophilic amine functionality are treated with electron-deficient bromoarenes, the Catellani reaction affords fused heterocycles (Scheme 59).[89] In this case, *ortho*-arylation is followed by an intramolecular termination event, in which a new carbon−nitrogen bond is formed. Notably, when methyl 2-bromobenzoate is used as an arylating reagent, a polycyclic δ-lactam is obtained in a single step.

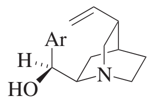
Ortho chelating groups can also be appended to bromoarenes to enable selective cross-coupling of iodoarenes and bromoarenes. For example, *ortho*-substituted aryl iodides react with 2-bromophenols in a highly selective manner, furnishing



Scheme 59

cross-coupling/oxa-Michael addition products in a single step (Scheme 60).[90] The desired reaction does not occur when the 2-bromophenol is replaced by 4-bromophenol or 2-bromoanisole, suggesting that chelation between the *ortho* hydroxyl group and the palladium(II) complex is necessary to favor reaction with the aryl bromide rather than with the aryl iodide. Using the *Cinchona* alkaloid derivative **cat.3** as a Michael addition organocatalyst provides dibenzopyran derivatives with enantiomeric ratios of up to 98.5:1.5 er.[91]



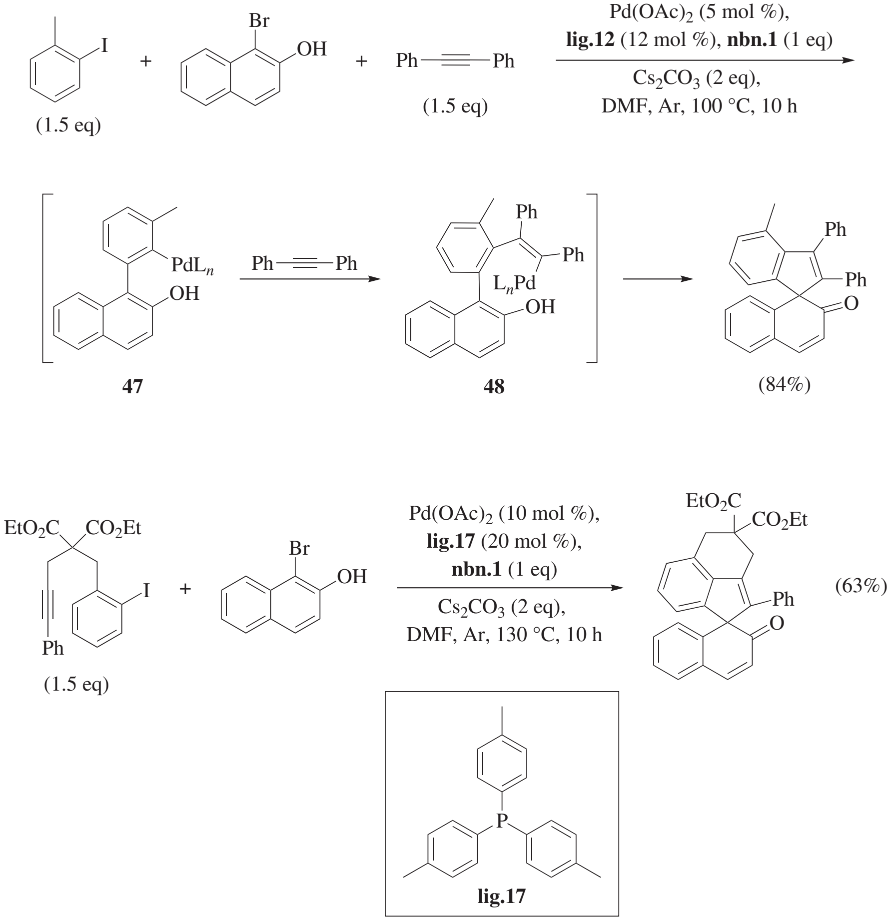


Ar = 1-naphthyl
cat.3

x	Time (h)	Yield (%)	er
0	24	83	50.0:50.0
50	96	75	97.5:2.5

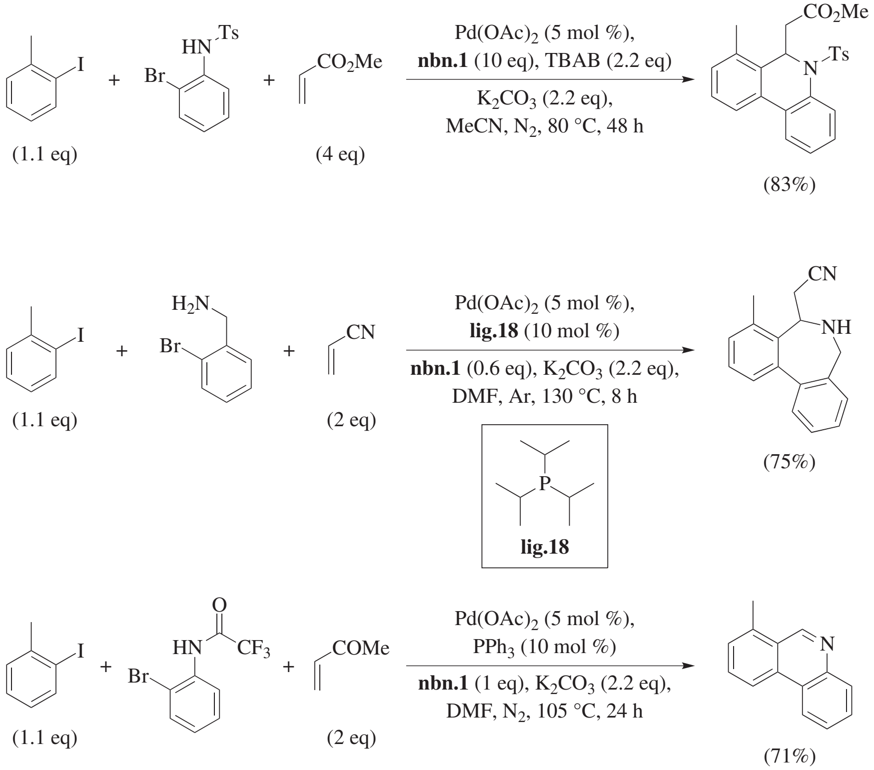
Scheme 60

The Catellani reaction affords spirocarbocyclic products in a single step by using internal alkynes as the terminating reagents in combination with *ortho*-substituted iodoarenes and 1-bromo-2-naphthols (Scheme 61).[92] After the *ortho*-arylation event, alkyne migratory insertion and arene dearomatization occur to deliver the final products in moderate-to-excellent yields via the intermediacy of **47** and **48**. By tethering the alkyne moiety to the aryl iodide, the corresponding two-component reaction proceeds smoothly to afford polycyclic skeletons in a similar fashion (Scheme 61, bottom reaction).



Scheme 61

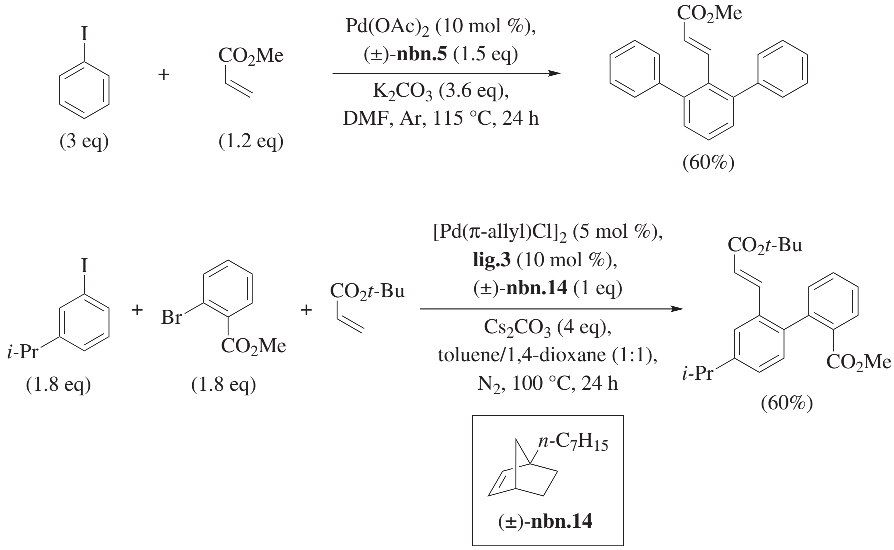
Nitrogen-containing functionalities can also serve as *ortho* chelating groups for selective cross-coupling reactions. For example, in the presence of a Heck acceptor, 2-bromo-*N*-sulfonyl-protected anilines undergo a Catellani-type reaction with 2-substituted aryl iodides, providing 5,6-dihydrophenanthridine derivatives (Scheme 62).[93] In the top reaction shown in Scheme 62, a two-component cyclization product is formed in significant quantities; the addition of TBAB prevents formation of this byproduct and accelerates the oxidative addition of the aryl iodide to palladium(0). In an analogous manner, dibenzoazepine derivatives are generated from 2-bromobenzylamines (Scheme 62, middle reaction).[94] Using methyl vinyl ketone as the Heck acceptor and a trifluoroacetyl protecting group on nitrogen, the *ortho*-arylation/aza-Michael addition sequence is followed by a retro-Mannich reaction to form phenanthridine derivatives as the final products (Scheme 62, bottom reaction).[95]



Scheme 62

Another approach to selective aryl–aryl coupling involves the use of substituted norbornene derivatives. For instance, the *ortho*-arylation of iodobenzene in the presence of a Heck acceptor and 2-carbomethoxynorbornene (**nbn.5**) affords the *ortho*-bis-arylated vinylarene product in 60% yield (Scheme 63, top reaction).[12] When the aryl iodide is both *meta*-substituted and *ortho*-unsubstituted, cross-couplings with electron-poor bromoarenes have been achieved using norbornene derivative **nbn.14**, which contains an alkyl substituent at the bridgehead (Scheme 63, bottom reaction).[96] Mono *ortho*-arylation occurs regioselectively at the less hindered *ortho* position due to unfavorable steric interactions between the bulky **nbn.14** and the *meta* substituent.

Axially chiral biaryl compounds can be prepared by employing enantioenriched norbornene derivatives to mediate *ortho*-arylation reactions. For example, the enantioenriched norbornene derivative (+)-**nbn.15** facilitates the coupling of

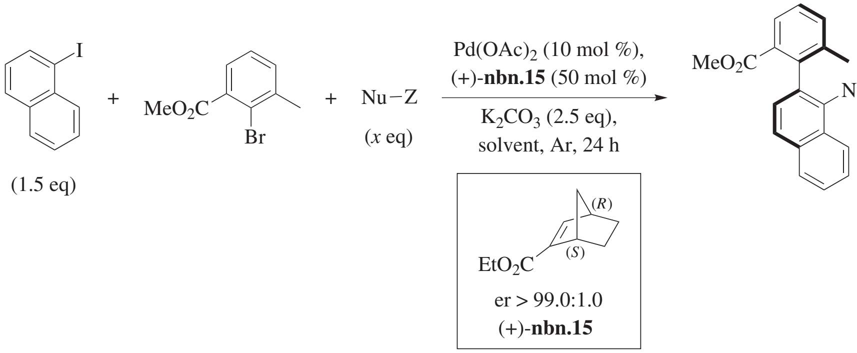


Scheme 63

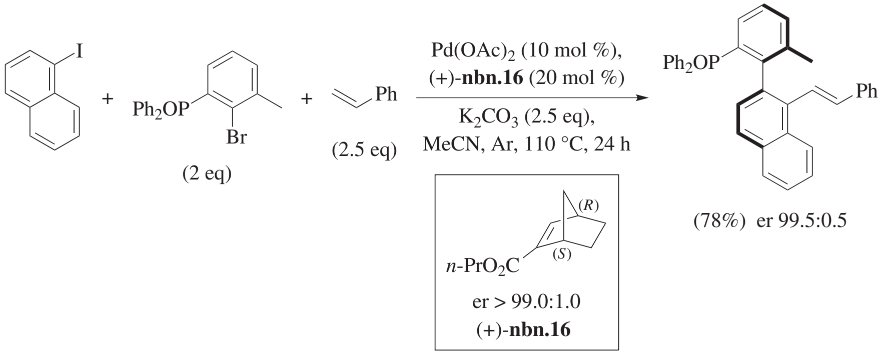
iodoarenes with 2,6-disubstituted aryl bromides to afford axially chiral biaryl compounds in modest-to-good yields and with high enantiomeric ratios (Scheme 64, top reaction).[97] This approach exhibits broad functional-group tolerance and is compatible with a wide range of terminating reagents such as Heck acceptors, terminal alkynes, boronic acids, and cyanide. A similar procedure using the *n*-propyl ester analog **nbn.16** permits a highly enantioselective synthesis of axially chiral biaryl monophosphine oxides (Scheme 64, bottom reaction).[98] DFT calculations reveal that oxidative addition of the aryl bromide to the palladacycle is the enantiodetermining step.

An analogous strategy using *ortho*-substituted potassium aryl trifluoroborates as the terminating reagents affords biaryls with excellent enantioselectivities along two stereogenic axes (Scheme 65).[99] Computational studies indicate that the diastereoselectivity, which ranges from 3:1 to >20:1, is dictated by the substitution pattern of the aryl trifluoroborates.

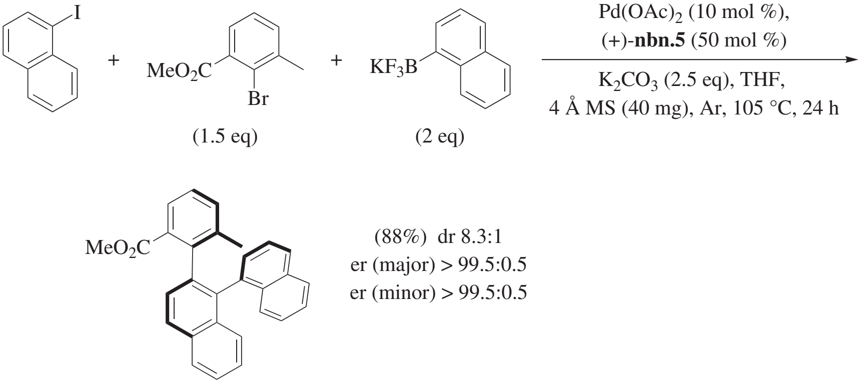
With Bifunctional Arylating Reagents. In the absence of an external terminating reagent, bifunctional arylating reagents can be used to prepare fused heterocycles in a single step (Scheme 66). For example, reaction of a 2-substituted iodoarene with a 2-bromobenzamide affords the 6-phenanthridinone in high yield.[100] When 2-chloro-*N*-silylaldimines or *N*-silylketimines are used as the bifunctional reagents, phenanthridine derivatives are obtained via *ortho*-arylation/*ipso*-amination followed by in situ desilylation.[101] Aryl chlorides, which are typically more readily available but less reactive than aryl bromides and iodides, are successful arylating reagents in this reaction, presumably because a chelation between the imine nitrogen and palladium accelerates the otherwise challenging oxidative addition to the carbon−chlorine bond. Phenanthridine products can also be prepared from the



Nu–Z	x	Solvent	Temp (°C)	Nu	Yield (%)	er
t-BuO$_2$C	1.5	MeCN	105	t-BuO$_2$C	78	98.0:2.0
TIPS–≡	2.0	DME	90	TIPS–≡	70	>99.5:0.5
MeB(OH)$_2$	2.0	THF	105	Me	43	>99.5:0.5
K$_4$[Fe(CN)$_6$]	1.5	MeCN	105	NC–	48	89.5:10.5

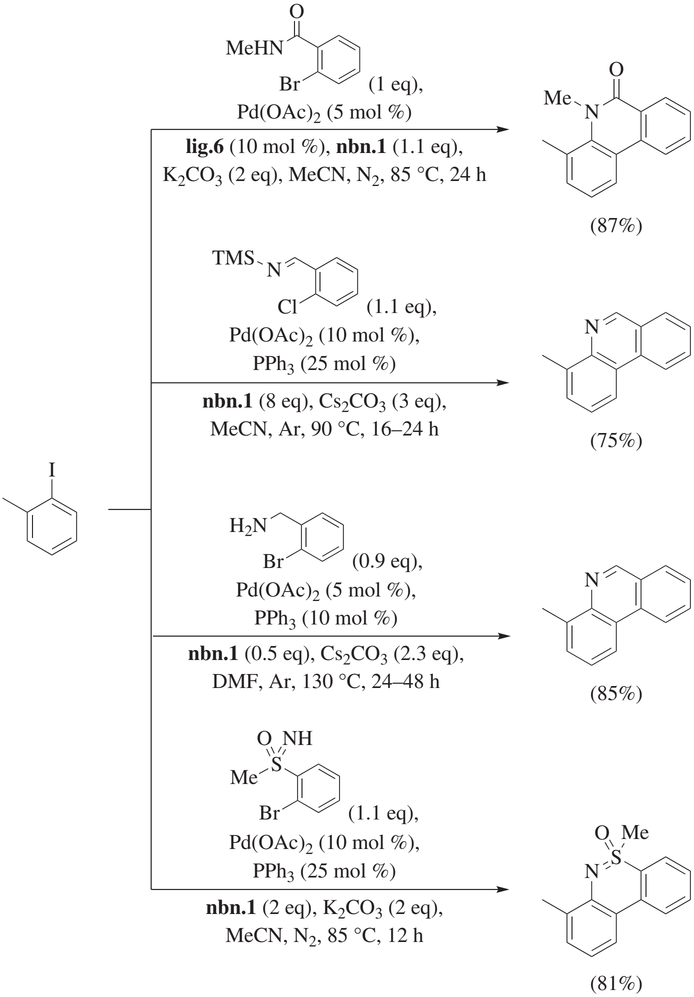


Scheme 64



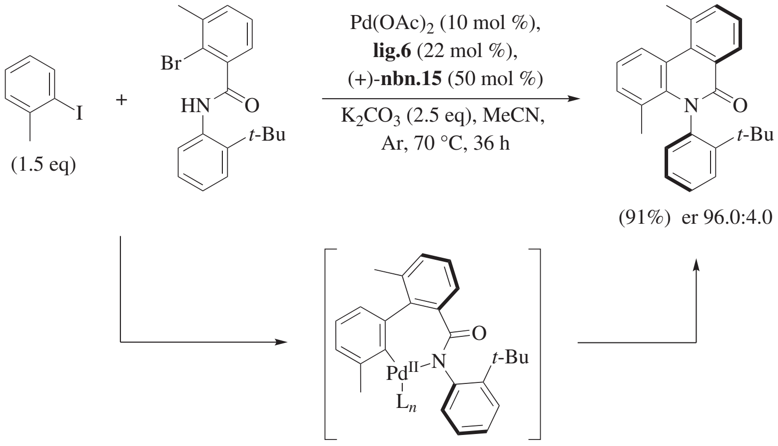
Scheme 65

corresponding 2-bromobenzylamines: in this case, the arylation reaction is followed by a palladium(II)-catalyzed oxidative dehydrogenation.[102] Using bromoarenes containing an *ortho* NH-sulfoximine moiety, tricyclic dibenzothiazines are obtained in good yields.[103]



Scheme 66

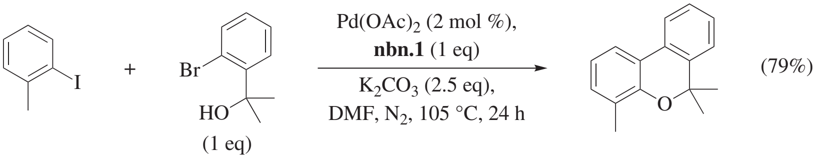
This strategy can be applied to the synthesis of enantioenriched phenanthridinones by using enantioenriched norbornene derivative (+)-**nbn.15**. Starting from 2-substituted iodoarenes and 2-bromobenzamides, axially chiral phenanthridinones are obtained with high enantioselectivities when a bulky substituent is present *ortho* to the aniline (Scheme 67).[104] Notably, a rare axial-to-axial chirality transfer event is involved in this transformation: the C–N axial chirality is generated from the initially formed C–C axial chirality via **49**. The C–C reductive elimination step, showing a strong preference for (*S*)-axial chirality formation, allows the preformed C–C axial chirality to dictate the formation of C–N axial chirality in the final product. Computational studies reveal that the bulky substituent (e.g., *tert*-butyl) of the aniline moiety makes the carbon–nitrogen bond configurationally stable.



49

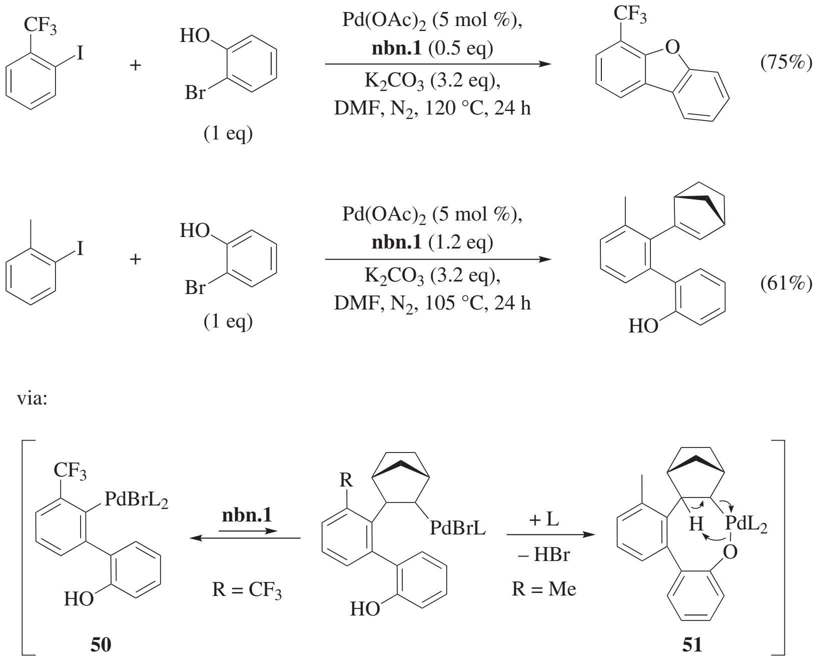
Scheme 67

In addition to the aforementioned *ipso*-C–N couplings, *ipso*-C–O couplings can also be achieved after *ortho*-arylation. For example, the hydroxyl group of 2-bromobenzyl alcohols can terminate the reaction, furnishing 6*H*-dibenzopyrans in good yields (Scheme 68).[105] However, only tertiary alcohols are suitable substrates because primary and secondary alcohols undergo β-hydrogen elimination to deliver biaryl 2-carbaldeydes or ketones.



Scheme 68

In a similar manner, the Catellani reaction between a 2-bromophenol and an iodoarene should afford a dibenzofuran product. However, 2-trifluoromethyliodobenzene is the only substrate that delivers the desired dibenzofuran in a synthetically useful yield (75%) (Scheme 69).[106] A major side reaction is the formation of norbornene-containing hydroxybiphenyl products via an unusual β-hydrogen elimination, which is facilitated by chelation of the phenol to generate intermediate **51**. In contrast, the electron deficiency of the trifluoromethyl-containing aryl ring favors the β-carbon-eliminated species **50** and subsequent intramolecular C(sp^2)–O bond formation.



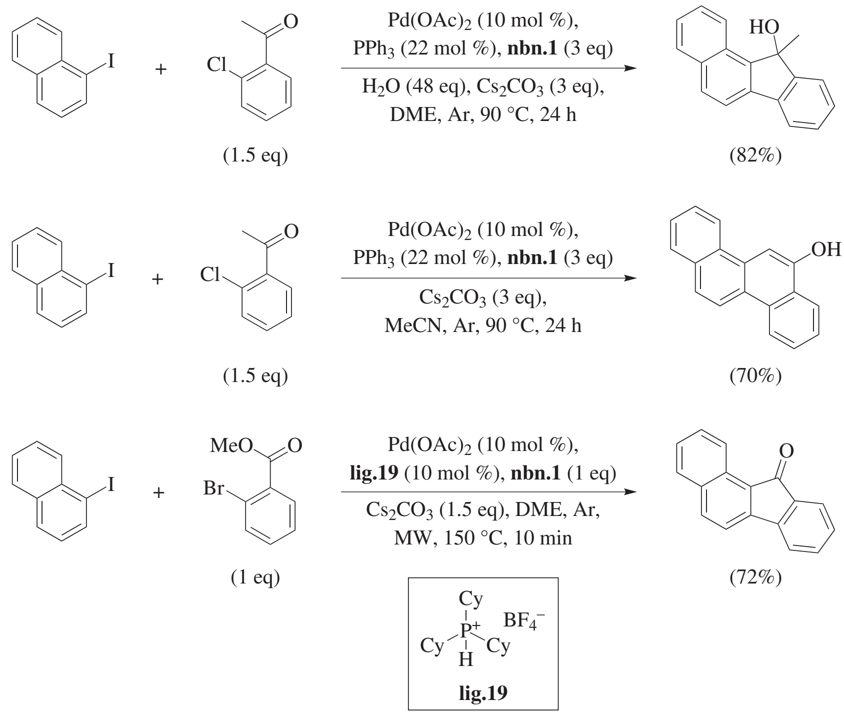
Scheme 69

In addition to acting as an electrophilic coupling partner, the *ortho*-arylated arylpalladium(II) species can also serve as a nucleophile and react with carbonyl groups under certain conditions (Scheme 70).[107] Using wet 1,2-dimethoxyethane as the solvent, 2′-chloroaryl ketones react with 2-substituted iodonaphthalenes to afford 9*H*-fluoren-9-ols via an *ortho*-arylation/*ipso*-1,2-addition sequence. However, in the absence of water, the *ortho*-arylated arylpalladium(II) species is electrophilic, and the expected phenanthren-9-ol derivatives are formed in good yields. Under microwave irradiation, 2′-bromoaryl esters yield 9*H*-fluoren-9-ones as the final products via *ipso*-1,2-addition to the carbonyl group.

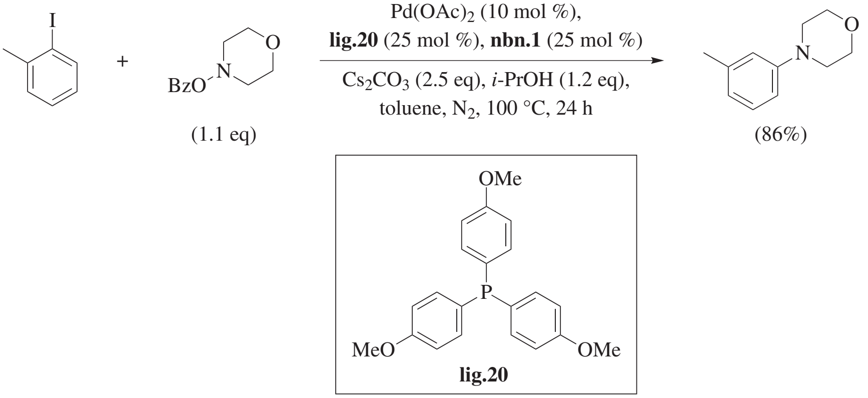
Ortho-Amination of Aryl (Pseudo)Halides.

With Simple Aminating Reagents. Aryl halides are common precursors to aryl amines. Whereas the Buchwald–Hartwig cross-coupling reaction enables carbon–nitrogen bond formation at the *ipso* position of aryl (pseudo)halides, *ortho*-amination of aryl (pseudo)halides under Catellani conditions offers a complementary route to *meta*-substituted aryl amines. The first such example uses *N*-benzoyloxyamines as the aminating reagents and isopropyl alcohol as the terminating hydride source, providing aniline derivatives in good yields (Scheme 71).[108]

Other terminating reagents are also compatible with this *ortho*-amination reaction (Scheme 72), including alkenes,[109] boronic esters,[110] bis(pinacolato)diboron,[111]



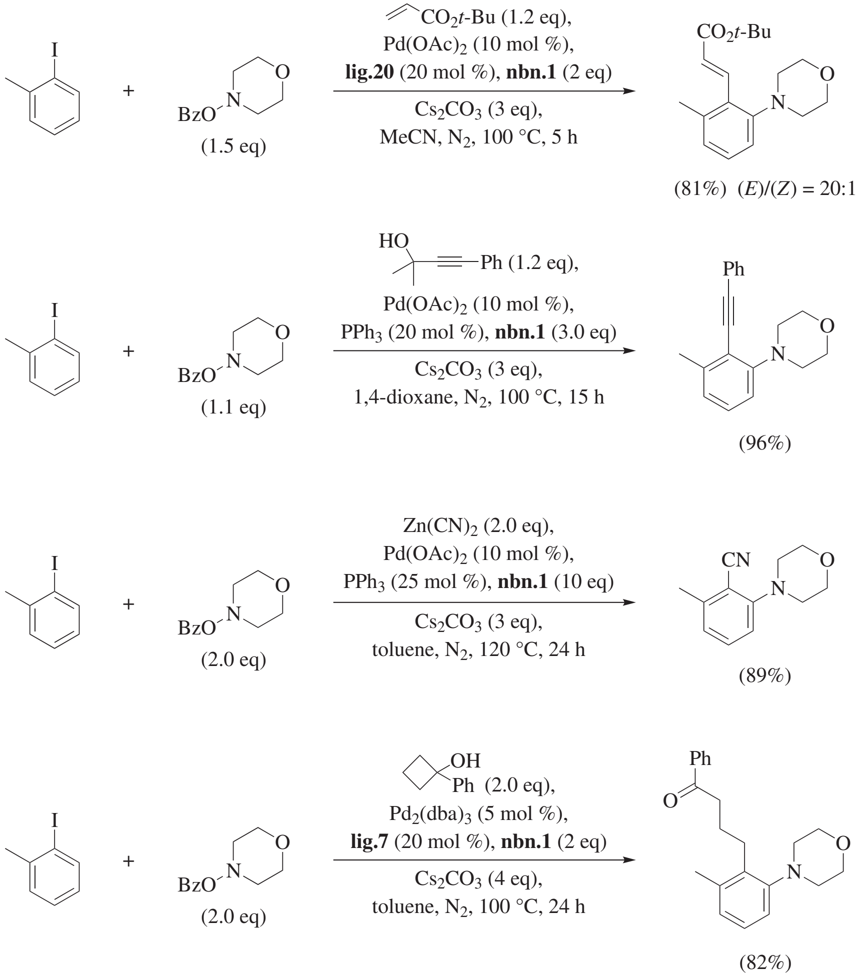
Scheme 70



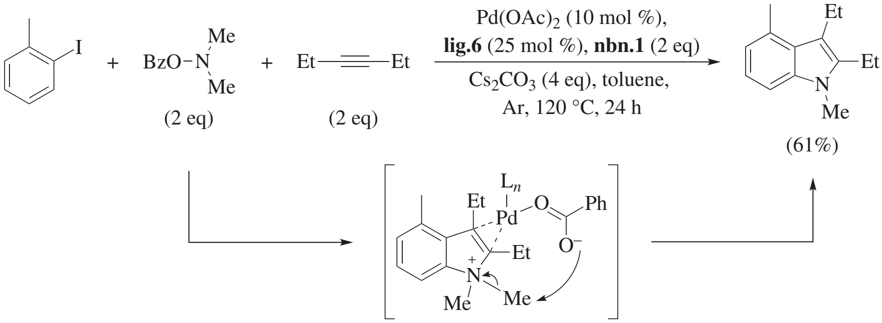
Scheme 71

carbene precursors,[112] 1,1-dimethyl-2-alkynols,[113] propiolic acids,[114] acetone,[115] cyanides,[116,117] and cyclobutanols.[61]

When internal alkynes are employed as the terminating agents in the presence of *O*-benzoyl-*N*,*N*-dimethylhydroxylamine, C2,C3,C4-trisubstituted indoles are obtained unexpectedly (Scheme 73).[118] The mechanism is thought to involve



Scheme 72

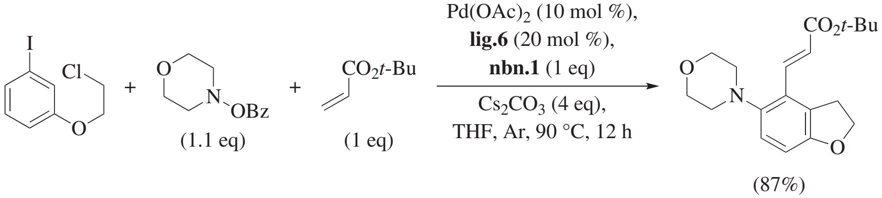


52

Scheme 73

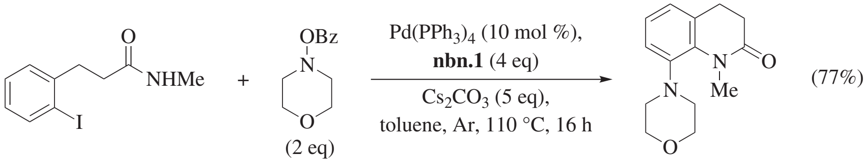
ortho-amination, norbornene (**nbn.1**) extrusion, and intermolecular carbopalladation. From the vinylpalladium intermediate, carbon-nitrogen-bond formation affords indole quaternary ammonium salts **52**, and the final products are generated from carbon-nitrogen-bond cleavage, which occurs via an S_N2 process with the benzoate anion.

The introduction of different functionalities at the two *ortho* positions of an aryl iodide is challenging. A solution involves tethering one of the electrophiles to the *meta* position of the iodoarene.[119] Using this strategy, *ortho*-amination and *ortho*-alkylation occur consecutively to afford polysubstituted benzoheterocyclic scaffolds in a single step (Scheme 74).[120]



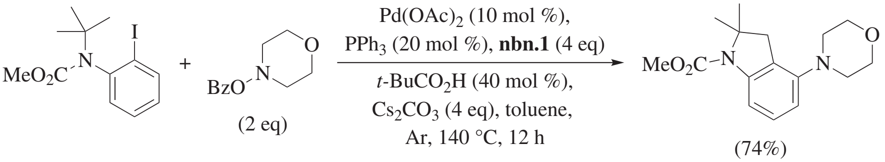
Scheme 74

When the iodoarene contains a terminating functionality, *ortho*-amination is followed by intramolecular termination to provide fused aniline derivatives. For example, an *ortho*-amination/*ipso*-amidation sequence affords dihydroquinolinone derivatives via two sequential carbon−nitrogen bond-forming events (Scheme 75).[121]



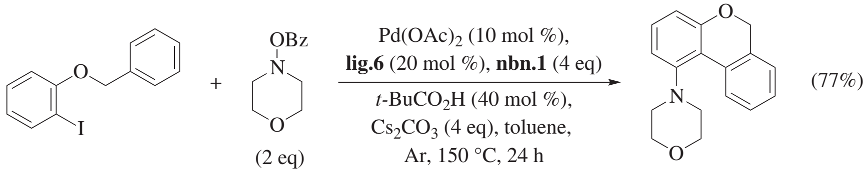
Scheme 75

Unactivated C(sp^3)−H bonds of a methyl group can also be utilized to terminate the reaction in a similar fashion, providing access to 4-aminoindoline derivatives (Scheme 76).[122] The use of pivalic acid as an additive is critical: the pivalate ligates to palladium and promotes an intramolecular arylation of the proximate methyl carbon−hydrogen bond via a concerted metalation–deprotonation (CMD) process.



Scheme 76

Pivalic acid also accelerates the rate of C(sp^2)–H activation, which enables the preparation of benzochromene derivatives via an *ortho*-amination/*ipso*-arylation sequence (Scheme 77).[123]



Scheme 77

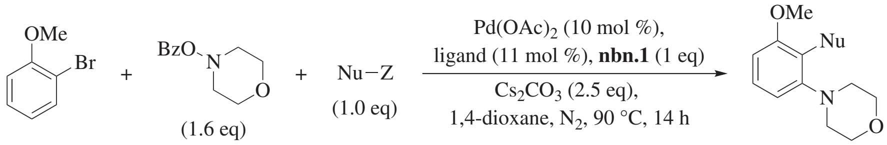
Bromoarenes are generally cheaper and more accessible than their iodide counterparts, and thus, are more attractive substrates. By judicious choice of phosphine ligands, *ortho*-aminations of aryl bromides occur with good efficiency in the presence of a diverse range of terminating reagents (Scheme 78, top reaction).[51] Although a more common hydride source for *ipso*-hydrogenation, isopropyl alcohol results in formation of norbornene-containing **53**, which is generated via hydride transfer from isopropyl alcohol to the norbornylpalladium species (Scheme 78, bottom reaction). The more sterically hindered (–)-borneol is thought to significantly decrease the rate of the undesired β-hydride elimination, thereby diminishing side-product formation.

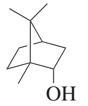
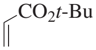
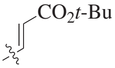
When norbornadiene (**nbn.17**) is used in place of norbornene (**nbn.1**) in the absence of an external terminating reagent, phenol-tethered iodoarenes afford diversely functionalized spiroindenes in good yields (Scheme 79).[124] After the initial *ortho*-amination step, phenol dearomatization is proposed to occur instead of norbornadiene extrusion; the slower rate of norbornadiene extrusion might be attributed to its higher ring-strain energy (32.4 kcal/mol) compared to that of norbornene (21.6 kcal/mol). Notably, using TADDOL-derived chiral ligand **lig.23**, the desired product is obtained with enantiomeric ratios of up to 92.0:8.0.

Unexpectedly, the use of 2-iodoaniline derivatives and norbornadiene (**nbn.17**) under the amination conditions leads to 4-aminoindoles (Scheme 80).[125] After the *ortho*-amination event, **54** undergoes an intramolecular Buchwald–Hartwig coupling instead of norbornadiene extrusion. From **55**, a *retro*-Diels–Alder reaction affords the indole product. This protocol works best for 2-iodoanilines with a sterically demanding substituent (e.g., *tert*-butyl) attached to the nitrogen.

With Bifunctional Aminating Reagents. By using *N*-benzoyloxy allylamines as bifunctional aminating reagents, sequential *ortho*-amination and *ipso*-Heck cyclization provide C3,C4-disubstituted indoles (Scheme 81).[126] This method complements those depicted in Schemes 73 and 80.[127]

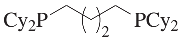
Larger benzo-fused heterocyclic ring systems can be prepared using the same approach. For example, the *N*-pentenyl aminating reagent **56** affords benzene-fused seven-membered rings in moderate-to-good yields in the presence of norbornene derivative **nbn.18** (Scheme 82).[128]



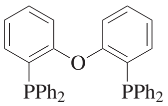
Nu−Z	Ligand	Nu	Yield (%)
	**lig.21**	H	88
	**lig.22**		63
B_2pin_2	**lig.21**	Bpin	62[a], 47[b]

[a] ^{1}H NMR yield.

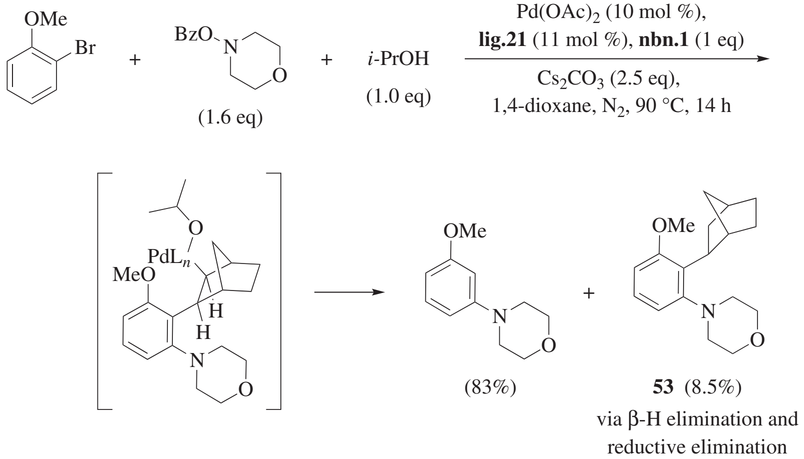
[b] Isolated yield of the bromide formed via in situ bromination of the Bpin ester: $CuBr_2$ (3 eq), MeOH/H_2O (1:1), 80 °C.



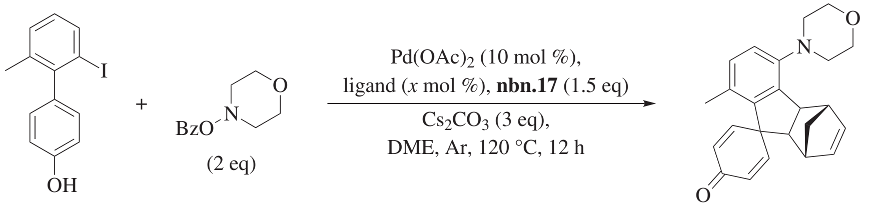
lig.21



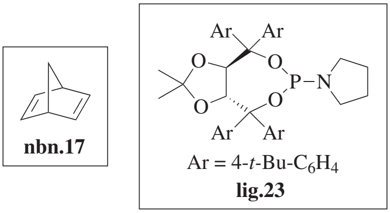
lig.22



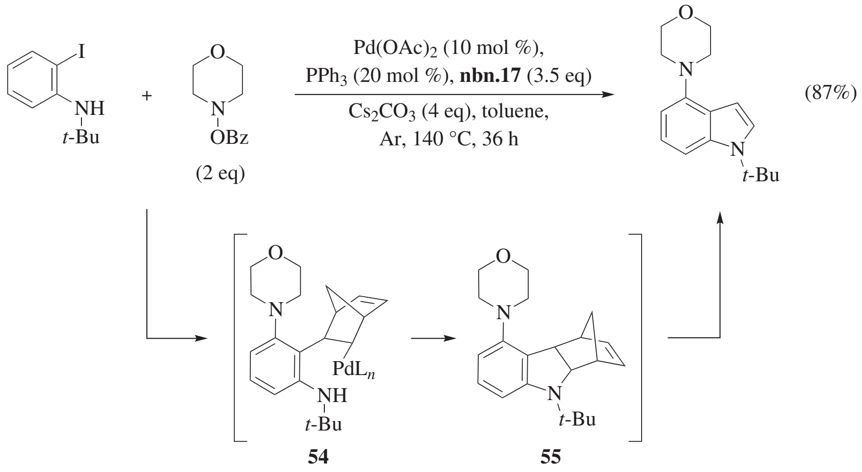
Scheme 78



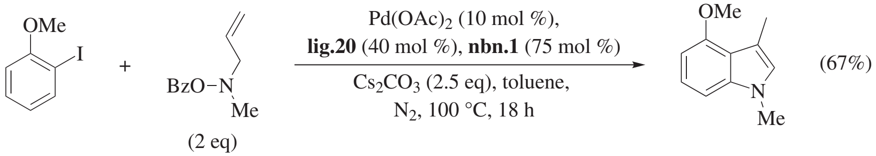
Ligand	*x*	Yield (%)	er
lig.20	25	73	50.0:50.0
lig.23	20	56	92.0:8.0



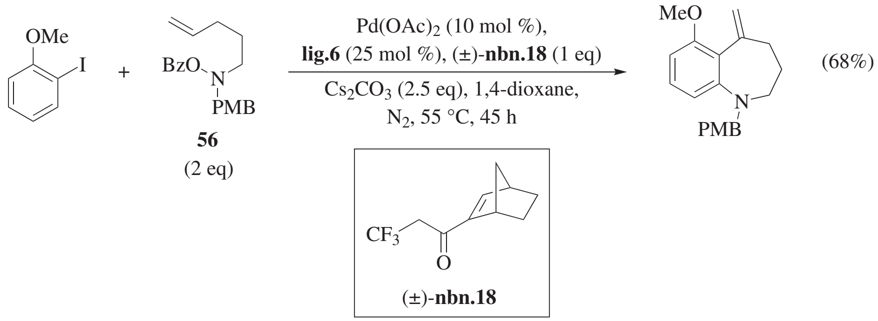
Scheme 79



Scheme 80

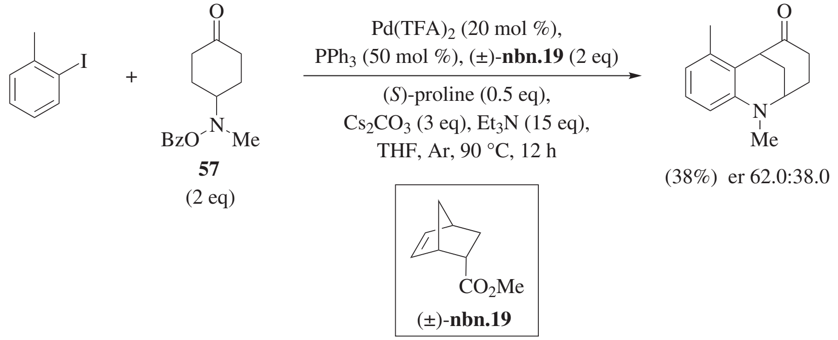


Scheme 81



Scheme 82

A single example of an enantioselective *ortho*-amination/*ipso*-alkylation reaction has been reported (Scheme 83).[129] Using (*S*)-proline as the chiral catalyst, 1-iodo-2-methylbenzene undergoes a Catellani-type reaction with *O*-benzoylhydroxylamine **57** as the aminating reagent to furnish an enantioenriched, nitrogen-containing bridged product in low yield and with low enantioselectivity.

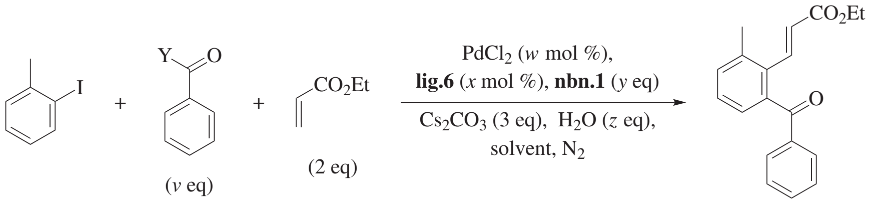


Scheme 83

Ortho-Acylation of Aryl (Pseudo)Halides.

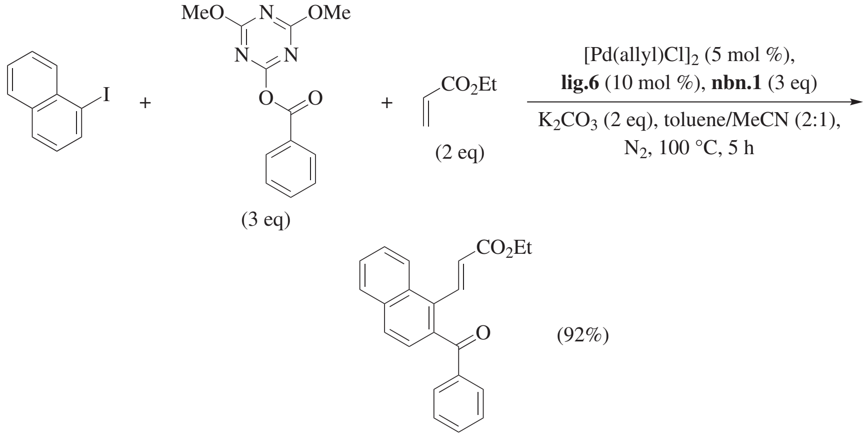
With Simple Acylating Reagents. When anhydrides (preformed[130] or generated in situ from acyl chlorides and water[131]) are used as the electrophiles for the Catellani reaction, *ortho*-acylation delivers functionalized diaryl (Scheme 84)[130,131] and aryl alkyl ketones. In addition to Heck acceptors, copper cyanide,[132] alkynes,[133] benzoxazoles, and benzo[*d*]thiazoles[134] can also be utilized as terminating reagents. Bench-stable 1,3,5-triazine esters can be employed in place of acyl chlorides and anhydrides to effect the same reaction (Scheme 85).[135]

When both an anhydride and a benzyl bromide are present, two different functionalities can be introduced at the two *ortho* positions of a 2-unsubstituted



Y	*v*	*w*	*x*	*y*	*z*	Solvent	Temp (°C)	Time (h)	Yield (%)
PhC(O)O	2	10	20	1	0	DME	90	20	88
Cl	3	5	10	2	2	1,4-dioxane	100	12	85

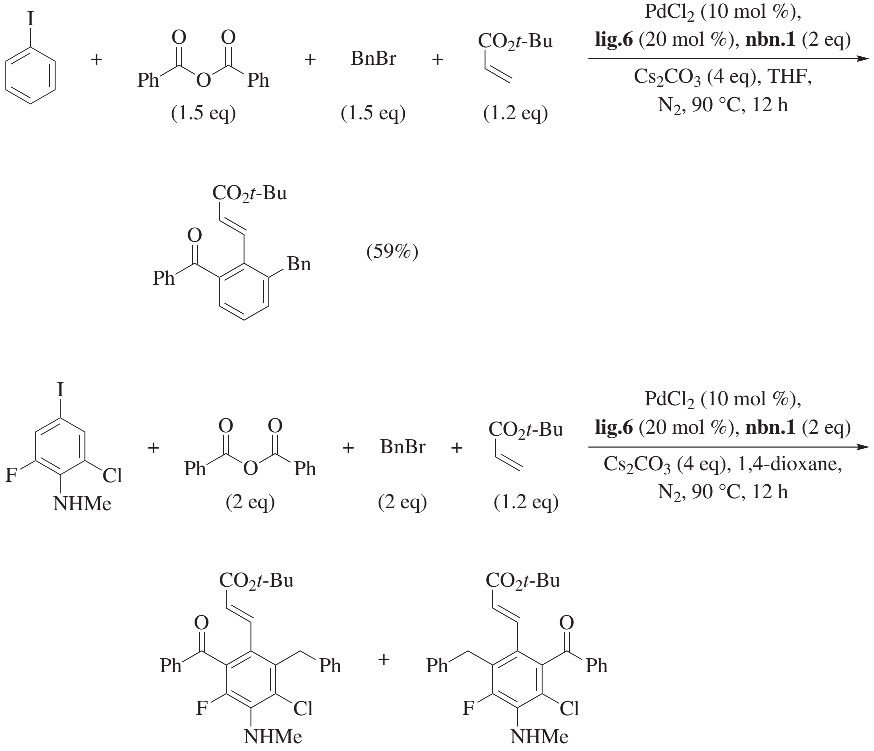
Scheme 84



Scheme 85

iodoarene, albeit with moderate selectivities (Scheme 86).[136] The electronic nature of the 4-substituent on the iodoarene has a profound influence on the reaction selectivity, with strongly electron-withdrawing groups favoring dibenzylation and strongly electron-donating groups favoring diacylation. It is notable that arenes with six different substituents can be prepared in a single step using this approach.

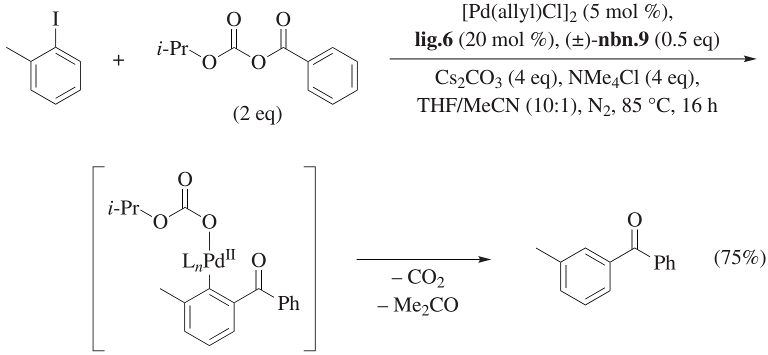
With Bifunctional Acylating Reagents. Employing isopropyl carbonate anhydrides as the acylating reagents in the presence of **nbn.9** yields *meta*-substituted aryl ketone products (Scheme 87).[137] In this case, *ortho*-acylation is followed by an *ipso*-reduction event wherein the isopropyl carbonate anhydride serves as a hydride source to terminate the reaction. The use of **nbn.9** has two main advantages over norbornene (**nbn.1**): product yields are higher, and the polar amide group facilitates chromatographic purification of the desired product from norbornene-containing side products.



58 **59**

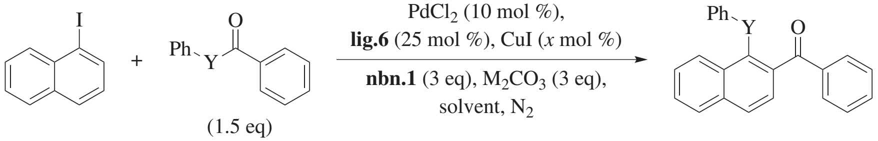
58 + **59** (41%), **58**/**59** = 17:1

Scheme 86



Scheme 87

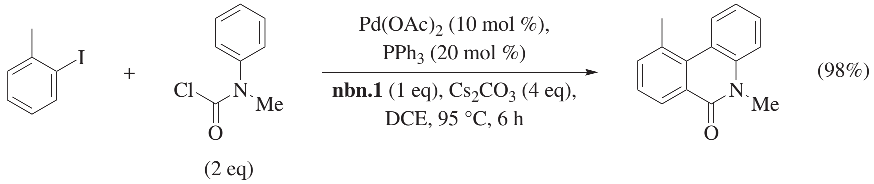
Using thioesters and selenoates as bifunctional acylating reagents, *ortho*-acylation is followed by *ipso*-thiolation[138] or *ipso*-selenation[139] (Scheme 88). This strategy has also been applied to the synthesis of aryl thio- and selenoglycosides from 1-thiosugars and 1-selenosugars, respectively.[140]



Y	x	M	Solvent	Temp (°C)	Time (h)	Yield (%)
S	20	Cs	1,4-dioxane	120	12	85
Se	0	K	DCP	100	16	56

Scheme 88

Phenanthridinones are obtained in a single step using aryl carbamoyl chlorides as the bifunctional acylating reagents (Scheme 89).[29] In this sequence, aryl C−H functionalization is the terminating step.

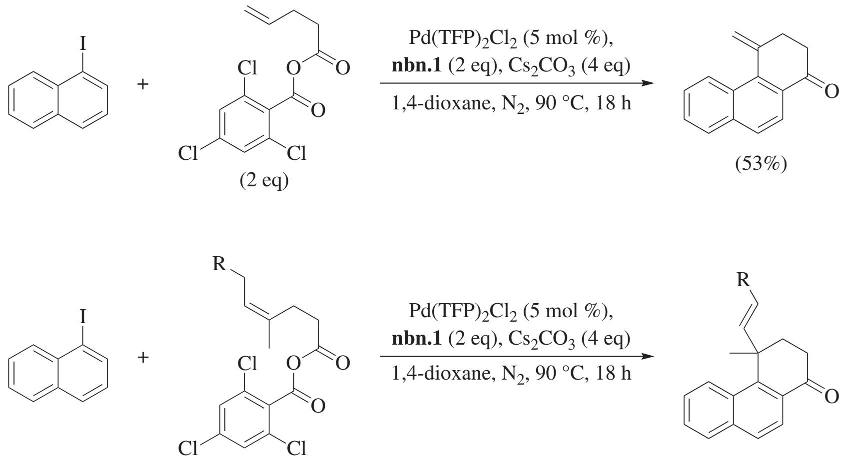


Scheme 89

Similarly, acylating reagents with a tethered alkene can be utilized to construct various cyclic aryl ketones (Schemes 90[141] and 91[142]). Termination of the reaction occurs when the arylpalladium intermediate undergoes an *ipso*-Heck cyclization.

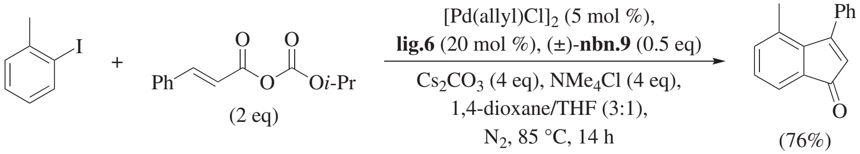
Ortho-alkoxy- or aminocarbonylation is possible by employing mixed carbonate anhydrides or carbamoyl anhydrides that contain a sterically hindered acyl group: the bulky acyl group facilitates chemoselective transfer of the alkoxycarbonyl group rather than the acyl group (Scheme 92).[143] Using this approach, 11- and 12-membered macrolactones can be generated when the carbonate anhydride possesses an electron-deficient alkene moiety, which undergoes an intramolecular Heck reaction as the terminating step.

***Ortho*-Thiolation of Aryl (Pseudo)Halides.** Although *ortho*-amination has been achieved using Catellani-type reactions, *ortho*-thiolation is considerably more difficult: this transformation requires an electrophilic thiolating reagent that will ensure selective C(Ar)−SR bond formation during reductive elimination of the palladium(IV) intermediate. The first reported *ortho*-thiolation uses a thiosulfonate



R	Yield (%)
n-Pr	51
Ph	48
Bn	56

Scheme 90

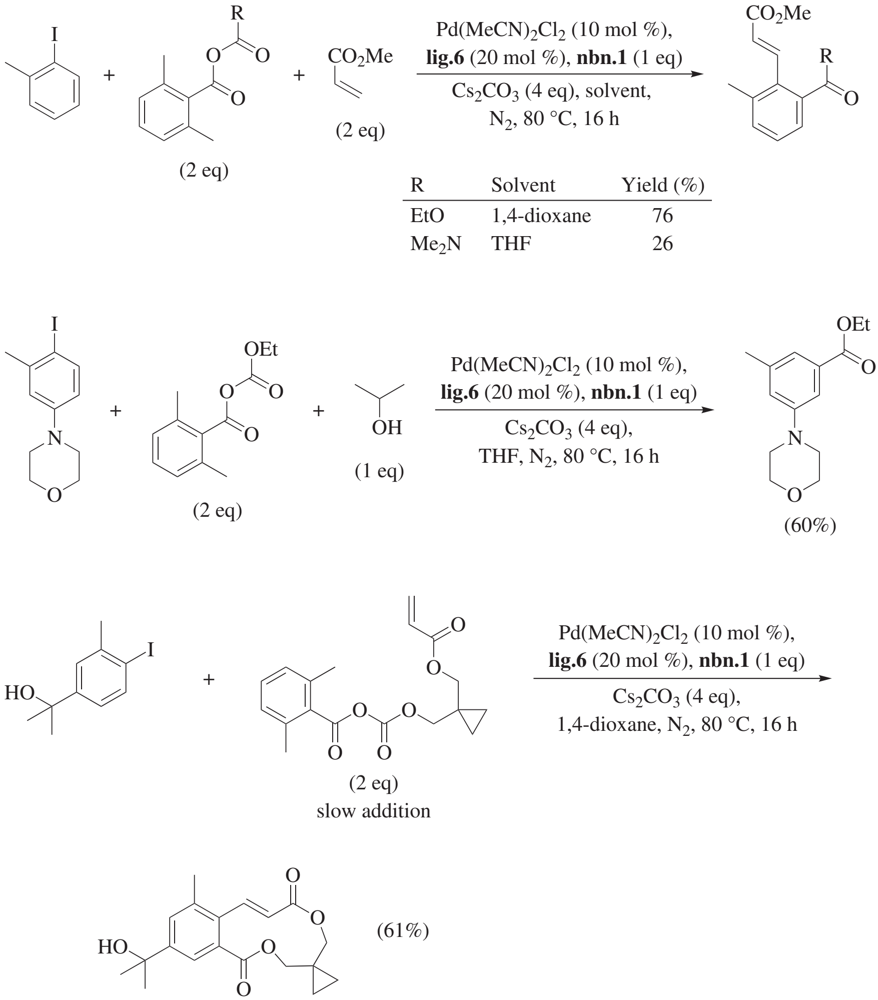


Scheme 91

as the thiolating reagent and **nbn.4** as the mediator to prepare both diaryl sulfides and aryl alkyl sulfides (Scheme 93).[144]

An alternative approach to *ortho*-thiolation employs sulfenamide **60**, which is derived from a seven-membered lactam as the thiolating reagent (Scheme 94).[145] In addition to using Heck acceptors to terminate the reaction, *ipso* functionalization via Suzuki or Sonogashira coupling is also feasible. The copper(I) thiophene-2-carboxylate (CuTC) additive improves the yield and is proposed to function as a thiolate scavenger.

***Ortho*-Alkylation, Arylation, and Amination of Alkenyl (Pseudo)Halides.** In the alkenyl Catellani reaction, aryl (pseudo)halides are replaced with alkenyl (pseudo)halides, and the ensuing palladium(0)/norbornene-catalyzed reaction delivers poly-substituted alkenes in a unique and stereoselective manner. The first two studies prepare fused tri- and tetracyclic ring systems by treating uracil- and 2-quinolone-derived iodides, which have aromatic character, with bifunctional alkylating or arylating agents (Schemes 95[10] and 96[146]).

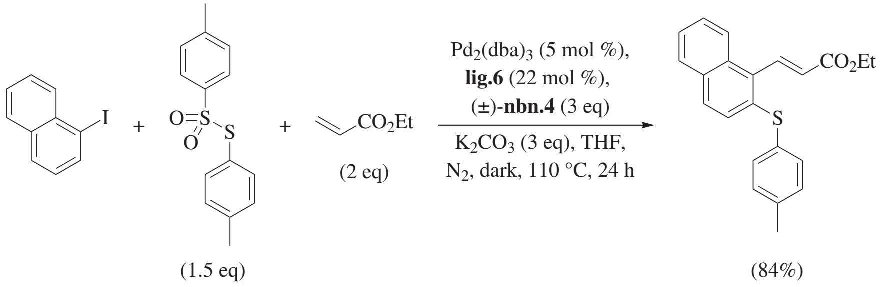


R	Solvent	Yield (%)
EtO	1,4-dioxane	76
Me_2N	THF	26

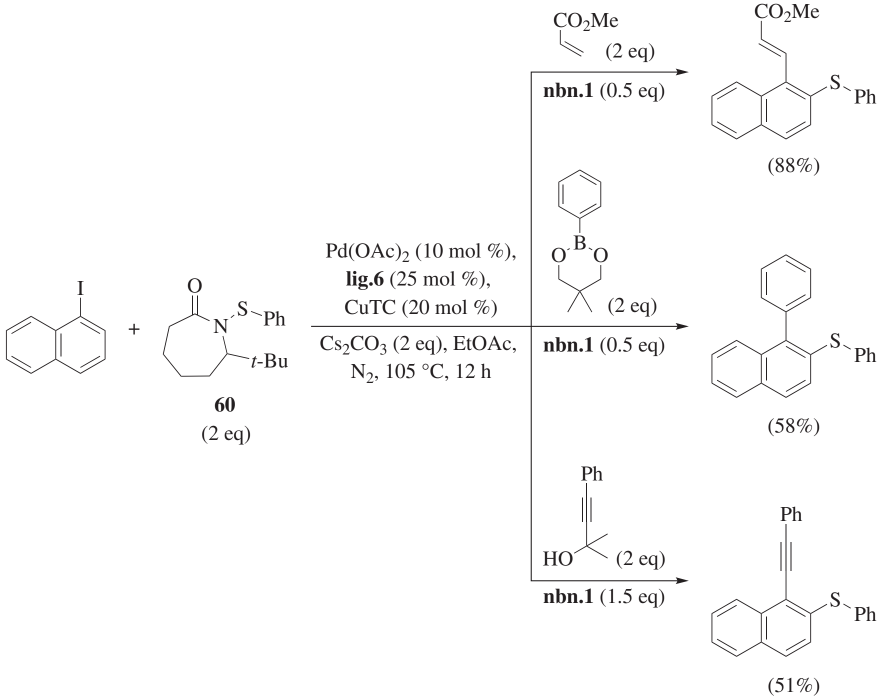
Scheme 92

Alkenyl iodides derived from 2-pyridones and uracils are also suitable substrates for three-component Catellani-type reactions. Using amide- or ester-substituted norbornenes as the mediators, both *ortho*-alkylation and *ortho*-arylation can be accomplished, and terminating reagents for *ipso* functionalization include Heck acceptors, H/DCO_2Na, boronic acids and esters, and terminal alkynes (Scheme 97). Notably, when the reaction is mediated by enantioenriched norbornene derivative (−)-**nbn.15**, the *ortho*-arylation/*ipso*-olefination sequence generates axially chiral products in good yields and with high enantioselectivities.[147]

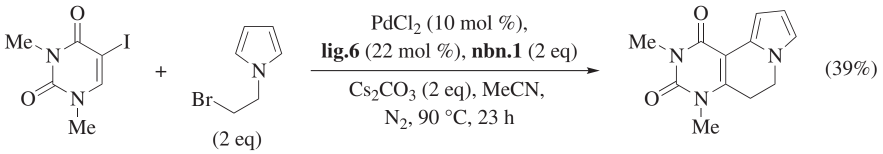
Although simple aliphatic alkenyl bromides and triflates are more readily available than the corresponding iodides, these substrates are less reactive and, like the



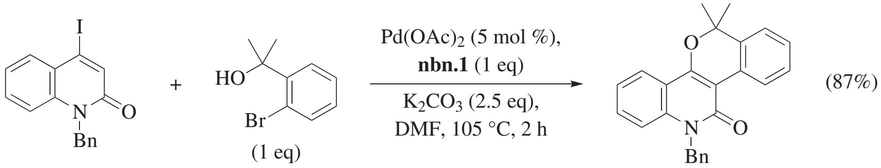
Scheme 93



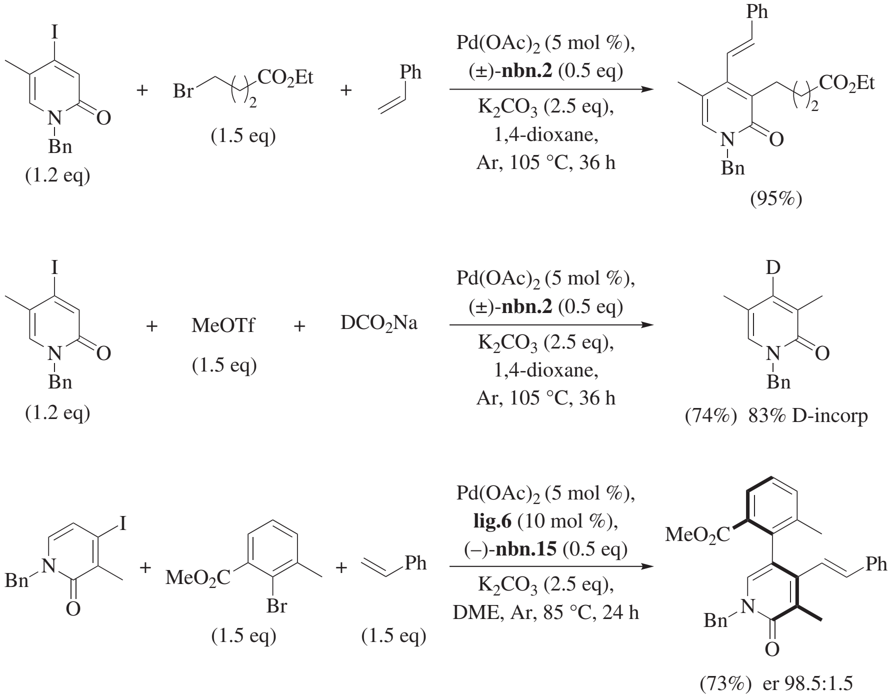
Scheme 94



Scheme 95



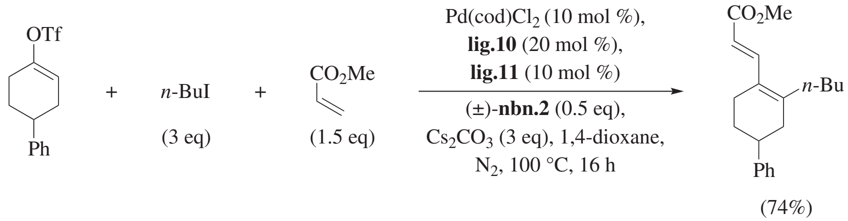
Scheme 96



Scheme 97

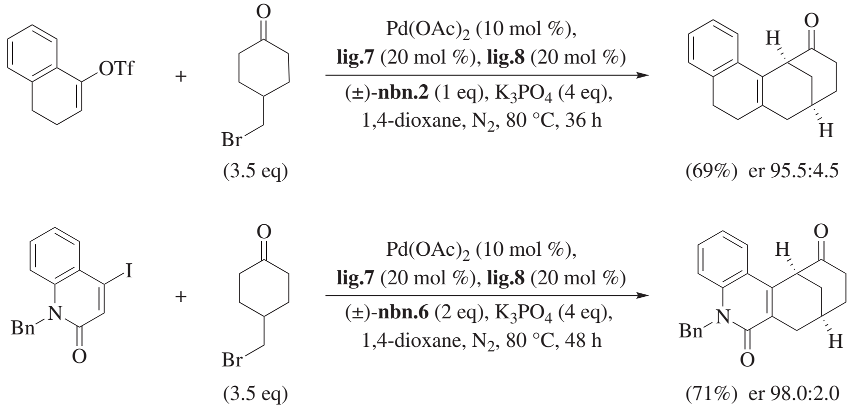
iodides, can undergo multiple undesired reaction pathways (e.g., cyclopropanation and β-hydride elimination). The lower reactivity can be addressed with modified reaction conditions wherein amide-substituted norbornene **nbn.2** serves as the mediator, Buchwald's Ph-DavePhos (**lig.11**) as the ligand, and 2-hydroxypyridine derivative **lig.10** as an excellent cocatalyst (Scheme 98).[148] This method affords all-carbon tetrasubstituted alkenes in an efficient and modular manner, starting from cyclic and acyclic alkenyl substrates. Both alkylation and arylation are possible at the α-position, and compatible terminating reagents include Heck acceptors, boronic esters and methyl boronic acid, and hydride donors.

Like aryl iodides, alkenyl triflates and conjugated vinyl iodides undergo a Catellani-type reaction with the bifunctional alkylating reagent 4-(bromomethyl)



Scheme 98

cyclohexanone (Scheme 99[46]; see also Scheme 22). Using a chiral amine catalyst, such as indoline-2-carboxylic acid (**lig.8**), *ortho*,*ipso*-dialkylation can be achieved with modest-to-excellent enantioselectivities.

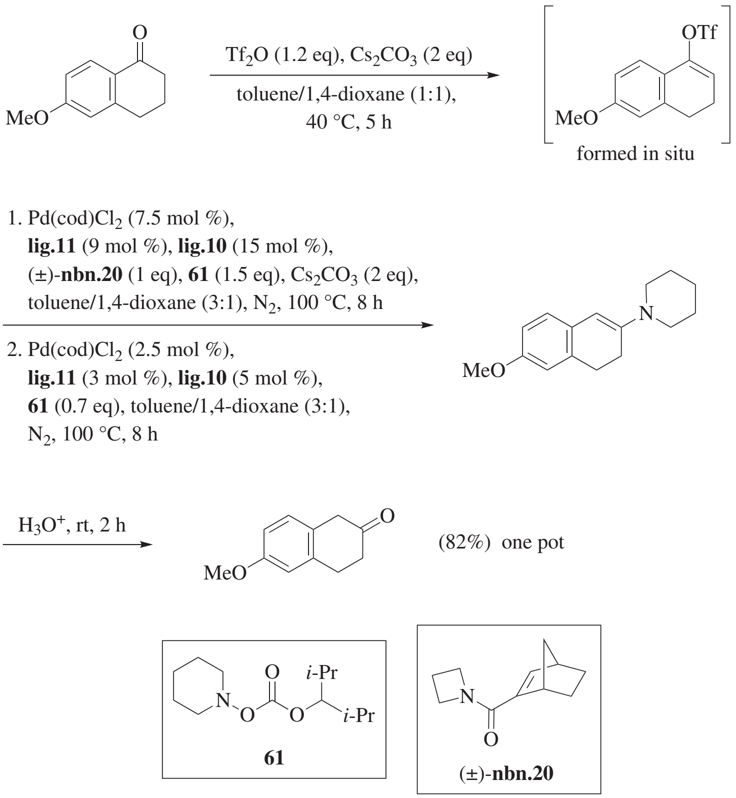


Scheme 99

α-Amination and *ipso*-hydrogenation of in situ generated cyclic alkenyl triflates is accomplished using the carbonate-based bifunctional aminating reagent **61** in which the secondary alcohol liberated in the *ortho*-amination serves as the hydride donor in the termination step (Scheme 100).[149] Azetidine-amide derived-norbornene **nbn.20** is the optimal cocatalyst for this reaction, and the presence of pyridone additive **lig.10** improves the yield. Notably, the enamine products can be hydrolyzed to the corresponding ketones, thereby resulting in a formal 1,2-carbonyl migration. The alkenyl triflate substrates are prepared from the corresponding β-unsubstituted cyclic ketones or from enones and alkyl nucleophiles.

Palladium(II)-Catalyzed Reactions

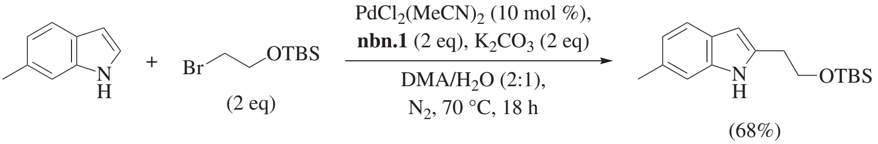
Palladium(II) catalysts provide an alternative to palladium(0) catalysts for initiating Catellani-type reactions. The required arylpalladium(II) species can be generated using palladium(II) catalysts by either nucleopalladation or transmetallation. The catalytic cycle then progresses in a manner analogous to the



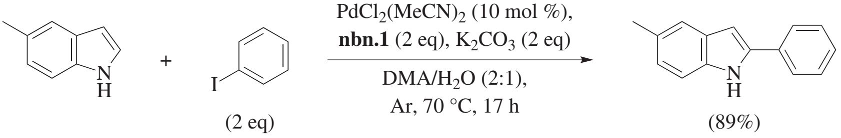
Scheme 100

palladium(0)/palladium(II) cycle, however, in certain scenarios, an oxidant is required to regenerate the catalytically active palladium(II) species. In the majority of instances, the process remains redox-neutral, culminating in the protonolysis of palladium(II)–carbon or palladium(II)–nitrogen bonds. Nevertheless, an oxidant is added in some cases to reoxidize any palladium (0) species that may be formed. Five types of palladium(II)-catalyzed reactions are discussed below.

Monofunctionalization of Unprotected Indoles and Pyrroles. The first reported palladium(II)-catalyzed Catellani-type reaction was the direct C2-alkylation of NH-indoles with primary alkyl bromides using $PdCl_2(MeCN)_2$ as the catalyst (Scheme 101).[11,38,150,151] Interestingly, neither *N*- nor C3-alkylation of the indole occurs, although over-alkylated products (i.e., 2,3-dialkylindoles) are observed as byproducts when sterically less-demanding alkyl bromides are employed. *N*-Protected indoles are unreactive, which is consistent with the proposed mechanism wherein the *N*-palladated indole is a precursor to the arylpalladium(II) species **23** (Scheme 13). This strategy can also be extended to the C2-arylation of indoles (Scheme 102).[152]

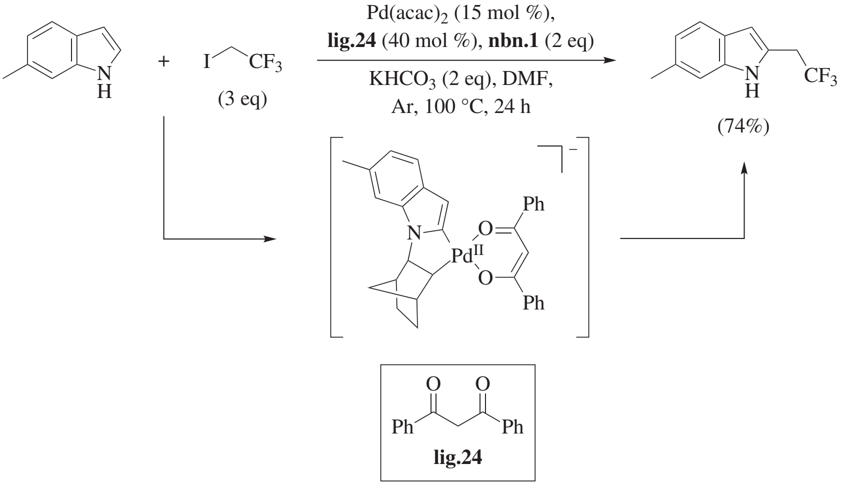


Scheme 101



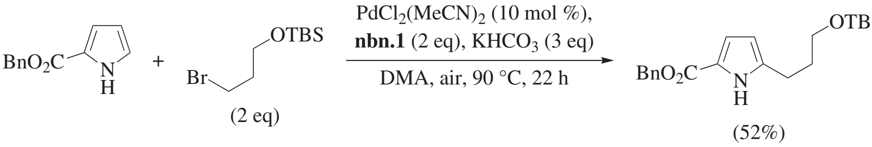
Scheme 102

Using a similar approach, a trifluoroethyl group can be introduced at the 2-position of NH-indoles using trifluoroethyl iodide as the alkylating reagent (Scheme 103).[153] In this case, Pd(acac)$_2$ and dibenzoylmethane (**lig.24**) are the optimal catalyst and ligand, respectively.



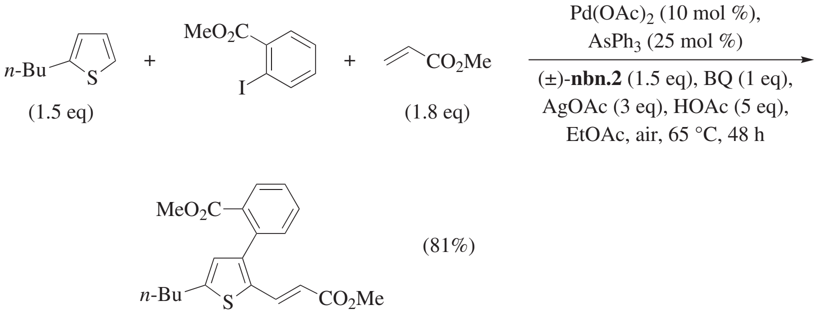
Scheme 103

Electron-deficient NH-pyrroles are also amenable to direct alkylation at the C5 position (Scheme 104).[151] The electron-withdrawing substituent is proposed to increase the acidity of the pyrrole N−H, thereby facilitating the required *N*-palladation step. This approach complements established methods for pyrrole C5-alkylation, which typically require an electron-rich pyrrole to serve as a π-nucleophile.



Scheme 104

Difunctionalization of Electron-Rich Heteroarenes. Electron-rich heteroarenes such as thiophenes and furans undergo C−H palladation readily in the presence of a palladium(II) species, and therefore, such substrates can be difunctionalized at vicinal positions by employing palladium/norbornene catalysis. For example, in the presence of **nbn.2** and an arsine ligand, C4-arylation and C5-olefination of thiophenes proceeds smoothly to produce polysubstituted thiophenes in good yields (Scheme 105).[39] The combination of silver acetate and 1,4-benzoquinone (BQ) is required for efficient oxidation of palladium(0) to palladium(II) to close the catalytic cycle.

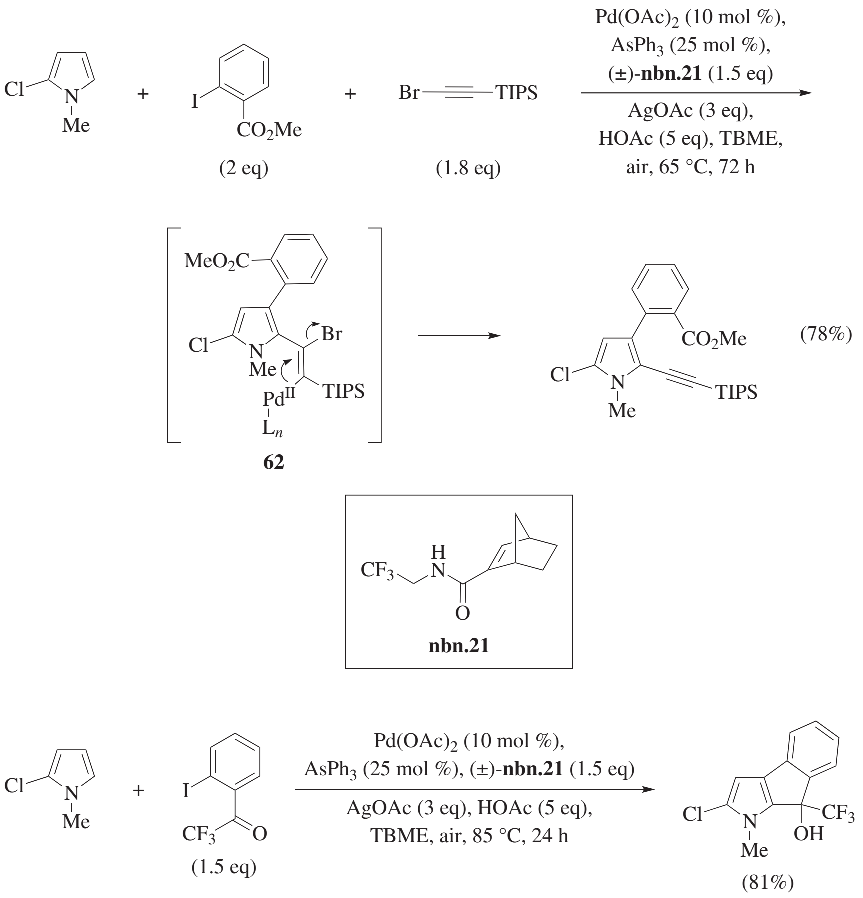


Scheme 105

Vicinal difunctionalization of electron-rich heteroarenes is also possible using an alkynyl bromide in place of the Heck acceptor in a site-selective and redox-neutral manner, which is distinct from the prior oxidative difunctionalization (Scheme 106).[154] In this case, a stoichiometric amount of oxidant is not necessary: the reaction is terminated by *ipso*-alkynylation and thus regenerates palladium(II) directly, presumably via Ar–Pd–X migratory insertion followed by β-bromide elimination from **62**. An iodoarene containing a 2-trifluoroacetyl group can act as a bifunctional arylating reagent, and the Catellani reaction with *N*-methyl-2-chloropyrrole produces tricyclic alcohols bearing a valuable trifluoromethyl moiety (Scheme 106, bottom reaction).[154]

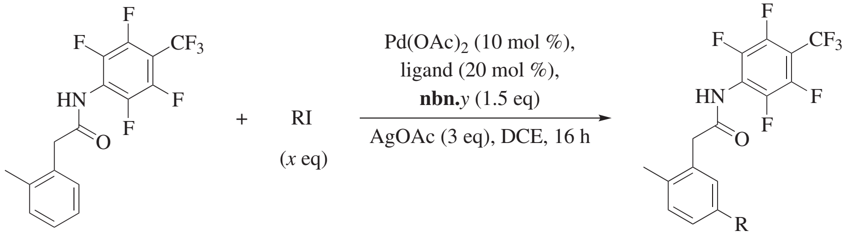
Meta-Selective C−H Functionalization of Arenes with an *Ortho* Directing Group.

Meta-C−H Alkylation. Palladium(II)/norbornene catalysis can be used for *meta*-C−H alkylation of arenes when an *ortho* directing group is present. For

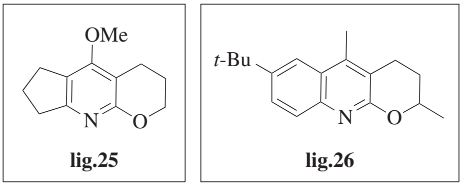


Scheme 106

example, Scheme 107 depicts the *meta*-C–H alkylation of phenylacetamides using norbornene (**nbn.1**) as the mediator in the presence of palladium(II) acetate and pyridine-based ligand **lig.25**.[13] Catalyst turnover occurs through protonolysis of the arylpalladium species by in situ generated acetic acid after norbornene elimination. Owing to the possibility of β-hydrogen elimination from palladium(IV) species **5**, the alkylating reagents are limited to those without β-hydrogen atoms (e.g., iodomethane, ethyl iodoacetate, and benzyl halides). The combination of **lig.26** and **nbn.5** inhibits formation of norbornyl benzocyclobutene side products, and under these conditions, a variety of aryl and alkyl electrophiles may be used in the *meta*-C–H functionalization reaction, including those with β-hydrogen atoms.[12] This transformation requires a unique fluorinated amide directing group, which is removed by hydrolysis under basic conditions and is installed by condensing the corresponding carboxylic acid with 4-aminoheptafluorotoluene.[155,156] The latter reagent is prepared by treating inexpensive octafluorotoluene with ammonium hydroxide in 1,4-dioxane at 80 °C.



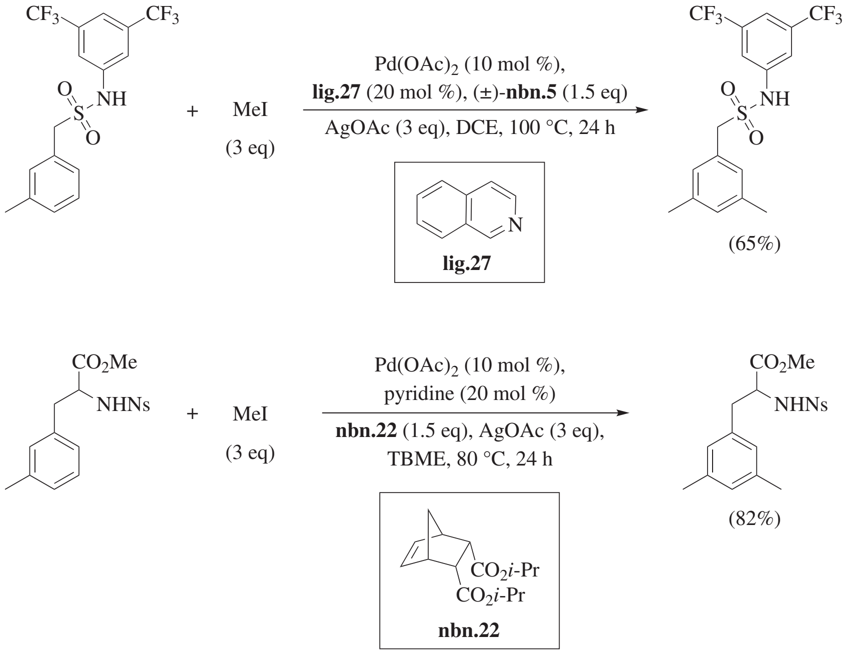
R	x	Ligand	y	Temp (°C)	Yield (%)
Me	3	**lig.25**	1	95	90
Et	2.5	**lig.26**	5	75	93



lig.25 **lig.26**

Scheme 107

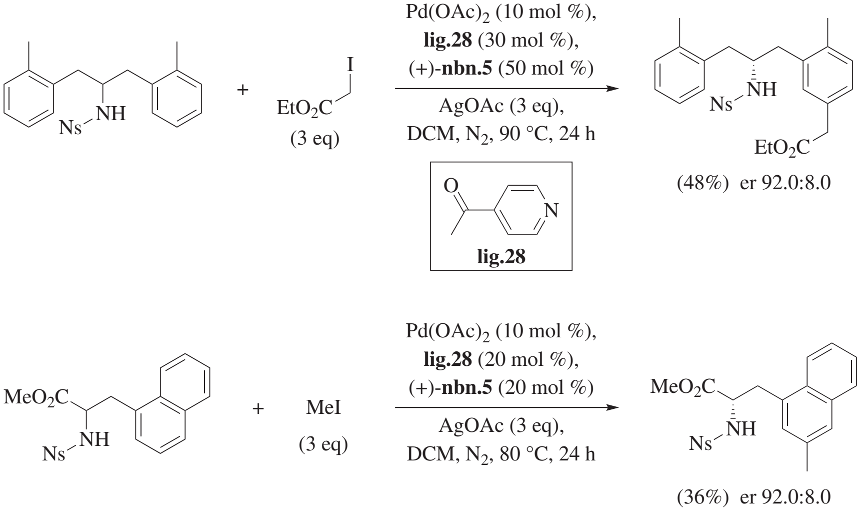
Using isoquinoline (**lig.27**) and 2-carbomethoxynorbornene (**nbn.5**) as the ligand and mediator, respectively, sulfonamides are viable alternative directing groups for the *meta*-C–H functionalization of arene rings (Scheme 108, top reaction).[157] Under



Scheme 108

similar conditions, phenylalanine derivatives are functionalized at the *meta* position (Scheme 108, bottom reaction).[158] The sulfonamide substrates can be accessed from the corresponding amines and arylsulfonyl chlorides, and following the reaction, the directing group is removed by hydrolysis under basic conditions.[157,159]

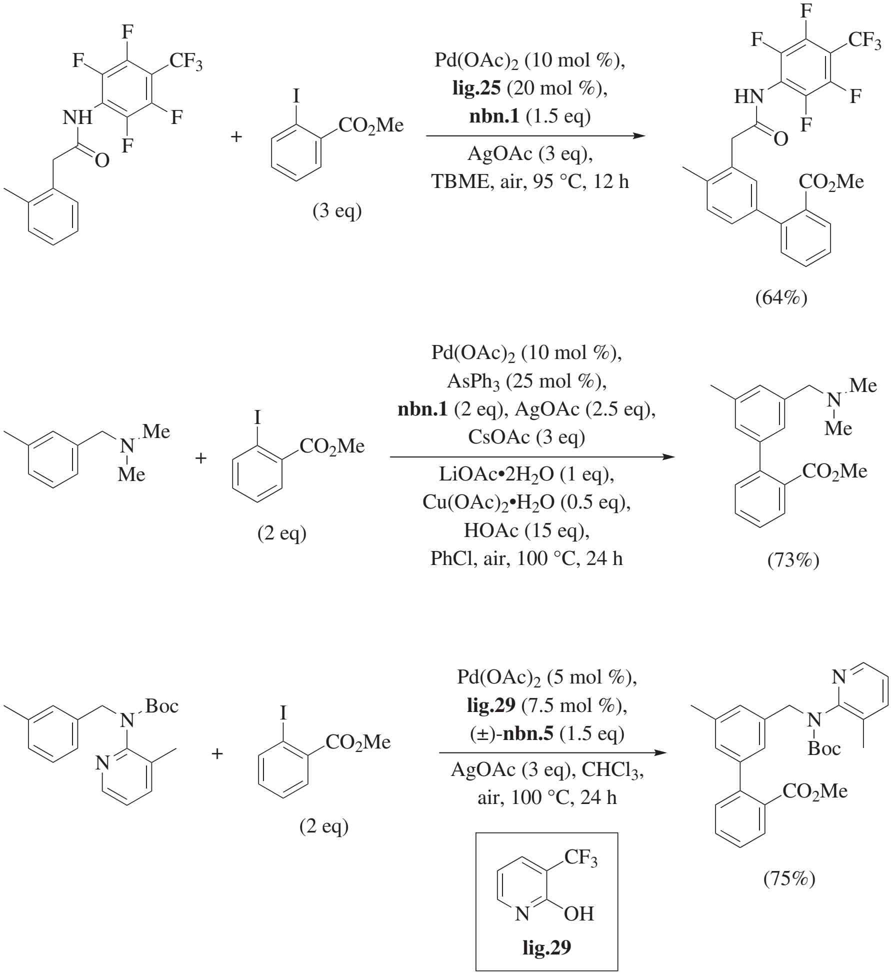
As shown earlier in the context of benzylamine desymmetrization (Scheme 20), the enantioenriched norbornene derivative (+)-**nbn.5** facilitates desymmetrization of homobenzylamine derivatives via remote *meta*-C–H arylation (Scheme 109).[44] In this case, the pyridine derivative **lig.28** serves as the ligand. These *meta*-C–H alkylation conditions have also been used for the kinetic resolution of homobenzylamines and β-arylamino acid derivatives.



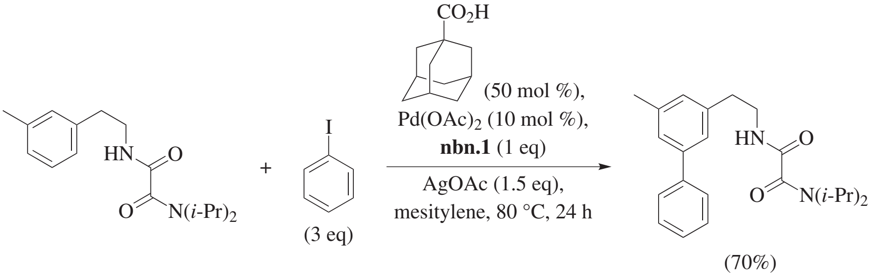
Scheme 109

Meta-C–H Arylation. With an appropriate directing group, phenylacetic amides and tertiary benzylamines can be arylated at the *meta* position (Scheme 110),[13,14,160] although the arylating reagents are mostly limited to those with an *ortho* electron-withdrawing substituent (to facilitate oxidative addition to the key palladacycle). A handful of directing groups have been evaluated, including the heptafluorotoluene amide[13] discussed above (see Scheme 107). Both *N*,*N*-dimethylamino[14] and an *N*-(3-methyl-2-pyridyl) group[160] afford good yields of the desired product, but removal of the *N*,*N*-dimethylamino directing group is challenging. The *N*-pyridyl directing group can be removed via a two-step procedure: *N*-methylation of the pyridyl group followed by hydrolysis of the pyridinium salt.[160]

Using a bidentate oxalyl-amide-based directing group, β-arylethylamine derivatives undergo *meta*-arylation to provide biaryl products in moderate-to-high yields (Scheme 111).[161] Electron-rich, -neutral, and -withdrawing aryl iodides are all suitable substrates for this protocol. The oxalyl amide directing group is installed by treating the amine with *N*,*N*-diisopropyloxamoyl chloride,[162] but the removal of this directing group has not been reported.

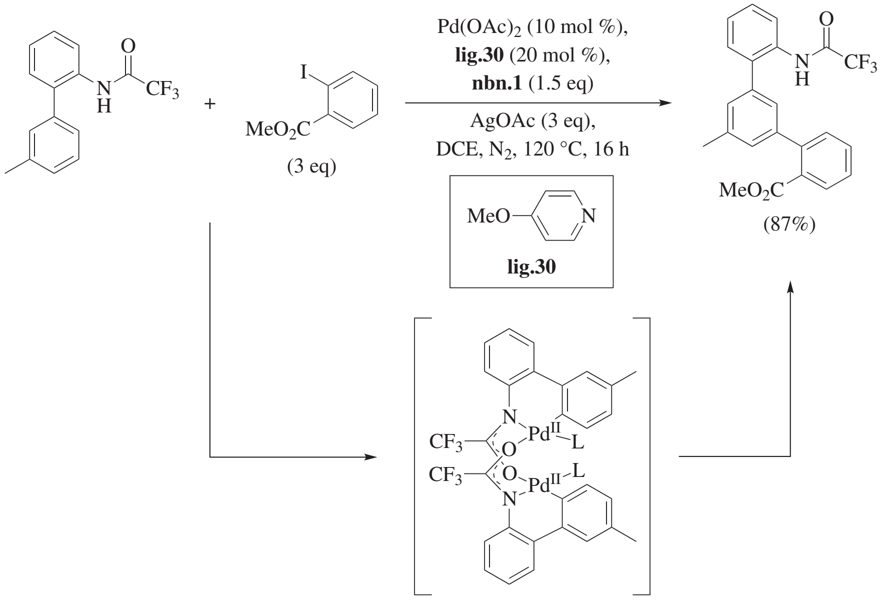


Scheme 110



Scheme 111

N-Trifluoroacetyl is an attractive directing group for C–H functionalizations because it is removed under very mild conditions (e.g., using potassium carbonate). Scheme 112 illustrates the use of this directing group in the palladium-catalyzed, interannular *meta*-C–H arylation of biaryl aniline derivatives.[163] The electronic properties and binding abilities of the trifluoroacetamide group are critical for achieving the desired interannular C–H activation in preference to the undesired intraannular *ortho*-C–H activation, presumably via the dimeric palladacycle intermediate **63**. As with similar reactions, iodoarenes with an *ortho* electron-withdrawing substituent exhibit much higher reactivities.

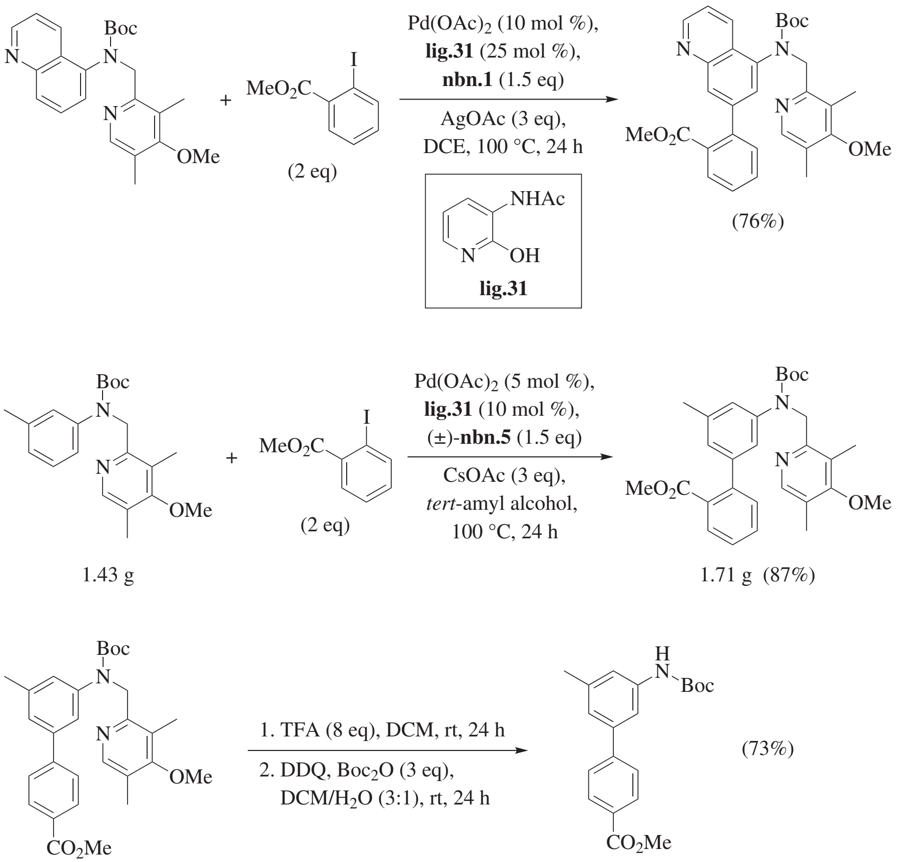


63

Scheme 112

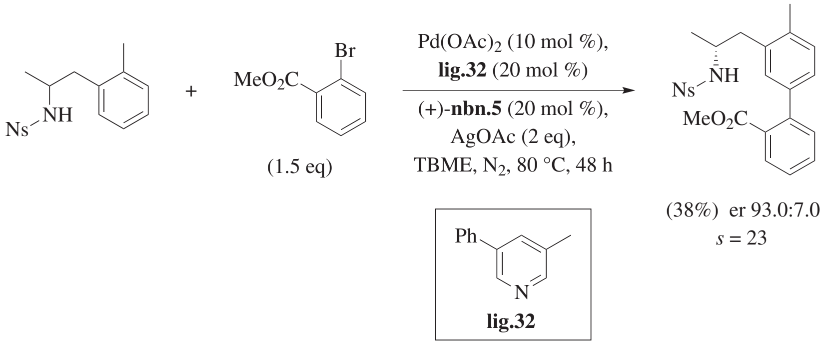
A benzylic pyridine-based directing group has been used in the *meta*-C–H arylation of aniline derivatives in the presence of a 2-hydroxypyridine derivative as the ligand (Scheme 113).[54] This protocol is successful with both heteroarene substrates and heteroaryl halide coupling partners. Electron-neutral aryl iodides, which are typically less reactive arylating reagents, are also compatible. The reaction can be conducted on a gram scale using cesium acetate (a less expensive reagent) as a substitute for silver(I) acetate, which improves the scalability of the process. To install the directing group, the *N*-Boc-protected aniline substrates are treated with 2-chloromethyl-4-methoxy-3,5-dimethylpyridine; removal is achieved by sequential treatment with TFA and DDQ.

As shown earlier (Scheme 20), enantioselective *meta*-C–H arylation of prochiral substrates can be accomplished when the enantioenriched norbornene derivative (+)-**nbn.5** is employed as the cocatalyst.[44] The same norbornene derivative also



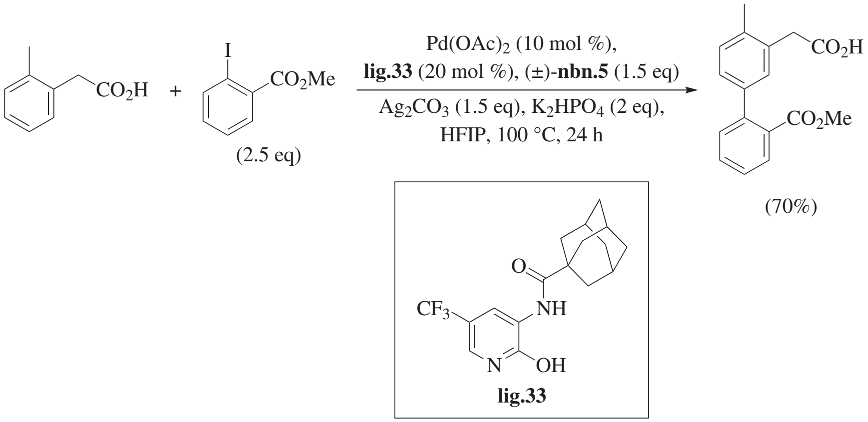
Scheme 113

effects kinetic resolution of racemic secondary nosyl-protected homobenzylamines with enantiomeric ratios of up to 93.0:7.0 and with selectivity factors (*s*) ranging from 17 to 37 (Scheme 114).[44]



Scheme 114

2-Hydroxypyridine-type ligands are often optimal for *meta*-C−H arylation reactions. As in Scheme 113, the 3-amino-2-hydroxypyridine-derived ligand is critical in the *meta*-C−H arylation of free arylacetic acids (Scheme 115).[164] In this case, the free carboxylic acid serves as the directing group, and after the arylation reaction, it can be easily functionalized or used as a handle for further reactions.

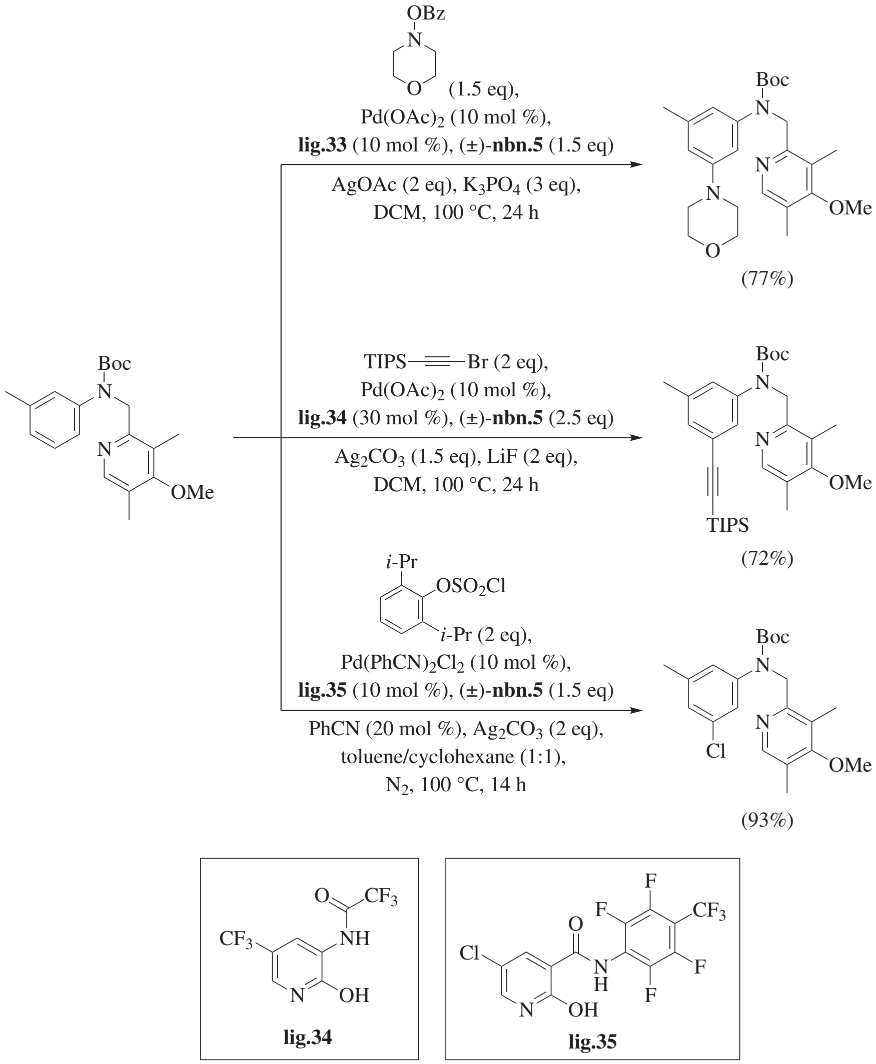


Scheme 115

Meta-C−H Functionalizations with Other Electrophiles. The pyridine-based group shown in Scheme 113 can also direct aminations, alkynylations,[165] and chlorinations.[166] A well-designed pyridyl directing group and a 2-hydroxypyridine ligand are both critical for achieving the desired reactivity and site-selectivity in *meta*-C−H functionalizations of aniline and phenol derivatives (Scheme 116).[165,166]

Remote Functionalization of Arenes or Alkenes with a Directing Group. Site-selective functionalization of C–H bonds that are distal to a functional group is highly desirable but very challenging. One such example is the *para*-selective arylation of arenes, which is accomplished using a cyanophenol-based *meta*-directing group (Scheme 117).[167] After directed *meta*-C–H palladation, norbornene facilitates one-bond relay palladation, ultimately resulting in *para*-C–H arylation. This protocol is compatible with a wide range of sulfonates, phosphonates, and phenol substrates that are derived from 2,6-disubstituted arenes. The directing groups are installed by treating the corresponding sulfonyl chlorides with phenols, and hydrolysis with lithium hydroxide delivers the corresponding sulfonic acids after the C–H functionalization event.

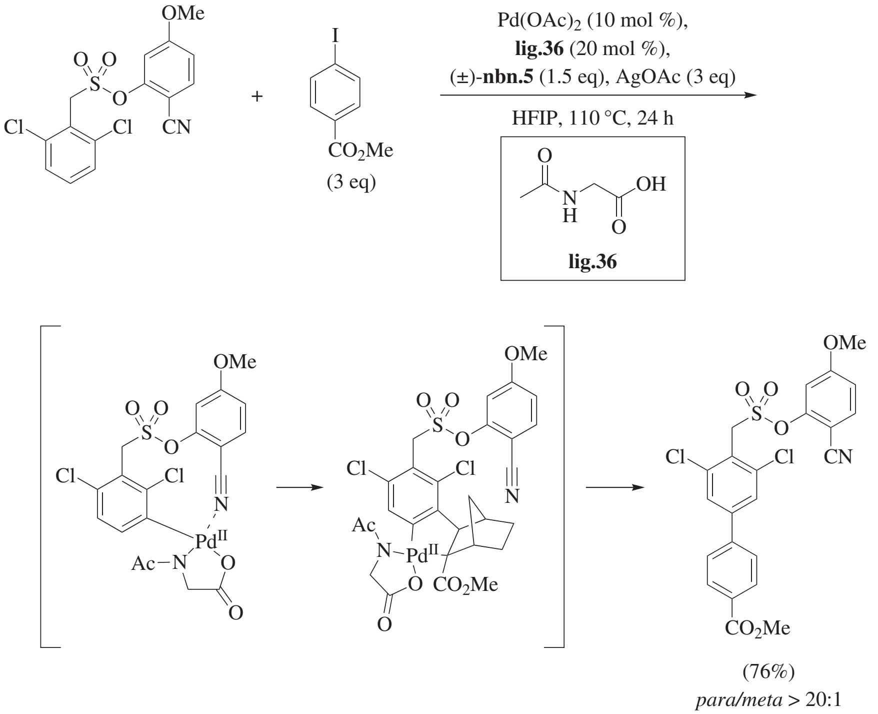
Remote C–H functionalizations of quinolines and isoquinolines are possible via Catellani-type reactions by using a specifically designed palladium “template” that holds both substrates in the proper orientation, much like an enzyme. For example, in the presence of **nbn.5**, template **cat.4** enables the C6 arylation of quinolines and isoquinolines with high regioselectivity (Scheme 118). Although stoichiometric



Scheme 116

amounts of the palladium-containing template **cat.4** are used, the palladium atom is fully coordinated to four nitrogen atoms and is unable to undergo C–H palladation. Thus, catalytic quantities of another palladium source (such as palladium(II) acetate) must be included.

In an analogous manner, a nitrile group can be used to direct the C–H functionalization when present on one of the substrates (Scheme 119). For example, C7 arylation of tetrahydroisoquinolines can be accomplished by appending a nitrile-containing directing group to the nitrogen atom.[168] Coordination of palladium(II)

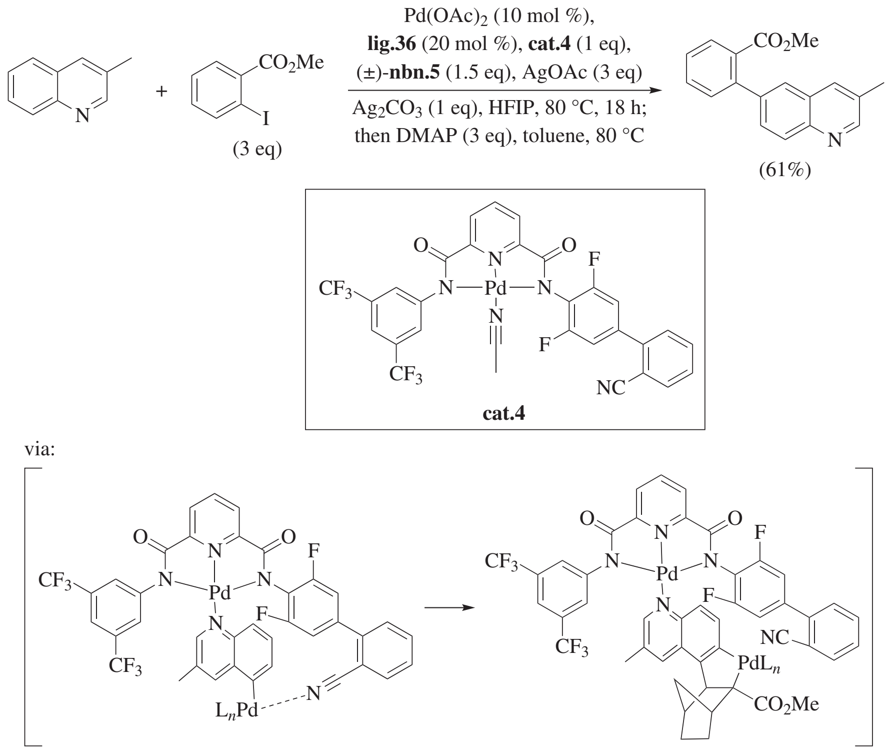


Scheme 117

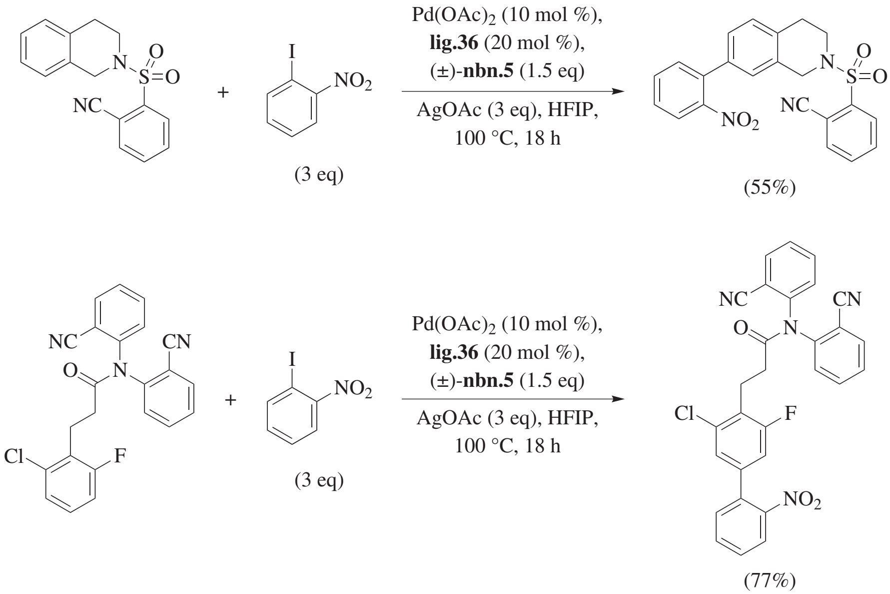
with the nitrile results in a U-shaped molecule that places palladium directly adjacent to the C7–H bond. A similar directed reaction occurs with phenylpropanoic acid derivatives, which undergo *para*-arylation (Scheme 119, bottom reaction). These nitrile-containing directing groups are installed by treating the corresponding amines with acid chlorides or sulfonyl chlorides, and removal is generally carried out via hydrolysis under basic conditions (for example, using lithium hydroxide in methanol at room temperature).[169]

Remote alkenyl C−H bonds can also be functionalized by combining directed C−H palladation with palladium(II)/norbornene cooperative catalysis. For instance, an oxime-ether-based directing group facilitates distal-selective alkenyl C−H arylation of (*Z*)-alkenes (both acyclic and cyclic) to deliver a variety of trisubstituted alkenes in a highly regio- and stereoselective manner (Scheme 120).[40] Alkenyl C−H alkylation using iodomethane or methyl bromoacetate is also possible, albeit with lower efficiency. Following the C–H functionalization reaction, treatment with zinc under acidic conditions removes the oxime ether to generate the alcohol product.

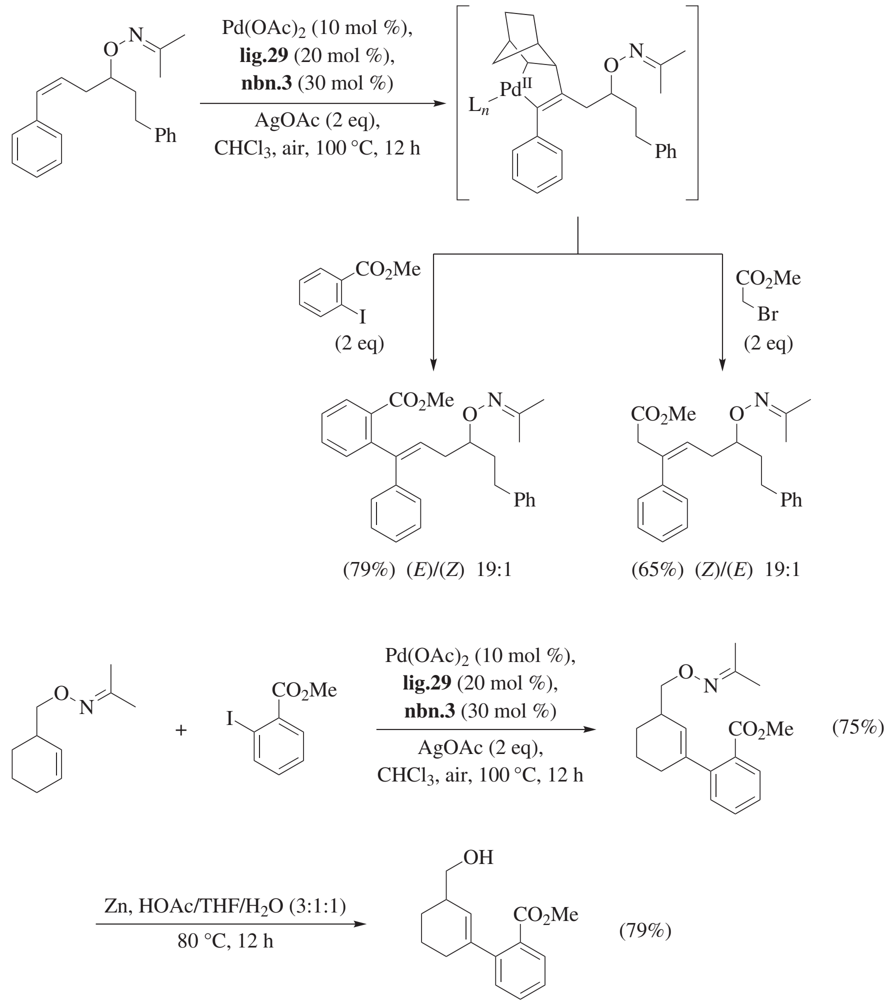
***Ortho*-Functionalization of Arylboron Species.** Arylboronic acids undergo an *ortho*-alkylation/*ipso*-Heck reaction in the presence of a palladium(II) catalyst and



Scheme 118



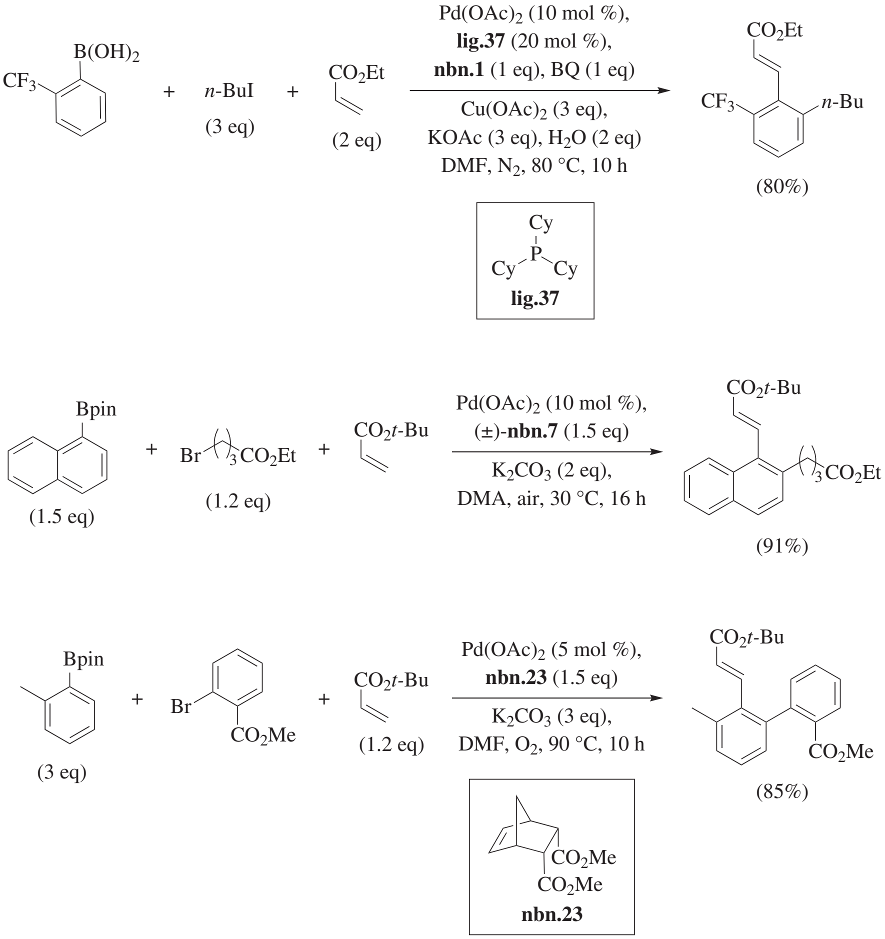
Scheme 119



Scheme 120

an oxidant (BQ and copper(II) acetate) (Scheme 121, top reaction).[15] Starting with arylboronic esters, oxygen can be used as the oxidant to carry out the same reaction sequence (Scheme 121, middle reaction),[16] or an *ortho*-arylation/*ipso*-Heck reaction combination (Scheme 121, bottom reaction).[42]

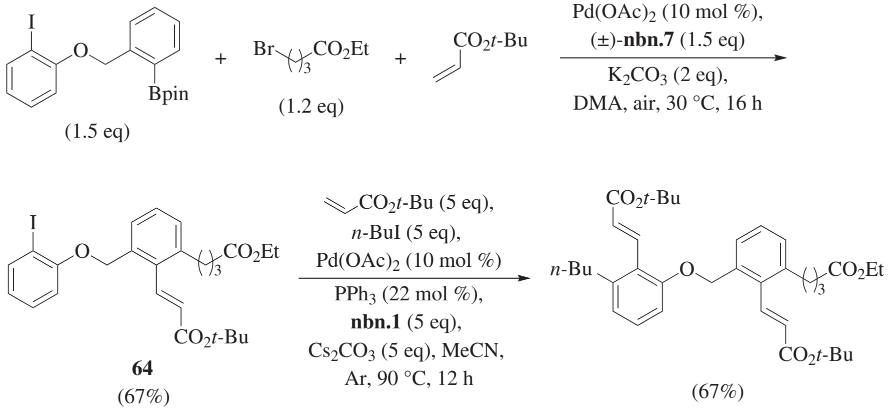
Because aryl iodides and arylboronic esters exhibit orthogonal reactivities under palladium(0) and palladium(II) catalyses, complex molecules can be prepared from arylboronic esters tethered to an iodoarene moiety (Scheme 122).[16] Under palladium(II) catalysis, bis-functionalization of the boron-containing aryl ring occurs preferentially, leading to the formation of intermediate **64**. A conventional palladium(0)-catalyzed *ortho*-alkylation/*ipso*-olefination then affords the final product.



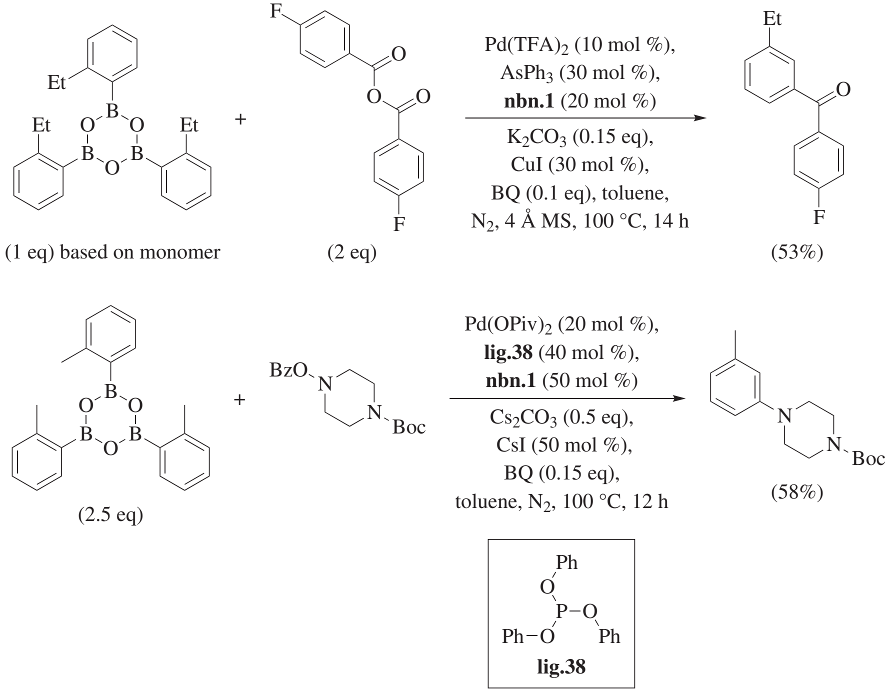
Scheme 121

Using a triarylboroxine as the starting material, palladium(II)-catalyzed *ortho*-acylation or amination delivers an aryl ketone or arylamine, respectively (Scheme 123).[41] Because these transformations are terminated by protodepalladation, they are redox-neutral and do not require an external oxidant. However, higher yields are obtained in the presence of a catalytic amount of BQ; in this context, BQ may serve as a palladium(0) scavenger or as a π-ligand to prevent catalyst decomposition.

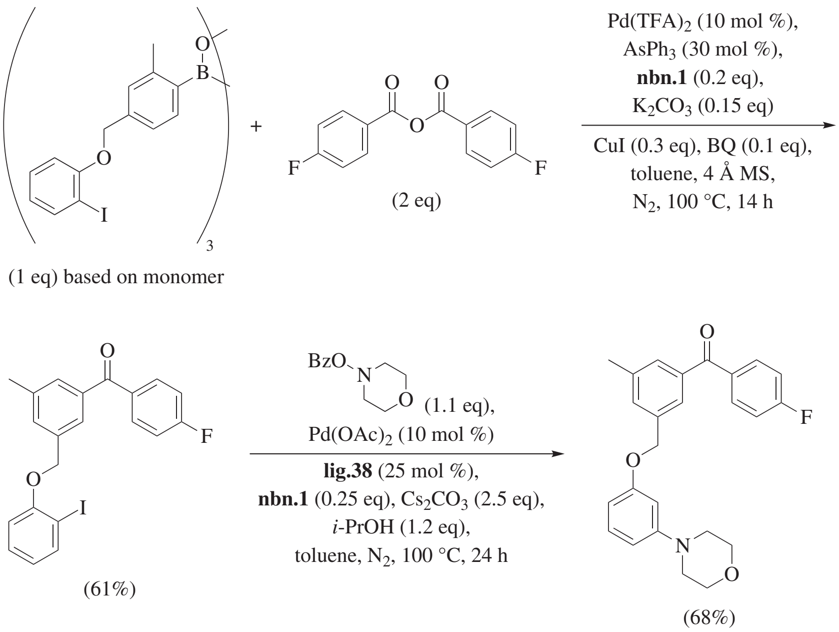
As with boronic esters (Scheme 122), the orthogonal reactivity of a boroxine and an aryl iodide can be exploited for sequential functionalization reactions. In Scheme 124, the boroxine undergoes an acylation reaction to generate a diaryl



Scheme 122



Scheme 123



Scheme 124

ketone, and the aryl iodide then participates in an amination reaction to afford the final product.[41]

APPLICATIONS TO SYNTHESIS

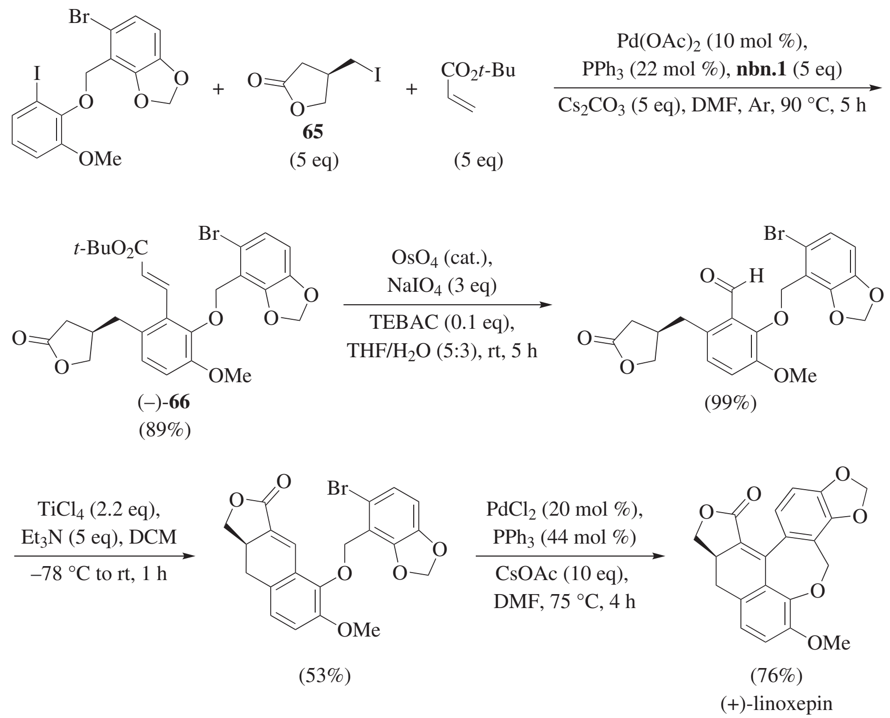
Densely substituted aromatic compounds are ubiquitous scaffolds in natural products, pharmaceuticals, and synthetic materials. Owing to their modular nature and high efficiencies, Catellani-type reactions have greatly improved the syntheses of many complex natural products and biologically active molecules. Selected examples are highlighted in this section.

(+)-Linoxepin

The first synthetic application of a Catellani-type reaction is demonstrated in the total synthesis of (+)-linoxepin, where the enantioenriched iodo lactone **65** is used as the alkylating reagent, and *tert*-butyl acrylate is employed as the terminating reagent. The key intermediate (−)-**66** is obtained in 89% yield on a gram scale and is then converted to the natural product (+)-linoxepin in three additional steps (Scheme 125).[170]

Psymberin

Psymberin is a cytotoxic natural product that exhibits antineoplastic activity.[171] A key intermediate for its synthesis is pentasubstituted arene **67**. Using an



Scheme 125

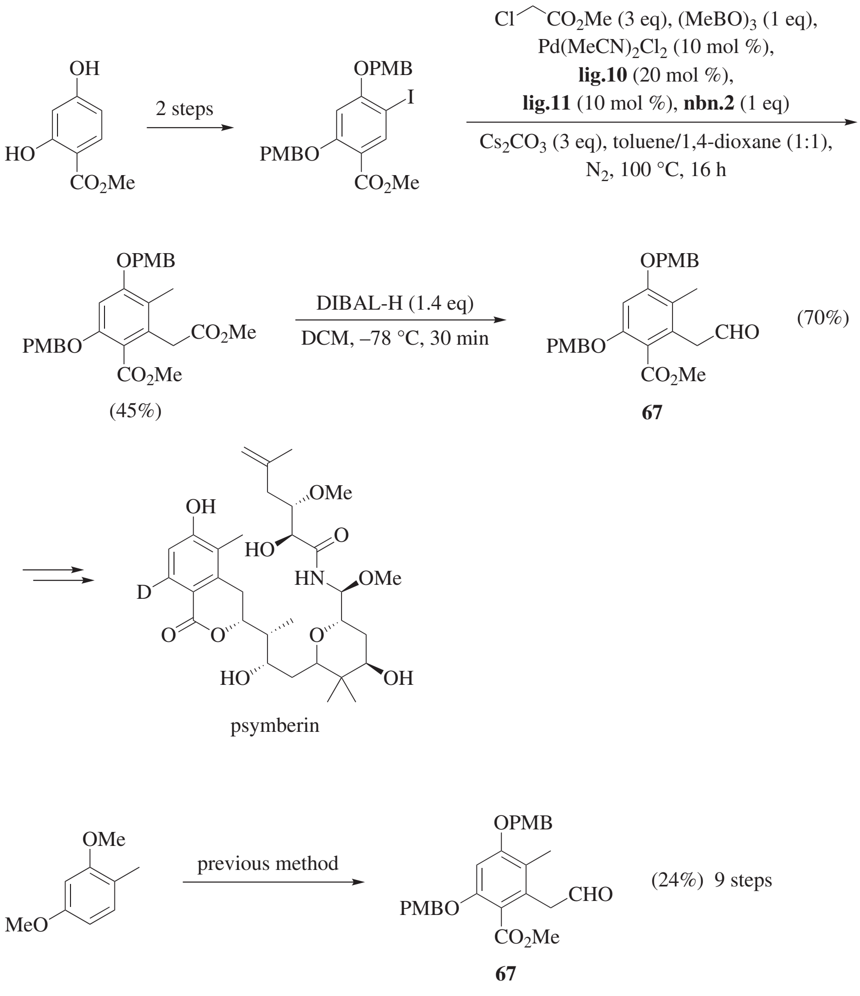
ortho-alkylation/*ipso*-methylation Catellani strategy (Scheme 126),[53] the key intermediate **67** can be accessed in four steps from a commercially available resorcinol derivative; in contrast, a previous route affords **67** in nine steps from 2,4-dimethoxy-1-methylbenzene.[171]

Tetrahydronaphthalene Derivatives

The herbicidal tetrahydronaphthalene derivative **69** can be prepared in 72% yield over two steps from methyl 3-iodo-4-methoxybenzoate and bifunctional alkylating agent **68**, which contains an alkyl bromide tethered to an allylic alcohol moiety (Scheme 127).[53] Alternatively, **69** can be generated in a single step by employing 5-iodo-2-methyl-1-pentene (**70**) in a three-component Catellani reaction. The termination step involves a novel reductive Heck reaction in which isopropyl alcohol quenches the final alkylpalladium(II) species. This approach represents a dramatic improvement in efficiency: using an earlier method, **69** is prepared in 3% yield over seven steps.[172]

Dalesconol A

The alkyne-tethered alkyl bromide **71** is used as a bifunctional alkylating reagent to prepare **72**, which contains the heptacyclic core of dalesconol A, a natural product

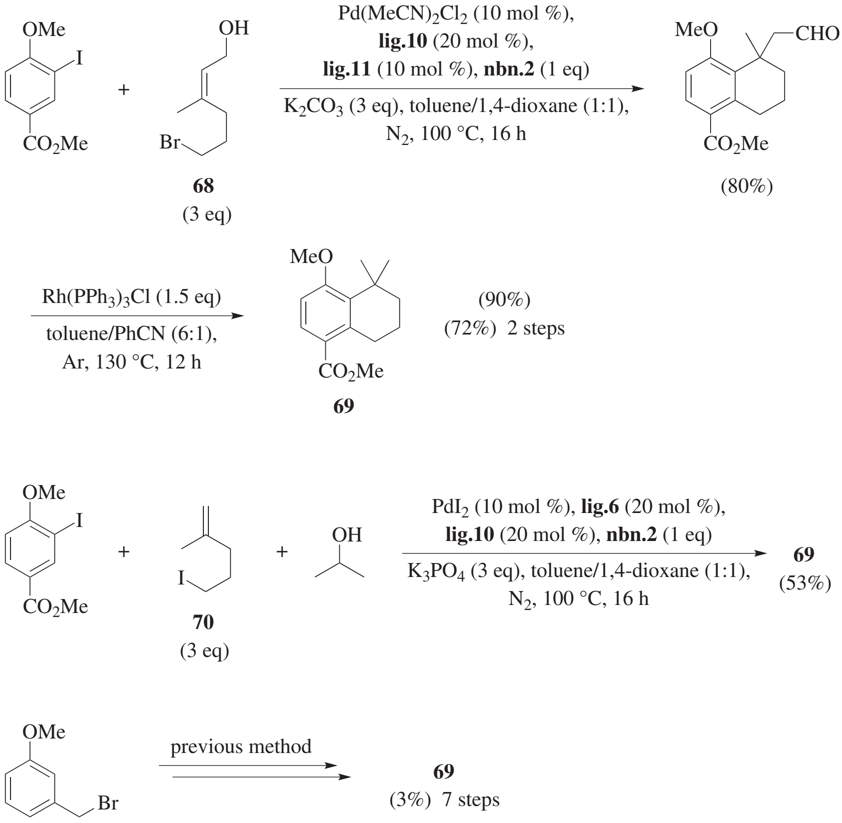


Scheme 126

that exhibits immunosuppressive activity (Scheme 128).[173] This highly efficient cascade reaction takes place in one pot to afford **72** in 65% yield on a gram scale via a sequence that involves *ortho*-alkylation/*ipso*-alkyne insertion, dearomatization of the naphthylamine, hydrolysis, and an intramolecular Michael addition. Subsequent oxidations then provide dalesconol A in a total of five steps.

(–)-Berkelic Acid

A Catellani reaction is used to prepare a key intermediate in the synthesis of (–)-berkelic acid (**74**) (Scheme 129).[174] Starting from a tetrasubstituted arene,

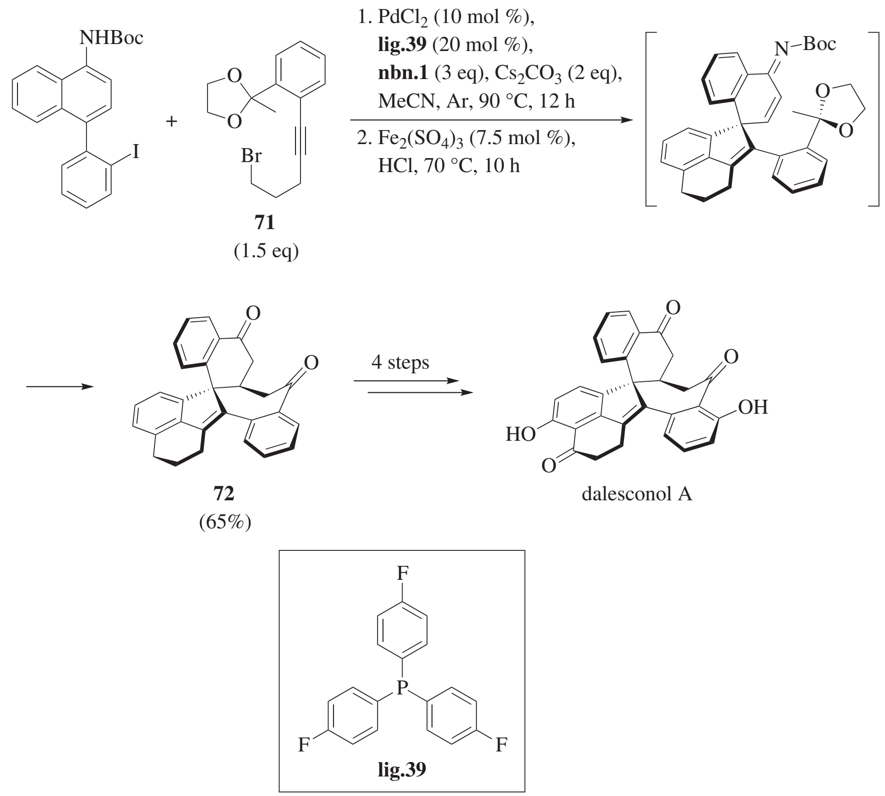


Scheme 127

ortho-alkylation with an epoxide is followed by *ipso*-olefination. A subsequent base-promoted oxa-Michael reaction affords intermediate **73**, which can be converted to (−)-berkelic acid **74** over four additional steps.

Rhazinal

The preparation of the pyrrole-based natural product rhazinal centers around a Catellani reaction that forms the fused two-ring system and installs a nitrophenyl group that will ultimately become the aniline moiety (Scheme 130).[175] Using 1-bromo-2-nitrobenzene as the arylating reagent, the 2-iodopyrrole substrate undergoes an *ortho*-arylation followed by a Heck reaction with the tethered alkene to afford intermediate **75**, which is converted to (±)-rhazinal over three additional steps. An asymmetric synthesis of (+)-rhazinal is enabled by using phosphoramidite **lig.40** as a chiral ligand in the Catellani reaction, leading to enantioenriched (*S*)-**75** in 65% yield and with an enantiomeric ratio of 94.0:6.0.[176]



71
(1.5 eq)

72
(65%)

dalesconol A

lig.39

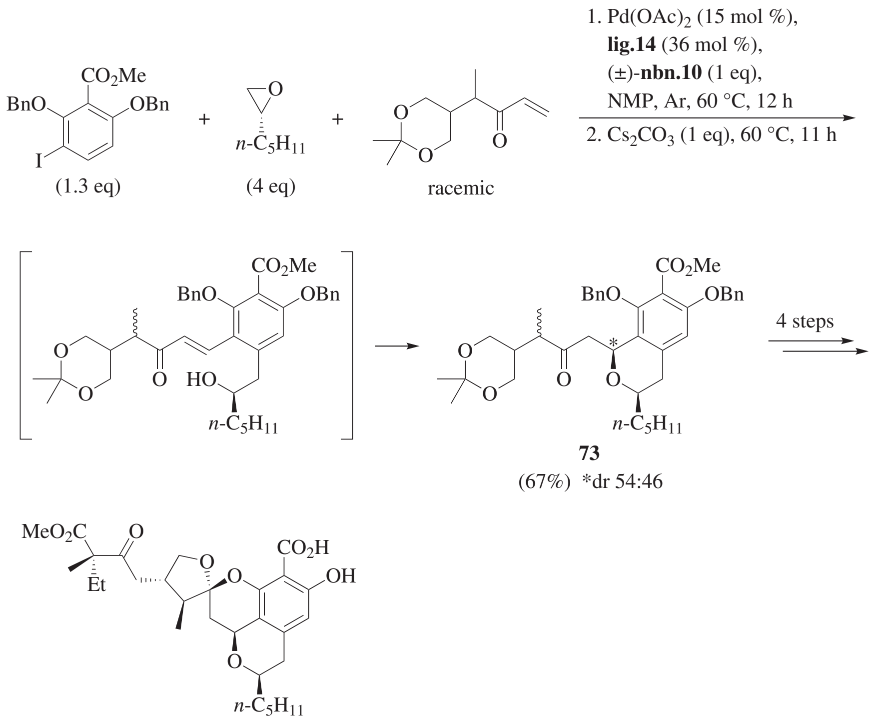
Scheme 128

P70S6 Kinase Inhibitor

The 1,3,5-trisubstituted aniline derivative **78** is a building block for the synthesis of a P70S6 kinase inhibitor.[177,178] Although **78** can be prepared from 3-chloro-5-bromoanisole via conventional coupling methods, the high cost of this starting material precludes its use on a large scale.[179] A Catellani-type amination strategy provides an alternative route to this building block. Iodination of 3-chloroanisole, which is significantly less expensive, provides the required iodoarene as an inseparable mixture of regioisomers **76** and **77**. This mixture is directly subjected to the *ortho*-amination/*ipso*-hydrogenation reaction conditions as both regioisomers afford **78**, which can be elaborated to a P70S6 kinase inhibitor in two additional steps (Scheme 131).[108]

GOT1 Inhibitor

4-Piperazinylindole (**79**) is a key intermediate in the synthesis of a GOT1 inhibitor used to treat pancreatic ductal adenocarcinoma.[180] Using conventional



73
(67%) *dr 54:46

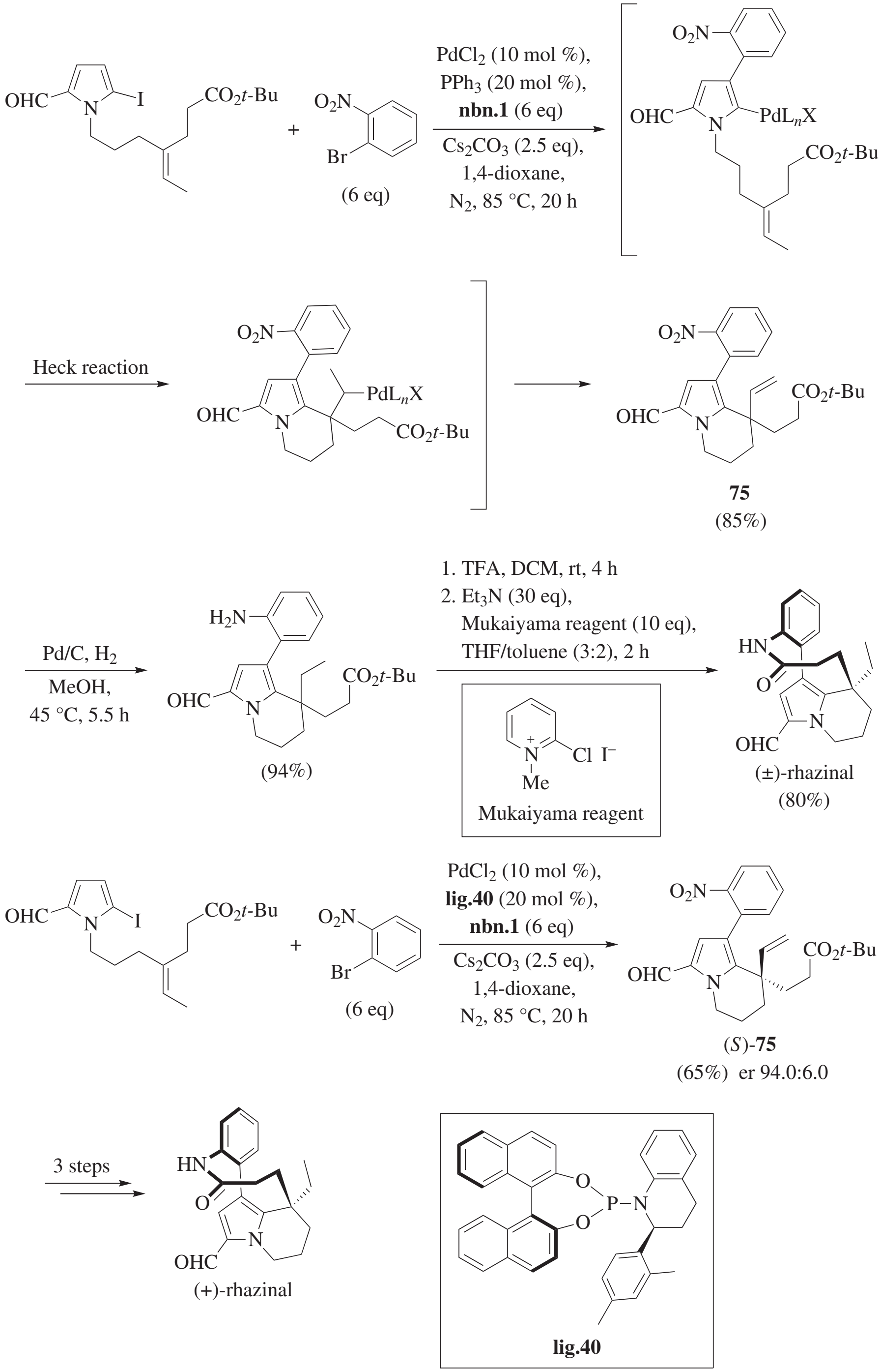
74
(−)-berkelic acid

Scheme 129

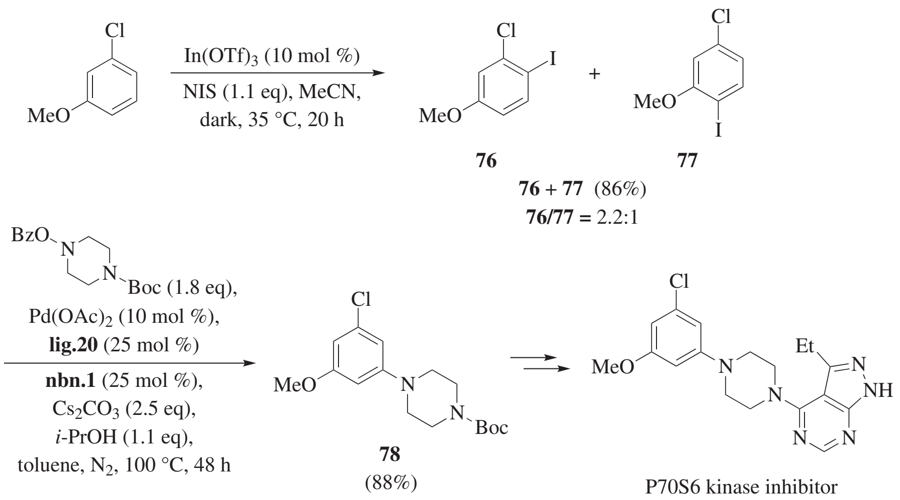
synthetic approaches, **79** is prepared from 2-nitrotoluene in four-to-six steps, but yields are less than 4%.[181−183] A sequence involving a Catellani-type amination and a retro-Diels−Alder reaction provides **79** in 48% yield over three steps (Scheme 132).[125] Treatment with 4-chlorophenyl isocyanate then affords the GOT1 inhibitor.

Acredinone A

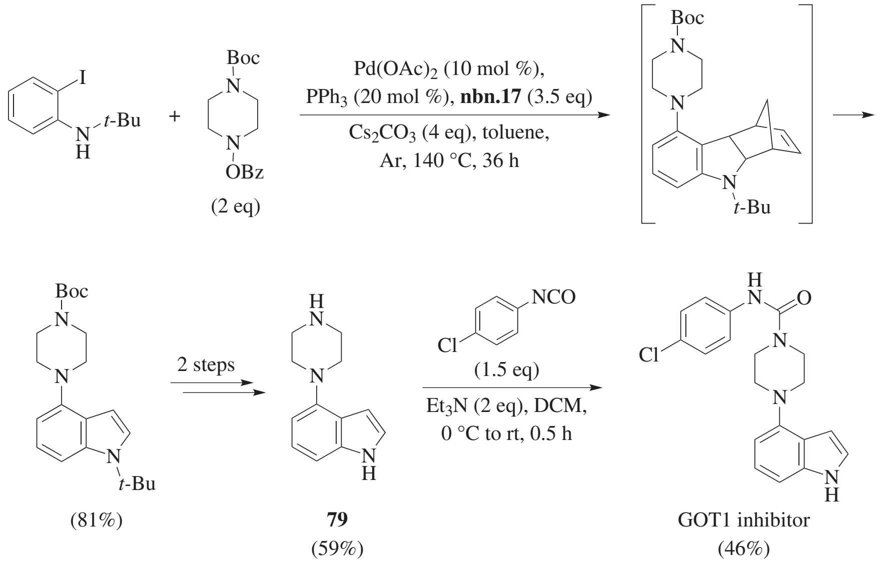
Two types of palladium(0)-catalyzed *ortho*-acylation reactions are employed in a concise synthesis of the natural product acredinone A (Scheme 133).[142] The two aryl iodide substrates, **80** and **82**, are prepared from the same aryl aldehyde and undergo *ortho*-acylation/*ipso*-Heck reaction and *ortho*-acylation/*ipso*-borylation, respectively. Functional-group interconversions generate the two fragments **81** and **83**, which are then coupled in a Suzuki–Miyaura reaction. Acid-mediated removal of the methoxymethyl ether affords acredinone A in 59% yield over two steps.


OHC
I
CO$_2$t-Bu
+
O$_2$N
Br
(6 eq)
PdCl$_2$ (10 mol %),
PPh$_3$ (20 mol %),
nbn.1 (6 eq)
Cs$_2$CO$_3$ (2.5 eq),
1,4-dioxane,
N$_2$, 85 °C, 20 h
PdL$_n$X
Heck reaction
75
(85%)
Pd/C, H$_2$
MeOH,
45 °C, 5.5 h
H$_2$N
(94%)
1. TFA, DCM, rt, 4 h
2. Et$_3$N (30 eq),
Mukaiyama reagent (10 eq),
THF/toluene (3:2), 2 h
Cl I$^-$
Me
Mukaiyama reagent
HN
O
(±)-rhazinal
(80%)
lig.40 (20 mol %),
(*S*)-**75**
(65%) er 94.0:6.0
3 steps
(+)-rhazinal
O
P
N
lig.40

Scheme 130



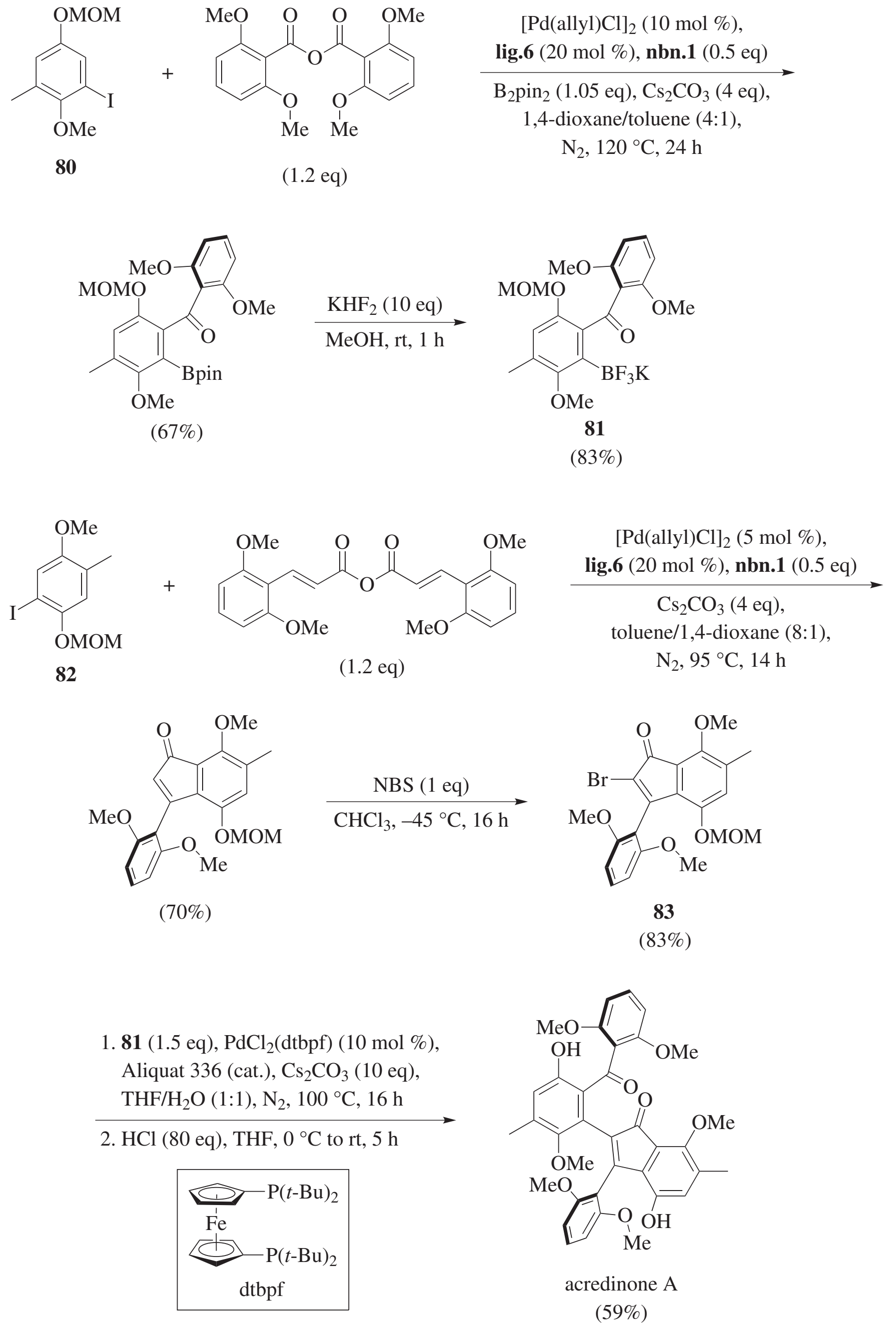
Scheme 131



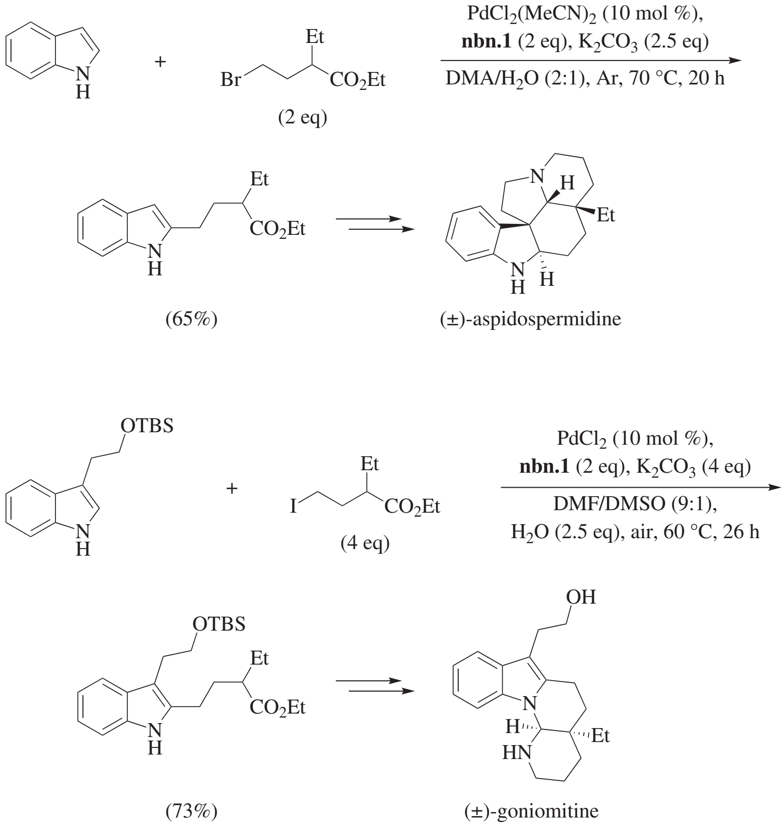
Scheme 132

(±)-Aspidospermidine and (±)-Goniomitine

Few palladium(II)-catalyzed Catellani-type reactions have been applied to syntheses of natural products. Two notable examples are the total syntheses of (±)-aspidospermidine and (±)-goniomitine, both of which utilize palladium(II)-catalyzed C2-alkylation of indoles as the key steps (Scheme 134).[38]


OMOM
I
OMe
80
+
MeO
O
O
OMe
O
O
Me
O
Me
(1.2 eq)
[Pd(allyl)Cl]$_2$ (10 mol %),
lig.6 (20 mol %), **nbn.1** (0.5 eq)
B$_2$pin$_2$ (1.05 eq), Cs$_2$CO$_3$ (4 eq),
1,4-dioxane/toluene (4:1),
N$_2$, 120 °C, 24 h
MeO
MOMO
OMe
O
Bpin
OMe
(67%)
KHF$_2$ (10 eq)
MeOH, rt, 1 h
MeO
MOMO
OMe
O
BF$_3$K
OMe
81
(83%)
OMe
I
OMOM
82
+
OMe
O
O
OMe
O
OMe
MeO
(1.2 eq)
[Pd(allyl)Cl]$_2$ (5 mol %),
lig.6 (20 mol %), **nbn.1** (0.5 eq)
Cs$_2$CO$_3$ (4 eq),
toluene/1,4-dioxane (8:1),
N$_2$, 95 °C, 14 h
O
OMe
MeO
OMOM
O
Me
(70%)
NBS (1 eq)
CHCl$_3$, –45 °C, 16 h
O
OMe
Br
MeO
OMOM
O
Me
83
(83%)
1. **81** (1.5 eq), PdCl$_2$(dtbpf) (10 mol %),
Aliquat 336 (cat.), Cs$_2$CO$_3$ (10 eq),
THF/H$_2$O (1:1), N$_2$, 100 °C, 16 h
2. HCl (80 eq), THF, 0 °C to rt, 5 h
P(t-Bu)$_2$
Fe
P(t-Bu)$_2$
dtbpf
MeO
OH
OMe
O
O
OMe
OMe
MeO
O
OH
Me
acredinone A
(59%)

Scheme 133



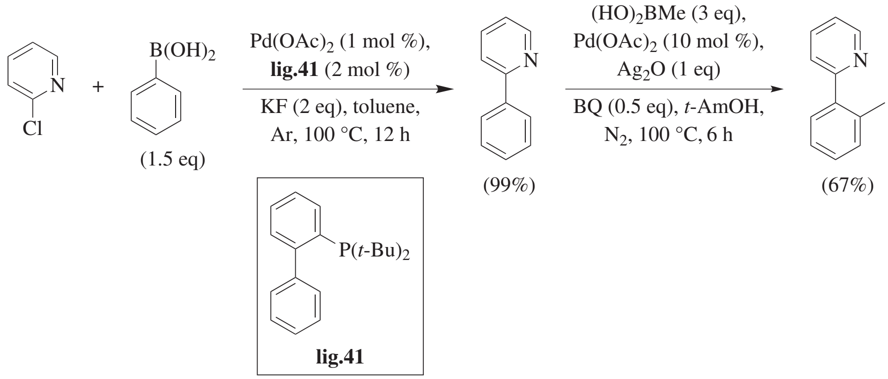
Scheme 134

COMPARISON WITH OTHER METHODS

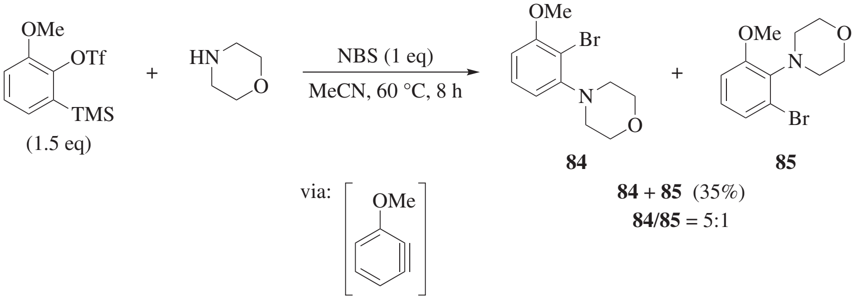
Catellani-type reaction products can be accessed using transition-metal-catalyzed cross-coupling reactions of aryl halides or direct C−H functionalization of arenes. Generally, only mono-functionalization of an arene is possible, and multiple synthetic steps are required for 1,2-difunctionalization (Scheme 135).[184]

Arene 1,2-difunctionalization is possible in a single step from a benzyne derivative, but the requisite starting materials (typically an arene ring with triflate and trialkylsilyl groups in an *ortho* arrangement) are not readily available and often require several synthetic steps to prepare. Moreover, controlling the regioselectivity of the addition step is nontrivial (Scheme 136).[185]

Catellani-type reactions are among the most efficient approaches for the synthesis of polysubstituted aryl rings and offer the following advantages: (1) high step economy (both the *ortho* and *ipso* positions are functionalized in a single operation); (2) excellent regioselectivities (an electrophile is introduced at the *ortho* position, and a nucleophile is coupled at the *ipso* position); (3) modularity (a variety of combinations of electrophiles and nucleophiles can be employed).



Scheme 135



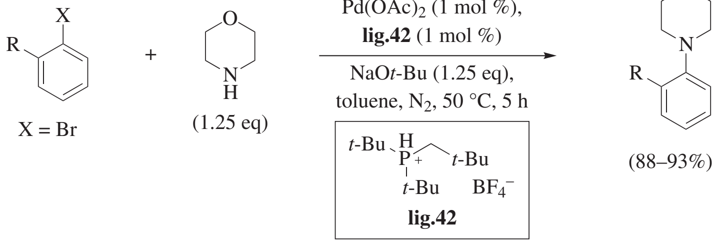
Scheme 136

However, there are also some limitations to Catellani-type reactions. For example, mono-*ortho*-functionalization of unsubstituted aryl halides (e.g., iodobenzene) remains a challenge, although the use of structurally modified norbornenes is beginning to address this problem. Moreover, the introduction of heteroatoms such as oxygen, halogens, and phosphorous via Catellani-type reactions is difficult, leaving much room for additional reaction development. Construction of aryl carbon–nitrogen bonds via *ipso*-amination has so far been restricted to intramolecular aminations, that is, the nucleophilic amine functionality has been integrated into arenes in preceding steps through the use of bifunctional reagents. Intermolecular *ipso*-amination remains an unresolved challenge, presumably because of the competing direct carbon–nitrogen coupling reactions.

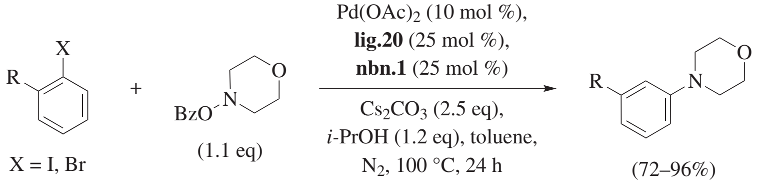
Amination of Aryl Halides

The closest analogue to the palladium(0)-catalyzed *ortho*-amination of aryl halides is the well-established Buchwald–Hartwig amination reaction.[186,187] Both reaction classes use aryl halides as starting materials and provide aniline derivatives under palladium(0) catalysis. However, they exhibit complementary site-selectivity: Buchwald–Hartwig reactions deliver *ipso*-amination products whereas Catellani reactions afford *ortho*-amination products. When the Catellani reactions are terminated by a hydride, the two different reaction products are regioisomers (Scheme 137).[108]

Buchwald–Hartwig amination



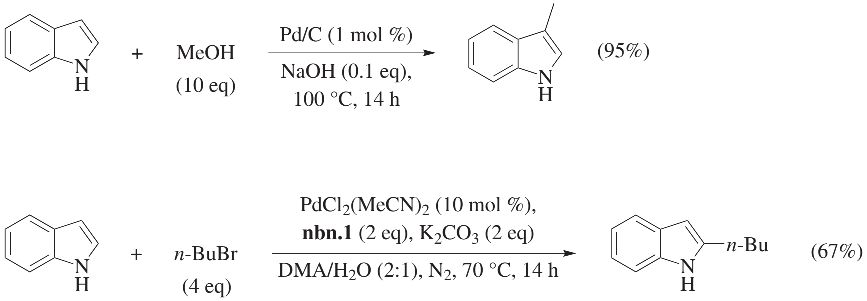
Catellani-type amination



Scheme 137

Alkylation of Indoles

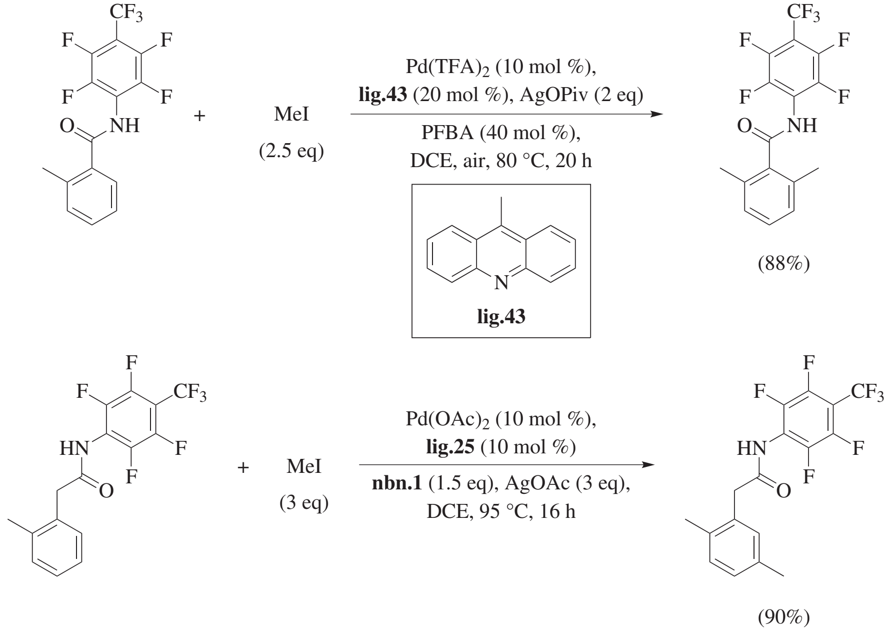
Indole alkylation typically occurs at the C3 position under conventional C–H functionalization conditions (Scheme 138, top reaction).[188] In this case, again, the Catellani-based alkylation reaction is complementary to existing methods, providing C2-alkylated products instead (Scheme 138, bottom reaction; see also Scheme 13) and only small amounts of 2,3-dialkylated side products.[11]



Scheme 138

C−H Functionalization of Arenes with a Directing Group

In the context of transition-metal-catalyzed C−H functionalization of arenes, directing groups generally place the metal in close proximity to the *ortho*-C−H bond, thereby providing *ortho*-substituted products (Scheme 139, top reaction).[189] However, when arenes with an *ortho*-directing group are subjected to palladium(II)-catalyzed Catellani-type reaction conditions, palladium is first introduced at the *ortho* position and is then relayed by norbornene (**nbn.1**) to the *meta* position, ultimately leading to *meta*-substituted products exclusively (Scheme 139, bottom reaction).[13]

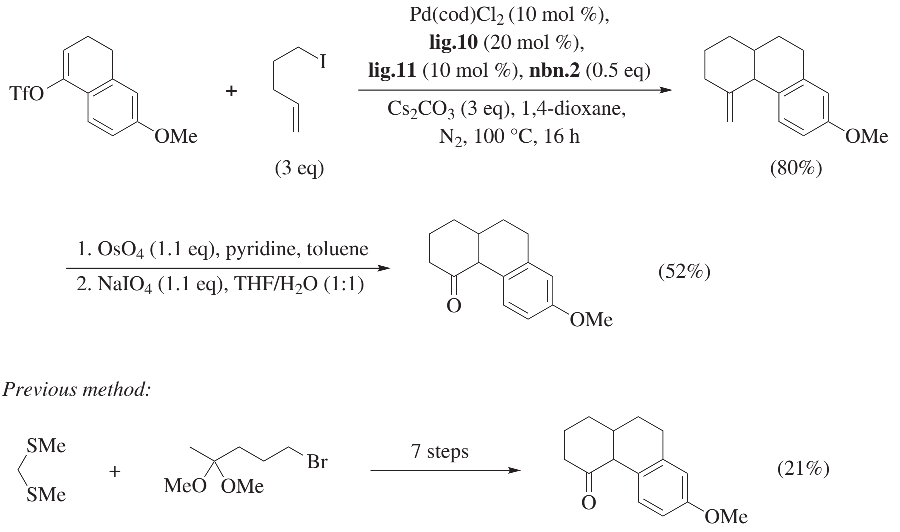


Scheme 139

Synthesis of Complex Molecules

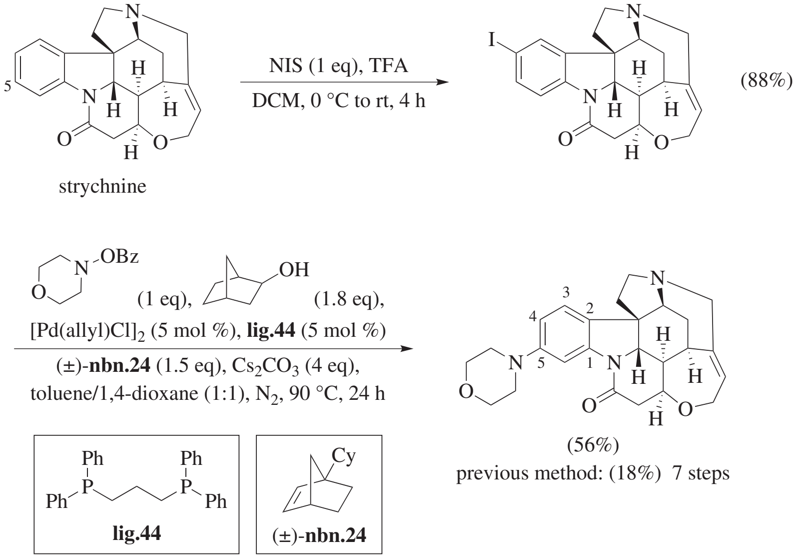
In several instances, the Catellani reaction has been used to synthesize complex molecules that previously have been prepared by alternative methods. The three case studies below provide direct comparisons between Catellani and non-Catellani approaches to the same target molecule.

***Ortho*-Alkylation Reactions.** En route to the phenanthrene nucleus, the tricyclic enone is prepared in three steps and 42% overall yield using an alkenyl Catellani reaction with a bifunctional alkylating reagent (Scheme 140).[148] In contrast, a previous method requires seven steps, and the enone is obtained in 21% overall yield.[190]



Scheme 140

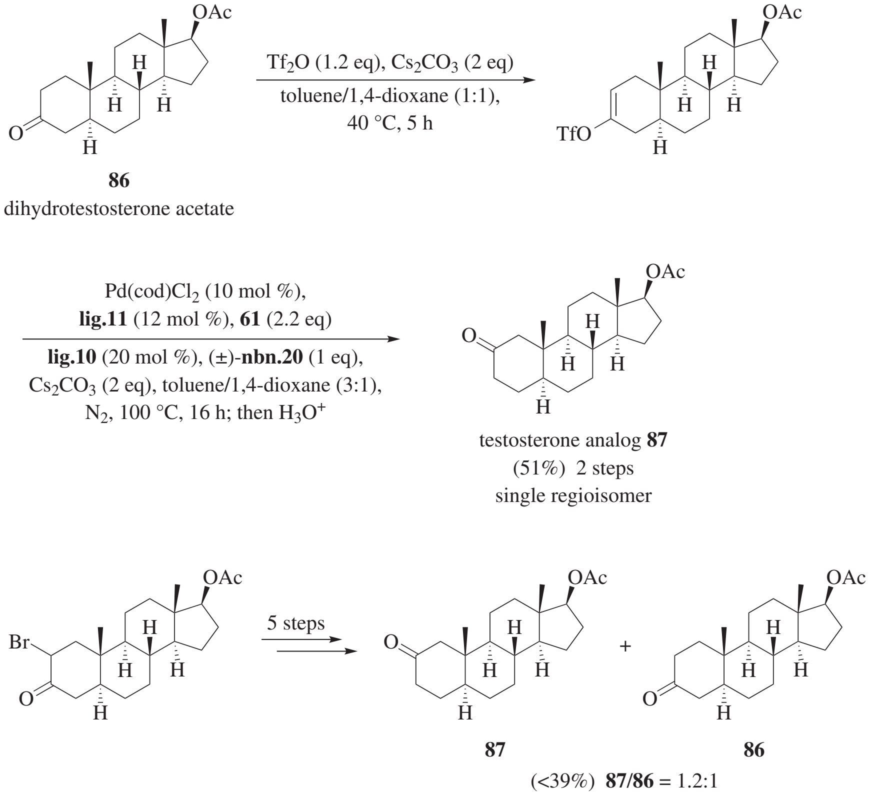
***Ortho*-Amination Reactions.** Site-selective amination of strychnine at the C5 position can be achieved via a two-step sequence that involves iodination and a Catellani-type *ortho*-amination reaction (Scheme 141).[96] With this method, the



Scheme 141

product is obtained in 56% overall yield; in contrast, the product may be accessed in 18% yield using a more traditional, seven-step route that includes acetylation, diazotization, and reduction.[191]

Carbonyl Transposition. A carbonyl 1,2-transposition process involving a Catellani-type amination reaction of an alkenyl triflate simplifies the synthesis of complex ketones (Scheme 142).[149] For example, the bioactive testosterone analog **87** is synthesized from dihydrotestosterone acetate (**86**) as a single regioisomer in 51% yield over two steps. A previous route accessed **87** in five steps and <39% yield,[149] but as a 1.2:1 mixture of regioisomers that complicates purification of the desired isomer.

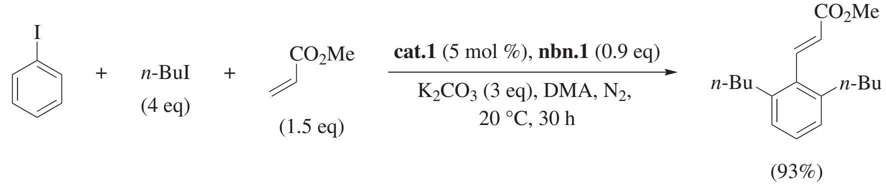


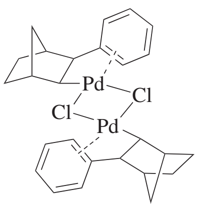
Scheme 142

EXPERIMENTAL CONDITIONS

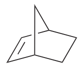
Most of the reagents used for Catellani-type reactions are air- and moisture-compatible. However, palladium(0) sources are not air- or moisture-stable, and reactions employing these reagents require anhydrous, inert-atmosphere conditions. Unless otherwise noted, reactions were run in flame-dried flasks or vials. Sealed tubes are often used when the reaction temperature is higher than the solvent boiling point. Norbornene and its derivatives are frequently used in stochiometric amounts to prevent side reactions, although catalytic amounts have been successfully employed on several occasions. Acetonitrile is the most commonly used solvent, and inorganic carbonate salts such as potassium or cesium carbonate are the most frequently used bases for the reactions.

EXPERIMENTAL PROCEDURES



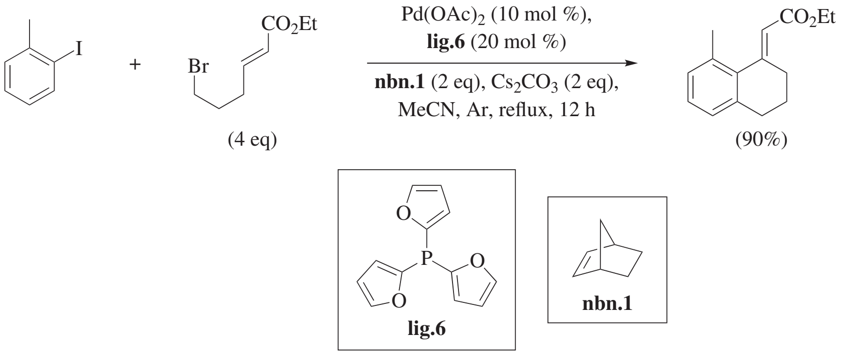


cat.1

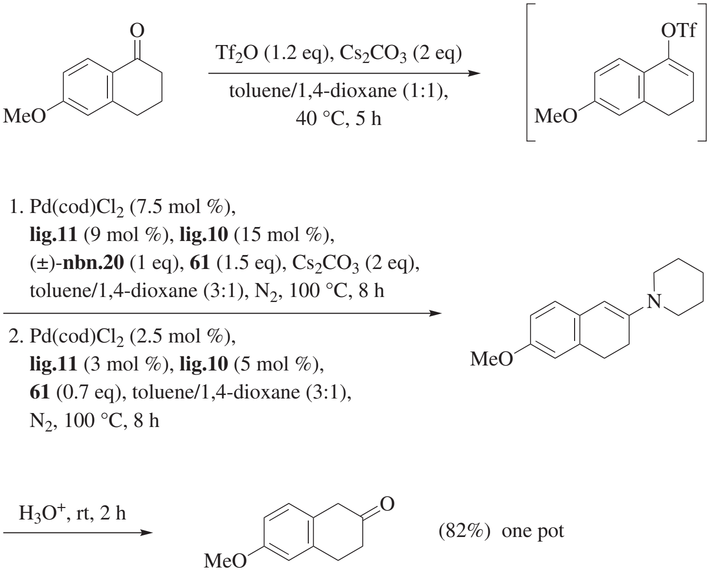


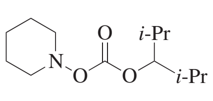
nbn.1

Methyl (*E*)-3-(2,6-Dibutylphenyl)acrylate [*Ortho*-Alkylation of an Aryl Halide].[1] In a Schlenk-type flask, iodobenzene (71 mg, 0.35 mmol), phenylnorbornylpalladium(II) (PNP) dimer **cat.1** (1.1 mg, 0.017 mmol), K_2CO_3 (146 mg, 1.05 mmol), *n*-butyl iodide (258 mg, 1.40 mmol), norbornene (**nbn.1**, 30 mg, 0.32 mmol), and methyl acrylate (45 mg, 0.52 mmol) were dissolved in DMA (7.0 mL) under nitrogen. The tube was sealed, and the mixture was stirred at 20 °C for 30 h. When the reaction had reached completion (determined by TLC and GC), 5% H_2SO_4 was added, the organic layer was separated, and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) to afford the title compound as a white solid (98 mg, 93%): IR (neat) 1724, 1636, 986 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 16.3 Hz, lH), 7.16–7.05 (m, 3H), 6.00 (d, *J* = 16.3 Hz, lH), 3.81 (s, 3H), 2.60 (m, 4H), l.49 (m, 4H), 1.38 (sextet, *J* = 7.1 Hz, 4H), 0.90 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.9, 144.2, 141.0, 133.6, 128.0, 126.9, 123.7, 51.7, 33.4, 33.3, 22.5, 13.9.

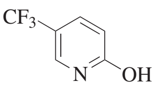


Ethyl (*E*)-2-(8-Methyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)acetate [*Ortho*-Alkylation of an Aryl Halide].[2] In a flame-dried, round-bottom flask, 2-iodotoluene (20 mL, 0.157 mmol), ethyl (*E*)-6-bromohex-2-enoate (138 mg, 0.624 mmol), Cs_2CO_3 (105 mg, 0.322 mmol), norbornene (**nbn.1**, 30.2 mg, 0.32 mmol), tri(2-furyl)phosphine (**lig.6**, 7.5 mg, 0.032 mmol), and $Pd(OAc)_2$ (4 mg, 0.017 mmol) were dissolved in acetonitrile (1.5 mL) under Ar. The reaction mixture was heated at reflux for 12 h. Saturated aqueous ammonium chloride solution was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After filtration and evaporation, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 30:1) to afford the title compound as a colorless oil (32.6 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2–7.1 (m, 2H), 7.1–6.9 (m, 1H), 5.9 (t, *J* = 2.0 Hz, 1H), 4.2 (q, *J* = 7.2 Hz, 2H), 3.1 (td, *J* = 7.0, 2.0 Hz, 2H), 2.6 (br t, *J* = 6.1 Hz, 2H), 2.47 (s, 3H), 1.8–1.7 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 154.7, 141.8, 136.3, 134.9, 129.5, 127.8, 125.2, 118.2, 59.7, 30.2, 28.2, 21.7, 21.6, 14.3; HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{18}O_2$, 230.1311; found, 230.1306.

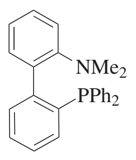




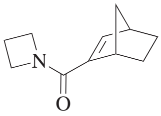
61



lig.10

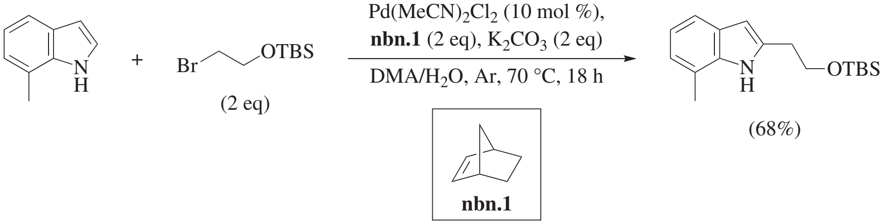


lig.11

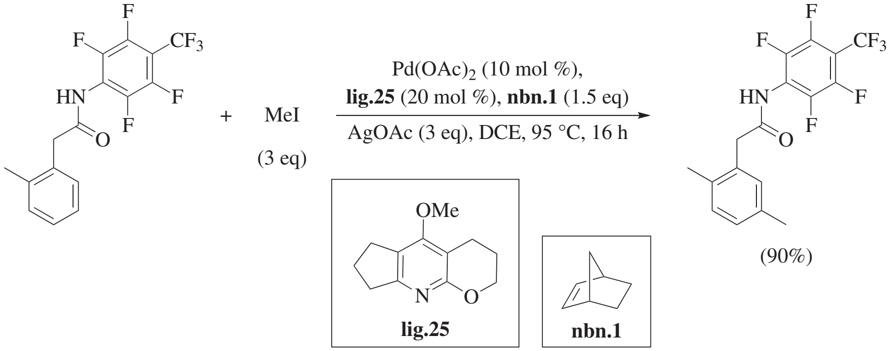


(±)-**nbn.20**

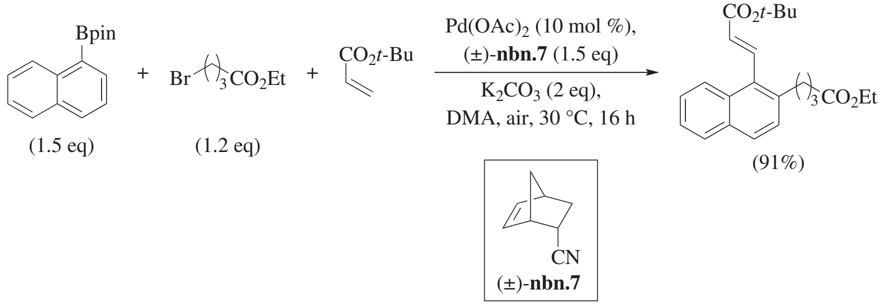
6-Methoxy-3,4-dihydronaphthalen-2(1*H*)-one [*Ortho*-Amination of an Alkenyl Pseudohalide].[149] In a flame-dried 4-mL vial, the ketone substrate (17.6 mg, 0.1 mmol), Cs_2CO_3 (65.2 mg, 0.2 mmol), dry toluene (0.4 mL), and dry 1,4-dioxane (0.4 mL) were added in a glovebox under an N_2 atmosphere. Next, Tf_2O (33.9 mg, 0.12 mmol) was added in one portion at rt. The reaction mixture was stirred at 40 °C for 5 h. To the reaction vial were then added sequentially: $Pd(cod)Cl_2$ (2.2 mg, 0.0075 mmol), Ph-DavePhos (**lig.11**) (3.5 mg, 0.008 mmol), **lig.10** (2.5 mg, 0.015 mmol), **nbn.20** (17.7 mg, 0.1 mmol), **61** (36.5 mg, 0.15 mmol), Cs_2CO_3 (65.2 mg, 0.2 mmol), and dry toluene (1.0 mL). The reaction vial was sealed with a cap, removed from the glovebox, and the mixture was stirred at 100 °C for 8 h before being returned to the glovebox, where a solution of Ph-DavePhos (**lig.11**, 1.1 mg, 0.003 mmol) and **lig.10** (0.8 mg, 0.005 mmol) in toluene (0.15 mL) and 1,4-dioxane (0.05 mL) were added followed by the addition of $Pd(cod)Cl_2$ (0.7 mg, 0.0025 mmol) and the electrophilic nitrogen source **61** (17.1 mg, 0.07 mmol) under an N_2 atmosphere. The reaction mixture was then stirred at 100 °C for another 8 h before it was diluted with 1 mL of THF. Acetate buffer (0.5 mL, prepared from NaOAc (10 g), AcOH (20 mL), and H_2O (20 mL)) was added, and the resulting mixture was stirred for 2 h at rt. The crude reaction mixture was then extracted with EtOAc (3×). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine. The solution was dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting residue was purified by column chromatography on silica gel (hexanes/EtOAc 4:1) to afford the title compound as a colorless liquid (29.0 mg, 82%): IR (NaCl) 2954, 2837, 1715, 1610, 1500, 1270, 1243, 1158, 1037, 809 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, J = 8.2 Hz, 1H), 6.83–6.73 (m, 2H), 3.81 (s, 3H), 3.52 (s, 2H), 3.03 (t, J = 6.7 Hz, 2H), 2.54 (t, J = 6.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.0, 158.7, 138.0, 129.3, 125.3, 113.4, 112.5, 55.5, 44.4, 38.3, 28.8; HRMS–ESI–TOF (*m/z*): $[M + H]^+$ calcd for $C_{11}H_{12}O_2$, 177.0910; found, 177.0910.



2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-7-methyl-1*H*-indole [Palladium(II)-Catalyzed C2-Functionalization of an NH Indole].[11] A flame-dried, round-bottom flask was charged with 7-methyl-1*H*-indole (131 mg, 1.00 mmol), (2-bromoethoxy)(*tert*-butyl)dimethylsilane (474 mg, 1.98 mmol), $Pd(MeCN)_2Cl_2$ (25.9 mg, 10 mol %), K_2CO_3 (276 mg, 2.00 mmol), and norbornene (**nbn.1**, 188 mg, 2.00 mmol). A solution of water in DMA (DMA/H_2O = 2:1, 5 mL) was added (0.2 M substrate concentration), and the resulting solution was briefly evacuated and then backfilled with Ar (3×). The flask was placed in a preheated oil bath at 70 °C for 18 h, at which point the mixture was cooled to rt, diluted with ether, and filtered. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (pentane/ethyl acetate, 40:1 to 30:1) to afford the title compound as a pale-yellow oil (196 mg, 68%): TLC R_f 0.65 (pentane/ether, 9:1); IR (ATR) 3437, 2954, 2927, 2856, 1614, 1559, 1496, 1461, 1329, 1254, 1086, 1054 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 6.22 (s, 1H), 3.94 (t, *J* = 5.6 Hz, 2H), 2.98 (t, *J* = 5.6 Hz, 2H), 2.45 (s, 3H), 0.97 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 138.3, 135.7, 127.9, 121.7, 119.70, 119.68, 117.7, 100.3, 63.3, 31.2, 26.1, 18.3, 16.9, –5.3; HRMS–EI (*m/z*): $[M]^+$ calcd for $C_{17}H_{27}NOSi$, 289.1856; found, 289.1856.



2-(2,5-Dimethylphenyl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl) acetamide [*Meta*-Selective C–H Functionalization of an Arene with an *Ortho* Directing Group].[13] A flame-dried, round-bottom flask was charged with *N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-2-(2-tolyl)acetamide (36.2 mg, 0.10 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), **lig.25** (4.1 mg, 0.02 mmol), AgOAc (50 mg, 0.30 mmol), and **nbn.1** (14.1 mg, 0.15 mmol). Methyl iodide (19 μL, 0.30 mmol) and DCE (1.5 mL) were added. The vial was capped tightly, and the reaction mixture was stirred at 95 °C for 16 h. The crude mixture was then cooled to rt, diluted with acetone, and filtered. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 4:1) to afford the title compound as a white solid (34 mg, 90%): ^{1}H NMR (400 MHz, acetone-d^6) δ 9.38 (br s, 1H), 7.13 (s, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 3.85 (s, 2H), 2.30 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (150 MHz, acetone-d^6) δ 206.2, 169.6, 136.1, 134.8, 134.1, 131.9, 131.0, 128.8, 41.2, 29.8, 20.9, 19.2; HRMS–ESI–TOF (m/z): $[M - H]^-$ calcd for $C_{17}H_{11}F_7NO^-$, 378.0734; found 378.0737.



Ethyl (*E*)-4-(1-(3-(*tert*-Butoxy)-3-oxoprop-1-en-1-yl)naphthalen-2-yl) butanoate [*Ortho*-Functionalization of an Arylboron Species].[16] An oven-dried, 25-mL Schlenk tube equipped with a magnetic stir bar was charged with the arylboron compound (76.2 mg, 0.3 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), K_2CO_3 (55.3 mg, 0.4 mmol), the alkyl bromide (46.8 mg, 0.24 mmol), alkene (25.6 mg, 0.2 mmol), 5-norbornene-2-carbonitrile **(nbn.7)** (35.7 mg, 0.3 mmol), and DMA (1 mL) under air. The reaction mixture was then stirred at 30 °C for 16 h. When the reaction was complete, the mixture was diluted with EtOAc (15 mL) and filtered. The filtrate was washed sequentially with water and brine, and then was dried over Na_2SO_4 and filtered. After concentration of the solution in vacuo, the residue was purified by column chromatography on silica gel to afford the title compound as a colorless oil (91%): TLC R_f 0.4 (petroleum ether/EtOAc, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.03 (m, 2H), 7.83–7.75 (m, 2H), 7.51–7.43 (m, 2H), 7.34 (d, J = 8.5 Hz, 1H), 6.14 (d, J = 16.4 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H), 2.01–1.93 (m, 2H), 1.59 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 165.9, 141.3, 137.3, 132.3, 131.5, 131.3, 128.7, 128.3, 127.9, 127.7, 126.6, 125.5, 125.3, 80.9, 60.5, 33.9, 33.1, 28.4, 26.3, 14.4; HRMS–ESI–TOF (m/z): $[M + Na]^+$ calcd for $C_{23}H_{28}NaO_4$, 391.1880; found 391.1884.

LIST OF ABBREVIATIONS

In addition to those listed in "*The Journal of Organic Chemistry* Standard Abbreviations and Acronyms", the following abbreviations are used in the chapter.

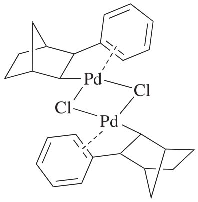
Ad	adamantyl
ANP	arylnorbornylpalladacycle
BQ	1,4-benzoquinone
CMD	concerted metalation–deprotonation
cod	1,5-cyclooctadiene
CuTC	copper(I) thiophene-2-carboxylate
dba	dibenzylideneacetone
DCP	1,3-dichloropropane
DG	directing group
DMI	1,3-dimethyl-2-imidazolidinone
dtbpf	1,1′-bis(di-*tert*-butylphosphino)ferrocene
EDG	electron-donating group
EWG	electron-withdrawing group
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
MS	molecular sieves
MW	microwave irradiation
Np	naphthyl
Ns	4-nitrobenzenesulfonate, nosyl
PFBA	pentafluorobenzoic acid
Phth	phthalyl
pin	pinacolato
PNP	phenylnorbornylpalladium
rr	regioisomeric ratio
TEBAC	benzyltriethylammonium chloride
TFP	tri(2-furyl)phosphine
TS	transition structure

TABULAR SURVEY

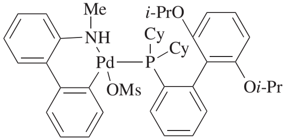
The following tables contain representative examples of Catellani-type reactions in the literature up to September 2021; supplemental references for the period of October 2021 to March 2024 are provided at the end of the Reference section. The tables are organized by the type of reaction (e.g., *ortho*-alkylation, *ortho*-acylation, *ortho*-amination, *ortho*-acylation, etc.), and in some cases, the type of co-reactant. For example, Tables 1–3 describe the palladium(0)-catalyzed *ortho*-alkylation of aryl (pseudo)halides with simple alkyl halides (Table 1), bifunctional alkylating reagents (Table 2), and three-membered heterocycles (Table 3). Tables 4–5 cover the palladium(0)-catalyzed *ortho*-arylation of aryl (pseudo)halides with simple aryl halides and bifunctional arylating reagents, respectively. Tables 6–8 survey palladium(0)-catalyzed *ortho*-amination, *ortho*-acylation and alkoxycarbonylation, and *ortho*-thiolation of aryl (pseudo)halides, respectively. Table 9 encompasses *ortho*-functionalization of alkenyl (pseudo)halides with both alkyl and aryl halides. Tables 10–12 detail different types of substrates that are functionalized under palladium(II) catalysis. Specifically, functionalization of unprotected NH indoles and pyrroles is listed in Table 10. Table 11 describes *meta*-C−H functionalization of arenes with an *ortho*-directing group, and *ortho*-functionalization of arylboron species is covered in Table 12. Reactions shown in the text section of the chapter are not repeated in the tables.

Within each table, entries are arranged by increasing carbon count of the substrate. Aryl halides with the same carbon count are ordered by the number of substituents on the aryl ring. For entries employing the same aryl halide, the carbon count of the electrophile is used as a secondary ordering rubric. Protecting groups, directing groups, and substituents on heteroatoms are not included in the carbon count unless the group is modified in the reaction.

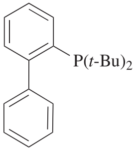
Chart 1. Structures of Catalysts and Ligands Used in Tables



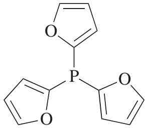
C1



C2



L1



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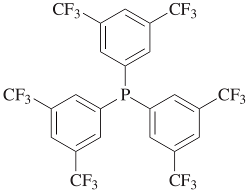

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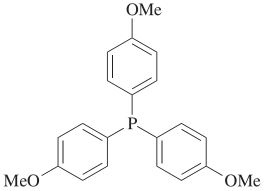

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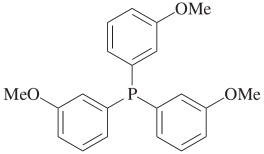

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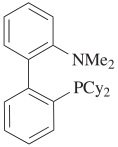

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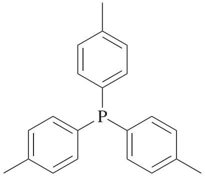

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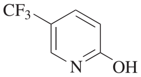

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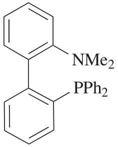

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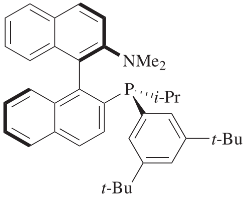

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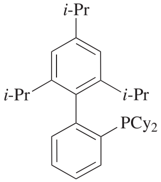

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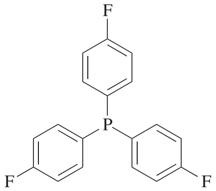
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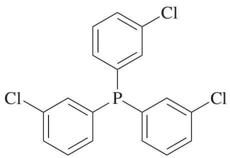
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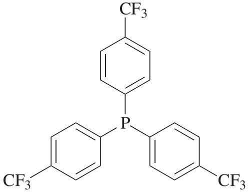
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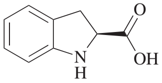
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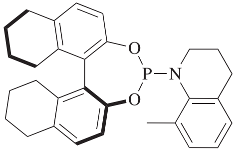
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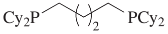
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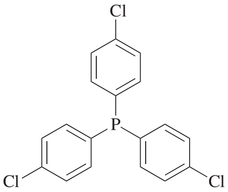
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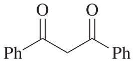
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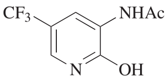
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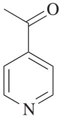
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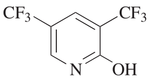
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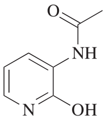
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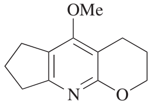
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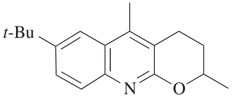
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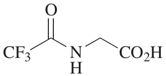
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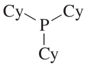
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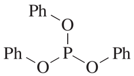
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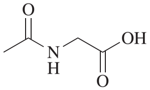
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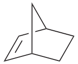
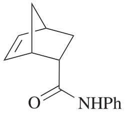
CHART 2. NORBORNENE AND DERIVATIVES USED IN TABLES



N1

N2



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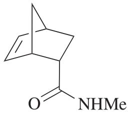

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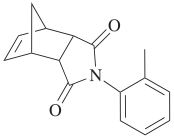

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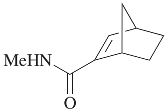

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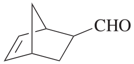

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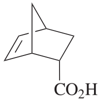

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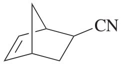

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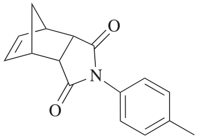

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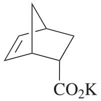

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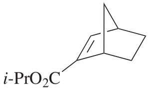

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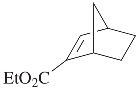

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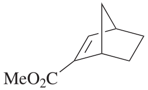

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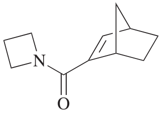

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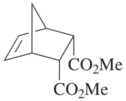
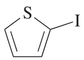
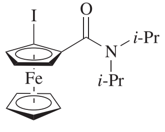
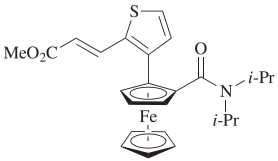
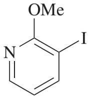
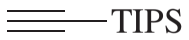
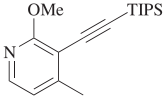
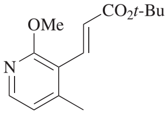
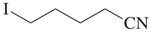
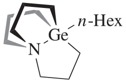
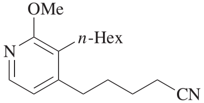
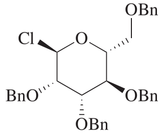


N16

TABLE 1. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH SIMPLE ALKYL HALIDES

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_4					
	 1.0 eq	 2.0 eq	$Pd(OAc)_2$ (20 mol %), **L1** (20 mol %), **N1** (1.5 eq), K_2CO_3 (3 eq), DMF, N_2, 105 °C	 (37%) er = 97.0:3.0	192
C_5					
 2.0 eq	MeOTs 2.0 eq		$Pd_2(dba)_3$ (5 mol %), **L2** (11 mol %), (±)-**N2** (2 eq), K_2CO_3 (2.5 eq), MeCN, Ar, 100 °C, 15 h	 (66%)	52
2.0 eq	$PO(OMe)_3$ 2.0 eq		$Pd(OAc)_2$ (10 mol %), **L2** (22 mol %), **N1** (2 eq), Cs_2CO_3 (2.5 eq), DMA, Ar, 80 °C, 15 h	 (86%)	52
	 2.0 eq	 1.0 eq	$PdBr_2$ (5 mol %), **L3** (10 mol %), **N1** (2 eq), Cs_2CO_3 (2 eq), MeCN, Ar, 100 °C, 14 h	 (74%)	60

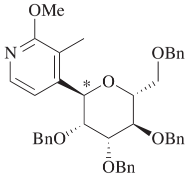


1.5 eq

(HO)$_2$BMe

2.0 eq

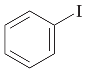
Pd(OAc)$_2$ (10 mol %),
L2 (20 mol %),
(±)-**N3** (2 eq),
Cs_2CO_3 (3 eq),
THF, N_2, 100 °C, 24 h



(43%) *α/β > 20:1

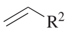
58

C$_6$



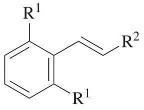
R^{1}I

4.0 eq



1.5 eq

C1 (5 mol %),
N1 (1 eq), K_2CO_3 (3 eq),
DMA, N_2, 20 °C, 30 h



1

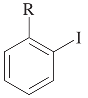
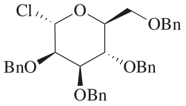
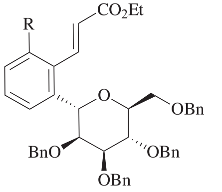
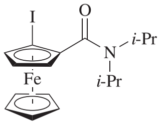
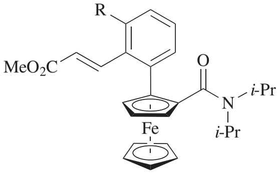
R^1	R^2	Conv (%)	Selectivity (%)[a]
n-Bu	MeCO	42	90
n-Bu	*n*-Hex	43	90
n-Bu	Ph	31	91
n-Oct	MeO_2C	86	95
$PhCH_2CH_2$	MeO_2C	100	93

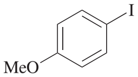
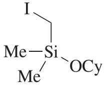
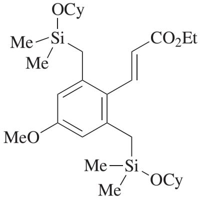
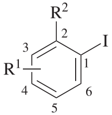
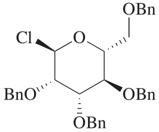
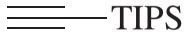
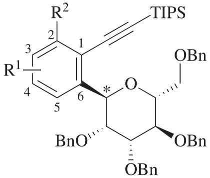
[a] Although unclear in the paper, the selectivity is presumably the ratio of products to byproducts.

TABLE 1. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH SIMPLE ALKYL HALIDES (*Continued*)

*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*

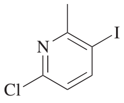
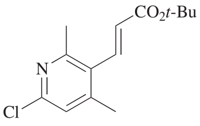
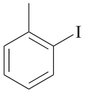
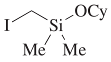
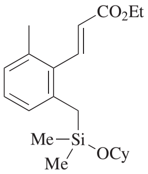
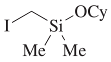
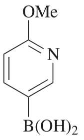
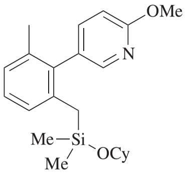
C_{6-7}

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
 2.0 eq	 2.0 eq		$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), (±)-**N2** (2 eq), Cs_2CO_3 (2.5 eq), 1,4-dioxane, Ar, 95 °C, 13 h	 α-isomer only R / Yield (%) F / 91 MeO / 96 *i*-PrO / 96 Me / 96	57
	 1.0 eq	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L5** (20 mol %), **N1** (1.5 eq), K_2CO_3 (2.4 eq), DMF, N_2, 105 °C	 R / Yield (%) / er Me_2N / 16 / 97.0:3.0 MeO / 78 / 97.0:3.0 BnO / 70 / 96.5:3.5 Me / 92 / 99.0:1.0	192

C_6		 5.0 eq	 3.5 eq	$Pd(OAc)_2$ (10 mol %), **L4** (20 mol %), **N1** (4 eq), K_2CO_3 (4.5 eq), MeCN, N_2, 95 °C, 30 h		(25%)	193
$C_{6–8}$	 1.5 eq	 1.5 eq		$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %), (±)-**N4** (2 eq), K_2CO_3 (3 eq), MeCN, N_2, 100 °C, 24 h			58

R^1	R^2	Yield (%)	*α/β
H	F	27	>20:1
H	Me	32	>20:1
3-F	Me	35	>20:1
4-F	Me	26	>20:1
3-Cl	Me	37	>20:1
4-Cl	Me	33	>20:1
3-Me	Me	36	>20:1

TABLE 1. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH SIMPLE ALKYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_6					
 2.0 eq	MeOTs 2.0 eq		$Pd(OAc)_2$ (10 mol %), **L2** (22 mol %), **N1** (2 eq), Cs_2CO_3 (2.5 eq), DMA, Ar, 80 °C, 15 h	 (90%)	52
C_7					
	 2.5 eq	 3.5 eq	$Pd(OAc)_2$ (10 mol %), **L4** (20 mol %), **N1** (4 eq), K_2CO_3 (3 eq), MeCN, N_2, 95 °C, 30 h	 (81%)	193
	 2.5 eq	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L4** (20 mol %), **N1** (4 eq), K_2CO_3 (3 eq), MeCN, N_2, 95 °C, 30 h	 (90%)	193

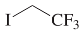
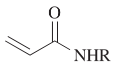
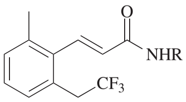
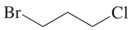
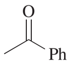
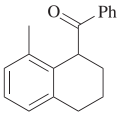
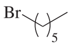
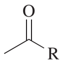
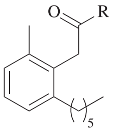
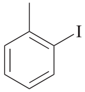
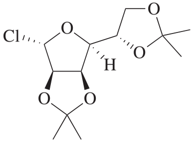
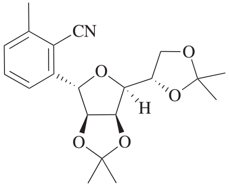
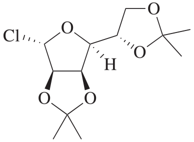
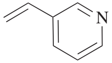
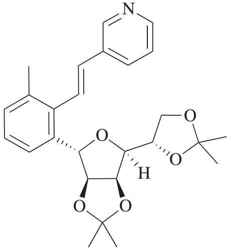
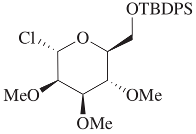
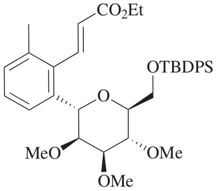
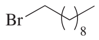
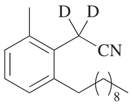
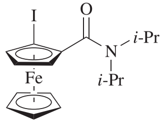
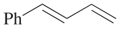
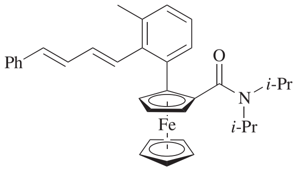
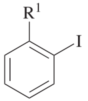
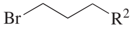
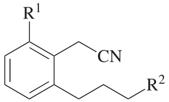
 7.0 eq	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L6** (20 mol %), **N1** (3 eq), Cs_2CO_3 (4 eq), HOAc (1 eq), MeCN/DMI (20:1), Ar, 110 °C, 8 h	 R / Yield (%) *i*-Pr 65 *t*-Bu 68	55
 4.0 eq	 2.0 eq	$PdBr_2$ (10 mol %), **L5** (20 mol %), **N1** (2 eq), NaOH (3 eq), THF, Ar, 100 °C, 24 h	 (46%)	194
 4.0 eq	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L7** (20 mol %), **N1** (2 eq), NaI (2 eq), NaOH (2 eq), 1,4-dioxane, Ar, 90 °C, 24 h	 R / Yield (%) Me 73 2-thienyl 47 Cy 45 1-Np 56	194

TABLE 1. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH SIMPLE ALKYL HALIDES (*Continued*)

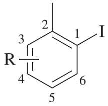
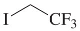
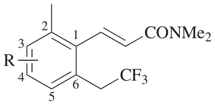
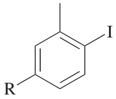
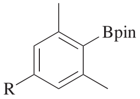
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)		Refs
C$_7$						
	 2.0 eq	$Zn(CN)_2$ 2.0 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), (±)-**N2** (2 eq), Cs_2CO_3 (2.5 eq), toluene, Ar, 95 °C, 13 h	 α-isomer only	(48%)	57
2.0 eq	 2.0 eq		$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), (±)-**N2** (2 eq), Cs_2CO_3 (2.5 eq), 1,4-dioxane, Ar, 95 °C, 13 h	 α-isomer only	(98%)	57
2.0 eq	 2.0 eq		$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), (±)-**N2** (2 eq), Cs_2CO_3 (2.5 eq), 1,4-dioxane, Ar, 95 °C, 13 h	 α-isomer only	(99%)	57

	 4.0 eq	CD_3CN 10.0 eq	$Pd(OAc)_2$ (10 mol %), **L7** (20 mol %), **N1** (2 eq), NaI (2 eq), LiO*t*-Bu (4 eq), 1,4-dioxane, Ar, 90 °C, 24 h	 (41%)	194
	 1.0 eq	 2.0 eq	$Pd(OAc)_2$ (20 mol %), **L1** (20 mol %), **N1** (1.5 eq), K_2CO_3 (3 eq), DMF, N_2, 105 °C	 (74%) er = 99.0:1.0	192
C_{7-9}					
	 4.0 eq	MeCN 10.0 eq	$Pd(OAc)_2$ (10 mol %), **L7** (20 mol %), **N1** (2 eq), NaI (2 eq), LiO*t*-Bu (4 eq), 1,4-dioxane, Ar, 90 °C, 24 h		194

R^1	R^2	Yield (%)
Me	CF_3	34
i-Pr	*n*-Pr	47

TABLE 1. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH SIMPLE ALKYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_{7-8}					
	 7.0 eq	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L6** (20 mol %), **N1** (3 eq), Cs_2CO_3 (4 eq), HOAc (1 eq), MeCN/DMI (20:1), Ar, 110 °C, 8 h	 R — Yield (%) H — 80 3-Cl — 48 3-MeO — 66 4-MeO — 82 3-Me — 60 4-Me — 60 4-MeO_2C — 50	55
	MeOTs 2.0 eq	B_2pin_2 3.0 eq	$Pd(OAc)_2$ (10 mol %), **L4** (22 mol %), **N1** (2 eq), Cs_2CO_3 (2.5 eq), KOAc (2.5 eq), MeCN, MW, Ar, 140 °C, 0.5 h	 R — Yield (%) H — 47 MeO_2C — 43 MeHNOC — 49	52

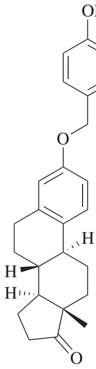
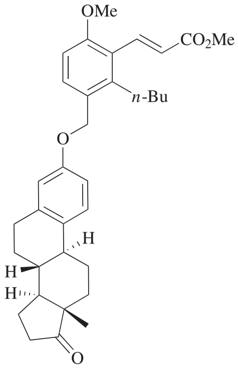
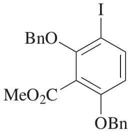
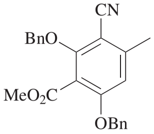
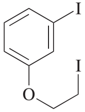
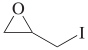
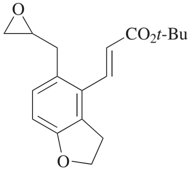
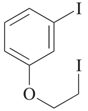
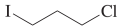
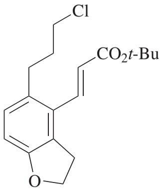
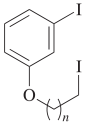
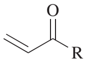
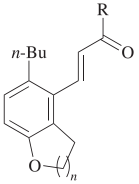
C_7						
	n-BuI 3.0 eq	 1.5 eq	$Pd(MeCN)_2Cl_2$ (10 mol %), **L8** (10 mol %), **L9** (20 mol %), (±)-**N6** (1 eq), Cs_2CO_3 (3 eq), toluene/1,4-dioxane (1:1), N_2, 100 °C, 16 h		(86%)	53
	MeOTs 3.0 eq	$Zn(CN)_2$ 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L6** (11 mol %), (±)-**N2** (3 eq), KOAc (2.5 eq), DME, Ar, 80 °C, 15 h		(36%)	52
C_8						
	 10.0 eq	 5.0 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), **N1** (5 eq), Cs_2CO_3 (5 eq), DME, N_2, 80 °C, 6 h		(35%)	49

TABLE 1. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH SIMPLE ALKYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_8					
	 10.0 eq	 5.0 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), **N1** (5 eq), Cs_2CO_3 (5 eq), DME, N_2, 80 °C, 6 h	 (53%)	49
C_{8-10}					
	*n*-BuI 10.0 eq	 5.0 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), **N1** (5 eq), Cs_2CO_3 (5 eq), DME, N_2, 80 °C, 6 h		49

n	R	Yield (%)
1	Me_2N	60
1	*t*-BuHN	87
1	*t*-BuO	85
1	Et	37
2	*t*-BuO	62
3	*t*-BuO	69

C$_8$

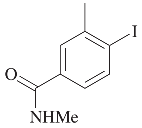
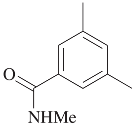
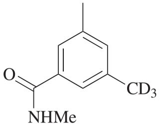
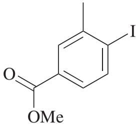
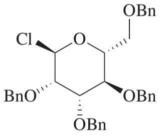
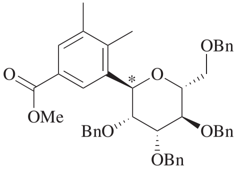
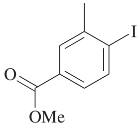
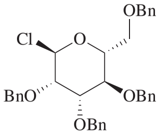
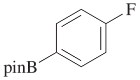
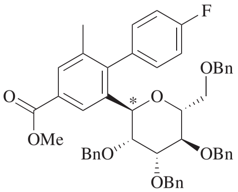
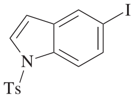
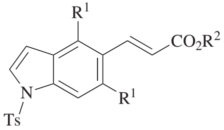
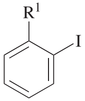
	MeOTs 3.0 eq	HCOONa 2.0 eq	$Pd_2(dba)_3$ (10 mol %), **L2** (11 mol %), **N5** (2 eq), Cs_2CO_3 (2.5 eq), DME, Ar, 80 °C, 15 h		(72%)	52
	CD_3OTs 3.0 eq	HCOONa 2.0 eq	$Pd_2(dba)_3$ (10 mol %), **L2** (11 mol %), **N5** (2 eq), Cs_2CO_3 (2.5 eq), DME, Ar, 80 °C, 15 h		(80%)	52
	 1.5 eq	$(HO)_2BMe$ 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %), (±)-**N3** (2 eq), Cs_2CO_3 (3 eq), THF, N_2, 100 °C, 24 h		(56%) *α/β > 20:1	58

TABLE 1. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH SIMPLE ALKYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_8					
	 1.5 eq	 2.0 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), (±)-**N4** (2 eq), Cs_2CO_3 (3 eq), toluene, N_2, 100 °C, 24 h	 (36%) *α/β > 20:1	58
	R^1I 6.0 eq	 2.0 eq	$Pd(OAc)_2$ (20 mol %), PPh_3 (20 mol %), **N1** (2 eq), Cs_2CO_3 (2 eq), DME, 90 °C, 24 h		195

R^1	R^2	Yield (%)
Et	Me	70
n-Bu	Me	88
n-Bu	Et	51
n-Bu	*t*-Bu	68

C_{9-10}

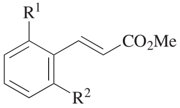


R^2I

13.2 eq

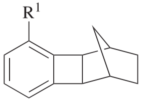
2.0 eq

$Pd(OAc)_2$ (20 mol %),
N1 (2 eq),
K_2CO_3 (5.2 eq),
KOAc (5.2 eq),
DMF, N_2, 55 °C, 72 h



I

+

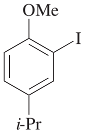


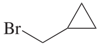
II

R^1	R^2	Conv (%)	**I/II**
i-Pr	*n*-Bu	59	60:40
n-Bu	*n*-Pr	100	76:24
n-Bu	*i*-Pr	31	25:75
n-Bu	*n*-Oct	62	73:27
t-Bu	*n*-Pr	20	42:58

47

C_9

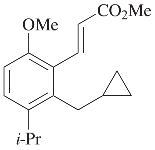




3.0 eq

1.5 eq

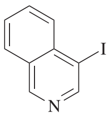
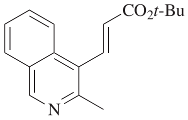
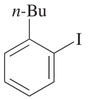
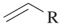
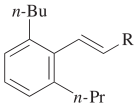
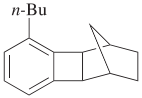
$Pd(MeCN)_2Cl_2$ (10 mol %),
L8 (20 mol %),
L9 (10 mol %),
(±)-**N6** (1 eq),
Cs_2CO_3 (3 eq),
toluene/1,4-dioxane (1:1),
N_2, 100 °C, 16 h



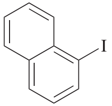
(71%)

53

TABLE 1. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH SIMPLE ALKYL HALIDES (*Continued*)

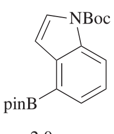
Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_9					
 2.0 eq	$PO(OMe)_3$ 2.0 eq		$Pd(OAc)_2$ (10 mol %), **L2** (22 mol %), **N1** (2 eq), Cs_2CO_3 (2.5 eq), DMA, Ar, 80 °C, 15 h	 (41%)	52
C_{10}					
	*n*-PrI 6.6 eq	 1.2 eq	$Pd(OAc)_2$ (20 mol %), **N1** (2 eq), K_2CO_3 (5.2 eq), KOAc (5.2 eq), DMF, N_2, 55 °C, 72 h	 **I** +  **II**	47

R	Conv (%)	**I/II**
MeOC	43	71:29
Ph	22	46:54
$4\text{-}FC_6H_4$	43	67:33
$4\text{-}MeC_6H_4$	21	50:50



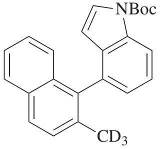
CD_3OTs

2.0 eq



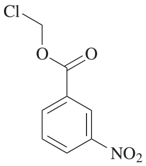
2.0 eq

$Pd(OAc)_2$ (10 mol %),
PPh_3 (11 mol %),
(±)-**N2** (2 eq),
Cs_2CO_3 (2.5 eq),
toluene, Ar, 80 °C, 15 h

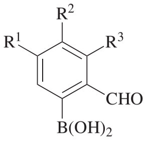


(83%)

52

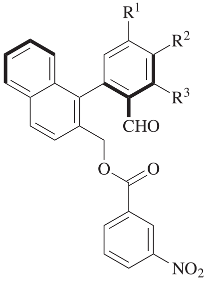


2.5 eq



2.0 eq

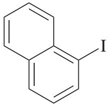
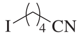
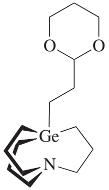
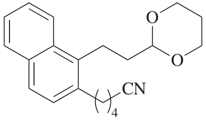
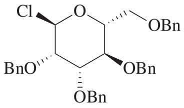
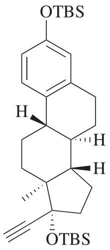
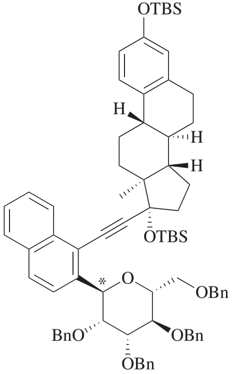
$Pd(TFA)_2$ (10 mol %),
L10 (11 mol %),
(±)-**N7** (2 eq),
K_2CO_3 (3 eq),
MeCN, N_2, 60 °C, 22 h



43

R^1	R^2	R^3	Yield (%)	er
H	H	H	76	91.0:9.0
H	H	F	61	94.0:6.0
H	F	H	54	90.0:10.0
H	H	Cl	58	95.0:5.0
H	Cl	H	60	90.0:10.0
H	H	MeO	28	93.0:7.0
H	CF_3	H	54	90.0:10.0
Me	H	H	75	88.0:12.0

TABLE 1. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH SIMPLE ALKYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_{10}					
	 2.0 eq	 1.0 eq	$PdBr_2$ (5 mol %), **L3** (10 mol %), **N1** (2 eq), Cs_2CO_3 (2 eq), MeCN, Ar, 100 °C, 14 h	 (75%)	60
1.5 eq	 1.5 eq		$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %), (±)-**N4** (2 eq), K_2CO_3 (3 eq), MeCN, N_2, 100 °C, 24 h	 (31%) *α/β > 20:1	58

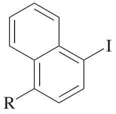
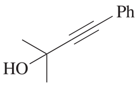
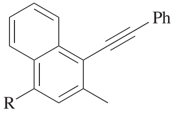
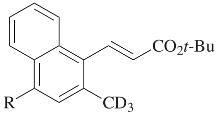
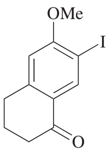
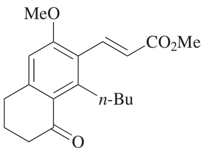
 2.0 eq	MeOTs 2.0 eq		$Pd_2(dba)_3$ (5 mol %), **L2** (11 mol %), (±)-**N2** (2 eq), Cs_2CO_3 (2.5 eq), MeCN, Ar, 100 °C, 15 h	 R Yield (%) H 58 Br 60	52
2.0 eq	CD_3OTs 2.0 eq		$Pd_2(dba)_3$ (5 mol %), **L2** (11 mol %), (±)-**N2** (2 eq), Cs_2CO_3 (2.5 eq), MeCN, Ar, 80 °C, 15 h	 R Yield (%) H 96 Br 94	52
	*n*-BuI 3.0 eq	 1.5 eq	$Pd(MeCN)_2Cl_2$ (10 mol %), **L8** (20 mol %), **L9** (10 mol %), (±)-**N6** (1 eq), K_2CO_3 (3 eq), toluene/1,4-dioxane (1:1), N_2, 100 °C, 16 h	 (52%)	53

TABLE 1. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH SIMPLE ALKYL HALIDES (*Continued*)

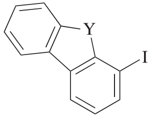
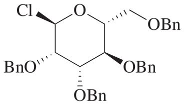
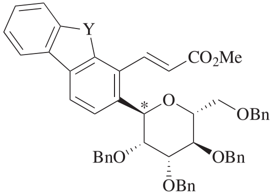
Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_{12}					
	 1.5 eq	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %), (±)-**N3** (2 eq), Cs_2CO_3 (3 eq), THF, N_2, 100 °C, 24 h	 Y · Yield (%) · *α/β O · 46 · >20:1 S · 38 · >20:1	58

TABLE 2. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ALKYLATING REAGENTS

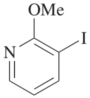
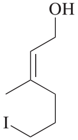
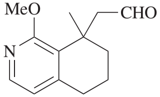
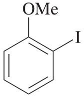
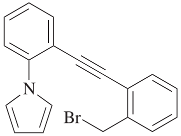
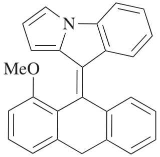
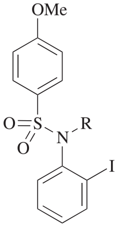
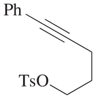
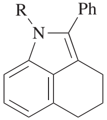
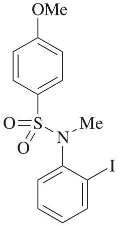
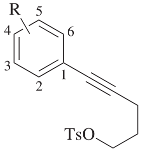
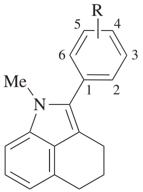
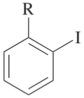
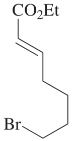
Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_5				
 1.2 eq		$[Pd(allyl)Cl]_2$ (5 mol %), **L11** (11 mol %), (±)-**N8** (20 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 70 °C, 5–24 h	 (62%)	7
C_6				
 2.0 eq		$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %), **N1** (2 eq), Cs_2CO_3 (3 eq), MeCN, Ar, 90 °C, 24 h	 (41%) (*Z*)/(*E*) = 1:1	4
	 2.0 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), **N1** (2 eq), Cs_2CO_3 (4 eq), CsI (2 eq), DMF, Ar, 130 °C, 20 h	 R — Yield (%) Et — 49 *n*-Pr — 40	73

TABLE 2. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ALKYLATING REAGENTS (*Continued*)

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_6				
	 2.0 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), **N1** (2 eq), Cs_2CO_3 (4 eq), CsI (2 eq), DMF, Ar, 130 °C, 20 h	 R — Yield (%) 3-F — 56 4-F — 58 4-Cl — 52 $4-O_2N$ — 50 3-MeO — 51 4-MeO — 47 2-Me — 23 3-Me — 53 4-Me — 57 $4-CF_3$ — 45 $4-MeO_2C$ — 42 4-*t*-Bu — 52 4-Ph — 54	73

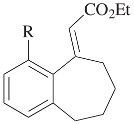
$C_{6–7}$





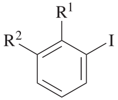
4.0 eq

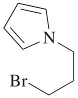
$Pd(OAc)_2$ (10 mol %),
L2 (20 mol %),
N1 (2 eq), Cs_2CO_3 (2 eq),
MeCN, Ar, reflux, 12 h



R	Yield (%)
MeO	93
Me	83
$TBSOCH_2$	47
$MeOCH_2$	25

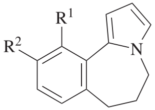
2





2.0 eq

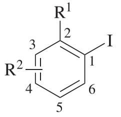
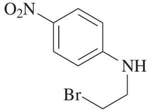
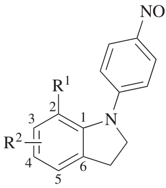
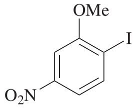
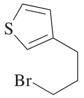
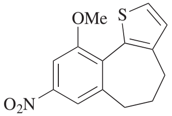
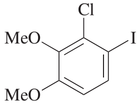
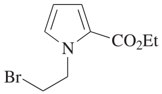
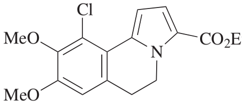
$Pd(OAc)_2$ (10 mol %),
L2 (22 mol %),
N1 (2 eq), Cs_2CO_3 (2 eq),
MeCN, N_2, 90 °C, 23 h

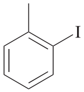
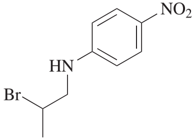
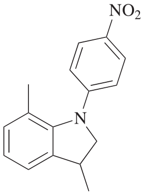
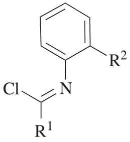
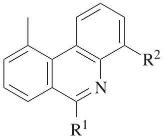


R^1	R^2	Yield (%)
TsMeN	H	69
Me	O_2N	74

10

TABLE 2. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ALKYLATING REAGENTS (*Continued*)

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_{6-8}				
 2.0 eq		$Pd(OAc)_2$ (10 mol %), **L2** (22 mol %), **N1** (4 eq), Cs_2CO_3 (4 eq), MeCN, N_2, 135 °C, 20 h	 R^1 / R^2 / Yield (%) Cl / 5-Cl / 50 Me / 3-Cl / 80 Me / 5-F / 64 Me / 5-Me / 24	66
C_6				
	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %), **N1** (2 eq), Cs_2CO_3 (2 eq), MeCN, N_2, 85 °C	 (52%)	65
 1.0 eq	 2.0 eq	$PdCl_2$ (10 mol %), **L2** (22 mol %), **N1** (2 eq), Cs_2CO_3 (2 eq), MeCN, N_2, 90 °C, 23 h	 (59%)	10

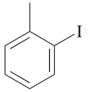
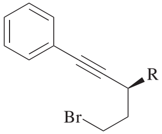
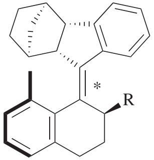
C_7	 2.0 eq		$Pd(OAc)_2$ (10 mol %), **L7** (22 mol %), **N1** (3 eq), Cs_2CO_3 (4 eq), DMF, N_2, 135 °C, 16 h		(55%)	66
		 1.2 eq	$Pd(OAc)_2$ (10 mol %), **L12** (20 mol %), **N1** (1 eq), K_3PO_4 (4 eq), toluene, N_2, 100 °C, 12 h			196

R^1	R^2	Yield (%)
$CClF_2$	H	79
$CBrF_2$	H	58
C_2F_5	H	65
CHF_2	Me	94
$CClF_2$	Me	93
C_2F_5	Me	97

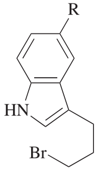
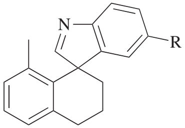
TABLE 2. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ALKYLATING REAGENTS (*Continued*)

*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*

C$_7$

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
 2.0 eq	 **I**	Pd(OAc)$_2$ (10 mol %), **L2** (20 mol %), **N1** (8 eq), Cs$_2$CO$_3$ (3 eq), MeCN, Ar, 90 °C, 16 h	 **II**	70

R	er **I**	**II** Yield (%)	**II** *dr	**II** er
CbzHN	99.25:0.75	77	5.3:1	97.0:3.0
BnO	>99.5:0.5	71	6.6:1	99.5:0.5

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
	 1.5 eq	[Pd(allyl)Cl]$_2$ (5 mol %), **L2** (10 mol %), **N1** (3 eq), K$_2$CO$_3$ (3 eq), MeCN, N$_2$, 90 °C		64

R	Yield (%)
F	54
Me	48
Et	50
t-Bu	63

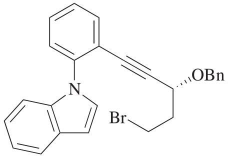
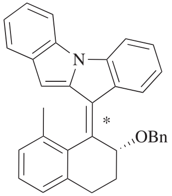
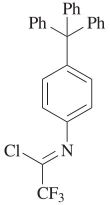
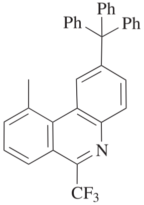
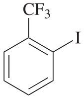
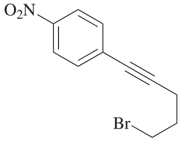
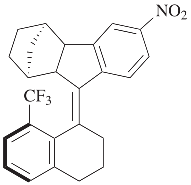
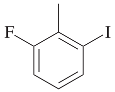
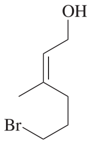
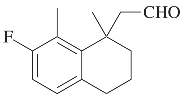
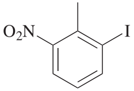
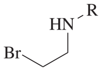
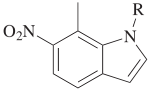
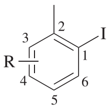
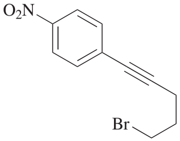
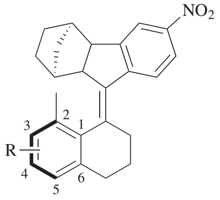
2.0 eq		Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), **N1** (2 eq), Cs$_2$CO$_3$ (3 eq), MeCN, Ar, 90 °C, 24 h		(90%) *dr = 10:1 er > 99.0:1.0	4
	 1.2 eq	Pd(OAc)$_2$ (10 mol %), **L12** (20 mol %), **N1** (1 eq), K$_3$PO$_4$ (4 eq), toluene, N$_2$, 100 °C, 12 h		(65%)	196
	 2.0 eq	Pd(OAc)$_2$ (10 mol %), **L2** (20 mol %), **N1** (3 eq), Cs$_2$CO$_3$ (3 eq), MeCN, Ar, 90 °C, 24 h		(87%)	3

TABLE 2. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ALKYLATING REAGENTS (*Continued*)

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
Please refer to the Charts preceding the tables for structures corresponding to the ***bold*** *numbers.*				
C_7				
 1.2 eq		$[Pd(allyl)Cl]_2$ (5 mol %), **L11** (11 mol %), (±)-**N8** (20 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 70 °C, 5–24 h	 (72%)	7
 2.0 eq		$Pd(OAc)_2$ (10 mol %), **L2** (22 mol %), **N1** (3 eq), Cs_2CO_3 (4 eq), MeCN, N_2, 135 °C, 20 h	 R — Yield (%) Ph — 53 $4\text{-}O_2NC_6H_4$ — 70	66
	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %), **N1** (3 eq), Cs_2CO_3 (3 eq), MeCN, Ar, 90 °C, 24 h	 R — Yield (%) 3-Cl — 62 3-AcHN — 60 5-F — 85	3

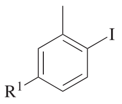
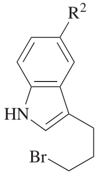
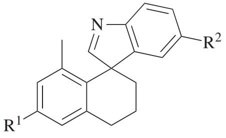
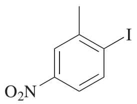
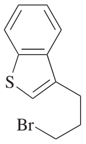
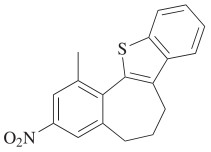
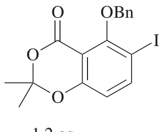
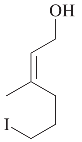
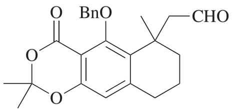
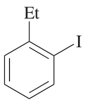
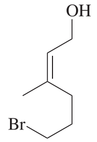
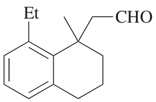
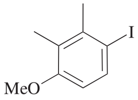
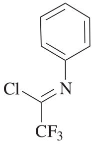
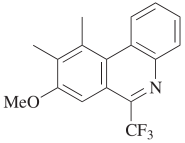
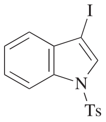
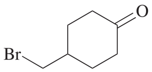
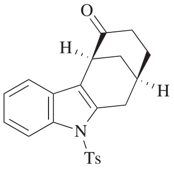
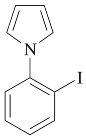
	 1.5 eq	[Pd(allyl)Cl]$_2$ (5 mol %), **L2** (10 mol %), **N1** (3 eq), K$_2$CO$_3$ (3 eq), MeCN, Ar, 90 °C	 R^1 R^2 Yield (%) Cl *t*-Bu 50 Br Et 44		64
	 2.0 eq	Pd(OAc)$_2$ (10 mol %), **L2** (20 mol %), **N1** (2 eq), Cs$_2$CO$_3$ (2 eq), MeCN, N$_2$, 105 °C, 18 h		(63%)	65
 1.2 eq		[Pd(allyl)Cl]$_2$ (5 mol %), **L11** (11 mol %), (±)-**N8** (20 mol %), K$_2$CO$_3$ (2.5 eq), MeCN, Ar, 70 °C, 12 h		(76%)	7

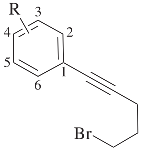
TABLE 2. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ALKYLATING REAGENTS (*Continued*)

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_8				
 1.2 eq		[Pd(allyl)Cl]$_2$ (5 mol %), **L11** (11 mol %), (±)-**N8** (20 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 70 °C, 5–24 h	 (73%)	7
	 1.2 eq	Pd(OAc)$_2$ (10 mol %), **L12** (20 mol %), **N1** (1 eq), K_3PO_4 (4 eq), toluene, N_2, 100 °C, 12 h	 (78%)	196
	 3.5 eq	Pd(OAc)$_2$ (10 mol %), **L14** (20 mol %), **L15** (20 mol %), (±)-**N9** (2 eq), K_3PO_4 (4 eq), 1,4-dioxane, N_2, 100 °C, 48 h	 (48%) er = 95.5:4.5	46

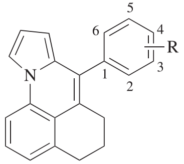
C$_{10}$



2.0 eq



PdCl$_2$ (5 mol %),
L2 (10 mol %),
N1 (1 eq), Cs$_2$CO$_3$ (3 eq),
MeCN, Ar, 90 °C, 24 h



LKB

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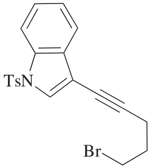
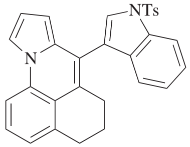
R	Yield (%)
2-Cl	72
2-O$_2$N	81
4-O$_2$N	72
2-AcHN	25
2-MeO	90
2,6-(MeO)$_2$	47
2-CF$_3$	51
3-EtO$_2$C	60
4-Me	85

2.0 eq



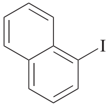
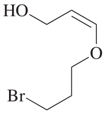
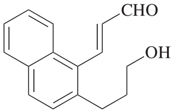
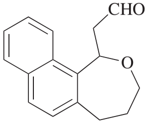
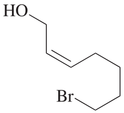
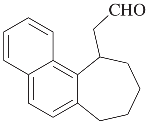
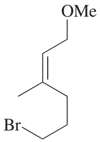
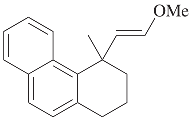
PdCl$_2$ (5 mol %),
L2 (10 mol %),
N1 (1 eq), Cs$_2$CO$_3$ (3 eq),
MeCN, Ar, 90 °C, 24 h



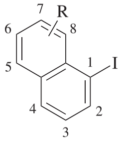
(75%)

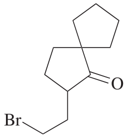
71

TABLE 2. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ALKYLATING REAGENTS (*Continued*)

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
Please refer to the Charts preceding the tables for structures corresponding to the ***bold*** *numbers.*				
C_{10}				
 1.2 eq		[Pd(allyl)Cl]$_2$ (5 mol %), **L11** (11 mol %), (±)-**N8** (20 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 70 °C, 12 h	 (44%) +  (21%)	7
1.2 eq		[Pd(allyl)Cl]$_2$ (5 mol %), **L11** (11 mol %), (±)-**N8** (20 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 70 °C, 15 h	 (76%)	7
1.2 eq		[Pd(allyl)Cl]$_2$ (5 mol %), **L11** (11 mol %), (±)-**N8** (20 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 70 °C, 15 h	 (81%) (*E*)/(*Z*) = 1.8:1	7

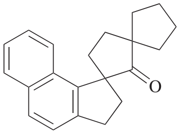
C$_{10-11}$





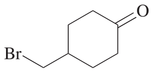
3.5 eq

Pd(OAc)$_2$ (10 mol %),
L13 (20 mol %),
N1 (2 eq),
Cs$_2$CO$_3$ (4 eq),
THF, Ar, 60 °C, 18 h



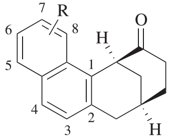
(40%)

5



3.5 eq

Pd(OAc)$_2$ (10 mol %),
L14 (20 mol %),
L15 (20 mol %),
(±)-**N9** (2 eq), K$_3$PO$_4$ (4 eq),
1,4-dioxane, N$_2$, 80 °C, 36 h



R	Yield (%)	er
H	69	97.5:2.5
5-Br	53	98.0:2.0
4-MeO	60	97.0:3.0
5-MeO	66	96.0:4.0
7-MeO	69	98.5:1.5
5-*i*-PrO	53	96.5:3.5
5-BnO	50	97.5:2.5
7-BnO	69	98.0:2.0
7-TIPSO	58	96.5:3.5
4-Me	62	98.0:2.0

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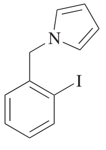
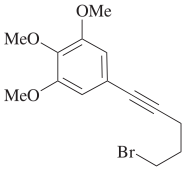
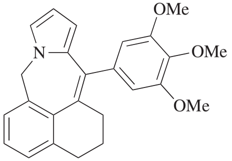
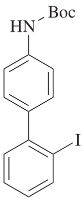
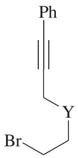
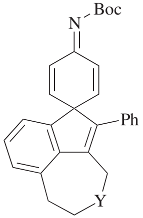
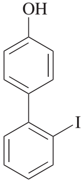
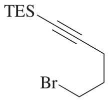
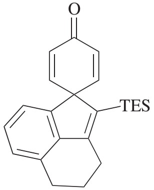
TABLE 2. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ALKYLATING REAGENTS (*Continued*)

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_{11}				
 1.2 eq		$PdCl_2$ (10 mol %), **L2** (20 mol %), **N1** (1 eq), Cs_2CO_3 (3 eq), MeCN, Ar, 90 °C, 24 h	 (20%)	72
C_{12}				
	 1.5 eq	$Pd(OAc)_2$ (5 mol %), **L2** (10 mol %), **N1** (30 mol %), Cs_2CO_3 (2 eq), DMF, Ar, 90 °C, 10 h	 Y — Yield (%) TsN — 87 O — 79	8
	 1.5 eq	$Pd(OAc)_2$ (5 mol %), **L2** (10 mol %), **N1** (30 mol %), Cs_2CO_3 (2 eq), DMF, Ar, 90 °C, 10 h	 (79%)	8

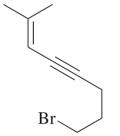
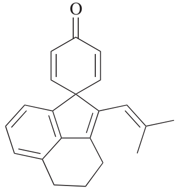
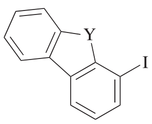
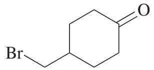
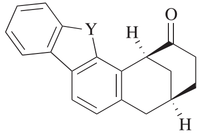
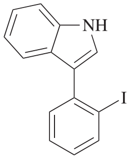
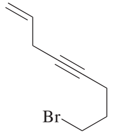
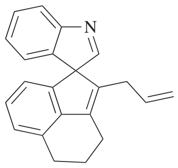
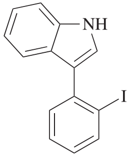
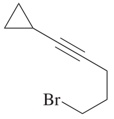
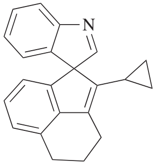
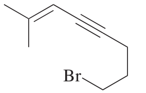
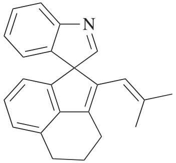
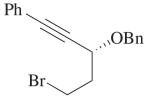
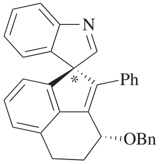
	 1.5 eq	Pd(OAc)$_2$ (5 mol %), **L2** (10 mol %), **N1** (30 mol %), Cs$_2$CO$_3$ (2 eq), DMF, Ar, 90 °C, 10 h		(81%)	8
		 3.5 eq	Pd(OAc)$_2$ (10 mol %), **L14** (20 mol %), **L15** (20 mol %), (±)-**N9** (2 eq), K$_3$PO$_4$ (4 eq), 1,4-dioxane, N$_2$, 80 °C, 36 h	 Y Yield (%) er O 68 93.5:6.5 S 51 97.5:2.5		46
C$_{14}$		 1.5 eq	Pd(OAc)$_2$ (10 mol %), **L2** (20 mol %), **N1** (0.5 eq), K$_3$PO$_4$ (2 eq), THF/DMF (4:1), Ar, 65 °C, 10 h		(87%)	6

TABLE 2. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ALKYLATING REAGENTS (*Continued*)

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C$_{14}$ 	 1.5 eq	Pd(OAc)$_2$ (5 mol %), **L2** (10 mol %), **N1** (0.5 eq), K$_3$PO$_4$ (2 eq), THF/DMF (4:1), Ar, 65 °C, 10 h	 (88%)	6
	 1.5 eq	Pd(OAc)$_2$ (5 mol %), **L2** (10 mol %), **N1** (0.5 eq), K$_3$PO$_4$ (2 eq), THF/DMF (4:1), Ar, 65 °C, 10 h	 (90%)	6
	 1.5 eq	Pd(OAc)$_2$ (10 mol %), **L2** (20 mol %), **N1** (0.5 eq), K$_3$PO$_4$ (2 eq), THF/DMF (4:1), Ar, 65 °C, 10 h	 (71%) *dr = 4:1	6

C_{16}

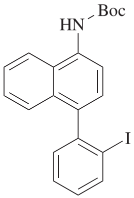
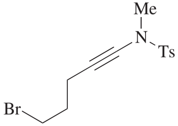
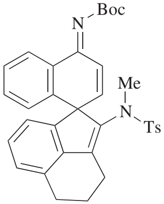
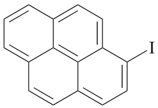
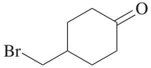
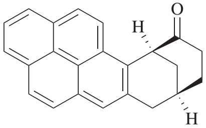
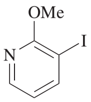
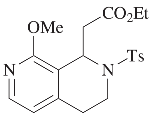
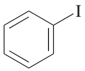
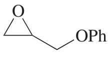
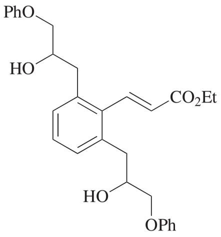
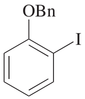
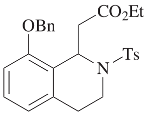
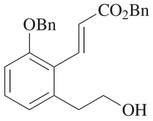
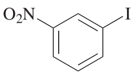
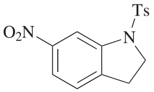
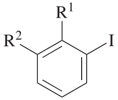
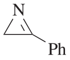
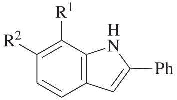
	 1.5 eq	$Pd(OAc)_2$ (5 mol %), **L2** (10 mol %), **N1** (0.3 eq), Cs_2CO_3 (2 eq), DMF, Ar, 90 °C, 10 h	 (91%)	8
	 3.5 eq	$Pd(OAc)_2$ (10 mol %), **L14** (20 mol %), **L15** (20 mol %), (±)-**N9** (2 eq), K_3PO_4 (4 eq), 1,4-dioxane, N_2, 80 °C, 36 h	 (52%) er = 98.0:2.0	46

TABLE 3. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH THREE-MEMBERED HETEROCYCLES

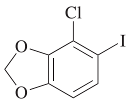
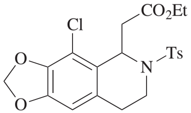
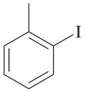
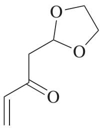
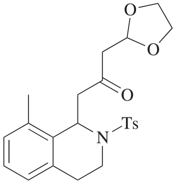
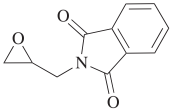
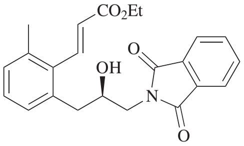
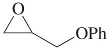
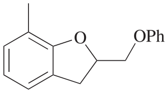
Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_5					
 1.2 eq		 1.5 eq	$Pd(OAc)_2$ (10 mol %), **L2** (24 mol %), **N10** (20 mol %), K_2CO_3 (2 eq), MeCN, Ar, 70 °C, 16–24 h	 (74%)	76
C_6					
 1.3 eq	 2.0 eq		$Pd(OAc)_2$ (2.5 mol %), **L11** (6 mol %), (±)-**N11** (50 mol %), NMP, Ar, 60 °C, 12 h	 (76%) dr = 1:1	62
 1.2 eq		 1.5 eq	$Pd(OAc)_2$ (10 mol %), **L2** (24 mol %), **N10** (20 mol %), K_2CO_3 (2 eq), MeCN, Ar, 70 °C, 16–24 h	 (71%)	76

	1.3 eq	 2.0 eq		Pd(OAc)$_2$ (10 mol %), **L11** (24 mol %), (±)-**N11** (50 mol %), NMP, Ar, 60 °C, 12 h		(90%)	62
		 2.5 eq	Intramolecular	Pd(OAc)$_2$ (10 mol %), **L13** (20 mol %), **N1** (50 mol %), K$_2$CO$_3$ (2 eq), toluene, N$_2$, 100 °C, 24 h		(58%)	75
C$_{6–8}$		 1.0 eq	Intramolecular	Pd(OAc)$_2$ (10 mol %), **L13** (25 mol %), **N1** (2 eq), Cs$_2$CO$_3$ (3 eq), MeCN, Ar, 110 °C, 16 h			74

R^1	R^2	Yield (%)
Cl	H	64
MeO	H	54
Me	H	55
Me	F	55
Me	CF$_3$	64

TABLE 3. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH THREE-MEMBERED HETEROCYCLES (*Continued*)

*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
C_6					
 1.2 eq		 1.5 eq	$Pd(OAc)_2$ (10 mol %), **L2** (24 mol %), **N10** (20 mol %), K_2CO_3 (2 eq), MeCN, Ar, 70 °C, 16–24 h	 (86%)	76
C_7					
 1.2 eq		 1.5 eq	$Pd(OAc)_2$ (10 mol %), **L2** (24 mol %), **N10** (20 mol %), K_2CO_3 (2 eq), MeCN, Ar, 70 °C, 16–24 h	 (50%)	76
1.3 eq	 2.0 eq		$Pd(OAc)_2$ (5 mol %), **L11** (12 mol %), (±)-**N11** (50 mol %), NMP, Ar, 60 °C, 12 h	 (75%) er > 99.5:0.5	62
	 4.0 eq	Intramolecular	**C2** (10 mol %), (–)-**N12** (20 mol %), NaOAc (1.5 eq), DMF, N_2, 120 °C, 24 h	 (92%) er = 69.0:31.0	78

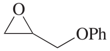
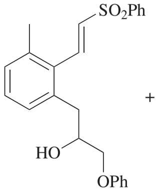
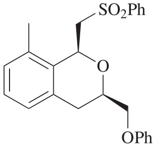
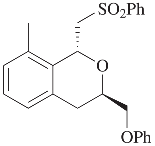
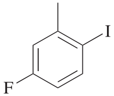
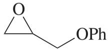
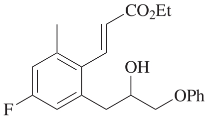
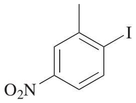
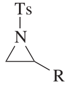
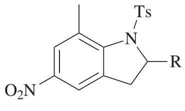
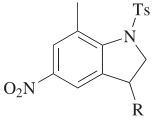
1.3 eq	 2.0 eq		$Pd(OAc)_2$ (5 mol %), **L11** (12 mol %), (±)-**N11** (50 mol %), NMP, Ar, 60 °C, 12 h	 **I** +  **II** +  **III** **I–III** (91%) **I/II/III** = 63:25:12	62
 1.3 eq	 2.0 eq		$Pd(OAc)_2$ (2.5 mol %), **L11** (6 mol %), (±)-**N11** (50 mol %), NMP, Ar, 60 °C, 12 h	 (69%)	62

TABLE 3. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH THREE-MEMBERED HETEROCYCLES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
Please refer to the Charts preceding the tables for structures corresponding to the ***bold*** *numbers.*					
C_7					
	 2.0 eq	Intramolecular	$Pd(OAc)_2$ (10 mol %), **L13** (20 mol %), **N1** (50 mol %), H_2O (2 eq), K_2CO_3 (2 eq), toluene/DME (1:1), N_2, 105 °C, 30 h	 **I** +  **II**	75

R	Yield (%) I + II	I/II
Me	71	>20:1
Et	61	>20:1
Ph	75	1:2.7
4-ClC_6H_4	74	1:2
2-MeC_6H_4	61	1:1.6
3-MeC_6H_4	66	1:1.9
4-MeC_6H_4	75	1:4
4-$MeO_2CC_6H_4$	66	1:1.3
Bn	41	>20:1
2-Np	78	1:2.9

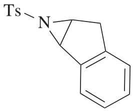
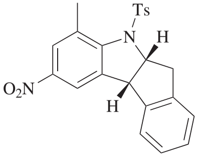
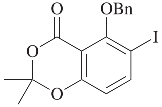
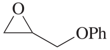
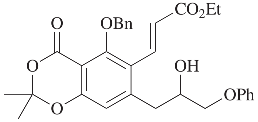
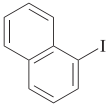
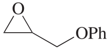
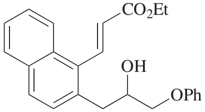
		 2.0 eq	Intramolecular	Pd(OAc)$_2$ (10 mol %), **L13** (20 mol %), **N1** (50 mol %), H_2O (2 eq), K_2CO_3 (2 eq), toluene/DME (1:1), N_2, 105 °C, 30 h		(66%)	75
	 1.3 eq	 2.0 eq		Pd(OAc)$_2$ (10 mol %), **L11** (24 mol %), (±)-**N11** (50 mol %), NMP, Ar, 60 °C, 12 h	 (95%)		62
C_{10}	 1.3 eq	 2.0 eq		Pd(OAc)$_2$ (2.5 mol %), **L11** (6 mol %), (±)-**N11** (50 mol %), NMP, Ar, 60 °C, 12 h		(85%)	62

TABLE 3. PALLADIUM(0)-CATALYZED *ORTHO*-ALKYLATION OF ARYL HALIDES WITH THREE-MEMBERED HETEROCYCLES (*Continued*)

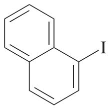
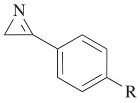
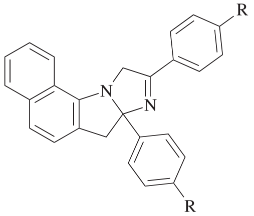
Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_{10}					
	 4.0 eq	Intramolecular	$Pd(OAc)_2$ (10 mol %), **L13** (45 mol %), **N1** (8 eq), Cs_2CO_3 (3 eq), MeCN, Ar, 90 °C, 16 h	 R Yield (%) H 86 F 63 MeO 41	74

TABLE 4. PALLADIUM(0)-CATALYZED *ORTHO*-ARYLATION OF ARYL HALIDES WITH SIMPLE ARYL HALIDES

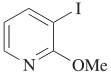
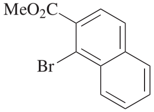
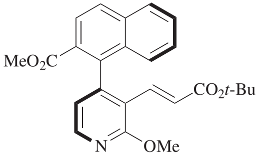
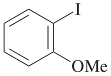
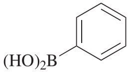
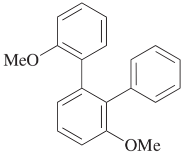
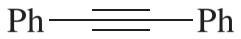
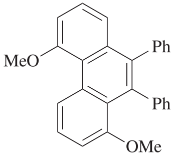
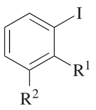
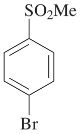
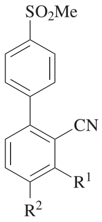
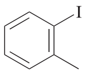
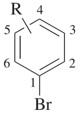
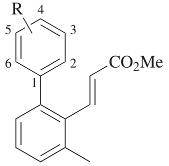
Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_5					
 1.5 eq		 1.5 eq	$Pd(OAc)_2$ (10 mol %), (+)-**N13** (50 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 105 °C, 24 h	 (53%) er = 98.0:2.0	97
C_6					
 2.0 eq	—	 1.2 eq	$Pd(OAc)_2$ (1 mol %), **N1** (1 eq), K_2CO_3 (4 eq), DMF, N_2, 105 °C, 90 h	 (82%)	83
2.0 eq	—		$Pd(OAc)_2$ (10 mol %), **N1** (0.5 eq), *n*-Bu_4NBr (6 eq), K_2CO_3 (3 eq), DMF, N_2, 105 °C, 24 h	 (64%)	81

TABLE 4. PALLADIUM(0)-CATALYZED *ORTHO*-ARYLATION OF ARYL HALIDES WITH SIMPLE ARYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_{6-7}					
	 1.5 eq	$K_4[Fe(CN)_6]•3H_2O$ 5.5 eq	$Pd(OAc)_2$ (2.5 mol %), **L2** (6 mol %), **N1** (1.5 eq), Cs_2CO_3 (1.5 eq), MeCN, 130 °C, MW, 2 h	 R^1 / R^2 / Yield (%) Cl / H / 31 MeO / H / 54 Me / H / 78 Me / Cl / 62	50
C_7					
	 1.0 eq	 1.6 eq	$Pd(OAc)_2$ (2 mol %), **N1** (1 eq), K_2CO_3 (2.4 eq), DMF, N_2, 105 °C, 24 h	 R / Yield (%) 2-MeO_2C / 80 3-CF_3 / 71 4-CF_3 / 80 4-NC– / 79	87

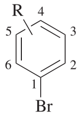
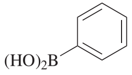
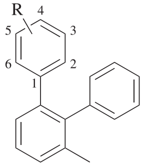
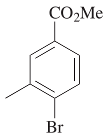
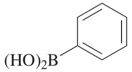
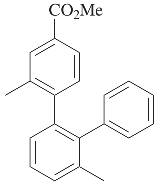
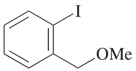
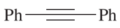
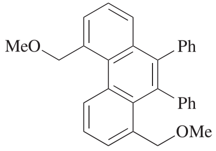
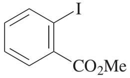
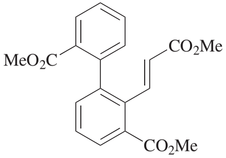
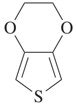
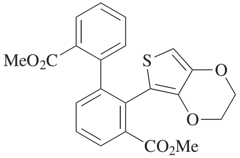
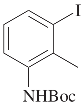
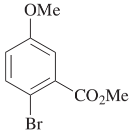
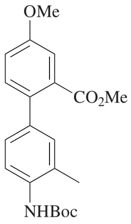
	 1.0 eq	 1.2 eq	Pd(OAc)$_2$ (2 mol %), **N1** (0.5 eq), K$_2$CO$_3$ (4 eq), DMF, N$_2$, 105 °C, 24 h	 R — Yield (%) 2-O$_2$N — 40 3-CF$_3$ — 60 4-CF$_3$ — 66 4-MeO$_2$C — 61	88
	 1.0 eq	 1.2 eq	Pd(OAc)$_2$ (2 mol %), **N1** (0.5 eq), K$_2$CO$_3$ (4 eq), DMF, N$_2$, 105 °C, 24 h	 (55%)	88
 2.0 eq	—		Pd(OAc)$_2$ (10 mol %), **N1** (0.5 eq), *n*-Bu$_4$NBr (6 eq), K$_2$CO$_3$ (3 eq), DMF, N$_2$, 105 °C, 24 h	 (51%)	81

TABLE 4. PALLADIUM(0)-CATALYZED *ORTHO*-ARYLATION OF ARYL HALIDES WITH SIMPLE ARYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_7					
 1.7 eq	—		$Pd(OAc)_2$ (4 mol %), **N1** (0.5 eq), K_2CO_3 (1.7 eq), DMF, N_2, 105 °C, 6 h	 (98%)	82
	—	 5.0 eq	$Pd(OAc)_2$ (1 mol %), **N1** (0.25 eq), K_2CO_3 (1 eq), DMF, N_2, 105 °C, 24 h	 (82%)	86
	 1.0 eq	DME	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), **N1** (1 eq), Cs_2CO_3 (2 eq), DME, Ar, 90 °C, 14 h	 (56%)	20

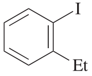
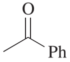
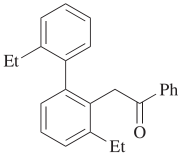
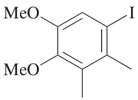
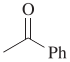
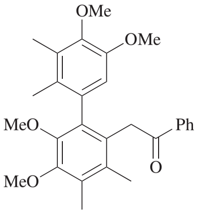
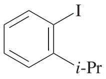
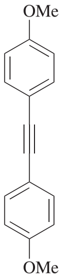
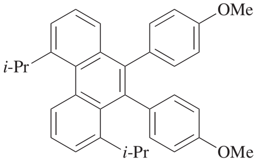
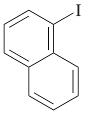
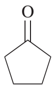
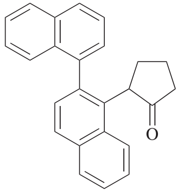
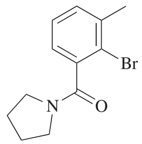
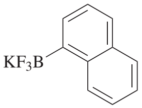
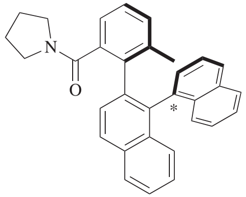
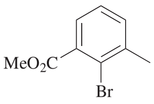
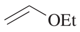
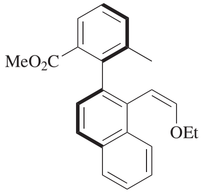
C_8							
		—	 1.25 eq	$Pd(OAc)_2$ (1 mol %), **N1** (0.25 eq), KOPh (0.1 eq), K_2CO_3 (1.1 eq), DMF, N_2, 105 °C, 16 h		(74%)	85
		—	 1.25 eq	$Pd(OAc)_2$ (2.5 mol %), **N1** (0.25 eq), KOPh (0.1 eq), K_2CO_3 (1.1 eq), DMF, N_2, 105 °C, 48 h		(79%)	85
C_9							
	 2.0 eq	—		$Pd(OAc)_2$ (5 mol %), **N1** (0.5 eq), *n*-Bu_4NBr (6 eq), K_2CO_3 (3 eq), DMF, N_2, 105 °C, 24 h		(80%)	81

TABLE 4. PALLADIUM(0)-CATALYZED *ORTHO*-ARYLATION OF ARYL HALIDES WITH SIMPLE ARYL HALIDES (*Continued*)

*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
C_{10}					
	—	 1.25 eq	$Pd(OAc)_2$ (2.5 mol %), **N1** (0.5 eq), KOPh (0.1 eq), K_2CO_3 (1.1 eq), DMF, N_2, 105 °C, 6 h	 (71%)	85
	 1.5 eq	 3.0 eq	$Pd(OAc)_2$ (10 mol %), (+)-**N14** (50 mol %), K_2CO_3 (2.5 eq), 4 Å MS, DCE, Ar, 120 °C, 24 h	 (63%) *dr > 20:1 er > 99.5:0.5	99
1.5 eq		 1.5 eq	$Pd(OAc)_2$ (10 mol %), (+)-**N13** (50 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 105 °C, 24 h	 (53%) (*Z*)/(*E*) = 1.2:1 er (*Z*) = 98.5:1.5 er (*E*) = 99.5:0.5	97

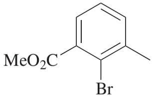
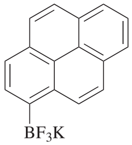
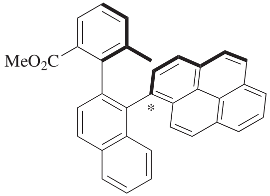
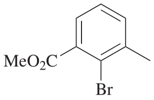
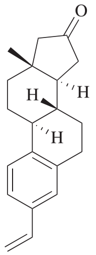
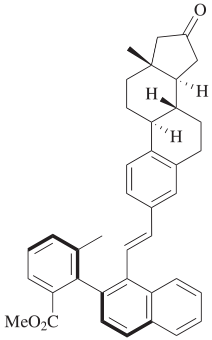
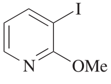
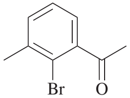
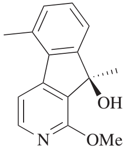
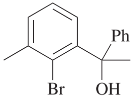
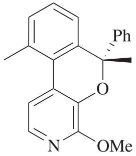
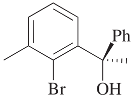
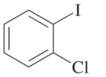
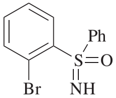
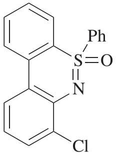
	 1.5 eq	 2.0 eq	Pd(OAc)$_2$ (10 mol %), (+)-**N14** (50 mol %), K_2CO_3 (2.5 eq), 4 Å MS, THF, Ar, 110 °C, 24 h	 (86%) *dr = 8.3:1 er (major) > 99.0:1.0 er (minor) > 98.5:1.5	99
1.5 eq		 1.5 eq	Pd(OAc)$_2$ (10 mol %), (+)-**N13** (50 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 105 °C, 24 h	 (88%) dr = 98.0:2.0	97

TABLE 5. PALLADIUM(0)-CATALYZED *ORTHO*-ARYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ARYL HALIDES

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_5				
 1.5 eq		$Pd(OAc)_2$ (10 mol %), **L2** (22 mol %), (+)-**N14** (20 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 120 °C	 (68%) er > 99.5:0.5	97
	 1.25 eq	$Pd(OAc)_2$ (2.5 mol %), **L2** (10 mol %), (+)-**N14** (0.3 eq), K_2CO_3 (1.2 eq), toluene, Ar, 105 °C	 **I** +  **II** **I** + **II** (90%) **I/II** = 51:49 er **I** = 95.0:5.0 er **II** = 97.0:3.0	45
C_6				
 1.2 eq		$Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), **N1** (2 eq), K_2CO_3 (2 eq), MeCN, N_2, 105 °C, 24 h	 (67%)	103

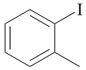
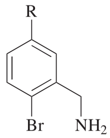
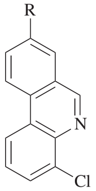
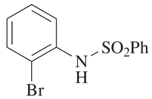
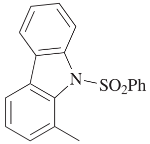
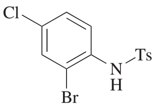
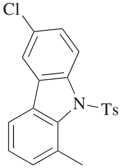
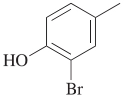
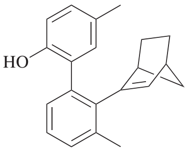
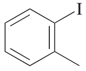
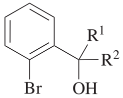
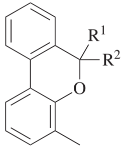
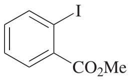
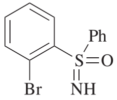
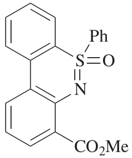
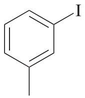
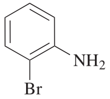
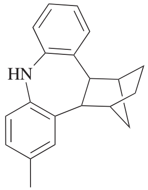
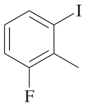
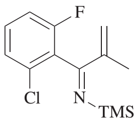
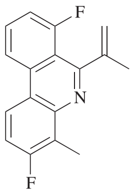
C_7	 1.1 eq		$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), **N1** (50 mol %), Cs_2CO_3 (2.1 eq), DMF, Ar, 130 °C		R Yield (%) H 31 F 46	102
	1.1 eq		$Pd(OAc)_2$ (5 mol %), **N1** (25 mol %), K_2CO_3 (2.2 eq), DMF, N_2, 105 °C, 96 h		(92%)	197
	1.1 eq		$Pd(OAc)_2$ (5 mol %), **N1** (25 mol %), K_2CO_3 (2.2 eq), DMF, N_2, 105 °C, 48 h		(90%)	197
		 1.0 eq	$Pd(OAc)_2$ (4 mol %), **N1** (1.2 eq), K_2CO_3 (3.2 eq), DMF, N_2, 105 °C, 24 h		(71%)	106

TABLE 5. PALLADIUM(0)-CATALYZED *ORTHO*-ARYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ARYL HALIDES (*Continued*)

Please refer to the Charts preceding the tables for structures corresponding to the ***bold*** *numbers.*

C_7

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
	 1.0 eq	$Pd(OAc)_2$ (2 mol %), **N1** (0.5 eq), K_2CO_3 (2.5 eq), DMF, N_2, 105 °C, 24 h	 R^1 R^2 Yield (%) Me Me 79 Me Et 84 Et Et 95	105
 1.2 eq		$Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), **N1** (2 eq), K_2CO_3 (2 eq), MeCN, N_2, 105 °C, 24 h	 (74%)	103
 1.1 eq		$Pd(OAc)_2$ (5 mol %), PPh_3 (12.5 mol %), **N1** (1.2 eq), Cs_2CO_3 (2.25 eq), DMF, N_2, 105 °C, 24 h	 (60%)	198
	 1.1 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), **N1** (8 eq), Cs_2CO_3 (3 eq), MeCN, Ar, 90 °C, 16–24 h	 (91%)	101

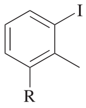
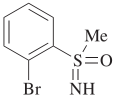
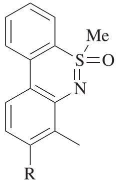
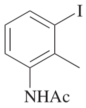
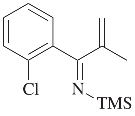
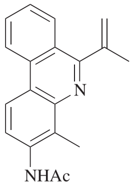
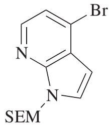
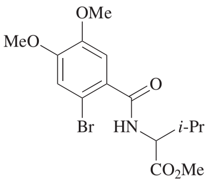
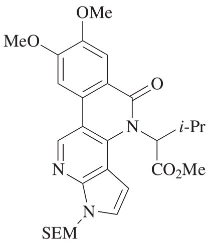
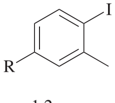
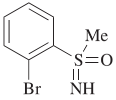
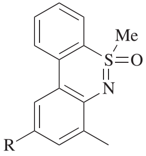
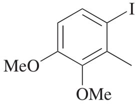
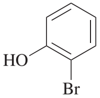
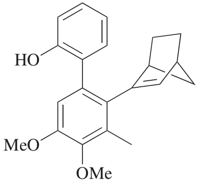
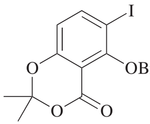
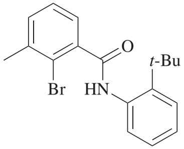
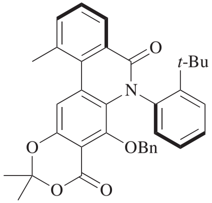
 1.2 eq		Pd(OAc)$_2$ (10 mol %), PPh$_3$ (25 mol %), **N1** (2 eq), K$_2$CO$_3$ (2 eq), MeCN, N$_2$, 85 °C, 12 h		R Yield (%) F 56 Cl 50	103
	 1.1 eq	Pd(OAc)$_2$ (10 mol %), PPh$_3$ (25 mol %), **N1** (8 eq), Cs$_2$CO$_3$ (3 eq), MeCN, Ar, 90 °C, 16–24 h		(98%)	101
	 1.05 eq	Pd(TFA)$_2$ (10 mol %), **L11** (20 mol %), **N1** (1.2 eq), Cs$_2$CO$_3$ (3 eq), toluene, Ar, 110 °C		(69%)	199

TABLE 5. PALLADIUM(0)-CATALYZED *ORTHO*-ARYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ARYL HALIDES (*Continued*)

Please refer to the Charts preceding the tables for structures corresponding to the ***bold*** *numbers.*

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
C_{7-8}				
 1.2 eq		$Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), **N1** (2 eq), K_2CO_3 (2 eq), MeCN, N_2, 85 °C, 12 h	 R — Yield (%) F — 80 Cl — 74 O_2N — 95 MeO_2C — 92	103
C_7				
	 1.0 eq	$Pd(OAc)_2$ (4 mol %), **N1** (1.2 eq), K_2CO_3 (3.2 eq), DMF, N_2, 105 °C, 66 h	 (74%)	106
 1.5 eq		$Pd(OAc)_2$ (10 mol %), **L2** (22 mol %), (+)-**N13** (50 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 70 °C, 36 h	 (45%) er = 94.5:5.5	104

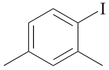
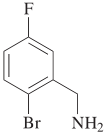
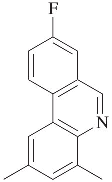
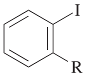
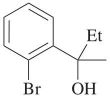
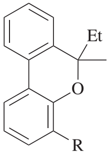
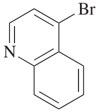
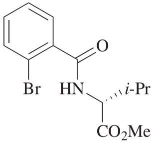
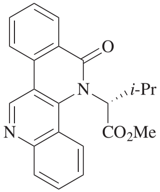
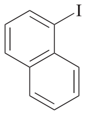
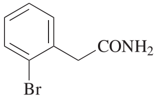
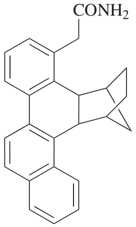
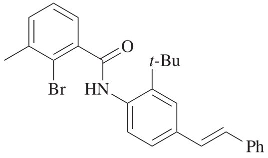
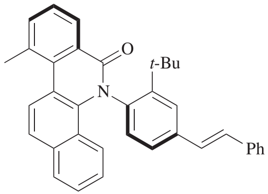
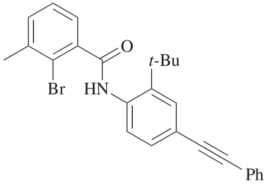
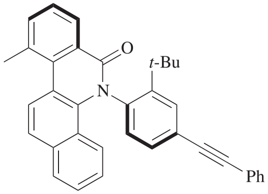
C_8	 1.1 eq		Pd(OAc)$_2$ (5 mol %), PPh$_3$ (10 mol %), **N1** (0.5 eq), Cs$_2$CO$_3$ (2.1 eq), DMF, Ar, 130 °C, 120 h		(86%)	102
C_9		 1.0 eq	Pd(OAc)$_2$ (5 mol %), **N1** (0.5 eq), K$_2$CO$_3$ (2.5 eq), DMF, N$_2$, 105 °C, 24 h		R Yield (%) *n*-Pr 90 *i*-Pr 92	105
		 1.05 eq	Pd(TFA)$_2$ (10 mol %), **L11** (20 mol %), **N1** (1.2 eq), Cs$_2$CO$_3$ (3 eq), toluene, Ar, 110 °C, 18 h		(79%)	199

TABLE 5. PALLADIUM(0)-CATALYZED *ORTHO*-ARYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ARYL HALIDES (*Continued*)

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_{10}				
	 1.0 eq	Pd(OAc)$_2$ (10 mol %), **L2** (20 mol %), **N1** (1 eq), Cs$_2$CO$_3$ (2 eq), DMF, Ar, 130 °C, 48 h	 (61%)	200
1.5 eq		Pd(OAc)$_2$ (10 mol %), **L2** (22 mol %), (+)-**N13** (50 mol %), K$_2$CO$_3$ (2.5 eq), MeCN, Ar, 70 °C, 24 h	 (91%) er = 98.5:1.5	104
1.5 eq		Pd(OAc)$_2$ (10 mol %), **L2** (22 mol %), (+)-**N13** (50 mol %), K$_2$CO$_3$ (2.5 eq), MeCN, Ar, 60 °C, 36 h	 (78%) er = 98.5:1.5	104

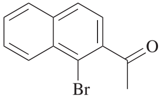
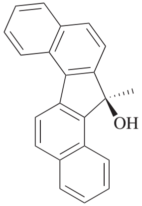
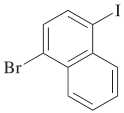
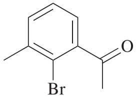
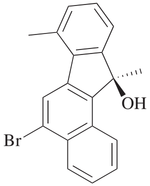
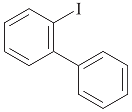
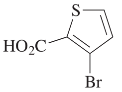
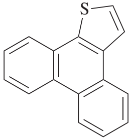
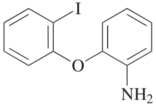
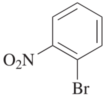
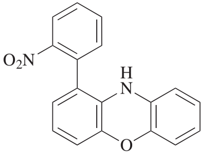
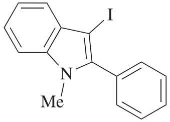
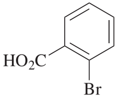
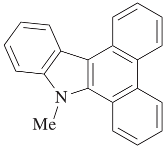
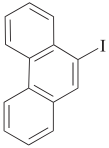
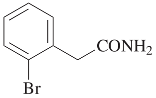
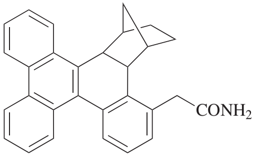
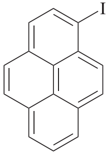
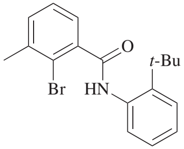
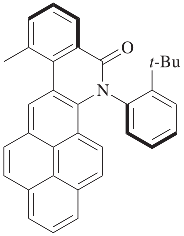
	1.5 eq		Pd(OAc)$_2$ (10 mol %), **L2** (22 mol %), (+)-**N13** (10 mol %), K$_2$CO$_3$ (2.5 eq), MeCN, Ar, 120 °C		(95%) er = 99.5:0.5	97
	 1.5 eq		Pd(OAc)$_2$ (10 mol %), **L2** (22 mol %), (+)-**N13** (20 mol %), K$_2$CO$_3$ (2.5 eq), MeCN, Ar, 120 °C		(71%) er > 99.5:0.5	97
C$_{12}$		 1.1 eq	PdCl$_2$(PPh$_3$)$_2$ (5 mol %), **N1** (2 eq), K$_2$CO$_3$ (3 eq), DMSO, N$_2$, 140 °C, 24 h		(99%)	201
		 1.5 eq	Pd(OAc)$_2$ (10 mol %), **L13** (22 mol %), **N1** (2 eq), K$_2$CO$_3$ (6 eq), MeCN, Ar, 135 °C, 18 h		(60%)	89

TABLE 5. PALLADIUM(0)-CATALYZED *ORTHO*-ARYLATION OF ARYL HALIDES WITH BIFUNCTIONAL ARYL HALIDES (*Continued*)

Substrate	Bifunctional Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_{14}				
	 1.1 eq	$PdCl_2(PPh_3)_2$ (5 mol %), **N1** (2 eq), K_2CO_3 (3 eq), DMSO, N_2, 140 °C, 9 h	 (99%)	201
	 1.0 eq	$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %), **N1** (1 eq), Cs_2CO_3 (2 eq), DMF, Ar, 130 °C, 48 h	 (81%)	200
C_{16}				
 1.5 eq		$Pd(OAc)_2$ (10 mol %), **L2** (22 mol %), (+)-**N13** (50 mol %), K_2CO_3 (2.5 eq), MeCN, Ar, 70 °C, 36 h	 (55%) er = 97.0:3.0	104

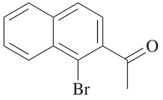
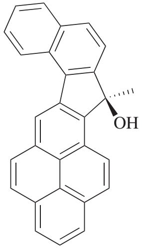
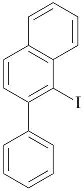
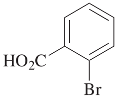
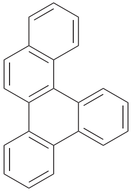
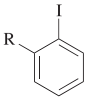
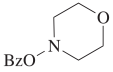
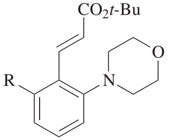
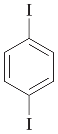
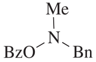
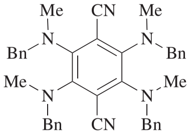
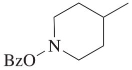
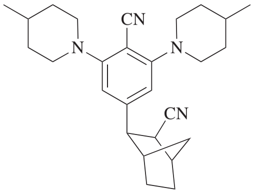
1.5 eq		Pd(OAc)$_2$ (10 mol %), **L2** (22 mol %), (+)-**N13** (10 mol %), K$_2$CO$_3$ (2.5 eq), MeCN, Ar, 120 °C		(71%) er > 99.5:0.5	97
	 2.2 eq	PdCl$_2$(PPh$_3$)$_2$ (5 mol %), **N1** (2 eq), K$_2$CO$_3$ (3 eq), BQ (1 eq), DMSO, N$_2$, 140 °C, 3 h		(78%)	201

TABLE 6. PALLADIUM(0)-CATALYZED *ORTHO*-AMINATION OF ARYL HALIDES

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_6					
	 1.5 eq	 1.2 eq	$Pd(OAc)_2$ (10 mol %), **L4** (20 mol %), **N1** (2 eq), Cs_2CO_3 (3 eq), toluene, N_2, 100 °C, 3–5 h	 R — Yield (%) — (*E*)/(*Z*) F — 79 — 2:1 Cl — 64 — 1:2	109
	 5.0 eq	$K_4[Fe(CN)_6]•3H_2O$ 10.0 eq	$Pd(OAc)_2$ (15 mol %), PPh_3 (30 mol %), **N1** (6 eq), Cs_2CO_3 (6 eq), toluene, Ar, 100 °C, 18 h	 (70%)	117
	 2.5 eq	$K_4[Fe(CN)_6]•3H_2O$ 10.0 eq	$Pd(OAc)_2$ (15 mol %), PPh_3 (30 mol %), **N1** (6 eq), Cs_2CO_3 (6 eq), toluene, Ar, 100 °C, 18 h	 (71%)	117

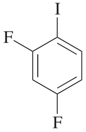
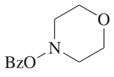
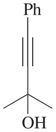
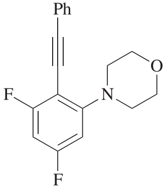
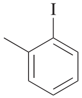
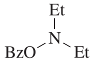
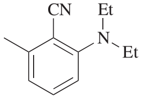
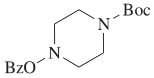
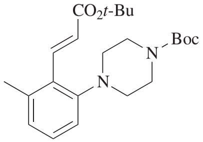
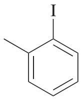
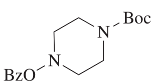
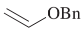
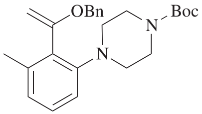
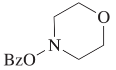
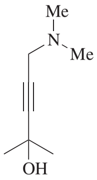
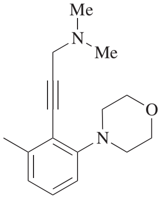
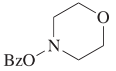
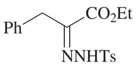
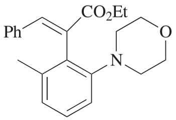
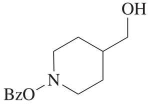
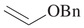
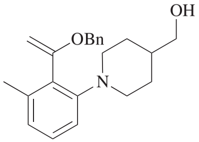
C_7		 1.1 eq	 1.2 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), **N1** (3 eq), Cs_2CO_3 (3 eq), 1,4-dioxane, N_2, 100 °C, 18 h	 (74%)	113
		 2.0 eq	$Zn(CN)_2$ 2.0 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), **N1** (10 eq), Cs_2CO_3 (3 eq), toluene, Ar, 120 °C, 24 h	 (29%)	116
		 1.5 eq	 1.2 eq	$Pd(OAc)_2$ (10 mol %), **L4** (20 mol %), **N1** (2 eq), Cs_2CO_3 (3 eq), MeCN, N_2, 100 °C, 3–5 h	 (65%) (*E*)/(*Z*) = 10:1	109

TABLE 6. PALLADIUM(0)-CATALYZED *ORTHO*-AMINATION OF ARYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_7					
	 1.5 eq	 3.0 eq	$PdCl_2$ (5 mol %), PPh_3 (10 mol %), **N1** (3 eq), Cs_2CO_3 (3 eq), 1,4-dioxane, N_2, 90 °C, 24 h	 (85%)	203
	 1.1 eq	 1.2 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), **N1** (3 eq), Cs_2CO_3 (3 eq), 1,4-dioxane, N_2, 100 °C, 18 h	 (63%)	113
	 1.5 eq	 1.2 eq	$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %), **N1** (2 eq), Cs_2CO_3 (2.2 eq), DCE, Ar, 60 °C, 30 h	 (57%)	112
	 1.5 eq	 3.0 eq	$PdCl_2$ (5 mol %), PPh_3 (10 mol %), **N1** (3 eq), Cs_2CO_3 (3 eq), 1,4-dioxane, N_2, 90 °C, 24 h	 (57%)	203

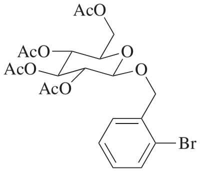
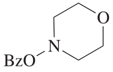
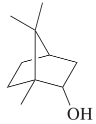
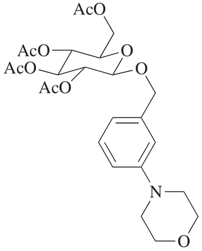
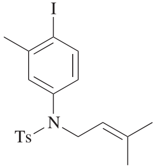
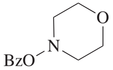
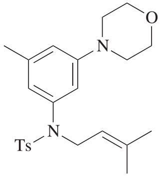
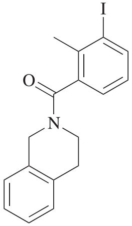
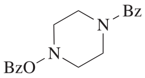
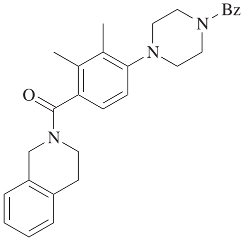
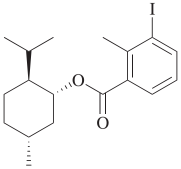
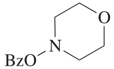
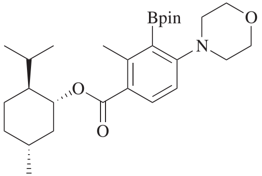
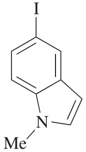
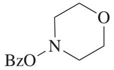
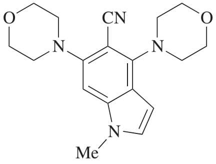
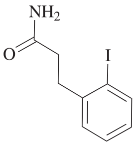
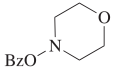
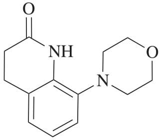
C$_8$		 1.6 eq	 1.0 eq	Pd(OAc)$_2$ (10 mol %), **L17** (11 mol %), **N1** (1 eq), Cs$_2$CO$_3$ (2.5 eq), 1,4-dioxane, N$_2$, 90 °C, 14 h		(71%)	51
		 1.1 eq	*i*-PrOH 1.2 eq	Pd(OAc)$_2$ (10 mol %), **L4** (25 mol %), **N1** (25 mol %), Cs$_2$CO$_3$ (2.5 eq), toluene, N$_2$, 100 °C, 24 h		(69%)	108
		 1.1 eq	MeB(OH)$_2$ 1.1 eq	Pd(OAc)$_2$ (5 mol %), **L4** (11 mol %), **N1** (1 eq), Cs$_2$CO$_3$ (3 eq), 1,4-dioxane, N$_2$, 100 °C, 18 h	 (48%)		204

TABLE 6. PALLADIUM(0)-CATALYZED *ORTHO*-AMINATION OF ARYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_8					
	 1.05 eq	B_2Pin_2 1.0 eq	$Pd(OAc)_2$ (5 mol %), **L4** (10.5 mol %), **N1** (1 eq), Cs_2CO_3 (2.5 eq), toluene, N_2, 100 °C, 16.5 h	 (70%)	111
	 2.5 eq	$K_4[Fe(CN)_6]•3H_2O$ 5.0 eq	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), **N1** (3 eq), Cs_2CO_3 (3 eq), toluene, Ar, 100 °C, 16 h	 (54%)	117
C_9					
	 2.0 eq	Intramolecular	$Pd(PPh_3)_4$ (10 mol %), **N1** (4 eq), Cs_2CO_3 (5 eq), toluene, Ar, 110 °C, 16 h	 (35%)	121

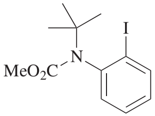
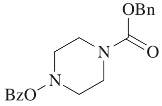
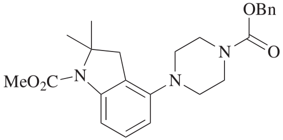
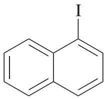
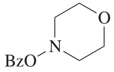
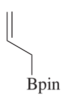
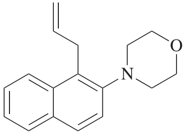
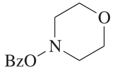
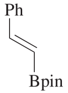
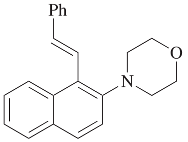
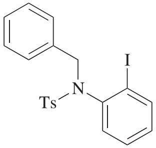
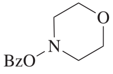
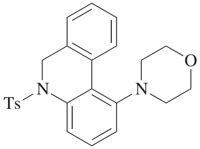
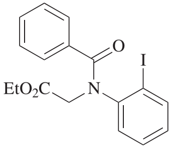
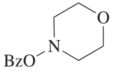
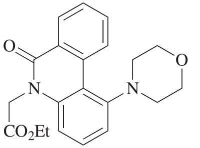
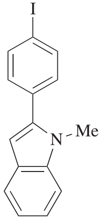
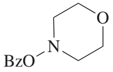
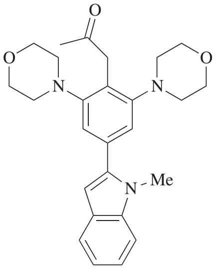
C_{10}					
	 2.0 eq	Intramolecular	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), **N1** (4 eq), *t*-$BuCO_2H$ (40 mol %), Cs_2CO_3 (4 eq), toluene, Ar, 140 °C, 12 h	 (45%)	122
	 1.5 eq	 1.5 eq	$Pd(OAc)_2$ (5 mol %), **L2** (20 mol %), **N1** (0.5 eq), Cs_2CO_3 (3 eq), toluene, N_2, 80 °C, 5 h	 (20%)	110
	 1.5 eq	 1.5 eq	$Pd(OAc)_2$ (5 mol %), **L2** (20 mol %), **N1** (0.5 eq), Cs_2CO_3 (3 eq), toluene, N_2, 80 °C, 5 h	 (67%)	110

TABLE 6. PALLADIUM(0)-CATALYZED *ORTHO*-AMINATION OF ARYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_{13}					
	 1.2 eq	Intramolecular	Pd(PPh$_3$)$_4$ (5 mol %), **N1** (4 eq), K_2CO_3 (3 eq), toluene, Ar, 110 °C, 16 h	 (42%)	202
	 1.2 eq	Intramolecular	Pd(PPh$_3$)$_4$ (5 mol %), **N1** (4 eq), K_2CO_3 (3 eq), toluene, Ar, 100 °C, 16 h	 (82%)	202
C_{14}					
	 2.4 eq	Acetone	Pd(OAc)$_2$ (10 mol %), **L2** (25 mol %), **N1** (1 eq), Cs_2CO_3 (5 eq), acetone, N_2, 100 °C, 18 h	 (63%)	115

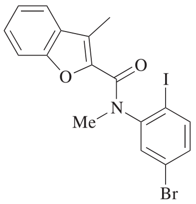
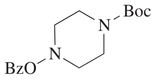
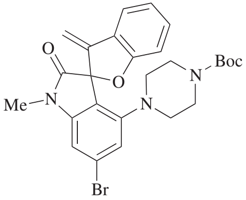
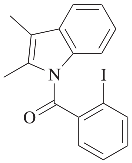
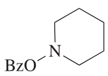
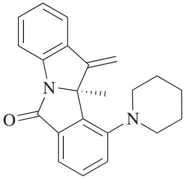
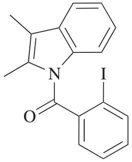
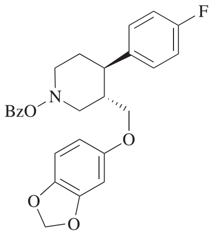
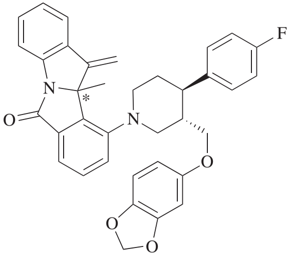
C_{16}		 2.0 eq	Intramolecular	$Pd(OAc)_2$ (10 mol %), **L11** (20 mol %), **N1** (4 eq), Cs_2CO_3 (4 eq), DCE, Ar, 120 °C, 18 h	 (51%)	205
C_{17}		 2.0 eq	Intramolecular	$Pd(OAc)_2$ (10 mol %), **L16** (20 mol %), **N1** (4 eq), Cs_2CO_3 (4 eq), toluene, Ar, 80 °C, 48 h	 (32%) er = 66.0:34.0	205
		 2.0 eq	Intramolecular	$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %) **N1** (4 eq), Cs_2CO_3 (4 eq), toluene, Ar, 80 °C, 48 h	 (75%) *dr = 1:1	205

TABLE 6. PALLADIUM(0)-CATALYZED *ORTHO*-AMINATION OF ARYL HALIDES (*Continued*)

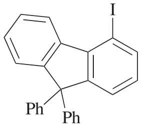
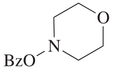
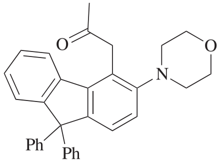
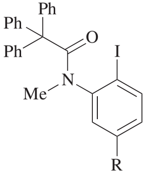
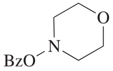
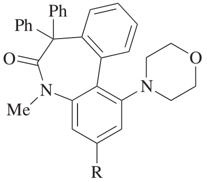
Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_{25}					
	 1.2 eq	Acetone	$Pd(OAc)_2$ (10 mol %), **L2** (25 mol %), **N1** (25 mol %), Cs_2CO_3 (3 eq), acetone, N_2, 100 °C, 18 h	 (98%)	115
C_{26-27}					
	 1.2 eq	Intramolecular	$Pd(PPh_3)_4$ (10 mol %), **N1** (4 eq), Cs_2CO_3 (3 eq), toluene, Ar, 100 °C, 16 h	 R — Yield (%) H — 55 Me — 55	202

TABLE 7. PALLADIUM(0)-CATALYZED *ORTHO*-ACYLATION AND *ORTHO*-ALKOXYCARBONYLATION OF ARYL HALIDES

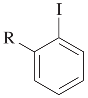
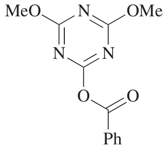
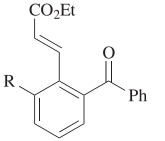
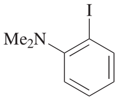
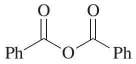
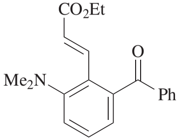
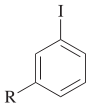
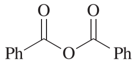
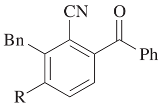
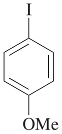
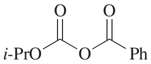
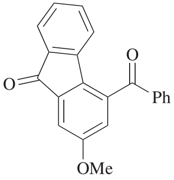
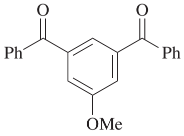
Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
$C_{6–9}$					
	 3.0 eq	 2.0 eq	[Pd(allyl)Cl]$_2$ (5 mol %), **L2** (10 mol %), **N1** (3 eq), K_2CO_3 (2 eq), toluene/MeCN (2:1), N_2, 100 °C, 5 h	 R — Yield (%) Cl — 37 TBSO — 64 MeO — 89 Me — 88 CF_3 — 42 Et — 89 *i*-Pr — 80	135
C_6					
	 3.0 eq	 2.0 eq	$PdCl_2$ (10 mol %), **L2** (20 mol %), **N1** (1 eq), Cs_2CO_3 (3 eq), DME, N_2, 90 °C, 20 h	 (74%) (*E*)/(*Z*) = 6:1	130

TABLE 7. PALLADIUM(0)-CATALYZED *ORTHO*-ACYLATION AND *ORTHO*-ALKOXYCARBONYLATION OF ARYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_6					
	 (1.5 eq), BnBr (1.5 eq)	CuCN 1.2 eq	$PdCl_2$ (10 mol %), **L2** (20 mol %), **N1** (2 eq), Cs_2CO_3 (4 eq), 1,4-dioxane, N_2, 90 °C, 12 h	 R — Yield (%) F — 69 Cl — 71 Br — 58	136
	 1.5 eq	Intramolecular	$[Pd(allyl)Cl]_2$ (5 mol %), **L2** (20 mol %), (±)-**N4** (0.5 eq), Cs_2CO_3 (4 eq), Bz_2O (2 eq), Me_4NCl (4 eq), THF/MeCN (10:1), N_2, 85 °C, 16 h	 **I** +  **II** **I** + **II** (80%) **I/II** = 56:44	137

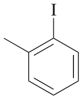
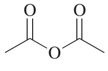
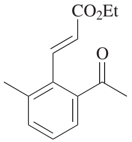
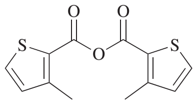
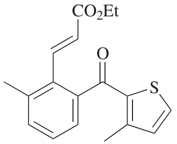
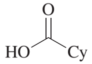
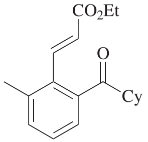
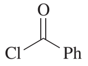
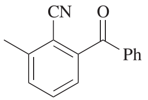
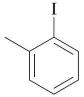
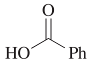
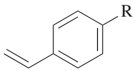
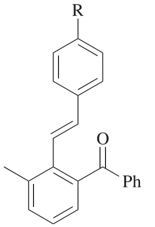
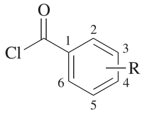
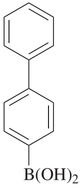
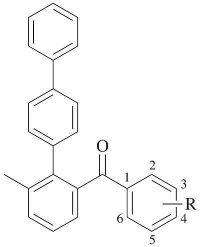
C_7 	 2.0 eq	 2.0 eq	$PdCl_2$ (10 mol %), **L2** (20 mol %), **N1** (1 eq), Cs_2CO_3 (3 eq), toluene, N_2, 100 °C, 20 h		(46%)	130
	 2.0 eq	 2.0 eq	$PdCl_2$ (10 mol %), **L2** (20 mol %), **N1** (1 eq), Cs_2CO_3 (3 eq), DME, N_2, 90 °C, 20 h		(63%)	130
	 4.0 eq	 1.5 eq	$[Pd(allyl)Cl]_2$ (2.5 mol %), **L2** (10 mol %), **N1** (2.5 eq), Cs_2CO_3 (3 eq), DCC (4.5 eq), toluene, N_2, 90 °C, 10 h		(71%)	206
	 3.0 eq	CuCN 1.2 eq	$PdCl_2$ (10 mol %), **L2** (20 mol %), **N1** (2 eq), Cs_2CO_3 (3 eq), H_2O (2 eq), 1,4-dioxane, N_2, 100 °C, 12 h		(65%)	132

TABLE 7. PALLADIUM(0)-CATALYZED *ORTHO*-ACYLATION AND *ORTHO*-ALKOXYCARBONYLATION OF ARYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_7					
	 4.0 eq	 1.5 eq	$[Pd(allyl)Cl]_2$ (2.5 mol %), **L2** (10 mol %), **N1** (2.5 eq), Cs_2CO_3 (3 eq), DCC (4.5 eq), toluene, N_2, 90 °C, 10 h	 R — Yield (%) H — 87 F — 72	206
	 3.0 eq	 2.0 eq	$PdCl_2$ (10 mol %), **L2** (20 mol %), **N1** (2 eq), Cs_2CO_3 (3 eq), MeCN, N_2, 100 °C, 12 h	 R — Yield (%) 3-F — 38 4-F — 45 3-Cl — 54 4-Cl — 60 3-MeO — 30 4-MeO — 75 4-Me — 62 4-Et — 50	207

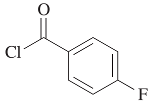
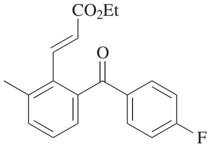
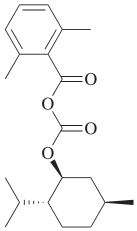
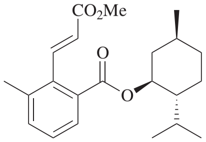
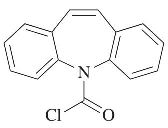
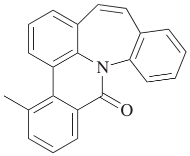
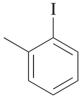
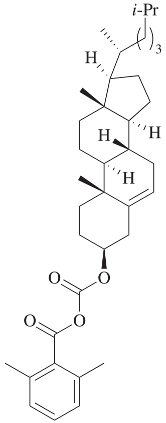
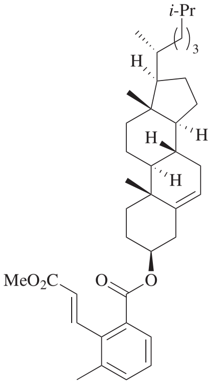
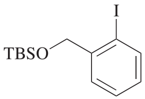
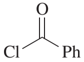
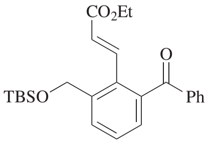
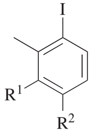
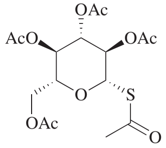
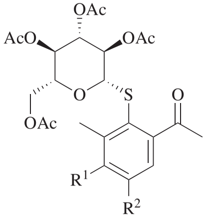
 3.0 eq	 2.0 eq	$PdCl_2$ (5 mol %), **L2** (10 mol %), **N1** (2 eq), Cs_2CO_3 (3 eq), H_2O (2 eq), 1,4-dioxane, N_2, 100 °C, 12 h		(45%)	131
 2.0 eq	 2.0 eq	$Pd(MeCN)_2Cl_2$ (10 mol %), **L2** (20 mol %), **N1** (1 eq), Cs_2CO_3 (4 eq), 1,4-dioxane, N_2, 80 °C, 16 h		(51%)	143
 2.0 eq	Intramolecular	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), **N1** (1 eq), Cs_2CO_3 (4 eq), toluene, 95 °C, 6 h		(41%)	29

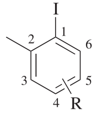
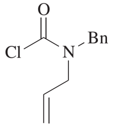
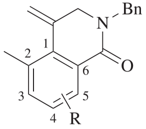
TABLE 7. PALLADIUM(0)-CATALYZED *ORTHO*-ACYLATION AND *ORTHO*-ALKOXYCARBONYLATION OF ARYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_7					
	 2.0 eq	 2.0 eq	$Pd(MeCN)_2Cl_2$ (10 mol %), **L2** (20 mol %), **N1** (1 eq), Cs_2CO_3 (4 eq), 1,4-dioxane, N_2, 80 °C, 16 h	 (76%)	143
	 3.0 eq	 2.0 eq	$PdCl_2$ (5 mol %), **L2** (10 mol %), **N1** (2 eq), Cs_2CO_3 (3 eq), H_2O (2 eq), 1,4-dioxane, N_2, 100 °C, 12 h	 (48%)	131

C_{7-8}

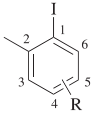
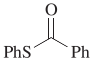
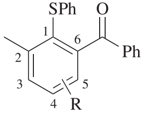
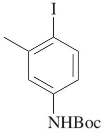
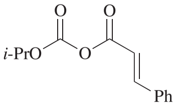
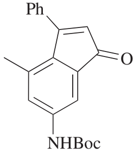
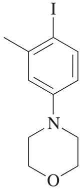
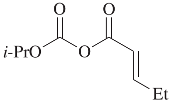
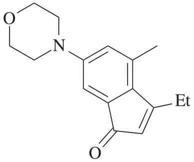
 2.0 eq		Intramolecular	$Pd(TFA)_2$ (10 mol %), **L18** (20 mol %), **N1** (4 eq), K_3PO_4 (3 eq), 1,4-dioxane, Ar, 100 °C, 17 h		140

R^1	R^2	Yield (%)
H	H	61
H	Me	58
Me	H	70

 2.0 eq		Intramolecular	$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %), **N1** (1 eq), Cs_2CO_3 (4 eq), THF, N_2, 30 °C, 12 h		208

R	Yield (%)
H	73
3-Cl	88
3-Me	78
4-Me	31

TABLE 7. PALLADIUM(0)-CATALYZED *ORTHO*-ACYLATION AND *ORTHO*-ALKOXYCARBONYLATION OF ARYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_7					
	 1.5 eq	Intramolecular	$PdCl_2$ (10 mol %), **L2** (25 mol %), CuI (20 mol %), **N1** (3 eq), Cs_2CO_3 (3 eq), 1,4-dioxane, N_2, 120 °C, 12 h	 R — Yield (%) H — 76 3-F — 78 4-F — 53 3-Cl — 72 4-O_2N — 53	138
	 2.0 eq	Intramolecular	$[Pd(allyl)Cl]_2$ (5 mol %), **L2** (20 mol %), (±)-**N4** (50 mol %), Cs_2CO_3 (4 eq), NMe_4Cl (4 eq), 1,4-dioxane/THF (3:1), N_2, 85 °C, 14 h	 (76%)	142
	 2.0 eq	Intramolecular	$[Pd(allyl)Cl]_2$ (5 mol %), **L2** (20 mol %), (±)-**N15** (50 mol %), Cs_2CO_3 (4 eq), Me_4NCl (4 eq), 1,4-dioxane/THF (3:1), N_2, 85 °C, 3 h	 (58%)	142

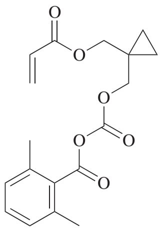
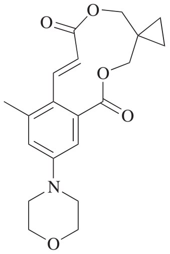
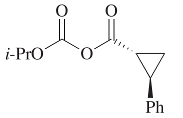
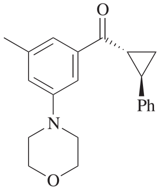
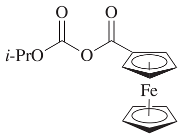
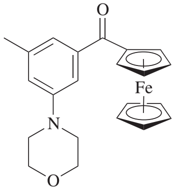
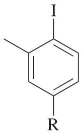
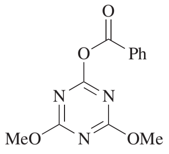
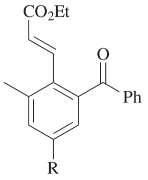
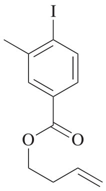
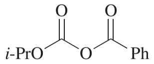
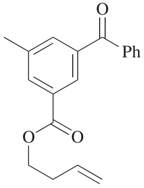
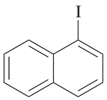
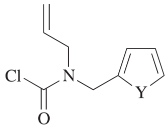
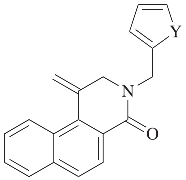
 2.0 eq (slow addition)	Intramolecular	$Pd(MeCN)_2Cl_2$ (10 mol %), **L2** (20 mol %), **N1** (1 eq), Cs_2CO_3 (4 eq), 1,4-dioxane, N_2, 80 °C, 16 h		(43%)	143
 2.0 eq	Intramolecular	$[Pd(allyl)Cl]_2$ (5 mol %), **L2** (20 mol %), (±)-**N4** (0.5 eq), Cs_2CO_3 (4 eq), Me_4NCl (4 eq), THF/MeCN (10:1), N_2, 85 °C, 16 h		(69%)	137
 2.0 eq	Intramolecular	$[Pd(allyl)Cl]_2$ (5 mol %), **L2** (20 mol %), (±)-**N4** (0.5 eq), Cs_2CO_3 (4 eq), Me_4NCl (4 eq), THF/MeCN (10:1), N_2, 85 °C, 16 h		(86%)	137

TABLE 7. PALLADIUM(0)-CATALYZED *ORTHO*-ACYLATION AND *ORTHO*-ALKOXYCARBONYLATION OF ARYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_8					
	 3.0 eq	 2.0 eq	$[Pd(allyl)Cl]_2$ (5 mol %), **L2** (10 mol %), **N1** (2 eq), K_2CO_3 (2 eq), toluene/MeCN (2:1), N_2, 100 °C, 5 h	 R — Yield (%) Me — 64 MeO_2C — 90	135
	 1.5 eq	Intramolecular	$[Pd(allyl)Cl]_2$ (5 mol %), **L2** (20 mol %), (±)-**N4** (1 eq), Cs_2CO_3 (4 eq), Bz_2O (2 eq), THF, N_2, 70 °C, 20 h	 (58%)	137
C_{10}					
 2.0 eq		Intramolecular	$Pd(OAc)_2$ (10 mol %), **L2** (20 mol %), **N1** (1 eq), Cs_2CO_3 (4 eq), THF, N_2, 30 °C, 12 h		208

Y	Yield (%)
O	80
S	43

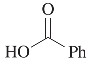
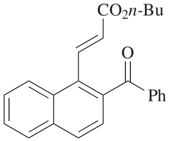
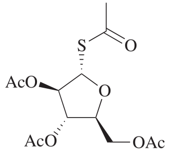
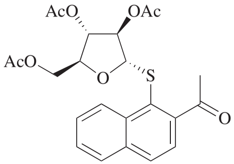
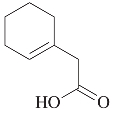
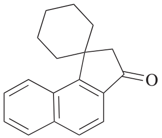
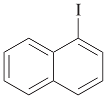
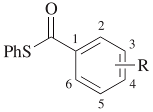
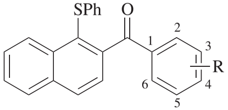
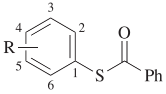
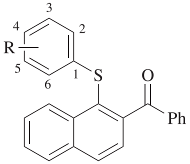
	 4.0 eq	 1.5 eq	$[Pd(allyl)Cl]_2$ (2.5 mol %), **L2** (10 mol %), **N1** (2.5 eq), Cs_2CO_3 (3 eq), DCC (4.5 eq), N_2, 90 °C, 10 h		(69%)	206
2.0 eq		Intramolecular	$Pd(TFA)_2$ (10 mol %), **L16** (20 mol %), **N1** (4 eq), K_3PO_4 (3 eq), 1,4-dioxane, Ar, 100 °C, 17 h	 (84%)		140
	 4.0 eq	Intramolecular	1. $Pd(TFP)_2Cl_2$ (5 mol %), Yamaguchi reagent (2 eq), **N1** (2 eq), Cs_2CO_3 (4 eq), 1,4-dioxane, N_2, 90 °C, 10 h 2. Pd/C, H_2, rt, 2 h		(46%)	141

TABLE 7. PALLADIUM(0)-CATALYZED *ORTHO*-ACYLATION AND *ORTHO*-ALKOXYCARBONYLATION OF ARYL HALIDES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_{10}					
	 1.5 eq	Intramolecular	$PdCl_2$ (10 mol %), **L2** (25 mol %), CuI (20 mol %), **N1** (3 eq), Cs_2CO_3 (3 eq), 1,4-dioxane, N_2, 120 °C, 12 h	 R — Yield (%) 4-F — 79 2-Cl — 81 3-O_2N — 78 2,6-$(MeO)_2$ — 92 2-Me — 94 4-Ph — 76	138
	 1.5 eq	Intramolecular	$PdCl_2$ (10 mol %), **L2** (25 mol %), CuI (20 mol %), **N1** (3 eq), Cs_2CO_3 (3 eq), 1,4-dioxane, N_2, 120 °C, 12 h	 R — Yield (%) 4-F — 42 2-Cl — 93 4-Cl — 82 4-MeO — 41 2-Me — 66 2,6-$(Me)_2$ — 46 4-*t*-Bu — 66	138

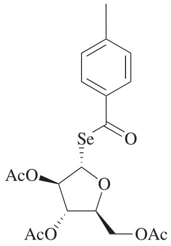
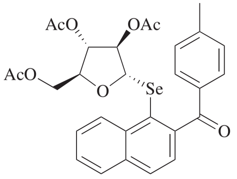
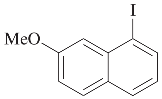
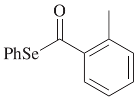
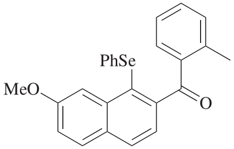
2.0 eq		Intramolecular	Pd(MeCN)$_2$Cl$_2$ (10 mol %), **L18** (20 mol %), (±)-**N2** (4 eq), K$_2$CO$_3$ (3 eq), DCP, Ar, 95 °C, 16 h	 (55%)	140
	 1.5 eq	Intramolecular	PdCl$_2$ (10 mol %), **L2** (25 mol %), **N1** (3 eq), K$_2$CO$_3$ (3 eq), DCP/DMI (20:1), N$_2$, 100 °C, 16 h	 (82%)	139

TABLE 8. PALLADIUM(0)-CATALYZED *ORTHO*-THIOLATION OF ARYL HALIDES

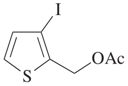
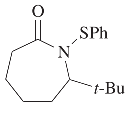
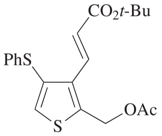
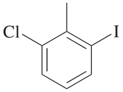
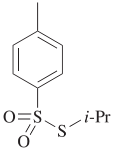
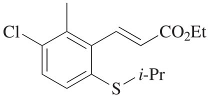
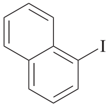
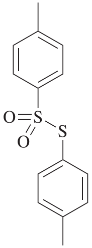
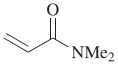
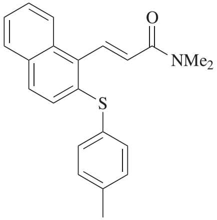
Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_5					
	 2.0 eq	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L2** (25 mol %), **N1** (0.5 eq), CuTC (20 mol %), Cs_2CO_3 (2 eq), EtOAc, N_2, 105 °C, 12 h	 (36%)	145
C_7					
	 1.5 eq	 2.0 eq	$Pd_2(dba)_3$ (5 mol %), **L2** (22 mol %), (±)-**N7** (3 eq), K_2CO_3 (3 eq), THF, N_2, dark, 110 °C, 24 h	 (55%)	144
C_{10}					
	 1.5 eq	 2.0 eq	$Pd_2(dba)_3$ (5 mol %), **L2** (22 mol %), (±)-**N7** (3 eq), K_2CO_3 (3 eq), THF, N_2, dark, 110 °C, 24 h	 (48%)	144

TABLE 9. PALLADIUM(0)-CATALYZED *ORTHO*-FUNCTIONALIZATION OF ALKENYL (PSEUDO)HALIDES

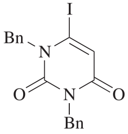
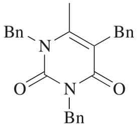
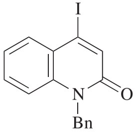
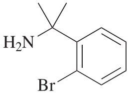
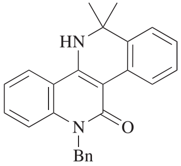
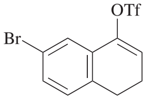
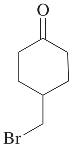
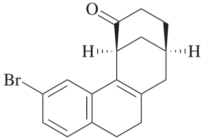
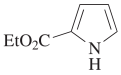
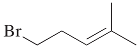
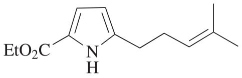
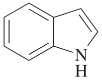
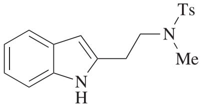
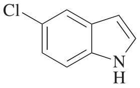
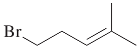
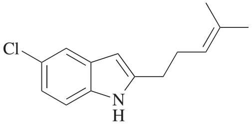
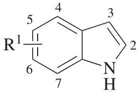
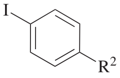
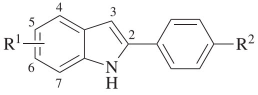
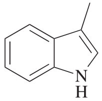
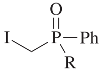
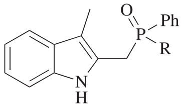
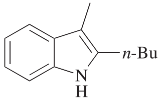
Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_4					
	BnCl 1.5 eq	$(HO)_2BMe$ 2.0 eq	$Pd(OAc)_2$ (10 mol %), (±)-**N6** (1 eq), K_2CO_3 (2.5 eq), 1,4-dioxane, Ar, 130 °C, 48 h	 (50%)	147
C_9					
	 1.0 eq	Intramolecular	$Pd(OAc)_2$ (10 mol %), **N1** (1 eq), K_2CO_3 (2.5 eq), DMF, 105 °C, 20 h	 (88%)	146
C_{10}					
	 3.5 eq	Intramolecular	$Pd(OAc)_2$ (10 mol %), **L14** (20 mol %), **L15** (20 mol %), (±)-**N6** (2 eq), K_3PO_4 (4 eq), 1,4-dioxane, N_2, 80 °C, 36 h	 (64%) er = 95.5:4.5	46

TABLE 10. PALLADIUM(II)-CATALYZED MONOFUNCTIONALIZATION OF UNPROTECTED INDOLES AND PYRROLES

Substrate	Electrophile	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_5				
	 2.0 eq	$Pd(MeCN)_2Cl_2$ (10 mol %), **N1** (2 eq), $KHCO_3$ (3 eq), DMA, air, 90 °C, 22 h	 (50%)	151
C_8				
	 2.0 eq	$Pd(MeCN)_2Cl_2$ (10 mol %), **N1** (2 eq), K_2CO_3 (2 eq), DMA/H_2O (2:1), Ar, 90 °C, 68 h	 (43%)	11
	 2.0 eq	$Pd(MeCN)_2Cl_2$ (10 mol %), **N1** (2 eq), $KHCO_3$ (3 eq), DMA/H_2O (2:1), N_2, 70 °C, 38 h	 (56%)	11
C_{8-9}				
	 2.0 eq	$Pd(MeCN)_2Cl_2$ (10 mol %), **N1** (2 eq), K_2CO_3 (2 eq), DMA/H_2O (2:1), 70 °C, 17 h		152

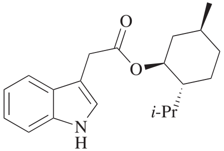
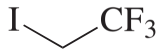
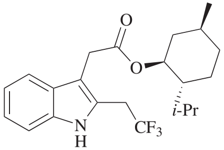
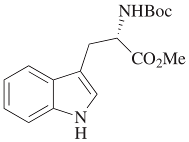
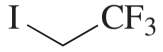
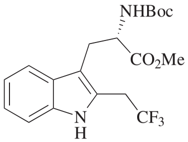
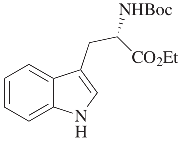
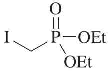
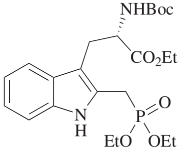
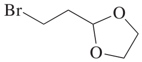
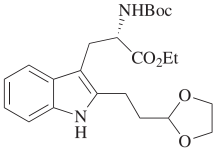
R^1	R^2	Yield (%)
H	H	83
H	Br	89
H	CF_3	90
5-F	H	49

6-F	H	41
5-Br	H	78
5-MeO	H	99
3-Me	H	89
4-Me	H	63

C_9	 1.5 eq		$Pd(acac)_2$ (10 mol %), **N1** (2 eq), K_2CO_3 (2 eq), DMF, air, 80 °C, 36 h			209
	n-BuBr 2.3 eq		$Pd(MeCN)_2Cl_2$ (10 mol %), **N1** (2 eq), K_2CO_3 (2 eq), H_2O (0.5 M), DMA, Ar, 70 °C, 14 h		(46%)	38

R	Yield (%)
EtO	89
n-BuO	88
i-Pr	80
Cy	78
Ph	92

TABLE 10. PALLADIUM(II)-CATALYZED MONOFUNCTIONALIZATION OF UNPROTECTED INDOLES AND PYRROLES (*Continued*)

Substrate	Electrophile	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_{10}				
	 3.0 eq	Pd(acac)$_2$ (15 mol %), **L19** (40 mol %), **N1** (2 eq), KHCO$_3$ (2 eq), DMF, Ar, 100 °C, 8 h	 (58%)	153
C_{11}				
	 3.0 eq	Pd(acac)$_2$ (15 mol %), **L19** (40 mol %), **N1** (2 eq), KHCO$_3$ (2 eq), DMF, Ar, 100 °C, 8 h	 (56%) er = 99.0:1.0	153
 1.5 eq		Pd(acac)$_2$ (10 mol %), **N1** (2 eq), K$_2$CO$_3$ (2 eq), DMF, air, 80 °C, 36 h	 (56%)	209
	 4.0 eq	PdCl$_2$ (10 mol %), **N1** (2 eq), K$_2$CO$_3$ (4 eq), DMF/H$_2$O (2:1), air, 60 °C, 24 h	 (62%)	150

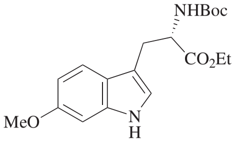
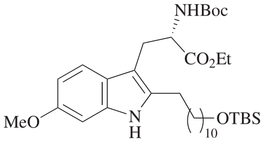
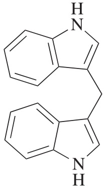
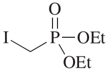
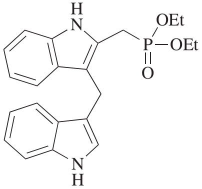
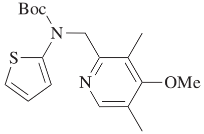
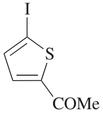
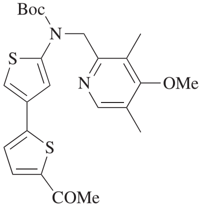
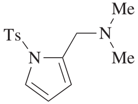
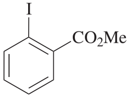
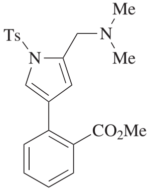
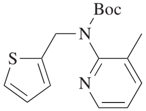
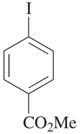
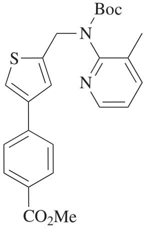
	 4.0 eq	$PdCl_2$ (10 mol %), **N1** (2 eq), K_2CO_3 (4 eq), DMF/H_2O (2:1), air, 60 °C, 24 h	 (80%)	150
C_{17}				
	 1.0 eq	$Pd(acac)_2$ (10 mol %), **N1** (2 eq), K_2CO_3 (2 eq), DMF, air, 80 °C, 36 h	 (60%)	209

TABLE 11. PALLADIUM(II)-CATALYZED *META*-SELECTIVE C–H ALKYLATION OF ARENES WITH A DIRECTING GROUP

Substrate	Electrophile	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_4				
	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L23** (20 mol %), (±)-**N14** (1.5 eq), AgOAc (3 eq), DCE, air, 100 °C, 24 h	 (47%)	54
C_5				
	 3.0 eq	$Pd(OAc)_2$ (10 mol %), $AsPh_3$ (25 mol %), **N1** (2 eq), CsOAc (3 eq), $LiOAc•2H_2O$ (1 eq), $Cu(OAc)_2•H_2O$ (0.5 eq), HOAc (15 eq), AgOAc (3.5 eq), PhCl, 130 °C, 24 h	 (48%)	14
	 2.0 eq	$Pd(OAc)_2$ (5 mol %), **L22** (7.5 mol %), (±)-**N14** (1.5 eq), AgOAc (3 eq), $CHCl_3$, air, 100 °C, 24 h	 (61%)	160

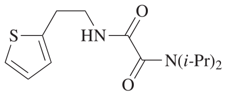
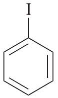
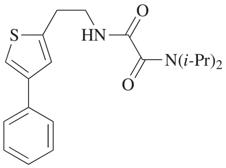
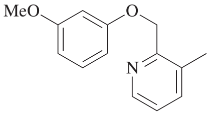
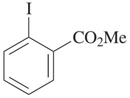
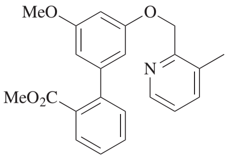
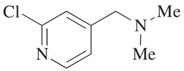
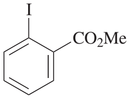
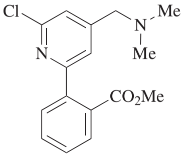
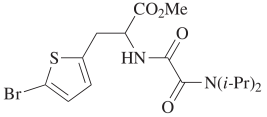
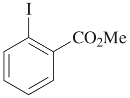
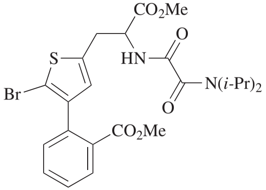
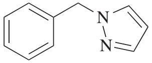
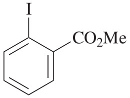
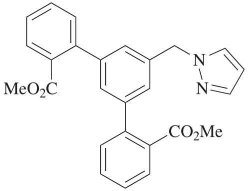
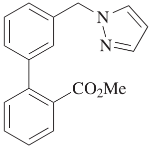
C_6				
	 3.0 eq	$Pd(OAc)_2$ (10 mol %), **N1** (1 eq), AgOAc (3 eq), 1-$AdCO_2H$ (0.5 eq), mesitylene, 100 °C, 24 h	 (87%)	161
	 3.0 eq	$Pd(OAc)_2$ (10 mol %), **L20** (10 mol %), (±)-**N14** (1.5 eq), AgOAc (3 eq), $CHCl_3$, air, 100 °C, 24 h	 (91%)	54
	 3.0 eq	$Pd(OAc)_2$ (10 mol %), $AsPh_3$ (25 mol %), **N1** (2 eq), CsOAc (3 eq), LiOAc•$2H_2O$ (1 eq), Cu(OAc)•$2H_2O$ (0.5 eq), HOAc (15 eq), AgOAc (3.5 eq), PhCl, 130 °C, 24 h	 (66%)	14

TABLE 11. PALLADIUM(II)-CATALYZED *META*-SELECTIVE C–H ALKYLATION OF ARENES WITH A DIRECTING GROUP (*Continued*)

Substrate	Electrophile	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_7				
	 3.0 eq	$Pd(OAc)_2$ (10 mol %), **N1** (1 eq), AgOAc (3 eq), 1-$AdCO_2H$ (0.5 eq), mesitylene, 100 °C, 24 h	 (80%)	161
	 3.0 eq	$Pd(OAc)_2$ (10 mol %), **L20** (20 mol %), **N1** (1.5 eq), AgOAc (3 eq), $CHCl_3$, air, 95 °C, 24 h	 **I** +  **II** **I** + **II** (84%), **I**/**II** = 2:1	54

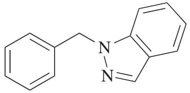
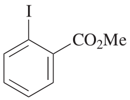
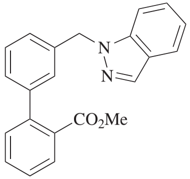
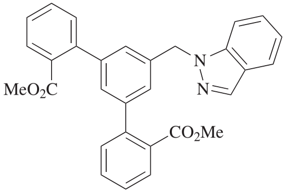
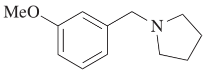
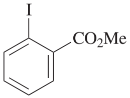
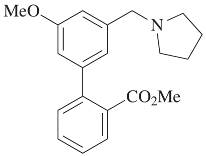
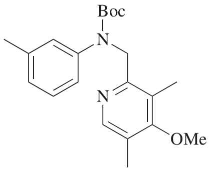
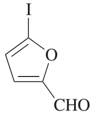
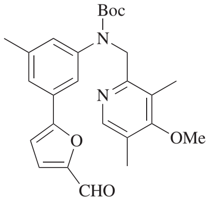
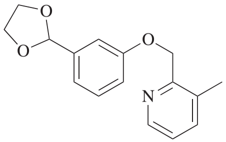
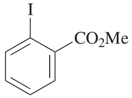
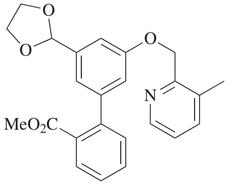
	 3.0 eq	$Pd(OAc)_2$ (10 mol %), **L20** (20 mol %), **N1** (1.5 eq), AgOAc (3 eq), $CHCl_3$, air, 95 °C, 24 h	 **I** +  **II** **I** + **II** (50%), **I**/**II** = 3:1		54
	 2.0 eq	$Pd(OAc)_2$ (10 mol %), $AsPh_3$ (25 mol %), **N1** (2 eq), CsOAc (3 eq), $LiOAc•2H_2O$ (1 eq), $Cu(OAc)_2•H_2O$ (0.5 eq), HOAc (15 eq), AgOAc (2.5 eq), PhCl, 100 °C, 24 h		(17%)	14

TABLE 11. PALLADIUM(II)-CATALYZED *META*-SELECTIVE C–H ALKYLATION OF ARENES WITH A DIRECTING GROUP (*Continued*)

*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*

C_7

Substrate	Electrophile	Conditions	Product(s) and Yield(s)	Refs
	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L23** (20 mol %), (±)-**N14** (1.5 eq), AgOAc (3 eq), DCE, air, 100 °C, 24 h	 (87%)	54
	 3.0 eq	$Pd(OAc)_2$ (10 mol %), **L20** (10 mol %), (±)-**N14** (1.5 eq), AgOAc (3 eq), $CHCl_3$, air, 100 °C, 24 h	 (53%)	54

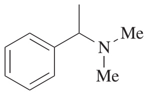
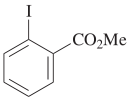
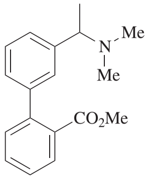
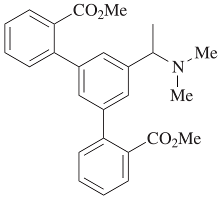
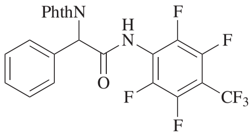
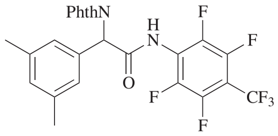
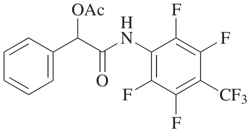
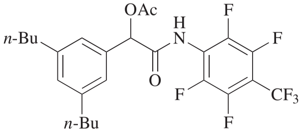
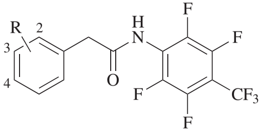
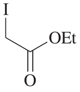
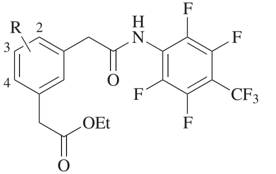
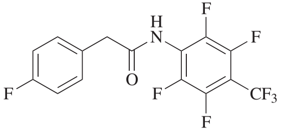
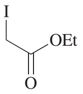
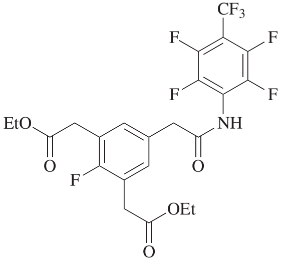
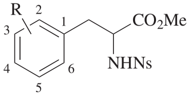
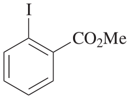
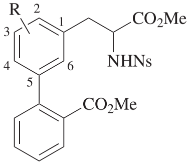
C_8		 4.0 eq	$Pd(OAc)_2$ (10 mol %), $AsPh_3$ (25 mol %), **N1** (2 eq), CsOAc (3 eq), LiOAc•$2H_2O$ (1 eq), $Cu(OAc)_2$•H_2O (0.5 eq), HOAc (15 eq), AgOAc (4.5 eq), PhCl, 100 °C, 36 h	 **I** +  **II** **I** + **II** (64%), **I**/**II** = 1.1:1		14
		MeI 5.0 eq	$Pd(OAc)_2$ (20 mol %), **L24** (40 mol %), **N1** (3 eq), AgOAc (5 eq), DCE, 95 °C, 16 h		(82%)	13

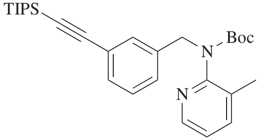
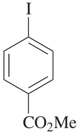
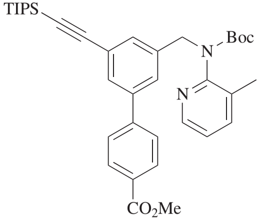
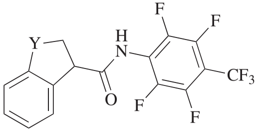
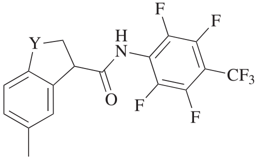
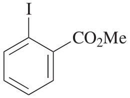
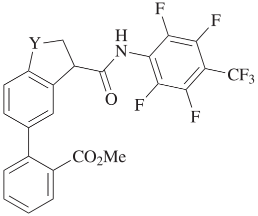
TABLE 11. PALLADIUM(II)-CATALYZED *META*-SELECTIVE C–H ALKYLATION OF ARENES WITH A DIRECTING GROUP (*Continued*)

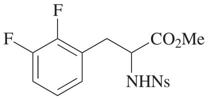
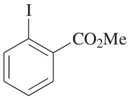
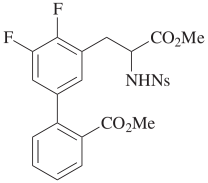
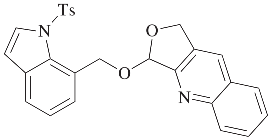
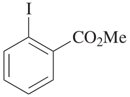
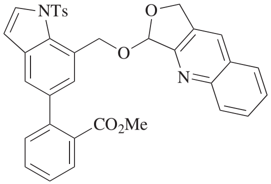
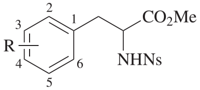
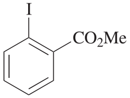
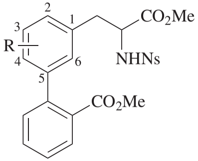
Substrate	Electrophile	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_8				
	*n*-BuI 5.0 eq	$Pd(OAc)_2$ (20 mol %), **L25** (20 mol %), (±)-**N14** (3 eq), AgOAc (6 eq), DCE, 75 °C, 16 h	 (80%)	12
	 3.0 eq	$Pd(OAc)_2$ (10 mol %), **L24** (20 mol %), **N1** (1.5 eq), AgOAc (3 eq), DCE, 95 °C, 16 h	 R — Yield (%) 2-F — 68 3-F — 86 2-Cl — 63 2-Br — 81	13

		 5.0 eq	$Pd(OAc)_2$ (20 mol %), **L24** (40 mol %), **N1** (3 eq), AgOAc (5 eq), DCE, 95 °C, 16 h	 (59%)	13
C_9		 3.0 eq	$Pd(OAc)_2$ (10 mol %), **L21** (20 mol %), **N1** (20 mol %), AgOAc (3 eq), MTBE, 80 °C, 12 h		159

R	Yield (%)
2-F	87
2-Cl	92
3-Cl	92
2-Br	85
3-Br	82
2-MeO	88
3-MeO	85

TABLE 11. PALLADIUM(II)-CATALYZED *META*-SELECTIVE C–H ALKYLATION OF ARENES WITH A DIRECTING GROUP (*Continued*)

Substrate	Electrophile	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*				
C_9				
	 2.0 eq	$Pd(OAc)_2$ (5 mol %), **L22** (7.5 mol %), (±)-**N14** (1.5 eq), AgOAc (3 eq), $CHCl_3$, air, 100 °C, 24 h	 (50%)	160
	MeI 3.0 eq	$Pd(OAc)_2$ (20 mol %), **L24** (40 mol %), **N1** (1.5 eq), AgOAc (3 eq), DCE, 95 °C, 16 h	 Y — Yield (%) TsN — 73 O — 81	13
	 3.0 eq	$Pd(OAc)_2$ (15 mol %), **L24** (30 mol %), **N1** (1.5 eq), AgOAc (3 eq), MTBE, 95 °C, 12 h	 Y — Yield (%) TsN — 69 O — 82	13

		 3.0 eq	$Pd(OAc)_2$ (10 mol %), **L21** (20 mol %), **N1** (20 mol %), AgOAc (3 eq), MTBE, 80 °C, 12 h		(86%)	159
		 4.0 eq	$Pd(TFA)_2$ (10 mol %), **L26** (20 mol %), (±)-**N14** (1.5 eq), AgOAc (4 eq), DCE, air, 100 °C, 24 h	 (47%)		210
C_{10}						
		 3.0 eq	$Pd(OAc)_2$ (10 mol %), **L21** (20 mol %), **N1** (20 mol %), AgOAc (3 eq), MTBE, 80 °C, 12 h			159

R	Yield (%)
2-Me	90
3-Me	84
2-CF_3	91
3-CF_3	92

TABLE 11. PALLADIUM(II)-CATALYZED *META*-SELECTIVE C–H ALKYLATION OF ARENES WITH A DIRECTING GROUP (*Continued*)

*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*

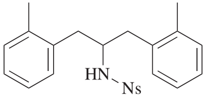
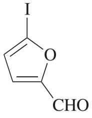
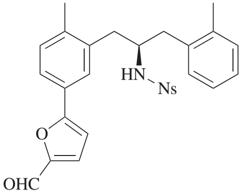
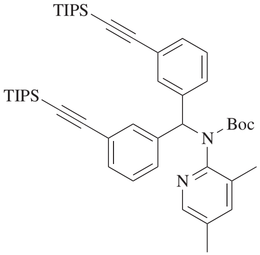
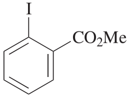
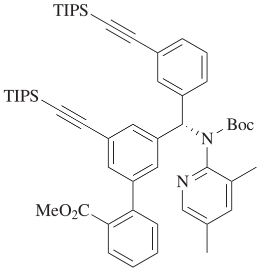
Substrate	Electrophile	Conditions	Product(s) and Yield(s)	Refs
C_{17}				
	 3.0 eq	$Pd(OAc)_2$ (15 mol %), **L21** (30 mol %), (+)-**N14** (50 mol %), AgOAc (3 eq), MTBE, N_2, 90 °C, 24 h	 (53%) er = 96.0:4.0	44
	 3.0 eq	$Pd(OAc)_2$ (10 mol %), **L22** (15 mol %), $(PhO)_2PO_2H$ (15 mol %), (+)-**N14** (20 mol %), AgOAc (3 eq), $CHCl_3$, N_2, 80 °C, 12 h	 (40%) er = 93.0:7.0	44

TABLE 12. PALLADIUM(II)-CATALYZED *ORTHO*-FUNCTIONALIZATION OF ARYLBORON SPECIES

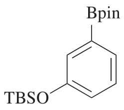
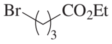
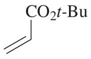
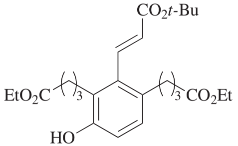
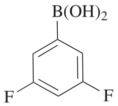
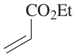
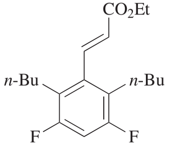
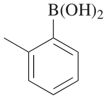
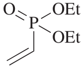
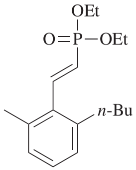
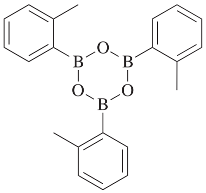
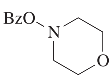
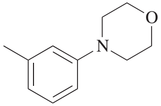
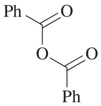
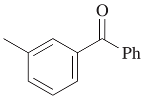
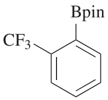
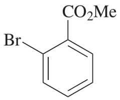
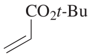
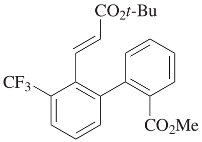
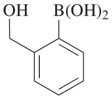
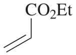
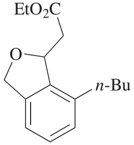
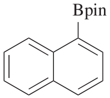
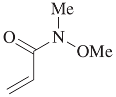
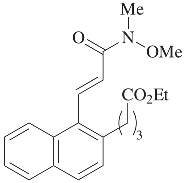
Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_6					
 1.5 eq	 2.4 eq		$Pd(OAc)_2$ (10 mol %), (±)-**N2** (1.5 eq), K_2CO_3 (3 eq), DMA, air, 30 °C, 16 h	 (40%)	16
	*n*-BuI 3.0 eq	 2.0 eq	$Pd(OAc)_2$ (10 mol %), **L27** (20 mol %), **N1** (1 eq), BQ (0.25 eq), $Cu(OAc)_2$ (2 eq), KOAc (3 eq), DMF, N_2, 80 °C, 10 h	 (93%)	15
C_7					
	*n*-BuI 3.0 eq	 3.0 eq	$Pd(OAc)_2$ (10 mol %), **L27** (20 mol %), **N1** (1 eq), BQ (0.25 eq), H_2O (2 eq), $Cu(OAc)_2$ (2 eq), KOAc (3 eq), DMF, N_2, 80 °C, 10 h	 (49%)	15

TABLE 12. PALLADIUM(II)-CATALYZED *ORTHO*-FUNCTIONALIZATION OF ARYLBORON SPECIES (*Continued*)

Substrate	Electrophile	Terminating Reagent	Conditions	Product(s) and Yield(s)	Refs
*Please refer to the Charts preceding the tables for structures corresponding to the **bold** numbers.*					
C_7					
 2.5 eq (monomer)		Intramolecular	Pd(OPiv)$_2$ (20 mol %), **L28** (40 mol %), **N1** (50 mol %), Cs_2CO_3 (50 mol %), CsI (50 mol %), BQ (15 mol %), toluene, N_2, 100 °C, 12 h	 (66%)	41
1.0 eq (monomer)	 2.0 eq	Intramolecular	Pd(TFA)$_2$ (10 mol %), $AsPh_3$ (30 mol %), **N1** (20 mol %), K_2CO_3 (15 mol %), CuI (30 mol %), BQ (10 mol %), 4 Å MS, toluene, N_2, 100 °C, 14 h	 (65%)	41
 4.0 eq		 1.2 eq	Pd(OAc)$_2$ (5 mol %), **N16** (2.5 eq), K_2CO_3 (3 eq), DMF, O_2, 100 °C, 10 h	 (44%)	42

	n-BuI 3.0 eq	 2.0 eq	Pd(OAc)$_2$ (10 mol %), **L29** (20 mol %), **N1** (1 eq), BQ (0.25 eq), H$_2$O (2 eq), Cu(OAc)$_2$ (2 eq), KOAc (3 eq), DMF, N$_2$, 80 °C, 10 h	 (41%)	15
C$_{10}$					
 1.5 eq	 1.2 eq		Pd(OAc)$_2$ (10 mol %), (±)-**N2** (1.5 eq), K$_2$CO$_3$ (2 eq), DMA, air, 30 °C, 16 h	 (75%)	16

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